Total Synthesis of (+)-Preussin, a Novel Antifungal Agent

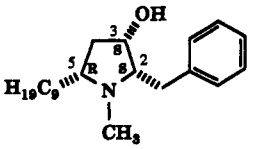
Chwang Siek Pak* and Ge Hyeong Lee

Korea Research Institute of Chemical Technology, P.O. Box 9, Daedeog-Danji, Chungnam, Korea

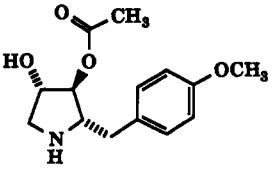
Received May 4, 1990

The total synthesis of (+)-preussin, (2*S*,3*S*,5*R*)-1-methyl-5-nonyl-2-(phenylmethyl)-3-pyrrolidinol, was achieved by using D-glucose as the starting material. The key synthetic steps involved the sequential reduction and cyclization of azido triflate **6** to construct the pyrrolidine moiety **7** with the proper stereochemistry.

L-657,398[1] (also known as (+)-preussin)[2] is a naturally occurring pyrrolidine alkaloid isolated from the fermentation of *Aspergillus ochraceus* ATCC 22947 and *Preussia* sp. which by comparison to anisomycin has a significantly broader spectrum of antifungal activity. After this compound was identified as 1-methyl-5-nonyl-2-(phenylmethyl)-3-pyrrolidinol,[1] its absolute configuration was determined to be 2*S*,3*S*,5*R*.[2]



(+)-Preussin (12)



Anisomycin

Our purpose for undertaking the total synthesis of (+)-preussin was to develop rapid derivatization methods to enable us to explore its structure–activity relationships and stereochemical requirements for antifungal activity. Numerous synthetic approaches employing different strategies and starting materials[3] have been used to produce chiral pyrrolidines but we envisioned a total synthesis of (+)-preussin (**12**) shown retrosynthetically in Scheme I.

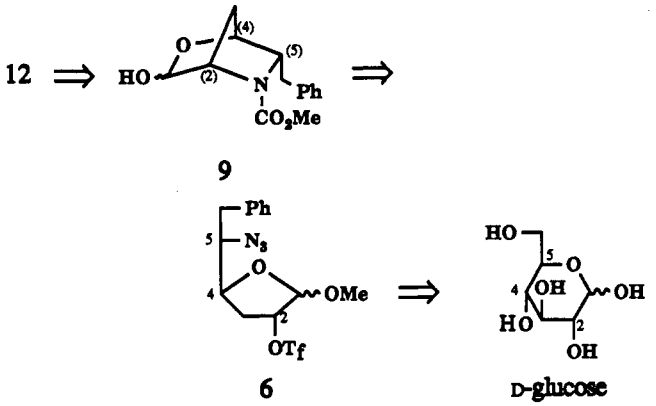
We had planned to prepare (+)-preussin (**12**) from oxazabicyclic compound **9** which was expected to be accessible via intramolecular reductive cyclization with azido triflate **6** to be derived from D-glucose. D-Glucose incorporates the requisite C-2, C-4, and C-5 stereochemistry for **12**.

Utilizing a one-pot reductive cyclization reaction and D-glucose as the chiral precursor to introduce the correct stereogenic centers at the pyrrolidine ring carbons, we have accomplished the first total synthesis of (+)-preussin (**12**).

Results and Discussion

Based on our retrosynthetic scheme, D-glucose was chosen as the starting material with its chirality at C-2,

Scheme I



C-4, and C-5 being transferred into the C-2, C-3, and C-5 of (+)-preussin (**12**) as shown in Scheme II.

Our synthesis commenced with the synthesis of the known epoxyfuranose **1** which was easily accessible via known procedures[4] from D-glucose. The copper ion catalyzed Grignard reaction[5] was performed with phenylmagnesium chloride to give secondary alcohol **2** as the only detectable product. Formation of undesired isomeric primary alcohol was not detected according to the analysis of ^1H and ^{13}C NMR spectra of the product.[6] The methine proton and the carbon at C-5 appear at 4.07 ppm as a multiplet and at 111.25 ppm as a doublet, respectively. Tosylation (95%) of **2** followed by reaction with sodium azide in dimethyl sulfoxide[7] afforded a mixture of substitution product **4a** and elimination product **4b**, which were subsequently separated by silica gel column chromatography to give **4a** (90%) and **4b** (8%) as white solids. The structure assigned to the azide **4a** is based on the method of preparation and ^1H NMR data including decoupling experiments. The coupling constant ($J_{5,6}$ = 15.9 Hz) of two vinyl protons H-5 and H-6 indicates that **4b** is an *E* isomer. Azide **4a** was subjected to methanolic hydrogen chloride solution at room temperature, which removed the acetonide protecting group. A mixture of anomers was obtained in quantitative yield which was subsequently separated by silica gel column chromatography (hexane/EtOAc, 3:1) to give β-anomer **5a** (84%) as a white solid and α-anomer (16%) as a colorless oil.[8] While the anomeric proton of **5a** appears as a singlet (4.84 ppm), that of **5b** appears as a doublet (4.92 ppm, $J_{1,2}$ =

(1) (a) Schwartz, R. E.; Liesch, J.; Hensens, O.; Zitano, L.; Honeycutt, S.; Garrity, G.; Fromtling, R. A. *J. Antibiot.* **1988**, *41*, 1774. (b) Schwartz, R. E.; Onishi, J. C.; Monaghan, R. L.; Liesch, J. M.; Hensens, O. D. U.S. Patent 4,847,284, 1989.

(2) Johnson, J. H.; Phillipson, D. W.; Kahle, A. D. *J. Antibiot.* **1989**, *42*, 1184.

(3) Previous syntheses of chiral pyrrolidines. (a) From amino acids: Rapoport, H.; Shiosaki, K. *J. Org. Chem.* **1985**, *50*, 1229. Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539. Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511. (b) From amino alkenes: Tokuda, M.; Yamada, Y.; Suginome, H. *Chem. Lett.* **1988**, 1289. Barluenga, J.; Jimenez, C.; Najera, C.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 721. Marman, T. H.; Harding, K. E. *J. Org. Chem.* **1984**, *49*, 2838. (c) From sugars: Gurjar, M. K.; Patil, V. J. *Indian J. Chem.* **1985**, *24B*, 1282. Buchanan, J. G.; MacLean, K. A.; Wightman, R. H.; Paulsen, H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1463. Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guedin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954. (d) Miscellaneous: Backvall, J. E.; Schink, H. E.; Renko, Z. D. *J. Org. Chem.* **1990**, *55*, 826. Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755. Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396. Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1988**, *29*, 5767.

(4) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) Szabo, P.; Szabo, L. *J. Chem. Soc.* **1964**, 5139.

(5) Huynh, C.; Boumechal, F. D.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, *17*, 1503.

