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Asymmetric synthesis of methyl 6-deoxy-3-*O*-methyl-α-L-mannopyranoside from a non-carbohydrate precursor

Wenting Du and Yongzhou Hu*

ZJU-ENS Joint Laboratory of Medicinal Chemistry, School of Pharmaceutical Sciences, Zhejiang University, Hubin campus, Hangzhou 310031, China

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Abstract—A novel method is reported for preparing methyl 6-deoxy-3-*O*-methyl-α-L-mannopyranoside (**1**) by asymmetric synthesis, using 2-acetylfuran (**2**), a non-chiral simple molecule, as the starting material and achieving high yields via (*S*)-1-(2-furyl)ethanol and (*S*)-1-(2,5-dihydro-2,5-dimethoxy-2-furyl)ethanol.

Keywords: Methyl 6-deoxy-3-*O*-methyl-α-L-mannopyranoside; 6-Deoxy-L-mannose; L-Rhamnose; (*S*)-1-(2-Furyl)ethanol; 2-Acetylfuran

1. Introduction

6-Deoxy-L-mannose (L-rhamnose) derivatives occur naturally in complex carbohydrates from many organisms: in polysaccharides of the cell wall of prokaryotes,[1] and as building blocks of many natural products. Steroidal glycoalkaloids isolated from many *Solanum* species have 6-deoxy-L-mannose as the sugar subunit.[2] 6-Deoxy-L-mannose is found in lepidimoide, isolated from the exudate of germinated cress (*Lepidium sativum* L.) seeds and serves as a potent novel allelopathic substance that promotes the shoot growth of different plant species.[3,4] Neuroprotective phenylpropanoid esters of 6-deoxy-L-mannoses isolated from roots of *Scrophularia buergeriana* may exert significant protective effects against glutamate-induced neurode generation in primary cultures of cortical neurons.[5] Methyl 6-deoxy-3-*O*-methyl-α-L-mannopyranoside (**1**), is a subunit of the antitumor antibiotic calicheamicin γ_1^I.[6,7] Various methods for synthesis of 6-deoxy-L-mannose have been developed,[7–9] but all have started with preformed sugars. For example, Halcomb et al. reported the synthesis of dimethylsilyl-3-*O*-methyl-α-L-mannopyranose from a preformed sugar, 3,4-di-*O*-acetyl-6-deoxy-L-glucal.[7] Herein we report a method for preparing methyl 6-deoxy-3-*O*-methyl-α-L-mannopyranoside (**1**) by asymmetric synthesis, using 2-acetylfuran (**2**), a nonchiral simple molecule, as the starting material, and most of the steps achieved high yields.

2. Results and discussion

The synthetic route for 6-deoxy-3-*O*-methyl-α-L-mannopyranoside (**1**) is depicted in Scheme 1. Asymmetric-transfer hydrogenation of 2-acetylfuran (**2**) under previously described conditions[10] gave (*S*)-1-(2-furyl)-ethanol (**3**). The (*S*)-furan alcohol **3** was oxidized to (*S*)-1-(2,5-dihydro-2,5-dimethoxy-2-furyl)ethanol (**4**) by use of bromine in methanol. Treatment of **4** with formic acid under strictly anhydrous conditions gave a mixture of the desired pyranosidulose **5** (61%) and its β anomer **6** (20%), which could be separated by flash chromatography. Both could be used in the synthesis of target compound **1**.

Reduction of ketone **5** with lithium aluminium hydride or sodium borohydride proceeded with the desired stereochemical result, giving **7** in high yield

* Corresponding author. Fax: +86 571 87217412; e-mail: huyz@zjuem.zju.edu.cn

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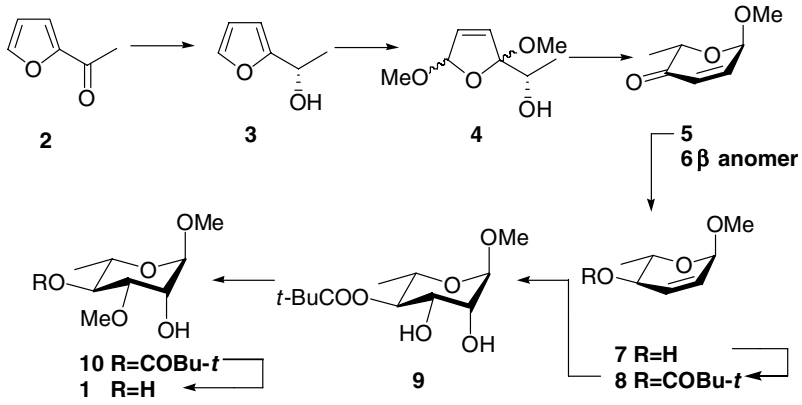
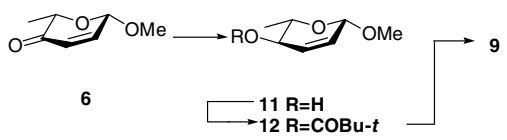


