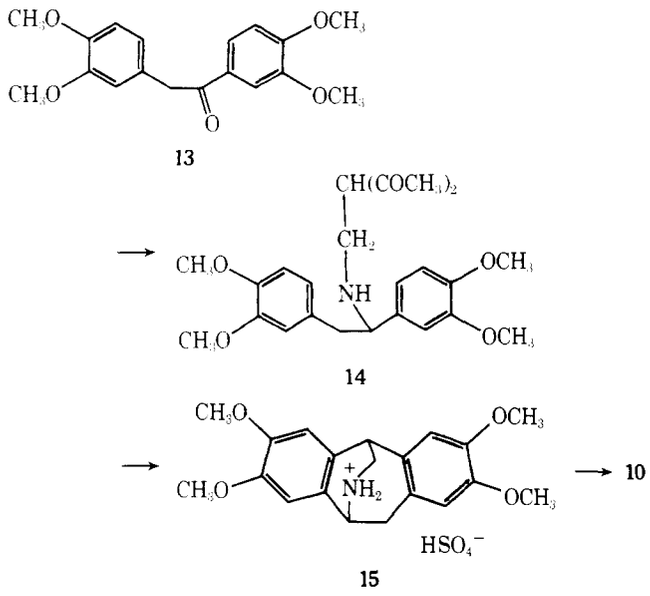
Scheme II. Alternative Synthesis of (±)-*O*-Methylthalisopavine



Experimental Section[9]

2,3,7,8-Tetramethoxy-13-oxo-10,5-(epoxymethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane (5). A solution of the lactone **4** (1.8 g) in CH_3CN (100 mL) was stirred mechanically and cooled in an ice bath, and a slurry of VOF_3 (3.5 g) in CH_3CN (15 mL) was added over a 2-min period. After stirring for 3 h, the mixture was diluted with CH_2Cl_2 (100 mL) and poured into water (300 mL) containing citric acid (10 g). The layers were separated, and the CH_2Cl_2 solution was evaporated. The crude product was recrystallized from EtOH–C_6H_6, and the bridged lactone **5** (1.27 g, 71%) was obtained in two crops, mp 247–249 °C. This oxidation product was identified as **5** by infrared and mass spectral comparison with a sample prepared by anodic oxidation.[5]

2,3,7,8-Tetramethoxy-12-methyl-13-oxo-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane (7). By the procedure described for the preparation of **5**, the 3-isoquinolone **6** (1.5 g) was oxidized by VOF_3 (2.9 g) in CH_3CN (50 mL). The crude product recrystallized very slowly from aqueous MeOH in three crops: 0.6 g; mp 231–233 °C; MS *m/e* 369 (M^+); UV λ_{max} (EtOH) 290 nm (log ϵ 4.0). Anal. Calcd for $C_{21}H_{23}NO_5 \cdot 0.5H_2O$: C, 66.69; H, 6.39; N, 3.71. Found: C, 66.96; H, 6.29; N, 3.60.

(±)-*O*-Methylthalisopavine. (a) By Reduction of 7. The lactam **7** (0.9 g) was added to BH_3–THF complex (100 mL), and the solution was allowed to stand 18 h. Addition of cold water and evaporation of the THF left a gum that, after unsuccessful attempts to purify as the HCl salt, was finally converted back to the base with aqueous NaOH and recrystallized from MeOH–H_2O as a colorless solid, 0.1 g, mp 163–165 °C, after drying over KOH pellets: MS *m/e* 355 (30), 354 (28), 312 (39), 204 (100). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.80; H, 6.95; N, 3.77.

(b) From Deoxyveratroin. Deoxyveratroin (5 g) was condensed with aminoacetaldehyde dimethyl acetal (20 g) and immediately hydrogenated to the amine acetal (**14**) by the procedure of Battersby and Yeowell.[8a] Compound **14** was cyclized by sulfuric acid, and thalisopavine sulfate (1.0 g), mp 185–188 °C, was isolated. A solution of the salt (0.8 g) in 40% HCHO (3 mL)–EtOH (5 mL) was treated after 5 min with $NaBH_4$ (0.3 g). The reaction mixture was diluted with water (15 mL) after 3 h, and a colorless solid (0.3 g) was collected. The isopavine **10** was recrystallized from aqueous MeOH, mp 165–166 °C (lit.[3] mp 165–166 °C); this compound proved to be identical with the product from part a by melting point, IR, and MS comparisons.

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Registry No.—**4**, 68890-14-2; **5**, 68890-15-3; **6**, 30048-23-8; **7**, 68890-17-5; **10**, 33579-95-2; **13**, 4927-55-3; **14**, 68890-18-6; **15**, 68907-93-7; aminoacetaldehyde dimethyl acetal, 22483-09-6.

