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Note

Stereospecific synthesis of (+)-oxybiotin from D-xylose☆

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Abstract

A new 14-step synthesis of (+)-oxybiotin, an oxygen analogue of (+)-biotin, was achieved starting from D-xylose by use of selected 2,5-anhydro sugar derivatives as key intermediates.

Keywords: (+)-Oxybiotin; Protected 2,5-anhydro pentoses; 2,3,4-Trisubstituted tetrahydrofuranes; D-Xylose

Oxybiotin, a biotin analogue in which oxygen replaces sulfur, was synthesized by Hofmann[2] and shown to exhibit a high biotin-like activity towards some microorganisms.[3] Accordingly, it was assumed that the biologically active oxybiotin has the same absolute configuration as that of the natural biotin. This assumption was definitely proved by a stereospecific synthesis of (+)-oxybiotin (**18**, Scheme 3) from D-glucose.[4] Apart of this 19-steps sequence, no further attempts were made directed towards more efficient preparations of the enantiopure (+)-**18**. Herein we report a new 14-step stereospecific synthesis of (+)-oxybiotin, based on D-xylose as a chiral precursor,[1] by way of selected 2,5-anhydro sugars† as convenient intermediates.

Earlier we have described[6,7] the five-step conversion of D-xylose to the 2,5-anhydro-D-xylose ethylene acetal derivative **1** (Scheme 1). The key step of the sequence (stereospecific formation of the trisubstituted tetrahydrofuran system) has been achieved according to the methodology similar to that developed by Defaye and Hildesheim.[8] Compound **1** has the correct stereochemistry at C-2, as well as the functionalities suitable for further introduction of the carboxyalkyl side chain, as well as for building the final (+)-oxybiotin ureido system.

Hydrolytic removal of the dioxolane protective group in **1** gave a hydrated form of the corresponding aldehyde **2**. Due to its instability,‡ the intermediate **2** was promptly treated with 3-methoxycarbonyl-2-propenylidene triphenylphosphorane,[9] (generated in situ from the corresponding phosphonium bromide), to afford the α,β-unsaturated ester **3** as a mixture of *E* and *Z* isomers. Subsequent catalytic hydrogenation of **3** over PtO_2 gave the corresponding saturated ester **4** (32% from **1**). Solvolysis of **4** in wet *N*,*N*-dimethylformamide, in the presence of calcium carbonate as a proton acceptor, gave a mixture of regioisomers **5** with inverted configuration at C-3. *O*-Debenzoylation of **5** with sodium methoxide in methanol afforded the expected diol **6**. Reaction of **6** with mesyl chloride in dichloromethane, in the presence of triethylamine, gave the corresponding di-*O*-mesyl derivative **7** (15.3% from **1**), a potential intermediate for the further introduction of two azide functions with inversion of configuration at C-3 and C-4.

An alternative six-step sequence for the preparation of intermediate **7** is presented in Scheme 2. Solvolysis of **1** in wet *N*,*N*-dimethylformamide, under the same reac-

☆ For a preliminary account, see Ref. 1.

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† For a review on 2,5-anhydro sugars, see Ref. 5.

‡ Compound **2** decomposes slowly on prolonged standing at room temperature turning into tar.

