Model Studies of Histrionicotoxin. The Synthesis of the 1-Azaspiro[5.5]-undecane Rings System from Carbohydrate Starting Materials

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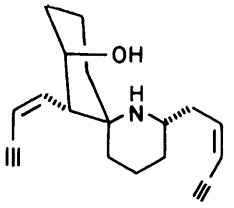
The base-catalysed condensation of nitroethane with dimethyl-t-butylsilyl 2,3-*O*-isopropylidene-α-D-lyxopentodialdo-1,4-furanoside (**2**) gives a diastereoisomeric mixture of nitro alcohols, which on desilylation with fluoride ion in tetrahydrofuran rearranges stereospecifically to 1L-[1,2,5/3,4,6(NO_2)]-3,4-*O*-isopropylidene-6-methyl-6-nitrocyclohexane-1,2,3,4,5-pentaol. The analogous condensation of the tetrahydropyranyl ether of 5-nitropentan-1-ol with aldehyde (**2**) and the subsequent desilylation and rearrangement occur similarly although the degree of stereoselectivity is lower. The major product, 1L-[1,2,5/3,4,6(NO_2)]-3,4-*O*-isopropylidene-6-nitro-6-[4'-(tetrahydropyranyloxy)butyl]cyclohexane-1,2,3,4,5-pentaol (**9**), is converted into (6*S*,7*R*,8*R*,9*R*,10*R*,11*S*)-7,8,11-tri-*o*-acetyl-9,10-*o*-isopropylidene-1-azaspiro[5.5]undecane-7,8,9,10,11-pentaol (**13**), which has the ring skeleton of histrionicotoxin (**1**).

Over one hundred alkaloids, many of which have novel pharmacological properties, have been characterised in the skin extracts from dendrobatid frogs. An important component of the mixture is histrionicotoxin (**1**) which interacts with the acetylcholine receptor-channel complex, reversibly blocking ion conductance whilst leaving acetylcholine binding unaffected. This alkaloid has a unique spiro piperidine ring system, and its low natural abundance (*ca.* 183 mg isolated from the extract of 1 200 frog skins[1]) dictates the need for a synthesis to allow a full biological evaluation of the compound be be made.

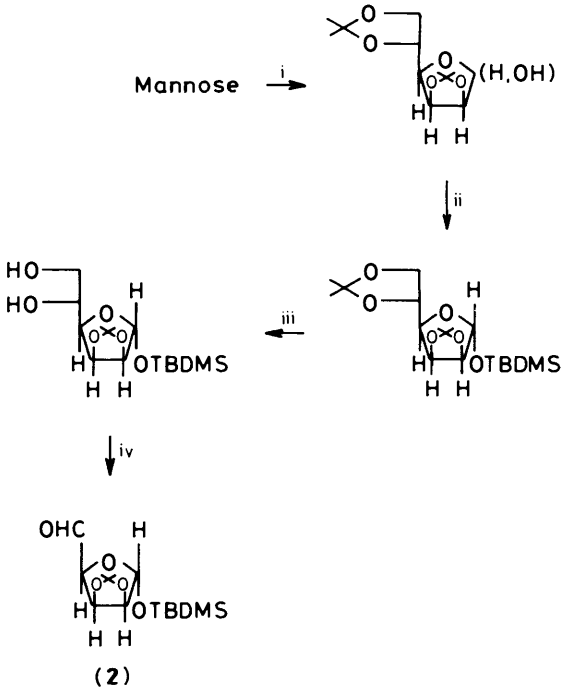


(**1**)

Whilst many syntheses[2,3] of racemic and a synthesis[4] of (+)- and (−)-perhydrohistrionicotoxin have been reported, the first synthesis of racemic histrionicotoxin has only recently been accomplished.[5] Several annelation procedures have been used for the construction of the ring skeleton but the major problems remain the generation of the *cis*-enyne side-chains with the correct absolute stereochemistry.

The use of carbohydrates as chiral starting materials is now well recognised[6,7] as an important method for the synthesis of enantiomerically pure natural products. This paper describes, as a model study for histrionicotoxin, a synthesis of the 1-azaspiro-[5.5]undecane ring system using mannose as the chiral starting material.

Aldehyde (**2**) was readily synthesised by a four-step sequence from mannose illustrated in Scheme 1. Preliminary studies (Scheme 2) demonstrated that a carbocyclic ring could be readily formed from aldehyde (**2**) by means of successive inter- and intra-molecular Henry reactions (nitro aldol condensation). Base-catalysed condensation of aldehyde (**2**) with nitroethane afforded a diastereoisomeric mixture of nitro alcohols (**3**), which on treatment with fluoride ion in tetrahydrofuran (THF) was readily desilylated to afford the furanose (**4**), which then underwent a rapid intramolecular base-catalysed Henry reaction at the newly formed aldehyde carbon to give the nitrocyclitol (**5**).

