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Synthesis of an ent-Halimanolide from ent-Halimic Acid

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Abstract: An efficient synthesis of ent-halimanolide 2 (15,16-epoxy-12-oxo-ent-halima-5(10),13(16),14-trien-18,2β-olide), from ent-halimic acid has been achieved, corroborating the structure of the natural compound and establishing its absolute configuration.

Keywords: Ent-halimanolides, ent-halimic acid, diterpenoids, Cladogynos orientalis.

Introduction

Euphorbiaceae plants are a rich source of bioactive substances [1-2] and certain genera of this family have attracted much interest, since they contain a group of antitumor compounds [3]. Cladogynos orientalis Zipp. ex Span. (syn. Adenochlaena siamensis Ridl.) (Euphorbiaceae), known in Thailand as “Chettaphangki,” is the only member of the genus Cladogynos and the roots are used as a carminative in Thai folk medicine. Chettaphanin I [4-5] and II [6-7], are the main components from their roots of this plant and the first to be known. Recently, in addition to chettaphanin I and II,
isolation from the root extract of a series of furan diterpenes 2-4 with ent-halimane skeletons has been described [8].

**Figures 1.** Structures of furo-ent-halimanes from *Cladogynos orientalis* and ent-halimic acid.

Our group has transformed *ent*-halimic acid 1, a diterpene of known structure and absolute configuration, into chettaphanin I and II, which confirmed their structure and absolute configuration [4, 6]. In this paper, we report the synthesis of *ent*-halimanolide 2, in order to confirm the structure of the natural compound and do SAR studies. *ent*-Halimanolide is a furan diterpene like chettaphanin I and II, but in this case the carboxylic acid at C-18 has formed a γ-butanolide with the hydroxyl at C-2.

**Results and Discussion**

In order to synthesise compound 2, from *ent*-halimic acid 1 it is necessary to functionalize C-2 and C-12, add a furan group in the side chain, isomerize the double bond to the more stable tetrasubstituted position and to form the lactone ring.

Two synthetic routes have been explored for the synthesis of 2: Route A and Route B, which differ in the strategy followed for the preparation of the γ-lactone, before or after of the introduction of the furan ring.

In Route A (Scheme 1) three fundamental parts can be differentiated: elaboration of the adequate *ent*-halimic acid tetranorderivative 9; γ-lactone formation as 12, necessary for the final introduction of the furan fragment and to prepare the functional groups required to achieve the natural product 2.
The *ent*-halimic acid tetranorderivative 6 was obtained in excellent yield as described in the synthesis of chettaphanin I and II [4] [6]. Carbonyl protection of 6 with ethylene glycol in acid media gives the tetranorderivative 7, that already contains the tetrasubstituted double bond in the required position. The carbonyl deprotection should be done very carefully (controlling the acid and time) and in this manner ketone 8 can be obtained, which by NaBH₄ reduction gives a 1:1 mixture of hydroxyderivative 9 and \( \gamma \)-lactone 10.

The required aldehyde 12 was obtained by hydrolysis of 10 followed by TPAP [9] oxidation of the hydroxy derivative 11. Addition of 3-furyl lithium [10-12] to 12 gives a mixture of the hydroxy derivatives 13 and 14. The C-12 configuration in 13 and 14 was established by comparation of their physical properties with the ones of similar compounds [13-14]. Oxidation of the mixture of 13 and 14 with TPAP gives 2, \([\alpha]_D^{22} -101.4\) (c 0.2, CHCl₃), that was identical in all its physical properties to the natural compound 15,16-epoxy-12-oxo-\( \text{ent} \)-halima-5(10),13(16),14-trien-18,2\( \beta \)-olide, \([\alpha]_D^{22} -151.5\) (c 0.017, CHCl₃), already described [8].

Route B (Scheme 2) involves first a new procedure for the synthesis of the key intermediate, the tetranorderivative 19 already used by our group in the synthesis of chettaphanin I and II, and secondly the transformation of this intermediate into the natural compound 2. Our new route for the synthesis of...
intermediate 19 gives a better global yield than one based on a Baeyer-Villiger reaction as a key step [4, 6], and can be done in a multigram scale.

Starting from 15, previously obtained from *ent*-halimic acid, 1 [4], by chemoselective Wittig reaction [15-17], we obtained 16. Treatment of 16 under acidic conditions allows the isomerization of the side chain terminal double bond into the more stable trisubstituted position in quantitative yield, to give compound 17. The protection of the carbonyl group gives the dioxolane 18, with concomitant isomerization of the double bond in the bicyclic system to the tetrasubstituted position. Chemoselective oxidation of the side chain of 18 was achieved by treatment with OsO₄ [18-21], followed by cleavage of the resulting diol with Pb(AcO)₄ to give aldehyde 19 in excellent overall yield (84%) from *ent*-halimic acid 1. In this manner we have opened a new and versatile route to
intermediate 19, a key compound for the synthesis of many natural products. Once this compound was available in large quantities in a reliable fashion it was decided to synthesize compound 2.

Reaction of 19 with 3-furyl lithium gives 20 and 21, that were separated and characterised as their acetyl derivatives 22 and 23. The careful hydrolysis in acid medium of 22 and 23 led to ketones 24 and 25. Alkaline hydrolysis of 24 gives the hydroxyderivative 26. Reduction of 26 with NaBH4 produced 27 and lactone 13. Oxidation of 13 gives the desired ent-halimanolide 2 [α]22D -101.4 (c 0.2, CHCl3). The overall yield for the synthesis of ent-halimanolide 2 from ent-halimic acid 1 by route B was 26%. Compound 2 has been tested against human tumor cell lines: HL-60, IC50 >10-5M, HeLa, IC50, 1.6±0.1 10-5M, A549, IC50 >10-5M, HT-29, IC50 >10-5M. As can be seen, compound 2, is only moderately active against HeLa (human cervix cancer).

Conclusions

The synthesis of the natural ent-halimanolide 2 has been achieved starting from ent-halimic acid 1, confirming in this way its structure and establishing its absolute configuration. A new and versatile route to the key intermediate 19 [84% from 1] for the synthesis of natural ent-halimanolides is described. Other biological tests for 2 and several intermediates are in progress and will be reported in due course.

