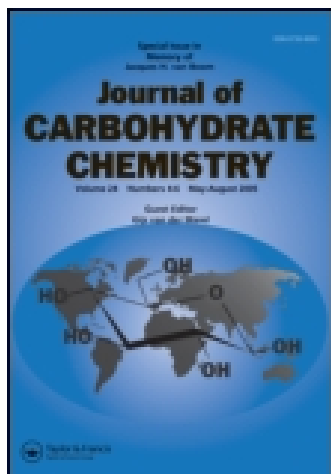


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SYNTHESIS OF BRANCHED-CHAIN HEXULOSE DERIVATIVES AS MODEL FOR THE SYNTHESIS OF TALAROMYCINS

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SYNTHESIS OF BRANCHED-CHAIN HEXULOSE DERIVATIVES AS MODEL FOR THE SYNTHESIS OF TALAROMYCINS

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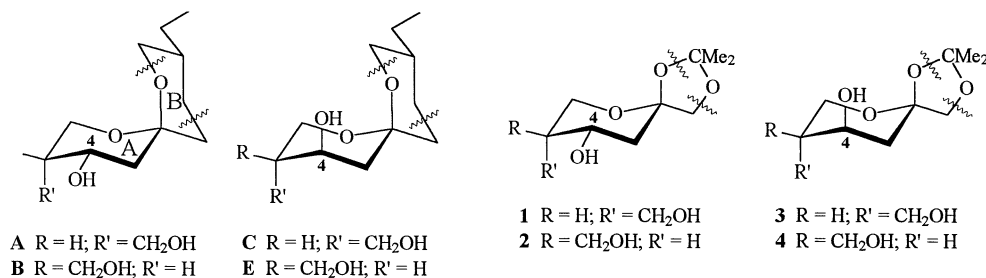
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ABSTRACT

The synthesis of 3,5-dideoxy-1,2-*O*-isopropylidene-5-*C*-hydroxymethyl- β -D-*erythro*- (**1**) and α -L-*threo*-hexulopyranose (**2**) from 3-deoxy-1,2-*O*-isopropylidene- β -D-*erythro*-hexulopyranose (**5**) from D-fructose is described, as well as their respective transformation into 3,5-dideoxy-1,2-*O*-isopropylidene-5-*C*-hydroxymethyl- β -D-*threo*- (**3**) and - α -L-*erythro*-hexulopyranose (**4**) by inversion of configuration at C-4.

INTRODUCTION

Talaromycins A and B are spiroketalic micotoxins produced by the fungus *Talaromyces stipitatus* and were isolated and identified for the first time by Lynn *et al.*¹ In a reinvestigation carried out by the same group,² they detected the presence of additional diastereoisomers talaromycins C and E as represented in Scheme 1. Enantiospecific syntheses of talaromycins A and B can be found in the literature,³ including that reported by our group⁴ which used D-fructose as chiral starting material. However, to the best of our knowledge synthesis of talaromycins C and E has not been communicated at this time. Since the only difference between talaromycins C-E and A-B is that of the C-4 configuration at the A ring, it is reasonable to think that transformation of the latter compounds into the former ones, could be easily achieved by inversion of configuration at this position.



Talaromycins

5-C-Branched-chain hexuloses

Scheme 1.

An examination of the 3,5-dideoxy-5-*C*-hydroxymethylhexulose derivatives (**1–2**) (Scheme 1) clearly indicated that these less elaborated molecules could act as a model in order to see if the above mentioned inversion could be feasible. With this objective in mind, the synthesis of **1–2** from D-fructose as well as their respective transformations into **3–4** are communicated herein.

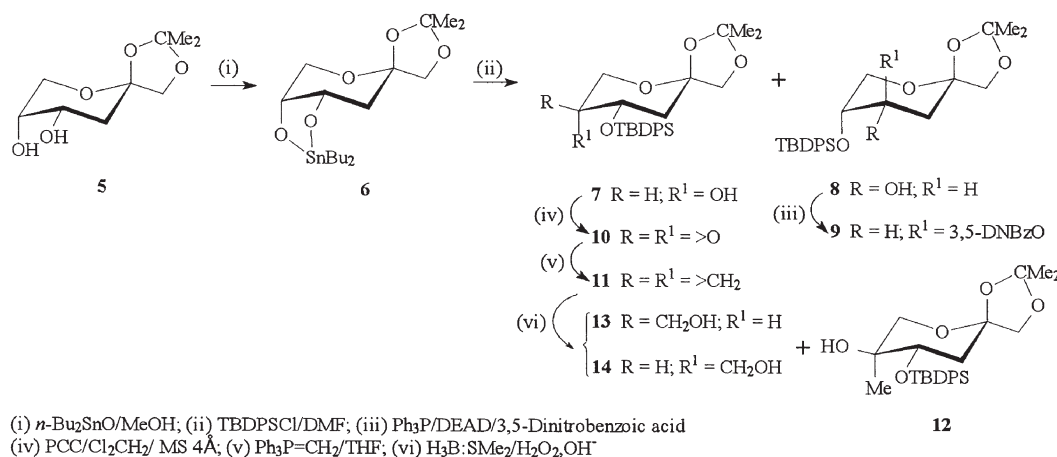
RESULTS AND DISCUSSION

The reaction of 3-deoxy-1,2-*O*-isopropylidene-β-D-*erythro*-hexulopyranose⁵ (**5**) with di-*n*-butyltin oxide in anhydrous methanol afforded 4,5-*O*-dibutylstannylene-3-deoxy-1,2-*O*-isopropylidene-β-D-*erythro*-hexulopyranose (**6**). Treatment of **6** with *tert*-butylchlorodiphenylsilane in dry DMF yielded 4-*O*-*tert*-butyldiphenylsilyl-3-deoxy-1,2-*O*-isopropylidene-β-D-*erythro*-hexulopyranose (**7**) together with a small amount of the related 5-*O*-*tert*-butyldiphenylsilyl regioisomer (**8**). The position of the silyl protecting group in **7** and **8** could be determined from their ¹H NMR spectra. Thus, the resonance signal for H-4 in **7** appeared as a ddd, from coupling with H-3_{ax}, 3_{eq}, 5, whereas H-4 in **8** appeared as a complex multiplet indicating additional coupling (*J* = 8.9 Hz) with HO-4. On the other hand, the chemical shift for H-4, which is geminal to the silyloxy group in **7**, exhibits a downfield shift (0.23 ppm) with respect to its position in compound **8**.

