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ent-Hydrohalimic acid transformations: synthesis of a diterpenic bislactone

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Abstract—A new diterpenic lactone has been synthesized starting from *ent*-hydrohalimic acid and its biological activity has been tested.

1. Introduction

In the course of our studies on the chemical constitution of Portuguese *Halimium* species, we have isolated from the aerial parts of *Halimium viscosum* (Wilk) P. da Silva, several bicyclic diterpenes, with either labdane or *ent*-halimane[1–5] skeletons along with several tricyclic diterpenic compounds belonging to the valparane or valparolane[6,7] class. Some minor components possess rearranged skeletons of the covilanone type.[8]

We are involved in the transformation of the main compounds obtained from the *Halimium* genus into biologically active compounds,[9] thus providing added value to areas of our region unsuitable for the production of other crops.

Our group has recently reported the transformation of *ent*-halimic acid into biologically active compounds such as, hydroxybutenolide **I**[9] with antifeedant activity, or biologically active *ent*-halimanolides such as **II**.[10,11] In order to do SAR studies on this kind of compound we decided to synthesize the bislactone **1** (Fig. 1). Our strategy was threefold: to conformationally constrain and deactivate the ester moiety of **I**, to further rigidify the decalin ring system (which has been shown in similar system, to have some conformational mobility) and to maintain the α,β-unsaturated lactone moiety, which could be used to produce a wide range of derivatives.

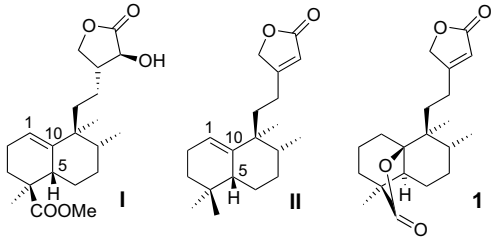

Figure 1.

2. Results and discussion

The major component of *Halimium viscosum* (Celorico da Beira) is *ent*-hydrohalimic acid (15-hydroxy-*ent*-halim-1(10)-en-18-oic acid) **3**,[1] which has been previously described and whose stereochemistry was proposed based upon comparison the $[\alpha]_D$ values between the methyl ester derivative of **3** and hydrogenated *ent*-halimic acid. Now we have established the absolute stereochemistry of **3** by X-ray diffraction[12] studies, as shown in Figure 2.

The retrosynthetic analysis for the synthesis of compound **1**, starting from *ent*-hydrohalimic acid **3**, is shown in Scheme 1. It requires the use of a Bestman ketene for the butenolide ring-formation via intermediate **2**, that

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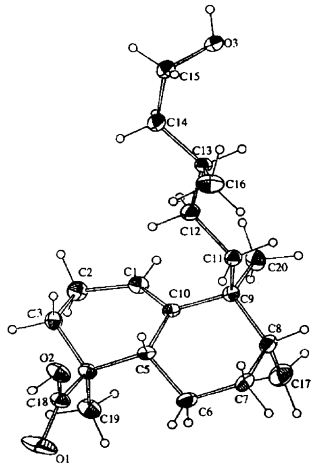
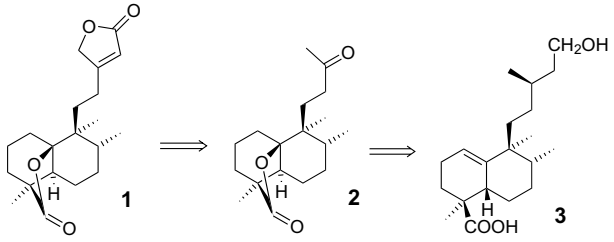


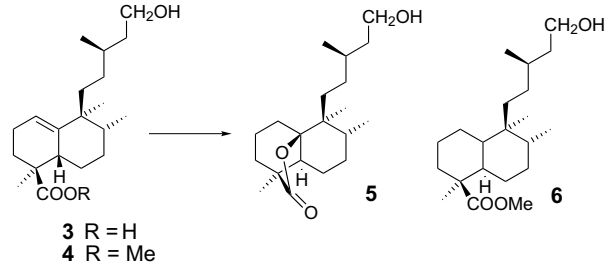
Figure 2. ORTEP view of *ent*- hydrohalimic acid **3**.



Scheme 1.

already has a suitably degraded side chain and the annular lactone ring.

Our initial studies were focused on the preparation of butenolide **5**, which we anticipated would proceed via acid catalyzed or iodine-mediated oxidative cyclization of ester **4** or and **3**. However, attempted cyclization of **4** under either set of conditions (Scheme 2) gave rise mainly to isomeric olefin **6**. Attempted iodolactonization of **3** gave rise to **5** as the major product; since no iodine was incorporated in the product, we attempted the acid-mediated cyclization of **3** and found that the yield improved still further to almost quantitative levels. The change of stereochemistry at C5 that accompanied this cyclization was established by X-ray crystallography as discussed below.



