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An efficient synthesis of (+)-oxybiotin from D-arabinose

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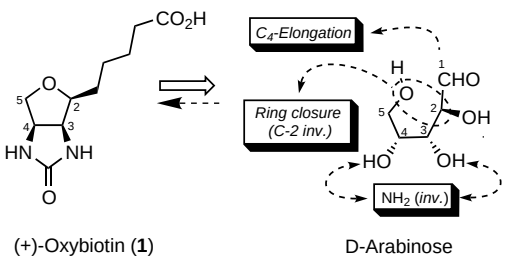
Abstract—A novel stereospecific synthesis of (+)-oxybiotin a biologically active analogue of (+)-biotin has been achieved starting from D-arabinose through ten synthetic steps.

The oxygenated analogue of biotin in which oxygen replaces sulphur was synthesised by Hofmann[1] and named oxybiotin.[2] Like biotin itself, oxybiotin supports the growth of some microorganisms whereupon it has been confirmed that the analogue is not converted to biotin in vivo.[3] On the basis of such a similar biological activity it was assumed that oxybiotin has the same absolute configuration as that of biotin.[1] This assumption was definitely confirmed by a total synthesis of optically active (+)-oxybiotin (**1**, Scheme 1), which was achieved starting from D-glucose in 19 synthetic steps.[4] An alternative synthesis of (+)-**1** was recently accomplished in our laboratory starting from D-xylose.[5,6] This approach consists of 14 synthetic steps, but contains a low-yielding step in the final stage of the synthesis.[6] We now report on an efficient ten-step synthesis of (+)-oxybiotin (**1**) based on D-arabinose as a chiral precursor.



Scheme 1. Functional and stereochemical relationship of (+)-oxybiotin (**1**) and D-arabinose.

A visual examination of the target molecule **1** reveals a chiral tetrahydrofuran system containing three contiguous substituents including the carboxybutyl side chain at C-2, as well as the C-3 and C-4 nitrogen functions incorporated into a *cis*-fused imidazolidinone ring. At first glance this leads to a pentose-type precursor in which the desired carboxyalkyl side chain should be elaborated at C-1, while the tetrahydrofuran ring should be closed between the O-5 and C-2. In view of the configuration at C-2 in (+)-**1** and the O-5/C-2 cyclisation step that should occur, the absolute configuration at this particular stereocentre in the starting monosaccharide is crucial. It corresponds to the (*S*)-configuration at C-2 in D-arabinose, if the inversion of configuration occurs at this centre during the ring closure step. The absolute configuration at C-3 and C-4 in D-arabinose is also suitable for successive introduction of two nitrogen functions, with inversion of configuration at these positions that would enable completion of the synthesis. Hence, a novel stereospecific synthesis of (+)-oxybiotin from D-arabinose was planned based on the trisubstituted tetrahydrofuran **7** as a possible intermediate. It was further assumed that the key intermediate **7** could be obtained from the 2,5-anhydro-D-ribose derivative **4**, by a sequential C-1 deprotection/Wittig elongation manoeuvre. Compound **4** should be available by a ring contraction in the arabinopyranoside 2-triflate **3**, analogously to similar literature precedents.[7] An alternative approach to **7** assumes an intramolecular displacement of the allylic C-2 mesyloxy group in the acyclic ester **10a** (Scheme 3), which should be available from the protected D-arabinose derivative **10** via a Wittig reaction.

The five-step route to the key intermediate **7** via the 2,5-anhydro-D-ribose derivative **4** is outlined in Scheme 2.

Keywords: D-arabinose; 2,5-anhydro-D-ribose; (+)-oxybiotin; stereospecific synthesis; Wittig reaction; ring contraction.

