Deoxygenation at C-4 and Stereospecific Branched-Chain Construction at C-3 of a Methyl Hexopyranuloside. Synthetic Approach to the Amipurimycin Sugar Moiety†

Amélia P. Rauter,*,‡ Ana C. Fernandes,‡ Stanislas Czernecki,§ and Jean-Marc Valery§

Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Edifício C1, 5° Piso, Campo Grande, 1700 Lisboa, Portugal, and Laboratoire de Chimie des Glucides, Université Pierre et Marie Curie, 4 Place Jussieu, 75005 Paris, France

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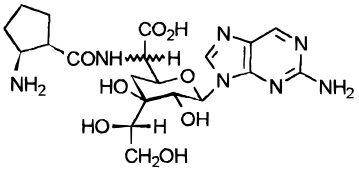
A five-step synthesis from **3** leading to a partially protected amipurimycin sugar moiety **14** in an overall yield of 47% is described and includes deoxygenation at C-4 and regio- and stereoselective construction of the branched chain. Deoxygenation at C-4 of **3** was possible by three different methods. Radical reduction with tri-*n*-butyltin hydride of the appropriate phenoxythiocarbonyl derivative afforded the desired deoxysugar **5** in 47% overall yield together with the secondary products **6** and **7** due to depivaloylation at C-2 and elimination of methanol. The most adequate deoxygenation procedure used the system Ph_3P/I_2/imidazole which led to the preparation of **5** in one step in 61% yield. When the system Ph_3PBr_2/Ph_3P was tried, only **8** was formed due to elimination of methanol. The synthesis of **5** was then accomplished by reaction of **8** with methanol in the presence of triphenylphosphine hydrobromide in 37% overall yield. Branched-chain construction was accomplished by Wittig reaction of **5** with [(ethoxycarbonyl)methylene]triphenylphosphorane, followed by osmilation and reduction with lithium aluminum hydride. Isopropylidenation of **14** afforded **16** with a free hydroxy group at C-6 for chain elongation and further synthesis of amipurimycin.

Introduction

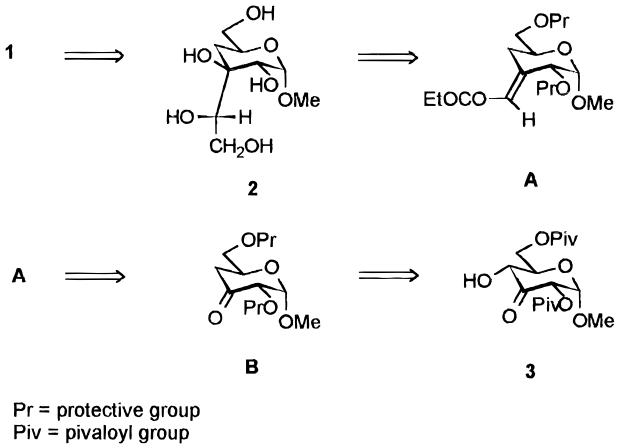
Amipurimycin (**1**) is a natural nucleoside antibiotic which was isolated from *Streptomyces novoguineensis* nov. sp.[1] It displays a remarkable activity *in vitro* and *in vivo* against *Pyricularia oryzae*, which is responsible for the rice blast disease, and also *in vitro* against other pathogenic fungi, such as *Alternaria kikuchiana* and *Helminthosporium sigmoideum* var. *irregulare*, among others.[2] The structure of amipurimycin, as previously



1 Amipurimycin

reported by Goto *et al.*,[3] contains *inter alia* a nucleic base attached to the anomeric carbon of a branched chain deoxy sugar. The chain of the latter is also extended by a dipeptide. We describe in this paper a stereospecific synthesis of the sugar moiety **2** of **1** from D-glucose**.** A synthesis of derivatives of this moiety was already reported by deoxygenation at C-4 of derivatives of the sugar moiety of miharamycin, prepared from D-glucose.[4] Our straightforward route resulted from the retrosynthetic analysis depicted in Scheme 1. Dihydroxylation

Scheme 1



of **A** from the β face insured good stereocontrol and afforded the desired configuration at C-3. The control of the C-3′ stereogenic center was obtained through the (*E*)-stereoisomer **A** which was expected to be the major product of the Wittig reaction from deoxygenated keto sugar **B**.[5] This compound was obtained by deoxygenation of known **3**.[6]

Results and Discussion

We deoxygenated, at C-4, methyl 2,6-di-*O*-pivaloyl-α-D-*ribo*-hexopyranosid-3-ulose (**3**),[6] which was synthesized by oxidation of methyl 2,6-di-*O*-pivaloyl-α-D-glucopyranoside[7] in dichloromethane, with pyridinium chlorochro-

† In memoriam of Professor Felix Serratosa.
‡ Universidade de Lisboa.
§ Université Pierre et Marie Curie.
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(5) In their synthesis of amipurimycin sugar moiety, Hara *et al.*[4] carried out the Wittig reaction before deoxygenation at C-4 and obtained a mixture of *Z*/*E* stereoisomers in which the wrong one (*Z*) was the major compound.
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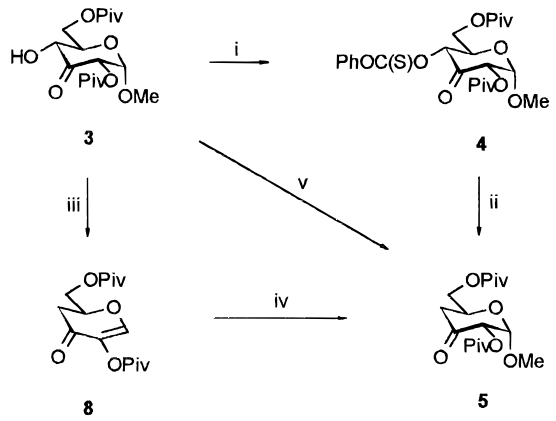
S0022-3263(95)02220-1 CCC: $12.00

