Abstract: The addition of α-halo-α-aminoacyl chlorides to ethyl indolenine-2-carboxylates followed by reaction with sulfur nucleophiles and a final ring closure provides a convenient and new synthetic scheme to analogues of gliotoxin, the simplest of the natural products containing the epidithiodiketopiperazine system. Illustrative of this approach, adducts of ethyl 3,3-dimethyldihydroindolene-2-carboxylate (17) with acid chlorides, α-halo acid chlorides, and N-trifluoroacetyl-α,α-dichlorosarcosyl chloride (44) have been studied. The last adduct when treated with a sulfide-poly sulfide mixture gave a monosulfide 49 (30% yield) but no disulfide 50. Reduction of 49 with NaCNBH3 proceeded stereoselectively to afford mainly the secoglotoxin analog 51 in addition to the diastereoisomer 52. Cyclization of this mixture presumably led to the strained epimonothiodiketopiperazine 41, which easily opened to the isomeric lactam 55 in addition to lactam 56 formed by epimerization.

The number of natural products containing the epidithiodiketopiperazine ring 1 continues to grow with the recent reports on the two fungal metabolites chaetocin (2) and verticillin A (3). Both are highly active against gram-positive bacteria. Chaetocin is cytostatic but lacks antiviral activity, while verticillin A is cytotoxic and active against mycobacteria. Other members of this group of fungal metabolites are the sporidesmins A through G (4-6) several of which display strong antibacterial activity. Noteworthy in this regard is the gietokotoxin (7-9) and apoaranotins (10-11) which have no antibacterial activity but do have potent antiviral activity, while verticillin A (3) is active against gram-positive bacteria. Chaetocin is active against RNA viruses, while the latter has only antifungal and antiviral activity.

Several syntheses of simple epidithiodiketopiperazines have been reported, which feature the addition of sulfur substituents to a preformed diketopiperazine. Surprisingly, the simple model 1a is highly active in inhibiting viral RNA synthesis, in support of the view that the activity of the more complex natural products resides in the epidithiodiketopiperazine ring. Another approach to this ring system started with 2-benzamido-2-mercaptopropanoic acid (13) as a possible precursor.

The drastic reaction conditions of all of these methods preclude their successful extension to the polycyclic epidithiodiketopiperazines. A synthetic approach of general applicability, we feel, would feature the initial construction of the disulfide bridge and then ring closure to a bridged diketopiperazine.

The addition of acyl chlorides to indolines (Chart I), a reaction first reported by Leuchs, who studied compounds 14-16, served as our first step. The 2-chloro substituent in Leuchs’ adducts 18-20 is known to undergo easy nucleophilic displacement, and known structure, probably contain the epidithiodiketopiperazine ring. The former is active against gram-positive bacteria and viruses while the latter has only antifungal and antiviral activity.

The mechanism of antiviral action of gliotoxin and aranotin depends upon the specific inhibition of RNA-dependent DNA polymerases from tumor-producing viruses or blocking of the synthesis of viral RNA in the case of chetomin.

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reaction of sulfur nucleophiles (e.g., SCOCH$_3^-$, SCN$^-$, S$_2$O$_3^{2-}$, etc) on the adduct 21 derived from 17 was first investigated as a route to 1-acylindoline-2-carboxylic acid derivatives having a thio function in the 2 position. The indolenine ester 17 was prepared as outlined in Chart II.

The azo ester 23, when prepared from ethyl α-isopropylacetooacetate and benzenediazonium chloride under mildly alkaline conditions, was stable enough to permit isolation. Careful treatment with ethanolic solutions of sodium hydroxide or preferably ammonium hydroxide gave the hydrazone ester 24, which was converted into 17 by refluxing in HCl-saturated ethanol. The yields are much higher than reported in the published procedure$^{31}$ where the coupling and hydrazone

1. a, R = R' = CH$_3$; R'' = R''' = H
2. chaetocin
3. verticillin A

Chart I

4. sporidesmin
A, R' = OH; R = S-S (active)$^1$
B, R' = H; R = S-S (active)$^1$
D, R' = OH; R = SCH$_3$, CH$_3$S (inactive)$^8$
E, R' = OH; R = S-S-S (active)$^9$
G, R' = OH; R = S$_2$$^10$

