43 (102 mg, 0.32 mmol), HF·Et_3N (3 mL), and BEMP on polystyrene (150 mg) was heated to 95 °C for 2 days and then poured into a saturated aqueous $NaHCO_3$ solution (30 mL). The mixture was extracted with AcOEt (30 mL, four times); the extracts were combined and dried ($MgSO_4$), and the solvent was evaporated. The yellowish residue (150 mg) was mixed with Ac_2O (0.5 mL), pyridine (0.5 mL), and 2-(dimethylamino)pyridine (1 mg) and stirred at 20 °C for 4 days. The solvent was removed by azeotropic distillation with toluene (twice), and the residue was purified by column chromatography on silica gel (4 g, AcOEt). The main fraction was purified by column chromatography (SiO_2, Lobar B, AcOEt). After crystallization from Et_2O, 66 mg (52%) was obtained: colorless crystals; mp 132–138 °C (for the racemate (±)-47: mp 178–179 °C); ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.22 (m, 5 H), 5.62 (ddd, $^3J(H,F)$ = 14.5, ^3J = 8.5, 9.5, HC(7)), 5.36 (m, HC(1)), 4.82 (dd, $^2J(H,F)$ = 48, $^3J(H,H)$ = 8.5, HC(6)), 4.65 and 4.55 (2 d, ^2J = 11.5, CH_2Ph), 3.84 (td, $^3J(H,H)$ = 9.5, $^4J(H,F)$ = 1.5, HC(8)), 3.75 (dd, $^3J(H,H)$ = 9.5, 3.0, HC(8a)), 3.62 (m, $H_2C(3)$), 2.19–2.10 (m, $H_2C(2)$), 2.13 and 1.97 (2 s, 2 Ac); $[\alpha]^{25}_{589}$ = +162°, $[\alpha]^{25}_{578}$ = +168°, $[\alpha]^{25}_{546}$ = +192°, $[\alpha]^{25}_{436}$ = +331°, $[\alpha]^{25}_{365}$ = +531° (c = 10 g/dm³, CH_2Cl_2).

(1*S*,6*S*,7*S*,8*R*,8a*R*)-8-(Benzyloxy)-6-fluoro-1,7-dihydroxyoctahydroindolizidine ((+)-48). A 10 M solution BH_3·Me_2S in THF (0.4 mL) was added to a solution of (+)-47 (207 mg, 0.55 mmol) in anhydrous THF (3 mL). After the mixture was stirred at 20 °C for 24 h, 3 N HCl (1 mL) was added dropwise and then MeOH (3 mL) was also added. After the mixture was heated to 70 °C for 4 h, the solvent was evaporated and the residue was dissolved in MeOH (3 mL). $NaHCO_3$ (1 g) was added portionwise, and the mixture was diluted with CH_2Cl_2 (5 mL). The precipitate was filtered off (Celite), and the solvent was evaporated. The residue was purified by column chromatography on silica gel (10 g, CH_2Cl_2/MeOH, 10:1). The main fraction (R_f = 0.5) was purified further by column chromatography on silica gel (Lobar B, CH_2Cl_2/MeOH 15:1, R_f = 0.3), yielding 127 mg (83%) of colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.50–7.26 (m, 5 H), 4.88 and 4.84 (2 d, ^2J = 11.5, CH_2Ph), 4.54 (dddd, $^2J(H,F)$ = 51, ^3J = 14, 8.5, 5.5, HC(6)), 4.30 (m, HC(1)), 3.75 (ddd, $^3J(H,F)$ = 15, ^3J = 9, 8.5, HC(7)), 3.60 (t, ^3J = 9.0, HC(8)), 3.33 (ddd, ^2J = 10.0, ^3J = 5.5, 2.0, $H_{eq}C(5)$), 3.4 (m, $H_{eq}C(3)$), 2.33–2.13 (m, $H_{ax}C(3)$, HC(2), $H_{ax}C(5)$), 2.00 (dd, ^3J = 9.0, 3.5, HC(8a)), 1.87–1.74 (m, $H_bC(2)$); $[\alpha]^{25}_{589}$ = +52°, $[\alpha]^{25}_{578}$ = +54°, $[\alpha]^{25}_{546}$ = +61°, $[\alpha]^{25}_{436}$ = +98°, $[\alpha]^{25}_{365}$ = +149° (c = 4.2 g/dm³, CH_2Cl_2).

