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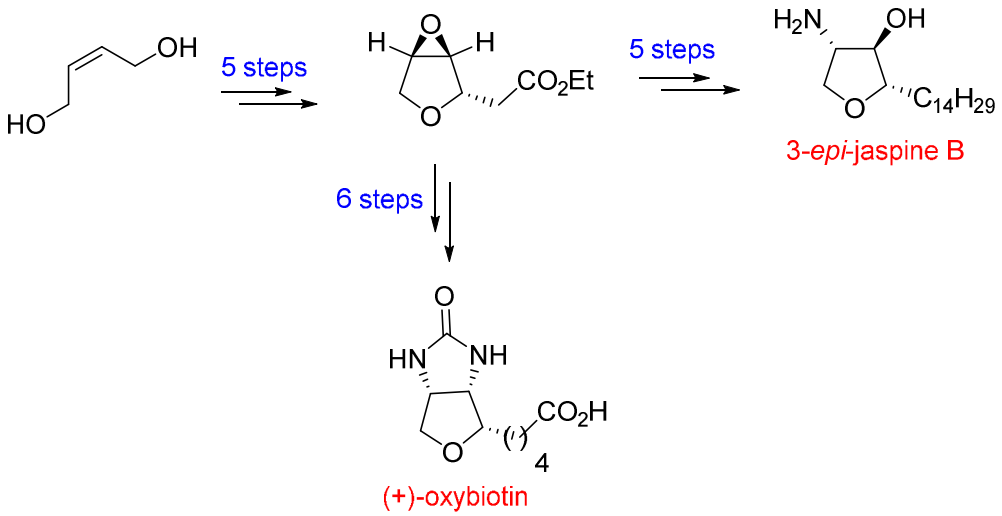

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ARTICLE TYPE

A short enantioselective synthesis of 3-*epi*-jaspine B and (+)-oxybiotin *via* intramolecular tandem desilylation oxa-Michael addition strategy †

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A new synthesis of cytotoxic anhydrophytosphingosine 3-*epi*-jaspine B (34.7% overall yield; 97% ee) and (+)-oxybiotin (21.2% overall yield; 97% ee) bioactive oxygen analogue of biotin; is described starting from commercially available *cis*-2-butene-1,4-diol. The key reactions employed in the synthesis include Sharpless asymmetric epoxidation and a novel tandem desilylation oxa-Michael addition reaction strategy to construct tetrahydrofuran core (dr >99%).

Introduction

Jaspine B (**1**), a naturally occurring anhydrophytosphingosine, was isolated independently from two marine sponges (*Pachastrissa* sp. and *Jaspis* sp.).[1] This marine sponge molecule and its diastereomers (**2** & **3**) have been reported to possess a strong anticancer and cytotoxic properties against several cancer cell lines with IC_{50} values in the submicromolar range.[2] In addition, these bioactive natural products (**1-3**) have been found to inhibit sphingosine kinases (SphKs) and atypical protein kinase C.[3] In structural modification studies, (+)-oxybiotin (**5**), an oxygenated analogue of (+)-biotin (**4**) was found to retain the growth stimulatory activity of natural biotin, indicating that replacement of the sulphur atom with oxygen atom does not adversely effect the biological activity of biotin. In view of their biological importance, different synthetic methods involving a chiral pool approaches like Garner aldehyde,[4] isoascorbic acid,[5] D-glucose,[6] D-xylose,[7] D-arabinose,[8] and 3,4,6-*tri*-O-benzyl-D-glucal,[9] as the starting materials and in other cases asymmetric catalysis[10] have been developed for the total synthesis of jaspine B (**1**), its isomers (**2** & **3**) & (+)-oxybiotin (**5**) (**Figure 1**). However, many of the reported methods suffer from one or more disadvantages, which include use of chiral pool strategy,[4-10] longer reaction sequence with exotic reagents and low yields.