Scheme 1.

(94%). The stereochemistry at OH-4 was determined to be the desired orientation on the basis of the H-4, H-5 coupling constant ($J_{4,5}$ 8.6 Hz). At this point, the optical purity of compound **7** was confirmed by ^{19}F NMR comparison of its Mosher ester with the corresponding material made from racemic **3**. The 4-OH group of allylic alcohol **7** was protected by *t*-BuCOCl to give the pivaloyl ester **8** in 93% yield, and dihydroxylation of **8** with OsO_4, according to Halcomb's method, produced diol **9** as the sole product,[7] which could be selectively and efficiently methylated (Bu_2SnO, MeI) at OH-3 (**9**→**10**, 95%).[11] Finally, mild basic hydrolysis of **10** gave the target compound **1**. The properties of compound **1** have been described.[12]

The ring-closure step from **4** afforded the β anomer **6** as a byproduct, but its stereochemistry could be adjusted (Scheme 2). Reduction of ketone **6** with sodium borohydride in THF afforded **11**, and then pivaloylation of **11** gave **12** as the major product. This was subjected without purification, to conditions for acetal exchange with methanol in the presence of camphorsulfonic acid (CSA), so as to form mainly the α-glycal. Finally, dihydroxylation with *N*-methylmorpholine oxide (NMO) and OsO_4 gave pure **9** in 75% overall yield from **12**.

In summary, we have developed a novel method to prepare methyl 6-deoxy-3-*O*-methyl-α-L-mannopyranoside, an important building block of calicheamicin γ_1^I; starting not from a preformed sugar but from a nonchiral simple compound. This method also offers additional possibilities for incorporating isotopic labels.



Scheme 2.

3. Experimental

3.1. General methods

Melting points were determined on a Kofler block apparatus. Optical rotations were measured at 25 °C with a Perkin–Elmer 241/MS polarimeter at the sodium D line. FTIR spectra were obtained for casts made by depositing the compound from solution on a KBr plate. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DMX spectrometer at 400 or 300 MHz using Me_4Si as the internal standard. Chemical shifts are expressed in δ (ppm). Mass spectra were recorded with an AEI Model MS-50 mass spectrometer.

3.2. (*S*)-1-(2-Furyl) ethanol (3)

A mixture of $[RuCl_2\ (\eta^6\text{-mesitylene})]_2$ (23 mg, 0.04 mmol), (1*S*,2*S*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine (29 mg, 0.08 mmol) and Et_3N (22 μL, 0.16 mmol) in 2-propanol (0.8 mL) was stirred and heated at 80 °C for 1 h. The mixture was cooled to room temperature, and evaporation of the solvent gave the crude Ru(II) complex, which could be used in the next step without further purification.

2-Acetylfuran (1.15 g, 10.44 mmol) was added to a stirred mixture of the foregoing Ru(II) complex in an anhydrous mixture of formic acid (3.8 mL) and Et_3N (1.5 mL), and stirring was continued at room temperature for 42 h. The mixture was cooled to 0 °C, made neutralized with saturated aq $NaHCO_3$, extracted with ether (2 × 20 mL), and the extract washed with brine (10 mL). The combined organic layer was dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (silica gel, 1:3 EtOAc–hexane) to afford **3** (1.00 g, 85%, ee = 99%) as an analytically pure oil; $[\alpha]_D^{25}$ −23.42 (*c* 1.08, EtOH); FTIR (CH_2Cl_2 cast): 3355, 2980, 1149, 1068, 1009, 737 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.54 (d, 3H, *J* 6.5 Hz), 1.98 (br, 1H), 4.88 (q, 1H, *J* 6.5 Hz), 6.23 (d, 1H, *J* 3.2 Hz), 6.33 (dd,

1H, *J* 3.0, 1.9 Hz), 7.37 (d, 1H, *J* 1.3 Hz); ^{13}C NMR ($CDCl_3$): δ 21.13 (q′), 63.36 (d′), 104.96 (d′), 110.00 (d′), 141.67 (d′), 157.65 (s′).

