(±)-**8e**, 125331-29-5; (±)-**8f**, 125331-30-8; (±)-**8g**, 125331-31-9; (±)-**8h**, 125331-32-0; (±)-**8i**, 125331-33-1; (±)-**8j**, 125331-34-2; (±)-**8k**, 125331-35-3; (±)-**8l**, 125331-36-4; (±)-**9**, 125331-37-5; $CH_3C(O)CH_2CH_3$, 78-93-3; PhCHO, 100-52-7; *o*-ClC_6H_4CHO, 89-98-5; $CH_3C(O)CH_3$, 67-64-1; $CH_3C(O)CH(CH_3)_2$, 563-80-4; $CH_3C(O)Ph$, 98-86-2; PhC(O)Ph, 119-61-9; PhC(O)C(O)Ph, 134-81-6; cyclohexanone, 108-94-1; *N,N*-diphenylhydrazine hydrochloride, 530-47-2; *N,N*-diphenylhydrazine, 530-50-7; *N,N*-dimethylhydrazine, 57-14-7; cinnamaldehyde, 104-55-2; 1,3-benzodioxole-5-carboxaldehyde, 120-57-0; phenoxyacetyl chloride, 701-99-5; methoxyacetic acid, 625-45-6; phenoxyketene, 107855-45-8.

Intramolecular Pictet–Spengler Reaction of *N*-Alkoxytryptophans and Tryptamines. 2.[1] Synthesis of Corynanthe Alkaloid Derivatives Containing a Tetrahydro-1,2-oxazine as the D Ring

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The *N*-hydroxtryptamines **1–3** were converted into the *N*-alkoxy derivatives **26–29** by successive protection with 2-(trimethylsilyl)ethyl chloroformate providing **19–21**, reaction with functionalized alkylhalides, and deprotection with tetrabutylammonium fluoride. Intramolecular cyclization of **26–29** under acidic or reductive conditions gave the corynanthe analogues **4–6** in good yields.

Introduction

The tetrahydro-β-carboline nucleus is a structural feature present in many indole alkaloids. Common to all these indole bases is a tryptamine unit, which in a convincing variety of alkaloids has been found to have its genesis in tryptophan.[2]

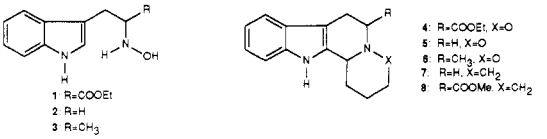
Due to the interesting biological effects such as inhibition of monoamine oxidase (MAO) enzymes,[3] neurotransmitter reuptake,[3] binding to benzodiazepine receptors,[3] carcinogenic properties,[3b] and antiviral activity[4] a wide array of β-carbolines have been prepared starting from various tryptamine and tryptophan derivatives. However, rare are those starting from *N*-hydroxytryptophan[5] (**1**) or *N*-hydroxytryptamine[6] (**2**) to give *N*(2)-hydroxy-1,2,3,4-tetrahydro-β-carboline derivatives. Because of the central significance of *N*-hydroxytryptophan in biotransformation pathways[7] which is substantiated by the detection of *N*-hydroxytryptamine in rabbit and guinea pig liver[8] and the isolation of secondary metabolites containing the *N*-hydroxytryptophan (e.g. astechrome[9]) or the *N*-hydroxytryptamine moiety (e.g. geneserine,[10] eudistomins[4]), we wanted to study the pharmacological impact of the introduction of a N–O bond in the β-carboline alkaloids.

Interesting target structures are **4–6** since these contain the structural feature of the *N*-hydroxy compounds **1–3**. These molecules are direct analogues of the simple corynanthe alkaloids **7**[11,12] and **8**,[12e,13] containing a tetrahydro-1,2-oxazine as the D ring (Chart I).

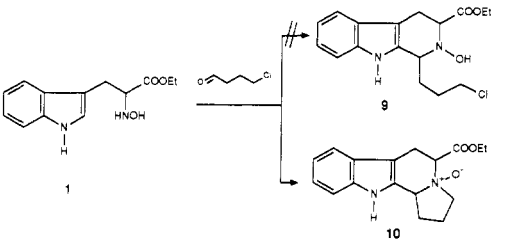
Strategy

The standard methods for the construction of the C ring in the corynanthe alkaloids are the Bischler–Napieralski[3b] and the Pictet–Spengler[3b] reactions or cyclization via pyridinium salts.[3b,14] Recently the conversion of **1** into 1,3-disubstituted *N*(2)-hydroxy-1,2,3,4-tetrahydro-β-carbolines via the Pictet–Spengler reaction has been reported.[5e] Therefore our first approach to compounds **4–6**

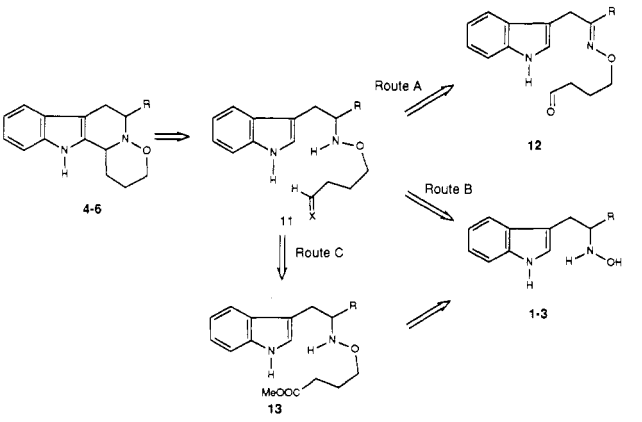
Chart I



Scheme I



Scheme II



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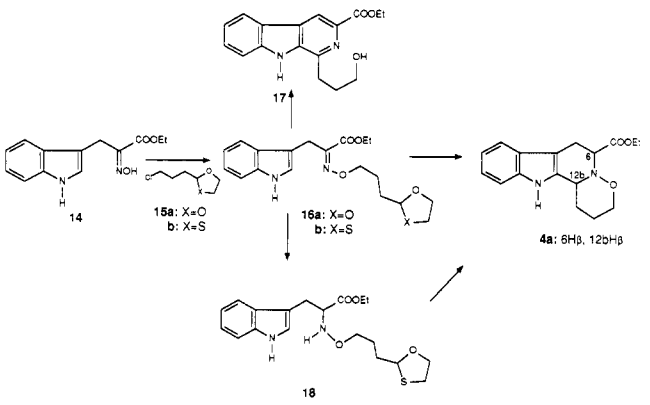
[‡] Department of Crystallography, University of Nijmegen.
[§] Duphar Research Laboratories.

(1) Hermkens, P. H. H.; Maarseveen, J. H. v.; Kruse, C. G.; Scheeren, J. W. *Tetrahedron Lett.*, submitted for publication.

0022-3263/90/1955-2200$02.50/0

Scheme III

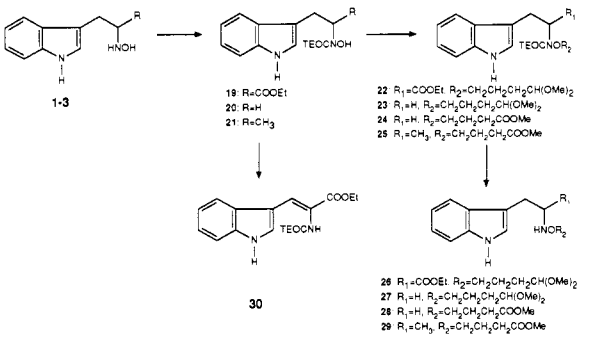


consisted of a Pictet–Spengler reaction with 4-chlorobutanal, followed by a cyclization to form ring D. However condensation of *N*-hydroxytryptophan (**1**) with 4-chlorobutanal did not give the desired compound **9** but the *N*-oxide **10**, which has been formed by an undesired intramolecular cyclization[15] (Scheme I).

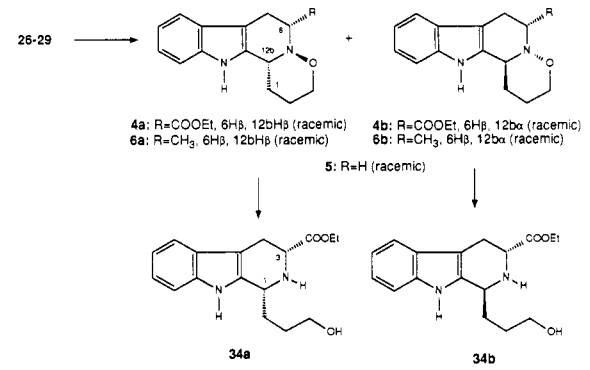
We reasoned that an intramolecular Pictet–Spengler reaction should be a better approach to the target molecules. The intermediate for this synthetic pathway to compounds **4–6** consists of a *N*-alkoxytryptamine derivative such as **11** having a potential aldehyde function in the δ-position of the alkoxy chain (Scheme II). Three routes as depicted in Scheme II might give access to such an intermediate: (1) selective reduction of the O-alkylated oxime function present in **12** (route A), (2) selective O-alkylation of the *N*-hydroxy compounds **1–3** with a functionalized four-carbon substrate (route B), or (3) selective reduction of the ester function in **13** (route C).[16]

In this report it is highlighted that compounds **11** are highly valuable intermediates for the corynanthe N_b-oxo analogues **4–6**, via an intramolecular Pictet–Spengler condensation.[1] The most suitable approaches to this intermediates **11** are routes B and C, whereas route A gave poor yields.

