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A brief and stereoselective synthesis of limonoid models, with antifeedant activity against *Locusts migratoria*

A. Fernández-Mateos,[a,*] A. I. Ramos Silvo,[a] R. Rubio González[a] and M. S. J. Simmonds[b]

[a]*Universidad de Salamanca, Facultad de C. Químicas, Departamento de Química Orgánica, Plaza de los Caídos 1-5, 37008 Salamanca, Spain*
[b]*Jodrell Laboratory, Royal Botanic Gardens, Kew, Richmond, Surrey, UK*

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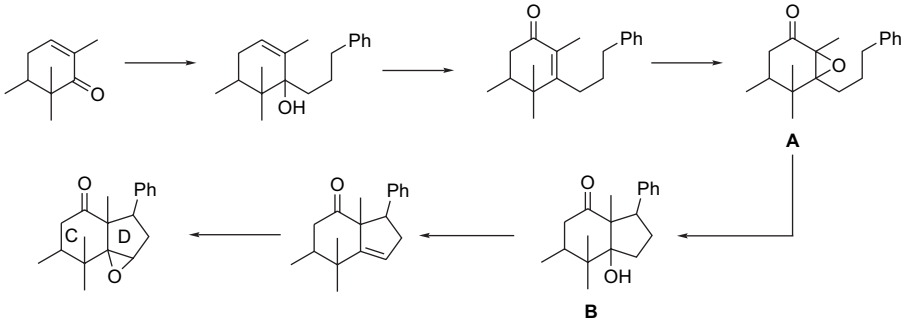
Abstract—A short stereoselective preparation of havanensin-type limonoid models is reported. The synthesis is based on a radical domino reaction of an epoxyketone to a bicyclic hydroxyketone, and is achieved in six and nine steps from simple cyclohexenones. The epoxyhavanensin derivatives show significant antifeedant activity against *Spodoptera littoralis* and *Spodoptera frugiperda*, and the epoxyketone **21** shows potent antifeedant activity against *Locusts migratoria*.

1. Introduction

The hydrindane structural unit is ubiquitous in biologically active molecules such as triterpenoids, steroids and related natural products. Limonoids are a family of degraded triterpenoids with a wide range of biological properties, that contains a structural unit of hydrindane bonded to a heterocycle, constituting the C, D and E rings. Work focused on the hydrindane angular methyl group is relatively limited, with few modes of access to a functionalized ring C, particularly on carbon C-12. Limonoids with an oxygenated function at position C-12 are among the most active of this family of natural products.[1] In connection with synthetic studies directed to the CDE structural fragments of limonoids,[2] we have delineated a new approach directed towards the synthesis of 12-oxo-14,15-epoxy havanensin derivatives, depicted in Scheme 1.

Our strategy is based on a stereoselective construction of ring D by a radical domino sequence from epoxyketone **A** to hydroxyketone **B**, in which the oxygenated functions are situated in the right position and the relative orientation of the methyl and phenyl substituents is the same as in natural limonoids. We have carried out a synthesis of two-keto epoxy limonoid analogues, that differs only on a *gem*-dimethyl group, following the sequence in the Scheme 1.

For the first synthesis, the readily available 2-methylcyclohexenone **1** was selected as the starting material.[3] Conversion of enone **1** into the key intermediate epoxyenone **4**



Scheme 1.

Keywords: Limonoids; Antifeedant; Radical domino cyclization.
* Corresponding author. Tel.: +34923294481; fax: +34923294574; e-mail: afmateos@usal.es

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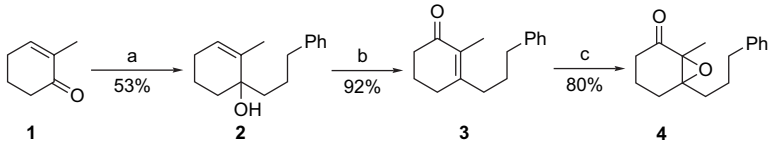
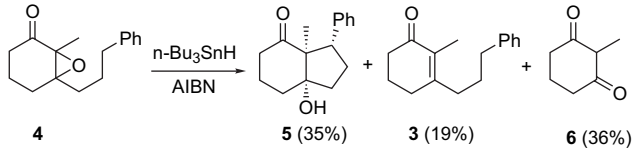


Scheme 2. Reaction conditions: (a) $BrCH_2CH_2CH_2Ph$, Li, THF, 25 °C; (b) PCC, CH_2Cl_2, 25 °C and (c) H_2O_2, NaOH, 20 °C.

was achieved in a three-step sequence. Thus, a Barbier reaction[4] of enone **1** with 1-bromo-3-phenylpropane and lithium furnished the allylic alcohol **2** in 53% yield. Oxidation of alcohol **2** using PCC in CH_2Cl_2 afforded the unsaturated ketone **3** in quantitative yield,[5] which was subsequently converted into epoxyketone **4** by treatment with alkaline hydrogen peroxide in 80% yield (Scheme 2).[6]

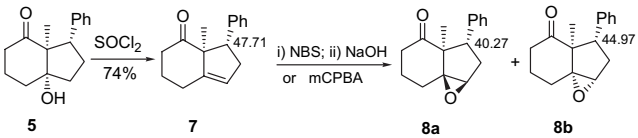
The radical domino reaction of epoxyketone **4** was carried out with AIBN and tributyltin hydride in toluene at reflux. The reaction rate of the epoxyketone **4** was slower as compared to the demethyl derivative in the literature.[7] After 8 h, a 70% conversion of the starting material was achieved (Scheme 3).



Scheme 3.

The expected bicyclic hydroxyketone **5** was obtained in 35% yield, together with another two compounds: the deoxygenation product, enone **3** (19%) and the side-chain fragmentation product, diketone **6** (36%). Other reaction conditions, longer times and several AIBN/*n*-Bu_3SnH/substrate ratios, furnish poorer yields of **5**. The structure assigned to **5** was based on the ^1H NMR signal: the methyl group at 0.78 ppm appears highly shielded by the phenyl ring, and the hydrogen geminal to the phenyl ring at 4.09 ppm as a quartet is deshielded by the nearby carbonyl group.

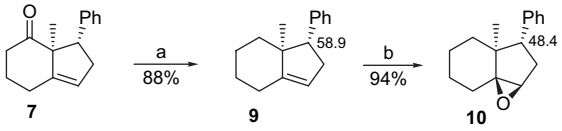
Although the yield of the hydroxyketone **5** in the latter domino reaction was not very high, the sequence is short, easy and stereoselective, and would be competitive with respect to other classic methods. In addition, the two side-products from the domino reaction could be readily recycled. Fortunately, the dehydration of hydroxyketone **5** with thionyl chloride at 0 °C was totally regioselective, affording the desired unsaturated ketone **7** in 74% yield (Scheme 4). The epoxidation of hydrindenone **7** was achieved by two methods, which respectively afforded the two different diastereomers. Treatment of **7** with NBS in water followed by NaOH addition afforded epoxyketone **8b** in 63% yield. In other way, treatment of **7** with *m*-CBPA at 20 °C furnished epoxyketone **8a** in 94% yield.