Scheme 2



Reagents and conditions: (i) PhOC(S)Cl, DMAP, pyr., r.t. (73%); (ii) Bu_3SnH, toluene, Δ (65%); (iii) Ph_3PBr_2, toluene, Δ, then Ph_3P (45%); (iv) Ph_3P.HBr, MeOH, r.t. (83%); (v) Ph_3P, I_2, imidazole, Δ (61%).

mate adsorbed on neutral alumina.[8] Heating at reflux (48 h) gave a 75% yield based on the reacted diol, which was partially recovered (24%). The workup by simple filtration is clean and improved considerably the access to **3** when compared to the procedure described in the literature.[6]

Methods known in the literature to synthesize such 4-deoxy derivatives involve mainly free radical reactions or reduction of intermediate epoxides,[4,9] triflates,[10] or halogenides[11] with metallic hydrides. The activation of the hydroxyl group by reaction with *N,N′*-thiocarbonyldiimidazole,[12] 4-fluorophenyl chlorothionocarbonate, and *N*-hydroxysuccinimide,[13] or by formation of thiocarbonates[14] or cyclic thiocarbonates,[15,16] was followed in all cases by radical reduction with tri-*n*-butyltin hydride under neutral conditions and was tried to obtain **5** (Scheme 2). Treatment of the α-hydroxy keto sugar **3** with phenoxythiocarbonyl chloride[17,18] in pyridine with 4-(dimethylamino)pyridine (DMAP) catalysis at room temperature gave clean conversion to the *O*-phenoxythiocarbonyl derivative **4** in 73% yield. Reductive deoxygenation with tri-*n*-butyltin hydride and 2,2′-azoisobutyronitrile (AIBN) as free radical initiator in warm toluene afforded the deoxy sugar **5** in 65% yield, together with two secondary products (Chart 1), a dideoxy keto sugar **6** due to the reduction of the pivaloyl ester at position 2, isolated in 25% yield and its enol ether **7**, formed by elimination of methanol and isolated in 10% yield. The overall yield of **5** was comparable to previously reported

Chart 1

ones for deoxygenation at C-4 of other pyranosidic sugar derivatives.[12−14] Reduction of pivaloyl groups under these experimental conditions has not been reported in the literature, although reduction of benzoyl groups in position α to the carbonyl group with *n*-Bu_3SnH was previously mentioned by Redlich *et al.*[19] For confirmation, **5** was submitted to the same experimental conditions in a parallel experience and after recovering 30% of the starting material, the expected products **6** and **7** were isolated in 29% and 43% yield, respectively, on the basis of the reacted starting material.

The system triphenylphosphine/X_2 (X = Br, I) is now reported to be suitable to synthesize **5**. When X = Br, a one-pot reaction led to the isolation of **8** (45%), formed by elimination of methanol. This procedure dehydroxylates α-hydroxylactones[20] via an intermediate bromide, which is transformed, in our case, into the deoxy sugar by the hydrogen bromide formed in the first step. The methyl glycoside was obtained by addition of methanol in the presence of triphenylphosphine hydrobromide at room temperature overnight, leading to **5** in 37% overall yield. More convenient was reduction by Ph_3P/iodine in the presence of imidazole, which gave **5** in only one step in 61% yield. This procedure is known in the literature to afford iodide derivatives from the corresponding alcohols.[21] When compared to those reported in the literature for radical and nonradical deoxygenation of other 4-deoxy sugar derivatives, our new reduction method allowed us to achieve easily the preparation of **5**, a valuable precursor for the synthesis of the amipurimycin sugar moiety. The presence of the carbonyl group does not only activate position 4 to the desired deoxygenation reaction but it is also an appropriate group for the construction of the branched chain at C-3 of the amipurimycin precursor.

In general, a two-carbon unit is introduced into an appropriate keto sugar by reaction with vinylmagnesium bromide,[22] 2-lithio-2-methyl-1,3-dithiane,[23] or with a suitable Wittig reagent. The first two options would lead to the undesired configuration at C-3, as described in the literature.[22,23]

Stereoselective branched-chain construction was possible by means of a Wittig reaction with [(ethoxycarbonyl)methylene]triphenylphosphorane (Scheme 3). Only the Wittig product **9** with the (*E*)-configuration was isolated (95%) due to the presence of the bulky pivaloyloxy group. Due to the neighborhood of the ethoxycarbonyl group, the equatorial methylene proton at C-4 in the ^{1}H NMR of **9** was included in the multiplet at δ 4.23−3.99, while the axial proton appeared at δ 2.12. This result is similar to the one previously reported by Rosenthal *et al.*[24] for a methylene group at position 2 of