References and Notes

(1) S. F. Dyke, "Rodd's Chemistry of Carbon Compounds", Vol. 4H, S. Coffey, Ed., Elsevier, New York, N.Y., 1978, p 1.
(2) T. Kametani and K. Fukumoto, *Synthesis*, 657 (1972); I. D. Spenser, "Chemistry of the Alkaloids", S. W. Pelletier, Ed., Van Nostrand Reinhold, New York, N.Y., 1970, p 669.
(3) S. F. Dyke and A. C. Ellis, *Tetrahedron*, **27**, 3803 (1971).
(4) (a) I. W. Elliott, *J. Heterocycl. Chem.*, **7**, 1229 (1970) (b) *ibid.*, **9**, 453 (1972).
(5) I. W. Elliott, *J. Org. Chem.*, **42**, 1090 (1977).
(6) These yields are reproducible under the conditions described but not necessarily optimized. A mechanism was suggested in ref 5 for the mode of oxidative coupling represented by the conversion of **4** to **5** or of **6** to **7**. The effects of solvent and of activation of the benzylic positions in **4** or **6** by the adjacent carbonyl groups are probably the same for oxidation by VOF_3 as for anodic oxidation.
(7) S. M. Kupchan and A. Yoshitake, *J. Org. Chem.*, **34**, 1062 (1969).
(8) (a) A. R. Battersby and D. A. Yeowell, *J. Chem. Soc.*, 1988 (1958); (b) E. Waldmann and C. Chwala, *Justus Liebigs Ann. Chem.*, **609**, 125 (1957); (c) D. A. Guthrie, A. W. Frank, and C. B. Purves, *Can. J. Chem.*, **33**, 729 (1955).
(9) Melting points were determined on a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Spectra were recorded on the following instruments: Perkin-Elmer 337 IR; Cary 14 UV, LKB 2091 MS, and Varian XL100 NMR.

Stereospecific Synthesis of (*R*)- and (*S*)-Isophosphamide

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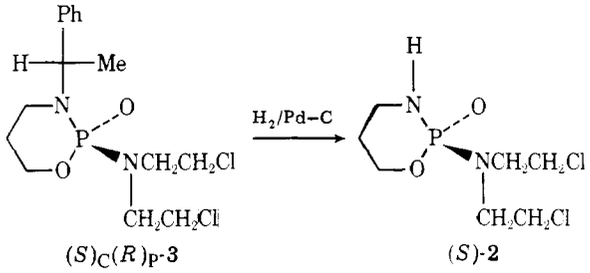
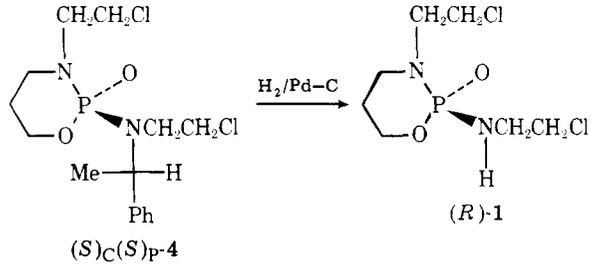
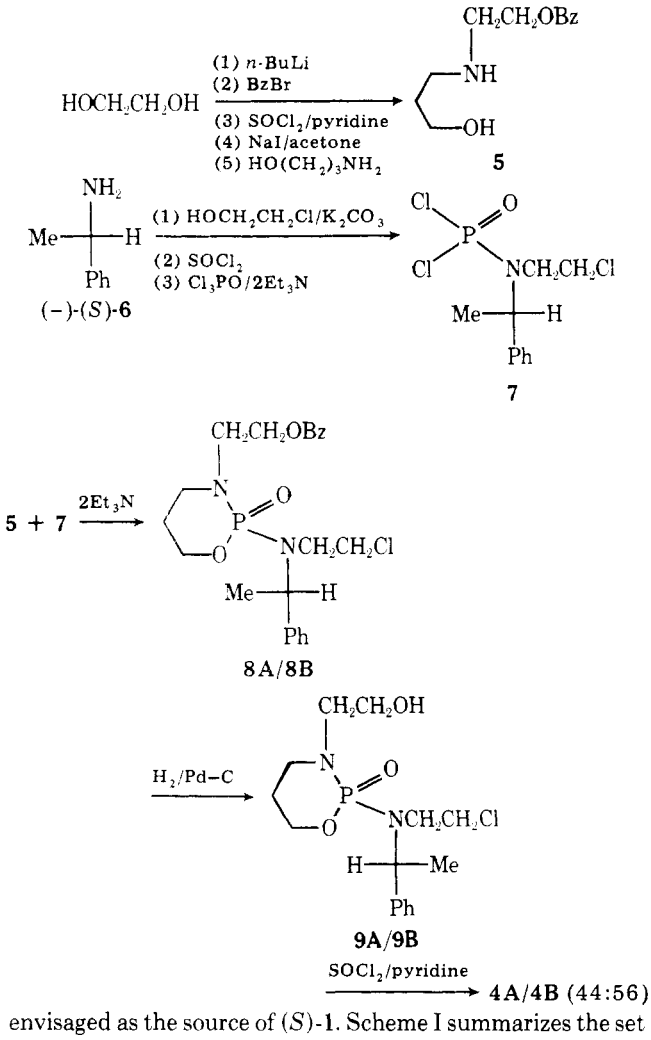
Isophosphamide (**1**) is a constitutional isomer of the clinically established anticancer drug cyclophosphamide (**2**, "Cytoxan"),[1] and **1** has been found to elicit therapeutic response in human breast, ovarian, and lung cancer.[2] The chirality of **1** and **2** necessitates consideration of stereochemical factors within the mechanisms of action for these drugs and, moreover, the clinical significance thereof. Recent progress in this direction has been achieved only in the case of **2**,[3-5] as the *R* and *S* enantiomers of **1** have been heretofore unavailable except as the racemate. We now wish to report the stepwise construction of separable diastereomers which serve as precursors to (*R*)- and (*S*)-**1** via a hydrogenolysis reaction that is unquestionably stereospecific according to ^{31}P NMR data.

