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Silylmethylene radical cyclization. A stereoselective approach to branched sugars *

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ABSTRACT

Ethyl 6-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**2**) was converted, in three steps and in 73% overall yield, into ethyl 6-*O*-benzyl-2,3-dideoxy-3-*C*-(hydroxymethyl)-α-D-*ribo*-hex-2-enopyranoside. This transformation involved silylation of **2** with (bromomethyl)chlorodimethylsilane and application of the Nishiyama–Stork radical cyclisation, followed by Tamao oxidation of the sila cycle. Ethyl 6-*O*-benzyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside and benzyl 2,6-di-*O*-benzyl-α-L-*threo*-hex-4-enopyranoside were similarly transformed into, respectively, ethyl 6-*O*-benzyl-2,3-dideoxy-3-*C*-(hydroxymethyl)-α-D-*lyxo*-hex-2-enopyranoside (50%), and benzyl 2,6-di-*O*-benzyl-4-deoxy-4-*C*-(hydroxymethyl)-β-D-galactopyranoside (71%).

INTRODUCTION

The regio- and stereo-selective synthesis of branched sugars has originally mainly been stimulated by their occurrence in a large variety of natural products, especially antibiotics. In 1983, we reported[1] a method to synthesize the first *C*-disaccharide, a class of compound that is of growing importance[2]. In order to extend[3] this approach, we attempted a stereoselective anchoring of a hydroxymethyl group to a deoxy position of a sugar. In addition to a variety of approaches[4], a typical one is based on the hydroboration–oxidation of a *C*-methylene group[3,5,6]. The yield of this last-mentioned process was usually low[5] or moderate[6], and its stereochemical outcome rather difficult to predict. As a rule, a mixture of the two possible diastereoisomers was obtained, together with the undesired, Markovnikov adduct. Recently, Nishiyama et al.[7] and Stork et al.[8] reported the regio- and stereo-selective addition of the elements of methanol ("hydrohydroxymethylation") to the double bound of an allylic alcohol (Scheme 1). This method involves

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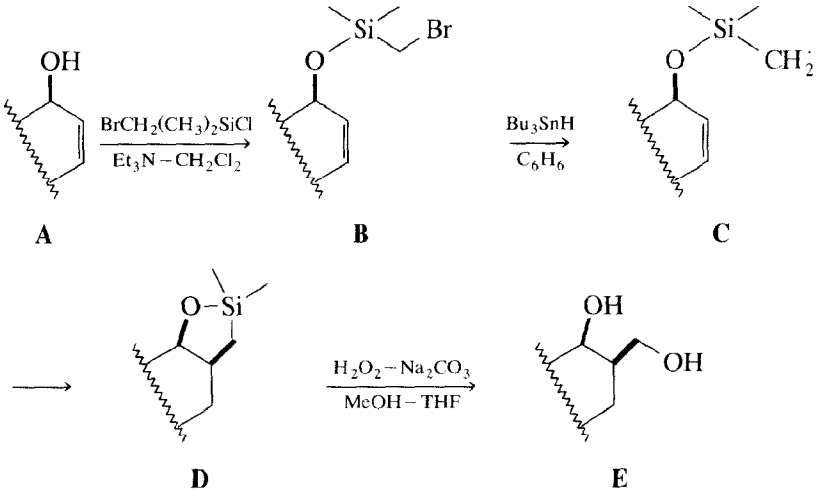


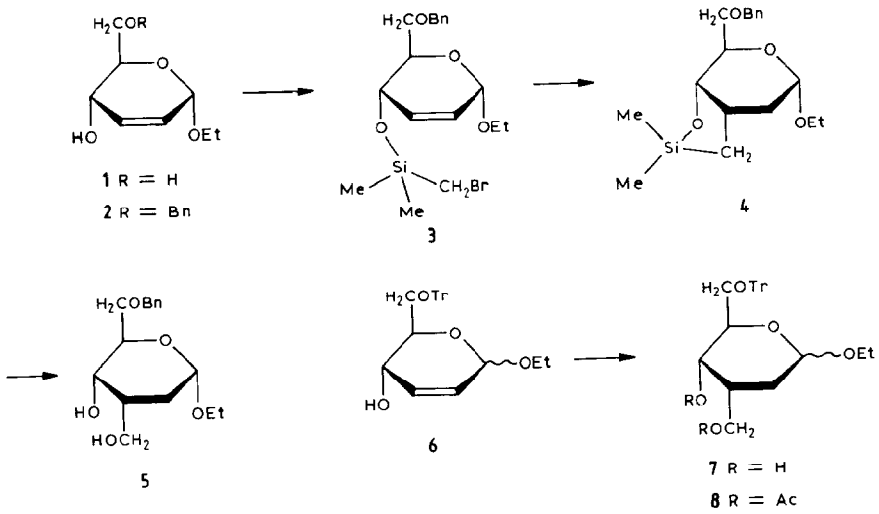
Scheme 1.

connection, to an allylic hydroxy group, of a temporary silylmethylene radical (**C**) capable of cycle formation into a five member ring (**D**). The sila cycle was then cleaved according to the Tamao–Kumada oxidative method[9] to give the diol **E**. This is an extension of a related process where an acetal link was independently suggested by Ueno et al.[10] and by Stork et al.[11] as a detachable connector, and used by others[12–14] in the carbohydrate field. We describe herein the application, to various sugar derivatives, of the Nishiyama–Stork silylmethylene radical cyclization.

