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An improved synthesis of evernitrose*

Peter Jütten and Hans-Dieter Scharf†
Institut für Organische Chemie der RWTH Aachen, Prof.-Pirlet-Strasse 1, D-5100 Aachen (F.R.G.)

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ABSTRACT

Evernitrose (**13**, 2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-L-*arabino*-hexopyranose), a constituent of the everninomicin oligosaccharide antibiotics, was synthesised from methyl 2,4-di-*O*-acetyl-3,6-dideoxy-3-*C*-methyl-3-nitro-α-L-*gluco*-hexopyranoside (**2**) in a yield of 16% on a gram scale and avoiding chromatographic separations. Nitro diacetate **2**, obtained by the dialdehyde–nitroethane cyclisation of methyl α-L-rhamnopyranoside (**1**), was subjected in sequence to hydrogenolysis, *N*-acetylation, regioselective 2-*O*-pivaloylation, and 4-*O*-methylation, to give methyl 3-acetamido-3,6-dideoxy-3-*C*-methyl-4-*O*-methyl-2-*O*-pivaloyl-α-L-glucopyranoside (**6**). Photodeoxygenation (254 nm) of ester **6** in a mixture of hexamethylphosphoric triamide and water gave methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-α-L-*arabino*-hexopyranoside (**8**). Reductive deprotection of **8** afforded methyl 3-amino-2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-α-L-*arabino*-hexopyranoside (**9**), a constituent of antibiotic complex 13-384 component 5. Oxidation of **9** with 3-chloroperoxybenzoic acid furnished the methyl glycoside **11**, hydrolysis of which gave **13**. Reduction of **11** with zinc/ammonium chloride gave methyl 2,3,6-trideoxy-3-hydroxyamino-3-*C*-methyl-4-*O*-methyl-α-L-*arabino*-hexopyranoside (**12**). Whereas acetamido groups considerably enhanced the rate of photodeoxygenation, nitro groups were not compatible with the reaction conditions.

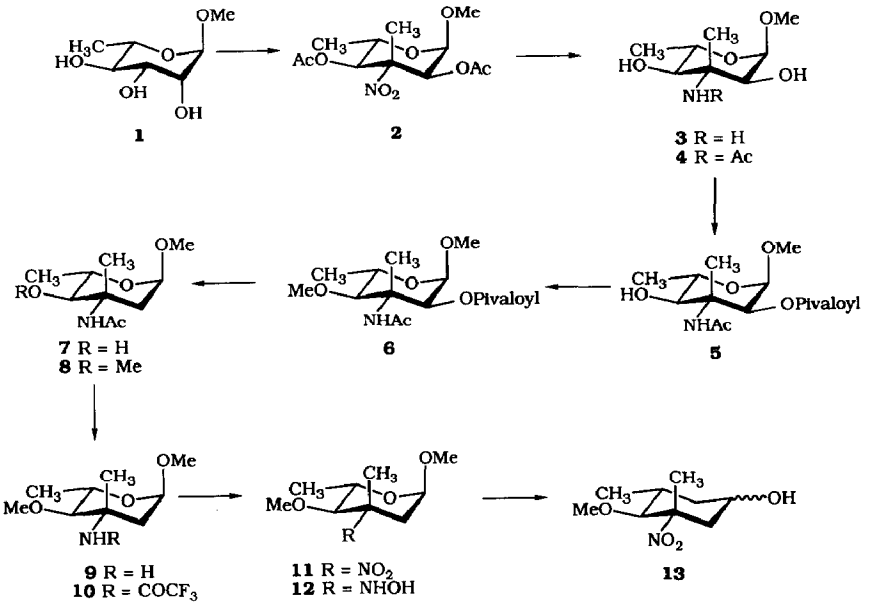
INTRODUCTION

Evernitrose (**13**) is a branched-chain nitro sugar that is a constituent[2,3] of everninomicins B, C, and D, and the related antibiotic 13-384-1, produced by strains of *Micromonospora carbonacea* of the variants *carbonacea* (NRRL 2972), *aurantiaca* (NRRL 2997), and *africana* (NRRL 15099), respectively. The L-*arabino* structure of **13** was assigned unambiguously by X-ray analysis of the 3-acetamido derivative[4].

With few exceptions, syntheses of naturally occurring branched-chain nitro and aminodeoxy sugars[5] rely on the introduction of a geminal methyl group and nitrogen functionality at C-3 *via* intermediate spiro-aziridines and subsequent reductive ring opening. The cyanomesylation approach to spiro-aziridines was used in the first synthesis of both enantiomers of evernitrose[6–8]. However, the preparation of spiro-aziridines invariably involves 2-deoxyhexopyranosid-3-uloses, which, in the L-series, are obtained only by tedious multi-step sequences with a poor overall yield.

Our studies[9,10] of the synthesis of everninomicin subunits that contain an L-evernitrose residue led to the dialdehyde–nitroethane cyclisation[11] as applied[12,13] to methyl α-L-rhamnopyranoside. The resulting *C*-nitroglycoside had already been trans-

* Reactions of Partial Acylated Aldohexopyranosides, Part VII. For Part VI, see ref. 1.
† Author for correspondence.



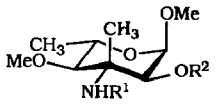
formed[14] into methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-α-L-*arabino*-hexopyranoside (**8**), a fairly good precursor of evernitrose. Deoxygenation at C-2, however, *via* the traditional glycal route or following the procedure developed by Barton and McCombie[15] was unsatisfactory because of the need for chromatographic separations in the former method and the low yield in the latter. On the other hand, the photochemical deoxygenation of sugar esters in mixtures of hexamethylphosphoric triamide and water with light of 254 nm has been used[1,16,17] successfully for the preparation of various deoxy sugars.

RESULTS AND DISCUSSION

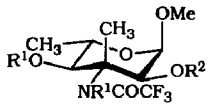
Oxidation of methyl α-L-rhamnopyranoside[18] (**1**) with aqueous sodium periodate and Henry reaction of the resulting dialdehyde with nitroethane gave[12,13] a mixture of diastereoisomers from which methyl 2,4-di-*O*-acetyl-3,6-dideoxy-3-*C*-methyl-3-nitro-α-L-*gluco*-hexopyranoside (**2**) was crystallised. Some modifications of this reaction[13] and acetylation of the products with acetic anhydride either in pyridine or in the presence of a catalytic amount of boron trifluoride afforded a solid mixture from which **2** (25–26%) was isolated by fractional crystallisation. Although the yield was modest, large amounts (42–45 g) of **2** could be prepared from L-rhamnose hydrate (100 g), the cheapest commercially available L sugar.

Reduction of the nitro group in **2** over Raney nickel occurred with concomitant deacetylation to give the aminodeoxy sugar **3** (85%). Chemoselective protection with acetic anhydride in ethanol[19] gave the acetamido derivative **4** (75%).

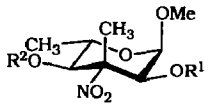
Esters of sterically hindered aliphatic carboxylic acids such as pivalates are deoxygenated more efficiently by irradiation (254 nm) in mixtures of hexamethyl-



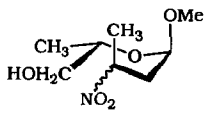
14 R^1 = Ac; R^2 = Me
15 R^1 = H; R^2 = Pivaloyl



16 R^1 = R^2 = H
17 R^1 = H; R^2 = Pivaloyl
18 R^1 = Me; R^2 = Pivaloyl



19 R^1 = R^2 = H
20 R^1 = H; R^2 = Ac
21 R^1 = Pivaloyl; R^2 = H
22 R^1 = Pivaloyl; R^2 = Me
23 R^1 = Ts; R^2 = H
24 R^1 = Ts; R^2 = Ac
25 R^1 = Ms; R^2 = Ac
26 R^1 = Ms; R^2 = H



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phosphoric triamide and water than acetates and aromatic esters[20,21]. Treatment of **4** with pivaloyl chloride at low temperature afforded the 2-pivalate **5** in a yield of 81%. No trace of the 4-pivalate was detected (t.l.c.). Sterically unfavourable *gauche* interactions with the adjacent methyl groups at C-3,5 and with the nitrogen functionality, together with the neopentyl structure in **4**, might explain the low reactivity of HO-4 (see below).

Controlled treatment of **5** with iodomethane and sodium hydride in tetrahydrofuran gave methyl 3-acetamido-3,6-dideoxy-3-*C*-methyl-4-*O*-methyl-2-*O*-pivaloyl-α-L-glucopyranoside (**6**, 76%). With iodomethane and silver(I) oxide in *N,N*-dimethylformamide, **5** afforded 64% of **6**, after crystallisation, and 20% of the di-*O*-methyl derivative **14**.

