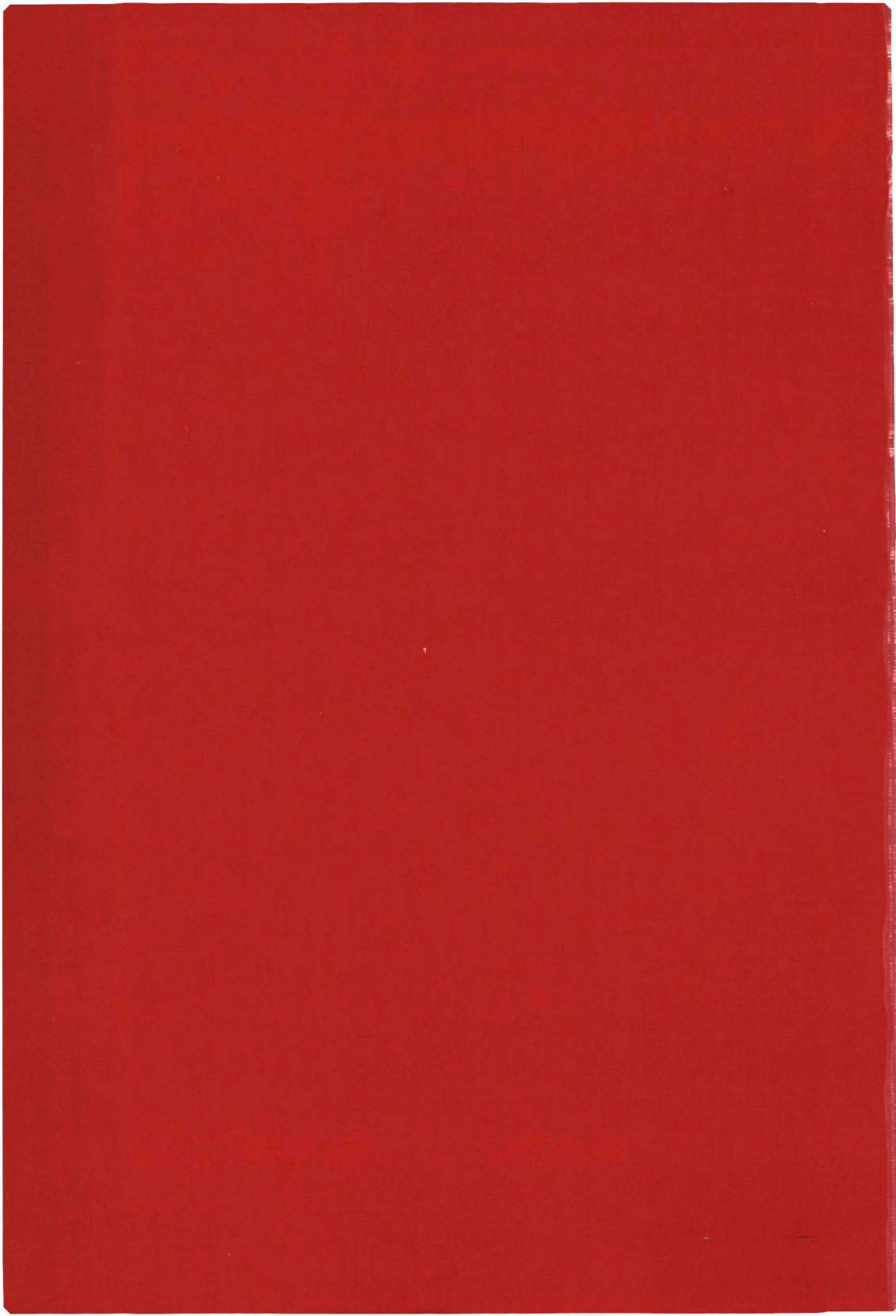


3434

**1,1-Dimethoxypropene
as a Propionate Equivalent
in the Synthesis of γ - and δ -Lactones**

Rob Hofstraat



1,1-DIMETHOXYPROPENE AS A PROPIONATE EQUIVALENT
IN THE SYNTHESIS OF γ - AND δ -LACTONES

ISBN 90-9001650-3

1,1-DIMETHOXYPROPENE AS A PROPIONATE EQUIVALENT
IN THE SYNTHESIS OF γ - AND δ -LACTONES

Proefschrift
ter verkrijging van de graad van doctor
in de wiskunde en natuurwetenschappen
aan de Katholieke Universiteit te Nijmegen,
op gezag van de Rector Magnificus
Prof.Dr. B.M.F. van Iersel
volgens besluit van het College van Decanen
in het openbaar te verdedigen
op donderdag 7 mei 1987
des namiddags te 3.30 uur

door

Robert Gerrit Hofstraat
geboren te Arnhem

Quick Service Drukkerij, Enschede

promotor : Prof.Dr. R.J.F. Nivard

co-referent: Dr. J.W. Scheeren

Voor mijn ouders en Wilma

Bij de voltooiing van dit proefschrift wil ik graag iedereen bedanken die mee heeft gewerkt aan de totstandkoming ervan.

Allereerst gaat mijn erkentelijkheid uit naar mijn ouders, die het mij mogelijk hebben gemaakt deze studie te volgen, en naar Wilma voor de morele en praktische steun.

René Aben wil ik bedanken voor wezenlijke bijdragen aan hoofdstukken 3 en 6 en Wim van Luyn en Wilma voor assistentie bij het tekenwerk. De Analytische Afdeling (Ad, Peter, Peter, Pieter) ben ik erkentelijk voor de vele, snelle analyses. De afdeling Fotografie dank ik voor de verkleining van de schema's en Henny Wigman-Roeffen voor het snelle typewerk en de lay-out.

Tot slot ben ik alle medewerkers van de afdeling Organische Chemie, in het bijzonder die van de kamers 358, 360 en 371, erkentelijk voor de uitstekende sfeer en de collegiale behulpzaamheid.

CONTENTS

CHAPTER I

Introduction	1
Synthesis of ketene acetals	2
Scope of (2+2)-cycloadditions with ketene acetals	2
Mechanistic aspects	4
Synthetic aspects	5
Outline of this investigation	7
References	9

CHAPTER II

Introduction	11
Reactions of 1,1-dimethoxypropene (1a) with benzaldehyde (2a) ...	12
Reactions of 1,1-dimethoxypropene (1a) with other aldehydes R ³ CHO	13
Mechanistic aspects	16
Experimental	18
References	22

CHAPTER III

Introduction	23
Synthetic aspects	25
Stereochemical aspects	26
Experimental	30
References	37

CHAPTER IV

Introduction	39
Synthesis of β -oxygenated aldehydes	40
Synthesis of 4-hydroxy- δ -lactones and 5,6-dihydro-2-pyrones	43
Synthesis of a chiral 5,6-dihydro-2-pyrone	47
Experimental	49
References	59

CHAPTER V

Introduction	61
Reactions of (1) with epoxyketones (5-9)	63
Synthesis of type I lactones	68
Synthesis of lactones of type II	72
Conclusions	74
Experimental	75
References	83

CHAPTER VI

Introduction	85
Stereochemical aspects	87
Synthesis of the monolactones (16), (20)-(23), and the bis-lactone (17) from (1) and glyoxal (13a)	90
Synthesis of bislactones (25) and (27) from (1a) and cisoid 1,2-diketones (14) and (15)	93
Synthesis of the bislactones (40) from a 1,2-dicarbonyl compound in which one of the carbonyl groups is protected or masked	95
Conclusion	99
Experimental	100
References	109
SUMMARY	111
SAMENVATTING	121
CURRICULUM VITAE	131

Introduction

This thesis deals with the application of 1,1-dimethoxypropene (1a) in the synthesis of various types of γ - and δ -lactones. 1,1-Dimethoxypropene is an electron-rich alkene and a representative member of the class of ketene acetals, $R^1R^2C=C(OMe)_2$. All syntheses studied in this thesis have in common that (1a) is used in a cycloaddition with an α - or β -oxygenated carbonyl compound. In this way (1a) functions as a propionate equivalent which is introduced under neutral or mildly acidic conditions. The chemistry of (1a-1c) (Figure 1) and other ketene acetals has been studied in our department for more than ten years, and recently the results obtained have been reviewed¹. Yet, in order to offer good insight into the present work the more important features of ketene acetal chemistry in general and of (1a) in particular are summarized here, before the objectives of the present study are outlined.

Figure 1

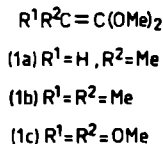
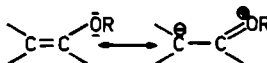


Figure 2

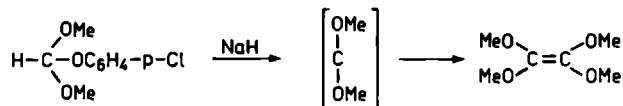


Ketene acetals (1) belong to the electron-rich olefins in which the electron-density of the double bond is increased by one or more electron-donating substituents (*e.g.* -OR, -NR₂). In the case of an enol ether this can be represented by the canonical structures, illustrated in Figure 2, which show that the electron-density is highest on the β -carbon atom. In orbital terms the HOMO's of ketene acetals have high energies and the largest HOMO coefficient is on the β -carbon atom with respect to the electron-donating substituent. The nucleophilicity of ketene acetals is between that of enol ethers and enamines.

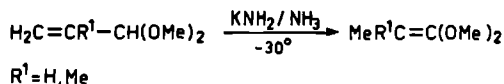
Synthesis of ketene acetals

The detailed study of the chemistry of ketene acetals followed on McElvain's general preparation in 1936 of the compounds $\text{H}_2\text{C}=\text{C}(\text{OR})_2$ by elimination of HX from the corresponding α -halogenated acetals² $\text{H}_2\text{XC}-\text{CH}(\text{OR})_2$. During the following 15 years, the chemistry of these compounds was studied mainly by McElvain and coworkers³. Our laboratory became interested in the chemistry of ketene acetals after we had developed large scale syntheses for tetramethoxyethene (1c)⁴ (Scheme 1) and for ketene acetals (1a) and (1b)⁵ (Scheme 2). Recently

Scheme 1



Scheme 2



van der Gen *et al.*⁶ published a general synthesis of ketene acetals in which the dialkoxymethylene group was introduced *via* a phosphine oxide reagent in a Horner-Emmons reaction.

In general, ketene acetals are very sensitive to moisture and traces of acid. They tend to polymerize at room temperature.

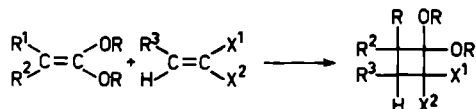
Scope of (2+2)-cycloadditions with ketene acetals

Ketene acetals react with a variety of electrophiles and enophiles⁷. The research in our laboratory is centred on cycloaddition reactions⁸ of these compounds, in particular (2+2)-cycloadditions.

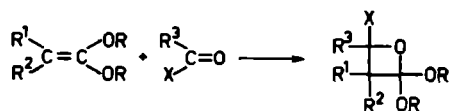
Ketene acetals react with electron-poor alkenes and carbonyl compounds *via* (2+2)-cycloaddition reactions to cyclobutanes (Scheme 3) and oxetanes (Scheme 4), respectively. The reactivity of ketene

acetals in such (2+2)-cycloadditions with electron-poor alkenes is dependent both on the substituents R^1 and R^2 of the ketene acetal and the number of electron-withdrawing groups (X) of the olefin. (1a) Reacts at elevated temperatures with alkenes having at least one electron-withdrawing substituent (*e.g.* $X^1 = \text{CN}, \text{COOMe}$) at the double bond whereas (1c) reacts only with electron-poor alkenes having two electron-withdrawing substituents⁹.

Scheme 3



Scheme 4



Ooms *et al.*¹⁰ have found that carbonyl compounds require at least one electron-withdrawing group at the carbonyl function in order to yield 2,2-dialkoxyoxetanes in the reaction with ketene acetals (Scheme 4).

A major break through came when it was found that in the presence of ZnCl_2 all kinds of aldehydes and even several ketones can be converted in this way⁵ with a variety of ketene acetals. In the presence of this catalyst the polymerisation of ketene acetals is relatively slow. A systematic examination of several Lewis acids showed that two aluminium catalysts, *i.e.* $\text{AlCl}_2\text{OR}^{11}$ and AlCl_2Et , in some cases gave similar results as ZnCl_2 when the reactions were performed at low temperature (-78°C). BF_3 -etherate, AlCl_3 and TiCl_4 appeared too harsh in most cases, resulting in polymerisation of the ketene acetals¹².

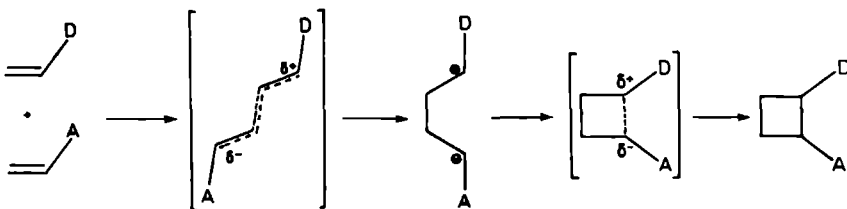
The use of the Lewis acid ZnCl_2 strongly extends the scope of the reactions of ketene acetals and electron-poor alkenes. With ZnCl_2 catalysis simple electron-poor alkenes having only one elec-

tron-withdrawing group (*i.e.* $X^1 = \text{COOMe}$, $X^2 = \text{H}$, Scheme 3) can be readily converted into cyclobutane derivatives¹³.

Mechanistic aspects

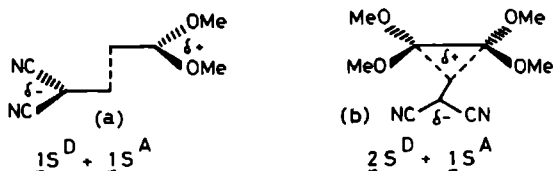
The mechanism and stereochemistry of the (2+2)-cycloaddition reactions of ketene acetals have recently been studied in the cyclobutane formation of dicyanostyrenes¹⁴. This study showed that the generally accepted mechanism for polar, thermal (2+2)-cycloadditions, in which a cisoid dipolar intermediate¹⁵ is an essential feature (Scheme 5), has to be refined for the reactions of ketene acetals.

Scheme 5



It appeared that the F.M.O. theory¹⁶ can explain the obtained results adequately. According to this theory two limiting geometries of addend approach are possible in the reaction of electron-rich alkenes with electron-poor compounds having the higher LUMO coefficient on the β -carbon atom (Figure 3). The $1S^D + 1S^A$ approach is preferred by ketene acetals having a much larger HOMO coefficient on C(β) than on C(α) (*e.g.* (1a)). The $2S^D + 1S^A$ approach becomes more probable

Figure 3



when the difference between the HOMO coefficients becomes smaller. In this case (*e.g.* (1c)) the developing charges at the dipolar ends arise rather close together and subsequent rotation and ring closure to the cyclobutane is much faster than other reactions of the dipolar intermediate. The energy profile must have a rather broad and flat maximum, so that a dipolar intermediate, if occurring, should be a short-lived species. In the $1S^D + 1S^A$ approach, the unsymmetrically substituted cycloaddends start their interaction in a *trans* arrangement¹⁷. The developing charges are far apart and have to rotate around the primary formed C-C bond into a cisoid *gauche* conformation for completion of the cyclobutane formation.

Conclusively, it can be stated that both the stereochemical outcome of the cyclobutane formation and the stabilities of the obtained cyclobutanes are determined by the π -electron distribution of the ketene acetals used; most stable cyclobutanes are obtained from (1c), having a symmetrical π -electron distribution and a high HOMO energy.

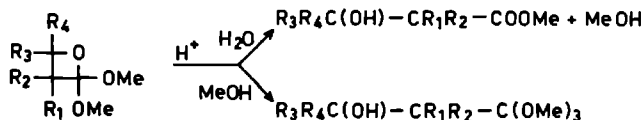
It is to be expected that the reactions of ketene acetals with carbonyl compounds also proceed *via* dipolar intermediates. Generally, the reaction of (1a) with aldehydes leads to mixtures of *cis* and *trans* oxetanes, and on the basis of preliminary experiments (*e.g.* with benzaldehyde) it was expected that *cis* oxetanes are the main products when the reactions are performed under kinetic conditions and that *trans* oxetanes are obtained in excess under thermodynamic conditions.

Synthetic aspects

This thesis deals only with the reaction of ketene acetals and carbonyl compounds. Therefore, the synthetic aspects of the cyclobutane formation will not be discussed here; an overview of these aspects is presented in reference 1.

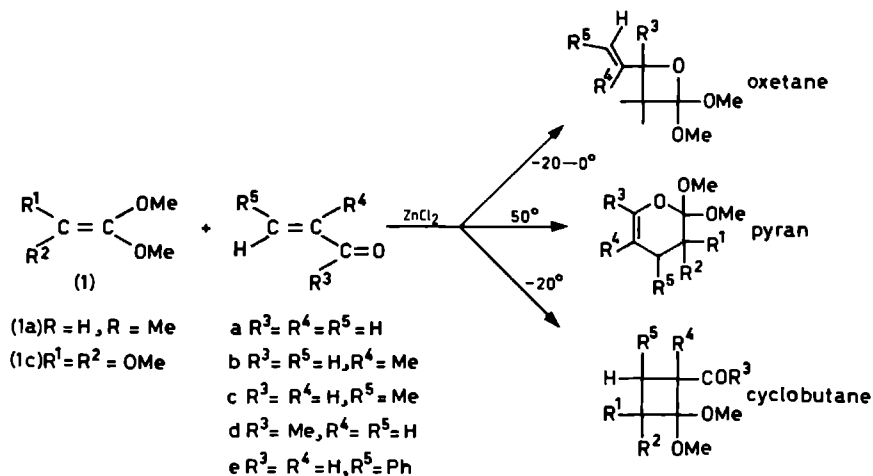
At first, the use of the 2,2-dialkoxyoxetanes was restricted to hydrolysis and methanolysis. Since oxetanes are reactive cyclic orthoesters, reactions with water or alcohols are easily accomplished (Scheme 6). They yield β -hydroxyesters and β -hydroxyorthoesters in which the stereochemistry of the oxetane formation is maintained.

Scheme 6



The use of weak Lewis acids as ZnCl_2 or AlCl_3OR results in a high chemical selectivity in the conversion of carbonyl compounds with ketene acetals. Aldehydes are selectively converted in the presence of ketones and other functions, which might react in the presence of acids (*e.g.* an epoxy function), are not affected. This principle was nicely demonstrated by Bakker *et al.* who investigated the reactions of ketene acetals with α,β -unsaturated aldehydes¹⁹. A priori three different cycloproducts are possible (Scheme 7)

Scheme 7

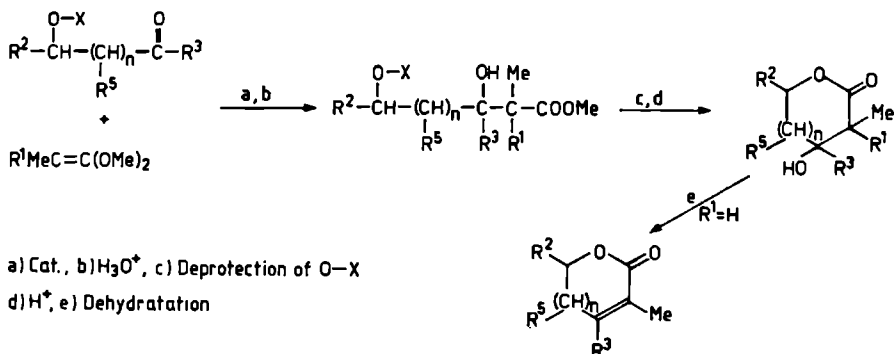


and competition between the various routes was observed. Generally, however, the formation of the different products could be controlled.

Outline of this investigation

The high chemical selectivity of the 2,2-dialkoxyoxetane synthesis and the ease of the conversion of these oxetanes into the corresponding β -hydroxyesters was the motive to start an investigation into the synthesis of γ - and δ -lactones. The presence of a protected hydroxy function in the starting aldehyde or ketone might enable the synthesis of various types of lactones after hydrolysis of the oxetane and deprotection of the hydroxy function (Scheme 8); protection of the hydroxy function is necessary, since, as already argued, ketene acetals react with alcohols (*vide infra*).

Scheme 8



In order to test this concept we planned reactions of several types of protected hydroxy aldehydes and -ketones with 1,1-dimethoxypropene (1a).

Ketene acetal (1a) can be considered as an equivalent of the enolate of propionic acid methyl ester. Recently, a lot of research has been done on the subject of stereoselective aldol reactions²⁰ with, among other synthons, propionate equivalents. Since a lot of natural products can be considered as constructed from propionate

equivalents (polypropionates)²⁰, there is a large interest in reactions of all sorts of propionate equivalents. As shown in Scheme 8 the use of (1a) would result in lactone rings having a methyl group in the α -position; this is often encountered in naturally occurring lactones²¹. As Grieco²² presented a method to convert such α -methyl groups into an α -methylene function, the use of (1a) might give access to naturally occurring α -methylene lactones. The use of (1a) has additional advantages: it is easily available on large scale (ca. 100 ml) and it has a high reactivity.

In the present work the (2+2)-cycloaddition of (1a) with various types of aldehydes and ketones, leading to 2,2-dimethoxyoxetanes, is the key-reaction of all the lactone syntheses. Therefore, first the stereochemical outcome of the oxetane formation and the effect of α -substituents in aldehydes on the stereochemistry of these reactions were examined, as has been described in chapter 2. Chapter 3 deals with the reaction of α -acyloxyaldehydes and -ketones with (1a) and with the conversion of the resulting products to 2,2-dimethoxy-4-hydroxy-3-methyltetrahydrofurans, 4-hydroxy-3-methyl- γ -butyrolactones and 2-butenolides. In chapter 4 the syntheses of 4-hydroxy- δ -lactones and 5,6-dihydropyrones from β -oxygenated aldehydes are described. Chapter 5 extends the concept to reactions of (1a) with α,β -oxygenated ketones, *viz.* epoxyketones. These reactions are aggravated to the synthesis of possible precursors of eudesmanolides. Chapter 6 describes the efforts to synthesize bis- γ -lactones from (1a) and the bis-aldehyde glyoxal, 1,2-diketones or ketoaldehydes in which one carbonyl group is masked or protected. A summary concludes this thesis.

References

1. J.W. Scheeren, *Recl. Trav. Chim. Pays-Bas*, 1986, 105, 71.
2. F. Beyerstadt and S.M. McElvain, *J. Am. Chem. Soc.*, 1936, 58, 529.
3. S.M. McElvain, *Chem. Rev.*, 1949, 45, 453.
4. J.W. Scheeren, R.J.F. Staps and R.J.F. Nivard, *Recl. Trav. Chim. Pays-Bas*, 1973, 92, 11.
5. J.W. Scheeren, R.W.M. Aben, P.H.J. Ooms and R.J.F. Nivard, *J. Org. Chem.*, 1977, 42, 3128.
6. T.A.M. van Schaik, A.V. Henzen and A. van der Gen, *Tetrahedron Lett.*, 1983, 24, 1303.
7. Houben-Weyl, 'Methoden der Organische Chemie', ed. E. Mueller, Thieme Verlag, Stuttgart, 1968, Band IV/4, 4. Aufl.
8. a. C.G. Bakker, Thesis, K.U. Nijmegen, 1983.
b. P.H.J. Ooms, Thesis, K.U. Nijmegen, 1976.
9. P.H.J. Ooms, J.W. Scheeren and R.J.F. Nivard, *Synthesis*, 1975, 260.
10. P.H.J. Ooms, J.W. Scheeren and R.J.F. Nivard, *J. Chem. Soc. Perkin I*, 1976, 1048.
11. R.W.M. Aben and H.W. Scheeren, *Synthesis*, 1982, 779.
12. R.W.M. Aben and J.W. Scheeren, unpublished results.
13. J.W. Scheeren and A.E. Frissen, *Synthesis*, 1983, 794.
14. J.W. Scheeren, A.J.R. van Rossum and R.J.F. Nivard, *Tetrahedron*, 1983, 39, 1345.
15. R. Huisgen, *Acc. Chem. Res.*, 1979, 10, 117; 199.
16. a. K.N. Houk in 'Pericyclic Reactions', eds. A.P. Marchand and R.E. Lehr, Academic Press, New York, 1977, vol. II.
b. I.F. Fleming, 'Frontier Orbitals and Organic Chemical Reactions', Wiley, London, 1976.
17. M.D. Epiotis, R.L. Yates, D. Carlberg and F. Bernardi, *J. Am. Chem. Soc.*, 1976, 98, 453.
18. R.W.M. Aben and J.W. Scheeren, *Synthesis*, 1978, 401.
19. C.G. Bakker, J.W. Scheeren and R.J.F. Nivard, *Recl. Trav. Chim. Pays-Bas*, 1981, 100, 13.

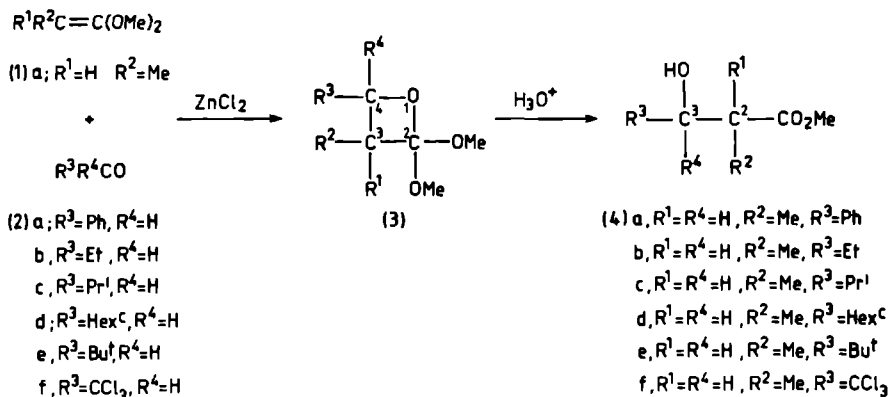
20. a. C.H. Heathcock in 'Asymmetric Synthesis', ed. J.D. Morrison, Academic Press, New York, 1984, vol. 3B.
b. S. Danishefsky and D.F. Harvey, *J. Am. Chem. Soc.*, 1985, 107, 6647.
21. a. Y.S. Rao, *Chem. Rev.*, 1976, 76, 625.
b. N.H. Fischer, E.J. Olivier and H.D. Fischer, in 'Prog. Chem. Org. Nat. Prod.', ed. L. Zechmeister, Springer Verlag, Wien, 1979, 38, 47.
22. P.A. Grieco and M. Nishizawa, *J. Org. Chem.*, 1977, 42, 1717.

Stereochemistry of the Reaction of 1,1-Dimethoxypropene with Aldehydes

Introduction

In previous papers¹⁻⁴ we have demonstrated the synthetic utility of cycloadditions between ketene acetals ($R^1R^2C=C(OMe)_2$ (1) and carbonyl compounds R^3R^4CO (2). In the presence of a Lewis acid (*e.g.* $ZnCl_2$) a variety of carbonyl compounds can be converted in this way into 2,2-dimethoxyoxetanes (3) under mild conditions. These cycloadducts can easily be hydrolysed into β -hydroxyesters¹ (4), or into lactones^{2,3} (*e.g.* γ -butyrolactones) when a suitably protected hydroxy group is present in R^3 (Scheme 1).

Scheme 1

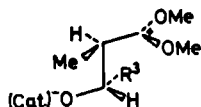


The chemical selectivity of the cycloadditions is rather high. Aldehydes can be converted selectively in the presence of other carbonyl compounds, olefinic double bonds, or substituents which are sensitive to nucleophilic attack. With α,β -unsaturated aldehydes

These results have been published in *J. Chem. Soc. Perkin I*, 1985, 561.

an oxetane is in most cases the primary product when the reaction is performed at low temperature⁵.

The stereoselectivity of the cycloadditions is apparent in reactions of unsymmetrically substituted carbonyl compounds (*e.g.* aldehydes) with ketene acetals in which R¹ and R² are different, *e.g.* 1,1-dimethoxypropene (1a). In previous studies on these reactions, of the two possible *cis-trans* isomers of the oxetane one was favoured as the main product. We supposed that the *cis* oxetane would always be formed in excess, because it arises *via* the more favourable transoid approach of the reactants leading to the *anti* conformation (Figure). Further experiments showed, however, that



the stereochemistry of the reactions depends on the reaction conditions used. Therefore, the stereochemical course of the reactions of (1a) with several aldehydes has now been studied under different conditions.

Reactions of 1,1-Dimethoxypropene (1a) with Benzaldehyde (2a)

In the cycloadditions with benzaldehyde the *cis:trans* ratio in the product mixture can easily be determined from the ¹H n.m.r. spectrum in which the 4-H absorptions are well separated ($\delta_{\text{H}(cis)}$ 5.27, $\delta_{\text{H}(trans)}$ 4.65). Equimolar solutions of benzaldehyde (2a) and (1a) (5.0 mmol) in diisopropyl ether (15 ml) were treated at -78°C with such an amount of AlCl₂Et or AlCl₂Obornyl⁶ that 20% conversion had been reached in 2 min. At that time the reaction was stopped by the addition of triethylamine (TEA) and the product ratio was determined: *cis:trans* 80:20 with AlCl₂Obornyl, 70:30 with AlCl₂Et.

A similar experiment, using ZnCl₂ as the catalyst, was performed at -15°C, because the reaction rate decreases substantially below -20°C with this less acidic catalyst⁷. The *cis:trans* ratio in this experiment was 85:15. Apparently, the nature of the catalyst has no important influence on the product ratio.

It appeared, however, that the *cis:trans* ratio in these experiments is reduced when the product yield is increased by prolongation of the reaction time. Table 1 gives *cis:trans* ratios and

percentages of conversion after several time intervals for the reaction of equimolar amounts (5.0 mmol) of benzaldehyde (2a) and (1a) at -78°C in the presence of 1 mol% of AlCl_2Et . Ultimately the product ratio is completely reversed.

Table 1: *cis-trans* Ratios and percentages of conversion as a function of time for the reaction of benzaldehyde (2a) and 1,1-dimethoxypropene (1a) at -78°C in diisopropyl ether, using AlCl_2Et as catalyst.

Time (min)	0.5	5	20	60	120
<i>cis:trans</i> Ratio	80:20	65:35	60:40	45:55	30:70
Conversion (%)	40	50	60	70	70

The results suggest that the *cis* oxetane is the kinetically and the *trans* oxetane the thermodynamically determined product. The latter can be expected to be the main product under circumstances which enable the catalyst to effect strong equilibration of the *cis* and *trans* oxetane.

Indeed, treatment of equimolar amounts of benzaldehyde (2a) and (1a) (5 mmol) dissolved in 1 ml of the polar solvent acetonitrile, at room temperature, for 2 h with a saturated solution of ZnCl_2 gave again a large excess of the *trans* oxetane over the *cis* oxetane (overall yield 75%, *cis:trans* ratio 1:4).

Preparation of the *cis* oxetane in high yield is apparently not possible. Even at low temperature (-78°C , using AlCl_2Et) and in a non-polar solvent the initially large *cis:trans* ratio is already reduced after relatively short reaction times, before the reaction has been completed.

Reactions of 1,1-dimethoxypropene (1a) with other aldehydes R^3CHO

In order to establish a possible influence of the residue R in the aldehyde on the *cis:trans* ratio, oxetane formation was investigated with a series of aldehydes (2b-f). The reactions were performed: (i) under thermodynamic conditions: equimolar (2.5 M) solution of the reactants in acetonitrile, ZnCl_2 as the catalyst, 2 h at room temperature; (ii) under 'kinetic' conditions: an equimolar (0.3 M) solution of the reactants in diisopropyl ether, AlCl_2Et

as the catalyst, 15 min at -35°C . Because of the lower reactivity of some of the aldehydes in comparison with benzaldehyde (2a), standardization of the circumstances at lower temperature was not possible. In both cases the reactions were stopped by the addition of TEA.

In some cases (aldehydes without a proton at C- α) determination of the *cis:trans* ratio could be based on the difference between the doublets of the 4-H proton⁴ in the ^1H n.m.r. spectrum of the *cis:trans* mixture (J_{cis} ca. 8 Hz, J_{trans} ca. 6 Hz). With the other aldehydes these signals cannot easily be assigned to the individual isomers either because of further splitting by protons in R^3 or because the 3-H and 4-H absorptions are hidden under other resonances.

Since separation of the isomers by distillation would change the *cis:trans* ratio, and separation by chromatography leads to hydrolysed products, the product mixture was then subjected to methanolysis at -78°C and the resulting acyclic orthoesters were hydrolysed at room temperature with dilute hydrochloric acid into β -hydroxyesters $\text{R}^3\text{CH}(\text{OH})\text{CH}(\text{Me})\text{CO}_2\text{Me}$ (4; $\text{R}^1 = \text{R}^4 = \text{H}$, $\text{R}^2 = \text{Me}$). In this way the *cis* oxetane gives an *erythro*, the *trans* oxetane a *threo* β -hydroxyester. Determination of the *erythro:threo* ratio from ^1H n.m.r. spectra can be based on the 2-H or 3-H signal because of the large difference between the 2-H-3-H coupling constants⁸ (J 7-8 Hz for *threo*, 2-3 Hz for *erythro* compounds); the 2-H signal often appears as a quintet for *threo* compounds and as a double quartet for *erythro* compounds. The *erythro:threo* ratios in the β -hydroxyesters can also be determined by separation of the isomers by h.p.l.c. In those cases where *cis:trans* as well as *erythro:threo* ratios could be determined, agreement between the results showed that the hydrolytic procedure did not alter the product ratio seriously.

The results of these experiments are given in Table 2. Product ratios of cycloadditions with benzaldehyde (2a) have been included for comparison.

TABLE 2 Product ratios of reactions between aldehydes (2) and 1,1-dimethoxypropene (1a) under different conditions

Aldehyde	Thermodynamic conditions				'Kinetic' conditions			
	<i>cis:trans</i> Ratio of oxetanes (3)	<i>erythro:threo</i> Ratio of β -hydroxy esters		Yield of β -hydroxy ester (4) (%)	<i>cis:trans</i> Ratio of oxetanes (3)	<i>erythro:threo</i> Ratio of β -hydroxy esters		Yield of β -hydroxy ester (4) (%)
	($^1\text{H-NMR}$)	($^1\text{H-NMR}$)	(HPLC)		($^1\text{H-NMR}$)	($^1\text{H-NMR}$)	(HPLC)	
(2a) PhCHO	20:80	20:80	15:85	70	60:40	60:40	65:35	60
(2b) EtCHO		45:55		70		50:50		65
(2c) Pr ⁱ CHO		5:95		65		45:55		60
(2d) Ben ^o CHO	5:95	5:95	5:95	70		50:50	50:50	70
(2e) Bu ⁱ CHO	5:95	5:95	5:95	50	50:50	45:55	40:60	50
(2f) CCl ₃ CHO	25:75	25:75	25:75	80	25:75	25:75	25:75	50

Table 2 reveals that under equilibrating conditions the oxetane is always the main product. With most aldehydes the cycloaddition provides a useful procedure for the stereoselective preparation of *threo* β -hydroxyesters in good yields. A low stereoselectivity is only found in the cycloaddition of EtCHO (2b). Because of the absence of branching at C- α the difference in thermodynamic stability of the *cis* and *trans* oxetane must be relatively small.

The *cis:trans* ratio, obtained with chloral (2f), is notable because for the bulky residue CCl₃ we expect an extreme preference for the *trans* isomer on equilibration. Moreover, the ratio is equal to that found under 'kinetic' conditions. It appeared that the same product ratio (30:70) was obtained on treating chloral (2f) and (1a) in acetonitrile for 2 h without the addition of a catalyst. Besides, the ratio did not alter when the mixture was left at room temperature for a longer period. On the other hand heating of this mixture (with or without a catalyst) to 70°C for 2 h gave the *trans* oxetane as the sole product. Apparently, equilibration of the oxetane of chloral (2f) and (1a) proceeds very slowly, so that even in a polar solvent at room temperature the product ratio after long reaction times is mainly kinetically determined.

Under 'kinetic' conditions high stereoselectivity cannot easily be realised with most of the aldehydes. This can be ascribed to increasing equilibration during the progress of the reaction in those cycloadditions in which the kinetically and thermodynamically determined products are different, as was demonstrated in the experiments with benzaldehyde (2a). This is not always the case,

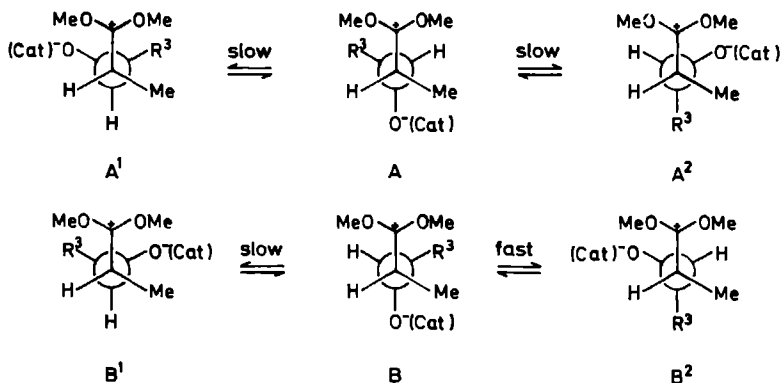
however; the kinetically determined cycloadduct of chloral (2f) and (1a) appeared to be the more stable adduct. Therefore, in some cases the low stereoselectivity under kinetic conditions may be due to a small difference between the rate constants for the formation of the *cis* and *trans* adduct. In the next section it is argued that this can be expected in cycloadditions of aldehydes having large residues R^3 .

Mechanistic aspects

It is generally accepted¹ that the oxetane formation from electron-donating ketene acetals and electron-accepting carbonyl compounds proceeds in two steps *via* a dipolar intermediate. In cycloadditions of ketene acetals like 1,1-dimethoxypropene (1a), in which the HOMO coefficient on C- β is much larger than on C- α , the preferred geometry of addend approach is according to FMO theory⁹ as indicated in the Figure. The transoid approach of the reactants leads to a dipolar intermediate in which the charges are far apart¹⁰, and the oxetane formation requires, in a second step, rotation around the primary formed C-C bond to a cisoid *gauche* conformation.