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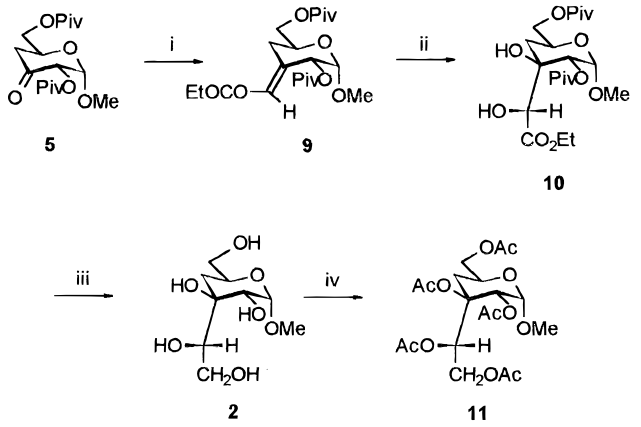
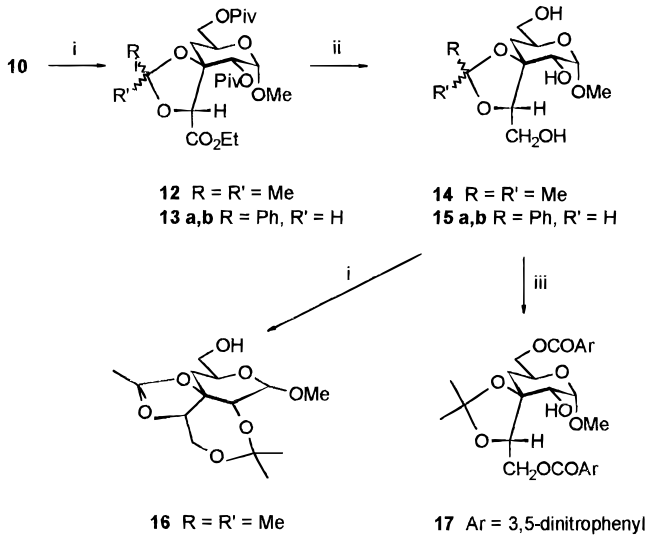
Scheme 3



Reagents and conditions: (i) $Ph_3P{=}CHCO_2Et$, $CHCl_3$, Δ (95%); (ii) OsO_4, pyr., r.t. (100%); (iii) $LiAlH_4$, THF, r.t.; (iv) Ac_2O, pyr., r.t. (45% from **10**).

Scheme 4



Reagents and conditions: (i) for **12** and **16**: 2,2-dimethoxypropane, TsOH, Me_2CO, r.t. (84% for **12**, 54% for **16**); for **13 a,b**: PhCHO, $ZnCl_2$, r.t. (67%); (ii) $LiAlH_4$, THF (96% for **14**, 93% for **15a, b**); (iii) 3,5-dinitrobenzoyl chloride, pyr., 4 °C (75%).

a pyranosidic derivative containing a *cis* methoxycarbonyl group on a vicinal double bond. The correct assignment of the signals was confirmed by 2D heteronuclear correlation and by COSY. Our synthesis is a considerable improvement over the one reported previously by Hara *et al.*,[4] who obtained a mixture of *E*/*Z* isomers.

Osmium tetraoxide in pyridine or in the presence of 4-methylmorpholine *N*-oxide in acetone−water,[25] *cis*-hydroxylated **9** to **10** in quantitative yield, with the branched chain with the proper configuration at C-3 and C-3′. Attempts to oxidize **9** with potassium permanganate[26] led only to a 20% yield of the expected diol. Reduction of **10** with lithium aluminum hydride in THF at room temperature afforded **2**, which was isolated in the form of its pentaacetate **11**. *O*-Isopropylidenation of **10** (2,2-dimethoxypropane−*p*-TsOH in acetone[22]) gave **12** in 84% yield (Scheme 4). Benzaldehyde ($ZnCl_2$)[27] gave a mixture of the protected derivatives **13a** and **13b** (67%). Reduction with lithium aluminum hydride led to the desired sugar moiety of amipurimycin **14**, and the mixture **15a** and **15b** protected at positions 3 and 3′ with the isopropylidene and benzylidene groups in 96% and 93% yield, respectively. Introduction of a second isopropylidene group gave **16** (54%), which has a free hydroxymethyl group for further chain elongation at C-6. Characterization of **14** was possible by synthesis of the solid (mp 117−118 °C) 3,5-dinitrobenzoate derivative **17** (75%).

The method developed by us constitutes a significant improvement (five steps, 47% overall) for the synthesis of the carbohydrate unit. In a previous attempt Hara *et al.*[5] synthesized it in 16 steps from D-glucose (12 steps from a 3-keto sugar) with an overall yield of 9.6%.

Experimental Section

Melting points were determined with a melting point apparatus (Tottoli) and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 60 MHz, respectively. Chemical shifts are expressed in ppm downfield from TMS. Analytical TLC was performed on Riedel aluminum precoated plates of silica gel $60F_{254}$ (thickness of 0.5 mm) with detection by UV and by spraying with a 3% vanillin−sulfuric acid solution. Column chromatography was performed using silica gel (0.043−0.063 mm, Riedel) and elution under medium pressure. Evaporation of solvents was carried out under reduced pressure at 40 °C. Elemental analysis was conducted at the Service of Microanalyses of Instituto Superior Técnico da Universidade Técnica de Lisboa. Mass spectra were obtained with a FTICR spectrometer either by laser desorption (1064 nm) or by electron impact. Molecular modeling of **16** was performed using PC Model from Serena Software.