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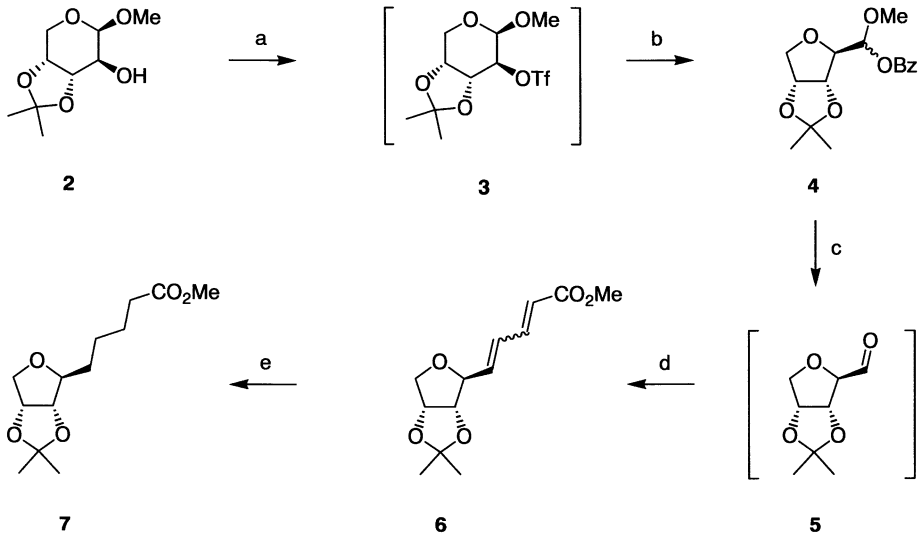
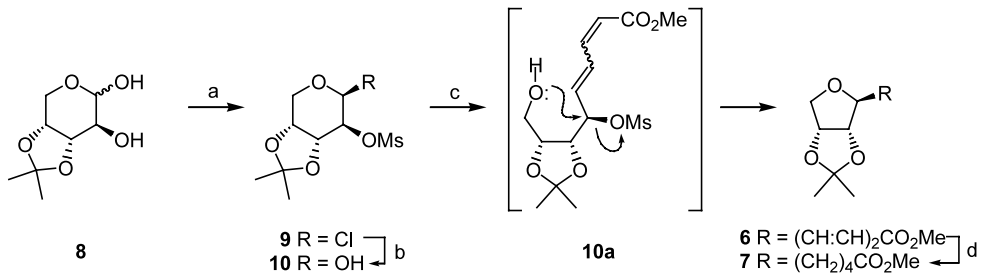


Scheme 2. (a) Tf_2O, Py, CH_2Cl_2, −10°C, 0.5 h; (b) KOBz, DMF, rt, 24 h, 99% from **2**; (c) MeONa, MeOH, rt, 1.5 h; (d) Ph_3P:CHCH:$CHCO_2Me$, MeOH, rt, 1.5 h, 41% from **4**; (e) H_2, PtO_2, MeOH, rt, 24 h, 88%.

In 1989 Baer, Mateo and Siemsen[7] reported a facile formation of 2,5-anhydro-6-deoxy-L-talose derivatives by ring contraction in methyl 2-*O*-trifluoromethanesulfonyl-β-L-fucopyranoside under solvolytic conditions. It was therefore assumed that utilisation of similar methodology in the D-arabinopyranose series would lead to the formation of the desired intermediate **4**. Accordingly, the preparation of the 2-triflic ester **3** was attempted. The known[8] methyl 3,4-*O*-isopropylidene-β-D-arabinopyranoside (**2**) was treated with triflic anhydride to afford the expected 2-*O*-triflic ester **3**. Compound **3** was characterised from NMR spectroscopic data, but was rather unstable on storage, similar to its fucopyranoside analogues.[7] It was therefore, immediately after its rapid isolation, treated with potassium benzoate in *N*,*N*-dimethylformamide for 24 h at room temperature. The desired product **4** was obtained as an inseparable 2:1 mixture of C-1 epimers in an almost quantitative yield. Treatment of **4** with sodium methoxide, followed by a Wittig reaction with 3-(methoxycarbonyl)-2-propenylidene triphenylphosphorane[9] in methanol, gave the unsaturated ester **6** as an inseparable mixture of several *E*- and *Z*-isomers. Catalytic hydrogenation of **6** over PtO_2 in methanol furnished the corresponding saturated ester **7** in 36% overall yield with respect to the starting compound **2**.