Conditions	Starting material	5	6
I_2 / benzene reflux	**3**	93%	
HI (57%) / $CHCl_3$, reflux	**3**	99%	
I_2 / benzene reflux	**4**	2%	90%
HI (57%) / $CHCl_3$, reflux	**4**	19%	72%

Scheme 2.

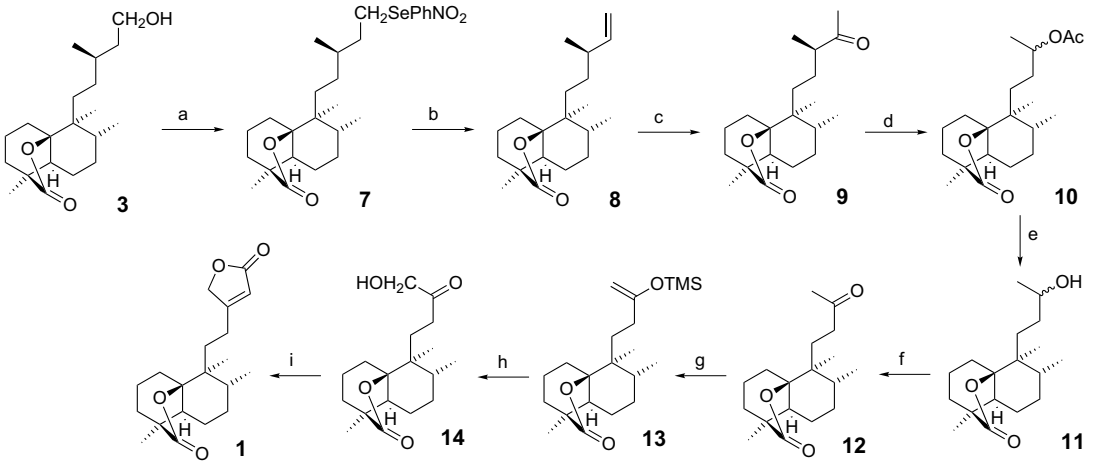
With compound **5** available to us, in gram quantities we decided to continue our route to bislactone **1**. The synthesis was carried out as depicted in Scheme 3. The transformation of **3** into **7** was carried out with *o*-nitrophenylselenocyanate.[13] X-ray diffraction studies[14] on this compound (Fig. 3) confirmed the β-relationship between the lactone ring formed by HI treatment and the α-stereochemistry of H-5, the inverse configuration with respect to the same hydrogen in *ent*-hydrohalimic acid **3**.

Oxidation of **7** with H_2O_2[15] gives olefin **8**, which after Wacker[16] oxidation afford methylketone **9**. The side-chain degradation was done by a Baeyer–Williger oxidation[17] with *m*-CPBA leading to the acetyl derivative **10**. Subsequent alkaline hydrolysis with Na_2CO_3 gives **11**, which was further oxidized with PCC[18] to afford ketone **2**. After treatment with LDA and TMSCl this ketone gives **12** oxidized in the presence of *m*-CPBA[19] to obtain hydroxyketone **13**. The reaction of the latter with Bestmann[20] ketene gives the desired bislactone **1**.

Compound **1**, and intermediates **7** to **14** has been tested against cytotoxicity in a wide range of biological assays, including a broad antifungal and antibacterial, antiviral assays against HIV, RSV, and influenza viruses, receptor based assays against CNS targets such as neurotransmitter uptake site Gly-1,VR1, Nac, and GABA-B receptors, and metabolic targets such as MC-4, and gastrointestinal targets such as GHSR. Compound **1** was further evaluated a wide range of oncology targets α2, D2, 5HT, or NPY5, others neurotransmitter uptake sites, signal transduction protein such as CCR2B or CRF1, and some enzymes such as BACE (implicated in Alzheimer's disease). However in all of these, and in one in vivo histone acetyl transferase assay, no activity was observed for any compound. This is in striking contrast to many similar compounds (e.g., dysidiolide,[21] etc.). We speculate that this may be due to locking of the butenolide side-chain equatorial as it has been previously suggested that an axial disposition may be required for the activity of some of these related compounds.

3. Experimental

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra were recorded on a MATTSON–GENESIS II FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were performed in deuterochloroform and referenced to the residual peak of $CHCl_3$ at δ 7.26 and 77.0 ppm, for ^1H and ^{13}C, respectively, at a Bruker WP-200 SY and a Bruker DRX 400 MHz. Chemical shifts are reported in δ ppm and



Scheme 3. Reagents and conditions: (a) *o*-$NO_2PhSeCN$/TBF, 92%; (b) H_2O_2/THF, 94%; (c) $PdCl_2/CuCl/O_2$/DMF, 89%; (d) *m*-CPBA/CH_2Cl_2, 79%; (e) K_2CO_3/MeOH, 95%; (f) PCC/CH_2Cl_2; (g) LDA/TMSCl, 63%; (h) *m*-CPBA/CH_2Cl_2, 50%; (i) $Ph_3P{=}C{=}C{=}O$/toluene, 75%.

