Tetrahedron Letters, Vol. 33, No. 34, pp. 4917-4920, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

TOTAL SYNTHESES OF 1,5-DIDEOXY-1,5-IMINO-D-*erythro*-L-*allo*-OCTITOL AND (1S,2R,6R,7R,8S,8aS)-PENTAHYDROXYINDOLIZIDINE

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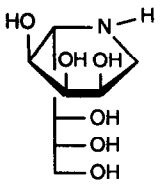
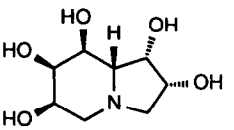
Summary: *The title compounds* (-)-**1** *and* (-)-**2** *were derived from the optically pure Diels-Alder adduct* (-)-**3** *of furan to 1-cyanovinyl (1R')-camphanate.*

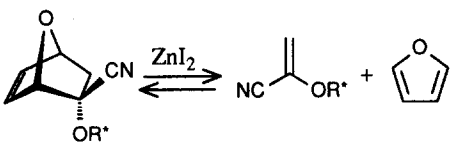
Polyhydroxyindolizidines belong to an important class of alkaloids which includes (-)-swainsonine and (+)-castanospermine, two potent inhibitors of mannosidases and glucosidases, respectively.[1] We report the total, asymmetric synthesis of the new 1,5-dideoxy-1,5-iminooctitol (-)-**1** and its conversion to the corresponding pentahydroxyindolizidine (-)-**2**.



