Synthesis of 2-Hydroxy-3-(ethoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolines from N-Hydroxytryptophans. An Approach to the Eudistomin Series

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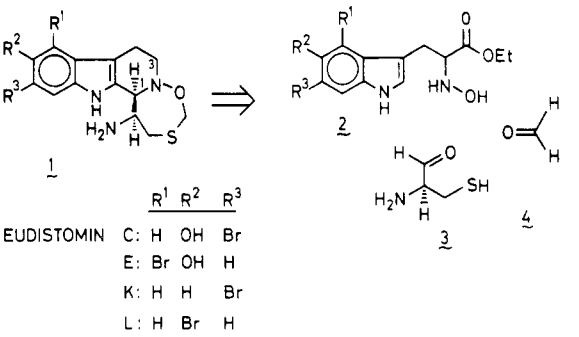
Pictet–Spengler condensations of the *N*-hydroxytryptophan ethyl esters **5a** and **5b** with acetals **6a–c** and aldehydes **9a,b** have been evaluated. These reactions provide an access to the 2-hydroxy-β-carbolines **7a–d**, **8a–d**, and **10a,b–12a,b**. Removal of the sulfur protection group of **10b–12b** gave **10c–12c**, respectively. Compound **11b** is a plausible chemosynthetic precursor for the class of eudistomins and may be of biogenetic relevance.

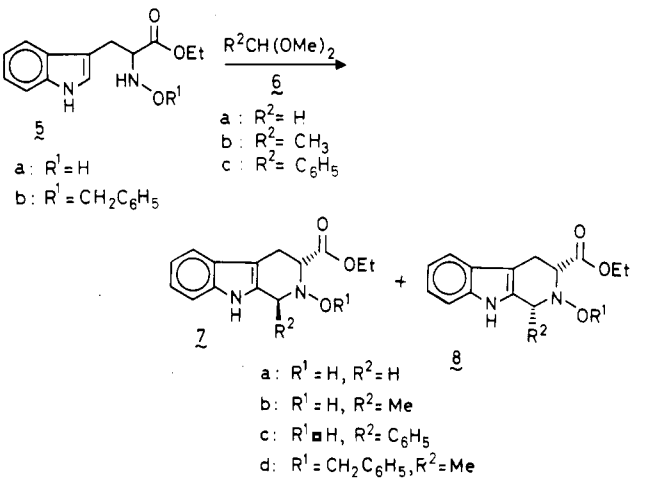
Introduction

Indole alkaloids are prominent secondary metabolites, derived predominantly from the amino acid tryptophan.[1] Recently, we reported[2] a scheme in which the non-protein amino acid *N*-hydroxytryptophan links *L*-tryptophan to several other non-protein tryptophan derivatives.[3] The central significance of *N*-hydroxytryptophan in biotransformation pathways, proposed in that report, is substantiated by the isolation of secondary metabolites containing this N-hydroxylated amino acid (e.g., astechrome[4a]) or containing *N*-hydroxytryptophan derivatives.[4b] A recent report[5] described the isolation and structure elucidation of a class of marine alkaloids, i.e., the eudistomins **1**. They are characterized by a *N*-hydroxytryptophan moiety and were found to have a potent activity against the herpes simplex virus, type HSV-1. The eudistomins, possessing an oxathiazepine ring unprecedented in natural products and a 2-oxy-1,2,3,4-tetrahydro-β-carboline moiety, present a distinct challenge for the synthetic organic chemist. They can be considered to be biosynthetically derived from *N*-hydroxytryptophan derivatives **2**, a cysteinal derivative **3**, and an activated methylene derivative **4**[6] as indicated in Scheme I. It was our aim to develop a useful, biosynthetically patterned approach to the eudistomins based on this scheme. The approach should feature, we thought, a Pictet–Spengler reaction of a properly protected cysteinal moiety **3** with an *N*-hydroxytryptophan ester **2** to yield a C(1)-substituted 2-hydroxy-1,2,3,4-tetrahydro-β-carboline moiety. In this reaction the chirality of tryptophan[7] might be used to control the chirality at C(1) of the β-carboline ring. Subsequently the ethoxycarbonyl group, having fulfilled its function, might be removed.[8] Here we report that the first part of this approach is viable indeed. The Pictet–Spengler reaction of the *N*-hydroxytryptophan derivative **5** with the acetals **6** and the aldehydes **9** affords the 2-hydroxy-1,2,3,4-tetrahydro-β-carboline derivatives **7** and **8** and **10–12**, respectively.[9]

Scheme I



Scheme II



Results

Pictet–Spengler Reactions of 5a,b with the Acetals 6a–c (Scheme II). The general synthetic potential of the Pictet–Spengler reaction of tryptophan esters or *N*-benzyltryptophan esters with a variety of aldehydes has been demonstrated.[10] At the onset of our investigations no example had been reported, however, of a Pictet–Spengler reaction yielding 2-hydroxy-1,2,3,4-tetrahydro-β-carboline derivatives.[9] Recently, we reported that the hydroxylamine function of **5a** reacts readily with formaldehyde dimethyl acetal **6a** to yield (91%) the 2-hydroxy-1,2,3,4-tetrahydro-β-carboline **7a**[11] (Scheme II).

Table I. 2-Hydroxy-1,2,3,4-tetrahydro-β-carbolines 7, 8, and 10–12 from 5

compd	product ratio	yield, %	^{13}C NMR, δ (decoupled) C(1)	C(3)
7a	**7a = 8a**	91		
7b	1:2	95	57.3	60.2
8b			58.7	66.7
7c	3:2	77	65.8	60.3
8c			69.0	68.1
7d	1:1	96		
8d				
10a				
11a	1:1:2	53		
12a				
10b			61.2	66.3
11b	1:1:2	54	62.1	62.7
12b			62.3	74.1

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We found that this reaction is also feasible with higher homologues of the acetal. Treatment of **5a** with the acetals **6b,c** in the presence of CF_3CO_2H yields mixtures of the 2-hydroxy-1,2,3,4-tetrahydro-β-carbolines **7b,c** and **8b,c**, which could be separated by column chromatography. The yields are given in Table I. The product ratios were determined by means of analytical HPLC technique.

The structures of the condensation products and in particular their relative stereochemistry were assigned on the basis of ^{13}C NMR data. It has been noted[10a-c] that in the off-resonance-decoupled ^{13}C NMR spectra of trans-1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines the chemical shift values for the C(1) and C(3) atoms are smaller the the values of the corresponding C atoms in the cis isomers. The compression effect, resulting from 1,3-diaxial interactions in the trans isomer, has been invoked to explain this observation.[10a] Consequently, trans structures **7b,c** were assigned to the isomers showing more shielded C(1) and C(3) carbon atoms in the ^{13}C NMR spectrum. Relevant features of the ^{13}C NMR spectra are given in Table I.

Recently, it has been pointed out[12] that in 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines only the C(1) chemical shift is invariably indicative of the stereochemistry; the chemical shift value of the C(3) carbon atom was found to be not reliable for this purpose because it also depends on the N(b) substituent. However, the chemical shifts of C(1) as well as of C(3) in the ^{13}C NMR spectrum 2-hydroxy-1,2,3,4-tetrahydro-β-carbolines **7b,c** and **8b,c** are a reliable guide to the stereochemistry. Further support for the structure assignment is based on single-crystal X-ray analysis of **11b** (vide infra).