Although various hydroxyl-protecting groups are compatible[16,21] with the photochemical deoxygenation process, little is known[21,22] about *N*-protecting groups. Therefore, the photolysis of methyl 3-amino-3,6-dideoxy-3-*C*-methyl-4-*O*-methyl-2-*O*-pivaloyl-α-L-glucopyranoside (**15**) was studied first.

Trifluoroacetyl is a readily removable[23] *N*-protecting group. Mild *N*-trifluoroacetylation[24] of **3** with ethyl trifluoroacetate and triethylamine in methanol gave **16**, reaction of which with pivaloyl chloride, as described for the acetamido derivative **4**, afforded the 2-pivalate **17**. However, the strong inductive effect of the trifluoromethyl group enhanced the acidity of the amide proton, so that treatment of **17** with iodomethane and silver oxide in *N,N*-dimethylformamide gave the *N,O*-dialkylated compound **18**.

Reaction of **6** with triethyloxonium tetrafluoroborate[25] effected *N*-deacetylation and gave the amine **15**, leaving the 2-pivalate group unaffected. Photodeoxygenation of **15** in hexamethylphosphoric triamide and water was complete within 24 h, but, due to the polarity of the free amino group, isolation of the product **9** was difficult and the yield was low.

The photolysis of sugar esters often required prolonged reaction times, typically 24 to 72 h and more, and sometimes complete conversion was difficult to achieve.

However, irradiation of the 2-pivaloylated acetamidoglycosides **5** and **6** in a Gräntzel reactor[26], under the usual conditions, was complete within 3 h to give **7** (58%) and **8** (79%), respectively, with no side reactions. A simple reactor has been described[27] for large-scale reactions, and photolysis of **6** was conducted in an improved[28] photoreactor made of quartz glass in which the circulating solution was irradiated by four mercury-vapour luminescent tubes. In this way, **8** was accessible easily on a gram scale. Methylation of **7** with iodomethane and sodium hydride also afforded **8**.

Whereas branched-chain sugars frequently resisted attempts to hydrolyse the acetamido group, using a variety of strong bases under aqueous conditions, *N*-deacetylation of **8** was accomplished readily with calcium in liquid ammonia[29] to give methyl 3-amino-2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-α-L-*arabino*-hexopyranoside (**9**), a constituent[3] of component 5 of the everninomicin antibiotic 13-384. *N*-Trifluoroacetylation of **9** gave **10**.

The oxidation of amines with 3-chloroperoxybenzoic acid is a convenient method for obtaining nitro compounds[30]. For large-scale preparations, the oxidation of **9**, obtained by *N*-deacetylation of **8**, and avoiding any purification step, was preferred. In this way, methyl evernitroside (**11**), hitherto known as a syrup[6-8], was obtained crystalline, after distillation, in a yield of 74% from **8**. The ^{1}H-n.m.r. spectrum of **11** indicated a $^1C_4$(L) conformation, and a W-coupling of 0.7 Hz of the axial H-2 with Me-3 was observed, thus proving the stereochemistry at the tertiary carbon. Hydrolysis of **11** in 0.05M sulfuric acid gave L-evernitrose (**13**).

In order to improve the pharmacokinetics of everninomicin antibiotics with retention of antimicrobial activity, Ganguly *et al.*[31,32] investigated modifications of the nitro sugar moiety, including the hydroxyamino derivatives. Hydroxylamines have been obtained from amines by mild oxidation[33], and reduction of nitro compounds with inexpensive metal reagents provides a reasonable alternative[34]. Reaction of **11** with zinc in the presence of ammonium chloride gave methyl 2,3,6-trideoxy-3-*C*-hydroxyamino-3-*C*-methyl-4-*O*-methyl-α-L-*arabino*-hexopyranoside (**12**, 71%).

The simple and efficient synthesis for L-evernitrose (**13**) described above prompted a synthesis of methyl 3,6-dideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-2-*O*-pivaloyl-α-L-*gluco*-hexopyranoside (**22**) from the parent diol **19**, thus avoiding the reduction of the nitro group before 2-deoxygenation. Although oxidation of the amine **3** with 3-chloroperoxybenzoic acid gave **19**, the yield was unsatisfactory. Hydrolysis of **2** could provide a more concise approach, but, in alkaline media, such nitro sugars as **19** would be susceptible to epimerisation at C-2,3,4 *via* a retro-Henry reaction and subsequent recyclisation. The greater reactivity of HO-2 on treatment with pivaloyl chloride in pyridine has been noted above. Conversely, the greater reactivity at position 2 is reflected in an enhanced lability of AcO-2 in **2** towards acid-catalysed methanolysis which afforded a mixture of the 4-acetate **20** (53%) and the diol **19** (45%) after 3 h. Complete *O*-deacetylation required longer reaction times and gave methyl 3,6-dideoxy-3-*C*-methyl-3-nitro-α-L-*gluco*-hexopyranoside (**19**, 84%).

Pivaloylation of **19** and subsequent 4-*O*-methylation gave the 2-pivalate derivatives **21** and **22**, respectively. The photodeoxygenation of sugar esters in hexamethyl-

phosphoric triamide and water is initiated by photoionisation of the amide[17]. The resulting solvated electrons reduce the ester to its radical anion, which decomposes to give carboxylate anions and a radical of the deoxy sugar. Hydrogen abstraction then yields the alkane. On the other hand, tertiary nitro compounds can be reduced electrochemically[31,35] and by alkali metals[35] to give unstable nitro anions, which cleave to yield nitrite ion and a free radical. Competition of photodeoxygenation and denitrohydrogenation might explain the complex mixture of products obtained by photolysis (254 nm) of **21** and **22**.

2-Sulfonyloxy groups of hexopyranosides are highly resistant to intermolecular nucleophilic displacement because of unfavourable alignment of dipoles in the transition state[36]. The replacement of 2-substituents in unbranched 3-deoxy-3-nitro sugars with various nucleophiles involves[37] an elimination–addition mechanism and an intermediate nitro-olefin. The 2-*O*-tosyl (**23**) and 2-*O*-mesyl (**26**) derivatives were prepared by regioselective sulfonylation of **19** and from the 4-acetate **20** in two steps (**20**→**25**→**26**), respectively. Attempted deoxygenation of both compounds with sodium borohydride in ethanol[38] gave the acyclic compound **27**, presumably *via* β-elimination of the 4-alkoxide and rapid reduction of the aldehyde and nitro-olefin functionality.

EXPERIMENTAL

General methods. — Melting points were determined with a Büchi 510 melting-point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. N.m.r. spectra were recorded with a Varian VXR 300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) instrument. I.r. spectra were recorded with a Perkin–Elmer FT 1750 spectrophotometer. E.i.-mass spectra were obtained with a Varian MAT 212 spectrometer (70 eV, 1 mA, 200°). T.l.c. was performed on Alugram SIL G/UV$_{254}$ (Macherey–Nagel). For column chromatography, Silica Gel 60 (0.063–0.1 mm; Merck) was used.

*Methyl 2,4-di-*O*-acetyl-3,6-dideoxy-3-*C*-methyl-3-nitro-α-*L*-gluco-hexopyranoside* (**2**). — A solution of methyl α-L-rhamnopyranoside (**1**, 92 g), prepared[18] from L-rhamnose hydrate (100 g, 0.55 mol), in water (750 mL) was treated in portions with sodium periodate (200 g) during 30 min whilst crushed ice was added to maintain a temperature of 20–30°. After 30 min, the mixture was neutralised with solid sodium hydrogen carbonate (~47 g), poured into ethanol (4 L), filtered, and concentrated. The residue was extracted with boiling ethanol (1 L), and the extract was cooled, filtered, and treated with nitroethane (100 mL) followed by a solution of sodium ethoxide (from 12 g of sodium) in ethanol (500 mL). The mixture was stirred at room temperature overnight, neutralised with powdered potassium hydrogen sulfate, filtered, and concentrated. The syrupy residue was extracted with ether (1.5 L), and the extract was concentrated to give a pale-yellow, syrupy mixture of nitrodiols (~66 g) which crystallised partially on scratching or seeding. The mixture was treated at room temperature either with acetic anhydride (180 mL) and pyridine (240 mL) for 24 h or acetic anhydride (300 mL) and boron trifluoride etherate (1 mL) for 2 h at <40°. Conventional work-up gave a solid mixture (92–96 g), and fractional crystallisation from 2:1 ether–hexane afforded **2**