(1*S*,6*S*,7*S*,8*R*,8a*R*)-6-Fluoro-1,7,8-trihydroxyoctahydroindolizidine (6-Deoxy-6-fluorocastanospermine, (+)-3). Same procedure as for (+)-2, starting with (+)-48 (127 mg, 0.45 mmol). Yield: 80 mg (93%) of a white solid. Recrystallization from EtOH (0.3 mL) and Et_2O (3 mL) at −20 °C gave 60 mg of colorless crystals: mp 142–143 °C. For the racemic (±)-3: mp 154–155 °C dec; IR (KBr) ν 3360, 2980, 2960, 2935, 2910, 2800, 1475, 1435, 1380, 1315, 1295, 1275, 1250, 1225, 1200, 1170, 1145, 1130, 1090, 1075, 1055, 1000, 980, 955, 855 cm^{-1}; ^1H NMR (250 MHz, D_2O) δ 4.44 (dddd, 1 H, $^2J(H,F)$ = 50, $^3J(H,H)$ = 10.5, 9.0, 5.5, HC(6)), 4.36 (m, HC(1)), 3.64–3.50 (m, HC(7), HC(8)), 3.30 (ddd, ^2J = 10.5, ^3J = 5.5, $^3J(H,F)$ = 2.2, $H_{eq}C(D)$), 3.09–3.04 (m, $H_{eq}C(3)$), 2.37–2.17 (m, $H_{ax}C(5)$, $H_{ax}C(3)$, $H_aC(2)$), 2.03 (dd, ^3J = 9.5, 4.5, HC(8a)), 1.94–1.83 (m, HC(2)); ^{13}C NMR (62.9 MHz, D_2O) δ 91.0 (dd, $^1J(C,F)$ = 174, $^1J(C,H)$ = 155, C(6)), 77.4 (dd, $^2J(C,F)$ = 17.3 $^1J(C,H)$ = 145, C(7)), 71.3 (d, $^1J(C,H)$ = 130, C(8a)), 69.6 (d, $^1J(C,H)$ = 155, C(1)), 68.4 (dd, $^3J(C,F)$ = 11.1, $^1J(C,H)$ = 145, C(8)), 52.8 (td, $^1J(C,H)$ = 140, $^2J(C,F)$ = 26.0, C(5)), 51.6 (t, $^1J(C,H)$ = 140, C(3)), 33.0 (t, $^1J(C,H)$ = 135, C(2)); MS (CI, NH_3) 193 (10), 192 (M + 1, 100), 191 (15), 190 (10), 174 (24), 173 (23), 154 (14), 147 (50), 118 (9), 86 (9), 82 (9); $[\alpha]^{25}_{589}$ = +88°, $[\alpha]^{25}_{578}$ = +92°, $[\alpha]^{25}_{546}$ = +104°, $[\alpha]^{25}_{436}$ = +170°, $[\alpha]^{25}_{365}$ = +267° (c = 1.6 g/dm³, EtOH). Anal. Calcd for $C_8H_{14}FNO_3$ (191.20): C, 50.25; H, 7.38; N, 7.33. Found: C, 50.36; H, 7.37; N, 7.28.

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Registry No. (+)-1, 79831-76-8; (±)-1, 123284-48-0; (+)-2, 130948-07-1; (+)-3, 131635-62-6; (±)-3, 131722-90-2; (−)-5, 94482-75-4; (±)-5, 94482-73-2; (±)-17, 131635-63-7; (±)-18, 131635-64-8; (−)-24, 131722-80-0; (±)-24, 115140-08-4; (+)-25, 131722-81-1; (±)-25, 123190-65-8; (+)-26, 131697-89-7; (±)-26, 123190-66-9; (−)-27, 131635-65-9; (±)-27, 123190-67-0; (+)-28, 131635-66-0; (±)-28, 123190-63-6; (−)-29, 131635-67-1; (−)-30, 131635-68-2; (−)-32, 131724-03-3; (+)-33, 131722-82-2; α-34, 131722-83-3; β-34, 131722-91-3; (+)-38, 131722-84-4; (±)-38, 123190-72-7; (±)-39, 131635-69-3; 40, 131722-85-5; (+)-41, 131722-86-6; 43, 131722-87-7; (+)-44, 131722-88-8; (±)-44, 123190-76-1; 45, 131722-89-9; (+)-46, 131635-70-6; (+)-46 diacetate, 131635-73-9; (+)-47, 131635-71-7; (±)-47, 131722-92-4; (+)-48, 131635-72-8.

Supplementary Material Available: IR, ^{13}C NMR, and MS spectral data, as well as elemental analyses of all new compounds (+)-25 to (−)-30, (−)-32 to 34, (−)-38 to (+)-41, 43 to (+)-48; X-ray crystallographic results on (+)-3, with stereoview of unit cell (16 pages). Ordering information is given on any current masthead page.

Ascent of the Aldose Series by Four Carbon Atoms: Total Synthesis of D-*glycero*-D-*talo*-L-*talo*-Undecose Pentaacetonide

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Enantiomerically pure undecose acetonide **9** was synthesized, through heptose intermediate **5**, starting with D-glyceraldehyde acetonide (**1**). The key steps were two consecutive four-carbon homologations, each consisting of four reactions: (i) stereoselective elongation of the aldehyde precursor with 2-(trimethylsiloxy)furan, giving C_{n+4} butenolide templates **2** and **6**, (ii) anti-selective cis-dihydroxylation of the butenolide double bond, giving fully functionalized lactones **3** and **7**, (iii) lactone ring opening and protection, giving open-chain methyl esters **4** and **8**, and (iv) DIBAL reduction to aldoses **5** and **9**. At the end of the eight-step sequence, undecose **9** was prepared in a 5.1% overall yield, which corresponded to a 69.5% average yield per step.

