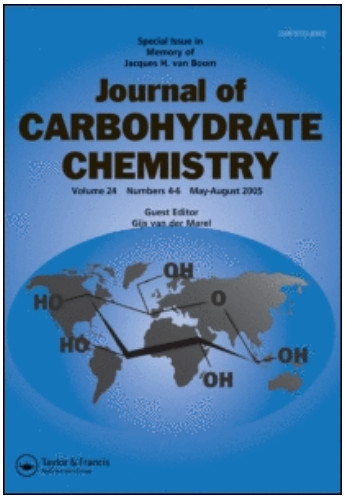

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthetic Studies on the Carbohydrate Moiety of Amipurimycin

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To cite this Article Xue, Jie and Guo, Zhongwu(2008) 'Synthetic Studies on the Carbohydrate Moiety of Amipurimycin', Journal of Carbohydrate Chemistry, 27: 2, 51 — 69
To link to this Article: DOI: 10.1080/07328300802030787
URL: http://dx.doi.org/10.1080/07328300802030787

Journal of Carbohydrate Chemistry, 27:51–69, 2008

ISSN: 0732-8303 print 1532-2327 online
DOI: 10.1080/07328300802030787

Synthetic Studies on the Carbohydrate Moiety of Amipurimycin

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The carbohydrate core of amipurimycin in its fully acetylated form was synthesized in 24 steps starting from commercially available methyl 4,6-*O*-benzylidene-α-D-glucopyranoside to give an overall yield of 1.5%. The late-stage intermediates involved were suitable for total synthesis of amipurimycin. It was further discovered that the branches and the protecting groups on the sugar rings of involved intermediates had a significant influence on their conformations, which in turn resulted in new and interesting cyclization reactions.

Keywords Amipurimycin, Antibiotics, Nucleoside, Carbohydrate, Conformation

INTRODUCTION

Amipurimycin is a nucleoside antibiotic isolated from *Streptomyces novoguineensis* by Iwasa et al.[1,2] in 1977, that was shown to be particularly active toward *Pyricularia oryzae*. Several years later, Goto et al.[3] proposed its primary structure. Amipurimycin has a unique carbohydrate core (i.e., an α-amino glycuronic acid having a two-carbon branch on *C*-3) and has the nucleic base β-linked to its anomeric center. Amipurimycin also contains a β-amino acid attached to the carbohydrate amino group. However, the stereochemistry of carbohydrate *C*-6 has not been determined. Amipurimycin is representative of a unique class of natural nucleosides, thus its carbohydrate core has drawn significant attention, as demonstrated by a number of reports on its synthesis.[4–10] Garner and coworkers[4–6] prepared the carbohydrate core of amipurimycin based on cyclocondensation of penaldic acid and an electron-rich diene. Others used readily accessible carbohydrates as the synthetic precursors, which could make use of the carbohydrate skeleton

Received August 1, 2007; accepted November 19, 2007.
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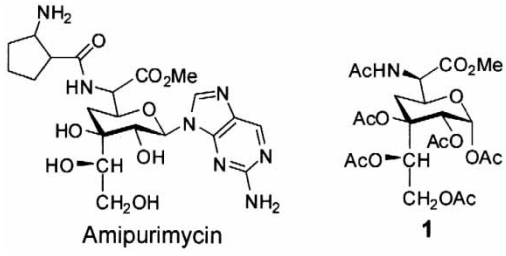


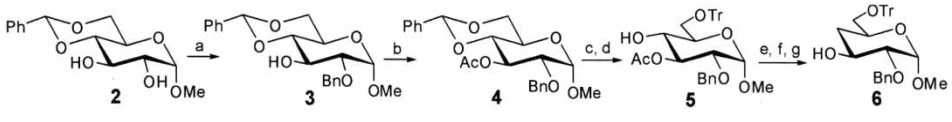
and chirality.[7–10] However, only Garner and coworkers[6] obtained the intact carbohydrate moiety of amipurimycin, and others were focused on partial or model structures.

Herein, we report a synthesis of the fully acetylated carbohydrate moiety **1** of amipurimycin with a commercially available and inexpensive derivative of D-glucose as the starting material. In this synthesis, we have observed the critical influence of side chains and protecting groups on the ring conformation of carbohydrates and novel reactions that were determined by the ring conformation. The results should be generally useful for the synthesis of branched sugars.

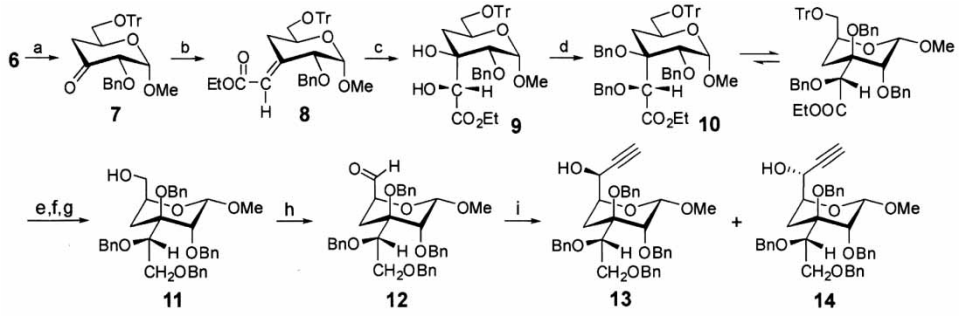
RESULTS AND DISCUSSION

The synthesis started from commercially available D-glucose derivative **2** (Sch. 1). Unbiased monobenzylation of **2** led to compound **3**[11] and its regioisomer with little discrimination, but the two products were easily separable. Acetylation of **3** was followed by removal of the benzylidene group under mild acidic conditions and then selective protection of the 6-OH by a trityl group to afford **5** in an excellent overall yield (95%). To deoxygenate the 4-position, **5** was first converted to the corresponding triflate and then treated with $NaBH_4$.[12] The product was then deacetylated to give **6** (74%, last three steps).

Oxidation of **6** using PCC gave ketone **7**, to which the two-carbon branch was introduced to *C*-3 through reaction with [(ethoxycarbonyl)methylene]triphenylphosphorane (Sch. 2). This Wittig reaction turned out to be extremely slow but highly stereoselective to afford only the (*E*)-isomer **8**, which was isolated in a 99% yield. The (*E*)-configuration of **8** was characterized by means of ^1H NMR. Similar



Scheme 1: Reagents and conditions. (a) BnBr, NaOH, *n*-Bu_4NI, rt, overnight, 54%; (b) Ac_2O, DMAP, pyridine, rt, 95%; (c) HOAc, H_2O, 80°C, 2 h; (d) TrCl, pyridine, 40°C, 36 h, 100%; (e) Tf_2O, pyridine, 0°C, 1 h; (f) $NaBH_4$, DMF, rt, 2 h; (g) NaOH, MeOH, H_2O, rt, 2 h, 74% three steps).

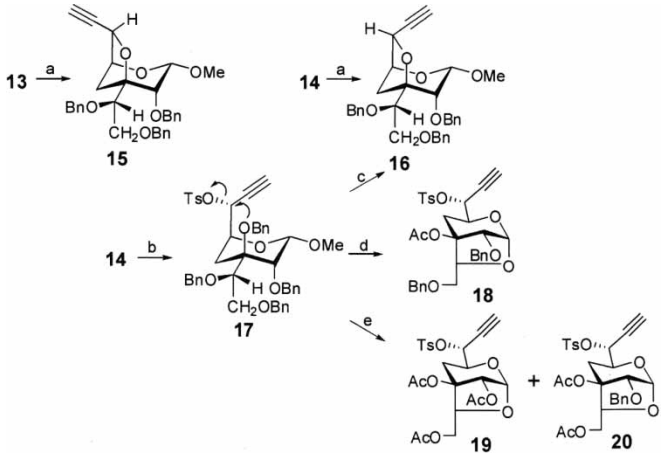


Scheme 2: Reagents and conditions. (a) PCC, MS 4Å, DCM, rt, 3 h, 84%; (b) $Ph_3P{=}CHCO_2Et$, $CHCl_3$, reflux, 3 d, 99%; (c) OsO_4, NMO, Acetone, THF, water, rt, overnight, 98%; (d) BnBr, NaH, DMF, rt, 1 h, 100%; (e) $LiAlH_4$, THF, rt, 4 h; (f) BnBr, NaH, DMF, rt, 2 h; (g) HCOOH, Et_2O, rt, 1 h, 93%; (h) SO_3·Pyr, Et_3N, DMSO, DCM, 0°C, 45 min; (i) HC≡CMgBr, THF, 40% each.

