Jan van Maarseveen

Syntheses and Biological Activity of some Tetracyclic Eudistomins and Analogs

A Study of Intramolecular Pictet-Spengler Condensations

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EEN WETENSCHAPPELIJKE PROEVE OP HET GEBIED VAN DE NATUURWETENSCHAPPEN

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR AAN DE KATHOLIEKE UNIVERSITEIT NIJMEGEN, VOLGENS BESLUIT VAN HET COLLEGE VAN DECANEN IN HET OPENBAAR TE VERDEDIGEN OP MAANDAG 9 MEI 1994 DES NAMIDDAGS TE 1.30 UUR PRECIES

DOOR

JAN HERMAN VAN MAARSEVEEN

GEBOREN OP 6 FEBRUARI 1963 TE ENSCHEDE

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Dr. C.G. Kruse

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Ter nagedachtenis aan Elna Oberyé

Aan mijn ouders

Voor Ine

Een woord van dank

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Dr B B Shankar (Schering-Plough, Bloomfield, NJ, USA) sent me without hesitation spectral data of eudistomin analogs These data were invaluable to me Without Prof Dr Andy Davis (Univ of Wollongong, NSW, Australia), I still woudn't know what tunicates are and how *Eudistoma Olivaceum* looks like

Ik heb veel geleerd van, ondersteuning gehad van, en plezier beleefd met vele collega's

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De illustratie op de omslag was een idee van Ine en is gerealiseerd door Jan Ibelings

Zonder Ine zou dit alles een ware sisyfusarbeid geweest zijn Jij hebt ervoor gezorgd dat thuis altijd een sfeer hing waarin ik mij optimaal concentreren en ontspannen kon

Jan

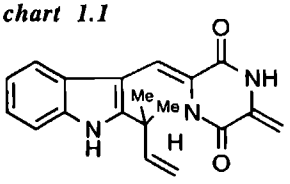
CONTENTS

1 Introduction

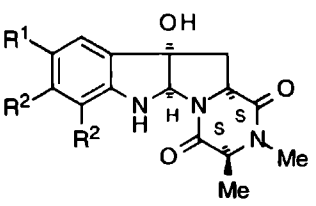
1.1 General

The study of the utility of *N_b-hydroxy*tryptophan and its derivatives in the synthesis of natural compounds has been ongoing in Nijmegen since 1981 [1] Initially N-hydroxytryptophan was studied in approaches to neoechinulin B **1**,[2] sporidesmin B **2**,[3] fumitremorgin C **3**[4,5] and verruculogen TR-2 (**4**)[4,5] indole alkaloids, which all have the tryptophan α-carboxyl and -amino groups incorporated into a dioxopiperazine moiety (chart 1 1) Of these fungal-derived secondary metabolites, the β-carbolines fumitremorgin C **3** and verruculogen TR-2 (**4**) in particular, have interesting biological (CNS) activities In 1984 the total synthesis of the tetracyclic eudistomin series (*e g* debromo-eudistomin K **5**) was begun Eudistomins, first isolated from the colonial tunicate *Eudistoma Olivaceum*, display potent antitumor and antiviral activities [6] In addition to their promising biological activity, tetracyclic eudistomins possess remarkable structural features such as the N_b-oxotryptamine moiety combined with an unprecedented 7-membered [1,6,2]-oxathiazepine ring

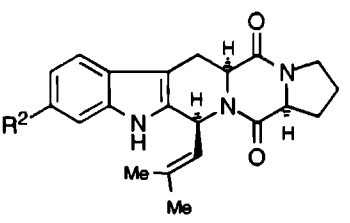
chart 1.1



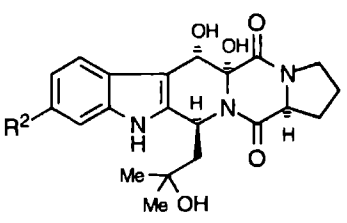
1 *Neoechinulin B*



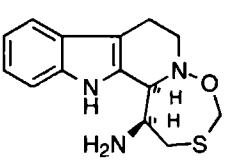
2 *Sporidesmin B*



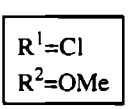
3 *Fumitremorgin C*



4 *Verruculogen TR-2*



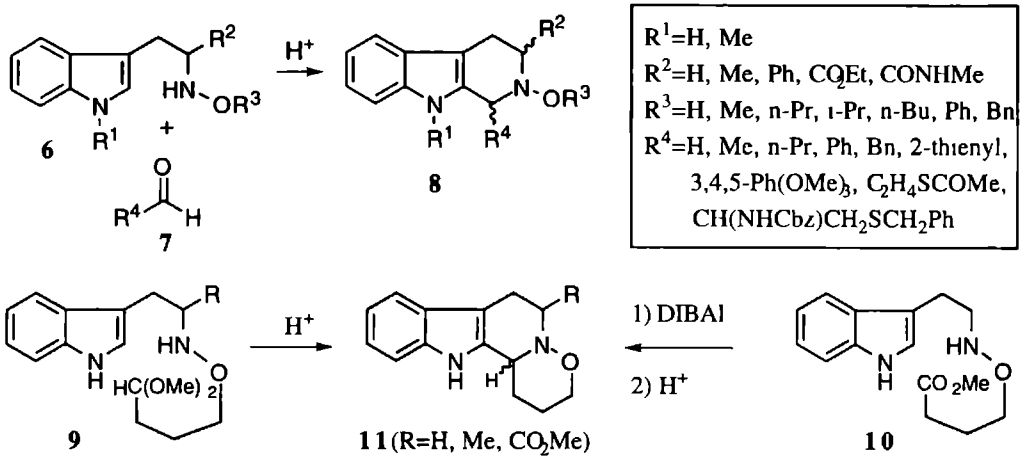
5 *Debromoeudistomin K*



In an approach to the synthesis of eudistomin **5**, first the Pictet-Spengler condensation of N_b-alkoxytryptophans **6** with several aldehydes **7**, to give N_b-alkoxy-β-carbolines **8**, was studied (scheme 1 1) [7] This study was extended toward the total synthesis of eudistomins by the preparation of N_b-alkoxytryptophans **9** and N_b-alkoxytryptamine **10**, both containing N_b-alkoxy chains with terminal groups which could easily be transformed into an aldehyde moiety These N_b-alkoxytryptophan derivatives **9** and **10** smoothly underwent the *intra*molecular Pictet-Spengler (PS)

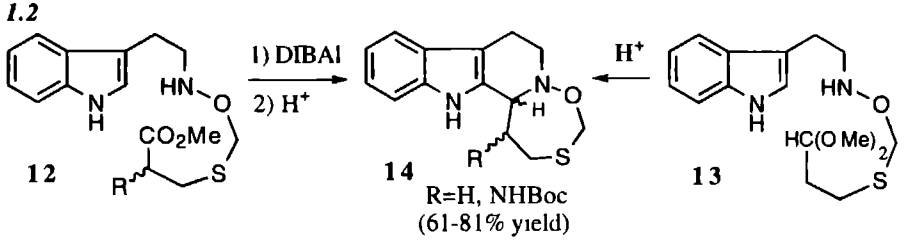
condensation smoothly to give the tetracyclic 1,3-disubstituted β-carbolines **11** in high yields [8] As is depicted in scheme 1 1, the aldehyde from **10** was generated by selective diisobutylaluminium hydride (DIBAl) reduction of the methyl ester

Scheme 1.1



By application of this type of intramolecular PS condensation to the precursors **12** or **13** closure of the 7-membered [1,6,2]-oxathiazepine ring, present in the tetracyclic eudistomin series, was also performed in high yields (scheme 1 2) [9]

scheme 1.2



The closure of the 7-membered ring proceeded smoothly, but resulted in unfavored diastereoselectivity to give the *un*natural trans eudistomin diastereomer with a diastereomeric excess of 40% [10] In the same study all four possible stereoisomers were synthesized and an antiviral and antitumor structure-activity relationship (SAR) study revealed that only the *natural* stereoisomer exhibited biological activity [11] Both debromo eudistomin K **5** and particulary a 10-methoxy derivative thereof showed pronounced antiviral and antitumor activities (in the nanomolar region) thus reconfirming their status as potent lead compounds in the development of antiviral and/or antitumor drugs

In this thesis our continuing research concerning eudistomins employing the intramolecular PS condensation is described The research goals which were set at the beginning are

GOALS OF THIS THESIS

1 - To study the factors controlling the diastereoselectivity of the intramolecular PS condensation in order to arrive at a diastereoselective synthetic route toward the natural C(1)H-C(13b)H cis eudistomins

2 - To prepare eudistomin derivatives designed to establish the essential structural elements that are necessary for both antiviral and antitumor activity

3 - To investigate the synthetic scope and the mechanism of the intramolecular PS condensation by the synthesis of the tetracyclic skeleton of the naturally occurring canthines

1.2 Literature Survey of Eudistomins

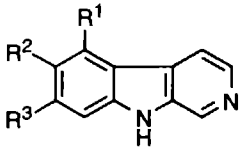
1.2.1 Isolation and Biological Activity

Marine natural products have been an important source of drug leads for almost 30 years [12] A variety of biologically active compounds has been isolated including CNS membrane-active toxins, ion channel affectors, anti-inflammatory agents, anticancer agents, tumor promotors and antiviral agents [13] The majority of the marine products have been isolated from sponges, soft corals, molluscs, coelenterates, algae or ascidians Of these species the ascidians (= tunicates) in particular distinguish themselves because of their biosynthesis of unprecedented, mainly amino acid derived, secondary metabolites [14]

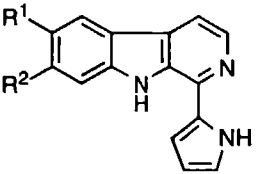
Tunicates (or sea squirts) are members of the *Phylum Chordata* which also include the vertebrates In the Phylum Chordata, the tunicates are incorporated in the subphylum Urochordata (= Tunicata) Adult tunicates are sessile filter feeders which live either alone or in colonies and are hermaphrodite They range in size from about 1 mm (colonial type) to over 40 cm (solitary type) in diameter and are common in all seas

The colonial tunicate genus *Eudistoma* proved to be a rich source of biologically active alkaloids Until now over 40 different compounds have been isolated belonging to six structural classes The majority of these compounds are indole alkaloids Those belonging to the β-carboline class, the eudistomins and eudistomidins, are depicted in chart 1 2 [15]

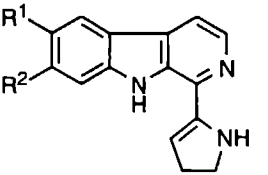
The tetracyclic eudistomins C **30** and E **31**, bearing the 7-membered oxathiazepine ring, are highly active against HSV-1 (5-10 ng/disk) and HSV-2 (25 ng/disk) viruses [6b] Moderate activities for the same viruses were reported for the eudistomins D **15**, H **23**, K **33**, $K_{(sulfoxide)}$ **34**, $K_{(debromo)}$ **35**, L **36**, N **17** and P **25** (100-500 ng/disk) [6b,c,d] Low antiviral activities were found for the eudistomins O **18** and the β-carboline **19** (500-2000 ng/disk) [6d] Antitumor activity has also been reported Eudistomin K **33** gave, *in vitro*, an IC_{50} against P388 cell lines of 0 01 μg/mL The *in vivo* assay gave a *T/C* of 137% at 100 mg/kg In the same report additional *in vitro* antitumor activities were reported against L1210 A549, and HCT-8 cell lines [6d] Of the several biological activities exhibited by the eudistomidins and woodinine only their antitumor activity will be noted here [16]



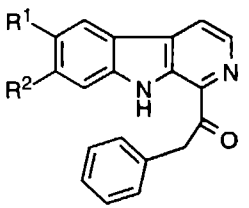
		R^1	R^2	R^3
D	**15**	Br	OH	H
J	**16**	H	OH	Br
N	**17**	H	Br	H
O	**18**	H	H	Br
	19	H	H	H



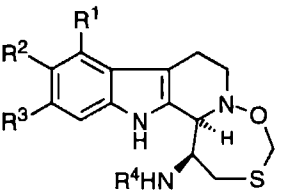
		R^1	R^2
A	**20**	OH	Br
M	**21**	OH	H



		R^1	R^2
G	**22**	H	Br
H	**23**	Br	H
I	**24**	H	H
P	**25**	OH	Br
Q	**26**	OH	H

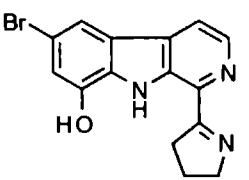


		R^1	R^2
R	**27**	H	Br
S	**28**	Br	H
T	**29**	H	H

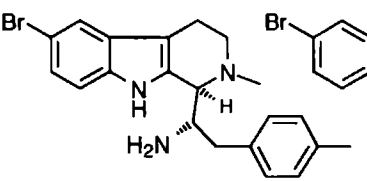


		R^1	R^2	R^3	R^4
C	**30**	H	OH	Br	H
E	**31**	Br	OH	H	H
F	**32**	H	OH	Br	$C_2H_3O_2$
K	**33**	H	H	Br	H
K(sulfoxide)	**34**	H	H	Br	H
K(debromo)	**35**	H	H	H	H
L	**36**	H	Br	H	H

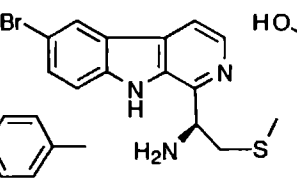
eudistomidines and woodinine



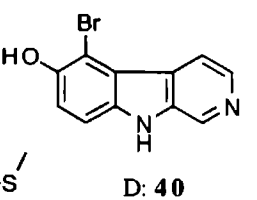
A: **37**



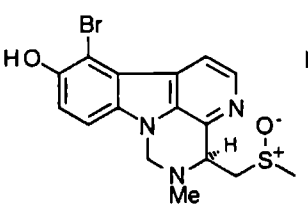
B: **38**



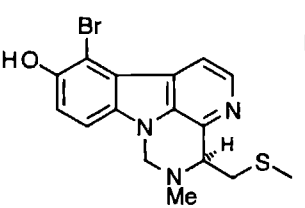
C: **39**



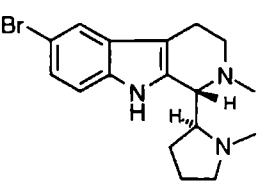
D: **40**



E: **41**



F: **42**



woodinine: **43**

The eudistomidins B **38**, C **39** and D **40** showed cytotoxic activity against L1210 (IC_{50} of 3 4, 0 36, and 2 4 µg/mL) and L5178Y (IC_{50} of 3 1, 0 42, and 2 4 µg/mL) cells, respectively

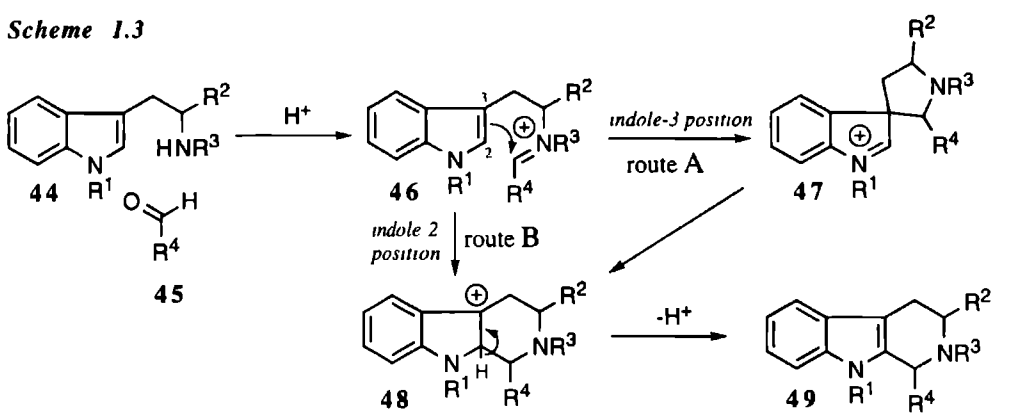
A closer look at the structures depicted in chart 1 2 shows some interesting resemblances Although knowledge of the biosynthetic pathways leading to marine alkoloids is limited, some statements seem to be valid With the exception of the structures **15-19**, **27-29** and **40** all eudistomins, eudistomidines and woodinine are derived from a PS reaction of tryptophan with the aldehydes of cysteine (**30-36**, **39**, **41**, **42**), phenylalanine (**38**) or proline (**20-26**, **37** and **43**) Furthermore, with the exception of eudistomidine B **38** and woodinine **43**, all stereogenic centers are derived from *D*-amino acids The cysteine derived structures **31**, **41**, **42** and **36**, **39** show the same substitution pattern in the aromatic part as well Finally, comparison of the cysteine derived structures suggest that biosynthetically the oxathiazepine eudistomins **30-36** are the result of an *inter*molecular PS condensation followed by closure of the D-ring

The endogenous function of eudistomins is most likely to provide a chemical defense against parasitical (micro)organisms The eudistomins G **22** and H **23** play an important role in the prevention of settlement of fouling organisms [17]

1.2.2 Syntheses

The PS condensation is the key reaction in the syntheses of eudistomins Since the beginning of this century, the PS condensation has been the method of choice for the construction of the tricyclic β-carboline moiety [18] The PS condensation may take place via two pathways from the iminium ion intermediate **46** (scheme 1 3)

Scheme 1.3

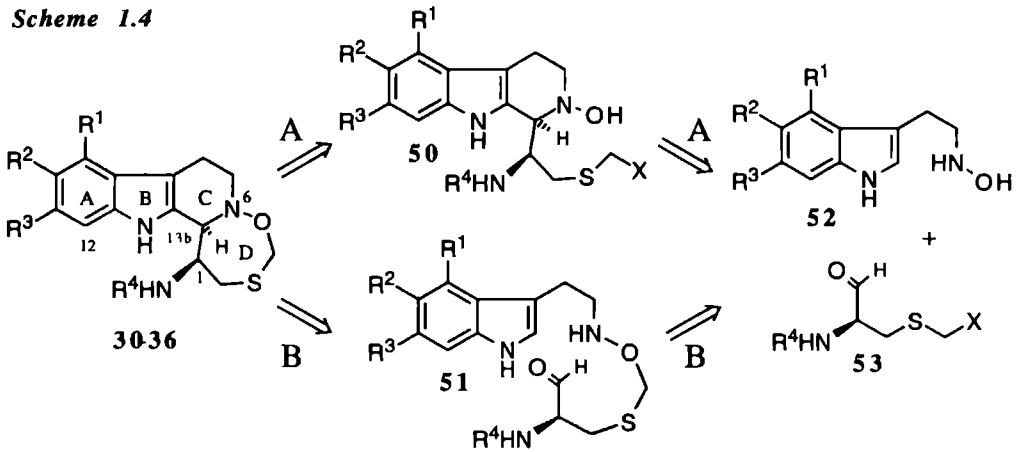


Although the intermediate spiroindolenine 47 (route A) has been detected or isolated in several cases, it cannot be ruled out that the ultimate β-carboline formation takes place via direct attack at the indole-2 position (route B) [19] According to Baldwin's rules for ring closures, attack at the indole-2 position proceeds via the favored 6-*endo*-trig pathway while attack at the indole 3-position proceeds via the disfavored 5-*endo*-trig pathway [20] The *exact* mechanism of the PS condensation is at present

still under investigation [21] The influence of the substituents R^{1-4} on the rate and the stereochemical outcome of the PS condensation has been studied thoroughly [22]

For the construction of the β-carboline moiety in the eudistomins **30-36** with the PS condensation two different strategies are possible (scheme 1 4)

Scheme 1.4



A. *Inter*molecular PS condensation of cysteine aldehydes **53** with N_b-hydroxytryptamines **52** to give the tricyclic β-carbolines **50**, followed by closure of the 7-membered oxathiazepine D ring (scheme 1 4, route A)

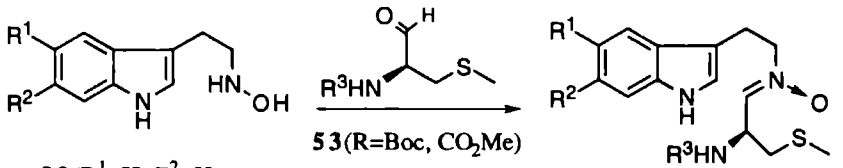
B *Intra*molecular PS condensation of tryptamine **51**, to which the cysteine fragment is already coupled via the oxathioacetal moiety, to close the CD-rings in a simultaneous fashion (scheme 1 4, route B)

Both approaches are described in the literature and will be discussed separately Only those approaches which succeeded in constructing the tetracyclic eudistomin skeleton will be discussed here [23]

Intermolecular PS approach (route A in scheme 1 4)

The intermolecular PS approach seems most straightforward for the synthesis of the tetracyclic eudistomins The first total synthesis of the eudistomins L **36** and K(debromo) **35** was indeed accomplished using this strategy by Nakagawa and coworkers [24] By application of the same methodology the total synthesis of eudistomin F **32** had also been achieved [25] In both syntheses the crude aldehydes **53** (after purification by column chromatography the aldehydes were obtained as racemates) were first condensed with the N_b-hydroxytryptamines **52** under neutral conditions to give the crystalline nitrones **54** (scheme 1 5) Subsequent acid treatment of the nitrones **54** at -78°C for 1 h gave the diastereomeric cis/trans β-carbolines **50** optically pure in nearly quantitative yields with d e 's of 82-95%, in favor of the desired cis isomer (scheme 1 6)

Scheme 1.5

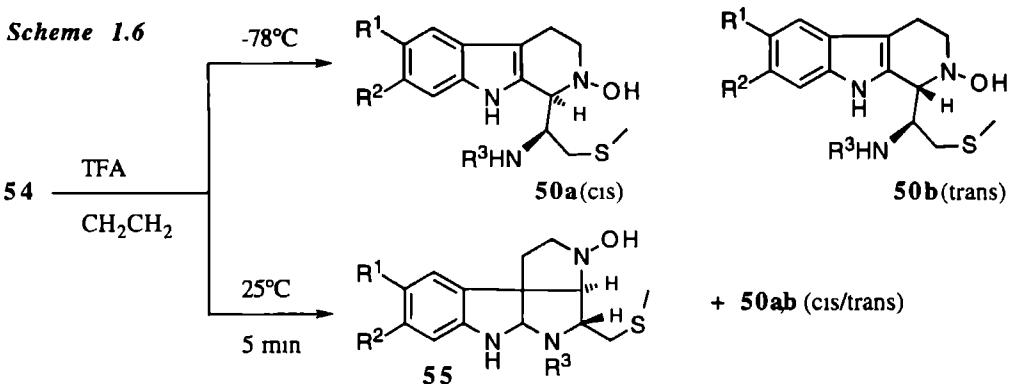


52(R^1=H, R^2=H, R^1=OMe, R^2=Br)

53(R=Boc, CO_2Me)

54

Scheme 1.6



50a(cis)

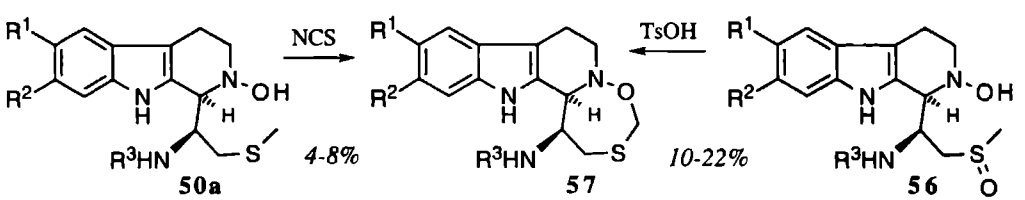
50b(trans)

+ **50a,b** (cis/trans)

55

After quenching of the reaction mixture after 5 min at room temperature, the trans spiro compound **55** was isolated and characterized as well as both diastereomeric β-carbolines **50a,b** Bromination of the spiro intermediate was selectively accomplished at the R^1 position thus opening a synthetic route toward eudistomin L **36** The bottleneck in this synthesis was closure of the 7-membered oxathiazepine ring As is depicted in scheme 1 7, Pummerer type cyclizations of **56** gave the eudistomins **57** in only 22% yield at best, while NCS mediated ring closure of **50a** resulted in yields below 10% [25]

Scheme 1.7



4-8%

10-22%

50a

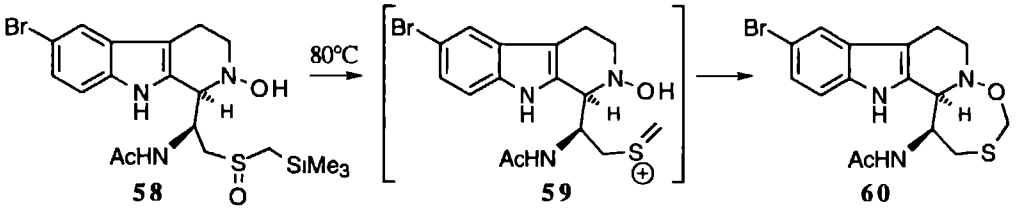
57

56

Removal of the protective groups in **57** afforded the, optically pure, eudistomins L **36**, K **33** and K(debromo) **35** [24 25]

A similar approach was used by Still and Strautmanis in their synthesis of N(1)-acetyleudistomin L **60** (scheme 1 8) [26] Closure of the oxathiazepine ring was achieved in 17-21% yield using a sila-Pummerer reaction via the dicoordinate S-methylene sulfonium ion **59**

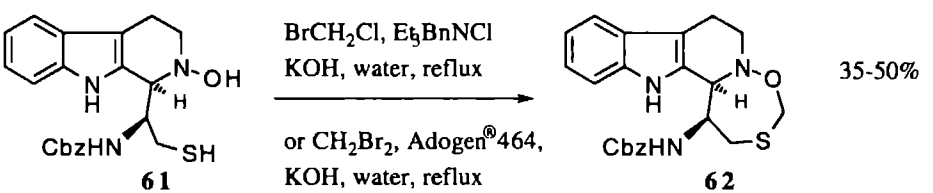
Scheme 1.8



Although both the syntheses of the cysteinal derivative and the PS condensation had been carried out exactly as described by Nakagawa and coworkers, it was reported that for unknown reasons the β-carboline **58** was obtained as a racemate [26]

Yoon and coworkers closed the oxathiazepine ring in 35-50% yield by nucleophilic insertion of a methylene moiety between the thiol and hydroxyl moieties in **61** under 2-phase conditions to give the Cbz-protected eudistomin K(debromo) **62** using dibromomethane (scheme 1 9) [27] The β-carboline **61** had again been synthesized based on the method described by Nakagawa and coworkers

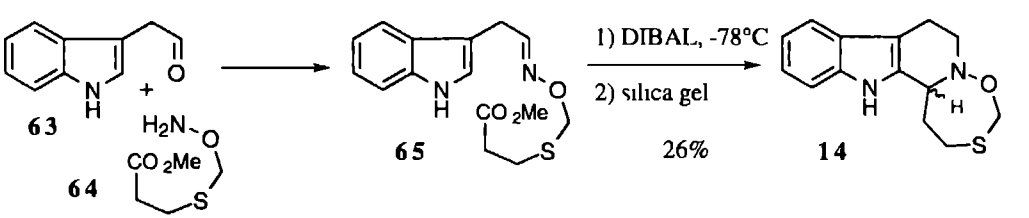
Scheme 1.9



Intramolecular PS approach (route B in scheme 1 4)

This approach has been used only by our group[8 11] (*vide supra*) and concurrently by Kirkup and coworkers [28] Build up of the N_b-alkoxytryptamine skeleton in Kirkup's approach was accomplished via oxim formation of indole-3-acetaldehyde **63** and aminoalkoxy compound **64** (scheme 1 10)

Scheme 1.10



Reduction of both the oxim and the methyl ester group in **65** was accomplished simultaneously by treatment with DIBAL After quenching of the excess of reducing agent with methanol, silica gel was added to induce acid catalyzed the PS cyclization affording desamino debromoeudistomin K **14** in 26% yield

1.3 Introduction to the Chapters

In *chapter 2* a study of the factors controlling the stereochemical outcome of the intramolecular PS condensation in the synthesis of tetracyclic eudistomins is presented. In *chapter 3* an attempted diastereoselective synthesis of natural cis eudistomins starting from a trans derivative with a C(1)-hydroxy group is presented. The hydroxy group in the trans diastereomer may be substituted by a suitable masked amino group via an S_n2 reaction, *e.g.* by application of the Mitsunobu reaction, to give the desired cis diastereomer. The synthesis of an eudistomin derivative with the sulfur atom in the oxathiazepine ring replaced by a methylene group is described in *chapter 4*. Also an attempted diastereoselective approach to this derivative via its trans C(1)-hydroxy precursor and the Mitsunobu procedure is described. In *chapter 5* an attempted synthesis of an eudistomin derivative with the oxygen atom in the oxathiazepine ring substituted by a methylene group is presented. The synthesis of an eudistomin derivative with the indole moiety substituted by a dimethoxyphenyl group to give the isoquinoline skeleton by applying the intramolecular PS condensation, is described in *chapter 6*. In *chapter 7* a study of the intramolecular PS condensation of tryptamine derivatives with alkylaldehyde chains at the indole nitrogen, to give the naturally occurring canthine type skeleton, is presented. *Chapter 8* deals with the conformations of the oxathiazepine ring present in eudistomins based on X-ray crystallographic and ^{1}H-NMR data. The antiviral and antitumor activities of the newly synthesized eudistomin derivatives together with the known activities from previous studies is presented in *chapter 9*. This thesis is concluded with a summary in English and Dutch.

References and Notes

1 a) Plate, R *"N-hydroxytryptophan in Synthetic Approaches to Indole Alkaloids. A Lustrum of N-hydroxy-tryptofun"*, **1986**, Thesis, University of Nijmegen. b) Hermkens, P.H.H *"N-hydroxy-β-carbolines Syntheses, Applications, and Biological Activities"*, **1990**, Thesis, University of Nijmegen.

2 a) Ottenheijm, H.C.J., Plate, R.; Noordik, J H.; Herscheid, J.D M. *J Org.Chem.*, **1982**, 47, 2147 b) Plate, R., Nivard, R.J.F.; Ottenheijm, H.C.J. *J.Chem.Soc Perkin Trans. I.*, **1987**, 11, 2473

3 a) Plate, R , Akkerman, M A J , Smits, J.M M.; Ottenheijm, H.C J. *J.Chem.Soc.Perkin Trans I.*, **1987**, 11, 2481 b) Plate, R., Theunisse, A.W.G.; Nivard, R.J.F.; Ottenheijm, H.C J. *Tetrahedron*, **1986**, 42, 6511

4 Plate, R , Hermkens, P H H., Behm, H , Ottenheijm, H.C.J. *J Org Chem.*, **1987**, 52, 560

5 TR-2· a) Hermkens, P H.H.; Plate, R ; Ottenheijm, H.C J. *Tetrahedron Lett.*, **1988**, 29, 1323. b) Hermkens, P.H H ; Plate, R.; Kruse, C G.; Scheeren, H.W ; Ottenheijm, H C.J. *J.Org.Chem.*, **1992**, 57, 3881. Fumitremorgine-C: c) Hermkens, P.H H ; Plate, R., Ottenheijm, H.C.J *Tetrahedron*, **1988**, 44, 1991

6 a) Rinehart, K L Jr.; Kobayashi, J.; Harbour, G.C., Hughes, R.G. Jr.; Mizsak, S.A., Scahill, T A. *J Am Chem Soc* , **1984**, 106, 1524. b) Rinehart, K.L. Jr.; Kobayashi, J., Harbour, G C.; Gilmore, J , Mascal, M.; Holt, T.G , Shield, L.S.; Lafargue, F *J Am Chem Soc* , **1987**, 109, 3378. c) Lake, R.J.; Brennan, M.M ; Blunt, J W , Munro, M.H.G., Pannell, L.K. *Tetrahedron Lett.*, **1988**, 29, 2255. d) Lake, R.J , Blunt, J W., Munro, M.H G. *Aust J Chem.*, **1989**, 42, 1201

7 a) Behm, H ; Beurskens, P T ; Plate, R , Ottenheijm, H C J. *Recl.Trav.Chim.Pays-Bas.*, **1986**, 105, 238. b) Plate, R ; Hout, R.H M van; Behm, H ; Ottenheijm, H.C.J. *J.Org Chem* , **1987**, 52, 555 c) Hermkens, P H.H , Maarseveen, J H., Cobben, P.L.H.M., Ottenheijm, H.C.J., Kruse, C.G.; Scheeren, J.W *Tetrahedron*, **1990**, 45, 833

8 Hermkens, P H H , Maarseveen, J H van, Berens, H W , Smits, J M M , Kruse, C G , Scheeren, H W *J Org Chem* , **1990**, 55, 2200

9 Hermkens, P H H , Maarseveen, J H van, Kruse, C G , Scheeren, J W *Tetrahedron Lett* , **1989**, 30, 5009

10 Hermkens, P H H , Maarseveen, J H van, Ottenheijm, H C J , Kruse, C G , Scheeren, J W *J Org Chem* , **1990**, 55, 3998

11 Maarseveen, J H van, Hermkens, P H H , DeClercq, E , Balzarini, J , Scheeren, J W , Kruse, C G *J Med Chem* , **1992**, 35, 3223

12 *Pharmaceutical and Bioactive Natural Products*, Attaway, D A , Zabosky, O R , Eds , Plenum Press New York, **1992**

13 *Chem Rev* , **1993**, 93(5) fully deals with marine derived natural products

14 Davidson, B S *Chem Rev* , **1993**, 93, 1771

15 Alvarez, M , Salas, M , Joule, J A *Heterocycles*, **1991**, 32, 1391

16 a) Kobayashi, L , Nakamura, H , Ohizumi, Y , Hirata Y *Tetrahedron Lett* , **1986**, 27, 1191 b) Kobayashi, J Cheng, J , Ohta, T , Nozoe, S , Ohizumi, Y , Sasaki, T *J Org Chem* **1990**, 55, 3666 c) Murata, O , Shigemori, H , Ishibashi, M , Sugama, K , Hayashi, K , Kobayashi, J *Tetrahedron Lett* , **1991**, 32, 3539 d) Debitus, C , Laurent, D , Pais, M *J Nat Prod* , **1988** 51, 799

17 Davis, A R , Wright, A E *J Chem Ecol* , **1990**, 16(4), 1349

18 Pictet, A , Spengler, T *Ber* , **1911**, 44, 2030

19 a) Bailey, P D *J Chem Res (S)*, **1987**, 202 b) Maarseveen, J H van, Scheeren, J W , Kruse, C G *Tetrahedron*, **1993**, 49, 2325

20 Bailey, P D , Hollinshead, S P , McLay, N R , Morgan, K , Palmer, S J , Prince, S N , Reynolds, C D Wood, S D *J Chem Soc Perkin Trans I* **1993**, 431

21 Kawate, T , Nakagawa, M , Ogata, K , Hino, T *Heterocycles*, **1992**, 33, 801

22 a) Sandrin, J , Hollinshead, S P , Cook, J M *J Org Chem* , **1989**, 54, 5636 b) Deng, L , Czerwinsky, K Cook, J M *Tetrahedron Lett* , **1991**, 32, 175 c) Speckamp, W N , Hiemstra, H *Tetrahedron*, **1985**, 41, 4367 d) Czerwinsky, K M , Deng, L , Cook, J M *Tetrahedron Lett* , **1992**, 33, 4721

23 For intermolecular PS approaches which only succeeded in constructing the tricyclic β-carboline skeleton see a) Han, S Y , Lakshmikantham, M V , Cava, M P *Heterocycles*, **1985**, 23, 1671 b) Nakagawa, M , Liu, J J , Ogata, K , Hino, T *Tetrahedron Lett* , **1986**, 27, 6087 c) Nakagawa, M , Liu, J J , Ogata K Hino, T *J Chem Soc Chem Commun* , **1988**, 463 d) Liu, J J , Nakagawa, M , Hino, T *Tetrahedron*, **1989**, 45, 7729

24 Nakagawa, M , Liu, J -J , Hino, T *J Am Chem Soc* , **1989**, 111, 2721

25 Liu, J J , Nakagawa, M , Harada, N , Tsuruoka, A , Hasegawa, A , Ma, J , Hino, T *Heterocycles*, **1990** 31 229

26 a) Still, I W J , Strautmanis, J *Tetrahedron Lett* , **1989**, 30, 1041 b) Still, I W J , Strautmanis, J *Can J Chem* , **1990**, 68, 1408

27 Yoon, B H , Lyu, H S , Hahn, J H , Ahn, C M *Bull Korean Chem Soc* , **1992**, 13, 290-296 In this article many serious errors are present

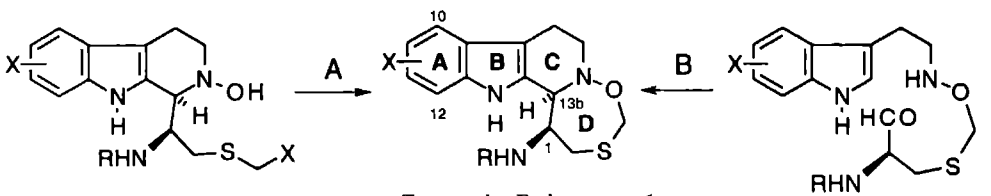
28 Kirkup, M P , Shankar, B B , McCombie, S , Ganguly, A K , McPhail, A *Tetrahedron Lett* , **1989**, 30, 6809

2 Diastereocontrol in the Synthesis of Tetracyclic Eudistomins

2.1 Introduction

Since their isolation in 1984 by Rinehart and coworkers, tetracyclic eudistomins have been an intriguing target for total synthesis in a number of research laboratories [1] These efforts have resulted in two successful synthetic routes, namely an *inter*molecular Pictet-Spengler (PS) condensation (route A) by the groups of Nakagawa[2a,b], Still,[2c] and Yoon[3] and an *intra*molecular PS condensation (route B) by Kirkup and coworkers,[4] and our group (scheme 2 1) [5]

scheme 2.1



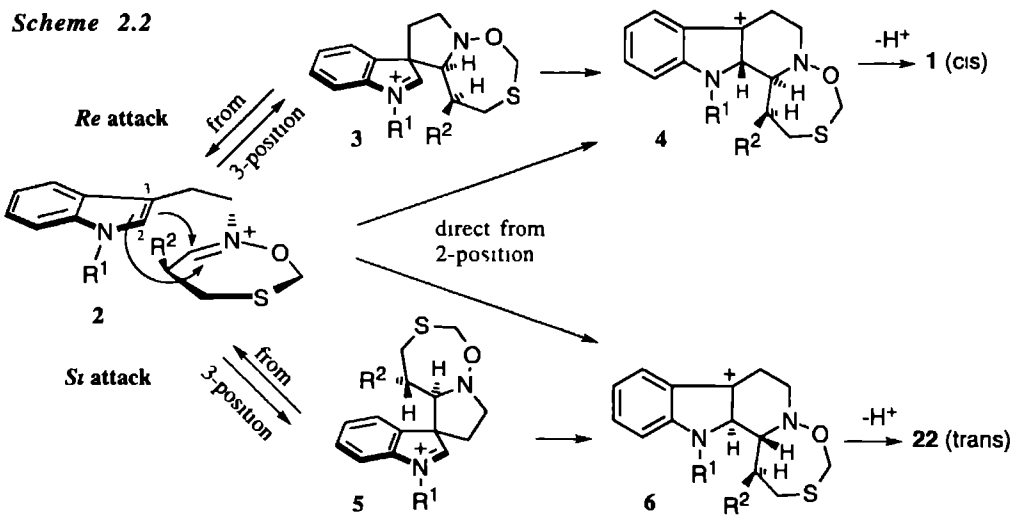
Tetracyclic Eudistomins **1**

In the intermolecular approach (route A) the PS condensation offers the correct cis configuration for H(1) and H(13b) It turns out, however, that closure of the 7-membered oxathiazepine ring (D-ring) is the crucial step The optimized yield of a modified Pummerer-type cyclization was only 22% [2b c] Better results (50% yield) were recently obtained by nucleophilic closure of the 7-membered ring In this approach the reactant in route A (X=Cl, scheme 2 1) was initially formed from the corresponding thiol and bromochloromethane, followed by a nucleophilic attack of the oxygen atom to give the tetracyclic structure **1** [3]

We were able to close the C and D rings *simultaneously* by means of the intramolecular PS condensation (route B) in good to excellent overall yields (66-98%) In contrast to the intermolecular approach, the intramolecular approach affords predominantly the *unnatural* C(1)H-C(13b)H *trans* diastereomer Our recently published structure-activity relationship study reveales that only eudistomins with the correct natural stereochemistry at both C(1) and (C13b) exhibit biological activity [6] Therefore, a diastereoselective high-yield process is needed for the synthesis of *cis* eudistomins In this chapter a study of the factors controlling the diastereoselectivity of the intramolecular PS condensation is described The results also contribute to a better understanding of the mechanistic details of the PS condensation in general

As is illustrated in scheme 2 2 the nucleophilic 3-position of the indole nucleus can attack the iminium-ion carbon in structure **2** on the two possible diastereotopic faces of the oxathiazepine ring giving the spiro intermediates **3** or **5**, respectively Attack on the more accessible *Si* side in **2** will lead to the undesired C(1)H-(C13b)H trans isomer **5**, while attack on the R^2-hindered *Re* side in **2** will give the desired C(1)H-C(13b)H cis isomer **3** This relationship is further maintained in the rearrangement to **4** and **6**, respectively, and the subsequent loss of a proton to give the final β-carbolines **1** and **22** with an aromatized indole nucleus [7]

Scheme 2.2

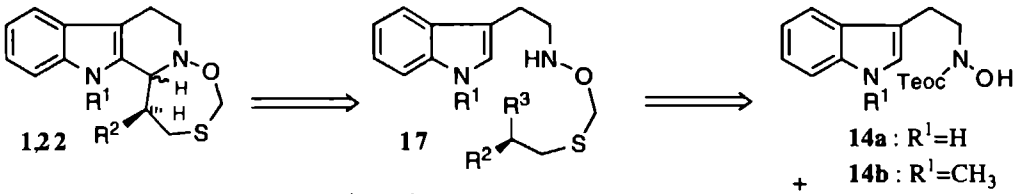


Taking into account that product formation occurs only via attack of the indole-3 position at the iminium ion and assuming that the final aromatization step is not rate determining, diastereoselective formation of the desired cis isomer can only be expected when the rate of the reaction **3**→**4** is much higher than the rate of the reaction **5**→**6** However, it has not been established yet whether or not the PS condensation occurs exclusively via a spiro intermediate Nakagawa and coworkers recently suggested in their intermolecular approach toward the eudistomin series that direct attack of the indole 2-position at the iminium-ion carbon could also lead to product formation [8,23] In this case **4** and **6** are formed directly from **2** and formation of the trans diastereomer will clearly predominate

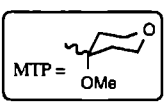
To rationalize steric effects of substituents at C(1) on the diastereocontrol of the intramolecular PS condensation, we synthesized derivatives with different sized groups R^2 at the oxathiazepine ring Indole N-methylated derivatives (R^1=CH_3) have also been prepared to investigate the possible role of the hydrogen bond which is present between the indole N-proton and the amino substituent at C(1) in the undesired trans product (see scheme 2 3) [5 9]

The intramolecular PS condensation was mostly carried out with aldehydes generated *in situ* by DIBAL reduction of the corresponding methyl esters **17a-j** In addition to earlier results,[13] we present here the use of acetal protected aldehydes **17k-o** as precursors, thus extending the scope of this reaction

scheme 2.3



17	R^1	R^2	R^3	17	R^1	R^2	R^3
a	H	OMe	COOMe	**i**	H	HNTFA	COOMe
b	H	OMTP	,,	**j**	Boc	HNBoc	,,
c	H	HNBoc	,,	**k**	H	HNBoc	$CH(OEt)_2$
d	H	CH_3	,,	**l**	H	HNAloc	,,
e	H	NH_2	,,	**m**	H	CH_3	,,
f	CH_3	NH_2	,,	**n**	H	NH_2	,,
g	H	HNBoc	,,	**o**	H	HNTFA	,,
h	CH_3	HNBoc	,,				



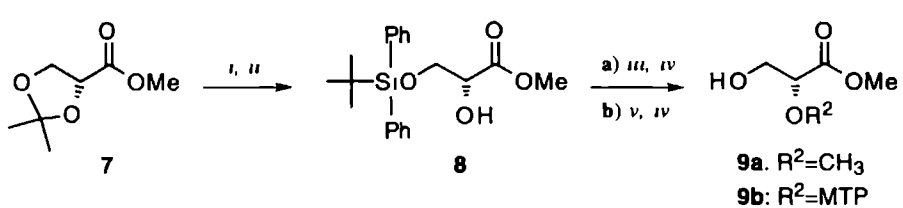
To build up N_b-alkoxytryptamine derivatives **17a-o** we used the established coupling method of chloromethyl sulfides **12** with the N_b-[2-(trimethylsilyl)ethyloxycarbonyl] (Teoc) protected N_b-hydroxytryptamines **14a** and **14b** (scheme 2.3) [5,6,10]

2.2 Synthesis of the Required Chloromethyl Sulfides

2.2.1 Synthesis of 2-Substituted Methyl 3-(chloromethylthio)-Propanoates

The chloromethyl sulfides **12** were synthesized according to our previously published procedure [5] The α-methoxy and α-4-methoxytetrahydropyranoxy derivatives were both synthesized from **8**. The ester **8** was obtained from the commercially available methyl α,β-isopropylidene-D-glycerate **7** (see scheme 2 4).[6]

scheme 2.4

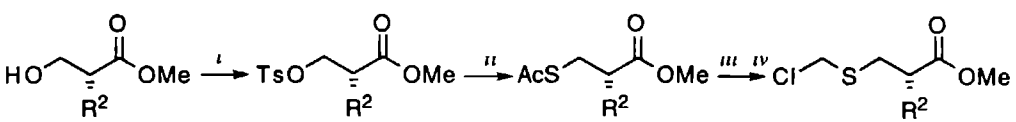


i) 80% HOAc, 5d at RT, ii) t-BudiPhSi-Cl, imidazole, DMF, iii) MeI, Ag_2O, glass beads, 4Å molecular sieves, reflux, iv) TBAF, THF, v) 5,6-dihydro-4-methoxy 2H-pyran, TsOH, THF

Methylation of **8** by using Ag_2O and MeI method[11] and subsequent removal of the silyl group with tetrabutylammonium fluoride (TBAF) afforded **9a** in an overall yield of 74% Protection with the bulky and fairly acid stable 4-methoxytetrahydropyranyl (MTP) group was carried out by treatment of **8** with 5,6-dihydro-4-methoxy-2*H*-pyran and a catalytic amount *p*-toluenesulfonic acid (TsOH) in THF, followed by removal of the silyl group to give **9b** in 96% yield

In the derivatives **9a,b** as well as in **9i** and commercially available **9d**, the sulfur moiety is introduced by conversion of the primary alcohol group in the corresponding tosylates **10a,b,d,i** followed by treatment with cesium thioacetate to give the thioacetates **11a,b,d,i** in overall yields of 59%, 61%, 48% and 59%, respectively (scheme 2 5). After removal of the acetate to give the free thiol, the chloromethyl sulfides **12a,b,d,i** were prepared by a phase-transfer alkylation with bromochloromethane employing powdered KOH, and the catalyst triethylbenzylammonium chloride in yields of 77%, 99%, 71% and 63%, respectively

scheme 2.5



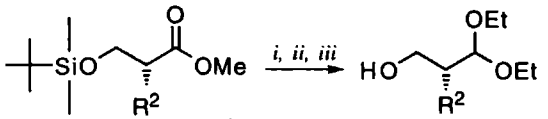
9-12	R^2
a	OMe
b	OMTP
d	CH_3
i	HNTFA

i) TsCl, pyridine 0°C, ii) Cs_2CO_3, HSAc DMF, iii) NaOMe, MeOH, iv) $BrCH_2Cl$ Et_3BnNCl, KOH (powdered)

2.2.2 Synthesis of the 2-Substituted 3-(chloromethylthio)-Propanal Diethyl Acetals

The N-(*tert*-butyloxycarbonyl) (NBoc), N-(allyloxycarbonyl) (NAloc) and N-(benzyloxycarbonyl) (NCbz) protected serinal diethyl acetals **9k,l,p** were prepared by DIBAL reduction of the corresponding methyl esters **13k,l,p** followed by treatment with triethyl orthoformate in ethanol in the presence of TsOH as a catalyst In order to remove the TBDMS group completely, further treatment with TBAF was neccessary to give **9k,l,p** in yields of 78%, 44% and 24%,[12] respectively, after purification by column chromatography (scheme 2 6) Due to the lability of the trifluoroacetyl protective group, this reductive approach to **9o** proved to be impossible Therefore, **9o** was synthesized via **9p** and **9n** in a standard manner from **9p** in 73% overall yield

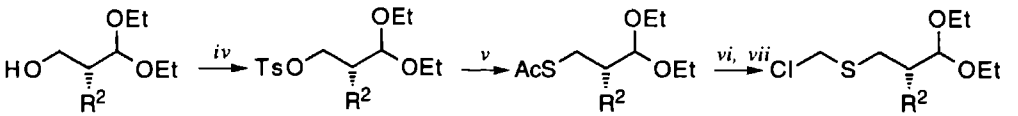
scheme 2.6



13	R^2	9
k	HNBoc	**k**
l	HNAloc	**l**
	NH_2	**n**[a]
	HNTFA	**o**[b]
p	HNCbz	**p**

[a] **9n** by deprotection of **9p** with Pd(C)/H_2 in MeOH

[b] **9o** by treatment of **9n** with TFA_2O / $EtN(iPr)_2$ in THF



9k,l,o **10** **11** **12**

9-12	R^2
k	HNBoc
l	HNAloc
m	CH_3
o	HNTFA

10m** was synthesized starting from **10d

i) DIBAL,-75°C; ii) $HC(OEt)_3$, EtOH, TsOH; iii) n-Bu_4NF, THF; iv) TsCl, pyridine, 0°C; v) Cs_2CO_3, HSAc, DMF; vi) NaOMe, MeOH; vii) $BrCH_2Cl$, Et_3BnNCl, KOH (powdered)

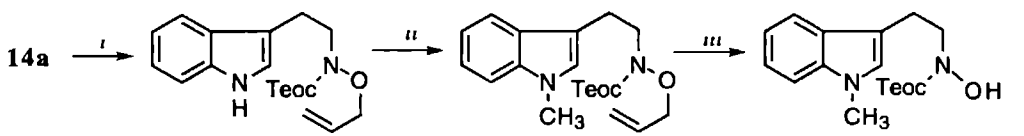
The thioether group was again introduced by conversion of the alcohols **9k,l,o** into the corresponding tosylates followed by treatment with cesium thioacetate to give the thioacetates **11k,l,o** in yields of 30%, 61% and 51%, respectively. DIBAL reduction of tosylate **10d** (scheme 2.5), followed by treatment with triethyl orthoformate in ethanol catalyzed by TsOH gave the tosylate **10m** in 39% overall yield. The tosylate **10m** was transformed into the thioacetate **11m** in a similar manner as described for **11k,l,o** in 55% yield.

After removal of the acetate with sodium methoxide to give the thiol, the chloromethyl sulfides **12k-m** were prepared by a phase-transfer alkylation with bromochloromethane, powdered KOH, and triethylbenzylammonium chloride as a catalyst in overall yields of 97%, 99% and 94%, respectively. NMR analysis of the chloromethyl sulfide **12o** thus obtained showed that 44% of **12o** was present and, in addition, two other products in yields of 32% and 20%, respectively, which were characterized as **20** and **21** (*vide infra*, scheme 2.9).

2.3 Alkylation of N_b-Teoc-N_b-hydroxytryptamine with the Chloromethyl Sulfides

N_b-Teoc-N_b-hydroxytryptamine **14a** (scheme 2.3) was prepared as described by Hermkens et. al [13] For the synthesis of the indole N-methyl derivative **14b**, **14a** was chosen as the starting material (scheme 2.7) To methylate the indole nitrogen selectively it was necessary to protect the more reactive hydroxamic oxygen as an allyl ether Treatment of **14a** with sodium hydride in 1,2-dimethoxyethane (DME) and subsequent addition of allyl bromide afforded **15a** in a quantitative yield, which was methylated to give **15b** by reaction with methyl iodide and powdered KOH in DMSO Removal of the allyl group was carried out using a cocktail of palladium(II)acetate/triphenyl-phosphine/triethyl-ammonium formate in refluxing acetonitrile/water[14] to give **14b** in an overall yield of 98% (scheme 2.7)

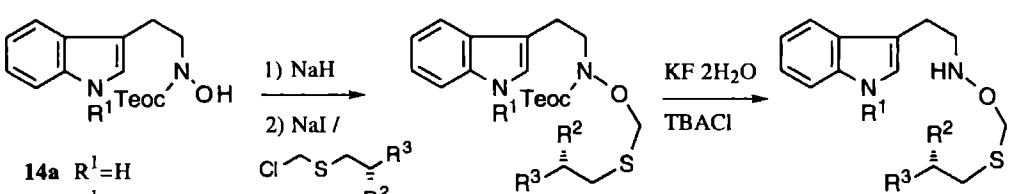
scheme 2.7



i) allylbromide, NaH, DME ii) MeI, KOH (powdered), DMSO, iii) $Pd(OAc)_2$, PPh_3, HCO_2NHEt_3

The sodium salt of N_b-Teoc protected N_b-hydroxytryptamines **14a,b** were alkylated with the chloromethyl sulfides **12a,b,d,h**[5],**i,k,l,m** and **o** in DME under controlled conditions (scheme 2.8)

scheme 2.8

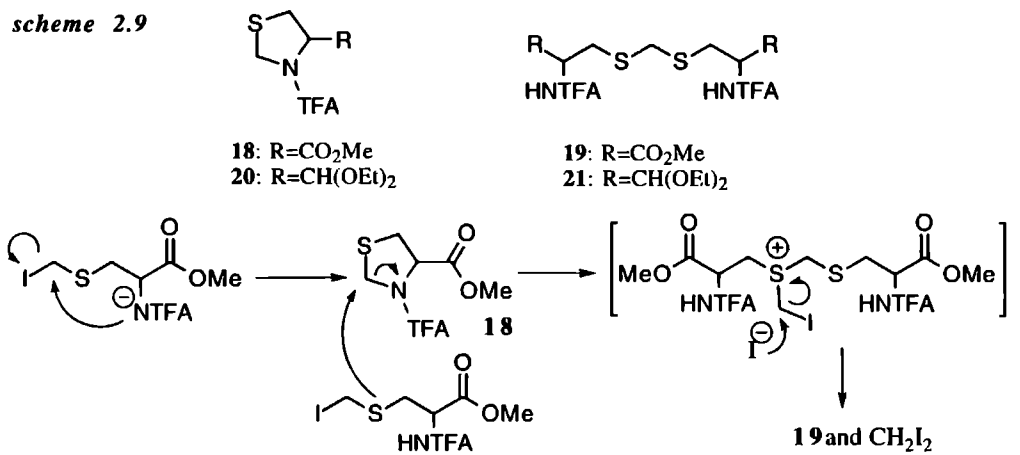


16	R^1	R^2	R^3	17
a	H	OMe	COOMe	**a**
b	H	OMTP	,,	**b**
d	H	CH_3	,,	**d**
h	CH_3	HNBoc	,,	**h**
k	H	HNBoc	$CH(OEt)_2$	**k**
l	H	HNAloc	,,	**l**
m	H	CH_3	,,	**m**

A solution of the sodium alkoxide derived from **14a** or **14b** was dropped into the stirred solution of *in situ* formed iodomethyl sulfides from **12a,b,d,h,i,k,l,m** and **o** at such rate (4-5 h.) that the pH remained near to neutral to avoid undesired elimination and racemization reactions, thus affording the tryptamines **16a,b,d,h,i,k,l,m** and **o**.[5,6] After removal of the Teoc group in **16a,b,d,h,k,l** and **m** with tetrabutylammonium chloride (TBACl) and KF•2H_2O in acetonitrile at elevated temperature (45°C), **17a,b,d,h,k,l** and **m** were isolated in yields of 26%[15], 84%, 54%, 56%, 88%, 63% and 94%, respectively based on **14a** or **14b** (scheme 2.8).

It should be noted that alkylations with the N-TFA protected chloromethyl sulfides **12i,o** was not accomplished. After work-up followed by purification of the product mixture by column chromatography it became clear that the chloromethyl sulfides **12i,o** had cyclized to give **18** and **20**, respectively, followed by the formation of the dithioacetals **19** and **21** (scheme 2.9).

scheme 2.9



The sodium salt of **14a** had acted only as a base and was recovered in both reactions in yields of 95% and 75%, respectively. Since chloromethyl sulfide **12i**, used in the alkylation approach to **16i** was pure, both side products **18** and **19** must have arisen from **12i** during the alkylation. The strong electron withdrawing trifluoroacetyl protective group must play a role in the formation of both **18** and **19**. Most likely **18** is formed by a base-induced intramolecular nucleophilic ring closure (scheme 2.9). As shown in scheme 2.9, the 5-membered ring of **18** is opened by nucleophilic attack of the thioether moiety of iodomethyl sulfide **12i** to yield the intermediate sulfonium ion as shown which then reacts with I^- to give dimer **19**. The compounds **20** and **21** were already present as contaminants of chloromethyl sulfide **12o** (*vide supra*) and are presumably formed in an analogous manner as suggested for **18** and **19**.

The α-hydroxy derivative **17c** (scheme 2.10) was prepared from **16b** by removal of the MTP group by treatment with TsOH in MeOH followed by removal (TBACl/KF•2H_2O) of the Teoc group in 77% overall yield. The free amino derivatives **17e, f** were prepared from **16g**[5] and **16h** by the simultaneous removal of the Boc and Teoc groups by stirring in TFA/dichloromethane (1/1, v/v) for

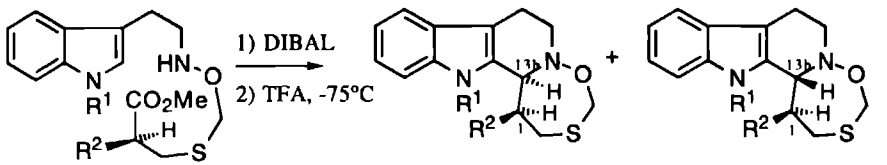
30 min in yields of 92% and 66%, respectively TFA protected compound **17i** was synthesized from **16g**[5] by selective removal of the Boc protective group by treatment with TMSI in acetonitrile at -25°C followed by treatment with TFA_2O and $EtN(iPr)_2$ in ether and removal of the Teoc group (TBACl/KF•$2H_2O$) in 50% overall yield The N_a-Boc derivative **17j** (scheme 2 10) was prepared from **16g**[1c] by treatment with di-*tert*-butyl dicarbonate and 4-dimethylaminopyridine in acetonitrile, followed by removal of the Teoc group (TBACl/KF•$2H_2O$) in 90% overall yield The free α-amino derivative **17n** (scheme 2 11) was prepared from **16l** by removal of the Aloc group with $Pd(OAc)_2$ and triethylammonium formate in refluxing acetonitrile/water (4/1, v/v), followed by removal of the Teoc group in 72% overall yield TFA protected compound **17o** was synthesized from **16n** by treatment with TFA_2O and $EtN(iPr)_2$ in ether and removal of the Teoc group (TBACl/KF•$2H_2O$) in overall 85% yield

2.4 Cyclization Reactions via DIBAL Reduction of Methyl Esters

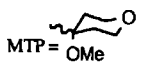
As described previously, the intramolecular PS-condensation proceeds smoothly with aldehydes [5 6 10] These aldehydes were prepared *in situ* by reduction of the methyl esters **17a-h** with DIBAL at -75°C After all starting material was consumed, TFA was added to induce the PS-condensation After work-up, the product ratio **1/22** was determined by analytical HPLC [16] The stereochemistry of the products **1** and **22** was confirmed by NMR techniques at 400 MHz (**1/22a,c,h**, see chapter 8) or X-ray diffraction analysis (**22d**, see chapter 8) The remaining eudistomins **1/22e,g** have been described elsewhere [5] The yields of **1** and **22** were determined after purification by column chromatography

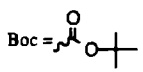
As indicated in scheme 2 10, the C(1)H-C(13b)H trans diastereomer **22** is formed predominantly in all cases In scheme 2 2 it is shown that diastereoselectivity in the intramolecular PS condensation is controlled by the R^2 substituents Larger R^2 substituents result in a higher trans diastereoselectivity The differences in diastereoselectivity described in scheme 2 10 cannot simply be explained by the size of the R^2 substituents, as is evident from entry 4 (R^2=CH_3) where the trans diastereomer is formed exclusively Although a methyl group seems small in comparison to an OMTP or HNBoc group (entries 2,7 and 8) it exerts the largest steric hindrance [17] With C(1) alkoxy groups the alkyl group can move in such a position that it exerts minimal steric hindrance by rotation around the C(1)-O bond When studied in more detail, it is thus the *minimum* steric hindrance of the substituent R^2 that will influence the diastereoselectivity With the smallest group, i e R^2=OH in entry 3, indeed the lowest trans selectivity was found By comparing the entries 6 and 8, where the N_a atom carries a methyl group with the entries 5 and 7 with NH groups it is clear that the hydrogen bond between the indole N_a-proton and the carbonyl oxygen atom of the Boc protected nitrogen on C(1) in the C(1)H-C(13b)H trans isomer (*vide supra*) has no influence on the diastereoselectivity

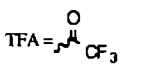
scheme 2.10



17 **1** (cis) **22** (trans)

MTP = 

Boc = 

TFA = 

entry	**17**	R^1	R^2	yield	ratio **1** / **22**	**1** / **22**
1	**a**	H	OCH_3	91	10 / 90 [a]	**a**
2	**b**	H	OMTP	98	11 / 89 [b]	**c**
3	**c**	H	OH	66	38 / 62	**c**
4	**d**	H	CH_3	69	0 / 100	**d**
5	**e**	H	NH_2	75	9 / 91	**e**
6	**f**	CH_3	NH_2	66	18 / 82	**f**
7	**g**	H	HNBoc	73	30 / 70	**g**
8	**h**	CH_3	HNBoc	79	31 / 69	**h**
9	**i**	H	HNTFA	0	--	
10	**j**	Boc	HNBoc	0	--	

[a] The ratio **1a/22a** was determined gravimetrically after separation by column chromatography [b] The ratio **1b/22b** was determined after removal of the MTP group by treatment of the crude reaction mixture with TsOH in MeOH

In entry 9, with R^2=HNTFA, no cyclized products were found. Again the TFA protective group proved to be unstable during the DIBAL reduction of the methyl ester. Due to the electron withdrawing ability of the Boc protecting group (R^1 in entry 10) the electron density of the indole C(2)-C(3) double bond is not sufficient to give an intramolecular nucleophilic attack on the intermediate iminium-ion **2**.[18]

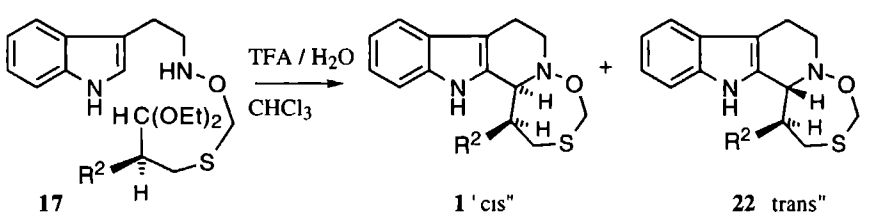
At this stage a few comments should be made concerning the stereochemical integrity of the final tetracyclic compounds. Although it is known that of all α-amino aldehydes, cysteinals racemize extremely fast,[19] in the entries 5-8 no excessive racemization had occurred, as was described in our previous study.[5,20] No determination of the optical purity was carried out for the entries 1 and 4. For entry 2 an e.e. of 45% was found, calculated from the optical rotation of nearly optically pure **1c**,**22c** described in chapter 3. The e.e.'s of the products obtained in entry 3 wer not determined, but are most likely the same as to those found in entry 2. As is described in section 3.4, the optical purity in the entries 2 and 3 was mainly lost during both the alkylation under basic conditions of the tryptamine fragment with the chloromethyl sulfide, and the DIBAL reduction prior to the cyclization reaction.

2.5 Cyclization Reactions by Hydrolysis of Diethyl Acetals

It is important to study the influence of the temperature on the diastereoselectivity of the intramolecular PS condensation These temperature dependent experiments are not possible when the aldehydes are generated by DIBAL reduction of methyl esters because the aldehyde must be liberated from the initially formed aluminum complex with acid at low temperature, which is immediately followed by PS condensation Earlier it was found that the use of acetals as such was not successful in the intramolecular PS condensation toward the natural tetracyclic eudistomins [5] Therefore, we turned our attention to the *in situ* hydrolysis of diethyl acetals to the more reactive aldehydes [21] The condition of choice for cyclization was stirring of the acetals in the two-phase system chloroform/TFA/water (98/1/1, v/v/v) The relatively slow hydrolysis of the acetals is followed by a rapid PS condensation The results are collected in scheme 2 11 Measurement of the product ratios and yields were performed as mentioned in the previous section

The observations presented in scheme 2 11 show large differences in the rate of hydrolysis between the different acetals This was in particular evident in entry 14 where hydrolysis only occurred at elevated temperatures due to the presence of the strongly electron-withdrawing NH_3^+ group under these acidic reaction conditions The electron-releasing methyl group in entries 13 and 18 resulted in a fast hydrolysis even at room temperature

scheme 2.11



17 **1** 'cis" **22** trans"

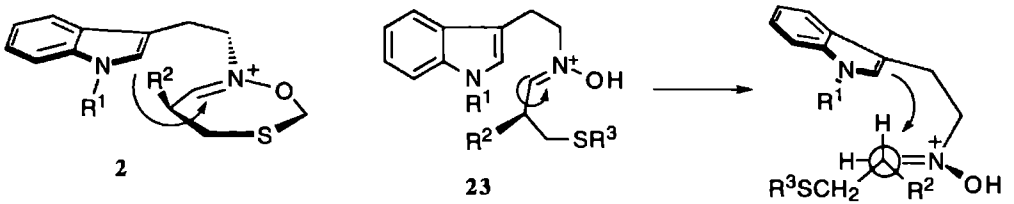
			room temperature				reflux			
17	R^2	**1/22**	entry	react time	yield	ratio **1/22**	entry	react time	yield	ratio **1/22**
k	HNBoc	**g**	11	7 days	71 %	29 / 71	16	8 h	32 %	6 / 94
l	HNAloc	**l**	12	9 days	48 %	23 / 77	17	8 h	83 %	10 / 90
m	CH_3	**d**	13	90 min	82 %	0 / 100	18	15 min	95 %	0 / 100
n	NH_2	**e**	14	*after 9 days ± 5% conversion*			19	9 h	44 %	5 / 95
o	HNTFA	**o**	15	4 days	45 %	33 / 67	20	10 h	68 %	10 / 90

At reflux temperature the hydrolysis proceeded much faster and higher yields were obtained (with the exception of entry 16) The diastereoselectivities at room temperature in entries 11 and 13 were similar to those obtained at -75°C (scheme 2 10, entries 4 and 7, respectively), suggesting no

temperature dependence. Due to the low yields obtained in the entries 14, 16 and 19 comparison of the diastereomeric ratios with the corresponding data in scheme 2.10 is not justified.

The results shown in scheme 2.10 and 2.11 indicate that the intramolecular approach predominantly leads to the trans diastereomer, in contrast to the intermolecular approach, which gives mainly the cis diastereomer as was shown recently by Nakagawa and coworkers.[8] This observation may be explained by assuming that in the cyclic iminium ion **2**, there is no rotational freedom around the $(R^2)C\text{-}C(=N^+)$ bond (chart 2.1). In contrast however, with the intermolecular approach, the R^2 substituent in **23** will rotate in such a manner that attack on the side leading to the cis isomer is preferred according to Cram's rule.[22] It was also described that in the intermolecular approach, the carbamate carbonyl group of the protected amines in R^2 of **23** may act as a hydrogen bond acceptor for the N-OH proton, thus stabilizing this favored conformation.[22b]

Chart 2.1

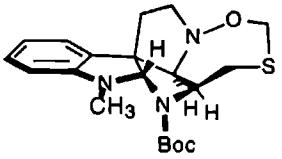


2.6 Isolation of Pentacyclic Spiro Intermediates

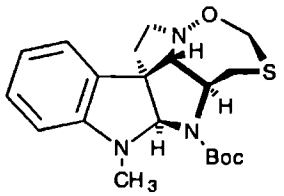
Under specific reaction conditions the N_a-methylated derivative **17h** (entry 8 in scheme 2.10) gave surprising by-products. Besides the expected cis/trans β-carboline eudistomin derivatives **1h** and **22h**, two pentacyclic spiro compounds **24** and **25** were isolated (chart 2.2).[23] These spiro compounds were formed by trapping of the tetracyclic spiro intermediates **3** and **5** (scheme 2.2) by an intramolecular nucleophilic attack of the Boc protected nitrogen on the electrophilic imino carbon at the indole 2-position. In the indole N-methylated spiro intermediates **3** and **5** (scheme 2.2) the positive charge in the indole nucleus is retained, in contrast to the unfunctionalized (R^1=H) indole nitrogen intermediates in which the spiro intermediate will lose this proton to give an uncharged species which is much less electrophilic.

The stereochemistry of these spiro compounds was confirmed by 2D-NMR COSY and NOESY techniques. Immediate neutralization of a sample of the reaction mixture taken at -75°C by filtration over sodium bicarbonate and subsequent analysis by reversed phase HPLC showed that only the trans spiro compound **25** was formed. A sample taken at -30°C showed the presence of both **24** and **25**. Upon standing at room temperature with 16 equiv. TFA for 15 minutes only the β-carboline eudistomin derivatives **1h** (cis) and **22h** (trans) were present in the ratio as mentioned in entry 8 in scheme 2.10.

chart 2.2



Pentacyclic cis isomer **24**



Pentacyclic trans isomer **25**

The isolated cis spiro compound **24** was more sensitive toward acid and was isolated after deactivation of the silica used for flash chromatography, by triethylamine Treatment once again of the pure spiro compounds **24** or **25** at room temperature with trifluoroacetic acid in dichloromethane gave in both cases the diastereomeric eudistomin cis/trans diastereomers **1h** and **22h** in a ratio of 35/65, in quantitative yields

This finding strongly suggests that both spiro compounds first rearrange back to the common iminium ion **2** and most probably a subsequent direct kinetically controlled attack from the indole 2-position then leads to β-carboline formation (see scheme 2 2) A further support for this assumption is the observation that treatment of the pure cis or trans eudistomins **1h** or **22h** with 3 equiv trifluoroacetic acid in dichloromethane at room temperature for days did not show any cis/trans isomerization [24] These results with the N_a-methylated substrate **17h** are in agreement with the suggestion of Nakagawa that, although attack at the indole 3-position is kinetically favored, the ultimate β-carboline formation in the PS condensation is the result of a direct attack at the 2-position [8,23] The diastereomeric ratio is only determined during the, kinetically controlled, nucleophilic attack of indole moiety on the intermediate cyclic iminium ion in **2** (see scheme 2 2)

2.7 Conclusion

In conclusion, the factors which control the diastereoselectivity in the intramolecular Pictet-Spengler condensation route toward the biological important tetracyclic eudistomin class natural compounds are well understood The extent of steric hindrance exerted by the substituent R^2 (see scheme 2 2) controls the diastereoselectivity The diastereoselectivity is determined during nucleophilic attack of the indole 2-position at the iminium-ion carbon This iminium-ion is incorporated in a 7-membered ring system, which has two diastereotopic faces due to the presence of R^2 The desired and naturally occurring C(1)H-C(13b)H cis diastereomer can only result from an unfavorable attack at the side hindered by the substituent R^2 As a consequence of this mechanism of the ring closure the intramolecular approach will lead to the formation of the unnatural trans isomer predominantly

2.8 Experimental Section

Ultraviolet spectra were measured with a Perkin-Elmer spectrometer, model Lambda 5. Protor magnetic resonance spectra were measured on a Bruker WH-90, Bruker AC-100 or a Bruker AM 400 spectrometer. Chemical shift values are reported as δ-values relative to tetramethylsilane as ar internal standard; deuteriochloroform was used as solvent. Mass spectra were obtained with a double focussing VG 7070E spectrometer. For the determination of optical rotations a Perkin-Elmer 241 polarimeter was used. Melting points were measured with a Reichert Thermopan microscope and are uncorrected. All solvents were commercially obtained and used unpurified unless stated otherwise Thin-layer chromatography (TLC) was carried out by using silica gel F-254 plates (thickness 0,2 mm). Spots were visualized with a UV hand lamp, iodine vapor, ninhydrine solution containing 1 mL acetic acid and 0.3 g ninhydrin in 100 mL *n*-butanol, or Cl_2-TDM.[25] Column chromatography was carried out using silica 60H (Merck). Analytical HPLC analysis was carried out with a LKB 2150 system equipped with a Waters RCM 8x10, reversed phase C-18 column and a Pye Unican LC-UV detector. All compounds described were purified by column chromatography when needed and were pure according to TLC, NMR and HPLC (from **17a** both at 254 and 280 nm). Also high resolution mass spectra were taken for the compounds **1**,**22** and **24** as a final proof. The 400 MHz NMR data of the newly synthesized eudistomins are collected in the tables 2.1 and 2.2.

Methyl (*R*)-2-hydroxy-3-*tert*-butyldiphenylsilyloxypropanoate (8). Methyl α,β-isopropylidene D glycerate **7** (10 g, 62 mmol) was dissolved in HOAc/H_2O=4/1 (v/v) (25 mL) and the solution was kept at room temperature for 5 days The solvent was removed under high vacuum to yield 7.5 g (100%) methyl D-glycerate as a colorless oil; ^{1}H NMR (90 MHz) δ 4 32 (t, 1H, J=4.0 Hz, CHOH), 4 00-3 83 (m, 4H, 2OH and CH_2OH), 3.83 (s 3H, OCH_3) Methyl D-glycerate (1.0 g, 8.3 mmol), *tert*-butyldiphenylsilyl chloride (2 5 g, 9 1 mmol), and imidazole (1.7 g, 25 mmol) were dissolved in dry DMF (25 mL) and stirred for 25 h The reaction mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc (50 mL) and subsequently washed with 0.1N HCl and brine. The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The residue was subjected to column chromatography (chloroform) to give 2 73 g (92%) of **8** as an oil; R_f 0.34 ($CHCl_3$/MeOH=99.5/0.5, v/v), ^{1}H NMR (90 MHz) δ 7.78 7 54 (M, 4H, 2xPhH_2), 7.44-7.25 (M, 6H, 2xPhH_3), 4.30-4 18 (m, 1H, CH), 3 97 and 3 91 (AB part of ABX spectrum, 2H, J_{AB}=11.4 Hz, J_{AX}=2.8 Hz and J_{BX}=3.3 Hz, CH_2), 3 77 (s, 3H, OCH_3), 3 18 (d, 1H, J=7.7 Hz, OH) 1.01 (s, 9H, $C(CH_3)_3$).

Methyl (*R*)-3-hydroxy-2-methoxypropanoate (9a). To **8** (2.0 g, 5.6 mmol) in MeI (50 mL) were successively added Ag_2O (2.2 g, 9.5 mmol), molecular sieves 3Å (2 g) and glass beads (2 g) The reaction mixture was heated at reflux for 6h. The reaction mixture was filtered over hyflo and concentrated *in vacuo* The residue was dissolved in dry THF (25 mL) and tetrabutylammonium fluoride (6 1 mL of a 1M solution in THF) was added. After 2h the solvent was evaporated *in vacuo* and the residue was subjected to column chromatography (MeOH/$CHCl_3$=3/97, v/v) to yield 560 mg (75%) of **9a** as an oil; R_f 0.49 (MeOH/$CHCl_3$=1/9, v/v); α_D^{22}=+67.4 (c=2 70, MeOH); CIMS(70eV) m/z (relative intensity) 135 ([M+1]$^+$, 7), 104 ([M-OCH_2]$^+$, 36), 75 ([$C_3H_7O_2$]$^+$, 100) , ^{1}H NMR (90 MHz) δ 3 98 3 78 (m, 3H, CH_2CH), 3.78 (s, 3H, $COOCH_3$), 3 50 (s, 3H, OCH_3), 2 73 (br s, 1H, OH).

Methyl (*R*)-3-hydroxy-2-(4-methoxy-tetrahydropyranyl-4-oxy)propanoate (9b). To **8** (2 6 g, 7. mmol) and 5,6-dihydro-4-methoxy-2*H*-pyran (1.7 g, 2eq.) in THF (25 mL) was added a catalytic amount TsOH•H_2O (2 mg). After 2h. the reaction mixture was diluted with EtOAc (50 mL) and washed with 2 portions sat $NaHCO_3$/brine =1/1, v/v (25 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in THF (50 mL) and tetrabutylammonium fluoride (8 mL of a 1M solution in THF) was added After completion of the reaction (2 h), which was monitored by TLC (EtOAc/hexanes=1/2, v/v), the reaction mixture was concentrated *in vacuo* an

subjected to column chromatography (MeOH/$CHCl_3$=3/97, v/v) to yield 1 64 g (96%) of **9b** as an oil, R_f 0 26 (MeOH/$CHCl_3$=3/97, v/v), α_D^{22}=+44 9 (c=4 52, MeOH), CIMS(70eV), m/z (relative intensity) 235 ($[M+1]^+$,1), 203($[M-OCH_3]^+$, 53), 115 ($[C_6H_{11}O_2]^+$, 100), ^{1}H NMR (90 MHz) δ 4 42 (t, 1H, J=4 8 Hz, CH), 4 04-3 46 (m, 6H, CH_2 and -CH_2OCH_2-), 3 76 (s, 3H, $COOCH_3$), 3 25(s, 3H, OCH_3), 2 48 (br t, 1H, OH), 1 93-1 75 (m, 4H, -CH_2CCH_2-)

N-(*tert*-butyloxycarbonyl)-*D*-serinal diethyl acetal (9k) To a stirred and cooled (-75°C) solution of **13k**[1c] (5 9 g, 17 7 mmol) in freshly distilled dichloromethane (50 mL) under an argon atmosphere, DIBAL (25 mL of a 1M solution in dichloromethane) was added at such rate that the temperature remained below -70°C The reaction mixture was stirred for 1 h at -75°C and subsequently quenched with an aqeous solution of citric acid (50 mL of a 20% solution) After allowing the resulting suspension to warm up to room temperature the organic layer was washed with 2 portions of water and neutralized with sat $NaHCO_3$ and washed with brine After drying ($MgSO_4$) the solvent was evaporated *in vacuo* and the residue was dissolved in dry ethanol (100mL) to which triethyl orthoformate (10 mL) and trifluoroacetic acid (0 5 mL) were added After standing over night at room temperature 20 mL sat $NaHCO_3$ was added and the volatiles were evaporated *in vacuo* The residue was dissolved in EtOAc and subsequently washed with brine and dried ($MgSO_4$) The solvent was evaporated *in vacuo* and the residue was dissolved in THF (50 mL) To the resulting solution Bu_4NF (18 mL of a 1M solution in THF) was added After stirring for 3 h the reaction mixture was diluted with EtOAc and washed with 3 portions of water, brine and dried ($MgSO_4$) After evaporation of the solvent *in vacuo* the residue was subjected to column chromatography (EtOAc/hexanes=1/1, v/v) to give 3 63 g (78%) of **9k** as an oil, R_f=0 27 (EtOAc/hexanes=1/1, v/v), ^{1}H NMR (90 MHz) δ 5 20 (br d, 1H, J=7 5 Hz, NH), 4 57 (d, 1H J=2 8 Hz, $CH(OEt)_2$), 4 08-3 36 (m, 7H, 2x$O\underline{CH_2}CH_3$ and CH_2CH), 2 78 (very br s, 1H, OH), 1 44 (s, 9H, $C(CH_3)_3$), 1 20 (t, 6H, J=7 0 Hz, 2x$OCH_2\underline{CH_3}$)

N-(Allyloxycarbonyl)-*D*-serinal diethyl acetal (9l) The same procedure was followed as described for **9k** using **13l** (8 7 g, 27 4 mmol), DIBAL (55 mL of a 1M solution in dichloromethane) and Bu_4NF (25 mL of a 1M solution in THF) Work-up gave 5 6 g of a residue which was subjected to column chromatography (EtOAc/hexanes=1/4, v/v), followed by MeOH/$CHCl_3$=3/7, v/v) to give 3 0 g (44%) **9l** as an oil, R_f=0 46 (EtOAc/hexanes=1/1), CIMS(70eV), m/z (relative intensity) 202 ($[M\ C_2H_5O]^+$, 30), 103 ($[CH(C_2H_5O)_2]^+$, 100), ^{1}H NMR (90 MHz) δ 6 16-5 74 (m, 1H, CH_2=$\underline{CH}$ CH_2), 5 48-5 15 (m, 3H, $\underline{CH_2}$=CH-CH_2 and NH), 4 60 4 52 (m, 3H, CH_2=CH-$\underline{CH_2}$ and $CH(OEt)_2$), 4 04 3 40 (m, 7H, CH_2CH and 2x$O\underline{CH_2}CH_3$), 2 61 (br s, 1H, OH), 1 20 (t, 6H, J=6 9 Hz, 2x$OCH_2\underline{CH_3}$)

D-serinal diethyl acetal (9n) To **9p** (3 5 g, 11 8 mmol) in MeOH (40 mL) was added a catalytic amount Pd(C) (10%) and the resulting mixture was shaken vigorously in a hydrogen atmosphere for 3 h The formed CO_2 was trapped by a 2M NaOH solution After filtration of the reaction mixture over Hyflo the solvent was evaporated *in vacuo* to give 1 91 g (99%) of **9n** as a colorless oil, CIMS(70eV), m/z (relative intensity) 164 ($[M+1]^+$, 20), 118 ($[M-C_2H_5O]^+$, 60), 103 ($[CH(C_2H_5O)_2]^+$, 100), ^{1}H NMR (90 MHz) δ 4 31 (d, 1H, J=5 7 Hz, $CH(OEt)_2$), 3 86-3 30 (m, 6H, $\underline{CH_2}CH$ and 2x$O\underline{CH_2}CH_3$), 2 87 (q, 1H, J=5 2 Hz, $CH_2\underline{CH}$), 2 16 (br s, 3H OH and NH_2), 1 14 (t, 6H, J=6 9 Hz, 2x$OCH_2\underline{CH_3}$)

N-(Trifluoroacetyl)-D-serinal diethyl acetal (9o) To **9n** (1 91 g, 11 7 mmol) and diisopropylethylamine (2 3 g, 17 8 mmol) in THF (50 mL) at 0°C was added trifluoroacetic anhydride (7 4 g, 35 2 mmol) over a period of 10 min After stirring for ±15 min another portion diisopropylethylamine (3 0 g, 23 2 mmol) was added together with MeOH (10 mL) The reaction mixture was diluted with EtOAc (50 mL) and extracted with 3 portions 0 1N HCl The organic layer was neutralized with sat $NaHCO_3$ and washed with brine and dried ($MgSO_4$) The solvent was evaporated *in vacuo* to give 2 2 g (73%) of **9o** which was homogeneous according to TLC, R_f 0 25 (EtOAc/hexanes=1/1, v/v), α_D^{22}=+14 5 (c=3 30, MeOH), CIMS(70eV), m/z (relative intensity) 214 ($[M\ C_2H_5O]^+$, 44), 103 ($[CH(C_2H_5O)_2]^+$, 100), ^{1}H NMR (90 MHz) δ 7 00 (very br s, 1H, NH), 4 66 (d 1H, J=3 0 Hz, $CH(OEt)_2$), 4 17-3 42 (m 7H, CH_2CH and 2x$O\underline{CH_2}CH_3$), 2 64 (very br s, 1H, OH), 1 24 (dt, 6H, J=2 1 Hz and J=6 9 Hz)

N-(Benzyloxycarbonyl)-D-serinal diethyl acetal (9p) The same procedure was followed as described for **9k** using **13p** (16 5 g, 45 0 mmol), DIBAL (55 mL of a 1M solution in dichloromethane) Work-up gave a mixture of compounds (as was monitored by TLC (EtOAc/hexanes=1/2 v/v)) which were separated by column chromatography (EtOAc/hexanes=1/4, v/v) to give 3 61 g (22%) of the starting compound **13p** (R_f 0,51), 1 17 g (8%) aldehyde (R_f

0 40) and 5.99 g (32%) of the silyl protected acetal (R_f 0 59) Treatment of the acetal with Bu_4NF (15 mL of a 1M solution in THF) gave after column chromatography (MeOH/CH_2Cl_2=3/97, v/v) 3 23 g (75%) of **9p** as a colorless oil, R_f 0 39 (MeOH/$CHCl_3$=3/97, v/v), α_D^{22}=+7.1 (c=1.55, MeOH), ClMS(70eV), m/z (relative intensity) 299 ($[M+1]^+$, 0.1), 252 ($[M-C_2H_5O]^+$, 2), 103 ($[CH(C_2H_5O)_2]^+$, 100), 91 ($[C_7H_7]^+$, 83), ^{1}H NMR (90 MHz) δ 7.32 (s, 5H, C_6H_5), 5.46 (br d, 1H, J=6.2 Hz, NH), 5 09 (s, 2H, CH_2Ph), 4.56 (d, 1H, J=2.9 Hz, $CH(OEt)_2$), 4 02-3.31 (m, 7H, HO$\underline{CH_2}$CH and 2xO$\underline{CH_2}CH_3$), 2.72 (br d, 1H, J=8.0 Hz, OH), 1.17 (dt, 6H, J=1.2 Hz and J=6 9 Hz, 2xOCH$_2\underline{CH_3}$).

Synthesis of tosylates **10**:

Methyl (*S*)-2-methoxy-3-(*p*-tolylsulfonyloxy)propanoate (10a). To freshly distilled pyridine (10 mL) was added **9a** (0.52 g, 3 9 mmol) and tosyl chloride (0.82 g, 4.3 mmol) and the resulting solution was kept over night at 4°C The volatiles were evaporated at 0°C at high vacuum. It is essential to keep the reaction mixture at low temperatures in order to avoid undesired β-elimination and/or racemization The residue was dissolved in EtOAc and subsequently washed with 0.1N HCl, sat. $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* The residue was subjected to column chromatography (dichloromethane) to yield 820 mg (73%) of **10a** as a colorless oil, R_f 0.55 (MeOH/$CHCl_3$=3/97, v/v), α_D^{22}=+22.0 (c=2 32, MeOH), ClMS(70eV), m/z (relative intensity) 289 ($[M+1]^+$,7), 229 ($[M-C_2H_3O_2]^+$, 100), 155 ($[C_7H_7SO_3]^+$, 59); ^{1}H NMR (90 MHz) δ 7 78 and 7.36 (AB, 4H, J_{AB}=8 4 Hz, C_6H_4), 4 32 and 4.22 (AB part of ABM spectrum, 2H, J_{AB}=10.3 Hz, J_{AM}=4.1 Hz and J_{BM}=6 0 Hz, O$\underline{CH_2}$CH), 4 01 (M part of ABM spectrum, 1H, OCH$_2\underline{CH}$), 3.72 (s, 3H, CO_2CH_3), 3.39 (s, 3H, OCH_3), 2 44 (s, 3H, p-C_6H_4-$\underline{CH_3}$)

Methyl (*S*)-2-(4-methoxytetrahydropyranyl-4-oxy)-3-(*p*-tolylsulfonyloxy)propanoate (10b). The same procedure as described for **10a** was followed using **9b** (1.35 g, 5.8 mmol) and tosyl chloride (1 23 g, 6.4 mmol) Purification by column chromatography (MeOH/$CHCl_3$=2/98, v/v) gave 1 72 g (77%) of **10b** as an oil, R_f 0 56 (MeOH/$CHCl_3$=3/97, v/v); α_D^{22}=+19.3 (c=2 18, MeOH), ClMS(70eV), m/z (relative intensity) 389 ($[M+1]^+$,1), 155 ($[C_7H_7SO_3]^+$, 57), 115($[C_6H_{11}O_2]^+$,100), ^{1}H NMR (90 MHz) δ 7 80 and 7 37 (AB, 2H, J=8.1 Hz, C_6H_4), 4.53 (t, 1H, J=5.3 Hz, OCH$_2\underline{CH}$), 4 20 (d, 2H, J=5.3 Hz, O$\underline{CH_2}$CH), 3 86-3 41 (m, 4H, -CH_2OCH_2-), 3 69 (s, 3H, $COOCH_3$), 3.18 (s, 3H, OCH_3), 2 45 (s, 3H, p- C_6H_4-$\underline{CH_3}$), 1 81-1 67 (m, 4H, -CH_2CCH_2-).