In view of elucidating the effect of stereochemistry and substitution on the biological activity as well as study of mode of action of jaspine and its stereoisomers, a useful synthetic route with high flexibility, yield and stereoselectivity is required. In continuation of our interest in the asymmetric synthesis of bioactive molecules,[11] we report, in this paper an efficient synthesis of 3-*epi*-jaspine B **3** and (+)-oxybiotin **5** by employing Sharpless asymmetric epoxidation (AE) and diastereoselective tandem desilylation oxa-Michael addition reaction as the key steps. Because of the presence of tri-substituted THF ring in

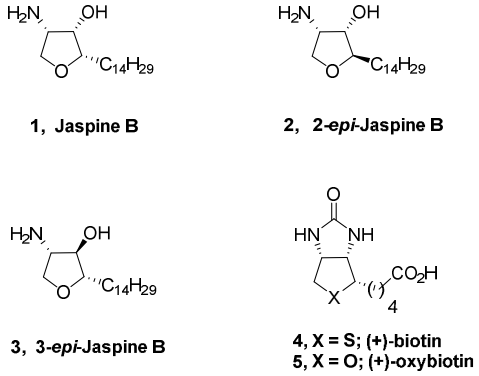

Figure 1 Structure's of some of the bioactive molecules

3-*epi*-jaspine B **3** and (+)-oxybiotin **5**, a common structural motif present in a large number of bioactive molecules, we envisioned cyclic epoxide **7** as the key precursor in the synthesis of 3-*epi*-jaspine B **3** and (+)-oxybiotin **5**.

Results and discussion

During our initial attempt in the synthesis of (-)-oseltamivir, we came across unexpectedly a one-pot tandem desilylation oxa-Michael addition reaction for the facile construction of optically & diastereochemically pure tetrahydrofurans. The synthesis of α,β-unsaturated epoxy ester **6**, which is a key intermediate in the synthesis of Tamiflu, was recently reported[12] by us starting from *cis*-2-butene-1,4-diol essentially involving 4 straightforward steps with 97%ee: (i) monosilylation of *cis*-2-butene-1,4-diol; (ii) AE of allylic alcohol; (iii) oxidation of epoxy alcohol; & (iv) Wittig olefinatin reaction. When silyl deprotection in epoxy ester **6** was attempted with TBAF at room temprature to our surprise, the corresponding THF epoxy core **7**, a Michael adduct was obtained in 93% yield;> 99%de. Its enantio & diastereoselectivity was confirmed by chiral HPLC, ^{1}H NMR and 2D NMR spectral analysis.[13] The relative stereochemistry of the three stereocentres generated were unambiguously determined using 2D homonuclear (COSY, and NOESY) and heteronuclear (HSQC and HMBC) NMR spectroscopy. The 2D NOESY spectrum of

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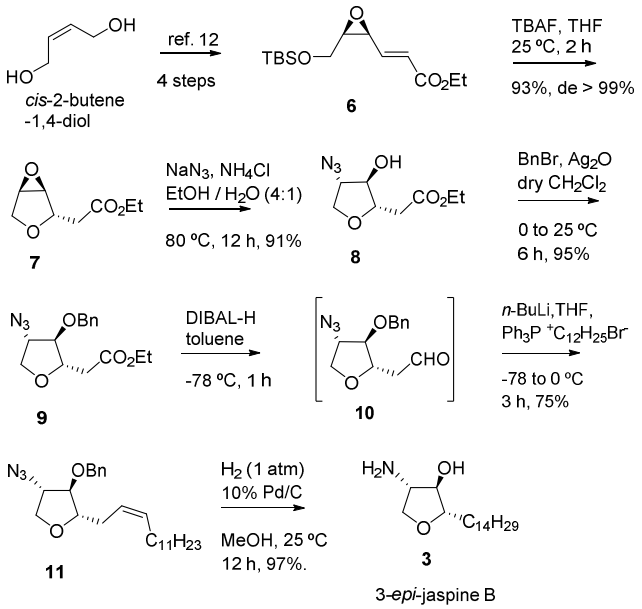
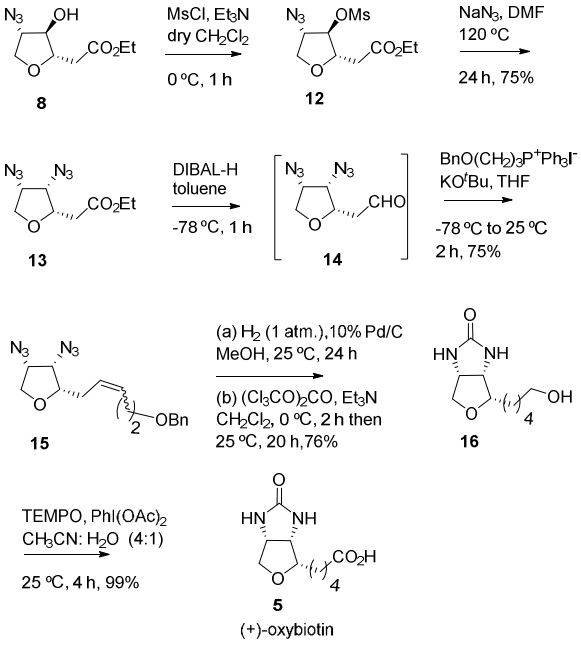
† Electronic Supplementary Information (ESI) available
Experimental details and spectral data of all the new compounds.