Experimental

General

Unless otherwise stated, all chemicals were purchased were of the highest purity commercially available and were used without further purification. IR spectra were recorded on a BOMEM 100 FT-IR or an AVATAR 370 FT-IR Thermo Nicolet spectrophotometers. 1H- and 13C-NMR spectra were recorded for CDCl3 solutions and referenced to the residual peak of CHCl3 at δ 7.26 ppm and δ 77.0 ppm, for 1H and 13C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ ppm and coupling constants (J) are given in Hz. MS were performed at a VG-TS 250 spectrometer at 70 eV ionising voltage. Mass spectra are presented as m/z (% rel. int.). HRMS were recorded on a VG Platform (Fisons) spectrometer using chemical ionization (ammonia as gas) or Fast Atom Bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionization (ESI). Optical rotations were determined on a Perkin-Elmer 241 polarimeter in 1 dm cells. Diethyl ether and THF were distilled from sodium, and dichloromethane was distilled from calcium hydride under Ar atmosphere.

Methyl 12-acetoxy-2-ethylenedioxy-13,14,15,16-tetranor-ent-halim-5(10)-en-18-oate (7)

Acetate 6 (1.02 g, 3.28 mmol) dissolved in benzene (33 mL), was refluxed in the presence of p-toluenesulfonic acid (17 mg, 0.10 mmol) and ethylene glycol (2.0 mL, excess) at 138 ºC for 16 h, then the solution was diluted with AcOEt, washed with 6% aqueous NaHCO3 and water and dried over Na2SO4. The solvent was evaporated to yield 7 (546 mg, 97%) as a colourless oil; [α]22D -19.1 (c 1.3,
CHCl₃); IR (film) ν (cm⁻¹) 1738, 1458, 1373, 1238, 1080, 1032; ¹H-NMR (200 MHz): 4.20-3.80 (6H, m, -OC₂H₄O-, H-12), 3.63 (3H, s, -COOMe), 2.41 (1H, d, J = 13.2 Hz, H₆-3), 2.24 (2H, s, H-1), 2.01 (3H, s, MeCOO-), 1.80-1.50 (4H, m), 1.50-1.20 (3H, m), 1.33 (3H, s, Me-19), 0.88 (3H, s, Me-20), 0.87 (3H, d, J = 6.7 Hz, Me-17); ¹³C-NMR (50 MHz): 177.2 (C-18), 170.9 (MeCOO-), 132.7 (C-10), 130.9 (C-5), 107.5 (C-2), 64.3/64.1 (-OC₂H₄O-), 61.6 (C-12), 51.9 (-COOMe), 48.9 (C-4), 42.0 (C-3), 39.8 (C-9), 35.8 (C-1), 35.6 (C-11), 34.1 (C-8), 26.5 (C-7), 24.9 (C-6), 23.7 (C-19), 20.9 (C-20), 20.8 (MeCOO-), 15.9 (C-17); HRMS (EI) m/z calcd. for C₂₁H₃₂O₆ (M⁺): 380.2199; found 380.2191.

Methyl 12-acetoxy-2-oxo-13,14,15,16-tetranor-ent-halim-5(10)-en-18-oate (8)

To a solution of acetate 7 (48 mg, 0.13 mmol) in EtOH (2.0 mL), aq. HCl (2M, 1.7 mL) was added. The reaction mixture was stirred for 3 h at room temperature, then it was diluted with Et₂O, extracted with Et₂O, washed with water and dried over Na₂SO₄. Evaporation of the organic layer yielded 8 (41 mg, 92%) as a colourless oil; [α]₂²D -9.8 (c 1.0, CHCl₃); IR (film) ν (cm⁻¹) 2963, 1736, 1680, 1459, 1238, 1033; ¹H-NMR (200 MHz): 4.09-3.95 (1H, m, H-12), 3.83-3.74 (1H, m, H-12), 3.68 (3H, s, -COOMe), 2.92 (1H, d, J = 12.2 Hz, H₆-1), 2.90 (1H, d, J = 15.0 Hz, H₆-3), 2.25 (1H, d, J = 15.0 Hz, H₆-3), 2.25 (1H, d, J = 15.0 Hz, H₆-3), 2.15-1.98 (3H, m), 2.01 (3H, s, MeCOO-), 1.92-1.49 (5H, m), 1.27 (3H, s, Me-19), 0.90 (3H, d, J = 6.6 Hz, Me-17), 0.86 (3H, s, Me-20); ¹³C-NMR (50 MHz): 208.2 (C-2), 174.3 (C-18), 170.7 (MeCOO-), 133.3 (C-10), 133.0 (C-5), 60.7 (C-12), 52.0 (-COOMe), 48.9 (C-1), 48.4 (C-4), 39.4 (C-9), 38.8 (C-3), 34.2 (C-11), 33.3 (C-8), 26.0 (C-7), 25.1 (C-6), 21.8 (C-19), 20.5 (C-20), 20.2 (MeCOO-), 15.4 (C-17); HRMS (EI) m/z calcd. for C₁₉H₂₆O₅(M⁺): 336.1937; found 336.1928.

12-Acetoxy-13,14,15,16-tetranor-ent-halim-5(10)-en-18,2β-olide (10) and methyl 12-acetoxy-2R-hydroxy-13,14,15,16-tetranor-ent-halim-5(10)-en-18-oate (9)

To an ice cooled solution of 8 (0.15 g, 0.43 mmol) in EtOH (4.3 mL), NaBH₄ (16.2 mg, 0.43 mmol) was added. After being stirred at room temperature for 3 h, the reaction mixture was recooled to 0ºC and quenched with a few drops of 2 M aqueous HCl solution, diluted with EtOAc and water and extracted with EtOAc. The organic layer was washed with water. Evaporation of the dried extract gave a residue which was chromatographed on silica gel (hex/EtOAc 9:1) to afford 10 (73 mg, 49%) and 9 (70 mg, 47%). Compound 10: a colourless oil; [α]₂²D -103.1 (c 0.4, CHCl₃); IR (film) ν (cm⁻¹) 2959, 1710.1 (MeCOO-), 169.41 (C-18), 133.3 (C-10), 133.0 (C-5), 74.2 (C-2), 60.9 (C-12), 43.4 (C-4), 41.1 (C-1), 39.0 (C-9), 36.1 (C-3), 33.0 (C-8), 31.2 (C-11), 25.9 (C-7), 23.8 (C-6), 21.6 (C-19), 20.8 (MeCOO-), 16.8 (C-20), 20.2 (MeCOO-), 15.5 (C-17); HRMS (EI) m/z calcd. for C₁₉H₂₈O₄Na (M⁺): 336.1723; found 336.1716; Compound 9: a colourless oil; [α]₂²D -88.0 (c 0.7, CHCl₃); IR (film) ν (cm⁻¹) 2938, 1732, 1460, 1368, 1273, 1162, 1045; ¹H-NMR (200 MHz): 4.01 (3H, m, H-2, H-12), 3.64 (3H, s, -COOMe), 2.48-2.10 (4H, m), 2.01 (3H, s, MeCOO-), 1.85-1.40 (6H, m), 1.30 (3H, s, Me-19), 0.90
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12-Hydroxy-13,14,15,16-tetranor-ent-halim-5(10)-en-18,2β-olide (11)

