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Note

An improved synthesis of a key intermediate for (+)-biotin from D-mannose

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Abstract—An efficient and reproducible process for the synthesis of methyl 2,3,4,5-tetradeoxy-7,8-*O*-isopropylidene-D-*arabino*-nanonate (**2**), a key intermediate in the total synthesis of (+)-biotin (**1**), starting from readily available D-mannose is described. The crucial part of this synthesis was the development of a practical route to a novel *O*-benzyl protected unsaturated ester methyl (benzyl 5,6,7,8-tetradeoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-nona-5,7-dienofuranosid) uronate (**7**), allowing the one-step preparation of hydroxy ester methyl 5,6,7,8-tetradeoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-nanofuranuronate (**8**) by the catalytic debenzylation and hydrogenation over palladium on carbon catalyst. This procedure requires no chromatographic purification, which makes it ideal for synthetic preparation on an industrial scale.

Keywords: (+)-Biotin; Methyl 2,3,4,5-tetradeoxy-7,8-*O*-isopropylidene-D-*arabino*-nanonate; D-Mannose; Horner–Emmons olefination; Chiral pool

Carbohydrates are especially useful starting materials for the total synthesis of chiral natural products because they provide an almost unlimited combinatorial source of stereocenters, and allow facile introduction of nitrogen after activation–substitution of hydroxyl groups.[1] A large effort has been devoted to the development of elegant methods for the total synthesis of (+)-biotin (**1**) (Fig. 1), a water-soluble vitamin, based on a carbohydrate approach to generate the (+)-biotin skeleton with excellent stereocontrol. Of the various chiron strategies described toward this vitamin synthesis,[2] the synthetic methods utilizing methyl 2,3,4,5-tetradeoxy-7,8-*O*-isopropylidene-D-*arabino*-nanonate (**2**) as a key intermediate seems to be one of the most expedient approach to **1** to date.

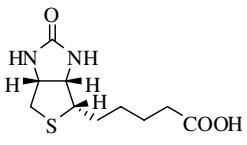

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Figure 1.

Some synthetic methods for **2**, using carbohydrates including D-mannose,[3] D-arabinose,[4] and D-glucose,[5] have been developed. Among them, one of the very convenient approaches which attracted our attention is the D-mannose process developed by Ohrui and Emoto[3] However, one of the serious limitations in this procedure is the formation of considerable amount of a side product, triphenylphosphine oxide, on use of Wittig reaction as a key step toward introduction of the desired C_4 side chain into 1-*O*-benzoyl-2,3-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanose, making it very difficult for large-scale production.

As a part of our continuing program to explore a practical total synthesis of **1**,[6] herein, we disclose an improved and scalable method for the preparation of **2** starting from commercially available D-mannose.

Our strategy for the preparation of **2** is depicted in Scheme 1. 2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose (**3**) was readily prepared in 88% yield by treatment