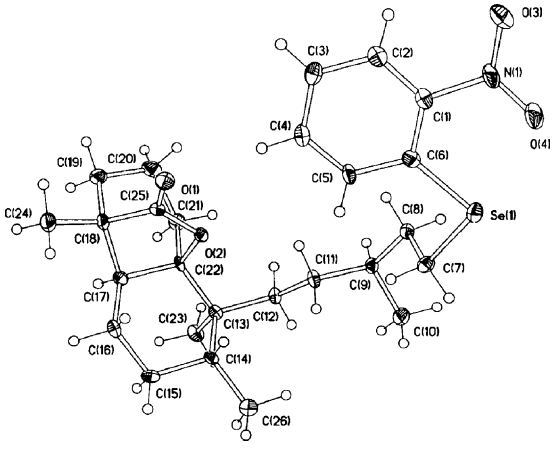


Figure 3. ORTEP view of compound **7**.

coupling constants (*J*) are given in Hz. MS were performed at a VG-TS 250 spectrometer at 70 eV ionizing 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). Optical rotations were determined at a digital ADP 220 polarimeter in 1 dm cells. Crystallographic data were obtained with Seifert XRD 3000 S diffractometer. Diethyl ether, THF, and benzene were distilled from sodium, and pyridine and dichloromethane were distilled from calcium hydride under an Ar atmosphere.

The raw material **3** was isolated from a hexane extract of *Halimium viscosum* as reported in Ref. 1.

3.1. Reaction of 3 with iodine: synthesis of 5

To a solution of **3** (1.0 g, 3.11 mmol) in benzene (45 mL) was added I_2 (3.5 g, 15.55 mmol). The reaction mixture was refluxed during 20 h. After cooling the solvent was evaporated, water added (50 mL) and extracted with ether (3×50 mL). The organic phase was washed with 10% $NaHSO_3$, 6% $NaHCO_3$, and water (until neutral); dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The crude product was chromatographed through silica gel yielding with hexane/EtOAc 8:2, 931 mg (93%) of **5**.

3.2. Reaction of 3 with HI: synthesis of 5

To a solution of **3** (1.0 g, 3.11 mmol) in benzene (50 mL) was added 2 mL a solution (57%) of HI (1.9 g, 15.16 mmol). The reaction mixture was refluxed during 5 h. After cooling the solvent was evaporated and added water (50 mL). The products reaction was extracted with ether (3×50 mL) and the organic phase washed with 10% $NaHSO_3$, 6% $NaHCO_3$, water, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The crude product was chromatographed through silica gel, to give with hexane/EtOAc 8:2, 1.0 g (99%) of **5**.

3.2.1. 5-*epi*-15-Hydroxy-*ent*-haliman-18,10β-olide, 5. $[\alpha]_D^{22} = -24.6$ (*c* 0.90, $CHCl_3$). IR ν_{max}^{film}: 3435, 2931, 2875, 1768, 1452, 1382, 1265, 1198, 1165, 1182, 1131, 1056, 1026, 942 cm^{-1}. ^1H NMR ($CDCl_3$): 3.67 (2H, m, H-15), 2.08 (2H, dd, $J_1 = 11.7$ Hz, $J_2 = 3.1$ Hz, H-1), 1.90–1.00 (18H, m), 1,07 (3H, s, Me-19), 0.87 (3H, d, $J = 6.3$ Hz, Me-16), 0.82 (3H, d, $J = 6.7$ Hz, Me-17), 0.73 (3H, s, Me-20). ^{13}C NMR ($CDCl_3$): 29.2 (C-1); 20.1 (C-2); 34.7 (C-3); 49.6 (C-4); 49.4 (C-5); 25.7 (C-6); 27.9 (C-7); 32.4 (C-8); 40.4 (C-9); 89.5 (C-10); 33.3 (C-11); 31.6 (C-12); 30.7 (C-13); 39.8 (C-14); 61.0 (C-15); 19.8 (C-16); 16.2 (C-17); 181.5 (C-18); 16.8 (C-19); 17.0 (C-20). MS, *m*/*z*: 322 ($[M]^+$, 1), 279 (1), 261 (1), 249 (2), 221 (16), 207 (2), 193 (3), 177 (24), 175 (7), 163 (4), 149 (16), 135 (6), 122 (20), 109 (20), 107 (20), 95 (31), 93 (27), 81 (40), 79 (33), 69 (42), 67 (55), 55 (100), 43 (52), 41 (19). HRMS calcd for $C_{20}H_{34}O_3$: 322.2508; found 322.2520.

3.3. Reaction of 4 with iodine: synthesis of 5 and 6

To a solution of **4** (1.0 g, 3.01 mmol) in benzene (45 mL) was added I_2 (3.8 g, 15.05 mmol). The reaction mixture

was refluxed for 20 h. After cooling the solvent was evaporated, water added (50 mL), and extracted with ether (3×50 mL). The organic phase was washed with 10% $NaHSO_3$, 6% $NaHCO_3$, and water (until neutral); dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The crude product was chromatographed with hexane/EtOAc 8:2, to give 19 mg (2%) of **5** and 910 mg (90%) of **6**.