3.3. (*S*)-1-(2,5-Dihydro-2,5-dimethoxy-2-furyl)ethanol (4)

A solution of **3** (1.52 g, 13.56 mmol) in a mixture of MeOH (5.4 mL) and ether (3.8 mL) was stirred and cooled to −40 °C. Br_2 (0.718 mL, 13.98 mmol) in dry MeOH (5.4 mL) was added dropwise over 20 min. After addition, stirring was continued for an additional 10 min. The mixture was saturated with NH_3 to pH 8, allowed to warm to room temperature, diluted with ether and evaporated. The residue was purified by flash chromatography (neutral alumina, 1:4 EtOAc–hexane) to afford **4** (2.11 g, 89%) as a pure mixture of isomers; ^{1}H NMR ($CDCl_3$): δ 1.13 (m, 3H), 2.24 (br, 1H), 3.16–3.53 (m, 6H), 3.85 (m, 1H), 5.45 (dt 1H, *J* 20.0, 1.2 Hz), 5.95 (m, 1H), 6.13 (m, 1H); Exact mass *m*/*z* calcd for $C_8H_{13}O_3$ (M^+-OH): 157.08647; found: 157.08680.

3.4. Methyl 2,3,6-trideoxy-α-L-*glycero*-hex-2-enopyanosid-4-ulose (5) and methyl 2,3,6-trideoxy-β-L-*glycero*-hex-2-enopyranosid-4-ulose (6)

A solution of **4** (810 mg, 4.65 mmol) in MeOH (0.35 mL) was added dropwise over 10 min to a stirred mixture of anhydrous formic acid (3.5 mL) and MeOH (0.2 mL) at room temperature. Stirring was continued for an additional 5 min. Water (8.0 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 15 mL), and washed with saturated aq $NaHCO_3$ (10.0 mL) and brine (10.0 mL). The combined organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (silica gel, EtOAc–hexane, 2:98 to 1:20) to afford the α anomer **5** (403 mg, 61%) as an analytically pure white solid; mp 55–56 °C; $[\alpha]_D^{25}$ −14.5 (*c* 1.04, $CHCl_3$); FTIR (CH_2Cl_2 cast): 2939, 1700, 1374, 1231, 1104, 1088, 1048 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.39 (d, 3H, *J* 6.7 Hz), 3.52 (s, 3H), 4.54 (q, 1H, *J* 6.8 HZ), 5.08 (d, 1H, *J* 3.5 Hz, H-1), 6.07 (d, 1H, *J* 10.2 Hz), 6.83 (dd, 1H, *J* 10.2, 3.4 Hz); ^{13}C NMR ($CDCl_3$): δ 15.28 (q′), 56.54 (q′), 70.30 (d′), 94.22 (d′), 127.36 (d′), 143.30 (d′), 196.95 (s′).

The β anomer **6** (129 mg, 20%) was also obtained by chromatography as an analytically pure oil; $[\alpha]_D^{25}$ +41.4 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.48 (d, 3H, *J* 6.8 Hz), 3.55 (s, 3H), 4.22 (q, 1H, *J* 6.8 Hz), 5.24 (dd, 1H, *J* 2.5, 1.7 Hz, H-1), 6.13 (dd, 1H, *J* 10.3, 1.5 Hz), 6.88 (dd, 1H, *J* 10.3, 1.9 Hz).