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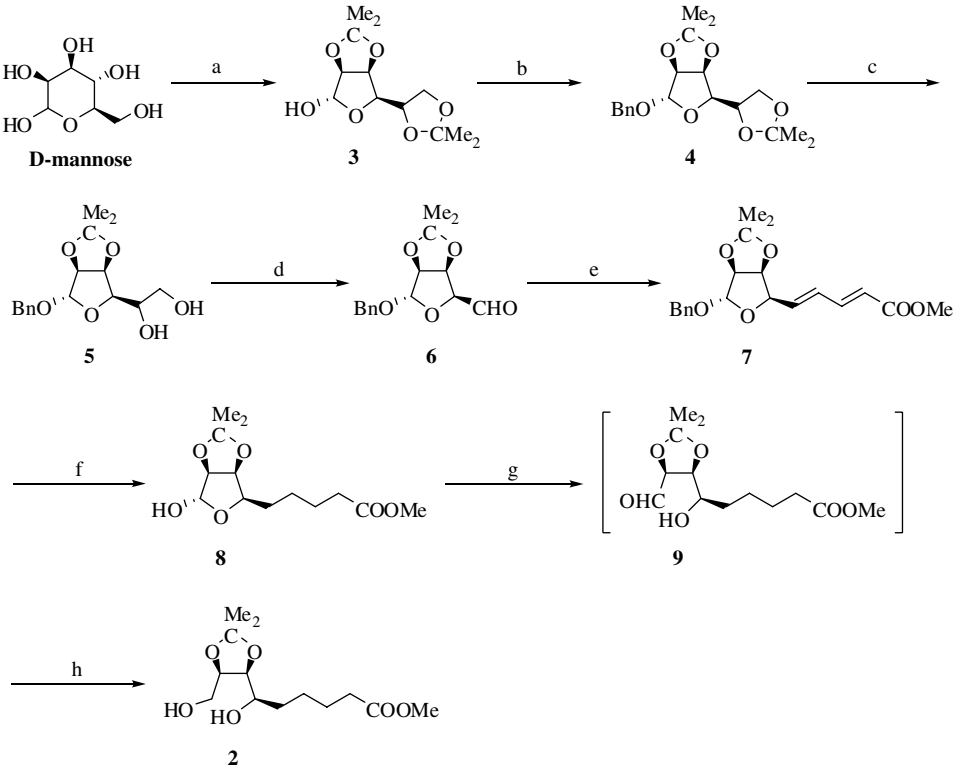

Scheme 1. Reagents and conditions: (a) Acetone, $FeCl_3$, rt, 4 h, 88%; (b) KOH, BnBr, PEG-600, THF, rt, overnight, 90.3%; (c) 70%HOAc, rt, 18 h, 97.5%; (d) silica gel-supported $NaIO_4$, CH_2Cl_2, 0 °C, 1.5 h, 99.5%; (e) $(EtO)_2POCHCH{=}CHCOOMe$, MS 4 Å, $LiOH{\cdot}H_2O$, THF, reflux, 12 h, 80%; (f) 5% Pd/C, EtOH/HOAc, 1 atm H_2, rt, 18 h, 90%; (g) NaOMe, MeOH, 0 °C, 15 min; (h) $NaBH_4$, MeOH, rt, 2 h, 96.4% (two steps from **8**).

of D-mannose with an excess acetone in the presence of a catalytic amount of anhydrous $FeCl_3$ according to the procedure described by Singh et al.[7] The phase transfer-catalyzed O-benzylation of hydroxyl group at C-1 in **3** with benzyl bromide and powdered KOH in THF using a catalytic amount of polyethylene glycols 600 (PEG-600) was carried out to provide a crystalline benzyl ether **4** in 90.3% yield. Hydrolytic removal of the 5,6-*O*-isopropylidene group was regioselectively achieved with 70% aqueous acetic acid at 25 °C for 18 h to afford the desired diol **5** as a single product in almost quantitative yield. It is worth mentioning that several attempts to this deprotection at elevated reaction temperature (50–70 °C) failed to give any product, and decreasing the concentration of acetic acid to 40% lowered the yield of **5** considerably. Shing's protocol[8] using Silica Gel-supported sodium metaperiodate in CH_2Cl_2 was eventually found to effect the oxidative cleavage of the glycol in **5** to give the expected aldehyde **6** in quantitative yield. The Horner–Emmons olefination of **6** in anhydrous THF with diethyl 3-methoxycarbonyl-2-propenylidine using MS 4 Å as catalyst in the presence of $LiOH{\cdot}H_2O$ under reflux for 12 h worked well to give α,β-unsaturated esters **7** as an inseparable mixture of several *E*- and *Z*-isomers. One-pot catalytic debenzylation and hydrogenation of the resulting **7** with 5% Pd/C in mixed solvents of ethanol/glacial acetic acid (1:1) at room temperature led to the corresponding saturated hemiacetal **8** in 90% isolated yield. Treatment of **8** with 50% sodium methoxide in methanol at 0 °C, followed by the reduction of the resulting aldehyde **9** with sodium borohydride at room temperature for 2 h, furnished methyl 2,3,4,5-tetradeoxy-7,8-*O*-isopropylidene-D-*arabino*-nanonate (**2**) in 96.4% yield (two steps from **8**).