RESULTS AND DISCUSSION

The allylic alcohol **2**[15] was first selected as a typical model to establish the feasibility of this approach when applied to carbohydrates. Firstly, Fraser-Reid et al.[15] attempted the selective monobenzylation of diol **1**[16], but the mixture of the two resulting ethers was found unresolvable. Valverde et al.[17] successfully obtained **2** in 87% yield through regioselective activation of CH_2OH-5 of **1** with dibutyltin oxide[18], followed by benzylation, a procedure that was subsequently used by Al Neirabeyeh and Rollin[19]. But none of these authors disclosed data on compound **2**. Using the tin method, we easily obtained analytically pure **2** in 86% yield, whose ^1H NMR spectrum was in complete agreement with the proposed structure.

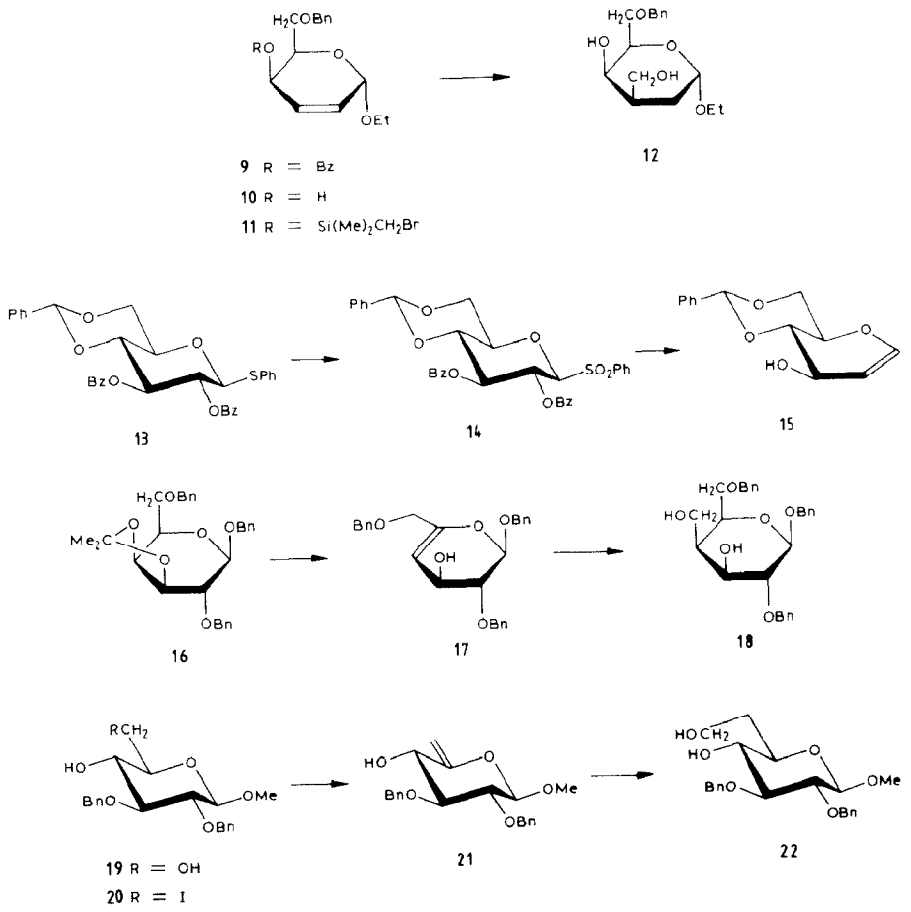
Alcohol **2** was converted into the required (bromomethyl)dimethylsilyl ether **3**. Such ethers have previously been purified by column chromatography on silica gel[7], but Stork and Sofia[8b] observed severe streaking (possible decomposition) during this process. We found that column chromatography on basic silica gel (see General methods) gave pure **3**; this purification was then routinely adopted. The



rather unstable silyl ether was immediately treated with tributyltin hydride and azobis(isobutyronitrile) (AIBN) (dropwise addition during 1 h) in benzene under reflux to afford the cyclisation product **4**. This was oxidized in a one-pot reaction according to Tamao et al.[9] to provide diol **5** in an overall 73% yield from starting alcohol **2**. The ^{1}H NMR spectrum of **5** (after addition of CCl_3CONCO) was in agreement with an axial orientation of CH_2OH-3 (δ 5.23, 1 H, $J_{3,4}$ 5.1, $J_{4,5}$ 8.5 Hz, H-4). The values observed for H-1 (δ 4.91, 1 H, $J_{1,2a}$ 3.3, $J_{1,2b}$ 3.3 Hz) and H-3 (δ 2.82–2.69, 1 H, $J_{2a,3}$ 5, $J_{2b,3}$ 5 Hz) demonstrated a departure from the $^1C_4$ (D) chair conformation. Such a distortion is the result of the 1,3-diaxial interaction between OEt-1 and CH_2OH-3 in the $^1C_4$ (D) chair conformation. Similar results were obtained with the trityl derivative **6**[20], which was processed as an α,β mixture, to give the branched sugar **7** in a 78% yield. ^{1}H NMR data of the α anomers of **7** and **8** were anologous to those reported for **5** and, thus, in agreement with the proposed structures.

