Selective Reactions using *N*-(*tert*-Butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole: Concise Asymmetric Syntheses of (+)-1-Deoxy-8-*epi*-castanospermine and its Enantiomer

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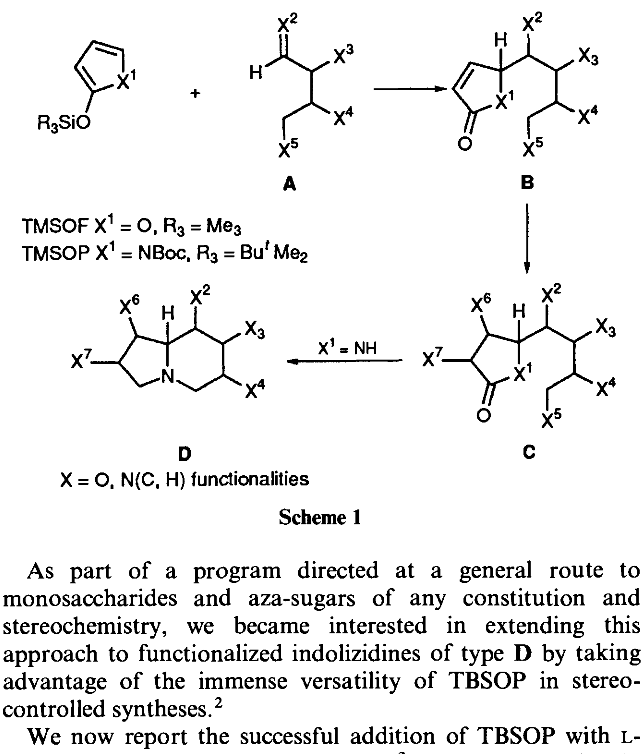
Advantage being taken of the versatility of the siloxydiene TBSOP in asymmetric synthesis, (6*S*,7*R*,8*S*,8a*R*)-6,7,8-trihydroxyindolizidine **11** has been assembled from the L-threose derivative **1** in six or eight steps in 22–30% overall yield. Pivotal to the success of this total synthesis venture is the ready availability of unsaturated lactam **2** with complete stereocontrol. As a corollary, the synthesis of the known indolizidine enantiomer *ent*-**11** confirms the feasibility of the procedure. The structure of compound **5** has been determined by X-ray crystallography.

Diastereoselective addition reactions of the heterocyclic siloxydienes 2-(trimethylsiloxy)furan (TMSOF)[1] and *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole (TBSOP)[2] with enantiopure aldehydo or imino precursors have been shown to be a key step in a flexible method for the construction of complex molecules bearing multiple contiguous chiral centres. In numerous ways, shown in Scheme 1, through various combinations of oxygen and nitrogen substitutions and accurate stereocontrolled manipulations, a wide variety of molecular assemblies can be constructed endowed with all-oxygen, N,O-mixed and all-nitrogen functionalities.



Scheme 1

As part of a program directed at a general route to monosaccharides and aza-sugars of any constitution and stereochemistry, we became interested in extending this approach to functionalized indolizidines of type **D** by taking advantage of the immense versatility of TBSOP in stereocontrolled syntheses.[2]

We now report the successful addition of TBSOP with L- and D-threose derivatives **1** and *ent*-**1**[3] and its application in concise asymmetric syntheses of (6*S*,7*R*,8*S*,8a*R*)-6,7,8-trihydroxyindolizidine [(+)-1-deoxy-8-*epi*-castanospermine] **11** and its enantiomer *ent*-**11**. Because of the potential value of monocyclic and bicyclic aza-sugar compounds and alkaloids as glycoprocessing inhibitors and therapeutic agents,[4] the efficient preparation of this important family of inhibitors has been of extreme interest to organic and medicinal chemists.[5,6]

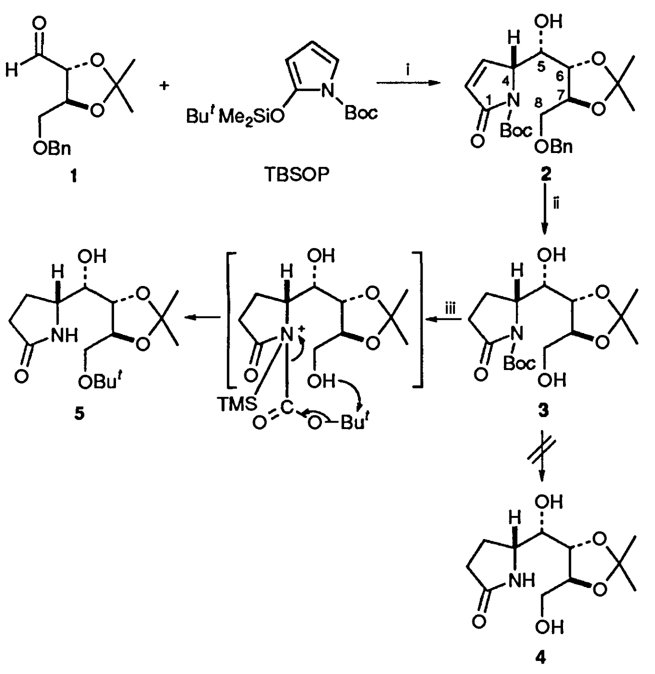
Results and Discussion

Synthesis.—The required protected *aldehydo*-threoses **1** and *ent*-**1** were prepared from the corresponding tartrate esters according to the literature,[3] while large-scale preparation of TBSOP was achieved from pyrrole as previously reported by us.[2] Optimally, compound **1** was treated with TBSOP in diethyl ether at −80 °C in the presence of 1.2 mol equiv. of $SnCl_4$ (Scheme 2). The addition occurred regio- and stereo-selectively at the C-5 carbon of TBSOP to form crystalline α,β-unsaturated lactam **2** exclusively, in 80% isolated yield. The determination of the relative stereochemistry of the newly created stereocentres C(4) and C(5) was based on a single-crystal X-ray analysis of a more advanced intermediate, namely lactam **5** (*vide infra*), while the absolute 4*R*,5*S* configuration was inferred from the chirality of the employed threose **1**.

