Synthesis of a 3-Deoxy-D-*arabino*-2-heptulosonic Acid Derivative

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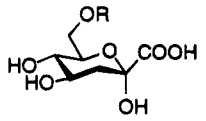
The synthesis of a selectively protected 3-deoxy-D-*arabino*-2-heptulosonic acid, **9**, from a non-carbohydrate precursor was achieved in six steps (19% yield) from a chiral, γ,δ-epoxy β-hydroxy ester, **3a**, readily available from the corresponding α,β-epoxy aldehyde. The product was obtained through a Lewis acid-mediated stereocontrolled lactonization of **3a** followed by a two-step procedure: synthesis of Weinreb's amide **5a** and lithiothiazole nucleophilic attack allowing the introduction of the masked aldehydo frame.

3-Deoxy-2-ulosonic acids are natural carbohydrates which participate in various important biological processes.[1,2] The 7-phosphate of the 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH, **1**) is an important intermediate in the shikimic acid pathway[3] along which the aromatic amino acids and a multitude of other aromatic and alicyclic compounds are biosynthesized in bacteria, fungi, and plants.



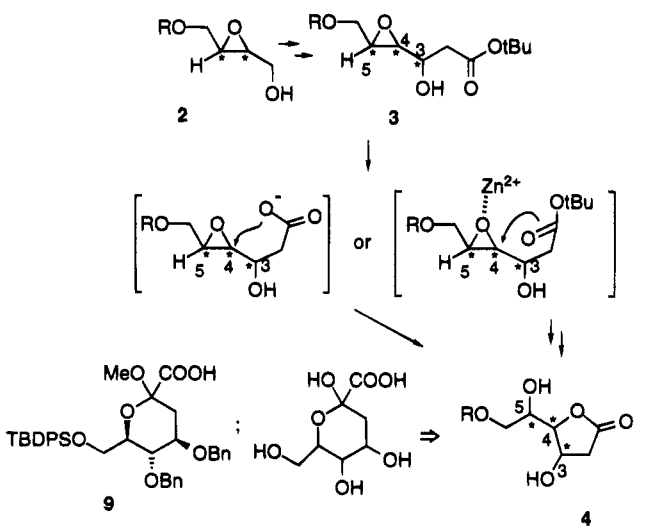
R = H DAH **1**

R = PO_3H^- DAHP

The biosynthesis of **1** as well as of ulosonic acids in general, which is thought to involve specific aldol condensation of pyruvic acid with aldoses catalyzed by the appropriate aldolase, has stimulated enzymatic syntheses over the last 10 years. Frost and co-workers[4] have used an enzymatic system to produce DAHP from D-fructose. Whitesides et al.[5] have utilized a combined chemical and enzymatic synthetic route from *N*-acetyl-D/L-aspartate β-semialdehyde and dihydroxyacetone phosphate in the presence of rabbit muscle aldolase to catalyze the formation of the C_4-C_5 bond.

In contrast chemical synthesis of this compound has always employed aldehydes derived from the sugars 2-deoxy-D-glucose[6] or D-mannitol.[7] Dondoni et al.[7] recently reported an elegant synthesis of DAH in which thiazole was used as a surrogate for the introduction of the carboxyl group.

We here report a synthesis of a protected form of DAH starting from a non-carbohydrate precursor. Recently we described a versatile synthesis of chiral susbtituted β-hydroxy-γ-butyrolactones[8] **4** through a Lewis acid-mediated stereocontrolled lactonization of chiral γ,δ-epoxy β-hydroxy esters[9] **3**. The epoxy alcohol precursors were prepared via an enantioselective Sharpless epoxidation.



The usefulness of the method resides in the exceptional versatility of the choice of the absolute configuration of the stereocenters. In fact the C_3, C_4, and C_5 carbon centers of the 5-ring lactone are controlled by (1) C_3, the aldolization reaction for obtention of the γ,δ-epoxy β-hydroxy esters and the choice of the chiral catalyst for the Sharpless enantiomeric epoxidation, (2) C_4, the epoxidation and lactonization reactions, and (3) C_5, the nature of the starting allylic alcohol (*E* or *Z*) and the Sharpless epoxidation reaction.

The methodology used for the synthesis of DAH derivative **9** is outlined in Scheme 1. Treatment of chiral γ,δ-epoxy β-hydroxy ester **3a** with zinc powder and trimethylsilyl chloride (1 min) in anhydrous methylene chloride gave the γ-butyrolactone **4a** in quantitative yield. The differently protected (R = *p*-BrBn) enantiomer **4b** was also obtained from the corresponding epoxy ester.