Scheme 4.

The structural assignation of the epoxides was based on experience gained with analogous compounds described by us elsewhere, in which oxidation with *m*-CBPA afforded always the *endo*-epoxide isomer **8a**.[2a,c,g,j,l,m] Additionally, the γ effect in ^{13}C NMR was considered.[2a,c,g,j,l,m] The difference in the chemical displacement of benzylic carbon between **8a** and **7** (7.5 ppm) was enhanced with respect to the pair **8b** and **7** (2.7 ppm). The shielding effect of the phenyl ring on the protons of the angular methyl group determined the cis relationship between both groups in diastereomers **8a** and **8b,** which appear in ^1H NMR at 0.97 and 0.81, respectively. The benzylic proton is observed to a lower field for **8b** (4.30 ppm) than for isomer **8a** due to deshielding effect of carbonyl group. The δ values in ^{13}C NMR of the isomer **8a** are in agreement with those *endo*-epoxides described by us elsewhere.[2a,c,g,j,l,m] The oxirane carbon (CH) chemical shift for the isomer **8b** are at a lower field (64.3 ppm) than the value observed for *endo*-epoxides,[2a,c,g,j,l,m] which are in the range 56–60 ppm.

For studies of structure–activity relationships (SAR) we obtained deoxoderivative **10** from **7**, following the sequence depicted in (Scheme 5).

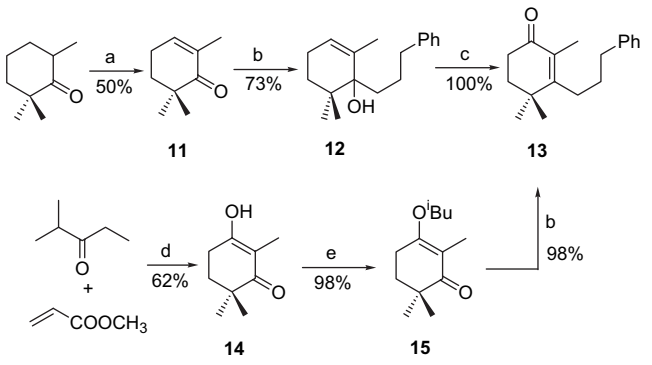


Scheme 5. Reaction conditions: (a) diethylene glycol, Na, N_2H_4 and (b) *m*-CPBA, CH_2Cl_2.

Synthesis of the trimethyl epoxyketone **21** was achieved in two parallel ways through epoxyketone **16**. The first method started with the readily available 2,6,6-trimethylcyclohexenone and comprised four steps: bromination followed by dehydrobromination introduced the required double bond. Addition of the side chain in **11** was done by the Barbier reaction with 1-bromo-3-phenylpropane and lithium. Finally oxidation of the allylic alcohol **12** with PCC/SiO_2 afforded enone **13** in 36% overall yield.

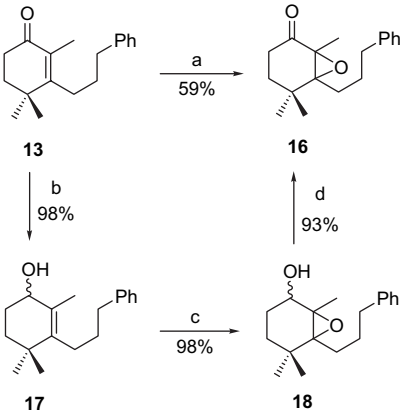
The alternative procedure is easier than the previous one, and only required three steps from 2-methyl-3-pentanone and methyl acrylate: double condensation with sodium methoxide following the M.P. Sammes conditions[8] afforded diketone **14**. Selective ketone protection through enol ether formation[9] to **15** followed by Barbier reaction afforded, after hydrolysis, the required enone **13** in 59% overall yield (Scheme 6).

Epoxidation of enone **13** was accomplished using two alternative methods: the direct one with alkaline water peroxide, which afforded epoxyketone **16** in 59% yield, and the longer indirect route through the allylic alcohol **17**, followed by



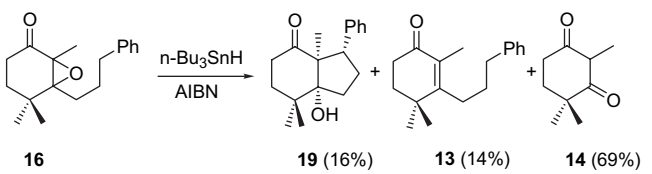
Scheme 6. Reaction conditions: (a) i. NBS, CCl_4 and ii. Li_2CO_3, 25 °C; (b) $BrCH_2CH_2CH_2Ph$, Li, THF, 25 °C; (c) PCC, CH_2Cl_2, 25 °C; (d) NaOMe, xylene, 25 °C and (e) ^{i}BuOH, *p*-TsOH, benzene, 80 °C.

epoxidation with *m*-CPBA and Jones oxidation, in a 89% overall yield (Scheme 7).



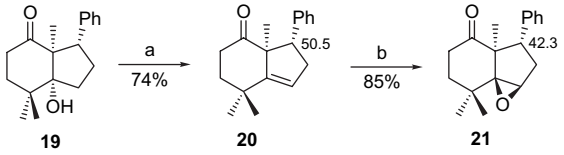
Scheme 7. Reaction conditions: (a) H_2O_2, NaOH, 25 °C; (b) $LiAlH_4$, diethyl ether, 25 °C; (c) *m*-CPBA, CH_2Cl_2, 25 °C and (d) Jones reagent, acetone 0 °C.

After 8 h, the domino reaction of epoxyketone **16** carried out under the same conditions as the demethyl analogue **4**, afforded a mixture of the expected hydroxyketone **19** (16%), the unsaturated ketone **13** (14%) and the diketone **14** (69%). On comparing the results of the domino reaction of epoxyketones **4** and **16**, we observed low conversion for the trimethylketone **16** with respect to the monomethylketone **4**, together an increase in the product arising from the side-chain cleavage. From these results it may be inferred that an increase in substituents around the oxirane slows down the radical reaction and promotes fragmentation of the alkoxyl radical before the 1,5 hydrogen transfer. In spite of these negative aspects, the reaction has other positive aspects such as brevity and stereoselectivity. Additionally, the byproducts could be recycled (Scheme 8).



Scheme 8.

In order to obtain the CDE 12-oxo-14,15-epoxyazadirone fragment **21** from hydroxyketone **19**, only two steps were needed. Dehydration of **19** with thionyl chloride at 0 °C afforded the unsaturated ketone **20** almost quantitatively. Epoxidation of **20** with *m*-CPBA finally afforded the target compound **21** in 85% yield (Scheme 9).