In a different approach towards the intermediate **7**, 3,4-*O*-isopropylidene-D-arabinose (**8**), readily available from D-arabinose,[10] was used as the starting material (Scheme 3). Treatment of **8** with mesyl chloride and triethylamine in dry dichloromethane gave the crystalline glycosyl chloride **9** as the only reaction product. Although compound **9** could be stored at −20°C for weeks without change, it tended to decompose on standing at room temperature turning into a tar. Hence, the intermediate **9** was immediately treated with silver oxide in aqueous acetone, in the presence of a catalytic amount of silver triflate, to give the stable lactol **10** (94% from **8**). Treatment of **10** with 3-(carbomethoxy)-2-propenylidene triphenylphosphorane in *N*,*N*-dimethylformamide, in the presence of calcium carbonate as a proton acceptor, gave an inseparable mixture of unsaturated esters **6** (*E*- and *Z*-isomers), as a result of the sequential Wittig reaction/intramolecular displacement process.[11] Neither the acyclic intermediate **10a** nor the products of the competitive Michael addition could be detected in the reaction mixture. The ^1H and ^{13}C NMR spectra of the mixture of **6** obtained displayed essentially the same signals as the sample **6** prepared according to Scheme 2, but indicated a somewhat different ratio of *E*- and *Z*-isomers. Moreover, catalytic hydrogenation of **6**, under the same reaction



Scheme 3. (a) MsCl, Et_3N, CH_2Cl_2, −10°C, 0.5 h; (b) Ag_2O, AgOTf, aq. Me_2CO, rt, 24 h, 94% from **8**; (c) Ph_3P:CHCH:$CHCO_2Me$, $CaCO_3$, DMF, 135°C, 2 h; (d) H_2, PtO_2, MeOH, rt, 24 h, 67% from **10**.

conditions as described above, gave a good yield of the corresponding saturated ester **7** (67% from **10**).

The four-step sequence outlined in Scheme 3 represents a more convenient route towards the key intermediate **7**, since it provided a considerably higher overall yield (63% from **8**) compared to the alternative five-step sequence presented in Scheme 2 (36% from **2**). Final conversion of the intermediate **7** into (+)-oxybiotin (**1**) is shown in Scheme 4.

Hydrolytic removal of the isopropylidene protective group in **7** gave an excellent yield of the expected diol **11** (95%). The optical rotation, as well as the IR and NMR spectral data of product **11** thus obtained were in good agreement with those already reported.[5,6] Compound **11** was further converted to the corresponding 3,4-diazido derivative **13** under reaction conditions similar to those reported earlier.[5] Reaction of **11** with triflic anhydride in pyridine and dichloromethane gave the corresponding 3,4-ditriflate **12**, isolated by flash column chromatography in 50% yield. Subsequent treatment of **12** with sodium azide in HMPA afforded the corresponding 3,4-diazido derivative **13** as the only reaction product (47% from **11**). However, when the last two-step sequence was carried out without purification of the intermediate **12**, the desired product **13** was obtained in a considerably higher overall yield (68% from **11**).[12]

Compound **13** represents a convenient intermediate for the completion of the synthesis of target **1**, since it has the correct absolute configuration at all the stereocentres, as well as the *cis* azido functions suitable for the final imidazolidinone ring closure. This requires conversion of **13** into the corresponding diamine, followed by subsequent cyclisation of the intermediate upon treatment with phosgene or its equivalent. Diazide **13** was therefore reduced over PtO_2 in dichloromethane and after 22 h, when the TLC indicated complete conversion of **13**, the reaction mixture was treated with triphosgene, under reaction conditions similar to those recently applied for the conversion of vicinal amino alcohols to oxazolidinones,[13] whereby the imidazolidinone **14** was obtained in 66% yield. Treatment of **14** with an aqueous solution of sodium hydroxide, followed by neutralisation with Amberlyst 15, gave an almost quantitative yield of (+)-oxybiotin (**1**), with physical constants[14] in excellent agreement with those already reported.[4] Spectroscopic data[15] of the final product thus obtained were consistent with structure **1**.

