Carbohydrate Research, 134 (1984) 332–336
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

A modified synthesis of (+)-biotin from D-glucose†

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(Received March 28th, 1984; accepted for publication, May 16th, 1984)

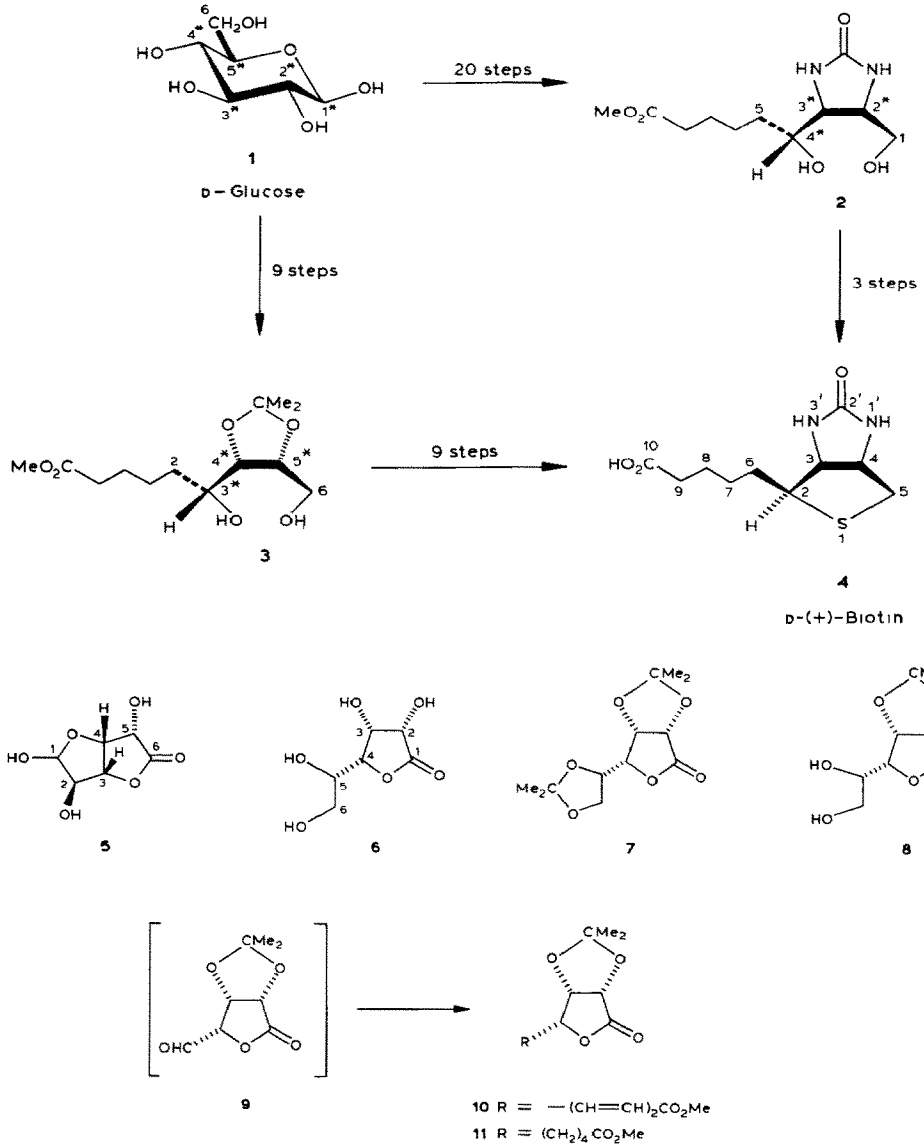
Four syntheses of (+)-biotin (**4**), using sugars as chiral substrates, have been reported[1–4]. In one of these syntheses[2], D-glucose (**1**) was converted into (+)-biotin in 23 steps where C-1/5 of D-glucose became C-5,4*,3*,2*,6 of (+)-biotin (biotin numbering) *via* the intermediate diol **2**. We now report a shorter synthesis whereby C-2/6 of D-glucose become C-6,2*,3*,4*,5 of **4** *via* the key intermediate **3**, which has also been prepared from D-mannose[1] and D-arabinose[4].