5. sporidesmin F (inactive)$^9$
6. sporidesmin C (active)$^9$

7. aranotin; R' = H, R'' = Ac; R = S-S (active)
8. acetylaranotin; R' = R'' = Ac; R = S-S (active)
9. bisdethiodi(methylthio)acetylaranotin; R' = R'' = Ac; R = CH$_3$S, SCH$_3$ (inactive)

10. apoaranotin; R' = H; R = S-S (active)
11. bisdethiodi(methylthio)acetylapoaranotin; R' = Ac; R = -SCH$_3$, CH$_3$S- (inactive)

12a. gliotoxin
12b. dehydrogliotoxin

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formation steps are carried out under such strongly alkaline conditions that only the hydrazone 25 can be isolated. This, on Fischer cyclization, gives a mixture of 17 and 26 accompanied by 2,3-dimethylindole, the product of decarboxylation and rearrangement of 26. The indolenine 17 can also be prepared by refluxing 23 in absolute alcoholic hydrogen chloride. This indicates that the transformation (23 $\rightarrow$ 24) in the Japp-Klingemann reaction can also be acid catalyzed.

We first examined the reaction of 17 with simple acid chlorides, such as acetyl chloride and chloroacetyl chloride, and found that when freshly purified reagents were employed, the Leuchs addition proceeded in high yield at room temperature. Interestingly, this is the first instance of addition of acyl chlorides to an indolenine-2-carboxylic acid derivative, the previous examples being limited to indolenine with 2-hydrogen, 2-methyl, or 2-phenyl substituents. The indolenine 17 is less reactive than unconjugated ones, since benzoyl chloride could not be added. Reaction of 17 with ethoxy carbonyl chloride or benzyloxycarbonyl chloride was very slow, and trifluoroacetyl chloride did not react at all.

Two isomeric thioacetates, 28 and 29, were isolated when potassium thioacetate was allowed to react with the product from acetyl chloride and 17 which had been allowed to warm to 40°, presumably as the result of a Plancher rearrangement (21 $\rightarrow$ 27, Chart III). With potassium thiocyanate on 21, the 2-isothiocyanate compound 30 (Chart IV) was isolated instead of the expected 2-thiocyanate compound. Therefore, we expected the 2-isothioureido derivative 34, but, under these conditions, isolated starting material 17.

The $pK_a$ of 33 was measured and found to be 7.7. When the solvolysis of 33 was attempted at pH 9.5 in the hope that 34 might be more stable as a neutral species, still only 17 was isolated. This suggests that unacetylated indolines are inherently unstable. Likewise, 2-indolinols are known only as N-acyl or N-alkyl derivatives. At least these reactions prove that no Plancher rearrangement occurs at room temperature during acyl chloride additions or subsequent displacement reactions.

When 32 reacted with inorganic sulfides, such as ammonium sulfide, sodium mono-, di-, or tetrasulfide, or thiocarbonate, two products resulted: a mono- (37) are removed by thiourea in refluxing aqueous ethanol at pH 5 with the formation of pseudothiohydantoin. Therefore, we expected the 2-isothioureido derivative 34, but, under these conditions, isolated starting material 17.

The $pK_a$ of 33 was measured and found to be 7.7. When the solvolysis of 33 was attempted at pH 9.5 in the hope that 34 might be more stable as a neutral species, still only 17 was isolated. This suggests that unacetylated indolin-2-thiols are inherently unstable. Likewise, 2-indolinols are known only as N-acyl or N-alkyl derivatives. At least these reactions prove that no Plancher rearrangement occurs at room temperature during acyl chloride additions or subsequent displacement reactions.

When 32 reacted with inorganic sulfides, such as ammonium sulfide, sodium mono-, di-, or tetrasulfide, or thiocarbonate, two products resulted: a mono- (37)
and a disulfide (38) in yields varying with the reactant (Chart VI). Sodium sulfide and sodium thiocarbonate

**Chart VI**

![Chemical structures](image)

gave mainly the monosulfide 37 (ca. 40% yield), whereas ammonium sulfide and sodium di- and tetrasulfide, which all exist as mixtures of mono- and polysulfides, gave the mono- and disulfide in proportions of 2:1, 1:4, and 2:7, respectively.

None of the thiol 36 could be detected; this together with the observation that sodium sulfide gives mainly (>90%) the monosulfide 37 suggests that 37 as well as 38 arise from an intramolecular displacement of chlorine in the sulphydryl intermediate 35 (n = 1 or 2) and not via the dithiol 36. A tetrasulfide 39 could not be detected although such a ring system forms easily in thio-bridged diketopiperazines.

