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Synthesis of 3-deoxyaldulosonic acid esters by one-carbon chain extension of glycal-derived lactone precursors

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ABSTRACT

A convenient preparative route is described for 3-deoxyaldulosonic acids. Glycal precursors are oxidatively converted into 2-deoxyaldonolactones, which react with 1,3-dithian-2-yl anion to afford 1,3-propanediyl dithioacetals of higher 3-deoxyaldosuloses. Deprotection with mercuric salts in wet or dry alcohols gave high yields of the corresponding alkyl aldulosonates. Preparative reaction conditions were optimized and the anomeric configurations of the ketopyranose products were established by ^{13}C NMR.

INTRODUCTION

The biological importance of aldulosonic acids, and especially their 3-deoxy derivatives, is well known. For example (Chart I), 3-deoxy-D-*arabino*-2-heptulosonic acid 7-phosphate (**1**) is an intermediate in the shikimic acid pathway for the synthesis of aromatic amino acids in living organisms[1–3]. 3-Deoxy-D-*manno*-2-octulosonic acid (Kdo, **2**) is a constituent of the cell-wall lipopolysaccharides of Gram-negative bacteria[4–7], and *N*-acetylneuraminic acid (NeuAc, **3**) is a component of the capsular polysaccharides of certain bacteria[8], and is of profound significance in molecular recognition processes in viruses, bacteria, and the cells of higher animals[9].

Many different reaction sequences have been used to prepare 3-deoxyaldulosonic acids. Among these are: (*a*) direct condensation of aldoses with oxaloacetic acid. The disadvantages of this method are: either low yields[10] and/or mixtures[11] of isomers obtained, and separation can be tedious; (*b*) selective oxidation of the

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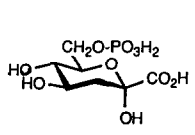
Chart I



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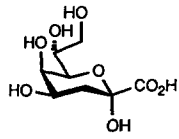

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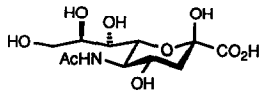

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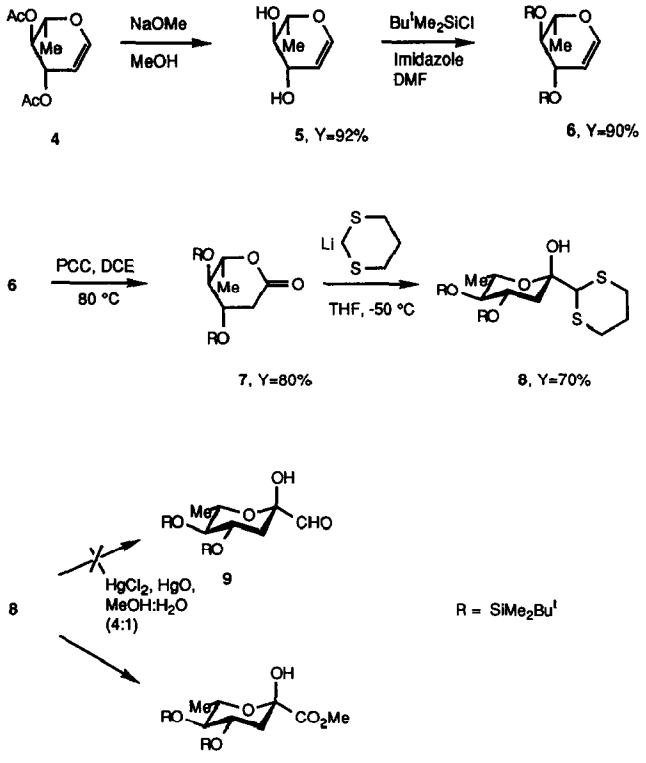
C-2 hydroxyl group to carbonyl with potassium chlorate in the presence of vanadium(V) oxide[12–14]. Only one isomer is obtained, but the drawbacks are that the reaction may be slow and the yields are mediocre; (*c*) conversion of aldoses into imidolactones of enamines, which are then sequentially hydrolyzed to 3-deoxyaldulosonic acids[15]; and (*d*) other methods that involve long synthetic procedures and/or tedious separations of isomers[16]. In our laboratory, a convenient short sequence has employed[17] a one-step conversion of a free aldose into the bis(benzoylhydrazone) of the corresponding 3-deoxyaldosulose, with subsequent transhydrazonation; the resultant 3-deoxyaldosulose may then be oxidized to the aldulosonic acid.

The present work demonstrates a convenient alternative route to these higher-carbon sugars, and is exemplified in the synthesis of alkyl esters of 3,7-dideoxy-L-*arabino*-2-heptulosonic acid.

RESULTS AND DISCUSSION

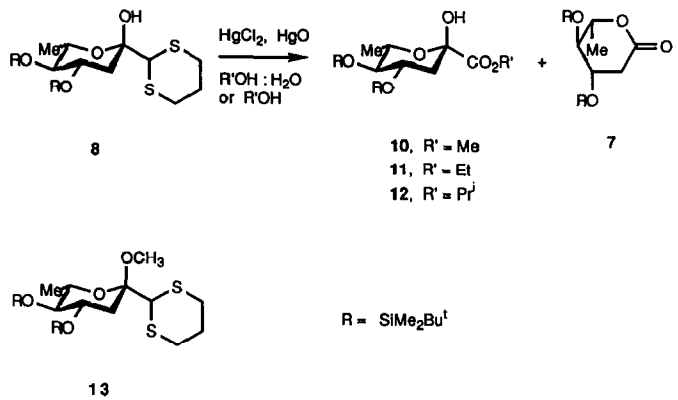
Synthesis of alkyl aldulosonates.—The general sequence used to obtain alkyl aldulosonates is shown in Scheme 1. Commercially available di-*O*-acetyl-L-rhamnal (**4**) was deacetylated with sodium methoxide in methanol to give L-rhamnal (**5**) in 92% yield. Silylation of **5** with *tert*-butylchlorodimethylsilane afforded the protected glycal **6** in 90% yield, and this was oxidized with pyridinium chlorochromate[18] in 1,2-dichloroethane at 80°C to give the crystalline lactone **7**, isolated in 80% yield after purification by column chromatography *. Lactone **7** was then treated with 2-lithio-1,3-dithiane to afford the 1-*C*-(1,3-dithiane-2-yl) derivative **8** in 70% yield. This approach was earlier developed by Horton and Priebe[20] as a useful route to higher-carbon sugars. In the final step, compound **8** was hydrolyzed by mercuric salts in 4:1 methanol–water. The methyl aldulosonate **10** was obtained in 80% yield, and no traces of the aldehyde **9** were detected.