D-Glucurono-6,3-lactone[5] (**5**) was catalytically reduced to L-gulono-1,4-lactone†† (**6**) using Raney nickel[6]. Compound **6** was converted into the 2,3:5,6-di-*O*-isopropylidene derivative[7] (**7**) which was selectively hydrolysed to the 2,3-*O*-isopropylidene derivative (**8**) using methanol–hydrochloric acid. Periodate oxidation of **8** in acetone–water at 0° furnished the aldehyde **9** which, on treatment with excess of (3-methoxycarbonyl-2-propenylidene)triphenylphosphorane[8] in dichloromethane afforded the crystalline, unsaturated lactone **10** (10%). Hydrogenation[1,3] of **10** over 10% Pd-C gave a very poor yield of the desired saturated lactone **11**. However, when the borohydride-reduced palladium catalyst[9] was used at 0° and atmospheric pressure, **11** was obtained in almost quantitative yield. Borohydride reduction of **11** in methanol at 0° then gave the required intermediate diol **3** (80%) as a syrup. The ^{1}H-n.m.r. data of **3** accorded with those reported[4].

Since the yield of the lactone **10** in the Wittig reaction was poor, **3** was prepared by another route starting from **7**. Treatment of **7** with sodium borohydride in methanol at 0° gave the lactol **12** which, with benzoyl chloride in pyridine, furnished the crystalline benzoate **13** (96%). Selective hydrolysis of **13** with methanol–hydrochloric acid afforded the diol **14** (95%), periodate oxidation of which in acetone–water at 0° gave the aldehyde **15**. Application of the Wittig reaction to **15**,

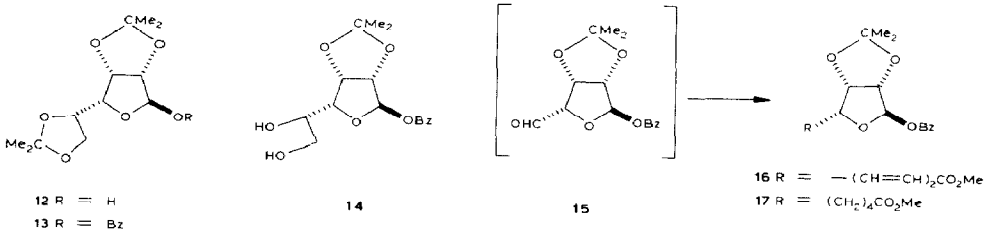
†NCL Communication No. 3505.
††L-Gulono-1,4-lactone and its mono- and di-*O*-isopropylidene derivatives had optical rotations lower than expected, possibly because of partial epimerisation at C-1 of D-glucuronolactone during the hydrogenation.

0008-6215/84/$ 03.00



using excess of (3-methoxycarbonyl-2-propenylidene)triphenylphosphorane in dichloromethane, gave the unsaturated lactol benzoate **16** (79%). Catalytic hydrogenation (borohydride-reduced palladium catalyst) of **16** then furnished the saturated lactol benzoate[1] **17** in quantitative yield.

Since the conversions **17**→**3**→**4** have been reported[1,4], this work constitutes the total synthesis of (+)-biotin (**4**) from D-glucose.



EXPERIMENTAL

All melting points are uncorrected. Optical rotations were measured with a Jasco DiP 181 digital polarimeter. I.r. spectra were recorded with a Perkin–Elmer Infrared-683 spectrophotometer with sodium chloride optics. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Varian FT-80A or WH-90 Bruker spectrometer.

Commercial D-glucurono-6,3-lactone was converted into 2,3:5,6-di-*O*-isopropylidene-L-gulono-1,4-lactone by literature procedures[6,7].

2,3-O-Isopropylidene-L-gulono-1,4-lactone (**8**). — A solution of 2,3:5,6-di-*O*-isopropylidene-L-gulono-1,4-lactone (**7**, 5.2 g) in methanol (100 mL) containing conc. hydrochloric acid (1 mL) was stirred at room temperature for 0.5 h, neutralised with conc. ammonia, and concentrated under reduced pressure. The residue was extracted with dry acetone, the extract was concentrated, and the residue was crystallised from ethyl acetate–light petroleum to give **8** (2.4 g, 48%), m.p. 143–146°, $[\alpha]_D^{26}$ +30° (*c* 2, ethanol).

Anal. Calc. for $C_9H_{14}O_6$: C, 49.54; H, 6.42. Found: C, 49.23; H, 6.58.