compound **7** was used to find out the relative *anti* stereochemistry in cyclic epoxide **7**. This novel tandem reaction has taken place *via* TBAF mediated desilylation followed by intramolecular oxa-Michael addition reaction. After determining the relative stereochemistry in compound **7**, we proceeded to the synthesis of target molecules 3-*epi*-jaspine B **3** and (+)-oxybiotin **5**.The regioselective ring opening of epoxide **7** with azide ion in the presence of NH_4Cl as a coordinating salt in ethanol/water system was accomplished to give *anti*-azido alcohol **8** in 91% yield. The OH group in **8** was then protected as its benzyl ether **9**, using silver oxide and benzyl bromide under neutral reaction condition which was selectively reduced to give aldehyde **10** (DIBAL-H, toluene, -78 ^oC). The crude aldehyde compound **10** was then immediately subjected to Wittig olefination reaction (*n*-BuLi, $PPh_3^+C_{12}H_{25}Br^-$, THF, -78 to 0 ºC) to give the olefinic azide **11** in 75% yield. Finally, the catalytic hydrogenation of compound **11** led to the global reduction of three functional groups (azide, C=C bond and benzyl ether) all occuring in a single step affording 3-*epi*-jaspine B **3** with an overall yield of 34.7% (**Scheme 1**). The physical constant, optical rotation & spectroscopic data of **3** was in complete agreement with the reported values.[14]



Scheme 1. Synthesis of *3-epi*-jaspine B **3**

After the successful completion of the synthesis of 3-*epi*-jaspine B, synthesis of (+)-oxybiotin **(5)** was undertaken starting from the common intermediate azido alcohol **8** (**Scheme 1).** Alcohol **8** was protected as its mesylate **12** using mesyl chloride and NEt_3 as a base which was then subjected to S_N2 displacement with azide ion (NaN_3, DMF, 120 ^oC, 75%) to produce the diazide **13** with complete stereochemical inversion. Ester **13** was selectively reduced (DIBAL-H, toluene, -78 ^oC) to give an aldehyde **14** *in situ* which was transformed to a inseparable mixture of *E* and *Z* olefins **15** under Wittig reaction conditions (KO^tBu, $BnO(CH_2)_3P^+Ph_3I^-$, THF, 0 ^oC, 75%). The Pd catalyzed hydrogenation of diazido derivative **15** was carried out in MeOH for 24 h which generates diamine followed by its *in situ* protection with triphosgene gave the oxazolidinone derivative **16** in 76% yield. The complete oxidation of alcohol **16** under TEMPO/BAIB in CH_3CN:H_2O (4:1) conditions was achieved to furnish final compound (+)-oxybiotin **(5)** in quantitative yield (**Scheme 2**). The physical constant, optical rotation & spectral data of **5** were in excellent agreement with the reported values.[6b]



Scheme2. Synthesis of (+)-oxybiotin **5**

Conclusion

In conclusion, we have accomplished a new enantioselective synthesis of 3-*epi* jaspine B (**3**) (34.7% overall yield) and (+)-oxybiotin **(5)** (21.2% overall yield) starting from readily available *cis*-2-butene-1,4-diol. This method comprises operationally simple reactions with fewer steps, high overall yields with the use of inexpensive & non toxic reagents.The strategy of the diastereoselective tandem desilylation oxa-Michael addition reaction employed here can be applied to the synthesis of other THF based bioactive molecules and studies pertaining to that are currently underway.

Acknowledgments

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Experimental Section

Ethyl 2-((1*S*, 2*S*, 5*R*)-3,6-dioxabicyclo[3.1.0]hexan-2-yl)acetate (7)

To a well stirred solution of silyl ether **6** (6 g, 20.97 mmol) in THF (40 mL) was added 1 M solution of tetrabutylammonium fluoride (30 mL, 41.95 mmol) at 25 ^oC. The reaction mixture was stirred at this temperature for 2 h after which the solvent was removed under reduced pressure and the residue was subjected to column chromatography purification with petroleum ether/EtOAc (5:5 v/v) to afford furan derivative **7** (3.34 g) as a single diastereomer.

