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Total Synthesis of 2,3-Dideoxy-*C*-methylheptose Derivatives

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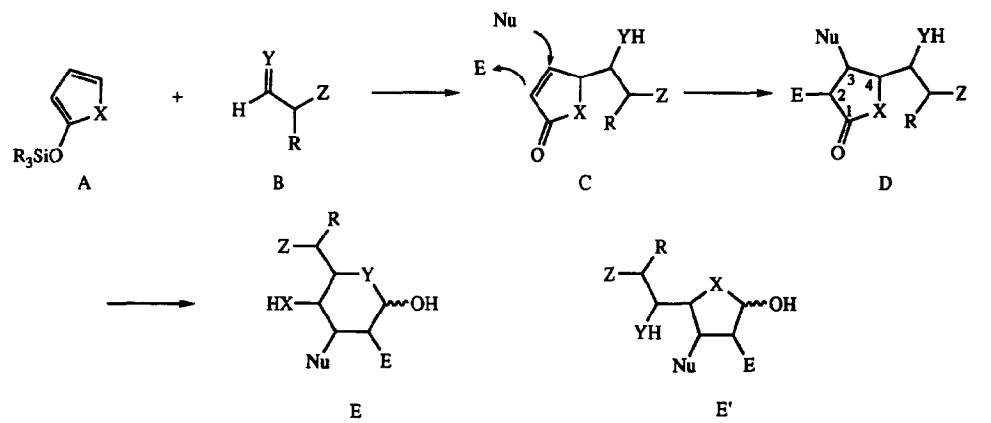
Abstract: *2,3-Dideoxy-3-C-methyl-D-manno-heptose (6) and 2,3-dideoxy-2,3-di-C-methyl-D-glycero-D-galacto-heptose (7) have been synthesized from 2,3-O-isopropylidene-D-glyceraldehyde (2), by taking advantage of a flexible synthetic strategy utilizing 2-(trimethylsiloxy)furan (1) as four-carbon homologative reagent.*

One of the relevant issues in the total synthesis of complex carbohydrates is that of devising a method of some flexibility to achieve the construction of sugars equipped with differentiated functionalities and chirality by utilizing a common modular reaction protocol.[1] Our general approach to this problem is illustrated in the Chart .[2]

Chart



Homochiral synthon B is homologated by four carbon atoms with siloxydiene A to give enantiomerically pure α,β-unsaturated γ-lactone (X=O) or γ-lactam (X=NR) precursors C. Double bond functionalization with, for example, a nucleophilic reagent Nu on carbon-3 and with an electrophilic reagent E on carbon-2 then gives rise to the advanced intermediates D, which are finally transformed into pyranosidic or

furanosidic targets E, E' by suitable manipulations. Precise chirality transfer from B to C, D, E, E', coupled with rational tuning of the atom involved X, Y, and Z, ensures synthetic efficiency and flexibility to our plan.

We now report the implementation of this scheme, in which X, Y, and Z are oxygen functionalities and Nu and E are methyl groups, in the construction of 2,3-dideoxy-*C*-methylheptoses of type **6** and **7**. They were selected as targets because they are known to be rare compounds and difficult to make by conventional chemistry.[3]

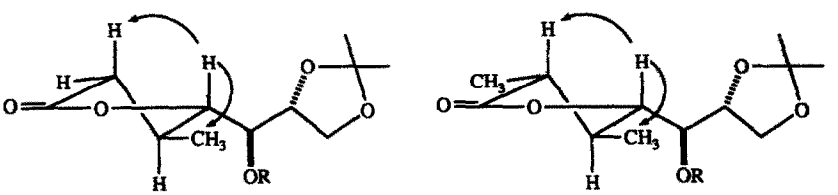
Since we had developed highly efficient asymmetric methodology for the synthesis of α,β-unsaturated γ- lactones via homologation of homochiral aldehydo precursors using 2-(trimethylsiloxy)furan (**1**),[2] we chose to commence synthesizing enantiomerically pure heptenonolactone **3** by using 2,3-*O*-isopropylidene-D-glyceraldehyde (**2**) as a chiral template to guide the overall synthesis (Scheme).

Reaction of **1** with **2** occurred under the previously reported conditions (BF_3 etherate, CH_2Cl_2, -80°C),[2] generating a single C-4 substituted lactone, which reacted with TMSCl in pyridine at room temperature. This afforded 5-*O*-silylated D-*arabino*-configurated butenolide **3** in a good 76% overall yield. We adopted an asymmetric conjugate addition reaction (Me_2CuLi, CH_2Cl_2, -80°C) to install a methyl group at C-3 of intermediate **3**.[4] The presence of a bulky substituent on C-4 precisely governed the stereochemical course (*anti*) of this reaction, affording an 86% yield of **4** as a single diastereoisomer.