By analogy to the previously reported[3d,4a] catalytic conversion of $(S)_C(R)_P$-**3** to (*S*)-**2** (eq 1) and of diastereomer $(S)_C(S)_P$-**3** to (*R*)-**2**, $(S)_C(S)_P$-**4** represented the logical precursor to (*R*)-**1** (eq 2), while its $(S)_C(R)_P$-**4** diastereomer was





Scheme I



envisaged as the source of (*S*)-**1**. Scheme I summarizes the set of reactions which was subsequently explored as a route to the target-diastereomers (**4A/4B**). Benzyl bromide was combined with the lithium salt of ethylene glycol, and the ethylene glycol monobenzyl ether[6] product (65%) was chlorinated[6] with $SOCl_2$/pyridine (60%) and then refluxed with NaI in acetone to provide benzyl 2-iodoethyl ether (78%) for N-alkylation of 3-aminopropanol (30-fold excess in refluxing EtOH) to give **5** (62%).[7] Introduction of the chiral "resolving group" began with the reaction of enantiomerically pure (−)-(*S*)-α-methylbenzylamine (**6**) and 2-chloroethanol (1 equiv) in a refluxing (1 day) 1,2-dimethoxyethane/H_2O (77:1) suspension of K_2CO_3 (1.4 equiv). Vacuum distillation led to recovery of unreacted **6** (41%) and gave a pot residue of crude 2-hydroxyethylated amine (30%), which was refluxed (3 h) with $SOCl_2$ (5 equiv) in $CHCl_3$ to afford (56%) the corresponding 2-chloroethylated amine hydrochloride as analytically pure white crystals, mp 213–216 °C. A $CHCl_3$ solution of this salt and Cl_3PO (10 equiv) was then reacted (1 day, 25 °C) with Et_3N (2 equiv), and the concentrated filtrate yielded (30%) **7** after silica gel chromatography (R_f 0.68, $CHCl_3$).

Reaction of **5** and **7** in EtOAc/Et_3N according to the usual procedures[8] was followed by silica gel chromatography ($CHCl_3$/MeOH, 98:2) with simultaneous elution of a ~55:45 mixture of diastereomeric products **8A/8B** (67%, R_f 0.39), as evidenced by ^1H NMR data (220 MHz, $CDCl_3$, Me_4Si) which featured two partially overlapped methyl doublets at δ 1.55 and 1.54. A lack of success which we encountered in numerous attempts to effect either silica gel or alumina TLC separation of **8A** and **8B** was also a frustration in the attempted silica gel and cellulose chromatographic separation of intermediates **9A/9B**, which had been obtained (82%) by medium-pressure (50 psi) hydrogenolysis of **8A/8B** over 10% Pd–C catalyst (Pd/8 = 0.3, 4:1 EtOH/H_2O, 25 °C, 6 h). These somewhat unexpected difficulties in diastereomer separation by chromatographic techniques were, nevertheless, eventually overcome by $SOCl_2$/pyridine conversion of **9A/9B** into **4A/4B** (35%), as multiple-elution TLC on silica gel (EtOAc, 4–5 times) gave samples which were ≥95% diastereomerically pure by both ^1H (220 MHz, $CDCl_3$) and ^{31}P NMR (40.25 MHz, 4:1 EtOH/H_2O): **4A** (faster eluting), δ_{1H}^{Me} 1.56 and δ_{31P} 13.92; **4B** (slower eluting), δ_{1H}^{Me} 1.58 and δ_{31P} 14.47.[9] In this connection it is worthwhile to note that conversion of **9A** and **9B** into their respective tosylates afforded a pair of more easily separable diastereomers (silica gel, 1:1 THF/CH_2Cl_2); however, these were unexpectedly resistant to chloride substitution via reactions with either NaCl/acetone,[10] KCl/Me_2SO, $SOCl_2$, or KCl/dicyclohexyl 18-crown-6.[11]

The final synthetic step (**4** → **1**, eq 2) was first attempted using medium-pressure hydrogenolysis conditions identical with those successfully used for conversion of **3** to **2**:[3d] Pd/**3** = 0.3 equiv as 10% Pd–C, 4:1 EtOH/H_2O, 1 day, 25 °C. Surprisingly, ^{31}P NMR analysis of the reaction solution showed only a trace of product, and with Pd/**4** = 0.6 equiv there was ~4% reaction after 5 days. The eventual use of 2 equiv of "catalyst" and a 3-day contact period finally resulted in ~25% conversion of **4** into **1** (δ_{31P} 13.38 ppm) accompanied by ~50% material loss evidenced by quantitative ^{31}P NMR measurements with suppression of differential nuclear Overhauser effects. Control studies with authentic **1** and 10% Pd–C revealed that decomposition and/or surface absorption of **1** produced from **4** were *not* factors in the poor material balance, and only trace amounts of EtOH/H_2O-soluble byproducts were detected by ^{31}P NMR. Adventitious acidic hydrolysis of **1** was likewise eliminated by ^{31}P NMR control experiments.