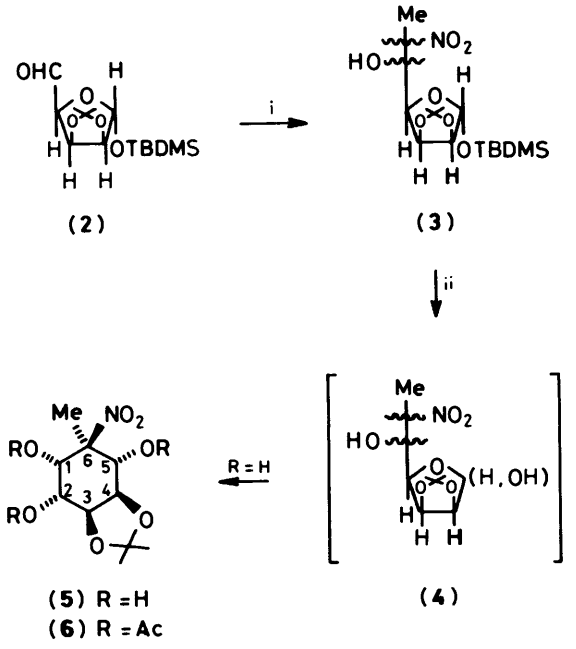


(**2**)

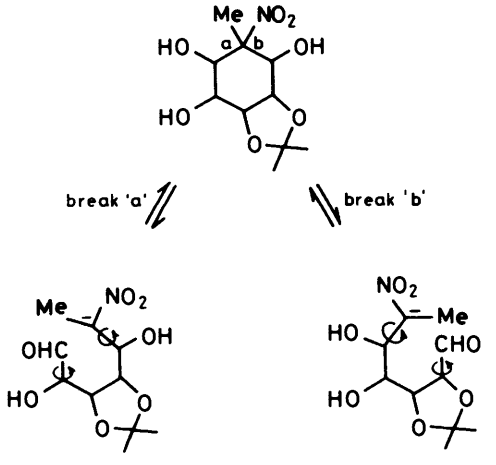
Scheme 1. *Reagents:* i, MeCOMe–H^+; ii, Bu^tMe_2SiCl (TBDMSCl), DMF, imidazole; iii, H^+; iv, $NaIO_4$, aq. EtOH

This reaction was notable in that of eight possible diastereoisomers available from a process involving the formation of three new asymmetric centres, only one stereoisomer was obtained. The stereochemistry was deduced from a combination of spectroscopic and chemical methods applied to the acetate (**6**). (These results will be discussed later). The fact that the diastereoisomeric mixture of nitro alcohols (**3**) after disilylation rearranged [*via* (**4**)] to a sole nitro cyclitol (**5**) is a consequence of the reversibility of the Henry reaction which allows equilibration of isomers through ring-opened intermediates such as those illustrated in Scheme 3. Mechanisms for the ring closure and equilibration of such systems have been discussed by Baer[8] and more recently by Funabashi.[9]

Having constructed one carbocyclic ring, we readily envisaged the extension of the procedure to allow the elaboration of



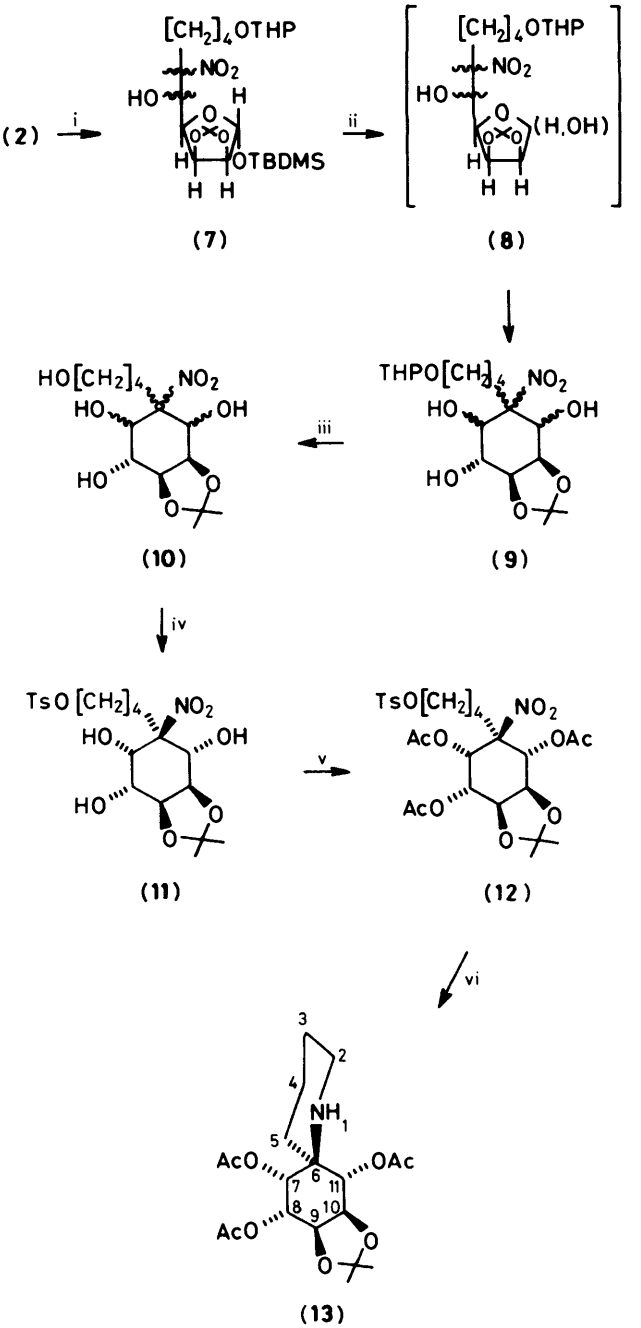
Scheme 2. *Reagents:* i, $EtNO_2$, KOH, EtOH; ii, Bu_4NF



Scheme 3.

a second spiro piperidine ring and hence the histrionicotoxin skeleton, and this involved condensation of a suitably protected nitropentanol with aldehyde (**2**) as shown in Scheme 4.