Methylation via enolate formation (LiHDMS, THF, then MeI) was adopted to convert **4** into **5**.[5] The diastereoselection was moderate (85:15) due to the presence of the mismatched 3β, 4α-substituents in the furan ring. Nonetheless, the major crystalline trans-trans diastereoisomer **5** was obtained in 60% yield after chromatographic separation.

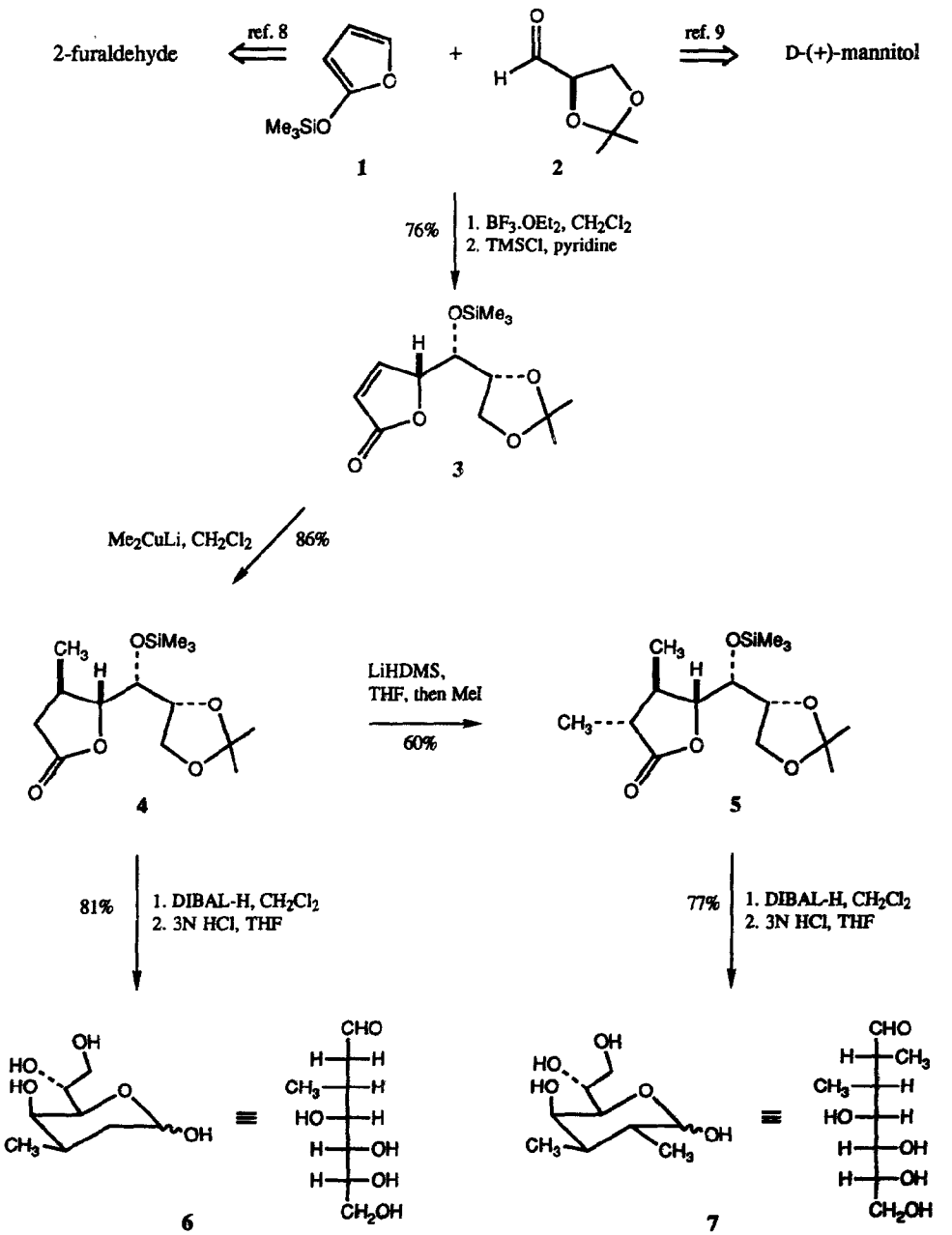
The absolute configuration of the advanced intermediates **4** and **5** is correlated to the 4*R*, 5*S*, 6*R* chirality of their common progenitor **3**, which has been firmly established by single crystal X-ray analysis.[6] The stereochemistry of the additional chiral centres in **4** and **5** follows from NOE measurements (Figure).[7] The significant NOEs observed for the C-4 proton, C-3 methyl, and C-2 β-proton in compound **4** indicate a cis orientation of these groups; in comparison, the trans protons at C-3 and C-4 have a NOE of only 1%. In compound **5**, the two trans methyl groups do not exhibit any NOE, whilst detectable effects are observed for the cis-oriented C-2 and C-4 protons in β-position and for β-located C-3 methyl and HC-4.