In order to examine the possibility of an inversion of the C-4 configuration by a Mitsunobu reaction,⁶ compound **8** was treated with Ph₃P/3,5-dinitrobenzoic acid/DEAD, giving the expected 5-*O*-*tert*-butyldiphenylsilyl-3-deoxy-1,2-*O*-isopropylidene-4-*O*-(3,5-dinitrobenzoyl)-β-D-*threo*-hexulopyranose (**9**). Inversion of the configuration at C-4 in **9** was evident from the NMR signal of H-4.

The introduction of the branched-chain at C-5 in **7** was carried out by oxidation to 2,5-diulose (**10**) followed by reaction with methylenetriphenylphosphorane to afford the 5-*C*-methylene derivative **11**. Hydroboration-oxidation of **11** was regio and stereoselective and gave a mixture of 4-*O*-*tert*-butyldiphenylsilyl-3-deoxy-1,2-*O*-isopropylidene-5-*C*-methyl-α-L-*threo*-hexulopyranose (**12**, 12%), 4-*O*-*tert*-



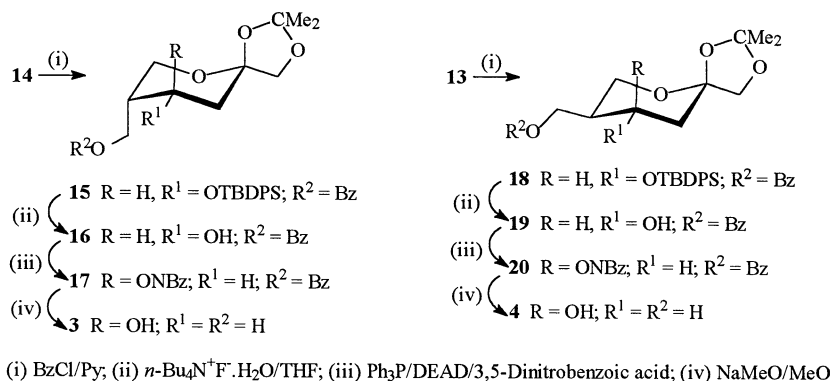


Scheme 2.

butyldiphenylsilyl-3,5-dideoxy-5-*C*-hydroxymethyl-1,2-*O*-isopropylidene- α -*L*-threo-hexulopyranose (**13**, 8.5%), and 4-*O*-*tert*-butyldiphenylsilyl-3,5-dideoxy-5-*C*-hydroxymethyl-1,2-*O*-isopropylidene- β -*D*-erythro-hexulopyranose (**14**, 55%). Compound **14** results from equatorial attack at C-5 in **11** by the hydroborating reagent.

Inversion of the configuration at C-4 in **13** and **14** required the previous protection of the hydroxymethyl group at C-5. With this aim both compounds were benzoylated to the corresponding 5-*C*-benzoyloxymethyl derivatives **18** and **15** respectively.

Treatment of **15** with tetrabutylammonium fluoride in THF caused *O*-desilylation to 5-*C*-benzoyloxymethyl-3,5-dideoxy-1,2-*O*-isopropylidene- β -*D*-erythro-hexulopyranose (**16**) concomitant with $O_7 \rightarrow O_4$ benzoyl group migration (see Experimental) that could be avoided in the analogous reaction on compound **18** to give **19**, by addition of ammonium chloride.



Scheme 3.



Compounds **16** and **19** were transformed into the fully protected 4-epimers 5-*C*-benzoyloxymethyl-3,5-dideoxy-1,2-*O*-isopropylidene-4-*O*-(3,5-dinitrobenzoyl)- β -D-*threo*- (**17**) and - α -L-*erythro*-hexulopyranose (**20**), by the above mentioned Mitsunobu reaction, and finally debenzoylated to the expected 3,5-dideoxy-5-*C*-branched-chain hexulopyranose derivatives **3** and **4**.

EXPERIMENTAL

General methods. Melting points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried over MgSO_4 before concentration under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300, and ARX-400 spectrometers for solutions in CDCl_3 (internal Me_4Si). IR spectra were recorded with a Perkin-Elmer 782 instrument and mass spectra with a Hewlett-Packard HP-5988-A and Fisons model Platform II and VG Autospec-Q mass spectrometers. Optical rotations were measured for solutions in CHCl_3 (1-dm tube) with a Jasco DIP-370 polarimeter. GLC was performed on a Hewlett-Packard 6890 gas chromatograph equipped with split/splitless injector, a flame-ionization detector and a capillary HP-5 column (30 m $\times$ 0.25 mm i.d. $\times$ 0.25 μm film thickness) at 3 min at 180 $^\circ\text{C}$, program to 250 $^\circ\text{C}$, 10 $^\circ\text{C}/\text{min}$. The He flow rate was 1.1 mL/min, the injection port and the zone-detector temperatures were 275 $^\circ\text{C}$. TLC was performed on precoated silica gel 60 F_{254} aluminium sheets and detection by charring with H_2SO_4 . Column chromatography was performed on silica gel (Merck, 7734). The noncrystalline compounds, for which elemental analyses were not obtained were shown to be homogeneous by chromatography and characterized by NMR and HRMS.

