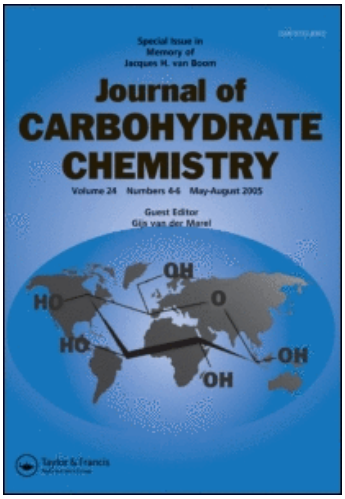

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Stereocontrolled Synthesis of Methyl (Methyl-5-Acetamido-4-*O*-Benzoyl-7-*O*-Benzyl-3,5-Dideoxy-α-D-Arabino-2-Heptulopyranosid)Onate, a Model Compound for Sialic Acids

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STEREOCONTROLLED SYNTHESIS OF METHYL (METHYL-5-ACETAMIDO-4-*O*-BENZOYL-7-*O*-BENZYL-3,5-DIDEOXY-α-D-ARABINO-2-HEPTULOPYRANOSID)ONATE, A MODEL COMPOUND FOR SIALIC ACIDS

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ABSTRACT

Thiophenyl 2,3-dideoxy-6-*O*-benzyl-α-**D**-*erythro*-hex-2-enopyranoside has been converted into a sialic acid analog, by means of methoxycarbonylation at the anomeric center and a [2,3]-*sigmatropic rearrangement* of the allylic glycosyl sulfoxide.

INTRODUCTION

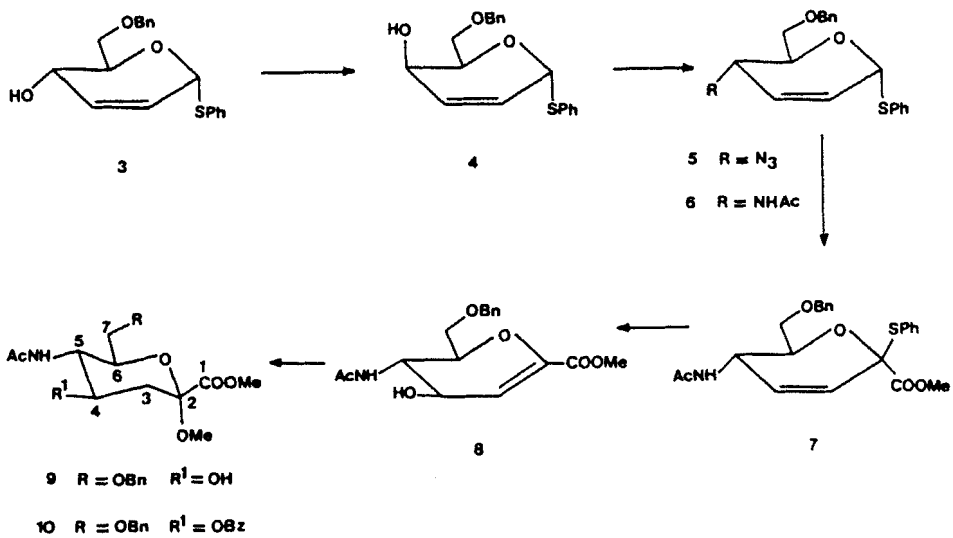
Sialic acids are components of biologically important glycoproteins and glycolipids,[1-3] as reflected by their widespread occurrence in nature.[4] Several microorganisms also contain large polymers of sialic acids as a part of their capsular polysaccharides.[5] Cell-surface sialic acids have been implicated in several cellular functions involving the plasma membrana. These functions include masking of the cell surface antigens and cell-to-cell recognition.[6] There is also increasing evidence that sialic acids are involved in the process of metastasis.[7]

It is obvious that the stereocontrolled synthesis of this type of substance, especially glycosides of sialic acids, or the preparation in an enantioselective manner of unnatural isomers would be of greatest interest. Our primary purpose has been to establish a facile and stereoselective route for the preparation of such molecules. In addition it would be important to devise a good procedure to prepare glycosyl-derivatives of these sugars. The following describes the results obtained in the stereocontrolled preparation of a model

