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A versatile route for the stereoselective synthesis of oxybiotin ☆

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ABSTRACT

An efficient 10-step synthesis of oxybiotin, an oxygen analogue of biotin, is disclosed starting from 3,4,6-tri-*O*-benzyl-D-glucal.

1. Introduction

Carbohydrates represent the single most abundant class of organic compounds associated with living matter. They can be considered as an important resource for synthetic organic chemists due to the wealth of functional, conformational, and stereochemical information associated with them.[1] The advantages of using carbohydrates include that they display a high density of functional groups, are available as single enantiomers, and contain multiple sites for attachment of recognition groups.[2] Hence, for the past few decades, the generation of enantiopure, biologically active natural and non-natural products from readily available carbohydrates has become a topic of intensive research activity.[3,4]

Recently, we have accomplished a practical and efficient method for the stereoselective synthesis of jaspine B, a marine natural product, starting from 3,4,6-tri-*O*-benzyl-D-galactal utilizing the intramolecular asymmetric ring opening (ARO) of the 2,3-epoxy alcohol as a pivotal step.[5] While working on the synthesis of jaspine B, we envisioned that some more biologically important compounds having the tetrahydrofuran backbone can be easily synthesized by using the glycal derived enantiopure THFs[6] as key intermediates. In this endeavor, we adeptly developed a general stereoselective method for the synthesis of γ-azido tetrahydrofuran carboxylic acids starting from glycals.[7] As a part of our continuing efforts to fully explore and exploit our recently synthesized versatile THF's[6a] toward the synthesis of biologically important compounds, we herein report the stereoselective synthesis of oxybiotin using one of the THFs as an enantiopure key intermediate.

Oxybiotin is an oxygenated analogue of biotin in which the sulfur atom is replaced by oxygen (Fig. 1). This oxygen analogue of biotin has been named oxybiotin, because of its structural relationship to biotin and its ability to replace biotin as an essential metabolite for various species of microorganisms and higher animals.[8] Hoffman achieved the first total synthesis of oxybiotin in its *dl*-form.[9] Later, Ohrui et al.[10] reported the total synthesis of optically active (+)-oxybiotin in 19 steps starting from D-glucose. It showed biotin-like activity for several species of bacteria, yeast, rats, and chickens.[11] Afterwards, only Popsavin et al. have devoted much effort toward its synthesis starting from D-xylose and D-arabinose as chiral sources.[12–16] Notably, among the numerous biotin analogues, the only one which has been shown to exhibit growth promoting activity without being transformed into biotin is oxybiotin.[17] This shows that oxybiotin is intrinsically active.

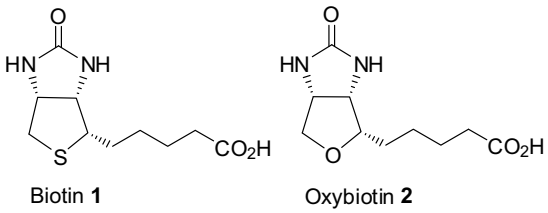

Figure 1.

Our retrosynthetic plan (Fig. 2) relies on the consecutive approach toward the synthesis of trisubstituted THF domains, a method recently developed by us.[6a] The THF domain **4** is easily available in a single step from glucal-derived allylic alcohol involving the intramolecular ARO of the in situ formed enantiomerically pure 2,3-epoxy alcohol, and carries the right stereochemistry at C1 of the tetrahydrofuran.

The isopropylidene protected side-chain diol at C1 of **4** can be easily transformed into an aldehyde group for introduction of the valeric acid side chain. The replacement of hydroxyl functionalities at C2 and C3 by the nitrogen atoms in an S_N2 fashion can provide the required ureido system of the oxybiotin.