(-)-**1**



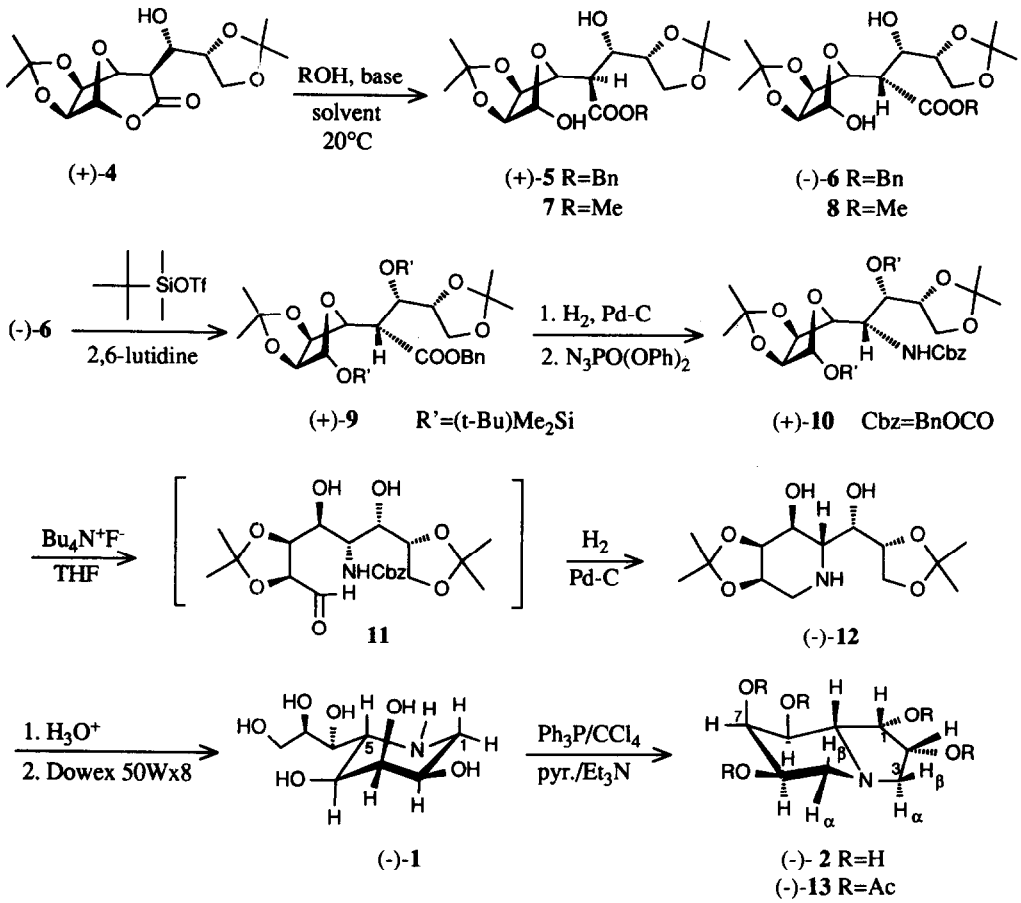
(-)-**2**



(-)-**3** R*=(1R)-camphanoyl

The "naked sugar" (-)-**3** (Diels-Alder adduct of furan to 1-cyanovinyl (1R')-camphanate)[2] was converted to the branched uronolactone (+)-**4** with high stereoselectivity as already described.[3] Treatment of (+)-**4** with benzylic alcohol (BnOH) in THF with K_2CO_3 led to mixtures of the equilibrating benzyl uronates (+)-**5** and (-)-**6**. When run in DMSO (6 equiv. of BnOH) in the presence of 3 equivalents of anhydrous CsF (20°C) (-)-**6** (76%, isolated)[4] was the major epimer (>10:1). In pure MeOH and in the presence of anhydrous K_2CO_3, (+)-**4** led to **7**, the product favored under kinetically controlled conditions. On staying at 20°C with K_2CO_3 in MeOH, it was slowly equilibrated with **8**. Hydrogenolysis of (-)-**6**, which could be isolated pure by flash chromatography on silica gel, gave the corresponding uronic acid that was esterified into **8** with CH_2N_2 in $CHCl_3$. While **7** and **8** had similar stabilities in MeOH, (-)-**6** appears to be more stable than (+)-**5** in DMSO.[5] This phenomenon is not yet understood.

Silylation of (-)-**6** with (t-Bu)$Me_2SiOSO_2CF_3$ and 2,6-lutidine (CH_2Cl_2, 0°C) gave (+)-**9** (mostly β-anomer).[6] Hydrogenolysis (H_2/10% Pd-C, EtOAc, 20°C) of (+)-**9** followed by treatment with $N_3PO(OPh)_2$ in toluene containing 5 equiv. of Et_3N induced a Curtius rearrangement[7] providing the corresponding isocyanate that was quenched with BnOH (100°C, 15 h) to give (+)-**10**[8] in 92% yield. Desilylation with $Bu_4N^+F^-$ (1 M in THF, 0-20°C), followed by hydrogenolysis (H_2, 10% Pd-C, EtOAc, 20°C, 24 h) furnished (-)-**12** (83%). This process implies the intermediacy of sugar **11** which generates the corresponding cyclic imine upon debenzylation of the NHCbz moiety. Hydrolysis of (-)-**12** (CF_3COOH/H_2O 8:1, 20°C, 5 h) followed by purification by chromatography on Dowex 50 Wx8 (H^+ form) gave



1,5-dideoxy-1,5-imino-D-*erythro*-L-*allo*-octitol ((-)-**1**) in 96% yield.[9] Treatment of (-)-**1** with pyridine, Ph_3P, CCl_4, Et_3N (20°C, 15 h) and then quenching with MeOH,[10] provided the pentahydroxyindolizidine (-)-**2** (82%) which was characterized in the form of the corresponding pentaacetate (-)-**13**[11] obtained by treatment with Ac_2O, pyridine and 4-(Me_2N)-pyridine.