Methyl (*S*)-2-methyl-3-(*p*-tolylsulfonyloxy)propanoate (10d). The same procedure as described for **10a** was followed using (R)-methyl-3-hydroxy-2-methylpropionate (2.5 g, 21 mmol) and tosyl chloride (4 40 g, 1 1 eq.). Purification by column chromatography (EtOAc/hexanes=35/65, v/v) gave 5 1 g (89%) of **10d** as an oil, R_f 0 25 (EtOAc/hexanes=1/4, v/v); ClMS(70eV), m/z (relative intensity) 273 ($[M+1]^+$,63%), 155 ($[C_7H_7SO_3]^+$, 46), 117 ($[M-C_7H_7SO_3]^+$, 46), 91 ($[C_7H_7]^+$,57), 69(100); ^{1}H NMR (90 MHz) δ 7 82 and 7 38 (AB, 4H, J=8 4 Hz, C_6H_4), 4 33-3 99 (m, 2H, $\underline{CH_2}$CH), 3 67 (s, 3H, $COOCH_3$), 3 02-2.64 (m, 1H, $CH_2\underline{CH}CH_3$), 2.45 (s, 3H, p- C_6H_4-$\underline{CH_3}$), 1 20 (d, 3H, J=7 0 Hz, CH$\underline{CH_3}$).

Methyl (*S*)-3-(*p*-tolylsulfonyloxy)-2-(trifluoroacetylamino)propanoate (10i). The same procedure as described for **10a** was followed using **9i** (3,72 g, 18,7 mmol) and tosyl chloride (5,60 g, 29,5 mmol). Purification by column chromatography (EtOAc/hexanes=20/80, v/v) gave 8 5 g (78%) of **10i** as a white solid , R_f 0 34 (EtOAc/hexanes=1/2, v/v), α_D^{22}=-7 3 (c=4.80, MeOH), ^{1}H NMR (90 MHz) δ 7 78 and 7 37 (AB, 4H, J_{AB}=8.0 Hz, C_6H_4), 7 5-7 2 (br d, 1H, NH), 4.86-6 67 (m, 1H, $CH_2\underline{CH}$), 4 47 and 4 36 (AB part of ABX spectrum, 2H, J_{AB}=10.9 Hz, J_{AX}=2.5 Hz and J_{BX}=2 8 Hz, $\underline{CH_2}$CH), 3 80 (s, 3H, OCH_3), 2 45 (s, 2H, CH_2Ph).

N-(*tert*-Butyloxycarbonyl)-O-(*p*-tolylsulfonyloxy)-*D*-serinal diethyl acetal (10k) The same procedure was followed as described for **10a**, with the exception that the pyridine is removed at room temperature because the acetal is much less susceptible toward elimination and/or racemization than the corresponding methyl ester. **9k** (3 5 g, 13 3 mmol) and tosyl chloride (2 54 g, 13.3 mmol) gave after column chromatography (EtOAc/hexanes=1/2, v/v) 1 32 g (52%) regained tosyl chloride and 2 35 g (42%) of **10k** as an oil; R_f 0 46 (EtOAc/hexanes=1/3, v/v), ^{1}H NMR (90 MHz) δ 7.79 and 7 34 (AB, 4H, J_{AB}=8 0 Hz, C_6H_4), 4 80 (br d, 1H, J=7 6 Hz, NH), 4 48 (d, 1H, J=4.0 Hz, CH(OEt)$_2$), 4 15-3 28 (m, 7H, OCH_2CH and 2xO$\underline{CH_2}CH_3$), 2 43 (s, 3H, H_3CPh), 1 40 (s, 9H, $C(CH_3)_3$), 1.13 (t, 6H, J=7 0 Hz, 2xOCH$_2\underline{CH_3}$)

N-allyloxycarbonyl-O-(*p*-tolylsulfonyloxy)-*D*-serinal diethyl acetal (10l). The same procedure was followed as described for **10k** using **9l** (3 0 g, 12.1 mmol) and tosyl chloride (2 4 g, 12.2 mmol) Purification by column chromatography (EtOAc/hexanes=1/3, v/v) gave 4.0 g (82%) of **10l** as an oil; R_f 0 62 (EtOAc/hexanes=1/2,

v/v); CIMS(70eV), m/z (relative intensity) 356.9 ($[M^+-C_2H_5O]^+$, 0.1), 213 (7), 155 (62), 103 ($[CH(C_2H_5O)_2]^+$, 4), 91 ($[C_7H_7]^+$, 100); ^{1}H NMR (90 MHz) δ 7.80 and 7.35 (AB, 4H, J_{AB}=8.0 Hz, C_6H_4), 6.13-5 71(m, 1H, H_2C=CH-CH_2), 5 38-5 13 (m, 2H, H_2C=CH-CH_2), 5 04 (br d, 1H, J=7.0 Hz, NH), 4 56-4 49 (m, 3H, H_2C=CH-CH_2 and $CH(OEt)_2$), 4 24-3.85 (m, 3H, CH_2CH), 3.79-3.35 (m, 4H, 2xOCH_2CH_3), 2 44 (s, 3H, H_3CPh), 1 14 (t, 6H, J=6.6 Hz, 2xOCH_2CH_3).

(*R*)-2-methyl-3-(*p*-tolylsulfonyloxy)-propanal diethyl acetal (10m). For transformation of the methyl ester into the diethyl acetal the same procedure was followed as for **9k** using **10d** (3.4 g, 12.5 mmol), DIBAL (21 mL of a 1M solution in dichloromethane), triethyl orthoformate (10 mL), EtOH (100 mL) and TFA (0.5 mL) Purification by column chromatography (EtOAc/hexanes=1/2, v/v) gave 1.55 g (39%) of **10m** as an oil, R_f 0,44 (EtOAc/hexanes=1/2, v/v); CIMS(70eV), m/z (relative intensity) 316 ($[M]^+$,0.3), 173 (100), 103 ($[CH(C_2H_5O)_2]^+$, 7), 91 ($[C_7H_7]^+$, 50), ^{1}H NMR (90 MHz) δ 7.81 and 7.34 (AB, 4H, J_{AB}=8.4 Hz, C_6H_4), 4.32 (d, 1H, J=5.9 Hz, $CH(OEt)_2$), 4 05 and 3.97 (AB part of ABX spectrum, 2H, J_{AB}=9.5 Hz, J_{AX}=4 9 Hz and J_{BX}=6.1 Hz,)CH_2CH), 3.75-3.24 (m, 4H, OCH_2CH_3). 2.46 (s, 3H, H_3CPh), 2.21-1.95 (m, 1H, CH_2CHCH), 1.14 (dt, 6H, J=2.3 Hz and J=7 0 Hz, 2xOCH_2CH_3) , 0.96 (d, 3H, J=6 9 Hz, $CHCH_3$) and 750 mg (22%) starting compound.

O-(*p*-tolylsulfonyloxy)-N-(trifluoroacetyl)-D-serinal diethyl acetal (10o). The same procedure was followed as described for **10a** using **9o** (2.2 g, 8.5 mmol) and tosyl chloride (1 65 g, 8.6 mmol) Purification by column chromatography (EtOAc/hexanes=1/2, v/v) gave 330 mg (20%) of recovered tosyl chloride, 250 mg (11%) of recovered **9o** and 2 1 g (58%) of **10o** as an oil, R_f 0.47 (EtOAc/hexanes=1/1, v/v), CIMS(70eV), m/z (relative intensity) 368 ($[M-C_2H_5O]^+$, 14), 196 (62), 103 ($[CH(C_2H_5O)_2]^+$, 100), 91 ($[C_7H_7]^+$, 27); ^{1}H NMR (90 MHz) δ 7.78 and 7.35 (AB, 4H, J_{AB}=8 1 Hz, C_6H_4), 6.62 (br d, 1H, J=4 0 Hz, NH), 4.60 (d, 1H, J=3.9 Hz, $CH(OEt)_2$), 4.39-4.00 (m, 2H, OCH_2CH), 3.86-3 29 (m, 5H, CH_2CH and 2xOCH_2CH_3), 2 44 (s, 3H, H_3CPh), 1.16 (t, 6H, J=6 9 Hz, 2xOCH_2CH_3)

Synthesis of thioacetates **11**:

Methyl (*S*)-3-acetylthio-2-methoxypropanoate (11a). To DMF[26] (10 mL) was successively added Cs_2CO_3 (630 mg, 2 0 mmol) and thioacetic acid (280 mg, 3.7 mmol). The suspension was stirred in the darkness until all Cs_2CO_3 had dissolved. To this solution tosylate **10a** (800 mg, 2.8 mmol), dissolved in DMF (2 mL), was added and the reaction mixture was allowed to stand over night at room temperature in the dark. The solvent of the resulting yellowish solution was removed *in vacuo*. The residue was dissolved in EtOAc (20 mL) and subsequently washed with 0.1N HCl and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was subjected to column chromatography (dichloromethane) to yield 440 mg (81%) of thioacetate **11a** as a yellowish oil; R_f 0 28 (MeOH/$CHCl_3$=3/97, v/v), α_D^{22}=+6.0 (c=1.5, MeOH); ^{1}H NMR (90 MHz) δ 3.93 (X part of ABX spectrum, 1H, CH_2CH), 3 78 (s, 3H, $COOCH_3$), 3.36 and 3.22 (AB part of ABX spectrum, 2H, J_{AX}=4.5 Hz, J_{BX}=7.3 Hz and J_{AB}=13 9 Hz, CH_2CH), 3 43 (s, 3H, OCH_3), 2.35 (s, 3H, $SCOCH_3$)

Methyl (*S*)-3-acetylthio-2-(4-methoxytetrahydropyranyl-4-oxy)propanoate (11b). The same procedure was followed as described for **11a** using Cs_2CO_3 (1.0 g, 3 1 mmol), thioacetic acid (440 mg, 5 8 mmol) and **10b** (1.72 g, 4.43 mmol). Purification by column chromatography (MeOH/$CHCl_3$=3/97, v/v) gave 1 02 g (79%) of **11b** as a yellowish oil; R_f 0.39 (MeOH/$CHCl_3$=3/97, v/v), α_D^{22}=-14 0 (c=2 5, MeOH), CIMS(70eV), m/z (relative intensity) 293 ($[M+1]^+$, 4), 161 ($[C_6H_9O_3S]^+$, 91), 115($[C_6H_{11}O_2]^+$, 100), ^{1}H NMR (90 MHz) δ 4.39 (t, 1H, CH_2CH), 3 87-3.48 (m, 4H, -CH_2OCH_2-), 3.74 (s, 3H, $COOCH_3$), 3.27-3.18 (m, 2H, CH_2CH), 3 23 (s, 3H, OCH_3), 2 34 (s, 3H, $SCOCH_3$), 1 91-1.73 (m, 4H, -CH_2CCH_2-)

Methyl (*S*)-3-acetylthio-2-methylpropanoate (11d). The same procedure was followed as described for **11a** using Cs_2CO_3 (4.13 g, 0.7 eq), thioacetic acid (2.08 g, 1.5 eq.) and **10d** (5 10 g, 18 3 mmol). Purification by column chromatography (hexanes/$CHCl_3$=15/85, v/v) gave 1.74 g (54%[26]) of thioacetate **5c**, R_f 0.41 ($CHCl_3$), ^{1}H NMR (90 MHz) δ 3.71 (s, 3H, $COOCH_3$), 3.12 and 3.05 (AB part of ABX spectrum, 2H, J_{AX}=7.8 Hz, J_{BX}=3 5 Hz and J_{AB}=13 5 Hz, CH_2CH), 2 89-2.51 (m, 1H, CH_2CH), 2.32 (s, 3H, $SCOCH_3$), 1 23 (d, 3H, J=7.0 Hz, $CHCH_3$)

Methyl (2*S*)-3-acetylthio-2-(trifluoroacetylamino)propanoate (11i). The same procedure was followed as described for **11a** using Cs_2CO_3 (4.94 g, 15 2 mmol), thioacetic acid (2.14 g, 28.2 mmol) and **10i** (8.0 g, 21.7 mmol). Purification by column chromatography (EtOAc/hexanes=1/3, v/v) gave 4.53 g (76%) of **11i** as a colorless oil, R_f 0 42 (EtOAc/hexanes=1/2, v/v), α_D^{22}=+12 0 (c=4.25, MeOH); ^{1}H NMR (90 MHz) δ 7 28 (br d, 1H, NH), 4 91-4 65

(m, 1H, $CH_2\underline{CH}$), 3.85 (s, 3H, OCH_3), 3 47 and 3.40 (AB part of ABX spectrum, 2H, J_{AB}=14.6 Hz, J_{AX}=4 0 Hz and J_{BX}=6.5 Hz, $\underline{CH_2}CH$), 2.40 (s, 3H, $SCOCH_3$).

S-acetyl-N-(*tert*-butyloxycarbonyl)-*D*-cysteinal diethyl acetal (11k). The same procedure was followed as described for **11a** using **10k** (2.35 g, 5.6 mmol), Cs_2CO_3 (1 28 g, 3 9 mmol) and thioacetic acid (560 mg, 7.4 mmol) Purification by column chromatography (EtOAc/hexanes=1/4, v/v) gave 1.25 g (70%) of **11k** as a yellowish oil; R_f 0.32 (EtOAc/hexanes=1/3, v/v), α_D^{22}=+67 0 (c=6.10, MeOH); CIMS(70eV), m/z (relative intensity) 322 ($[M+1]^+$, 1), 276 ($[M-C_2H_5O]^+$, 12), 220 (39), 103 ($[CH(C_2H_5O)_2]^+$, 100), 57 ($[C_4H_9]^+$, 20); ^{1}H NMR (90 MHz) δ 4.82 (br d, 1H, J=9.0 Hz, NH), 4.43 (d, 1H, J=3.5 Hz, $CH(OEt)_2$), 4.02-3.38 (m, 5H, $CH_2\underline{CH}$ and 2x$O\underline{CH_2}CH_3$), 3.19 and 3.02 (AB part of ABX spectrum, J_{AB}=13.8 Hz, J_{AX}=6.1 Hz and J_{BX}=7.3 Hz, $\underline{CH_2}CH$), 2.32 (s, 3H, $SCOCH_3$), 1.42 (s, 9H, $C(CH_3)_3$), 1.20 (t, 6H, J=7.0 Hz, 2x$OCH_2\underline{CH_3}$).

S-acetyl-N-(allyloxycarbonyl)-*D*-cysteinal diethyl acetal (11l) The same procedure was followed as described for **11a** using **10l** (3.9 g, 9 7 mmol), Cs_2CO_3 (2.22 g, 6.8 mmol) and thioacetic acid (1.03 g, 13.5 mmol). Purification by column chromatography (EtOAc/hexanes=1/3, v/v) gave 2.18 g (74%) of **11l** as a yellowish oil; R_f 0 35 (EtOAc/hexanes=1/3, v/v); α_D^{22}=+75.8 (c=2.40, MeOH); CIMS(70eV), m/z (relative intensity) 306 ($[M+1]^+$, 0.2), 260 ($[M-C_2H_5O]^+$, 45), 184 (49), 103 ($[CH(C_2H_5O)_2]^+$, 100); ^{1}H NMR (90 MHz) δ 6.17-5.74 (m, 1H, CH_2=$\underline{CH}$-CH_2), 5 40-5 04 (m, 3H, $\underline{CH_2}$=CH-CH_2 and NH), 4.58 (br d, 2H, J=5.1 Hz, CH_2=CH-$\underline{CH_2}$), 4 46 (d, 1H, J=3 1Hz, $CH(OEt)_2$), 4.09-3.44 (m, 5H, CH_2CH and 2x$O\underline{CH_2}CH_3$), 3.21 and 3.04 (AB part of ABX spectrum, 2H, J_{AB}=14.3 Hz, J_{AX}=3.9 Hz and J_{BX}=10.3 Hz), 2.33 (s, 3H, $COCH_3$), 1.21 (t, 6H, J=6.8 Hz, 2x$OCH_2\underline{CH_3}$)

(*R*)-3-acetylthio-2-methyl-propanal diethyl acetal (11m). The same procedure was followed as described for **11a** using **10m** (1.55 g, 4.9 mmol), Cs_2CO_3 (1.12 g, 3.4 mmol) and thioacetic acid (560 mg, 7.4 mmol). Purification by column chromatography (EtOAc/hexanes=1/3, v/v) gave 595 mg (55%) of **11m** as a yellowish oil; R_f 0.15 (hexanes/CH_2Cl_2=1/4, v/v); CIMS(70eV), m/z (relative intensity) 175 ($[M-C_2H_5O]^+$, 0 2), 103 ($[CH(C_2H_5O)_2]^+$, 6), 41 ($[C_3H_5]^+$, 100); ^{1}H NMR (90 MHz) δ 4.27 (d, 1H, J=5 8 Hz, $CH(OEt)_2$), 3 89-3.32 (m, 4H, 2x$O\underline{CH_2}CH_3$), 3.10 and 2 80 (AB part of ABX spectrum, 2H, J_{AB}=13 8 Hz, J_{AX}=6.8 Hz and J_{BX}=6 6 Hz, $S\underline{CH_2}CH$), 2 29 (s, 3H, H_3CCOS), 2 14-1.87 (m, 1H, $CH_2\underline{CH}$), 1.18 (t, 6H, J=7.1 Hz, 2x$OCH_2\underline{CH_3}$), 0 98 (d, 3H, J=6.7 Hz, $CH\underline{CH_3}$)

S-acetyl-N-trifluoroacetyl-D-cysteinal diethyl acetal (11o). The same procedure was followed as described for **11a** using **10o** (2.05 g, 5.0 mmol), Cs_2CO_3 (1.13 g, 3.5 mmol) and thioacetic acid (490 mg, 6.4 mmol). Purification by column chromatography (EtOAc/hexanes=1/3, v/v) gave 1.39 g (88%) of **11o** as an oil; R_f 0.49 (EtOAc/hexanes=1/2, v/v), α_D^{22}=+29.0 (c=2 45, MeOH); CIMS(70eV), m/z (relative intensity) 318 ($[M+1]^+$, 0 5), 272 ($[M-C_2H_5O]^+$, 96), 196 (77), 103 ($[CH(C_2H_5O)_2]^+$, 100), ^{1}H NMR (90 MHz) δ 6.72 (very br d, 1H, J=8 0 Hz, NH), 4 51 (d, 1H, J=3.2 Hz, $CH(OEt)_2$), 4.20 (dq, 1H, J=2.9 Hz and J=7.5 Hz, $CH_2\underline{CH}$), 3.95-3.36 (m, 4H, 2x$O\underline{CH_2}CH_3$), 3.19 (d, 2H, J=7 0 Hz, $\underline{CH_2}CH$), 2 34 (s, 3H, CH_3), 1.22 (dt, 6H, J=1.7 Hz and J=6.9 Hz, 2x$OCH_2\underline{CH_3}$).

Synthesis of chloromethyl sulfides **12**.

Methyl (*S*)-3-chloromethylthio-2-methoxy-propanoate (12a). To dry MeOH (10 mL) sodium (52 mg, 2.3 mmol) was added. This NaOMe solution was added dropwise to a stirred solution of thioacetate **11a** (440 mg, 2 3 mmol) in dry MeOH (5 mL) under an argon atmosphere. After stirring for 15 minutes, sat. NH_4Cl (10 mL) was added and the volatiles were evaporated *in vacuo*. The residue was dissolved in EtOAc (25 mL) and washed with satd NH_4Cl The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to yield 336 mg (98%) of the crude thiol, R_f 0 53 (EtOAc/hexanes=1/1, v/v); ^{1}H NMR (90 MHz) δ 3.60 (t, 1H, J=5.2 Hz + fine splitting <1 Hz, $S\underline{CH}CH_2$), 3.46 (s, 3H, $COOCH_3$), 3 14 (s, 3H, OCH_3), 2.71-2 56 (m, 2H, $SCH\underline{CH_2}$), 1.64 (t, 1H, J=8.2 Hz + fine splitting <1Hz, SH) The crude thiol was dissolved in $BrCH_2Cl$ (50 mL) To this solution triethylbenzylammonium chloride (TEBAC) (52 mg, 0 23 mmol) and powdered KOH (192 mg, 3 4 mmol) were added. The suspension was stirred vigorously for 30 min The reaction mixture was subsequently washed with NH_4Cl (20 mass%) and brine The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to yield 350 mg (77%) of the chloromethyl sulfide **12a** as a yellow oil which was not further purified Although most chloromethyl sulfides were obtained pure according to TLC, purification by column chromatography is not possible due the lability of chloromethyl sulfides; R_f 0.53 (EtOAc/hexanes=1/1, v/v); ^{1}H NMR

(90 MHz) δ 4 80 (s, 2H, SCH_2Cl), 4 07 (t, 1H, J=5 5 Hz, $S\underline{CH}CH_2$), 3 76 (s, 3H, $COOCH_3$), 3 44 (s, 3H, OCH_3) 3 10-3 00 (m, 2H, $SCH\underline{CH_2}$)

Methyl (*S*)-3-(chloromethylthio)-2--(4-methoxytetrahydropyranyl-4-oxy)propanoate (12b). The same procedure was followed as described for **12a** using dry MeOH (25 mL), sodium (102 mg, 4 43 mmol) and **11b** (1 30 g, 4 45 mmol) to give after work-up 1 12 g of the crude thiol, R_f 0 54 (MeOH/$CHCl_3$=3/97, v/v) The crude thiol, $BrCH_2Cl$ (40 mL), TEBAC (101 mg , 0 44 mmol) and powdered KOH (374 mg, 6 70) mmol) gave 1 32 g (99%) crude chloromethyl sulfide **12b**, R_f 0 68 (MeOH/$CHCl_3$=3/97, v/v), CIMS(70eV), m/z (relative intensity) 298 ($[M]^+$, 0 1), 183 ($[C_5H_6O_3SCl+2]^+$,3), 181 ($[C_5H_6O_3SCl]^+$,9), 115($[C_6H_{11}O_2]^+$,100), ^1H NMR (90 MHz) δ 4 97-4 65 (AB pattern, 2H, SCH_2Cl), 4 58 (t, 1H, J=5 7 Hz, $CH_2\underline{CH}$), 3 92-3 45 (m, 4H, $-CH_2OCH_2-$), 3 76 (s, 3H $COOCH_3$),3 24 (s, 3H, OCH_3), 3 09 (d, 2H, J=5 7 Hz, $\underline{CH_2}CH$), 1 92-1 74 (m, 4H, $-CH_2CCH_2$)

Methyl (*S*)-3-(chloromethylthio)-2-methylpropanoate (12d). The same procedure as described for **12a** was followed using **11d** (1 7 g, 9 7 mmol) and sodium (223 mg, 1 eq) to give after work-up the corresponding thiol (not weighed), ^1H NMR (90 MHz) δ 3 73 (s, 3H, $COOCH_3$), 2 93-2 53 (m, 3H, $CHCH_2$), 1 60-1 18 (m, 4H, $CHCH_3$ and SH), This crude thiol together with $BrCH_2Cl$ (100 mL), TEBAC 313 mg (0 1 eq) and powdered KOH (815 mg, 1 5 eq) gave 1 26 g of **12d** (71% overall from **5c**), CIMS(70eV), m/z (relative intensity) 147 ($[M-Cl]^+$, 100), 101 ($[C_5H_9O_2]^+$, 29), ^1H NMR (90 MHz) δ 4 75 (s, 2H, SCH_2Cl), 3 73 (s, 3H, $COOCH_3$), 3 22-2 63 (m, 3H $CHCH_2$), 1 29 (d, 3H, J=6 2 Hz, CCH_3)

Methyl S-(chloromethyl)-*N*-(trifluoroacetyl)-D-cysteinate (12i) The same procedure was followed as described for **12a** using sodium (355 mg, 15 4 mmol) and **11i** (4 21 g, 15 4 mmol) to give after work-up 3 23 g (91%) of the crude thiol, ^1H NMR (90 MHz) δ 7 27 (very br s, 1H, NH), 4 98-4 80 (m, 1H, $CH_2\underline{CH}$), 3 84 (s, 3H OCH_3), 3 15-3 01 (m, 2H, $\underline{CH_2}CH$), 1 39 (t, 1H, J=9 1 Hz, SH) The crude thiol together with TEBAC (318 mg, 1 40 mmol), $BrCH_2Cl$ (140 mL) and powdered KOH (1 17 g, 20 9 mmol) gave 2 47 g (63%) of chloromethyl sulfide **12i**, ^1H NMR (90 MHz) δ 7 25 (very br s, 1H, NH), 5 02-4 82 (m, 1H, $CH_2\underline{CH}$), 4 68 (d, 2H, J=1 2 Hz, OCH_2S), 3 85 (s, 3H, OCH_3), 3 34 and 3 26 (AB part of ABX spectrum, 2H, J_{AB}=14 7 Hz, J_{AX}=4 3 Hz and J_{BX}=5 1 Hz, $\underline{CH_2}CH$)

N-(*tert*-butyloxy)carbonyl)-S-(chloromethyl)-D-cysteinal diethyl acetal (12k) The same procedure was followed as for **12a** using **11k** (1 35 g, 4 2 mmol) and Na (97 mg, 4 2 mmol) to give after work-up 1 14 g (97%) of the crude thiol, ^1H NMR (90 MHz) δ 4 90 (br d, 1H, J=8 0 Hz, NH), 4 58 (d, 1H, J=3 5 Hz, $CH(OEt)_2$), 3 97-3 37 (m, 5H, $CH_2\underline{CH}$ and 2x$O\underline{CH_2}CH_3$), 2 81-2 65 (m, 2H, $\underline{CH_2}CH$), 1 44 (t, 1H, J=8 7 Hz, SH), 1 44 (s, 9H, $C(CH_3)_3$), 1 20 (t, 6H, J=6 8 Hz, $OCH_2\underline{CH_3}$) This crude thiol together with $BrCH_2Cl$ (50 ml), TEBAC (95 mg , 0 42 mmol) and powdered KOH (235 mg, 4 2 mmol) gave 1 3 g (94%) of the chloromethyl sulfide **12b** as a yellow oil, ^1H NMR (90 MHz) δ 4 87 (br d, 1H, J=9 2 Hz, NH), 4 79 (d, 2H, J=1 4 Hz, OCH_2S), 4 53 (d, 1H, J=3 3 Hz, $CH(OEt)_2$), 4 14-3 89 (m, 1H, $CH_2\underline{CH}$), 3 85-3 37 (m, 4H, $O\underline{CH_2}CH_3$), 3 06 and 2 85 (AB part of ABX spectrum, 2H, J_{AB}=13 9 Hz, J_{AX}=5 1 Hz and J_{BX}=7 5 Hz, $\underline{CH_2}CH$), 1 44 (s, 9H, $C(CH_3)_3$), 1 21 (t, 6H, J=6 9 Hz, 2x$OCH_2\underline{CH_3}$)

N-(allyloxycarbonyl)-S-(chloromethyl)-*D*-cysteinal diethyl acetal (12l) The same procedure was followed as described for **12a** using **11l** (2 15 g, 7 0 mmol) and sodium (161 mg, 7 0 mmol) to give after work-up the crude thiol (not weighed), ^1H NMR (90 MHz) δ 6 16-5 75 (m, 1H, $CH_2=\underline{CH}-CH_2$), 5 41 5 13 (m, 3H, $\underline{CH_2}=CH-CH_2$), 4 60-4 56 (m, 3H, $CH_2=CH-\underline{CH_2}$ and $CH(OEt)_2$), 4 25-3 38 (m, 5H, $CH_2\underline{CH}$ and 2x$O\underline{CH_2}CH_3$), 2 83-2 66 (m, 2H, $CH\underline{CH_2}$), 1 45 (t, 1H, J=8 5 Hz, SH), 1 20 (t, 6H, J=6 9 Hz, 2x$OCH_2\underline{CH_3}$) This crude thiol together with $BrCH_2Cl$ (150 mL), TEBAC (160 mg , 0 70 mmol) and powdered KOH (600 mg, 10 7 mmol) gave 2 17 g (99%) of chloromethyl sulfide **12l** as a yellow oil, CIMS(70eV), m/z (relative intensity) 313 9 ($[M+2]^+$, 0 2), 311 9 ($[M+2]^+$ 0 4), 276 ($[M+1-Cl]^+$, 3), 230 ($[M-C_2H_5OCl]^+$, 10), 184 (26), 103, ($[HC(OC_2H_5)_2]^+$, 100), ^1H NMR (90 MHz) δ 6 17-5 74 (m, 1H, $CH_2=\underline{CH}-CH_2$), 5 41-5 06 (m, 3H, $\underline{CH_2}=CH-CH_2$ and NH), 4 77 (d, 2H, J<1 Hz, $ClCH_2S$), 4 61 4 53 (m, 3H, $CH_2=CH\ \underline{CH_2}$ and $CH(OEt)_2$), 4 20-3 90 (m, 1H, $CH_2\underline{CH}$), 3 97-3 38 (m, 4H, 2x$O\underline{CH_2}CH_3$), 3 08 and 2 87 (AB part of ABX spectrum, 2H, J_{AB}=13 8 Hz, J_{AX}=5 3 Hz and J_{BX}=7 9 Hz, $\underline{CH_2}CH$), 1 22 (t, 6H, J=6 8 Hz 2x$OCH_2\underline{CH_3}$)

(*R*)-3-(Chloromethylthio)-2-methyl-propanal diethyl acetal (12m) The same procedure was followed as described for **12a** using **11m** (595 mg, 2 7 mmol), sodium (62 mg, 2 7 mmol), $BrCH_2Cl$ (50 mL), TEBAC (61

mg, 0 27 mmol) and powdered KOH (227 mg, 4 1 mmol) to give after work-up 572 mg (94%) of **12m** as a yellow oil; ^{1}H NMR (90 MHz) δ 4.74 (s, 2H, $ClCH_2S$), 4.34 (d, 1H, J=5.7 Hz, $CH(OEt)_2$), 3.90-3 34 (m, 4H, 2x$O\underline{CH_2}CH_3$), 2.99 and 2 63 (AB part of ABX spectrum, 2H, J_{AB}=12.6 Hz, J_{AX}=4.8 Hz and J_{BX}=7 9 Hz, $S\underline{CH_2}CH$), 2.29-1 95 (m, 1H, $CH_2\underline{CH}$), 1.21 (dt, 6H, J=0.5 Hz and J=7.0 Hz, 2x$OCH_2\underline{CH_3}$), 1.04 (d, 3H, J=6 7 Hz, $CH\underline{CH_3}$)

S-(Chloromethyl)-N-(trifluoroacetyl)-D-cysteinal diethyl acetal (12o), 20 and 21. The same procedure was followed as described for **12o** using **11o** (1 39 g, 4.38 mmol) and sodium (101 mg, 4.38 mmol) to give after work-up 1 16 g (96%) of the crude thiol; ^{1}H NMR (90 MHz) δ 6.69 (very br d, 1H, J=6.0 Hz, NH), 4.67 (d, 1H, J=3.3 Hz, $CH(OEt)_2$), 4 29-4 02 (m, 1H, $CH_2\underline{CH}$), 3 88-3 37 (m, 4H, 2x$O\underline{CH_2}CH_3$), 2 71 and 2.51 (AB part of ABX spectrum, 2H, J_{AB}=14.6 Hz, J_{AX}=6 3 Hz and J_{BX}=6.8 Hz, $\underline{CH_2}CH$), 1.47 (t, 1H, J=8.7 Hz, SH), 1.20 (dt, 6H, J=0 9 Hz and J=7 0 Hz, 2x$OCH_2\underline{CH_3}$) This crude thiol together with $BrCH_2Cl$ (100 mL), TEBAC (95 mg , 0 42 mmol) and powdered KOH (354 mg, 6.3 mmol) gave 1 22 g of an impure oil. Comparison of the NMR of this oil with the NMR's of the isolated products in the alkylation attempt toward **17o** showed that the oil consisted of **12o** (44%) (the 90 MHz NMR spectrum was too complicated for exact assignments), **20** (32%), CIMS(70eV), m/z (relative intensity) 562.8 ($[M+1]^+$, 0.2), 516.8 ($[M-C_2H_5O]^+$, 32), 470.8 ($[M-1-2xC_2H_5O]^+$, 50), 196 (100), 103 ($[HC(C_2H_5O)_2]^+$, 100), ^{1}H NMR (90 MHz) δ 6.95 (br d, 1H, J=9.0 Hz, NH), 6.72 (br d, 1H, J-9.0 Hz, NH), 4.60 (d, 1H, J=3.0 Hz, $CH(OEt)_2$), 4 55 (d, 1H, J=3.3 Hz, $CH(OEt)_2$), 4.47-4.10 (m, 2H, 2x$CH_2\underline{CH}$), 3.97-3 38 (m, 10H, 4x$O\underline{CH_2}CH_3$ and SCH_2S), 3 13-2.64 (m, 4H, 2x$\underline{CH_2}CH$), 1.20 (dt, 12H, J=1.2 Hz and J=6.9 Hz, 4x$OCH_2\underline{CH_3}$) and **21** (20%); CIMS(70eV), m/z (relative intensity) 288 ($[M+1]^+$, 15), 242 ($[M-C_2H_5O]^+$, 97), 103 ($[HC(C_2H_5O)_2]^+$, 100); ^{1}H NMR (90 MHz) δ 5 07-4.27 (m, 3H, $CH_2\underline{CH}$ and NCH_2S), 4 84 (d, 1H, J=3.2 Hz, $CH(OEt)_2$), 3.97-3.42 (m, 4H, 2x$O\underline{CH_2}CH_3$), 3.39 and 3.07 (AB part of ABX spectrum, 2H, J_{AB}=13.3 Hz, J_{AX}=7 0 Hz and J_{BX}=9.5 Hz, $\underline{CH_2}CH$), 1.18 (dt, 6H, J=4 0 Hz and J=7 0 Hz, 2x$OCH_2\underline{CH_3}$)

3-[N-(2-trimethylsilylethyloxycarbonyl)-N-(allyloxy)-2-aminoethyl]indole (15a). To **14a**[5] (1 g, 3.1 mmol) in freshly distilled DME (25 mL) was added NaH (125 mg of a 60% oil dispersion, 3 1 mmol) and the suspension was stirred until a clear solution appeared (hydrogen gas evolved). To this solution allyl bromide (1 5 g, 12.4 mmol) was added in one portion (immediate NaBr formation). After 2 h the suspension was concentrated *in vacuo* in order to remove the remaining poisonous allylbromide The residue was dissolved in EtOAc and subsequently washed with water and brine The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to yield 1.12 g (100%) of the allyl ether **15a**.; R_f 0.63 (EtOAc/ hexanes =1/1, v/v), CIMS(70eV), m/z (relative intensity) 360 ($[M]^+$, 18), 318 ($[M-C_3H_6]^+$, 54), 158 (100), 144 ($[C_{10}H_{10}N]^+$, 96), 130 ($[C_9H_8N]^+$, 52), 73 (60); ^{1}H NMR (60 MHz) δ 8.03 (br s, 1H, indole-NH), 7 70-7.00 (m, 5H, indole C(2)H and C(4)H-C(7)H), 6 35-5 80 (m, 1H, -$CH_2\underline{CH}=CH_2$), 5.40-5.20 (m, 2H,-$CH_2CH=\underline{CH_2}$), 4 40-3.70 (m, 6H,-$\underline{CH_2}CH=CH_2$, $O\underline{CH_2}CH_2Si$ and indole-C(3)$CH_2\underline{CH_2}N$), 3 15-3 00 (m, 2H, indole C(3)$CH_2\underline{CH_2}N$), 0 95-0 75 (m, 2H, $OCH_2\underline{CH_2}Si$), 0 00 (s, 9H, $Si(CH_3)_3$)

1-Methyl-3-[N-(2-trimethylsilylethyloxycarbonyl)-N-(allyloxy)-2-aminoethyl]indole (15b). To DMSO (20 mL) was added **15a** (1.2 g, 3 3 mmol), MeI (1.0 g, 7 0 mmol) and powdered KOH (370 mg, 6.6 mmol) The, in the beginning dark solution, became clearer as the reaction proceeded. After stirring for 1 5 h the reaction mixture was diluted with EtOAc (50 mL) and subsequently washed with 1N HCl, 3 portions water and brine. The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* The residue was subjected to column chromatography (EtOAc/hexanes=1/4, v/v) to yield 1.22 g (99%) **15b** as an oil, R_f 0.30 (EtOAc/hexanes= 1/4, v/v); ^{1}H NMR (90 MHz) δ 7.62-7.52 (m, 1H, indole C(7)H), 7.28-6.96 (m, 3H indole C(4)-C(6)H), 6.84 (s, 1H, indole C(2)H), 6 22-5 77 (m, 1H, $\underline{CH}=CH_2$), 5 37-5 17 (m, 2H, $CH=\underline{CH_2}$), 4.34(d, 2H, J=6.0 Hz, $\underline{CH_2}CH=CH_2$), 4.16-3.96 (m, 2H, $O\underline{CH_2}CH_2Si$), 3 86-3 69 (m, 2H, CH_2N), 3 71(s, 3H, NCH_3), 3.12-2 96 (m, 2H, indole C(3)CH_2), 0.94-0 75 (m, 2H, $OCH_2\underline{CH_2}Si$), 0 00 (s, 9H, $SiC(CH)_3$)

1-Methyl-3-[N-(2-trimethylsilylethyloxycarbonyl)-N-hydroxy-2-aminoethyl]indole (14b). A solution of **15b** (980 mg, 2 62 mmol), $Pd(OAc)_2$ (6 mg, 0 03 mmol), PPh_3 (27 mg, 0 1 mmol) and $HCOOHNEt_3$ (3.4 g, 23 mmol) in acetonitrile/water=4/1, v/v (50 mL) was heated at reflux. After completion of the reaction (30 min.) (monitored by TLC (EtOAc/hexanes=4/1, v/v)), the reaction mixture was diluted with EtOAc (50 mL) and subsequently washed with 2 portions water and brine. The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* The residue was subjected to column chromatography (MeOH/$CHCl_3$=3/97, v/v) to yield 870 mg (99%) of **14b** as an oil R_f 0 13 (EtOAc/hexanes=1/4, v/v), CIMS(70eV), m/z (relative intensity) 334 ($[M]^+$, 39), 144

($[C_{10}H_{10}N]^+$,100), ^{1}H NMR (90 MHz) δ 7 67-7 58 (m, 1H, indole C(7)H), 7 35-7 03 (m, 3H, indole C(4)-C(6)H), 6 92 (s, 1H, indole C(2)H), 4 13 3 93 (m, 2H, $O\underline{CH_2}CH_2Si$), 3 84 (t, 2H, J=7 0 Hz, CH_2N), 3 73 (s, 3H, NCH_3), 3 12 (t, 2H, J=7 0 Hz, indole C(3)CH_2), 0 87-0 67 (m, 2H, $OCH_2\underline{CH_2}Si$), 0 00 (s, 9H, $SiC(CH)_3$)

Synthesis of N_b-Teoc- or N_b-Aloc-N_b-alkoxytryptamines **16**.

Compound 16a NaH (80 mg of a 60% oil dispersion, 2 0 mmol) was added to a stirred solution of **14b** (640 mg, 2 0 mmol) in freshly distilled DME (20 mL) The suspension was stirred until a clear solution appeared (10-30 min) (hydrogen gas evolved) This solution was added dropwise (over a period of 4 5 h) to a stirred solution of chloromethyl sulfide **12a** (540 mg, 2 7 mmol) and NaI (408 mg, 2 7 mmol) in freshly distilled DME (50 mL) (after approx 30 sec after the addition of NaI, the formation of iodomethylsulfide was observable by precipitation of the formed NaCl) at 0°C After additional stirring for 1 h , sat NH_4Cl (1 mL) was added and the suspension was concentrated *in vacuo* The residue was dissolved in EtOAc (50 mL) and subsequently washed with water and sat NH_4Cl The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* The residue was subjected to column chromatography (EtOAc/hexanes=1/2, v/v) to give 340 mg (53%) starting material **14b** and 400 mg (41%) **16a** as an oil, R_f 0 41 (EtOAc/hexanes=1/2, v/v), CIMS(70eV), m/z (relative intensity) 482 ($[M]^+$, 7), 130 ($[C_9H_8N]^+$, 66), 73 ($[SiC(CH)_3]^+$, 100), ^{1}H NMR (90 MHz) δ 8 14 (br s, 1H, indole NH), 7 65-7 02 (m, 5H, indole C(7)H_3 and C(4)-C(7)H_3), 4 98 (s, 2H, OCH_2S), 4 24-3 76 (m, 5H, $\underline{CH}CH_2$, $O\underline{CH_2}CH_2Si$ and NCH_2), 3 76 (s, 3H, $COOCH_3$), 3 43 (s, 3H, OCH_3), 3 18-2 94 (m, 4H, indole C(3)CH_2 and $CH\underline{CH_2}$), 0 93-0 73 (m, 2H, $OCH_2\underline{CH_2}Si$), 0 00 (s, 9H, $SiC(CH)_3$)

Compound 16b. The same procedure was followed as described for **16a** using **14b** (930 mg, 2 9 mmol), NaH (116 mg of a 60% oil dispersion, 2 9 mmol), chloromethyl sulfide **12b** (1 3 g, 4 3 mmol) and NaI (650 mg, 4 3 mmol) in freshly distilled DME (100 mL) Purification by column chromatography (chloroform) gave 1 5 g (89%) of **16b** as an oil, R_f 0 42 (MeOH/$CHCl_3$=2/98, v/v), CIMS(70eV), m/z (relative intensity) 468 ($[M+1-C_6H_{11}O_2]^+$,1), 130 ($[C_9H_8N]^+$, 30), 115 ($[C_6H_{11}O_2]^+$, 55), 73 ($[SiC(CH)_3]^+$, 36), 41(100), ^{1}H NMR (90 MHz) δ 8 11 (br s, 1H, indole-NH), 7 67-7 04 (m, 5H, indole C(2)H and C(4)-C(7)H), 4 98 (s, 2H, OCH_2S), 4 51 (t, 1H, J=6 4 Hz,$\underline{CH}CH_2$), 4 12-3 39 (m, 8H, CH_2OCH_2, $O\underline{CH_2}CH_2Si$ and NCH_2), 3 73 (s, 3H, $COOCH_3$), 3 22 (s, 3H, OCH_3), 3 18-2 95 (m, 4H, indole C(3)CH_2 and $CH\underline{CH_2}$), 1 91-1 74 (m, 4H, CH_2CCH_2), 0 91-0 72 (m, 2H, $OCH_2\underline{CH_2}Si$), 0 00 (s, 9H, $SiC(CH)_3$)

Compound 16d. The same procedure was followed as described for **16a** using **14b** (1 3 g, 4 0 mmol), NaH (160 mg of a 60% oil dispersion, 4 0 mmol), chloromethyl sulfide **12d** (1 1 g, 6 0 mmol) and NaI (900 mg, 6 0 mmol) in freshly distilled DME (200 mL) Purification by column chromatography (EtOAc/hexanes=1/2, v/v) gave 1 50g (80%) of **16d** as an oil, R_f 0 59 (EtOAc/hexanes=1/1, v/v), CIMS(70eV), m/z (relative intensity) 480 ($[M+CH_4]^+$, 1), 466 ($[M]^+$, 4), 130 ($[C_9H_8N]^+$, 64), 73 ($[SiC(CH)_3]^+$, 100), ^{1}H NMR (90 MHz) δ 8 16 (br s, 1H, indole NH), 7 68-7 02 (m, 5H, indole C(2)H and C(4)-C(7)H), 4 91 (s, 2H, OCH_2S), 4 14-3 80 (m, 4H, $O\underline{CH_2}CH_2Si$ and NCH_2), 3 68 (s, 3H, $COOCH_3$), 3 18-2 73 (m, 5H, indole C(3)CH_2 and $CHCH_2$), 1,26 (d, 3H, J=6 3 Hz, $CH\underline{CH_3}$), 0 94-0 74 (m, 2H, $OCH_2\underline{CH_2}Si$), 0 00 (s, 9H, $SiC(CH)_3$)

Compound 16h. The same procedure was followed as described for **16a** using **14b** (1 9 g, 6 7 mmol), NaH (175 mg of a 60% oil dispersion, 4 4 mmol), chloromethyl sulfide **12h**[5] (1 9 g, 6 7 mmol) and NaI (990 mg, 6 6 mmol) in freshly distilled DME (250 mL) Purification by column chromatography (EtOAc/hexanes=1/2, v/v) gave 1 53 g (60%) of **16h** as an oil, R_f 0 52 (EtOAc/hexanes=1/1, v/v), CIMS(70eV), m/z (relative intensity) 581 ($[M]^+$, 32), 158 ($[C_{11}H_{12}N]^+$, 79), 144 ($[C_{10}H_{10}N]^+$, 100), 73 ($[SiC(CH)_3]^+$, 75), 57 ($[C(CH)_3]^+$, 82), ^{1}H NMR (90 MHz) δ 7 62-7 53 (m, 1H, indole C(7)H), 7 31-6 98 (m, 3H, indole C(4)- C(6)H), 6 89 (s, 1H, indole C(2)H), 5 60 (br d, 1H, J=9 0 Hz, HNBoc), 4 87 (s, 2H, OCH_2S), 4 66-4 46 (m, 1H, CHCOOMe), 4 26-3 49 (m, 4H, $O\underline{CH_2}CH_2Si$ and NCH_2) 3 69 (s, 6H, $COOCH_3$ and NCH_3), 3 22 2 98 (m, 4H, indole C(3)CH_2 and $CH\underline{CH_2}S$), 1 38 (s, 9H, $C(CH)_3$), 0 91 0 71 (m, 2H, $OCH_2\underline{CH_2}Si$), 0 00 (s, 9H, $SiC(CH)_3$)

Compounds 16i, 18 and 19. Attempted alkylation. The same procedure was followed as described for **16a** using NaH (275 mg of a 60% oil dispersion, 6 9 mmol), **14b** (2 20 g, 6 9 mmol), **12i** (2 47 g, 10 7 mmol) and NaI (1 20 g, 8 0 mmol) After work-up purification by column chromatography (EtOAc/hexanes=1/2, v/v) gave two fractions 690 mg (27 %) **19**, R_f 0 50 (EtOAc/hexanes=1/1, v/v), ^{1}H NMR (90 MHz) δ 5 07 (t, 1H, J=5 9 Hz) $CH_2\underline{CH}$), 4 91-4 58 (m, 2H, SCH_2N), 3 80 (s, 3H, OCH_3), 3 54-3 14 (m, 2H, $\underline{CH_2}CH$) and a second fraction of 3 5 g

weight; NMR and TLC (MeOH/$CHCl_3$=3/97) analyses showed that the second fraction contained 2 products. Another purification by column chromatography (MeOH/$CHCl_3$=3/97, v/v) gave the two pure fractions. 712 mg (28%) of **18**; R_f 0.70 (MeOH/$CHCl_3$=3/97, v/v), ^1H NMR (90 MHz) δ 7.29 (br s, 2H, 2xNH), 4.97-4 76 (m, 2H, 2xCH_2CH), 3 81 (s, 6H, 2xOCH_3), 3 68 (s, 2H, SCH_2S), 3.38-2.97 (AB part of ABX spectrum, 4H, 2xCH_2CH) and 2 1 g (95%) of recovered **14b**

Approach from **16g** In acetonitrile (100 mL) **16g**[5] (4.10 g, 7.20 mmol) was dissolved and cooled to -25°C. To this solution Me_3SiI (1 02 mL, 1.44 g, 7.20 mmol) was added over a 10 min. period with a syringe. Monitoring of the reaction by TLC (MeOH/$CHCl_3$=7/93, v/v) showed that after 30 min still some starting material was present Therefore another portion Me_3SiI (140 µL, 200 mg, 1 0 mmol) was added. After stirring for another 15 min water (1 mL) was added and the reaction mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc and washed with brine and dried ($MgSO_4$). After evaporation of the solvent *in vacuo* the residue was subjected to column chromatography to give 250 mg (6%) starting compound **16g**, 100 mg (4%) totally deprotected compound **17e** and 1 98 g (59%) **16e**; R_f 0.42 (MeOH/$CHCl_3$=7/93, v/v); α_D^{22}=-9.3 (c=3.0, MeOH); CIMS(70eV), m/z (relative intensity) 468 ($[M+1]^+$, 3), 148 (90), 144 ($[C_{10}H_{10}N]^+$, 43), 143 (100), 130 ($[C_9H_8N]^+$, 89), 73 ($[C_3H_9Si]^+$, 95), ^1H NMR (90 MHz) δ 8.33 (br s, 1H, indole NH), 7 67-7.57 (m, 1H, C(7)H_3), 7.40-7.01 (m, 4H, C(2)H-C(4)-C(6)H_3), 4 93 (s, 2H, OCH_2S), 4 12-3 67 (m, 5H, C(3)CH_2CH_2N, CH_2CH and OCH_2CH_2Si), 3 73 (s, 3H, OCH_3), 3 26-2.80 (m, 4H, C(3)CH_2CH_2N and CH_2CH), 1.80 (br s, 2H, NH_2), 0.90-0 72 (m, 2H, OCH_2CH_2Si), 0.00 (s, 9H, $Si(CH_3)_3$).

To a cooled (0°C) and stirred solution of **16e** (1.8 g, 3.8 mmol) and diethylisopropylamine (500 mg, 3.8 mmol) in THF (100 mL) was added TFA_2O (0.53 mL, 800 mg, 3.8 mmol) with a syringe. After 30 min , the reaction mixture was poured into sat. $NaHCO_3$/brine (1/1, v/v) After another extraction with this aqueous mixture the organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to give 2.08 g (97%) of **16e** as a colorless oil which was homogeneous according to TLC and NMR, R_f 0 46 (EtOAc/hexanes=1/1, v/v); CIMS(70eV), m/z (relative intensity) 562.9 ($[M]^+$, 1 2), 165 9 (100), 144 ($[C_{10}H_{10}N]^+$, 52), 130 ($[C_9H_8N]^+$, 72), 73 ($[C_3H_9Si]^+$, 77), ^1H NMR (90 MHz) δ 8 54 (br d, 1H, J=7.0 Hz, NH), 8.18 (br s, 1H, indole NH), 7 63-7.54 (m, 1H, C(7)H_3), 7.40-7.00 (m, 4H, C(2)H-C(4)-C(6)H_3), 5.02-4.70 (m, 1H, CH_2CH), 4.71 (s, 2H, OCH_2S), 4.23-3.61 (m, 4H, C(3)CH_2CH_2N and OCH_2CH_2Si), 3 77 (s, 3H, OCH_3), 3 51-3.00 (m, 4H, C(3)CH_2CH_2N and CH_2CH), 0 88-0.69 (m, 2H, OCH_2CH_2Si), 0 00 (s, 9H, $Si(CH_3)_3$).

Compound 16k. The same procedure was followed as for **16a** using **14b** (850 mg, 2 7 mmol), NaH (106 mg of a 60% oil dispersion, 2.7 mmol), chloromethyl sulfide **12k** (1.3 g, 4 0 mmol), NaI (595 mg, 3.9 mmol) and freshly distilled DME (100 mL). After work-up 2 02 g of an oil was afforded which was not purified further; R_f 0 29 (EtOAc/hexanes=1/2, v/v), 0.49 (EtOAc/hexanes=1/1, v/v); ^1H NMR (90 MHz) δ 8 14 (br s, 1H, indole NH), 7.66-7 56 (m, 1H, C(7)H), 7 38-7 02 (m, 4H, C(2)H and C(4)-C(6)H_3), 5.04 (br d, 1H, J=8.4 Hz, BocNH), 4.92 (s, 2H, OCH_2S), 4 54 (d, 1H, J=3 5 Hz, $CH(OEt)_2$), 4 12-3 36 (m, 9H, C(3)CH_2CH_2N, CH_2CH, OCH_2CH_2Si and 2xOCH_2CH_3), 3 18-2 71 (m, 4H, C(3)CH_2CH_2N and CH_2CH), 1 42 (s, 9H, $C(CH_3)_3$), 1.17 (t, 6H, J=7 0 Hz, 2xOCH_2CH_3), 0 95-0 66 (m, 2H, OCH_2CH_2Si), 0.00 (s, 9H, $Si(CH_3)_3$).

Compound 16l The same procedure was followed as for **16a** using **14b** (1.50 g, 4.7 mmol), NaH (190 mg of a 60% oil dispersion, 4 7 mmol), chloromethyl sulfide **12l** (2 15 g, 6.9 mmol), NaI (1 0 g, 6.7 mmol) and freshly distilled DME (100 mL). After work-up 3.02 g of an oil was obtained which was not purified further, R_f 0.27 (EtOAc/hexanes=1/2, v/v), CIMS(70eV), m/z (relative intensity) 594.8 ($[M]^+$, 0 03), 230 (21), 130 ($[C_9H_8N]^+$, 52), 103 ($[HC(C_2H_5O)]^+$, 100), 73 ($[Si(CH_3)_3]^+$, 44), ^1H NMR (90 MHz) δ 8.11 (br s, 1H, indole NH), 7 67-7 57 (m, 1H, C(7)H), 7.40-7.04 (m, 4H, C(2)H and C(4)-C(6)H_3), 6.14-5.72 (m, 1H, CH_2=CH-CH_2), 5 38-5.12 (m, 3H, CH_2=CH-CH_2 and NH), 4.93 (s, 2H, OCH_2S), 4.59-4.53 (m, 3H, CH_2=CH-CH_2 and $CH(OEt)_2$), 4 16-3.37 (m, 9H, C(3)CH_2CH_2N, CH_2CH, OCH_2CH_2Si and 2xOCH_2CH_3), 3 17-2 75 (m, 4H, C(3)CH_2CH_2N and CH_2CH), 1.19 (t, 6H, J=7.0 Hz, 2xOCH_2CH_3), 0 87-0 68 (m, 2H, OCH_2CH_2Si), 0.00 (s, 9H, $Si(CH_3)_3$)

Compound 16m. The same procedure was followed as for **16a** using **14b** (550 mg, 1 7 mmol), NaH (70 mg of a 60% oil dispersion, 1 7 mmol), chloromethyl sulfide **12m** (560 mg, 2.5 mmol), NaI (370 mg, 2.5 mmol) and freshly distilled DME (50 mL) After work-up 904 mg (100%) of **16m** was obtained as an oil which was not purified further, R_f 0 40 (EtOAc/hexanes=1/2, v/v); α_D^{22}=+13 8 (c=2 40, MeOH), ^1H NMR (90 MHz) δ 8.14 (br s, 1H, indole

NH), 7.67-7.58 (m, 1H, C(7)H), 7.40-7.00 (m, 4H, C(2)H and C(4)-C(6)H_3), 4.94 (s, 2H, OCH_2S), 4.34 (d, 1H, J=5.4 Hz, CH$(OEt)_2$), 4.13-3.32 (m, 8H, 2x$O\underline{CH_2}CH_3$, C(3)$CH_2\underline{CH_2}$ and $O\underline{CH_2}CH_2Si$), 3.08 (br t, 2H, J=7.5 Hz, C(3)$\underline{CH_2}CH_2$), 2 95 and 2.61 (AB part of ABX spectrum, 2H, J_{AB}=12.8 Hz, J_{AX}=5.1 Hz and J_{BX}=8 2 Hz, $S\underline{CH_2}CH$), 2.20-1 93 (m, 1H, $CH_2\underline{CH}$), 1.18 (t, 6H, J=6.9 Hz, 2x$OCH_2\underline{CH_3}$), 1.04 (d, 3H, J=6.6 Hz, $CH\underline{CH_3}$), 0.89-0.68 (m, 2H, $OCH_2\underline{CH_2}Si$), 0.00 (s, 9H, $Si(CH_3)_3$).

Compound 16o. Alkylation approach: The same procedure was followed as for the alkylation of **16i** using **14b** (804 mg, 2.5 mmol), NaH (101 mg of a 60% oil dispersion, 2.5 mmol), chloromethyl sulfide **12o** (1.22 g, 3.8 mmol, not pure see **12o**) and NaI (565 mg, 3.8 mmol) in freshly distilled DMF (100 mL). Purification by column chromatography (EtOAc/hexanes=1/1, v/v) gave 240 mg (22%) of **20**, 270 mg (27%) of **21** and 600 mg (75%) of recovered **14b**.

Approach via **16l**. A solution of **16l** (2.13 g, 3,6 mmol), $Pd(OAc)_2$ (9 mg, 0 04 mmol), PPh_3 (38 mg, 0.15 mmol) and $HCOOHNEt_3$ (4.7 g, 11 mmol) in acetonitrile/water=4/1, v/v (50 mL) was refluxed under an argon atmosphere After completion of the reaction (30 min , monitored by TLC (EtOAc/hexanes=1/4, v/v)), the reaction mixture was diluted with EtOAc (50 mL) and subsequently washed with 2 portions water and brine. The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The residue was subjected to column chromatography (MeOH/$CHCl_3$=3/97, v/v) to yield 1.70 g (93%) of **16n** as a colorless oil; R_f 0.39 (MeOH/$CHCl_3$=7/93, v/v); CIMS(70eV), m/z (relative intensity) 512 ($[M+1]^+$, 2), 466 ($[M-C_2H_5O]^+$, 5), 144 ($[C_{10}H_{10}N]^+$, 41), 130 ($[C_9H_8N]^+$, 56), 103 ($[HC(C_2H_5O)]^+$, 58), 73 ($[Si(CH_3)_3]^+$, 52), 41 (100); ^{1}H NMR (90 MHz) δ 8.31 (br s, 1H, indole NH), 7.67-7.51 (m, 1H, C(7)H), 7.39-7.00 (m, 4H, C(2)H and C(4)-C(6)H_3), 4.95 (s, 2H, OCH_2S), 4 36 (d, 1H, J=5.0 Hz, CH$(OEt)_2$), 4.11-3.44 (m, 9H, C(3)$CH_2\underline{CH_2}N$, $CH_2\underline{CH}$, $O\underline{CH_2}CH_2Si$ and 2x$O\underline{CH_2}CH_3$), 3 17-2 40 (m, 4H, C(3)$\underline{CH_2}CH_2N$ and $\underline{CH_2}CH$), 1.88 (br s, 2H, NH_2), 1.21 (dt, 6H, J=1.3 Hz and J=7 0 Hz, 2x$OCH_2\underline{CH_3}$), 0.88-0.68 (m, 2H, $OCH_2\underline{CH_2}Si$), 0 00 (s, 9H, $Si(CH_3)_3$).

To THF (50 mL) **16n** (550 mg, 1.1 mmol) and $EtN(iPr)_2$ (140 mg, 1.1 mmol) were added and the solution was cooled to 0°C. To this stirred solution TFA_2O (0 15 mL, 230 mg, 1.1 mmol) was added with a syringe. After 30 min. the reaction mixture was poured into sat. $NaHCO_3$/brine (1/1, v/v). The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to give 650 mg (100%) of **16o** as a colorless oil which was homogeneous according to TLC and NMR, R_f 0.67 (MeOH/$CHCl_3$=7/93, v/v), CIMS(70eV), m/z (relative intensity) 608 ($[M+1]^+$, 3), 607 ($[M]^+$, 562 ($M-C_2H_5O]^+$, 4), 144 ($[C_{10}H_{10}N]^+$, 52), 130 ($[C_9H_8N]^+$, 88), 103 ($[HC(C_2H_5O)]^+$, 74), 73 ($[Si(CH_3)_3]^+$, 100), ^{1}H NMR (90 MHz) δ 8 11 (br s, 1H, indole NH), 7.89 (br d, 1H, J=8.4 Hz, NH), 7 64-7.00 (m, 5H, C(2)H and C(4)-C(7)H_3), 4 84 (s, 2H, OCH_2S), 4.71 (d, 1H, J=4.2 Hz, CH$(OEt)_2$), 4.42-4 13 (m, 1H, $CH_2\underline{CH}$), 4.11-3.44 (m, 8H, C(3)$CH_2\underline{CH_2}N$, $O\underline{CH_2}CH_2Si$ and 2x$O\underline{CH_2}CH_3$), 3.26-3 01 (m, 4H, C(3)$\underline{CH_2}CH_2N$ and $\underline{CH_2}CH$), 1 18 (t, 6H, J=7.0 Hz, 2x$OCH_2\underline{CH_3}$), 0.88-0.68 (m, 2H, $OCH_2\underline{CH_2}Si$), 0.00 (s, 9H, $Si(CH_3)_3$).

Synthesis of N_b-alkoxytryptamines **17**:

Compound 17a. A solution of **16a** (400 mg, 0.83 mmol), Bu_4NCl (690 mg, 2.5 mmol) and KF $2H_2O$ (312 mg, 3.3 mmol) in dry acetonitrile (25 mL) was stirred at 45°C for 10 h. The solvent was evaporated *in vacuo* and the residue was dissolved in EtOAc and subsequently washed with water and sat NH_4Cl. The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* The residue was subjected to column chromatography (EtOAc/hexanes=1/1, v/v) to yield 178 mg (63%) of **17a** as a colorless oil; R_f 0 25 (EtOAc/hexanes=1/1, v/v); α_D^{22}=+19 1 (c=2.98, MeOH), CIMS(70eV), m/z (relative intensity) 339 ($[M+1]^+$, 8), 308 ($[M-OCH_3]^+$, 3), 144 ($[C_{10}H_{10}N]^+$, 63), 130 ($[C_9H_8N]^+$, 83), 103 ($[C_4H_7O_3]^+$, 100); ^{1}H NMR (90 MHz) δ 8.13 (br s, 1H, indole NH), 7.67-7 03 (m, 5H, indole C(2)H and C(4)-C(7)H_4), 5.91 (very br s, 1H, NH), 4.91 (s, 2H, OCH_2S), 4.00 (t, 1H, J=6 0 Hz, $\underline{CH}CH_2S$), 3.76 (s, 3H, $COOCH_3$), 3.42 (s, 3H, OCH_3), 3 37-2 92 (m, 6H, $CH\underline{CH_2}$, NCH_2 and indole C(3)CH_2)

Compound 17b. The same procedure was followed as described for **17a** using **16b** (520 mg, 0.89 mmol), Bu_4NCl (750 mg, 2.7 mmol) and KF.$2H_2O$ (340 mg, 3 6 mmol) Purification by column chromatography (MeOH/Et_3N/$CHCl_3$=2/0.5/97.5, v/v/v) gave 366 mg (94%) of **17b** as a colorless oil; R_f 0.28 (MeOH/$CHCl_3$=3/97, v/v), HPLC (acetonitrile/water=3/2, v/v, flow=1 mL/min., λ=282 nm, retention time (min)) 6 2, α_D^{22}=+17 5 (c=3 25, MeOH); CIMS(70eV), m/z (relative intensity) 325 ($[M-C_6H_{13}O_2]^+$, 3), 144 ($[C_{10}H_{10}N]^+$, 32), 130 ($[C_9H_8N]^+$, 55),

115($[C_6H_{11}O_2]^+$, 100), ^{1}H NMR (90 MHz) δ 8 16 (br s, 1H, indole NH), 7 65-7 04 (m, 5H, indole C(7)H3 and C(4)-C(7)H3), 4 89 (s, 2H, OCH_2S), 4 49 (t, 1H, J=6 2 Hz, $\underline{CH}CH_2S$), 3 93-2 95 (m, 10H , $CH\underline{CH_2}$, CH_2OCH_2, NCH_2 and indole C(3)CH_2), 3 71 (s, 3H, $COOCH_3$), 3 21 (s, 3H, OCH_3), 1 89-1 73 (m, 4H, CH_2CCH_2)

Compound 17c. To a solution of **16b** (650 mg, 1 12 mmol) in MeOH (30 mL) was added a catalytic amount of $TsOH•H_2O$ (20 mg) After completion of the reaction (50 min) (monitored by TLC (MeOH/$CHCl_3$=2/98, v/v)), sat $NaHCO_3$ (1 mL) was added and the solvent was evaporated *in vacuo* The residue was dissolved in EtOAc (50 mL) and subsequently washed with sat $NaHCO_3$ and brine The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to yield 515 mg (98%) of crude **16c** as a colorless oil, R_f 0 29 (MeOH/$CHCl_3$=2/98, v/v), ^{1}H NMR (90 MHz) δ 8 09 (br s, 1H, indole NH), 7 68-7 06 (m, 5H, indole C(2)H and C(4)-C(7)H), 4 98 (s, 2H, OCH_2S), 4 53 (br s, 1H, OH), 4 18-4 66 (m, 5H, $\underline{CH}CH_2$, $O\underline{CH_2}CH_2Si$ and NCH_2), 3 80 (s, 3H, $COOCH_3$), 3 34-2 86 (m, 4H, indole C(3)CH_2 and $CH\underline{CH}2S$), 0 84-0 65 (m, 2H, $OCH_2\underline{CH_2}Si$), 0 00 (s, 9H, $SiC(CH)_3$), For the removal of the Teoc protective group the same procedure was followed as described for **17a 16c** (540 mg, 1 15 mmol), Bu_4NCl (960 mg, 3 5 mmol) and KF $2H_2O$ (434 mg, 4 6 mmol) in acetonitrile (25 mL) gave, after column chromatography (MeOH/$CHCl_3$=1/99, v/v), 296 mg (79%) of **17c** as a colorless oil which was not purified further, R_f 0 32 (MeOH/$CHCl_3$=3/97, v/v), α_D^{22}=+3 9 (c=3 6, MeOH), CIMS(70eV), m/z (relative intensity) 325 ($[M+1]^+$, 0 2), 294 ($[M\ OCH_3]^+$,11), 144 ($[C_{10}H_{10}N]^+$, 34), 130 ($[C_9H_8N]^+$, 100), ^{1}H NMR (90 MHz) δ 8 15 (br s, 1H, indole NH), 7 66-7 02 (m, 5H, indole C(2)H and C(4)-C(7)H), 5 55 (br s, 2H, NH and OH), 4,90 (AB, 2H, J=11 9 Hz, OCH_2S), 3 76 (s, 3H, $COOCH_3$), 3 42-2 95 (m, 6H, indole C(3)CH_2CH_2 and $CH\underline{CH_2}S$)

Compound 17d. The same procedure was followed as described for **17a** using **16d** (1 5g, 3 2 mmol), Bu_4NCl (2 7 g, 9 7 mmol) and KF $2H_2O$ (1 21 g, 12 9 mmol) in acetonitrile (50 mL) Purification by column chromatography (EtOAc/hexanes=1/2, v/v) afforded 693 mg (67%) of **17d** as a colorless oil, R_f 0 45 (EtOAc/hexanes=1/2, v/v), α_D^{22}=-30 4 (c=2 50, MeOH), CIMS(70eV), m/z (relative intensity) 323 ($[M+1]^+$, 10), 188 ($[C_{11}H_{12}N_2O]^+$, 72), 144 ($[C_{10}H_{10}N]^+$, 81), 130 ($[C_9H_8N]^+$, 100), ^{1}H NMR (90 MHz) δ 8 15 (br s, 1H, indole NH), 7 63 7 03 (m, 5H, indole C(2)H and C(4)-C(7)H), 5 91 (very br s, 1H, NH), 4 86 (s, 2H, OCH_2S), 3 68 (s, 3H, $COOCH_3$), 3 40-2 56 (m, 7H, indole C(3)CH_2CH_2 and $CHCH_2S$), 1 24 (d, 3H, J=6 2 Hz, $CH\underline{CH_3}$)

Compound 17e To **16g**[5] (400 mg, 0 71 mmol) and 2 drops of 1,2-ethanedithiol was added a mixture of TFA/CH_2Cl_2 (1/1, v/v, 25 mL) with stirring After standing for 20 min at room temperature the solvent was removed *in vacuo* The residue was dissolved in EtOAc and washed with sat $NaHCO_3$ and brine After drying ($MgSO_4$) the solvent was evaporated *in vacuo* and the residue was subjected to column chromatography (MeOH/Et_3N/$CHCl_3$= 3/0 1/96 9 v/v) to give 210 mg (92%) of **17e** as a colorless oil, R_f 0 31 (MeOH/$CHCl_3$=7/93, v/v), α_D^{22}=-7 8 (c=2 45, MeOH), ^{1}H NMR (90 MHz) δ 8 17 (br s, 1H, indole NH), 3 67-7 02 (m, 5H, indole C(2)H and C(4)-C(7)H_4), 4 88 (s, 2H, OCH_2S), 4 5-1 5 (very br s, 3H, indole NH and NH_2), 3 78-3 64 (m, 1H, $\underline{CH}CH_2S$), 3 72 (s, 3H, $COOCH_3$), 3 39-2 78 (m, 6H, indole C(3)CH_2CH_2 and $CH\underline{CH_2}S$)

Compound 17f The same procedure was followed as described for **17e** using **16h** (1 5 g, 2 6 mmol), 1 drop of dithioglycol and TFA/CH_2Cl_2 (1/1, v/v, 50 mL) Purification by column chromatography (MeOH/Et_3N/CH_2Cl_2 =4/0 5/95 5 v/v/v) afforded 577 mg (66%) of **17f** as a colorless oil, R_f 0 36 (MeOH/$CHCl_3$=7/93, v/v), ^{1}H NMR (90 MHz) δ 7 64-7 55 (m, 1H, C(7)H), 7 34-7 00 (m, 3H, C(4)-C(6)H_3), 6 89 (s, 1H, C(2)H), 4 87 (s, 2H, OCH_2S), 3 83 3 66 (m, 1H, $CH_2\underline{CH}$), 3 75 (s, 6H, NCH_3 and OCH_3), 3 45 2 77 (m, 9H, C(3)CH_2CH_2N, NH_2 and $\underline{CH_2}CH$)

Compound 17h The same procedure was followed as described for **17a** using **16h** (1 52 g, 2 6 mmol), Bu_4NCl (2 2 g, 7 9 mmol) and KF $2H_2O$ (991 mg, 10 5 mmol) Purification by column chromatography (EtOAc/hexanes=1/1, v/v) gave 1 07 g (93%) of **17h** as a colorless oil, R_f 0 37 (EtOAc/hexanes=1/1, v/v), CIMS(70eV), m/z (relative intensity) 438 ($[M+1]^+$, 70), 437 ($[M]^+$, 18) 327 (86), 203 (71), 158 ($[C_{11}H_{12}N]^+$, 100), 144 ($[C_{10}H_{10}N]^+$, 89), 57 ($[C_4H_9]^+$, 88), ^{1}H NMR (90 MHz) δ 7 63-7 49 (m, 1H, indole C(7)H), 7 34-7 03 (m, 3H, indole C(4)-C(6)H), 6 96 (s, 1H, indole C(2)H), 5 99 (very br d, 2H, J=9 0 Hz, HNBoc and ONH), 4 85 (AB, 2H, OCH_2S), 4 68-4 53 (m, 1H, $\underline{CH}CH_2S$), 3 74 (s, 3H, $COOCH_3$), 3 71 (s, 3H, indole NCH_3), 3 36-2 86 (m, 6H, indole C(3)CH_2CH_2 and $CH\underline{CH_2}S$), 1 42 (s, 9H, $C(CH)_3$)

Compound 17i The same procedure was followed as described for **17a** using **16i** (2 0 g, 3 6 mmol), Bu_4NCl (2 96 g, 10 7 mmol) and KF $2H_2O$ (1 33 g, 14 2 mmol) Purification by column chromatography (EtOAc/hexanes=1/1, v/v) gave 1 31 g (88%) of **17i** as a colorless oil, R_f 0 32 (EtOAc/hexanes=1/1, v/v), HPLC

retention time (acetonitrile/water=7/3, v/v, flow=1 mL/min., λ=282 nm.) 4 4 min , CIMS(70eV), m/z (relative intensity) 420 ([M+1]$^+$, 18), 374 (14), 144 ([$C_{10}H_{10}N$]$^+$, 100), 130 ([C_9H_8N]$^+$, 63); ^{1}H NMR (90 MHz) δ 8 31 (br d, 1H, J=8.0 Hz, TFANH), 8.11 (br s, 1H, indole NH), 7.65-7.52 (m, 1H, C(7)H3), 7 42-7 02 (m, 4H, C(2)H and C(4)-C(6)H3), 6 11 (very br s, 1H, $CH_2\underline{NH}$), 5 09-4 94 (m, 1H, $CH_2\underline{CH}$), 4 92 and 4.79 (AB, 2H, J_{AB}=11.8 Hz, OCH_2S), 3.76 (s, 3H, OCH_3), 3 41-2.87 (m, 6H, C(3)CH_2CH_2N and $\underline{CH_2}CH$).

Compound 17j. **16g**[5] (0.5 g, 0.88 mmol) was dissolved in acetonitrile (10 mL). To the stirred solution di-*tert*-butyldicarbonate (0.23 g, 1.1 mmol) and a catalytical amount DMAP (11 mg, 0.09 mmol) was added. After 2 h the reaction was complete (monitored by TLC (EtOAc/hexanes=1/2, v/v)) and the solvent was evaporated *in vacuo*. The residue was subjected to column chromatography ($CHCl_3$) to give 584 mg (99 %) of the N_a-Boc protected compound **16j** as a colorless oil, Rf 0.47 (EtOAc/hexanes=1/2, v/v); CIMS(70eV), m/z (relative intensity) 668 ([M+1]$^+$, 5), 148 (42), 130 ([C_9H_8N]$^+$, 37), 73 ([C_3H_9Si]$^+$, 100); ^{1}H NMR (90 MHz) δ 8 15-8 05 (m, 1H, C(7)H), 7 58-7 04 (m, 4H, C(2)H and C(4)-C(6)H3), 5.55 (br d, 1H, J=9.6 Hz, NH), 4.89 (S, 2H, OCH_2S), 4.66-4.47 (m, 1H, $\underline{CH}CH_2$), 4 22-4 02 (m, 2H, $O\underline{CH_2}CH_2Si$), 3.91-3.66 (m, 2H, C(3)$CH_2\underline{CH_2}N$), 3.78 (s, 3H, $COOCH_3$), 3.17-2 93 (m, 4H, C(3)$\underline{CH_2}CH_2N$ and $CH\underline{CH_2}$), 1 62 (s, 9H, indole $NCO_2C(CH_3)_3$), 1.40 (s, 9H, $HNCO_2C(CH_3)_3$), 0.98-0 79 (m, 2H, $OCH_2\underline{CH_2}Si$), 0 00 (s, 9H, $Si(CH_3)_3$). For removal of the Teoc group the same procedure was followed as described for **17a** using **16j** (570 mg, 0.85 mmol), Bu_4NCl (713 mg, 2.6 mmol), $KF.2H_2O$ (322 mg, 3 4 mmol) and acetonitrile (25 mL). Purification by column chromatography ($CHCl_3$) afforded 360 mg (81 %) of **17j** as a colorless oil, R_f 0.34 (EtOAc/hexanes=1/2, v/v), CIMS(70eV), m/z (relative intensity) 423 ([M+1-$C_5H_9O_2$]$^+$, 0.3), 322 ([M-2$C_5H_9O_2$]$^+$, 0.4), 130 ([C_9H_8N]$^+$, 34), 57 ([C_5H_9]$^+$, 100), ^{1}H NMR (90 MHz) δ 8.18-8.08 (m, 1H, C(7)H), 7 60-7.16 (m, 4H, C(2)H and C(4)-C(6)H3), 5 91 (br d, 1H, J=9.1 Hz, HNBoc), 5 00-4.74 (AB, 2H, OCH_2S), 4 74-4 55 (m, 1H, $\underline{CH}CH_2$), 3.74 (s, 3H, $COOCH_3$), 3.40-2.89 (m, 6H, C(3)CH_2CH_2N and $CH\underline{CH_2}$), 1.66 (s, 9H, indole $NCO_2C(CH_3)_3$), 1 42 (s, 9H, $HNCO_2C(CH_3)_3$)

Compound 17k. The same procedure was followed as described for **17a** using **16k** (2 02 g), Bu_4NCl (2.0 g, 7.2 mmol) and $KF\ 2H_2O$ (940 mg, 10.0 mmol). Purification by column chromatography (EtOAc/hexanes=2/3, v/v) afforded 1 09 g (88 % from **14b**) of **17k** as a colorless oil. R_f 0 37 (EtOAc/hexanes=1/1, v/v), HPLC (acetonitrile/water=1/9, v/v, flow=1 mL/min., λ=280 nm), retention time (min.). 4.0, α_D^{22}=+29.8 (c=3.15, MeOH), CIMS(70eV), m/z (relative intensity) 469 ([M+2]$^+$, 0.03), 243 (88), 144 ([$C_{10}H_{10}N$]$^+$, 24), 130 ([C_9H_8N]$^+$, 38), 103 ([$HC(C_2H_5O)$]$^+$, 100), 57 ([$C(CH_3)_3$]$^+$, 23); ^{1}H NMR (90 MHz) δ 8.28 (br s, 1H, indole NH), 7.63-7.51 (m, 1H, C(7)H), 7.40-7 00 (m, 4H, C(2)H and C(4)-C(6)H3), 6.06 (br s, 1H, $CH_2\underline{NH}$), 5.06 (br d, 1H, J=9.2 Hz, NH), 4 87 (s, 2H, OCH_2S), 4 54 (d, 1H, J=3.6 Hz, $CH(OEt)_2$), 4 11-2.66 (m, 11H, C(3)CH_2CH_2, CH_2CH and 2x$O\underline{CH_2}CH_3$), 1 44 (s, 9H, $C(CH_3)_3$), 1 18 (t, 6H, J=7.0 Hz, 2x$OCH_2\underline{CH_3}$).

Compound 17l. The same procedure was followed as described for **17a** using **16l** (1.07 g, 2.1 mmol), Bu_4NCl (1 7 g, 6 1 mmol) and $KF.2H_2O$ (790 mg, 8 4 mmol) Purification by column chromatography (MeOH/Et_3N/$CHCl_3$= 3/0.5/96.5, v/v) afforded 596 mg (63%) of **17l** as a colorless oil, R_f 0 49 (MeOH/$CHCl_3$=3/97, v/v), 0 65 (MeOH/$CHCl_3$=7/93, v/v); HPLC (acetonitrile/water=1/9, v/v, flow=1 mL/min , λ=280 nm), retention time (min) 12.1, α_D^{22}=+28.3 (c=2.90, MeOH); CIMS(70eV), m/z (relative intensity) 452 ([M+1]$^+$, 1), 144 ([$C_{10}H_{10}N$]$^+$, 47), 130 ([C_9H_8N]$^+$, 64), 103 ([$HC(C_2H_5O)$]$^+$, 90), 41 ([C_3H_5]$^+$, 100), ^{1}H NMR (90 MHz) δ 8 12 (br s, 1H, indole NH), 7 64-7.54 (m, 1H, C(7)H), 7.42-7 01 (m, 4H, C(2)H and C(4)-C(6)H_3), 6.14-5.72 (m, 1H, CH_2=$\underline{CH}$-CH_2), 6.02 (br s, 1H, $CH_2\underline{NH}$), 5.38-5.12 (m, 3H, $\underline{CH_2}$=CH-CH_2 and NH), 4.87 (s, 2H, OCH_2S), 4.58-4.52 (m. 3H, CH_2=CH-$\underline{CH_2}$ and $CH(OEt)_2$), 3 84-2.67 (m, 11H, C(3)CH_2CH_2N, CH_2CH and 2x$O\underline{CH_2}CH_3$), 1.17 (t, 6H, J=7 0 Hz, 2x$OCH_2\underline{CH_3}$).

Compound 17m. The same procedure was followed as described for **17a** using **16m** (900 mg, 1 8 mmol), Bu_4NCl (1 47 g, 5 3 mmol) and $KF\ 2H_2O$ (663 mg, 7.0 mmol). Work-up afforded 654 mg (100%) **17m** as a colorless oil which was homogeneous by TLC; R_f 0 10 (EtOAc/hexanes=1/4, v/v); HPLC (acetonitrile/water=9/1, v/v, flow=1 mL/min., λ=282 nm), retention time (min.) 4.7; α_D^{22}=+14.4 (c=4 25, MeOH); ^{1}H NMR (90 MHz) δ 8 07 (br s, 1H, indole NH), 7 65-7 55 (m, 1H, C(7)H), 7.42-7 02 (m, 4H, C(2)H and C(4)-C(6)H_3), 6.2-5.5 (very br s, 1H, NH), 4 33 (d, 1H, J=5.6 Hz, $CH(OEt)_2$), 3.78-3.00 (m, 8H, 2x$O\underline{CH_2}CH_3$ and C(3)CH_2CH_2N), 2.89 and 2 53 (AB part of ABX spectrum, 2H, J_{AB}=12 6 Hz, J_{AX}=4 9 Hz and J_{BX}=8 3 Hz, S$\underline{CH_2}$CH), 2.16-1 91 (m, 1H, $CH_2\underline{CH}$), 1.17 (t, 6H, J=7 0 Hz, 2x$OCH_2\underline{CH_3}$), 1 03 (d, 3H, J=6.8 Hz, $CH\underline{CH_3}$).

Compound 17n. The same procedure was followed as described for **17a** using **16n** (460 mg, 0.9 mmol), Bu_4NCl (730 mg, 2.6 mmol) and KF $2H_2O$ (340 mg, 3.6 mmol) gave after work-up 254 mg (77%) **17n** as a colorless oil which was homogeneous according to TLC; R_f 0.14 (MeOH/$CHCl_3$=3/97, v/v), 0.37 (MeOH/$CHCl_3$=7/93, v/v); HPLC (methanol/0.1 m $(NH_4)_2SO_4$ in water=6/4, v/v, flow=1 mL/min., λ=280 nm), retention time (min) 7.9; α_D^{22}=+24.7 (c=3 20, MeOH), CIMS(70eV), m/z (relative intensity) 368 ($[M+1]^+$, 1), 144 ($[C_{10}H_{10}N]^+$, 40), 130 ($[C_9H_8N]^+$, 74), 103 ($[HC(C_2H_5O)]^+$, 100); ^1H NMR (90 MHz) δ 8.26 (br s, 1H, indole NH), 7.64-7.55 (m, 1H, C(7)H), 7 42-7.01 (m, 4H, C(2)H and C(4)-C(6)H_3), 4.86 (s, 2H, OCH_2S), 4.33 (d, 1H, J=5.3 Hz, $CH(OEt)_2$), 3.94-2.47 (m, 14H, C(3)CH_2CH_2NH, NH_2, CH_2CH and 2xOCH_2CH_3), 1.17 (dt, 6H, J=1.5 Hz and J=7 0 Hz, 2xOCH_2CH_3).

Compound 17o. The same procedure was followed as described for **17a** using **16o** (600 mg, 1 0 mmol), Bu_4NCl (823 mg, 3.0 mmol) and KF $2H_2O$ (370 mg, 3.94 mmol). Work-up afforded 390 mg (85%) of **17o** as a colorless oil which was homogeneous by TLC, R_f 0.46 (MeOH/$CHCl_3$=3/97, v/v), 0.63 (MeOH/$CHCl_3$=7/93, v/v); α_D^{22}=+24 1 (c=1 95, MeOH); CIMS(70eV), m/z (relative intensity) 368 (1.4), 144 ($[C_{10}H_{10}N]^+$, 45), 130 ($[C_9H_8N]^+$, 75), 103 ($[HC(C_2H_5O)]^+$, 100); ^1H NMR (90 MHz) δ 8 08 (br s, 1H, indole NH), 7.69-7.51 (m, 1H, C(7)H), 7.42-7.00 (m, 4H, C(2)H and C(4)-C(6)H_3), 6 94 (br d, 1H, J=9 2 Hz, NH), 5.96 (very br s, 1H, CH_2NH), 4.87 (s, 2H, OCH_2S), 4.64 (d, 1H, J=3.5 Hz, $CH(OEt)_2$), 4.47-4 18 (m, 1H, CH_2CH), 3 86-2 86 (m, 10H, C(3)CH_2CH_2N, CH_2CH and 2xOCH_2CH_3), 1.17 (dt, 6H, J=1 9 Hz and J=7.0 Hz, 2xOCH_2CH_3).

Cyclization reactions:

Entry 1 Procedure A: The cyclization reaction was carried out in flame dried glass equipment in an argon atmosphere To a cooled (-75°C) and stirred solution of **17a** (170 mg, 0.50 mmol) in dry dichloromethane (20 mL) was added DIBAL (1.5 mL of a 1M solution in dichloromethane) in a period of 10 min. After completion of the reaction (15-60 min.), (monitored by TLC (EtOAc/hexanes=1/1, v/v)) TFA (0.3 mL, 3.9 mmol) was added in ± 2 min. The reaction mixture was allowed to warm up to room temperature and poured into 1M HCl/brine=1/4 (25 mL, v/v) The organic layer was successively washed with 1M HCl/brine=1/4), water and sat $NaHCO_3$/brine=1/1 and dried (Na_2SO_4). The organic layer was concentrated *in vacuo* and subjected to column chromatography (EtOAc/hexanes=1/2, v/v) to give 119 mg (82%) of **22a**; R_f 0 59 (EtOAc/hexanes=1/1, v/v); α_D^{22}=+52.7 (c=1.88, MeOH), CIMS(70eV) exact mass calcd for $C_{15}H_{18}N_2O_2S$ m/z, 290 1089 ($[M]^+$) Found. 290 1090; m/z (relative intensity) 290 ($[M]^+$, 25), 186 ($[C_{11}H_{10}N_2O]^+$, 100), 144 ($[C_{10}H_{10}N]^+$, 6), 130 ($[C_9H_8N]^+$, 11) Anal. Calcd for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25 N, 9.65. Found: C, 61.84; H, 6.38; N, 9 49. and 13 mg (9%) **1a**, R_f 0 53 (EtOAc/hexanes=1/1, v/v); α_D^{22}=-85.7 (c=2.38, MeOH); CIMS(70eV) exact mass calcd for $C_{15}H_{18}N_2O_2S$ m/z, 290 1089 ($[M]^+$). Found· 290.1090; m/z (relative intensity) 290 ($[M]^+$, 45), 186 ($[C_{11}H_{10}N_2O]^+$, 100), 144 ($[C_{10}H_{10}N]^+$, 11), 130 ($[C_9H_8N]^+$, 18) both as amorphous white solids on which failed to crystallize.

