View Article Online / Journal Homepage / Table of Contents for this issue

ARTICLE

OBC
www.rsc.org/obc

Conformation inversion of an inositol derivative by use of silyl ethers: a modified route to 3,6-di-*O*-substituted-L-*ido*-tetrahydroxyazepane derivatives

Gavin F. Painter,* Andrew Falshaw and Herbert Wong
Carbohydrate Chemistry, Industrial Research Limited, P O Box 31-310, Lower Hutt, New Zealand

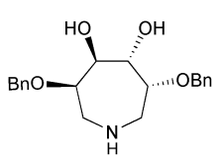
Received 22nd December 2003, Accepted 9th February 2004
First published as an Advance Article on the web 27th February 2004

Published on 27 February 2004. Downloaded by Northeastern University on 30/10/2014 20:34:31.

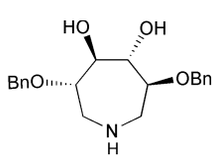
The *trans*-diequatorial 3,4-diol of 2,5-di-*O*-benzyl-D-*chiro*-inositol cleaved selectively with the periodate ion in the presence of the *trans*-diaxial 1,6-diol to give a dialdehyde (dialdose) from which 3,6-di-*O*-benzyl-D-*manno*-tetrahydroxyazepane (**1**) was made. The *trans*-diaxial 1,6-diol of 3,4-di-*O*-allyl-2,5-di-*O*-benzyl-D-*chiro*-inositol was not cleaved satisfactorily by periodate, but replacement of the allyl substituents with *tert*-butyldimethylsilyl groups caused conformational inversion of the inositol ring, and the resulting *trans*-diequatorial 1,6-diol cleaved efficiently to give a dialdehyde from which 3,6-di-*O*-benzyl-L-*ido*-tetrahydroxyazepane (**2**) can be prepared.

Introduction

The specific inhibition of selected enzymes represents a major means by which control can be gained over biological function and malfunction, and oligosaccharide processing glycosidases and glycosyl transferases are important targets.[1] Many imino sugars, having nitrogen as the ring hetero atom, inhibit these enzymes,[2] the tetrahydroxyazepanes with seven-membered rings, several syntheses of which have been reported,[3–13] showing significant activities.[7–9,13] Wong and colleagues have indicated that the introduction of hydrophobic substituents on the hydroxyl groups at the 3,6-positions of these compounds can alter their bioactivities making them protease rather than glycosidase inhibitors.[8] Our previously reported approach to the tetrahydroxyazepanes is unusual in starting from the *chiro*-inositols,[13,14] and we have now utilised it to prepare the 3,6-di-*O*-dibenzyl compounds **1** and **2** from two hexodialdoses made by periodate oxidation of α-diols of two D-*chiro*-inositol-based derivatives. We now report that compound **1** can be made from the dialdehyde **6** obtained by selective oxidative cleavage of the diequatorial C-3, C-4 diol of 2,5-di-*O*-benzyl-D-*chiro*-inositol (**5**) in the presence of the diaxial 1,6-diol. Complementarily, the latter product (**2**) can be obtained from dialdehyde **12**, derived from compound **4** by a reluctant and inefficient oxidative fission of the diaxial C-1, C-6 diol. An improved route to compound **2** was opened when the allyl groups of compound **4** were replaced by *t*-butyldimethylsilyl ethers. This alteration afforded compound **18** with the inositol ring conformationally inverted and the 1,6-diol consequently diequatorial and efficiently oxidisable to give dialdehyde **19**. We are not aware that silyl ether groups have been used for this purpose previously.



1



2

Results and discussion

Following the observation that 3,4-di-*O*-benzyl-D-*chiro*-inositol can be converted to the 2,3,4,5-tetrasubstituted compound by benzylation of a 1,2;5,6-bis-stannylene intermediate,[15] the diallyl ether **3**, made from the 1,2:5,6-diisopropylidene diol, was benzylated at the equatorial C-2, C-5 hydroxyl groups to give compound **4** which, as expected, was shown to adopt the $^4C_1$ chair conformation with the 1,6-diol oriented diaxially (Scheme 1, Table 1). Deallylation gave the known dibenzyl ether **5**[16] (32% from the diisopropylidene diol) that, alternatively, could be obtained, but only in low yield, by reductive cleavage of the acetal groups of 1,2:5,6-di-*O*-benzylidene-D-*chiro*-inositol[17] with DIBAL in dichloromethane.[18]

Tetraol **5** was selectively oxidised with sodium periodate at the diequatorial diol site to give dialdehyde **6** in high yield. Some of the features of this product merit comment. During its formation from tetraol **5** it resisted reaction with periodate at the remaining C-3, C-4 diol (hexodialdose numbering) although excess of the reagent was present, and it did not exist as the dialdehyde, but as a >90% single isomer of a cyclic modification, as evidenced by the absence of formyl group resonances in the ^{1}H and ^{13}C NMR spectra and the presence of two identical anomeric (hemiacetal) proton and carbon atom resonances (δ_H 5.3, d, J = 4.8 Hz; δ_C = 103.2). The latter point would follow had compound **6** been present as the symmetrical cyclic hydrate (**7**), but this also would probably be reactive towards periodate, and therefore, it is proposed, the dialdehyde may have existed in the symmetrical 1,4:6,3-difuranose modification **8**—a proposal supported by the mass spectrometrically derived molecular weight. On reductive amination with benzylamine and sodium cyanoborohydride, compound **6** afforded the *N*-benzyl compound **9** and hence the required diether **1** by a selective *N*-debenzylation by use of palladium hydroxide in methanol containing aqueous ammonia.[19] Proof of the structure compound **1**, and hence of the position of oxidation of tetraol **5**, is provided later.

Periodate cleavage of vicinal diols involves the intermediacy of cyclic iodine-containing ions which do not form with *trans*-diaxial diols on conformationally locked, saturated six-membered rings. Consequently, for example, the fused ring compounds methyl 4,6-*O*-benzylidene-α-D-altropyranoside (**10**)[20] and the D-*chiro*-inositol derivative **11**[13] are stable to the reagent. We found that **11** was also unreactive towards lead tetra-acetate. As a potential precursor of tetrahydroxyazepane **2**, the conformationally unlocked diallyldibenzyl compound **4**, which has a 1,6-diaxial diol in the preferred chair conformation, was tested for its susceptibility to periodate oxidation and, on treatment with excess of reagent in refluxing aqueous

DOI: 10.1039/b316506j

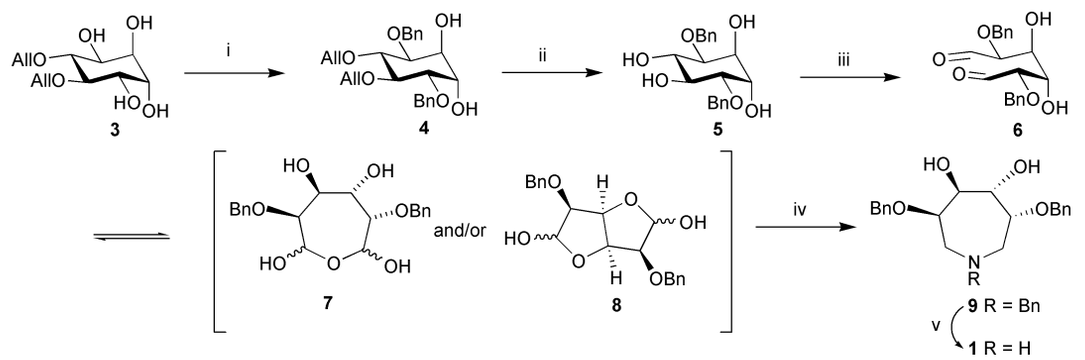
View Article Online

Published on 27 February 2004. Downloaded by Northeastern University on 30/10/2014 20:34:31.