Due to the low optical rotatory power anticipated for **1**[3b] and the relatively small amount of crude **1** which was available by the present hydrogenolysis route, the enantiomeric composition of **1** was best assessed by use of the chiral shift reagent $Eu(hfc)_3$.[3d,5] "Titration" studies with $Eu(hfc)_3$ and simulated mixtures of racemic **1** and **4** in $CDCl_3$ demonstrated that at relatively high $Eu(hfc)_3$/organophosphorus molar ratios (≥2) narrow ($\omega_{1/2} \cong 8$ Hz) ^{31}P NMR absorptions were clearly evident for the individual enantiomers of **1** (δ −68.57 and −70.93, $\Delta\delta = 95$ Hz) and that there was no problem of overlap between these signals and the further upfield-shifted absorptions of **4A/4B** (δ ~−100).

According to the above procedures, hydrogenolysis of a known diastereomerically enriched mixture of **4A/4B** (10:90) was found to afford enantiomerically enriched **1** having $Eu(hfc)_3$-shifted ^{31}P NMR absorptions at −68.57 and −70.93 ppm in a relative abundance of 10 and 90, respectively, while oppositely enriched **4A/4B** (82:18) starting material under duplicate conditions led to a 90 and 10 relative abundance of these NMR absorptions. These observations and the fact that **4A** and **4B** were seen by ^{31}P NMR to react at essentially identical rates (constant **4A/4B** signal intensities) collectively establish the complete stereospecificity (±~5%) of the final hydrogenolysis step. Absolute configurational assignments have yet to be determined.

The overall yield of (*R*)- and (*S*)-**1** via Scheme I is very low (~0.14%), and improvements in the efficiency of **4** → **1** deserve particular attention. We intend to investigate a variety of alternative methods for removing the α-methylbenzyl group and to obtain quantities of enantiomerically homogeneous (*R*)- and (*S*)-**1** sufficient for comparative anticancer screening tests, which will be reported in the future.

Experimental Section

Melting points were obtained with a Thomas-Hoover capillary

melting point apparatus and are uncorrected, as are reported boiling points. Elemental analyses were performed by Chemalytics, Inc. A Paar shaker hydrogenator was used for hydrogenolysis. Analytical thin-layer chromatography utilized either 2.5 × 10 cm or 5 × 20 cm Analtech plates with a 0.25-mm layer of silica gel GF, while analogous preparative separations were performed with 20 × 20 cm plates having a 1-mm coating; component visualization was achieved by exposure either to iodine vapor or to ultraviolet light. Column chromatography employed Baker 60–200 mesh silica gel. All of the reported R_f values are approximate. All reactions performed in nonaqueous media were conducted with protection from atmospheric moisture. Racemic samples of authentic isophosphamide were obtained from the National Cancer Institute and were used without further purification.

^{1}H NMR spectra at 60 MHz were recorded on a Varian A 60 instrument at ambient probe temperature. ^{1}H NMR spectra at 220 MHz were obtained in either the continuous wave or the Fourier transform mode on a Varian HR 220 spectrometer equipped with a Fourier accessory and 620 L computer. The accumulated free induction decay signal (8K data points) was transformed to give spectra with either 2500- or 1000-Hz sweep widths; ambient probe temperature was 20 ± 1 °C.

^{13}C NMR spectra at 24.05 MHz were obtained with a JEOL FX-100 spectrometer equipped with quadrature phase detection and utilizing alternating pulse sequence. Spectral parameters were as follows: 12-μs ($\pi/2$) pulse, 2.5-s pulse repetition rate, 5-kHz spectral window and filter, and 8K data points and zero-filling with this same number of points.

^{13}C NMR spectra at 68 MHz were obtained in the pulse Fourier transform mode utilizing a Bruker superconducting magnet with a "homebuilt" spectrometer and probe. A Nicolet 1080 computer system, modified for quadrature phase detection, was used for data collection and transformation. The accumulated free induction decay signal (32K data points) was transformed to give a spectrum with a 15 151.5-Hz sweep width. A 90° ^{13}C pulse was approximately 27μs. Spectra were recorded under broad-band pseudo-random-noise proton decoupling conditions at a probe temperature of 28 ± 2 °C.

^{31}P NMR spectra were recorded at 40.25 MHz on a JEOL FX-100 spectrometer. Normal operating conditions were as follows: a 26-μs ($\pi/2$) pulse, 5 kHz spectral window and filter, 8K data points. Prior to Fourier transformation, the free induction decay signal was zero-filled with 8K points and exponentially multiplied so as to result in an additional 1.0 Hz line broadening in the frequency domain spectrum. Broad-band ^{1}H decoupling was employed, but gated off except during data acquisition; this was done to suppress differential nuclear Overhauser effects. The ambient probe temperature was ~20 °C.