Scheme 9. Reaction conditions: (a) $SOCl_2$, CH_2Cl_2, 0 °C and (b) *m*-CPBA, CH_2Cl_2, −10 °C.

2. Biological results

Larvae of the African leafworms *Spodoptera littoralis* and *Spodoptera frugiperda* were used to assess the antifeedant activity of our molecular fragments.[10] In the series of model compounds related to havanensin, the racemic β-epoxide **8a** was slightly more active than α-epoxide **8b**, and less active than the racemic trimethyl derivative **21** against *S. littoralis* and *S. frugiperda*. The deoxo β-epoxide **10** was the most active of the series.

The 12-oxo-14,15-epoxy havanensin derivative **21** was found to be a very potent antifeedant against *Locusts migratoria*. The larvae died when they had ingested some of the epoxyketone **21**; this is a species of locusts that does not find azadirachtin a very potent insect antifeedant (Table 1).

Table 1. Antifeedant index of the compounds tested in choice bioassays

	Antifeedant index at 100 ppm[a]	
	S. littoralis	*S. frugiperda*
8a	22 (5.7)	22 (3.7)
8b	20 (5.7)	14 (7.6)
10	43 (4.9)	23 (6.8)
21	30 (3.6)	21 (5.4)

[a] Antifeedant index=$[(C-T)/(C+T)]$% of compounds tested in choice bioassays with glass fibre discs (control (C) vs treatment (T)) (n=20).

3. Experimental

3.1. General

Commercial reagents were used as received. Dichloromethane and pyridine were distilled under nitrogen over calcium hydride. Ether and THF were distilled from sodium. Acetone, benzene and hexane were distilled before use. Melting points were determined on a hot-stage apparatus and are not corrected. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 200 and 50 MHz, respectively. IR spectra were obtained as films. Mass spectra were obtained on a VG-TS 250 instrument. All reactions were carried out under an atmosphere of nitrogen in glassware dried overnight and cooled under nitrogen. TLC monitored reactions. Column chromatography was performed on using silica gel 60 (0.040–0.063 mm, Merck). Organic extracts

were washed with saturated NaCl solution, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure with the aid of rotary evaporator.

3.1.1. 2-Methyl-1-(3-phenyl-propyl)-cyclohex-2-enol 2. A solution of 2-methylcyclohex-2-enone **1** (15.5 g, 137 mmol) and 1-bromo-3-phenylpropane (41 g, 206 mmol) in THF (13 mL) was added via a dropping funnel to a stirred suspension of lithium (3.4 g, 480 mmol) in THF (152 mL) at room temperature under argon. The reaction mixture was vigorously stirred for 7 h. The mixture was filtered to remove excess lithium and the solvent was evaporated at reduced pressure. The residue was hydrolyzed with hydrochloric acid, and the two-phase system was extracted with ether. The combined ethereal extracts were washed with aqueous $NaHCO_3$ (5%) and brine. Removal of the solvent afforded a crude residue, which was purified by chromatography. Eluting with hexane–ethyl acetate (9:1) furnished enone **1** (1 g, 7%), as a colourless oil. Eluting with hexane–ether (8:2) afforded the unsaturated alcohol **2** (8 g, 53%), as a colourless oil: IR 3408, 2941, 1086 cm^{-1}; ^1H NMR δ: 1.65 (3H, s), 1.3–1.7 (8H, m), 1.95 (2H, m), 2.61 (2H, m), 5.52 (1H, br s), 7.1–7.2 (5H, m) ppm; ^{13}C NMR δ: 17.5 (CH_3), 18.9 (CH_2), 25.5 (CH_2), 25.9 (CH_2), 35.2 (CH_2), 38.2 (CH_2), 38.6 (CH_2), 71.8 (C), 125.5 (CH), 126.1 (CH), 128.1 (2CH), 128.2 (2CH), 137.1 (C), 142.2 (C) ppm; MS *m*/*z* (relative intensity) 212 (11, M^+-18), 121 (49), 11 (58), 93 (80), 91 (100), 79 (52), 65 (42), 55 (31); HRMS (ESI): 231.1768 (M^++H, $C_{16}H_{23}O$), calcd 231.1744.

3.1.2. 2-Methyl-3-(3-phenyl-propyl)-cyclohex-2-enone 3. To a stirred suspension of PCC (9.97 g, 46.2 mmol) and silica (10 g) in CH_2Cl_2 (300 mL) was added dropwise a solution of the alcohol **2** (7 g, 30.4 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was vigorously stirred at room temperature under argon for 1 h. The resulting dark brown slurry was filtered through a short column of silica and eluted with CH_2Cl_2. Removal of the solvent afforded cyclohexenone **3** (6.9 g, 98%), as a colourless oil: IR 2950, 1661, 1450 cm^{-1}; ^1H NMR δ: 1.73 (3H, s), 1.7–2.0 (4H, m), 2.35 (6H, m), 2.65 (2H, m), 7.1–7.4 (5H, m) ppm; ^{13}C NMR δ: 9.8 (CH_3), 21.8 (CH_2), 28.2 (CH_2), 30.1 (CH_2), 34.1 (CH_2), 35.2 (CH_2), 37.0 (CH_2), 125.3 (CH), 127.6 (4CH), 130.3 (C), 140.9 (C), 157.6 (C), 198.2 (C) ppm; MS *m*/*z* (relative intensity) 228 (3, M^+), 124 (49), 104 (100), 91 (69), 65 (39), 53 (51); HRMS (ESI): 229.1542 (M^++H, $C_{16}H_{21}O$), calcd 229.1587.

3.1.3. 1-Methyl-6-(3-phenyl-propyl)-7-oxa-bicyclo-[4.1.0]heptan-2-one 4. To a stirred solution of enone **3** (6.1 g, 26.7 mmol) in methanol (232 mL) at 0 °C under argon, were added dropwise H_2O_2 (40 mL, 30%) and a solution of NaOH (14 mL, 6 N). This resulting solution was stirred for 6 h at room temperature, and then poured into a solution of $Na_2S_2O_3$ (10%). The methanol was evaporated off and the aqueous solution was extracted with ether. The organic extracts were washed with brine, dried and filtered. Removal of the solvent afforded a crude residue, which was purified by chromatography. Eluting with hexane–ethyl acetate (8:2) furnished epoxyketone **4** (5.2 g, 80%), as a colourless oil: IR 3027, 2961, 1710, 1459 cm^{-1}; ^1H NMR δ: 1.36 (3H, s), 1.6–2.2 (10H, m), 2.60 (2H, m), 7.1–7.4 (5H, m) ppm; ^{13}C NMR δ: 11.3 (CH_3), 17.6 (CH_2), 26.8 ($2CH_2$), 33.0 (CH_2), 35.5 (CH_2), 35.9 (CH_2), 64.4 (C), 68.5 (C), 125.7 (CH), 128.1 (4CH), 141.3 (C), 207.1 (C) ppm; MS *m*/*z* (relative intensity) 244 (2, M^+), 104 (35), 91 (100), 77 (25), 65 (38), 55 (46); HRMS (ESI): 245.1512 (M^++H, $C_{16}H_{21}O_2$), calcd 245.1536.