To 10 (73.0 mg, 0.24 mmol) a 3% solution of K₂CO₃ in methanol (5 ml) was added. After 2 h the solvent was evaporated and diluted with Et₂O. The organic layer was successively washed with a 2N aqueous solution of HCl and water, dried over Na₂SO₄ and evaporated to yield the expected compound 11 (61 mg, 97%) as a colourless oil; [α]²υD -105.5 (c 0.4, CHCl₃); IR (film) ν (cm⁻¹) 3419, 2938, 1770, 1457, 1381, 1189, 1162, 948; ¹H-NMR (200 MHz): 4.82 (1H, m, H-2), 3.67-3.48 (1H, m, HA-12), 3.42-3.28 (1H, m, HB-12), 2.45-2.05 (5H, m), 1.96-1.43 (5H, m), 1.28 (3H, s, Me-19), 0.88 (3H, s, Me-20), 0.86 (3H, d, J = 6.1 Hz, Me-17); ¹³C-NMR (50 MHz): 179.2 (C-18), 134.0 (C-10), 133.3 (C-5), 74.6 (C-2), 59.2 (C-12), 43.7 (C-4), 41.3 (C-1), 40.3 (C-3), 39.3 (C-9), 33.7 (C-8), 31.4 (C-11), 26.4 (C-6), 24.5 (C-7), 21.8 (C-20), 17.1 (C-19), 16.0 (C-17); HRMS (EI) m/z calcd. for C₁₆H₂₄O₃Na 287.1618; found 287.1612.

12-Oxo-13,14,15,16-tetranor-ent-halim-5(10)-en-18,2β-olide (12)

To a mixture of 11 (32 mg, 0.12 mmol) N-methylmorpholine-N-oxide (NMO) (49 mg, 0.36 mmol) and molecular sieves (60 mg, 500 mg/mmol) in anhydrous CH₂Cl₂ (1.2 mL) under an Ar atmosphere and at room temperature, TPAP (2 mg, 5x10⁻³ mmol) was added. The reaction mixture was stirred for 30 min. and then filtered on silica gel and Celite (DCM and EtOAc). Evaporation of the solvent yielded 12 (31 mg, 96%) as a colourless oil, IR (film) ν (cm⁻¹) 1078, 1024, 1460, 1189, 1162, 948; ¹H-NMR (200 MHz): 9.56 (1H, m, H-12), 4.80 (1H, m, H-2), 2.48-2.41 (3H, m), 2.19-2.14 (2H, m), 1.96 (1H, d, J = 13.0 Hz, H-11β), 1.77-1.20 (5H, m), 1.30 (3H, s, Me-19), 1.02 (3H, s, Me-20), 0.90 (3H, d, J = 6.6 Hz, Me-17); HRMS (EI) m/z calcd. for C₁₆H₂₂O₃Na 285.1461; found 281.1476.

15,16-Epoxy-12S-hidroxy-ent-halima-5(10),13(16),14-trien-18,2β-olide (13) and 15,16-epoxy-12R-hydroxy-ent-halima-5(10),13(16),14-trien-18,2β-olide (14)

A solution of 3-bromofuran in THF 1M (0.14 mL, 0.14 mmol), was treated dropwise with n-BuLi (1.6 M in hexane, 0.09 mL, 0.14 mmol) at –78°C under Ar atmosphere. After the reaction mixture was stirred for 30 min. at this temperature, a solution of 12 (30 mg, 0.11 mmol) in dry THF (1.1 mL) was added and stirred for an additional 30 minutes at the same temperature. The reaction mixture was treated with 10% aqueous NH₄Cl solution, warmed to room temperature and extracted with EtOAc. The organic layer was washed with 6% NaHCO₃, brine and dried over Na₂SO₄. The solvent was evaporated to afford a residue which was purified by chromatography (Hex/AcOEt 9/1) to yield 13 (20 mg, 54%) and 14 (13 mg, 36%). Compound 13: colourless oil; [α]²υD -31.1 (c 0.4, CHCl₃). IR (film) ν (cm⁻¹) 3400, 2927, 1769, 1460, 1070, 1024. ¹H-NMR (200 MHz): 7.39 (1H, s, H-15), 7.36 (1H, s, H-
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16, 6.40 (1H, d, J = 2.20 Hz, H-14), 4.76 (1H, dd, J = 5.6, 2.7 Hz, H-2), 4.43 (1H, d, J = 7.9 Hz, H-12), 2.38-1.93 (4H, m), 1.30 (3H, s, Me-19), 0.92 (3H, d, J = 6.6 Hz, Me-17), 0.91 (3H, s, Me-20). 13C-NMR (50 MHz): 178.6 (C-18), 143.5 (C-16), 138.5 (C-15), 134.0 (C-10), 133.6 (C-5), 130.9 (C-13), 108.0 (C-14), 74.5 (C-2), 64.0 (C-12), 45.3 (C-11), 43.3 (C-4), 41.0 (C-3), 40.4 (C-9), 33.0 (C-8), 31.1 (C-1), 26.0 (C-7), 24.1 (C-6), 21.1 (C-20), 16.9 (C-19), 15.8 (C-17); HRMS (EI) m/z calcd. for C20H26O4Na: 353.1723; found 353.1718.