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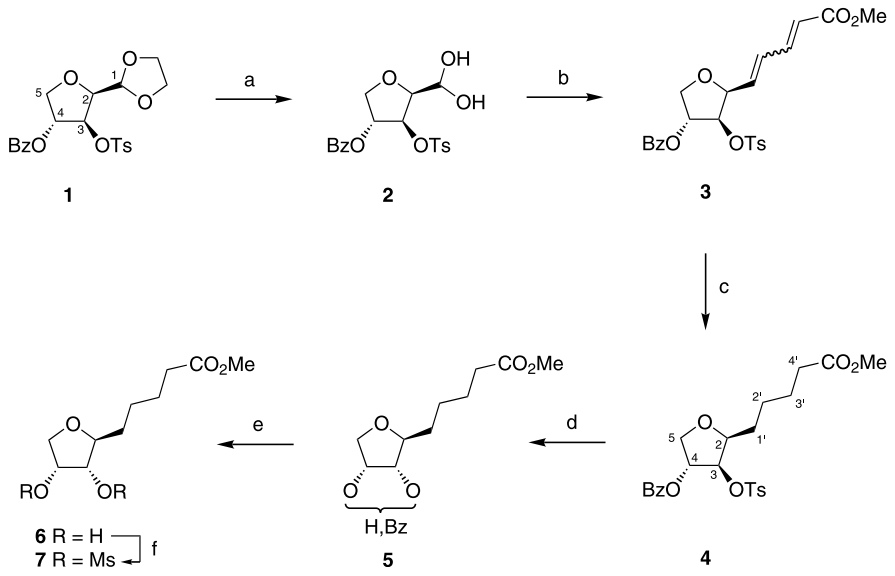
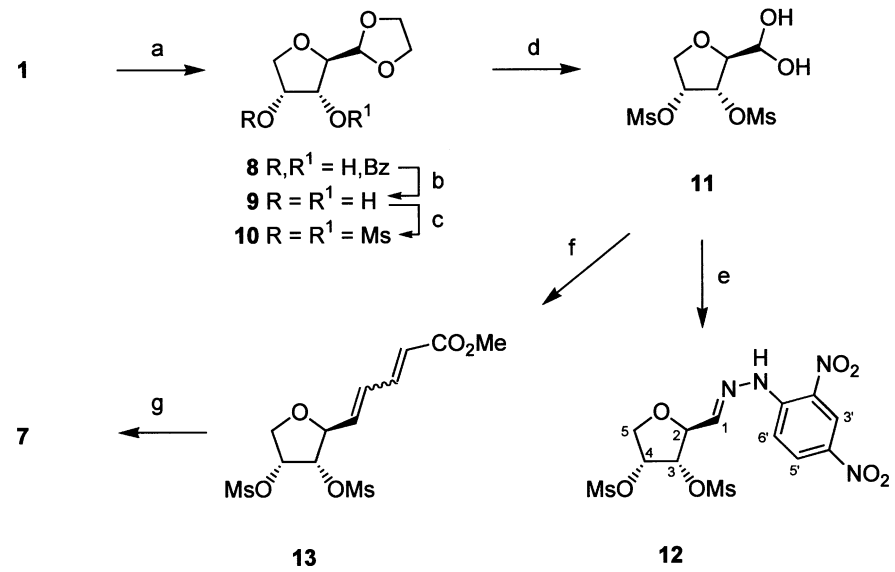
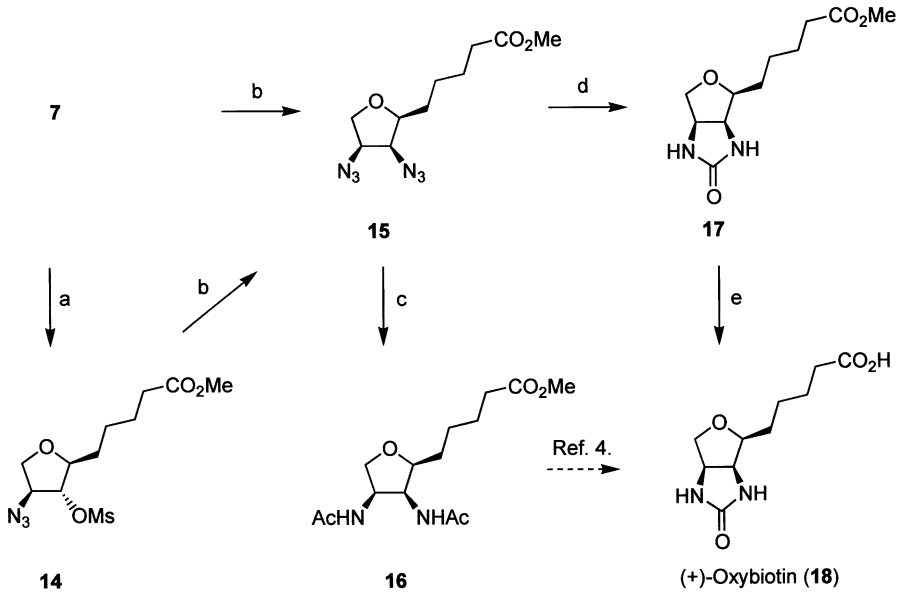


Scheme 1. Reagents and conditions: (a) TFA, 6 M HCl, rt, 12 h, 60%; (b) $[Ph_3PCH_2CH{:}CHCO_2Me]^+$ Br^-, CH_2Cl_2, NaOH, H_2O, rt 1 h, 59%; (c) H_2/PtO_2, AcOH, rt, 20 h, 90%; (d) $CaCO_3$, 95% aq DMF, 150 °C, 10 h, 65%; (e) NaOMe, MeOH, rt, 1 h, 81%; (f) MsCl, Et_3N, CH_2Cl_2, −10 °C, 0.5 h, 91%.



Scheme 2. Reagents and conditions: (a) $CaCO_3$, 95% aq DMF, 150 °C, 10 h; (b) KOH/MeOH, 60 °C, 0.5 h; (c) MsCl, Py, rt, 24 h, 64% from **1**; (d) TFA, 6 M HCl, rt, 24 h; (e) 2,4-DNPH, MeOH, H_2SO_4, rt, 0.5 h, 72%; (f) $[Ph_3PCH_2CH{:}CHCO_2Me]^+$ Br^-, CH_2Cl_2, NaOH, H_2O, rt 45 min; (g) H_2/PtO_2, AcOH, rt, 18 h, 54% from **10**.

tion conditions already used for the preparation of **5** (Scheme 1), afforded a mixture of regioisomers **8**. Subsequent *O*-debenzoylation of **8** with potassium hydroxide gave the corresponding diol **9**, which was finally converted into the known[7,10] di-*O*-mesyl derivative **10** by treatment with mesyl chloride in pyridine. All three steps concerning the conversion of **1** to **10** were carried out by a one-pot procedure, whereupon the intermediates **8** and **9** were used without any purification or separation from accompanying inorganic impurities. Pure **10** was isolated by short-column chromatography in an overall yield of 64% with respect to the starting compound **1**. Hydrolysis of **10** with a mixture of hydrochloric and trifluoroacetic acid afforded the unstable hydrated aldehyde **11**, which was fully characterized after its conversion to the corresponding 2,4-dinitrophenylhydrazone **12**. Wittig olefination of **11**, under the conditions as described above, yielded **13** as an inseparable mixture of *E* and *Z* isomers, which were then converted to the desired intermediate **7** (54% from **10**) by catalytic hydrogenation over PtO_2. Obviously the six-step sequence realized via the 3,4-di-*O*-mesyl deriva-



