141091-51-2; (Z)-4f, 141091-50-1; 5, 93303-13-0; 7, 141091-41-0; 10, 141091-52-3; 11, 141091-53-4; 12, 141091-54-5; (E)-17, 141091-56-7; (Z)-17, 141091-55-6; 18, 141091-57-8; (E)-19, 141091-58-9; (Z)-19, 141091-59-0; 20, 141091-60-3; $PhPCl_2$, 644-97-3.

Supplementary Material Available: X-ray data for (E)-2f (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Stereoselective Synthesis of Verruculogen TR-2 Featuring the Mild Formation of a Dihydro-β-carboline as an Intermediate

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Reaction of indolyldiketopiperazine **5** with 2,3,4,5,6,6-hexachlorocyclohexadien-1-one (**25**) in dichloromethane/methanol provided the methoxyindolenine **29**, which in the presence of TFA rearranged to the dehydrodiketopiperazine **6**. This compound was elaborated to verruculogen TR-2 (**2**) employing osmium tetroxide oxidation.

Increased research on mycotoxins has led to the discovery of fungal metabolites that induce neurological manifestations in vertebrate animals that include sustained or intermittent tremors.[1-13] Fungi capable of producing tremorgic metabolites can be found on a variety of important agricultural commodities. The fungal tremorgens can be classified into six groups based on their chemical relationship.[9] The compounds of one of these groups—the fumitremorgin–verruculogen group—are biochemically derived from tryptophan, proline, and one or more mevalonic acid moieties.[6,13] Seven members of this group are at the moment isolated and identified, including in most cases their stereochemistry; two members are given in Chart I. In efforts to determine the mode of action of fungal tremorgens, it has become apparent that they provide useful tools in the study of central nervous system functions. In general, they interfere in mechanisms responsible for the release of CNS neurotransmitters.[14-19] Although particular molecular features responsible for the 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.[17]

We became interested in the fumitremorgins as attractive synthetic targets not only because of their biological activity but also because of their structure.

Recently, we reported[20,21] the total synthesis of fumitremorgin C (**1**) and three of its epimers. Our approach was based on the reaction sequence **3** → **4** → **5** → **1** (Scheme I).

The target of this study is the more functionalized verruculogen TR-2 (**2**),[3,6,8,9,11] a mycotoxin initially isolated from *Aspergillus fumigatus*. Recently, it was suggested[22] that the biogenetic relationship between tryptophan on one hand and α-substituted and α,β-dehydrotryptophan derivatives on the other hand might proceed via *N*-hydroxytryptophan derivatives. Moreover, it was demonstrated[22] that *N*-hydroxytryptophan derivatives deserve attention as synthons in the preparation of natural products having α-functionalized and α,β-dehydrotryptophan as structural elements.

On the basis of these considerations we wondered whether the *N*-hydroxytryptophan derivative **4** could be

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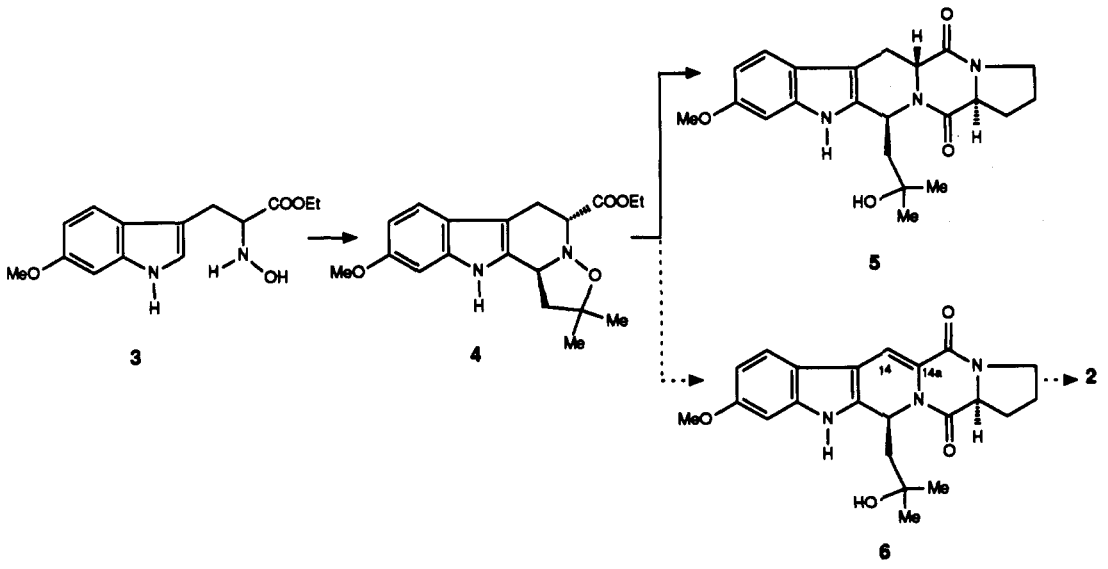
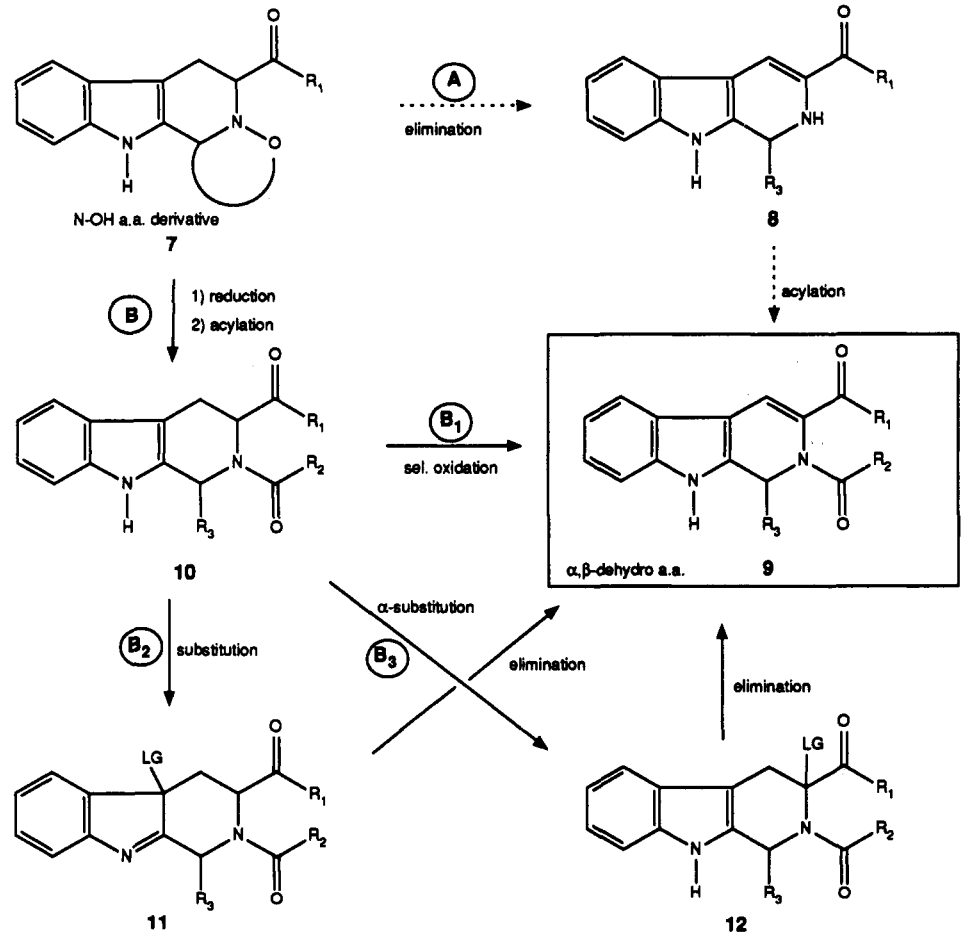
Scheme I