The elongation of "short" homochiral progenitors by suitable carbon fragments is a prominent method of ascending the carbohydrate series.[1] Ingenious approaches to the stereocontrolled assembly of natural and synthetic

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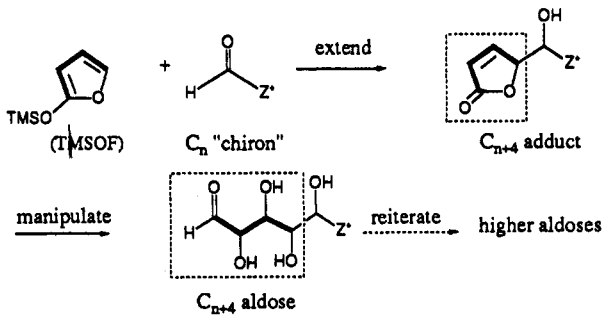
Scheme I[a]



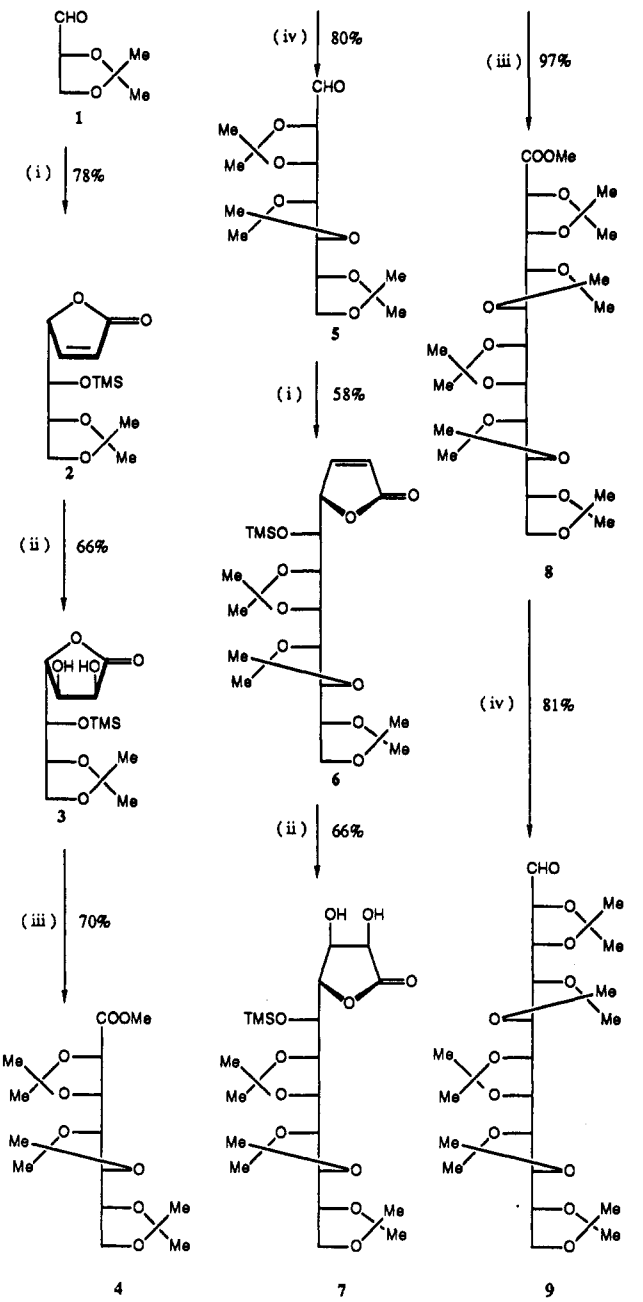
[a] Z* = cyclic or acyclic dissymmetric fragment.

structures have emerged in recent years,[2] and, often, reiterative application of a stereoselective homologation cycle constitutes an exceedingly powerful device for growing the catenated hydroxymethine units of a carbohydrate in a rational manner.[3]

Recently,[4] we exploited commercially available 2-(trimethylsiloxy)furan (TMSOF) for the four-carbon extension of both cyclic and acyclic homochiral C_n *aldehydo* derivatives (Scheme I). The butenolide group of the C_{n+4} adducts that were produced with high stereoselectivity served as "tetrose equivalents", which, by stereoselective double-bond functionalization and reductive elaboration, ultimately furnished full tetrose units appended to the starting C_n frameworks.[4c]

We now describe the sequential synthesis of seven- and 11-carbon aldoses **5** and **9** via the reiterative application of our TMSOF-based C_4 elongation protocol.

Scheme II[a]



[a] Reagents: (i) TMSOF, $BF_3{\cdot}OEt_2$, −90 °C, then Me_3SiCl, pyridine; (ii) $KMnO_4$, DCH-18-crown-6, CH_2Cl_2, 15 °C, (iii) dimethoxypropane, TsOH, room temperature; (iv) DIBAL, CH_2Cl_2, −90 °C.

Results and Discussion

The total synthesis of the title 11-carbon aldose **9** starts with a three-carbon unit, 1,2-*O*-isopropylidene-D-glyceraldehyde (**1**), freshly prepared from commercially available 1,2:5,6-di-*O*-isopropylidene-D-mannitol by periodate fission.[5] The entire reaction sequence is presented in Scheme II.

For this scheme to be synthetically useful, a high level of diastereofacial selectivity during the carbon–carbon bond formation would have to be realized. Indeed, the stereogenic carbon C-2 does control the sense of the TMSOF addition reaction (step i). Treatment of **1** in

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dichloromethane with TMSOF at −90 °C in the presence of an equimolecular amount of BF_3 etherate, protection of the crude product as its TMS ether (TMSCl, pyridine), and flash chromatography afforded the seven-carbon butenolide **2** as the major component (78% isolated yield) along with a minor amount (<5%) of its C-4 epimer *epi*-**2**. Butenolide **2** exhibited a large dextrorotation while *epi*-**2** was levorotatory and, based upon an empirical rule for α,β-unsaturated γ-lactones of this sort,[4b] the configurations of **2** and *epi*-**2** are assigned as 4*R* and 4*S* respectively. The 4,5-*threo*:5,6-*erythro* relationship of the three stereogenic centres in **2** was proven by an X-ray crystallographic structure determination of fully deprotected **2**, namely, 2,3-dideoxy-D-*arabino*-hept-2-enono-1,4-lactone.[4b] Anti-selective cis-dihydroxylation of the double bond in **2** (step ii) was performed by using the $KMnO_4$/dicyclohexano-18-crown-6/CH_2Cl_2 system at 10 °C.[6] There was obtained, after chromatographic purification, crystalline D-*glycero*-D-*talo*-heptonolactone **3** in 66% yield, with no trace of any diastereoisomeric material. The stereochemistry of the newly created C-2 and C-3 centers follows from mechanistic analogy to a similar reaction developed by Mukaiyama[6,7] and was corroborated by a strong NOE between H-2 and H-3 and by the absence of an effect between H-2 and H-4.

