11.61 (q), 14.41 (q), 32.42 (q), 51.69 (q), 60.55 (t), 65.85 (t), 116.46 (s), 116.74 (s), 121.37 (s), 126.86 (s), 128.03 (d), 128.23 (d), 128.23 (s), 128.60 (d), 130.47 (s), 135.84 (s), 160.77 (s), 163.56 (s), 164.19 (s); IR (neat) 3268, 2983, 2953, 1710, 1455, 1376, 1304, 1263, 1214, 1147, 1061, 736 cm^{-1}; MS (FAB) m/e (relative intensity) 768 [(M + H)$^+$, 9], 767 (M^+, 12), 91 (100); HRMS (FAB) m/e (M^+) calcd 767.2690, obsd 767.2670.

***trans*- and *cis*-2′,3′-Dihydro-2,2′-bipyrroles (20a,b).** A solution of mesomeric betaine **10e** (70.8 mg, 0.20 mmol) and dimethyl maleate (63.4 mg, 0.44 mmol) in benzene (4 mL) was heated at reflux for 6 h. The solvent was evaporated, and the residue was purified by PTLC [(hexanes–EtOAc, 3:1)–ether, 1:1] to afford **20a** (69.5 mg, 70%) and **20b** (8.3 mg, 8%) as a pale yellow oils. In a similar experiment, a solution of **10e** (70.8 mg, 0.20 mmol) and dimethyl fumarate (63.4 mg, 0.44 mmol) in benzene (4 mL) at reflux (3 h) afforded **20a** (77.2 mg, 77%) and **20b** (14.6 mg, 15%). **20a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, 3 H, J = 7.2 Hz), 1.41 (t, 3 H, J = 7.1 Hz), 2.54 (s, 3 H), 2.59 (s, 3 H), 3.47 (s, 3 H), 3.79 (s, 3 H), 3.85 (d, 1 H, J = 8.1 Hz), 4.18–4.28 (m, 1 H), 4.31–4.41 (m, 1 H), 4.38 (q, 2 H, J = 7.1 Hz), 5.47 (d, 1 H, J = 8.1 Hz), 7.44–7.48 (m, 5 H), 9.30 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.75 (q), 14.36 (q), 14.36 (q), 35.74 (q), 50.40 (q), 52.18 (q), 54.85 (d), 59.93 (t), 60.58 (t), 64.81 (d), 99.39 (s), 114.20 (s), 119.67 (s), 128.18 (d), 128.93 (d), 129.62 (d), 130.77 (s), 130.99 (s), 139.30 (s), 161.33 (s), 163.67 (s), 164.43 (s), 164.90 (s), 173.82 (s); IR (neat) 3250, 2981, 2949, 1744, 1699, 1671, 1615, 1572, 1437, 1305, 1247, 1198, 1076 cm^{-1}; MS (EI) m/e (relative intensity) 498 (M^+, 47), 466 (96), 438 (18), 393 (100), 347 (31), 315 (38), 118 (30); HRMS (EI) m/e (M^+) calcd 498.2002, obsd 498.1992. **20a**, ^{13}C-enriched: ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (s), $^3J_{C\text{-}5',H\text{-}3'}$ = 3.3 Hz, $^3J_{C\text{-}5',H\text{-}2'}$ = 0 Hz. **20b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, 3 H, J = 7.2 Hz), 1.43 (t, 3 H, J = 7.2 Hz), 2.44 (s, 3 H), 2.58 (s, 3 H), 3.37 (s, 3 H), 3.48 (s, 3 H), 4.36 (q, 4 H, J = 7.2 Hz), 4.45 (d, 1 H, J = 11.9 Hz), 5.52 (d, 1 H, J = 11.9 Hz), 7.45–7.47 (m, 5 H), 9.33 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.77 (q), 14.42 (q), 14.42 (q), 36.24 (q), 50.58 (q), 51.72 (q), 51.80 (d), 60.00 (t), 60.56 (t), 64.97 (d), 101.81 (s), 115.29 (s), 119.73 (s), 128.23 (d), 128.79 (d), 129.46 (d), 130.49 (s), 131.47 (s), 136.15 (s), 161.28 (s), 164.66 (s), 164.66 (s), 165.05 (s), 171.84 (s); IR (neat) 3256, 2983, 2947, 1742, 1699, 1620, 1590, 1436, 1371, 1245, 1191, 1072 cm^{-1}; MS (EI) m/e (relative intensity) 498 (M^+, 34), 466 (58), 438 (10), 393 (100), 347 (21), 315 (25), 118 (14); HRMS (EI) m/e (M^+) calcd 498.2002, obsd 498.1999. **20b**,^{13}C-enriched: ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1 (s), $^3J_{C\text{-}5',H\text{-}3'}$ = 3.7 Hz, $^3J_{C\text{-}5',H\text{-}2'}$ = 0 Hz.

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Supplementary Material Available: ^{1}H NMR spectra of **17i** at 25 °C, 65 °C, and 130 °C; ^{1}H NMR and ^{13}C NMR spectra of **10a,f–h**, **12b**, **17a–j**, and **20a,b**; and ^{13}C NMR spectra of ^{13}C-enriched samples of **10e**, **17b,d** and **20a,b** (42 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-7-Epi-20-desethylgelsedine

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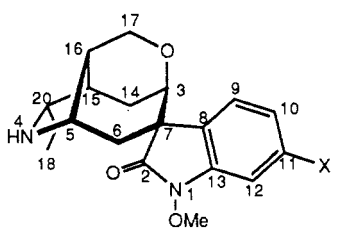
The oxindole alkaloid gelsedine contains a unique molecular architecture. The synthetic approach to this pentacyclic molecule involved the efficient preparation of the all-cis trisubstituted pyrrolidine intermediate **14**. The lactone system **18**, an excellent precursor of the pentacyclic cage framework of gelsedine, was prepared in an efficient and highly convergent manner by reaction of pyrrolidine **16** and the readily available *N*-methoxyindole system **5**. Subsequent steps led to the formation of the title compound.

Gelsedine (**1**) is an oxindole alkaloid that was isolated from *Gelsemium sempervirens* in 1953 by Schwarz and Marion.[1] Its structure was elucidated by Wenkert in 1962 through spectroscopic comparison with the related alkaloid gelsemicine (**2**).[2,3] Since that time synthetic studies toward the total synthesis of gelsedine or gelsemicine have received scant attention in the literature, and to date a successful synthesis of these alkaloids has not been reported.[4] Very recent activity toward the total synthesis of the Gelsemium alkaloids[5] prompts us to describe our progress toward the total synthesis of gelsedine.[6]



1, gelsedine (X = H)

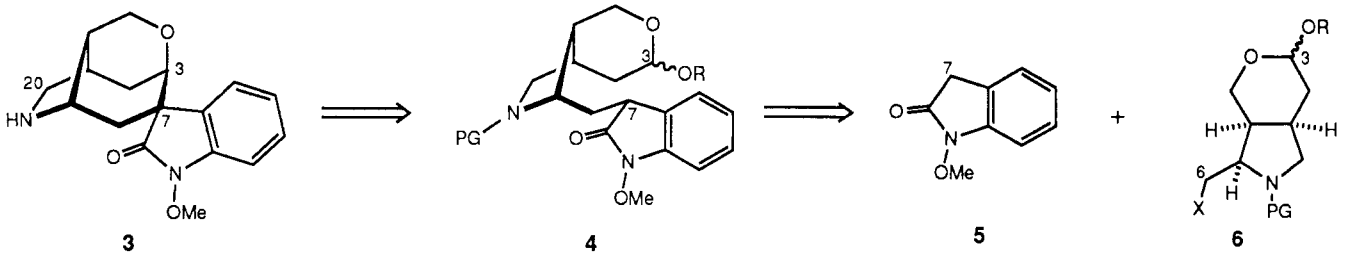
2, gelsemicine (X = OMe)