Our first approach to the indolizidine **11** envisaged double-bond saturation in lactam **2** to form compound **3**, followed by selective removal of the N-Boc protecting group to furnish compound **4** and subsequent reduction of the lactam and ring closure to create the indolizidine skeleton. Thus, catalytic hydrogenation of lactam **2** using Pd on charcoal in NaOAc-buffered tetrahydrofuran (THF) at ambient temperature and pressure yielded saturated lactam **3** (95%); however, the subsequent deprotection reaction using trimethylsilyl trifluromethanesulfonate (TMSOTf) failed to produce target compound **4**. When the reaction was performed in CH_2Cl_2 at 0 °C, a single crystalline compound could be isolated in 94% yield. This product was shown spectroscopically to contain the expected amidic NH function (singlet at δ 6.02) along with a singlet integrating to 9 H at δ 1.23, presumably due to the presence of an oxygen-linked *tert*-butyl substituent. The structure **5** was assigned to this lactam, based on a single-crystal X-ray analysis (*vide infra*). This scheme was not further pursued.

Our second attempt utilized lactam **6** prepared *via* selective N-Boc deprotection of unsaturated lactam **2** as shown in Scheme 3.

Treatment of compound **2** with TMSOTf in CH_2Cl_2 in the presence of thiophenol cleanly afforded lactam **6** (75%), which



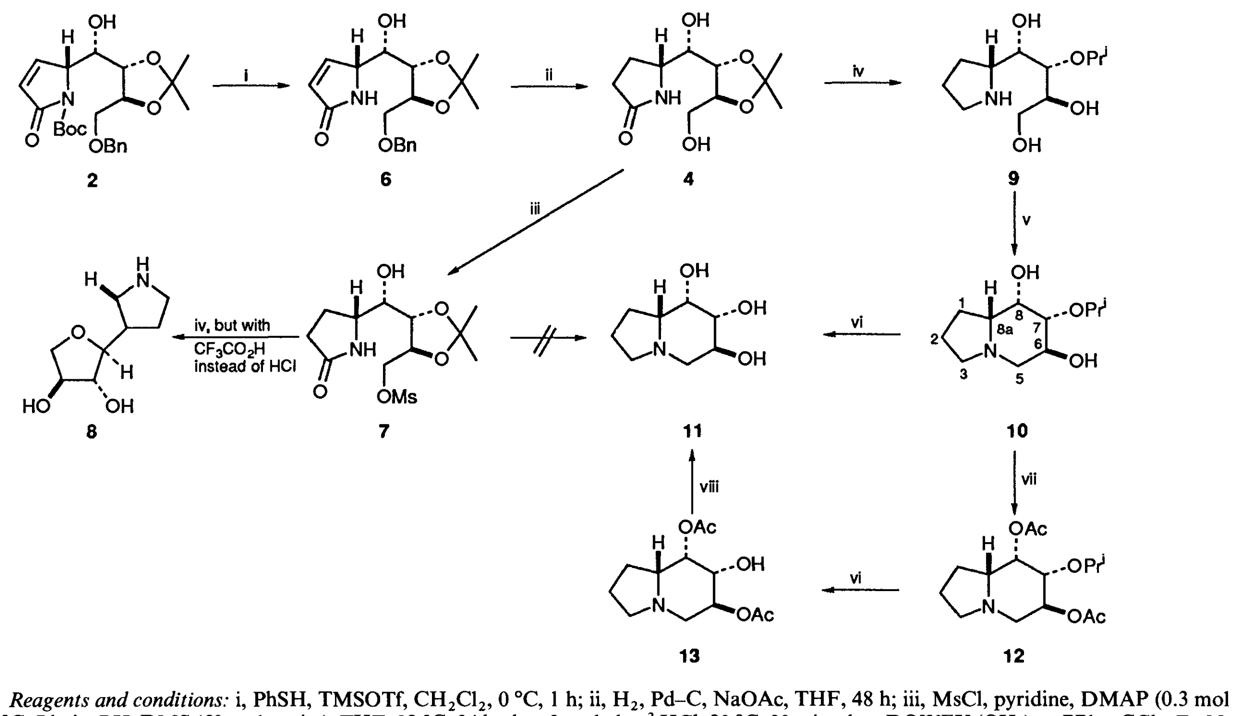
Scheme 2 *Reagents and conditions:* i, $SnCl_4$, Et_2O, −80 °C, 5 h; ii, H_2, Pd–C, NaOAc, THF, 22 °C, 48 h; iii, TMSOTf, CH_2Cl_2, 0 °C, 6 h

was hydrogenated and deprotected to compound **4** (Pd on charcoal, NaOAc, THF) in 95% isolated yield. Having the desired alcohol **4** in hand, we next examined its conversion into the indolizidine **11**. We first pursued a conventional ring-closure methodology based on conversion of compound **4** into mesate **7** followed by reduction of the lactam and N–C(8) ring closure. Selective monomesylation was thus successfully conducted by using 1.1 mol equiv. of MsCl in pyridine in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) to furnish mesate **7** in 74% yield. Unfortunately, exposure of compound **7** to BH_3·dimethyl sulfide (DMS) complex in THF, a reagent known to reduce selectively the lactam carbonyl function in similar structures,[6t] met with complete failure, the unwanted *C*-nucleoside-like furanose **8** being solely generated in 45% yield with no trace of the expected indolizidine **11**. One possible explanation for this competitive and preferential O(5)–C(8) annulation might be steric factors at the C(6) and C(7) carbon atoms of the dioxolane which prevent nitrogen from attacking C(8) to form a six-membered piperidine endowed with a strained *trans*-disposed acetonide ring.

Having thus abandoned this path, we envisaged a third plan involving prior carbonyl reduction in lactam **4**, removal of the acetonide, and final NH–C(8) annulation. This route was shown to be satisfactory although some conversions were not as anticipated. As shown in Scheme 3, lactam **4** was directly exposed to an excess of BH_3·DMS in THF at room temperature and the crude amine–borane adduct thus formed was subjected to acidic treatment with 2 mol dm^{-3} HCl at room temperature. Surprisingly enough, this treatment afforded isopropyl ether **9** (71%), likely to have arisen from reduction of the lactam with concomitant regioselective opening of the acetonide at the O(7)–$C(Me)_2$ linkage and over-reduction.