* This compound was first prepared by Dr. Albert V. Thomas in this laboratory[19].



Scheme 1.

The high yields prompted a further study of this reaction as summarized in Scheme 2 and Table I. As already noted, the reaction in 4:1 methanol–water (entry 1, Table I and Scheme 1) afforded the methyl aldulosonate **10** as the sole product, obtained in 80% yield after 12 h of reaction. However, when the reaction



Scheme 2.

TABLE I

Product distribution in the treatment of **8** under the conditions shown in Scheme 1

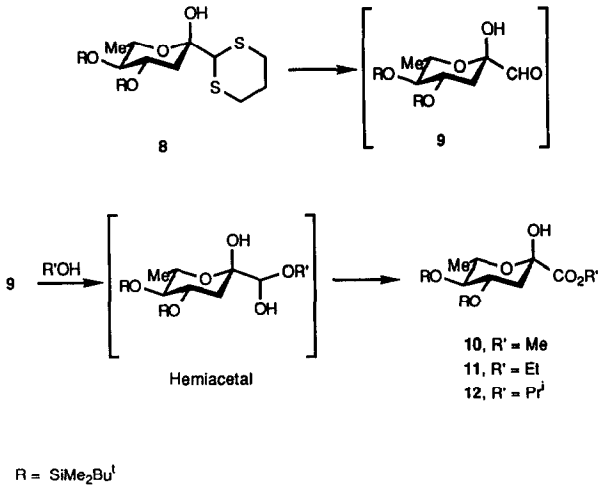
Entry	Solvent	Product distribution	Reaction time (h)	Yield [a] (%)
1	4:1 MeOH–H_2O	**10**:**7** = 100:0	12	80
2	4:1 EtOH–H_2O	**11**:**7** = 80:20	12	75
3	4:1 *i*-PrOH–H_2O	**12**:**7** = 20:80	12	68
4	4:1 *t*-BuOH–H_2O	**7** = 100	12	60
5	MeOH	**10**:**7** = 100:0	48	85 [b]
6	EtOH	**11**:**7** = 100:0	72	82
7	*i*-PrOH	**12**:**7** = 90:10	96	70
8	*t*-BuOH	**7** = 100	96	20

[a] When mixtures were obtained, the value denotes the total combined yield. [b] Minor amounts of compound **13** were isolated (see Experimental).

was conducted in 4:1 ethanol–water (entry 2), the ethyl aldulosonate **11** was accompanied by lactone **7** (the precursor of the dithiane adduct) as a minor component. In 4:1 2-propanol–water (entry 3), the lactone **7** was the major component, and in 4:1 *tert*-butyl alcohol–water it was the sole product. The second part of Table I (entries 5–8) shows the results of conducting the reaction in dry alcohols. In dry methanol (entry 5), again no lactone was detected, but a minor amount of the methyl glycoside **13** was isolated. In dry ethanol (entry 6) no lactone was detected and the ethyl aldulosonate **11** was obtained in 82% yield. In dry 2-propanol (entry 7), a 9:1 mixture of the isopropyl aldulosonate **12** and the lactone **7** was isolated; here the isopropyl aldulosonate was the major product, in contrast to the result obtained in wet 2-propanol (entry 3). Finally, in dry *tert*-butyl alcohol (entry 8), lactone **7** was again the only isolated product, but its yield was very low (20%), and the reaction time very long (96 h). Higher proportions of alkyl aldulosonates are thus obtained in dry alcohols, although longer reaction times are required.

These results demonstrate that two competing reactions are involved: one which gives the alkyl aldulosonate and the other that involves displacement of the 1,3-dithianyl group to re-form the lactone **7**. The relative rates of these two reactions will determine the proportion of products. If a hemiacetal (Scheme 3) is one of the intermediates in the mechanism of the first reaction, the more highly substituted the alcohol (R'OH) the more difficult it is to form this intermediate. This factor could explain the decrease in the proportion of alkyl aldulosonates when higher alcohols are used. As regards formation of the lactone, some precedents in the literature[21] relate to our results (Scheme 4). When the α-keto-dithioacetal **14** was treated with KOH in *tert*-butyl alcohol, the 1,3-dithianylcarboxylic acid **15** was obtained in 93% yield. When the same reaction was performed in methanol, no reaction was detected and only starting material was recovered.

In a similar procedure[22] tris(methylthio)methane was used as the reagent, to afford methyl aldulosonates from lactones in a two-step synthesis, but the yields were lower (33–49%) as compared with ours (55–60% for the two steps from

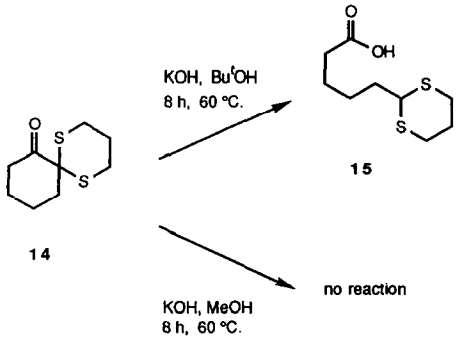


Scheme 3.

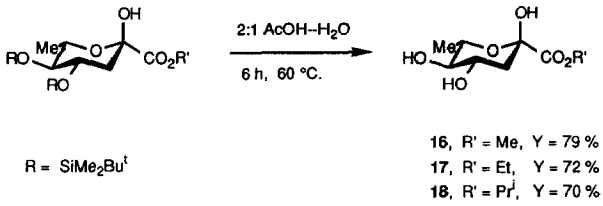
lactone **7** to methyl aldulosonate **10**). The present method also establishes that there is no need to utilize intermediates in higher oxidation states, such as orthothioesters, for preparing alkyl aldulosonates.

Final deprotection was accomplished with 2:1 acetic acid–water for 6 h at 60°C, which hydrolyzed the *O*-silyl groups to furnish the alkyl aldulosonates in good yield (Scheme 5). The reactivity of these products with sodium borohydride (Scheme 6) was examined. The reaction gave a mixture of three compounds, the 3,7-dideoxyketose **19** and the two C-2-stereoisomeric alditols **20** and **21**. The proportion of products did not change appreciably when the reaction time was extended.