Models indicate that a cyclic sulfide is possible only in structures 37 and 38. For the disulfide, but not the monosulfide, an alternate structure 40 may be envisaged. The disulfide 38, however, could be converted quantitatively into the monosulfide 37 with trisulfide ions (pathway B2). At the moment, we were unable to detect the disulfide 50, possibly because it is either inherently unstable, or unable to survive the strongly alkaline conditions of the tetrasulfide reaction.

As we have proposed elsewhere, 44 may decompose spontaneously to form 47, which may then react with 17 to give 48 which in turn forms 49 with polysulfide ions in an intramolecular reaction (pathway A). Alternatively, pathway B proceeds via 45, the addition product of 44 and 17, which may then react in either or both of two ways: base-catalyzed hydrolysis of the N-trifluoroacetyl group to yield 49 via 48 (pathway B1) or removal of the N-trifluoroacetyl group following reaction with polysulfide ions (pathway B2). At the moment, we lack the definitive evidence necessary for a decision among these mechanistic possibilities.

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The monosulfide 49 was reduced with sodium cyanoborohydride to the amines 51 and 52 (Chart VIII), which are secogliotoxin analogs.

The course of the reduction is guided by steric induction of the carbethoxy group. The nmr spectrum of the reduction mixture showed two signals for the C9 proton, at δ 5.65 and 5.29 in the ratio 2:1, respectively, and two signals at δ 2.54 with a separation of 2 Hz for the N-methyl group. It is assumed that the C9 proton in the stereoisomer 52 is more shielded than in 51, so that the signals at δ 5.65 and 5.29 can be assigned to structures 51 and 52, respectively, of which 51 is the major (66%) and the diastereomer 52 the minor product (33%). An

(37) This method has been used to convert dehydrogliotoxin (12b) and sporidesmin (44) into monosulfides.


(42) The alkaline decomposition of organic disulfides very often produces monosulfides.


epithiodiketopiperazine can be formed only from 51 in which ester and amine functions are in a cis relationship. A bulkier hydride donor might make the reduction even more stereoselective.

Surprisingly the conversion of 49 into 51 and 52 led to no change in the ir spectrum of the amide carbonyl absorption (1705 cm⁻¹). This suggests that conjugation in O=CC=NCH₃ has little effect. The mixture of monosulfides 51 and 52 was heated with ethanol in an attempt to form the epimonthiodiketopiperazine 41 (n = 1). Only in a sealed tube at 125°C did a reaction occur yielding, besides starting material, a compound with a slightly higher R₄ value on tlc.⁴⁴ This compound had nearly the same mass spectrum as the starting mixture, with differences only in peak intensities, indicative of closely related isomers of 51 and/or 52. The nmr spectrum could best be interpreted as a mixture of structures 55 and 56 (Chart IX).

The two signals assigned to the N-methyl groups were shifted downfield (δ 3.23 and 3.13) and show a larger difference in chemical shifts than in 51 and 52 (Δδ = 5 and 2 Hz, respectively). Surprisingly only one broad signal was observable for the C₂'=CH₂ proton. Therefore, the possibility that we had in hand only one pair of enantiomers, 55 or 56, had also to be considered; the two signals for the N-methyl group could be explained by a conformational or long-range coupling effect.

However, nmr spectra at -20 or -40°C and irradiation of the C₂'=CH₂ proton failed to change the relative intensities of the two N-methyl signals and indicated that the isolated material was most likely a mixture of two pairs of enantiomers, 55 and 56. An nmr of the recovered starting material mixture indicated that the proportion of 52 in the mixture had increased greatly and was now twice that of 51.

Particular attention was given to these considerations, for if only one pair of enantiomers had been formed, this probably would have been 55, derived only from the reactive starting material 51, via the desired diketopiperazine 41 (pathway A, Chart IX). A Dreiding model shows that the epimonthiodiketopiperazine ring system in 41 is a highly strained though not an impossible one as has been shown by Taylor.⁹⁸ The occurrence of two pairs of enantiomers could then be explained by epimerization at C₂' in 55. A deuterium-exchange study is planned to check this possibility.