Nonetheless, amino alcohol **9** was ready for the final and crucial cyclization step. This was achieved by subjecting compound **9** to PPh_3–CCl_4–Et_3N in pyridine at room temperature, as suggested by Vogel.[6u] There was obtained, after ion-exchange resin purification, the 7-isopropoxyindolizidine **10** in 79% isolated yield. This compound was recognized as such mainly through ^{13}C NMR analysis, showing the expected eleven carbon signals in the appropriate positions for two methyls, four methylenes, and five methines. Cleavage of the oxygen–carbon bond in the isopropyl ether **10** was finally accomplished, as anticipated, in a simple manner by using BBr_3 in CH_2Cl_2. This treatment afforded the indolizidine **11** in 67% yield, which showed ^1H and ^{13}C NMR characteristics identical with those reported by St-Denis and Chan for its enantiomer *ent*-**11**.[6q]

The conversion of isopropyl ether **10** into triol **11** was also possible through a slightly longer but cleaner reaction sequence. Conventional acetylation of compound **10** (Ac_2O, pyridine, DMAP) quantitatively afforded diacetate **12**, suitable for



Scheme 3 *Reagents and conditions:* i, PhSH, TMSOTf, CH_2Cl_2, 0 °C, 1 h; ii, H_2, Pd–C, NaOAc, THF, 48 h; iii, MsCl, pyridine, DMAP (0.3 mol equiv.), 22 °C, 7 h; iv, BH_3DMS (50 mol equiv.), THF, 22 °C, 24 h; then 2 mol. dm^{-3} HCl, 20 °C, 30 min; then DOWEX (OH^-); v, PPh_3, CCl_4, Et_3N, pyridine, 20 °C, 20 h; then DOWEX (H^+) 2 mol dm^{-3} NH_4OH; vi, BBr_3, CH_2Cl_2, 20 °C, 20 h; vii, Ac_2O, pyridine, DMAP (0.3 mol equiv.), 22 °C, 5 h; viii, NaOMe (0.1 mol equiv.), MeOH, 20 °C, 5 h

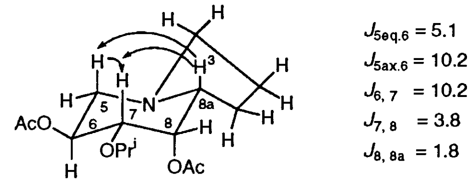


Fig. 1 Compound **12** in its ${}^{8a}C_6$ configuration. Diagnostic coupling constants (Hz) and NOE interactions (arrows).

accurate structural and conformational ^{1}H NMR analyses. The study allowed complete assignments of all the proton resonances as indicated in Fig. 1, and was consistent with the piperidine ring adopting a ${}^{8a}C_6$ conformation in solution with no significant distortion to accommodate the *trans*-fused five-membered heterocycle.

Selective removal of the 7-*O*-isopropyl group in compound **12** was smoothly accomplished by acidic treatment (BBr_3) to furnish diacetate **13** (95%), which was converted into triol **11** by catalytic NaOMe in methanol in quantitative yield.

(−)-(6*R*,7*S*,8*R*,8a*S*)-6,7,8-Trihydroxyindolizidine *ent*-**11** has been recently prepared by St-Denis and Chan, who claim $[\alpha]_D^{20}$ − 17.3 × 10^{-1} deg cm^2 g^{-1} in methanol.[6q] This compound offered us the opportunity to test the feasibility of our synthetic procedure, as applied to a known target molecule. Indeed, starting from *ent*-**1** and paralleling exactly the chemistry exploited for triol **11**, *ent*-**11** was prepared in 24% overall yield, *via* intermediates *ent*-**2**, *ent*-**6**, *ent*-**4** and *ent*-**10**. The measured optical rotation in methanol was − 19.1 at 22 °C, in accord with the reported value. Obviously, the spectroscopic properties of compound **11** and its enantiomer *ent*-**11** were indistinguishable and matched well those reported for *ent*-**11**.[6q]

Overall, concise asymmetric syntheses of the indolizidine **11** and its enantiomer *ent*-**11** from tartaric acid-derived L- and D-threoses **1** and *ent*-**1** were established, involving only six (or eight) steps, in 22% and 26% yield, respectively.

X-Ray Study.—An X-ray analysis of compound **5** allowed its unambiguous structural determination establishing, as a consequence, the chirality of the related precursor **2**, the several intermediates, and the indolizidine **11**. The absolute configuration of lactam **5** was determined as 4*R*,5*S*,6*S*,7*S* based on the chirality of its precursor (2*R*,3*S*)-4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose **1** as in Scheme 2. An ORTEP view of the molecule in its correct absolute configuration is shown in Fig. 2.

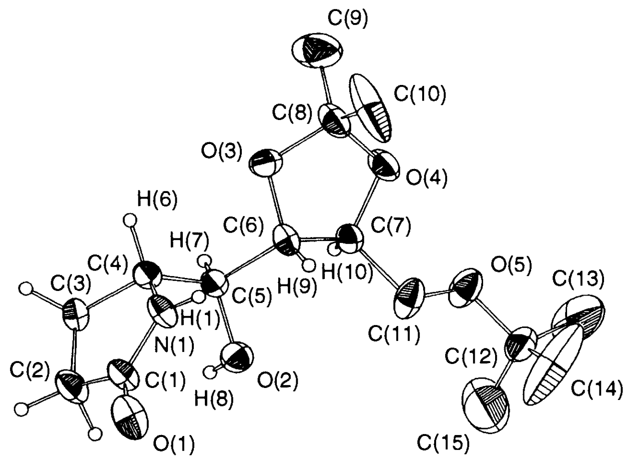


Fig. 2 ORTEP drawing of compound **5** showing the atomic-numbering scheme. Thermal ellipsoids enclose 30% probability.

The fractional atomic co-ordinates obtained from the crystallographic analysis and the subsequently derived interatomic distances and bond angles have been deposited as a supplementary publication.* In the solid-state structure the least-squares planes of the two rings form an angle of 88.7(2)°. The lactam ring assumes an envelope conformation with q_2 = 0.204(7) Å, φ_2 = −68(2)°,[7a] while in the dioxolane ring is present a quasi-twist conformation with the diad axis passing through the O(4) oxygen atom [q_2 = 0.298(5) Å, φ_2 = 11(1)°], maybe the most probable for rings with adjacent carbon atoms which are substituted.[7b] Both rings present significant displacements from their least-squares planes: a maximum deviation of 0.13 Å for C(2) in the lactam ring and of 0.19 Å for C(6) in the dioxolane. The angle C(1)–N(1)–C(4), of 115.5(5)°, is similar to the values found in the literature for pyrrolidine rings with an N–H bond.[7c] A certain charge delocalization can be observed in the C(4)N(1)C(1)O(1) moiety of the lactam ring,

* *Supplementary publication* (see Instructions for Authors, in the January issue). Tables of atomic co-ordinates, bond lengths and bond angles have been deposited at the Cambridge Crystallographic Data Centre.