The transoid approach of the unsymmetrically substituted alkene dimethoxypropene and an aldehyde will lead to two intermediates A and B (Scheme 2). Because of less crowding, stereoisomer A, having

Scheme 2: Newman projections of dipolar intermediates A and B.



R^3 and Me in an *anti* relationship, will be of lower energy. Therefore, the *cis* oxetane resulting from A will be the kinetically determined product, when the formation of the intermediate is rate determining.

Bond rotation in the second step, leading to a *cisoid gauche* conformation, is possible in two directions. Starting from A both rotations are accompanied with an increase of crowding. With B, however, rotation into B" leads to release of crowding. The formation of a *trans* oxetane from B will, therefore, be easier than the conversion of A into a *cis* oxetane. In those cases in which the second step is rate determining the *trans* adduct may even become the kinetically determined product. The occurrence of the transition state of the overall reaction in the second step is more probable when R^3 is a large group. So the formation of the *trans* oxetane as the main product for $R^3 = CCl_3$ under circumstances in which the cycloaddition is not reversible can be explained. The low stereoselectivity of the cycloadditions of aldehydes in which R^3 is a secondary or tertiary alkyl residue might also be due to a dependence of the product ratio on both reaction steps. The stereochemistry of product formation in the related reactions of ketene acetals with dicyanostyrene has previously been explained in a similar way¹¹.

Experimental

General methods

M.p.s are uncorrected. ^1H n.m.r. spectra were recorded on a Bruker 90 Mz spectrometer in CDCl_3 solution with SiMe_4 as internal reference. All OH resonances could be exchanged with D_2O . Mass spectra were obtained with a VG 7070E mass spectrometer. Preparative h.p.l.c. was performed on a Miniprep LC Jobin Yvon apparatus using Merck silica gel 60H as stationary phase. Acetonitrile and diisopropyl ether were stored over CaH_2 . Ether refers to diethylether. 1,1-Dimethoxypropene (1a) was prepared as described in the literature¹. AlCl_3Et was commercially available as a 25% standard solution in hexane (Alfa products) and was diluted with ether, previously dried over LiAlH_4 , to a 0.3 M ether-hexane solution before use. $\text{AlCl}_3\text{Obornyl}$ was prepared as described in the literature⁶.

Preparation of β -hydroxyesters, $\text{R}^3\text{CH}(\text{OH})\text{CH}(\text{Me})\text{CO}_2\text{Me}$ from aldehydes R^3CHO and (1a) via the corresponding oxetanes

(a) Experiments under 'kinetic' conditions, general procedure

To a vigorously stirred mixture of the aldehyde (5 mmol) and 1,1-dimethoxypropene (1a) (0.56 g, 5.5 mmol) in diisopropyl ether (15 ml) was added AlCl_3Et (1 ml of a 0.3 M solution) at the temperature indicated in the text. After 15 min the reaction was terminated by the addition of triethylamine (0.5 ml) and the reaction mixture was allowed to come to room temperature. After evaporation of the solvent *n*-pentane (ca. 30 ml) was added until a light precipitate was formed. The precipitate was filtered off. Evaporation of the solvent gave the crude oxetane.

To obtain the β -hydroxyesters (4; $\text{R}^1 = \text{R}^4 = \text{H}$, $\text{R}^2 = \text{Me}$) the crude oxetane was dissolved in diisopropyl ether (15 ml) and stirred and cooled to -78°C . A mixture of methanol (0.48 g, 15 mmol) and toluene-*p*-sulphonic acid monohydrate (pinpoint, ca. 15 mg) was added. The reaction mixture was kept at -78°C for 1 h, and then allowed to come to room temperature. To the stirred mixture was added hydrochloric acid (10 ml of a 1 M solution) and the mixture was stirred

for 1 h. After addition of brine (25 ml) the diisopropyl ether layer was separated and the aqueous layer was extracted with ether (3 x 25 ml). The combined ethereal extracts were dried (MgSO_4) and the solvent was evaporated to give the β -hydroxyester as a faint yellow oil. Preparative h.p.l.c. using chloroform-acetonitrile (99:1) yielded the pure diastereoisomers.

In the case of chloral (2f) the aldehyde (5.0 mmol) was dissolved in diisopropyl ether (15 ml) and the solution was cooled to -35°C . 1,1-Dimethoxypropene (1a) (0.56 g, 5.5 mmol) was dissolved in diisopropyl ether (1 ml) and the solution was added to the cooled solution of the aldehyde without a catalyst. Work-up was performed as described above.

(b) *Experiments under thermodynamic conditions, general procedure*

To a stirred mixture of the aldehyde (5.0 mmol) and 1,1-dimethoxypropene (1a) (0.56 g, 5.5 mmol) in acetonitrile (1 ml) was added ZnCl_2 (1 ml of a saturated solution in acetonitrile) at room temperature; in some cases immediate cooling with an ice-bath was necessary. After the addition of ZnCl_2 the mixture was left for 2 h whilst being vigorously stirred. Triethylamine (0.5 ml) was then added and the solvent was evaporated off. *n*-Pentane (ca. 30 ml) was added until a light precipitate was formed; the precipitate was filtered off. Evaporation of the solvent gave the crude oxetane. To obtain the β -hydroxyesters the same procedure as previously described was followed. In the case of chloral (2f) again no catalyst was used; a solution of the aldehyde (5.0 mmol) in acetonitrile (1 ml) was mixed at room temperature with a solution of 1,1-dimethoxypropene (1a) (0.56 g, 5.5 mmol) in acetonitrile (1 ml) and worked up as described above.

All β -hydroxyesters were characterized by ^1H n.m.r., mass spectroscopy, and C,H-analyses, or by comparison with literature data. The following esters were prepared.

Methyl 3-hydroxy-2-methyl-3-phenylpropanoate (4a), *threo*: m.p. 49–50°C (lit.³: 52°C) (Found: C, 68.1; H, 7.25%; M^+ +1, 195.1028. Calc. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27%; M +1, 195.1021); m/z 195 (M +1, 16%), 194 (M , 6), 177 (M -OH, 100), 163 (M -OMe, 7), 121 (75); δ_H : see supplementary material cited in ref. 13. *erythro*: δ_H ($CDCl_3$) 1.12 (3H, d, J 7 Hz, Me), 2.78 (1H, dq, J 7 and 3 Hz, 2-H), 2.94 (1H, br.s, OH), 3.66 (3H, s, OMe), 5.08 (1H, d, J 3 Hz, 3-H), 7.30 (5H, br.s, Ph).

Methyl 3-hydroxy-2-methylpentanoate (4b), diastereomeric mixture: (Found: M^+ +1, 147.1016. Calc. for $C_7H_{14}O_3$: M +1, 147.1021); m/z 147 (M +1, 100%), 129 (M -OH, 100), 115 (M -OMe, 50); δ_H ($CDCl_3$) 0.97 (3H, br.t, J 7 Hz, 5- H_3), 1.18 and 1.21 (3H, 2d, J 7 Hz, Me), 1.30–1.78 (2H, m, 4- H_2), 2.46 (1H, s, OH), 2.36–2.70 (1H, m, 2-H), 3.43–3.90 (1H, m, 3-H), 3.70 (3H, s, OMe).

Methyl 3-hydroxy-2,4-dimethylpentanoate (4c), *threo*: (Found: M^+ +1, 161.1168. Calc. for $C_8H_{16}O_3$: M +1, 161.1178); m/z 161 (M +1, 15%), 147 (24), 143 (M -OH, 82), 129 (M -OMe, 100), 127 (25), 111 (M -CO₂Me, 13); δ_H see supplementary material cited in ref. 13.

Methyl 3-cyclohexyl-3-hydroxy-2-methylpropanoate (4d), *threo*: (Found: C, 65.76; H, 10.15%; M^+ +1, 201.1494. Calc. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07%; M +1, 201.1491); m/z 201 (M +1, 100%), 200 (M , 1), 184 (50), 183 (M -OH, 100), 169 (M -OMe, 15), 151 (47); δ_H see supplementary material cited in ref. 13. *Erythro*: δ_H ($CDCl_3$) 0.71–2.18 (11H, m, Hex^C), 1.16 (3H, d, J 7 Hz, Me), 2.44 (1H, br.s, OH), 2.68 (1H, dq, J 7 and 3.3 Hz, 2-H), 3.64 (1H, dd, J 7.6 and 3.3 Hz, 3-H), 3.69 (3H, s, OMe).

Methyl 3-hydroxy-2,4,4-trimethylpentanoate (4e), *threo*: (Found: M^+ +1, 175.1339. Calc. for $C_9H_{18}O_3$: M +1, 175.1334; m/z 175 (M +1, 100%), 175 (M , 1), 159 (M -Me, 40), 157 (M -OH, 100), 155 (16), 145 (15), 143 (M -OMe, 50); δ_H see supplementary material cited in ref. 13. We found, however, a smaller value for the 2-H-3-H coupling

constant: J 2 Hz*. *Erythro*: δ_{H} (CDCl₃) 0.95 (9H, s, Bu^t), 1.23 (3H, d, J 7 Hz, Me), 2.22 (1H, br.s, OH), 2.75 (1H, dq, J 7 Hz and 4.5 Hz*, 2-H), 3.68 (3H, s, OMe); 3-H resonance hidden under ester resonance.

Methyl 4,4,4-trichloro-3-hydroxy-2-methylbutanoate (4f), *threo*:

m.p. 81-91°C. (Found: C, 30.75; H, 3.8%; M⁺+1, 234.9692. C₆H₉Cl₃O₃ requires C, 30.60; H, 3.85%; M+1, 234.9696); m/z 235 (M+1, 48%), 203 (M-OMe, 24), 201 (37), 177 (100), 117 (M-CCl₃, 30); δ_{H} (CDCl₃) 1.47 (3H, d, J 7 Hz, Me), 3.31 (1H, dq, J 7 and 2 Hz*, 2-H), 3.73 (3H, s, OMe), 4.06 (1H, d, J 2 Hz, 3-H), 5.39 (1H, s, OH).

Erythro: δ_{H} (CDCl₃) 1.40 (3H, d, J 7 Hz, Me), 3.31 (1H, dq, J 7 and 5 Hz*, 2-H), 3.23 (1H, br.s, OH), 3.73 (3H, s, OMe), 4.66 (1H, d, J 5 Hz, 3-H).

*These observed values for the *erythro* and *threo* coupling constants are a notable example in which the *threo* coupling constant is smaller than that of the *erythro* due to the presence of bulky tertiary groups (see ref. 9b).

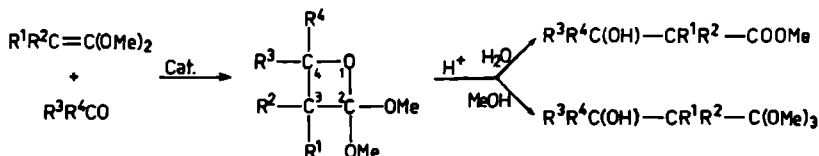
References

1. J.W. Scheeren, R.W. Aben, P.H.J. Ooms and R.J.F. Nivard, *J. Org. Chem.*, 1977, 42, 3188.
2. R.W. Aben, R.G. Hofstraat and J.W. Scheeren, *Recl. Trav. Chim. Pays-Bas*, 1981, 100, 355.
3. R.W. Aben and J.W. Scheeren, *Synthesis*, 1978, 401.
4. R.W.M. Aben and H.W. Scheeren, *Tetrahedron Lett.*, 1983, 24, 4613.
5. C.G. Bakker, J.W. Scheeren and R.J.F. Nivard, *Recl. Trav. Chim. Pays-Bas*, 1981, 100, 13.
6. R.W. Aben and H.W. Scheeren, *Synthesis*, 1982, 779.
7. M.T. Reetz, K. Kessler and A. Jung, *Tetrahedron Lett.*, 1984, 25, 729.
8. a. H.O. House, D.S. Crumrine, A.Y. Teranishi and H.I. Olmstead, *J. Am. Chem. Soc.*, 1973, 95, 3310.
b. C.H. Heathcock, M.C. Pirrung and J.E. Sohn, *J. Org. Chem.*, 1979, 44, 4294.
9. K.N. Houk, in 'Pericyclic Reactions', eds. A.P. Marchand and R.E. Lehr, Academic Press, New York, 1977, vol. II; I. Fleming, 'Frontier Orbitals and Organic Chemical Reactions', Wiley, London, 1976.
10. N.D. Epiotis, R.L. Yates, D. Carlberg and F. Bernardi, *J. Am. Chem. Soc.*, 1976, 98, 453.
11. H.W. Scheeren, A.J.R. van Rossum and R.J.F. Nivard, *Tetrahedron*, 1983, 39, 1345.
12. A.I. Meyers and P.J. Reider, *J. Am. Chem. Soc.*, 1979, 101, 2501.

A Simple and General Method for the Preparation of
4-Hydroxy- γ -Butyrolactones and 2-Butenolides from
1,1-Dimethoxypropene and α -Acyloxy Aldehydes and Ketones

Introduction

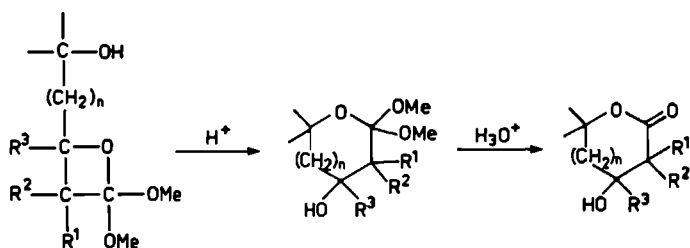
In a previous paper¹ we reported that aldehydes and ketones react with ketene acetals under very mild conditions in the presence of ZnCl_2 to yield 2,2-dimethoxyoxetanes (Scheme 1). The reaction shows relatively large solvent effects, is strongly influenced by the electronic properties of the residues R^3, R^4 at the carbonyl group and is thought to proceed *via* a dipolar intermediate. Hydrolysis or alcoholysis² of the 2,2-dimethoxyoxetanes under acidic conditions delivers β -hydroxyesters or β -hydroxyorthoesters (Scheme 1).

Scheme 1

The formation of β -hydroxyesters and β -hydroxyorthoesters suggests a possible route to cyclic orthoesters and lactones by ring enlargement of the oxetanes when the acid treatment is applied to oxetanes having a hydroxy group in one of the side chains (Scheme 2). The reaction sequence of Scheme 2 thus would provide an attractive route to *e.g.* 2,2-dimethoxy-tetrahydrofurans or -pyrans in the case of $n = 0$ or 1, respectively. We now present our results of applying this method for $n = 0$.

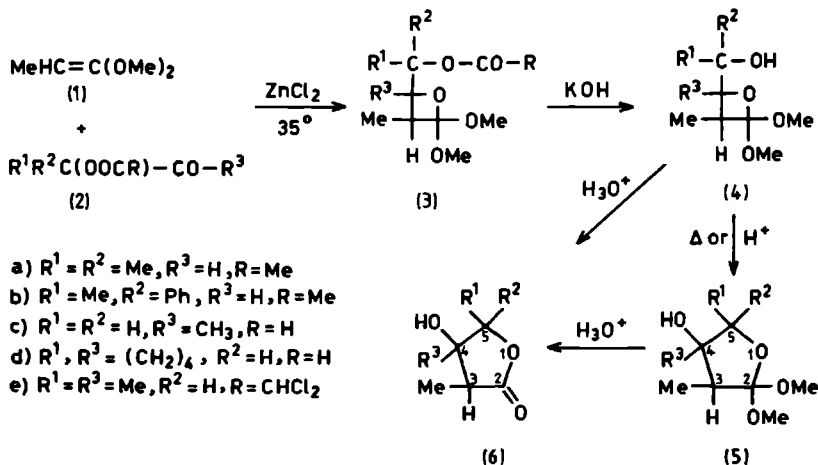
Major parts of these results have been published in *Recl. Trav. Chim. Pays-Bas*, 1981, 100, 355.

Scheme 2



Since ketene acetals react rapidly with alcohols the hydroxy groups in the starting aldehydes or ketones have to be protected by groups which can be removed without hydrolysis of the orthoester function. Since orthoesters are stable to base, we used as starting materials the readily accessible α -acyloxy carbonyl compounds* (2) from which the protecting group can be removed by basic hydrolysis³ (Scheme 3). In all experiments 1,1-dimethoxypropene (1) was used as the ketene acetal since γ -butyrolactones having a 3-methyl group are both important constituents of sesquiterpene lactones⁵ and important precursors of (naturally occurring) 2-methylene- γ -butyrolactones^{4,6}.

Scheme 3



* α -Acetoxy aldehydes have been used recently in a related basic method for the synthesis of 4-hydroxy- and 4-acetoxy- γ -butyrolactones out of methyl 2-(phenylthio) propionate⁴.

Synthetic aspects

The α -acetoxyaldehydes (2a) and (2b) were prepared as described³ from the corresponding enol acetates which were epoxidized and rearranged under the influence of acid. Reaction of (1) with (2a) and (2b) in acetonitrile at 35°C and under ZnCl_2 catalysis proceeded well. The corresponding oxetanes (3a) and (3b) (Scheme 3) could be isolated in moderate yields after neutralisation of the catalyst with triethylamine (TEA) and subsequent distillation; these compounds could be identified by the characteristic position (δ_{H} 2.5-2.9 ppm) of their 3-H signals in the ^1H n.m.r. spectra. It is known that cycloadditions of ketones with (1) proceed more slowly than the reactions of aldehydes with (1) and that the reaction can be accelerated by the introduction of electron-withdrawing substituents on the position next to the carbonyl group¹. Therefore, we used stronger electron-withdrawing groups for the hydroxyl protection in the reactions of α -hydroxyketones, viz. the formyl group⁷ in ketones (2c) and (2d) and the dichloroacetyl group in the ketone (2e). However, 3-hydroxy-3-methyl-2-butanone did not even react when we used the trifluoro acetyl residue as the protective group. The use of these protecting groups having a rather high leaving ability increased the risk of elimination of the protective group on heating the reaction mixture. Since the liberated acids (e.g. HCOOH and CHCl_2COOH) catalyze the polymerization of (1) we kept the reaction temperature during oxetane formation as low as possible (i.e. below 35°C for (1) and (2e)). In this way we could synthesize oxetanes (3c)-(3e) in moderate to good yields. Unfortunately, (3d) and (3e) could not be purified by distillation, but the crude products were sufficiently pure to use them for further reaction.

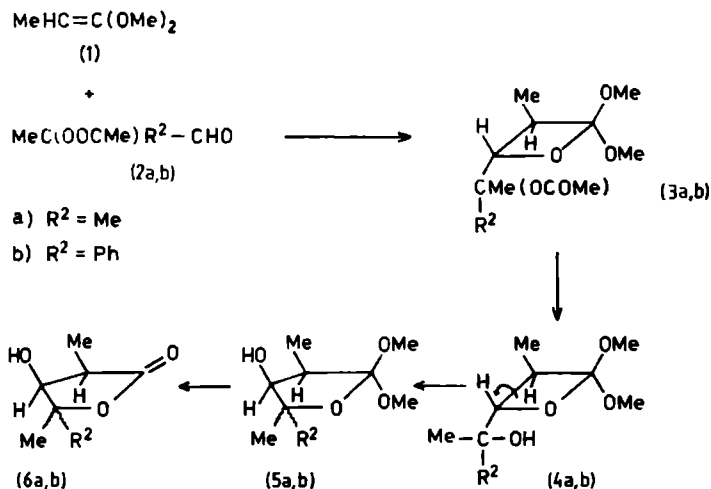
Deprotection of the hydroxy function was executed in a two phase system using ether and 40% aqueous potassium hydroxide. The resulting compounds (4) are very labile and were not purified, but directly rearranged to 2,2-dimethoxyfurans. This can be done either by heating the α -hydroxyoxetanes (4a)-(4e) in the presence of a base (e.g. *t*-BuOK) or by treatment with an acid (e.g. ZnCl_2) at room temperature. The latter method is favoured since it delivers less side products. The conversion of (3) into (4) and (4) into (5) is always accompanied by some loss of cyclic products (10-30%) since the cycloaddition is partly reversed under the applied reaction circumstances. This leads to polymerization

of (1). The compounds (5) could not easily be separated from these side products since the thermal instability of (5) prevents its purification on a good fractionating column. Attempts to purify (5) with m.p.l.c. resulted in complete conversion into γ -butyrolactones (6). Hence, compounds (5) were purified by a quick bulb to bulb distillation affording these compounds in a purity of ca. 90% according to ^1H n.m.r. The 3-methylbutyrolactones (6) could be obtained by mild acidic hydrolysis of the α -hydroxyoxetanes (4) or the 2,2-dimethoxyfurans (5). The conversion of (3) into (6) can be performed as a one-pot synthesis by neutralizing the potassium hydroxide solution and subsequently acidifying with HCl (10%) to pH < 3.

Stereochemical aspects

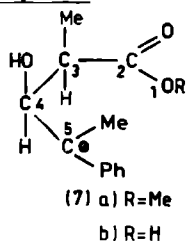
The preparation of γ -butyrolactones (6) from the aldehydes (2a) and (2b) proceeds with high stereoselectivity. The ^1H n.m.r. spectra of the intermediate oxetanes ((3a) and (3b), (4a) and (4b)) show one sharp doublet for the 3-Me group. Oxetane (3a) shows a doublet for the 4-H signal at δ_{H} 3.82 with a coupling constant of 6 Hz. This value for J points to a *trans* oxetane structure⁸. Since either (2a) reacted with (1) under thermodynamic conditions (*viz.* 8 h at 30°C in acetonitrile with ZnCl_2 catalysis) and the $\text{C}(\text{Me})_2\text{OAc}$ group is very bulky, this finding is in full agreement with the proposed mechanism for oxetane formation⁸. Consequently, (4a) also has a *trans* oxetane structure and (5a) and (6a) thus have likely a *cis* relationship for the 3-Me group with respect to the 4-hydroxy group as is demonstrated in Scheme 4.

The value of the 3-H-4-H coupling constant in (5a) is 5 Hz and 5.6 Hz in (6a). These values do not allow to decide between a *cis* and a *trans* orientation. In the literature⁹ configurations of γ -lactones were generally determined on the basis of a value of 2-4 Hz for vicinal *trans* oriented protons and a value of ca. 9 Hz for *cis* oriented protons. The measured value 5.6 Hz for (6a) is just in between these values. Very recently Font *et al.*¹⁰ made an extensive conformational study of di- and trisubstituted γ -lactones. From an analysis of the calculated and measured coupling constants in these compounds, they concluded that the rule $J_{\text{cis}} > J_{\text{trans}}$ can only be applied in combination with some other evidence, such as *e.g.* chemical proof. In several of the products studied they showed that $J_{\text{cis}} < J_{\text{trans}}$.



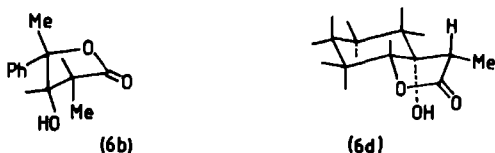
The compounds (3b) and (4b) also show a value of 6 Hz for the ^1H -4-H coupling constant, which points to a *trans* structure⁸. Rearrangement of (4b) to (5b) was expected to give a 1:1 diastereomeric mixture of the *cis* 3-methyl-4-hydroxyfurans due to the presence of a chiral centre at C-5. Indeed, in the ^1H n.m.r. spectrum of (5b) the existence of two diastereomers was demonstrated by the very broad signal for the phenyl group and by the two signals for the 4-H at δ_{H} 3.93 and 4.10 ppm. Yet, hydrolysis of (4b) to the butyrolactone (6b) delivered only one diastereomer with regard to C-4 and C-5 as the ^1H n.m.r. spectrum showed only one doublet for the 4-H signal. Hence, hydrolysis of the oxetane (4b) to the butyrolactone (6b) had proceeded with equilibration at C-5. Equilibration at C-5 is likely due to the formation of the stable¹¹ carbocations (7a,b) (Fig. 1). If rearrangement of (4b) into (5b) proceeds before further hydrolysis to (6b) equilibration may take place *via* (7a) which may be formed during hydrolysis of ortho-ester (5b). On the other hand, (7b) may be formed by protonation of (6b) under the acidic reaction conditions. In both cations (7a,b) the carbonyl function may attack the flat carbocation from either site and consequently (7) will cyclize

Figure 1



to the most stable lactone in which the phenyl group is in a pseudo equatorial position. Thus, the configuration of (6b) is likely as indicated in Fig. 2. The ^1H n.m.r. spectrum of (6b) shows that the proton at C-4 is more downfield in (6b) than in (6a) ($\Delta\delta_{\text{H}}$ 0.45). This points to a deshielding effect of the phenyl group and suggests a *trans* position of this group relative to 4-H, in accordance with the proposed structure for (6b).

Figure 2



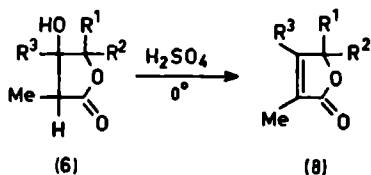
The stereochemical control of the oxetane formation from (1) and the ketones (2c-2e) is less pronounced than in the reaction of (1) with aldehydes (2a) and (2b). This appears clearly from the occurrence of double doublets for the 3-Me groups in the products (3c-3e), (4c-4e) and (5c-5e). Besides, in the case of (5c) small amounts of both diastereomers could be obtained in pure form by a separation *via* distillation. Apparently the steric demands of the different alkyl residues in the ketones (2c-2e) do not cause a large preference for the formation of a single oxetane. The ratio between the isomers in the compounds (3c-3e)-(5c-5e) varies from 1.5:1 (5c) to 3:1 (4d) as determined by ^1H n.m.r., and there is no equilibration to the more stable isomers under the applied reaction conditions.

Stereochemical control seems to be best during reaction of (1) with the cyclic ketone (2d). From this ketone one diastereomer (6d) (Figure 2) could be obtained in pure form *via* repeated crystallizations in an overall yield of 40% based on (2d). On the other hand (6c) and (6e) were obtained as mixtures of diastereomers.

The configuration of (6d) can be deduced both from its ^1H n.m.r. spectrum and the mechanism of the formation of the intermediate oxetane (3d). It is very likely that in (3d) the ketene acetal moiety is in an equatorial position with respect to the cyclohexane ring. Furthermore, in the more stable oxetane the 3-Me group of the oxetane ring

is probably in a *trans* position with respect to the α -formoxy substituted alkyl chain, *i.e.* the main isomer of (3d) is likely a *trans* oxetane. The position of the α -formoxy group is uncertain, but it is known that in the related α -acetoxy cyclohexanones the acetoxy group is exclusively in an equatorial position¹². In combination with the just mentioned suppositions this would imply that (6d) has a *trans* diequatorial-fused lactone ring. This is confirmed by the ¹H n.m.r. spectrum of (6d). The O-lactonic methine proton of (6d) is seen as a multiplet centered at δ_H 3.92*. These signals reflect the X-part of an ABX spectrum and from this multiplet it can be measured¹³ that $J_{AX} + J_{BX}$ is 15.6 Hz. Since the sum of an axial-equatorial and an equatorial-equatorial coupling constant is at most 14 Hz, this indicates that the lactonic methine proton is in an axial position. In combination with the equatorial position of the ketene acetal moiety this points to a *trans* diequatorial-fused lactone ring; likely (6d) has the configuration as depicted in Fig. 2.

Scheme 5



The butyrolactones (6a) and (6c-e) were converted into 2-(5H)-furanones (8) by treatment with concentrated sulfuric acid at 0°C. Since dehydration under these conditions probably proceeds *via* a pure *E*₁ mechanism the dehydration proceeds equally well with the pure butyrolactones (6a) and (6d) as with the mixture of diastereomers (6c) and (6e). Therefore, the simple procedure, described in this paper, seems to be a promising method for the preparation of a variety of 2-butenolides¹⁵ occurring in nature (Scheme 5).

*Danishefsky and coworkers¹⁴ noticed that in a set of seven isomeric *cis*- and *trans*-fused lactones structurally related to (6d), the configuration of the ring junction could be determined on the basis of the chemical shift of the oxygen-bound lactonic methine proton. So, in the case of a *cis*-fused γ -lactone ring this proton absorbs in the region δ_H 4.6-5.0, while that of the *trans* series absorbs in the region δ_H 3.8-4.1 ppm. Since we measured a multiplet centered at δ_H 3.92 ppm this finding might support the proposed structure for (6d).

Experimental

General methods - ^1H n.m.r. spectra were recorded on a Varian T-60 spectrometer in CDCl_3 or CCl_4 solution with SiMe_4 as internal reference. Mass spectra were obtained using a double focussing Varian SM1-B mass spectrometer. Melting and boiling points are uncorrected. Distillations were performed using a vacuum jacketed 25 x 1.5 cm Vigreux column or a Büchi Kugelrohrföfen. Products which could be purified by distillation or crystallization gave satisfactory elemental analyses ($\text{C} \pm 0.4$, $\text{H} \pm 0.2$). 3-Hydroxy-2-butanone and 3-hydroxy-3-methyl-2-butanone were commercially available (Aldrich) and were dried over molecular sieves 4 Å before use. 2-Hydroxycyclohexanone¹⁶, 1-acetoxy-2-methylpropene¹⁷, 1-acetoxy-2-phenylpropene¹⁷ and 1,1-dimethoxypropene¹ were prepared according to literature methods.

Synthesis of starting materials (2a-2e)

2-Acetoxy aldehydes (2a) and (2b)

1-Acetoxy-2-methylpropene was treated with *m*-chloroperbenzoic acid as described for the synthesis of 2-acetoxyketones¹⁸. The resulting 2-acetoxy-3,3-dimethyloxirane, b.p. 65-70°C/15 mmHg (yield 80%) was maintained at 90°C for 2 h in the presence of ZnCl_2 (1 mol%) giving (2a). A similar oxidation of 1-acetoxy-2-phenylpropene at room temperature gave (2b) in one step. The aldehydes (2a,b) were used without purification.

2-Formyloxy ketones (2c) and (2d)

The corresponding α -hydroxyketones were formylated with a formic acid-acetic anhydride mixture as described for the formylation of alcohols⁷. In this way (2c), b.p. 62°C/15 mmHg, yield 75%, and (2d), b.p. 110°C/15 mmHg, yield 60%, were obtained.

3-(Dichloroacetoxy)-2-butanone

3-Hydroxy-2-butanone was acylated with dichloroacetyl chloride in the presence of Et_3N according to a standard method for the acylation of alcohols ; b.p. 68°C/0.5 mmHg, yield 65%.

Synthesis of 2,2-dimethoxy-3-methyloxetanes (3a-3e), general method

ZnCl₂ (2 ml of a saturated solution in acetonitrile) was added to a stirred solution of an α -acetoxy carbonyl compound (50 mmol) and 1,1-dimethoxypropene (1) (7 g, 70 mmol). The mixture was maintained at 30°C for several hours; 8 h for (2a) and (2b), 24 h for (2c) and (2e), and 40 h for (2d). *n*-Pentane (50 ml) and TEA (5 g) were added and the mixture was stirred vigorously until a light precipitate was formed. The precipitate was removed by filtration and the filtrate concentrated *in vacuo* to yield the crude product. Crude (3a-3c) were distilled to give the pure products which had satisfactory elemental analyses; (3b) could be crystallized from hexane. The oxetanes (3d) and (3e) could not be purified by distillation because of their thermal instability. According to their ¹H n.m.r. spectra they were present in the concentrated reaction mixture for at least 80% and were converted into (4d) and (4e) without purification. Yields, boiling points and spectral data are given in Table I.

Synthesis of 2,2-dimethoxy-3-methyloxetanes (4a-4e), general procedure

Each of the products (3a-3e) obtained as described, was added dropwise to a mixture of KOH (50 ml of a 40% aqueous solution) and diethylether (70 ml). The mixture was stirred vigorously for 2 h at room temperature and the ethereal layer was separated. The aqueous layer was extracted with ether (2 x 25 ml) and the combined ethereal layers were dried (Na₂CO₃ and CaH₂). The solvent was evaporated to yield the crude products. Attempts to purify the products by distillation gave (4a), (4b) and (4d) contaminated with 10-40% of the corresponding (5). The oxetanes (4c) and (4e) have not been distilled and were used without purification in the next step. Yields, boiling points and spectral data are given in Table I.

Synthesis of 2,2-dimethoxy-3-methyl-tetrahydrofurans (5a-5e), general methods

Method A: Crude (4a-4e) were heated in the presence of *t*-BuOK (1 g) for 5 h; in the case of (4d) 24 h. Distillation at reduced pressure delivered (5a-5e) in purities of ca. 90% according to their ¹H n.m.r. spectra. Attempts to purify (5a-5e) with m.p.l.c. lead to decomposition

of the products under formation of 3-methyl- γ -butyrolactones (6).

Method B: Crude (4a-4e) were treated with ZnCl_2 (1 ml of a saturated solution in acetonitrile) for 20 min at room temperature. *t*-BuOK (2 g) was added and the mixture was distilled under reduced pressure.

Methods A and B gave equal yields, calculated on the basis of the starting aldehyde. Yields, boiling points and spectral data are given in Table II.

Method C: Slightly better yields were obtained when the oxetanes (3c) and (3d) were hydrolysed with KOH (75 ml of a 10% aqueous solution) for 4 h. Work up as described for (4a-4e) delivered the tetrahydrofurans (5c) and (5d).

Synthesis of 3-methyl- γ -butyrolactones (6a-6e)

Ethereal extracts obtained in the preparation of (4a-4e) were concentrated to 50 ml, and hydrochloric acid (20 ml of an 0.5 M solution) was added. The resulting two-phase mixture was stirred vigorously for 2 h at room temperature. The ethereal layer was separated and the aqueous layer was extracted with dichloromethane (2 x 50 ml). The combined organic layers were dried (Na_2SO_4) and the solvents were evaporated. The crude products were distilled *in vacuo* or crystallized from hexane-ethyl acetate to yield the pure products. All products had satisfactory elemental analyses (C, H). Yields were calculated based on the starting aldehyde. Yields, physical constants and spectral data are given in Table II.

Synthesis of 3-methyl-(5H)-dihydro-2-furanones (8a), (8c-8e)

A 3-methyl- γ -butyrolactone (6) (30 mmol) was added dropwise to sulfuric acid (50 ml of a 96% solution) at 0°C under vigorously stirring. After stirring for 1 h the mixture was poured on ice (250 g). The resulting mixture was extracted with CH_2Cl_2 (3 x 25 ml). The combined organic layers were dried (Na_2SO_4), concentrated and distilled. In the case of (6a) extraction with CH_2Cl_2 was executed after neutralization of the aqueous layer with NaHCO_3 . Yields, spectral data and physical constants of the obtained butenolides are given in Table III.

Table I: Yield, physical constants and spectral data for oxetanes (3) and (4).

Compound	Molecular formula	B.p. (°C/mmHg)	M.p. (°C) (solvent)	Peak Match, Found; Calc.	Yield (%)	¹ H n.m.r. (CDCl ₃) δ _H (ppm)
3a	C ₁₁ H ₂₀ O ₅	49-51/0.1		201.0970; 201.0998 (M-OCH ₃)	45	1.10 (3H, d, J 7 Hz, 3-Me), 1.38 (3H, s, COAc(Me) ₂), 1.41 (3H, s, COAc(Me) ₂), 1.90 (3H, s, OCOMe), 2.83 (1H, dq, J 7 and 6 Hz, 3-H), 3.25 and 3.29 (6H, 2s, OMe), 3.83 (1H, d, J 6 Hz, 4-H).
3b	C ₁₆ H ₂₂ O ₅	115-120/0.1 ^a	97-98 (hexane)	294.1456; 294.1467	44	0.83 (3H, d, J 7 Hz, 3-Me), 1.90 (3H, s, OCOMe), 2.10 (3H, s, C(OAc)(Ph)Me), 3.10 (1H, dq, J 7 and 6 Hz, 3-H, signal partly hidden under OMe signals), 3.23 and 3.28 (6H, 2s, OMe), 3.83 (1H, d, J 6 Hz, 4-H).
3c ^b	C ₉ H ₁₆ O ₅	54/0.1		204.1085; 204.1076	85	1.03 and 1.07 (3H, d, J 7 Hz, 3-Me), 1.23 and 1.40 (3H, s, 4-Me, isomer ratio 2:3), 2.57-3.00 (1H, m, 3-H), 3.20 (6H, br.s, OMe), 4.06 and 4.15 (2H, br.s and s, CH ₂ COOH), 8.00 (1H, br.s, COOH).
4a	C ₉ H ₁₈ O ₄	55/0.5				1.00 and 1.12 (6H, 2s, C(OH)Me ₂), 1.09 (3H, d, J 7 Hz, 3-Me), 2.50 (1H, br.s, OH), 2.60-3.10 (1H, m, 3-H), 3.13 and 3.20 (6H, 2s, OMe).
4b	C ₁₄ H ₂₀ O ₄					(from a mixture with 5b): 0.63 (3H, d, J 7 Hz, 3-Me), 1.50 (3H, s, C(OH)(Ph)Me), 3.13 and 3.23 (6H, 2s, OMe), 3.83 (1H, d, J 6 Hz, 4-H).
4d ^b	C ₁₁ H ₂₀ O ₄	100/0.4 ^a				1.00 and 1.17 (3H, 2d, J 7 Hz, 3-Me), 0.87-2.00 (8H, m, (5-8)-H), 2.25 (1H, br.s, OH), 2.35-2.83 (1H, m, 3-H), 3.15 and 3.16 (6H, 2s, OMe), 3.27-3.60 (1H, m, 9-H)

^aKugelrohr distillation^bDiastereomeric mixture

Table II: Yields, physical data and spectral data for furans (5) and γ -lactones (6).