Attention was now directed toward elaborating the lactone framework into an open-chain *aldehydo* sugar. Compound **3** was directly transformed into methyl ester **4** (70% yield) by treatment with a large excess of dimethoxypropane (DMP) in the presence of 3 molar equiv of *p*-toluenesulfonic acid (TsOH) at room temperature (step iii). The intermediate lactone (2,3:6.7-di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,4-lactone) could be isolated, characterized, and quantitatively converted into **4** by using the same DMP/TsOH reagent. Controlled reduction of methyl ester **4** into our subtarget **5** was achieved (80% isolated yield), without any epimerization, by careful addition of DIBAL (3 equiv) in CH_2Cl_2 at −90 °C (step iv). The structure of heptose **5** was indeed as shown, based upon its transformation ($NaBH_4$/MeOH, then 10% HCl/THF 1:1), into the known natural D-*glycero*-D-*talo*-heptitol (volemitol), which was fully characterized as its crystalline heptaacetate, mp 65 °C, $[\alpha]^{20}_D$ = +37.9° (*c* 1.1, $CHCl_3$) [lit.[8] mp 63–64 °C, $[\alpha]_D$ = +36.1° ($CHCl_3$)].

The first cycle of our sequence was thus completed and the setting for proper installation of four additional contiguously oxygenated carbon atoms was at hand. Thus, we started the second iteration of the i–iv sequence, where now each new center was to be related to the C-2 of heptose **5**. Four-carbon elongation with TMSOF (i) generated levorotatory 11-carbon unsaturated lactone **6** as the main component, which required two chromatographic separations to obtain a 58% yield of pure material. A second dextrorotatory diastereoisomer was also isolated (9% yield), to which 4-*epi*-**6** structure was attributed on the basis of its clean epimerization (Et_3N/DMAP, CH_2Cl_2, rt) into **6**. On the basis of the aforementioned lactone rule,[4b] the major component **6** (levorotatory) should possess the 4*S* configuration and the minor C-4 epimer *epi*-**6** (dextrorotatory) the 4*R* configuration. The 4,5-*erythro*-5,6-*erythro* stereochemistry in 4-*epi*-**6** was firmly established via an X-ray structure analysis of the 5-*O*-desilyl derivative obtained from deblocking 4-*epi*-**6** with citric acid–methanol,[9] confirming the assignments based on rotation data.

Hydroxylation of **6** (ii) afforded **7** as a crystalline material in 66% yield,[10] which was then subjected to the DMP/TsOH treatment (iii). The resultant open-chain methyl undeconate **8** (57% yield), upon DIBAL reduction (iv), finally generated the undecose pentaacetonide **9** (91% isolated yield), whose D-*glycero*-D-*talo*-L-*talo* configuration was assigned on the basis of the known stereoselectivity of the synthetic sequence. An overall yield of 5.1% was obtained for the eight steps of the complete operation sequence with all the intermediates **2**–**8** separated (69.5% average yield per step). However, during a second preparation of **9**, where only **4**, **6**, and **8** were chromatographically purified, an improved 8.5% overall yield was attained.

Thus, an expeditious and selective route for the preparation of totally synthetic 11-carbon aldose **9** has been established, demonstrating that the single chirality element of the starting "chiron" **1** can be propagated, in a continuous fashion, to create all of the nine contiguous stereocentres of the final target structure.

Experimental Section

^1H NMR spectra were obtained at 300 MHz with a Varian XL-300 instrument. Chemical shifts are reported in ppm units, by reference to Me_4Si. When necessary, unambiguous assignments were made by decoupling experiments. ^{13}C NMR spectra were recorded with the same instrument at 75.45 MHz. FT-IR spectra were measured with a Bruker IFS 66 spectrophotometer in $CDCl_3$ solution. $[\alpha]_D$ values were measured with a Perkin-Elmer 241 polarimeter at 20 ± 1 °C using a 1-cm cell. Microanalyses were performed by Mr. A. Canu, Microanalytical Laboratory of Sassari University. Chromatographic separations were performed on silica gel (230–400 mesh, Merck). TLC was done on precoated silica gel plates (Merck 60 F_{254}) with detection by ethanolic 7% phosphomolybdic acid. All solvents were purified by standard procedures and manipulations involving air/moisture-sensitive substances were carried out under an argon atmosphere using vacuum line, syringe/septum techniques.

2-(Trimethylsiloxy)furan (TMSOF) was purchased from Aldrich and used as received. 2,3-*O*-Isopropylidene-D-glyceraldehyde (**1**) was prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannitol (Fluka) by periodate fission[5] and used immediately.

