

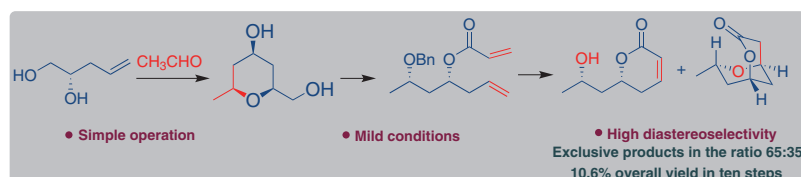
# Stereoselective Synthesis of Euscapholide and Tetraketide via Prins Cyclisation and Ring-Closing Metathesis

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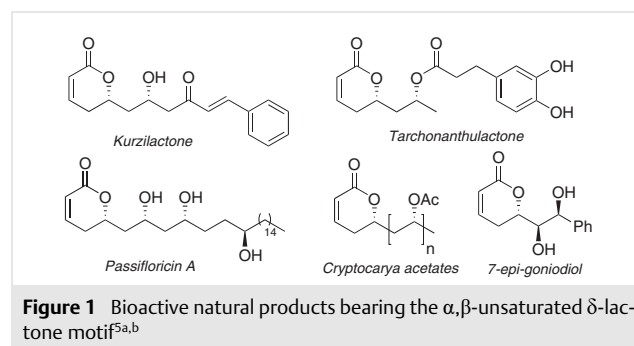
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**Abstract** A concise and diastereoselective total synthesis of tetraketide and euscapholide is described in ten steps in 10.6% overall yield from acetaldehyde and (*S*)-pent-4-ene-1,2-diol. Jacobsen hydrolytic kinetic resolution, Prins cyclization, ring-closing metathesis and oxa-Michael addition reactions are the key steps involved in the synthesis.

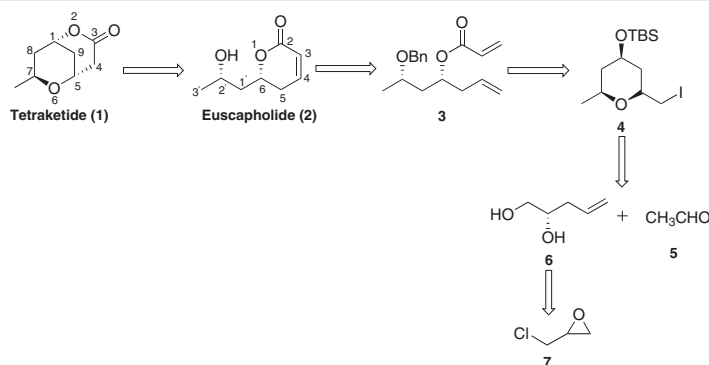
**Key words** Prins cyclization, euscapholide, tetraketide, ring-closing metathesis

Natural products from terrestrial plant sources have been a source of discovery for numerous biologically active compounds.<sup>1</sup> Along this line, tetraketide (**1**) and euscapholide (**2**) are a dioxabicyclo[3.3.1]nonan-3-one derivative and a  $\alpha,\beta$ -unsaturated  $\delta$ -lactone that were obtained from the leaves of *Euscaphis japonica*.<sup>2</sup> Natural products containing  $\alpha,\beta$ -unsaturated  $\delta$ -lactone and bicyclic lactone/pyrone structural motifs have attracted attention because of their unusual structural architecture, electrophilic nature as Michael acceptors, and range of biological properties including analgesic, antibacterial, antifungal, anti-inflammatory, antiparasitic, antidiabetic, and cytotoxic activities (Figure 1).<sup>3,4</sup> In addition, some of them have been used in traditional medicine for treating arthritis, headache, and hepatitis infections,<sup>4h</sup> headaches, morning sickness, cancer, pulmonary diseases, and a variety of other bacterial and fungal infections.<sup>4d</sup> Owing to their interesting chemical framework and promising biological profiles, these compounds have attracted much attention from the chemical synthesis community over the past decade.<sup>5</sup> Recently

O'Doherty *et al.* reported the total synthesis of euscapholide (**2**)<sup>6</sup> and Mohapatra *et al.* reported the total synthesis of tetraketide (**1**).<sup>7</sup> The absolute structures of **1** and **2** were assigned based on NMR spectroscopic and circular dichroism analyses. Compound **2** shows anti-inflammatory activity; whereas its analogue, 3,7-dihydroxy-5-octenolide, which lacks the Michael acceptor, does not show any anti-inflammatory activity and the biological activity of **1** remains to be assessed.<sup>4j,k</sup> However, further biological evaluation of compounds **1** and **2** is hindered due to their limited availability from natural sources. Hence, a concise, unified, and efficient approach has been developed toward the total synthesis of **1** and **2**, which can provide sufficient amounts of the target compounds for further biological evaluation.



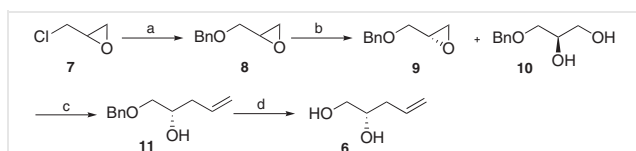
The retrosynthetic analysis of **1** and **2** is illustrated in Scheme 1. An assessment of the structures of tetraketide (**1**) and euscapholide (**2**) showed that bicyclic lactone **1** could be derived from an intramolecular oxa-Michael addition reaction of **2**, which could be accessed from acrylated compound **3** through ring-closing metathesis (RCM). Precursor **3** could be obtained from iodopyran **4**, which could, in turn, be accessed from acetaldehyde **5** and homoallylic alcohol **6**



**Scheme 1** Retrosynthetic analysis of tetraketide (1) and euscapholide (2)

via Prins cyclization. Finally, homoallylic alcohol **6** could be obtained from epichlorohydrin **7** using Jacobsen hydrolytic kinetic resolution.