Structural assignment at the anomeric center of alkyl aldulosonates.—The ^{13}C and ^{1}H NMR spectra of the alkyl aldulosonates **10**, **11**, and **12** showed two set of signals in a 10:1 ratio ($CDCl_3$), corresponding to the α (equatorial ester group) and β anomer (axial ester group), respectively. The absolute configuration at the anomeric center of the major component was established by SFORD (single



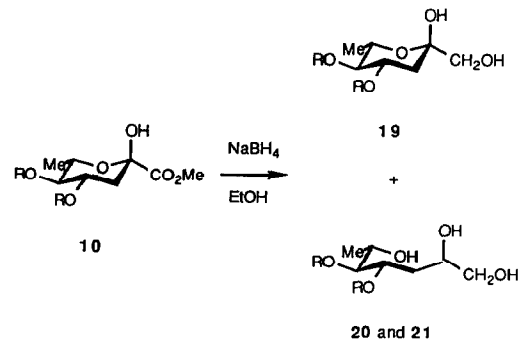
Scheme 4.



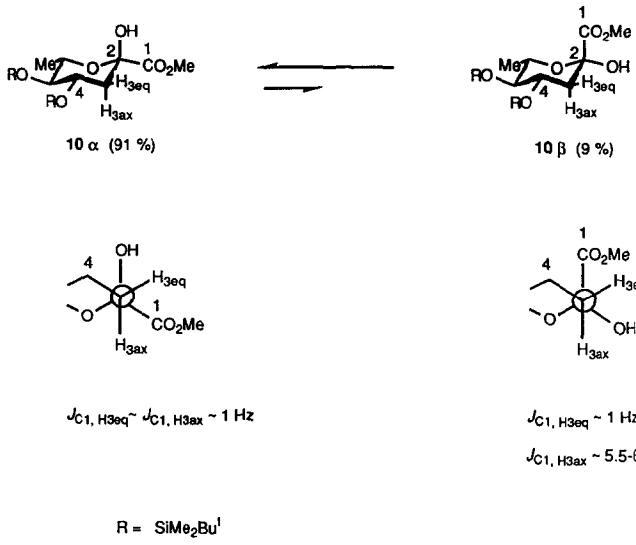
Scheme 5.

frequency off-resonance decoupling) ^{13}C NMR spectroscopy. The spectra showed the C-1 signal as a double quartet reflecting a constant of 3.5 Hz for the coupling between C-1 and the three protons of the methyl group, and of 1.2 Hz for the coupling between C-1 and H-3*eq* or C-1 and H-3*ax*. The remaining coupling (< 1 Hz) was not resolved. A Karplus-type equation[23–26] has been proposed that correlates the vicinal coupling constants for ^{13}C and ^{1}H with their dihedral angle, in the same way as for ^{1}H–^{1}H couplings. For example (Scheme 7), in the α anomer the expected constant for the coupling between C-1 and H-3*eq*, and C-1 and H-3*ax*, should be ~ 1 Hz. In the β anomer, the expected coupling between C-1 and H-3*eq* would again be ~ 1 Hz, but between C-1 and H-3*ax* the coupling should be ~ 5.5–6.0 Hz. The small coupling constants for C-1–H-3*eq* and C-1–H-3*ax* establish the α configuration at C-2, with the ester group in an equatorial orientation. The $\alpha:\beta$ ratio (10:1) was determined by integration of the signals of H-3*eq* and H-3*ax* for both isomers in the proton spectrum. Scheme 8 shows these values and the coupling constants involving H-4. The large coupling constant for H-3*ax*–H-4 in both anomers establishes the *trans*-diaxial orientation of these two protons and also the $^{2}C_{5}$ conformation. All of these values are concordant with data previously reported[28] for *N*-acetylneuraminic acid (**3**).

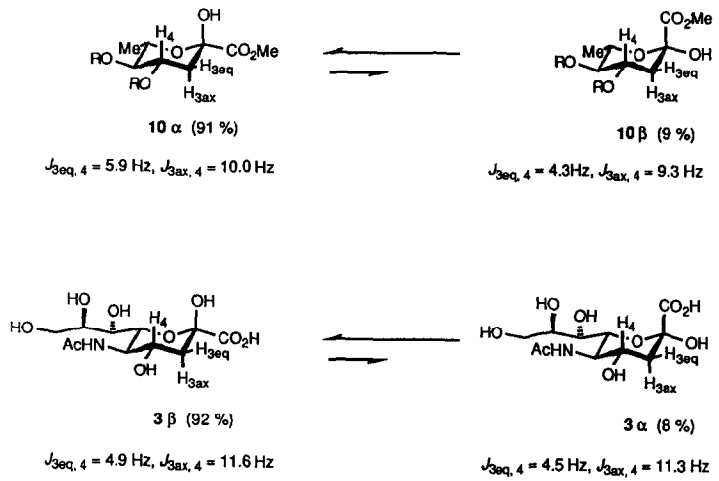
A similar ratio of isomers was observed in the ethyl (**11**) and isopropyl (**12**) aldulosonates. The free hydroxy derivatives **16**, **17**, and **18** showed an $\alpha:\beta$ ratio of 9:1 in acetone.



Scheme 6.



Scheme 7.



Scheme 8.

EXPERIMENTAL

General methods.—Solvents were dried and redistilled just prior to use. Melting points were determined in open glass capillaries by use of a Thomas–Hoover

apparatus, and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 141 polarimeter, ^{1}H NMR spectra were recorded at 500 MHz with a Bruker AM-500 spectrometer by C.E. Cottrell. The samples were dissolved in $CDCl_3$ or acetone-d_6 and the chemical shifts refer to an internal standard of Me_4Si ($\delta = 0.0$ ppm). Evaporations were performed under diminished pressure. TLC was performed on precoated aluminum sheets (0.2 mm) and glass plates (0.25 mm) coated with Silica Gel $60F_{254}$ (E. Merck, Darmstadt); components were detected by spraying the plates with 0.1 M ceric sulfate in 2 M H_2SO_4, with subsequent heating. Column chromatography was performed with Silica Gel 60 (230–400 mesh, E. Merck, Darmstadt). High pressure liquid chromatography was performed with a Waters apparatus equipped with a Model 6000A solvent delivery system and Model 440 absorbance detector. Elemental analyses were done by Atlantic Microlab (Atlanta, GA).