4-*O*- (7) and 5-*O*-*Tert*-butyldiphenylsilyl-3-deoxy-1,2-*O*-isopropylidene- β -D-*erythro*-hexulopyranose (8). To solution of 3-deoxy-1,2-*O*-isopropylidene- β -D-*erythro*-hexulopyranose⁵ (**5**, 6.2 g, 30.4 mmol) in dry methanol (200 mL), was added dibutyltin oxide (7.95 mg, 32 mmol) and the suspension was heated for 2 h under reflux. The clear solution was concentrated to afford the 4,5-dibutylstannylene derivative **6** as a solid foam that was dried under vacuum over P_2O_5 overnight. A solution of **6** in dry DMF (250 mL) was treated at room temperature with *tert*-butylchlorodiphenylsilane (8.8 g, 32 mmol) for 20 h. TLC (ether-hexane 3:1) then revealed the absence of **6** and the presence of a further running main product. GLC 22.4 min (major) and 24.2 (minor) in a 87:13 ratio. The mixture was filtered and the filtrate concentrated to a residue that was partitioned into toluene-water. The organic phase was concentrated, and the residue subjected to flash chromatography (ether-hexane 1:6 $\rightarrow$ 1:3) to afford first **7** (6.63 g, 50% from **5**) as a thick syrup; $[\alpha]_{\text{D}}^{23} -36.5$ (c 1); $\nu_{\text{max}}^{\text{film}}$ 3570 (OH), 3073 and 3049 (aromatic), 1373 (CMe_2), and 703 cm^{-1} (aromatic). NMR data: ^1H , δ 7.6–.64 and 7.4–.37 (2 m, 10 H, Ph), 4.20 (ddd, 1 H, $J_{3\text{ax},4}$ 11.3, $J_{3\text{eq},4}$ 5, $J_{4,5}$ 3.3 Hz, H-4), 3.99 (d, 1 H, $J_{1,1'}$ 8.7 Hz, H-1), 3.82 (dd, 1 H, $J_{5,6\text{ax}}$ 2, $J_{6\text{ax},6\text{eq}}$ 12.7 Hz, H-6ax), 3.75 (dt, 1 H, $J_{5,6\text{eq}} = J_{4,6\text{eq}} = 1.7$ Hz, H-6eq), 3.64 (bs, 1 H, H-5), 3.62 (d, 1 H, H-1'), 2.60 (bs, 1 H, OH-5), 2.05 (t, 1 H,



H-3ax), 1.42 (dd, 1 H, $J_{3ax,3eq}$ 10.3 Hz, H-3eq), 1.36 and 1.19 (2 s, 6 H, CMe_2) and 1.10 (s, 9 H, Me_3C); ^{13}C , δ 135.77, 135.68, 133.47, 133.35, 133.10, 127.90, and 127.86 (aromatic), 111.10 (CMe_2), 104.38 (C-2), 74.97 (C-1), 68.41 and 67.80 (C-4,5), 63.74 (C-6), 36.09 (C-3), 26.98 and 26.55 (Me_2C and Me_3C), and 19.18 (Me_3C). Mass spectrum (LSIMS): m/z 465.2079 ($M^+ + Na$). For $C_{25}H_{34}O_5NaSi$ 465.2073 (deviation -1.3 ppm).

Eluted second was **8** (350 mg, 2.6% from **5**) as a syrup; $[\alpha]_D^{25} - 58$ (c 1); ν_{max}^{film} 3591 (OH), 3139 and 3055 (aromatic), 1372 (CMe_2), and 703 cm^{-1} (aromatic). NMR data: 1H , δ 7.7–.67 and 7.4–.38 (2 m, 10 H, Ph), 4.17 (d, 1 H, $J_{1,1'}$ 8.9 Hz, H-1), 3.97 (m, 1 H, H-4), 3.89 (bq, 1 H, H-5), 3.81 (d, 1 H, H-1'), 2.62 (dd, 1 H, $J_{5,6ax}$ 2, $J_{6ax,6eq}$ 12.5 Hz, H-6ax), 3.53 (dd, 1 H, $J_{5,6eq}$ = 3.6 Hz, H-6eq), 2.19 (d, 1 H, $J_{HO,4}$ = 8.9 Hz, OH-4), 2.10 (dd, 1 H, $J_{3ax,4}$ 10.2, $J_{3ax,3eq}$ 12.4 Hz, H-3ax), 1.91 (dd, 1 H, $J_{3eq,4}$ 4.4 Hz, H-3eq), 1.41 and 1.37 (2 s, 6 H, CMe_2) and 1.10 (s, 9 H, Me_3C); ^{13}C , δ 135.87, 135.84, 133.48, 133.01, 130.12, 130.04, 128.01 and 127.85 (aromatic), 111.00 (CMe_2), 104.23 (C-2), 74.41 (C-1), 69.76 and 67.16 (C-4,5), 64.14 (C-6), 36.80 (C-3), 27.11 and 26.52 (Me_2C and Me_3C), and 19.57 (Me_3C). Mass spectrum (LSIMS): m/z 465.2077 ($M^+ + Na$). For $C_{25}H_{34}O_5NaSi$ 465.2073 (deviation -0.7 ppm).

5-*O*-*Tert*-butyldiphenylsilyl-3-deoxy-1,2-*O*-isopropylidene-4-*O*-(3,5-dinitrobenzoyl)- β -D-*threo*-hexulopyranose (9**).** To a stirred solution of **8** (80 mg, 0.18 mmol) in dry THF (3 mL) were added Ph_3P (178 mg, 0.68 mmol), 3,5-dinitrobenzoic acid (144 mg, 0.68 mmol) and diethylazodicarboxylate (DEAD, 118 mg, 0.68 mmol). The mixture was left at room temperature for 22 h. TLC (ether-hexane 1:1) then revealed the presence of a slower-running product. The mixture was diluted with ether and washed with saturated aqueous Na_2CO_3 solution and with water, then concentrated. Column chromatography (ether-hexane 1:5) of the residue gave syrupy **9** (70 mg, 61%); $[\alpha]_D^{26} - 16$ (c 1); ν_{max}^{film} 3093 and 3043 cm^{-1} (aromatic), 1735 ($C=O$), 1346 (CMe_2), 725 and 704 cm^{-1} (aromatic). NMR data: 1H , δ 9.19 (t, 1 H, J 2.1 Hz, H-4 of 3,5-DNBzO group), 9.14 (d, 2 H, H-2,6 of DNBzO group), 7.7–.64 and 7.4–.34 (2 m, 10 H, Ph), 5.31 (m, 1 H, H-4), 4.21 (d, 1 H, $J_{1,1'}$ 8.7 Hz, H-1), 4.08 (dd, 1 H, $J_{6ax,6eq}$ 12.6, $J_{5,6ax}$ 1.6 Hz, H-6ax), 3.82 (d, 1 H, H-1'), 3.78 (m, 1 H, H-5), 3.50 (dd, 1 H, $J_{5,6eq}$ 1.5 Hz, H-6eq), 2.54 (dd, 1 H, $J_{3,4}$ 3.4, $J_{3,3'}$ 14.3 Hz, H-3), 1.97 (dd, 1 H, $J_{3',4}$ 3.9 Hz, H-3'), 1.55 and 1.32 (2 s, 6 H, CMe_2), and 1.10 (s, 9 H, Me_3C); ^{13}C , δ 161.54 ($C=O$), 148.68, 135.80, 135.73, 134.24, 133.16, 132.99, 130.16, 130.08, 129.68, 127.98, 127.95, and 122.41 (aromatic), 111.91 (CMe_2), 102.49 (C-2), 74.99 (C-1), 71.94 (C-4), 66.33 (C-5), 62.66 (C-6), 31.89 (C-3), 27.14 and 26.59 (Me_2C), 26.94 (Me_3C), and 19.37 (Me_3C). Mass spectrum (LSIMS): m/z 659.2033 ($M^+ + Na$). For $C_{32}H_{36}N_2O_{10}NaSi$ 659.2037 (deviation 0.7 ppm).