The synthesis of tetraketide (**1**) and euscapholide (**2**) commenced with the synthesis of starting material (*S*)-pent-4-ene-1,2-diol **6** as depicted in Scheme 2. Epichlorohydrin can act as a versatile source of both (*R*)- and (*S*)-homoallylic alcohols **6**. Thus, racemic epichlorohydrin **7** was treated with NaH and BnOH in THF solvent to furnish racemic oxirane **8** in 94% yield. Oxirane **8**, on Jacobsen hydrolytic kinetic resolution using (*R,R*)-(salen)Co(II) complex<sup>9</sup> in aqueous acetic acid, afforded (*S*)-oxirane **9** in 46% yield (ee 96%) and (*R*)-1,2-diol **10** in 48% yield (ee 98%). Regioselective ring opening of (*S*)-oxirane **9** using vinyl magnesium bromide<sup>10</sup> in the presence of CuCN afforded (*S*)-1-(benzyloxy)pent-4-en-2-ol (**11**) in 92% yield, which was then subjected to debenzoylation<sup>11</sup> by treatment with Li in liquid NH<sub>3</sub> to provide the homoallylic alcohol **6** in 90% yield, being the requisite precursor for the Prins cyclization reaction.

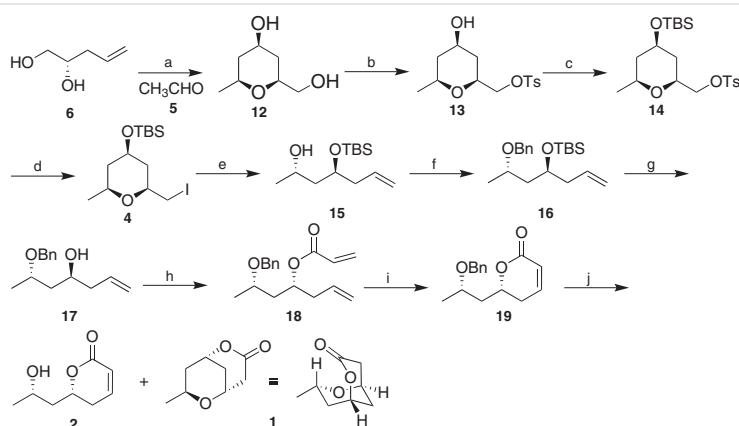


**Scheme 2** Reagents and conditions: (a) NaH, BnOH, THF, 0 °C to rt, 12 h, 94%; (b) (*R,R*)Co-Salen, AcOH, H<sub>2</sub>O, THF, 0 °C to rt, 36 h, 46%; (c) CH<sub>2</sub>=CH-Br, Mg, THF, CuCN, 1,2-dibromoethane, -78 to -40 °C, 4 h, 92%; (d) Li, Liq. NH<sub>3</sub>, THF, -33 °C, 20 min, 90%.

With quantities of homoallylic alcohol **6** readily available, the key intermolecular Prins cyclization<sup>12,13</sup> reaction was carried out between acetaldehyde **5** and homoallylic alcohol **6** using TFA in CH<sub>2</sub>Cl<sub>2</sub> to afford the resultant tetrahydropyran, which, on hydrolysis with K<sub>2</sub>CO<sub>3</sub> in MeOH, furnished 2,6-*cis*-tetrahydropyran **12** as the exclusive product in 52% yield. The stereochemical aspects of such Prins cyclizations leading to structurally similar compounds to **12** have been discussed in detail previously.<sup>12,13</sup> Tosylation<sup>14</sup> of

the primary hydroxy functionality of **12** furnished **13** in 85% yield. Silylation<sup>15</sup> of the secondary alcohol of **13** produced *tert*-butyldimethylsilyl ether **14** in 94% yield and subsequent nucleophilic substitution of the tosylate group using NaI/acetone<sup>16</sup> afforded the corresponding iodide **4** in 91% yield. Reductive ring opening<sup>17</sup> of iodo-intermediate **4** using Zn/EtOH furnished the key open chain *anti*-1,3-diol **15** in 88% yield (de 97%). Benzoylation<sup>18</sup> of the secondary alcohol **15** led to **16** in 85% yield. Desilylation<sup>19</sup> of **16** to its homoallylic alcohol **17** in 84% yield and subsequent acylation<sup>20</sup> under Mitsunobu conditions<sup>20</sup> using acrylic acid, TPP and DEAD afforded ester **18** in 75% yield. Having succeeded in achieving the key intermediate **18** with desired relative and absolute stereochemistry, the bis-olefinic compound **18** was subjected to RCM reaction using Grubbs' second generation catalyst<sup>21</sup> to afford  $\alpha,\beta$ -unsaturated  $\delta$ -lactone **19** in 70% yield. Debenzoylation<sup>22</sup> of  $\alpha,\beta$ -unsaturated  $\delta$ -lactone **19** using TiCl<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> afforded euscapholide (**2**) and tetraketide (**1**), through an intramolecular oxa-Michael addition reaction, in a 65:35 ratio, with 89% combined yield, as shown in Scheme 3. A comparison of the <sup>1</sup>H NMR spectroscopic and analytical data of synthetic compounds **1** and **2** with those of the natural products showed that they were in agreement. The specific rotation of compound **1** (synthetic [ $\alpha$ ]<sub>D</sub><sup>25</sup> -11.5 (c 0.8, MeOH); Lit.<sup>7</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> -12.7 (c 0.9, MeOH)) and compound **2** (synthetic [ $\alpha$ ]<sub>D</sub><sup>25</sup> +113.8 (c 0.24, MeOH); Lit.<sup>23</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> +115.5 (c 1.52 MeOH))<sup>23</sup> were in good agreement with the reported values.