Compound	Molecular formula	B.p. (°C/mmHg)	M.p. (°C) (solvent)	Peak Match; Found;Calc.	Yield (%)	^1H n.m.r. (CDCl_3) δ_{H} (ppm)
5a	$\text{C}_9\text{H}_{18}\text{O}_4$	55/0.2 ^a		173.1155; 173.1178 (M-OH)	50 ^c	0.97 (3H, d, J 7 Hz, 3-Me), 1.21 (6H, s, 5-Me), 2.13-2.60 (2H, m, 3-H, OH), 3.20 (6H, s, OMe), 3.50 (1H, d, J 5 Hz, 4-H).
5b	$\text{C}_{14}\text{H}_{20}\text{O}_4$	140/0.4 ^a		252.1380; 252.1361	45 ^c	1.08 (3H, d, J 7 Hz, 3-Me), 1.53 (3H, br.s, 5-Me), 2.00-2.53 (1H, m, 3-H), 2.70 and 2.82 (1H, br.s, OH), 3.37 and 3.40 (6H, 2s, OMe), 3.93 and 4.10 (1H, 2d, J 6 Hz, 4-H), 7.10-7.50 (5H, m, Ph).
5c	$\text{C}_8\text{H}_{16}\text{O}_4$	78/15 (<i>trans</i>) 85-90/15 (<i>cis</i>)			65 ^c	<i>trans</i> : 0.93 (3H, d, J 7 Hz, 3-Me), 1.17 (3H, s, 4-Me), 2.00 (1H, q, J 7 Hz, 3-H), 2.75 (1H, br.s, OH), 3.20 and 3.27 (6H, 2s, OMe), 3.73 (2H, br.s, 5H). <i>cis</i> ^d : 0.90 (3H, d, J 7 Hz, 3-Me), 1.17 (3H, s, 4-Me), 2.17 (1H, q, J 7 Hz, 3-H), 3.20 and 3.23 (6H, 2s, OMe), 3.33 (1H, br.s, OH), 3.67 (2H, br.s, 5-H).
5d	$\text{C}_{11}\text{H}_{20}\text{O}_4$	50/0.2 ^a		216.1391; 216.1361	60 ^c	0.83-1.10 (11H, m, 3-Me, (4-7)-H), 2.00-2.30 (1H, m, 3-H), 3.20 and 3.25 (6H, 2s, OMe), 3.60 (1H, br.s, OH), 3.83 (1H, br.q, J 7 Hz, 7a-H).
5e ^b	$\text{C}_9\text{H}_{18}\text{O}_4$	72/0.2			60 ^c	1.07 (3H, d, J 7 Hz, 3 or 5-Me), 1.20-2.40 (8H, m, 3 or 5-Me, 4-Me, 3-H, OH), 3.30 and 3.37 (6H, 2s, OMe), 3.37-3.80 (1H, m, 5-H).

Table II (continued)

Compound	Molecular formula	B.p. (°C/mmHg)	M.p. (°C) (solvent)	Peak Match, Found;Calc.	Yield (%)	¹ H n.m.r. (CDCl ₃) δ _H (ppm)
6a	C ₇ H ₁₂ O ₃	140/0.2 ^a		144.0773; 144.0786	60 ^c	1.25 (3H, d, J 7 Hz, 3-Me), 1.37 and 1.47 (6H, 2s, 5-Me), 2.67-3.20 (1H, m, 3-H), 3.05 (1H, br.s, OH), 4.05 (1H, d, J 5.6 Hz, 4-H).
6b	C ₁₂ H ₁₄ O ₃		96-98 (hexane-ethyl acetate)	206.0913; 206.0943	55 ^c	1.23 (3H, d, J 7 Hz, 3-Me), 1.75 (3H, s, 5-Me), 2.33-2.83 (1H, m, 3-H), 3.50 (1H, br.s, OH), 4.50 (1H, d, J 6 Hz, 4-H), 7.36 (5H, br.s, Ph).
6c ^b	C ₆ H ₁₀ O ₃	90/0.2		130.0644; 130.0630	40 ^c	1.16 and 1.18 (3H, d, J 7 Hz, 3-Me), 1.30 and 1.40 (3H, s, 4-Me, ratio 2:3), 2.37 and 2.67 (1H, q, J 7 Hz, 3-H), 3.30 and 3.70 (1H, br.s, OH), 3.97-4.40 (2H, m, 5-H).
6d	C ₉ H ₁₄ O ₃	150/0.2 ^a	124-125 (hexane-ethyl acetate)	170.0940; 170.0943	40 ^c	1.17 (3H, d, J 7 Hz, 3-Me), 1.30-2.20 (8H, m, Hex ^c -H), 2.33 (1H, br.s, OH), 2.50 (1H, q, J 7 Hz, 3-H), 3.84-4.08 (1H, m, 7aH).
6e ^b	C ₇ H ₁₂ O ₃	120-130/0.2		144.0773 144.0786	60 ^c	1.00-1.43 (9H, m, 3,4,5-Me), 2.50 and 2.73 (1H, 2q, J 7 Hz, 3-H), 3.40 and 3.67 (1H, br.s, OH), 4.10-4.50 (1H, m, 5-H).

^aKugelrohr distillation. ^bMixture of diastereomers. ^cBased on the amount of (2) used.

^dThe 3-H quartet is 0.17 ppm downfield compared to the stereoisomer which points to a *cis* position of this proton and the neighbouring OH group.

Table III: Yields, physical constants and spectral data for butenolides (8).

Compound	Molecular formula	B.p. (°C/mmHg)	M.p. (°C) (solvent)	Peak match, Found;Calc.	Yield (%)	¹ H n.m.r. (CDCl ₃) δ _H (ppm)
8a	C ₇ H ₁₀ O ₂	90-95/15 ^a	50-54 (hexane-diisopropyl ether)	126.0686; 126.0681	50	1.43 (6H, s, 5-Me), 1.87 (3H, d, J 2 Hz, 3-Me), 7.00-7.10 (1H, m, 4-H).
8c	C ₆ H ₈ O ₂	108/15 (lit. ¹⁹ : 75-85/0.1)	29-32/32-35 (hexane)	112.0526; 112.0524	75	1.80 (3H, br.s (with fine splitting), 4-Me), 2.00 (3H, d, J 1 Hz, 3-Me), 4.60 (2H, br.s (with fine splitting), 5-Me).
8d	C ₉ H ₁₂ O ₂	130/0.2 ^a (lit. ²⁰ : 65-68/0.05)		152.0835; 152.0837	70	1.80 (3H, d, J 1 Hz, 3-Me), 1.00-3.00 (8H, m, (CH ₂) ₄ -H), 4.33-4.73 (1H, m, CH ₂ -C(C)(H)-OCO).
8e	C ₇ H ₁₀ O ₂	48/0.2 ^a (lit. ²¹ : 60-80/1)		126.0702; 126.0681	60	1.37 (3H, d, J 7 Hz, 5-Me), 1.73 (3H, d, J 1 Hz, 4-Me), 1.97 (3H, d, J 1 Hz, 3-Me), 4.60-4.90 (1H, m, 5-H).

^aKugelrohr distillation^bbased on (6)

References

1. J.W. Scheeren, R.W.M. Aben, P.H.J. Ooms and R.J.F. Nivard, *J. Org. Chem.*, 1977, 42, 3128.
2. R.W.M. Aben and J.W. Scheeren, *Synthesis*, 1978, 401.
3. a. G.M. Rubottom, J.M. Gruber and G.M. Mong, *J. Org. Chem.*, 1976, 41, 1673.
b. A. Hassner, P.H. Reuss and H.W. Rinnick, *J. Org. Chem.*, 1975, 40, 3427.
4. P. Barbier and C. Benezra, *J. Org. Chem.*, 1983, 48, 2705.
5. H.D. Fischer, M.H. Fischer, R.W. Franck and E.J. Olivier in 'Prog. Chem. Org. Nat. Prod.', ed. L. Zechmeister, Springer Verlag, Wien, 1979, 38, 47.
6. P.A. Grieco and M. Miyasita, *J. Org. Chem.*, 1974, 39, 120.
7. A. v. Es and W. Stevens, *Recl. Trav. Chim. Pays-Bas*, 1965, 84, 704.
8. R.G. Hofstraat, J.W. Scheeren and R.J.F. Nivard, *J. Chem. Soc. Perkin I*, 1985, 561.
9. a. B.N. Ravi and R.J. Wells, *Aust. J. Chem.*, 1982, 35, 105.
b. J.B. Lowry and N.V. Riggs, *Tetrahedron Lett.*, 1964, 2911.
10. C. Jaime, R.M. Ortuño and J. Font, *J. Org. Chem.*, 1986, 51, 3946.
11. C. Wentrup, 'Reaktive Zwischenstufen', Thieme Verlag, Stuttgart, 1979, Teil II.
12. D. Cantacuzene and M. Tordeux, *Can. J. Chem.*, 1976, 54, 2759.
13. H. Günther, 'NMR-Spektroskopie', Thieme Verlag, Stuttgart, 1973.
14. S. Danishefsky, M.-Y. Tsai, T. Kitahara, *J. Org. Chem.*, 1977, 42, 394.
15. Y.S. Rao, *Chem. Rev.*, 1976, 76, 625.
16. J.J. Bloomfield, D.C. Owsley and J.M. Nelke, in 'Organic Reactions', J. Wiley, New York, 1976, 23, 259.
17. T.J. Cousineau, S.L. Cook and J.A. Secrist, *Synth. Commun.*, 1979, 9, 157.
18. K.L. Williamson, J.I. Coburn and M.F. Herr, *J. Org. Chem.*, 1967, 32, 3934.
19. W.W. Epstein and A.C. Sontag, *J. Org. Chem.*, 1967, 32, 3390.
20. A.E. Greene, J.C. Muller and G. Ourisson, *J. Org. Chem.*, 1977, 39, 186.
21. K. Iwai, H. Kosugi, H. Uda and M. Kawai, *Bull. Chem. Soc. Jpn.*, 1977, 50, 242.

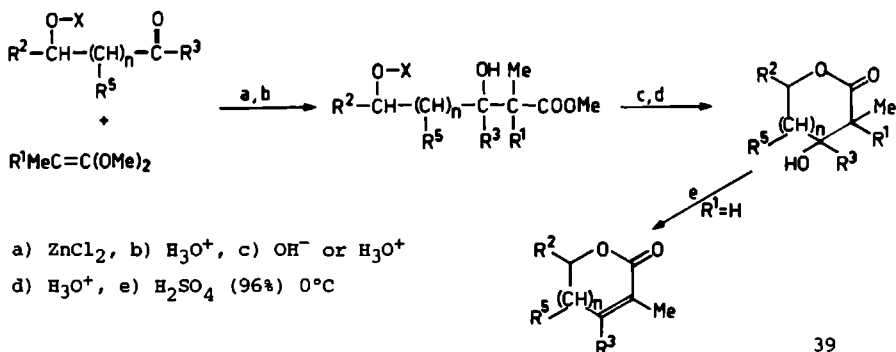
A Simple 'One-Pot' Synthesis
of 4-Hydroxy- δ -Lactones and 5,6-Dihydro-2-Pyrones
from 1,1-Dimethoxypropene and β -Oxyaldehydes

Introduction

δ -Lactones are versatile, synthetic intermediates and are widely spread in nature; whereas γ -lactones occur preferentially in plants, δ -lactones are mainly found in animal products¹. Some δ -lactones are significant in insect behaviour² and recently there has been a lot of synthetic effort concerning the synthesis of these pheromones³⁻⁵. However, general synthetic routes to δ -lactones are relatively scarce. Besides most syntheses that have been published use strongly basic conditions and yield 5,6-dihydro-2-pyrones⁶⁻⁹. A relatively mild, basic method was presented by Giese *et al.*¹⁰, who used radical C-C bond formation as the critical step. Paterson *et al.*¹¹ used the Lewis acid-catalyzed reaction of ketene bis-trimethylsilyl acetals with α -chloro thioethers as the key reaction. However, the products of the latter procedure were also transformed into 5,6-dihydro-2-pyrones in order to reduce the number of diastereomeric products.

In previous work¹² we showed that hydroxy-substituted γ -lactones can easily be obtained out of ketene acetals (1) and α -oxygenated aldehydes or -ketones (Scheme 1, $n = 0$, $X = \text{Ac}$). In order to extend

Scheme 1



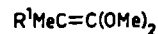
this strategy we undertook an investigation into the synthetic applications of reactions between β -oxygenated carbonyl compounds and (1). These would give access to 4-hydroxy- δ -lactone derivatives. Elimination of the 4-hydroxy function might then allow the synthesis of substituted 5,6-dihydro-2-pyrones (Scheme 1, $n = 1$).

We now present a mild, acidic route to 4-hydroxy-3-methyl- δ -lactones and their corresponding 5,6-dihydro-2-pyrones based on readily available β -oxygenated aldehydes and ketene acetals¹³.

Synthesis of β -oxygenated aldehydes

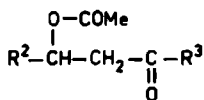
In the first instance we concentrated on the synthesis of β -hydroxyaldehydes since we expected β -hydroxyketones lacking an activating substituent on the α -position to be unreactive¹³. β -Hydroxyaldehydes are very labile compounds and dehydration to the corresponding α,β -unsaturated aldehydes is a severe problem. Thus, most synthetic routes provide β -hydroxyaldehydes in a protected form. The protection of the hydroxy group is, however, necessary in any case in order to avoid a competing reaction of the free hydroxy group with (1). Two methods are known to us which deliver directly protected compounds in a one-step synthesis.

Tsumara *et al.*¹⁴ described the synthesis of 3-acetoxypropanal (2) from propenal, acetic acid and barium acetate *via* a Michael addition reaction. Reaction of propenal under the described conditions delivered (2) in an overall yield of 43% after careful distillation. A further study of the method showed that instead of barium acetate sodium acetate could be used as well. Besides the formoxy- and propionyxy-analogues of (2) could be prepared in about the same yield, using formic acid and propionic acid, respectively. This method enabled us to synthesize (3) and the β -acetoxyketone (4) as well, in yields of 5 and 50-54%, respectively. 2-Methyl-propenal was, however, entirely unreactive under these conditions. The low yield in the case of (3) and the nonreactivity of the methyl-substituted propenal are possibly due to a greater stability of the double bonds in these compounds, containing a disubstituted instead of a monosubstituted double bond.



(1) a, $R^1=H$

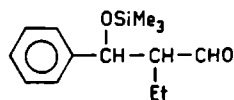
b, $R^1=Me$



(2) $R^2=R^3=H$

(3) $R^2=Me, R^3=H$

(4) $R^2=H, R^3=Me$



(5)

Yamamoto and coworkers¹⁵ described a synthesis of β -silyloxyketones from benzaldehyde or substituted benzaldehydes. Although the scope of this reaction is limited with respect to the starting aldehydes, it is still an attractive method as it delivers the products in a single step out of easy available silylenolethers of ketones. We tried this route starting with benzaldehyde and a silylenolether of an aldehyde. Thus, benzaldehyde and the silylenolether of butyraldehyde in acetonitrile were pressurized in the presence of $ZnCl_2$ to 12 kbar for 96 h at 50°C. In this way a reaction mixture was obtained containing *ca.* 75% of the β -silyloxyaldehyde (5). Bulb to bulb distillation afforded (5) in a yield of 30-35% based on benzaldehyde as a 1:1 diastereomeric mixture. Attempts to synthesize an analogue of (5) using cinnamic aldehyde as the starting compound failed.

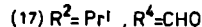
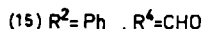
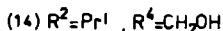
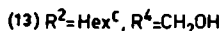
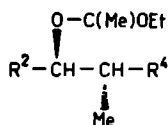
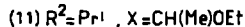
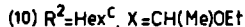
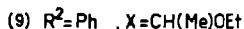
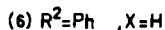
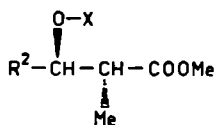
Although both direct methods are easy to perform and probably can still be optimized there are drawbacks. The method of Tsumara has a very small scope and the method of Yamamoto leads to 1:1 diastereomeric mixtures. Hence, the known, direct syntheses appear to be rather limited. Therefore, we investigated some other methods.

In the literature four more laborious methods of potentially broader scope for the synthesis of (protected) β -hydroxyaldehydes have been published. First, there is the imine anion route as originally conceived by Wittig and coworkers¹⁶. Second, there is an approach based on the chemistry of thiazolines as pursued by Meyers *et al.*¹⁷. However, in our hands both these methods failed as a convenient synthesis of β -hydroxyaldehydes when we used simple aldehydes as starting compounds¹⁸. The third method for the synthesis of β -oxygenated aldehydes is based on the selective reduction of

suitable, protected β -hydroxyesters as for instance demonstrated by Corey *et al.*¹⁹. The fourth method is based on 1,3-dithiane chemistry as developed by Masamune and coworkers²⁰.

We have concentrated on the third method since stereoselective methods for the synthesis of β -hydroxyesters have recently been described by us and others^{21,22}. A priori, the use of these compounds implies the synthesis of δ -lactones with defined stereochemistry at the 5- and 6-position. Thus, *threo* β -hydroxyesters (6-8) were chosen as the starting compounds. After reduction these esters deliver aldehydes with an α -branched side-chain. On account of previous results it could be expected that reaction with a ketene acetal should deliver a *threo* configuration around the 3- and 4-position of the product after hydrolysis²². Hence, δ -lactones with entirely defined stereochemistry might be synthesized.

The pure *threo* compound (6) was isolated by crystallization from petroleum ether²³ (b.p. 40-60°C) after it had been synthesized as a 3:1 *threo-erythro* mixture²². Compounds (7) and (8) were obtained as 19:1 *threo-erythro* mixtures²² and were used without further purification. The hydroxy function was protected as an acetal with ethyl vinyl ether according to the method of Tufariello²⁴ and this functionality appeared to be perfectly stable under the applied reaction conditions.



Reduction of the ester function in (9) was performed with diisobutylaluminium hydride (DIBAH) in methylene chloride at -78°C according to the protocol of Keck *et al.*^{25a}. However, the product was a mixture containing both the starting material and the corresponding alcohol¹²; only a few percents of the desired aldehyde* were present. Scolastico and coworkers^{25c} showed that reduction of an ester to the alcohol using LiAlH_4 followed by a Collins oxidation to afford the aldehyde delivers even slightly better yields than selective reduction of the ester with DIBAH at -90°C . Hence, we decided to circumvent the DIBAH reduction.

Reduction of (9-11) with LiAlH_4 in ether proceeded straightforward and delivered the alcohols (12-14) in good yields. Oxidation of the alcohols to aldehydes (15-17) was tested with alcohol (12) both by a modification of the Collins oxidation²⁶ and by the dimethylsulfoxide (DMSO)-oxalyl chloride oxidation according to Swern²⁷. Both methods delivered the desired aldehyde (15) but since the Swern oxidation is easier to perform and gives slightly better yields we further used this oxidation. *Via* this method aldehydes (15-17) were obtained in good yield.

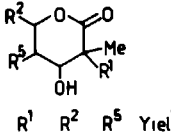
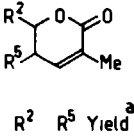
Synthesis of 4-Hydroxy- δ -lactones and 5,6-dihydro-2-pyrones

The protected aldehydes thus obtained were converted with the ketene acetals (1a) and (1b) into 4-hydroxylactones and 5,6-dihydropyrones as depicted in Scheme 1. A survey of the results has been given in Table 1.

A test reaction of (2) with (1a) under ZnCl_2 catalysis and in acetonitrile at room temperature gave instead of the expected products rapid dimerisation of (1a). Probably ZnCl_2 catalyses the elimination of acetic acid out of (2), and (1a) dimerizes readily under the influence of proton acids. However, using $\text{AlCl}_3\cdot\text{O}$ -

*Careful investigation of the literature indicated that reduction of an ester with DIBAH is a delicate reaction, for which various solvents, *e.g.* hexane, toluene, methylene chloride and various reaction temperatures, *e.g.* -78°C , -90°C , -100°C are used; see reference 25.

Table 1

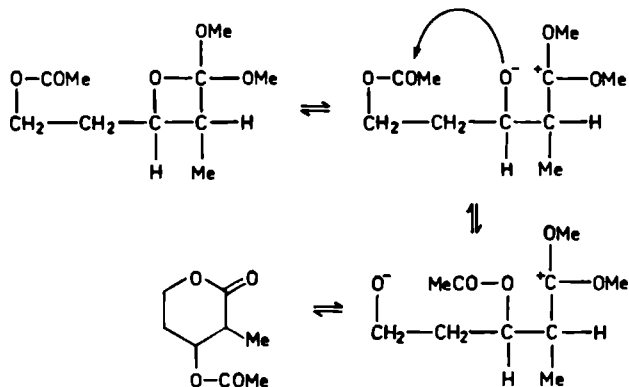
$\begin{array}{c} \text{OX} \\ \\ \text{R}^2\text{CH}-\text{CH}(\text{R}^5)-\text{CHO} \\ \text{R}^2 \quad \text{R}^5 \quad \text{X} \end{array}$	Ketene Acetal	 $\text{R}^1 \quad \text{R}^2 \quad \text{R}^5 \quad \text{Yield}^a$	 $\text{R}^2 \quad \text{R}^5 \quad \text{Yield}^a$
(2) H H Ac	(1a)	(21) H H H 50	(22) H H 30
(3) Me H Ac	(1a)		(25) Me H 28
(5) Ph Et SiMe ₃	(1a)		(27) Ph Et 70 ^b
(15) Ph Me CHMeOEt	(1a)	(28) H Ph Me 61 ^b	
(15) Ph Me CHMeOEt	(1b)	(31) Me Ph Me 12 ^c	
(16) Hex ^c Me CHMeOEt	(1a)	(29) H Hex ^c Me 40 ^c	
(17) Pr ^l Me CHMeOEt	(1a)	(30) H Pr ^l Me 44 ^c	
(35) Me H CHMeOEt	(1a)		(37) Me H 38

a) yield in % based on the aldehyde b) diastereomeric mixture

c) one diastereomer

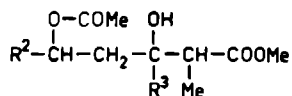
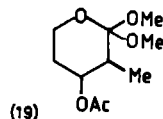
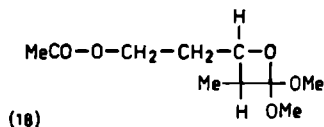
bornyl²⁸ and dichloromethane at low temperature, (2) could be converted in a product which, when isolated at room temperature in the presence of the catalyst, appeared to be the 2,2-dimethoxytetrahydropyran (19). The ¹H n.m.r. spectrum of the crude product showed no signals in the region 2.5–2.9 ppm, which is the characteristic interval of the 3-H signals in 2,2-dialkoxyoxetanes¹⁴. The formation of (19) may be explained by a shift of the acetoxy group, as already noticed in the reactions of analogous α-acetoxyaldehydes^{28c}

(Scheme 2). However, hydrolysis of the crude reaction product at -10°C in a two-phase system dichloromethane-water delivered in good yield (20) as a 8:1 *threo-erythro* mixture, indicating that the oxetane (18) is the initially formed product. Although (20) could be obtained analytically pure in a small amount *via* bulb to bulb distillation, purification of (20) is rather tricky since elimination



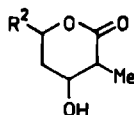
of acetic acid and subsequent dehydration during distillation is a substantial problem. Consequently, in a repeated experiment we pursued the reaction route with the crude product (85-90%).

Saponification of the acetoxy protective group and the methyl-ester of (20) with 30% KOH proceeded without considerable elimination of the acetoxy group and careful acidification with 30% sulphuric acid to pH < 2 delivered the 4-hydroxy- δ -lactone (21) in a yield of 75-80%. Besides a few percents of the 5,6-dihydropyrone (22) could

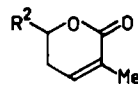


(20) $\text{R}^2=\text{R}^3=\text{H}$

(23) $\text{R}^2=\text{Me}, \text{R}^3=\text{H}$



(24) $\text{R}^2=\text{Me}$



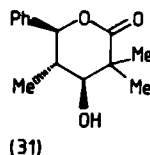
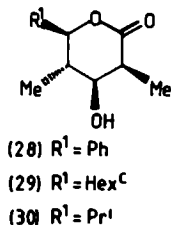
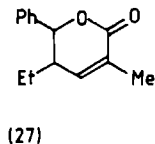
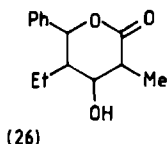
(25) $\text{R}^2=\text{Me}$

be detected in the crude reaction mixture.

Reaction of (3) with (1a) under the same conditions as used in the reaction of (2) gave (23) in good yield. Since the crude product was sufficiently pure (*ca.* 90%), the deprotection was carried out without previous purification. After acidification (30% sulphuric acid) a mixture containing (24) and (25) in approximately a 1:1 ratio was isolated. Unfortunately, (24) could not be obtained completely free from (25). Hence, we converted the product mixture into (25) *via* dehydration. Dehydration of both (21) and the mixture of (24) and (25) was accomplished by reaction in concentrated sulphuric acid at 0°C. Work-up and subsequent bulb to bulb distillation afforded both (22) and (25) in a yield of 55-60%.

As expected reaction of (4) with (1a) did not proceed at all; (4) appeared to be inert during reflux with (1a) in acetonitrile and under ZnCl_2 catalysis.

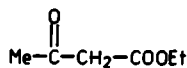
Reaction of the diastereomeric mixture (5) with (1a) and subsequent hydrolysis of (22) gave a complex mixture of δ -lactones (26). Because of the presence of much diastereomers, dehydration was executed directly. Using a Dean-Stark apparatus and benzene and toluene-*p*-sulphonic acid, the 5,6-dihydropyrone (27) was isolated as a 1:1 diastereomeric mixture in a yield of 60% based on (5).



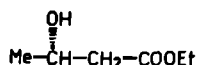
Reaction of the pure *threo* aldehyde (15) and the almost (95%) pure *threo* aldehydes (16) and (17) with (1a) in acetonitrile under ZnCl_2 catalysis and at room temperature delivered the corresponding 2,2-dimethoxyoxetanes. These compounds were not isolated but directly hydrolyzed²² to the 4-hydroxy- δ -lactones using THF and hydrochloric acid (18%) (Scheme 1, $n = 1$, $\text{R}^3 = \text{H}$, $\text{R}^5 = \text{Me}$). In this way (15) and (16) gave a 4:1 diastereomeric mixture of δ -lactones; crystallization of the lactones from hexane-ethyl acetate in the case of (16) afforded the major diastereomer (29) in pure form in a moderate yield. The product of (15), lactone (28), was obtained as a solid 4:1 mixture with its C-3-C-4 *erythro* isomer. The depicted structures (28) and (29) represent the major isomers of the synthesized 4-hydroxy-lactones; this assignment is based on the stereochemistry observed in the formation of oxetanes²⁹. For the same reason aldehyde (17) was expected to give the analogous lactone (30) as the main diastereomer after reaction with (1a) and subsequent hydrolysis. However, now the isomer ratio was 3:1 and (30) was purified by m.p.l.c. We did not isolate any products originating from the *erythro* isomers of (16) and (17). When (15) was reacted with (1b) in acetonitrile at 50°C and under ZnCl_2 catalysis (31) could be isolated after hydrolysis and crystallization, but now in low yield; the low yield of (31) compared to (28) is likely due to the lower reactivity of (1b) with regard to (1a).

Synthesis of a chiral 5,6-dihydro-2-pyrone

Eventually we tested the synthesis of optically active 5,6-dihydro-2-pyrones starting with a chiral β -hydroxyester. Seebach and coworkers³⁰ recently described an enantioselective preparation of S(+)- β -hydroxyesters from the corresponding β -ketoesters by yeast reduction. We followed this method using the ketobutyrate (32). Yeast reduction delivered the optically active alcohol (33) as described in a yield of 61% and with an e.e. of 84% ($[\alpha]_{\text{D}}^{20} + 36.6$ ($c = 4.5$, CHCl_3)). Protection with ethyl vinyl ether and subsequent reduction with LiAlH_4 delivered the protected diol (34) in good

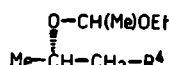


(32)



S(+)

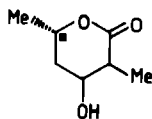
(33)



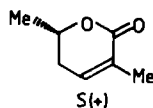
S(+)

(34) $\text{R}^4 = \text{CH}_2\text{OH}$

(35) $\text{R}^4 = \text{CHO}$



(36)



S(+)

(37)

yield. Oxidation of (34) with DMSO and oxalyl chloride proceeded well and gave the aldehyde (35) in a yield of 75% based on (33). Reaction of (35) with (1a) in acetonitrile at room temperature and under ZnCl_2 catalysis was complete within half an hour. We did not isolate the product of this reaction, but directly carried out a hydrolysis using THF and hydrochloric acid (18%) in order to isolate the 4-hydroxylactone (36). Dehydration of (36) to the desired (37) was tried without purification of (36). We used diisopropyl ether and toluene-*p*-sulphonic acid in a Dean-Stark apparatus for this purpose⁴. This procedure delivered a crude product containing *ca.* 50% (37). It was isolated in a moderate yield after an m.p.l.c. purification using cyclohexane-ethyl acetate (3:1). The specific rotation $[\alpha]_{\text{D}}^{20}$ was $+160^\circ$ (CHCl_3 , $c = 0.81$); the ^1H n.m.r. spectrum of (37) showed an e.e. of 80-85% in the presence of an optically active shift reagent ($\text{Eu}(\text{hfc})_3$). Although the method needs optimization the synthesis of (37) shows that the presented route has a good potential and that the chirality present in the starting β -hydroxyester is maintained in the formation of a 5,6-dihydro-2-pyrone (37).

Experimental

General methods

^1H n.m.r. spectra were recorded on a Varian T60 60 Mz, a Hitachi Perkin Elmer R-24B 60 Mz or a Bruker WH90 90 Mz spectrometer using CCl_4 or CDCl_3 with SiMe_4 as internal reference. Mass spectra were measured with a Varian SM1-B double focussing mass spectrometer or with a VG 7070E mass spectrometer. Elemental analyses were performed by Mr. P. van Galen (Microanalytical Department of our University). All other general methods were identical with those described previously^{13b,22}. Compounds (7-9) were synthesized as reported²². The silylenolether of butyraldehyde was prepared as described by House *et al.*³¹, b.p. 42-54°C/70 mmHg (lit.³¹: 52-62°C/75 mmHg).

3-Acetoxypropanal (2)

A mixture of propenal (56 g, 1.0 mole), glacial acetic acid (120 g, 2.0 mol) and sodium acetate (8.2 g, 0.1 mol) is stirred at room temperature for 16 h. Then the excess of acetic acid is largely evaporated *in vacuo*. The remaining oil is treated with ether (100 ml) and the precipitate (sodium acetate) is filtered off. After the filtrate has been concentrated *in vacuo* the remaining oil is distilled at low pressure using an oil pump to yield (2) (50.2 g, 43%), b.p. 35-40°C/0.5 mmHg; δ_{H} (CCl_4) 1.98 (3H, s, OCOMe), 2.67 (2H, d.tr, J 6 and 1.5 Hz, 2-H), 4.22 (2H, tr, J 6 Hz, 3-H), 9.60 (1H, tr, J 1.5 Hz, 1-H).

3-Acetoxybutanal (3)

A mixture of 2-butenal (70 g, 1.0 mole), glacial acetic acid (120 g, 2.0 mol) and sodium acetate (8.2 g, 0.1 mol) is stirred at 50°C for 72 h. After cooling to room temperature the reaction mixture is treated as described for (2) to yield (3) (6.5 g, 5%), b.p. 45-50°C/0.4 mmHg; δ_{H} (CCl_4) 1.30 (3H, d, J 6 Hz, 4-H), 1.95 (3H, s, OCOMe), 2.56 (2H, d.tr, J 6 and 1.5 Hz, 2-H), 5.20 (1H, br.sextet, J 6 Hz, 3-H), 9.52 (1H, tr, J 1.5 Hz, 1-H).

2-Ethyl-3-phenyl-3-trimethylsilyloxypropan-1-ol (5)

ZnCl₂ (0.5 ml of a saturated solution in acetonitrile) was added to a mixture of benzaldehyde (1.90 g, 18 mmol) and 1-trimethylsilyloxy-1-butene (3.20 g, 22 mmol) in acetonitrile (1.5 ml). The mixture was placed in a 7.5 ml teflon ampoule and acetonitrile (a few drops) was added to fill the ampoule completely. The closed ampoule was placed in a one wall piston-in-cylinder high-pressure apparatus³² and was pressurized at 12 kbar and 50°C for 96 h. After depressurising and cooling to room temperature triethylamine (TEA) (0.5 ml) was added and the solvent was evaporated. *n*-Pentane (*ca.* 40 ml) was added until a light precipitate was formed. The precipitate was filtered off. Evaporation of the solvent delivered the crude product. Bulb to bulb distillation afforded a (1:1) diastereomeric mixture of (5) (1.55 g, 34%), b.p. 95-105°C/0.6 mmHg; (Found: M⁺+1, 251.1115; C₁₄H₂₂O₂Si requires M+1, 251.1108); m/z 251 (M+1, 12%), 235 (M-Me, 16), 205 (18), 180 (22), 179 (M-CH(Et)CHO, 100), 177 (18), 161 (M-OSiMe₃, 20). δ_H (CDCl₃) 0.04 (9H, br.s, OSiMe₃), 0.84 and 0.87 (3H, 2 tr, J 9 Hz, Me), 1.16-2.00 (2H, m, -CH₂-Me), 2.36-2.67 (1H, m, 2-H), 4.86 and 5.04 (1H, 2d, J 7 and 5 Hz, 3-H), 7.32 (5H, br.s, Ph), 9.65 and 9.69 (1H, 2d, J 3 and 4 Hz, 1-H).

Synthesis of alcohols (12-14), general procedure

Ethyl vinyl ether (30 ml) and a β-hydroxyester (40 mmol) were mixed and cooled to 0°C. Trifluoroacetic acid (1 ml) was carefully added under vigorous stirring. The mixture was stirred at 0°C for 2 h and then left at 5°C for 16 h. Then TEA (7 ml) was added and the excess ethyl vinyl ether was evaporated. Diisopropyl ether (100 ml) was added and the mixture was washed with water (2 x 30 ml) and brine (30 ml). The combined aqueous layers were extracted with diisopropyl ether (25 ml) and the combined ethereal layers were dried (Na₂SO₄). After evaporation of the solvent crude products were isolated with purities >92% according to G.C. The crude products were solved in dry ether (40 ml) and dropped into a suspension of LiAlH₄ (1.6 g, 42 mmol) in dry ether (200 ml) at room temperature. After the addition was complete the mixture was refluxed for 4 h and allowed to come to room temperature. Then the

excess LiAlH_4 was destroyed carefully by addition of water (ca. 3 ml) and potassium hydroxide (ca. 4 ml of a 15% solution). The resulting suspension was filtered and the remaining salts were washed with ether (2 x 15 ml). The combined filtrates were dried (Na_2SO_4) and the solvent was evaporated to yield the crude products. Distillation on a short vigreux column (10 x 1 cm) or bulb to bulb distillation afforded the pure products as (1:1) diastereomeric mixtures.

In this way were prepared:

3-(1-Ethoxyethoxy)-2-methyl-3-phenylpropan-1-ol (12) (7.2 g, 76%), b.p. 100–110°C/0.4 mmHg; (Found: $M^+ + 1$, 239.1652. $\text{C}_{14}\text{H}_{22}\text{O}_3$ requires $M + 1$, 239.1647); m/z (CI) 239 ($M + 1$, 1%), 221 ($M - \text{OH}$, 2), 193 ($M - \text{EtOH}$, 3), 149 ($M - \text{OCH}(\text{Me})\text{OEt}$, 40), 131 ($M - \text{OCH}(\text{Me})\text{OEt}$, $-\text{H}_2\text{O}$, 22), 73 ($\text{C}(\text{Me})\text{OEt}^+$, 100); ν_{max} (CHCl_3) 3600–3300 (OH), 3140–2860 (C–H), 1510–1370 (C–H), 1170–1010 cm^{-1} (C–O); δ_{H} (CDCl_3) 0.71 and 0.73 (3H, 2d, J 7 Hz, 2-Me), 0.93 and 1.22 (3H, 2tr, J 7 Hz, $\text{OCH}_2\text{-Me}$), 1.24 and 1.31 (3H, 2d, J 7 Hz, $\text{OCH}(\text{Me})\text{OEt}$), 1.78 (1H, br.s, OH), 1.76–2.31 (1H, m, 2-H), 2.99–3.98 (4H, m, $\text{OCH}_2\text{-Me}$, 3-H), 4.22 and 4.45 (1H, 2d, J 9 Hz, 1-H), 4.44 and 4.58 (1H, 2q, J 5 Hz, $\text{OCH}(\text{Me})\text{OEt}$), 7.31 (5H, br.s, Ph).

3-Cyclohexyl-3-(1-ethoxyethoxy)-2-methylpropan-1-ol (13) (7.0 g, 72%), b.p. 120–130°C/0.5 mmHg; (Found: $M^+ - \text{OEt}$, 199.1699. $\text{C}_{12}\text{H}_{23}\text{O}_2$ requires 199.1698); m/z (CI) 245 ($M + 1$, 1%), 199 ($M - \text{OEt}$, 74), 155 ($M - \text{OCH}(\text{Me})\text{OEt}$, 100), 153 (18), 137 (30); ν_{max} (CHCl_3) 3600–3300 (OH), 3020–2860 (C–H), 1480–1380 (C–H), 1170–970 cm^{-1} (C–O); δ_{H} (CDCl_3) 0.84–2.09 (21H, m, *c*-Hex-H, 2-H, 2-Me, $\text{OCH}(\text{Me})\text{OCH}_2\text{-Me}$), 2.59 (1H, br.tr, J 6 Hz, OH), 3.20–4.03 (5H, m, 1-H, 3-H, $\text{OCH}_2\text{-Me}$), 4.60 and 4.72 (1H, 2q, J 6 Hz, $\text{OCH}(\text{Me})\text{OEt}$).

