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ENANTIOMERIC SYNTHESIS OF POLYHYDROXYLATED INDOLIZIDINE ANALOGUES RELATED TO CASTANOSPERMINE: 1-DEOXY-7-EPICASTANOSPERMINE AND 1,7-DIDEOXY-7-FLUOROCASTANOSPERMINE[1]

C.-Kuan Lee*, K.Y. Sim and Jun Zhu

Department of Chemistry, National University of Singapore, Kent Ridge Crescent, Singapore 0511

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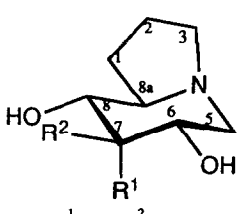
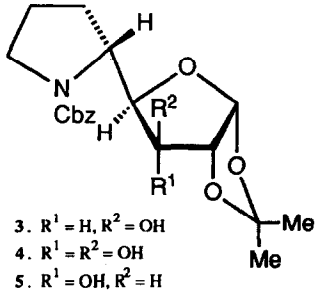
Abstract: (6S,7S,8R,8aR)-6,7,8-Trihydroxyindolizidine (1) and its (7R)-deoxyfluoro analogue (2) was synthesised from 5,8-benzyloxycarbonylimino-5,6,7,8-tetradeoxy-1,2-*O*-isopropylidene-α-D-*gluco*-octose (3). The key step is an oxidation-reduction sequence. Introduction of a fluoro substituent at C-3 (6) was readily effected by displacement of the 3-trifluoromethanesulfonyl (triflate) group with tris-(dimethylamino)-sulfonium-difluorotrimethylsilicate (TASF).

INTRODUCTION

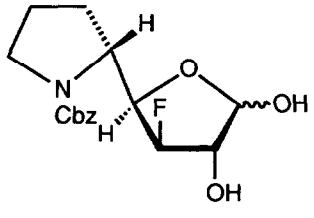
The discovery that certain naturally occurring mono- and bi-cyclic polyhydroxylated alkaloids are specific and potent inhibitors of several glycosidases[2], including those involved in the processing of glycoproteins[3], has generated considerable interest in analogues of 1-deoxynojirimycin and castanospermine as glycosidase inhibitors and potential therapeutic agents for the treatment of AIDS[4]. Fluorinated analogues of these compounds could be important because like fluorosugars, they could show potential or enhanced inhibitory activity[5] against DNA and RNA synthesis and potential antitumour and antiviral agents[5c,6] thereby providing the prospect of an alternative chemotherapeutic agent against HIV and related viruses[4c,7]. Few synthetic methods exists for the selective functionalization and transformation of the individual hydroxyl groups of these alkaloids. As part of a synthetic programme on analogues of mono- and bi-cyclic polyhydroxylated piperidines and indolizidines, we now report the synthesis of 1-deoxy-7-epicastanospermine (1) and 1,7-dideoxy-7-fluorocastanospermine (2).



1. $R^1 = OH, R^2 = H$
2. $R^1 = H, R^2 = F$



3. $R^1 = H, R^2 = OH$
4. $R^1 = R^2 = OH$
5. $R^1 = OH, R^2 = H$
6. $R^1 = H, R^2 = F$



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RESULTS AND DISCUSSION

5,8-Benzyloxycarbonylimino-5,6,7,8-tetradeoxy-1,2-*O*-isopropylidene-α-D-*gluco*-octose[8] (**3**) was readily converted to the *allo*-isomer by an oxidation (→**4**) - reduction (→**5**) sequence in about 65% yield. Compound (**4**) was isolated as the hydrate as was evident from the ^{1}H- and ^{13}C-n.m.r.spectra. The ^{1}H-n.m.r. spectrum indicated the presence of two hydroxyl groups, the proton of one appearing downfield (δ 7.11) indicating that it is probably fairly strongly hydrogen bonded. Its ^{13}C-n.m.r. spectrum also did not show a carbonyl C signal at δ ~210

Reaction of (**5**) with triflic anhydride followed by displacement of the triflate group with TASF[9] in cold dichloromethane gave the 3-deoxyfluoro derivative (**6**). The ^{1}H-n.m.r. spectrum of (**6**) was not well resolved but it was observed that the H-3 signal has been deshielded (cf. **5**). The presence of a fluorine substituent at C-3 (δ_F -129.7) was further confirmed by its ^{19}F-n.m.r. spectrum while the ^{13}C-^{19}F couplings ($J_{2,F}$ 32 $J_{3,F}$ 186.4, $J_{4,F}$ 10.0 Hz) were similar to those of 3-deoxy-3-fluoro-D-glucofuranoid derivatives[9,10]. Additional evidence was provided by the mass spectrum of (**6**) which displayed the ions m/z 365 [M$^+$] and 350 [M$^+$-15].