4-*O*-*Tert*-butyldiphenylsilyl-3,5-dideoxy-1,2-*O*-isopropylidene-5-*C*-methylene- β -D-*glycero*-hexulopyranose (11**).** To a stirred and cooled (ice-water) solution of **7** (4.75 g, 10.74 mmol) in dry dichloromethane (50 mL) were added sodium acetate (315 mg, 3.84 mmol), molecular sieve (4 Å powder, 5 g) and pyri-



dinium chlorochromate (4.5 g, 20.6 mmol). Stirring was maintained at room temperature overnight. TLC (ether-hexane 3:1) then revealed a new compound of higher mobility. The mixture was diluted with ether (150 mL), filtered through silica gel G and concentrated to a residue that was chromatographed (ether) to afford **10** (3.4 g, 72%) that was not investigated but used in the next step.

To a stirred solution of $\text{NaCH}_2\text{SOCH}_3$ (from 350 mg of an 80% dispersion of sodium hydride in oil) and imidazole (62 mg, 1 mmol) in anhydrous methyl sulfoxide (20 mL) under argon was added methyltriphenylphosphonium bromide (3.54 g, 10 mmol). The mixture was stirred for 20 min and a solution of **10** (1.75 g, 4 mmol) in dry ether (20 mL) was added dropwise and the reaction mixture left for 2.5 h. TLC (ether-hexane 1:3) then showed a new compound of higher mobility. The mixture was treated with ether saturated with water, the organic phase was separated, the aqueous phase extracted with ether, and the combined extracts were washed with brine and concentrated. Column chromatography (ether-hexane 1:5) of the residue gave **11** (1.38 g, 79%) as a colorless syrup; $[\alpha]_D^{25} -64$ (*c* 1); $\nu_{\text{max}}^{\text{film}}$ 3057 and 3048 (aromatic), 1382 and 1372 (CMe_2), and 702 cm^{-1} (aromatic). NMR data: ^1H , δ 7.7–.63 and 7.4–.34 (2 m, 10 H, Ph), 5.38 (t, 1 H, *J* 1.9 Hz, H-7), 5.02 (bs, 1 H, H-7'), 4.68 (m, 1 H, H-4), 4.26 (d, 1 H, $J_{6\text{ax},6\text{eq}}$ 12.3 Hz, H-6ax), 4.02 (d, 1 H, H-6eq), 3.88 (d, 1 H, $J_{1,1'}$ 8.7 Hz, H-1), 3.53 (d, 1 H, H-1'), 1.63 (m, 2 H, H-3,3'), 1.38 and 1.14 (2 s, 6 H, CMe_2), and 1.11 (s, 9 H, CMe_3); ^{13}C , δ 145.73 (C-5), 135.91, 135.78, 134.37, 133.77, 129.88, 129.79, 127.74, and 127.70 (aromatic), 111.11 (CMe_2), 108.25 (C-7), 104.92 (C-2), 74.57 (C-1), 68.68 (C-4), 65.80 (C-6), 44.05 (C-3), 27.07 (Me_3C), 26.86 and 26.40 (Me_2C), and 19.37 (Me_3C). Mass spectrum (LSIMS): m/z 461.2122 ($\text{M}^+ + \text{Na}$). For $\text{C}_{26}\text{H}_{34}\text{O}_4\text{NaSi}$ 461.2124 (deviation 0.5 ppm).

Hydroboration-oxidation of 11. To a stirred and cooled (ice-water) solution of **11** (1.34 g, 3.1 mmol) in anhydrous THF (20 mL) was added dropwise under argon 10M $\text{BH}_3\text{-SMe}_2$ (0.7 mL). The mixture was allowed to reach room temperature and stirring was maintained for 30 min. 3M NaOH (3 mL) and aqueous 30% H_2O_2 (3 mL) were added dropwise to the stirred and ice-cooled mixture. Stirring was continued for 30 min at room temperature, ether (20 mL) was added, the organic phase was separated, and the aqueous phase was extracted with ether. The combined extracts were washed with brine and water, then concentrated. Flash-chromatography (ether-hexane 1:6) gave first crystalline 4-*O*-*tert*-butyldiphenylsilyl-3-deoxy-1,2-*O*-isopropylidene-5-*C*-methyl- α -L-*threo*-hexulopyranose (**12**, 170 mg, 12%), mp 106–108 °C; $[\alpha]_D^{25} -36$ (*c* 1); $\nu_{\text{max}}^{\text{KBr}}$ 3488 (OH), 3074 and 3044 (aromatic), 1388 and 1378 (CMe_2), and 705 cm^{-1} (aromatic). NMR data: ^1H , δ 7.7–.37 (2 m, 10 H, Ph), 4.12 (dd, 1 H, $J_{3\text{eq},4}$ 6.5, $J_{3\text{ax},4}$ 9.6 Hz, H-4), 3.92 (d, 1 H, $J_{1,1'}$ 8.8 Hz, H-1), 3.58 (d, 1 H, H-1'), 3.56 (d, 1 H, $J_{6\text{ax},6\text{eq}}$ 11.2 Hz, H-6ax), 3.36 (d, 1 H, H-6eq), 1.73 (bs, 1 H, OH-5), 1.64 (m, 2 H, H-3ax,3eq), 1.37 and 1.18 (2 s, 6 H, CMe_2), 1.35 (s, 3 H, Me-5), and 1.11 (s, 9 H, CMe_3); ^{13}C , δ 135.97, 135.88, 134.21, 133.61, 130.02, 129.94, 127.89, and 127.80 (aromatic), 111.22 (CMe_2), 104.44 (C-2), 74.27 (C-4), 74.23 (C-1), 71.54 (C-5), 68.59 (C-6), 39.47 (C-3), 27.13



(Me_3C), 26.82 and 26.41 (Me_2C), 19.50 (Me_3C), and 18.72 (Me -5). Mass spectrum (LSIMS): m/z 479.2230 ($M^+ + Na$). For $C_{26}H_{36}O_5NaSi$ 479.2230 (deviation -0.1 ppm).