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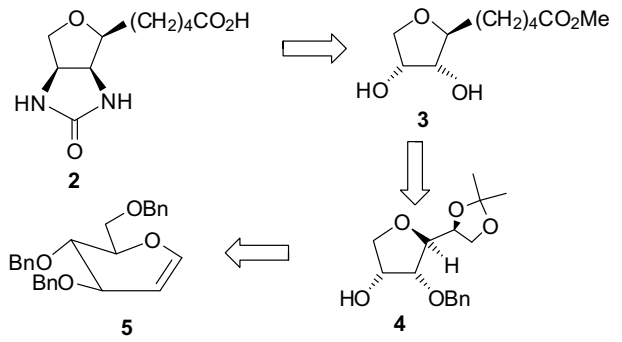


Figure 2. Retrosynthetic pathway.

2. Results and discussion

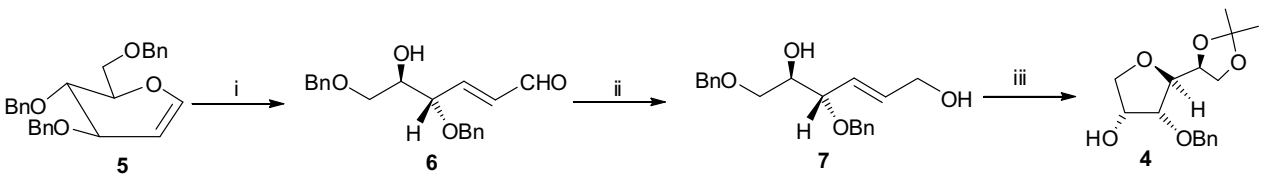
The synthesis of oxybiotin began with an inexpensive starting material 3,4,6-tri-*O*-benzyl-D-glucal to obtain the THF domain **4** in a one-pot process, as shown in Scheme 1. The isopropylidene in domain **4** was then smoothly converted to an aldehyde group in a single step using 1.3 equiv of periodic acid. Notably, aldehyde **8** could be easily stored for long periods unlike the intermediate aldehyde used by Popsavin et al.[16] The Wittig olefination of the crude aldehyde **8** with the freshly prepared 3-(carbomethoxy-2-propenylidene) triphenylphosphorane gave the expected dienoate **9** as an inseparable mixture of isomers (^{1}H NMR).

The catalytic hydrogenation of the C2 benzyl and two double bonds in the side chain of **9** over $Pd(OH)_2$ in methanol was carried out to obtain **3** in a single step. Although the specific rotation $\{[\alpha]_D^{28} = -26.6$ (c 0.42, $CHCl_3$)$\}$ of the sample is different from the literature value $\{[\alpha]_D^{28} = -39.4$ (c 1.0, $CHCl_3$)$\}$,[16] the IR, ^{1}H, and ^{13}C NMR data are consistent with structure **3**. However, the physico-chemical data of the 3,4-ditriflate **10** prepared from **3** by using triflic anhydride and pyridine in dichloromethane under dry condition is in full agreement with the reported values.[16] The crude 3,4-ditriflate **10** was then treated with sodium azide in HMPA to afford the corresponding diazido derivative **11** as the only reaction product (68% yield for two steps).