Scheme IV



Scheme V



Results

Route A (Scheme III). Alkylation of oxime **14** with the protected 4-chlorobutanals **15** in DMSO with potassium *tert*-butoxide as the base gave the O-alkylated products **16** in 64–68% yield. Selective reduction of the oxime double bond of the dioxolane protected compound **16a** failed. Treatment with trimethylamineborane in dioxane saturated with HCl gave a mixture of compounds. One of the products appeared to be the desired **4a**,[17] presumably as a result of reduction of the oxime double bond[18] and intramolecular cyclization under the acidic conditions. The yield however was low (10%)[19] as a result of side reactions due to cationic ring opening of the dioxolane ring. This was followed either by reduction (24%) or by intramolecular cyclization, ring opening of the D ring, and aromatization to give product **17** (16%). Reaction of

(2) For a review, see: Herbert, R. B. In *The Chemistry of Heterocyclic Compounds*; Saxton, J. E., Ed.; J. Wiley: New York, 1983; Vol. 25, Part 4, p 2 and references cited therein.

(3) Recent reviews: (a) Airaksinen, M. M.; Kari, I. *Med. Biol.* **1981**, *59*, 190. (b) Torreilles, J.; Guérin, M.-C.; Previero, A. *Biochemie* **1985**, *67*, 929.

(4) (a) Rinehart, K. L., Jr.; Kobayashi, J.; Harbour, G. C.; Hughes, R. G.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 1524. (b) Rinehart, K. L., Jr.; Kobayashi, J.; Harbour, G. C.; Gilmore, J.; Mascal, M.; Holt, T. G.; Shield, L. S.; Larfargue, F. *J. Am. Chem. Soc.* **1987**, *109*, 3378. (c) Blunt, J. W.; Lake, R. J.; Munro, M. H. G. *Tetrahedron Lett.* **1987**, *28*, 1825. (d) Lake, R. J.; Brennan, M. M.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K. *Tetrahedron Lett.* **1988**, *29*, 2255.

(5) (a) Plate, R.; Hermkens, P. H. H.; Smits, J. M. M.; Ottenheijm, H. C. J. *J. Org. Chem.* **1986**, *51*, 309. (b) Plate, R.; Nivard, R. J. F.; Ottenheijm, H. C. J. *Heterocycles* **1986**, *24*, 3105. (c) Plate, R.; Hermkens, P. H. H.; Behm, H.; Ottenheijm, H. C. J. *J. Org. Chem.* **1987**, *52*, 560. (d) Plate, R.; Hermkens, P. H. H.; Smits, J. M. M.; Nivard, R. J. F.; Ottenheijm, H. C. J. *J. Org. Chem.* **1987**, *52*, 1047. (e) Plate, R.; Hout, v. R. H. M.; Behm, H.; Ottenheijm, H. C. J. *J. Org. Chem.* **1987**, *52*, 555. (f) Hermkens, P. H. H.; Plate, R.; Ottenheijm, H. C. J. *Tetrahedron* **1988**, *44*, 1991. (g) Hermkens, P. H. H.; Maarseveen, v. J. H.; Kruse, C. G.; Scheeren, J. W. *Tetrahedron* **1988**, *44*, 6491.

(6) (a) Han, S. Y.; Lakshmikantham, M. V.; Cava, M. P. *Heterocycles* **1985**, *23*, 1671. (b) Nakagawa, M.; Liu, J. J.; Ogata, K.; Hino, T. *Tetrahedron Lett.* **1986**, *27*, 6087. (c) Nakagawa, M.; Liu, J. J.; Ogata, K.; Hino, T. *J. Chem. Soc., Chem. Commun.* **1988**, 463. (d) Still, I. W. J.; Strautmanis, J. R. *Tetrahedron Lett.* **1989**, *30*, 1041. (e) Nakagawa, M.; Liu, J. J.; Hino, T. *J. Am. Chem. Soc.* **1989**, *111*, 2721.

(7) (a) Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, J. D. M. *J. Org. Chem.* **1982**, *47*, 2147. (b) See also references cited therein.

(8) Jaccarini, A.; Felice, M. A. In *Biological Oxidation of Nitrogen*; The Metabolism of Pyrroles and Indoles: Ring Nitrogen Oxidation; Gorrod, J. W., Ed.; Elsevier: North-Holland, 1978.

(9) Arai, K.; Sato, S.; Shimizu, S.; Nitta, K.; Yamamoto, Y. *Chem. Pharm. Bull.* **1981**, *29*, 1510.

(10) (a) Hootele, C. *Tetrahedron Lett.* **1969**, 2713. (b) Robinson, B.; Moorcroft, D. *J. Chem. Soc. C* **1970**, 2077.

(11) Isolation from *Dracontomelum mangiferum* Bl. Johns, S. R.; Lamberton, J. A.; Occolowitz, J. L. *J. Chem. Soc., Chem. Commun.* **1966**, 421.

(12) Syntheses: (a) Groves, L. H.; Swan, G. A. *J. Chem. Soc.* **1952**, 650. (b) Prasad, K. B.; Swan, G. A. *J. Chem. Soc.* **1958**, 2024. (c) Wenkert, E.; Dave, K. G.; Haglid, F. *J. Am. Chem. Soc.* **1965**, *87*, 5461. (d) Gribble, G. W. *J. Org. Chem.* **1972**, *37*, 1833. (e) Johansen, J. E.; Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 4914.

(13) Brown, R. T.; Chapple, C. L.; Lee, G. K. *J. Chem. Soc., Chem. Commun.* **1972**, 1007.

(14) For a review, see: Brown, T. B. In *The Chemistry of Heterocyclic Compounds*; Saxton, J. E., Ed.; J. Wiley: New York, 1983; Vol. 25, Part 4, p 119 and references cited therein.

(15) The undesired cyclization is a result of the ambident nucleophilic properties of the N-OH moiety, unpublished result.

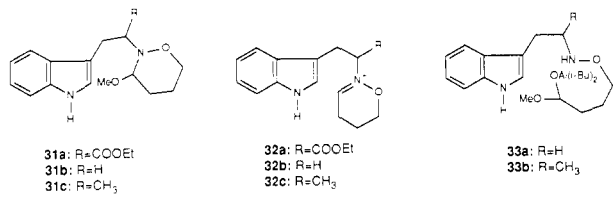
(16) This approach is mentioned for a corynanthe alkaloid containing a piperidine as the D ring by Winterfeldt, E. *Synthesis* **1975**, 617, reference 129 as an unpublished result.

(17) The relative stereochemistry was established by single-crystal X-ray analysis, see ref 26.

(18) An analogous *N*-alkoxamine derivative of **11** was never detected.

(19) The highest reached yield of **4a** was 34%, but it was not reproducable.

Chart II



31a: R=COOEt
31b: R=H
31c: R=CH_3

32a: R=COOEt
32b: R=H
32c: R=CH_3

33a: R=H
33b: R=CH_3

16a under the same reaction conditions with exclusion of the reductive reagent gave **17** quantitatively.

Reduction of the oxime double bond of the 1,3-oxathiolane protected compound **16b** with TMA/BH_3 in ethanolic HCl gave the *N*-alkoxytryptophan derivative **18** in 56% yield. In this case intramolecular cyclization was not observed. Deprotection of the oxathiolane moiety of **18** failed under treatment with $HgCl_2$/NaOH,[20b] Raney nickel,[20a,b] and various acidic conditions. Deprotection with Chloramine-T[20c] gave the cyclized product **4a** in only 22% yield. Attempts to improve these results were unsuccessful.

Routes B and C (Scheme IV). In both routes B and C we faced the problem of a selective O-alkylation of the N-substituted hydroxylamines **1–3**. In general N,O-disubstituted hydroxylamines are prepared by alkylation of *N*-hydroxyurethanes followed by acidic hydrolysis.[21] By adjusting the protective group this method could be suitable for our goal. The protective group has to be easily incorporated and removed and has to survive the alkylation conditions. For example, the trichloroethoxycarbonyl (TrOC) group satisfied the first two criteria, but failed with respect to the last one. The protective group of choice which met all the criteria was the (2-(trimethylsilyl)ethoxy)carbonyl[22] (TEOC) group. Treatment of the hydroxylamines **1–3** with 2-(trimethylsilyl)ethyl chloroformate in dichloromethane/dioxane[23] at room temperature gave **19**, **20**, and **21** in 96%, 91%, and 80% yields, respectively. The reaction conditions for the O-alkylation of these TEOC-protected compounds depend on the α-substituent in the tryptamine moiety. An *N*-acyl-*N*-hydroxytryptophan derivative such as **19** is sensitive to elimination reactions under basic conditions. In the absence of a nucleophile, rearrangements to the corresponding enamine acid derivative have been reported.[7a,24] It occurred that alkylation attempts with **19** using DMSO/KOtBU or DME/NaH with 4-bromo-1,1-dimethoxybutane yielded the dehydro acid **30** almost quantitatively. With K_2CO_3 as the base in DMSO at 45 °C the desired **22** was obtained in 67% yield. The TEOC-protective group was removed with tetrabutylammonium fluoride (Bu_4NF) in THF to give the *N*-alkoxytryptophan **26** in 78% yield. Since **20** and **21** do not undergo this elimination reaction these compounds could be smoothly converted at room temperature in DME with functionalized alkyl bromides in the presence of NaI using NaH as the base to give **23–25**. These compounds were not purified, but immediately deprotected with Bu_4NF in THF yielding the compounds **27–29** in an overall yields of 67%, 74%, and 64%, respectively.