Eluted second was 4-*O*-*tert*-butyldiphenylsilyl-3,5-dideoxy-5-*C*-hydroxymethyl-1,2-*O*-isopropylidene- α -L-*threo*-hexulopyranose (**13**, 120 mg, 8.5%); $[\alpha]_D^{24} -21$ (c 1); ν_{max}^{film} 3489 (OH), 3074 and 3052 (aromatic), 1379 and 1371 (CMe_2), and 702 cm^{-1} (aromatic). NMR data: 1H , δ 7.7–.35 (2 m, 10 H, Ph), 4.16 (dt, 1 H, $J_{3ax,4} = J_{4,5} = 10.1$, $J_{3eq,4}$ 5.3 Hz, H-4), 3.89 (d, 1 H, $J_{1,1'}$ 8.8 Hz, H-1), 3.79 (dd, 1 H, $J_{5,7}$ 4.8, $J_{7,7'}$ 11.0 Hz, H-7), 3.76 (dd, 1 H, $J_{5,6eq}$ 4.8, $J_{6ax,6eq}$ 11.5 Hz, H-6eq), 3.60 (t, 1 H, $J_{5,6ax}$ 11.5 Hz, H-6ax), 3.59 (dd, 1 H, $J_{5,7'}$ 8.5 Hz, H-7'), 3.53 (d, 1 H, H-1'), 1.91 (m, 2 H, H-5, OH), 1.69 (dd, 1 H, $J_{3ax,3eq}$ 12.3 Hz, H-3eq), 1.63 (t, 1 H, H-3ax), 1.37 and 1.16 (2 s, 6 H, CMe_2), and 1.08 (s, 9 H, CMe_3); ^{13}C , δ 135.95, 135.83, 134.88, 134.32, 129.99, 127.89, and 127.83 (aromatic), 111.03 (CMe_2), 104.46 (C-2), 74.72 (C-1), 69.46 (C-4), 62.47 and 61.83 (C-6,7), 46.33 (C-5), 41.79 (C-3), 27.12 (Me_3C), 26.81 and 26.44 (Me_2C), and 19.39 (Me_3C). Mass spectrum (LSIMS): m/z 479.2228 ($M^+ + Na$). For $C_{26}H_{36}O_5NaSi$ 479.2230 (deviation 0.4 ppm).

The last eluted fraction contained 4-*O*-*tert*-butyldiphenylsilyl-3,5-dideoxy-5-*C*-hydroxymethyl-1,2-*O*-isopropylidene- β -D-*erythro*-hexulopyranose (**14**, 773 mg, 55%); $[\alpha]_D^{25} -37$ (c 1); ν_{max}^{film} 3438 (OH), 3049 and 3015 (aromatic), 1383 and 1373 (CMe_2), and 702 cm^{-1} (aromatic). NMR data: 1H , δ 7.7–.36 (2 m, 10 H, Ph), 4.47 (dt, 1 H, $J_{3ax,4}$ 11.5, $J_{3eq,4} = J_{4,5} = 4.9$ Hz, H-4), 4.23 (dd, 1 H, $J_{5,7}$ 8.0, $J_{7,7'}$ 11.2 Hz, H-7), 3.89 (d, 1 H, $J_{1,1'}$ 8.7 Hz, H-1), 3.88 (dd, 1 H, $J_{5,6ax}$ 2.7, $J_{6ax,6eq}$ 12.0 Hz, H-6ax), 3.78 (dd, 1 H, $J_{5,7'}$ 6.6 Hz, H-7'), 3.63 (dd, 1 H, $J_{5,6eq}$ 1.8 Hz, H-6eq), 3.55 (d, 1 H, H-1'), 2.10 (m, 2 H, H-5, OH), 1.88 (t, 1 H, $J_{3ax,3eq}$ 12.5 Hz, H-3ax), 1.45 (dd, 1 H, H-3eq), 1.34 and 1.13 (2 s, 6 H, CMe_2), and 1.08 (s, 9 H, CMe_3); ^{13}C , δ 135.94, 135.83, 133.49, 133.28, 130.09, 130.06, 129.97, and 127.87 (aromatic), 111.11 (CMe_2), 104.42 (C-2), 74.84 (C-1), 69.57 (C-4), 62.10 and 61.25 (C-6,7), 41.89 (C-5), 37.79 (C-3), 27.06 (Me_3C), 26.80 and 26.40 (Me_2C), and 19.08 (Me_3C). Mass spectrum (LSIMS): m/z 479.2233 ($M^+ + Na$). For $C_{26}H_{36}O_5NaSi$ 479.2230 (deviation -0.6 ppm).