5-*O*-(Trimethylsilyl)-6,7-*O*-isopropylidene-2,3-dideoxy-D-*arabino*-hept-2-enono-1,4-lactone (2). 2,3-*O*-Isopropylidene-D-glyceraldehyde (**1**) (13.0 g, 0.1 mol) and 2-(trimethylsiloxy)furan (TMSOF) (21.5 mL, 0.13 mol) were dissolved in dry CH_2Cl_2 (250 mL) under argon, and the mixture was cooled to −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 (3 × 50 mL) and the organic layer washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was dissolved in pyridine (100 mL) and TMSCl (31.7 mL, 0.25 mol) was added. Distilled water (200 mL) was then added and the mixture extracted (3 × 50 mL) with CH_2Cl_2. The organic extracts were combined, washed with water, dried ($MgSO_4$), and concentrated in vacuo. This furnished crude lactone **2** contaminated by ca. 4–5% (^1H NMR) of minor C-4 epimer *epi*-**2**. The major component was purified by flash chromatography (80:20 hexane/ethyl acetate) to afford **2** (22.3 g, 78%) as a colorless oil that solidified on standing: mp 39–41 °C; $[\alpha]_D$ = +106.2° (*c* 4.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 5.9, 1.7 Hz, 1 H), 6.16 (dd, *J* = 2.2, 1.7 Hz, 1 H), 5.12 (dt, *J* = 4.1, 1.9 Hz, 1

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(10) A 2D-NOE experiment was done on this compound. No correlation was observed between H-2 and H-4 (anti relationship), while a definite NOE was observed between the two cis hydrogens H-2 and H-3.

H), 4.15 (ddd, J = 7.3, 6.1, 5.9 Hz, 1 H), 4.06 (dd, J = 8.4, 6.1 Hz, 1 H), 3.83 (dd, J = 8.4, 5.9 Hz, 1 H), 3.75 (dd, J = 7.3, 4.1 Hz, 1 H), 1.40 and 1.35 (2 s, each 3 H), 0.12 (s, 9 H). Anal. Calcd for $C_{13}H_{22}O_5Si$: C, 54.52; H, 7.74. Found: C, 54.66; H, 7.90.

5-*O*-(Trimethylsilyl)-6,7-*O*-isopropylidene-2,3-dideoxy-D-*ribo*-hept-2-enono-1,4-lactone (*epi*-2): $[\alpha]_D$ = −115.4°; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (dd, J = 5.6, 1.5 Hz, 1 H), 5.25 (m, 1 H), 4.09 (m, 1 H), 4.02 (m, 2 H), 3.86 (dd, J = 7.8, 4.2 Hz, 1 H), 1.44 and 1.36 (2 s, each 3 H), 0.27 (s, 3 H), 0.20 (s, 6 H). Anal. Calcd for $C_{13}H_{22}O_5Si$: C, 54.52; H, 7.74. Found: C, 54.39; H, 7.86.

5-*O*-(Trimethylsilyl)-6,7-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,4-lactone (3). To a CH_2Cl_2 (150 mL) solution of **2** (20.0 g, 70 mmol) and dicyclohexano-18-crown-6-ether (2.0 g, 5.4 mmol) was added finely powdered $KMnO_4$ (12.6 g, 80 mmol) in several portions at −10 °C with stirring, and the mixture was allowed to stir at 10 °C until compound **2** could not be detected by TLC (ca. 1 h). Next, solid sodium sulfite (15 g) and water (200 mL) were added and the dark brown mixture was extracted with CH_2Cl_2 (3 × 50 mL) and filtered through a Celite pad. The filtrates were dried ($MgSO_4$) and evaporated under vacuum, and the residue was flash chromatographed on silica (20:80 hexane/ethyl acetate) to yield 14.8 g (66%) of **3** as a white solid: mp 116–118 °C; $[\alpha]_D$ = −5.0° (*c* 1.4, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.62 (d, J = 2.2 Hz, 1 H), 4.55 (d, J = 5.7 Hz, 1 H), 4.34 (d, J = 5.7 Hz, 1 H), 4.14 (q, J = 6.3 Hz, 1 H), 4.05 (dd, J = 8.3, 6.3 Hz, 1 H), 3.99 (dd, J = 6.3, 2.2 Hz, 1 H), 3.79 (dd, J = 8.3, 6.3 Hz, 1 H), 3.55 (bs, 2 H), 1.42 and 1.34 (2 s, each 3 H), 0.18 (s, 9 H). Anal. Calcd for $C_{13}H_{24}O_7Si$: C, 48.73; H, 7.55. Found: C, 48.96; H, 7.41.