Cyclization (Scheme V). It has been demonstrated that dimethoxy acetals easily react with **1** in the presence of trifluoroacetic acid to give *N*-hydroxy-1,2,3,4-tetrahydro-β-carbolines.[5e] So by preparing the compounds **26** and **27**, which bare all necessary features of intermediate **11**, route B seems to be feasible. Indeed, treatment of **26** and **27** with trifluoroacetic acid in dichloromethane caused an intramolecular Pictet–Spengler reaction and presumably via intermediates **31a,b** → **32a,b** (Chart II) the cyclized products **4** and **5** were isolated in 97% and 92% yield, respectively. The corynanthe analogue **4** was obtained as a 79/21 (**4a**/**4b**) mixture of the two possible diastereomers, which were readily separated by column chromatography. The relative stereochemistry at the C(6) and C(12b) centers were established as **4a** cis and **4b** trans (vide infra).

Route C implies the selective reduction of the ester function in **28** and **29** in the presence of the labile N–O bond. Therefore, we were pleased to find that reduction of the methyl ester function of **28** with DIBAL in toluene at −70 °C, followed by addition of trifluoroacetic acid gave the cyclized product **5** in 76% yield. Under the anhydrous acidic conditions intermediate **33** cyclized either via **31** → **32** → **5** or via an aldehyde intermediate to **32** → **5** (Chart II).

Under the same conditions, reduction of **29** gave the two diastereomers **6a** and **6b** (HPLC ratio 83/17) which were separated by column chromatography in respectively 68% and 9% yields. The stereochemistry was assigned by extending the results of **4a** and **4b**. The major isomer, **6a**, was assumed to be cis given that the predominant isomer in the cyclization of **26** was unambiguously demonstrated to be **4a** (cis).

The observed stereochemistry seems to be the result of a kinetically controlled reaction. Prolonged treatment of either the cis isomers **4a** and **6a** or the trans isomers **4b** and **6b**, respectively, under the reaction conditions caused no formation of the other isomer. Higher temperature (65 °C) led to serious decomposition of the starting materials. In the formed reaction mixtures the other isomer could be only detected in less than 5% by means of analytic HPLC techniques.

Stereochemistry. The relative configurations of the two diastereomers of **4a** and **4b** were established as follows. Reductive ring opening of the tetrahydro-1,2-oxazine was accomplished by cleaving the N–O bond. Treatment of **4a** and **4b** with zinc dust in acetic acid at elevated temperature (80 °C) gave the 1,3-disubstituted tetrahydro-β-carbolines **34a** and **34b** in 85% and 89% yield, respectively (Scheme V). Their relative stereochemistry was assigned on basis of ^{13}C NMR data. It has been noted[25] 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 upfield of the values of the corresponding C atoms in the cis isomer. Consequently, structure **34b** was assigned trans because of its more shielded C(3) δ 51.90 and C(1) δ 50.30 carbon atoms, compared to C(3) δ 56.38 and C(1) δ 52.60 of **34a**. Thus the relative stereochemistry at C(12b) and C(6) of the two diastereomers **4a** and **4b** is as depicted in Scheme V. Recently Rapoport[12e] reported that cyclization to the corynanthe alkaloid **8** via an in situ generated iminium ion

(20) (a) Djerassi, C.; Shamma, M.; Kan, T. Y. *J. Am. Chem. Soc.* **1958**, *80*, 4723. (b) Romo, J.; Rosenkranz, G.; Djerassi, C. *J. Am. Chem. Soc.* **1951**, *73*, 4961. (c) Emerson, D. W.; Wynberg, H. *Tetrahedron Lett.* **1971**, 3445.

(21) For a review see: Roberts, J. S. In *Comprehensive Organic Chemistry*; Sutherland, I. O., Ed.; Pergamon Press: Oxford, 1979; Vol. 2, Chapter 6.4, p 185.

(22) (a) Carpino, L. A.; Tsao, J.-H.; Ringsdorf, H.; Fell, E.; Hettrich, G. *J. Chem. Soc. Chem. Commun.* **1978**, 358. (b) Carpino, L. A.; Sau, A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514.

(23) The ether function of dioxane obviously acts as a weak lewis base, resulting in selective N-acylation, see: Plate, R.; Akkerman, M. A. J.; Smits, J. M. M.; Ottenheijm, H. C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2481.

(24) Plate, R.; Nivard, R. J. F.; Ottenheijm, H. C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2473.

(25) (a) Ungemach, F.; Soerens, D.; Weber, R.; Dipierro, M.; Campos, O.; Mokry, P.; Cook, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 6967. (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.

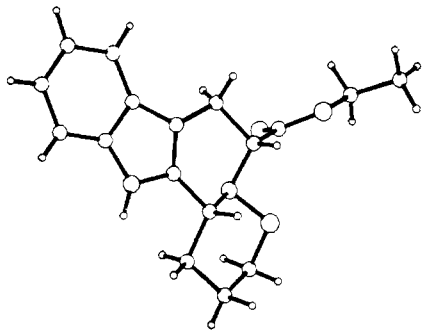


Figure 1. PLUTO drawing of **4a**.

showed the same relative stereochemistry at C(12b) and C(6) as well as the same ratio of the diastereomers. So it seems to be reasonable to suppose that cylization of **26** proceeds via the in situ generation of intermediate **32a**. The structure of **4a** is verified by single-crystal X-ray analysis.[26]

Interesting is the stereochemistry at N(5) (Figure 1). The crystal structure clearly shows that the tetrahydro-1,2-oxazine ring has a chair conformation with the N(5) and C(12b) carbon substituents in an equatorial position. This implies a trans juncture of ring C and D as depicted in Scheme V. The ethyl ester at C(6) is also in an equitorial position.

Conclusions

In conclusion corynanthe analogues **4–6** in which the D ring is a tetrahydro-1,2-oxazine have been synthesized by an intramolecular Pictet–Spengler reaction of **26–29** in excellent yields (routes B and C). The cyclizations occur with high stereoselectivity of the product with a cis conformation of the C(6) and C(12b) substituents.

In general, this method is appropriate for constructing tetracylic indole alkaloids of which the D ring contains an N–O moiety. Therefore, we are currently pursuing the synthesis of the natural product *Eudistomin*,[4] an indole alkaloid with an oxathiazepine as the D ring.

Experimental Section

Melting points were taken on a Koefler hot stage apparatus (Leitz-Wetzlar) and are uncorrected. Ultraviolet spectra were measured with a Perkin-Elmer spectrometer, Model lambda 5. Proton magnetic resonance spectra were measured on a Bruker WH-90 or on a Bruker AM 400 spectrometer. Chemical shifts are reported as δ values relative to tetramethylsilane as an internal standard; deuteriochloroform was used as solvent unless stated otherwise. Mass spectra were obtained with a double-focusing VG 7070E spectrometer. Thin-layer chromatography (TLC) was carried out by using silica gel F-254 plates (thickness 0.25 mm). Spots were visualized with a UV hand lamp, iodine vapor, or Cl_2-TDM.[27] For column chromatography Merck silica gel (type 60H) was used. Solvent systems used are as follows: A, MeOH/$CHCl_3$ (3/97, v/v); B, MeOH/$CHCl_3$ (7/93, v/v); C, EtOAc/*n*-hexane (25/75, v/v); D, EtOAc/*n*-hexane (40/60, v/v).

Ethyl α-[[3-(1,3-Dioxolan-2-yl)propyl]oximido]-β-(indol-3-yl)propanoate (16a). Potassium *tert*-butoxide (0.74 g, 6.6 mmol) was added portionwise to a stirred solution of **14**[4a] (1.63 g, 6.6 mmol) and **15a**[28] (1 g, 6.6 mmol) in DMSO (25 mL). After stirring for 2 h at 50 °C the reaction was complete. The reaction mixture was diluted with CH_2Cl_2 (100 mL), and most of the DMSO was removed by washing three times with 100 mL of water. The resulting organic layer was washed with brine and dried with Na_2SO_4. Evaporation of the solvent gave an oil, which was subjected to column chromatography ($CHCl_3$) to give 1.52 g (64%) of **16a**: oil; R_f 0.62 (solvent system A); UV (MeOH) λ_{max} 224, 274 (sh), 281, 289 nm; CIMS (100 eV) *m/z* (relative intensity) 361 ($[M + 1]^+$, 30), 360 (M^+, 33), 229 ($[C_{13}H_{13}N_2O_2]^+$, 26), 130 ($[C_9H_8N]^+$, 100); ^{1}H NMR δ 8.08 (br s, 1 H, NH), 7.76–7.04 (m, 5 H, indole C(2)H and C(4)–C(7)H), 4.91 (t, 1 H, OCHO), 4.32 (m, 4 H, OCH_2CH_3 and $NOCH_2$), 4.07 (s, 2 H, C(3)CH_2), 4.00–3.82 (m, 4 H, OCH_2CH_2O), 2.04–1.71 (m, 4 H, CH_2CH_2CH), 1.27 (t, 3 H, OCH_2CH_3).

