

Full Paper

Synthetic Studies Towards the *ent*-Labdane Diterpenoids: Rearrangement of *ent*-Halimanes

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Abstract: For the first time *ent*-labdanes have been synthesised starting from *ent*-halimic acid, following a route that is the reverse of the biosynthetic one leading to the former compounds.

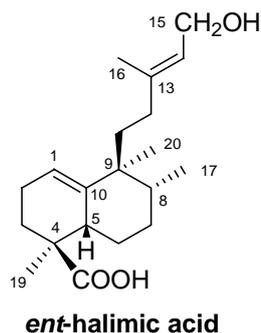
Keywords: Rearrangement, *ent*-labdanes, *ent*-halimic acid.

Introduction

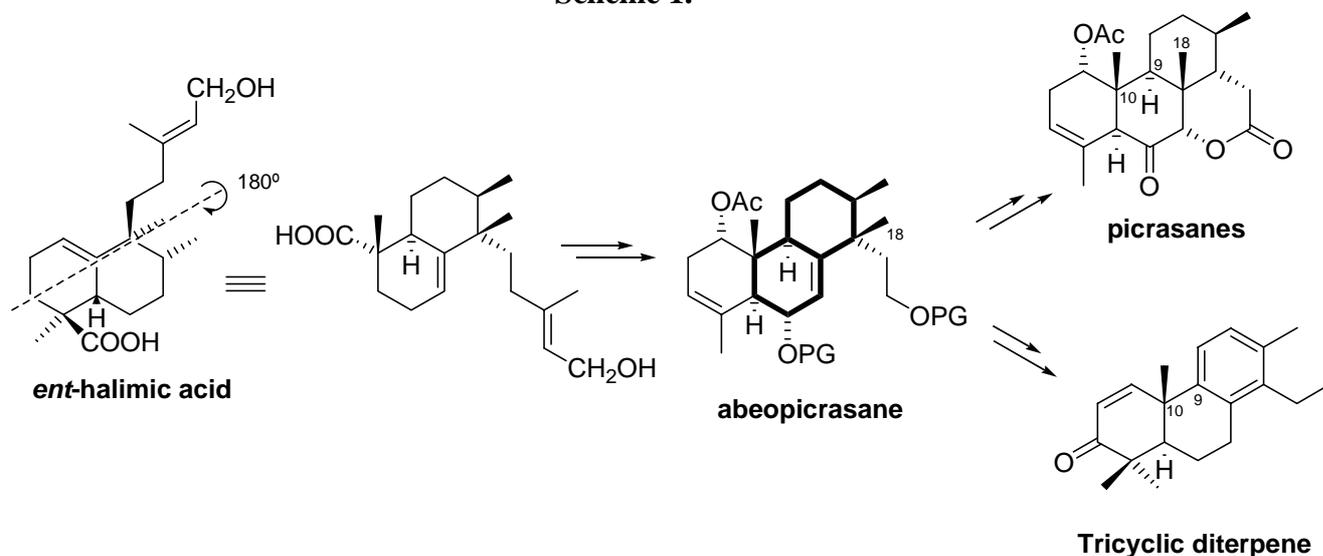
ent-Halimic acid (Figure 1) is a bicyclic diterpene that has been used as a starting material for the synthesis of different bioactive molecules such as the *ent*-halimanolides [1], chettaphanin I and chettaphanin II [2], (+)-agelasine C [3] and sesterterpenolides with an disydiolane skeleton [4].

Due to its functionality, *ent*-halimic acid can be viewed as an excellent synthon for the synthesis of new natural products. For example, the bicyclic system of *ent*-halimic acid can be visualized as the basis for the BC rings of tricyclic diterpenes or quassinoids with a picrasane skeleton (Scheme 1) whereby the C-4 quaternary carbon and the C-5 carbon of the starting material are incorporated with the correct configuration as C-10 and C-9, respectively, in the targets. However, to the best of our knowledge, a diterpene of the antipodal series has not been used previously as a starting material for the synthesis of diterpenes of the normal series or quassinoids with a picrasane skeleton.

Figure 1.