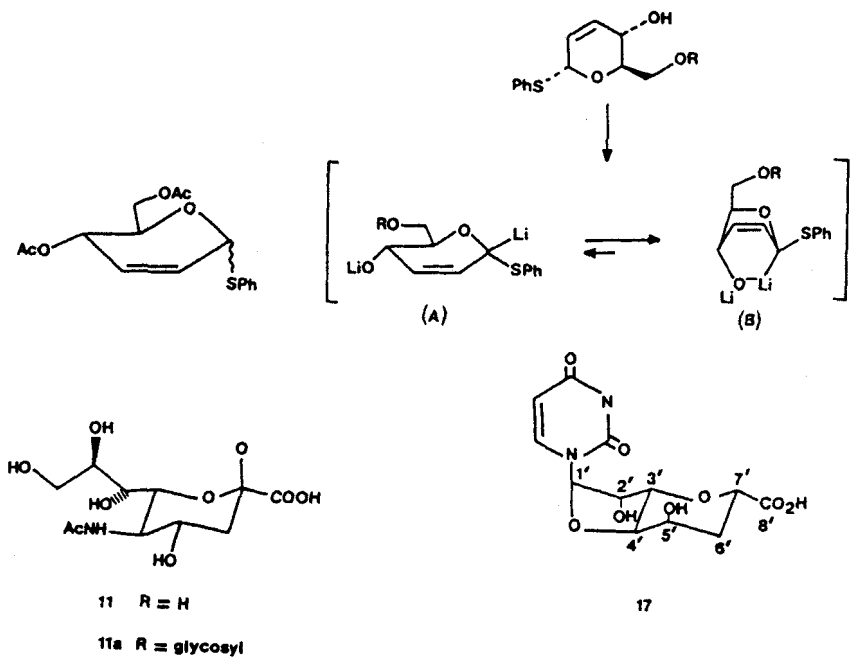
compound (**9**) containing all the substituents present in the ring of *N*-acetyl neuraminic acid (**11**), and with identical relative stereochemistry.

RESULTS AND DISCUSSION

The reaction of 3,4,6-tri-*O*-acetyl-**D**-glucal with thiophenol in the presence of catalytic amounts of BF_3-etherate affords the corresponding Ferrier's products (**1**) (74 % yield, α : β , 8 : 1). Methanolysis with potassium carbonate in methanol and selective benzylation of the primary hydroxyl group of the α-anomer of **1** using a mixture of di-*n*-butyltin oxide, benzyl bromide and tetra-*n*-butylammonium bromide gave compound **3** (78 %). In order to obtain the desired stereochemistry of the required acetamido group, it was necessary to invert the configuration of the hydroxyl group at C-4 (see Scheme 1). This was achieved under Mitsunobu's conditions[8,9] (triphenylphosphine, diethyl azodicarboxylate, benzoic acid). Compound **4** (81 % overall yield) was thus obtained by hydrolysis, with potassium carbonate in methanol, of the corresponding C-4 benzoate. Mesylation of compound **4**, with mesyl chloride in the presence of triethylamine, followed by treatment with sodium azide in dimethylformamide resulted in the preparation of **5** (83 %). Reduction of the azide group ($LiAlH_4$) and subsequent acetylation finally provided the desired acetamido-derivative **6** (93 %).



