resolution mass spectrum, calcd for $C_{14}H_{21}O_8$ m/z 317.1234, found M + H, 317.1222. Anal. Calcd for $C_{14}H_{20}O_8$: C, 53.11; H, 6.37. Found: C, 53.31; H, 6.61.

From **54**. Compound **54** (8 mg) was hydrolyzed with 80% aqueous acetic acid at ambient temperature for 48 h and evaporated. The residue was acetylated. Compound **55** (7 mg, 79%) was obtained after silica gel chromatography.

(1*S*,2*S*,3*S*,4*S*)-2,3,4-Trihydroxy-1-(hydroxymethyl)-cyclopentane (56). To a stirred solution of **55** (142 mg, 0.45 mmol) in methanol (4 mL) was added sodium methoxide (1 M in methanol, 1.3 mL, 1.3 mmol), and the mixture was stirred at 0 °C for 3 h. The solution was neutralized with Amberlite IR 120 (H^+), and the resin was removed by filtration to afford **56** (64 mg, 97%) as crystals. **56**: mp 103-104 °C; $[\alpha]^{23}_D$ -8.8° (*c* 0.56, MeOH); ^{1}H NMR (CD_3OD) δ 1.23-1.67 (1 H, m, H-1), 1.70-2.40 (2 H, m, H-5,5'), 3.30-5.43 (5 H, m, H-2,3,4, CH_2OH); high-resolution mass spectrum, calcd for $C_6H_{13}O_4$ m/z 149.0812, found M + H, 149.0783. Anal. Calcd for $C_6H_{12}O_4 \cdot {}^1/_4H_2O$: C, 47.20; H, 8.26. Found: C, 47.12; H, 8.16.

Acknowledgment. We express our sincere thanks to Professor Seiichiro Ogawa of Keio University for his valuable discussion on the structural identification of the pseudo-sugars synthesized in the present work.

Total Synthesis of (+)-Codonopsinine and Its Stereoisomers: Stereochemical Assignment of Natural (-)-Codonopsinine

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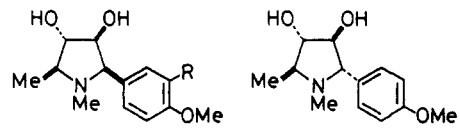
(+)-Codonopsinine [(+)-**1b**], the enantiomer of natural (-)-codonopsinine, and its stereoisomers, (2*R*,3*S*,4*S*,5*S*)-**1a**, (2*R*,3*S*,4*S*,5*R*)-**1c**, and (2*S*,3*S*,4*S*,5*R*)-**1d**, were synthesized in enantiomerically pure forms from diethyl L-tartrate via the common intermediate 4-*O*-benzyl-2,3-*O*-bis(methoxymethyl)-L-threose (**3**), thus leading to both stereochemical revision of codonopsinine from **1a** to **1b** and confirmation of the absolute configuration of natural codonopsinine to be 2*R*,3*R*,4*R*,5*R* [(-)-**1b**].

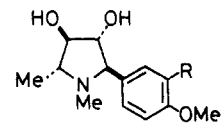
Codonopsinine and codonopsine, a new class of the 1,2,3,4,5-pentasubstituted pyrrolidine alkaloids isolated[1,2] from *Codonopsis clematidea*, have been shown to have structures assigned as **1** and **2**, respectively, by Russian workers.[3,4] In animal tests the latter has been found to possess hypotensive pharmacological activity with no effect on the central nervous system.[5] Shortly after the structure elucidation, in 1972 the Russian group[6] reported the relative stereochemistry for these alkaloids to be 2*R**,3*S**,4*S**,5*S** as shown in **1a** and **2a**, based on analyses of ^{1}H NMR coupling constants using the Karplus equation. However, vicinal coupling constants have been shown to be unreliable for assigning configurations of substituted pyrrolidines.[7] Thus, it seemed to us that the proposed assignments rested on dubious spectral interpretation, and hence, additional verification was desirable. In view of this, we recently reinvestigated the relative structure of codonopsinine by means of NOE experiments and chemical correlation that led to the revised structure **1b** for codonopsinine.[8] That study also revealed that the phthalimide intermediate for the synthesis of (+)-codonopsinine, originally assigned structure **6**,[9] actually possessed structure **7**, based on X-ray crystallographic analysis. In order to provide direct evidence for the structure of codonopsinine, we aimed to synthesize codonopsinine (**1b**) and all possible diastereoisomers (e.g., **1a**, **1c**, **1d**) with the vicinal hydroxy groups in the threo configuration (3*S*,4*S*) by utilizing the structurally established intermediates **6** and **7**.

In this paper, we describe the total synthesis of (+)-codonopsinine [(+)-**1b**] in detail[10] and its stereoisomers **1a**,

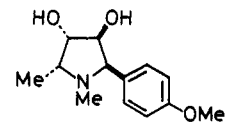


1a R = H
2a R = OMe

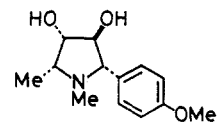
(+)-**1b**



(-)-**1b** R = H
(-)-**2b** R = OMe



1c



1d

(1) Matkhalikova, S. F.; Malikov, V. M.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1969**, *5*, 607.
(2) Matkhalikova, S. F.; Malikov, V. M.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1969**, *5*, 30.
(3) Matkhalikova, S. F.; Malikov, V. M.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1969**, *5*, 606.
(4) Matkhalikova, S. F.; Malikov, V. M.; Yagudaev, M. R.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1971**, *7*, 210.
(5) Khanov, M. T.; Sultanov, M. B.; Egorova, M. R. *Farmakol. Alkaloidov Serdech. Glikoyidov.* **1971**, 210; *Chem. Abstr.* **1972**, *77*, 135091r.
(6) Yagudaev, M. R.; Matkhalikova, S. F.; Malikov, V. M. *Khim. Prir. Soedin.* **1972**, *8*, 495.
(7) Booth, H. In *Progress in Nuclear Magnetic Resonance Spectroscopy*; Emsley, J. W., Feeney, J., Sutcliffe, L. H., Eds.; Pergamon: Oxford, 1969; Vol. 5, pp 220-225.
(8) Iida, H.; Yamazaki, N.; Kibayashi, C.; Nagase, H. *Tetrahedron Lett.* **1986**, *27*, 5393.
(9) Iida, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1985**, *26*, 3255.
(10) In the preceding communication,[9] (+)-codonopsinine [(+)-**1b**] synthesized was represented by the wrong formula **1a**.

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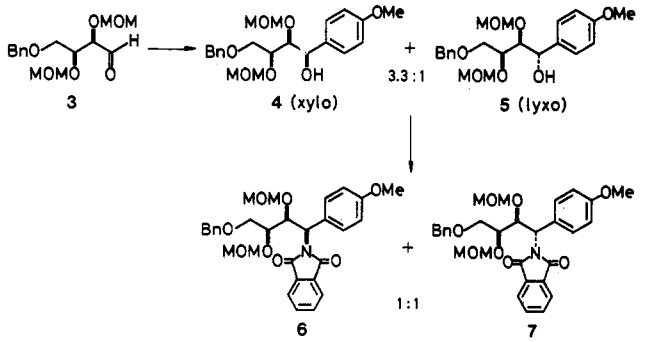
Scheme I



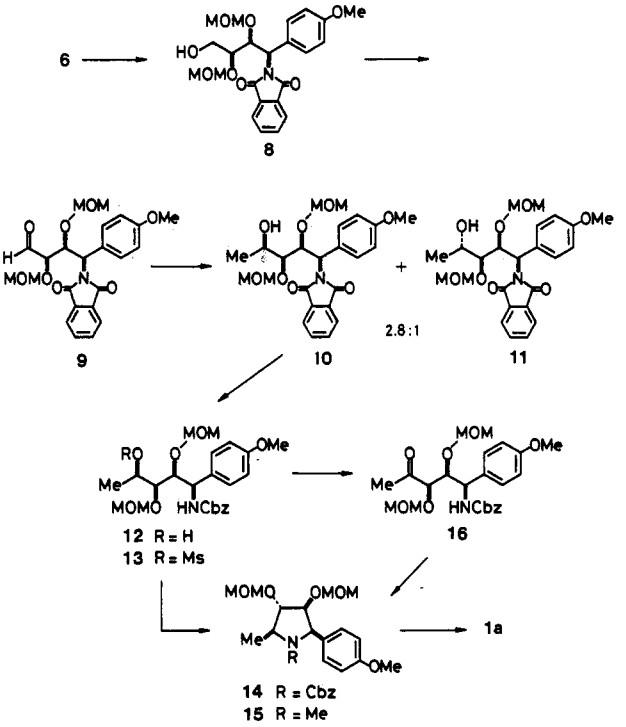
1c, and **1d** in enantiomerically pure forms from diethyl L-tartrate via the syn (**6**) and anti (**7**) phthalimides. The present invetigation provides additional evidence for the revised structure (+)-**1b** of (+)-codonopsinine, thus establishing the absolute stereochemistry of the naturally occurring levorotatory enantiomer of codonopsinine as 2*R*,3*R*,4*R*,5*R* or (−)-**1b**.