to what was reported by Rauter et al.[8] the ^{1}H NMR signal of the equatorial proton on *C*-4 shifted downfield to δ 3.91 due to strong deshielding effect of the adjacent ethoxycarbonyl group, while the axial proton on *C*-4 was at δ 1.97. The preferred formation of the (*E*)-isomer was probably due to the presence of a rather bulky benzyl group at the 2-*O*-position which was likely to point away from the methoxyl group on *C*-1. Treatment of **8** with 4-methylmorpholine *N*-oxide and osmium tetraoxide, gave the *cis*-dihydroxylation product **9** stereospecifically in a 98% yield. While the *cis* selectivity was determined by the mechanisms of the oxidation reaction, the facial selectivity was possibly due to steric effect, as the bottom side of the C=C bond might be shielded by the adjacent benzyl and the anomeric methoxyl groups, which forces the oxidizing reagent to approach C=C bond from the top only. Thereafter, **9** was benzylated to afford **10**. We noticed that the coupling constants between H-5 and H-4/4′ in **10** were substantially different from that of **8**, **9**, and other compounds that have the conventional $^4C_1$ conformation. For example, $J_{4a,5}$ and $J_{4e,5}$ for **9** were 12.4 and 2.0 Hz, respectively, but they were 4.8 and 6.4 Hz for **10**. Based on these results, we suggested that **10** might adopt the $_4C^1$ conformation or that the $^4C_1$ and $_4C^1$ conformers were in rapid equilibrium. Other subsequent intermediates also adopted $_4C^1$ conformation, which might account for many new and interesting reactions observed in this research.

The carboxyl group in **10** was reduced to alcohol by lithium aluminum hydride smoothly, which was followed by benzylation of the product using benzyl bromide and removal of the trityl group under mild acidic conditions to yield **11** (93%). Swern oxidation of **11** gave aldehyde **12**, which was treated with an excess of ethynylmagnesium bromide at 0°C to afford **13** and **14** in a nearly 1:1 ratio. The stereochemistry of **13** and **14** was assigned later on.

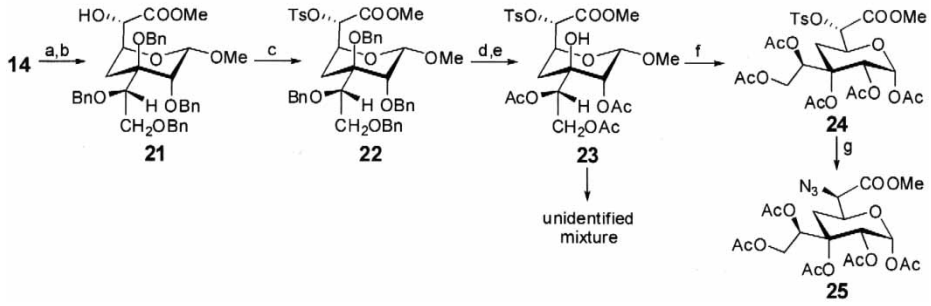
The efforts to directly azidonate *C*-6 of **13** and **14** via activation of 6-OH and azido substitution were unsuccessful, because the reactions always led to



Scheme 3: Reagents and conditions. (a) Tf_2O, pyridine, rt, 100%; (b) Ts_2O, pyridine, rt, 100%, (c) NaN_3, DMF, 80°C; (d) H_2SO_4, Ac_2O, AcOH, 0°C; (e) BCl_3, Ac_2O, THF, −50°C.

intramolecular substitution (Sch. 3). Treating **13** and **14** with triflic anhydride gave **15** and **16** quantitatively and stereospecifically, instead of the desired triflates, even at low temperature. We believe that triflates were formed, but they were prone to intramolecular substitution with simultaneous 3-*O*-debenzylation to give **15** and **16**. Trying to overcome this problem, we transformed **14** into tosylate **17**, in which the *C*-6 should be less electrophilic. The tosylation reaction indeed gave isolable **17**; however, treatment of **17** with sodium azide in DMF still produced **16** as the major product. We believe that the $_4C^1$ conformation of **13** and **14** made *O*-3 perfectly situated to attack *C*-6 to facilitate intramolecular substitution. Consequently, intermolecular substitution reactions would not happen. These results were disappointing for the target synthesis, but the reactions were new and interesting. Moreover, because the products **15** and **16** had rigid structures, they were useful for assignments of the sterochemistry of **13** and **14**. For example, strong NOEs between H-6 and H-1 in **15** and strong NOEs between H-6 and H-4 in **16** all supported the assigned structures of **13** and **14**. Considering that benzyl group, which can depart as a stabilized cation, might have enabled the intramolecular reaction, we then attempted to substitute all benzyl groups in **17** with acetyl groups. For acetolysis of benzyl ethers, **17** was treated with BCl_3 or sulfuric acid in acetic acid and acetic anhydride, but neither of these conditions would afford the desired products. Instead, cyclization products **18**, **19**, and **20**, which were also derived from an intramolecular reaction, were obtained.

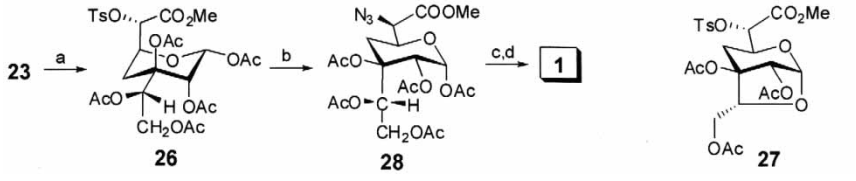
After these frustrations, we decided to attempt a procedure involving oxidation of the triple bond first and then replacement of benzyl groups with acetyl groups in two steps including catalytic hydrogenolysis and acetylation (Sch. 4). Oxidation of **14** by $NaIO_4$ using osmium tetraoxide as the catalyst



Scheme 4: Reagents and conditions. (a) OsO_4, $NaIO_4$, THF, H_2O, 40°C, overnight; (b) CH_2N, CH_2Cl_2, rt, 66% two steps); (c) TsCl, pyr., CH_2Cl_2, 0°C to rt, quant.; (d) 10% Pd/C, H_2, THF, 1 d; (e) Ac_2O, pyr. (1:3), rt, overnight, 89% two steps); (f) H_2SO_4, AcOH, Ac_2O, EtOAc, 0°C, overnight, 60%; (g) NaN_3, DMF, 30°C, 1 d, 51%.

and methylation of the resultant carboxylic group afforded a moderate yield (66%) of **21**. Subsequent tosylation of **21** gave **22** quantitatively. Hydrogenolysis to remove the benzyl groups in **22** and peracetylation of the product went smoothly to give **23**, in which the 3-OH could not be acetylated even after prolonged reaction, probably because of the severe steric hindrance at this position. When **23** reacted with sodium azide in DMF, an inseparable mixture was obtained, and it seemed that the 3-OH was involved. To avoid this problem, we subjected **23** to acetylation using acetic anhydride and a catalytic amount of sulfuric acid. The reaction indeed gave a 3-*O*-acetyl product with acetolysis of the anomeric center, but this product was identified as **24** with inverted stereochemistry at *C*-3, which was probably derived from an acid-catalyzed and thermodynamically controlled S_N1 reaction. Compound **24** was then used as a model to study the reaction conditions for *C*-6 azidonation. We found that the reaction of **24** with sodium azide in DMF at 30°C afforded an acceptable yield (51%) of **25**.

Next, we examined the 3-*O*-acetylation and anomeric acetolysis of **23** with Lewis acid $SnCl_4$ as catalyst (Sch. 5). This reaction turned out to be rather complex, but the desired compound **26** (28%) and a side product 27 (11%) were isolated as the major products. It should be possible to optimize this



Scheme 5: Reagents and conditions. (a) $SnCl_4$, Ac_2O, CH_2Cl_2, 0°C to rt, overnight, 11% and 28%, respectively; (b) NaN_3, DMF, 30°C, 1 d, 85%; (c) 10% Pd/C, H_2, THF, MeOH, overnight; (d) Ac_2O, pyr., rt, overnight, 92% (two steps).

reaction by carefully monitoring the reaction progress and promptly quenching the reaction. For subsequent azidonation of **26**, the reaction conditions established in the preparation of **25** were utilized to offer a good yield (85%) of **28**. It was assumed that the azidonation reaction under basic condition would follow an S_N2 mechanism with configurational inversion of *C*-6. It is worth noting that the azidonation product **28** resumed conventional $^4C_1$ conformation, supported by its $J_{4a,5}$ and $J_{4e,5}$ values of 12.4 and 2.4 Hz, respectively. Compound **28** with an azido group as a latent amino group can be very useful for total synthesis of amipurimycin. For instance, **28** may be directly glycosidated to introduce the nucleic base, which would be followed by reduction of the azido group and regioselective *N*-acylation to introduce the β-amino acid to eventually afford amipurimycin. In this research, **28** was subjected to hydrogenation and then *N*-acetylation to give **1**, the peracetylated carbohydrate moiety of amipurimycin. In conclusion, **1** was synthesized from commercially available **2** in 24 steps and in an overall yield of 1.5%.