(42–45 g, 25–26%). Recrystallisation from ethanol gave material with m.p. 135–137°, $[\alpha]_D^{22}$ −135° (*c* 1.06, chloroform); lit.[12] m.p. 137.5–138°, $[\alpha]_D^{20}$ −133° (chloroform); lit.[13] m.p. 137–138°, $[\alpha]_D$ −130° (chloroform); ν_{max}^{KBr} 1750 (C=O), 1545, 1380 cm^{-1} (NO_2). N.m.r. data ($CDCl_3$): ^1H, δ 1.22 (d, 3 H, Me-5), 1.87 (s, 3 H, Me-3), 2.07 (2 s, 6 H, OAc), 3.39 (s, 3 H, OMe), 3.86 (dq, 1 H, H-5), 5.02 (d, 1 H, H-1), 5.33 (d, 1 H, H-4), 5.59 (d, 1 H, H-2); $J_{1,2}$ 4.2, $J_{4,5}$ 9.9, $J_{5,6}$ 6.3 Hz; ^{13}C, δ 13.20 (Me-3), 17.27 (C-6), 20.40, 20.51 (CH_3COO), 55.86 (OMe), 64.07 (C-5), 71.74 (C-2), 74.31 (C-4), 91.42 (C-3), 96.38 (C-1), 168.73, 169.29 (Me*C*OO).

Anal. Calc. for $C_{12}H_{19}NO_8$ (305.3): C, 47.21; H, 6.27; N, 4.59. Found: C, 47.10; H, 6.29; N, 4.66.

Methyl 3-amino-3,6-dideoxy-3-C-methyl-α-L-glucopyranoside (**3**). — A mixture of **2** (42.5 g, 139.2 mmol), methanol (500 mL), and Raney nickel (70 g) was hydrogenated at 40 bar for 24 h. Celite (20 g) was added, the mixture was filtered and concentrated, and the residue was recrystallised from chloroform to give **3** (22.7 g, 85%), m.p. 152–154°, $[\alpha]_D^{24}$ −136° (*c* 1.01, methanol); lit.[12] m.p. 151–152°, $[\alpha]_D^{20}$ −130° (acetone); ν_{max}^{KBr} 3300–3500 cm^{-1} (NH_2 and OH). N.m.r. data [$(CD_3)_2SO$]: ^1H, δ 1.00 (s, 3 H, Me-3), 1.11 (d, 3 H, Me-5), 2.87 (d, 1 H, H-4), 3.23 (s, 3 H, OMe), 3.28 (d, 1 H, H-2), 3.43 (dq, 1 H, H-5), 4.42 (d, 1 H, H-1); $J_{1,2}$ 4.2, $J_{4,5}$ 9.7, $J_{5,6}$ 6.0 Hz; ^{13}C, δ 17.32, 18.11 (Me-3 and C-6), 54.68 (OMe), 56.03 (C-3), 65.33, 74.15, 77.80 (C-2,4,5), 99.75 (C-1).

Anal. Calc. for $C_8H_{17}NO_4$ (191.2): C, 50.26; H, 8.96; N, 7.33. Found: C, 50.05; H, 8.99; N, 7.32.

Methyl 3-acetamido-3,6-dideoxy-3-C-methyl-α-L-glucopyranoside (**4**). — To a solution of **3** (23.0 g, 120.3 mmol) in ethanol (240 mL) at 50° was added acetic anhydride (25 mL). The mixture was concentrated, and toluene was evaporated several times from the residue, which was crystallised from ethyl acetate to give **4** (20.3 g, 75%), m.p. 141–143°, $[\alpha]_D^{24}$ −119° (*c* 1.03, chloroform); lit.[13] m.p. 144–145°, $[\alpha]_D$ −118° (chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.31 (d, 3 H, Me-5), 1.38 (s, 3 H, Me-3), 2.03 (s, 3 H, NAc), 3.38 (d, 1 H, H-4), 3.40 (s, 3 H, OMe), 3.60 (d, 1 H, H-2), 3.67 (dq, 1 H, H-5), 4.67 (d, 1 H, H-1), 6.41 (bs, 1 H, NH); $J_{1,2}$ 4.2, $J_{4,5}$ 9.4, $J_{5,6}$ 6.0 Hz; ^{13}C, δ 13.66 (Me-3), 17.99 (C-6), 24.02 (CH_3CON), 55.51 (OMe), 63.12 (C-3), 65.76, 72.86, 76.03 (C-2,4,5), 98.74 (C-1), 171.52 (CONH).

Anal. Calc. for $C_{10}H_{19}NO_5$ (233.3): C, 51.48; H, 8.21; N, 6.00. Found: C, 51.57; H, 8.15; N, 6.14.

Methyl 3-acetamido-3,6-dideoxy-3-C-methyl-2-O-pivaloyl-α-L-glucopyranoside (**5**). — To a stirred solution of **4** (20.1 g, 86.2 mmol) in dry pyridine (260 mL) at −15° was added, during 90 min with exclusion of moisture, a solution of pivaloyl chloride (15.8 g, 129.5 mmol) in dry dichloromethane (40 mL). Stirring was continued overnight, and the mixture was allowed to attain room temperature slowly. T.l.c. (ethyl acetate) then indicated that the reaction was complete. Dichloromethane and pyridine were distilled-off under reduced pressure, dichloromethane was added to the residue, and the solution was washed successively with cold aqueous 10% sulfuric acid (half-saturated with brine), saturated aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and concentrated. Recrystallisation of the residue from ethyl acetate–hexane gave **5**

(22.2, 81%), m.p. 180–182°, $[\alpha]_D^{24}$ −84° (*c* 1.05, chloroform); ν_{max}^{KBr} 3200–3400 (CONH and OH), 1730 (^{t}BuC=O), 1660 cm^{-1} (CONH). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.27 (s, 9 H, ^{t}Bu), 1.32 (d, 3 H, Me-5), 1.49 (s, 3 H, Me-3), 1.95 (s, 3 H, NAc), 3.36 (s, 3 H, OMe), 3.57 (dd, 1 H, H-4), 3.70 (dq, 1 H, H-5), 4.67 (d, 1 H, H-1), 4.82 (d, 1 H, H-2), 6.20 (d, 1 H, OH), 6.58 (bs, 1 H, NH); $J_{1,2}$ 4.3, $J_{4,5}$ 9.5, $J_{4,HO-4}$ 1.0, $J_{5,6}$ 6.1 Hz; ^{13}C, δ 13.86 (Me-3), 17.84 (C-6), 24.05 (*C*H$_3$CON), 27.04 (*Me*$_3$C), 39.31 (Me$_3$*C*), 55.59 (OMe), 62.77 (C-3), 65.76, 73.57, 77.43 (C-2,4,5), 96.97 (C-1), 171.54 (CONH), 179.92 (^{t}Bu*C*OO).

Anal. Calc. for $C_{15}H_{27}NO_6$ (317.4): C, 56.76; H, 8.57; N, 4.41. Found: C, 56.93; H, 8.57; N, 4.45.

*Methyl 3-acetamido-3,6-dideoxy-3-*C*-methyl-4-*O*-methyl-2-*O*-pivaloyl-α-*L*-gluco-pyranoside* (**6**). — (*a*) A stirred solution of **5** (31.0 g, 97.7 mmol) in dry tetrahydrofuran (300 mL) was treated with oil-free sodium hydride (2.8 g, 116.7 mmol) until the evolution of gas ceased. The mixture was cooled in an ice-bath, a solution of iodomethane (45.0 g, 317.0 mmol) in tetrahydrofuran (50 mL) was added dropwise, and the mixture was stirred at room temperature until t.l.c. (3:1 chloroform–acetone) indicated that all starting material had disappeared. The excess of the reagents was destroyed with a few drops of conc. hydrochloric acid, the solvents were evaporated, and a solution of the residue in dichloromethane (300 mL) was washed with saturated aqueous sodium hydrogen carbonate, dilute aqueous sodium thiosulfate, and water, dried ($MgSO_4$), and concentrated. Recrystallisation of the residue from ethyl acetate–hexane gave small fine needles of **6** (24.9 g, 76%), m.p. 233–235°, $[\alpha]_D^{23}$ −96° (*c* 1.02, chloroform); ν_{max}^{KBr} 3300, 3200 (NH), 1730 (^{t}BuC=O), 1650 and 1560 cm^{-1} (CONH). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.22 (s, 9 H, ^{t}Bu), 1.29 (d, 3 H, Me-5), 1.36 (s, 3 H, Me-3), 1.92 (s, 3 H, NAc), 3.31 (s, 3 H, MeO-1), 3.49 (s, 3 H, MeO-4), 3.68 (dq, 1 H, H-5), 4.17 (d, 1 H, H-4), 4.86 (d, 1 H, H-1), 5.31 (bs, 1 H, NH), 5.77 (d, 1 H, H-2); $J_{1,2}$ 4.4, $J_{4,5}$ 9.8, $J_{5,6}$ 6.3 Hz; ^{13}C, δ 16.63 (Me-3), 18.00 (C-6), 24.32 (*C*H$_3$CON), 27.14 (*Me*$_3$C), 39.01 (Me$_3$*C*), 55.50 (MeO-1), 60.10 (C-3), 61.14 (MeO-4), 65.44, 69.27, 80.82 (C-2,4,5), 97.41 (C-1), 169.88 (CONH), 177.36 (^{t}Bu*C*OO).