Ethyl α-[[3-(1,3-Oxathiolan-2-yl)propyl]oximido]-β-(indol-3-yl)propanoate (16b). The same procedure was followed as described for **16a**. **14**[4a] (10 g, 41 mmol), potassium *tert*-butoxide (4.6 g, 41 mmol), and **15b**[29] (10 g, 60 mmol) in DMSO (100 mL) gave after column chromatography ($CHCl_3$) 10.5 g (68%) of **16b** as an oil: R_f 0.76 (solvent system A); UV (MeOH) λ_{max} 224, 274 (sh), 281, 289 nm; CIMS (100 eV) *m/z* (relative intensity) 376 (M^+, 6), 230 ($[C_{13}H_{14}N_2O_2]^+$, 16), 144 ($[C_{10}H_{10}N]^+$, 48), 130 ($[C_9H_8N]^+$, 100); ^{1}H NMR δ 8.11 (br s, 1 H, NH), 7.64–7.00 (m, 5 H, indole C(2)H and C(4)-C(7)H), 5.03 (br t, 1 H, OCHS), 4.38–4.11 (m, 5 H, OCH_2CH_3, $NOCH_2$, and SCHOCH_A), 4.02 (s, 2 H, C(3)CH_2), 3.87–3.51 (m, 1 H, SCHOCH_B), 3.08–2.87 (m, 2 H, CH_2S), 2.00–1.70 (m, 4 H, CH_2CH_2CH), 1.23 (t, 3 H, OCH_2CH_3).

1-(3-Hydroxypropyl)-3-(ethoxycarbonyl)-β-carboline (17). Through a stirred solution of **16a** (150 mg, 0.42 mmol) in THF (10 mL) was passed a stream of HCl for 2 min. Stirring was continued for 4 h. The reaction mixture was washed with saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was subjected to column chromatography (solvent system A) to give 120 mg (96%) of **17**. Crystallization attempts were unsuccessful: R_f 0.17 (solvent system B); EIMS (70 eV) *m/z* (relative intensity) 298 (M^+, 1), 254 ($[C_{15}H_{14}N_2O_2]^+$, 19), 169 ($[C_{11}H_9N_2]^+$, 14), 69 (100); ^{1}H NMR ($CDCl_3/CD_3OD$) δ 11.14 (br s, 1 H, NH exchangeable), 8.71 (s, 1 H, C(4)H), 8.14 (d, 1 H, C(5)H), 7.62–7.22 (m, 3 H, C(6)–C(8)H), 4.51 (q, 2 H, OCH_2CH_3), 3.76 (t, 2 H, CH_2OH), 3.30 (t, 2 H, C(1)CH_2), 2.24–1.98 (m, 2 H, $CH_2CH_2CH_2OH$), 1.51 (t, 3 H, OCH_2CH_3).

Ethyl α-[[[3-(1,3-Oxathiolan-2-yl)propyl]oxy]amino]-β-(indol-3-yl)propanoate (18). A solution of HCl in ethanol (2 mL, 7 N solution) was added dropwise to a stirred solution of **16b** (0.5 g, 1.3 mmol) and $(CH_3)_3N{\cdot}BH_3$ (Aldrich Chemical Co; 300 mg, 4.16 mmol) in EtOH (10 mL) at room temperature and in an argon atmosphere. Stirring was continued for 5 h. The mixture was then concentrated to near dryness. The residue was dissolved in CH_2Cl_2. This solution was neutralized with $NaHCO_3$ and filtered. The filtrate was washed with 0.1 N HCl and dried over Na_2SO_4. Evaporation of the solvent gave an oil which after column chromatography ($CHCl_3$) yielded 273 mg (56%) of **18**: oil; R_f 0.57 (solvent system A); UV (MeOH) λ_{max} 224, 274 (sh), 281, 289 nm; EIMS (70 eV) *m/z* (relative intensity) 378 (M^+, 2), 305 ($[M - COOEt]^+$, 4), 227 ($[C_{14}H_{15}N_2O]^+$, 18), 130 ($[C_9H_8N]^+$, 100); ^{1}H NMR δ 8.11 (br s, 1 H, NH), 7.67–7.04 (m, 5 H, indole C(2)H and C(4)–C(7)H), 5.82 (br s, 1 H, HNO), 5.07 (br t, 1 H, OCHS), 4.40–3.90 (m, 4 H, OCH_2CH_3, HCCOOEt, and SCHOCH_A), 3.88–3.60 (m, 3 H, $NOCH_2$ and SCHOCH_B), 3.12–2.92 (m, 4 H, C(3)CH_2 and CH_2S), 2.02–1.55 (m, 4 H, CH_2CH_2CH), 1.17 (t, 3 H, OCH_2CH_3).

Ethyl α-[*N*-(((2-(Trimethylsilyl)ethyl)oxy)carbonyl)-*N*-hydroxyamino]-β-(indol-3-yl)propanoate (19). 2-(Trimethylsilyl)ethyl chloroformate[21] (1.08 g, 6 mmol) was added dropwise to a stirred solution of **1**[6a] (1.0 g, 4 mmol) in CH_2Cl_2/dioxane, 1/1, v/v (25 mL). The reaction was monitored by TLC (solvent system B). Stirring was continued for 2 h. The reaction mixture was concentrated to near dryness, dissolved in CH_2Cl_2, subsequently washed with saturated $NaHCO_3$ and brine, and dried with Na_2SO_4. Evaporation of the solvent gave a crystalline material which was subjected to column chromatography ($CHCl_3$/*n*-hexane, 99.5/0.5, v/v) to yield 1.51 g (96%) of **19**. Crystallization from CH_2Cl_2/*n*-hexane: mp 101–102.5 °C; R_f 0.45 (solvent system A); UV (MeOH) λ_{max} 224, 274 (sh), 281, 289 nm; CIMS (100 eV) *m/z* (relative intensity) 393 ($[M + 1]^+$, 9), 392 (M^+, 23), 365 (28), 349 (49), 321 (27), 247 ($[M - C_6H_{13}O_2Si]^+$, 11), 231 (53), 216 (67),

(26) Smits, J. M. M.; Beurskens, P. T.; Hermkens, P. H. H.; Maarseveen, J. M. *J. Crystallogr. Spectrosc. Res.*, in press.
(27) Arx, E.; Faupel, M.; Bruggen, M. *J. Chromatogr.* **1976**, *120*, 224.
(28) Forbes, C. P.; Wenteler, G. L.; Wiechers, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2353.
(29) Prepared under the same conditions as **15a**, with mercaptoethanol, see ref 28.

215 (95), 130 ($[C_9H_8N]^+$, 100); ^{1}H NMR δ 8.23 (br s, 1 H, NH), 7.77–7.19 (m, 5 H, indole C(2) and C(4)–C(7)H), 6.53 (br s, 1 H, NOH), 5.11 (t, 1 H, J = 7.8 Hz, HCCOOEt), 4.37 (q, 2 H, OCH_2CH_3), 3.91 (m, 2 H, OCH_2CH_2Si), 3.51 (d, 2 H, J = 7.8 Hz, indole C(3)CH_2), 1.39 (t, 3 H, OCH_2CH_3), 0.71 (m, 2 H, CH_2Si), 0.0 (s, 9 H, $Si(CH_3)_3$). Anal. Calcd for $C_{19}H_{28}N_2O_5Si$ (MW 392.531): C, 58.14; H, 7.19; N, 7.14. Found: C, 57.83; H, 7.14; N, 7.16.

3-[2-(*N*-(((2-(Trimethylsilyl)ethyl)oxy)carbonyl)-*N*-hydroxyamino)ethyl]indole (20). The same procedure was followed as described for **19**. 2-(Trimethylsilyl)ethyl chloroformate[21] (675 mg, 3.75 mmol) and **2**[30] (440 mg, 2.5 mmol) gave after column chromatography (EtOAc/*n*-hexane, 40/60, v/v) 750 mg (91%) of **20**. Crystallization from EtOAc/*n*-hexane: mp 95–97 °C; R_f 0.39 (solvent system B); UV (MeOH) λ_{max} 224, 274 (sh), 281, 289 nm; EIMS (70 eV) m/z (relative intensity) 320 (M^+, 1), 157 ($[C_{10}H_9N_2]^+$, 11), 130 ($[C_9H_8N]^+$, 100); ^{1}H NMR δ 8.02 (br s, 1 H, NH), 7.70–7.04 (m, 5 H, indole C(2) and C(4)–C(7)H), 6.25 (br s, 1 H, NOH), 4.11–3.87 (m, 2 H, OCH_2CH_2Si), 3.90 (t, 2 H, CH_2N), 3.13 (t, 2 H, indole C(3)CH_2), 0.89–0.68 (m, 2 H, CH_2Si), 0.0 (s, 9 H, $Si(CH_3)_3$). Anal. Calcd for $C_{16}H_{24}N_2O_3Si$ (MW 320.469): C, 59.97; H, 7.55; N, 8.74. Found: C, 59.91; H, 7.62; N, 8.70.