5-*C*-Benzoyloxymethyl-4-*O*-*tert*-butyldiphenylsilyl-3,5-dideoxy-1,2-*O*-isopropylidene- β -D-*erythro*-hexulopyranose (15**).** Conventional benzoylation of **14** (310 mg, 0.7 mmol) with benzoyl chloride (0.25 mL, 2.2 mmol) in dry dichloromethane (10 mL) in the presence of triethylamine (0.4 mL, 2.9 mmol) at room temperature overnight gave, after work-up and column chromatography (hexane $\rightarrow$ ether-hexane 1:15), pure **15** (280 mg, 74%) as a syrup; ν_{max}^{film} 3062 (aromatic), 1718 ($C=O$, benzoate), 1377 (CMe_2), and 715 cm^{-1} (aromatic). NMR data: 1H , δ 8.1–.38 (5 m, 15 H, Ph), 4.80 (dd, 1 H, $J_{5,7}$ 3.6, $J_{7,7'}$ 10.7 Hz, H-7), 4.56 (t, 1 H, $J_{5,7'}$ 10.6 Hz, H-7'), 4.43 (dt, 1 H, $J_{3ax,4}$ 11.5, $J_{3eq,4} = J_{4,5} = 5.1$ Hz, H-4), 3.96 (d, 1 H, $J_{1,1'}$ 8.8 Hz, H-1), 3.86 (dd, 1 H, $J_{5,6}$ 1.8, $J_{6,6'}$ 12.0 Hz, H-6), 3.80 (dd, 1 H, $J_{5,6'}$ 1.8 Hz, H-6'), 3.62 (d, 1 H, H-1'), 2.10 (m, 1 H, H-5), 1.80 (t, 1 H, $J_{3ax,3eq}$ 12.6 Hz, H-3ax), 1.60 (dd, 1 H, H-3eq), 1.38 and 1.21 (2 s, 6 H, CMe_2), and 1.11



(s, 9 H, CMe₃); ¹³C (*inter alia*) δ166.72 (PhCO), 111.14 (CMe₂), 104.35 (C-2), 74.84 (C-1), 67.34 (C-4), 60.94 and 60.67 (C-6,7), 40.05 (C-5), 38.32 (C-3), 27.02 (Me₃C), 26.81 and 26.45 (Me₂C), and 19.20 (Me₃C).

5-C-Benzoyloxymethyl-3,5-dideoxy-1,2-O-isopropylidene-β-D-erythro-hexulopyranose (16). To a stirred solution of **15** (220 mg, 0.4 mmol) in THF (5 mL) was added tetrabutylammonium fluoride trihydrate (730 mg, 2.3 mmol) under argon. The mixture was stirred at room temperature 8 h. TLC (ether-hexane 1:1) then revealed a slower-running product. The solvent was evaporated and a solution of the residue in ether was washed with brine and water, then concentrated. Column chromatography (ether-hexane 3:1) gave first crystalline **16** (80 mg, 64%), mp 122–124 °C; [α]_D²⁴ –100 (*c* 1.1); *v*_{max}^{KBr} 3307 (OH), 3070 (aromatic), 1717 (C=O, benzoate), 1386 and 1373 (CMe₂), and 713 cm^{–1} (aromatic). NMR data: ¹H, δ8.0–.41 (3 m, 5 H, Ph), 4.68 (dd, 1 H, J_{5,7} 5.5, J_{7,7'} 11.1 Hz, H-7), 4.36 (dd, 1 H, J_{5,7'} 8.7 Hz, H-7'), 4.35 (dt, 1 H, J_{3eq,4} = J_{4,5} = 4.7 Hz, H-4), 4.11 (d, 1 H, J_{1,1'} 9.0 Hz, H-1), 3.93 (dd, 1 H, J_{5,6} 3, J_{6,6'} 12.0 Hz, H-6), 3.86 (dd, 1 H, J_{5,6'} 3.9 Hz, H-6'), 3.76 (d, 1 H, H-1'), 2.29 (m, 1 H, H-5), 1.95 (dd, 1 H, J_{3ax,3eq} 13 Hz, H-3eq), 1.84 (dd, 1 H, J_{3ax,4} 10 Hz, H-3ax), 1.48 and 1.37 (2 s, 6 H, CMe₂); ¹³C, δ167.01 (PhCO), 133.21, 130.92, 129.66, and 128.48 (Ph), 111.11 (CMe₂), 104.17 (C-2), 74.28 (C-1), 65.62 (C-4), 61.34 and 60.99 (C-6,7), 39.87 (C-5), 37.85 (C-3), 27.14 and 26.52 (Me₂C). Mass spectrum (LSIMS): *m/z* 345.1316 (M⁺ + Na). For C₁₇H₂₂O₆Na 345.1314 (deviation –0.4).

Anal. Calcd for C₁₇H₂₂O₆: C, 63.37; H, 6.87. Found: C, 63.60; H, 6.84.

Eluted second was 4-*O*-benzoyl-3,5-dideoxy-5-*C*-hydroxymethyl-1,2-*O*-isopropylidene-β-D-erythro-hexulopyranose (10 mg) contaminated with **16**. NMR data (*inter alia*): ¹H, 5.67 (dt, 1 H, J_{3eq,4} = J_{4,5} = 5.0, J_{3ax,4} 9.5 Hz, H-4), 4.62 (dd, 1 H, J_{5,7} 5.9, J_{7,7'} 11.6 Hz, H-7), and 4.37 (dd, 1 H, J_{5,7'} 3.5 Hz, H-7'). Mass spectrum (LSIMS): *m/z* 345.1315 (M⁺ + Na). For C₁₇H₂₂O₆Na 345.1314 (deviation –0.3 ppm).

5-C-Benzoyloxymethyl-3,5-dideoxy-1,2-O-isopropylidene-4-O-(3,5-dinitrobenzoyl)-β-D-threo-hexulopyranose (17). Treatment of **16** (116 mg, 0.36 mmol) with Ph₃P (188 mg, 0.72 mmol), 3,5-dinitrobenzoic acid (153 mg, 0.72 mmol) and DEAD (125 mg, 0.72 mmol) in dry THF (3 mL) as above gave, after work-up and column chromatography (ether-hexane 1:3), crystalline **17** (100 mg, 54%); mp 115–116 °C (from ether-hexane); [α]_D²⁷ –83 (*c* 1); *v*_{max}^{KBr} 3097 (aromatic), 1725 (C=O benzoate), 1382 (CMe₂), and 719 cm^{–1} (aromatic). NMR data: ¹H, δ9.3–.47 (4 m, 8 H, Bz and 3,5-DNBz), 5.58 (m, 1 H, H-4), 4.6–.51 (m, 3 H, H-6,7,7'), 4.14 (d, 1 H, J_{1,1'} 8.7 Hz, H-1), 3.8–.78 (m, 2 H, H-1',6'), 2.40 (m, 1 H, H-5), 2.30 (dd, 1 H, J_{3,4} 3.5, J_{3,3'} 14.9 Hz, H-3), 2.10 (dd, 1 H, J_{3',4} 3.1 Hz, H-3'), 1.64 and 1.40 (2 s, 6 H, CMe₂); ¹³C, δ166.42 (Bz), 161.76 (3,5-DNBz) 148.83, 134.39, 133.42, 129.71, 128.61, and 122.54 (aromatic), 112.27 (CMe₂), 102.47 (C-2), 75.17 (C-1), 69.95 (C-4), 63.09 (C-6), 58.57 (C-7), 37.19 (C-5), 32.66 (C-3), 27.13 and 26.62 (Me₂C). Mass spectrum (LSIMS): *m/z* 539.1277 (M⁺ + Na). For C₂₄H₂₄N₂O₁₁Na 539.1278 (deviation 0.2 ppm).