Methyl 2,3:4,5:6,7-Tri-*O*-isopropylidene-D-*glycero*-D-*talo*-heptonate (4). A solution of 12.0 g (37 mmol) of lactone **3** and 7.6 g (40 mmol) of *p*-toluenesulfonic acid in 200 mL of dimethoxypropane was stirred at room temperature for 8 h. The solution was evaporated under vacuum, then additional dimethoxypropane (200 mL) and *p*-toluenesulfonic acid (7.6 g, 40 mmol) were added, and the resulting solution was stirred at room temperature overnight. The reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (3 × 50 mL), and dried over $MgSO_4$. The organic layer was evaporated and the residue was chromatographed on silical gel (70:30 hexane/ethyl acetate) to afford 9.3 g (70% yield) of methyl ester **4** as a pale yellow oil: $[\alpha]_D$ = +10.6° (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 (d, J = 6.1 Hz, 1 H), 4.33 (dd, J = 9.1, 6.1 Hz, 1 H), 4.21 (q, J = 6.1 Hz, 1 H), 4.14 (t, J = 6.1 Hz, 1 H), 4.05 (dd, J = 8.1, 6.1 Hz, 1 H), 3.96 (dd, 1 H, J = 8.1, 6.1 Hz, 1 H), 3.95 (dd, J = 9.1, 6.1 Hz, 1 H), 3.75 (s, 3 H), 1.57, 1.42, 1.37, 1.36, 1.35, and 1.34 (6 H, each 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) DEPT sequence, CH_3 δ 25.39, 25.59, 26.44, 27.22, 27.67, 27.84, and 51.91, CH_2 δ 65.75, CH δ 75.86, 75.91, 76.44, 78.21, and 80.10, C_q δ 109.50, 110.47, 110.99, and 168.79. Anal. Calcd for $C_{17}H_{28}O_8$: C, 56.66; H, 7.83. Found: C, 56.76; H, 8.02.

2,3:6,7-Di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,4-lactone: a minor component (ca. 10% yield) of the above reaction, as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (d, J = 6.0 Hz, 1 H), 4.78 (d, J = 6.0 Hz, 1 H), 4.75 (bs, 1 H), 4.17 (q, J = 6.0 Hz, 1 H), 4.08 (dd, J = 9.0, 6.0 Hz, 1 H), 3.94 (dd, J = 9.0, 6.0 Hz, 1 H), 3.85 (bd, J = 6.0 Hz, 1 H), 2.80 (bs, 1 H), 1.45, 1.40, 1.37, and 1.34 (4 s, each 3 H). Treatment of this byproduct in dimethoxypropane in the presence of *p*-toluenesulfonic acid (3 molar equiv) at room temperature for 8 h resulted in quantitative formation of open-chain ester, which was identical in all respects with compound **4** obtained in the above reaction.

2,3:4,5:6,7-Tri-*O*-isopropylidene-D-*glycero*-D-*talo*-heptose (5). To a stirred solution of the methyl ester **4** (8.5 g, 23.5 mmol) in 200 mL of anhydrous CH_2Cl_2 was slowly added a 1 M solution of DIBAL in CH_2Cl_2 (70 mL) via cannula at −90 °C. After the reaction was stirred at this temperature for 3 h, methanol (5.0 mL) and then solid sodium–potassium tartrate (10.0 g) and water (100 mL) were added and the mixture was stirred at room temperature for 2 h. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), which was dried over $MgSO_4$ and then evaporated, and the residue was chromatographed on silica (70:30 hexane/ethyl acetate) to afford 6.2 g (80% yield) of aldose **5** as a colorless oil: $[\alpha]_D$ = +16.3° (*c* 0.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (d, J = 2.7 Hz, 1 H), 4.57 (dd, J = 6.6, 6.0 Hz, 1 H), 4.50 (dd, J = 6.8, 2.7 Hz, 1 H), 4.15 (dd, J = 6.8, 6.0 Hz, 1 H), 4.09 (dt, J = 6.6, 3.9 Hz, 1 H), 4.08 (dd, J = 11.1, 6.6 Hz, 1 H), 3.97 (dd, J = 11.1, 3.9 Hz, 1 H), 3.89 (t, J = 6.6 Hz, 1 H), 1.59, 1.42, 1.40, 1.38, 1.36, and 1.34 (6 s, each 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) DEPT sequence, CH_3 δ 25.25, 25.32, 26.57, 26.86, and 27.28 (2 C), CH_2 δ 66.68, CH δ 76.46, 77.56, 78.87, 79.49, 81.20, and 197.80, C_q δ 109.70, 110.86, and 111.02; FTIR ($CDCl_3$) 1734, cm^{-1}. Anal. Calcd for $C_{16}H_{26}O_7$: C, 58.17; H, 7.93. Found: C, 58.29; H, 8.11.

1,2,3,4,5,6,7-Hepta-*O*-acetyl-D-*glycero*-D-*talo*-heptitol (Volemitol Heptaacetate). To a solution of aldose **5** (200 mg, 0.6 mmol) in methanol (5.0 mL) was added solid $NaBH_4$ (0.4 g) at room temperature and the solution was stirred for 2 h. The reaction was then quenched by addition of pH 7 buffer and the resulting mixture was extracted (3 × 10 mL) with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford a colorless oil. This was dissolved in a 1:1 THF/1 N HCl mixture (5.0 mL) and stirred for 3 h at room temperature. The solution was evaporated to dryness under vacuum and the residue treated with acetic anhydride (2.0 mL) in dry pyridine (5.0 mL) at room temperature. The solution was neutralized with 1 N HCl and the resulting mixture extracted (3 × 10 mL) with CH_2Cl_2. The organic extracts, dried over $MgSO_4$, were concentrated in vacuo and the residue chromathographed over silica to give pure heptitol heptaacetate as colorless crystals (pentane/ether 1:1): mp 65 °C; $[\alpha]_D$ = +37.9° (*c* 1.1, $CHCl_3$) [lit.[8] mp 63–64 °C; $[\alpha]_D$ = +36.1° ($CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.9–5.4 (m, 5 H), 3.9–4.4 (m, 4 H), 2.09, 2.06, and 2.05 (3 s, each 3 H), 2.02 and 1.99 (2 s, each 6 H).