*6-Deoxy-*L*-glucal* (L*-rhamnal,* **5**).—Conventional *O*-deacetylation[28] of 3,4-di-*O*-acetyl-L-rhamnal (Pfanstiehl, **4**, 12.0 g, 56 mmol) with NaOMe in MeOH gave 6.74 g (92%) of **5** in two crops, mp 71–73°C (EtOAc–hexane).

*3,4-Di-*O-tert*-butyldimethylsilyl-*L*-rhamnal* (**6**).—This compound was prepared[29] from L-rhamnal (**5**, 6.4 g, 49 mmol) as an oil (15.7 g, 90%); $[\alpha]_D^{20}$ 44.7° (*c* 1.0, $CHCl_3$); lit.[29] 44°.

*3.4,-Di-*O-tert*-butyldimethylsilyl-2,6-dideoxy-*L-arabino*-hexono-1,5-lactone* (**7**).—A mixture of compound **6** (2.0 g, 5.6 mmol) and pyridinium chlorochromate (2.43 g, 11.3 mmol, 2 molar equiv) in 60 mL of 1,2-dichloroethane was stirred for 20 h at 80%C. The mixture was cooled and poured through a short column of silica gel (50 g, 1:1 hexane–EtOAc). Evaporation of the solvent yielded an oil that solidified into a waxy material. Crystallization from MeOH gave 7 as a pure solid (1.7 g, 80%); mp 76–78°C, $[\alpha]_D^{20}$ −36.5° (*c* 1.0 $CHCl_3$); lit.[30] mp 77–78°C, $[\alpha]_D^{20}$ −38.4° (*c* 1.0, $CHCl_3$).

*4,5-Di-*O-tert*-butyldimethylsilyl-3,7-dideoxy-α-*L-arabino*-heptos-2-ulo-2,6-pyranose 1,3-propanediyl dithioacetal* (**8**).—To a well-stirred solution of 1,3-dithiane (1.57 g, 13.0 mmol) in dry THF (60 mL), was slowly added a solution of butyllithium (6.0 mL, 2.6 M in hexane, 15 mmol) at −55°C under Ar. The mixture was kept with stirring for 2 h at −35 to −20°C. It was then cooled (−50°C), whereupon a solution of lactone 7 (4.9 g, 13.0 mmol) in dry THF (25 mL) was added. The mixture was stirred for 4 h at −50 to −45°C, and then kept for 36 h at −14°C. TLC (10:1 hexane–EtOAc) showed one major product (R_f 0.55). The mixture was poured into ice–water (200 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined extracts were successively washed with 7% KOH solution and water, and then dried (Na_2SO_4). Evaporation gave a yellowish oil that was purified by column chromatography (150 g silica gel, 20:1 hexane–EtOAc). A syrup was obtained that crystallized from MeOH to give **8** as a pure white solid (4.5 g, 70%); mp 100–102°C, $[\alpha]_D^{20}$ 6.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.02 (ddd, 1 H, H-4), 3.98 (d, 1 H, $J_{2\text{-}OH,3ax}$ 2.7 Hz, O*H*-2), 3.82 (dq, 1 H, $J_{6,7}$ 6.4 Hz, H-6), 3.39 (s, 1 H, H-1), 3.33 and 3.30 (two symmetrical ddd, 2 H, $J_{1'ax,1'eq}$ 15.9, $J_{1'ax,2'ax}$ 11.5,

$J_{1'ax,2'eq}$ 2.7 Hz, H-1′*ax* and H-3′*ax*) *, 3.17 (t, 1 H, $J_{4,5}$ 8.4, $J_{5,6}$ 9.1 Hz, H-5), 2.46 (m, 2 H, $J_{3'ax,3'eq}$ 15.9 Hz, H-1′*eq* and H-3′*eq*), 2.35 (ddd, 1 H, $J_{3ax,3eq}$ 12.7, $J_{3ax,4}$ 11.1 Hz, H-3*ax*), 2.08 (m, 1 H, $J_{2'eq,3'ax}$ 2.7 Hz, H-2′*eq*), 1.98 (m, 1 H, $J_{1'eq,2'ax}$ 3.0, $J_{2'eq,2'ax}$ 14.0, $J_{2'ax,3'ax}$ 11.5, $J_{2'ax,3'eq}$ 3.0 Hz, H-2′*ax*), 1.82 (dd, 1 H, $J_{3eq,4}$ 4.8 Hz, H-3*eq*), 1.24 (d, 3 H, CH_3), 0.91 [s, 18 H, (CH_3)$_3$CSi], 0.12 (s, 3 H, CH_3Si), 0.10 (s, 6 H, CH_3Si), and 0.09 (s, 3 H, CH_3Si); ^{13}C NMR ($CDCl_3$): δ 100.3 (C-2), 78.5 (C-5), 71.8 (C-4), 70.2 (C-6), 49.5 (C-1), 40.5 (C-3), 26.6 and 26.3 (C-1′ and C-3′), 26.1 [(*C*H$_3$)$_3$CSi], 24.9 (C-2′), 19.5 (C-7), 18.3 and 18.1 [(CH$_3$)$_3$*C*Si], −2.6, −3.0, −3.9, and −4.3 (*C*H$_3$Si). All assignments were verified by ^{13}C–^{1}H correlations. Anal. Calcd for $C_{22}H_{46}O_4S_2Si_2$: C, 53.39; H, 9.37; S, 12.96. Found: C, 53.22; H, 9.43; S, 13.01.