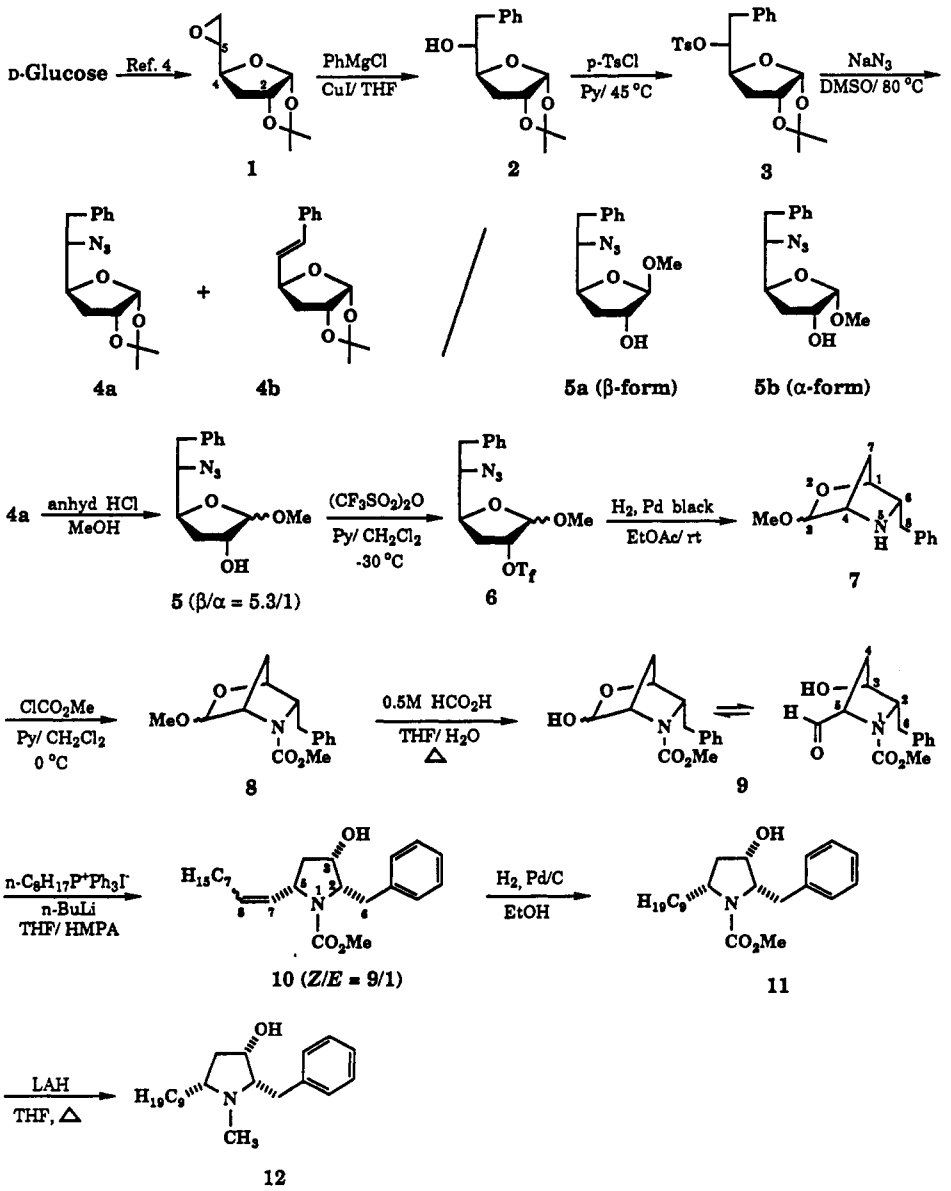
(6) Sanders, J. M.; Hunter, B. K. *Modern NMR Spectroscopy*; Oxford University Press: Oxford, 1987; p 253. DEPT (distortionless enhancement by polarization transfer) technique was used for **2**, **4a**, **6b**, **8a**, and **12** to determine the type of carbon atom (primary, secondary, and tertiary).

(7) Kinoshita, M.; Mariyama, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2081.

(8) Steric hindrance exerted by group attached at C-2 on the incoming nucleophile (CH_3OH) to the generated carbocation must be greater than by side chain at C-4 (see ref 12d).

0022-3263/91/1956-1128$02.50/0

Scheme II

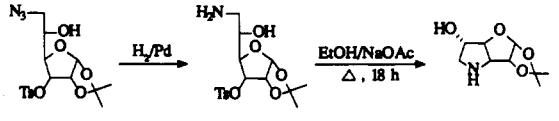


4.3 Hz). The NOEs between H-1 and H-2 and between H-2 and H-3 establish the configuration of **5a** and **5b**. A 3% NOE at H-1 of **5b** upon irradiation of H-2 was observed, but H-1 of **5a** did not exhibit any enhancement. Each anomer was subjected to triflating condition[9] to produce triflates **6a** (95%) as a purple solid and **6b** (98%) as a colorless oil. These triflates were not stable enough to be kept at room temperature for 2–3 days. However, **6a**, once decolorized (active charcoal) and recrystallized, remained stable for 1 month in the refrigerator as needle type white crystals.

Using the same methodology as the Syntex group had used for the synthesis of anisomycin,[10] we attempted to reduce the azido group of **6** into its corresponding primary amine via hydrogenation with palladium black for 6 h. Interestingly, reduction and nucleophilic displacement causing cyclization occurred in one pot to afford *exo*-methoxy bicyclic amine **7a** (66%) and *endo*-methoxy bicyclic amine **7b** (70%), respectively. A typical AB quartet coupling pattern is observed for bridgehead H-7 and H-7′ of **7b** centered at 1.96 and 1.62 ppm, respectively. It was further confirmed by decoupling experiments irradiating H-1. However, the bridgehead protons of **7a** appear as a multiplet centered at 1.94 ppm with small coupling constants (~1 Hz). Our efforts to isolate the expected primary amine intermediately after a basic workup were fruitless. The relatively low yields (66–70%) might have been due to the formation of a triflate–primary amine salt,[11] but none could be isolated from the reaction mixture. The spectral data (^{1}H and ^{13}C NMR, mass, and IR) of the

(9) Stang, P. J.; White, M. R. *Aldrichimica Acta* **1983**, *16*, 15.

(10) Verhyden, J. P. H.; Richardson, A. C.; Bhatt, R. S.; Grant, B. D.; Fitch, W. L.; Moffat, J. G. *Pure Appl. Chem.* **1978**, *50*, 1363. They isolated the expected primary amine from the hydrogenation of 6-C-azido-3-tosyl-6-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose prior to base-induced intramolecular nucleophilic displacement cyclization reaction.



(11) Bruce, I.; Fleet, G. W. J.; di Bello, I. C.; Winchester, B. *Tetrahedron Lett.* **1989**, *30*, 7257. Primary amine-triflate salt was isolated during reductive cyclization of 2-amino-7-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-3,4-*O*-isopropylidene-6-*O*-[(trifluoromethyl)sulfonyl]-D-*glycero*-D-*talo*-heptono-1,5-lactone trifluoromethanesulfonate. We thank Dr. George W. J. Fleet for disclosing the isolation procedure in private communication prior to publication.

reaction products are consistent with the proposed structures of **7a** and **7b**. From a report by Fleet et al.[12] we learned that similar oxazabicyclic skeletons, i.e., oxazabicyclo[3.2.1]octane and oxazabicyclo[2.2.1]heptane, have been made via a reductive intramolecular nucleophilic displacement reaction for the synthesis of a polyhydroxylated piperidine and a pyrrolidine alkaloid. In spite of the above mentioned cyclization, the formation of an oxazabicyclic [2.2.1] ring via intramolecular nucleophilic attack of the nitrogen at C-5 onto the C-2 carbon to produce a chiral pyrrolidine ring has not been previously reported in the literature. The yields of **7a** and **7b** were evidently not affected by the configuration of the anomeric carbon where steric repulsion between the β-methoxy and phenyl groups might have influenced the cyclization reaction. Carbomethoxylation of **7a** and **7b** gave *exo*-methoxy **8a** (86%) and *endo*-methoxy **8b** (87%),[13] each being subsequently demethylated by treatment with 0.5 M formic acid in THF to give the identical equilibriated hemiacetal–aldehyde mixture of **9** in quantitative yield. According to ^{1}H NMR analysis, the hemiacetal and free aldehyde forms exist as an equilibrium mixture in solution.[14] Without separating the isomeric mixture, **9** was subjected to a Wittig reaction[15] of the ylide derived from *n*-octyltriphenylphosphonium iodide and *n*-butyllithium which afforded a mixture of *Z* and *E* isomers that was separated by silica gel column chromatography to give *Z* isomer **10a** (81%) and *E* isomer **10b** (9%). The structures of the *Z* and *E* isomers were confirmed by ^{1}H NMR[16] spectroscopy which shows the vinylic proton, H-6, of the *Z* isomer as a doublet of doublets at 5.38 ppm ($J_{7,8}$ = 10.9 Hz) while the vinylic proton of the *E* isomer appears as a doublet of doublets at 5.11 ppm ($J_{7,8}$ = 15.4 Hz). Upon hydrogenation both isomers gave compound **11**, which was subsequently reduced by lithium aluminum hydride to afford the target compound (+)-preussin (**12**). Spectral (^{1}H and ^{13}C NMR) properties of the synthetic (+)-preussin (**12**) are identical with those of the natural product.[1] The optical rotation, $[\alpha]^{25}_D$ +31.08° (*c* 1.0, $CHCl_3$), is significantly higher than that reported for natural **12**, $[\alpha]^{25}_D$ +22.0° (*c* 1.0, $CHCl_3$).[2] The discrepancy in optical rotation might be due to the purity of natural (+)-preussin, which was obtained from fermentation as a yellow oil, while synthetic (+)-preussin was obtained as a white solid.