2,4-Dimethyl-3-(1-ethoxyethoxy)-pentan-1-ol (14) (5.95 g, 73%), b.p. 65–68°C/0.5 mmHg; (Found: $M^+ + 18$, 222.2084. $\text{C}_{11}\text{H}_{24}\text{O}_3$ requires $M + 18$, 222.2069); m/z (CI, NH_3) 222 ($M + 18$, 6%), 176 (72), 159 ($M - \text{OEt}$, 81), 150 (100), 133 (32); ν_{max} (NaCl) 3610–3160 (OH), 3000–2780 (C–H), 1450 (C–H), 1380 (C–H), 1180–990 cm^{-1} (C–O); δ_{H} (CDCl_3)

0.73-1.39 (15H, m, 2,4-Me, 5-H, CH(Me)OCH₂-Me), 1.56-2.09 (2H, m, 2-H, 4-H), 2.49 (1H, br.s, OH), 3.21-3.73 (5H, m, 1-H, 3-H, OCH₂-Me), 4.62 and 4.73 (1H, 2q, J 5 Hz, OCH(Me)).

Synthesis of aldehydes (15-17), general procedure

Aldehydes (15-17) were prepared as described by Swern *et al.*²⁷, using DMSO and oxalyl chloride in dichloromethane; the procedure was executed on a 20 mmole scale.

In this way were prepared:

3-(1-Ethoxyethoxy)-2-methyl-3-phenylpropan-1-al (15) (4.1 g, 86%), b.p. 100-110°C/0.5 mmHg; m/z (CI) 221 (M-Me, 2), 191 (M-OEt, 9), 147 (M-OCH(Me)OEt, 59), 135 (16), 119 (27), 73 (100); ν_{\max} (CHCl₃) 3100-2810 (C-H), 1730 (CO), 1500-1370 (C-H), 1170-1000 cm⁻¹ (C-O); δ_{H} (CDCl₃) 0.86 and 0.87 (3H, 2d, J 7 Hz, 2-Me), 0.91 and 1.19 (3H, 2tr, J 7 Hz, OCH₂-Me), 1.23 and 1.25 (3H, 2d, J 7 Hz, OCH(Me)), 2.56-3.64 (3H, m, 2-H, OCH₂-Me), 4.39-4.84 (2H, m, 1-H, OCH(Me)), 7.31 (5H, br.s, Ph), 9.83 (1H, d, J 3 Hz, CHO).

3-Cyclohexyl-3-(1-ethoxyethoxy)-2-methylpropan-1-al (16) (3.95 g, 81%), b.p. 100-110°C/0.3 mmHg; (Found: M⁺-OEt, 197.1537. C₁₂H₂₁O₂ requires 197.1542); m/z (CI, NH₃) 260 (M+18, 4*), 216 (11), 215 (20), 214 (44), 198 (13), 197 (M-OEt, 100), 196 (15), 188 (11), 170 (18), 153 (M-OCH(Me)OEt, 31), 73 (20); ν_{\max} (CHCl₃) 3010-2810 (C-H), 1725 (CO), 1450 (C-H), 1200-1070 cm⁻¹ (C-O); δ_{H} (CDCl₃) 0.82-2.07 (20H, m, *c*-Hex-H, 2-Me, OCH(Me)OCH₂-Me), 2.44-2.84 (1H, m, 2-H), 3.33-3.76 (3H, m, 1-H, OCH₂-Me), 4.51-4.82 (1H, m, OCH(Me)), 9.76 (1H, d, J 2 Hz, CHO).

Methyl 5-acetoxy-3-hydroxy-2-methylpentenoate (20)

AlCl₃Obornyl (1.0 ml of a 0.55 M solution in ether) was added to a stirred mixture of (2) (4.65 g, 40 mmol) and (1a) 4.45 g, 44 mmol) in dry dichloromethane (15 ml) at -78°C. After 30 min the mixture was allowed to warm up to -10°C, and water (15 ml) was added. This mixture was stirred vigorously for 1 h at -10°C and then allowed to come to room temperature. The dichloromethane layer was separated

and the aqueous layer was extracted with dichloromethane (3 x 20 ml). The combined dichloromethane layers were dried (Na_2SO_4) and the solvent was evaporated to yield a crude mixture containing ca. 90% (20). Bulb to bulb distillation, using a container and receivers previously treated with base (TEA), afforded (20) as an 8:1 diastereomeric mixture (6.9 g, 84%), b.p. 90–100°C/0.5 mmHg; (Found: C, 52.84; H, 7.91; $\text{C}_9\text{H}_{16}\text{O}_5$ requires C, 52.93; H, 7.90%); ν_{max} (CCl_4) 3660–3220 (OH), 3010–2840 (C–H), 1750–1710 (CO), 1450 and 1380 (C–H), 1235 cm^{-1} (C–O); δ_{H} (CCl_4) (major isomer) 1.20 (3H, d, J 7 Hz, 2-Me), 1.73 (2H, d.tr, J 6 and 6 Hz, 4-H), 2.05 (3H, s, OCOMe), 2.30–2.77 (1H, m, 2-H), 2.83 (1H, br.s, OH), 3.67 (3H, br.s, COOMe), 3.95 (1H, d.tr, J 6 and 4 Hz, 3-H), 4.18 (2H, br.tr, J 6 Hz, 5-H).

4-Hydroxy-3-methyl-tetrahydro-2-pyrone (21)

(20) (4.1 g, 20 mmol) Was added to a vigorously stirred solution of KOH (15 ml of a 30% solution). The mixture was stirred at room temperature for 16 h and than carefully acidified to pH < 1 with sulphuric acid (ca. 14 ml of a 30% solution), whereas the temperature of the reaction mixture was not allowed to rise above 30°C. The water was almost completely evaporated and the resulting mixture was extracted with dichloromethane (5 x 30 ml). The combined dichloromethane layers were dried (Na_2SO_4) and the solvent was evaporated. Bulb to bulb distillation of the crude product afforded (21) as an 8:1 diastereomeric mixture (1.56 g, 60%), b.p. 120–130°C/0.3 mmHg; m/z (EI) 130 (M^+ , 54%), 112 (M– H_2O , 65), 102 (M–CO, 14), 74 (M– $\text{C}_3\text{H}_4\text{O}$, 25), 71 (M– $\text{CO}_2\text{-Me}$, 100); ν_{max} (CHCl_3) 3600 (OH), 3650–3250 (OH), 3010–2850 (C–H), 1730 (CO), 1400 (C–H), 1280–1080 cm^{-1} (C–O); δ_{H} (CDCl_3) 1.30 and 1.36 (3H, 2d, J 7 Hz, 3-Me), 1.58–2.71 (3H, m, 5-H, 3-H), 3.49 (1H, br.s, OH), 3.71–3.94 (1H, m, 4-H), 4.09–4.64 (2H, m, 6-H).

3-Methyl-5,6-dihydro-2-pyrone (22)

(21) (1.3 g, 10 mmol) Was added dropwise to concentrated sulphuric acid (5.0 g) at 0°C. The mixture turns into dark brown within 10 min. After stirring for 45 min the mixture was poured on ice (50 g) and carefully neutralized with sodium hydrogen carbonate (8.5 g).

Dichloromethane (20 ml) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 x 20 ml). The combined dichloromethane layers were dried (Na_2SO_4) and the solvent was evaporated. Bulb to bulb distillation affords (22) (0.71 g, 56%), b.p. 42-44°C/2 mmHg; m/z (EI) 112 (M, 100%), 97 (M-Me, 5), 84 (M-CO, 18), 68 (M-CO₂, 11); ν_{max} (CCl₄) 3040-2880 (C-H), 1730 (CO), 1470-1360 (C-H), 1130 cm⁻¹ (C-O); δ_{H} (CDCl₃) 1.91 (3H, q, J 2 Hz, 3-Me), 2.21-2.61 (2H, m, 5-H), 4.35 (2H, tr, J 6 Hz, 6-H), 6.61 (1H, m, 4-H).

3,6-Dimethyl-5,6-dihydro-2-pyrone (25)

AlCl₃Obornyl (0.5 ml of a 0.55 M solution in ether) was added to a stirred mixture of (3) (2.0 g, 15.4 mmol) and (1a) (1.75 g, 17 mmol) in dichloromethane (5 ml) at -78°C. The mixture was stirred for 30 min and then treated as described for (20). After work-up the product was directly saponified, cyclized and dehydrated as described for (21) and (22), respectively, without purification of the intermediate products. After final work-up the crude product (750 mg) was purified by bulb to bulb distillation to yield (25) (610 mg, 28%), b.p. 75-90°C/0.6 mmHg (lit.⁴: 55-60°C/0.2 mmHg, m.p. 31-33°C); (Found: C, 65.86; H, 8.09. Calc. for C₇H₁₀O₂: C, 66.65; H, 7.99%); m/z (EI) 126 (M⁺, 85%), 111 (M-Me, 10), 82 (M-CO₂, 100), 54 (25); ν_{max} (CCl₄) 3010-2810 (C-H), 1720 (CO), 1380-1330 (C=C), 1250 and 1120 cm⁻¹ (C-O); δ_{H} (CDCl₃) 1.41 (3H, d, J 6 Hz, 6-Me), 1.91 (3H, q, J 1.8 Hz, 3-Me), 2.20-2.40 (2H, m, 5-H), 4.52 (1H, br.sextet, J 6 Hz, 6-H), 6.47-6.64 (1H, m, 4-H).

5-Ethyl-3-methyl-6-phenyl-5,6-dihydro-2-pyrone (27)

ZnCl₂ (0.5 ml of a saturated solution in acetonitrile) was added to a stirred mixture of (5) (1.15 g, 4.6 mmol) and (1a) (1.65 g, 16 mmol) in acetonitrile (5 ml) at room temperature. The mixture was stirred for 2 h and the work-up was performed as previously described²². Toluene (100 ml) and toluene-p-sulphuric acid (ca. 100 mg) were added to the crude product and the mixture was refluxed for 16 h in a Dean-Stark apparatus. After cooling the mixture was extracted with water (2 x 25 ml) and brine (25 ml).

The combined aqueous layers were extracted with toluene (25 ml) and the combined organic layers were dried (Na_2SO_4). Evaporation of the solvent yielded a crude product (1.4 g). M.p.l.c. of a part of the crude product (500 mg) using silica gel and hexane-diisopropyl ether (5:3) afforded an 1:1 diastereomeric mixture of (27) (250 mg); this corresponded to a yield of 70%, b.p. 125-145°C/0.4 mmHg; (Found: $M^+ + 1$, 217.1231. $\text{C}_{14}\text{H}_{16}\text{O}_2$ requires $M + 1$, 217.1228); m/z (CI) 217 ($M + 1$, 100%), 199 ($M - 17$, 24), 171 ($M - 45$, 13), 139 ($M - \text{Ph}$, 16), 110 ($M - \text{Ph}$, $-\text{Et}$, 30); ν_{max} (CCl_4) 3100-2840 (C-H), 1725 (CO), 1610-1480 (C-H), 1280-1200 cm^{-1} (C-O); δ_{H} (CDCl_3) 0.68-1.53 (5H, m, Et), 1.99 (3H, q, J 1.5 Hz, Me), 2.27-2.82 (1H, m, 5-H), 5.09 and 5.58 (1H, 2d, J 10 and 4 Hz, 6-H), 6.56 and 6.87 (1H, 2dq, J 2.5 and 1.5 Hz, J 6 and 1.5 Hz, 4-H), 7.36 (5H, br.s, Ph).

Synthesis of 4-hydroxy-3-methyl- δ -lactones (28-30)

ZnCl_2 (0.5 ml of a saturated solution in acetonitrile) was added to a stirred mixture of the appropriate aldehyde (15-17) (2 mmol) and (1a) (310 mg, 3 mmol) in acetonitrile (1 ml) at room temperature. The mixture was stirred for 1 h and TEA (0.5 ml) and THF (15 ml) were added. The mixture was cooled to -78°C and a solution of toluene-*p*-sulphonic acid (15 mg) in MeOH (1.5 ml) was added. The mixture was kept at -78°C for 0.5 h and allowed to warm up to room temperature. Hydrochloric acid (10 ml of a 18.5% solution) was added and the mixture was stirred for 36 h. Then brine (20 ml) was added and the ethereal layer was separated. The aqueous layer was extracted with ether (4 x 25 ml). The combined ethereal layers were washed with brine (25 ml), dried (Na_2SO_4) and the solvent was evaporated. The resulting faint yellow oils in the case of (28) and (29) contained a 4:1 diastereomeric mixture of δ -lactones according to capillary G.C. Crystallization from hexane-diisopropyl ether-ethyl acetate afforded the major diastereomer in the case of (29) in pure form. In the case of (30) the resulting oil contained a 3:1 diastereomeric mixture of δ -lactones and the major isomer was purified *via* m.p.l.c. using silica gel and *c*-hexane-ethyl acetate (3:1).

In this way were prepared:

3,5-Dimethyl-4-hydroxy-6-phenyl-3,4,5,6-tetrahydro-2-pyrone (28), 4:1 diastereomeric mixture (270 mg, 61%), m.p. 134-137°C (hexane-ethyl acetate); (Found: C, 70.52; H, 7.28%; M^+ , 220.1097. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%; M , 220.1099); m/z (EI) 220 (M , 2%), 118 (16), 117 (12), 107 (Ph-CHOH, 100); ν_{max} (CHCl₃) 3600 (OH), 3620-3300 (OH), 3110-2860 (C-H), 1735 (CO), 1470 (C-H), 1370 cm⁻¹ (C-H); δ_H (CDCl₃) 0.92 and 0.97 (3H, 2d, J 7 Hz, 5-Me), 1.36 and 1.41 (3H, 2d, J 7 Hz, 3-Me), 1.59 (1H, br.s, OH), 1.93-2.32 (1H, m, 5-H), 2.68-3.02 (1H, m, 3-H), 3.86 (1H, dd, J 5 and 4 Hz, 4-H), 4.74 and 5.27 (1H, 2d, J 11 Hz, 6-H), 7.36 (5H, br.s, Ph).

3,5-Dimethyl-6-cyclohexyl-4-hydroxy-3,4,5,6-tetrahydro-2-pyrone (29) (182 mg, 40%), m.p. 124-126°C (hexane-ethyl acetate); (Found: C, 68.66; H, 9.75%; M^+ +1, 227.1648. $C_{13}H_{22}O_3$ requires C, 68.99; H, 9.80%; M +1, 228.1647); m/z (CI) 227 (M +1, 23%), 209 (M -OH, 13), 191 (12), 153 (M -C₃H₄O₂, 100), 143 (M -Hex^C, 13), 135 (20); ν_{max} (CHCl₃) 3640-3300 (OH), 3020-2860 (C-H), 1740 (CO), 1450 (C-H), 1400-1370 (C-H), 1260-1180 cm⁻¹ (C-O); δ_H (CDCl₃) 1.06 (3H, d, J 7 Hz, 5-Me), 1.27 (3H, d, J 7 Hz, 3-Me), 0.97-2.20 (12H, m, Hex^C-H, 5-H), 1.58 (1H, br.s, OH), 2.69 (1H, dq, J 7 and 4 Hz, 3-H), 3.62-3.78 (2H, m, 4-H and 6-H).

3,5-Dimethyl-6-(α -methyl)ethyl-4-hydroxy-3,4,5,6-tetrahydro-2-pyrone (30) (165 mg, 44%), m.p. 67-69°C (hexane-ethyl acetate); (Found: C, 64.33; H, 9.69%; M^+ +1, 187.1330. $C_{10}H_{18}O_3$ requires C, 64.49; H, 9.74%; M +1, 187.1334); m/z (CI) 187 (M +1, 24%), 169 (M -OH, 12), 143 (M -Prⁱ, 8), 126 (M -OH, -Prⁱ, 15), 113 (M -Prⁱ, -2Me, 100), 69 (15); δ_H (CDCl₃) 0.97 and 1.06 and 1.09 (9H, 3d, J 7 Hz, Prⁱ and 5-Me), 1.29 (3H, d, J 7 Hz, 3-Me), 1.56 (1H, br.s, OH), 1.74-2.13 (2H, m, α -H, 5-H), 2.69 (1H, dq, J 7 and 2 Hz, 3-H), 3.64-3.82 (2H, m, 4-H, 6-H).

4-Hydroxy-6-phenyl-3,3,5-trimethyl-3,4,5,6-tetrahydro-2-pyrone (31)
 ZnCl_2 (0.5 ml of a saturated solution in acetonitrile) was added to a stirred mixture of (15) (475 mg, 2 mmol) and (1b) (465 mg, 4 mmol) in acetonitrile (2 ml), and the mixture was heated at 50°C for 16 h. TEA (0.5 ml) was added and the temperature was allowed to come to room temperature. Then the mixture was treated as described for (30-32). The crude product was crystallized using hexane-diisopropyl ether-ethyl acetate to yield (31) (55 mg, 12%), m.p. 152-154°C (hexane-ethyl acetate). (Found: C, 71.87; H, 7.80%; M^+ , 235.1332. $\text{C}_{14}\text{H}_{18}\text{O}_3$ requires C, 71.77; H, 7.74%; M^+ , 235.1334); m/z 235 (M^+ , 6%), 217 ($M-\text{OH}$, 7), 171 ($M-3\text{Me}$, $-\text{H}_2\text{O}$, 16), 145 (13), 139 ($M-\text{Ph}$, $-\text{H}_2\text{O}$, 25), 119 (78), 118 (22), 117 (100); ν_{max} (CHCl_3) 3700 (OH), 3600 (OH), 3580-3360 (OH), 3140-2860 (C-H), 1725 (CO), 1530 (C-H), 1430 (C-H), 1280-1160 cm^{-1} (C-O); δ_{H} (CDCl_3) 0.93 (3H, d, J 6 Hz, 5-Me), 1.40 and 1.46 (6H, 2s, 3-Me), 1.83 (1H, br.d, J 5 Hz, OH), 2.04-2.38 (1H, m, 5-H), 3.61 (1H, dd, J 11 and 5 Hz, 4-H), 4.74 (1H, d, J 11 Hz, 6-H), 7.36 (5H, br.s, Ph).

S(+)-3,6-Dimethyl-5,6-dihydro-2-pyrone (37)

Pyrone (37) was synthesized from 3-hydroxybutyrate (33) which was prepared by yeast reduction of the corresponding β -ketobutyrate (32) as described by Seebach *et al.*³⁰, yield 61%, b.p. 74-76°C/15 mmHg, $[\alpha]_{\text{D}}^{21} + 36.6^\circ$ (CHCl_3 , $c = 4.1$) (lit.³⁰: b.p. 71-73°C/12 mmHg, $[\alpha]_{\text{D}}^{25} + 37.2^\circ$ (CHCl_3 , $c = 1.3$)).

Alcohol (34) and aldehyde (35) were synthesized as described for (12) and (15). The products were distilled and identified on the basis of their ^1H n.m.r. spectra; 3-(1-ethoxyethoxy)-butan-1-ol (34), yield 86%, b.p. 98-100°C/15 mmHg; δ_{H} (CDCl_3) 1.09-1.37 (9H, m, 4-H, $\text{OCH}(\text{Me})\text{OCH}_2\text{Me}$), 1.58-1.83 (2H, m, 2-H), 2.29 and 2.96 (1H, br.tr, J 6 Hz, OH), 3.31-4.16 (5H, m, 1-H, 3-H, OCH_2Me), 4.69 and 4.73 (1H, 2q, J 5 Hz, OCHOEt);

3-(1-ethoxyethoxy)-butan-1-al (35), yield 82%, b.p. 95-105°C/14 mmHg; δ_{H} (CDCl_3) 1.09-1.37 (9H, m, 4-H, $\text{OCH}(\text{Me})\text{OCH}_2\text{Me}$), 2.49-2.69 (2H, m, 2-H), 3.32-3.78 (2H, m, OCH_2Me), 4.24 (1H, br.septet, Me-CH-CH_2), 4.77 (1H, br.q, $\text{OCH}(\text{Me})\text{OEt}$).

Aldehyde (35) was reacted with (1a) as described for (15). The crude product was refluxed with diisopropyl ether (50 ml) and toluene-*p*-sulphuric acid (100 mg) in a Dean-Stark apparatus for 16 h. After cooling to room temperature the diisopropyl ether solution was washed with brine (3 x 20 ml) and dried (Na_2SO_4). After evaporation of the solvent the crude product (500 mg, prepared from 5 mmol of (35)) was purified by m.p.l.c. using silica gel and *c*-hexane-ethyl acetate (3:1) to yield (37) as an colorless oil (240 mg, 38%), $[\alpha]_{\text{D}}^{21} + 160^\circ$ (CHCl_3 , $c = 0.8$). An ^1H n.m.r. spectrum in the presence of $\text{Eu}(\text{hfc})_3$ showed an e.e. of 80-85% (6-Me signal) indicating that the chirality was maintained during the reaction sequence. ^1H n.m.r. mass and i.r. spectra were identical with those of (25).

References

1. G. Ohloff, in 'Prog. Chem. Org. Nat. Prod.', ed. L. Zechmeister, Springer Verlag, Wien, 1978, vol. 35, p. 431.
2. J.M. Brand, J. Young and R.M. Silverstein, in 'Prog. Chem. Org. Nat. Prod.', ed. L. Zechmeister, Springer Verlag, Wien, 1980, vol. 37, p. 1.
3. W.H. Pirkle and P.E. Adams, *J. Org. Chem.*, 1979, 44, 2169.
4. R. Bacardit and M. Moreno-Mañas, *J. Chem. Ecol.*, 1983, 9, 703.
5. K. Mori and S. Senda, *Tetrahedron*, 1985, 41, 541.
6. M. Pohmakotr and P. Jarupan, *Tetrahedron Lett.*, 1985, 26, 2253.
7. R.W. Dugger and C.H. Heathcock, *J. Org. Chem.*, 1980, 45, 1181.
8. R.M. Carlson, A.R. Oyler and J.R. Peterson, *J. Org. Chem.*, 1975, 40, 1610.
9. N.C. Barua and R.R. Schmidt, *Synthesis*, 1986, 1067.
10. D.B. Gerth and B. Giese, *J. Org. Chem.*, 1986, 51, 3726.
11. H.A. Khan and I. Paterson, *Tetrahedron Lett.*, 1982, 23, 5083.
12. R.W.M. Aben, R.G. Hofstraat and J.W. Scheeren, *Recl. Trav. Chim. Pays-Bas*, 1981, 100, 355.
13. J.W. Scheeren, R.W.M. Aben, P.H.J. Ooms and R.J.F. Nivard, *J. Org. Chem.*, 1977, 42, 3128.
14. R. Tsumara, M. Kanemura and N. Ishii, Jap. Pat. Kokai 75 05.315, (Cl. 16B602.2, 21 Jan. 1975); *C.A.*, 1975, 83, P27573q.
15. Y. Yamamoto, K. Maruyama and K. Matsumoto, *J. Am. Chem. Soc.*, 1983, 105, 6963.
16. a. G. Wittig, H.D. Frommelt and P. Suchanek, *Angew. Chem.*, 1963, 75, 978.
b. W.G. Dauben, G.H. Beasley, M.D. Broadhurst, B. Muller, D.J. Peppard, P. Pesnelle and C. Suter, *J. Am. Chem. Soc.*, 1975, 97, 4793.
17. A.I. Meyers, J.L. Durandetta and R. Munavu, *J. Org. Chem.*, 1975, 40, 2025.
18. Hydrolysis according to the method of Dauben^{16b} of the β -hydroxy-imine obtained from 2-methylpropionaldehyde and N-ethylidene cyclohexylamine resulted in a mixture of the starting hydroxy-imine and the α,β -unsaturated aldehyde.

By following the method of Meyers using butyraldehyde, we could isolate the MOM-protected β -hydroxyaldehyde, albeit in very low yield (ca. 10%); reduction of the thiazoline to the thiazolidine with aluminium amalgam appeared in our hands not to be straightforward

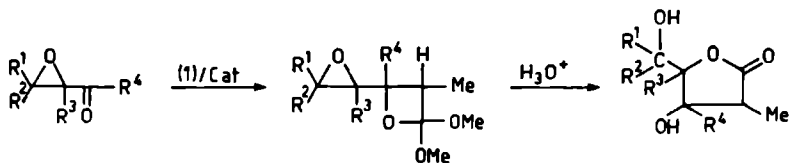
19. E.J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 19, 2317.
20. a. S. Masamune, H. Murase, N. Matsue and A. Murai, *Bull. Chem. Soc. Jpn.*, 1979, 52, 135.
b. R.-T. Gröbel and D. Seebach, *Synthesis*, 1977, 357.
21. C.H. Heathcock, in 'Asymmetric Synthesis', ed. J.D. Morrison, Academic Press, New York, 1984, vol. 3B, p. 111; A.I. Meyers, *Ibid.*, p. 213.
22. R.G. Hofstraat, J.W. Scheeren and R.J.F. Nivard, *J. Chem. Soc. Perkin I*, 1985, 561.
23. R.W.M. Aben and J.W. Scheeren, *Synthesis*, 1978, 401.
24. J.J. Tufariello and E.J. Trybulski, *J. Org. Chem.*, 1974, 39, 3378.
25. a. G.E. Keck, D.F. Kachensky and E.J. Enholm, *J. Org. Chem.*, 1985, 50, 4317.
b. R.W. Hoffmann and U. Weidmann, *Chem. Ber.*, 1985, 118, 3966.
c. L. Banfi, A. Bernardi, L. Colombo, C. Gennari and C. Scolastico, *J. Org. Chem.*, 1984, 49, 3784.
26. R. Ratcliff and R. Rodehorst, *J. Org. Chem.*, 1970, 35, 4000.
27. A.J. Mancuso and D. Swern, *Synthesis*, 1981, 165.
28. a. E.L. Eliel and D. Nasipuri, *J. Org. Chem.*, 1965, 30, 3812.
b. R.W. Aben and H.W. Scheeren, *Synthesis*, 1982, 779.
c. P. Barbier and C. Benezra, *J. Org. Chem.*, 1983, 48, 2705.
29. It has been demonstrated that under the applied reaction circumstances aldehydes having an α -branched side chain can be selectively converted into *trans* oxetanes with (1a). These *threo* oxetanes yield *threo* β -hydroxyesters after hydrolysis. See ref. 22.
30. D. Seebach, M.A. Sutter, R.H. Weber and M.F. Züger, *Org. Synth.*, 1985, 63, 1.
31. H.O. House, L.J. Czuba, M. Gall, H.D. Olmsteadt, *J. Org. Chem.*, 1969, 34, 2324.
32. R.W.M. Aben and J.W. Scheeren, *J. Org. Chem.*, 1987, in press.

The use of 1,1-Dimethoxypropene
as Propionate Equivalent in the Synthesis of some
Eudesmanolide Precursors from α,β -Epoxyketones

Introduction

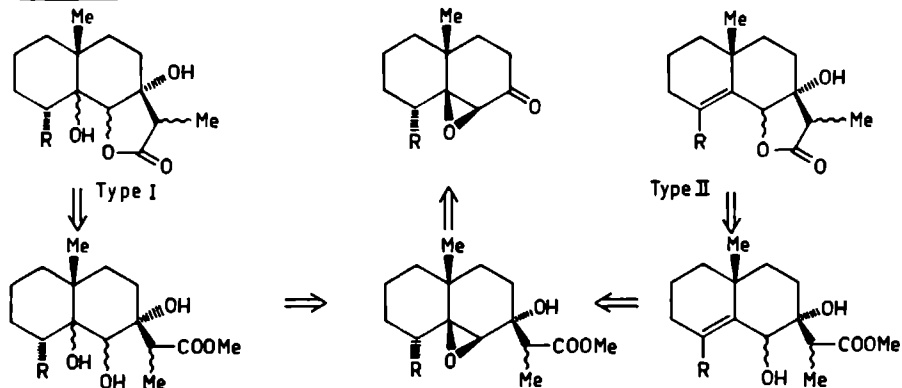
In a preceding paper we showed that 1,1-dimethoxypropene (1a) is a very useful synthon for the preparation of α -methyl- β -hydroxy- γ -(1-hydroxyalkyl)- γ -lactones *via* the corresponding 2,2-dialkoxyoxetanes (Scheme 1)^{1,2}.

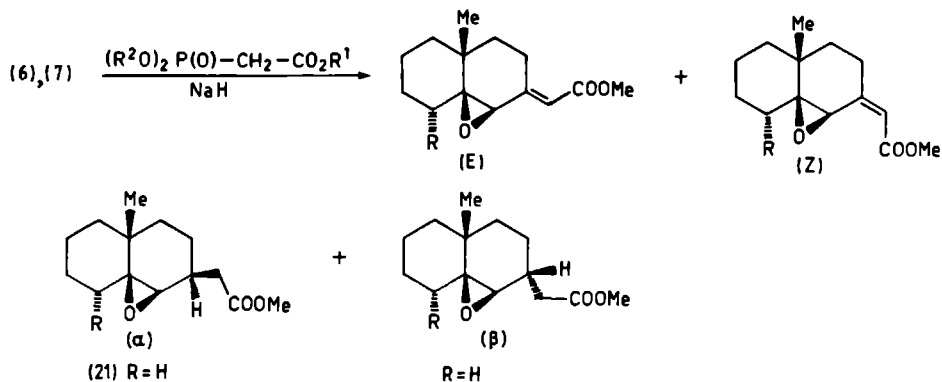
Scheme 1



The method provides a very mild, acidic route to this type of γ -lactones starting from readily available compounds. In order to extend the scope of this reaction and to judge the versatility of this lactone synthesis we decided to test it in the preparation of sesquiterpene lactones. As a first objective we chose the synthesis of some simple eudesmanolide precursors of type I and II (Scheme 2).

Scheme 2





Reactions of (1) with epoxyketones (5-9)

Epoxyketones (5), (6) and (7) are easily available through a base-catalyzed epoxidation of the corresponding enones (2-4)^{5,6} with hydroperoxide⁷. In the case of (3) and (4) the epoxidation yields a mixture of a *cis*- and a *trans*-epoxyketone in which the *cis*-isomer predominates^{7,8}. The *cis*-*trans* isomers can be separated by crystallization from petroleum ether.

A priori, reaction of (1) with an epoxyketone may give a mixture of four 'epoxyoxetanes', as a consequence of either α- or β-attack of (1), and the formation of *cis*- and *trans*-oxetanes. Regarding the two conformations of the model compound (5) which have the lowest energy⁹ (Figure 1), attack by (1) should be equally possible from

Figure 1

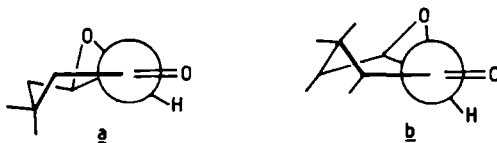
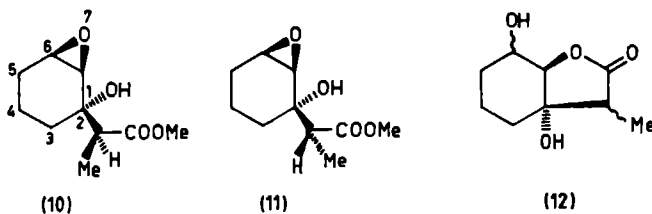


Figure 1: Lowest, energy half-chair conformations⁹ of (5).

either site (α and β) with nearly equal rate; consequently we expected a low selectivity. In the case of epoxyketones (6) and (7) the *cis*-decaline structure will probably introduce such steric requirements that the reaction with (1) will proceed with higher selectivity. Epoxyketones (8) and (9) having a rather flat *trans*-decaline structure are not expected to react very selectively.

Introductory experiments with epoxyketone (6) indicated that (6) is less reactive than (5); under the conditions previously described (*i.e.* at low temperature, in dichloromethane, under AlCl_3OR -catalysis and using 1.1 equivalent of (1a)) (6) showed only a low degree of conversion (30-40%). Hence, conditions were changed. Better conversions were obtained at room temperature using a fourfold excess of (1a), ZnCl_2 -catalysis and acetonitrile as the solvent.

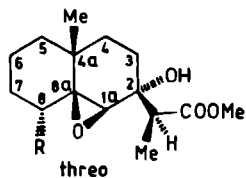
Under these conditions reaction of (1a) with the model compound (5) gave a mixture of diastereomeric oxetanes. Subsequent methanolysis and hydrolysis in a one-pot procedure¹⁰ afforded a mixture of only two diastereomeric epoxyesters in a ratio of about 1:1 according to the ^1H n.m.r. spectrum; capillary G.C. gave only one broad signal. Thus the reaction of (5) with (1a) was more selective than expected. The isolated epoxy-



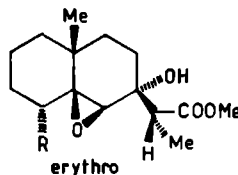
esters have tentatively been assigned the structures (10) and (11). As the oxetane formation is reversible under the acidic conditions we suppose that both epoxyesters are derived from an oxetane having the ketene acetal moiety in an equatorial position relative to the six-membered ring. We anticipated a low *threo* vs *erythro* selectivity as molecular models* of (5) showed that in the cyclohexane ring steric hindrance at both sides of the carbonyl group is about the same (Fig. 1).

*Orbit molecular building system, cochrans of Oxford, Fairspear House, Leafield, Oxford, U.K. Available *via* Aldrich.

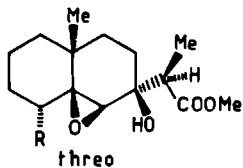
Reaction of (6) under the improved conditions gave a mixture of oxetanes in good yield (conversion 85%). The compounds were relatively stable and could be isolated as a mixture; hydrolysis *via* the 'one-pot procedure' furnished a mixture of the four possible epoxyesters (13-16).



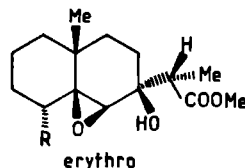
(13) R = H
(17) R = Me



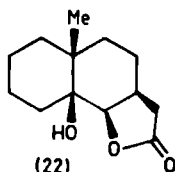
(14) R = H
(18) R = Me



(15) R = H
(19) R = Me



(16) R = H
(20) R = Me



The ratio of the epoxyesters in this case could be determined by capillary G.C.¹¹ and appeared 14:7:1:1. Medium pressure column chromatography (m.p.l.c.) using silica gel and a chloroform-hexane mixture afforded the two main diastereomers in pure form, and a mixture of the two minor diastereomers as a third fraction. Fortunately, the less abundant of the main diastereomers, crystallized; its configuration (14) was established by X-ray analysis¹² (Figure 2). It was now secured that (14) had arisen from an equatorial β -attack of (1a).

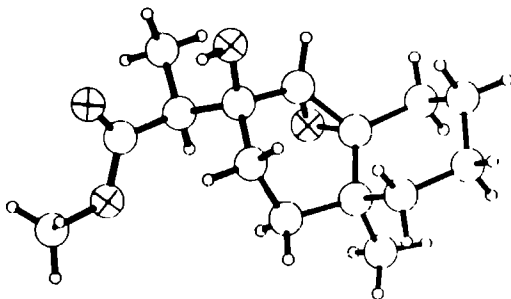


Figure 2: X-ray structure of (14);
 ⊗ = oxygen

On the basis of the X-ray analysis we assumed that the main product has the configuration (13). Later on this was confirmed independently (*vide*). The *threo:erythro* ratio (2:1) could equally be anticipated on account of the results obtained in the reaction of (5) with (1a). Molecular models show that in the more rigid (6) the larger steric hindrance is at the epoxy site of the carbonyl group. This favours the formation of a *trans*-oxetane and thus of a *threo* ester (13). It is noteworthy that the *cis*-configuration of the C₂-alkyl substituent relative to the angular methyl group in the main products (13) and (14) is a structural feature of the naturally occurring eudesmanolides¹³. Attempts to increase the excess of (13) with regard to diastereomers (14-16) failed; the use of diethylketene acetal (1b) gave essentially the same yields and isomer distribution of the resulting ethyl esters. High pressure conditions (12 kbar, 18 h) gave after work up also a 2:1 diastereomeric mixture of the esters (13) and (14).

The *trans*-epoxyketone (8) showed the same reactivity as (6), but it reacted less stereoselective with (1a); as expected it gave a smaller ratio of equatorial- *versus* axial-attack as appeared from capillary G.C.¹¹. For that reason we concentrated our further studies on the use of (6) and (7).

Reaction of (7) with (1a) under the standard conditions furnished in good yield a mixture of three epoxyesters in a ratio of 12:6:1¹¹, which probably have configurations (17-19), respectively. We suppose that the ester (20), which should arise from α -attack of (1a) under formation of a *cis*-oxetane was not formed. This may be due to a steric

interaction of the C(8)-Me group with the Me-group at the imaginary *cis*-oxetane as shown by molecular models. M.p.l.c. with a diisopropyl ether-hexane mixture afforded the pure diastereomers (17) and (18), and a mixture of (19) and (18).

Lactonization of the acquired epoxyesters may occur *via* two routes: *i.* Acid hydrolysis of the epoxy group will afford a *trans*-diol which is capable of ring closure to either a γ - or a δ -dihydroxylactone^{4b}; however, we demonstrated previously that γ -lactones are formed exclusively when 20% formic acid is used. *ii.* Rearrangement of the epoxy function to an allylic alcohol moiety and subsequent lactonization will deliver a mono-hydroxylactone (Scheme 2). This second route has the theoretical advantage of reducing the number of possible products whereas the double bond in the product can be used for further functionalization. Both methods were tested.