Our retrosynthetic analysis to **1** is illustrated in Scheme I. We defined 20-desethylgelsedine (**3**) as a penultimate precursor of the target alkaloid, assuming that the C-20 ethyl (gelsedine numbering throughout the paper) could be introduced at the end of the sequence. The formation of the quaternary spirocyclic center at C-7 is the key structural problem in this pentacyclic skeleton. Recog-

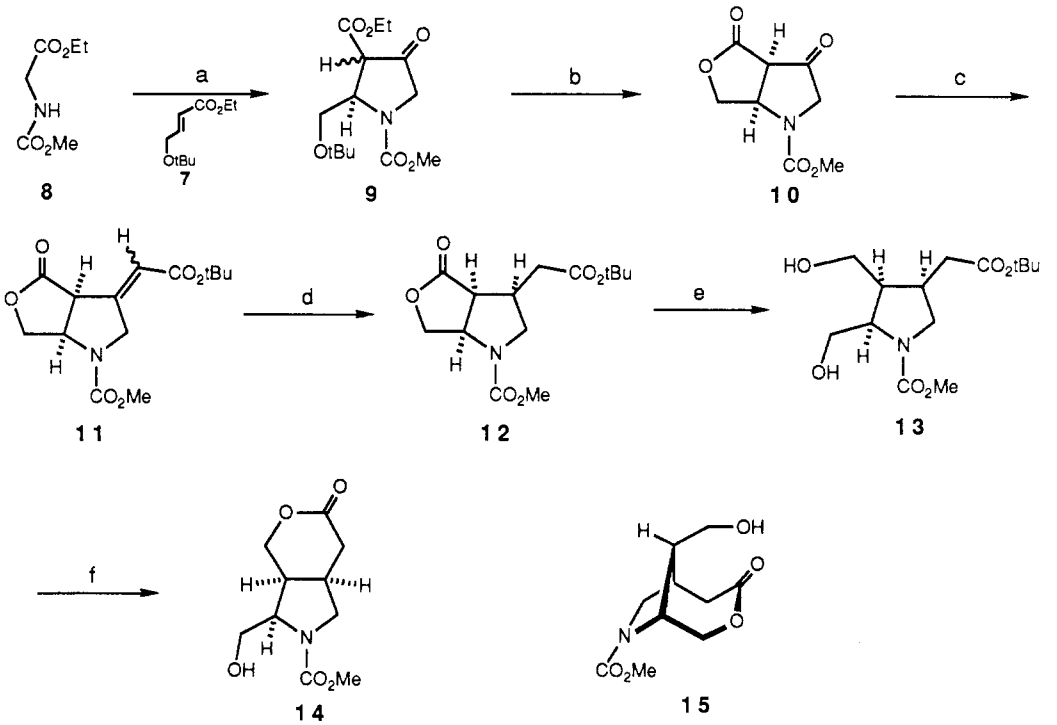
(1) Schwarz, H.; Marion, L. *Can. J. Chem.* **1953**, *31*, 958.
(2) Wenkert, E.; Orr, J. C.; Garratt, S.; Hansen, J. H.; Wickberg, B.; Leicht, C. L. *J. Org. Chem.* **1962**, *27*, 4123.
(3) For reviews of literature related to *Gelsemium* alkaloids, see: (a) Saxton, J. E. In *The Alkaloids*; Manske, R. H. F., Eds.; Academic Press: New York, 1965; Vol. 8, pp 93–117. (b) Bindra, J. S., ref 3a, 1973, Vol. 14, pp 83–91.
(4) Baldwin, S. W.; Doll, R. J. *Tetrahedron Lett.* **1979**, 3275.
(5) Choi, J. K.; Ha, D. C.; Hart, D. J.; Lee, C. S.; Ramesh, S.; Wu, S. *J. Org. Chem.* **1989**, *54*, 279.
(6) Taken in part from Luzzio, M. J. Ph.D. Thesis, University of Rochester, 1987.

0022-3263/90/1955-0918$02.50/0

Scheme I



Scheme II[a]



[a] (a) NaH, PhH, Δ; (b) TFA–H_2O (4:1), room temperature, 24 h; (c) $(Ph)_3PCHCO_2tBu$, THF, Δ; (d) H_2, Pd/C, EtOAc/CH_2Cl_2; (e) $LiBH_4$, THF; (f) aqueous TFA (cat.), CH_2Cl_2.

nizing that the oxindole "C-7" position is enolic and thus a potential nucleophilic synthon, and given that the C-3 carbon adjacent to pyran oxygen is a potential electrophile, the formation of this quaternary center by a C-7 to C-3 ionic reaction seemed to be a feasible key reaction. This permits the retrosynthetic stream to give the seco acetal **4**. A further disconnection involving the oxindole β-carbon would yield the known[7] *N*-methoxyindole **5** and the *all-cis*-2,3,4-trisubstituted-pyrrolidine **6**. It is evident that the efficient and stereocontrolled construction of this pyrrolidine unit is a prerequisite to the successful test of the key cyclization step **4** to **3**.