Scheme 1



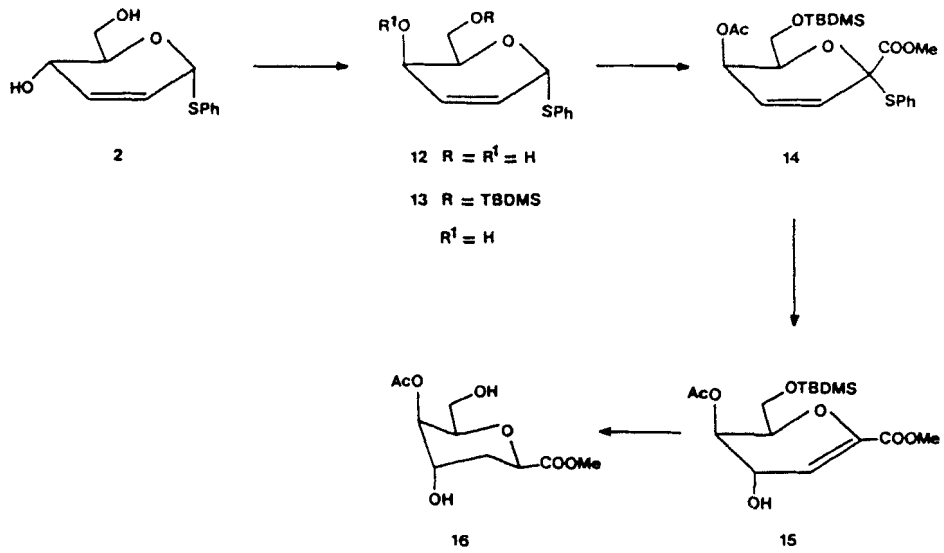
Scheme 2

We have previously shown[10] that the stereochemical outcome of alkylation or acylation at C-1 of phenyl thioglycosides such as **3** or **4** was controlled by the stereochemistry of the hydroxyl group at C-4. According to our previous results,[10] the incoming alkyl or acyl group would preferentially adopt the same configuration as the hydroxyl group at C-4. We have assumed that the reaction takes place through intermediate B (Scheme 2) in which the 4-OH group interacts with lithium at C-1 as indicated.

In our approach to a stereocontrolled synthesis of the title compound, we considered that in the following step the nitrogen atom of the C-4 acetamido group would play a similar role to the one postulated for the C-4 hydroxyl group with regard to the stereochemical control of the reaction. In fact, compound **6** upon metallation (n-BuLi) and quenching of the reaction with dimethyl carbonate yielded the carbomethoxy derivative **7** (59%). The configuration of **7** could not be determined by spectroscopic methods at this point, but was later confirmed by the NMR results obtained with the compound derived from it, namely the final product **10.** The product (or products) obtained by

oxidation of **7** (*m*-$ClC_6H_4CO_3H$) (assumed to be a mixture of sulfoxides or sulfoxides and sulfone but not characterized) underwent the expected rearrangement.[11] Methanolysis (Et_3N/MeOH) of the rearranged products led to the isolation of **8** (90%). We have postulated the configuration depicted in the formula for the configuration of the C-4 hydroxyl group of **8**, in agreement with the β-configuration of the thiophenyl group of **7**. The ^1H NMR spectrum of **8** showed a signal at δ 4.30 (dd, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 5.8 Hz) which did not settle this question. These results are hardly surprising considering the half-chair conformation of **8**. This compound is a good substrate to carry out glycosidation reactions. The sialic acid analog of **8** has been recently used by Thiem et al.[12] for this purpose. Methoxymercuration of **8** with mercuric trifluoroacetate in methanol followed by reduction with triphenyltin hydride afforded methyl (methyl-5-acetamido-7-*O*-benzyl-3,5-dideoxy-α-D-*arabino*-2-heptulopyranosid)onate (**9**, 65%), an analog of sialic acid glycosides (**11a**) as the only reaction product. Compound **9** was benzoylated with benzoyl chloride in the presence of triethylamine affording the corresponding benzoyl-derivative (**10**). The stereochemistry assigned to **10** at C-4 was clearly confirmed by ^1H NMR data (δ 5.48, ddd, J = 11.1, 10.4, 4.9 Hz, H-4) (δ 4.17, ddd, J = 10.4, 9.8, 9.5 Hz, H-5). The stereochemistry at C-2 was tentatively assigned by analogy with previous results (see ref. 12 among others). Provided that our postulated mechanisms are correct, these results support our contention that the configuration of **6** at C-4 determines the chirality of **7** at C-2, and this chirality is latter transferred to the C-4 center of **8** through a [2,3]-sigmatropic rearrangement.[11]

In order to further illustrate the potential of the method here described and also to test the postulated stereochemical control in the previous sequence of reactions, we prepared compound **16** following Scheme 3. Diol **2** (δ 4.3, dd, J = 9, 2 Hz, H-4) was prepared by deacetylation of the α-anomer of **1** with potassium carbonate in methanol. Application of Mitsunobu's conditions[8,9] to **2** afforded compound **12** (δ 4.2-3.9, m, H-4), the primary hydroxyl group of which was regioselectively protected by treatment with *tert*-butyldimethylsilyl chloride[13] affording compound **13**. Acylation of **13** at the anomeric center with *n*-butyllithium and dimethyl carbonate and further acetylation with acetic anhydride-triethylamine led to a single product **14** (38%). Oxidation of **14** (*m*-$ClC_6H_4CO_3H$) provided compound **15** as expected (79%). Catalytic reduction of **15** (Pd/C) gave a single product **16** (82%). The ^1H NMR spectrum of **16** confirms the stereochemistry assigned (δ 4.80, dd, J = 3.3, 1.1 Hz, H-5), (δ 4.55, dd, J = 8.9, 5.7 Hz, H-2).