The occurrence of 55 and 56 would also be explained by pathway B, Chart IX. If the amide groups in 51 and 52 were cleaved by ethanol, the α-thio-bridged α-amino acid esters 53 and 54 would result. These could lactamize in two ways, yielding besides the starting materials the structures 55 and 56, respectively. Structures 53 and 54 with an unacylated α-thio amino acid moiety are undoubtedly unstable⁴⁶ (see also Chart V and accompanying text), and should break down to the indolenine ester 17. However, the reaction mixture 51 + 52 ⇌ 55 + 56 showed only two spots on tlc with no trace of side products,⁴⁷ making this mechanism unlikely.

Milder reaction temperatures and the use of nonprotic solvents provided no new information. At 90° the formation of the new isomers is very slow and no new component could be detected; diglyme as solvent at 90 or 120°C failed to give any identifiable product. At present there is no evidence permitting a choice between pathways A and B.

Experimental Section

Infrared spectra were measured with Perkin-Elmer spectrophotometers, Models 237B (CHCl₃ or CC1₄) and 421 (KBr), and uv spectra with a Cary Model 11 (95% EtOH). Mass spectra were obtained with the double-focusing Hitachi RMU-6E mass spectrometer. Proton magnetic resonance spectra were measured on the Varian Associates Model A-60 spectrometer. Chemical shifts are reported as δ values (ppm) relative to tetramethylsilane as an internal standard; deuteriochloroform was used as solvent unless stated.

(45) Under these conditions compound 37 was found to be stable.

(46) Pojer and Rae described the synthesis of 13 and 2,2'-dibenzamido-2,2'-dithiodipropanoic acid, in which the amino function is acylated. Interestingly, the decacylated products were not mentioned.

(47) A Plancher rearrangement producing 57 and 58 cannot be completely ruled out. The shift in amide carbonyl absorption from 1690 to 1640 cm⁻¹ which accompanies this reaction is somewhat unexpected. Although the latter absorption is normal for a tertiary amide, it could also indicate that the amide is part of a six-membered ring. Arguing against this possibility, however, is the similarity of the 3-methyl signals in the nmr spectra of starting materials and products.
otherwise. Melting points were taken on a Kofler hot stage and are corrected. Thin layer chromatography (tlc) was carried out using Merck precoated silica gel F-254 plates (thickness: 0.25 mm for analytical, 2.0 mm for preparative); spots were visualized with a uv hand lamp, iodine vapor, or a 0.1% solution of ninhydrin in methanol–1-butanol–2 N acetic acid (20:10:1 v/v).

Ethyl α-isopropylacetoacetate (23). This compound was prepared from ethyl acetocacetate and 2-bromopropane following the procedure for the synthesis of ethyl n-propylacetoacetate. Acetic acid distillation (34 mm) on a Vigreux column yielded two fractions, bp 83–105° and 105–108°, the latter being the desired compound, the former being the O-alkylated product. When freshly distilled ethyl α-isopropylacetoacetate (23) was used, only the second fraction (22 g) resulted in 40% yield (m/e 184, 24.1% (H₂, CH₂CH₂CH₂), 2.15 (s, 3 H, CH₃CO), 1.21 (t, 3 H, CH₂), 0.9 (d, 2 H, CH₂CH₂CH₂), J = 6 Hz, spacing 2 Hz). O-Alkylated product: m/e 184.12, 2.42 (s, 1 H, CH=CH₂), 2.18 (s, 3 H, CH₃CO), 1.21 (t, 3 H, CH₂CH₂), 0.90 (2 d, 6 H, CH₂CH₂CH₂), J = 6 Hz, spacing 2 Hz.

Ethyl α-Phenylazopyropylacetoacetate (23). Solution A. A solution of 51.0 g (0.30 mol) of ethyl α-isopropylacetoacetate (22) in 200 ml of ethanol was cooled at —15° (ice–salt bath). Just before the addition of solution B to A, 232.5 ml of 5 M NaOH (1.15 mol), cooled to — 15°, was added at once.

Solution B. A solution of benzenediazonium chloride was prepared by the addition of solution B to A, 232.5 ml of 5 M NaOH (1.15 mol), and finally water until neutral, dried (Na₂CO₃), and the ether was removed to yield 38.5 g (0.163 mol, 94%) of a dark red solid, which was purified by vacuum sublimation at 90° (1.0 Torr). This compound was prepared according to Robinson and Suginome.11 From the hydrazone ester 24 mentioned in the preparation of isomer 2,0 g sample of the azo ester 23 was converted into 17 in 48% yield by the treatment given to the hydrazone ester 24 mentioned above. Both procedures led to material which was found to be identical in all respects with the specimen previously obtained.