Figure. Diagnostic NOE contacts for lactones **4** and **5**



4 **5**

Scheme. Synthesis of 2,3-Dideoxy-*C*-methylheptoses **6** and **7**



At this point, all that remained was to convert the intermediates **4** and **5** into *C*-methylheptoses **6** and **7**, respectively. A common enantioconservative protocol of two sequential reactions ensured clean transformations. Lactone-to-lactol reduction occured under the usual conditions using DIBAL-H in CH_2Cl_2 at -80°C, while complete cleavage of the silyl and acetonide linkages was quickly accomplished by treatment with 3N HCl in THF at room temperature. In this manner, the expected heptoses **6** and **7** were obtained in 81% and 77% yields, respectively, for the two final steps.

The free sugars exhibited somewhat complex ^1H NMR spectra in D_2O, due to the expected presence of anomeric furanose and pyranose equilibrium structures; nonetheless, the anomeric region (4.4-5.6 ppm) was clean enough to permit rough estimation of the sugar compositions. Ratios of 0:0:1:12 for **6** and 1:2:15:18 for **7** were determined of the corresponding β-furanose, α-furanose, β-pyranose, and α-pyranose isomers.

In summary, a flexible stereospecific route from D-glyceraldehyde to certain *C*-methyl 2,3-dideoxyheptoses has been established, which is presumably applicable to a wide variety of 2,3-substituted and branched chain deoxy sugars. The C-2 and C-3 unsaturated carbons of our butenolide intermediates, like **3**, can be substituted by several combinations of carbon, nitrogen, and oxygen functionalities and with varied stereochemistry. Applications of this type are currently underway.

EXPERIMENTAL SECTION

Materials. 2-(Trimethylsiloxy)furan (**1**) was prepared on a multigram scale from 2-furaldehyde (Aldrich) following the Brimble procedure.[8] 2,3-*O*-Isopropylidene-D-glyceraldehyde (**2**) was prepared from D-mannitol (Aldrich) by following the recently developed improved procedure of Schmidt.[9]

Instrumentation. ^1H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded on a Varian XL 300 instrument (δ in ppm referred to TMS, unless otherwise stated, *J* in Hz). Rotations were measured on a Perkin-Elmer 241. Mp were determined (uncorrected) on a Dr. Tottoli melting point apparatus. Flash chromatography was performed using silica gel 70-230 Mesh purchased from Merck. Kieselgel 60 F_{254} (from Merck) was used for TLC. All the solvents were distilled before use: THF over Na/benzophenone; Et_2O over $LiAlH_4$; CH_2Cl_2 over CaH_2. Elemental analyses were performed by the Microanalytical Laboratory of University of Sassari.

(*4R*, *5S*, *6R*)-5-*O*-Trimethylsilyl-6,7-*O*-isopropylidene-2,3-dideoxy-hept-2-enono-1,4-lactone (3). 2-(Trimethylsiloxy)furan (**1**) (21.5 mL, 0.13 mol) and 2,3-*O*-isopropylidene-D-glyceraldehyde (**2**) (13.0 g, 0.1 mol) were dissolved in dry CH_2Cl_2 (250 mL) under argon, and the mixture was cooled at -90 °C. With stirring, BF_3 etherate (12.3 mL, 0.1 mol) cooled to the same temperature was added via cannula over 10 min, and the solution was allowed to stir for 6 h. The reaction was then quenched at -90 °C by addition of an aqueous saturated $NaHCO_3$ solution and, after ambient temperature was reached, the mixture was extracted with CH_2Cl_2 (3x50 mL) and the organic layer washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The crude product was dissolved in pyridine (100mL) and TMSCl (31.7 mL, 0.25 mol) was added. Distilled water (200 mL) was then added and the mixture extracted with CH_2Cl_2 (3x50 mL). The organic extracts were combined, washed with water, dried ($MgSO_4$), and concentrated in vacuo. This