Benzyl 2-Hydroxyethyl Ether. To chilled (−10 °C) ethylene glycol (0.36 mol) was added *n*-butyllithium (0.10 mol), whereupon a white precipitate formed. After being stirred overnight at room temperature, benzyl bromide (0.10 mol) was added and the reaction mixture was heated (120 °C) for 2 h, which was followed by the addition of acetone (100 mL), filtration, and concentration in vacuo. Excess ethylene glycol was removed by Kugelrohr distillation, and the pot residue was treated with H_2O (100 mL) and extracted three times with equal volumes of ether. The combined ether layers were dried ($MgSO_4$) and concentrated in vacuo to give the expected ether product (65%): ^{1}H NMR (60 MHz, $CDCl_3/Me_4Si$) δ 7.38 (s, 5 H, aromatic), 4.58 (s, 2 H, benzylic), 3.87–3.44 (m, 4 H), and 2.97–2.63 (br s, hydroxyl); ^{13}C NMR (68 MHz, $CDCl_3/Me_4Si$) δ 137.90, 128.43, 127.79 (aromatic), 73.25 (benzylic), 71.44 ($\mathbf{C}H_2CH_2OH$), and 61.77 ($CH_2\mathbf{C}H_2OH$).

Benzyl 2-Chloroethyl Ether. To a chilled (−10 °C) solution of benzyl 2-hydroxyethyl ether (12.1 mmol) and pyridine (12.1 mmol) was added $SOCl_2$ (13.9 mmol) in $CHCl_3$ (11.5 mL). Upon complete addition, the mixture was refluxed (30 min) and then cooled and poured cautiously into 0.1 M HCl (170 mL). The $CHCl_3$ layer was diluted (50 mL) and then removed, while the aqueous layer was extracted two times with equal volumes of $CHCl_3$. The original $CHCl_3$ layer was washed twice with 0.1 M HCl (170 mL) and twice with H_2O (170 mL). All $CHCl_3$ layers were then combined, dried ($MgSO_4$), and concentrated in vacuo. Kugelrohr distillation gave the product (60%) as a colorless liquid (bp 124 °C (20 mm)): ^{1}H NMR (220 MHz, $CDCl_3/Me_4Si$) δ 7.35 (s, 5 H, aromatic), 4.59 (s, 2 H, benzylic), and 3.6 (AA′BB′, 4 H); ^{13}C NMR (68 MHz, $CDCl_3/Me_4Si$) δ 137.62, 128.44, 127.71 (aromatic), 73.17 (benzylic), 69.99 ($\mathbf{C}H_2CH_2Cl$), and 42.89 ($CH_2\mathbf{C}H_2Cl$).

Benzyl 2-Iodoethyl Ether. A suspension of benzyl 2-chloroethyl ether (35.5 mmol) and dry NaI (355 mmol) in anhydrous acetone (115 mL) was refluxed (4 days) and then concentrated in vacuo. Ether (85 mL) was added to the residue and was removed in vacuo a total of three times before final addition of ether, filtration of NaI/NaCl, and concentration in vacuo. The product was obtained as an oil in 78% yield: ^{1}H NMR (60 MHz, $CDCl_3/Me_4Si$) δ 7.38 (s, 5 H, aromatic), 4.61 (s, 2 H, benzylic), and 3.55 (AA′BB′, 4 H).

***N*-(2-Benzyloxyethyl)-3-hydroxypropylamine (5).** A solution of benzyl 2-iodoethyl ether (1.6 mmol) and 1-amino-3-propanol (48 mmol) in ethanol (2 mL) was refluxed (12 h), and the excess 1-amino-3-propanol was removed by Kugelrohr distillation. The pot residue was treated with H_2O and was twice extracted with ether. The combined ether layers were dried (Na_2SO_4) and then concentrated in vacuo to give **5** (62%), which was generally used without further purification; the small amount of bisalkylated contaminant could be removed by chromatography on silica gel ($CHCl_3$/MeOH, 9:1), as its R_f value (0.73) was twice that of the desired monoalkylated product: ^{1}H NMR (60 MHz, $CDCl_3/Me_4Si$) δ 7.33 (s, 5 H, aromatic), 4.51 (s, 2 H, benzylic), 3.87–3.48 (m, 4 H, CH_2O), 3.44 (s, 2 H, NH, OH), 2.95–2.68 (m, 4 H, CH_2N), and 1.90–1.43 (quintet, 2 H, $CH_2C\mathbf{H}_2CH_2$).

(*S*)-*N*-(2-Hydroxyethyl)-*N*-α-methylbenzylamine. A suspension of (−)-(*S*)-methylbenzylamine (**6**, 0.20 mol), 2-chloroethanol (0.20 mol), and K_2CO_3 (0.14 mol) in H_2O (2.6 mL) and 1,2-dimethoxyethane (200 mL) was refluxed (4 days), and solvent was then removed in vacuo. $CHCl_3$ was added to the residue, undissolved solids were removed by filtration, and the filtrate was concentrated in vacuo. Unreacted **6** (41%) was removed by vacuum distillation, and the product (30%, 52% corrected) was obtained as the pot residue: ^{1}H NMR (60 MHz, $CDCl_3/Me_4Si$) δ 7.38 (s, 5 H, aromatic), 4.10–3.18 (m, 5 H), 2.82–2.54 (m, 2 H, CH_2N), and 1.42 (d, J_{HH} = 6.5 Hz, 3 H, CH_3).