As appears from Table I the reaction of **5** with **6** yields mixtures of trans/cis isomers (i.e., **7** and **8**). Recently Cook et al.[10b] reported that the Pictet–Spengler condensation occurs in a completely stereospecific fashion when N-benzyltryptophan esters are employed. Stereoelectronic effects have been employed to explain the stereospecificity of this reaction. Therefore we examined the reaction of O-benzylated *N*-hydroxytryptophan ester **5b**[2] with **6b**. However, again a cis/trans mixture was found; the ratio of **7d** and **8d** was even 1:1 now. The *O*-benzyl group clearly fails to direct the condensation in a stereospecific fashion.

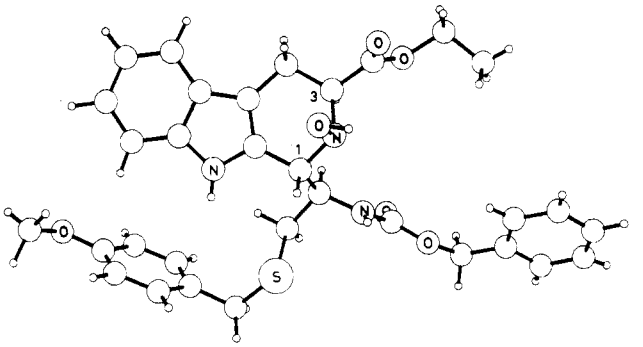
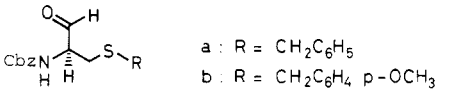


Figure 1. ORTEP drawing of **11b**.

Pictet–Spengler Reactions of 5a with the Cysteinals 9a and 9b. In an attempt to direct the above results on the preparation of possible eudistomin precursors, the reaction of **5a** with cysteinal derivatives was studied. Two N,S-protected derivatives of **3** were prepared from L-cysteine, one being the known *S*-benzyl derivative **9a**[13] and the other the *S*-*p*-methoxybenzyl derivative **9b**.



a: R = $CH_2C_6H_5$
b: R = $CH_2C_6H_4$ p-OCH_3

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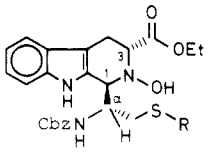
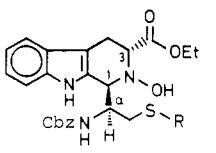
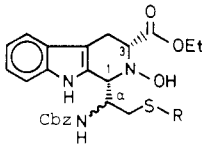
These aldehydes reacted easily with **5a** in the presence of an acid (CF_3CO_2H) to yield mixtures of the 2-hydroxy-1,2,3,4-tetrahydro-β-carbolines **10a–12a** and **10b–12b**, respectively. The diastereomers were separated by flash column chromatography. The product ratio and yields are given in Table I.



10



11



12

a: R = $CH_2C_6H_5$
b: R = $CH_2C_6H_4$ p-OCH_3
c: R = H

Unfortunately, it had to be accepted that the products obtained were racemates; the specific rotations of the product mixtures were zero. Subsequently we observed that the aldehydes **9a** and **9b** racemize under the conditions of their preparation.[13] It might be worthwhile to point out here, that should homochiral cysteine derivatives be accessible they would be prone to racemization during the acid-induced Pictet–Spengler reaction.

(1) For reviews, see: (a) *The Alkaloids—a Biogenetic Approach*; Dalton, D. R., Ed.; Dekker: New York, 1979; p 215. (b) *Indoles*; Saxton, J. E., Ed.; Wiley: New York, 1983; Part IV.

(2) Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, J. D. M. *J. Org. Chem.* **1982**, *47*, 2147.

(3) *N*-hydroxytryptophans have been proposed moreover as intermediates in the glucosinolate formation of Glucobrassicins; see: Møller, B. L. In *Cyanide in Biology*; Vennesland, B., Conn, E. E., Knowles, C. J., Westley, J., Eds.; Academic: London, 1981; p 197. Mahadevan, S. *Annu. Rev. Plant Physiol.* **1973**, *24*, 69.

(4) Arai, K.; Sato, S.; Shimizu, S.; Nitta, K.; Yamamoto, Y. *Chem. Pharm. Bull.* **1981**, *29*, 1510. Hootele, C. *Tetrahedron Lett.* **1969**, 2713. Robinson, B.; Moorcroft, D. *J. Chem. Soc. C* **1970**, 2077. Morita, Y.; Hesse, M.; Schmid, H.; Hofmann, A. *Helv. Chim. Acta* **1962**, *45*, 611.

(5) Rinehart, K. L.; Kobayashi, J.; Harbow, G. L.; Hughes, R. G.; Mizak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 1524.

(6) For the biochemical transfer of a one-carbon fragment, see: Bieraeugel, H.; Plemp, R.; Hiemstra, H. C.; Pandit, U. K. *Tetrahedron* **1983**, *39*, 3971 and references cited therein.

(7) The synthesis of optically active *N*-hydroxytryptophan is currently under investigation in our laboratory.

(8) Several methods have been developed to remove the ethoxycarbonyl function from related systems, e.g.: Tamelen, E. E. van; Olivier, L. K. *J. Am. Chem. Soc.* **1970**, *92*, 2136. Yamada, S.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1976**, 61. Yamada, S.; Murato, K.; Shioiri, T. *Tetrahedron Lett.* **1976**, 1605. Bobbitt, J. M.; Willes, J. P. *J. Org. Chem.* **1980**, *45*, 1978. Massiot, G.; Mulamba, T. *J. Chem. Soc., Chem. Commun.* **1983**, 1147. Barton, D. H. K.; Herve, Y.; Portier, P.; Thierry, J. *J. Chem. Soc., Chem. Commun.* **1984**, 1298.

(9) During the course of this research a related Pictet–Spengler reaction involving *N*-hydroxytryptamine has been reported: Han, S.-Y.; Lakshmikantham, M. V.; Cava, M. P. *Heterocyles* **1985**, *23*, 1671.

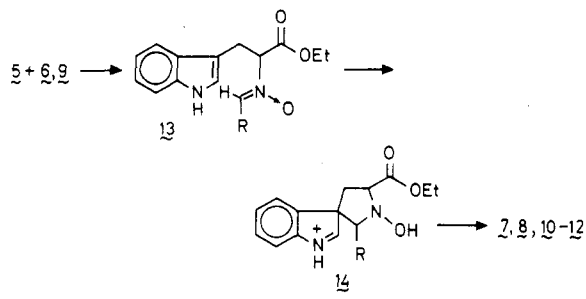
(10) (a) Ungemach, F.; Soerens, D.; Weber, R.; Dipierro, M.; Campos, O.; Mokry, P.; Cook, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 6976. (b) Ungemach, F.; Dipierro, M.; Weber, R.; Cook, J. M. *J. Org. Chem.* **1981**, *46*, 164. (c) Jawdosiuk, M.; Cook, J. M. *J. Org. Chem.* **1984**, *49*, 2699. (d) Massiot, G.; Mulamba, T. *J. Chem. Soc., Chem. Commum.* **1984**, 1147.

(11) Plate, R.; Hermkens, P. H. H.; Smits, J. M. M.; Ottenheijm, H. C. J. *J. Org. Chem.* **1986**, *51*, 309.

(12) Bailey, P. D.; Hollinshead, S. P.; Dauter, Z. *J. Chem. Soc., Chem. Commun.* **1985**, 1575.

(13) The aldehydes were prepared from the corresponding N,S-protected L-cysteine methyl ester by reduction with diisobutylaluminum hydride according to: Ito, A.; Takahashi, R.; Baba, Y. *Chem. Pharm. Bull.* **1975**, *23*, 3081. The authors report that cysteinal derivatives are exceedingly prone to racemization.