Anal. Calc. for $C_{16}H_{29}NO_6$ (331.4): C, 57.99; H, 8.82; N, 4.23. Found: C, 58.06; H, 8.83; N, 4.33.

(*b*) To a solution of **5** (23.0 g, 72.5 mmol) in dry *N,N*-dimethylformamide (200 mL) and iodomethane (51.4 g, 362 mmol) was added freshly prepared silver oxide[39] (43.6 g, 188 mmol) during 60 min with vigorous stirring and cooling (ice–water). Stirring was continued overnight at room temperature, when t.l.c. (ethyl acetate) revealed **6** and the more polar compound **14**. The solids were collected, and washed with a small amount of *N,N*-dimethylformamide and then with chloroform. The combined filtrate and washings were diluted with chloroform (500 mL), filtered with the aid of Celite, and concentrated under reduced pressure at 40°→90° (bath). A solution of the solid residue in chloroform was washed twice with half-saturated brine and then water, dried ($MgSO_4$), and concentrated. Recrystallisation of the residue from ethyl acetate–hexane gave small needles of **6** (15.4 g, 64%).

Column chromatography (2:1 ethyl acetate–cyclohexane) of the material in the mother liquor gave **14** (3.8 g, 20%), m.p. 126–128° (from ethyl acetate–hexane), $[\alpha]_D^{23}$

$-103.5°$ (*c* 1.01, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.28 (d, 3 H, Me-5), 1.28 (s, 3 H, Me-3), 2.01 (s, 3 H, NAc), 3.38 (s, 3 H, MeO-1), 3.46, 3.49 (2 s, 6 H, MeO-2,4), 3.61 (dq, 1 H, H-5), 4.05 (d, 1 H, H-4), 4.50 (d, 1 H, H-2), 4.81 (d, 1 H, H-1), 5.66 (bs, 1 H, NH); $J_{1,2}$ 4.4, $J_{4,5}$ 10.1, $J_{5,6}$ 6.0 Hz; ^{13}C, δ 16.05 (Me-3), 18.07 (C-6), 24.55 (CH_3CON), 55.20 (MeO-1), 59.08, 61.15 (MeO-2,4), 61.20 (C-3), 65.25, 76.66, 81.00 (C-2,4,5), 97.47 (C-1), 170.26 (CONH).

Anal. Calc. for $C_{12}H_{23}NO_5$ (261.3): C, 55.16; H, 8.87; N, 5.36. Found: C, 55.07; H, 8.59; N, 5.42.

*Methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-α-*L*-arabino-hexopyranoside* (**7**). — A solution of **5** (1.60 g, 5 mmol) in hexamethylphosphoric triamide–water (50 mL; 97:3) was irradiated (254 nm) in a Gräntzel model 400 photoreactor[26] for 3 h in a slow stream of nitrogen. The solution was diluted with ether (500 mL), and washed with half-saturated brine (50 mL) and saturated brine (4 × 100 mL). The aqueous solutions were extracted with ether (2 × 100 mL) and the same ethereal solutions were used for the extraction of all aqueous layers. The combined ethereal solutions were dried ($MgSO_4$) and concentrated. Column chromatography (ethyl acetate) of the residue gave syrupy **7** (0.64 g, 58%), $[\alpha]_D^{21}$ $-128°$ (*c* 0.91, chloroform); lit.[14] $[\alpha]_D$ $-104°$ (chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.31 (d, 3 H, Me-5), 1.51 (s, 3 H, Me-3), 1.86 (dd, 1 H, H-2*ax*), 2.00 (s, 3 H, NAc), 2.03 (dd, 1 H, H-2*eq*), 3.31 (s, 3 H, OMe), 3.41 (d, 1 H, H-4), 3.63 (dq, 1 H, H-5), 4.71 (d, 1 H, *J* 4.0 Hz, H-1), 5.99 (bs, 1 H, NH); $J_{1,2ax}$ 4.0, $J_{1,2eq}$ 1.7, $J_{2ax,2eq}$ 13.4, $J_{4,5}$ 9.4, $J_{5,6}$ 6.0 Hz; ^{13}C, δ 18.17, 19.78 (Me-3 and C-6), 23.98 (CH_3CON), 41.33 (C-2), 54.77 (OMe), 57.56 (C-3), 65.63, 77.55 (C-3,5), 97.38 (C-1), 171.37 (CONH).

Anal. Calc. for $C_{10}H_{19}NO_4$ (217.3): C, 55.28; H, 8.81; N, 6.45. Found: C, 55.04; H, 8.82; N, 6.11.

*Methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-α-*L*-arabino-hexopyranoside* (**8**). — (*a*) A solution of **6** (24.85 g, 75 mmol) in hexamethylphosphoric triamide–water (820 mL; 97:3) was irradiated (254 nm) for 24 h in a quartz glass-photoreactor[27,28], using four tubular low-pressure mercury-vapour lamps (Philips TUV, 40 W, 254 nm). The mixture was diluted with ether (4 L), and washed with half-saturated (1 L) and then saturated brine (4 × 1 L). Each aqueous solution was extracted with ether (2 × 1 L) and the same ethereal solutions were used for the extraction of all aqueous layers. The combined ethereal layers were dried ($MgSO_4$) and concentrated. Filtration (ethyl acetate–cyclohexane, 5:1) of the residue on a column of silica gel and recrystallisation from di-isopropyl ether–hexane gave **8** (13.7 g, 79%), m.p. 141–143°, $[\alpha]_D^{21}$ $-74°$ (*c* 1.03, chloroform); lit.[8] m.p. 140–141°, $[\alpha]_D^{22}$ $-75°$ (chloroform); lit.[14] m.p. 136–138°, $[\alpha]_D$ $-71°$ (chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.29 (d, 3 H, Me-5), 1.36 (s, 3 H, Me-3), 1.76 (dd, 1 H, H-2*eq*), 1.96 (s, 3 H, NAc), 2.99 (s, 1 H, H-2*ax*), 3.29 (s, 3 H, MeO-1), 3.49 (s, 3 H, MeO-4), 3.64 (dq, 1 H, H-5), 3.91 (d, 1 H, H-4), 4.68 (d, 1 H, *J* 4.4 Hz, H-1), 5.71 (bs, 1 H, NH); $J_{1,2ax}$ 4.5, $J_{1,2eq}$ 1.0, $J_{2ax,2eq}$ 14.1, $J_{4,5}$ 9.7, $J_{5,6}$ 6.4 Hz; ^{13}C, δ 18.41 (C-6), 21.87 (Me-3), 24.63 (CH_3CON), 38.53 (C-2), 54.65 (MeO-1), 56.35 (C-3), 61.20 (MeO-4), 65.61, 82.21 (C-4,5), 98.41 (C-1), 169.87 (CONH).

Anal. Calc. for $C_{11}H_{21}NO_4$ (231.3): C, 57.12; H, 9.15; N, 6.06. Found: C, 57.20; H, 9.20; N, 6.21.

(*b*) Oil-free sodium hydride (0.10 g, 4.2 mmol) was added to a solution of **7** (0.50 g, 2.3 mmol) in dry tetrahydrofuran (20 mL) followed, after 30 min, by iodomethane (0.70 g, 4.9 mmol). The solution was stirred for 18 h at room temperature, excess of reagent was destroyed by the addition of a few drops of methanol, and solvents were removed. The residue was partitioned between ether and half-saturated brine, and the organic layer was dried ($MgSO_4$) and concentrated. Recrystallisation of the residue from di-isopropyl ether–hexane gave **8** (0.44 g, 82%).