(2S,3S,4R)-2,3-Isopropylidenedioxy-4-[(1E,3E)-4-methoxycarbonyl-1,3-butadienyl]-4-butanolide (**10**). — To a solution of **8** (1.744 g, 8 mmol) in acetone–water (60 mL, 1:1) at 0° was added dropwise during ~5 min a solution of sodium metaperiodate (27 mL, 0.7M), and the mixture was stirred at 0° for 0.5 h. Ethylene glycol (2.5 mL) was then added and stirring continued for 0.5 h at 0°. Ethanol (150 mL) was added and the resulting solid was collected. The filtrate was concentrated to ~5 mL under reduced pressure at 25–30° and extracted with dichloromethane (5 × 20 mL). The combined extracts were dried (Na_2SO_4) and added dropwise to a solution of (3-methoxycarbonyl-2-propenylidene)triphenylphosphorane (5.77 g, 16 mmol) in dichloromethane (30 mL). The mixture was stirred for 4 h, and then concentrated under reduced pressure at room temperature. The residue was eluted from a column (75 g) of silicic acid with light petroleum–ethyl acetate (1:1) to give **10** (0.195 g, 9.28%), m.p. 137–138°, $[\alpha]_D^{25}$ +2° (*c* 1.4, chloroform); ν_{max}^{Nujol} 1790 and 1720 cm^{-1} (lactone and ester C=O, respectively). ^{1}H-N.m.r. data: δ 1.38 and 1.48 (2 s, 6 H, CMe_2), 3.74 (s, 3 H, CO_2Me), 4.82 (d, 1 H, $J_{6,7}$ 3.15, $J_{7,8}$ 0 Hz, H-7), 4.84 (s, 1 H, $J_{8,7}$ 0 Hz, H-8), 5.43 (dd, 1 H, $J_{6,7}$ 3.15, $J_{6,5}$ 8.66 Hz, H-6), 5.94 (dd, 1 H, $J_{5,6}$ 8.66, $J_{5,4}$ 11.02 Hz, H-5), 6.02 (d, 1 H, $J_{2,3}$ 15.7 Hz, H-2), 6.42 (dd, 1 H, $J_{4,3}$ 11, $J_{4,5}$ 11 Hz, H-4), and 7.48 (dd, 1 H, $J_{3,4}$ 11, $J_{3,2}$ 15.7 Hz, H-3).

Anal. Calc. for $C_{13}H_{16}O_6$: C, 58.20; H, 5.96. Found: C, 58.55; H, 5.82.

(2S,3S,4R)-2,3-Isopropylidenedioxy-4-(4-methoxycarbonylbutyl)-4-butanolide (**11**). — A solution of **10** (0.2 g) in methanol (10 mL) was hydrogenated at 1 atmosphere and 0° for 0.5 h using borohydride-reduced Pd catalyst (5 mg). The mixture was then filtered and concentrated to furnish **11** as a syrup (0.195 g), $[\alpha]_D^{25}$ +74° (*c* 1, chloroform); ν_{max}^{liquid} 1790 and 1740 cm^{-1} (lactone and ester C=O, respectively). ^{1}H-N.m.r. data: δ 1.41 and 1.48 (2 s, 6 H, CMe_2), 1.5–1.9 (m, 6 H, CH_2-3,4,5), 2.36 (t, 2 H, $COCH_2$), 3.7 (s, 3 H, CO_2Me), 4.3–4.5 (m, 1 H, H-6), and 4.68–4.86 (m, 2 H, H-7,8).

Methyl (6R,7S,8R)-6,9-dihydroxy-7,8-(isopropylidenedioxy)nonanoate (**3**). — To a solution of **11** (0.2 g) in methanol (15 mL) at 0° was added sodium borohydride (0.2 g) in portions. The mixture was stirred for 4 h at 0°, poured into cold water, and extracted with dichloromethane (5 × 20 mL). The combined extracts were washed with saturated aqueous ammonium chloride, dried, and concentrated, and the residual liquid (0.19 g) was eluted from a column of silicic acid with light petroleum–ethyl acetate (1:1) to furnish **3** (0.165 g, 81.3%), $[\alpha]_D^{26}$ +14° (*c* 1, chloroform) {lit.[1,4] $[\alpha]_D^{20}$ +12.3° (*c* 2, chloroform)}; ν_{max}^{film} 3430 (OH) and 1745 cm^{-1} (CO_2Me). ^{1}H-N.m.r. data: δ 1.3 and 1.43 (2 s, 6 H, CMe_2), 2.28 (m, 2 H, $COCH_2$), 1–1.9 (m, 6 H, CH_2-3,4,5), and 3.6 (s, 3 H, CO_2Me).

Anal. Calc. for $C_{13}H_{24}O_6$: C, 56.52; H, 8.69. Found: C, 56.28; H, 8.90.