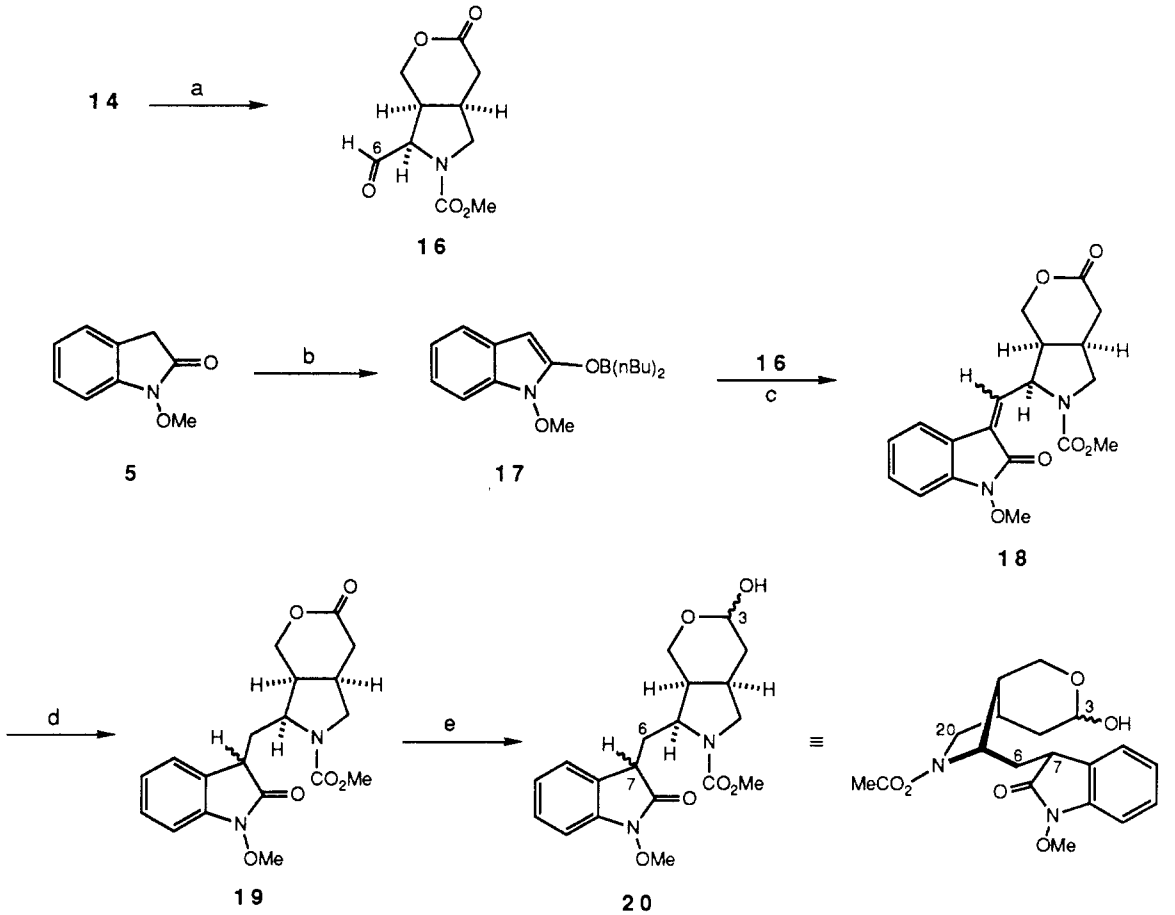
Our entry to the requisite pyrrolidine system commenced with the Michael–Dieckmann route for synthesis of 3-pyrrolidinones. Following the precedents of Kuhn and Rozing,[8,9] the ethyl ester of 4-*tert*-butoxycrotonic acid (**7**) was allowed to react with the ethyl ester of *N*-carbomethoxyglycine (**8**) by using NaH in benzene at reflux to give the 3-pyrrolidinone ester **9** in 42% yield (Scheme II). Treatment of **9** with 80% aqueous trifluoroacetic acid at room temperature gave the keto lactone **10** in 77% yield, setting the first two ring substituents exclusively in the thermodynamically favored cis configuration.[10,11] Reaction of **10** with (carbo-*tert*-butoxymethylene)triphenylphosphorane in tetrahydrofuran at 55 °C gave a 10:1 mixture of the *Z* to *E* isomers **11** in 72% yield. Proton NMR studies showed that the double bond is entirely exocyclic, and that it did not migrate to the Δ^3 position under a variety of reaction conditions.

The presence of the γ-lactone unit in both isomers of **11** was crucial for the stereochemistry of the subsequent catalytic reduction. As anticipated, catalytic reduction of the mixture **11** with hydrogen over palladium on carbon in ethyl acetate gave a quantitative yield of a single crystalline compound. By analogy with the stereochemistry of reduction of related [3.3.0] systems,[12] the catalyst must deliver the hydrogen from the sterically less encumbered convex face of the molecule to yield only the *all-*

(7) Wright, W. B.; Collins, K. H. *J. Am. Chem. Soc.* **1956**, *78*, 221.
(8) Kuhn, R.; Osswald, G. *Chem. Ber.* **1956**, *89*, 1423.
(9) (a) Rozing, G. P.; De Koning, H.; Huisman, H. O. *Heterocycles* **1977**, *7*, 123; (b) **1976**, *5*, 325.

(10) Proton NMR in $CDCl_3$ shows **9** to be 90% enolized. When **9** was reacted with aqueous trifluoroacetic acid, the *tert*-butyl ether group cleaved to the primary alcohol. The ketone is undergoing keto–enol tautomerization followed by acid-catalyzed lactonization, giving the cis lactone **10**.
(11) All compounds reported were homogeneous by TLC analysis and provided 300-MHz ^1H NMR, IR, and mass spectra consistent with those expected for the compounds. The molecular composition of key compounds was determined by high-resolution mass spectrometry or elemental analysis.
(12) Ho, T. L.; Gopalan, B.; Nestor, J. J. *J. Org. Chem.* **1986**, *51*, 2405.

Scheme III[a]



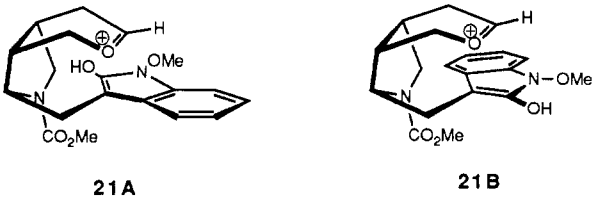
[a] (a) $(COCl)_2$, DMSO, CH_2Cl_2; TEA; (b) $(iPr)_2NEt$, $(nBu)_2BOTf$, CH_2Cl_2, −78 °C; (c) CH_2Cl_2, −70 °C; SiO_2 chromatography; (d) H_2, Pd/C, EtOAc/CH_2Cl_2 (3:1); (e) $Li(sBu)_3BH$, CH_2Cl_2, 0 °C.

cis-pyrrolidine derivative **12**. Selective reduction of the γ-lactone unit in the presence of the *tert*-butyl ester was accomplished by using lithium borohydride in tetrahydrofuran at room temperature to yield 98% of hygroscopic diol **13**, which was directly treated with a catalytic amount of aqueous trifluoroacetic acid in methylene chloride to give the rearranged δ-lactone **14** in 79% yield. The formation of this δ-lactone, whose structure was confirmed by 300-MHz ^1H NMR analysis, is driven by the stability of the planar δ-lactone system of **14** relative to the transannular ε-lactone alternative **15**.

With lactone **14** in hand, the next objective became the first carbon–carbon bond formation between the *N*-methoxyindole **5** and the lactone **14** (Scheme III). Treatment of **14** under Swern oxidation conditions[13] gave in 86% yield the moderately sensitive aldehyde **16**. Reaction of *N*-methoxyindole **5** with di-*n*-butylboron triflate at −78 °C in the presence of diisopropylethylamine gave the vinyloxyborane **17**[14] in nearly quantitative yield. This was allowed to react with the aldehyde **16** to afford directly after neutral workup and silica gel chromatography a mixture of *E* and *Z* olefins **18** in an overall 42% yield. This mixture (predominantly *Z*) was reduced over 5% palladium on carbon to give in 67% yield the oxindoles **19** as a mixture of C-7 epimers. Such a mixture of epimers is of no consequence in view of the subsequent enolization step.

After the initial success in the connection of the *all-cis*-pyrrolidine lactone with the oxindole unit, the final cyclization to a pentacyclic cage was contemplated. Chemoselective reduction of the lactone vs lactam ring was carried out by using lithium tri-*sec*-butylborohydride[15] in methylene chloride at 0 °C. The lactols **20** were obtained as a mixture of C-7 and C-3 epimers, again inconsequential in view of the subsequent cyclization step between these two carbons under acidic conditions.