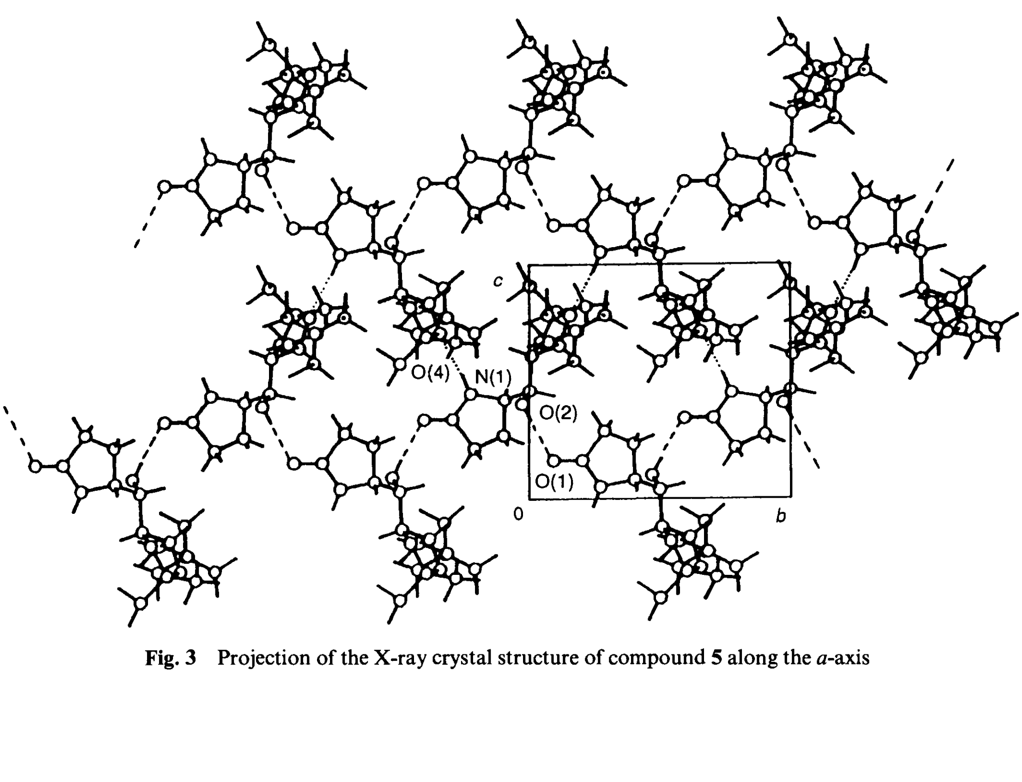


Fig. 3 Projection of the X-ray crystal structure of compound **5** along the *a*-axis

evidenced by both bond lengths and the torsion angle of 176.9(6)°.[7c–e]

The orientation of the OH group with respect to the pyrrolidine and dioxolane rings is shown by the following torsion angles: N(1)C(4)C(5)O(2) = 54.5(6)°, C(3)C(4)C(5)-O(2) = −61.1(6)°; O(3)C(6)C(5)O(2) = 177(5)°, C(7)C(6)C(5)-O(2) = 63.3(6)°. The distance H(6) ··· H(7) is 2.27(8) Å and the torsion angle H(6)C(4)C(5)H(7) = −50(5)°. corresponds to a synclinal conformation.

The distance H(7) ··· H(8) = 1.94(8) Å is extremely short, probably as a consequence of the excessive closeness of the H(8) hydrogen to the O(2) oxygen atom, and the torsion angle of −38(7)° corresponds to an intermediate conformation between synperiplanar and synclinal. The C–O distances in the dioxolane ring are similar to the values found in the literature.[1b,2b,7b] The orientation of the *tert*-butyl ether group is evidenced by the following torsion angles: O(4)C(7)C(11)O(5) = −64.9(7), C(6)C(7)C(11)O(5) = 178.7(5), C(7)C(11)O(5)C(12) = −172.8(6)°.

The packing is determined by a strong hydrogen bond O(2)–H(8) ··· O(1)(I) = 2.716(7) Å (I = 1 − *x*, 1/2 + *y*, 1/2 − *z*) between molecules related by a diad screw-axis. The helicoidal chains so formed stretching along the *y*-axis are joined among themselves by a weaker hydrogen bond N(1)–H(1) ··· O(4)(II) = 3.277(7) Å (II = 1 − *x*, *y* − 1/2, 3/2 − *z*) (Fig. 3).

Experimental

M.p.s. were determined on a Büchi melting-point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were performed with a Varian XL 300 spectrometer. *J* Values are given in Hz and chemical-shift values in ppm referred to tetramethylsilane (0.0 ppm), DOH (4.80 ppm), CD_3OD (3.35 and 49.0 ppm) and 1,4-dioxane (67.4 ppm). *N-tert*-Butoxycarbonyl-2-(*tert*-butyldimethylsiloxy)pyrrole (TBSOP) was prepared from pyrrole according to a recently described protocol.[2] 4-*O*-Benzyl-2,3-*O*-isopropylidene-L- and D-threose **1** and *ent*-**1** were prepared from the corresponding diethyl tartrates according to literature.[3] $[\alpha]_D$ Values were measured on a Perkin-Elmer 241 polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed by the Microanalytical Laboratory of the University of Sassari.