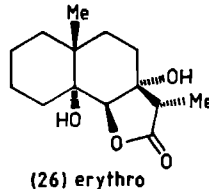
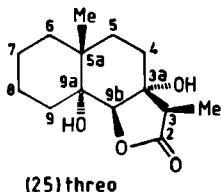
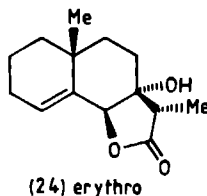
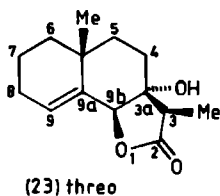
Acid hydrolysis of the mixture of esters (10) and (11) was performed according to the method previously described using 20% HCOOH¹¹. It delivered a mixture of only two diastereomeric dihydroxy- γ -lactones. Repeated crystallization from hexane-ethyl acetate provided one diastereomer (12) of unknown configuration in pure form. The shift of the oxygen-bound lactonic methine proton in (12) (δ_H 4.08 ppm) supports* the *cis*-orientation of the γ -lactone ring since this proton absorbs in the same region (δ_H 3.90-4.18 ppm) as the analogous protons of the related *cis*-fused lactones (25), (26), (29) and (30) (*v.i.*). This result strongly contrasts with the outcome of the hydrolysis of the epoxyesters (10) and (11) according to the method of Weyerstahl *et al.*⁴. These authors used dilute sulfuric acid in acetone; application of this procedure to several γ,δ -epoxyesters^{4b} gave a mixture of γ - and δ -lactones. Hydrolysis of (10) and (11) with 1 M H₂SO₄ in acetone furnished a mixture of several products as indicated by the ¹H n.m.r. spectrum. Efforts to analyze this mixture with the aid of capillary G.C. were not successful; apart from a small signal of about

*We realize, however, that this shift correspondence can only be applied to structurally closely related compounds. Small changes in the surrounding of the lactonic methine proton can cause a considerable change in shift, see also Chapter III.

5% of the dihydroxylactones we had isolated before, there was found only one broad signal. I.r. spectra of the reaction mixture showed by far the largest CO absorptions between $1710-1745\text{ cm}^{-1}$ indicating that a γ -lactone was scarcely present.

Synthesis of type I lactones

With the experiences just mentioned, hydrolysis of compounds (13-19) was attempted according to the formic acid method. However, hydrolysis of the crude mixture of (13-16) under these conditions did not proceed at all. Addition of THF (15%) did not accelerate the conversion. Therefore we tried the method of Weyerstahl *et al.*⁴ since these authors showed that the analogous epoxyester (21), synthesized as depicted in Scheme 3, is converted into monohydroxylactone (22) under the influence of H_2SO_4 in acetone at room temperature. Hydrolysis of the crude mixture of (13-16) under these conditions gave after crystallization from chloroform-hexane in a total yield of 55-60% the monohydroxylactones



(23) and (24) as a 2:1 *threo-erythro* mixture, and the dihydroxylactones (25) and (26) likewise as a 2:1 *threo-erythro* mixture. M.p.l.c. of this mixture using silica gel and diisopropyl ether-hexane gave the pure diastereomers (23), (24) and (25), and a mixture of (26) with (25).

As expected products originating from the epoxyesters (15) and (16) were not found. It was not possible to assign a *cis*- or a *trans*-decaline structure to (25) and (26) on the basis of ^1H n.m.r. spectroscopy due to the intermediate positions of the resonances of the angular Me-group at 1.07 and 1.08 ppm, respectively¹⁴. X-ray analysis of (25)¹², however, confirmed not only a *trans*-decaline structure and a *cis*-lactone configuration but also the β -attack of (1a) on (6) and the *threo*-configuration of the intermediate (13) (Figure 3).

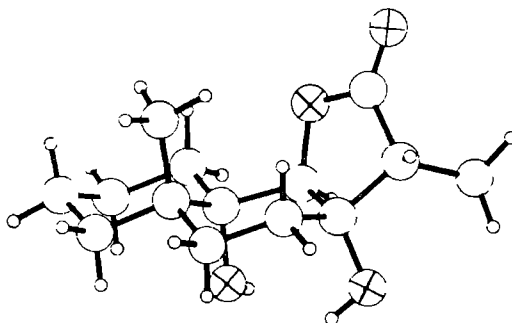
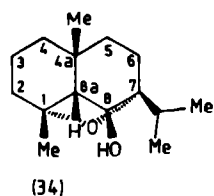
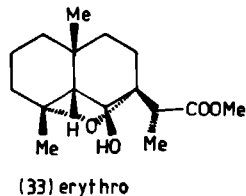
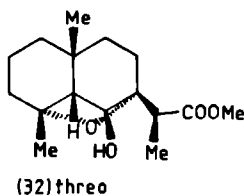
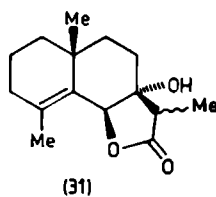
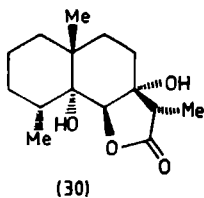
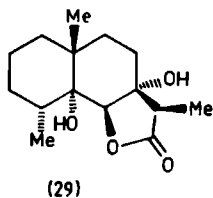
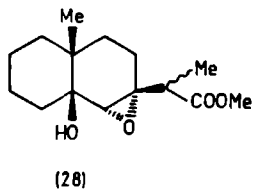
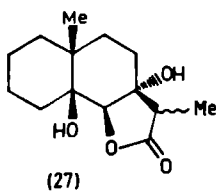


Figure 3: X-ray structure of (25); \otimes = oxygen.

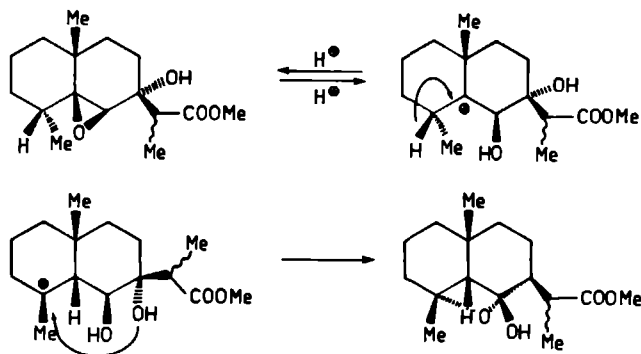
The outcome of the hydrolysis of epoxyesters (13-16) strongly contrasts with the results obtained by Weyerstahl *et al.* for the analogous compound (21a)^{4a} (see Scheme 3). These authors got a *cis*-decaline from (21). The formation of (23-26) cannot be explained by anchimeric assistance of the tertiary hydroxy function since this would deliver (27) having a *cis*-decaline structure *via* the intermediate epoxide (28)¹⁵. The different results may be due to a different mechanism for the epoxide hydrolysis¹⁶. Lactone (22) is probably formed *via* an $\text{S}_{\text{N}}2$ -type reaction of water at the less-hindered 1a-position¹⁷, followed by attack of the ester carbonyl group at the same carbon, resulting in a *cis*-decaline structure and a *cis*-lactone ring. Due to the presence of the vicinal α -OH function in (13-16) epoxide opening *via* an $\text{S}_{\text{N}}2$ -type reaction with water is apparently not possible.



Thus the epoxide ring will be opened *via* an SN_1 -type reaction which leads to both the monohydroxylactones (23) and (24) and the dihydroxy lactones (25) and (26). Although it cannot be excluded that the hydrolysis in the case of the formation of (25) and (26) proceeds *via* an SN_2 -type reaction at C-8a (for numbering see (13), (17)) of the epoxy-esters, this pathway is very unlikely, as it concerns attack at a tertiary carbon atom. Besides Weyerstahl *et al.* did not isolate any lactone with a *trans*-decaline structure after hydrolysis of (21). Increase of the acid concentration to 3 M did not influence the product distribution although hydrolysis was now complete within 4 h; a further increase to 6 M led to substantial loss of product. Hydrolysis with 1 M H_2SO_4 in refluxing dimethoxyethane⁴ led to destruction of both products and starting esters under formation of a black, tarry material.

Hydrolysis of the mixture of epoxyesters (17-19) under the standard conditions (1 M H_2SO_4) did not proceed at all; after 48 h the starting compounds could be regained almost quantitatively. When the epoxyesters were treated with 6 M H_2SO_4 in acetone the dihydroxylactones (29) and (30) were obtained in *ca.* 30% yield. The monohydroxylactones (31) could not be detected, but two other products were isolated in *ca.* 20% yield. The use of stronger acidic conditions raised the yield of the latter products substantially, as will be described further on. The structures (32) and (33) have been assigned tentatively to them on the basis of spectroscopic and analytical data. Since these compounds have not been described in the literature we compared their spectroscopic data with those of compound (34)¹⁸, which bears a strong resemblance to the supposed structures. Compound (34) shows a resonance at δ 4.55 ppm for the H(8) signal in the ^1H n.m.r. spectrum. The corresponding hydrogen atoms in (32) and (33) show δ -values 4.76 and 4.80 ppm. The higher values may be due to a deshielding effect of the side chain ester function. On the basis of the crystallographic data of (34) we calculated¹⁹ a *trans*-diequatorial J-coupling of 4.5 Hz for the H(8) signal, which matches nicely with the observed values (5 Hz) in the ^1H n.m.r. spectrum of (32) and (33). Compounds (32) and (33) are apparently formed *via* an $\text{S}_{\text{N}}1$ opening of the epoxide followed by a rearrangement of the intermediate carbonium ion (Scheme 4).

Scheme 4

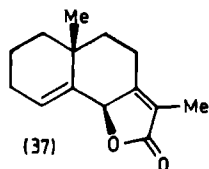
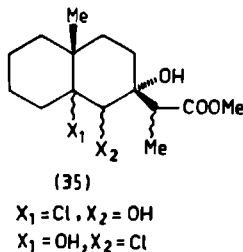
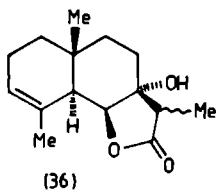


Synthesis of lactones of type II

Rearrangement of the epoxide function to an allylic alcohol can proceed both *via* basic and acidic routes¹⁶. The strongly basic route using lithium diethylamide²⁰ was not our first choice as we expected to get a *retro* reaction; later on this was confirmed by Carda *et al.*²¹, who reported destruction of material in a related case. In an alternative procedure the epoxide can be opened by acidic and/or nucleophilic reagents to afford an adduct which after addition of an amine-base gives an allylic alcohol.

Simple acid-catalyzed rearrangement was examined first. Indeed reaction of crude (13-16) with trifluoroacetic acid (TFA) in dry THF at 0°C and subsequent pouring out into water gave *ca.* 20% (23) and (24), according to G.C. and G.C./M.S. Lowering of the reaction temperature to -78°C did not improve the result. Treatment of the esters (17-19) with TFA/THF gave a mixture of the compounds (32) and (33) in good yield (65-70%). Reaction of (13-16) with BF₃-etherate²² in benzene at 0°C resulted in a complex reaction mixture with complete disappearance of the starting material.

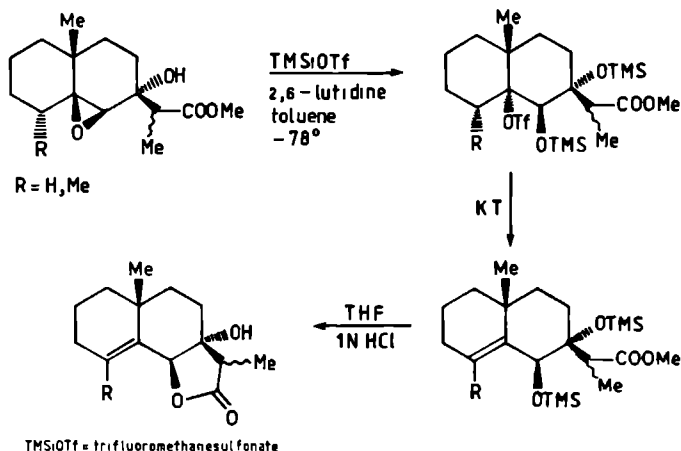
Then we tried to convert the epoxide ring into a chlorohydrin using the Lewis acids SnCl₄ and TiCl₄²³. Treatment of (13-16) with SnCl₄ and TiCl₄ was performed in CH₂Cl₂ at -78°C. It afforded neither the desired chlorohydrins nor allylic alcohols but a mixture of three, rearranged products which were not further characterized. The modification of Spawn *et al.*²⁴, who added DBU, did not lead to spectacular improvement, but G.C./M.S. showed the presence of 4 isomeric



chlorohydrins (35) in small amounts. The procedure of Caron and Sharpless²⁵ was not tried out, since the position of the tertiary

hydroxy function is mainly *trans* with regard to the epoxy function. Eventually the method of Noyori²⁶ was tested (Scheme 5).

Scheme 5



Submitting the crude esters (13-16) to an excess of trimethylsilyl-trifluoromethane sulfonate and 2,6-lutidine delivered almost quantitatively the expected products. Subsequent hydrolysis with 1 M HCl in THF afforded after m.p.l.c. a 2:1 mixture of (23) and (24) in a good overall yield of 50-52% based on (6). The epoxyesters (17-19) were submitted to the same reaction conditions; GC/MS showed the presence of 34% (36) after work up, and after two recrystallizations 90 mg of an analytical sample of (36) were obtained. Since (36) is not the primary product of the elimination of the trifluoromethane sulfonic acid group, a secondary reaction must have taken place. This may be either a carbonium ion rearrangement during a pure E_1 elimination, or a double bond migration under the influence of the acid or during work up on silica gel.

In a preliminary experiment we tested whether lactones (23-26) could be dehydrated to (37). According to the method of Godfrey and Schultz¹⁴ we used methane sulfonic acid and phosphorous pentoxide for this purpose but treatment of a mixture of lactones (23-26) with these reagents resulted in complete decomposition of the starting material.

Conclusions

In a previous study we have shown that epoxyketones are easily converted with 1,1-dimethoxypropene into the corresponding γ,δ -epoxy- β -hydroxyesters *via* a mild acidic one-pot reaction. This study has shown that this reaction is equally applicable to decaline type epoxyketones. Cyclization of the used model compounds furnishes various lactones which likely all have a *cis*-fused lactone ring. In the case of the decaline structures the lactone ring is also *cis* oriented with regard to the angular methyl group which is generally present in eudesmanolides. The presence of a *trans*-fused lactone ring in the majority of the eudesmanolides is a drawback of the method in the synthesis of this type of compounds. However, when necessary inversion of configuration of the 9b-hydroxyl function is probably possible by several general methods²⁷.

Experimental

General methods

M.p.'s are uncorrected. ^1H n.m.r. spectra were recorded on a Bruker WH-90 90 Mz spectrometer in CDCl_3 solution with SiMe_4 as internal reference. All OH-resonances could be exchanged with D_2O or CD_3OD . I.r. spectra were measured with a Perkin-Elmer spectrophotometer model 397. Mass spectra were obtained with a VG 7070E mass spectrometer. Capillary GC was performed on a Hewlett Packard 5790A apparatus equipped with a 25 m x 0.31 mm cross-linked methyl silicone column using a Hewlett Packard 3390A integrator, or on a Dani 3800 apparatus (GC/MS) equipped with a Chrompack 25 m x 0.32 mm CpSil-5CB column. Preparative m.p.l.c. was executed on a miniprep L.C. Jobin Yvon apparatus using Merck silica gel 60H as the stationary phase.

Acetonitrile and diisopropyl ether were stored over CaH_2 . Dry diethyl ether and tetrahydrofuran were obtained by distilling from sodium benzophenone ketyl, whereas dichloromethane was distilled over CaH_2 . Ether refers to diethyl ether. Compounds (1) and (3-9) were prepared according to literature procedures (*v.i.*). Compound (2) is commercially available.

Preparation of epoxyesters (10)-(11) and (13)-(19), general method

ZnCl_2 (0.5 ml of a saturated solution in acetonitrile) was added to a vigorously stirred mixture of the epoxyketone (2.5 mmol) in acetonitrile (0.5 ml) and 1,1-dimethoxypropene (1a) (1.01 g, 10 mmol) at room temperature, and stirring was continued for 1.5 h. Triethylamine (TEA) (0.5 ml) was added, followed by diisopropyl ether (30 ml), and the mixture was cooled to -78°C . Then a solution of toluene-*p*-sulfonic acid monohydrate (*ca.* 15 mg) in methanol (1.5 ml) was added; the reaction mixture was kept at -78°C for 0.5 h, and was then allowed to come to room temperature. Hydrochloric acid (20 ml of a 0.1 M solution) was added to the stirred mixture, and stirring was continued for 2 h. After the addition of brine (25 ml) the diisopropyl ether layer was separated and the aqueous layer was extracted with ether (2 x 25 ml). The combined ethereal extracts were dried (Na_2SO_4) and the solvent was evaporated to yield a crude mixture containing 85-90% epoxyesters.

Bulb to bulb distillation afforded the diastereomeric mixtures, yield 55-60%. M.p.l.c. using hexane-chloroform (65-35) for compounds (13-16) or diisopropyl ether-hexane (90:10) for compounds (17-19) delivered the more abundant diastereomers in pure form in total yields of 50-55%.

2 α -hydroxy-7-oxabicyclo[4.1.0]-heptane-2 β -(2'-methyl)-acetic acid methyl ester, (1:1) diastereomeric mixture (10, 11). B.p. 140-150°C/0.5 mmHg. (Found: C, 59.9; H, 8.1%; M⁺, 200.1046; Calc. for C₁₀H₁₆O₄: C, 59.98; H, 8.05%; M, 200.1049); m/z (EI) 200 (M, 169 (M-OCH₃), 151 (M-OCH₃, -H₂O). ν_{\max} (CHCl₃): 3600-3800 (OH), 3050-2850 (C-H), 1715 (COOMe), 1220-1150 cm⁻¹ (C-O); δ_{H} 1.22 and 1.38 (3H, 2d, J 7 Hz, 2'-Me), 1.17-1.66 (4H, m, (3-4)-H), 1.60 (1H, br.s, OH), 1.74-2.00 (2H, m, 5-H), 2.78 (1H, br.q, J 7 Hz, 2'-H), 2.98 and 3.06 (1H, 2d, J 8 Hz, 1-H), 3.19-3.33 (1H, m, 6-H), 3.71 and 3.74 (3H, 2s, COOMe).

threo (1 α ,2 α ,4 α)-2-hydroxy-4 α -methyl-1 α ,2,4,4 α ,5,6,7,8-octahydro-3H-naphth-[1,8 α -b]-oxirene-2 β -(2'-methyl)-acetic acid methyl ester (13). B.p. 125-140°C/0.3 mmHg. (Found: C, 66.97; H, 9.34%; M⁺+1, 269.1746; C₁₅H₂₄O₄ requires C, 67.14; H, 9.01%; M+1, 269.1753); m/z (CI) 269 (M+1, 91%), 268 (M, 2), 251 (M-OH, 100), 237 (M-OCH₃, 5), 233 (20), 219 (M-H₂O, -OCH₃, 30); ν_{\max} (CHCl₃): 3680 (OH), 3690-3360 (OH), 3080-2870 (C-H), 1710 (COOMe), 1300-1180 cm⁻¹ (C-O); δ_{H} 1.07 (3H, s, 4 α -Me), 1.23 (3H, d, J 7 Hz, 2'-Me), 0.84-2.19 (12H, m, (3-4)-H, (5-8)-H), 2.84 (1H, br.s, 1 α -H), 2.85 (1H, q, J 7 Hz, 2'-H), 3.76 (3H, s, COOMe), 3.98 (1H, br.s, OH).

erythro (1 α ,2 α ,4 α)-2-hydroxy-4 α -methyl-1 α ,2,4,4 α ,5,6,7,8-octahydro-3H-naphth-[1,8 α -b]-oxirene-2 β -(2'-methyl)-acetic acid methyl ester (14). B.p. 125-140°C/0.3 mmHg; m.p. 74-76°C (hexane). δ_{H} 1.06 (3H, s, 4 α -Me), 1.37 (3H, d, J 7 Hz, 2'-Me), 0.86-2.20 (12H, m, (3-4)-H, (5-8)-H), 2.82 (1H, br.s, 1 α -H), 2.87 (1H, q, J 7 Hz, 2'-H), 3.71 (3H, s, COOMe), 3.91 (1H, br.s, OH).

(1 α ,2 β ,4 $\alpha\beta$)-2-hydroxy-4 α -methyl-1 α ,2,4,4 α ,5,6,7,8-octahydro-3H-naphth-[1,8 α -b]-oxirene-2 α -(2'-methyl)-acetic acid methyl ester (15-16), (2:1) diastereomeric mixture, b.p. 125-140°C/0.3 mmHg. δ_{H} 1.09 (3H, br.s., 4 α -Me), 1.30 and 1.33 (3H, 2d, J 7 Hz, 2'-Me), 0.82-2.27 (12H, m, (3-4)-H, (5-8)-H), 2.80 and 2.82 (1H, 2q, J 7 Hz, 2'-H), 2.89 and 3.01 (1H, 2 br.s, OH), 3.06 and 3.19 (1H, 2 br.s, 1 α -H), 3.72 (3H, br.s, COOMe).

threo (1 α ,2 α ,4 $\alpha\beta$,8 α)-4 α ,8-dimethyl-2-hydroxy-1 α ,2,4,4 α ,5,6,7,8-octahydro-3H-naphth-[1,8 α -b]-oxirene-2 β -(2'-methyl)-acetic acid methyl ester (17). B.p. 125-140°C/0.3 mmHg. (Found: C, 67.87; H, 9.60; C₁₆H₂₆O₄ requires C, 68.06; H, 9.28%); m/z (CI) 283 (M⁺+1, 1%), 282 (M, 2), 265 (M-OH, 24), 263 (8), 251 (M-OCH₃, 8), 247 (26), 234 (15), 233 (M-H₂O-OCH₃, 100), 205 (19); ν_{max} (CHCl₃) 3600-3400 (OH), 3020-2850 (C-H), 1710 (COOMe), 1300-1180 cm⁻¹ (C-O); δ_{H} 0.67 (3H, d, J 7 Hz, 8-Me), 1.06 (3H, s, 4 α -Me), 1.22 (3H, d, J 7 Hz, 2'-Me), 0.90-2.29 (11H, m, (3-4)-H, (5-8)-H), 2.87 (1H, q, J 7 Hz, 2'-H), 3.00 (1H, br.s, 1 α -H), 3.75 (3H, s, COOMe).

erythro (1 α ,2 α ,4 $\alpha\beta$,8 α)-4 α ,8-dimethyl-2-hydroxy-1 α ,2,4,4 α ,5,6,7,8-octahydro-3H-naphth-[1,8 α -b]-oxirene-2 β -(2'-methyl)-acetic acid methyl ester (18). B.p. 125-140°C/0.3 mmHg, m.p. 85-87°C (hexane-diisopropyl ether). δ_{H} 0.72 (3H, d, J 7 Hz, 8-Me), 1.06 (3H, s, 4 α -Me), 1.38 (3H, d, J 7 Hz, 2'-Me), 1.54 (1H, br.s, OH), 0.86-2.29 (11H, m, (3-4)-H, (5-8)-H), 2.89 (1H, q, J 7 Hz, 2'-H), 3.02 (1H, br.s, 1 α -H), 3.71 (3H, s, COOMe).

threo (1 α ,2 β ,4 $\alpha\beta$,8 α)-4 α ,8-dimethyl-2-hydroxy-1 α ,2,4,4 α ,5,6,7,8-octahydro-3H-naphth-[1,8 α -b]-oxirene-2 α -(2'-methyl)-acetic acid methyl ester (19). δ_{H} (from a 2:1 mixture with (17)) 0.72 (3H, d, J 7 Hz, 8-Me), 1.09 (3H, s, 4 α -Me), 1.29 (3H, d, J 7 Hz, 2'-Me), 1.56 (1H, br.s, OH), 2.82 (1H, q, J 7 Hz, 2'-H), 3.40 (1H, br.s, 1 α -H), 3.70 (3H, s, COOMe).

Hydrolysis of epoxyesters (10) and (11)

Hydrolysis was performed according to the method previously described¹. A crude mixture of (10) and (11) (1.8 g) was converted into a diastereomeric mixture of dihydroxylactones (12) (1.4 g, 80%). After repeated crystallization from hexane-ethyl acetate one diastereomer was obtained in pure form (270 mg, 15%). The configuration of this isomer (12a) could not be established by X-ray analysis because it was not possible to obtain single crystals.

3a,7-dihydroxy-3-methyl-3a,4,5,6,7,7a-hexahydro-benzo-[b]-furan-(3H)-2-on (12a). M.p. 123-124°C (hexane-ethyl acetate). (Found: C, 58.1; H, 7.69; Calc. for $C_9H_{14}O_4$: C, 58.05; H, 7.58%). m/z (EI) 186 (M^+), 168 ($M-H_2O$), 150 ($M-2H_2O$); ν_{max} ($CHCl_3$) 3640-3250 (OH), 3080-2880 (C-H), 1780 (CO), 1270-1030 cm^{-1} (C-O); δ_H 1.17 (3H, d, J 7 Hz, 3-Me), 1.31-2.00 (6H, m, (4-6)-H), 1.57 (1H, br.s, OH), 2.70 (1H, br.s, OH), 2.78 (1H, q, J 7 Hz, 3-H), 4.08 (1H, d, J 3 Hz, 7a-H), 4.22-4.40 (1H, m, 7-H).

Hydrolysis of epoxyesters (13-16)

Hydrolysis was performed according to the method of Weyerstahl *et al.*⁴. In a typical experiment a crude mixture of (13-16) (720 mg, obtained from 400 mg of (6)) was dissolved in acetone p.a. (4.0 ml) and under continuous stirring sulfuric acid (0.5 ml of a 1.0 M solution) was added. Stirring was continued for 18 h at room temperature. Then diisopropyl ether (30 ml) and brine (30 ml) were added. The ethereal layer was separated and the aqueous layer extracted with ether (2 x 25 ml). The combined ethereal extracts were dried (Na_2SO_4) and the solvent was evaporated. Crystallization from chloroform-hexane at -20°C afforded a solid mixture (450 mg) consisting of (23) (22%), 24 (12%), 25 (43%) and (26) (22%), as determined by capillary GC¹¹. Chromatography (m.p.l.c.) of the crude reaction mixture using diisopropyl ether-hexane (9:1) delivered the pure diastereomers (23), (24), (25) and a mixture of (26) and (25).

threo (3a α , 5a β , 9b α)-3, 5a-dimethyl-3a-hydroxy-3a, 4, 5, 5a, 6, 7, 8, 9b-octahydronaphtho-[1, 2-b]-furan-2-(3H)-on (23). M.p. 114-116°C (hexane-diisopropyl ether). (Found: C, 70.72; H, 8.48; C₁₄H₂₀O₃ requires C, 71.16; H, 8.53%). m/z (CI) 237 (M⁺+1, 11%), 236 (M, 2), 219 (M-OH, 100), 191 (M-OH, -CO, 19), 163 (15); ν_{\max} (CHCl₃) 3610-3240 (OH), 3550 (OH), 3030-2820 (C-H), 1770 (γ -lactone), 1660 (C=C), 1310-1170 cm⁻¹ (C-O); δ_H 1.12 (3H, s, 5a-Me), 1.29 (3H, d, J 7 Hz, 3-Me), 1.67 (1H, br.s, OH), 1.02-2.44 (10H, m, (4-5)-H, (6-8)-H), 2.56 (1H, q, J 7 Hz, 3-H), 4.42 (1H, br.s, 9b-H), 5.96 (1H, br.tr, J 3.5 Hz, 9-H).

erythro (3a α , 5a β , 9b α)-3, 5a-dimethyl-3a-hydroxy-3a, 4, 5, 5a, 6, 7, 8, 9b-octahydronaphtho-[1, 2-b]-furan-2-(3H)-on (24). M.p. 120-121°C (hexane-diisopropyl ether). δ_H 1.10 (3H, s, 5a-Me), 1.20 (3H, d, J 7 Hz, 3-Me), 1.67 (1H, br.s, OH), 1.00-2.31 (10H, m, (4-5)-H, (6-8)-H), 2.76 (1H, q, J 7 Hz, 3-H), 4.31 (1H, br.s, 9b-H), 5.96 (1H, br.tr, J 3.5 Hz, 9-H).

threo (3a α , 5a β , 9a α , 9b α)-3a, 9a-dihydroxy-3, 5a-dimethyl-3a, 4, 5, 5a, 6, 7, 8, 9, 9a, 9b-decahydronaphtho-[1, 2-b]-furan-2-(3H)-on (25). M.p. 151-153°C (diisopropyl ether-hexane). (Found: C, 66.0; H, 8.75%; M⁺+1 255.1592; C₁₄H₂₂O₄ requires C, 66.12; H, 8.75%; M+1 255.1596); m/z (CI) 255 (M+1, 4%), 237 (M-OH, 38), 220 (M-2OH, 15), 219 (M-H₂O, -OH, 100), 191 (M-H₂O, -OH, -CO, 13); ν_{\max} (CHCl₃) 3640-3200 (OH), 3010-2820 (C-H), 1760 (γ -lactone), 1250-1110 cm⁻¹ (C-O); δ_H 1.07 (3H, s, 5a-Me), 1.27 (3H, d, J 7 Hz, 3-Me), 1.54 (1H, br.s, OH), 0.92-2.20 (12H, m, (4-5)-H, (6-9)-H), 2.48 (1H, q, J 7 Hz, 3-H), 3.34 (1H, br.s, OH), 3.90 (1H, s, 9b-H).

erythro (3a α , 5a β , 9a α , 9b α)-3a, 9a-dihydroxy-3, 5a-dimethyl-3a, 4, 5, 5a, 6, 7, 8, 9, 9a, 9b-decahydronaphtho-[1, 2-b]-furan-2-(3H)-on (26). δ_H (from a 1:1 mixture with (25)) 1.08 (3H, s, 5a-Me), 1.28 (3H, d, J 7 Hz, 3-Me), 2.56 (1H, q, J 7 Hz, 3-H), 3.93 (1H, s, 9b-H).

Hydrolysis was performed according to the described method for (13-16), except that 6 M sulphuric acid was used. In this way a one-pot experiment afforded 475 mg (out of 300 mg of (7)) of a crude product containing 23% of (32) and (33), and 46% of (29) and (30).

threo (3 α ,5 α ,9 α ,9 α ,9 β a)-3 α ,9 α -dihydroxy-3,5 α ,9-trimethyl-3 α ,4,5,5 α ,6,7,8,9,9 α ,9 β -decahydronaphtho-[1,2-*b*]-furan-2-(3H)-on (29). M.p. 147-151°C (diisopropyl ether-hexane). (Found: C, 66.87; H, 8.98%; M⁺+1 269.1748; C₁₅H₂₄O₄ requires C, 67.14; H, 9.01%; M+1 269.1753); ν_{\max} (KBr) 3620-3280 (OH), 3010-2820 (C-H), 1755 (γ -lactone), 1250-1110 cm⁻¹ (C-O); δ_{H} 0.93 (3H, d, J 7 Hz, 9-Me), 1.08 (3H, s, 5a-Me), 1.29 (3H, d, J 7 Hz, 3-Me), 0.73-2.31 (11H, m, (4-5)-H, (6-9)-H), 1.56 (1H, br.s, OH), 2.49 (1H, q, J 7 Hz, 3-H), 3.22 (1H, br.s, OH), 4.18 (1H, s, 9b-H).

erythro (3 α ,5 α ,9 α ,9 α ,9 β a)-3 α ,9 α -dihydroxy-3,5 α ,9-trimethyl-3 α ,4,5,5 α ,6,7,8,9,9 α ,9 β -decahydronaphtho-[1,2-*b*]-furan-2-(3H)-on (30). M.p. (of a 2:1 mixture with (29)) 156-166°C (diisopropyl ether-hexane). δ_{H} (from a 2:1 mixture with (29)) 0.92 (3H, d, J 7 Hz, 9-Me), 1.05 (3H, s, 5a-Me), 1.20 (3H, d, J 7 Hz, 3-Me), 1.58 (1H, br.s, OH), 2.79 (1H, q, J 7 Hz, 3-H), 3.46 (1H, br.s, OH), 4.04 (1H, s, 9b-H).

threo (1 β ,4 α ,7 β ,8 β ,8 α ,8 β)-1,4 α -dimethyl-8-hydroxy-perhydro-1,7-epoxy-naphthalene-7-(2'-methyl)-acetic acid methyl ester (32). M.p. 116-119°C (diisopropyl ether-hexane). (Found: C, 68.11; H, 9.31; C₁₆H₂₆O₄ requires C, 68.06; H, 9.28%; m/z (CI) 283 (M⁺+1, 33%), 282 (M, 6), 267 (M-CH₃, 20), 265 (M-OH, 66), 251 (M-OCH₃, 10), 249 (M-CH₃, -H₂O, 12), 247 (28), 233 (M-H₂O, -OCH₃, 100); ν_{\max} (CHCl₃) 3620 (OH), 3680-3410 (OH), 3010-2840 (C-H), 1730-1700 (CO), 1450 (C-H), 1280-1120 cm⁻¹ (C-O); δ_{H} 1.15 (3H, s, 1-Me or 4a-Me), 1.22 (3H, s, 1-Me or 4a-Me), 1.30 (3H, d, J 7 Hz, 2'-Me), 1.09-2.02 (11H, m, (2-4)-H, (5-6)-H, 8a-H), 2.82 (1H, q, J 7 Hz, 2'-H), 3.72 (3H, s, COOMe), 3.88 (1H, br.s, OH), 4.76 (1H, d, J 5 Hz, 8-H).

erythro (1 β ,4 $\alpha\beta$,7 β ,8 β ,8 $\alpha\beta$)-1,4a-dimethyl-8-hydroxy-perhydro-1,7-epoxy-naphthalene-7-(2'-methyl)-acetic acid methyl ester (33). M.p. 114-117°C (hexane-diisopropyl ether). δ_H 1.14 (3H, s, 1-Me or 4a-Me), 1.17 (3H, s, 1-Me or 4a-Me), 1.26 (3H, d, J 7 Hz, 2'-Me), 1.05-2.11 (11H, m, (2-4)-H, (5-6)-H, 8a-H), 2.56 (1H, br.s, OH), 2.72 (1H, q, J 7 Hz, 2'-Me), 3.71 (3H, s, COOMe), 4.80 (1H, d, J 5 Hz, 8-H).

Reactions with trimethylsilyl trifluoromethane sulfonate; preparation of (23), (24) and (36)

The reactions were performed according to the method of Noyori²⁶, with the omission of DBU, however. To a stirred mixture of toluene p.a. (10 ml) and 2,6-lutidine (2 ml), cooled to 0°C and under an atmosphere of nitrogen, TMSOTf (2 ml, 10.3 mmol) was added. The resulting mixture was cooled to -78°C and crude epoxyester (450 mg, ca. 1.5 mmol) in toluene p.a. (5 ml) was added in 5 min. The mixture was stirred for 4 h at -78°C and then allowed to come to room temperature. Stirring was continued for another 64 h and work up was performed as described in reference 26. The products were dissolved in THF (35 ml) and 1 M hydrochloric acid (25 ml) was added. After stirring for 4 h brine (25 ml) and diisopropyl ether (35 ml) were added and the organic layer was separated off. The aqueous layer was extracted with diisopropyl ether (2 x 25 ml) and the combined ethereal extracts were dried (Na₂SO₄). Evaporation of the solvent delivered the crude products.

In the case of the epoxyesters (13)-(16) m.p.l.c. of the crude product, using diisopropyl ether-hexane (9:1), afforded a 2:1 mixture of (23) and (24) (220 mg, 62%). In the case of the epoxyesters (17-19) the crude product was purified by distillation under reduced pressure using a Büchi Kugelrohr oven. The fraction collected at 125-165°C/0.9 mmHg was crystallized using diisopropyl ether-hexane yielding 90 mg (20%) of (36). Recrystallization from diisopropyl ether-hexane afforded 70 mg of an analytically pure sample.

(3 α , 5 α , 9 α , 9 β)-3 α -hydroxy-3, 5 α , 9-trimethyl-3 α , 4, 5, 5 α , 6, 7, 9 α , 9 β -octa-hydronaphtho-[1, 2- b]-furan-2-(3H)-on (36). M.p. 148-151°C (diisopropyl ether-hexane). (Found: C, 71.98; H, 8.90%; $M^+ + 1$, 251.1646; $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%; $M + 1$ 251.1647); m/z (CI) 252 ($M + 2$, 15%), 251 ($M + 1$, 90), 233 ($M - OH$, 100), 205 ($M - OH$, $-CO$, 22), 177 ($M - CO_2$, $-2Me$, 69); ν_{max} (KBr) 3610-3280 (OH), 3590 (OH), 3060-2820 (C-H), 1765 (γ -lactone), 1270-1150 cm^{-1} (C-O); δ_H 0.92 (3H, s, 5 α -Me), 1.00-1.97 (7H, m, (4-5)-H, 6-H, 9 α -H), 1.19 (3H, d, J 7 Hz, 3-Me), 1.57 (1H, br.s, OH), 1.81 (3H, br.s, 9-Me), 1.97-2.30 (2H, m, 7-H), 2.76 (1H, q, J 7 Hz, 3-H), 4.21 (1H, d, J 9 Hz, 9 β -H), 5.36-5.48 (1H, m, 8-H).

Reaction with TFA; preparation of (23), (24), (32) and (33)

To a vigorously stirred mixture of TFA (10 ml) and THF (5 ml), cooled to 0°C, the crude epoxyester (450 mg, *ca.* 1.5 mmol) in THF (5 ml) was added in 10 min. The color of the reaction mixture turned into dark blue and stirring was continued for 1.5 h at 0°C. The reaction mixture was then poured into a mixture of brine (50 ml) and crushed ice (100 g) and the resulting mixture was stirred for 0.5 h. Diisopropyl ether (35 ml) was added and the organic layer was separated. The aqueous layer was extracted with diisopropyl ether (2 x 25 ml). The combined ethereal layers were washed with brine to neutral and dried (Na_2SO_4), and the solvent was evaporated. M.p.l.c. using silica gel and diisopropyl ether-hexane (9:1) afforded the pure products. In this way a mixture of (23) and (24) (30 mg, 6%), and a mixture of (32) and (33) (140 mg, 38%) were obtained.