Methyl 2,6-Di-*O*-Pivaloyl-α-D-*ribo*-hexopyranosid-3-ulose (3). A solution of methyl 2,6-di-*O*-pivaloyl-α-D-glucopyranoside[7] (2.0 g, 5.5 mmol) in dry dichloromethane (20 mL) was heated with pyridinium chlorochromate absorbed on alumina[8] (10.8 g, 8.8 mmol) under reflux for 48 h. The solids were filtered off and were washed with ether. The combined filtrates were evaporated to dryness. Column chromatography with EtOAc−toluene (1:8) afforded **3** (1.13 g, 75%, on the basis of the reacted alcohol). The starting material was recovered in 24% yield. Physical and spectroscopic data of **3** agreed with those given in the literature.[6]

Methyl 4-*O*-(Phenoxythiocarbonyl)-2,6-di-*O*-pivaloyl-α-D-*ribo*-hexopyranosid-3-ulose (4). Phenoxythiocarbonyl chloride (0.68 mL, 5 mmol) was added dropwise to a solution of **3** (1.2 g, 3.3 mmol) and DMAP (40 mg, 0.3 mmol) in pyridine (3 mL) at 0 °C under argon. The mixture was stirred overnight at room temperature and was evaporated. The residue was purified by column chromatography with EtOAc−petroleum ether (1:7) giving **4** as a syrup (1.19 g, 73%): $[\alpha]_D^{20}$ +49.2 (*c* 1, CH_2Cl_2); IR (neat) 1737 cm^{-1} (C═O), 1599 cm^{-1} (Ph), 1212 cm^{-1} (C═S); ^1H NMR δ 7.42−7.14 (m, 5H), 5.93 (d, 1H, $J_{4,5}$ = 9.0 Hz), 5.40 (d, 1H, $J_{1,2}$ = 4.2 Hz), 5.20 (d, 1H), 4.44−4.37 (m, 3H), 3.48 (s, 3H), 1.29 (s, 9H), 1.26 (s, 9H); ^{13}C NMR δ 193.7 (C-3), 191.6 (C═S), 177.9 (C═O), 177.0 (C═O), 153.5 (Cq, Ph), 129.6, 126.8, 121.6 (Ph), 99.9 (C-1), 79.3 (C-4), 76.5 (C-2), 69.5 (C-5), 62,0 (C-6), 55.9 (OMe), 38.9 (Cq), 27.2 (Me), 27.1 (Me); HRMS calcd for $C_{24}H_{32}O_9S$ 496.571, found 496.569.

Methyl 4-Deoxy-2,6-di-*O*-pivaloyl-α-D-*erythro*-hexopyranosid-3-ulose (5). Method a. Tri-*n*-butyltin hydride (890 mg, 3.06 mmol) was added dropwise to a solution of **4** (1.0 g, 2.02 mmol) and AIBN (66 mg, 0.4 mmol) in dry toluene (13.5 mL) at 90 °C under argon. After 3 h the mixture was evaporated. The residue was purified by column chromatography with EtOAc−toluene (1:9) to give **5** (452 mg, 65% yield): mp 92−95 °C; $[\alpha]_D^{20}$ +54.6 (*c* 1, CH_2Cl_2); IR ($CHCl_3$) 1740 cm^{-1} (C═O); ^1H NMR δ 5.19 (d, 1H, $J_{1,2}$ = 4.08 Hz), 5.06

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(d, 1H), 4.26−4.08 (m, 3H), 3.37 (s, 3H), 2.58−2.41 (m, 2H), 1.21 (s, 9H), 1.16 (s, 9H); ^{13}C NMR δ 197.2 (C-3), 179.3 (C=O), 177.5 (C=O), 100.3 (C-1), 75.2 (C-2), 67.5 (C-5), 65.0 (C-6), 55.5 (OMe), 43.0 (C-4), 41.1 (Cq), 38.8 (Cq), 27.1 (Me), 27.1 (Me). Anal. Calcd for $C_{17}H_{28}O_7$: C, 59.29; H, 8.19. Found: C, 59.47; H, 8.29. Further elution afforded methyl 2,4-dideoxy-6-*O*-pivaloyl-α-D-*glycero*-hexopyranosid-3-ulose (**6**) as a syrup (123 mg, 25%): $[\alpha]_D^{20}$ +84 (*c* 3, CH_2Cl_2); IR (neat) 1734 cm^{-1} (C=O); ^{1}H NMR δ 5.08 (br d, 1H), 4.23−4.13 (m, 3H), 3.30 (s, 3H), 2.58 (dd, 1H, $J_{1,2a}$ = 4.35 Hz), 2.43 (br d, 1H, $J_{2a,2e}$ = 15.12 Hz), 2.34−2.31 (m, 2H), 1.16 (s, 9H); ^{13}C NMR δ 203.5 (C-3), 178.1 (C=O), 99.4 (C-1), 66.5 (C-5), 65.7 (C-6), 54.7 (OMe), 46.2 (C-2), 43.3 (C-4), 38.8 (Cq), 27.1 (Me). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.27; H, 8.46. Also resulting was 1,5-anhydro-2,4-dideoxy-6-*O*-pivaloyl-D-*glycero*-hex-1-enul-3-itol (**7**) as a syrup (43 mg, 10%): $[\alpha]_D^{20}$ +60.4 (*c* 0.5, CH_2Cl_2); IR (neat) 1734 cm^{-1} (C=O), 1686 cm^{-1} (C=O), 1600 cm^{-1} (C=C); ^{1}H NMR δ 7.30 (d, 1H, $J_{1,2}$ = 6.02), 5.38 (d, 1H), 4.64−4.54 (m, 1H), 4.30−4.19 (m, 2H), 2.60 (dd, 1H, $J_{4a,5}$ = 12.61 Hz, $J_{4a,4e}$ = 16.77 Hz), 2.40 (dd, 1H, $J_{4e,5}$ = 3.88 Hz), 1.16 (s, 9H); ^{13}C NMR δ 191.2 (C-3), 177.9 (C=O), 162.7 (C-1), 107.2 (C-2), 76.8 (C-5), 64.2 (C-6), 38.9 (Cq), 38.0 (C-4), 27.1 (Me). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.26; H, 7.55.