Scheme III



The relative configurations of the products were established as follows. The structure of **11b** is based on single-crystal X-ray analyses[14] (Figure 1). The substituents at C(1) and C(3) are in a trans relationship.

Subsequently, the off-resonance-decoupled ^{13}C NMR spectra of **10b–12b** were compared (see Table I). The cis structure **12b** was assigned to the only compound lacking the compression effect for the C(1) and C(3) carbon atoms (vide supra). Structure **10b** was assigned to the remaining compound—having δ values for the C(1) and C(3) carbon atoms rather similar to those of **11b**; the only difference with **11b** being the relative stereochemistry at the C(α) carbon. Surprisingly only one cis stereoisomer, i.e., **12b**, could be detected. As a consequence we cannot establish the relative stereochemistry of its C(α) carbon atom on the basis of the abovementioned information.

Finally, structures **10a–12a** were assigned by comparison of their ^1H NMR spectra with those of **10b–12b**. Characteristic differences observed between the spectra of **10b**, **11b**, and **12b** were also found in the series **10a–12a**.

When the reaction leading to **10b–12b** was interrupted after 6 h it was found not to be complete. A fourth fraction was isolated consisting of a mixture of two stereomers.[15] The ^1H NMR spectrum of this mixture exhibits a pattern typical for indolenines (δ 7.29–6.44, indolenine C(4)C(7)H). So we assigned tentatively structure **14**—a spiro compound—to these two isomers. Treatment of this fourth fraction with CF_3CO_2H in CH_2Cl_2 supports the structure assignment. It caused formation of a mixture of **10b** and **11b**.

This finding may suggest that all of the Pictet–Spengler reactions under consideration proceed via an *N*-hydroxyspiroindoleninium intermediate **14**, formed via the nitrone **13** (Scheme III). It cannot be excluded, however, that this structure **14** only participates in a ring–chain equilibrium (i.e. **13** $\rightleftharpoons$ **14**) without leading itself to 2-hydroxy-1,2,3,4-tetrahydro-β-carbolines.[16]

In view of the other reactive functionalities present in the compounds **10–12** the S-protecting groups had to be removed as mildly as possible. We found that the method of choice for the preparation of **10c–12c** was treatment of the corresponding *p*-methoxybenzyl derivatives **10b–12b** with freshly prepared $(CF_3CO_2)_2Hg$[17] in a mixture of aqueous acetic acid (80%) and ethanol containing anisole as a scavenger of the intermediate benzyl cation. The resulting mercuric sulfides were treated with H_2S to liberate the mercaptans **10c–12c** in 50–64% yield.

Encouraged by these results we anticipated that the next step in our approach to the eudistomin skeleton would be reaction of **11c** with an activated methylene derivative. So far we have not been able, however, to form the oxathiazepine ring system. The three reagents used up to now, i.e., dimethoxy methane, methoxychloromethane, and the one-carbon-unit transfer reagent 1-tosyl-3,4,4-trimethylimidazolidine,[6] failed to give identifiable products. It is difficult to rationalize this failure, as no literature exists on oxathiazepines. Currently we are investigating whether the formation of this seven-membered heterocycle has to take place prior to or subsequent to the removal of the ethoxycarbonyl function.

Conclusions

The synthesis of **11c** demonstrates the utility of the *N*-hydroxytryptophan derivative **5a** for an approach to eudistomins **1**. The formation of the oxathiazepine ring system in **11c** and the removal of the ethoxycarbonyl group are currently under investigation. When these conversions can be accomplished, a total synthesis of racemic eudistomins seems feasible by using a derivative of **5a**, having the proper substituents in the indole moiety. Recently we have shown that the procedure used for the preparation of **5**—i.e., reaction of indole with a nitrosoolefin—can also be employed for derivatives of **5** having substituents in the indole moiety.

Having optically active **5** at hand, our approach will provide optically active **11c**. We regard this as an essential asset of our approach, as the homochirality of the cysteine derivative is lost during the synthesis of **11c**. As a consequence of which C(α)–C(1) induction is bound to fail. We anticipate therefore that optically active **11c** has to be derived by C(3)→C(1) induction.

^{13}C NMR spectroscopy can reliably be employed to assign the stereo structures of the 2-hydroxy-1,2,3,4-tetrahydro-β-carbolines **7**, **8**, and **10–12**.

Experimental Section

Melting points were taken on a Koefler hot stage (Leitz-Wetzlar) and are uncorrected. Ultraviolet spectra were measured with a Perkin-Elmer spectrometer, Model 555.

Proton magnetic resonance spectra were measured on a Varian Associates Model T-60 or a Bruker WH-90 spectrometer. Chemical shifts are reported as δ values (parts per million) relative to tetramethylsilane as an internal standard. ^{13}C NMR resonance spectra were measured on a Bruker WP-60 spectrometer. Mass spectra were obtained with a double-focusing VG 7070E spectrometer. Thin-layer chromatography (TLC) was carried out by using Merck precoated silica gel F-254 plates (thickness, 0.25 mm). Spots were visualized with a UV hand lamp, iodine vapor, Cl_2/TDM,[18] cinnamaldehyde/HCl for indole detection,[19] or ninhydrin. A Miniprep LC (Jobin Yvon) was used for preparative HPLC; as stationary phase Merck silica gel H (Type 60) was used. Merck silica gel (Type 60) was used for flash column chromatography. HPLC analysis was performed with solvent delivery system (Spectra Physics Sp 8700), stationary phase (Chrompack Cptm Spher G18250 × 4.6 mm), and MeOH/H_2O, (9/1, v/v) as an eluent.

1-Methyl-2-hydroxy-3-(ethoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolines [7b (trans) and 8b (cis)]. To a stirred solution of **5a**[11] (1 mmol, 250 mg) and **6b** (2 mmol, 180 mg) in dichloromethane (30 mL) was added dropwise CF_3COOH (150 mg). The reaction mixture was monitored by TLC. After the mixture was stirred for 3 days the sovent was evaporated, and the residue was dissolved in dichloromethane and washed with

(14) Behm, H.; Beurskens, P. T.; Plate, R.; Ottenheijm, H. C. J. *Recl. Trav. Chim. Pays-Bas.* **1986**, *105*, 238.

(15) FAB-MS of **14** (7 kV, 1.4 mA), *m/e* (relative intensity) 590 (M + 1, 1), 289 (2), 277 (2), 215 (3), 185 (39), 121 (14), 93 (100). Anal. Calcd for $C_{32}H_{35}N_3O_6S$ (M_r 589.711): C, 65.18; H, 5.98; N, 7.04. Found: C, 65.04; H, 5.97; N, 7.04.

(16) Grigg, R.; Gunaratne, H. Q. N.; McNaghten, E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 185.

(17) Nishimura, O.; Kitada, G.; Fujino, M. *Chem. Pharm. Bull.* **1978**, *26*, 1576.

(18) Arx, E. von; Faupel, M.; Bruggen, M. *J. Chromatogr.* **1976**, *120*, 224.

(19) *Anfaerbereagentien fuer Papier- and Duennschichtchromatographie*; Merck; Darmstadt, F.R.G., 1970; p 108.

water. The solution was dried, and the solvent was removed in vacuo. Flash column chromatography (Merck Silica 60, ethyl acetate/*n*-hexane, 1/1, v/v) gave the diastereomers **7b** and **8b**: 90 mg (33%), R_f 0.33 (ethyl acetate/*n*-hexane, 3/2, v/v), and 170 mg (62%), R_f 0.42, respectively.