5-*O*-(Trimethylsilyl)-6,7:8,9:10,11-tri-*O*-isopropylidene-2,3-dideoxy-D-*arabino*-L-*altro*-undec-2-enono-1,4-lactone (6). The reaction was conducted as described for lactone **2**, by starting with 5.0 g (15 mmol) of aldose **5**. This furnished **6** as a major component along with ca. 9% (^{1}H NMR) of C-4 epimer *epi*-**6**. The major lactone **6** was purified by flash chromatography (50:50 hexane/ethyl acetate) to afford pure **6** (4.22 g, 58% yield) as a colorless oil: $[\alpha]_D$ = −62.0° (*c* 2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, J = 5.7, 1.5 Hz, 1 H) 6.17 (dd, J = 5.7, 1.8 Hz, 1 H), 5.23 (dt, J = 4.8, 1.8 Hz, 1 H), 4.10–4.40 (5 H, m), 4.01 (d AB_q, J_{AB} = 8.0 Hz, $\Delta\nu$ = 7.8 Hz, J_{AX} = 6.6 Hz, J_{BX} = 7.2 Hz, 2 H), 3.88 (dd, J = 8.4, 6.3 Hz, 1 H), 1.43 (s, 6 H), 1.42, 1.39, 1.36, and 1.34 (4 s, each 3 H), 0.15 (s, 6 H), 0.11 (s, 3 H). Anal. Calcd for $C_{23}H_{38}O_9Si$: C, 56.77; H, 7.87. Found: C, 56.98; H, 8.10.

5-*O*-(Trimethylsilyl)-6,7:8,9:10,11-tri-*O*-isopropylidene-2,3-dideoxy-D-*arabino*-L-*allo*-undec-2-enono-1,4-lactone (*epi*-6): $[\alpha]_D$ = +71.4° (*c* 0.42, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, J = 5.8, 1.3 Hz, 1 H), 6.14 (dd, J = 5.7, 2.1 Hz, 1 H), 5.27 (dt, J = 3.0, 1.8 Hz, 1 H), 4.64 (t, J = 3.9 Hz, 1 H), 4.17–4.36 (m, 4 H), 4.04 (d AB_q, J_{AB} = 8.4 Hz, $\Delta\nu$ = 7.0 Hz, J_{AX} = 6.6 Hz, J_{BX} = 6.6 Hz, 2 H), 3.95 (dd, J = 9.0, 6.0 Hz, 1 H), 1.46, 1.44, 1.42, 1.41, 1.37, and 1.36 (6 s, each 3 H), 0.12 (s, 6 H), 0.09 (s, 3 H). Anal. Calcd for $C_{23}H_{38}O_9Si$: C, 56.77; H, 7.87. Found: C, 56.81; H, 7.69.

5-*O*-(Trimethylsilyl)-6,7:8,9:10,11-tri-*O*-isopropylidene-D-*glycero*-D-*talo*-L-*talo*-undecono-1,4-lactone (7). The reaction was conducted as described for lactone **3**, by starting with 3.5 g (7.2 mL) of lactone **6**. This furnished a crude product, which was purified by flash chromatography on silica gel (20:80 hexane/ethyl acetate), giving pure **7** (2.48 g, 66% yield) as a white solid: mp 102–104 °C; $[\alpha]_D$ = +20.0° (*c* 2.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (d, J = 3.0 Hz, 1 H), 4.56 (bd, J = 5.0 Hz, 1 H), 4.14–4.22 (m, 1 H), 3.95–4.07 (m, 2 H), 3.80 (dd, J = 3.9, 8.0 Hz, 1 H), 3.60 (bs, 2 H), 1.45, 1.41, 1.37, and 1.33 (4 s, each 3 H), 1.42 (s, 6 H), 0.18 (s, 6 H), 0.12 (s, 3 H). Anal. Calcd for $C_{23}H_{40}O_{11}Si$: C, 53.06; H, 7.74. Found: C, 53.30; H, 7.64.

Methyl 2,3:4,5:6,7:8,9:10,11-Penta-*O*-isopropylidene-D-*glycero*-D-*talo*-L-*talo*-undeconate (8). The reaction was conducted as described for methyl ester **4**, by starting with 2.0 g (3.8 mmol) of lactone **7**. This furnished a crude product, which was purified by flash chromatography on silica gel (60:40 hexane/ethyl acetate), giving pure **8** (1.22 g, 57%) as a colorless oil: $[\alpha]_D$ = −32.7° (*c* 2.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.64 (d, J = 6.3, 1 H), 4.40–4.50 (m, 7 H), 4.02 (d AB_q, J_{AB} = 8.1 Hz, $\Delta\nu$ = 20.0 Hz, J_{AX} = 6.3 Hz, J_{BX} = 7.2 Hz, 2 H), 3.92 (dd, J = 9.6, 5.1 Hz, 1 H), 3.74 (s, 3 H), 1.55, 1.49, 1.47, and 1.39 (4 s, each 3 H), 1.44 (s, 6 H), 1.37 (s, 12 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) DEPT sequence, CH_3 δ 25.45, 25.47, 25.58, 25.78, 26.33, 26.68, 27.69, 27.87, 27.93, 27.97, and 51.80, CH_2 δ 65.28, CH δ 75.27, 75.29, 75.39, 75.50, 75.89,

76.14, 76.84, 78.25, and 80.24, C_q 109.04 (2 C), 109.41, 110.58, 111.68, and 169.96. Anal. Calcd for $C_{27}H_{44}O_{12}$: C, 57.84; H, 7.91. Found: C, 57.96; H, 8.09.