EXPERIMENTAL

NMR spectra were recorded on a 200-, 300-, 400- or 600-MHz machine. Chemical shifts of protons are reported in ppm (δ) downfield from tetramethylsilane (TMS) if not specified otherwise, and chemical shifts of carbons are reported in ppm (δ) in reference to the solvent peak of $CDCl_3$ (δ 77.16). Coupling constants (J) are reported in hertz (Hz). Thin layer chromatography (TLC) was performed on silica gel GF_{254} plates detected by charring with phosphomolibdic acid/EtOH or 5% H_2SO_4/EtOH solutions. Molecular sieves were dried under high vacuum at 170 to 180°C for 6 to 10 h before use. Commercial anhydrous solvents and other reagents were used without further purification.

Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (3)[11]

A mixture of **2** (25 g, 88.6 mmol), *n*-Bu_4NI (7.4 g, 20 mmol), and benzyl bromide (13 mL, 109 mmol) in CH_2Cl_2 (600 mL) and aq. NaOH solution (0.68 M, 200 mL) was stirred at rt for 24 h. The organic phase was separated and washed once with water and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product, which was purified by silica gel column chromatography to yield **3** as a major product 17.9 g (48 mmol, 54%). ^1H NMR ($CDCl_3$, 200 MHz): 7.32–7.54 (m, 10H), 5.53 (s, 1H), 4.80 (d, $J = 12.2$ Hz, 1H), 4.71 (d, $J = 12.2$ Hz, 1H), 4.62 (d, $J = 3.6$ Hz 1H), 4.28 (dd, $J = 9.2$, 4.0 Hz, lH), 4.17 (t, $J = 9.2$ Hz, 1H), 3.81 (m, 1H), 3.71 (t, $J = 9.6$ Hz, 1H), 3.50 (m, 2H), 3.39 (s, 3H).

Methyl 3-*O*-Acetyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (4)[13]

The mixture of **3** (17.9 g, 48 mmol), acetic anhydride (100 mmol), and dimethylaminopyridine (61 mg, 0.5 mmol) in pyridine (150 mL) was stirred at rt overnight. The reaction was quenched with water and the mixture was extracted with CH_2Cl_2. After washing with water and saturated $NaHCO_3$ solution, the organic phase was dried over Na_2SO_4 and then condensed in vacuum. The residue was subjected to column chromatography to give **4** (19 g, 45.8 mmol, 95%) as a white solid. ^{1}H NMR ($CDCl_3$, 200 MHz): 7.32–7.48 (m, 10H), 5.57 (t, $J = 9.6$ Hz, 1H), 5.46 (s, 1H), 4.70 (d, $J = 3.6$ Hz, 1H), 4.66 (s, 2H), 4.2 (dd, $J = 9.9$, 4.6 Hz, 1H), 3.90 (td, $J = 9.9$, 4.6 Hz, 1H), 4.73 (d, $J = 9.9$ Hz, 1H), 3.58 (m, 2H), 3.41 (s, 3H), 2.05 (s, 3H).

Methyl 3-*O*-Acetyl-2-*O*-benzyl-6-*O*-trityl-α-D-glucopyranoside (5)

Compound **4** (19 g, 45.8 mmol) was dissolved in a mixture of HOAc and H_2O (150 mL, 1:1), The solution was stirred at 80°C for 2 h and then concentrated to dryness. The resulting residue was dissolved in 150 mL of pyridine. To this solution was added trityl chloride (15.3 g, 55 mmol) at rt and the mixture was stirred at 40°C for 36 h, when TLC indicated the completion of reaction. After the mixture was concentrated, to the mixture was added CH_2Cl_2, and the solution was washed with water, dried over Na_2SO_4, and then concentrated. The resulting syrup was purified with a silica gel column to afford **5** (26 g, 100%). [α]=+42 (1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): 7.20–7.50 (m, 20H), 5.25 (t, $J = 9.5$ Hz, 1H, H-3), 4.71 (d, $J = 3.5$ Hz, 1H, H-1), 4.66 (s, 2H, H-Bn), 3.72 (m, 1H, H-5), 3.48–3.58 (m, 2H), 3.42 (s, 3H, OMe), 3.33–3.38 (m, 2H), 2.08 (s, 3H, Ac); HR FAB MS (m/z): calc. for $C_{35}H_{36}NaO_7(M + Na^+)$ 591.2359, found 591.2354.

Methyl 2-*O*-Benzyl-4-deoxy-6-*O*-trityl-α-D-*xylo*-hexopyrnaoside (6)

To the solution of **5** (2.4 g, 4.22 mmol) in CH_2Cl_2 (30 mL) and pyridine (1 mL) at −10°C was added triflic anhydride (1.0 mL, 5.9 mmol). The mixture was allowed to warm n-Bu_4NI to rt gradually and then stirred for 1 h. The mixture was subsequently washed with diluted HCl solution, aq. $NaHCO_3$ solution and water, dried over Na_2SO_4, and concentrated to give the crude product as syrup. After this crude product was dissolved in 20 mL of anhydrous DMF, $NaBH_4$ (1.6 g, 42.2 mmol) was added at rt. The reaction mixture was stirred at rt for 2 h and then diluted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was dissolved in a mixture of MeOH and H_2O, and to this solution was added NaOH. After the solution was stirred at rt for 2 h, the reaction

mixture was concentrated and diluted with CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, and concentrated. The resulting syrup was subjected to silica gel column chromatography to afford **6** (1.6 g, 74%) **6**: $[\alpha] = +48.6$ (1.0, $CHCl_3$); ^{1}H NMR ($CDC1_3$, 400 MHz): 7.20–7.45 (m, 20H), 4.73 (d, $J = 3.6$ Hz, 1H, H-1), 4.69 (d, $J = 12.0$ Hz, 1H, H-Bn), 4.64 (d, $J = 12.0$ Hz, 1H, H-Bn), 4.04 (m, 1H, H-3), 3.90 (m, 1H, H-5), 3.38 (s, 3H, OMe), 3.30 (dd, $J = 9.6$, 3.6 Hz, 1H, H-2), 3.21 (dd, $J = 9.6$, 6.0 Hz, 1H, H-6), 3.03 (dd, $J = 9.6$, 4.8 Hz, 1H), 2.35 (d, $J = 2.0$ Hz, 1H, OH), 2.04 (ddd, $J = 12.4$, 5.2, 2.4 Hz, 1H, H-4e), 1.43 (q, $J = 12.0$ Hz, lH, H-4a); ^{13}C NMR ($CDCl_3$, 100 MHz): 144.2, 138.2, 128.9, 128.8, 128.3, 128.0, 127.2, 98.0, 86.7, 82.1, 72.8, 67.1, 66.4, 55.2, 35.4; HR FAB MS (m/z): calc. for $C_{33}H_{34}NaO_5$ ($M + Na^+$) 533.2304, found 533.2307.

Methyl 2-*O*-Benzyl-4-deoxy-6-*O*-trityl-α-D-*erythro*-hexopyranoside-3-ulose (7)

To a mixture of **6** (1.6 g, 3.14 mmol) and molecular sieves 4Å (3.0 g) in dry DCM (20 mL) was slowly added PCC (1.7 g, 7.85 mmol). After stirring at rt for 3 h, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and then concentrated. Column chromatography of the residue afforded **7** (1.35 g, 84%). $[\alpha] = -22.6$ (1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.20–7.45 (m, 20H), 5.03 (d, $J = 4.0$ Hz, 1H, H-1), 4.93 (d, $J = 12.4$ Hz, 1H, H-Bn) 4.54 (d, $J = 12.4$ Hz, 1H, H-Bn), 4.12 (m, 1H, H-5), 4.04 (d, $J = 4.0$ Hz, 1H, H-2), 3.40 (s, 3H OMe), 3.24 (dd. $J = 10.0$, 6.0 Hz, 1H, H-6), 3.14 (dd, $J = 10.0$, 4.4 Hz, 1H, H-6), 2.43 (d, $J = 6.4$ Hz, 2 H, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz); 202.9, 143.9, 137.6, 128.9, 128.7, 128.3, 128.1, 127.3, 101.5, 86.9, 81.0, 72.8, 69.1, 65.9, 55.5, 44.4; HR FAB MS (m/z): calc. for $C_{33}H_{32}NaO_5$ ($M + Na^+$) 531.2147, found 531.2146.