*Methyl 3-amino-2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-*α*-*L*-*arabino*-hexopyranoside* (**9**). — (*a*) A solution of **8** (3.31 g, 14.3 mmol) in 1,2-dimethoxyethane (150 mL) that contained ethanol (3 mL) was added at −78° to liquid ammonia (~ 500 mL), followed by calcium turnings (4.17 g, 0.104 g-atom). The deep blue solution was stirred at −78° for 5 h and the excess of reagent was destroyed with ethanol. Chloroform (500 mL) and water (60 mL) were added, the ammonia was allowed to evaporate, and the white precipitate was collected and washed with chloroform. The filtrate was dried ($MgSO_4$) and concentrated, and column chromatography (9:1 chloroform–methanol) of the residue gave **9** (1.60 g, 59%) as an oil, $[\alpha]_D^{23}$ −136° (*c* 1.39, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.28 (s, 3 H, Me-3), 1.29 (d, 3 H, Me-5), 1.74 (dd, 1 H, H-2*ax*), 1.89 (dd, 1 H, H-2*eq*), 2.74 (d, 1 H, H-4), 3.1 (b, 2 H, NH_2), 3.30 (s, 3 H, MeO-1), 3.58 (s, 3 H, MeO-4), 3.64 (dq, 1 H, H-5), 4.66 (d, 1 H, H-1); $J_{1,2ax}$ 4.4, $J_{1,2eq}$ 1.0, $J_{2ax,2eq}$ 13.8, $J_{4,5}$ 9.7, $J_{5,6}$ 6.4 Hz; ^{13}C, δ 18.47 (C-6), 22.61 (Me-3), 43.06 (C-2), 52.75 (C-3), 54.70 (MeO-1), 62.21 (MeO-4), 65.99 (C-5), 90.49 (C-4), 98.18 (C-1).

(*b*) A solution of **15** (0.50 g, 1.7 mmol) in hexamethylphosphoric triamide–water (20 mL; 97:3) was irradiated at 254 nm in a Gräntzel model 400 photoreactor[26] for 24 h. The mixture was diluted with ether (150 mL), washed with saturated brine (3 × 50 mL), dried ($MgSO_4$), and concentrated. Column chromatography (chloroform–methanol, 50:1→10:1) of the residue gave **9** (0.05 g, 15%).

*Methyl 2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-3-trifluoroacetamido-α-L-arabino-hexopyranoside* (**10**). — To a solution of **9** (2.0 g, 10.6 mmol) in dry pyridine (25 mL) at 0° was added dropwise trifluoroacetic anhydride (6.5 mL). The mixture was stirred for 3 h at room temperature, poured into ice–water, and extracted with dichloromethane. The extract was washed successively with cold aqueous 10% sulfuric acid, water, saturated aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and concentrated. Recrystallisation of the residue from di-isopropyl ether–hexane gave **10** (2.4 g, 84%), m.p. 102–104°, $[\alpha]_D^{25}$ −50.5° (*c* 1.02, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.31 (m, 3 H, Me-5), 1.48 (s, 3 H, Me-3), 1.96 (dd, 1 H, H-2*eq*), 2.77 (dd, 1 H, H-2*ax*), 3.30 (s, 3 H, MeO-1), 3.49 (s, 3 H, MeO-4), 3.70 (m, 2 H, H-4,5), 4.71 (d, 1 H, *J* 3.7 Hz, H-1), 6.17 (bs, 1 H, NH); $J_{1,2ax}$ 4.7, $J_{1,2eq}$ 1.0, $J_{2ax,2eq}$ 13.8 Hz; ABX_3 system with virtual coupling for Me-5 (1.31), H-4 (3.68), and H-5 (3.70): $J_{4,5}$ 9.7, $J_{5,6}$ 6.0 Hz; ^{13}C, δ 18.38 (C-6), 21.36 (Me-3), 38.25 (C-2), 54.81 (MeO-1), 58.21 (C-3), 61.43 (MeO-4), 65.54 (C-5), 82.69 (C-4), 97.95 (C-1), 115.54 (q, $^1J_{C,F}$ 288 Hz, CF_3), 156.20 (q, $^2J_{C,F}$ 36 Hz, CF_3CON).

Anal. Calc. for $C_{11}H_{18}F_3NO_4$ (285.3): C, 46.31; H, 6.36; N, 4.91. Found: C, 46.35; H, 6.34; N, 5.01.

*Methyl 2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-α-L-arabino-hexopyrano-*

side (**11**, *methyl evernitroside*). — A solution of **8** (13.7 g, 59.2 mmol) in 1,2-dimethoxyethane (250 mL) and ethanol (12 mL) was added to liquid ammonia (~1200 mL) at −78°, followed by calcium turnings (21.8 g, 0.545 g-atom). The resulting deep-blue solution was stirred at −78° for 24 h and excess of reagent was destroyed by the addition of ethanol. Chloroform (750 mL) and water (40 mL) were added, the ammonia was allowed to evaporate, and the white precipitate was collected with the aid of Celite (20 g) and washed with chloroform. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude amine **9** as a yellow oil, a solution of which in dichloromethane (250 mL) was added during 60 min to a boiling solution of 3-chloroperoxybenzoic acid (54.6 g, 316.3 mmol) in dichloromethane (650 mL). The mixture was washed successively with aqueous 10% sodium hydrogen sulfite, aqueous 10% sodium hydroxide, and water, dried ($MgSO_4$), and concentrated. The residual oil was distilled at 61–63°/0.01 mbar to give solid **11** (9.7 g, 74%), recrystallisation of which from hexane gave needles with m.p. 42–43°, $[\alpha]_D^{22}$ −115° (*c* 1.19, chloroform); lit.[8] $[\alpha]_D^{22}$ −103° (chloroform); lit.[7] for D-**11**, $[\alpha]_D^{22}$ +95.4° (chloroform); ν_{max} 1545, 1350 cm^{-1} (NO_2). N.m.r. data ($CDCl_3$): ^1H, δ 1.34 (d, 3 H, Me-5), 1.76 (d, 3 H, Me-3), 2.15 (dd, 1 H, H-2*eq*), 2.44 (ddd, 1 H, H-2*ax*), 3.31 (s, 3 H, MeO-1), 3.42 (s, 3 H, MeO-4), 3.66 (dq, 1 H, H-5), 3.76 (d, 1 H, H-4), 4.75 (dd, 1 H, H-1); $J_{1,2ax}$ 4.7, $J_{1,2eq}$ 1.3, $J_{2ax,2eq}$ 13.4, $J_{2ax,Me\text{-}3}$ 0.7, $J_{4,5}$ 9.7, $J_{5,6}$ 6.0 Hz; ^{13}C, δ 18.30, 18.47 (Me-3 and C-6), 40.97 (C-2), 54.94 (MeO-1), 60.76 (MeO-4), 65.90, 84.64 (C-4,5), 90.39 (C-3), 97.12 (C-1).

Anal. Calc. for $C_9H_{17}NO_5$ (219.2): C, 49.30; H, 7.82; N, 6.39. Found: C, 49.24; H, 7.78; N, 6.13.

*Methyl 2,3,6-trideoxy-3-hydroxyamino-3-C-methyl-4-O-methyl-α-*L-arabino-*hexopyranoside* (**12**). — To a solution of **11** (0.33 g, 1.5 mmol) in peroxide-free tetrahydrofuran (30 mL) was added zinc powder (0.90 g) followed, dropwise, by aqueous 10% ammonium chloride (3 mL). The slurry was stirred under argon for 30 min at room temperature, when monitoring by t.l.c. (1:1 ethyl acetate–cyclohexane) indicated that the reaction was complete. The mixture was filtered and concentrated, and the residue was partitioned between dichloromethane and saturated brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (ethyl acetate) of the residue gave **12** (0.22 g, 71%), $[\alpha]_D^{24}$ −126° (*c* 0.98, chloroform); ν_{max}^{liquid} 3440, 3260 cm^{-1} (NH and OH). N.m.r. data ($CDCl_3$): ^1H, δ 1.11 (s, 3 H, Me-3), 1.31 (d, 3 H, Me-5), 1.67 (d, 1 H, H-2*eq*), 2.18 (dd, 1 H, H-2*ax*), 3.26 (d, 1 H, H-4), 3.31 (s, 3 H, MeO-1), 3.55 (s, 1 H, MeO-4), 3.72 (dq, 1 H, H-5), 4.73 (d, 1 H, H-1), 5–7 (b, OH and NH); $J_{1,2ax}$ 4.7, $J_{2ax,2eq}$ 13.8, $J_{4,5}$ 9.7, $J_{5,6}$ 6.4 Hz; ^{13}C, δ 17.80, 18.55 (Me-3 and C-6), 37.49 (C-2), 54.73 (MeO-1), 59.73 (C-3), 61.30 (MeO-4), 65.38, 81.42 (C-4,5), 98.65 (C-1). Mass spectrum: *m/z* 206 (0.3%, $[M^+ + H]$), 205 (0.4, M^+), 174 (12, $[M^+ - OMe]$), 134 (16), 130 (15), 116 (68), 102 (32), 97 (10), 86 (12), 74 (11), 73 (38), 72 (100), 71 (11), 57 (20), 56 (16), 45 (10), 43 (16), 42 (25), 41 (21).