*4-Amino-8-O-benzyl-N-(*tert*-butoxycarbonyl)-2,3,4-trideoxy-6,7-O-isopropylidene-*L-galacto-*oct-2-enonic Acid* 1,4-*Lactam* **2**.—TBSOP (3.35 g, 11.27 mmol) and L-threose derivative **1** (2.32 g, 11.27 mmol) were dissolved in anhydrous Et_2O (50 cm^3) under argon and the mixture was cooled to −80 °C. A 1 mol dm^{-3} solution of $SnCl_4$ in CH_2Cl_2 (16.90 mmol, 16.90 cm^3) was added at room temperature, *via* a cannula, during 10 min and the solution was stirred for 5 h. The reaction was quenched at this temperature by addition of an excess of saturated aq. $NaHCO_3$. Then the mixture was warmed to room temperature and extracted with Et_2O (3 × 15 cm^3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to furnish the crude lactam, which was purified by flash chromatography over silica gel and eluted with 65:35 EtOAc–hexane to afford lactam **2** (3.42 g, 80%) as a solid, m.p. 96–98 °C; $[\alpha]_D^{20}$ +134.66 (*c* 0.88 in $CHCl_3$) (Found: C, 63.65; H, 7.1; N, 3.15. $C_{23}H_{31}NO_7$ requires C, 63.73; H, 7.21; N, 3.23%); δ_H(300 MHz; $CDCl_3$) 1.28 (3 H, s, Me), 1.30 (3 H, s, Me), 1.53 (9 H, s, Bu^t), 3.52 (1 H, dd, *J* 8.8 and 7.5, 6-H), 3.53 (1 H, dd, *J* 9.3 and 6.9, 8-H^b), 3.73 (1 H, dd, *J* 9.3 and 4.5, 8-H^a), 4.07 (1 H, dd, *J* 6.9 and 4.5, 7-H), 4.15 (1 H, ddd, *J* 9.0, 5.1 and 3.3, 5-H), 4.30 (1 H, d, *J* 3.0, OH), 4.58 (2 H, s, C*H*$_2$Ph), 4.76 (1 H, dt, *J* 4.8 and 1.8, 4-H), 6.12 (1 H, dd, *J* 6.0 and 1.8, 2-H) and 7.31 (6 H, m, *Ph*, 3-H); δ_C(75.4 MHz; $CDCl_3$) 26.52, 28.05, 65.65, 70.54, 72.38, 73.83, 78.93, 79.56, 82.99, 109.86, 127.65, 128.09, 136.78, 150.31 and 169.06.

*4-Amino-N-(*tert*-butoxycarbonyl)-2,3,4-trideoxy-6,7-O-isopropylidene-*L-galacto-*octonic Acid* 1,4-*Lactam* **3**.—To a solution of unsaturated lactam **2** (1 g, 2.3 mmol) in THF (40 cm^3) were added Pd–C (100 mg) and AcONa (50 mg). The mixture was stirred for 48 h at room temperature, then was filtered and the resulting solution was evaporated under reduced pressure. The crude product was purified by flash chromatography over silica gel and eluted with EtOAc to afford compound **3** (755 mg, 95%) as an oil; $[\alpha]_D^{20}$ +45.83 (*c* 0.24 in $CHCl_3$) (Found: C, 55.4; H, 7.8; N, 4.0. $C_{16}H_{27}NO_7$ requires C, 55.62; H, 7.88; N, 4.06%); δ_H(300 MHz; $CDCl_3$) 1.39 (3 H, s, Me), 1.41 (3 H, s, Me), 1.52 (9 H, s, Bu^t), 2.28–2.07 (2 H, m, 3-H$_2$), 2.37 (1 H, ddd, *J* 17.7, 9.0 and 1.5, 2-H^b), 2.66 (1 H, ddd, *J* 16.2, 12.0 and 9.0, 2-H^a), 3.81–3.70 (3 H, m, 5- and 6-H, 8-H^b), 3.86 (1 H, dd, *J* 11.7 and 3.9, 8-H^a), 4.08 (1 H, td, *J* 6.3 and 3.9, 7-H) and 4.37 (1 H, ddd, *J* 8.1, 5.7 and 1.8, 4-H); δ_C(75.4 MHz; $CDCl_3$) 20.87, 26.68. 26.82, 27.97, 31.81, 61.20, 63.07, 74.29, 79.34, 80.93, 83.62, 109.54, 151.76 and 174.90.

*4-Amino-8-O-(*tert*-butyl)-2,3,4-trideoxy-6,7-O-isopropylidene-*L-galacto-*octonic Acid* 1,4-*Lactam* **5**.—To a solution of compound **3** (500 mg, 1.45 mmol) in CH_2Cl_2 (30 cm^3) under argon at O °C was added TMSOTf (644.5 mg, 2.9 mmol). The mixture was stirred at this temperature for 6 h, then saturated aq. $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc and the organic phase, dried over $MgSO_4$, was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel and eluted with 8:2 EtOAc–MeOH to afford compound **5** (411 mg, 94%) as crystals, m.p. 170–171 °C; $[\alpha]_D^{24}$ −11.1 (*c* 0.20 in $CHCl_3$) (Found: C, 59.7; H, 9.1; N, 4.6. $C_{15}H_{27}NO_5$ requires C, 59.76; H, 9.03; N, 4.65%); δ_H(300 MHz; $CDCl_3$) 1.23 (9 H, s, Bu^t), 1.37 (3 H, s, Me), 1.38 (3 H, s. Me), 2.10 (1 H, m, 2-H^b), 2.26 (2 H, m, 3-H$_2$), 2.44 (1 H, m, 2-H^a), 3.34 (1 H, t, *J* 8.7, 8-H^b), 3.46 (1 H, m, 5-H), 3.63 (1 H, t, *J* 7.8, 6-H), 3.77 (1 H, dd, *J* 8.4 and 3.9, 8-H^a), 3.84 (1 H, m, 4-H), 3.49 (1 H, dq, *J* 9.0, 7.5 and 3.9, 7-H), 4.21 (1 H, d, *J* 1.8, OH) and 6.02 (1 H, s, NH).

*4-Amino-8-O-benzyl-2,3,4-trideoxy-6,7-O-isopropylidene-*L-galacto-*oct-2-enonic Acid* 1,4-*Lactam* **6**.—To a solution of compound **2** (3.0 g, 6.92 mmol) in anhydrous CH_2Cl_2 (130 cm^3) were added, under argon, at 0 °C, PhSH (1.14 g, 10.38 mmol) and TMSOTf (2.307 g, 10.38 mmol). The mixture was stirred for 1 h at this temperature, then was quenched by addition of saturated aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc and the organic phase was evaporated under reduced pressure. The crude product was then purified by flash chromatography over silica gel and eluted with 95:5 EtOAc–MeOH to afford *title compound* **6** (1.73 g, 75%) as an oil; $[\alpha]_D^{25}$ +23.49 (*c* 3.1 in EtOAc) (Found: C, 64.8; H, 6.8; N, 4.35. $C_{18}H_{23}NO_5$ requires C, 64.85; H, 6.95; N, 4.20%); δ_H(300 MHz; $CDCl_3$) 1.36 (3 H, s, Me), 1.41 (3 H, s, Me), 3.48 (1 H, td, *J* 6.6 and 6.3, 5-H), 3.64 (1 H, dd, *J* 9.0 and 6.6, 8-H^b), 3.70 (1 H, dd, *J* 6.6 and 4.5, 6-H), 3.83 (1 H, t, *J* 9, 8-H^a), 4.18 (1 H, m, 7-H), 4.29 (1 H, d, *J* 6.6, 4-H), 4.58 (2 H, s, C*H*$_2$Ph), 4.77 (1 H, d, *J* 6.3, OH), 6.05 (1 H, d, *J* 5.7, 2-H), 7.17 (1 H, d, *J* 5.7, 3-H), 7.29 (5 H, m, *Ph*) and 7.90 (1 H, s, NH); δ_C(75.4 MHz; $CDCl_3$) 26.83, 26.89, 64.13, 70.87, 73.41, 73.84, 78.95, 79.41, 109.79, 127.26, 127.62, 128.22, 137.51 and 175.06.