The structures of the new compounds described above were given by their mode of formation, their reactivity, their elemental analyses and their spectral data.[12] The $^1C_4$ chair conformation of (-)-**1** as well as the $^4C_7$-chair conformation of the six-membered ring in (-)-**13** were confirmed by the 360 MHz ^{1}H-NMR spectra with the help of double irradiation experiments including NOE measurements. In particular, irradiation of proton H-C(8a) in (-)-**13** (δ_H = 2.47 ppm, ^3J(H-C(8),H-C(8a)) = 10.0 Hz, ^3J(H-C(1),H-C(8a)) = 4.5 Hz) led to significant NOE's at signals δ_H = 2.14 and 2.17 ppm attributed to H_β-C(3) and H_β-C(5), respectively.

This work demonstrates the potential of the "naked sugars" in the total, asymmetric synthesis of complicated sugars and alkaloids. The biological properties of (-)-**1** and (-)-**2** and their derivatives are under scrutinity.

Acknowledgments. We are grateful to the *Swiss National Science Foundation*, the *Fonds Herbette* (Lausanne) and *Hoffmann-La Roche & Co.*, AG (Basel) for financial support.

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4. Data of (-)-**6**: m.p. 100-101°C. $[\alpha]^{25}_{589}$ = -12 (c = 0.91, $CHCl_3$). ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 7.37 (m, Ph); 5.47 (d, *J* = 3.5 Hz, H-C(1)); 5.28, 5.30 (2d, ^2J = 12.5 Hz); 4.73 (dd,*J* = 6.0, 1.0 Hz, H-C(3)); 4.63 (d, *J* = 6.0 Hz, H-C(2)); 4.62 (dd, *J* = 11.0, 1.0 Hz, H-C(4)); 4.10-3.90 (m, 4 H, H-C(6), H-C(7), H'-C(8), H-C(8)); 3.19 (dd, *J* = 11.0, 2.0 Hz, H-C(5)); 3.14 (d, *J* = 3.5 Hz, HO-C(1)); 3.04 (br.s, HO-C(6)); 1.49, 1.37, 1.30, 1.28 (4s, 2 Me_2C). IR (KBr) v: 3600-3300, 3020, 2980, 1710 (COO), 1370 cm^{-1}. Data of (+)-**5**: oil; $[\alpha]^{25}_{589}$ = +16 (c = 0.74, $CHCl_3$); IR (film) v: 1730 cm^{-1} (COO). ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 7.38 (m, Ph); 5.37 (d, *J* = 8.0 Hz, H-C(1)); 5.27, 5.13 (2d, ^2J = 12.0 Hz); 4.86 (dd, *J* = 6.0, 1.0 Hz, H-C(3)); 4.64 (d, *J* = 6.0 Hz, H-C(2)); 4.65 (dd, *J* = 6.0, 1.0 Hz, H-C(4)); 4.21 (d, *J* = 8.0 Hz, HO-C(1)); 4.04 (m, H-C(6), H-C(7), H_2-C(8)); 3.23 (d, *J* = 6.0 Hz, HO-C(6)); 3.07 (dd, *J* = 6.0, 6.0 Hz, H-C(5)), 1.49, 1.38, 1.31, 1.30 (4s, 2 Me_2C).

5. In DMSO/BnOH (6 equiv.) and CsF (3 equiv.), pure (+)-**5** was converted to (-)-**6** at 20°C in 2 h. Under these conditions H_2O elimination was a slow process.

6. Data of (+)-**9**: oil; $[\alpha]^{25}_{589}$ = +27 (c = 1.065, $CHCl_3$). IR (CH_2Cl_2) v: 3030, 2950, 2930, 2890, 1730, 1460 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H : 7.38 (m, C_6H_5); 5.40 (s, H-C(1)); 5.22, 5.12 (2d, ^2J = 12.0 Hz); 4.57 (dd, *J* = 10.5, 1.5 Hz, H-C(4)); 4.50 (dd, *J* = 6.0, 1.5 Hz, H-C(3)); 4.47 (d, *J* = 6.0 Hz, H-C(2)); 4.40 (dd, *J* = 4.0, 1.8 Hz, H-C(6)); 4.12 (ddd, *J* = 8.0, 6.5, 4.0 Hz, H-C(7)); 3.90 (dd, *J* = 8.0, 6.5 Hz, H-C(8)); 3.67 (t, *J* = 8.0 Hz, H'-C(8)); 2.84 (dd, *J* = 10.5, 1.8 Hz, H-C(5)); 1.49, 1.39, 1.30, 1.26 (4s, 2 Me_2C); 0.89, 0.85 (2s, 2 t-Bu); 0.15, 0.14, 0.13, 0.08 (4s, 2 Me_2Si).

