Synthesis of *ent*-Halimanolides from *ent*-Halimic Acid

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This paper is dedicated to Prof. S. V. Ley on occasion of his 60th birthday.

Abstract: Three natural *ent*-halimanolides have been synthesized from *ent*-halimic acid. Their structures have been confirmed as well as their absolute configurations established. Bestmann methodology has been used for the synthesis of butenolides and for the synthesis of γ-hydroxybutenolides the Boukouvalas method has been employed.

Key words: diterpenes, alkaloids, *ent*-halimanolides, reduction

Annonaceae plants are a rich source of bioactive substances such as acetogenins.[1–4] The occurrence of natural diterpenes possessing hydroxybutenolide units has been reported frequently in plants of the genera *Polyalthia*, *Acritopappus*, *Premna*, and *Cyathocalux* (*Annonaceae*).[5–7] It is interesting to note that many species of these genera are widely used in folk medicine.[8]

Genus *Polyalthia* has been widely studied,[9] in particular several alkaloids[11] and a large number of clerodane and *ent*-halimane diterpenes were isolated from *Polyalthia longifolia*.[10] In 1995 Hara et al. reported the isolation of three *ent*-halimanolides **1**, **2**, and **3**. These compounds are the first *ent*-halimane diterpenes which have been isolated from *Annonaceae* plants. Their structures were elucidated by spectroscopic methods. Recently, the synthesis of the enantiomer[12] of **3** from (+)-hardwickiic acid (clerodane diterpene) was reported. In the present work, we report the synthesis of **1**, **2**, and **3**, starting from *ent*-halimic acid, confirming the structure and establishing the absolute configuration of these natural products.

ent-Halimic acid is the main component of *Halimium viscosum* (Villarino de los Aires) and has been used as the starting material in the synthesis of *ent*-halimanolides[13] and sesterterpenolides[14] similar to dysidiolide,[15] that show high anti-tumor activity, and chettaphanin I and II.[16]

The synthesis of **1–3** is carried out in three parts:

1. Reduction of C-18 and side chain degradation;

2. Functionalization of C-16; and

3. Synthesis of the butenolides and γ-hydroxybutenolides.

In the first part (reduction of C-18 and degradation of the side chain), the objective is the synthesis of methylketone **20**. Several conditions and even strategies were developed in order to achieve this objective, first reduction and then degradation (Scheme 1) or vice versa (Scheme 2).

For the transformation of the ester at C-18 several routes were attempted. The first employed a Huang-Minlon[17] reduction as the key step (Scheme 1). The hydroxyl group at C-15 was protected satisfactorily as methyl ether **5** or as the OTHP derivative **6**; the subsequent reduction of C-18 with $LiAlH_4$ gave **7** and **8**, respectively. tetra-*n*-Propylammonium perruthenate (TPAP) oxidation of these alcohols gave unstable aldehydes **9** and **10**, respectively. These aldehydes were treated under Huang-Minlon conditions to produce **11** and **12** in 85% and 81%, respectively.

The hydroxy derivatives **7** and **8** were subjected to other reduction procedures. The hydroxy derivative **8** was transformed into the xantogenate **13** by treatment with CS_2 and MeI. Reduction of **13** with *n*-Bu_3SnH[18] gave **12** in a low 31% yield (Scheme 1).

Reaction of **7** with *N*,*N*-dimethylphosphoramidic chloride and *n*-BuLi gives the corresponding TMPDA derivative **14**, which after reduction with lithium naphthalenide (LN) gave a mixture of **15**, **16**, and **17**.[19] Both **17** (36% yield) and alcohol **16** (12% yield) result from the cleavage of the oxygen–phosphorus bond along with reduction of the side chain. TMPDA derivative **15** (10% yield) resulted from reduction of the side chain. Compounds **15** and **16** can be recycled to give **17** and consequently can be used later in the synthesis. Due to the behavior of the side chain with LN an alternative route was tried which involved one less step.

Diol **18** which resulted from the reduction of **4** with $LiAlH_4$, was treated with *N*,*N*-dimethylphosphoramidic chloride in *n*-BuLi and gave the di-TMPDA derivative **19** (97% yield). Once again, reduction with LN gave a mixture of **15** (35%), **16** (25%), and **17** (38%).

Transformation of **11**, **12**, and **17**, into methylketone **20** was achieved by chemoselective epoxidation with MCPBA and H_5IO_6[20] which gave **20** in 90%, 92%, and 85% yields respectively for the two steps.

The reaction with MCPBA was totally regioselective, with no derivative resulting from oxidation of the annular double bond being observed.

The other strategy for the synthesis of **20** (Scheme 2) would be to reverse the strategy described above, first carry out the degradation and then C-18 reduction. Oxidation of **4** with OsO_4 and $Pb(OAc)_4$[16b,21] gave methylketone **21**,

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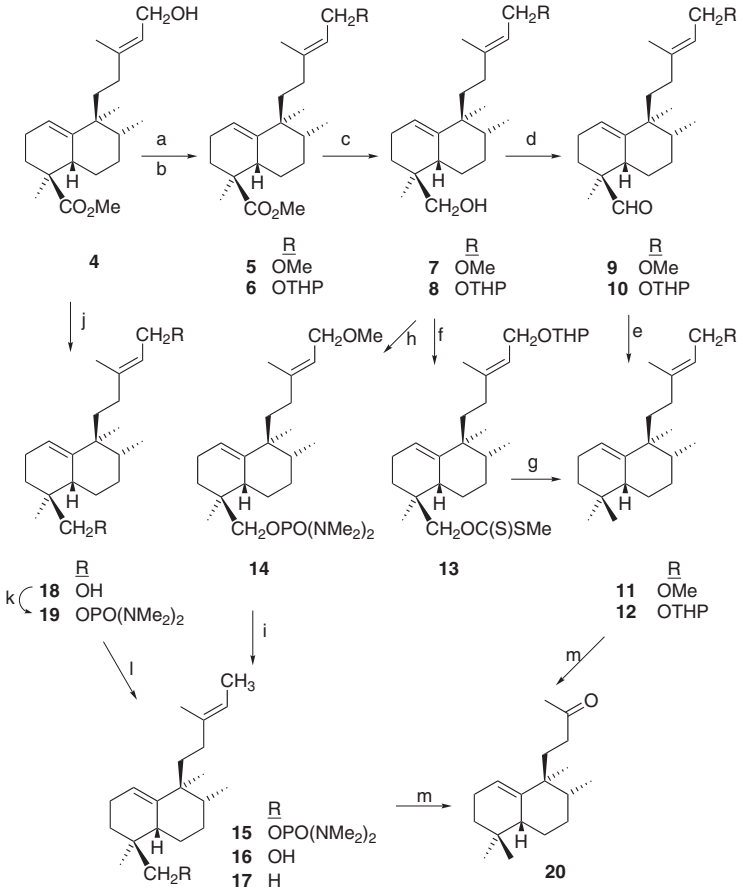


Scheme 1 *Reagents and conditions*: a) NaH, MeI, THF, 2 h, r.t. (92%); b) DHP, *p*-TsOH, benzene, 15 min, r.t. (74%); c) $LiAlH_4$, Et_2O, r.t., 1 h [**7** (96%); **8** (93%]; d) TPAP, NMO, CH_2Cl_2, 30 min [**9** (91%); **10** (94%)]; e) diethylene glycol, $NH_2NH_2{\cdot}H_2O$, KOH, 175–230 °C, 23 h [**11** (85%); **12** (81%)]; f) CS_2, *n*-BuLi, THF, MeI, –78 °C→r.t. (98%); g) *n*-Bu_3SnH, AIBN, toluene, 120 °C, 20 min, (31%); h) $(NMe_2)_2POCl$, *n*-BuLi, TMDEA,THF, –78 °C→r.t., 1 h (99%); i) LN (0.66 M), THF, r.t., 1 h [**15** (10%); **16** (12%); **17** (36%)]; j) $LiAlH_4$, Et_2O, r.t., 50 min (97%); k) $(NMe_2)_2POCl$, *n*-BuLi, TMDEA,THF, –78 °C→r.t., 1 h (97%); l) LN (0.24 M), THF, r.t., 6 h [**15** (35%); **16** (25%); **17** (38%)]; m) 1) MCPBA, CH_2Cl_2, r.t., 1 h; 2) H_5IO_6, THF, H_2O, r.t., 12 h [from **11** (90%); from **12** (92%); from **17** (85%) two steps].

that was protected as its dioxolane derivative **22** by reduction with ethylene glycol and *p*-TsOH. Reduction of **22** followed by oxidation of the alcohol **23** with TPAP[22] gave aldehyde **24** that was submitted immediately to Huang-Minlon reduction to give **25** in excellent yield. Deprotection of C-13 by reaction of **25** with *p*-TsOH and acetone gave **20** in 73% overall yield.

In order to introduce the butenolide ring side chain by means of a Bestmann reaction[23] it is necessary to functionalize C-16 as a hydroxy group. This was achieved by reaction of **20** with LDA in the presence of TMSCl[24] followed by oxidation[25] of the intermediate silyl enol ether with OsO_4 to afford the hydroxy ketone **26** in excellent yield.