Compound 7b (trans): mp 165–168 °C (CH_2Cl_2/*n*-hexane); UV (MeOH) λ_{max} 285 (sh), 276, 270 (sh), 220 nm, λ_{min} 243 nm; EIMS (70 eV), *m/e* (relative intensity) 274 ($[M]^+$, 19), 259 ($[M - CH_3]^+$, 8), 257 ($[M - OH]^+$, 43), 243 ($[C_{13}H_{11}N_2O_3]^+$, 4), 201 ($[M - COOC_2H_5]^+$, 17), 183 ($[C_{12}H_{11}N_2]^+$, 90), 169 (35), 157 ($[C_{11}H_{11}N]^+$, 100), 143 ($[C_{10}H_9N]^+$, 23); exact mass calcd for $C_{15}H_{18}N_2O_3$ 274.1317, found 274.1313; ^1H NMR (90 MHz, $CDCl_3$) δ 7.89–6.88 (m, 5 H, Ar H and NH), 6.18 (s, 1 H, NO*H*), 4.51 (q, ^3J = 6.9 Hz, 1 H, C(1)*H*), 4.22 (q, 2 H, OCH_2CH_3), 4.09 (X part of ABX spectrum, $^3J_{AX}$ = 6.5 Hz, $^3J_{BX}$ = 7.8 Hz, 1 H, C(3)*H*), 3.42–2.89 (AB part of ABX spectrum, 2 H, C(4)H_2), 1.47 (d, 3 H, CHCH_3), 1.24 (t, 3 H, OCH_2CH_3); ^{13}C NMR (15.08 MHz, $CDCl_3$) δ 172.6 ($COOC_2H_5$), 136.4 (C(8a)), 134.5 (C(9a)), 126.8 (C(4b)), 121.8 (C(7)), 119.6 (C(6)), 118.2 (C(5)), 110.9 (C(8)), 105.7 (C(4a)), 61.2 (OCH_2CH_3), 60.2 (C(3)), 57.3 (C(1)), 21.1 (C(4)), 19.4 (C(1)CH_3), 14.1 (OCH_2CH_3).

Compound 8b (cis): mp 158–160 °C (CH_2Cl_2/*n*-hexane); UV (MeOH) λ_{max} 285 (sh), 275, 270 (sh), 222 nm, λ_{min} 241 nm; EIMS (70 eV), *m/e* (relative intensity) 274 ($[M]^+$, 28), 259 ($[M - CH_3]^+$, 8), 257 ($[M - OH]^+$, 10), 215 ($[C_{12}H_{11}N_2O_2]^+$, 11), 201 ($[M - COOC_2H_5]^+$, 27), 183 ($[C_{12}H_{11}N_2]^+$, 11), 157 ($[C_{11}H_{11}N]^+$, 100), 143 ($[C_{10}H_9N]^+$, 12); exact mass calcd for $C_{15}H_{18}N_2O_3$ 274.1317, found 274.1321; ^1H NMR (90 MHz, $CDCl_3$) δ 7.84–6.84 (m, 5 H, Ar H and NH), 6.00 (br s, 1 H, NOH), 4.24 (q, 2 H, OCH_2CH_3), 4.06 (q, ^3J = 6.3 Hz, 1 H, C(1)H), 3.79 (X part of ABX spectrum, $^3J_{AX}$ = 8.1 Hz, $^3J_{BX}$ = 8.1 Hz, 1 H, C(3)*H*), 3.18–2.78 (AB part of ABX spectrum, 2 H, C(4)H_2), 1.53 (d, 3 H, CHCH_3), 1.31 (t, 3 H, OCH_2CH_3); ^{13}C NMR (15.08 MHz, $CDCl_3$), δ 172.6 ($COOC_2H_5$), 136.0 (C(8a)), 133.3 (C(9a)), 126.0 (C(4b)), 121.5 (C(7)), 119.3 (C(6)), 117.9 (C(5)), 110.6 (C(8)), 105.3 (C(4a)), 66.7 (C(3)), 61.0 (OCH_2CH_3), 58.7 (C(1)), 23.3 (C(4)), 16.7 (C(1)CH_3), 14.0 (OCH_2CH_3).

1-Phenyl-2-hydroxy-3-(ethoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolines [7c (trans) and 8c (cis)]. To a stirred solution of **5a** (1 mmol, 250 mg) in dichloromethane (30 mL) and **6c** (1.2 mmol, 180 mg) was added CF_3COOH (150 mg) dropwise. After the mixture was stirred for 6 h at room temperature the products **7c** (47%, 160 mg) and **8c** (30%, 100 mg) were isolated as described for **7b** and **8b**.

Compound 7c (trans): mp 195–197 °C (CH_2Cl_2/*n*-hexane); UV (MeOH) λ_{max} 286 (sh), 277, 271 (sh), 220 nm, λ_{min} 246 nm; EIMS (70 eV), *m/e* (relative intensity) 336 ($[M]^+$, 9), 319 ($[M - OH]^+$, 49), 291 ($[M - OC_2H_5]^+$, 5), 263 ($[M - COOC_2H_5]^+$, 15), 245 ($[C_{17}H_{13}N_2]^+$, 100), 244 ($[C_{17}H_{12}N_2]^+$, 33), 219 ($[C_{16}H_{13}N]^+$, 73), 218 (62), 144 ($[C_{10}H_{10}N]^+$, 6); exact mass calcd for $C_{20}H_{20}N_2O_3$ 336.1474, found 336.1465; ^1H NMR (90 MHz, $CDCl_3$) δ 7.64–6.94 (m, 10 H, C(5)C(8)*H*, N*H* and C_6H_5), 5.93 (s, 1 H, C(1)*H*), 5.62 (br s, 1 H, NOH), 4.35–4.00 (m, 3 H, OCH_2CH_3 and X part of ABX spectrum, C(3)*H*), 3.38 and 3.18 (AB part of ABX spectrum, C(4)H_2), 1.24 (t, 3 H, OCH_2CH_3); ^{13}C NMR (15.08 MHz, $CDCl_3$), δ 172.7 (CO), 139.4 (C(1′)), 136.8 (C(8a)), 131.8 (C(9a)), 130.1 (C(2′) and C(6′)), 128.7 (C(3′) and C(5′)), 128.2 (C(4′)), 126.6 (C(4b)), 122.2 (C(7)), 119.8 (C(6)), 118.5 (C(5)), 111.1 (C(8)), 107.5 (C(4a)), 65.8 (C(1)), 61.0 (OCH_2CH_3), 60.3 (C(3)), 22.1 (C(4)), 14.1 (OCH_2CH_3). Anal. Calcd for $C_{20}H_{20}N_2O_3$ (M_r 336.391): C, 71.41; H, 5.99; N, 8.33. Found: C, 71.21; H, 6.00; N, 8.26.