Methyl 2-*O*-Benzyl-4-dexoy-3-*C*-((E)-(ethoxycarbonyl) methylene)-6-*O*-trityl-α-D-*erythro*-hexopyranoside (8)

After [(ethoxycarbonyl)methylene]triphenylphosphorane (20 g, 57.4 mmol) was added to a solution of **7** (8.0 g, 15.7 mmol) in dry $CHCl_3$ (200 mL), the mixture was stirred under reflux for 3 d. Evaporation of the solvent in vacuum and purification of the crude product by column chromatography afforded **8** (9.0 g, 99%). $[\alpha] = +1.6$ (1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.20–7.43 (m, 20H), 6.18 (t, $J = 2.0$ Hz, 1H, =CH), 4.88 (d, $J = 3.6$ Hz, 1H, H-1), 4.78 (d, $J = 12.4$ Hz, 1H, H-Bn), 4.56 (d, $J = 12.4$ Hz, 1H H-Bn), 4.15 (m, 2-H, Et), 4.01 (dd, $J = 3.6$, 2.0 Hz, 1H, H-2), 3.97 (m, 1H, H-5), 3.91 (dd, $J = 12.0$, 2.0 Hz, 1H, H-4e), 3.47 (s, 3H, OMe), 3.18 (dd, $J = 10.0$, 6.0 Hz, 1H, H-6), 3.08 (dd, $J = 10.0$, 3.2 Hz, 1H, H-6), 1.97 (t, $J = 12.0$ Hz, 1H, H-4a), 1.27 (t, $J = 7.2$ Hz, 3H, Et); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.8, 152.8, 144.2,

137.9. 128.9, 128.7, 128.2, 128.0, 127.2, 113.8, 99.7, 86.6, 78.1, 72.4, 69.4, 66.4, 60.0, 55.3, 31.9, 14.5; HR FAB MS (m/z): calc. for $C_{37}H_{38}NaO_6$ ($M + Na^+$) 601.2566, found 601.2567.

Methyl 2-*O*-Benzyl-4-deoxy-3-*C*-[(R)-(ethoxycarbonyl) hydroxymethyl]-6-*O*-trityl-α-D-*xylo*-hexopyranoside (9)

After **8** (9.0 g, 15.5 mmol) and 4-methylmorpholine *N*-oxide (3.63 g, 31 mmol) were dissolved in a mixture of acetone, THF, and water (250 mL, 8:2:1), osmium tetraoxide (197 mg, 0.775 mmol) was added, and the reaction mixture was stirred overnight at rt. The mixture was then poured into H_2O and extracted with $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4, and concentrated to dryness. The residue was purified with flash column chromatography to give **9** (9.3 g, 98%) as syrup. $[\alpha] = +26.6$ (1.0, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz): 7.20–7.45 (m, 20H), 4.82 (d, $J = 5.2$ Hz, 1H, C<u>H</u>-CO_2Et), 4.81 (d, $J = 3.6$ Hz, lH, H-l), 4.65 (s, 2H, H-Bn), 4.51 (d, $J = 5.2$ Hz, 1H, OH), 4.31 (s, lH, OH), 4.17 (m, 1H, H-5), 4.08 (qd, $J = 7.2$, 1.2 Hz, 2H, Et), 3.70 (d, $J = 3.6$ Hz, 1H, H-2), 3.47 (s, 3H, OMe), 3.16 (dd, $J = 9.6$, 6.0 Hz, 1H, H-6), 3.02 (dd, $J = 9.6$, 4.4 Hz, 1H, H-6), 1.92 (dd, $J = 14.0$, 2.0 Hz, 1H, H-4e), 1.68 (dd, $J = 14.0$, 12.4 Hz, 1H, H-4a), 1.16 (t, $J = 7.2$ Hz, 3H, Et); ^{13}C NMR ($CDCl_3$, 100 MHz): 172.0, 144.1, 137.4, 128.9, 128.8, 128.4, 128.3, 128.0, 127.2, 98.1, 86.7, 84.6, 75.2, 74.1, 73.2, 67.2, 66.3, 61.4, 55.7, 38.5, 14.3; HR FAB MS (m/z): calc. for $C_{37}H_{40}NaO_8$ ($M + Na^+$) 635.2621, found 635.2641.

Methyl 2,3-di-*O*-Benzyl-4-deoxy-3-*C*-[(R)-(ethoxycarbonyl) benzyloxymethyl]-6-*O*-trityl-α-D-*xylo*-hexopyranoside (10)

To the solution of **9** (50 mg, 0.079 mmol) and benzyl bromide (24 mg, 0.2 mmol) in DMF (3 mL) was added NaH (8 mg, 0.2 mmol) at 0°C. The mixture was stirred at rt for 1 h. The reaction was quenched with methanol and diluted with CH_2Cl_2. The reaction mixture was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified with flash column chromatography to give **10** (64 mg, 100%) as white foam. $[\alpha] = +43.0$ (1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.05–7.40 (m, 30H), 5.08 (d, $J = 11.6$ Hz, 1H, H-Bn), 5.01 (d, $J = 11.2$ Hz, 1H, H-Bn), 4.76 (d, $J = 2.0$ Hz, 1H, H-1), 4.54 (d, $J = 10.4$ Hz, 1H, H-Bn), 4.53 (d, $J = 10.8$ Hz, 1H, H-Bn), 4.48 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.45 (s, 1H, C<u>H</u>-CO_2Et), 4.41 (m, 1H, H-5), 4.18 (qd, $J = 7.2$, 10.8 Hz, 1H, Et), 4.16 (d, $J = 2.0$ Hz, 1H, H-2), 4.15 (d $J = 10.8$ Hz 1H-Bn), 4.01 (qd, $J = 7.2$, 10.8 Hz, 1H, Et), 3.55 (s, 3 H, OMe), 3.49 (dd, $J = 10.4$, 8.0 Hz, 1H, H-6), 2.81 (dd, $J = 10.4$, 3.6 Hz, 1H, H-6), 2.20 (dd, $J = 14.0$, 6.4 Hz, 1H, H-4e), 1.73

(dd, $J = 14.0, 4.8$ Hz, 1H, H-4a), 1.06 (t, $J = 7.2$ Hz, 3H, Et); HR FAB MS (m/z); calc. for $C_{51}H_{52}NaO_8$ ($M + Na^+$) 815.3560, found 815.3563.

Methyl 2,3-di-*O*-Benzyl-4-deoxy-3-*C*-((S)-1,2-dibenzyloxyethyl)-α-D-xylo-hexopyranoside (11)

Lithium aluminum hydride (3.8 g, 100 mmol) was added to a solution of **10** (14.9 mmol) in dry THF (200 mL) at 0°C, and the mixture was warmed to rt and stirred for 4 h. Then, the reaction was quenched with $Na_2SO_4 \cdot 10H_2O$, and the reaction mixture was filtered off, dried over Na_2SO_4 and concentrated. The residue was dissolved in dry DMF (100 mL), and to this solution was added benzyl bromide (4.5 mL, 37.5 mmol) and NaH (40%, 2.0 g, 50 mmol) at 0°C. The reaction mixture was stirred at rt for 2 h and quenched with methanol. The mixture was poured into H_2O and extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was dissolved in a mixture of HCOOH and Et_2O (100 mL, 1:1). After stirring at rt for 1 h, evaporation of the solvent and purification of the product by chromatography afforded **11** (8.3 g, 93%). $[\alpha] = +55.2$ (1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.20–7.40 (m, 20H), 5.05 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.95 (d, $J = 11.2$ Hz, 1H H-Bn), 4.90 (d, $J = 12.0$ Hz, 1H, H-Bn), 4.87 (d, $J = 2.4$ Hz, 1H, H-l), 4.63 (d, $J = 6$ Hz, 1H, H-Bn), 4.46 (s, 2H, H-Bn), 4.42 (d, $J = 10.0$ Hz, 1H, H-Bn), 4.39 (d, $J = 11.2$ Hz, 1H, H-Bn), 4.29 (d, $J = 2.0$ Hz, 1H, H-2), 4.25 (m, 1H, H-5), 4.13 (dd, $J = 6.0, 3.6$ Hz, 1H, H-l′), 3.91 (dd, $J = 10.4, 3.6$ Hz, 1H, H-2′), 3.73 (dd, $J = 10.4, 6.0$ Hz, 1H, H-2′), 3.69 (m, 1H, H-6), 3.53 (ddd, $J = 11.2. 4.0, 3.2$ Hz, 1H, H-6) 3.44 (s, 3H, OMe), 2.04 (m, 1H, OH), 2.00 (dd, $J = 14.0, 6.0$ Hz, 1H, H-4e), 1.66 (dd, $J = 14.0, 6.4$ Hz, 1H, H-4a), 1.06 (t, $J = 7.2$ Hz, 3 H, Et); ^{13}C NMR ($CDCl_3$, 100 MHz): 139.5, 139.3, 139.0, 138.3, 128.6, 128.4, 128.3, 127.9, 27.6, 127.5, 127.4, 127.2, 127.1, 98.7, 83.2, 79.8, 74.8, 74.0, 73.6, 71.9, 70.9, 67.3, 65.1, 56.4, 33.0; HR FAB MS (m/z): calc. for $C_{37}H_{43}O_7$ ($M + H^+$) 599.3009, found 599.2992.