3-[2-(*N*-(((2-(Trimethylsilyl)ethyl)oxy)carbonyl)-*N*-hydroxyamino)propyl]indole (21). The same procedure was followed as described for **19**. 2-(Trimethylsilyl)ethyl chloroformate[21] (1625 mg, 9 mmol) and **3**[30] (1.14 g, 6 mmol) gave after column chromatography ($CHCl_3$/*n*-hexane, 99/1, v/v) 1.61 g (80%) of **21**. Crystallization from $CHCl_3$/*n*-hexane: mp 122–125 °C; R_f 0.29 (solvent system B); UV (MeOH) λ_{max} 224, 274 (sh), 281, 289 nm; CIMS (100 eV) m/z (relative intensity) 334 (M^+, 2), 291 (14), 230 (9), 158 ($[C_{11}H_{12}N]^+$, 100), 130 ($[C_9H_8N]^+$, 85), 73 ($[Si(CH_3)_3]^+$, 100); ^{1}H NMR δ 8.07 (br s, 1 H, NH), 7.68–7.07 (m, 5 H, indole C(2) and C(4)–C(7)H), 6.20 (br s, 1 H, NOH), 4.53 (m, 1 H, $HCCH_3$), 3.84 (m, 2 H, OCH_2CH_2Si), 3.18 and 2.94 (AB part of ABX spectrum, 2 H, ^2J = 14.3 Hz, J = 8.1 Hz, J = 6.0 Hz, indole C(3)CH_2), 1.36 (d, 3 H, J = 7.0 Hz, $HCCH_3$), 0.63 (m, 2 H, CH_2Si), 0.0 (s, 9 H, $Si(CH_3)_3$). Anal. Calcd for $C_{17}H_{26}N_2O_3Si$ (MW 334.494): C, 61.04; H, 7.83; N, 8.37. Found: C, 60.83; H, 7.93; N, 8.16.

Ethyl α-(((4,4-Dimethoxybutyl)oxy)amino)-β-(indol-3-yl)propanoate (26) via 19 → 22. A stirring solution of **19** (1568 mg, 4 mmol), 4-bromo-1,1-dimethoxybutane[31] (1575 mg, 8 mmol), and K_2CO_3 (828 mg, 6 mmol) in DMSO (25 mL) was kept at 45 °C for 24 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL), and most of the DMSO was removed by washing with water and 0.1 N HCl. The resulting organic layer was washed with brine and dried with Na_2SO_4. Evaporation of the solvent gave a oil, which was subjected to column chromatography ($CHCl_3$/*n*-hexane, 90/10, v/v) to give 1.37 g (67%) of **22**: oil; R_f 0.58 (solvent system A); EIMS (70 eV) m/z (relative intensity) 508 (M^+, 4), 476 ([M – MeOH]$^+$, 5), 215 ($[C_{13}H_{13}NO_2]^+$, 95), 130 ($[C_9H_8N]^+$, 100); ^{1}H NMR δ 8.07 (br s, 1 H, NH), 7.70–7.10 (m, 5 H, indole C(2) and C(4)–C(7)H), 4.98 (X part of ABX spectrum, 1 H, J = 6.0 Hz, J = 8.9 Hz, $HCCOOEt$), 4.37–3.74 (m, 7 H, OCH_2CH_3, OCH_2CH_2Si, $NOCH_2$, and $HC(OMe)_2$), 3.50–3.30 (AB part of ABX spectrum, 2 H, indole C(3)–CH_2), 3.30 (s, 6 H, 2 OCH_3), 1.65 (m, 4 H, $OCH_2CH_2CH_2CH$), 1.30 (t, 3 H, OCH_2CH_3), 0.78 (m, 2 H, CH_2Si), 0.0 (s, 9 H, $Si(CH_3)_3$). A solution of **22** (1.35 g, 2.65 mmol) and tetrabutylammonium fluoride (5.3 mL, 1 N solution in THF) in THF (25 mL) was stirred for 2 h. The reaction mixture was washed with saturated $NaHCO_3$ and brine and dried with $MgSO_4$. Evaporation of the solvent gave crude **26**, which was subjected to column chromatography ($CHCl_3$) to yield 706 mg (78%) of **26**: oil; R_f 0.33 (solvent system A); UV (MeOH) λ_{max} 224, 274 (sh), 281, 289 nm; CIMS (100 eV) m/z (relative intensity) 365 ([M + 1]$^+$, 33), 332 ([M – MeOH]$^+$, 41), 301 ($[C_{17}H_{21}N_2O_3]^+$, 95), 216 ($[C_{13}H_{14}NO_2]^+$, 94), 130 ($[C_9H_8N]^+$, 100); ^{1}H NMR δ 8.06 (br s, 1 H, NH), 7.67–7.07 (m, 5 H, indole C(2) and C(4)–C(7)H), 5.88 (br s, 1 H, N_bH), 4.35 (br t, 1 H, $HC(OMe)_2$), 4.11 (q, 2 H, OCH_2CH_3), 4.00 (m, 1 H, $HCCOOEt$), 3.69 (br t, 2 H, $NOCH_2$), 3.28 (s, 6 H, 2 OCH_3), 3.13–2.96 (m, 2 H, indole C(3)CH_2), 1.60 (m, 4 H, $OCH_2CH_2CH_2CH$), 1.46 (t, 3 H, OCH_2CH_3).

3-[2-(((4,4-Dimethoxybutyl)oxy)amino)ethyl]indole (27) via 20 → 23. Sodium hydride (41 mg, 1.7 mmol) was added to a cooled (−10 °C) stirred solution of **20** (500 mg, 1.56 mmol) in dry DME (10 mL) in an argon atmosphere. The reaction mixture was allowed to warm to room temperature by which H_2 evolution occurred. The resulting clear solution was added dropwise to a stirred solution of 4-bromo-1,1-dimethoxybutane[31] (368 mg, 1.87 mmol) and NaI (260 mg, 1.75 mmol) in DME (10 mL). After being stirred for 24 h, the reaction mixture was diluted with EtOAc (25 mL), washed with 0.1 N HCl and brine, and then dried with $MgSO_4$. Evaporation of the solvent gave crude **23**, which was added to a solution of Bu_4NF (2 equiv) in THF. After the reaction mixture was stirred for 2 h, the solution was washed with saturated $NaHCO_3$ and brine and dried with $MgSO_4$. Evaporation of the solvent gave crude **27**, which was subjected to column chromatography ($CHCl_3$/MeOH, 99/1, v/v) to yield 306 mg (67%) of **27**: oil; R_f 0.28 (solvent system A); UV (MeOH) λ_{max} 224, 274 (sh), 281, 289 nm; EIMS (70 eV) m/z (relative intensity) 292 (M^+, 7), 260 ([M – MeOH]$^+$, 14), 229 ($[C_{14}H_{17}N_2O]^+$, 16), 216 ($[C_{14}H_{16}N_2O]^+$, 14), 130 ($[C_9H_8N]^+$, 100); ^{1}H NMR δ 8.08 (br s, 1 H, indole NH), 7.70–7.07 (m, 5 H, indole C(2) and C(4)–C(7)H), 5.35 (br s, 1 H, NH), 4.44 (br t, 1 H, $HC(OMe)_2$), 3.78 (br t, 2 H, $NOCH_2$), 3.36 (s, 6 H, 2 OCH_3), 3.36–2.93 (m, 4 H, indole C(3)-CH_2CH_2), 1.71 (m, 4 H, $OCH_2CH_2CH_2CH_3$).

3-[2-(((3-Carbomethoxypropyl)oxy)amino)ethyl]indole (28) via 20 → 24. The same procedure was followed as described for **27**. **20** (640 mg, 2 mmol), methyl 4-bromobutanoate[32] (400 mg, 2.2 mmol), NaH (53 mg, 2.2 mmol), and NaI (300 mg, 2 mmol) gave crude **24**. Deprotection with Bu_4NF (2 equiv) in THF gave after column chromatography ($CHCl_3$/MeOH, 99/1, v/v) 406 mg (74%) of **28**: oil; R_f 0.30 (solvent system A); UV (MeOH) λ_{max} 224, 274 (sh), 281, 289 nm; EIMS (70 eV) m/z (relative intensity) 276 (M^+, 7), 146 ($[C_6H_{12}NO_3]^+$, 26), 144 ($[C_{10}H_{10}N]^+$, 11), 130 ($[C_9H_8N]^+$, 100); ^{1}H NMR δ 8.04 (br s, 1 H, indole NH), 7.64–7.05 (m, 5 H, indole C(2) and C(4)–C(7)H), 5.56 (br s, 1 H, NH), 3.73 (t, 2 H, $NOCH_2$), 3.68 (s, 3 H, OCH_3), 3.31–2.90 (m, 4 H, indole C(3)CH_2CH_2), 2.44 (t, 2 H, CH_2COOMe), 1.91 (m, 2 H, $OCH_2CH_2CH_2$).