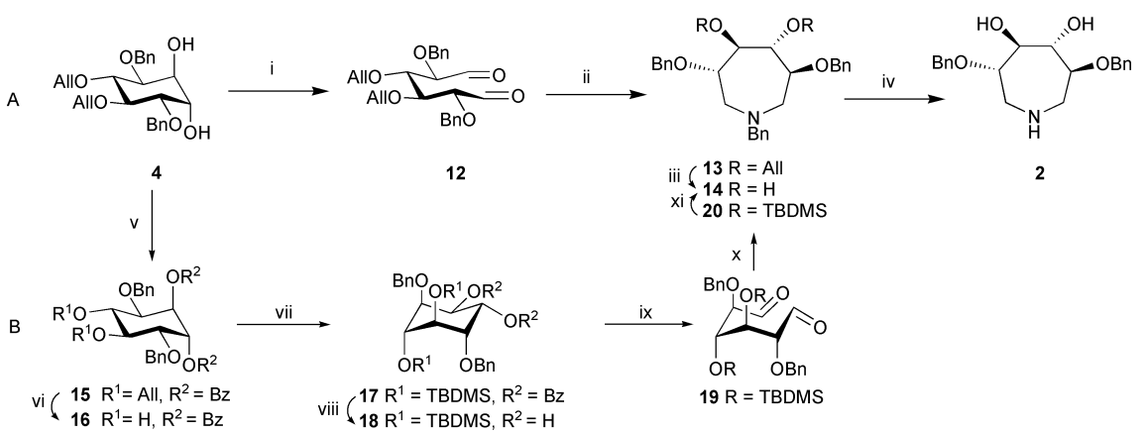
Table 1 Inositol ring ^{1}H and ^{13}C chemical shifts (δ) and $J_{H,H}$ values for compounds **3**, **4**, **15**, **16** and **17**, **18**[a]

		^{1}H δ values			$^3J_{H,H}$ values (Hz)[b]				^{13}C δ values		
Compound	Solvent	H-1,6	H-2,5	H-3,4	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{1,6}$	(not specifically assigned)		
3	MeOH	3.90	3.78	3.47	3.0	10	8.0	2.0	72.7	74.0	75.6
4	$CDCl_3$	4.12	3.75	3.60	3.0	10	8.0	2.0	69.5	80.2	81.4
15	$CDCl_3$	5.72	3.92	3.75	3.0	10	8.0	2.0	68.1	78.2	81.7
16	$CDCl_3$	5.84	4.04	3.8[c]	3.0	10	8.0	2.0	67.6	72.6	77.0
17	$CDCl_3$	6.00	3.96	3.96	3.3	4.2	5.0	9.0	70.0	72.7	80.0
18	$CDCl_3$	4.07	3.70	3.98	3.3	4.2	5.0	9.0	69.2	72.0	81.9

[a] All compounds showed other resonances in keeping with the assigned structures. [b] All obtained by spectral simulation. As well as the given J values, for compounds **17** and **18** $J_{2,4} = J_{3,5} = 1$ Hz were used in the simulations. The method employed allowed the estimation of J values for coupling between chemically (but not magnetically) identical vicinal protons. [c] Poorly resolved because of OH coupling.

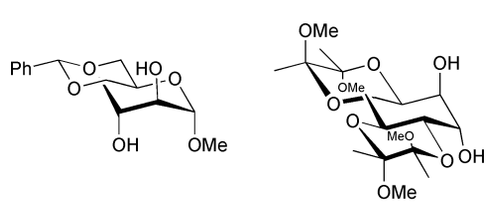


Scheme 1 *Reagents, conditions and yields:* i, $(Bu_3Sn)_2O$, PhMe, 110 °C, 1.5 h, then BnBr, Bu_4NBr, PhMe, 110 °C, 2 h (53%); ii, Pd/C, TsOH, MeOH, 64 °C, 12 h (60%); iii, $NaIO_4$, H_2O, MeCN, rt, 15 h, (86%); iv, $BnNH_2$, $NaCNBH_3$, AcOH, sieves, MeOH, −78 °C – rt, 10 h (60%); v, $Pd(OH)_2$, NH_4OH, MeOH, H_2, rt, 12 h (57%).



Scheme 2 *Reagents, conditions and yields:* i, $NaIO_4$, H_2O, MeCN, 90 °C, 20 h, (35%); ii, $BnNH_2$, $NaCNBH_3$, AcOH, sieves, MeOH, −78 °C–rt, 14 h (58%); iii, Pd/C, TsOH, MeOH, 64 °C, 5 h (50%); iv, $Pd(OH)_2$, NH_4OH, MeOH, H_2, rt, 2 h (74%); v, BzCl, DMAP, Py, 0 °C–rt, 0.5 h, (53%); vi, Ir(I), THF, rt, 1.5 h, then AcCl, MeOH, then Et_3N (60%); vii, TBDMSCl, imidazole, DMF, 85 °C, 18 h, then TBDMSOTf, lutidine, 65 °C, 18 h (60%); viii, MeONa, MeOH, rt, 18 h (83%); ix, $NaIO_4$, H_2O, MeCN, 65 °C, 6 h, (82%); x, $BnNH_2$, $NaCNBH_3$, AcOH, sieves, MeOH, −78 °C–rt, 18 h (59%); xi, MeOH, HCl (concd), rt, 2 h, (93%).

acetonitrile for 20 h, it did undergo diol cleavage but, as implied by these conditions, the reaction was very slow, and 3,4-di-*O*-allyl-2,5-di-*O*-benzyl-L-*ido*-hexodialdose (**12**) was obtained, but in only 35% yield (Scheme 2, route A). Reductive amination with benzylamine and sodium cyanoborohydride afforded the *N*-benzyl compound **13**; deallylation and selective *N*-debenzylation gave the target L-*ido* azepane **2**. Attention then turned to improving the efficiency of the diol cleaving step.