Methyl (6R)-2,3-di-*O*-Benzyl-4-deoxy-3-*C*-((S)-l,2-dibenzyloxyethyl)-6-*C*-ethynyl-α-D-xylo-hexopyranoside (13) and Methyl (6S)-2,3-di-*O*-benzyl-4-deoxy-3-*C*-((S)-l,2-dibenzyloxyethyl)-6-*C*-ethynyl-α-D-xylo-hexopyranoside (14)

To a solution of **11** (8.3 g, 13.9 mmol) and Et_3N (19.5 mL, 139 mmol) in DCM (75 mL) at 0°C was added SO_3·Pyr (17.8 g, 111.2 mmol) in DMSO (150 mL). After the reaction mixture was stirred at 0°C for 45 min, it was diluted with ethyl acetate, washed with aqueous $NaHCO_3$ and brine, dried

over Na_2SO_4, and then concentrated. The residue was dissolved in THF (50 mL) and directly treated with HC≡CMgBr (100 mL, 0.5 M) at 0°C. The reaction mixture was stirred at 0°C until the starting material disappeared (monitored by TLC). Evaporation of the solvent under vacuum and purification of the product by column chromatography afforded **13** (3.5 g, 40%) and **14** (3.5 g, 40%). **13** (more polar product): $[\alpha] = +53.3$ (1.0, $CHCl_3$); ^{1}H NMR ($CDCI_3$, 400 MHz): 7.20–7.40 (m, 20H), 5.07 (d, $J = 11.2$ Hz, 1H, H-Bn), 4.99 (d, $J = 12.0$ Hz, 1H, H-Bn), 4.90 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.84 (d, $J = 2.4$ Hz, 1H, H-1), 4.65 (d, $J = 12.0$ Hz, 1H, H-Bn), 4.59 (ddd, $J = 6.4$, 4.0, 2.0 Hz, 1H, H-6), 4.48 (s, 2H, H-Bn), 4.42 (d, $J = 11.2$ Hz, 1H, H-Bn), 4.38 (d, $J = 11.6$ Hz, lH, H-Bn), 4.31 (d. $J = 1.6$ Hz, 1H, H-2), 4.19 (q, $J = 6.0$ Hz, 1H H-5), 4.12 (dd, $J = 6.0$, 3.6 Hz, 1H, H-1′), 3.94 (dd, $J = 10.4$, 3.6 Hz, 1H, H-2′), 3.74 (dd, $J = 10.4$, 6.0 Hz, 1H, H-2′), 3.46 (s, 3H, OMe), 2.61 (d, $J = 4.4$ Hz, 1H, OH), 2.42 (d, $J = 2.4$ Hz, 1H, HC≡C), 2.13 (dd, $J = 14.0$, 6.4 Hz, 1H, H-4e), 1.97 (dd, $J = 14.0$, 5.6 Hz, 1H, H-4a); ^{13}C NMR ($CDCl_3$, 100 MHz): 139.3, 139.2, 139.0, 138.2, 128.6, 128.5, 128.4, 127.9, 127.6, 127.4, 127.2, 127.1, 98.6, 83.0, 82.3, 80.0, 74.9, 74.2, 73.8, 73.7, 73.6, 73.4, 71.7, 67.1, 64.2, 56.6, 32.2; HR FAB MS (m/z): calc. for $C_{39}H_{43}O_7$ ($M + H^+$) 623.3003, found 623.3008. **14** (less polar product): $[\alpha] = +56.5$ (1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.20–7.40 (m, 20 H), 5.07 (d, $J = 11.6$ Hz. 1H, H-Bn), 5.01 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.96 (d, $J = 2.4$ Hz, 1H, H-1), 4.93 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.66 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.57 (ddd, $J = 7.2$, 5.2, 2.4 Hz, 1H, H-6), 4.52 (d, $J = 12.0$ Hz, 1H, H-Bn), 4.49 (d, $J = 12.0$ Hz, 1H, H-Bn), 4.44 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.42 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.30 (d, $J = 2.0$ Hz, 1H, H-2), 4.27 (q, $J = 6.0$ Hz, 1H, H-5), 4.18 (dd, $J = 6.0$, 3.6 Hz, 1H, H-l′), 3.98 (dd, $J = 10.4$, 3.6 Hz, 1H, H-2′), 3.79 (dd, $J = 10.4$, 6.0 Hz, 1H, H-2′), 3.48 (s, 3H, OMe), 2.83 (d, $J = 7.2$ Hz, 1H, OH), 2.43 (d, $J = 2.4$ Hz, 1H, HC≡C), 2.09 (d, $J = 6.4$ Hz, 2H, H-4); ^{13}C NMR ($CDCl_3$ 100 MHz): 139.4, 139.2, 138.6, 138.2, 128.7, 128.6, 128.4, 128.3, 127.9, 127.8, 127.6, 127.4, 127.2, 127.1, 98.2, 83.0, 82.5, 79.9, 74.8, 74.3, 73.7, 73.6, 72.4, 71.9, 67.5, 64.8, 56.5, 31.0; HR FAB MS (m/z): calc. for $C_{39}H_{43}O_7$ ($M + N^+$) 623.3003, found 623.3009.

(1S,3S,4R,5R,7R)-4-Benzyloxy-5-((S)-l,2-dibenzyloxyethyl)-7-ethynyl-3-methoxy-2,6-dioxabicyclo(3.2.1)octane (15)

To the solution of **13** (120 mg, 0.2 mmol) in pyridine (0.1 mL) and dichloromethane (5 mL) was added triflic anhydride (67.3 μL, 0.4 mmol) at 0°C. After the mixture was stirred for 0.5 h, water was added to quench the reaction. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was subjected to column chromatography to afford **15** (99 mg, 100%) $[\alpha] = +86.3$ (1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.20–7.35 (m, 15H), 4.97 (d, $J = 11.6$ Hz, 1H,

H-Bn), 4.79 (d, $J = 2.4$ Hz, 1H, H-l), 4.75 (d, $J = 2.0$ Hz, 1H, H-6), 4.71 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.51 (s, 2H, H-Bn), 4.50 (m, 1H, H-5), 4.31 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.24 (d, $J = 11.6$ Hz, 1H, H-Bn), 3.98 (br, 1H, H-2), 3.95 (m, 2H, H-1′,2′), 3.72 (dd, $J = 12.0$, 6.0 Hz, 1H, H-2′), 3.54 (s, 3H, OMe), 2.47 (d, $J = 2.0$ Hz, 1H, HC≡C), 2.47 (ddd, $J = 12.4$, 1.2, 1.2 Hz, 1H, H-4e), 2.12 (ddd $J = 12.4$, 2.8, 1.2 Hz, 1H, H-4a); ^{13}C NMR ($CDCl_3$, 100 MHz): 139.1, 138.5, 138.3, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 101.3, 87.5, 80.8, 79.3, 77.2, 75.9, 75.2, 74.6, 73.6, 73.1, 72.7, 70.0, 57.7, 32.1; HR FAB MS (m/z): calc. for $C_{32}H_{35}O_6$ ($M + H^+$) 515.2434, found 515.2430.

