

Article

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-18,2 β -olide), from *ent*-halimic acid has been achieved, corroborating the structure of the natural compound and establishing its absolute configuration.

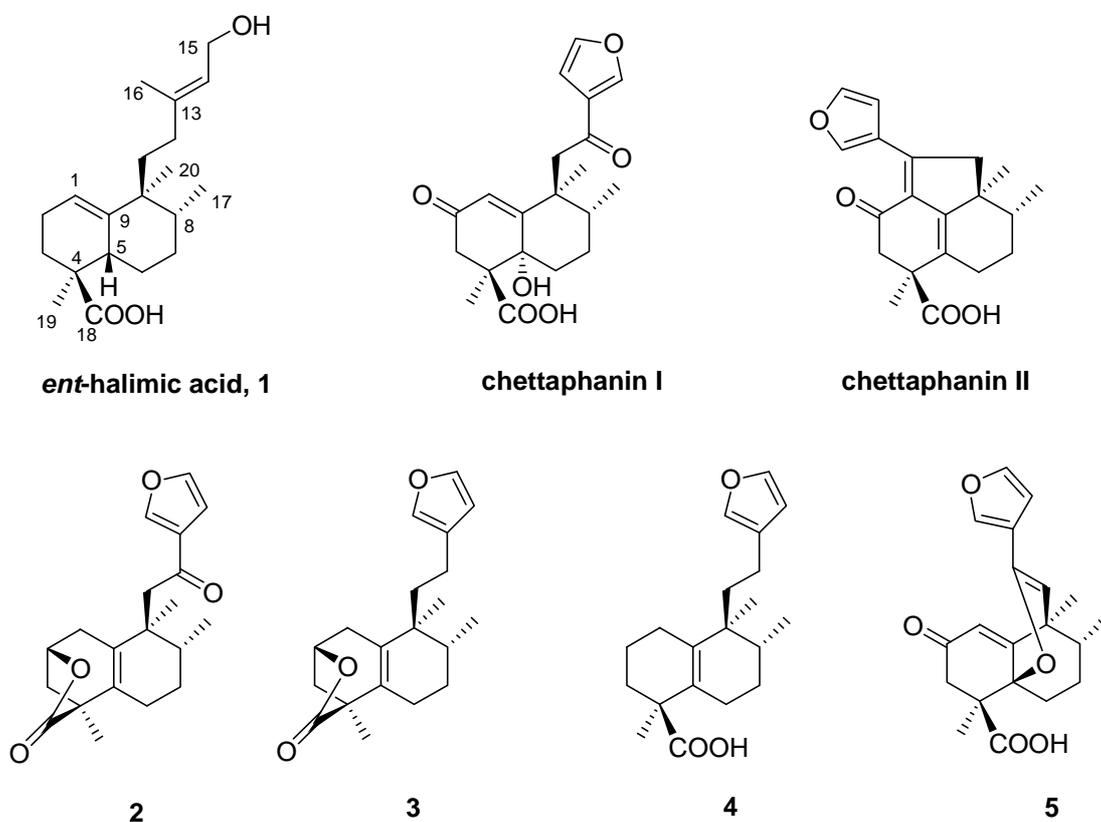
Keywords: *Ent*-halimanolides, *ent*-halimic acid, diterpenoids, *Cladogynos orientalis*.

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.