In conclusion, a concise, enantio- and diastereoselective total synthesis of tetraketide (**1**) and euscapholide (**2**) has been accomplished in ten steps with an overall yield of over 10%. Jacobsen hydrolytic kinetic resolution, ring-closing metathesis, Prins cyclisation reaction and oxa-Michael addition reaction are the key steps. The operational expediency, synthetic efficiency, and high diastereoselectivity make the synthetic process practicable. We believe the current strategy provides a reliable route for the synthesis of structural analogues of  $\alpha,\beta$ -unsaturated  $\delta$ -lactones and  $\alpha$ -pyrones for structure-activity studies.



**Scheme 3** Reagents and conditions: (a) i. TFA,  $\text{CH}_2\text{Cl}_2$ , 0 °C to rt, 3 h; ii.  $\text{K}_2\text{CO}_3$ , MeOH, r.t., 0.5 h, 52%; (b) TEA, TsCl,  $\text{CH}_2\text{Cl}_2$ , 0 °C to rt, 6 h, 85%; (c) TBSCl, imidazole, DMAP,  $\text{CH}_2\text{Cl}_2$ , 0 °C to rt, 4 h, 94%; (d) NaI, acetone, reflux, 24 h, 91%; (e) Zn, EtOH, reflux, 4 h, 88%; (f) NaH, BnBr, TBAI, THF, 0 °C to rt, 4 h, 85%; (g) CSA, MeOH, 0 °C to rt, 2 h, 84%; (h) Acrylic acid, TPP, DEAD, 0 °C to rt, 6 h, 75%; (i) Grubbs' second generation catalyst,  $\text{CH}_2\text{Cl}_2$ , reflux, 18 h, 70%; (j)  $\text{TiCl}_4$ , DCM, 0 °C, 0.5 h, 89%.

Commercial reagents were used without further purification and all solvents were purified by standard techniques. Infrared spectra were recorded with a Perkin–Elmer 683 spectrometer. Specific rotations were obtained with a Jasco Dip 360 digital polarimeter. NMR spectra were recorded in  $\text{CDCl}_3$  with Varian Unity 400 and 500 MHz NMR spectrometers. Chemical shifts ( $\delta$ ) are quoted in parts per million and are referenced to tetramethylsilane (TMS) as an internal standard. Coupling constants ( $J$ ) are quoted in Hertz and the resonance multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; dt, doublet of triplets; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, double double doublet of doublets; m, multiplet. Column chromatographic separations were carried out on silica gel (60–120 mesh) and flash chromatographic separations were carried out using 230–400 mesh, silica gel. Mass spectra were recorded with Micromass VG-7070H for EI and VG Autospec M FABMS spectrometers.

### 2-[(Benzyloxy)methyl]oxirane (**8**)

To a stirred suspension of NaH (8 g, 333 mmol) in anhydrous THF (400 mL) at 0 °C, was added dropwise benzyl alcohol (24 g, 222 mmol) dissolved in anhydrous THF (100 mL). After 30 minutes, epichlorohydrin **7** (20.5 g, 222 mmol) was added and the reaction mixture was allowed to rise to r.t. and stirred for 12 hours. After completion of the reaction (monitored by TLC), the reaction mixture was quenched at 0 °C with saturated aqueous ammonium chloride (100 mL), diluted with EtOAc (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with brine (100 mL) and dried over  $\text{Na}_2\text{SO}_4$ . After filtration and removal of solvent under reduced pressure, the crude oxirane was purified by column chromatography eluting with 5% EtOAc/hexane to give pure product **8** (34.4 g, 94% yield) as a colourless liquid.

IR (neat): 3031, 2999, 2926, 2864, 1725, 1453, 1267, 1096, 742, 699  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.35–7.24 (m, 5 H), 4.62–4.46 (m, 2 H), 3.71 (dd,  $J$  = 11.2, 3.1 Hz, 1 H), 3.41 (dd,  $J$  = 11.4, 5.7 Hz, 1 H), 3.14 (tt,  $J$  = 5.9, 3.2 Hz, 1 H), 2.77–2.71 (m, 1 H), 2.58 (dd,  $J$  = 5.2, 2.6 Hz, 1 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 137.6, 127.2, 127.1, 72.5, 70.1, 50.2, 43.2.

MS-ESIMS:  $m/z$  165  $[\text{M} + \text{H}]^+$ , 187  $[\text{M} + \text{Na}]^+$ .

HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd. for  $\text{C}_{10}\text{H}_{12}\text{O}_2\text{Na}$ : 187.21680, found: 187.21690.