3.4. Reaction of 4 with HI: synthesis of 5 and 6

To a solution of **4** (1.0 g, 2.98 mmol) in benzene (50 mL) was added 2 mL to a solution, 57%, of HI (1.9 g, 15.16 mmol). The reaction mixture was refluxed during 5 h. After cooling the solvent was evaporated, water added (50 mL) and extracted with ether. The organic phase was washed with 10% $NaHSO_3$, 6% $NaHCO_3$ and water, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The crude product was chromatographed through silica gel, eluted with hexane/EtOAc 8:2 afforded 189 mg (19%) of **5** and 651 mg (72%) of **6**.

3.4.1. Methyl 15-hydroxy-*ent*-halim-5(10)-en-18-oate, 6. $[\alpha]_D^{22} = -32.2$ (*c* 0.25, $CHCl_3$). IR ν_{max}^{film}: 3430, 2931, 2875, 1732, 1460, 1433, 1377, 1250, 1188, 1081, 1057, 1007 cm^{-1}. ^1H NMR ($CDCl_3$): 3.66 (2H, m, H-15), 3.63 (3H, s, COOMe), 2.10–1.20 (17H, m), 1,26 (3H, s, Me-19), 1.17–0.91 (2H, m), 0.88 (3H, d, $J = 6.3$ Hz, Me-16), 0.80 (3H, d, $J = 7.3$ Hz, Me-17), 0.79 (3H, s, Me-20). ^{13}C NMR ($CDCl_3$): 25.0 (C-1); 19.4 (C-2); 35.2 (C-3); 47.4 (C-4); 131.0 (C-5); 25.9 (C-6); 26.7 (C-7); 33.2 (C-8); 40.6 (C-9); 135.9 (C-10); 33.5 (C-11); 30.5 (C-12); 30.8 (C-13); 40.1 (C-14); 60.9 (C-15); 19.6 (C-16); 15.9 (C-17); 178.5 (C-18); 22.9 (C-19); 20.8 (C-20), 51.7 ($COOCH_3$). MS, *m/z*: 336 ($[M]^+$, 1), 277 (3), 235 (42), 203 (2), 175 (100), 161 (9), 147 (7), 133 (11), 119 (19), 105 (18), 91 (10), 81 (7), 69 (9), 55 (40), 41 (33). HRMS calcd for $C_{21}H_{38}O_3$: 338.2821; found 338.2832.

3.5. Reaction of 5: synthesis of 7

To a solution of **5** (1.0 g, 3.14 mmol) in dry THF (10 mL) was added *o*-nitrophenylselenocyanate (8.9 g, 3.77 mmol) and stirred under inert atmosphere for 20 min at 48 °C. TBF (760 mg, 3.77 mmol) was added to reactional mixture, stirred for 48 min, the solvent was removed at reduced pressure and the residue chromatographed yielding with hexane/EtOAc 9:1, 1.46 g (92%) of **7**.

3.5.1. 5-*epi*-15-*o*-Nitrophenylseleno-*ent*-haliman-18,10β-olide, 7. Mp 127–128 °C. $[\alpha]_D^{22} = -20.3$ (*c* 1.48, $CHCl_3$). IR ν_{max}^{film}: 3512, 3072, 2979, 1590, 1566, 1198, 1127, 1048, 1026, 972, 943, 921, 850, 789, 737 cm^{-1}. ^1H NMR ($CDCl_3$): 8.26 (1H, d, $J = 8.2$ Hz, H-3′), 7.55 (2H, m, H-4′ and H-5′), 7.28 (1H, m, H-6′), 2.98 (1H, m, H-15a), 2.91 (1H, m, H-15b), 2.07 (2H, dd, $J_1 = 11.7$ Hz, $J_2 = 3.1$ Hz, H-1), 1.90–1.05 (17H, m), 1.06 (3H, s, Me-19), 0.96 (3H, d, $J = 6.4$ Hz, Me-16), 0.83 (3H, d, $J = 6.8$ Hz, Me-17), 0.75 (3H, s, Me-20). ^{13}C NMR ($CDCl_3$): 29.0 (C-1); 19.9 (C-2); 34.5 (C-3); 49.3 (C-4); 49.2 (C-5); 25.5 (C-6); 27.8 (C-7); 32.0 (C-8); 40.2 (C-9); 89.2 (C-10); 33.3 (C-11); 31.7 (C-12); 34.6 (C-13); 34.7 (C-14); 23.8 (C-15); 19.3 (C-16); 16.0 (C-17); 181.1 (C-18); 16.8 (C-19); 16.8 (C-20), 134.0 (C-1′), 146.6 (C-2′), 126.3 (C-3′), 129.1 (C-4′), 133.7 (C-5′), 125.1 (C-6′). HRMS calcd for $C_{26}H_{37}NO_4Se$: 507.1888; found 507.1892.

3.6. Oxidation of 7 with H_2O_2: synthesis of 8

To a solution of **7** (1.0 g, 1.98 mmol) in THF (7 mL) was added 30% H_2O_2 (0.40 mL, 134 mg, 3.96 mmol) and stirred for 12 h. The solvent was evaporated at reduced pressure and the crude product chromatographed yielding with hexane/EtOAc 95:5, 566 mg (94%) of **8**.