Scheme 3

It appears that the methodology here described provides good control of the required stereochemistry. On the other hand, compounds **9** and **16** are good models for the preparation of sialic acid (**11**) and octosilic acid A (**17**) two natural compounds of undoubted interest.

EXPERIMENTAL

General Methods. Melting points were determined on a Kofler hot-stage apparatus. Optical rotations were measured in chloroform solution with a Perkin-Elmer 141 polarimeter. Flash chromatography was performed according to the procedure of Still[14] on silica gel, 0.040-0.063 mm (Merck); analytical thin-layer chromatography was routinely used to monitor reactions, plates precoated with silica gel 60 F_{254} of 0.25 mm thickness (Merck) were used. Proton nuclear magnetic resonance (^{1}H NMR) spectra were measured for $CDCl_3$ solutions with a Varian EM-390 (90 MHz), XL-300 (300 MHz) or Bruker AM-200 (200 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard. Multiplicities are abbreviated as follow: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Carbon NMR spectra were measured at 20.1, 50.3 or 75.4 MHz as indicated. Chemical shifts are reported in parts per million (δ) relative to

tetramethylsilane. All the reactions with sensitive substrates were run in flame-dried vessels under an atmosphere of dry argon or nitrogen. Stated yields refer to purified products.

Preparation of Thiophenyl 4,6-Di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranoside (1). To a stirred solution of 3,4,6-tri-*O*-acetyl-D-glucal (12.4 g) in dry benzene (400 mL), cooled at 0 °C, was added thiophenol (4.6 mL) and boron trifluoride etherate (0.2 mL). Stirring was continued for 48 h at room temperature. Solid potassium carbonate was then added. The solids were filtered off and the solvent evaporated under reduced pressure. Chromatography of the residue gave **1** (mixture of α and β-anomers, 8:1 ratio) (10.9 g, 74%) and 3-deoxy-3-thiophenyl-D-glucal (400 mg, 3%).

A pure sample of the α-anomer was obtained by crystallization of **1** (hexane:ethyl eter). The β-anomer was obtained by careful chromatography of the mixture.

1 (α-anomer): $[\alpha]_D$ +391° (c 0.29). ^{1}H NMR (200 MHz), δ 7.57-7.52 (2H, m, phenyl-H), 7.31-7.27 (3H, m, phenyl-H), 6.06 (1H, ddd, J = 10.0, 3.1, 1.9 Hz, H-2), 5.86 (1H, dt, J_d = 10.0 Hz, J_t = 1.7 Hz, H-3), 5.76-5.73 (1H, m, H-1), 5.36 (1H, dq, J_d = 9.4 Hz, J_q = 1.9 Hz, H-4), 4.52- 4.43 (1H, m, H-5), 4.33-4.16 (2H, m, H_2-6), 2.09 (3H, s, Me-acetate), 2.05 (3H, s, Me-acetate). ^{13}C NMR (50 MHz) δ 170.2, 169.8, 134.7, 131.5, 128.7, 128.4, 127.5, 127.4, 83.4, 67.3, 65.1, 62.9, 20.7, 20.4.

Anal. Calcd for $C_{16}H_{18}O_5S$: C, 59.61; H, 5.63; S, 9.94. Found: C, 60.03; H, 5.84; S, 10.06.

Thiophenyl 2,3-Dideoxy-α-D-*erythro*-hex-2-enopyranoside (2). Solid potassium carbonate (0.5 g) was added to a solution of **1** (α-anomer) (10.0 g) in methanol (200 mL). This mixture was stirred for 5 h at 25 °C. Evaporation of the solvent and chromatography of the residue gave pure **2** (7.74 g, 97%).

2: Syrup, $[\alpha]_D$ +331° (c 0.58). ^{1}H NMR (90 MHz) δ 7.6-7.1 (5H, m, phenyl-H), 5.9 (2H, s, H-2, H-3), 5.7 (1H, br s, H-1), 4.3 (1H, dd, J = 9, 2 Hz, H-4), 4.0 (1H, dt, J_d = 9 Hz, J_t = 4 Hz, H-5), 3.8 (2H, d, J = 4 Hz, H_2-6), 3.0-2.8 (2H, 2OH). ^{13}C NMR (20 MHz) δ 135.2, 131.9, 131.7, 129.0, 127.5, 126.7, 83.7, 72.0, 63.6.