Scheme II



converted into the α,β-dehydrotryptophan moiety present in **6**. We reasoned that this conversion might well be an avenue to the title compound **2**, as hydroxylation of α,β-dehydrotryptophan derivatives into the corresponding cis-diols has been reported before by others.[23-26]

Strategy

So the problem we faced here was the conversion of the tetrahydro-β-carboline **4** into the dihydro-β-carboline **6**. This is not a trivial reaction, as 1,2-dihydro-β-carbolines are relatively unstable and prone to undergo oxidative

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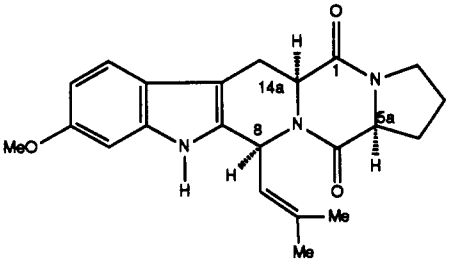
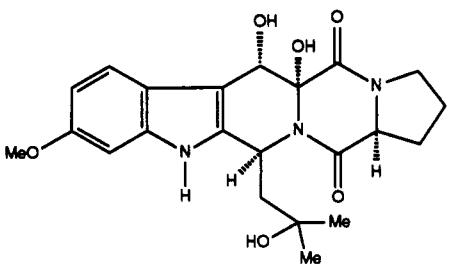
Chart I



1

Fumitremorgin C



2

Verruculogen TR-2

aromatization to give β-carbolines.[27] We reasoned that two, fundamentally different approaches might yield this conversion (Scheme II). These approaches were explored with a more readily available analogue lacking the methoxy substituent in the indole moiety.

Initially, we studied the base-catalyzed elimination of the alkoxy group in N(2)-alkoxy derivatives (e.g., 7) to give—after isomerization of the double bond—the dihydro β-carboline 8 (route A). Acylation of the amine function might then give the desired dihydro-β-carboline 9.

Our second approach (route B) deviated from route A in that first the N–O bond was cleaved by reduction to yield a ring-opened amino alcohol of which the amino group was acylated to provide 10. Several methods were studied for the formal dehydrogenation of the latter to give 9.

First, selective dehydrogenation of 10 with the oxidizing reagent DDQ was explored (route B_1). A second method (route B_2) features the introduction of a leaving group at the 3-position of the indole moiety providing the indolenine 11, which—after elimination of the leaving group and rearrangement—should give the dihydro compound 9. A third method (route B_3) has been explored successfully by Boyd et al.,[26] who introduced the benzeneseleninic function at the β-carboline C(3) position to yield 12 (LG = SeOPh) and subsequently eliminated this function to give 9.

The most suitable approach to 9 was found to be route B_2, which was subsequently successfully applied in the total synthesis of 2.[28]

Results

Route A. It has been reported[20] that treatment of the isoxazolidine tetrahydro-β-carboline 13 with base (NaH or KOtBu in dimethoxyethane) gave the aromatized β-carboline 17 instead of the desired dihydro compound 8 (Scheme III). In a related reaction Harrison[29] has shown that this aromatization can be prevented by acylation of the NH function. We therefore set out to prepare the proline amides 19 and 20 anticipating that the proline ester moiety might capture intramolecularly the NH formed in the dihydro-β-carboline moiety to give the desmethoxy analogue of 6. Coupling of the isoxazolidine fragment 13 with L-proline methyl ester was achieved as follows. The acid chloride 16 was prepared from 13 in three steps. The first one was transesterification of 13 to give the benzyl ester 14 (yield 92%) by a mild method[30] using titanium(IV) isopropoxide in an excess of benzyl alcohol. Selective removal of the benzyl group was achieved by hydrogenation in the presence of catalytic Pd/C to give 15 quantitatively.[31] The carboxylic acid was converted into the acid chloride 16 by oxalyl chloride in dichloromethane in the presence of a catalytic amount of DMF.

In order to prevent epimerization of the acid chloride 16 or its conversion into a ketene during the coupling procedure a solution of L-proline methyl ester 18 and triethylamine were added together and dropwise to a cooled (−20 °C) solution of 16. This procedure provided (76% yield) the amides 19 and 20 in a ratio of 1:1, which were easily separated by column chromatography. In order to assign the absolute stereochemistry of 19 and 20 these compounds were converted into the known pentacycles 21 and 22.[32]

Unfortunately, our attempts to convert 19 and 20 to an α,β-dihydro derivative (e.g., 8) failed.[33]

Route B_1. Attempted selective dehydrogenation of the pentacycles 21 and 22 with DDQ failed to give the corresponding 14,14a-dehydro derivative, i.e., the desmethoxy analogue of 6. Reaction of 21 or 22 with DDQ (1 equiv) in dichloromethane gave 50% starting material and 50% of 23 instead (Scheme III). Subsequent addition of a second equivalent DDQ to the reaction mixture gave quantitatively 23. The desired desmethoxy analogue of 6 is probably an intermediate in this reaction. Attempts to prevent the overoxidation (i.e., 6 → 23) by temperature control or by the use of other solvents or a milder oxidation reagent—such as *p*-chloranil—failed.