Scheme 3. Reagents and conditions: (a) NaN_3, HMPA, 80 °C, 5 h, 71%; (b) NaN_3, NH_4Cl, DMF, 150 °C, 20 h, 47%; (c) H_2/PtO_2, AcOH, Ac_2O, rt, 23 h, 85%; (d) Ph_3P, BnOCOCl, THF, rt, 5 h, then NH_4OH, H_2O, rt, 18 h, 24%; or H_2/PtO_2, CH_2Cl_2, rt, 6 h, then Et_3N, triphosgene, 0 °C, 1 h, rt 18 h, 68%; (e) $Ba(OH)_2$, H_2O, 100 °C, 1.5 h, 98%.

tive **10** (Scheme 2) represents a more convenient procedure for the preparation of **7**, since it provided a considerably higher overall yield (34.6% from **1**), compared to the six-step route presented in Scheme 1 (15.3% from **1**).

Conversion of the intermediate **7** into the (+)-oxybiotin (**18**) is outlined in Scheme 3. In 1975 Ohrui and Emoto[11] described a solvolytic reaction of a thiophane analogue of **7** (NaN_3, HMPA, 80 °C) whereupon the corresponding 3,4-diazido derivative was obtained in high yield. The same reaction conditions were therefore applied to the intermediate **7**, but instead of the expected 3,4-diazido derivative **15**, the 4-monoazide **14** was exclusively formed in 71% yield. However, a reaction of **7** with sodium azide in *N*,*N*-dimethylformamide at 150 °C for 20 h, in the presence of ammonium chloride, gave the key intermediate **15** (37%) along with **14** (26%) as a byproduct.[§] Compound **14**, under similar reaction conditions gave the same yield of **15** (37%). Accordingly, by combining the last two procedures, the desired product **15** can be prepared in 47% total yield, which is comparable to that achieved earlier[1] from the triflic analogue of **7**. Catalytic hydrogenation of **15** over PtO_2 in a mixture of glacial acetic acid and acetic anhydride gave the corresponding diacetamido derivative **16**, that can be converted to (+)-oxybiotin (**18**) according to the reported procedure.[4] Although the preparation of **16** formally represents a new stereospecific synthesis of (+)-oxybiotin (**18**) from D-xylose, alternative procedures for the conversion of **15** into **18** were also considered, in order to avoid the hazards of handling of phosgene.[4] At first, we have checked up if the Staudinger reaction[¶] in the presence of a chloroformate[13] could be used for the direct conversion of **15** into the imidazolidinone **17**, analogously to the one-pot conversion of vicinal azido alcohols to oxazolidinones.[14] Treatment of **15** with triphenylphosphine and benzyl chloroformate, under reaction conditions similar to those recently reported,[13] afforded a low yield of the desired imidazolidinone **17** (24%). However, one-pot catalytic reduction of **15** followed by a subsequent triphosgene treatment provided the desired intermediate **17** in 68% yield. Compound **17** was finally converted to (+)-oxybiotin (**18**) by hydrolysis with barium hydroxide in an almost quantitative yield. The physical constants (mp and $[\alpha]_D$) of (+)-**18** thus obtained were in excellent agreement with those already reported.[4]

In summary, a new stereospecific synthesis of (+)-oxybiotin has been developed starting from D-xylose, by utilizing cheap and readily available reagents and by applying simple experimental procedures. Although this new synthesis of **18** contains some low-yielding steps (**7**→**15**, **14**→**15**), it consists of less synthetic steps (14) then the earlier preparation from D-glucose (19 steps).[4] In addition, the new approach provided a convenient one-pot procedure for the (+)-oxybiotin ureido system building utilizing triphosgene, a safe and stable replace-

[§] Prolongation of the reaction time did not increase the yield of the desired product **15** presumably due to its instability under the applied reaction conditions.

[¶] For a review on the Staudinger reaction, see Ref. 12.

ment of phosgene.[15] Novel and more efficient approaches towards the key intermediate **15** and to the target **18** itself are currently being investigated, and the results will be reported in due course. Moreover, appropriate C-1 functionalization of the 2,5-anhydro derivatives **2** or **11**, may provide access to potential divergent intermediates for the preparation of (+)-oxybiotin analogues with the side chain containing an additional heteroatom (e.g., O or S) instead of the C-2′ methylene group.[16]

1. Experimental

General methods.—Melting points were determined on a Büchi 510 apparatus and were not corrected. Optical rotations were measured on a Polamat A (Carl–Zeiss, Jena) polarimeter at rt. IR spectra were recorded with a Specord 75IR spectrophotometer and band positions (ν_{max}) are given in cm^{-1}. NMR spectra were recorded on a Bruker AC 250 E instrument and chemical shifts are expressed in ppm downfield from tetramethylsilane. Mass spectra were recorded on Finnigan-MAT 8230 (CI), VG AutoSpec (FAB) and Micromass LCT KA111 (ES+) mass spectrometers. TLC was performed on DC Alufolien Kieselgel 60 F_{254} (E. Merck). Short-column chromatography was carried out using Kieselgel 60 (under 0.063 mm; E. Merck). Typical sample/adsorbent ratio was 1:30. Flash-column chromatography was performed using ICN silica 32–63. All organic extracts were dried with anhyd Na_2SO_4. Organic solutions were concentrated in a rotary evaporator under diminished pressure at a bath temperature below 35 °C.