At this point we were faced with a stereochemical question regarding the key cyclization from C-7 to C-3. Two transition states (**21A** and **21B**) can be envisioned for this cyclization reaction. It is transition state A that will

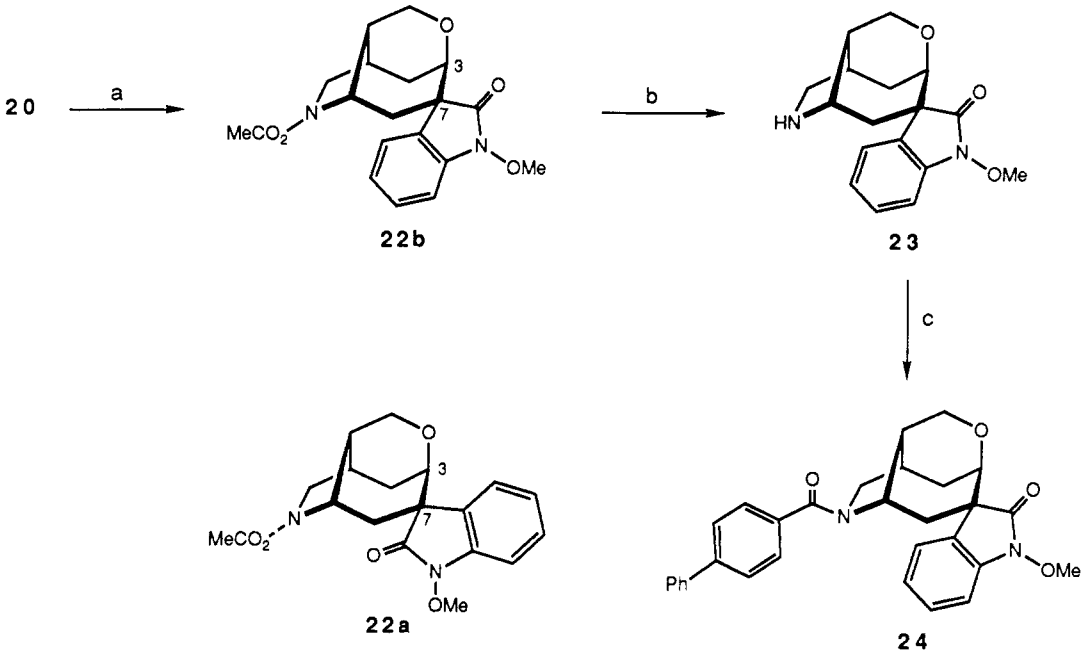


21A **21B**

lead to the natural gelsedine stereochemistry.[16] Dreiding models indicate that transition state **21A**, with the benzene ring "exo", should be favored over the alternative transition state **21B**, in which the "endo" benzene ring C-9 proton

(13) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(14) (a) Mukaiyama, T.; Inoue, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174. (b) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559.
(15) Other hydride reagents such as diisobutylaluminum hydride or lithium tri-*tert*-butoxyborohydride were unsuccessful in our hands.
(16) Molecular mechanics calculations comparing the ground-state energy of structures **22a** and **22b** show the product **22a** to be more stable.

Scheme IV[a]



[a] (a) TFAA/TFA (1:1), $CHCl_3$, room temperature; (b) HMDS, I_2, $PhCH_3$, Δ; (c) PhBzCl, CH_2Cl_2, TEA.

would be virtually embedded in the C-20 methylene group. Treatment of lactols **20** with 1:1 trifluoroacetic acid–trifluoroacetic anhydride mixture in chloroform gave a single pentacyclic product in 53% yield.[17] The structure of this molecule was originally assigned as the "natural" diastereomer **22a** on the basis of the preceding argument.

Selective cleavage of the carbamate protecting group using an in situ preparation of trimethylsilyl iodide[18] gave 61% yield of a single compound, again tentatively designated as **3**; no evidence of a second diastereomer was observed. The mass spectrum, IR spectrum, and proton NMR spectrum supported the overall structure of **3**. However, comparison of the ^1H NMR spectrum of **3** with that of authentic gelsedine[19] showed a major difference. The aromatic proton at C-9 of gelsedine was at higher field than that of the tentative structure **3** (e.g. H-9 d, at δ 7.41 for gelsedine; δ 8.18 for tentative structure **3**). The unexpected downfield shift caused by removal of the carbamate group suggested steric proximity between the pyrrolidine nitrogen and the aromatic ring, throwing doubt on the original structural assignment. Finally, the correct structures, **22b** and **23**, were deduced from the X-ray crystallographic analysis of the protected amine **24** (Scheme IV). The molecular structure of **24** is shown in Figure 1.[20]

A possible destabilizing electronic interaction present in the desired conformation **21A** is the repulsion between the carbamate group and the C-2 oxygen of the oxindole, possibly both in protonated form. This could be an important factor responsible for the formation of the unnatural spirocyclic carbon framework of gelsedine.[21] We

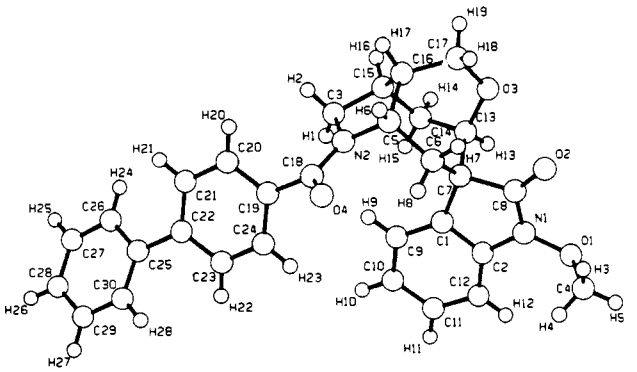


Figure 1. X-ray structure of compound **24**.

are currently exploring modifications in our synthetic strategy involving the C-3 to C-7 bond formation to overcome the unexpected generation of the incorrect stereochemistry in the formation of this spirocyclic center.

Experimental Section

General Procedures. All melting points are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 1310 spectrophotometer as either thin films or in chloroform solutions. Nuclear magnetic resonance spectra were determined on a Nicolet QE 300-MHz spectrometer. All chemical shifts are reported in ppm from tetramethylsilane as internal standard and described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), or broad (br). ^{13}C NMR spectra were recorded on a Nicolet QE-300 MHz spectrometer at 75.5 MHz. Low-resolution mass spectra were recorded on either a VG-7035 or a Nermag R10-10C mass spectrometer. High-resolution mass spectra were determined

(17) The cyclized product was recovered unchanged in almost quantitative yield after it was resubmitted to the reaction conditions, indicating a kinetically formed product.

(18) Raucher, S.; Bray, B. L. *J. Org. Chem.* **1985**, *50*, 3236 and references cited therein.

(19) An authentic sample of gelsedine was kindly provided by Dr. F. Khuong-Huu, Institut de Chimie des Substances Naturelles, C.N.R.S., Gif-sur-Yvette, France.

(20) Details of the X-ray study may be found in the supplementary material. We are grateful to Prof. William D. Jones for his advice and assistance in the single-crystal X-ray analysis.

(21) The synthesis of the spirocyclic unnatural compound contradicts the results expected on the basis of both Dreiding models and molecular mechanics calculations. Further modeling studies and force field calculations are currently in progress. For some alternative methodologies leading to spirocyclic oxindoles, see: (a) Kende, A. S.; Koch, K.; Smith, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 2210. (b) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (c) Jones, K.; Thompson, M.; Wright, C. *J. Chem. Soc., Chem. Commun.* **1986**, 115. Leading citations to other syntheses of 3-spiro-2-oxindoles can be found in ref 3 of this paper.

on a VG-7035 mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc. The purity of all titled compounds was shown to be at least 95% by NMR and TLC analyses.

Solvents and reagents were dried and purified prior to use when it was deemed necessary: tetrahydrofuran, benzene, and diethyl ether (distilled from sodium metal); methylene chloride (distilled from CaH_2). All reaction temperatures refer to those of the reaction mixtures unless indicated otherwise. All reactions were run in flame-dried flasks under an atmosphere of nitrogen except in those reactions where water was present. Analytical thin-layer chromatography was performed utilizing Baker hard-surfaced layer glass plates of 0.25-mm thickness with a 254-nm fluorescent indicator. Column chromatography was carried out on SiO_2 (silica gel, Merck, 230–400 mesh).