As the sizes of alkyl or aryl groups attached to the silicon atoms of cyclohexyl silyl ethers increase, the ring conformations with the substituents axial become increasingly favoured[21]—contrary to the effects of such substituents on analogously C–O–C bonded compounds. This may relate to the longer Si–O bond length (1.65 Å) relative to C–O (1.41 Å). When two such silyl ether groups are attached to vicinal diequatorial oxygen substituents on saturated six-membered rings the effect is markedly enhanced, and the silyloxy groups have a strong tendency to assume the diaxial orientation and to cause conformational inversion of the rings. This striking phenomenon was first reported by Tius and Busch-Petersen in 1994,[22] and by K. Suzuki and coworkers in 1996[23] who, respectively, observed that the sugar rings of 3,4-bis-*O*-*tert*-butyldimethylsilyl-2-deoxy- and 3,4-bis-*tert*-butyldiphenylsilyl-2,6-dideoxy-D-glucopyranose derivatives adopt the unusual $^1C_4$ conformation with the silyloxy groups axial. This conform-

View Article Online

Published on 27 February 2004. Downloaded by Northeastern University on 30/10/2014 20:34:31.

ational inversion appreciably alters the α,β-ratio of *C*-glycosides produced from the glycosyl acetates of these series relative to analogues having other (equatorial) substituents at O-3 and O-4,[23] and the general observation pertaining to silyloxy groups carrying bulky substituents has been corroborated with pyranoid compounds having the D-*manno*-,[24] D-*gluco*-[25] and D-*xylo*[26] configurations.

Given this propensity for bulky silyloxy groups to cause conformational change, the allyl protecting groups of compound **4** were exchanged for *tert*-butyldimethylsilyl groups with the intention of increasing the susceptibility of the 1,6-diol to oxidative fission. To this end, diol **4** was converted to the dibenzoate **15**, which was deallylated with iridium(I) to give **16** (Scheme 2 route B). Surprisingly, attempted selective deallylation of **15** with palladium on carbon in the presence of toluenesulfonic acid, as was applied successfully to compound **4** (Scheme 1), caused concomitant debenzylation. Forcing conditions, involving the use of *tert*-butyldimethylsilyl chloride in DMF at 85 °C[24] followed by *tert*-butyldimethylsilyl triflate[27] at 65 °C for a total of 34 h, were required to install the *tert*-butyldimethylsilyl protecting groups and give **17**. Finally the benzoate groups were removed to afford diol **18**. Unlike the diallyl analogue **4** (see above), this diol oxidised efficiently with sodium periodate to dialdehyde **19** (82% yield) although the reaction had to be conducted at an elevated temperature (65 °C). From this dialdehyde the L-*ido*-tetrahydroxyazepanes **20** and hence **14** were made by normal reductive amination followed by desilylation. Although the route to compound **2** illustrated in route 2B is several steps longer than that shown in route 2A, it is likely to afford better access—particularly if the steps were all optimised.

The structures of compounds **3** and **4** follow from the method of their synthesis (Scheme 1), and establish **2** as having the L-*ido* configuration. The fact that the tetrahydroxyazepanes **1** and **2** are different compounds proves the former is the D-*manno* isomer and identifies the site of oxidation of the tetraol **5** as the diequatorial 3,4-diol as expected. This assumes that aldehydes **6**, **12** and **19** do not epimerise. Epimerisation of the aldehydes would give mixtures of products and we obtained single products. It is possible that cyclised hydrated forms of the aldehydes, *e.g.* **7**, are less susceptible to epimerisation than the free aldehydes. Furthermore, and consistent with expectations based on the shielding effects of *cis*-oxygen-bonded substituents at vicinal positions on protons of saturated 5-membered[28] and 6-membered[29] cyclic compounds, H-3,6 and H-4,5 of the *manno*-compounds **1** as well as the unsubstituted tetrahydroxyazepane[13,14] resonate downfield (δ 3.8–3.9, 4.1–4.2, respectively) relative to the corresponding protons of the L-*ido*-analogues (δ 3.5 and 3.8–3.9 respectively).

Conformational analysis of compounds **3**, **4**, **15** and **16**, and of the silylated **17** and **18**, by attempted use of $^3J_{H,H}$ values obtained directly from NMR spectra was significantly impeded by second order effects, and coupling constants of the ring protons could not be measured directly. Consequently, the simulation methods described in the Experimental section were employed and gave spectra which were effectively identical to those produced experimentally. The derived coupling values are recorded in Table 1, and show clearly that the first set of compounds adopted the $^4C_1$ conformation ($J_{1,2} = J_{5,6} = 3$ Hz; $J_{2,3} = J_{4,5} = 10$ Hz; $J_{3,4} = 8$ Hz; $J_{1,6} = 2$ Hz), while the introduction of the silyl groups resulted in the desired chair inversion in the cases of compounds **17** and **18** ($J_{1,6} = 9$ Hz; other values = 4 ± 1 Hz).

Conformations of flexible molecules like inositols can alter with solvent and, in consequence, their optical activities can change.[30,31] It was therefore notable that conformational inversion of D-*chiro*-inositol derivatives from the $^4C_1$ chair (compounds **3**, **4**, **15**, **16**) to the $^1C_4$ form (**17**, **18**) results in dramatic rotational change, the respective molecular rotations ([Φ]) ([α] × mol wt/100) being +114, +134, +105, +125 for the former group and −219 and −188 for the latter. This is in keeping with predictions based on an empirical method, developed from the work of Whiffen and Brewster, by which molecular rotations of inositols can be estimated by summing the rotational contributions of the constituent asymmetric gauche vicinal diols, the *R*,*S* and *R*,*R* (diequatorial) moieties, for example, being assigned the values +45 and −45, respectively.[32] By this process the values for D-*chiro*-inositol in the $^4C_1$ and $^1C_4$ chair conformations are determined to be +135 and −135, respectively (although the two chairs are not enantiomers), whereas the observed value is +117. As expected, therefore, the compound exists predominantly in the former conformation as do its non-silylated derivatives (Table 1). Consideration of molecular rotations ([Φ]) rather than specific rotations ([α]) suppresses the effects of the substituent groups and enhances the validity of comparisons of the above type.

Experimental

General experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer at 300 and 75 MHz respectively, using tetramethylsilane as internal standard unless otherwise indicated. In the ^{13}C spectra the numbers of attached protons were determined by DEPT experiments. Spin simulations were calculated using the Bruker-supplied *NMRSIM* programme. The *chiro*-inositol ring protons were treated as a strongly coupled AA′BB′CC′ six spin system in which A and A′ *etc.* denote protons that are chemically equivalent in consequence of the C_2 symmetry.[33] They are, however, not magnetically equivalent as they have different coupling constants to the similarly chemical shift equivalent pair BB′. That is, $J_{AB} \neq J_{AB'}$ and $J_{A'B} \neq J_{A'B'}$.