3.6.1. 5-*epi*-*ent*-Halim-14-en-18,10β-olide, 8. $[\alpha]_D^{22} = -27.5$ (*c* 0.80, $CHCl_3$). IR ν_{max}^{film}: 3076, 2955, 2936, 2875, 1771, 1640, 1452, 1382, 1263, 1196, 1165, 1125, 1025, 996, 941, 923 cm^{-1}. ^1H NMR ($CDCl_3$): 5.68 (1H, ddd, $J_1 = 17.3$ Hz, $J_2 = 10.3$ Hz, $J_3 = 7.7$ Hz, H-14), 4.97 (1H, ddd, $J_1 = 17.3$ Hz, $J_2 = 2.1$ Hz, $J_3 = 0.9$ Hz, H-15a), 4.87 (1H, ddd, $J_1 = 10.3$ Hz, $J_2 = 2.1$ Hz, $J_3 = 1.0$ Hz, H-15b), 2.07 (2H, dd, $J_1 = 11.7$ Hz, $J_2 = 3.1$ Hz, H-1), 2.00–1.04 (15H, m), 1.06 (3H, s, Me-19), 0.98 (3H, d, $J = 6.7$ Hz, Me-16), 0.80 (3H, d, $J = 6.8$ Hz, Me-17), 0.73 (3H, s, Me-20). ^{13}C NMR ($CDCl_3$): 29.2 (C-1); 20.1 (C-2); 34.7 (C-3); 49.6 (C-4); 49.4 (C-5); 25.8 (C-6); 28.0 (C-7); 32.5 (C-8); 40.4 (C-9); 89.5 (C-10); 33.6 (C-11); 31.4 (C-12); 39.3 (C-13); 145.0 (C-14); 112.7 (C-15); 20.6 (C-16); 16.2 (C-17); 181.4 (C-18); 16.8 (C-19); 17.1 (C-20). MS, *m/z*: 304 ($[M]^+$, <1), 289 (0.8), 276 (0.9), 261 (2), 249 (3), 243 (3), 222 (86), 221 (46), 207 (11), 193 (8), 177 (83), 161 (8), 149 (25), 135 (14), 122 (35), 109 (52), 95 (75), 93 (43), 81 (68), 79 (41), 69 (62), 67 (72), 55 (100). HRMS calcd for $C_{20}H_{32}O_2$: 304.2402; found 304.2413.

3.7. WACKER oxidation of 8: synthesis of 9

To a solution of $PdCl_2$ (128 mg, 0.72 mmol) and CuCl (3.6 g, 3.60 mmol) in DMF (10 mL) and H_2O (1 mL) was activated for 30 min with O_2. A solution of **8** (1.1 g, 3.62 mmol) in DMF (8 mL) was added and stirred with O_2 atmosphere at room temperature for 36 h. Then was added a cool solution of 3 N HCl, extracted with CH_2Cl_2 (3×30 mL), and washed successively with 10% $NaHCO_3$ and water, dried, filtered, evaporated, and chromatographed gave (hexane/EtOAc 9:1) 1.0 g (89%) of **9**.

3.7.1. 5-*epi*-14-Oxo-*ent*-haliman-18,10β-olide, 9. $[\alpha]_D^{22} = -26.4$ (*c* 0.76, $CHCl_3$). IR ν_{max}^{film}: 2960, 2939, 1762, 1711, 1458, 1379, 1358, 1265, 1248, 1198, 1167, 1026, 941 cm^{-1}. ^1H NMR ($CDCl_3$): 2.35 (1H, sex, $J = 7.1$ Hz, H-13), 2.12 (3H, s, H-15), 2.09–1.12 (16H, m), 1.07 (3H,

d, $J = 6.8$ Hz, Me-16), 1.05 (3H, s, Me-19), 0.81 (3H, d, $J = 6.8$ Hz, Me-17), 0.72 (3H, s, Me-20). ^{13}C NMR ($CDCl_3$): 29.0 (C-1); 19.9 (C-2); 34.5 (C-3); 49.3 (C-4); 49.2 (C-5); 25.5 (C-6); 27.7 (C-7); 32.0 (C-8); 40.2 (C-9); 89.1 (C-10); 33.1 (C-11); 28.0 (C-12); 48.4 (C-13); 213.3 (C-14); 27.3 (C-15); 16.0 (C-16); 16.2 (C-17); 181.0 (C-18); 16.8 (C-19); 16.2 (C-20). MS, m/z: 320 ([M]$^+$, 1), 292 (2), 277 (4), 259 (3), 249 (69), 231 (9), 221 (30), 203 (29), 193 (12), 177 (49), 161 (13), 149 (30), 135 (12), 122 (20), 121 (26), 119 (27), 109 (34), 99 (47), 95 (54), 93 (48), 81 (59), 79 (55), 69 (52), 67 (73), 55 (100). HRMS calcd for $C_{20}H_{32}O_3$: 320.2351; found 320.2362.