Ethyl 4-*tert*-Butoxycrotonate (7). To a 500-mL Parr shaker bottle were added ethyl 4-hydroxycrotonate[22] (70.98 g, 546 mmol) and dry methylene chloride (75 mL). The bottle was cooled to −78 °C and isobutylene (75 g, 1340 mmol) was condensed into the flask under a nitrogen atmosphere. Concentrated sulfuric acid (5 g) was added to the resultant solution at −78 °C. The flask was removed from the bath and as quickly as possible placed on a Parr apparatus, sealed, and shaken while the reaction warmed to room temperature. The reaction was shaken for 36 h. The reaction mixture was removed from the Parr apparatus and poured into a 10% sodium bicarbonate solution (300 mL) and stirred at room temperature for 30 min. The mixture was extracted with ether (4 × 250 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a quantitative yield (101.5 g) of **7** as an essentially pure oil, which was carried through directly to next step: bp 95–98 °C/6 mmHg; IR (film) 2970, 1710, 1360, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.96 (dt, J = 15.0, 4.2 Hz, 1 H), 6.06 (br d, J = 15.0 Hz, 1 H), 4.15 (q, J = 7.5 Hz, 2 H), 4.04 (m, 2 H), 1.25 (t, J = 7.5 Hz, 3 H), 1.18 (s, 9 H).

Ethyl *N*-(Methoxycarbonyl)glycinate (8). A solution of glycine ethyl ester hydrochloride (139.58 g, 1.0 mol) in distilled water (200 mL) cooled to −5 °C was carefully neutralized with a 40% aqueous sodium hydroxide solution (100 mL), keeping the internal temperature below 5 °C. Methyl chloroformate (103.95 g, 1.1 mol) was then added dropwise with vigorous stirring at a rate so as to maintain the internal temperature below 5 °C. After all the methyl chloroformate was added, the reaction mixture was stirred at 0 °C for 45 min, at which time a second portion of a 40% aqueous sodium hydroxide solution (110 mL) was added. The reaction mixture was extracted with ether (3 × 300 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo to give a crude clear liquid. This liquid was then Kugelrohr distilled to afford 138.68 g (87%) of **8** as a clear liquid: bp 135–139 °C/15 mmHg; IR ($CHCl_3$) 3440, 3000, 1730, 1520, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.70 (br s, 1 H), 4.22 (q, J = 6.9 Hz, 2 H), 3.95 (d, J = 4.8 Hz, 2 H), 3.70 (s, 3 H), 1.30 (t, J = 6.9 Hz, 3 H).

(2α)-(±)-2-[(1,1-Dimethylethoxy)methyl]-1-(methoxycarbonyl)-4-oxopyrrolidine-3-carboxylic Acid Ethyl Ester (9). To a suspension of sodium hydride (14 g of a 50% oil dispersion) in dry benzene (200 mL) heated at 60–65 °C (internal temperature) was added dropwise over a 45-min period the protected glycine **8** (46.32 q, 287.7 mmol) in benzene (120 mL) under a nitrogen atmosphere. After all the protected amino acid was added, the reaction mixture was mechanically stirred for 30 min. The crotonate ester **7** (53.51 g, 287.7 mmol) in benzene (120 mL) was added dropwise over a 45-min period. The blackish red reaction mixture was stirred at 60–65 °C for 90 min, cooled to room temperature, and poured into a mixture of water–ice (500 g) and 2 N aqueous hydrochloric acid solution (200 mL). The resulting mixture was extracted with ethyl acetate (3 × 300 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over silica gel (hexane–ethyl acetate, 7:3) to give 36.37 g (42%) of **9** as an amber oil, the spectral characteristics of which were identical with those reported in the literature for this compound:[9a] IR (film) 3340, 2980, 1775, 1725, 1420, 1380, 1250, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.69 (br m, enol H), 4.15 (q, J = 7.8 Hz, 2 H, $CO_2CH_2CH_3$), 3.99–3.90 (m, 1 H), 3.80–3.70 (m, 2 H), 3.69 (s, 3 H, NCO_2CH_3), 3.39 (d, J = 9.0 Hz, 2 H), 1.24 (t, J = 7.8 Hz, 3 H, $CO_2CH_2CH_3$), 1.06 (s, 9 H, $C(CH_3)_3$); MS (CI, ammonia), m/e (rel intensity) 302 ($M^+ + 1$, 13), 260 (32), 246 (100), 228 (27), 214 (51), 200 (16), 168 (35).

***cis*-(±)-Hexahydro-3,4-dioxo-1*H*-furo[3,4-*b*]pyrrole-1-carboxylic Acid Methyl Ester (10).** A solution of **9** (25.5 g, 84.6 mmol) in trifluoroacetic acid–water (4:1, 100 mL) was stirred at room temperature for 24 h. The reaction mixture was concentrated in vacuo to dryness and the resultant solid residue was then purified by chromatography over silica gel (ethyl acetate–hexane, 1:1) to afford 12.98 g (77%) of **10** as a white crystalline solid: mp 148–150 °C (ethyl acetate–hexane); IR ($CHCl_3$) 1810, 1760, 1710, 1450, cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.96 (m, 1 H, C*H*N), 4.68 (m, 1 H, CO_2CH_2), 4.59 (m, 1 H, CO_2CH_2), 3.95 (s, 2 H, NCH_2CO), 3.76 (s, 3 H, NCO_2CH_3), 3.72 (d, J = 8.5 Hz, 1 H, COC*H*CO); MS, m/e (rel intensity) 201 ($M^+ + 2$, 0.9), 200 (2.9), 199 (M^+, 25.8), 171 (50.4), 168 (6.2), 167 (6.7), 141 (34.8), 140 (4.7), 99 (25.8), 88 (22.0), 85 (100.0), 82 (35.4), 69 (6.7), 68 (15.9); high-resolution mass spectrum for $C_8H_9NO_5$ requires 199.0480, measured 199.0474. Anal. Calcd for $C_8H_9NO_5$: C, 48.24; H, 4.55; N, 7.03. Found: C, 48.48; H, 4.79; N, 6.91.

***cis*-(±)-3-[2-(1,1-Dimethylethoxy)-2-oxoethylidene]hexahydro-4-oxo-1*H*-furo[3,4-*b*]pyrrole-1-carboxylic Acid Methyl Ester (11).** To a solution of pyrrolidinone **10** (13 g, 65.3 mmol) in dry tetrahydrofuran (350 mL) was added (carbo-*tert*-butoxymethylene)triphenylphosphorane (30.1 g, 80 mmol), and the solution was stirred until all solids had dissolved, followed by heating at 55 °C for 12 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and concentrated in vacuo. The thick oil was chromatographed over silica gel (hexane–ethyl acetate, 6:4) to yield 13.97 g (72%) of olefins **11** as a 10:1 mixture of *Z* to *E* isomers: mp 154–157 °C (ethyl acetate–hexane); IR ($CHCl_3$) 1780, 1705, 1449, 1370, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, major isomer) δ 6.10 (br s, 1 H), 4.69 (m, 2 H), 4.61 (m, 1 H), 4.50 (m, 2 H), 3.80 (br d, 1 H), 3.72 (s, 3 H), 1.45 (s, 9 H); ^{13}C NMR ($CDCl_3$, major isomer) δ 173.44, 164.43, 156.01, 149.63, 119.02, 81.01, 72.39, 57.72, 52.79, 51.16, 49.46, 28.00; MS, m/e (rel intensity) 297 (M^+, 0.3), 241 (0.7), 223 (25.1), 195 (3.1), 166 (3.8), 152 (5.5), 138 (7.3), 56 (20.5).