*Methyl 4,5-di-*O-tert-*butyldimethylsilyl-3,7-dideoxy-*L-arabino-*2-heptulosonate* (**10**) —(Table I, entry 1). To a well-stirred suspension of $HgCl_2$ (0.24 g, 0.88 mmol) and HgO (0.19 g, 0.88 mmol) in 4:1 MeOH–water (5 mL), was added compound **8** (0.22 g, 0.44 mmol). After 12 h, TLC (10:1 hexane–EtOAc) showed one major compound (R_f 0.53). The mixture was filtered through Celite, and the filtrate was diluted with water and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried (Na_2SO_4) and evaporated, and the resultant mixture was purified by column chromatography (20 g of silica gel, 20:1 hexane–EtOAc) to give pure **10** (0.155 g, 80%, 10:1 mixture of α and β anomers) as a syrup; bp 100°C (0.04 mmHg), $[\alpha]_D^{20}$ −5.7° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$), signals of the α anomer: δ 3.99 (ddd, 1 H, $J_{3ax,4}$ 10.0, $J_{3eq,4}$ 5.9, $J_{4,5}$ 8.4 Hz, H-4), 3.87 (dq, 1 H, $J_{5,6}$ 8.6, $J_{6,7}$ 6.3 Hz, H-6), 3.83 (s, 3 H, CH_3O), 3.79 (bs, 1 H, O*H*-2), 3.22 (t, 1 H, H-5), 2.10 and 2.00 (m, 2 H, H-3*eq* and H-3*ax*), 1.22 (d, 3 H, CH_3), 0.91 [s, 9 H, (CH_3)$_3$CSi], 0.90 [s, 9 H, (CH_3)$_3$CSi], 0.11 (s, 3 H, CH_3Si), 0.10 (s, 3 H, CH_3Si), 0.09 (s, 3 H, CH_3Si), and 0.08 (s, 3 H, CH_3Si); signals of the β anomer: δ 2.50 (dd, 1 H, $J_{3eq,3ax}$ 12.5, $J_{3eq,4}$ 4.3 Hz, H-3*eq*) and 1.80 (dd, 1 H, $J_{3ax,4}$ 9.3 Hz, H-3*ax*); ^{13}C NMR ($CDCl_3$) δ 170.8 (C-1α), 169.1 (C-1β), 95.3 (C-2β), 94.7 (C-2α), 78.1 (C-5α), 73.4 and 71.8 (C-4β and C-6β), 71.1 (C-6α), 70.8 (C-4α), 53.3 (*C*H$_3$O α), 52.7 (*C*H$_3$O β), 40.1 (C-3α), 38.0 (C-3β), 26.3 and 26.1 [(*C*H$_3$)$_3$CSi α], 19.4 (C-7β), 18.6 (C-7α), 18.3 and 18.1 [(CH$_3$)$_3$*C*Si α], −2.7, −3.1, −3.9, and −4.4 (*C*H$_3$Si α). All assignments were verified by ^{13}C–^{1}H correlations. Anal. Calcd for $C_{20}H_{42}O_6Si_2$: C, 55.26; H, 9.74. Found: C. 55.30; H, 9.80.

*Ethyl 4,5-di-*O-tert-*butyldimethylsilyl-3,7-dideoxy-*L-arabino-*2-heptulosonate* (**11**). —(Table I, entry 2). The same conditions and same scale as described in the preceding experiment were used, except that 4:1 EtOH–water was the solvent instead of 4:1 MeOH–water. Column chromatography gave a mixture of two compounds which was resolved by HPLC (10:1 hexane–EtOAc at a flow rate of 5.0 mL/min). The faster-moving component (t_R 19.0 min), identified as the ethyl aldulosonate **11** (10:1 mixture of α and β anomers), was isolated as a syrup (0.12

* Primed locants refer to positions in the propanediyl group.

g, 60%); bp 100°C (0.04 mmHg), $[\alpha]_D^{20}$ −10.0° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$), signals of the α anomer: δ 4.26 (m, 2 H, $J_{CH2,CH3}$ 7.0 Hz, OCH_2CH_3), 3.99 (m, 1 H, H-4), 3.86 (dq, 1 H, $J_{6,7}$ 6.4 Hz, H-6), 3.69 (s, 1 H, O*H*-2), 3.22 (t, 1 H, $J_{4,5}$ 8.7, $J_{5,6}$ 8.7 Hz, H-5), 2.04 and 2.03 (m, 2 H, H-3*eq* and H-3*ax*), 1.33 (t, 3 H, OCH_2CH_3), 1.22 (d, 3 H, CH_3), 0.91 [s, 9 H, $(CH_3)_3CSi$], 0.90 [s, 9 H, $(CH_3)_3CSi$], 0.11 (s, 3 H, CH_3Si), 0.10 (s, 3 H, CH_3Si), 0.09 (s, 3 H, CH_3Si), and 0.08 (s, 3 H, CH_3Si); signals of the β anomer: δ 2.51 (dd, 1 H, $J_{3eq,3ax}$ 12.0, $J_{3eq,4}$ 4.0 Hz H-3*eq*) and 1.78 (dd, 1 H, $J_{3ax,4}$ 9.1 Hz, H-3*ax*); ^{13}C NMR ($CDCl_3$): δ 170.2 (C-1α), 169.8 (C-1β), 95.0 (C-2β), 94.7 (C-2α), 78.2 (C-5α), 73.3 and 71.5 (C-4β and C-6β), 71.1 (C-6α), 71.0 (C-4α), 62.5 (OCH_2CH_3 α), 61.9 (OCH_2CH_3 β), 40.0 (C-3α), 39.0 (C-3β), 26.3 and 26.1 [$(CH_3)_3CSi$ α], 19.0 (C-7β), 18.3 (C-7α), 17.9 and 17.8 [$(CH_3)_3CSi$ α], 14.0 (OCH_2CH_3 β), 13.9 (OCH_2CH_3 α), −2.7, −3.1, −3.9, and −4.4 (CH_3Si α). All assignments were verified by ^{13}C–^1H correlations. Anal. Calcd for $C_{21}H_{44}O_6Si_2$: C, 56.21; H, 9.88. Found: C, 56.29; H, 9.89.

The slower-moving component (t_R 25.0 min) was identified as lactone **7** (25 mg, 15%).