Our approach to the synthesis of (+)-codonopsinine [(+)-**1b**] and its stereoisomers **1a**, **1c**, and **1d** was based on utilization of the L-threose derivative **3** as a chiral synthon in the synthesis of natural products, to which we have devoted some of our recent efforts.[11,12] Thus, we chose first to synthesize the codonopsinine isomer **1a**, the original relative structure assigned for natural codonopsinine, starting from **3** as outlined in Scheme I. Compound **3**, readily available from diethyl L-tartrate,[11] was allowed to react with the Grignard reagent (*p*-$MeOC_6H_4MgBr$) to afford a chromatographically separable mixture of the L-xylo (**4**) and L-lyxo (**5**) alcohols in a ratio of 3.3:1, favoring the L-xylo isomer in agreement with the prediction based on the α-chelation cyclic model,[13] wherein neither β-chelation cyclic nor Felkin[14] models, both providing anti selectivity, should be eliminated.[15] Interestingly, the observed syn selectivity is opposite to the stereochemical outcome reported by Mukaiyama et al.[16] in the nucleophilic addition of organotin compounds to the 2,3-*O*-isopropylidene analogue of **3** where the reaction is antiselective, affording L-lyxo isomers predicted by the acyclic Felkin model.

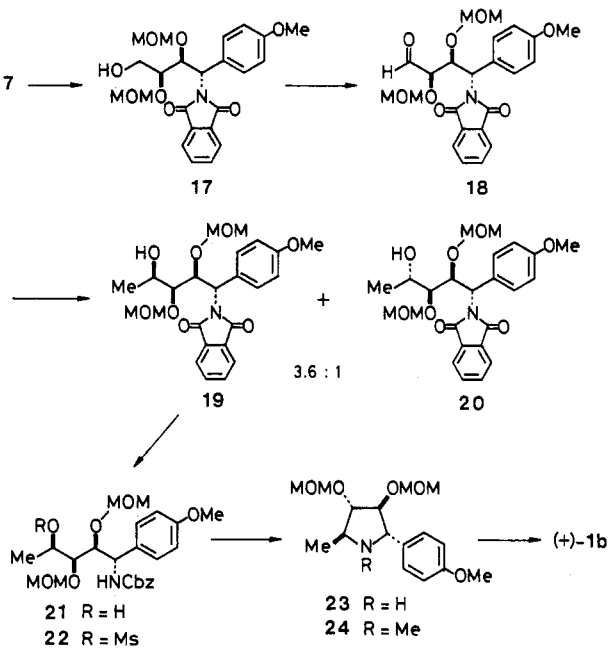
Application of the Mitsunobu method with phthalimide to the L-xylo alcohol **4** resulted in complete epimerization at C_1, providing a 1:1 mixture of the syn (**6**) and anti (**7**) phthalimide derivatives. When this reaction was carried out with the mixture of **4** and **5**, a 1:1 epimeric mixture of **6** and **7** was obtained as well. Column chromatography of this mixture afforded **7** and **6** as less polar and more polar products, respectively. In the preceding paper[9] we had mistakenly assigned the syn structure **6** to the less polar component. The recent study,[8] however, has disclosed that the less polar epimer is actually the anti isomer **7**, and thus, the more polar epimer has the syn structure **6**.

Preparation of the codonopsinine isomer **1a** from the syn epimer **6** is outlined in Scheme II. Thus, **6** was converted to the aldehyde **9** in 70% yield via debenzylation (H_2, Pd/C) followed by Swern oxidation of the resulting alcohol **8**. Syn selective Grignard addition (MeMgBr, ether) to **9** based on the α-chelation model as described above for **3** provided a 2.8:1 diastereomeric mixture of the syn (**10**) and anti (**11**) alcohols in 76% yield. The chiral precursor **10** with the four contiguous asymmetric centers properly arranged for **1a** was now obtained as a major product that was then converted to the hydroxy carbamate **12** by removal of the phthaloyl group by hydrazine hydrate followed by benzyloxycarbonylation. Cyclization to **14** was performed in 47% yield by intramolecular nucleophilic displacement of the mesylate **13**, prepared from **12** by a standard procedure, by using potassium *tert*-butoxide in THF at room temperature. Subsequent $LiAlH_4$ reduction of **14** led to the *N*-methyl derivative **15** (90% yield). For an alternative to the formation of **15**, **12** was converted to

Scheme II



Scheme III



(11) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 1069.
(12) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 4245.
(13) Still, W. C.; MacDonald, J. H., III *Tetrahedron Lett.* **1980**, *21*, 1031.
(14) Cherest, M.; Felkin, M.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.
(15) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 3769.
(16) Mukaiyama, T.; Suzuki, K.; Yamada, T. *Chem. Lett.* **1982**, 929.

Table I. ^{1}H NMR Spectral Data for (+)-Codonopsinine [(+)-1b] and Its Stereoisomers 1a, 1c, and 1d[a,b]

compd	H-2	H-3	H-4	H-5	NMe	CMe	OMe	aromatic
1a[c]	3.73 (d, J = 6.4)	4.59 (ddd, J = 6.4, 3.0, 1.0)	4.38 (dd, J = 6.4, 3.0)	2.60 (quint, J = 6.4)	2.21 (s)	1.50 (d, J = 6.4)	3.66 (s)	7.01, 7.60 (AB q, J = 7.8)
(+)-1b[d]	4.06 (d, J = 6.3)	4.64 (dd, J = 6.3, 4.0)	4.39 (t, J = 4.0)	3.70 (qd, J = 6.6, 4.0)	2.23 (s)	1.34 (d, J = 6.6)	3.67 (s)	6.98, 7.61 (AB q, J = 8.6)
1c[c]	4.14 (d, J = 6.5)	4.79 (t, J = 6.5)	4.90 (t, J = 6.5)	3.74 (quint, J = 6.5)	2.32 (s)	1.33 (d, J = 6.5)	3.66 (s)	7.03, 7.60 (AB q, J = 8.8)
1d[d]	3.41 (d, J = 6.9)	4.52 (dd, J = 6.9, 3.6)	4.58 (dd, J = 6.5, 3.6)	2.86 (quint, J = 6.5)	2.20 (s)	1.48 (d, J = 6.5)	3.66 (s)	6.98, 7.62 (AB q, J = 7.9)

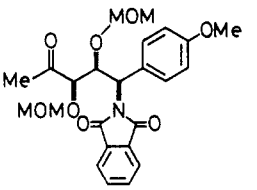
[a] In pyridine-d_5. [b] The chemical shifts are given in δ values measured from C_5H_5N (7.20 ppm) as an internal standard, and the J values are given in hertz. [c] At 200 MHz. [d] At 400 MHz.

the ketone **16** by the Swern method. Catalytic hydrogenation of **16** over palladium on carbon in methanol resulted in direct generation of **15** as a single diasteromer in 50% yield.[17] Deprotection of **15** by acidic workup furnished quantitatively (−)-2-epicodonopsinine (**1a**), whose ^{1}H NMR spectrum (Table I) and physical properties (except for the sign of optical rotation) were clearly different from those reported[1,6] for natural codonopsinine.

The synthesis of **1a** showed that the earlier stereochemistry assigned to codonopsinine was incorrect. We therefore undertook the synthesis of codonopsinine represented by the revised formula **1b**. The procedure for the synthesis of (+)-**1b** was based on utilization of the anti phthalimide **7** as a starting material, which had the proper configuration to form the D-gulo framework (**19**) required for (+)-**1b** (Scheme III). Debenzylation of **7** by hydrogenolysis followed by Swern oxidation of the resulting alcohol **17** yielded aldehyde **18**. Compound **18** suffered α-chelation-controlled addition of the Grignard reagent (MeMgBr, ether), which proceeded with a diastereoselectivity of 3.6:1 in 62% yield, providing the desired D-gulo alcohol **19** as the major epimer. Removal of the phthaloyl group with hydrazine hydrate followed by benzyloxycarbonylation gave the carbamate **21** in quantitative overall yield, which was then transformed into the mesylate **22** by the usual procedure. Catalytic hydrogenolysis of **22** over palladium on carbon in methanol resulted in exclusive formation of **23** via in situ cyclization. N-Methylation of **23** by catalytic hydrogenation over palladium on carbon in methanol in the presence of formaldehyde gave **24**, which was deprotected by treatment with hydrochloride acid to afford (+)-codonopsinine (**1b**) in 58% overall yield from **23**. Synthetic (+)-**1b** proved to be identical with natural codonopsinine[6] by ^{1}H NMR (Table I) and mass spectra and had $[\alpha]^{20}_D$ + 12.5° (c 2.55, MeOH) while the natural product is reported[1] to have $[\alpha]^{20}_D$ −8.8° (c 0.1, MeOH). It follows therefore, that the naturally occurring levorotatory enantiomer of codonopsinine has the opposite absolute configuration to (+)-**1b** and should be depicted by (−)-**1b**.