Route B_2. Electrophiles are easily incorporated at the 3-position of the indole unit of simple tetrahydro-β-carbolines.[34] Therefore, for our initial investigations we selected the sulfonamide derivative 24[21] as a model compound. An attractive Cl^+-donor appeared to us to be 2,3,4,5,6,6-hexachlorocyclohexadien-1-one (25, C_6Cl_6O).[35] This expectation was based on the reported selectivity and

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(31) The isoxazolidine moiety of 14 and 15 is remarkably stable under these catalytic hydrogenation conditions; see ref 32.

(32) Reductive ring opening of the isoxazolidine moiety of 19 and 20 by zinc dust in acetic acid at 50 °C gave—after workup and subsequent addition of the base DBU in chloroform—cyclization to the pentacycles 21 and 22 in 87% and 83% yield, respectively. Comparison of the ^1H NMR data of 21 with those published earlier (ref 20) allowed assignment of the structures as indicated in Scheme III.

(33) Treatment of 19 with several bases (MeOH/NaOMe, KOtBu/MeOH, NaH/DME, DBU/THF, pyridine, KOtBu/CH_2Cl_2) or acids (H_2SO_4/MeOH, HCl(g)/dioxane, $TiCl_4/CH_2Cl_2$, TMSI/CH_3CN) gave only untractable reaction mixtures or starting material. This failure blocked the, in our opinion, most elegant approach for the conversion 4 → 6.

(34) With *tert*-butyl hypochlorite: (a) Maindreville, M. D.; Levy, J.; Tillequin, F.; Koch, M. *J. Nat. Prod.* **1983**, *46*, 310. (b) Hershenson, F. M.; Swenton, L.; Prodan, K. A. *Tetrahedron Lett.* **1980**, *21*, 2617. (c) Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705. (d) Owellen, R. J. *J. Org. Chem.* **1974**, *39*, 69. By halogenation: (e) Gassman, P. G.; Campbell, G. A.; Mehta, G. *Tetrahedron* **1972**, *28*, 2749. (f) Gross, E. A.; Vice, S. F.; Dmitrienko, G. I. *Can. J. Chem.* **1981**, *59*, 635.

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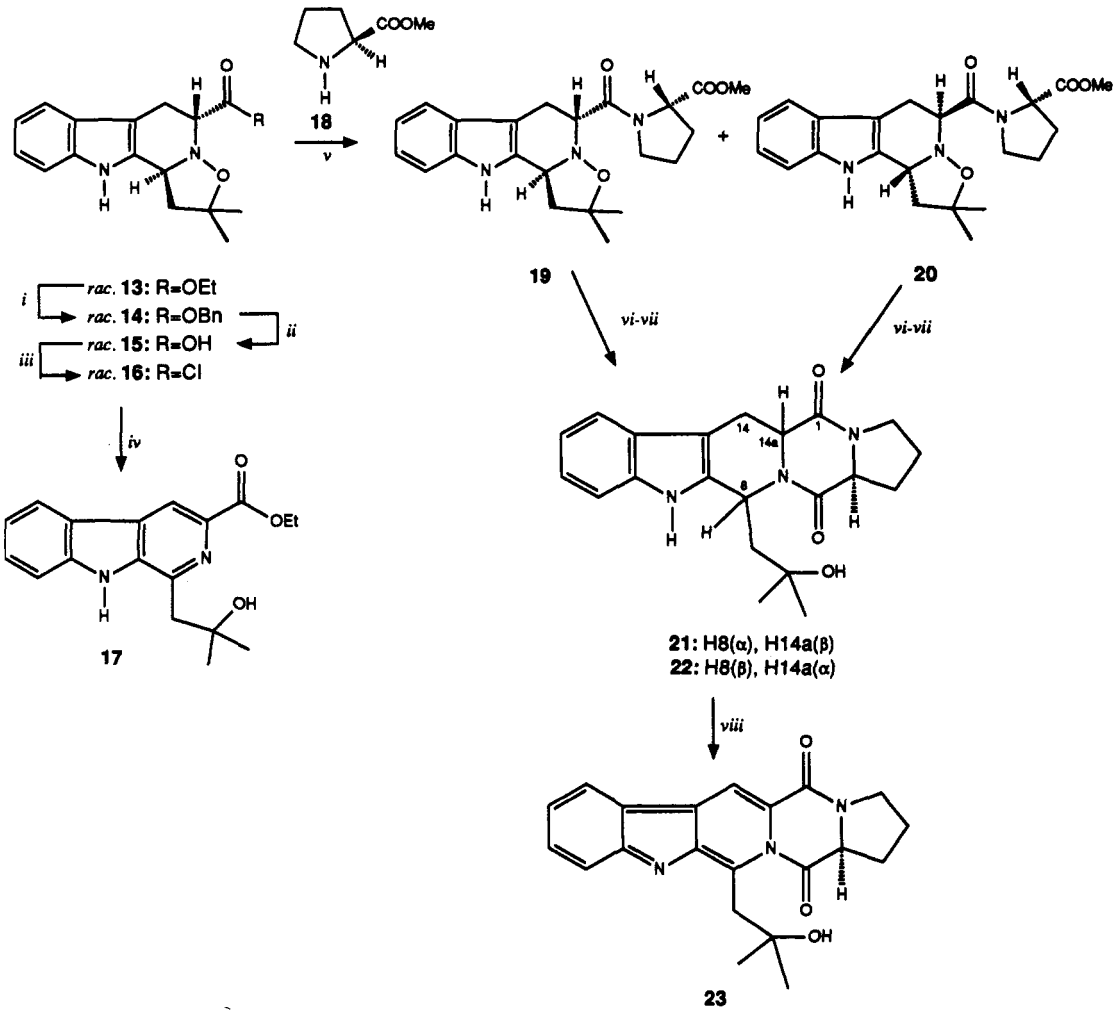
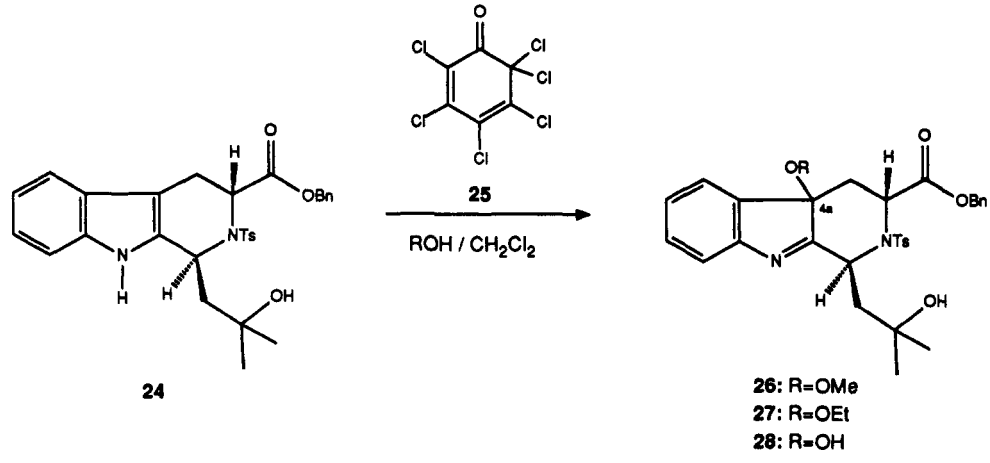
Scheme III[a]