Method b. Bromine (0.3 mL) was added dropwise to a stirred solution of triphenylphosphine (1.5 g, 5.72 mmol) in toluene (15 mL). After 10 min, a solution of **3** (1.33 g, 3.70 mmol) in CH_2Cl_2 (4 mL) was added dropwise at room temperature. The reaction mixture was heated 30 min at 50 °C. A solution of triphenylphosphine (1.5 g, 5.72 mmol) in toluene (3 mL) was added and the mixture was stirred at 60 °C for 30 min. Filtration and neutralization with lead carbonate was followed by filtration and evaporation of the solvent. The residue was fractionated on a column of silica gel with EtOAc−toluene (1:15) to give 1,5-anhydro-4-deoxy-2,6-di-*O*-pivaloyl-D-*glycero*-hex-1-enul-3-itol (**8**) (519 mg, 45%): mp 65−66 °C, $[\alpha]_D^{20}$ +86.4 (*c* 1, CH_2Cl_2); IR ($CHCl_3$) 1728 cm^{-1} (C=O), 1694 cm^{-1} (C=O), 1628 cm^{-1} (C=C); ^{1}H NMR δ 7.28 (s, 1H), 4.72−4.65 (m, 1H), 4.31−4.26 (m, 2H), 2.72 (dd, 1 H, $J_{4a,4b}$ = 16.9 Hz, $J_{4a,5}$ = 13.8 Hz), 2.49 (dd, 1H, $J_{4b,5}$ = 3.6 Hz), 1.23 (s, 9H), 1.15 (s, 9H); ^{13}C NMR δ 183.9 (C-3), 177.9 (C=O), 154.8 (C-1), 131.9 (C-2), 77.6 (C-5), 63.9 (C-6), 38.9 (Cq), 38.7 (Cq), 37.6 (C-4), 27.1 (Me). Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.64; H, 7.85. A solution of triphenylphosphine hydrobromide (THPB) (40 mg, 0.128 mmol) in CH_2Cl_2 (13 mL) was added to a solution of **8** (800 mg, 2.56 mmol) in methanol (0.3 mL, 7.68 mmol). After being stirred for 24 h at room temperature, the reaction mixture was washed with aqueous saturated $NaHCO_3$ and brine, dried, and evaporated. The residue was purified by column chromatography with *n*-hexane−acetone (3:1) to give **5** (730 mg, 83%).

Method c. A mixture of triphenylphosphine (293 mg, 1.12 mmol), iodine (213 mg, 0.84 mmol), and imidazole (68 mg, 1.12 mmol) in dry toluene (3 mL) was stirred at room temperature for 10 min. A solution of **3** (100 mg, 0.28 mmol) in toluene (2 mL) was added, and the temperature was kept at 60 °C for 3.5 h. After filtration and evaporation, the residue was purified by column chromatography with EtOAc−toluene (1:15) to give **5** (59 mg, 61%).

Methyl 3,4-Dideoxy-3-*C*-[(*E*)-(ethoxycarbonyl)methylene]-2,6-di-*O*-pivaloyl-α-D-*erythro*-hexopyranoside (9). [(Ethoxycarbonyl)methylene]triphenylphosphorane (1.21 g, 3.47 mmol) was added to a solution of **5** (0.6 g, 1.74 mmol) in dry $CHCl_3$ (15 mL) and the mixture was stirred under reflux for 20 h. Evaporation of the solvent and purification by column chromatography with EtOAc−petroleum ether (1:7) afforded **9** as a solid (685 mg, 95%): mp 54−56 °C; $[\alpha]_D^{20}$ +31.2 (*c* 1, CH_2Cl_2); IR ($CHCl_3$) 1731 cm^{-1} (C=O), 1686 cm^{-1} (C=O), 1623 cm^{-1} (C=C); ^{1}H NMR δ 5.90 (t, 1H, $J_{3',4a}$ = 1.89 Hz), 5.34 (t, 1H, $J_{2,3'}$ = 1.47 Hz), 4.92 (d, 1H, $J_{1,2}$ = 3.75 Hz), 4.23−3.99 (m, 6H), 3.38 (s, 3H), 2.12 (t, 1H, $J_{4a,4e}$ = $J_{4a,5}$ = 12.75 Hz), 1.29 (s, 9H), 1.23 (m, 12H); ^{13}C NMR δ 178.0 (C=O), 177.1 (C=O), 165.8 (C-3″), 149.5 (C-3), 113.6 (C-3′), 98.4 (C-1), 71.5 (C-2), 67.5 (C-5), 65.5 (C-6), 59.9 (CH_2), 55.3 (OMe), 38.9 (Cq), 38.7 (Cq), 30.9 (C-4), 27.2 (Me), 27.1 (Me), 14.2 (Me). Anal. Calcd for $C_{21}H_{34}O_8$: C, 60.84; H, 8.27. Found: C, 60.36; H, 7.81.