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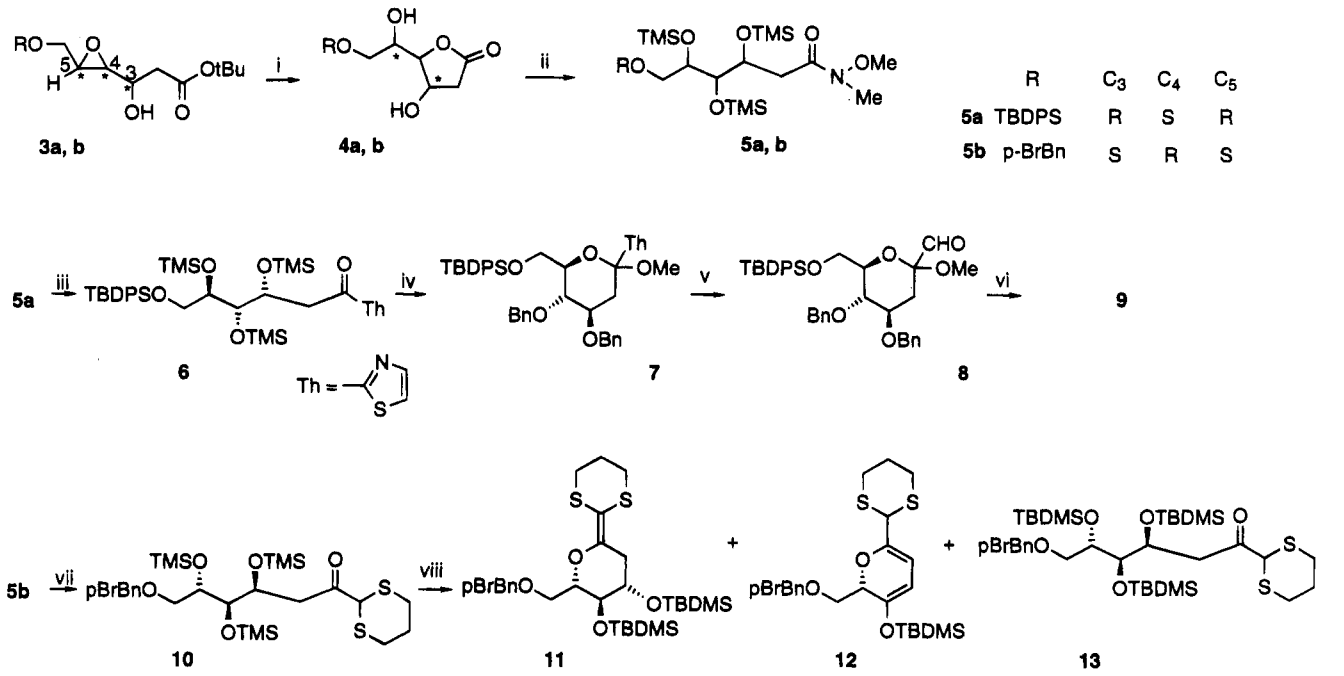
Scheme 1[a]



[a] (i) Zn°/Me_3SiCl/CH_2Cl_2/rt, 96% for **4a**, 93% for **4b**; (ii) MeNHOMe·HCl/$AlMe_3/CH_2Cl_2$/0 °C → rt, then Me_3SiCl/HMDS/pyridine, 79% for **5a**, 90% for **5b**; (iii) thiazole/*n*-BuLi/Et_2O/−78 °C → rt, 87%; (iv) PTSA/MeOH/50 °C, then BnBr/NaH/*n*-Bu_4NI/THF/0 °C → rt, 70%; (v) methyl triflate/molecular sieves, 4 Å/CH_3CN/rt, then $NaBH_4$/MeOH/0 °C, then $CuO/CuCl_2/CH_3CN/H_2O$/rt, 69%; (vi) NaOH/$AgNO_3/H_2O$/THF, 79%; (vii) dithiane/*n*-BuLi/THF/−78 °C → rt, 71%; (viii) PTSA/MeOH/rt, Et_3N, TBDMS-SO_3CF_3, CH_2Cl_2, 20% for **12**, 12% for **11**, 16% for **13**.

Compounds carrying a *tert*-butyl ester function as a suitable nucleophilic participating group have also been reported by Paterson and others[10] in the ring opening of various bi- and triepoxides, a method that leads toward the synthesis of polyether ionophores. The stereoelectronically preferred *anti* periplanar attack of the epoxide leads to the specific synthesis of the lactone **4** with an inversion of the configuration on the C_4 carbon of the epoxy ester.

We first proposed[8] an isobutene elimination and an intramolecular attack of the carboxylate oxygen atom[11a] on the epoxide function, analogous to that proposed by Evans[11b] for an intramolecular cyclopropyl ring opening by a *tert*-butyl ester, in the presence of a Lewis acid. A mechanism involving an intramolecular attack of the Lewis acid-complexed epoxide group by the ester carbonyl, leading to the same lactone **4** through an oxonium intermediate,[11c] is a possible alternative.

Formally the heptulosonic acid could be synthesized through the nucleophilic attack by a carboxyl (or formyl) equivalent on the lactone **4**. A large number of readily accessible carboxyl or formyl anion equivalents have been reported. Among them, we tried lithium thioorthoformate and the classical aldehyde equivalents lithio-1,3-dithiane[12] and lithiothiazole. The latter has been reported[13] to add successfully to fully protected polyhydroxylated lactones. All three equivalents failed to react with lactones **4a,b** even when the C_3 hydroxyl group was silylated; this is probably due to *in situ* enolization of the 2-deoxylactones **4a,b**.

This problem was overcome by introducing the carboxyl (or formyl) equivalent in a two-step procedure: formation of the Weinreb's amide **5** and nucleophilic displacement of the amide function. Ring opening of the lactone using the Weinreb's procedure[14] proved to be very convenient. Reaction of compounds **4a,b** with the aluminum reagent generated *in situ* from the hydrochloride salt of *N*-methoxy-*N*-methylamine and trimethylaluminum in dry methylene chloride leads to the corresponding amides **5a,b** in high yields. It is noteworthy that the reaction proceeds cleanly even if the hydroxy functions of lactones are kept unprotected.