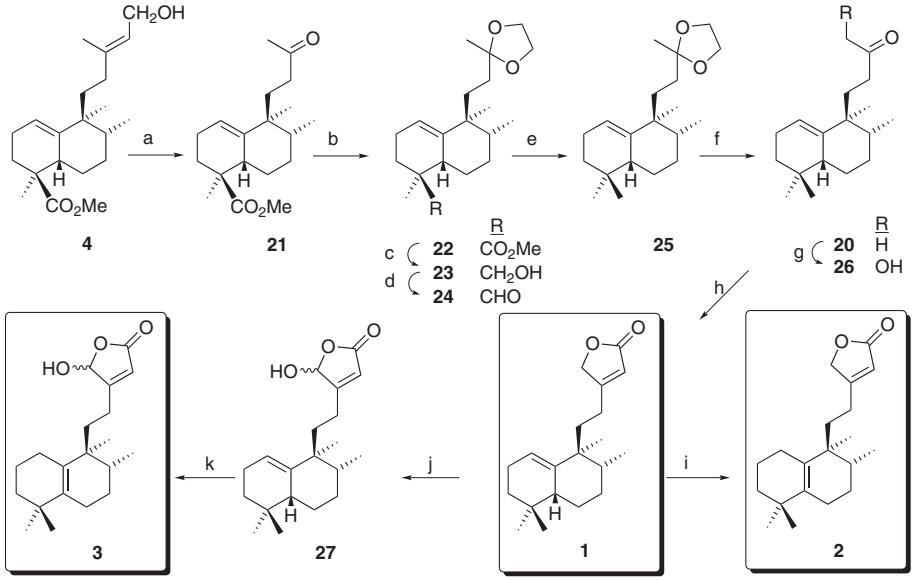
Thus hydroxy ketone **26** adds to $Ph_3P{=}C{=}C{=}O$ giving an intermediate ylide, which cyclized by intramolecular Wittig reaction with the formation of a double bond to give butenolide **1**.

Butenolide **2** was obtained from **1** by isomerization of the double bond. The isomerization was carried out by heating a solution of butenolide **1** and I_2 in benzene (0.1 M) at 85 °C affording **2** in almost quantitative yield. Physical properties of the synthesized compounds, **1** and **2** are identical to those described for the natural products *ent*-halima-1(10),13*E*-dien-15,16-olide[10] and *ent*-halima-5(10),13*E*-dien-15,16-olide,[10] respectively.

The synthesis of the γ-hydroxybutenolide **3** was performed using the Boukouvalas[26] method. Thus, reaction of **1** with TBDMSTf[27] in the presence of LDA followed by reaction of the intermediate 2-trialkylsilyloxyfurane with MCPBA afforded **27** in good yield, after chromatography.

Finally, compound **3** was obtained in quantitative yield by acidic isomerization of **27** using HI in benzene at 85 °C. Physical and spectroscopic data of the synthetic product **3** were in good agreement with those reported for the natural product 16-hydroxy-*ent*-halima-5(10),13-dien-15,16-olide.[10]

In conclusion *ent*-halimic acid, a diterpene of known absolute configuration,[28] has been transformed into natural *ent*-halimanolides **1**, **2**, and **3**, confirming their structure and establishing their absolute configuration.



Scheme 2 *Reagents and conditions:* a) 1) OsO_4, NMO, *t*-BuOH–THF–H_2O (7:2:1), 20 h; 2) $Pb(OAc)_4$, C_6H_6, 20 min (90%); b) ethylene glycol, *p*-TsOH, benzene, reflux, 16 h (96%); c) $LiAlH_4$, Et_2O, r.t., 45 min (98%); d) TPAP, NMO, CH_2Cl_2, r.t., 1 h (95%); e) diethylene glycol, $NH_2NH_2{\cdot}H_2O$, KOH, 175–230 °C, 20 h (91%); f) *p*-TsOH, acetone, r.t., 3.33 h (94%); g) 1) LDA, TMSCl, THF, –78 °C, 1 h (97%); 2) OsO_4, NMO, *t*-BUOH–THF–H_2O (7:2:1), r.t., 20 h (96%); h) $Ph_3P{=}C{=}C{=}O$, benzene, 85 °C, 3 h (91%); i) I_2 (benzene, 0.1 M), 85 °C 16 h (99%); j) 1) LDA, TBDMSTf, THF, –78 °C, 1 h (94%); 2) MCPBA, CH_2Cl_2, r.t., 4 h (77%); k) HI (benzene, 0.05 M), 85 °C, 4 h (99%).

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ (reference 7.26 and 77.0 ppm, respectively) at 200 and 400 MHz on Varian 200 VX and BRUKER DRX 400 instruments, respectively. Multiplicities were determined by DEPT experiments. IR spectra were recorded on a BOMEM 100 FTIR spectrophotometer. Optical rotations were determined using a Perkin-Elmer 241 polarimeter and 1 dm cells. EI mass spectra were run on a VG-TS 250 spectrometer at 70 eV. HRMS were recorded in a VG Platform (Fisons) spectrometer using CI (NH_3) or FAB techniques. Column chromatography was performed with Merck silica gel 60 (70–230 mesh). Solvents and reagents were generally distilled immediately prior to use: THF from sodium benzophenone ketyl, CH_2Cl_2 from CaH_2.

Methyl 15-Methoxy-*ent*-halima-1(10),13*E*-dien-18-oate (5)

To a solution of *ent*-halimic methyl ester **4** (792 mg, 2.37 mmol) in THF (12 mL) was added NaH (60%; 582 mg, 24.25 mmol) and after 10 min MeI (1.5 mL, 24.10 mmol) was added under argon. The reaction mixture was stirred for 2 h, quenched with ice (20 mL), and extracted with Et_2O (3 × 50 mL). The organic phase was washed with an aq solution of HCl (2 M, 3 × 25 mL), brine (25 mL), H_2O (2 × 25 mL), and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (hexane–EtOAc, 9:1) to afford **5**.

Yield: 758 mg (92%); $[\alpha]_D^{22}$ +54.6 (*c* 1.15, $CHCl_3$).

IR (neat): 2934, 1728, 1462, 1362, 1381, 1113 cm^{-1}.

^{1}H NMR (200 MHz): δ = 5.38–5.24 (2 H, m, H-1, H-14), 3.87 (2 H, d, *J* = 7.0 Hz, H-15), 3.60 (3 H, s, CO_2Me), 3.28 (3 H, s, OMe), 2.70–2.54 (1 H, m, H-5), 1.64 (3 H, s, Me-16), 2.09–1.12 (13 H, m), 1.07 (3 H, s, Me-19), 0.87 (3 H, s, Me-20), 0.76 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 141.6 (C-10), 141.3 (C-13), 120.2 (C-14), 119.6 (C-1), 69.1 (C-15), 57.7 (OMe), 51.6 (CO_2Me), 44.9 (C-4), 42.8 (C-9), 38.5 (C-5), 38.4 (C-8), 37.8 (C-11), 34.0 (C-12), 30.7 (C-3), 28.4 (C-7), 22.9 (C-6), 22.8 (C-2), 22.4 (C-20), 19.8 (C-19), 178.3 (C-18), 16.6 (C-16), 15.5 (C-17).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{36}O_3$ $(M)^+$: 348.2664; found: 348.2670.

15-Methoxy-*ent*-halima-1(10),13*E*-dien-18-ol (7)

A solution of methoxy ester **5** (1.1 g, 3.16 mmol) in Et_2O (35 mL) was reduced with $LiAlH_4$ (130 mg, 3.42 mmol) at 0 °C for 1 h. Then wet Et_2O (50 mL) was added. The organic phase was dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (hexane–EtOAc, 85:15) to afford methoxy alcohol **7**.

Yield: 972 mg (96%); $[\alpha]_D^{22}$ +64.6 (*c* 1.13, $CHCl_3$).

IR (neat): 3451, 2930, 1667, 1464, 1379, 1105 cm^{-1}.

^{1}H NMR (200 MHz): δ = 5.34–5.20 (2 H, m, H-1, H-14), 3.85 (2 H, d, *J* = 7.0 Hz, H-15), 3.41 (1 H, d, *J* = 10.5 Hz, H_A-18), 3.26 (3 H, s, OMe), 3.19 (1 H, d, *J* = 10.5 Hz, H_B-18), 1.60 (3 H, s, Me-16), 2.21–1.09 (14 H, m), 0.84 (3 H, s, Me-19), 0.79 (3 H, s, Me-20), 0.76 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 141.5 (C-13), 141.5 (C-10), 120.2 (C-14), 120.0 (C-1), 69.4 (C-18), 69.0 (C-15), 57.6 (OMe), 43.0 (C-9), 39.0 (C-8), 37.8 (C-5), 37.5 (C-11), 36.4 (C-4), 34.3 (C-12), 28.9 (C-3), 28.6 (C-7), 23.2 (C-6), 22.6 (C-2), 22.3 (C-20), 20.5 (C-19), 16.5 (C-16), 15.5 (C-17).

MS (EI): *m*/*z* (%) = 320 (M^+, 2), 289 (50), 257 (60), 207 (100), 177 (84), 105 (29), 81 (33).

15-Methoxy-*ent*-halima-1(10),13*E*-dien-18-al (9)

To a mixture of **8** (6.5 g, 20.31 mmol), NMO (4.2 g, 31.10 mmol), and molecular sieves (5.0 g, 500 mg/mmol) in anhyd CH_2Cl_2 (40 mL) under argon at r.t. was added TPAP (210 mg, 0.6 mmol). The reaction mixture was stirred for 15 min and then filtered through silica gel and celite (EtOAc). The solvent was evaporated and the residue was purified by column chromatography (hexane–EtOAc, 95:5→85:15) to afford aldehyde **9**.