Compound 14: colourless oil; [α]22\(_D\)–63.1 (c 0.3, CHCl3); IR (film) \(\nu\) (cm\(^{-1}\)) 3407, 2927, 1769, 1460, 1075, 1024; 1H-NMR (200 MHz): 7.40 (1H, d, J = 1.6 Hz, H-15), 7.36 (1H, s, H-16), 6.41 (1H, dd, J = 2.13, 0.61 Hz, H-14), 4.76 (1H, ddd, J = 5.6, 2.9, 2.7 Hz, H-2), 4.44 (1H, dd, J = 7.7, 1.7 Hz, H-12), 2.34-1.93 (7H, m), 1.90-1.40 (4H, m), 1.32 (3H, s, Me-19), 0.94 (3H, d, J = 6.8 Hz, Me-17), 0.93 (3H, s, Me-20); 13C-NMR (50 MHz): 178.7 (C-18), 143.5 (C-16), 138.7 (C-15), 134.0 (C-10), 133.7 (C-5), 130.7 (C-13), 108.2 (C-14), 74.3 (C-2), 64.2 (C-12), 45.6 (C-11), 43.5 (C-4), 41.2 (C-3), 40.5 (C-9), 33.1 (C-8), 31.4 (C-1), 26.2 (C-7), 24.3 (C-6), 21.4 (C-20), 16.9 (C-19), 15.8 (C-17); HRMS (EI) m/z calcd. for C20H26O4Na: 353.1723; found 353.1712.

15,16-Epoxy-12-oxo-ent-halima-5(10),13(16),14-trien-18,2\(\beta\)-olide (2)

To a mixture of 13/14 (3 mg, 0.01 mmol) N-methylmorpholine-N-oxide (NMO, 4 mg, 0.03 mmol) and molecular sieves (10 mg) in anhydrous CH\(_2\)Cl\(_2\) (0.3 mL) under an Ar atmosphere and at room temperature, TPAP (1.0 mg, 3x10\(^{-3}\) mmol) was added. The reaction mixture was stirred for 30 min. and then filtered on silica gel and Celite (DCM and EtOAc). Evaporation of the solvent yielded 2 (3.0 mg, 92%) as a colourless oil; [α]\(_D\)^22 -63.1 (c 0.3, CHCl3); IR (film) \(\nu\) (cm\(^{-1}\)) 2928, 1733, 1240, 1077, 1023; 1H-NMR (200 MHz): 7.94 (1H, dd, J = 1.6, 0.8 Hz, H-16), 7.41 (1H, dd, J = 12.0, 1.6 Hz, H-15), 6.73 (1H, dd, J = 1.6, 0.8 Hz, H-14), 4.76 (1H, ddd, J = 5.6, 2.8, 2.8 Hz, H-2), 2.85 (1H, d, J = 15.6 Hz, H\(_A\)-11), 2.74 (1H, d, J = 15.6 Hz, H\(_B\)-11), 2.39-2.35 (2H, m, H-1), 2.19-2.10 (2H, m, H-6), 2.13 (1H, dd, J = 10.8, 6.8 Hz, H\(_A\)-3), 2.08-2.04 (1H, m, H-8), 1.94 (1H, d, J = 10.8 Hz, H\(_B\)-3), 1.81-1.42 (2H, m, H-7), 1.32 (3H, s, Me-19), 1.09 (3H, s, Me-20), 0.86 (3H, d, J = 7.0 Hz, Me-17); 13C-NMR (50 MHz): 193.5 (C-12), 178.2 (C-18), 146.9 (C-16), 144.1 (C-15), 132.4 (C-10), 132.1 (C-5), 129.3 (C-13), 108.7 (C-14), 73.9 (C-2), 47.7 (C-11), 43.5 (C-4), 41.1 (C-3), 40.3 (C-9), 33.1 (C-8), 31.6 (C-1), 25.2 (C-7), 22.1 (C-6), 21.8 (C-20), 16.4 (C-19), 15.1 (C-17); HRMS (EI) m/z calcd. for C20H24O4Na: 351.1567; found 351.1567.

Methyl 2-oxo-15-nor-ent-halima-1(10),13(14)-dien-18-oate (16)

To a suspension of MeOCH\(_2\)PPh\(_3\)Cl (1.24 g, 3.15 mmol) in THF (10 mL) at –20ºC under an Ar atmosphere, 1.0 M NaHMDS in THF (3.15 mL, 3.15 mmol) was added dropwise and the solution was stirred for 30 min. A solution of the aldehyde 15 (1.0 g, 3.12 mmol) in THF (15 mL) was added dropwise at –78ºC. The mixture was stirred for 1 h at room temperature. Then, it was quenched with aqueous NH\(_2\)Cl and extracted with AcOEt. The organic layer was washed with brine and dried over Na\(_2\)SO\(_4\). The solvent was evaporated to afford a residue which was purified by chromatography (Hex/AcOEt 97/3) to yield 16 (933 mg, 94%) as a colourless oil; [α]\(_D\)^22 +179.9 (c 1.4, CHCl3); IR (film) \(\nu\)
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(\text{cm}^{-1}) 2964, 1732, 1676, 1455, 1267, 1160, 1113, 883; \textsuperscript{1}H-NMR (200 MHz): 5.81 (1H, s, H-1), 4.68 (2H, s, H-14), 3.60 (3H, s, -COOMe), 3.00 (1H, dd, \(J = 12.1, 4.7\) Hz, H-5), 2.66 (1H, d, \(J = 16.2\) Hz, H-3\(\alpha\)), 2.24 (1H, d, \(J = 16.2\) Hz, H-3\(\beta\)), 2.18-1.97 (3H, m), 1.83-1.36 (6H, m), 1.70 (3H, s, Me-16), 1.20 (3H, s, Me-19), 0.98 (3H, s, Me-20), 0.78 (3H, d, \(J = 7.4\) Hz, Me-17); \textsuperscript{13}C-NMR (50 MHz): 196.3 (C-2), 175.9 (C-18) 168.7 (C-10), 145.2 (C-13), 124.2 (C-1), 108.9 (C-14), 51.6 (-COOMe), 45.5 (C-4), 44.4 (C-9), 42.2 (C-5), 39.9 (C-8), 36.4 (C-12), 31.1 (C-11), 27.5 (C-7), 22.8 (C-6), 21.9 (C-19), 21.2 (C-16), 20.0 (C-20), 14.8 (C-17); HRMS (EI) m/z calcd. for C\(_{20}\)H\(_{30}\)O\(_3\)Na: 341.2087; found 341.2073.