Having established that 1,2,3,4,5-pentasubstituted pyrrolidines can be stereoselectively elaborated by using syn and anti phthalimide intermediates, we next applied this method to the preparation of the other codonopsinine stereoisomers **1c** and **1d**. These syntheses would offer further evidence for confirmation of the stereochemical relationship between codonopsinine and its stereoisomers with respect to C-2 and C-5. To this end, we proposed utilizing the L-gluco (**11**) and L-manno (**20**) alcohols as precursors of **1c** and **1d**, respectively; however, both of these were, obtained only as minor diastereoisomers in the Grignard addition described above. Therefore we first sought a practical route to these intermediates **11** and **20**.

Thus, the diastereomeric mixture of **10** and **11** from the Grignard reaction of **9** was subjected to Swern oxidation to give the ketone **25**. Reduction of **25** with $NaBH_4$



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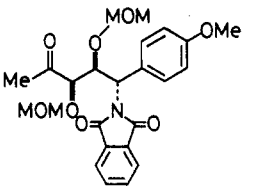

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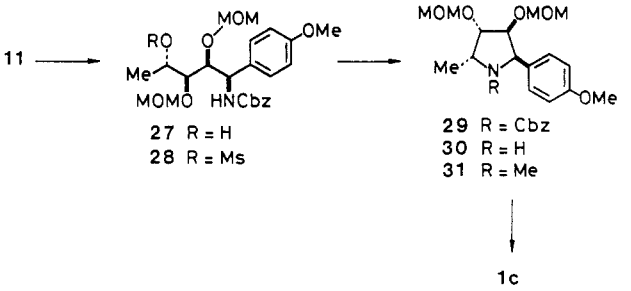
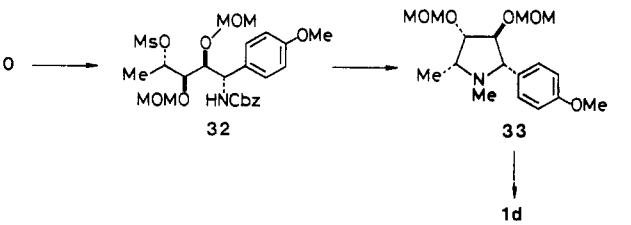
proceeded in diastereoselective manner (2.7:1), thus affording the desire alcohol **11** as a major product as predicted by the α-chelate cyclic model. Similarly, when the tandem sequence involving Swern oxidation–hydride addition was applied to the mixture of **19** and **20**, the chelation-controlled product **20** was isolated with a diastereoselectivity of 3:1.

After removal of the phthaloyl group by hydrazine hydrate, **11** was converted to the mesylate **28** by benzyloxycarbonylation followed by mesylation. Intramolecular



cyclization of **28** was carried out by using potassium *tert*-butoxide in THF at 0 °C and produced **29**, which was converted to **31** in 47% yield from **28** by $LiAlH_4$ reduction. Alternatively, **31** was formed from **28** in 48% yield by hydrogenolytic cyclization (H_2, Pd/C, MeOH) followed by N-methylation (H_2, Pd/C, HCHO, MeOH). The cleavage of the MOM ethers afforded **1c**, physical and ^{1}H NMR (Table I) data of which were not identical with those reported[1,6] for natural codonopsinine as expected.

Finally, the synthesis of the codonopsine stereoisomer **1d** was achieved as follows. The mesylate **32**, prepared from **20** in three steps involving dephthaloylation, N-benzyloxycarbonylation, and mesylation, was subjected to



(17) A clear mechanistic rationalization of the formation of **15** from **16** has not been made at present.

cyclization via hydrogenolysis and subsequent Nh-methylation (H_2, Pd/C, HCHO, MeOH) to form exclusively **33** in 71% overall yield from **20**. Deprotection of **33** afforded **1d**, which was found to have ^{1}H NMR (Table I) clearly different from that of natural codonopsinine.[6]

In conclusion, these syntheses of (+)-codonopsinine and its stereoisomers have proven that the relative stereochemistry of codonopsinine has to be revised from **1a** to **1b**, thus establishing the absolute configuration of the natural levorotatory enantiomer as *2R3R,4R,5R*. This work also results in the revision of the stereochemistry of codonopsine from **2a** to **2b** and allows the absolute stereostructure of the naturally occurring levoratatory enantiomer to be assigned as (−)-**2b**.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were measured at 90, 200, or 400 MHz. ^{13}C NMR spectra were recorded at 50.1 or 100.6 MHz. Mass spectra were obtained at an ionizing potential of 70 eV. Optical rotations were measured at the sodium D line in a 0.1-dm cell at the designated concentration in grams/100 mL. TLC was run on Wako precoating silica gel 70 FM plates. Column chromatography refers to flash chromatography on Merck silica gel (230–400 mesh).

Grignard Reaction of 4-*O*-Benzyl-2,3-*O*-bis(methoxymethyl)-L-threose (3). A solution of (*p*-methoxyphenyl)magnesium bromide in THF (100 mL), prepared from magnesium turnings (1.40 g, 58 mmol) and *p*-bromoanisole (13.00 g, 70 mmol) at reflux temperature by the usual Grignard technique, was cooled to −10 °C, and to this was added dropwise **3** (6.90, 23 mmol) in THF (20 mL) under N_2 with stirring. The mixture was allowed to reach room temperature and was stirred for 10 h. The reaction was quenched by addition of water (5 mL). Ether (150 mL) was added, and the reaction mixture was filtered through Celite, dried ($MgSO_4$), and evaporated to dryness. The residue was purified by chromatography on silica gel with 3:1 hexane–ethyl acetate. The first fraction gave (1*S*,2*S*,3*S*)-4-(benzyloxy)-2,3-bis[(methoxymethyl)oxy]-1-(*p*-methoxyphenyl)-1-butanol [**5**; 1.83 g (20%)] as an oil: $[\alpha]^{21}_D$ −61.3° (*c* 0.32, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ ($CHCl_3$) 3.09 (3 H, s), 3.42 (3 H, s), 3.66 (1 H, d of $^1/_2$ AB q, *J* = 5.2, 9.7 Hz), 3.68 (1 H, d of $^1/_2$ AB q, *J* = 6.5, 9.7 Hz), 3.73 [0.5 H, d (a part of dd), *J* = 2.8 Hz], 3.75 [3 H, s; including 0.5 H (a part of dd)], 3.79 (1 H, d, *J* = 4.0 Hz), 4.04 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.13 (1 H, td, *J* = 5.6, 2.8 Hz), 4.27 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.50 (1 H, $^1/_2$ AB q, *J* = 11.9 Hz), 4.54 (1 H, $^1/_2$ AB q, *J* = 11.9 Hz), 4.70 (1 H, dd, *J* = 7.8, 3.9 Hz), 4.75 (1 H, $^1/_2$ AB q, *J* = 6.5 Hz), 4.84 (1 H, $^1/_2$ AB q, *J* = 6.5 Hz), 6.84 (2 H, $^1/_2$ AB q, *J* = 8.7 Hz), 7.20–7.40 (7 H, m); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 55.05, 55.85, 70.35, 72.64, 73.25, 76.61, 81.23, 97.32, 97.60, 113.49,127.55, 128.24, 128.30, 133.67, 137.90, 159.07.

The second fraction gave (1*R*,2*S*,3*S*)-4-(benzyloxy)-2,3-bis[(methoxymethyl)oxy]-1-(*p*-methoxyphenyl)-1-butanol [**4**; 6.03 g (64%)] as an oil: $[\alpha]^{19}_D$ −26.0° (*c* 1.07 , MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ ($CHCl_3$) 3.29 (3 H, s), 3.35 (3 H, s), 3.50–3.72 (3 H, m), 3.78 (3 H, s; including 1 H), 3.87 (1 H, dd, *J* = 5.9, 3.0 Hz), 4.40–4.75 (6 H, m), 4.83 (1 H, dd, *J* = 5.6, 3.3 Hz), 6.86 (2 H, $^1/_2$ AB q, *J* = 8.6 Hz), 7.28 ($^1/_2$ AB q, *J* = 8.6 Hz), 7.30 (5 H, s); mass spectrum, *m/e* (relative intensity) 389 (M^+ − 17, 12), 313 (32), 295 (21), 253 (16), 207 (72), 181 (68), 163 (65), 137 (55), 121 (37), 91 (100). Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 64.85; H, 7.41.