### (S)-2-[(Benzyloxy)methyl]oxirane (**9**)

To (*R,R*)-(salen)Co(II) precatalyst (604 mg, 1 mmol) in a round-bottom flask were added sequentially racemic oxirane **8** (32.8 g, 200 mmol) and AcOH (0.228 mL, 4 mmol) at r.t. After the reaction mixture turned from a red suspension to a dark-brown solution, the flask was cooled to 0 °C and THF (2 mL) followed by  $\text{H}_2\text{O}$  (1.98 g, 110 mmol, 0.55 equiv) were added over a period of 20 minutes and the reaction mixture was allowed to stir at r.t. for 36 hours. After completion of reaction, monitored by TLC, the mixture was directly purified by column chromatography eluting with 5% EtOAc/hexane to afford epoxide **9** (15.08 g, 46%, 96% ee) as a colorless liquid and enantiomerically pure diol **10** (17.05 g, 52%, 98% ee) as a viscous liquid.

$[\alpha]_D^{22} +5.2$  (c 1.1,  $\text{CHCl}_3$ ); Lit.  $[\alpha]_D^{25} +5.1$  (c 1.0,  $\text{CHCl}_3$ ).

IR (Neat): 3454, 3031, 2999, 2926, 2864, 1725, 1453, 1267, 1096, 742, 699  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.36–7.23 (m, 5 H), 4.64–4.48 (m, 2 H), 3.70 (dd,  $J$  = 11.4, 3.1 Hz, 1 H), 3.41 (dd,  $J$  = 11.4, 5.7 Hz, 1 H), 3.12 (tt,  $J$  = 5.8, 3.1 Hz, 1 H), 2.78–2.72 (m, 1 H), 2.57 (dd,  $J$  = 5.2, 2.6 Hz, 1 H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 137.5, 127.2, 127.0, 72.4, 70.2, 50.1, 43.27.

MS-ESIMS:  $m/z$  165  $[\text{M} + \text{H}]^+$ , 187  $[\text{M} + \text{Na}]^+$ .

HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd. for  $\text{C}_{10}\text{H}_{12}\text{O}_2\text{Na}$ : 187.21680; found: 187.21690.

### (S)-1-(Benzyloxy)pent-4-en-2-ol (**11**)

To magnesium turnings (6.6 g, 274.4 mmol) in anhydrous THF (35 mL) at r.t. were sequentially added, 1,2-dibromoethane (3 drops) and freshly prepared vinyl bromide (13.1 mL, 182.9 mmol) in a dropwise manner, and CuCN (40.9 mg, 5 mol%). The reaction mixture was stirred for 30 minutes and cooled to –78 °C, then epoxide **9** (15 g, 91.46 mmol) in THF (60 mL) was added, the mixture allowed to warm to –40 °C and stirred for 4 h. The reaction was then quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (50 mL) and extracted with EtOAc (2 × 100

mL). The combined organic extracts were washed with brine (120 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. Purification by column chromatography eluting with 12% EtOAc/hexane afforded **11** (16.2 g, 92%) as a colourless liquid.

$[\alpha]_{\text{D}}^{22} +2.6$  (c 1.1,  $\text{CHCl}_3$ );  $[\alpha]_{\text{D}}^{25} +2.3$  (c 1.0,  $\text{CHCl}_3$ ).

IR (neat): 3426, 3070, 3030, 2910, 2862, 1718, 1640, 1451, 1275, 1103, 997, 915, 741, 698, 608  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.42–7.27 (m, 5 H), 5.82 (ddt,  $J$  = 17.2, 10.2, 7.1 Hz, 1 H), 5.18–5.05 (m, 2 H), 4.55 (s, 1 H), 3.88 (dt,  $J$  = 6.7, 9.9 Hz, 1 H), 3.51 (dd,  $J$  = 9.5, 3.4 Hz, 1 H), 3.38 (dd,  $J$  = 9.5, 7.4 Hz, 1 H), 2.38 (s, 1 H), 2.25 (dd,  $J$  = 17.2, 10.8 Hz, 2 H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 137.8, 134.1, 128.2, 127.5, 117.4, 73.7, 73.1, 69.5, 37.7.

MS-ESIMS:  $m/z$  193  $[\text{M} + \text{H}]^+$ , 215  $[\text{M} + \text{Na}]^+$ .

HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd. for  $\text{C}_{12}\text{H}_{16}\text{O}_2\text{Na}$ : 215.21640; found: 215.21650

#### (S)-Pent-4-ene-1,2-diol (**6**)

To a stirred suspension of lithium (16 g, 250 mmol) in liquid  $\text{NH}_3$  (160 mL) was added **11** (16 g, 83.3 mmol) dissolved in anhydrous THF (100 mL). The mixture was stirred for 20 minutes and quenched with solid  $\text{NH}_4\text{Cl}$  (15 g). The ammonia was allowed to evaporate at r.t., ether (100 mL) was added to the residue and the mixture was filtered through Celite®. The filtrate was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography eluting with 70% EtOAc/hexane to afford diol **6** (7.6 g, 90% yield) as a colourless liquid.

$[\alpha]_{\text{D}}^{25} -3.5$  (c 2.5,  $\text{CHCl}_3$ ); Lit  $[\alpha]_{\text{D}}^{25} -3.4$  (c 2.8,  $\text{CHCl}_3$ ).

IR (neat): 3419, 2926, 1840, 1640, 1431, 1073, 915, 848, 765, 654  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.91–5.63 (m, 1 H), 5.20–5.08 (m, 2 H), 3.75–3.55 (m, 1 H), 3.71–3.42 (m, 2 H), 2.93 (s, 1 H), 2.33–2.15 (m, 2 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 134.1, 117.5, 71.4, 65.9, 37.6.