The same procedure was next applied to the rather unstable allylic alcohol **10**, which was easily prepared in two steps from **2** by use of epimerization at C-4 with benzoic acid under Mitsunobu's conditions[21] to give **9**, followed by debenzoylation. In this case, an acceptable yield of the cyclization of the silyl derivative **11** was only achieved upon very slow, syringe addition (17 h) of tributyltin hydride; the diol **12** was obtained in crystalline form in 50% overall yield from **10**. Reduction of **11** occurred as a competing reaction; ^{1}H NMR data were in agreement with a $^1C_4$ (D) chair conformation for **12** (see Experimental) with an equatorial orientation for CH_2OH-3 (δ 1.88, 1 H, $J_{2a,3}$ 13.2 Hz, H-2a).

Crystalline 1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-D-*arabino*-hex-1-enitol was originally prepared in poor yield[22,23] from 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol. We synthesized **15** through the reductive lithiation-elimination sequence[24].



Phenyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside[25] was benzoylated in pyridine in the presence of 4-dimethylaminopyridine to give crystalline **13** in 89% yield. This was oxidized (92%) within 15 min at room temperature by sodium periodate and a catalytic amount of ruthenium trichloride, in a biphasic system[26], to give the crystalline sulfone **14**, and reductive lithiation gave **15** in 86% yield. Radical cyclization of **15** was unsuccesful as reduction of the (bromomethyl)-dimethylsilyl ether was observed. This contrasts with a successful free-radical cyclization of a related bromoacetal[13].

The allylic alcohol **17** was then investigated; it was prepared in 46% yield from benzyl 2,6-di-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranoside[18,27] (**16**) by treatment with potassium *tert*-butoxide in *N*,*N*-dimethylformamide at 80°C for 24 h[28]. This rather unstable alcohol was immediately cyclized to give the branched D-*galacto* derivative **18** in 71% yield. The salient feature of this regiocontrolled synthesis lies in the generation of two stereocentres at C-4 and C-5 in a single-radical cyclization step. It provided a selective formation of a 4-branched D-*galacto* derivative which is a starting material for the potential synthesis of C-disacchar-

ides[3]. The orientation of CH_2OH-4 is axial in view of the coupling constant $J_{3,4}$ 5.6 Hz, close to the 5–5.1 Hz values reported by Fraser-Reid et al.[6] for similar derivatives prepared by another route. The coupling constant $J_{4,5}$ 1.4 Hz corroborated the configurational assignment.

The crystalline *exo*-methylene derivative **21** was finally investigated. It was easily prepared in two steps from the known diol **19**[29], by selective iodination[30] at C-6 (**19** → **20**) followed by elimination in *N*,*N*-dimethylformamide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene. When **21** was submitted to the aforementioned reaction conditions (very slow addition of Bu_3SnH–AIBN during 17 h through a syringe technique), selective hydroxymethylation at C-6 occurred albeit in a low yield (13%), and **22** was the only detectable product of the cycle formation. The major course of the reaction was the reduction of the silylmethylene radical. 5-*Exo*-cyclization of a radical originating from a (bromomethyl) dimethylsilyl ether predominates[7], but the 6-*endo* mode can also be observed for allylic systems devoid of a terminal functionality[7], or with a lower degree of terminal substitution[31].

EXPERIMENTAL

Methods.—Melting points were determined with a Büchi model 510 melting point apparatus and are uncorrected. Optical rotations were measured in chloroform at 20 ± 2°C with a Perkin–Elmer Model 241 polarimeter, using a 10-cm, 1-mL cell. CI(NH_3)-mass spectra were obtained with a Nermag R10-10 spectrometer. Elemental analyses were performed by Service Central d'Analyse du C.N.R.S, Vernaison, France. ^{1}H NMR spectra were recorded with Cameca 250 and Brüker AM-400 spectrometers (internal Me_4Si). H-7a and H-7b refer to the branched CH_2OH group. Reactions were monitored by TLC on Silica Gel 60 F_{254} (Merck) and detection by charring with H_2SO_4. Flash-column chromatography was performed on Silica Gel 60 (230–400 mesh, Merck). Basic silica gel was prepared from Silica Gel 60 (230–400 mesh, Merck) by successive washings with satd aq $NaHCO_3$, water, MeOH, EtOAc, and hexane, and activated at 120°C for 15 h.

*Ethyl 6-O-benzyl-2,3-dideoxy-α-*D-erythro-*hex-2-enopyranoside* (**2**).—A mixture of ethyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside[16] (**1**; 9.2 g, 52.8 mmol) and Bu_2SnO (13.3 g, 52.7 mmol) was refluxed for 16 h in benzene (200 mL) with azeotropical removal of water. After one half of the benzene had evaporated, Bu_4NBr (17 g, 52.85 mmol) and benzyl bromide (15.8 mL, 132.2 mmol) were added, and the suspension was refluxed for 20 h and evaporated. The residue was eluted from a column of silica gel with 5:1 hexane–EtOAc to afford **2**, syrup (12.1 g, 86%), $[\alpha]_D$ +35° (*c* 1); ^{1}H NMR ($CDCl_3$): δ 7.37–7.24 (m, 5 H, Ph), 5.92 (ddd, 1 H, $J_{2,3}$ 10.2, $J_{3,4}$ 1.5, $J_{1,3}$ 0.7 Hz, H-3), 5.73 (ddd, 1 H, $J_{1,2}$ 2.8, $J_{2,4}$ 2.5 Hz, H-2), 4.98 (dd, 1 H, H-1), 4.62 and 4.57 (2 d, 2 H, *J* 12.0 Hz, CH_2Ph), 4.20 (dd, 1 H, $J_{4,5}$ 8.9 Hz, H-4), 3.89–3.42 (m, 5 H, H-5,6a,6b, OCH_2Me), and 1.23 (t, 3 H, *J* 7.0 Hz, CH_3); MS: *m/z* 264 $(M)^+$, 281 $(M + 17)^+$, and 282 $(M + 18)^+$.