Yield: 5.90 g (91%).

IR (neat): 2930, 1726, 1464, 1379, 1107 cm^{-1}.

^{1}H NMR (200 MHz): δ = 9.41 (1 H, s, H-18), 5.42–5.27 (2 H, m, H-1, H-14), 3.90 (2 H, d, *J* = 7.0 Hz, H-15), 3.30 (3 H, s, OMe), 2.49–2.31 (1 H, m, H-5), 1.67 (3 H, s, Me-16), 2.20–1.16 (13 H, m), 0.95 (3 H, s, Me-19), 0.90 (3 H, s, Me-20), 0.79 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 205.7 (C-18), 141.1 (C-13), 141.1 (C-10), 120.3 (C-14), 120.2 (C-1), 69.0 (C-15), 57.6 (OMe), 47.8 (C-4), 43.0 (C-9), 38.6 (C-8), 37.6 (C-11), 36.0 (C-5), 34.0 (C-12), 28.4 (C-3), 27.6 (C-7), 23.0 (C-6), 22.2 (C-20), 22.2 (C-2), 17.2 (C-19), 16.6 (C-16), 15.4 (C-17).

MS (EI): *m*/*z* (%) = 318 (M^+, 2), 286 (23), 257 (66), 240 (60), 205 (70), 177 (100), 161 (41), 145 (32), 107 (68), 91 (75), 77 (80).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{34}O_2$ $(M)^+$: 318.2559; found: 318.2564.

15-Methoxy-*ent*-halima-1(10),13*E*-diene (11)

$NH_2NH_2{\cdot}H_2O$ (25%; 2 mL, 40 mmol) and KOH (297 mg, 4.95 mmol) were added to a solution of **9** (380 mg, 1.19 mmol) in diethylene glycol (10 mL), the mixture was heated at 175 °C for 18.5 h, and then the condenser was removed. After 15 min the mixture was warmed to 230 °C for 4.5 h. It was allowed to cool to r.t., quenched with H_2O (5 mL) and an aq solution of HCl (6 M; 5 mL), and extracted with Et_2O (3 × 50 mL). The organic phase was washed with H_2O (3 × 50 mL) and dried over Na_2SO_4. The solvent was removed and the residue was purified by column chromatography (hexane–EtOAc, 98:2) to afford **11**.

Yield: 307 mg (85%); $[\alpha]_D^{22}$ +79.9 (*c* 1.2, $CHCl_3$).

IR (neat): 1464, 1379, 1109, 953 cm^{-1}.

^{1}H NMR (200 MHz): δ = 5.35–5.20 (2 H, m, H-1, H-14), 3.90 (2 H, d, *J* = 7.0 Hz, H-15), 3.32 (3 H, s, OMe), 2.05–1.05 (14 H, m), 1.66 (3 H, s, Me-16), 0.89 (3 H, s, Me-20), 0.87 (3 H, s, Me-19), 0.82 (3 H, s, Me-18), 0.80 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 141.7 (C-10), 141.5 (C-13), 120.1 (C-14), 119.7 (C-1), 69.0 (C-15), 57.7 (OMe), 43.4 (C-5), 42.7 (C-9), 39.1 (C-8), 37.6 (C-11), 34.2 (C-12), 33.3 (C-3), 31.4 (C-4), 29.1 (C-7), 28.2 (C-19), 25.9 (C-18), 23.6 (C-6), 23.1 (C-2), 22.2 (C-20), 16.6 (C-16), 15.6 (C-17).

MS (EI): *m*/*z* (%) = 304 (M^+, 2), 272 (6), 245 (8), 191 (100), 135 (18), 107 (19), 68 (18).

14,15-Dinor-*ent*-halima-1(10)-en-13-one (20)

A solution of MCPBA (169 mg, 0.98 mmol) in anhyd CH_2Cl_2 (3 mL) was added to an ice-cooled solution of **11** (300 mg, 0.99 mmol) in anhyd CH_2Cl_2 (3 mL). After 1 h the reaction mixture was diluted with H_2O (25 mL) and extracted with Et_2O (3 × 25 mL). The organic phase was washed with an aq solution of Na_2SO_3 (10%; 2 × 25 mL), an aq solution of $NaHCO_3$ (6%, 2 × 25 mL), and H_2O (3 × 25 mL). The organic phase was dried over Na_2SO_4. The solvent was evaporated to give a mixture of epoxide derivatives (285 mg), which were used in the next step. To a solution of the epoxide derivatives (209 mg, 0.65 mmol) in THF (2.5 mL) was added a suspension of H_5IO_6 (303 mg, 1.32 mmol) in THF–H_2O (2:1, 4.5 mL). The reaction mixture was stirred for 16 h at r.t., H_2O (20 mL) was added, and extracted with Et_2O (3 × 25 mL). The organic phase was washed with an aq solution of Na_2SO_3 (10%; 2 × 25 mL), H_2O (3 × 25 mL), and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (hexane–EtOAc, 98:2) to afford ketone **20**.

Yield: 167 mg (90%, two steps); $[\alpha]_D^{22}$ +65.1 (*c* 1.24, $CHCl_3$).

IR (neat): 2928, 1721, 1466, 1379 cm^{-1}.

^{1}H NMR (200 MHz): δ = 5.31 (1 H, t, *J* = 3.8 Hz, H-1), 2.11 (3 H, s, Me-16), 2.30–1.05 (14 H, m), 0.85 (6 H, s, Me-20, Me-19), 0.82 (3 H, s, Me-18), 0.80 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 209.7 (C-13), 141.1 (C-10), 120.2 (C-1), 43.2 (C-9), 43.2 (C-5), 39.0 (C-8), 38.9 (C-12), 33.2 (C-11), 32.2 (C-3), 31.3 (C-4), 29.9 (C-16), 28.9 (C-7), 28.0 (C-19), 25.7 (C-18), 23.4 (C-6), 23.0 (C-2), 22.2 (C-20), 22.2 (C-20), 16.6 (C-16), 15.6 (C-17), 15.6 (C-17).

MS (EI): *m*/*z* (%) = 262 (M^+, 2), 191 (100), 135 (12), 95 (8), 69 (7).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{30}O$ (M^+): 262.2297; found: 262.2262.

Methyl-15-tetrahydropyranyloxy-*ent*-halima-1(10),13*E*-dien-18-oate (6)

To a solution of **4** (2.1 g, 6.23 mmol) in benzene (25 mL), *p*-TsOH (237 mg, 1.25 mmol) and DHP (1.75 mL, 18.68 mmol) were added. After stirring for 15 min at r.t., K_2CO_3 (200 mg) was added. The reaction mixture was stirred for an additional 30 min, filtered, and extracted with EtOAc (250 mL). The organic phase was washed with an aq solution of Na_2CO_3 (6%; 3 × 50 mL), brine (2 × 40 mL), H_2O (2 × 40 mL), and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (hexane–EtOAc, 95:5) to afford **6**.

Yield: 2.0 g (74%); $[\alpha]_D^{22}$ +24.5 (*c* 0.4, $CHCl_3$).

IR (neat): 2940, 1732, 1456, 1256, 1117, 1024 cm^{-1}.

^{1}H NMR (200 MHz): δ = 5.35–5.31 (2 H, m, H-1, H-14), 4.98–4.93, 4.66–4.60 (1 H, 2 m , H-1′), 4.23 (1 H, dd, *J* = 12.1, 6.4 Hz, H-15_A), 4.00 (1 H, dd, *J* = 12.1, 7.5 Hz, H-15_B), 3.93–3.88 (1 H, m, H-5′), 3.66 (3 H, s, COOMe), 3.58–3.53 (1 H, m, H-5′), 2.72–2.55 (1 H, m, H-5), 2.15–1.00 (19 H, m), 1.69 (3 H, s, Me-16), 1.11 (3 H, s, Me-19), 0.91 (3 H, s, Me-20), 0.80 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 178.4 (C-18), 141.3 (C-13), 141.3 (C-10), 120.1 (C-14), 119.6 (C-1), 97.9 (C-1′), 63.8 (C-15), 62.2 (C-5′), 51.6 (CO_2Me), 44.9 (C-4), 42.8 (C-9), 38.4 (C-8), 38.4 (C-5), 37.7 (C-11), 34.0 (C-12), 30.7 (C-3), 30.7 (C-2′), 28.3 (C-7), 25.5 (C-3′), 22.9 (C-6), 22.9 (C-2), 22.4 (C-20), 19.7 (C-4′), 19.6 (C-19), 16.7 (C-16), 15.5 (C-17).

MS (EI): *m*/*z* (%) = 418 (M^+, 1), 235 (35), 175 (35), 137 (15), 85 (100).

HRMS (EI): *m*/*z* calcd for $C_{26}H_{42}O_4$ $(M)^+$: 418.3083; found: 418.3090.

15-Tetrahydropyranyloxy-*ent*-halima-1(10),13*E*-dien-18-ol (8)

To a stirred solution of **6** (3.5 g, 8.37 mmol) at 0 °C in Et_2O (80 mL), $LiAlH_4$ (477 mg, 12.50 mmol) was added. The mixture was stirred at r.t. for 15 min, cooled to 0 °C, and excess $LiAlH_4$ was decomposed by the slow addition of wet Et_2O (150 mL). The organic phase was dried over Na_2SO_4, The solvent was evaporated and the residue was purified by column chromatography (hexane–EtOAc, 85:15) to afford alcohol **8**.