Mitsunobu Reaction of 4. To a stirred, ice-cold solution of **4** (9.3 g, 23 mmol), phthalimide (8.4 g, 57 mmol), and triphenylphosphine (15.0 g, 57 mmol) in THF (300 mL) was added diethyl azodicarboxylate (10.0 g, 57 mmol). The mixture was allowed to reach room temperature and was stirred for 12 h. After the solvent was evaporated, the residue was subjected to chromatography on silica gel with 4:1 hexane–ethyl acetate to remove most of the triphenylphosphine oxide from the reaction product. To the oily product was added benzene (100 mL), and a separated solid was filtered off. The filtrate was evaporated, and the same treatment with benzene (50 mL) was repeated to give a pale yellow syrup that was chromatographed on silica gel with 5:1 hexane–ethyl acetate. The first fraction gave (1*S*,2*S*,3*S*)-4-(benzyloxy)-2,3-bis[(methoxymethyl)oxy]-1-(*p*-methoxyphenyl)-1-(1,3-dioxo-2-azindan-2-yl)butane [**7**; 3.9 g (32%)] as an oil: $[\alpha]^{20}_D$ −64.3° (*c* 4.20, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ ($CHCl_3$) 2.96 (3 H, s), 3.24 (3 H, s), 3.60–4.05 (3 H, m; including 3 H, s at δ 3.76), 4.21 (1 H, d, *J* = 6.8 Hz), 4.34 (1 H, d, *J* = 6.8 Hz), 4.52 (1 H, d, *J* = 6.8 Hz), 4.54 (2 H, br s), 4.70 (1 H, d, *J* = 6.6 Hz), 5.18 (1 H, d, *J* = 10.7 Hz), 5.39 (1 H, d, *J* = 10.7 Hz), 6.83 (2 H, $^1/_2$ AB q, *J* = 8.5 Hz), 7.32 (5 H, br s), 7.47–7.90 (4 H, m; including 2 H, $^1/_2$ AB q, *J* = 8.5 Hz at δ 7.60); mass spectrum, *m/e* (relative intensity) 428 (1.5), 352 (6.5), 311 (3.5), 266 (100), 218 (10), 176 (30), 148 (20), 130 (17), 91 (25).

The second fraction gave (1*R*,2*S*,3*S*)-4-(benzyloxy)-2,3-bis[(methoxymethyl)oxy]-1-(*p*-methoxyphenyl)-1-(1,3-dioxo-2-azindan-2-yl)butane [**6**; 3.9 g (32%)] as an oil: $[\alpha]^{23}_D$ −61.9° (*c* 7.2, MeOH); ^{1}H NMR (90 MHz, $CDCl_3$) δ (Me_4Si) 2.85 (3 H, s), 2.92–3.42 (2 H, m, including 3 H, s at δ 3.30), 3.62 (2 H, br s), 3.75 (3 H, s), 4.15 (1 H, d, *J* = 7.5 Hz), 4.47–4.78 (2 H, m; including 2 H, br s at δ 4.48), 5.23 (1 H, d, *J* = 11.1 Hz) 5.63 (1 H, d, *J* = 11.1 Hz), 6.83 (2 H, $^1/_2$ AB q, *J* = 9.0 Hz), 7.33 (5 H, br s), 7.48–7.95 (6 H, m); mass spectrum, *m/e* (relative intensity) 352 (8), 266 (100), 151 (18), 91 (43).

(2*S*,3*S*,4*R*)-2,3-Bis[(methoxymethyl)oxy]-4-(*p*-methoxyphenyl)-4-(1,3-dioxo-2-azindan-2-yl)-1-butanol (8). A methanolic solution (10 mL) of **6** (400 mg, 0.747 mmol) including 10% palladium on carbon (400 mg) was hydrogenolyzed at 1 atm for 3.5 h. Filtration followed by evaporation left an oil that was purified by chromatography on silica gel with 2:1 hexane–ethyl acetate to give **8** [250 mg (75%)] as a colorless oil: $[\alpha]^{18}_D$ −186.8° (*c* 0.66, MeOH); ^{1}H NMR (90 MHz, $CDCl_3$) δ (Me_4Si) 3.07 (3 H, s), 3.15–4.10 (5 H, m; including 3 H, s at δ 3.38, 3 H, s at δ 3.77), 4.50–4.72 (3 H, m), 5.13 (1 H, $^1/_2$ AB q, *J* = 10.5 Hz, with further fine spliting), 5.63 (1 H, $^1/_2$ AB q, *J* = 10.5 Hz), 6.83 (2 H, $^1/_2$ AB q, *J* = 9.0 Hz), 7.52–7.88 (4 H, m; including 2 H, $^1/_2$ AB q, *J* = 9.0 Hz at δ 7.57); mass spectrum, *m/e* (relative intensity) 353 (7.0), 308 (6.5), 266 (100).

(2*R*,3*S*,4*R*)-2,3-Bis[(methoxymethyl)oxy]-4-(*p*-methoxyphenyl)-4-(1,3-dioxo-2-azindan-2-yl)butanal (9). To a stirred solution of oxalyl chloride (286 mg, 2.25 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added dropwise a solution of Me_2SO (352 mg, 4.50 mmol) in CH_2Cl_2 (3 mL) over a period of 5 min, and the mixture was stirred for another 15 min at −78 °C. To this mixture was added dropwise a soltuion of **8** (251 mg, 0.56 mmol) in CH_2Cl_2 (3 mL), and stirring was continued at −78 °C. After 1 h, triethylamine (684 mg, 6.76 mmol) was added to the reaction mixture and the reaction was allowed to warm to ambient temperature. After addition of water (5 mL) the mixture was stirred for 15 min, extracted with CH_2Cl_2 (3 × 20 mL), and washed with brine, and the extract was dried ($MgSO_4$). Removal of the solvent by evaporation followed by chromatography of the residue on silica gel with 3:1 hexane–ethyl acetate gave **9** (233 mg, 93%) as a colorless oil: $[\alpha]^{21}_D$ −76.8° (*c* 1.28, MeOH); IR ($CHCl_3$) 1760, 1705 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ (Me_4Si) 3.00 (3 H, s), 3.43 (3 H, s), 3.70 (1 H, br s), 3.77 (3 H, s), 4.28 (1 H, $^1/_2$ AB q, *J* = 6.9 Hz), 4.57 (2 H, br s), 4.75 (1 H, $^1/_2$ AB q, *J* = 6.9 Hz), 5.45 (1 H, $^1/_2$ AB q, *J* = 10.5 Hz, with further fine spliting), 5.65 (1 H, $^1/_2$ AB q, *J* = 10.5 Hz), 6.88 (2 H, $^1/_2$ AB q, *J* = 9.0 Hz), 7.50–7.90 (6 H, m), 9.67 (1 H, s); mass spectrum, *m/e* (relative intensity) 352 (1.9), 339 (1.9), 336 (1.6), 308 (2.6), 292 (1.8), 280 (4.6), 279 (6.3), 266 (100).

Reation of 9 with Methylmagnesium Bromide. To a stirred solution of MeMgBr, prepared from 95 mg (1.0 mmol) of methyl bromide and 16 mg (0.66 mmol) of Mg, in ether (5 mL) was added at −78 °C a solution of **9** (190 mg, 0.43 mmol) in ether (3 mL) via syringe under N_2. After the reaction mixture was stirred at −78 °C for 2 h, it was quenched with water (1 mL) and extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated, and the residue was chromatographed on silica gel with $CHCl_3$. The first fraction gave (2*R*,3*S*,4*S*,5*R*)-3,5-bis[(methoxymethyl)oxy]-5-(*p*-methoxyphenyl)-5-(1,3-dioxo-2-azidan-2-yl)-2-pentanol [**10**; 110 mg (56%)] as a colorless oil: $[\alpha]^{20}_D$ −70.5° (*c* 0.41, MeOH); ^{1}H NMR (200 Hz, $CDCl_3$) δ ($CHCl_3$) 1.23 (3 H, d, *J* = 6.3 Hz), 2.99 (3 H, s), 3.01–3.14 (1 H, m), 3.47 (3 H, s), 3.77 (3 H, s), 3.83–4.00 (2 H, m), 4.10 (1 H, d, *J* = 6.8 Hz), 4.58–4.80 (3 H, m), 5.15 [1 H, $^1/_2$ AB q, *J* = 10.6 Hz, with further fine spliting (*J* = 1.0 Hz)], 5.61 (1 H, $^1/_2$ AB q, *J* = 10.6 Hz), 6.85 (2 H, $^1/_2$ AB q, *J* = 8.8 Hz), 7.54 (2 H, $^1/_2$ AB q, *J* = 8.8 Hz), 7.60–7.88 (4 H, m);

mass spectrum, m/e (relative intensity) 429 ($M^+ - 30$, 1.5), 355 (2.2), 353 (2.6), 308 (5), 266 (100).

The second fraction gave (2*S*,3*S*,4*S*,5*R*)-3,4-bis[(methoxymethyl)oxy]-5-(*p*-methoxyphenyl)-5-(1,3-dioxo-2-azidan-2-yl)-2-pentanol [11; 40 mg (20%)] as a colorless oil: $[\alpha]^{20}_D$ −135.5° (*c* 2.43, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ ($CHCl_3$) 1.26 (3 H, d, *J* = 6.4 Hz), 3.04 (3 H, s), 3.15–3.32 (2 H, m), 3.48 (3 H, s), 3.76 (3 H, s), 3.90 (1 H, dd, *J* = 12.6, 6.2 Hz), 4.28 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.55–4.75 (3 H, m), 5.30 [1 H, $^1/_2$ AB q, *J* = 10.8 Hz, with further fine spliting (*J* = 0.7 Hz)], 5.64 (1 H, $^1/_2$ AB q, J = 10.8 Hz), 6.84 (2 H, $^1/_2$ AB q, J = 8.5 Hz), 7.55 (2 H, $^1/_2$ AB q, *J* = 8.5 Hz), 7.58–7.85 (4 H, m); mass spectrum, m/e (relative intensity) 353 (2.5), 308 (0.6), 266 (100).