Weinreb amides are now well known as useful intermediates for a variety of synthetic transformations.[15] In our hands the amides **5a,b** thus obtained, after quantitative silylation of their hydroxy functions, were subjected to nucleophilic attack by formyl or carboxyl anion equivalents. Amides **5a,b** reacted very sluggishly with the lithium thioorthoformate and lithium 2-(methylthio)-1,3-dithiane. When amide **5b** was treated with the formyl equivalent lithium 1,3-dithiane in THF at −78 °C, it readily gave the ketone **10** in 71% yield. Protection of the ketone function of **10** by intramolecular acetalization and subsequent silylation of the hydroxy function were attempted. The reaction yields the dehydration products **11** (12% yield) and **12** (20%) aside from the starting material **13** (16%), as has been previously observed for benzylic α-hydroxyl thioacetals.[16] Treatment of **10** with

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N-bromosuccinimide[17] failed to give the desired pyruvaldehyde frame. The use of lithiothiazole as a formyl equivalent proved not unexpectedly[7,18] to be more efficient. Its usefulness has already been demonstrated in the synthesis of carbohydrates[18] and ulosonic acids.[7] Addition of an ether solution of the amide **5a** to lithium thiazole thus leads to the ketone **6** in high yield (87%). Cleavage of the trimethylsilyl protecting groups by TsOH-catalyzed methanolysis and then benzylation of the hydroxy functions gave compound **7** in 75% yield as a mixture of anomers (82:18).

The major anomer **7**[19] was then subjected to one-pot thiazole to formyl transformation according to a known procedure[20] —*N*-methylation, reduction, and hydrolysis in the presence of CuO and $CuCl_2$—to produce aldehyde **8** in 69% isolated yield (after chromatographic purification). Oxidation of **8** with wet Ag_2O and purification through a Sephadex column gave the heptulosonic acid derivative **9** in 79% yield.

In conclusion, this methodology based on the use of suitably substituted and enantiomerically controlled β-hydroxy-γ-butyrolactones, obtained from non-carbohydrate starting compounds, can easily lead in good yield (yield 19% over eight steps) to the protected 3-deoxy-D-*arabino*-heptulosonic acid derivative **9**.

Experimental Section

The epoxy esters **3a,b** were obtained by aldolic condensation of the lithio-*tert*-butyl acetate on the optically active epoxy aldehyde[9] (yield **3a**, 64%; **3b**, 61%).

(4*R*,5*S*,1′*R*)-5-[2′-[(*tert*-Butyldiphenylsilyl)oxy]-1′-hydroxyethyl]-4-hydroxy-2-oxo-1-oxacyclopentane (4a). To a stirred solution of *tert*-butyl (3*R*,4*R*,5*R*)-6-[(*tert*-butyldiphenylsilyl)oxy]-4,5-epoxy-3-hydroxyhexanoate (**3**) in anhydrous methylene chloride (620 mg, 1.36 mmol, 7 mL/mmol) were added activated zinc powder (2 equiv) and chlorotrimethylsilane (2 equiv). After 2 min the reaction mixture was hydrolyzed with saturated aqueous $NaHCO_3$ and extracted with methylene chloride. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel with CH_2Cl_2/AcOEt (8/2, v/v) to give 5-ring lactone **4a** (522 mg, 96% yield). IR ($CHCl_3$): ν (cm^{-1}) 3568 (OH), 3075, 3049 (=CH), 1789 (C=O), 1166, 1112 (C−O). ^1H NMR (250 MHz, $CDCl_3$): δ 7.67−7.62 (m, 4H, phenyl), 7.46−7.24 (m, 6H, phenyl), 4.69 (m, 1H, H_4), 4.33 (dd, 1H, J = 8.4, 3.8 Hz, H_5), 4.07 (m, 1H, $H_{1'}$), 3.96 and 3.85 (AB(X), dq, 2H, J = 4.6, 3.3, 10.6 Hz, CH_2-O), 2.78 (m, 2H, OH), 2.76 and 2.59 (AB(X), dq, 2H, J = 5.8, 0.8, 17.9 Hz, CH_2-CO), 1.09 (s, 9H, *t*-Bu). ^{13}C NMR (63 MHz, $CDCl_3$): δ 175.2, 135.5, 132.5, 130.1, 128.0, 81.3, 69.7, 68.5, 64.8, 37.8, 26.9, 19.3. MS (DCI, NH_3): 418 (M + 18, 100), 281 (17), 240 (24). $[\alpha]^{25}_D$ = +28.5° (c = 0.5, $CHCl_3$). Anal. Calcd (found): C, 65.96 (66.15); H, 7.04 (7.07).