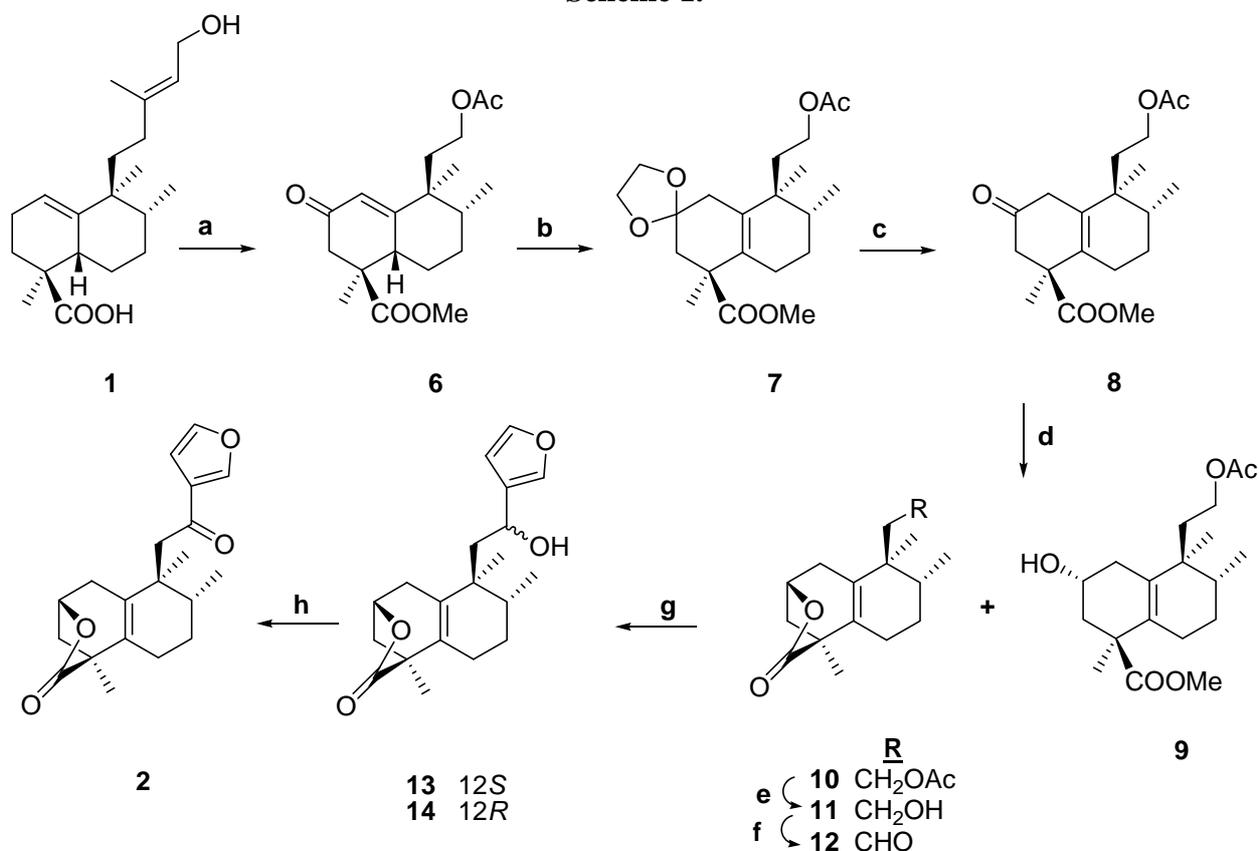
Results and Discussion

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**.

Scheme 1.



a) Ref. 3a; b) ethylene glycol, *p*-TsOH, C₆H₆, reflux, 8h (97%); c) HCl 2M, EtOH, 3h (92%); d) NaBH₄, EtOH, rt, 3h (**9**: 47%, **10**: 49%); e) Na₂CO₃, MeOH, rt, 5 h (97%); f) TPAP, NMO, DCM, rt, 30 min (96%); g) 3-bromofuran, *n*-BuLi (1/1), -78°C, 30 min (**13** : 54%, **14** : 36%); h) TPAP, NMO, DCM, rt, 50 min (92%).