[a] Key: (i) $Ti(OiC_3H_7)_4/BnOH$; (ii) H_2, Pd/C; (iii) $(COCl)_2$, DMF/CH_2Cl_2; (iv) NaH/DME; (v) Et_3N/CH_2Cl_2; (vi) Zn/HOAc, 60 °C; (vii) DBU/CH_2Cl_2; (viii) DDQ/CH_2Cl_2.

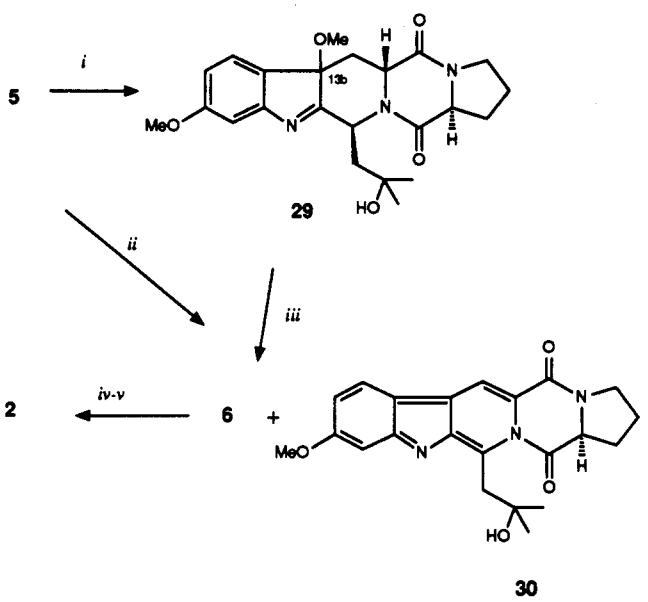
Scheme IV



mildness of this reagent which is due to its ability to form a donor–acceptor complex as well as a hydrogen bond which leads to a well defined "recognition" between this reagent and the substrate (vide infra). So far this reagent has not been studied in substitution reactions at an indole nucleus.

Suprisingly, we found that reaction of tetrahydro-β-carboline **24** in dichloromethane/methanol (1/1, v/v) with C_6Cl_6O (**25**) at room temperature gave not the expected 3-chloroindolenine but the 3-methoxyindolenine **26** in quantitative yield (Scheme IV). Reaction of tetrahydro-β-carboline **24** with C_6Cl_6O under identical conditions but now in a dichloromethane/ethanol or a dimethoxyethane/water mixture gave the 3-ethoxyindolenine **27** (80%) and the 3-hydroxyindolenine **28** (78%), respectively. Whereas this reaction proceeded with complete stereoselectivity we did not establish—for obvious reasons—the stereochemistry at C(4a) of the alkoxy indolenines **26–28**.

Scheme V[a]



[a] Key: (i) CH_2Cl_2/MeOH/C_6Cl_6O; (ii) EtOH/C_6Cl_6O; (iii) CH_2Cl_2/TFA; (iv) OsO_4/pyridine; (v) $NaHSO_3$.

Although examples of the introduction of a nucleophile at this position are extremely rare,[36] we could not escape the conclusion that the above-described conditions cause incorporation of a nucleophile at C(3) of the indole nucleus.[37]

Application of this methodology to the pentacycle **5**[20]—a precursor of one of the epimers of fumitremorgin C (**1**)—gave the 3-methoxyindolenine **29** (73%) with complete stereoselectivity (Scheme V). Subsequently, a solution of **29** in dichloromethane containing a catalytic amount of trifluoroacetic acid was stirred at room temperature to give the dehydrodipeptide **6** (46%), together with the aromatized product **30** (6%) and recovered indolenine **29** (43%). This mixture was separated easily by column chromatography whereupon the starting material **29** was treated again with TFA. By this procedure the overall yield of **6** could be raised to 80%.[38]

Finally, osmylation of key intermediate **6** using OsO_4 in pyridine, followed by a reductive workup with sodium bisulfite,[26] gave verruculogen TR-2 (**2**) in 22% yield (Scheme V). The spectroscopical data of **2** are identical[8] to those of the natural verruculogen TR-2.[39]

Conclusion

This work constitutes the first total synthesis of verruculogen TR-2 and provides further proof of its structure. Reaction of pentacycle **5** with 2,3,4,5,6,6-hexachlorocyclohexadien-1-one (**25**) in dichloromethane/methanol provided the methoxyindolenine **29**, which in the presence of TFA rearranged to the dehydrodipeptide **6**. This compound was elaborated to **2** employing osmium tetroxide followed by reductive workup.

Experimental Section

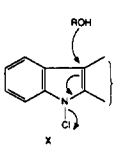
Melting points were taken on a Koefler hot stage (Leitz-Wetzlar) and are uncorrected. Ultraviolet spectra were measured with a Perkin-Elmer spectrophotometer, Model λ 5. Proton magnetic resonance spectra were measured on a Bruker WH-90 or on a Bruker AM 200 spectrometer. Chemical shifts are reported as δ values (parts per million) relative to tetramethylsilane as an internal standard. 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.[40] For column chromatography Merk silica gel 60H was used.