Hydrolysis of the 1,2-acetal group of (**6**) using Amberlite IR-120 (H$^+$) resin proceeded slowly to afford the free furanose (**7**) as an anomeric mixture. Catalytic hydrogenation of the mixture effected hydrogenation of the benzyloxycarbonyl group followed by intramolecular reductive amination of the C-1 aldehyde to yield (**2**) (78% yield). Evidence of the structure of (**2**) was provided by its ^{1}H-, ^{13}C- and ^{19}F-n.m.r. spectra. Its n.m.r. signals and the ^{1}H-^{1}H, ^{19}F-^{1}H and ^{13}C-^{19}F couplings of the piperidine ring are consistent with those found in 1,3-dideoxy-3-fluoronojirimycin[1]. The ^{1}H-n.m.r. spectrum showed a low field signal (δ 4.23) containing two triplets, each of intensity 0.5 protons. This was assigned to H-7. The separation between these two triplets (52.9 Hz) is characteristic of a geminal ^{19}F-^{1}H coupling. That the fluorine substituent at this position is equatorial is reflected by the large $J_{6,7}$ and $J_{7,8}$ couplings (9.0 Hz). The ^4J couplings between F-7 and H-5eq and C-8a (5.0 and 8.0 Hz, respectively) accord with the stereospecificity of such couplings[5a], giving further confirmation of the equatorial orientation of the fluoro substituent. The presence of a deoxy group at C-5 was reflected by the H-5eq and H-6 signals at δ 3.17 ($J_{5ax,5eq}$ 11.0 Hz) and 3.90 ($J_{5ax,6}$ 10.4 Hz), respectively. The H-5ax signal overlapped with the H-8a signal at δ 2.7. The signals due to the protons of the pyrrolidine ring are much as would be anticipated. The presence of a deoxy group at C-1 was reflected by the signals at δ 1.52 ($J_{1a,1b}$ 12.0, $J_{1b,8a} = J_{1b,2a} = J_{1b,2b}$ = 9.0 Hz, H-1b) and 2.05. In addition, accurate mass measurement gave a fragment m/z 175.0997 corresponding to $C_8H_{14}FNO_2$ [M$^+$].

Synthesis of 1-deoxy-7-epicastanospermine (**1**) was carried out by a similar procedure as for (**2**), by first hydrolysing the acetal group followed by catalytic hydrogenation. The ^{1}H n.m.r. spectrum showed coupling constants $J_{6,7} = J_{7,8}$ = 2.7 Hz, indicative of an axial substituent at C-7.

EXPERIMENTAL

Optical rotations were determined at 22-25°C in 1 dm tube with a Perkin Elmer 141 polarimeter. The ^{1}H-, ^{13}C- and ^{19}F- n.m.r. spectra (internal Me_4Si) were recorded on a Brucker ACS-300 (300 MHz) or AMX-500 (MHz) spectrometers. E.i. mass spectra (70 eV) were determined with a Micromass VG 7035 spectrometer. Melting points were determined using a Büchi 512 melting point apparatus and are uncorrected.

Microanalyses were carried out using a Perkin Elmer 2400 Elemental Analyser. Reactions were monitored by t.l.c. on silica gel 60 F_{254} (Merck) with detection by charring with sulphuring acid. Flash column chromatography was performed on Kieselgel 60 (Merck 230-400 mesh) at 5-10 p.s.i.

*5,8-Benzyloxycarbonylimino-5,6,7,8-tetradeoxy-1,2-*O*-isopropylidene-*α*-*D*-octofuranosid-3-ulose-hydrate* (**4**). A solution of (**3**) (140 mg) in N,N-dimethylformamide (6 ml) and dimethylsulfoxide (0.15 ml) was heated with phosphorus pentaoxide (160 mg) at 65-70°C for 2.5 h. T.l.c. (ethyl acetate-hexane, 1:2) revealed the presence of a slower-moving product. The cooled mixture was poured into ice-water and extracted with ether (3 x 5 ml). The ether extract was washed once with water, dried (Na_2SO_4) and concentrated to give, after flash column chromatography (ethyl acetate-hexane, 1:2), crystalline (**3**) (110 mg, 75%), m.p. 75-76°C (from methanol), $[\alpha]_D$ +84° (c 0.6, chloroform), ν 3470, 3300, 1660 cm^{-1}. ^{1}H-N.M.R. δ_H 7.11 [s, 1 H, 3-$(OH)_2$]; 5.78 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1); 5.0-5.2 (m, 2 H, $ArCH_2$); 4.20 (d, 1 H, H-2); 4.0-4.2 (m, 2 H, H-5, 3-$(OH)_2$]; 3.70 (d, 1 H, $J_{4,5}$ 10.0 Hz, H-4); 3.4-3.6 (m, 1 H, H-8a,8b); 1.8-2.2 (m, 4 H, H-6a,6b,7a,7b); 1.40, 1.56 [d, 6 H, $C(CH_3)_2$]. ^{13}C-N.M.R. δ_C. 114.3 (CMe_2); 102.8/103.4 (C-1/C-3); 79.5/79.2 (C-2/C-4); 67.7 (C-5); 67.0 ($ArCH_2$); 47.0 (C-8); 28.6 (C-6); 27.3, 27.1 [$C(CH_3)_2$], 23.9 (C-7). Anal. calc. for $C_{19}H_{25}NO_8$ (395.41): C-57.71; H 6.37, N 3.54%; found: C 57.72; H 6.71; N 3.92.