2,3:4,5:6,7:8,9:10,11-Penta-*O*-isopropylidene-D-*glycero*-D-*talo*-L-*talo*-undecose (9). The reaction was conducted as described for heptose **5**, by starting with 1.0 g (1.78 mmol) of methyl ester **8**. This furnished the crude aldehyde **9**, which was purified by flash chromatography on silica gel (70:30 hexane/ethyl acetate) to give pure undecose **9** (0.76 g, 81%) as a colorless oil: $[\alpha]_D$ = -42.5° (c 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.79 (d, J = 1.5 Hz, 1 H), 4.65 (dd, J = 6.6, 1.5 Hz, 1 H), 4.56 (dd, J = 9.6, 6.6 Hz, 1 H), 4.46 (dd, J = 7.8, 4.8 Hz, 1 H), 4.36 (t, J = 5.1 Hz, 1 H), 4.34 (m, 1 H), 4.30 (t, J = 6.3 Hz, 1 H), 4.25 (t, J = 5.1 Hz, 1 H), 4.17 (dd, J = 9.9, 5.1 Hz, 1 H), 4.06 (dd, J = 8.1, 6.3 Hz, 1 H), 3.98 (dd, J = 8.1, 7.0 Hz, 1 H), 3.92 (dd, J = 10.0, 5.1 Hz, 1 H), 1.55, 1.53, 1.49, 1.43, 1.41, 1.40, 1.38, 1.37, 1.36, and 1.34 (10 s, each 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) DEPT sequence, CH_3 δ 25.51, 25.55, 25.56, 25.63, 26.36, 27.09, 27.72, 27.97, 28.01, and 28.07, CH_2 δ 65.31, CH δ 75.13 (2 C), 75.25, 75.94 (2 C), 76.10, 78.19, 80.37, 82.18, and 198.56, C_q δ 109.25, 109.49 (2 C), 110.64, and 111.86; FTIR ($CDCl_3$) 1738 cm^{-1}. Anal. Calcd for $C_{26}H_{42}O_{11}$: C, 58.85; H, 7.98. Found: C, 58.70; H, 7.69.

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Registry No. 1, 15186-48-8; 2, 132046-98-1; *epi*-2, 132047-05-3; 3, 132046-99-2; 3 2,3-*O*-isopropylidene-5-desilyl derivative, 132047-06-4; 4, 132047-00-8; 5, 132077-98-6; 6, 132047-01-9; *epi*-6, 132047-07-5; 7, 132047-02-0; 8, 132047-03-1; 9, 132047-04-2; TMSOF, 61550-02-5; volemitol, 488-38-0; volemitol heptaacetate, 6893-85-2.

A Simple and Efficient Synthesis of 9-Substituted Guanines. Cyclodesulfurization of 1-Substituted 5-[(Thiocarbamoyl)amino]imidazole-4-carboxamides under Aqueous Basic Conditions

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5-Aminoimidazole-4-carboxamide (AICA) (**1a**) is 1-alkylated by an improved method. The resulting 5-amino-1-alkylimidazole-4-carboxamides (**1b-i**) are converted to the corresponding 1-alkyl-5-[(thiocarbamoyl)amino]imidazole-4-carboxamides (**3**). These compounds are ring closed under alkaline conditions to 9-substituted guanines (**5**) in very high yields by treatment with heavy-metal salts in aqueous sodium hydroxide, or, in somewhat lower yields, by S-oxidation with hydrogen peroxide or sodium perborate in aqueous sodium hydroxide.

Introduction

The search for new or improved synthetic routes leading to nucleoside analogues of guanosine has attracted much attention during recent years.[1]

One of the classic routes to 9-substituted guanines is the Yamazaki ring closure. In 1967 Yamazaki and co-workers first reported the synthesis of guanosine from 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICA-riboside) (**1b**),[2] and since then Yamazaki as well as others have attempted to improve this method or to develop new, related methodologies.[3-6]

There are several examples in the literature of cyclodesulfurization of thioureas leading to various heterocyclic compounds. Among reagents used in this type of reactions are dicyclohexylcarbodiimide (DCC) and mercury salts. These ring closure reactions are believed to proceed via intermediate cyanamides or carbodiimides, respectively.[7] However, attempts to prepare guanines by direct cyclodesulfurization of thioureido derivatives of 5-aminoimidazole-4-carboxamides have failed. Thus Yamazaki was unsuccessful in an attempt to prepare guanine by desulfurization of **3a** using mercury(II) oxide, although he was able to demonstrate that **4a**, prepared by another route, underwent cyclization when treated with aqueous base. An interesting finding was that the ring closure product was dependent on base strength, viz. guanine was formed in 6 N sodium hydroxide, while **4a** ring closed to isoguanine in 0.1 N sodium hydroxide. Different reaction mechanisms were suggested. The formation of isoguanine was explained by the initial cyclization to an unstable [1,3]-oxazine derivative with subsequent ring opening to 5-[(carbamoyl)amino]imidazole-4-carbonitrile, the ring closure of which would lead to the observed isoguanine.[3] The proposed mechanism has later been supported by other workers. Townsend et al. unexpectedly isolated 5-[[*N'*-(methoxycarbonyl)carbamoyl]amino]imidazole-4-carbonitrile riboside after treatment of 1-ribosyl-5-[[*N'*-(methoxycarbonyl)(thiocarbamoyl)]amino]imidazole-4-carboxamide with DCC. Isotope labeling experiments indicated

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