*2,3,6-Trideoxy-3-C-methyl-4-O-methyl-3-nitro-*L-arabino-*hexopyranose* (**13**, L-*evernitrose*). — A solution of **11** (4.4 g, 20.1 mmol) in 0.05M sulfuric acid in 1:1 water–1,4-dioxane (250 mL) was heated at 90° for 28 h, neutralised with barium carbonate, filtered, and extracted with dichloromethane, and the extract was dried

($MgSO_4$) and concentrated. Column chromatography (10:1 toluene–acetone) of the residue gave α,β-**13** (3.0 g, 73%; α,β-ratio 1:1), m.p. 85–89°, $[\alpha]_D^{22}$ −11° (10 min)→ −14° (*c* 1.07, ethanol; 24 h); lit.[2] m.p. 88–93°, $[\alpha]_D^{25}$ −4.9°→ −19.4° (ethanol; 24 h); lit.[6] m.p. 85–89°, $[\alpha]_D$ −34°; lit.[8] m.p. 85–89°, $[\alpha]_D^{22}$ −22° (ethanol; 24 h). ^{1}H-N.m.r. data ($CDCl_3$): δ 4.89 (dd, $J_{1,2ax}$ 9.8, $J_{1,2eq}$ 4.5 Hz, H-1β), 5.33 (b, H-1α).

Anal. Calc. for $C_8H_{15}NO_5$ (205.2): C, 46.82; H, 7.37; N, 6.83. Found: C, 46.93; H, 7.42; N, 6.55.

*Methyl 3-amino-3,6-dideoxy-3-*C*-methyl-4-*O*-methyl-2-*O*-pivaloyl-α-*L*-glucopyranoside* (**15**). — A solution of **6** (1.00 g, 3.0 mmol) in dry dichloromethane (20 mL) was treated portionwise with triethyloxonium tetrafluoroborate[40] (1.42 g, 7.5 mmol) during 10 min. The resulting colorless solution was stirred at room temperature for 24 h under anhydrous conditions, washed with cold aqueous 10% sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated. The residue was dissolved in the minimum volume of ethyl acetate. Dropwise addition of hexane gave colorless crystals of unreacted **6** (0.09 g). Evaporation of the solvents left syrupy **15** (0.56 g, 64%) that was homogeneous in t.l.c. N.m.r. data ($CDCl_3$): ^{1}H, δ 1.25 (s, 9 H, ^{t}Bu), 1.28 (s, 3 H, Me-3), 1.29 (d, 3 H, Me-5), 1.47 (b, 2 H, NH_2), 2.76 (d, 1 H, H-4), 3.31 (s, 3 H, MeO-1), 3.60 (s, 3 H, MeO-4), 3.68 (dq, 1 H, H-5), 4.55 (d, 1 H, H-2), 4.76 (d, 1 H, H-1); $J_{1,2}$ 4.1, $J_{4,5}$ 9.7, $J_{5,6}$ 6.1 Hz; ^{13}C, δ 18.10, 18.27 (Me-3 and C-6), 27.13 (Me_3C), 39.09 (Me_3C), 55.47 (MeO-1), 56.33 (C-3), 62.29 (MeO-4), 65.65, 76.05, 88.54 (C-2,4,5), 96.90 (C-1), 177.97 (^{t}BuCOO).

*Methyl 3,6-dideoxy-3-*C*-methyl-3-trifluoroacetamido-α-*L*-glucopyranoside* (**16**). — To a solution of **3** (5.74 g, 30.0 mmol) in dry methanol (60 mL) was added triethylamine (3.06 g, 30.0 mmol), followed by ethyl trifluoroacetate[41] (5.33 g, 37.5 mmol). The mixture was stirred under nitrogen for 24 h at room temperature, then cooled (ice-bath), and Amberlite IR-120 (H^+) resin (20 g) was added. The mixture was stirred for 30 min, filtered, and concentrated. Recrystallisation of the residue from ethyl acetate–hexane gave platelets of **16** (6.70 g, 77%), m.p. 117–118°, $[\alpha]_D^{21}$ −85° (*c* 1.07, chloroform). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.33 (d, 3 H, Me-5), 1.42 (s, 3 H, Me-3), 3.0 (b, 1 H, OH), 3.42 (s, 3 H, OMe), 3.60 (d, 1 H, H-4), 3.71 (dq, 1 H, H-5), 3.79 (d, 1 H, H-2), 3.9 (b, 2 H, OH), 4.70 (d, 1 H, H-1), 5.85 (bs, 1 H, OH), 6.99 (bs, 1 H, NH); $J_{1,2}$ 4.4, $J_{4,5}$ 9.4, $J_{5,6}$ 6.0 Hz; ^{13}C, δ 14.13 (Me-3), 17.96 (C-6), 55.66 (OMe), 64.70 (C-3), 65.76, 71.90, 74.34 (C-2,4,5), 98.54 (C-1), 115.95 (q, $^1J_{C,F}$ 286 Hz, CF_3), 157.19 (q, $^2J_{C,F}$ 37 Hz, CF_3CON).

Anal. Calc. for $C_{10}H_{16}F_3NO_5$ (287.2): C, 41.82; H, 5.61; N, 4.88. Found: C, 41.89; H, 5.67; N, 4.90.

*Methyl 3,6-dideoxy-3-*C*-methyl-2-*O*-pivaloyl-3-trifluoroacetamido-α-*L*-glucopyranoside* (**17**). — To a solution of **16** (5.90 g, 20.5 mmol) in dry pyridine (30 mL) was added a solution of pivaloyl chloride (3.71 g, 30.8 mmol) in dichloromethane (15 mL) at −15° during 30 min, and stirring was continued overnight. The mixture was concentrated and toluene was evaporated several times from the residue. A solution of the residue in dichloromethane was washed with half-saturated brine and water, dried ($MgSO_4$), and concentrated. Recrystallisation of the residue from di-isopropyl ether–hexane gave **17** (5.34 g, 70%), m.p. 123–125°, $[\alpha]_D^{23}$ −58° (*c* 1.04, chloroform). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.26 (s, 9 H, ^{t}Bu), 1.34 (d, 3 H, Me-5), 1.53 (s, 3 H, Me-3), 3.38 (s, 3 H, OMe), 3.74

(dq, 1 H, H-5), 3.80 (d, 1 H, H-4), 4.74 (d, 1 H, H-1), 5.04 (d, 1 H, H-2), 7.26 (bs, 1 H, NH); $J_{1,2}$ 4.2, $J_{4,5}$ 9.4, $J_{5,6}$ 5.7 Hz; ^{13}C, δ 14.28 (Me-3), 17.83 (C-6), 26.97 (Me_3C), 39.28 (Me_3C), 55.74 (OMe), 64.04 (C-3), 65.59, 72.25, 75.52 (C-2,4,5), 97.00 (C-1), 115.77 (q, $^1J_{C,F}$ 286 Hz, CF_3), 157.57 (q, $^2J_{C,F}$ 36 Hz, CF_3CON), 179.71 (^{t}BuCOO).

Anal. Calc. for $C_{15}H_{24}F_3NO_6$ (371.4): C, 48.51; H, 6.51; N, 3.77. Found: C, 48.45; H, 6.54; N, 3.96.