In summary, an efficient and convenient synthesis of methyl 2,3,4,5-tetradeoxy-7,8-*O*-isopropylidene-D-*arabino*-nanonate (**2**) amenable to scale-up has been accomplished in an overall yield of 53% starting form D-mannose by utilizing cheap and readily available reagents and by applying simple experimental procedures. Further developments of (+)-biotin (**1**) using this key intermediate are in process and will be reported in due course.

1. Experimental

1.1. General methods

Melting points were determined on a WRS-1 digital melting point apparatus and uncorrected. IR spectra were recorded on a JASCO FT/IR-4200 spectrometer. NMR spectra were taken on a Bruker AVANCEII 400 MHz spectrometer using TMS as an internal stan-

dard. Mass spectra were measured on Agilent Technologies 6890 N. Optical rotations were recorded with a JASCO P-1020 Polarimeter at 25 °C. All chemicals and solvents were of reagent grade and were used without further purification, silica gel-supported $NaIO_4$ reagent was prepared according to the method of Shing et al.[8]

1.2. Benzyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside (4)

To a vigorously stirred suspension of powdered KOH (10.0 g, 0.18 mol), PEG-600 (0.2 g) and **3** (26 g, 0.1 mol) in THF (200 mL) was added benzyl bromide (17.1 g, 0.1 mol) in one portion. The reaction mixture was stirred overnight at room temperature. CH_2Cl_2 (200 mL) and water (200 mL) were added into the reaction mixture, the organic phase was separated, washed with water (150 mL), dried ($MgSO_4$) and concentrated under diminished pressure. The crude product a yellowish syrup became solid on storing in the cold. Recrystallization of the crude product from petroleum ether (60–90 °C) afford pure **4** (31.6 g, 90.3%) as a white solid. Mp 54.9–55.6 °C, lit.:[9] mp 55–56 °C; $[\alpha]_D^{25}$ +74.8 (*c* 1.0, acetone), lit.:[9] $[\alpha]_D^{25}$ +76.5 (*c* 1.0, acetone); IR(KBr): *v* 2988, 2933, 1380, 1086, 737, 517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H); 1.38 (s, 3H), 1.45 (s, 3H), 1.46 (s, 3H), 3.97 (dd, 1H, *J* 6.4, 8.8 Hz), 3.98 (dd, 1H, *J* 3.6, 6.8 Hz), 4.10 (dd, 1H, *J* 5.5 Hz, 1.0 Hz), 4.40 (m, 1H), 4.49 (d, 1H, *J* 12 Hz), 4.64 (d, 1H, *J* 12 Hz), 4.66 (d, 1H, *J* 6.0 Hz), 4.79 (dd, 1H, *J* 3.6, 6.0 Hz), 5.07 (s, 1H), 7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3, 128.4, 128.0, 127.8, 112.5, 109.2, 105.7, 85.1, 80.5, 79.6, 73.1, 69.1, 66.9, 26.8, 25.9, 25.2, 24.5. GC–MS: (*m*/*z*, %): 335 $(M-CH_3)^+$, 229, 214, 91 (100).