3.5. Methyl 2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (7)

Method A. A mixture of $NaBH_4$ (24 mg, 0.63 mmol) in water (1.8 mL) was stirred and cooled to 0 °C. A solution of **5** (180 mg, 1.26 mmol) in THF (0.4 mL) was added dropwise over 5 min, and stirring was continued for an additional 5 min. The mixture was quenched with saturated aq NH_4Cl (2.0 mL), extracted with ether (3 × 10 mL) and washed with brine (5.0 mL). The combined organic layer was dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (silica gel, 1:6 EtOAc–hexane) to afford **7** (163 mg, 90%) as an analytically pure oil; $[\alpha]_D^{25}$ −105.1 (*c* 1.1, $CHCl_3$); FTIR (CH_2Cl_2 cast): 3419, 2893, 1399, 1189, 1146, 1103, 1055, 963 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (d, 3H, *J* 5.7 Hz), 1.60 (br, 1H), 3.43 (s, 3H), 3.69 (m, 1H), 3.84 (t, 1H, *J* 8.6 Hz, H-4), 4.83 (d, 1H, *J* 1.5 Hz, H-1), 5.75 (dq, 1H, *J* 10.2, 2.5 Hz), 5.93 (dd, 1H, *J* 10.2, 0.7 Hz); ^{13}C NMR ($CDCl_3$): δ 17.97 (q′), 55.62 (q′), 68.00 (d′), 69.64 (d′), 95.35 (d′), 126.43 (d′), 133.67 (d′); Exact mass *m*/*z* calcd for $C_7H_{11}O_2$ (M^+-OH): 127.075895; found: 127.07577.

Method B. A mixture of **5** (153 mg, 1.08 mmol) in ether (6.0 mL) was stirred and cooled to −50 °C. Lithium aluminium hydride (41 mg, 1.08 mmol) was added and stirring was continued for 45 min at this temperature. Potassium fluoride (100 mg) and water (0.1 mL) were then added and the mixture was allowed to warm to room temperature. The mixture was filtered over Celite (0.5 × 2 cm), and the pad was washed with ether. The filtrate was concentrated under reduced pressure and purified by flash chromatography (silica gel, 1:6 EtOAc–hexane) to afford **7** (147 mg, 94%) as an analytically pure oil.

3.6. Methyl 4-*O*-pivaloyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (8)

A solution of **7** (130 mg, 0.90 mmol), pyridine (0.29 mL, 3.61 mmol) and DMAP (33.0 mg, 0.27 mmol) in CH_2Cl_2 (2.5 mL) was stirred and cooled to 0 °C. *t*-BuCOCl (0.22 mL, 1.80 mmol) was added dropwise. After the addition, the mixture was allowed to warm to room temperature and stirring was continued overnight (~12 h). The mixture was quenched with saturated aq $NaHCO_3$ (1.0 mL), extracted with ether (15 mL × 2) and washed with brine (5.0 mL). The combined organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography (silica gel, 2:98 EtOAc–hexane) to afford **8** (192 mg, 93%) as an analytically pure oil; $[\alpha]_D^{25}$ −167.4 (*c* 1.1, $CHCl_3$); FTIR (CH_2Cl_2 cast): 2978, 2934, 1733, 1398, 1275, 1156, 1082, 1057, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.19 (s, 9H), 1.21 (d, 3H, *J* 6.3 Hz), 3.44 (s, 3H), 3.57 (dq, 1H, *J* 9.2, 6.3 Hz), 4.86 (d, 1H, *J* 1.5 Hz, H-1), 5.04 (ddd, 1H, *J* 9.2, 1.1, 1.1 Hz, H-4), 5.76–5.84 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 17.87 (q′), 26.98 (q′), 38.74 (s′), 55.67 (q′), 64.79 (d′), 70.46 (d′), 95.42 (d′), 127.42 (d′), 129.97 (d′), 177.83 (s′); Exact mass *m*/*z* calcd $C_{11}H_{17}O_3$ (M^+-OMe): 197.117755; found: 197.117795.