Anal. Calcd for $C_{15}H_{20}O_4$ (264.32): C, 68.16; H, 7.63. Found: C, 68.30; H, 7.63.

*Ethyl 2,3-dideoxy-6-O-triphenylmethyl-α,β-*D-erythro-*hex-2-enopyranoside* (**6**).—A solution of ethyl 2,3-dideoxy-α,β-D-*erythro*-hex-2-enopyranoside[20] (650.6 mg, 3.73 mmol) and chlorotriphenylmethane (1.13 g, 4.05 mmol) in pyridine (12 mL) was stirred for 48 h at room temperature. Water (15 mL) and CH_2Cl_2 (15 mL) were added. The organic layer was washed successively with 5% aq HCl, satd aq $NaHCO_3$, water, dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel with 5:1 hexane–EtOAc to afford **6**, syrup (1.27 g, 82%); ^{1}H NMR ($CDCl_3$): δ 7.51–7.18 (m, 15 H, Ph), 5.90 (dd, 1 H, $J_{2,3}$ 10.2, $J_{3,4}$ 1.6 Hz, H-3), 5.75 (ddd, 1 H, $J_{1,2} = J_{2,4}$ 2.7 Hz, H-2), 4.98 (dd, 1 H, $J_{1,3}$ 1.4 Hz, H-1), 4.17–4.04 (m, 1 H, H-4), 3.92–3.78 (m, 2 H, H-5, OCH_2Me), 3.61–3.50 (m, 1 H, OCH_2Me), 3.45 (dd, 1 H, $J_{5,6a}$ 5.3, $J_{6a,6b}$ 9.1 Hz, H-6a), 3.36 (dd, 1 H, $J_{5,6b}$ 5.3 Hz, H-6b), and 1.24 (t, 3 H, *J* 7.0 Hz, CH_3).

Anal. Calcd for $C_{27}H_{28}O_4$ (416.52): C, 77.86; H, 6.78. Found: C, 77.66; H, 6.48.

*Ethyl-4-O-benzoyl-6-O-benzyl-2,3-dideoxy-α-*D-threo-*hex-2-enopyranoside* (**9**).—Diethyl diazodicarboxylate (1.26 mL, 6.61 mmol) was slowly added (5 min) at room temperature under Ar to a solution of **2** (970 mg, 3.67 mmol), triphenylphosphine (2.07 mg, 6.61 mmol) and benzoic acid (982.6 mg, 6.61 mmol) in dry THF (12 mL). The solvent was evaporated and the residue was eluted from a column of silica gel with 5:1 hexane–EtOAc to afford **9**, syrup (740 mg, 55%), $[\alpha]_D$ −210° (*c* 1); ^{1}H NMR ($CDCl_3$): δ 8.09–7.17 (m, 10 H, Ph), 6.24 (ddd, 1 H, $J_{2,3}$ 10.1, $J_{1,3} < 1$, $J_{3,4}$ 5.4 Hz, H-3), 6.06 (dd, 1 H, $J_{1,2}$ 2.8 Hz, H-2), 5.28 (dd, 1 H, $J_{4,5}$ 2.4 Hz, H-4), 5.15 (d, 1 H, H-1), 4.62–4.42 (m, 3 H, H-5, CH_2Ph), 3.96–3.85 (m, 1 H, OCH_2Me), 3.73 (d, 2 H, $J_{5,6}$ 6.2 Hz, H-6a,6b), 3.65–3.53 (m, 1 H, OCH_2Me), and 1.25 (t, 3 H, *J* 7.0 Hz, CH_3).

Anal. Calcd for $C_{22}H_{24}O_5$ (368.43): C, 71.72; H, 6.57. Found: C, 71.43; H, 6.58.

*Methyl 2,3-di-O-benzyl-6-O-deoxy-β-*D-xylo-*hex-5-enopyranoside* (**21**).—A toluene solution (250 mL) of methyl 2,3-di-*O*-benzyl-β-D-glucopyranoside (**19**, 5 g, 13.3 mmol), triphenylphosphine (5.2 g, 20 mmol), imidazole (2.7 g, 39.9 mmol), and I_2 (4.7 g, 18.6 mmol) was stirred for 2.5 h at 70°C, and concentrated. A solution of the residue in EtOAc (200 mL) was filtered, washed with aq $Na_2S_2O_3$ solution, aq NaCl solution, dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel with 1:1 hexane–EtOAc to give crystalline methyl 2,3-di-*O*-benzyl-6-deoxy-6-iodo-β-D-glucopyranoside (**20**: 5.1 g, 80%), mp 78°C (hexane–EtOAc). A solution of **20** (1.45 g, 3 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.88 mL, 6 mmol) in DMF (20 mL) was stirred at 50°C for 2 h. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic phases were washed successively with cold diluted aq HCl solution, water, satd aq $NaHCO_3$ solution, water, dried ($MgSO_4$), and concentrated. The residue crystallized from EtOH to give **21** (734 mg, 72%), mp 98–99°C (EtOH), $[\alpha]_D$ −40° (*c* 1.1); ^{1}H NMR ($CDCl_3$): δ 7.41–7.25 (m, 10 H, Ph), 4.87 (d, 1 H, *J* 11.5 Hz, CH_2Ph), 4.82 (d, 1 H, *J* 11.4 Hz, CH_2Ph), 4.70 (s, 2 H, H-6a,6b), 4.67 (d, 1 H, *J* 11.5 Hz, CH_2Ph), 4.65 (d, 1 H, *J* 11.4 Hz, CH_2Ph), 4.54 (d, 1 H, $J_{1,2}$ 5.3 Hz, H-1),