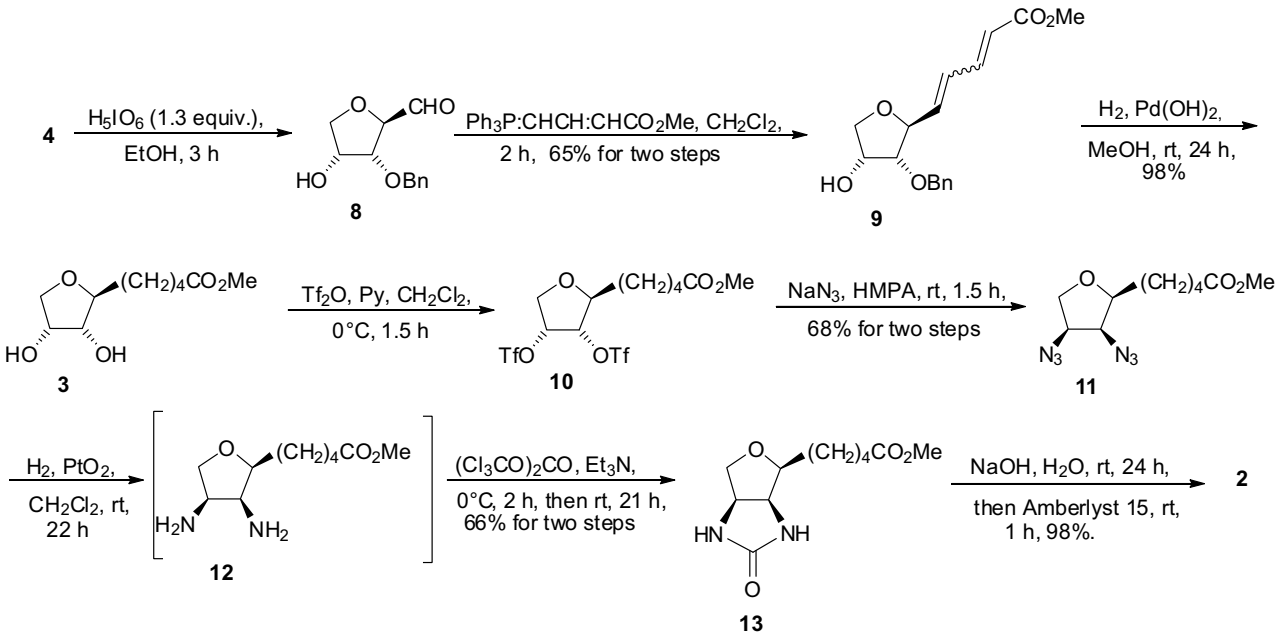
In a one-step sequence, diazide **11** was hydrogenated in the presence of catalytic amount of PtO_2 to the intermediate diamine **12**, which was subsequently protected with triphosgene to obtain the methyl ester of the oxybiotin **13**. Treatment of **13** with 1 M NaOH followed by neutralization with properly cleaned Amberlyst 15 resin[18] furnished the target compound **2** in quantitative yield (Scheme 2). The physical and spectroscopic data of the title compound are in good agreement with the literature values.

3. Conclusion

In conclusion, a versatile approach for the synthesis of oxybiotin, the analogue of biotin, was achieved starting from 3,4,6-tri-



Scheme 1. Synthesis of **4**. Reagents and conditions: (i) $HgSO_4$ (cat.), 0.01 N H_2SO_4, 1,4-dioxane, 0 °C–rt, 8 h; (ii) $NaBH_4$ (0.5 equiv), $CeCl_3{\cdot}7H_2O$ (1.0 equiv), EtOH, 0 °C–rt, 3 h, 57% for two steps; (iii) Ti(*O*-*i*-Pr)$_4$ (1.0 equiv), L-(+)-DET (1.2 equiv), *t*-BuOOH (2.0 equiv), MS 4 Å, CH_2Cl_2, −25 °C to 0 °C, 2.5 h, satd citric acid in acetone, 2 h, 51%.



Scheme 2. Synthesis of oxybiotin **2**.

O-benzyl-D-glucal. It is noteworthy that key intermediate THF domain **4**,[6a] which can be prepared in multi-gram scale, showed its versatility toward the synthesis of compounds of biological importance.

4. Experimental

4.1. General

CH_2Cl_2 was distilled from calcium hydride. Ti(*O*-*i*-Pr)$_4$, (+)-diethyltartrate, 6.0 M solution of *t*-BuOOH in nonane, triflic anhydride, sodium azide, and triphosgene were purchased from Aldrich Chemical Co., whereas **5** was synthesized in a laboratory. All the products were characterized by ^{1}H, ^{13}C, IR, ESI-MS, EI-HRMS, and DART-HRMS (C, H, O, N, S).