*Isopropyl 4,5-di-*O-tert-*butyldimethylsilyl-3,7-dideoxy-*L-arabino-*2-heptulosonate* (**12**).—(Table I, entry 3). The same conditions and same scale as described in the preceding experiment were used, except that 4:1 2-propanol–water was the solvent instead of 4:1 EtOH–water. Column chromatography gave a mixture of two compounds which was resolved by HPLC (10:1 hexane–EtOAc at a flow rate of 5.0 mL/min). The faster-moving component (t_R 18.0 min), identified as the isopropyl aldulosonate **12** (10:1 mixture of α and β anomers), was isolated as a syrup (28 mg, 13.6%); bp 100°C (0.04 mmHg), $[\alpha]_D^{20}$ −4.2° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) signals of the α anomer: δ 5.06 [m, 1 H, $J_{CH,CH3}$ 6.3 Hz, $OCH(CH_3)_2$], 3.98 (ddd, 1 H, $J_{3ax,4}$ 9.6, $J_{3eq,4}$ 6.4, $J_{4,5}$ 8.5 Hz, H-4), 3.84 (dq, 1 H, $J_{5,6}$ 8.6, $J_{6,7}$ 6.4 Hz, H-6), 3.70 (s, 1 H, O*H*-2), 3.21 (t, 1 H, H-5), 2.06 and 2.00 (m, 2 H, H-3*eq* and H-3*ax*), 1.31 [d, 3 H, $OCH(CH_3)_2$], 1.30 [d, 3 H, $OCH(CH_3)_2$], 0.91 [s, 9 H, $(CH_3)_3CSi$], 0.90 [s, 9 H, $(CH_3)_3CSi$], 0.11 (s, 3 H, CH_3Si), 0.10 (s, 3 H, CH_3Si), 0.09 (s, 3 H, CH_3Si), and 0.08 (s, 3 H, CH_3Si); signals of the β anomer: δ 2.47 (dd, 1 H, $J_{3eq,3ax}$ 12.1, $J_{3eq,4}$ 4.3 Hz, H-3*eq*) and 1.77 (dd, 1 H, $J_{3ax,4}$ 9.3 Hz, H-3*ax*); ^{13}C NMR ($CDCl_3$): δ 169.8 (C-1α), 94.7 (C-2α), 78.3 (C-5α), 73.1 and 71.1 (C-4β and C-6β), 71.0 and 70.9 (C-6α and C-4α), 70.5 [$OCH(CH_3)_2$ α], 69.9 [$OCH(CH_3)_2$ β], 39.9 (C-3α), 39.4 (C-3β), 26.3 and 26.1 [$(CH_3)_3CSi$ α], 21.6 [$OCH(CH_3)_2$ β], 21.5 [$OCH(CH_3)_2$ α], 19.3 (C-7β), 18.6 (C-7α), 18.3 and 18.1 [$(CH_3)_3CSi$ α], −2.7, −3.1, −3.9, and −4.4 (CH_3Si α). All assignments were verified by ^{13}C–^1H correlations. Anal. Calcd for $C_{22}H_{46}O_6Si_2$: C, 57.10; H, 10.02. Found: C, 57.00; H, 10.06.

The slower-moving component (t_R 25.0 min) was identified as lactone **7** (89 mg, 54%).

Reaction of 8 in 4:1 t-*BuOH–water*.—(Table I, entry 4). The same conditions and same scale as described in the preceding experiment were used, except that

4:1 *t*-BuOH–water was the solvent instead of 4:1 2-propanol–water. Column chromatography gave one compound, identified as lactone **7** (98 mg, 60%).

Reaction of 8 in dry alcohols.—In the following procedures, the same conditions and same scale as previously described were used, except that the indicated dry alcohol (MeOH, EtOH, 2-propanol, or *t*-BuOH) was used as a solvent.

Dry MeOH.—(Table I, entry 5). After 48 h the reaction was stopped by the usual procedure. Column chromatography gave two compounds, the faster-moving of which was identified as 4,5-di-*O*-*tert*-butyldimethylsilyl-3,7-dideoxy-2-*O*-methyl-α-L-*arabino*-heptos-2-ulo-2,6-pyranose 1,3-propanediyl dithioacetal (**13**), isolated as a syrup (20 mg, 10%); $[\alpha]_D^{20}$ −10.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.50 (s, 1 H, H-1), 3.90 (ddd, 1 H, $J_{3eq,4}$ 4.9, $J_{4,5}$ 8.6, H-4), 3.48 (dq, 1 H, $J_{5,6}$ 8.8, $J_{6,7}$ 6.4 Hz, H-6), 3.23 (s, 3 H, OCH_3), 3.12 (t, 1 H, H-5), 2.81–2.93 (m, 4 H, H-1′*ax*, H-1′*eq*, H-3′*ax*, and H-3′*eq*), 2.21 (dd, 1 H, H-3*eq*), 2.07 (m, 1 H, H-2′*eq*), 1.83 (m, 2 H, H-2′*ax* and $J_{3ax,3eq}$ 13.3, $J_{3ax,4}$ 11.0 Hz, H-3*ax*), 1.25 (d, 3 H, CH_3), 0.91 [s, 18 H, $(CH_3)_3CSi$], 0.12 (s, 3 H, CH_3Si), 0.10 (s, 6 H, CH_3Si), and 0.09 (s, 3 H, CH_3Si); ^{13}C NMR ($CDCl_3$): δ 100.7 (C-2), 78.1 (C-5), 71.1 (C-4), 70.8 (C-6), 52.5 (C-1), 47.5 (OCH_3), 39.6 (C-3), 30.7 and 30.6 (C-1′ and C-3′), 26.4 [two overlapped signals, C-2′ and (CH_3CSi], 26.1 [$(CH_3)_3CSi$], 18.6 (C-7), 18.3 and 18.1 [$(CH_3)_3CSi$], −2.7, −3.0, −3.9, and −4.1 (CH_3Si). All assignments were verified by ^{13}C–^{1}H correlations. Anal. Calcd for $C_{23}H_{48}O_4S_2Si_2$: C, 54.28; H, 9.51; S, 12.60. Found: C, 53.99; H, 9.48; S, 12.51.

The slower-moving component was identified as the methyl aldulosonate **10** (0.14 g, 75%).

Dry EtOH.—(Table I, entry 6). After 72 h the reaction was stopped by the usual procedure. Column chromatography gave one compound, identified as the ethyl aldulosonate **11** (0.16 g. 82%).

Dry 2-propanol.—(Table I, entry 7). After 96 h the reaction was stopped by the usual procedure. Column chromatography gave a mixture of two compounds which was resolved by HPLC (10:1 hexane–EtOAc at a flow rate of 5.0 mL/min). The faster-moving component (t_R 18.0 min), identified as the isopropyl aldulosonate **12** (10:1 mixture of α and β anomers), was isolated as a syrup (0.13 g, 63%). The slower-moving component (t_R 25.0 min) was identified as lactone **7** (10 mg, 7%).

Dry ^{t}BuOH.—(Table I, entry 8). After 96 h the reaction was stopped by the usual procedure. Column chromatography gave one compound, identified as lactone **7** (30 mg, 20%).