The overall yield of (+)-oxybiotin (**1**) from D-arabinose by the combined routes presented in Schemes 3 and 4 was 22%.

In conclusion, this paper reports a convenient ten-step synthesis of (+)-oxybiotin by chirality transfer from D-arabinose. The synthesis was realised by using simple and conventional experimental procedures, as well as a cheap and readily available starting material.[16] In addition, the new approach provided a convenient one-pot procedure for the construction of the (+)-oxybiotin ureido system by using triphosgene, a safe and stable replacement of phosgene.[17]

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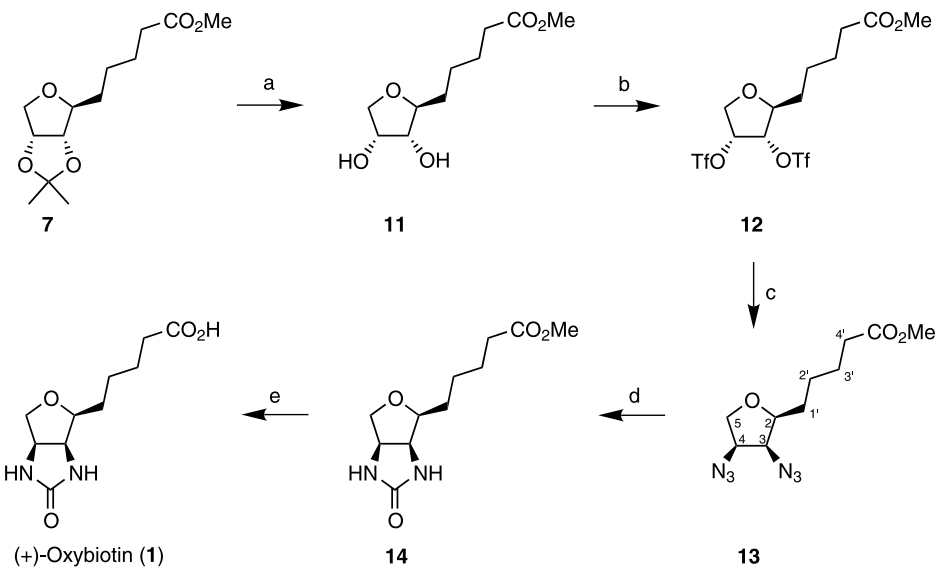

Scheme 4. (a) 9:1 TFA–H_2O, rt, 0.5 h, 95%; (b) Tf_2O, Py, CH_2Cl_2, 0°C, 1.5 h; (c) NaN_3, HMPA, rt, 1.5 h, 68% from **11**; (d) H_2, PtO_2, CH_2Cl_2, rt, 24 h, then $(Cl_3CO)_2CO$, Et_3N, 0°C, 2 h, rt 22 h, 66%; (e) NaOH, H_2O, 100°C, 1 h, then Amberlyst 15, rt, 0.5 h, 99%.