Thiophenyl 6-*O*-Benzyl-2,3-Dideoxy-α-D-*erythro*-hex-2-enopyranoside (3). Compound **2** (525 mg, 2.2 mmol) and di-*n*-butyltin oxide (548 mg, 2.2 mmol) were dissolved in anhydrous benzene (15 mL). This solution was heated under reflux for 15 h using a Dean-Stark trap to separate water. Benzyl bromide (0.55 mL) and tetra-*n*-butylammonium bromide (708 mg) were then added. Evaporation of the solvent under reduced pressure and chromatographic separation of the residue afforded **3** (564 mg, 78%) as a thick oil which slowly crystallized.

3: mp 53-54°C (hexane); $[\alpha]_D$ +241° (c 0.79). ^{1}H NMR (90 MHz) δ 7.6-7.1 (5H, m, phenyl-H), 6.9 (2H, s, H-2, H-3), 5.7 (1H, d, J = 1 Hz, H-1), 4.6 (2H, s, benzylic CH_2), 4.3-4.0 (2H, m, H-4, H-5), 3.8-3.6 (2H, m, H_2-6), 2.5-2.3 (1H, OH).

Thiophenyl 6-*O*-Benzyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (4). To a solution of 3 (2.6 g, 7.92 mmol) in diethyl ether (30 mL) was added triphenylphosphine (3.1 g, 11.9 mmol). This solution was stirred for 10 min and cooled at 0 °C. To this mixture was sequentially added: benzoic acid (1.5 g, 11.9 mmol), and diethyl azodicarboxylate (1.9 mL , 11.9 mmol) previously dissolved in diethyl ether (20 mL). The whole mixture was left at 25 °C with stirring for 3 h. The solvent was removed under reduced pressure. Column chromatography of the residue gave the benzoate ester of 4 (2.9 g), which was then treated with potassium carbonate in methanol to afford 4, used without further purification in the next step.

Thiophenyl 4-Azide-6-*O*-benzyl-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside (5). To a solution of 4 (1.0 g, 3.0 mmol) in dry dichloromethane at 0 °C, was added triethylamine (0.63 mL, 4.5 mmol) and methylsulfonyl chloride (0.35 mL, 4.5 mmol). This mixture was stirred for 1 h. The reaction was diluted with dry dimethylformamide (25 mL) and sodium azide (585 mg, 9 mmol) was added, stirring the whole mixture overnight. The organic solution was washed with brine, dried and concentrated under reduced pressure. Column chromatography of the residue yielded 5 (0.9 g, 83 %).

5: oil, $[\alpha]_D$ +369° (c 0.52). ^{1}H NMR (90 MHz) δ 7.6-7.1 (10H, m, 2 phenyl-H), 6.1 (1H, dd, J = 10, 3 Hz, H-3 or H-2), 5.9 (1H, br d, J = 10 Hz, H-2 or H-3), 5.8-5.7 (1H, m, H-1), 4.7 (1H, d, J = 12 Hz, benzyl-CH_2), 4.4 (1H, d, J = 12 Hz, benzyl-CH_2), 4.3-4.1 (2H, m, H-4 and H-5), 3.7 (2H, d, J = 3 Hz, H_2-6). ^{13}C NMR (20 MHz) δ 138.0, 135.1, 131.8, 129.2, 129.0, 128.4, 127.8, 126.9, 83.7, 73.6, 69.7, 69.2, 54.4.

Thiophenyl 4-Acetamido-6-*O*-benzyl-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside (6). A solution of 5 (0.8 g, 2.27 mmol) in dry diethyl ether (10 mL) was added to a suspension of lithium aluminium hydride (173 mg, 4.54 mmol) in diethyl ether (15 mL) at 0 °C. The solution was stirred for 1.5 h, under argon atmosphere; it was then diluted with diethyl ether, and excess hydride was destroyed by the addition of an aqueous saturated sodium sulfate solution. Solids were filtered off through a Celite layer and the solvent was evaporated. The residue was acetylated (triethyl amine, 0.9 mL; acetic anhydride, 0.65 mL) at 0 °C. Excess reagents were distilled off and the residue gave, after chromatographic separation, pure **6** (0.77 g, 93 %).