1.3. Benzyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (5)

A soln of **4** (21 g, 12 mmol), glacial AcOH (91 mL), and water (39 mL) was stirred for 18 h at room temperature, and concentrated under diminished pressure. The residue was dissolved in EtOAc (200 mL), washed sequentially with satd aq $NaHCO_3$ (2 × 50 mL), water (2 × 20 mL), and brine (2 × 30 mL), dried ($MgSO_4$), and the solvent was concentrated under diminished pressure to a colorless oil which was crystallized upon cooling to afford **5** (18.1 g, 97.5%) as a white solid. Mp 59.4–61.0 °C, lit.:[9] mp 60–61 °C; $[\alpha]_D^{25}$ +88.6 (*c* 1.0, acetone), lit.:[9] $[\alpha]_D^{25}$ +90 (*c*1.0, acetone); IR(KBr): *v* 3520, 3364, 3063, 2934, 1736, 1454, 1381, 1207, 1085, 893, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.47 (s, 3H), 2.01 (s, 1H), 2.76 (s, 1H), 3.66 (m, 1H), 3.82 (m, 1H), 3.96 (dd, 1H, *J* 3.6, 8.0 Hz), 4.02 (m, 1H), 4.50 (d, 1H, *J* 12 Hz), 4.62 (d, 1H, *J* 12 Hz), 4.66 (d, 1H, *J* 6.0 Hz), 4.86 (dd, 2H, *J* 3.6, 6.0 Hz), 5.12 (s, 1H), 7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4, 128.5, 128.0, 127.9, 112.7, 105.6, 84.9, 80.2, 79.4, 70.5, 69.3, 64.5, 25.9, 24.6. GC–MS: (*m*/*z*, %): 295 $(M-CH_3)^+$, 246, 222, 91 (100).

1.4. Benzyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside (6)

To a vigorously stirred suspension of silica gel-supported $NaIO_4$ reagent (110 g) was added a soln of **5** (17.05 g, 55 mmol) in CH_2Cl_2 (700 mL) at room temperature. The reaction mixture was stirred at 0 °C for 1.5 h, and filtered. The residue was washed twice with MeOH (400 mL). The combined filtrates were concentrated under diminished pressure and allowed to stand at 5 °C overnight to give **6** (15.2 g, 99.5%) as a white solid and was pure enough to be used immediately for the next step. Mp 81.4–82.7 °C, lit.:[10] mp 81–82 °C; $[\alpha]_D^{25}$ +28 (*c* 1.0, acetone); IR(KBr): *v* 2935, 1750, 1377, 1211, 1092, 864, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (s, 3H), 1.43 (s, 3H), 4.43 (d, 1H, *J* 4.8 Hz), 4.52 (d, 1H, *J* 11.6 Hz), 4.69 (d, 1H, *J* 6.0 Hz), 4.70 (d, 1H, *J* 11.6 Hz), 5.09 (dd, 1H, *J* 4.8, 6.0 Hz), 5.31 (s, 1H), 7.31 (m, 5H), 9.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 136.8, 128.5, 128.0, 127.9, 113.9, 105.9, 84.7, 84.1, 80.9, 69.3, 25.8, 24.5. GC–MS: (*m*/*z*, %): 295 $(M-CH_3)^+$, 246, 222, 91 (100).

1.5. Methyl (benzyl 5,6,7,8-tetradeoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-nona-5,7-dienofuranosid) uronate (7)

Activated MS 4 Å (25 g, beads, 4–8 mesh) and $LiOH\cdot H_2O$ (2.21 g, 52.5 mmol) were added to a vigorously stirred soln of **6** (13.9 g, 50 mmol) and methyl diethyl-4-phosphonocrotonate (12.4 g, 52.5 mmol) in THF (500 mL). The reaction mixture was heated under reflux for 12 h, and filtered. The filtrate was evaporated under diminished pressure. The residual oil was dissolved in EtOAc (200 mL), washed with water (3 × 80 mL), dried ($MgSO_4$). The solvent was concentrated under diminished pressure to a dark brown syrup, which was crystallized from aq CH_3OH to afford **7** (14.4 g, 80%) as a yellow solid. Mp 41.7–43.4 °C, $[\alpha]_D^{25}$ +9.5 (*c* 1.0, acetone); IR(KBr): *v* 2990, 2918, 1719, 1619, 1497, 1376, 1232, 860, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.44 (s, 3H), 3.75 (s, 3H), 4.50 (d, 1H, *J* 12 Hz), 4.56 (dd, 1H, *J* 3.6, 6.8 Hz), 4.68 (d, 1H, *J* 5.6 Hz), 4.69 (d, 1H, *J* 12 Hz), 4.72 (dd, 1H, *J* 3.6, 5.6 Hz), 5.13 (s, 1H), 5.93 (d, 1H, *J* 15.2 Hz), 6.21 (dd, 1H, *J* 6.8. 15.2 Hz), 6.46 (dd, 1H, *J* 11.2, 15.2 Hz), 7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 143.7, 135.6, 137.2, 131.2, 128.4, 127.8, 127.6, 122.0, 112.7, 105.3, 85.3, 81.3, 80.3, 69.0, 51.5, 26.0, 24.8. GC–MS: (*m*/*z*, %): 360 (M^+), 246, 222, 91 (100).