Methyl 4-Deoxy-3-*C*-[(*R*)-(ethoxycarbonyl)hydroxymethyl]-2,6-di-*O*-pivaloyl-α-D-*xylo*-hexopyranoside (10). Method a. Osmium tetraoxide (250 mg, 0.97 mmol) was added to a solution of **9** (400 mg, 0.97 mmol) in pyridine (4 mL), and the mixture was stirred at room temperature for 2 h. A solution of $NaHSO_3$ (480 mg) in H_2O (7 mL) and pyridine (5 mL) was added to the reaction mixture and within 5 min the complex was cleaved to give an orange solution, which was extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was dried (Na_2SO_4) and evaporated to give **10** (434 mg, 100%) as a syrup: $[\alpha]_D^{20}$ +26.4 (*c* 2, CH_2Cl_2); IR ($CHCl_3$) 3490 cm^{-1} (OH), 1743 cm^{-1} (C=O); ^{1}H NMR δ 4.92 (t, 2H), 4.75 (d, 1H, $J_{3',OH}$ = 6.83 Hz), 4.35−4.08 (m, 6H), 3.59 (d, 1H), 3.42 (s, 3H), 2.02 (dd, 1H, $J_{4e,5}$ = 2.88 Hz, $J_{4a,4e}$ = 14.04 Hz), 1.76 (dd, 1H, $J_{4a,5}$ = 10.32 Hz), 1.33 (t, 3H, $J_{CH_2,Me}$ = 7.13 Hz), 1.23 (s, 9H), 1.22 (s, 9H); ^{13}C NMR δ 178.2 (C=O), 171.7 (C-3″), 97.0 (C-1), 75.6 (C-2), 73.9 (C-3′), 72.2 (C-3), 66.2 (C-5), 65.4 (C-6), 61.8 (CH_2), 55.8 (OMe), 38.9, 38.8 (Cq), 36.3 (C-4), 27.1 (Me), 27.0 (Me), 14.1 (Me). Anal. Calcd for $C_{21}H_{36}O_{10}$: C, 56.24; H, 8.09. Found: C, 56.10; H, 8.24.

Method b. Compound **9** (660 mg, 1.6 mmol) and 4-methylmorpholine *N*-oxide (375 mg, 3.2 mmol) were dissolved in acetone−water (8:1; 13 mL). Osmium tetraoxide (20 mg, 0.08 mmol) was added, and the reaction mixture was stirred overnight at room temperature. The mixture was poured into H_2O and extracted with $CHCl_3$. The organic layer was washed with H_2O, was dried, and was evaporated. The residue was purified as in method a to give **10** (695 mg, 97%).

Method c. To the solution of **9** (200 mg, 0.48 mmol) in THF (2 mL) at −10 °C under nitrogen was added dropwise, with vigorous stirring, $KMnO_4$ (76 mg, 0.48 mmol) in H_2O (3 mL) at such a rate that the temperature did not exceed 5 °C. The mixture was stirred at room temperature for 12 h. MnO_2 was removed by filtration and washed with THF. The extracts were dried (Na_2SO_4) and evaporated. Purification as in method a gave **10** (43 mg, 20%).

Methyl 2,3,3′,3″,6-Penta-*O*-acetyl-4-deoxy-3-*C*-[(*S*)-1,2-dihydroxyethyl]-α-D-*xylo*-hexopyranoside (11). Lithium aluminum hydride (13.3 mg, 0.35 mmol) was added to an ice-cold solution of **10** (45 mg, 0.1 mmol) in dry THF (3 mL), and the mixture was stirred at room temperature for 1 h. After addition of Na_2SO_4·10H_2O and stirring for 15 min, the solution was filtered, was dried (Na_2SO_4), was evaporated, and was acetylated by stirring with acetic anhydride (0.01 mL), DMAP (1 mg, 0.008 mmol), and 1 mL of pyridine at room temperature overnight. Evaporation and column chromatography with EtOAc−toluene (2:1) gave **11** as a syrup (18 mg, 40%); $[\alpha]_D^{20}$ +6 (*c* 0.3, CH_2Cl_2); ^{1}H NMR δ 5.75 (1H, dd, $J_{3',3''a}$ = 2.7 Hz, $J_{3',3''b}$ = 2.4 Hz), 5.56 (1H, d, $J_{1,2}$ = 3.6 Hz), 4.78 (1H, d), 4.54 (1H, dd, $J_{3''a,3''b}$ = 11.9 Hz), 4.16−3.95 (m, 4H), 3.30 (s, 3H), 2.24 (dd, 1H, $J_{4a,4e}$ = 14.1 Hz, $J_{4e,5}$ = 3.6 Hz), 2.15 (dd, 1H, $J_{4a,5}$ = 8.0 Hz), 2.03 (s, 3H), 2.01 (s, 6H), 1.98 (s, 3H), 1.97 (s, 3H); HRMS calcd for $C_{19}H_{28}O_{12}$ 448.423, found 448.420.

Methyl 4-Deoxy-3-*C*-[(*R*)-(ethoxycarbonyl)hydroxymethyl]-3,3′-*O*-isopropylidene-2,6-di-*O*-pivaloyl-α-D-*xylo*-hexopyranoside (12). 2,2-Dimethoxypropane (1.2 mL, 9.8 mmol) and *p*-toluenesulfonic acid (9 mg, 0.047 mmol) were added to a solution of **10** (200 mg, 0.46 mmol) in dry acetone (0.6 mL). The reaction mixture was stirred at room temperature for 3 days. The mixture was neutralized with solid $NaHCO_3$, was filtered, and was concentrated. Chromatography of the residue with EtOAc/petroleum ether (1:5) gave **12** as a syrup (140 mg, 84%, on the basis of reacted alcohol) and recuperation of the diol gave **10** (46 mg, 23%): $[\alpha]_D^{20}$ +30.7 (*c* 1.2, CH_2Cl_2); IR (neat) 1740 cm^{-1} (C=O), 1380 cm^{-1} (isop); ^{1}H NMR δ 4.93 (s, 1H), 4.84 (d, 1H, $J_{1,2}$ = 3.29 Hz), 4.77 (d, 1H), 4.27−3.91 (m, 5H), 3.24 (s, 3H), 2.31 (dd, 1H, $J_{4e,5}$ = 2.41 Hz, $J_{4a,4e}$ = 13.93 Hz), 1.68, (dd, 1H, $J_{4a,5}$ = 11.67 Hz), 1.45 (s, 3H), 1.30 (s, 3H), 1.26 (t, 3H, $J_{CH_2,Me}$ = 7.30 Hz), 1.19 (s, 9H), 1.15 (s, 9H); ^{13}C NMR δ 178.1 (C=O), 177.4 (C=O), 170.2 (C-3″), 110.1 (Cq), 96.8 (C-1), 82.4 (C-3), 77.3 (C-3′), 72.7 (C-2), 65.4 (C-6), 65.2 (C-5), 61.2 (CH_2), 54.7 (OMe), 39.0 (Cq), 38.8 (Cq),