2,2-Dimethyl-5-(benzoxycarbonyl)-4,5,6,11b-tetrahydroisoxazolidino[2,3-*a*]-β-carboline (14). A solution of **13**[19] (3.7 g, 11.8 mmol), benzyl alcohol (20 mL), and 0.3 equiv of titanium(IV) isopropoxide (Aldrich Chemical Co., 1.0 g, 3.5 mmol) in dioxane (30 mL) was kept for 18 h at 100 °C and in an argon atmosphere. The reaction was monitored by TLC ($CHCl_3$/MeOH (99/1), v/v). After dilution with CH_2Cl_2 (100 mL) the mixture was washed with 1 N HCl. The turbid, organic layer was filtered, and the filtrate was washed with brine and dried with Na_2SO_4; subsequently, the solvent was evaporated. Crystallization of the residue from $CHCl_3$/*n*-hexane gave 2.5 g (57%) of **14**. Removal of the solvent and the remaining benzyl alcohol by vacuum distillation and crystallization of the resulting residue gave an additional 1.15 g (26%) of product: total yield 83%; mp 210–212 °C ($CHCl_3$); R_f 0.64 ($CHCl_3$/MeOH (93/7), v/v); CIMS (100 eV) *m/z* (relative intensity) 377 ($[M + 1]^+$, 100), 241 ($[C_{15}H_{17}N_2O]^+$, 91), 91 ($[C_7H_7]^+$, 72); exact mass for $C_{23}H_{25}N_2O_3$ calcd 377.187, found 377.189; ^1H NMR ($CDCl_3$) δ 7.95 (br s, 1 H, NH), 7.60–7.18 (m, 9 H, C(7)-C(10)H and Ph), 5.45 and 5.30 (AB spectrum, 2 H, ^2J = 14 Hz, OCH_2), 5.03 (X part of ABX spectrum, 1 H, C(11b)H, 4.28 (t, 1 H, J = 6.6 Hz, C(5)H), 3.21 (d, 2 H, J = 6.6 Hz, C(6)H_2), 2.60 and 2.38 (AB part of ABX spectrum, 2 H, ^2J = 21.3, 6.3, 9.9 Hz, C(1)H_2), 1.53 and 1.50 (2×s, 6 H, 2×CH_3). Anal. Calcd for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44. Found: C, 73.03; H, 6.41; N, 7.32.

Compounds 19 and 20. Hydrogenation of **14** (1.28g, 3.4 mmol) in EtOH/CH_2Cl_2 (95/5, v/v) (200 mL) using catalytic Pd–C at room temperature and atmospheric pressure gave 996 mg (100%) of **15** as a crystalline material. As a solid and kept under argon it was stable: R_f = 0.12 ($CHCl_3$/MeOH (93/7), v/v); CIMS (100 eV) *m/z* 287 ($[M + 1]^+$, 2), 285 ($[M - 1]^+$, 4), 269 ($[M - OH]^+$, 3), 241 ($[M - COOH]^+$, 20), 183 ($[C_{12}H_{11}N_2]^+$, 24), 169 ($[C_{11}H_9N_2]^+$, 19), 59 (100); ^1H NMR (DMSO-d_6) δ 10.97 (br s, 1 H, NH),

(36) Awang, D. V. C.; Vincent, A. *Can. J. Chem.* **1989**, *58*, 1589 and references cited therein.

(37) These findings can be rationalized as follows. Initially, **25** reacts with **24** to form a donor–acceptor complex, directed by a H-bridge between the indole NH proton and the oxygen of **25**. This is followed by the formation of pentachlorophenol and the *N*-chloro-substituted intermediate **X**,



X

which is now prone to undergo a nucleophilic attack at the indole C-(3)-position. For the reaction of 2,3-disubstituted indoles to 3-alkoxyindolenines, the involvement of a reactive N-substituted intermediate has been proposed earlier (see ref 36). The completeness of the observed stereoselectivity of this reaction sequence renders a S_N1 type reaction less likely. It is also unlikely that first a 3-chloroindolenine is generated which subsequently undergoes nucleophilic substitution of the chlorine by ROH as neutral reaction conditions are employed, whereas strongly alkaline (see ref 34d) or acidic (see ref 34f) conditions have been reported to be required for this conversion. Whereas C_6Cl_6O has been proposed (ref 35) to act as a Cl^+ donor, an alternative mode of action of this reagent has been suggested by a reviewer. Attack by the β-indole position at the oxygen of the carbonyl group of C_6Cl_6O (**25**) might result in a pentachlorophenol ether and a chloride anion. The next step should then be substitution of the pentachlorophenol ether.

(38) Treatment of **5** with C_6Cl_6O in ethanol (neat) at room temperature gave directly the dehydrogenated product **6** in 37% yield. However, formation of the side product **30** in up to 23% yield made this route less attractive.

(39) Recently, the synthesis of desmethoxy TR-2 has been reported (ref 26). However, we are puzzled about the ^1H NMR spectrum of the compound reported in that study. It differs substantially from the spectrum we observed for **2**. It is unlikely that this difference can be attributed to the absence of the indole methoxy group in the compound the authors prepared for the following reason. The ^1H NMR spectrum of **6** resembles the spectrum of the corresponding desmethoxy compound prepared by Boyd and Thompson. The discrepancy occurs in the last step, i.e., the osmylation. Moreover, we observed with analogs of **1** (refs 20 and 21) that the 11-methoxy group exerts no long-range effects in the ^1H NMR spectra.

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7.50–6.88 (m, 4 H, C(7)–C(10)H), 4.79 (X part of ABX spectrum, 1 H, C(11b)H), 4.30 (X part of ABX spectrum, 1 H, C(5)H, 3.19–2.78 (AB part of ABX spectrum, 2 H, $C(6)H_2$), 2.67–1.94 (AB part of ABX spectrum, 2 H, $C(1)H_2$), 1.34 (s, 6 H, 2×CH_3). To a cooled (−20 °C) and stirring mixture of **15** in dry CH_2Cl_2 (100 mL) and a few drops of DMF was added dropwise oxalyl chloride (475 mg, 3.75 mmol). The reaction mixture became clear while CO and CO_2 evolution occurred. After completion of the reaction a solution of L-Pro-OMe (485 mg, 3.75 mmol) and Et_3N (760 mg, 7.52 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise during which time the cooled (−20 °C) reaction mixture was stirred and kept in an argon atmosphere. The reaction mixture was allowed to warm to room temperature. After completion of the reaction (1 h) as was monitored by TLC ($CHCl_3$/MeOH (93/7), v/v) the reaction mixture was successively washed with 0.1 N $NaHCO_3$, 0.1 N HCl, and brine. The organic layer was dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was subjected to column chromatography ($CHCl_3$/MeOH (98.5/1.5), v/v) to give 530 mg (39%) of **19** and 498 mg (37%) of **20**.