Condensation of the tetrahydropyranyl ether of 5-nitropentan-1-ol with aldehyde (**2**) gave compound (**7**) as a complex mixture of several nitro alcohols in 73% yield. The broad unresolved ^1H n.m.r. spectrum did not allow detailed assessment of the isomer ratios, and chromatographic separation of the mixture was not attempted. Treatment of furanoside (**7**) with fluoride ion in THF caused a rapid desilyation to afford the corresponding furanose (**8**), which then rearranged more slowly to give the cyclitol (**9**) as a mixture of isomers. In this instance the rearrangement step occurred more slowly than in the simple case and with a lower degree of stereoselectivity so that the product (**9**) was a mixture of several diastereoisomers. Longer reaction times did not result in a simplification of the product mixture *via* equilibration. Again no attempt was made to separate the isomeric mixture, which was treated directly with aqueous acetic acid to remove the tetrahydropyranyl group [to afford the nitro alcohol (**10**)], and the product was then selectively tosylated at the newly exposed primary hydroxy



Scheme 4. *Reagents:* i, $O_2N[CH_2]_5OTHP$, KOH, EtOH; ii, Bu_4NF; iii, AcOH; iv, TsCl, py; v, Ac_2O, py; vi, Al/Hg

group. At this stage, some resolution of the mixture of isomers was possible by column chromatography to give the toluene sulphonate (**11**) as an isomerically homogenous major component separate from the several minor stereoisomers which remained as a mixture. Treatment of compound (**11**) with aluminium amalgam resulted in a rapid loss of starting material but no products could be isolated. However, acetylation of compound (**11**) gave a triacetate (**12**) which, with aluminium amalgam, was smoothly reduced, and the product ring-closed spontaneously to afford the required azaspiro[5.5]undecane (**13**) in 72% yield [from (**12**)].

An assignment of the stereochemistry of compounds (**6**), (**12**), and (**13**) was possible from the ^1H n.m.r. spectrum at 360 MHz.*

* We thank Dr Parsons for these spectra.

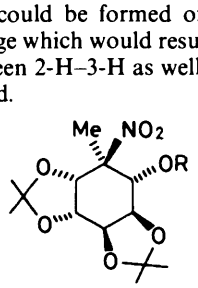
Table. Chemical shifts (p.p.m.) and coupling constants (Hz) measured at 360 MHz for compounds (**6**), (**12**), and (**13**)

	Proton	5-H	4-H	3-H	2-H	1-H
(**6**)	Chemical shift	5.77	4.19—4.25		5.85	5.95
	Coupling constants	$J_{4,5}$ 7.6			$J_{2,3}$ 2.1	$J_{1,2}$ 4.2
	Proton	5-H	4-H	3-H	2-H	1-H
(**12**)	Chemical shift	5.67	4.24		5.67	6.07
	Coupling constants	$J_{4,5}$ 7.8	$J_{3,4}$ 5.5		$J_{2,3}$ 3.8	$J_{1,2}$ 3.6
	Proton	11-H	10-H	9-H	8-H	7-H
(**13**)	Chemical shift	5.40	4.39	4.46	5.34	5.91
	Coupling constants	$J_{10,11}$ 10	$J_{9,10}$ 7.7		$J_{8,9}$ 7.7	$J_{7,8}$ 3.2

The chemical shifts and coupling constants of the cyclitol ring protons are shown in the Table.* Since it is likely that the main product in the mixture of cyclitols (**9**) has the same stereochemistry as the sole product (**5**) in the simpler reaction, it was expected that compounds (**6**), (**12**), and (**13**) would have the same stereochemistry.

The configuration at C-2, C-3, and C-4 in compounds (**6**) and (**12**), and C-8, C-9, and C-10 in compound (**13**), remains unchanged from that of C-2, C-3, and C-4 in the parent D-mannose and is as shown in Schemes 2 and 4. The configuration at C-6 in compounds (**6**) and (**12**) [and therefore in (**13**)] can only be inferred from the fact that the nitro group has a very strong preference for an equatorial position in six-membered rings.[10] With this information, consideration of the ^{1}H n.m.r. data (Table) allows assignment of the configuration at C-1 and C-5 and the ring conformation in compounds (**6**) and (**12**).

The values $J_{4,5}$ 7.6 Hz for (**6**) and 7.8 Hz for (**12**) is consistent with 5-H and 6-H being in a *trans*-diaxial relationship. That 3-H–4-H are *cis* and 2-H–3-H are *trans* pairs follows from their origin in mannose and from the coupling constants observed. The coupling constants suggest only a small distortion from a $_1C^4$ chair conformation. In such a conformation with 2-H equatorial the $J_{1,2}$ value of 4.2 Hz for (**6**) and 3.6 Hz for (**12**) cannot distinguish between an axial or equatorial proton at C-1. Evidence that 1-H is axial was obtained when compound (**5**) condensed readily with acetone under mild conditions in the presence of copper(II) sulphate–toluene-*p*-sulphonic acid (PTSA) to form the di-*O*-isopropylidene derivative (**14**). Such ready formation of a second dioxolane ring only occurs with *cis* hydroxy groups. Compound (**14**) gave a crystalline triacetate (**15**) which gave a clear first-order n.m.r. spectrum at 100 MHz. The coupling constants ($J_{4,5}$ 8.8, $J_{3,4}$ 6.3, $J_{2,3}$ 1.9, and $J_{1,2}$ 7.2 Hz) indicated distortion to a half-chair conformation by decreasing the dihedral angle between 1-H and 2-H and increasing the angle between 2-H and 3-H. Had 1-H been equatorial an isopropylidene ring could be formed only by a more major conformational change which would result in essentially a *trans* diaxial relation between 2-H–3-H as well as between 1-H–2-H. This was not observed.