(1S,3S,4R,5R,7S)-4-Benzyloxy-5-((1S)-1,2-dibenzyloxyethyl)-7-ethynyl-3-methoxy-2,6-dioxa bicyclo(3.2.1)octane (16)

To the solution of **14** (120 mg, 0.2 mmol) in pyridine (0.1 mL) and dichloromethane (5 mL) was added triflic anhydride (67.3 μL, 0.4 mmol) at 0°C. After the mixture was as stirred for 0.5 h, water was added to quench the reaction. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with water, dried over Na_2SO_4, and concentrated. The resides was subjected to column chromatography to afford **16** (100 mg, 100%). $[\alpha] = +110.2$ (1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.20–7.38 (m, 15H), 5.40 (d, $J = 2.4$ Hz, 1H, H-l), 5.00 (d, $J = 11.2$ Hz, 1H, H-Bn), 4.69 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.49 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.48 (d, $J = 2.4$ Hz, 1H, H-6), 4.43 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.41 (m, 1H, H-5), 4.33 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.24 (d, $J = 11.6$ Hz, 1H, H-Bn), 3.96 (d, $J = 2.0$ Hz, 1H, H-2), 3.89 (dd, $J = 5.2$, 4.8 Hz, 1H), 3.78 (dd, $J = 6.4$, 4.8 Hz, 1H), 3.64 (dd, $J = 6.4$, 5.2 Hz, 1H), 3.58 (s, 3H, OMe), 2.62 (d, $J = 2.8$ Hz, 1H, HC≡C), 2.52 (dd, $J = 12.4$, 1.2 Hz, 1H, H-4e), 1.82 (dd, $J = 12.4$, 1.6 Hz, 1H, H-4a); HR FAB MS (m/z): calc. for $C_{32}H_{35}O_6$ ($M + H^+$) 515.2434, found 515.2430.

Methyl (6S)-2,3-di-*O*-Benzyl-4-deoxy-3-*C*-((S)-l,2-dibenzyloxyethyl)-6-*C*-ethynyl-6-*O*-tosyl-α-D-xyl*o*-hexopyranoside (17)

To a solution of **14** (120 mg, 0.2 mmol) in pyridine (0.1 mL) and dichloromethane (5 mL) was added TsCl (0.8 mmol) at 0°C. After the reaction mixture was warmed to rt, it was stirred overnight, and then water was added to quench the reaction. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was subjected to column chromatography to afford **17** (150 mg, 100%). $[\alpha] = +36.7$ (1.0, $CHCl_3$); ^{1}H NMR ($CDC1_3$, 400 MHz): 7.67

(d, $J = 7.6$ Hz, 2H, Ts), 7.24–7.38 (m, 20H), 7.19 (d, $J = 7.6$ Hz, 2H, Ts), 5.53 (d, $J = 6.8$ Hz, 1H, H-6), 5.09 (d, $J = 11.2$ Hz, 1H, H-Bn), 4.99 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.95 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.71 (br, 1H, H-l), 4.66 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.51 (d, $J = 12.0$ Hz, 1H, H-Bn), 4.45 (d, $J = 12.0$ Hz, 1H, H-Bn), 4.40 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.37 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.28 (br, 1H, H-2), 4.24 (dd, $J = 12.0$, 6.0 Hz, 1H, H-5) 4.06 (dd, $J = 2.8$, 2.0 Hz, 1H, H-1′), 3.90 (dd, $J = 10.4$, 2.8 Hz, 1H, H-2′), 3.76 (dd, $J = 10.4$, 2.0 Hz, 1H, H-2′), 3.38 (s, 3H, OMe), 2,43 (s, 3H, CH_3), 2.40 (br, 1H, HC≡C), 2.08 (dd, $J = 14.4$, 4.8 Hz, 1H, H-4), 1.93 (dd, $J = 14.4$, 4.4 Hz, 1H, H-4); HR FAB MS (m/z): calc. for $C_{46}H_{49}O_9S$ ($M + H^+$) 777.3097, found 777.3114.

(1S,3S,5R,6S,8R)-5-Acetoxy-8-benzyloxy-6-benzyloxymethyl-3-((R)-(ethynyl)tosyloxymethyl)-2,7-dioxabicyclo(3.2.1)octane (18)

To a solution of **17** (80 mg, 0.1 mmol) in acetic acid and acetic anhydride (1:1, 5 mL) was added sulfuric acid (1 drop) at 0°C. The reaction mixture was stirred at 0°C for 0.5 h and then diluted with CH_2C1_2. The mixture was washed with water, dried over Na_2SO_4, and concentrated. The residue was finally subjected to column chromatography to afford **18**. ^{1}H NMR ($CDCl_3$, 600 MHz): 7.81 (d, $J = 7.8$ Hz, 2H, Ts), 7.20–7.38 (m, 12H), 5.35 (s, 1H, H-l), 5.22 (t, $J = 3.6$ Hz, 1H, H-6), 4.64 (d, $J = 12.0$ Hz, 1H, H-Bn), 4.60 (dd, $J = 12.0$, 2.4 Hz, 1H, H-2′), 4.55 (d, $J = 10.8$ Hz, 1H, H-Bn), 4.54 (d, $J = 12.0$ Hz, 1H, H-Bn), 4.45 (d, $J = 10.8$ Hz, 1H, H-Bn), 4.43 (dd, $J = 12.0$, 9.0 Hz, 1H, H-2′), 4.25 (dd, 9.0, 2.4 Hz, 1H, H-1′), 4.09 (dt, $J = 10.8$, 3.6 Hz, 1H, H-5), 3.58 (S, 1H, H-2), 2.47 (d, $J = 1$ 3.6 H2, 1H, HC≡C), 2.44 (S, 3H, CH_3), 2.23 (t, $J = 13.2$ Hz, 1H, H-4a), 1.93 (dd, 13.2, 6.0 Hz, 1H, H-4e), 2.05 (s, 3H, Ac).

(1S,3S,5R,6S,8R)-5,8-di-Acetoxy-6-acetoxymethyl-3-((R)-(ethynyl)tosyloxymethyl)-2,7-dioxabicyclo(3.2.1) octane (19) and (1S,3S,5R,6S,8R)-5,8-di-Acetoxy-6-benzyloxymethyl-3-((R)-(ethynyl)tosyloxymethyl)-2,7-dioxabicyclo(3.2.1)octane (20)

To the solution of **17** (160 mg, 0.2 mmol) in THF and acetic anhydride (9:1, 10 mL) was added BCl_3, at −50°C. After it was stirred for 1 h, CH_2CI_2 was added, and the mixture was washed with water, dried over Na_2SO_4, and concentrated. The residue was subjected to column chromatography to give **19** and **20**. **19**: $[\alpha] = -49.0$ (0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.81 (d, $J = 8.0$ Hz, 2 H, Ts), 7.34 (d, $J = 8.0$ Hz, 2H, Ts), 5.20 (s, 1H, H-1), 5.18 (dd, $J = 3.6$, 2.4 Hz, 1H, H-6), 4.97 (s, 1H, H-2), 4.62 (dd, $J = 7.2$, 4.0 Hz, IH,

H-2′), 4.27 (dd, $J = 12.0$, 7.2 Hz, 1H, H-l′), 4.24 (dd, $J = 12.0$, 4.0 Hz, lH, H-l′), 4.09 (dt, $J = 11.2$, 4.0 Hz, 1H, H-5), 2.61 (dd, $J = 12.8$, 4.4 Hz, 1H, H-4′), 2.50 (d, $J = 2.0$ Hz, 1H, HC≡C), 2.44 (s, 3H, CH_3), 2.28 (t, $J = 12.8$ Hz, lH, H-4a), 2.12 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.08 (s, 3H, Ac); HR FAB MS (m/z): cacl. for $C_{23}H_{27}O_{11}S$ ($M + H^+$) 511.1274, found 511.1262. **20**: [α] = −50.0 (0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.80 (d, $J = 8.0$ Hz, 2H, Ts), 7.27–7.36 (m, 7 H), 5.22 (s, lH, H-l), 5.18 (dd, $J = 3.6$, 2.0 Hz, 1H, H-6), 4.58 (s, 2H, H-Bn), 4.44 (dd, $J = 8.4$, 2.8 Hz, 1H, H-l′), 4.39 (dd, $J = 12.0$, 3.2 Hz, 1H, H-2′), 4.31 (dd, $J = 12.0$, 8.4 Hz, lH, H-2′), 4.04 (m, 1H, H-5), 3.92 (s, 1H, H-2), 2.45 (d, $J = 2.4$ Hz, lH, HC≡C), 2.43 (s, 3H, CH_3), 2.37 (dd, $J = 14.4$, 12.8 Hz, 1H, H-4a), 2.34 (d, $J = 14.4$ Hz, 1H, H-4e), 2.08 (s, 3H, Ac), 2.07 (s, 3H, Ac); HR FAB MS (m/z): calc. for $C_{28}H_{31}O_{10}S$ ($M + H^+$) 559.1638, found 559.1637.