Compound 8c (cis): mp 117–119 °C (CH_2Cl_2/*n*-hexane); UV (MeOH) λ_{max} 286 (sh), 276, 271 (sh), 223 nm, λ_{min} 243 nm; EIMS (70 eV), *m/e* (relative intensity) 336 ($[M]^+$, 14), 319 ($[M - OH]^+$, 22), 316 ($[C_{20}H_{16}N_2O_2]^+$, 34), 263 ($[M - COOC_2H_5]^+$, 15), 245 ($[C_{17}H_{13}N_2]^+$, 95), 244 ($[C_{17}H_{12}N_2]^+$, 100), 220 (19), 219 ($[C_{16}H_{13}N]^+$, 89), 218 (48); exact mass calcd for $C_{20}H_{20}N_2O_3$ 336.1474, found 336.1742; ^1H NMR (90 MHz, $CDCl_3$) δ 7.58–7.00 (m, 10 H, C(5)C(8)*H*, N*H*, and C_6H_5), 5.62 (br s, 1 H, NOH), 5.00 (br s, 1 H, C(1)*H*), 4.31 (q, 2 H, OCH_2CH_3), 4.02 (X part of ABX spectrum, $^3J_{AX}$ = 8.8 Hz, $^3J_{BX}$ = 7.0 Hz, 1 H, C(3)*H*), 3.22 and 3.19 (AB part of ABX spectrum, $^3J_{AX}$ = 8.8 Hz, $^3J_{BX}$ = 7.0 Hz, $^2J_{AB}$ = 10.8 Hz, 2 H, C(4)H_2), 1.33 (t, 3 H, OCH_2CH_3); ^{13}C NMR (15.08 MHz, $CDCl_3$) δ 173.0 (CO), 139.3 (C(1′)), 136.7 (C(8a)), 132.7 (C(9a)), 129.5 (C(2′) and C(6′)), 128.6 (C(3′), (C(4′), and C(5′)), 126.4 (C(4b)), 122.0 (C(7)), 119.7 (C(6)), 118.2 (C(5)), 111.0 (C(8)), 107.0 (C(4a)), 69.0 (C(1)), 68.1 (C(3)), 61.0 (OCH_2CH_3), 25.4 (C(4)), 14.2 (OCH_2CH_3). Anal. Calcd for $C_{20}H_{20}N_2O_3$ (M_r 336.391): C, 71.41; H, 5.99; N, 8.33. Found: C, 71.46; H, 6.04; N, 8.30.

1-Methyl-2-(benzyloxy)-3-(ethoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline [7d (trans) and 8d (cis)]. To a stirred and cooled (0 °C) solution of **5b** (0.6 mmol, 203 mg) and **6b** (1 mL) in dichloromethane was added dropwise CF_3COOH (100 mg). The mixture was allowed to warm to room temperature and stirred for 3 h. Then the solvents were removed in vacuo, and the residue was dissolved into CH_2Cl_2. The resulting solution was washed with brine, dried (Na_2SO_4), and concentrated to dryness to give a mixture of two isomers in a ratio of 1:1 in 96% yield as an oil. Attempts to separate these isomers failed: R_f (**7d** and **8d**) 0.5 (CH_2Cl_2); UV (MeOH) λ_{max} 286 (sh), 278, 220 nm, λ_{min} 245 nm; EIMS (70 eV), *m/e* (relative intensity) 364 ($[M]^+$, 17), 205 (17), 291 ($[M - COOC_2H_5]^+$, 16), 273 ($[M - C_7H_7]^+$, 36), 257 ($[M - C_7H_7O]^+$, 51), 243 (38), 183 (51), 157 ($[C_{11}H_{11}N]^+$, 100); exact mass calcd for $C_{22}H_{24}N_2O_3$ 364.1787, found 364.1795.

***S*-(*p*-Methoxybenzyl)-*N*-(benzyloxycarbonyl)cysteine Aldehyde (9b).** To a cooled (−60 °C) and stirred solution of *S*-(*p*-methoxybenzyl)-*N*-(benzyloxycarbonyl)cysteine methyl ester[20] (33 mmol, 13.0 g) in dry toluene (400 mL) was added dropwise diisobutylaluminum hydride (73 mL, 1 M solution in *n*-hexane, Aldrich Chem. Co.) over a period of 1 h in an argon atmosphere. After the mixture was stirred for another 1.5 h at −60 °C, the excess of reagent was decomposed by careful addition of a mixture of ethanol/concentrated aqueous HCl (40 mL, 10/1, v/v). Then water was added (500 mL), and the organic layer was separated. The aqueous layer was washed with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated to give a white solid. Flash column chromatography (hexane/ethyl acetate, 5/2, v/v) gave **9b** (67%, 8.0 g) as an amorphous white solid which was homogeneous on TLC: R_f 0.33 (hexane/ethyl acetate, 3/2, v/v); UV (MeOH) λ_{max} 281 (sh), 274, 225 nm, λ_{min} 255, 212 nm; CIMS (100 eV), (relative intensity) *m/e* 360 ($[M + 1]^+$, 5), 358 (2), 268 ($[M - CH_2C_6H_5]^+$ 12), 252 ($[M - OCH_2C_6H_5]^+$, 6), 251 (10), 250 (67), 241 (6), 212 (6), 211 (36), 149 (14), 121 (100); ^1H NMR (60 MHz, $CDCl_3$) δ 9.42 (s, 1 H, C*H*O), 7.33–6.60 (m, 9 H, C_6H_5 and C_6H_4), 5.62 (d, 1 H, N*H*CO), 5.00 (s, 1 H, $CH_2C_6H_5$), 4.25 (X part of ABX spectrum, 1 H, C*H*NH), 3.70 (s, 3 H, OCH_3), 3.60 (s, 2 H, $SCH_2C_6H_4$), 2.83 and 2.72 (AB part of ABX spectrum, 2 H, SCH_2CH).

1-[1-(*N*-(Benzyloxycarbonyl)amino)-2-(benzylthio)-ethyl]-2-hydroxy-3-(ethoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolines (10a, 11a, and 12a). To a stirred solution of **9a**[13] (0.9 mmol, 330 mg) and **5a** (0.7 mmol, 182 mg) in CH_2Cl_2 (30 mL) was added dropwise CF_3COOH (3.5 mmol, 400 mg) at room temperature in an argon atmosphere. The reaction was monitored by TLC. After 60 h the reaction mixture was concentrated to dryness. The residue was dissolved in CH_2Cl_2 (80 mL). The resulting solution was washed with water, dried (Na_2SO_4), filtered, and concentrated to dryness to give a yellow oil consisting mainly of three compounds, which were separated by column chromatography (0.5/99.5, MeOH/CH_2Cl_2, v/v). The product ratio of **10a**/**11a**/**12a** determined by analytical HPLC was 1:1:2. Recrystallization (CH_2Cl_2/*n*-hexane) gave 35 mg of **10a** (9%; R_f 0.42; *n*-hexane/ethyl acetate, 2/1, v/v), 70 mg of **11a** (18%; R_f 0.31), and 100 mg of **12a** (26%; R_f 0.39).

Compound 10a: mp 104–106 °C (CH_2Cl_2/*n*-hexane); UV (MeOH) λ_{max} 287 (sh), 275, 220 nm, λ_{min} 243 nm; CIMS (100 eV), *m/e* (relative intensity) 560 ($[M + 1]^+$, 1), 544 ($[M - CH_3]^+$, 3), 542 ($[M - OH]^+$, 3), 540 (2) 420 (5), 418 (10), 310 (2), 259 ($[C_{14}H_{15}N_2O_3]^+$, 2), 243 (17), 169 (5), 91 (71); ^1H NMR (90 MHz, $CDCl_3$) δ 8.73 (s, 1 H, N(9)*H*), 7.53–6.96 (m, 15 H, C(5)C(8)*H*, $SCH_2C_6H_5$, $OCH_2C_6H_5$, NO*H*), 5.77 (d, 1 H, N*H*CO), 5.13 (s, 2 H, $OCH_2C_6H_5$), 4.53 (X part of ABX spectrum, 1 H, SCH_2CH), 4.35 (br s, 1 H, C(1)*H*), 4.26 (q, 2 H, OCH_2CH_3), 3.79 (X part of ABX spectrum, $^3J_{AX}$ = 5.7 Hz, $^3J_{BX}$ = 10.4 Hz, 1 H, C(3)*H*), 3.60 (s, 2 H, $SCH_2C_6H_5$), 3.21–2.38 (2 AB part of ABX spectrum, 4 H, SCH_2CH, C(4)H_2), 1.31 (t, 3 H, OCH_2CH_3).