MS-ESIMS:  $m/z$  103  $[\text{M} + \text{H}]^+$ , 125  $[\text{M} + \text{Na}]^+$ .

#### (2S,4R,6S)-Tetrahydro-2-(hydroxymethyl)-6-methyl-2H-pyran-4-ol (**12**)

TFA (21.5 mL) was added slowly to a solution of homoallylic alcohol **6** (2.5 g, 24.5 mmol) and acetaldehyde **5** (3.24 g, 73.5 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (50 mL) at 25 °C and the reaction mixture was stirred for 6 h at r.t. After completion of reaction, as monitored by TLC, the reaction was quenched with saturated aqueous  $\text{NaHCO}_3$  (60 mL) and the pH was adjusted to >7 by addition of triethylamine. The two layers were separated, the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (4 × 50 mL) and the combined organic layers were concentrated under reduced pressure. The crude residue was dissolved in MeOH (40 mL), potassium carbonate (10.16 g, 73.52 mmol) was added, and the mixture was stirred for 0.5 h. The MeOH was removed under reduced pressure and water (25 mL) was added. The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 × 50 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent was removed under reduced pressure. Purification of the crude material by column chromatography eluting with 60% EtOAc/hexane afforded pure **12** (1.86 g, 52%) as a pale-yellow solid.

$[\alpha]_{\text{D}}^{22} +15.8$  (c 1.1,  $\text{CHCl}_3$ ).

IR (neat): 3382, 2937, 2872, 1652, 1452, 1375, 1323, 1148, 1115, 1024, 953  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 3.82–3.72 (m, 1 H), 3.61–3.54 (m, 1 H), 3.53–3.38 (m, 3 H), 2.10 (s, 1 H), 1.95–1.88 (m, 1 H), 1.83–1.76 (m, 1 H), 1.66–1.55 (m, 2 H), 1.22 (d,  $J$  = 6.2 Hz, 3 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 76.1, 71.8, 67.4, 65.3, 42.4, 36.4, 21.5.

MS-ESIMS:  $m/z$  147  $[\text{M} + \text{H}]^+$ .

HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd. for  $\text{C}_7\text{H}_{15}\text{O}_3$ : 147.09780; found: 147.09790.

#### (2S,4R,6S)-Tetrahydro-6-methyl-2-p-toluenesulfonyloxymethyl-2H-pyran-4-ol (**13**)

To a stirred solution of alcohol **12** (1.8 g, 12.3 mmol), triethylamine (5.2 mL, 36.9 mmol) and DMAP (cat) in anhydrous dichloromethane (25 mL) at 0 °C was added *p*-toluenesulfonyl chloride (2.8 g, 14.8 mmol) portionwise. After stirring for 2 h at r.t., the resulting mixture was quenched with sat aqueous  $\text{NaHCO}_3$  and extracted with dichloromethane (2 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and filtered. Removal of solvent under reduced pressure and purification by silica gel chromatography eluting with 20% EtOAc/hexane afforded **13** (3.14 g 85%) as a viscous liquid.

$[\alpha]_{\text{D}}^{22} +34.8$  (c 3,  $\text{CHCl}_3$ ).

IR (neat): 3395, 2973, 2859, 1597, 1451, 1358, 1176, 1095, 975, 817  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.76 (d,  $J$  = 8.2 Hz, 2 H), 7.32 (d,  $J$  = 8.0 Hz, 2 H), 4.03–3.87 (m, 2 H), 3.70 (dt,  $J$  = 15.3, 5.3 Hz, 1 H), 3.53 (dd,  $J$  = 10.8, 4.9 Hz, 1 H), 3.37 (dd,  $J$  = 10.9, 6.0 Hz, 1 H), 2.62 (s, 1 H), 2.45 (s, 3 H), 1.86 (dd,  $J$  = 12.0, 2.5 Hz, 1 H), 1.13 (d,  $J$  = 6.2 Hz, 3 H), 1.09–0.95 (m, 2 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 145.0, 133.3, 130.1, 128.4, 73.2, 72.6, 72.2, 68.4, 43.4, 37.5, 21.9, 21.8.

MS-ESIMS:  $m/z$  323  $[\text{M} + \text{Na}]^+$ .

HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd. for  $\text{C}_{14}\text{H}_{20}\text{O}_5\text{NaS}$ : 323.0929; found: 323.0915.

#### (2S,4R,6S)-4-((tert-Butyldimethylsilyloxy)-6-methyltetrahydro-2H-pyran-2-yl Methyl *p*-Toluene Sulfonate (**14**)

To a stirred solution of **13** (3.05 g, 10.2 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (12 mL) was added DMAP (0.248 g, 2.03 mmol), imidazole (2.1 g, 30.5 mmol) and TBSCl (2.38 g, 15.2 mmol) at 0 °C. The resulting mixture was allowed to stir for 4 h at r.t. After completion of reaction as monitored by TLC, the reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (40 mL) and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (2 × 50 mL). The organic layers were washed with brine (100 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and evaporated under reduced pressure. The resulting crude product on purification with silica gel column chromatography eluting with 10% EtOAc/hexane afforded TBS ether **14** (3.94 g, 94%) as a colourless oil.

$[\alpha]_{\text{D}}^{22} +8.1$  (c 1.0,  $\text{CHCl}_3$ ).