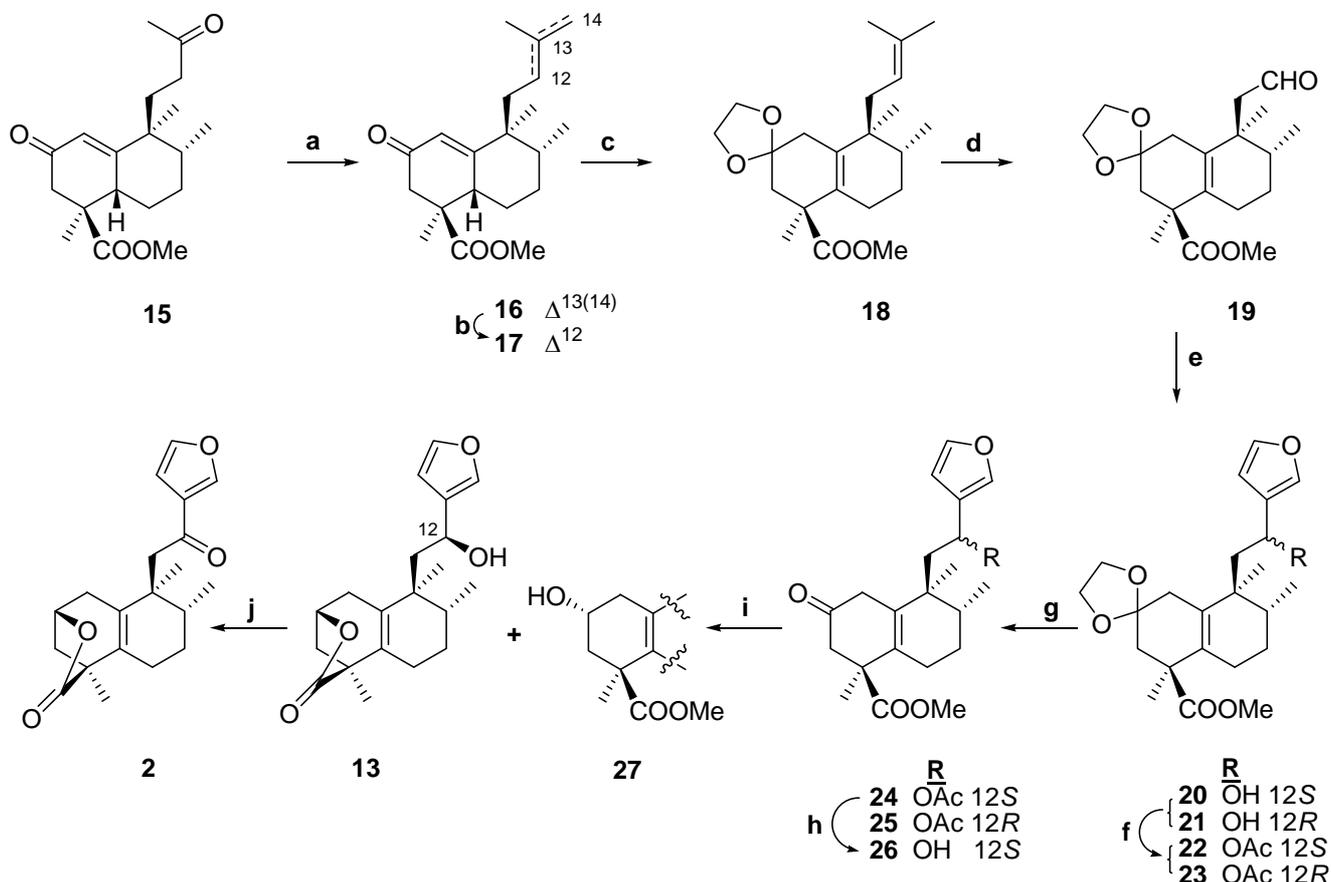
The *ent*-halimic acid tetranorderivative **6** was obtained in excellent yield as described in the synthesis of chettaphanin I and II [4] [6]. Carbonyl protection of **6** with ethylene glycol in acid media gives the tetranorderivative **7**, that already contains the tetrasubstituted double bond in 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 γ -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 comparison 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-*ent*-halima-5(10),13(16),14-trien-18,2 β -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 chetaphanin 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.