(3α,3aβ,6aβ)-(±)-Hexahydro-1-(methoxycarbonyl)-4-oxo-1*H*-furo[3,4-*b*]pyrrole-3-acetic Acid 1,1-Dimethylethyl Ester (12). To a solution of olefins **11** (11.95 g, 40.2 mmol) in methylene chloride (30 mL) and ethyl acetate (200 mL) was added 10% palladium on carbon (1.5 g), and the solution was stirred at room temperature under 1 atm of hydrogen. After hydrogen uptake ceased, the reaction mixture was filtered through Celite, and the filter cake was washed with methylene chloride (200 mL). The filtrate was concentrated in vacuo to give 11.91 g (99%) of ester lactone **12** (a 2:1 mixture of conformers) as a colorless oil that crystallized upon standing: mp 69–71 °C; IR ($CHCl_3$) 1770, 1720, 1700, 1420, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, major conformer) δ 4.58 (dd, J = 6.8, 5.4 Hz, 1 H, C*H*N), 4.52 (d, J = 11.0 Hz, 1 H, CO_2CH_2), 4.37 (m, 1 H, CO_2CH_2), 3.83 (m, 1 H, CH_2N), 3.70 (s, 3 H, NCO_2CH_3), 3.38 (t, J = 6.8 Hz, 1 H, C*H*CO_2), 2.93 (m, 3 H), 2.51 (dd, J = 18.0, 5.8 Hz, 1 H, $CH_2CO_2C(CH_3)_3$), 1.45 (s, 9 H, $C(CH_3)_3$); MS, m/e (rel intensity) 299 (M^+, 0.3), 286 (2.3), 243 (16.7), 242 (9.6), 226 (33.0), 196 (57.0), 184 (100.0), 152 (23.0), 126 (39.9), 56 (68.0).

(3α,4α,5α)-(±)-4,5-Bis(hydroxymethyl)-1-(methoxycarbonyl)pyrrolidine-3-acetic Acid 1,1-Dimethylethyl Ester (13). To a solution of pyrrolidine lactone **12** (11.97 g, 40.03 mmol) in dry tetrahydrofuran (200 mL) cooled to 0 °C was added lithium borohydride (0.963 g, 44.22 mmol) cautiously. When all the reducing agent was added, the reaction was stirred at 0 °C for 30 min, then at room temperature for 24 h. The reaction mixture was cooled to 0 °C and a 90% aqueous acetic acid solution (65 mL) was carefully and cautiously added. After gas evolution ceased, the reaction was concentrated in vacuo. The residue was dissolved in ethyl acetate (200 mL) and washed with saturated sodium bicarbonate solution (3 × 75 mL). The aqueous layers were combined and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford 11.9 g (98%) of essentially pure diol **13**: IR (film) 3400, 2985, 1720, 1680, 1420, 1150 cm^{-1}; ^1H NMR

(22) For the preparation of this compound, see: Kende, A. S.; Fludzinski, P. *Org. Synth.* **1985**, *64*, 104.

($CDCl_3$) δ 4.61 (br, 1 H), 4.00–3.91 (m, 2 H), 3.82 (m, 1 H), 3.76–3.62 (m, 4 H), 3.68 (s, 3 H), 3.20 (dd, J = 12.5, 9.0 Hz, 1 H), 2.63–2.28 (m, 4 H), 1.41 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 171.79, 156.71, 80.70, 62.10, 61.40, 58.77, 52.42, 52.21, 44.81, 35.83, 34.77, 27.94; MS, m/e (rel intensity) 272 (M^+ – 31, 0.3), 216 (90.8), 198 (21.1), 186 (24.7), 126 (25.1).

(3α,3aβ,7aβ)-(±)-Hexahydro-3-(hydroxymethyl)-6-oxopyrano[3,4-*c*]pyrrole-2(3*H*)-carboxylic Acid Methyl Ester (14). To a solution of diol ester **13** (9.8 g, 32.34 mmol) in methylene chloride (100 mL) was added a solution of aqueous trifluoroacetic acid (1:1, 0.75 mL), and the solution was heated to reflux for 23 h. The solution was cooled to room temperature and concentrated in vacuo. The resultant syrup was chromatographed over silica gel (ethyl acetate) to give 5.86 g (79%) of **14** as a white crystalline solid: mp 116–117 °C (ethyl acetate–hexane); IR ($CHCl_3$) 3440, 2960, 1750, 1690, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.38 (m, 2 H), 4.12 (m, 1 H), 3.99 (m, 1 H), 3.88 (m, 1 H), 3.70 (m, 1 H), 3.69 (s, 3 H), 3.11 (dd, J = 11.5, 7.7 Hz, 1 H), 2.88–2.63 (m, 4 H), 2.44 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 172.80, 154.43, 66.07, 59.68, 59.57, 52.40, 51.77, 38.68, 33.41, 31.85; MS, m/e (rel intensity) 229 (M^+, 0.7), 199 (23.9), 198 (100.0), 170 (28.7), 169 (21.4), 154 (41.0), 152 (14.6), 140 (69.7), 139 (40.0), 126 (56.5), 99 (45.9). Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.39; H, 6.60; N, 6.11. Found: C, 52.30; H, 6.50; N, 6.27.

(3α,3aβ,7aβ)-(±)-Hexahydro-3-formyl-6-oxopyrano[3,4-*c*]pyrrole-2(3*H*)-carboxylic Acid Methyl Ester (16). To a solution of oxalyl chloride (1.56 g, 1.1 mL, 12.26 mmol) in methylene chloride (20 mL) cooled to –72 °C was added dropwise a solution of dimethyl sulfoxide in methylene chloride (1:2, 9 mL), keeping the internal temperature of the reaction below –65 °C. After all the dimethyl sulfoxide solution was added, a solution of the alcohol lactone **14** (1.874 g, 8.2 mmol) in dry methylene chloride (10 mL) was added dropwise at –70 °C. The resultant solution was stirred under a nitrogen atmosphere for 1 h. The reaction mixture, which at the end of this time period was a thick white slurry, was carefully quenched with triethylamine (5.14 mL, 36.9 mmol), keeping the temperature below –65 °C. The reaction mixture was stirred at –70 °C for 10 min, then allowed to warm to –10 °C (internal temperature), poured into a saturated salt water solution (60 mL), and extracted. The organic layer was washed with an additional 60 mL of saturated salt water solution. The aqueous layers were combined and extracted with methylene chloride (3 × 75 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo with the bath temperature at 10 °C. The resulting aldehyde **16** (1.6 g, 86%) was shown to be pure by high-field ^1H NMR and used directly in the following reaction without purification: IR ($CHCl_3$) 2960, 1730, 1685, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.56 (s, 1 H), 4.41–4.21 (m, 3 H), 4.00 (m, 1 H), 3.69 (s, 3 H), 3.30 (dd, J = 11.6, 7.4 Hz, 1 H), 3.18–2.90 (m, 2 H), 2.73 (dd, J = 16.2, 7.4 Hz, 1 H), 2.46 (dd, J = 16.2, 4.2 Hz, 1 H); MS, m/e (rel intensity) 227 (M^+, 0.6), 198 (100.0).