3.1.4. Cyclization of the epoxyketone 4 with *n*-Bu_3SnH. A solution of tributyltin hydride (1.7 mL, 6.3 mmol) in benzene (85 mL) was added via a dropping funnel to a refluxing solution of the epoxyketone **4** (5.1 g, 20.9 mmol) and AIBN (1.04 mmol) in benzene (700 mL) under argon. The reaction mixture was refluxed for 8 h. Removal of the solvent afforded a crude residue, which was purified by chromatography. Eluting with hexane–ethyl acetate (9:1) furnished epoxyketone **4** (1.5 g, 30%), as a colourless oil. Eluting with hexane–ethyl acetate (8:2) furnished enone **3** (605 mg, 19%), as a colourless oil. Eluting with hexane–ethyl acetate (1:1) furnished 7a-hydroxy-3a-methyl-3-phenyl-octahydro-inden-4-one **5** (1.25 g, 35%), as a colourless oil: IR 3440, 2865, 1710 cm^{-1}; ^1H NMR δ: 0.79 (3H, s), 1.6–2.4 (8H, m), 2.47 (1H, m), 2.61 (1H, m), 4.07 (1H, t, J=9 Hz), 7.1–7.4 (5H, m) ppm; ^{13}C NMR δ: 14.3 (CH_3), 21.3 (CH_2), 27.0 (CH_2), 34.7 (CH_2), 37.4 (CH_2), 37.6 (CH_2), 48.5 (CH), 62.9 (C), 85.2 (C), 126.4 (CH), 127.9 (2CH), 129.1 (2CH), 141.1 (C), 213.6 (C) ppm; MS *m*/*z* (relative intensity) 244 (4, M^+), 170 (91), 155 (51), 115 (94), 91 (100), 77 (63), 65 (37), 55 (83); HRMS (ESI): 245.1571 (M^++H, $C_{16}H_{21}O_2$), calcd 245.1536. Eluting with ethyl acetate furnished 2-methyl-1,3-cyclohexanodione **6** (0.66 g, 36%), as a white solid identified by comparison with a standard.

3.1.5. 3a-Methyl-3-phenyl-2,3,3a,5,6,7-hexahydro-inden-4-one 7. To a solution of the hydroxyketone **5** (1.13 g, 4.65 mmol) in dry CH_2Cl_2 (23 mL) at 0 °C under argon were gradually added pyridine (1.3 mL) and $SOCl_2$ (0.67 mL, 9.3 mmol). The mixture was stirred at 0 °C for 20 min and then poured into ice water. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with $NaHCO_3$ (5%) and brine, and then dried (Na_2SO_4). Evaporation of the solvent left a crude, which was purified by flash chromatography. Elution with hexane–ethyl acetate (93:7) afforded the unsaturated ketone **7** (774 mg, 74%), as a colourless oil: IR 2950, 1711 cm^{-1}; ^1H NMR δ: 0.92 (3H, s), 1.63 (1H, m), 2.10 (1H, m), 2.2–2.8 (6H, m), 4.06 (1H, t J= 9.5 Hz), 5.46 (1H, s), 7.1–7.6 (5H, m) ppm; ^{13}C NMR δ: 19.9 (CH_3), 25.7 (CH_2), 26.3 (CH_2), 34.9 (CH_2), 38.6 (CH_2), 47.7 (CH), 63.5 (C), 121.92 (CH), 126.0 (CH), 127.7 (2CH), 129.8 (2CH), 141.0 (C), 146.5 (C), 214.0 (C) ppm; MS *m*/*z* (relative intensity) 226 (82, M^+), 211 (58), 169 (100), 155 (81), 115 (70), 91 (81), 77 (56), 65 (930), 55 (41); HRMS (ESI): 227.1439 (M^++H, $C_{16}H_{19}O$), calcd 227.1431.

3.1.6. 3a-Methyl-3-phenyl-hexahydro-1-oxa-cyclopropa-[*c*]inden-4-one 8. To a stirred solution of ketone **7** (210 mg, 0.9 mmol) in acetone (5 mL) and water (0.5 mL) at 0 °C under argon was added NBS (739 mg, 4.1 mmol). The resulting mixture was gradually warmed to room temperature and then, stirred for 1 h, after this hours was poured into water (3 mL) and extracted three times with ether. The combined extracts were washed with brine and then dried (Na_2SO_4). The solvent was evaporated off at reduced

pressure to afford a colourless residue (276 mg), which was dissolved in THF (3 mL). To this stirred solution, at 0 °C, under argon was added NaOH (0.5 mL, 5 M). The reaction mixture was stirred for 45 min, and then H_2O was added, and extracted with ether. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography over silica gel (hexane–ether, 80:20) gave epoxyketone **8b** (133 mg, 63%), as a white solid: mp 109 °C; IR 3023, 2955, 1707, 1460 cm^{-1}; ^1H NMR δ: 0.81 (3H, s), 1.71 (2H, m), 2.0–2.6 (6H, m), 3.41 (1H, s), 4.30 (1H, dd, J=6 Hz, J'=5.5 Hz), 7.1–7.4 (5H, m) ppm; ^{13}C NMR δ: 18.0 (CH_3), 21.2 (CH_2), 26.0 (CH_2), 34.1 (CH_2), 37.2 (CH_2), 44.9 (CH), 61.0 (C), 64.3 (CH), 71.0 (C), 125.8 (CH), 127.7 (2CH), 130.4 (2CH), 143.6 (C), 211.9 (C) ppm; Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.30; H, 7.49. Found: C, 79.39; H, 7.38; MS m/z (relative intensity) 242 (23, M^+), 227 (59), 199 (43), 169 (37), 143 (49), 128 (59), 115 (78), 104 (44), 91 (93), 77 (74), 65 (39), 55 (100); HRMS (ESI): 243.1404 (M^++H, $C_{16}H_{19}O_2$), calcd 243.1380. The second compound, epoxyketone **8a** (45 mg, 22%), was a white solid: mp 120–121 °C; IR 3022, 1707 cm^{-1}; ^1H NMR δ: 0.97 (3H, s), 1.55 (1H, m), 2.0–2.8 (7H, m), 3.60 (1H, dd, J=7.5 Hz, J'=11.5 Hz), 3.66 (1H, s), 7.1–7.5 (5H, m) ppm; ^{13}C NMR δ: 17.2 (CH_3), 23.9 (CH_2), 24.5 (CH_2), 30.0 (CH_2), 37.9 (CH_2), 40.2 (CH), 56.7 (C), 60.5 (CH), 73.3 (C), 126.2 (CH), 127.8 (2CH), 129.7 (2CH), 138.9 (C), 211.6 (C) ppm; Anal. calcd for $C_{16}H_{18}O_2$: C, 79.30; H, 7.49. Found: C, 79.69; H, 7.78; MS m/z (relative intensity) 242 (20, M^+), 169 (100), 155 (26), 141 (34), 115 (44), 91 (50), 77 (37), 65 (20), 55 (41).