Methyl 3,7-dideoxy-L-arabino-*2-heptulosonate* (**16**).—A solution of compound **10** (0.23 g, 0.52 mmol), 8 mL of AcOH, and 4 mL of water was kept for 6 h at 60°C and then evaporated to dryness. Column chromatography (4 g silica gel, 2:1 hexane–acetone) gave one compound, as a syrup, identified as the methyl aldulosonate **16** (90 mg, 79%) (9:1 mixture of α and β anomers); $[\alpha]_D^{20}$ −36.7° (*c* 1.0, acetone); ^{1}H NMR (acetone-d_6), signals of the α anomer: δ 3.85–3.77 (m, 2 H $J_{6,7}$ 6.3 Hz, H-4 and H-6), 3.69 (s, 3 H, CH_3O), 2.97 (t, 1 H, $J_{4,5}$ 9.1, $J_{5,6}$ 9.1 Hz, H-5), 2.04 (m, 1 H, H-3*eq*), 1.86 (dd, 1 H, $J_{3ax,3eq}$ 11.8, $J_{3ax,4}$ 11.6 Hz, H-3*ax*), 1.16 (d, 3

H, CH_3); signals of the β anomer: δ 2.51 (dd, 1 H, $J_{3eq,3ax}$ 12.8, $J_{3eq,4}$ 5.0 Hz, H-3*eq*) and 1.57 (dd, 1 H, $J_{3ax,4}$ 9.5, H-3*ax*); ^{13}C NMR (acetone-d_6) δ 171.2 (C-1α), 95.6 (C-2α), 77.6 (C-5α), 77.0 (C-5β), 72.4 (C-6β), 70.1 (C-6α), 70.0 (C-4β), 69.0 (C-4α), 53.3 (CH_3O α), 52.7 (CH_3O β), 41.0 (C-3β), 39.6 (C-3α), 18.1 (C-7β), and 17.8 (C-7α). All assignments were verified by ^{13}C–^1H correlations. Anal. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.72; H, 6.85.

*Ethyl 3,7-dideoxy-*L*-*arabino*-2-heptulosonate* (**17**).—Compound **11** (0.23 g, 0.52 mmol) was treated as described in the preceding experiment. Column chromatography (4 g silica gel, 2:1 hexane–acetone) gave one compound, as a syrup, identified as the ethyl aldulosonate **17** (80 mg, 72%) (9:1 mixture of α and β anomers); $[\alpha]_D^{20}$ −32.0° (*c* 1.0, acetone); ^1H NMR (acetone-d_6), signals of the α-anomer: δ 4.15 (m, 2 H, OCH_2CH_3), 3.84–3.78 (m, 2 H, $J_{6,7}$ 6.3 Hz, H-4 and H-6), 2.96 (t, 1 H, $J_{4,5}$ 9.0, $J_{5,6}$ 9.0 Hz, H-5), 2.05 (m, 1 H, H-3*eq*), 1.87 (dd, 1 H, $J_{3ax,3eq}$ 12.7, $J_{3ax,4}$ 11.7 Hz, H-3*ax*), and 1.16 (d, 3 H, CH_3); signals of the β anomer: δ 2.53 (dd, 1 H, $J_{3eq,3ax}$ 12.4, $J_{3eq,4}$ 4.1 Hz, H-3*eq*) and 1.56 (dd, 1 H, $J_{3ax,4}$ 10.1, H-3*ax*); ^{13}C NMR (acetone-d_6): δ 170.6 (C-1α), 95.8 (C-2α), 78.4 (C-5α), 72.5 (C-6β), 70.3 (C-6α), 69.7 (C-4α), 62.1 ($OCH_2CH_3\alpha$), 61.7 (OCH_2CH_3 β), 41.3 (C-3β), 39.9 (C-3α), 18.5 (C-7β), 18.2 (C-7α), 14.3 (OCH_2CH_3 β), and 14.2 (OCH_2CH_3 α). All assignments were verified by ^{13}C–^1H correlations. Anal. Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 48.96; H, 7.37.

*Isopropyl 3,7-dideoxy-*L*-*arabino*-2-heptulosonate* (**18**).—Compound **12** (0.24 g, 0.52 mmol) was treated as described in the preceding experiment. Column chromatography (4 g silica gel, 2:1 hexane–acetone) gave one compound, as a syrup, identified as the isopropyl aldulosonate **18** (90 mg, 70%) (9:1 mixture of α and β anomers); $[\alpha]_D^{20}$ −26.5° (*c* 1.0, acetone); ^1H NMR (acetone-d_6), signals of the α anomer: δ 4.94 [m, 1 H, $J_{CH,CH3}$ 6.2 Hz, $OCH(CH_3)_2$], 3.84–3.77 (m, 2 H, $J_{6,7}$ 6.3 Hz, H-4 and H-6), 2.96 (t, 1 H, $J_{4,5}$ 9.1, $J_{5,6}$ 9.1 Hz, H-5), 2.03 (m, 1 H, H-3*eq*), 1.87 (dd, 1 H, $J_{3ax,3eq}$ 12.7, $J_{3ax,4}$ 11.6 Hz, H-3*ax*), 1.21 [d, 3 H, $OCH(CH_3)_2$], 1.20 [d, 3 H, $OCH(CH_3)_2$], and 1.16 (d, 3 H, CH_3); ^{13}C NMR (acetone-d_6): δ 170.1 (C-1α), 95.8 (C-2α), 78.5 (C-5α), 77.9 (C-5β), 72.5 (C-6β), 70.8 (C-4β), 70.3–69.8 and 69.7 [C-6α, C-4α, and $OCH(CH_3)_2$ α], 69.4 [$OCH(CH_3)_2\beta$], 41.4 (C-3β), 39.8 (C-3α), 21.8 and 21.7 [$OCH(CH_3)_2$ β], 21.8 and 21.7 [$OCH(CH_3)_2$ α], 18.5 (C-7β), and 18.2 (C-7α). All assignments were verified by ^{13}C–^1H correlations. Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found: C, 51.17; H, 7.78.