Ethyl 1-Acetyl-2-thioacetyl-3,3-dimethylindoline-2-carboxylate and Isoemer (28 and 29). A 2.0-g sample of the azo ester 23 was converted into 17 in 48% yield by the treatment given to the hydrazone ester 24 mentioned above. Both procedures led to material which was found to be identical in all respects with the specimen previously obtained.

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The product with lower purified by vacuum sublimation (110° (0.7 mm)) followed by re-

(37) and 40 mg (12.4%) of disulfide 38 were isolated.

The last aliquot was allowed to react with 20 ml of 1.1 M aque- ouso solution of sodium monosulfide (20 ml of a 1.1 M solution), or freshly prepared sodium thio carbonate (38) (20 ml of a 1.1 M solution), respectively. Reaction conditions and work-up were as described above.

3.70 (d, 1 H, Q-Hp), 1.45 (s, 3 H, C H3), 3.31 (s, 2 H, -COCH2-), 1.50 (s, 6 H, CH3(CCH3)), 1.42 (t, 3 H, -CH2CH3).

Reaction mixture was monitored by tic.

3.46 (s, 3 H, NCH3), 1.51 (s, 3 H, C H3), 4.18 (q, 2 H, CH2CH3), 4.07 (d, 1 H, CH-C=H, J6 = 15 Hz, AB spectrum), 3.70 (d, 1 H, CH-C=H), 1.45 (s, 3 H, C H3-C=H), 1.35 (s, 3 H, CH3-C=H), 1.21 (t, 3 H, CH2CH3); mass spectrum (180°), m/e 291 (M+), 218 (M+ - COCH3).

The reaction mixture was poured into 20 ml of 1.1 M aqueous sodium monosulfide solution (20 ml of 1.1 M solution) and extracted with ethyl acetate. The organic layer was dried (Na2SO4) and the solvent was removed, yielding 270 mg of a still impure, ninhydrin-positive material. The latter was chromatographed on five plates as before yielding 320 mg (0.7 mmol, 30%) of crystalline material (ninhydrin-positive) which could be further purified by vacuum sublimation at 100° (0.5 mm): tic (5% ethanol–benzene), one spot Rf 0.41. A small sample was crystallized from slowly evaporating chloroform: mp 101–103°; ir (CHC13) 2960, 1730 (ester), 1705 (amide), 1690, 1582, 1570, 1480, 1460, 1450, 1410, 1350, 1265, 1250, 1210, 1150, 1105, and 1025 cm⁻¹; νmax 377 (mult), 1 H, C-H), 7.18 (mult, 3 H, C-H), 4.18 (q, 2 H, CH2CH3), 4.07 (d, 1 H, CH-C=H, J6 = 15 Hz, AB spectrum), 3.70 (d, 1 H, CH-C=H), 1.45 (2 H, CH2CH2); mass spectrum (180°), m/e 291 (M+), 218 (M+ - COCH3), 205, 185, 170, 145, 144.

To a solution of 285 mg (0.9 mmol) of the

2-Carboxy-3,3-dimethylindolin-2-one (37) and 38). The reaction mixture was kept at 0° and stirred for 5 min, after which it was extracted with ethyl acetate. The organic layer was dried (Na2SO4) and the solvent was removed to yield 1.94 g of a dark brown oil: 0.65 g of this oil was subjected to preparative tic on five plates (developed two times with 4% ethanol–benzene) to yield 192 mg (0.88 mmol, 38%) of starting material and 270 mg of a still impure, ninhydrin-positive material. The latter was chromatographed on five plates as before yielding 320 mg (0.7 mmol, 30%) of crystalline material (ninhydrin-positive) which could be further purified by vacuum sublimation at 100° (0.5 mm): tic (5% ethanol–benzene), one spot Rf 0.41. A small sample was crystallized from slowly evaporating chloroform: mp 101–103°; ir (CHC13) 2960, 1730 (ester), 1705 (amide), 1690, 1582, 1570, 1480, 1460, 1450, 1410, 1350, 1265, 1250, 1210, 1150, 1105, and 1025 cm⁻¹; νmax 377 (mult), 1 H, C-H); 7.18 (mult, 3 H, C-H); 4.18 (q, 2 H, CH2CH3); 4.07 (d, 1 H, CH-C=H, J6 = 15 Hz, AB spectrum); 3.70 (d, 1 H, CH-C=H); 1.45 (2 H, CH2CH2); mass spectrum (180°), m/e 291 (M+), 218 (M+ - COCH3); 205, 185, 170, 145, 144.