6: mp 113-116 °C (hexane : ethyl acetate); $[\alpha]_D$ +284° (c 0.58). ^{1}H NMR (300 MHz) δ 7.58-7.20 (10H, m, 2-phenyl-H), 6.06-6.01 (1H, m, H-2), 5.77-

5.74 (1H, m, H-3), 5.74 (1H, d, J = 2.4 Hz, H-1), 5.44 (1H, br d, J = 9.5 Hz, NH), 4.64 (1H, tq, J_q = 2.4 Hz, J_t = 9.5 Hz, H-4), 4.56 (2H, s, benzyl-CH_2), 4.23 (1H, ddd, J = 2.9, 6.0, 9.3 Hz, H-5), 3.72 (1H, dd, J = 2.9, 10.7 Hz, H-6). ^{13}C NMR (50 MHz) δ 169.7, 138.1, 134.7, 132.1, 129.5, 128.8, 127.9, 127.5, 83.2, 73.4, 70.6, 70.2, 44.5, 23.3.

Anal. Calcd for $C_{21}H_{23}O_3NS$: C, 68.27; H, 6.27; N, 3.79; S, 8.68. Found: C, 68.13; H, 6.40; N, 3.93; S, 9.09.

Methyl (Thiophenyl-5-acetamido-7-*O*-benzyl-3,4,5-trideoxy-β-D-*erythro*-hept-3-en-2-ulopyranosid)onate (7). To a solution of **6** (530 mg, 1.44 mmol) in dry tetrahydrofuran (7.0 mL) cooled at -78 °C and kept under argon was added a 1.5 M hexane solution of *n*-butyl lithium (1.92 mL, 2.28 mmol). After 40 s, dimethyl carbonate (1.2 mL, 14.4 mmol) was quickly added to the previous solution. The reaction was stirred for 15 min and then diluted with diethyl ether, washed with brine, dried and concentrated. Column chromatography of the residue yielded **7** (361 mg, 59 %) and starting material (60 mg, 11 %).

7: $[\alpha]_D$ +64° (c 1.02). ^1H NMR (300 MHz) δ 7.50-7.15 (10H, m, 2 phenyl -H), 5.98 (1H, dd, J = 2.3, 10.0 Hz, H-3 or H-4), 5.70 (1H, dd, J = 2.3, 10.0 Hz, H-4 or H-3), 5.50 (1H, br d, J = 8.6 Hz, NH), 4.57 (1H, d, J = 11.6 Hz, benzyl-CH_2), 4.48 (1H, d, J = 11.6 Hz, benzyl-CH_2), 4.22 (1H, dd, J = 8.6, 2.3 Hz, H-5), 3.72 (1H, dt, J_t = 4.5 Hz, J_d = 8.6 Hz, H-6), 3.65 (2H, d, J = 4.5 Hz, H_2-7), ^{13}C NMR (50 MHz) δ 169.8, 168.6, 138.2, 136.3, 132.2, 130.8, 129.5, 128.5, 128.2, 127.8, 127.5, 127.2, 87.2, 77.2, 73.5, 70.2, 52.8, 43.8, 23.1.

Methyl 5-Acetamido-2,6-anhydro-7-*O*-benzyl-3,5-dideoxy-D-*arabino*-hept-2-enopyranosonate (8). To a solution of **7** (235 mg., 0.55 mmol) in dichloromethane at 0 °C was added m-chloroperbenzoic acid (232 mg, 1.21 mmol). This solution was stirred during 1.5 h. Solid sodium sulphite (100 mg) and saturated aqueous sodium bicarbonate (4 mL) were added. The organic layer was washed with brine, dried and concentrated. The residue was taken in methanol (10 mL) and triethylamine (1 mL). This solution was stirred for 1 h and concentrated. Column chromatography of the residue gave **8** (167 mg, 91 %).

8: mp 120-123 °C (hexane : ethyl acetate; $[\alpha]_D$ +56° (c 0.24). ^1H NMR (300 MHz) δ 7.35-7.26 (5H, m, phenyl-H), 6.48 (1H, br d, J = 5.8 Hz, NH), 6.09 (1H, d, J = 3.5 Hz, H-3), 4.58 (2H, s, benzyl-CH_2), 4.31 (1H, dd, J = 3.5, 5.8 Hz, H-4), 4.19 (1H, dt, J_t = 6.5 Hz, J_d = 4.1 Hz, H-6), 3.94 (1H, dt, J_t = 5.8 Hz, J_d = 6.5 Hz, H-5), 3.93 (1H, dd, J = 4.1, 10.1 Hz, H-7), 3.82 (1H, dd, J = 6.5, 10.1 Hz, H-7), ^{13}C NMR (50 MHz) δ 171.7, 171.7, 143.3, 137.1, 128.6, 128.6, 128.2, 128.0, 128.0, 111.8, 75.6, 73.8, 69.0, 66.5, 54.0, 52.5, 23.1.