2,3:5,6-Di-O-isopropylidene-L-gulose (**12**). — To an ice-cold solution of **7** (2.58 g) in methanol (25 mL) was added sodium borohydride (0.39 g) slowly with stirring. After 0.5 h, the solvent was removed under vacuum and the residue was crystallised from ethyl acetate–light petroleum to give **12** (2.4 g, 92%), m.p. 113–115° (lit.[10] 114–115°), $[\alpha]_D^{24}$ +51° (*c* 1, chloroform).

Anal. Calc. for $C_{12}H_{20}O_6$: C, 55.38; H, 7.69. Found: C, 55.63; H, 8.06.

1-O-Benzoyl-2,3:5,6-di-O-isopropylidene-L-gulose (**13**). — To an ice-cold mixture of pyridine (1.6 mL, 0.02 mol) and dry dichloromethane (5 mL) was added with stirring a solution of benzoyl chloride (1.8 mL, 0.015 mol) in dichloromethane (10 mL). After 5 min, a solution of **12** (2.64 g, 0.01 mol) in dichloromethane (15 mL) was added dropwise. The mixture was stirred at 0° for 4 h and then poured into ice–water, the aqueous layer was extracted with dichloromethane (2 × 20 mL), and the combined extracts and dichloromethane layer were washed with water, aqueous sodium hydrogen carbonate, and water, dried, and concentrated. Recrystallisation of the residue from ethyl acetate gave **13** (3.6 g, 96%), m.p. 127–128°, $[\alpha]_D^{25}$ +13° (*c* 1.6, chloroform).

Anal. Calc. for $C_{19}H_{24}O_7$: C, 62.63; H, 6.59. Found: C, 62.34; H, 6.60.

1-O-Benzoyl-2,3-O-isopropylidene-L-gulose (**14**). — A solution of **13** (3.6 g) in methanol (50 mL) containing conc. hydrochloric acid (0.5 mL) was stored at room temperature for 1.5 h, neutralised with conc. ammonia, and concentrated under vacuum at room temperature. The residue was extracted with dry ethyl acetate, the extract was concentrated to 20 mL, and light petroleum (b.p. 60–80°) was added to slight turbidity. On cooling, **14** (3.1 g, 95%) separated; m.p. 174–175°,

$[\alpha]_D^{25}$ +91° (*c* 1,2, ethanol); ν_{max}^{Nujol} 3390 (OH) and 1730 cm^{-1} (benzoate C=O).

Anal. Calc. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.17. Found: C, 59.55; H, 6.23.

*Methyl 1-O-benzoyl-5,6,7,8-tetradeoxy-2,3-O-isopropylidene-*D-lyxo*-non-5,7-dienofuranuronate* (**16**). — The procedure was essentially similar to that described above for **10**, and gave **16** (79.6%), m.p. 89–90°, $[\alpha]_D^{25}$ −33° (*c* 1.46, chloroform); lit.[1] m.p. 91–92°, $[\alpha]_D^{20}$ −33.6° (*c* 0.3, chloroform). ^{1}H-N.m.r. data: δ 1.34 and 1.5 (2 s, 6 H, CMe_2), 3.78 (s, 3 H, CO_2Me), 4.89 (m, 2 H, H-2,3), 5.13 (d, 1 H, H-4), 5.85–6.5 (m, 4 H, H-1,5,6,8), 7.3–7.7 (m, 4 H, 3 Ar-H, H-7), and 8.08 (m, 2 H, 2 Ar-H).

Anal. Calc. for $C_{20}H_{22}O_7$: C, 64.17; H, 5.88. Found: C, 64.50; H, 5.88.

*Methyl 1-O-benzoyl-5,6,7,8-tetradeoxy-2,3-O-isopropylidene-*D-lyxo*-nono-furanuronate* (**17**). — A solution of **16** (200 mg) in methanol (20 mL) was hydrogenated at room temperature and atmospheric pressure over borohydride-reduced Pd catalyst (5 mg). After hydrogen absorption ceased (~0.5 h), the solution was decanted and concentrated to furnish **17** (0.195 g) as a liquid which crystallised on storage; m.p. 66–67°, $[\alpha]_D^{25}$ +30° (*c* 3.2, chloroform). ^{1}H-N.m.r. data: δ 1.0–1.8 (m, 6 H, CH_2-5,6,7), 1.28 and 1.43 (2 s, 6 H, CMe_2), 2.3 (t, 2 H, -CH_2CO_2Me), 3.6 (s, 3 H, CO_2Me), 4.1 (m, 1 H, H-4), 4.75 (m, 2 H, H-2,3), 6.3 (s, 1 H, H-1), and 7.25–8.05 (2 m, 5 H, Ph).

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