Entry 2. Procedure A was followed using **17b** (160 mg, 0 37 mmol) and DIBAL (1.1 mL of a 1M solution in hexanes or CH_2Cl_2). Work-up gave a mixture of products caused by partly removal of the MTP protective group. Therefore the crude reaction mixture was dissolved in methanol (50 mL) and a catalytic amount of TsOH (15 mg) was added After standing at room temperature for 2 h. the removal of the MTP group was complete, sat $NaHCO_3$ (1 mL) was added and the solvent was evaporated *in vacuo*. The residue was dissolved in EtOAc (50 mL) and washed with saturated $NaHCO_3$ and brine The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The product ratio was determined at this stage by analytical HPLC (acetonitrile/water=55/45, v/v, flow=1 mL/min., λ=282 nm), retention time (min); **1c** (4.9) and **22c** (5.4)· Ratio **1c**/**22c**=11/89. The residue was subjected to column chromatography (EtOAc/hexanes=1/4, v/v) to yield 88 mg (88%) **22c**; R_f 0.18 (MeOH/$CHCl_3$=1/99, v/v), 0.24 (EtOAc/hexanes=1/2, v/v); α_D^{22}=-5.8 (c=4.15, MeOH); CIMS(70eV), exact mass calcd for $C_{14}H_{16}N_2O_2S$ m/z, 276.0933 ($[M]^+$). Found 276.0932; m/z (relative intensity) 276 ($[M]^+$, 13), 186 ($[C_{11}H_{10}N_2O]^+$, 100), Anal. Calcd for $C_{14}H_{16}N_2O_2S$. C, 60.85; H, 5.84; N, 10.14, S, 11.60. Found: C, 60.68, H, 5.88, N, 10.34, S, 11.55, and 10 mg (10%) **1c**; R_f 0.18 (EtOAc/hexanes=1/2, v/v), α_D^{22}=-75.0 (c=0.4, EtOAc, e.e.=45%, see table 3 3 in the exp. part of chapter 3); CIMS(70eV) exact mass calcd for $C_{14}H_{16}N_2O_2S$ m/z, 276 0933 ($[M]^+$) Found 276.0930, m/z (relative intensity), 276 ($[M]^+$,17), 186 ($[C_{11}H_{10}N_2O]^+$, 100), both as amorphous white solids

Entry 3 Cyclization procedure A was followed from **17c** (150 mg, 0 46 mmol) Purification by column chromatography (EtOAc/hexanes=1/4, v/v) gave 21 mg (17%) of **1c** and 62 mg (49%) of **22c** The product ratio was determined by analytical HPLC (see entry 2) Ratio **1c/22c**=38/62 For spectroscopical and analytical data, see entry 2

Entry 4 Cyclization procedure A was followed from **17d** (215 mg, 0 67 mmol) Purification by column chromatography (EtOAc/hexanes=1/4, v/v) gave 125 mg (69%) of **22d** as an amorphous white solid and 13 mg of an unidentified, but by NMR (90 MHz) clearly not cyclized product Both by TLC (EtOAc/hexanes=1/2, v/v) as by analytical HPLC (acetonitrile/water=4/1, v/v, flow=1 mL/min , λ=254 nm), retention time (min), **1l** (6 1)) the other possible formed diastereomer was not detected **22d** crystallized from CH_2Cl_2/hexanes (mp 135-141°C), R_f 0 50 (EtOAc/hexanes=1/2, v/v), α_D^{22}=+94 8 (c=1 55, MeOH), CIMS(70eV), m/z (relative intensity) 274 ($[M]^+$, 38), 186 ($[C_{11}H_{10}N_2O]^+$, 100), 170 ($[C_{11}H_{10}N_2]^+$, 25), 144 ($[C_{10}H_{10}N]^+$, 16), 130 ($[C_9H_8N]^+$, 16), Anal Calcd for $C_{15}H_{18}N_2OS$ C, 65 66, H, 6 61, N, 10 21, S, 11 69 Found C, 65 50, H, 6 75, N, 9 96, S, 11 65

Entry 5 Procedure A was followed starting from **17e** (135 mg, 0 42 mmol) and DIBAL (1 25 mL of a 1M solution in dichloromethane). After warming up to room temperature the reaction mixture was poured into a mixture of water/brine (4/1, v/v, 50 mL) The organic layer was subsequently washed with sat $NaHCO_3$/brine (1/1, v/v, 50 mL) and dried ($MgSO_4$) and the product ratio was determined at this stage by analytical HPl C (methanol/0 1M $(NH_4)_2SO_4$ in water=3/2, v/v, flow=1 mL/min , λ=280 nm), retention time (min) **1e** (5 7), **22e** (7 8)) ratio **1e/22e**=9/91 The residue was subjected to column chromatography (MeOH/CHCl/Et_3N=2 0/97 6/0 4, v/v/v) to yield 74 mg (64%) **22e** and 13 mg (11%) **1e** both as amorphous white solids whose spectroscopical data were identical as published previously [5]

Entry 6 Procedure A was followed together with the work-up procedure as described in entry 5 **17f** (383 mg, 1 14 mmol) and DIBAL (2 2 mL of a 1M solution in hexanes) gave after work up 300 mg of a residue The product ratio was determined at this stage by analytical HPLC (methanol/0 1M $(NH_4)_2SO_4$ in water=6/4, v/v, flow=1 mL/min , λ=280 nm), retention time (min) **1f** (8 4), **22f** (10 3)) ratio **1f/22f**=18/82 The residue was subjected to column chromatography (CH_2Cl_2/MeOH/ Et_3N=96 5/3/0 5, v/v/v) to give 169 mg (51%) **22f**, R_f 0 14 (EtOAc/hexanes=1/1, v/v), 0 55 (MeOH/$CHCl_3$=7/93, v/v), α_D^{22}=-93 9 (c=1 5, MeOH), CIMS(70eV) exact mass calcd for $C_{15}H_{19}N_3OS$ m/z, 289 1249 ($[M]^+$) Found 289 1248, m/z (relative intensity) 290 ($[M+1]^+$, 3 8), 289 ($[M]^+$, 1 0), 200 ($[C_{12}H_{12}N_2O]^+$, 100), 184 ($[C_{12}H_{12}N_2]^+$, 28), and 49 mg (15%) **1f**, R_f 0 37 (MeOH/$CHCl_3$=7/93, v/v), α_D^{22}=+63 9 (c=1 8, MeOH), CIMS(70eV) exact mass calcd for $C_{15}H_{19}N_3OS$ m/z, 289 1249 ($[M]^+$) Found 289 1250, m/z (relative intensity) 289 ($[M]^+$, 0 4), 200 ($[C_{12}H_{12}N_2O]^+$, 100), 184 ($[C_{12}H_{12}N_2]^+$, 26) both as amorphous white solids

Entry 7 was published previously [5] The revised NMR assignments of **22g** are described in table 2 2 The one dimensional and NOESY spectrum of **22g** is shown in chapter 8

Entry 8 Procedure B To a cooled (-74°C) and stirred solution of **17h** (558 mg, 1 28 mmol) in dry dichloromethane (50 mL) employing dry glass equipment under an argon atmosphere was added DIBAL (3 8 mL of a 1M solution in dichloromethane) in 10 min After completion of the reaction (15-60 min) which was monitored by TLC (EtOAc/hexanes=1/1, v/v), TFA (1 mL, 13 mmol) was added in 2 min After allowing the reaction mixture to warm to -30°C, the reaction mixture was poured into a mixture of 1N HCl/brine=1/4 (50 mL, v/v) and the organic layer was immediately washed with water followed by another washing with a mixture of sat $NaHCO_3$/brine=1/1 and dried (Na_2SO_4) The product ratio was determined at this stage by analytical HPLC (acetonitrile/water=9/1, v/v, flow=1 mL/min , λ=282 nm and λ=250 nm), retention time (min) **24** (5 1), **1h** (5 6), **22h** (6 5), **25** (8 0)) ratio **24 / 25 / 1h / 22h** = 21 / 52 / 9 / 18 The organic layer was subsequently concentrated *in vacuo* and subjected to column chromatography (hexanes/EtN_3/$CHCl_3$=19/1/80) to yield 264 mg (53%) **24**, 75 mg (15%) **25**, 23 mg (5%) **1h** and 31 mg (6%) **22h** (overall 79% cyclisation) all as amorphous white solids

Compound 1h R_f 0 43 ($CHCl_3$) α_D^{22}= 152 5 (c=2 05, MeOH), CIMS(70eV) exact mass calcd for $C_{20}H_{27}N_3O_3S$ m/z, 389 1773 ($[M]^+$) Found 389 1774, m/z (relative intensity) 390 ($[M+1]^+$, 12), 200 ($[C_{12}H_{12}N_2O]^+$, 100), 57 ($[C(CH)_3]^+$, 21), UV (acetonitrile) λ_{max} 277 0(sh), 284 7 (7180), 292 5(sh), ε_{250} = 1940 and ε_{282} = 7030

Compound 22h R_f 0 58 ($CHCl_3$), α_D^{22}=+90 2 (c=2 35, MeOH), CIMS(70eV) exact mass calcd for $C_{20}H_{27}N_3O_3S$ m/z, 389 1773 ($[M]^+$) Found 389 1773, m/z (relative intensity) 389 ($[M]^+$, 14), 200 ($[C_{12}H_{12}N_2O]^+$, 100), 57 ($[C(CH)_3]^+$, 13), UV (acetonitrile) λ_{max} 277 5(sh), 284 5 (7030), 292(sh), ε_{250} = 1860 and ε_{282} = 6900

Compound 24 R_f 0 49 (EtOAc/hexanes=1/2, v/v), α_D^{22}=-55 1 (c=1 85, MeOH), CIMS(70eV) exact mass calcd for $C_{20}H_{27}N_3O_3S$ m/z, 389 1773 ($[M]^+$) Found 389 1770, m/z (relative intensity) 389 ($[M]^+$, 59), 290 (18), 200 ($[C_{12}H_{12}N_2O]^+$, 33), 144 ($[C_{10}H_{10}N]^+$, 18), 57 ($[C(CH)_3]^+$, 18), 51 5(100), ^{1}H NMR (400 MHz) (all assignments are based on COSY) δ 7 18 (dt, 1H, J=7 7 Hz and J=1 3 Hz, C(10)H), 7 12 (dd, 1H, J=7 4 Hz and J=0 9 Hz, C(12)H), 6 76 (dt, 1H, J=7 4 and J=0 9 Hz, C(11)H), 6 47 (d, 1H, J=7 8 Hz, C(9)H), 5 36 (s, 1H, C(13a)H), 5 22 (d, 1H, J=13 8 Hz, C(4)H) 4 91 (dd, 1H, J=13 8 Hz and J=1 0 Hz, C(4)H), 4 63 (ddd, 1H, J=10 3 Hz, J=7 2 Hz and J=2 3 Hz, C(1)H), 3 91 (d, 1H, J=7 2 Hz, C(13b)H), 3 58 (ddd, 1H, J=10 0 Hz, J=8 7 Hz and J=3 0 Hz, C(7)H), 3 28 (br d, 1H, J=10 3 Hz, C(2)H), 3 24 (t, 1H, J=9 8 Hz, C(7)H), 2 91 (s, 3H, CH_3), 2 80 (dd, 1H, J=11 7 Hz and J=10 6 Hz, C(2)H), 2 40 (dt, 1H, J=14 3 Hz and J=9 0 Hz, C(8)H), 2 17 (ddd, 1H, J=13 8 Hz, J=10 3 Hz and J=2 9 Hz, C(8)H), 1 54 (s, 9H $C(CH_3)_3$), ^{13}C NMR (100 MHz) δ 155 43 C(=O)OtBu, 149 67 C(12a), 132 36 C(8b), 128 95 C(11), 122 16 C(10), 118 40 C(9), 106 89 C(12), 93 42 C(13a), 82 61 C(13b), 81 35 CMe_3, 72 36 C(4), 61 46 C(1), 56 75 C(8a), 53 04 C(7), 35 04 C(2), 33 96 NCH_3, 31 10 C(8), 28 38 $C(\underline{C}H_3)_3$, UV (acetonitrile) λ_{max} 251 7 (7870), 300 0 (2570), ε_{282} = 1200

Compound 25 R_f 0 59 (EtOAc/hexanes=1/2, v/v), α_D^{22}=-161 4 (c=2 20, MeOH), CIMS(70eV), m/z (relative intensity) 389 ($[M]^+$, 100), 290(28), 200 ($[C_{12}H_{12}N_2O]^+$, 37), 144 ($[C_{10}H_{10}N]^+$, 37), 57 ($[C(CH)_3]^+$, 27), ^{1}H NMR (400 MHz) (all assignments are based on NOESY) δ 7 26 7 10 (m, 2H, C(10) and C(12)H), 6 73 (dt, 1H, J=7 5 Hz and J=0 9 Hz), C(11)H), 6 40 (d, 1H, J=7 8 Hz, C(13)H), 5 38 (very br s, 1H, C(14a)H), 5 19 (d, 1H, J=11 6 Hz, C(5)Hα), 4 83 (dd, 1H, J=11 9 Hz and J=1 2 Hz, C(5)Hβ), 4 50-3 50 (very br s, 1H, C(2)H, 4 10-4 04 (m 1H, C(3)Hβ), 3 98 (d 1H, J=5 4 Hz, C(1)Hβ), 3 54 (dd, 1H, J=6 7 and J=9 0 Hz, C(8)Hα), 3 29 (dd, 1H, J=10 9 and J=14 1 Hz, C(3)Hα), 3 27-3 20 (m 1H, C(8)Hβ), 2 91 (s, 3H, NCH_3), 2 28 (dd, 1H, J=6 5 Hz and J=13 1 Hz, C(9)Hβ), 1 97 (dt, 1H, J=6 6 Hz and J=13 4 Hz, C(9)Hα), 1 52 (s, 9H, $C(CH)_3$), UV (acetonitrile) λ_{max} 251 6 (10500), 305 1 (3200), ε_{282} = 1280

Procedure A After stirring for an additional 15 min at room temperature the reaction mixture was worked up as described in procedure A **17h** (160 mg, 0 37 mmol) and DIBAL (1 1 mL of a 1M solution hexanes) gave after column chromatography (hexanes/$CHCl_3$=1/4, v/v) 37 mg (25%) **1h** and 81 mg (57%) **22h.** The product ratio was determined by analytical HPLC **1h/17l**=31/69

Entry 9 Procedure A was followed Only the formation of by products was detected which could not be characterized

Entry 10 Procedure A was followed using **17j** (110 mg) and DIBAL (0 6 mL of a 1M solution in hexanes) Purification by column chromatography (EtOAc/hexanes=1/4, v/v) gave 3 unidentified fractions which were clearly not cyclized according to NMR (90 MHz) This experiment was repeated several times at different temperatures (-75°C to -60°C) and using different DIBAL amounts (up to 6 equivalents) without major changes in the product composition

Entry 11 Procedure C **17k** (200 mg, 0 43 mmol) was dissolved in $CHCl_3$ (50 mL) To this vigourously stirred solution TFA/H_2O (1/1, v/v, 2 mL) was added The resulting 2-phase system was stirred at room temperature The progress of the reaction was monitored by TLC (MeOH/$CHCl_3$=7/93, v/v) After 7 days all starting material had been consumed The reaction mixture was neutralized by careful addition of $NaHCO_3$ while stirring Brine was added and the organic layer was dried (Na_2SO_4) The product ratio was determined at this stage by analytical HPLC (acetonitrile/water=85/15, v/v, flow=1 mL/min , λ=280 nm), retention time (min) **1g** (7 8), **22g** (5 3)) **1g / 22g** =

29 / 71. After evaporation of the solvent *in vacuo* the residue was subjected to column chromatography (EtOAc/hexanes=1/2, v/v) to yield 82 mg (51%) of **22g** and 33 mg (20%) of **1g**

Entry 12: Procedure C was followed from **17l** (220 mg, 0.49 mmol) which was consumed after stirring for 9 days The product ratio was determined by analytical HPLC (acetonitrile/water=9/1, v/v, flow=1 mL/min., λ=280 nm), retention time (min.) **1l** (4 5), **22l** (5 9)) ratio **1l / 22l** = 23 / 77. The residue was subjected to column chromatography (EtOAc/hexanes=1/2, v/v) to yield 64 mg (36%) **22l**, R_f 0.56 (EtOAc/hexanes=1/2, v/v); α_D^{22}=+1.6 (c=2.50, MeOH); CIMS(70eV) exact mass calcd for $C_{18}H_{21}N_3O_3S$ m/z, 359.1304 ($[M]^+$). Found 359.1304, m/z (relative intensity) 359 ($[M]^+$, 18), 202 (31), 186 ($[C_{11}H_{10}N_2O]^+$, 100), 144 ($[C_{10}H_{10}N]^+$, 10), 130 ($[C_9H_8N]^+$, 5), 41 ($[C_3H_5]^+$, 26). Anal. Calcd for $C_{18}H_{21}N_3O_3S$: C, 60 14; H, 5 89: N, 11.69 Found: C, 59 78; H, 5.95, N, 11.38. and 23 mg (12%) **1l**.; R_f 0 31 (EtOAc/hexanes=1/2, v/v), α_D^{22}=-58 8 (c=1.65, MeOH), CIMS(70eV) exact mass calcd for $C_{18}H_{21}N_3O_3S$ m/z, 359.1304 ($[M]^+$). Found. 359 1302, m/z (relative intensity) 359 ($[M]^+$, 13), 186 ($[C_{11}H_{10}N_2O]^+$, 100), 144 ($[C_{10}H_{10}N]^+$, 8), 130 ($[C_9H_8N]^+$, 5), 41 ($[C_3H_5]^+$, 32) both as white amorphous solids

Entry 13: Procedure C was followed from **17m** (250 mg, 0.68 mmol) which was consumed after stirring for 1 5 hours By HPLC (acetonitrile/water=7/3, v/v, flow=1 mL/min , λ=280 nm) only 1 product could be detected with a retention time of 8.1 minutes The residue was subjected to column chromatography (EtOAc/hexanes=1/4, v/v) to yield 172 mg (92%) of **22d** as a white crystalline solid In contrast to entries 11,12,14 and 15 no water was necessary to induce the PS condensation. A small scale (± 10 mg **17m**) experiment was carried out according to procedure C *without* the addition of water. After 2.5 hours all starting material had been converted. Both TLC and HPLC showed that a clean reaction had occurred without the formation of side products.

Entry 14: Procedure C was followed from **17n** (75 mg, 0 2 mmol) which was stirred for 9 days. The progress of the reaction was monitored both by TLC (MeOH/$CHCl_3$=7/93, v/v) and HPLC (for conditions see entry 5) After this period only 5% of the starting material had been consumed, as was confirmed by 90 MHz NMR after work-up.

Entry 15: Procedure C was followed from **17o** (100 mg, 0.21 mmol) which was stirred for 4 days The progress of the reaction was monitored both by TLC (EtOAc/hexanes=1/2, v/v) and HPLC (acetonitrile/water=9/1). After work-up and column chromatography (EtOAc/hexanes=15/85, v/v) 22 mg (30%) of **22o**, R_f 0.48 (EtOAc/hexanes=1/2, v/v); HPLC (acetonitrile/water=9/1, v/v, flow=1 mL/min , λ=282 nm), retention time (min) 4 4, α_D^{22}=+29.6 (c=2 70, MeOH), CIMS(70eV) exact mass calcd for $C_{16}H_{16}N_3O_2SF_3$ m/z, 371 0915 ($[M]^+$) Found 371.0916; m/z (relative intensity) 371 ($[M]^+$, 56), 186 ($[C_{11}H_{10}N_2O]^+$, 100), 144 ($[C_{10}H_{10}N]^+$, 32), 130 ($[C_9H_8N]^+$, 34) and 11 mg (15%) **1o**; R_f 0 26 (EtOAc/hexanes=1/2, v/v), HPLC (acetonitrile/water=9/1, v/v, flow=1 mL/min., λ=282 nm), retention time (min.) 3.9; α_D^{22}=-43.2 (c=0.95, MeOH); CIMS(70eV) exact mass calcd for $C_{16}H_{16}N_3O_2SF_3$ m/z, 371 0915 ($[M]^+$). Found: 371.0910 m/z (relative intensity) 371 ($[M]^+$, 37), 186 ($[C_{11}H_{10}N_2O]^+$, 100), 144 ($[C_{10}H_{10}N]^+$, 21), 130 ($[C_9H_8N]^+$, 24) were both obtained as white solids.

Entries 16-20· Procedure C was followed in combination with heating of the reaction mixtures at reflux The entries 16-20 were carried out on resp. 0.43 mmol, 0.40 mmol, 0 21 mmol, 0.38 mmol and 0.33 mmol scales. Workup was carried out identical to the corresponding entries 11-15. For the reaction times, product ratios and yields, see scheme 2 11.

Table 2.1. ^{1}H-NMR data of H(1)-H(13b) cis eudistomins **1** (All spectra were recorded at 400 MHz in $CDCl_3$).

	δ, ppm, multiplicity (J, Hz)														
natural isomers	H1$^{\alpha}$	H2$^{\alpha}$	H2$^{\beta}$	H4$^{\alpha}$	H4$^{\beta}$	H7$^{\alpha}$	H7$^{\beta}$	H8$^{\alpha}$	H8$^{\beta}$	H9	H10	H11	H12	H13bα	N(13)H	Miscel.
1a	**4.25** dd (8 5, 5 8)	**3.22-3.11** m	**2.68** d (14 3)	**5.10** AB (9 8)	**4.92** AB (9 8)	**3.15** ddd (11 6, 10 2, 4 3)	**3.75-3.70** m	**2.78-2.73** m	**3.22-3.11** m	**7.32** d (8 0)	**7.14** dt (8 1, 1 2)	**7.08** dt (7 9, 0 9)	**7.47** d (7 8)	**4.58** br d (4 1)	**8.73** br s	**3.56** s OCH_3
1c[a]	**4.32** br s	**3.32** br d (12 5)	**2.97** dd (14 4, 6 0)	**4.93** AB (8 7)	**4.80** AB (9 1)	**3.15** m (11 8, 10 2, 4 3)	**3.61** m (10 0, 4 3)	**2.82** dd (15 2)	**2.97** m	**7.28** d (8 0)	**7.14** dt (8 2, 1 3)	**7.08** dt (8 0, 1 1)	**7.45** d (7 7)	**4.04** br s	**7.91** br s	**3.39** d (3 5) OH
1f	**3.61** m	**3.35** dd (14 5, 2 2)	**2.83** dt (14 8, 3 0)	**4.92** AB (9 4)	**4.84** AB (9 4)	**3.08** m (11 3, 9 5, 4 0)	**3.54** m (9 3, 4 2, 2 4)	**2.93-2.88** m	**2.93-2.88** m	**7.29** d (8 1)	**7.22** dt (7 8, 1 0)	**7.13** dt (7 8, 1 0)	**7.49** d (7 8)	**4.38** br s	**3.69** s N-CH_3	**1.59** br s, NH_2
1h[b]	**4.66** very br s	**3.28** d (14 5)	**2.95-2.79** m	**4.93** AB(9 2)	**4.82** AB (9 2)	**3.07** ddd (11 6, 9 7, 3 7)	**3.52** ddd (9 2, 3 8, 2 2)	**2.95-2.79** m	**2.95-2.79** m	**7.24** d (8 2)	**7.16** d (7 5)	**7.06** t (7 4)	**7.45** d (7 8)	**4.39** br s	**3.74** s, CH_3	**5.29** br d (10 0) BocN-H
1i[c]	**4.70-4.66** m	**3.32** d(14 5)	**2.87-2.82** m	**4.95** AB (9 1)	**4.82** AB (9 1)	**3.18-3.12** m	**3.60** dd (9 6, 4 4)	**2.87-2.82** m	**2.87-2.82** m	**7.30** d (8 0)	**7.14** dt (7 4, 1 2)	**7.08** dt (7 5, 0 9)	**7.44** d (7 7)	**4.17** br s	**8.42** br s	**5.89** br d (10 2) AlocN H
1o	**4.94** m	**3.39** d (14 7)	**2.98-2.83** m	**4.96** AB(9 1)	**4.85** AB (9 1)	**3.17** ddd (11 8, 10 4 4 4)	**3.48** dd (10 0, 4 1)	**2.98-2.83** m	**2.98-2.83** m	**7.29** d (8 2)	**7.15** dt (7 5, 1 3)	**7.09** dt (7 5, 1 0)	**7.44** d (7 8)	**4.27** br s	**8.07** br s	**7.44** br d TFAN-H (9 4)

a To sharpen up the broadened spectrum recorded at 38°C

b Boc protective group $C(CH)3)3$ singlet at 1.00 ppm

c Aloc protective group protons 5 62 (ddd, 1H, J=22.5 Hz, J=10 5 Hz and J=5.3 Hz, H_2C=C<u>H</u>), 4 95-4 87 (m, 2H, <u>H_2</u>C=CH), 4 35 (br d, 2H, J=5.3 Hz, H_2C=CH-C<u>H_2</u>)

Table 2.2: ^{1}H-NMR data of H(1)-H(13b) trans eudistomins **22** (All spectra were recorded at 400 MHz in $CDCl_3$).

	δ, ppm, multiplicity (J, Hz)															
unnatural isomers	H1$^{\beta}$	H2$^{\alpha}$	H2$^{\beta}$	H4$^{\alpha}$	H4$^{\beta}$	H7$^{\alpha}$	H7$^{\beta}$	H8$^{\alpha}$	H8$^{\beta}$	H9	H10	H11	H12	H13bα	N(13)H	Miscel
22a[a]	**3.65-3.59**	**2.90**	**3.12-3.00**	**4.90**	**5.07**	**3.12-3.00**	**3.65-3.59**	**2.74**	**3.12-3.00**	**7.34**	**7.16**	**7.09**	**7.49**	**4.07**	**8.48**	**3.56**
	m	d (14 2)	m	AB(9 8)	very br s	m	m	br d (13 9)	m	d (8 0)	dt (8 2, 1 2)	dt (7,9, 1 1)	d (7 8)	br d (8 4)	br s	s OCH_3
22c[b]	**4.10**	**2.77**	**2.88**	**4.95**	**4.99**	**3.23**	**3.60**	**2.98**	**3.10**	**7.32**	**7.15**	**7.09**	**7.47**	**4.02**	**8.76**	**2.23**
	m	m	dd (14 2, 2 0)	AB (10 0)	AB (10 0)	m	m	m	m	d (8 0)	dt (8 1, 1 1)	dt (7 9, 1 0)	d (7 7)	d (7 3)	br s	br s OH
22d	**2.55**	**2.72**	**3.37-3.01**	**5.01**	**5.01**	**3.08**	**3.64**	**3.37-3.01**	**3.01**	**7.32**	**7.15**	**7.10**	**7.46**	**3.95**	**7.77**	**1.47**
	m	m	m	br s	br s	m	br s	m	m	d (7 9)	dt (8 2, 1 2)	dt (8 0, 1 0)	d (7 7)	dd(6 0, 2 0)	br s	d (3 5) CH_3
22f	**3.64**	**2.54**	**3.86**	**4.71**	**5.17**	**2.98**	**3.47**	**2.88**	**2.75**	**7.28**	**7.20**	**7.09**	**7.45**	**4.09**	**3.91**	**1.82**
	m (4 9, 3 4, 1 5)	ddd (14 3, 5 2, 1 7)	dd (14 3, 1 4)	dAB (11 2, 1 7)	AB(11 2)	ddd (11 7 9 9, 3 3)	ddd (9 2, 4 3, 2 0)	dddd (14 1, 12 0, 4 3, 2 2)	br d (14 2)	d (8 2)	dt (8 2, 1 0)	dt (7 8, 0 9)	d (7 8)	m (2 3)	s N-CH_3	br s, NH_2
22g[c]	**4.50**	**2.73**	**3.78**	**4.77**	**5.26**	**3.06**	**3.53**	**2.78**	**2.94**	**7.44-**	**7.15**	**7.07**	**7.44-**	**4.12**	**9.98**	**6.24**
	dddd (9 2, 5 4 2 4)	br dd (14 4, 4 2)	br d (14 8)	dAB (11 4 1 6)	AB(11 4)	ddd (11 8, 9 8 4 0)	ddd (9 8, 4 3 1 7)	m	dddd (14 6, 11 9, 4 9, 2 5)	7.42 m	dt (7 6, 1 2)	dt (7 5, 0 9)	7.42 m	s	br s	br d (8 6) BocN-H
22h[d]	**4.66**	**2.79-2.72**	**3.67**	**4.71**	**5.18**	**3.02-2.89**	**3.51-3.48**	**2.79-2.72**	**3.02-2.89**	**7.28**	**7.21**	**7.10**	**7.45**	**4.13**	**3.76**	**5.84** br d
	very br s	m	d (14 2)	dAB (11 1, 1 5)	AB(11 1)	m	m	m	m	d (8 2)	dt (7 0, 1 1)	dt (7 4 0 9)	d (7 8)	d (2 1)	s, CH_3	(10 2) BocN-H
22l[e]	**4.56**	**2.80-2.72**	**3.81**	**4.77**	**5.26**	**3.05**	**3.54**	**2.80-2.72**	**2.94**	**7.40**	**7.15**	**7.08**	**7.44**	**4.15**	**9.78**	**6.49** br d
	m	m	dd(14 4)	dAB (11 4, 1 7)	AB (11 3)	ddd (11 8 9 8, 3 9)	ddd (9 8, 4 9, 1 8)	m	dddd (14 4 11 9, 4 9 2 5)	d (8 1)	dt (7 6, 1 2)	dt (7 5, 1 0)	d (7 8)	br s	br s	(8 7) AlocN-H
22o	**4.82**	**2.74**	**3.93**	**4.79**	**5.30**	**3.07**	**3.55**	**2.82-2.78**	**2.96**	**7.38**	**7.18**	**7.10**	**7.44**	**4.12**	**9.42**	**8.25**
	m	ddd (14 7, 5 9 1 8)	d (14 7)	dAB (11 3, 1 9)	AB(11 3)	ddd (11 8 9 9 3 8)	ddd (9 8, 4 8, 1 6)	m	dddd (14 6 11 8, 4 8, 2 4)	d (8 1)	dt (7 6 1 1)	dt (7 5 0 8)	d (7 8)	br s	br s	br d TFAN H (7 7)

[a] To sharpen up the broadened spectrum recorded at 43°C [b] To sharpen up the broadened spectrum recorded at 57°C [c] Boc protective group $C(CH)3)3$ singlet at 1 52 ppm. [d] Boc protective group $C(CH)3)3$ singlet at 1 49 ppm [e] Aloc protective group protons 5 99 (ddd, 1H, J=22 6 Hz, J=10 8 Hz and J=5 4 Hz, H_2C=C<u>H</u>), 5 39 (dd, 1H, J=17 2 and J=1 3 Hz, H<u>H</u>C=CH), 5 29 (m, 1H, <u>H</u>HC=CH), 4 69 (ddd, 2H, J=19 6 Hz, J=13 3 Hz and J=5 7 Hz, H_2C=CH-C<u>H_2</u>)

References and Notes

1 a) Han, S Y , Lakshmikantham, M V , Cava, M P *Heterocycles*, **1985**, 23, 1671-1673 b) Nakagawa, M , Liu, J J , Ogata, K , Hino, T *Tetrahedron Lett* **1986**, 27, 6087 c) Plate, R , Hout, v R H M , Behm, H , Ottenheijm, H C J *J Org Chem* **1987**, 52, 555 d) Nakagawa, M , Liu, J J , Ogata, K , Hino, T *J Chem Soc , Chem Commun* **1988**, 463

2 a) Nakagawa, M , Liu, J J Hino, T *J Am Chem Soc* **1989**, 111, 2721 b) Liu, J J , Nakagawa, M , Harada, N , Tsuruoka, A , Hasegawa, A , Ma, J , Hino, T *Heterocycles* **1990**, 31, 229 c) Still, I W J , Strautmanis, J R *Tetrahedron Lett* **1989**, 30, 1041

3 Yoon, B H , Lyu, H S , Hahn, J H , Ahn, C M *Bull Korean Chem Soc* , **1992**, 13, 290

4 Kirkup, M P , Shankar, B B , McCombie, S , Ganguly, A K *Tetrahedron Lett*, **1989**, 30, 6809

5 Hermkens, P H H , Maarseveen, J H van, Ottenheijm, H C J , Kruse, C G , Scheeren, J W *J Org Chem* **1990**, 55, 3998

6 Maarseveen, J H van, Hermkens, P H H , De Clercq, E , Balzarini, J , Scheeren, J W , Kruse, C G , *J Med Chem* **1992**, 35, 3223

7 a) Ungemach, F , Cook, J M *Heterocycles* **1978**, 9, 1089 b) Bailey, P D *Tetrahedron Lett* **1987**, 28, 5181

8 Liu, J J Nakagawa M , Ogata, K , Hino, T *Chem Pharm Bull* **1991**, 39, 1672

9 Hermkens, P H H , Maarseveen, J H van, Bosman, W P , Smits, J M M , Beurskens, P T *J Crystallogr Spectrosc Res* **1990**, 20, 313

10 Hermkens, P H H , Maarseveen, J H van, Kruse, C G , Scheeren, J W *Tetrahedron Lett* **1989**, 30, 5009

11 Bonner, W A *J Am Chem Soc* **1951**, 73, 3126

12 The poor yield was due to the bad quality of the DIBAL solution and no further optimization has been attempted

13 Hermkens, P H H , Maarseveen, J H van, Berens, H W , Smits, J M M , Kruse, C G , Scheeren, J W *J Org Chem* **1990**, 55, 2200

14 Yamada, T , Goto, K Mitsuda, Y , Tsuji, J *Tetrahedron Lett* , **1987**, 28, 4557

15 The low yield of **15a** was due to moisture in the sodium iodide used for the *in situ* generation of the more reactive iodomethylsulfides and was not further optimized

16 The extinction coefficients of **1h/22h** were determined for the wavelengths used in the HPLC analysis and are identical It was assumed that this observation can be extrapolated to the other eudistomin derivatives Also the extinction coefficients were determined for the pentacyclic spiro derivatives **24** and **25**

17 Verloop, A , Hoogenstraaten, W , Tipker, J in *"Drug Design"* (Ariens, E J , ed), Vol VII, pp 165 207 Academic Press, New York, 1976

18 Hermkens, P H H , Maarseveen, J H van, Cobben, P L H M , Ottenheijm, H C J , Kruse, C G , Scheeren, J W *Tetrahedron* **1990**, 46, 833

19 Jurczak, J, Golebiowski, A *Chem Rev* **1989**, 89, 149

20 Kuijpers, P H , Gerding, T K , De Jong, G J *J Chromatogr* **1992** 625, 223

21 As we published earlier[5] treatment of the dimethyl acetal of **15b** with trifluoroacetic acid in dry dichloromethane only gave uncyclized by-products This was mainly caused by intramolecular trapping of the intermediate alkoxy-carbonium ion by the Boc carbonyl We reasoned that the addition of water to the reaction mixture should quench the rather stable intermediate methoxy-carbonium ion to give the very reactive aldehyde In addition we synthesized diethyl acetals which can be transformed more facile into aldehydes than dimethyl acetals

22 Eliel, E L in *Asymmetric Synthesis*, Vol 2 Ed by Morrison, J D , Academic Press, Inc New York, **1983**, Chapter 5 For a specific example in the PS condensation see a) eudistomin synthesis Still, I W J , Strautmanis, J R *Can J Chem* , **1990**, 68, 1408 b) isoquinoline skeleton synthesis Czarnocki, Z , Maclean, D B , Szarek, W , *Can J Chem* **1986**, 64, 2205

23 An analogous trans tetracyclic spiro compound was isolated by Nakagawa et al [2a,b,8] and Ottenheijm et al [1c] in their intermolecular approach towards the eudistomin series Nakagawa isolated the spiro compounds at room temperature At lower temperatures only β-carbolines were formed From these results the assumption was made that at low temperatures (kinetic control) direct electrophilic attack at the indole 2-position leads to β-carboline formation Nakagawa also found that when N_a-methyl-N_b-hydroxytryptamines were used only the spiro compounds were formed independent of the reaction temperature

24 In cases where epimerization at C(1) in β-carbolines was observed, scission occurred of the bond between the β carboline-C(1) and the indole-C(2) atoms, see Zhang, L H , Cook, J M *Heterocycles*, **1988**, 27, 1357

25 Arx, E v , Faupel, M , Brugger, M J *J Chromatogr* **1976**, 120, 224

26 The reason for the moderate yield was the bad quality of the used DMF The DMF should be purified as described in Perrin, D D and Armarego, W L F , *Purification of Laboratory Chemicals*, 3rd ed , Pergamon Press, p 157

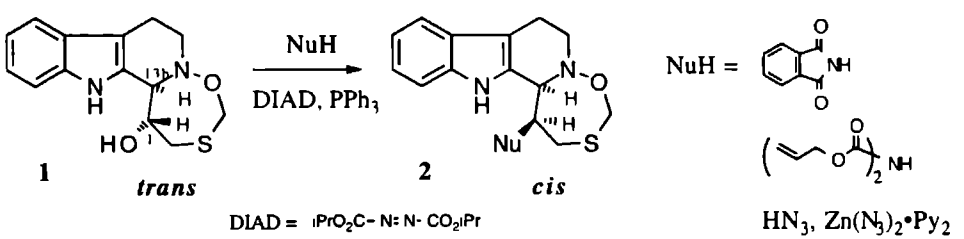
3 A Study toward the Diastereoselective Synthesis of Cis Tetracyclic Eudistomins via a 1-Hydroxy Trans Derivative

3.1 Introduction

In the preceding chapter it was concluded that the intramolecular Pictet-Spengler (PS) condensation approach predominantly leads to the undesired trans eudistomin diastereomer [1] The best cis/trans ratio obtained was 30/70 for N(1)-Boc protected debromo eudistomin K (see scheme 2 10 in chapter 2) As the yield of the intramolecular PS condensation in the eudistomin series is 70% in average, only 20% of the desired cis N(1)-Boc protected eudistomin is obtained Consequently, the efficiency of the intramolecular PS condensation is canceled out by a poor diastereoselectivity

It should be possible however to take advantage of the fact that selectivity toward only the trans diastereomer can be achieved As depicted in scheme 3 1 diastereoselective synthesis of a *trans* C(1)-hydroxy eudistomin derivative **1**, followed by the introduction of the amino functionality by an S_n2 type reaction, such as the Mitsunobu reaction, should give eudistomins **2** with the natural C(1)H-C(13b)H cis configuration In this chapter this approach will be worked out

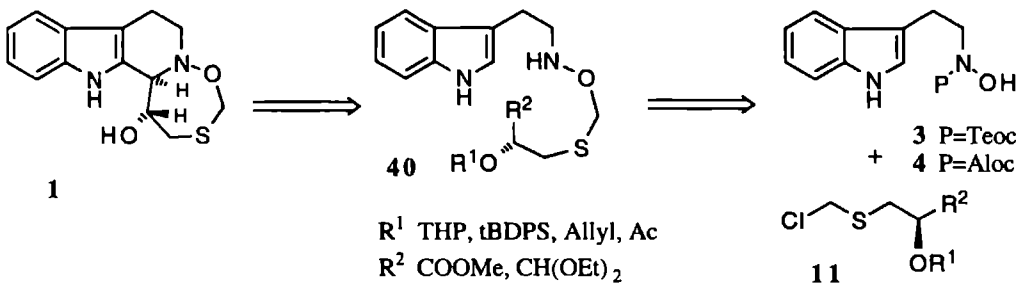
scheme 3.1



Mainly because its exclusive S_n2 type substitution the Mitsunobu reaction was chosen for the introduction of the amino group [2] Also activation of the hydroxyl group takes place *in situ* in the Mitsunobu approach, avoiding an extra step Appropriate nitrogen nucleophiles, which can be conveniently transformed into a primary amine group are phthalimide[3], diallyloxy imidodicarbonate[4] and hydrazoic acid[5] or zinc azide bipyridate [6]

In scheme 3 2 the retrosynthesis of the required trans C(1)-hydroxy eudistomin is presented The build up of the N_b-functionalized tryptamines **40** was accomplished by nucleophilic coupling of the N_b-protected N-hydroxytryptamines **3** or **4** with the chloromethyl sulfides **11**

scheme 3.2



As is depicted in scheme 3 2, approaches from both α-alkoxy-β-chloromethylthio esters and acetals **11** were studied As described in chapter 2, free aldehydes, which are essential in the intramolecular PS condensation, can be generated *in situ* by DIBAL reduction of methyl esters at low temperature or by hydrolysis of acetals Gram scale quantities of eudistomins are needed for extensive biological studies Therefore, it is necessary that the corresponding methyl ester and acetal precursors can conveniently be synthesized in optically pure form in multigram quantities In this chapter several asymmetric approaches will be discussed toward both the methyl ester and the acetal type 2-alkoxy-3-(chloromethylthio)-propionaldehyde precursors **11** illustrated in scheme 3 2

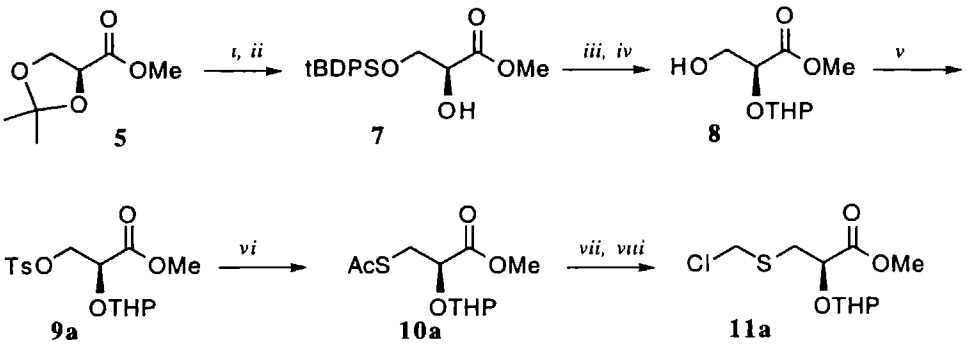
Several protective groups R^1 were introduced in order to achieve a high trans selectivity during the PS condensation

3.2 Synthesis of the 2-Alkoxy-3-(chloromethylthio)-Propionaldehyde Precursors

3.2.1 Synthesis of a Chloromethyl Sulfide Derived from Methyl L-Glycerate

For the synthesis of chloromethyl sulfide **11a** (scheme 3 3) commercially available methyl α,β-isopropylidene-*L*-glycerate **5** was chosen as the starting compound After removal of the acetonide by treatment with aqueous acetic acid it was necessary to protect the primary alcohol (as a tBDMS ether) since direct tosylation of the primary alcohol led to extensive elimination Introduction of the THP protective group on the remaining secondary alcohol followed by removal of the tBDMS group gave **8** in 69% yield The primary alcohol was converted into the chloromethyl sulfide **11a** in a standard manner via the tosylate **9a** and thioacetate **10a** in an overall yield of 53%

scheme 3.3



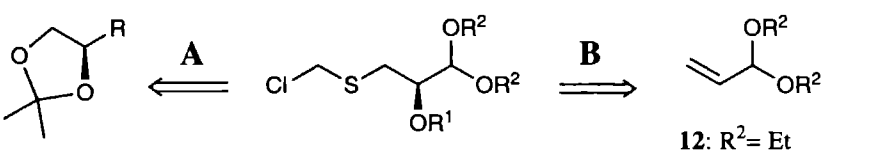
i) 80% HOAc, 5 days; ii) tBDPS-Cl, imidazole, DMF; iii) DHP, PTS, CH_2Cl_2; iv) Bu_4NF, THF; v) TsCl pyridine; vi) CsSAc, DMF; vii) NaOMe, MeOH, viii) $BrCH_2Cl$, KOH(s), Et_3BnNCl

3.2.2 Synthesis of Chloromethyl Sulfides Derived from (*L*)-Glyceraldehyde Acetal

As will be discussed in section 3.4, the approach from methyl esters suffered from base induced racemization. In chapter 2 it was already mentioned that acetals also give smooth PS cyclization after *in situ* formation of the more reactive aldehyde by acid catalyzed hydrolysis of the acetals. Therefore our attention was focussed on the synthesis of (*L*)-glyceraldehyde acetal derived chloromethyl sulfides, lacking the acidic α-proton. For the synthesis of these (*L*)-glyceraldehyde derivatives two fundamentally different pathways were investigated (scheme 3.4):

- Route A: Chiral pool approach from commercially available enantiopure acetonides **5** and **6**.
- Route B: Introduction of chirality by asymmetric dihydroxylation of acrolein acetals **12-15**.

scheme 3.4



5: R = COOMe
6: R = CH_2OH

11

12: R^2= Et
13: R^2= iPr
14: R^2= Bn
15: R^2,R^2=

- **Chiral Pool Approach (route A)**

As is shown in scheme 3.4 both commercially available enantiopure methyl α,β-isopropylidene-(*L*)-glycerate **5** and (*R*)-2,2-dimethyl-1,3-dioxolane-4-methanol **6** were studied as possible glyceraldehyde precursors. Because the chloromethyl sulfide moiety is introduced by our own

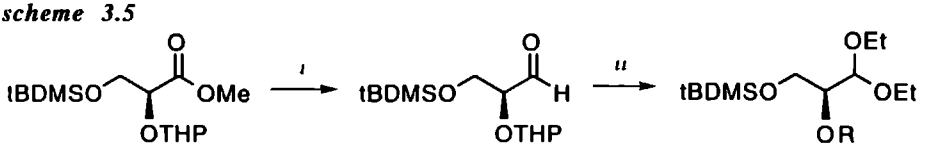
standard manner from the primary hydroxyl group, (*L*)-glyceraldehyde itself seems to be the most straightforward starting compound Although enantiopure α,β-isopropylidene-*L*-glyceraldehyde (*i e* **5** or **6** with R=CHO, scheme 3 4) can be obtained conveniently in multigram quantities by degradation of ascorbic acid[7], it cannot be used as a starting compound because the essential acetonide protective group is not compatible with the acetal protected aldehyde

Synthesis from methyl α,β-isopropylidene-*L*-glycerate **5**.

The objective was synthesis of the chloromethyl sulfide **11e** (see scheme 3.11) with the hydroxy group, positioned α toward the diethyl acetal, protected as a THP ether Unfortunately direct DIBAL reduction of the previously described primary tosylate **9a** (see scheme 3.3) gave a mixture of compounds Most probably elimination of the tosyl group caused the side reactions Therefore the primary alcohol was first protected as a tBDMS ether followed by the introduction of the THP protective group to give **17** in overall 65% yield from **5**

DIBAL reduction of tBDMS protected **17** gave the aldehyde **18** in 76% yield Subsequent treatment of the aldehyde with triethyl orthoformate and TsOH in ethanol led to considerable removal of the THP protective group to give the free secondary alcohol **20** as the main product in 50% yield By substituting TsOH by the milder citric acid in the acetalization no conversion of the aldehyde could be observed

scheme 3.5

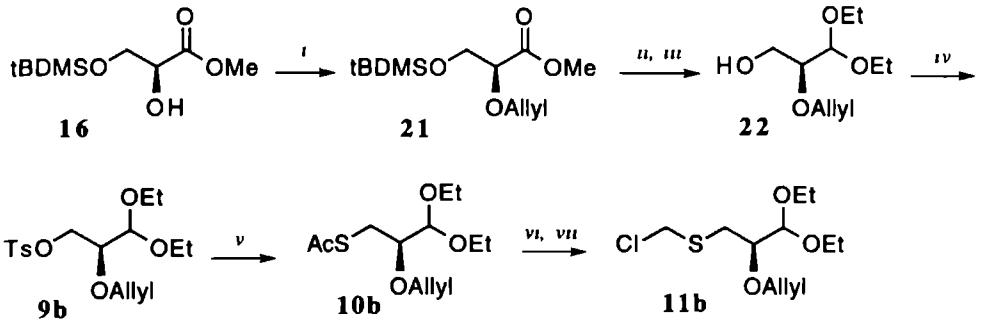


17 **18** **19** R = THP, 15%
20: R = OH, 50%

i) DIBAl, CH_2Cl_2 75°C, ii) $HC(OEt)_3$, TsOH, EtOH

To circumvent this deprotection, the acid labile THP group was replaced by the allyl protective group Allylation of **16** (scheme 3 6) had to be carried out under neutral conditions in order to avoid base induced racemization This was accomplished in quantitative yield with allylethyl carbonate in the presence of a catalytic amount of Pd(0) [8] It should be noted however that this method proved not to be reproducible Although the reaction was always carried out in dried glass equipment under an argon atmosphere with freshly distilled THF (over NaH) it failed several times It did not become clear which impurity caused inhibition of the Pd(0) catalyzed allylation [9] After reduction of the methyl ester **21** with DIBAL, the crude aldehyde was treated with triethyl orthoformate and TsOH in ethanol to yield the free primary alcohol **22** in 79% This alcohol was converted to the chloromethyl sulfide **11b** in a standard fashion in overall 48% yield Because the Pd(0) catalyzed allylation could not be reproduced this promising approach had to be abandoned Nevertheless, the chloromethyl sulfide **11b** was converted to the final tetracyclic eudistomin skeleton.

scheme 3.6

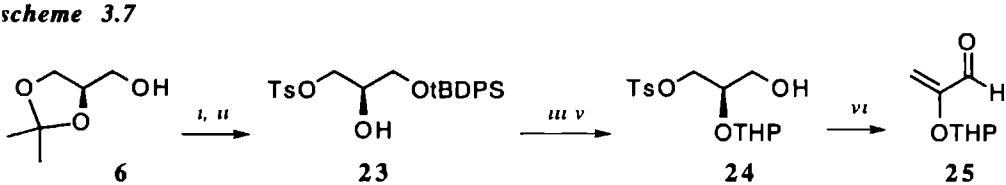


i) $Pd(0)_2dba_3$, allylethyl carbonate, THF, reflux ii) DIBAL, CH_2Cl_2, -75°C, iii) $HC(OEt)_3$, TsOH, EtOH, iv) TsCl, pyridine, v) CsSAc, DMF, vi) NaOMe, MeOH, vii) $BnCH_2Cl$, KOH(s), Et_3BnNCl

Synthesis from (R)-2,2-dimethyl-1,3-dioxolane-4-methanol **6:**

The objective was the synthesis of the chloromethyl sulfide **11e** (scheme 3 11) First, **6** was converted into (R)-1-tosyloxy-3-(*tert*-butyldiphenylsilyloxy)-2-propanol **23** as described in the literature [10] Protection of the remaining secondary alcohol as a THP ether and removal of the tBDPS group gave **24** in 76% yield It turned out that tosylate **24** decomposes over night at room temperature but storage is possible in the refrigerator Selective oxidation of the primary alcohol to the corresponding aldehyde could not be accomplished Both Swern[11] and PCC[12] oxidation gave a complex mixture of products The only product that could be isolated in both approaches was the α,β-unsaturated aldehyde **25**, formed by elimination of the tosyloxy group

scheme 3.7



i) tBDPS-Cl, imidazole, DMF, ii) 90% HOAc, ΔT, iii) TsCl, pyridine, iv) DHP, TsOH, CH_2Cl_2, v) Bu_4NF, THF, $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N or PCC, CH_2Cl_2

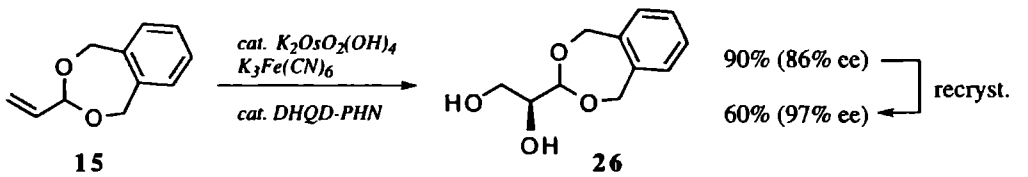
This undesired elimination can be avoided by substitution of the tosyl group in **24** by a protective group, compatible with the tBDPS and THP group (*i e* an allyl group) However, this route was abandoned because the extra reaction steps necessary would give an unacceptable long synthesis path toward the final chloromethyl sulfide

- **Asymmetric Dihydroxylation of Acrolein Acetals (route B)**

Asymmetric dihydroxylation (AD) of acrolein acetals directly yields a stable masked glyceraldehyde derivative. Synthesis of a glyceraldehyde acetal with high optical purity by means of catalytic AD of 3-vinyl-1,5-dihydro-3*H*-2,4-benzodioxepine **15** was recently published by Sharpless

and coworkers.[13] The osmium tetroxide catalyzed dihydroxylation is accelerated and asymmetrically steered by the ligand hydroquinidine-O-(9'-phenanthryl) ether (DHQD-PHN).[14]

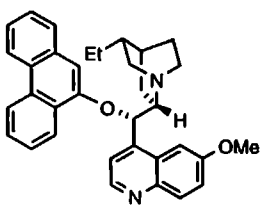
scheme 3.8



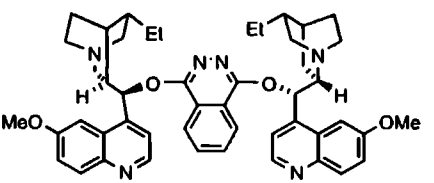
15 **26**

High enantioselectivity could only be achieved with the benzodioxepine protected aldehyde. AD of open acetals just like other cyclic acetals gave lower ee's. Recently, Sharpless and coworkers published a highly improved AD procedure using the newly designed ligand hydroquinidine 1,4-phtalazinediyl ether ($(DHQD)_2PHAL$).[15] In chart 3.1 both the old and new ligands are shown.

chart 3.1



hydroquinidine-0-O-(9'-phenanthryl) ether (DHQD-PHN)

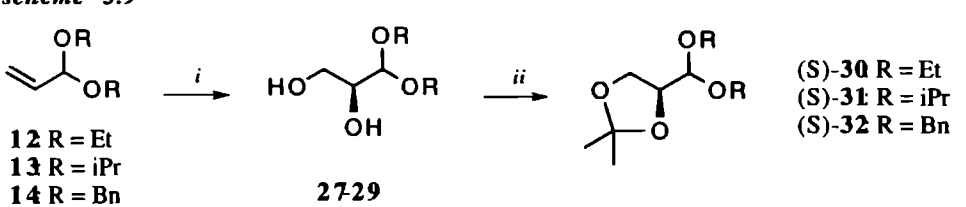


hydroquinidine 1,4-phtalazinediyl ether $(DHQD)_2PHAL$ ligand used in AD-mix β

Because the newly designed ligand outperformed its predecessors in every way, AD's of diethyl, diisopropyl and dibenzyl acrolein acetals **12-14** were investigated. The benzodioxepine protected aldehyde cannot be hydrolyzed mildly, eliminating the possibility of *in situ* formation of the free aldehyde as is necessary for the PS condensation.

Synthesis of both diisopropyl and dibenzyl acrolein acetals **13** and **14** were performed in a standard manner from the corresponding orthoesters and acrolein. AD of **12-14** using the improved ligand gave the diols **27-29** in yields of 92%, 84% and 99%, respectively (scheme 3.9).

scheme 3.9



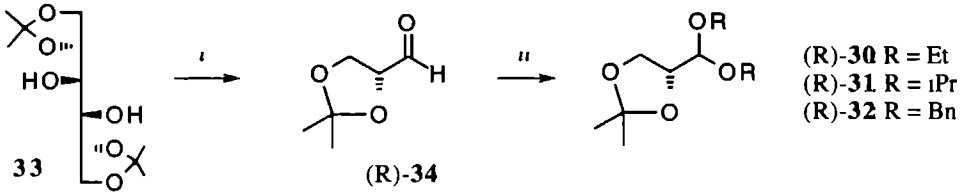
12 R = Et
13 R = iPr
14 R = Bn

27-29

i) AD-mix β ($K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, DHQD-PHAL, K_2CO_3), tBuOH/H_2O, 4°C; ii) 1,2-DMP, PPTS, CH_2Cl_2

To define the e e of the AD the resulting diols were protected as their acetonides (S)-**30-32** Acetalization of the readily available α,β-isopropylidene-*D*-glyceraldehyde from *D*-mannitol[7] gave the optically pure acetals (R)-**30-32**, enabling the exact determination of both the ee and absolute stereochemistry of the AD (scheme 3 10)

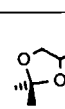
Scheme 3.10



i) $NaIO_4$, aq $NaHCO_3$, ii) $HC(OR)_3$ PPTS ROH

The data shown in table 3 1 show that the ee's of the AD of open acrolein acetals were also disappointing with the new ligand $(DHQD)_2PHAL$ The absolute configuration is however in accordance with the mnemonic picture designed by Sharpless used for selection of the correct AD-mix [16]

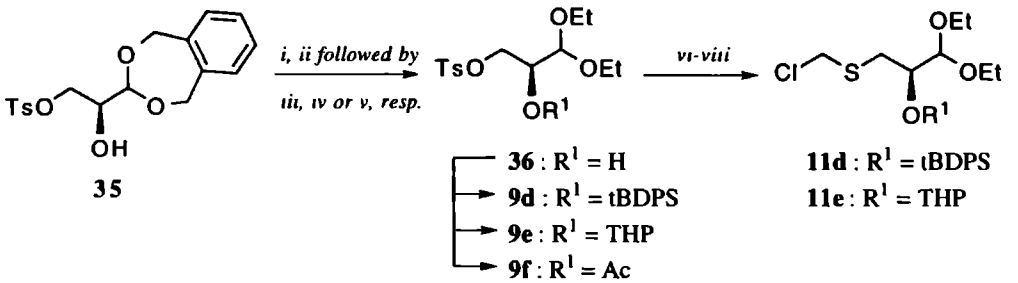
table 3.1

	α_D (Mannitol) *(R) configuration*	α_D (AD-mix β) *(S)-configuration*	ee AD (%)
30 R=Et	+28 7	-15 6	54
31 R=iPr	+31 5	-3 4	11
32 R=Bn	+25 2	-15 0	60

As mentioned in the beginning of the chapter optical purity of the chloromethyl sulfides is essential and the ee's should exceed at least 90% Therefore, AD of open acetals was abandoned and the original route explored by Sharpless and coworkers was followed [13]

After tosylation of the primary alcohol in diol **26** (scheme 3 8) to give **35** (scheme 3 11) the benzodioxepine ring was removed by catalytic hydrogenation, to give the aldehyde which was re-protected without purification as a diethyl acetal by treatment with triethyl orthoformate and TsOH in ethanol to give **36** in overall quantitative yield Acid-catalyzed acetalization of α-hydroxy aldehydes can be performed without loss of optical purity [17] The secondary hydroxyl group in **36** has been protected with several groups The THP group was introduced quantitatively by treatment with dihydropyran and PPTS in dichloromethane to give **9e** TsOH instead of PPTS gave a mixture of compounds caused by decomposition of the diethyl acetal moiety Both tBDPS and acetyl protective groups were introduced using standard procedures giving **9d** and **9f** in yields of 94% and 95%, respectively Transformation of the tosylates **9d**, **9e** into the chloromethylsulfides **11d**, **11e** was carried out by standard procedures in overall yields of 68% and 66%, respectively

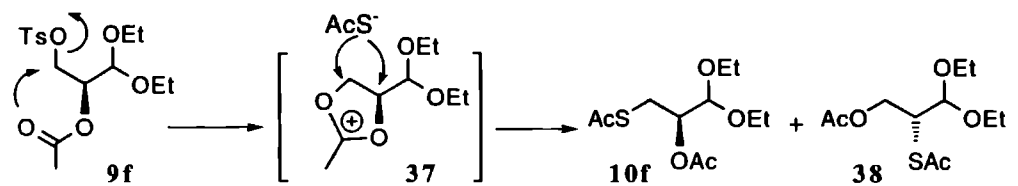
scheme 3.11



i) Pd/C, H_2; ii) $HC(OEt)_3$, TsOH, EtOH, iii) tBDPS-Cl, imidazole, DMF; iv) Ac_2O, pyridine v) DHP, PPTS, CH_2Cl_2; vi) CsSAc, DMF; vii) NaOMe, MeOH; viii) $BrCH_2Cl$, KOH(s), Et_3BnNCl

During thioacylation of tosylate **9f** neighboring group participation played a role (scheme 3.12).

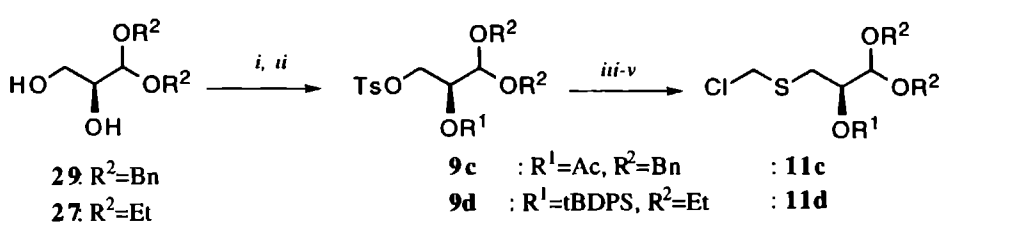
scheme 3.12



Intramolecular nucleophilic attack of the acetyl carbonyl at the electrophilic carbon to which the tosyl group is attached gives the relatively stable oxonium-ion **37**.[18] Subsequent nucleophilic attack of cesium thiolate takes place at both electrophilic carbon atoms, giving the thioacetates **10f** and **38** in 71% yield in about the same ratio. Thioacetate **10f** was not transformed into the corresponding chloromethyl sulfide because its synthesis was not efficient.

To check the optical integrity during the reaction steps toward the eudistomin skeleton, diols **29** and **27**, obtained by direct AD of the corresponding acyclic acrolein acetals whith known optical purities (see table 3.1), were converted into the chloromethyl sulfides **11c,d**, respectively (scheme 3.13).

scheme 3.13

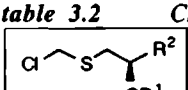


i) TsCl, pyridine, ii) tBDPS-Cl, imidazole, DMF or Ac_2O, pyridine, iii) CsSAc, DMF; iv) NaOMe, MeOH, v) $BrCH_2Cl$, KOH(s), Et_3BnNCl

After transformation of the primary alcohols in **27** and **29** into their tosylates, the secondary alcohols were functionalized. The secondary alcohol in **27** was silylated by treatment with tert-butyl diphenylsilyl chloride to give **9d** in 80% yield. The secondary alcohol in **29** was acylated by treatment with acetic acid anhydride to give **9c** in 94% yield. Transformation of the tosylates **9c,d** into the chloromethyl sulfides **11c,d** was accomplished via our established procedure in overall 53% and 68% yields, respectively. It should be noted here that no side products were detected resulting from neighboring group participation during thioacylation of dibenzyl acetal **9c** as was observed for diethyl acetal **9f**. Apparently, steric repulsion of the more bulky O-benzyl groups combined with the electron withdrawing ability of the dibenzyl acetal prevents attack of the thioacetate at the central carbon atom.

In table 3.2 all chloromethyl sulfides described in this section are summarized. It is important to note that the optical purity of none of these chloromethyl sulfides has been determined. It was checked however, by measurement of the optical rotation of the thioacetates that no complete racemization had occurred. Complete optical characterization has been omitted because it is unclear if the enantiomeric excess will be retained in the synthesis sequence leading to the final eudistomins. The optical purities of the final trans hydroxy eudistomins will indicate which chloromethyl sulfide is most suitable.

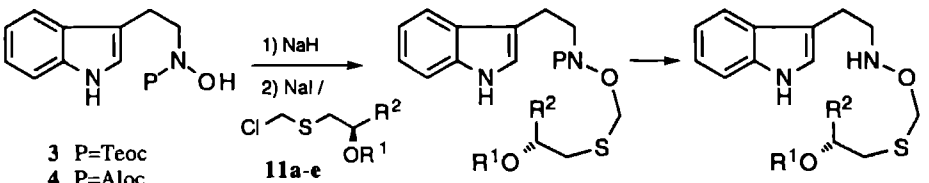
table 3.2 *Chloromethyl sulfides 11*

 **11**	R^1	R^2	Source
a	THP	COOMe	methyl-α,β-isopropylidene-*L*-glycerate
b	Allyl	$CH(OEt)_2$	,,
c	Ac	$CH(OBn)_2$	AD of acrolein dibenzyl acetal
d	tBDPS	$CH(OEt)_2$	AD of acrolein diethyl acetal and acrolein benzodioxepine acetal
e	THP	,,	AD of acrolein benzodioxepine acetal

3.3 Alkylation of N_b-Protected N_b-Hydroxy-tryptamines with Chloromethyl Sulfides Derivatived from Glyceraldehyde

Alkylation of the N_b-protected N_b-hydroxytryptamines **3**[29] or **4** (see exp. part) with chloromethyl sulfides **11a-e** was carried out using the procedure described in chapter 2. Replacement of the Teoc group in **3** by the Aloc group as in **4** was necessary because the Teoc protective group in **3** is not compatible with the tBDPS group in the synthesis of **40d**. The synthesis of **39c,e** was also performed from **4**.

scheme 3.14

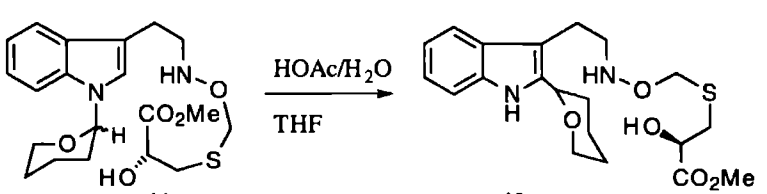


39	R^1	R^2	40
a	THP	COOMe	**a**
b	Allyl	$HC(OEt)_2$	**b**
c	Ac	$HC(OBn)_2$	**c**
d	tBDPS	$HC(OEt)_2$	**d**
e	THP	,,	**e**

It should be mentioned here that only in the approach to **39a** 1,5 equivalent chloromethyl sulfide (*i e* **11a**) was used with respect to N_b-Teoc-N_b-hydroxytryptamine **3**. In the approaches to **39b-e** the chloromethyl sulfides **11b-e** can be used in equimolar amounts because no acidic α-proton is present.[19] The solution of the sodium alkoxides from **3** or **4** was dropped into the stirred solution of the *in situ* formed iodomethyl sulfides from **11a-e** at such rate (3-6 hours) that the pH remained near to neutral After removal of the Teoc (**39a,b**) or Aloc (**39c-e**) groups, **40a-e** were isolated in overall yields of 86%, 61%, 45%, 65% and 81%, respectively

For the initial alkylation experiments leading to THP protected **39a** (or **39e**), TLC analysis showed clean product formation, but after removal of the solvent under reduced pressure several side products had been formed In addition to small amounts of the desired **39a** (or **39e**) and some undefined compounds, a product was isolated in 58% yield, which showed no indole-NH in the ^{1}H-NMR spectrum After subsequent removal of the N_b-Teoc group, this product was identified as **41** (scheme 3 15) based on NMR, UV and CIMS spectroscopy [20]

scheme 3.15



41 **42**

As is shown in scheme 3.15, attempted removal of the THP group in **41**, by treatment with $HOAc/H_2O$ in THF, failed, due to another shift of the THP group, now to the indole 2-position giving **42** in a 96% yield

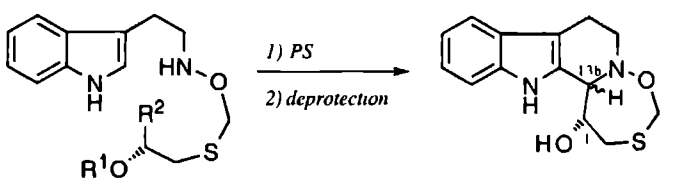
Most likely the formation of products of the type **41** occurs after the formation of small amounts of hydroiodic acid, liberated after decomposition of the rather unstable iodomethyl sulfide (which is used in excess in the preparation of **39a**). When concentrated, the strong acid induces the transfer of

the THP group from oxygen to the indole nitrogen. It was found that this problem could be solved easily by addition of a few mL sat. $NaHCO_3$ before removal of the solvent. Also the silica used for flash chromatography was precautionary deactivated with triethylamine.

3.4 Cyclization Reactions

The availability of **40a-e** now sets the scene for the study of the diastereoselectivity of the intramolecular PS reaction In entry 1 (scheme 3.16) the aldehyde is generated by DIBAL reduction of the methyl ester at -75°C followed by addition of trifluoroacetic acid at the same temperature to induce the PS condensation. The favored trans diastereomer was formed in an outstanding excess of 92%. After removal of the THP protective group the cis/trans diastereomers could be separated by flash column chromatography. The reaction was carried out several times and it was found that the yield of the DIBAL reduction varied (42-59%). Unfortunately, also the ee is disappointing and racemization has most probable occurred during both alkylation of the tryptamine fragment with the chloromethyl sulfide and the DIBAL reduction.

scheme 3.16



40a-e **43 / 1**
cis trans

Entry	R^1	R^2	ratio **43 / 1** cis / trans [a]	cyclization yield (%) [b]	ee (%)[c]	chiral source
1	THP	COOMe	4 / 96	59	30	(*D*)-glycerate
2	Allyl	$CH(OEt)_2$	19 / 81	82	70	(*D*)-glycerate
3	Ac	$CH(OBn)_2$	20 / 80	45	60	AD of **14**
4	TBDPS	$CH(OEt)_2$	32 / 68	83	54	AD of **12**
5	TBDPS	$CH(OEt)_2$	30 / 70	81	97	AD of **15**
6	THP	$CH(OEt)_2$	--	--	--	AD of **15**

[a] The cis/trans ratios were determined by analytical HPLC [b] After removal of protective group R^2

[c] The ee's stated in the entries 3, 4 and 5 are those found after the AD The ee's stated in entries 1 and 2 are calculated from these

Therefore, the approach from methyl esters had to be abandoned. In chapter 2 it was already mentioned that acetals give smooth PS cyclization only after *in situ* hydrolysis to the more reactive aldehydes. Also it was found that the best yields were obtained using an efficiently stirred 2-phase system chloroform/water/trifluoroacetic acid (98/1/1, v/v/v). Application of this 2-phase system in entry 2, however, gave a complex mixture of products. The method of choice turned out to be hydrolysis of the acetals in formic acid/water (9/1, v/v). The reactions in entries 2, 4, 5 and 6 were

completed within one hour at room temperature Removal of the respective allyl and tBDPS protective groups followed by separation of the diastereomers by flash chromatography gave the free hydroxy eudistomins in good overall yields In entry 3 the acetyl protective group with its electron withdrawing ability, retards hydrolysis of the acetal function The reaction now took 1,5 hours at 60°C to come to completion leading to a decreased yield It was also necessary to exclude oxygen from the reaction mixture to avoid oxidation of the released benzyl alcohol to benzaldehyde leading to a competitive PS condensation Removal of the acetyl group was carried out under mild transesterification conditions using a catalytic amount of potassium cyanide in methanol [21]

The trans diastereomers in entries 2 and 3 are formed in a moderate 60% excess Although the tBDPS group in entry 4 is the most bulky protective group used it gave the lowest d e (40%) As is discussed in the preceding chapter the minimum steric hindrance exerted by the substituent R^1 is mainly responsible for the cis/trans ratio [22] Probably, the long O-Si bond length (1 75 Å) compared to the O-C bond length (1 40 Å) is responsible for the bad diastereoselectivity in entry 4

It is evident that the ee's in entries 2-5 are significantly higher than in entry 1 The ratio of the measured optical rotations of the cis/trans hydroxy eudistomins **43,1**, isolated in entries 3, 4 and 5, were identical with those found directly after the AD s of the corresponding acrolein acetals as stated in table 3 3 (see exp part) This justifies the supposition that no further racemization has occurred and the ee s in entries 3, 4 and 5 remained 60%, 54% and 97%, respectively The ee's in entries 1 and 2 are thus calculated from the data found in entries 3, 4 and 5 From entry 2 it can be concluded that the DIBAL reduction of methyl glycerates also suffers from considerable racemization It is very unlikely that racemization has taken place elswhere in the reaction sequence to the tetracyclic skeleton (*vide supra)* Thus, the method of choice for the synthesis of nearly optically pure 1-hydroxy-eudistomins starts from acrolein benzodioxepine acetal followed by the novel Sharpless catalytic AD

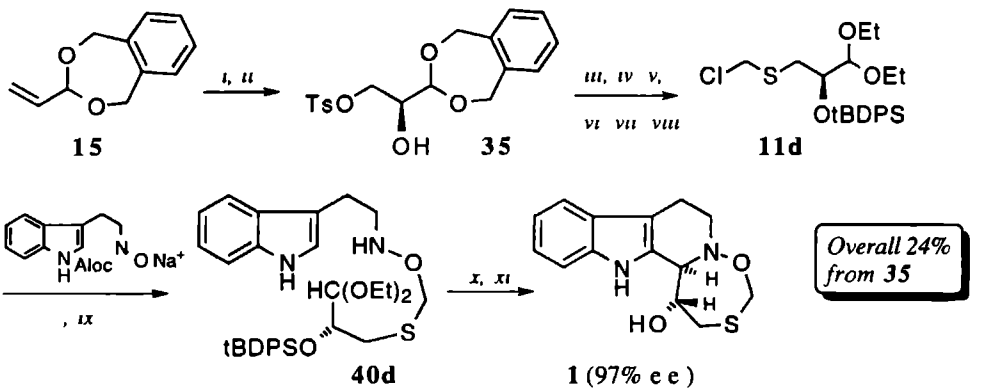
In entry 6 the objective was to combine the optical purity found in entry 5 with the high trans selectivity found in entry 1 But again the THP protective group caused problems No cyclized products were isolated in entry 6 Like the side reactions mentioned in section 3 3, the NMR spectra of the two main products isolated in entry 6 showed migration of the THP group In entry 1 however, were a free aldehyde, obtained by DIBAL reduction of the methyl ester, is used the PS condensation occurred without THP group migration Addition of trifluoroacetic acid after the DIBAL reduction immediately gives the intermediate cyclic iminium-ion Reaction of the indole unit with the highly reactive iminium ion is apparantly faster than attack of the indole nitrogen on the protonated THP group Once the rigid tetracyclic eudistomin skeleton is formed, intramolecular attack of the indole part on the protonated THP group is impossible Therefore it is concluded that intramolecular migration of the THP group proceeds much faster than hydrolysis of the diethyl acetal in entry 6 to give the corresponding aldehyde

Thus, despite giving the best diastereomeric excess toward the wanted trans 1-hydroxy-eudistomin derivative, the THP protective group is not applicable in the acetal approach In spite of the moderate d e , the tBDPS group is the only usable secondary hydroxy protective group fulfilling all remaining requirements, being (next page)

- Protection must be carried out under near neutral conditions (basic conditions will lead to elimination of the tosyloxy group while the lability of the acetal functionality causes problems in acidic conditions)
- Stable toward base treatment during the alkylation of N_b-hydroxy-tryptamine with the iodomethyl sulfide
- Stable toward acid treatment used in the cyclization reaction

In scheme 3 17 the best synthesis route to nearly optically pure **1** is presented

scheme 3.17



40d **1** (97% e e)

i) AD mix β, tBuOH/H_2O=1/1, 4°C, ii) TsCl pyridine RT iii) Pd/C, H_2, EtOH, iv) HC(OEt)$_3$, EtOH, TsOH, v) tBDPS Cl, imidazole DMF, RT vi) CsSAc, DMF vii) NaOMe, MeOH, viii) $BrCH_2Cl$, KOH(s) Et_3BnNCl ix) Et_3NHCO_2H, Pd(OAc)$_2$, PPh_3, MeCN/H_2O=4/1, reflux, x) HCO_2H/H_2O=9/1 xi) Bu_4NF, THF

3.5 Introduction of the Amino Group via the Mitsunobu Reaction

For the introduction of an amino group by S_n2 type nucleophilic substitution of an activated hydroxyl group the following methods can be applied·

- Substitution of a tosylate, mesylate or triflate by Gabriel or azide type nucleophiles, followed by transformation into the free amine or via direct nucleophilic displacement with amines [3]
- The Mitsunobu reaction with Gabriel type *acids* or hydrazoic acid followed by transformation into the free amine [3 4]

The Mitsunobu reaction was chosen mainly because of its very reliable stereochemical course combined with good yields [2] In the few cases mentioned in the literature where retention was found after the Mitsunobu reaction, always neighboring group participation was involved and not a competitive S_n1 process [23] The Mitsunobu reaction was also chosen because the hydroxyl group is transformed into the very efficient phosphonium leaving group *in situ*, avoiding an extra step It is described in the literature that the yield of the Mitsunobu reaction depends highly on the pK_a of the

used acids incorporating the nucleophiles as their conjugated bases [24] To obtain satisfactory yields the pK_a must be ≤14 Suitable acids which were studied and meet this requirement, combined with ease of transformation to free amines are phthalimide (pK_a=13 4), $(Aloc)_2NH$ (pK_a=≈13), HN_3 (pK_a=4 7) and $Zn(N_3)_2$•2Py

Successful experiments were carried out with phthalimide The yield of phthalimide introduction was optimized to 83% However, all attempts to remove the phthalimide group failed By hydrazinolyses with hydrazine monohydrate or hydrazine acetate at room temperature over night no conversion of the starting material could be detected Raising the temperature with hydrazine monohydrate in THF to 50°C gave conversion of the starting material into a product with a lower R_f-value than the desired debromo eudistomin K Similar observations were made by addition of an aqeous methylamine solution to **45a** in benzene It was reasoned that this side product emerged from fission of the N-O bond in the 7-membered ring system That this was not the case will be discussed further on in this section

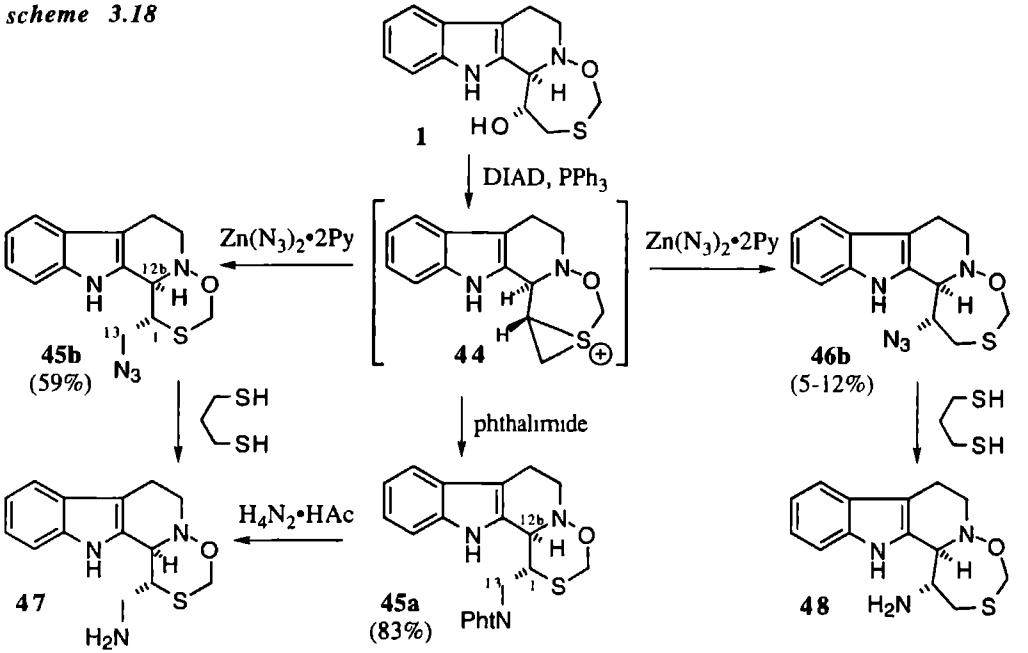
Next, our attention was focussed on $(Aloc)_2NH$ which is an acyclic imide containing two easy removable Aloc protective groups Synthesis of $(Aloc)_2NH$ was accomplished from diallyl dicarbonate and formamide following a literature procedure [25] Although several attempts were made, no succesful Mitsunobu reaction with the acyclic imide could be accomplished It was reasoned that steric factors prevented the acyclic imide to attack the intermediate phosphonium salt

This assumption could however be disproved because the very small azide nucleophile derived from hydrazoic acid also failed to give the desired product Introduction of the azide group was however possible with the stable metal salt $Zn(N_3)_2$•2Py which was synthesized according to a literature procedure [6] Two products were isolated in yields of 41-59% and 5 12%, respectively, both incorporating the β-carboline moiety as shown by NMR Later these products were characterized as **45b** and **46b**, respectively

Several methods were applied to reduce the azide group into the amine group but in neither case formation of the cis eudistomin skeleton was detected by TLC After reduction of the azide moiety in **45b** with the very mild and selective reducing agent propane-1,3-dithiol[26] product **47** was formed which had a smaller TLC R_f-value then the desired cis debromo eudistomin K and turned out to be identical with the product obtained after the removal of the phthalimide group The side product **46b** was also treated with propane-1,3-dithiol yielding *trans* debromo eudistomin K **48**

Now it became clear that during the Mitsunobu reaction transannular anchimeric assistance had taken place from the sulfur atom positioned β with respect to the phosphonium leaving group (scheme 3 18) After formation of the highly reactive phosphonium group immediate transannular attack of the sulfur atom occurs to give the thiirane containing intermediate **44** Now nucleophilic attack at the secondary or tertiary (electrophilic) carbon atoms is possible to give the ring contracted compound **45b** or the *trans* eudistomin derivative **46b**, respectively Formation of the ring contracted products **45a,b** is favored because of the less hindered attack at a secondary carbon atom in combination with the formation of a favored 6-membered oxathiapyridine ring system, which is most pronounced for the larger phthalimide nucleophile

scheme 3.18



It must be concluded now that transformation of the C(1)-hydroxy in a good leaving group inevitably gives neighboring group participation of the β-positioned sulfur atom followed by the formation of side products

3.6 Concluding Remarks

A diastereoselective synthesis (d e =92%) of a *trans*-C(1)-hydroxy eudistomin is possible by using the THP group as a directing group in the intramolecular PS condensation Unfortunately, by generation of the aldehyde needed in the PS condensation by DIBAL reduction of the α-alkoxy-ester most of the optical purity is lost High optical purity (e e=97%) is however possible by utilizing α-alkoxy-acetals, obtained by asymmetric dihydroxylation of a specific acrolein acetal, which is hydrolyzed *in situ* to the free aldehyde as is necessary in these PS condensations Under these conditions however, the THP group cannot be used and has to be replaced by the acid-stable tBDPS group However, the tBDPS group gives only a moderate diastereoselectivity (d e =36%) Finally, transformation of *trans*-C(1)-hydroxy eudistomin into the naturally occurring and biological active *cis*-C(1)-amino-eudistomin failed due to an inevitable transannular neighboring group participation

Combining these facts with the conclusion drawn in chapter 2 that via the *intra*molecular PS condensation no cis diastereoselectivity required for the natural tetracyclic eudistomin series can be achieved one may question the use of this strategy In chapter 1 it was already mentioned that in the intermolecular PS approach as applied by Nakagawa and coworkers, diastereoselectivity toward the

desired cis diastereomer was achieved. However, ringclosure of the 7-membered [1,6,2]-oxathiazepine could not be optimized further than 22% using the Pummerer reaction [27] The approach by Yoon and coworkers who closed the oxathiazepine in 50% yield by utilizing our 2-phase reaction with bromochloromethane and powdered KOH catalyzed by benzyltriethylammonium chloride might be promising [28] Therefore, it seems obvious that further optimizing of this ringclosure after the *inter*molecular PS condensation gives the best prospects to synthesis of multigram quantities of tetracyclic eudistomins.