Analytical TLC was performed using 2.5 × 5 cm plates coated with a 0.25 mm thickness of silica gel (60F-254), and visualization was accomplished with $CeSO_4$, or in some cases 30% (v/v) H_2SO_4 in MeOH and subsequent charring over the hotplate. ^{1}H NMR spectra were recorded at 300 MHz with TMS as the internal reference. ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$, D_2O, or DMSO-d_6 as the internal reference. Chemical shifts were given in parts per million downfield from internal standard Me_4Si. IR spectra were recorded on Perkin–Elmer 881 and FTIR-8210 PC Shimadzu Spectrophotometers. Mass spectra were recorded on a JEOL JMS-600H high-resolution spectrometer using EI mode at 70 eV. Optical rotations were determined on an Autopol III polarimeter using a 1 dm cell at 28 °C; concentrations mentioned are in g/100 mL.

4.2. Procedure for the preparation of the Wittig salt

To a solution of PPh_3 (1 equiv) in toluene was added methyl 4-bromocrotonate (1 equiv) in toluene and the reaction was left for stirring at rt overnight. The precipitate formed was filtered, washed with toluene thrice, and dried. The salt thus obtained was dissolved in water, and to it 10% NaOH was added dropwise until the yellow precipitate of the ylide formed (solution should be alkaline). The ylide was filtered, washed with water, dried, and used for the reaction.

4.2.1. (2*R*,3*R*,4*R*)-3-(Benzyloxy)-4-hydroxytetrahydrofuran-2-carbaldehyde 8

A solution of **4**[6a] (500 mg, 1.70 mmol) and periodic acid (504 mg, 2.21 mmol) in 10 mL of dry ethyl acetate was allowed to stir at room temperature for 1.5 h. After the completion of reaction (TLC), the reaction mixture was quenched with saturated solution of $NaHCO_3$ and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford 380 mg of crude aldehyde **8** (>95% pure from ^{1}H NMR) as a colorless syrup which was immediately used for the next step. IR (neat, cm^{-1}): 3402 (O–H str), 2926 (=C–H str), 1738 (C=O str), 1631, 1456, (C=C str), 1216, 1114, 1066 (C–O str). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92–4.10 (m, 3H, H-3 and H-5), 4.19 (dd, *J* = 4.3, 8.9 Hz, 1H, H-4), 4.30 (dd, *J* = 1.0, 5.5 Hz, 1H, H-2), 4.64, 4.74 (2d, *J* = 11.7 Hz, 2H, C*H*$_2$Ph), 7.32–7.41 (m, 5H, ArH), 9.69 (d, *J* = 1.3 Hz, 1H, –C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.6 (C-5), 73.2 (*C*H$_2$Ph), 74.1 (C-4), 79.9 (C-3), 85.6 (C-2), 128.4 (ArC), 128.8 (ArC), 129.1 (ArC), 136.9 (Ar qC), 201.3 (–*C*HO). DART-HRMS: calcd for [M+NH_4^+], $C_{12}H_{18}N_1O_4$ *m*/*z* 240.12358, measured 240.12530.

4.2.2. Methyl 5-((2*S*,3*S*,4*R*)-3,4-dihydroxytetrahydrofuran-2-yl) pentanoate 3

To the solution of aldehyde **8** (380 mg, 1.71 mmol) in CH_2Cl_2, freshly prepared 3-(carbomethoxy-2-propenylidene) triphenylphosphorane (1.23 g, 3.4 mmol) was added in one portion (15 mL) and left for stirring. After 1.5 h of stirring, change in color of the reaction mixture from yellow to orange was observed. The solvent was evaporated under reduced pressure and passed through a short column to furnish 338 mg of pure compound **9** as a mixture of diastereomers.