Mass spectra were recorded at the Mass Spectrometry Unit, HortResearch, Palmerston North, New Zealand on a VG70-250S double focusing, magnetic sector mass spectrometer under chemical ionization conditions using isobutene or ammonia as the ionizing gas, or under high-resolution FAB conditions in a glycerol or nitrobenzyl alcohol matrix. Microanalyses were carried out by the Campbell Microanalytical Laboratory, University of Otago. Melting points were determined using a Buchi 510 melting point apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter, in a 1 dm path length cell. Analytical thin layer chromatography (TLC) was carried out on pre-coated 0.25 mm thick Merck 60 F254 silica gel plates. Visualization was by UV exposure, or by thermal development after spraying with basic potassium permanganate or ethanolic phosphomolybdic acid. Flash chromatography was carried out using Merck Kieselgel 60 (230–400 mesh) under air pressure.

3,4-Di-*O*-allyl-1,2:5,6-di-*O*-isopropylidene-D-*chiro*-inositol

A solution of 1,2:5,6-di-*O*-isopropylidene-D-*chiro*-inositol[34] (5.17 g, 19.9 mmol) in DMF (20 mL) was added under an argon atmosphere to a stirred suspension of sodium hydride (1.70 g, 60% dispersion in mineral oil, 42.5 mmol) in DMF (25 mL) cooled in an ice bath. After 30 min allyl bromide (4.20 mL, 48.6 mmol) was added dropwise and the ice bath was removed. After being stirred at 20 °C for 2 h the reaction mixture was quenched with water (150 mL) and then extracted with diethyl ether (3 × 100 mL). The combined extracts were washed with water (3 × 100 mL) and dried ($MgSO_4$). Evaporation under reduced pressure afforded a thick yellow oil which was purified by column chromatography with CH_2Cl_2–hexanes (1:1 ⟶ 1:0) as eluants to give the title diether (5.44 g, 16.0 mmol, 80%) as a colourless gum; $[\alpha]_D^{22}$ +6.0 (*c* 1.7, $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.34 (6 H, s), 1.50 (6 H, s), 3.38–3.42 (2 H, m), 4.10–4.30 (8 H, m), 5.13–5.19 (2 H, m), 5.27–5.35 (2 H, m), 5.88–6.02 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 25.7 (q), 28.2 (q), 73.2 (t), 76.8 (d), 79.4

View Article Online

Published on 27 February 2004. Downloaded by Northeastern University on 30/10/2014 20:34:31.

(d), 79.9 (d), 109.9 (s), 117.0 (t), 135.5 (d); *m/z* (FAB) 341.1967 [(M + H)$^+$, $C_{18}H_{29}O_6$ requires 341.1964], 341 (60%), 283 (40), 81 (20), 41 (100).

3,4-Di-*O*-allyl-D-*chiro*-inositol (3)

To a stirred solution of 3,4-di-*O*-allyl-1,2:5,6-di-*O*-isopropylidene-D-*chiro*-inositol (1.00 g, 2.94 mmol) in methanol (5 mL) was added HCl (1 mL, concd). After 1 h at room temperature the solvents were evaporated under reduced pressure and the residual syrup was purified by column chromatography with ethyl acetate–MeOH (1:0 ⟶ 1:20) as eluants to afford the diallyl ether (**3**) (760 mg, 2.92 mmol, 99%) as a syrup; $[a]_D^{22}$ *m/z* (FAB) 261.1347 [(M + H)$^+$, $C_{12}H_{21}O_6$ requires 261.1338], 261 (100%), 127 (20), 41 (20). NMR data are in Table 1.

3,4-Di-*O*-allyl-2,5-di-*O*-benzyl-D-*chiro*-inositol (4)

A solution of 3,4-di-*O*-allyl-D-*chiro*-inositol (**3**) (1.30 g, 4.99 mmol), and bistributyltin oxide (5.95 mL, 11.7 mmol) was heated under reflux in toluene (50 mL) under argon for 90 min with the water generated removed by use of a Dean–Stark distillation head. Benzyl bromide (3.50 mL, 29.4 mmol) and tetrabutylammonium bromide (950 mg, 2.95 mmol) were added and, after 2 h, the reaction mixture was cooled to room temperature and applied directly to a column of silica gel. Gradient elution with hexanes–ethyl acetate (1:0 ⟶ 1:1.5) afforded diol (**4**) (1.35 g, 3.06 mmol, 53%) as a syrup, $[a]_D^{22}$ +26 (*c* 0.22, $CDCl_3$); *m/z* (FAB) 441.2268 [(M + H)$^+$, $C_{26}H_{33}O_6$ requires 441.2277], 441 (5%), 242 (100), 91 (60). NMR data are in Table 1.

2,5-Di-*O*-Benzyl-D-*chiro*-inositol (5)

A mixture of 3,4-di-*O*-allyl-2,5-di-*O*-benzyl-D-*chiro*-inositol (**4**) (1.38 g, 3.45 mmol), Pd on carbon (10%, 800 mg) and *p*-toluenesulfonic acid (800 mg, 4.6 mmol) in methanol (30 mL)–water (6 mL) was heated under reflux for 12 h. After being cooled to room temperature the reaction mixture was filtered through Celite and stirred with Amberlyst A-21 to adjust the pH to *ca.* 6. After filtration, the solvent was removed at reduced pressure to give the crude product which was crystallized from ethyl acetate to give the title compound **5** (750 mg, 2.08 mmol, 60%) as white prisms, mp 201–202 °C; $[a]_D^{22}$ + 39 (*c* 0.55, EtOH); lit.[16] $[a]_D^{22}$ +37.2 (*c* 0.6, EtOH); ^{1}H NMR (DMSO-d_6) literature;[16] ^{13}C NMR (DMSO-d_6) δ 69.35, 71.4, 73.1, 79.45, 127.4, 127.8, 128.3, 139.8.

2,5-Di-O-benzyl-D-*manno*-hexodialdose (6)

A solution of sodium periodate (30 mg, 0.14 mmol) in water (1.0 mL) was added to a stirred suspension of 2,5-di-*O*-benzyl-D-*chiro*-inositol (**5**) (50 mg 0.14 mmol) in acetonitrile (5.0 mL). After 1 h, additional sodium periodate (30 mg, 0.14 mmol) in water (1.0 mL) was added, and after further stirring for 14 h the reaction mixture was partitioned between ethyl acetate (100 mL) and water (50 mL). The organic extract was washed with brine (50 mL) and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure to afford the crude product that was purified by column chromatography. Gradient elution with CH_2Cl_2–MeOH (1:0 ⟶ 20:1) afforded dialdehyde **6** (43 mg, 0.12 mmol, 86%) as a syrup; ^{1}H NMR (CD_3OD) (dominant isomer) δ 3.77 (2 H, t, *J* = 4.8 Hz, 2,5-H), 4.58–4.80 (6 H, m, 3,4-H, PhC*H*$_2$), 5.30 (2 H, d, *J* = 4.8 Hz, 1,6-H), 7.24–7.42 (10 H, m, Ar); ^{13}C NMR (CD_3OD) (dominant isomer) δ 73.8 (t), 79.7 (d), 85.7 (d), 103.2 (d), 129.2 (d), 129.5 (d), 129.8 (d), 139.7 (s); *m/z* (FAB) 359.1496 [(M + H)$^+$, $C_{20}H_{23}O_6$ requires 359.1495], 359 (10%), 233 (5), 181 (15), 91 (60).