Compound 19: crystallized from MeOH/$CHCl_3$; mp 263–265 °C; R_f 0.46 ($CHCl_3$/MeOH (93/7), v/v); $[\alpha]^{22}_D$ + 4° (*c* = 2.6, methanol); EIMS (70 eV) *m/z* (relative intensity) 397 (M^+, 2), 382 ($[M - CH_3]^+$, 8), 338 ($[M - COOMe]^+$, 6), 241 ($[C_{15}H_{17}N_2O]^+$, 100), 183 ($[C_{12}H_{11}N_2]^+$, 82); ^1H NMR δ 8.16 (br s, 1 H, NH), 7.48–7.00 (m, 4 H, C(7)–C(10)H), 4.81 (t, 1 H, C(11b)H), 4.57 (t, 1 H, C(5)H), 4.32 (t, 1 H, C(2′)HCOOMe), 3.94 (br t, 2 H, $C(5')H_2$), 3.71 (s, 3 H, OCH_3), 3.08 (d, 2 H, $C(6)H_2$), 2.60–1.82 (m, 6 H, $C(1)H_2$ and $C(3')H_2$–$C(4')H_2$), 1.36 (s, 6 H, 2×CH_3). Anal. Calcd for $C_{22}H_{27}N_3O_4$ (MW 397.496): C, 66.48; H, 6.85; N, 10.57. Found: C, 66.80; H, 6.72; N, 10.30.

Compound 20: crystallized from CH_2Cl_2/*n*-hexane; mp 286–288 °C; R_f 0.43 ($CHCl_3$/MeOH (93/7), v/v); $[\alpha]^{22}_D$ −86° (*c* = 1.6, methanol); EIMS (70 eV) *m/z* (relative intensity) 397 (M^+, 2), 241 ($[C_{15}H_{17}N_2O]^+$, 75), 183 ($[C_{12}H_{11}N_2]^+$, 100); ^1H NMR δ 7.87 (br s, 1 H, NH), 7.54–7.07 (m, 4 H, C(7)–C(10)H), 4.96 (t, 1 H, C(11b)H), 4.67 (t, 1 H, C(5)H), 4.37 (t, 1 H, C(2′)HCOOMe), 3.89–3.58 (m, 2 H, $C(5')H_2$), 3.64 (s, 3 H, OCH_3), 3.11 (d, 2 H, $C(6)H_2$), 2.67–1.92 (m, 6 H, $C(1)H_2$ and $C(3')H_2$–$C(4')H_2$), 1.39 and 1.32 (2×s, 6 H, 2×CH_3). Anal. Calcd for $C_{22}H_{27}N_3O_4$ (MW 397.496): C, 66.48; H, 6.85; N, 10.57. Found: C, 66.12; H, 6.75; N, 10.41.

Pentacyclic Skeleton 21 and 22. To a warmed (50 °C) and stirred solution of **19** (or **20**) (40 mg, 0.1 mmol) in acetic acid (1 mL) was added activated zinc dust. After completion of the reaction (30 min) as was monitored by TLC ($CHCl_3$/MeOH (93/7), v/v) the reaction mixture was filtered and the filtrate was evaporated in vacuo. The residue was dissolved in dichloromethane, and this solution was successively washed with 0.1 N $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and concentrated to dryness. The residue was dissolved in dry dichloromethane, and DBU (1 equiv) was added. After completion of the reaction (3 days) as was monitored by TLC ($CHCl_3$/MeOH (93/7), v/v) the reaction mixture was washed with 1 N HCl and brine. The organic layer was dried (Na_2SO_4), and evaporation of the solvent in vacuo gave 35 mg (95%) of crystalline **21** (or **22**). Spectroscopical data are identical with those published earlier.[20]

Attempted Oxidation of 21 (or 22) with DDQ. Compound 23. To a stirred solution of **21** (or **22**) (92 mg, 0.25 mmol) in dry dichloromethane (5 mL) was added dropwise a solution of DDQ (125 mg, 0.55 mmol) in dichloromethane (10 mL). After completion of the reaction (1 h) as was monitored by TLC ($CHCl_3$/MeOH (93/7), v/v) the reaction mixture was washed with 0.1 N NaOH and brine. The organic layer was dried (Na_2SO_4) and concentrated to dryness. The residue was subjected to column chromatography ($CHCl_3$/MeOH (99/1), v/v) to give 86 mg (95%) of **23**: R_f 0.56 ($CHCl_3$/MeOH (93/7), v/v); UV (MeOH) λ_{max} 210, 237, 271, 285 (sh), 304 (sh), 316 (sh), 335, 350 nm; EIMS (70 eV) *m/z* (relative intensity) 363 (M^+, 15), 222 (100); ^1H NMR δ 8.37 (s, 1 H, C(14)H), 7.92 (d, 1 H, C(10)H), 7.47 (m, 1 H, C(13)H), 7.31–7.05 (m, 2 H, C(11)–C(12)H), 4.11 (m, 1 H, C(5a)H), 3.90–3.60 (m, 2 H, $C(3)H_2$), 3.44 and 3.28 (AB spectrum, 2 H, ^2J = 16.0 Hz, $C(15)H_2$), 2.22–1.76 (m, 4 H, $C(4)H_2$–$C(5)H_2$), 1.60 and 1.13 (2×s, 6 H, 2×CH_3).

General Procedure to the 3-Alkoxyindolenines 26–28. A solution of 2,3,4,5,6,6-hexachloro-2,4-cyclohexandien-1-one (**25**; Janssen Chimica; 33 mg, 0.11 mmol) in dichloromethane (2 mL) was added dropwise to a stirred solution of **24**[21] (53 mg, 0.1 mmol) in CH_2Cl_2/ROH (1/1, v/v) (8 mL). After completion of the reaction (2–4 h) as was monitored by TLC (EtOAc/*n*-hexane (40/60), v/v) the reaction mixture was washed with 1 N NaOH and brine. The organic layer was dried (Na_2SO_4) and concentrated to dryness. The residue was subjected to column chromatography ($CHCl_3$) to give the 3-substituted indolenines **26–28**.

Compound 26 (R = Me): yield 56 mg (100%); oil; R_f 0.48 (EtOAc/*n*-hexane, (40/60), v/v); UV (MeOH) λ_{max} 205, 231 nm; EIMS (70 eV) *m/z* (relative intensity) 562 (M^+, 14), 407 ($[M - SO_2C_7H_7]^+$, 34), 91 ($[C_7H_7]^+$, 100); ^1H NMR δ 7.78 (d, 2 H, p-$C_6Ha_2Hb_2(CH_3)$), 7.41–6.93 (m, 9 H, C_6H_5, *p*-$C_6Ha_2Hb_2(CH_3)$ and C(6)-C(7)H), 6.78–6.40 (m, 2 H, C(5)H and C(8)H, 4.74 (X part of ABX spectrum, 1 H, C(1)H), 4.56 and 4.27 (AB spectrum, 2 H, ^2J = 12.4 Hz, OCH_2Ph), 4.21 (br t, 1 H, C(3)H), 3.11 (s, 3 H, OCH_3), 2.70–1.75 (m, 4 H, $C(4)H_2$ and $C(1)CH_2$), 2.42 (s, 3 H, *p*-$C_6H_4(CH_3)$), 1.58 (br s, 1 H, OH (exchangeable)), 1.34 and 1.28 (2×s, 6 H, 2×CH_3).