*4-Amino-2,3,4-trideoxy-6,7-O-isopropylidene-*L-galacto-*octonic Acid* 1,4-*Lactam* **4**.—To a solution of compound **6** (1.8 g, 5.4 mmol) in THF (80 cm^3) were added Pd–C (200 mg) and NaOAc (100 mg). The mixture was stirred for 48 h under

H_2, then the solution was filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography over silica gel and eluted with 8:2 EtOAc–MeOH to afford *saturated lactam* **4** (1.26 g, 95%) as an oil; $[\alpha]_D^{21}$ −24.28 (*c* 0.7 in MeOH) (Found: C, 53.6; H, 7.8; N, 5.6. $C_{11}H_{19}NO_5$ requires C, 53.87; H, 7.81; N, 5.71%); δ_H(300 MHz; $CDCl_3$) 1.35 (3 H, s, Me), 1.37 (3 H, s, Me), 2.43–2.02 (4 H, m, 2- and 3-H_2), 3.42 (1 H, td, *J* 8.4 and 3.6, 5-H), 3.66 (3 H, m, 6-H, 8-H_2), 3.82 (1 H, m, 4-H), 3.96 (1 H, m, 7-H), 5.31 (2 H, br, OH) and 6.80 (1 H, s, NH); δ_C(75.4 MHz; $CDCl_3$) 23.41, 26.81, 30.54, 56.90, 62.57, 75.19, 78.17, 80.70, 109.23 and 180.25.

4-*Amino*-2,3,4-*trideoxy*-6,7-O-*isopropylidene*-8-O-*methylsulfonyl*-L-galacto-*octonic Acid* 1,4-*Lactam* **7**.—To a solution of compound **6** (500 mg, 2.04 mmol) in anhydrous CH_2Cl_2 (10 cm^3) under argon at room temperature were sequentially added pyridine (483 mg, 6.12 mmol), MsCl (257 mg, 2.24 mmol) and DMAP (25 mg, 0.20 mmol). The mixture was stirred for 7 h, then was quenched with water and evaporated under reduced pressure. The crude product was purified by flash chromatography over silica gel and eluted with 8:2 AcOEt–MeOH to afford the *mesate* **7** (488 mg, 74%) as an oil (Found: C, 44.3; H, 6.55; N, 4.65. $C_{12}H_{21}NO_7S$ requires C, 44.57; H, 6.55; N, 4.33%); δ_H(300 MHz; $CDCl_3$) 1.40 (3 H, s, Me), 1.42 (3 H, s, Me), 2.14–2.06 (1 H, m, 3-H^b), 2.40–2.20 (3 H, m, 2-H_2, 3-H^a), 3.09 (3 H, s, SMe), 3.47 (1 H, ddd, *J* 8.4, 8.0 and 5.0. 5-H), 3.81 (1 H, dd, *J* 8.4, 6-H), 3.87 (1 H, q, *J* 5.1, 4-H), 4.38–4.22 (2 H, m, 7-H, 8-H^b), 4.54 (1 H, dd, *J* 11.1 and 1.8, 8-H^a), 4.72 (1 H, d, *J* 7.9, OH) and 7.19 (1 H, s, NH).

(2R)-2-(α-L-threo-*Pentofuranosyl*)*pyrrolidine* **8**.—To a solution of lactam **7** (500 mg, 1.55 mmol) in anhydrous THF (20 cm^3), under argon at room temperature, was added a 10 mol dm^{-3} solution of BH_3•DMS (7.75 cm^3, 77.5 mmol). The mixture was stirred for 15 h, then quenched with MeOH and evaporated under reduced pressure. The crude product was treated with CF_3CO_2H–water 4:1 (12 cm^3), then was purified by passage through a DOWEX (OH^- form) column eluted with water, to afford compound **8** (120 mg, 45%) as an oil (Found: C, 55.4; H, 8.4; N, 7.85 $C_8H_{15}NO_3$ requires C, 55.47; H, 8.73; N, 8.09%); δ_H(300 MHz; D_2O) 1.82–1.32 (4 H, m, 2- and 3-H_2), 2.62 (2 H, m, 1-H_2), 3.08 (1 H, q, *J* 7.5, 4-H), 3.47 (1 H, dd, *J* 7.0 and 3.0, 5-H), 3.63 (1 H, ddd, *J* 10.2, 1.5 and 0.9, 8-H^b), 3.77 (1 H, dd, *J* 10.2 and 3.6, 8-H^a), 3.82 (1 H, ddd, *J* 3.0, 1.5 and 0.9 6-H) and 3.94 (1 H, dt, *J* 3.9 and 1.5, 7-H); δ_C(75.4 MHz; CD_3OD) 27.56, 29.08, 47.72, 61.01, 75.00, 78.63, 81.18 and 90.48.

1,2,3,4-*Tetradeoxy*-1,4-*imino*-6-O-*isopropyl*-L-galacto-*octitol* **9**.—To a solution of compound **4** (1.0 g, 4.01 mmol) in anhydrous THF (60 cm^3) under argon was added a 10 mol dm^{-3} solution of BH_3•DMS complex (28.6 cm^3, 285.6 mmol) at room temperature. The mixture was stirred at this temperature for 24 h, then MeOH was added and the solution was evaporated under reduced pressure. The crude product was purified by flash chromatography over silica gel and eluted with 9:1 EtOAc–MeOH to afford an oil (698 mg, 74%). To this material was added 2 mol dm^{-3} HCl (10 cm^3), then the solution was stirred for 30 min and evaporated under reduced pressure, and the crude product was purified by passage through a DOWEX (OH^- form) column to afford *compound* **9** (676 mg, 96%) as an oil; $[\alpha]_D^{19}$ +1.54 (*c* 1.3 in MeOH) (Found: C, 56.6; H, 9.9; N, 6.1 $C_{11}H_{23}NO_4$ requires C, 56.63; H, 9.94; N, 6.0%); δ_H(300 MHz; D_2O) 1.21 (6 H, t, CH*Me*$_2$), 1.63 (1 H, m, 3-H^b), 1.83 (2 H, m, 2-H_2), 1.92 (1 H, m, 3-H^a), 2.90 (1 H, m, 1-H^b), 3.04 (1 H, m, 1-H^a), 3.30 (1 H, m, 4-H), 3.52 (1 H, dd, *J* 5.4 and 2.7, 6-H), 3.66 (2 H, m, 8-H_2), 3.72 (1 H, t, *J* 5.4, 5-H) and 3.88 (2 H, m, 7-H, C*H*Me$_2$); δ_C(75.4 MHz; CD_3OD) 22.82, 23.20, 26.25, 29.53, 47.23, 61.03, 63.91, 73.08, 73.54, 74.73 and 78.01.