3.8. Treatment of 9 with *m*-CPBA: synthesis of 10

Compound **9** (500 mg, 1.49 mmol) was dissolved in CH_2Cl_2 (10 mL) and *m*-CPBA (935 mg, 2.98 mmol) was added. The mixture was stirred at 40 °C and monitored by TLC. After 24 h the reaction was complete and the solvent evaporated. Work-up afforded 480 mg of crude product that after chromatography on silica gel gave 470 mg (79%) of **10** in the hexane/EtOAc 9:1 fractions.

3.8.1. 5-*epi*-13-Acetoxy-14,15-di-*nor*-*ent*-haliman-18,10β-olide, 10. $[\alpha]_D^{22} = -25.0$ (*c* 0.48, $CHCl_3$). IR ν_{max}^{film}: 2973, 2938, 2878, 1768, 1736, 1452, 1374, 1246, 1198, 1127, 1054, 1016, 952 cm^{-1}. ^{1}H NMR ($CDCl_3$): 4.73 (1H, sex, $J = 6.1$ Hz, H-13), 1.97 (3H, s, Me-15), 1.88–1.00 (16H, m), 1.14 (3H, d, $J = 6.1$ Hz, Me-16), 1.01 (3H, s, Me-19), 0.70 (3H, s, Me-20). ^{13}C NMR ($CDCl_3$): 28.9 (C-1); 19.9 (C-2); 34.6 (C-3); 49.4 (C-4); 49.2 (C-5); 25.6 (C-6); 27.8 (C-7); 31.8 (C-8); 40.1 (C-9); 89.1 (C-10); 30.8 (C-11); 31.2 (C-12); 72.1 (C-13); 19.8 (C-16); 15.8 (C-17); 181.1 (C-18); 16.9 (C-19); 16.9 (C-20); 170.9 (OOCMe), 21.4 (OOCCH_3). MS, m/z: 334 ([M]$^+$, <0.8), 302 (2), 263 (5), 211 (8), 179 (37), 124 (32), 109 (100), 105 (20), 95 (16), 93 (16), 91 (32), 81 (26), 79 (32), 77 (17), 69 (26), 67 (17), 59 (12), 55 (30). HRMS calcd for $C_{20}H_{32}O_4$: 336.2301; found 336.2313.

3.9. Alkaline hydrolysis of 10: synthesis 11

To a solution of **10** (455 mg, 1.35 mmol) in methanol (45 mL) was added K_2CO_3 (43 mg). The reaction mixture was stirred at room temperature for 3 h, water was added, and the mixture extracted with ether washed with 2 N HCl and H_2O, dried, filtered, and evaporated yielding 375 mg (95%) of **11**.

3.9.1. 5-*epi*-14,15-Di-*nor*-13-hydroxy-*ent*-haliman-18,10β-olide, 11. $[\alpha]_D^{22} = -13.4$ (*c* 0.89, $CHCl_3$). IR ν_{max}^{film}: 3419, 2960, 2878, 1764, 1453, 1381, 1283, 1264, 1198, 1166, 1131, 943, 755 cm^{-1}. ^{1}H NMR ($CDCl_3$): 3.63 (1H, sext, $J = 6.1$ Hz, H-13), 2.09 (2H, d, $J = 11.8$ Hz, H-1), 1.90–1.00 (15H, m), 1.19 (3H, d, $J = 6.1$ Hz, Me-16), 1.07 (3H, s, Me-19), 0.83 (3H, d, $J = 6.7$ Hz, Me-17), 0.76 (3H, s, Me-20). ^{13}C NMR ($CDCl_3$): 28.9 (C-1); 19.8 (C-2); 34.4 (C-3); 49.3 (C-4); 49.2 (C-5); 25.5 (C-6); 27.7 (C-7); 31.9 (C-8); 40.0 (C-9); 89.3 (C-10); 31.6 (C-11); 34.1 (C-12); 69.2 (C-13); 23.2 (C-16); 15.9 (C-17); 181.3 (C-18); 16.8 (C-19); 16.8 (C-20). MS, m/z: 294 ([M]$^+$, <1), 276 (0.8), 261 (0.6), 248 (1), 221 (12), 205 (1), 193 (3), 177 (32), 163 (8), 149 (17), 133 (8), 122 (30), 107 (31), 95 (39), 81 (52), 67 (73), 55 (100), 45 (90), 41 (88). HRMS calcd for $C_{18}H_{30}O_3$: 294.2145; found 294.2156.

3.10. Oxidation of 11 with PCC: synthesis of 12

To a stirred suspension of powdered molecular sieves (4 Å) and PCC (1.7 g, 7.74 mmol) in dry CH_2Cl_2 (30 mL) was added **11** (758 mg, 2.58 mmol). The reaction mixture was stirred at 40 °C for 1 h. The reaction mixture was cooled to room temperature, was added ether (250 mL), the mixture was filtered through a pad of Florisil, and concentrated. It was obtained 640 mg (85%) of **12**.