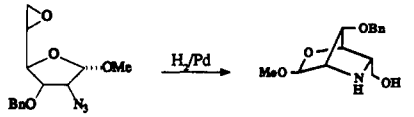
Experimental Section

General Procedure. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solution unless otherwise specified. Optical rotations were measured at the 589-nm sodium D line. GC analyses were performed on a 1 m × $^1/_8$ in. column (5% Dexil 300 on Gas Chrom W, 100–120 mesh), working in the range 60–230 °C (10–20 deg min^{-1}), using N_2 as carrier gas (flow rate 60 mL min^{-1}). Column chromatography was performed with Merck Kieselgel 60 (70–230 mesh ASTM) silica. Tetrahydrofuran (THF) was distilled from sodium benzophenone immediately prior to use. Dichloromethane was distilled from P_2O_5 prior to use. All reactions were monitored by thin-layer chromatography with E-Merck 60F-254 precoated silica (0.2 mm) on glass.

6-*C*-Phenyl-3,6-dideoxy-1,2-*O*-isopropylidene-α-D-allofuranose (2). To a stirred solution of CuI (2.86 g, 15.0 mmol) in dry THF (250 mL) at −50 °C under nitrogen was added dropwise phenylmagnesium chloride (50.0 mL of 3.0 M in ether, 150.0 mmol) over a period of 10 min. The resulting solution was stirred for 10 min, at which time a solution of 5,6-anhydro-3-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose **1** (18.6 g, 100 mmol) in dry THF (50 mL) was added dropwise over a period of 30 min. After additional stirring for 1 h, the solution was allowed to warm to −30 °C over a period of 45 min, stirred for a further 30 min, and then warmed to 0 °C. The solution was then quenched by addition of saturated aqueous NH_4Cl (50 mL). The solvent was removed in vacuo and then diluted with ether (300 mL) and water (300 mL). The organic layer was separated, and the aqueous layer was extracted with ether (250 mL × 2). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford a pale yellow oil, which was purified by flash column chromatography on silica gel (elution with hexane/EtOAc, 3:1) to give 26.4 g (100%) of **2** as a nearly colorless oil, which slowly crystallized to white crystal on standing at room temperature. An analytical sample was obtained by recrystallization from hexane as white crystals: TLC R_f 0.18 (hexane/AcOEt, 3:1); mp 72–73 °C; $[\alpha]^{25}_D$ −15.47° (*c* 2.5 in $CHCl_3$); IR (KBr) 3441 (OH), 3044, 2927, 1559, 1378, 1016 cm^{-1}; ^{1}H NMR δ 7.37–7.15 (m, 5 H, aromatic), 5.77 (d, $J_{1,2}$ = 3.7 Hz, 1 H, H-1), 4.71 (dd, $J_{1,2}$ = 3.7, $J_{2,3}$ = 4.6 Hz, 1 H, H-2), 4.17 (m, 1 H, H-4), 4.07 (m, 1 H, H-5), 2.74 (dd, $J_{6,6'}$ = 13.8, $J_{6,5}$ = 9.0 Hz, 1 H, H-6), 2.66 (dd, $J_{6,6'}$ = 13.8, $J_{6',5}$ = 5.5 Hz, 1 H, H-6′), 2.38 (d, *J* = 3.1 Hz, 1 H, OH), 2.01 (dd, $J_{3,3'}$ = 13.5, $J_{3,4}$ = 4.8 Hz, 1 H, H-3), 1.90 (ddd, $J_{3,3'}$ = 13.5, $J_{3',4}$ = 10.4, $J_{3',2}$ = 4.6 Hz, 1 H, H-3′), 1.46, 1.30 (singlets, 3 H each, acetonide); ^{13}C NMR δ 137.76, 129.07, 128.29, 126.30, 110.96, 105.06, 80.39, 80.24, 71.56, 39.24, 31.93, 26.56, 25.99; MS *m/z* (rel intensity) 265 (M^+ + 1, 2.5), 264 (M^+, 5.8), 173 (52.8), 143 (100), 91 (68.8), 85 (85.1), 59 (57.2). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.29; H, 7.57.

6-*C*-Phenyl-3,6-dideoxy-5-*O*-(*p*-tolylsulfonyl)-1,2-*O*-isopropylidene-α-D-allofuranose (3). A stirred mixture of **2** (25.9 g, 98.0 mmol), dry pyridine (250 mL), and *p*-toluenesulfonyl chloride (37.4 g, 196 mmol) was heated at 45 °C for 24 h. The reaction mixture was cooled to room temperature and quenched with ice chips, diluted with water, and then extracted with ether (400 mL × 2). The combined organic layer was sequentially washed with 1 N HCl and saturated aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated in vacuo to afford a pale yellow solid, which was purified by column chromatography on silica gel (elution with hexane/EtOAc, 5:1) to give 39.0 g (95%) of **3** as a white solid. An analytical sample was obtained by recrystallization from 2-propanol, which gave fine white needles: TLC R_f 0.27 (hexane/AcOEt, 4:1); mp 99–100 °C; $[\alpha]^{25}_D$ −30.80° (*c* 2.5 in $CHCl_3$); IR (KBr) 3009, 2932, 1594, 1337, 1020, 888 cm^{-1}; ^{1}H NMR δ 7.66–7.55 (m, 2 H, aromatic), 7.29–7.05 (m, 7 H, aromatic), 5.52 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1), 4.91 (m, 1 H, 5-H), 4.63 (dd, $J_{1,2}$ = 3.6, $J_{2,3}$ = 4.6 Hz, 1 H, H-2), 4.17 (m, 1 H, H-4), 2.99 (dd, $J_{6,6'}$ = 13.5, $J_{6,5}$ = 5.0 Hz, 1 H, H-6), 2.93 (dd, $J_{6,6'}$ = 13.5, $J_{6',5}$ = 8.6 Hz, 1 H, H-6′), 2.39 (s, 3 H, CH_3), 2.02 (dd, $J_{3,3'}$ = 13.3, $J_{3,2}$ = 4.6 Hz, 1 H, H-3), 1.73 (ddd, $J_{3,3'}$ = 13.3, $J_{3,4}$ = 10.6, $J_{3',2}$ = 4.6 Hz, 1 H, H-3′), 1.37, 1.25 (singlets, 3 H each, acetonide); ^{13}C NMR δ 144.24,

(12) (a) Fleet, G. W. J.; Carpenter, N. M.; Petursson, S.; Ramsden, N. G. *Tetrahedron Lett.* **1990**, *31*, 409. (b) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 327. (c) Fleet, G. W. J.; Fellows, L. E.; Smith, P. W. *Tetrahedron* **1987**, *43*, 979. (d) Fleet, G. W. J.; Smith, P. W. *Tetrahedron Lett.* **1985**, *26*, 1469. In ref (d), the azido epoxide was hydrogenated to obtain the bicyclic amine selectively by a 5-*exo*-*tet* process.



(13) Due to restricted rotation about N–CO bond, two conformers were present approximately in the ratio of 6:4 both in **8a** and **8b**. While conformer signals for H-4 of **8a** (endo-OCH_3) appeared as two slightly broadened singlets centered at 4.59 and 4.46 ppm, respectively, those of **8b** (exo-OCH_3) appeared at 5.31 and 4.37 ppm as severely broadened two singlets.

(14) Depending on the solvents, the ratio of the equilibrium mixture of **9** changed dramatically, i.e., in $CDCl_3$ the ratio of hemiacetal to aldehyde was approximately 1:1 while in DMSO-d_6 it was 1:4. Other proton peaks were difficult to assign since severe line broadening occurred (see the Experimental Section). The difficulty might be due to the combined effects of hindered rotation of carbomethoxy group and puckering of the pyrrolidine ring on the NMR time scale. Efforts to determine the ratio by GC and HPLC were not successful.