3-[2-(((3-Carbomethoxypropyl)oxy)amino)propyl]indole (29) via 21 → 25. The same procedure was followed as described for **27**. **21** (300 mg, 0.9 mmol), methyl 4-bromobutanoate[32] (180 mg, 1 mmol), NaH (24 mg, 1 mmol), and NaI (150 mg, 1 mmol) gave crude **25**. Deprotection with Bu_4NF (2 equiv) in THF gave after column chromatography ($CHCl_3$/MeOH, 99/1, v/v) 167 mg (64%) of **29**: oil; R_f 0.33 (solvent system A); UV (MeOH) λ_{max} 224, 274 (sh), 281, 289 nm; EIMS (70 eV) m/z (relative intensity) 290 (M^+, 14), 223 (34), 160 (165), 131 (85), 130 ($[C_9H_8N]^+$, 100); ^{1}H NMR δ 8.01 (br s, 1 H, indole NH), 7.67–7.02 (m, 5 H, indole C(2) and C(4)–C(7)H), 3.73 (t, 2 H, $NOCH_2$), 3.66 (s, 3 H, OCH_3), 3.34 (m, 1 H, $CHCH_3$), 2.93 and 2.78 (AB part of ABX spectrum, 2 H, ^2J = 14.0 Hz, J = 7.0 Hz, J = 5.8 Hz, indole C(3)CH_2), 2.41 (t, 2 H, CH_2COOMe), 1.89 (m, 2 H, $CH_2CH_2CH_2COOMe$), 1.56 (br s, 1 H, NH), 1.13 (d, 3 H, $CHCH_3$).

Ethyl α-[*N*-(((2-(Trimethylsilyl)ethyl)oxy)carbonyl)-amino]-β-(indol-3-yl)propenoate (30). A solution of **19** (157 mg, 0.4 mmol), 4-bromo-1,1-dimethoxybutane[31] (158 mg, 0.8 mmol), and KOtBu (67 mg, 0.6 mmol) in DMSO (5 mL) was stirred for 24 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and most of the DMSO was removed by washing with water and 0.1 N HCl. The resulting organic layer was washed with brine and dried with Na_2SO_4. Evaporation of the solvent gave an oil, which was subjected to column chromatography ($CHCl_3$) to give 145 mg (97%) of **30**: R_f 0.37 ($CHCl_3$/MeOH, 97/3, v/v); EIMS (70 eV) m/z (relative intensity) 374 (M^+, 18), 287 (9), 258 (8), 155 (15), 73 (100); ^{1}H NMR δ 8.73 (br s, 1 H, indole NH), 7.89 (s, 1 H, indole C(3)CH=C), 7.89–7.71 and 7.50–7.23 (2 m, 5 H, indole C(2)H and C(4)–C(7)H), 6.09 (br s, 1 H, HNTEOC), 4.35 (q, 2 H, OCH_2CH_3), 4.24 (m, 2 H, OCH_2CH_2Si), 1.38 (t, 3 H, OCH_2CH_3), 1.00 (m, 2 H, OCH_2CH_2Si), 0.00 (s, 9 H, $Si(CH_3)_3$). Anal. Calcd for $C_{19}H_{26}N_2O_4Si$ (MW 374.516): C, 60.94; H, 7.00; N, 7.48. Found: C, 60.98; H, 7.01; N, 7.44.

Cyclization of Dimethoxy Acetals under Acid Conditions.

(30) Cohen, A.; Heath-Brown, B. *J. Chem. Soc.* **1965**, 7179.
(31) Orsini, F.; Pelizzoni, F. *Gazz. Chim. Ital.* **1980**, *110*, 499.
(32) Olah, G. A.; Karpeles, R.; Narang, S. C. *Synthesis* **1982**, 963.

***rel*-(6*R*,12b*R*)-6-(Ethoxycarbonyl)-2,3,6,7,12,12b-hexahydro-1*H*-[1,2]oxazino[2′,3′:1,2]pyrido[3,4-*b*]indole (4a) and *rel*-(6*R*,12b*S*)-6-(Ethoxycarbonyl)-2,3,6,7,12,12b-hexahydro-1*H*-[1,2]oxazino[2′,3′:1,2]pyrido[3,4-*b*]indole (4b).** A solution of **26** (650 mg, 1.79 mmol) and TFA (228 mg, 2 mmol) in dichloromethane (20 mL) was stirred for 4 h. The reaction mixture was monitored by TLC (*n*-hexane/EtOAc, 75/25, v/v). The reaction mixture was washed with 0.1 N $NaHCO_3$ and brine and dried with Na_2SO_4. After evaporation of the solvent the crystalline material was subjected to column chromatography (*n*-hexane/EtOAc, 75/25, v/v) to yield 415 mg (77%) of **4a** and 110 mg (20%) of **4b**.

Compound 4a: crystallized from EtOAc/*n*-hexane; mp 156–158 °C; R_f 0.16 (solvent system C); UV (MeOH) λ_{max} 225, 272 (sh), 281, 289 nm; EIMS (70 eV) *m/z* (relative intensity) 300 (M^+, 22), 227 ([M – COOEt]$^+$, 100), 169 ([$C_{11}H_9N_2$]$^+$, 24), 130 ([C_9H_8N]$^+$, 48); ^{1}H NMR (400 MHz) δ 7.77 (br s, 1 H, NH), 7.42 (d, 1 H, C(11)H), 7.32 (d, 1 H, C(8)H), 7.18–7.08 (m, 2 H, C(9) and C(10)H), 4.32 (m, 2 H, OCH_2CH_3), 4.15–3.99 (m, 3 H, C(12b)H, $NOCH_2$), 3.81 (X part of ABX spectrum, 1 H, *J* = 5.1 Hz, *J* = 10.8 Hz, C(6)H), 3.18 and 3.10 (AB part of ABX spectrum, 2 H, ^2J = 15.1 Hz, *J* = 5.1 Hz, *J* = 10.8 Hz, C(7)H_2), 2.20 (m, 1 H, C(1)*H*), 1.96 (m, 2 H, C(1)*H* and C(2)*H*), 1.76 (m, 1 H, C(2)*H*), 1.34 (t, 3 H, OCH_2CH_3). Anal. Calcd for $C_{17}H_{20}N_2O_3$ (MW 300.358): C, 67.98; H, 6.71; N, 9.33. Found: C, 68.21; H, 6.72; N, 9.25. The structure has been secured by single-crystal X-ray crystallography.[26]

Compound 4b: crystallized from EtOAc/*n*-hexane; mp 145–147 °C; R_f 0.21 (solvent system C); UV (MeOH) λ_{max} 225, 272 (sh), 281, 289 nm; CIMS (100 eV) *m/z* (relative intensity) 301 ([M + 1]$^+$, 86), 300 (M^+, 52), 256 (34), 231 (75), 227 ([M – COOEt]$^+$, 100), 216 (60); ^{1}H NMR (400 MHz) δ 7.77 (br s, 1 H, NH), 7.44 (d, 1 H, C(11)H), 7.30 (d, 1 H, C(8)H), 7.16–7.07 (m, 2 H, C(9) and C(10)H), 4.99 (d, 1 H, *J* = 10.4 Hz, C(12b)H), 4.35 (X part of ABX spectrum, 1 H, *J* = 1.25 Hz, *J* = 7.45 Hz, C(6)H), 4.18–4.04 (m, 4 H, OCH_2CH_3, $NOCH_2$), 3.36 (A part of ABX spectrum, 1 H, ^2J = 16.0 Hz, *J* = 7.45 Hz, C(7)H_A), 3.09 (B part of ABX spectrum, 1 H, ^2J = 16.0 Hz, *J* = 1.25 Hz, C(7)H_B), 2.21 (m, 1 H, C(1)H), 1.91 (m, 1 H, C(1)H), 1.74 (m, 2 H, C(2)H_2), 1.23 (t, 3 H, OCH_2CH_3). Anal. Calcd for $C_{17}H_{20}N_2O_3$ (MW 300.358): C, 67.98; H, 6.71; N, 9.33. Found: C, 68.16; H, 6.70; N, 9.23.