(2*R*,3*S*,4*S*,5*R*)-5-[[(Benzyloxy)carbonyl]amino]-3,4-bis[(methoxymethyl)oxy]-5-(*p*-methoxyphenyl)-2-pentanol (12). A solution of **10** (210 mg, 0.46 mmol) and hydrazine hydrate (57 mg, 1.14 mmol) in ethanol (8 mL) was refluxed for 2.5 h. After cooling, the reaction mixture was diluted with ether (15 mL) and filtered. The filtrate was concentrated in vacuo to give an oily product that was dissolved in CH_2Cl_2 (3 mL). To the resulting solution was added a solution of Na_2CO_3 (48 mg, 0.45 mmol) in H_2O (2 mL), and to this at 0 °C with stirring was added dropwise a solution of benzyl chloroformate (78 mg, 0.46 mmol) in CH_2Cl_2 (1 mL) via syringe. The mixture was stirred at room temperature for 2 h, extracted with CH_2Cl_2 (3 × 20 mL), and dried ($MgSo_4$). The solvent was removed, and the residue was purified by chromatography on silica gel with 2:1 hexane–ethyl acetate to give **12** [200 mg (94%)] as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ (Me_4Si) 1.22 (3 H, d, *J* = 6.0 Hz), 2.77 (1H, br d, *J* = 6.0 Hz), 2.95–5.22 (8 H, m; including 3 H, s at δ 3.10, 3 H, s at δ 3.43, 3 H, s at δ 3.78, 2 H, br s at δ 5.08), 5.88 (1 H, br d, *J* = 9.0 Hz), 6.87 (2 H, $^1/_2$ AB q, *J* = 9.0 Hz), 7.23 (2 H, $^1/_2$ AB q, *J* = 9.0 Hz).

(1*R*,2*S*,3*R*,4*R*)-1-[[(Benzyloxy)carbonyl]amino]-2,3-bis[(methoxymethyl)oxy]-1-(*p*-methoxyphenyl)-4-[(methylsulfonyl)oxy]pentane (13). To a stirred, cold (0 °C) solution of **12** (68 mg, 0.15 mmol) and triethylamine (1 mL) in CH_2Cl_2 (1 mL) was added a solution of mesyl chloride (21 mg, 0.18 mmol) in CH_2Cl_2 (0.5 mL) via syringe. After being stirred at 0 °C for 5 min and at room temperature for 5 min, the mixture was diluted with ether (5 mL) and filtered to remove the salt separated. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel with 2:1 hexane–ethyl acetate to give **13** [46 mg (58%)] as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ (Me_4Si) 1.52 (3 H, d, *J* = 9.6 Hz), 3.02 (6 H, s), 3.43 (3 H, s), 3.51–5.25 (8 H, m; including 3 H, s at δ 3.78, 2 H, br s at δ 5.07), 5.75 (1 H, br d, *J* = 9.0 Hz), 6.87 (2 H, $^1/_2$ AB q, *J* = 9.3 Hz), 7.32 (2 H, $^1/_2$ AB q, *J* = 9.3 Hz), 7.35 (5 H, br s).

(2*R*,3*S*,4*S*,5*S*)-*N*-[(Benzyloxy)carbonyl]-3,4-bis[(methoxymethyl)oxy]-2-(*p*-methoxyphenyl)-5-methylpyrrolidine (14). To a stirred, ice-cold solution of **13** (17 mg, 0.031 mmol) in THF (3 mL) was added potassium *tert*-butoxide (4 mg, 0.036 mmol), and the mixture was stirred at 0 °C for 20 min and then at room temperature for 10 min. The reaction was quenched by addition of water (1 mL) under cooling. The resulting mixture was extracted with ether, and the ether extract was washed with water and dried ($MgSO_4$). Removal of the solvent left an oil that was purified by chromatography on silica gel with 3:1 hexane–ethyl acetate to afford **14** [6.6 mg (47%)] as a colorless oil: $[\alpha]^{20}_D$ −20.3° (*c* 0.74, MeOH); ^{1}H NMR (90 MHz, $CDCl_3$) δ Me_4Si 1.55 (3 H, d, *J* = 6.9 Hz), 3.02 (3 H, s), 3.40 (3 H, s), 3.78 (3 H, s), 3.85–5.22 (8 H, m; including 2 H, s at δ 4.71), 6.83 (2 H, $^1/_2$ AB q, *J* = 9.0 Hz), 7.20 (2 H, $^1/_2$ AB q, *J* = 9.0 Hz), 7.28 (5 H, br s); mass spectrum, m/e (relative intensity) 445 (0.6), 414 (0.3), 383 (1.6), 323 (12), 310 (18), 278 (6), 162 (22), 91 (100); exact mass calcd for $C_{24}H_{31}NO_7$ (M^+) 445.2097, found 445.2064.

(3*R*,4*S*,5*R*)-5-[[(Benzyloxy)carbonyl]amino]-3,4-bis[(methoxymethyl)oxy]-5-(*p*-methoxyphenyl)pentan-2-one (16). In a manner similar to the preparation of **9** above, the reaction of **12** was run. Identical workup followed by chromatography on silica gel with 3:1 hexane–ethyl acetate gave **16**. From 140 mg (0.30 mmol) of **12** was obtained 118 mg (85%) of **16** as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ ($CHCl_3$) 2.21 (3 H, s), 3.16 (3 H, s), 3.40 (3 H, s), 3.78 (3 H, s), 3.80–5.25 (7 H, m), 5.90 (1 H, br s), 6.85 (2 H, $^1/_2$ AB q, *J* = 9.1 Hz), 7.23 (2 H, $^1/_2$ AB q, *J* = 9.1 Hz), 7.32 (5 H, br s).

(2*R*,3*S*,4*S*,5*S*)-Bis[(methoxymethyl)oxy]-2-(*p*-methoxyphenyl)-1,5-dimethylpyrrolidine (15). A. From 14. To a stirred cold (0 °C) slurry of $LiAlH_4$ (10 mg, 0.26 mmol) in THF (4 mL) was added a solution of **14** (13.8 mg, 0.031 mmol) in THF (1 mL) via syringe. The mixture was refluxed for 3 h, quenched with water (0.5 mL) under cooling, and diluted with ether (20 mL). This was filtered through a silica gel pad, dried ($MgSO_4$), and evaporated in vacuo. The residue was chromatographed on silica gel eluted initially with 99:1 $CHCl_3$–ammoniacal methanol and then with ethyl acetate, affording **15** [9.1 mg (90%)] as a colorless oil: $[\alpha]^{21}_D$ −89.7° (*c* 1.19, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ ($CHCl_3$) 1.32 (3 H, d, *J* = 6.2 Hz), 2.09 (3 H, s), 2.25 (1 H, quint, *J* = 6.2 Hz), 3.00 (3 H, s), 3.40 (1 H, d, *J* = 5.4 Hz), 3.41 (3 H, s), 3.77 (1 H, dd, *J* = 6.1, 1.7 Hz), 3.80 (3 H, s), 3.95 (1 H, dd, *J* = 5.4, 1.7 Hz), 3.99 (1 H, $^1/_2$ AB q, *J* = 6.9 Hz), 4.25 (1 H, $^1/_2$ AB q, *J* = 6.9 Hz), 4.68 (1 H, $^1/_2$ AB q, *J* = 6.7 Hz), 4.81 (1 H, $^1/_2$ AB q, *J* = 6.7 Hz), 6.85 (2 H, $^1/_2$ AB q, *J* = 8.8 Hz), 7.29 (2 H, $^1/_2$ AB q, *J* = 8.8 Hz); mass spectrum, m/e (relative intensity) 325 (M^+, 10), 310 (16), 294 (10), 280 (30), 264 (18), 194 (26), 177 (84), 176 (100), 162 (34), 121 (38), 45 (79).

B. From 16. A methanolic solution (5 mL) of **16** (48 mg 0.10 mmol) was vigorously stirred under 1 atm hydrogen in the presence of 10% palladium on carbon for 48 h. Filtration, concentration, and purification by silica gel chromatography (99:1 $CHCl_3$–ammoniacal methanol followed by ethyl acetate) gave **15** (17 mg, 50%), in all respects identical with the sample obtained from **14**.

(2*R*,3*S*,4*S*,5*S*)-3,4-Dihydroxy-2-(*p*-methoxyphenyl)-1,5-dimethylpyrrolidine (Codonopsinine Stereoisomer 1a). A solution of **15** (7 mg, 0.022 mmol) in methanol (1 mL) and 3 N HCl (0.5 mL) was heated at 50 °C for 2.5 h. The volatile components of the mixture were removed in vacuo. The residue was dissolved in water (1 mL), made basic by addition of solid Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried ($MgSO_4$). Evaporation of the solvent in vacuo afforded 5 mg (98%) of an oil (**1a**): $[\alpha]^{22}_D$ −33.0° (*c* 1.0, MeOH); ^{1}H NMR, Table I; mass spectrum, m/e (reative intensity) 237 (26), 222 (10), 177 (64), 176 (100), 164 (16), 162 (46), 121 (25); exact mass calcd for $C_{13}H_{19}NO_3$ (M^+) 237.1363, found 237.1362.