3.7. Methyl 6-deoxy-4-*O*-pivaloyl-α-L-mannopyranoside (9)

Osmium tetraoxide (2.5% w/v in *t*-BuOH, 150 μL, 0.015 mmol) was added to a stirred mixture of **8** (171 mg, 0.75 mmol) and NMO (97 mg, 0.83 mmol) in 9:1 acetone–water (1.7 mL) at room temperature. Stirring was continued for 22 h, and the mixture was quenched with 10% aq $NaHSO_3$ (1.0 mL), extracted with EtOAc (3 × 10 mL), and washed with 10% aq $NaHSO_3$ (2.0 mL) and brine (5.0 mL). The combined organic layer was dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (silica gel, 2:3 EtOAc–hexane) to afford **9** (191 mg, 97%) as an analytically pure white solid; mp 81–83 °C; $[\alpha]_D^{25}$ −90.2 (*c* 1.07, $CHCl_3$); FTIR (CH_2Cl_2 cast): 3449, 2978, 2936, 1734, 1187, 1158, 1101, 1067, 1039, 1013, 973 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.18 (d, 3H, *J* 6.3 Hz), 1.2 (s, 9H), 3.15 (br, 2H), 3.36 (s, 3H), 3.76 (dq, 1H, *J* 9.2, 6.2 Hz), 3.81 (dd, 1H, *J* 9.6, 3.5 Hz), 3.91 (dd, 1H, *J* 3.5, 1.6 Hz), 4.69 (d, 1H, *J* 1.5 Hz, H-1), 4.77 (t, 1H, *J* 9.6 Hz); ^{13}C NMR ($CDCl_3$): δ 17.43 (q′), 27.08 (q′), 39.00 (s′), 55.07 (q′), 65.46 (d′), 70.44 (d′), 70.87 (d′), 75.32 (d′), 100.53 (d′), 179.74 (s′); Exact mass *m*/*z* calcd $C_{11}H_{19}O_5$ (M^+−OMe): 231.12325; found: 231.12353.

3.8. Methyl 6-deoxy-3-*O*-methyl-4-*O*-pivaloyl-α-L-mannopyranoside (10)

A mixture of **9** (181 mg, 0.69 mmol) and Bu_2SnO (206 mg, 0.83 mmol) in a mixture of MeOH (3.0 mL) and benzene (0.3 mL) was refluxed until all of the Bu_2SnO had dissolved and the solution became clear. The mixture was diluted with benzene (2.5 mL) and concentrated under reduced pressure. Methyl iodide (1.5 mL) was added to the residue, and the mixture was stirred for 17 h at 45 °C. The mixture was concentrated and the residue was diluted with saturated aq NH_4Cl (3.0 mL). The mixture was stirred at room temperature for 30 min, extracted with EtOAc (3 × 10 mL) and the extract washed with brine (10.0 mL). The combined organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (silica gel, 1:4 EtOAc–hexane) to afford **10** (181 mg, 95%) as an analytically pure white solid; mp 80–81 °C; $[\alpha]_D^{25}$ −66.6 (*c* 1.1, $CHCl_3$); FTIR (CH_2Cl_2 cast): 3467, 2979, 2935, 1736, 1280, 1155, 1135, 1117, 1087, 1059 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.17 (d, 3H, *J* 6.3 Hz), 1.22 (s, 9H), 2.46 (br, 1H), 3.38 (s, 3H), 3.39 (s, 3H), 3.48 (dd, 1H, *J* 9.5, 3.4 Hz), 3.76 (dq, 1H, *J* 9.2, 6.3 Hz), 4.06 (dd, 1H, *J* 2.5, 1.7 Hz), 4.76 (d, 1H, *J* 1.5 Hz, H-1), 4.98 (t, 1H, *J* 9.7 Hz); ^{13}C NMR ($CDCl_3$): δ 17.20 (q′), 27.00 (q′), 38.74 (s′), 54.93 (q′), 57.44 (q′), 65.88 (d′), 67.37 (d′), 71.86 (d′), 79.12 (d′), 100.70 (d′), 177.49 (s′); Exact mass *m*/*z* calcd $C_{12}H_{21}O_5$ (M^+−Me): 245.138875; found: 245.138847.

3.9. Methyl 6-deoxy-3-*O*-methyl-α-L-mannopyranoside (1)

Lithium hydroxide monohydrate (102 mg, 2.43 mmol) was added to a stirred solution of **10** (103 mg, 0.37 mmol) in a mixture of MeOH (13.6 mL) and water (3.4 mL). The mixture was stirred at room temperature for 5 days, then acidified with 10:1 MeOH–AcOH to pH ∼ 5–6, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 2:1 EtOAc–hexane) to afford recovered **10** (11 mg) and **1** (62 mg, 85%, not corrected for recovered **10**) as an analytically pure oil; $[\alpha]_D^{25}$ −65.5 (*c* 1.0, $CHCl_3$); lit.[13–15] −51.1°, −61° ($CHCl_3$), −60° ($CHCl_3$); FTIR (CH_2Cl_2 cast): 3442, 2934, 2908, 113, 1118, 1078, 1057, 982 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.32 (d, 3H, *J* 6.2 Hz), 2.31 (br s, 2H), 3.37 (dd, 1H, *J* 9.1, 3.3 Hz), 3.37 (s, 3H), 3.46 (s, 3H), 3.50 (t, 1H, *J* 9.3 Hz), 3.56 (dq, 1H, *J* 10.2, 6.2 Hz), 4.05 (dd, 1H, *J* 3.1, 1.6 Hz), 4.72 (d, 1H *J* 1.5 Hz, H-1); ^{13}C ($CDCl_3$) δ 17.64 (q′), 54.93 (q′), 56.97 (q′), 66.77 (d′), 67.97 (d′), 71.59 (d′), 81.35 (d′), 100.47 (d′); Exact mass *m*/*z* calcd for $C_8H_{15}O_4$ (M^+−OH): 175.097015; found: 175.097019.