(15) Moustakis, C. A.; Viala, J.; Capdevila, J.; Falck, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 5283.

(16) Decoupling experiments with **10a** further confirmed the assigned structure. Signals of CO_2CH_3, H-6, and H-4 of **10b** exhibited severe line broadening.

135.22, 133.93, 129.53, 129.37, 128.28, 127.55, 126.70, 111.25, 105.02, 82.57, 80.05, 77.04, 37.90, 33.57, 26.58, 26.06, 21.43; MS m/z (rel intensity) 403 ($M^+ - CH_3$, 19.1), 246 (55.8), 143 (100), 91 (64.9), 85 (43.4). Anal. Calcd for $C_{22}H_{26}O_6S$: C, 63.14; H, 6.26. Found: C, 63.45; H, 6.19.

6-*C*-Phenyl-5-azido-3,5,6-trideoxy-1,2-*O*-isopropylidene-β-L-talofuranose (4a). A stirred mixture of **3** (38.7 g, 92.4 mmol), dimethyl sulfoxide (250 mL), and sodium azide (18.0 g, 277 mmol) was heated at 80 °C for 3 h. The reaction mixture was cooled to room temperature and then diluted with ether (300 mL) and water (200 mL). The organic layer was separated, and the aqueous layer was extracted with ether (250 mL × 2). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford a pale yellow oil, which slowly solidified on standing at room temperature and was purified by column chromatography on silica gel (elution with hexane/CH_2Cl_2, 1:2) to give 23.3 g (90%) of **4a** as a white solid and 1.76 g (8%) of **4b** as a white solid. Analytical samples of **4a** and **4b** were obtained by recrystallization from 2-propanol and hexane, which separately gave white needles.

4a: TLC R_f 0.56 (hexane/CH_2Cl_2, 1:3); mp 78–78.5 °C; $[\alpha]^{25}_D$ −36.40° (c 2.5 in $CHCl_3$); IR (KBr) 3043, 2978, 2104 (N_3), 1015, 696 cm^{-1}; ^1H NMR δ 7.40–7.20 (m, 5 H, aromatic), 5.87 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1), 4.75 (dd, $J_{2,3}$ = 4.7, $J_{2,1}$ = 3.6 Hz, 1 H, H-2), 4.25 (m, 1 H, H-4), 3.37 (m, 1 H, H-5), 3.04 (dd, $J_{6,6'}$ = 13.5, $J_{6,5}$ = 5.3 Hz, 1 H, H-6), 2.98 (dd, $J_{6,6'}$ = 13.5, $J_{6',5}$ = 9.6 Hz, 1 H, H-6'), 2.02 (dd, $J_{3,3'}$ = 13.3, $J_{3,4}$ = 4.7 Hz, 1 H, H-3), 1.90 (ddd, $J_{3,3'}$ = 13.3, $J_{3',4}$ = 10.5, $J_{3',2}$ = 4.6 H, 1 H, H-3'), 1.46, 1.32 (singlets, 3 H each, acetonide); ^{13}C NMR δ 137.15, 129.25, 128.58, 126.84, 111.46, 105.27, 80.38, 78.63, 64.12, 37.36, 35.30, 26.75, 26.23; MS m/z (rel intensity) 274 ($M^+ - CH_3$, 11.8), 143 (100), 91 (72.8), 85 (55.0). Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.57; N, 14.52. Found: C, 62.51; H, 6.70; N, 14.53.

4b: TLC R_f 0.28 (hexane/CH_2Cl_2, 1:3); mp 105–106 °C; $[\alpha]^{25}_D$ −54.16° (c 2.5 in $CHCl_3$); IR (KBr) 3121, 2999, 1375, 1007, 749 cm^{-1}; ^1H NMR δ 7.18–7.48 (m, 5 H, aromatic), 6.68 (d, $J_{5,6}$ = 15.9 Hz, 1 H, H-6), 6.17 (dd, $J_{5,6}$ = 15.9, $J_{4,5}$ = 7.1 Hz, 1 H, H-5), 5.89 (d, $J_{1,2}$ = 3.7 Hz, 1 H, H-1), 4.75–4.88 (m, 2 H, H-2, H-4), 2.24 (dd, $J_{3,3'}$ = 13.4, $J_{3',4}$ = 4.2 Hz, 1 H, H-3'), 1.71 (ddd, $J_{3,3'}$ = 13.4, $J_{2,3}$ = 11.0, $J_{3,4}$ = 4.2 Hz, 1 H, H-3), 1.57, 1.34 (singlets, 3 H each, acetonide); ^{13}C NMR δ 136.31, 132.46, 128.51, 127.82, 127.25, 126.50, 110.99, 105.32, 80.51, 78.41, 39.68, 26.62, 26.04; MS m/z (rel intensity) 247 (M^+ + 1, 3.8), 246 (M^+, 20.7), 131 (51.9), 130 (48.4), 104 (97.9), 43 (100). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.10; H, 7.39.

Methyl 6-*C*-Phenyl-5-azido-3,5,6-trideoxy-β-L-talofuranoside (5a) and Methyl 6-*C*-Phenyl-5-azido-3,5,6-trideoxy-α-L-talofuranoside (5b). A solution of azide **4a** (24.1 g, 83.3 mmol) in anhydrous methanolic hydrogen chloride (300 mL, 1 M in HCl) was stirred at room temperature for 12 h. The solution was neutralized by addition of excess anhydrous Na_2CO_3, filtered, and concentrated in vacuo to afford a pale orange oil, which slowly solidified on standing, and was purified by column chromatography on silica gel (elution with hexane/AcOEt, 4:1) to give 18.3 g (84%) of β-isomer **5a** as a white solid and 3.62 g (16%) of α-isomer **5b** as a colorless oil. An analytical sample of β-isomer **5a** was obtained by recrystallization from hexane–isopropyl ether (1:1) as white needles.

5a: TLC R_f 0.11 (hexane/AcOEt, 3:1); mp 68–68.5 °C; $[\alpha]^{25}_D$ −21.84° (c 2.5 in $CHCl_3$); IR (KBr) 3401 (OH), 3064, 2958, 2099 (N_3), 1015, 912 cm^{-1}; ^1H NMR δ 7.46–7.12 (m, 5 H, aromatic), 4.84 (s, 1 H, H-1), 4.34 (m, 1 H, H-2), 4.26 (m, 1 H, H-4), 3.52–3.30 (m, 1 H, H-5), 3.41 (s, 3 H, OCH_3), 2.84 (dd, $J_{6,6'}$ = 13.9, $J_{6,5}$ = 4.3 Hz, 1 H, H-6), 2.67 (dd, $J_{6,6'}$ = 13.9, $J_{6',5}$ = 9.4 Hz, 1 H, H-6'), 2.38 (d, J = 3.6 Hz, 1 H, OH), 2.12–1.90 (m, 2 H, H-2); ^{13}C NMR δ 137.18, 129.24, 128.53, 126.77, 109.37, 81.58, 75.71, 66.42, 55.12, 37.06, 35.44; MS m/z (rel intensity) 235 ($M^+ - N_2$, 0.8), 117 (100), 91 (66.3), 85 (21.1), 45 (57.1). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.61; H, 6.61; N, 15.89.

5b: TLC R_f 0.22 (hexane/AcOEt, 3:1); $[\alpha]^{25}_D$ +105.01° (c 2.5 in $CHCl_3$); IR (NaCl, neat) 3409 (OH), 3089, 2900, 2086 (N_3), 1024, 696 cm^{-1}; ^1H NMR δ 7.39–7.18 (m, 5 H, aromatic), 4.92 (d, $J_{1,2}$ = 4.3 Hz, 1 H, H-1), 4.34 (m, 1 H, H-2), 4.20 (m, 1 H, H-4), 3.48 (s, 3 H, OCH_3), 3.30 (m, 1 H, H-5), 2.98 (dd, $J_{6,6'}$ = 13.3, $J_{6,5}$ = 8.6 Hz, 1 H, H-6), 2.95 (dd, $J_{6,6'}$ = 13.3, $J_{6',5}$ = 6.2 Hz, 1 H, H-6'), 2.09 (m, 1 H, H-3), 1.88 (m, 1 H, H-3); ^{13}C NMR δ 137.09, 129.12, 128.51, 126.71, 102.58, 77.27, 71.56, 65.46, 55.26, 36.67, 35.08; MS m/z (rel intensity) 235 ($M^+ - N_2$, 0.4), 117 (100), 91 (85.8), 85 (21.9), 45 (61.6). Anal. Calcd for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.49; H, 6.44; N, 16.03.