Scheme 2



a) MePPh₃Br, NaHMDS, THF, -78° C, 30 min (94%); b) *p*-TsOH, C₆H₆, 60° C, 2h (96%); c) (CH₂OH)₂, *p*-TsOH, C₆H₆, Dean Stark, 16 h, (97%), d) 1.- OsO₄, NMO, ^tBuOH, THF, H₂O, rt, overnight; 2.- Pb(AcO)₄, C₆H₆, rt, 39 min (96%, two steps); e) 3-bromofuran, *n*-BuLi, THF, 30 min (**20** : 54%, **21** : 39%); f) Ac₂O, pyridine 12 h (98%); g) HCl·2M, EtOH, rt, 3 h (96%); h) Na₂CO₃, MeOH, 2 h, (96%); i) NaBH₄, EtOH, rt, 3h (**13**: 38%, **27**: 43%); j) TPAP, NMO, DCM, rt, 50 min (92%).

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]_D²² -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 °C 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]_D²² -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, H_A-3), 2.24 (2H, s, H-1), 2.01 (3H, s, MeCOO-), 1.80-1.50 (4H, m), 1.72 (1H, d, J = 13.2 Hz, H_B-3), 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; $[\alpha]_D^{22}$ -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, H_A-1), 2.90 (1H, d, J = 15.0 Hz, H_A-3), 2.25 (1H, d, J = 15.0 Hz, H_B-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 C₁₉H₂₈O₅ (M)⁺: 336.1937; found 336.1928.

12-Acetoxy-13,14,15,16-tetranor-ent-halim-5(10)-en-18,2 β -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 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 **10** (73 mg, 49%) and **9** (70 mg, 47%). *Compound 10*: a colourless oil; $[\alpha]_D^{22}$ -103.1 (c 0.4, CHCl₃); IR (film) ν (cm⁻¹) 2959, 1769, 1732, 1456, 1238, 1081, 1031; ¹H-NMR (400 MHz): 4.81 (1H, m, H-2), 4.03 (1H, m, H-12), 3.84 (1H, m, H-12), 2.61-2.24 (4H, m), 2.15-2.01 (3H, m), 2.02 (3H, s, OCOMe), 1.95- 1.69 (4H, m), 1.30 (3H, s, Me-19), 0.91 (3H, s, Me-20), 0.88 (3H, d, J = 7.0 Hz, Me-17); ¹³C-NMR (100 MHz): 171.10 (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 C₁₈H₂₆O₄Na 329.1723; found 329.1716; *Compound 9*: a colourless oil; $[\alpha]_D^{22}$ -88.0 (c 0.7, CHCl₃); IR (film) ν (cm⁻¹) 3440, 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

(3H, s, Me-20), 0.87 (3H, d, $J = 7.0$ Hz, Me-17); ^{13}C -NMR (50 MHz): 176.8 (C-18), 170.7 (MeCOO-), 132.7 (C-10), 130.1 (C-5), 65.0 (C-2), 61.3 (C-12), 51.7 (-COOMe), 48.2 (C-4), 43.9 (C-1), 39.3 (C-9), 36.2 (C-3), 33.6 (C-8), 34.2 (C-11), 25.8 (C-7), 24.6 (C-19), 23.4 (C-6), 20.7 (MeCOO-), 20.7 (C-20), 20.7 (MeCOO-), 15.4 (C-17); HRMS (EI) m/z calcd. for $\text{C}_{19}\text{H}_{30}\text{O}_5\text{Na}$ 361.1985; found 361.1976.