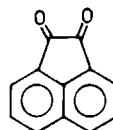
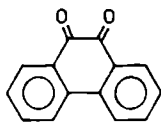
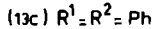
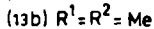
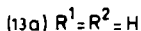
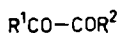
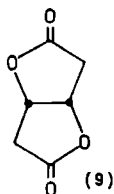
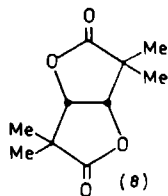
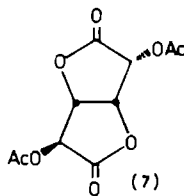
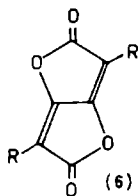
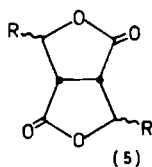
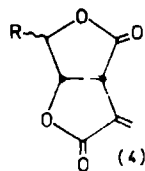
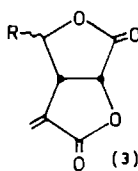
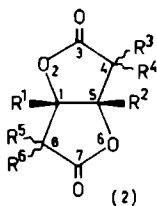
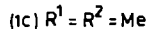
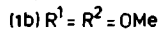
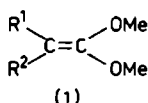
References

1. J.W. Scheeren and J. Lange, *Tetrahedron Lett.*, 1984, 25, 1609.
2. J.W. Scheeren, *Recl. Trav. Chim. Pays-Bas*, 1986, 105, 71.
3. a. C.H. Heathcock, in 'The Total Synthesis of Natural Products', J. Apsimon ed., Vol. 2, John Wiley, New York, 1973.
b. C.H. Heathcock, S.L. Graham, M.C. Pirrung, F. Plavec and C.T. White, in 'The Total Synthesis of Natural Products', J. Apsimon ed., Vol. 5, John Wiley, New York, 1983.
4. a. N. Bensen, H. Marschall, P. Weyerstahl and R. Zeisberg, *L. Ann. Chem.*, 1982, 1781.
b. B. Bardili, H. Marschall-Weyerstahl and P. Weyerstahl, *L. Ann. Chem.*, 1985, 275.
5. a. C.H. Heathcock and J.E. Ellis, *Tetrahedron Lett.*, 1971, 12, 4995.
b. W.C. Clark Still and Fl. van Middlesworth, *J. Org. Chem.*, 1977, 42, 1258.
6. The enones (3) and (4) themselves appeared completely unreactive towards (1); however, under Lewis acid catalysis and high pressure conditions (12 kbar) (2) was almost quantitatively converted into a bicyclo-[4.2.0]-octanone derivative. See R.W.M. Aben and J.W. Scheeren, *Tetrahedron Lett.*, 1985, 26, 1889.
7. a. M.E. Kuehne and J.A. Nelson, *J. Org. Chem.*, 1970, 35, 161.
b. D. Felix, C. Wintner and A. Eschenmoser, *Org. Synth.*, 1976, 55, 52.
8. H.B. Henbest and W.R. Jackson, *J. Chem. Soc. C*, 1967, 2459.
9. J.L. Pierre and P. Chautemps, *Tetrahedron Lett.*, 1972, 13, 4371.
10. R.G. Hofstraet, J.W. Scheeren and R.J.F. Nivard, *J. Chem. Soc. Perkin I*, 1985, 561.
11. Ratios were determined with capillary GC and GC/MS assuming equal response factors (flame ionization detector) for the diastereomers. The data are the average of at least 4 experiments.
12. R.P.F. Kanters, J.M.M. Smits, R.G. Hofstraet and P.T. Beurskens, to be published.
13. N.H. Fischer, E.J. Olivier, H.D. Fischer, in *Fortschr. Chem. Org. Naturst.*, L. Zechmeister ed., Springer Verlag, Wien, 1979, 38, 47.

14. In general, the stereochemistry of the decaline ring fusion in such compounds can be assigned with a high degree of reliability by consideration of the ^1H n.m.r. chemical shift of the angular methyl group. The position of the C(8a) methyl resonance in a *trans*-8a-methyldecaline is at higher field (δ 0.73-0.90) than that of a *cis* compound (δ 1.05-1.20). Due to the presence of deshielding substituents these values may shift somewhat to lower field. See: R.B. Carlson and A.G. Zey, *J. Org. Chem.*, 1972, 47, 1327; F. Bohlmann, H.-J. Förster and C.-H. Fisher, *L. Ann. Chem.*, 1976, 1487; A.G. Schultz and J.D. Godfrey, *J. Am. Chem. Soc.*, 1980, 102, 2414.
15. G.A. Morrison and J.B. Wilkinson, *Tetrahedron Lett.*, 1975, 16, 2713.
16. J. Gorzinsky Smith, *Synthesis*, 1984, 629, and references cited therein.
17. A.R. Davies and G.H.R. Summers, *J. Chem. Soc. C*, 1966, 1012.
18. Yu.V. Gatilov and Zh.V. Dubovenko, *Zh. Strukt. Khim.*, 1979, 20, 325.
19. D.H. Williams and I. Fleming in 'Spektroskopische Methoden zur Strukturaufklärung', Thieme Verlag, Stuttgart, 1975.
20. J.K. Crandall and M. Appar, *Org. React.*, 1983, 29, 345.
21. M. Carda, M. Arnó and J.A. Marco, *Tetrahedron*, 1986, 42, 3655.
22. M.S. Jelenick and T.A. Bryson, *J. Org. Chem.*, 1986, 51, 802.
23. a. H.O. House, *J. Am. Chem. Soc.*, 1954, 76, 1235.
b. G. Dittus in Houben-Weyl, 'Methoden der Organischen Chemie', Teil VI/3, Georg Thieme Verlag, Stuttgart, 1965.
c. J. Kagan, B.E. Firth, N.J. Shih and C.G. Boyagian, *J. Org. Chem.*, 1977, 42, 343.
d. See reference 16.
24. C.L. Spawn, G.J. Drtina and D.F. Wiemer, *Synthesis*, 1986, 315.
25. M. Caron and K.B. Sharpless, *J. Org. Chem.*, 1985, 50, 1557.
26. a. S. Murata, M. Suzuki and R. Noyori, *J. Am. Chem. Soc.*, 1979, 101, 2738.
b. R. Noyori, S. Murata and M. Suzuki, *Tetrahedron*, 1981, 37, 3899.
27. W.H. Kruizinga, B. Strijtveen, R.M. Kellogg, *J. Org. Chem.*, 1981, 46, 4321.

Introduction

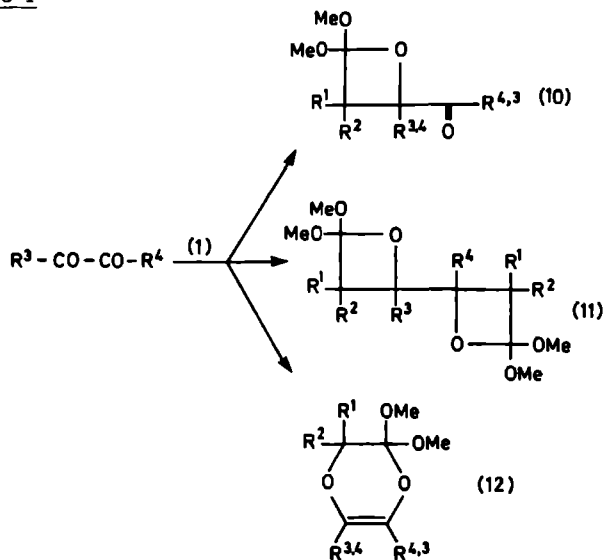
Within the class of bis- γ -lactones (bislactones) various types (2-5) can be distinguished. For several of them, *e.g.* the avenaciolides (3), the canadensolides (4) and the lignanolides (5) synthetic routes have been published in the literature¹⁻³. Bislactones of type (2), occurring in only two classes of natural products, *viz.* the pulvinic acid anhydrides⁴ (6) and glucaric acid derivatives⁵ like (7), have attracted much less attention until now. The rather simple representative D-glucaric acid 1,4-3,6-bislactone (2, $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = R^6 = OH$) is well investigated⁶. Weyerstahl and coworkers⁷ published the synthesis of (8); Elvidge *et al.*⁸ as well as Janda *et al.*⁹ that of (9). A general procedure for the preparation of (2) has not been described, however. It may be noted that all bislactones mentioned here, are *cis* compounds; to our knowledge the corresponding



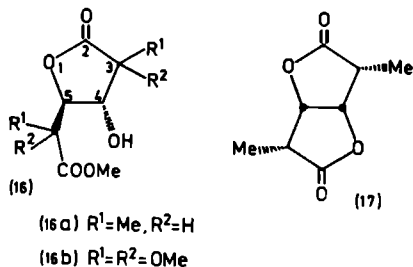
trans compounds, probably highly strained, have not been described in the literature.

During a systematic study of the reactions of ketene acetals (1) with a variety of 1,2-diketones¹⁰ we discovered a potential, simple and general route to bislactones of type (2). A priori, 1,2-diketones may yield three different types of cycloaddition products, *viz.* oxetanes (10), bisoxetanes (11) and dihydrodioxins (12) (Scheme 1). It was shown that bisoxetanes (11) are obtained in the ZnCl_2 -catalyzed reaction of (1a) or (1b) with glyoxal (13a) and in the ZnCl_2 -catalyzed reaction of (1a) with phenanthrenequinone (14) or acenaphthenequinone (15). Hydrolysis of (11, $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$) obtained from the

Scheme 1



reaction of (13a) with (1a) gave apart from a diastereomeric mixture of monolactones in the moderate yield of about 30% a bislactone. As the hydrolysis conditions were very mild we suppose that the bislactone has the *cis* structure (17) as a consequence of the presence of two *trans* oxetanes in (11). In the monolactone (16a) the hydroxy function and the propionic acid moiety probably show a *trans* relation. A retrosynthetic analysis of the target molecule (2) yields two



complementary and related approaches for the synthesis of such compounds.

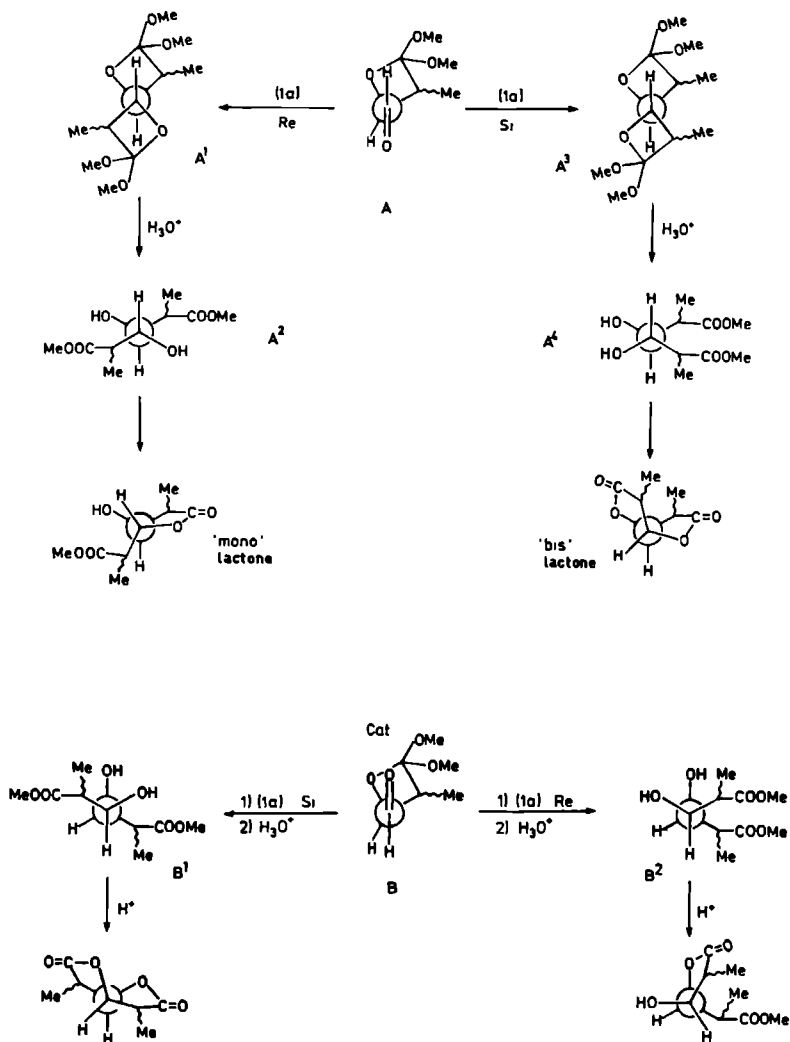
- (i) Starting from either glyoxal or a suitable 1,2-diketone reaction with 2 equivalents of (1) under Lewis acid catalysis might yield a bisoxetane; subsequent hydrolysis should yield symmetrically substituted bislactones (2) ($R^3 = R^5, R^4 = R^6$). The route is restricted to dicarbonyl compounds which cannot enolize, since enols add readily to (1) under formation of orthoesters.
- (ii) The use of a precursor of a 1,2-diketone or α -ketoaldehyde in which one of the carbonyl functions is protected or masked might enable to introduce two different ketene acetal moieties and may be applied in the synthesis of bislactones (2) in which R^3 and R^4 are not identical with R^5 and R^6 . In this chapter we will discuss the results of a study of both these routes.

Stereochemical aspects

The stereochemical aspects of the reaction of (1a) and glyoxal (13a) leading to the lactone (16a) and the bislactone (17) have been outlined in Scheme 2. Apparently, two factors determine the configuration of the products. First, during oxetane formation a *trans* oxetane or a mixture of a *cis* and a *trans* oxetane can be formed. This determines only the relative configuration at C-4 and C-8 (for numbering see formula (2)) of the bislactone and at C-3 and C- α (for numbering see formula (16)) of the lactone, and by that the number of diastereomers and their ratio. Secondly, during the addition of the second ketene acetal residue attack of the free carbonyl group may occur

from two different sides with respect to the ketene acetal moiety which is already present (*e.g.* $A \rightarrow A_1$ or A_3 in Scheme 2). This determines whether a mono- or a bislactone ((16) or (17)) will be formed.

Scheme 2

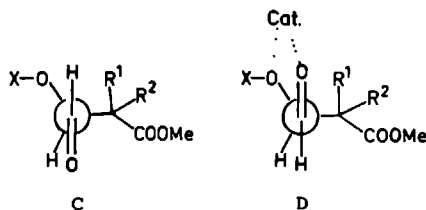


Under conditions which do not imply chelation-control¹¹ the primary formed mono-oxetane will have the preferential conformation A, due to electrostatic repulsion of the oxygen atoms. Attack of the second ketene acetal residue can be described by the Felkin model^{11,12}. Approach of (1a) from the less-hindered Re-face leads to A¹ and after hydrolysis to A², in which only one lactone ring can be closed under the mild acidic conditions (\rightarrow (16a))* . Attack of (1a) on A at the more-hindered Si-side yields A³, and after hydrolysis A⁴, which will readily close to a bislactone.

Under chelation-controlled conditions^{11,13}, the primary formed oxetane will likely adopt the conformation B due to the α -chelation of the Lewis acid catalyst used. Chelation of the catalyst with the carbonyl function and one of the methoxy oxygen atoms is rather unlikely since the formation of a 7-membered ring is rather unfavoured. As depicted in Scheme 2 attack of (1a) on B from the less-hindered Si-face leads now *via* the intermediate B¹ to the bislactone (2) ($R^1 = R^2 = R^3 = R^5 = H$, $R^4 = R^6 = Me$), whereas attack from the more-hindered Re-face now leads to the monolactone (16a).

The same reasoning holds for reactions of (1) with OH-protected α -hydroxyaldehydes or -ketones, which proceed *via* conformation C ('Felkin' conditions) or conformation D (chelation-controlled conditions (Figure 1)).

Figure 1



*Closure of two lactone rings in A² should lead to a highly strained *trans* bislactone. When possible this should need anyhow extreme, and forcing reaction conditions.

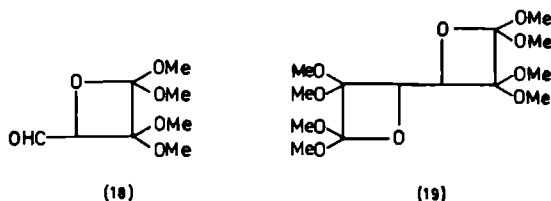
In conclusion, it can be stated that for routes to *cis* bislactones (2), either from non-cyclic 1,2-diketones or from protected α -hydroxyaldehydes or -ketones, chelation-controlled reaction conditions are necessary during the introduction of the second ketene acetal moiety. The formation of chelates is delicately influenced by factors as size and coordination sphere of the Lewis acid, the solvent and the reaction temperature¹¹.

Synthesis of the monolactones (16), (20-23), and the bislactone (17) from (1) and glyoxal (13a)

In a previous paper¹⁰ it was demonstrated that non-cyclic 1,2-diketones other than (13a), *e.g.* (13b,c), yield only oxetanes (10) (Scheme 1) in the reaction with (1), even when ZnCl_2 is used as a catalyst. Only in one case an α -ketoaldehyde, having $\text{R}^3 = \text{H}$, $\text{R}^4 = \text{Me}$ (Scheme 1) could be converted into a bisoxetane (11) in reaction with an excess of (1a) and in the presence of ZnCl_2 as a catalyst. Therefore we concentrated in our study on the reaction of (13a) with (1). Glyoxal (13a) was prepared according to the method of Harries and Temme¹⁴ by heating the anhydrous polymer with P_2O_5 . The greenish-yellow glyoxal was directly introduced into a cooled (-30 – -40°C) solution of an excess of (1a) in an appropriate solvent *via* a wide and short connector. This led to immediate decolouration. Repeated experiments showed that dry THF is the solvent most suited; the rate of polymerization of (13a) in this solvent is definitely lower than in the formerly used acetonitrile. In dichloromethane, the solvent most-suited for reactions under chelation-controlled conditions¹³, roughly the same rate of polymerization was observed as in acetonitrile. Since (1a) and (13a) react already without a Lewis acid catalyst the stereochemical outcome of the reaction cannot well be influenced. Addition of a Lewis acid (*e.g.* ZnCl_2 or MgBr_2) resulted only in faster polymerization of (13a). Hydrolysis of both the bisoxetanes obtained *via* reaction in THF and *via* reaction in CH_2Cl_2 gave 25–30% bislactone (17), just like the outcome of the reaction in acetonitrile. Product (17) is supposed to be formed from

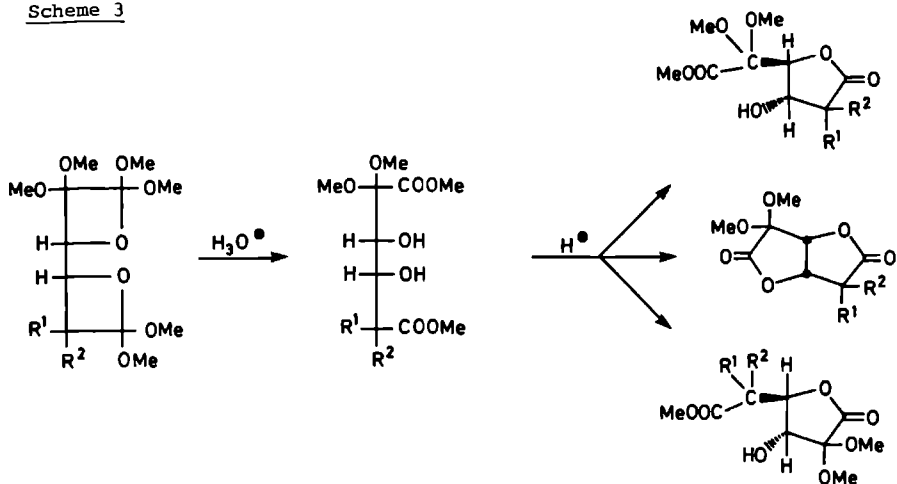
a bis-*trans* oxetane having conformation A³. The accompanying monolactones (16a) in both cases were isolated in *ca.* 50% yield and as a mixture of isomers.

The reaction of an excess of (1b) with (13a) appeared rather slow; the greenish-yellow colour of the reaction mixture remained for *ca.* 2½ h. After decolouration the ¹H n.m.r. spectrum of the crude reaction mixture showed that the glyoxal signal had disappeared but another aldehyde signal (a doublet at δ_{H} *ca.* 9.5 ppm) had appeared, indicating that the oxetane (18) had been formed. The oxetane appeared to be rather stable; it could even be purified to *ca.* 90% by rapid bulb to bulb distillation.

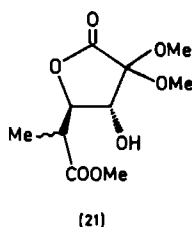
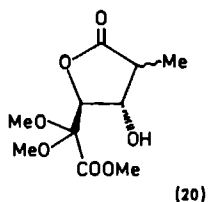


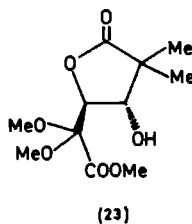
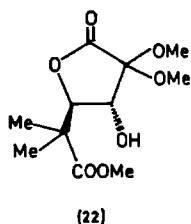
Addition of ZnCl₂ to the colourless reaction mixture gave in good yield the bisoxetane (19) which could be purified by crystallization. The product (19) could be synthesized directly by introducing (13a) into a THF solution containing an excess of (1b) in the presence of ZnCl₂. Hydrolysis of (19) gave no bislactone but only the monolactone (16b) in good yield.

The unexpected stability of (18) gave an unforeseen opportunity to test the synthesis of bislactones from (13a) and two different ketene acetals (1). It was uncertain whether the Lewis acids used were capable of complexation with the oxetane ring and the aldehyde function in an intermediate like (18). However, there are examples in which one of the chelating groups is part of a three-membered ring (*e.g.* an epoxide or aziridine) or a five-membered ring (*e.g.* a tetrahydrofuran)¹¹. When no chelation takes place a complex mixture of monolactones is to be expected (Scheme 3).



Reaction of (18) with (1a) was tried with the Lewis acids ZnCl_2 and MgBr_2 ¹⁵, other catalysts (*e.g.* AlCl_2Et and $\text{AlCl}_2\text{Obornyl}$) appeared too harsh resulting in polymerization of (13a) formed in the retroreaction of (18). Acetonitrile or dichloromethane were used as the solvent and the reaction temperature was varied from 0°C to -40°C . Unfortunately, the freshly prepared MgBr_2 catalyst appeared rather unreactive as it gave only substantial conversion at temperatures higher than 0°C . In all cases the product (yield 70-80%) after hydrolysis was a *ca.* 4:5 mixture according to capillary GC. The ^1H n.m.r. spectrum of the mixture showed that a bislactone was not present and that a mixture of monolactones had been formed. However, the ^1H n.m.r. spectrum did not allow to decide whether a mixture of two lactones (20) and (21) had been formed or a mixture of diastereomers of one of them, different at the centre bearing the Me-group.





Reaction of (18) with (1b) under ZnCl_2 catalysis in dichloromethane at 0°C gave after hydrolysis the monolactone (16b); MgBr_2 was not active enough to catalyze the reaction of (18) with (1b) and (1c) (*v.i.*), probably due to the much lower reactivity of (1b) and (1c) with respect to (1a).

Reaction of (18) with (1c) under ZnCl_2 catalysis at 20°C in dichloromethane resulted in the formation of a 3:1 mixture of monolactones according to capillary GC and the ^1H n.m.r. spectrum of the product mixture. The lactones were assigned the structures (22) and (23), since the ^1H n.m.r. spectrum showed three singlets for the Me-groups present in a ratio of 6:1:1, indicating that the lactone (22), having the $-\text{C}(\text{Me})_2$ -group in the side chain, is probably in excess.

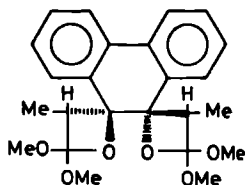
The experiments described above demonstrate that at least under the conditions used chelation does not play an important role in controlling the oxetane formation. Formation of bisoxetanes *via* conformation A^3 is apparently not possible with disubstituted ketene acetals according to the stereochemistry outlined in Scheme 2. This can be ascribed to crowding of the substituents in the 3-position of these oxetanes.

Synthesis of bislactones (25) and (27) from (1a) and cisoid 1,2-diketones (14) and (15)

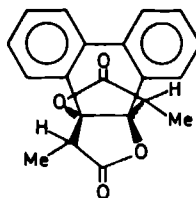
In a previous paper, it was already shown that fixed cisoid diaryl-1,2-diketones (*e.g.* (14)) are more reactive towards ketene acetals than their corresponding acyclic analogues (*e.g.* (13c))¹⁰. In order to check the stereochemical control in the oxetane formation from

1,2-diketones having the carbonyl function in a fixed cisoid position we reinvestigated the reaction of (1a) with phenanthrenequinone (14) and acenaphthenequinone (15). We expected that the attack of the second ketene acetal in these flat diketones should always be on the side opposite to the already present oxetane ring. Consequently, hydrolysis of the bisoxetane should deliver the corresponding bis-lactones in high yield.

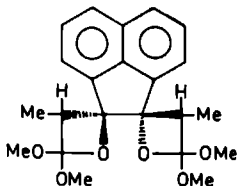
Reaction of (1a) with (14) under the conditions previously described gave the bisoxetane (24) in good yield. The ^1H n.m.r. spectrum of the product showed only one doublet at δ_{H} 1.40 ppm for the Me-resonances, pointing to a single diastereomer. Hydrolysis of (24) with hydrochloric acid in THF gave a bislactone in high yield. Again, we isolated only one diastereomer and assigned configuration (25) to it, as this configuration arises from (24) having the most stable *trans* configuration for the oxetane rings.



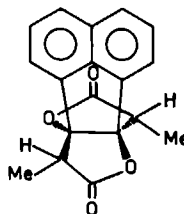
(24)



(25)



(26)

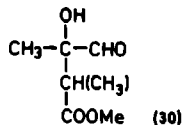
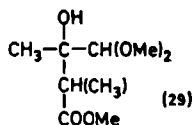
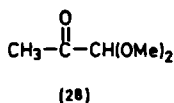


(27)

In the same way (15) was converted into (26) *via* a similar reaction sequence and then after hydrolysis into a 9:1 mixture of two diastereomeric bislactones in an overall yield of 45%. The major isomer of the two bislactones was assigned configuration (27) *via* a similar reasoning as given for (25).

Synthesis of the bislactones (40) from a 1,2-dicarbonyl compound in which one of the carbonyl groups is protected or masked

In order to judge the usefulness of a route in which one carbonyl group is protected we chose the commercially available protected pyruvaldehyde (28) as the starting compound. Reaction of (28) with (1a) in acetonitrile and under ZnCl_2 catalysis resulted *via* a one-pot reaction¹⁶ in a good overall yield of the corresponding β -hydroxy-ester (29) as a 2:1 diastereomeric mixture. Deprotection of the carbonyl function using dilute acid, in order to get the α -hydroxy-aldehyde, proved to be a very tricky procedure. Various acidic conditions led either to the starting material or to a complex mixture of products in which at most *ca.* 25% of the desired aldehyde (30) was present. Therefore, we changed to a route in which the second carbonyl group can be introduced under mild acidic or neutral conditions.

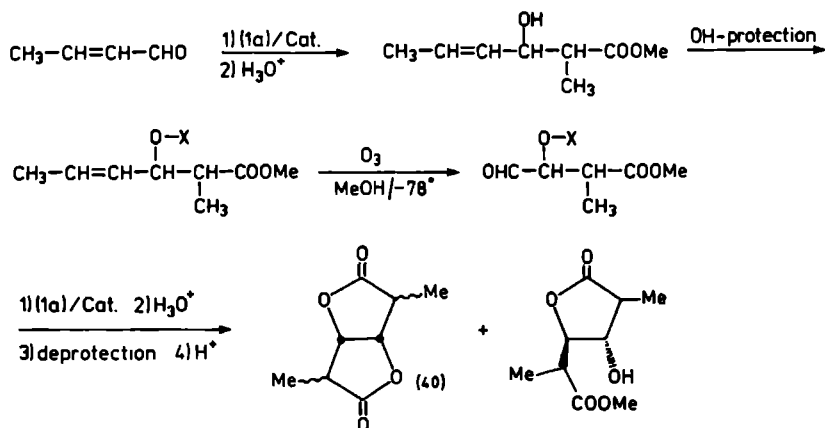


In this route the starting compound is an α,β -unsaturated carbonyl compound*. As a variety of such compounds is readily available this

*In the reactions of α,β -unsaturated compounds with (1) there is always a risk of a competing (4+2) cycloaddition reaction. In general, the (4+2) cycloaddition occurs at higher temperatures and requires stronger Lewis acids as catalysts, see C.G. Bakker, J.W. Scheeren and R.J.F. Nivard, *Recl. Trav. Chim. Pays-Bas*, 1981, 100, 13.

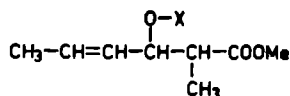
choice for the parent compound guarantees a wide applicability of the procedure. The olefinic double bond in the compounds is used as a masked carbonyl function, which is liberated by ozonolysis at a suitable step of the procedure. The ozonolysis, a rather mild technique, is the key reaction in the procedure. In Scheme 4 the route is outlined starting with crotonaldehyde, a simple, masked glyoxal equivalent.

Scheme 4



Crotonaldehyde reacts regioselective with (1a); in THF at -78°C and in the presence of $\text{AlCl}_2\text{Obornyl}^{18}$ in diethylether as a catalyst the expected oxetane was formed. Addition of an excess of methanol and subsequent hydrolysis of the intermediate orthoester gave the β -hydroxyester (31) in good yield (70-76%) as a 2:1 *threo-erythro* mixture. This low temperature method gives somewhat better yields than the method previously described using ZnCl_2 and acetonitrile at 10°C^{19} . The hydroxy group in the β -hydroxyester had to be protected to prevent reaction of the OH-group in a latter stage; the protection is also useful because it avoids dimerisation. In our first experiments we used the acetoxy group for the OH-protection. The function is stable during ozonolysis and its presence or absence can easily be recognized by ^1H n.m.r..

The hydroxyester (31) was quantitatively acylated using acetic acid anhydride and dimethylaminopyridine (DMAP) according to the method of Steglich²⁰. Ozonolysis of the resulting product (32) in methanol at -78°C gave, after reduction with dimethylsulfide (DMS) and subsequent distillation, the protected (33) in good yield (70-75%). Reaction of (33) with (1a) in acetonitrile as the solvent and under ZnCl_2 catalysis gave after hydrolysis of the intermediate oxetane the crude monolactone (34). However, direct saponification of this crude product in dioxane with sodium hydroxide delivered after acidification to pH 3 neither the hydroxylactone (16a) nor the bislactone (40), but the butenolide (35) as a consequence of elimination of the acetoxy group. Change of the solvent from dioxane-water to dioxane-methanol led to the corresponding methylester (36).



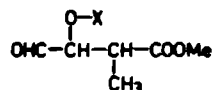
(31) X = H

(32) X = Ac

(37) X = CH(Me)OEt

(38) X = THP

(41) X = CH₂Ph

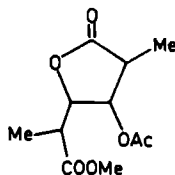


(33) X = Ac

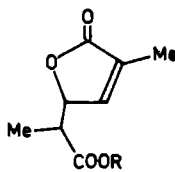
(38) X = CH(Me)OEt

(42) X = THP

(43) X = CH₂Ph



(34)



(35) R = H

(36) R = Me

At first sight the quick elimination of the acetoxy group seemed to be advantageous; it reduced the number of diastereomeric products,

and according to the Baldwin rules²¹ a compound like (35) should be capable of ring-closure via a 5-exo-trig reaction and might be converted completely in this way into the bislactone (40). Unfortunately, (35) appeared to be extremely unreactive. Ring-closure to (40) could neither be attained by acid activation of the double bond (conc. sulphuric acid^{8,9}, trifluoroacetic acid, mercury(I)oxide in acetone-sulphuric acid), nor *via* bromo- or iodolactonization²², nor *via* epoxidation of the double bond (hydrogen peroxide/NaOH, sodium hypochlorite in pyridine²³, *m*-CPBA in refluxing CHCl₃). In all these attempts (35) was regained quantitatively.

So, introduction of another protective group (X) in (31) was necessary. We chose the ethoxyethyl group (CH(Me)OEt, see (37)) which appeared more easy to handle than the THP group (see (38)) in the further reaction sequence. Compound (37) was obtained in good yield according to the method of Tufariello²⁴. Ozonolysis of (37) delivered the aldehyde (39) in a yield of 58% after distillation.

Reaction of (39) with (1a) both in acetonitrile and in dichloromethane under ZnCl₂ catalysis at 0°C resulted in a diastereomeric mixture of lactones (16a). However, reaction of (39) with (1a) under MgBr₂ catalysis at room temperature both in acetonitrile and dichloromethane gave in low yield (ca. 17%) a mixture of mainly three of the four possible diastereomeric bislactones (40) according to capillary GC and ¹H n.m.r. Capillary G.C. also showed that one of these isomers was possibly identical with the isomer (17) obtained from (1a) and (13a). The reaction of (39) with (1a) could not be performed at lower temperature due to the low activating power of the MgBr₂ catalyst. A low temperature (-78°C) experiment with (39) and (1a) using AlCl₃O-bornyl as the catalyst resulted in the formation of monolactones (16a). The results demonstrate that the Lewis acid MgBr₂ is most apt for α -complexation¹⁵, but that it is not very active as a catalyst. Therefore, it has to be used at relatively high temperatures. As a consequence the yield of bislactones is low.

Conclusion

Further studies have to reveal whether the yield can be increased by the use of another protective group, having better chelating power and not introducing an additional chiral centre. In this respect the benzyl group (compounds (41) and (42)) seems promising as it is especially suited for reactions under chelation-controlled conditions¹³. Furthermore, the use of MgBr_2 in equimolar amounts may enable a lowering of the reaction temperature; this may result in a better stereoselectivity and a higher yield of bislactones. These reactions are currently under investigation.

Experimental

General methods

M.p.s are uncorrected. ^1H n.m.r. spectra were recorded on a Varian T60, Varian EM-390, or a Hitachi Perkin-Elmer R-24B spectrometer in CDCl_3 solution with SiMe_4 as internal reference. All OH-resonances could be exchanged with D_2O or CD_3OD . Mass spectra were obtained with a Varian SM1-B double focussing mass spectrometer, or with a VG 7070E mass spectrometer. IR spectra were measured with a Perkin-Elmer spectrophotometer model 397. Ozone was produced with a Fischer Ozone-generator. MgBr_2 was freshly prepared according to the protocol of Brandsma²⁶. All other general methods were identical with those described in previous chapters.

Preparation of the lactones (16a) and the bislactone (17)

Thoroughly dried glyoxal polymer (2.5 g) was mixed with P_2O_5 (12.5 g) and depolymerized as described¹⁴. The resulting green-yellow glyoxal (13a) was condensed in a cooled (-40°C) flask containing a vigorously stirred solution of (1a) (ca. 1.5 g) in THF (20 ml). After the production of glyoxal had stopped the cooling bath was removed and the THF solution was allowed to come to room temperature. The polymeric side products were filtered off and the colourless solution was cooled to -10°C . Hydrochloric acid (2 ml of a 10% solution) was added and the mixture was stirred vigorously for 2 h at -10°C . The mixture was allowed to come to room temperature, and brine (10 ml) and CH_2Cl_2 (40 ml) were added. The aqueous layer was separated and the organic layer was dried (Na_2SO_4). After evaporation of the solvents a crude mixture of products (ca. 1.3 g) was obtained which contained 25-30% (17) and 40-50% (16a). Crystallization from THF, diisopropyl ether and hexane afforded pure (17) (325-290 mg). Bulb to bulb distillation of the residue afforded (16a) (520-650 mg).

cis 4,8-Dimethyl-2,6-dioxabicyclo[3.3.0]octane-3,7-dione (17), m.p. 139–141°C (diisopropyl ether-hexane); (Found: C, 56.13; H, 6.01. Calc. for $C_8H_{10}O_4$: C, 56.47; H, 5.92%); m/z (EI) 170 (M^+ , 100%), 126 ($M-CO_2$, 28), 104 (10), 97 (14), 85 (41); ν_{max} (KBr) 3000–2850 (C–H), 1785 (γ -lactone), 1160 cm^{-1} (C–O); δ_H 1.37 (6H, d, J 7 Hz, 4-Me, 8-Me), 2.60–3.12 (2H, m, 4-H, 8-H), 4.83–5.05 (2H, m, 1-H, 5-H).

4-Hydroxy-3-methyl-5-(α -methylacetic acid methyl ester)-tetrahydrofuran-2-on (16a), b.p. 180–190°C/0.5 mmHg; ν_{max} ($CHCl_3$) 3450 (OH), 3000–2860 (C–H), 1790 (γ -lactone), 1735 (COOMe), 1160–1080 cm^{-1} (C–O); δ_H 1.20–1.42 (6H, m, 3-Me, α -Me), 2.45–3.10 (2H, m, \underline{CH} (Me)), 3.20–3.50 (1H, br.s, OH), 3.70 (3H, s, COOMe), 3.82–4.55 (2H, m, 4-H, 5-H).

Preparation of 2-formyl-3,3,4,4-tetramethoxyoxetane (18)

Compound (18) was prepared according to the protocol for (16a) and (17) using (1b) (2.0 g) instead of (1a). After the cooling bath had been removed, the mixture was stirred at room temperature until the yellow colour had disappeared (*ca.* 2.5 h). Triethylamine (TEA) (0.5 ml) was added and the polymeric side products were filtered off. Evaporation of the solvent and subsequent bulb to bulb distillation afforded (18) with a purity of *ca.* 90% (600 mg), b.p. 180–190°C/0.5 mmHg; δ_H 3.28–3.43 (12H, m, OMe), 4.50 (1H, d, J 2 Hz, 2-H), 9.57 (1H, d, J 2 Hz, CHO).

Synthesis of lactones (16b), (20)–(23) from (18) and (1a), (1b) and (1c), general procedure.

$ZnCl_2$ (0.25 ml of a saturated solution in acetonitrile) was added to a stirred mixture of (18) (1.2 g, 5.8 mmol) and (1) (2 eq.) in acetonitrile (5 ml) at 0°C or –40°C (for (1a) only). The mixture was stirred vigorously (2 h for (1a), 16 h for (1b) and 24 h for (1c)). Then THF (30 ml) was added and the mixture was cooled to –10°C. HCl (2 ml of a 10% solution) was added and stirring was continued at –10°C for 2 h. The mixture was allowed to come to room temperature, and brine (10 ml) and dichloromethane (40 ml) were added. The aqueous layer was separated off and the organic layer was dried (Na_2SO_4).