(3α,3aβ,7aβ)-(±)-3-[(1,2-Dihydro-1-methoxy-2-oxo-3*H*-indol-3-ylidene)methyl]hexahydro-6-oxopyrano[3,4-*c*]-pyrrole-2(3*H*)-carboxylic Acid Methyl Ester (18). To a solution of 1-methoxy-2-indolone **5** (2.68 g, 16.4 mmol) in dry methylene chloride (20 mL) and diisopropylethylamine (2.12 g, 16.4 mmol) cooled to –78 °C was added dropwise and under a nitrogen atmosphere a 1 M solution of dibutylboron triflate (16.4 mL, 16.4 mmol). The resultant solution was stirred at –78 °C for 1 h and then treated with a solution of aldehyde **16** (1.6 g, 7.04 mmol) in methylene chloride (20 mL) added dropwise while maintaining an internal temperature below –70 °C. The reaction mixture was stirred at –78 °C for 1 h and then poured into distilled water (60 mL). The layers were separated, and the organic solution was washed with water (60 mL). The aqueous layers were combined and extracted with methylene chloride (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The resultant crude syrup after standing overnight at room temperature was chromatographed over silica gel (ethyl acetate–hexane, 8:2) to give 1.1 g (42%) of olefins **18** as a 8:1 mixture of isomers: IR ($CHCl_3$) 2995, 1720, 1690, 1550, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, major isomer) δ 7.47–7.28 (m, 2 H), 7.10–6.92 (m, 2 H), 6.77 (d, J = 9.2 Hz, 1 H), 5.44 (t, J = 9.1 Hz, 1 H), 4.15 (m, 3 H), 4.05 (s, 3 H), 3.65 (s, 3 H), 3.25 (m, 2 H), 2.96 (m, 1 H), 2.76 (m, 1 H), 2.49 (m, 1 H); MS, m/e (rel intensity) 372 (M^+, 2.4), 341 (64.8), 283 (30.4), 281 (11.6), 251 (12.8), 237 (13.6); high-resolution mass spectrum for $C_{19}H_{20}N_2O_6$ requires 372.1321, measured 372.1332.

(3α,3aβ,7aβ)-(±)-3-[(2,3-Dihydro-1-methoxy-2-oxo-1*H*-indol-3-yl)methyl]hexahydro-6-oxopyrano[3,4-*c*]pyrrole-2-(3*H*)-carboxylic Acid Methyl Ester (19). A solution of the olefins **18** (0.665 g, 1.787 mmol) in ethyl acetate (30 mL) and methylene chloride (10 mL) to which 5% of palladium on carbon (0.4 g) had been added was stirred at room temperature under 1 atm of hydrogen. After no more hydrogen uptake, the reaction mixture was filtered through Celite, and the filter cake was washed with methylene chloride (100 mL). The filtrate was concentrated in vacuo. The residue was chromatographed over silica gel (ethyl acetate) to afford 0.446 g (67%) of lactone **19** as a 1:1 mixture of diastereomers: IR (film) 2960, 1745, 1720, 1695, 1445 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60, 7.35–7.19 (each m, 2 H), 7.09 (m, 1 H), 6.95 (m, 1 H), 4.80–4.65 (m, 1 H), 4.31 (m, 2 H), 4.21–4.19 (m, 1 H), 4.01, 3.98 (each s, 3 H), 3.60 (m, 1 H), 3.57 (s, 3 H), 3.05–2.65 (m, 4 H), 2.50–2.15, 2.01, 1.78 (each m, 3 H); MS, m/e (rel intensity) 375 (M^+ + 1, 1.7), 374 (M^+, 7.2), 344 (4.2), 343 (4.1), 341 (6.8), 283 (7.3), 212 (19.7), 199 (15.0), 198 (49.8), 176 (30.5), 163 (34.3); high-resolution mass spectrum for $C_{19}H_{22}N_2O_6$ requires 374.1478, measured 374.1479.

(3α,3aβ,7aβ)-(±)-3-[(2,3-Dihydro-1-methoxy-2-oxo-1*H*-indol-3-yl)methyl]hexahydro-6-hydroxypyrano[3,4-*c*]-pyrrole-2(3*H*)-carboxylic Acid Methyl Ester (20). To a solution of lactone **19** (0.446 g, 1.19 mmol) in dry methylene chloride (20 mL) cooled to 0 °C was added dropwise a 1 M solution of lithium tri-*sec*-butylborohydride in THF (1.4 mL, 1.4 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 30 min followed by a second addition of lithium tri-*sec*-butylborohydride (1.4 mL, 1.4 mmol). The reaction mixture was stirred at 0 °C for 60 min and then quenched by the addition of a solution of saturated salt water and 2 M HCl (10:1, 40 mL). The organic solution was washed with brine (30 mL). The aqueous layers were combined and extracted with methylene chloride (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The resulting resinous residue was chromatographed over silica gel (ethyl acetate) to give 0.263 g (59%) of lactols **20** as a mixture of four diastereomers: IR (film) 3450, 2980, 1720, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58, 7.30, 7.05, 6.95 (each m, 4 H), 5.15–5.10, 4.92 (each m, 1 H), 4.52–4.37 (m, 1 H), 4.20 (m, 1 H), 4.00, 3.98 (each s, 3 H), 3.80–3.50, 3.30 (each m, 7 H), 2.70–2.20 (m, 4 H), 1.95, 1.80 (each m, 3 H); MS, m/e (rel intensity) 376 (M^+, 0.9), 358 (2.1), 246 (2.9), 245 (1.3), 244 (6.4), 328 (7.0), 300 (12.7), 283 (4.7), 214 (21.8), 200 (15.4), 196 (66.6), 182 (52.4), 168 (51.3), 146 (100.0), 145 (78.3).

(±)-7-Epi-4-(methoxycarbonyl)-20-desethylgelsedine (22b). To a solution of lactols **20** (0.18 g, 0.479 mmol) in chloroform (18 mL) was added a solution of trifluoroacetic anhydride–trifluoroacetic acid (1:1, 9 mL), and the resulting mixture was stirred at room temperature for 3 days and then concentrated in vacuo. The residue was chromatographed over silica gel (ethyl acetate) to give 0.091 g (53%) of **22b**: IR ($CHCl_3$) 2990, 1720, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26 (m, 1 H), 7.08–6.97 (m, 2 H), 6.94 (d, J = 7.2 Hz, 1 H), 4.36 (m, 2 H), 4.12 (dd, J = 9.1, 4.2 Hz, 1 H), 4.00 (br s, 3 H), 3.74 (s, 1 H), 3.60 (m, 5 H), 2.60 (m, 1 H), 2.54–2.20 (m, 4 H), 1.80 (dd, J = 13.2, 4.1 Hz, 1 H); MS, m/e (rel intensity) 360 (M^+ + 2, 0.9), 359 (4.4), 358 (M^+, 16.9), 329 (0.8), 328 (1.6), 295 (4.4), 267 (2.2), 196 (32.2), 182 (100.0), 176 (13.1), 144 (20.1); high-resolution mass spectrum for $C_{19}H_{22}N_2O_5$ requires 358.1549, measured 358.1549.