(2*S*,3*S*,4*S*)-2,3-Bis[(methoxymethyl)oxy]-4-(*p*-methoxyphenyl)-4-(1,3-dioxo-2-azindan-2-yl)-1-butanol (17). Compound **7** (1.26 g, 2.35 mmol) was dissolved in methanol (50 mL) and hydrogenolyzed in the presence of 10% palladium on carbon (1.26 g) at 1 atm for 1 h. The catalyst was filtered off and the solution evaporated to dryness. Purification of the residue by chromatography on silica gel with 2:1 hexane–ethyl acetate gave **17** [740 mg (71%)] as a colorless oil: $[\alpha]^{20}_D$ −83.0° (*c* 22.4, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ ($CHCl_3$) 3.20 (3 H, s), 3.30 (3 H, s), 3.35–3.88 (4 H, m; including 3 H, s at δ 3.76), 4.11 (1 H, d, *J* = 6.8 Hz), 4.25 (1 H, d, J = 7.1 Hz), 4.35 (1 H, d, *J* = 7.1 Hz), 4.65 (1 H, d, *J* = 6.8 Hz), 5.15 (1 H, dd, *J* = 10.4, 1.8 Hz), 5.46 (1 H, d, *J* = 10.5 Hz), 6.83 (2 H, $^1/_2$ AB q, *J* = 8.8 Hz), 7.59 (2 H, $^1/_2$ AB q, *J* = 8.8 Hz), 7.64–7.85 (4 H, m); mass spectrum, m/e (relative intensity) 353 (1.5), 308 (1.6), 280 (1.3), 266 (100), 130 (10).

(2*R*,3*S*,4*S*)-2,3-Bis[(methoxymethyl)oxy]-4-(*p*-methoxyphenyl)-4-(1,3-dioxo-2-azindan-2-yl)butanal (18). In the exactly same manner as described above for the preparation of **9**, **17** was subjected to Swern oxidation. From 387 mg (3.05 mmol) of **17** was obtained 302 mg (89%) of **18** as a colorless oil: $[\alpha]^{20}_D$ −85.7° (*c* 12.3, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ ($CHCl_3$) 3.06 (3 H, s), 3.27 (3 H, s), 3.74 (3 H, s), 4.00–4.23 (3 H, m), 4.53 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.70 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 5.40–5.62 (2 H, m), 6.82 (2 H, $^1/_2$ AB q, *J* = 8.8 Hz), 7.56 (2 H, $^1/_2$ AB q, *J* = 8.8 Hz), 7.59–7.85 (4 H, m), 9.72 (1 H, s); mass spectrum, m/e (relative intensity) 308 (1.3), 280 (1.5), 266 (100).

Reaction of 18 with Methylmagnesium Bromide. The reaction was conducted in exactly the same manner as for the Grignard reaction of **9**. The same workup and chromatography, from 280 mg (0.63 mmol) of **18**, afforded as the less polar fraction 180 mg (62%) of (2*R*,3*S*,4*S*,5*S*)-3,4-bis[(methoxymethyl)oxy]-5-(*p*-methoxyphenyl)-5-(1,3-dioxo-2-azidan-2-yl)-2-pentanol (**19**): colorless oil; $[\alpha]^{20}_D$ −57.8° (*c* 3.2, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ ($CHCl_3$) 1.32 (3 H, d, *J* = 6.3 Hz), 3.18 (3 H, s), 3.44 (3 H, s), 3.76 (3 H, s), 3.88–4.23 (4 H, m), 4.38 (1 H, $^1/_2$ AB q, *J* = 7.1 Hz), 4.84 (1 H, $^1/_2$ AB q, *J* = 7.1 Hz), 5.14 (1 H, $^1/_2$ AB q, *J* = 10.3 Hz), 5.44 (1 H, $^1/_2$ AB q, *J* = 10.3 Hz), 6.83 (2 H, $^1/_2$ AB

q, J = 8.8 Hz), 7.57 (2 H, $^1/_2$ AB q, J = 8.8 Hz), 7.60–7.88 (4 H, m); mass spectrum, m/e (relative intensity) 353 (1.1), 308 (4), 267 (20), 266 (100); mass spectrum (isobutane CI), m/e (relative intensity) 396 (5), 353 (2), 308 (2), 267 (20), 266 (100), 121 (40).

The more polar fraction afforded 50 mg (17%) of (2*S*,3*S*,4*S*,5*S*)-3,4-bis[(methoxymethyl)oxy]-5-(*p*-methoxyphenyl)-5-(1,3-dioxo-2-azidan-2-yl)-2-pentanol (**20**): $[\alpha]^{20}_D$ −85.1° (*c* 2.1, MeOH); ^{1}H NMR (90 MHz, $CDCl_3$) δ (Me_4Si) 1.27 (3 H, d, J = 6.0 Hz), 3.14 (3 H, s), 3.20–4.00 (3 H, unresolved; including 3 H, s at δ 3.30, 3 H, s at δ 3.70), 4.07 (1 H, $^1/_2$ AB q, J = 6.6 Hz), 4.22 (1 H, $^1/_2$ AB q, J = 6.6 Hz), 4.45 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.64 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 5.35 (2 H, br s), 6.81 (2 H, $^1/_2$ AB q, J = 9.0 Hz), 7.55 (2 H, $^1/_2$ AB q, J = 9.0 Hz), 7.55–7.90 (4 H, m); mass spectrum, m/e (relative intensity) 396 (0.1), 353 (1 .2), 321 (0.4), 308 (4), 267 (21), 266 (100).

(2*R*,3*S*,4*S*,5*S*)-5-[[(Benzyloxy)carbonyl]amino]-3,4-bis[(methoxymethyl)oxy]-5-(*p*-methoxyphenyl)-2-pentanol (21). This compound was prepared from **19** by the same procedure used for the preparation of **12** above. From 80 mg (0.17 mmol) of **19** was obtained 75 mg (93%) of **21** as a colorless oil: $[\alpha]^{20}_D$ +4.5° (*c* 2.4, MeOH); ^{1}H NMR (90 MHz, $CDCl_3$) δ (Me_4Si) 1.10 (3 H, d, J = 6.3 Hz), 2.85–3.25 (2 H, m), 3.30 (3 H, s), 3.40 (3 H, s), 3.77 (3 H, s), 3.78–4.02 (2 H, m), 4.40–4.80 (4 H, m), 5.07 (2 H, br s), 6.27 (1 H, unresolved), 6.86 (2 H, $^1/_2$ AB q, J = 8.7 Hz), 7.10–7.40 (7 H, unresolved).

(1*S*,2*S*,3*S*,4*R*)-1-[[(Benzyloxy)carbonyl]amino]-2,3-bis[(methoxymethyl)oxy]-1-(*p*-methoxyphenyl)-4-[(methylsulfonyl)oxy]pentane (22). As in the preparation of **13** from **12**, **21** (50 mg, 0.11 mmol) was subjected to mesylation to give **22** (42 mg, 72%) as a colorless oil: $[\alpha]^{20}_D$ +6.6° (*c* 4.8, MeOH); ^{1}H NMR (90 MHz, $CDCl_3$) δ (Me_4Si) 1.37 (3 H, d, J = 6.0 Hz), 2.93 (3 H, s), 3.33 (3 H, s), 3.40 (4 H, s, with broadening), 3.73 (3 H, s), 3.97 (1 H, t, J = 5.0 Hz), 4.53–5.17 (6 H, m; including 2 H, s at δ 5.07), 6.28 (1 H, br d, J = 8.7 Hz), 6.87 (2 H, $^1/_2$ AB q, J = 8.7 Hz), 7.20–7.47 (7 H, unresolved); mass spectrum, m/e (relative intensity) 383 (5), 370 (1.9), 356 (3.9), 354 (2.3), 340 (2.3), 339 (4.1), 323 (38), 322 (26), 310 (50), 278 (26), 270 (37), 226 (32), 162 (100).

(2*S*,3*S*,4*S*,5*S*)-3,4-Bis[(methoxymethyl)oxy]-2-(*p*-methoxyphenyl)-5-methylpyrrolidine (23). A solution of **22** (40.5 mg, 0.075 mmol) in methanol (4 mL) was vigorously stirred in the presence of 10% palladium on carbon (40 mg) under hydrogen at 1 atm for 1 h. Addition of two drops of triethylamine, filtration, and evaporation in vacuo gave an oil. It was chromatographed on silica gel and eluted with 99:1 $CHCl_3$–ammoniacal methanol followed by ethyl acetate to afford **23** (17.5 mg, 75%) as a colorless oil: $[\alpha]^{20}_D$ −29.5° (*c* 2.5, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ ($CHCl_3$) 1.30 (3 H, d, J = 6.8 Hz), 3.24 (3 H, s), 3.30–3.50 (1 H, unresolved; including 3 H, s at δ 3.38), 3.79 (3 H, s), 3.85 (1 H, t, J = 3.5 Hz), 4.09–4.13 (2 H, unresolved), 4.54 (1 H, $^1/_2$ AB q, J = 6.6 Hz), 4.59–4.88 (3 H, m), 6.86 (2 H, $^1/_2$ AB q, J = 8.8 Hz), 7.34 (2 H, $^1/_2$ AB q, J = 8.8 Hz); mass spectrum, m/e (relative intensity) 312 (0.1), 311 (0.4), 267 (2), 266 (22), 251 (6), 250 (37), 180 (31), 163 (100), 162 (72), 148 (24), 121 (29).