Yield: 93%; colorless liquid; $[\alpha]_D^{25}$ -6.2 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): ν_{max} 838, 1256, 1719, 2876 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.0 Hz, 3H), 2.47 (m, 2H), 3.72-3.78 (m, 3H), 3.96 (d, *J* = 10.5 Hz, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 4.46 (t, *J*

= 6.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 36.2, 55.6, 58.2, 60.4, 66.1, 73.7, 169.5; HRMS (*m/z*): calculated $[M+Na]^+$ for $C_8H_{12}O_4Na$: 195.0633, found: 195.0636.

Ethyl 2-((2*S*,3*R*,4*S*)-4-azido-3-hydroxytetrahydrofuran-2-yl) acetate (8)

To a solution of epoxide **7** (3 g, 17.43 mmol) in EtOH/H_2O (80:20 mL) was added NaN_3 (6.83 g, 104.59 mmol) and NH_4Cl (5.6 g, 104.59 mmol) at 25°C. The mixture was then stirred at 80 °C for 12 h. After completion of reaction (monitored by TLC), EtOH was removed by rotary evaporation. The reaction mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with H_2O (20 mL x 3), brine (20 mL x 3) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified using column chromatography with petroleum ether/EtOAc (6:4 v/v) to give the azido alcohol **8** (3.41 g).

Yield: 91%; Yellow liquid; $[\alpha]_D^{25}$ +10.2 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): ν_{max} 1073, 1725, 2105, 3439 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.0 Hz, 3H), 2.65 (dd, *J* = 8.9, 16.8 Hz, 1H), 2.84 (dd, *J* = 5.3, 16.8 Hz, 1H), 3.38 (br s, 1H), 3.88-4.03 (m, 5H), 4.18 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 37.8, 61.2, 67.5, 70.4, 81.2, 81.4, 172.0; HRMS (*m/z*): calculated $[M+Na]^+$ for $C_8H_{13}N_3O_4Na$:238.0803 found: 238.0806.

Ethyl 2-((2*S*,3*R*,4*S*)-4-azido-3-(benzyloxy)tetrahydrofuran-2-yl)acetate (9)

To a solution of azido alcohol **8** (2.1 g, 9.76 mmol) in dry CH_2Cl_2 (60 mL) was added Ag_2O (3.39 g, 14.64 mmol) followed by BnBr (2.0 g, 11.71 mmol) at 0 °C. The reaction mixture was stirred for 6 h at 25 °C and then filtered through a pad of Celite. The filtrate was evaporated to dryness and the residue was purified by column chromatography with petroleum ether/EtOAc (8:2 v/v) to give **9** (2.82 g).

Yield: 95%; yellow oil; $[\alpha]_D^{25}$ +15.8 (*c* 1.0, $CHCl_3$) {lit.[5] $[\alpha]_D^{25}$ +15.4 (*c* 1.1, $CHCl_3$)}; IR ($CHCl_3$): ν_{max} 747, 1020, 1171, 1436, 1497, 1737, 2105, 3031 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.2 Hz, 3H), 2.59 (dd, *J* = 1.9, 7.1 Hz, 2H), 3.79 (d, *J* = 2.1 Hz, 1H), 3.95-4.27 (m, 6H), 4.61 (s, 2H), 7.29-7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 38.2, 60.7, 65.8, 70.8, 72.3, 80.2, 86.9, 127.8, 128.1, 128.6, 137.2, 170.3; HRMS (*m/z*): calculated $[M+Na]^+$ for $C_{15}H_{19}N_3O_4Na$:328.1259 found: 328.1261.

2-((2S,3R,4S)-4-azido-3-(benzyloxy)tetrahydrofuran-2yl)acetaldehyde (10)

To a stirred solution of ester **9** (1.0 g, 3.27 mmol) in dry toluene (50 mL), a solution of diisobutylaluminium hydride (3.6 mL, 3.6 mmol, 1M in cyclohexane) was added dropwise at -78 °C and stirred at this temperature for 1 h. After completion of reaction (monitored by TLC), it was diluted with a saturated solution of potassium sodium tartrate (Rochelle salt) and stirred for further 3 h. The organic phase was separated and the aqueous phase extracted twice with CH_2Cl_2. The combined organic phase was then washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude aldehyde which was purified by column chromatography with petroleum ether/EtOAc (9:1 v/v) to give aldehyde **10** and then it was used for the next reaction.