Methyl 2-oxo-15-nor-ent-halima-1(10),12(13)-dien-18-oate (17)

To a solution of 16 (1.06 g, 3.35 mmol) in benzene (33 mL), \(p\)-TsOH (0.16 g, 0.91 mmol) was added. The reaction mixture was stirred at 60ºC for 2 h, then it was cooled and diluted with Et\(_2\)O. The organic layer was washed with 6% aqueous NaHCO\(_3\) and brine and dried over Na\(_2\)SO\(_4\). The solvent was evaporated to yield 17 (1.01 g, 96%) as a colourless oil; \([\alpha]_{D}^{22} +45.4\) (c 1.0, CHCl\(_3\)); IR (film) \(\nu\) (\text{cm}^{-1}) 2929, 1732, 1676, 1457, 1269, 1116; \textsuperscript{1}H-NMR (200 MHz): 5.74 (1H, s, H-1), 4.71 (1H, m, H-12), 3.57 (3H, s, -COOMe), 3.00 (1H, dd, \(J = 12.4, 4.5\) Hz, H-5), 2.63 (1H, d, \(J = 16.0\) Hz, H-3\(\alpha\)), 2.19 (1H, d, \(J = 15.6\) H-3\(\beta\)), 2.10-1.90 (3H, m), 1.85-1.22 (5H, m), 1.53 (3H, s, Me-16), 1.47 (3H, s, Me-14), 1.16 (3H, s, Me-19), 0.86 (3H, s, Me-20), 0.72 (3H, d, \(J = 7.0\) Hz, Me-17); \textsuperscript{13}C-NMR (50 MHz): 197.4 (C-2), 176.8 (C-18) 169.8 (C-10), 133.9 (C-13), 124.9 (C-1), 120.0 (C-12), 52.5 (-COOMe), 46.5 (C-4), 46.1 (C-9), 43.6 (C-3), 41.2 (C-5), 40.3 (C-8), 37.7 (C-11), 28.6 (C-7), 26.2 (C-20), 23.7 (C-6), 21.7 (C-19), 21.7 (C-16), 18.2 (C-14), 15.8 (C-17); HRMS (EI) m/z calcd. for C\(_{20}\)H\(_{30}\)O\(_3\)Na: 341.2087; found 341.2097.

Methyl 2-ethylenedioxy-15-nor-ent-halima-5(10),12(13)-dien-18-oate (18)

Compound 17 (1 g, 3.15 mmol) dissolved in benzene (32 mL), was refluxed in the presence of \(p\)-toluenesulfonic acid (19 mg, 0.11 mmol) and ethylene glycol (1.9 ml, excess) at 138ºC for 16 h. The solution was then diluted with AcOEt and washed with 6% aqueous NaHCO\(_3\) and water and dried over Na\(_2\)SO\(_4\). The solvent was evaporated to yield 18 (1.11 g, 97%) as a colourless oil; \([\alpha]_{D}^{22} -20.3\) (c 1.4, CHCl\(_3\)); IR (film) \(\nu\) (\text{cm}^{-1}) 2964, 1733, 1237, 1118, 1078; \textsuperscript{1}H-NMR (200 MHz): 4.98 (1H, m, H-12), 3.96 (4H, m, -OC\(_2\)H\(_4\)O-), 3.64 (3H, s, -COOMe), 2.31 (2H, s, H-3), 2.20-1.95 (4H, m), 1.92-1.30(5H, m), 1.66 (3H, s, Me-16), 1.57 (3H, s, Me-14), 1.33 (3H, s, Me-19), 0.84 (3H, s, Me-20), 0.80 (3H, d, \(J = 7.0\) Hz, Me-17); \textsuperscript{13}C-NMR (50 MHz): 197.4 (C-2), 176.8 (C-18) 169.8 (C-10), 133.9 (C-13), 124.9 (C-1), 120.0 (C-12), 52.5 (-COOMe), 46.5 (C-4), 46.1 (C-9), 43.6 (C-3), 41.2 (C-5), 40.3 (C-8), 37.7 (C-11), 28.6 (C-7), 26.2 (C-20), 23.7 (C-6), 21.7 (C-19), 21.7 (C-16), 18.2 (C-14), 15.8 (C-17); HRMS (EI) m/z calcd. for C\(_{22}\)H\(_{34}\)O\(_4\)Na: 385.2349; found 385.2362.

Methyl 2-ethylenedioxy-12-oxo-13,14,15,16-tetranor-ent-halim-5(10)-en-18-oate (19)

To a solution of 18 (1.05 g, 2.90 mmol) in \(t\)-BuOH/THF/H\(_2\)O (7:2:1, 30.5 ml) was added \(N\)-methylmorpholine \(N\)-oxide (NMO, 1.18 g, 8.70 mmol) and a solution of OsO\(_4\) 2.5% (0.3 ml, 0.01mmol) in
t-BuOH. The reaction mixture was stirred at room temperature for 20 h and a saturated aqueous solution of Na$_2$SO$_3$ (30 mL) was added. The mixture was extracted with AcOEt, and the organic layer was washed with 10% aqueous Na$_2$SO$_3$, 2N aqueous HCl, water and brine and dried over Na$_2$SO$_4$. The solvent was evaporated to yield the expected mixture of hydroxy derivatives. To a solution of the hydroxy derivatives (1.15g, 3.06 mmol) in benzene (16 ml) was added LTA (3.0 g, 6.68 mmol). The reaction mixture was stirred at room temperature for 30 min and then filtered off through Celite. The solution was diluted with EtOAc and washed with 6% aqueous NaHCO$_3$, water and brine and then dried and evaporated to yield 19 (980 mg, 96%) as a colourless oil; [α]$_D^{22}$ +2.1 (c 0.9, CHCl$_3$); IR (film) ν (cm$^{-1}$) 1734, 1717, 1456, 1375, 1238, 1152, 1078, 1032; $^1$H-NMR (200 MHz): 9.63 (1H, s, H-12), 4.00-3.80 (4H, m, -OC$_2$H$_4$O-), 3.60 (3H, s, -COOMe), 2.60-2.20 (5H, m, H-11, H-1, H$_A$-3), 2.10-1.90 (1H, m), 1.62 (1H, d, J = 13.2 Hz, H$_B$-3), 1.80-1.60 (2H, m), 1.40-1.20 (2H, m), 1.31 (3H, s, Me-19), 0.96 (3H, s, Me-20), 0.88 (3H, d, J = 6.7 Hz, Me-17); $^{13}$C-NMR (50 MHz): 204.3 (C-12), 177.0 (C-18), 131.7 (C-10), 131.3 (C-5), 107.2 (C-2), 64.3/64.1 (-OC$_2$H$_4$O-), 51.9 (-COOMe), 51.2 (C-11), 48.8 (C-4), 42.2 (C-3), 40.1 (C-9), 36.4 (C-1), 36.4 (C-8), 26.2 (C-7), 24.5 (C-6), 23.9 (C-19), 21.1 (C-20), 15.7 (C-17); HRMS (EI) m/z calcd. for C$_{19}$H$_{28}$O$_5$ (M$^+$): 336.1937; found 336.1916.