2S-(4′-Methoxycarbonyl-1′-butyl)-3R-p-toluenesulfonyloxy-4R-benzoyloxy-tetrahydrofuran (**4**).—A suspension of **1** (2.12 g, 4.88 mmol) in a mixture of trifluoroacetic acid (20 mL) and 6 M HCl (2 mL) was kept at rt for 12 h. The mixture was concentrated to one third of the initial volume, treated with satd aq $NaHCO_3$ (to pH 9), and extracted with CH_2Cl_2. The extract was washed successively with satd aq $NaHCO_3$ and water, dried and evaporated. Column chromatography (PhMe) of the residue gave pure **2** (1.2 g, 60%) as a pale yellow oil: $[\alpha]_D$ −76.04° (*c* 0.89, $CHCl_3$); ν_{max} (film): 3480, 1730, 1600, 1370, 1195 cm^{-1}. To a solution of **2** (1.17 g, 2.86 mmol) in CH_2Cl_2 (25 mL) was added a solution of (3-methoxycarbonyl-2-propenyl)triphenylphosphonium bromide[9] (2.02 g, 4.58 mmol) in water (105 mL). To this mixture, a solution of NaOH (0.19 g, 4.75 mmol) in water (11 mL) was added dropwise while stirring for 15 min at rt. The reaction mixture was stirred under nitrogen at rt for 1 h, and then transferred into a separatory funnel. The organic phase was separated, washed with water, dried and evaporated. Column chromatography (PhMe) of the residue gave **3** (0.804 g, 59%) as a bright-yellow syrup: $[\alpha]_D$ −9.78° (*c* 0.87, $CHCl_3$); ν_{max} (film): 1725, 1655, 1600, 1375, 1200–1180 cm^{-1}. A solution of **3** (0.74 g, 1.57 mmol) in glacial AcOH (15 mL) was hydrogenated over PtO_2 (0.08 g, 0.35 mmol) for 20 h at rt. The mixture was filtered and the catalyst washed with CH_2Cl_2 (20 mL). The organic solution was washed successively with satd aq $NaHCO_3$ (5 × 20 mL) and water (3 × 20 mL), dried and evaporated. Chromatographically homogenous **4** (0.67 g, 90%) was thus obtained as a white solid. Recrystallization from MeOH afforded an analytical sample **4**: mp 102–103 °C; $[\alpha]_D$ −65.7° (*c* 1.04, $CHCl_3$); ν_{max} (KBr): 1735, 1600, 1360, 1200–1185 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.32–1.75 (m, 6 H, 3 × CH_2), 2.30 (t, 2 H, C**H**$_2$CO$_2$Me), 2.38 (s, 3 H, **Me**C$_6$H$_4$SO$_2$), 3.66 (s, 3 H, CO$_2$**Me**), 3.70 (dd, 1 H, $J_{5a,5b}$ 10.5, $J_{4,5a}$ 3 Hz, H-5a), 4.04 (ddd, 1 H, $J_{1a',2}$ 7.2, $J_{1b',2}$ 5.1, $J_{2,3}$ 3.5 Hz, H-2), 4.32 (dd, 1 H, $J_{4,5b}$ 5.2 Hz, H-5b), 5.05 (dd, 1 H, $J_{3,4}$ 1.5 Hz, H-3), 5.29 (ddd, 1 H, H-4), 7.28–7.98 (m, 9 H, C$_6$**H**$_5$CO and MeC$_6$**H**$_4$SO$_2$); ^{13}C NMR ($CDCl_3$): δ 21.73 (**Me**C$_6$H$_4$SO$_2$), 24.95, 25.67 and 28.26 (3 × CH_2), 33.99 (**C**H$_2$CO$_2$Me), 51.62 (CO$_2$**Me**), 71.22 (C-5), 78.00 (C-4), 80.19 (C-2), 83.33 (C-3), 127.92, 128.18, 128.45, 129.71, 129.95 and 133.45 (aromatic), 165.14 (Ph**C**=O), 174.05 (**C**O$_2$Me); FABMS: *m*/*z* 499 [MNa^+], 477 [MH^+]. Anal. Calcd for $C_{24}H_{28}O_8S$: C, 60.50; H, 5.91; S, 6.72. Found: C, 60.77; H, 6.03; S, 6.39.