Methyl 6-*C*-Phenyl-5-azido-3,5,6-trideoxy-2-*O*-[(trifluoromethyl)sulfonyl]-β-L-talofuranoside (6a). To a stirred solution of β-isomer **5a** (17.5 g, 66.5 mmol) and dry pyridine (10.8 mL, 134 mmol) in dry CH_2Cl_2 (200 mL) at −50 °C under nitrogen was added dropwise trifluoromethanesulfonic anhydride (22.5 g, 79.8 mmol) over a period of 30 min. After being stirred for another 1 h, the solution was allowed to warm to 0 °C over a period of 30 min and was further stirred for a further 30 min, after which methanol (5 mL) was added and warmed to room temperature. The solvent was removed in vacuo, and the resulting residue was diluted with ether (200 mL) and water (150 mL). The organic layer was separated, and the aqueous layer was extracted with ether (150 mL × 2). The combined organic layer was washed with 1 N HCl and saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo to afford a dark purple oil, which was purified by flash column chromatography on silica gel (elution with hexane/ether, 1:3) to give 25.0 g (95%) of **6a** as a pale orange oil, which rapidly changed on standing to a purple solid. The solid was directly used in the next step without further purification even though the purple color could be removed by treatment with activated charcoal. An analytical sample was obtained by recrystallization from 2-propanol–hexane (1:2) as fine white needles: TLC R_f 0.57 (hexane/ether, 3:1); mp 49.5–50 °C; $[\alpha]^{25}_D$ −16.63° (c 2.5 in $CHCl_3$); IR (KBr) 3047, 2902, 2105 (N_3), 1407, 1243, 1199, 920 cm^{-1}; ^1H NMR δ 7.46–7.10 (m, 5 H, aromatic), 5.22 (d, $J_{2,3}$ = 4.1 Hz, 1 H, H-2), 5.11 (s, 1 H, H-1), 4.36 (m, 1 H, H-4), 3.46 (s, 3 H, OCH_3), 3.46–3.35 (m, 1 H, H-5), 3.00–2.71 (m, 2 H, H-6), 2.42–2.16 (m, 2 H, H-3); ^{13}C NMR δ 136.65, 129.21, 128.70, 127.04, 118.37, 106.23, 89.63, 81.11, 66.61, 55.67, 37.00, 33.13; MS m/z (rel intensity) 367 ($M^+ - N_2$, 1.9), 99 (84.0), 91 (100). Anal. Calcd for $C_{14}H_{16}F_3N_3O_5S$: C, 42.53; H, 4.08; N, 10.63. Found: C, 42.51; H, 4.21; N, 10.59.

Methyl 6-*C*-Phenyl-5-azido-3,5,6-trideoxy-2-*O*-[(trifluoromethyl)sulfonyl]-α-L-talofuranoside (6b). The reaction was carried out as described above, using **5b** (3.00 g, 11.4 mmol) to give 4.41 g (98%) of **6b** as a colorless oil: TLC R_f 0.44 (hexane/ether, 3:1); $[\alpha]^{25}_D$ +118.61° (c 2.5 in $CHCl_3$); IR (NaCl, neat) 3040, 2908, 2090 (N_3), 1408, 1199, 1029, 920 cm^{-1}; ^1H NMR δ 7.40–7.13 (m, 5 H, aromatic), 5.18 (m, 1 H, H-2), 5.10 (d, $J_{1,2}$ = 4.1 Hz, 1 H, H-1), 4.22 (m, 1 H, H-4), 3.46 (s, 3 H, OCH_3), 3.38 (td, $J_{5,6}$ = 7.5, $J_{5,4}$ = 2.8 Hz, 1 H, H-5), 3.01 (d, $J_{6,5}$ = 7.5 Hz, 2 H, H-6), 2.37–2.17 (m, 2 H, H-3); ^{13}C NMR δ 136.51, 129.14, 128.66, 126.98, 118.38, 100.76, 83.07, 75.77, 64.67, 55.35, 36.27, 31.02; MS m/z (rel intensity) 367 ($M^+ - N_2$, 3.5), 249 (54.4), 99 (72.8), 91 (100). Anal. Calcd for $C_{14}H_{16}F_3N_3O_5S$: C, 42.53; H, 4.08; N, 10.63. Found: C, 42.65; H, 4.07; N, 10.69.

(3*R*,6*S*)-6-(Phenylmethyl)-3-methoxy-2-oxa-5-azabicyclo[2.2.1]heptane (7a). A mixture of **6a** (22.9 g, 58.0 mmol), palladium black (1.00 g), and EtOAc (500 mL) was stirred in 1 atm of hydrogen for 6 h. The reaction mixture was diluted with cold 6.0 N NaOH solution (150 mL) and filtered through a pad of Celite. The organic layer was separated, and the aqueous layer was extracted with EtOAc (200 mL × 2). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford a brown oil, which was purified by flash column chromatography on silica gel (elution with CH_2Cl_2/MeOH, 9:1) to give 8.39 g (66%) of **7a** as a pale yellow oil: TLC R_f 0.54 (CH_2Cl_2/MeOH, 9:1); $[\alpha]^{25}_D$ +36.31° (c 2.5 in $CHCl_3$); IR (NaCl, neat) 3299 (NH), 3039, 2934, 1113, 1027, 919 cm^{-1}; ^1H NMR δ 7.35–7.06 (m, 5 H, aromatic), 5.04 (d, $J_{3,4}$ = 1.1 Hz, 1 H, H-3), 4.14 (m, 1 H, H-1), 3.56 (s, 3 H, OCH_3), 3.43–3.22 (m, 2 H, H-4, H-6), 3.01 (dd, $J_{8,8'}$ = 13.0, $J_{6,8}$ = 8.5 Hz, 1 H, H-8), 2.90 (dd, $J_{8,8'}$ = 13.0, $J_{6,8'}$ = 6.7 Hz, 1 H, H-8'), 2.09 (br s, 1 H, NH), 1.94 (m, 2 H, H-7); ^{13}C NMR δ 138.93, 128.84, 128.18, 125.85, 107.53, 78.99, 63.21, 58.67, 55.51, 37.73, 35.67; MS m/z (rel intensity) 221 (M^+ + 2, 0.5), 220 (M^+ + 1, 3.1), 219 (M^+, 0.8), 68 (100). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.30; H, 7.91; N, 6.28.

(3*S*,6*S*)-6-(Phenylmethyl)-3-methoxy-2-oxa-5-azabicyclo[2.2.1]heptane (7b). The reaction was carried out as described above, using **6b** (4.00 g, 10.1 mmol) to give 1.55 g (70%) of **7b** as a pale yellow oil: TLC R_f 0.54 (CH_2Cl_2/MeOH, 9:1); $[\alpha]^{25}_D$

+155.03° (c 2.5 in $CHCl_3$); IR (NaCl, neat) 3285 (NH), 3091, 2970, 1445, 1191, 1091, 902 cm^{-1}; ^1H NMR δ 7.43–7.10 (m, 5 H, aromatic), 4.56 (s, 1 H, H-3), 4.22 (m, 1 H, H-1), 3.50–3.33 (m, 1 H, H-4), 3.39 (s, 3 H, OCH_3), 3.20 (ddd, $J_{6,8}$ = 8.2, $J_{6,8'}$ = 6.2, $J_{1,6}$ = 1.0 Hz, 1 H, H-6), 2.80 (dd, $J_{8,8'}$ = 13.1 Hz, $J_{6,8}$ = 8.2 Hz, 1 H, H-8), 2.69 (dd, $J_{8,8'}$ = 13.1, $J_{6,8'}$ = 6.2 Hz, 1 H, H-8′), 1.96 (ddd, $J_{7,7'}$ = 10.0, $J_{4,7'}$ = 2.4, $J_{1,7'}$ = 0.9 Hz, 1 H, H-7), 1.62 (dd, $J_{7,7'}$ = 10.0, $J_{4,7}$ = 2.0 Hz, 1 H, H-7′), 1.32 (br s, 1 H, NH); ^{13}C NMR δ 138.84, 128.97, 128.25, 125.99, 107.09, 76.68, 62.31, 59.33, 54.59, 37.43, 34.81; MS m/z (rel intensity) 121 (M^+ + 2, 1.1), 120 (M^+, 6.6), 219 (M^+, 0.7), 68 (100). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.29; H, 7.70; N, 6.38.