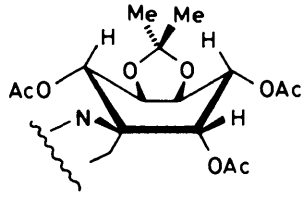


(**14**) R = H

(**15**) R = Ac

* It should be noted that 5-H in compounds (**6**) and (**12**) corresponds to 11-H in spiro compound (**13**) *etc.*, and that $J_{4,5}$ corresponds to $J_{10,11}$ *etc.*

For the spiro compound (**13**), which must have the same absolute configuration as its precursor (**12**), the best fit of the ^{1}H n.m.r. data is obtained when a $^{2,5}B$ conformation (**16**) is assumed. In this conformation 10-H and 11-H are *trans* diaxial, 9-H and 10-H are eclipsed, and 8-H and 9-H are *trans* diaxial so that large (7—10 Hz) couplings constants are observed in all cases. The small ($J_{7,8}$ 3.2 Hz) coupling is consistent with 7-H and 8-H in a *cis* relationship. Thus on the reasonable assumption that conversion of a nitro group into an amino group which is incorporated into a spiro ring causes a change in ring conformation, the changes in ^{1}H n.m.r. data in compounds (**12**) and (**13**) confirm the configurational assignments.



(**16**)

The assignment of alternative configurations to C-1 or C-5 with chair or non-chair conformations does not give a good fit to the available data. These stereochemical assignments for base-promoted intramolecular nitro alcohol condensations are consistent with those of other workers,[9,11,12] which generally result in the formation of cyclitols in which the groups at the newly formed asymmetric centres adopt an equatorial position.

The work described shows the feasibility of the approach as a practical method for the synthesis of the histrionicotoxin skeleton from chiral starting materials.

Experimental

T.l.c. was performed by upward irrigation of microscope slides coated with silica gel G (particle size 0.015—0.040 mm). Column chromatography was performed over silica gel G, particle size 0.063—0.200 mm or 0.040—0.063 mm ('flash grade').[13] N.m.r. spectra were determined in deuteriochloroform solution unless otherwise stated. Proton spectra were determined on a JEOL MH100 instrument except for those in the Table. ^{13}C Spectra were determined at 15 MHz on a JEOL FX60Q instrument. All solvents were routinely distilled prior to use. The term light petroleum refers to the fraction boiling 60—80 °C. Extracts were dried over anhydrous magnesium sulphate. Rotations were determined in chloroform solution unless otherwise stated, c = 1.

Dimethyl-t-butylsilyl 2,3:5,6-*Di*-O-*isopropylidene*-α-D-*mannofuranoside*.†—To a solution of di-*O*-isopropylidene mannofuranose[14] (40.g 0.15 mol) and imidazole (28 g, 0.48 mol) in dry dimethylformamide (DMF) (80 ml) was added dimethyl-t-butylsilyl chloride (27 g, 0.18 mol) in one portion. The mixture was kept at room temperature for 1 h, when t.l.c. [light petroleum–acetone (4:1)] showed no starting material and one major product spot. Water was added and the product was extracted into chloroform. The extract was washed with water, dried, and concentrated, and the residual DMF was removed under reduced pressure. The crude product (51 g, 90%) was sufficiently pure for use in the next step. An aliquot was purified

† The TBDMS group was assigned the α configuration on the basis of the zero vicinal coupling constant ($J_{1,2}$ 0). For a β-anomer, a value of J 7—8 Hz would be expected. However, the assignment of the stereochemistry from the ^{13}C chemical shift of C-1 gave the opposite results. See R. G. S. Ritchie, N. Cyr, B. Korcsh, H. J. Koch, and A. J. Perkin, *Can. J. Chem.*, 1975, **53**, 1424.

by column chromatography [light petroleum–diethyl ether, (19:1)] to afford a syrup which had $[\alpha]_D$ +33°; δ_H 0.10 (6 H, s, $SiMe_2$), 0.80 (9 H, s, SiBu^t), 1.22, 1.26, 1.33, 1.34 (each 3 H, s, isopropylidene Me), 4.0 (3 H, m, CH_2O and 4-H), 4.34 (1 H, m, 5-H), 4.51 (1 H, d, *J* 6.0 Hz, 2-H), 4.76 (1 H, dd, *J* 4.0 and 6.0 Hz 8-H), and 5.26 (1 H, s, 1-H).

Dimethyl-t-butylsilyl 2,3-O-*Isopropylidene*-α-D-*mannofuranoside*.—A solution of the crude di-isopropylidene compound (50 g) in a mixture of acetic acid (400 ml) and water (200 ml) was stirred and heated at *ca.* 50 °C for 3 h. The mixture was diluted with water, extracted with ether, and the extract was concentrated to afford the crude diol (39 g, 87%) as a pale yellow syrup that gave essentially one spot by t.l.c. An aliquot was purified by chromatography [chloroform–methanol (38:1)] to afford the title diol as a white waxy solid, m.p. 67 °C; $[\alpha]_D$ +45°; δ_H 0.10 (6 H, s, $SiMe_2$), 0.76 (9 H, s, SiBu^t), 1.22 and 1.36 (each 3 H, s, isopropylidene Me), 3.38 (2 H, br s, OH), 3.56 (1 H, m, 5-H), 3.68 (1 H br d *J* 2.4 Hz, 4-H), 3.86 (2 H, m, 5-H_2), 4.42 (1 H, d, *J* 6.0 Hz, 2-H), 4.80 (1 H, m, 3-H), and 5.19 (1 H, s, 1-H).