Anal. Calcd for C33H30N3O5S: C, 61.83; H, 5.88; N, 4.81; S, 10.76. Found: C, 61.78; H, 5.82; N, 4.54; S, 10.76.

Disulfide 38: ir (CHCl3) 2970, 1732 (ester), 1650 (amide), 1595, 1475, 1455, 1390, 1284, 1100, and 1025 cm⁻¹; νmax 377 (mult), 1 H, C-H); 7.18 (mult, 3 H, C-H); 4.18 (q, 2 H, CH2CH3); 4.07 (d, 1 H, CH-C=H, J6 = 15 Hz, AB spectrum); 3.70 (d, 1 H, CH-C=H); 1.45 (2 H, CH2CH2); mass spectrum (180°), m/e 291 (M+), 218 (M+ - COCH3), 205, 185, 170, 145, 144.

Anal. Calcd for C33H30N3O5S: S, 55.70; H, 5.30; N, 4.33; S, 19.82. Found: C, 55.93; H, 5.17; N, 4.39; S, 19.50.

One 5-ml aliquot was treated with 20 ml of an aqueous ammonium sulfide solution (7%). Reaction conditions and work-up were the same as described above. After preparative tic, 80 mg (27%) of monosulfide 37 and 40 mg (12.4%) of disulfide 38 were isolated.

Two other 5-ml aliquots were allowed to react with an aqueous solution of sodium monosulfide (20 ml of a 1.1 M solution), or freshly prepared sodium thio carbonate (38) (20 ml of a 1.1 M solution), respectively. Reaction conditions and work-up were as described above. The crude material was purified by vacuum sublimation (110° (0.7 mm)) (material that sublimed at a lower temperature was found to be starting material 37) and recrystallization from ethanol–water to yield 120 (40%) and 123 mg (42%), respectively, of the monosulfide 37. The crude of the material showed only traces of the disulfide 38.

Conversion of Disulfide 38 into Monosulfide 37. A solution of 13 mg (4.1 × 10⁻⁴ mol) of 38 and 22 mg (8.4 × 10⁻⁴ mol) of triphenylphosphine in 1 ml of absolute ethanol was kept, wrapped in aluminum foil, at room temperature for 20 days. The rate of reaction was monitored by tic. The solvent was removed and the residue subjected to preparative tic (developed two times, 3% ethanol–benzene), to yield 9.5 mg (3.25 × 10⁻⁴ mol, 80%) of 37. Identification was based upon nmr and infrared spectroscopic data.

N-Trifluoroacetyl-α,α-dichlorosarcosyl Chloride (44). The synthesis of this compound (bp 54–58° (40 mm)) is described elsewhere.

mmlol) of the mixture of 51 and 52 in 5 ml of absolute ethanol was heated in a sealed ampoule at 108° for 24 hr and then at 125° for 16 hr. TLC (6% ethanol–benzene) showed the presence of only two products, the starting material and a product with larger Rf. The solvent was removed and the brown oily residue subjected to preparative TLC (developed three times with 5% ethanol–benzene), to yield 26 mg (65%) of “starting material” and 14 mg (35%) of isomerized product: TLC (6% ethanol–benzene) only one spot, Rf 0.50; ir (CHCl₃) 3400 (sharp, NH), 2980, 2940, 2860, 1730 (ester), 1640 (amide), 1600, 1525, 1480, 1370 cm⁻¹; nmr δ 8.15 (mult, 1 H, Cr-H), 7.20 (mult, 3 H, C₄–H), 5.50 (broad singlet, 1 H, C₄’–H), 4.17 (q, 2 H, CH₃CH₂), 3.23 and 3.13 (2 singlets, separated 5 Hz, 3 H, N–CH₃), 2.0 (broad S, 1 H, NH), 1.47 and 1.29 (2 singlets, 6 H, CH₃(CH₂)₃), 1.29 (t, 3 H, CH₃CH₂); mass spectrum (160°), m/e 320 (M⁺), identical with that for 51 and 52, except for a stronger signal at m/e 304 (M⁺ − CH₄) and a weaker one at m/e 247 (M⁺ − CO₂C₆H₅) and 245.

The nmr spectrum of the isolated “starting material” showed a change in that the ratio of the two signals from the C₆-proton was reversed (now δ 5.65/5.29 = 1:2), indicating that only the cis enantiomers 51 have been isomerized.

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