Anal. Calcd for $C_{24}H_{24}N_2O_5$: C, 52.94; H, 4.44; N, 10.29. Found: C, 52.35; H, 4.31; N, 10.52.

3,5-Dideoxy-5-C-hydroxymethyl-1,2-O-isopropylidene- α -D-threo-hexulopyranose (3). A stirred suspension of **17** (37 mg, 0.08 mmol) in anhydrous methanol (5 mL) was treated with 0.8M sodium methoxide (0.5 mL) in the same solvent for 1 h. TLC (ether-hexane 3:1) then revealed a compound of lower mobility. The reaction mixture was neutralized (acetic acid), supported on silica gel and finally chromatographed (ether $\rightarrow$ ether-methanol 5:1) to yield pure **3** (17 mg, quantitative) as a clear thick syrup; $[\alpha]_D^{28} - 101$, $[\alpha]_{405}^{28} - 228.5$ (c 0.45). NMR data: 1H , δ 4.21 (dd, 1 H, $J_{5,6}$ 3.3, $J_{6,6'}$ 12.3 Hz, H-6), 4.00 (d, 1 H, $J_{1,1'}$ 8.7 Hz, H-1), 4.01 (bs, 1 H, H-4), 3.75 (dd, 1 H, $J_{5,7}$ 3.8, $J_{7,7'}$ 10.8 Hz, H-7), 3.70 (d, 1 H, H-1'), 3.67 (dd, 1 H, $J_{5,7'}$ 7.1 Hz, H-7'), 3.58 (dd, 1 H, $J_{5,6'}$ 2.4 Hz, H-6'), 2.02 (dd, 1 H, $J_{3,4}$ 3.7, $J_{3,3'}$ 14.0 Hz, H-3), 1.85 (m, 1 H, H-5), 1.83 (dd, 1 H, $J_{3',4}$ 4.4 Hz, H-3'), 1.47 and 1.39 (2 s, 6 H, CM_e_2); ^{13}C , δ 111.84 (CM_e_2), 103.84 (C-2), 74.52 (C-1), 66.68 (C-4), 62.57 (C-6), 59.02 (C-7), 43.21 (C-5), 35.99 (C-3), 27.03 and 26.55 (Me_2C). Mass spectrum (LSIMS): m/z 241.1053 ($M^+ + Na$). For $C_{10}H_{18}O_5Na$ 241.1055 (deviation -0.5 ppm).

5-C-Benzoyloxymethyl-4-O-tert-butylidiphenylsilyl-3,5-dideoxy-1,2-O-isopropylidene- α -L-threo-hexulopyranose (18). Conventional benzylation of **13** (120 mg, 0.26 mmol) with benzoyl chloride (120 μ L) in dry dichloromethane (2 mL) in the presence of triethylamine (300 μ L) at room temperature overnight gave, after work-up and column chromatography (ether-hexane 1:5), pure **18** (60 mg, 41%) as a syrup; $[\alpha]_D^{25} + 86$ (c 0.4); ν_{max}^{film} 3065 and 3011 (aromatic), 1726 (C=O, benzoate), 1382 (CM_e_2), and 708 cm^{-1} (aromatic). NMR data: 1H , δ 7.9–.28 (4 m, 15 H, Ph), 4.65 (dd, 1 H, $J_{5,7}$ 3.4, $J_{7,7'}$ 11.2 Hz, H-7), 4.27 (dd, 1 H, $J_{5,7'}$ 7.4 Hz, H-7'), 4.17 (dt, 1 H, $J_{3eq,4}$ 5.1, $J_{3ax,4} = J_{4,5} = 10$ Hz, H-4), 3.90 (d, 1 H, $J_{1,1'}$ 8.7 Hz, H-1), 3.85 (dd, 1 H, $J_{5,6eq}$ 4.8, $J_{6ax,6eq}$ 11.6 Hz, H-6eq), 3.69 (t, 1 H, $J_{5,6ax}$ 11.4 Hz, H-6ax), 3.54 (d, 1 H, H-1'), 2.2–.13 (m, 1 H, H-5), 1.72 (dd, 1 H, $J_{3ax,3eq}$ 12.3 Hz, H-3eq), 1.65 (dd, 1 H, H-3ax), 1.35 and 1.16 (2 s, 6 H, CM_e_2), and 1.07 (s, 9 H, CM_e_3); ^{13}C (*inter alia*) δ 166.39 (PhCO), 111.09 (CM_e_2), 104.46 (C-2), 74.77 (C-1), 68.00 (C-4), 63.08 and 62.61 (C-6,7), 43.81 (C-5), 41.86 (C-3), 27.04 (Me_3C), 26.81 and 26.43 (Me_2C), and 19.41 (Me_3C).