3.7 Experimental part

For general remarks see the experimental part of chapter 2

3-[2-(N-allyloxycarbonyl-N-hydroxy)amino)ethyl]indole (4) To 3-(2-hydroxyaminoethyl)-indole[29] (6 14 g, 35 7 mmol) in dioxane/dichloromethane (150 mL, 1/1, v/v) was added Aloc-ONSu (7 81 g, 39 3 mmol), causing a slight raise in temperature After 3 h all starting material had been consumed as was indicated by TLC ($CHCl_3$/MeOH=93/7, v/v) The reaction mixture was concentrated to dryness, dissolved in EtOAc (150 mL) and washed with sat $NaHCO_3$ (2 x 50 mL) and brine After drying ($MgSO_4$) the solvent was evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/1, v/v) to yield 8 0 g (86%) of **4** as colorless crystals, mp 79 82°C, R_f 0 40 (EtOAc/hexanes=1/1, v/v), ^{1}H NMR (90 MHz) δ 8 82 (br s, 1H, indole-NH), 7 76-7 52 (m, 1H, indole-C(7)H), 7 42-7 03 (m, 4H, indole-C(2)H and C(4)-C(6)H_3), 5 96-5 54 (m, 1H, H_2C=C<u>H</u>-CH_2), 5 19-5 07 (m, 2H, H_2<u>C</u>=CH-CH_2), 4 42 (dt, 2H, J=5 8 Hz and J=1 0 Hz, H_2C=CH-C<u>H_2</u>), 4-2 5 (very br s, 1H, NOH), 3 94-3 76 (m, 2H, C(3)CH_2C<u>H_2</u>N), 3 20 3 04 (m, 2H, C(3)C<u>H_2</u>CH_2N), Anal Calcd for $C_{14}H_{16}N_2O_3$•1/2H_2O C, 62 44, H, 6 36, N, 10 40 Found C, 62 66, H, 6 19, N, 10 34

Methyl (*S*)-3-hydroxy-2-(2-tetrahydropyranyloxy)propanoate (8) To 7[30] (19 2 g, 53 6 mmol) and 2,3-dihydro-2*H*-pyran (9 0 g, 108 mmol) in dry THF (50 mL) was added TsOH•H_2O (10 mg) After completion of the reaction (15 h) sat $NaHCO_3$ (1 mL) was added and the volatiles were evaporated *in vacuo* The residue was dissolved in EtOAc and subsequently washed with sat $NaHCO_3$ and brine The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* The residue (R_f 0 54, EtOAc/hexanes=1/2, v/v) was dissolved in dry THF (25 mL) and Bu_4NF (54 mL of a 1M solution in THF) was added After TLC analysis showed complete conversion of the starting material (1 h) the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/1, v/v) to yield 7 6 g (69% from **7**) of **8** as a mixture of diastereomers, R_f 0 12 (EtOAc/hexanes=1/1, v/v), ^{1}H NMR (90 MHz) δ 4 93 4 49 (m, 1H O<u>C</u>H$(CH_2)_3$), 4 42 and 4 29 (t and dd, 1H, J=5 1 Hz resp J=3 8 Hz and J=5 8 Hz, OCH_2<u>C</u>H), 4 09-3 74 (m, 2H, O<u>CH_2</u>CH), 3 80 and 3 78 (2xs, 3H, OCH_3), 3 63-3 43 (m, 2H, O<u>CH_2</u>$(CH_2)_3$), 2 75 (very br s, exchangeable, 1H, OH), 1 93-1 39 (m, 6H, OCH_2(<u>CH_2</u>)$_3$)

The acrolein acetals **13** and **14** were prepared according to a literature procedure[31] from acrolein and the corresponding orthoesters The orthoesters were prepared by an exchange reaction from triethyl orthoformate and the corresponding alcohols in the presence of a catalytic amount TsOH•H_2O and removal of the formed ethanol by distillation [32] For the preparation of **15**, see ref [33]

Methyl (*S*)-2-hydroxy-3-(*tert*-butyldimethylsilyloxy)propanoate (16) To methyl *L*-glycerate[30] (6 5 g, 54 mmol) and imidazole (11 g, 162 mmol) in DMF (50 mL) was added *tert*-butyldimethylsilyl chloride (8 1 g, 54 mmol) After standing for 2 h at room temperature the solvent was evaporated *in vacuo* The residue was dissolved in EtOAc and subsequently washed was 20% citric acid (2x50 mL), sat $NaCO_3$ and brine After drying ($MgSO_4$) the solvent was evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/5, v/v) to yield 9 7 g (77%) of **16** as a colorless oil, R_f 0 24 (EtOAc/hexanes=1/4, v/v), ^{1}H NMR (90 MHz) δ 4 28-4 14 (m, 1H, CH_2<u>C</u>H), 4 00-3 74 (m, 2H, <u>CH_2</u>CH), 3 70 (s, 3H, OCH_3), 3 00 (d, exchangeable, 1H, J=7 4 Hz, OH), 0 79 (s, 9H, C$(CH_3)_3$) 0 00 (s, 6H, Si$(CH_3)_2$)

Methyl (*S*)-3-(*tert*-butyldimethylsilyloxy)-2-(2-tetrahydropyranyloxy)propanoate (17) The same procedure was followed as described for **8** **16** (8 0 g, 34 mmol) and 2,3-dihydro-2*H*-pyran (5 7 g, 68 mmol) gave after column chromatography (EtOAc/hexanes=1/4, v/v) 8 9 g (85%) of **17** as a colorless oil (obtained as a mixture of diastereomers), R_f 0 38 (EtOAc/hexanes=1/4, v/v), ^{1}H NMR (90 MHz) δ 4 76-4 66 (m, 1H, OC<u>H</u>$(CH_2)_3$), 4 39-4 09 (t and dd, 1H, OCH_2C<u>H</u>), 3 87-3 18 (m, 4H, O<u>CH_2</u>CH and O<u>CH_2</u>$(CH_2)_3$), 3 64 (s, 3H, OCH_3), 1 82-1 31 (m, 6H, OCH_2(<u>CH_2</u>)$_3$), 0 78 (s, 9H, $C(CH_3)_3$), 0 00 (s, 6H, $Si(CH_3)_2$

(*S*)-3-(*tert*-butyldimethylsilyloxy)-2-(2-tetrahydropyranyloxy)propanal (18) To a stirred solution of **17** (4 1 g, 12 9 mmol) in dry dichloromethane (25 mL) employing flame dried glass equipment under an argon atmosphere at -75°C was added DIBAL (25 mL of a 1M solution in dichloromethane) at such a rate that T<-70°C Then the solution was stirred in the cold for an additional 2 hours and subsequently quenched with aqeous citric acid (20 mL of a 20% solution) After allowing the resulting suspension to warm up to room temperature the resulting clear 2-phase system was separated and the organic layer was washed with 2 portions of water and neutralized with sat $NaHCO_3$ The solution was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* The residue was subjected to column chromatography (EtOAc/hexanes=1/4, v/v) to yield 2 8 g (75%) **18** as a colorless oil with a typical aldehyde odour (obtained as a mixture of diastereomers), R_f 0 38 (EtOAc/hexanes=1/4, v/v), CIMS(70eV), m/z (relative intensity) 289 ($[M+1]^+$, 0 01), 175 (1), 117 ($[C_5H_{13}SiO]^+$, 14), 85 ($[C_5H_9O]^+$, 100), ^{1}H NMR (90 MHz) δ 9 66-9 58 (m, 1H, HC=O), 4 73-4 56 (m, 1H, OC<u>H</u>$(CH_2)_3$), 4 23-3 36 (m, 5H, CH_2CH and O<u>CH_2</u>$(CH_2)_3$), 1 84-1 33 (m, 6H, OCH_2(<u>CH_2</u>)$_3$), 0 79 (s, 9H, $C(CH_3)_3$), 0 00 (s, 6H, $Si(CH_3)_2$)

(*S*)-3-(*tert*-butyldimethylsilyloxy)-2-(2-tetrahydropyranyloxy)propanal diethyl acetal (19) and (*S*)-3-(*tert*-Butyldimethylsilyloxy)propanal diethyl acetal (20) In a mixture of dry ethanol (50 mL) and triethyl orthoformate (3 mL) was dissolved **18** (1 1 g, 3 8 mmol) and $TsOH•H_2O$ (10 mg) After standing over night at room temperature sat $NaHCO_3$ (2 mL) was added and the volatiles were evaporated *in vacuo* The residue was dissolved in EtOAc en washed with water and brine After drying ($MgSO_4$) the solvent was evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/5, v/v) to yield two clear oily fractions 210 mg (15%) **19** (obtained as a mixture of diastereomers), R_f 0 44 (EtOAc/hexanes=1/4, v/v), CIMS(70eV), m/z (relative intensity) 317 ($[M-OC_2H_5]^+$, 5), 175 (21), 117 ($[C_5H_{13}SiO]^+$, 7), 103 ($[HC(OC_2H_5)_2]^+$, 100), 85 ($[C_5H_9O]^+$, 97), 75 ($[C_3H_7O_2]^+$, 32), 57 ($[C_4H_9]^+$, 9), ^{1}H NMR (90 MHz) δ 4 86 and 4 59 (2xbr t, 1H, OC<u>H</u>$(CH_2)_3$), 4 53 4 45 and 4 35-4 26 (2xm, 1H, OCHO), 3 94-3 27 (m, 9H, OCH_2CH, O<u>CH_2</u>$(CH_2)_3$ and 2xO<u>CH_2</u>CH_3), 1 84-1 36 (m, 6H OCH_2(<u>CH_2</u>)$_3$), 1 11 (t, 6H, J=6 9 Hz, 2xOCH_2<u>CH_3</u>), 0 78 (s, 9H, $C(CH_3)_3$), 0 00 (s, 6H, $Si(CH_3)_2$) and 540 mg (50%) of **20**, R_f 0 29 (EtOAc/hexanes=1/4, v/v), CIMS(70eV), m/z (relative intensity) 233 ($[M\ OC_2H_5]^+$, 6), 175 (41), 117 ($[C_5H_{13}SiO]^+$, 48), 103 ($[HC(OC_2H_5)_2]^+$, 100), 75 ($[C_3H_7O_2]^+$, 66), 57 ($[C_4H_9]^+$, 12), ^{1}H NMR (90 MHz) δ 4 41 (d, 1H, J=5 3 Hz, CH_2C<u>H</u>C<u>H</u>), 3 82-3 31 (m, 7H, <u>CH_2</u>C<u>H</u>CH and 2x<u>CH_2</u>CH_3), 2 37 (d, exchangeable, 1H, J=4 2 Hz, OH), 1 15 and 1 13 (2xt, 6H, J=7 1 Hz, 2xOCH_2<u>CH_3</u>), 0 80 (s, 9H, $C(CH_3)_3$), 0 00 (s, 6H, $Si(CH_3)_2$)

Methyl (*S*)-3-(*tert*-butyldimethylsilyloxy)-2-(allyloxy)propanoate (21) In freshly distilled (from NaH) THF (200 mL) employing flame dried glass equipment under an argon atmosphere was dissolved **16** (9 9 g, 42 mmol), tris(dibenzylideneacetone)dipalladium(0) (240 mg, 0 27 mmol), 1,4 bis(diphenylphosphino)-butane (455 mg, 1 1 mmol) and allyl ethyl carbonate (10 5 g, 81 mmol) After heating at reflux for 2 hours all starting material had been converted and the reaction mixture was filtered over a short path of hyflo After evaporation of the volatiles the residue was subjected to column chromatography (EtOAc/hexanes=15/85, v/v) to yield 11 5 g (99%) **21** as a colorless oil, R_f 0 63 (EtOAc/hexanes=1/4, v/v), α_D^{22}=-28 5 (c=3 96, MeOH), CIMS(70eV), m/z (relative intensity) 275 ($[M+1]^+$, 1), 217 ($[M-C_3H_5O]^+$, 79), 117 ($[C_5H_{13}SiO]^+$, 100), ^{1}H NMR (90 MHz) δ 6 09-5 67 (m, 1H, H_2C=C<u>H</u>-CH_2), 5 39-5 10 (m, 2H, <u>H_2</u>C=CH-CH_2), 4 28-3 78 (m, 5H, OCH_2CH and H_2C=CH-<u>CH_2</u>), 3 68 (s, 3H, OCH_3), 0 79 (s, 9H $C(CH_3)_3$), 0 00 (s, 6H, $Si(CH_3)_2$)

(*S*)-2-(allyloxy)propanal diethyl acetal (22) For the DIBAL reduction of **21** to the aldehyde the same procedure was followed as described for **18** using **21** (10 g, 36 5 mmol) and DIBAL (74 mL of a 1M solution in dichloromethane) After work-up 9 2 g of a residue was obtained which was dissolved in ethanol (150 mL) To this solution triethyl orthoformate (25 mL) and $TsOH•H_2O$ (0 5 g, 2 6 mmol) were added and the reaction mixture was

allowed to stand over night at room temperature. Sat. $NaHCO_3$ (20 mL) was added and the volatiles were evaporated *in vacuo*. The residue was dissolved in EtOAc and subsequently washed with sat. $NaHCO_3$ and brine. After drying ($MgSO_4$) the solvent was evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/2, v/v) to yield 5.9 g (79%) **22** as a colorless oil; R_f 0.25 (EtOAc/hexanes=1/2, v/v); α_D^{22}=-24 8 (c=2 06, MeOH), CIMS(70eV), m/z (relative intensity) 159 ($[M\text{-}OC_2H_5]^+$, 28), 103 ($[HC(OC_2H_5)_2]^+$, 100), 75 ($[C_3H_7O_2]^+$, 98), ^{1}H NMR (90 MHz) δ 6.16-5.74 (m, 1H, H_2C=C<u>H</u>-CH_2), 5 40-5 10 (m, 2H, $\underline{H_2C}$=CH-CH_2), 4.49 (d, 1H, J=6 0 Hz, OCHO), 4.23-4 14 (m, 2H, H_2C=CH-$\underline{CH_2}$) 4.00-3.33 (m, 7H, 2x$O\underline{CH_2}CH_3$ and $HO\underline{CH_2}CH$), 2.37 (t, exchangeable, 1H, J=6.3 Hz, OH), 1.22 and 1.20 (2xt, 6H, J=7.0 Hz, 2x$OCH_2\underline{CH_3}$)

(*R*)-1-tosyloxy-2-(2-tetrahydropyranyloxy)-1-propanol (24): To **23**[10] (10.4 g, 21 mmol) in dry dichloromethane was added 2,3-dihydro-2*H*-pyran (3.5 g, 42 mmol) and $TsOH•H_2O$ (5 mg) After standing for 30 min. at room temperature the reaction mixture was washed with sat. $NaHCO_3$ and brine. After drying ($MgSO_4$) the volatiles were removed *in vacuo* and the residue was dissolved in THF (25 mL). To this solution Bu_4NF (35 mL of a 1M solution in THF) was added. After standing at room temperature for 1 h the solvent was evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/1, v/v) to yield 5 3 g (76%) of **24** as a colorless oil (obtained as a mixture of diastereomers); R_f 0.25 (EtOAc/hexanes=1/1, v/v), ^{1}H NMR (90 MHz) δ 7.77 and 7.39 (AB, 4H, J_{AB}=7 8 Hz, C_6H_4), 4 72-4 51 (m, 1H, OCHO), 4.36-3.11 (m, 7H, CH_2CHCH_2 and $O\underline{CH_2}(CH_2)_3$), 2.45 (s, 3H, H_3CPh), 2.13-2.05 (br t, exchangeable, 1H, OH), 1.84-1 36 (m, 6H, $OCH_2(\underline{CH_2})_3$)

2-(2-Tetrahydropyranyloxy)propenal (25). <u>Swern approach:</u> To dry dichloromethane (25 mL) under an argon atmosphere employing flame dried glass equipment stoppered with a septum was added with a syringe oxalyl chloride (0 53 mL, 0.77 g, 6.1 mmol). After cooling of this solution to -75°C, dry dimethyl sulfoxide (0.43 mL, 0.47 mg, 6 1 mmol) was added. After stirring for 5 min. **24** (1.0 g, 3 0 mmol), dissolved in dichloromethane (10 mL), was added over a period of 15 min. and stirred for an additional 15 min. In the cold triethylamine (3 mL) was added dropwise and the solution was allowed to warm up to -25°C at which temperature citric acid (25 mL of a 20% solution) was added. The organic layer was neutralized with sat. $NaHCO_3$ and dried ($MgSO_4$). After evaporation of the solvent the residue was subjected to column chromatography (EtOAc/hexanes) to yield 35 mg (8%) of **25** as an oil; R_f 0 45 (EtOAc/hexanes=1/1, v/v), ^{1}H NMR (90 MHz) δ 9.25 (s, 1H, HC=O), 5.66 (d, 1H, J=2.2 Hz, $\underline{H}$HC=C), 5.33-5.25 (m, 1H, OCHO), 5 24 (d, 1H, J=2.2 Hz, $\underline{H}$HC=C), 3.94-3.47 (m, 2H, $O\underline{CH_2}(CH_2)_3$), 2 08-1.50 (m, 6H, $OCH_2(\underline{CH_2})_3$) and 450 mg of an impure fraction containing miscellaneous unidentified products.
<u>PCC approach.</u> In dry dichloromethane (35 mL) **24** (1.0 g, 3 0 mmol) was dissolved. This solution was added in one portion to a suspension of pyridinium chlorochromate (0 98 g, 4.5 mmol) and sodium acetate (0 5 g, 6 0 mmol) in dichloromethane (25 mL) After stirring of this suspension for 2 days TLC analysis (EtOAc/hexanes=1/1, v/v) showed the presence of the alkene **25** besides unreacted starting material.

(*L*)-glyceraldehyde diethyl acetal (27). To a well stirred solution of *tert*-butylalcohol (50 mL) and water (50 mL) was added potassium osmate (VI) dihydrate (7.4 mg, 0.02 mmol), hydroquinidine 1,4-phtalazinediyl diether (78 mg, 0 1 mmol), potassium carbonate (4.12 g, 30 mmol) and potassium ferricyanide (9 8 g, 30 mmol). After a clear two-layer system appeared, the solution was cooled to 0°C To this well stirred and cold mixture, acrolein diethyl acetal **12** (1.3 g, 10 mmol) was added in one portion After stirring in the refrigerator at 4°C over night sodium sulfite (1 5 g, 11.9 mmol) was added and the reaction mixture was allowed to warm to room temperature After stirring for an additional hour EtOAc (100 mL) was added together with brine (25 mL) The organic phase was separated and the water phase was subsequently washed with 3 portions of EtOAc. The combined organic phases were washed with brine and dried ($MgSO_4$). After removal of the solvent *in vacuo* 1.51 g (92%) crude **27** was obtained as a yellowish oil: ^{1}H-NMR (90 MHz) δ 4.51 (d, 1H, J=5.4 Hz, $CH_2C\underline{H}CH$), 3.98-3.43 (m, 7H, $\underline{CH_2}\underline{C}HCH$ and 2x$O\underline{CH_2}CH_3$), 2.49 (very br s, 2H, 2xOH), 1.24 and 1 23 (2xt, 6H, J=7 0 Hz, 2x$OCH_2\underline{CH_3}$)

(*L*)-glyceraldehyde diisopropyl acetal (28): Following the same procedure on a 29.6 mmol scale, 4.80 g (84%) crude **28** was obtained as a yellowish oil which was not further purified and transformed into **31**.

(*L*)-glyceraldehyde dibenzyl acetal (29). Following the same procedure on a 19.5 mmol scale, 5.66 g (99%) crude **29** was obtained as a yellowish oil, EIMS(70eV). m/z (relative intensity) 227 ($[HC(OCH_2Ph)_2]^+$, 0 23), 163 ($[M\text{-}C_7H_7]^+$, 10), 147 ($[M\text{-}C_7H_7O]^+$, 17), 107 ($[C_7H_7O]^+$, 46), 91 ($[C_7H_7]^+$, 100) ^{1}H-NMR (90 MHz) δ 7 31 (s,

10H, 2x-C_6H_5), 4 85 - 4 38 (m, 6H, 2xO$\underline{CH_2}$Ph and -$CH_2\underline{CHCH}$-), 3 92 - 3 68 (AB, 2H, -$\underline{CH_2}$CHCH-), 2 17 (very br s, 2H, 2xOH),

Synthesis of α,β-isopropylidene-glyceraldehyde acetals (for optical rotations of **30-32**, see table 3 1)

α,β-isopropylidene-*L*-glyceraldehyde diethyl acetal ((S)-30) To **27** (1 62 g, 9 9 mmol) in dichloromethane (50 mL) was added 2,2-dimethoxypropane (10 3 g, 12 1 mL, 99 mmol) and PPTS (20 mg) The progress of the reaction was monitored by GC After 2 h the reaction mixture was washed with sat $NaHCO_3$ and brine After drying ($MgSO_4$) the volatiles were evaporated *in vacuo* The residue (1 94 g) was purified by kugelrohr distillation (5 mmHg) to yield 1 25 g (64%) of **(S)-30** as a colorless oil which was homogeneous by GC CIMS(70eV), m/z (relative intensity) 203 ($[M-1]^+$, 0 1),189 ($M-CH_3]^+$, 0 5), 159 ($[M-C_2H_5O]^+$, 4), 103($[HC(OC_2H_5)_2]^+$, 9), 75 ($[C_3H_7O_2]^+$, 4), 42 (100), ^{1}H NMR (90 MHz) δ 4 43 (d, 1H, J=5 9 Hz, OCHO), 4 25-3 41 (m, 7H, 2xO$\underline{CH_2}$$CH_3$ and OCH_2CH), 1 44 and 1 37 (2xs, 6H, $C(CH_3)_2$), 1 25 and 1 21 (2xt, 6H, J=7 1 Hz, 2x$OCH_2\underline{CH_3}$)

α,β-isopropylidene-*L*-glyceraldehyde diisopropyl acetal ((S)-31) Following the same procedure **28** (0 8 g, 4 2 mmol) gave after column chromatography (EtOAc/hexanes=1/5, v/v) 470 mg (49%) of **(S)-31** as a colorless oil which was homogeneous by GC R_f 0 63 (EtOAc/hexanes=1/2, v/v), CIMS(70eV), m/z (relative intensity) 217 (M $CH_3]^+$, 0 3), 173 ($[M-C_3H_7O]^+$, 9), 131 ($[HC(OC_3H_7)_2]^+$, 7), 73 ($[C_4H_9O]^+$, 73), 42 (100), ^{1}H NMR (90 MHz) δ 4 46 (d, 1H, J=5 1 Hz, OCHO), 4 09-3 83 (m, 5H, 2xO$\underline{CH}(CH_3)_2$ and O$\underline{CH_2}$CH), 1 36 and 1 28 (2xs, 6H, $C(CH_3)_2$), 1 16-1 03 (m, 12H, 2xOCH($\underline{CH_3}$)$_2$)

α,β-isopropylidene-*L*-glyceraldehyde dibenzyl acetal ((S)-32) Following the same procedure **29** (1 62 g, 5 6 mmol) gave after column chromatography (EtOAc/hexanes=1/4, v/v) 1 53 g (83%) of **(S) 31** as a colorless oil which was homogeneous by GC R_f 0 61 (EtOAc/hexanes=1/2, v/v), EIMS(70eV), m/z (relative intensity) 313 ([M-$CH_3]^+$, 1), 227 ($[HC(OCH_2Ph)_2]^+$, 4), 181 (16), 107 ($[C_7H_7O]^+$, 91 ($[C_7H_7]^+$, 100), ^{1}H NMR (90 MHz) δ 7 35 (s, 5H, C_6H_5), 7 32 (s, 5H, C_6H_5), 4 78 - 4 48 (m, 5H, 2xOCH_2Ph and OCHO), 4 29 (q, 1H, J = 5 8 Hz, $OCH_2\underline{CH}$), 4 06 and 3 89 (AB part of ABX spectrum, 2H, J_{AX} = 5 4 Hz, J_{BX} = 5 3 Hz and J_{AB} = 8 3 Hz, O$\underline{CH_2}$CH), 1 38 (s, 3H, CH_3), 1 35 (s, 3H, CH_3)

The optically pure *D*-glyceraldehyde antipodes were synthesized in excellent yields from α,β isopropylidene-*D*-glyceraldehyde (R)-**34**[7] following the standard acetalization procedure from the corresponding orthoesters as described for **22** (after the DIBAL reduction of **21**)

(*S*)-2-hydroxy-3-(*p*-tolylsulfonyloxy)propanal diethyl acetal (36) From **35** To **35**[13] (8 6 g, 23 6 mmol) in ethanol (150 mL) under a nitrogen atmosphere was added 10% Pd(C) (500 mg) and the resulting suspension was stirred in a hydrogen atmosphere until all starting material had been consumed (2-48 h) according to TLC ($R_{f(35)}$ 0 38, $R_{f(aldehyde)}$ 0 21, EtOAc/hexanes=1/1 v/v) The Pd(C) catalyst was removed by filtration over hyflo and subsequently triethyl orthoformate (25 mL) and TFA (0,2 mL) were added After standing for 1,5 h sat $NaHCO_3$ (50 mL) was added and the volatiles were removed *in vacuo* After purification of the residue by column chromatography (EtOAc/hexanes=1/2, v/v) 7 4 g (99 %) of **36** was obtained as a colorless oil R_f 0 46 (EtOAc/hexanes=1/1, v/v), EIMS(70eV), m/z (relative intensity) 317 ($[M-1]^+$, 0 01), 273 ($[M-OC_2H_5]^+$, 0 4), 103 ($[HC(OC_2H_5)_2]^+$, 100), 91 ($[C_7H_7]^+$, 26), 75 ($[C_3H_7O_2]^+$, 50), ^{1}H NMR (90 MHz) δ 7 80 and 7 35 (AB, 4H, J_{AB}=8 4 Hz, C_6H_4), 4 47 (d, 1H, J=5 7 Hz, OCHO), 4 20 and 4 11 (AB part of ABX spectrum, 2H, J_{AX}=3 4 Hz, J_{BX}=5 5 Hz and J_{AB}=10 2 Hz O$\underline{CH_2}$CH), 3 95-3 36 (m, 5H, 2xO$\underline{CH_2}$$CH_3$ and $OCH_2\underline{CH}$), 2 42 (s, 4H, H_3CPh and OH), 1 20 and 1 17 (2xt, 6H, J=7 0 Hz, 2x$OCH_2\underline{CH_3}$) From **27** **27** (1 29 g, 7 9 mmol), TsCl (1 55 g, 8 1 mmol) and pyridine (25 mL) gave after column chromatography 2 1 g (84%) of **36**

Syntheses of tosylates **9**

The tosylates **9a,b** were prepared as described in chapter 2 from **8** and **22**, respectively, and tosyl chloride in pyridine to afford

Methyl (*R*)-2-(2-tetrahydropyranyloxy)-3-(*p*-tolylsulfonyloxy)propanoate (9a) obtained after purification by column chromatography (EtOAc/hexanes=1/2, v/v) as a mixture of diastereomers in 70% yield (18 8 g scale) as a colorless oil, R_f 0 26 (EtOAc/hexanes=1/2, v/v), CIMS(70eV), m/z (relative intensity) 359 ($[M+C_2H_5]^+$, 16), 275 (51), 215 (51), 155 ($[C_7H_7SO_3]^+$, 85), 91 $[C_7H_7]^+$, 59), 85 ($[C_5H_9O]^+$, 100), ^{1}H NMR (90 MHz) δ 7 70

7 67 and 7 47, 7 45 (2xAB, 4H, J_{AB}=9 0 Hz, C_6H_4), 4 80 and 4 71 (2xbr t, 1H, O<u>CH</u>$(CH_2)_3$), 4 58-4 47 (m, 1H, OCH_2<u>CH</u>), 4 40-2 38 (m, 4H, O<u>CH_2</u>$(CH_2)_3$), 3 68 (s, 3H, OCH_3), 1 66-1 51 (m, 6H, OCH_2(<u>CH_2</u>)$_3$)

(*R*)-2-allyloxy-3-(*p*-tolylsulfonyloxy)propanal diethyl acetal (9b) obtained after column chromatography (EtOAc/hexanes=1/4, v/v) in 77 % yield (7 7 g scale) as a colorless oil, R_f 0 43 (EtOAc/hexanes=1/2, v/v), α_D^{22}=-16 5 (c=4 3, MeOH), CIMS(70eV), m/z (relative intensity) 313 ([M OC_2H_5]$^+$, 1), 103 ([HC$(OC_2H_5)_2$]$^+$, 100), 91 ([C_7H_7]$^+$, 12), 75 ([$C_3H_7O_2$]$^+$, 23), ^{1}H NMR (90 MHz) δ 7 79 and 7 33 (AB, 4H, J_{AB}=8 4 Hz, C_6H_4), 5 97-5 52 (m, 1H H_2C=<u>CH</u>-CH_2), 5 20-4 99 (m, 2H, <u>H_2C</u>=CH-CH_2), 4 30 (d, 1H, J=5 3 Hz, OCHO), 4 25-3 88 (m, 4H, H_2C=CH-<u>CH_2</u> and SO<u>CH_2</u>CH), 3 78-3 22 (m, 5H, 2xO<u>CH_2</u>CH_3 and $SOCH_2$<u>CH</u>), 2 33 (s, 3H, H_3CPh), 1 11 and 1 06 (2xt, 6H, J=6 9 Hz, 2xOCH_2<u>CH_3</u>)

(*R*)-2-acetoxy-3-(*p*-tolylsulfonyloxy)propanal dibenzyl acetal (9c) 29 (1 6 g, 5 6 mmol) was tosylated following the standard procedure from TsCl (1 07 g, 5 6 mmol) and pyridine as described in chapter 2 to yield 2 44 g (96%) of the tosylate (R_f 0 21 (EtOAc/hexanes=1/2, v/v)) This tosylate was dissolved in freshly distilled pyridine (25 mL) and acetic anhydride (2 9 g, 2 7 mL, 28 0 mmol) was added Upon standing over night at room temperature the volatiles were evaporated *in vacuo* and the residue was dissolved in EtOAc and subsequently washed with citric acid (50 mL of a 10% sol), sat $NaHCO_3$ and brine After drying ($MgSO_4$) the solvent was evaporated *in vacuo* to yield 2 12 g (81%) of **9c** as a colorless oil, R_f 0 42 (EtOAc/hexanes=1/2, v/v), α_D^{22}=-9 8 (c=5 51, MeOH), EIMS(70eV), m/z (relative intensity) 377([M C_7H_7]$^+$, 17), 227 ([HC$(OCH_2Ph)_2$]$^+$ 0 5), 172 (9), 107 ([C_7H_7O]$^+$, 50), 91 ([C_7H_7]$^+$, 100), 43 ([C_2H_3O]$^+$, 49), ^{1}H NMR (100 MHz) δ 7 76 (A part of AB spectrum, 2H, J_{AB}=8 5 Hz, p-Me-C_6H_2), 7 40-7 14 (m, 12H, 2xC_6H_5 and p-Me-C_6H_2), 5 20-5 08 (m, 1H, CH_2<u>CH</u>CH), 4 78 (d, 1H, J=5 6 Hz, CH_2CH<u>CH</u>), 4 57-4 28 (m, 6H, <u>CH_2</u>CHCH and 2xOCH_2Ph), 2 43 (s, 3H, H_3CPh), 1 95 (s, 3H, $COCH_3$)

(*R*)-2-(*tert*-butyldiphenylsilyl)-3-(*p*-tolylsulfonyloxy)propanal diethyl acetal (9d) To **36** (1 41 g, 4 4 mmol, derived from **27**) and imidazole (0 6 g, 8 8 mmol) in DMF (25 mL) was added *tert* butyldiphenylsilyl chloride (1 46 g, 5 3 mmol) After standing at room temperature over night the reaction mixture was diluted with EtOAc (100 mL) and successively washed with citric acid (20% aq sol), water (2x) and brine After drying ($MgSO_4$) the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/4, v/v) to yield 2 29 g (94%) of **9d** as a colorless oil R_f 0 37 (EtOAc/hexanes=1/4 v/v), α_D^{22}=-4 37 (c=5 26, MeOH), EIMS(70eV), m/z (relative intensity) 353([M-203]$^+$, 14), 199 ([M-Ph_2SiOH]$^+$, 100), 103 ([HC$(OC_2H_5)_2$]$^+$, 31), 91 ([C_7H_7]$^+$ 9), 75 ([$C_3H_7O_2$]$^+$, 10), ^{1}H NMR (90 MHz) δ 7 76-7 56 and 7 39-7 19 (m, 14H, 2xC_6H_5 and C_6H_4), 4 24 (d, 1H, J=4 6 Hz, OCHO), 4 16-3 74 (m, 3H, OCH_2CH), 3 67-3 08 (m, 4H, 2xO<u>CH_2</u>CH_3), 2 40 (s, 3H, H_3CPh), 1 16 and 0 92 (2xt, 6H, J=7 3 Hz, 2xOCH_2<u>CH_3</u>), 1 04 and 1 00 (2xs, 9H, $C(CH_3)_3$)

(*R*)-2-(2-tetrahydropyranyloxy)-3-(*p*-tolylsulfonyloxy)propanal diethyl acetal (9e) To **36** (8 2 g, 25 8 mmol) and 2,3-dihydro-2*H*-pyran (8 7 g, 104 mmol) in dichloromethane (200 ml) was added PPTS (0 5 g, 2 0 mmol) After 30 min the reaction mixture was washed with sat $NaHCO_3$ (50 mL) and brine After drying (Na_2SO_4) the volatiles were removed *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/2, v/v) to yield 9 6 g (95%) of **9e** as a colorless oil as a mixture of diastereomers, R_f 0 62 (EtOAc/hexanes=1/1, v/v), CIMS(70eV), m/z (relative intensity) 401 ([M-1]$^+$, 0 6), 357 ([M-OC_2H_5]$^+$, 15), 103 ([HC$(OC_2H_5)_2$]$^+$, 100), 85 ([C_5H_9O]$^+$, 92), 75 ([$C_3H_7O_2$]$^+$, 14), ^{1}H NMR (90 MHz) δ 7 81, 7 79 and 7 33 (2xAB, 4H, J_{AB}=8 4 Hz, C_6H_4), 4 86 and 4 69 (2xbr t, 1H, O<u>CH</u>$(CH_2)_3$), 4 54 and 4 48 (2xd, 1H, J=4 4 Hz and J=6 0 Hz, OCHO), 4 40-4 04 (m, 2H, O<u>CH_2</u>CH), 3 97-3 31 (m, 7H, 2xO<u>CH_2</u>CH_3 O<u>CH_2</u>$(CH_2)_3$ and OCH_2<u>CH</u>), 2 44 (s, 3H, H_3CPh), 1 91-1 43 (m, 6H, OCH_2(<u>CH_2</u>)$_3$), 1 27-1 05 (m, 6H, 2xOCH_2<u>CH_3</u>)

(*R*)-2-acetoxy-3-(*p*-tolylsulfonyloxy)propanal diethyl acetal (9f) To **36** (2 0 g, 6 3 mmol) in freshly distilled pyridine (25 mL) was added acetic anhydride (3 22 g, 3 0 mL, 31 5 mmol) After standing over night at room temperature the volatiles were evaporated *in vacuo* The residue was dissolved in EtOAc and successively washed with citric acid (25 mL of a 10% sol) sat $NaHCO_3$ and brine After drying ($MgSO_4$) the solvent was evaporated *in vacuo* to yield 2 18 g (96%) **9f** as a yellowish oil which was homogeneous by TLC, R_f 0 46 (EtOAc/hexanes=1/1, v/v), EIMS(70eV), m/z (relative intensity) 315 ([M-OC_2H_5]$^+$, 1 8), 103 ([HC$(OC_2H_5)_2$]$^+$, 100), 91 ([C_7H_7]$^+$, 16), ^{1}H NMR (90 MHz) δ 7 79 and 7 35 (AB, 4H, J_{AB}=8 4 Hz, C_6H_4), 5 06-4 92 (m, 1H, CH_2<u>CH</u>CH), 4 56 (d, 1H, J=5 6 Hz CH_2CH<u>CH</u>), 4 25 (d, 2H, J=4 1 Hz, <u>CH_2</u>CHCH), 3 84 3 38 (m, 4H, 2xO<u>CH_2</u>CH_3), 2 45 (s, 3H, $PhCH_3$), 2 03 (s, 3H, $COCH_3$), 1 16 and 1 14 (2xt, 6H J=7 0 Hz, 2xOCH_2<u>CH_3</u>)

Syntheses of thioacetates **10**

The thioacetates **10a-f** were prepared following the same procedure as described in chapter 2

Methyl (*R*)-3-acetylthio-2-(2-tetrahydropyranyloxy)propanoate (10a) Obtained from **9a** as a mixture of diastereomers and purified by column chromatography (EtOAc/hexanes=1/3, v/v) in 75% yield (10 4 g scale) as a yellowish oil, R_f 0 38 (EtOAc/hexanes=1/2, v/v), CIMS(70eV), m/z (relative intensity) 203 ([M-COOMe]$^+$, 2), 85 ([C_5H_9O]$^+$, 100), ^{1}H NMR (90 MHz) δ 4 77 (br t, 1H, OC<u>H</u>(CH_2)$_3$), 4 45 and 4 24 (dd and t, 1H, J=4 6 Hz, J=6 6 Hz and J=6 2 Hz, SCH_2C<u>H</u>), 4 09-3 07 (m, 4H, O<u>CH_2</u>(CH_2)$_3$ and S<u>CH_2</u>CH)), 3 76 (s, 3H, CO_2CH_3), 2 36 (s, 3H, $SCOCH_3$), 1 71-1 52 (m, 6H, OCH_2(<u>CH_2</u>)$_3$)

(*R*)-3-acetylthio-2-allyloxy-propanal diethyl acetal (10b) Obtained from **9b** and purified by column chromatography (EtOAc/hexanes=1/4, v/v) in 71% yield (4 0 g scale) as a yellowish oil, R_f 0 30 (EtOAc/hexanes=1/4, v/v), CIMS(70eV), m/z (relative intensity) 261 ([M-1]$^+$, 0 01), 217 ([M-OC_2H_5]$^+$, 15), 103 ([$HC(OC_2H_5)_2$]$^+$, 100), 75 ([$C_3H_7O_2$]$^+$, 82), ^{1}H NMR (90 MHz) δ 6 16-5 72 (m, 1H, H_2C=C<u>H</u>-CH_2), 5 40-5 09 (m, 2H, <u>H_2C</u>=CH-CH_2), 4 39 (d, 1H, J=5 3 Hz, OCHO), 4 19-4 09 (m, 2H, H_2C=CH-<u>CH_2</u>), 3 84-3 42 (m, 5H, 2xO<u>CH_2</u>CH_3 and SCH_2C<u>H</u>), 3 31 and 3 01 (AB part of ABX spectrum, 2H, J_{AX}=3 8 Hz, J_{BX}=7 1 Hz and J_{AB}=13 5 Hz, S<u>CH_2</u>CH), 2 33 (s, 3H, $SCOCH_3$), 1 21 (t, 6H, J=7 0 Hz, 2xOCH_2<u>CH_3</u>)

(*R*)-2-acetoxy-3-acetylthio-propanal dibenzyl acetal (10c) Obtained from **9c** and purified by column chromatography (EtOAc/hexanes=1/4, v/v) in 54% yield (1 2 g scale) as a yellowish oil, R_f 0 54 (EtOAc/hexanes=1/2, v/v), EIMS(70eV), m/z (relative intensity) 281 ([M-C_7H_7O]$^+$, 6), 227 ([$HC(OCH_2Ph)_2$]$^+$, 16), 181 (21), 91 ([C_7H_7]$^+$, 100), 43 ([C_2H_3O]$^+$, 68), ^{1}H NMR (90 MHz) δ 7 33 (s, 10H, 2xC_6H_5), 5 30-5 13 (m, 1H, CH_2C<u>H</u>CH), 4 78-4 48 (m, 5H, 2OCH_2Ph and CH_2CHC<u>H</u>), 3 46 and 3 03 (AB part of ABX spectrum (2H, J_{AX}=6 0 Hz, J_{BX}=11 6 Hz and J_{AB}=14 2 Hz, <u>CH_2</u>CHCH), 2 32 (s, 3H, $SCOCH_3$), 2 01 (s, 3H, $OCOCH_3$)

(*R*)-3-acetylthio--2-(*tert*-butyldiphenylsilyloxy)propanal diethyl acetal (10d) Obtained from **9d** and purified by column chromatography (EtOAc/hexanes=1/9, v/v) in 70% yield (3 5 g scale) as a yellowish oil, R_f 0 53 (EtOAc/hexanes=1/4, v/v), α_D^{22}=-16 2 (c=2 6, MeOH), ^{1}H NMR (90 MHz) δ 7 78-7 62 and 7 44-7 30 (m, 10H, 2xC_6H_5), 4 24 (d, 1H, J=4 4 Hz, OCHO), 3 98-3 81 (m, 1H, CH_2C<u>H</u>), 3 72-3 12 (m, 6H, 2xO<u>CH_2</u>CH_3 and <u>CH_2</u>CH), 2 24 (s, 3H, $COCH_3$), 1 17 and 0 95 (2xt, 6H, J=7 2 Hz, 2xOCH_2<u>CH_3</u>), 1 04 (s, 9H, $C(CH_3)_3$)

(*R*)-3-acetylthio--2-(2-tetrahydropyranyloxy)propanal diethyl acetal (10e) Obtained from **9e** and purified by column chromatography (EtOAc/hexanes=1/4, v/v) in 68% yield (3 9 g scale) as a mixture of diastereomers as a yellowish oil, R_f 0 36 (EtOAc/hexanes=1/4, v/v), CIMS(70eV), m/z (relative intensity) 305 ([M-1]$^+$ 0 3), 261 ([M-OC_2H_5]$^+$, 6), 103 ([$HC(OC_2H_5)_2$]$^+$, 100), 85 ([C_5H_9O]$^+$, 92), 75 ([$C_3H_7O_2$]$^+$, 19), ^{1}H NMR (90 MHz) δ 4 92 and 4 80 (2xbr t, 1H, OC<u>H</u>(CH_2)$_3$), 4 53 and 4 43 (2xd, 1H, J=4 6 Hz and J=6 2 Hz, OCHO), 4 10-2 86 (m, 9H 2xO<u>CH_2</u>CH_3, O<u>CH_2</u>(CH_2)$_3$ and SCH_2CH), 2 32 (s, 3H, $COCH_3$), 1 96-1 50 (m, 6H, OCH_2(<u>CH_2</u>)$_3$), 1 21 and 1 19 (2xt, 6H, J=7 1 Hz, 2xOCH_2<u>CH_3</u>)

(*R*)-2-acetoxy-3-acetylthio-propanal diethyl acetal (10f) Obtained from **9f** and purified by column chromatography (EtOAc/hexanes=1/8, v/v) in 31% yield, R_f 0 17 (EtOAc/hexanes=1/7, v/v), EIMS(70eV), m/z (relative intensity) 219 ([M-OC_2H_5]$^+$, 4), 103 ([$HC(OC_2H_5)_2$]$^+$, 100), ^{1}H NMR (90 MHz) δ 5 16-4 97 (m, 1H, CH_2C<u>H</u>CH), 4 52 (d, 1H, J=5 4 Hz, CH_2CHC<u>H</u>), 3 94-3 46 (m, 4H, 2xO<u>CH_2</u>CH_3), 3 38-2 78 (m, 2H, <u>CH_2</u>CHCH), 2 33 (s, 3H, $SCOCH_3$), 2 08 (s, 3H, $OCOCH_3$), 1 22 and 1 21 (2xt, 6H, J=7 0 Hz, 2xOCH_2<u>CH_3</u>) and **(*R*)-3-acetoxy-2-acetylthio-propanal diethyl acetal (38)** in 40% yield, R_f 0 26 (EtOAc/hexanes=1/7, v/v), ^{1}H NMR (90 MHz) δ 5 30-5 09 (m, 1H, CH_2C<u>H</u>CH), 4 53 (d, 1H, J=4 9 Hz, CH_2CHC<u>H</u>), 3 92-3 28 (m, 6H, <u>CH_2</u>CHCH and 2xO<u>CH_2</u>CH_3), 2 84 (s, 3H, $SCOCH_3$), 2 09 (s, 3H, $OCOCH_3$), 1 24 (t, 6H, 2xOCH_2<u>CH_3</u>)

Syntheses of chloromethyl sulfides **11**

The chloromethyl sulfides **11a-e** were prepared via the corresponding thiols in yields of 96%, 89%, 99%, 97% and 97%, respectively, based on the thioacetates **10a-e**, following the same procedure as described in chapter 2

(*R*) Methyl-3-(chloromethylthio)-2-(2-tetrahydropyranyloxy)propanoate (11a): Thiol obtained as a mixture of diastereomers, ^{1}H NMR (90 MHz) δ 4 84-4 75 (m, 1H, OC<u>H</u>(CH_2)$_3$), 4 38 and 4 23 (2xt, 1H, J=5 4 Hz and J=6 0 Hz, SCH_2C<u>H</u>), 4 16-3 33 (m, 2H, O<u>CH_2</u>(CH_2)$_3$), 3 02-2 77 (m, 2H, S<u>CH_2</u>CH), 3 78 (s, 3H, CO_2CH_3), 1 89-1 50 (m, 7H, OCH_2(<u>CH_2</u>)$_3$ and SH), **11a** obtained as a mixture of diastereomers, ^{1}H NMR (90 MHz) δ 5 06-4 56 (m, 3H, OC<u>H</u>(CH_2)$_3$ and $ClCH_2S$), 4 66 and 4 39 (dd and t, 1H, J=5 0 Hz, J=7 0 Hz and J=6 1 Hz, SCH_2C<u>H</u>),

4 08-3 31 (m, 2H, O$\underline{CH_2}(CH_2)_3$), 3 78 (s, 3H, CO_2CH_3), 3 23-3 07 (m, 2H, S$\underline{CH_2}$CH), 1 89-1 54 (m, 6H, $OCH_2(\underline{CH_2})_3$)

(*R*)-2-allyloxy-3-(chloromethylthio)propanal diethyl acetal (11b) Thiol ^{1}H NMR (90 MHz) δ 6 19-5 76 (m, 1H, H_2C=$\underline{CH}$ CH_2), 5 42-5 11 (m, 2H, $\underline{H_2C}$=CH-CH_2), 4 48 (d, 1H, J=5 7 Hz, OCHO), 4 39-4 02 (m, 2H, H_2C=CH-$\underline{CH_2}$), 3 86-3 36 (m, 5H, 2xO$\underline{CH_2}CH_3$ and S$CH_2\underline{CH}$), 3 04-2 48 (m, 2H, S$\underline{CH_2}$CH), 1 63 (dd, 1H, J=7 3 Hz and J=9 0 Hz, SH), 1 24 and 1 22 (2xt, 6H, J=6 9 Hz, 2xO$CH_2\underline{CH_3}$), **11b** EIMS(70eV), m/z (relative intensity) 223 ([M-OC_2H_5]$^+$, 0 8), 103 ([HC(OC_2H_5)$_2$]$^+$, 16), 75 ([$C_3H_7O_2$]$^+$, 9), 41 ([C_3H_5]$^+$, 100), ^{1}H NMR (90 MHz) δ 6 22-5 79 (m, 1H, H_2C=$\underline{CH}$ CH_2), 5 46-5 13 (m, 2H, $\underline{H_2C}$=CH-CH_2), 4 84 (s, 2H, SCH_2Cl), 4 48 (d, 1H, J=5 6 Hz, OCHO), 4 26-4 17 (m, 2H, H_2C=CH-$\underline{CH_2}$), 3 98-3 41 (m, 5H, 2xO$\underline{CH_2}CH_3$ and S$CH_2\underline{CH}$), 3 06 and 2 89 (AB part of ABX spectrum, 2H, J_{AX}=3 2 Hz, J_{BX}=7 3 Hz and J_{AB}=13 9 Hz, S$\underline{CH_2}$CH), 1 24 and 1 22 (2xt, 6H, J=7 0 Hz, 2xO$CH_2\underline{CH_3}$)

(*R*)-2-acetoxy-3-(chloromethylthio)propanal dibenzyl acetal (11c) Thiol ^{1}H NMR (90 MHz) δ 7 29 (s, 10H, 2xC_6H_5), 5 23-5 04 (m, 1H, $CH_2\underline{CH}CH$), 4 83 (d, 1H, J=5 8 Hz, $CH_2CH\underline{CH}$), 4 78-4 48 (m, 4H, 2x$\underline{CH_2}$Ph), 3 11-2 58 (m, 2H, $\underline{CH_2}$CHCH), 2 06 (s, 3H, $OCOCH_3$), 1 36 (t, 1H, J=8 5 Hz, SH), **11c** ^{1}H NMR (90 MHz) δ 7 29 (s, 10H, 2xC_6H_5), 5 36-5 17 (m, 1H, $CH_2\underline{CH}CH$), 4 85-4 49 (m, 7H, $ClCH_2S$, 2xOCH_2Ph and $SCH_2CH\underline{CH}$), 3 22 and 2 93 (AB part of ABX spectrum, 2H, J_{AX}=3 3 Hz, J_{BX}=8 4 Hz and J_{AB}=14 4 Hz, S$\underline{CH_2}$CHCH), 2 04 (s, 3H, CH_3)

(*R*)-2-(*tert*-butyldiphenylsilyloxy)-3-(chloromethylthio)propanal diethyl acetal (11d) Thiol ^{1}H NMR (90 MHz) δ 7 82-7 67 and 7 47-7 30 (m, 10H, 2xC_6H_5), 4 50 (d, 1H, J=5 6 Hz, OCHO), 3 95-3 80 (m, 1H, $CH_2\underline{CH}$), 3 76-3 24 (m, 4H, 2xO$\underline{CH_2}CH_3$), 2 70-2,55 (m, 2H, $\underline{CH_2}$CH), 1 53 (dd, 1H, J=7 8 Hz and J=9 0 Hz, SH), 1 18 and 1 00 (2xt, 6H, J=7 2 Hz, 2xO$CH_2\underline{CH_3}$), 1 07 (s, 9H, C(CH_3)$_3$), **11d** ^{1}H NMR (90 MHz) δ 7 80-7 67 and 7 47-7 31 (m, 10H, 2xC_6H_5), 4 55 (s, 2H, SCH_2Cl), 4 36 (d, 1H, J=4 6 Hz, OCHO), 4 04-3 88 (m, 1H, $CH_2\underline{CH}$), 3 75-3 16 (m, 4H, 2xO$\underline{CH_2}CH_3$), 3 09-2 74(m, 2H, $\underline{CH_2}$CH), 1 19 and 0 97 (2xt, 6H, J=7 1 Hz, 2xO$CH_2\underline{CH_3}$), 1 05 (s, 9H, C(CH_3)$_3$)

(*R*)-3-(chloromethylthio)-2-(2-tetrahydropyranyloxy)propanal diethyl acetal (11e) Thiol ^{1}H NMR (90 MHz) δ 4 91 (m, 1H, O$\underline{CH}(CH_2)_3$), 4 67-4 57 (m, 1H, OCHO), 4 13 3 40 (m, 7H, 2xO$\underline{CH_2}CH_3$, $SCH_2\underline{CH}$ and O$\underline{CH_2}(CH_2)_3$), 3 08-2 57 (m, 2H, S$\underline{CH_2}$CH), 2 06-1 40 (m, 7H, $OCH_2(\underline{CH_2})_3$ and SH), 1 22 and 1 21 (2xt, 6H, J=7 1 Hz, 2xO$CH_2\underline{CH_3}$), **11e** obtained as a mixture of diastereomers, CIMS(70eV), m/z (relative intensity) 313 ([M-1]$^+$, 0 09), 311 ([M-1]$^+$, 0 16), 269 ([M-OC_2H_5]$^+$, 2), 267 ([M-OC_2H_5]$^+$, 4), 103 ([HC(OC_2H_5)$_2$]$^+$, 99), 85 ([C_5H_9O]$^+$, 100, 75 ([$C_3H_7O_2$]$^+$, 16), ^{1}H NMR (90 MHz) δ 5 18-4 54 (m, 4H, $ClCH_2Cl$, OCHO and $SCH_2\underline{CH}$), 3 16, 3 13 and 2 95 (2xAB part of ABX spectrum, 2H, J_{AX}=3 2 Hz, J_{BX}=7 2 Hz and J_{AB}=13 9 Hz, S$\underline{CH_2}$CH), 1 97-1 52 (m, 6H, OCH($\underline{CH_2}$)$_3$), 1 23 and 1 21 (2xt, 6H, J=7 2 Hz, 2xO$CH_2\underline{CH_3}$)

Alkylation of the N_b-protected N_b-oxo tryptamines **3**,**4** with the chloromethyl sulfides **11a-e** followed by removal of the N_b-Teoc or N_b-Aloc groups to give **40a e**

40a and **41** Nucleophilic coupling was carried out as described in chapter 2 on a 7 0 mmol scale from **3** and **11a** To prevent side reactions caused by acid induced THP-group migration it is essential to add sat $NaHCO_3$ (10 mL) before removal of the solvent after the coupling of **3** and **11a** After work-up crude **39a** was obtained as a mixture of diastereomers as an oil R_f 0 48 (EtOAc/hexanes=1/1, v/v), CIMS(100eV), m/z (relative intensity) 552 ([M]$^+$, 0 3), 144 ([$C_{10}H_{10}N$]$^+$, 24), 130 ([C_9H_8N]$^+$, 38), 85 ([C_5H_9O]$^+$, 86), 73 ([$Si(CH_3)_3$]$^+$, 38), ^{1}H NMR (90 MHz) δ 8 14 (br s, 1H, indole-NH), 7 69-7 59 (m, 1H, indole-C(7)H), 7 37-7 05 (m, 4H, indole-C(2)H and C(4) C(6)H_3), 5 06 and 4 97 (2xs, 2H, SCH_2O), 4 81 (br t, 1H, OCHO), 4 61 and 4 36 (2xd, 1H, J=5 0 Hz and J=6 8 Hz, $SCH_2\underline{CH}$), 4 18-3 73 (m, 6H, O$\underline{CH_2}CH_2Si$, O$\underline{CH_2}(CH_2)_3$ and C(3)$CH_2\underline{CH_2}$N), 3 73 (s, 3H, $COOCH_3$), 3 17-3 02 (m, 4H, C(3)$\underline{CH_2}CH_2$N and S$\underline{CH_2}$CH), 1 71-1 51 (m, 6H, $OCH_2(\underline{CH_2})_3$), 0 93-0 74 (m, 2H, $OCH_2\underline{CH_2}Si$), 0 00 ($Si(CH_3)_3$) Followed by removal of the Teoc group of **39a** as described in chapter 2 to give 2 5 g (86% from **3**) of **40a** after column chromatography (EtOAc/hexanes/triethylamine=1/1/0 01, v/v) as a mixture of diastereomers as a colorless oil R_f 0 32 (EtOAc/hexanes=1/1, v/v), ^{1}H NMR (90 MHz) δ 8 20 (br s, 1H, indole NH), 7 66-7 57 (m, 1H, indole-C(7)H), 7 40-7 04 (m, 4H, indole-C(2)H and C(4)-C(6)H_3), 4 97 and 4 91 (2xs, 2H, SCH_2O), 4 77 (br t, 1H, OCHO), 4 57 and 4 30 (2xdd, 1H, J=6 3 Hz, J=6 3 Hz and J=5 4 Hz, 6 3 Hz, $SCH_2\underline{CH}$), 3 74 (s, 3H, $COOCH_3$), 3 96-2 95 (m, 6H, C(3)$\underline{CH_2}CH_2$N and S$\underline{CH_2}$CH), 1 72-1 49 (m, 6H, $OCH_2(\underline{CH_2})_3$)

41 The alkylation was carried out as described for **39a** with the exception of the addition of sat $NaHCO_3$ after the alkylation The reaction mixture was further worked-up in the standard manner and the residue was subjected to column chromatography (EtOAc/hexanes=1/2, v/v) to yield (besides several undefined side products) 1 2 g (58%) of a product as a colorless oil (R_f 0 32, EtOAc/hexanes=1/1, v/v, not further characterized) Of 1 0 g (1 85 mmol) of this product the Teoc group was removed following the standard procedure described in chapter 2, to yield 558 mg (73%) of **41** after purification by column chromatography (EtOAc/hexanes=1/2, v/v) as a colorless oil as mixture of diastereomers, R_f 0 18 (EtOAc/hexanes=1/1, v/v), UV (methanol) λ_{max} 275 0 (sh), 280 0, 291 1 (sh), CIMS(100eV), m/z (relative intensity) 408 ($[M]^+$, 1 4), 214 ($[C_{14}H_{16}NO]^+$, 11), 144 ($[C_{10}H_{10}N]^+$, 17), 130 ($[C_9H_8N]^+$, 100), 85 ($[C_5H_9O]^+$, 50), ^1H NMR (90 MHz) δ 7 67-7 02 (m, 5H, indole C(2)H and C(4)-C(7)H_4), 6-4 5 (very br s, exchangeable, 2H, NH and OH), 5 46 and 5 43 (2xm, NCHO), 4 97 and 4 89 (AB, 2H, J_{AB}=11 7 Hz, OCH_2S), 4 50 and 4 49 (2xt, 1H, J=8 5 Hz, $SCH_2\underline{CH}$), 4 22-4 04 (m, 1H, $OC\underline{H}H(CH_2)_3$), 3 88-3 59 (m, 1H, $OCH\underline{H}(CH_2)_3$), 3 75 and 3 74 (2xs, 3H, OCH_3), 3 40-3 23 (m, 2H, $C(3)CH_2\underline{CH_2}$), 3 07-2 93 (m, 4H, $C(3)\underline{CH_2}CH_2$ and $S\underline{CH_2}CH$), 2 43-1 58 (m, 6H, $OCH_2(\underline{CH_2})_3$)

40b The same procedure was followed as described for **39a** starting from **3** and **11b**, with the exception that an equimolar amount chloromethyl sulfide **11b** was used with respect to tryptamine derivative **3**, to yield 83% (3 8 mmol scale) of **39b** after purification by column chromatography (EtOAc/hexanes=1/2, v/v) as a colorless oil, R_f 0 33 (EtOAc/hexanes=1/2, v/v), EIMS(70eV), m/z (relative intensity) 552 ($[M]^+$, 0 4), 189 (13), 144 ($[C_{10}H_{10}N]^+$, 14), 130 ($[C_9H_8N]^+$, 63), 103 ($[HC(OC_2H_5)_2]^+$, 100), ^1H NMR (90 MHz) δ 8 04 (br s, 1H, indole-NH), 7 69-7 58 (m, 1H, indole-C(7)H), 7 40-7 02 (m, 4H, indole-C(2)H and C(4)-C(6)H_3), 6 15-6 73 (m, 1H, $H_2C=\underline{CH}\text{-}CH_2$), 5 36 5 07 (m, 2H, $\underline{H_2C}$=CH CH_2), 5 00 (s, 2H, OCH_2S), 4 47 (d, 1H, J=5 6 Hz, $SCH_2CH\underline{CH}$), 4 22-4 13 (m, 2H, H_2C=CH-$\underline{CH_2}$), 4 09-3 45 (m, 9H, $2xO\underline{CH_2}CH_3$, indole-C(3)$CH_2\underline{CH_2}$, $SCH_2\underline{CH}CH$ and $SiCH_2\underline{CH_2}$), 3 18-2 73 (m, 4H,indole-C(3)$\underline{CH_2}CH_2$ and $S\underline{CH_2}CHCH$), 1 21 and 1 19 (2xt, 6H, J=7 0 Hz, $2xOCH_2\underline{CH_3}$), 0 91-0 72 (m, 2H, $Si\underline{CH_2}CH_2$), 0 00 (s, 9H, $Si(CH_3)_3$) Followed by removal of the Teoc group as described in chapter 2 to yield 73% of **40b** after purification by column chromatography (EtOAc/hexanes=1/2, v/v) as an oil, R_f 0 25 (EtOAc/hexanes=1/2, v/v), α_D^{22}= 16 1 (c=5 85, MeOH), CIMS(70eV), m/z (relative intensity) 409 ($[M+1]^+$, 1 2), 144 ($[C_{10}H_{10}N]^+$, 21), 130 ($[C_9H_8N]^+$, 91), 103 ($[HC(OC_2H_5)_2]^+$, 100), ^1H NMR (90 MHz) δ 8 24 (br s, 1H, indole-NH), 7 77-7 66 (m, 1H, indole C(7)H), 7 53-7 11 (m, 4H, indole-C(2)H and C(4)-C(6)H_3), 6 24-5 83 (m, 1H, $H_2C=\underline{CH}\text{-}CH_2$), 6 03 (br s, 1H, ONH), 5 44-5 16 (m, 2H, $\underline{H_2C}$=CH-CH_2), 4 99 (s, 2H, OCH_2S), 4 56 (d, 1H, J=5 7 Hz, $SCH_2CH\underline{CH}$), 4 29-4 16 (m, 2H, H_2C=CH-$\underline{CH_2}$), 3 91-3 54 (m, 5H, $2xO\underline{CH_2}CH_3$ and $SCH_2\underline{CH}CH$), 3 47-2 76 (m, 6H, indole-C(3)CH_2CH_2 and $S\underline{CH_2}CHCH$), 1 33 and 1 29 (2xt, 6H, J=7 0 Hz, $2xOCH_2\underline{CH_3}$)

40c For the coupling reaction the same procedure was followed as described for **39b** starting from **4** and **11c** and after workup the crude product (±5 mmol) was dissolved in acetonitrile/water (50 mL, 4/1, v/v) and triethylammonium formate (20 g, 46 5 mmol) was added An argon stream was passed through the resulting solution for 15 min to remove oxygen and palladium(II)acetate (30 mg, 0 13 mmol) and triphenylphosphine (170 mg, 0 65 mmol) were added After heating at reflux for 45 min all starting material had disappeared and subsequently the volatiles were removed *in vacuo* The residue was dissolved in EtOAc (75 mL) and washed with water (2x50 mL) and dried with brine and $MgSO_4$ The solvent was removed *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/1, v/v) to yield 1 2 g (45%) of **39c** as a colorless oil, R_f 0 50 (EtOAc/hexanes=1/1, v/v), CIMS(70eV), m/z (relative intensity) 535 ($[M+1]^+$, 0 03), 427 ($[M-C_7H_7O]^+$, 0 3), 227 ($[HC(OC_7H_7)_2]^+$, 1), 179 (13), 144 ($[C_{10}H_{10}N]^+$, 20), 130 ($[C_9H_8N]^+$, 23), 91 ($[C_7H_7]^+$, 100), ^1H NMR (90 MHz) δ 7 97 (br s, 1H, indole-NH), 7 63-7 50 (m, 1H, indole-C(7)H), 7 38-7 00 (m, 4H, indole-C(2)H and C(4)-C(6)H_3), 7 28 (s, 10H, $2xC_6H_5$), 5 96 (br s, 1H, HNO), 5 40-5 21 (m, 1H, $SCH_2\underline{CH}CH$), 4 86-4 47 (m, 7H, $2xOCH_2Ph$, $SCH_2CH\underline{CH}$ and SCH_2O), 3 33-2 73 (m, 6H, $S\underline{CH_2}CHCH$ and indole-C(3)CH_2CH_2), 2 04 (s, 3H, CH_3)

40d The same procedure was followed as described for **39b** starting from **4** and **11d** to yield after column chromatography (EtOAc/hexanes=1/3, v/v) 83% (2 4 mmol scale) of **39d** as a colorless oil, R_f 0 18 (EtOAc/hexanes=1/4, v/v), CIMS(70eV), m/z (relative intensity) 644 ($[M+1\text{-}OC_2H_5]^+$, 0 9), 199 ($[C_{13}H_{11}SiO]^+$, 100), 144 ($[C_{10}H_{10}N]^+$, 11), 130 ($[C_9H_8N]^+$, 27), 103 ($[HC(OC_2H_5)_2]^+$, 38), ^1H NMR (90 MHz) δ 8 02 (br s, 1H indole-NH), 7 80-7 56 and 7 39-6 95 (m, 15H, $2xC_6H_5$, indole-C(2)H and C(4)-C(7)H_4), 5 98-5 56 (m, 1H, $H_2C=\underline{CH}\text{-}CH_2$), 5 32-5 07 (m, 2H, $\underline{H_2C}$=CH-CH_2), 4 82 (s, 2H, OCH_2S), 4 47-4 32 (m, 3H, H_2C=CH-$\underline{CH_2}$ and $SCH_2CH\underline{CH}$), 3 96-2 89 (m, 11H, $2xO\underline{CH_2}CH_3$, indole-C(3)CH_2CH_2 and SCH_2CHCH), 1 16 and 0 94 (2xt, 6H

J=6 9 Hz, 2xOCH$_2$CH$_3$), 1 05 (s, 9H, C(CH$_3$)$_3$) Followed by removal of the Aloc group as described for **40c** to give 1 13 g (78%) of **40d** after column chromatography (EtOAc/hexanes=1/4, v/v) as a colorless oil, R_f 0 18 (EtOAc/hexanes=1/4, v/v), CIMS(70eV), m/z (relative intensity) 576 ([M 30]$^+$, 4), 144 ([C$_{10}$H$_{10}$N]$^+$, 15), 130 ([C$_9$H$_8$N]$^+$, 79), 103 ([HC(OC$_2$H$_5$)$_2$]$^+$, 100), ^{1}H NMR (90 MHz) δ 8 00 (br s, 1H, indole-NH), 7 81-7 54 and 7 37-6 96 (m, 15H, 2xC$_6$H$_5$ and indole C(2)H and C(4)-C(7)H$_4$), 5 76 (br s, 1H, HNO), 4 69 (s, 2H, OCH$_2$S), 4 40 (d, 1H, J=4 2 Hz, SCH$_2$CHCH), 4 00 3 86 (m, 1H, SCH$_2$CHCH), 3 71-2 80 (m, 10H, indole-C(3)CH$_2$CH$_2$, SCH$_2$CHCH and 2xOCH$_2$CH$_3$), 1 16 and 0 97 (2xt, 6H, J=6 9 Hz, 2xOCH$_2$CH$_3$), 1 07 (s, 9H, C(CH$_3$)$_3$)

40e The same procedure was followed as described for **39b** starting from **4** and **11e** For removal of the N$_b$-Aloc group an alternative method was used The crude **39e** (±1 6 mmol) was dissolved in EtOAc/dimethyl sulfoxide/morpholine (50 mL, 2/1/1, v/v) and oxygen was removed from the resulting solution by passing an argon stream through the solution for 15 min After addition of Pd(PPh$_3$)$_4$ (30 mg, 0 026 mmol) the reaction mixture was allowed to stand over night at room temperature The reaction mixture was diluted with EtOAc (50 mL) and washed with 5 portions water (50 mL) and brine The organic layer was dried (MgSO$_4$) and the solvent was removed *in vacuo* The residue was subjected to column chromatography (EtOAc/hexanes/Et$_3$N=3/7/0 01, v/v) to yield 422 mg (81%) of **40e** as a mixture of diastereomers as a colorless oil, R_f 0 37 (EtOAc/hexanes=1/1), CIMS(70eV), m/z (relative intensity) 453 ([M+1]$^+$, 0 6), 144 ([C$_{10}$H$_{10}$N]$^+$, 22), 130 ([C$_9$H$_8$N]$^+$, 31), 103 ([HC(OC$_2$H$_5$)$_2$]$^+$, 65), 85 ([C$_5$H$_9$O]$^+$, 100), ^{1}H NMR (90 MHz) δ 8 20 (br s, 1H, indole NH), 7 66-7 52 (m, 1H, indole-C(7)H), 7 41-7 00 (m, 4H, indole-C(2)H and C(4)-C(6)H$_3$), 5 96 (br s, 1H, HNO), 4 97-4 82 (m, 1H, OCH(CH$_2$)$_3$), 4 88 (s, 2H, OCH$_2$S), 4 62 and 4 55 (2xd, 1H, J=4 4 Hz and J=5 8 Hz, SCH$_2$CHCH), 3 97-2 76 (m, 13H, 2xOCH$_2$CH$_3$, indole-C(3)CH$_2$CH$_2$, OCH$_2$(CH$_2$)$_3$ and SCH$_2$CHCH), 1 91 1 44 (m, 6H, OCH$_2$(CH$_2$)$_3$), 1 34 1 13 (m, 6H, 2xOCH$_2$CH$_3$)

42 To a mixture of HOAc/THF/H$_2$O (5 mL, 4/2/1, v/v/v) was added **41** (120 mg, 0 29 mmol) The resulting clear solution was allowed to stand over night at room temperature EtOAc (50 mL) was added and the solution was neutralized by the careful addition of solid NaHCO$_3$ The organic layer was washed with brine and dried (MgSO$_4$) and the volatiles were evaporated *in vacuo* to yield 115 mg (96%) of **42** as a mixture of diastereomers as a colorless oil which was essentially homogeneous on TLC, R_f 0 08 (EtOAc/hexanes=1/1, v/v), CIMS(70eV), m/z (relative intensity) 408 ([M]$^+$, 0 1), 171 (100), 144 ([C$_{10}$H$_{10}$N]$^+$, 21), 130 ([C$_9$H$_8$N]$^+$, 24), ^{1}H NMR (90 MHz) δ 8 17 (br s, 1H, indole NH), 7 43 6 92 (m, 4H, indole-C(2)H and C(4) C(7)H$_4$), 4 95 and 4 84 (AB, 2H, J_{AB}=11 8 Hz, OCH$_2$S), 4 40 (br t, 1H, J=4 6 Hz, SCH$_2$CH), 4 22 4 04 (m, 1H, C(2)CHO), 3 74-2 69 (m, 8H, OCH$_2$(CH$_2$)$_3$, C(3)CH$_2$CH$_2$N and SCH$_2$CH), 3 74 and 3 72 (2xs, 3H, OCH$_3$), 1 87-1 50 (m, 6H, OCH$_2$(CH$_2$)$_3$)

Cyclization reactions

Entry 1 Procedure A was followed as described in the exp part of chapter 2 **40a** (2 65 g, 6 5 mmol), DIBAL (19 5 mL of a 1M solution in dichloromethane) and TFA (0 5 mL), followed by work-up Removal of the THP protective group was accomplished by treatment with HOAc/THF/H$_2$O (4/2/1, v/v/v, 100 mL) at 45°C for 5 h The volatiles were evaporated *in vacuo* and the residue was dissolved in EtOAc (50 mL) This solution was washed with sat NaHCO$_3$ and brine After drying (MgSO$_4$) and evaporation of the solvent *in vacuo* the residue was subjected to column chromatography (EtOAc/hexanes=1/4, v/v) to yield 1 00 g (56%) of **1**, α_D^{22}=-8 0 (c=4 24, EtOAc, ee=31%) and 50 mg (3%) of **43**, α_D^{22}=+49 0 (c=3 70, EtOAc, ee=29%) For further spectroscopic and analytical data of **1** and **43**, see chapter 2

Entry 2 **1** (0 94 g, 2 30 mmol) was dissolved in HCO$_2$H/H$_2$O (9/1, v/v, 100 mL) and stored in the refrigerator (5°C) over night The volatiles were evaporated at high vacuum (0 5 mmHg) and the residue was dissolved in EtOAc This solution was washed with sat NaHCO$_3$, brine and dried (MgSO$_4$) The residue was dissolved in acetonitrile/water (4/1, v/v, 25 mL) and triethylammonium formate (3 g) was added The solution was saturated with argon (to remove oxygen) and triphenylphosphine (25 mg, 0 095 mmol) and palladium(II)acetate (8 mg, 0 036 mmol) were added, followed by heating at reflux for 2 h The volatiles were evaporated *in vacuo* and the residue was dissolved in EtOAc and subsequently washed with sat NaHCO$_3$ and brine After drying (MgSO$_4$) the solvent was evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/4, v/v) to yield 421 mg (66%) **1**, α_D^{22}=-17 9 (c=3 20, EtOAc, ee=69%) and 99 mg (16%) **43**, α_D^{22}=+117 9 (c=2 62, EtOAc, ee=70%) For further spectroscopic and analytical data of **1** and **43** see chapter 2

Entry 3 **40c** (1 00 g, 1 87 mmol) was dissolved in HCO_2H/H_2O (9/1, v/v, 100 mL) and an argon stream was passed through the resulting solution for 15 min in order to remove oxygen The reaction mixture was heated at 60°C under an argon atmosphere and the progress of the reaction was monitored by TLC (EtOAc/hexanes=1/2, v/v) After completion of the reaction (1 5 h) the solution was diluted with EtOAc (100 mL) and subsequently neutralized by the careful addition of $NaHCO_3$ The organic layer was then washed with brine and dried ($MgSO_4$), followed by evaporation of the volatiles*in vacuo* The residue was dissolved in MeOH, and KCN (100 mg, 1 54 mmol) was added After standing over night the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/4, v/v) to yield 185 mg (38%) of **1** and 35 mg (7%) of **43** For further spectroscopical and analytical data of **1** and **43** see chapter 2 and table 3 3

Entry 4 In HCO_2H/H_2O (9/1, v/v, 90 mL) was dissolved **40d** (770 mg, 1 27 mmol, obtained by AD of acrolein diethyl acetal) After 1 h the reaction mixture was diluted with EtOAc (100 mL) and neutralized by the careful addition of $NaHCO_3$ The organic layer was then washed with brine and dried ($MgSO_4$), followed by evaporation of the volatiles *in vacuo* The residue was dissolved in dry THF (25 mL) and tetrabutylammonium fluoride (1 5 mL of a 1 M solution in THF) was added After 30 min the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/4, v/v) to yield 190 mg (54%) of **1** and 100 mg (28%) of **43** For further spectroscopical and analytical data of **1** and **43** see chapter 2 and table 3 3

Entry 5 The same procedure was followed as described for entry 5 on a 1 80 mmol scale The used **40d** was derived from the AD of acrolein benzodioxepine acetal For further spectroscopic and analytical data of **1** and **43**, see chapter 2, scheme 3 16 and table 3 3

Entry 6 When the same procedure was followed as described for entry 2, only 2 products emerged which moved slower on TLC than **1** or **43** Therefore, an alternative procedure was followed as described for the PS condensations of acetals in chapter 2 **40e** (280 mg, 0 62 mmol) was dissolved in chloroform (20 mL) and TFA/H_2O (1/9, v/v, 1 0 mL) was added The resulting suspension was stirred over night at room temperature On TLC (EtOAc/hexanes=1/1 v/v), besides the presence of starting material, again the 2 slow moving fractions were visible The solution was neutralized with $NaHCO_3$, washed with brine and dried (Na_2SO_4) After evaporation of the solvent *in vacuo* the residue was subjected to column chromatography (EtOAc/hexanes=1/1, v/v) to yield 36 mg (13%) starting material **40e** (fraction 1), R_f 0 50, 115 mg (41%), R_f 0 28 (fraction 2), and 65 mg (23%), R_f 0 12 (fraction 3) The 90 MHz NMR spectrum of the 3rd fraction showed close resemblence with compound **42** In the NMR spectra of both the 2nd and 3rd fractions the diethyl acetal moiety was visible Most probably the THP-group of the components in fraction 2 shifted to the alkoxyamine nitrogen The CIMSspectra of the 2nd and 3rd fractions both showed $[M\text{-}C_2H_5O]^+$ peaks (M=407) indicating only a shift of the THP group in the starting compound

Table 3.3 Optical rotations and ee values of **1** and **43** derived from AD of acrolein acetals

	entry[a]	source	ee after AD[b]	α_D^{22} (c, mg/mL)[c]	calcd α_D^{22} (100% ee)
1	3	AD dibenzyl acetal **14**	60 %	-14 7 (3 00)	-24 5
(trans)	4	AD diethyl acetal **12**	54 %	-13 8 (4 85)	-25 6
	5	AD benzodioxepine acetal **15**	97 %	-26 8 (4 78)	-27 6
43	3	AD dibenzyl acetal **14**	60 %	+100 4 (2 45)	+167 3
(cis)	4	AD diethyl acetal **12**	54 %	+88 5 (4 60)	+163 9
	5	AD benzodioxepine acetal **15**	97 %	+166 5 (3 40)	+171 6

[a] See scheme 3 16 [b] See table 3 1 [c] All measured in EtOAc The optical rotations of **1** varied greatly in MeOH

Introduction of the amino group via the Mitsunobu reaction.

45a To **1** (100 mg, 0 36 mmol, ee=30%), phthalimide (80 mg, 0 54 mmol) and triphenylphosphine (190 mg 0 72 mmol) in dry THF (0 5 mL), diisopropylazodicarboxylate (0 11 mL, 110 mg, 0 54 mmol) was added dropwise

with a syringe over a period of 5 min causing a slight exothermic reaction The progress of the reaction was monitored by HPLC (acetonitrile/water =3/7, v/v, flow=1 mL/min , λ=254 nm), retention time (min) phthalimide (3 0), triphenylphosphine oxide (4 0), **1** (4 8), **45a** (6 4) and triphenylphosphine 8 8)) After 2 h the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/3, v/v) to yield 129 mg (84%) of **45a** as a white amorphous solid which failed to crystallize, R_f 0 47 (EtOAc/hexanes=1/1, v/v), α_D^{22}=+77 6 (c=1 65, MeOH), CIMS(70eV) exact mass calcd for $C_{22}H_{19}N_3O_3S$ m/z, 405 1147 ([M]$^+$) Found 405 1149, m/z (relative intensity) 405 ([M]$^+$, 0 3), 186 ([$C_{11}H_{10}N_2O$]$^+$, 3), 144 ([$C_{10}H_{12}N$]$^+$, 4 3), 130 ([$C_9H_{10}N$]$^+$, 7 2), 41 (100), ^{1}H NMR (400 MHz) (all assignments are based on NOESY) δ 8 34 (very br s, 1H, indole-NH), 7 90-7 85 (m, 2H, Pht-H_2), 7 73 7 70 (m, 2H, Pht-H_2), 7 49 (d, 1H, J=7 6 Hz, C(8)H), 7 31 (d, 1H, J=7 9 Hz, C(11)H), 7 14 (dt, J=7 1 Hz and J=1 2 Hz, C(9)H), 7 09 (dt, 1H, J=7 8 Hz and J=0 9 Hz, C(10)H), 5 67 (very br s, 1H, C(3)Hα), 4 86 (br t, 1H, J=14 1 Hz, C(13)H), 4 69 (very br s, 1H, C(3)Hβ), 4 32 (s, 1H, C(12b)Hα), 5 15 (dd, 1H, J=14 0 Hz and J=5 3 Hz, C(13)H), 3 94-3 90 (m, 1H, C(1)Hβ), 3 86 (dd, 1H, J=13 0 Hz and J=4 0 Hz, C(6)Hβ), 3 24-3 16 (m, 1H, C(7)Hβ), 3 12 (ddd, 1H, J=12 7 Hz, J=11 7 Hz and J=5 3 Hz, C(6)Hα), 2 66 (dd, 1H, J=15 0 Hz and J=4 7 Hz, C(7)Hα)

45b and **46b** To **1** (50 mg, 0 18 mmol), $Zn(N_3)_2$•2Py (167 mg, 0 54 mmol) and triphenylphosphine (190 mg, 0 72 mmol) in dry toluene (1 0 mL), diisopropylazodicarboxylate (0 14 mL, 150 mg, 0 74 mmol) was added dropwise via a syringe over a period of 5 min causing a slight exothermic reaction The progress of the reaction of the reaction was monitored by TLC (EtOAc/hexanes=1/2, v/v) After 2 h the volatiles were evaporated in vacuo and the residue was subjected to column chromatography (EtOAc/hexanes=1/4) to yield 7 mg (13%) of **46b**, R_f 0 58 (EtOAc/hexanes=1/2, v/v), ^{1}H NMR (90 MHz) δ 8 07 (br s, 1H, indole NH), 7 53 7 00 (m, 4H, indole-C(9)-C(12)H_4), 5 29 and 5 00 (br AB, 2H, J_{AB}=11 4 Hz, C(4)H_2), 4 43 (br d, 1H, J=5 0 Hz, C(13b)H), 4 04-3 93 (m, 2H), 3 77-3 58 (m, 1H), 3 57 3 25 (m, 1H), 3 20-2 47 (m, 3H) and 23 mg (42%) of **45b**, R_f 0 44 (EtOAc/hexanes=1/2, v/v), IR (NaCl), ν (cm^{-1}) 2110 (N_3), CIMS(70eV) exact mass calcd for $C_{14}H_{15}N_5OS$ m/z, 301 0997 ([M]$^+$) Found 301 0995, m/z (relative intensity) 301 ([M]$^+$, 32), 259 ([M-N_3]$^+$, 100), 144 ([$C_{10}H_{10}N$]$^+$, 12), 130 ([C_9C_8N]$^+$, 4) ^{1}H NMR (400 MHz) (all assignments are based on NOE difference spectroscopy) δ 8 03 (br s, 1H, indole-NH), 7 49 (d, 1H, J=7 8 Hz, C(8)H), 7 34 (d, 1H, J=8 0 Hz, C(11)H), 7 18 (dt, 1H, J=7 5 Hz and J=1 1 Hz, C(9)H) 7 11 (dt, 1H, J=7 4 Hz and J=0 9 Hz, C(10)H), 5 30 (br s, 1H, C(3)Hα), 5 06 (very br s, 1H, C(3)Hβ), 4 45 (d, 1H, J=4 9 Hz, C(12b)Hα), 4 04 3 99 (m, 2H, C(1)Hβ and C(13)H), 3 71 (br s, 1H, C(6)Hβ), 3 40 (br s, 1H, C(13)H), 3 15 3 04 (m, 2H, C(7)Hβ and C(6)Hα), 2 68 (br d, 1H, J=10 5 Hz, C(7)Hα) and 15 mg (30%) of recovered **1**

References and Notes

1 Maarseveen, J H van, Scheeren, J W , Kruse, C G *Tetrahedron*, **1993**, 49, 2325
2 a) Mitsunobu, O *Synthesis*, **1981**, 1 b) Hughes, D L *Organic Reactions*, **1992**, vol 42, 335
3 Ragnarsson, U , Grehn, L *Acc Chem Res* , **1991**, 24, 285
4 Arnould, J C , Landier, F , Pasquet, M J *Tetrahedron Lett* , **1992**, 33(47), 7133
5 a) Chen, C-P , Prasad, K and Repic, O *Tetrahedron Lett* , **1991**, 32, 7175 b) Fabiano, E , Golding, B T , Sadeghi, M M *Synthesis*, **1987**, 190
6 Viaud, M-C , Rollin, P *Synthesis*, **1990**, 130
7 Jurczak, J, Pikul S , Bauer, T *Tetrahedron* **1986**, 42, 447
8 Lakhmiri, R Lhoste, P , Sinou, D *Synthetic Comm* , **1990**, 20, 1551
9 It is known that this reaction can fail for unknown reasons (Prof Sinou, *personal communication*)
10 Leftheris, K , Goodman, M *Synthesis*, **1989**, 564
11 Mancuso, A J , Swern, D *Synthesis*, **1981**, 165
12 Corey, E J , Suggs, J W *Tetrahedron Lett* , **1975**, 31, 2647
13 Oi, R , Sharpless, K B *Tetrahedron Lett* , **1992**, 33, 2095
14 Corey, E J , Noe, M C , Sarshar, S *J Am Chem Soc* , **1993**, 115, 3828
15 Sharpless, K B , Amberg, W , Bennani, Y L , Crispino, G A , Hartung, J , Jeong, K-S , Kwong, H-L , Morikawa, K , Wang, Z-M Xu, D , Zhang, X L *J Org Chem* , **1992**, 57, 2768

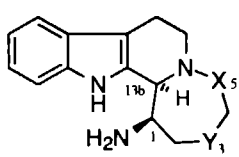
16 An opposite stereochemical outcome of the AD to that predicted by Sharpless' mnemonic picture has been published for 2-substituted allylethers Hale, K J , Manaviazar, S , Peak, S A *Tetrahedron Lett* , **1994**, 35, 425
17 Effenberger, F , Null, V , Ziegler, T *Tetrahedron Lett* , **1992**, 33, 5157
18 Winstein, S , Hanson, C , Grunwald, E *J Am Chem Soc* , **1948**, 70, 812
19 Hermkens, P H H , Maarseveen, J H van, Ottenheijm, H C J , Kruse, C,G , Scheeren, J W *J Org Chem* , **1990**, 55, 3998
20 Compared to the desired product **40a**, in the NMR spectrum of **41** also alterations were visible in the aliphatic part of the THP group in combination with a downfield shift of ±0 7 ppm of the acetal-H signal, which was also present now as a double multiplet (arising from a mixture of diastereomers) The UV spectrum confirmed no disturbance of the aromatic indole moiety
21 Herzig, J , Nudelman, A , Gottlieb, H E , Fischer, B *J Org Chem* , **1986**, 51, 727
22 Verloop, A , Hoogenstraaten, W , Tipker, J , in *"Drug Design"* (E J Ariens, ed), Vol VII, pp 165-207 Academic Press, New York, **1976**
23 a) Ghosh, A , Wang, W , Freeman, J P , Althaus, J S , Von Voigtlander, P F , Scahill, T A , Mizsak S A , Szmuszkovicz, J *Tetrahedron*, **1991**, 47, 8653 b) Freedman, J , Vaal, M J , Huber, E W *J Org Chem* **1991**, 56, 670
24 Koppel, I , Koppel, J , Degerbeck, F , Grehn, L , Ragnarsson, U *J Org Chem* , **1991**, 56, 7172
25 $(Aloc)_2NH$ was synthesized from $(Aloc)_2O$ (Sennyey, G , Barcelo, G , Senet, J-P *Tetrahedron Lett* , **1987**, 28, 5809) as described for $(Boc)_2NH$ by Grehn, L , Ragnarsson, U *Synthesis*, **1987**, 275 A more convenient method is described in ref 4
26 Bayley, H , Standring, D N , Knowles, J R *Tetrahedron Lett* **1978**, 3633
27 Liu, J J , Nakagawa, M , Harada, N , Tsuruoka, A , Hasegawa, A , Ma, J , Hino, T *Heterocycles*, **1990**, 31, 229
28 Yoon, B H , Lyu, H S , Hahn, J H , Ahn, C M *Bull Korean Chem Soc* , **1992**, 13(3), 290
29 Hermkens, P H H , Maarseveen, J H van, Berens, H W , Smits, J M M , Kruse, C G , Scheeren, J W *J Org Chem* , **1990**, 55, 2200
30 Maarseveen, J H van, Hermkens, P H H , De Clercq, E , Balzarini, J , Scheeren, J W , Kruse, C G *J Med Chem* , **1992**, 35, 3223
31 VanAllan, J A *Org Synth Coll Vol IV*, 21
32 DeWolfe, A T *Carboxylic Ortho Acid Derivatives*, Blomquist, A T ed , Academic Press, 1970
33 Machinaga, N , Kibayashi, C *Tetrahedron Lett* , **1989**, 30, 4165

4 Synthesis of a Tetracyclic Eudistomin Desthia Carba Analog

4.1 Introduction

The most intriguing structural unit of the tetracyclic eudistomins is the unprecedented 7-membered [1,6,2]-oxathiazepine ring Probably, this remarkable ring system, which also contains two stereogenic centers, plays an important role in the interaction with the biological target In previous work it was demonstrated that the absolute stereochemistry (*i e* 1*S*,13b*S*), which determines the absolute spatial position of the two basic amino atoms, is essential for biological activity [1] To investigate the relevance of the oxathio acetal moiety for biological activity we considered the synthesis of analogs in which either the sulfur-3 or oxygen-5 atom is replaced by a methylene moiety

chart 4.1



	X	Y
debromo eudistomin K	O	S
desthia carba analog	O	CH_2
desoxa carba analog	CH_2	S

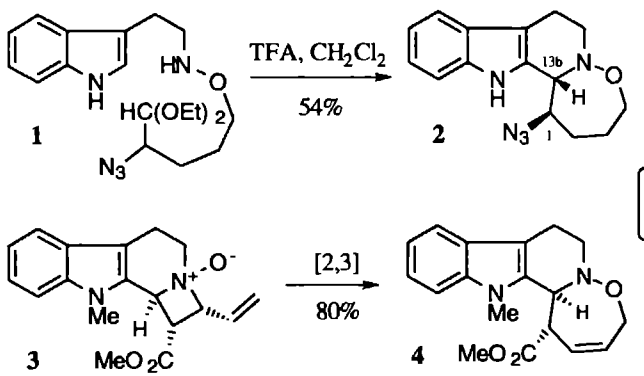
Because the synthesis of these eudistomin carba analogs differs significantly they will be discussed separately In this chapter the synthesis of the desthia carba analog using the *intra*molecular Pictet-Spengler (PS) approach will be described An attempted synthesis of the desoxa carba analog will be presented in chapter 5

For the synthesis of the desthia carba analog the *inter*molecular PS condensation strategy was first considered The most straightforward strategy for closure of the seven membered D-ring is formation of the NO-C bond Earlier studies concerning this type of closure of the D-ring failed due to the higher nucleophilicity of the nitrogen atom giving a cyclic N-oxide [2] Selective alkylation of the hydroxy group in N_b-hydroxy β-carbolines also failed due to the ambident nucleophilicity of the hydroxylamine moiety [3] Therefore, this approach is unlikely to be successful

In the literature two successful approaches to the eudistomin desthia carba skeleton have been described (scheme 4 1) Kirkup and coworkers prepared the 7-membered 1,2-oxazine ring using the intramolecular PS condensation giving **2** in 54% yield [4] Kurihara and coworkers used the Meisenheimer [2,3] sigmatropic rearrangement to obtain **4**, which contains the 2,3-dehydro desthia

carba eudistomin skeleton, in 80% yield.[5] It is important to note that both approaches merely yielded the undesired H(1)-H(13b) trans diastereomers as racemates.

scheme 4.1

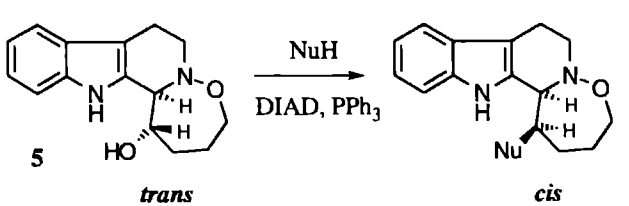


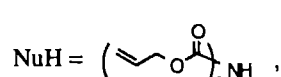
Both approaches only gave the H(1)-H(13b) trans diastereomers

From the experience described in the preceding chapters it may be assumed that in the intramolecular PS approach performed by Kirkup and coworkers some cis diastereomer may be formed because the trans diastereomer was isolated in 54% yield only. Therefore, we undertook the synthesis of the cis desthia carba analog using the same strategy with the azide functionality replaced by a Boc protected amino group. The results are described in section 4.2.

As it was expected that this approach would predominantly result in the undesired trans diastereomer another route was at the same time explored (scheme 4.2). The objective was to synthesize the cis diastereomer **6** by introducting the amino functionality via the *trans*-hydroxy derivative **5** using an S_n2 type reaction. In chapter 3 it was demonstrated that diastereoselective formation of trans-hydroxy eudistomins can be achieved with the intramolecular PS condensation. In this chapter it was also mentioned that the S_n2 strategy failed for the natural eudistomin series because the highly nucleophilic sulfur atom brought about a transannular neighboring group participation leading to the formation of undesired products. In the case of the conversion of **5** into **6** the prospects are much better because of the absence of the sulfur atom.

scheme 4.2



NuH =  , HN_3

6a: Nu=$(Aloc)_2N$
6b: Nu=N_3

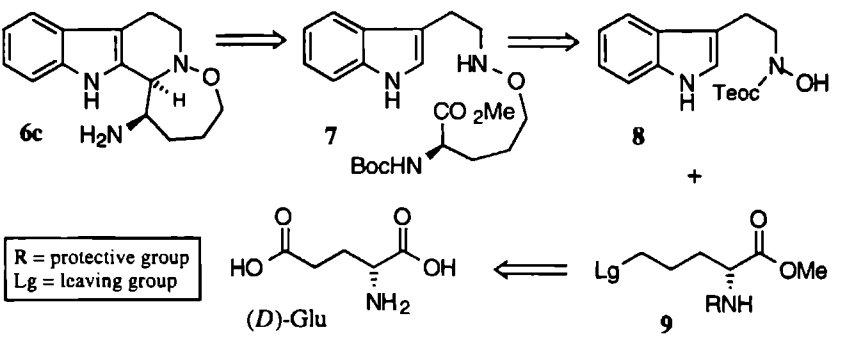
For the introduction of the amino group with inversion the Mitsunobu procedure was again followed. Both diallyl imidodicarbonate and hydrazoic acid were investigated as nucleophiles in the

Mitsunobu reaction, as is depicted in scheme 4.2. The results of these experiments are described in section 4.3.

4.2 Direct Approach Based on *D*-glutamic Acid

Retrosynthetic analysis of the intramolecular PS approach (scheme 4.3) shows that for the tryptamine part N_b-Teoc-N_b-hydroxytryptamine **8** can be used. For the chiral five-carbon α-amino ester fragment **9**, *D*-glutamic acid is a suitable optically pure synthon.

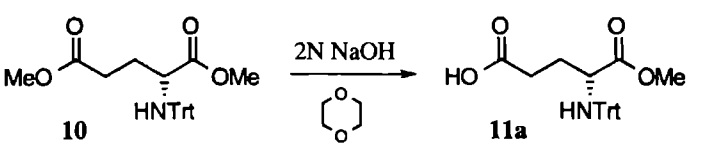
scheme 4.3



4.2.1 Synthesis of the (*D*)-Glutamic Acid Derived Fragment

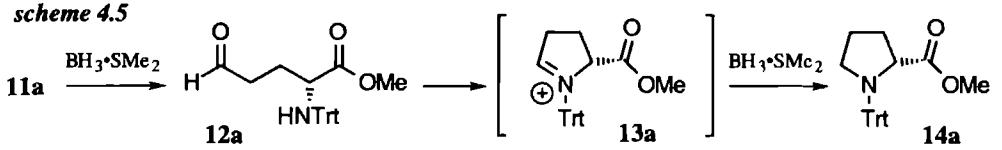
Several strategies are known to discriminate between the two carboxyl groups in glutamic acid. The carboxyl moiety of α-amino acids can be shielded by trityl protection of the amino group. In the case of glutamic acid this gives the possibility for selective chemical manipulation of the γ-carboxyl group. Using this strategy, (*D*)-Trt-Glu(OH)-OMe **11** was synthesized in 76% yield by selective saponification of the γ-ester in (*D*)-Trt-Glu(OMe)-OMe **10** following a modified literature procedure (scheme 4.4).[6]

scheme 4.4



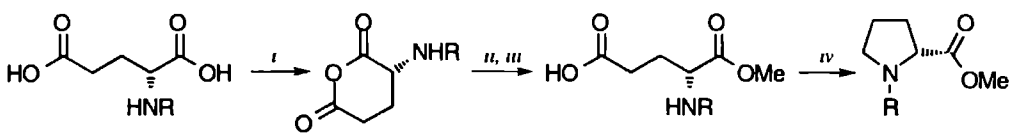
Selective reduction of the terminal carboxyl group with borane dimethylsulfide surprisingly gave Trt-Pro-OMe **14a** in a nearly quantitative yield (scheme 4.5).[7] As shown in scheme 4.5 this can be explained by the formation of a cyclic iminium-ion from the intermediate aldehyde, probably catalyzed by the borane reagent. The highly electrophilic iminium ion is then reduced by the borane dimethylsulfide complex to yield the proline derivative.

scheme 4.5



This surprisingly efficient side reaction can probably be avoided by using an electron withdrawing carbamate type amino protective group thus lowering the nucleophilicity of the nitrogen atom. Therefore, (*D*)-Boc-Glu(OH)-OMe **11b** and (*D*)-Z-Glu(OH)-OMe **11c** were synthesized from the corresponding N-protected (*D*)-Glu derivatives **15b,c** via the cyclic anhydrides **16b,c** by a method described in the literature. This procedure is based on the selective crystallization of the dicyclohexylammonium (DCHA) salt of the γ-carboxylate from a mixture containing the α-carboxylate salt as well (scheme 4.6). [8,9]

scheme 4.6



15b. R=Boc
15c R=Z

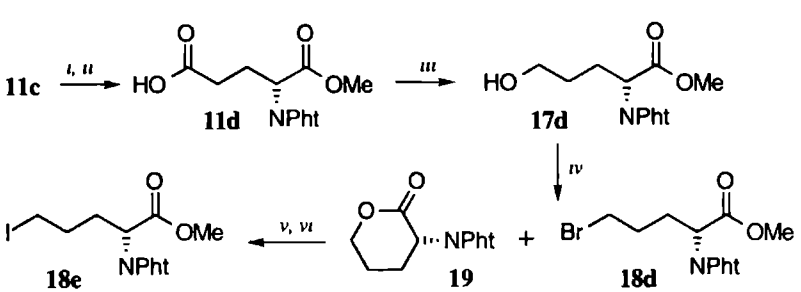
16b,c **11b,c** **14b,c**

i) DCC or acetic anhydride, ii) N,N-dicyclohexyl amine, methanol, iii) 10% aqueous citric acid, iv) BH_3•SMe_2

However, selective reduction of the γ-carboxyl groups in **11b,c** again gave the corresponding protected proline methyl esters **14b,c**[10] in nearly quantitative yields.