(2*S*,3*S*,4*S*,5*S*)-3,4-Bis[(methoxymethyl)oxy]-2-(*p*-methoxyphenyl)-1,5-dimethylpyrrolidine (24). To a methanolic (3 mL) solution of **23** (17 mg, 0.055 mmol) was added 37% aqueous formaldehyde (0.5 mL) and 10% palladium on carbon (17 mg), and the mixture was vigorously stirred under hydrogen at 1 atm for 30 min. Filtration and concentration left a product that was chromatographed on silica gel with 2:1 hexane–ethyl acetate to give **24** (10.7 mg, 60%) as a colorless oil: $[\alpha]^{20}_D$ +7.2° (*c* 2.9, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ $CHCl_3$ 1.15 (3 H, d, J = 6.8 Hz), 2.09 (3 H, s), 3.19 (3 H, s), 3.25–3.42 (1 H, unresolved; including 3 H, s at δ 3.41), 3.60 (1 H, d, J = 5.4 Hz), 3.80 (3 H, s), 3.84 (1 H, s), 4.04 (1 H, d, J = 5.1 Hz), 4.51 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.63 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.73 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.78 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 6.86 (2 H, $^1/_2$ AB q, J = 8.7 Hz), 7.29 (2 H, $^1/_2$ AB q, J = 8.7 Hz); mass spectrum, m/e (relative intensity) 325 (M^+, 6), 310 (11), 294 (3), 281 (5), 280 (26), 264 (16), 194 (22), 177 (76), 176 (100), 162 (37).

(+)-Codonopsinine [(+)-1b]. Tretment of **24** (10.6 mg, 0.033 mmol) with an acid according to the procedure described for deprotection of **15** (formation of **1a**) provided, after recrystallization from methanol, (+)-**1b** [7.5 mg (97%)] as white needles: mp 172.5–173.5 °C [for (−)-**1b**, lit.[1] mp 169–170 °C (methanol)]; $[\alpha]^{20}_D$ +12.5° (*c* 2.55, MeOH) [for (−)-**1b**, lit.[1] $[\alpha]^{20}_D$ −8.8° (*c* 0.1, MeOH)]; ^{1}H NMR, Table I; mass spectrum, m/e (relative intensity) 237 (M^+, 15), 222 (7), 178 (6), 177 (59), 176 (100), 162 (50), 121 (30); exact mass calcd for $C_{13}H_{19}NO_3$ (M^+) 237.1363, found 237.1353.

(3*R*,4*S*,5*R*)-3,4-Bis[(methoxymethyl)oxy]-5-(*p*-methoxyphenyl)-5-(1,3-dioxo-2-azidan-2-yl)pentan-2-one (25). To a stirred and cooled (−78 °C) solution of oxalyl chloride (119 mg, 0.94 mmol) in CH_2Cl_2 (5 mL) was added a solution of Me_2SO (147 mg, 1.88 mmol) in CH_2Cl_2 (3 mL) over a period of 5 min. After 15 min with stirring at −78 °C, a solution of **10** (108 mg, 0.24 mmol) in CH_2Cl_2 (3 mL) was added to the reaction mixture over a period of 5 min. After 1 h of stirring at −78 °C, triethylamine (285 mg, 2.82 mmol) was added to the reaction mixture and the mixture was stirred for further 5 min. The reaction was allowed to warm to room temperature, and the mixture was diluted with CH_2Cl_2 (20 mL) and washed with water. The CH_2Cl_2 solution was dried ($MgSO_4$) and evaporated to dryness. Purification of the oily residue by silica gel chromatography (elution with 3:1 hexane–ethyl acetate) gave **25** [62 mg (58%)] as a colorless oil: $[\alpha]^{21}_D$ −135.7° (*c* 0.49, MeOH); IR ($CHCl_3$) 1700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ ($CHCl_3$) 2.24 (3 H, s), 2.92 (3 H, s), 3.41 (3 H, s), 3.76 (3 H, s), 3.82 (1 H, br s), 4.22 (1 H, d, J = 6.8 Hz), 4.37–4.73 (3 H, m), 5.46 (1 H, $^1/_2$ AB q, J = 12.1 Hz), 5.64 (1 H, $^1/_2$ AB q, J = 12.1 Hz), 6.86 (2 H, $^1/_2$ AB q, J = 9.1 Hz), 7.48–7.93 (6 H, m); mass spectrum, m/e (relative intensity) 394 (0.9), 352 (2.6), 340 (2), 339 (9), 266 (100).

A similar result was obtained when this procedure was applied to the diastereomeric mixture of **10** and **11** obtained by the Grignard reaction of **9** above.

Sodium Borohydride Reduction of 25. To a stirred cold (0 °C) solution of **25** (50 mg, 0.11 mmol) in ethanol (5 mL) was added $NaBH_4$ (8 mg, 0.21 mmol) in small portions. The mixture was stirred for 1 h at 0 °C, and the solvent was removed in vacuo. After addition of water (3 mL), a product was extracted with $CHCl_3$ and the extract was dried over $MgSO_4$. Removal of the solvent followed by chromatography on silica gel with 2:1 hexane–ethyl acetate afforded **10** [11 mg (22%)], identical with that prepared by Grignard addition to **9**. Further elution gave **11** [30 mg (60%)], identical with the sample derived from **9**.

(3*R*,4*S*,5*S*)-3,4-Bis[(methoxymethyl)oxy]-5-(*p*-methoxyphenyl)-5-(1,3-dioxo-2-azindan-2-yl)pentan-2-one (26). This compound was prepared from **19** by the exactly same procedure used for the preparation of **25** above. From 79 mg (0.17 mmol) of **19** was obtained 46 mg (58%) of **26** as a colorless oil: $[\alpha]^{20}_D$ −114.1° (*c* 3.1, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ ($CHCl_3$) 2.32 (3 H, s), 3.04 (3 H, s), 3.23 (3 H, s), 3.76 (3 H, s), 3.95 (1 H, d, J = 7.2 Hz), 4.11 (1 H, d, J = 7.2 Hz), 4.27 (1 H, s), 4.53 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.59 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 5.46 (1 H, $^1/_2$ AB q, J = 10.6 Hz), 5.55 (1 H, $^1/_2$ AB q, J = 10.6 Hz), 6.84 (2 H, $^1/_2$ AB q, J = 8.8 Hz), 7.55 (2 H, $^1/_2$ AB q, J = 8.8 Hz), 7.62–7.90 (4 H, m); mass spectrum, m/e (relative intensity) 394 (0.3), 352 (1.3), 340 (1.1), 339 (4.9), 280 (2.4), 279 (4.0), 267 (19), 266 (100), 130 (7).

A similar result was obtained when this procedure was applied to the diastereomeric mixture of **19** and **20** obtained by Grignard addition to **18**.

Sodium Borohydride Reduction of 26. This was conducted in exactly the same manner as described above for reduction of **25**. From 39 mg (0.085 mmol) of **26** were obtained 24 mg (61%) of **20** and 8 mg (20%) of **19**, both of which were identical with those derived from **18**.

(1*R*,2*S*,3*R*,4*S*)-1-[[(Benzyloxy)carbonyl]amino]-2,3-bis[(methoxymethyl)oxy]-1-(*p*-methoxyphenyl)-4-[(methylsulfonyl)oxy]pentane (28). In the same manner as for the preparation of **12**, removal of the phthaloyl group and benzyloxycarbonylation of **11** (160 mg, 0.35 mmol) were run to give (2*S*,3*S*,4*S*,5*R*)-5-[[(benzyloxy)carbonyl]amino]-3,4-bis[(methoxymethyl)oxy]-5-(*p*-methoxyphenyl)-2-pentanol [**27**; 131 mg (81%)] as a colorless oil: $[\alpha]^{20}_D$ −55.3° (*c* 3.3, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ ($CHCl_3$) 1.22 (3 H, d, J = 6.4 Hz), 3.11 (3 H, s), 3.25 (1 H, d, J = 7.6 Hz), 3.45 (3 H, s), 3.54 (1 H, dd, J = 5.6, 4.2 Hz), 3.79 (3 H, s), 3.80–4.04 (2 H, m), 4.31 (1 H, $^1/_2$ AB q, J = 6.6 Hz), 4.56 (1 H, $^1/_2$ AB q, J = 6.6 Hz), 4.65 (1 H, $^1/_2$ AB q, J = 6.6 Hz), 4.72 (1 H, $^1/_2$ AB q, J = 6.6 Hz), 4.83 (1 H, br s), 5.06 (1 H, $^1/_2$ AB q, J = 12.5 Hz), 5.10 (1 H, $^1/_2$ AB q, J = 12.5 Hz), 5.85 (1 H, br s), 6.86 (2 H, $^1/_2$ AB q, J = 8.9 Hz), 7.20

(2 H, $^1/_2$ AB q, J = 8.9 Hz), 7.34 (5 H, br s).