Compound 11a: mp 174–176° ($CHCl_3$/hexane); UV (MeOH) λ_{max} 286 (sh), 271, 220 (sh) nm, λ_{min} 246 nm; CIMS (100 eV), *m/e* (relative intensity) 560 ($[M + 1]^+$, 5), 544 ($[M - CH_3]^+$, 4), 542

(20) Akabori, S.; Sakakibara, S.; Shimonishi, Y.; Nobuhara, Y. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 433.

([M - OH]$^+$, 2), 452 ([M - $OCH_2C_6H_5$]$^+$, 2), 418 (6), 259 ([$C_{14}H_{15}N_2O_3$]$^+$, 13), 243 (35), 241 (13), 195 (5), 169 (18), 91 (100); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.56–6.95 (m, 15 H, C(5)C(8)*H*, N(9)H, $OCH_2C_6H_5$, $SCH_2C_6H_5$), 6.16 (s, 1 H, NO*H*), 5.49 (d, 1 H, N*H*CO), 5.02 (s, 2 H, $OCH_2C_6H_5$), 4.91 (d, ^3J = 3.9 Hz, 1 H, C(1)H), 4.31–3.89 (2 X parts of ABX spectrum, C(3*H*, NC*H*), 4.13 (q, 2 H, OCH_2CH_3), 3.82 (d, 2 H, $SCH_2C_6H_5$), 3.38–2.67 (2 AB parts of ABX spectrum, 4 H, C(4)H_2, $CHCH_2S$), 1.20 (t, 3 H, OCH_2CH_3).

Compound 12a: mp 72–74 °C (ethyl acetate/hexane); UV (MeOH) λ_{max} 286 (sh), 272, 220 (sh) nm, λ_{min} 246 nm; CIMS (100 eV) *m/e* 560 ([M + 1]$^+$, 2), 544 ([M - CH_3]$^+$, 1), 542 ([M - OH]$^+$, 1), 452 ([M - $OCH_2C_6H_5$]$^+$, 1), 259 ([$C_{14}H_{15}N_2O_3$]$^+$, 7), 243 (15), 241 (20), 195 (8), 169 (10), 91 (100); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.56–6.95 (m, 16 H, C(5)C(8)*H*, N(9)*H*, NO*H*, $SCH_2C_6H_5$, $OCH_2C_6H_5$), 5.74 (d, 1 H, NHCO), 5.00 (s, 2 H, $OCH_2C_6H_5$), 4.60 (br s, 1 H, C(1)*H*), 4.29 (q, 2 H, CH_2CH_3), 3.95–3.64 (2 X parts of ABX spectrum, C*H*NH, C(3)*H*), 3.82 (s, 2 H, $SCH_2C_6H_5$), 3.29–2.64 (2 AB parts of ABX spectrum, 4 H, SCH_2CH, C(4)H_2), 1.33 (t, 3 H, OCH_2CH_3).

1-[1-(*N*-(Benzyloxycarbonyl)amino)-2-((4-methoxybenzyl)thio)ethyl]-2-hydroxy-3-(ethoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolines (10b, 11b, and 12b). To a stirred solution of **9b** (22 mmol, 8.0 g) and **5a** (20 mmol, 5.0 g) in CH_2Cl_2 (450 mL) was added dropwise CF_3COOH (53 mmol, 6.0 g) at room temperature in an argon atmosphere. The reaction was monitored by TLC. After 24 h the reaction mixture was concentrated to dryness. The residue was dissolved in CH_2Cl_2 (500 mL). The resulting solution was washed with water, dried (Na_2SO_4), filtered, and concentrated to dryness to give a yellow oil consisting mainly of three compounds, which were separated by means of HPL chromatography (ethyl acetate/hexane, 2/5, v/v). The product ratio of **10b**/**11b**/**12b** determined by analytical HPLC was 1:1:2. Recrystallization (CH_2Cl_2/*n*-hexane) gave 1.3 g of **10b** (11%; R_f 0.49; ethyl acetate/*n*-hexane, 1/1, v/v), 1.9 g of **11b** (16%; R_f 0.40), and 3.2 g of **12b** (27%; R_f 0.47).

Compound 10b: mp 125–127 °C (CH_2Cl_2/*n*-hexane); UV (MeOH) λ_{max} 286 (sh), 275, 220 nm, λ_{min} 246 nm; FAB$^+$ mass spectrum (7 kV, 1.4 mA), *m/e* (relative intensity) 590 ([M + 1]$^+$, 1), 461 ([$C_{25}H_{23}N_3O_4S$]$^+$, 3), 369 ([$C_{18}H_{15}N_3O_4S$]$^+$, 6), 301 ([$C_{15}H_{15}N_3O_2S$]$^+$, 4), 277 (45), 275 (3), 259 (6), 257 (3), 245 (3), 243 (4), 223 (6), 213 (7), 187 (10), 186 (41), 185 (100), 147 (7), 121 (30); ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.51 (br s, 1 H, N(9)*H*), 7.80–6.50 (m, 14 H, C(5)C(8)*H*, $C_6H_4OCH_3$, C_6H_5, NO*H*), 5.73 (d, 1 H, N*H*CO), 5.13 (s, 2 H, $CH_2C_6H_5$), 4.54 (X part of ABX spectrum, 1 H, NC*H*), 4.34 (br s, 1 H, C(1)*H*), 4.29 (q, 2 H, oCH_2CH_3), 3.80 (X part of ABX spectrum, 1 H, $^3J_{AX}$ = 5.7 Hz, $^3J_{BX}$ = 10.4 Hz, C(3)*H*), 3.66 (s, 3 H, OCH_3), 3.60 (s, 2 H, $SCH_2C_6H_4$), 3.22–2.38 (2 AB parts of ABX spectra, 4 H, $CHCH_2S$, C(4)H_2), 1.31 (t, 3 H, OCH_2CH_3); ^{13}C NMR (15.08 MHz, $CDCl_3$), δ 172.5 (*C*(O)OCH_2CH_3), 158.8 (C(O)N), 136.7 (C(8a)), 136.4 (C(9a)), 156.3, 130.2, 130.2, 130.2, 130.2, 128.5, 128.5, 127.9, 127.9, 127.9, 113.7, 113.7, (C_6H_5, C_6H_4), 126.3 (C(4b)), 122.0 (C(7)), 119.4 (C(6)), 118.0 (C(5)), 111.2 (C(8)), 108.1 (C(4a)), 67.0 ($CH_2C_6H_5$), 66.3 (C(3)), 61.2 (C(1) and CH_2CH_3), 55.1 (OCH_3), 53.6 ($CHCH_2S$), 35.6 ($SCH_2C_6H_4$), 31.9 ($CHCH_2S$), 24.8 (C(4)), 14.1 (CH_2CH_3). Anal. Calcd for $C_{32}H_{35}N_3O_6S$ (M_r 589.711): C, 65.18; H, 5.98; N, 7.13. Found: C, 65.00; H, 5.97; N, 7.06.