By blocking the nucleophilicity of the amino group completely with the phthaloyl protective group the γ-alcohol **17d** was obtained indeed in good yields (scheme 4.7). (*D*)-Pht-Glu(OH)-OMe **11d** was prepared from (*D*)-Z-Glu(OH)-OMe **11c** (scheme 4.6) by hydrogenolytic removal of the Z group followed by re-protection with the phthaloyl group by treatment with N-carbethoxyphthalimide and sodium carbonate to give **11d** in overall 63% yield [11] Reduction of the γ-carboxyl group with borane dimethylsulfide gave γ-alcohol **17d** in quantitative yield

scheme 4.7

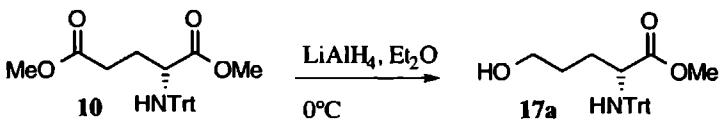


i) 10% Pd(C), H_2, ii) N-carbethoxyphthalimide, Na_2CO_3, H_2O, iii) BH_3•SMe_2, THF, iv) TMSCl, LiBr, MeCN, reflux v) TMSI, CH_2Cl_2, EtOH, vi) CH_2N_2, CH_2Cl_2/Et_2O

For conversion of γ-alcohol **17d** into the γ-bromide **18d** the mild and selective reagent bromotrimethylsilane was chosen.[12] Besides the formation of some γ-bromide **18d** (28%) the main product was the lactone **19** (47%). Probably, the lactonization was catalyzed by the presence of small amounts HBr in the reaction mixture. Ringopening of the lactone **19** with iodotrimethylsilane gave the γ-iodo acid. Treatment of the acid with diazomethane gave **18e** in quantitative yield based on **19**.

Finally, we found that the terminal primary alcohol **17a** could be obtained in one step by selective reduction of (*D*)-Trt-Glu(OMe)-OMe **10** with lithiumaluminum hydride under controlled conditions (scheme 4.8).

scheme 4.8

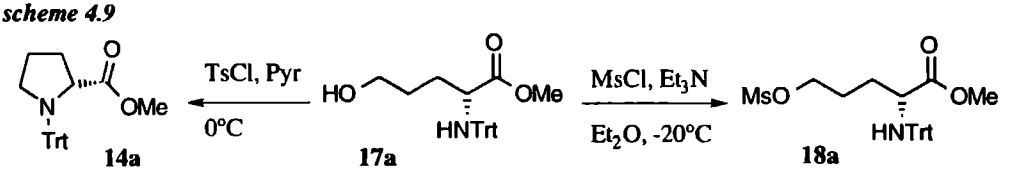


Addition of lithiumaluminum hydride, while carefully monitoring the progress of the reaction by TLC, to a stirred solution (at 0°C) of the dimethyl ester **10** in ether gave **17a** in 85% yield.

As is shown in scheme 4.9 attempted transformation of the alcohol into the tosylate gave Trt-Pro-OMe **14a** as the main product. Although the tosylate was visible on TLC as an intermediate it was not possible to optimize the reaction conditions.

Surprisingly treatment of the alcohol **17a** at low temperature (-20°C) with methanesulfonyl chloride and triethylamine in ether gave the mesylate **18a** in high yield. It should however be noted that mesylate **18a** was only stable below -20°C. At higher temperatures intramolecular nucleophilic ringclosure takes place, yielding some **14a**. The simultaneously formed methanesulfonic acid causes disintegration of the acid labile trityl protected amino acid.

scheme 4.9



Both mesylate **18a** (scheme 4.9) and iodide **18e** (scheme 4.7) have been used in the coupling reaction with the tryptamine fragment.

4.2.2 Coupling of (*D*)-Glutamic Acid Derived Fragments with N_b-Teoc-N_b-hydroxytryptamine, Followed by the PS Condensation

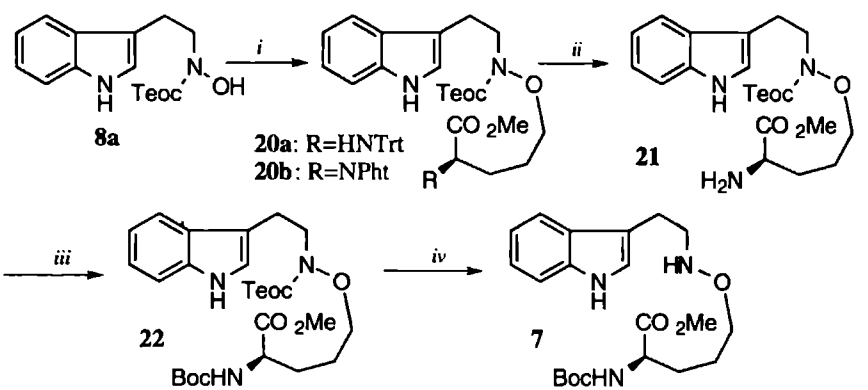
Coupling: Alkylation of the sodium alkoxide of N_b-Teoc-N_b-hydroxytryptamine **8a** with alkyl iodide **18e** was carried out as described for the iodomethyl sulfides in the preceding chapters. In contrast to the iodomethyl sulfides alkyl iodide **18e** reacted very slowly. After allowing the reaction

mixture to stand over night, **20b** was obtained in 62% yield together with 22% recovered alkyliodide **18e**.

Nucleophilic coupling of mesylate **18a** with the sodium alcoholate of N_b-Teoc-N_b-hydroxy tryptamine **8a** in DME was initially carried out at 0°C but at this temperature no conversion of the starting material could be observed. Surprisingly, no proline formation was detected (*vide supra*). However, after standing of the reaction mixture at room temperature over night all starting material had been consumed (scheme 4.10) to give **20a** in 67% yield. As a consequence of the long time of exposure to the basic conditions used in the nucleophilic coupling reaction **20** was isolated as a near racemate in both approaches from.

The phthaloyl and trityl protective groups in **20b** and **20a**, respectively, will not survive the reductive and acid catalyzed steps used in the PS condensation. Therefore, at this stage the phthaloyl and trityl groups were replaced by the Boc group. This Boc group was chosen because it gave the best cis/trans ratio in the intramolecular PS condensation (see chapter 2).

scheme 4.10



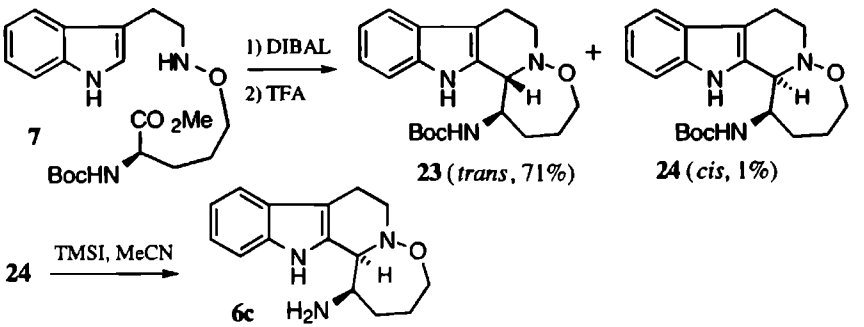
*i) **18a** or **18e**, NaH, DME, rt; ii) **20a**: 1M HCl in F_3CCH_2OH, **20b**: MeOH, H_2N-$NH_3^+OAc^-$; iii) Boc_2O, Et_3N CH_2Cl_2; iv) n-Bu_4NCl, $KF{\cdot}2H_2O$, MeCN, 45°C*

Dephthaloylation was carried out by treatment of **20b** with hydrazine acetate in methanol to give **21** in 70% yield. The trityl group was removed by titration of **20a** with 0.1M HCl in 2,2,2-trifluoroethanol giving **21** in 70% yield. Subsequent treatment of the free amine in **21** with di-*tert*-butyl dicarbonate and triethylamine in dichloromethane gave the Boc-protected **22** in 92% yield. Removal of the Teoc protective group with tetrabutyl ammoniumchloride and potassium fluoride in acetonitrile gave the desired substrate **7** in 95% yield.

PS condensation: As shown in scheme 4.11, reduction of the methyl ester with DIBAL at -75°C followed by treatment of the obtained aldehyde with TFA resulted in cyclization in 72% yield. At first glance inspection of the crude reaction mixture by both TLC and NMR spectroscopy only indicated the presence of the trans diastereomer **23**. Close examination of the isolated fractions obtained after purification of the reaction mixture by flash chromatography showed however the presence of the desired cis diastereomer **24** as well in 1.3% yield.

Subsequent removal of the Boc group from the isolated cis diastereomer **24** by treatment with iodotrimethylsilane gave the desthia carba eudistomin analog **6c** in 64% yield.

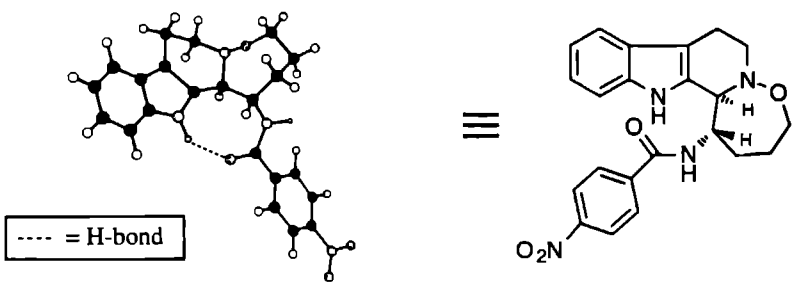
scheme 4.11



The cis/trans structure assignments were made using 400 MHz ^{1}H-NMR data In the natural eudistomin series it was found that cis/trans assignment was possible using the δ-values of the indole-NH protons In the X-ray crystal structure of the trans diastereomer it was deduced that the C(1)-amino group occupies an equatorial position (see chapter 8) which allows formation of an intramolecular hydrogen bond between the indole-N proton and the C(1)-amino nitrogen From the X-ray structure of the cis diastereomer it was concluded that the amino substituent occupies an axial position in which no intramolecular hydrogen bond is possible This difference in spatial position of the C(1)-amino group and its ability to form a hydrogen bond with the indole-NH is clearly seen in the ^{1}H-NMR spectra The indole-NH of the trans diastereomer absorbs 1.4 ppm lower than in the cis isomer

Shankar and coworkers succeeded in obtaining an X-ray crystal structure from the trans desthia carba analog with the NH_2 group functionalized with a 4-nitrobenzoyl group to facilitate crystallization (chart 4 2) [13]

chart 4.2 X-ray structure of trans N(1)-4-nitrobenzoyl desthia carba eudistomin.



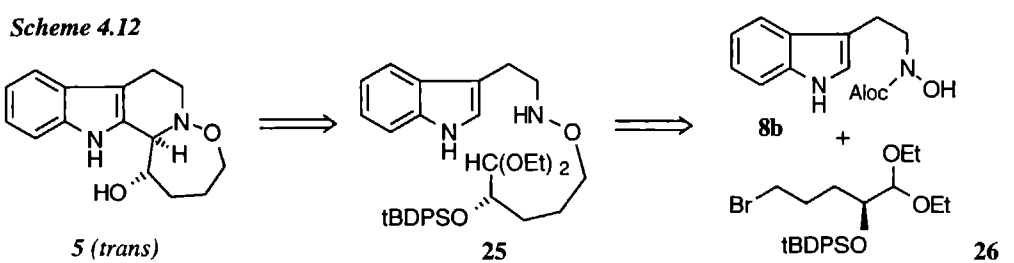
This X-ray analysis reveals that the functionalized C(1)-amino sidechain occupies an equatorial position, and that there is a hydrogen bond between the amide carbonyl and the indole-N proton In the NMR spectrum of the trans carba analog also a downfield shift was observed for the indole NH proton (*i e* Δδ=1 0 ppm), suggesting the same spatial orientation of the C(1)-amino side groups in cis/trans desthia carba derivatives as is found in both 'natural' eudistomin diastereomers (see

paragraph 4.3.2 and chapter 8). It is also noteworthy that the (Boc) t-butyl singlets in the NMR spectra of the natural and desthia carba series are located at exact the same δ values (*viz.* 1.17 ppm in the cis diastereomer and 1.52 ppm in the trans diastereomer). Due to broadening and overlap of the NMR signals no cis/trans assignments could be made on the basis of the vicinal coupling constants of H(1) and H(13b).

4.3 Approach Based on the Displacement of the OH-group in a C(1)-hydroxy Desthia Carba Eudistomin Analog

As outlined in the introductory section an alternative method for the synthesis of the desired cis desthia carba eudistomin analog involves a displacement of the C(1)-OH group in a corresponding trans diastereomer using a S_n2 type reaction (see scheme 4.2). The retrosynthesis of the required C(1)-hydroxy trans eudistomin analog is depicted in scheme 4.12.

Scheme 4.12



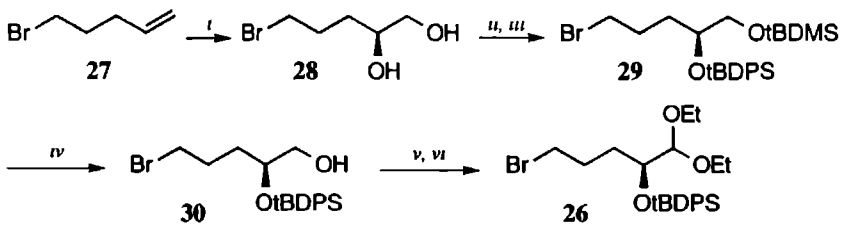
5 (trans) **25** **26**

The *tert*-butyldiphenylsilyl (tBDPS) group was selected as a directing group in the PS cyclization, and therefor the Aloc group was chosen for the protection of the N_b amine group. For the chiral five carbon fragment (S)-5-bromo-2-(*tert*-butyldiphenylsilyloxy)-pentanal diethyl acetal **26** no chiral pool derived synthon is available. A synthesis of **26** is conceivable starting from 5-bromo-1-pentene using the Sharpless asymmetric dihydroxylation (AD).

4.3.1 Synthesis of (S)-5-Bromo-2-(*tert*-Butyldiphenylsilyloxy)-pentanal Diethyl Acetal and its Coupling with N_b-Aloc-N_b-hydroxytryptamine

The synthesis of (S)-5-bromo-2-(*tert*-butyldiphenylsilyloxy)-pentanal diethyl acetal **26** was accomplished from 5-bromo-1-pentene **27** (scheme 4.13). According to Sharpless and coworkers, catalytic asymmetric dihydroxylation of 1-alkenes proceeds with high chemical and optical yields.[14] Treatment of 5-bromo-1-pentene with AD-mix α gave diol **28** in an outstanding yield of 94% but with a disappointing e.e. of 65%. The optical purity of the diol was determined by transformation into the di-(*R*)-MTPA ester and subsequent ^{19}F and ^{1}H-NMR analysis.[15]

scheme 4.13

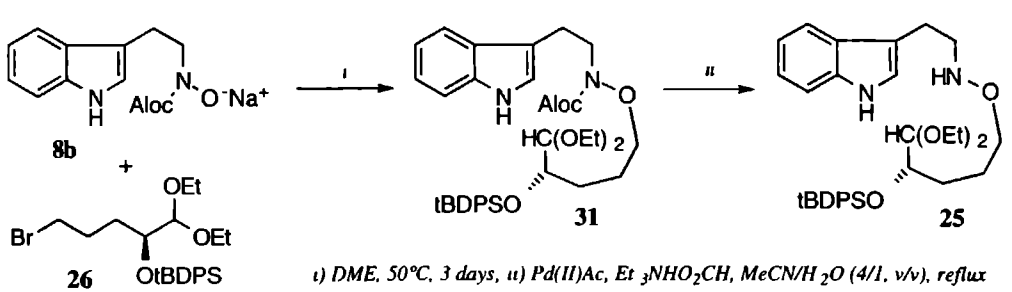


i) AD mix α, tBuOH/H2O=1/1, 4°C ii) tBDMS Cl, imidazole, DMF, rt, iii) tBDPS-Cl, imidazole, DMF, rt, iv) PPTS, EtOH, 40°C 12 h , v) (COCl)2, DMSO, CH2Cl2 Et3N, vi) HC(OEt)3, EtOH, TsOH

The primary alcohol in **28** was protected as a tBDMS ether followed by protection of the secondary alcohol as a tBDPS ether to give **29** in 64% overall yield Selective removal of the tBDMS group by treatment with the mild acid pyridinium-*p*-toluene sulfonic acid (PPTS) proceeded sluggishly and the primary alcohol **30** was obtained after column chromatography in 53% [16] Subsequent Swern oxidation and protection of the obtained aldehyde by conversion into the diethyl acetal by treatment with triethyl orthoformate in ethanol gave **26** in overall 94% yield from **30** Although we did not check the preservation of the e e in the reaction sequence **28→29→30→26** it may be assumed that no racemization has been occurred based on related transformations which have been described in both the literature[17] and chapter 3

Coupling Substitution of the primary bromide with the sodium salt of N_b-Aloc-N_b-hydroxytryptamine **8b** was accomplished after stirring for 3 days at 50°C to give **31** in 50% yield After that time no further progress of the reaction could be detected by TLC analysis, although both starting compounds **8b** and **26** were still present and could be recovered after column chromatography Removal of the Aloc group by treatment with palladium(II)acetate, triphenylphosphine and triethylammonium formate (TEAF) afforded **25** in 88% yield At this point it is interesting to note that about 10 eq TEAF were necessary in order to avoid allylation of the unprotected N_b-amine Clearly, the very nucleophilic α-alkoxy amine[18] competes with the formate anion in trapping the allyl cations [19]

scheme 4.14

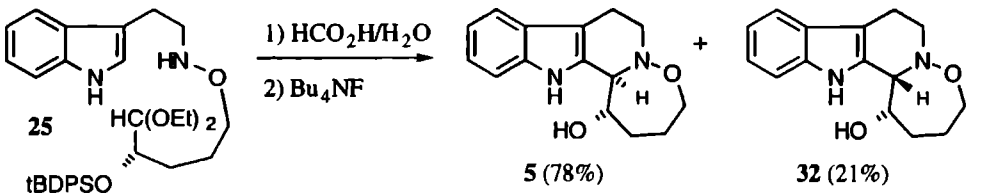


i) DME, 50°C, 3 days, ii) Pd(II)Ac, Et 3NHO2CH, MeCN/H 2O (4/1, v/v), reflux

4.3.2 Pictet-Spengler Condensation

The PS condensation of α-*tert*-butyldiphenyl-silyloxy diethyl acetal **25** took place smoothly in formic acid/water (9/1, v/v) at room temperature

Scheme 4.15



5 (78%) **32** (21%)

After removal of the silyl protective group with tetrabutylammonium fluoride the cis/trans diastereomers **32/5** were isolated in 99% overall yield in a 21/78 ratio

Unexpectedly, in contrast with the direct approach using the *tert*-butyloxycarbonylamino group, with the *tert*-butyldiphenylsilyloxy group no exclusive trans diastereoselectivity was found In the natural eudistomin series the diastereomeric ratio obtained in the PS condensation was the same for *tert*-butyldiphenylsilyloxy (chapter 3) and *tert*-butyloxycarbonylamino (chapter 2) groups

In the 400 MHz NMR spectra a downfield shift was observed for the indole NH proton (*i e* Δδ=1 1 ppm) in the trans diastereomer due to the presence of a hydrogen bond between the oxygen atom and the indole NH proton (*vide supra*) The NOESY spectrum of the cis diastereomer **32**, suggested the same conformation of the [1,2]-oxazepine ring as is found for the [1,6,2]-oxathiazepine ring in natural eudistomins (see chapter 8), for H(13b)α connectivities were found with both H(2)α and H(7)α, indicating that these protons are all axially orientated in space, in combination with the connectivity between H(1)α and the indole-N proton, indicating that H(1)α occupies an equatorial position

4.3.3 Introduction of the Amino Functionality via the Mitsunobu Reaction

As outlined in chapter 3, for the S_n2 type introduction of the amino group the Mitsunobu reaction is appropriate Initially the promising acidic Mitsunobu nucleophile diallyl imidodicarbonate[20] was chosen After work-up both NMR and mass spectroscopy showed however incorporation of the reduced form of diisopropyl azodicarboxylate (*viz* 1,2 diisopropoxy-carbonylhydrazine) instead of diallyl imidodicarbonate, giving a product in 42% yield whose structure will be elucidated later Substitution of THF by toluene did not alter the outcome of the reaction Also with phthalimide the same side product was formed in 24% yield

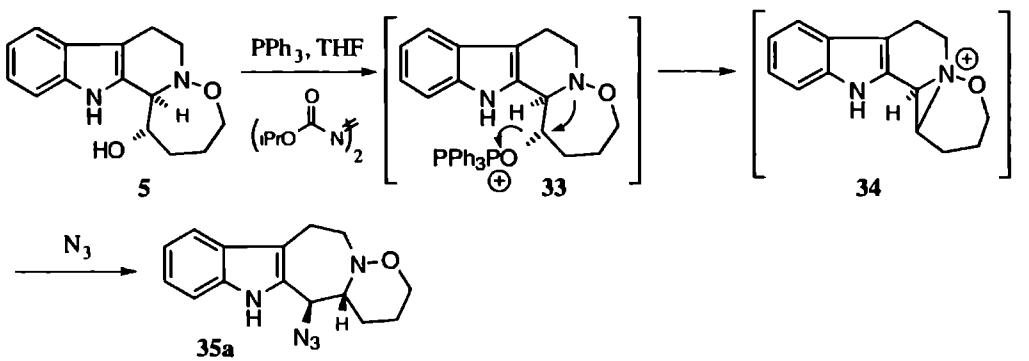
For this side reaction a literature precedent was found [21] Alcohols can give smooth reactions with triphenylphosphine/dialkyl azodicarboxylate when the reacting alcohol is capable of forming

stable carbonium ions That the formation of a stable carbonium ion occurred during the Mitsunobu reactions described in this chapter will be discussed later in this paragraph

Use of the very small nucleophile formed from hydrazoic acid gave a clean substitution reaction and the azide was isolated after column chromatography in 81% yield Comparison of the 90 MHz NMR spectrum of this isolated azide with the NMR spectrum of the *trans* desthia carba-eudistomin azide, synthesized by Kirkup and coworkers, was reason to be suspicious [13] In the ^{1}H-NMR spectrum of the azide obtained a broadened doublet (J=9 4 Hz) is present at 5 1 ppm Since in all isolated tetracyclic eudistomins the ^{1}H-NMR signal of H(13b) is located in the 3 9-4 6 ppm region (see tables 2 1 and 2 2 in chapter 2) this doublet must arise from H(1) In the ^{1}H-NMR spectrum of the trans azide analog, obtained by Kirkup and coworkers, H(1) is part of a multiplet in the 3 4-4 0 ppm region Because a $\Delta\delta$ of 1 1 ppm for the H(1) signals in the cis/trans diastereomers is very unlikely it must be concluded that during the Mitsunobu reactionthe target compound has not been formed [22]

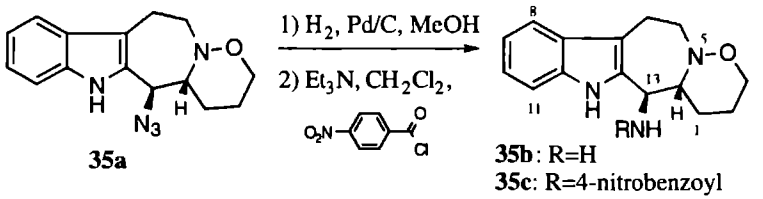
Apparently, as in the diastereoselective approach of the natural eudistomin series, transannular neighboring group participation had occurred After formation of the phosphonium leaving group the bridge-head nitrogen (which is highly nucleophilic due to the alpha-effect of the alkoxy substituent[16]) attacks to form the pentacyclic aziridinium intermediate **34** (scheme 4 16) Subsequent attack of the present azide anion takes place only at the benzylic position (*vide infra*) yielding the azepine **35a** in 81% yield

scheme 4.16



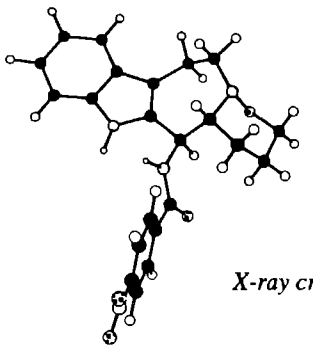
The incontrovertible proof of structure **35a** was given by X-ray crystal structure determination (scheme 4 17) For this purpose the azide group was reduced by catalytic hydrogenation with Pd/C to give **35b** in 49% yield followed by treatment with 4-nitrobenzoyl chloride to give **35c** in 63% yield of which a single crystal was obtained suitable for X-ray crystal structure determination

scheme 4.17



35a

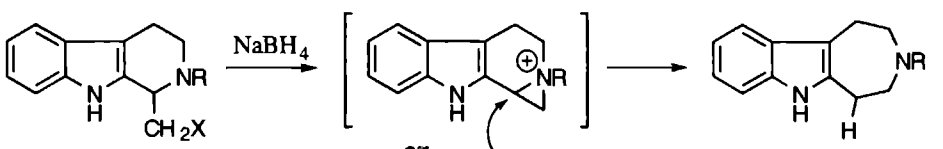
35b: R=H
35c: R=4-nitrobenzoyl



X-ray crystal structure of 35c

A related reaction is described in the literature (scheme 4.18).[23] Reduction of **36a** (HCl salt) and **36b** with sodium borohydride in DME gave unexpectedly the azepines **38a** and **38b** in yields of 52% and 30%, respectively. Although not stated in the original paper one can assume that the azepines are formed by hydride attack on the intermediate aziridinium-ion **37**.

Scheme 4.18



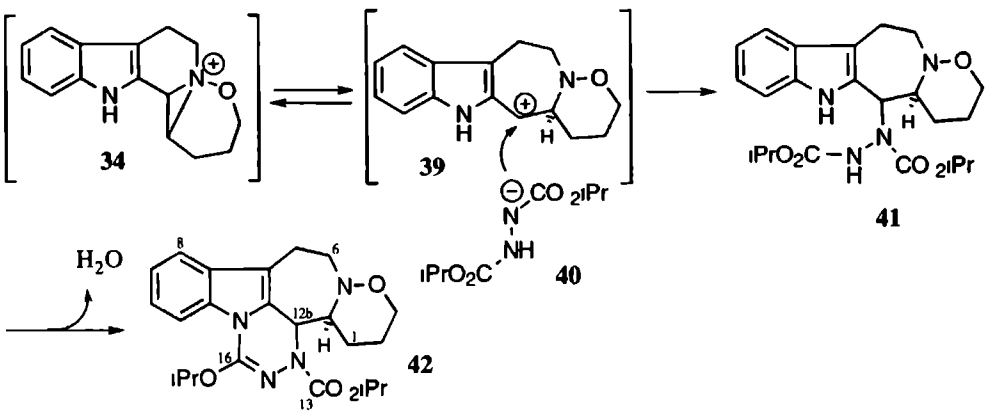
36a: R=H, X=Cl
36b: R=Ts, X=OTs

37

38a: R=H
38b: R=Ts

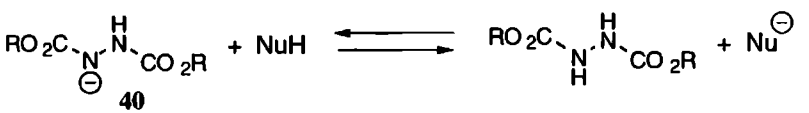
With this information at hand also the formation of the earlier mentioned side product formed when diallyl imidodicarbonate or phthalimide were used as nucleophiles in the Mitsunobu reaction, can be explained. As mentioned above incorporation of the elements of 1,2-dialkoxycarbonylhydrazine only takes place when the reacting alcohol can form stable carbonium ions. That formation of a stable carbonium in our reaction sequence is very likely is shown in scheme 4.19. After formation of the aziridium-ion **34** ringopening occurs to yield the relatively stable secondary and benzylic carbocation **39**. Attack of 1,2-diisopropoxycarbonyl-hydrazide **40** gives the intermediate compound **41**, which immediately undergoes an intramolecular condensation to give **42**.

scheme 4.19



The reason that this side reaction is only found with the two imide type nucleophiles and not with hydrazoic acid, is probably a combination of two factors the presence of an intermediate carbonium ion and the difference in pK_a of the nucleophiles Firstly, the phosphonium salt **33** (see scheme 4 16) *rapidly* forms the aziridinium intermediate **34** (scheme 4 19) [24] This reactive species may have a different preference for nucleophiles than phosphonium salts **33**

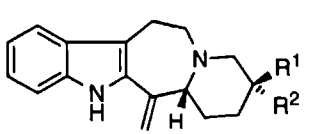
The position of the following equilibrium is decisive for the outcome of the Mitsunobu reaction



Apparently, in the case of NuH=imide the more nucleophilic **40** is present in sufficient concentrations to form the hydrazide adduct **41**, whereas with NuH=hydrazoic acid the equilibrium is immediately shifted to the right, leading to product **35a** exclusively

An interesting adventitious circumstance is the resemblance of the skeleton of the tetracyclic azepines **35** with the naturally occurring ngouniensines, which were isolated as the major indole alkaloids of *Strychnos Ngouniensis* (scheme 4 20)[25]

scheme 4.20



Ngouniensine R^1=H, R^2=Et
epingouniensine R^1=Et, R^2=H

Finally, it is of interest to note that during the PS condensation shown in scheme 4 15 and the subsequent reaction under Mitsunobu conditions the optical integrity is predominantly retained as was apparant from the optical purity of product **35b** By means of analytical HPLC the optical purity of **35b** was determined[26] to be 78%, corresponding with an e e of 56% The starting material **28** had an e e of 65%, implying that in the sequence of **28** to **35b** only 9% of e e was sacrificed

4.4 Conclusion

The synthesis of the target cis desthia carba analog was accomplished using the intramolecular PS condensation albeit in only 1% yield. The substrate needed for this PS condensation was obtained by coupling of a tryptamine fragment and a fragment derived from D-glutamic acid. However, due to the conditions used during this coupling almost complete racemization of the stereogenic center present in the glutamic acid fragment had to be accepted.

The attempted displacement of the C(1)-OH group in the trans desthia carba eudistomin analog by an amino function using the Mitsunobu methodology was not successful. A deviating reaction was observed in which the bridgehead nitrogen atom took part by formation of an intermediate aziridinium ion, which ultimately resulted in the formation of 6/5/6/7 tetracyclic ring system. The anchimeric effect of the bridgehead N prevented the planned S_n2 displacement during the Mitsunobu reaction.

4.5 Experimental Part

For general remarks see the experimental part of chapter 2.

Synthesis of the (*D*)-glutamic acid derived compounds:

Dimethyl *N*-trityl-D-glutamate (10): To cooled (0°C) dry methanol (35 mL) was added with stirring thionyl chloride (12.5 mL, 7.7 g, 64 mmol) over a period of 30 min. To the resulting solution D-glutamic acid (5 g, 34 mmol) was added in one portion. The resulting white suspension became a clear solution after ca.1 hour After standing of the reaction mixture over night the volatiles were evaporated *in vacuo*. The residue was dissolved in methanol (2.5 mL) and poured into ether/hexanes (30 mL, 1/1, v/v). The product was collected by filtration and dried (KOH), to yield 7 0 g (96%) of (*D*)-HCl-Glu(OMe)-OMe as a white crystalline solid which was then dissolved in dry DMF (40 mL) To this stirred solution, triethylamine (9.1 mL, 6 6 g, 66 mmol) and trityl chloride (9.1 g, 33 mmol) were added. After stirring of the reaction over night the volatiles were evaporated *in vacuo*. The residue was dissolved in EtOAc (50 mL) and successively washed with 10% citric acid, sat. $NaHCO_3$ and brine. After drying ($MgSO_4$) the solvent was evaporated *in vacuo* to yield 12 7 g (93%) of **10** as a white solid; R_f 0.53 (EtOAc/hexanes=1/2, v/v); ^1H NMR (90 MHz) δ 7.56-7 09 (m, 16H, 3xC_6H_5 and NH), 3.70 (s, 3H, γ-OCH_3), 3.58-3.31 (m, 1H, α-H), 3.16 (s, 3H, α-OCH_3), 2.76-2.13 (m, 4H, CH_2CH_2)

α-Methyl-*N*-trityl-D-glutamate (11a): To dioxane (50 mL) was added **10** (5.0 g, 12.0 mmol) and 2N NaOH (50 mL). The resulting 2-phase system was efficiently stirred over night at room temperature. The reaction mixture was acidified with $NaHSO_4$ and the product was extracted with ether (50 mL). The organic layer was washed with brine and dried ($MgSO_4$). The volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (MeOH/$CHCl_3$=7/93) to yield 3.7 g (76%) of **11a** as a white crystalline solid, R_f 0.61 (MeOH/$CHCl_3$=15/85); ^1H NMR (90 MHz) δ 7 53-7.09 (m, 16H, 3xC_6H_5 and NH), 3.29 (t, 1H, J=6.0 Hz, α-H), 3.17 (s, 3H, OCH_3), 2.59-2 40 (m, 4H, CH_2CH_2)

Borane dimethyl sulfide reduction of **11a-c**: **Methyl *N*-Trityl-D-prolinate (14a)**: Glutamate **11a** (2.5 g, 6.2 mmol) was dissolved in freshly distilled THF (25 mL) employing flame dried glass equipment under an argon atmosphere. BH_3•SMe_2 (6 8 mL of a 1M solution) was gradually added with stirring When this addition was completed stirring was continued for another 30 min., then sat aq. $NaHCO_3$ (50 mL) was cautiously added The organic layer was washed with sat. aq $NaHCO_3$ and brine, then dried ($MgSO_4$) and concentrated *in vacuo* to give 2.38 g (99%) of **14a** as a colorless solid; R_f 0 65 (MeOH/$CHCl_3$=7/93, v/v); α_D^{22}=+55.0 (c=3.80, MeOH); ^1H NMR (90 MHz) δ 7.62-7.14 (m, 15H, 3xPhH_5), 3.92 (dd, 1H, J=8.5 Hz and J=2.2 Hz, α-H), 3.69 (s, 3H, OCH_3), 3.56-3.30 (m, 1H, NC<u>H</u>H), 2.98-2.73 (m,

1H, NCHH), 1 73-0 83 (m, 4H, CH_2CH_2), CIMS(70eV), m/z (relative intensity) 372 ($[M+1]^+$, 1), 243 ($[CPh_3]^+$, 100), 165(17) 84(6), 49(18)

Methyl *N*-(*tert*-butyloxycarbonyl)-D-prolinate (14b) Obtained in 98% yield on a 15 mmol scale using the same procedure as described for **14a**, R_f 0 36 (EtOAc/hexanes=1/2, v/v), α_D^{22}=+65 7 (c=3 00, MeOH), ^1H NMR (90 MHz) δ 4 39-4 16 (m, 1H, α-H), 3 72 (s, 3H, OCH_3), 3 65-3 26 (m, 2H, NCH_2), 2 38-1 75 (m, 4H, CH_2CH_2), 1 40 (s, 9H, $C(CH_3)_3$), CIMS(70eV), m/z (relative intensity) 230 ($[M+1]^+$, 37), 174 (46), 130 (60), 114 (40), 70 ($[C_4H_8N]^+$, 100), 57 ($[C_4H_9]^+$, 48)

Methyl *N*-(benzyloxycarbonyl)-D-prolinate (14c) Obtained in 96% yield on a 9 mmol scale using the same procedure as described for **14a** All spectroscopical data were identical with those described in the literature [9]

α-Methyl *N*-phthaloyl-D-glutamate (11d) To (*D*)-H-Glu(OH)-OMe[6] (2 5 g, 15 5 mmol) dissolved in water (20 mL) was added Na_2CO_3 (1 65 g, 15 5 mmol) and N carbethoxyphthalimide (3 6 g, 16 4 mmol) After stirring for 1 5 h the reaction mixture was acidified with 2N $KHSO_4$ and EtOAc (50 mL) was added After washing with brine and drying ($MgSO_4$) the solvent was evaporated *in vacuo* followed by purification of the residue by column chromatography (MeOH/CH_2Cl_2=2/98, v/v followed by MeOH/CH_2Cl_2=1/9, v/v) to yield 2 85 g (63%) of **11d** as a white solid, R_f 0 29 (MeOH/CH_2Cl_2=7/93, v/v), R_f 0 14 (EtOAc/hexanes=2/1, v/v), α_D^{22}=+48 3 (c=8 4, MeOH), ^1H NMR (90 MHz) δ 9 02 (very br s, 1H, COOH), 7 97-7 66 (m, 4H, C_6H_4), 5 03-4 87 (m, 1H, α-H), 3 76 (s, 3H, $COOCH_3$), 2 93 2 32 (m, 4H, CH_2CH_2), EIMS(70eV), m/z (relative intensity) 292 ($[M+1]^+$, 2), 259 (13), 186 (100)

Methyl (R)-5-hydroxy-2-tritylamino-pentanoate (17a) To a cooled (0°C) solution of **10** (5 0 g, 12 0 mmol) in dry ether (100 mL) employing flame dried glass equipment under an argon atmosphere was added $LiAlH_4$ (0 36 g, 9 6 mmol) in 3 portions over a period of 10 min The reaction was monitored by TLC (EtOAc/hexanes=1/1) After consumption of the starting material (30 min) NaOH (5 mL of a 1M solution) was added cautiously and the resulting grey suspension was stirred until a white color appeared The salts were removed by filtration over hyflo and after drying ($MgSO_4$) the solvent was evaporated *in vacuo* The residue was subjected to column chromatography (EtOAc/hexanes=1/1) to yield 3 94 g (85%) of **17a** as a white foam, R_f 0 29 (EtOAc/hexanes=1/1, v/v), α_D^{22}=-53 0 (c=2 85, MeOH), ^1H NMR (90 MHz) δ 7 56-7 16 (m, 16H, $3xC_6H_6$ and NH), 3 64 (t, 2H, J=6 0 Hz, $HOCH_2$), 3 39 (t, 1H, J=5 9 Hz, α H), 3 18 (s, 3H, $COOCH_3$), 2 28 (very br s 1H, exchangeable, OH), 1 96-1 40 (m, 4H, CH_2CH_2), CIMS(70eV), m/z (relative intensity) 390 ($[M+1]^+$, 1), 243 ($[CPh_3]^+$, 100), 146 (M-$CPh_3]^+$, 3 5)

Methyl (R)-5-hydroxy-2-phthaloylamino-pentanoate (17d) To a stirred solution of **11d** (2 85 g, 9 8 mmol) in freshly distilled THF (50 mL) employing flame dried glass equipment under an argon atmosphere BH_3•SMe_2 (25 mL of a 1M solution in THF) was added dropwise (evolution of H_2) After completion of the reaction (1 h) the reaction was worked-up as mentioned for **14a** to yield 2 7 g (99%) of **17d** as a white solid which was homogeneous by TLC, R_f 0 36 (EtOAc/hexanes=2/1, v/v), ^1H NMR (90 MHz) δ 7 92-7 68 (m, 4H, C_6H_4), 4 90 (dd, 1H, J=6 6 Hz and J=8 9 Hz, α H), 3 74 (s, 3H, $COOCH_3$), 3 67 (t, 2H, J=6 3 Hz, $HOCH_2$), 2 47-2 20 (m, 2H, $HOCH_2CH_2CH_2$), 1 95 (br s, 1H, exchangeable, OH), 1 73 1 44 (m, 2H, $HOCH_2CH_2CH_2$), EIMS(70eV), m/z (relative intensity) 277 ($[M]^+$, 1), 245 (13), 218 (35), 148 (49), 71 ($[C_4H_7O]^+$, 100)

Methyl (R)-5-methylsulfonyloxy-2-tritylamino-pentanoate (18a) To a cooled (-20°C) and stirred solution of **17a** (0 5 g 1 29 mmol) and triethylamine (0 54 mL, 0 39 g, 3 86 mmol) in ether (20 ml) methanesulfonyl chloride (0 25 mL, 0 37 g, 2 57 mmol) was gradually added (over a period of 20 min) After additionally stirring for 15 min , the salts were removed by filtration over hyflo The resulting solution was then washed with 10% citric acid, sat $NaHCO_3$, and brine After drying ($MgSO_4$) the solvent was evaporated *in vacuo* to yield 0 6 g (99%) of **18a** as a colorless oil which decomposes at room temperature Storage is however possible for a few days in the refrigator (T<-20°C), R_f 0 15 (EtOAc/hexanes=1/2, v/v), ^1H NMR (90 MHz) δ 7 54-7 15 (m, 16H, $3xC_6H_6$ and NH), 4 31-4 18 (m, 2H, J=6 0 Hz, $MsOCH_2$), 3 34-3 31 (m, 1H, α-H), 3 18 (s, 3H, $COOCH_3$), 3 00 (s, 3H, H_3CSO_3), 1 89-1 76 (m, 4H, CH_2CH_2)

Methyl (R)-5-bromo-2-(phthaloylamino)-pentanoate (18d) and (R)-α-(phthaloylamino)-δ-valerolactone (19) To a stirred solution of chlorotrimethylsilane (3 14 mL, 2 7 g, 25 mmol) and lithium bromide (1 74 g, 20 mmol) in dry acetonitrile (10 mL) was added **14a** (2 7 g, 9 8 mmol) The reaction mixture was heated at reflux over night After evaporation of the volatiles *in vacuo* the residue was subjected to column chromatography (EtOAc/hexanes=1/2, v/v) to yield 0 93 g (28%) of **18d** as a white solid, R_f 0 47 (EtOAc/hexanes=2/3 v/v), ^1H NMR (90 MHz) δ 7 93-7 70 (m, 4H, C_6H_4), 4 86 (dd, 1H, J=6 9 Hz and J=8 7 Hz, α-H), 3 73 (s, 3H, $COOCH_3$), 3 40 (t, 2H, J=6 5 Hz, $BrCH_2$), 2 56-2 28

(m, 2H, $BrCH_2CH_2\underline{CH_2}$), 2 04-1 74 (m, 2H, $BrCH_2\underline{CH_2}CH_2$), EIMS(70eV), m/z (relative intensity) 340/342 ($[M+1]^+$ 2), 280/282 (95), 200 (100) and 1 18 g (47%) of **19** also as a white solid, R_f 0 21 (EtOAc/hexanes=2/3, v/v), ^1H NMR (90 MHz) δ 7 93-7 68 (m, 4H, C_6H_4), 4 94 (dd, 1H, J=7 8 Hz and J=11 0 Hz, α H), 4 52 (t, 2H, J=6 0 Hz, OCH_2), 2 76-1 99 (m, 4H, CH_2CH_2)

Methyl (R)-5-iodo-2-(phthaloylamino)-pentanoate (18e) from 19 To **19** (1 18 g, 4 8 mmol) dissolved in dry dichloromethane (10 mL) was added iodotrimethylsilane (0 68 mL, 0 96 g, 4 8 mmol) After stirring for 1 h another portion iodotrimethylsilane (0 34 mL, 0 48 g, 2 4 mmol), together with EtOH (0 73 mL, 0 55 g, 12 mmol) were added After standing for 2 h no conversion of the intermediate product (*i e* the α-acid) was detected by TLC The reaction was worked-up by evaporation of the volatiles *in vacuo* The residue was dissolved in EtOAc (50 mL) and washed with two portions of water, brine and dried ($MgSO_4$) Removal of the volatiles *in vacuo* gave the crude acid which was subsequently dissolved in CH_2Cl_2/Et_2O (1/1, v/v, 50 mL) To this solution was added diazomethane (20 mL of a 0 3M solution) which brought about immediately evolution of nitrogen After standing for 10 min a few drops of formic acid were added to quench the excess diazomethane and the volatiles were evaporated *in vacuo* The residue was dissolved in EtOAc (50 mL) and subsequently washed with 10% Na_2CO_3 and dried (sat NH_4Cl and $MgSO_4$) The solvent was evaporated *in vacuo* to yield 1 86 g (99%) of **18e** as a colorless oil, R_f 0 59 (EtOAc/hexanes=1/1, v/v), ^1H NMR (90 MHz) δ 7 94-7 71 (m, 4H, C_6H_4), 4 87 (t, 1H, J=7 8 Hz, α-H), 3 74 (s, 3H, $COOCH_3$), 3 19 (t, 2H, J=7 0 Hz, ICH_2), 2 51-2 25 (m, 2H, $ICH_2\underline{CH_2}CH_2$), 2 01-1 69 (m, 2H, $ICH_2CH_2\underline{CH_2}$)

Alkylations of the N_b-Teoc-N_b-hydroxytryptamine **8a** with the glutamic acid derivatives **18**

Methyl (*rac*)-5-{N-[2-(1H-indol-3-yl)-ethyl]-N-(2-trimethylsilylethyloxycarbonyl)-aminooxy}-2-(tritylamino)-pentanoate (20a) NaH (35 mg of a 80% oil dispersion, 1 18 mmol) was added in 2 portions to a stirred solution of **8a** (340 mg, 1 07 mmol) in freshly distilled DME (20 ml) employing flame dried glass equipment under an argon atmosphere The suspension was stirred until a clear solution appeared (10-30 min) (hydrogen gas evolved) This solution was added dropwise to a stirred solution of **18a** (500 mg, 1 07 mmol) in freshly distilled DME (50 ml) at 0°C After additional stirring over night at room temperature EtOAc (50 ml) was added and the reaction mixture was subsequently washed with water and sat NH_4Cl The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* The residue was subjected to column chromatography (EtOAc/hexanes=1/2, v/v) to give 740 mg (67%) of **20a** as an oil, R_f 0 28 (EtOAc/hexanes=1/2, v/v), CIMS(70eV), m/z (relative intensity) 243 ($[CPh_3]^+$, 29), 144 ($[C_{10}H_{10}N]^+$, 23), 130 ($[C_9H_8N]^+$, 29), 73 ($[Si(CH_3)_3]^+$, 100), ^1H NMR (100 MHz) δ 8 02 (br s, 1H, indole NH), 7 71-6 96 (m, 20H, $3xC_6H_5$, indole C(2)H and C(4)-C(7)H_4), 4 18-3 66 (m, 6H, H_2CNOCH_2 and $O\underline{CH_2}CH_2Si$), 3 53-3 29 (m, 1H, α-H), 3 21-3 01 (m, 2H, indole C(3)CH_2), 3 13 (s, 3H, $COOCH_3$), 1 96-1 62 (m, 3H, $NOCH_2\underline{CH_2}CHH$), 1 33-1 18 (m, 1H, $NOCH_2CH_2CH\underline{H}$), 1 00-0 76 (m, 2H, $SiCH_2$), 0 00 (s, 9H, $Si(CH_3)_3$)

Methyl-(*rac*)-5-{N-[2-(1H-indol-3-yl)-ethyl]-N-(2-trimethylsilylethyloxycarbonyl)-aminooxy}-2-(phthaloylamino)-pentanoate (20b) The same procedure followed as described for **20a** using NaH (160 mg of a 80% oil dispersion, 5 3 mmol), **8a** (1 7 g, 5 3 mmol) and **18e** (2 04 g, 5 2 mmol) Work up and purification by column chromatography (EtOAc/hexanes=1/4, v/v) gave 1 9 g (62%) of **20b** as an oil, R_f 0 47 (EtOAc/hexanes=1/1, v/v), R_f 0 50 (MeOH/CH_2Cl_2=1/9, v/v), EIMS(70eV), m/z (relative intensity) 579 ($[M]^+$, 6), 130 ($[C_9H_8N]^+$, 100), 73 ($[Si(CH_3)_3]^+$, 71), ^1H NMR (90 MHz) δ 8 15 (br s, 1H, indole NH), 7 92-7 56 (m, 5H, C_6H_4 and indole C(7)H), 7 39-7 00 (m, 4H, indole C(2)H and C(4)-C(6)H_3), 4 90 (dd, 1H, J=6 6 Hz and J=9 0 Hz, α H), 4 17-3 98 (m, 2H, $O\underline{CH_2}CH_2Si$), 3 96 3 69 (m, 4H, CH_2NOCH_2), 3 73 (s, 3H, $COOCH_3$), 3 13-2 97 (m, 2H, indole C(3)CH_2), 2 53-2 27 (m, 2H, $OCH_2CH_2\underline{CH_2}$), 1 81-1 50 (m, 2H, $OCH_2\underline{CH_2}CH_2$), 0 96-0 77 (m, 2H, $SiCH_2$), 0 00 (s, 9H, $Si(CH_3)_3$ together with 0 45 g (22%) recovered **18e**

Methyl-(*rac*)-2-amino-5-{N-[2-(1H-indol-3-yl)-ethyl]-N-(2-trimethylsilylethyloxycarbonyl)-aminooxy-pentanoate (21) From **20a** To **20a** (0 33 g, 0 48 mmol) in 2,2,2-trifluoroethanol/water (9/1, v/v, 10 mL) was added 0 1N HCl in 2,2,2-trifluoroethanol/water (9/1, v/v) in 100 µL portions until the pH remained ca 3 5 After additional stirring for 1 h the reaction mixture was neutralized with sat $NaHCO_3$ and dichloromethane (50 mL) was added The organic layer was washed with brine and dried ($MgSO_4$) After evapoation of the volatiles *in vacuo* the residue was subjected to column chromatography (MeOH/CH_2Cl_2/Et_3N=1/99/0 05, v/v/v) to yield 150 mg (70%) of **21** as a colorless oil, R_f 0 37 (MeOH/CH_2Cl_2=1/9, v/v), ^1H NMR (90 MHz) δ 8 36 (br s, 1H, indole NH), 7 67 7 56 (m, 1H,

indole C(7)H), 7 38-6 99 (m, 4H, indole C(2)H and C(4)-C(6)H_3), 4 16-3 97 (m, 2H, $SiCH_2\underline{CH_2}$), 3 93-3 68 (m, 5H, H_2CNOCH_2 and α-H), 3 70 (s, 3H, $COOCH_3$), 3 15-2 97 (m, 2H, indole C(3)CH_2), 2 11-1 58 (m, 6H, $NOCH_2\underline{CH_2}\underline{CH_2}$ and NH_2), 0 96-0 76 (m, 2H, $SiCH_2$), 0 00 (s, 9H, $Si(CH_3)_3$) From **20b** Hydrazine monohydrate (0 95 mL, 0 98 g, 19 5 mmol) and acetic acid (1 11 mL, 1 17 g, 19 5 mmol) were dissolved in methanol (10 mL) This solution was added in one portion to **20b** (2 3 g, 3 9 mmol) dissolved in methanol (45 mL) The reaction mixture was stirred over night at 40°C The volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (MeOH/CH_2Cl_2/Et_3N=1/99/0 05, v/v/v) affording 1 23 g (70%) of **21** as a colorless oil

Methyl-(*rac*)-2-(*tert*-butyloxycarbonylamino)-5-{N-[2-(1H-indol-3-yl)-ethyl]-N-(2-trimethylsilylethyloxy-carbonyl)-aminooxy-pentanoate (22) To **21** (1 23 g, 2 74 mmol) in dichloromethane (15 mL) was added di-*tert*-butyl dicarbonate (0 65 g, 2 98 mmol) and 5 drops of triethylamine After 2 h the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/3, v/v) to yield 1 38 g (92%) of **22** as a colorless oil, R_f 0 53 (EtOAc/hexanes=1/1, v/v), CIMS(70eV), m/z (relative intensity) 549 ($[M]^+$, 5), 130 ($[C_9H_8N]^+$, 100), 73 ($[C_3H_9Si]^+$, 73), 57 ($[C_4H_9]^+$, 42), ^{1}H NMR (90 MHz) δ 8 14 (br s, 1H, indole NH), 7 66-7 57 (m, 1H, indole C(7)H), 7 40-7 00 (m, 4H, indole C(2)H and C(4)-C(6)H_3), 5 11 (br d, 1H, J=8 2 Hz, HNBoc), 4 41-3 71 (m, 7H, H_2CNOCH_2, $SiCH_2\underline{CH_2}$ and α-H), 3 71 (s, 3H, $COOCH_3$), 3 16-2 98 (m, 2H, indole C(3)CH_2), 2 04-1 56 (m, 4H, $NOCH_2\underline{CH_2}\underline{CH_2}$), 1 44 (s, 9H, $C(CH_3)_3$), 0 93-0 76 (m, 2H, $SiCH_2$), 0 00 (s, 9H, $Si(CH_3)_3$)

Methyl-(*rac*)-2-(*tert*-butyloxycarbonyl)-amino-5-{N-[2-(1H-indol-3-yl)-ethyl]-aminooxy}-pentanoate (7) A suspension of **22** (1 38, 2 51 mmol), Bu_4NCl (2 1 g, 7 6 mmol) and $KF\cdot 2H_2O$ (950 mg, 10 1 mmol) in dry acetonitrile (50 mL) was stirred at 45°C for 10 h The solvent was evaporated *in vacuo* The residue was dissolved in EtOAc and subsequently washed with water and sat NH_4Cl The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* The residue was subjected to column chromatography (EtOAc/hexanes=1/1, v/v) to yield 0 96 g (95%) of **7** as a colorless oil, R_f 0 23 (EtOAc/hexanes=1/1, v/v), CIMS(70eV), m/z (relative intensity) 406 ($[M+1]^+$, 4), 144 ($[C_{10}H_{10}N]^+$, 37), 130 ($[C_9H_8N]^+$, 100), 57 ($[C_4H_9]^+$, 69), ^{1}H NMR (90 MHz) δ 8 08 (br s, 1H, indole NH), 7 71 7 53 (m, 1H, indole C(7)H), 7 43-7 02 (m, 4H, indole C(2)H and C(4)-C(6)H_3), 5 51 (very br s, ONH), 5 14 (br d, 1H, J=8 0 Hz, HNBoc), 4 42-4 09 (m, 1H, α-H), 3 76-3 64 (m, 2H, $NOCH_2$), 3 73 (s, 3H, $COOCH_3$), 3 33-3 13 (m, 2H, CH_2NO), 3 13-2 91 (m, 2H, indole C(3)CH_2), 1 89-1 60 (m, 4H, $NOCH_2\underline{CH_2}\underline{CH_2}$), 1 47 (s, 9H, $C(CH_3)_3$)

PS cyclization to **trans (*rac*)-1-[[(*tert*-Butyloxy)carbonyl]amino]-1,2,3,4,7,8,13,13b-octahydro-[1,2]-oxazepino-[2',3':1,2]pyrido[3,4-*b*]indole (23)** and **cis (*rac*)-1-[[(*tert*-Butyloxy)carbonyl]-amino]-1,2,3,4,7,8,13,13b-octahydro-[1,2]-oxazepino[2',3':1,2]pyrido[3,4-*b*]indole (24)** followed by removal of the Boc group to give **cis (*rac*)-1-Amino-1,2,3,4,7,8,13,13b-octahydro-[1,2]-oxazepino-[2',3':1,2]pyrido[3,4-*b*]indole (6c)** The cyclization reaction was carried out employing flame dried glass equipment under an argon atmosphere To a cooled (-75°C) stirred solution of **7** (820 mg, 2 02 mmol) in dry dichloromethane (100 mL) was added DIBAL (5 0 mL of a 1M solution in dichloromethane) over a period of 20 min After completion of the reaction (15 min), as was indicated by TLC (EtOAc/hexanes=1/4, v/v), TFA (0 5 mL) was added The reaction mixture was allowed to warm to room temperature and then 10% citric acid (20 mL) was added The organic layer was washed with water and sat $NaHCO_3$/brine=1/1, dried (Na_2SO_4), filtered, and concentrated *in vacuo* The residue was subjected to column chromatography (EtOAc/hexanes=1/6, v/v) to give 510 mg (71%) of **23** as a white crystalline solid, R_f 0 29 (EtOAc/hexanes=1/4), mp=173-175°C (EtOAc/ether), ^{1}H NMR (400 MHz) (to sharpen up the broadened spectrum recorded at 57°C) δ 9 42 (br d, 1H, indole NH), 7 42 (d, 1H, J=7 8 Hz, C(12)H), 7 33 (d, 1H, J=8 0 Hz, C(9)H), 7 11 (t, 1H, J=7 4 Hz, C(10)H), 7 04 (t, 1H, J=7 4 Hz C(11)H), 5 08 (br d, 1H, J=9 2 Hz, BocNH), 4 23-4 17 (m, 1H, C(1)Hα), 3 97-3 91 (m, 3H, C(13b)Hβ and C(4)H_2), 3 62 3 52 (m, 1H, C(7)Hβ), 3 03-2 94 (M, 2H, C(7)Hα and C(8)Hβ), 2 76-2 67 (m, 1H, C(8)Hα), 2 21-2 15 (m, 1H, C(3)H), 2 02-1 94 (m 1H, C(3)H), 1 83-1 73 (m, 2H, C(2)H_2), 1 52 (s, 9H, $C(CH_3)_3$), ^{13}C NMR (100 MHz) (to sharpen up the broadened spectrum recorded at 57°C) δ 156 29 C=O, 136 65 C(12a), 133 09 C(13a), 126 65 C(8b), 121 47 C(11) 119 22 C(10), 118 07 C(9), 111 31 C(12), 107 77 C(8a), 80 50 CMe_3, 72 18 C(4), 71 10 C(13b), 55 34 C(1), 53 91 C(7), 30 28 C(3), 28 49 $(CH_3)_3$, 26 65 C(2), 20 52 C(8), Anal Calcd for $C_{20}H_{27}N_3O_3$ C, 67 20, H, 7 61, N, 11 76 Found C, 67 18, H, 7 39, N, 11 58 together with 9 2 mg (1 3%) of **24** as a white solid, R_f 0 22 (EtOAc/hexanes=1/4), ^{1}H NMR (400 MHz) δ ^{1}H NMR (400 MHz) δ 8 38 (br s, 1H, indole NH), 7 44 (d, 1H, J=7 3 Hz, C(12)H), 7 26 (d, 1H, J=7 4 Hz, C(9)H), 7 10 (t, 1H, J=7 2 Hz, C(10)H), 7 05 (t, 1H, J=7 3 Hz,

C(11)H), 4.97 (br d, 1H, J=9.2 Hz, BocNH), 4.50 (br s, 1H, C(1)Hα), 4.15-4.06 (m, 2H, C(13b)Hα and C(4)H), 3.75 (very br s, 1H, C(4)H), 3.52 (very br s, 1H, C(7)Hβ), 3.11-2.92 (br m, 2H, C(7)Hα and C(8)Hβ), 2.81-2.78 (br m, 1H, C(8)Hα), 2.11-1.98 (br m, 3H, C(2)H and C(3)H_2), 1.75 (br s, 1H, C(2)H), 1 17 (s, 9H, C(CH_3)$_3$). Both **23** and **24** are near racemates.

6c: To a stirred solution of **24** (8.9 mg, 0.025 mmol) in dry acetonitrile (1 mL) was added NaI (11.2 mg, 0.075 mmol) together with chlorotrimethylsilane (1 mL of a 0.074M solution in acetonitrile). After stirring for 2 h MeOH/Et_3N (1/1, v/v, 0.5 mL) was added to quench the formed HI and the volatiles were evaporated *in vacuo*. The residue was subjected to column chromatography (MeOH/CH_2Cl_2/Et_3N=3/97/0.05, v/v/v) to yield 19 mg of contaminated **6c**. NMR analysis showed a mixture of Et_3NHI and **6c** which could not be separated by extraction (CH_2Cl_2/water) or straight phase (Si60H) chromatography (*in future attempts quenching of HI should be performed with sat. $NaHCO_3$*). The salt was removed by preparative reversed phase column chromatography (RP-8, water/methanol=7/3, v/v), followed by another Si60H column (MeOH/CH_2Cl_2/Et_3N=2/98/0.05, v/v/v) to yield 4,1 mg (64%) of **6c** as a white solid which was still contaminated with impurities which were dominantly present in the NMR spectrum in the δ 0.99-3 ppm region; R_f 0.24 (MeOH/CH_2Cl_2=1/9, v/v); α_D^{22}=-2.9 (c=2 05, MeOH/CH_2Cl_2=1/1, v/v); CIMS(70eV), m/z (relative intensity) 258 ([M+1]$^+$, 100), 241 ([M-NH_2]$^+$, 8), 171 (29), 144 ([$C_{10}H_{10}N$]$^+$, 9), 130 ([C_9H_8N]$^+$, 5); ^{1}H NMR (400 MHz) δ δ 9.07 (br d, 1H, indole NH), 7.46 (d, 1H, J=7.1 Hz, C(12)H), 7 44 (d, 1H, J=8 2 Hz, C(9)H), 7.17 (t, 1H, J=7.3 Hz, C(10)H), 7.11 (t, 1H, J=7.3 Hz, C(11)H), 3.99 (br s, 1H, C(13b)Hα), 3.86-3 80 (br m, 1H, C(1)Hα), 3.73-3.59 (m, 2H, C(4)H_2), 3.38 (br d, 1H, J=6.6 Hz, C(7)Hβ), 2.93 (dt, 1H, J=3.5Hz and J=8.8 Hz, C(7)Hα), 2.80 (br t, 1H, J=13.4 Hz, C(8)Hβ), 2 74 (br dt, 1H, J=2.3 Hz and J=12.6 Hz, C(8)Hα), 1 94 (s, 1H), 1.76-1.60 (m, 3H)

(*S*)-**5-bromo-1,2-pentanediol** (**28**): Asymmetric approach To a well stirred solution of *tert*-butyl alcohol (100 mL) and water (100 mL) was added potassium osmate (VI) dihydrate (14,5 mg, 0.039 mmol), hydroquinidine 1,4-phtalazinediyl diether (150 mg, 0.19 mmol), potassium carbonate (8.2 g, 59 mmol) and potassium ferricyanide (19 3 g, 59 mmol). After a clear two-layer system appeared, the solution was cooled to 0°C. To this well stirred cold 2-phase system was added 5-bromo-1-pentene **27** (2.4 mL, 3.0 g, 20 mmol) in one portion. After stirring in the refrigerator at 4°C over night sodium sulfite (30.0 g, 24 mmol) was added to the bright yellow suspension, and the reaction mixture was allowed to warm up to room temperature After stirring for an additional hour EtOAc (200 mL) and brine (25 mL) were added to the, now almost colorless, reaction mixture. The organic phase was separated and the water phase was subsequently extracted with 3 portions EtOAc. The combined organic phases were washed with brine and dried ($MgSO_4$). After removal of the solvent *in vacuo* 3.43 g (94%) crude **28** was obtained as a yellowish oil To determine the e.e. (*vide infra*) a small part of the reaction mixture was further purified by column chromatography (MeOH/CH_2Cl_2=3/97, v/v) to obtain pure **28** as a colorless oil; R_f 0.26 (MeOH/CH_2Cl_2=7/93, v/v); α_D^{22}=-10.7 (c=3.92, MeOH, e e =65%); ^{1}H-NMR (90 MHz) δ 3.87-3.32 (m, 5H, OCH_2CH and $BrCH_2$), 3.24 (br s, 2H, exchangeable, 2xOH), 2.20-1.44 (m, 4H, $BrCH_2\underline{CH_2}\underline{CH_2}$); EIMS(70eV), m/z (relative intensity) 153 ([M-CH_3O]$^+$ 17), 151 ([M-CH_3O]$^+$, 17), 71 (84), 43 ([C_2H_3O]$^+$, 100) Symmetric approach (to obtain both enantiomers to facilitate the e.e. determination): To a stirred solution of 5-bromo-1-pentene **27** (0 25 mL, 0.32 g, 2.1 mmol) and 4-methylmorpholine *N*-oxide (0.42 g, 3.55 mmol) in THF/H_2O (2/1, v/v, 10 mL) was added osmium tetroxide (2 6 mL of a 2 5% solution in *tert*-butyl alcohol). After stirring for 12 h. sodium sulfite (0.4 g, 3.2 mmol) was added and the reaction mixture was filtered over hyflo. After evaporation of the volatiles *in vacuo* the residue was subjected to column chromatography (MeOH/CH_2Cl_2=3/97, v/v) to yield 35 mg (9%) of racemic **28**. Determination of the enantiomeric purity Both optically active and racemic **28** were converted into their di-(*R*)-MTPA esters following the procedure described by Mosher and coworkers.[15] Determination of the e.e. by ^{1}H-NMR (400 MHz) gave an e.e of 64%, calculated from the double doublets at 4 56 ppm (*R*-enantiomer) and 4 28 ppm (*S*-enatiomer). ^{19}F-NMR (376 MHz, 325°K) gave an e.e. of 66%, calculated from the singlets at 8.50/8.28 ppm (*R*-enantiomer) and 8.36/8 31 ppm (*S*-enantiomer).

29: To a stirred solution of **28** (2.84 g, 15.5 mmol) in DMF (25 mL) was added imidazole (1 6 g, 23 mmol) and *tert*-butyldimethylsilyl chloride (2 34 g, 15 5 mmol). After standing of the reaction mixture over night *tert*-butylchlorodiphenylsilane (4.27 g, 15.5 mmol) together with another portion imidazole (1.6 g, 23 mmol) were added

After additional stirring over night the volatiles were evaporated at high vacuum The residue was dissolved in EtOAc (50 mL) and subsequently washed with 2 portions 10% citric acid, sat. $NaHCO_3$ and brine. After drying ($MgSO_4$) the solvent was evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/8, v/v) affording 5.0 g (64%) of **29** as a colorless oil, R_f 0.69 (EtOAc/hexanes=1/4, v/v); ^1H NMR (90 MHz) δ 7.87-7.71 (m, 4H, 2xPhH_2), 7 55-7 43 (m, 6H, 2xPhH_3), 4.10-3 35 (m, 5H, OCH_2CH and $BrCH_2$), 2 18-1.64 (m, 4H, $BrCH_2CH_2CH_2$), 1.18 (s, 9H, $C(CH_3)_3$), 0.93 (s, 3H,$C(CH_3)_3$), 0.04 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$)

(*S*)-5-bromo-2-(*tert*-butyldimethylsilyloxy-pentane-1-ol (30): To **29** (5 0 g, 9.8 mmol) in dry ethanol (25 mL) was added PPTS (0.82 g, 3.3 mmol) After standing of the reaction mixture over night no conversion of the starting material was detected by TLC Subsequent heating of the reaction mixture over night at 40°C gave complete consumption of the starting material The volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/4, v/v) to give 2.19 g (53%) of **30** as a colorless oil; R_f 0 31 (EtOAc/hexanes=1/4, v/v); R_f 0.45 (EtOAc/hexanes=1/2, v/v), α_D^{22}=+5.9 (c=2 56, acetone); ^1H NMR (90 MHz) δ 7.69-7.47 (m, 4H, 2xPhH_2), 7 43-7 22 (m, 6H, 2xPhH_3), 3.82-3.62 (m, 1H, $HOCH_2CH$), 3.42-3.05 (m, 4H, $BrCH_2$ and $HOCH_2$), 1.75-1 43 (m, 4H, $BrCH_2CH_2CH_2$), 0 96 (s, 9H, $C(CH_3)_3$); CIMS(70eV), m/z (relative intensity) 391 ([M-CH_3O]$^+$, 0.07), 389 ([M-CH_3O]$^+$, 0 06), 199 (100)

(*S*)-5-bromo-2-(*tert*-butyldiphenylsilyloxy-pentanal diethyl acetal (26): Oxalyl chloride (0 29 mL, 0.42 g, 3 31 mmol) was dissolved in dichloromethane (25 mL) employing flame dried glass equipment under an argon atmosphere After cooling to -75°C, dry dimethyl sulfoxide (0.47 mL, 0.51 g, 6.54 mmol) was added over a 5 min period and the reaction mixture was stirred for 5 min. at that temperature. Subsequently **30** (0 92 g, 2 2 mmol), dissolved in dry dichloromethane (5 mL), was added and after additional stirring for 10 min., triethylamine (1.5 mL, 1 1 g, 10.9 mmol) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was washed with 10% citric acid, sat. $NaHCO_3$ and brine After drying (Na_2SO_4) the volatiles were evaporated *in vacuo* to yield the crude aldehyde; R_f 0 58 (EtOAc/hexanes=1/2, v/v); R_f 0 50 (EtOAc/hexanes=1/6, v/v), ^1H NMR (90 MHz) δ 9.59 (d, 1H, J=1.3 Hz, HCO), 7 72-7 32 (m, 10H, 2xC_6H_5), 4 11-4.02 (m, 1H, CH), 3.56-3 23 (m, 2H, $BrCH_2$), 1 87-1 76 (m, 4H, CH_2CH_2), 1.11 (s, 9H, $C(CH_3)_3$) The aldehyde was dissolved in dry ethanol (25 mL), and triethyl orthoformate (2 mL) and $TsOH•H_2O$ (±5 mg) were added. After standing for 3 h sat. $NaHCO_3$ (10 mL) was added and the volatiles were evaporated *in vacuo*. The residue was dissolved in EtOAc (50 mL) and washed with water and brine and then dried ($MgSO_4$). After evaporation of the solvent *in vacuo* the residue was subjected to column chromatography (EtOAc/hexanes=1/8, v/v) to yield 1 02 g (94%) of **26** as a colorless oil; R_f 0 63 (EtOAc/hexanes=1/6, v/v), α_D^{22}=-5 40 (c=2.24, MeOH), ^1H NMR (90 MHz) δ 7 78-7 66 (m, 4H, 2xPhH_2), 7.42-7.30 (m, 6H, 2xPhH_3), 4.24 (d, 1H, J=4.8Hz, $CH(EtO)_2$), 3 84-3.03 (m, 7H, $BrCH_2$, $CHCH(OEt)_2$ and 2xOCH_2CH_3), 2.05-1 50 (m, 4H, $BrCH_2CH_2CH_2$), 1 19 and 0 95 (2xt, 6H, J=7.1 Hz, 2xOCH_2CH_3), 1.06 (s, 9H, $C(CH_3)_3$), CIMS(70eV), m/z (relative intensity) 449 ([M-CH_3O]$^+$, 0.8), 447 ([M-CH_3O]$^+$, 0.7), 161 (71), 103 ([$HC(OC_2H_5)_2$]$^+$, 100)

Alkylation of N_b-Teoc-N_b-hydroxytryptamine **8a** with **26** followed by the PS cyclization

(S)-2-(*tert*-butyldiphenylsilyl)oxy-5-[N-[2-(1H-indol-3-yl)-ethyl]-N-(2-allyloxycarbonylaminooxy)-pentanal diethyl acetal (31) The same procedure was followed as described for **20a**. NaH (120 mg of a 80% oil dispersion, 4.0 mmol), **26** (2,0 g, 4 0 mmol), NaI (100 mg, 0.7 mmol) and **8b** (1 0 g, 3.8 mmol) were stirred for 3 days at 50°C and gave after work-up and purification by column chromatography (EtOAc/hexanes=3/7, v/v) 1.28 g (50%) of **31** as an oil, R_f 0.38 (EtOAc/hexanes=1/2, v/v), ^1H NMR (90 MHz) δ 8 07 (br s, 1H, indole-NH), 7 80-7.58 (m, 5H, indole-C(7)H and 2xPhH_2), 7.39-6 99 (m, 10H, 2xPhH_3 and indole C(2)H and C(4)-C(6)H_3), 6.04-5.62 (m, 1H, H_2C= CH-CH_2), 5.34-5 10 (m, 2H, H_2C=CH-CH_2), 4 49 (dt, 2H, J=1 2 Hz and J=5.6 Hz, H_2C=CH-CH_2), 4.23 (d, 1H, J=4 6 Hz, $HC(OEt)_2$), 3 86-2.97 (m, 11H, indole-C(3)-$CH_2CH_2NOCH_2$-, $CHCH(OEt)_2$ and 2xOCH_2CH_3), 1 89-1.53 (m, 4H, $OCH_2CH_2CH_2CH$-), 1 17 and 0.94 (2xt, 6H, J=7.2 Hz, 2xOCH_2CH_3), 1.06 (s, 9H, $C(CH_3)_3$), CIMS(70eV), m/z (relative intensity) 569 ([M-$HC(OC_2H_5)_2$]$^+$, 0.2), 144 ([$C_{10}H_{10}N$]$^+$, 3), 130 ([C_9H_8N]$^+$, 5), 103 ([$HC(OC_2H_5)_2$]$^+$, 4), 91 ([C_7H_7N]$^+$, 14), 41 ([C_3H_5]$^+$, 100) together with 1 18 g (59%) recovered **26**.

(S)-2-(*tert*-butyldiphenylsilyl)oxy-5-[N-[2-(1H-indol-3-yl)-ethyl-aminooxy]-pentanal diethyl acetal (25): To a mixture of acetonitrile/water (4/1, v/v, 25 mL) under an argon atmosphere was added **31** (1 28 g, 1.90 mmol), triethylammonium formate (10 g), palladium(II)acetate (7 mg, 0.03 mmol) and triphenylphosphine (23 mg, 0.09 mmol)

The reaction mixture was heated at reflux for 45 min and then poured into EtOAc (100 mL) The organic layer was extracted with sat $NaHCO_3$, water and brine After drying (brine and $MgSO_4$) the solvents were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/2, v/v) to give 980 mg (88%) of **25** as a colorless oil, R_f 0 26 (EtOAc/hexanes=1/2, v/v), ^1H NMR (90 MHz) δ 8 07 (br s, 1H, indole-NH), 7 80-7 57 (m, 5H, indole-C(7)H and 2xPhH_2), 7 38-7 00 (m, 10H, 2xPhH_3 and indole C(2)H and C(4)-C(6)H_3), 5 45 (very br s, ONH), 4 24 (d, 1H, J=4 8 Hz, $HC(OEt)_2$), 3 81 2 91 (m, 11H, indole-C(3)-$CH_2CH_2NOCH_2$-, $\underline{CH}CH(OEt)_2$ and 2x$O\underline{CH_2}CH_3$), 1 84-1 46 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH$-), 1 25 and 0,94 (2xt, 6H, J=7 2 Hz, 2x$OCH_2\underline{CH_3}$), 1 05 (s, 9H $C(CH_3)_3$)

(1*S*,13b*R*)-1-hydroxy-1,2,3,4,7,8,13,13b-octahydro-[1,2]-oxazepino-[2',3':1,2]pyrido[3,4-*b*]indole (5) and **(1*S*,13b*S*)-1-hydroxy-1,2,3,4,7,8,13,13b-octahydro-[1,2]-oxazepino-[2',3':1,2]pyrido[3,4-*b*]indole (32)** **25** (1 2 g, 2 04 mmol) was dissolved in a mixture of formic acid/water (9/1, v/v, 100 mL) After standing at room temperature for 30 min all starting material had been consumed The volatiles were evaporated at high vacuum and the residue was dissolved in EtOAc (50 mL) and subsequently washed with sat $NaHCO_3$, water and brine After drying ($MgSO_4$) and evaporation of the solvent *in vacuo* the residue was dissolved in dry THF (15 mL) and tetrabutylammonium fluoride (2 5 mL of a 1M solution in THF) was added After completion of the reaction (30 min) the solvent was evaporated *in vacuo* The product ratio was determined at this stage by analytical HPLC (acetonitrile/water=3/7, v/v, flow=1 mL/min , λ=280 nm), retention time (min), **32** (4 5) and **5** (5 6) ratio **32/5**=18/82 The residue was subjected to column chromatography (EtOAc/hexanes=1/2, v/v) to give 413 mg (78%) of **5** as a white solid, R_f 0 39 (EtOAc/hexanes=1/1, v/v), 0 22 (EtOAc/hexanes=1/2, v/v), α_D^{22}=-23 2 (c=3 40, EtOAc), CIMS(70eV), exact mass calcd for $C_{15}H_{18}N_2O_2$ m/z , 258 1368 ($[M]^+$) Found 258 1467, (relative intensity) 258 ($[M]^+$, 100), 241 ($[M\text{-}OH]^+$, 12), 169 (78), 144 ($[C_{10}H_{10}N]^+$, 42), 130 ($[C_9H_8N]^+$, 7), ^1H NMR (400 MHz) (all assignments are based on NOESY) δ 9 00 (br s, 1H, indole NH), 7 47 (d, 1H, J=7 7 Hz, C(12)H), 7 32 (d, 1H, J=8 0 Hz, C(9)H), 7 14 (t, 1H, J=7 4 Hz, C(10)H), 7 07 (t, 1H, J=7 4 Hz, C(11)H), 4 12-4 08 (m, 1H, C(1)Hβ), 3 78-3 71 (br m, 3H, C(13b)Hα and $C(4)H_2$), 3 05-2 92 (m, 2H, C(7)Hα and C(8)Hα), 2 78 (br d, 1H, J=13 4 Hz, C(8)Hβ), 2 05-1 95 (m, 2H, $C(3)H_2$), 1 80-1 73 (m, 2H, $C(2)H_2$), Anal Calcd for $C_{15}H_{18}N_2O_2$ C, 69 75, H, 7 02 N, 10 84 Found C, 69 59, H, 6 95, N, 10 57 together with 110 mg (21%) of **32** as a white solid, R_f 0 30 (EtOAc/hexanes=1/1, v/v), α_D^{22}=+62 3 (c=3 10, EtOAc), CIMS(70eV), exact mass calcd for $C_{15}H_{18}N_2O_2$ m/z , 258 1368 ($[M]^+$) Found 258 1467, (relative intensity) 258 ($[M]^+$, 85), 241 ($[M\text{-}OH]^+$, 12), 227 (41), 169 (84), 149 (100), 144 ($[C_{10}H_{10}N]^+$, 51), 130 ($[C_9H_8N]^+$, 8) ^1H NMR (400 MHz) (all assignments are based on NOESY) δ 7 91 (br s, 1H, indole NH), 7 46 (d, 1H, J=7 7 Hz, C(12)H), 7 29 (d, 1H, J=8 0 Hz C(9)H), 7 15 (t, 1H, J=7 4 Hz, C(10)H), 7 09 (t, 1H, J=7 4 Hz, C(11)H), 4 31 (br s, 1H, C(1)Hβ), 4 13-4 08 (m, 2H, C(13b)Hβ and C(4)Hα), 3 75 (dt, 1H, J=10 6 Hz and J=7 6 Hz, C(4)Hβ), 3 56-3 54 (m, 1H, C(7)Hα), 3 08-3 01 (m, 1H, C(7)Hβ), 2 99-2 91 (m, 1H, C(8)Hβ), 2 78 (br d, 1H, J=15 2 Hz, C(8)Hα), 2 32-2 24 (m, 1H, C(3)Hα), 2 17-2 09 (m, 1H, C(2)Hα), 2 04-1 95 (m, 2H, C(2)Hβ and OH), 1 69-1 62 (m, 1H, C(3)Hβ)

Introduction of the amino group via the Mitsunobu reaction

35a The same procedure was used as described for **42** using **5** (195 mg, 0 76 mmol), hydrazoic acid (0 7 mL of 1 6 m solution in benzene[27]), triphenylphosphine (300 mg, 1 15 mmol) and diisopropyl azodicarboxylate (0 23 mL, 230 mg, 1 14 mmol) Work-up and purification by column chromatography (EtOAc/hexanes=1/4, v/v) afforded 174 mg (81%) of **35a** as a white solid, R_f 0 52 (EtOAc/hexanes=1/2, v/v), IR (KBr pellet) ν (cm $^{-1}$) 2105 (N_3), ^1H NMR (90 MHz) δ 8 33 (br d, 1H, indole-NH), 7 53-7 00 (m, 4H, C(8)-C(11)H_4), 5 07 (br d, 1H, J=9 4 Hz, C(13)H), 3 68-2 68 (m, 5H, NCH_2CH_2 and C(13a)H), 2 36-1 43 (m, 4H, $\underline{CH_2}\underline{CH_2}CH_2O$)

35b To **35a** (90 mg, 0 32 mmol) in methanol (25 mL) was added 10% Pd(C) (500 mg) and the resulting suspension was stirred in a hydrogen atmosphere for 30 min The Pd(C) catalyst was removed by filtration over hyflo and the volatiles were evaporated *in vacuo* The residue was subjected to column chromatography (MeOH/$CHCl_3$/Et_3N =5/94 75/0 25, v/v/v) to yield 40 mg (49%) of **35b** as a white solid, R_f 0 24 (MeOH/$CHCl_3$=7/93, v/v) α_D^{22}=+1 6 (c=4 95, MeOH),, CIMS(70eV), exact mass calcd for $C_{15}H_{19}N_3O$ m/z , 257 1528 ($[M]^+$) Found 257 1528, (relative intensity) 257 ($[M]^+$, 21), 241 ($[M\text{-}NH_2]^+$, 10), 169 (70), 158 ($[C_{10}H_{10}N_2]^+$, 100), 144 ($[C_{10}H_{10}N]^+$, 13), 130 ($[C_9H_8N]^+$, 23), ^1H NMR (400 MHz) δ 8 91 (br s, 1H, indole-NH), 7 47 (d, 1H, J=7 7 Hz, C(11)H), 7 31 (d, 1H, J=7 8 Hz, C(8)H), 7 12 (t, 1H, J=7 4 Hz, C(9)H), 7 07 (t, 1H, J=7 3 Hz, C(10)H), 4 09 (br s, 1H, C(13)H), 4 00-3 97 (m, 2H,

$NOCH_2$), 3 54-3 41 (m, 2H, C(6)HH and C(7)HH), 3 04-2 86 (m, 3H, C(6)HH, C(7)HH and C(13a)H), 2 07-2 04 (m, 1H, CH_2CHH), 1 77-1 66 (m, 5H, NH_2 and CH_2CHH), ^{13}C NMR (100 MHz) δ 138 13 C(11a), 133 66 C(12a), 128 33 C(8b), 121 12 C(10), 119 06 C(9), 117 85 C(8), 111 45 C(7a), 110 66 C(11), 69 62 C(3), 68 56 C(13), 57 72 C(6), 49 45 C(13a), 27 18 C(2), 24 42 C(1), 19 52 C(7), Anal Calcd for $C_{20}H_{27}N_3O_3 \cdot 1/4H_2O$ C, 68 81, H, 7 51, N, 16 05 Found C, 68 96, H, 7 50, N, 14 37

35c To **35b** (18 mg, 0 07 mmol) dissolved in dichloromethane (1 mL) was added 4-nitrobenzoyl chloride (19 mg, 0 10 mmol) and triethylamine (19 µL, 14 mg, 0 14 mmol) After stirring of the reaction mixture for 2 h the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/2, v/v) to give 18 mg (63%) of **35c** as yellow crystals (mp=252°C, decomp , CH_2Cl_2/EtOH by very slow evaporation of CH_2Cl_2), R_f 0 30 (EtOAc/hexanes=1/1, v/v), EIMS(70eV), m/z (relative intensity) 406 ($[M]^+$, 19), 195 (74), 28 (100), ^1H NMR (400 MHz) δ 8 39 (br s, 1H, indole-NH), 8 28 (d, 2H, J=8 7 Hz, O_2NPhH_2), 7 94 (d, 2H, J=8 7 Hz, O_2NPhH_2), 7 50 (d, 1H, J=7 8 Hz, C(11)H), 7 31 (d, 1H, J=8 0 Hz, C(8)H), 7 29 (br d, 1H, NH), 7 18 (t, 1H, J=7 3 Hz, C(9)H), 7 12 (t, J=7 4 Hz, C(10)H), 5 38 (dd, 1H, J=8 0 Hz and J=5 5 Hz, C(13)H), 4 15 (dt, 1H, J≈11 Hz, NOCHH), 3 85-3 78 (m, 2H, C(13a)H and C(6)HH), 3 71 (dt, 1H, J=11 3 Hz and J=2 1 Hz, NOCHH), 3 44 (ddd, 1H, J=12 2 Hz, J=6 7 Hz and J=2 5 Hz, C(6)HH), 3 15 (ddd, 1H, J=15 9 Hz, J=6 6 Hz and J=2 2 Hz, C(7)HH), 2 96 (ddd, 1H, J=16 1 Hz, J=10 3 Hz and J=2 4 Hz, C(7)HH), 1 92-1 78 (m, 3H, CH_2CHH), 1 65-1 58 (m, 1H, CH_2CHH)

42 To **5** (100 mg, 0 39 mmol), diallyl iminodicarbonate (110 mg, 0 59 mmol), and triphenylphosphine (200 mg, 0 76 mmol) in dry THF (0 5 mL) was added diisopropyl azodicarboxylate (0 115 mL, 120 mg, 0 59 mmol) gradually over a period of 5 min causing a slight exothermic reaction After stirring for 1 5 h the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/4, v/v) to yield 70 mg (42%) of **42** as a colorless oil, R_f 0 31 (EtOAc/hexanes=1/2, v/v), CIMS(70eV), m/z (relative intensity) 426 ($[M+1]^+$, 100), ^1H NMR (400 MHz, to sharpen up the severely broadened spectrum recorded at 58°C) δ 7 84-7 79 (m, 1H, C(11)H), 7 47-7 42 (m, 1H, C(8)H), 7 24-7 19 (m, 2H, C(9)H and C(10)H), 6 07 (br s, 1H, C(12b)H), 5 32 (heptet, 1H, J=6 1 Hz, $OCH(Me)_2$), 5 02 (heptet, 1H, J=6 2 Hz, $OCH(Me)_2$), 4 01-3 92 (m, 2H, OCH_2), 3 59 (ddd, 1H, J=12 9 Hz, J=4 9 Hz and J=1 6 Hz, C(6)HH), 3 18 (t, 1H, J=13 7 Hz, C(7)HH), 2 87-2 82 (br m, 1H, C(12c)H), 2 73 (dd, 1H, J=15 6 Hz and J=4 2 Hz, C(7)HH), 2 58 (t, 1H, J=12 1 Hz, C(6)HH), 2 01 (br s, 1H, C(2)HH), 1 94-1 82 (m, 2H, $C(1)H_2$), 1 59 (d, 3H, J=6 1 Hz, CH_3), 1 46 (d, 3H, J=6 3 Hz, CH_3), 1 51-1 44 (m, 1H, C(2)HH), 1 36 (d, 3H, J=6 2 Hz, CH_3), 1 32 (d, 3H, J=6 2 Hz, CH_3), ^{13}C NMR (100 MHz) δ 154 54 C(13), 147 84 C(16), 135 77 C(11a), 133 41 C(12a), 129 10 C(7b), 123 24 C(9), 122 73 C(10), 118 35 C(8), 115 39 C(7a), 115 18 C(11), 72 74 C(14), 70 22 C(3), 69 84 C(16), 64 61 C(12b), 57 46 C(6), 50 11 C(12c), 25 59 C(2), 23 35 C(1), 22 27 CH_3, 22 14 CH_3, 22 00 CH_3, 21 45 CH_3, 19 88 C(7)

References and Footnotes

1 Hermkens, P H H *"N-hydroxy β-carbolines Syntheses, Applications, and Biological Activities"*, **1990**, Thesis, University of Nijmegen

2 Hermkens, P H H , Maarseveen, J H van, Berens, H W , Smits, J M M , Kruse, C G , Scheeren, J W *J Org Chem* **1990**, 55, 2200

3 Hermkens, P H H , Maarseveen, J H van Unpublished results

4 Kirkup, M P , Shankar, B B , McCombie, S , Ganguly, A K *Tetrahedron Lett*, **1989**, 30, 6809

5 Kurihara, T , Doi, M , Hamaura, K , Ohishi, H , Harusawa, S , Yoneda, R *Chem Pharm Bull* **1991**, 39, 811

6 Amiard, G , Heymès, R , Velluz, L *Bull Soc Chim Fr* **1956**, 97

7 Although **14a** has been mentioned in the literature no spectroscopic data are given see Webb, R G , Haskell, M W , Stammer, C H *J Org Chem* **1969**, 34, 576

8 Schroder, E , Klieger, E *Liebigs AnnnChem* **1964**, 673, 196

9 Klieger, E , Gibian, H *Liebigs Ann Chem* **1962**, 655, 195

10 To the best of our knowledge Boc-Pro-OMe has not been described before For (*L*)-Pro-OMe see Cassal, J-M , Furst, A , Meier, W *Helv Chim Acta* **1976**, 59, 1919

11 Nefkens, G H L , Tesser, G I , Nivard, R J F *Recl Trav Chim Pays Bas*, **1960**, 79, 688

12 Olah, G A , Gupta, B B G , Malhotra, R , Narang, S C *J Org Chem* **1980**, 45, 1638

13 Dr. B.B. Shankar of Schering Plough Research Institute (NJ, USA) is greatly acknowledged for providing the X-ray crystallography and NMR data of several desthia carba eudistomin analogs.