(4*S*,5*R*,1′*S*)-5-[2′-[(4-Bromobenzyl)oxy]-1′-hydroxyethyl]-4-hydroxy-2-oxo-1-oxacyclopentane (4b). Using the same procedure described above, **3b** (832 mg, 2.1 mmol) was converted into **4b** (662 mg, 93%). Purification: silica gel (Et_2O/EtOH, 95/5; R_f = 0.32). IR ($CHCl_3$): ν (cm^{-1}) 3604 (OH), 3016 (=CH), 1784 (C=O), 1163, 1111 (C−O). ^1H NMR (250 MHz, $CDCl_3$): δ 7.68−7.37 (m, 10H, phenyl), 4.62 (m, 1H, J = 2.4, 4.6, 6.2 Hz, H_4), 4.46 (t, 1H, J = 4.6 Hz, H_5), 4.22 (m, 1H, J = 4.6, 5.4, 7.3 Hz, $H_{1'}$), 3.83 and 3.76 (AB(X), dq, 2H, J = 5.4, 7.3, 10.7 Hz, CH_2-O), 3.69 (m, 2H, OH), 2.77 and 2.62 (AB(X), dq, 2H, J = 6.2, 2.4, 18.1, CH_2-CO), 1.08 (s, 9H, *t*-Bu). ^{13}C NMR (63 MHz, $CDCl_3$): δ 175.9, 135.5, 132.4, 130.1, 128.0, 83.7, 70.4, 69.0, 64.3, 38.9, 26.8, 19.2. MS (DCI, CH_4): 333 (M − *t*-Bu, 38), 305 (50), 199 (100), 161 (94), 127 (75). $[\alpha]^{25}_D$ = −37.4° (c = 0.9, $CHCl_3$). Anal. Calcd (found): C, 47.14 (47.34); H, 4.56 (4.62).

(3*R*,4*S*,5*R*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-3,4,5-tris-[(trimethylsilyl)oxy]-*N*-methoxy-*N*-methylhexanamide (5a). To a stirred suspension of N-methoxy-*N*-methylamine chlorohydrate (0.34 g, 3.5 mmol) in anhydrous methylene chloride (15 mL) was slowly added at 0 °C trimethylaluminum (1.75 mL of a 2 M solution, 3.5 mmol). After 30 min at room temperature, lactone **4a** (280 mg, 0.7 mmol) in methylene chloride (3.5 mL) was introduced. The mixture was stirred for 12 h and then hydrolyzed with HCl (0.5 M, 15 mL) and diluted with methylene chloride (20 mL). The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated. The residue was dissolved in pyridine (10 mL); hexamethyldisilazane (1.6 mL) and chlorotrimethylsilane (1 mL) were added. After 3 h at rt, the mixture was hydrolyzed with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and evaporated, and the crude product was chromatographed on silica gel (Et_2O/petroleum ether, 4/6) to give **5a** (369 mg, 79% for the two steps). IR ($CHCl_3$): ν (cm^{-1}) 3074, 3056, 3002 (=CH), 1651 (C=O). ^1H NMR (250 MHz, C_6D_6): δ 7.90−7.84 (m, 4H, phenyl), 7.28−7.23 (m, 6H, phenyl), 4.67 (ddd, 1H, J = 3.2, 5.2, 8.5 Hz, H_3), 4.29 (ddd, 1H, J = 2, 3.6, 7.7 Hz, H_5), 4.17 and 4.05 (AB(X), dq, 1H, J = 3.6, 7.7, 10.7 Hz, CH_2-O), 3.99 (dd, 1H, J = 2, 5.2 Hz, H_4), 3.13 (s, 3H, OMe), 3.11−2.80 (m, 2H, H_2), 2.86 (s, 3H, NMe), 1.22 (s, 9H, *t*-Bu), 0.32 (s, 9H, $SiMe_3$), 0.21 (s, 9H, $SiMe_3$), 0.16 (s, 9H, $SiMe_3$). ^{13}C NMR (63 MHz, C_6D_6): δ 136.2, 134.2, 134.1, 130.0, 129.9, 128.5, 77.6, 77.2, 71.9, 66.9, 60.8, 36.1, 32.0, 27.3, 19.5, 0.8, 0.6, 0.5. MS (DCI, NH_3): 680 (M + 3, 29), 679 (M+2, 57), 678 (M + 1, 100), 108 (58). $[\alpha]^{25}_D$ = +22.6° (c = 1.5, $CHCl_3$). Anal. Calcd (found): C, 59.45 (59.81); H, 8.77 (8.95); N, 2.07 (2.23).

(3*S*,4*R*,5*S*)-6-[(4-Bromobenzyl)oxy]-3,4,5-tris[(trimethylsilyl)oxy]-*N*-methoxy-*N*-methylhexanamide (5b). Using the same procedure described above (for **5a**), **4b** (574 mg, 1.73 mmol) was converted to **5b** (929 mg, 90%). IR ($CHCl_3$): ν (cm^{-1}) 3002 (=CH), 1653 (C=O), 1100 (C−O). ^1H NMR (250 MHz, C_6D_6): δ 7.26−7.24 (m, 2H, phenyl), 6.97−6.94 (m, 2H, phenyl), 4.65 (m, 1H, H_3), 4.24 (m, 1H, H_5), 4.20 (2H, PhCH_2), 3.94 (dd, 1H, J = 2.6, 4.8 Hz, H_4), 3.85 and 3.61 (AB(X), dq, 2H, J = 2.7, 7.3, 10 Hz, CH_2-O), 3.12 (s, 3H, OMe), 2.94 and 2.77 (AB(X), dq, 2H, J = 3.7, 8, 16 Hz, CH_2-CO), 2.86 (s, 3H, NMe), 0.26 (s, 9H, $SiMe_3$), 0.24 (s, 9H, $SiMe_3$), 0.21 (s, 9H, $SiMe_3$). ^{13}C NMR (63 MHz, C_6D_6): δ 172.0, 136.1, 131.6, 129.4, 121.5, 78.5, 74.7, 73.6, 72.6, 71.4, 60.7, 36.3, 32.0, 0.7, 0.6. MS (DCI, NH_3): 610 (M + 1, 100), 530 (14). $[\alpha]^{25}_D$ = −20.0° (c = 0.6, $CHCl_3$). Anal. Calcd (found): C, 47.35 (47.05); H, 7.62 (7.50).