Compound 11b: mp 128–129 °C ($CHCl_3$/hexane); UV (MeOH) λ_{max} 286 (sh), 275, 220 nm, λ_{min} 247 nm; FAB$^+$ mass spectrum (7 kV, 1.4 mA), *m/e* (relative intensity) 590 ([M + 1]$^+$, 6), 450 ([$C_{24}H_{24}N_3O_4S$]$^+$, 2), 418 ([$C_{22}H_{32}N_3O_3S$]$^+$, 3), 333 ([$C_{16}H_{19}N_3O_3S$]$^+$, 3), 302 ([$C_{15}H_{16}N_3O_2S$]$^+$, 3), 299 (30), 285 (4), 273 (4), 269 (5), 259 (21), 185 (35), 169 (26), 129 (10), 121 (53), 115 (21), 93 (100); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.60–6.64 (m, 14 H, C(5)C(8)*H*, N(9)*H*, $C_6H_4OCH_3$, C_6H_5), 6.20 (s, 1 H, NO*H*), 5.53 (d, 1 H, N*H*CO), 4.98 (s, 2 H, $CH_2C_6H_5$), 4.89 (d, ^3J = 4.1 Hz, 1 H, C(1)*H*), 4.40–3.83 (2 X parts of ABX spectrum, 2 H, C(3)*H*, N*H*CO), 4.13 (q, 2 H, OCH_2CH_3), 3.73 (s, 3 H, OCH_3), 3.69 (d, 2 H, $SCH_2C_6H_4$), 3.42–2.51 (2 AB parts of ABX spectrum, 4 H, C(4)H_2, $CHCH_2S$), 1.18 (t, 3 H, OCH_2CH_3); ^{13}C NMR (15.08 MHz, $CDCl_3$) δ 172.5 (*C*(O)OCH_2CH_3), 158.8 (C(O)N), 136.7 (C(8a)), 136.4 (C(9a)), 156.3, 131.4, 130.4, 130.2, 130.2, 128.5, 128.5, 128.0, 127.9, 127.9, 114.2, 114.2 (C_6H_5 and C_6H_4), 126.3 (C(4b)), 122.0 (C(7)), 119.4 (C(6)), 118.0 (C(5)), 111.2 (C(8)), 107.7 (C(4a)), 66.8 ($CH_2C_6H_5$), 62.7 (C(3)), 62.1 (C(1)), 61.2 (CH_2CH_3), 53.3 ($CHCH_2S$), 36.6 ($SCH_2C_6H_4$), 35.4 ($CHCH_2S$), 21.9 (C(4)), 14.0 (CH_2CH_3). Anal. Calcd for $C_{32}H_{35}N_3O_6S$ (M_r 589.711): C, 65.18; H, 5.98; N, 7.13. Found: C, 64.99; H, 5.93; N, 7.13.

Compound 12b: mp 72–74 °C (ethyl acetate/hexane); UV (MeOH) λ_{max} 285 (sh), 270, 221 nm, λ_{min} 246 nm; FAB$^+$ mass spectrum (7 kV, 1.4 mA), *m/e* (relative intensity) 590 ([M + 1]$^+$, 1), 461 ([$C_{25}H_{23}N_3O_4S$]$^+$, 1), 369 ([$C_{18}H_{15}N_3O_4S$]$^+$, 3), 277 (9), 259 (2), 215 (1), 187 (2), 186 (10), 185 (100), 183 (2), 167 (2), 121 (3); ^{1}H NMR (90 MHz, CD_2Cl_2) δ 7.47–6.53 (m, 15 H, C(5)C(8)*H*, N(9)*H*, $C_6H_4OCH_3$, C_6H_5, NO*H*), 5.60 (d, 1 H, N*H*CO), 4.87 (s, 2 H, $CH_2C_6H_5$), 4.49 (br s, 1 H, C(1)*H*), 4.13 (q, 2 H, OCH_2CH_3), 3.96–3.42 (2 X parts of ABX spectrum, 2 H, NC*H*, C(3)*H*), 3.63 (s, 2 H, OCH_3), 3.63 (s, 2 H, $SCH_2C_6H_4$), 3.14–2.47 (2 AB parts of ABX spectrum, 4 H, $CHCH_2S$, C(4)H_2), 1.20 (t, 3 H, OCH_2CH_3); ^{13}C NMR (15.08 MHz, $CDCl_3$) δ 172.7 (*C*(O)OCH_2CH_3), 158.8 (*C*(O)N), 136.7 (C(8)), 136.3 (C(9a)), 156.9, 130.2, 130.2, 130.2, 130.2, 128.4, 128.4, 128.0, 127.8, 127.8, 114.1, 114.1 (C_6H_5 and C_6H_4), 126.5 (C(4b)), 122.0 (C)7)), 119.6 (C(6)), 117.8 (C(5)), 111.4 (C(8)), 108.1 (C(4a)), 74.1 (C(3)), 66.8 ($CH_2C_6H_5$), 62.3 (C(1)), 61.0 CH_2CH_3), 55.3 (OCH_3), 52.3 ($CHCH_2S$), 36.4 ($SCH_2C_6H_4$), 35.2 ($CHCH_2S$), 21.4 (C(4)), 14.2 (CH_2CH_3).

1-[1-(*N*-(Benzyloxycarbonyl)amino)-2-mercaptoethyl]-2-hydroxy-3-(ethoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolines (10c, 11c, and 12c). Compound 10c. To a stirred solution of **10b** (1.2 mmol, 0.7 g) in a mixture of acetic acid and 80% aqueous ethanol (5/9, v/v) were added freshly prepared[17] $(CF_3COO)_2Hg$ (2.3 mmol, 1.0 g) and anisole (0.5 mmol) as a scavenger. The reaction was monitored by TLC. After 24 h water (100 mL) was added. Then hydrogen sulfide was bubbled through this solution for 1 h. The resulting mercuric sulfide was filtered off and was washed several times with ethanol. Evaporation of the solvents at room temperature in vacuo gave a yellow oil, which was subjected to flash column chromatography (toluene/ethyl acetate/formic acid, 40/1/1, v/v/v). Recrystallization gave **10c** in 50% (0.28 g) yield: mp 98–100 °C (CH_2Cl_2/*n*-hexane); R_f 0.60 (toluene/ethyl formate/formic acid, 10/7/3, v/v/v); UV (MeOH) λ_{max} 286 (sh), 277, 271 (sh), 221 nm, λ_{min} 245 nm; CIMS (100 eV), *m/e* (relative intensity) 470 ([M + 1]$^+$, 1), 454 ([M - CH_3]$^+$, 3), 452 ([M - OH]$^+$, 6), 450 ([M - H_2O]$^+$, 4), 420 (18), 418 (25), 417 (5), 346 (4), 310 (4), 274 (3), 243 (16), 169 (5), 121 (8); ^{1}H NMR (90 MHz, CD_2Cl_2) δ 8.93 (s, 1 H, N(9)*H*), 7.50–6.90 (m, 10 H, C(5)C(8)*H*, C_6H_5, NO*H*), 6.04 (d, 1 H, N*H*CO), 5.09 (s, 2 H, $OCH_2C_6H_5$), 4.51 (X part of ABX spectrum, 1 H, SCH_2CH), 4.33 (br s, 1 H, C(1)*H*), 4.18 (q, 2 H, O|cH_2CH_3), 3.76 (X part of ABX spectrum, 1 H, C(3)*H*), 3.24–2.43 (2 AB parts of ABX spectrum, 1 H, SCH_2CH, C(4)H_2), 1.38 (t, ^3J = 8.0 Hz, 1 H, S*H*), 1.27 (t, 3 H, OCH_2CH_3).