5-C-Benzoyloxymethyl-3,5-dideoxy-1,2-O-isopropylidene- α -L-threo-hexulopyranose (19). Treatment of **18** (60 mg, 0.11 mmol) in THF (3 mL) with tetrabutylammonium fluoride trihydrate (200 mg, 0.64 mmol) and ammonium chloride (20 mg, 0.4 mmol) under argon as above gave, after work-up and column chromatography (ether-hexane 3:15), pure **19** (25 mg, 71%) as a syrup; $[\alpha]_D^{25} - 38$ (c 1.3); ν_{max}^{film} 3274 (OH), 3063 (aromatic), 1718 (C=O, benzoate), 1378 (CM_e_2), and 710 cm^{-1} (aromatic). NMR data: 1H , δ 8.0–.10 (3 m, 5 H, Bz), 4.62 (dd, 1 H, $J_{5,7}$ 5.8, $J_{7,7'}$ 11.6 Hz, H-7), 4.38 (dd, 1 H, $J_{5,7'}$ 3.4 Hz, H-7'), 4.01 (d, 1 H, $J_{1,1'}$ 8.7 Hz, H-1), 3.93 (dt, 1 H, $J_{3eq,4}$ 4.8, $J_{3ax,4} = J_{4,5} = 10.9$ Hz, H-4), 3.86 (dd, 1 H, $J_{5,6eq}$ 4.9, $J_{6ax,6eq}$ 11.5 Hz, H-6eq), 3.78 (d, 1 H, H-1'), 3.76 (t, 1 H, $J_{5,6ax}$ 11.0 Hz, H-



6ax), 2.08 (dd, 1 H, $J_{3ax,3eq}$ 12.3 Hz, H-3eq), 1.98 (m, 1 H, H-5), 1.70 (dd, 1 H, H-3ax), 1.45 and 1.36 (2 s, 6 H, CMe_2); ^{13}C , δ 167.18 (PhCO), 133.4, 129.97, and 128.58 (aromatic), 111.54 (CMe_2), 104.62 (C-2), 74.99 (C-1), 65.79 (C-4), 63.00 and 62.30 (C-6,7), 44.22 (C-5), 40.89 (C-3), 27.07 and 26.65 (Me_2C). Mass spectrum (LSIMS): m/z 345.1314 ($M^+ + Na$). For $C_{17}H_{22}O_6Na$ 345.1315 (deviation -0.1 ppm).

5-C-Benzoyloxymethyl-3,5-dideoxy-1,2-O-isopropylidene-4-O-(3,5-dinitrobenzoyl)- α -L-erythro-hexulopyranose (20). Treatment of **19** (60 mg, 0.19 mmol) with Ph_3P (100 mg, 0.38 mmol), 3,5-dinitrobenzoic acid (80 mg, 0.38 mmol) and DEAD (66 mg, 0.38 mmol) in dry THF (3 mL) as above gave, after work-up and column chromatography (ether-hexane 1:3) crystalline **20** (95 mg, quantitative); mp 133–135 °C (from dichloromethane-ether); $[\alpha]_D^{28} -57$ (c 1); ν_{max}^{KBr} 3116 (aromatic), 1720 ($C=O$ benzoate), 1380 (CMe_2), and 714 cm^{-1} (aromatic). NMR data: 1H , δ 9.2–.40 (4 m, 8 H, Bz and 3,5-DNBz), 5.75 (bs, 1 H, H-4), 4.37 (dd, 1 H, $J_{5,7}$ 6.3, $J_{7,7'}$ 11.3 Hz, H-7) 4.35 (t, 1 H, $J_{5,6ax} = J_{6ax,6eq} = 11.6$ Hz, H-6ax), 4.28 (dd, 1 H, $J_{5,7'}$ 7.5 Hz, H-7') 4.14 (d, 1 H, $J_{1,1'}$ 8.7 Hz, H-1), 3.94 (dd, 1 H, $J_{5,6eq}$ 4.7 Hz, H-6eq), 3.80 (d, 1 H, H-1'), 2.59 (m, 1 H, H-5), 2.22 (dd, 1 H, $J_{3,4}$ 3.0, $J_{3,3'}$ 14.8 Hz, H-3), 2.12 (dd, 1 H, $J_{3',4}$ 3.0 Hz, H-3'), 1.66 and 1.27 (2 s, 6 H, CMe_2); ^{13}C , δ 166.80 (Bz), 162.13 (3,5-DNBz), 148.71, 134.50, 133.36, 129.66, 129.59, 128.52, and 122.43 (aromatic), 112.27 (CMe_2), 102.34 (C-2), 75.26 (C-1), 69.46 (C-4), 62.07 (C-6), 59.01 (C-7), 38.00 (C-5), 35.68 (C-3), 27.17 and 26.63 (Me_2C). Mass spectrum (LSIMS): m/z 539.1282 ($M^+ + Na$). For $C_{24}H_{24}N_2O_{11}Na$ 539.1278 (deviation -0.8 ppm).

Anal. Calcd for $C_{24}H_{24}N_2O_5$: C, 52.94; H, 4.44; N, 10.29. Found: C, 52.66; H, 4.25; N, 10.83.

3,5-Dideoxy-5-C-hydroxymethyl-1,2-O-isopropylidene- α -L-erythro-hexulopyranose (4). Treatment of **20** (190 mg, 0.4 mmol) with 0.8M sodium methoxide (0.5 mL) in anhydrous methanol (5 mL) as above afforded pure **4** (75 mg, quantitative) as a clear thick syrup; $[\alpha]_D^{27} -91$ (c 0.6), $[\alpha]_{405}^{27} -241$ (c 0.4). NMR data: 1H , δ 4.31 (bd, 1 H, H-4), 4.14 (t, 1 H, $J_{5,6ax} = J_{6ax,6eq} = 12.0$ Hz, H-6ax), 4.01 (d, 1 H, $J_{1,1'}$ 8.8 Hz, H-1), 3.81 (dd, 1 H, $J_{5,7}$ 4.4, $J_{7,7'}$ 11.3 Hz, H-7), 3.76 (d, 1 H, H-1'), 3.7–.70 (m, 2 H, H-6eq,7'), 1.95 (d, 2 H, $J_{3,4}$ 3.1 Hz, H-3,3), 1.85 (m, 1 H, H-5), 1.51 and 1.40 (2 s, 6 H, CMe_2); ^{13}C , δ 111.65 (CMe_2), 103.52 (C-2), 75.10 (C-1), 68.11 (C-4), 63.08 (C-6), 59.17 (C-7), 40.71 (C-5), 38.27 (C-3), 27.00 and 26.64 (Me_2C). Mass spectrum (LSIMS): m/z 241.1053 ($M^+ + Na$). For $C_{10}H_{18}O_5Na$ 241.1055 (deviation -0.4 ppm).

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