Methyl (3*R*,6*S*)-6-(Phenylmethyl)-3-methoxy-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (8a). To a stirred solution of **7a** (8.00 g, 36.5 mmol) and dry pyridine (8.9 mL, 110 mmol) in dry CH_2Cl_2 (150 mL) at −78 °C was added dropwise methyl chloroformate (4.14 g, 43.8 mmol) over a period of 30 min. The solution was allowed to warm to room temperature over a period of 1 h. The solvent was removed in vacuo, and the resulting residue was diluted with ether (200 mL) and water (100 mL). The organic layer was separated, and the aqueous layer was extracted with ether (150 mL × 2). The combined organic layer was washed with 1 N HCl and saturated aqueous NH_4Cl solution, dried (Na_2SO_4), and concentrated in vacuo to afford a pale yellow oil, which was purified by column chromatography on silica gel (elution with hexane/EtOAc, 2:1) to give 8.70 g (86%) of **8a** as a colorless oil: TLC R_f 0.31 (hexane/AcOEt, 2:1); $[\alpha]^{25}_D$ −29.18° (c 2.5 in $CHCl_3$); IR (NaCl, neat) 2974, 1698 (C=O), 1454, 1177, 1105 cm^{-1}; ^1H NMR δ 7.42–7.12 (m, 5 H, aromatic), 5.01, 5.07 (singlets, 1 H, H-3), 4.59, 4.46 (singlets, 1 H, H-4), 4.23 (s, 1 H, H-1), 3.90–3.70 (m, 1 H, H-6), 3.78, 3.74 (singlets, 3 H, CO_2CH_3), 3.58 (s, 3 H, OCH_3), 3.55–2.98 (m, 2 H, H-8), 1.98 (d, $J_{7,7'}$ = 10.2 Hz, 1 H, H-7), 1.70 (d, $J_{7,7'}$ = 10.2 Hz, 1 H, H-7′); ^{13}C NMR δ 155.83, 155.37, 138.59, 129.48, 129.36, 128.24, 126.00, 106.72, 106.41, 78.87, 78.59, 65.01, 64.91, 60.03, 59.95, 56.05, 52.34, 52.23, 37.34, 33.85, 32.94; MS m/z (rel intensity) 277 (M^+, 1.3), 186 (12.7), 126 (100). Anal. Calcd $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.03; H, 6.84; N, 4.99.

Methyl (3*S*,6*S*)-6-(Phenylmethyl)-3-methoxy-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (8b). The reaction was carried out as described above, using **7b** (3.50 g, 15.9 mmol) to give 3.85 g (87%) of **8b** as a colorless oil: TLC R_f 0.51 (hexane/AcOEt, 2:1); $[\alpha]^{25}_D$ +88.83° (c 2.5 in $CHCl_3$); IR (NaCl, neat) 2980, 1697 (C=O), 1439, 1383, 1094, 698 cm^{-1}; ^1H NMR δ 7.42–7.12 (m, 5 H, aromatic), 4.73 (s, 1 H, H-3), 4.51, 4.37 (singlets, 1 H, H-4), 4.24 (s, 1 H, H-1), 3.74 (s, 3 H, CO_2CH_3), 3.70–3.51 (m, H, H-6), 3.42 (s, 3 H, OCH_3), 3.50–3.10 (m, 1 H, H-8), 2.85–2.60 (m, 1 H, H-8′), 1.96 (d, $J_{7,7'}$ = 10.2 Hz, 1 H, H-7), 1.51 (d, $J_{7,7'}$ = 10.2 Hz, 1 H, H-7′); ^{13}C NMR δ 155.80, 155.12, 138.14, 129.45, 128.29, 126.17, 104.85, 76.32, 64.36, 60.60, 54.90, 52.26, 34.91, 33.85, 33.56; MS m/z (rel intensity) 277 (M^+, 1.1), 186 (12.2), 126 (100). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.91; H, 6.91; N, 5.05. Found: C, 65.01; H, 6.93; N, 5.01.

(2*S*,3*S*,5*S*)-5-Formyl-2-(phenylmethyl)-1-carbomethoxy-3-pyrrolidinol (9). A stirred solution of **8a** (8.60 g, 31.0 mmol) and 0.5 M aqueous formic acid (50 mL) in THF (50 mL) was refluxed for 2 h. The reaction mixture was cooled to room temperature, neutralized by addition of anhydrous $NaHCO_3$, and then diluted with ether (200 mL). The organic layer was separated, and the aqueous layer was extracted with ether (100 mL × 2). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford a pale yellow oil, which was purified by column chromatography on silica gel (elution with hexane/EtOAc, 1:2) to give 8.20 g (100%) of **9** as a colorless oil. The following analytical data are for the equilibrium mixture: TLC R_f 0.37 (CH_2Cl_2/MeOH, 9:1); IR (NaCl, neat) 3396 (OH), 3037, 2925, 1669 (C=O), 1443, 1377, 1112 cm^{-1}; ^1H NMR (DMSO-d_6) 9.46 (s, 0.8 H, CHO), 7.05–7.40 (m, aromatic, 5 H), 5.37 (br doublet, 1 H, OH), 3.75–4.40 (m, 3 H, H-2, H-3, H-5), 3.60, 3.43 (br singlets, 3 H, CO_2CH_3), 2.99 (m, 2 H, H-6), 2.13 (m, 1 H, H-4), 1.88 (m, 1 H, H-4′); ^{13}C NMR (DMSO-d_6) 2?3.46, 202.32, 156.27, 155.54, 139.42, 129.86, 129.57, 129.25, 128.44, 128.04, 127.82, 125.89, 125.50, 69.32, 68.31, 64.52, 63.86, 62.75, 52.26, 37.01, 34.52, 34.03, 32.95; MS m/z (rel intensity) 264 (M^+ + 1, 0.3), 263 (M^+, 1.9), 234 (100), 172 (44.0), 91 (39.7). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.57; H, 6.55; N, 5.35. The reaction with exo isomer **8b** was carried out as described above to afford the same hemiacetal **9** quantitatively.

(2*S*,3*S*,5*S*)-2-(Phenylmethyl)-1-carbomethoxy-5-[(*Z*)-nonen-1-yl]-3-pyrrolidinol (10a). To a stirred solution of octyltriphenylphosphonium iodide (30.6 g, 60.8 mmol) in dry THF (250 mL) and dry HMPA (30 mL) at −78 °C under nitrogen was added dropwise *n*-butyllithium (38.0 mL of 1.6 N in hexane, 60.8 mmol) over a period of 15 min. After additional stirring for 15 min, the reaction mixture was allowed to warm to 0 °C and stirred for 30 min, and then cooled to −78 °C, at which time a solution of **9** (8.01 g, 60.8 mmol) in dry THF (20 mL) was added dropwise over a period of 20 min. The reaction mixture was stirred for 30 min, the cooling bath was removed, and then the mixture was allowed to warm to room temperature over a period of 1 h and further stirred for 12 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution (20 mL), and the solvent was removed in vacuo and then diluted with ether (300 mL) and water (200 mL). The organic layer was separated, and the aqueous layer was extracted with ether (200 mL × 2). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford a purple oil, which was purified by column chromatography on silica gel (elution with hexane/EtOAc, 3:1) to give 8.83 g (81%) of *Z* isomer **10a** as a colorless oil and 0.98 g (9%) of *E* isomer **10b** as a colorless oil.