2,3,6,7,12,12b-Hexahydro-1*H*-[1,2]oxazino[2′,3′:1,2]pyrido-[3,4-*b*]indole (5). The same procedure was followed as described for **4**. **27** (570 mg, 1.95 mmol) and TFA (250 mg, 2.2 mmol) in dichloromethane (20 mL) gave 410 mg (92%) of **5**: mp 178–180 °C (EtOAc/*n*-hexane); R_f 0.49 (solvent system A); UV (MeOH) λ_{max} 225, 273 (sh), 281, 289 nm; EIMS (70 eV) *m/z* (relative intensity) 228 (M^+, 100), 197 (21), 169 ([$C_{11}H_9N_2$]$^+$, 81), 156 (34), 144 (26), 130 ([C_9H_8N]$^+$, 18); ^{1}H NMR (400 MHz) δ 7.77 (br s, 1 H, NH), 7.46 (d, 1 H, C(11)H), 7.31 (d, 1 H, C(8)H), 7.17–7.08 (m, 2 H, C(9) and C(10)H), 4.06 (br s, 2 H, C(3)H_2), 3.86 (br s, 1 H, C(12b)H), 3.57 (br s, 1 H, C(6)H), 3.11–2.97 (m, 2 H, C(6)H and C(7)H), 2.83 (d, 1 H, C(7)H), 2.18 (d, 1 H, C(1)H), 1.79 (m, 3 H, C(1)H and C(2)H_2). Anal. Calcd for $C_{14}H_{16}N_2O$ (MW 228.295): C, 73.66; H, 7.06; N, 12.27. Found: C, 73.44; H, 7.70; N, 11.94.

Reductive Ring Closure. 2,3,6,7,12,12b-Hexahydro-1*H*-[1,2]oxazino[2′,3′:1,2]pyrido[3,4-*b*]indole (5). DIBAL (1 N, 3 mL) in toluene was added dropwise to a cooled (–70 °C) stirring solution of **28** (390 mg, 1.4 mmol) in dry toluene (75 mL) in an argon atmosphere. After stirring for 1.5 h at –70 °C, TFA (640 mg, 5.6 mmol) in dichloromethane (5 mL) was added carefully. Stirring was continued for 30 min at –70 °C. After completion of the reaction as was monitored by TLC (solvent system A), the reaction mixture was poured into ice–water (100 mL). The organic layer was separated. The neutralized aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$, and filtered, and the solvent was evaporated to give crude **5**. Column chromatography ($CHCl_3$MeOH, 99/1, v/v) gave 241 mg (76%) of **5** (for spectroscopic data, vide supra).

***rel*-(6*R*,12b*R*)-6-Methyl-2,3,6,7,12,12b-hexahydro-1*H*-[1,2]oxazino[2′,3′:1,2]pyrido[3,4-*b*]indole (6a) and *rel*-(6*R*,12b*S*)-6-Methyl-2,3,6,7,12,12b-hexahydro-1*H*-[1,2]oxazino[2′,3′:1,2]pyrido[3,4-*b*]indole (6b).** The same procedure was followed as described for **5**. From **29** (165 mg, 0.57 mmol) and DIBAL (2 equiv) was obtained a mixture of two diastereomers, which were separated by column chromatography ($CHCl_3$) to yield 93 mg (68%) of **6a** and 13 mg (9%) of **6b**.

Compound 6a: mp 194–196 °C (EtOAc/*n*-hexane); R_f 0.34 (solvent system D); UV (MeOH) λ_{max} 224, 273 (sh), 281, 289 nm; EIMS (70 eV) *m/z* (relative intensity) 242 (M^+, 100), 227 ([M – CH_3]$^+$, 10), 200 (15), 183 ([$C_{12}H_{11}N_2$]$^+$, 53), 169 ([$C_{11}H_9N_2$]$^+$, 59), 168 ([$C_{11}H_8N_2$]$^+$, 45), 156 (28); ^{1}H NMR (400 MHz) δ 7.72 (br s, 1 H, NH), 7.44 (d, 1 H, *J* = 7.6 Hz, C(11)H), 7.29 (d, 1 H, *J* = 7.9 Hz, C(8)H), 7.16–7.07 (m, 2 H, C(9)–C(10)H), 4.12–4.00 (m, 2 H, $NOCH_2$), 3.89 (d, 1 H, *J* = 9.7 Hz, C(12b)H), 3.14–3.06 (m, 1 H, C(6)H), 2.88 and 2.67 (AB part of a ABX spectrum, 2 H, ^2J = 15.6 Hz, *J* = 4.5 Hz, *J* = 10.7 Hz, C(7)H_2), 2.14 (d, 1 H, *J* = 9.7 Hz, C(1)H), 1.87–1.71 (m, 3 H, C(1)H and C(2)H_2), 1.39 (d, 3 H, *J* = 6.2 Hz, CH_3); ^{13}C NMR (400 MHz) δ 136.33 (C(11a)), 132.92 (C(12a)), 126.70 (C(7b)), 121.51 (C(10)), 119.53 (C(9)), 118.18 (C(8)), 110.82 (C(11)), 107.54 (C(7a)), 70.11 (C(3)), 62.35 (C(6)), 57.95 (C(12b)), 29.82 (C(1)), 28.10 (C(2)), 25.15 (C(7)), 19.46 (CH_3). Anal. Calcd for $C_{15}H_{18}N_2O$ (MW 242.322): C, 74.35; H, 7.49; N, 11.56. Found: C, 74.34; H, 7.37; N, 11.47.

Compound 6b: mp 173–176 °C (EtOAc/*n*-hexane); R_f 0.25 (solvent system D); UV (MeOH) λ_{max} 224, 273 (sh), 281, 289 nm; EIMS (70 eV) *m/z* (relative intensity) 242 (M^+, 100), 227 ([M – CH_3]$^+$, 14), 200 (18), 183 ([$C_{12}H_{11}N_2$]$^+$, 56), 169 ([$C_{11}H_9N_2$]$^+$, 72), 168 ([$C_{11}H_8N_2$]$^+$, 51), 156 (36); ^{1}H NMR (400 MHz) δ 7.76 (br s, 1 H, NH), 7.46 (d, 1 H, *J* = 7.6 Hz, C(11)H), 7.32 (d, 1 H, *J* = 7.9 Hz, C(8)H), 7.17–7.08 (m, 2 H, C(9)–C(10)H), 4.03 (br s, 2 H, $NOCH_2$), 3.81 (m, 1 H, C(12b)H), 3.24–3.18 (m, 1 H, C(6)H), 2.57 (br d, 1 H, C(7)H), 2.22–2.18 (m, 1 H, C(7)H), 1.89–1.67 (m, 4 H, C(1)H_2 and C(2)H_2), 1.16 (d, 3 H, *J* = 6.6 Hz, CH_3). Anal. Calcd for $C_{15}H_{18}N_2O$ (MW 242.322): C, 74.35; H, 7.49; N, 11.56. Found: C, 74.16; H, 7.41; N, 11.36.

***cis*-1-(3-Hydroxypropyl)-3-(ethoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (34a).** Activated zinc dust (100 mg) was added to a stirred solution of **4a** (90 mg, 0.3 mmol) in glacial acetic acid (20 mL). Subsequently the reaction mixture was kept at 80 °C and monitored by TLC (solvent system B). The reaction was completed after 5 h. The reaction mixture was filtered, and the filtrate was concentrated to dryness. The residue was dissolved in dichloromethane, and this solution was washed successively with saturated $NaHCO_3$, water, and brine and then dried with Na_2SO_4. The solvent was evaporated, and the residue was subjected to column chromatography ($CHCl_3$/MeOH, 99/1, v/v) to yield 77 mg (85%) of **34a**: R_f 0.20 (solvent system B); CIMS (100 eV) *m/z* (relative intensity) 303 ([M + 1]$^+$, 74), 302 (M^+, 41), 286 (25), 243 ([$C_{14}H_{15}N_2O_2$]$^+$, 100), 233 (40), 202 (37), 169 ([$C_{11}H_9N_2$]$^+$, 21); ^{1}H NMR δ 8.57 (br s, 1 H, N(9)H), 7.52–7.05 (m, 4 H, C(5)–C(8)H), 4.24 (q, 2 H, OCH_2CH_3), 4.24–4.13 (m, 1 H, C(1)H), 3.74 (X part of ABX spectrum, 1 H, C(3)H), 3.60 (t, 2 H, $CH_2CH_2CH_2OH$), 3.27 (s, 2 H, N(2)H and OH), 3.08 and 2.78 (AB part of ABX spectrum, 2 H, ^2J = 15.8 Hz, *J* = 12 Hz, *J* = 4.1 Hz, C(4)H_2), 2.12–1.58 (m, 4 H, $CH_2CH_2CH_2OH$), 1.33 (t, 3 H, OCH_2CH_3); ^{13}C NMR (400 MHz) δ 172.85 (COOEt), 136.13 (C(8a)), 134.74 (C(9a)), 127.08 (C(4b)), 121.74 (C(7)), 119.49 (C(6)), 117.90 (C(5)), 110.91 (C(8)), 108.18 (C(4a)), 62.23 (CH_2OH), 61.26 (OCH_2CH_3), 56.38 (C(3)), 52.60 (C(1)), 32.26 (C(1)CH_2), 28.72 ($CH_2CH_2CH_2OH$), 25.62 (C(4)), 14.18 (OCH_2CH_3).