Dimethyl-t-butylsilyl 2,3-O-*Isopropylidene*-α-D-lyxo-*pentodialdo*-1,4-*furanoside* (**2**).*—A solution of sodium metaperiodate (31 g) in water (200 ml) was added to a stirred solution of the crude diol (35 g) in ethanol (200 ml) during 30 min. A thick heavy white precipitate was obtained. After an additional 30 min, the mixture was diluted with water, and extracted with chloroform, and the extract was dried and concentrated to afford a pale yellow liquid that was distilled *in vacuo* to give the aldehyde (**2**) as a syrup (23 g, 70%), b.p. 100—112 °C at 0.8 mmHg; $[\alpha]_D$ +26°; δ_H 0.1 (6 H, s, $SiMe_2$), 0.90 (9 H, s, SiBu^t), 1.28 and 1.43 (each 3 H, s, isopropylidene Me), 4.42 (1 H, dd, *J* 1.2 and 4.2 Hz, 4-H), 4.56 (1 H, d, *J* 5.6 Hz, 2-H), 5.10 (1 H, dd, *J* 4.2 and 5.6 Hz, 3-H), 5.50 (1 H, s, 1-H), and 9.61 (1 H, d, *J* 1.2 Hz, CHO); δ_C −5.5 and −4.5 ($SiMe_2$), 17.8 ($SiCMe_3$), 24.5 (CMe_2), 25.6 ($SiCMe$), 81.1, 83.9, and 86.4 (C-2, -3, and -4), 102 (C-1), 113.1 (CMe_2), and 198 (CHO). The aldehyde was characterised as a semicarbazone derivative m.p. 204 °C (from aqueous ethanol); $[\alpha]_D$ −30° (Found: C, 50.2; H, 8.1; N, 11.5. $C_{15}H_{29}N_3O_5Si$ requires C, 50.12; H, 8.13; N, 11.69%).

Dimethyl-t-butylsilyl 6,7-*Dideoxy*-2,3-O-*isopropylidene*-6-*nitroheptofuranosides* (**3**).—Nitroethane (10 ml) was added to a solution of aldehyde (**2**) (3.04 g, 0.01 mol) in ethanol (20 ml) and the pH was adjusted to 9 by the dropwise addition of 2M-aqueous potassium hydroxide. The mixture was stored at room temperature until t.l.c. [light petroleum–ethyl acetate (9:1)] indicated an absence of aldehyde (**2**); the mixture was then neutralised and concentrated to a small volume. The residue was diluted with chloroform, and the solution was washed with water, dried, and concentrated to give the title heptofuranosides (**3**) (3.4 g, 90%) as a syrupy mixture of essentially two diastereoisomers in a ratio of *ca.* 70:30 which was readily separated by column chromatography [light petroleum–diethyl ether (4:1)] into a faster isomer (2.12 g, 56%), $[\alpha]_D$ +33.3°; δ_H 0.1 (6 H, s, $SiMe_2$), 0.76 (9 H, s, SiBu^t), 1.22 and 1.36 (each 3 H, s, isopropylidene Me), 1.54 (3 H, d, *J* 7.0 Hz, 7-H_3), 2.9 (1 H, d, *J* 4.4 Hz, OH), 3.81 (1 H, dd, *J* 3.6 and 9.2, 4-H), 4.4—4.82 (4 H, m, 2-, 3-, 5-, and 6-H), and 5.2 (1 H, s, 1-H); δ_C −5.5 and −4.5 ($SiMe_2$), 11.4 (C-7), 17.9 ($SiCMe_3$), 25.6 ($SiCMe_2$), 24.7 and 25.9 (CMe_2), 69.6 (C-5), 78.6, 79.6, 83.6, and 86.6 (C-2, -3, -4, and -6), 101.5 (C-1), and 112.8 (CMe_2); and a slower isomer (0.91 g, 25%), $[\alpha]_D$ +34°; δ_H 0.1 (6 H, s, $SiMe_2$), 0.76 (9 H, s, SiBu^t), 1.20 and 1.34 (each 3 H, s, isopropylidene Me) 1.57 (3 H, d, *J* 7.5 Hz, 7-H_3), 3.06 (1 H, br s, OH), 3.8—4.1 (2 H, m, not assigned), 4.42 (1 H, d, *J* 6.0 Hz, 2-H), 4.54—4.84 (2 H, m, not assigned), and 5.20 (1 H, s, 1-H); δ_C −5.5 and −4.6 ($SiMe_2$), 16.2 (C-7), 17.8 ($SiCMe_3$), 24.5 and 25.8 (isopropylidene CMe_2), 25.8 ($SiCMe_3$), 71.1 (C-5), 79, 80, 84.6, and 86.2 (C-2, -3, -4, and -6), 101.5 (C-1), and 112.6 (CMe_2). The configuration at C-5 and C-6 was not determined.