3.10. Methyl 4-*O*-pivaloyl-2,3,6-trideoxy-β-L-*erythro*-hex-2-enopyranoside (12)

A solution of sodium borohydride (19 mg, 0.50 mmol) in water (1.4 mL) was stirred and cooled to 0 °C. A solution of **6** (143 mg, 1.00 mmol) in THF (0.3 mL) was added dropwise, and stirring was continued for 5 min. The mixture was quenched with saturated aq NH_4Cl (1.0 mL), extracted with ether (3 × 10 mL) and washed with brine (2.0 mL). The combined organic layer was dried (Na_2SO_4), and evaporated. The resulting crude alcohol was used directly in the next step.

A solution of the foregoing crude alcohol **11**, pyridine (0.3 mL, 3.61 mmol) and DMAP (30 mg, 0.26 mmol) in CH_2Cl_2 (2.5 mL) was stirred and cooled to 0 °C and *t*-BuCOCl (0.22 mL, 1.80 mmol) was added dropwise. After the addition, the mixture was allowed to warm to room temperature and stirring was continued overnight (∼12 h). The mixture was quenched with saturated aq $NaHCO_3$ (2.0 mL), extracted with ether (2 × 15 mL) and washed with brine (5.0 mL). The combined organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (silica gel, 2:98 EtOAc–hexane) to afford **12** (152 mg, 66%) as an analytically pure oil and the C-4 epimer (50.7 mg, 22%), also as an analytically pure oil; Compound **12** had: $[\alpha]_D^{25}$ −117.9 (*c* 1.05, $CHCl_3$); FTIR (CH_2Cl_2 cast): 2977, 2935, 1728, 1396, 1281, 1152, 1112, 1098, 1062, 1038 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.20 (s, 9H), 1.29 (d, 3H, *J* 6.4 Hz), 3.46 (s, 3H), 3.81 (q, 1H, *J* 6.6 Hz), 5.04 (dq, 1H, *J* 6.9, 2.1 Hz, H-4), 5.08 (d, 1H, *J* 1.5 Hz, H-1), 5.82–5.87 (m, 2H); ^{13}C NMR ($CDCl_3$,):

δ 18.42 (q′), 38.77 (s′), 54.90 (q′), 69.57 (d′), 71.40 (d′), 97.28 (d′), 128.78 (d′), 129.96 (d′), 177.93 (s′); Exact mass m/z calcd $C_{11}H_{17}O_3$ (M^+-OMe): 197.117755; found: 197.117795.

3.11. Methyl 6-deoxy-4-*O*-pivaloyl-α-L-mannopyranoside (9)

Camphorsulfonic acid (15 mg, 0.06 mmol) was added to a stirred solution of **12** (110 mg, 0.48 mmol) in MeOH (4.0 mL), and stirring was continued at room temperature for 4 h. The solution was concentrated, and saturated aq $NaHSO_3$ (1.0 mL) was added. The mixture was extracted with ether (2×15 mL), and the extract washed with water (4.0 mL) and brine (4.0 mL). The combined organic layer was dried (Na_2SO_4) and evaporated. The crude material was used immediately in the next step.

N-Methylmorpholine oxide (57 mg, 0.48 mmol) and OsO_4 (2.5% w/v in *t*-BuOH, 97 μL, 0.0097 mmol) were added to a stirred solution of the foregoing crude material in a mixture of acetone (0.9 mL) and water (0.1 mL), and stirring was continued for 20 h. The mixture was quenched with 10% aq $NaHSO_3$ (2.0 mL) and washed with brine (5.0 mL). The combined organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (silica gel, 2:3 EtOAc–hexane) to afford **9** as a white solid (95 mg, 75%).

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