Methyl {Methyl 2,3-di-*O*-Benzyl-4-deoxy-3-*C*-[(S)-(l,2-dibenzyloxyethyl)]-α-D-*gluco*-heptopyranosid} uronate (21)

After **14** (2.0 g, 3.21 mmol) and $NaIO_4$ (3.2 g, 15 mmol) were dissolved in a mixture of THF and water (5:3, 160 mL), osmium tetraoxide (76 mg, 0.3 mmol) was added, and the reaction mixture was stirred at 45°C overnight. After the mixture was concentrated to remove THF, the residue was poured into water and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The crude product was directly subjected to methylation using freshly prepared CH_2N_2 in CH_2Cl_2 to give **21** (1.4 g, 66%). [α] = +69.7 (1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.20–7.38 (m, 20 H), 5.05 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.97 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.92 (d, $J = 2.0$ Hz, 1H, H-l), 4.89 (d, $J = 12.0$ Hz, 1H, H-Bn), 4.65 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.52 (m, 1H, H-6), 4.48 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.45 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.41 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.35 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.26 (d, $J = 2.0$ Hz, 1H, H-2), 4.22 (m, 1H, H-5), 4.09 (dd, $J = 6.4$, 3.2 Hz, 1H, H-1′), 3.95 (dd, $J = 10.8$, 3.2 Hz, 1H, H-2′), 3.73 (dd, $J = 10.8$, 6.4 Hz, 1H, H-2′), 3.71 (s, 3H, OMe), 3.42 (s, 3H, OMe), 2.79 (d, $J = 8.0$ Hz, 1H, OH), 1.99 (m, 2H, H-4e, H-4a); HR FAB MS (m/z): calc. for $C_{39}H_{45}O_9$ ($M + H^+$) 657.3064, found 657.3017.

Methyl {Methyl 2,3-di-*O*-Benzyl-4-deoxy-3-*C*-[(S)-(1,2-dibenzyloxyethyl)]-6-*O*-tosyl-α-D-*gluco*-heptopyranosid} uronate (22)

To the solution of **21** (0.6 g, 0.91 mmol) in pyridine and CH_2Cl_2 (1:1, 20 mL) was added TsCl (5 eq., 4.5 mmol) at 0°C. The reaction mixture was allowed to warm to rt and stirred overnight. Then, CH_2Cl_2 was added to dilute the reaction mixture, and the mixture was washed with water, dried over

Na_2SO_4, and concentrated. The residue was subjected to column chromatography to give **22** (0.74 g, 100%). $[\alpha] = +36.8$ (1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.49 (d, $J = 8.4$ Hz, 2H, Ts), 7.20–7.44 (m, 20H), 7.08 (d, $J = 8.4$ Hz, 2H, Ts), 5.46 (d, $J = 9.2$ Hz, 1H, H-6), 5.08 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.90 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.86 (d, $J = 2.0$ Hz, 1H, H-1), 4.85 (d, $J = 11.2$ Hz, 1H, H-Bn), 4.69 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.49 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.44 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.37 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.28 (d, $J = 11.6$ Hz, 1H, H-Bn), 4.28 (m, 2H, H-2, H-5), 3.96 (dd, $J = 6.0$, 3.6 Hz, 1H, H-1′), 3.73 (dd, $J = 10.4$, 3.6 Hz, 1H, H-2′), 3.68 (dd, $J = 10.4$, 6.0 Hz, 1H, H-2′), 3.61 (s, 3H, OMe), 3.34 (s, 3H, OMe), 2.36 (s, 3H, CH_3), 2.04 (dd, $J = 14.4$, 6.8 Hz, 1H, H-4e), 2.04 (d, $J = 14.4$ Hz, 1H, H-4a), HR FAB MS (m/z): calc. for $C_{46}H_{51}O_{11}S$ $(M + H^+)$. 811.3152, found 811.3151.

Methyl {Methyl 2-*O*-Acetyl-4-deoxy-3-*C*-[(S)-(1,2-diacetyloxyethyl)]-6-*O*-tosyl-α-D-*gluco*-heptopyranosid} uronate (23)

To the solution of **22** (0.73 g, 0.9 mmol) in THF (15 mL) was added 10% Pd/C (0.2 g). After stirred under hydrogen atmosphere for 1 d, the reaction mixture was filtered off, and the filtrate was concentrated. The residue was dissolved in the mixture of pyridine and acetic anhydride (3:1, 12 mL), and a catalytic amount of DMAP was added. The reaction mixture was stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and then concentrated. The residue was subjected to column chromatography to give **23** (460 mg, 89% yield). $[\alpha] = +16.5$ (1.0, $CHCl_3$); ^1H NMR ($CDCl_3$), 400 MHz): 7.81 (d, $J = 8.0$ Hz, 2H, Ts), 7.37 (d, $J = 8.0$ Hz, 2H, Ts), 5.39 (d, $J = 8.8$ Hz, 1H, H-6), 5.13 (dd, $J = 6.8$, 3.6 Hz, 1H, H-l′), 4.96 (br, 1H, H-2) 4.94 (d, $J = 2.0$ Hz, 1H, H-S). 4.31 (m, 2H, H-5, H-2′), 4.04 (dd, $J = 12.0$, 6.8 Hz, 1H, H-2′), 3.66 (s, 3H, OMe), 3.36 (s, 3H, OMe), 2.75 (s, 1H, OH), 2.46 (s, 3H, CH_3), 2.08 (s, 3H, Ac), 2.07 (s, 3H, Ac), 2.05 (s, 3H, Ac), 1.99 (dd, $J = 14.4$, 6.4 Hz, 1H, H-4e), 1.85 (dd, $J = 14.4$, 3.2 Hz, 1H, H-4a); HR FAB MS (m/z): calc. for $C_{24}H_{33}O_{14}S$ $(M + H^+)$ 577.1591, found 577.1590.

Methyl {Methyl 2,3-di-*O*-Acetyl-4-deoxy-3-*C*-[(S)-(l,2-diacetyloxyethyl)]-6-*O*-tosyl-α-D-*allo*-heptopyranosid} uronate (24)

To the solution of **23** (0.45 g, 0.78 mmol) in the mixture of ethyl acetate, acetic anhydride, and acetic acid (35 mL, 8:3:2) was added sulfuric acid (0.03 mL) under nitrogen atmosphere at 0°C. The reaction mixture was stirred overnight and then poured into water and extracted with ethyl

acetate. The organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified with flash column chromatography to give **24** (0.305 g, 60%). ^{1}H NMR ($CDCl_3$, 400 MHz): 7.81 (d, J = 8.0 Hz, 2H, Ts), 7.35 (d, J = 8.0 Hz, 2H, Ts), 6.01 (d, J = 4.0 Hz, 1H, H-1), 5.94 (dd, J = 8.8, 2.8 Hz, 1H, H-1′), 5.45 (d, J = 4.0 Hz, 1H, H-2), 5.04 (d, J = 4.4 Hz, 1H, H-6), 4.58 (dd, J = 12.0, 2.8 Hz, 1H, H-2′), 4.56 (m, 1H, H-5), 4.06 (dd, J = 12.0, 8.8 Hz, 1H, H-2′), 3.71 (s, 3H, OMe), 2.46 (s, 3H, CH_3), 2.44 (m, 2H, H-4e, H-4a), 2.10 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.03 (s, 3H, Ac), 2.02 (s, 3H, Ac), 2.00 (s, 3H, Ac); HR FAB MS (m/z): calc. for $C_{25}H_{31}O_{14}S$ (M^+ − OAc) 587.1435, found 587.1438.

Methyl {Methyl 2,3-di-*O*-Acetyl-6-*C*-azido-3-*C*-[(S)-(1,2-diacetyloxyethyl)]-4,6-dideoxy-α-L-*talo*-heptopyranosid}urinate (25)

To the solution of **24** (220 mg, 0.34 mmol) in dry DMF (10 mL) was added NaN_3 (218 mg, 3.4 mmol) and NH_4Cl (22 mg). The reaction mixture was stirred at 30°C for 1 d and then poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified with flash column chromatography to give **25** (90 mg, 51%). [α] = −4.5 (1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 6.25 (d, J = 4.4 Hz, 1H, H-l), 5.93 (dd, J = 8.4, 2.4 Hz, 1H, H-l′), 5.64 (d, J = 4.4 Hz, 1H, H-2), 4.67–4.72 (m, 2H, H-5, H-2′). 4.09 (dd, J = 12.0, 8.8 Hz, 1H, H-2′), 3.83 (s, 3H, OMe), 2.76 (dd, J = 10.4, 7.2 Hz, 1H, H-4e), 2.47 (dd, J = 10.4, 4.0 Hz, 1H, H-4a), 2.11 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.08 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.04 (s, 3H, Ac); HR FAB MS (m/z): calc. for $C_{18}H_{24}N_3O_{11}$ (M^+ − OAc) 458.1411, found 458.1418.