Compound **27** (140 mg, 0.30 mmol) was mesylated under the standard conditions stated above, giving the title compound **28** [140 mg (86%)] as a colorless oil: $[\alpha]^{20}_D$ -42.0° (c 3.3, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ ($CHCl_3$) 1.45 (3 H, d, J = 6.3 Hz), 2.97 (3 H, s), 3.03 (3 H, s), 3.44 (3 H, s), 3.79 (3 H, s), 3.86 (2 H, br s), 4.37 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.62 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.65-5.19 (4 H, m), 5.92 (1 H, br d, J = 8.6 Hz), 6.87 (2 H, $^1/_2$ AB q, J = 8.6 Hz), 7.21 (2 H, $^1/_2$ AB q, J = 8.6 Hz), 7.34 (5 H, br s); mass spectrum, m/e (relative intensity) 464 (0.8), 374 (1.0), 324 (4.2), 283 (6.0), 278 (4.2), 266 (4.0), 234 (4.8), 204 (3.0), 148 (40), 121 (20), 91 (100).

(2*R*,3*S*,4*S*,5*R*)-*N*-[(Benzyloxy)carbonyl]-3,4-bis[(methoxymethyl)oxy]-2-(*p*-methoxyphenyl)-5-methylpyrrolidine (29). The compound **28** (35 mg, 0.065 mmol) was treated in the same manner as described for the preparation of **14** to give **29** [16 mg (56%)] as a colorless oil: $[\alpha]^{20}_D$ +68.0° (c 0.41, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ ($CHCl_3$) 1.33 (3 H, d, J = 6.1 Hz), 3.28 (3 H, s), 3.38 (3 H, s), 3.81 (3 H, s), 4.20-5.20 (10 H, m), 6.65-7.40 (9 H, m); mass spectrum, m/e (relative intensity) 445 (M^+, 2.7), 414 (2.1), 400 (1.4), 383 (22), 324 (16), 323 (74), 322 (38), 310 (40), 278 (28), 234 (26), 162 (100).

(2*R*,3*S*,4*S*,5*R*)-3,4-Bis[(methoxymethyl)oxy]-2-(*p*-methoxyphenyl)-1,5-dimethylpyrrolidine (31). A. From 29. In the same manner for the preparation of **15** from **14**, **29** (8 mg, 0.018 mmol) was subjected to $LiAlH_4$ reduction to give **31** [4.9 mg (84%)] as a colorless oil: $[\alpha]^{20}_D$ -18.7° (c 1.1, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ $CHCl_3$) 1.01 (3 H, d, J = 6.6 Hz), 2.13 (3 H, s), 3.06 (3 H, s), 3.41 (3 H, s), 3.50 (1 H, quint, J = 6.5 Hz), 3.80 (3 H, s), 3.84 (1 H, br s), 4.04-4.38 (4 H, m), 4.69 (1 H, $^1/_2$ AB q, J = 6.3 Hz), 4.78 (1 H, $^1/_2$ AB q, J = 6.3 Hz), 6.85 (2 H, $^1/_2$ AB q, J = 8.8 Hz), 7.24 (2 H, $^1/_2$ AB q, J = 8.8 Hz); mass spectrum, m/e (relative intensity) 325 (M^+, 12), 310 (12), 294 (10), 280 (38), 264 (22), 207 (14), 194 (32), 178 (12), 177 (94), 176 (100), 162 (32); exact mass calcd for $C_{17}H_{27}NO_5$ (M^+) 325.1887, found 325.1877.

B. From 28 via 30. Compound **28** (47 mg, 0.087 mmol) was hydrogenolyzed in the same manner as described for the preparation of **23**. As in the preparation of **24** from **23**, the crude product [20 mg (74%)] of (2*R*,3*S*,4*S*,5*R*)-3,4-bis[(methoxymethyl)oxy]-2-(*p*-methoxyphenyl)-5-methylpyrrolidine (**30**) obtained was subsequently alkylated to afford **31** [14 mg (67%)], in all respects identical with the sample obtained from **29**.

(2*R*,3*S*,4*S*,5*R*)-3,4-Dihydroxy-2-(*p*-methoxyphenyl)-1,5-dimethylpyrrolidine (Codonopsinine Stereoisomer 1c). In the same manner as for the preparation of **1a** from **15**, **31** (10 mg, 0.031 mmol) was treated under the acidic condition to provide **1c** [7.2 mg (99%)] as white needles: mp 110-111 °C; $[\alpha]^{20}_D$ -40.4° (c 3.4, MeOH); ^{1}H NMR, Table I; mass spectrum, m/e (relative intensity) 237 (M^+, 22), 222 (8), 178 (6), 177 (65), 176 (100), 162 (40), 150 (10), 121 (23); exact mass calcd for $C_{13}H_{19}NO_3$ (M^+) 237.1364, found 237.1376.

(1*S*,2*S*,3*R*,4*S*)-1-[[(Benzyloxy)carbonyl]amino]-2,3-bis[(methoxymethyl)oxy]-1-(*p*-methoxyphenyl)-4-[(methylsulfonyl)oxy]pentane (32). By the same procedure as used for the formation of **13** from **10**, **20** (11 mg, 0.024 mmol) was subjected so sequential treatment involving dephthaloylation, benzyloxycarbonylation, and mesylation to give **32** [11 mg (85% overall yield)] as a colorless oil.

(2*S*,3*S*,4*S*,5*R*)-3,4-Bis[(methoxymethyl)oxy]-2-(*p*-methoxyphenyl)-1,5-dimethylpyrrolidine (33). As in the preparation of **24** from **22** via **23**, **32** (2 mg, 0.0037 mmol) was subjected to hydrogenolysis followed by N-methylation to give **33** [1 mg (83% overall yield from **32**)] as a colorless oil.

(2*S*,3*S*,4*S*,5*R*)-3,4-Dihydroxy-2-(*p*-methoxyphenyl)-1,5-dimethylpyrrolidine (Codonopsinine Stereoisomer 1d). Acid treatement of **33** (1 mg, 0.0031 mmol), as described for the formation of **1a**, afforded **1d** [0.5 mg (69%)] as a colorless oil: ^{1}H NMR, Table I.

Total Syntheses of the Amaryllidaceae Alkaloids (±)-Haemanthidine and (±)-Pretazettine†[1]

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The concise total synthesis of the Amaryllidaceae alkaloid (±)-haemanthidine (**2**) has been completed in 3.1% overall yield from piperonal (**11**) by a linear sequence of 12 chemical operations. Thus, piperonal (**11**) was converted via Grignard addition followed by oxidation into the monoprotected 1,4-dione **12**. Elaboration of **12** into the key intermediate 4,4-disubstituted cyclohexenone **18d** was conveniently achieved by exploiting a general method developed in these laboratories for the efficient construction of quaternary carbon atoms at a carbonyl center by the net replacement of the two carbon-oxygen bonds with carbon-carbon bonds. Bromination of **18d** followed by dehydrobromination then furnished the cyclohexadienone **26**, which was transformed into a mixture of the hydroindolenones **27** and **28** upon the palladium(0)-catalyzed removal of the nitrogen protecting group. Treatment of this mixture of **27** and **28** with DIBAL followed by methanolysis of the mesylates that were derived from the mixture of allylic alcohols thus produced afforded a mixture of the hydroindoles **36** and **37**. After conversion of **37** into the *N*-formylindole **46**, Bischler-Napieralski cyclization and subsequent saponification of the ester protecting group from the hydroxyl function at C(11) delivered (±)-haemanthidine (**2**). Methylation of **2** followed by basic workup according to the Wildman protocol gave (±)-pretazettine (**3**).

Introduction

The alkaloids of the Amaryllidaceae family[3,4] comprise a group of over 100 architecturally interesting natural bases that may be classified into seven principal, skeletally homogeneous subgroups. Of these, the alkaloids possessing the 5,10-ethanophenanthridine and the [2]benzopyrano[3,4-*c*]hydroindole ring systems as structural subunits have captured a significant degree of attention, and crinine (**1**),[5] haemanthidine (**2**),[6] and pretazettine (**3**)[7] have emerged as attractive objects for the development of new synthetic

† Dedicated to Professor George H. Büchi on the occasion of his 65th birthday.

(1) For a preliminary account of a portion of this work, see: Martin, S. F.; Davidsen, S. K. *J. Am. Chem. Soc.* **1984**, *106*, 6431.

(2) Recipient of a National Institutes of Health (National Cancer Institute) Research Career Development Award, 1980-1985.

(3) For a review of the chemistry of the Amaryllidaceae alkaloids, see: (a) Fuganti, C. "The Amaryllidaceae Alkaloids" In *The Alkaloids, Chemistry and Physiology*; Manske, R. H. F., Ed.; Academic Press: New York, 1975; Vol. 15, pp 83-164. (b) Grundon, M. F. In *Specialist Periodical Reports, The Alkaloids*; The Chemical Society: London, 1983; Vol. 13, p 187. See also Vol. 1-12. (c) Grundon, M. F. *Nat. Prod. Rep.* **1985**, *2*, 249; **1984**, *1*, 247.

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