12-Hydroxy-13,14,15,16-tetranor-ent-halim-5(10)-en-18,2 β -olide (11)

To **10** (73.0 mg, 0.24 mmol) a 3% solution of K_2CO_3 in methanol (5 ml) was added. After 2 h the solvent was evaporated and diluted with Et_2O . The organic layer was successively washed with a 2N aqueous solution of HCl and water, dried over Na_2SO_4 and evaporated to yield the expected compound **11** (61 mg, 97%) as a colourless oil; $[\alpha]_{\text{D}}^{22}$ -105.5 (c 0.4, CHCl_3); 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, H_A -12), 3.42-3.28 (1H, m, H_B -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); ^{13}C -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 $\text{C}_{16}\text{H}_{24}\text{O}_3\text{Na}$ 287.1618; found 287.1612.

12-Oxo-13,14,15,16-tetranor-ent-halim-5(10)-en-18,2 β -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 CH_2Cl_2 (1.2 mL) under an Ar atmosphere and at room temperature, TPAP (2 mg, 5×10^{-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** (30 mg, 96%) as a colourless oil, IR (film) ν (cm^{-1}) 2937, 1770, 1719, 1460, 1189, 1078, 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-11 $_B$), 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 $\text{C}_{16}\text{H}_{22}\text{O}_3\text{Na}$ 285.1461; found 281.1476.

15,16-Epoxy-12S-hidroxy-ent-halima-5(10),13(16),14-trien-18,2 β -olide (13) and 15,16-epoxy-12R-hidroxy-ent-halima-5(10),13(16),14-trien-18,2 β -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 NH_4Cl solution, warmed to room temperature and extracted with EtOAc. The organic layer was washed with 6% NaHCO_3 , brine and dried over Na_2SO_4 . 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; $[\alpha]_{\text{D}}^{22}$ -31.1 (c 0.4, CHCl_3). 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-

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 (7H, m), 1.91-1.42 (4H, m), 1.30 (3H, s, Me-19), 0.92 (3H, d, $J = 6.6$ Hz, Me-17), 0.91 (3H, s, Me-20). $^{13}\text{C-NMR}$ (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 $\text{C}_{20}\text{H}_{26}\text{O}_4\text{Na}$: 353.1723; found 353.1718. **Compound 14**: colourless oil; $[\alpha]_{\text{D}}^{22} -63.1$ (c 0.3, CHCl_3); IR (film) ν (cm^{-1}) 3407, 2927, 1769, 1460, 1075, 1024; $^1\text{H-NMR}$ (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); $^{13}\text{C-NMR}$ (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 $\text{C}_{20}\text{H}_{26}\text{O}_4\text{Na}$: 353.1723; found 353.1712.

15,16-Epoxy-12-oxo-ent-halima-5(10),13(16),14-trien-18,2 β -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_2Cl_2 (0.3 mL) under an Ar atmosphere and at room temperature, TPAP (1.0 mg, 3×10^{-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; $[\alpha]_{\text{D}}^{22} -101.4$ (c 0.2, CHCl_3); IR (film) ν (cm^{-1}) 2928, 1733, 1240, 1077, 1023; $^1\text{H-NMR}$ (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); $^{13}\text{C-NMR}$ (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), 33.2 (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 $\text{C}_{20}\text{H}_{24}\text{O}_4\text{Na}$: 351.1567; found 351.1567.

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

To a suspension of $\text{MeOCH}_2\text{PPh}_3\text{Cl}$ (1.24 g, 3.15 mmol) in THF (10 mL) at -20°C 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 -78°C . The mixture was stirred for 1 h at room temperature. Then, it was quenched with aqueous NH_4Cl and extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_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; $[\alpha]_{\text{D}}^{22} +179.9$ (c 1.4, CHCl_3); IR (film) ν