2S-(4′-Methoxycarbonyl-1′-butyl)-3S,4R-dihydroxytetrahydrofuran (**6**).—To a solution of **4** (0.50 g, 1.05 mmol) in 95% aq *N*,*N*-dimethylformamide (20 mL, 5% of water) was added $CaCO_3$ (0.33 g, 3.3 mmol). The mixture was stirred for 10 h at 150 °C, then concentrated in vacuo, and the remaining residue was extracted with boiling CH_2Cl_2 (20 mL). The suspension was filtered and evaporated to a brown syrup. Short-column chromatography (9:1 toluene–EtOAc) of the residue gave oily **5** (0.22 g, 65%): $[\alpha]_D$ −47.8° (*c* 1.17, $CHCl_3$); ν_{max} (film): 3430, 1720–1710 cm^{-1}. To a solution of **5** (0.20 g, 0.62 mmol) in dry MeOH (1 mL) was added the solution of 0.1 M NaOMe in MeOH (0.4 mL). The mixture was stirred for 1 h at rt, then acidified with glacial AcOH (to pH 5) and evaporated by co-distillation with toluene (30 mL). The remaining oily residue (0.16 g) was purified by short-column chromatography (4:1 toluene–Me_2CO) to afford pure **6** (0.11 g; 81%) as a colorless syrup: $[\alpha]_D$ −37.6° (*c* 0.95, $CHCl_3$); ν_{max} (film): 3380, 1730 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$): δ 1.38–1.65 (m, 6 H, 3 × CH_2), 2.35 (t, 2 H, C**H**$_2$CO$_2$Me), 3.62 (s, 3 H, CO$_2$**Me**), 3.58–3.80 (m, 3 H, H-2, H-3 and H-5a), 4.01 (dd, 1 H, $J_{5a,5b}$ 10, $J_{4,5b}$ 5 Hz, H-5b), 4.21 (m, 1 H $J_{4,5a}$ 4.6 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 24.85, 25.34 and 32.91 (3 × CH_2), 33.97 (**C**H$_2$CO$_2$Me), 51.65 (CO$_2$**Me**), 71.01 (C-4), 72.63 (C-5), 75.84 and 82.09 (C-2 and C-3), 174.57 (**C**O$_2$Me); LRMS (CI): *m*/*z* 219 [MH^+]. ES^+ HRMS: Calcd for $C_{10}H_{18}NaO_5$: 241.1052. Found: *m*/*z* 241.1057 [MNa^+].

2,5-Anhydro-3,4-di-O-*methanesulfonyl*-D-*ribose ethylene acetal* (**10**).—To a solution of **1** (2.00 g, 4.60 mmol) in 95% aq *N*,*N*-dimethylformamide (20 mL, 5% of water) was added $CaCO_3$ (1.00 g, 9.99 mmol), and the mixture was stirred for 4 h at 150 °C. Examination of the reaction mixture by TLC (4:1 toluene–Me_2CO) proved a complete conversion of **1** into **8**. To the reaction mixture was then added 10% KOH in MeOH (6 mL) and the resulting mixture was stirred at 60 °C for 30 min, whereupon the intermediate **8** was fully converted to the diol **9** as established by TLC (3:2 toluene–Me_2CO). The mixture was concentrated under diminished pressure and dried by co-distillation with 1:1 toluene–EtOH (4 × 30 mL). The crude residue was dissolved in dry pyridine (15 mL) and treated with MsCl (2 mL). The mixture was stored for 24 h at rt, then poured onto ice (100 g), acidified with 6 M aq HCl (100 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with water, dried and evaporated. Short-column chromatography (CH_2Cl_2) of the residue gave pure **10** (0.98 g, 64% form **1**) as a white solid. Recrystallization from EtOH gave an analytical sample **10** as needles: mp 108–109 °C, lit.[7] 107–108 °C; $[\alpha]_D$ −46.5° (*c* 0.77, $CHCl_3$); ν_{max} (KBr): 1370–1330, 1180–1170 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.12 and 3.13 (2 × s, each 3 H, 2 × $MeSO_2$), 3.88–4.28 (m, 7 H, 2 × CH_2-dioxolane, 2 × H-5 and H-2), 5.05 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 5.15–5.28 (m, 2 H, H-3 and H-4); ^{13}C NMR ($CDCl_3$): δ 38.55 and 38.65 (2 × $MeSO_2$), 65.40 and 65.65 (2 × CH_2-dioxolane), 70.48 (C-5), 76.28 (C-4), 76.34 (C-3), 80.98 (C-2), 102.06 (C-1).

2,5-Anhydro-3,4-di-O-*methanesulfonyl*-D-*ribose 2′,4′-dinitrophenylhydrazone* (**12**).—A solution of 2,5-anhydro derivative **10** (0.66 g, 1.99 mmol) in a mixture of trifluoroacetic acid (10 mL) and concd HCl (1 mL) was kept at rt for 24 h. The solvent was evaporated and traces of acids were removed by co-distillation with toluene (3 × 30 mL). The remaining brown oil was purified by short-column chromatography (4:1 toluene–Me_2CO) whereupon pure **11** (0.38 g, 62.5%) was obtained as an unstable colorless syrup: $[\alpha]_D$ −46.8° (*c* 0.65, $CHCl_3$); ν_{max} (film): 3560, 1380–1360, 1180 cm^{-1}. To a solution of compound **11** (0.10 g, 0.33 mmol) in MeOH (2 mL) was added a freshly prepared solution of 2,4-dinitrophenylhydrazine hydrochloride (0.25 g, 1.07 mmol) in MeOH (5 mL) and concd H_2SO_4 (0.5 mL). The reaction mixture was stirred at rt for 0.5 h. The separated yellow precipitate was filtered, washed with cold MeOH and recrystallized from MeOH, to afford pure **12** (0.11 g, 72%) as yellow needles. Short-column chromatography (7:3 toluene–Me_2CO) followed by recrystallization from MeOH, gave an analytical sample **12**: mp 137–138 °C; ν_{max} (KBr): 3280, 1595, 1510, 1360–1320, 1175 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.18 (s, 6 H, 2 × $MeSO_2$), 4.21 (dd, 1 H, $J_{5a,5b}$ 11.1, $J_{4,5a}$ 3 Hz, H-5a), 4.33 (dd, 1 H, $J_{4,5b}$ 4.5 Hz, H-5b), 4.81 (dd, 1 H, $J_{1,2}$ 4.7, $J_{2,3}$ 6.4 Hz, H-2), 5.36 (ddd, 1 H, $J_{3,4}$ 5 Hz, H-4), 5.41 (dd, 1 H, H-3), 7.50 (dd, 1 H, $J_{1,NH}$ 0.9 Hz, H-1), 8.02 (d, 1 H, $J_{5',6'}$ 9.5 Hz, H-6′), 8.38 (ddd, 1 H, $J_{3',5'}$ 2.4, $J_{5',NH}$ 0.6 Hz, H-5′), 9.13 (d, 1 H, H-3′), 11.30 (bs, 1 H, exchangeable with D_2O, NH); FABMS: *m*/*z* 491 [MNa^+], 469 [MH^+]. Anal. Calcd for $C_{13}H_{16}N_4O_{11}S_2 \times MeOH$: C, 33.60; H, 4.03; N, 11.20; S, 12.81. Found: C, 33.90; H, 3.85; N, 10.83; S, 13.20.