1L-[1,2,5/3,4,6(NO_2)]-3,4-O-*Isopropylidene*-6-*methyl*-6-*nitrocyclohexane*-1,2,3,4,5-*pentaol* (**5**).†—A solution of nitro alcohol (**3**) (mixed diastereoisomers) (1.0 g, 0.0033 mol) in THF (5 ml) was stirred and cooled in an ice–water-bath. A solution of 1M-tetrabutylammonium fluoride in THF (3.4 ml, 0.0034 mol) was added, and the reaction was monitored by t.l.c. [chloroform–methanol (9:1)]. After *ca.* 15 min, the reaction mixture was carefully neutralised with dil. sulphuric acid, and was then diluted with water, and extracted with chloroform; the extract was dried and concentrated to give an off-white solid which was a sole stereoisomer by n.m.r. spectroscopy. Column chromatography gave the *cyclitol derivative* (**5**) as white solid (0.61 g, 70%), m.p. 186—187 °C (from benzene–methanol); $[\alpha]_D$ +118° (*c* = 0.3 in MeOH); δ_H(CD_3OD) 1.34 and 1.50 (each 3 H, s, isopropylidene Me), 1.56 (3 H, s, Me), 3.80—4.5 (5 H, br m, ring H), and 4.76 (3 H, s, OH); δ_C(CD_3OD) 12.2 (6-Me), 26.3 and 28.4 (CMe_2), 70.5, 72.7, 75.7 and 79.8 (C-1, -2, -3, -4, and -5), 97.3 (C-6), and 110 (CMe_3) (Found: C, 45.4; H, 6.4; N, 5.1. $C_{10}H_{17}NO_7$ requires C, 45.63; H, 6.57; N, 5.23%).

1L-[1,2,5/3,4,6(NO_2)]-1,2,5-*Tri*-O-*acetyl*-3,4-O-*isopropylidene*-6-*methyl*-6-*nitrocyclohexane*-1,2,3,4,5-*pentaol* (**6**).—A solution of nitro alcohol (**5**) (0.26 g, 0.001 mol) in pyridine (3 ml) was cooled in an ice–water bath. Acetic anhydride (1 ml) was added and the mixture was allowed to warm to room temperature. After 3.5 h, water was added and the product was extracted into chloroform; the extract was dried and concentrated. Column chromatography [light petroleum–diethyl ether (1:1)] gave a syrup (0.3 g, 77%), $[\alpha]_D$ +85°; δ_H 1.36 and 1.62 (each 3 H, s, isopropylidene Me), 1.73 (3 H, s, 6-Me), 2.00, 2.10, 2.14 (each 3 H, s, MeCO), 4.19—4.25 (2 H, m, 3- and 4-H), 5.77 (1 H, d, *J* 7.6 Hz, 5-H), 5.85 (1 H, dd, *J* 2.1 and 4.2 Hz, 2-H), and 5.95 (1 H, d, *J* 4.2 Hz, 1-H); δ_C 13.3 (6-Me), 20.1 and 20.4 ($MeCO$), 26.1 and 27.4 (CMe_2), 67, 70.1, 73.5, 75.5, and 75.8 (C-1, -2, -3, -4, and -5), 91.1 (C-6), 110.9 (CMe_2), and 168.2 and 168.6 ($MeCO$). Alternatively, to the crude reaction mixture solution of the triol (**5**) [prepared from (**3**), 1.0 g] in THF (see previous experiment) were added pyridine (6 ml) and acetic anhydride (3 ml). The mixture was stored at room temperature for 4 h. Work-up as above and column chromatography gave the triacetate (**6**) (1.03 g, 80%) as a homogeneous syrup, indistinguishable from that above.

5-*Nitropentyl Tetrahydropyran*-2-*yl Ether*.—A mixture of 5-bromopentyl acetate[15] (12 g, 0.057 mol) and sodium nitrite (10 g) in dry dimethyl sulphoxide DMSO (60 ml) was stirred for 2.5 h at room temperature, when t.l.c. [light petroleum–acetone (4:1)] showed no starting material. The precipitate was filtered off and the filtrate was diluted with water, and extracted with diethyl ether, and the extract was dried and concentrated. Column chromatography [light petroleum–acetone (9:1)] gave 5-nitropentyl acetate (7.0 g, 67%), a solution of which in methanol (10 ml) was treated with 2M-sodium hydroxide (5 ml) until t.l.c. [chloroform–methanol (38:1)] showed an absence of starting material. The reaction mixture was neutralised with dil. hydrochloric acid, and was then concentrated and extracted

* Dimethyl-t-butylsilyl (5*R*)-3,4-*O*-isopropylidene-D-*arabino*-pentodialdo-5,2-furanoside.

† Nomenclature follows 'IUPAC-IUB 1973 Recommendations for Cyclitols,' *Pure Appl. Chem.*, 1974, **37**, 285; *Eur J. Biochem.*, 1975, **57**, 1.

with chloroform to afford, on distillation, 5-nitropentan-1-ol (4.6 g, 86%), b.p. 88 °C at 0.3 mmHg, which on treatment with an excess of 2,3-dihydropyran in the presence of PTSA at room temperature in the usual way gave 5-nitropentyl tetrahydropyran-2-yl ether (6.0 g, 75%), b.p. 111—113 °C at 0.9 mmHg.

Dimethyl-t-butylsilyl 6,7,8,9-*Tetradeoxy*-2,3-O-*isopropylidene*-6-*nitro*-10-O-(*tetrahydropyran-2-yl*)-*decofuranosides* (**7**).—A solution of tetrahydropyran-2-yl 5-nitropentyl ether (6.0 g, 0.028 mol) and aldehyde (**2**) (8.0 g, 0.026 mol) in ethanol (19 ml) was brought to pH 9 by the addition of aqueous 1M-potassium hydroxide. After 4 h, when only a trace of starting material remained, the mixture was neutralised with acetic acid, and diluted with water, and the product was extracted into chloroform. The extract was dried and concentrated. Column chromatography [light petroleum–acetone (19:1)] gave the decofuranosides (**7**) (10.0 g, 73%) as a mixture of diastereoisomers, δ_H 0.10 (6 H, s, $SiMe_2$), 0.76 (9 H, s, $SiBu^t$), 1.23 and 1.36 (each 3 H, s, isopropylidene Me) overlapping with 1.0—2.2 (12 H, br m, various CH_2), and 3.08—5.3 (12 H, br m, remaining H).