Yield: 3.1 g (93%); $[\alpha]_D^{22}$ +36.2 (*c* 0.8, $CHCl_3$).

IR (neat): 3468, 2940, 1454, 1379, 1117, 1022 cm^{-1}.

^{1}H NMR (200 MHz): δ = 5.35–5.31 (2 H, m, H-1, H-14), 4.63–4.58 (1 H, m, H-1′), 4.23 (1 H, dd, *J* = 11.8, 6.5 Hz, H-15_A), 3.97 (1 H, dd, *J* = 11.8, 7.5 Hz, H-15_B), 3.90–3.85 (1 H, m, H-5′), 3.53–3.47 (1 H, m, H-5′), 3.47 (1 H, d, *J* = 10.8 Hz, H-18_A), 3.24 (1 H, d, *J* = 10.8 Hz, H-18_B), 2.10–1.10 (20 H, m), 1.64 (3 H, s, Me-16), 0.88 (3 H, s, Me-19), 0.83 (3 H, s, Me-20), 0.79 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 141.5 (C-10), 141.2 (C-13), 120.2 (C-14), 120.0 (C-1), 97.9 (C-1′), 69.6 (C-18), 63.8 (C-15), 62.2 (C-5′), 43.0 (C-9), 39.0 (C-8), 37.8 (C-5), 37.5 (C-11), 36.5 (C-4), 34.4 (C-12), 30.7 (C-2′), 29.0 (C-3), 28.6 (C-7), 25.5 (C-3′), 23.3 (C-6), 22.6 (C-2), 22.3 (C-20), 20.6 (C-19), 19.6 (C-4′), 16.6 (C-16), 15.6 (C-17).

MS (EI): *m*/*z* (%) = 390 (M^+, 1), 257 (25), 207 (40), 177 (25), 149 (10), 85 (100).

HRMS (EI): *m/z* calcd for $C_{25}H_{42}O_3$ $(M)^+$: 390.3133; found: 390.3140.

15-Tetrahydropyranyloxy-*ent*-halima-1(10),13*E*-dien-18-al (10)

To a mixture of **8** (3.3 g, 8.46 mmol), NMO (1.7 g 12.69 mmol), and molecular sieves (4.2 g) in anhyd CH_2Cl_2 (40 mL) under argon, at r.t. was added TPAP (148 mg, 0.42 mmol). The reaction mixture was stirred for 45 min and then filtered through a short pad of silica gel and celite (EtOAc). The solvent was evaporated and the residue was purified by column chromatography (hexane–EtOAc, 85:15) to afford aldehyde **10**.

Yield: 3.1 g (94%).

IR (neat): 2940, 2872, 1724, 1672, 1456, 1381, 1123, 1024 cm^{-1}.

^1H NMR (200 MHz): δ = 9.43 (1 H, s, H-18), 5.45–5.25 (2 H, m, H-1, H-14), 4.65–4.55 (1 H, m, H-1′), 4.20 (1 H, dd, *J* = 11.8, 6.5 Hz, H-15_A), 3.97 (1 H, dd, *J* = 11.8, 7.5 Hz, H-15_B), 3.90–3.80 (1 H, m, H-5′), 3.55–3.40 (1 H, m, H-5′), 2.50–2.35 (1 H, m, H-5), 2.20–1.20 (19 H, m), 1.66 (3 H, s, Me-16), 0.95 (3 H, s, Me-19), 0.90 (3 H, s, Me-20), 0.79 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 205.9 (C-18), 141.2 (C-10), 141.1 (C-13), 120.4 (C-1), 120.3 (C-14), 97.9 (C-1′), 63.9 (C-15), 62.3 (C-5′), 48.0 (C-4), 43.2 (C-9), 38.9 (C-8), 37.6 (C-11), 36.2 (C-5), 34.4 (C-12), 30.9 (C-2′), 28.7 (C-3), 27.9 (C-7), 25.8 (C-3′), 23.2 (C-6), 22.6 (C-2), 22.5 (C-20), 19.9 (C-4′), 17.6 (C-19), 16.9 (C-16), 15.8 (C-17).

HRMS (EI): *m/z* calcd for $C_{25}H_{40}O_3$ $(M)^+$: 388.2977; found: 388.2982.

15-Tetrahydropyranyloxy-*ent*-halima-1(10),13*E*-diene (12)

$NH_2NH_2{\cdot}H_2O$ (25%; 6 mL, 120 mmol) and KOH (1.6 g, 26.6 mmol) were added to a solution of **10** (1.76 g, 4.53 mmol) in diethylene glycol (40 mL); the mixture was heated at 175 °C for 18.5 h and then the condenser was removed. After 15 min the mixture was warmed to 230 °C for 4.5 h. Following the same procedure described for **9** the residue obtained was purified by column chromatography (hexane–EtOAc, 98:2) to afford **12**.

Yield: 1.37 g (81%).

IR (neat): 2940, 2870, 1653, 1454, 1379, 1200, 1132, 1117, 1042, 907, 870 cm^{-1}.

^1H NMR (200 MHz): δ = 5.34–5.30 (2 H, m, H-1, H-14), 4.63–4.58 (1 H, m, H-1′), 4.20 (1 H, dd, *J* = 11.8, 6.5 Hz, H-15_A), 3.97 (1 H, dd, *J* = 11.8, 7.5 Hz, H-15_B), 3.90–3.85 (1 H, m, H-5′), 3.53–3.47 (1 H, m, H-5′), 2.15–1.00 (20 H, m), 1.66 (3 H, s, Me-16), 0.89 (3 H, s, Me-20), 0.87 (3 H, s, Me-19), 0.82 (3 H, s, Me-18), 0.80 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 141.7 (C-10), 141.4 (C-13), 120.2 (C-14), 119.8 (C-1), 97.9 (C-1′), 63.9 (C-15), 62.3 (C-5′), 43.6 (C-5), 43.1 (C-9), 39.4 (C-8), 37.7 (C-11), 34.5 (C-12), 33.5 (C-3), 31.6 (C-4), 31.0 (C-2′), 29.4 (C-7), 28.4 (C-19), 26.3 (C-18), 25.8 (C-3′), 23.9 (C-6), 23.4 (C-2), 22.6 (C-20), 19.9 (C-4′), 16.9 (C-16), 15.9 (C-17).

MS (EI): *m/z* (%) = 374 (M^+, 8), 272 (15), 191 (90), 121 (14), 85 (100).

HRMS (EI): *m/z* calcd for $C_{25}H_{42}O_2$ $(M)^+$: 374.3185; found: 374.3178.

Methyl-15-tetrahydropyranyloxy-*ent*-halima-1(10),13*E*-dien-18-dithiocarbonate (13)

To a solution of alcohol **8** (33 mg, 0.09 mmol) in THF (2 mL), cooled to –78 °C under argon, a solution of *n*-BuLi (1.6 M in hexane; 0.06 mL, 0.10 mmol) was added and the mixture was stirred at 0 °C for 30 min. After addition of CS_2 (0.05 mL, 0.85 mmol), the mixture was stirred for an additional 2 h at r.t., and MeI (0.02 mL, 0.25 mmol) was added. After 1 h the reaction mixture was quenched with ice-water (5 mL) and extracted with EtOAc (3 × 25 mL). The extracts were washed with an aq solution of HCl (0.5 M; 3 × 20 mL), water (2 × 20 mL), brine (2 × 20 mL), and dried over Na_2SO_4. The solvent was evaporated to afford **13**.

Yield: 40 mg (98%); $[\alpha]_D^{22}$ +38.0 (*c* 0.3, $CHCl_3$).

IR (neat): 1464, 1380, 1215, 1069, 1023, 666 cm^{-1}.

^1H NMR (200 MHz): δ = 5.37–5.30 (2 H, m, H-1, H-14), 4.63–4.58 (1 H, m, H-1′), 4.42 (1 H, d, *J* = 10.6 Hz, H-18_A), 4.26 (1 H, d, *J* = 10.6 Hz, H-18_B), 4.18 (1 H, dd, *J* = 11.8, 7.2 Hz, H-15_A), 3.98 (1 H, dd, *J* = 11.8, 7.4 Hz, H-15_B), 3.94–3.83 (1 H, m, H-5′), 3.56–3.45 (1 H, m, H-5′), 2.54 (3 H, s, MeS), 2.26–1.11 (20 H, m), 1.66 (3 H, s, Me-16), 0.95, 0.91 (3 H, 2 s, Me-19, Me-20), 0.81 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 215.9 (CS_2), 141.3 (C-10), 141.1 (C-13), 120.2 (C-14), 120.1 (C-1), 98.0 (C-1′), 80.5 (C-18), 63.9 (C-15), 62.3 (C-5′), 43.2 (C-9), 39.4 (C-8), 38.4 (C-5), 37.2 (C-11), 35.9 (C-4), 34.3 (C-12), 30.9 (C-2′), 29.1 (C-7), 29.0 (C-3), 25.7 (C-3′), 23.5 (C-2), 22.7 (C-6), 22.5 (C-20), 21.6 (C-19), 19.8 (C-4′), 19.0 (MeS), 17.0 (C-16), 15.8 (C-17).

MS (EI): *m/z* (%) = 447 (M^+ – 33, 3), 331 (15), 270 (15), 189 (70), 85 (100).