Anal. Calcd for $C_{17}H_{21}O_6N$: C, 60.88; H, 6.31; N, 4.18. Found: C, 60.99; H, 6.50; N, 4.44.

Methyl (Methyl-5-acetamido-4-*O*-benzoyl-7-*O*-benzyl-3,5-dideoxy-α-D-*arabino*-2-heptulopyranosid)onate (10). To a solution of **8** (52 mg, 0.15 mmol) in tetrahydrofuran-methanol (3 : 1) (3.0 mL) was added mercuric trifluoroacetate (127 mg, 0.3 mmol) in four consecutive portions. The solution was stirred for 1 h, excess potassium chloride was then added and the stirring continued for 1 h. Solids were filtered off and the solution was concentrated. The residue was taken in a mixture of tetrahydrofuran-toluene (1 : 5) (3.0 mL). To this mixture was added an excess of anhydrous sodium acetate and triphenyltin hydride (0.15 mL, 0.6 mmol). The reaction was stirred under argon during 16 h. The mixture was diluted with diethyl ether and washed with water, dried and concentrated. Column chromatography of the residue afforded **9** (37 mg, 65 %). Compound **9** was benzoylated (benzoyl chloride-pyridine) to yield **10.**

10: mp 138-142 °C (hexane-diethyl ether); $[\alpha]_D$ +35° (c 0.20). ^{1}H NMR (300 MHz) δ 8.10-7.90 (2H, m, benzoyl-H), 7.60-7.20 (8H, m, benzoyl and benzyl-H), 5.58 (1H, br d, J = 9.5 Hz, NH), 5.49 (1H, ddd, J = 10.4, 11.1, 4.9 Hz, H-4), 4.64 (1H, d, J = 12.0 Hz, benzyl-CH_2), 4.56 (1H, d, J = 12.0 Hz, benzyl-CH_2), 4.17 (1H, ddd, J = 10.4, 9.8, 9.5 Hz, H-5), 3.82 (3H, s, Me-ester), 3.83-3.81 (1H, m, H-6), 3.76-3.72 (2H, m, H_2-7), 3.33 (3H, s, Me-glycoside), 2.55 (1H, dd, J = 12.7, 4.9 Hz, H-3 eq.), 2.04 (1H, dd, J = 12.7, 11.1 Hz, H-3_{ax}), 1.79 (3H, s, Me-acetamido). ^{13}C NMR (75 MHz) δ 170.4, 168.0, 166.8, 138.2-127.6 (C-aromatic), 98.5, 73.6, 73.5, 70.1, 69.5, 52.7, 51.3, 51.0, 37.6, 23.2.

Thiophenyl 2,3-Dideoxy-α-D-*threo*-hex-2-enopyranoside (12). A solution of **2** (3.0 g, 12.6 mmol) and triphenylphosphine (9.9 g, 37.8 mmol) in tetrahydrofuran (60 mL) was stirred for 5 min. This solution was cooled (0 °C) and benzoic acid (4.6 g, 37.7 mmol) was added, followed by the slow addition of a solution of diethyl azodicarboxylate (5.95 mL, 37.8 mmol) in tetrahydrofuran (20 mL). The solution was allowed to reach room temperature and stirred for 24 h. The residue obtained by evaporation of the solvent yielded the dibenzoyl derivative of **12.** Methanolysis (methanol, sodium methoxide) and chromatographic separation of the resulting crude product yielded **12** (2.6 g, 86 %).

12: white solid, mp 108-110 °C (hexane-ethyl acetate); $[\alpha]_D$ +132° (c 0.25). ^{1}H NMR (90 MHz) δ 7.7-7.2 (5H, m, phenyl-H), 6.3-6.0 (2H, m, H-2, H-3), 5.8 (1H, br s, H-1), 4.4 (1H, dt, J_d = 3 Hz, J_t = 6 Hz, H-5), 4.2-3.9 (1H, m, H-4), 3.9 (2H, d, J = 6 Hz, H_2-6), 2.3-2.1 (2H, 2OH).