Reduction of **10** *with* $NaBH_4$.—To a solution of compound **10** (0.34 g, 0.78 mmol) in EtOH (20 mL) $NaBH_4$ (1.62 g) was added at 0°C. After 30 min, when no starting material was detected by TLC (2:1 hexane–EtOAc), the mixture was diluted with 20 mL of water and neutralized with H_2SO_4 (50%). The solution was extracted with CH_2Cl_2 (2 × 50 mL). The organic solution was washed with aq $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated. The resultant mixture was resolved by column chromatography (30 g silica gel, 5:1 hexane–EtOAc). The faster-migrating fraction (50 mg, 15%) was isolated as an amorphous solid and identified as *4,5-di-*O*-*tert*-butyldimethylsilyl-3,7-dideoxy-α-*L*-*arabino*-2-heptulo-*

pyranose (**19**); $[\alpha]_D^{20}$ −24.2° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.03 (ddd, 1 H, $J_{3eq,4}$ 4.9, $J_{4,5}$ 8.3 Hz, H-4), 3.79 (dq, 1 H, $J_{5,6}$ 8.5, $J_{6,7}$ 6.4 Hz, H-6), 3.53 (d, 1 H, $J_{1a,1b}$, 11.1 Hz, H-1a), 3.37 (d, 1 H, H-1b), 3.12 (t, 1 H, H-5), 1.96 (dd, 1 H, H-3*eq*), 1.47 (dd, 1 H, $J_{3eq,3ax}$ 12.7, $J_{3ax,4}$ 11.0 Hz, H-3*ax*), 1.20 (d, 3 H, CH_3), 0.91 [s, 9 H, $(CH_3)_3CSi$], 0.90 [s, 9 H, $(CH_3)_3CSi$], 0.11 (s, 3 H, CH_3Si), 0.10 (s, 3 H, CH_3Si), 0.09 (s, 3 H, CH_3Si), and 0.08 (s, 3 H, CH_3Si); ^{13}C NMR ($CDCl_3$) δ 96.0 (C-2), 76.6 (C-5), 71.0 (C-4), 69.9 (C-6), 68.9 (C-1), 39.9 (C-3), 26.3 and 26.1 [$(CH_3)_3CSi$], 18.8 (C-7), 18.3 and 18.1 [$(CH_3)_3CSi$], −2.7, −3.1, −3.9, and −4.3 (CH_3Si). All assignments were verified by ^{13}C–^1H correlations. Anal. Calcd for $C_{19}H_{42}O_5Si_2$: C, 56.11; H, 10.41. Found: C, 56.01; H, 10.42.

The second fraction (70 mg, 23%) was isolated as a syrup and identified as *4,5-di*-O-tert-*butyldimethylsilyl-3,7-dideoxy*-L-gluco- or L-manno-*heptitol* (**20** or **21**); $[\alpha]_D^{20}$ −52.0° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.10 (m, 1 H, $J_{3b,4}$ 8.0, $J_{4,5}$ 4.0 Hz, H-4), 3.95 (dq, 1 H, $J_{5,6}$ 8.6, $J_{6,7}$ 6.1 Hz, H-6), 3.80 (m, 1 H, $J_{1,2}$ 3.3, $J_{2,3a}$ 10.5, $J_{2,3b}$ 1.8 Hz, H-2), 3.65 (dd, 1 H, H-1a), 3.47 (dd, 1 H, $J_{1a,1b}$ 10.9 and $J_{1b,2}$ 7.3 Hz, H-1b), 3.44 (dd, 1 H, H-5), 1.90 (ddd, 1 H, $J_{3a,3b}$ 14.4, $J_{3a,4}$ 4.0 Hz, H-3a), 1.58 (ddd, 1 H, H-3b), 1.18 (d, 3 H, CH_3), 0.91 [s, 9 H, $(CH_3)_3CSi$], 0.90 [s, 9 H, $(CH_3)_3CSi$], 0.17 (s, 3 H, CH_3Si), 0.14 (s, 3 H, CH_3Si), 0.13 (s, 3 H, CH_3Si), and 0.12 (s, 3 H, CH_3Si); ^{13}C NMR ($CDCl_3$) δ 76.1 (C-5), 73.7 (C-4), 68.8 (C-6), 68.2 (C-2), 67.4 (C-1), 34.7 (C-3), 25.7 and 25.69 [$(CH_3)_3CSi$], 20.8 (CH_3), 17.9 and 17.8 [$(CH_3)_3CSi$], −4.1, −4.4, −4.7, and −5.1 (CH_3Si). Anal. Calcd for $C_{19}H_{44}O_5Si_2$: C, 55.83; H, 10.85. Found: C, 55.60; H, 10.89.

The third fraction was isolated as as syrup (65 mg, 20.5%) and identified as *4,5-di*-O-tert-*butyldimethylsilyl-3,7-dideoxy*-L-gluco- or L-manno-*heptitol* (**20** or **21**); $[\alpha]_D^{20}$ −32.0° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.99 (m, 1 H, $J_{3b,4}$ 8.9 and $J_{4,5}$ 3.9 Hz, H-4), 3.93 (dq, 1 H, $J_{5,6}$ 8.2, $J_{6,7}$ 6.1 Hz, H-6), 3.89 (m, 1 H, $J_{2,3a}$ 4.1, $J_{2,3b}$ 8.0 Hz, H-2), 3.60 (dd, 1 H, H-1a), 3.48 (dd, 1 H, $J_{1a,1b}$ 9.3, $J_{1b,2}$ 4.0 Hz, H-1b), 3.42 (dd, 1 H, H-5), 1.99 (m, 1 H, $J_{3a,3b}$ 14.5, $J_{3a,4}$ 4.0 Hz, H-3a), 1.75 (m, 1 H, H-3b), 1.17 (d, 3 H, CH_3), 0.91 [s, 9 H, $(CH_3)_3CSi$], 0.88 [s, 9 H, $(CH_3)_3CSi$], 0.19 (s, 3 H, CH_3Si), 0.16 (s, 3 H, CH_3Si), 0.10 (s, 3 H, CH_3Si), and 0.09 (s, 3 H, CH_3Si); ^{13}C NMR ($CDCl_3$) δ 76.2 (C-5), 75.6 (C-4), 70.8 (C-2), 68.7 (C-6), 66.7 (C-1), 34.5 (C-3), 25.8 [$(CH_3)_3CSi$], 20.7 (CH_3), 15.9 and 15.8 [$(CH_3)_3CSi$], −4.1, −4.2, −4.8, and −5.0 (CH_3Si). Anal. Calcd for $C_{19}H_{44}O_5Si_2$: C, 55.83; H, 10.85. Found: C, 55.73; H, 10.89.

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