furnished crude lactone **3** contaminated by ca. 4-5% (^{1}H NMR) of minor C-4 epimer. The major component was purified by flash chromatography (80:20 hexane/ethyl acetate) to afford **3** (22.3 g, 78%) as a colorless oil that solidified on standing: mp 39-41 °C; $[\alpha]_D^{20}$ +106.2 (*c* 4.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, 1H, *J* = 5.9, 1.7 Hz), 6.16 (dd, 1H, *J* = 2.2, 1.7 Hz), 5.12 (dt, 1H, *J* = 4.1, 1.9 Hz), 4.15 (ddd, 1H, *J* = 7.3, 6.1, 5.9 Hz), 4.06 (dd, 1H, *J* =8.4, 6.1 Hz), 3.83 (dd, 1H, *J* = 8.4, 5.9 Hz), 3.75 (dd, 1H, *J* = 7.3, 4.1 Hz), 1.40 and 1.35 (2s, each 3H), 0.12 (s, 9H). Anal. Calcd for $C_{13}H_{22}O_5Si$: C, 54.52; H, 7.74. Found: C, 54.66; H, 7.90.

(3*R*, 4*R*, 5*S*, 6*R*)-3-*C*-Methyl-5-*O*-trimethylsilyl-6,7-*O*-isopropylidene-2,3-dideoxy-heptono-1,4-lactone (4). To a suspension of $CuBr{\cdot}Me_2S$ (3.60 g, 17.5 mmol) in anhydrous diethyl ether (40 mL) was added a solution of methyl lithium (21.97 mL of a 5% solution in ether, 35.0 mmol) at 0 °C over 5-10 min. The initial yellow precipitate redissolved to give a pale-buff colored solution. After cooling the solution to -80 °C, the enone **3** (1.00 g, 3.5 mmol) in anhydrous diethyl ether (40 mL) was slowly added via cannula and the reaction was stirred for 3 h before being quenched by the cautious addition of satd NH_4Cl solution. After vigorous extraction to remove copper compounds, the colorless ethereal layer was evaporated to give the crude product. Flash column chromatography (AcOEt/hexane 3:7) gave pure **4** as a colorless oil (0.90 g, 85%); $[\alpha]_D^{22}$ -13.4 (*c* 3.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (dd, 1H, *J* = 5.4, 1.8 Hz, H-4), 4.15 (dd, 1H, *J* = 6.3, H-6), 4.04 (dd, 1H, *J* = 8.4, 6.3 Hz, H-7a), 3.82 (dd, 1H, *J* = 8.4, 6.3 Hz, H-7b), 3.79 (dd, 1H, *J* = 6.3, 1.8 Hz, H-5), 2.73 (dd, 1H, *J* = 17.1, 8.7 Hz, H-2a), 2.46 (m, 1H, H-3), 2.12 (dd, 1H, *J* = 17.1, 6.6 Hz, H-2b), 1.40 and 1.33 (2s, each 3H, Me), 1.15 (d, 3H, *J* = 6.9 Hz, Me), 0.15 (s, 9H, $SiMe_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 178.16, 109.24, 86.98, 76.30, 72.93, 66.44, 36.74, 31.11, 26.62, 25.18, 18.74, 0.65. Anal. Calcd for $C_{14}H_{26}O_5Si$: C, 55.60; H, 8.67. Found: C, 55.86; H, 8.48.

(2*R*, 3*R*, 4*R*, 5*S*, 6*R*)-2,3-Di-*C*-methyl-5-*O*-trimethylsilyl-6,7-*O*-isopropylidene-2,3-dideoxy-heptono-1,4-lactone (5). To a stirring solution of **4** (0.57 g, 1.9 mmol) in anhydrous THF (10ml) under argon atmosphere at -80 °C was added lithium hexamethyldisilazide (1.6 equiv.). The resulting solution was stirred at -80 °C for 1 h, followed by addition of methyl iodide (1.1 equiv.). The reaction was allowed to stir for 1 h at -80 °C, then allowed to warm to room temperature over a period of 1 h. The reaction mixture was then added to ether followed by extraction with water and brine, and then dried over magnesium sulphate. The product was then purified by flash column chromatography on silica gel (AcOEt/hexane 4:6) giving an oil (0.36 g, 60%); $[\alpha]_D^{24}$ -1104.8 (*c* 0.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (d, 1H, *J* =6.3 Hz), 4.07 (m, 2H), 3.84 (m, 2H), 2.22 (m, 1H), 2.07 (m, 1H), 1.43 and 1.35 (2s, each 3H, Me), 1.24 (d, 3H, *J* = 6.9 Hz, Me), 1.14 (d, 3H, *J* = 6.6 Hz, Me), 0.16 (s, 9H, $SiMe_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 178.21, 108.93, 84.30, 76.39, 70.94, 66.53, 42.80, 38.68, 26.67, 25.19, 15.01, 13.21, 0.69. Anal. Calcd for $C_{15}H_{28}O_5Si$: C, 56.93; H, 8.92. Found: C, 57.13; H, 8.85.