3.1.7. 3a-Methyl-3-phenyl-hexahydro-1-oxa-cyclopropa-[*c*]inden-4-one 8a. To a stirred solution of ketone **7** (200 mg, 0.88 mmol) in CH_2Cl_2 (10 mL), under argon, were added catalytic Na_2CO_3 and *m*-CPBA (150 mg, 0.88 mmol). The reaction mixture was stirred for 7 h at room temperature. Then, a 5% solution of $Na_2S_2O_3$ was added and the resulting heterogeneous mixture was stirred for 15 min. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated $NaHCO_3$, water and brine and then dried (Na_2SO_4). Evaporation of the solvent and purification by flash chromatography over silica gel (hexane–ether, 80:20) gave the epoxyketone **8b** (5 mg, 2%) and epoxyketone **8a** (188 mg, 94%).

3.1.8. 7a-Methyl-1-phenyl-2,4,5,6,7,7a-hexahydro-1*H*-indene 9. To anhydrous diethylene glycol (17 mL), under an atmosphere of argon, was added sodium metal (561 mg) and the mixture was stirred until all of the sodium had reacted. Anhydrous hydrazine (prepared by refluxing hydrazine hydrate over sodium hydroxide) was distilled directly into the resulting solution until the latter refluxed freely at 165 °C. The solution was cooled and the bicyclic ketone **7** (350 mg, 1.55 mmol) was added. The mixture was refluxed for 14 h and excess hydrazine was distilled from the mixture until the internal temperature of the latter reached 210 °C. Refluxing was then continued for an additional 8 h. The mixture was cooled, combined with the distillate (see above), and poured into water. The resulting mixture was extracted with hexane. The combined extracts were washed with water and dried over Na_2SO_4. Removal of the solvent gave the bicyclic olefin **9** (300 mg, 88%), as a colourless oil: IR 2928, 2868, 1654, 772 cm^{-1}; ^1H NMR δ: 0.61 (3H, s), 1.2–2.1 (6H, m), 2.42 (2H, m), 2.72 (2H, m), 3.18 (1H, dd, J=8 Hz, J'=10.7 Hz), 5.34 (1H, br s), 7.2–7.4 (5H, m) ppm; ^{13}C NMR δ: 18.2 (CH_3), 22.5 (CH_2), 26.9 (CH_2), 27.0 (CH_2), 33.9 (CH_2), 41.0 (CH_2), 48.1 (C), 58.9 (CH), 118.4 (CH), 126.0 (CH), 127.8 (2CH), 128.7 (2CH), 141.6 (C), 148.3 (C) ppm; HRMS (ESI): 213.1697 (M^++H, $C_{16}H_{21}$), calcd 213.1638.

3.1.9. 3a-Methyl-3-phenyl-octahydro-1-oxa-cyclopropa-[*c*]indene 10. To a stirred solution of alquene **9** (130 mg, 0.6 mmol) in CH_2Cl_2 (10 mL) at room temperature, under argon, were added catalytic Na_2CO_3 and *m*-CPBA (110 mg, 0.6 mmol). The reaction mixture was stirred for 10 min. Then, a 5% solution of $Na_2S_2O_3$ was added and the resulting heterogeneous mixture was stirred for 15 min. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated $NaHCO_3$, water and brine, and then dried (Na_2SO_4). Evaporation of the solvent afforded the epoxyketone **10** (130 mg, 94%) as a colourless oil: IR 2943, 2870, 2454, 758 cm^{-1}; ^1H NMR δ: 0.58 (3H, s), 1.2–2.2 (10H, m), 2.80 (1H, dd, J=7 Hz, J'=11 Hz), 3.55 (1H, s), 7.0–7.4 (5H, m) ppm; ^{13}C NMR δ: 16.1 (CH_3), 21.3 (CH_2), 25.9 (CH_2), 23.6 (CH_2), 25.9 (CH_2), 34.3 (CH_2), 41.8 (C), 48.4 (CH), 60.9 (CH), 70.4 (C), 126.0 (CH), 127.9 (2CH), 128.9 (2CH), 139.6 (C) ppm; HRMS (ESI): 229.1619 (M^++H, $C_{16}H_{21}O$), calcd 229.1587.

3.1.10. 2,6,6-Trimethyl-1-(3-phenyl-propyl)-cyclohex-2-enol 12. A solution of 2,6,6-trimethyl-cyclohex-2-enone (1.27 g, 10.2 mmol) and 1-bromo-3-phenylpropane (3.06 g, 15.4 mmol) in THF (3 mL) was added via a dropping funnel to a stirred suspension of lithium (250 mg, 35.8 mmol) in dry THF (12 mL), at room temperature under argon. The reaction mixture was vigorously stirred for 5 h. The mixture was filtered to remove excess lithium and the solvent was evaporated at reduced pressure. The residue was hydrolyzed with hydrochloric acid, and the two-phase system was extracted with ether. The combined ethereal extracts were washed with aqueous $NaHCO_3$ (5%) and brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography. Eluting with hexane–ether (8:2) afforded the alcohol **12** (1.93 g, 73%), as a colourless oil: IR 3499, 2951 cm^{-1}; ^1H NMR δ: 0.93 (3H, s), 0.94 (3H, s), 1.3–1.8 (6H, m), 1.65 (3H, s), 1.95 (2H, m), 2.56 (2H, m), 5.40 (1H, s), 7.1–7.4 (5H, m) ppm; ^{13}C NMR δ: 18.9 (CH_3), 22.4 (CH_2), 23.1 (CH_3), 24.1 (CH_3), 27.6 (CH_2/C), 34.0 (CH_2), 36.9 (CH_2), 37.2 (CH_2), 77.2 (C), 123.5 (CH), 125.5 (CH), 128.8 (2CH), 128.2 (2CH), 137.2 (C), 142.2 (C) ppm; MS m/z (relative intensity) 240 (5, M^+-18), 202 (7), 139 (27), 121 (31), 91 (100), 77 (22), 65 (26), 55 (20); HRMS (ESI): 259.2111 (M^++H, $C_{18}H_{27}O$), calcd 259.2057.