*5,8-Benzyloxycarbonylimino-5,6,7,8-tetradeoxy-1,2-*O*-isopropylidene-*α*-*D*-allo-octose* (**5**). A solution of (**4**) in aqueous ethanol (3:7) was treated with sodium borohydride (12 mg) over 15 min and stirred for 2 h at room temperature when t.l.c. (ether-hexane, 1:1) revealed a slower moving product. Ethanol was removed by distillation and the aqueous solution was extracted with dichloromethane, dried (Na_2SO_4) and concentrated. Flash column chromatography (ether-hexane-methanol, 2:2:1) of the syrupy residue gave (**5**), (73 mg, 78%), $[\alpha]_D$ +91° (c 0.95, chloroform). ^{1}H-N.M.R. ($CDCl_3$) δ_H 5.73 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1); 5.0-5.3 (m, 2 H, $ArCH_2$); 4.61 (m, 1 H, H-2); 3.4-4.2 (m, 6 H, H-3,4,5,8a,8b,3-OH); 1.8-5.3 (m, 4 H, H-6a,6b,7a,7b); 1.35, 1.56 [2 s, 6 H, $C(CH_3)_2$]. ^{13}C-N.M.R. δ_H 112.7 (CMe_2); 103.4 (C-1); 79.8/77.6 (C-2/C-4); 74.9 (C-3); 67.1 ($ArCH_2$); 59.3 (C-5); 47.0 (C-8); 27.1 (C-6); 26.4, 26.6 [$C(CH_3)_2$]; 23.8 (C-7). Anal. calc. for $C_{19}H_{25}NO_6$ (363.40): C 62.80, H 6.93, N 3.85%; found: C 62.35, H 6.52, N 3.44.

*5,8-Benzyloxycarbonylimino-3,5,6,7,8-tetradeoxy-3-fluoro-1,2-*O*-isopropylidene-*α*-*D*-gluco-octose* (**6**). A solution of (**5**) (0.31 g) in a mixture of dry dichloromethane (15 ml) and pyridine (0.5 ml), cooled in an ice-salt bath, was treated with triflic anhydride (0.55 ml). The solution was stirred for 20 min when t.l.c. (ether-hexane, 1:1) revealed only one faster-moving product. The solution was washed successively with dil. HCl, water (thrice) and dried (Na_2SO_4). The solution was filtered, cooled in ice-bath and treated with TASF (0.9 g) for 1 h when t.l.c. (ether-hexane, 1:1) showed the presence of a faster -moving product. The reaction mixture was washed with water, the organic extract dried (Na_2SO_4) and concentrated to give, after flash column chromatography (ether-hexane, 1:1), (**2**) (0.24 g, 78%), $[\alpha]_D$ +48.5° (c 0.9, chloroform). ^{1}H-N.M.R. ($CDCl_3$) δ_H 5.95 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1); 5.0-5.1 (m, 2 H, $ArCH_2$); 4.2-5.0 (m, H-2,3,4,5); 3.4-3.5 (m, 1 H, H-8); 1.8-2.3 (m, 4 H, H-6a,6b,7a,7b); 1.31, 1.59 [2 s, 6 H, $C(CH_3)_2$]. ^{13}C-N.M.R. δ_C 112.2 (s, CMe_2), 104.7 (s, C-1); 94.8 (d, $J_{3,F}$ 186.4 Hz, C-3); 82.6 (d, $J_{2,F}$ 32.0 Hz, C-2); 80.4 (d, $J_{4,F}$ 10.0 Hz, C-4); 66.9 (s, $ArCH_2$); 55.75 (s, C-5); 46.6 (s, C-8); 26.3, 26.7 [2 s, $C(CH_3)_2$]; 24.6/23.75 (C-6/C-7). ^{19}F-N.M.R. δ_F -129.7. Anal. calc. for $C_{19}H_{24}FNO_5$: C 62.45, H 6.62, F 5.20, N 3.83%; found: C 62.64, H 6.34, F 5.26, N 3.67.