Compound 11c. Thiol **11c** was prepared from **11b** (2.5 mmol, 1.5 g) by treatment with $(CF_3COO)_2Hg$ (1.8 g, 4.1 mmol) as described for the preparation of **10c**. Recrystallization gave **11c** in 56% (0.66 g) yield: mp 97–99 °C (CH_2Cl_2/*n*-hexane); R_f 0.57 (toluene/ethyl formate/formic acid, 10/7/3, v/v/v); UV (MeOH) λ_{max} 286 (sh), 276, 271 (sh), 221 nm, λ_{min} 245 nm; CIMS (100 eV), *m/e* (relative intensity) 470 ([M + 1]$^+$, 1), 454 ([M - CH_3]$^+$, 3), 452 ([M - OH]$^+$, 8), 450 ([M - H_2O)]$^+$,4), 446 (4), 420 (10), 419 (10), 418 (31), 346 (4), 310 (16), 269 (7), 243 (18), 169 (9), 119 (4), 108 (10), 91 (100); ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.33 (s, 9 H, N(7)*H*), 7.53–6.97 (m, 9 H, C(5)C(8)*H*, C_6H_5), 6.43 (s, 1 H, NO*H*), 5.62 (d, 1 H, N*H*CO), 5.00 (d, 1 H, ^3J = 4.0 Hz, C(1)H), 4.92 (s, 2 H, $OCH_2C_6H_5$), 4.34–3.91 (2 X parts of ABX spectrum, 2 H, C(3)H_2, SCH_2CH), 4.09 (q, 2 H, OCH_2CH_3), 3.31–2.60 (2 AB parts of ABX spectrum, 4 H, C(4)H_2, SCH_2CH), 1.58 (t, *J* = 8.0 Hz, 1 H, S*H*), 1.17 (t, 3 H, OCH_2CH_3).

Compound 12c. Thiol **12c** was prepared from **12b** (5 mmol, 2.9 g) by treatment with $(CF_3COO)_2Hg$ (3.5 g, 8 mmol) as has been described for the preparation of **10c**. Recrystallization gave **12c** in 64% (1.51 g) yield: mp 93–96 °C (CH_2Cl_2/*n*-hexane); R_f 0.58 (toluene/ethyl formate/formic acid, 10/7/3, v/v/v); UV (MeOH) λ_{max} 286 (sh), 270, 220 nm, λ_{min} 247 nm; CIMS (100 eV), *m/e* (relative intensity) 470 ([M + 1]$^+$, 5), 454 ([M - CH_3]$^+$, 5), 452 ([M - OH]$^+$, 26), 450 ([M - H_2O)]$^+$, 4), 420 (8), 418 (9), 346 (4), 344 (4), 312 (6), 310 (4), 274 (14), 259 (7), 243 (19), 169 (8), 139 (11), 121 (19), 91 (100); exact mass calcd for $C_{24}H_{28}N_3O_5S$ (M + 1) 470.175, found 470.174; ^{1}H NMR (90 MHz, CD_2Cl_2) δ 8.62 (s, 1 H, N(9)H), 7.50–6.87 (m, 10 H, C(5)C(8)*H*, NO*H*, C_6H_5), 5.87 (d, 1 H, N*H*CO), 4.88 (s, 2 H, $OCH_2C_6H_5$), 4.62 (br s, 1 H, C(1)*H*), 4.18 (q, 2 H, OCH_2CH_3), 3.97–3.58 (2 X parts of ABX spectrum,

2 H, C(3)*H*, SCH_2CH), 3.24–2.62 (2 AB parts of ABX spectrum, 4 H, C(4)H_2, SCH_2CH), 1.62 (t, J = 8.0 Hz, 1 H, S*H*), 1.27 (t, 3 H, OCH_2CH_3).

Registry No. **5a**, 106268-32-0; **5b**, 106268-38-6; **6b**, 534-15-6; **6c**, 1125-88-8; **7b**, 106268-33-1; **7c**, 106268-35-3; **7d**, 106268-50-2; **8b**, 106268-34-2; **8c**, 106268-36-4; **8d**, 106268-37-5; **9a**, 89093-55-0; **9b**, 106268-40-0; (±)-**10a**, 106268-41-1; (±)-**10b**, 106268-44-4; (±)-**10c**, 106268-47-7; (±)-**11a**, 106268-42-2; (±)-**11b**, 106268-45-5; **11c**, 106268-48-8; **12a**, 106268-43-3; **12b**, 106268-46-6; **12c**, 106268-49-9; *S*-(*p*-methoxybenzyl)-*N*-(benzyloxycarbonyl)cysteine methyl ester, 106268-39-7.

Application of an Isoxazolidine in a Stereoselective Approach to the Fumitremorgin Series†

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Reduction of the isoxazolidine **5** provides **7**, which was coupled with the N-protected proline derivative **8**. Subsequent deprotection of the amino group affords **11** which undergoes ring closure and dehydration to yield **6** in good yield. The ^{1}H NMR spectrum of **6** compares unfavorably with that of fumitremorgin C (**1**), indicating that **6** may be the C(14a) epimer of the natural product.

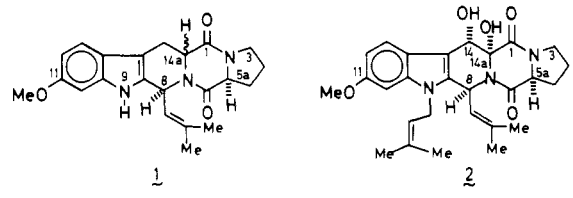
Introduction

Increased research on mycotoxins, in general over the past 15 years, has led to the discovery of fungal metabolites capable of eliciting sustained or intermittent tremors in vertebrate animals.[1-10] All of these tremorgenic mycotoxins, which share an indole moiety as chemical feature, can be conveniently classified into four groups on the basis of structural relationships. The compounds of one of these groups—the fumitremorgin–verruculogen group, two members of which are given in Scheme I—contain three nitrogen atoms per molecule and are biosynthetically derived from tryptophan, proline, and one or more mevalonic acid moieties.[4] In efforts to determine the mode of action of fungal tremorgins, it has become apparent that they provide valuable tools in the study of central nervous system functions.[11-14] Although particular molecular features responsible for tremorgenic activity in the fumitremorgin–verruculogen group have not been completely identified, there are indications that the conformation and configuration of the dioxopiperazine moiety affects tremorgenic activity.[14]

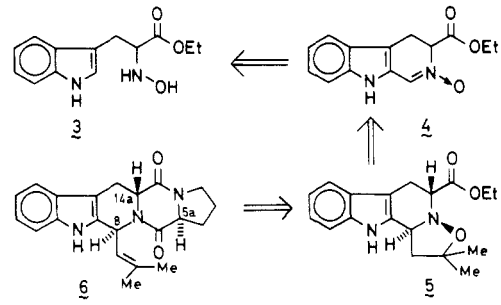
We became interested in the fumitremorgins as attractive synthetic targets because of their biological activity and unique structure. The first target we settled upon was fumitremorgin C (**1**).[1,2,4,6] The structure of this fumitremorgin, as first reported in 1977,[2] contains three chiral carbon atoms. The absolute configuration at C(5a) and C(8) is as depicted in formula **1**.[2-10] The stereochemistry at C(14a) has not been ascertained[15] and at least in one literature report[5] the C(8)-substituent has been presented as being a saturated, tertiary alcohol.

Thus, the total synthesis of fumitremorgin C is desirable for at least two reasons. First, a synthesis would confirm the assigned structure and would allow the chirality to be determined. Second, an efficient synthesis of fumitremorgin C constitutes a challenge, because of its unique structure. Despite some attempts at fumitremorgin synthesis,[16-20] no member of this class of compounds has yet been synthesized. Recently we evaluated the cycloaddition chemistry of nitrone **4**, obtained from the *N*-hydroxy-

Scheme I



Scheme II



† Dedicated to J. H. Ottenheijm, on the occasion of his 65th birthday.

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§ Department of Crystallography.

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