Evaporation of the solvents afforded the crude products. Bulb to bulb distillation afforded product mixtures free from polymeric and other side products. For all reactions the same product mixtures were isolated, when dichloromethane instead of acetonitrile was used as the solvent. In this way were obtained:

Compounds (20) and (21) from (18) and (1a), 4:5 mixture (900 mg, 62%), b.p. 180-200°C/0.8 mmHg; (Found: $M^+ - OMe$, 217.0711. $C_9H_{13}O_6$ requires 217.0712); m/z (CI) 218 (10%), 217 ($M - OMe$, 100), 185 ($M - OMe$, $-MeOH$, 18), 119 (12); ν_{max} ($CHCl_3$) 3550 (OH), 3040-2900 (C-H), 1795 (γ -lactone), 1735 (COOMe), 1460 (C-H), 1280 (C-O), 1180-1160 cm^{-1} (C-O); δ_H 1.30 (3H, br.d, J 5 Hz, Me), 2.80 and 2.88 (1H, 2dq, J 5 and 1.5 Hz, $-CH(Me)$), 3.45 (6H, br.s, OMe), 3.65 (1H, br.s, OH), 3.72 (3H, s, COOMe), 4.10-4.53 (2H, m, $-CH(OH)$ and $-CHO-CO-)$.

Compound (16b) from (18) and (1b)

Crystallization of the crude product from diisopropyl ether afforded pure (16b) (750 mg, 44%), m.p. 90-92°C (CCl_4 - n -pentane); (Found: C, 44.94; H, 6.11. $C_{11}H_{18}O_9$ requires C, 44.90; H, 6.17%); m/z (EI) 263 ($M - OMe$, 100%), 235 ($M - COOMe$, 37), 203 ($M - COOMe$, $-MeOH$, 62), 133 (17); ν_{max} (KBr) 3600-3450 (OH), 3050-2850 (C-H), 1800 (γ -lactone), 1730 (COOMe), 1450 (C-H), 1200-1030 cm^{-1} (C-O); δ_H 2.82 (1H, d, J 6 Hz, OH), 3.40-3.48 (12H, 4s, OMe), 3.77 (3H, s, COOMe), 4.33 (1H, d, J 5 Hz, 5-H), 4.46-4.68 (1H, m, 4-H).

(3:1) Mixture of (22) and (23) from (18) and (1c), (800 mg, 52%), b.p. 150-160°C/0.5 mmHg; (Found: $M^+ + 1$, 263.1136. $C_{11}H_{19}O_7$ requires 263.1131); m/z (CI) 263 ($M+1$, 1%), 231 ($M - OMe$, 100), 203 ($M - COOMe$, 24), 199 (16), 171 (27), 133 (53), 119 (88); ν_{max} ($CHCl_3$) 3550 (OH), 3600-3250 (OH), 3060-2880 (C-H), 1810-1780 (γ -lactone), 1745-1710 (COOMe), 1470-1430 (C-H), 1275 (C-O), 1180-1030 cm^{-1} (C-O); δ_H 1.17, 1.25 and 1.28 (6H, 3s, (signal ratio 1:1:6), Me), 2.72 and 2.99 (1H, br.d, J 6 Hz, OH), 3.35-3.47 (6H, 4s, OMe), 3.67 and 3.77 (3H, 2s (signal ratio 3:1), COOMe), 4.07-4.77 (2H, m, 4-H, 5-H).

Preparation of bisoxetane (19)

Compound (19) could be synthesized using the procedure for (16a). After addition of ZnCl_2 the mixture was stirred for 16 h. The solvent was evaporated and the resulting solid product was recrystallized twice from tetrachloromethane-hexane, yield 88%, m.p. 161-164°C (lit.¹⁰: 163-165°C). Spectral data were identical with those described¹⁰.

*Preparation of cis phenanthro[4,5-*i*]-4,8-dimethyl-2,6-dioxabicyclo[3.3.0]octane-3,7-dione (25)*

ZnCl_2 (0.5 ml of a saturated solution in acetonitrile) was added to a mixture of phenanthrenequinone (14) (2.1 g, 10 mmol) and (1a) (3.03 g, 30 mmol). The mixture was refluxed for 4.5 h. After cooling to room temperature THF (30 ml) was added and the mixture was cooled to -10°C. HCl (2 ml of a 10% solution) was added and the mixture was stirred for 2 h. Brine (10 ml) and CH_2Cl_2 (40 ml) were added and the aqueous layer was separated off. The organic layer was dried (Na_2SO_4) and the solvent was evaporated to give the crude product. Crystallization from dichloromethane- CCl_4 afforded (25), (2.75 g, 85%), m.p. 185-187°C (CH_2Cl_2 - CCl_4); (Found: C, 74.88; H, 4.97. $\text{C}_{20}\text{H}_{16}\text{O}_4$ requires C, 74.99; H, 5.03%); m/z (EI) 320 (M^+ , 81%), 248 (M^+ -CH(Me)COO, 100), 2.09 (42); ν_{max} (KBr) 3100-2980 (C-H), 1785 (γ -lactone), 1180 cm^{-1} (C-O); δ_{H} 1.40 (6H, d, J 7 Hz, Me), 2.81 (2H, q, J 7 Hz, -CHMe), 7.27-7.94 (8H, m, phenanthrene-H).

*Preparation of cis acenaphtheno[1,2-*i*]-4,8-dimethyl-2,6-dioxabicyclo[3.3.0]octane-3,7-dione (27)*

ZnCl_2 (0.5 ml of a saturated solution in acetonitrile) was added to a mixture of acenaphthenequinone (1.82 g, 10 mmol) and (1a) (3.03 g, 30 mmol) in acetonitrile (20 ml). The mixture was refluxed for 4 h. After cooling to room temperature TEA (1 ml) was added and the solvent was evaporated. THF (40 ml) was added and work-up as described for (25) yielded a crude product. Crystallization from diisopropyl ether gave a mixture (1.5 g) of two diastereomeric bislactones and a mono-ester. After repeated crystallization (27) could be obtained completely free from the mono ester. (27), (9:1 diastereomeric mixture) (1.1 g,

37%), m.p. 176-181°C (diisopropyl ether-CCl₄); (Found: C, 73.46; H, 4.76. C₁₈H₁₄O₄ requires C, 73.46; H, 4.80%); m/z (EI) 294 (M⁺, 82%), 221 (M-C₃H₅O₂, 48), 210 (70), 209 (49), 194 (100), 165 (93), 154 (77), 126 (C₁₀H₆, 85); ν_{\max} (KBr) 3090-2930 (C-H), 1790 (γ -lactone), 1220-1150 cm⁻¹ (C-O); δ_{H} 1.00 and 1.57 (6H, 2d, J 7 Hz, Me), 2.82, 2.86 and 3.33 (2H, 3q, J 7 Hz, CH(Me)), 7.45-8.00 (6H, m, acenaphthene-H). Careful recrystallization of this 9:1 diastereomeric mixture from diisopropyl ether-hexane-dichloromethane afforded a small amount of the major isomer in pure form; m.p. 190-194°C; (Found: C, 72.9; H, 4.80. C₁₈H₁₄O₄ requires C, 73.46; H, 4.80%); δ_{H} 1.56 (6H, d, J 7 Hz, Me), 2.86 (2H, q, J 7 Hz, CH(Me)), 7.48-7.97 (6H, m, acenaphthene-H). The spectral data of the mono ester were identical with those given by Bakker *et al.*¹⁰.

Synthesis of methyl 1,3-dimethyl-4,4-dimethoxy-3-hydroxybutanoate (29)
ZnCl₂ (0.5 ml of a saturated solution in acetonitrile) was added to a mixture of freshly distilled pyruvaldehyde dimethylacetal (2.51 g, 25 mmol) and (1a) (3.03 g, 30 mmol) in acetonitrile (15 ml). The mixture was stirred at 30°C for 16 h. After addition of TEA (0.5 ml) the solvent was evaporated and THF (30 ml) was added. The mixture was cooled to -10°C and hydrochloric acid (5 ml of a 1 M solution) was added. The mixture was stirred for 2 h, dichloromethane (40 ml) was added, and the aqueous layer was separated off. The organic layer was dried (Na₂SO₄) and the solvent was evaporated. Distillation afforded (29) as a 2:1 diastereomeric mixture (4.1 g, 78%), b.p. 66°C/0.8 mmHg; δ_{H} 1.12-1.28 (6H, m, 2-Me, 3-Me), 2.55-2.83 (1H, m, 2-H), 2.92 (1H, br.s, OH), 3.45 and 3.52 (6H, 2s, OMe), 3.67 (3H, s, COOMe), 4.02 and 4.15 (1H, 2s (signal ratio 1:2), 4-H).

Synthesis of methyl 3-hydroxy-2-methyl-4-hexenoate (31)

A mixture of 2-butenal (7 g, 0.1 mol) and (1a) (12.5 g, 123 mmol) in THF (50 ml) was cooled to -78°C and AlCl₂Obornyl (2 ml of a 0.55 M solution in ether) was added under vigorous stirring. The mixture was stirred for 6 h and after 3 h additional AlCl₂Obornyl (1 ml) was added. MeOH (6.4 g, 0.2 mol) was added and the mixture was

allowed to come to room temperature. Sulphuric acid (10 ml of a 0.75 M solution) was added and the mixture was stirred for 30 min at room temperature. CH_2Cl_2 (75 ml) and brine (20 ml) were added and the organic layer was separated off. The aqueous layer was extracted with CH_2Cl_2 (25 ml) and the combined organic layers were dried (Na_2SO_4). Evaporation of the solvent and subsequent distillation afforded (31) as a 2:1 diastereomeric mixture (11.5 g, 72%), b.p. $54^\circ\text{C}/0.5 \text{ mmHg}$ (lit.¹⁹: $98\text{--}100^\circ\text{C}/15 \text{ mmHg}$); δ_{H} 1.12 and 1.17 (3H, 2d, J 7 Hz, 2-Me), 1.71 (3H, d, J 6 Hz, 6-H), 1.92 (1H, br.s, OH), 2.32–2.54 (1H, m, 2-H), 3.70 (3H, s, COOMe), 3.95–4.38 (1H, m, 3-H), 5.25–5.93 (2H, m, 4-H, 5-H).

Synthesis of protected β -hydroxyesters (32), (37) and (38)

Methyl 3-acetoxy-2-methyl-4-hexenoate (32)

Compound (32) was prepared according to the method of Steglich²⁰, yield 92%, b.p. $65\text{--}70^\circ\text{C}/0.4 \text{ mmHg}$; δ_{H} 1.11 and 1.16 (3H, 2d, J 7 Hz, 2-Me), 1.71 (3H, d, J 6 Hz, 6-H), 2.00 and 2.04 (3H, 2s, OAc), 2.70 (1H, br.q, J 7 Hz, 2-H), 3.67 (3H, s, COOMe), 5.23–6.04 (3H, m, 3-H, 4-H, 5-H).

Methyl 3-(1-ethoxyethoxy)-2-methyl-4-hexenoate (37)

Compound (37) was prepared according to the protocol of Tufariello²⁴, yield 84%, b.p. $75^\circ\text{C}/0.5 \text{ mmHg}$; δ_{H} 0.97–1.32 (9H, m, 2-Me, $\text{CH}(\text{Me})\text{OCH}_2\text{-Me}$), 1.62–1.78 (3H, m, 6-H), 2.33–2.83 (1H, m, 2-H), 3.13–4.25 (3H, m, $\text{OCH}_2\text{-Me}$, 3-H), 3.63 (3H, br.s, COOMe), 4.45–4.80 (1H, m, $\text{OCH}(\text{Me})$), 4.97–5.75 (2H, m, 4-H and 5-H).

Methyl 2-methyl-3-tetrahydropyranyloxy-4-hexenoate (38)

Compound (38) was prepared according to the method of Olah²⁸ using acidic DOWEX W-50 as the ion exchange resin, yield 77%, b.p. $95\text{--}104^\circ\text{C}/0.2 \text{ mmHg}$; (Found: C, 64.21; H, 8.99. $\text{C}_{13}\text{H}_{22}\text{O}_4$ requires C, 64.44; H, 9.15%); m/z (CI) 243 ($\text{M}^+ + 1$, 16%), 159 ($\text{M-C}_5\text{H}_8\text{O}$, 63), 142 (17), 141 (M-OTHP , 100), 85 (100); δ_{H} 1.04 and 1.08, 1.24 and 1.27 (3H, 4d, J 7 Hz, 2-Me), 1.42–1.83 (6H, m, 3'-5'-H), 2.42–2.80 (1H, m, 2-H),

3.31-3.91 (2H, m, 6'-H), 3.64-3.72 (3H, 4s, COOMe), 3.99-4.31 (1H, m, 3-H), 4.60-4.79 (1H, m, 2'-H), 4.97-5.97 (2H, m, 4-H, 5-H).

Synthesis of aldehydes (33), (39), and (42), general procedure

TBA (3 ml) was added to a stirred solution of the appropriate methyl hexenoate (30 mmol) in MeOH (150 ml). The mixture was cooled to -78°C . A stream of ozonised oxygen (2.5 g O_3 per h) was passed through the solution, until a blue colour persisted (ca. 0.6 h). The solution was then flushed with N_2 for 5 min to remove the excess of ozone. Dimethylsulfoxide (2.5 ml) was added dropwise to the solution and the mixture was stirred for another 30 min at -78°C . After the solution had come to room temperature the MeOH was largely evaporated. Water (100 ml) and dichloromethane (50 ml) were added and the aqueous layer was separated. The organic layer was washed with water (3 x 25 ml) in order to remove all dimethylsulfoxide. The combined aqueous layers were extracted with dichloromethane (35 ml) and this dichloromethane layer was extracted with water (35 ml). The combined organic layers were dried (Na_2SO_4) and the solvents were evaporated. Distillation afforded the pure products. In this way were prepared:

Methyl 3-acetoxy-2-methyl-4-oxobutanoate (33), (4.1 g, 72%), b.p. $58-60^{\circ}\text{C}/0.5 \text{ mmHg}$; m/z (CI) 189 ($\text{M}^+ + 1$, 100%), 157 (M-OMe, 100), 129 ($\text{M}-\text{C}_2\text{H}_3\text{O}_{23}$, 25), 43 (36); δ_{H} 1.18 and 1.23 (3H, 2d, J 7 Hz, 2-Me), 2.13 (3H, br.s, OAc), 2.75-3.37 (1H, m, 2-H), 3.63 (3H, s, COOMe), 4.97 and 5.15 (1H, 2d, J 5 Hz, 3-H), 9.45 (1H, br.s, CHO).

Methyl 3-(1-ethoxyethoxy)-2-methyl-4-oxo-butanoate (39), (3.8 g, 58%), b.p. $95-100^{\circ}\text{C}/0.8 \text{ mmHg}$; δ_{H} 1.05-1.38 (9H, m, 2-Me, $\text{CH}(\text{Me})\text{OCH}_2\text{-Me}$), 2.70-3.08 (1H, m, 2-H), 3.48 (2H, br.q (signal partially hidden under COOMe signal), J 4 Hz, $\text{OCH}_2\text{-Me}$), 3.65 (3H, s, COOMe), 3.66-3.90 (signal partially hidden under COOMe signal) and 4.02-4.28 (1H, 2m, 3-H), 4.55-4.90 (1H, m, $\text{OCH}(\text{Me})\text{OEt}$), 9.53-9.67 (1H, m, CHO).

Methyl 2-methyl-4-oxo-3-tetrahydropyranyloxybutanoate (42), (4.25 g, 61%), b.p. 90-92°C/0.5 mmHg; δ_{H} 1.16-1.32 (3H, m, 2-Me), 1.40-1.90 (6H, m, 3'-5'-H), 2.78-3.19 (1H, m, 2-H), 3.31-4.03 (2H, m, 6'-H), 3.69 (3H, br.s, COOMe), 4.17-4.60 (1H, m, 3-H), 4.68-4.79 and 4.87-4.99 (1H, 2m, 2'-H), 9.67 (1H, br.s (with fine splitting), CHO).

Synthesis of (35) from (33) and (1a)

ZnCl₂ (1 ml of a saturated solution in acetonitrile) was added to a mixture of (33) (2.82 g, 15 mmol) and (1a) (2.05 g, 20 mmol) in acetonitrile (10 ml). The mixture was stirred for 3 h at room temperature. Then TEA (1 ml) and THF (30 ml) were added. The mixture was cooled to -10°C and sulphuric acid (10 ml of a 0.75 M solution) was added. After stirring at -10°C for 2 h dichloromethane (40 ml) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (25 ml) and the organic layers were combined. The solvents were evaporated and dioxane (30 ml) and water (5 ml) were added. Sodium hydroxide (10 ml of a 2 M solution) was added and the mixture was stirred again for 16 h at room temperature. The mixture was then extracted with chloroform (50 ml) and hydrochloric acid (a 6 M solution) was added until the pH was *ca.* 2. Chloroform (50 ml) was added and the organic layer was separated off. The aqueous layer was extracted with chloroform (2 x 20 ml) and the combined organic layers were dried (Na₂SO₄). Evaporation of the solvent delivered (35) with a purity of *ca.* 95%; it was used without further purification.

m/z (CI) 171 (M+1, 100%), 153 (M-OH, 46), 125 (M-COOH, 34), 97 (M-CH(Me)COOH, 23); δ_{H} 1.15 and 1.27 (3H, 2d, J 6 Hz, 2'-Me), 1.93 (3H, br.s, Me), 2.53-3.15 (1H, m, 2'-H), 4.98-5.30 (1H, m, 5-H), 7.13 (1H, br.s (with fine splitting), 4-H), 9.30 (1H, br.s, COOH).

Synthesis of cis 4,8-dimethyl-2,6-dioxabicyclo[3.3.0]octane-3,7-dione (40) (mixture of diastereomers) from (39) and (1a)

MgBr₂ (0.5 ml of a saturated solution in acetonitrile) was added to a mixture of (39) (0.5 g, 2.3 mmol) and (1a) (0.4 g, 3.96 mmol) in dichloromethane (5 ml) at 25°C. The mixture was stirred for 3 h, then

cooled to -78°C and finally MeOH (2 ml) was added. The mixture was stirred at -78°C for 30 min and then allowed to come to room temperature. The solvents were evaporated and THF (30 ml) and H_2SO_4 (5 ml of an 0.5 M solution) were added. The mixture was stirred again for 1 h and dichloromethane (40 ml) and brine (10 ml) were added. The organic layer was separated off and the aqueous layer was extracted with dichloromethane (15 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. Crystallization of the products with diisopropyl ether afforded (40) (mixture of 3 diastereomers) (70 mg, 17%), m.p. $85-98^{\circ}\text{C}$ (diisopropyl ether-hexane); ν_{max} (CHCl_3) 3020-2800 (C-H), 1810-1780 (γ -lactone), 1450 and 1390 (C-H), 1190-1070 cm^{-1} (C-O); δ_{H} 1.37 (6H, d, J 5 Hz, 3-Me), 2.70-3.12 (2H, m, 3-H and 6-H), 4.73 and 4.82 (0.37H, 2d, J 3 and 4 Hz, 1-H, 5-H), 4.93-5.22 (0.63H, m, 1-H, 5-H).

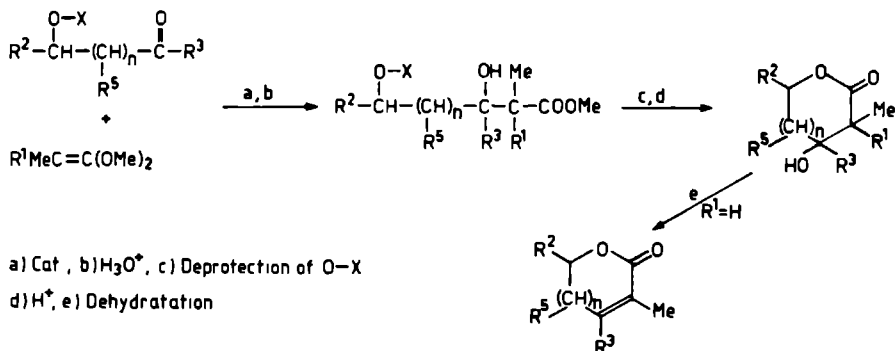
References

1. a. R.C. Anderson and B. Fraser-Reid, *J. Org. Chem.*, 1985, 50, 4781.
b. J.L. Hermann, M.H. Berger and R.H. Schlessinger, *J. Am. Chem. Soc.*, 1979, 101, 1544.
2. R.M. Carlson and A.R. Oyler, *J. Org. Chem.*, 1976, 41, 4065.
3. A. Pelter, R.S. Ward, P. Collins, R. Venkateswarlu and I.T. Kay, *J. Chem. Soc. Perkin I*, 1985, 587.
4. G. Pattenden in 'Prog. Chem. Org. Nat. Prod.', L. Zechmeister ed., Springer Verlag, Wien, 1978, 35, 133.
5. S. Harigaya, *J. Biochem.*, 1964, 56, 392; see also ref. 6.
6. D. Horton and Z. Wataszek, *Carbohydrate Res.*, 1982, 105, 95.
7. H.R. Krüger, P. Weyerstahl, H. Marschall and F. Nerdel, *Chem. Ber.* 1972, 105, 3553.
8. J.A. Elvidge and R.P. Linstead, *J. Chem. Soc.*, 1950, 2228.
9. M. Janda, E. Korblova and I. Stilber, *Coll. Czech. Chem. Commun.*, 1983, 48, 96.
10. C.G. Bakker, J.W. Scheeren and R.J.F. Nivard, *Recl. Trav. Chim. Pays-Bas*, 1983, 102, 96.
11. a. E.L. Eliel in 'Asymmetric Synthesis', J.D. Morrison ed., Academic Press, New York, Vol. II, 1983, 125.
b. K. Mead and T.L. MacDonald, *J. Org. Chem.*, 1985, 50, 422 and references cited therein.
12. M. Cherest, H. Felkin and N. Prudent, *Tetrahedron Lett.*, 1968, 9, 2199; see also ref. 11b.
13. a. M.T. Reetz, K. Kessler and A. Jung, *Tetrahedron*, 1984, 40, 4327.
b. M.T. Reetz, *Angew. Chem.*, 1984, 96, 542.
c. M.T. Reetz and K. Kessler, *J. Org. Chem.*, 1985, 50, 5436.
14. C. Harries and P. Temme, *Chem. Ber.*, 1907, 40, 165.
15. K. Takai and C.H. Heathcock, *J. Org. Chem.*, 1985, 50, 3247.
16. R.G. Hofstraat, J.W. Scheeren and R.J.F. Nivard, *J. Chem. Soc. Perkin I*, 1985, 561.

17. a. A. Haneda, H. Uenaki, T. Imagawa and M. Kawanisi, *Synthetic Commun.*, 1976, 6, 141.
b. L. Schuster and J. Paust, Ger. Offen. P 2514001.6 (C 07 C 47/02, 29 Mar. 1975), *C.A.*, 1978, 86, P 71908p.
18. R.W.M. Aben and J.W. Scheeren, *Synthesis*, 1982, 779.
19. R.W.M. Aben and J.W. Scheeren, *Synthesis*, 1978, 400.
20. G. Höfle, W. Steglich and H. Vorbrüggen, *Angew. Chem.*, 1978, 602.
21. J. Baldwin, *J. Chem. Soc. Chem. Commun.*, 1976, 734.
22. a. M.D. Dowle and D.I. Davies, *Chem. Soc. Rev.*, 1979, 8, 171.
b. J. Mulzer, *Nachr. Chem. Techn. Lab.*, 1984, 32, 226.
23. A.A. Jakubowski, F.S. Guziec, M. Sugira, C. Chan Tan, M. Tischler, and S. Omura, *J. Org. Chem.*, 1982, 47, 1221.
24. J.J. Tufariello and E.J. Trybulski, *J. Org. Chem.*, 1974, 39, 3378.
25. G.A. Olah, A. Husain, B.P. Singh and A.K. Mehrita, *J. Org. Chem.* 1983, 48, 3667.
26. L. Brandsma and H.D. Verkruysse, 'Preparative Polar Organometallic Chemistry', Vol. I, Springer Verlag, Berlin, 1987.

This thesis deals with the application of the ketene acetal 1,1-dimethoxypropene (1a) (Fig. 1) in the synthesis of various types of γ - and δ -lactones. In the introductory chapter the more important synthetic and mechanistic aspects of (2+2) cycloadditions of ketene acetals (1) in general, and in particular of (1a), are discussed. A variety of aldehydes and ketones can be converted with (1) under ZnCl_2 catalysis into 2,2-dimethoxyoxetanes. These can easily be hydrolyzed to the corresponding β -hydroxyesters. When a protected hydroxy function is present in the starting aldehyde or ketone reaction with (1a) and subsequent hydrolysis enables after deprotection to synthesize various types of hydroxylactones. This reaction sequence is the common theme of the various chapters of the thesis (Scheme 1).

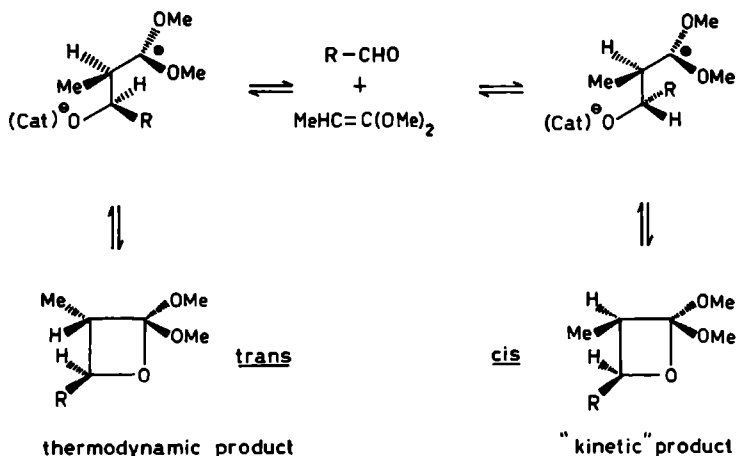
Scheme 1



The stereochemical outcome of the (2+2) cycloaddition of (1a) with the starting aldehyde or ketone determines the overall stereochemistry of the lactone synthesis. Therefore, the reactions of (1a) with several

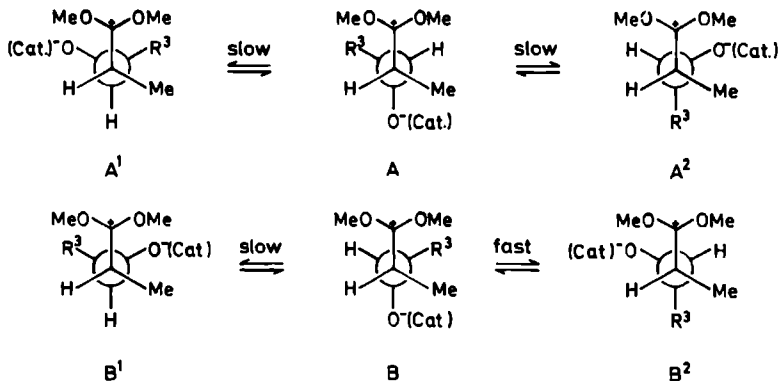
aldehydes, R-CHO, have been examined and the results have been presented in chapter 2. It is shown (Scheme 2) that oxetane formation occurs *via* a dipolar intermediate and that the reaction is reversible in the presence of the catalysts used. The influence of the reaction

Scheme 2



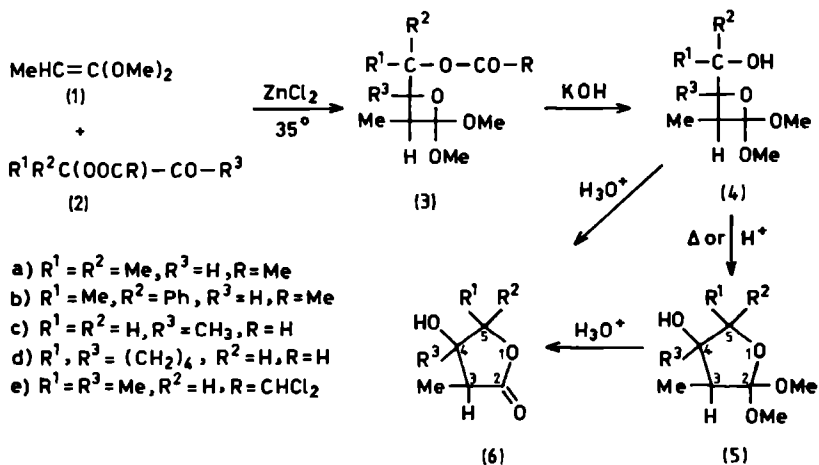
conditions and of the size of the group R on the stereochemistry have been discussed. It appears that under 'kinetic' conditions the *cis:trans* ratio of the oxetanes is not only determined by the most favourable transoid approach of the cycloaddends, but also by the rotation of the dipolar intermediate to a cisoid *gauche* conforma-

Figure 2

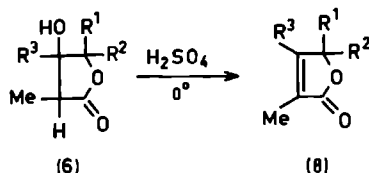


tion (Figure 2). Under thermodynamic conditions the most stable *trans* oxetane is formed in excess. When the side-chain R of the aldehyde is branched at C- α *cis:trans* ratios of 5:95 can be obtained. Since the stereochemistry of the oxetanes is maintained during hydrolysis this allows the stereoselective preparation of *threo* β -hydroxyesters in good yields and with high selectivity.

Scheme 3

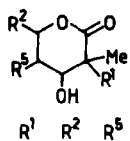
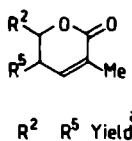


In chapter 3 the preparation of 2,2-dimethoxy-4-hydroxy-3-methyl-tetrahydrofurans and 4-hydroxy-3-methyl- γ -butyrolactones from (1a) and α -acyloxyaldehydes and -ketones has been described (Scheme 3). α -Acyloxyaldehydes react with (1a) in the presence of ZnCl_2 to yield 4-(α -acyloxy)alkyl-2,2-dimethoxy-3-methyloxetanes. For the analogous conversion of α -acyloxyketones stronger electron-withdrawing acyl groups are necessary. Hydrolysis of the acyloxy groups with potassium hydroxide yields the corresponding hydroxy compounds which rearrange under neutral or weakly acidic conditions to 2,2-dimethoxytetrahydrofurans. Mild acidic hydrolysis of the latter compounds affords the γ -butyrolactones which can be dehydrated to 3-methyl-2-(5H)-furanones in moderate to good overall yields (Scheme 4).



Chapter 4 deals with the use of (1a) in the synthesis of δ -lactones from hydroxy-protected β -hydroxyaldehydes (Scheme 1, $n = 1$). These protected β -hydroxyaldehydes are synthesized *via* various methods. β -Acetoxy- and β -silyloxyaldehydes are synthesized in one step, *via* the addition of acetic acid to an α,β -unsaturated aldehyde, and *via* the reaction of a silyl enoether with benzaldehyde under high pressure, respectively. These methods have, however, a restricted scope. The reduction of a protected β -hydroxyester to a protected β -hydroxyaldehyde is a more general route to β -oxygenated aldehydes. Using protected *threo* β -hydroxyesters as a starting material, protected β -hydroxyaldehydes (Scheme 1, $n = 1$, $X = \text{CH}(\text{Me})\text{OEt}$) of defined stereochemistry are prepared in good yields. Reaction of the prepared aldehydes with (1a), subsequent hydrolysis of the formed oxetane, deprotection of the hydroxy function and lactonization deliver 4-hydroxy-3-methyl- δ -lactones in moderate to good yields *via* a 'one-pot' procedure. When β -oxyaldehydes of defined stereochemistry are used, δ -lactones with defined chemistry are isolated. Dehydration of the obtained 4-hydroxylactones with concentrated sulphuric acid delivers 5,6-dihydropyrones. The results are presented in Table 1.

Table 1

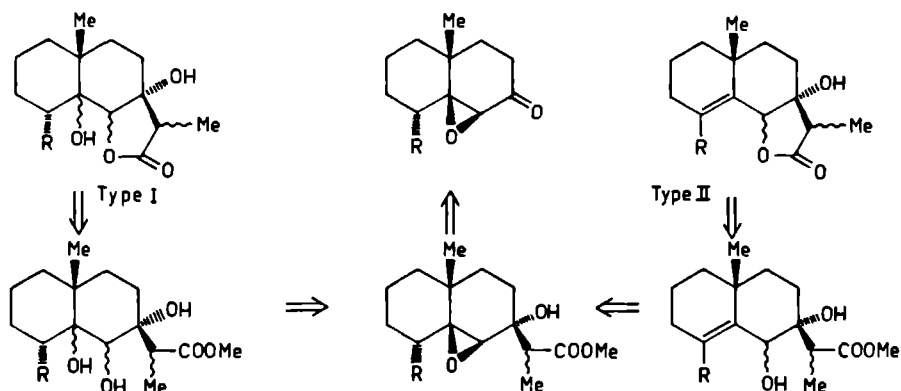
OX R ² CH-CH(R ⁵)-CHO R ² R ⁵ X	Ketene Acetal		
		R ¹ R ² R ⁵ Yield ^a	R ² R ⁵ Yield ^a
(2) H H Ac	(1a)	(21) H H H 50	(22) H H 30
(3) Me H Ac	(1a)		(25) Me H 28
(5) Ph Et SiMe ₃	(1a)		(27) Ph Et 70 ^b
(15) Ph Me CHMeOEt	(1a)	(28) H Ph Me 61 ^b	
(15) Ph Me CHMeOEt	(1b)	(31) Me Ph Me 12 ^c	
(16) Hex ^c Me CHMeOEt	(1a)	(29) H Hex ^c Me 40 ^c	
(17) Pr ^l Me CHMeOEt	(1a)	(30) H Pr ^l Me 44 ^c	
(35) Me H CHMeOEt	(1a)		(37) Me H 38

a) yield in % based on the aldehyde b) diastereomeric mixture

c) one diastereomer

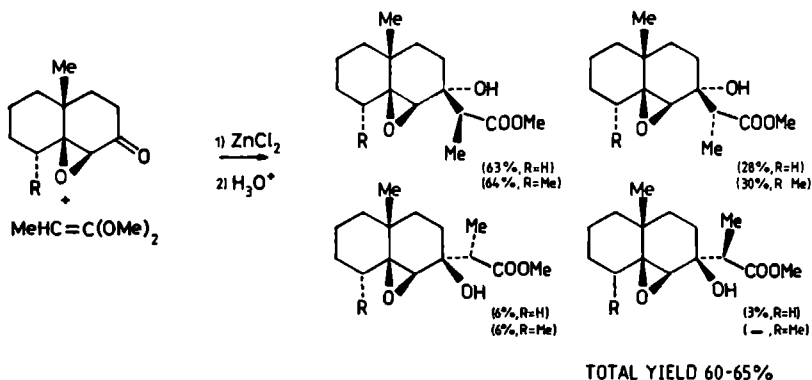
The synthesis of some precursors for the preparation of eudesmanolides of type I and type II (Scheme 5) is presented in chapter 5. Two deca-

Scheme 5



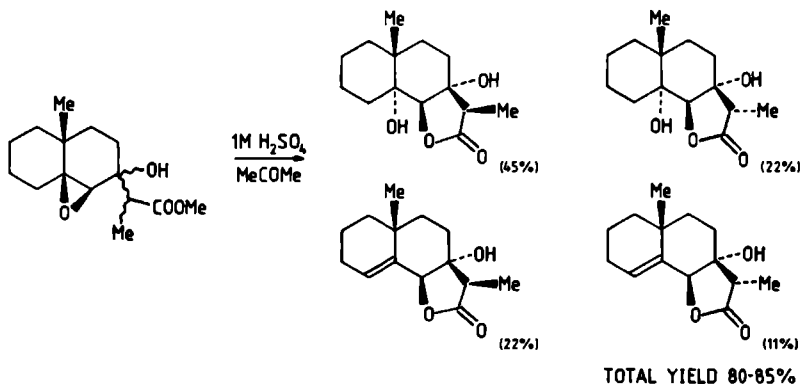
line-type epoxyketones (Scheme 6, R = H or Me) have been chosen as starting material. These ketones are easily converted into γ,δ -epoxy- β -hydroxyesters *via* reaction with (1a) and subsequent hydrolysis of the oxetanes. Both epoxyketones deliver epoxyesters in which the introduced ketene acetal moiety is mainly in an equatorial position with respect to the decaline structure. Hydrolysis of these epoxyesters occurs in one case (R = H) *via* reaction with 1 M H_2SO_4 in

Scheme 6



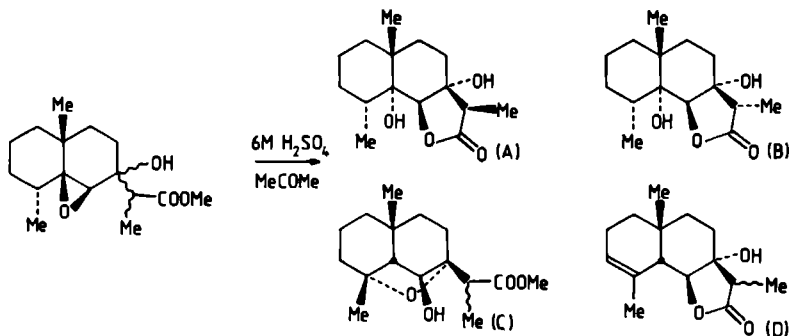
acetone and delivers a mixture of two monohydroxy- and two dihydroxy-lactones (Scheme 7). In the other case (R = Me) hydrolysis requires

Scheme 7



6 M H_2SO_4 in acetone and yields a mixture of two dihydroxylactones and two 1,7-epoxynaphthalene derivatives (Scheme 8). Furthermore,

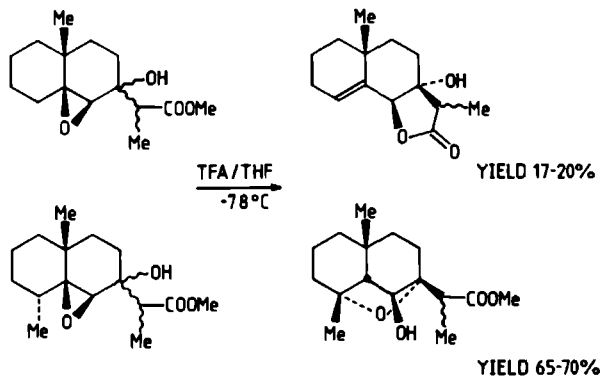
Scheme 8



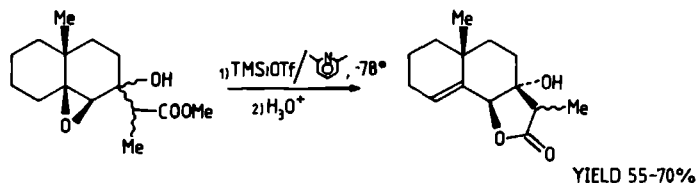
YIELD (A+B)30%,(C)20%

reaction with trifluoroacetic acid (Scheme 9) and with trimethylsilyl-trifluoromethanesulfonate (TMSOTf) (Scheme 10 and 11) have been carried out. The latter reaction gives in one case (Scheme 10) easy access to a valuable eudesmanolide precursor in good overall yield.