Thiophenyl 6-*O*-*tert*-Butyldimethylsilyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (13). To a solution of **12** (524 mg, 2.20 mmol), triethylamine (0.42 mL, 3.0 mmol) and 4-dimethylaminopyridine (30 mg) in dry dichloromethane (25 mL) was added *tert*-butyldimethylsilyl chloride (431 mg, 2.86 mmol) and the mixture was stirred for 4 h. Column chromatography of the crude product obtained by evaporation of the solvents gave **13** (580 mg, 78 %).

13: oil, $[\alpha]_D$ +113° (c 0.76). ^{1}H NMR (90 MHz) δ 7.6-7.2 (5H, m, phenyl-H), 6.2-5.9 (2H, m, H-2, H-3), 5.8 (1H, br s, H-1), 4.3 (1H, dt, J_d = 2 Hz, J_t = 6 Hz, H-5), 4.1-3.9 (1H, m, H-4), 3.8 (2H, d, J = 6 Hz, H_2-6), 2.2 (1H, br d, J = 7 Hz, OH), 0.8 (9H, s, *t*-butyl), 0.0 (6H, s, 2 Me-Si).

Methyl (Thiophenyl 6-*O*-*tert*-Butyldimethylsilyl-3,4-dideoxy-α-D-*threo*-hept-3-enopyranosyl)onate (14). A cooled solution (-78 °C) of **13** (151 mg, 0.43 mmol) in tetrahydrofuran (3.0 mL) was treated as described above for the preparation of **7**. Chromatographic separation of the crude reaction product yielded **14** (63 mg, 38%) and **13** (57 mg, 38%).

14: $[\alpha]_D$ +79° (c 0.41). ^{1}H NMR (90 MHz) δ 7.6-7.2 (5H, m, phenyl-H), 6.5-6.2 (2H, m, H-2, H-3), 4.5 (1H, dt, J_d = 3 Hz, J_t = 6 Hz, H-5), 4.2-4.0 (1H, m, H-4), 4.0 (2H, d, J = 6 Hz, H_2-6), 3.5 (3H, s, Me-ester), 2.2-2.0 (1H, OH), 0.9 (9H, s, ^{t}Bu), 0.0 (6H, s, 2 Me-Si).

Methyl 5-*O*-Acetyl-2,6-anhydro-7-*O*-*tert*-Butyldimethylsilyl-3-deoxy-D-xylo-hept-2-enoate (15).

14 was acetylated (acetic anhydride-triethylamine) to yield the *O*-acetyl derivative. To a solution of the *O*-acetyl derivative of **14** (60 mg, 0.13 mmol) in dichloromethane (2.0 mL) at 0 °C was added solid *m*-chloroperbenzoic acid (60 mg, 0.31 mmol). The reaction was elaborated as in the case of **8** (see above) to yield **15** (38 mg, 79%) after chromatographic separation.

15: $[\alpha]_D$ +31° (c 0.30). ^{1}H NMR (90 MHz) δ 6.2 (1H, dd, J = 5, 1 Hz, H-3), 5.1-5.0 (1H, m, H-5), 4.3-4.1 (3H, m, H-5, H_2-6), 4.0-3.8 (1H, m, H-3), 3.8 (3H, s, Me-ester), 2.1 (3H, s, Me-acetate), 0.9 (9H, s, *t*-butyl), 0.0 (6H, s, 2 Me-Si). ^{13}C NMR (50 MHz) δ 170.2, 162.6, 145.6, 107.8, 73.2, 68.5, 61.7, 60.4, 52.4, 25.7, 20.8, 18.2.

Methyl 5-*O*-Acetyl-2,3-anhydro-3-deoxy-D-guloheptenoate (16). A solution of **15** (30 mg, 0.08 mmol) in ethyl acetate was hydrogenated over palladium/carbon (30 mg) at 45 psi during 24 h. Solids were removed by filtration and the solvent was evaporated yielding **16** (17 mg, 82%).

16: mp 158-160 °C (hexane : ethyl acetate); $[\alpha]_D$ +27° (c 0.19). ^{1}H NMR (300 MHz) δ 4.80 (1H, dd, J = 3.3, 1.1 Hz, H-5), 4.55 (1H, dd, J = 8.9, 5.7 Hz, H-2), 4.17-4.11 (2H, m, H-4, H-6), 3.81 (1H, dd, J = 7,4, 11.7 Hz, H-7), 3.81 (3H, s, Me-ester), 3.57 (1H, dd, J = 5.6, 11.7 Hz, H-7), 2.15 (3H, s, Me-acetate), 2.13-2.04 (2H, m, H_2-3).

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