*2*S-*(4′-Methoxycarbonyl-1′-butyl)-3*S,*4*R-*dimethanesulfonyloxy-tetrahydrofuran* (**7**).—(a) To a stirred and cooled solution (−10 °C) of **6** (0.103 g, 0.47 mmol) in dry CH_2Cl_2 (5 mL) was added Et_3N (0.20 mL, 1.44 mmol) and MsCl (0.08 mL, 1.03 mmol). Stirring was continued for 0.5 h and the mixture diluted with CH_2Cl_2 (10 mL), washed successively with aq 5% HCl (2 × 10 mL), satd aq $NaHCO_3$ (10 mL) and water (10 mL). The organic solution was dried and evaporated to a yellow syrup. Flash-column chromatography (CH_2Cl_2) of the residue gave pure **7** (0.1615 g, 91%) as a white solid, which upon crystallization from EtOH gave colorless needles, mp 70–71 °C.

(b) A solution of **10** (1.00 g, 3.01 mmol) in trifluoroacetic acid (10 mL) and 6 M aq HCl (1 mL) was kept at rt for 24 h. The solution was concentrated under diminished pressure and traces of acids were removed by co-distillation with toluene (25 mL). To a solution of remaining crude **11** in dry CH_2Cl_2 (20 mL) was added a solution of (3-methoxycarbonyl-2-propenyl)triphenylphosphonium bromide[9] (2.02 g, 4.58 mmol) in water (11 mL) and to thus prepared mixture was added a solution of NaOH (0.19 g, 4.75 mmol) in water (11 mL). The reaction mixture was stirred at rt for 45 min, and then transferred to a separatory funnel. The aqueous phase was separated and the organic layer was washed with water (50 mL), dried and evaporated. Short-column chromatography (CH_2Cl_2) of the residue (2.45 g) gave pure **13** (0.68 g, 61% from **10**) as a bright-yellow syrup: $[\alpha]_D$ −37.5° (*c* 1.52, $CHCl_3$); ν_{max} (film): 1725, 1660, 1630, 1370, 1190 cm^{-1}. A solution of **13** (0.5374 g, 1.45 mmol) in glacial AcOH (3 mL) was hydrogenated over PtO_2 (0.05 g, 0.22 mmol) at rt for 18 h. The suspension was filtered and the catalyst washed with CH_2Cl_2 (15 mL). The combined organic solution was washed with satd aq $NaHCO_3$ (2 × 20 mL), dried and evaporated to give chromatographically homogenous **7** (0.4841 g, 89%) as a white solid. Recrystallization from EtOH gave an analytical sample **7** as colorless needles: mp 68–69 °C; $[\alpha]_D$ −62.6° (*c* 1.06, $CHCl_3$); ν_{max} (KBr): 1745, 1350, 1180 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.35–1.87 (m, 6 H, 3 × CH_2), 2.34 (t, 1 H, C**H**$_2$$CO_2Me$), 3.13 and 3.15 (2 × s, each 3 H, 2 × **Me**SO_2), 3.67 (s, 3 H, CO_2**Me**), 3.99 (dt, 1 H, $J_{2,3}$ = $J_{1a',2}$ = 7.2, $J_{1b',2}$ 4.2 Hz, H-2), 4.01 (dd, 1 H, $J_{5a,5b}$ 11, $J_{4,5a}$ 3.8 Hz, H-5a), 4.28 (dd, 1 H, $J_{4,5b}$ 5.2 Hz, H-5b), 4.70 (dd, 1 H, $J_{3,4}$ 5.2 Hz, H-3), 5.17 (dt, 1 H, H-4); ^{13}C NMR ($CDCl_3$): δ 24.60, 24.80 and 31.91 (3 × CH_2),

33.74 (**C**H_2CO_2Me), 38.58 ($MeSO_2$), 51.36 (CO_2**Me**), 70.36 (C-5), 76.15 (C-4), 78.60 (C-2), 79.43 (C-3), 173.71 (**C**O_2Me). Anal. Calcd for $C_{12}H_{22}O_9S_2$: C, 38.49; H, 5.92; S, 17.13. Found: C, 38.39; H, 6.06; S, 17.34.