Methyl {l,2,3-tri-*O*-Acety-4-deoxy-3-*C*-[(S)-(l,2-diacetoxhyl)]-6-*O*-tosyl-α-*O*-tosoyl-α-D-*gluco*-heptopyranosid}uronate (26)

To the solution of **23** (300 mg, 0.52 mmol) in acetic anhydride (2.6 mmol) and anhydrous dichloromethane (20 mL) was added $SnCl_4$ (0.52 mmol) at 0°C. The mixture was allowed to warm to rt and stirred at rt overnight. The mixture was neutralized with triethyl amine and then poured into H_2O and extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was finally purified by silica gel column chromatography to afford **26** (90 mg, 28%) and (1S, 3S,5R,6S,8R)-5,8-di-acetoxy-6-acetoxymethyl-3-[(S)-(methoxycarbonyl)tosyloxy-methyl]-2,7-dioxabicyclo[3.2.1]octane **27** (30 mg, 11%). **26**: [α] = −4.4 (1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.78 (d, J = 8.4 Hz, 2H, Ts), 7.31 (d, J = 8.4 Hz, 2H, Ts), 5.84 (d, J = 2.4 Hz, 1H, H-1), 5.80 (dd, J = 6.8, 4.0 Hz, 1H, H-1′), 5.39 (d, J = 1.2 Hz, 1H, H-2), 4.97 (d, J = 4.8 Hz, 1H, H-6), 4.49 (dd,

$J = 12.4$, 4.0 Hz, 1H, H-2′), 4.32 (ddd, $J = 11.6$, 4.8, 2.8 Hz, 1H, H-5), 3.94 (dd, $J = 12.0$, 6.8 Hz, 1H, H-2′), 3.68 (s, 3H, OMe), 2.44 (s, 3H, CH_3), 2.31 (dd, $J = 14.4$, 4.0 Hz, 1H, H-4e), 2.22 (dd, $J = 14.4$, 2.4 Hz, 1H, H-4a), 2.08 (s, 3H, Ac), 2.04 (s, 3H, Ac), 2.03 (s, 3H, Ac), 2.02 (s, 3H, Ac), 2.01 (s, 3H, Ac); ^{13}C NMR ($CDCl_3$, 100 MHz): 171.0, 169.9, 169.1, 168.9, 168.5, 166.6, 145.6, 133.2, 129.8, 128.5, 90.7, 79.8, 78.2, 71.0, 68.1, 66.8, 62.9, 53.3, 29.8, 21.9, 21.8, 21.1, 20.9, 20.8, 20.8; HR FAB MS (m/z): calc. for $C_{25}H_{31}O_{14}S$ ($M^+ - OAc$) 587.1435, found 587.1438. **27**: $[\alpha] = -18.4$ (1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.79 (d, $J = 8.4$ Hz, 2H, Ts), 7.33 (d, $J = 8.4$ Hz, 2H, Ts), 5.70 (s, 1H, H-l), 5.14 (s, 1H, H-2), 4.87 (d, $J = 4.4$ Hz, 1H, H-6), 4.39–4.45 (m, 2H, H-5, H-1′), 4.26 (dd, $J = 8.4$, 3.2 Hz, 1H, H-2′), 4.14 (dd, $J = 12.0$, 8.4 Hz, 1H, H-2′), 3.63 (s, 3H, OMe), 2.43 (m, 2H, H-4e, H-4a), 2.41 (s, 3H, CH_3), 2.09 (s, 3H, Ac), 2.04 (s, 3H, Ac), 2.03 (s, 3H, Ac); ^{13}C NMR ($CDCl_3$, 100 MHz): 170.6, 169.4, 169.3, 166.6, 145.6, 132.8, 129.9, 128.7, 100.4, 78.5, 78.0, 77.7, 72.7, 67.3, 63.5, 53.2, 30.1, 21.9, 21.4, 21.0, 20.8; HR FAB MS (m/z): cacl. for $C_{23}H_{29}O_{13}S$ ($M + H^+$) 545.1329, found 545.1325.

Methyl {1,2,3-tri-*O*-Acetyl-3-*C*-[(*S*)-(l,2-diacetyloxyethyl)]-4,6-dideoxy-6-*C*-azido-α-L-*ido*-heptopyranosid}uronate (28)

To the solution of **26** (80 mg, 0.14 mmol) in dry DMF (5 mL) was added NaN_3 (91 mg, 1.4 mmol) and NH_4Cl (10 mg). The reaction mixture was stirred at 30°C for 1 d and was then poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified with flash column chromatography to afford **28** (62 mg, 85%). $[\alpha] = +6.5$ (1.0, $CHCl_3$); ^{1}H NMR ($CDC1_3$, 400 MHz): 6.04 (d, $J = 2.4$ Hz, 1H, H-1), 5.89 (dd, $J = 7.6$, 3.2 Hz, 1H, H-1′), 5.47 (d, $J = 1.6$ Hz, 1H, H-2), 4.62 (dd, $J = 12.4$, 3.2 Hz, 1H, H-2′), 4.50 (dt, $J = 12.4$, 2.8 Hz, 1H, H-5), 3.97 (dd, $J = 12.4$, 7.6 Hz, 1H, H-2′), 3.80 (s, 3H, OMe), 3.78 (d, $J = 3.2$ Hz, 1H, H-6), 2.56 (dd, $J = 14.0$, 12.4 Hz, 1H, H-4a), 2.30 (dd, $J = 14.0$, 2.4 Hz, 1H, H-4a), 2.13 (s, 3H, Ac), 2.12 (s, 3H, Ac), 2.07 (s, 3H, Ac), 2.07 (s, 3H, Ac), 2.06 (s, 3H, Ac); HR FAB MS (m/z): calc. for $C_{20}H_{27}N_3NaO_{13}$ ($M + Na^+$) 540.1442, found 540.1450.

Methyl {6-*C*-Acetamido-1,2,3-tri-*O*-acetyl-3-*C*-[(*S*)-1,2-diacetyloxyethyl)]-4,6-dideoxy-α-L-*ido*-heptopyranosid}uronate (1)

To a solution of **28** (10 mg, 0.02 mmol) in a mixture of MeOH, THF, and DCM (6 mL, 1:1:1) was added 10% Pd/C (5 mg) under hydrogen atmosphere, and the mixture was stirred overnight. After filtration of the reaction mixture to remove the catalyst, the filtrate was concentrated, and the residue was dissolved in pyridine and acetic anhydride (3:1, 4 mL) containing

a catalytic amount of DMAP. The reaction mixture was stirred at rt overnight and then diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and finally concentrated. The residue was subjected to column to chromatography give, (9 mg, 92%). $[\alpha] = -3.6$ (0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 6.17 (d, $J = 9.2$ Hz, 1H, NH), 5.97 (d, $J = 2.0$ Hz, 1H, H-l), 5.88 (dd, $J = 6.8$, 4.0 Hz, 1H, H-1′). 5.54 (d, $J = 2.0$ Hz, 1H, H-2), 4.83 (dd, $J = 8.8$, 2.4 Hz, 1H, H-6), 4.58 (dd, $J = 12.0$, 3.6 Hz, 1H, H-2′), 4.52 (ddd, $J = 9.6$, 4.8, 2.8 Hz, 1H, H-5), 3.99 (dd, $J = 12.0$, 6.8 Hz, 1H, H-2′), 3.73 (s, 3H, OMe), 2.15–2.19 (m, 2H, H-4a, H-4e), 2.11 (s, 6 H, 2 Ac), 2.08 (s, 3H, Ac), 2.07 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.04 (s, 3H, Ac); HMQC ($CDCl_3$, ^{1}H 400 MHz/^{13}C 100 MHz): 5.97/91.0 (H-1/C-2), 5.88/71.5, (H-1′/C-1′), 5.54/66.5 (H-2/C-2), 4.83/54.5 (H-6/C-6), 4.58/62.5 (H-2′/C-2′), 4.52/68.5 (H-5/C-5), 3.99/62.5 (H-2′/C-2′), 3.73/52.5 (OMe), 2.17/32.0 (H-4/C-4); HR FAB MS (m/z): calc. for $C_{22}H_{32}NO_{14}$ ($M + H^+$) 534.1823, found 534.1830.

ACKNOWLEDGMENT

This work is supported by research grants from the National Science Foundation (CHE-0407144 and CHE-0715275). Z.G. thanks Professor Philip Garner for helpful and stimulating suggestions and discussion about this project.

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