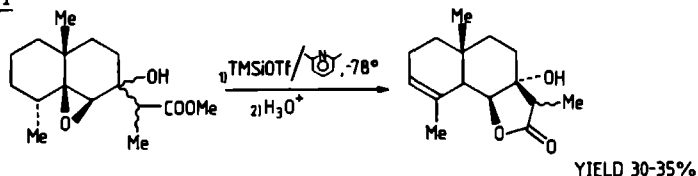
Scheme 9



Scheme 10



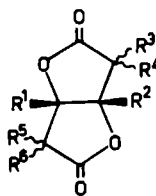
Scheme 11



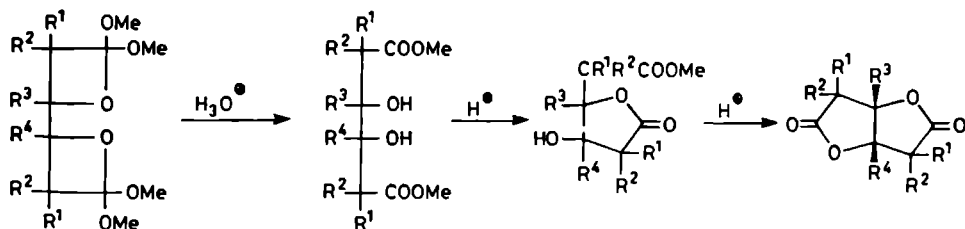
Attempts to synthesize bis- γ -lactones (bislactones) (Fig. 3) from

(1) and various types of α -dicarbonyl compounds or analogues of them are described in chapter 6. Only the more stable *cis*-fused bislactones are obtained *via* these routes. α -Dicarbonyl compounds can be converted with (1a) into bisoxetanes and hydrolysis of these compounds gives either a bislactone, or a 'monolactone', or a mixture of both compounds (Scheme 12).

Figure 3

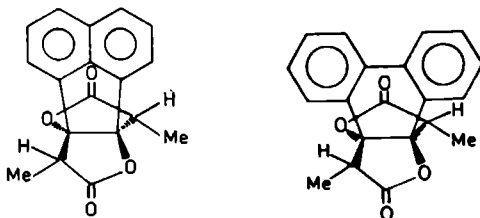


Scheme 12



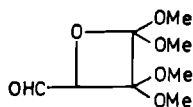
Reaction of (1a) with the most simple α -dicarbonyl compound, glyoxal, affords a mixture containing *ca.* 25% bislactone and *ca.* 50% monolactones. Stereochemical analysis shows that the formation of bislactones demands that the two carbonyl compounds are in a cisoid position. This can be arranged by either the use of a Lewis acid which complexes with both carbonyl groups (chelation) or by the use of α -dicarbonyl compounds in which these carbonyl groups are already in such a position. Only the latter route delivers bislactones as main products; both phenanthrenequinone and acenaphthenequinone have been converted with (1a) into their corresponding bislactones (Fig. 4).

Figure 4



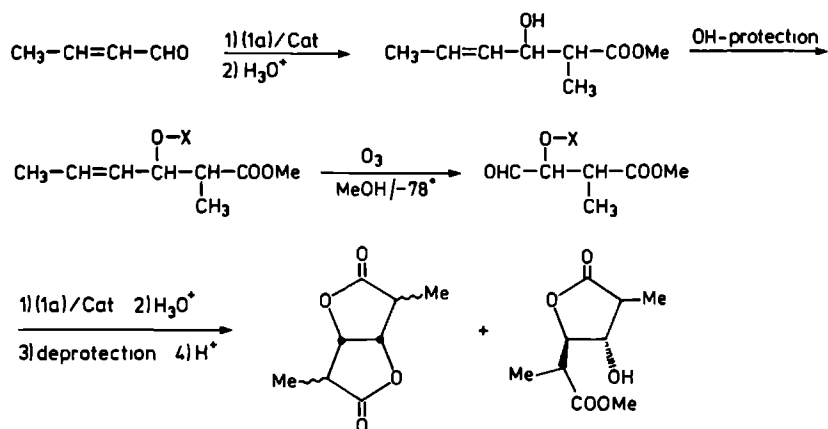
Another way to bislactones starts with dicarbonyl compounds, in which one carbonyl group is protected or masked. For this route too chelation controlled reaction conditions are necessary. In a first attempt, the oxetane synthesized from glyoxal and (1b) (Fig. 5) has

Figure 5



been used, but reaction of this oxetane could not be achieved under chelation controlled conditions. Then, a strategy using crotonaldehyde as the starting compound was followed (Scheme 13). Crotonaldehyde can be regarded as a masked glyoxal analogue, since ozonolysis of the double bond yields a second carbonyl function. *Via*

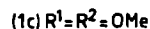
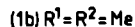
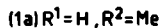
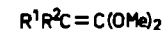
this route a few 3-hydroxy-4-oxo-butanoates have been synthesized, which after reaction with (1a) and subsequent hydrolysis might give a bislactone. Indeed, using $MgBr_2$ as the catalyst and ethyl vinyl ether as the protecting agent this has been achieved, and a mixture of diastereomeric bislactones has been isolated in a yield of *ca.* 17%.



Further study will concentrate on the use of protective groups having a stronger chelating power and not introducing an additional centre (*e.g.* the benzyl group). Currently, these reactions are under investigation.

Deze dissertatie beschrijft de toepassing van het keteenacetaal 1,1-dimethoxypropaan (1a) (Fig. 1) in de synthese van diverse γ - en δ -lactonen. In hoofdstuk 1 worden de belangrijkste synthetische en mechanistische aspecten van (2+2)

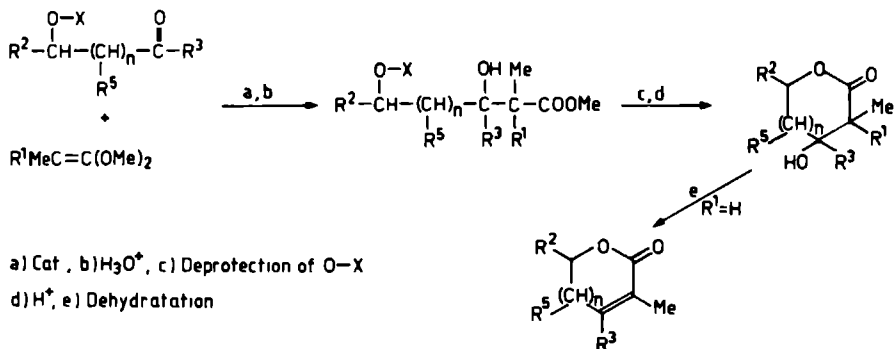
Figuur 1



het algemeen, en van (1a) in het bijzonder, toege-
licht. Onder invloed van $ZnCl_2$ als katalysator
kan een groot aantal aldehyden en ketonen met (1)
reageren tot 2,2-dimethoxyoxetanen en deze oxetanen
kunnen gemakkelijk gehydrolyseerd worden tot
 β -hydroxyesters (Schema 1). Indien in de uitgangs-

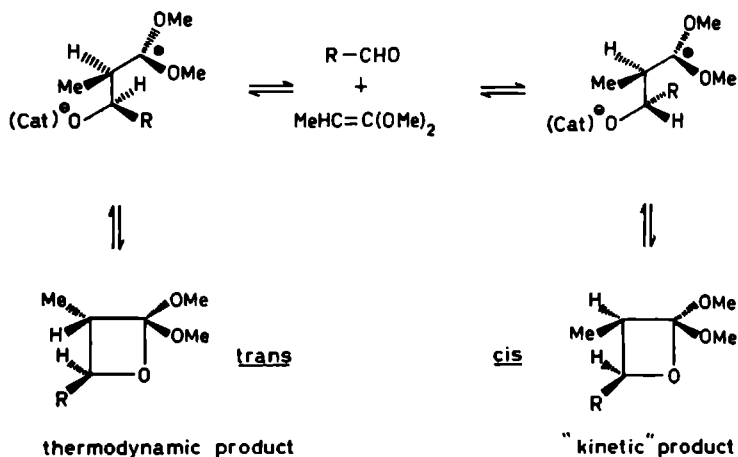
verbindingen een beschermde hydroxyfunctie aanwezig is, dan biedt
reactie met (1a), gevolgd door hydrolyse van het gevormde oxetaan
en ontscherming van de hydroxygroep, de mogelijkheid tot de synthese
van diverse typen hydroxylactonen. Deze serie reacties ligt ten grond-
slag aan elk der opeenvolgende hoofdstukken en vormt zodoende het
thema van deze dissertatie.

Schema 1

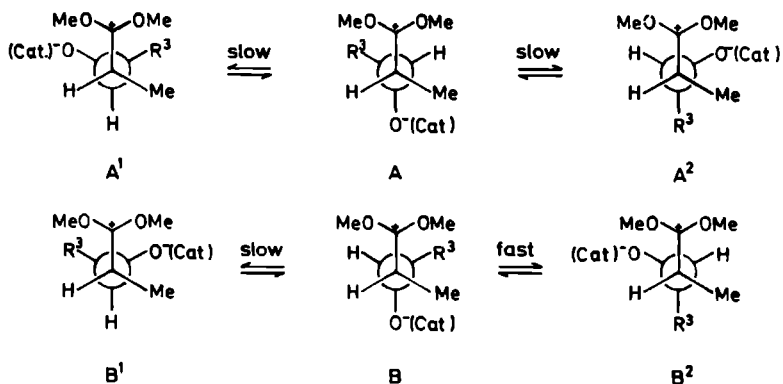


De stereochemie van deze lactonsynthese wordt bepaald door de (2+2) cycloadditie van (1a) met het betreffende aldehyde of keton. Daarom is de stereochemie van de reactie van (1a) met diverse aldehyden, R-CHO, nader bestudeerd, en de resultaten zijn gepresenteerd in hoofdstuk 2. Het blijkt dat de vorming van het oxetaan verloopt via een dipolair intermediair (Schema 2) en dat de reactie reversibel is onder invloed van de gebruikte katalysator. Zowel de invloed van de reactiecondities als van de grootte van de groep R zijn bestudeerd. Onder 'kinetische' condities blijkt de *cis:trans* ratio van de gevormde oxetanen niet alleen bepaald te worden door de meest gunstige nadering van de reactanten, maar ook door rotatie van het dipolair intermediair tot de *cisoid gauche* conformatie (Figuur 2). Onder thermodynamische omstandigheden wordt het meest stabiele *trans* oxetaan in overmaat gevormd. Indien de zijketen R van het aldehyde vertakt is op C- α dan zijn *cis:trans* verhoudingen van 5:95 mogelijk. Aangezien de stereochemie van de oxetanen behouden blijft tijdens de hydrolyse van de verbindingen is de stereoselectieve bereiding van *threo* β -hydroxyester in goede opbrengsten en met hoge selectiviteit mogelijk.

Schema 2

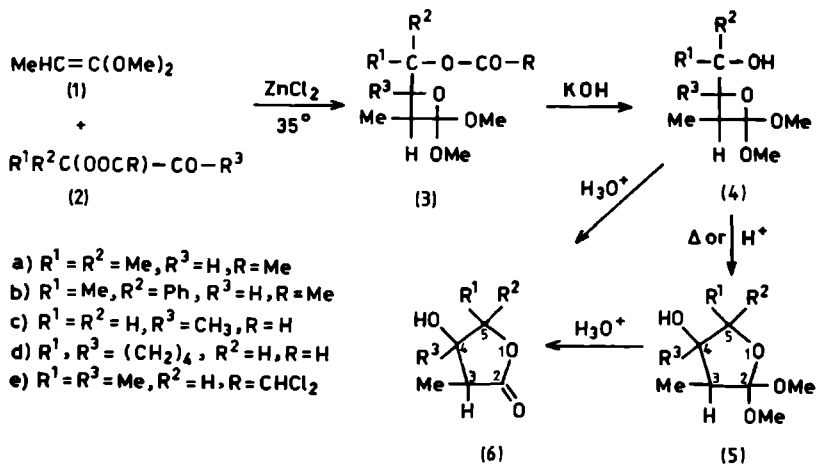


Figuur 2



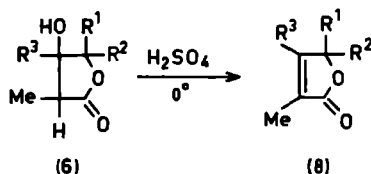
In hoofdstuk 3 wordt de bereiding van 2,2-dimethoxy-4-hydroxy-3-methyl-tetrahydrofuranen en 4-hydroxy-3-methyl- γ -butyrolactonen beschreven, uitgaande van (1a) en α -acyloxyaldehyden en -ketonen (Schema 3). α -Acyloxyaldehyden reageren met (1a) onder invloed van $ZnCl_2$ tot 4-(α -acyloxy) alkyl-2,2-dimethoxy-3-methyloxetanen. Voor de overeenkomstige omzetting van α -acyloxyketonen blijken sterkere elektronen-

Schema 3



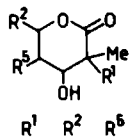
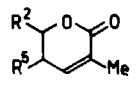
zuigende acyloxy groepen nodig. Verzeping van de acyloxy groepen met kaliumhydroxide levert de corresponderende hydroxyverbindingen en deze kunnen onder neutrale of mild-zure omstandigheden omleggen tot 2,2-dimethoxytetrahydrofuranen (5). Mild-zure hydrolyse van deze laatste verbindingen levert γ -butyrolactonen (6), welke in redelijke tot goede opbrengsten gedehydrateerd kunnen worden tot 3-methyl-2-(5H)-furanonen (Schema 4).

Schema 4



De synthese van δ -lactonen uitgaande van hydroxyl-beschermd β -hydroxyaldehyden en (1a) wordt besproken in hoofdstuk 4 (Schema 1, $n = 1$). De beschermde β -hydroxyaldehyden worden via een aantal methoden gesynthetiseerd. β -Acetoxy- en β -silyloxyaldehyden worden in één stap gemaakt door, respectievelijk, de additie van azijnzuur aan een α,β -onverzadigd aldehyde, en de hoge-druk reactie van een silylenolether met benzaldehyde. Deze directe methoden hebben echter een beperkte scope. De reductie van een beschermde β -hydroxyester tot een beschermd β -hydroxyaldehyde is een algemenere route naar β -oxyaldehyden. Indien gestart wordt met beschermde *threo* β -hydroxyesters dan kunnen beschermde β -hydroxyaldehyden (Schema 1, $n = 1$, $X = \text{CH}(\text{Me})\text{OEt}$) met een gedefinieerde stereochemie (*threo*) gesynthetiseerd worden. Reactie van de gesynthetiseerde aldehyden met (1a) en achtereenvolgens hydrolyse van het gevormde oxetaan, ontscherming van de hydroxyfunctie en lactonisering, levert 4-hydroxy-3-methyl- δ -lactonen in redelijke tot goede opbrengsten via een eenpots synthese. Indien β -oxyaldehyden met gedefinieerde stereochemie worden gebruikt, dan worden ook δ -lactonen met geheel gedefinieerde stereochemie geïsoleerd. Dehydratatie van de verkregen 4-hydroxylactonen met geconcentreerd zwavelzuur levert 5,6-dihydro-2-pyronen. Een overzicht van de resultaten geeft Tabel 1.

Tabel 1

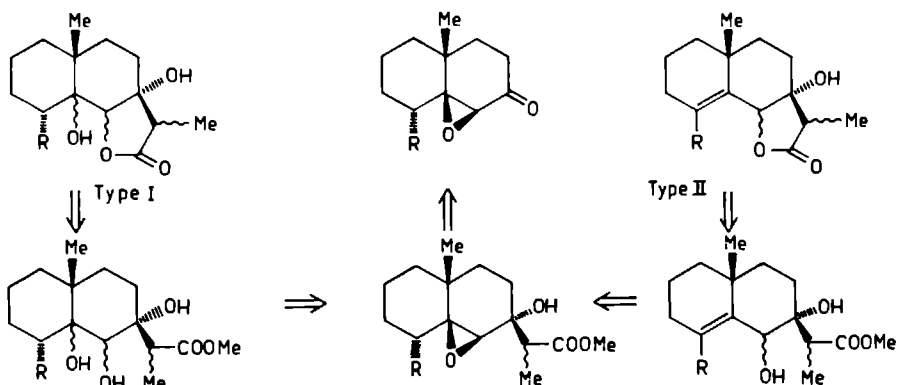
$\begin{array}{c} \text{OX} \\ \\ \text{R}^2\text{CH}-\text{CH}(\text{R}^5)-\text{CHO} \\ \text{R}^2 \quad \text{R}^5 \quad \text{X} \end{array}$	Ketene Acetal	 $\begin{array}{c} \text{R}^1 \quad \text{R}^2 \quad \text{R}^5 \quad \text{Yield}^a \end{array}$	 $\begin{array}{c} \text{R}^2 \quad \text{R}^5 \quad \text{Yield}^a \end{array}$
(2) H H Ac	(1a)	(21) H H H 50	(22) H H 30
(3) Me H Ac	(1a)		(25) Me H 28
(5) Ph Et SiMe ₃	(1a)		(27) Ph Et 70 ^b
(15) Ph Me CHMeOEt	(1a)	(28) H Ph Me 61 ^b	
(15) Ph Me CHMeOEt	(1b)	(31) Me Ph Me 12 ^c	
(16) Hex ^c Me CHMeOEt	(1a)	(29) H Hex ^c Me 40 ^c	
(17) Pr ^l Me CHMeOEt	(1a)	(30) H Pr ^l Me 44 ^c	
(35) Me H CHMeOEt	(1a)		(37) Me H 38

a) yield in % based on the aldehyde b) diastereomeric mixture

c) one diastereomer

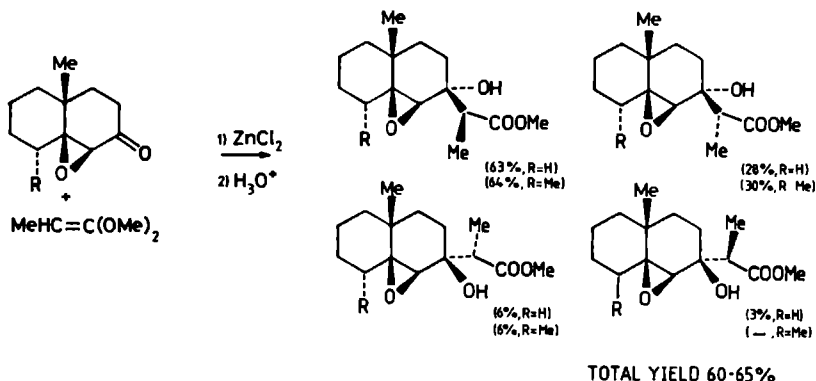
De synthese van enkele precursors voor de bereiding van eudesmanolides van het type I en het type II (Schema 5) wordt beschreven

Schema 5



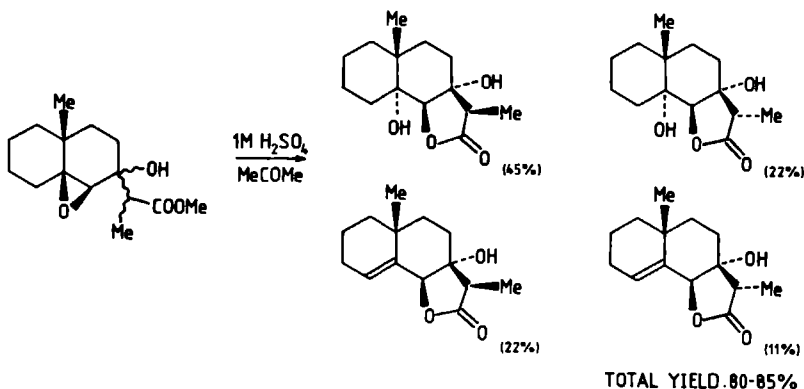
in hoofdstuk 5. Twee epoxyketonen (R = H of Me) van het decaline type zijn als uitgangsstof gebruikt (Schema 6). Deze ketonen worden op eenvoudige wijze omgezet in γ,δ -epoxy- β -hydroxyesters, via reactie met (1a) en directe hydrolyse van de gevormde oxetanen. In beide epoxyesters komt de geïntroduceerde keteenacetaal eenheid hoofdzakelijk in een equatoriale positie met betrekking tot de decaline ring. Hydrolyse van deze epoxyesters gebeurt in het ene geval (R = H) via

Schema 6



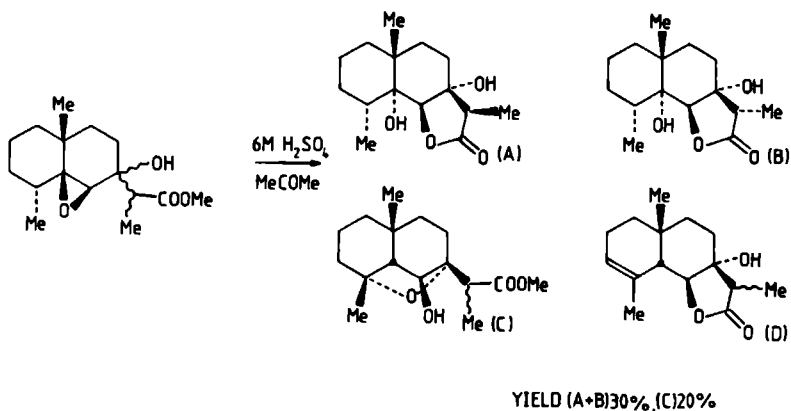
reactie met 1 M H_2SO_4 in aceton en levert een mengsel van twee mono-hydroxy- en twee dihydroxylactonen (Schema 7). In het andere geval

Schema 7

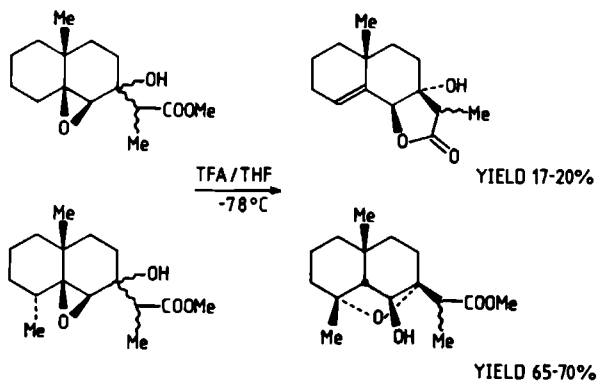


(R = Me) verloopt de hydrolyse slechts bij sterkere zuurconcentraties (6 M H_2SO_4 in aceton) en levert een mengsel van twee dihydroxylactonen en twee 1,7-epoxynaftaleen derivaten (Schema 8). Bovendien zijn reacties met trifluoroazijnzuur (Schema 9) en met trimethylsilyltrifluoromethaansulfonaat (TMSOTf) (Schema 10 en 11) uitgevoerd. Deze laatste reactie geeft in één geval (Schema 10) op eenvoudige wijze toegang tot een eudesmanolide precursor in goede overall opbrengst.

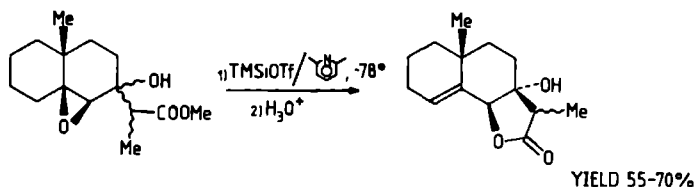
Schema 8



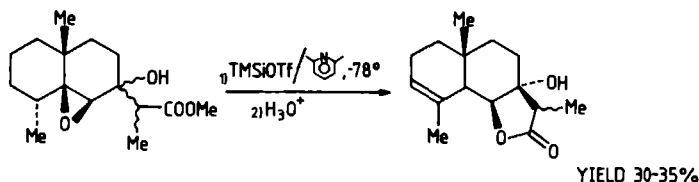
Schema 9



Schema 10

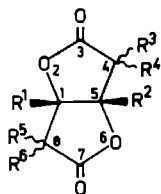


Schema 11



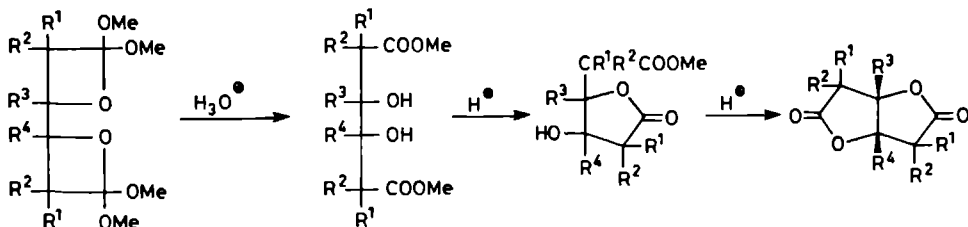
Pogingen tot synthese van bis- γ -lactonen (bislactonen) (Figuur 3)

Figuur 3



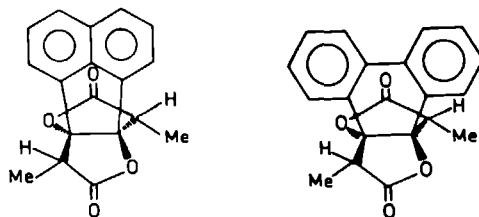
uit (1) en verschillende typen α -dicarbonylverbindingen en analoga hiervan zijn beschreven in hoofdstuk 6. Alleen de stabiele *cis*-verknoopte bislactonen worden via deze route gesynthetiseerd en geïsoleerd. α -Dicarbonylverbindingen kunnen met (1a) omgezet worden in bisoxetanen en hydrolyse van deze verbindingen levert een bislacton, een 'monolacton' of een mengsel van deze twee verbindingen (Schema 12).

Schema 12



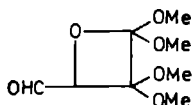
Reactie van (1a) met de meest eenvoudige dicarbonylverbinding, glyoxaal, levert een mengsel dat ca. 25% bislacton en ca. 50% monolactonen bevat. Stereochemische analyse van de synthese van de bislactonen laat zien, dat in een dicarbonylverbinding de twee carbonylgroepen zich in een cisoide positie dienen te bevinden om bislactonvorming mogelijk te maken. Dit kan beïnvloed worden door het gebruik van een Lewiszuur dat met beide carbonylgroepen complexeert (chelatie) of door het gebruik van α -dicarbonylverbindingen, waarin de carbonylgroepen reeds in zo'n positie zitten. Alleen deze laatste route levert bislactonen als hoofdproducten. Zowel phenanthreenchinon als acenaphtheenchinon zijn met (1a) omgezet in hun respectievelijke bislactonen (Figuur 4).

Figuur 4



Een andere mogelijkheid tot de synthese van bislactonen is het gebruik van dicarbonylverbindingen die in één carbonylfunctie beschermd of gemaskeerd zijn. Ook voor deze route zijn chelatie-gecontroleerde reactiecondities nodig. Als eerste is het oxetaan gesynthetiseerd uit glyoxaal en (1b) (Figuur 5), maar reactie van dit oxetaan

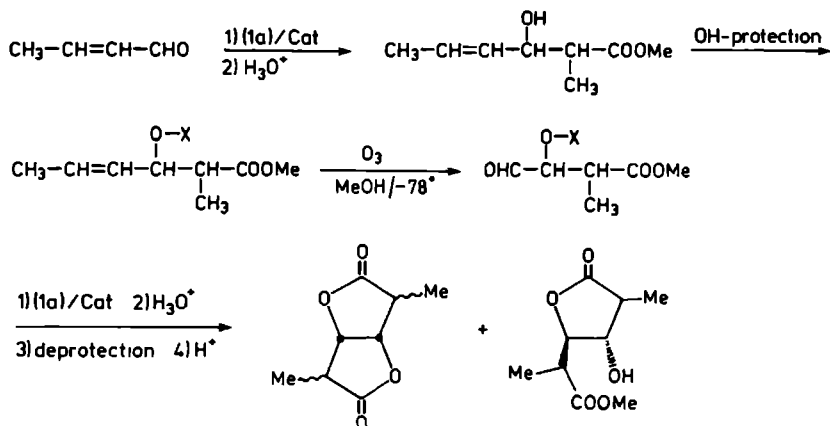
Figuur 5



kan niet bewerkstelligd worden onder chelatie-gecontroleerde condities. Vervolgens is een strategie uitgaande van crotonaldehyde onderzocht. Crotonaldehyde kan beschouwd worden als een gemaskeerd glyoxaal analogon, aangezien ozonolyse van de dubbele binding een tweede carbonylfunctie oplevert. Via deze route (Schema 13) zijn enkele 3-hydroxy-4-oxobutanoatesters gesynthetiseerd welke na reactie met (1a) en hydrolyse een bislacton kunnen opleveren. Indien MgBr_2

als katalysator wordt gebruikt en ethylvinylether om de hydroxygroep te beschermen, dan kan in een opbrengst van ca. 17% een mengsel van diastereomere bislactonen verkregen worden.

Schema 13



Het onderzoek aan deze reacties duurt nog voort en concentreert zich op beschermgroepen die geen extra asymmetrisch centrum introduceren en sterkere chelatiserende eigenschappen hebben (bijv. de benzylgroep).

Rob Hofstraat werd geboren op 28 maart 1957 te Arnhem. Van 1969 tot 1975 werd het Baudartius College te Zutphen bezocht en in 1975 werd het diploma Gymnasium- β behaald. In datzelfde jaar werd begonnen met de studie Scheikunde aan de Katholieke Universiteit te Nijmegen. Het kandidaatsexamen Scheikunde (S_2) werd afgelegd in september 1978. De doctoraalstudie omvatte de hoofdvakken Organische Chemie (Prof.Dr. R.J.F. Nivard) en Biofysische Chemie (Prof.Dr. C.W. Hilbers), alsmede het caputgedeelte Chemische Technologie (Prof.Dr. C. van Heerden). Tevens werd de eerstegraads lesbevoegdheid verkregen (drs. F.C.J.M. Arnold). Na het behalen van het doctoraalexamen Scheikunde op 25 oktober 1982 werd hij op 1 november 1982 aangesteld als wetenschappelijk assistent aan het Laboratorium voor Organische Chemie van de Katholieke Universiteit Nijmegen en werd het in dit proefschrift beschreven onderzoek begonnen onder leiding van dr. J.W. Scheeren en Prof.Dr. R.J.F. Nivard. Gedurende zijn studie en promotie-onderzoek was hij betrokken bij het onderwijs aan scheikundestudenten als assistent bij diverse practica. Sinds 1 april 1987 is hij werkzaam bij DIOSYNTH B.V. te Oss.

Publicaties

- Chemistry of Ketene Acetals, part IV. A simple and general Method for the Preparation of 4-Hydroxy- γ -Butyrolactones and 2-Butenolides from 1,1-Dimethoxypropene and α -Acyloxy Aldehydes and Ketones, R.W.M. Aben, R.G. Hofstraat and J.W. Scheeren, *Recl. Trav. Chim. Pays-Bas*, 1981, 100, 355.
- Chemistry of Ketene Acetals, part VIII. Stereochemistry of the Reaction of 1,1-Dimethoxypropene with Aldehydes, R.G. Hofstraat, J.W. Scheeren and R.J.F. Nivard, *J. Chem. Soc. Perkin I*, 1985, 561.
- Chemistry of Ketene Acetals, Part IX. The Use of 1,1-Dimethoxypropene as Propionate Equivalent in the Synthesis of some Eudesmanolide Precursors from α, β -Epoxyketones, R.G. Hofstraat, J.L. Pompl, J.W. Scheeren and R.J.F. Nivard, submitted to *J. Chem. Soc. Perkin I*.
- Chemistry of Ketene Acetals, Part X. A simple 'One-Pot' Synthesis of 4-Hydroxy- δ -Lactones and 5,6-Dihydro-2-Pyrones from 1,1-Dimethoxypropene and β -Oxyaldehydes, R.G. Hofstraat, J. Lange, J.W. Scheeren and R.J.F. Nivard, submitted to *J. Chem. Soc. Perkin I*.

1

De verhouding van de producten die Lamaty et al. vinden bij de hydrolyse van 2,2-diethoxy-3,4-dihydrobenzopyranen kunnen beter verklaard worden door de invloed van het gebruikte oplosmiddel (MeOH/H₂O, 4:1) dan door de stereo-electronische controle tijdens deze hydrolyse.

- . G. Lamaty, P. Lorente, C. Moreau,
Can. J. Chem., 1983, 61, 2651.
- . P. Deslongchamps, R. Chenevert, R.J. Taillefer,
C. Moreau, J.K. Saunders,
Can. J. Chem., 1975, 53, 1601.
- . J.W. Scheeren en C.G. Bakker,
Tetrahedron Lett., 1987, accepted in press.

2

De waarnemingen die Schultz en Ming Shen beschrijven ter ondersteuning van hun conclusie dat de Diels-Alder reactie van N,N-dimethylamino-2,3,4,5-tetramethylpyrrool en N-fenyl-maleïmide reversibel is, kunnen ook verklaard worden door de aanwezigheid van een electron donor-acceptor complex.

- . A.G. Schultz en Ming Shen,
Tetrahedron Lett., 1979, 2969.
- . R. Forster,
Organic Charge-Transfer Complexes,
Acad. Press, London, 1969.

3

In hun publicatie over de base geïnduceerde racemisatie van de door dicyclohexylcarbodiimide geactiveerde component in een peptide condensatie. gaan de auteurs voorbij aan de mogelijkheid van intramoleculaire racemisatie van hun reactie intermediair.

- . A.M. Kołodziejczyk en M. Ślebioda,
Int. J. Peptide Protein Res., 1986, 28, 444.

Onderzoek naar de invloed van ultrasone geluidsgolven op chemische reacties verdient meer aandacht dan tot nu toe het geval is geweest.

- . D. Bremner,
Chem. in Britain, 1986, 633.
- . P. Boudjouk,
J. Chem. Ed., 1986, 427.

Voor het fitten van de smeltcurven van Dimeer-Coil overgangen maken Albergo et al. gebruik van niet-lineaire regressie. De door hen gebruikte parameters (ΔH , ΔS , ϵ_s , ϵ_d en c_t) kunnen echter niet alle uit smeltmetingen verkregen worden. Het is dan ook verbazingwekkend dat zij toch een éénduidige oplossing voor alle parameters vinden.

- . D.DP. Albergo, L.A. Marky, K.J. Breslauer
en D.H. Turner,
Biochemistry, 1981, 20, 1409.

Clore et al. gebruiken voor de bepaling van de driedimensionale structuur in oplossing van het B DNA hexameer 5'd(CGTACG)₂ uitsluitend een combinatie van Nuclear Overhauser Enhancement Spectroscopie en een kleinste kwadraten fit-procedure.

De resultaten van deze methode lijken niet zo betrouwbaar als gesuggereerd, aangezien geen rekening wordt gehouden met locale bewegingen in het DNA fragment.

- . C.M. Clore, A.M. Gronenborn, D.S. Moss en
I.J. Tickle,
J. Mol. Biol., 1985, 185, 219.

De opbrengsten die Fuji et al. opgeven voor de kinetische resolutie van D,L-pantolactone met S-kamfersulfonzuur zijn misleidend.

- . K. Fuji, M. Node, M. Murata,
Tetrahedron Lett., 1986, 27, 5381.

De door Lewis et al. beschreven nucleotide sequentie van het muize GFAPcDNA moet met een zekere terughoudendheid worden gehanteerd, aangezien de restrictieenzymen Sac, Kpn en Stu I in een aantal gevallen niet knippen op plaatsen die, uit de door de auteurs opgegeven nucleotide volgorde, afgeleid kunnen worden als restrictie-site voor de betreffende enzymen.

- . Z. van Eupen, persoonlijke mededeling.
- . S.A. Lewis, J.M. Balcarek, V. Krek, M. Shelanski
en N.J. Cowan,
Proc. Natl. Acad. Sci. USA, 1984, 81, 2743.

De verhouding van de hoeveelheden polyfosfaat en orthofosfaat in intacte gistcellen, zoals die met behulp van ³¹P Nuclear Magnetic Resonance kan worden bepaald is waarschijnlijk sterk ondergewaardeerd.

- . I.S. Kulaev en V.M. Vagabov,
Adv. Microbiol. Physiology, 1983, 24, 83.
- . B.G.F. Kessels,
Dissertatie, K.U. Nymegen, 1987.

Tot teleurstelling van velen leidt afslanken vaak tot een algemene figuur-correctie in plaats van een locale figuur-correctie.

Het gemak waarmee zowel toluen als "dioxine" als vergif werden aangeduid in de berichtgeving van het NOS journaal over de ramp met de Harold of Free Enterprise, doet een zekere twijfel ontstaan omtrent de nuancering van andere berichten van het journaal.

- . E.R. Koch en F. Vahrenholt, Seveso ist überall, Kiepenheuer und Witsch, Köln, 1978.
- . N.I. Sax, Dangerous Properties, Reinhold, New York, 1965 (sec. ed.).

Nymegen, 7 mei 1987

Rob Hofstraat