4.21–4.17 (m, 1 H, H-4), 3.60 (dd, 1 H, $J_{2,3}$ 7.3 Hz, H-2), 3.57 (s, 3 H, OCH_3), and 3.46 (dd, 1 H, $J_{3,4}$ 8.8 Hz, H-3).

Anal. Calcd for $C_{21}H_{24}O_5$ (356.42): C, 70.77; H, 6.79. Found: C, 70.43; H, 7.11.

Phenyl 2,3-di-O-benzoyl-4,6-O-benzylidene-1-thio-β-D-glucopyranoside (**13**).—Benzoyl chloride (3.5 mL, 30 mmol) was added dropwise at 0°C to a solution of phenyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (3.6 g, 10.0 mmol) and 4-dimethylaminopyridine (4 mg) in pyridine (40 mL). Stirring was continued for 15 min. Methanol (5 mL) was added to the solution which was then concentrated and the residual solvent coevaporated with toluene. The residue crystallized from EtOH–EtOAc to give **13** (5.09 g, 89%), mp 204–205°C (EtOH–EtOAc), $[\alpha]_D$ +40° (*c* 1); ^{1}H NMR ($CDCl_3$): δ 8.10–7.30 (m, 20 H, Ph), 5.86 (dd, 1 H, $J_{3,4} = J_{2,3}$ 9.5 Hz, H-3), 5.62 (s, 1 H, C*H*Ph), 5.54 (dd, 1 H, $J_{1,2}$ 10.0 Hz, H-2), 5.10 (d, 1 H, H-1), 4.52 (dd, 1 H, $J_{5,6a}$ 4.5, $J_{6a,6b}$ 10.5 Hz, H-6a), and 4.00–3.70 (m, 3 H, H-4,5,6b).

Anal. Calcd for $C_{28}H_{34}O_6$ (568.65): C, 69.70; H, 4.96. Found: C, 69.71; H, 4.79.

(2,3-di-O-Benzoyl-4,6-O-benzylidene-β-D-glucopyranosyl) phenyl sulfone (**14**).—To a solution of **13** (4.0 g, 7.04 mmol) in CCl_4 (70 mL), MeCN (70 mL), and water (105 mL) was added $RuCl_3 \cdot 3H_2O$ (7 mg) and $NaIO_4$ (6.3 g, 29.5 mmol). This biphasic mixture was vigorously stirred for 15 min at room temperature, and then diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the organic layer dried ($MgSO_4$), and concentrated. A solution of the residue in CH_2Cl_2 was filtered through silica gel to remove Ru salts and concentrated. The residue crystalized from EtOH–EtOAc to give **14** (3.90 g, 92%), mp 228–230°C, $[\alpha]_D$ −28° (*c* 1). ^{1}H NMR ($CDCl_3$): δ 8.06–7.30 (m, 20 H, Ph), 5.88–5.78 (m, 2 H, H-2,3), 5.64 (s, 1 H C*H*Ph), 4.98 (d, 1 H, $J_{1,2}$ 10.0 Hz, H-1), 4.48–4.36 (m, 1 H, H-5), and 3.82–3.70 (m, 3 H, H-4,6a,6b).

Anal. Calcd for $C_{33}H_{28}O_9S$ (600.64): C, 65.99; H, 4.70. Found: C, 65.88; H, 4.55.

1,5-Anhydro-4,6-O-benzylidene-2-deoxy-D-arabino-hex-2-enitol (**15**).—To a solution of **14** (3.0 g, 4.99 mmol) in dry THF (50 mL) was added a solution of ~M lithium naphthalene in THF at −78°C under Ar untill disappearance of the starting material. The reaction was monitored by TLC (4:1 toluene–EtOAc). The base was neutralized at 0°C with 20% acetic acid in THF and the solvent evaporated. A solution of the residue in CH_2Cl_2 was washed with water, dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel with 4:1 toluene–EtOAc containing 1% of Et_3N to give **15** (1.0 g, 86%), mp 140–142°C (hexane–ether) [lit.[22] mp 142–143°C (hexane–ether)]; ^{1}H NMR ($CDCl_3$): δ 7.60–7.40 (m, 5 H, Ph), 6.41 (dd, 1 H, $J_{1,2}$ 6.0, $J_{1,3}$ 1.8 Hz, H-1), 5.67 (s, 1 H, C*H*Ph), 4.83 (dd, 1 H, $J_{2,3}$ 2.2 Hz, H-2), 4.56 (m, 1 H, H-3), 4.43 (dd, 1 H, $J_{5,6a}$ 4.0, $J_{6a,6b}$ 10.5 Hz, H-6a), and 4.02–3.80 (m, 3 H, H-4,5,6b).