(3*R*,4*S*,5*R*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-3,4,5-tris-[(trimethylsilyl)oxy]-1-(2′-thiazolyl)-1-hexanone (6). To a stirred solution of thiazole (80 μL, 1.1 mmol) in anhydrous ether (25 mL) under argon was added at −78 °C a solution of *n*-butyllithium (690 μL, 1.1 mmol; 1.6 M solution). After 10 min of stirring, compound **5a** (350 mg, 0.517 mmol) in ether (5 mL) was added. The reaction mixture was kept at −78 °C for 15 min and then allowed to warm to rt. The mixture was filtered through silica gel (4 g). The silica gel was washed with a solution of ether/petroleum ether (2/8), and the solvents were evaporated to give compound **6** (316 mg, 87% yield). IR ($CHCl_3$): ν (cm^{-1}) 3074, 3040 (=CH), 1684 (C=O), 1589 (C=C), 1478 (C=N). ^1H NMR (250 MHz, C_6D_6): δ 7.90−7.86 (m, 4H, phenyl), 7.46 (d, 1H, J = 3 Hz, H_{th}), 7.30−7.21 (m, 6H, phenyl), 6.56 (d, 1H, J = 3 Hz, H_{th}), 4.82 (m, 1H, ΣJ = 17.2 Hz, H_3), 4.30 (m, 1H, ΣJ = 13.4 Hz, H_5), 4.23 and 3.99 (AB(X), dq, 2H, J = 4.1, 7.2, 10.7 Hz, CH_2-O), 4.04 (dd, 1H, J = 2.1, 5.4 Hz, H_4), 3.80 and 3.70 (AB(X), dq, 2H, J = 4.1, 7.7, 16.4 Hz, CH_2-CO), 1.22 (s, 9H, *t*-Bu), 0.31 (s, 9H, $SiMe_3$), 0.15 (s, 9H, $SiMe_3$), 0.14 (s, 9H, $SiMe_3$). ^{13}C NMR (63 MHz, C_6D_6): δ 192.6, 168.1,

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(19) The major anomer **7** was desilylated, and the spectral data (^1H and ^{13}C NMR) were found identical with the values reported for compound **20a** in ref 7.
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144.7, 136.2, 134.1, 134.0, 130.0, 129.9, 128.6, 128.4, 125.9, 77.5, 76.8, 71.4, 66.6, 43.1, 30.1, 27.3, 19.5, 0.8, 0.6, 0.5. MS (DCI, NH_3): 703 (M + 1, 62), 702 (M, 100), 612 (9), 316 (6), 119 (10). $[\alpha]^{25}_D$ = +22° (*c* = 0.7, $CHCl_3$). Anal. Calcd (found): C, 58.15 (58.20); H, 7.89 (7.90).

Methyl (3*R*,4*S*,5*R*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-3,4-bis(benzyloxy)-2-deoxy-1-[(2′-thiazolyl)methyl]hexopyranoside (7). A catalytic amount of *p*-toluenesulfonic acid (1.4 mg) was added to a solution of compound **6** (251 mg, 0.36 mmol) in methanol (4 mL). The reaction mixture was stirred at 50 °C for 4 h and then hydrolyzed with saturated aqueous $NaHCO_3$ (0.5 mL) and concentrated. The residue was diluted in ether, filtered through silica gel, and evaporated. To a stirred solution of this crude product of two anomers (178 mg) in anhydrous THF at 0 °C were added sodium hydride (41 mg, 1.71 mmol), a catalytic amount of tetra-*n*-butylammonium iodide, and benzyl bromide (304 mg, 1.78 mmol). The reaction mixture was stirred at rt overnight. It was then concentrated and the residue chromatographed on silica gel (petroleum ether/CH_2Cl_2/AcOEt, 55/40/5) to give the major anomer **7** (169 mg, 70% for two steps). IR ($CHCl_3$): ν (cm^{-1}) 3072, 3004 (=CH), 1588 (C=C). ^1H NMR (250 MHz, C_6D_6): δ 7.99–7.88 (m, 4H, phenyl), 7.68 (d, 1H, J = 3.2 Hz, H_{th}), 7.32–7.10 (m, 16H, phenyl), 6.71 (d, 1H, J = 3.2 Hz, H_{th}), 5.11 and 4.67 (AB, 2H, J_{AB} = 11.4 Hz, OCH_2Ph), 4.38 and 4.33 (AB, 2H, J_{AB} = 11.6 Hz, OCH_2Ph), 4.29 (m, 1H), 4.08 (d, 2H, J = 3.0 Hz, CH_2-O), 3.94 (td, 1H, J = 3.0, 8.9 Hz, H_5), 3.81 (t, 1H, J = 8.9 Hz, H_4), 3.27 (dd, 1H, J = 13.0, 5.0 Hz, H_{2eq}), 3.05 (s, 3H, OMe), 1.88 (dd, 1H, J = 13.0, 11.3 Hz, H_{2ax}), 1.21 (s, 9H, *t*-Bu). ^{13}C NMR (63 MHz, C_6D_6): δ 170.3, 143.5, 139.6, 139.3, 136.3, 136.1, 134.0, 133.8, 130.0 (2C), 128.6, 128.3, 128.2 (2C), 127.9 (2C), 127.8, 127.6, 119.9, 100.7, 78.4, 78.2, 75.2, 74.6, 71.3, 63.4, 49.6, 41.2, 27.1, 19.6. MS (DCI, NH_3): 683 (M + 4, 6), 682 (M + 3, 21), 681 (M + 2, 51), 680 (M + 1, 100), 274 (6). $[\alpha]^{25}_D$ = +38.4° (*c* = 0.47, $CHCl_3$). Anal. Calcd (found): C, 70.66 (70.35); H, 6.67 (6.80).