14 Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J., Jeong, K-S.; Kwong, H-L.; Morikawa, K.; Wang, Z-M.; Xu, D.; Zhang, X-L., *J.Org.Chem.* **1992**, 57, 2768

15 Dale, J.A.; Mosher, H.S. *J.Am.Chem.Soc.*, **1973**, 95, 512

16 Prakash, C.; Saleh, S.; Blair, I.A. *Tetrahedron Lett.*, **1989**, 30, 19

17 Jurczak, J; Pikul, S.; Bauer, T. *Tetrahedron*, **1986**, 42, 447

18 Roberts, J.S. in *Comprehensive Organic Chemistry*, Barton, D.H.R.; Ollis, W.D. Eds., Pergamon Press: Oxford. **1979**, Vol. 2; pp. 185

19 Undesired nucleophilic competition during palladium(0) catalyzed deprotection of Aloc groups has been described before: Hayakawa, Y ; Kato, H., Uchiyama, M.; Kajino, H.; Noyori, R. *J.Org.Chem.* **1986**, 51, 2400

20 Arnould, J.C.; Landier, F.; Pasquet, M.J. *Tetrahedron Lett.*, **1992**, 33, 7133, $(Aloc)_2NH$ was synthesized from $(Aloc)_2O$ (Sennyey, G.; Barcelo, G.; Senet, J-P. *Tetrahedron Lett*, **1987**, 28, 5809) as described for $(Boc)_2NH$ by Grehn, L.; Ragnarsson, U. *Synthesis*, **1987**, 275 The method described by Arnould and coworkers is probably the most convenient.

21 Grynkiewicz, G.; Jurczak, J.; Zamojski, A. *Bull.Acad.Pol.Sci.*, **1976**, 24, 83

22 The greatest difference of the positions of the signals H(1) in the NMR spectra of cis/trans eudistomins was 0.63 ppm for the 1-methoxy-debromoeudistomins K (**1a**/**22a** in chapter 2)

23 a) Julia, M.; Bagot, J.; Siffert, O. *Bull.Soc.Chim.Fr.* **1973**, 1424. In a recent paper this ring expansion was named a 'Homo-Pictet-Spengler' cyclization: b) Laronze, J-Y.; Gauvin-Hussenet, C ; Lévy, J. *Tetrahedron Lett.*, **1991**, 32, 619

24 Indeed the reaction between the phosphonium salt and the nucleophile is a slow process in the Mitsunobu reaction. See :Varasi, M.; Walker, K.A M.; Maddox, M.L. *J.Org.Chem.*, **1987**, 52, 4235

25 Massiot, G.; Thépenier, P.; Jacquier, M-J.; Lounkokobi, J.; Mirand, C.; Zèches, M.; Le Men-Olivier, L *Tetrahedron*, **1982**, 39, 3645. Total synthesis: Bosch, J.; Bennasar, M-L.; Zulaica, E.; Massiot, G.; Massoussa, B. *Tetrahedron Lett.*, **1987**, 28, 231

26 Kuijpers, P.H.; Gerding, T.K.; De Jong, G.J. *J.Chromatogr.* **1992**, 625, 223

27 Wolff, H. *Organic Reactions*, Adams, R. Ed. John Wiley & Sons, Inc., New York, **1946**, part III, 327

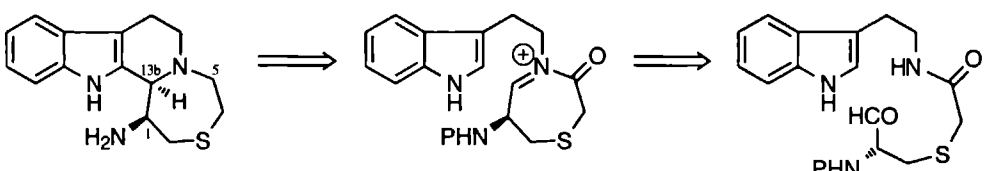
5 Attempted Synthesis of a Tetracyclic Eudistomin Desoxa Carba Analog

5.1 Introduction

The justification for the synthesis of the tetracyclic eudistomin carba-analog lacking the oxygen atom was given in the introductory section of chapter 4, where the synthesis of a desthia carba eudistomin analog is described This chapter deals with the (attempted) synthesis of a desoxa carba analog

The intramolecular Pictet-Spengler (PS) condensation strategy was chosen for closure of the 7-membered ring, as is shown in a retrosynthetic manner in scheme 5 1 [1]

Scheme 5.1



1

2a P=Boc
2b P=Cbz

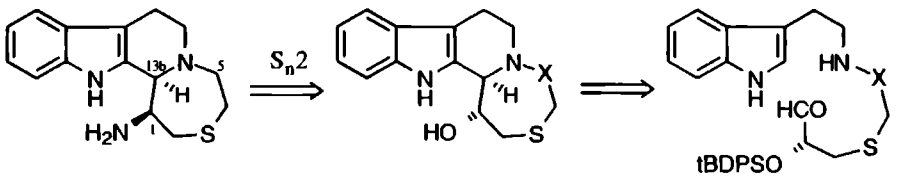
3a P=Boc
3b P=Cbz

The PS cyclizations are planned with secondary amides, giving the highly reactive intermediate N-acyl iminium ions **2** [2] Besides the Boc protective group also the more acid stable Cbz group was used as the amine protective group Because formation of N-acyliminium ions proceeds more slowly than formation of N-alkoxyiminium ions racemization is likely to occur It is known that cysteinal derivatives racemize extremely fast and it may be expected that the optical activity will be completely lost [3] Therefore, for the build-up of the cysteine fragment, which has the *D*-configuration in natural eudistomin, inexpensive *L*-cystine was used

As it was expected that the undesired C(13b)H-C(1)H trans diastereomer would be formed in excess in the intramolecular PS condensation we studied the approach from α-alkoxy aldehydes at the same time S_n2 type introduction of the amino functionality in the thus obtained trans 1-hydroxy eudistomin analog would give then the desired cis eudistomin derivative This approach failed for the syntheses of the natural eudistomins as well as for the desthia-carba eudistomins because of transannular neighboring group participation from the sulfur or N_b nitrogen atoms, respectively (chapters 3 and 4) In the case of the desoxa carba analog neighboring group participation from the N_b nitrogen atom in **4a** is impossible due to the low nucleophilicity of the amide nitrogen

Participation from the sulfur atom also may be less likely to occur because of the increased rigidity of the 7-membered lactam in **4a**

scheme 5.2



1 **4a** X= C=O **5a** X= C=O
4b X=CH_2 **5b** X=CH_2

In addition to the approach via a highly reactive N-acyliminium ion from **5a** also cyclization via the dialkyl iminium ion from **5b** has been investigated, with the primary aim to study the synthetic scope of the intramolecular PS condensation (scheme 5 2)

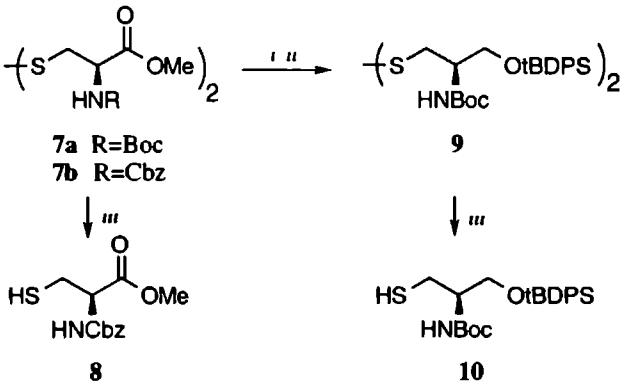
5.2 Direct Approach Based on *L*-Cystine

5.2.1 Build up of the Cystine Derived Fragment and its Coupling with Tryptamine

As shown in scheme 5 1 the PS cyclization requires a free aldehyde as essential substrate Access to such aldehydes by DIBAL reduction of the corresponding ester is not conceivable in this case because of the presence of the amido function in **3** Hydrolysis of an acetal is not feasible either because α-amino acetals only sluggishly undergo such a reaction (see chapter 2) Therefore the oxidative approach from β-amino alcohols was chosen

For the synthesis of N-Boc protected cystinol derivative **9** (see scheme 5 3) the strategy developed by Ottenheijm and coworkers was followed starting from *L*-cystine [4] Boc-cystine methylester **7a** and Cbz-cystine methylester **7b** were prepared according to literature procedures [5] Reduction of **7a** with lithium borohydride followed by protection of the primary alcohols as their *tert*-butyldiphenylsilyl ethers gave **9** in 99% yield Cleavage of the disulfide bond in **7b** and **9** was accomplished by treatment with erythro-1,4 dimercapto-2,3-pentanediol (dithiothreitol) and triethylamine Thiol **10** was isolated in 99% yield and was used in the next reaction without further purification It is interesting to note that the reduction of the disulfide in cystinol derivative **9** was approx 200x slower than the reduction of cystine derivative **7b** (*viz* 3 weeks compared to 2 hours)

scheme 5.3



7a R=Boc
7b R=Cbz

9

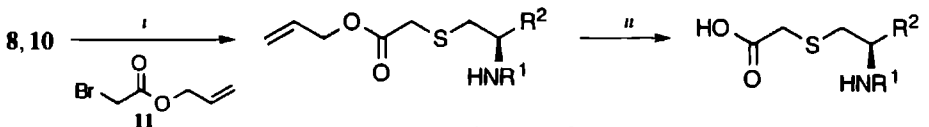
8

10

i) $LiBH_4$, MeOH, Et_2O, ii) tBDPS-Cl imidazole DMF iii) erythro 1,4 dimercapto-2,3 pentanediol Et_3N, Et_2O

The thiols **8,10** were then alkylated with allyl bromoacetate **11** using 1,8-diazabicyclo[5 4 0]-undec-7-ene (DBU) as the base to give the thioethers **12a,b** from which the carboxylic acids were liberated by treatment with $Pd(PPh_3)_4$/morpholine to give **13a,b** in overall yields of 72% (from the corresponding diol of **7a**) and 69% (from **7b**), respectively

scheme 5.4

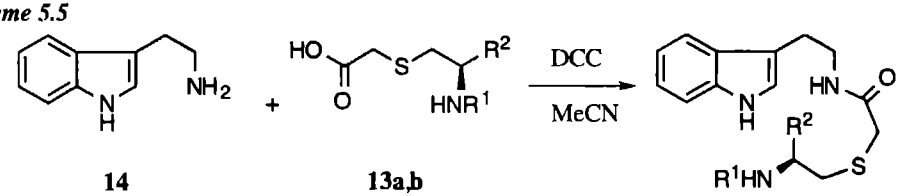


12a R^1=Boc, R^2=$CH_2OtBDPS$ **13a**
12b R^1=Cbz, R^2=CO_2Me **13b**

i) DBU benzene, ii) $Pd(PPh_3)_4$ morpholine

Both acids **13a,b** were coupled with tryptamine **14** by activation with 1,3-dicyclohexylcarbodiimide to give the amides **15a** (after subsequent removal of the tBDPS protective group with tetrabutylammonium fluoride) and **16** in 61% and 62% yield, respectively (scheme 5 5)

scheme 5.5



14

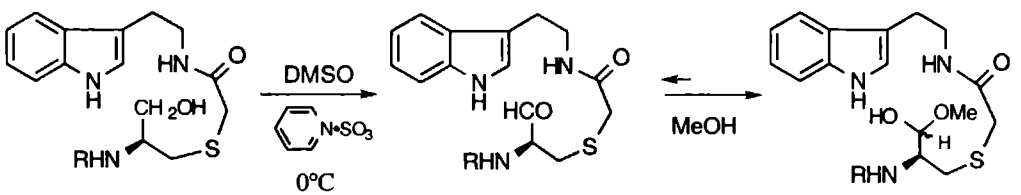
13a,b

15a R^1=Boc, R^2=CH_2OH
16 R^1=Cbz, R^2=CO_2Me
15b R^1=Cbz, R^2=CH_2OH

The primary β-amino alcohol **15b** was obtained after selective reduction of the methyl ester in **16** by treatment with lithium borohydride in 78% yield Oxidation of the alcohols in **15a,b** to the

corresponding aldehydes using pyridinium chlorochromate or a Swern procedure failed [3] The method of choice for this oxidation was a slightly modified procedure as described for the oxidative approach to carbamate protected α-amino aldehydes [6] This procedure is also based on activated DMSO, by an electrophilic pyridine-sulfur trioxide complex, followed by a reaction sequence analogous to the Swern oxidation. Following this procedure combined with cooling of the reaction mixture to 0°C the aldehydes **3a,b** were obtained in 56% and 64% yield, respectively (scheme 5 6) NMR spectroscopy of the crude reaction mixture of **3a** clearly showed the presence of the aldehyde After purification of the aldehydes by column chromatography ($MeOH/CH_2Cl_2$=3/97, v/v) NMR spectroscopy revealed almost complete disappearance of the aldehyde The methanol used in the eluent had reacted with the aldehyde to give the methyl hemiacetal (scheme 5.6)

Scheme 5.6



15a. R=Boc
15b R=Cbz

3a,3b

3a',b'

The presence of a second chiral center in the hemiacetal was detectable in the NMR spectrum, The BocNH proton was now present as a double doublet (δ=5 07 and 4 92 ppm, J=9 4 Hz) in combination with the presence of two singlets (δ=3 37 and 3 36 ppm) from the methoxy protons in both diastereomers. Similar observations were made for aldehyde **3b** After standing for 6 hours in $CDCl_3$ containing 4Å molsieves the aldehydes **3a,b** could be regenerated completely NMR analysis showed that in deuteriochloroform both hemiacetals **3a',b'** were in equilibrium with the corresponding aldehydes **3a,b** in a 95/5 ratio

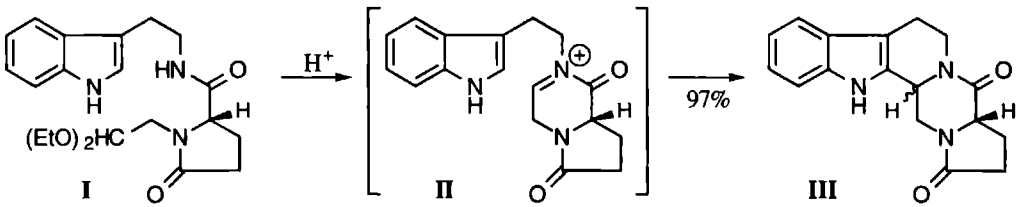
The aldehydes were isolated as racemates as was expected from literature data (*vide supra*) [3]

5.2.2 Pictet-Spengler Condensation

The initial cyclization experiments were carried out with the Boc protected α-amino aldehyde derivative **3a** By application of the standard cyclization conditions, *viz* dichloromethane/trifluoro-acetic acid, formic acid or heating in acetic acid, TLC indicated only slow moving products which may indicate the presence of a primary amine group resulting from removal of the Boc group Substitution of the Boc group in **3a** by the more acid stable Cbz group in **3b** did not lead to cyclized products Application of the above mentioned conditions indeed showed the higher stability of the Cbz group toward acid treatment, but further activation by heating under PS conditions only led to decomposition of the starting material It was also thought that the presence of the aldehydes as their methyl hemiacetals contributed to the low reactivity Transformation, however, of the

hemiacetal into the aldehyde by treatment with 4Å molecular sieves prior to the addition of trifluoroacetic acid (2-5 eq) or acetic acid/acetic anhydride (95/5, v/v, as solvent) did not alter the outcome of the reaction The reason for this failure is most probably the difficult formation of the highly unfavored intermediate 7-membered cyclic acyliminium ion **2** (in combination with other factors, *vide infra*) A similar cyclization of **I**, in which a 6-membered cyclic iminium ion intermediate **II** is formed, has been described and proceeded smoothly in high yields (scheme 5 7) to give the yohimbine derivative **III** [7]

Scheme 5.7

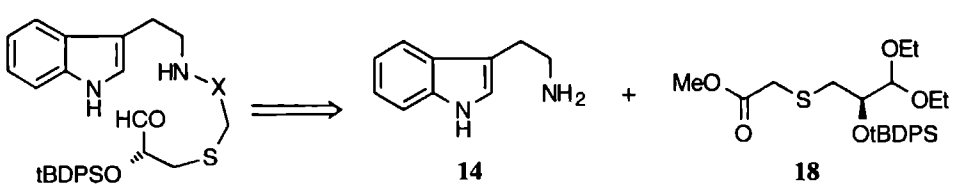


5.3 Approach via the Trans 1-Hydroxy Eudistomin Analog

5.3.1 Synthesis of the α-Alkoxy Aldehyde Fragment and its Coupling with Tryptamine

According to the retrosynthetic sequence shown in scheme 5 2 the compounds **5** are required as starting material for the PS condensation Build up of the N_b-functionalized tryptamines **5a,b** was accomplished with an amide coupling of tryptamine **14** with the chiral methyl ester **18** (scheme 5 8)

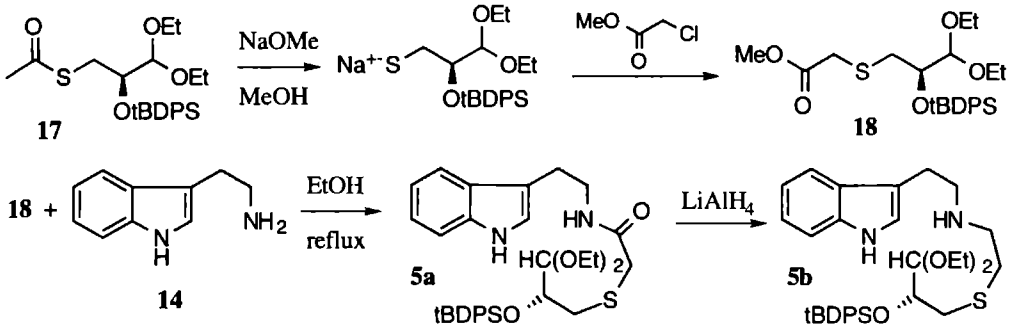
Scheme 5.8



5a X= C=O
5b X=CH_2

The chiral methyl ester **18** was synthesized in two steps from nearly optically pure (R)-3-(acetylthio)-2-(*tert*-butyldiphenylsilyloxy)-propanal diethyl acetal **17** (scheme 5 9) The synthesis of **17** has been described in chapter 3 Deprotection of thioacetate in **17** by treatment with sodium methoxide in methanol gave the sodium thiolate, which was alkylated *in situ* with methyl chloroacetate to give **18** in 96% yield The methyl ester **18** was coupled with tryptamine **14** by heating at reflux in methanol for 1 week to give desired **5a** in 74% yield

Scheme 5.9



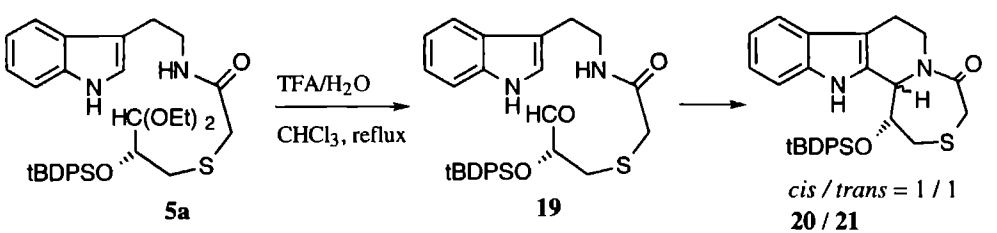
To study the PS cyclization also with a classical iminium-ion the amide moiety in **5a** was reduced with lithiumaluminium hydride to give **5b** in 25% yield.

5.3.2 Pictet-Spengler Condensation

The initial cyclization experiments were carried out with the *amine* **5b**. Using the reaction conditions successfully applied in the chapters 2 and 3 for the *in situ* generation of aldehydes from diethyl acetals (*viz.* trifluoroacetic acid/water in chloroform or formic acid/water) only the formation of numerous side products took place. It is known that the driving force in the PS condensation is the electrophilic nature of the intermediate iminium ion double bond.[8] Therefore, it may be assumed that no cyclization products were formed due to the low reactivity of the intermediate dialkyliminium ion formed from **5b** (*vide infra*).

Indeed with amide **5a**, giving the highly reactive N-acyliminium ion intermediate, cyclization was accomplished, albeit in low yield. By treatment with formic acid/water at room temperature only deprotection of the diethyl acetal to the aldehyde was observed. After heating at reflux of **5a** in chloroform in the presence of trifluoroacetic/water for 18 hours all starting material had been consumed and the two diastereomeric tetracyclic products were isolated in 36% yield in a 50/50 ratio.

Scheme 5.10

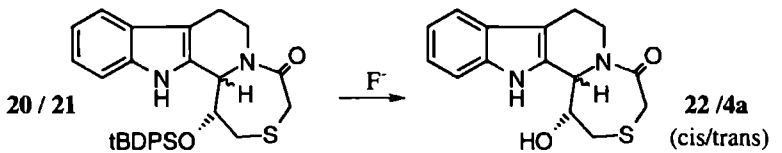


In contrast to the natural eudistomin series, the cis/trans assignments were now reliable be made on the basis of the coupling constants between the C(13b)H and C(1)H protons. Due to the amide-

moiety the tetracyclic structure in **20/21** is almost rigid. This is readily deduced from the NMR spectra because no peak-broadening was observed, in contrast to the spectra of the eudistomins with an oxathiazepine moiety (see chapter 8). In the cis diastereomer H(13b) gives a sharp singlet, corresponding with a dihedral angle with H(1) of ≈90°. In the trans diastereomer H(13b) gives a doublet (J=8.0 Hz), corresponding with a dihedral angle with H(1) of ≈180°.

The tBDPS protective group in **20/21** was removed by treatment with tetrabutylammonium fluoride to give the alcohols **4a/22** in nearly quantitative yields.

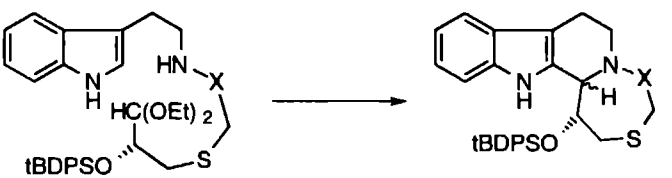
scheme 5.11



Mechanistic intermezzo:

At this point it is interesting to compare the reactivity of the N_b-alkoxyiminium ions as were used in related PS cyclizations in chapter 3, with the reactivity of the N_b-acyl- and N_b-alkyliminium ions used in this chapter. The results of these related cyclizations are summarized in scheme 5.12.

scheme 5.12



entry	X	reaction conditions	reaction time	yield	cis/trans ratio
1	O[a]	formic acid/water (9/1, v/v), 22°C	1 h.	83%	3/7
2	C=O	trifluoroacetic acid/water/ chloroform (1/1/98, v/v/v), reflux (60°C)	18 h.	36%	1/1
3	CH_2	various	various	--	--

[a] See entries 4 and 5 in scheme 3.15 in chapter 3.

By considering the information collected in scheme 5.12, a recapitulation can be made of the efficiency of the PS condensation in relation to the nature of intermediate iminium ion. The discussion of the rate of the reaction in relation to the nature of the iminium ion can be devided into two independent parameters which can be rate determining in the PS condensation:

- The rate of formation of the iminium ion.
- The electrophilicity of the once formed iminium ion.

For clarity reasons we will start discussing the latter parameter. Recently, Cook and coworkers described the relation between the pK_a-values of amines and the reactivity of the corresponding electrophilic iminium ions.[9] A lower pK_a-value of the amine is indicative for a more electrophilic

and thus more reactive iminium ion $(CH_3)HNR + R'-CHO \rightarrow (CH_3)RN^{\oplus}=CHR'$ In table 5 1 some representative amines and their pK_a-values are shown From table 5 1 an increasing reactivity is thus expected in the order CH_3<Bn<OCH_3<Ac

Table 5.1 $(CH_3)HNR$ (pK_a's from ref 10)

R	pK_a	R	pK_a
CH_3	10 7	OCH_3	5 2
Bn	9 54	Ac	-0 46

The reactivity order CH_3<Bn<OCH_3 was confirmed experimentally by Cook and coworkers [9] The reactivity order CH_3<Ac is also established in this chapter with the cyclizations of **5a** and **5b** (entries 3 and 2, respectively, in scheme 5 12) From the data in table 5 1, however, it follows that the fastest PS condensation can be expected when using N-acyliminium ions due to the low electron density at the amide nitrogens, this in contrast with the experimental data shown in scheme 5 12 Although the pK_a of N-alkoxy nitrogen atoms is 5 7 logarithmic magnitudes higher than the pK_a of amide nitrogen atoms, with N-alkoxy amines much higher PS cyclization rates were found (compare entries 1 and 2 in scheme 5 12)

The reason for this deviation may be that with amides the reactivity of the formed N-acyliminium ion is not rate determining in the PS condensation Due to the relative low nucleophilicity of amide nitrogen atoms compared to N-alkoxy nitrogen atoms the formation of N-acyliminium ions is probably rate determining The inductive electron withdrawing N-alkoxy substituent lowers the pK_a of the amine but increases the nucleophilicity of the nitrogen atom due to the alpha-effect [11] This synergistic effect is in particular important in our specific cyclization because a disfavored intermediate 7-membered cyclic iminium ion must be formed

Also the inability of the aldehydes **3a,b** (section 5 2 2) to give a PS cyclization can be explained now As is discussed above cyclizations via N-alkoxyiminium ions proceed much faster than cyclizations via N-acyliminium ions Comparison of the data in scheme 2 11 (chapter 2) with the data in scheme 5 12 shows that the rate of the PS cyclization with α-alkoxy aldehydes is much faster than with carbamate protected α-amino aldehydes Therefore, formation of a disfavored 7-membered N-acyliminium ion intermediate from an α amino aldehyde will occur at a very slow rate

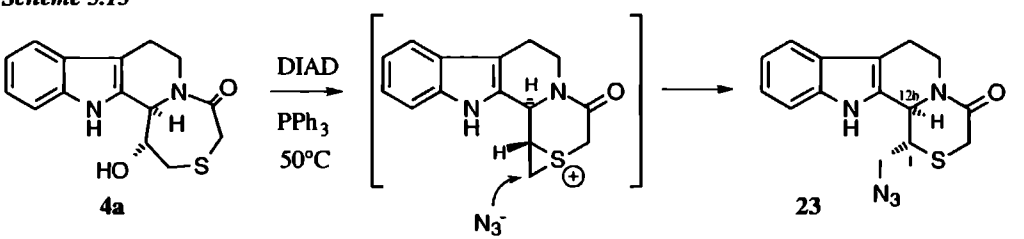
Therefore, at this point, the highly important conclusion can be drawn that the intramolecular PS condensation is in retrospect the strategy of choice for the construction of the [1,6,2]-oxathiazepine 7-membered ring system In chapter 1 it was mentioned that the crucial step in the synthesis of tetracyclic eudistomins is the closure of this 7-membered ring system As was demonstrated in the chapters 2-4 and 6, indeed, with help of the versatile N-alkoxyiminium ion, which is both easily formed and highly electrophilic, ring closure was accomplished in high yields In chapter 7 the versatility of N-alkoxyiminium ion will be emphasized in the synthesis of the canthine type skeleton

5.3.3 Introduction of the Amino Functionality via the Mitsunobu Reaction

Initially the Mitsunobu reaction was performed with hydrazoic acid as the nucleophile but no conversion of the starting material could be observed Analogous to the results in chapter 3, introduction of the azide moiety could be accomplished with $Zn(N_3)_2$•2Py, although only at an elevated temperature (50°C), to give **23** in 80% yield The reason that the reaction only occurs at elevated temperature is merely due to the low solubility of **4a** in the toluene/THF (5/2, v/v) solvent mixture

From the structure of **23** as deduced from the NMR spectrum it is evident that, unfortunately, transannular neighboring group participation of the β-positioned sulfur atom has played a dominant role (scheme 5 13) The proton at C(12b) was present as a doublet with a coupling constant of 7 3 Hz, thus indicating a trans relationship with the proton at C(1). None of the desired eudistomin analog could be detected in the reaction mixture

Scheme 5.13



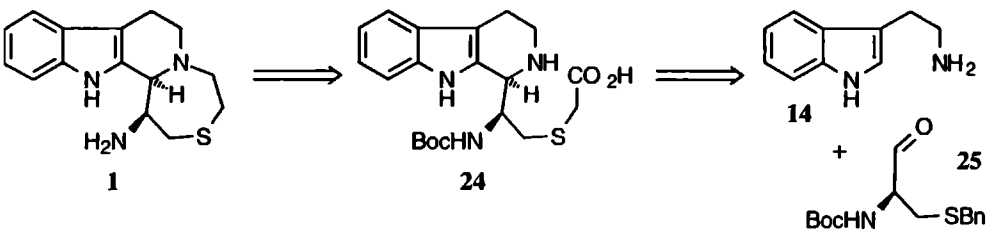
5.4 Concluding Remarks

The PS condensation to produce an eudistomin analog in which the oxygen atom in the 7-membered ring unit is replaced by a carbonyl group was accomplished when the precursor aldehydes contain an α-oxygen function The diastereomeric ratio of cis/trans eudistomin analogs amounted 1 1 When an α-amino group is present in the aldehyde precursor no PS cyclization could be realized The N-acyliminium ions which are intermediates in the above PS condensation are reactive species However, their formation will be hampered due to relative low nucleophilicity of amide nitrogen atoms and the strain exerted by the 7-membered ring in which the N-acyliminium ion is incorporated As in all PS condensations α-amino aldehydes are less reactive than α-alkoxy aldehydes Attempts to substitute the C(1)-OH function in eudistomin carba analog **4a** by employing the Mitsunobu conditions was not successful due to the involvement of neighboring group participation of the β-positioned sulfur atom leading to a 6/5/6/6 membered tetracyclic ring system instead of the desired 6/5/6/7 membered ring system

Work is now in progress to synthesize the desoxa carba-eudistomin derivative via the *inter*molecular PS approach starting from **24** as the precursor, which is accessible by reaction of

tryptamine **14** with the known aldehyde **25**, followed by closure of the 7-membered [1,4]-thiazepine ring (scheme 5 14) An advantage of the intermolecular PS approach is the expected high diastereoselectivity to the desired cis diastereomer [12]

Scheme 5.14



5.5 Experimental Part

For general remarks see the experimental part of chapter 2.

N-(*tert*-butyloxycarbonyl)-O-(*tert*-butyldiphenylsilyl)-*L*-cystinol (9) The methyl ester in **7a** was reduced to the corresponding alcohol following a literature procedure [4] To this alcohol (6 4 g, 15 5 mmol) dissolved in DMF (50 mL) was added *tert*-butylchlorodiphenylsilane (9 6 g, 28 6 mmol) and imidazole (6 8 g, 100 mmol) After standing for 2 days all starting material had been consumed The reaction was worked-up by the addition of EtOAc (100 mL) followed by removal of DMF and imidazole by 5 extractions with 5% aqueous citric acid The organic layer was neutralized with sat $NaHCO_3$, washed with brine and dried ($MgSO_4$) The volatiles were removed *in vacuo* to yield 13 7 g (99%) of crude **9** as a colorless oil which was homogeneous by TLC, R_f 0 46 (EtOAc/hexanes=1/8, v/v), FABMS(70eV), m/z (relative intensity) 889 ($[M+1]^+$, 1 2), 733 ($[M-C_{12}H_{11}]^+$, 32), 199 ($[C_{13}H_{11}SiO]^+$, 42), 135 ($[C_{10}H_{15}]^+$, 100), ^1H NMR (90 MHz) δ 7 78-7 58 (m, 8H, 4xPhH_2), 7 46 7 30 (m, 12H, 4xPhH_3), 5 04 (br d, 2H, J=6 2 Hz, 2xNH), 3 96 3 64 (m, 6H, 2xOCH_2CH), 2 99-2 91 (m, 4H, 2xSCH_2), 1 44 (s, 9H, OC(CH_3)$_3$), 1 06 (s, 9H, SiC(CH_3)$_3$)

N-(*tert*-butyloxycarbonyl)-O-(*tert*-butyldipenylsilyl)-*L*-cysteinol (10) To **9** (9 1 g, 10 2 mmol) dissolved in ether (100 mL) was added triethylamine (3 6 mL, 2 6 g, 26 mmol) and dithiothreitol (3 2 g, 21 mmol) The reaction needed 3 weeks to reach completion (the resulting cyclic disulfide of dithiothreitol gave colorless cubic crystals) The volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography to afford 9 03 g (99%) of the thiol **10** as a colorless oil, R_f 0 55 (EtOAc/hexanes=1/8, v/v), ^1H NMR (90 MHz) δ 7 78 7 55 (m, 4H, 2xPhH_2), 7 48-7 30 (m, 6H, 2xPhH_3), 4 88 (br d, 2H, J=5 0 Hz, NH), 3 90-3 63 (m, 3H, OCH_2CH), 2 90-2 63 (m, 2H, SCH_2), 1 44 (s, 9H, OC(CH_3)$_3$), 1 18 (t, 1H, J=10 0 Hz, SH), 1 05 (s, 9H, SiC(CH_3)$_3$)

Allyl bromoacetate (11) To bromoacetic acid (25 mL, 48 g, 0 34 mole) and allyl alcohol (24 mL, 20 g, 0 34 mole) in cyclohexane (200 mL) was added TsOH•H_2O (10 mg) and the resulting reaction mixture was heated at reflux for 3 hours with azeotropic removal of the formed water employing a Dean and Stark apparatus The reaction mixture was neutralized by washing with dil Na_2CO_3 After washing with brine and drying ($MgSO_4$) the volatiles were evaporated *in vacuo* and the residue was purified by vacuum distillation to give 51 g (82%) of **11** as a colorless very irritating liquid (bp=73°C/15 mmHg), ^1H NMR (90 MHz) δ 6 61-5 75 (m, 1H, H_2C=CH), 5 48-5 21 (m, 2H, H_2C=CH), 4 69 (dt, 2H J=5 6 Hz and J=1 2 Hz, OCH_2), 3 86 (s, 2H, CH_2Br)

3-Allyloxycarbonylmethylthio-1-*tert*-butyldiphenylsilyloxy-2-(*tert*-butyloxycarbonylamino)-propane (12a) To **10** (9 0 g, 20 2 mmol) dissolved in benzene (10 mL) was added 1,8-diazabicyclo[5 4 0]undec-7 ene (3 0 mL, 3 1 g, 20 mmol) and allyl bromoacetate **11** (3 6 g, 20 mmol) causing a slight exothermic reaction (ca 30°C raise in temperature) The reaction was completed within 15 min and worked-up by extraction with 10% citric acid, sat $NaHCO_3$ and brine After drying ($MgSO_4$) the solvent was evaporated *in vacuo* to yield 10 9 g (99%) of **12a** as a colorless oil, R_f 0 38

(EtOAc/hexanes=1/8, v/v), CIMS(70eV), m/z (relative intensity) 544 ($[M+1]^+$, 5), 430 ($[M-113]^+$, 100), 199 ($[C_{13}H_{11}SiO]^+$, 42), 57 ($[C_4H_9]^+$, 68), ^{1}H NMR (90 MHz) δ 7 76-7 52 (m, 4H, 2xPhH$_2$), 7 47 7 29 (m, 6H, 2xPhH$_3$), 6 14-5 71 (m, 1H, H$_2$C=CH), 5 46-5 15 (m, 2H, H$_2$C=CH), 4 90 (br d, 2H, J=8 2 Hz, NH), 4 72-4 56 (m, 2H, C(O)OCH$_2$), 3 94-3 67 (m, 3H, OCH$_2$CH), 3 27 (s, 2H, SCH$_2$COOMe), 2 88 (d, 2H, J=6 0 Hz, SCH$_2$), 1 43 (s, 9H, OC(CH$_3$)$_3$), 1 06 (t, 1H, J=10 0 Hz, SH), 1 05 (s, 9H, SiC(CH$_3$)$_3$)

Methyl 3-Allyloxycarbonylmethylthio-2-(benzyloxycarbonylamino)-propionate (12b) For reduction of the disulfide in **7b** the same procedure was followed as decribed for the synthesis of **10** Disulfide **7b** (9 86 g, 18 4 mmol), triethylamine (5 1 mL, 3 74 g, 37 0 mmol) and dithiothreitol (5 67 g, 37 0 mmol) in ether (100 mL) gave complete formation of the thiol in 2 hours, $R_{f(7b)}$ 0 06, $R_{f(8)}$ 0 21 (both EtOAc/hexanes=1/2, v/v) The crude thiol **8** was alkylated with allyl bromoacetate **11** (6 6 g, 37 0 mmol) using DBU (5 6 g, 37 0 mmol) as the base as described for the synthesis of **12a**, to give after purification by column chromatography (EtOAc/hexanes=1/2, v/v) 9 43 g (69%) of **12b** as a colorless oil, R_f 0 15 (EtOAc/hexanes=1/2, v/v), CIMS(70eV), m/z (relative intensity) 368 ($[M+1]^+$, 32), 324 ($[M-44]^+$, 16), 91 ($[C_7H_7]^+$, 100), ^{1}H NMR (100 MHz) δ 7 34 (s, 5H, PhH$_5$), 6 12-5 73 (m, 2H, H$_2$C=CH and NH), 5 41-5 19 (m, 2H, H$_2$C=CH), 5 12 (s, 2H, CH$_2$Ph), 4 7-4 58 (m, 2H, OCH$_2$CH=CH$_2$), 3 75 (s, 3H, OCH$_3$), 3 27 (s, 2H, SCH$_2$COOMe), 3 12-3 06 (m, 2H, SCH$_2$CH)

3-carboxymethylthio-1-*tert*-butyldiphenylsilyloxy-2-(*tert*-butyloxycarbonylamino)-propane (13a) To **12a** (9 8 g, 19 2 mmol) under an argon atmosphere in EtOAc (100 mL) was added morpholine (15 mL) and tetrakis(triphenylphosphine)palladium(0) (15 mg, 0 013 mmol) After stirring at room temperature for 12 hours the reaction mixture was extracted with 2 portions 1N KHSO$_4$, brine and dried (MgSO$_4$) The volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (MeOH/CH$_2$Cl$_2$) to give 6 6 g (73%) of **13a** as a colorless oil, R_f 0 15 (EtOAc/hexanes=1/1, v/v), CIMS(70eV), m/z (relative intensity) 504 ($[M+1]^+$, 6), 390 ($[M-113]^+$, 100), 199 ($[C_{13}H_{11}SiO]^+$, 82), 57 ($[C_4H_9]^+$, 84), ^{1}H NMR (90 MHz) δ 7 76-7 52 (m, 4H, 2xPhH$_2$), 7 46-7 31 (m, 6H, 2xPhH$_3$), 4 96 (very br s, 1H, NH), 3 88-3 66 (m, 3H, OCH$_2$CH), 2 87 (d, 2H, J=5 8 Hz, SCH$_2$), 1 42 (s, 9H, OC(CH$_3$)$_3$), 1 05 (s, 9H, SiC(CH$_3$)$_3$)

Methyl 2-(benzyloxycarbonylamino)-3-carboxymethylthio-propionate (13b) For liberation of the acid from the allyl ester the same procedure was followed as described for **13a** using **12b** (6 0 g, 16 4 mmol), morpholine (15 mL) and tetrakis(triphenylphosphine)palladium(0) (15 mg, 0 013 mmol) After work-up 5 3 g (100%) of crude **13b** was obtained which was not further purified It should be noted here that initially the palladium catalyzed reaction did not proceed at all Several new attempts were made but only after careful purification of the starting material (*i e* **12b**) by column chromatography deprotection of the allyl ester succeeded, CIMS(70eV), m/z (relative intensity) 328 ($[M+1]^+$, 77), 284 ($[M+1-CO_2]^+$, 45), 91 ($[C_7H_7]^+$, 100), ^{1}H NMR (90 MHz) δ 9 11 (br s, 1H, COOH), 7 33 (s, 5H, PhH$_5$), 5 87 (very br d, 1H, J=8 1 Hz, NH), 5 12 (s, 2H, CH$_2$Ph), 4 77-4 55 (m, 1H, CHCH$_2$), 3 76 (s, 3H, OCH$_3$), 3 26 (s, 2H, SCH$_2$CO$_2$), 3 22 2 94 (m, 2H, SCH$_2$CH)

2-(3-hydroxy-2-(*tert*-butyloxycarbonylamino)-propylthio)-N-[2-(1*H*-indole-3-yl)-ethyl]-acetamide (15a) To **13a** (6 5 g, 13 8 mmol) and tryptamine **14** (2 2 g, 13 8 mmol) dissolved in acetonitrile (100 mL) was added dicyclohexylcarbodiimide (2 84 g, 13 8 mmol), giving the immediate precipitation of dicyclohexylureum The reaction was completed within 30 min ($R_{f(product)}$=0 33, EtOAc/hexanes=1/1, v/v) Work-up was accomplished by filtration of the reaction mixture over hyflo followed by removal of the solvent *in vacuo* The residue was dissolved in THF (25 mL) followed by the addition of tetrabutylammonium fluoride (15 mL of a 1M solution in THF) After 30 min the solvent was evaporated *in vacuo* and the residue was subjected to column chromatography (MeOH/CH$_2$Cl$_2$=5/95, v/v) to give 3 45 g (61%) of **15a** as a colorless oil, R_f 0 38 (MeOH/CH$_2$Cl$_2$=7/93, v/v), α_D^{22}=-6 9° (c=4 50, MeOH), CIMS(70eV), m/z (relative intensity) 407 ($[M]^+$, 1), 143 ($[C_{10}H_9N]^+$, 86), 130 ($[C_9H_8N]^+$, 37), 57 ($[C_4H_9]^+$, 100), ^{1}H NMR (90 MHz) δ 8 76 (br s, 1H, indole NH), 7 62-7 48 (m, 1H, indole C(7)H), 7 40-7 00 (m, 5H, indole C(2) and C(4)-C(6)H$_3$ and CH$_2$NH), 5 24 (br d, 1H, J=7 8 Hz, BocNH), 3 71 3 36 (m, 5H, CH$_2$CH$_2$N and OCH$_2$CH), 3 11 (s, 2H, SCH$_2$C(O)), 2 97 (t, 2H, J=6 4 Hz, CH$_2$CH$_2$N), 2 68-2 36 (m, 3H, SCH$_2$CH and OH), 1 41 (s, 9H, C(CH$_3$)$_3$)

Methyl 2-(benzyloxycarbonylamino)-3-[2-(1*H*-indol-3-yl)-ethylcarbamoylmethylsulfanol]-propionate (16) The same procedure was followed as described for **15a** using **13b** (5 3 g, 16 2 mmol), tryptamine **14** (2 6 g, 16 2 mmol)

and dicyclohexylcarbodiimide (3 4 g, 16 2 mmol) Work-up and purification by column chromatography (MeOH/CH_2Cl_2=5/95, v/v) afforded 4 6 g (62%) of **16** as a white foam, R_f 0 53 (MeOH/CH_2Cl_2=7/93, v/v), CIMS(70eV), m/z (relative intensity) 470 ([M+1]$^+$, 100), 426 (M+1-CO_2]$^+$, 41), 235 ([$C_{12}H_{15}N_2O_5$]$^+$, 4), 203 ([$C_{12}H_{15}N_2O$]$^+$, 35), 130 ([C_9H_8N]$^+$, 17), 91 ([C_7H_7, 51), ^{1}H NMR (90 MHz) δ 8 42 (br s, 1H, indole NH), 7 64-7 49 (m, 1H, indole C(7)H), 7 38-6 99 (m, 4H, indole C(2) and C(4)-C(6)H_3), 7 38 (s, 5H, PhH_5), 6 74 (very br t, 1H, J=7 1 Hz, $CH_2CH_2\underline{NH}$), 5 80 (br d, 1H, J=8 0 Hz, CbzNH), 5 09 (s, 2H, CH_2Ph), 4 59-4 38 (m, 1H, $\underline{CH_2}CH$), 3 74-3 49 (m, 2H, $CH_2\underline{CH_2}NH$), 3 69 (s, 3H, OCH_3), 3 11 (s, 2H, SCH_2CO), 3 04-2 61 (m, 4H, $\underline{CH_2}CH_2NH$ and $S\underline{CH_2}CH$)

2-(3-hydroxy-2-(benzyloxycarbonylamino-propylthio)-N-[2-(1*H*-indole-3-yl)-ethyl]-acetamide (15b) To **16** (4 5 g, 9 9 mmol) in dry ether/THF (1/1, v/v, 50 mL) was added dry methanol (0 60 mL, 0 48 g, 14 9 mmol) and lithium borohydride (330 mg, 15 0 mmol) A rather insoluble sticky white syrup emerged from the solution After stirring for 30 minutes all starting material had been consumed Work up was accomplished by the careful addition of sat $NaHCO_3$ The organic layer was washed with brine and dried ($MgSO_4$) followed by evaporation of the volatiles *in vacuo* The residue was subjected to column chromatography (MeOH/CH_2Cl_2=5/95, v/v) to give 3 3 g (78%) of **15b** as a white foam, R_f 0 23 (MeOH/CH_2Cl_2=7/93, v/v), 0 39 (MeOH/CH_2Cl_2=1/9, v/v), CIMS(70eV), m/z (relative intensity) 442 ([M+1]$^+$, 38), 398 (M+1-CO_2]$^+$, 12), 308 ([$C_{15}H_{22}N_3O_2S$]$^+$, 100), 203 ([$C_{12}H_{15}N_2O$]$^+$, 79), 91 ([C_7H_7, 68), ^{1}H NMR (90 MHz) δ 8 52 (br s, 1H, indole NH), 7 60-7 47 (m, 1H, indole C(7)H), 7 37-6 97 (m, 4H, indole C(2) and C(4)-C(6)H_3), 7 31 (s, 5H, PhH_5), 6 97-6 80 (m, 1H, $CH_2CH_2\underline{NH}$), 5 51 (br d, 1H, J=8 2 Hz, CbzNH), 5 04 (s, 2H, CH_2Ph), 3 77-3 30 (m, 6H, 1H exchangeable, $CH_2\underline{CH_2}NH$ and $CHCH_2OH$), 3 07 (s, 2H, SCH_2CO), 2 95 (t, 2H, J=6 3 Hz, $\underline{CH_2}CH_2NH$), 2 57-2 46 (m, 2H, $S\underline{CH_2}CH$)

2-(2-(*tert*-butyloxycarbonylamino)-3-oxo-propylthio)-N-[2-(1*H*-indole-3-yl)-ethyl]-acetamide (3a) and **2-(3-hydroxy-3-methoxy-2-(*tert*-butyloxycarbonylamino-propylthio))-N-[2-(1*H*-indole-3-yl)-ethyl]-acetamide (3a')** To a cooled (-5°C) solution of **15a** (2 46 g, 6 0 mmol) in DMSO/CH_2Cl_2 (1/1, v/v, 40 mL) was added triethylamine (1 83 g, 2 51 mL, 18 mmol) To the efficiently stirred solution was added sulfur trioxide pyridine complex (2 9 g, 18 2 mmol, dissolved in 10 mL DMSO/CH_2Cl_2 (1/1, v/v)) at once After additional stirring in the cold for 30 minutes all starting material had been consumed Work-up was accomplished by the addition of 1N $KHSO_4$ (100 mL) and CH_2CH_2 (50 mL) After another extraction with dil $KHSO_4$, water and brine the organic layer was dried (Na_2SO_4) The volatiles were evaporated *in vacuo* to give 2 6 g of the crude racemic aldehyde **3a**, R_f 0 41 (MeOH/CH_2Cl_2=7/93, v/v), FABMS(70eV), m/z (relative intensity) 405 ([M]$^+$, 2), 143 (100), 130 ([C_9H_8N]$^+$, 59), ^{1}H NMR (90 MHz) δ 9 31 (s, 1H, HCO), 8 37 (br s, 1H, indole NH), 7 58-7 44 (m, 1H, indole C(7)H), 7 35-6 94 (m, 4H, indole C(2) and C(4)-C(6)H_3), 6 66 (very br t, 1H, J=6 0 Hz, $CH_2CH_2\underline{NH}$), 5 42 (br d, 1H, J=6 8 Hz, BocNH), 4 07 (q, 1H J=6 0 Hz, $CH_2\underline{CH}$), 3 57 (q, 2H, J=6 4 Hz, $CH_2\underline{CH_2}N$), 3 07 (s, 2H, $SCH_2C(O)$), 2 93 (t, 2H, J=6 1 Hz, $\underline{CH_2}CH_2N$), 2 66 (dd, 2H J=2 2 Hz and J=6 0 Hz, $S\underline{CH_2}CH$), 1 36 (s, 9H, $C(CH_3)_3$) The crude aldehyde **3a** was purified by column chromatography (MeOH/CH_2CH_2=3/97, v/v) to give 1 41 g (56%) of the methyl hemiacetal **3a'** as a mixture of diastereomers as a white foam, R_f 0 41 (MeOH/CH_2Cl_2=7/93, v/v), ^{1}H NMR (90 MHz) δ 8 52 (br s, 1H, indole NH), 7 64-7 54 (m, 1H, indole C(7)H), 7 42-6 94 (m, 5H, indole C(7) and C(4)-C(6)H_3 and $CH_2CH_2\underline{NH}$), 5 07 and 4 92 (2xbr d, 1H, J=9 4 Hz, BocNH), 4 58-4 42 (m, 1H, $SCH_2CH\underline{CH}$), 3 92 3 53 (m, 3H, $CH_2\underline{CH_2}N$ and $CH_2\underline{CH}CH$), 3 37 and 3 36 (2xs, 3H, OCH_3), 3 16 (s, 2H, $SCH_2C(O)$), 3 00 (t, 2H, J=6 1 Hz, $\underline{CH_2}CH_2N$), 2 78-2 50 (m, 2H $S\underline{CH_2}CHCH$), 1 44 (s, 9H, $C(CH_3)_3$) The hemiacetal **3a'** was converted to the aldehyde **3a** by treatment with 4Å molecular sieves for 6 hours Anal Calcd for $C_{20}H_{27}N_3O_4S\cdot H_2O$ C, 56 72, H, 6 90 N, 9 92 S, 7 57 Found C 56 92, H, 6 66, N, 9 66 S, 7 51

2-(2-(benzyloxycarbonylamino-3-oxo-propylthio)-N-[2-(1*H*-indole-3-yl)-ethyl]-acetamide (3b) and **2-(3-hydroxy-3-methoxy-2-(benzyloxycarbonylamino-propylthio))-N-[2-(1*H*-indole-3-yl)-ethyl]-acetamide (3b')** The same procedure was followed as described for **3a** using **15b** (3 3 g, 7 7 mmol) and sulfur trioxide pyridine complex (3 7 g, 23 2 mmol) Purification by column chromatography (MeOH/CH_2Cl_2=5/95, v/v) afforded 2 24 g (64%) of the aldehyde methyl hemiacetal **3b'** as a white foam as a racemic mixture of two diastereomers, R_f 0 50 (MeOH/CH_2Cl_2=1/9, v/v), ^{1}H NMR (90 MHz) δ 8 40 (br s, 1H, indole NH), 7 62-7 50 (m, 1H, indole C(7)H), 7 39-6 99 (m, 4H, indole C(7) and C(4)-C(6)H_3), 7 30 (s, 5H, PhH_5), 6 94-6 75 (m, 1H, $CH_2CH_2\underline{NH}$), 5 40 and 5 24 (2xbr d, 1H, J=9 0 Hz, CbzNH), 5 07 (s, 2H, CH_2Ph), 4 57-4 44 (m, 1H, $SCH_2CH\underline{CH}$), 3 99-3 49 (m, 3H, $CH_2\underline{CH_2}N$ and

$CH_2\underline{CH}CH$), 3 33 and 3 32 (2xs, 3H, OCH_3), 3 12 (s, 2H, $SCH_2C(O)$), 2 96 (t, 2H, J=6 2 Hz, $\underline{CH_2}CH_2N$), 2 67-2 47 (m, 2H, $S\underline{CH_2}CHCH$) The hemiacetal **3b'** was converted to the aldehyde **3b** by treatment with 4Å molecular sieves in $CDCl_3$ for 8 hours, R_f 0 50 ($MeOH/CH_2Cl_2$=1/9, v/v), EIMS(70eV), m/z (relative intensity) 439 ($[M]^+$, 0 07), 234 ($[C_{12}H_{14}N_2OS]^+$, 4), 130 ($[C_9H_8N]^+$, 50), 91 ($[C_7H_7$, 100), ^1H NMR (90 MHz) δ 9 94 (s, 1H, CHO), 8 23 (br s, 1H, indole NH), 7 63-7 52 (m, 1H, indole C(7)H), 7 32 (s, 5H, PhH_5), 7 33-6 99 (m, 4H, indole C(2) and C(4)-C(6)H_3), 6 56 (very br t, 1H, J=6 1 Hz, $CH_2CH_2\underline{NH}$), 5 83 (very br d, 1H, J=6 2 Hz, CbzNH), 5 08 (s, 2H, CH_2Ph), 4 18 (q, 1H, J=6 2 Hz, $SCH_2\underline{CH}$), 3 62 (q, 2H, J=6 3 Hz, $CH_2\underline{CH_2}NH$), 3 09 (s, 2H, SCH_2CO), 2 97 (t, 2H, J=6 3 Hz, $\underline{CH_2}CH_2NH$), 2 73 dd, 2H, J=1 8 Hz and J=5 8 Hz, $S\underline{CH_2}CH$), Anal Calcd for $C_{23}H_{24}N_3O_4S\cdot H_2O$ C, 60 51, H, 5 74 N, 9 20 S, 7 02 Found C, 60 49, H, 5 96, N, 9 09 S, 6 85

Methyl (3,3-diethoxy-2-*tert*-butyldiphenylsilyloxy-propylthio)-acetate (18) To dry methanol (10 mL) was added sodium (50 mg, 2 2 mmol) in one portion This NaOMe solution was added to a stirred solution of **17** (0 90 g, 1 96 mmol) dissolved in dry methanol (20 mL) After 15 min NaI (20 mg) and methyl chloroacetate (0 26 mL, 0 33 g, 3 0 mmol) were added (immediate NaCl formation) and the solution was stirred for 1 hour Work up was accomplished by removal of the volatiles *in vacuo* followed by addition of EtOAc (50 mL) and washing of the solution with water and sat NH_4Cl After drying ($MgSO_4$) the volatiles were removed at high vacuum (in order to remove the excess methyl chloroacetate) to yield 0 93 g (96%) of **18** as a colorless oil, R_f 0 34 (EtOAc/hexanes=1/5, v/v), CIMS(70eV), m/z (relative intensity) 519 ($[M+29]^+$, 1 4), 445 ($[M\text{-}OEt]^+$, 0 5), 103 ($[CH(OEt)_2]^+$, 100), ^1H NMR (90 MHz) δ 7 80-7 68 (m, 4H, $2xPhH_2$), 7 43-7 24 (m, 6H, $2xPhH_3$), 4 36 (d, 1H, J=4 7 Hz, $CH_2CH\underline{CH}$), 3 91 (q, 1H, J=4 9 Hz, $CH_2\underline{CH}CH$), 3 76-3 16 (m, 4H, $2xO\underline{CH_2}CH_3$), 3 66 (s, 3H, OCH_3), 3 04 (s, 2H, SCH_2COOMe), 2 85 (d, 1H, J=4 8 Hz, $\underline{CH_2}CHCH$), 1 17 and 0 97 (2xt, 6H, J=7 1 Hz, $2xOCH_2\underline{CH_3}$), 1 07 (s, 9H, $C(CH_3)_3$)

2-(3,3-diethoxy-2-*tert*-butyldiphenylsilyloxy-propylthio)-N-[2-(1*H*-indole-3-yl)-ethyl]-acetamide (5a) A solution of tryptamine **14** (1 0 g, 6 3 mmol) and **17** (0 92 g, 1 9 mmol) in methanol (25 mL) was heated at reflux for 7 days The volatiles were subsequently removed *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/1, v/v) to give 0 86 g (74%) of **5a** as a colorless oil, R_f 0 17 (EtOAc/hexanes=1/2, v/v), CIMS(70eV), m/z (relative intensity) 618 ($[M]^+$, 2), 573 ($[M\text{-}OEt]^+$, 1), 130 ($[C_9H_8N]^+$, 40), 103 ($[CH(OEt)_2]^+$, 100), ^1H NMR (90 MHz) δ 8 16 (br s, 1H, indole NH), 7 77-7 51 (m, 5H, $2xPhH_2$ and indole C(7)H), 7 43-6 89 (m, 11H, $2xPhH_3$, indole C(2)H and C(4)-C(6)H_3 and NH), 4 29 (d, 1H, J=4 2 Hz, $CH_2CH\underline{CH}$), 3 84 (q, 1H, J=4 8 Hz, $CH_2\underline{CH}CH$), 3 71-3 12 (m, 6H, $2xO\underline{CH_2}CH_3$ and $CH_2\underline{CH_2}N$), 3 04 (s, 2H, $SCH_2C(O)N$), 2 94 (t, 2H, J=6 2 Hz, $\underline{CH_2}CH_2N$), 2 62 (d, 2H, J=5 1 Hz, $S\underline{CH_2}CHCH$), 1 16 and 0 97 (2xt, 6H, J=7 2 Hz and J=7 1 Hz, $2xOCH_2\underline{CH_3}$), 1 06 (s, 9H, $C(CH_3)_3$)

[2-(3,3-diethoxy-2-*tert*-butyldiphenylsilyloxy-propylthio)-ethyl]-[2-(1*H*-indole-3-yl)-ethyl]-amine (5b) To **5a** (0 86 g, 1 4 mmol) in dry THF (50 mL) under an argon atmosphere was added $LiAlH_4$ (80 mg, 2 1 mmol), and the resulting reaction mixture was heated at reflux for 12 hours, after which time still some starting material was detected by TLC Another portion $LiAlH_4$ (80 mg 2 1 mmol) was added and after 30 min all starting material had been consumed Work up was accomplished by the careful addition of dil NaOH (10 mL of a 2m solution) followed by 3 washings with water and sat NH_4Cl After drying ($MgSO_4$) the solvent was removed *in vacuo* and the residue was subjected to column chromatography ($Et_3N/MeOH/CHCl_3$=0 5/5/94 5, v/v/v) to give 210 mg (25%) of **5b** as a colorless oil, R_f 0 56 ($MeOH/CHCl_3$=1/9, v/v), CIMS(70eV), m/z (relative intensity) 605 ($[M+1]^+$, 0 4), 559 ($[M\text{-}OEt]^+$, 0 7), 143 (100), 130 ($[C_9H_8N]^+$, 80), 103 ($[CH(OEt)_2]^+$, 95), ^1H NMR (90 MHz) δ 8 09 (br s, 1H, indole NH), 7 83-7 57 (m, 5H, $2xPhH_2$ and indole C(7)H), 7 36-6 99 (m, 10H, indole C(3)H and C(4)-C(6)H_3 and $2xPhH_3$), 4 33 (d, 1H, J=5 3 Hz, $CH_2CH\underline{CH}$), 3 94-2 19 (m, 15H, $CH_2CH_2NCH_2CH_2SCH_2CH$ and $2xO\underline{CH_2}CH_3$), 1 18 and 0 99 (2xt, 6H, J=6 8 Hz, $2xOCH_2\underline{CH_3}$), 1 08 (s, 9H, $C(CH_3)_3$)

20 and 21 To **5a** (0 5 g, 0 81 mmol), dissolved in chloroform (100 mL), was added a mixture of trifluoroacetic acid/water (4 mL of a 1/1, v/v, solution) and the resulting 2-phase system was heated at reflux for 24 hours under an argon atmosphere After cooling to room temperature the reaction mixture was cautiously neutralized by the portion wise addition of $NaHCO_3$ After washing with brine and drying (Na_2SO_4) the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/5, v/v) to give 75 mg (18%) of **20** as a white

solid R_f 0 17 (EtOAc/hexanes=1/3, v/v), HPLC (acetonitrile, flow=1 mL/min , λ=280 nm), retention time (min) 8 3, α_D^{22}=-47 1 (c=4 35, MeOH), CIMS(70eV), m/z (relative intensity) 527 ([M+1]$^+$, 12), 526 ([M]$^+$, 10), 270 ([$C_{15}H_{14}N_2OS$]$^+$, 72), 244 (100), 169 ([$C_{11}H_9N_2$]$^+$, 36), ^{1}H NMR (90 MHz) δ 7 56-7 04 (m, 15H, indole-NH, indole C(4)-C(7)H_4 and 2xPhH_5), 5 10 (br s, 1H, C(13b)H), 5 03-4 96 (m, 1H, C(7)Hβ), 4 31-4 07 (m, 1H, C(1)H), 3 61 and 3 41 (AB, 2H, J_{AB}=13 2 Hz, C(4)H_2), 3 79-3 45 (m, 1H, C(7)Hα), 2 99-2 52 (m, 4H, C(2)H_2 and C(8)H_2), 0 66 (s, 9H, C(CH_3)$_3$), Anal Calcd for $C_{31}H_{34}N_2O_2SSi$ C, 70 68, H, 6 51, N, 5 32, S, 6 09 Found C, 69 79, H, 6 44, N, 5 47, S, 6 13 and 76 mg (18%) of **21** as a white solid R_f 0 23 (EtOAc/hexanes=1/3, v/v), HPLC (acetonitrile, flow=1 mL/min , λ=280 nm), retention time (min) 9 1, α_D^{22}=-2 8 (c=5 30, MeOH), CIMS(70eV), m/z (relative intensity) 528 ([M+2]$^+$, 13), 527 ([M+1]$^+$, 11), 244 (100), 169 ([$C_{11}H_9N_2$]$^+$, 34), ^{1}H NMR (90 MHz) δ 8 19 (br s, 1H, indole-NH), 7 50-7 02 (m, 13H, indole PhH_3 and 2xPhH_5), 6 87-6 72 (m, 1H, indole-PhH_1), 5 00 (d, 1H, J=8 4 Hz, C(13b)H), 4 91-4 73 (m, 1H, C(7)Hβ), 4 27-4 06 (m, 1H, C(1)H), 3 83 and 3 28 (AB, 2H, 2H, J_{AB}=13 2 Hz, C(4)H_2), 2 77-2 31 (m, 5H, C(7)Hα, C(8)H_2 and C(2)H_2), 1 06 (s, 9H, C(CH_3)$_3$), Anal Calcd for $C_{31}H_{34}N_2O_2SSi$ C, 70 68, H, 6 51, N, 5 32, S, 6 09 Found C, 69 52, H, 6 28, N, 5 15, S, 6 07

4a and **22** An equimolar mixture of **20** and **21** (310 mg, 0 59 mmol) was dissolved in THF (5 mL) and n-Bu_4NF (0 7 mL of a 1M solution in THF) was added After 1 h the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (MeOH/$CHCl_3$=5/95, v/v) affording 80 mg (49%) of **4a** as a white solid R_f 0 39 (MeOH/$CHCl_3$/H_2O=5/95/0 2, v/v/v), HPLC (acetonitrile/water=1/1, v/v, flow=1 mL/min , λ=280 nm), retention time (min) 3 5, α_D^{22}=+94 9 (c=3 35, MeOH), CIMS(70eV), m/z (relative intensity) 288 ([M]$^+$, 24), 271 ([M-17]$^+$, 3), 244 (100), 169 ([$C_{11}H_9N_2$]$^+$, 54), ^{1}H NMR (400 MHz, acetonitrile d_3/methanol-d_4/$CDCl_3$=2/2/1, v/v/v) δ 7 52 (d, 1H, J=7 8 Hz, C(12)H), 7 45 (d, 1H, J=8 0 Hz, C(9)H), 7 17 (t, 1H, J=7 4 Hz, C(10)H), 7 09 (t, 1H, J=7 5 Hz, C(11)H), 4 96 (d, 1H, J=9 0 Hz, C(13b)H), 4 89 (dd, 1H, J=12 9 Hz and J=5 1 Hz, C(7)Hβ), 4 18 (dt 1H, J=9 0 Hz and J=3 3 Hz, C(1)H), 4 06 (d, 1H, J=12 8 Hz, C(4)H), 3 24 (d, 1H, J=12 8 Hz, C(4)H), 3 03 (dd, 1H, J=15 1 Hz and J=2 9 Hz, C(2)H), 2 96 (dt, 2H, J=12 4 Hz and J=4 0 Hz, C(7)Hα), 2 88 (dd, J=15 3 Hz and J=3 9 Hz, C(8)H), 2 75 (dddd, 1H, J=15 4 Hz, J=12 0 Hz, J=5 4 Hz and J=1 3 Hz, C(8)H), ^{13}C NMR (100 MHz, acetonitrile-d_3/methanol-d_4/$CDCl_3$=2/2/1, v/v/v) δ 169 47 C(5), 138 00 C(12a), 132 80 C(13a), 127 48 C(8b), 122 85 C(11), 120 20 C(10), 119 19 C(9), 112 43 C(12), 109 59 C(8a), 70 98 C(13b), 58 48 C(1), 39 35 C(7), 37 25 C(4), 33 76 C(2), 21 95 C(8) together with 82 mg (49%) of **22** as a white solid R_f 0 15 (MeOH/$CHCl_3$/H_2O=5/95/0 2, v/v/v), HPLC (acetonitrile/water=1/1, v/v, flow=1 mL/min , λ=280 nm), retention time (min) 3 2, α_D^{22}=-44 6 (c=3 70, MeOH), CIMS(70eV), m/z (relative intensity) 288 ([M]$^+$, 15), 244 (100), 169 ([$C_{11}H_9N_2$]$^+$, 54), ^{1}H NMR (400 MHz) δ 8 15 (br s, 1H, indole-NH), 7 53 (d, 1H, J=7 7, C(12)H), 7 37 (d, 1H, J=8 0 Hz, C(9)H), 7 15 (t, 1H, J=7 5 Hz, C(10)H), 7 08 (t, 1H, J=7 5 Hz, C(11)H), 5 13 (s, 1H, C(13b)Hα), 4 98 (ddd, 1H, J=12 8 Hz, J=5 3 Hz and J=1 2 Hz, C(7)Hβ), 4 42 (br m, 1H, C(1)Hα), 3 71 (d, 1H, J=13 5 Hz, C(4)H), 3 37 (d, 1H, J=13 5 Hz, C(4)H), 3 34 (dt, 1H, J=12 3 Hz and J=4 3 Hz, C(7)Hα), 3 14 (dd, 1H, J=14 5 Hz and J=4 1 Hz, C(2)H), 2 91 2 85 (m, 2H, C(8)H and C(2)H), 2 75 (dddd, 1H, J=15 5 Hz, J=11 7 Hz, J=5 4 Hz and J=1 6 Hz, C(8)H), 2 42 (br s, 1H, OH)

23 To **4a** (96 mg, 0 33 mmol), $Zn(N_3)_2$•2Py (77 mg, 0 25 mmol) and triphenylphosphine (175 mg, 0 67 mmol) dissolved in toluene/THF (7 mL of a 5/2, v/v, mixture) was added via a syringe over a period of 5 min diisopropylazodicarboxylate (0 135 mL, 135 mg, 0 67 mmol) The reaction mixture was warmed to 50°C for 1 hour The volatiles were evaporated *in vacuo* and the residue was subjected column chromatography (EtOAc/hexanes=1/1, v/v) to give 83 mg (80%) of **23** as a white solid, R_f 0 45 (EtOAc/hexanes=4/1, v/v), α_D^{22}=-7 8 (c=2 05, MeOH), CIMS (70eV), m/z (relative intensity) 314 ([M+1]$^+$, 19), 313 ([M]$^+$, 17), 285 ([M-N_2]$^+$, 98), 271 ([M N_3]$^+$, 46), 144 ([$C_{10}H_{10}N$]$^+$, 23), 43 ([HN_3]$^+$, 100), ^{1}H NMR (90 MHz, methanol-d_4/$CDCl_3$=5/95, v/v) δ 7 59-7 02 (m, 4H, indole C(4)-C(7)H_4), 5 08 (d, 1H, J=7 3 Hz, C(12b)H), 4 69-4 48 (m, 1H, C(6)Hβ), 3 78 (d, 1H, J=15 5 Hz, C(3)H), 3 76 (d, 2H, J=5 5 Hz, CH_2N_3), 3 60-2 87 (m, 4H, C(6)H, C(7)H_2 and C(1)H), 3 17 (d, 1H, J=15 5 Hz, C(3)H

References and Notes

1 It should however be noted here that the *inter*molecular Pictet-Spengler strategy (route B in scheme 5.1) seems also applicable for the synthesis of this particular derivative, lacking the N-alkoxy moiety (see the introductory paragraph of chapter 4).

2 Speckamp, W.N.; Hiemstra, H. *Tetrahedron*, **1985**, 41, 4367. For a recent paper describing the specific use of N-acyliminium ions in the Pictet-Spengler condensation, see. Maryanoff, B.E.; Rebarchak, M.C. *Synthesis*, **1992**, 1245 and references cited therein

3 Jurczak, J , Golebiowski, A. *Chem.Rev.*, **1989**, 89, 149

4 Ottenheijm, H.C.J ; Liskamp, R.M.J.; Nispen, S.P.J M. van; Boots, H A.; Tijhuis, M.W. *J.Org.Chem.* **1980**, 46, 3273

5 Liskamp, R.M.J.; Zeegers, H J.M.; Ottenheijm, H C J. *J Org.Chem.* **1981**, 46, 5408

6 Konradi, A W., Pedersen, S.F *J.Org.Chem.* **1992**, 57, 28

7 Valls, N.; Bonjoch, J.; Del Alamo, C.; Bosch, J *Helv Chim.Acta*, **1992**, 75, 137. Another representative example of the intramolecular Pictet-Spengler condensation employing an N-acyliminium ion intermediate has been described by: Pancrazi, A.; Kervagoret, J., Khuong-Huu, Q. *Synlett*, **1991**, 589

8 Soerens, D ; Sandrin, J.; Ungemach, F., Mokry, P., Wu, G.S ; Yamahaka, E.; Hutchins, L.; DiPierro, M.; Cook, J.M. *J.Org Chem.*, **1979**, 44, 535

9 Sandrin, J ; Hollinshead, S.P., Cook, J.M. *J.Org.Chem.* **1989**, 54, 5636

10 Perrin, D. *Dissociation Constants of Organic Bases in Organic Solutions;* Butterworths London, **1965**

11 Roberts, J S. in *Comprehensive Organic Chemistry*, Barton, D.H.R , Ollis, W.D. Eds., Pergamon Press: Oxford. **1979**, Vol. 2; pp. 185

12 Melnyk, P.; Ducrot, P.; Thal, C. *Tetrahedron*, **1993**, 49, 8589

6 Synthesis of an Isoquinoline Type Eudistomin Analog

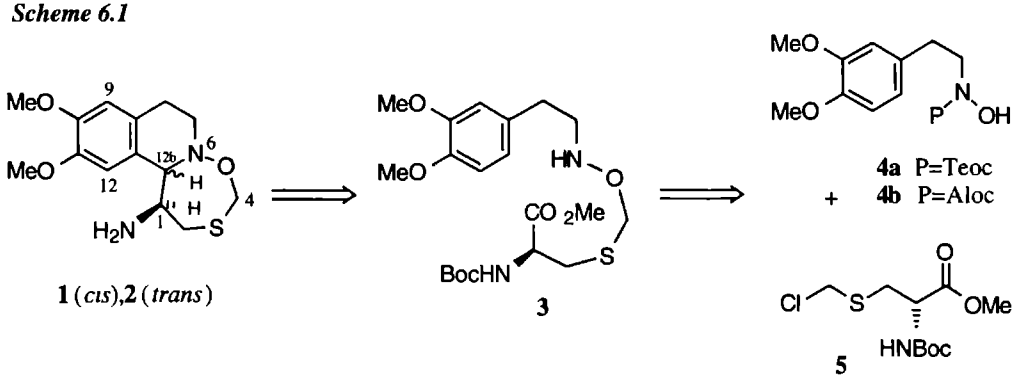
6.1 Introduction

As an extension of our study about the antiviral and antitumor structure-activity relationship of the tetracyclic eudistomin series the tricyclic isoquinoline analog, lacking the 5-membered pyrrole ring system, is a logical choice From structure-activity relationship studies of biological active compounds containing the indole ring system it is known that substitution of the indole moiety by a substituted phenyl group is an often allowed bioisosteric structural replacement [1] Especially in the field of biologically active β-carbolines it is known that isoquinolines behave often bioisosterically Moreover, the isoquinoline analog might be interesting as our preceding study revealed that substitution of the indole-N proton by a methyl group did not lead to a dramatic decrease in biological activity of eudistomins (see also chapter 9) [2]

As is pointed out in the introductory chapter, the intramolecular Pictet-Spengler (PS) condensation strategy is fully applicable in the synthesis of isoquinoline eudistomin analogs It is known that the PS condensation is less effective in the isoquinoline series than in the β-carboline series [3] The electron-rich pyrrole ring in indole is much more susceptible toward electrophilic species than an unsubstituted phenyl group Therefore in our approach the electron-rich 2-(3,4-dimethoxyphenyl)-ethyl amine was used as a tryptamine isostere

The build up of the tricyclic isoquinoline eudistomin skeleton was accomplished in an analogous manner as described in chapter 2 for the natural eudistomins from the N-Teoc or N-Aloc protected hydroxylamines **4a,b** and the (*D*)-cysteine derived chloromethyl sulfide **5** (scheme 6 1)

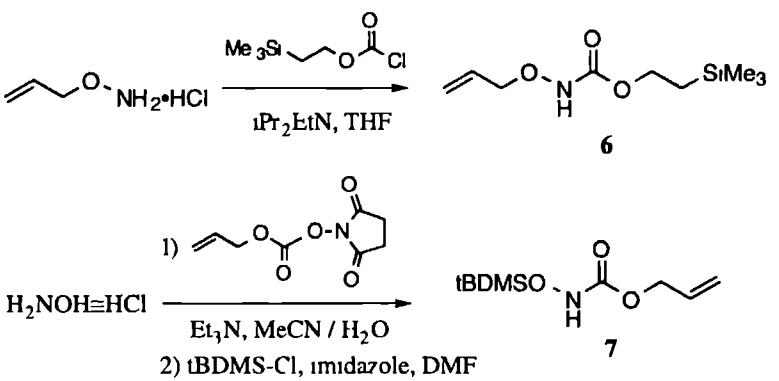
Scheme 6.1



6.2 Synthesis of Functionalized *N*-2-(3,4-dimethoxyphenyl)ethyl-hydroxylamines

For the synthesis of the unprecedented N-Teoc or N-Aloc protected secondary hydroxylamines **4a,b** a modification of the method described by Miller and Maurer was used [4] In the original paper it was described that O-benzyl-N-Cbz-hydroxylamine gives efficient Mitsunobu reactions with primary alcohols, yielding only the N-alkylated products A drawback of this method is that hydrogenolysis is accompanied by reduction of the N-O bond In contrast, O-benzyl-N-Ac-hydroxylamine only gave minor N-alkylation in the Mitsunobu reaction but during hydrogenolysis no reduction of the N-O bond took place Therefore, it was reasoned that other carbamate type N-protective groups (*e g* Teoc or Aloc) in combination with an compatible O-protective group (*e g* Allyl or tBDMS) which all can be removed under non-reductive conditions should give access to our target compounds

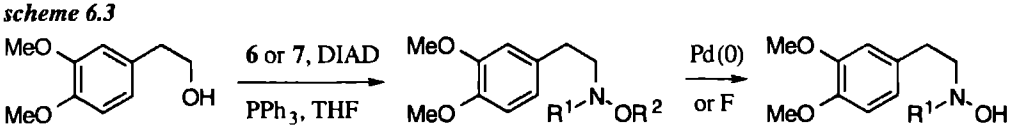
scheme 6.2



O-Allyl-N-Teoc-hydroxylamine **6** was synthesized from O-allylhydroxylamine hydrochloride hydrate and Teoc-Cl in 98% yield O-tBDMS N-Aloc-hydroxylamine **7** was synthesized in two steps from hydroxylamine hydrochloride by treatment with Aloc-ONSu to give N-Aloc-hydroxylamine followed by protection of the hydroxyl group by treatment with *tert*-butyldimethylsilyl chloride to give **7** in overall 71% yield

With the hydroxamates **6** and **7** efficient Mitsunobu reactions could indeed be accomplished (scheme 6 3)

scheme 6.3

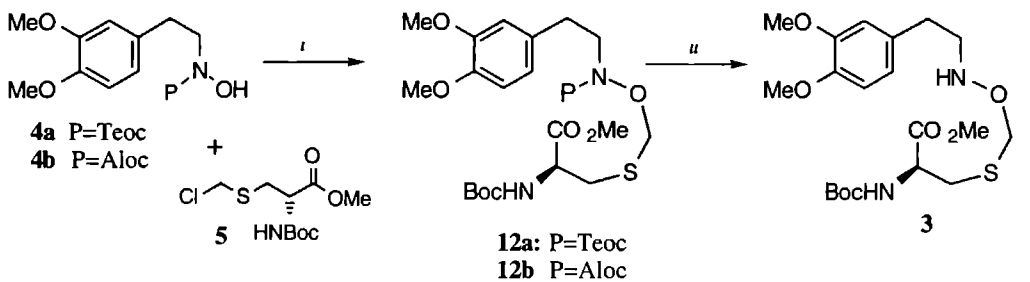


Triphenylphosphine/diisopropyl azodicarboxylate mediated alkylation of **6** and **7** with 2-(3,4-dimethoxyphenyl)ethanol **8** afforded **9** and **10** in yields of 64% and 88%, respectively, after purification by column chromatography Deprotection of the hydroxyl groups in **9** and **10** by treatment with palladium(II)acetate/triethylammonium formate or tetrabutylammonium fluoride, gave **4a,b** in yields of 98% and 74%, respectively

6.3 Nucleophilic Coupling of the N-functionalized Hydroxylamines with a Chloromethyl Sulfide.

The nucleophilic coupling of the chloromethyl sulfide **5** with the sodium salts of the hydroxamates of **4a,b** gave (crude) **12a** and **12b** in yields of 73% and 69%, respectively To avoid racemization the sodium alkoxides **4a,b** were added at such a rate (ca 6 hours) that the pH of the reaction mixture remained near neutral as was previously described in chapter 2

scheme 6.4



i) NaH DME NaI ii) 12a $KF{\equiv}2H_2O/n\text{-}Bu_4NCl$ *12b* $Pd(PPh_3)_4$*/morpholine*

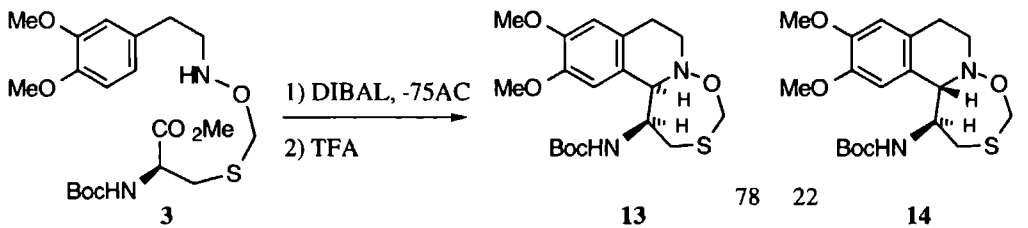
Removal of the Teoc protective group in **12a** was accomplished by treatment with $KF{\equiv}2H_2O$/n-Bu_4NCl/MeCN to give **3** in 98% yield Removal of the Aloc group in **12b** by treatment with $Pd(PPh_3)_4$/morpholine was sluggish and **3** was isolated in only 35% yield Although the optical integrity was not determined after the above-described reaction steps, from previous work it may be assumed that no appreciable racemization had occurred [5]

6.4 Pictet-Spengler Cyclization

The PS condensation was carried out as described in chapter 2 The aldehyde was generated *in situ* by DIBAL reduction of the methyl ester **3** at -75AC, immediately followed by addition of TFA to induce the PS condensation In contrast to the cyclizations in the β-carboline series described in chapter 2, after warming to room temperature still starting material (aldehyde) was present in the reaction mixture (TLC) After additional stirring for 30 minutes at room temperature all starting material had been consumed Work-up and purification by column chromatography gave the two diastereomeric isoquinolines (**13/14**) in 60% yield in a 78/22 ratio As a consequence of the slow

cyclization reaction both **13** and **14** were obtained as near racemates It is likely that racemization can be avoided in future attempts by allowing the reaction to proceed at low temperature (-20AC) and prolonged reaction times

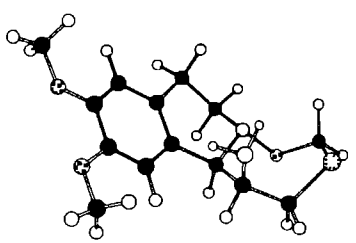
Scheme 6.5



Comparison of the NMR and TLC data with the β-carboline series showed that almost certain the desired cis diastereomer had been formed in excess In the cis diastereomer a smaller geminal (^2J) coupling constant was observed for the thioacetal protons at C(4) (*viz* ca 9 Hz for the cis and ca 11 Hz for the trans diastereomer) Also the δ-values of the (Boc) t-butyl singlets in the cis/trans diastereomers (*viz* at 1 24 and 1 47 ppm) correspond with the δ-values found for the Boc protected cis/trans natural and desthia carba eudistomins (*viz* at 1 17 and 1 52, see chapter 8) In the β-carboline series without exception the cis diastereomer was the low moving component on TLC

This assignment was unambiguously proven by an X-ray crystal structure determination of **13** (chart 6 1)

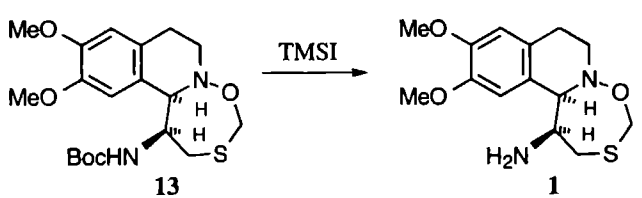
chart 6.1 *X-ray crystal structure of **13***



For clarity reasons the originally present C(1)-NBoc protective group has been replaced by a hydrogen atom

The Boc-group was removed using the TMSCl/NaI method to generate TMSI *in situ* giving the eudistomin isoquinoline analog **1** in 81% yield (scheme 6 6)

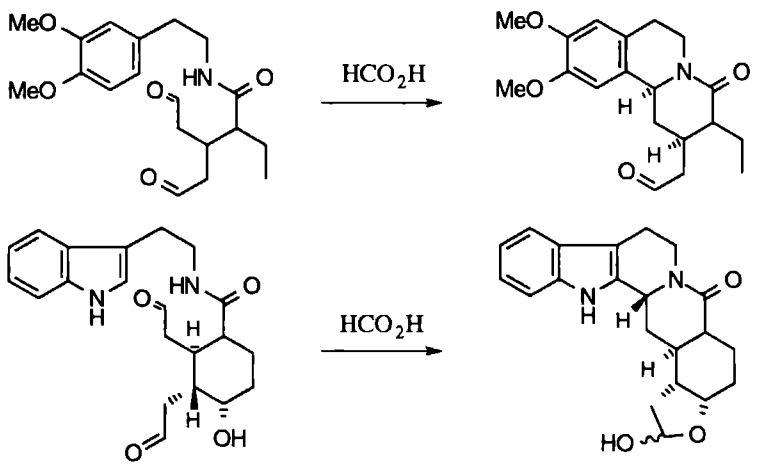
Scheme 6.6



In the isoquinoline series a reversal of diastereoselectivy has been found compared to the β-carboline series Great take great care should be taken in giving an explanation for these results The ΔΔG (at room temperature) between the two transition states leading to a 20/80 diastereomeric product ratio is 0 77 kcal/mol Thus at room temperature the energy difference between a 20/80 or 80/20 diastereomeric ratio is only 1 54 kcal/mol

It is interesting to note that in synthesis of yohimbine derivatives also a complete reversal of product formation was found for an intramolecular PS cyclization in the β-carboline and isoquinoline series (scheme 6 7) [6]

scheme 6.7



For the reversal of diastereoselectivity in these cyclizations no detailed explanation was given It was only stated that the matter of product formation in these cases reflects a delicate energy balance

As is worked out in chapter 2 the main reason for trans diastereoselectivity in the β-carboline series is hindered attack of the indole-β bond on the side of a cyclic iminium-ion where the (amino) substituent is present Consequently, the diastereomeric outcome of the reaction in the β-carboline series is determined in the beginning of the reaction sequence and is kinetically controlled Because the electronic and steric nature of the dimethoxy phenyl group differs fundamentally from an indole moiety, the mechanistic conclusions drawn in chapter 2 for the β-carboline series are not applicable for the isoquinoline series To explain the reversal in diastereoselectivity in the isoquinoline series further investigations will be necessary

6.5 Conclusions

For the synthesis of the unknown N-protected 3,4-dimethoxyphenethyl hydroxylamines **4a,b** a very effcient method was developed from commercialy available 2-(3,4-dimethoxyphenyl)ethanol The hydroxyl groups in **4a,b** were selectively alkylated with the chloromethyl sulfide **5**, previously

described in chapter 2. The PS cyclization, very surprisingly, gave a 56% d.e. to the desired C(1)H-C(12b)H cis diastereomer. The structure assignment was made by X-ray crystal structure determination.

6.6 Experimental Part

For general remarks see the experimental part of chapter 2.