12; Reaction of 13 with *n*-Bu_3SnH

A solution of **13** (373 mg, 0.78 mmol), AIBN (13 mg, 0.08 mmol), and *n*-Bu_3SnH (0.52 mL, 1.94 mmol) in toluene (10 mL) was heated at 120 °C for 20 min. During heating the solution changed color from dark red through pale yellow to black. The solution was cooled to r.t., filtered through a short pad of silica gel (hexane–EtOAc, 98:2), and the solvent was evaporated to afford diene **12** (91 mg, 31%).

20; Reaction of 12 with MCPBA/H_5IO_6

A solution of MCPBA (32 mg, 0.18 mmol) in anhyd CH_2Cl_2 (2 mL) was added to an ice-cooled solution of **12** (53 mg, 0.18 mmol) in anhyd CH_2Cl_2 (2 mL). After 1 h the reaction mixture was diluted with H_2O (6 mL) and extracted with Et_2O (3 × 25 mL). The organic phase was washed with an aq solution of Na_2SO_3 (10%; 10 mL), an aq solution of $NaHCO_3$ (6%; 2 × 15 mL), H_2O (3 × 15 mL), and dried over Na_2SO_4. The solvent was evaporated to give a mixture of epoxide derivatives (53 mg), which were used in the next step. To a solution of the epoxide derivatives (50 mg, 0.16 mmol) in THF (2 mL) was added a suspension of H_5IO_6 (98 mg, 0.43 mmol) in THF–H_2O (4:3, 3.5 mL). The reaction mixture was stirred for 12 h at r.t. Following the same procedure described above the residue obtained, was purified by column chromatography (hexane–EtOAc, 98:2) to afford ketone **20**.

Yield: 40 mg (92%, two steps).

15-Methoxy-*ent*-halima-1(10),13*E*-dien-18-*N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidate (14)

To a stirred solution of **7** (128 mg, 0.40 mmol) in a mixture of anhyd THF (3 mL) and TMEDA (0.1 mL) cooled to –78 °C under argon, *n*-BuLi (1.6 M in hexane; 1 mL, 1.6 mmol) was added slowly. The reaction mixture was stirred at –78 °C for 15 min and $(NMe_2)_2POCl$ (0.23 mL, 1.6 mmol) was added. After stirring at –78 °C for 5 min, the reaction mixture was allowed to warm to r.t., and was stirred for 1 h. After being quenched with wet Et_2O (30 mL) and H_2O (30 mL), the mixture was extracted with Et_2O (3 × 25 mL). The organic phase was washed with H_2O (3 × 20 mL) and dried over Na_2SO_4. The solvent was evaporated to afford **14**.

Yield: 180 mg (99%).

IR (neat): 2928, 2876, 1462, 1379, 1304, 1227, 1044, 993, 870, 754, 675 cm^{-1}.

^1H NMR (200 MHz): δ = 5.31–5.27 (2 H, m, H-1, H-14), 3.88 (2 H, d, *J* = 7.0 Hz, H-15), 3.74 (1 H, dd, *J* = 9.4, 4.5 Hz, H_A-18), 3.47 (1 H, dd, *J* = 9.4, 4.3 Hz, H_B-18), 3.29 (3 H, s, OMe), 2.64, 2.63, 2.60, 2.59 [12 H, 4 s, $(NMe_2)_2$], 2.05–1.05 (14 H, m), 1.63 (3 H, s, Me-16), 0.88 (3 H, s, Me-19), 0.85 (3 H, s, Me-20), 0.79 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 141.3 (C-10), 141.0 (C-13), 120.1 (C-14), 120.1 (C-1), 71.0 (C-18), 69.0 (C-15), 57.7 (OMe), 42.7 (C-9), 38.6 (C-8), 37.6 (C-5), 37.5 (C-11), 36.6 [$(NMe_2)_2$], 36.2 (C-4), 34.2 (C-12), 29.4 (C-3), 28.6 (C-7), 22.5 (C-20), 22.5 (C-2), 22.3 (C-6), 19.8 (C-19), 16.7 (C-16), 15.5 (C-17).

HRMS (EI): *m*/*z* calcd for $C_{25}H_{47}N_2O_3P$ $(M)^+$: 454.3324; found: 454.3329.

15, 16, and 17; Reduction of 14 with LN

A solution of LN (0.66 M) in THF was prepared by the addition of pieces of Li (25 mg, 3.57 mmol) to a solution of naphthalene (413 mg, 3.23 mmol) in THF (5 mL). The solution of LN thus prepared was added to a solution of TMPDA derivative **14** (79 mg, 0.17 mmol) in THF (2 mL). The reaction mixture was stirred at r.t. under argon for 1 h. H_2O (20 mL) was added and the resulting mixture was extracted with Et_2O (3 × 15 mL). The organic phase was washed with H_2O (3 × 10 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography to afford hydrocarbon **17**, alcohol **16**, and **15**.

***ent*-Halima-1(10),13*E*-dien-18-*N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidate (15)**

Yield: 7 mg (10%).

IR (neat): 2926, 1464, 1379, 1304, 1227, 997, 870, 754, 669 cm^{-1}.

^1H NMR (400 MHz): δ = 5.35–5.31 (1 H, m, H-1), 5.14 (1 H, complex, *J* = 6.8 Hz, H-14), 3.75 (1 H, dd, *J* = 9.6, 4.5 Hz, H_A-18), 3.48 (1 H, dd, *J* = 9.6, 4.5 Hz, H_B-18), 2.65, 2.64, 2.60, 2.59 [12 H, 4 s, $(NMe_2)_2$], 2.06–1.20 (14 H, m), 1.54 (3 H, s, Me-16), 1.51 (3 H, d, *J* = 6.8 Hz, Me-15), 0.88 (3 H, s, Me-19), 0.85 (3 H, s, Me-20), 0.79 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 141.1 (C-10), 136.7 (C-13), 119.9 (C-1), 117.5 (C-14), 70.9 (C-18), 42.7 (C-9), 38.4 (C-8), 37.8 (C-11), 37.7 (C-5), 36.6 [$(NMe_2)_2$], 36.1 (C-4), 34.2 (C-12), 29.4 (C-3), 28.6 (C-7), 22.5 (C-20), 22.5 (C-2), 22.3 (C-6), 19.8 (C-19), 15.9 (C-16), 15.6 (C-17), 13.3 (C-15).

HRMS (EI): *m*/*z* calcd for $C_{24}H_{45}N_2O_2P$ $(M)^+$: 424.3219; found: 454.3225.

***ent*-Halima-1(10),13*E*-dien-18-ol (16)**

Yield: 6 mg (12%); $[\alpha]_D^{22}$ +56.1 (*c* 1.35, $CHCl_3$).

IR (neat): 3422, 2932, 1454, 1379, 1125 cm^{-1}.

^1H NMR (200 MHz): δ = 5.33–5.16 (1 H, 2 m, H-1, H-14), 3.50 (1 H, d, *J* = 10.2 Hz, H_A-18), 3.28 (1 H, d, *J* = 10.2 Hz, H_B-18), 2.10–1.02 (14 H, m), 1.58 (3 H, s, Me-16), 1.53 (3 H, d, *J* = 6.7 Hz, Me-15), 0.90 (3 H, s, Me-19), 0.86 (3 H, s, Me-20), 0.81 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 141.8 (C-10), 137.0 (C-13), 119.8 (C-1), 117.7 (C-14), 69.7 (C-18), 43.0 (C-9), 39.0 (C-8), 37.9 (C-5), 37.9 (C-11), 36.5 (C-4), 34.3 (C-12), 29.0 (C-3), 28.5 (C-7), 23.3 (C-6), 22.6 (C-2), 22.3 (C-20), 20.7 (C-19), 15.9 (C-16), 15.6 (C-17), 13.3 (C-15).

MS (EI): *m*/*z* (%) = 290 (M^+, 2), 259 (15), 208 (25), 177 (100), 105 (25), 91 (23), 69 (27).

***ent*-Halima-1(10),13*E*-diene (17)**

Yield: 17 mg (36%); $[\alpha]_D^{22}$ +67.4 (*c* 0.89, $CHCl_3$).

IR (neat): 2926, 2870, 1462, 1379, 1090, 814 cm^{-1}.

^1H NMR (200 MHz): δ = 5.33–5.29 (1 H, m, H-1), 5.20–5.16 (1 H, m, H-14), 2.10–1.10 (14 H, m), 1.58 (3 H, s, Me-16), 1.56 (3 H, d, *J* = 6.7 Hz, Me-15), 0.90 (3 H, s, Me-20), 0.89 (3 H, s, Me-19), 0.83 (3 H, s, Me-18), 0.80 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 141.9 (C-10), 137.0 (C-13), 119.5 (C-1), 117.5 (C-14), 43.4 (C-5), 42.9 (C-9), 39.1 (C-8), 38.0 (C-11), 34.3 (C-12), 33.4 (C-3), 31.4 (C-4), 29.1 (C-7), 28.2 (C-19), 26.0 (C-18), 23.7 (C-6), 23.1 (C-2), 22.3 (C-20), 15.8 (C-16), 15.6 (C-17), 13.3 (C-15).

MS (EI): *m*/*z* (%) = 274 (M^+, 1), 245 (2), 191 (15), 177 (15), 135 (8), 121 (8), 107 (10), 91 (30), 70 (29), 69 (50), 55 (100).

