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

Dhanraj O. Biradar*ab
Yogesh D. ManeOD
Basi V. Subba Reddy*ab

* Indian Institute of Chemical Technology, Hyderabad-500007, Telangana, India
drajict@gmail.com
basireddy@iict.res.in

b Maharashtra Mahavidyalaya, Nilanga-413521, Dist. Latur, M.S, India
b BSS Arts, Science & Commerce College, Makni, Tq. Lohara-413604, Dist. Osmanabad, M.S., India

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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-ene-1,2-diol. Jacobsen hydrolytic kinetic resolution, Prins cyclization, ring-closing metathesis and oxadiazirine/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).3,4 In addition, some of them have been used in traditional medicine for treating arthritis, headache, and hepatitis infections,4b headaches, morning sickness, cancer, pulmonary diseases, and a variety of other bacterial and fungal infections.4d 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.5 Recently O’Doherty et al. reported the total synthesis of euscapholide (2)6 and Mohapatra et al. reported the total synthesis of tetraketide (1).7 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.4l 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.

Natural products from terrestrial plant sources have been a source of discovery for numerous biologically active compounds.1 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.2 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 analgesic, antibacterial, antifungal, anti-inflammatory, antiparasitic, antidiabetic, and cytotoxic activities (Figure 1).3,4 In addition, some of them have been used in traditional medicine for treating arthritis, headache, and hepatitis infections,4b headaches, morning sickness, cancer, pulmonary diseases, and a variety of other bacterial and fungal infections.4d 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.5 Recently

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Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany
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-(benzyloxy)pent-4-en-2-ol (11) in 92% yield, which was then subjected to debenzylolation 11 by treatment with Li in liquid NH3 to provide the homoallylic alcohol 8 in 90% yield, being the requisite precursor for the Prins cyclization reaction.

With quantities of homoallylic alcohol 6 readily available, the key intermolecular Prins cyclization 12,13 reaction was carried out between acetaldehyde 5 and homoallylic alcohol 6 using TFA in CH2Cl2 to afford the resultant tetrahydroxyran, which, on hydrolysis with K2CO3 in MeOH, furnished 2,6-cis-tetrahydroxypyrane 12 as the exclusive product in 52% yield. The stereochemical aspects of such Prins cyclisations leading to structurally similar compounds to 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 83% 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 oxa-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]D20 +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 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 α,β-unsaturated δ-lactones and α-pyrones for structure–activity studies.

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**Diagram:**

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

Scheme 2 Reagents and conditions: (a) NaH, BnOH, THF, 0 °C to rt, 12 h, 94%; (b) (R,R)-(salen)Co-Salen, AcOH, H2O, THF, 0 °C to rt, 36 h, 46%; (c) CH2=CH-Br, Mg, THF, CuCN, 1,2-dibromobutane, –78 to –40 °C, 4 h, 92%; (d) Li, Liq. NH3, THF, –33 °C, 20 min, 90%.
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 with a Varian Unity 400 and 500 MHz NMR spectrometers. Chemical shifts (δ) 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; q, quintet; dd, doublet of triplets; ddd, doublet of doublet of triplets; 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-[(Benzoxyl)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 (20.5 g, 222 mmol) was added and the reaction mixture was allowed to stir at 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 Na2SO4. After filtration and removal of solvent under reduced pressure, the crude residue 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): 3301, 2999, 2926, 2864, 1725, 1453, 1267, 1096, 742, 699 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 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), 3.41 (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).

13C NMR (100 MHz, CDCl3): δ = 137.6, 127.2, 127.1, 72.5, 70.1, 50.2, 43.2.

### Scheme 3

Reagents and conditions: (a) i. TFA, CH3Cl2, 0 °C to rt, 3 h; ii. K2CO3, MeOH, r.t., 0.5 h, 52%; (b) TEA, TsCl, CH2Cl2, 0 °C to rt, 6 h, 85%; (c) TBSCI, imidazole, DMAP, CH2Cl2, 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, CH2Cl2, reflux, 18 h, 70%; (j) TiCl4, DCM, 0 °C, 0.5 h.

MS-ESIMS: m/z 165 [M + H]+, 187 [M + Na]+, 209 [M + K]+.

HRMS (ESI): m/z [M + Na]+ calcd. for C10H12O2Na: 187.21680, found: 187.21690.

(5)-2-[(Benzoxyl)methyl]oxirane (9)

To (RR)-([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 H2O (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.

[a]23 + 5.2 (c 1.1, CHCl3); Lit. [a]23 + 5.1 (c 1.0, CHCl3).

IR (Neat): 3454, 3131, 2926, 2864, 1725, 1453, 1267, 1096, 742, 699 cm⁻¹.

HRMS (ESI): m/z [M + Na]+ calcd. for C10H12O2Na: 187.21680; found: 187.21690.

(5)-1-(Benzoxyl)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, 0.5 mmol). 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 NH4Cl (50 mL) and extracted with EtOAc (2 × 100
ml. The combined organic extracts were washed with brine (120 ml), dried over Na2SO4, 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.

[a]D22 +26.6 (c 1.2, CHCl3); [α]D22 +23.2 (c 1.0, CHCl3).

IR (neat): 3419, 2926, 1840, 1640, 1431, 1073, 915, 848, 765, 654 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 3.82–3.72 (m, 3 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).

13C NMR (100 MHz, CDCl3): δ = 76.1, 71.8, 67.4, 65.3, 42.4, 36.4, 21.5.

MS-ESIMS: m/z 147 [M + H]+.