1L-[1,2,5/3,4,6(NO_2)]-3,4-O-*Isopropylidene*-6-*nitro*-6-[4-(*tetrahydropyran*-2-*yloxybutyl*]*cyclohexane*-1,2,3,4,5-*pentaol* (**9**).—A solution of adduct (**7**) (5 g 0.0096 mol) in dry THF (15 ml) was stirred in an ice–water-bath whilst 1M-tetrabutylammonium fluoride in THF (10 ml; 0.01 mol) was added. The reaction was monitored by t.l.c. [benzene–acetone–methanol (80:17:3)] which showed a rapid desilylation of the furanoside (**7**) to afford the intermediate furanose (**8**) (which could be isolated by work-up after a suitable time) which then rearranged more slowly to afford the cyclitol (**9**) after longer reaction times (*ca.* 3 h). The reaction mixture was neutralised with 2M-sulphuric acid, diluted with water, and extracted with chloroform. The extract was dried and concentrated and the residue was chromatographed to afford the nitrocyclitols (**9**) (2.5 g, 61%) as a mixture of diastereoisomers. Resolution of the isomers was not attempted at this time. Compounds (**9**) showed δ_H 1.32, 1.41, 1.48 (all s, isopropylidene Me), overlapping with 1.2—1.8 (br m), and 1.85—2.5 (br m).

1L-[1,2,5/3,4,6(NO_2)]-6-(4-*Hydroxybutyl*)-3,4-O-*isopropylidene*-6-*nitrocyclohexane*-1,2,3,4,5-*pentaol* (**10**).—A solution of the nitrocyclitol (**9**) (1.6 g, 0.0044 mol) in acetic acid–water (1:1; 25 ml) was stored at room temperautre for 6 h. The mixture was diluted with water and the product was extracted into chloroform; the extract was dried and concentrated. Column chromatography [benzene–acetone–methanol (8:1:1)] gave the title product (**10**) (1.0 g, 71%) as a mixture of diastereoisomers; $\delta_H(CD_3OD)$ 1.32 and 1.48 (each s, isopropylidene Me) overlapping with 1.2—2.5 (12 H, br resonances, side-chain CH_2), and 3.24—4.6 (7 H, br multiplets, ring H and CH_2O).

1L-[1,2,5/3,4,6(NO_2)]-3,4-O-*Isopropylidene*-6-*nitro*-6-(4′-*tosyloxybutyl*)*cyclohexane*-1,2,3,4,5-*pentaol* (**11**).—A solution of the nitrocyclitol (**10**) (0.45 g, 0.0014 mol) in dry pyridine (3 ml) was cooled and stirred, and a solution of toluene-*p*-sulphonyl chloride (0.40 g, 0.0021 mol) in pyridine (2 ml) was added. After 3.5 h, the reaction mixture was poured into water, and extracted with chloroform, and the extract was dried and evaporated to afford, after column chromatography [chloroform–methanol (38:1)], the major toluene sulphonate (**11**) as a homogeneous fraction (0.32 g, 48%), and a lesser fraction (0.24 g, 35%) of mixed composition. The major tosylate (**11**) was a syrup with $[\alpha]_D$ −20°; δ_H 1.32 and 1.38 (each 3 H, s, isopropylidene Me) overlapping with 1.1—2.3 (6 H, br m, side-chain CH_2), 2.43 (3 H, s, tosyl Me), 3.8—4.7 (7 H, br m, 2 × ring H, CH_2OTs, and 3 × OH), and 7.32 and 7.74 (4 H, ABq, *J* 8 Hz, ArH); δ_C 19.6 (C-1′), 21.7 (Ar*Me*), 25.3 and 27.3 (CMe_2), 28.7 (C-2′), 31.8 (C-3′), 70.2 (C-4′), 71.7, 71.9 and 76 (C-1, -2, -3, -4, and -5), 93.3 (C-6), 109.8 (*CMe*), and 127.8, 129.9, 132.7 and 148 (arom. C).

1L-[1,2,5/3,4,6(NO_2)]-1,2,5-*Tri*-O-*acetyl*-3,4-O-*isopropylidene*-6-*nitro*-6-(4′-*tosyloxybutyl*)*cyclohexane*-1,2,3,4,5-*pentaol* (**12**).—To a solution of the nitro tosylate (**11**) (0.24 g, 0.005 mol) in pyridine (2 ml) was added acetic anhydride (1 ml) and the mixture was stored at room temperature for 2 h. Work-up in the usual way and column chromatography [benzene–acetone (9:1)] gave the triacetate (**12**) (0.2 g, 66%) as a syrup $[\alpha]_D$ +35°; δ_H 1.25 (1 H, m, side-chain H), 1.35 and 1.54 (each 3 H, s, isopropylidene Me), 1.68 (3 H, m, side-chain H), 2.0 (1 H, m, side-chain H), 2.07, 2.13, and 2.14 (each 3 H, s, MeCO), 2.36 (1 H, m, side-chain H), 2.48 (3 H, s, tosyl *Me*), 4.04 (2 H, m, CH_2OTs), 4.24 (1 H, dd, *J* 5.5 and 7.8 Hz, 4-H), 4.29 (1 H, dd, *J* 3.8 and 5.5 Hz, 3-H), 5.67 (2 H, d, *J* 7.8 Hz overlapping with dd, *J* 8.6 and 3.8 Hz, 2- and 5-H), 6.07 (1 H, d, *J* 3.6 Hz, 1-H), and 7.38 and 7.79 (4 H, ABq, *J* 8 Hz, ArH); δ_C 20.5 (C-1′), 21.6 (Ar*Me*), 20.5 (*Me*CO), 25.9 and 27.4 (CMe_2), 29.4 and 29.8 (C-2′ and C-3′), 69.8 (C-4′), 68.5, 72.8, 75.0, and 79.2 (C-2, -3, -4, and -5), 92.3 (C-6), 110.9 (CMe_2), 127.9, 129.9, 133.1, and 145 (arom. C), and 168.6 and 169 (Me*C*O).