General procedure for silylation, cyclization, and oxidation.—A solution of alcohol, (bromomethyl)chlorodimethylsilane (1.3 eq) and Et_3N (2 eq) in dry CH_2Cl_2 (5 mL/mmol) was stirred at room temperature for 3 h, and the solvent evaporated at < 30°C. The residue was eluted from a column of basic silica gel with 3:1 hexane–EtOAc to afford an unstable syrup. This silyl ether was heated under Ar

in dry, degazed benzene (15 mL/mmol). Tributylstannane (1.5 eq) and AIBN (2%) in benzene (1 mL) were added slowly (1 h, unless otherwise stated) to the refluxed solution. Heating was continued for 3 h, and benzene was evaporated. Methanol (1.5 mL/mmol), THF (1.5 mL/mmol), 30% H_2O_2 (2.1 mL/mmol), and Na_2CO_3 (120 mg/mmol) were added to the residue. The mixture was refluxed for 4 h, concentrated, and the residue was eluted from a column of silica gel to give the diol.

*Ethyl-6-*O*-benzyl-2,3-dideoxy-3-*C*-(hydroxymethyl)-α-*D*-ribo-hexopyranoside* (**5**). —Compound **5** (86.4 mg, 73%) was obtained from **2** (144.5 mg, 0.55 mmol) after column chromatography (1:1 hexane–EtOAc) as a white foam, $[\alpha]_D$ +71° (*c* 1); ^{1}H NMR ($CDCl_3$): δ 7.42–7.30 (m, 5 H, Ph), 4.77 (dd, 1 H, $J_{1,2a}$ 4.0, $J_{1,2b}$ 1.7 Hz, H-1), 4.62 and 4.57 (2 d, 2 H, *J* 12.0 Hz, CH_2Ph), 4.19 (dd, 1 H, $J_{3,7a}$ 8.3, $J_{7a,7b}$ 11.6 Hz, H-7a), 4.04–3.91 (m, 2 H, H-4,7b), 3.80–3.62 (m, 4 H, H-5,6a,6b, OCH_2Me), 3.52–3.33 (m, 1 H, OCH_2Me), 2.40–2.26 (m, 1 H, H-3), 1.94 (ddd, 1 H, $J_{2a,2b}$ 14.3, $J_{2a,3}$ 6.0 Hz, H-2a), 1.71 (ddd, 1 H, $J_{2b,3}$ 3.5 Hz, H-2b), and 1.22 (t, 3 H, *J* 7.0 Hz, CH_3); ^{1}H NMR ($CDCl_3$ + CCl_3CONCO): δ 7.39–7.19 (m, 5 H, Ph), 5.23 (dd, 1 H, $J_{3,4}$ 5.1, $J_{4,5}$ 8.5 Hz, H-4), 4.91 (dd, 1 H, $J_{1,2a} = J_{1,2b}$ 3.3 Hz, H-1), 4.66 (d, 1 H, *J* 12.1 Hz, CH_2Ph), 4.59 (dd, 1 H, $J_{3,7a}$ 7.4, $J_{7a,7b}$ 11.5 Hz, H-7a), 4.52 (dd, 1 H, $J_{3,7b}$ 5.3 Hz, H-7b), 4.46 (d, 1 H, *J* 12.1 Hz, CH_2Ph), 4.07 (ddd, 1 H, $J_{5,6a} = J_{5,6b}$ 4.0 Hz, H-5), 3.82–3.70 (m, 1 H, OCH_2Me), 3.70–3.61 (m, 2 H, H-6a,6b), 3.54–3.37 (m, 1 H, OCH_2Me), 2.82–2.69 (m, 1 H, H-3), 2.04 (ddd, 1 H, $J_{2a,2b}$ 14, $J_{2a,3}$ 4.6 Hz, H-2a), 1.91 (ddd, 1 H, $J_{2b,3}$ 5.4 Hz, H-2b), and 1.22 (t, 3 H, *J* 7 Hz, CH_3).

Anal. Calcd for $C_{16}H_{24}O_5$ (296.37): C, 64.80; H, 8.16. Found: C, 64.93; H, 8.31.

*Ethyl 2,3-dideoxy-3-*C*-(hydroxymethyl)-6-*O*-triphenylmethyl-α,β-*D*-ribo-hexopyranoside* (**7**).—Compound **7** (876.3 mg, 78%) was obtained from **6** (1.08 g, 2.60 mmol) after column chromatography (10:1 CH_2Cl_2–acetone,) as a white foam; ^{1}H NMR ($CDCl_3$): δ 7.52–7.15 (m, 15 H, Ph), 4.69 (dd, 1 H, $J_{1,2a}$ 4.1, $J_{1,2b}$ 2.1 Hz, H-1), 4.10 (dd, 1 H, $J_{3,7a}$ 8.3, $J_{7a,7b}$ 11.7 Hz, H-7a), 3.91–3.25 (m, 7 H, H-4,5,6a,6b,7b, OCH_2Me) 2.30–2.19 (m, 1 H, H-3), 1.86 (ddd, 1 H, $J_{2a,2b}$ 14.2, $J_{2a,3}$ 6.0 Hz, H-2a), 1.69 (ddd, 1 H, $J_{2b,3}$ 3.7 Hz, H-2b), and 1.20 (t, 3 H, *J* 7.0 Hz, CH_3); ^{1}H NMR ($CDCl_3$ + CCl_3CONCO): δ 7.50–7.10 (m, 15 H, Ph), 5.19 (dd, 1 H, $J_{3,4}$ 4.8, $J_{4,5}$ 8.2 Hz, H-4), 4.88 (dd, 1 H, $J_{1,2a}$ 3.8, $J_{1,2b}$ 2.5 Hz, H-1), 4.54–4.47 (2 dd, 2 H, $J_{7a,7b}$ 11.5, $J_{3,7a}$ 5.1, $J_{3,7b}$ 6.3 Hz, H-7a,7b), 4.10–4.00 (m, 1 H, H-5), 3.82 (dq, 1 H, J_{gem} 14.1, J_{vic} 7 Hz, OCH_2Me), 3.48 (dq, 1 H, OCH_2Me), 3.26–3.34 (2 dd, 2 H, $J_{6a,6b}$ 10.1, $J_{5,6b}$ 4.6, $J_{5,6a}$ 3.5 Hz, H-6a,6b), 2.69–2.58 (m, 1 H, H-3), 2.03 (ddd, 1 H, $J_{2a,2b}$ 14.0, $J_{2a,3}$ 5.1 Hz, H-2a), 1.89 (ddd, 1 H, $J_{2b,3}$ 6.0 Hz, H-2b), and 1.22 (t, 3 H, *J* 7.0 Hz, CH_3).