Methyl 15,16-epoxy-2-ethylenedioxy-12S-hydroxy-ent-halima-5(10),13(16),14-trien-18-oate (20) and methyl 15,16-epoxy-2-ethylenedioxy-12R-hydroxy-ent-halima-5(10),13(16),14-trien-18-oate (21)

A solution of 3-bromofuran in THF 0.89M (1.45 mL, 1.28 mmol), was treated dropwise with n-BuLi (1.6 M in hexane, 0.85 ml, 1.35 mmol) at –78°C under an Ar atmosphere. After the reaction mixture was stirred for 30 minutes at this temperature, a solution of 19 (430 mg, 1.28 mmol) in dry THF (1.1 mL) was added and stirred for an additional 30 min. at the same temperature. The reaction mixture was then treated with 10% aqueous NH$_4$Cl solution, warmed to room temperature and extracted with EtOAc. The organic layer was washed with 6% NaHCO$_3$, brine and dried over Na$_2$SO$_4$. The solvent was evaporated to afford a residue which was purified by chromatography (hex/AcOEt 95/5) to yield 20 (279 mg, 54%) and 21 (202 mg, 39%). Compound 20: a colourless oil; [α]$_D^{22}$ +4.6 (c 0.8, CHCl$_3$); IR (film) ν (cm$^{-1}$) 3500, 1724, 1458, 1375, 1262, 1157, 1078, 1030, 665; $^1$H-NMR (200 MHz): 7.34 (2H, s, H-15, H-16), 6.39 (1H, s, H-14), 4.85 (1H, dd, J = 9.0, 2.2 Hz, H-12), 4.00-3.80 (4H, m, -OC$_2$H$_4$O-), 3.67 (3H, s, -COOMe), 2.38 (1H, d, J = 12.5 Hz, HA-3), 2.35 (1H, d, J = 10.5 Hz, H$_A$-1), 2.15 (1H, d, J = 10.5 Hz, H$_B$-1), 2.00 (1H, dd, J = 15.0, 9.4 Hz, H$_A$-11), 1.72 (1H, dd, J = 15.0, 2.2 Hz, H$_B$-11), 1.71-1.68 (2H, m, H-6), 1.70 (1H, d, J = 12.5 Hz, H$_B$-3), 1.63-1.56 (1H, m, H-8), 1.37-1.27 (2H, m, H-7), 1.35 (3H, s, Me-19), 0.93 (3H, s, Me-20), 0.92 (3H, d, J = 6.8 Hz, Me-17); $^{13}$C-NMR (50 MHz): 177.6 (C-18), 143.0 (C-16), 138.2 (C-15), 133.2 (C-10), 131.7 (C-5), 130.8 (C-13), 108.6 (C-14), 107.3 (C-2), 64.4 (C-12), 64.4/64.2 (-OC$_2$H$_4$O-), 52.0 (-COOMe), 48.6 (C-4), 46.5 (C-11), 42.7 (C-3), 40.6 (C-9), 36.7 (C-1), 35.3 (C-8), 26.8 (C-7), 25.2 (C-6), 24.5 (C-19), 21.3 (C-20), 16.1 (C-17); HRMS (EI) m/z calcd for C$_{23}$H$_{32}$O$_6$ (M$^+$): 404.2199; found 404.2191. Compound 21: a colourless oil; [α]$_D^{22}$ -17.2 (c 0.5, CHCl$_3$); IR (film) ν (cm$^{-1}$) 3500, 1730, 1464, 1377, 1159, 1089, 1030, 665; $^1$H-NMR (200 MHz): 7.38 (2H, s, H-15, H-16), 6.38 (1H, s, H-14), 4.91 (1H, dd, J = 9.4, 2.3 Hz, H-12), 4.00-3.80 (4H, m, -OC$_2$H$_4$O-), 3.65 (3H, s, -COOMe), 2.60-2.00 (5H, m), 1.90-1.60 (3H, m), 1.40-1.20 (3H, m), 1.36 (3H, s, Me-19), 0.91 (3H, s, Me-20), 0.89 (3H, d, J = 6.9 Hz, Me-17); $^{13}$C-
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NMR (50 MHz): 177.6 (C-18), 143.0 (C-16), 138.4 (C-15), 133.4 (C-10), 132.0 (C-5), 130.0 (C-13), 108.7 (C-14), 107.4 (C-2), 64.6/64.3 (-OC$_2$H$_4$O-, 64.2 (C-12), 52.1 (-COOMe), 48.7 (C-4), 47.7 (C-11), 42.9 (C-3), 46.0 (C-9), 36.1 (C-1), 35.8 (C-8), 26.9 (C-7), 25.1 (C-6), 24.5 (C-19), 21.8 (C-20), 16.4 (C-17), HRMS (EI) m/z calcd. for C$_{23}$H$_{32}$O$_6$ (M)$^+$: 404.2199; found 404.2193.

*Methyl 12S-acetoxy-15,16-epoxy-2-ethylenedioxy-ent-halima-5(10),13(16),14-trien-18-oate (22)*