Oil, eluent for column chromatography: EtOAc/hexane (1/5, v/v), R_f 0.48 (1/2 EtOAc/hexane). IR (neat, cm^{-1}): 3432 (–OH str), 1712 (C=O, ester), 1647, 1520, 1437 (C=C str), 1216. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.67, 2.72 (2d, 2H, –OH and –OH$_D$), 3.70–3.77 (m, 7H, CO_2Me, CO_2Me_D, H-3), 3.86–3.90 (m, 2H, H-5a, H$_D$-5a), 4.09–4.13 (m, 2H, H-5b, H$_D$-5b), 4.26 (br s, 2H, H-4, H$_D$-4) 4.40 (t, *J* = 6.4 Hz, 1H, H$_D$-2) 4.54–4.69 (m, 4H, C*H*$_2$Ph, C*H*$_2$Ph$_D$) 4.83 (t, *J* = 7.8 Hz, 1H, H-2) 5.78 (t, *J* = 8.5 Hz, 1H, H-1′) 5.88–6.07 (m, 3H, H$_D$-1′, H-4′, H$_D$-4′) 6.29 (t, *J* = 11.2 Hz, 1H, H-2′), 6.42 (dd, *J* = 11.8, 15.2 Hz, 1H, H$_D$-2′), 7.28–7.39 (m, 11H, ArH, Ar$_D$H, H$_D$-3′), 7.69 (dd, *J* = 12.3, 15.1 Hz, 1H, H-3′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.9 (CO_2Me), 70.1 (C-4), 70.2 (C$_D$-4), 73.4 (*C*H$_2$Ph), 73.7 (C$_D$-5), 73.9 (C-5), 76.3 (C-2), 80.2 (C$_D$-2), 83.7 (C$_D$-3), 84.1 (C-3), 122.0 (C$_D$-4′), 123.72 (C-4′), 128.3 (ArH), 128.4 (Ar$_D$H), 128.6 (ArH), 128.8 (Ar$_D$H), 128.9 (ArH), 129.0 (Ar$_D$H), 129.5 (C$_D$-2′), 130.0 (C-2′), 137.2 (Arqc), 137.6 (C-1′), 139.5 (C-3′), 140.1 (C$_D$-1′), 143.9 (C$_D$-3′), 167.4 (*C*O$_2$Me), 167.6 (*C*O$_2$Me$_D$); mass (ESI-MS) *m*/*z* 304, found 343 [M+K]$^+$. DART-HRMS: calcd for [M+1]$^{+\cdot}$, $C_{17}H_{21}O_5$, *m*/*z* 305.13890, measured 305.13840.

To the mixture of pure dienoate **9** (338 mg, 1.1 mmol) in dry methanol, degassed with argon, was added 10% $Pd(OH)_2$ on carbon (30 mg). The resulting mixture was stirred under 1 atm H_2 using a balloon at room temperature for 24 h. After the completion of the reaction (TLC), the catalyst was filtered, washed with methanol twice, and the filtrate was concentrated to afford the diol **3** as a colorless oil.

$[\alpha]_D^{28} = -26.6$ (*c* 0.42, $CHCl_3$), R_f 0.26 (Et_2O). IR (neat, cm^{-1}): 3405 (O–H str), 1726 (C=O, ester). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37–1.71 (m, 6H, 3 × CH_2), 2.32 (t, *J* = 7.2 Hz, 2H, C*H*$_2$CO$_2$Me), 3.42–3.71 (br s, 8H, CO_2CH_3, 2 × OH, H-2, H-3 and H-5a), 4.05 (dd, *J* = 4.6, 9.7 Hz, 1H, H-5b), 4.17 (br s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4) δ 25.2, 25.7 and 33.3 (3 × CH_2), 34.3 (*C*H$_2$CO$_2$Me), 51.9 (CO_2CH_3), 71.4 (C-4), 73.0 (C-5), 76.3 (C-2), 82.3 (C-3), 174.5 (*C*O$_2$CH$_3$); mass (EI-MS) *m*/*z* 218, found 219 [M+1]$^{+\cdot}$. DART-HRMS: calcd for [M+1]$^{+\cdot}$, $C_{10}H_{19}O_5$, *m*/*z* 219.12325, measured 219.12275.