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8. Data of (+)-**10**: oil, $[\alpha]^{25}_{589}$ = +46 (c = 0.99, $CHCl_3$). IR (CH_2Cl_2) v : 3430, 3030, 2950, 2930, 2890,

2850, 1720, 1500, 1470 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 7.35 (m, C_6H_5); 5.42 (s, H-C(1)); 5.18, 5.10 (2d, ^2J = 12.0 Hz); 5.0 (d, J = 9.5 Hz, NH); 4.82 (d, J = 6.0 Hz, H-C(2)); 4.58 (d, J = 6.0 Hz, H-C(3)); 4.48 (d, J = 2.2 Hz, H-C(6)); 3.96 (ddd, J = 8.5, 6.5, 2.2 Hz, H-C(7)); 3.88 (d, J = 0.6 Hz, H-C(4)); 3.82 (dd, J = 9.5 Hz, 0.6, H-C(5)); 3.72 (m, H_2-C(8)); 1.48, 1.40, 1.32, 1.25 (4s, 2 Me_2C); 0.92, 0.90 (2, 2 t-Bu); 0.12, 0.15 (2s, 2 Me_2Si).

9. Data of (-)-**1**: colourless crystals, m.p. 205°C (dec.). $[\alpha]^{25}_{589}$ = -27 (c = 0.3, H_2O). IR (KBr) ν : 3700 - 3100, 2920, 1630, 1560, 1400, 1070, 1020, 900 cm^{-1}. ^{1}H-NMR (360 MHz, D_2O, CH_3CN as internal standard) δ_H: 4.17 (t, J = 2.5 Hz, H-C(3)); 3.92 (dd, J = 8.0, 1.0 Hz, H-C(6)); 3.84 (dd, J = 10.5, 3.5 Hz, H-C(8)); 3.78 (m, H-C(7)); 3.70 (ddd, J = 10.5, 5.0, 2.5 Hz, H-C(2)); 3.63 (dd, J = 10.5, 6.0 Hz, H'-C(8)); 3.62 (dd, J = 10.5, 2.5 Hz, H-C(4)); 2.93 (dd, J = 10.5, 1.0 Hz, H-C(5)); 2.86 (dd, J = 12.5, 5.0 Hz, H-C(1)); 2.68 (dd, J = 12.5, 10.5 Hz, H'-C(1)). ^{13}C-NMR (62.9 MHz, pyridine-D_5) δ_C: 75.9, 73.9, 71.0, 70.5, 70.45 (5d, ^1J(C,H) = 140-150 Hz, C(2), C(3), C(4), C(6), C(7)); 64.7 (t, ^1J(C,H) = 140 Hz, C(8)); 56.3 (d, ^1J(C,H) = 135 Hz, C(5)); 46.3 (t, ^1J(C,H) = 135 Hz, C(1)). MS-CI (NH_3) m/z : 224 ([M + 1]$^+$, 59), 207 (3), 204 (3), 203 (7), 192 (10), 162 (9), 145 (27), 132 (100).