N-Benzyl-3,6-di-*O*-benzyl-D-*manno*-3,4,5,6-tetrahydroxyazepane (9)

Benzylamine (44 μL, 0.41 mmol) was added to a stirred mixture of dialdehyde **6** (149 mg, 0.40 mmol), $NaCNBH_3$ (55 mg, 0.88 mmol), AcOH (50 μL, 0.83 mmol) and 3 Å sieves (500 mg) in MeOH (40 mL) cooled to −78 °C under argon. The reaction mixture was allowed to warm to room temperature over 10 h, then filtered through Celite. The solvent was removed from the filtrate under reduced pressure and the residue partitioned between ethyl acetate (100 mL) and water (60 mL). The aqueous phase was further extracted with ethyl acetate (80 mL). The combined organic extracts were washed with $NaHCO_3$ (saturated, aqueous, 80 mL) and dried ($MgSO_4$). After filtration the solvent was removed under reduced pressure to give the crude product that was purified by column chromatography. Gradient elution with CH_2Cl_2–MeOH (1 : 0 ⟶ 25 : 1) as eluant followed by a second column eluted with hexanes–ethyl acetate (8 : 2 ⟶ 7 : 3) afforded the title compound (106 mg, 0.24 mmol, 60%) as a syrup; $[a]_D^{22}$ +2.5 (*c* 2.0, $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.70 (2 H, dd, *J* = 12.7, 8.4 Hz, 2,7-H), 2.85 (2 H, dd, *J* = 12.8, 5.3 Hz, 2′,7′-H), 3.51, 3.67 (2 H, 2d, *J* = 12 Hz, PhCH_2N), 3.84 (2 H, dd, *J* = 8.4, 5.3 Hz, 3,6-H), 4.20 (2H, s, 4,5-H), 4.38, 4.42 (4 H, 2d, *J* = 11.7 Hz, PhCH_2O), 7.1–7.4 (15 H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 54.8 (t), 63.5 (t), 71.8 (t), 72.2 (d), 76.4 (d), 128.0 (d), 128.1 (d), 128.8 (d), 129.0 (d), 129.4 (d), 138.5 (s); *m/z* (FAB) 434.2368 [(M + H)$^+$, $C_{27}H_{32}NO_4$ requires 434.2332], 434 (95), 342 (15), 326 (15), 91 (100).

3,6-Di-*O*-benzyl-D-*manno*-3,4,5,6-tetrahydroxyazepane (1)

$Pd(OH)_2$ (20%, 10 mg) was added to a stirred solution of compound **9** (38 mg, 0.088 mmol) and aqueous NH_4OH (28%, 15 μL) in MeOH (5.0 mL). After gentle evacuation the reaction vessel was charged with hydrogen, these processes were repeated (×2) and the suspension was stirred at room temperature for 12 h. After removal of the hydrogen the reaction mixture was filtered through Celite, the solvent was removed at reduced pressure and the product was purified by column chromatography. Gradient elution with CH_2Cl_2–acetone (4 : 1 ⟶ 0.7 : 1) afforded the title compound (15 mg, 0.050 mmol, 57%) as an oil; $[a]_D^{22}$ −34 (*c* 0.2, $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.57 (3 H, bs, OH, NH), 3.05 (4 H, d, *J* = 6 Hz, 2,2′,7,7′-H), 3.85 (2 H, t, *J* = 4 Hz, 3,6-H), 4.08 (2 H, s, 4,5-H), 4.62 (4 H, s, PhCH_2), 7.22–7.38 (10 H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 48.3 (t), 72.4 (t), 72.5 (d), 78.6 (d), 128.1 (d), 128.2 (d), 128.9 (d), 138.5 (s); *m/z* (FAB) 344.1861 [(M + H)$^+$, $C_{20}H_{26}NO_4$ requires 344.1862], 344 (80%), 225 (80), 185 (90), 93 (100).

3,4 Di-*O*-allyl-2,5-di-*O*-benzyl-L-*ido*-hexodialdose (12)

A solution of sodium periodate (1.60 g, 7.48 mmol) in water (15 mL) was added to a stirred solution of 3,4-di-*O*-allyl-2,5-di-*O*-benzyl-D-*chiro*-inositol (**4**) (1.08 g, 2.44 mmol) in MeCN (50 mL) and the mixture was heated to 90 °C for 20 h, when TLC showed complete consumption of the starting material. After being cooled, the reaction mixture was filtered and the residue was washed with toluene. The combined filtrate and washings were partitioned between ethyl acetate (200 mL) and brine (100 mL), the aqueous phase was extracted with further ethyl acetate (2 × 100 mL) and the combined organic extracts were dried ($MgSO_4$). After filtration, the solvent was removed at reduced pressure to give a syrup that was purified by column chromatography. Gradient elution with hexanes-ethyl acetate (4 : 1 ⟶ 7 : 3) afforded the dialdehyde **12** (370 mg, 0.844 mmol, 35%) as a syrup; $[a]_D^{22}$ −6.7 (*c* 0.52, $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.82–4.03 (8 H, m, 2,3,4,5-H, CH_2CH=CH_2), 4.47, 4.82 (4 H, 2d, *J* = 12 Hz, PhCH_2), 5.07–5.23 (4 H, m, CH_2=C), 5.80 (2 H, m, C*H*=CH$_2$), 7.20–7.38 (10 H, m, Ar), 9.72 (2 H, s, C*H*O); ^{13}C NMR ($CDCl_3$) δ 73.3, 73.4, 78.6, 80.5, 118.6, 128.4(8), 128.5(4), 128.9, 134.2, 137.6, 200.5; *m/z* (EI) 438.2061 [(M)$^+$, $C_{26}H_{30}O_6$ requires 438.2042], 438 (5%), 347 (80), 335 (90), 317 (90), 203 (60), 131 (50), 105 (60), 91 (65), 41 (100).

View Article Online

Published on 27 February 2004. Downloaded by Northeastern University on 30/10/2014 20:34:31.