(±)-7-Epi-20-desethylgelsedine (23). To a solution of **22b** (0.065 g, 0.182 mmol) in toluene (16 mL) were added hexamethyldisilane (0.219 g, 1.461 mmol) and iodine (0.185 g, 0.731 mmol), and the resulting mixture was heated at 105 °C for 4 h under a nitrogen atmosphere, cooled to room temperature, and concentrated in vacuo. The brown residue was dissolved in dry methanol (5 mL) and stirred at room temperature for 15 min. The solution was concentrated in vacuo and the residue was purified by preparative thin-layer chromatography (2-mm silica gel plate, ethyl acetate–methanol, 2:1) to afford 0.033 g (61%) of the free amine **23** as a white hygroscopic solid: IR ($CHCl_3$) 3400, 2920, 1720, 1600, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18 (d, J = 7.4 Hz, 1 H, C(9)-H), 7.25 (t, J = 7.6 Hz, 1 H, C(11)-H), 7.01 (t, J = 7.2 Hz, 1 H, C(10)-H), 6.90 (d, J = 7.6 Hz, 1 H, C(12)-H), 4.29 (d, J = 10.8 Hz, 1 H, C(17)-H), 4.13 (dd, J = 10.8, 4.4 Hz, 1 H,

C(17)-H), 3.98 (s, 3 H, OCH_3), 3.85 (dt, J = 9.6, 3.1 Hz, 1 H, C(5)-H), 3.52 (d, J = 6.8 Hz, 1 H, C(3)-H), 3.18 (dd, J = 8.2, 4.0 Hz, 1 H, C(20)-H), 2.96 (d, J = 8.2 Hz, 1 H, C(20)-H), 2.42 (m, 2 H, C(6)-H and C(16)-H), 2.36-2.10 (m, 2 H, C(14)-H and C-(15)-H), 1.81-1.69 (m, 3 H, C(6)-H, C(14)-H, and N*H*); ^{13}C NMR ($CDCl_3$) δ 176.52, 140.09, 129.42, 128.98, 127.95, 122.57, 106.92, 74.48, 63.52, 62.51, 57.48, 54.20, 39.46, 35.31, 31.30, 29.98; MS, m/e (rel intensity) 301 (M^+ + 1, 1.3), 300 (M^+, 6.8), 271 (1.2), 270 (7.7), 185 (2.2), 158 (3.6), 149 (10.9), 124 (100.0), 111 (10.9), 85 (20.0); high-resolution mass spectrum for $C_{17}H_{20}N_2O_3$ requires 300.1473, measured 300.1450.

(±)-4-(1,1'-Biphenyl-4-ylcarbonyl)-7-epi-20-desethylgelsedine (24). To a solution of **23** (0.008 g, 0.0266 mmol) in methylene chloride (3 mL) cooled to -70 °C was added *p*-phenylbenzoyl chloride (0.0144 g, 0.0665 mmol), and the solution was stirred at -78 °C for 10 min. Triethylamine (0.02 mL) was added and the reaction was allowed to warm to room temperature and stirred for 30 min. The reaction mixture was poured into water (3 mL) and the layers were separated. The aqueous layer was extracted with methylene chloride (3 × 3 mL). The combined organic solution was concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (ethyl acetate-ether, 9:1) to give 0.009 g (70%) of **24** as a mixture of conformers: mp 248-249 °C dec; IR ($CHCl_3$) 3020, 1735, 1620, 1420, 1220 cm^{-1}; MS, m/e (rel intensity) 481 (M^+ + 1, 12.5), 480 (M^+, 38.5), 450 (28.2), 449 (30.0), 305 (55.5), 181 (100.0), 152 (53.0), 124 (16.1).

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Registry No. **5**, 65816-14-0; **7**, 124155-67-5; **7** (hydroxy ester), 10080-68-9; **8**, 5602-94-8; **9**, 124155-68-6; (±)-**10**, 124155-69-7; (±)-(*E*)-**11**, 124155-66-4; (±)-(*Z*)-**11**, 124223-45-6; (±)-**12**, 124155-70-0; (±)-**13**, 124155-71-1; (±)-**14**, 124155-72-2; (±)-**16**, 124155-73-3; (±)-(*E*)-**18**, 124155-65-3; (±)-(*Z*)-**18**, 124223-46-7; (±)-**19** (isomer 1), 124223-47-8; (±)-**19** (isomer 2), 124155-74-4; (±)-**20** (isomer 1), 124155-75-5; (±)-**20** (isomer 2), 124223-50-3; (±)-**20** (isomer 3), 124223-51-4; (±)-**20** (isomer 4), 124223-52-5; (±)-**22b**, 124223-48-9; (±)-**23**, 124223-49-0; (±)-**24**, 124242-39-3; $Ph_3P{=}CHCO_2Bu$-*t*, 35000-38-5; $H_2NCH_2CO_2Et{\cdot}HCl$, 623-33-6; *p*-PhBzCl, 14002-51-8.

Supplementary Material Available: Crystal data parameters, fractional coordinates, bond distances, bond angles, torsional angles, nearest intermolecular contacts, and anisotropic temperature factors for compound **24** (16 pages); observed and calculated structural factor amplitudes for the X-ray crystallographic determination of compound **24** (10 pages). Ordering information can be found on any current masthead page.

Facile Synthesis of 3'-*O*-Methylthymidine and 3'-Deoxythymidine and Related Deoxygenated Thymidine Derivative: A New Method for Selective Deoxygenation of Secondary Hydroxy Groups

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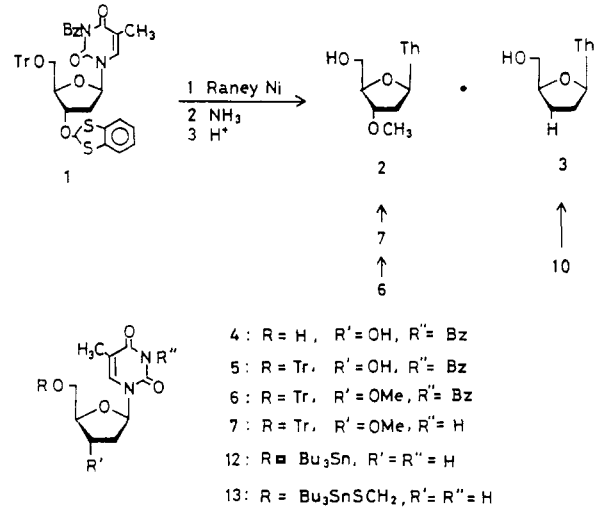
This paper deals with convenient syntheses of 3'-*O*-methylthymidine (**2**) and 3'-deoxythymidine (**3**), which involve Ag_2O-promoted methylation and Barton-Robins reductive deoxygenation, respectively. New methods for the regioselective 3'- and 5'-deoxygenation of thymidine have also been developed. Namely, compound **3** was synthesized by the 3',5'-O-diacylation of thymidine with phenyl chlorothionoformate (PTCF) followed by the selective 3'-reduction with tributyltin hydride and successive alkaline hydrolysis. 5'-Deoxythymidine (**18**) was obtained by the 5'-selective acylation of thymidine with PTCF followed by reduction with tributyltin hydride.

A wide variety of nucleoside derivatives have been synthesized to find biologically active species such as antivirus, antitumor, and antimicrobial agents.[1-5] Among them, deoxyribonucleotide derivatives with 3'-blocked structures are of great importance as inhibitors specific for various enzyme reactions that catalyze nucleic acid metabolism[6-11] and are useful particularly for molecular biology as shown in M13 DNA sequencing[12] which utilizes dideoxyribonucleotide triphosphates as chain termina-

Scheme I



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