***O*-Allyl-*N*-(2-trimethylsilylethyloxycarbonyl)-hydroxylamine (6)**: To *O*-allylhydroxylamine hydrochloride hydrate (1 9 g, 16 8 mmol) and Teoc-Cl (3 7 g, 20 5 mmol) dissolved in dry THF (15 mL) was added gradually diisopropylethylamine (6.5 mL, 4 8 g, 37 5 mmol). After stirring of the reaction mixture for 6 h., EtOAc (50 mL) was added and the mixture was subsequently washed with 2 portions 10% citric acid, sat $NaHCO_3$ and brine. After drying ($MgSO_4$) and evaporation of the volatiles *in vacuo* the residue was subjected to column chromatography (EtOAc/hexanes=1/4, v/v) to give 3.6 g (98%) of **6** as a colorless oil; R_f 0.50 (EtOAc/hexanes=1/4, v/v); EIMS(70eV), m/z (relative intensity) 174 ([M-C_3H_7]$^+$, 12), 73 ([C_3H_9Si]$^+$, 100), 41 ([C_3H_5]$^+$, 38); ^{1}H NMR (90 MHz) δ 7 35 (br s, 1H, NH), 6 20-5.74 (m, 1H, H_2C=CH), 5 41-5 19 (m, 2H, H_2C=CH), 4.37-4 12 (m, 4H, 2xOCH_2), 1 08-0.89 (m, 2H, $SiCH_2$), 0.00 (s, 9H, $Si(CH_3)_3$)

***O*-(*tert*-Butyldimethylsilyl)-*N*-(2-allyl]oxycarbonyl)-hydroxylamine (7)** To hydroxylamine hydrochloride (2 0 g, 28.8 mmol) and Aloc-ONSu (6.0 g, 30.2 mmol) dissolved in a mixture of acetonitrile/water (4/1, v/v, 25 mL) was added gradually triethylamine (8 mL, 5.8 g, 58 mmol) causing a slightly exothermic reaction (15AC raise in temp.) After stirring for 1 h the reaction mixture was acidified with 10% aqueous citric acid and then EtOAc (50 mL) was added. The organic layer was washed with another portion dil. citric acid and subsequently neutralized (sat. $NaHCO_3$), washed with brine and dried ($MgSO_4$) The volatiles were evaporated *in vacuo* to give 2 54 g (75%) of the crude *N*-Aloc-hydroxylamine, R_f 0 10 (EtOAc/hexanes=1/2, v/v), EIMS(70eV), m/z (relative intensity) 117 ([M]$^+$, 3), 41 ([C_3H_5]$^+$, 100), ^{1}H NMR (90 MHz) δ 7.75 (br s, 1H, HNOH), 6 13-5 70 (m, 1H, H_2C=CH), 5 42-5 15 (m, 2H, H_2C=CH), 4.61 (dt, 2H, J=6.0 Hz and J=1.4 Hz, OCH_2). This crude *N*-Aloc-hydroxylamine (1 4 g, 12 0 mmol) was dissolved in DMF (5 mL) together with *tert*-butyldimethylsilyl chloride (1 8 g, 11.9 mmol) and imidazole (2 4 g, 35 mmol). After standing for 3 h., EtOAc (50 mL) was added and the reaction mixture was extracted with 10% citric acid, water, brine and dried ($MgSO_4$) The volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes =1/3, v/v) to give 2 6 g (94%) of **7** as a colorless oil; R_f 0 53 (EtOAc/hexanes=1/2, v/v), EIMS(70eV), m/z (relative intensity) 174 ([M-C_4H_9]$^+$, 12), 130 ([$C_6H_{14}SiO$]$^+$, 100), 41 ([C_3H_5]$^+$, 97), ^{1}H NMR (90 MHz) δ 7 00 (br s, 1H, NH), 6 15-5 72 (m, 1H, H_2C=CH), 5.53-5 15 (m, 2H, H_2C=CH), 4.62 (dt, 2H, J=5 6 Hz and J=1 3 Hz, OCH_2), 0.94 (s, 9H, $Si(CH_3)_3$), 0.16 (s, 6H, $Si(CH_3)_2$)

***N*-[2-(trimethylsilyl)ethyloxycarbonyl]-*N*-(allyloxy)-2-(3,4-dimethoxyphenyl)ethylamine (9)** To 2-(3,4-dimethoxyphenyl)ethanol (1.0 g, 5.5 mmol), **6** (1.6 g, 7 1 mmol) and triphenylphosphine (1 87 g, 7 1 mmol) dissolved in dry THF (10 mL) was added gradually diisopropyl azodicarboxylate (1.40 mL, 1 44 g, 7 1 mmol) causing a slightly exothermic reaction After 1 h. the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/6, v/v) to yield 0 86 g (64%) of **9** as a colorless oil, R_f 0 30 (EtOAc/hexanes=1/4, v/v), EIMS(70eV), m/z (relative intensity) 381 ([M]$^+$, 6), 338 ([M-C_3H_7]$^+$, 2), 151 ([$C_9H_{11}O_2$]$^+$, 22), 73 ([C_3H_9Si]$^+$, 100), 41 ([C_3H_5]$^+$, 6); ^{1}H NMR (90 MHz) δ 6.76 (s, 3H, PhH_3), 6 24-5 78 (m, 1H, H_2C=CH), 5 44-5 19 (m, 2H, H_2C=CH), 4.33 (d, 2H, J=5 9 Hz, $NOCH_2$), 4 23-4.04 (m, 2H, OCH_2CH_2Si), 3 84 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3 67 (dd, 2H, J=8 0 Hz and J=6 7 Hz, NCH_2), 2.85 (dd, 2H, J=7.8 Hz and J=6.5 Hz, $PhCH_2$), 1 04-0 86 (m, 2H, $SiCH_2$), 0.00 (s, 9H, $Si(CH_3)_3$) together with 0.48 g of an impure fraction, contaminated with **6** Because the R_f values of the starting compound **6** and product **9** only differ slightly (*i e* 0.36 and 0.30) purification by flash chromatography was difficult and it is therefore recommended not to use an excess of **6**.

***N*-(allyloxycarbonyl)-*N*-(*tert*-butyldimethylsilyloxy)-2-(3,4-dimethoxyphenyl)ethylamine (10)** The same procedure was followed as described for **9** using 2-(3,4-dimethoxyphenyl)ethanol (1 0 g, 5 5 mmol), **7** (1 6 g, 6 9 mmol), triphenylphosphine (1 9 g, 7 3 mmol) and diisopropyl azodicarboxylate (1 44 mL, 1 4 g, 6 9 mmol) Work-up followed by purification by column chromatography (EtOAc/hexanes=1/5, v/v) afforded 1 91 g (88%) of **10** as a colorless oil, R_f 0 33 (EtOAc/hexanes=1/4, v/v), EIMS(70eV), m/z (relative intensity) 395 ($[M]^+$, 1), 338 ($[M\text{-}C_4H_9]^+$, 46), 151 ($[C_9H_{11}O_2]^+$, 99 7), 115 ($[C_6H_{15}Si]^+$, 7), 41 ($[C_3H_5]^+$, 100), ^{1}H NMR (90 MHz) δ 6 75 (m, 3H, PhH_3), 6 07-5 65 (m, 1H, CH_2=C<u>H</u>), 5 37-5 11 (m, 2H, <u>CH_2</u>=CH), 4 51-4 42 (m, 2H, OCH_2), 3 86 (s, 3H, OCH_3), 3 84 (s, 3H, OCH_3), 3 67 (dd, 2H, J=9 0 Hz and J=5 4 Hz, NCH_2), 2 88 (dd, 2H, J=9 0 Hz and J=5 4 Hz, $PhCH_2$), 0 98 (s, 9H, $C(CH_3)_3$), 0 17 (s, 6H, $Si(CH_3)_2$)

***N*-[2-(trimethylsilyl)ethyloxy)carbonyl]-*N*-hydroxy-2-(3,4-dimethoxyphenyl)ethylamine (4a)** To **9** (1 3 g, 3 4 mmol) dissolved in acetonitrile/water (4/1, v/v, 25 mL) under an argon atmosphere was subsequently added triethylammonium formate (4 4 g, 10 mmol), triphenylphosphine (40 mg, 0 15 mmol) and $Pd(OAc)_2$ (11 mg, 0 05 mmol) The reaction mixture was heated at reflux for 30 minutes Work-up was accomplished by the addition of EtOAc (50 mL) and subsequent washings with 3 portions of water and brine After drying ($MgSO_4$), the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/2, v/v) to give 1 14 g (98%) of **4a** as a colorless oil, R_f 0 35 (EtOAc/hexanes=1/1, v/v), EIMS(70eV), m/z (relative intensity) 341 ($[M]^+$, 0 5), 151 ($[C_9H_{11}O_2]^+$, 31), 73 ($[C_3H_9Si]^+$, 100), ^{1}H NMR (90 MHz) δ 7 21 (br s, 1H, OH), 6 78-6 70 (m, 3H, PhH_3), 4 19 4 01 (m, 2H, OCH_2), 3 85 (s, 3H, OCH_3), 3 82 (s, 3H, OCH_3), 3 71 (t, 2H, J=6 8 Hz, NCH_2), 2 87 (t, 2H, J=6 8 Hz, $PhCH_2$), 0 99-0 80 (m, 2H, $SiCH_2$), 0 00 (s, 9H, $Si(CH_3)_3$)

***N*-(allyloxycarbonyl)-*N*-hydroxy-2-(3,4-dimethoxyphenyl)ethylamine (4b)** To **10** (1 9 g, 4 8 mmol) dissolved in THF (25 mL) was added tetrabutylammonium fluoride (5 mL of a 1M solution in THF) The deprotection was completed within 30 minutes Work-up was accomplished by removal of the volatiles *in vacuo* followed by purification of the residue by column chromatography (EtOAc/hexanes=1/2, v/v) to give 1 0 g (74%) of **4b** as a colorless oil, R_f 0 33 (EtOAc/hexanes=1/1, v/v), CIMS(70eV), m/z (relative intensity) 281 ($[M]^+$, 64), 151 ($[C_9H_{11}O_2]^+$, 100), ^{1}H NMR (90 MHz) δ 6 77-6 75 (m, 3H, PhH_3), 6 04-5 62 (m, 1H, CH_2=C<u>H</u>), 5 33-5 10 (m, 2H, <u>CH_2</u>=CH), 4 54-4 46 (m, 2H, OCH_2), 3 84 (s, 6H, $2xOCH_3$), 3 67 (t, 2H, J=7 0, NCH_2), 2 90 (t, 2H, J=7 0 Hz, $PhCH_2$)

Methyl 2-(*tert*-butyloxycarbonylamino)-3-[*N*-(allyloxycarbonyl)-*N*-(2-(3.4-dimethoxyphenyl)-ethyl)aminooxy-methylsulfanyl]propionate (12b) This experiment was carried out under an argon atmosphere employing flame dried glass equipment To **4b** (0 69 g, 2 46 mmol) dissolved in freshly distilled 1,2-dimethoxyethane (10 ml), NaH (75 mg of a 60% oil dispersion, 2 46 mmol) was added and the suspension was stirred until a clear solution appeared (hydrogen gas evolved) This solution was added gradually (in ca 6 hours) to a stirred solution of **5**,[5] (1 0 g, 3 5 mmol) and NaI (0 55 g, 3 7 mmol) in freshly distilled 1,2-dimethoxyethane (50 mL) Work-up was accomplished by the addition of sat NH_4Cl (2 mL) followed by concentration of the suspension *in vacuo* The residue was dissolved in EtOAc and subsequently washed with water and brine The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to yield 0 87 g (69%) of crude **12b** which was homogeneous by TLC, R_f 0 21 ($MeOH/CH_2Cl_2$ =1/99, v/v), CIMS(70eV), m/z (relative intensity) 529 ($[M+1]^+$, 0 2), 151 ($[C_9H_{11}O_2]^+$, 58), 57 ($[C_4H_9]^+$, 100), 41 ($[C_3H_5]^+$, 62) ^{1}H NMR (90 MHz) δ 6 77 (broadened s, 3H, PhH_3), 6 10-5 69 (m, 1H, CH_2=C<u>H</u>), 5 60 (br d, 1H, J=8 1 Hz, NH), 5 39-5 16 (m, 2H, <u>CH_2</u>=CH), 4 91 (s, 2H, OCH_2S), 4 64-4 42 (m, 3H, $O\underline{CH_2}$-CH=CH_2 and $SCH_2\underline{CH}$), 3 88 (s, 3H, OCH_3), 3 87 (s, 3H, OCH_3), 3 77 (s, 3H, CO_2CH_3), 3 81-3 62 (m, 2H, $PhCH_2\underline{CH_2}$), 3 21-2 82 (m, 4H, $Ph\underline{CH_2}CH_2$ and $S\underline{CH_2}CH$), 1 43 (s, 9H, $C(CH_3)_3$)

Methyl 2-(*tert*-butyloxycarbonylamino)-3-[*N*-(2-(3.4-dimethoxyphenyl)ethyl)aminoxymethyl-sulfanyl]-propionate (3) <u>From **12b**</u> To **12b** (0 87 g, 1 7 mmol) dissolved in THF (15 mL) under an argon atmosphere was added morpholine (0 44 mL, 0 44 g, 5 1 mmol) and $Pd(PPh_3)_4$ (25 mg, 0 02 mmol) After standing of the reaction mixture for 2 days, work-up was accomplished by evaporation of the volatiles *in vacuo* followed by purification of the residue by column chromatography (EtOAc/hexanes=1/2, v/v) of the residue to yield 0 26 g (35%) of **3** as a colorless oil, R_f 0 40 (EtOAc/hexanes=1/1, v/v), CIMS(70eV), m/z (relative intensity) 445 ($[M+1]^+$, 6), 151 ($[C_9H_{11}O_2]^+$, 58), 148 (100),

57 ($[C_4H_9]^+$, 85), ^{1}H NMR (90 MHz) δ 6 78-6.72 (m, 3H, PhH_3), 5.95 (br d, 1H, J=8.8 Hz, NH), 4.91-4.81 (AB, 2H, OCH_2S), 3.89 (s, 3H, OCH_3), 3 89 (s, 3H, OCH_3), 3.78 (s, 3H, CO_2CH_3), 3.22-3 74 (m, 6H, $PhCH_2CH_2$ and SCH_2CH), 1.44 (s, 9H, $C(CH_3)_3$)

From **4a** For the alkylation the same procedure was followed as described for **12b** using **4a** (0 99 g, 2.9 mmol), **5** (1.4 g, 4 9 mmol), NaH (87 mg of a 80% suspension, 2.9 mmol) and NaI (0 7 g, 4 7 mmol). After work-up 1.24 g (73%) of crude **12a** was obtained which was then dissolved in dry acetonitrile (25 mL) To this solution tetrabutylammonium chloride (1.76 g, 6 3 mmol) and potassiumfluoride dihydrate (0 79 g, 8 4 mmol) were added and the resulting suspension was stirred at 50°C over night. Work-up was accomplished by evaporation of the volatiles *in vacuo* followed by purification of the residue by chromatography (EtOAc/hexanes=1/2, v/v) affording 0.85 g (98%) of **3** as a colorless oil

Cyclization reaction:

cis (*rac*)-1-(*tert*-Butyloxycarbonylamino)-10,11-dimethoxy-1,2,7,8,12b-pentahydro[1,6,2]-oxathiazepino-[2',3'-*a*]isoquinoline (13) and **trans (*rac*)-1-(*tert*-Butyloxycarbonylamino)-10,11-dimethoxy-1,2,7,8,12b-pentahydro-[1,6,2]oxathiazepino-[2',3'-*a*]isoquinoline (14)** To a cooled solution (-75°C) of **3** (830 mg, 1.93 mmol) in dry dichloromethane (150 mL) employing flame dried glass equipment under an argon atmosphere was added DIBAL (2 9 mL of a 1M solution in dichloromethane) at such rate that the temperature remained below -70°C. After stirring for 30 minutes trifluoroacetic acid (1 mL) was added and the reaction mixture was allowed to warm to room temperature After standing for 30 min. at room temperature all starting material had been consumed and the reaction mixture was successively washed with 10% citric acid, sat. $NaHCO_3$ and brine After drying ($MgSO_4$) the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/4) to give 100 mg (13%) of **14** as a white solid; R_f 0 31 (EtOAc/hexanes=1/2), CIMS(70eV), m/z (relative intensity) 395 ($[M-1]^+$, 0.5), 341 (11), 207 ($[C_{11}H_{13}NO_3]^+$, 100), 57 ($[C_4H_9]^+$, 24), ^{1}H NMR (400 MHz) δ 7.27 (br s, 1H, C(12)H), 6 54 (s, 1H, C(9)H), 5 93 (br d, 1H, J=9 9 Hz, NH), 5.15 (br AB, 1H, J_{AB}=10 9 Hz, C(4)Hα), 4.76 (AB, 1H, J_{AB}=10.9 Hz, C(4)Hβ), 4 58 (br s, 1H, C(1)Hα), 4 01 (s, 1H, C(12b)Hβ), 3.90 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3 60 (very br s, 1H, C(7)Hα), 3 43 (br s, 1H, C(2)Hα), 3 09-2.90 (m, 2H, C(7)Hβ and C(8)Hα), 2 73 (dd, 1H, J=5 1 Hz and J=14.1 Hz, C(8)Hβ), 2.62 (d, 1H, J=15 3 Hz, C(2)Hβ), 1.47 (s, 9H, $C(CH_3)_3$), ^{13}C NMR (100 MHz, the marked atoms may be interchanged) δ 154.90 (C=O), 147 70 C(11) and C(10), 127.73 C(12a#), 125 88 C(8a#), 110 39 C(12⁻), 110 39 C(9⁻), 79 46 $\underline{C}(CH_3)_3$, 74.49 C(12b) and C(4), 56 03 OCH_3, 56.2 C(1), 55.81 OCH_3, 53.28 C(7), 33.90 C(2), 29 25 C(8), 28 39 $C(\underline{C}H_3)_3$ and 360 mg (47%) of **13** as colorless crystals. Recrystallized from EtOAc/hexanes (mp=173-177°C); R_f 0 21 (EtOAc/hexanes=1/2), α_D^{22}=+13.0 (c=2.30, CH_2Cl_2/MeOH=1/1, v/v, near racemate), CIMS(70eV), m/z (relative intensity) 397 ($[M+1]^+$, 0 7), 207 ($[C_{11}H_{13}NO_3]^+$, 100), 57 ($[C_4H_9]^+$, 15), ^{1}H NMR (400 MHz, to sharpen up the broadened spectrum recorded at 46°C) δ 6.75 (s, 1H, C(12)H), 6.53 (s, 1H, C(9)H), 5 23 (br d, 1H, J=8.1 Hz, NH), 4 91 and 4.79 (AB, 2H, J_{AB}=9.1 Hz, OCH_2S), 4.63 (br m, 1H, H(1)α), 4 16 (br s, 1H, H(12b)β), 3.86 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3 46-3 38 (m, 1H, H(7)β), 3.25 (d, 1H, J=14.5 Hz, H(2)α), 3 06-2 95 (m, 2H, H(7)α and H(8)β), 2.85 (dd, 1H, J=14 5 Hz and J=6 1 Hz, H(2)β), 2 68-2 58 (m, 1H, H(8)α), 1 24 (s, 9H, $C(CH_3)_3$), ^{13}C NMR (100 MHz, the marked atoms may be interchanged) δ 155.30 (C=O), 147 57 C(11*), 147 44 C(10*), 126 42 C(12a#), 125 39 C(8a#), 110.37 C(12⁻), 109 97 C(9⁻), 78.98 $\underline{C}(CH_3)_3$, 71.33 C(12b) and C(4), 55.84 2xOCH_3, 53 40 C(7), 50 69 C(1), 33.08 C(2), 29 28 C(8), 28 17 $C(\underline{C}H_3)_3$, Anal Calcd for $C_{19}H_{28}N_2O_5S$· C, 57 56; H, 7.12; N, 7.07, S, 8 09 Found: C, 57.52; H, 6 94, N, 6.81; S, 7 66

cis (*rac*)-1-amino-10,11-dimethoxy-1,2,7,8,12b-pentahydro[1,6,2]-oxathiazepino-[2',3'-*a*]isoquinoline (1) To a stirred solution of **13** (300 mg, 0 76 mmol) in dry acetonitrile (50 mL) NaI (227 mg, 1.51 mmol) and chlorotrimethylsilane (0 19 mL, 164 mg, 1.51 mmol) were added After stirring for 4 hours all starting material had been consumed and triethylamine (0.5 mL) was added The volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (MeOH/CH_2Cl_2=2/98, v/v) to yield 183 mg (81%) of **1** as a white solid as a near racemate, mp=100-102°C, R_f 0.21 (MeOH/CH_2Cl_2=5/95, v/v), CIMS(70eV), m/z (relative intensity) 297 ($[M+1]^+$, 11), 280 ($[M-NH_2]^+$, 6), 207 ($[C_{11}H_{13}NO_3]^+$, 100); ^{1}H NMR (400 MHz) δ 6.61 (s, 1H, PhH), 6.59 (s, 1H, PhH), 4.91 and 4.82 (AB, 2H, J_{AB}=9.2 Hz, OCH_2S), 4 15 (d, 1H, J=2.1 Hz, H(12b)α), 3.86 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3 51-3 43 (m, 2H, H(1)α and H(7)β), 3 33 (d, 1H, J=14.4 Hz, H(2)α), 3 05-2 95 (m, 2H, H(7)α and H(8)β), 2 87 (dd,

1H, J=14 4 Hz and J=6 2 Hz, H(2)β), 2 68-2 58 (m, 1H, H(8)α), ^{13}C NMR (100 MHz, the marked atoms may be interchanged) δ 147 97 C(11*), 147 62 C(10*), 127 99 C(12a#), 126 23 C(8a#), 110 87 C(12~), 108 84 C(9~), 72 57 C(12b), 72 12 C(4), 55 96 (OCH_3), 55 79 (OCH_3), 52 83 C(7), 52 55 C(1), 35 04 C(2), 29 28 C(8), Anal Calcd for $C_{14}H_{20}N_2O_3S$ C, 56 73, H, 6 80, N, 9 45, S, 10 82 Found C, 56 05, H, 6 47, N, 9 12, S, 10 40

References

1 Cain, M , Weber, R W , Guzman, F , Cook, J M , Barker, S A , Rice, K C , Crawley, J N , Paul, S M , Skolnick, P *J Med Chem* , **1982**, 25, 1081

2 Maarseveen, J H van, Hermkens, P H H , De Clercq, E , Balzarini, J , Scheeren, J W , Kruse, C G *J Med Chem* , **1992**, 35, 3223

3 a) Tietze, L F , Schimpf, R , Wichmann, J *Chem Ber* **1992**, 125, 2571-2576 b) Maryanoff, B E , Rebarchak, M C *Synthesis*, **1992**, 1245

4 Maurer, P J , Miller, M J *J Am Chem Soc* **1982**, 104, 3096

5 Hermkens, P H H , Maarseveen, J H van, Ottenheijm, H C J , Kruse, C G , Scheeren, J W *J Org Chem* **1990**, 55, 3998

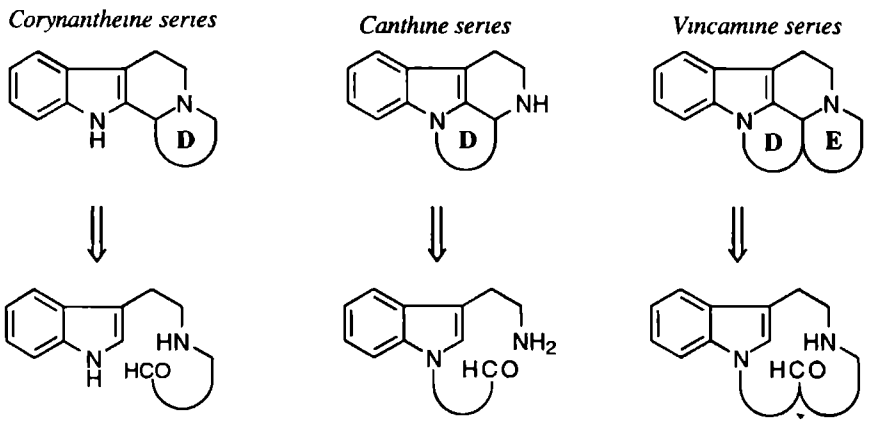
6 Van Tamelen, E E , Shamma, M , Burgstahler, A W , Wolinsky, J , Tamm, R , Aldrich, P E *J Am Chem Soc* **1969** 91 7315

7 An Approach to the Canthine series Using the Intramolecular Pictet-Spengler Condensation.

7.1 Introduction

For ring closures in the β-carboline series by means of the intramolecular Pictet-Spengler (PS) condensation three different target structures can be considered, which all are related to naturally occurring indole alkoloids.

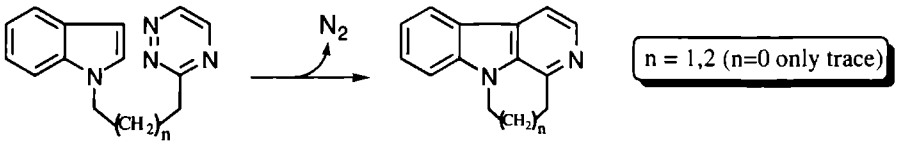
Scheme 7.1



The intramolecular PS approach in the synthesis of compounds containing the corynanthe-type skeleton has been extensively applied [1] The similar strategy toward the vincamine-type skeleton, giving the CDE ring systems simultaneously, is unknown. Build up of the vincamine-type skeleton via a corynanthe-type skeleton using the intramolecular PS strategy followed by closure of the D ring however is known [2] Closure of the D-ring, as illustrated in scheme 7 1, in the canthine-series using the intramolecular PS strategy is hitherto completely unknown.

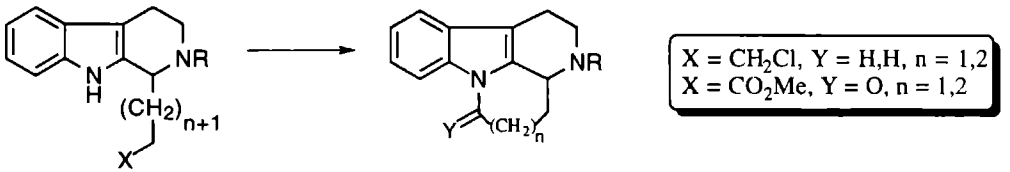
Access to the canthine series by closing the CD ring simultaneously has recently be accomplished by using an intramolecular Diels-Alder reaction [3]

Scheme 7.2



Closure of the D-ring in β-carboline skeletons has been accomplished on the indole nitrogen both by alkylation[4] and lactamization (scheme 7 3) [5]

Scheme 7.3

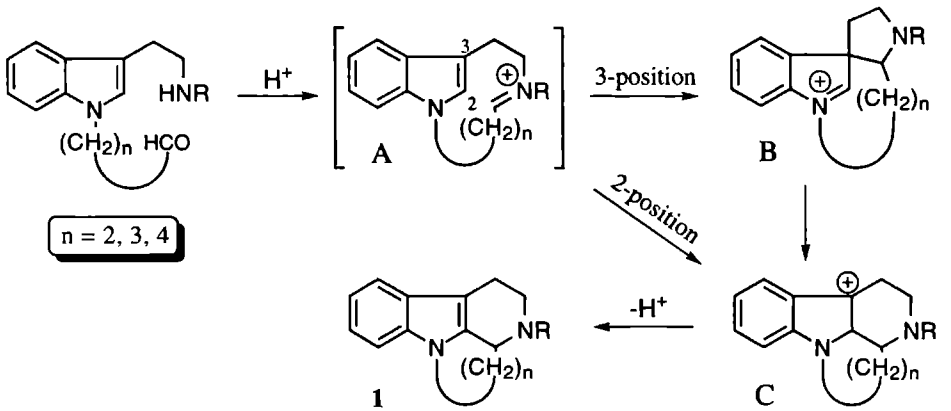


In this chapter access to the canthine-series using the intramolecular PS condensation will be described This approach is hitherto unknown and therefore, a more detailed study of the use of this new strategy is desirable In addition to the synthetic utility interesting mechanistic aspects are also connected to this approach

Since the late sixties the discussion has continued whether product formation in the PS takes place via electrophilic attack at the indole 3- or 2-position [6] In chapter 2 this topic was treated extensively The intermediate spiro compounds, the result of attack at the indole 3-position, have been isolated and characterized Although the spiro intermediate in the PS condensation was isolated and succesfully transformed into the β-carboline, product formation via direct attack at the indole 2-position still cannot be excluded [7] The argument that attack at the indole 2-position competes with attack at the 3-position was recently considered by Nakagawa[8], Cook[9] and our group[10] (see chapter 2) Nakagawa drew attention to the fact that the empirical Baldwin rules for ring closure show that only the process via the spiro intermediate involves the disfavored 5-*endo*-trig pathway

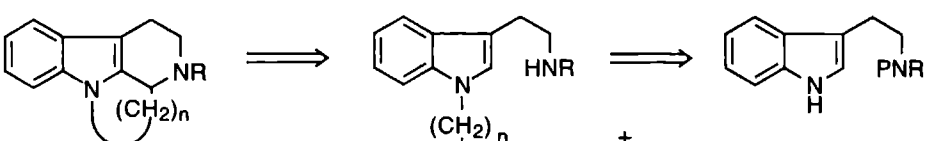
The intramolecular PS condensation in the synthesis of the canthine skeleton in particular may prove evidence for direct electrophilic attack at the indole 2-position From scheme 7 4 it is clear that for n=2 canthine formation is unlikely because the formation of the intermediate iminium-ion will be difficult as it will involve a highly strained 9-membered ring Therefore, for n=2 only oligomeric compounds may be expected rather than intramolecular PS cyclizations When canthine formation would occur for n=3 this would be a strong indication for a PS reaction via a direct attack at the indole 2 position, since product formation via attack at the indole 3-position is highly unfavorable due to the formation of a spiro intermediate with a 7-membered ring system containing a trans double bond[1]

Scheme 7.4



As indicated in scheme 7.5, in this study the chain length *n* was varied from 2-4. In chapter 5, it was described that the nature of the intermediate iminium ion in the PS condensation particulary dictates the efficiency of the reaction. Therefore, besides N_b-allyloxy cyclization studies were also performed with N_b-formyl and N_b-benzyl tryptamines with n=3 (see scheme 7.5). The aldehydes used in the PS reactions were generated by *in situ* hydrolysis of the corresponding dialkyl acetals **9a-e**, which are retrosynthetically derived from the corresponding tryptamines **2-4** and the alkyl bromides **5-7**.

Scheme 7.5



1	n	R
a	2	OCH_2-HC=CH_2
b	3	OCH_2-HC=CH_2
c	3	CHO
d	3	CH_2Ph
e	4	OCH_2-HC=CH_2

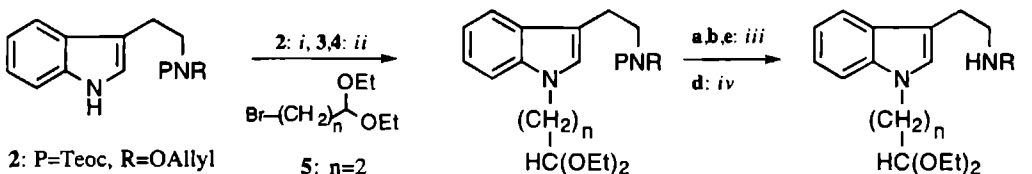
7.2 Synthesis of the Various N_a,N_b-Bifunctionalized Tryptamines

N_a-alkylation of the tryptamine derivative **2**[11] with the alkyl bromides **5-7** was accomplished under mild phase transfer conditions, using concentrated NaOH/toluene/n-Bu_4NBr at elevated

temperature (40°C) to give **8a,b,e** in 73-93% yield (scheme 7.6).[12] For N_a-alkylation of the tryptamines **3** and **4** the powdered KOH/DMSO method was used to give **8c** in 65% yield (the crude yield of **8d** was not determined). This method gave concomitant removal of the Teoc group.[13]

Deprotection of the Teoc group of **8a,b,e** was accomplished by treatment with tetrabutylammonium fluoride in THF to give **9a,b,e** in 73-99% yield. Reduction of the benzoyl group in **8d** with lithiumaluminium hydride in THF gave **9d** in 65% overall yield from **4**.

Scheme 7.6



2: P=Teoc, R=OAllyl
3: P=H, R=formyl
4: P=H, R=benzoyl

5: n=2
6: n=3
7: n=4

for n=2 the dimethyl acetal was used

8[a]	n	R	9
a	2	OCH_2-HC=CH_2	**a**
b	3	OCH_2-HC=CH_2	**b**
c	3	CHO	
d[b]	3	CH_2Ph	**d**
e	4	OCH_2-HC=CH_2	**e**

[a] P=Teoc in **8a,b,e**; P=H in **8c,d** [b] R=benzoyl

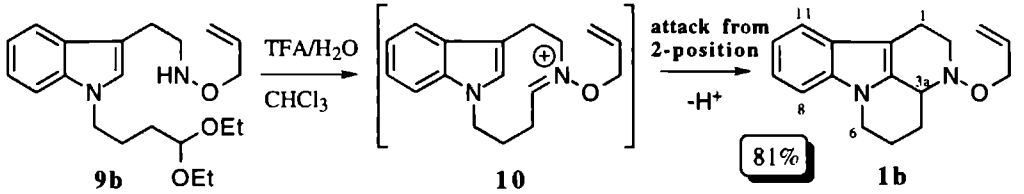
i) n-Bu_4NBr, 50% aq.NaOH, toluene, 40°C; ii) powdered KOH, DMSO, RT; iii) n-Bu_4NF, THF; iv) $LiAlH_4$, THF

7.3 Cyclization Reactions

Cyclizations with N_b-allyloxy tryptamines:

The initial cyclization experiments were carried out with **9b** (*i.e.* n=3) which would give the canthine skeleton. The intramolecular PS approach to the corynanthe series gave the best results by treatment of the acetals with trifluoroacetic acid in dichloromethane producing cyclized products in >90% yield.[1b] Application of this method to **9b** indeed gave the target canthine **1b**, although in a disappointing yield of 27%. TLC analysis showed, besides **1b**, the presence of several, unidentified, side products. In chapter 2 it was described that addition of water to the reaction mixture, which facilitates *in situ* formation of the more reactive aldehyde, may improve the cyclization yield. Indeed stirring of **9b** in the medium trifluoroacetic acid/water/chloroform (1/1/98, v/v/v) gave in a clean reaction of only 30 min. **1b** in 81% isolated yield. In contrast, under anhydrous conditions stirring for 2 days was necessary to convert all starting material.

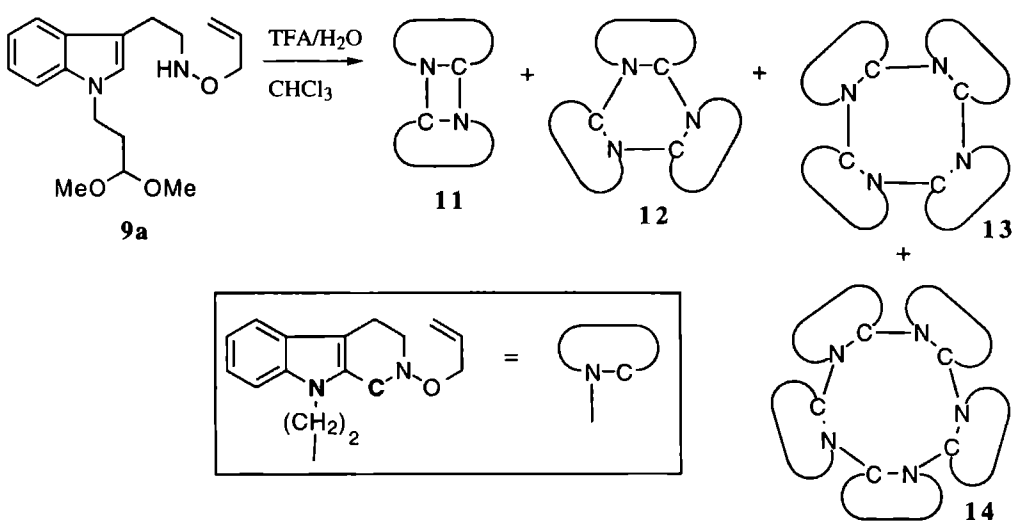
Scheme 7.7



Besides the efficiency of this approach to the canthine series it is also demonstrated that indeed direct attack of the indole 2-position at the intermediate iminium ion is a possible pathway in the PS condensation, even under mild conditions (see also paragraph 2.6).

The cyclization experiments with **9a** and **9e** (*i.e.* with n=1 and n=3, respectively) were also carried out under these optimized aqueous conditions (see schemes 7.8 and 7.9, respectively). As was expected **9a** failed to give the monomeric canthine skeleton. In only 24% yield dimer **11** was isolated in combination with 50% of a mixture of compounds. This mixture was again subjected to flash column chromatography to yield compounds which had more or less the same NMR spectra. Compared with the NMR spectrum of the pure dimeric compound the signals were at the same δ values but broadened. Fast atom bombardment mass spectroscopy (FABMS) showed that these products were indeed the tri-, tetra- and pentameric compounds **12-14**.

Scheme 7.8

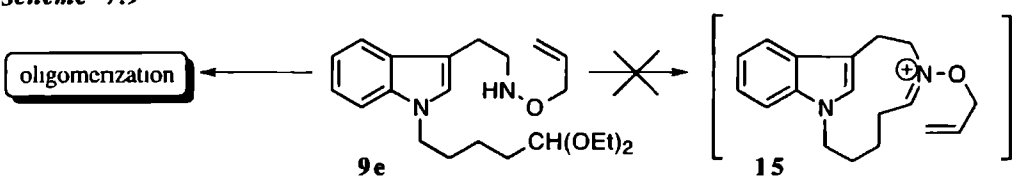


Although the cyclization of **9a** was performed at rather high dilution (0.01M) it is likely that the yield of dimer **11** may be improved by applying a higher dilution. This is suggested by the fact that by increasing the dilution from 0.02M→0.01M the yield of the dimer **11** improved from 15%→24%. It is not known to which of the two theoretically possible diastereomic forms, *i.e.* the meso or d,l-

pair, the isolated dimer **11** belongs, or if **11** is a mixture of both For pentamer **14**, the combination of NMR and FABMS spectroscopy suggested that at least two diastereomers had been formed

Cyclization reaction with **9e** gave, unexpectedly, a complex mixture of products (oligomers) which could not be separated and identified (scheme 7 9) The reason for this failure is most probably the involvement of the disfavored intermediate 11-membered ring iminium ion **15**

Scheme 7.9



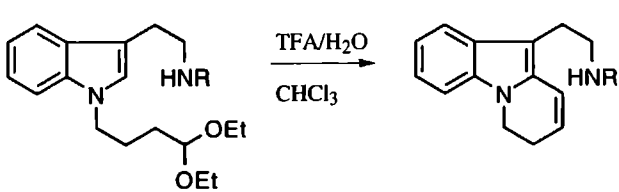
Cyclization reactions of the N_b-formyl- and N_b-benzyltryptamines **8c** and **9d**

From the literature[14] and our work it is known that the nature of the intermediate iminium ion is very important for the outcome of the PS reaction In chapter 5 the influence of N_b substituents on the PS reaction has been discussed in detail From this discussion it may be concluded that the high reactivity of an iminium ion can be cancelled out by the low rate of its formation due to the low nucleophilicity of the N_b nitrogen atom It was found that in particular alkoxyamines are versatile amines in the PS condensation because the high nucleophilicity is accompanied by a high electrophilicity of the corresponding iminium ions, both of these effects being exerted by the alkoxy substituent

To compare the utility of N_b-alkoxy tryptamines with N_b-formyl- and N_b-benzyltryptamines, which are known rate enhancing N_b-substituents in the PS condensation,[15] cyclizations were carried out with **8c** and **9d**

Both **8c** and **9d** gave a clean cyclization reaction under the standard TFA/H_2O/$CHCl_3$ conditions and all starting material had been consumed within 30 minutes Visualization of the TLC-spots of the products, however, showed an intense fluorescence at 365 nm which indicates the presence of some extra conjugation to the aromatic indole system Indeed, NMR spectroscopy revealed that a side reaction had occurred Instead of the N_b amine, the indole 2-position had directly attacked the electrophilic aldehyde species, followed by an elimination giving the 3,4-dihydro pyrimidino[1,2-*a*]indoles **16c** and **16d**, in quantitative yields (scheme 7 10) [16]

Scheme 7.10



8c R = CHO
9d R = CH_2Ph

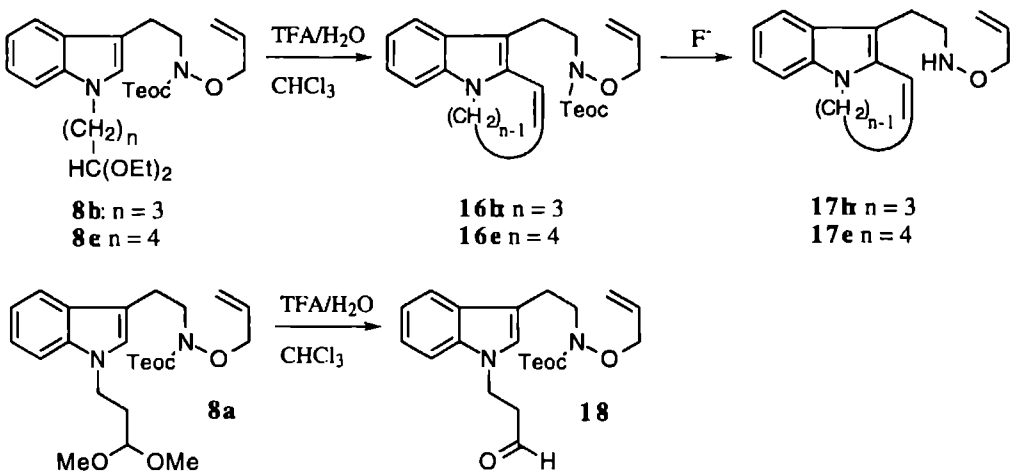
16c R = CHO
16d R = CH_2Ph

The failure of **8c** to give the canthine skeleton can be attributed to the low nucleophilicity of the formylated nitrogen atom. Although the benzylated amine in **9d** is highly nucleophilic it is also strongly basic (see table 5.1 in chapter 5) implying that under these acidic conditions the amine is predominantly present in its nonnucleophilic protonated form. The observation that the cyclizations to the 3,4-dihydro pyrimidino[1,2-*a*]indoles **16c,d** proceeded with rates comparable with the cyclization to the canthine **1b** underscores the high reactivity of the indole 2-position.

With these findings the statement previously made in chapter 5, *i.e.* that N_b-alkoxytryptamines ions are the most versatile substrates in the PS condensation, is reconfirmed.

To study the intramolecular cyclization reaction with aldehydes at the indole 2-position for different ring sizes this reaction was also performed with the N_b-Teoc protected tryptamines **8a,b** and **8e**. Both **8b** and **8e** gave a smooth cyclization reaction to give **16b** and **16e**, respectively, in quantitative yields (scheme 7.11).[17] **8a** failed to give the cyclization reaction. After stirring the reaction mixture for 16 hours the aldehyde **18** could be isolated in 43% yield together with 14% recovered starting material **8a**. Although no further attempts have been made to achieve cyclization of **18** it may be expected that stronger acidic conditions will lead to the desired cyclization.[18]

Scheme 7.11



The N_b-Teoc protective groups in **16b,e** were removed by treatment with tetrabutylammonium fluoride in THF to give **17b,e** in 75% and 72% yield. Subsequent treatment of **17b** with $TFA/H_2O/CHCl_3$ did not give any formation of canthine **1b**, proving that indeed canthine formation had occurred via the iminium ion pathway.

7.4 Conclusion

Treatment of N_a-(4-butanal diethyl acetal)-N_b-allyloxytryptamine **9b** with TFA/H_2O in chloroform gave the hexahydro canthine derivative **1b** in 81% yield. This result demonstrates that PS cyclization can indeed occur by direct attack of the indole 2-position at the intermediate iminium ion. With N_a-propanal chains, only dimeric and oligomeric compounds could be isolated. With the N_a-pentanal chain (unidentified) oligomeric compounds were also formed. The monomeric canthine-like product could not be detected, probably because its formation has to proceed via a disfavored intermediate cyclic iminium ion.

Cyclization of N_a-butanal functionalized N_b-formyl- or N_b-benzyltryptamines **8c** and **9d**, which are known rate enhancing substituents in the PS condensation, unexpectedly gave the 3,4-dihydro pyrimidino[1,2-*a*]indoles **16c,d**. The products **16c,d** were formed by a direct electrophilic attack of the protonated aldehydes on the indole 2-position, thus emphasizing the reactivity of the indole 2-position. The poor nucleophilicity of the corresponding N_b-atoms in **8c** and in the protonated form of **9d** is responsible for the inability to afford the canthine skeleton.

In summary, the intramolecular PS condensation to the canthine series is only possible with N_b-alkoxy tryptamines due to their highly nucleophilic N_b nitrogen atom

7.5 Experimental Part

For general remarks see the experimental part of chapter 2.

O-Allyl-N-[2-[1-(3,3-diethoxy-propyl)-1*H*-indol-3-yl]-ethyl]-N-[(2-(trimethylsilyl)ethoxy)-carbonyl]-hydroxylamine (8a) To **2** (3 0 g, 8 3 mmol), dissolved in a mixture of conc NaOH (24 mL of a 50% (by weight) solution in water) and toluene (100 mL) was added 3-bromopropionaldehyde dimethoxyacetal (2 0 g, 10 9 mmol) and tetrabutylammonium bromide (280 mg, 0 87 mmol) The resulting suspension was stirred vigorously at 40°C for 12 hours. The reaction mixture was diluted with EtOAc and water The organic layer was washed with sat NH_4Cl and dried ($MgSO_4$) The volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/3, v/v) to afford 2 8 g (73%) of **2** as a colorless oil, R_f 0 26 (EtOAc/hexanes=1/3, v/v), CIMS(70eV), m/z (relative intensity) 462 ([M]$^+$, 14), 232 ([$C_{14}H_{18}NO_2$]$^+$, 35), 73 ([$Si(CH_3)_3$]$^+$, 17), 49 (100), ^{1}H NMR (90 MHz) δ 7 64-7 56 (m, 1H, indole C(7)H), 7 36-7 00 (m, 3H, indole C(4)-C(6)H_3), 6 92 (s, 1H, indole C(2)H), 6.24-5 81 (m, 1H, H_2C=C<u>H</u>-CH_2), 5 40-5.20 (m, 2H, <u>H_2C</u>=CH-CH_2), 4.40-4 00 (m, 7H, H_2C=CH-<u>CH_2</u>, indole NCH_2, O<u>CH_2</u>CH_2Si and <u>C</u>H(OMe)$_2$), 3 78 (t, 2H, J=8.0 Hz, indole C(3)CH_2<u>CH_2</u>), 3 28 (s, 6H, 2xOCH_3), 3,06 (t, 2H, J=8 0 Hz, indole C(3)<u>CH_2</u>CH_2), 2 08 (q, 2H, J=6 4 Hz, indole NCH_2<u>CH_2</u>CH), 0 99-0 80 (m, 2H, OCH_2<u>CH_2</u>Si), 0 00 (s, 9H, $Si(CH_3)_3$)

O-Allyl-N-[2-[1-(4,4-diethoxy-butyl)-1*H*-indol-3-yl]-ethyl]-N-[(2-(trimethylsilyl)ethoxy)-carbonyl]-hydroxylamine (8b)· The same procedure was followed as described for **8a** using **2** (1.0 g, 2 8 mmol), conc NaOH (8 mL), toluene (35 mL), 4-bromo-1,1-diethoxybutane[19] **6** (2 0 g, 8 9 mmol) and n-Bu_4NBr (92 mg, 0 29 mmol) Work-up followed by purification by column chromatography (EtOAc/hexanes=1/4, v/v) gave 1 3 g (93%) of **8b** as a colorless oil, R_f 0.54 (EtOAc/hexanes=1/2, v/v), CIMS(70eV), m/z (relative intensity) 504 ([M]$^+$, 58), 458 ([M-1-C_2H_5O]$^+$, 8), 274 ([$C_{17}H_{24}NO_2$]$^+$, 100), 103 ([$HC(OEt)_2$]$^+$, 8), 73 ([$Si(CH_3)_3$]$^+$, 59), 49 (100), ^{1}H NMR (100 MHz) δ 7 63-7.54 (m, 1H, indole C(7)H), 7 33-6.97 (m, 3H, indole C(4)-C(6)H_3), 6 90 (s, 1H, indole C(2)H), 6 20-5.80 (m, 1H, H_2C=C<u>H</u>-CH_2), 5.38-5.20 (m, 2H, <u>H_2C</u>=CH-CH_2), 4 46-4 32 (m, 3H, H_2C=CH-<u>CH_2</u> and $CH(OEt)_2$), 4.17-3 99 (m, 2H, O<u>CH_2</u>CH_2Si), 3.81-3 30 (m, 8H, indole C(3)CH_2<u>CH_2</u>, indole NCH_2 and

2xO$\underline{CH_2}CH_3$), 3.11-2.96 (m, 2H, indole C(3)$\underline{CH_2}CH_2$), 2.00-1.47 (m, 4H, indole $NCH_2\underline{CH_2}\underline{CH_2}CH$), 1.15 (t, 6H, J=7.0 Hz, 2xO$CH_2\underline{CH_3}$), 0.97-0.79 (m, 2H, O$CH_2\underline{CH_2}Si$), 0.00 (s, 9H, $Si(CH_3)_3$)

N-[2-[1-(4,4-diethoxy-butyl)-1*H*-indol-3-yl]-ethyl]-formamide (8c): To N_b-formyl tryptamine **3**[20] (1.0 g, 5.3 mmol) dissolved in dimethyl sulfoxide (20 mL) was added 4-bromo-1,1-diethoxybutane **6** (1.2 g, 6.6 mmol) and powdered KOH (590 mg, 10.5 mmol). The reaction mixture was stirred vigorously for 1,5 hours at room temperature. Water (50 mL) and EtOAc (100 mL) were added and the organic layer was subsequently washed with 5 portions of water (50 mL) and brine. After drying ($MgSO_4$) the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography ($MeOH/CH_2Cl_2$=5/95, v/v) to give 1.0 g (57%) of **8c** as a colorless oil; R_f 0.48 ($MeOH/CH_2Cl_2$=1/9, v/v); ^1H NMR (90 MHz) δ 8.11 (br s, 1H, HCO), 7.65-7.50 (m, 1H, indole C(7)H), 7.41-7.00 (m, 3H, indole C(4)-C(6)H_3), 6.96 (s, 1H, indole C(2)H), 5.72 (very br s, 1H, NH), 4.38 (t, 1H, J=5.5 Hz, $HC(OEt)_2$), 4.12 (t, 2H, J=7.0 Hz, indole NCH_2), 3.80-3.26 (m, 6H, indole C(3)$CH_2\underline{CH_2}$ and 2xO$\underline{CH_2}CH_3$), 2.98 (t, 2H, J=6.6 Hz, indole C(3)$\underline{CH_2}CH_2$), 2.09-1.50 (m, 4H, indole $NCH_2\underline{CH_2}\underline{CH_2}CH$), 1.18 (t, 6H, J=7.3 Hz, 2xO$CH_2\underline{CH_3}$)

N-[2-[1-(4,4-diethoxy-butyl)-1*H*-indol-3-yl]-ethyl]-benzamide (8d): For the alkylation the same procedure was followed as described for **8c** using N_b-benzoyl tryptamine **4**[21] (1.0 g, 3.8 mmol), dimethyl sulfoxide (15 mL), 4-bromo-1,1-diethoxybutane **6** (1.0 g, 5.6 mmol) and powdered KOH (320 mg, 5.7 mmol). After stirring of the reaction mixture for 3 hours followed by work-up, crude **8d** (yield not determined; **8d** was immediately subjected to $LiAlH_4$ reduction to **9d**) was obtained as a colorless oil, R_f 0.42 (EtOAc/hexanes=1/1, v/v); ^1H NMR (90 MHz) δ 7.65-7.50 (m, 3H, indole C(7)H and PhH_2), 7.39-7.00 (m, 6H, indole C(4)-C(6)H_3 and PhH_3), 6.91 (s, 1H, indole C(2)H), 6.2 (very br s, 1H, NH), 4.46 (t, 1H, J=6.3 Hz, $\underline{CH}(OEt)_2$), 4.06 (t, 2H, J=7.0 Hz, indole NCH_2), 3.85-3.28 (m, 6H, indole C(3)$CH_2\underline{CH_2}$ and 2xO$\underline{CH_2}CH_3$), 3.04 (t, 2H, J=6.3 Hz, indole C(3)$\underline{CH_2}CH_2$), 2.00-1.47 (m, 4H, indole $NCH_2\underline{CH_2}\underline{CH_2}CH$), 1.20 (t, 6H, J=7.2 Hz, 2xO$CH_2\underline{CH_3}$)

O-Allyl-N-[2-[1-(5,5-diethoxy-pentyl)-1*H*-indol-3-yl]-ethyl]-N-[(2-(trimethylsilyl)ethoxy)-carbonyl]-hydroxylamine (8e). For the alkylation the same procedure was followed as described for **8a** using **2** (1.0 g, 2.8 mmol), conc NaOH (8 mL), toluene (35 mL), 5-bromo-1,1-diethoxypentane[22] **7** (2.6 g, 10.9 mmol) and n-Bu_4NBr (92 mg, 0.29 mmol). Work-up followed by purification by column chromatography (EtOAc/hexanes=1/4, v/v) afforded 1.3 g (90%) of **8e** as a colorless oil; R_f 0.49 (EtOAc/hexanes=1/2, v/v), CIMS(70eV), m/z (relative intensity) 518 ($[M]^+$, 66), 288 ($[C_{18}H_{26}NO_2]^+$, 100), 103 ($[HC(OEt)_2]^+$, 15), 73 ($[Si(CH_3)_3]^+$, 67), 41 ($[C_3H_5]^+$, 28); ^1H NMR (90 MHz) δ 7.65-7.54 (m, 1H, indole C(7)H), 7.34-6.97 (m, 3H, indole C(4)-C(6)H_3), 6.91 (s, 1H, indole C(2)H), 6.24-5.80 (m, 1H, H_2C=$\underline{CH}$-CH_2), 5.40-5.18 (m, 2H, $\underline{H_2C}$=CH-CH_2), 4.48-4.31 (m, 2H, H_2C=CH-$\underline{CH2}$), 4.42 (t, 1H, J=5.4 Hz, $CH(OEt)_2$), 4.20-3.97 (m, 4H, O$\underline{CH_2}CH_2Si$ and indole NCH_2), 3.86-3.33 (m, 6H, indole C(3)$CH_2\underline{CH_2}$ and 2xO$\underline{CH_2}CH_3$), 3.13-2.96 (m, 2H, indole C(3)$\underline{CH_2}CH_2$), 1.99-1.11 (m, 6H, indole $NCH_2(\underline{CH_2})_3CH$), 1.16 (t, 6H, J=7.1 Hz, 2xO$CH_2\underline{CH_3}$), 0.98-0.78 (m, 2H, O$CH_2\underline{CH_2}Si$), 0.00 (s, 9H, $Si(CH_3)_3$)

O-Allyl-N-[2-[1-(3,3-diethoxy-propyl)-1*H*-indol-3-yl]-ethyl]-hydroxylamine (9a): To **8a** (1.4 mg, 3.0 mmol) dissolved in THF (50 mL) was added tetrabutylammonium fluoride (4.5 mL of a 1M solution in THF). After 30 min all starting material had been consumed. The volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes/Et_3N=24.5/75/0.5, v/v/v) to yield 0.7 g (73%) of **9a** as a colorless oil; R_f 0.11 (EtOAc/hexanes=1/3, v/v); CIMS(70eV), m/z (relative intensity) 318 ($[M]^+$, 41), 233 ($[C_{14}H_{19}NO_2]^+$, 75), 232 ($[C_{14}H_{18}NO_2]^+$, 60), 144 ($[C_{10}H_{10}N]^+$, 100), 75 ($[C_3H_7O_2]^+$, 11), 41 ($[C_3H_5]^+$, 16); ^1H NMR (90 MHz) δ 7.64-7.54 (m, 1H, indole C(7)H), 7.39-6.99 (m, 3H, indole C(4)-C(6)H), 6.93 (s, 1H, indole C(2)H), 6.20-5.77 (m, 1H, H_2C=$\underline{CH}$-CH_2), 5.40 (very br s, 1H, NH), 5.36-5.12 (m, 2H, $\underline{H_2C}$=CH-CH_2), 4.32-4.07 (m, 5H, H_2C=CH-$\underline{CH_2}$, indole NCH_2 and $CH(OMe)_2$), 3.29 (s, 6H, 2xOCH_3), 3.23-2.91 (m, 4H, indole C(3)CH_2CH_2), 2.09 (q, J=6.5 Hz, indole-N-$CH_2\underline{CH_2}$CH)

O-Allyl-N-[2-[1-(4,4-diethoxy-butyl)-1*H*-indol-3-yl]-ethyl]-hydroxylamine (9b). For the deprotection the same method was used as described for **9a** using **8b** (1.5 g, 3.0 mmol) and Bu_4NF (5 mL of a 1M solution in THF). Work-up and purification by column chromatography (EtOAc/hexanes/Et_3N=24.5/75/0.5, v/v/v) afforded 1.07 g (99%) of **9b** as a colorless oil; R_f 0.26 (EtOAc/hexanes=1/2, v/v); CIMS(70eV), m/z (relative intensity) 360 ($[M]^+$, 16), 314 ($[M-1-C_2H_5O]^+$, 2), 274 ($[C_{17}H_{24}NO_2]^+$, 82), 183 ($[C_{13}H_{13}N]^+$, 100), 103 ($[HC(OEt)_2]^+$, 14), ^1H NMR (90 MHz) δ 7.66-7.54 (m, 1H, indole C(7)H), 7.38-7.04 (m, 3H, indole C(4)-C(6)H_3), 6.94 (s, 1H, indole C(2)H), 6.20-5.77 (m, 1H, H_2C=$\underline{CH}$-CH_2), 5.6 (very br s, 1H, NH), 5.39-5.10 (m, 2H, $\underline{H_2C}$=CH-CH_2), 4.43

(t, 1H, J=5 3 Hz, CH(OEt)$_2$), 4 26-4 03 (m, 4H, indole NCH$_2$ and H$_2$C=CH-CH2), 3 78-2 89 (m, 8H, indole C(3)CH$_2$CH$_2$ and 2xOCH$_2$CH$_3$), 2 08-1 49 (m, 4H, indole NCH$_2$CH$_2$CH$_2$CH), 1 17 (t, 6H, J=7 1 Hz, 2xOCH$_2$CH$_3$)

N-benzyl-2-[1-(4,4-diethoxy-butyl)-1*H*-indol-3-yl]-ethylamine (9d) Crude **8d** (ca 3 6 mmol) was dissolved in dry THF and LiAlH$_4$ (0 43 g, 11 3 mmol) was added The reaction mixture was heated at reflux for 8 hours The reaction mixture was cooled (0°C) and dil NaOH (2 mL of a 1M solution) was added cautiously The resulting suspension was filtered over hyflo The residue was subsequently washed with EtOAc (100 mL) and sat NH$_4$Cl The combined filtrates were dried (MgSO$_4$) and the volatiles were evaporated *in vacuo* The residue was subjected to column chromatography (EtOAc/hexanes/Et$_3$N=49 5/50/0 5, v/v/v) to give 0 91 g (65% from **4**) of **9d** as a colorless oil, R$_f$ 0 11 (EtOAc/hexanes=1/1, v/v), EIMS(70eV), m/z (relative intensity) 394 ([M]$^+$, 6), 275 ([C$_{17}$H$_{25}$NO$_2$]$^+$, 100), 103 ([HC(OEt)$_2$]$^+$, 14), 91 ([C$_7$H$_7$]$^+$, 81), ^{1}H NMR (90 MHz) δ 7 63-7 52 (m, 1H indole C(7)H), 7 37-6 96 (m, 3H, indole C(4)-C(6)H$_3$), 7 24 (s, 5H, PhH$_5$), 6 90 (s, 1H, indole C(2)H), 4 42 (t, 1H, J=5 4 Hz, CH(OEt)$_2$), 4 08 (t, 2H, J=7 2 Hz, indole NCH$_2$), 3 80 (s, 2H, CH$_2$Ph), 3 76-3 24 (m, 4H, 2xOCH$_2$CH$_3$), 2 97 (s, 4H, indole C(3)CH$_2$CH$_2$), 2 06-1 47 (m, 4H, indole NCH$_2$CH$_2$CH$_2$CH), 1 17 (t, 6H, J=6 8 Hz, 2xOCH$_2$CH$_3$)

O-Allyl-N-[2-[1-(5,5-diethoxy-pentyl)-1*H*-indol-3-yl]-ethyl]-hydroxylamine (9e) For deprotection the same procedure was followed as described for **9a** using **8e** (1 4 g, 2 7 mmol) and Bu$_4$NF (3 5 mL of a 1M solution in THF) Work-up and purification by column chromatography (EtOAc/hexanes/Et$_3$N=24 5/75/0 5, v/v/v) afforded 0 92 g (85%) of **9e** as a colorless oil, R$_f$ 0 31 (EtOAc/hexanes=1/2, v/v), CIMS(70eV), m/z (relative intensity) 374 ([M]$^+$, 27), 288 ([C$_{18}$H$_{26}$NO$_2$]$^+$, 83), 183 ([C$_{13}$H$_{13}$N]$^+$, 100), 103 ([HC(OEt)$_2$]$^+$, 43), ^{1}H NMR (90 MHz) δ 7 66-7 55 (m, 1H, indole C(7)H), 7 37-6 98 (m, 3H, indole C(4)-C(6)H$_3$), 6 95 (s, 1H, indole C(2)H), 6 20-5 78 (m, 1H, H$_2$C=CH-CH$_2$), 5 6 (very br s, 1H, NH), 5 40-5 11 (m, 2H, H$_2$C=CH-CH$_2$), 4 44 (t, 1H J=5 5 Hz, CH(OEt)$_2$), 4 28-4 18 (m 2H, H$_2$C=CH-CH2), 4 07 (t, 2H, J=7 0 Hz, indole NCH$_2$), 3 81-3 31 (m, 4H, 2xOCH$_2$CH$_3$), 3 31-3 18 (m, 2H, indole C(3)CH$_2$CH$_2$), 3 05-2 90 (m, 2H, indole C(3)CH$_2$CH$_2$), 2 02-1 19 (m, 6H, indole NCH$_2$(CH$_2$)$_2$CH), 1 18 (t, 6H, J=7 1 Hz, 2xOCH$_2$CH$_3$)

3-Allyloxy-2,3,3a,4,5,6-hexahydro-1*H*-indolo[3,2,1-*de*][1,5]naphthyridine (1b) To **9b** (1 18 g, 3 3 mmol) dissolved in chloroform (150 mL) was added trifluoroacetic acid/water (10 mL, 1/1, v/v) The resulting 2-phase system was stirred vigorously for 30 minutes Work-up was accomplished by the careful (portionwise) addition of sodium carbonate until the evolution of gas (CO$_2$) ceased The organic layer was washed with brine and dried (Na$_2$SO$_4$) The volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes=1/5, v/v) to give 0 71 g (81%) of **1b** as a white amorphous solid, mp=47-49°C, R$_f$ 0 55 (EtOAc/hexanes=1/2, v/v), CIMS(70eV) exact mass calcd for C$_{17}$H$_{20}$N$_2$O m/z 268 1576 ([M]$^+$) found 268 1574, m/z (relative intensity) 268 ([M]$^+$, 44), 183 ([C$_{13}$H$_{13}$N]$^+$, 100), 41 ([C$_3$H$_5$]$^+$, 11), ^{1}H NMR (400 MHz, to sharpen up the broadened spectrum recorded at 57°C, the numbering is according to scheme 7 7) δ 7 35 (d, 1H, J=7 7 Hz, C(8)H), 7 14 (d, 1H, J=7 8 Hz, C(11)H), 7 06 (t, 1H, J=7 2 Hz, C(10)H), 6 99 (t, 1H, J=7 3 Hz, C(9)H), 5 92 (ddt, 1H, J=16 7 Hz, J=10 6 Hz and J=6 2 Hz, H$_2$C=CH), 5 21 (dd, 1H, J=17 5 Hz and J=1 3 Hz, HHC=CH), 5 11 (d, 1H, J=10 3 Hz, HHC=CH), 4 27 4 18 (m, 2H, OCH$_2$), 4 11 (dd, 1H, J=11 4 Hz and J=5 8 Hz, C(6)H), 3 75 (br d, J=7 8 Hz C(3a)H), 3 64-3 55 (m, 1H, C(2)H), 3 54 (dt, 1H, J=11 9 Hz and J=5 1 Hz, C(6)H), 3 00-2 92 (m, 2H, C(2)H and C(1)H), 2 81-2 73 (m, 1H, C(1)H), 2 40 (br d, 1H, J=9 8 Hz, C(4)H), ^{13}C NMR (75 MHz) δ 137 9 C(7a), 134 1 C(14), 133 4 C(11c), 127 0 C(11a), 120 8 C(9), 119 4 C(10), 118 2 C(11), 118 0 C(15), 109 3 C(8), 105 0 C(11b), 74 7 C(13), 62 6 C(3a), 54 7 C(2), 42 0 C(6), 26 1 C(5), 21 7 C(1) and C(4), Anal Calcd for C$_{17}$H$_{20}$N$_2$O C, 76 09, H, 7 51, N, 10 45 Found C, 75 83, H, 7 47, N, 10 25

11 and 12-14 The same procedure was followed as described for **1b** using **9a** (580 mg, 1 8 mmol), chloroform (160 mL) and trifluoroacetic acid/water (8 mL, 1/1, v/v) After stirring for 18 hours at room temperature work-up and purification by column chromatography (EtOAc/hexanes=1/5, v/v) afforded two fractions 110 mg (24%) of **11** as colorless needles (evaporation of CH$_2$Cl$_2$), mp=189 193°C, R$_f$ 0 52 (EtOAc/hexanes=1/2, v/v), CIMS(70eV) exact mass calcd for C$_{32}$H$_{36}$N$_4$O$_2$ m/z 508 2838 ([M]$^+$) found 508 2838, m/z (relative intensity) 508 ([M]$^+$, 56), 451 ([M C$_3$H$_5$O]$^+$, 26), 49 (100), ^{1}H NMR (400 MHz, canthine numbering) δ 7 51 (d, 1H, J=7 7 Hz, C(7)H), 7 44 (d, 1H, J=8 1 Hz, C(10)H), 7 22 (t, 1H, J=7 5 Hz, C(9)H), 7 12 (t, 1H, J=7 4 Hz, C(8)H), 5 89 (ddt, 1H, J=16 7 Hz, J=10 6 Hz and J=6 2 Hz, H$_2$C=CH), 5 21 (d, 1H, J=17 3 Hz, HHC=CH), 5 11 (d, 1H, J=10 2 Hz HHC=CH), 4 24-4 15 (m, 4H, OCH$_2$, C(5)H and C(3a)H), 4 03-3 95 (m, 1H, C(5)H), 3 49-3 41 (m, 1H, C(2)H), 3 36-3 30 (m, 1H, C(2)H),

3 03-2 95 (m, 1H, C(1)H), 2 84-2 81 (br m, C(1)H and C(4)H), 2 54-2 45 (m, 1H, C(4)H), ^{13}C NMR (100 MHz, canthine numbering) δ 137 79 C(6a), 134 67 C(10c), 134 41 C(13), 127 18 C(10a), 121 60 C(8), 119 41 C(9), 118 30 C(10), 117 98 C(14), 109 96 C(7), 108 10 C(10b), 73 72 C(12), 57 56 C(3a), 47 83 C(2), 40 21 C(5), 33 51 C(4), 19 03 C(1) together with 230 mg (50%) of a fraction containing several products as was identified by TLC (EtOAc/hexanes=1/5, v/v) This fraction was again subjected to column chromatography (EtOAc/hexanes=1/7, v/v) to give in 1-9% yield 6 fractions which were identified by FABMS and NMR as the tri-, tetra- and pentamers and isomers thereof

O-Allyl-N-[2-(6,7-dihydro-pyrido[1,2-*a*]indol-10-yl)-ethyl]-N-[(2-(trimethylsily)ethoxy)-carbonyl]-hydroxylamine (16b) For the cyclization the same procedure was followed as described for **1b** using **8b** (1 5 g, 3 0 mmol), chloroform (100 mL) and trifluoroacetic acid/water (10 mL, 1/1, v/v) After stirring for 30 min , work-up and purification by column chromatography (EtOAc/hexanes=1/3, v/v) afforded 1 2 g (99%) of **16b** as a colorless oil, R_f 0 51 (EtOAc/hexanes=1/2, v/v), CIMS(70eV), m/z (relative intensity) 412 ($[M]^+$, 40), 182 ($[C_{13}H_{12}N]^+$, 100), 73 ($[Si(CH_3)_3]^+$, 20) 41 ($[C_3H_5]^+$, 16), ^{1}H NMR (90 MHz) δ 7 61-7 51 (m, 1H, indole C(7)H), 7 24-6 96 (m, 3H, indole C(4)-C(6)H$_3$), 6 68 (br dt, 1H, J=10 1 Hz, indole C(2)CH=CH), 6 23-5 80 (m, 2H, H_2C=CH and indole C(2)CH=CH), 5 42-5 19 (m, 2H, H_2C=CH), 4 35 (d, 2H, J=6 1 Hz, CH_2-CH=CH_2), 4 31-3 96 (m, 4H, indole NCH_2CH_2 and OCH_2CH_2Si), 3 77-3 59 (m, 2H, indole C(3)CH_2CH_2), 3 16 2 98 (m, 2H, indole C(3)CH_2CH_2), 2 70-2 50 (m, 2H, indole NCH_2CH_2), 1 00-0 80 (m, 2H, OCH_2CH_2Si), 0 00 (s, 9H, $Si(CH_3)_3$)

N-[2-(6,7-dihydro-pyrido[1,2-*a*]indol-10-yl)-ethyl]-formamide (16c) For the cyclization the same procedure was followed as described for **1b** using **8c** (0 78 g, 2 35 mmol), chloroform (40 mL) and trifluoroacetic acid/water (4 mL, 1/1, v/v) After stirring for 30 min , work-up and purification by column chromatography (MeOH/CH_2Cl_2=5/95, v/v) afforded 0 56 g (99%) of **16c** as a colorless oil, R_f 0 52 (MeOH/CH_2Cl_2=1/9, v/v), EIMS(70eV), m/z (relative intensity) 240 ($[M]^+$, 5), 182 ($[C_{13}H_{12}N]^+$, 31), 18 ($[H_2O]^+$, 100), ^{1}H NMR (90 MHz) δ 7 97 (br s, 1H, CHO), 7 50-7 39 (m, 1H, indole C(7)H), 7 21 6 89 (m, 3H, indole C(4)-C(6)H$_3$), 6 56 (dt, 1H, J=10 2 Hz and J=1 7 Hz, indole C(2)CH=CH), 5 96 (dt, 1H, J=10 0 Hz and J=4 4 Hz, indole C(2)CH=CH), 5 59 (very br s, 1H, NH), 3 99 (t 2H, J=7 1 Hz, indole NCH_2CH_2), 3 58-3 26 (m, 2H, indole C(3)CH_2CH_2), 2 90 (t, 2H, J=6 5 Hz, indole C(3)$CHCH_2$), 2 67-2 44 (m, 2H indole NCH_2CH_2)

Benzyl-[2-(6,7-dihydro-pyrido[1,2-*a*]indol-10-yl)-ethyl]-amine (16d) For the cyclization the same procedure was followed as described for **1b** using **9d** (0 90 g, 2 28 mmol), chloroform (40 mL) and trifluoroacetic acid/water (4 mL, 1/1, v/v) After stirring for 30 min , work-up and purification by column chromatography (EtOAc/hexanes=1/1, v/v) afforded 0 50 g (72%) of **16d** as a colorless oil The yield may be improved in future attempts by the addition of a small amount (0 5%) triethylamine to the eluent, R_f 0 18 (EtOAc/hexanes=1/1, v/v), EIMS(70eV), m/z (relative intensity) 302 ($[M]^+$, 3), 183 ($[C_{13}H_{13}N]^+$, 100), 91 ($[C_7H_7]^+$, 46), ^{1}H NMR (90 MHz) δ 7 60-7 50 (m, 1H, indole C(7)H), 7 31-6 94 (m, 3H, indole C(4) C(6)H$_3$), 7 23 (s, 5H, PhH_5), 6 69 (dt, 1H, J=9 9 Hz and J=1 7 Hz, indole C(2)CH=CH), 5 97 (dt, 1H, J=9 8 Hz and J=4 5 Hz, indole C(2)CH=CH), 4 04 (t, 2H, J=6 9 Hz, indole NCH_2CH_2), 3 79 (s, 2H, CH_2Ph), 3 13-2 80 (m, 4H, indole C(3)CH_2CH_2), 2 72 2 50 (m, 2H, indole NCH_2CH_2), 1 73 (s, 1H, NH)

O-Allyl-N-[2-(7,8-dihydro-6*H*-azepino[1,2-*a*]indol-11-yl)-ethyl]-N-[(2-(trimethylsily)ethoxy)-carbonyl]-hydroxylamine (16e) For the cyclization the same procedure was followed as described for **1b** using **8e** (1 4 g, 2 7 mmol), chloroform (60 mL) and trifluoroacetic acid/water (6 mL, 1/1, v/v) After stirring for 30 min , workup and purification by column chromatography (EtOAc/hexanes=1/3, v/v) afforded 1 15 g (99%) of **16e** as a colorless oil, R_f 0 56 (EtOAc/hexanes=1/2, v/v), CIMS(70eV), m/z (relative intensity) 426 ($[M]^+$, 26), 196 ($[C_{14}H_{14}N]^+$, 100), 73 ($[Si(CH_3)_3]^+$, 47), ^{1}H NMR (90 MHz) δ 7 71 7 50 (m, 1H, indole C(7)H), 7 25-7 00 (m, 3H, indole C(4)-C(6)H$_3$), 6 58 (br dt, 1H, J=13 0 Hz, indole C(2)CH=CH), 6 22-5 67 (m, 2H, H_2C=CH and indole C(2)CH=CH), 5 39-5 18 (m, 2H, H_2C=CH), 4 37-3 97 (m, 6H, CH_2-CH=CH_2, indole NCH_2CH_2 and OCH_2CH_2Si), 3 71-3 52 (m, 2H, indole C(3)CH_2CH_2), 3 15-3 00 (m, 2H, indole C(3)CH_2CH_2), 2 64-2 47 (m, 2H, indole N$CH_2CH_2CH_2$), 2 20-2 00 (m, 2H, indole N$CH_2CH_2CH_2$), 1 05-0 84 (m, 2H, OCH_2CH_2Si), 0 00 (s, 9H, $Si(CH_3)_3$)

O-Allyl-N-[2-(6,7-dihydro-pyrido[1,2-*a*]indol-10-yl)-ethyl]-hydroxylamine (17b) For the deprotection the same procedure was followed as described for **9a** using **16b** (1 2 g, 2 9 mmol) and Bu_4NF (4 4 mL of a 1M solution in THF) Work-up and purification by column chromatography (EtOAc/hexanes/Et_3N=24 5/75/0 5, v/v/v) afforded 0 59 g (75%) of **17b** as a colorless oil, R_f 0 44 (EtOAc/hexanes=1/2, CIMS(70eV) exact mass calcd for $C_{17}H_{20}N_2O$ m/z 268 1576 ($[M]^+$) found 258 1578, m/z (relative intensity) 268 ($[M]^+$, 32), 182 ($[C_{13}H_{12}N]^+$, 100), 41 ($[C_3H_5]^+$, 18), ^1H NMR (90 MHz) δ 7 62-7 51 (m, 1H, indole C(7)H), 7 29-6 96 (m, 3H, indole C(4)-C(6)H_3), 6 71 (dt, 1H, J=10 0 Hz and J=1 8 Hz, indole C(2)CH=CH), 6 20-5 76 (m, 2H, H_2C=CH and indole C(2)CH=CH), 5 55 (very br s, 1H, NH), 5 40-5 10 (m, 2H, H_2C=CH), 4 22 (dt, 2H, J=5 7 Hz and J=1 3 Hz, CH_2 CH=CH_2), 4 06 (t, 2H, J=7 0 Hz, indole NCH_2CH_2), 3 30-2 92 (m, 4H, indole C(3)CH_2CH_2), 2 73-2 32 (m, 2H, indole NCH_2CH_2)

O-Allyl-N-[2-(7,8-dihydro-6*H*-azepino[1,2-*a*]indol-11-yl)-ethyl]-hydroxylamine (17e) For the deprotection the same procedure was followed as described for **9a** using **16e** (1 4 g, 2 7 mmol) and Bu_4NF (4 1 mL of a 1M solution in THF) Work-up and purification by column chromatography (EtOAc/hexanes/Et_3N=24 5/75/0 5, v/v/v) afforded 0 55 g (72%) of **17b** as a colorless oil, R_f 0 49 (EtOAc/hexanes=1/2, CIMS(70eV) exact mass calcd for $C_{32}H_{36}N_4O_2$ m/z 282 1732 ($[M]^+$) found 282 1732, m/z (relative intensity) 282 ($[M]^+$, 24), 196 ($[C_{14}H_{14}N]^+$, 100), 41 ($[C_3H_5]^+$, 62), ^1H NMR (90 MHz) δ 7 63-7 54 (m, 1H, indole C(7)H), 7 34-6 96 (m, 3H, indole C(4)-C(6)H_3), 6 59 (dt, 1H, J=12 4 Hz and J=1 9 Hz, indole C(2)CH=CH), 6 20-5 70 (m, 2H, H_2C=CH and indole C(2)CH=CH), 5 40-5 11 (m, 2H, H_2C=CH), 4 26-4 17 (m, 4H, CH_2-CH=CH_2 and indole NCH_2CH_2), 3 32-2 94 (m, 4H, indole C(3)CH_2CH_2), 2 69-2 49 (m, 2H, indole N$CH_2CH_2CH_2$), 2 24-2 00 (m, 2H, indole N$CH_2CH_2CH_2$)

O-Allyl-N-[2-[1-(3-oxo-propyl)-1*H*-indol-3-yl]-ethyl]-hydroxylamine (18) For the attempted cyclization the same procedure was followed as described for **1b** using **8a** (1 4 g, 3 0 mmol), chloroform (80 mL) and trifluoroacetic acid/water (8 mL, 1/1, v/v) After stirring for 24 hours, some starting material was still present Only deprotection of the acetal toward the aldehyde **18** was detected The reaction mixture was worked-up and subjected to column chromatography (EtOAc/hexanes=1/3, v/v) to give 0 54 g (43%) of **18** as a colorless oil, R_f 0 24 (EtOAc/hexanes=1/3, v/v), CIMS(70eV) exact mass calcd for $C_{22}H_{32}N_2O_4Si$ m/z 416 2131 ($[M]^+$) found 416 2131, m/z (relative intensity) 416 ($[M]^+$, 40), 186 ($[C_{12}H_{12}NO]^+$, 100), 73 ($[C_3H_9Si]^+$, 69), ^1H NMR (90 MHz) δ 9 76 (s, 1H, CHO), 7 64-7 55 (m, 1H, indole C(7)H), 7 31 6 99 (m, 3H, indole C(4)-C(6)H_3), 6 94 (s, 1H, indole C(2)H), 6 24-5 80 (m, 1H, H_2C=CH), 5 43-5 15 (m, 2H, H_2C=CH), 4 45 4 30 (m, 4H, indole NCH_2 and OCH_2-CH=CH_2), 4 15-3 96 (m, 2H, OCH_2CH_2Si), 3 83-3 67 (m, 2H, indole C(3)CH_2CH_2), 3 11-2 85 (m, 4H, indole C(3)CH_2CH_2 and indole NCH_2CH_2), 0 97-0 77 (m, 2H, OCH_2CH_2Si), 0 00 (s, 9H, $Si(CH_3)_3$), together with 0 2 g (14%) recovered starting compound **8a**

References and Notes

1 a) Chapters 2-6 of this thesis b) Hermkens, P H H , Maarseveen, J H van, Berens, H W , Smits, J M M , Kruse, C G , Scheeren, J W *J Org Chem* , **1990**, 55, 2200 b) Mangeney, P , Gosmini, R , Alexakis, A *Tetrahedron Lett* , **1991**, 32, 3981 c) Brown, R T , Dauda, B E N , Santos, C A M *J Chem Soc Chem Comm* , **1991**, 825 d) Lounasmaa, M , Jokela, R , Tiainen, L -P *Tetrahedron*, **1990**, 46, 7873 e) Brown, R T , Duckworth, D M , Santos, C A M *Tetrahedron Lett* , **1991**, 32, 1987 (Bischler-Napieralsky type cyclization) f) Kuehne, M E , Muth, R S *J Org Chem* , **1991**, 56, 2701 g) Baxter, E W , Labaree D , Ammon, H L , Mariano, P S *J Am Chem Soc* , **1990**, 112, 7682 The reaction is considered to be an intramolecular Pictet-Spengler cyclization when ring D is formed prior to ring C

2 a) Takano, S , Sato, S , Goto, E , Ogasawara, K *J Chem Soc Chem Comm* , **1986**, 156 b) Soti, F , Kajtár-Peredy, M , Keresztury, G , Incze, M , Kardos-Balogh, Z , Szántay, Cs *Tetrahedron*, **1991**, 47, 271 (Bischler Napieralsky type cyclization)

3 Benson, S C , Li, J -H , Snyder, J K *J Org Chem* , **1992**, 57, 5285

4 a) Meyers, A I , Loewe, M F *Tetrahedron Lett* , **1984**, 25(25), 2641 b) Loewe, M F , Meyers, A I *Tetrahedron Lett* , **1985**, 26(28), 3291

5 a) Hagen, T.J.; Narayanan, K.; Names, J.; Cook, J.M. *J.Org.Chem.*, **1989**, 54, 2170. b) Bruyn, A. de; Eeckhaut, G.; Villaneuva, J.; Hannart, J. *Tetrahedron*, **1985**, 41(23), 5553

6 The possibility of rearrangement of spiro indolenines towards 2,3-disubstituted indoles has been proven by Jackson and coworkers: a) Jackson, A.H.; Smith, P. *Tetrahedron*, **1968**, 24, 2227. b) Jackson, A H.; Naidoo, B.; Smith, P. *Tetrahedron*, **1968**, 24, 6119. c) For a recent paper concerning this subject see: Ganesan, A.; Heathcock, C.H. *Tetrahedron Lett.*, **1993**, 34(3), 439. Only discussing the Pictet-Spengler condensation: d) Ungemach, F.; Cook, J.M. *Heterocycles* **1978**, 9, 1089. e) Bailey, P.D. *Tetrahedron Lett,*.**1987**, 28, 5181-5184. Direct electrophilic attack at the indole 2-position has been proven by Casnati and coworkers: Casnati, G.; Dossena, A.; Pochini, A. *Tetrahedron Lett.*, **1972**, 52, 5277

7 Bailey, P D.; Hollinshead, S.P.; McLay, N.R., Morgan, K.; Palmer, S J.; Prince, S.N.; Reynolds, C.D ; Wood, S.D. *J.Chem.Soc.Perkin Trans. I*, **1993**, 431

8 Kawate, T., Nakagawa, M.; Ogata, K.; Hino, T. *Heterocycles*, **1992**, 33(2), 801.

9 Czerwinsky, K.M., Deng, L.; Cook, J.M. *Tetrahedron Lett.*, **1992**, 33(33), 4721

10 Maarseveen, J.H. van; Kruse, C.G., Scheeren, J.W. *Tetrahedron*, **1993**, 49(11), 2325

11 See chapter 2 or: Maarseveen, J.H. van; Hermkens, P.H.H.; Clercq, E. de, Balzarini, J.; Scheeren, J.W.; Kruse, C.G. *J Med.Chem.*, **1992**, 35, 3223

12 Bourak, M.; Gallo, R *Heterocycles*, **1990**, 31(3), 447

13 It should however be noted here that the powdered KOH/DMSO method with the reactive electrophile MeI quantitatively gave the N_a-methyl derivative of tryptamine **2**. Due to the relatively low reactivity of the electrophiles **5-7** deprotection of the Teoc group occurred faster than N_a-alkylation.

14 Sandrin, J.; Hollinshead, S.P.; Cook, J M. *J.Org.Chem.* **1989**, 54, 5636-5640

15 Speckamp, W.N.; Hiemstra, H. *Tetrahedron*, **1985**, 41(20), 4367-4417. For a recent paper descibing the specific use of N-acyliminium ions in the Pictet-Spengler condensation, see. Maryanoff, B.E.; Rebarchak, M C. *Synthesis*, **1992**, 1245-1248 and references cited therein. For the use of N_b-benzyl groups see. Soerens, D.; Sandrin, J ; Ungemach, F.; Mokry, P.; Wu, G.S.; Yamahaka, E., Hutchins, L.; DiPierro, M.; Cook, J.M. *J.Org.Chem.*, **1979**, 44(4), 535-545

16 A similar cyclization to give pyrido[1,2-*a*]indoles was described for N-substituted 3-methyl indole: Eberle, M K. *J.Org Chem.*, **1976**, 41, 633

17 With this information at hand it is surprising that with **9e** only oligomers and polymers were formed instead of **17e**. Clearly the *inter*molecular iminium-ion formation is faster than the *intra*molecular cyclization at the indole-2 position.

18 Hoechst, P., Röder, E. *Arch.Pharmaz.*, **1975**, 308, 75, 779

19 Roush, W.R.; Hall,S.E. *J.Am.Chem.Soc.*, **1981**, 103, 5200

20 Nakagawa, M., Kaneko, T.; Yamaguchi, H.; Kawashima, T., Hino, T. *Tetrahedron*, **1974**, 30, 2591

21 Huang, H.T., Niemann, C. *J.Am.Chem.Soc.* **1952**, 74, 101

22 Boaventura, M.-A.; Drouin, J. *Bull.Soc.Chim.Fr.*, **1987**, 1015

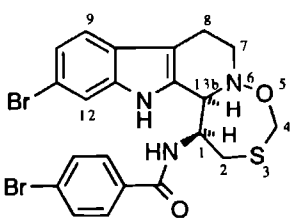
8 Conformational Analysis of the Oxathiazepine Ring in Eudistomins

8.1 Introduction

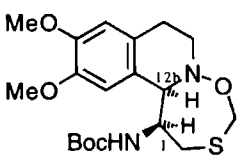
As pointed out in the introductory chapter, the correct absolute *configuration* of the two chiral centers, which also form part of the oxathiazepine ring in eudistomins, is essential for biological activity [1] Only with the (1*S*, 13b*S*) configuration were biological activies found It is likely that the *conformation* of the oxathiazepine system also has influence on the biological potency of tetracyclic eudistomins Therefore, for a thorough biological structure-activity relationship study, information about the conformation of the aliphatic CD ring systems in eudistomins is essential In this chapter a conformational analysis using X-ray diffraction analysis and NMR data is presented

In addition to the two X-ray crystal structures of the cis tetracyclic eudistomin **1** and the trans derivative **3**, published by Munro[2] and our group[3], the X-ray structure of the C(1)-deamino eudistomin derivative **5** has also been published by Kirkup and coworkers (chart 8 1) [4] In addition, crystal structure determinations have been performed for two eudistomins described in this thesis, *viz* the cis isoquinoline **2** (chapter 6) and the trans C(1)-methyl derivative **4** (chapter 2)

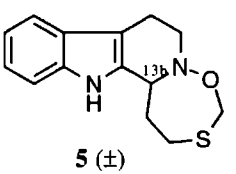
Chart 8.1 *The eudistomins of which the crystal structures have been determined*



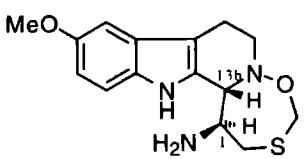
cis **1** (1*S*,13b*S*)



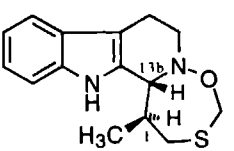
cis **2** (1*S*, 12b*S* + 1*R*, 12b*R*)



5 (±)



trans **3** (1*S*, 13b*R*)



trans **4** (1*S*,13b*S*)

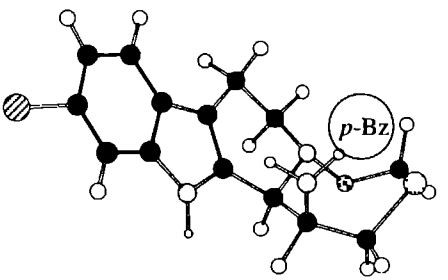
The two new crystal structures together with the known structures from the literature will be discussed in combination with NMR data

As is indicated in chart 8 1 the compounds **1**,**3** and **4** have been obtained enantiomerically pure and **2** and **5** were analyzed as racemates.