3.1.11. 2,4,4-Trimethyl-3-(3-phenyl-propyl)-cyclohex-2-enone 13. To a stirred suspension of PCC (1.8 g, 8.4 mmol) and silica (1 equiv of PCC) in dry CH_2Cl_2 (53 mL) was added a solution of the alcohol **12** (1.4 g, 5.6 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was vigorously stirred at room temperature under argon for 2 h. The resulting dark brown slurry was filtered though a short

column of silica gel and eluted with CH_2Cl_2. Removal of the solvent afforded unsaturated cyclohexenone **13** (1.4 g, 100%), as a colourless oil: IR 2957, 1667, 1352 cm^{-1}; ^1H NMR δ: 1.11 (6H, s), 1.70 (3H, s), 1.77 (4H, m), 2.15 (2H, m), 2.44 (2H, m), 2.70 (2H, t, J=7.4 Hz), 7.15–7.35 (5H, m) ppm; ^{13}C NMR δ: 11.1 (CH_3), 28.8 ($2CH_3$), 30.1 ($2CH_2$), 34.0 (CH_2), 35.9 (C), 36.3 (CH_2), 37.2 (CH_2), 125.7 (CH), 128.1 (4CH), 130.5 (C), 141.2 (C), 164.1 (C), 198.2 (C) ppm; MS *m/z* (relative intensity) 256 (4, M^+), 137 (29), 104 (100), 91 (98), 77 (32), 65 (33), 55 (29); HRMS (ESI): 257.1936 (M^++H, $C_{18}H_{25}O$), calcd 257.1900.

3.1.12. 2,4,4-Trimethyl-cyclohexane-1,3-dione 14. A mixture of 2-methyl-pentan-3-one (30 g, 300 mmol) and methyl acrylate (25.8 g, 300 mmol) was added dropwise at room temperature under argon to a stirred solution of NaOMe (65 mL, 360 mmol) in MeOH (5.5 M) and xylene (180 mL). The resulting mixture was stirred for 30 min at 25 °C. The solution was concentrated in vacuo to remove methanol and the residue was then acidified with HCl 6 N. The organic phase was separated and the aqueous layer was extracted with ether. The organic extracts were washed with brine, dried and concentrated. The residue was chromatographed over silica gel, eluting with AcOEt furnished the diketone **14** (28.4 g, 62%): IR 3208, 2965, 1711, 1092 cm^{-1}; ^1H NMR δ: 1.13 (6H, s), 1.71 (3H, s), 1.79 (2H, t, J=6.3 Hz), 2.49 (2H, t, J=6.3 Hz) ppm.

3.1.13. 3-Isobutoxy-2,6,6-trimethyl-cyclohex-2-enone 15. Diketone **14** (20.6 g, 133.7 mmol), ^{t}BuOH (24.6 mL, 267.6 mmol) and *p*-TsOH (168 mg, 0.9 mmol) in benzene (126 mL) were heated at reflux under argon for 9 h with a Dean and Stark apparatus. The solvent was distilled under reduced pressure, and the residue was diluted with ether and washed with aqueous Na_2CO_3 (10%) and brine, dried, and evaporated in vacuo to afford the ketone **15** (27.6 g, 98%), as a colourless oil: IR 2963, 1736, 1620, 1379 cm^{-1}; ^1H NMR δ: 0.91 (3H, d, J=6.6 Hz), 0.98 (3H, d, J=6.8 Hz), 1.08 (6H, s), 1.70 (3H, s), 1.80 (2H, t, J=6 Hz), 2.00 (1H, m), 2.55 (1H, t, J=6 Hz), 3.74 (2H, d, J=6.5 Hz) ppm; MS *m/z* (relative intensity) 210 (20, M^+), 155 (7), 127 (12), 99 (100), 83 (30), 70 (25), 57 (32); HRMS (ESI): 211.1704 (M^++H, $C_{13}H_{23}O_2$), calcd 211.1693.

3.1.14. 2,4,4-Trimethyl-3-(3-phenyl-propyl)-cyclohex-2-enone 13. A solution of the ketone **15** (18 g, 85.7 mmol) and 1-bromo-3-phenylpropane (25.5 g, 128.5 mmol) in THF (13 mL) was added via a dropping funnel to a stirred suspension of lithium (2.1 g, 300 mmol) in THF (108 mL) at room temperature under argon. The reaction mixture was vigorously stirred for 60 h. The mixture was filtered to remove excess lithium and the solvent was evaporated at reduced pressure. The residue was hydrolyzed with HCl 6 N, and the two-phase system was extracted with ether. The combined ethereal extracts were washed with aqueous $NaHCO_3$ (5%) and brine. The solvent was evaporated under reduced pressure to afford the enone **13** (21.4 g, 98%).

3.1.15. 1,5,5-Trimethyl-6-(3-phenyl-propyl)-7-oxa-bicyclo[4.1.0]heptan-2-one 16. To a stirred solution of enone **13** (14 g, 54.67 mmol) in methanol (491 mL) at 0 °C under argon were added dropwise H_2O_2 (112 mL, 30%) and NaOH (27 mL, 6 N). This resulting solution was stirred for 48 h at room temperature, and then poured into a solution of $Na_2S_2O_3$ (10%). The methanol was evaporated off and the aqueous solution was extracted with ether. The solution was washed with brine, dried and filtered. Evaporation of the solvent left a crude, which was purified by chromatography. Eluting with hexane–ether (9:1) furnished epoxyketone **16** (4.6 g, 59%) as a colourless oil: IR 2961, 1703, 1452 cm^{-1}; ^1H NMR δ: 0.98 (3H, s), 1.10 (3H, s), 1.21 (2H, m), 1.30 (3H, s), 1.74 (4H, m), 2.62 (2H, m), 2.89 (2H, m), 7.1–7.5 (5H, m) ppm; ^{13}C NMR δ: 12.5 (CH_3), 23.7 (CH_3), 25.9 (CH_3), 27.4 (CH_2), 27.7 (CH_2), 32.4 (CH_2), 33.6 (CH_2), 35.4 (C), 38.1 (CH_2), 65.7 (C), 73.2 (C), 125.9 (CH), 128.3 (4CH), 141.8 (C), 207.9 (C) ppm; MS *m/z* (relative intensity) 254 (2, M^+-18), 229 (6), 211 (5), 147 (10), 104 (42), 91 (100), 83 (28), 65 (19), 55 (36); HRMS (ESI): 273.1843 (M^++H, $C_{18}H_{25}O_2$), calcd 273.1849. Eluting with hexane–ether (8:2) furnished enone **13** (234 mg, 47%).