Compound 27 (R = Et): yield 46 mg (80%); oil; R_f 0.58 (EtOAc/*n*-hexane (40/60), v/v); UV (MeOH) λ_{max} 207, 231 nm; EIMS (70 eV) *m/z* (relative intensity) 576 (M^+, 4), 421 ($[M - SO_2C_7H_7]^+$, 11), 91 ($[C_7H_7]^+$, 100); ^1H NMR δ 7.73 (d, 2 H, *p*-$C_6Ha_2Hb_2(CH_3)$), 7.32–6.90 (m, 9 H, C_6H_5, *p*-$C_6Ha_2Hb_2(CH_3)$ and C(6)–C(7)H), 6.73–6.38 (m, 2 H, C(5)H and C(8)H), 4.69 (X part of ABX spectrum, 1 H, *J* = 3.3, 5.9 Hz, C(1)H), 4.50 and 4.34 (AB spectrum, 2 H, ^2J = 12.3 Hz, OCH_2Ph), 4.18 (X part of ABX spectrum, 1 H, *J* = 6.9, 11.7 Hz, C(3)H), 3.30 (m, 2 H, OCH_2CH_3), 2.76–1.71 (m, 4 H, $C(4)H_2$ and $C(1)CH_2$), 2.38 (s, 3 H, *p*-$C_6H_4(CH_3)$), 1.60 (br s, 1 H, OH (exchangeable)), 1.33 and 1.27 (2×s, 6H, 2×CH_3).

Compound 28 (R = H). Instead of dichloromethane, dimethoxyethane was used as the solvent in this experiment: yield 43 mg (78%); oil; R_f 0.41 (EtOAc/*n*-hexane (40/60), v/v); UV (MeOH) λ_{max} 205, 231 nm; exact mass for $C_{30}H_{33}N_2O_6S$ (FAB^+) calcd 549.2022, found 549.2032; EIMS (70 eV) *m/z* (relative intensity) 548 (M^+, 69), 413 ($[M - COOC_7H_7]^+$, 4), 393 ($[M - SO_2C_7H_7]^+$, 37), 337 (25), 230 (30), 91 ($[C_7H_7]^+$, 100); ^1H NMR δ 7.7$_7$ (d, 2 H, *p*-$C_6Ha_2Hb_2(CH_3)$), 7.36–6.97 (m, 9 H, C_6H_5, –$C_6Ha_2Hb_2(CH_3)$ and C(6)–C(7)H), 6.81–6.44 (m, 2 H, C(5)H and C(8)H), 4.93 and 4.76 (AB spectrum, 2 H, ^2J = 12.9 Hz, OCH_2Ph), 4.67–4.51 (2× X part of ABX spectrum, 2 H, C(1)H and C(3)H), 4.12 (br s, 1 H, C(4a)OH (exchangeable)), 2.56–1.88 (m, 4 H, $C(4)H_2$ and $C(1)CH_2$), 2.39 (s, 3 H, *p*-$C_6H_4(CH_3)$), 1.61 (br s, 1 H, OH (exchangeable)), 1.34 (s, 6 H, 2×CH_3).

Compound 29. A solution of 2,3,4,5,6,6-hexachloro-2,4-cyclohexandien-1-one (**25**: Janssen Chimica; 38 mg, 0.13 mmol) in dichloromethane (2 mL) was added dropwise to a stirred solution of **5**[20] (46 mg, 0.12 mmol) in CH_2Cl_2/MeOH (1/1), v/v) (15 mL). After completion of the reaction (30 min), as monitored by TLC (EtOAc), the reaction mixture was washed with 1 N NaOH and brine. The organic layer was dried (Na_2SO_4) and concentrated to dryness. The residue was subjected to column chromatography ($CHCl_3$) to give 37 mg (73%) of **29**: colorless oil; R_f 0.28 (EtOAc); $[\alpha]_D$ +95° (*c* = 3.5, methanol); UV (methanol) λ_{max} 210, 240, 296 nm; EIMS (70 eV) *m/z* (relative intensity) 427 (M^+, 35), 412 (22), 396 (4), 395 (3), 260 (37), 28 (100); ^1H NMR (90 MHz, $CDCl_3$) δ 7.00 (d, 1 H, C(13)H), 6.36–6.17 (m, 2 H, C(10) and C(12)H), 5.45 (dd, 1 H, C(8)H), 4.40 (dd, 1 H, C(14a)H), 4.10 (br s, 1 H, OH), 4.04–3.87 (m, 1 H, C(5a)H), 3.69 (s, 3 H, OCH_3), 3.53 (s, 3 H, OCH_3), 3.78–3.29 (m, 2 H, $C(3)H_2$), 2.60–1.16 (m, 8 H, $C(14)H_2$, $C(1')H_2$, $C(4)$–$C(5)H_2$), 1.36 (s, 6 H, 2×CH_3).

Dehydrodipeptide 6 and Overoxidation Product 30. To a stirred solution of **29** (35mg, 0.082 mmol) in dichloromethane (20 mL) at room temperature was added a few drops of trifluoroacetic acid. Stirring was continued for 1 h at room temperature after which the reaction mixture was washed with 0.1 N $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and evaporated to dryness. The residue was subjected to column chromatography (EtOAc) to give 15 mg (46%) of **6**, 15 mg (43%) of starting material **29**, and 2 mg (6%) of **30**.

Compound 6: amorphous, yellow-green solid; R_f 0.14 (EtOAc); $[\alpha]_D$ +87° (*c* = 1.3, methanol); UV (methanol) λ_{max} 227, 254, 363 nm; EIMS (70 eV) 395 (M^+, 13), 322 (40), 294 (18), 225 (21), 197 (27), 57 (100); ^1H NMR (90 MHz, $CDCl_3$) δ 9.25 (br s, 1 H, NH), 7.51 (d, 1 H, C(13)H), 7.34 (s, 1 H, C(14)H), 6.87 (s, 1 H, C(10)H), 6.82 (m, 1 H, C(12)H), 6.17 (t, 1 H, C(8)H), 4.22–4.00 (m, 1 H,

C(5a)H), 3.89–3.54 (m, 2 H, C(3)H_2), 3.82 (s, 3 H, OCH_3), 2.53–1.71 (m, 6 H, C(1')H_2, C(4)–C(5)H_2), 2.00 (br s, 1 H, OH), 1.42 and 1.18 (2×s, 6 H, 2×CH_3).