Methyl 3,6-dideoxy-3-C-*methyl-3*-N-*methyl-4*-O-*methyl-2*-O-*pivaloyl-3-trifluoroacetamido-α*-L-*glucopyranoside* (**18**). — To a solution of **17** (4.30 g, 11.6 mmol) in a mixture of dry *N,N*-dimethylformamide (30 mL) and iodomethane (13.40 g, 94.4 mmol) was added freshly prepared silver oxide[39] (7.00 g, 30.2 mmol) during 60 min with vigorous stirring and cooling (ice-bath). Stirring was continued overnight, chloroform (200 mL) was added, and the suspension was filtered with the aid of Celite and concentrated *in vacuo*. Column chromatography (10:1 cyclohexane–ethyl acetate) of the residue yielded syrupy **18** (2.69 g, 58%), $[\alpha]_D^{27}$ −66° (*c* 1.03, chloroform); ν_{max}^{liquid} 1740 cm^{-1} (C=O). N.m.r. data ($CDCl_3$): ^1H, δ 1.23 (s, 9 H, ^{t}Bu), 1.31 (d, 3 H, Me-5), 1.35 (s, 3 H, Me-3), 2.44 (s, 3 H, NMe), 3.32 (s, 3 H, MeO-1), 3.44 (d, 1 H, H-4), 3.49 (s, 3 H, MeO-4), 4.00 (dq, 1 H, H-5), 4.69 (d, 1 H, H-1), 5.01 (d, 1 H, H-2); $J_{1,2}$ 4.5, $J_{4,5}$ 10.1, $J_{5,6}$ 6.0 Hz; ^{13}C, δ 10.37 (Me-3), 17.35 (C-6), 27.03 (Me_3C), 38.85 (Me_3C), 51.97, 52.00 (NMe and MeO-4), 56.09 (MeO-1), 61.23 (C-3), 64.53, 77.88, 84.26 (C-2,4,5), 97.25 (C-1), 106.25 (q, $^2J_{C,F}$ 33 Hz, CF_3CON), 122.55 (q, $^1J_{C,F}$ 291 Hz, CF_3), 177.30 (^{t}BuCOO).

Methyl 3,6-dideoxy-3-C-*methyl-3-nitro-α*-L-gluco-*hexopyranoside* (**19**). — (*a*) Acetyl chloride (35 mL) was added dropwise to dry methanol (700 mL) with cooling (ice-bath). The resulting mixture was heated to ~45°, **2** (33.5 g, 109.7 mmol) was added, and the mixture was stirred at 40–50° for ~20 h, when t.l.c. (19:1 chloroform–methanol) revealed one major product. The red mixture was decolorised with carbon, filtered, and concentrated. Column chromatography (19:1 chloroform–methanol) of the residue and recrystallisation from chloroform–hexane gave **19** (20.4 g, 84%), m.p. 111–113°, $[\alpha]_D^{21}$ −152° (*c* 1.05, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.33 (d, 3 H, Me-5), 1.72 (s, 3 H, Me-3), 2.6 (bm, 2 H, OH), 3.43 (s, 3 H, OMe), 3.68 (dq, 1 H, H-5), 3.93 (dd, 1 H, H-2), 4.36 (dd, 1 H, H-4), 4.77 (d, 1 H, H-1); $J_{1,2}$ 4.7, $J_{2,HO-2}$ 9.4, $J_{4,5}$ 9.7, $J_{4,HO-4}$ 4.7, $J_{5,6}$ 6.4 Hz; ^{13}C, δ 11.85 (Me-3), 17.67 (C-6), 55.84 (OMe), 65.60, 71.50, 76.63 (C-2,4,5), 95.77 (C-3), 98.80 (C-1).

Anal. Calc. for $C_8H_{15}NO_4$ (221.2): C, 43.44; H, 6.84; N, 6.33. Found: C, 43.58; H, 6.83; N, 6.45.

(*b*) A solution of **3** (9.1 g, 47.6 mmol) in dichloromethane–methanol (250 mL; 3:2) was added during 30 min to a boiling solution of 3-chloroperoxybenzoic acid (57.5 g, 333 mmol) in dichloromethane (800 mL) and heating was continued for 30 min. The solvents were removed under reduced pressure and a solution of the residue in chloroform (500 mL) was cooled (−20°) to precipitate the bulk of acidic material. Concentration of the filtrate left a solid residue, a solution of which in methanol (300 mL) and water (120 mL) was stirred with Amberlite IRA-400 (HO^-) resin for 3 h, then filtered, and concentrated. The residue was recrystallised from di-isopropyl ether to give **19** (3.6 g, 34%).

Methyl 4-O-acetyl-3,6-dideoxy-3-C-methyl-3-nitro-α-L-gluco-hexopyranoside (**20**). — Acetyl chloride (5 mL) was added dropwise to dry methanol (100 mL) followed by dry acetone (10 mL), and **2** (10.00 g, 32.8 mmol) was dissolved in this mixture at 40°. The mixture was stirred for 3 h at the same temperature, when t.l.c. (19:1 chloroform–methanol) revealed no **2** but two slower-moving products. The solvents were evaporated to leave a syrupy mixture, column chromatography (19:1 chloroform–methanol) of which gave **20** (4.60 g, 53%), m.p. 124–126° (from ethyl acetate–hexane), $[\alpha]_D^{24}$ −166° (*c* 1.04, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.20 (d, 3 H, Me-5), 1.76 (s, 3 H, Me-3), 2.05 (s, 3 H, OAc), 2.77 (bd, 1 H, OH), 3.44 (s, 3 H, OMe), 3.80 (dq, 1 H, H-5), 4.54 (bdd, 1 H, H-2), 4.81 (d, 1 H, H-1), 5.34 (d, 1 H, H-4); $J_{1,2}$ 4.7, $J_{2,HO-2}$ 9.1, $J_{4,5}$ 10.1, $J_{5,6}$ 6.4 Hz; ^{13}C, δ 12.16 (Me-3), 17.31 (C-6), 20.45 (CH_3CO), 56.01 (OMe), 64.32, 71.58, 74.24 (C-2,4,5), 93.67 (C-3), 98.78 (C-1), 168.95 (CH_3COO).

Anal. Calc. for $C_{10}H_{17}NO_7$ (263.2): C, 45.64; H, 6.51; N, 5.32. Found: C, 45.73; H, 6.71; N, 5.38.

Further elution with the same solvent gave **19** (3.26 g, 45%).

Methyl 3,6-dideoxy-3-C-methyl-3-nitro-2-O-pivaloyl-α-L-gluco-hexopyranoside (**21**). — To a solution of **19** (3.00 g, 13.6 mmol) in dry pyridine (50 mL) was added pivaloyl chloride (3.28 g, 27.2 mmol) in dry dichloromethane (10 mL) at −20° during 30 min. The mixture was stirred overnight and then concentrated, and a solution of the residue in dichloromethane was washed with cold aqueous 10% sulfuric acid, saturated aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and concentrated. The resulting syrup was crystallised from ethyl acetate–hexane to give **21** (3.31 g, 79%), m.p. 76–78°, $[\alpha]_D^{23}$ −118° (*c* 1.02, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.19 (s, 9 H, ^{t}Bu), 1.34 (d, 3 H, Me-5), 1.83 (s, 3 H, Me-3), 2.99 (d, 1 H, OH), 3.36 (s, 3 H, OMe), 3.74 (dq, 1 H, H-5), 3.98 (dd, 1 H, H-4), 4.92 (d, 1 H, H-1), 5.34 (d, 1 H, H-2); $J_{1,2}$ 4.4, $J_{4,5}$ 9.7, $J_{4,HO-4}$ 5.0, $J_{5,6}$ 6.0 Hz; ^{13}C, δ 12.72 (Me-3), 17.58 (C-6), 26.90 (Me_3C), 38.99 (Me_3C), 55.89 (OMe), 65.54, 71.60, 75.46 (C-2,4,5), 93.80 (C-3), 96.54 (C-1), 177.15 (^{t}Bu*C*OO).

Anal. Calc. for $C_{13}H_{23}NO_7$ (305.3): C, 51.14; H, 7.59; N, 4.59. Found: C, 51.32; H, 7.71; N, 4.56.

Methyl 3,6-dideoxy-3-C-methyl-4-O-methyl-3-nitro-2-O-pivaloyl-α-L-gluco-hexopyranoside (**22**). — To a solution of **21** (3.70 g, 12.1 mmol) in dry *N,N*-dimethylformamide (35 mL) and iodomethane (17 g, 120 mmol) was added freshly prepared silver oxide[39] (7.30 g, 31.5 mmol) during 60 min with vigorous stirring and cooling (ice-bath). Stirring was continued overnight, chloroform (200 mL) was added, and the suspension was filtered with Celite and concentrated. Column chromatography (5:1 cyclohexane–ethyl acetate) of the residue gave **22** (2.70 g, 69%), $[\alpha]_D^{25}$ −121° (*c* 1.13, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.17 (s, 9 H, ^{t}Bu), 1.35 (d, 3 H, Me-5), 1.79 (s, 3 H, Me-3), 3.34, 3.37 (2 s, 6 H, MeO-1,4), 3.65–3.75 (m, 2 H, H-4,5), 4.90 (d, 1 H, H-1), 5.31 (d, 1 H, H-2); $J_{1,2}$ 4.2, $J_{5,6}$ 6.0 Hz; ^{13}C, δ 12.51 (Me-3), 17.75 (C-6), 26.90 (Me_3C), 38.97 (Me_3C), 55.85 (MeO-1), 60.80 (MeO-4), 65.65, 72.42, 85.29 (C-2,4,5), 93.29 (C-3), 96.37 (C-1), 176.93 (^{t}Bu*C*OO).