3.1.16. 2,4,4-Trimethyl-3-(3-phenyl-propyl)-cyclohexen-2-ol 17. Lithium aluminium hydride (892 mg, 23.46 mmol) was added to a solution of **13** (6 g, 23.46 mmol) in dry diethyl ether (216 mL) cooled to 0 °C. The mixture was vigorously stirred under argon for 1 h. Then, $Na_2SO_4\cdot 10H_2O$ was added and the resulting mixture was stirred for 30 min. The resulting mixture was filtered and the solvent was concentrated under reduced pressure to afford a solid identified as alcohol **17** (5.9 g, 98%): mp 55–60 °C; IR 3374, 2940, 1454 cm^{-1}; ^1H NMR δ: 0.93 (3H, s), 1.00 (3H, s), 1.34 (2H, m), 1.68 (3H, s), 1.5–2.1 (6H, m), 2.64 (2H, m), 3.87 (1H, m), 7.1–7.4 (5H, m) ppm; ^{13}C NMR δ: 16.6 (CH_3), 27.0 (CH_3), 28.4 (CH_3), 28.5 (CH_2), 28.8 (CH_2), 31.4 (CH_2), 34.7 (CH_2), 35.2 (C), 36.6 (CH_2), 70.1 (CH), 125.6 (CH), 128.1 (2CH), 128.3 (2CH), 128.7 (C), 142.1 (C), 142.1 (C) ppm; MS *m/z* (relative intensity) 240 (15, M^+-H_2O), 139 (14), 121 (45), 91 (100), 77 (27), 51 (12); HRMS (ESI): 259.2007 (M^++H, $C_{18}H_{27}O$), calcd 259.2057.

3.1.17. 1,5,5-Trimethyl-6-(3-phenyl-propyl)-7-oxa-bicyclo[4.1.0]heptan-2-ol 18. To a stirred solution of alcohol **17** (5.9 g, 23.2 mmol) in CH_2Cl_2 (357 mL) at −10 °C under argon, were added catalytic Na_2CO_3 and *m*-CPBA (4 g, 23.2 mmol). The reaction mixture was gradually warmed to room temperature, and stirred for 25 min. Then, a 5% solution of $Na_2S_2O_3$ was added and the resulting heterogeneous mixture was stirred for 15 min. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated $NaHCO_3$, water and brine, and then dried (Na_2SO_4). Evaporation of the solvent afforded the epoxy alcohol **18** (6 g, 98%): IR 3455, 2947, 1452 cm^{-1}; ^1H NMR δ: 1.00 (3H, s), 1.01 (3H, s), 1.35 (3H, s), 1.4–1.9 (8H, m), 2.61 (2H, m), 3.72 (1H, br s), 7.1–7.4 (5H, m) ppm; ^{13}C NMR δ: 18.6 (CH_3), 24.9 (CH_3), 25.7 (CH_3), 27.1 (CH_2), 28.1 (CH_2), 28.3 (CH_2), 31.7 (CH_2), 34.3 (C), 36.3 (CH_2), 66.1 (C), 69.1 (CH), 72.6 (C), 125.7 (CH), 128.2 (2CH), 128.3 (2CH), 141.8 (C) ppm; MS *m/z* (relative intensity) 256 (1, M^+-18), 190 (12), 147 (14), 104 (95), 91 (100), 77 (21), 65 (30), 55 (49); HRMS (ESI): 275.2019 (M^++H, $C_{18}H_{27}O_2$), calcd 275.2006.

3.1.18. 1,5,5-Trimethyl-6-(3-phenyl-propyl)-7-oxa-bicyclo[4.1.0]heptan-2-one 16. Jones reagent was added

dropwise with stirring to a solution of **18** (6 g, 21.89 mmol) in acetone (253 mL) at 0 °C. The resulting mixture was stirred at this temperature for an additional 30 min. Then, isopropilic alcohol was added. The solvent was evaporated under reduced pressure to afford a residue, which was dissolved in water and extracted with ether. The extracts were washed with brine, dried and evaporated to afford the epoxyketone **16** (5.5 g, 93%).

3.1.19. Cyclization of the epoxyketone 16 with *n*-Bu_3SnH. A solution of tributyltin hydride (2.8 mL, 10.5 mmol) in benzene (300 mL) was added via a dropping funnel (4.3 mmol/h) to a refluxing solution of the epoxyketone **16** (9.5 g, 34.9 mmol) and AIBN (1.7 mmol) in benzene (700 mL) under argon. The reaction mixture was refluxed for 8 h. Removal of the solvent afforded a crude residue, which was purified by chromatography. Eluting with hexane–ethyl acetate (9:1) furnished epoxyketone **16** (4.7 g, 50%), as a colourless oil. Eluting with hexane–ethyl acetate (8:2) furnished enone **13** (625 mg, 14%), as a colourless oil. Eluting with hexane–ethyl acetate (8:2) furnished 7a-hydroxy-3a,7,7-trimethyl-3-phenyl-octahydro-inden-4-one **19** (709 mg, 16%), as a colourless oil: IR 3518, 2965, 1694 cm^{-1}; ^1H NMR δ: 0.76 (3H, s), 1.06 (6H, s), 1.7–2.2 (6H, m), 2.61 (2H, m), 3.67 (1H, dd, J=6.8 Hz, J'=11.3 Hz), 7.1–7.3 (5H, m) ppm; ^{13}C NMR δ: 17.5 (CH_3), 22.4 (CH_3), 25.9 (CH_3), 28.4 (CH_2), 32.6 (CH_2), 34.2 (CH_2), 36.1 (CH_2), 37.6 (C), 51.0 (CH), 62.5 (C), 87.6 (C), 126.3 (CH), 127.8 (2CH), 129.5 (2CH), 141.0 (C), 214.5 (C) ppm; MS *m/z* (relative intensity) 254 (53, M^+-18), 198 (60), 173 (64), 159 (100), 115 (56), 91 (83), 70 (48), 55 (90); HRMS (ESI): 273.1858 (M^++H, $C_{18}H_{25}O_2$), calcd 273.1849. Eluting with ethyl acetate furnished 2-methyl-1,3-cyclohexanodione **14** (1.8 g, 69%), as a white solid identified by comparison with a standard.

3.1.20. 3a,7,7-Trimethyl-3-phenyl-2,3,3a,5,6,7-hexahydro-inden-4-one 20. To a solution of the hydroxyketone **19** (200 mg, 0.7 mmol) in dry CH_2Cl_2 (3.5 mL) at 0 °C under argon were gradually added pyridine (0.2 mL) and $SOCl_2$ (0.1 mL, 1.5 mmol). The mixture was stirred at 0 °C for 2 h and then poured into ice water. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with $NaHCO_3$ (5%) and brine, and then dried (Na_2SO_4). Evaporation of the solvent left a crude, which was purified by flash chromatography. Elution with hexane–ethyl acetate (93:7) afforded unsaturated ketone **20** (516 mg, 74%), as a white solid, mp 70–71 °C; IR 2926, 1717, 1458, 1377 cm^{-1}; ^1H NMR δ: 1.03 (3H, s), 1.23 (3H, s), 1.31 (3H, s), 1.65 (1H, m), 1.90 (1H, m), 2.32 (1H, m), 2.50 (1H, m), 2.72 (2H, m), 3.80 (1H, dd, J=8.4 Hz, J'=10.8 Hz), 5.63 (1H, dd, J=1.6 Hz, J'=3.2 Hz), 7.1–7.6 (5H, m) ppm; ^{13}C NMR δ: 21.0 (CH_3), 29.4 (CH_3), 30.2 (CH_3), 33.6 (C), 34.5 (CH_2), 36.2 (CH_2), 38.3 (CH_2), 50.5 (CH), 61.6 (C), 122.7 (CH), 126.2 (CH), 127.7 (2CH), 130.2 (2CH), 140.5 (C), 154.5 (C), 215.1 (C) ppm; MS *m/z* (relative intensity) 254 (30, M^+), 239 (12), 198 (100), 183 (40), 115 (45), 91 (84), 77 (53), 65 (24), 55 (63); HRMS (ESI): 255.1741 (M^++H, $C_{18}H_{23}O$), calcd 255.1744.