4,5-Di-*O*-allyl-*N*-benzyl-3,6-di-*O*-benzyl-L-*ido*-3,4,5,6-tetrahydroxyazepane (13)

Benzylamine (86 μL, 0.78 mmol) was added to a stirred mixture of the dialdehyde **12** (341 mg, 0.778 mmol), $NaCNBH_3$ (108 mg, 1.72 mmol), AcOH (100 μL, 1.66 mmol) and 3 Å sieves (1.00 g) in MeOH (70 mL) at −78 °C under argon. The reaction mixture was allowed to warm to room temperature over 14 h then filtered through Celite. The solvent was removed from the filtrate under reduced pressure and the residue was partitioned between ethyl acetate (200 mL) and $NaHCO_3$ (saturated, aqueous, 100 mL). The aqueous phase was further extracted with ethyl acetate (120 mL) and the combined organic extracts were dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure to give the crude product that was purified by column chromatography. Gradient elution with hexanes–ethyl acetate (9 : 1 ⟶ 4 : 1) afforded the title compound (232 mg, 0.452 mmol, 58%) as an oil; $[\alpha]_D^{22}$ +21.3 (*c* 1.34, $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.62 (2H, dd, *J* = 13.3, 7.3 Hz, 2,7-H), 2.75 (2H, dd, *J* = 13.3, 3.1 Hz, 2′,7′-H), 3.55–3.72 (6 H, m 3,4,5,6-H, PhCH_2N), 4.16, 4.25 (4H, 2dd, *J* = 12.5, 5.6 Hz, CH_2CH=C), 4.45, 4.58 (4H, 2d, *J* = 12 Hz, PhCH_2), 5.12 (2 H, dd, *J* = 10.5 Hz, CH_2=CH), 5.25 (2 H, dd, *J* = 17.2, 1.7 Hz, CH_2=CH), 5.90 (2 H, ddd, CH_2=C*H*), 7.15–7.35 (15 H, m, Ar); ^{13}C NMR. ($CDCl_3$) δ 55.2 (t), 63.2 (t), 72.6 (t), 73.4 (t), 79.2 (d), 80.2 (d), 84.3 (d), 116.7 (t), 127.5 (d), 127.7 (d), 128.1 (d), 128.6 (d), 129.0 (d), 129.4 (d), 139.2 (s), 139.5 (s); *m*/*z* (FAB) 514.2976 [(M + H)$^+$, $C_{33}H_{40}NO_4$ requires 514.2957], 514 (100%), 456 (10), 316 (10), 91 (90).

***N*-Benzyl-3,6-di-*O*-benzyl-L-*ido*-3,4,5,6-tetrahydroxyazepane (14)**

a. From compound 13. A stirred mixture of compound **13** (62 mg, 0.12 mmol), Pd on carbon (10%, 37 mg), TsOH (37 mg, 0.21 mmol) in MeOH (5 mL) and H_2O (1 mL) was heated under reflux for 5 h. After being cooled to room temperature the reaction mixture was filtered through Celite, the solvent was removed at reduced pressure and the residue partitioned between ethyl acetate (50 mL) and $NaHCO_3$ (saturated, aqueous, 50 mL). The aqueous phase was re-extracted with ethyl acetate (2 × 50 mL) and the combined organic extract dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure to give the crude product that was purified by column chromatography. Gradient elution with hexanes–ethyl acetate (2.3 : 1 ⟶ 0.7 : 1) afforded the title compound (26 mg, 0.060 mmol, 50%) as an oil; $[\alpha]_D^{22}$ +49 (*c* 0.52, $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.62 (2 H, dd, *J* = 13.3, 7.4 Hz, 2,7-H), 2.85 (2 H, dd, *J* = 13.3, 5.0 Hz, 2′,7′-H), 3.50 (2H, ddd, *J* = 7.4, 5.4, 5.0 Hz, 3,6-H), 3.63 (2H, s PhCH_2N), 3.78 (2 H, d, *J* = 5.4 Hz, 4,5-H), 4.48 (4 H, s, PhCH_2O), 7.1–7.3 (15 H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 56.8 (t), 63.7 (t), 72.7 (t), 75.4 (d), 80.7 (d), 127.7 (d), 128.1 (d), 128.2 (d), 128.8 (d), 129.3 (d), 138.5 (s), 139.0 (s); *m*/*z* (FAB) 434.2311 [(M + H)$^+$, $C_{27}H_{32}NO_4$ requires 434.2331], 434 (100%), 391 (20), 286 (20), 133 (25), 91 (25).

b. From compound 20. HCl (1 mL, concd) was added to a stirred solution of *N*-benzyl-3,6-di-*O*-benzyl-4,5-bis-*O*-(*tert*-butyldimethylsilyl)-L-*ido*-3,4,5,6-tetrahydroxyazepane (**20**) (10 mg, 0.015 mmol) in MeOH (5 mL) at 20 °C. After 2 h the volatiles were removed under reduced pressure and the residue was partitioned between diethyl ether (50 mL) and $NaHCO_3$ (saturated, aqueous, 50 mL). The aqueous phase was further extracted with diethyl ether (2 × 50 mL), and the combined organic extracts were dried ($MgSO_4$) and filtered. The solvent was removed from the filtrate under reduced pressure to give the crude product that was purified by column chromatography. Gradient elution with hexanes–ethyl acetate (9 : 1 ⟶ 4 : 1⟶ 0 : 1) afforded the title compound (5 mg, 0.014 mmol, 93%) as an oil; NMR (^{1}H and ^{13}C) identical to those of the sample made from compound **13**.

3,6-Di-*O*-benzyl-L-*ido*-3,4,5,6-tetrahydroxyazepane (2)

$Pd(OH)_2$ (20%, 7.0 mg) was added to a stirred solution of compound **14** (15 mg, 0.035 mmol) and NH_4OH (28%, 7 μL) in MeOH (3.0 mL). After gentle evacuation the reaction vessel was charged with H_2 (× 3) and the suspension stirred at room temperature for 2 h. After removal of the hydrogen the reaction mixture was filtered through Celite, the solvent was removed from the filtrate under reduced pressure and the product was purified by column chromatography. Elution with CH_2Cl_2–MeOH (19 : 1) afforded the title compound (9.0 mg, 0.026 mmol, 74%) as an oil; $[\alpha]_D^{22}$ +74 (*c* 0.18, $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.90 (2 H, dd, *J* = 14.2, 6.6 Hz, 2,7-H), 3.08 (2 H, dd, *J* = 14.2, 3.9 Hz, 2′,7′-H), 3.48 (2H, ddd, *J* = 6.6, 4.2, 3.9, 3,6-H), 3.79 (2 H, d, *J* = 4.2 Hz, 4,5-H), 4.65 (4 H, s, PhCH_2), 7.2–7.35 (10 H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 51.0 (t), 72.6 (t), 75.9 (d), 81.8 (d), 128.2 (d), 128.9 (d), 138.4 (s); *m*/*z* (FAB) 344.1849 [(M + H)$^+$, $C_{20}H_{26}NO_4$ requires 344.1862], 344 (100%), 236 (10), 149 (5), 91 (60).

3,4-Di-*O*-allyl-1,6-di-*O*-benzoyl-2,5-di-*O*-benzyl-D-*chiro*-inositol (15)

Benzoyl chloride (300 μL, 2.58 mmol) was added dropwise to a stirred solution of 3,4-di-*O*-allyl-2,5-di-*O*-benzyl-D-*chiro*-inositol (**4**) (100 mg, 0.227 mmol) and DMAP [(4-(dimethylamino)pyridine] (55 mg, 0.45 mmol) in pyridine (5 mL) under argon at 0 °C. After 10 min the cold bath was removed and the reaction mixture was stirred at ambient temperature for a further 30 min before dilution with ethyl acetate (100 mL) and acidification with HCl (1 M, 100 mL). The acidic phase was extracted with further ethyl acetate (2 × 100 mL) and the combined organic extracts were washed with HCl (1 M, 100 mL), $NaHCO_3$ (saturated, aqueous, 150 mL) and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure to give the crude product which was purified by column chromatography. Gradient elution with hexanes–ethyl acetate (9 : 1 ⟶ 6 : 1) followed by a second column eluted with hexanes–CH_2Cl_2 (1 : 1 ⟶ 0 : 1) afforded compound **15** (77 mg, 0.12 mmol, 53%) as an oil; $[\alpha]_D^{22}$ +16.1 (*c* 1.54, $CDCl_3$); *m*/*z* (FAB) 649.2807 [(M + H)$^+$, $C_{40}H_{41}O_8$ requires 649.2801], 649 (10%), 527 (35), 105 (95), 91 (100). NMR data are in Table 1.