Methyl 3,6-dideoxy-3-C-methyl-3-nitro-2-O-tosyl-α-L-gluco-hexopyranoside (**23**) *and its 4-acetate* (**24**). — To a stirred solution of **19** (18.0 g, 81.4 mmol) in dry pyridine

(300 mL) at −15° was added *p*-toluenesulfonyl chloride (45.7 g, 239.9 mmol) in small portions during 60 min. Stirring was continued for 30 h and the mixture was allowed to attain room temperature slowly. T.l.c. (4:1 chloroform–ethyl acetate) then revealed that the reaction was complete. The mixture was poured into ice–water (1.5 L) and extracted with dichloromethane (4 × 250 mL), and the combined extracts were washed with cold aqueous 10% sulfuric acid, saturated aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and concentrated. Column chromatography (ether) of the residue (~33 g) gave **23** as a pale-yellow syrup (29.6 g, 96%), $[\alpha]_D^{24}$ −88° (*c* 1.33, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.28 (d, 3 H, Me-5), 1.72 (s, 3 H, Me-3), 2.45 (s, 3 H, Ts Me), 3.05 (d, 1 H, OH), 3.24 (s, 3 H, OMe), 3.67 (dq, 1 H, H-5), 3.83 (dd, 1 H, H-4), 4.90, 5.02 (2 d, 2 H, H-1,2), 7.34 (m, 2 H, Ts *m*-H), 7.71 (m, 2 H, Ts *o*-H); $J_{1,2}$ 4.4, $J_{4,5}$ 9.7, $J_{4,HO\text{-}4}$ 6.0, $J_{5,6}$ 6.4 Hz; ^{13}C, δ 11.73 (Me-3), 17.38 (C-6), 21.71 (Ts *Me*), 56.09 (OMe), 65.39, 75.97, 77.07 (C-2,4,5), 93.93 (C-3), 97.21 (C-1), 127.94 (Ts *m*-C), 129.91 (Ts *o*-C), 132.28 (Ts *C*Me), 145.59 (Ts CSO_3).

Acetylation of **23** (1.88 g, 5 mmol) with acetic anhydride (5 mL) in pyridine (10 mL), in the usual way, gave **24** (1.69 g, 80%), m.p. 142–144° (from ethyl acetate–hexane), $[\alpha]_D^{23}$ −114° (*c* 1.0, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.17 (d, 3 H, Me-5), 1.78 (s, 3 H, Me-3), 2.00 (s, 3 H, OAc), 2.45 (s, 3 H, Ts Me), 3.40 (s, 3 H, OMe), 3.82 (dq, 1 H, H-5), 5.03, 5.09 (2 d, 2 H, H-1,2), 5.20 (d, 1 H, H-4), 7.34 (m, 2 H, Ts *m*-H), 7.71 (m, 1 H, Ts *o*-H); $J_{1,2}$ 4.4, $J_{4,5}$ 9.9, $J_{5,6}$ 6.4 Hz; ^{13}C, δ 12.54 (Me-3), 17.12 (C-6), 20.27 (CH_3COO), 21.73 (Ts *Me*), 56.36 (OMe), 63.86, 74.41, 76.69 (C-2,4,5), 91.57 (C-3), 97.32 (C-1), 128.02 (Ts *m*-C), 129.97 (Ts *o*-C), 131.91 (Ts *C*Me), 145.71 (Ts CSO_3), 168.48 (Me*C*OO).

Anal. Calc. for $C_{17}H_{23}NO_9S$ (417.4): C, 48.92; H, 5.55; N, 3.36. Found: C, 49.17; H, 5.57; N, 3.43.

*Methyl 4-*O*-acetyl-3,6-dideoxy-2-*O*-mesyl-3-*C*-methyl-3-nitro-α-*L*-gluco-hexopyranoside* (**25**). — To a stirred solution of **20** (4.60 g, 17.5 mmol) in pyridine (30 mL) was added methanesulfonyl chloride (2.40 g, 21.0 mmol) at 0°. After 30 min at room temperature, the mixture was concentrated and the residue partitioned between ether and water. The ether layer was dried ($MgSO_4$) and concentrated, and the residue was crystallised from ethanol to give large prisms of **25** (4.78 g, 80%), m.p. 74–76°, $[\alpha]_D^{21}$ −146° (*c* 1.04, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.22 (d, 3 H, Me-5), 1.86 (s, 3 H, Me-3), 2.08 (s, 3 H, OAc), 2.99 (s, 3 H, OMs), 3.47 (s, 3 H, OMe), 3.87 (dq, 1 H, H-5), 5.10, 5.36 (2 d, 2 H, H-1,2), 5.29 (d, 1 H, H-4); $J_{1,2}$ 4.4, $J_{4,5}$ 9.7, $J_{5,6}$ 6.4 Hz; ^{13}C, δ 12.86 (Me-3), 17.16 (C-6), 20.34 (CH_3COO), 37.97 (OMs), 56.45 (OMe), 63.97, 74.30, 76.70 (C-2,4,5), 91.66 (C-3), 97.62 (C-1), 168.61 (Me*C*OO).

Anal. Calc. for $C_{11}H_{19}NO_9S$ (341.3): C, 38.71; H, 5.61; N, 4.10. Found: C, 38.65; H, 5.59; N, 4.31.

*Methyl 3,6-dideoxy-2-*O*-mesyl-3-*C*-methyl-3-nitro-α-*L*-gluco-hexopyranoside* (**26**). — A solution of **25** (2.80 g, 8.2 mmol) in acetone (3 mL) and methanolic hydrogen chloride (42 mL, from 2 mL of acetyl chloride and 40 mL of dry methanol) was kept at 40–50° for 16 h, when t.l.c. (4:1 chloroform–ethyl acetate) revealed no **25**. The reaction was concentrated and short-column chromatography (ether) of the residue gave syrupy

26 (2.26 g, 92%), $[\alpha]_D^{24}$ −116° (*c* 1.05, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.33 (d, 3 H, Me-5), 1.80 (s, 3 H, Me-3), 3.01 (s, 3 H, OMs), 3.44 (s, 3 H, OMe), 3.73 (dq, 1 H, H-5), 3.92 (d, 1 H, H-4), 5.01, 5.22 (2 d, 2 H, H-1,2); $J_{1,2}$ 4.4, $J_{4,5}$ 9.4, $J_{5,6}$ 6.0 Hz; ^{13}C, δ 12.08 (Me-3), 17.43 (C-6), 38.06 (OMs), 56.20 (OMe), 65.48, 75.91, 76.94 (C-2,4,5), 94.02 (C-3), 97.51 (C-1).

Anal. Calc. for $C_9H_{17}NO_8S$ (299.3): C, 36.12; H, 5.73; N, 4.68. Found: C, 37.57; H, 5.94; N, 4.74.

(*2S,4R,6amphi*)-*4-Methoxy-2-methyl-6-nitro-3-oxaheptan-1-ol* (**27**). — Sodium borohydride (0.44 g, 11.6 mmol) was added portionwise during 5 min to a stirred solution of **26** (1.17 g, 3.9 mmol) in dry ethanol (20 mL), with cooling (ice-bath). After 30 min at room temperature, t.l.c. (4:1 chloroform–ethyl acetate) revealed that the reaction was complete. The solvent was evaporated, the residue was dissolved in the minimum amount of chloroform, the voluminous precipitate which formed upon addition of acetone was collected on a layer of Celite, and the filtrate was concentrated. Several portions of methanol were evaporated from the residue, short-column chromatography (2:1 cyclohexane–ethyl acetate) of which gave **27** (0.65 g, 80%). ^{13}C-N.m.r. data ($CDCl_3$): δ 16.52, 16.62 (Me-2), 20.01, 20.04 (C-7), 38.49, 38.79 (C-5), 53.44, 53.73 (MeO-4), 69.72 (C-1), 75.89, 76.35, 79.65, 79.73 (C-2,6), 100.27, 100.32 (C-4).

Anal. Calc. for $C_8H_{17}NO_5$ (207.2): C, 46.38; H, 8.27; N, 6.76. Found: C, 46.19; H, 8.22; N, 7.31.

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