3.1.21. 3a,7,7-Trimethyl-3-phenyl-hexahydro-1-oxacyclopropa[*c*]inden-4-one 21. To a stirred solution of ketone **20** (41 mg, 0.16 mmol) in CH_2Cl_2 (1 mL) at −10 °C under argon, were added catalytic Na_2CO_3 and *m*-CPBA (28 mg, 0.16 mmol). The reaction mixture was gradually warmed to room temperature, and stirred for 3 h at room temperature. Then, a 5% solution of $Na_2S_2O_3$ was added and the resulting heterogeneous mixture was stirred for 15 min. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated $NaHCO_3$, water and brine, and then dried (Na_2SO_4). Evaporation of the solvent afforded the epoxyketone **21** (30 mg, 85%) as a colourless solid: mp 97–100 °C; IR 2924, 1711, 1458 cm^{-1}; ^1H NMR δ: 0.94 (3H, s), 1.01 (3H, s), 1.35 (3H, s), 1.93 (2H, m), 2.11 (1H, m), 2.21 (1H, m), 2.46 (1H, m), 2.61 (1H, m), 3.44 (1H, dd, J=7 Hz, J'=11.4 Hz), 3.57 (1H, br s), 7.1–7.4 (5H, m) ppm; ^{13}C NMR δ: 17.8 (CH_3), 26.5 (CH_3), 27.6 (CH_3), 30.7 (CH_2), 32.7 (C), 36.6 (CH_2), 36.7 (CH_2), 42.3 (CH), 56.1 (C), 56.7 (CH), 74.1 (C), 126.3 (CH), 127.7 (2CH), 130.4 (2CH), 138.6 (C), 213.2 (C) ppm; Anal. Calcd for $C_{16}H_{22}O_2$: C, 79.30; H, 7.49. Found: C, 79.69; H, 7.78; MS *m/z* (relative intensity) 255 (25, M^+-15), 197 (100), 156 (66), 115 (46), 91 (67), 77 (46), 55 (52); HRMS (ESI): 271.1690 (M^++H, $C_{18}H_{23}O_2$), calcd 271.1693.

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References and notes

1. (a) Taylor, D. A. H. *Prog. Chem. Org. Nat. Prod.* **1984**, *45*, 1; (b) Champagne, D. E.; Koul, O.; Isman, M. B.; Scudder, G. G. E.; Towers, G. H. N. *Phytochemistry* **1992**, *31*, 377; (c) Akhila, A.; Rani, K. *Prog. Chem. Org. Nat. Prod.* **1999**, *78*, 48.
2. (a) Fernández-Mateos, A.; de la Fuente Blanco, J. A. *J. Org. Chem.* **1990**, *55*, 1349; (b) Fernández-Mateos, A.; López Barba, A. *J. Org. Chem.* **1995**, *60*, 3580; (c) de la Fuente Blanco, J. A.; Marugán, J. J.; Cross, S. S.; Fernández-Mateos, A.; García, S.; Menéndez, A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1471; (d) Fernández-Mateos, A.; Pascual Coca, G.; Rubio González, R.; Tapia Hernández, C. *Tetrahedron* **1996**, *52*, 4817; (e) Fernández Mateos, A.; Pascual Coca, G.; Pérez Alonso, J. J.; Rubio González, R. *Synlett* **1996**, 1134; (f) Fernández-Mateos, A.; Pascual Coca, G.; Rubio González, R.; Tapia Hernández, C. *J. Org. Chem.* **1996**, *61*, 9097; (g) Fernández Mateos, A.; Pascual Coca, G.; Pérez Alonso, J. J.; Rubio González, R.; Simmonds, M. S. J.; Blaney, W. M. *Tetrahedron* **1998**, *54*, 14989; (h) Fernández-Mateos, A.; López Barba, A.; Pascual Coca, G.; Rubio González, R.; Tapia Hernández, C. *Synlett* **1995**, 409; (i) Fernández-Mateos, A.; López Barba, A.; Pascual Coca, G.; Rubio González, R.; Tapia Hernández, C. *Synthesis* **1997**, 1381; (j) Fernández Mateos, A.; Martín de la Nava, E. M.; Pascual Coca, G.; Rubio González, R.; Ramos Silvo, A. I.; Simmonds, M. S. J.; Blaney, W. M. *J. Org. Chem.* **1998**, *63*, 9440; (k) Fernández-Mateos, A.; Martín de la Nava, E. M.; Rubio González, R. *Synthesis* **2002**, 1728; (l) Fernández-Mateos, A.; Mateos Burón, L.; Martín de la Nava, E. M.; Rubio González, R. *J. Org. Chem.* **2003**, *68*, 3585; (m)

Fernández-Mateos, A.; Martín de la Nava, E. M.; Rabanedo Clemente, R.; Rubio González, R. *Tetrahedron* **2005**, *61*, 12264.
3. (a) Kende, A. S.; Fludzinski, P.; Hill, J. H.; Swenson, W.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *108*, 3551; (b) Collinton, E. W.; Jones, G. *J. Chem. Soc., Chem. Commun.* **1968**, 958; (c) House, H. O.; Bashe, R. W. *J. Org. Chem.* **1965**, *30*, 2942.
4. Fieser, M.; Fieser, L. F. *Reagents for Organic Synthesis*; Wiley: New York, NY, 1974; Vol. IV, p 286.
5. Luzzio, F. A.; Moore, W. J. J. *Org. Chem.* **1993**, *58*, 2970.
6. All compounds synthesized were racemic, although only one enantiomer is depicted.
7. (a) Kim, S.; Koh, J. S. *J. Chem. Soc., Chem. Commun.* **1992**, 1377; (b) Rawal, V. H.; Krishnamurthy, V.; Fabre, A. *Tetrahedron Lett.* **1993**, *34*, 2899.
8. Maini, P. N.; Sammes, M. P. *Synth. Commun.* **1984**, *14*, 731.
9. Rosenberger, M.; McDougal, P.; Bahr, J. *J. Org. Chem.* **1982**, *47*, 2130.
10. Blaney, W. M.; Simmonds, M. S. J.; Ley, S. V.; Anderson, J. C.; Toogood, P. L. *Entomol. Exp. Appl.* **1990**, *55*, 149.