10a: TLC R_f 0.41 (hexane/AcOEt, 3:1); $[\alpha]^{25}_D$ +30.35° (c 2.5 in $CHCl_3$); IR (NaCl, neat) 3395 (OH), 3039, 2901, 1668 (C=O), 1445, 1377, 1084 cm^{-1}; ^1H NMR δ 7.40–7.10 (m, 5 H, aromatic), 5.55–5.32 (m, 1 H, H-8), 5.38 (dd, $J_{7,8}$ = 10.9, $J_{5,7}$ = 7.4 Hz, 1 H, H-7), 4.56 (td, $J_{5,6}$ = $J_{4,5}$ = $J_{4',5}$ = 7.5 Hz, H-5), 4.35–4.20 (m, 1 H, H-3), 4.20–4.06 (m, 1 H, H-2), 3.50 (s, 3 H, CO_2CH_3), 3.15–2.90 (m, 2 H, H-6), 2.33–2.00 (m, 3 H, H-4, H-9), 1.70–1.13 (m, 1 H, H-4′), 1.54–1.15 (m, 10 H, H-10–H-14), 0.88 (t, $J_{14,15}$ = 6.6 Hz, 3 H, H-15); ^{13}C NMR δ 156.06, 139.23, 131.78, 130.58, 129.45, 128.06, 125.88, 70.73, 65.71, 62.84, 53.19, 51.99, 38.67, 35.47, 31.71, 29.52, 29.21, 29.09, 27.16, 22.53, 13.98; MS m/z (rel intensity) 360 (M^+ + 1, 0.3), 359 (M^+, 2.0), 269 (24.2), 268 (100). Anal. Calcd for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.69; H, 9.11; N, 3.92.

10b: TLC R_f 0.33 (hexane/AcOEt, 3:1); $[\alpha]^{25}_D$ −19.60° (c 2.5 in $CHCl_3$); IR (NaCl, neat) 3399 (OH), 3038, 2901, 1670 (C=O), 1445, 1378, 1081 cm^{-1}; ^1H NMR δ 7.43–7.10 (m, 5 H, aromatic), 5.63 (td, $J_{7,8}$ = 15.4, $J_{8,9}$ = 6.4 Hz, 1 H, H-8), 5.51 (dd, $J_{7,8}$ = 15.4, $J_{5,7}$ = 6.0 Hz, 1 H, H-7), 4.40–4.26 (m, 1 H, H-5), 4.26–4.14 (m, 1 H, H-3), 4.14–4.00 (m, 1 H, H-2), 3.58 (s, 3 H, CO_2CH_3), 3.27–3.02 (m, 1 H, H-6), 2.30 (dd, $J_{6,6'}$ = 13.1, $J_{2,6'}$ = 8.7 Hz, 1 H, H-6′), 2.34 (br s, 1 H, OH), 2.27–2.01 (m, 1 H, H-4), 2.01–1.98 (m, 2 H, H-9), 1.90–1.77 (m, 1 H, H-4′), 1.50–1.13 (m, 10 H, H-10–H-14), 0.88 (t, $J_{14,15}$ = 6.7 Hz, 3 H, H-15); ^{13}C NMR δ 156.26, 139.25, 131.64, 131.43, 129.47, 128.12, 125.95, 71.36, 63.84, 58.29, 52.08, 38.55, 35.12, 31.97, 31.74, 29.09, 29.05, 28.99, 22.56, 14.01; MS m/z (rel intensity) 360 (M^+ + 1, 0.6), 359 (M^+, 2.0), 269 (20.2), 268 (100), 88 (15.1). Anal. Calcd for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.38; H, 9.20; N, 3.84.

(2*S*,3*S*,5*R*)-2-(Phenylmethyl)-1-carbomethoxy-5-nonyl-3-pyrrolidinol (11). A mixture of *Z* isomer **10a** (8.21 g, 22.9 mmol) and 5% palladium on charcoal (300 mg) in ethanol (150 mL) was stirred in 1 atm of hydrogen for 24 h. The reaction mixture was filtered through a pad of Celite, and the solvent was removed in vacuo to afford a colorless oil, which was purified by flash column chromatography on silica gel (elution with hexane/EtOAc, 3:1) to give 8.25 g (100%) of **11** as a colorless oil: TLC R_f 0.33 (hexane/AcOEt, 3:1); $[\alpha]^{25}_D$ −73.36° (c 2.5 in $CHCl_3$); IR (NaCl, neat) 3395 (OH), 3040, 2899, 1661 (C=O), 1380, 1078 cm^{-1}; ^1H NMR δ 7.38–7.08 (m, 5 H, aromatic), 4.32–4.19 (m, 1 H, H-3), 4.19–4.04 (m, 1 H, H-2), 3.79–3.62 (m, 1 H, H-5), 3.62–3.25 (br s, 3 H, CO_2CH_3), 3.10–2.60 (m, 2 H, H-6), 2.23 (br s, 1 H, OH), 2.20–1.92 (m, 1 H, H-4), 1.79–1.60 (m, 1 H, H-4′), 1.50–1.10 (m, 1 H, H-7–H-14), 0.89 (t, $J_{14,15}$ = 6.2 Hz, 3 H, H-15); ^{13}C NMR δ 156.08, 139.37, 129.35, 127.99, 125.81, 70.81, 62.57, 56.48, 51.86, 37.21, 36.27, 35.75, 31.77, 29.50, 29.45, 29.19, 26.22, 22.55, 13.98; MS m/z (rel intensity) 362 (M^+ + 1, 0.4), 361 (M^+, 0.9), 270 (100), 144 (15.3). Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.09; H, 9.76; N, 3.87. Found: C, 73.11; H, 9.81; N, 3.79. The reaction with *E* isomer **10b** was carried out as described above to afford **11** quantitatively.

(2*S*,3*S*,5*R*)-1-Methyl-5-nonyl-2-(phenylmethyl)-3-pyrrolidinol (12). To a stirred solution of lithium aluminum

hydride (1.01 g, 26.6 mmol) in dry THF (100 mL) was added dropwise a solution of 11 (8.00 g, 22.2 mmol) in dry THF (20 mL) over a period of 10 min. The reaction mixture was refluxed for 2 h, cooled to 0 °C, and then quenched by addition of saturated aqueous NH_4Cl solution (1 mL). The resulting mixture was diluted with ether (300 mL), dried (Na_2SO_4), and concentrated in vacuo to afford a colorless oil, which was purified by flash column chromatography on silica gel (elution with CH_2Cl_2/MeOH, 9:1) to give 7.02 g (100%) of **12** as a colorless waxy solid which was identical with natural one[1,2] in every aspect except optical rotation. The waxy solid slowly changed into a yellow oil on prolonged standing at room temperature. An analytical sample was obtained from silica gel preparative thick-layer chromatography (hexane/ether, 1:4) as a white solid: TLC R_f 0.37 (CH_2Cl_2/MeOH, 9:1); mp 25.5–26.5 °C; $[\alpha]^{25}_D$ +31.08° (*c* 1.0 in $CHCl_3$); IR (NaCl, neat) 3374 (OH), 3040, 2899, 1448, 1147, 695 cm^{-1}; ^1H NMR δ 7.37–7.13 (m, 5 H, aromatic), 3.82 (m, 1 H, H-3), 2.92 (dd, $J_{6,6'}$ = 13.2, $J_{6,2}$ = 10.2 Hz, 1 H, H-6), 2.83 (dd, $J_{6,6'}$ = 13.2, $J_{6',2}$ = 4.5 Hz, 1 H, H-6'), 2.48 (br s, 1 H, OH), 2.33 (s, 3 H, NCH_3), 2.26 (ddd, $J_{2,6}$ = 10.2, $J_{2,6'}$ = 4.5, $J_{2,3}$ = 4.0 Hz, 1 H, H-2), 2.18 (m, 1 H, H-4), 2.10 (m, 1 H, H-5), 1.72 (m, 1 H, H-7), 1.50–1.12 (m, 16 H, H-4', H-7', H-8–H-14), 0.88 (t, $J_{14,15}$ = 6.3 Hz, 3 H, H-15); MS *m/z* (rel intensity) 318 (M^+ + 1, 0.3), 317 (M^+, 0.6), 316 (M^+ - 1, 1.5), 227 (21.0), 226 (100); HRMS calcd for $C_{21}H_{35}NO$ *m/e* 317.2719, found 317.2699. Anal. Calcd for $C_{21}H_{35}NO$: C, 79.44; H, 11.11; N, 4.41. Found: C, 79.43; H, 11.28; N, 4.39.