Anal. Calcd for $C_{28}H_{32}O_5$ (448.56): C, 74.98; H, 7.19. Found: C, 74.41; H, 7.19.

The 3-*C*-acetoxymethyl derivative **8** (103 mg, 92%) was obtained by acetylation of **7** (95 mg, 0.21 mmol) with acetic anhydride (50 μL) and 4-dimethylaminopyridine (5 mg) in pyridine (2 mL); ^{1}H NMR ($CDCl_3$): δ 7.50–7.18 (m, 15 H, Ph), 5.03 (dd, 1 H, $J_{4,5}$ 7.7, $J_{3,4}$ 4.8 Hz, H-4), 4.83 (dd, 1 H, $J_{1,2a}$ 4.0, $J_{1,2b}$ 3.9 Hz, H-1),

4.25–4.12 (m, 2 H, H-7a,7b), 4.04–3.86 (m, 1 H, $J_{4,5}$ 7.7, $J_{5,6a}$ 3.6, $J_{5,6b}$ 5.3 Hz, H-5), 3.91–3.77 (m, 1 H, OCH_2Me), 3.54–3.40 (m, 1 H, OCH_2Me), 3.30–3.16 (2dd, 2 H, $J_{6a,6b}$ 9.9 Hz, H-6a,6b), 2.48–2.35 (m, 1 H, $J_{2,3a}$ 4.9, $J_{2,3b}$ 6.8 Hz, H-3), 2.00 (s, 3 H, OAc), 1.95–1.73 (m, 2 H, $J_{2a,2b}$ 13.6 Hz, H-2a,2b), 1.87 (s, 3 H, OAc), and 1.22 (t, 3 H, J 7.0 Hz, CH_3).

*Ethyl 6-O-benzyl-2,3,-dideoxy-3-C-(hydroxymethyl)-α-*D*-lyxo-hexopyranoside* (**12**). —Compound **9** (150 mg, 0.41 mmol) was dissolved in a 0.05 M solution of NaOMe in MeOH (5 mL). The solvent was evaporated and the residue was eluted from a column of basic silica gel with 5:1 hexane–EtOAc to afford ethyl 6-*O*-benzyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (**10**; 94 mg, 87%) as an unstable syrup, which was immediately used in the next step; ^{1}H NMR (C_5D_5N): δ 7.57–7.21 (m, 5 H, Ph), 6.31 (ddd, 1 H, $J_{1,3}$ 0.5, $J_{2,3}$ 10.0, $J_{3,4}$ 5.4 Hz, H-3), 5.97 (ddd, 1 H, $J_{1,2}$ 3.0 Hz, H-2), 5.12 (dd, 1 H, H-1), 4.67 (s, 2 H, CH_2Ph), 4.61–4.53 (m, 1 H, H-5), 4.23–4.07 (m, 3 H, H-4,6a,6b), 4.06–3.93 (m, 1 H, OCH_2Me), 3.60–3.45 (m, 1 H, OCH_2Me), and 1.18 (t, 3 H, J 7.0 Hz, CH_3).

Compound **12** (48 mg, 26%, for 1 h addition; 97.8 mg, 50%, for 17 h addition) was obtained from **10** (175.4 mg, 0.66 mmol) after column chromatography (1:1 hexane–EtOAc), mp 94–95°C (hexane–EtOAc), $[\alpha]_D$ +93° (*c* 1); ^{1}H NMR ($CDCl_3$ + CCl_3CONCO): δ 7.37–7.20 (m, 5 H, Ph), 5.37 (s, 1 H, H-4), 5.01 (dd, 1 H, $J_{1,2b} < 1$, $J_{1,2a}$ 3 Hz, H-1), 4.57 and 4.46 (2 d, 2 H, J 11.8 Hz, CH_2Ph), 4.19 (d, 2 H, $J_{3,7}$ 7.0 Hz, H-7a,7b), 4.10 (dd, 1 H, $J_{5,6} = J_{4,5}$ 5.7 Hz, H-5), 3.81–3.67 (m, 1 H, OCH_2Me), 3.61–3.42 (m, 1 H, OCH_2Me), 3.55 (d, 2 H, H-6a,6b), 2.81–2.66 (m, 1 H, H-3), 1.89 (ddd, 1 H, $J_{1,2a}$ 3, $J_{2a,3}$ 13, $J_{2a,2b}$ 13.3 Hz, H-2a), 1.67 (dd, 1 H, $J_{1,2b} < 1$, $J_{2b,3}$ 3.7 Hz, H-2b), and 1.23 (t, 3 H, J 7.0 Hz, CH_3).