*2*S-*(4′-Methoxycarbonyl-1′-butyl)-4*S-*azido-3*R-*methanesulfonyloxy-tetrahydrofuran* (**14**).—To a solution of **7** (0.2231 g, 0.6 mmol) in HMPA (4 mL) was added NaN_3 (0.4582 g, 7.05 mmol). The mixture was stirred at 80 °C for 5 h, then poured into cold water (50 mL) and extracted with 1:1 benzene–hexane (3 × 20 mL). The extract was washed with water, dried and evaporated to give crude **14** (0.2289 g) as a yellow oil. Short-column chromatography (9:1 toluene–EtOAc) of the residue afforded pure **14** (0.1356 g, 71%) as a colorless syrup: $[\alpha]_D$ +18.7° (*c* 1.63, $CHCl_3$); ν_{max} (film): 2100, 1735, 1360, 1180 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.38–1.82 (m, 6 H, 3 × CH_2), 2.34 (t, 2 H, C**H**$_2CO_2Me$), 3.09 (s, 3 H, $MeSO_2$), 3.66 (s, 3 H, CO_2**Me**), 3.89 (ddd, 1 H, $J_{2,3}$ 4.2, $J_{1a',2}$ 5.5, $J_{1b',2}$ 7.5 Hz, H-2), 3.94 (dd, 1 H, $J_{5a,5b}$ 10.2, $J_{4,5a}$ 2.5 Hz, H-5a), 4.02 (dd, 1 H, $J_{4,5b}$ 4.5 Hz, H-5b), 4.20 (ddd, 1 H, $J_{3,4}$ 2 Hz, H-4), 4.66 (dd, 1 H, H-3); ^{13}C NMR ($CDCl_3$): δ 24.55, 25.14 and 31.91 (3 × **C**H_2), 33.77 (**C**H_2CO_2Me), 38.54 ($MeSO_2$), 51.36 (CO_2**Me**), 65.78 (C-4), 70.25 (C-5), 83.18 (C-2), 86.19 (C-3), 174.00 (**C**O_2Me); FABMS: *m*/*z* 322 [MH^+]. ES^+ HRMS: Calcd for $C_{11}H_{20}N_3O_6S$: 322.1073. Found: *m*/*z* 322.1079 [MH^+].

*2*S-*(4′-Methoxycarbonyl-1′-butyl)-3*S,*4*R-*diacetamido-tetrahydrofuran* (**16**).—To a solution of **7** (0.1605 g, 0.43 mmol) in DMF (10 mL) was added NaN_3 (0.3890 g, 5.98 mmol) and NH_4Cl (0.0320 g, 0.6 mmol). The mixture was stirred at 150 °C for 20 h, and then evaporated under diminished pressure. Flash-column chromatography of the residue (4:1 light petroleum–EtOAc) gave pure **15** (0.0430 g, 37.4%) as colorless oil. Further elution afforded pure **14** (0.036 g, 26%). Compound **14** was dissolved in DMF (3.5 mL), and to the solution was added NaN_3 (0.0736 g, 1.13 mmol) and NH_4Cl (0.0064 g, 0.12 mmol). The mixture was stirred at 150 °C for 24 h. After the workup as described above, and flash purification on a column of silica, an additional amount of pure **15** (0.0112 g) was obtained. Total yield: 0.0542 g (47%) of **15**: $[\alpha]_D$ +35.5° (*c* 1.79, $CHCl_3$); ν_{max} (film): 2100, 1740 cm^{-1}; LRMS (CI): *m*/*z* 269 [MH^+]. A solution of **15** (0.1214 g, 0.54 mmol) in glacial AcOH (3 mL) and Ac_2O (3 mL) was hydrogenated over PtO_2 (0.04 g, 0.18 mmol) at rt for 23 h. The suspension was filtered and the catalyst washed with $CHCl_3$ (20 mL) and MeOH (10 mL). The combined filtrates were concentrated and residual AcOH removed by co-distillation with a 1:2 mixture of toluene–MeOH (4 × 15 mL), whereupon crude **16** remained as a white solid. Recrystallization from a mixture of CH_2Cl_2–hexane gave an analytical sample **16** (0.1160 g, 85%): mp 151–152 °C; $[\alpha]_D$ +8.8° (*c* 1.17, $CHCl_2$); ν_{max} (KBr): 3290–3080, 1730, 1550 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.35–1.64 (m, 6 H, 3 × CH_2), 1.97 and 2.06 (2 × s, each 3 H, 2 × **Me**CONH), 2.31 (t, 2 H, C**H**$_2CO_2Me$), 3.58 (dd, 1 H, $J_{5a,5b}$ 9.2, $J_{4,5a}$ 6.6 Hz, H-5a), 3.66 (CO_2**Me**), 3.82 (ddd, 1 H, $J_{1a,2}$ 6.9, $J_{1b,2}$ 6, $J_{2,3}$ 3.9 Hz, H-2), 4.05 (dd, 1 H, $J_{4,5b}$ 8.1 Hz, H-5b), 4.55 (ddd, 1 H, $J_{3,NH}$ 9, $J_{3,4}$ 6.1 Hz, H-3), 4.62 (m, 1 H, $J_{4,NH}$ 7 Hz, H-4), 6.71 (bs, 2 H, D_2O exchangeable, 2 × NH); ^{13}C NMR ($CDCl_3$): δ 22.27 (2 × **Me**CONH), 24.29, 24.99 and 28.76 (3 × CH_2), 33.23 (**C**H_2CO_2Me), 50.69 (CO_2**Me**), 51.09 (C-4), 52.11 (C-3), 69.00 (C-5), 80.36 (C-2), 169.85 and 170.27 (2 × Me**C**ONH), 173.19 (**C**O_2Me); FABMS: *m*/*z* 323 [MNa^+], 301 [MH^+]. Anal. Calcd for $C_{14}H_{24}N_2O_5$: C, 55.98; H, 8.05; N, 9.33. Found: C, 55.64; H, 8.00; N, 9.71.