1,6-Di-*O*-benzoyl-2,5-di-*O*-benzyl-D-*chiro*-inositol (16)

(1,5-Cyclooctadiene)bis(methyldiphenylphosphine)iridium(I) hexafluorophosphate (4.0 mg, 0.005 mmol) was added to a stirred solution of compound **15** (33 mg, 0.050 mmol) in THF (4 mL) under argon. The argon was replaced with hydrogen to activate the catalyst and stirring was continued for 2 min. The hydrogen was replaced with argon and the stirring was then continued for 90 min. Methanol (4 mL) and AcCl (0.10 mL, 1.4 mmol) were added, and after further stirring for 30 min triethylamine (1 mL) was added and the solvents were removed under reduced pressure to give the crude product that was purified by column chromatography. Gradient elution with hexanes–ethyl acetate (2.3 : 1 ⟶ 1 : 1 ⟶ 0 : 1) afforded compound **16** (17 mg, 0.030 mmol, 60%) as an oil; $[\alpha]_D^{22}$ +22 (*c* 0.34, $CDCl_3$); *m*/*z* (FAB) 569.2201 [(M + H)$^+$, $C_{34}H_{33}O_8$ requires 569.2175], 569 (50%), 391 (45), 105 (30), 91 (100). NMR data are given in Table 1.

1,6-Di-*O*-benzoyl-2,5-di-*O*-benzyl-3,4-bis-*O*-(*tert*-butyldimethylsilyl)-D-*chiro*-inositol (17)

Imidazole (102 mg, 1.50 mmol) was added to a stirred solution of diol **16** (122 mg, 0.215 mmol) and *tert*-butyldimethylsilyl chloride (122 mg, 0.809 mmol) in DMF (3 mL) under argon. After being heated at 85 °C for 18 h the reaction mixture was allowed to cool to room temperature and 2,6-lutidine (300 μL, 2.58 mmol) and *tert*-butyldimethylsilyl triflate (300 μL, 1.31 mmol) were added dropwise. The mixture was then heated at

View Article Online

Published on 27 February 2004. Downloaded by Northeastern University on 30/10/2014 20:34:31.

65 °C for 18 h. After being cooled to room temperature it was partitioned between diethyl ether (200 mL) and brine (200 mL). The aqueous phase was re-extracted with diethyl ether (2 × 150 mL) and the combined organic extracts were washed with water (3 × 150 mL), dried ($MgSO_4$) and filtered. The solvent was removed from the filtrate at reduced pressure to give the crude product that was purified by column chromatography. Gradient elution with hexanes–CH_2Cl_2 (2.3 : 1 ⟶ 1.5 : 1 ⟶ 1 : 1) afforded compound **17** (96 mg, 0.13 mmol, 60%) as an oil; $[\alpha]_D^{22}$ −27.5 (*c* 1.92, $CDCl_3$); *m*/*z* (FAB) 797.3919 [(M + H)$^+$, $C_{46}H_{61}O_8Si_2$ requires 797.3905], 797 (1%), 181 (10), 106 (95), 91 (100), 73 (15). NMR data are given in Table 1.

2,5-Di-*O*-benzyl-3,4-bis-*O*-(*tert*-butyldimethylsilyl)-D-*chiro*-inositol (18)

NaOMe (*ca.* 0.1–0.2 mL, 30% in MeOH) was added to a stirred mixture of compound **17** (94 mg, 0.12 mmol) in MeOH (10 mL) under argon such that the pH was maintained at *ca.* 12. After stirring of the mixture at room temperature for 18 h, Amberlite IR-50(H) was added to neutralise and the mixture was stirred for 15 min. The reaction mixture was filtered and the solvent was removed at reduced pressure to give the crude product that was purified by column chromatography. Elution with hexanes–ethyl acetate (2.3 : 1) afforded compound **18** (58 mg, 0.099 mmol, 83%) as an oil; $[\alpha]_D^{22}$ −32.0 (*c* 1.16, $CDCl_3$); *m*/*z* (FAB) 589.3380 [(M + H)$^+$, $C_{32}H_{53}O_6Si_2$ requires 589.3381], 589 (10%), 181 (25), 91 (100), 73 (25). NMR data are given in Table 1.

2,5-Di-*O*-benzyl-3,4-bis-*O*-(*tert*-butyldimethylsilyl)-L-*ido*-hexodialdose (19)

A solution of $NaIO_4$ (30 mg, 0.14 mmol) in water (2 mL) was added to a stirred solution of the diol **18** (40 mg, 0.068 mmol) in acetonitrile (5 mL) and the mixture was heated at 65 °C for 6 h. After cooling, toluene (10 mL) was added and the solvents were removed under reduced pressure. The residue was partitioned between ethyl acetate (100 mL) and brine (100 mL), the aqueous phase was re-extracted with ethyl acetate (2 × 100 mL) and the combined organic extracts were dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product that was purified by column chromatography. Gradient elution with hexanes–ethyl acetate (9 : 1 ⟶ 4 : 1) afforded dialdehyde **19** (33 mg, 0.056 mmol, 82%) as an oil; $[\alpha]_D^{22}$ +54 (*c* 0.66, $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ −0.04 (6 H, s, Me), 0.00 (6 H, s, Me), 0.82 (18 H, s, Me), 3.93–4.00 (2 H, m, 2,5- or 3,4-H), 4.03–4.10 (2 H, m, 3,4- or 2,5-H), 4.41 (2 H, d, *J* 11.6, PhCH_2), 4.62 (2 H, d, *J* 11.6, PhCH_2), 7.21–7.31 (10 H, m, Ar), 9.72 (2 H, s, C*H*O); ^{13}C NMR. ($CDCl_3$) δ −4.2 (q), 18.3 (s), 26.2 (q), 73.3 (t), 75.1 (d), 84.3 (d), 128.4 (d), 128.7 (d), 128.8 (d), 137.5 (s), 201.8 (d); *m*/*z* (FAB) 587.3214 [(M + H)$^+$, $C_{32}H_{51}O_6Si_2$ requires 587.3224], 797 (1%), 587 (1%), 277 (5), 181 (10), 91 (100), 73 (15).