Anal. Calcd for $C_{16}H_{24}O_5$ (296.37): C, 64.84; H, 8.16. Found: C, 64.63; H, 8.27.

*Benzyl 2,6-di-O-benzyl-4-deoxy-4-C-(hydroxymethyl)-β-*D*-galactopyranoside* (**18**). —A solution of benzyl 2,6-di-*O*-benzyl-3,4-*O*-isopropylidene-β-D-glucopyranoside (**16**, 197.1 mg, 0.40 mmol) and potassium *tert*-butoxide (198.4 mg, 1.80 mmol) in DMF (5 mL) was stirred for 24 h at 80°C. The solution was filtered through Celite and concentrated. The residue was eluted from a column of silica gel with 4:1 hexane–EtOAc to afford benzyl 2,6-di-*O*-benzyl-α-L-*threo*-hex-4-enopyranoside (**17**; 180 mg, 46%), unstable syrup, which was immediately used in the next step; ^{1}H NMR (C_6D_6): δ 7.53–7.22 (m, 15 H, Ph), 5.33 (d, 1 H, $J_{3,4}$ 4.5 Hz, H-4), 5.20 (dd, 1 H, $J_{1,2}$ 2.9, $J_{1,3}$ 1.2 Hz, H-1), 4.65 (d, 1 H, J 11.8 Hz, CH_2Ph), 4.40–4.30 (m, 5 H, CH_2Ph), 4.23–4.14 (m, 1 H, H-3), and 4.00–3.75 (m, 3 H, $J_{6a,6b}$ 12.7 Hz, H-2,6a,6b).

Compound **18** (40 mg, 71%) was obtained from **17** (55.3 mg, 0.13 mmol) after column chromatography (1:1 hexane–EtOAc), $[\alpha]_D$ −12° (*c* 1); ^{1}H NMR ($CDCl_3$): δ 7.34–7.14 (m, 15 H, Ph), 4.93 (d, H, J 11.8 Hz, CH_2Ph), 4.88 (d, H, J 12.4 Hz, CH_2Ph), 4.63–4.48 (m, 4 H, CH_2Ph), 4.38 (d, 1 H, $J_{1,2}$ 7.5 Hz, H-1), 3.96–3.58 (m, 5 H, H-3,5,6a,6b,7a,7b), 3.44 (dd, 1 H, $J_{2,3}$ 9.6 Hz, H-2), and 2.93–2.84 (m, 1 H, H-4); ^{1}H NMR ($CDCl_3$ + CCl_3CONCO): δ 7.40–7.20 (m, 15 H, Ph), 5.09 (dd, 1 H, $J_{2,3}$ 10.2, $J_{3,4}$ 5.6 Hz, H-3), 4.98 and 4.82 (2 d, 2 H, J 11.8 Hz, CH_2Ph), 4.72–4.53 (m, 6 H, H-1,7a, 2 CH_2Ph), 4.47 (dd, 1 H, $J_{4,7b}$ 6.3, $J_{7b,7a}$ 11.6 Hz, H-7b), 3.84

(ddd, 1 H, $J_{4,5}$ 1.4, $J_{5,6a} = J_{5,6b}$ 6.2 Hz, H-5), 3.79–3.62 (m, 2 H, H-6a,6b), 3.49 (dd, 1 H, $J_{1,2}$ 7.5 Hz, H-2), and 2.69 (m, 1 H, H-4).

Anal. Calcd for $C_{28}H_{34}O_6$ (466.58): C, 72.08; H, 7.35. Found: C, 72.27; H, 7.07.

*Methyl 2,3-di-O-benzyl-6-deoxy-β-*D*-gluco-heptopyranoside* (**22**).—Compound **22** (143.1 mg, 13%, 17 h addition) was obtained from **21** (1.0 g, 2.81 mmol) after column chromatography (50 : 1 CH_2Cl_2–acetone), mp 104–105°C (hexane–EtOAc), $[\alpha]_D$ −7° (*c* 3); ^{1}H NMR (C_6D_6): δ 7.39–7.05 (m, 10 H, Ph), 5.00 and 4.98 (2 d, 2 H, *J* 11.5 Hz, CH_2Ph), 4.73 and 4.69 (2 d, 2 H, *J* 11.5 Hz, CH_2Ph), 4.14 (d, 1 H, $J_{1,2}$ 7.4 Hz, H-1), 3.65–3.57 (m, 2 H, H-7a,7b), 3.50 (dd, 1 H, $J_{2,3}$ 7.4 Hz, H-2), 3.41 (dd, 1 H, $J_{3,4}$ 8.4 Hz, H-3), 3.34 (dd, 1 H, $J_{4,5}$ 8.2 Hz, H-4), 3.28–3.16 (m, 4 H, H-5, OMe), 2.03–1.90 (m, 1 H, H-6a), and 1.80–1.65 (m, 1 H, H-6b); MS: *m/z* 388 $(M)^+$, 389 $(M + 1)^+$, and 406 $(M + 18)^+$.

Anal. Calcd for $C_{22}H_{28}O_6 \cdot 0.5H_2O$ (397.47): C, 66.48; H, 7.35. Found: C, 66.94; H, 7.81.

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