(+)-Oxybiotin (**18**).—(a) To a solution of **15** (0.1860 g, 0.69 mmol) in dry THF (5 mL) was added Ph_3P (0.4550 g, 1.73 mmol) and benzyl chloroformate (0.3 mL of 50% solution in toluene, 1.19 mmol). The mixture was stirred at rt for 5 h, and then treated with concd aq NH_4OH (0.5 mL) while stirring at rt for the additional 18 h. The mixture was evaporated, and the residue partitioned between water (10 mL) and CH_2Cl_2 (5 mL). The aqueous solution was washed with CH_2Cl_2 (5 mL) to remove the Ph_3PO and concentrated by co-distillation with 1:1 toluene–EtOH (2 × 20 mL). Flash chromatography (9:1 EtOAc–MeOH) of the residue gave pure methyl ester **17** (0.040 g, 24%).

(b) A solution of **15** (0.1 g, 0.37 mmol) in dry CH_2Cl_2 (6 mL) was hydrogenated over PtO_2 (0.03 g, 0.13 mmol) for 6 h at rt, and then to the stirred and cooled (0 °C) mixture was added Et_3N (0.1 mL, 0.87 mmol) in one portion. A solution of triphosgene (0.054 g, 0.19 mmol) in dry CH_2Cl_2 (3 mL) was added dropwise while stirring the mixture at 0 °C for 1 h. After stirring at rt for additional 18 h, the suspension was filtered and the catalyst washed with CH_2Cl_2. The combined organic solution was concentrated and the residue purified by flash chromatography (9:1 EtOAc–MeOH) to afford pure **17** (0.061 g, 68%) as a colorless solid: ν_{max} (KBr): 3410–3120, 1750, 1710 cm^{-1}; ^1H NMR ($CDCl_3$); δ 1.21–1.80 (m, 6 H, 3 × CH_2), 2.32 (t, 2 H, C**H**$_2CO_2Me$), 3.40 (m, 1 H, $J_{2,3}$ 3.6, $J_{1',2}$ 6.4 Hz, H-2), 3.49 (dd, 1 H, $J_{5a,5b}$ 10.1, $J_{4,5a}$ 4.2 Hz, H-5a), 3.63 (s, 3 H, CO_2**Me**), 3.86 (d, 1 H, H-5b), 4.17 (dd, 1 H, $J_{3,4}$ 8.4 Hz, H-3), 4.34 (dd, 1 H, H-4), 5.98 and 6.18 (2 × bs, each 1 H, 2 × NH); ^{13}C NMR ($CDCl_3$): δ 24.81, 25.52 and 28.36 (3 × CH_2), 33.67 (**C**H_2CO_2Me), 51.42 (CO_2**Me**), 57.52 (C-4), 58.98 (C-3), 75.23 (C-5), 82.58 (C-2), 163.62 (NHCONH), 174.14 (**C**O_2Me). To a solution of **17** (0.0550 g, 0.23 mmol) in water (1.5 mL) was added $Ba(OH)_2 \times 8$ H_2O (0.080 g, 0.25 mmol). The mixture was stirred at 100 °C for 1.5 h, then acidified to Congo red with 1 M H_2SO_4, and then centrifuged to remove $BaSO_4$. The solution was concentrated by co-distillation with 1:1 toluene–MeOH to afford pure **18** (0.0517 g, 98%) as a white powder. Recrystallization

from water gave pure **18** as silky needles: mp 187–188 °C, lit.[4] 187–188 °C; $[\alpha]_D$ + 57.8° (*c* 0.65, 1 M aq NaOH); lit.[4] + 57.7°; ^{1}H NMR (Me_2SO-d_6): δ 1.18–1.58 (m, 6 H, 3 × CH_2), 2.20 (t, 2 H, C**H**$_2$CO$_2$Me), 3.33 (m, 1 H, $J_{2,3}$ 4 Hz, H-2), 3.39 (dd, 1 H, $J_{5a,5b}$ 9.8, $J_{4,5a}$ 4.6 Hz, H-5a), 3.65 (d, 1 H, H-5b), 4.07 (dd, 1 H, $J_{3,4}$ 8.7 Hz, H-3), 4.21 (dd, 1 H, H-4), 6.36 and 6.40 (2 × bs, 1 H each, 2 × NH); ^{13}C NMR (Me_2SO-d_6): δ 25.29, 25.99 and 28.83 (3 × CH_2), 34.35 (**C**H$_2$CO$_2$Me), 57.53 (C-4), 59.01 (C-3), 74.34 (C-5), 82.85 (C-2), 163.80 (NHCONH), 176.09 (CO_2H).

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