(*S*)-*N*-(2-Chloroethyl)-*N*-α-methylbenzylamine Hydrochloride. To a solution of the above amine (86 mmol) in $CHCl_3$ (65 mL) was added $SOCl_2$ (430 mmol) in $CHCl_3$ (45 mL). The mixture was refluxed for 3.5 h, and volatiles were then removed in vacuo. Cooling an ether solution of the residue resulted in precipitation of the product (56%, mp 213–216 °C): ^{1}H NMR (220 MHz, D_2O/TSP) δ 7.52 (s, 5 H, aromatic), 4.50 (q, J_{HH} = 7 Hz, 1 H, benzylic), 3.80 (apparent t, J_{HH} = 5 Hz, 2 H, CH_2Cl), 3.45–3.14 (symmetrical m, 2 H, CH_2N), and 1.72 (d, J_{HH} = 7 Hz, 3 H, CH_3).

(*S*)-*N*-(2-Chloroethyl)-*N*-α-methylbenzylamine Phosphoramidic Dichloride (7). To a suspension of $POCl_3$ (196 mmol) and the above hydrochloride (19.6 mmol) in $CHCl_3$ (90 mL) was added Et_3N (39.2 mmol) in $CHCl_3$ (10 mL). After being stirred overnight at room temperature, volatiles were removed in vacuo and an ether solution of the residue was filtered. Concentration of the filtrate in vacuo gave an oil which was chromatographed on silica gel ($CHCl_3$) and afforded the product (30%, R_f 0.68): ^{1}H NMR (60 MHz, $CDCl_3/Me_4Si$) δ 7.47 (s, 5 H, aromatic), 5.28 (apparent sextet, 1 H, benzylic), 3.66–2.76 (m, 4 H), and 1.71 (d, J_{HH} = 7 Hz, 3 H, CH_3).

2-[2-Chloroethyl-(*S*)-α-methylbenzylamino]-3-(2-benzyloxyethyl)-2*H*-1,3,2-oxazaphosphorinane 2-Oxide (8). To a solution of **5** (7.09 mmol) and Et_3N (14.18 mmol) in ethyl acetate (20 mL) was added **7** (7.09 mmol) in the same solvent (25 mL). The reaction mixture was stirred at room temperature for 3 days before filtration and chromatography of the concentrated filtrate on silica gel ($CHCl_3$/MeOH, 98:2). The product (R_f 0.39) was obtained (67%) as a ~55:45 mixture of diastereomers: ^{1}H NMR (220 MHz, $CDCl_3/Me_4Si$) δ 7.55–7.25 (aromatic), 5.16–4.91 (m, benzylic methine), 4.53 and 4.51 (two s, two benzylic methylenes in 55 and 45% relative abundance, respectively), 4.61–4.14, 3.80–3.55, and 3.48–2.95 (three m, 12 H), 2.14–1.75 (m, 2 H, $CH_2C\mathbf{H}_2CH_2$), and 1.55 and 1.54 (two d, J_{HH} = 7 Hz, two CH_3 in a relative abundance of ca. 55 and 45%, respectively); ^{13}C NMR (25 MHz, $CDCl_3/Me_4Si$) δ 128.10, 127.32, 127.23, 73.05, 68.57, 68.43, 67.06, 66.77, 53.69, 47.86, 44.45, 42.46, 42.07, 26.41, 26.21, 18.53, and 17.80.

2-[2-Chloroethyl-(*S*)-α-methylbenzylamino]-3-(2-hydroxyethyl)-2*H*-1,3,2-oxazaphosphorinane 2-Oxide (9). Medium-pressure hydrogenolysis (50 psi, 25 °C) of **8** (4.8 mmol, 2.13 g) using 10% Pd–C (2.13 g) and EtOH/H_2O (4:1, 30 mL) for 6 h was followed by filtration and in vacuo concentration to roughly half the original volume. Addition of EtOH (15 mL) followed by concentration to roughly half-volume was carried out a total of three times before final evaporation to afford an oily residue which was dissolved in $CHCl_3$, dried ($MgSO_4$), and concentrated in vacuo to give **9** (82%). Such samples of **9** could generally be used without further purification; however, chromatography on silica gel ($CHCl_3$/MeOH, 9:1) was found in one instance to afford purified **9** as a mixture of simultaneously eluting diasteromers (R_f 0.58): ^{1}H NMR (220 MHz, $CDCl_3/Me_4Si$) δ 7.52–7.23 (m, 5 H, aromatic), 5.16–4.80 (m, 2 H, methine and hydroxyl), 4.61–3.89 (three m, 4 H), 3.77–2.66 (m, 8 H, CH_2Cl and three NCH_2), 2.27–1.82 (m, 2 H, $CH_2C\mathbf{H}_2CH_2$), and 1.60 and 1.54 (two d, J_{HH} = 7 Hz, two CH_3 in a relative abundance of ca. 58 and 42%, re-

spectively).