(6S,7R,8S,8aR)-6,8-*Dihydroxy*-7-*isopropyloxyindolizidine* **10**.—Under rigorously anhydrous conditions in a vessel shielded from light, to a solution of compound **9** (260 mg, 1.11 mmol) in pyridine (6 cm^3) under argon at room temperature were added PPh_3 (716 mg, 2.72 mmol), CCl_4 (139 mm^3, 1.36 mmol) and, after 3 h, Et_3N (379 mm^3, 2.72 mmol). The mixture was stirred overnight then was quenched with MeOH (5 cm^3) and evaporated under reduced pressure. The crude product was purified by passage first through a DOWEX 50W X 8 (H^+ form) column eluted successively with MeOH, water and aq. NH_4OH, then by flash chromatography over silica gel and elution with 2:1 CH_2Cl_2–MeOH to afford compound **10** (188 mg, 79%) as an oil; $[\alpha]_D^{19}$ +21.1 (*c* 0.80 in MeOH) (Found: C, 61.15; H, 9.65; N, 6.3. $C_{11}H_{21}NO_3$ requires C, 61.37; H, 9.83; N, 6.51%); δ_H(300 MHz; D_2O) 1.15 (6 H, m), 2.04–1.75 (4 H, m), 2.14 (2 H, m), 2.87 (1 H, m), 3.10 (1 H, dd, *J* 10.8 and 10.4), 3.28 (1 H, dd, *J* 9.9 and 3.6), 3.76 (3 H, m) and 4.03 (1 H, m); δ_C(75.4 MHz; D_2O) 22.69, 23.08, 24.18, 25.47, 54.51, 57.18, 67.08, 67.40, 68.20, 72.39 and 82.74.

(6S,7R,8S,8aR)-6,7,8-*Trihydroxyindolizidine* **11**.—To a stirred solution of the ether **10** (150 mg, 0.70 mmol) in anhydrous CH_2Cl_2 (8 cm^3) was added BBr_3 (0.65 cm^3, 7.0 mmol at −78 °C and the mixture was treated for 20 h at room temperature. The reaction was quenched with saturated aq. NH_4OH and the resulting slurry was concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel and eluted with EtOH–CH_2Cl_2–NH_4OH 10:5:1 to give the *indolizidine* **11** (81 mg, 67%) as a glass; $[\alpha]_D^{20}$ +17.5 (*c* 0.30 in MeOH) (Found: C, 55.35; H, 8.6; N, 8.2. $C_8H_{15}NO_3$ requires C, 55.47; H, 8.73; N, 8.09%); δ_H(300 MHz; D_2O) 1.77 (3 H, m), 2.0 (1 H, m), 2.20 (2 H, m), 2.93 (1 H, br t, *J* 6.0), 3.17 (1 H, dd, *J* 10.5 and 5.1), 3.38 (1 H, m), 3.47 (1 H, dd, *J* 9.9 and 3.9), 3.82 (1 H, td, *J* 10.2 and 5.1) and 3.95 (1 H, dd, *J* 9.9 and 3.9); δ_C(75.4 MHz; CD_3OD) 23.00, 25.31, 54.59, 57.78, 67.82, 69.35, 69.85 and 77.99.

(6S,7R,8S,8aR)-6.8-*Diacetoxy*-7-*isopropoxyindolizidine* **12**.—To a stirred solution of the isopropyl ether **10** (54 mg, 0.31 mmol) in dry pyridine (1.0 cm^3) were added Ac_2O (20 cm^3) and DMAP (20 mg) at room temperature. After 5 h the solvent was removed and the residue was purified by flash chromatography over silica gel and eluted with 7:3 EtOAc–hexane to afford *diacetate* **12** (92 mg, 100%) as a glass (Found: C, 60.15; H, 8.2; N, 4.7 $C_{15}H_{25}NO_5$ requires C, 60.18; H, 8.42; N, 4.68%); δ_H(300 MHz; $CDCl_3$) 1.10 and 1.08 (2 × 3 H, d, *J* 6.0, CH*Me*$_2$), 1.1–2.2 (7 H, m), 2.17 and 2.04 (2 × 3 H, s, OAc), 3.10 (1 H, td, *J* 9.9 and 1.8), 3.38 (1 H, dd, *J* 10.2 and 3.9, 7-H), 3.41 (1 H, dd, *J* 10.2 and 5.1, 5-H^{eq}), 3.67 (1 H, m, C*H*Me$_2$), 5.10 (1 H, td, *J* 10.2 and 5.1, 6-H) and 5.45 (1 H, dd, *J* 3.6 and 1.8, 8-H); δ_C(74.5 MHz; $CDCl_3$) 20.93, 21.00, 21.53, 22.91, 24.70, 29.63, 53.23, 53.59, 64.44, 67.61, 69.71, 70.94, 77.49, 170.04 and 171.20.

(6S,7R,8S,8aR)-6,8-*Diacetoxy*-7-*hydroxyindolizidine* **13**.—To a stirred solution of the ether **12** (30 mg, 0.1 mmol) in CH_2Cl_2 (1 cm^3) at −78 °C was added BBr_3 (0.1 cm^3) and the mixture was allowed to react for 20 h at room temperature. The reaction was quenched with saturated aq. NH_4OH and the resulting mixture was evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel and eluted with 9:1 AcOEt–MeOH to afford *compound* **13** (24 mg, 95%) as a glass (Found: C, 55.9; H, 7.4; N, 5.3 $C_{12}H_{19}NO_5$ requires C, 56.02, 7.44; N, 5.44%); δ_H(300 MHz; CD_3OD) 2.05–1.60 (4 H, m), 2.10 and 1.96 (2 × 3 H, s, OAc), 2.31 (1 H, m), 3.07 (2 H, m), 3.26 (1 H, dd, *J* 11.1 and 5.0), 3.51 (1 H, dd, *J* 10.0 and 3.2), 3.86 (1 H, m), 5.31 (1 H, m) and 5.35 (1 H, m). To a solution of acetate **13** (20 mg. 0.08 mmol) in methanol (0.5 cm^3) were added a few drops of methanolic NaOMe at room temperature and the mixture was allowed to react for 1 h. Removal of the solvent and DOWEX (OH^-) column purification, elution with water, afforded the pure indolizidine **11** (~100%) which was identical in all respects $[\alpha]_D$, ^1H and ^{13}C NMR with the above compound.