Yield: 80%; Colorless liquid; $[\alpha]_D^{25}$ +23.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max} 750, 1030, 1168, 1430, 1490, 1710, 2107, 3036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12-2.19 (dd, *J* = 1.7, 6.8 Hz, 2H), 3.82-4.44 (m, 5H), 4.71 (s, 2H), 7.38-7.53 (m, 5H), 9.90 (dd, *J* = 5.4, 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.0, 70.1, 72.0, 82.0, 83.1, 86.0, 123.3, 125.5, 128.0, 138.4, 201.0; HRMS (*m/z*): calculated $[M+Na]^+$ for $C_{13}H_{15}N_3O_3Na$:285.1110 found: 285.1113.

(2*S*,3*R*,4*S*)-4-azido-3-(benzyloxy)-2-((*Z*)-tetradec-2-en-1-yl) tetrahydrofuran (11)

To a stirred solution of dodecyl triphenylphosphonium bromide (2.05 g, 4.0 mmol) in 20 mL of dry THF at -78 °C was added *n*-BuLi (1.6 M solution in hexane 2.5 mL, 3.8 mmol) dropwise and the resulting solution was stirred for 30 min. The aldehyde **10** obtained above was dissolved in dry THF (5 mL) and added dropwise with stirring to the ylide solution at -78 °C. The reaction mixture was then brought to 0 °C and stirred for 3 h. The reaction was quenched with 6 mL of saturated NH_4Cl solution at 0 °C, the solvent was evaporated under reduced pressure; the residue was extracted with EtOAc (2 x15 mL), and dried with anhydrous Na_2SO_4. After evaporation of ethyl acetate the residue was chromatographed (silica gel, 230-400 mesh, petroleum ether/EtOAc (9.5:0.5 v/v) to obtain **11** (1.02 g).

Yield: 75%; Colorless liquid; $[\alpha]_D^{25}$ +6.8 (*c* 2.5, $CHCl_3$) {lit.[5] $[\alpha]_D^{25}$ +6.7 (*c* 2.8, $CHCl_3$)}; IR ($CHCl_3$): ν_{max} 747, 1081, 1460, 1729, 2853, 2937 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, *J* = 7.1 Hz, 3H), 1.31-1.34 (m, 18H), 2.01-2.02 (m, 2H), 2.45-2.47 (m, 2H), 3.63 (dd, *J* = 3.2, 9.8 Hz, 1H), 3.83-3.85 (m, 2H), 3.97-4.01 (m, 1H), 4.14 (dd, *J* = 5.7, 9.5 Hz, 1H), 4.52 (d, *J* = 12.3 Hz, 1H), 4.62 (d, *J* = 11.1 Hz, 1H), 5.33-5.35 (m, 1H), 5.42-5.45 (m, 1H), 7.29-7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.8, 22.7, 27.3, 29.3, 29.5, 29.6, 30.9, 31.9, 65.9, 70.6, 72.2, 84.0, 87.1, 123.9, 127.7, 127.9, 128.4, 133.0, 137.2; HRMS (*m/z*): calculated $[M+Na]^+$ for $C_{25}H_{39}N_3O_2Na$: 436.1543 found: 436.1540.

3-*epi* Jaspine B (3)

To a stirred ethanolic solution of olefin **12** (50 mg, 0.12 mmol, 5 mL) was added Pd/C (10% on carbon, 5 mg) and the reaction mixture stirred under an H_2 atmosphere at room temperature for about 12 h. After the completion of reaction it was filtered over celite plug (EtOH eluent) and solvent evaporated under reduced pressure to give 3-*epi* jaspine B **3** (35 mg).