15; Reaction of 16 with $(NMe_2)_2POCl$/*n*-BuLi

To a stirred solution of **16** (85 mg, 0.29 mmol) in anhyd THF (2 mL) and TMEDA (0.1 mL), cooled to –78 °C under argon, *n*-BuLi (1.6 M in hexane; 0.7 mL, 1.16 mmol) was added slowly. The reaction mixture was stirred at –78 °C for 15 min and then $(NMe_2)_2POCl$ (0.17 mL, 1.2 mmol) was added. Following the same procedure described above, flash chromatography afforded **15**.

Yield: 115 mg (94%).

16 and 17; Reduction of 15 with LN

A solution of TMPDA derivative **15** (34 mg, 0.08 mmol) in THF (1 mL) was added to a solution of LN in THF (0.66 M, prepared as described above). The reaction mixture was stirred at r.t. under argon for 2 h. Following the same work-up described for **14**, the residue obtained was purified by column chromatography to afford the desired hydrocarbon **17** (10 mg, 46%) and alcohol **16** (9 mg, 39%).

21; Reaction of 17 with MCPBA/H_5IO_6

A solution of MCPBA (145 mg, 0.406 mmol) in anhyd CH_2Cl_2 (3 mL) was added to an ice-cooled solution of **17** (113 mg, 0.41 mmol) in anhyd CH_2Cl_2 (3 mL). After 1.5 h the reaction mixture was diluted with H_2O (40 mL) and extracted with Et_2O (3 × 50 mL). The organic phase was washed with an aq solution of Na_2SO_3 (10%; 25 mL), an aq solution of $NaHCO_3$ (6%; 3 × 20 mL), H_2O (3 × 20 mL), and dried over Na_2SO_4. The solvent was evaporated to give a mixture of epoxide derivatives (111 mg) which were used in the next step. To a solution of the epoxide derivatives (213 mg, 0.73 mmol) in THF (3 mL) was added a suspension of H_5IO_6 (341 mg, 1.49 mmol) in THF–H_2O (3:2, 5 mL). The reaction mixture was stirred for 12 h at r.t. Following the same procedure described above, the residue obtained was purified by column chromatography to afford ketone **20**.

Yield: 192 mg (85%, two steps).

***ent*-Halima-1(10),13*E*-dien-15,18-diol (18)**

To a stirred solution of **4** (10.4 g, 31.13 mmol) in Et_2O (300 mL) at 0 °C, $LiAlH_4$ (1.38 g, 36.36 mmol) was added. The mixture was stirred at r.t. for 50 min, then cooled to 0 °C, and excess $LiAlH_4$ was decomposed by slow addition of wet Et_2O (300 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated to afford alcohol **18**.

Yield: 9.2 g (97%); $[\alpha]_D^{22}$ +66.2 (*c* 0.84, $CHCl_3$).

IR (neat): 3360, 2930, 2872, 1464, 1379, 1045, 997, 743, 667 cm^{-1}.

^1H NMR (200 MHz): δ = 5.45–5.30 (2 H, m, H-1, H-14), 4.13 (2 H, d, *J* = 7.0 Hz, H-15), 3.48 (1 H, d, *J* = 10.4 Hz, H_A-18), 3.28 (1 H, d, *J* = 10.4 Hz, H_B-18), 2.15–1.70 (4 H, m), 1.66 (3 H, s, Me-16), 1.60–1.45 (3 H, m), 1.40–1.10 (7 H, m), 0.90 (3 H, s, Me-19), 0.86 (3 H, s, Me-20), 0.81 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 141.7 (C-10), 140.5 (C-13), 123.0 (C-14), 120.0 (C-1), 69.5 (C-18), 59.3 (C-15), 43.1 (C-9), 39.1 (C-8), 37.6 (C-5), 37.6 (C-11), 36.4 (C-4), 34.3 (C-12), 28.9 (C-3), 28.7 (C-7), 23.2 (C-6), 22.6 (C-2), 22.3 (C-20), 20.6 (C-19), 16.4 (C-16), 15.6 (C-17).

MS (EI): *m*/*z* (%) = 306 (M^+, 1), 275 (10), 257 (40), 207 (93), 177 (100), 105 (33), 81 (31).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{34}O_2$ $(M)^+$: 306.2558; found: 306.2568.

ent-Halima-1(10),13*E*-dien-15,18-di-*N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidate (19)

To a stirred solution of **18** (989 mg, 3.23 mmol) in anhyd THF (8 mL) and TMEDA (1 mL), cooled to –78 °C under argon, BuLi (1.6 M in hexane; 12.2 mL, 19.52 mmol) was added slowly. The reaction mixture was stirred at –78 °C for 15 min, and then $(NMe_2)_2POCl$ (3.7 mL, 25.6 mmol) was added. Following the same procedure described above, column chromatography afforded **19**.

Yield: 1.80g (97%).

IR (neat): 2930, 2807, 1462, 1379, 1302, 1215, 1034, 991, 872, 754 cm^{-1}.

^{1}H NMR (200 MHz): δ = 5.34–5.30 (2 H, m, H-1, H-14), 4.39 (1 H, d, *J* = 7.0 Hz, H_A-15), 4.37 (1 H, d, *J* = 7.0 Hz, H_B-15), 3.72 (1 H, dd, *J* = 9.5, 4.5 Hz, H_A-18), 3.45 (1 H, dd, *J* = 9.5, 4.5 Hz, H_B-18), 2.62, 2.57 [24 H, 2 s, $(NMe_2)_2$], 1.90–1.05 (14 H, m), 1.63 (3 H, s, Me-16), 0.87 (3 H, s, Me-19), 0.84 (3 H, s, Me-20), 0.77 (3 H, d, *J* = 7.0 Hz, Me-17).

HRMS (EI): *m*/*z* calcd for $C_{28}H_{56}N_4O_4P_2$ $(M)^+$: 574.3777; found: 574.3781.

15, 16 and 17; Reduction of 19 with LN

A 0.24 M solution of LN in THF was prepared by the addition of pieces of Li (25 mg, 3.57 mmol) to a solution of naphthalene (200 mg, 1.56 mmol) in THF (7 mL). The solution of LN thus prepared was added to a solution of TMPDA derivative **19** (155 mg, 0.27 mmol) in THF (4 mL). The reaction mixture was stirred at r.t. under argon for 6 h. H_2O (20 mL) was added and the resulting mixture was extracted with Et_2O (3 × 15 mL). The organic phase was washed with H_2O (3 × 10 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography to afford hydrocarbon **17** (28 mg, 38%), alcohol **16** (20 mg, 25%), and **15** (40 mg, 35%).

Methyl-13-ethylendioxy-14,15-dinor-*ent*-halima-1(10)-en-18-oate (22)

To a solution of compound **21** (3.71 g, 12.12 mmol) in benzene (100 mL) was added ethylene glycol (6.2 mL, 44.96 mmol) and a catalytic amount of *p*-TsOH (8 mg, 0.04 mmol). The solution was refluxed in a Dean–Stark apparatus for 16 h. The mixture was cooled and diluted with EtOAc (150 mL). The organic phase was washed with $NaHCO_3$ (6%; 3 × 25 mL), H_2O (2 × 50 mL), brine (2 × 50 mL), and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (hexane–EtOAc, 9:1) to afford dioxolane derivative **22**.

Yield: 4.08 g (96%); $[\alpha]_D^{22}$ + 49.4 (*c* 1.10, $CHCl_3$).

IR (neat): 3073, 2932, 1732, 1458, 1379, 1252, 1165, 1115 cm^{-1}.

^{1}H NMR (200 MHz): δ = 5.26 (1 H, t, *J* = 3.6 Hz, H-1), 3.86 (4 H, s, OC_2H_4O), 3.57 (3 H, s, CO_2Me), 2.69–2.52 (1 H, m, H-5), 1.25 (3 H, s, Me-16), 2.10–1.03 (13 H, m), 1.04 (3 H, s, Me-19), 0.82 (3 H, s, Me-20), 0.73 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 178.3 (C-18), 141.2 (C-10), 119.6 (C-1), 110.4 (C-13), 64.4 (OC_2H_4O), 51.5 (CO_2CH_3), 44.8 (C-4), 42.4 (C-9), 38.5 (C-5), 38.3 (C-8), 33.2 (C-12), 30.7 (C-3), 30.7 (C-11), 28.3 (C-7), 23.6 (C-16), 22.8 (C-2), 22.7 (C-6), 22.3 (C-20), 19.8 (C-19), 15.5 (C-17).

MS (EI): *m*/*z* (%) = 350 (M^+, 2), 288 (49), 235 (61), 213 (10), 175 (100), 115 (57), 87 (68).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{34}O_4$ $(M)^+$: 350.2457; found: 350.2452

13-Ethylendioxy-14,15-dinor-*ent*-halima-1(10)-en-18-ol (23)

To a stirred solution of **22** (4.05 g, 11.57 mmol) in Et_2O (115 mL) at 0 °C was added $LiAlH_4$ (485 mg, 3.95 mmol). The mixture was stirred at r.t. for 45 min, then cooled to 0 °C, and excess $LiAlH_4$ was decomposed by slow addition of wet Et_2O (120 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated to afford alcohol **23**.

Yield: 3.65 g (98%); $[\alpha]_D^{22}$ +80.9 (*c* 0.63, $CHCl_3$).

IR (neat): 3447, 3074, 2934, 1456, 1379, 1045 cm^{-1}.