N-Benzyl-3,6-di-*O*-benzyl-4,5-bis-*O*-(*tert*-butyldimethylsilyl)-L-*ido*-3,4,5,6-tetrahydroxyazepane (20)

Benzylamine (15 μL, 0.14 mmol) was added to a stirred mixture of the dialdehyde **19** (33 mg, 0.056 mmol), $NaCNBH_3$ (10 mg, 0.16 mmol), AcOH (17 μL, 0.30 mmol) and 3 Å sieves (200 mg) in MeOH (5 mL) at −78 °C under argon. The reaction mixture was allowed to warm to room temperature over 18 h, then filtered through Celite. The solvent was removed from the filtrate under reduced pressure and the residue was partitioned between ethyl acetate (50 mL) and $NaHCO_3$ (saturated, aqueous 50 mL). The aqueous phase was further extracted with ethyl acetate (2 × 50 mL) and the combined organic extracts were dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure to give the crude product that was purified by column chromatography. Gradient elution with CH_2Cl_2–MeOH (1 : 0 ⟶ 200 : 1) afforded the title compound (22 mg, 0.033 mmol, 59%) as an oil; $[\alpha]_D^{22}$ +9.1 (*c* 0.44, $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ −0.09 (6 H, s), 0.00 (6 H, s), 0.78 (18 H, s), 2.65–2.70 (2 H, m), 3.60–3.80 (4 H, m), 3.86–3.89 (2 H, m), 4.35–4.55 (4 H, m), 7.15–7.30 (15 H, m, Ar); ^{13}C NMR. ($CDCl_3$) δ −4.3 (t), −4.2 (t), 18.4 (s), 26.3 (q), 52.3 (t), 63.0 (t), 71.4 (t), 78.6 (d), 82.0 (d), 127.4 (d), 127.6 (d), 127.8 (d), 128.5 (d), 129.6 (d), 139.4 (s); *m*/*z* (FAB) 662.4046 [(M + H)$^+$, $C_{39}H_{60}NO_4Si_2$ requires 662.4061], 662 (30%), 171 (10), 91 (100), 73 (50).

Acknowledgements

The authors thank the Foundation for Research, Science and Technology for financial support (Science and Technology Post-Doctoral Fellowship, contract # C08821 to G. F. P. and Public Good Science Fund, contract # C08811-D, to A. F.) and Dr Richard Furneaux for his role as team leader. Prof Robin Ferrier assisted with the preparation of the manuscript.

References

1 B. G. Winchester and G. W. J. Fleet, *Glycobiology*, 1992, **2**, 199.
2 *Iminosugars as Glycosidase Inhibitors. Nojirimycin and Beyond*, ed. A. E. Stütz, Wiley-VCH, Weinheim, 1999.
3 H. Paulsen and K. Todt, *Chem. Ber.*, 1967, **100**, 512.
4 L. Poitout, Y. Le Merrer and J.-C. Depezay, *Tetrahedron Lett.*, 1994, **35**, 3293.
5 R. A. Farr, A. K. Holland, E. W. Huber, N. P. Peet and P. M. Weintraub, *Tetrahedron*, 1994, **50**, 1033.
6 B. B. Lohray, Y. Jayamma and M. Chatterjee, *J. Org. Chem.*, 1995, **60**, 5958.
7 F. Morís-Varas, X. Qian and C.-H. Wong, *J. Am. Chem. Soc.*, 1996, **118**, 7647.
8 X. Qian, F. Morís-Varas, M. C. Fitzgerald and C.-H. Wong, *Bioorg. Med. Chem.*, 1996, **4**, 2055.
9 Y. Le Merrer, L. Poitout, J.-C. Depezay, I. Dosbaa, S. Geoffroy and M.-J. Foglietti, *Bioorg. Med. Chem.*, 1997, **5**, 519.
10 P. R. Andreana, T. Sanders, A. Janczuk, J. I. Warrick and P. G. Wang, *Tetrahedron Lett.*, 2002, **43**, 6525.
11 C. C. Joseph, H. Regeling, B. Zwanenburg and G. J. F. Chittenden, *Tetrahedron*, 2002, **58**, 6907.
12 J. N. Tilekar, N. T. Patil, H. S. Jadhav and D. D. Dhavale, *Tetrahedron*, 2003, **59**, 1873.
13 G. F. Painter, P. J. Elridge and A. Falshaw, *Bioorg. Med. Chem.*, 2004, **12**, 225.
14 G. F. Painter and A. Falshaw, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1157.
15 A. Falshaw, J. B. Hart and P. C. Tyler, *Carbohydr. Res.*, 2000, **329**, 301.
16 C. Liu, R. J. Davis, S. R. Nahorski, S. Ballereau, B. Spiess and B. V. L. Potter, *J. Med. Chem.*, 1999, **42**, 1991.
17 E. A. Shneour and C. E. Ballou, *J. Am. Chem. Soc.*, 1958, **80**, 3960.
18 T. Mikami, H. Asano and O. Mitsunobu, *Chem. Lett.*, 1987, 2033.
19 B. M. Malle, I. Lundt and R. H. Furneaux, *J. Carbohydr. Chem.*, 2000, **19**, 573.
20 J. Honeyman and C. J. G. Shaw, *J. Chem. Soc.*, 1959, 2454.
21 E. L. Eliel and H. Satici, *J. Org. Chem.*, 1994, **59**, 688.
22 M. A. Tius and J. Busch-Petersen, *Tetrahedron Lett.*, 1994, **35**, 5181.
23 T. Hosoya, Y. Ohashi, T. Matsumoto and K. Suzuki, *Tetrahedron Lett.*, 1996, **37**, 663.
24 H. Yamada, M. Nakatani, T. Ikeda and Y. Marumoto, *Tetrahedron Lett*, 1999, **40**, 5573.
25 S. Shuto, M. Terauchi, Y. Yahiro, H. Abe, S. Ishikawa and A. Matsuda, *Tetrahedron Lett*, 2000, **41**, 4151.
26 H. Abe, S. Shuto and A. Matsuda, *J. Am. Chem. Soc.*, 2001, **123**, 11870.
27 E. J. Corey, H. Cho, C. Rücker and D. H. Hua, *Tetrahedron Lett.*, 1981, **22**, 3455.
28 J. D. Stevens and H. G. Fletcher, *J. Org. Chem.*, 1968, **33**, 1799.
29 G. Kotowycz and R. U. Lemieux, *Chem. Rev.*, 1973, **73**, 669.
30 R. U. Lemieux and A. A. Pavia, *Can. J. Chem.*, 1968, **46**, 1453.
31 R. U. Lemieux, A. A. Pavia, J. C. Martin and K. A. Watanabe, *Can. J. Chem.*, 1969, **47**, 4427.
32 D. H. Whiffen and J. H. Brewster, *J. Am. Chem. Soc.*, 1959, **81**, 5483; R. U. Lemieux and J. C. Martin, *Carbohydr. Res.*, 1970, **13**, 139.
33 A. Ault, *J. Chem. Educ.*, 1970, **47**, 812.
34 H. Paulsen, W. von Deyn and W. Röben, *Liebigs Ann. Chem.*, 1984, 433.