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

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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 (5)-pent-4-en-1,2-diol. Jacobsen hydrolytic kinetic resolution, Prins cyclization, ring-closing metathesis and ox-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. Along this line, tetraketide (1) and euscapholide (2) are a dioxabicyclo[3.3.1]nonan-3-one derivative and a α,β-unsaturated δ-lactone that were obtained from the leaves of Euscaphis japonica. Natural products containing α,β-unsaturated δ-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 algogenic, antibacterial, antifungal, anti-inflammatory, antiparasitic, antidiabetic, and cytotoxic activities (Figure 1). In addition, some of them have been used in traditional medicine for treating arthritis, headache, and hepatitis infections, headaches, morning sickness, cancer, pulmonary diseases, and a variety of other bacterial and fungal infections. 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. Recently, O’Doherty et al. reported the total synthesis of euscapholide (2) and Mohapatra et al. reported the total synthesis of tetraketide (1). 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. 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 ox-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.
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 9 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 10 in the presence of CuCN afforded (S)-1-(benzyl-oxiranylpent-4-en-2-ol (11) in 92% yield, which was then subjected to debenzylisation 11 by treatment with Li in liquid NH3 to provide the homoallylic alcohol 6 in 90% yield, being the requisite precursor for the Prins cyclization reaction.

With quantities of homoallylic alcohol 6 readily available, the key intermolecular Prins cyclisation 12,13 reaction was carried out between acetaldehyde 5 and homoallylic alcohol 6 using TFA in CH2Cl2 to afford the resultant tetrahydropyran, which, on hydrolysis with K2CO3 in MeOH, furnished 2,6-cis-tetrahydropyran 12 as the exclusive product in 52% yield. The stereochemical aspects of such Prins cyclisations leading to structurally similar compounds 12 have been discussed in detail previously.12,13 Tosylation 14 of the primary hydroxy functionality of 12 furnished 13 in 85% yield. Silylation 15 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 16 afforded the corresponding iodide 4 in 91% yield. Reductive ring opening 17 of iodo-intermediate 4 using Zn/ EtOH furnished the key open chain anti-1,3-diol 15 in 88% yield (de 97%). Benzylolation 18 of the secondary alcohol 15 led to 16 in 85% yield. Desilylation 19 of 16 to its homoallylic alcohol 17 in 84% yield and subsequent acylation 20 under Mitsunobu conditions 20 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 21 to afford α,β-unsaturated δ-lactone 19 in 70% yield. Debenzylation 22 of α,β-unsaturated δ-lactone 19 using TiCl4 in CH2Cl2 afforded euscapholide (2) and tetraketide (1), through an intramolecular oxo-Michael addition reaction, in a 65:35 ratio, with 89% combined yield, as shown in Scheme 3. A comparison of the 1H 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 [α]D25 –11.5 (c 0.8, MeOH); Lit.7 [α]D20 –12.7 (c 0.9, MeOH)) and compound 2 (synthetic [α]D25 +113.8 (c 0.24, MeOH); Lit.23 [α]D25 +115.5 (c 1.52 MeOH))23 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 oxo-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 α,β-unsaturated δ-lactones and α-pyrones for structure–activity studies.
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. Chemical shifts (δ) are referenced to tetramethylsilane (TMS) as an internal standard. Coupling constants (J) are quoted in Hertz and the resonance multiplicities abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; q, quintet; dt, doublet of triplets; dd, doublet of doublets; ddd, 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) and extracted with EtOAc (100 mL) and dried over Na2SO4. 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): 3454, 3031, 2999, 2926, 2864, 1725, 1453, 1267, 1096, 742, 699 cm−1.


2022 SynOpen D. O. Biradar et al.

(5S)-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 NaHCl (50 mL) and extracted with EtOAc (2 × 100
To a stirred suspension of lithium (16 g, 250 mmol) in liquid NH3 (160 mL), a solution of homoallylic alcohol (12 mL) was added DMAP (0.248 g, 2.03 mmol), imidazole (2.1 g, 30.5 mmol) and DMAP (cat) in anhydrous dichloromethane (5.2 mL, 36.9 mmol) at 0 °C was added to a stirred solution of alcohol (3.24 g, 73.5 mmol) in anhydrous THF (100 mL) at 25 °C and the reaction mixture was stirred for 2 h at r.t., the resulting mixture was quenched with saturated aqueous NH4Cl (40 mL) and the mixture was extracted with CH2Cl2 (2 × 50 mL). The organic layers were washed with brine (100 mL), dried over Na2SO4, filtered and concentrated under reduced pressure. Purification by column chromatography eluting with 20% EtOAc/hexane afforded 13 (3.14 g 85%) as a viscous liquid.

1H NMR (400 MHz, CDC13): δ = 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).

13C NMR (100 MHz, CDCl3): δ = 145.0, 133.3, 130.1, 128.4, 73.2, 72.6, 68.4, 43.4, 37.5, 21.9, 21.8.

MS-ESIMS: m/z 323 [M + Na]+.

HRMS (ESI): m/z [M + H]+ calcd. for C14H20O5NaS: 323.0929; found: 323.0915.
HRMS (ESI): m/z [M + Na]+ calcd. for C_{20}H_{30}O_{5}NaSiS: 437.1793; found: 437.1782.

tert-Butyl ((25,4R,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 acetonitrile (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 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_{2}SO_{4} and filtered. Evaporation of the solvent followed by column chromatography eluting with 15% EtOAc/hexane afforded pure 16 (1.92 g, 85%) as a colourless liquid.

[a]_{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\(^{-1}\).

HRMS (ESI): m/z [M + H]+ calcd. for C_{14}H_{20}O_{2}Na: 243.1360; found: 243.1356.

(45R,6S)-6-(Benzyloxy)hept-1-en-4-yl Acrylate (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_{2}SO_{4}), filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 10% EtOAc/hexane afforded pure 17 (0.99 g, 84%) as a colourless liquid.

[a]_{D}^{22} +59.75 (c 0.25, CHCl_{3}).

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

HRMS (ESI): m/z [M + Na]+ calcd. for C_{14}H_{20}O_{2}Na: 243.1360; found: 243.1356.
Euscapholide (2) colourless oil. Evaporation to dryness under reduced pressure gave a brown residue. To a stirred solution of R-6-(\((\text{Benzyloxy})\)-propyl)-5,6-dihydro-2H-pyran-2-one (19) A solution of compound 18 (0.70 g, 2.5 mmol) in anhydrous CH2Cl2 (50 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 major product 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.


(R)-6-(\((\text{S})-2\text{-Hydroxypropyl})\)-5,6-dihydro-2H-pyran-2-one (2) To a stirred solution of 19 (0.35 g, 14.2 mmol) in CH2Cl2 (6 mL), TiCl4 (1.0 mL, 1.80 mmol) was added at 0°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 CH2Cl2 (50 mL), washed with brine, dried over Na2SO4, 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) its [α]D25 +113.8 (c 0.24, MeOH); Lit.23 [α]D25 +115.5 (c 1.52 MeOH).


Conflict of Interest

The authors declare no conflict of interest.

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