IR (neat): 2932, 2856, 1598, 1461, 1363, 1254, 1179, 1121, 1073, 981, 835, 776, 667, 552  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.95 (d,  $J$  = 8.2 Hz, 2 H), 7.48 (d,  $J$  = 8.1 Hz, 2 H), 4.19–4.02 (m, 2 H), 3.94–3.79 (m, 1 H), 3.75–3.62 (m, 1 H), 3.59–3.45 (m, 1 H), 2.62 (s, 3 H), 1.90 (ddd,  $J$  = 8.2, 5.0, 1.9 Hz, 1 H), 1.29 (d,  $J$  = 6.1 Hz, 3 H), 1.04 (s, 9 H), 0.19 (s, 6 H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 144.7, 129.7, 128.0, 72.8, 72.2, 71.8, 68.0, 42.9, 37.1, 25.7, 21.4, –4.6.

MS-ESIMS:  $m/z$  437  $[\text{M} + \text{Na}]^+$ .

HRMS (ESI):  $m/z$   $[M + Na]^+$  calcd. for  $C_{20}H_{34}O_5NaSi$ : 437.1793; found: 437.1782.

**tert-Butyl (((2S,4R,6S)-2-(Iodomethyl)-6-methyltetrahydro-2H-pyran-4-yl)oxy) Dimethylsilane (4)**

To a stirred solution of **14** (3.8 g, 9.2 mmol) in acetone (40 mL) was added NaI (20.7 g, 137.7 mmol) and the mixture was heated to reflux for 24 hours. After completion of reaction as monitored by TLC, the acetone was removed under reduced pressure. To the resulting residue was added water and  $CH_2Cl_2$ , and the organic layer was extracted, dried over  $Na_2SO_4$ , filtered, concentrated under reduced pressure, and purified by silica gel chromatography eluting with 7% EtOAc/hexane to afford **15** (3.1 g, 91%) as a colourless liquid.

$[\alpha]_D^{22} +15.10$  (c 1.0,  $CHCl_3$ ).

IR (neat): 2932, 2855, 1632, 1465, 1381, 1253, 1158, 1120, 1072, 836, 775  $cm^{-1}$ .

$^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 3.76–3.61 (m, 1 H), 3.47–3.33 (m, 1 H), 3.32–3.19 (m, 1 H), 3.17–3.00 (m, 2 H), 2.02–1.92 (m, 1 H), 1.72–1.62 (m, 1 H), 1.22 (d,  $J$  = 6.3 Hz, 3 H), 1.18–1.07 (m, 2 H), 0.88 (s, 9 H), 0.05 (s, 6 H).

$^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 75.1, 72.0, 68.3, 43.0, 41.0, 25.8, 21.6, 9.1, –4.5.

MS-ESIMS:  $m/z$  393  $[M + Na]^+$ .

HRMS (ESI):  $m/z$   $[M + Na]^+$  calcd. for  $C_{13}H_{27}IO_2SiNa$ : 393.16930; found: 393.16922.

**(2S,4S)-4-((tert-Butyldimethylsilyl)oxy)hept-6-en-2-ol (15)**

To a stirred solution of iodide **4** (3.0 g, 8.1 mmol) in EtOH (60 mL), zinc dust (10.5 g, 162.16 mmol) was added, the mixture was heated to reflux for 3 h and then cooled to 25 °C. Solid  $NH_4Cl$  (6.5 g) and ether (100 mL) were added and the resultant mixture was stirred for 10 min to obtain a grey suspension. The resulting suspension was filtered through a pad of Celite® and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 12% EtOAc/hexane to give pure **15** (1.74 g, 88%, 97% de) as a colourless liquid.

$[\alpha]_D^{22} +36.8$  (c 2.5,  $CHCl_3$ ).

IR (neat): 3444, 2957, 2932, 2858, 1640, 1466, 1370, 1254, 1090, 1063, 1001, 913, 834, 774  $cm^{-1}$ .

$^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 5.84–5.54 (m, 1 H), 5.11–4.92 (m, 2 H), 4.13–3.78 (m, 2 H), 2.81 (s, 1 H), 2.35–2.16 (m, 2 H), 1.60–1.43 (m, 2 H), 1.11 (d,  $J$  = 6.2 Hz, 3 H), 0.87 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H).

$^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 134.6, 117.4, 71.2, 64.4, 43.1, 41.1, 29.7, 25.7, 23.8, –4.5, –4.8

MS-ESIMS:  $m/z$  245  $[M + Na]^+$ .

HRMS (ESI):  $m/z$   $[M + H]^+$  calcd. for  $C_{13}H_{28}O_2Si$ : 245.19650; found: 245.19510.

**(4S,6S)-6-(Benzyloxy)hept-1-en-4-yl)oxy(tert-butyl)dimethylsilane (16)**

To a cooled suspension of NaH (0.4 g, 16.9 mmol, 60% w/w dispersion in paraffin oil) in anhydrous THF (10 mL), was added dropwise a solution of alcohol **15** (1.7 g, 6.7 mmol) in THF (25 mL) at 0 °C and the mixture was stirred for 30 min. To this reaction mixture TBAI (0.124 g, 3.4 mmol) and benzyl bromide (0.96 mL, 8.1 mmol) were added sequentially and stirring was continued for another 15 minutes at the same temperature, followed by 3 hours at reflux. The reaction was

quenched with crushed ice until a biphasic solution formed. The reaction mixture was extracted with EtOAc (2 × 25 mL) and the organic extracts were washed with water (25 mL), brine (25 mL), dried over anhydrous  $Na_2SO_4$  and filtered. Evaporation of the solvent followed by column chromatography eluting with 4% EtOAc/hexane afforded pure **16** (1.92 g, 85%) as a colourless liquid.