4.2.3. Methyl 5-((2*S*,3*S*,4*R*)-3,4-bis(trifluoromethylsulfonyloxy) tetrahydrofuran-2-yl)pentanoate 10

To the precooled (−10 °C) solution of **3** (242 mg, 0.90 mmol) in dry CH_2Cl_2 and pyridine (0.36 mL, 4.5 mmol) was added dropwise, a cooled solution of trifluoromethane–sulfonic anhydride (0.9 mL, 5.4 mmol). The temperature of the reaction mixture was raised to 0 °C and then left for stirring for 1.5 h. After the completion of reaction (TLC), the reaction mixture was neutralized with 10 mL of saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 15 mL), dried, evaporated, and as such used for the next step without purification. A small amount of the compound was purified on silica gel column chromatography to obtain the physical data of **10**.

Oil, eluent for column chromatography: EtOAc/hexane (2/25, v/v), $[\alpha]_D^{28} = -36.6$ (*c* 0.18, $CHCl_3$), R_f 0.68 (CH_2Cl_2). IR (neat, cm^{-1}): 1730 (C=O, ester), 1425, 1217 (SO_2), 1144 (C–F). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45–1.77 (m, 6H, 3 × CH_2), 2.34 (t, *J* = 2.9 Hz, 2H, C*H*$_2$CO$_2$Me), 3.69 (s, 3H, CO_2CH_3), 4.04–4.14 (m, 2H, H-5a, H-2), 4.35 (dd, 1H, *J* = 5.3, 11.1 Hz, H-5b), 4.86 (t, 1H, *J* = 6.0 Hz, H-3), 5.32 (dd, *J* = 4.9, 9.7 Hz, 1H, H-4). ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4) δ 24.8, 25.0 and 31.8 (3 × CH_2), 34.0 (*C*H$_2$CO$_2$Me), 51.9 (CO_2CH_3), 69.7 (C-5), 79.7 (C-2), 81.6 (C-4), 84.0 (C-3), 116.6 (CF_3SO_2), 120.8 (CF_3SO_2), 174.1 (*C*O$_2$CH$_3$). EI-HRMS: calcd for [M+1]$^{+\cdot}$, $C_{12}H_{17}F_6O_9S_2$, *m*/*z* 483.0218, measured 483.0211.

4.2.4. Methyl 5-((2*S*,3*S*,4*R*)-3,4-diazidotetrahydrofuran-2-yl) pentanoate 11

To a solution of **10** (300 mg, 0.62 mmol) dissolved in a minimal amount of HMPA (2 mL) was added an excess amount of NaN_3 (1.0 g, 15.5 mmol) and left for stirring at room temperature. After 1.5 h of stirring, the reaction mixture was diluted with 20 mL of water and extracted with 1:1 benzene–hexane (3 × 15 mL). The combined organic layer collected was dried and evaporated to give the crude azide, which on column chromatography gave the pure compound **11** as a yellow oil. Oil, eluent for column chromatography: EtOAc/hexane (3/20, v/v), $[\alpha]_D^{28} = +31.3$ (*c* 0.15, $CHCl_3$), R_f 0.28 (CH_2Cl_2). IR (neat, cm^{-1}): 2105 ($-N_3$ str) 1731 (C=O, ester). ^1H NMR (300 MHz, $CDCl_3$) δ 1.39–1.48 (m, 2H, $-CH_2$), 1.64–1.74 (m, 4H, 2 × CH_2) 2.34 (t, *J* = 7.3 Hz, 2H, CH_2CO_2Me), 3.67 (s, 3H, CO_2CH_3), 3.80 (dd, 1H, *J* = 7.2, 9.0 Hz, H-5a), 3.86–3.92 (m, 1H, H-2), 3.99–4.04 (m, 2H, H-3 and H-5b), 4.25 (m, 1H, H-4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 25.9 and 30.1 (3 × CH_2), 34.1 (CH_2CO_2Me), 51.9 (CO_2CH_3), 63.4 (C-4), 65.6 (C-3), 68.9 (C-5), 81.2 (C-2), 174.3 (CO_2Me); mass (ESI-MS) *m*/*z* 268, found 269 $[M+1]^{+\cdot}$. DART-HRMS: calcd for $[M+1]^{+\cdot}$, $C_{10}H_{17}N_6O_3$, *m*/*z* 269.13621, measured 269.13360. DART-HRMS: calcd for $[M+NH_4]^{+\cdot}$, $C_{10}H_{20}N_7O_3$, *m*/*z* 286.16276, measured 286.15899.