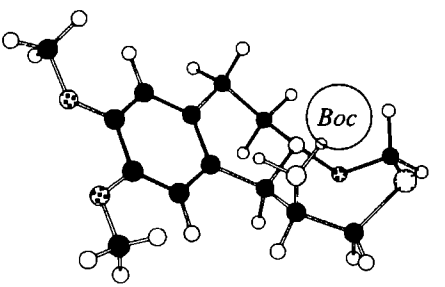
8.2 Discussion of the X-ray Crystal Structures

To facilitate comparison of the conformations of the structures, the bridgehead chiral centers (*i e.* C(13b) in **1**,**3**,**4** and **5**, and C(12b) in **2**) are all depicted with the *R*-configuration in chart 8 2 (the structures of **3** and **4** have thus been inverted)

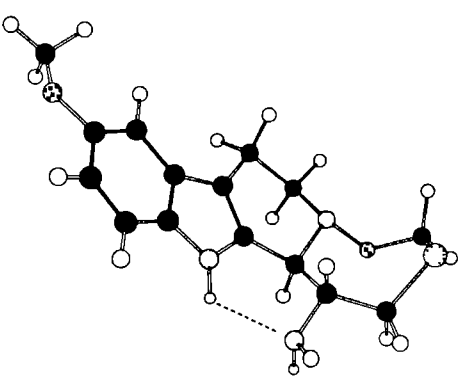
Chart 8.2



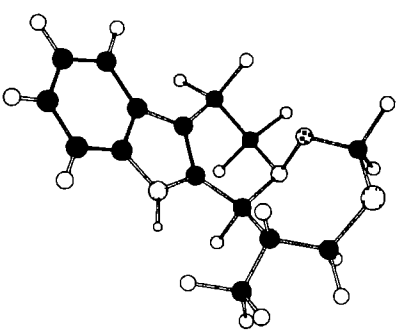
1 (*p*-Bz = *p*-bromobenzoyl)



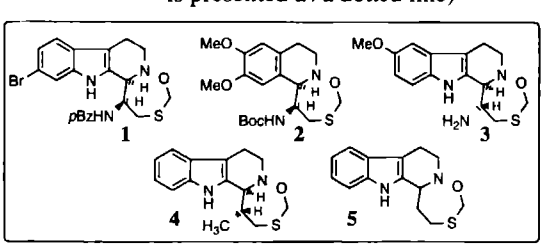
2 (Boc = *tert*-butyloxycarbonyl)

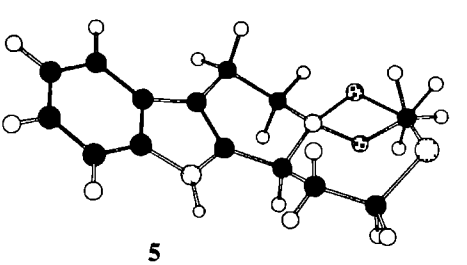


3 (the indole-NH-N-C(1) H-bond is presented as a dotted line)



4



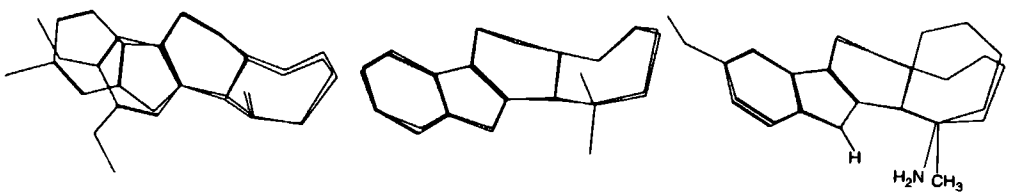


5

From the structures of the cis eudistomin derivative **1** and the cis isoquinoline derivative **2** it is noted at first glance that the aliphatic CD ring systems have exactly the same conformations. This conformation is also found in the trans derivative **3**, and in the C(1) unsubstituted derivative **5** as the major conformer (*vide infra*). These observations are illustrated in the overlay structures of **1** and **2** together with **1** and **3** in chart 8.3.

Chart 8.3 *Overlay structures*

1 and 2 **1 and 3** **3 and 4**



It is worth mentioning that in the structures **1** and **2**, with the natural configurations at the stereogenic centers, both the lone-pair at the bridgehead nitrogen atom and the C(1)-amino substituent are axially orientated in space.

A conformationally deviating oxathiazepine D-ring is found in the C(1)-unsubstituted eudistomin derivative **5** (chart 8.2). In the unit cell of the X-ray structure of **5** two different conformations were found in a 0.74/0.26 ratio. The conformation of the oxathiazepine ring in the major conformer was identical with the conformation found in the structures **1**-**3**. In the minor conformer the N_b bridgehead nitrogen atom was inverted. Clearly, the conformational energy difference between the two N_b inverted conformers is small.

The conformation of the oxathiazepine ring in the trans C(1)-methyl derivative **4** is entirely present in the N_b-inverted configuration as is indicated in chart 8.3. The reason for this inversion is the steric repulsion of the methyl group in **4** by the indole-N proton. As can be seen in chart 8.3 the distance between the C(1)-methyl group and the indole-N proton is elongated by inversion of the bridgehead nitrogen. Due to the presence of a hydrogen bond between the indole-N proton and the equatorially orientated C(1)-nitrogen atom in the trans derivative **3**, only the 'natural' configuration is found in the crystal structure (charts 8.2 and 8.3).

8.3 Discussion of the NMR Data

8.3.1 Conformations of the Oxathiazepine Ring in Solution

Cis diastereomer:

In the literature extensive NMR data are described for the natural eudistomins.[5] The assignment by Rinehart and coworkers of the cis relationship between the H(13b) and H(1) protons was based on the small vicinal coupling constant (*i.e.* $\leq$ 3Hz).[5a] However, as small coupling constants between H(13b) and H(1) protons correspond with dihedral angles between 50° and 120° these values may

also indicate a trans relationships between these protons (*vide infra*) That indeed a cis relationship between H(13b) and H(1) exists in natural eudistomins was confirmed by Munro and coworkers from the X-ray crystal structure determination of **1** [5b] In the same paper an extensive NOE study was presented which confirmed the same conformation of the CD ring system of **1** in solution as was found in the crystal structure

In table 8 1 the dihedral angles are presented for H(1)α with the neighboring H(13b)α (for **1**) or H(12b)α (for **2**) and H(2)αβ protons as found in the crystal structures of **1** and **2** together with the corresponding estimated vicinal coupling constants using a modified Karplus equation [6] Also the measured coupling constants are presented together with the estimated dihedral angles for the same protons in solution

Table 8.1 *Some dihedral angles (degrees) and in parentheses the corresponding vicinal coupling constants (Hz) of **1** and **2** in the crystalline and liquid states The estimated data are underlined and are calculated using a modified Karplus equation* [6]

1	H(1)α-H(2)α	H(1)α-H(2)β	H(1)α-H(13b)α
X-ray	72 (1 7)	39 (5 8)	54 (3 1)
NMR	80-90 (0)	40 (6 2)	80-90 (<1)
2	H(1)α-H(2)α	H(1)α-H(2)β	H(1)α-H(12b)α
X-ray	70 (1 8)	42 (5 5)	45 (4 0)
NMR	80-90 (0)	40 (6 1)	80-90 (<1)

Comparison of the NMR and X-ray data of **1** and **2** shows that the dihedral angles between H(1)α and H(2)αβ are similar in both the liquid and solid states A significant difference between the solid and liquid states is found for the dihedral angle between H(1)α and H(13b or 12b)α in **1** and **2** In the liquid state an opening of ≈40° is found for this dihedral angle, resulting in an even more pronounced axial orientation of the C(1)-amino group As will be discussed in chapter 9 the axial orientation of the C(1)-amino group in the natural cis diastereomer is considered to be essential for showing biological activity

The NMR spectrum of **2** was recorded at 46° to sharpen the slightly broadened spectrum observed at room temperature With only one additional exception (*i e* compound **1c** in table 2 1 in chapter 2) all signals in the NMR spectra of cis eudistomins and derivatives described in chapter 2 were sharp and corresponded with the NMR spectra of **1** and **2**

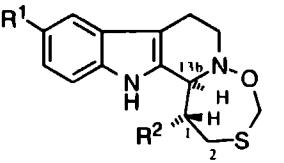
Trans diastereomer

Direct comparison of the NMR data of the trans derivatives **3** and **4** with the corresponding X-ray data is not possible due to the severe peak-broadening in the NMR spectra recorded at room temperature The NMR spectrum of **3** measured at -31°C showed the presence of two conformations in a 18/82 ratio [7] The spectrum was, however, too complicated to determine all required coupling constants In table 8 2 the dihedral angles as found in the crystal structures of **3** and **4** and the, from

these data, estimated vicinal coupling constants for the spin systems H(13b)α-H(1)β and H(1)β-H(2)αβ are presented Because direct comparison with the NMR data of **3** and **4** is not possible due to peak-broadening an alternative trans derivative was chosen The trans derivative **6** (table 8 2), which gave a sharp spectrum, structurally differs from **3** only by the presence of a Boc protected C(1)-amino group and the absence of the 10-methoxy group

Table 8.2 *Some dihedral angles (degrees)and in parentheses the corresponding vicinal coupling constants (Hz) of **3** and **4** in the crystalline state and of **6** in the liquid state The estimated data are underlined and were calculated using a modified Karplus equation* [6]

X-ray	H(1)β-H(2)α	H(1)β-H(2)β	H(1)β-H(13b)α
3	180 (11 8)	73 5 (1 5)	161 (9 4)
4	160 (10 4)	86 (1 2)	140 (6 2)
NMR	H(1)β-H(2)α	H(1)β-H(2)β	H(1)β-H(13b)α
6	40 (6.2)	80-90 (0)	80-90 (<1)



3 R^1=OCH_3, R^2=NH_2
4 R^1=H, R^2=CH_3
6 R^1=H, R^2=NHBoc

The data in table 8 2 reveal that the conformation of the oxathiazepine ring of **6** in solution differs significantly from the conformation found in the crystals of **3** and **4**

To determine the liquid conformation of **6** NOESY spectroscopy was performed For protons with spatially distances of less than ≈3Å, NOE connectivities may be expected [8] The most remarkable observation in the NOESY spectrum of **6** was the absence of the diaxial H(13b)α-H(2)α NOE connectivity as would be expected from the X-ray of the analogous structure **3** (in structure **3** the H(13b)α-H(2)α distance is 2 78Å) This remarkable observation points to a conformational deviation of the D ring around C(13b)-C(1)-C(2) To study this deviation, a molecular modeling study was performed on **6**, by minimization of the structure corresponding to the observed vicinal coupling constants of H(13b)α, H(1)β and H(2)αβ [9] The structure resulting of this study, which fits all observed NMR data, is presented in chart 8 4, together with the ^{1}H and NOESY NMR spectra Comparison with the X-ray structure of **3** shows that the conformation in solution of the oxathiazepine ring in **6** differs in the spatial orientation of C(2) and S(3) The reason for this conformational deviation is the presence of a hydrogen bond between the indole N proton and the Boc-carbonyl in an 8-membered ring The presence of this hydrogen bond in an 8 membered ring as in **6** reduces the dihedral angle between H(1)β-H(13b)α to ≈90°

A further support for the presence of this conformatial behaviour of **6** in solution is the X ray structure of **7** (see also chapter 4) depicted in chart 8 5 A similar conformation as assumed for **6** in solution was found for the 1,2-oxazine ring in the X-ray structure of the trans desthia carba eudistomin derivative **7** In the X-ray structure of **7** the amino group at C(1) was functionalized as an amide and the resulting hydrogen bond between the indole-N proton and the amide carbonyl is clearly visible

Chart 8.4 *One dimensional and NOESY ^{1}H-NMR spectra of 6*

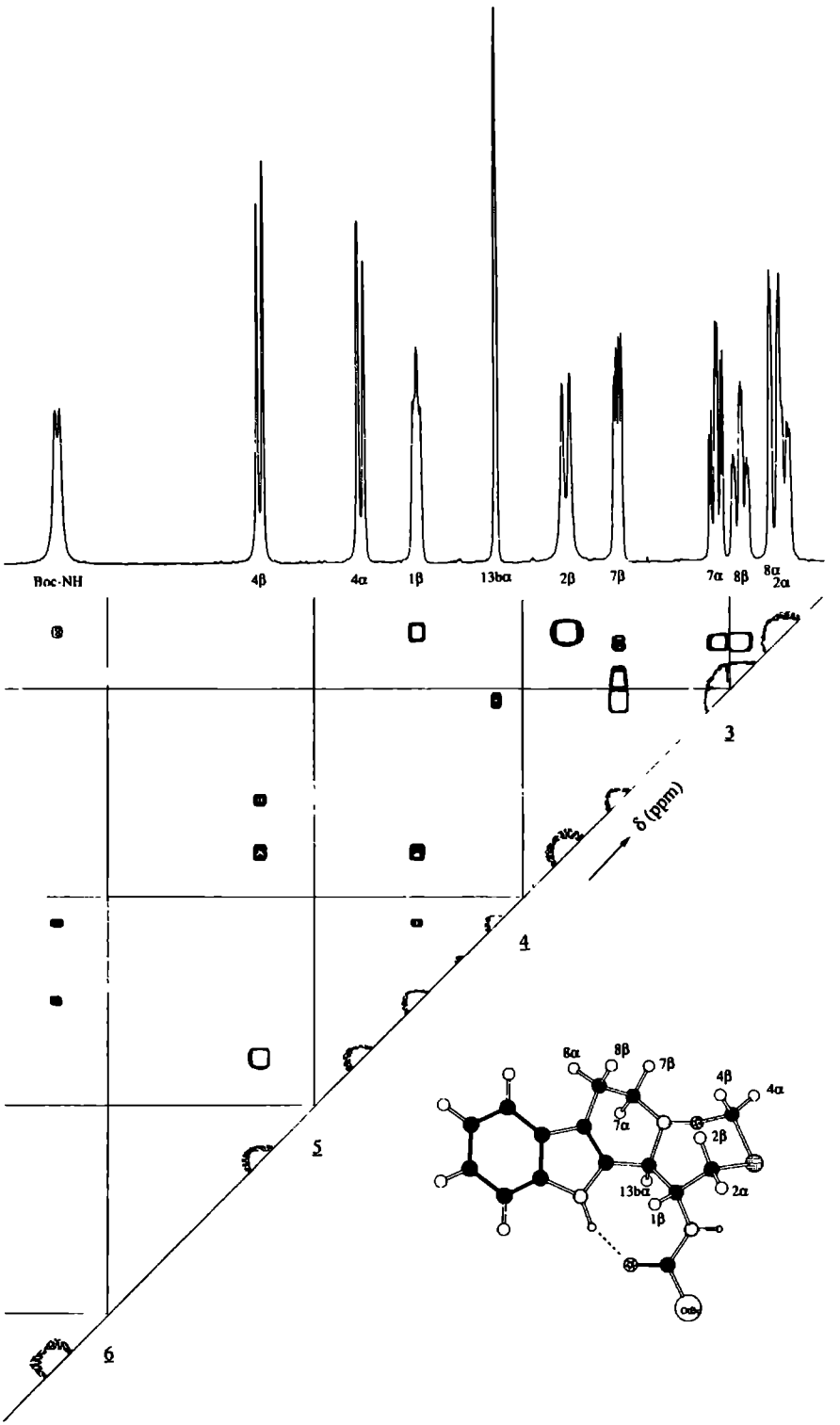
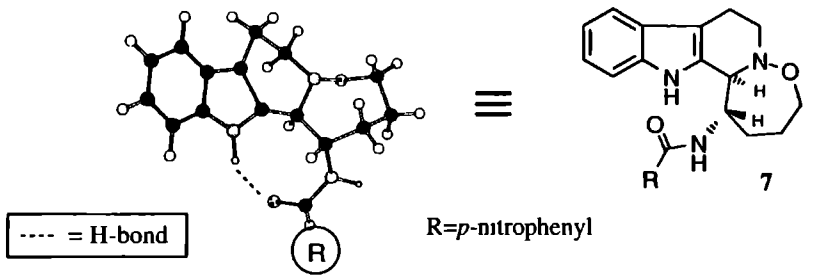
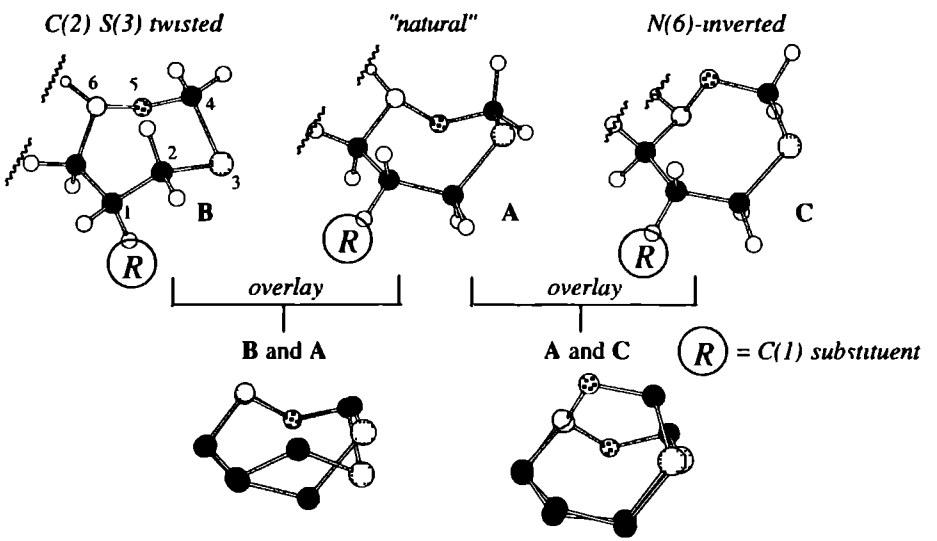


Chart 8.5 X ray structure of trans N(1)-p nitrobenzoyl desthia carba eudistomin 7



In summary, three different conformations of the oxathiazepine ring have been found now in the trans series which are depicted in chart 8 6 together with some overlay structures

Chart 8.6 The observed conformations of the oxathiazepine ring in the trans derivatives (eudistomin numbering)



Both deviations from the "natural" conformation **A**, *i e* the C(2)-S(3) twisted **B** and N(6)-inverted **C** conformations, are caused by the interaction of the equatorial substituent at C(1) and the indole-N proton in the unnatural trans diastereomers In the case of **3** and **4** these interactions of the C(1)-substituent (*i e* NH_2 in **3** and CH_3 in **4**) destabilize the 'natural' conformation **A**, causing an equilibrium between several other conformers which is apparent from the severely broadened NMR spectra This peak-broadening was also observed with trans derivatives with C(1)-hydroxy or C(1)-methoxy substituents (see table 2 2 at the end of the experimental part in chapter 2) Peak broadening due to a nitrogen inversion process occurring at the NMR timescale is known for cyclic 1,2-oxaza compounds [10] With all trans derivatives containing a carbamate protected amino group at C(1) a

strong hydrogen bond exists between the carbonyl oxygen and the indole-N proton favoring the C(2)-S(3) twisted conformation **B**.

8.3.2 Cis/Trans Assignments

From the preceding paragraph it may be concluded that due to presence of several conformations of the oxathiazepine ring in the trans diastereomer, cis/trans assignments only can be made with greatest care. As is evident from the structures depicted in the charts 8.2 and 8.4, differences in the vicinal coupling constants for cis/trans diastereomers may only be expected for the protons at C(13b), C(1) and C(2). Comparison of the vicinal coupling constants of H(1) with H(13b), and of H(1) with both protons H(2) in the cis derivatives **1** and **2** (table 8.1) with the corresponding data of the trans derivative **6** (table 8.2) shows that no significant differences are present. Therefore, it is not possible to carry out cis/trans assignments on the basis of analyzing vicinal coupling constants.

Another method for the cis/trans relationship assignment of the H(13b)-H(1) protons which has been considered is NOE spectroscopy. The spatial distance between these protons with a cis relationship (in 7-membered rings) is expected to be smaller than the distance between these protons in the case of a trans relationship. In table 8.3 the distances between the protons H(1) and H(13b) in the X-ray structures are presented. Also the data of the modeled structure of **6** are included.

Table 8.3 *The distances (Å) between the protons at C(1) and C(13b) in the X-ray structures.*

cis diastereomers			*trans diastereomers*		
	atoms	distance (Å)		atoms	distance (Å)
1	H(13b)α–H(1)α	2.69	**3**	H(13b)α–H(1)β	3.07
2	H(12b)α–H(1)α	2.38	**4**	H(13b)α–H(1)β	3.49
5	H(13b)α–H(1)α	2.52	**5**	H(13b)α–H(1)β	3.09
			6	H(13b)α–H(1)β	2.84

These data show that *both* with the cis and trans diastereomers NOE connectivities between the H(13b)-H(1) protons can be expected and were observed for **1**,**2**,**5** and **6**. Thus, the presence of a NOE connectivity between the H(1) and H(13b) protons is itself not indicative for cis/trans assignment. It may be concluded that, although the prefered conformations of the oxathiazepine ring are well understood, cis/trans assignments in new eudistomin derivatives should be made with great care. By NMR, only with a combination of techniques (calculation of the dihedral angles from the ^{3}J-values in combination with NOESY), reliable assignments could be made.

There is however one NMR parameter which has been of value in all cases for assignment of the cis/trans relationship.[11] The presence of a hydrogen bond between the indole-N proton and a hydrogen bond acceptor at C(1) in the trans diastereomers is expected to give an upfield shift of the indole-N proton. Indeed, in all NMR spectra of the trans derivatives described in this thesis and

before[3,7], with a hydrogen bond accepting substituent at C(1), an upfield shift of 0 9-1 7 ppm was observed for the indole-N proton

However, with both the trans analog of the isoquinoline derivative **2** -lacking the indole-N proton- and the C(1)-methyl derivative **4** -missing the hydrogen bond acceptor at C(1)- single crystal X-ray determination had to be performed to give the incontrovertible cis/trans assignments

8.3 Conclusion

For a thorough biological structure-activity relationship study, information about the conformation in solution is important. It has been described previously in the literature that the conformation of the oxathiazepine ring in natural *cis* eudistomins in solution is almost identical to the solid state structure found by single crystal X-ray diffraction

Due to interactions of the equatorial substituent at C(1) and the indole-N proton in the *trans* diastereomer, deviations of the 'natural' conformation of the oxathiazepine ring were found both in the solid and liquid states. Two deviating conformations were found due to inversion of the bridgehead nitrogen atom or to a twist in the C(2)-S(3) region. The energy barriers between the different conformers are small and the interconversion occurs at the NMR timescale resulting in severely broadened NMR peaks By NMR, only with a combination of techniques (calculation of the dihedral angles from the ^{3}J-values together with NOE spectroscopy), reliable cis/trans assignments can be made

References and Notes

1 Maarseveen, J H van, Hermkens, P H H , De Clercq, E , Balzarini, J , Scheeren, J W , Kruse, C G , *J Med Chem* **1992**, 35, 3223

2 Lake, R J , McCombs, J D , Blunt, J W , Munro, M H G , Robinson, W T *Tetrahedron Lett* , **1988**, 29, 4971

3 Hermkens, P H H , Maarseveen, J H van, Bosman, W P , Smits, J M M , Beurskens, P T *J Crystallogr Spectrosc Res* , **1990**, 20, 313

4 Kirkup, M P , Shankar, B B , McCombie, S , Ganguly, A K , McPhail, A T *Tetrahedron Lett* , **1989**, 30 6809

5 a) Rinehart , K L , Jr , Kobayashi, J , Harbour, G C , Hughes, R G , Jr , Mizsak, S A , Scahill, T A *J Am Chem Soc* , **1984**, 106, 1524 b) Blunt, J W , Lake, R J , Munro, M H G , Toyokuni, T *Tetrahedron Lett* , **1987**, 28, 1825 c) Lake, R J , Brennan, M M , Blunt, J W , Munro, M H G *Tetrahedron Lett* , **1988**, 29, 2255 d) Lake, R J , Blunt, J W , Munro, M H G *Aust J Chem* , **1989**, 42, 1201

6 Haasnoot, C A G , Leeuw, F A A M de, Altona, C *Tetrahedron*, **1980**, 36, 2783

7 See also Hermkens, P H H , Maarseveen, J H van, Ottenheijm, H C J , Kruse, C G , Scheeren, J W *J Org Chem* , **1990**, 55, 3998

8 Friebolin, H *"Ein- und zweidimensionale NMR-Spektroskopie"*, VCH, Weinheim, **1988**

9 The minimization was performed on a Macintosh SE/30 running Chem3D Plus™ (v 3 1 2) molecular modeling software of Cambridge Scientific Computing, Inc

10 Riddel, R G *Tetrahedron*, **1981**, 37, 849

11 Although not a spectroscopic parameter, the relative Rf-values found with straight phase TLC for the cis/trans diastereomers seems also indicative Without any exception the cis diastereomer had the smallest Rf value

9 Antiviral and Antitumor Structure-Activity Relationship Studies of Eudistomins

9.1 Introduction

A brief introduction concerning viruses is given before the antiviral properties of the synthetically derived eudistomins are discussed

Viruses are intracellular parasites that lack independent metabolism and can replicate only within living host cells Viruses consist of a protective protein coat which contain the packets of infectious nucleic acid Other more complex viruses are surrounded by an additional layer containing membrane lipids and glycoproteins, called the envelope Viruses contain either DNA or RNA, but not both They can be devided in four subclasses DNA viruses, (+)-RNA viruses (mRNA is defined as (+)-RNA), (-)-RNA viruses and the (±)-RNA viruses In table 9 1 some examples are given belonging to these four subclasses [1]

Table 9.1 *Some viruses devided in their subclasses*

DNA viruses	(+)-RNA viruses	(-)-RNA viruses	(±)-RNA viruses
Herpes (herpes simplex type-1, herpes simplex type-2, herpes simplex type-1 (TK), cytomegalo), Pox (vaccinia)	Picorna (polio, coxsackie, rhino), Toga (Sindbis, Semliki forest), Corona, Rous sarcoma*, HIV*	Orthomyxo (influenza), Paramyxo (parainfluenza, measles, respiratory syncytial), Arena (Junin, Tacaribe), Rhabdo (vesicular stomatitis)	Reo

* retroviruses

The replication cycle of viruses is intimately connected with the metabolic processes of the host cell For the replication of DNA-type viruses the complete host cell biosynthesis machinery is used to produce viral DNA, RNA and proteins RNA-type viruses replicate using a different mechanism than DNA-type viruses because the host cells lack RNA-directed RNA polymerase, which is essential for the transcription of viral RNA into virus derived mRNA RNA viruses contain genetic information for the synthesis of RNA-directed RNA polymerase or, for the retroviruses, RNA-directed DNA polymerase (or reverse transciptase) [2]

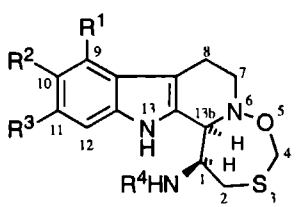
Since the replication of viruses is closely associated with the host cell metabolism it has been be difficult to develop selective antiviral drugs [3] Treatment of viral infections by chemotherapy began about three decades ago The first commercial antiviral drug idoxuridine -against herpes simplex

keratitis virus- was registered in the early sixties Besides idoxuridine, the U S Food and Drug Administration has approved acyclovir, amantadine, ribavirin, trifluridine, vidarabine, and zidovudine With the exception of amantadine all these drugs are nucleoside derivatives The applications of these drugs are rather limited, emphasizing the demand for new antiviral compounds with unique structures For the acquisition of biologically active lead compounds three approaches are valid

1 - General pharmacological screening of natural products
2 - General pharmacological screening of new chemical entities
3 - Rational design based on understanding of the biological target at a molecular level

In the search for antiviral lead compounds the first approach, especially from marine natural products, seems to be quite successful [4] Besides the indole alkaloid eudistomins, a variety of marine derived antiviral natural products have been isolated belonging to the terpenoid, nucleoside, alkaloid and polysaccharide classes [4] As stated in the introductory chapter, eudistomins were first isolated from the colonial tunicate *Eudistoma Olivaceum* [5] Of the five different classes of eudistomins which were isolated (see chapter 1), the oxathiazepine 7-membered ring containing tetracyclic eudistomins showed the most potent antiviral activities by far [6] In chart 9 1 the natural tetracyclic eudistomins are presented in combination with their antiviral activities in table 9 2 All these activities were determined using the same standardized procedure involving monkey kidney cells (CV-1 line), as described by Schroeder and coworkers [7]

Chart 9.1 *The isolated natural tetracyclic eudistomins and their antiviral activities*



Eudistomin	R^1	R^2	R^3	R^4
C	H	OH	Br	H
E	Br	OH	H	H
F	H	OH	Br	$C_2H_3O_2$
K	H	H	Br	H
K(sulfoxide)	H	H	Br	H
K(debromo)	H	H	H	H
L	H	Br	H	H

Table 9.2 *Antiviral activities of the natural eudistomins in ng/disk (active=no precise data given)*

	DNA viruses			*RNA viruses*			
eudistomin	Herpes simplex virus-1	Herpes simplex virus-2	Vaccinia virus	Coxsackie virus A-21	Equine rhino virus	Polio vaccine virus-1	reference
C	5-10	active	active	active	active		5,6a,6d
E	5-10	active	active	active	active		5 6a
K	200					200	5 6a 6c 6d
K(sulfoxide)	400					400	6c 6d
K(debromo)	400					400	6d
L	100						5 6a

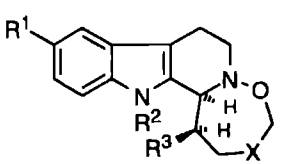
From table 9 2 it follows that the substituents in the phenyl ring influence the antiviral potency The highest activities were found with the eudistomins C,E with a 10-OH group The 11-Br substituent may also influence the antiviral potency Eudistomins are active against both DNA and RNA viruses and thus display broad-spectrum antiviral activity Both Rinehart[5] and Munro[6d] reported that acylation of the C(1)-amino group eliminate the antiviral activity

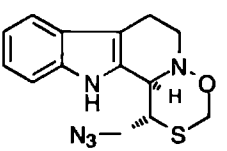
In addition to antiviral activity antitumor activity has also been reported for eudistomins Eudistomin K gave, *in vitro*, an IC_{50} for P388 of 0 01 µg/mL The *in vivo* assay gave a T/C of 137% at 100 mg/kg Further *in vivo* antitumor activities were reported against L1210, A549, and HCT-8 cell lines [6d] Apparently, eudistomins act on a biological target which is essential for the growth of both the viruses and the host cells No biological data have been reported yet for eudistomin F

Although three total syntheses of eudistomins have been developed,[8] hitherto only limited structure-activity relationship (SAR) investigations had been published [9] We already demonstrated that in debromoeudistomin K the correct natural absolute configuration at the two stereogenic centers, as depicted in chart 9 1, is essential for the biological activity [9] In the same study also the 10-OMe eudistomin K(debromo) derivative was discussed which shows a similar increase in activity as the most potent natural eudistomins C and E

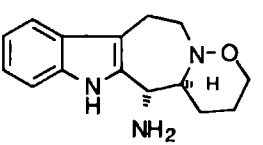
In this chapter we present the antiviral and antitumor results of compounds with a substituent at C(1) or N(13) as well as compounds in which either the indole system or elements of the oxathiazepine ring are replaced by bioisosteric groups In chart 9 2 the investigated derivatives are depicted

Chart 9 2



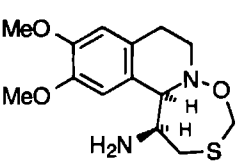


JM7 (chapter 3)



JM8 (chapter 4)

compound code	R^1	R^2	R^3	X	synthesis
PH77	H	H	NH_2	S	ref 9
JM2	H	CH_3	NH_2	S	chapter 2
JM3	H	H	OH	S	chapter 3
JM6	H	H	OCH_3	S	chapter 2
JM9	OCH_3	H	NH_2	S	ref 9
JM11	H	H	NH_2	CH_2	chapter 4



JM10 (chapter 6)

The inclusion of the compounds **PH77** (=debromo eudistomin K) and **JM9** (=10-methoxy debromo eudistomin K) allows the possibility to compare the activities of the new compounds with those reported for the isolated naturally occurring eudistomins and the data in our previously

performed SAR study Although the derivatives **JM7** and **JM8**, with 6/5/6/6 and 6/5/7/6 membered ring systems, respectively, cannot be considered directly as eudistomins, they have been included in the biological screening process because of their structural analogy with the naturally occurring 6/5/6/7 tetracyclic structures The optical purities of **PH77** and **JM8** have been determined by analytical HPLC methods and were ca 95% and ca 75%, respectively [10] The optical purities of **JM2,3,6,7** and **JM9** have not been determined, but it is not expected that excessive racemization has been occurred during their synthesis (see chapters 2 and 3) Both **JM10** and **JM11** have been obtained as racemates

9.2 Antiviral Activities

The derivatives depicted in chart 2 were evaluated for their inhibitory effects on the replication of a number of viruses at the Rega institute in Leuven (Belgium) [11]

- DNA viruses herpes simplex virus type-1 (HSV-1) (strains KOS, F, McIntyre), HSV 2 (strains G, 196, Lyons), vaccinia virus and thymidine kinase (TK) deficient (TK) HSV-1 (strain B2006)
- (+)-RNA viruses Coxsackie virus B4, polio virus-1, Sindbis virus, Semliki forest virus and human immunodeficiency virus (HIV) type 1 and 2
- (-) RNA viruses influenza virus A and B, respiratory syncytial virus, vesicular stomatitis virus and parainfluenza-3 virus
- (±) RNA viruses reovirus-1

HIV infection was carried out with the HTLV-III_B strain The virus was prepared from the culture supernatant of persistently HTLV-III_B-infected MT-4 cells The antiviral tests were performed in either MT-4 (HTLV-1 infected human T4 lymphocyte) or MDCK (Madin-Darby canine kidney) or HeLa (a human epithelial cell line derived from a cervix carcinoma) or Vero (a simian fibroblast cell line derived from African green monkey kidney) or PRK (primary rabbit kidney) or E_6SM (human embryonic skin muscle fibroblast) cell lines All antiviral tests were carried out following established procedures [12] To give the possibility to correct for alterations in the activity of the viral assays on different times, *E*-5-(2-bromovinyl)-2' deoxyuridine (BVDU), (S)-9-(2,3-dihydroxypropyl)adenine (DHPA), ribavirin and/or carbocyclic 3-deazaadenosine (C c^3 Ado) have been incorporated in the antiviral tests The observed antiviral data should always be considered in relation with the cytotoxic data The antiviral activities were considered significant if the ratio of the minimum cytotoxic concentration to the minimum viral inhibitory concentration (MCC/MIC ratio) is equal or greater than 10

Table 9 3 shows that against the influenza viruses A and B out of 5 compounds tested only synthetically derived debromo Eudistomin K (**PH77**) showed significant activity The MCC/MIC ratio of **PH77** is 10 Due to the highly cytocidal activity of **JM9** toward the MDCK host cells, its activity against influenza virus could not be detected

Table 9.4 shows that **PH77**, **JM9** and **JM10** are active against vesicular stomatitis virus (MCC/MIC=20). Surprisingly, activity was found for the deviating structure **JM8** against respiratory syncytial virus (MCC/MIC=17). **JM9** is extremely active against vesicular stomatitis, Coxsackie B4 and polio-1 virus, although its high cytotoxity against the HeLa host cells should be mentioned.

Table 9.3 *Cytotoxic and antiviral activity of the synthetically derived eudistomins in MDCK cell cultures:*

compound code	min. cytotoxic concentration (MCC)[a], (μg/mL)	Minimum inhibitory concentration (μg/mL)[b]	
		influenza virus A (Ishikawa)	influenza virus B (Singapore)
PH77	8	0.8	0.8
JM6	100	≥100	>100
JM7	40	6	30
JM8	100	14	>100
JM9	0.8	>0.32	>0.32
ribavirin	>200	15	15

[a] Required to cause a microscopically detectable alteration of normal cell morphology.
[b] Required to reduce virus-induced cytopathogenicity by 50%. Virus-induced cytopathogenicity was recorded at 5 days after infection

Table 9.4 *Cytotoxity and antiviral activity of the synthetically derived eudistomins in HeLa cell cultures:*

compound code	Minimum cytotoxic concentration (μg/mL)[a]	Minimum inhibitory concentration (μg/mL)[b]			
		Respiratory syncytial virus (long)	Vesicular stomatitis virus	Coxsackie virus B4	Polio virus-1
PH77	≥4	0.8	0.2	0.7	0.7
JM2	≥10		7	7	2
JM3	100		>100	>40	>100
JM6	100	20	>100	>100	>100
JM7	12	2.8	>10	>10	>10
JM8	100	6.0	>100	>100	>100
JM9	0.4	0.15	0.02	0.02	0.02
JM10	≥4		0.2	4	1
JM11	≥100		40	20	20
BVDU	>400		>400	>400	>400
DHPA	>400		300	>400	>400
Ribavirin	>400	3	20	70	70
C-c^3 Ado	>400		2	>400	>400

[a] Required to cause a microscopically detectable alteration of normal cell morphology.
[b] Required to reduce virus-induced cytopathogenicity by 50%. The data represent average values of two separate experiments

Table 9.5 shows that in Vero host cells, besides **JM9**, now also **JM2**, **JM10** and **JM11** show activity against Coxsackie B4 virus. The same compounds, together with **PH77** showed also activity against parainfluenza-3, reovirus-1, Sindbis and Semliki forest virus. Noteworthy are the promising MCC/MIC ratios ranging from 57-570 for the isoquinoline eudistomin derivative **JM10**. The same trends for **PH77**, **JM2**, **JM9**, **JM10** and **JM11** were found against HSV-1, HSV-2, vaccinia and vesicular stomatitis virus, presented in scheme 9.6. The MCC/MIC ratios of 1000-5000 for **JM10** for these viruses again emphasize its selective antiviral potency.

No significant anti-HIV 1 and anti-HIV 2 activities were found for any synthetically derived eudistomins (data not shown). For the derivatives **JM3**, **JM6** and **JM7** no antiviral activities were found in any assay.

Table 9.5 *Cytotoxity and antiviral activity of the synthetically derived eudistomins in Vero cell cultures:*

compound code	minimum cytotoxic conc. (μg/mL)[a]	Minimum inhibitory concentration (μg/mL)[b]				
		Para-influenza-3 virus	Reo-virus-1	Sindbis virus	Coxsackie virus B4	Semliki forest virus
PH77	≥4	0.2	0.4	0.2	0.4	0.2
JM2	≥20	0.7	1	2	0.7	2
JM3	≥100	>40	>40	20	>40	>40
JM6	≥200	>100	>100	>100	>100	>100
JM7	≥40	>10	>10	>10	>10	>10
JM8	≥40	>10	>10	>10	>10	>10
JM9	≥1	0.7	0.07	0.02	0.07	0.07
JM10	40	0.2	0.2	0.07	0.2	0.7
JM11	≥100	7	0.7	2	2	20
BVDU	>400	>400	>400	>400	>400	>400
DHPA	>400	70	70	150	70	>400
Ribavirin	>400	20	70	40	70	40
C-c[3] Ado	>400	2	2	20	20	>400

[a] Required to cause a microscopically detectable alteration of normal cell morphology
[b] Required to reduce virus-induced cytopathogenicity by 50% The data represent average values of two separate experiments

General discussion of the antiviral data:

The synthetic eudistomins **JM2,9,10** and **11** display broad-spectrum antiviral activity against both DNA- and RNA-type viruses, in contrast to the reference compounds. No activity was found against the retrovirus HIV. The general conclusion from previous work that the stereochemistry at both C(1) and C(13)b atoms must be the same as in the natural eudistomins, indicates at least a three point interaction at the receptor level. At this point it is interesting to take a closer look at the conformations of the CD ring systems in both eudistomin diastereoisomers. In chart 9.3 the spatial structure of the natural cis diastereomer as was determined both by X-ray analysis and in solution together with the X-ray structure of the inactive trans diastereomer are depicted (see chapter 8).[13]

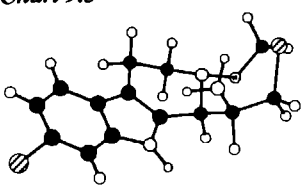
Table 9.6 *Cytotoxic and antiviral activity of the synthetically derived eudistomins in primary rabbit kidney (PRK) or E_6SM cell cultures:*

compound code	min. cytotoxic conc. (MCC) (μg/ml)[a]	Minimum inhibitory concentration (MIC) (μg/mL)[b]									
		Herpes simplex virus-1 (KOS)	Herpes simplex virus-1 (F)	Herpes simplex virus-1 (McIntyre)	Herpes simplex virus-2 (G)	Herpes simplex virus-2 (196)	Herpes simplex virus-2 (Lyons)	Vaccinia virus	Vesicular stomatitis virus	Herpes simplex virus-1 (TK^-) (B2006)	Herpes simplex virus-1 (TK^-) VMW1837
PH77	≥10	0.7	0.07	0.2	0.2	0.2	0.07	0.1	0.2	0.7	
JM2	≥40	3	2	0.7	0.7	1	0.7	1.5	7	7	
JM3	≥100	>100			>100			>100	>100		
JM6[c]	100	>40			>40			>40	>40	>40	>40
JM7[c]	100	>40			>40			>40	20	>40	>40
JM8[c]	100	>40			>40			>40	>40	10	>40
JM9	≥1	0.045	0.07	0.02	0.02	0.02	0.04	0.02	0.02	0.04	
JM10[c]	≥100	0.1			0.1			0.07	0.1	0.07	0.02
JM11[c]	100	2			2			1	7	0.04	1
BVDU	≥400	0.04	0.02	0.02	7	70	70	7	>200	150	10
DHPA	≥400	>100	>100	>100	>100	>100	>100	20	20	>100	>400
Ribavirin	≥400	>200	>200	>200	>200	>200	>200	20	>400	>200	100
C-c³ Ado	≥400	>200	>200	>200	>200	>200	>200	0.7	2	150	150

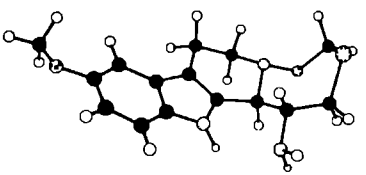
[a] Required to cause a microscopically detectable alteration of normal cell morphology.
[b] Required to reduce virus-induced cytopathogenicity by 50%. The data represent average values of two separate experiments
[c] Virus grown in E_6SM cell cultures.

Especially from the overlayed structures, it is clear that the only difference between both diastereomers is the position of the NH_2 group To obtain a significant activity it seems necessary that the NH_2 group occupies the axial position, as is found in the naturally occurring tetracyclic eudistomins

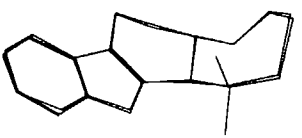
Chart 9.3



cis diastereomer



trans diastereomer



both diastereomers overlayed

In the natural stereoisomer the NH_2 group and the lone pair on N(6) are situated on the same side of the molecule, indicating that both could be involved in the binding process with the biological target The earlier reported observation that replacement of the NH_2 group by H (**1g**) results in loss of activity supports this supposition [9] Furthermore, the complete loss of activity when the NH_2 group is substituted by a hydroxyl group (**JM3**) or a methoxy group (**JM6**) may indicate that the amino group interacts in its protonated form, leading to an ionic interaction with the biological target This is further supported by the observation of Rinehart and Munro that N-acylation leads to loss of activity [5 6d] The strong influence of substituents at the phenyl ring in the indole part (compare **PH77** with **JM9**) demonstrates that the aromatic indole nucleus also contributes to the binding process at the receptor site Alterations at this site are allowed as is demonstrated by the observation that a methyl substituent at the indole-N (**JM2**) only moderately lowers the potency Substitution of the indole ring system by the dimethoxyphenyl group in the isoquinoline derivative **JM10** even increases the selectivity of the antiviral activity Structural alterations are also allowed in the 7-membered oxathiazepine ring Replacement of the sulfur atom by a methylene moiety (**JM11**) slightly diminished the antiviral activity compared to the natural occurring eudistomin **PH77** It can therefore be ruled out that the oxathio acetal moiety plays a crucial role in the antiviral mechanism of action From the NMR data of the derivatives **JM10** and **JM11** it was elucidated that the 7-membered ring had the same conformation in solution as was found in the natural eudistomins, further supporting the importance of an axially positioned C(1)-amino group

9.3 Cytostatic Activities

For the antitumor SAR study the inhibitory effects of the compounds **JM2**, **JM6**, **JM7**, **JM8**, **JM10** and **JM11** were studied in a similar manner as described previously for **PH77** and **JM9** [9] The inhibitory effects were evaluated on the proliferation of murine leukemia cells (L1210), HTLV I infected human T-lymphoblast cells (Molt/4F), human T-lymphocyte (MT-4), murine mammary

carcinoma cells (FM3A and human T-lymphocyte cells (CEM/0), following established procedures.[11,14] For **PH77** already a marked inhibitory effect was observed while **JM9** appeared to be a very potent cytostatic compound with ID_{50} values down to 0.005 μg/mL (16 nM) for the investigated tumor cells.[9] Similarly to the antiviral data, it was established that the correct natural configuration of the two stereogenic centers is essential for the antitumor activity. The data of **PH77** and **JM9** in combination with the data of the new derivatives described in this thesis are presented in table 9.7.

Table 9.7 *Inhibitory effects of eudistomins on the proliferation of murine leukemia cells (L1210), human T-lymphoblast cells (Molt/4F), human T-lymphocyte (MT-4), FM3A, and CEM/0 cells:*

compound code	ID_{50}[a] (ng/mL)				
	L1210	Molt-4F	MT-4	FM3A	CEM/0
PH77	110 ± 10[b]	120 ± 20	75 ± 7		
JM2	560 ± 3	370 ± 80	690 ± 15		
JM6	27200 ± 6100	23100 ± 6700		62000 ± 1670	15200 ± 1600
JM7	9210 ± 3980	38600 ± 1310		10300 ± 3200	10800 ± 1000
JM8	22800 ± 5100	17800 ± 5100		45300 ± 1540	10400 ± 70
JM9	5.0 ± 0.4[b]	6.2 ± 0.6	5.0 ± 0.1	7.3 ± 0.3	5.5 ± 2.1

[a] 50% Inhibitory dose or dose required to inhibit tumor cell proliferation by 50%.
[b] Similar results were obtained with the P388 cell line by Dr P Lelieveld from TNO-CIVO Institutes, Zeist , the Netherlands

For the new compounds the same trends are found as in the antiviral tests. It should be noted here that **JM10** is a racemate and it is therefore very likely that optically pure **JM10**, with the correct natural configuration at both stereogenic centers, is twice as active.

PH77 and **JM10** were subjected to further *in vitro* antitumor activity determinations against breast cancer (MCF7, EVSAT), colon cancer (WIDR), ovarian cancer (IGROV), melanoma (M19), renal cancer (A498), and non small cell lung cancer (HOP92) cell lines, following established procedures (table 9.8).[15]

Table 9.8 *Inhibitory effects of eudistomins on the proliferation of human breast cancer cells (MCF7, EVSAT), colon cancer (WIDR), ovarian cancer (IGROV), melanoma (M19), renal cancer (A498), non small cell lung cancer (HOP92).*[a]

compound code	ID_{50}[b] (ng/mL)						
	MCF7	EVSAT	WIDR	IGROV	M19	A498	HOP92
PH77	100	140	210	420	220	75	280
JM10	62	194	150	99	109	230	203
DOX	8	6	20	28	5	5	
5-FU	210	650	260	280	160	88	

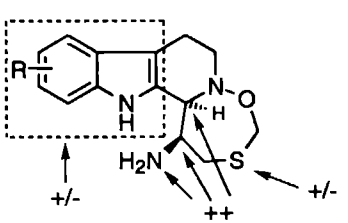
[a] These results were obtained in the Laboratory of Experimental Chemotherapy and Pharmacology, Department of Medical Oncology, Rotterdam Cancer Institute (Dr Daniel den Hoed Kliniek), the Netherlands
[b] 50% Inhibitory dose or dose required to inhibit tumor cell proliferation by 50% The assays were found to be reproducable with relative standard deviations of <20%.

As a reference the registered and clinical used antitumor drugs doxorubicin (**DOX**) and 5-fluorouracil (**5-FU**) were added to the assays. The antitumor activities of **PH77** and **JM10** are roughly in between the data for doxorubicin (**DOX**) and 5-fluorouracil (**5-FU**), reconfirming the potential of eudistomins as antitumor drugs. As was stated above, for the antitumor activity of eudistomins, roughly the same SAR conclusions can be drawn as for the antiviral activies. This indicates that possibly eudistomins act on a biochemical process that is essential for both virus growth and tumor cell growth which has been observed more often for antiviral compounds.[14] The exact mechanism of biological action of eudistomins is at present under investigation at the REGA institute in Leuven (Belgium).

9.4 Conclusions

In conclusion it can be stated that tetracyclic eudistomins and analogs may have promise as broad-spectrum antiviral and/or antitumor compounds. The correct natural configuration of the two stereogenic centers is essential for the biological activity together with the presence of the C(1)-amino group. The indole ring system may be substituted by the dimethoxyphenyl group, to give an isoquinoline eudistomin derivative, without losing antiviral or antitumor potency. The sulfur atom in the 7-membered oxathiazepine ring may also be substituted by a methylene moiety without appreciable loss of antiviral activity. Substituents at the phenyl ring alter both the antiviral and antitumor potency. The tricyclic isoquinoline derivative is, so far, the most promising antiviral analog; it combines a high potency (MIC at ≈100 ng/mL (340 nM)) with a high selectivity (MCC/MIC ratios ranging from 1000-5000 against HSV-1, HSV-2, vaccinia virus and vesicular stomatitis virus). The 10-methoxy debromoeudistomin K derivative is the most potent antitumor compound with ID_{50} values down to 5 ng/mL (16 nM). A summary of the SAR observations is depicted in chart 9.4.

Chart 9.4 *SAR observations regarding both antiviral and antitumor activities of eudistomin derivatives*



++ essential for activity

+/- structural modification allowed

References and Notes

1 De Clercq, E , Murase, J , Marquez, V E *Biochem Pharm* **1991**, 41, 1821

2 Stryer, L *Biochemistry*, third ed , W H Freeman and company, New York, 1988

3 Neal, M J *Medicinal Pharmacology at a Glance*, second ed , Blackwell Scientific Publications, Oxford, 1992

4 Che, C-t *Drug Dev Res* , **1991**, 23, 201

5 Rinehart, K L Jr , Kobayashi, J , Harbour, G C , Hughes, R G Jr , Mizsak, S A , Scahill, T A *J Am Chem.Soc* , **1984**, 106, 1524

6 a) Rinehart, K L Jr , Kobayashi, J , Harbour, G C , Gilmore, J , Mascal, M , Holt, T G , Shield, L S , Lafargue, F *J Am Chem Soc* , **1987**, 109, 3378 b) Blunt, J W , Lake, R J , Munro, M H G , Toyokuni, T *Tetrahedron Lett* , **1987**, 28, 1825 c) Lake, R J , Brennan, M M , Blunt, J W , Munro, M H G , Pannell, L K *Tetrahedron Lett* , **1988**, 29, 2255 d) Lake, R J , Blunt, J W , Munro, M H G *Aust J Chem* , **1989**, 42, 1201

7 Schroeder, A C , Hughes, R G Jr , Bloch, A J *J Med Chem* , **1981**, 24, 1078

8 a) Hermkens, P H H *'N-hydroxy-β-carbolines Syntheses, Applications and Biological Activities"*, **1990**, Thesis, Catholic University of Nijmegen b) Hermkens, P H H , Maarseveen, J H van, Ottenheijm, H C J , Kruse, C G , Scheeren, J W *J Org Chem* , **1990**, 55, 3998 c) Nakagawa, M , Liu, J -J , Hino, T *J Am Chem.Soc* , **1989**, 111, 2721 d) Liu, J -J , Nakagawa, M , Harada, N , Tsuruoka, A , Hasegawa, A , Ma, J , Hino, T *Heterocycles*, **1990**, 31, 229 e) Still, I W J , Strautmanis, J *Tetrahedron Lett* , **1989**, 30, 1041 f) Still, I W J , Strautmanis, J *Can J Chem* , **1990**, 68, 1408

9 Maarseveen, J H van, Hermkens, P H H , DeClercq, E , Balzarini, J , Scheeren, J W , Kruse, C G *J Med Chem.*, **1992**, 35 3223

10 Kuijpers, P H , Gerding, T K , Jong, G J de *J Chromatogr* , **1992**, 625, 223

11 The tests were performed under supervision of Prof Dr E DeClercq at the Rega Institute, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000, Leuven (Belgium)

12 a) De Clercq, E , Descamps, J , Verhelst, G , Walker, R T , Jones, A S , Torrence, P F and Shugar, D *J Infect Dis* , **1980**, 5, 563 b) De Clercq, E and Montgomery, J A , *antiviral Res* **1983**, 3, 17 c) Balzarini, J , Naesens, L , Herdewijn, P , Rosenberg, I , Holy, A , Pauwels, R , Baba, M , Johns, D G and De Clercq, E , *Proc Natl Acad Sci USA*, **1989**, 86, 332

13 By ^{1}H-NMR spectroscopy investigations of the trans diastereomer at least three different conformations of the 7-membered oxathiazepine ring have been established (see chapter 8) Besides the natural conformation also the bridgehead nitrogen atom inverted and C(2)-S(3) twisted conformations exist in solution All possible conformations of the trans diastereomer have, however, in common that the C(1)-amino group occupies the equatorial position

14 a) De Clercq, E , Balzarini, J , Torrence, P F , Mertes, M P , Schmidt, C L , Shugar, D , Barr, P J , Jones, A S , Verhelst, G , Walker, R T *Mol Pharmacol* **1981**, 19, 321 b) Balzarini, J , De Clercq, E , Torrence, P F , Mertes, M P , Park, J S , Schmidt, C L , Shugar, D , Barr, P J , Jones, A S , Verhelst, G , Walker, R T *Biochem. Pharmacol* **1982**, 31, 1089

15 a) Kepers, Y P , Pizao, P E , Peters, G J , Van Ark-Otte, J , Winograd, B , Pinedo, H M *Eur J Cancer* **1991**, 27, 897 b) Boyd, M R *Status of the NCI preclinical antitumor drug discovery screen Principles and practice of oncology* **1989**, 3, 1

Summary

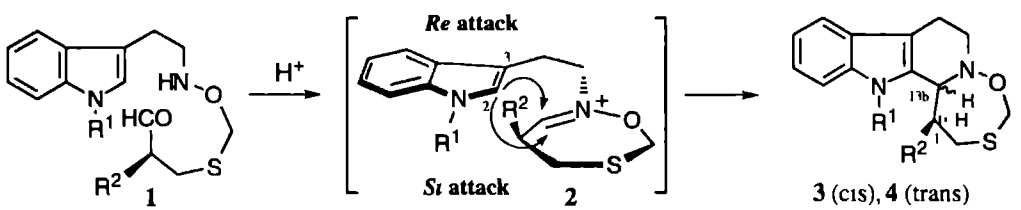
Tetracyclic eudistomins (**3**, R^1=H, R^2=NH_2), first isolated from the colonial tunicate *Eudistoma Olivaceum*, display potent antitumor and antiviral activities In a previous study, closure of the 7-membered [1,6,2]-oxathiazepine ring was performed in high yields by application of the intramolecular Pictet-Spengler (PS) condensation The high yield was cancelled out by an unfavored diastereoselectivity to give the *un*natural C(1)H-C(13b)H trans eudistomin diastereomer **4** in excess It was also discovered that only the natural *cis* isomer exhibits biological activity In this thesis further research on the total synthesis of eudistomins by application of the intramolecular PS condensation is described The research objectives for this thesis are

1 - To study the factors controlling the diastereoselectivity of the intramolecular PS condensation in order to arrive at a diastereoselective synthetic route to the natural C(1)H-C(13b)H cis eudistomins

2 - To prepare a series of eudistomin derivatives aimed to establish the necessary structural elements for both antiviral and antitumor structure-activity relationship (SAR) studies

3 - To investigate the synthetic scope and the mechanism of the intramolecular PS condensation in the synthesis of the tetracyclic skeleton of the naturally occurring canthines

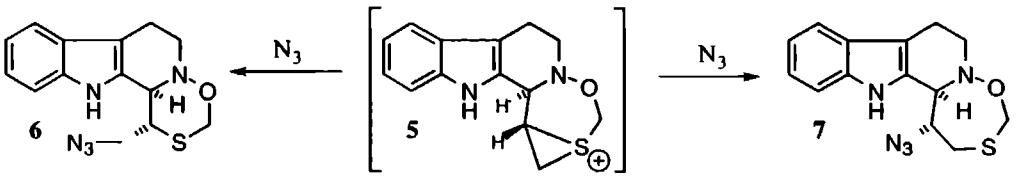
In chapter 2 a study of the factors controlling the stereochemical outcome of the PS condensation is presented Several cyclizations were performed with aldehydes of the type **1** to elaborate the influence of the size of the substituents R^1 and R^2 on the diastereoselectivity It was found that the diastereoselectivity is solely determined during the kinetically controlled nucleophilic attack of the indole-2 position at the intermediate cyclic iminium ion in **2**



Unfortunately, only attack at the side hindered by the substituent R^2 (*Re* attack) will lead to the natural cis eudistomins Therefore, with the intramolecular PS condensation in the natural eudistomin series, selectivity can only be achieved to the unnatural trans diastereomers The cyclization yields ranged from 68-98% Depending on the size of R^2 the d e 's of the trans diastereomers ranged from 24% (R^1=H, R^2=OH) to 100% (R^1=H, R^2=CH_3)

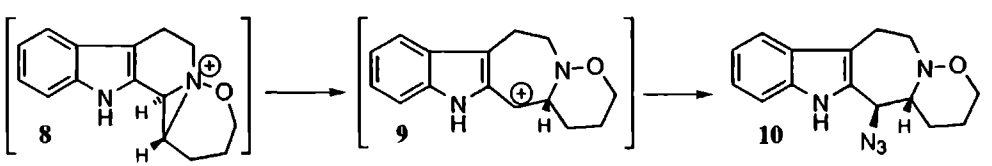
It was reasoned that this trans selectivity can become an advantage when the C(1)-amino functionality could be introduced after completion of the ring closure by means of an S_n2-type reaction resulting in the cis stereochemistry In chapter 3 this approach is worked out for the natural eudistomin series Transformation of the *trans* C(1)-hydroxy derivative into the *cis* C(1)-azido eudistomin derivative by means of the Mitsunobu reaction failed because of a transannular

neighboring group participation of the β-positioned sulfur atom, leading to a pentacyclic intermediate **5**



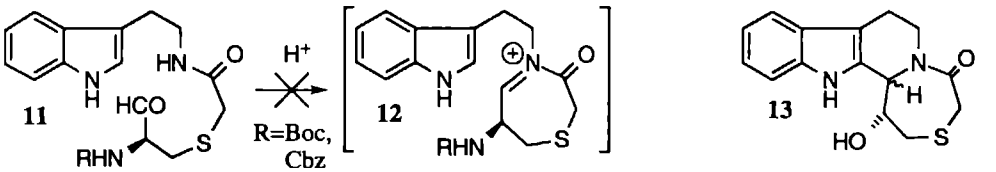
Subsequent attack of the azide nucleophile occurred at both electrophilic carbon atoms in the thiirane ring to give the D-ring contracted C(1)-azidomethylene product **6**, containing a 6/5/6/6 membered ring system, and the *trans* C(1)-azide eudistomin derivative **7**

In chapter 4 the synthesis of an eudistomin derivative with the sulfur atom replaced by a methylene group is described The diastereoselectivity of the intramolecular PS condensation was also unfavorable and the trans diastereomer was formed in an excess of 98% Moreover, during the synthesis the optical activity was lost The desired cis diastereomer was, however, obtained in sufficient quantities for biological testing purposes A diastereoselective approach to a cis desthia carba analog was also attempted using the S_n2 strategy via a trans C(1)-hydroxy derivative Once again, neighboring group participation thwarted this stategy Transannular nucleophilic attack now occurred from the β-positioned bridgehead nitrogen atom to give a pentacyclic intermediate **8** containing an aziridinium ring



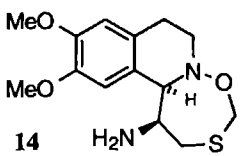
Subsequent attack of the azide ions occurred at the benzylic position only The resulting product **10**, with a 6/5/7/6 membered ring system instead of the 6/5/6/7 membered ring system originally present in the starting eudistomin derivative, was obtained in a stereospecific fashion in 81% yield

Besides the biological relevance of the sulfur atom, the function of the oxygen atom in the oxathiazepine moiety was also considered In chapter 5 the attempted syntheses of an eudistomin derivative with the oxygen atom in the 7-membered ring replaced by a methylene group are described Closure of the 7-membered thiazepine ring by means of the intramolecular PS condensation could not be accomplished, despite the use of the N_b-amides **11** which should give the highly reactive intermediate cyclic N acyliminium ions **12** Probably due to the low nucleophilicity of the amide nitrogen atoms the rate of formation of the acyliminium intermediates **12** is very slow and competitive deprotection of the carbamate protected C(1)-amino group occurred, followed by side reactions Also in this case a diastereoselective approach via a trans C(1)-hydroxy compound was carried out Ring closure via the intermediate N-acyliminium ions could now be performed giving the cis/trans tetracyclic lactams **13** in a 50 50 ratio in only 36% yield

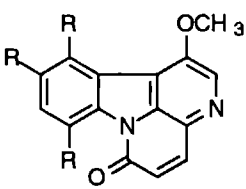


These disappointing cyclization results with the desoxo carba derivative emphasize the unique properties of N-alkoxyiminium ions in the PS condensation The S_n2 type introduction of the amino functionality by means of the Mitsunobu reaction again failed due to neighboring group participation of the nucleophilic sulfur atom, despite the anticipated rigidity of the 7-membered lactam in **13**

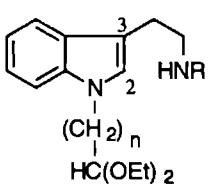
The intramolecular PS approach to the isoquinoline derivative of **14** described in chapter 6 Cyclization proceeded in 60% yield and, surprisingly, the desired cis diastereomer was obtained in a diastereomeric excess of 56% The stereochemical outcome of the PS condensation resulting in compound **14** is much better than in the case of tetracyclic eudistomin derivatives The subtile difference in nucleophilicity of the aromatic nucleus in the respective cases is probably responsible for this



The synthetic accessibility of the tetracyclic canthine skeleton as in **15**, using the intramolecular PS cyclization of the several N_a-functionalized tryptamines **16** is described in chapter 7

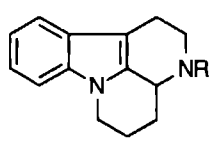


15 canthin-6-one
(R =H, OCH_3)



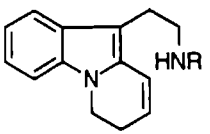
16

16	n	R
a	2	OCH_2 $HC{=}CH_2$
b	3	OCH_2 $HC{=}CH_2$
c	4	OCH_2 $HC{=}CH_2$
d	3	CHO
e	3	CH_2Ph



17 R=OAllyl

The chain-length ***n*** was varied to investigate both the synthetic scope and the reaction mechanism of this PS condensation It was found that only tryptamine derivative **16b**, after *in situ* hydrolysis of the diethyl acetal, cyclized to give the corresponding hexahydro canthine derivative **17** in 81% yield Product formation *must* have occurred by attack from the indole 2-position at the electrophilic iminium-ion Intramolecular attack from the indole-3 position is impossible because this process would give a spiro intermediate with a highly unfavorable 7-membered ring containing a trans double bond The tryptamine derivatives **16a** (n=2) and **16c** (n=4) only gave oligomeric compounds resulting from *inter*molecular PS condensations Instead of giving the hexahydro canthine skeleton, the N_b-formylated and N_b-benzylated tryptamines **16d**,**e**, gave the corresponding 3,4-dihydro pyrimidino[1,2-*a*]indoles **18** originating from direct attack from the indole 2-position at the protonated aldehydes



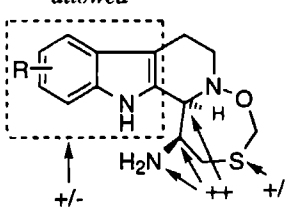
18 R=CHO, CH_2Ph

This prefered attack of the indole 2-position at the protonated aldehydes occurred due to the low nucleophilicities of the N_b-formylated or the protonated N_b-benzylated nitrogen atoms in **16d,e**, respectively, again emphasizing the unique usefullness of N-alkoxytryptamines in the PS condensation

In chapter 8 all known X-ray crystal structures of oxathiazepine ring containing eudistomin derivatives are discussed in combination with the ^{1}H-NMR data It was found that the conformation of the oxathiazepine ring in the natural cis eudistomins in solution was virtually the same as was found in the X-ray crystal structures Several conformations of the oxathiazepine ring were found for the trans diastereomers both in solution and in the solid state These conformational changes are caused by interactions of the equatorial C(1)-substituent with the indole-N substituent Due to the flexibility of the oxathiazepine ring, straightforward cis/trans assignments by ^{1}H-NMR spectroscopy may be hampered

The biological activities of the eudistomin derivatives described in this thesis are presented in chapter 9 The antiviral activity was determined against sixteen different viruses Also antitumor activities were determined against twelve different cell line classes From previous work it was already concluded that the correct natural configuration of the two stereogenic centers is essential for biological activity From the derivatives tested in this thesis it was established that also the presence of the C(1)-amino group is essential for biological activity

++ *essential for activity*
+/- *structural modification allowed*



The indole N proton may be replaced by a methyl group without appreciable loss of biological activity Furthermore, the indole ring system may be substituted by the dimethoxyphenyl group, to give the isoquinoline skeleton **14**, without losing antiviral or antitumor potency Replacement of the sulfur atom in the oxathiazepine ring by a methylene group is also allowed, since the antiviral activity is only slightly affected These observations are summarized in the chart at the left The tricyclic isoquinoline derivative **14** is, so far, the most promising antiviral analogue with MCC/MIC ratios (= cytostatic activity/antiviral activity ratio) ranging from 1000-5000 against the HSV-1, HSV-2, vaccinia and vesicular stomatitis viruses and activity in concentrations of ≈100 ng/mL (340 nM) The 10-methoxy debromoeudistomin K derivative is the most active antitumor compound with ID_{50} values down to 5 ng/mL (16 nM) It may therefore be concluded that tetracyclic eudistomins and analogs have promise as broad-spectrum antiviral or antitumor compounds

The major conclusions, regarding the three objectives of the research described in this thesis, that can be drawn are

1-With the intramolecular PS condensation in the β-carboline series, diastereoselectivity can only be achieved to the unnatural trans diastereomer Cis diastereoselectivity, however, can be achieved in the isoquinoline series S_n2-type substitution of activated C(1)-hydroxy groups in trans eudistomin derivatives by masked nitrogen nucleophiles, to give cis eudistomins, failed due to

transannullar neighboring group participation of either the nitrogen or sulfur atom in the 7-membered ring

2-By synthesis of appropriate derivatives it was shown that the indole-N proton, the indole ring system or the sulfur atom may be replaced by isosteric groups without losing antiviral or antitumor activity Both the correct natural stereochemistry and the C(1)-amino group are essential for biological activity

3-The tetracyclic skeleton, present in the canthine series, is synthetically accessible via the intramolecular PS condensation from N_a-butyraldehyde-N_b-alkoxytryptamines in high yields Substancial evidence has been presented for a direct nucleophilic attack of the indole-2 position at the intermediate iminium ion in the intramolecular PS condensation.

Samenvatting

Tetracyclische eudistomines (**3**.R^1=H,R^2=NH_2), die voor het eerst werden geisoleerd uit het in kolonies levende manteldier *Eudistoma Olivaceum*, bezitten een sterke antivirale en antitumor activiteit. Een uniek structuur kenmerk vormt de 7-voudige [1,6,2]-oxathiazepine ring. In een voorafgaande studie was de sluiting van deze 7-voudige ring in hoge opbrengsten bewerkstelligd d m v. de intramoleculaire Pictet-Spengler (PS) condensatie Echter, tegenover deze hoge opbrengst staat de ongunstige diastereoselectiviteit waarmee de onnatuurlijke C(1)H-C(13b)H trans eudistomines **4** in overmaat gevormd worden. Er was namelijk al gebleken dat slechts de natuurlijke cis stereoisomeren biologische activiteiten vertonen. In dit proefschrift is een voortgezette studie beschreven van de totaalsynthese van eudistomines d.m.v de intramoleculaire PS condensatie. De doelen die vooraf aan het onderzoek gesteld werden, zijn:

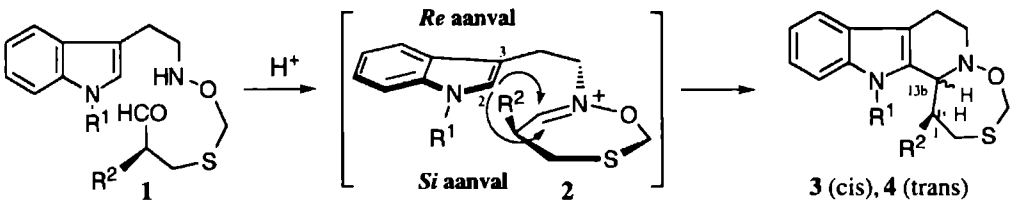
1- Het bestuderen van de factoren die de diastereoselectiviteit in de intramoleculaire PS condensatie beinvloeden, om te komen tot een betere diastereoselectieve synthese van natuurlijke C(1)H-C(13b)H cis eudistomines.

2- Het gericht ontwerpen en synthetiseren van eudistomine derivaten met de noodzakelijke structuur-elementen voor zowel een antivirale als een antitumor structuur activiteits relatie (SAR) onderzoek.

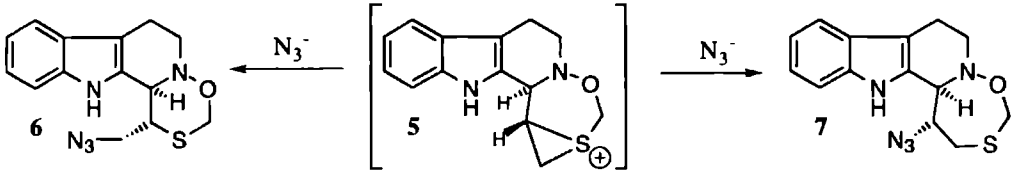
3- Het bestuderen van de toepasbaarheid en mechanistische aspecten van de intramoleculaire PS condensatie in de synthese van het tetracyclische skelet van de natuurlijk voorkomende canthines.

In hoofdstuk 2 is de studie beschreven naar de factoren die het stereochemische reactieverloop van de PS condensatie beinvloeden. Verschillende cyclisaties zijn uitgevoerd met aldehyden van het type **1** om de invloed van de grootte van de substituenten R^1 en R^2 op de diastereoselectiviteit te onderzoeken. Gevonden werd dat de diastereoselectiviteit geheel werd bepaald door de kinetisch bepaalde, nucleofiele aanval van de indool-2 positie op het intermediaire cyclische iminium ion in **2** Ongelukkigerwijs levert aanval op de door R^2 gehinderde zijde (*Re* aanval) de natuurlijke cis configuratie. Derhalve kan met de intramoleculaire PS condensatie, in de natuurlijke eudistomine

reeks, slechts de ongewenste trans diastereomeer selectief gesynthetiseerd worden. De opbrengsten van de cyclisaties variëerden van 68-98%. Afhankelijk van de grootte van R^2 werden diastereomere overmaten verkregen van 24% (R^1=H, R^2=OH) tot 100% (R^1=H, R^2=CH_3).

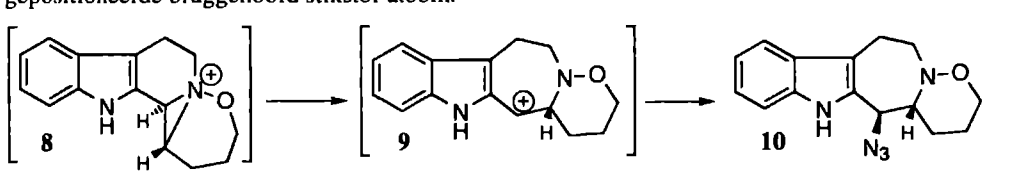


Er werd beredeneerd dat deze trans diastereoselectiviteit in ons voordeel gebruikt zou kunnen worden, indien de C(1)-amino substituent geïntroduceerd wordt d.m.v. een S_n2-type reactie, resulterend in een produkt met de gewenste cis stereochemie. In hoofdstuk 3 is deze benadering uitgewerkt voor de natuurlijke eudistomine klasse. Omzetting van het trans C(1)-hydroxy derivaat in het cis C(1)-azido eudistomine derivaat d.m.v. de Mitsunobu reactie mislukte t.g.v. transannulaire buurgroepparticipatie van het β-gepositioneerde zwavel atoom, resulterend in het pentacyclische intermediair **5**.



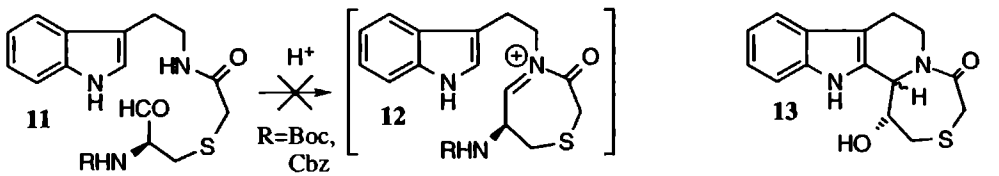
Aanval van de azide nucleofielen vond plaats op beide electrofiele koolstof atomen in de thiiraan ring, waarbij het D-ring verkleinde C(1)-azidomethyleen produkt **6** met een 6/5/6/6-voudig ring systeem, gevormd werd tesamen met het *trans* C(1)-azide eudistomine derivaat **7**.

In hoofdstuk 4 is de synthese beschreven van een eudistomine derivaat waarbij het zwavel atoom is vervangen door een methyleen eenheid. De diastereoselectiviteit van de intramoleculaire PS condensatie was uiterst ongunstig en de trans diastereomeer werd gevormd in een overmaat van 98%. Bovendien is tijdens de synthese de optische activiteit verloren gegaan. De gewenste cis diastereomeer is echter in voldoende hoeveelheden verkregen t.b.v. biologische testen. Gelijktijdig is geprobeerd om het desthia carba derivaat d.m.v. de S_n2 strategie diastereoselectief uit het trans C(1)-hydroxy derivaat te synthetiseren. Wederom werd deze strategie gedwarsboomd door transannulaire buurgroepparticipatie. Transannulaire nucleofiele aanval vond nu plaats door het β-gepositioneerde bruggehoofd stikstof atoom.



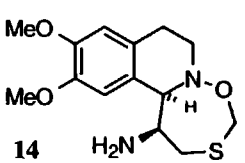
Het pentacyclische intermediair **8** met een aziridinium ring werd door de aanwezige azide ionen selectief op de benzylische positie aangevallen waarbij stereospecifiek product **10** met een 6/5/7/6-voudig ring systeem gevormd werd in een opbrengst van 81%

Naast de biologische relevantie van het zwavel atoom zijn wij tevens geïnteresseerd in de functie van het zuurstof atoom in de oxathiazepine ring In hoofdstuk 5 staan de synthese pogingen beschreven van het derivaat, waarbij het zuurstof atoom in de 7-voudige ring gesubstitueerd is door een methyleen eenheid Sluiting van de 7-voudige ring d m v de intramoleculaire PS condensatie kon niet bewerkstelligd worden, ondanks het gebruik van N_b-amides **11** die de uiterst reactieve intermediaire cyclische N-acyliminium ionen **12** zouden moeten geven



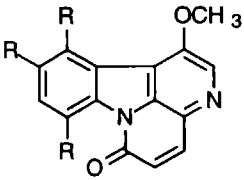
Waarschijnlijk wordt de PS condensatie erg vertraagd door de lage vormingssnelheid van de acyliminium intermediairen **12**, zodat competitieve ontscherming van de carbonaat beschermde C(1)-amino groepen plaats kan vinden, gevolgd door nevenreacties Ook in het geval van het desoxo carba derivaat is een diastereoselectieve benadering via een trans C(1)-hydroxy derivaat ondernomen Ringsluiting van het intermediaire N-acyliminium ion kon nu inderdaad bewerkstelligd worden waarbij de cis/trans tetracyclisch lactamen **13** in een gelijke verhouding in slechts 36% opbrengst geïsoleerd werden. Deze teleurstellende cyclisatie resultaten van het desoxo carba derivaat onderstrepen de unieke eigenschappen van N-alkoxyiminium ionen in de PS condensatie De S_n2 type introductie van de amino functie d m v de Mitsunobu reaktie is wederom mislukt t g v buurgroeppartïcipatie van het nucleofiele zwavel atoom, dit ondanks de voorziene grotere starheid van het 7-voudige lactam in **13**

De synthese van het isoquinoline derivaat **14** via de intramoleculaire PS condensatie is beschreven in hoofdstuk 6 De ringsluiting verliep in 60% opbrengst en, verrassenderwijs, werd de gewenste cis diastereomeer met een diastereomere overmaat van 56% gevormd De diastereoselectiviteit van de PS condensatie resulterend in verbinding **14** is veel beter dan in het geval van de tetracyclische eudistomine derivaten Het subtiele verschil in nucleofiliciteit van het aromatisch gedeelte in de respectievelijke gevallen is hiervan mogelijk de oorzaak

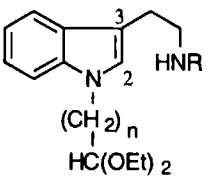


De synthetische toegankelijkheid van het canthine skelet zoals in **15** d m v de intramoleculaire PS cyclisatie van verschillende N_a-gefunctionaliseerde tryptamines **16** is beschreven in hoofdstuk 7 De ketenlengte *n* werd gevarieerd om de synthetische toepasbaarheid en het reactiemechanisme van deze PS condensatie te bestuderen Gevonden werd dat slechts tryptamine derivaat **16b**, na *in situ* hydrolyse van het diethyl acetaal, cycliseerde, waarbij het overeenkomstige hexahydro canthine

derivaat **17** in 81% opbrengst geïsoleerd werd De produktvorming *moet* hebben plaatsgevonden door aanval van de indool-2 positie op het electrofiele iminium ion

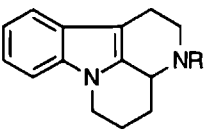


15 canthin-6-one
(R =H OCH_3)



16

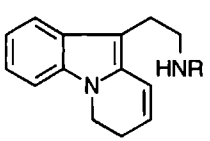
16	n	R
a	2	OCH_2 HC=CH_2
b	3	OCH_2 HC=CH_2
c	4	OCH_2 HC=CH_2
d	3	CHO
e	3	CH_2Ph



17 R=OAllyl

Intramoleculaire aanval vanaf de indool-3 positie is onmogelijk, omdat dan een spiro intermediair met een zeer ongunstige 7-voudige ring met een trans dubbele band zou ontstaan De tryptamine derivaten **16a** (n=2) en **16c** (n=4) gaven slechts de vorming van oligomeren te zien t g v *inter*moleculaire PS condensaties

In plaats van de vorming van het hexahydro canthine skelet werden vanuit de N_b-geformyleerde en



18 R=CHO, CH_2Ph

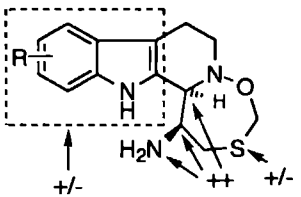
N_b-gebenzyleerde tryptamines **16d,e** de overeenkomstige 3,4-dihydro pyrimidino[1,2 *a*]indolen **18** verkregen, t g v directe aanval van de indool-2 positie op de geprotoneerde aldehyden Deze competitieve aanval vond plaats t g v de lage nucleofiliciteit van de N_b-geformyleerde of de geprotoneerde N_b-gebenzyleerde stikstof atomen in respectievelijk **16d,e** Dit onderstreept wederom de unieke toepasbaarheid van N_b alkoxytryptamines in de PS condensatie

In hoofdstuk 8 worden alle, tot nu toe bekende, kristalstructuren van oxathiazepine ring bevattende eudistomine derivaten bediscussieerd in relatie tot de ^{1}H-NMR data Verder wordt verduidelijkt dat de conformatie van de oxathiazepine ring in de natuurlijke cis eudistomines in oplossing vrijwel identiek is aan de conformatie in de kristalstructuren Verschillende conformaties voor de oxathiazepine ring werden gevonden voor de trans diastereomeren, zowel in oplossing als in de kristalstructuren De conformationele afwijkingen werden veroorzaakt door interacties van de equatoriale C(1)-substituent met de indool-N substituent T g v de grote flexibiliteit van de oxathiazepine ring wordt de cis/trans toekenning d m v ^{1}H-NMR spectroscopie vaak bemoeilijkt

De biologische activiteiten van de nieuwe eudistomine derivaten staan beschreven in hoofdstuk 9 De antivirale activiteit werd bepaald tegen zestien verschillende virussen Eveneens zijn de antitumor activiteiten bepaald tegen twaalf verschillende cellijnen Uit voorgaand onderzoek werd reeds geconcludeerd dat de correcte natuurlijke configuratie van de twee chirale centra essentieel is voor de biologische activiteit Het indool-N proton kan vervangen worden door een methyl groep zonder noemenswaardig verlies van de biologische activiteit Verder kan de gehele indool eenheid vervangen worden door een dimethoxyfenyl groep, zoals in het isoquinoline derivaat **14**, zonder verlies van antivirale of antitumorale potentie Eveneens heeft vervanging van het zwavel atoom in

de oxathiazepine ring door een methyleen groep weinig invloed op de antivirale activiteit Deze waarnemingen zijn schematisch samengevat in de onderstaande figuur

++ *essentieel voor activiteit*
+/- *structurele modificaties toegestaan*



Het tricyclische isoquinoline analogon is het tot nu toe meest veelbelovende antivirale derivaat met MCC/MIC ratio's (=cytostatische activiteit/antivirale activiteit) variërend van 1000-5000 tegen HSV-1, HSV-2, vaccinia en vesicular stomatitis virussen, waarbij reeds activiteiten in het ≈100 ng/mL (340 nM) concentratiegebied gevonden werden Het 10-methoxy debromoeudistomine K derivaat is de meest actieve antitumor verbinding met ID_{50} waarden tot 5 ng/mL (16 nM) Uit deze resultaten blijkt dat tetracyclische eudistomines en analoga een kans hebben als breed-spectrum antivirale of antitumor verbindingen

De hoofdconclusies die getrokken kunnen worden, m b t de doelstellingen die aan het begin van het onderzoek gesteld werden, zijn

1- Met gebruikmaking van de intramoleculaire PS condensatie in de β-carboline reeks kan slechts diastereoselectiviteit in de vorming van de onnatuurlijke trans diastereomeer bewerkstelligd worden Cis diastereoselectiviteit werd echter wel bereikt in de synthese van een isoquinoline type eudistomine derivaat Synthese van eudistomines via S_n2-type substitutie van een geactiveerde C(1) hydroxy groep in trans eudistomines door gemaskeerde stikstof nucleofielen is niet mogelijk t g v transannulaire buurgroep participatie van zowel het stikstof- alsmede het zwavelatoom in de 7-voudige ring

2- Door synthese van geschikte derivaten is opgehelderd dat het indool-N proton, de indool eenheid of het zwavelatoom vervangen kunnen worden door isostere groepen zonder belangrijk verlies van de antivirale of antitumor activiteit Zowel de correcte natuurlijke configuratie alsmede de C(1)-amino groep zijn essentieel voor de biologische activiteit

3- Het tetracyclische skelet, zoals aanwezig in de canthines, is synthetisch toegankelijk in hoge opbrengsten d m v de intramoleculaire PS condensatie vanuit N_a-butyraldehyde-N_b-alkoxytryptamines Eveneens is het bewijs geleverd dat inderdaad directe nucleofiele aanval vanaf de indool-2 positie op het intermediaire iminium ion tot productvorming in de PS condensatie kan leiden

List of Publications

1 1,3-Dipolar cycloaddition of nitrones with nitriles Scope and mechanistic study Hermkens, P H H , Van Maarseveen, J H , Kruse, C G , Scheeren, J W , *Tetrahedron*, **1988**, 44, 6491

2 Eur Pat 0 401 929 A2, Hermkens, P H H , Van Maarseveen, J H , Scheeren, J W , Kruse, C G to Duphar International Research B V , **1989**

3 Intramolecular Pictet-Spengler reaction of N-alkoxy tryptamines I Synthesis of (±)-Deamino-debromo-Eudistomin L Hermkens, P H H , Van Maarseveen, J H , Kruse, C G , Scheeren, J W , *Tetrahedron Letters*, **1989**, 30, 5009

4 Crystal structure determination of (1*S*,13b*R*)-1-amino-10-methoxy-1,2,7,8,13,13b-hexahydro-[1,6,2]oxathiazepino[2' 3' 1,2]pyrido[3,4-*b*]indole monohydrate, $C_{15}H_{19}N_3O_2S{\cdot}H_2O$ Hermkens, P H H , Van Maarseveen, J H , Bosman, W P , Smits, J M M , Beurskens, P T , *J Cryst Spectr Res* , **1990**, 20, 313

5 Intramolecular Pictet-Spengler reaction of *N*-Alkoxytryptophans and tryptamines 2 Synthesis of corynanthe alkaloid derivatives containing a tetrahydro-1,2-oxazine as the D ring Hermkens, P H H , Van Maarseveen, J H , Berens, H W , Smits, J M M , Kruse, C G , Scheeren, J W , *J Org Chem* , **1990**, 55, 2200

6 Syntheses of 1,3-disubstituted N-oxy-β-carbolines by the Pictet-Spengler reactions of N-oxy-tryptophan and -tryptamine derivatives Hermkens, P H H , Van Maarseveen, J H , Cobben, P L H M , Ottenheijm, H C J ,Kruse, C G , Scheeren, J W , *Tetrahedron*, **1990**, 46, 833

7 Intramolecular Pictet-Spengler reaction of *N*-Alkoxytryptamines 3 Stereoselective synthesis of (-)-debromoeudistomin L and (-)-*O*-methyldebromoeudistomin E and their stereoisomers Hermkens, P H H , Van Maarseveen, J H , Ottenheijm, H C J , Kruse, C G , Scheeren, J W , *J Org Chem* , **1990**, 55, 3998

8 Antiviral and antitumor structure-activity relationship studies on tetracyclic eudistomins Van Maarseveen, J H ,Hermkens, P H H , De Clercq, E , Balzarini, J , Scheeren, J W , Kruse, C G , *J Med Chem* , **1992**, 35, 3223

9 The intramolecular Pictet-Spengler reaction in the synthesis of tetracyclic eudistomins Van Maarseveen, J H , Oberyé, E H , in 't Groen, W H M , Scheeren, J W , Kruse, C G , *9th conference on Organic Synthesis, IUPAC, Montreal*, june **1992**

10 Intramolecular Pictet-Spengler Reaction of N_b-Alkoxytryptamines 4 A study towards diastereocontrol in the synthesis of tetracyclic eudistomins Van Maarseveen, J H , Kruse, C G , Scheeren, J W , *Tetrahedron*, **1993**, 49, 2325

11 Synthesis and receptor-affinity profile of *N*-hydroxytryptamine derivatives for serotonin and tryptamine receptors A molecular-modeling study Dijkstra, G D H , Tulp, M Th M , Hermkens, P H H , Van Maarseveen, J H , Scheeren, J W , Kruse, C G , *Recl Trav Chim.Pays Bas*, **1993**, 112, 131

12 Unexpected transannular neighboring group participations in an attempted diastereoselective approach to tetracyclic eudistomins using the Mitsunobu reaction Van Maarseveen, J H , Oberyé, E H H , Bolster, M B , Beurskens, P T , Smits, J M M , Kruse, C G , Scheeren, J W *Tetrahedron Lett* , in preparation

13 Synthesis of an isoquinoline type eudistomin analog Van Maarseveen, J H , Kruse, C G , Scheeren, J W *Tetrahedron Lett* , in preparation

14 Continued antiviral and antitumor structure-activity relationship studies on tetracyclic eudistomins Van Maarseveen, J H , in 't Groen, W H M , De Clercq, E Balzarini, J , Scheeren, J W , Kruse, C G *J Med Chem* in preparation

15 A mechanistic and synthetic study of the intramolecular Pictet-Spengler condensation in the synthesis of the tetracyclic canthine skeleton Van Maarseveen, J H , Mulders, S J E , Aben, R W M , Kruse, C G , Scheeren, J W *Tetrahedron*, in preparation

16 Conformational analysis of the oxathiazepine ring in eudistomins Van Maarseveen, J H , Beurskens, P T , Smits, J M M , Kruse, C G , Scheeren, J W *Recl Trav Chim Pays Bas*, in preparation

Curriculum Vitae

Jan van Maarseveen werd geboren op 6 februari 1963 te Enschede. In 1981 behaalde hij het HAVO-diploma aan de Scholengemeenschap Zuid te Enschede. In hetzelfde jaar begon hij zijn studie aan de Hogere Laboratorium Opleiding aan de S.V.L te Hengelo (O) waarvan het diploma, met als afstudeerrichting organische chemie, in 1985 behaald werd. Na het vervullen van de militaire dienstplicht is hij van juni 1986 tot juli 1990 werkzaam geweest als organisch chemisch analist op het laboratorium voor organische chemie van de Katholieke Universiteit Nijmegen (KUN) onder leiding van Dr. H.C.J Ottenheijm (1986) en Dr J W Scheeren (1987-1990) Daarnaast is hij in september 1988 gestart met de verkorte studie scheikunde (organische chemie) aan de KUN waarvan het doctoraal examen in augustus 1990 met succes is afgelegd. Van juli 1990 tot oktober 1993 is hij werkzaam geweest als toegevoegd onderzoeker onder leiding van Dr. J W. Scheeren en Dr. C.G. Kruse (Solvay-Duphar B V.) Tijdens deze periode is het in dit proefschrift beschreven onderzoek uitgevoerd. Vanaf 1 maart 1994 is hij in tijdelijke dienst van Solvay-Duphar B V te Weesp