36.0 (C-4), 28.6 (Me), 27.4 (Me), 27.1 (Me), 14.0 (Me); HRMS calcd for $C_{24}H_{40}O_{10}$ 488.574, found: 488.573.

Methyl 4-Deoxy-3-*C*-[(*R*)-(ethoxycarbonyl)hydroxymethyl]-3,3′-*O*-benzylidene-2,6-di-*O*-pivaloyl-α-D-*xylo*-hexopyranoside (13a and 13b). Anhydrous $ZnCl_2$ (68 mg, 0.50 mmol) was added to benzaldehyde (0.3 mL) and the mixture was stirred for 30 min at room temperature. A solution of **10** (135 mg, 0.3 mmol) in benzaldehyde (1 mL) was added. Stirring was continued for 5 days at room temperature. Evaporation and purification by column chromatography gave a mixture of both isomers **13a** and **13b** (105 mg, 67%) as a syrup, in proportion of 2:1: $[\alpha]_D^{20}$ +39.1 (*c* 3.4, CH_2Cl_2); IR (neat) 1742 cm^{-1} (C═O); ^{1}H NMR of **13a** δ 7.59−7.57 (m, Ph), 6.29 (s, 1H), 5.34 (s, 1H), 5.06 (d, 1H, $J_{1,2}$ = 2.88 Hz), 4.89 (d, 1H), 4.30−4.21 (m, CH_2), 4.13−4.07 (m, 3H), 3.36 (s, 3H), 2.27−2.20 (m, 2H), 1.34 (t, 3H), 1.22 (s, 9H), 1.07 (s, 9H); ^{13}C NMR of **13a** δ 178.1 (C═O), 177.5 (C═O), 170.9 (C-3″), 136.1 (Cq Ph), 129.7, 128.3, 126.5 (Ph), 102.7 (CH), 97.2 (C-1), 81.9 (C-3), 77.9 (C-3′), 72.5 (C-2), 65.7 (C-6), 65.0 (C-5), 61.3 (CH_2), 55.0 (OMe), 38.8 (Cq), 35.0 (C-4), 27.2 (Me), 27.0 (Me), 14.1 (Me). Anal. Calcd for $C_{27}H_{40}O_{10}$: C, 61.82; H, 7.69. Found: C, 61.94; H, 7.62.

Methyl 4-Deoxy-3-*C*-[(*S*)-1,2-dihydroxyethyl]-3,3′-*O*-isopropylidene-α-D-*xylo*-hexopyranoside (14). Lithium aluminum hydride (55 mg, 1.44 mmol) was added to an ice-cold solution of **12** (200 mg, 0.41 mmol) in dry THF (6 mL), and the mixture was stirred at room temperature for 1 h. The workup was the same described for **11**. Purification by column chromatography with EtOAc afforded **14** as a syrup (109 mg, 96%): $[\alpha]_D^{20}$ +14.8 (*c* 0.8, CH_2Cl_2); IR (neat) 3340 cm^{-1} (OH), 1380 cm^{-1} (isop); ^{1}H NMR δ 4.79 (d, 1H, $J_{1,2}$ = 3.48 Hz), 4.28 (dd, 1H, $J_{3',3''a}$ = 4.32 Hz, $J_{3',3''b}$ = 5.7 Hz), 3.95 (m, 1H), 3.84−3.71 (m, 3H), 3.61−3.55 (m, 2H), 3.38 (s, 3H), 2.68 (d, 1H, $J_{OH,2}$ = 6.48 Hz), 2.07 (dd, 1H, $J_{4e,5}$ = 3.69 Hz, $J_{4a,4e}$ = 14.58 Hz), 1.47 (dd, 1H, $J_{4a,5}$ = 11.13 Hz), 1.36 (s, 3H), 1.34 (s, 3H); ^{13}C NMR δ 106.8 (Cq), 99.2 (C-1), 81.7 (C-3), 77.3 (C-3′), 71.6 (C-2), 68.7 (C-5), 64.9 (C-6), 60.6 (C-3″), 55.2 (OMe), 33.4 (C-4), 28.7 (Me), 26.4 (Me). Anal. Calcd for $C_{12}H_{22}O_7$: C, 51.79; H, 7.97. Found: C, 52.26; H, 7.80.