3.10.1. 5-*epi*-14,15-Di-*nor*-13-oxo-*ent*-haliman-18,10β-olide, 12. $[\alpha]_D^{22} = -18.4$ (*c* 0.76, $CHCl_3$). IR ν_{max}^{film}: 2935, 2878, 2863, 1770, 1716, 1450, 1419, 1378, 1262, 1197, 1168, 1026, 940 cm^{-1}. ^{1}H NMR ($CDCl_3$): 2.91 (1H, ddd, $J_1 = 15.5$ Hz, $J_2 = 11.0$ Hz, $J_3 = 5.4$ Hz, H-12a), 2.35 (1H, ddd, $J_1 = 15.5$ Hz, $J_2 = 8.9$ Hz, $J_3 = 7.5$ Hz, H-12b), 2.13 (3H, s, Me-16), 2.00–1.05 (14H, m), 1.04 (3H, s, Me-19), 0.78 (3H, d, $J = 6.7$ Hz, Me-17), 0.76 (3H, s, Me-20). ^{13}C NMR ($CDCl_3$): 28.9 (C-1); 20.0 (C-2); 34.7 (C-3); 49.5 (C-4); 49.3 (C-5); 25.7 (C-6); 27.8 (C-7); 31.2 (C-8); 40.1 (C-9); 89.3 (C-10); 28.3 (C-11); 39.1 (C-12); 209.8 (C-13); 30.5 (C-16); 15.8 (C-17); 181.1 (C-18); 17.5 (C-19); 17.0 (C-20). MS, m/z: 292 ([M]$^+$, 6), 274 (11), 259 (5), 249 (28), 231 (36), 222 (56), 221 (48), 213 (11), 204 (18), 193 (15), 189 (17), 177 (83), 161 (17), 149 (50), 133 (21), 121 (54), 107 (51), 95 (65), 93 (57), 81 (56), 79 (50), 69 (39), 67 (58), 55 (76), 43 (100), 41 (77). HRMS calcd for $C_{18}H_{28}O_3$: 292.2038; found 292.2050.

3.11. Reaction of 12 with LDA/TMSCl: synthesis of 13

A mixture of LDA (0.8 mL, 5.68 mmol), 2 mL of dry THF, 1.8 mL of BuLi (1.36 mmol) and 0.5 mL of 2,2′-dipyridine, under argon atmosphere and at −75 °C was stirred during 5 min. The mixture was warmed till room temperature and 10 min later the solution become pink. It was then cooled to −78 °C again and it was added 1.8 mL of TMSCl (6.9 mmol) and the compound **12** (621 mg, 213 mmol). The reaction mixture was stirred for 1 h and it was warmed to −20 °C and 4 mL of triethylamine was added and reacted during 2 h. After was added 5 mL of a solution 6% $NaHCO_3$, extracted with EtOAc (3 × 15 mL), the organic phase was washed with a saturated solution of NaCl and water; dried over anhydrous Na_2SO_4, filtered, and the solvent evaporated. The crude product was chromatographed through silica gel yielding with hexane/EtOAc 9:1, 488 mg (63%) of **13**.

3.11.1. 5-*epi*-14,15-Di-*nor*-13-trimethylsililoxy-*ent*-halim-13(16)-en-18,10β-olide, 13. $[\alpha]_D^{22} = -21.4$ (*c* 0.80, $CHCl_3$). IR ν_{max}^{film}: 3109, 2956, 2938, 2879, 1774, 1635,

1450, 1384, 1296, 1262, 1122, 1029, 1012, 942, 848 cm^{-1}. ^1H NMR ($CDCl_3$): 4.04 (1H, s, H-16a), 3.98 (1H, s, H-16b), 2.42–1.20 (16H, m), 1.06 (3H, s, Me-19), 0.84 (3H, d, $J = 6.8$ Hz, Me-17), 0.76 (3H, s, Me-20), 0.14 (9H, s, $OSi(CH_3)_3$). ^{13}C NMR ($CDCl_3$): 29.0 (C-1); 20.0 (C-2); 34.7 (C-3); 49.5 (C-4); 49.3 (C-5); 25.7 (C-6); 28.0 (C-7); 31.8 (C-8); 40.4 (C-9); 89.3 (C-10); 32.2 (C-11); 33.3 (C-12); 160.6 (C-13); 89.8 (C-16); 15.8 (C-17); 181.2 (C-18); 17.1 (C-19); 17.0 (C-20); 1.0 and 0.3 ($OSi(CH_3)_3$). MS, m/z: 364 ($[M]^+$, 2), 355 (0.7), 294 (33), 279 (8), 251 (2), 229 (2), 222 (2), 204 (23), 176 (50), 161 (10), 143 (80), 136 (8), 119 (12), 105 (10), 91 (13), 73 (100), 67 (23), 55 (30), 45 (24), 43 (47), 41 (33). HRMS calcd for $C_{21}H_{36}O_3Si$: 364.2434; found 364.2445.