HRMS (ESI): m/z [M + H]+ calcd. for C11H15O4SNa: 315.0929; found: 315.0928.

(5S,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 (ca. 16.5 mmol) 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 saturated aqueous NaHCO3 and extracted with dichloromethane (2 × 25 ml). The combined organic layers were washed with brine, dried over anhydrous Na2SO4 and filtered. Removal of solvent under reduced pressure and purification by silica gel chromatography eluting with 20% EtOAc/hexane afforded 13 (3.1 g 85%) as a viscous liquid.

[a]D22 +34.8 (c 3, CHCl3).

IR (neat): 3382, 2937, 2872, 1652, 1452, 1373, 1148, 698, 608 cm⁻¹.

1H NMR (500 MHz, CDCl3): δ = 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 (dd, J = 9.5, 3.4 Hz, 1 H), 3.37 (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).

13C NMR (125 MHz, CDCl3): δ = 137.8, 134.1, 128.2, 127.5, 117.4, 73.7, 73.1, 69.5, 37.7.

MS-ESIMS: m/z 193 [M + H]+, 215 [M + Na]+.

HRMS (ESI): m/z [M + Na]+ calcd. for C14H20O5NaS: 323.0929; found: 323.0925.

(25S,4R,6S)-Tetrahydro-2-(hydroxymethyl)-6-methyl-2H-pyran-4-ol (12)

To a stirred suspension of lithium (16 g, 250 mmol) in liquid NH3 (160 ml) was added 11 (16 g, 83.3 mmol) dissolved in anhydrous THF (100 ml). 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 NaHCO3 and extracted with dichloromethane (25 ml) at 0 °C. The resulting mixture was washed with brine (120 ml) portionwise. After stirring for 2 h at r.t., the resulting mixture was quenched with saturated aqueous NaHCO3 and extracted with dichloromethane (2 × 25 ml). The combined organic layers were washed with brine, dried over anhydrous Na2SO4 and filtered. Removal of solvent under reduced pressure and purification by silica gel chromatography eluting with 20% EtOAc/hexane afforded 12 (1.66 g, 85%) as a viscous oil.

[a]D22 +15.8 (c 1.1, CHCl3).

IR (neat): 3382, 2937, 2872, 1652, 1452, 1375, 1323, 1148, 1115, 1024, 953 cm⁻¹.

H NMR (400 MHz, CDCl3): δ = 3.82–3.72 (m, 3 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).

13C NMR (100 MHz, CDCl3): δ = 76.1, 71.8, 67.4, 65.3, 42.4, 36.4, 21.5.

MS-ESIMS: m/z 147 [M + H]+.

HRMS (ESI): m/z [M + H]+ calcd. for C10H13O4: 164.0798; found: 164.0794.
To a stirred solution of 14 (3.8 g, 9.2 mmol) in acetonitrile (40 mL) was added NaN (20.7 g, 137.7 mmol) and the mixture was heated to reflux for 24 h. After completion of reaction as monitored by TLC, the mixture was cooled to r.t, diluted with water (50 mL) and extracted with EtOAc (2 × 50 mL). The organic extracts were washed with saturated aqueous NaHCO₃, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 10% EtOAc/hexane to give a grey suspension. The resulting suspension was filtered through a pad of Celite® and concentrated under reduced pressure to give pure 15 (1.7 g, 6.7 mmol) as a colourless liquid.

**HRMS (ESI):** m/z [M + Na]+ calcd. for C₁₃H₂₇IO₂SiNa: 393.16930; found: 393.1706.

**1H NMR (500 MHz, CDCl₃):** δ = 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), 0.90 (s, 9 H), 0.05 (s, 3 H).

**13C NMR (125 MHz, CDCl₃):** δ = 137.6, 133.6, 128.3, 127.7, 127.4, 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 C₁₃H₂₀O₂Na: 335.2406; found: 335.2398.

**HRMS (ESI):** m/z [M + Na]+ calcd. for C₁₄H₂₀O₂Na: 243.1360; found: 243.1365.

**HRMS (ESI):** m/z [M + Na]+ calcd. for C₁₄H₂₀O₂Na: 335.2406; found: 335.2398.

**HRMS (ESI):** m/z [M + Na]+ calcd. for C₉H₁₀O₂SiNa: 393.16930; found: 393.1706.

**HRMS (ESI):** m/z [M + Na]+ calcd. for C₁₃H₂₇IO₂SiNa: 393.16930; found: 393.1706.

To a stirred mixture of NaOH (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 washed with EtOAc (2 × 25 mL) and the organic extracts were washed with water (25 mL), brine (25 mL), dried over anhydrous Na₂SO₄ 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.

**HRMS (ESI):** m/z [M + Na]+ calcd. for C₁₄H₂₀O₂Na: 335.2406; found: 335.2398.
1H NMR (400 MHz, CDCl3): δ = 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).

13C NMR (100 MHz, CDCl3): δ = 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 + H]+ calcd. for C15H19O3: 247.1345; found: 247.1331.

(E)-6-(S)-2-(Benzyloxy)propyl)-5,6-dihydro-2H-pyran-2-one (2)

To a stirred solution of 19 (0.35 g, 14.2 mmol) in anhydrous CH2Cl2 (6 mL), TiCl4 (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 part 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.

[a]D25 +115.5 (c 0.6, CHCl3).

IR (neat): 3427, 2934, 1730, 1373, 1217, 797, 746 cm⁻¹.

1H NMR (500 MHz, CDCl3): δ = 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).

13C NMR (125 MHz, CDCl3): δ = 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 C15H19O3: 247.1345; found: 247.1331.

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Supporting Information

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