The ^{13}C NMR ($CDCl_3$), ^{13}C NMR (CD_3COOD), and ^1H NMR (CD_3COOD) spectral data are identical with those in the literature.[1]

Acknowledgment. We are pleased to acknowledge the Ministry of Science & Technology for financial support of this work. We thank Dr. Sueg-Geun Lee for his help in carrying out 2D and DEPT NMR experiments, and we are grateful to Dr. Vincent Crist for proofreading this paper.

Registry No. **1**, 2457-93-4; **2**, 131013-17-7; **3**, 131013-18-8; **4a**, 131013-19-9; **4b**, 131013-20-2; **5a**, 131013-21-3; **5b**, 131013-22-4; **6a**, 131013-23-5; **6b**, 131013-24-6; **7a**, 131013-25-7; **7b**, 131100-31-7; **8a**, 131013-26-8; **9**, 131013-27-9; **10a**, 131013-28-0; **10b**, 131013-29-1; **11**, 131013-30-4; **12**, 125356-66-3; *n*-$C_8H_{17}P^+Ph_3I^-$, 71344-40-6.

Supplementary Material Available: ^1H NMR spectra of all new compounds including NOE, DEPT, and decoupling experiments (36 pages). Ordering information is given on any current masthead page.

Highly Stereoselective Total Syntheses of Octoses and Derivatives[1a]

Suruliappa Jeganathan[1b] and Pierre Vogel*

Section de chimie de l'Université, 2, rue de la Barre, CH 1005 Lausanne, Switzerland

Received May 30, 1990

Mukaiyama cross aldolizations of (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**10**) with (1*R*,4*S*,5*R*,6*R*)-5-*exo*,6-*exo*-(isopropylidenedioxy)-7-oxabicyclo[2.2.1]heptan-2-one ((+)-**8**) and to its enantiomer ((−)-**8**) were highly diastereoselective and led to the corresponding u,u,l or SYNCAT ((+)-**11**) and u,u,u or ANCAT ((−)-**21**) aldols, respectively. The results were interpreted in terms of extended open transition state models with (ul,lk) and (ul,ul) topicities, respectively, which minimize steric repulsions. Aldols (+)-**11** and (−)-**21** were converted into (*tert*-butyl)dimethylsilyl 6-*O*-acetyl-2,3:7,8-di-*O*-isopropylidene-D-*glycero*-L-*talo*-α-octofuranosid-5-ulose ((−)-**18**) and its D-*talo* diastereomer ((+)-**28**), respectively. Reduction of (−)-**18** with $LiEt_3BH$ in THF gave, after deprotection, the known D-*threo*-L-*talo*-octose ((−)-**4**). Reduction of (−)-**18** with $(i\text{-Bu})_2AlH$/THF gave, after deprotection, the unknown D-*threo*-D-*allo*-octose ((+)-**5**) with high stereoselectivity. Similarly, the unknown D-*erythro*-D-*talo*-octose ((+)-**6**) and D-*erythro*-L-*allo*-octose ((−)-**7**) were derived from (+)-**28** through reduction with $LiB(s\text{-Bu})_3H$ and $(i\text{-Bu})_2AlH$, respectively.

Higher carbon sugars (monosaccharides with eight or more consecutive carbon atoms) have stirred a great interest in the recent years.[2] A few octoses have been found in plants,[3] and an octitol has been observed recently in human eye lenses.[4] Lincosamine, an amine octose, is a component of the antibiotics lincomycins[5] and ezoaminuroic acid is the octose nucleoside portion of ezomycins that are antifungal antibiotics.[6] The octosyl acids are eight-carbon bicyclic sugars which are N-glycosidically linked to pyrimidine bases;[7] some derivatives are powerful phosphodiesterase inhibitors.[8] Another octose, KDO (= 3-deoxy-D-*manno*-2-octulosonic acid), is an important connecting link in the membrane structures of Gram-negative bacteria.[9,10] Among the nine-carbon carbohy-

(1) (a) For a preliminary communication, see: Jeganathan, S.; Vogel, P. *J. Chem. Soc., Chem. Commun.* **1989**, 993. Enantiomerically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives ("naked sugars") as synthetic intermediates, Part XII. For Part XI, see: Le Drian, C.; Vionnet, J. P.; Vogel, P. *Helv. Chim. Acta* **1990**, *73*, 161. (b) Present address: Research Department, Ciba-Geigy SA, CH 1701 Fribourg, Switzerland.

(2) (a) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15. (b) Kishi, Y. *Pure Appl. Chem.* **1989**, *61*, 313. (c) Hanessian, S.; Sato, K.; Liak, T. J.; Danh, N.; Dixit, D.; Cheney, B. V. *J. Am. Chem. Soc.* **1984**, *106*, 6114. (d) Kominato, K.; Ogawa, S.; Suami, T. *Carbohydr. Res.* **1988**, *174*, 360. (e) Rosenbrook, W.; Lartey, P. A.; Riley, D. A. U.S. Patent; *Chem. Abstr.* **1987**, *106*, 50600y. (f) Secrist, J. A. III; Barnes, K. D.; Wu, S.-R. In *Trends in Synthetic Carbohydrate Chemistry*; ACS Symposium Series 386; Horton, D., Hawkins, L. D., McGarvey, G. J., Eds.; American Chemical Society: Washington, D.C., 1989; pp 93–106 and references cited therein.

(3) Charlson, A. J.; Richtmyer, N. K. *J. Am. Chem. Soc.* **1960**, *82*, 3428. Kull, U. *Naturw. Rundschau* **1963**, *16*, 483. Jones, J. K. N. Chim. Biochim. Lignine, Cellulose, Hemicelluloses, Actes Symp. Intern., Grenoble, France, 1964, 391; see *Chem. Abstr.* **1966**, *64*, 16291c.

(4) Barker, S. A.; Fish, F. P.; Tomana, M.; Garner, L. C.; Settine, R. L.; Prchal, J. *Biochem. Biophys. Res. Commun.* **1983**, *116*, 988; *Chem. Abstr.* **1984**, *100*, 20844a.

(5) Bycroft, B. W.; Higton, A. A.; Roberts, A. D. *Dictionary of Antibiotics and Related Substances*; Chapman and Hall: London, 1988; pp 443–444 and references cited therein; see also pp 206–207 (Celesticetin); p 263 (Desalicetin); p 479 (Mirincamycin);

(6) Sakata, K.; Sakurai, A.; Tamura, S. *Agric. Biol. Chem.* **1973**, *37*, 697. Sakata, K.; Sakurai, A.; Tamura, S. *Tetrahedron Lett.* **1974**, 4327. Hanessian, S.; Dixti, D. M.; Liak, T. J. *Pure Appl. Chem.* **1981**, *53*, 129. Sakanaka, O.; Ohmori, T.; Kozaki, S.; Suami, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1057. See also ref 5, pp 319–320 and references cited therein.

(7) Isono, K.; Crain, P. F.; McCloskey, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 943.

(8) Azuma, T.; Isono, K. *Chem. Pharm. Bull.* **1977**, *25*, 3347. Bloch, A. *Biochem. Biophys. Res. Commun.* **1975**, *64*, 210.

(9) Unger, F. M. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 323. See also: Norbeck, D. W.; Rosenbrook, W.; Kramer, J. B.; Grampovnik, D. J.; Nartey, P. A. *J. Med. Chem.* **1989**, *32*, 625. Claesson, A. *J. Org. Chem.* **1987**, *523*, 4414.

0022-3263/91/1956-1133$02.50/0