^{1}H NMR (200 MHz): δ = 5.30 (1 H, t, *J* = 3.4 Hz, H-1), 3.95 (4 H, s, OC_2H_4O), 3.45 (1 H, dd, *J* = 10.6, 5.8 Hz, H_A-18), 3.25 (1 H, dd, *J* = 10.6, 7.6 Hz, H_B-18), 2.26–1.87 (5 H, m), 1.28 (3 H, s, Me-16), 1.74–1.05 (9 H, m), 0.89 (3 H, s, Me-19), 0.87 (3 H, s, Me-20), 0.82 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 141.4 (C-10), 120.0 (C-1), 110.6 (C-13), 69.3 (C-18), 64.6–64.4 (OC_2H_4O), 43.1 (C-9), 39.7 (C-5), 36.8 (C-8), 36.3 (C-4), 33.8 (C-12), 32.4 (C-3), 32.4 (C-11), 28.6 (C-7), 23.8 (C-16), 22.6 (C-6), 22.6 (C-2), 21.9 (C-19), 21.7 (C-20), 15.6 (C-17).

MS (EI): *m*/*z* (%) = 322 (M^+, 1), 260 (27), 207 (100), 173 (16), 115 (38), 87 (99).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{34}O_3$ $(M)^+$: 322.2508; found: 322.2515

13-Ethylendioxy-14,15-dinor-*ent*-halima-1(10)-en-18-al (24)

To a mixture of **23** (1.19 g, 3.70 mmol), NMO (1.50 g, 11.10 mmol), and molecular sieves (1.85 g, 500 mg/mmol) in anhyd CH_2Cl_2 (38 mL) under argon, at r.t. was added TPAP (35 mg, 0.10 mmol). The reaction mixture was stirred for 1 h and then filtered through a short pad of silica gel and celite (EtOAc). The solvent was evaporated and the residue was purified by column chromatography (hexane–EtOAc, 85:15) to afford aldehyde **24**.

Yield: 1.12 g (95%); $[\alpha]_D^{22}$ +54.69 (*c* 0.90, $CHCl_3$).

IR (neat): 3050, 2936, 2693, 1724, 1458, 1379, 1262, 1221, 1109, 1059, 949 cm^{-1}.

^{1}H NMR (200 MHz): δ = 9.40 (1 H, s, H-18), 5.33 (1 H, t, *J* = 3.6 Hz, H-1), 3.91 (4 H, s, OC_2H_4O), 2.49–2.35 (1 H, m, H-5), 2.18–2.82 (4 H, m), 1.30 (3 H, s, Me-16), 1.64–1.03 (9 H, m), 0.95 (3 H, s, Me-19), 0.87 (3 H, s, Me-20), 0.79 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 206.7 (C-18), 141.1 (C-10), 120.7 (C-1), 110.7 (C-13), 64.7 (OC_2H_4O), 48.1 (C-4), 42.9 (C-9), 39.1 (C-5), 36.1 (C-8), 33.7 (C-12), 33.2 (C-11), 28.7 (C-3), 27.8 (C-7), 23.9 (C-16), 23.2 (C-6), 22.5 (C-20), 22.5 (C-2), 17.6 (C-19), 15.8 (C-17).

MS (EI): *m*/*z* (%) = 320 (M^+, 4), 230 (27), 205 (14), 177 (26), 115 (48), 87 (100).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{32}O_3$ $(M)^+$: 320.2351; found: 320.2341.

13-Ethylendioxy-14,15-dinor-*ent*-halima-1(10)-en (25)

$NH_2NH_2{\cdot}H_2O$ (25%; 3.2 mL, 64 mmol) and KOH (846 mg, 15.08 mmol) were added to a solution of **24** (760 mg, 2.37 mmol) in diethylene glycol (21 mL) and the mixture was heated at 175 °C for 20 h. The condenser was removed and after 15 min, the mixture was warmed to 230 °C for 3.5 h. The reaction mixture was allowed to

cool to r.t., quenched with H_2O (5 mL), an aq solution of HCl (2 M, 5 mL) was added, and extracted with Et_2O (3 × 75 mL). The organic phase was washed with H_2O (3 × 50 mL) and dried over $NaSO_4$. The solvent was removed to afford **25**.

Yield: 662 mg (91%); $[\alpha]_D^{22}$ +61.4 (*c* 0.11, $CHCl_3$).

IR (neat): 3047, 2900, 2872, 1452, 1378 cm^{-1}.

^1H NMR (200 MHz): δ = 5.28 (1 H, t, *J* = 3.6 Hz, H-1), 3.93–3.88 (4 H, s, OC_2H_4O), 2.10–1.90 (3 H, m), 1.30 (3 H, s, Me-16), 1.80–0.90 (11 H, m), 0.86 (6 H, s, Me-19 and Me-20), 0.82 (3 H, s, Me-18), 0.80 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 141.7 (C-10), 120.0 (C-1), 110.8 (C-13), 64.7 (OC_2H_4O), 43.3 (C-5), 42.8 (C-9), 39.5 (C-8), 33.7 (C-3), 33.5 (C-12), 33.2 (C-11), 31.6 (C-4), 29.3 (C-7), 28.3 (C-16), 26.4 (C-19), 23.9 (C-18), 23.3 (C-6), 23.3 (C-2), 22.5 (C-20), 15.9 (C-17).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{34}O_2$ $(M)^+$: 306.2559; found: 306.2554.

20; Deprotection of 25 with *p*-TsOH

To a solution of **25** (913 mg, 2.98 mmol) in acetone (distilled over $KMnO_4$, 15 mL) was added *p*-TsOH (54 mg, 0.33 mmol). The reaction mixture was stirred for 3.33 h, diluted with H_2O (200 mL), and extracted with EtOAc (3 × 75 mL). The organic phase was washed with an aq solution of $NaHCO_3$ (6%; 3 × 50 mL), H_2O (2 × 50 mL), brine (2 × 50 mL), and dried over Na_2SO_4. The solvent was evaporated to afford **20**.

Yield: 734 mg (94%).

16-Hydroxy-14,15-dinor-*ent*-halima-1(10)-en-13-one (26)

To a solution of *i*-Pr_2NH (0.4 mL, 2.85 mmol) in THF (0.5 mL) cooled to –78 °C under an argon atmosphere was added *n*-BuLi (1.6 M in hexane; 1.7 mL, 2.72 mmol) and 2,2′-dipyridine (1 mg, 0.006 mmol). The solution was stirred for 10 min at r.t. and then cooled to –78 °C. Distilled TMSCl (1.7 mL, 13.77 mmol) was added followed by **20** (363 mg, 1.38 mmol) in THF (4 mL) via cannula. The mixture was stirred for 1 h, Et_3N (2 mL) was added, then the reaction mixture was allowed to warm to –20 °C, and stirred for an additional 2 h. After that time, the resulting mixture was diluted with an aq solution of $NaHCO_3$ (6%; 2 mL) and extracted with EtOAc (150 mL). The organic phase was washed with H_2O (3 × 25 mL), brine (2 × 25 mL), and dried over Na_2SO_4. The solvent was evaporated to afford the corresponding silyl enol ether (447 mg, 97%).

To a solution of the latter compound (103 mg, 0.31 mmol) in *t*-BuOH–THF–H_2O (7:2:1, 10 mL) was added NMO (145 mg, 1.06 mmol) and a solution of OsO_4 in *t*-BuOH (2.5%, 0.15 mL). The reaction mixture was stirred at r.t. for 30 min and a sat. aq solution of $Na_2S_2O_3$ (3 mL) was added. The reaction mixture was extracted with EtOAc (50 mL). The organic phase was washed with an aq solution of $Na_2S_2O_3$ (10%, 25 mL), an aq solution of HCl (2 M, 2 × 25 mL), H_2O (2 × 25 mL), brine (2 × 25 mL), and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography to afford hydroxy ketone **26**.

Yield: 83 mg (96%); $[\alpha]_D^{22}$ +77.0 (*c* 0.86, $CHCl_3$).

IR (neat): 3462, 3048, 2928, 1721, 1456, 1379, 1285, 1115, 1067, 849 cm^{-1}.

^1H NMR (200 MHz): δ = 5.32 (1 H, t, *J* = 3.2 Hz, H-1), 4.20 (2 H, s, H-16), 2.45–1.02 (14 H, m), 0.86 (3 H, s, Me-20), 0.84 (3 H, s, Me-19), 0.81 (3 H, s, Me-18), 0.80 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 210.3 (C-13), 140.7 (C-10), 120.7 (C-1), 68.0 (C-16), 43.4 (C-5), 42.7 (C-9), 39.1 (C-8), 33.7 (C-12), 33.3 (C-11), 32.3 (C-3), 31.4 (C-4), 29.0 (C-7), 28.2 (C-19), 25.7 (C-18), 23.5 (C-6), 23.1 (C-2), 22.3 (C-20), 15.7 (C-17).

MS (EI): *m*/*z* (%) = 278 (M^+, 2), 191 (100), 135 (17), 107 (10), 91 (11), 69 (12).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{30}O_2$ $(M)^+$: 278.2246; found: 278.2231

***ent*-Halima-1(10),13-dien-15,16-olide (1)**

To a solution of the hydroxyketone **26** (32 mg, 0.12 mmol) in benzene (2.5 mL) was added $Ph_3P{=}C{=}C{=}O$ (84 mg, 0.28 mmol), which was prepared by the addition of a solution of NaHMDS (0.6 M in toluene; 25 mL, 15.0 mmol) to $Ph_3P{=}CHCOOMe$ (5.0 g, 14.95 mmol) under argon. The reaction mixture was heated at 85 °C with stirring for 3 h, allowed to cool to r.t., and then filtered through a short pad of celite (Et_2O). The solvent was evaporated and the residue was purified by column chromatography (hexane–EtOAc, 9:1) to afford butanolide **1**.