1.6. Methyl 5,6,7,8-tetradeoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-nanofuranuronate (8)

Compound **7** (13 g, 36.1 mmol) dissolved in a mixture of EtOH (75 mL) and glacial AcOH (75 mL) was hydrogenated under 1 atm of H_2 in the presence of 5% Pd/C (2.6 g). After stirring at room temperature for 24 h, the reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under diminished pressure. The residual syrup was solidified upon on storing in the cold storage to afford **8** (8.9 g, 90%) as a pale-yellow solid. Mp 50.4–52.0 °C, $[\alpha]_D^{25}$ +17.6 (*c* 1.0, acetone); IR(KBr): *v* 3467, 2952, 1720, 1381, 1244, 1202, 1066, 875 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.45 (s, 3H), 1.368–1.767 (m, 6H), 2.34 (t, 2H, *J* 7.6 Hz), 3.21 (s, 1H), 3.67 (s, 3H), 4.12 (dt, 1H, *J* 3.6, 6.8 Hz), 4.58 (d, 1H, *J* 6.0 Hz), 4.62 (dd, 1H, *J* 3.6, 6.0 Hz), 5.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 112.2, 100.8, 85.7, 80.4, 80.0, 51.4, 33.9, 28.0, 26.9, 26.0, 25.7, 25.6. GC–MS: (*m*/*z*, %): 259 $(M-CH_3)^+$, 227, 213, 59 (100).

1.7. Methyl 2,3,4,5-tetradeoxy-7,8-*O*-isopropylidene-D-*arabino*-nanonate (2)

A soln of **8** (8.22 g, 30 mmol) in anhyd MeOH (100 mL) and 50% sodium methoxide (0.54 g, 5 mmol) was stirred at 0 °C for 15 min, sodium borohydride (2.28 g, 60 mmol) was added into the resulting aldehyde **9**, stirring was continued at room temperature for an additional 2 h, the excess sodium borohydride was carefully quenched by the addition of glacial AcOH (3 mol) after cooling to −40 °C, and extracted CH_2Cl_2 (3×60 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (2×50 mL), water (2×35 mL), and brine (2×30 mL) and dried ($MgSO_4$). The solvent was concentrated under diminished pressure to afford **2** as a pale yellow oil (7.25 g, 96.4%); $[\alpha]_D^{25}$ +13.8 (*c* 1.92, $CHCl_3$), lit.:[3] $[\alpha]_D^{25}$ +12.3 (*c* 2.0, $CHCl_3$); IR(film): *v* 3431, 2939, 1735, 1642, 1439, 1372, 1217, 1044, 856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.50 (s, 3H), 1.401–1.747 (m, 6H), 2.34 (t, 2H, *J* 7.6 Hz), 2.69 (s, 2H), 3.67 (s, 1H), 3.73 (m, 1H), 3.78 (t, 2H, *J* 5.2 Hz), 4.05 (dd, 1H, *J* 3.2, 6.8 Hz), 4.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 108.2, 79.2, 77.3, 68.8, 61.0, 51.3, 34.6, 33.4, 27.2, 25.3, 24.9, 24.7. GC–MS: (*m*/*z*, %): 261 $(M-CH_3)^+$, 243, 227, 59 (100).

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