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11. Data of (-)-**2**: colourless crystals, m.p. 175°C (dec). $[\alpha]^{25}_{589}$ = -70 (c = 0.85, H_2O). ^{1}H-NMR (360 MHz, D_2O, pyridine-D_5 as internal standard) δ_H: 4.43 (ddd, J = 8.0, 6.0, 2.5 Hz, H-C(2)); 4.25 (dd, J = 6.0, 3.5 Hz, H-C(1)); 4.14 (dd, J = 3.0, 3.0 Hz, H-C(7)); 3.89 (dd, J = 10.5, 3.0 Hz, H-C(8)); 3.84 (ddd, J = 10.0, 5.0, 3.0 Hz, H-C(6)); 2.92 (dd, J = 11.0, 2.5 Hz, H_α-C(3)); 2.90 (dd, J = 11.0, 5.0 Hz, H_α-C(5)); 2.69 (dd, J = 11.0, 8.0 Hz, H_β-C(3)); 2.46 (dd, J = 10.5, 3.5 Hz, H-C(8a)); 2.32 (dd, J = 11.0, 10.0 Hz, H_β-C(5)); ^{13}C-NMR (62.9 MHz, D_2O, pyridine-D_5 as internal standard) δ_C: 73.0, 71.0, 70.7, 69.1, 68.3 (5d, ^1J(C,H) = 145-150 Hz, C(1), C(2), C(6), C(7), C(8)); 66.4 (d, ^1J(C,H) = 140 Hz, C(8a)); 61.1, 52.4 (2t, ^1J(C,H) = 140 Hz, C(3), C(5)). MS-CI (NH_3) m/z: 224 (8), 223 (M^+ + NH_4^+, 1.2), 206 (M^+ + 1, 100), 205 (M^+, 26), 188 (20), 187 (13), 170 (9), 145 (41), 116 (12), 102 (25), 98 (20), 80 (19). Data of (-)-**13**: colourless crystal, m.p. 150-151°C; $[\alpha]^{25}_{589}$ = -19 (c = 0.2, $CHCl_3$). ^{1}H-NMR (360 MHz, C_7D_8) δ_H: 5.76 (t, J = 3.0 Hz, H-C(7)); 5.41 (dd, J = 6.5, 4.5 Hz, H-C(1)); 5.27 (dd, J = 10.0, 3.0 Hz, H-C(8)); 4.91 (ddd, J = 10.0, 5.0, 3.0 Hz, H-C(6)); 4.90 (ddd, J = 8.0, 6.5, 2.5 Hz, H-C(2)); 2.79 (dd, J = 10.5, 2.5 Hz, H_α-C(3)); 2.75 (dd, J = 10.0, 5.0 Hz, H_α-C(5)); 2.47 (dd, J = 10.0, 4.5 Hz, H-C(8a)); 2.17 (t, J = 10.0 Hz, H_β-C(5)); 2.14 (dd, J = 10.5, 8.0 Hz, H_β-C(3)); 1.85, 1.83, 1.75, 1.68, 1.61 (5s, 5 Ac). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 170.1, 169.9, 169.8, 169.5, 169.4 (5s), 70.5, 69.2, 68.2, 67.6, 66.3 (5d, ^1J(C,H) = 150-160 Hz, C(1), C(2), C(6), C(7), C(8)); 62.3 (d, ^1J(C,H) = 135 Hz, C(8a)); 57.9, 48.9 (2t, ^1J(C,H) = 140 Hz, C(3), C(5)); 20.74, 20.7, 20.5, 20.4, 20.3 (5q, ^{1}J(C,H)=130 Hz). MS-EI m/z: 416 (M^+ + 1, 3), 356 (M^+ - OAc, 3); 355 (M^+ - HOAc, 24), 296 (55), 295 (9), 294 (26), 252 (24), 236 (100), 194 (10), 176 (7), 134 (34), 126 (4), 96 (13), 84 (12). Calc. Anal. for $C_{18}H_{25}NO_{10}$ (415.401): C 52.05, H 6.07, N 3.37; found: C 52.02, H 6.02, N 3.45.

12. Details will be given in a forthcoming full-paper.

(Received in France 21 April 1992)