To a solution of 20 (118 mg, 0.29 mmol) in dry pyridine (1.0 mL), Ac$_2$O (1.0 mL) was added and the mixture was stirred at room temperature overnight, then the reaction mixture was poured into ice-water and extracted with EtOAc. The organic layer was washed successively with 2M aqueous HCl, 6% aqueous NaHCO$_3$ and brine. It was dried over Na$_2$SO$_4$ and the solvent was evaporated to afford 22 (128 mg, 99%) as a colourless oil; [$\alpha$]$_D^{22}$-13.3 (c 0.7, CHCl$_3$); IR (film) ν (cm$^{-1}$) 1733, 1458, 1374, 1240, 1102, 1077, 1023, 874; $^1$H-NMR (200 MHz): 7.36 (1H, s, H-16), 7.31 (1H, s, H-15), 6.36 (1H, s, H-14), 5.71 (1H, dd, $J = 7.8, 2.2$ Hz, H-12), 4.00-3.80 (4H, m, -OC$_2$H$_4$O-), 3.69 (3H, s, -COOMe), 2.25 (1H, d, $J = 13.2$ Hz, H$_x$-3), 2.19-1.99 (4H, m), 1.96 (3H, s, -OCOMe), 1.95-1.39 (5H, m), 1.66 (1H, d, $J = 13.2$ Hz, H$_z$-3), 1.32 (3H, s, Me-19), 0.89 (3H, d, $J = 6.9$ Hz, Me-17), 0.87 (3H, s, Me-20); $^{13}$C-NMR (50 MHz): 177.6 (C-18), 170.2 (-OC$\_2$H$_4$OMe), 143.3 (C-16), 140.2 (C-12), 132.9 (C-10), 131.5 (C-5), 126.7 (C-13), 109.0 (C-14), 107.7 (C-2), 66.4 (C-12), 64.5/64.3 (-OC$_2$H$_4$O-, 52.2 (-COOMe), 49.0 (C-4), 42.1 (C-3), 41.9 (C-11), 41.1 (C-9), 36.2 (C-1), 33.8 (C-8), 26.4 (C-7), 25.1 (C-6), 24.0 (C-19), 21.6 (-OCOMe), 20.8 (C-20), 16.0 (C-17); HRMS (EI) m/z calcd. for C$_{23}$H$_{34}$O$_7$Na: 469.2197; found 469.2197.

*Methyl 12R-acetoxy-15,16-epoxy-2-ethylenedioxy-ent-halima-5(10),13(16),14-trien-18-oate (23)*

To a solution of 21 (22 mg, 0.05 mmol) in dry pyridine (0.5 mL), Ac$_2$O (0.5 mL) was added and the mixture was stirred at room temperature overnight. The reaction mixture was then poured into ice-water and extracted with EtOAc. The organic layer was washed successively with 2M aqueous HCl, 6% aqueous NaHCO$_3$ and brine. It was dried over Na$_2$SO$_4$ and the solvent was evaporated to afford 23 (128 mg, 99%) as a colourless oil; [$\alpha$]$_D^{22}$-51.8 (c 0.6, CHCl$_3$); IR (film) ν (cm$^{-1}$) 1733, 1458, 1374, 1240, 1102, 1077, 1023, 874; $^1$H-NMR (200 MHz): 7.39 (1H, s, H-16), 7.34 (1H, s, H-15), 6.39 (1H, s, H-14), 5.89 (1H, dd, $J = 8.8, 4.4$ Hz, H-12), 3.96-3.80 (4H, m, -OC$_2$H$_4$O-), 3.66 (3H, s, -COOMe), 2.60-2.00 (5H, m), 2.19-1.99 (4H, m), 2.02 (3H, s, -OCOMe), 1.93-1.62 (3H, m), 1.40-1.20 (3H, m), 1.36 (3H, s, Me-19), 0.87 (3H, s, Me-20), 0.82 (3H, d, $J = 6.6$ Hz, Me-17); $^{13}$C-NMR (50 MHz): 177.5 (C-18), 170.5 (-OCOMe), 143.3 (C-16), 140.4 (C-15), 133.3 (C-10), 129.7 (C-5), 126.6 (C-13), 109.1 (C-14), 107.9 (C-2), 65.4 (C-12), 64.6/64.2 (-OC$_2$H$_4$O-, 52.2 (-COOMe), 49.5 (C-4), 41.4 (C-3), 41.2 (C-11), 40.9 (C-9), 36.4 (C-1), 33.4 (C-8), 25.6 (C-7), 25.1 (C-6), 23.6 (C-19), 22.0 (-OCOMe), 21.4 (C-20), 16.1 (C-17); HRMS (EI) m/z calcd. for C$_{23}$H$_{34}$O$_7$Na: 469.2197; found 496.2197.
Methyl 12S-acetoxy-15,16-epoxy-2-oxo-ent-halima-5(10),13(16),14-trien-18-oate (24) and methyl 12R-acetoxy-15,16-epoxy-2-oxo-ent-halima-5(10),13(16),14-trien-18-oate (25)

To a solution of acetate 22 (118 mg, 0.27 mmol) in EtOH (2.6 mL), aq HCl. (2M, 3.6 mL) was added. The reaction mixture was stirred for 3 h at room temperature. Then it was diluted and extracted with EtO2, washed with water and dried over Na2SO4. Evaporation of the organic layer yielded 24 (102 mg, 96%) as a colourless oil; [α]22D -5.0 (c 0.9, CHCl3); IR (film) ν (cm-1) 2922, 1734, 1717, 1458, 1374, 1234, 1023; 1H-NMR (200 MHz): 7.39 (1H, s, H-16), 7.31 (1H, s, H-15), 6.37 (1H, s, H-14), 5.52 (1H, dd, J =7.0, 3.4 Hz, H-12), 3.76 (3H, s, -COOMe), 2.82-2.63 (2H, m), 2.23-2.06 (2H, m), 2.05-1.50 (5H, m), 1.96 (3H, s, -OCOMe), 1.40-1.20 (3H, m), 1.36 (3H, s, Me-19), 0.95 (3H, d, J = 6.2 Hz, Me-17), 0.84 (3H, s, Me-20); 13C-NMR (50 MHz): 208.9 (C-2), 174.9 (C-18), 170.2 (-OCOMe), 143.6 (C-16), 140.4 (C-15), 134.3 (C-13), 134.0 (C-10), 125.6 (C-5), 108.8 (C-14), 66.0 (C-12), 52.8 (-OCOMe), 49.2 (C-2), 48.8 (C-4), 41.3 (C-11), 41.3 (C-9), 39.8 (C-3), 33.9 (C-8), 26.7 (C-7), 26.0 (C-6), 22.2 (-OCOMe), 21.5 (C-19), 20.7 (C-20), 16.0 (C-17); HRMS (EI) m/z calcd. for C23H30O6 Na: 425.1935; found 425.1944.