Methyl 4-Deoxy-3-*C*-[(*S*)-1,2-dihydroxyethyl]-3,3′-*O*-benzylidene-α-D-*xylo*-hexopyranoside (15a and 15b). The same experimental procedure to prepare **14** was followed and afforded **15a** and **15b** in proportion 2:1 as a syrup (93%): $[\alpha]_D^{20}$ +65.6 (*c* 1.1, CH_2Cl_2); IR (neat) 3372 cm^{-1} (OH); ^{1}H NMR of **15a** δ 7.47−7.29 (m, 5H), 5.89 (s, 1H), 4.76 (d, 1H, $J_{1,2}$ = 3.48 Hz), 4.61 (t, 1H, $J_{3',3''a}$ = $J_{3',3''b}$ = 4.43 Hz), 3.97−3.77 (m, 4H), 3.57−3.47 (m, 2H), 3.34 (s, 3H), 2.15 (dd, 1H, $J_{4e,5}$ = 2.7 Hz, $J_{4a,4e}$ = 16.5 Hz), 1.66 (dd, 1H, $J_{4a,5}$ = 13.8 Hz); ^{13}C NMR δ 137.5 (Cq), 129.5 (CH), 128.5 (CH), 126.5 (CH), 100.3 (CH), 99.5 (C-1), 82.5 (C-3), 78.3 (C-3′), 73.9 (C-2), 68.5 (C-5), 64.9 (C-6), 60.2 (C-3″), 55.4 (OMe), 31.8 (C-4); HRMS calcd for $C_{16}H_{22}O_7$ 326.346, found 326.344.

Methyl 4-Deoxy-3-*C*-[(*S*)-1,2-dihydroxyethyl]-2,3″:3,3′-di-*O*-isopropylidene-α-D-*xylo*-hexopyranoside (16). The same procedure described for **12** was used to prepare **16,** which gave **16** as a syrup (54%, on the basis of reacted diol) after recovering unreacted **12** (17%): $[\alpha]_D^{20}$ +3.3 (*c* 0.3, CH_2Cl_2); IR (neat) 3436 cm^{-1} (OH), 1383 cm^{-1} (isop); ^{1}H NMR δ 4.76 (d, 1H, $J_{1,2}$ = 3.36 Hz), 4.35 (dd, 1H, $J_{3',3''a}$ = 2.9 Hz, $J_{3',3''b}$ = 7.7 Hz), 4.03 (dd, 1H, $J_{3''a,3''b}$ = 9.9 Hz), 3.86−3.76 (m, 2H), 3.53−3.37 (m, 6H), 2.07 (dd, 1H, $J_{4e,5}$ = 3.25 Hz, $J_{4a,4e}$ = 13.75 Hz), 1.52 (dd, 1H, $J_{4a,5}$ = 10 Hz), 1.37 (s, 3H), 1.33 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H); ^{13}C NMR δ 107.4 (Cq), 100.0 (Cq), 99.0 (C-1), 82.0 (C-3), 77.3 (C-3′), 72.1 (C-2), 67.8 (C-5), 63.2 (C-6), 59.6 (C-3″), 55.0 (OMe), 29.6 (C-isop), 29.5 (C-4), 29.3 (C-isop) 24.3 (C-isop); HRMS calcd for $C_{15}H_{26}O_7$ 318.366, found 318.365.

Methyl 4-Deoxy-3-*C*-[(*S*)-1,2-dihydroxyethyl]-3,3′-*O*-isopropylidene-3″,6-bis-*O*-(3,5-dinitrobenzoyl)-α-D-*xylo*-hexopyranoside (17). 3,5-Dinitrobenzoyl chloride (55 mg, 0.24 mmol) was added to an ice-cold solution of **14** (17 mg, 0.06 mmol) in dry pyridine (1 mL). After 48 h at 4 °C, the mixture was evaporated and purified by column chromatography with EtOAc−ether petroleum (1:2) to give **17** as a solid (30 mg, 75%): mp 117−118 °C; $[\alpha]_D^{20}$ +12.5 (*c* 0.6, CH_2Cl_2); IR (neat) 3460 cm^{-1} (OH), 1732 cm^{-1} (C═O), 1554 cm^{-1} (NO_2), 1470 cm^{-1} (NO_2), 1352 cm^{-1} (isop); ^{1}H NMR δ 9.25−9.17 (m, 6H), 5.04 (d, 1H, $J_{3''a,3''b}$ = 9.33 Hz), 4.97 (d, 1H, $J_{1,2}$ = 2.70 Hz), 4.83 (dd, 1H, $J_{5,6b}$ = 8.22 Hz, $J_{6a,6b}$ = 11.73 Hz), 4.68−4.58 (m, 2H), 4.43 (dd, 1H, $J_{5,6a}$ = 2.94 Hz), 4.32−4.27 (m, 1H), 3.85 (dd, 1H, $J_{2,OH}$ = 4.65 Hz), 3.52 (s, 3H), 2.53 (d, 1H, OH), 2.26 (dd, 1H, $J_{4e,5}$ = 4.35 Hz), 1.69 (dd, 1H, $J_{4a,5}$ = 8.16 Hz, $J_{4a,4e}$ = 14.07 Hz), 1.50 (s, 3H), 1.49 (s, 3H); ^{13}C NMR δ 162.4 (C═O), 162.2 (C═O), 148.6 (Cq, Ph), 133.5 (Cq, Ph), 129.6, 129.4, 122.6 (Ph), 108.6 (Cq), 97.7 (C-1), 81.1 (C-3), 76.6 (C-3′), 71.6 (C-2), 67.5 (C-5), 67.1 (C-6), 65.2 (C-3″), 55.9 (OMe), 31.6 (C-4), 28.7 (Me), 26.5 (Me). Anal. Calcd for $C_{26}H_{26}O_{17}N_4$: C, 46.78; H, 4.08; N, 8.39. Found: C, 46.91; H, 3.96; N, 8.16.

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