2-[2-Chloroethyl-(*S*)-α-methylbenzylamino]-3-(2-chloroethyl)-2*H*-1,3,2-oxazaphosphorinane 2-Oxide (4). To a solution of **9** (0.41 mmol) and pyridine (0.41 mmol) in benzene (1 mL) was added $SOCl_2$ (1.23 mmol) in an equal volume of the same solvent. The reaction mixture was allowed to stir at 70 °C for 17 h before concentration in vacuo and chromatography of the residue on silica gel ($CHCl_3$/MeOH, 95:5), which gave **4** (R_f 0.75, 35%) as a mixture (44:56) of diastereomers. Separation of the diastereomers of **4** was achieved by multiple-elution (4–5 times) thick-layer (1 mm) chromatography on silica gel using ethyl acetate as eluent. Methanol was used to remove the diastereomers of **4** from the silica gel; however, recovery was low (~60%). For **4A** (faster eluting): ^1H NMR (220 MHz, $CDCl_3$/Me_4Si) δ 7.45–7.25 (m, 5 H, aromatic), 5.07–4.86 (m, 1 H, benzylic), 4.50–4.11 (m, 2 H, CH_2O), 3.80–3.52 and 3.52–3.02 (two m, 10 H), 2.16–1.95 and 1.95–1.80 (two m, 2 H, $CH_2CH_2CH_2$), and 1.56 (d, J_{HH} = 7 Hz, 3 H, CH_3). For **4B** (slower eluting): ^1H NMR δ 7.45–7.27 (m, 5 H, aromatic), 5.14–4.98 (m, 1 H, benzylic), 4.51–4.35 and 4.35–4.14 (two m, 2 H, CH_2O), 3.77–3.57 and 3.48–3.05 (two m, 10 H), 2.18–1.82 (m, 2 H, $CH_2CH_2CH_2$), and 1.58 (d, J_{HH} = 7 Hz, 3 H, CH_3). ^{31}P NMR (40.25 MHz, 4:1 EtOH/H_2O, 25% H_3PO_4 as external reference) (for **4A**) δ 13.92, (for **4B**) δ 14.47.

Hydrogenolysis of 4. A diastereomerically enriched sample of **4A**/**4B** (10:90, 22.4 mg) in EtOH/H_2O (4:1, 5 mL) with 10% Pd–C (134.4 mg) was subjected to a medium-pressure (50 psi) of hydrogen for 3 days at 25 °C. The isophosphamide product (25%) was identified and quantified by direct ^{31}P NMR analysis of the filtered reaction mixture: δ 13.38 (25% H_3PO_4 external reference). Concentration of the reaction mixture, as in the case of **9**, was followed by drying in vacuo over P_2O_5 and gave an oily residue. This material (10 mg) was dissolved in $CDCl_3$ (1.7 mL), and the chiral shift reagent Eu(hfc)$_3$ (2 equiv based on total ^{31}P content) was added in portions for direct assessment of the enantiomeric composition of **1**. Narrow ($\omega_{1/2} \cong 8$ Hz) ^{31}P NMR absorptions were clearly evident for the individual enantiomers of **1** at δ −68.57 and −70.93, and these signals were in a relative abundance of 10 and 90, respectively. There was no problem of overlap between these signals and the further upfield-shifted absorptions of **4A**/**4B** (δ ~−100). Isolation of **1** was accomplished by thin-layer (0.25 mm) chromatography on silica gel (10 × 20 cm plate) using $CHCl_3$/MeOH (9:1) eluent. In this solvent system, Eu(hfc)$_3$ and unreacted **4A**/**4B** travel with the solvent front while **1** has a R_f value of 0.74. Isolation of the area corresponding to R_f ~0.74 followed by desorption with methanol gave material (3 mg) which had a ^1H NMR (220 MHz) spectrum essentially identical with that of authentic **1**.

Oppositely enriched **4A**/**4B** (82:18) starting material under duplicate hydrogenolysis conditions led to a 90 and 10 relative abundance of the ^{31}P signals at δ −68.57 and −70.93, respectively. Chromatographic purification as above likewise gave material (2 mg), which had a ^1H NMR (220 MHz) spectrum essentially identical with that of authentic **1**.

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Registry No.—(+)-**1**, 66849-34-1; (−)-**1**, 66849-33-0; **4A**, 68927-45-7; **4B**, 68927-46-8; **5**, 68927-47-9; **6**, 2627-86-3; **7**, 66921-28-6; **8A**, 68927-48-0; **8B**, 68927-49-1; **9A**, 68927-50-4; **9B**, 68927-51-5; benzyl 2-hydroxyethyl ether, 622-08-2; benzyl 2-chloroethyl ether, 35655-21-1; benzyl 2-iodoethyl ether, 54555-84-9; (*S*)-*N*-(2-hydroxyethyl)-*N*-α-methylbenzylamine, 66849-29-4; (*S*)-*N*-(2-chloroethyl)-*N*-α-methylbenzylamine hydrochloride, 66849-30-7, ethylene glycol, 107-21-1; benzyl bromide, 28807-97-8; 1-amino-3-propanol, 156-87-6; 2-chloroethanol, 107-07-3.