Yield: 33 mg (91%); $[\alpha]_D^{22}$ +82.7 (*c* 0.39, $CHCl_3$).

IR (neat): 2928, 1780, 1751, 1640, 1451, 1381, 1169, 1138, 1032, 885, 853 cm^{-1}.

^1H NMR (400 MHz): δ = 5.80 (1 H, s, H-14), 5.39–5.36 (1 H, m, H-1), 4.71 (2 H, s, H-16), 2.30–2.10 (1 H, m, H_A-12), 2.10–1.90 (2 H, m, H-2), 2.00–1.90 (1 H, m), 1.70–1.50 (3 H, m, H-5, H-8, H_A-6), 1.45–1.35 (1 H, m, H_B-12), 1.45–1.10 (5 H, m), 1.30–1.20 (1 H, m, H_B-6), 0.93 (3 H, s, Me-20), 0.86 (3 H, s, Me-19), 0.84 (3 H, s, Me-18), 0.83 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (100 MHz): δ = 174.1 (C-15), 171.5 (C-13), 140.5 (C-10), 120.9 (C-1), 114.9 (C-14), 73.0 (C-16), 43.6 (C-5), 43.0 (C-9), 39.0 (C-8), 36.2 (C-11), 33.1 (C-3), 31.4 (C-4), 29.0 (C-7), 28.1 (C-19), 25.9 (C-18), 23.6 (C-12), 23.5 (C-6), 23.0 (C-2), 22.1 (C-20), 15.6 (C-17).

MS (EI): *m*/*z* (%) = 302 (M^+, 1), 191 (37), 135 (28), 107 (33), 91 (62).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{30}O_2$ $(M)^+$: 302.2245; found: 302.2270.

UV (EtOH): λ = 210 nm.

***ent*-Halima-5(10),13-dien-15,16-olide (2)**

To a solution of butanolide **1** (25 mg, 0.08 mmol) in benzene (8.3 mL) was added I_2 (106 mg, 0.05 M). The reaction was heated at 85 °C with stirring for 16 h, allowed to cool to r.t., and extracted with Et_2O (40 mL). The organic phase was washed with an aq solution of $NaHSO_3$ (10%; 3 × 10 mL), an aq solution of $NaHCO_3$ (6%; 3 × 10 mL), H_2O (3 × 10 mL), and dried over Na_2SO_4. The solvent was evaporated to afford butanolide **2**.

Yield: 25 mg (99%); $[\alpha]_D^{22}$ + 14.3 (*c* 0.81, $CHCl_3$).

IR (neat): 2926, 2868, 1778, 1753, 1638, 1462, 1381, 1360, 1169, 1130, 1034, 885, 853 cm^{-1}.

^1H NMR (200 MHz): δ = 5.83 (1 H, s, H-14), 4.74 (2 H, s, H-16), 2.40–1.10 (15 H, m), 0.99 (3 H, s, Me-20), 0.97 (3 H, s, Me-19), 0.87 (3 H, s, Me-18), 0.86 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (50 MHz): δ = 173.9 (C-15), 171.2 (C-13), 138.6 (C-5), 131.3 (C-10), 115.0 (C-14), 73.0 (C-16), 40.8 (C-9), 39.9 (C-3), 34.6 (C-4), 33.8 (C-8), 33.6 (C-11), 29.6 (C-19), 27.6 (C-18), 27.1 (C-7), 25.8 (C-6), 25.2 (C-1), 23.7 (C-12), 20.9 (C-20), 19.9 (C-2), 16.0 (C-17).

MS (EI): *m*/*z* (%) = 302 (M^+, 1), 287 (1), 274 (1), 227 (8), 191 (60), 171 (8), 135 (8), 121 (7), 105 (9), 91 (14), 69 (20), 55 (60), 43 (80), 41 (100).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{30}O_2$ $(M)^+$: 302.2245, found: 302.2252.

UV (EtOH): λ = 207 nm.

16-Hydroxy-*ent*-halima-1(10),13-dien-15,16-olide (27)

To a solution of *i*-Pr_2NH (0.3 mL, 1.43 mmol) in THF (1 mL) cooled to –78 °C under argon was added *n*-BuLi (1.6 M in hexane;

0.7 mL, 1.13 mmol) and 2,2′-dipyridine (1 mg, 0.006 mmol). The solution was stirred for 10 min at r.t. and then cooled to –78 °C. TBDMSTf (0.3 mL, 1.3 mmol) was added followed by **1** (34 mg, 0.11 mmol) in THF (2 mL) via cannula. The mixture was stirred for 1 h, Et_3N (2 mL) was added, then the reaction mixture was allowed to warm to –20 °C, and stirred for an additional 2 h. After this time, the resulting mixture was diluted with an aq solution of $NaHCO_3$ (6%; 1 mL) and extracted with EtOAc (150 mL). The organic phase was washed with H_2O (2 × 25 mL), brine (2 × 25 mL), and dried over Na_2SO_4. The solvent was evaporated to afford the corresponding 2-trialkylsilyloxyfuran derivative (102 mg, 94%).

A solution of MCPBA (20 mg, 0.11 mmol) in anhyd CH_2Cl_2 (2 mL) was added to an ice-cooled solution of the later compound (46 mg, 0.11 mmol) in anhyd CH_2Cl_2 (1 mL). The reaction mixture was stirred for 4 h, diluted with H_2O (20 mL), and extracted with Et_2O (3 × 30 mL). The organic phase was washed with an aq solution of $NaHCO_3$ (6%; 3 × 10 mL), H_2O (2 × 10 mL), brine (2 × 10 mL), and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (hexane–EtOAc, 85:15) to afford γ-hydroxybutanolide **27**.

Yield: 26 mg (77%).

IR (neat): 3372, 2930, 2872, 1742, 1468, 1381, 1254, 1138, 953 cm^{-1}.

^1H NMR (400 MHz): δ = 6.00 (1 H, br s, H-16), 5.83 (1 H, br s, H-14), 5.40–5.36 (1 H, m, H-1), 2.40–1.10 (14 H, m), 0.94 (3 H, s, Me-20), 0.87 (3 H, s, Me-19), 0.85 (3 H, s, Me-18), 0.84 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (100 MHz): δ = 170.9 (C-15), 170.3 (C-13), 140.6 (C-10), 120.8/120.9 (C-1), 117.1 (C-14), 98.7 (C-16), 43.5 (C-5), 42.9 (C-9), 39.1 (C-8), 35.7/35.8 (C-11), 33.1/33.2 (C-3), 31.4 (C-4), 29.0 (C-7), 28.1 (C-19), 25.8/25.9 (C-18), 23.5 (C-6), 23.0 (C-2), 22.7 (C-12), 22.2 (C-20), 15.6 (C-17).

MS (EI): *m*/*z* (%) = 318 (M^+ – 1, 8), 301 (10), 191 (100), 135 (80), 121 (70), 107 (85), 91 (98), 69 (99), 55 (98).

16-Hydroxy-*ent*-halima-5(10),13-dien-15,16-olide (3)

γ-Hydroxybutanolide **27** (12 mg, 0.038 mmol) was treated with HI (0.05 M in benzene; 2 mL). The reaction was heated at 85 °C and stirred for 4 h. It was allowed to cool to r.t. and extracted with Et_2O (40 mL). The organic phase was washed with an aq solution of $NaHSO_3$ (10%, 3 × 10 mL), an aq solution of $NaHCO_3$ (6%; 3 × 10 mL), H_2O (3 × 10 mL), and dried over Na_2SO_4. The solvent was evaporated to afford γ-hydroxybutanolide **3**.

Yield: 12 mg (99%); $[\alpha]_D^{22}$ +22.8 (*c* 0.49, $CHCl_3$).

IR (neat): 3354, 2926, 1744, 1458, 1134, 951 cm^{-1}.

^1H NMR (400 MHz): δ = 5.98 (1 H, br s, H-16), 5.85 (1 H, br s, H-14), 2.45–2.10 (2 H, m), 2.05–1.90 (4 H, m), 1.70–1.10 (9 H, m), 0.99 (3 H, s, Me-20), 0.97 (3 H, s, Me-19), 0.87 (3 H, s, Me-18), 0.86 (3 H, d, *J* = 7.0 Hz, Me-17).

^{13}C NMR (100 MHz): δ = 171.6 (C-15), 170.7 (C-13), 16.1 (C-17), 138.4/138.5 (C-5), 131.3 (C-10), 117.1 (C-14), 98.5 (C-16), 40.6 (C-9), 39.8 (C-3), 34.5 (C-4), 33.7 (C-8), 32.8/32.9 (C-11), 29.2 (C-19), 27.6 (C-18), 27.0 (C-7), 25.6/25.7 (C-6), 25.2 (C-1), 22.6 (C-12), 20.9 (C-20), 19.8 (C-2).

MS (EI): *m*/*z* (%) = 256 [M^+ – (HOH + CO_2), 15], 191 (30), 149 (58), 128 (14), 105 (40), 77 (78).

MS (FAB): *m*/*z* (%) = 301 [M^+ + 1 – (HOH), 15], 191 (38), 95 (45), 69 (77).

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