Methyl (4*R*,5*S*,6*R*)-7-[(*tert*-Butyldiphenylsilyl)oxy]-4,5-bis(benzyloxy)-3-deoxy-2-heptuloso-2,6-pyranoside (8). To a suspension of activated molecular sieves (4 Å, 0.23 g) in CH_3CN (1 mL) was added compound **7** (79 mg, 0.116 mmol). The mixture was stirred for 10 min at rt. Then methyl triflate (17 μL, 0.15 mmol) was added and the solution stirred for an additional 15 min before concentrating. The residue, dissolved in methanol (1 mL), was treated at 0 °C with sodium borohydride (10 mg, 0.256 mmol). After 10 min of stirring, acetone (1 mL) was added and the solution was filtered through Celite and evaporated. The crude product was dissolved in CH_3CN/H_2O (8/1, 1 mL), and CuO (74 mg, 0.93 mmol) and $CuCl_2$ (16 mg, 0.12 mmol) were added. The solution was stirred for 15 min at rt and then filtered through Celite and evaporated at 40 °C to give a brown cake. The residue was dissolved in ether and filtered through Florisil to give a colorless solution. The Florisil was washed three times with AcOEt, and the combined organic phases were evaporated. The residue was chromatographed on silica gel (5 g of silica gel, petroleum ether/ether, 5/5) to give the desired aldehyde **8** (50 mg, 69%). IR ($CHCl_3$): ν (cm^{-1}) 3006 (=CH), 1747 (C=O). ^1H NMR (250 MHz, $CDCl_3$): δ 9.43 (s, 1H, CHO), 7.75–7.70 (m, 4H, phenyl), 7.45–7.26 (m, 16H, phenyl), 4.98 and 4.70 (AB, 2H, J_{AB} = 11 Hz, OCH_2Ph), 4.69 and 4.65 (AB, 2H, J_{AB} = 12 Hz, OCH_2Ph), 4.00 (m, 3H), 3.71 (m, 2H), 3.22 (s, 3H, OCH_3), 2.29 (dd, 1H, J = 13.0, 5.0 Hz, H_{3eq}), 1.60 (dd, 1H, J = 13.0, 11.0 Hz, H_{3ax}), 1.08 (s, 9H, *t*-Bu). ^{13}C NMR (63 MHz, $CDCl_3$): δ 198.0, 136.3, 136.2, 135.9, 135.7, 133.6, 133.3, 129.7, 128.5, 128.4, 128.0, 127.8, 127.7, 127.6, 99.8, 77.4, 75.2, 74.1, 72.1, 62.8, 50.4, 34.5, 29.8, 26.6, 19.4. MS (DCI, NH_3): 644 (M + 20, 15), 643 (M + 19, 48), 642 (M + 18, 100), 146 (23). $[\alpha]^{25}_D$ = +31.4° (*c* = 0.76, $CHCl_3$).