$[\alpha]_D^{22} +24.72$  (c 2.8,  $CHCl_3$ ).

IR (neat): 2930, 2857, 1640, 1461, 1371, 1251, 1145, 1068, 998, 913, 833, 773, 734  $cm^{-1}$ .

$^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  = 7.42–7.18 (m, 5 H), 5.84 (ddt,  $J$  = 17.4, 10.4, 7.0 Hz, 1 H), 5.17–5.01 (m, 2 H), 4.69–4.35 (m, 2 H), 4.15–3.99 (m, 1 H), 3.69 (dt,  $J$  = 10.0, 5.5 Hz, 1 H), 2.37 (dd,  $J$  = 6.9, 5.7 Hz, 2 H), 1.63–1.56 (m, 2 H), 1.15 (d,  $J$  = 6.2 Hz, 3 H), 0.92 (s, 9 H), 0.06 (s, 6 H).

$^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  = 138.8, 134.6, 128.2, 127.6, 127.3, 117.1, 75.6, 70.7, 65.4, 44.8, 38.2, 29.6, 25.8, 24.6, 18.1, –3.8, –4.6.

MS-ESIMS:  $m/z$  335  $[M + H]^+$ .

HRMS (ESI):  $m/z$   $[M + H]^+$  calcd. for  $C_{20}H_{35}O_2NaSi$ : 335.2406; found: 335.2398.

**(4S,6S)-6-(Benzyloxy)hept-1-en-4-ol (17)**

To a stirred solution of **16** (1.8 g, 5.38 mmol) in anhydrous MeOH (25 mL), CSA (0.12 g, 0.05 mmol) was added at 0 °C under a nitrogen atmosphere. The mixture was warmed to r.t. and stirred for 4 h, then the reaction was quenched with saturated aqueous  $NaHCO_3$ , and the mixture was extracted with EtOAc (25 mL), washed with brine, dried over ( $Na_2SO_4$ ), filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel eluting with 10% EtOAc/hexane afforded pure **17** (0.99 g, 84%) as a colourless liquid.

$[\alpha]_D^{22} +59.75$  (c 0.25,  $CHCl_3$ ).

IR (neat): 3424, 2966, 2927, 1639, 1495, 1453, 1349, 1093, 1065, 998, 914, 739  $cm^{-1}$ .

$^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 7.38–7.20 (m, 5 H), 5.87–5.69 (m, 1 H), 5.15–5.02 (m, 2 H), 4.74–4.40 (m, 2 H), 3.98–3.85 (m, 1 H), 3.71 (dt,  $J$  = 9.8, 4.1 Hz, 1 H), 2.48–2.30 (m, 2 H), 1.74–1.51 (m, 2 H), 1.12 (d,  $J$  = 6.2 Hz, 3 H).

$^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 137.6, 133.6, 128.3, 127.7, 127.4, 117.6, 78.9, 70.5, 67.4, 42.4, 37.8, 23.3.

MS-ESIMS:  $m/z$  243  $[M + Na]^+$ .

HRMS (ESI):  $m/z$   $[M + Na]^+$  calcd. for  $C_{14}H_{20}O_2Na$ : 243.1360; found: 243.1365.

**(4R,6S)-6-(Benzyloxy)hept-1-en-4-yl Acrylate (18)**

To a stirred mixture of **17** (0.9 g, 4 mmol), triphenylphosphine (3.75 g, 14.3 mmol) and acrylic acid (0.70 mL, 10.2 mmol) in anhydrous THF (20 mL) at 0 °C was added diethyl azodicarboxylate (2.2 mL, 14.3 mmol) via syringe. The reaction mixture was then stirred for 6 hours at r.t., diluted with water (50 mL) and extracted with EtOAc (2 × 50 mL). After removing the solvent, water (50 mL) was added and the mixture was extracted with diethyl ether (3 × 30 mL). Separation of the organic solvents, drying over  $Na_2SO_4$ , filtering and removal of solvent under reduced pressure followed by flash chromatography eluting with 15% EtOAc/hexane afforded ester **18** (0.84 g, 75%) as a colourless liquid.

$[\alpha]_D^{22} +12.66$  (c 0.42,  $CHCl_3$ ).

IR (neat): 2923, 2853, 1730, 1453, 1369, 1326, 1155, 1082, 1082, 923, 835, 750  $cm^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.32–7.18 (m, 5 H), 6.40–6.27 (m, 1 H), 6.03 (dd,  $J$  = 17.3, 10.4 Hz, 1 H), 5.89–5.70 (m, 2 H), 5.15–5.01 (m, 3 H), 4.60–4.40 (m, 2 H), 3.55–3.44 (m, 1 H), 2.38–2.26 (m, 2 H), 1.96 (dt,  $J$  = 14.1, 7.0 Hz, 1 H), 1.72–1.58 (m, 1 H), 1.21 (d,  $J$  = 6.3 Hz, 3 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 165.6, 138.4, 134.2, 130.2, 128.8, 128.3, 127.7, 127.5, 117.4, 75.2, 70.5, 68.7, 40.0, 38.0, 20.1.

MS-ESIMS:  $m/z$  297 [M + Na] $^+$ .