***trans*-1-(3-Hydroxypropyl)-3-(ethoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (34b).** The same procedure was followed as described for **34a**. From **4b** (90 mg, 0.3 mmol) was obtained 81 mg (89%) of **34b**: R_f 0.20 (solvent system B); CIMS (100 eV) *m/z* (relative intensity) 303 ([M + 1]$^+$, 100), 302 (M^+, 89), 286 (21), 243 ([$C_{14}H_{15}N_2O_2$]$^+$, 79), 233 (42), 202 (38), 169 ([$C_{11}H_9N_2$]$^+$, 26); ^{1}H NMR δ 8.28 (br s, 1 H, N(9)H), 7.54–7.04 (m, 4 H, C(5)–C(8)H), 4.31–4.09 (m, 1 H, C(1)H), 4.21 (q, 2 H, OCH_2CH_3), 3.94 (X part of ABX spectrum, 1 H, C(3)H), 3.68 (t, 2 H, $CH_2CH_2CH_2OH$), 3.29 (s, 2 H, N(2)H and OH), 3.12 and 2.92 (AB part of ABX spectrum, 2 H, ^2J = 15.0 Hz, *J* = 5.4 Hz, *J* = 7.6 Hz, C(4)H_2), 2.06–1.62 (m, 4 H, $CH_2CH_2CH_2OH$), 1.28 (t, 3 H, OCH_2CH_3); ^{13}C NMR (400 MHz) δ 173.35 (COOEt), 135.96 (C(8a)), 135.03 (C(9a)), 126.77 (C(4b)), 121.54 (C(7)), 119.15 (C(6)), 117.87 (C(5)), 110.84 (C(8)), 106.52 (C(4a)), 62.23 (CH_2OH), 61.13 (OCH_2CH_3), 51.90 (C(3)), 50.30 (C(1)), 33.16 (C(1)CH_2), 29.67 ($CH_2CH_2CH_2OH$), 24.93 (C(4)), 14.04 (OCH_2CH_3).

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Registry No. DL-1, 99708-04-0; **2**, 4761-34-6; (±)-**3**, 46276-79-3;

(±)-**4a**, 125108-97-6; (±)-**46**, 125109-01-5; (±)-**5**, 125108-98-7; (±)-**6a**, 125108-99-8; (±)-**6b**, 125109-00-4; **14**, 125109-04-8; **15a**, 16686-11-6; (±)-**15b**, 125109-03-7; **16a**, 125109-05-9; (±)-**16b**, 125109-02-6; **17**, 125109-06-0; DL-**18**, 125137-41-9; DL-**19**, 125109-07-1; **20**, 125109-08-2; (±)-**21**, 125109-09-3; DL-**22**, 125109-10-6; **23**, 125109-11-7; **24**, 125137-86-2; (±)-**25**, 125109-12-8; DL-**26**, 125109-13-9; **27**, 125109-14-0; **28**, 125109-15-1; (±)-**29**, 125109-16-2; **30**, 125137-87-3; (±)-**34a**, 125109-18-4; (±)-**34b**, 125109-17-3; $Br(CH_2)_3COOMe$, 4897-84-1; $Br(CH_2)_3CH(OMe)_2$, 24157-02-6.

Benzotriazole-Assisted Synthesis of Monoacyl Aminals and Their Peptide Derivatives

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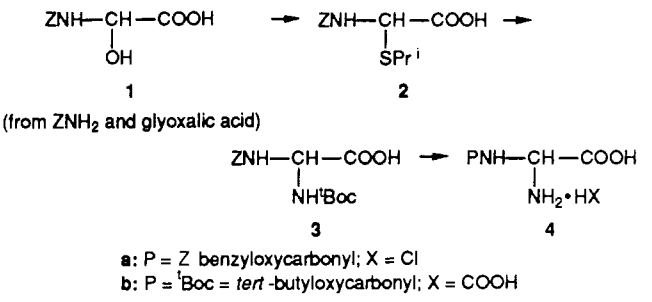
Adducts 8–11, derived from benzotriazole (**7**), an aldehyde (**6**), and an amide (**5**), react with ammonia to give various monoacylated aminals (**12–14**) and "*gem*-peptide"[2a] derivatives (**15**) in a novel, convenient route, useful for peptide analogue syntheses and studies.

Reversing one or more of the amide groups (i.e. CHRCONH to CHRNHCO) of a linear peptide gives a so-called "partially modified retro isomer" and represents an important strategy in peptide analogue research.[1a,2] The modified sequence requires both a malonic unit and a (much less easily available) α,α-diamino moiety. Such α,α-diamino units have been synthesized by Curtius-[1,3,5] or Hoffmann-type[2,3,4] rearrangements of protected amino acid derivatives. The appropriate "*gem*-peptides" are usually also synthesized by one of these degradations of a protected peptide amide,[2a-c,4] and only in a few cases have monoprotected aminals ($PNHCH(R)NH_2$) been used as (or synthesized for) building units for their preparation.[1a-b,5,6] In all cases, these monoprotected aminals have been synthesized via unsymmetrically bis-protected derivatives. Recently, α-carboxyl-substituted compounds were synthesized by Bock and co-workers[6] from α-hydroxy-*N*-(benzyloxycarbonyl)glycine (**1**) in three-step sequences as shown in Scheme I for **4a** and **4b**. These α-carboxyl-substituted aminals **4** are *gem*-analogues of aminomalonic acid derivatives, which are of only minor importance in peptide sequences.

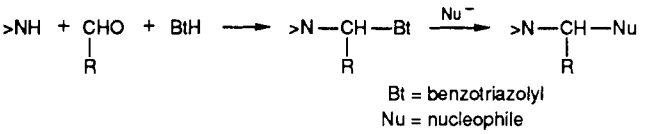
Earlier we reported[7] a convenient synthesis of compounds of type >NCH(R)X mediated by benzotriazole via the general route of Scheme II. More recently, this methodology with glyoxylic acid as the oxo component (R = COOH) and ammonia as the nucleophile allowed a convenient synthesis of monoacyl-α-aminoglycines of type **4**.[8]

We have now found that in adducts 8–11 (Scheme III), formed from various amides (including protected amino acid amides for compounds **11**) and aldehydes, the benzotriazole moiety can be replaced by NH_3 providing (i) a convenient and versatile method for the preparation of various simple α-substituted monoacyl aminals **12–14**, and (ii) a novel synthetic route to "*gem*-dipeptides" **15**.[2a]

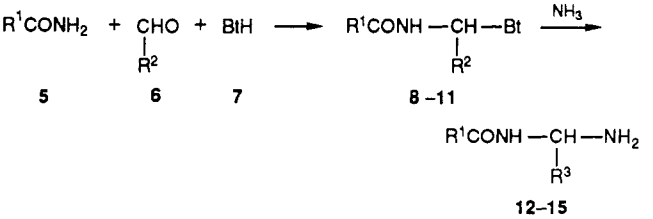
Scheme I



Scheme II



Scheme III[a]



[a] For designating of R^1, R^2, and R^3 see Tables I–IV (all can be alkyl or aryl, additionally R^1 can be OR or $RCONHCH_2$; R^2 can be CO_2H or CO_2R; R^3 can be CO_2H or $CONH_2$).

(1) (a) Goodman, M.; Chorev, M. *Acc. Chem. Res.* **1979**, *12*, 1. (b) DeBons, F. E.; Loudon, G. M. *J. Org. Chem.* **1980**, *45*, 1703. (c) Loudon, G. M.; Almond, M. R.; Jacob, J. N. *J. Am. Chem. Soc.* **1981**, *103*, 4508.

(2) (a) Chorev, M.; Shavitz, R.; Goodman, M.; Minick, S.; Guillemin, *Science (Washington D.C.)* **1979**, *204*, 1210. In the paper (Table I) the authors "suggest the following prefixes: g- for *gem*-diamino alkyl corresponding to the amino acid residue denoted", (e.g. g-Phe for -NH-CH-(Bzl)-NH- fragment). Correspondingly, we apply the "*gem*-peptide" terminology for peptides containing such "g-" units in the terminal position. (b) Verland, M. S.; Fuller, W. D.; Goodman, M. Eur. Pat. *Appl.*, EP (128,654, 1984; *Chem. Abstr.* **1984**, *102*, 185492c. (c) Fuller, W. D.; Goodman, M.; Verlander, M. S. *J. Am. Chem. Soc.* **1985**, *107*, 5821.

(3) Moutevelis-Minakakis, P.; Photaki, I. *J. Chem. Soc., Perkin Trans. 1* 1985, 2277.

(4) Pallai, P.; Goodman, M. *J. Chem. Soc., Chem. Commun.* **1982**, 280.

(5) Chorev, M.; Willson, C. G.; Goodman, M. *J. Am. Chem. Soc.* **1977**, *99*, 8075.

(6) Bock, M. G.; DiPardo, R. M.; Freidinger, R. M. *J. Org. Chem.* **1986**, *51*, 3718.

(7) (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 805. (b) Katritzky, A. R.; Yannakopoulou, K.,; Lue, P.; Rasala, D.; Urogdi, L. *J. Chem. Soc., Perkin Trans. 1* **1989**, 225. (c) Katritzky, A. R.; Drewniak, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2339. (d) Katritzky, A. R.; Drewniak, M. *Tetrahedron Lett.* **1988**, *29*, 1755. (e) Katritzky, A. R.; Urogdi, L.; Mayence, A. *Synthesis* **1989**, *323*.

(8) Katritzky, A. R.; Urogdi, L.; Mayence, A. *J. Chem. Soc., Chem. Commun.* **1989**, 337.

0022-3263/90/1955-2206$02.50/0