4.2.5. Methyl ester of oxybiotin 13

A 50 mL round-bottomed flask was charged with 85 mg of azide **11** (0.3 mmol), 10 mL of CH_2Cl_2, and 15 mg of PtO_2. The reaction mixture was stirred under 1 atm hydrogen for 21 h. After the complete consumption of starting material, the reaction mixture was cooled to 0 °C and to it were added Et_3N (0.13 mL, 0.93 mmol) and a solution of triphosgene (69 mg, 0.23 mmol) in dry CH_2Cl_2. After stirring for 2 h under the same temperature, the reaction mixture was left for stirring at room temperature. After 21 h, the catalyst was filtered off and washed thrice with CH_2Cl_2. Concentration of the filtrate under vacuum provided the crude residue which on column chromatography afforded pure **13**. Oil, eluent for column chromatography: methanol/EtOAc (2/25, v/v), $[\alpha]_D^{28} = +35.3$ (*c* 0.20, $CHCl_3$), R_f 0.29 (Me_2CO). IR (neat, cm^{-1}): 3020 (NH), 1710 (CO_2Me, NHCONH). ^1H NMR (300 MHz, $CDCl_3$) δ 1.37–1.70 (m, 6H, 3 × CH_2), 2.33 (t, *J* = 7.3 Hz, 2H, CH_2CO_2Me), 3.43 (br s, 1H, H-2), 3.52 (dd, *J* = 3.5, 9.7 Hz, 1H, H-5a), 3.65 (s, 3H, CO_2CH_3), 3.89 (d, *J* = 9.9 Hz, 1H, H-5b), 4.19–4.21 (m, 1H, H-3), 4.35 (br s, 1H, H-4), 5.90 and 6.09 (2 × br s, 1H each, 2 × NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 25.9 and 28.8 (3 × CH_2), 34.1 (CH_2CO_2Me), 51.8 (CO_2CH_3), 57.9 (C-4), 59.4 (C-3), 74.6 (C-5), 83.0 (C-2), 163.6 (NHCONH), 174.6 (CO_2Me). mass (ESI-MS) *m*/*z* 242, found 243 $[M+1]^{+\cdot}$; EI-HRMS: calcd for $[M+1]^{+\cdot}$, $C_{11}H_{18}N_2O_4$ 242.1267, measured 242.1261.

4.2.6. (+)-Oxybiotin 2

A freshly prepared 1 M solution of NaOH (2 mL) was added to **13** (55 mg, 0.2 mmol) and stirred for 24 h at room temperature. The reaction mixture was diluted with water and neutralized with properly cleaned Amberlyst-15 resin (3 g) catalyst by stirring at room temperature for an additional 1 h. The reaction mixture was filtered, the resin was washed with a minimal amount of water and the whole aqueous solution was co-evaporated with toluene to give **2**. Recrystallization of the crude product from water gave 40 mg of pure **2** as silky white crystals. Mp: 185–187 °C, $[\alpha]_D^{28} = +57.2$ (*c* 0.10, 1 M NaOH), IR (KBr, cm^{-1}): 3401 (COOH), 1704 (COOH), 1673 (NHCONH). ^1H NMR (300 MHz, D_2O): δ 1.40–1.63 (m, 6H, 3 × CH_2), 2.34 (t, *J* = 7.2 Hz, 2H, CH_2CO_2H), 3.53–3.60 (m, 2H, H-2 and H-5a), 3.81 (d, *J* =10.3 Hz, 1H, H-5b), 4.29 (dd, *J* = 3.9, 8.6 Hz, 1H, H-3), 4.45 (dd, *J* = 4.1, 8.6 Hz, 1H, H-4). ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 25.3, 25.9 and 28.9 (3 × CH_2), 34.2 (CH_2CO_2H), 57.2 (C-4), 58.7 (C-3), 74.3 (C-5), 82.7 (C-2), 163.2 (NHCONH), 175.1 (CO_2H); EI-HRMS: calcd for ($M^{+\cdot}$) $C_{10}H_{16}N_2O_4$, *m*/*z* 228.1110, measured 228.1104. EI-HRMS: calcd for [$M^{+\cdot}$−OH], $C_{10}H_{15}N_2O_3$, *m*/*z* 211.1083, measured 211.1099.