4-(*Amino*-8-O-*benzyl*-N-(tert-*butoxycarbonyl*)-2,3,4-*trideoxy*-6,7-O-*isopropylidene*-D-galacto-*oct-2-enonic Acid* 1,4-*Lactam* ent-**2**.—The *title compound* was prepared by starting with *ent*-**1** (2.0 g, 9.7 mmol) following the procedure described for its enantiomer **2**. Yield 3.27 g (78%); $[\alpha]_D^{20}$ −129.3 (*c* 1.2 in $CHCl_3$) (Found: C, 63.6; H, 7.15; N, 3.15. $C_{23}H_{31}NO_7$ requires C, 63.73; H, 7.21; N, 3.23%); ^1H and ^3C NMR, see compound **2**.

4-*Amino*-8-O-*benzyl*-2,3,4-*trideoxy*-6,7-O-*isopropylidene*-D-galacto-*oct-2-enonic Acid* 1,4-*Lactam* ent-**6**.—The *title compound* was prepared by starting with *ent*-**2** (2.0 g, 4.6 mmol) and following the procedure described for its enantiomer **6**. Yield 1.16 g (76%); $[\alpha]_D^{20}$ −22.5 (*c* 2.0 in EtOAc) (Found: C, 64.9; H, 6.8; N, 4.1. $C_{18}H_{23}NO_5$ requires C, 64.85; H, 6.95; N, 4.20%); ^1H and ^{13}C NMR, see compound **6**.

4-*Amino*-2,3,4-*trideoxy*-6,7-O-*isopropylidene*-D-galacto-*octonic Acid* 1,4-*Lactam* ent-**4**.—The *title compound* was prepared by starting with *ent*-**6** (1.5 g, 4.5 mmol) and following the procedure described for its enantiomer **4**. Yield 1.0 g (95%); $[\alpha]_D^{20}$ +25.1 (*c* 1.1 in MeOH) (Found: C, 54.0; H, 7.8; N, 5.65. $C_{11}H_{19}NO_5$ requires C, 53.87; H, 7.81; N, 5.71%); ^1H and ^{13}C NMR, see compound **4**.

1,2,3,4-*Tetradeoxy*-1-4-*imino*-6-O-*isopropyl*-D-galacto-*octitol* ent-**9**.—The *title compound* was prepared by starting with *ent*-**4** (800 mg, 3.26 mmol) and following the procedure described for its enantiomer **9**. Yield 676 mg (76%); $[\alpha]_D^{20}$ −1.7 (*c* 1.0 in MeOH) (Found: C, 55.7; H, 9.8; N, 5.8. $C_{11}H_{23}NO_4$ requires C, 55.63; H, 9.94; N, 6.0%); ^1H and ^{13}C NMR, see compound **9**.

(6R,7S,8R,8aS)-6,8-*Dihydroxy*-7-*isopropoxyindolizidine* ent-**10**.—The *title compound* was prepared by starting with *ent*-**9** (500 mg, 2.14 mmol) and following the procedure described for its enantiomer **10**. Yield 368 mg (80%); $[\alpha]_D^{20}$ −20.3 (*c* 1.1 in MeOH) (Found: C, 61.2; H, 9.8; N, 6.5. $C_{11}H_{21}NO_3$ requires C, 61.37; H, 9.83; N, 6.51%); ^1H and ^{13}C NMR, see compound **10**.

(6R,7S,8R,8aS)-6,7,8-*Trihydroxyindolizidine* ent-**11**.—The title compound was prepared by starting with *ent*-**10** (200 mg, 0.93 mmol) and following the procedure described for its enantiomer **11**. Yield 112 mg (70%); $[\alpha]_D^{20}$ −19.1 (*c* 0.1 in MeOH) {lit.,[6q] $[\alpha]_D^{20}$ −17.3 (*c* 0.85 in MeOH)} (Found: C, 55.4; H, 8.7; N, 8.1. $C_8H_{15}NO_3$ requires C, 55.47; H, 8.73; N, 8.09%); ^1H and ^{13}C NMR, see compound **11**.

X-Ray Crystal Structure Determination of Compound **5**.—*Crystal data*. $C_{15}H_{27}NO_5$, M = 301.4, prisms, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 16.663(5), b = 10.488(4), c = 9.869(3) Å, V = 1725(1) Å^3, Z = 4, $F(000)$ = 656, D_c = 1.161 g cm^{-3}, μ(Cu-Kα) = 6.752 cm^{-1}.

Data collection. The intensity data were collected on a Siemens AED diffractometer over a 3–70° θ range; h, 0–20; k, 0–12; l, 0–12, by using the Cu-Kα radiation (λ = 1.541 78) and θ–2θ scanning. Of the 1911 unique data measured, 1437 had $I > 2\sigma(I)$ and were used in the subsequent structural solution and refinement. The data were corrected for Lorentz and polarization effects, but not for absorption. The crystal dimensions were 0.47 × 0.47 × 0.23 mm.

Structure solution. The structural determination was carried out by direct methods using the SHELX-86[8a] program. The structure was then refined by full-matrix least-squares methods (SHELX-76)[8b] using anisotropic temperature factors for all the non-hydrogen atoms. Hydrogen atoms were located with a difference Fourier map with the exception of methyl and methylene hydrogens, which were calculated at idealized positions (d_{C-H} 1.008 Å). All H-atoms were included in the refinement. The weighting scheme adopted was $w = 0.5792/\sigma^2(F_o) + 0.013\,95(F_o)^2$. At convergence, the discrepancy indices R and R_w were 0.067 and 0.073, respectively. Scattering factors for C, H, N and O were taken from ref. 8*c*. Molecular-geometry calculations were carried out by using the computer program PARST[8d] and the structure drawing by using the ORTEP program.[8e]

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