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11. Conversely, the reaction of **10** with trimethyl-4-phosphono crotonate, in the presence of NaH in THF, at room temperature for 0.5 h, gave pure *E*,*E*-**6** (48%) as the only stereoisomer: mp 75°C (from CH_2Cl_2–hexane), $[\alpha]_D$ −108.2 (*c* 0.88 in $CHCl_3$); ν_{max} (KBr): 1710, 1650, 1630 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.32 and 1.51 (2×s, 3H each, Me_2C), 3.73 (s, 3H, CO_2Me), 3.83 (dd, 1H, $J_{5a,5b}$ 10.7, $J_{4,5a}$ 4.2 Hz, H-5a), 3.99 (dd, 1H, $J_{4,5b}$ 1 Hz, H-5b), 4.58 (dd, 1H, $J_{2,3}$ 1.7, $J_{3,4}$ 6.2 Hz, H-3), 4.62 (ddd, 1H, $J_{2,2'}$ 1.8, $J_{1',2}$ 4.6 Hz, H-2), 4.77 (m, 1H, H-4), 5.88 (d, 1H, $J_{3',4'}$ 15.4 Hz, H-4′), 5.97 (dd, 1H, $J_{1',2'}$ 15.5 Hz, H-1′), 6.39 (ddd, 1H, $J_{2',3'}$ 11 Hz, H-2′), 7.24 (dd, 1H, H-3′); ^{13}C NMR ($CDCl_3$): δ 24.91 and 26.48 (**Me**$_2$C), 51.53 (CO_2**Me**), 72.53 (C-5), 80.84 (C-4), 83.92 (C-2), 84.76 (C-3), 112.90 (Me_2**C**), 121.75 (C-4′), 128.83 (C-2′). 138.02 (C-1′), 143.23 (C-3′), 167.09 (**C**O_2Me). FAB MS: *m*/*z* 277 (M^++Na); HR MS (ES+): *m*/*z* 277.1052 (M^++Na). Calcd for $C_{13}H_{18}O_5Na$: 277.1052.
12. Compound **13** (oil): $[\alpha]_D$ +36.0 (*c* 1.95 in $CHCl_3$); ν_{max} (film): 2100, 1740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.29–1.78 (m, 6H, 3×CH_2), 2.33 (t, 2H, C**H**$_2$$CO_2$Me), 3.66 (s, 3H, CO_2Me), 3.78 (dd, 1H, $J_{5a,5b}$ 9.1, $J_{4,5a}$ 7.2 Hz, H-5a), 3.88 (ddd, 1H, $J_{1'a,2}$ 5.8, $J_{1'b,2}$ 7.3, $J_{2,3}$ 3.4 Hz, H-2), 3.95–4.05 (two partially overlapped dd, 2H, $J_{3,4}$ 7.7, $J_{4,5b}$ 4 Hz, H-3 and H-5b), 4.25 (td, 1H, H-4); ^{13}C NMR ($CDCl_3$): δ 24.76, 25.47 and 29.68 (3×CH_2), 33.72 (**C**$H_2$$CO_2$Me), 51.46 ($CO_2$**Me**), 62.96 (C-4), 65.24 (C-3), 68.52 (C-5), 80.78 (C-2), 173.87 (**C**O_2Me). FAB MS: *m*/*z* 291 (M^++Na); HR MS (ES+): *m*/*z* 291.1174 (M^++Na). Calcd for $C_{10}H_{16}N_6O_3Na$: 291.1182.
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14. Physical constants of (+)-**1**: mp 187–188°C (from H_2O), $[\alpha]_D$ +57.8 (*c* 0.65 in 1 M NaOH); Ref. 4: mp 187–188°C, $[\alpha]_D$ +57.7.
15. Spectroscopic data of (+)-**1**: ν_{max} (KBr): 3430–2500, 1700, 1670, 1490, 1460, 1250, 1200, 1070 and 1020 cm^{-1}; ^1H NMR (D_2O): δ 1.41–1.80 (m, 6H, 3×CH_2), 2.46 (t, 2H, *J* 7 Hz, C**H**$_2$$CO_2$H), 3.64–3.76 (partially overlapped dd and m, 2H, $J_{2,3}$ 4, $J_{5a,5b}$ 10.4, $J_{4,5a}$ 4.4 Hz, H-2 and H-5a), 3.94 (d, 1H, H-5b), 4.42 (dd, 1H, $J_{3,4}$ 8.7 Hz, H-3), 4.45 (dd, 1H, H-4); ^{13}C NMR (D_2O): δ 26.96, 27.66 and 30.42 (3×CH_2), 36.36 (**C**$H_2$$CO_2$H), 60.35 and 61.67 (C-3 and C-4), 76.55 (C-5), 85.64 (C-2), 167.63 (NHCONH), 181.73 (CO_2H). FAB MS: *m*/*z* 251 (M^++Na); HR MS (ES+): *m*/*z* 251.1007 (M^++Na). Calcd for $C_{10}H_{16}N_2O_4Na$: 251.1008.
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