Compound **5** has been desilylated by citric acid in methanol and its stereochemistry has been elucidated by NOE experiments (see text). $[\alpha]_D^{21}$ -46.0 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (dd, 1H, *J* = 6.0, 1.0 Hz, H-4), 4.12 (m, 2H, H-6 and H-7a), 4.02 (dd, 1H, *J* = 7.8, 3.0 Hz, H-7b), 3.61 (t, 1H, *J* = 6.6 Hz, H-5), 2.86 (q, 1H, *J* = 7.8 Hz, H-2), 2.75 (q, 1H, *J* = 7.5 Hz, H-3), 2.62 (d, 1H, *J* = 8.7 Hz, OH), 1.42 and 1.36 (2s, each 3H, Me), 1.17 (d, 3H, *J* = 7.5 Hz, Me), 1.05 (d, 3H, *J* =6.9 Hz, Me).

2,3-Dideoxy-3-*C*-methyl-D-*manno*-heptose (6). To a stirred solution of **4** (0.30 g, 1.0 mmol) at -80 °C in dry CH_2Cl_2 (10 mL) was added DIBAL-H (1.5 M in toluene, 2 mL, 3.0 mmol) under argon atmosphere. After stirring for 2 h at -80 °C, cold MeOH (1 mL) was slowly added to this solution at -80 °C and this was poured into a brine-water mixture and extracted with EtOAc three times, dried over $MgSO_4$, filtered and concentrated in vacuo to give a crude oil. After being purified by flash-column chromatography (AcOEt/hexane 3:7) it was stirred with HCl 3N in methanol overnight at room temperature and product **6** has been recovered after removal of the solvent followed by liophilization as a colorless foam (0.15 g, 81%). $[\alpha]_D^{21}$ +42.1 (*c* 0.29, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 5.45 (d, 1H, *J* = 4.8 Hz, H-1), 3.91 (d, 1H, *J* = 3.9 Hz, H-4), 3.78 (dd, 1H, *J* = 11.7, 2.1 Hz, H-7a), 3.61 (m, 2H, H-5 and H-7b), 3.51 (m, 1H, H-6), 2.51 (m, 1H, H-3), 2.27 (dd, 1H, *J* = 13.8, 8.4 Hz, H-2a), 1.56 (dt, 1H, *J* = 13.8, 4.8 Hz, H-2b), 1.12 (d, 3H, *J* = 6.6 Hz, Me); ^{13}C NMR (75.4 MHz, CD_3OD) δ 101.41, 85.74, 75.86, 65.47, 63.04, 39.66, 30.54, 22.11. Anal. Calcd for $C_8H_{16}O_5$: C, 49.99; H, 8.39. Found: C, 50.13; H, 8.55.

2,3-Dideoxy-2,3-di-C-methyl-D-*glycero*-D-*galacto*-heptose (7). To a stirred solution of desilylated **5** (40.0 mg, 0.16 mmol) at -80 °C in dry CH_2Cl_2 (3 mL) was added DIBAL-H (1.0 M in CH_2Cl_2, 480 μL, 0.48 mmol) under argon atmosphere. After stirring for 2 h at -80 °C cold MeOH (0.5 mL) was slowly added to this solution at -80 °C and this was poured into a brine-water mixture and extracted with EtOAc three times, dried over $MgSO_4$, filtered and concentrated in vacuo to give a crude oil. After being purified by flash-column chromatography (AcOEt/hexane 1:1) it was stirred with HCl 3N in methanol overnight at room temperature and product **7** has been recovered after removal of the solvent followed by liophilization as a colorless foam (25.4 mg, 77%). $[\alpha]_D^{20}$ -2.2 (*c* 0.59, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 4.8-4.4 (m, 1H), 4.2-3.3 (m, 5H), 3.0-2.7 (m, 1H), 2.0-1.6 (m, 1H), 1.3-0.9 (m, 6H). Anal. Calcd for $C_9H_{18}O_5$: C, 52.41; H, 8.80. Found: C, 52.23; H, 8.83.

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