Yield: 97%; Colorless solid; m.p. 75-77 °C; {lit.[14] m.p. 75-76 °C}; $[\alpha]_D^{25}$ -3.4 (*c* 0.6, $CHCl_3$) {lit.[14] $[\alpha]_D^{25}$ -3.2 (c 0.8, $CHCl_3$)}; IR ($CHCl_3$): ν_{max} 3359, 2924, 2857, 1637, 1435 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.25 (m, 24H), 1.55-1.67 (m, 2H), 2.12 (br s, 3H), 3.32 (dd, *J* = 4.9, 6.6Hz, 1H,), 3.60 (dd, *J* = 4.8, 9.4 Hz, 1H), 3.62-3.64 (m, 2H), 4.01 (dd, *J* = 5.9, 9.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.7, 26.0, 29.3, 29.57, 29.60, 29.65, 29.67, 31.9, 34.0, 60.5, 73.6, 84.1, 85.2; HRMS (*m/z*): calculated $[M+Na]^+$ for $C_{18}H_{37}NO_2Na$: 322.2722 found: 322.2725.

Ethyl 2-((2*S*,3*S*,4*R*)-3,4-diazidotetrahydrofuran-2-yl)acetate (13)

To a well stirred and cooled solution (0 °C) of azido alcohol **8** (2.0 g, 9.29 mmol) in dry CH_2Cl_2 (50 mL) was added Et_3N (3.8 mL, 27.5 mmol) and MsCl (0.84 mL, 11.15 mmol). Stirring was continued for 0.5 h and the mixture was diluted with CH_2Cl_2 (30 mL), washed successively with aq 5% HCl (2×15 mL), satd aq $NaHCO_3$ (15 mL) and water (15 mL). The organic solution was dried and evaporated to give a crude mesylate **12** as a yellow syrup which was used as such for the next reaction.

To a stirred solution of crude mesylate **12** (2.2 g, 7.50 mmol) in dry DMF (20 mL) were added NaN_3 (2.92 g, 45.05 mmol) & the resulting suspension was stirred at 120 °C for 24 h. After completion of reaction (monitored by TLC), the solution was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (20 mL x 3) and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified using column chromatography with petroleum ether/ethyl acetate (7:3 v/v) to give the diazide **13** (1.35 g).

Yield: 75%; yellow liquid; $[\alpha]_D^{25}$ +27.70 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): ν_{max} 1740, 2105, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.27-1.30 (t, *J* = 7.0 Hz, 3H), 2.57-2.62 (dd, *J* = 6, 16 Hz, 1H), 2.65-2.70 (dd, *J* = 6, 16 Hz, 1H), 3.75-3.78 (dd, *J* = 6, 16 Hz, 1H), 3.96-3.98 (m, 1H), 4.10-4.20 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 37.6, 60.8, 62.2, 65.6, 70.3, 169.6; HRMS (*m/z*): calculated $[M+Na]^+$ for $C_8H_{12}N_6O_3Na$:263.0868 found: 263.0886.

(2*S*,3*S*,4*R*)-3,4-diazido-2-(5-(benzyloxy)pent-2-en-1-yl)tetrahydrofuran (15)

To a stirred solution of ester **13** (1.0 g, 4.16 mmol) in dry toluene (50 mL), a solution of diisobutylaluminium hydride (4.5 mL, 4.57 mmol, 1M in cyclohexane) was added dropwise at -78 °C and stirred at this temperature for 1 h. After completion of the reaction (monitored by TLC), it was diluted with a saturated solution of potassium sodium tartrate (Rochelle salt) and stirred for further 3 h. The organic phase was separated and the aqueous phase extracted twice with CH_2Cl_2. The combined organic phase was then washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude aldehyde **14** which was used as such for the next reaction.

At 0 °C, a solution of the crude aldehyde **14** (0.500 g, 2.55 mmol) in ether (4 mL) was treated with a solution of the ylide [generated from $BnO(CH_2)_3P^+Ph_3I^-$ (4.2 g, 7.65 mmol) using KO^{t}Bu (0.714 g, 6.37 mmol) in THF (5 mL) at 0 °C] and stirred for 30 min. The reaction mixture was quenched with saturated NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude product by column chromatography (90:10 petroleum ether/EtOAc) gave olefin **15** (0.627 g).

Yield: 75%; colorless liquid; $[\alpha]_D^{25}$ +31.33 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max} 698, 737, 1095, 1262, 2106, 2855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.35-2.49 (m, 4H), 3.42-3.55 (m, 3H), 3.68-4.07 (m, 4H), 4.51 (s, 2H), 5.46-5.71 (m, 2H), 7.34 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.0, 35.2, 61.3, 65.2, 66.5, 73.5, 128.0, 128.7, 131.7, 133.2, 133.9; HRMS (*m/z*): calculated $[M+Na]^+$ for $C_{16}H_{20}N_6O_2Na$: 351.1648 found: 351.1650.