Methyl (4*R*,5*S*,6*R*)-7-[(*tert*-Butyldiphenylsilyl)oxy]-4,5-bis(benzyloxy)-3-deoxy-2-heptulopyranosidonic Acid (9). To a vigorously stirred mixture of silver nitrate (27.9 mg, 0.164 mmol), NaOH (13.44 mg, 0.336 mmol), and water (1.4 mL) was added a solution of **8** (44 mg, 0.07 mmol) in freshly distilled THF (1 mL). Stirring was continued for 2 days at rt. The mixture was then extracted with CH_2Cl_2 (10 mL); the aqueous phase was adjusted at pH = 5 with acetic acid and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried over $MgSO_4$; the solvent was evaporated and the residue chromatographed on a Sephadex LH20 column (3 × 30 cm) with MeOH/CH_2Cl_2 (3/7) as eluent to give the acid **9** (35 mg, 79%). IR ($CHCl_3$): ν (cm^{-1}) 3430 (OH), 1782 (C=O). ^1H NMR (400 MHz, C_6D_6): δ 7.92–7.83 (m, 4H, phenyl), 7.31–7.12 (m, 16H, phenyl), 5.01 and 4.64 (AB, 2H, J_{AB} = 11.4 Hz, OCH_2-Ph), 4.37 and 4.28 (AB, 2H, J_{AB} = 11.8 Hz, OCH_2Ph), 4.08 (m, 1H, ΣJ = 24.0 Hz, H_4), 3.97 (d, 2H, J = 2.85 Hz, H_7), 3.72 (td, 1H, J = 2.9, 9.7 Hz, H_6), 3.66 (dd, 1H, J = 8.3, 9.7 Hz, H_5), 3.14 (s, 3H, OCH_3), 2.74 (dd, 1H, J = 13.0, 4.8 Hz, H_{3eq}), 1.79 (dd, 1H, J = 13.0, 11.0 Hz, H_{3ax}), 1.17 (s, 9H, *t*-Bu). ^{13}C NMR (63 MHz, $CDCl_3$): δ 169.3, 138.1, 138.0, 135.7, 135.6, 133.2, 133.0, 130.0, 129.9, 128.5, 128.4, 128.0, 127.9, 98.9, 77.0, 76.9, 75.0, 74.4, 71.9, 62.7, 51.0, 37.0, 26.8, 19.3. MS (DCI, NH_3): 659 (48), 658 (M + 18, 100), 642 (M + 2, 20), 518 (45). $[\alpha]^{25}_D$ = +26.1° (*c* = 0.56, $CHCl_3$). Anal. Calcd (found): C, 71.22 (71.19); H, 6.92 (7.50).

(3*S*,4*R*,5*S*)-6-[(4-Bromobenzyl)oxy]-3,4,5-tris[(trimethylsilyl)oxy]-1-(1,3-dithia-2-cyclohexyl)-1-hexanone (10). To a stirred solution of dithiane (97 mg, 0.8 mmol) in THF (3 mL) at −78 °C was added *n*-butyllithium (504 μL, 0.82 mmol). After 30 min the silylated amide (410 mg, 0.67 mmol) in THF (2 mL) was added, and the reaction mixture was allowed to warm to rt (4 h). It was then hydrolyzed with saturated aqueous NH_4Cl, extracted with ether, and dried over $MgSO_4$ and the solvent evaporated. The residual dithiane was distilled under reduced pressure (55 °C/0.1 mmHg), and the crude product was chromatographed (petroleum ether/ether, 9/1) to leave 264 mg (71% yield) of compound **10**. IR ($CHCl_3$): ν (cm^{-1}) 1710 (C=O), 1594 (C=C), 1200 (C–O, C–S). ^1H NMR (250 MHz, C_6D_6): δ 7.27 and 6.94 (A_2B_2, 4H, J = 8 Hz, phenyl), 4.48 (ddd, 1H, J = 4, 5.4, 7.6 Hz, H_3), 4.20 and 4.16 (AB, 2H, J = 12 Hz, CH_2Ph), 4.22 (m, 1H, H_5), 3.92 (s, 1H, CHS_2), 3.89 (dd, 1H, J = 2.6, 5.4 Hz, H_4), 3.77 and 3.55 (AB(X), dq, 2H, J = 3.2, 7, 10 Hz, CH_2-O), 3.08 and 2.92 (AB(X), dq, 2H, J = 4, 7.6, 16 Hz, CH_2-CO), 3.10–2.83 (m, 2H, H_{eq}, SCH_2), 2.04–1.93 (m, 2H, H_{ax}, SCH_2), 1.69–1.50 (m, 2H, $CH_2CH_2CH_2$), 0.26 (s, 9H, $SiMe_3$), 0.21 (s, 9H, $SiMe_3$), 0.20 (s, 9H, $SiMe_3$). ^{13}C NMR (63 MHz, C_6D_6): δ 201.2, 137.9, 131.7, 129.4, 121.6, 76.2, 74.1, 73.2, 72.6, 71.2, 47.9, 44.4, 26.2, 25.4, 0.8, 0.6. $[\alpha]^{25}_D$ = −24.1° (*c* = 0.9, $CHCl_3$).

(6*S*)-6-[[(4-Bromobenzyl)oxy]methyl]-5-[(*tert*-butyldimethylsilyl)oxy]-2-(1,3-dithia-2-cyclohexyl)oxa-2,4-cyclohexadiene (12). A stirred solution of **10** (90 mg, 0.135 mmol) and Ts-OH (1 mg) in methanol (2 mL) was kept at rt for 3 h. After hydrolysis with saturated aqueous $NaHCO_3$ (0.5 mL), evaporation of the solvent, and filtration of a CH_2Cl_2 solution of the residue on silica gel, 67 mg of crude product was obtained. It was treated with triethylamine (65 μL) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (100 μL) in anhydrous CH_2Cl_2 (2 mL). After 4 h of stirring, the mixture was hydrolyzed with saturated aqueous NH_4Cl and extracted with ether. The organic phase was dried over $MgSO_4$, the solvent evaporated, and the residue chromatographed on silica gel (eluent petroleum ether/ether, 8/2) to leave 14 mg (20% yield) of **12** along with compounds **11** (11 mg, 12% yield) and **13** (17 mg, 16% yield).