(cm^{-1}) 2964, 1732, 1676, 1455, 1267, 1160, 1113, 883; $^1\text{H-NMR}$ (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_A), 2.24 (1H, d, $J = 16.2$ Hz, H-3_B), 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); $^{13}\text{C-NMR}$ (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-3), 40.2 (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 $\text{C}_{20}\text{H}_{30}\text{O}_3\text{Na}$: 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 60°C for 2 h, then it was cooled and diluted with Et_2O . The organic layer was washed with 6% aqueous NaHCO_3 and brine and dried over Na_2SO_4 . The solvent was evaporated to yield **17** (1.01 g, 96%) as a colourless oil; $[\alpha]_{\text{D}}^{22} +45.4$ (c 1.0, CHCl_3); IR (film) ν (cm^{-1}) 2929, 1732, 1676, 1457, 1269, 1116; $^1\text{H-NMR}$ (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_A), 2.19 (1H, d, $J = 15.6$ Hz, H-3_B), 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); $^{13}\text{C-NMR}$ (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 $\text{C}_{20}\text{H}_{30}\text{O}_3\text{Na}$: 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 138°C for 16 h. The solution was then diluted with AcOEt and washed with 6% aqueous NaHCO_3 and water and dried over Na_2SO_4 . The solvent was evaporated to yield **18** (1.11 g, 97%) as a colourless oil; $[\alpha]_{\text{D}}^{22} -20.3$ (c 1.4, CHCl_3); IR (film) ν (cm^{-1}) 2964, 1733, 1237, 1118, 1078; $^1\text{H-NMR}$ (200 MHz): 4.98 (1H, m, H-12), 3.96 (4H, m, -OC₂H₄O-), 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); $^{13}\text{C-NMR}$ (50 MHz): 176.1 (C-18), 132.5 (C-13), 131.0 (C-5), 129.2 (C-10), 120.6 (C-12), 106.7 (C-2), 63.2 (-OC₂H₄O-), 63.0 (-OC₂H₄O-), 50.7 (-COOMe), 48.0 (C-4), 40.8 (C-3), 39.8 (C-9), 34.8 (C-1), 34.7 (C-11), 32.8 (C-8), 25.6 (C-7), 25.1 (C-20), 23.9 (C-6), 22.6 (C-16), 19.4 (C-19), 17.0 (C-14), 15.2 (C-17); HRMS (EI) m/z calcd. for $\text{C}_{22}\text{H}_{34}\text{O}_4\text{Na}$: 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_2O (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 Na₂SO₃ (30 mL) was added. The mixture was extracted with AcOEt, and the organic layer was washed with 10% aqueous Na₂S₂O₃, 2N aqueous HCl, water and brine and dried over Na₂SO₄. 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 NaHCO₃, water and brine and then dried and evaporated to yield **19** (980 mg, 96%) as a colourless oil; $[\alpha]_D^{22} +2.1$ (c 0.9, CHCl₃); IR (film) ν (cm⁻¹) 1734, 1717, 1456, 1375, 1238, 1152, 1078, 1032; ¹H-NMR (200 MHz): 9.63 (1H, s, H-12), 4.00-3.80 (4H, m, -OC₂H₄O-), 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); ¹³C-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 (-OC₂H₄O-), 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 C₁₉H₂₈O₅ (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 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 95/5) to yield **20** (279 mg, 54%) and **21** (202 mg, 39%). *Compound 20*: a colourless oil; $[\alpha]_D^{22} +4.6$ (c 0.8, CHCl₃); IR (film) ν (cm⁻¹) 3500, 1724, 1458, 1375, 1262, 1157, 1078, 1030, 665; ¹H-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, -OC₂H₄O-), 3.67 (3H, s, -COOMe), 2.38 (1H, d, *J* = 12.5 Hz, H_A-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); ¹³C-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 (-OC₂H₄O-), 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 C₂₃H₃₂O₆ (M)⁺: 404.2199; found 404.2191. *Compound 21*: a colourless oil; $[\alpha]_D^{22} -17.2$ (c 0.5, CHCl₃); IR (film) ν (cm⁻¹) 3500, 1730, 1464, 1377, 1159, 1089, 1030, 665; ¹H-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, -OC₂H₄O-), 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); ¹³C-