(6S,7R,8R,9R,10R,11S)-7,8,11-*Tri*-O-*acetyl*-9,10-O-*isopropylidene*-1-*azaspiro*[5.5]*undecane*-7,8,9,10,11-*pentaol* (**13**).—A solution of the nitro triacetate (**12**) (210 mg, 0.000 34 mol) in ethanol (4 ml) was added to aluminium amalgam prepared from aluminium (250 mg) and 5% aqueous mercury(II) chloride (8 ml). The mixture was stirred for 20 min, then filtered, and the inorganic material was washed with several portions of ethanol. The combined filtrate and washings were concentrated and the residue was chromatographed [benzene–acetone (9:1)] to afford the 1-azaspiro[5.5]undecane (**13**) (100 mg, 72%) as a syrup $[\alpha]_D$ 12°; δ_H 1.00 (1 H, m, ring CH_2H), 1.37 and 1.48 (each 3 H, s, isopropylidene Me) overlapping with 1.3—1.85 (5 H, m, ring protons), 2.05, 2.12, 2.18 (each 3 H, s, MeCO), 2.88 and 3.08 (2 H, m, CH_2NH), 4.39 (1 H, dd, *J* 7.7 and 10.0 Hz, 10-H), 4.46 (1 H, t, *J* 7.7 Hz, 9-H), 5.34 (1 H, dd, *J* 3.4 and 7.7 Hz, 8-H), 5.40 (1 H, d, *J* 10.0 Hz, 11-H), 5.86 (1 H, s, NH), and 5.91 (1 H, d, *J* 3.2 Hz, 7-H); δ_C 20.0, 20.8, and 21.2 (*Me*CO), 24 and 25.1 (C-3, -4, and -5), 25.9 and 27.2 (CMe_2), 51.8 (C-2, 66.8 (C-6), 68.4, 71.8, 72.8, 73.4, and 74.5 (C-7, -8, -9, -10, and -11), 110.4 (CMe_2), and 169.3, 169.5, and 171.4 (Me*C*O).

1L-[1,2,5/3,4,6(NO_2)]-1,2:3,4-*Di*-O-*isopropylidene*-6-*methyl*-6-*nitrocyclohexane*-1,2,3,4,5-*pentaol* (**14**).—To a solution of the nitro cyclitol (**5**) (100 mg, 0.38 mmol) in acetone (3 ml) were added 2,2-dimethoxypropane (2 ml), anhydrous copper sulphate (0.5 g), and a catalytic amount of PTSA. The mixture was stirred at room temperature. T.l.c. [chloroform–methanol (19:1)] showed no trace of starting material (**5**) after 3 h, and one product spot. The mixture was added to water and the product was extracted into chloroform; the extract was dried and concentrated to afford, after column chromatography, the di-*O*-isopropylidene derivative (**14**) as a syrup (104 mg, 90%), $[\alpha]_D$ +88°; δ_H 1.36, 1.51, and 1.52 (15 H, 5 × Me), 3.8 (1 H br m, OH), 4.1—4.64 (4 H, m, 1-, 2-, 3-, and 4-H), and 4.89 (1 H, d, *J* 7.2 Hz, 5-H).

1L-[1,2,5/3,4,6(NO_2)]-5-O-*Acetyl*-1,2:3,4-*di*-O-*isopropylidene*-6-*methyl*-6-*nitrocyclohexane*-1,2,3,4,5-*pentaol* (**15**).—The di-*O*-isopropylidene derivative (**14**) (90 mg, 0.3 mmol) was dissolved in a mixture of pyridine (2 ml) and acetic anhydride (0.5 ml). After 2 h t.l.c. [light petroleum–ethyl acetate (9:1)] showed no trace of starting material (**14**) and essentially one

product spot. The mixture was evaporated to dryness under reduced pressure and the crystalline residue was chromatographed to afford *acetate* (**15**) as a white crystalline solid (89 mg, 86%), m.p. 189—190 °C (from cyclohexane–ethyl acetate); $[\alpha]_D$ +131°; δ_H 1.36, 1.53 and 1.77 (15 H, 5 × Me), 2.04 (3 H, s, COMe), 4.22 (1 H, dd, *J* 6.3 and 8.8 Hz, 4-H), 4.56 (1 H, dd, *J* 1.4 and 6.3 Hz, 3-H), 4.7 (1 H, dd, *J* 1.4 and 7.2 Hz, 2-H), 5.02 (1 H, d, *J* 7.2 Hz, 1-H), and 5.58 (1 H, d, *J* 8.8 Hz, 5-H) (Found: C, 52.1; H, 6.6; N, 4.0. $C_{10}H_{17}NO_7$ requires C, 52.17; H, 6.71; N, 4.06%).

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Received 21*st October* 1985; *Paper* 5/1818