Similarly, to a solution of acetate 23 (36 mg, 0.08 mmol) in EtOH (0.8 mL), aq HCl. (2M, 1.0 mL) was added. The reaction mixture was stirred for 3 h at room temperature. Then it was diluted with Et2O, extracted with Et2O, washed with water and dried over Na2SO4. Evaporation of the organic layer yielded 25 (31 mg, 96%) as a colourless oil; [α]22D -21.1 (c 0.6, CHCl3); IR (film) ν (cm-1) 2922, 1734, 1718, 1458, 1374, 1234, 1119, 1023; 1H-NMR (200 MHz): 7.39 (1H, s, H-16), 7.36 (1H, s, H-15), 6.37 (1H, s, H-14), 5.83 (1H, dd, J = 8.4, 4.8 Hz, H-12), 3.72 (3H, s, -COOMe), 3.27 (1H, d, J = 21.0 Hz, Hα-1), 2.83 (1H, d, J = 20.8 Hz, Hβ-1), 2.31 (1H, d, J = 14.2 Hz, Hβ-3), 2.20-1.60 (4H, m), 2.01 (3H, s, -OCOMe), 1.50-1.20 (3H, m), 1.24 (3H, s, Me-19), 0.85 (3H, s, Me-20), 0.83 (3H, d, J = 6.2 Hz, Me-17); 13C-NMR (50 MHz): 209.1 (C-2), 175.1 (C-18), 170.4 (-OCOMe), 143.6 (C-16), 140.4 (C-15), 134.0 (C-10), 125.6 (C-5), 108.8 (C-14), 66.0 (C-12), 52.8 (-OCOMe), 49.2 (C-2), 48.8 (C-4), 41.3 (C-11), 41.3 (C-9), 39.8 (C-3), 33.9 (C-8), 26.7 (C-7), 26.0 (C-6), 22.2 (-OCOMe), 21.5 (C-19), 20.7 (C-20), 16.0 (C-17); HRMS (EI) m/z calcd. for C23H30O6Na: 425.1935; found 425.1945.

Methyl 15,16-epoxy-12S-hydroxy-2-oxo-ent-halima-5(10),13(16),14-trien-18-oate (26)

To a solution of acetate 22 (50 mg, 0.12 mmol) in methanol (1.0 ml) Na2CO3 (23 mg, 0.21 mmol) was added. The mixture was stirred at room temperature. After 2 h, the solvent was evaporated and diluted with Et2O, extracted with Et2O, washed with water and dried over Na2SO4. Evaporation of the organic layer yielded 26 (42 mg, 96%) as a colourless oil; [α]22D +6.1 (c 1.0, CHCl3); IR (film) ν (cm-1) 3435, 2956, 1724, 1461, 1242, 1120, 1075; 1H-NMR (200 MHz): 7.34 (2H, m, H-15, H-16), 6.39 (1H, s, H-14), 4.51 (1H, m, H-12), 3.69 (3H, s, -COOMe), 2.78 (1H, d, J = 15.8 Hz, Hα-3), 2.71 (1H, m, Hα-1), 2.22 (1H, d, J = 15.4 Hz, Hβ-3), 2.19-1.95 (3H, m), 1.93-1.34 (5H, m), 1.25 (3H, s, Me-19), 0.95 (3H, d, J = 6.6 Hz, Me-17), 0-85 (3H, s, Me-20); 13C-NMR (50 MHz): 207.8 (C-2), 173.9 (C-18), 142.6 (C-16), 137.5 (C-15), 132.8 (C-13), 132.6 (C-10), 129.0 (C-5), 107.2 (C-14), 63.1 (C-12), 51.3 (-OCOMe), 48.5 (C-1), 47.7 (C-4), 43.1 (C-11), 39.9 (C-9), 38.5 (C-3), 32.7 (C-...
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8), 25.5 (C-7), 24.6 (C-6), 21.0 (C-19), 19.8 (C-20), 15.0 (C-17); HRMS (EI) m/z calcd. for C$_{21}$H$_{28}$O$_{5}$Na: 383.1829; found 383.1829.

Methyl 15,16-epoxy-2R,12S-dihydroxy-ent-halima-5(10),13(16),14-trien-18-oate (27) and 15,16-epoxy-12S-hydroxy-ent-halima-5(10),13(16),14-trien-18,2β-olide (13)

To an ice cooled solution of 26 (22.0 mg, 0.07 mmol) in EtOH (0.7 mL), NaBH$_4$ (13 mg, 0.33 mmol) was added. After being stirred at room temperature for 3h, the reaction mixture was recooled to 0°C and quenched with a few drops of 2 M aqueous HCl solution, diluted with EtOAc and water and extracted with EtOAc. The organic layer was washed with water. Evaporation of the dried extract gave a residue, which was chromatographed on silica gel (hex/EtOAc 9/1) to afford 13 (8 mg, 38%), and 27 (9 mg, 43%). Compound 27: a colourless oil; [α]$_D^{22}$ -41.1 (c 0.6, CHCl$_3$); IR (film) ν (cm$^{-1}$) 3408, 2929, 1727, 1460, 1274, 1161, 1024; $^1$H-NMR (200 MHz): 7.20 (2H, m, H-15, H-14), 6.41 (1H, bs, H-14), 3.66 (3H, s, -COOMe), 2.42- 1.95 (5H, m), 1.92-1.47 (6H, m), 1.33 (3H, s, Me-19), 0.93 (3H, s, Me-20), 0.85 (3H, d, $J = 6.6$ Hz, Me-17); $^{13}$C-NMR (50 MHz): 177.9 (C-18), 143.4 (C-16), 138.8 (C-15), 133.9 (C-10), 131.4 (C-5), 130.8 (C-13), 108.8 (C-14), 65.5 (C-2), 64.9 (C-12), 52.6 (-COOMe), 49.2 (C-4), 47.3 (C-3), 45.0 (C-1), 40.6 (C-9), 35.4 (C-8), 29.3 (C-7), 26.5 (C-6), 22.1 (C-20), 16.1(C-19), 14.3 (C-17); HRMS (EI) m/z calcd. for C$_{21}$H$_{30}$O$_{5}$Na: 385.1985; found 385.1969. Compound 13: see above.

15,16-Epoxy-12-oxo-ent-halima-5(10),13(16),14-trien-18,2β-olide (2)

To a mixture of 13 (3 mg, 0.01 mmol) N-methylmorpholine-N-oxide (NMO) (4 mg, 0.03 mmol) and molecular sieves (15 mg) in anhydrous CH$_2$Cl$_2$ (0.3 mL) under an Ar atmosphere and at room temperature, TPAP (3.0 mg, 3x10$^{-3}$ mmol) was added. The reaction mixture was stirred for 30 min. and then filtered on silica gel and Celite (DCM and EtOAc). Evaporation of the solvent yielded 2 (3.0 mg, 92%).

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*Sample Availability:* Samples of compounds 1 and 6 are available from the authors. Copies of the spectra for all compounds are also available on request.

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