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 (-OC₂H₄O-), 64.2 (C-12), 52.1 (-COOMe), 48.7 (C-4), 47.7 (C-11), 42.9 (C-3), 40.6 (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 C₂₃H₃₂O₆ (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), Ac₂O (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 NaHCO₃ and brine. It was dried over Na₂SO₄ and the solvent was evaporated to afford **22** (128 mg, 99%) as a colourless oil; $[\alpha]_D^{22}$ -13.3 (c 0.7, CHCl₃); IR (film) ν (cm⁻¹) 1733, 1458, 1374, 1240, 1102, 1077, 1023, 874; ¹H-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, -OC₂H₄O-), 3.69 (3H, s, -COOMe), 2.25 (1H, d, *J* = 13.2 Hz, H_A-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_B-3), 1.32 (3H, s, Me-19), 0.89 (3H, d, *J* = 6.9 Hz, Me-17), 0.87 (3H, s, Me-20); ¹³C-NMR (50 MHz): 177.6 (C-18), 170.2 (-OCOMe), 143.3 (C-16), 140.2 (C-15), 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 (-OC₂H₄O-), 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 C₂₅H₃₄O₇Na: 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), Ac₂O (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 NaHCO₃ and brine. It was dried over Na₂SO₄ and the solvent was evaporated to afford **23** (128 mg, 99%) as a colourless oil; $[\alpha]_D^{22}$ -51.8 (c 0.6, CHCl₃); IR (film) ν (cm⁻¹) 1733, 1458, 1374, 1240, 1102, 1077, 1023, 874; ¹H-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, -OC₂H₄O-), 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); ¹³C-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 (-OC₂H₄O-), 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 C₂₅H₃₄O₇Na: 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 Et₂O, washed with water and dried over Na₂SO₄. Evaporation of the organic layer yielded **24** (102 mg, 96%) as a colourless oil; $[\alpha]_D^{22}$ -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 (-COOMe), 49.2 (C-1), 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; $[\alpha]_D^{22}$ -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, H_A-1), 2.99 (1H, d, *J* = 14.2 Hz, H_A-3), 2.83 (1H, d, *J* = 20.8 Hz, H_B-1), 2.31 (1H, d, *J* = 14.2 Hz, H_B-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-13), 132.4 (C-10), 126.2 (C-5), 108.9 (C-14), 65.4 (C-12), 52.6 (-COOMe), 50.5 (C-1), 49.2 (C-4), 40.4 (C-9), 40.1 (C-11), 33.3 (C-8), 29.9 (C-3), 26.8 (C-7), 25.7 (C-6), 22.5 (-OCOMe), 22.5 (C-19), 21.8 (C-20), 16.1 (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 **24** (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. The organic layer was successively washed with a 2N aqueous solution of HCl and water, dried over Na₂SO₄ and evaporated to yield **26** (42 mg, 96%) as a colourless oil; $[\alpha]_D^{22}$ -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, H_A-3), 2.71 (1H, m, H_A-1), 2.22 (1H, d, *J* = 15.4 Hz, H_B-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 (-COOMe), 48.5 (C-1), 47.7 (C-4), 43.1 (C-11), 39.9 (C-9), 38.5 (C-3), 32.7 (C-

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 $C_{21}H_{28}O_5Na$: 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-18,2 β -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; $[\alpha]_D^{22}$ -41.1 (c 0.6, $CHCl_3$); IR (film) ν (cm^{-1}) 3408, 2929, 1727, 1460, 1274, 1161, 1024; 1H -NMR (200 MHz): 7.20 (2H, m, H-15, H-14), 6.41 (1H, bs, H-14), 3.97 (2H, m, H-2, H-12), 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-18,2 β -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_2Cl_2 (0.3 mL) under an Ar atmosphere and at room temperature, TPAP (3.0 mg, 3×10^{-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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