Compound 30: R_f 0.43 (EtOAc); UV (MeOH) λ_{max} 217, 236, 272, 285 (sh), 304 (sh), 317 (sh), 335, 354 nm; EIMS (70 eV) m/z (relative intensity) 393 (M^+, 18), 252 (100), 222 (86); ^1H NMR δ 8.38 (s, 1 H, C(14)H), 7.93 (d, 1 H, C(13)H), 6.96 (s, 1 H, C(10)H), 6.90 (d, 1 H, C(12)H), 4.13 (m, 1 H, C(5a)H), 3.98–3.71 (m, 2 H, C(3)H_2), 3.86 (s, 3 H, OCH_3), 3.57 and 3.18 (AB spectrum, 2 H, ^2J = 14.5 Hz, C(15)H_2), 2.23–1.75 (m, 4 H, C(4)H_2–C(5)H_2), 1.61 and 1.24 (2×s, 6 H, 2×CH_3).

(-)-Verrucculogen TR-2 (2). To a stirred and cooled (0 °C) solution of the dehydro compound **6** (5 mg, 0.0127 mmol) in dry pyridine (0.5 mL) was added a solution of osmium tetroxide (100 μL, 0.0195 M in pyridine, 0.0195 mmol). The resulting orange-colored solution was stirred at 0 °C for 2 h and was then treated with saturated aqueous $NaHSO_3$ (0.5 mL). This reaction mixture was stirred at room temperature for 30 min, after which the aqueous layer was separated. The mixture was extracted with chloroform. The organic layer was washed with brine and subsequently dried (Na_2SO_4) and concentrated to dryness. The residue was subjected to column chromatography ($CHCl_3$/MeOH (97/3), v/v) to give 1.2 mg (22%) of **2**: oil; R_f 0.39 ($CHCl_3$/MeOH (93/7), v/v); $[\alpha]_D$ -45° (c = 0.55, CH_2Cl_2); EIMS (70 eV) 429, (M^+, 4), 411 (8), 335 (45), 278 (47), 219 (100); exact mass for $C_{22}H_{27}N_3O_6$ calcd 429.1912, found 429.1910; UV (methanol) λ_{max} 224, 267, 295 nm; ^1H NMR (200 MHz, $CDCl_3$) δ 9.04 (br s, 1 H, NH), 7.82 (d, 1 H, C(13)H), 6.86–6.77 (m, 2 H, C(10)H and C(12)H), 5.72 (d, 1 H, J = 2.9 Hz, C(14)H), 5.46 (dd, 1 H, J_{AX} + J_{BX} = 11.2 Hz, C(8)H, 4.60 (d, 1 H, J = 2.9 Hz, C(14)OH, 4.45 (m, 1 H, C(5a)H), 4.02 (s, 1 H, C(14a)OH), 3.85 (s, 3 H, OCH_3), 3.70–3.61 (m, 2 H, C(3)H_2), 2.51 and 2.12–1.65 (m, 7 H, C(1')H_2, C(4)–C(5)H_2), 1.25 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3); (90 MHz, DMSO-d_6) δ 10.55 (br s, 1 H, NH), 7.60 (d, 1 H, J = 9 Hz, C(13)H), 6.83 (s, 1 H, C(10)H), 6.58 (d, 1 H, J = 9 Hz, C(12)H), 6.13 (br s, 1 H, OH), 5.48 (d, 1 H, C(14)H), 5.32 (m, 1 H, C(8)H, 5.16 (d, 1 H, C(14)OH), 4.33 (m, 1 H, C(5a)H), 4.17 (br s, 1 H, OH), 3.70 (s, 3 H, OCH_3), 3.55 (m, 2 H, C(3)H_2), 2.36–1.60 (m, 6 H, C(1')H_2, C(4)–C(5)H_2), 1.09 and 0.94 (2×s, 6 H, 2× CH_3).

Supplementary Material Available: Spectroscopic data (^1H NMR, MS) for compounds **2**, **6**, and **26–30** (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

A Highly Stereoselective Synthesis of Anti-HIV 2',3'-Dideoxy- and 2',3'-Didehydro-2',3'-dideoxynucleosides[1]

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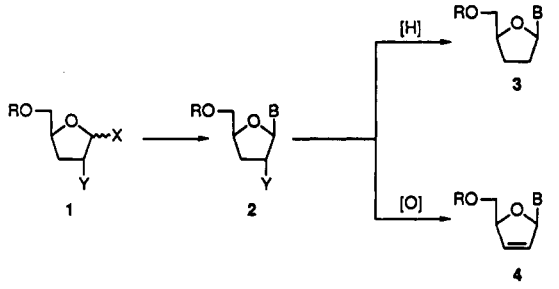
A general total synthetic method for the stereocontrolled synthesis of 2',3'-dideoxy- as well as 2',3'-didehydro-2',3'-dideoxynucleosides is presented. Introduction of an α-phenylselenenyl group at the 2-position of 2,3-dideoxyribosyl acetate directs the glycosyl bond formation to give ≥95% β-isomer. This 2'-phenylselenenyl nucleoside may be converted to either the 2',3'-dideoxynucleoside by treatment with n-Bu_3SnH and Et_3B at room temperature or to the unsaturated derivative by treatment with H_2O_2/cat. pyridine. The application of this method to the syntheses of pyrimidines (ddU, ddT, ddC), 6-substituted purines (ddA, ddI, 6-chloro-ddP, N^6-Me-ddA), and 2,6-disubstituted purines (2-F-ddA, 6-chloro-2-amino-ddP) as well as selected 2',3'-didehydro-2',3'-dideoxy derivatives is reported.

Since the discovery of 2',3'-dideoxy- and 2',3'-didehydro-2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine (ddC),[2] 2',3'-dideoxyadenosine (ddA),[2] 2',3'-dideoxyinosine (ddI),[3] and 3'-deoxy-2',3'-didehydrothymidine (d4T)[4-6] as anti-HIV agents, a number of laboratories, including ours, have been interested in developing efficient syntheses of these nucleosides. The simplest synthetic method for these nucleosides is the deoxygenation of the 3'-hydroxyl group of 5'-protected 2'-deoxynucleosides.[7] However, this method may not be economically feasible due to the limited availability as well as expense of the starting material, 2'-deoxynucleosides. As part of our effort to develop practical methods for anti-HIV nucleosides, we have reported a general synthetic method for the 2',3'-dideoxy- and 2',3'-didehydro-2',3'-dideoxynucleosides from

Scheme I



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