References and Notes

(1) D. L. Hill, "A Review of Cyclophosphamide", Charles C. Thomas, Springfield, Ill., 1975.
(2) P. J. Creaven, L. M. Allen, M. H. Cohen, and R. L. Nelson, *Cancer Treat. Rep.*, **60**, 445 (1976); G. Falkson and H. C. Falkson, *ibid.*, **60**, 955 (1976).
(3) (a) G. Zon, *Tetrahedron Lett.*, 3139 (1975); (b) G. Zon, J. A. Brandt, and W. Egan, *J. Natl. Cancer Inst.*, **58**, 1117 (1977); (c) I. L. Karle, J. M. Karle, W. Egan, G. Zon, and J. A. Brandt, *J. Am. Chem. Soc.*, **99**, 4803 (1977); (d) F. P. Tsui, J. A. Brandt, and G. Zon, *Biochem. Pharmacol.*, **28**, 367 (1979).
(4) (a) R. Kinas, K. Pankiewicz, and W. J. Stec, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **23**, 981 (1975). (b) P. J. Cox, P. B. Farmer, M. Jarman, M. Jones, W. J. Stec, and R. Kinas, *Biochem. Pharmacol.*, **25**, 993 (1976). (c) P. J. Cox, P. B. Farmer, A. B. Foster, L. J. Griggs, M. Jarman, R. Kinas, K. Pankiewicz, and W. J. Stec, *Biomed. Mass Spectrom.*, **4**, 371 (1977). (d) D. A. Adamiak, W. Saenger, R. Kinas, and W. J. Stec, *Z. Naturforsch., C*, **32**, 672 (1977). (e) For the synthesis and absolute configuration of 4-methylcyclophosphamide, see R. Kinas, K. Pankiewicz, W. J. Stec, P. B. Farmer, A. B. Foster, and M. Jarman, *J. Org. Chem.*, **42**, 1650 (1977).
(5) T. Kawashima, R. D. Kroshefsky, R. A. Kok, and J. G. Verkade, *J. Org. Chem.*, **43**, 1111 (1978).
(6) (a) G. Bennett and A. Hock, *J. Chem. Soc.*, **127**, 1277 (1925); (b) J. D. Genzer, C. P. Huttrer, and G. C. van Wessem, *J. Am. Chem. Soc.*, **73**, 3159 (1951).
(7) H. Schmid and K. Schmid, *Helv. Chim. Acta*, **35**, 1879 (1952).
(8) (a) S. M. Ludeman and G. Zon, *J. Med. Chem.*, **18**, 1251 (1975); (b) S. M. Ludeman, G. Zon, and W. Egan, *ibid.*, **22**, 151 (1979).
(9) All $\delta_{^{31}P}$ values refer to an external solution of 25% H_3PO_4 in water.
(10) R. S. Tipson, M. A. Clapp, and L. H. Cretcher, *J. Org. Chem.*, **12**, 133 (1947).
(11) H. K. Frensdorff, *J. Am. Chem. Soc.*, **93**, 4684 (1971).

N^2,N^3-Di-*tert*-butoxycarbonylspermidine. A Synthesis of the Aglycone of the LL-BM123 Antibiotics

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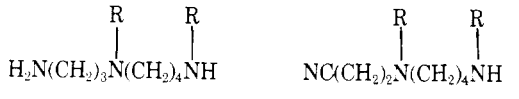
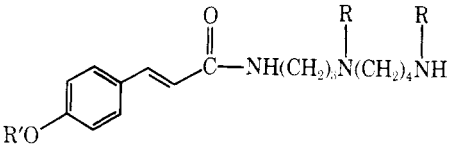
In recent years several alkaloids have been discovered that have spermidine (**1**) incorporated in their structures.[2] As part of our plan to synthesize several of these alkaloids, we required a derivative of spermidine in which the secondary amine and one of the primary amines were blocked by a group that is stable to base and to other vigorous, nonacidic conditions. Because the *tert*-butoxycarbonyl (BOC) group constitutes a base-stable, acid-labile nitrogen protecting group,[3] N^2,N^3-di-*tert*-butoxycarbonylspermidine (**2**) was prepared.[4]

Monoalkylation of 1,4-diaminobutane with acrylonitrile afforded the diaminonitrile **3**.[5] The BOC groups were introduced by treatment of **3** with 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON), a reagent previously utilized in peptide chemistry.[6] In nonpeptide applications such as this, the byproduct, 2-hydroxyimino-2-phenylacetonitrile, may be conveniently separated from the product, **4**,

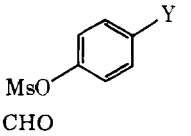


1, R = H
2, R = $(CH_3)_3COC(O)$– (BOC)

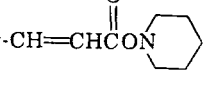
3, R = H
4, R = BOC



5, R = R′ = H
9, R = BOC; R′ = $-SO_2CH_3$ (Ms)
10, R = BOC; R′ = H
11, R = H·HCl; R′ = H



6, Y = CHO
7, Y = *t*-CH=CHCOOH



8, Y = *t*-CH=CHCON

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