(3*S*,4*S*,6*R*)-4-(5-hydroxypentyl)tetrahydro-1H-furo[3,4-d]imidazol-2(3H)-one (16)

To a stirred Methanolic solution of olefin **15** (150 mg, 0.45 mmol, 15 mL) was added Pd/C (10% on carbon, 15 mg) and the reaction mixture stirred under an H_2 atmosphere at room temperature for about 24 h. After the completion of reaction it was filtered over celite plug (MeOH eluent) and solvent evaporated under reduced pressure to give crude di-amino alcohol as a gummy liquid which was then diluted with dry CH_2Cl_2. the reaction mixture was cooled to 0 °C and to it were added Et_3N (0.2 mL, 1.47 mmol) and a solution of triphosgene (47 mg, 0.16 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 20 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 with ethyl acetate/methanol (8:2 v/v) afforded pure **16** (73 mg).

Yield: 76%; white solid; m.p. 162-164 °C; $[\alpha]_D^{25}$ +40.35 (*c* 1.5, MeOH); IR : ν_{max} 1700, 2935, 3445 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 1.40-1.46 (m, 4H), 1.51-1.63 (m, 3H), 1.69-1.77 (m, 1H), 2.69 (d, *J* = 13 Hz, 1H), 2.95 (dd, *J* = 4.8, 13 Hz, 1H), 3.24 (ddd, *J* = 4.6, 6.1 & 9.0 Hz, 1H), 3.56 (t, *J* = 6.2 Hz ,2H), 4.33 (dd, *J* = 5.0, 7.7 Hz, 1H), 4.50, (dd, *J* = 4.9, 8.1 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ 26.6, 29.5, 29.9, 33.1, 40.8, 56.9, 61.4, 62.6, 63.2, 163.4; HRMS (*m/z*): calculated $[M+Na]^+$ for $C_{10}H_{18}N_2O_3Na$: 237.1317 found: 237.1315.

(+)-oxybiotin (5)

To a stirred solution of alcohol **16** (60 mg, 0.28 mmol) in CH_3CN/H_2O (4:1) were added in one portion (diacetoxyiodo)benzene (196 mg, 0.61 mmol) and TEMPO (14 mg, 0.084 mmol). The reaction mixture was then allowed to stir at 25 °C for 4 h. After completion of the reaction (monitored by TLC), it was quenched by the addition of a saturated solution of aq. sodium thiosulfate. The combined aqueous solution was evaoprated by co-distillation with a mixture of 1:1 toluene : EtOH to give crude residue which was then subjected to column chromatographic purification with MeOH/EtOAc (5:5 v/v) to give **5** as a white powder which on recrystallization from water gave pure (+)-oxybiotin **5** (63 mg).

Yield: 99%; White Solid; m.p. 184-187 °C; {lit.[6b] m.p. 185-187 °C}; $[\alpha]_D^{25}$ +57.5 (*c* 0.65, in 1 M NaOH) {lit.[6b] $[\alpha]_D^{25}$ +57.7 (*c* 0.8, in 1 M NaOH)}; IR: ν_{max} 1670, 1705, 3405 cm^{-1}; ^1H NMR (400 MHz, Me_2SO-d_6): δ 1.16-1.56 (m, 6H), 2.21 (t, *J* = 6.0 Hz , 2H), 3.32 (m, 1H), 3.40 (dd, *J* = 9.8, 4.6 Hz 1H), 3.66 (d,1H), 4.09 (dd, *J* = 8.5 Hz, 1H), 4.22 (dd, 1H), 6.35 (br s , 1H) , 6.41 (br s , 1H); ^{13}C NMR (100 MHz, Me_2SO-d_6): δ 25.3, 26.0, 28.3, 34.4, 57.5, 59.2, 74.4, 82.9, 164.0, 174; HRMS (m/z): calculated [M+Na]+ for $C_{10}H_{16}N_2O_4Na$: 251.1008 found: 251.1006.

Notes & References

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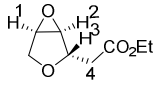
(13)The relative stereochemistry of **7** was confirmed by COSY & NOESY studies. A significant COSY & NOESY correlation was observed between H_4 and H_3 & H_4 and H_2, H_1.while no correlation is observed between H_3 and H_2 in **7.**



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