HRMS (ESI):  $m/z$  [M + Na] $^+$  calcd. for  $\text{C}_{17}\text{H}_{22}\text{O}_3\text{NaP}$ : 297.1466; found: 297.1461.

#### (R)-6-((S)-2-(Benzyloxy)propyl)-5,6-dihydro-2H-pyran-2-one (19)

A solution of compound **18** (0.70 g, 2.5 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (500 mL) was degassed and Grubbs' second generation catalyst (0.05 mg, 0.06 mmol) was added at r.t. under nitrogen atmosphere and the resulting pale-purple solution was heated to reflux for 12 hours. After completion of reaction (monitored by TLC), the majority of the solvent was distilled off and the concentrated solution was stirred at r.t. for 2 hours under air bubbling in order to decompose the catalyst. Evaporation to dryness under reduced pressure gave a brown residue that was purified by column chromatography on silica gel eluting with 40% EtOAc/hexane to afford cyclic lactone **19** (0.43 g, 70%) as a colourless oil.

$[\alpha]_{\text{D}}^{22}$  +87.65 (c 0.6,  $\text{CHCl}_3$ ).

IR (neat): 2938, 1730, 1373, 1217, 977, 746  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.36–7.22 (m, 5 H), 6.82–6.72 (m, 1 H), 5.9 (d,  $J$  = 9.7 Hz, 1 H), 4.64–4.50 (m, 2 H), 4.40 (d,  $J$  = 11.8 Hz, 1 H), 3.82–3.69 (m, 1 H), 2.38–2.08 (m, 3 H), 1.84–1.70 (m, 1 H), 1.28 (d,  $J$  = 6.2 Hz, 3 H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 164.6, 145.1, 128.4, 127.6, 121.3, 75.3, 70.6, 70.2, 41.4, 29.2, 19.3.

MS-ESIMS:  $m/z$  247 [M + H] $^+$ .

HRMS (ESI):  $m/z$  [M + H] $^+$  calcd. for  $\text{C}_{15}\text{H}_{19}\text{O}_3$ : 247.1345; found: 247.1331.

#### (R)-6-((S)-2-Hydroxypropyl)-5,6-dihydro-2H-pyran-2-one (2)

To a stirred solution of **19** (0.35 g, 14.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (6 mL),  $\text{TiCl}_4$  (1.0 mL, 1.80 mmol) was added at 0  $^\circ\text{C}$  under a nitrogen atmosphere. The reaction mixture was warmed to r.t. and stirred for 1 h. After completion of reaction (monitored by TLC), the reaction mixture was quenched with 1 M HCl, extracted with  $\text{CH}_2\text{Cl}_2$  (50 mL), washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with 2% MeOH/chloroform to give euscapholide **2** (15.37 mg, 65%) as a colourless oil and a tetraketide **1** (6.24 mg, 24%) as a white solid.

#### Euscapholide (2)

$[\alpha]_{\text{D}}^{25}$  +113.8 (c 0.24, MeOH); Lit.<sup>23</sup>  $[\alpha]_{\text{D}}^{25}$  +115.5 (c 1.52 MeOH).

IR (neat): 3427, 2934, 1730, 1370, 1245, 1219, 1172, 1096, 1034, 980, 864, 777  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 6.88 (ddd,  $J$  = 10.2, 5.1, 3.2 Hz, 1 H), 5.96 (dd,  $J$  = 9.7, 1.9 Hz, 1 H), 4.70–4.62 (m, 1 H), 4.10–4.00 (m, 1 H), 2.52–2.38 (m, 3 H), 2.22 (br, 1 H), 1.80–1.74 (m, 1 H), 1.24 (d,  $J$  = 6.3 Hz, 3 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 163.9, 145.1, 121.3, 76.9, 65.4, 43.6, 29.5, 23.8.

MS-ESIMS:  $m/z$  157 [M + H] $^+$ .

HRMS (ESI):  $m/z$  [M + H] $^+$  calcd. for  $\text{C}_8\text{H}_{13}\text{O}_3$ : 157.08592; found: 157.08611.

#### Tetraketide (1)

$[\alpha]_{\text{D}}^{25}$  –11.5 (c 0.8, MeOH); Lit.<sup>7</sup>  $[\alpha]_{\text{D}}^{20}$  –12.7 (c 0.9, MeOH).

IR (neat): 2925, 2855, 1725, 1504, 1457, 1381, 1252, 1223, 1118, 1066, 1023, 767  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 4.94–4.89 (m, 1 H), 4.45 (dd,  $J$  = 5.3, 2.5 Hz, 1 H), 3.93–3.85 (m, 1 H), 2.86 (dtd,  $J$  = 18.1, 2.5, 0.8 Hz, 1 H), 2.56–2.50 (m, 1 H), 2.32–2.26 (m, 1 H), 2.14 (ddd,  $J$  = 15.6, 7.8, 5.0 Hz, 1 H), 1.93–1.85 (m, 2 H), (d,  $J$  = 6.2 Hz, 3 H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 169.2, 72.5, 64.6, 64.0, 40.8, 39.4, 25.9, 21.6.

MS-ESIMS:  $m/z$  157 [M + H] $^+$ .

HRMS (ESI):  $m/z$  [M + H] $^+$  calcd. for  $\text{C}_8\text{H}_{13}\text{O}_3$ : 157.08592; found: 157.08594.

#### Conflict of Interest

The authors declare no conflict of interest.

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