(4*S*,5*R*,6*S*)-6-[[(4-Bromobenzyl)oxy]methyl]-4,5-bis[(*tert*-butyldimethylsilyl)oxy]-2-(1,3-dithia-2-cyclohexylidene)-oxacyclohexane (11). IR ($CHCl_3$): ν (cm^{-1}) 3047 (=CH), 1629 (C=C), 1597 (C=C). ^1H NMR (250 MHz, $CDCl_3$): δ 7.46–7.43 (m, 2H, phenyl), 7.23–7.19 (m, 2H, phenyl), 4.52–4.38 (m, 3H, H_6, CH_2-Ph), 4.19 (m, 2H, H_4, H_5), 3.75–3.57 (m, 2H, H_7), 3.04–2.69 (m, 6H, H_3, and CH_2S), 2.14 (m, 2H, CH_2), 0.9 (s, 9H, *t*-Bu), 0.86 (s, 9H, *t*-Bu), 0.11 (s, 3H, Me), 0.9 (s, 3H, Me), 0.06 (s, 6H, Me). ^{13}C NMR (63 MHz, $CDCl_3$): δ 158.9, 136.4, 131.4, 129.2, 121.5, 87.0, 72.6, 72.4, 70.7, 39.6, 31.3, 30.8, 26.5, 25.9, 18.2, −4.1, −4.2, −4.5, −4.7. MS (DCI, NH_3): 698–696 (M + 36, 19), 678–680 (M + 18, 72), 661–663 (M + 1, 4), 576–578 (54), 546–548 (71), 274 (22), 152 (100), 130 (21). $[\alpha]^{25}_D$ = −16.4° (*c* = 0.2, $CHCl_3$).

(6*S*)-6-[[(4-Bromobenzyl)oxy]methyl]-5-[(*tert*-butyldimethylsilyl)oxy]-2-(1,3-dithia-2-cyclohexyl)oxa-2,4-cyclohexadiene (12). IR ($CHCl_3$): ν (cm^{-1}) 1597 (C=C), 1549 (C=C). ^1H NMR (250 MHz, $CDCl_3$): δ 7.45 and 7.16 (A_2B_2,

4H, J = 8.4 Hz, phenyl), 6.33 and 6.21 (2d, 1H each, J = 3.2 Hz, H_3, H_4), 5.17 (s, 1H, HCS_2), 4.84 (m, 1H, H_6), 4.50 and 4.47 (AB, 2H, J = 12 Hz, H_{Bn}), 3.67 (m, 2H, H_7), 2.97–2.93 (m, 4H, CH_2S), 2.17–2.05 (m, 2H, CH_2), 0.87 (s, 9H, *t*-Bu), 0.06 (s, 3H, Me), −0.01 (s, 3H, Me). ^{13}C NMR (63 MHz, $CDCl_3$): δ 154.6, 151.0, 137.4, 131.4, 129.2, 121.3, 108.5, 107.9, 73.7, 72.5, 68.2, 42.3, 30.5, 25.8, 25.3, 18.2, −4.9. MS (DCI, NH_3): 546–548 (M + 18, 100), 468 (11). $[\alpha]^{25}_D = -25.7°$ (c = 0.3, $CHCl_3$).

(3*S*,4*R*,5*S*)-6-[(4-Bromobenzyl)oxy]-3,4,5-tris[(*tert*-butyldimethylsilyl)oxy]-1-(1,3-dithia-2-cyclohexyl)-1-hexanone (13). IR ($CHCl_3$): ν (cm^{-1}) 3052 (=CH), 1712 (C=O), 1594 (C=C). ^1H NMR (250 MHz, C_6D_6): δ 7.29 and 6.96 (A_2B_2, 4H, phenyl), 4.53 (ddd, 1H, J = 2.3, 4.8, 8.9 Hz, H_3), 4.37 (m, 1H, H_5), 4.25 and 4.17 (AB, 2H, J = 12.3 Hz, H_{Bn}), 4.04 (dd, 1H, J = 1.3, 4.8 Hz, H_4), 3.89 (s, 1H, HCS_2), 3.80 and 3.58 (AB(X), dq, 2H, J = 2.2, 7.4, 10.2 Hz, CH_2-O), 3.24 and 2.89 (AB(X), dq, 2H, J = 2.3, 8.9, 16.7 Hz, CH_2-CO), 3.14 and 2.79 (m, 2H, CH_2S eq), 2.00 (m, 2H, CH_2S ax), 1.40–1.20 (m, 2H, CH_2), 1.07 (s, 9H, *t*-Bu), 0.98 (s, 18H, *t*-Bu), 0.3, 0.26, 0.25, 0.22, 0.21, and 0.18 (s, 3H each, MeSi). ^{13}C NMR (63 MHz, C_6D_6): δ 201.4, 137.8, 131.7, 129.5, 121.4, 76.4, 74.5, 74.2, 72.6, 71.5, 46.2, 43.7, 26.3, 25.4, 18.6, 18.5, 18.2, −3.8, −3.9, −4.1, −4.3, −4.4, −4.7. MS (DCI, NH_3): 810–812 (M + 18, 100), 793–795 (M, 24), 446–444 (15). $[\alpha]^{25}_D = -53°$ (c = 0.3, $CHCl_3$).

Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **4a**, **5b**, **10**, **11n**, **12**, and **13** and ^{13}C NMR spectra of compound **8** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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