3.12. Treatment of 13 with *m*-CPBA: 14

Compound **13** (448 mg, 1.34 mmol) was dissolved in dry CH_2Cl_2 (10 mL), stirred at 0 °C and *m*-CPBA (230 mg, 1.34 mmol) was added. The mixture was stirred at room temperature and monitored by TLC. After 15 h the reaction was complete and the solvent evaporated. Work-up afforded 410 mg of crude product that after chromatography on silica gel gave 205 mg (50%) of **14** in the hexane/EtOAc 1:1 fractions.

3.12.1. 5-*epi*-14,15-Di-*nor*-16-hydroxy-13-oxo-*ent*-haliman-18,10β-olide, 14. $[\alpha]_D^{22} = -19.5$ (*c* 0.72, $CHCl_3$). IR ν_{max}^{film}: 3481, 2935, 2879, 1766, 1720, 1450, 1378, 1280, 1244, 1198, 1124, 1078, 1018, 939 cm^{-1}. ^1H NMR ($CDCl_3$): 4.28 (1H, d, $J = 17.5$ Hz, H-16a), 4.16 (1H, d, $J = 17.5$ Hz, H-16b), 3.20 (1H, br s, 16-OH), 2.88 (1H, m, H-12a), 2.26 (1H, m, H-12b), 2.22–1.91 (2H, m), 1.89–1.10 (12H, m), 1.02 (3H, s, Me-19), 0.77 (3H, d, $J = 7.9$ Hz, Me-17), 0.76 (3H, s, Me-20). ^{13}C NMR ($CDCl_3$): 28.9 (C-1); 19.9 (C-2); 34.5 (C-3); 49.4 (C-4); 49.3 (C-5); 25.6 (C-6); 27.8 (C-7); 31.0 (C-8); 40.1 (C-9); 89.1 (C-10); 27.6 (C-11); 33.6 (C-12); 210.6 (C-13); 68.3 (C-16); 15.7 (C-17); 180.9 (C-18); 17.4 (C-19); 16.8 (C-20). MS, m/z: 308 ($[M]^+$, 1), 277 (9), 260 (5), 250 (59), 249 (68), 231 (7), 222 (100), 221 (40), 204 (7), 189 (7), 177 (42), 167 (18), 153 (9), 149 (27), 135 (26), 121 (79), 107 (98), 95 (82), 93 (62), 91 (47), 81 (76), 79 (57), 69 (52), 67 (47), 55 (88), 43 (31), 41 (64). HRMS calcd for $C_{18}H_{28}O_4$: 308.1988; found 308.1996.

3.13. Reaction of 14 with Bestmann ketene: synthesis of 1

To a solution of **14** (189 mg, 0.61 mmol) in toluene (15 mL) was added at room temperature $Ph_3P{=}C{=}C{=}O$ (422 mg, 1.40 mmol) and stirred for 3 h at 85 °C. After the solution was filtered with ether under celite. The solvent was removed at reduced pressure and the residue chromatographed yielding with hexane/EtOAc 7:3, 153 mg (75%) of **1**.

3.13.1. 5-*epi*-*ent*-Halim-13-en-18,10β;15,16-diolide, 1. $[\alpha]_D^{22} = -15.4$ (*c* 0.26, $CHCl_3$). IR ν_{max}^{film}: 3103, 2937, 2878, 1768, 1747, 1637, 1448, 1377, 1263, 1244, 1197, 1124, 1026, 941, 887, 848 cm^{-1}. UV (EtOH) λ_{max}: 209 nm ($\varepsilon = 10,687$). ^1H NMR ($CDCl_3$): 5.79 (1H, s, H-14), 4.79 (1H, d, $J = 17.3$ Hz, H-16a), 4.71 (1H, d, $J = 17.3$ Hz, H-16b), 2.83 (1H, m, H-12a), 2.35 (1H, m, H-12b), 1.99–1.05 (14H, m), 1.07 (3H, s, Me-19), 0.83 (3H, d, $J = 6.7$ Hz, Me-17), 0.82 (3H, s, Me-20). ^{13}C NMR ($CDCl_3$): 29.1 (C-1); 19.9 (C-2); 34.6 (C-3); 49.4 (C-4); 49.3 (C-5); 25.6 (C-6); 27.7 (C-7); 31.2 (C-8); 40.4 (C-9); 89.0 (C-10); 32.7 (C-11); 24.1 (C-12); 171.9 (C-13); 114.4 (C-14); 174.3 (C-15); 73.4 (C-16); 15.8 (C-17); 180.9 (C-18); 17.4 (C-19); 16.9 (C-20). HRMS calcd for $C_{20}H_{28}O_4$: 332.1988; found 332.2009.

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rotating anode diffractometer with (Cu-K_α) radiation (graphite monochromator) using $2\theta - \omega$ scans at 293(2) K. The structure was solved by direct methods and the nonhydrogen atoms were refined anisotropically by full-matrix least squares based on F^2 to give the agreement factors $R_1 = 0.0352$, $wR_2 = 0.0629$. Full crystallographic details for the structures reported in this paper has been deposited at the Cambridge Crystallographic Data Centre as supplementary material no CCDC-203161.

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