1-Deoxy-7-epicastanospermine (**1**). A solution of (**5**) (0.28 g) in aqueous solution (50 ml, 1:10) was stirred with Amberlite IR-120 (H^+) resin at 45° for 3 h. The solution was concentrated, dissolved in methanol and hydrogenated in the presence of 10% Pd on activated charcoal for 20 hr at room temperature and 35 p.s.i pressure. The catalyst was filtered off and the filtrate concentrated to give, after flash-column chromatography, crystalline (**1**) (85 mg, 30%), m.p. 123-124° (from methanol-ether), $[\alpha]_D$ +18°+ (c 0.8, methanol). ^{1}H-N.M.R. (D_2O) δ_H 4.04 (t, 1 H, $J_{6,7} = J_{7,8}$ = 2.7 Hz. H-7); 3.89 (qd, 1 H, $J_{5eq,6}$ 5.5, $J_{5ax,6}$ 11.0 Hz, H-6); 3.55 (dd, 1 H, $J_{8,8a}$ 10.1 Hz, H-8); 3.17 (dddd, 1 H, $J_{3a,3b}$ 10.3, $J_{2a,3a}$ 7.3, $J_{2b,3a}$ 4.4 Hz, H-3a); 3.08 (dd, 1 H, $J_{5eq,5ax}$ 11.0 Hz, H-5eq); 2.5-2.8 (m, 2 H, H-1b,3b,5ax); 2.0-2.2 (m, 1 H, H-8a); 1.8-2.0 (m, 2 H, H-2a,2b); 1.4-1.6 (m, 1 H, H-1b). ^{13}C-N.M.R. δ_C 73.8/73.4 (C-7/C-8); 69.7 (C-6); 64.1 (C-8a); 55.1 (C-5); 52.35 (C-3); 29.0 (C-1); 22.85 (C-2). Anal. calc. for $C_8H_{15}NO_3$ (173.21): C 55.47, H 8.73, N 8.09%; found: C 55.86, H 8.54, N 7.76.

1,7-Dideoxy-7-fluorocastanospermine (**2**). A solution of (**5**) (140 mg) in methanol (15 ml) was treated as for (**1**) to give (**2**) (70 mg, 95%), m.p. 137-138° (from ether), $[\alpha]_D$ +44° (c 0.9, methanol). ^{1}H-N.M.R. (D_2O) δ_H 4.23 (dt, 1 H, $J_{6,7} = J_{7,8}$ = 9.0, $J_{7,F}$ 52.9 Hz, H-7); 3.90 (qd, 1 H, $J_{5eq,6}$ 5.5, $J_{5ax,6}$ 10.4, $J_{6,7}$ 9.0, $J_{6,F}$ 14.3 Hz, H-6); 3.50 (ddd, 1 H, $J_{8,8a}$ 9.0, $J_{8,F}$ 12.3 Hz, H-8); 3.17 (ddd, 1 H, $J_{5eq,5ax}$ 11.0, $J_{5eq,F}$ 5.0, H-5eq); 2.98 (dt, 1 H, $J_{3a,3b}$ 9.0, $J_{2,3eq}$ 5.5 Hz, H-3eq); 2.1-2.2 (m, 2 H, H-5ax,8a); 2.0-2.1 (m, 1 H, H-1a); 1.79-1.9 (m, 2 H, H-2a,2b); 1.52 (qd, 1 H, $J_{1a,1b}$ 12.0, $J_{1b,8a} = J_{1b,2a} = J_{1b,2b}$ = 9.0 Hz, H-1b). ^{13}C-N.M.R. δ_C 101.9 (d, $J_{7,F}$ 178.7 Hz, C-7); 75.4 (d, $J_{8,F}$ 17.3 Hz, C-8); 71.2 (d, $J_{6,F}$ 17.8 Hz, C-6); 68.8 (d, $J_{8a,F}$ 8.0 Hz, C-8a); 56.3 (d, $J_{5,F}$ 9.2 Hz, H-5); 55.3 (s, C-3); 29.9 (s, C-1); 23.9 (s, C-2). ^{19}F-N.M.R. δ_F -119.3. Anal. calc. for $C_8H_{14}FNO_2$ (175.20): C 54.85, H 8.05, F 10.84, N 7.99%; found: C 55.22, H 7.64, F 10.44, N 5.59.

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