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References

1. Leeuwenburgh, M. A.; Kulker, C.; Duynstee, H. I.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1999**, *55*, 8253–8262.
2. Wunberg, T.; Kallus, C.; Opatz, T.; Henke, S.; Schmidt, W.; Kunz, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 2503–2505.
3. (a) Hanessian, S. *Acc. Chem. Res.* **1979**, 159–165; (b) Fraser-Reid, B.; Sun, K. M.; Tam, T. F. *Bull. Soc. Chim. Fr.* **1981**, 238–246; (c) Inch, T. D. *Tetrahedron* **1984**, *40*, 3161–3213; (d) Hollingsworth, R. I.; Wang, G. *Chem. Rev.* **2000**, *100*, 4267–4282.
4. Hanessian, S. *Total Synthesis of Natural Products; The 'Chiron' Approach*; Pergamon: Oxford, 1983.
5. Reddy, L. V. R.; Reddy, P. V.; Shaw, A. K. *Tetrahedron: Asymmetry* **2007**, *18*, 542–546.
6. (a) Sagar, R.; Reddy, L. V. R.; Saquib, M.; Kumar, B.; Shaw, A. K. *Tetrahedron: Asymmetry* **2006**, *17*, 3294–3299; (b) Reddy, L. V. R.; Roy, A. D.; Roy, R.; Shaw, A. K. *Chem. Commun.* **2006**, 3444–3446.
7. Reddy, P. V.; Reddy, L. V. R.; Kumar, B.; Kumar, R.; Maulik, P. R.; Shaw, A. K. *Tetrahedron* **2008**, *64*, 2153–2159.
8. Axelrod, A. E.; Pilgrim, F. J.; Hofmann, K. *J. Biol. Chem.* **1946**, *163*, 191–194.
9. Hofmann, K. *J. Am. Chem. Soc.* **1945**, *67*, 1459–1462.
10. Ohrui, H.; Kuzuhara, H.; Emoto, S. *Agric. Biol. Chem.* **1971**, *35*, 752–755.
11. Potter, R. L.; Elvehjem, C. A. *J. Biol. Chem.* **1950**, *183*, 587–592.
12. Miljković, D.; Popsavin, V.; Harangi, J. *Tetrahedron Lett.* **1987**, *28*, 5733–5736.
13. Miljković, D.; Popsavin, V.; Harangi, J.; Batta, G. *J. Serb. Chem. Soc.* **1989**, *54*, 163–165.
14. Popsavin, V.; Benedeković, G.; Popsavin, M.; Miljković, D. *Carbohydr. Res.* **2002**, *337*, 459–465.
15. Popsavin, V.; Benedeković, G.; Popsavin, M. *Tetrahedron Lett.* **2002**, *43*, 2281–2284.
16. Popsavin, V.; Benedeković, G.; Popsavin, M.; Divjaković, V.; Armbruster, T. *Tetrahedron* **2004**, *60*, 5225–5235.
17. McCoy, R. H.; McKibben, J. N.; Axelrod, A. E.; Hofmann, K. *J. Biol. Chem.* **1948**, *176*, 1319–1326 and references cited therein.
18. Amberlyst 15 beads (≈100 gm) as received were soaked for 2 h in 500 mL of deionized water. After the 2 h soaking, the beads were placed in a glass column. Deionized water was passed through the column until the effluents ran clear. Six bed volumes of 10% (electronic grade) hydrochloric acid were passed through the column with a 10 min residence time for each bed. Finally, a large volume of deionized water was passed through the column until the conductivity of the water going into the column was the same as the effluents leaving the column. At this point the beads were considered ready for use and dried (see U.S. Patent 5,936,071).