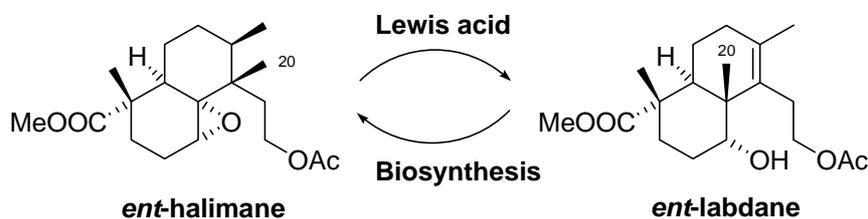


Scheme 1.



As can be observed in Scheme 1, the synthesis of the picrasane skeleton would require a rearrangement of the abeopicrasane skeleton, namely a 1,2 migration of the Me-18 group, in the same manner as seen in the biosynthetic pathway of euphane and tirucallane, biosynthetic precursors of the quassinoids [5].

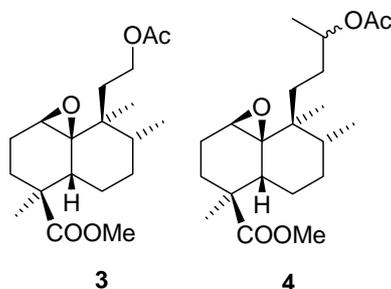
Scheme 2.



Scheme 2 shows the 1,2-shift of the Me-20 of *ent*-halimanes that leads to *ent*-labdanes. A rearrangement of this kind would be required to access the picrasane skeleton quassinoids. This rearrangement would be the opposite of the biosynthetic route, in which the *ent*-labdanes are the precursors of *ent*-halimanes [6].

In the present work we have explored the use of *ent*-halimic acid for the synthesis of biologically active compounds with different carbon skeletons. In particular we have studied the rearrangements with different Lewis acids of epoxides **3** and **4** (Figure 2), derived from *ent*-halimic acid.

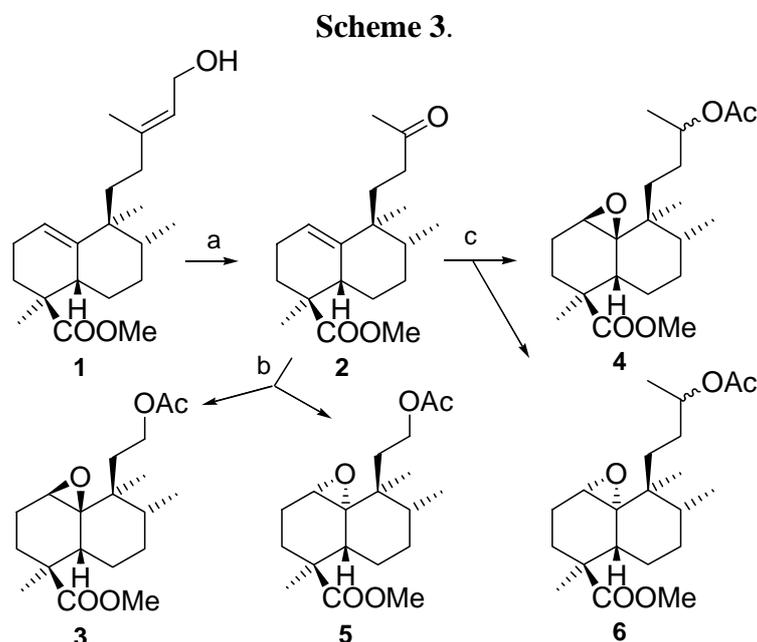
Figure 2. Starting materials obtained from *ent*-halimic acid.



Results and Discussion

Synthesis of the starting materials **3** and **4**.

The starting materials **3** and **4** were obtained from compound **1**, the methyl ester of *ent*-halimic acid, via two or four carbon atom side chain degradations, respectively, with methylketone **2** being the key intermediate in both syntheses (Scheme 3).

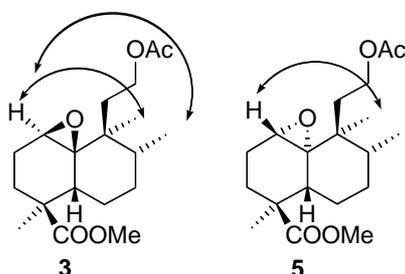


Reagents: (a) Ref [2]; (b) UHP, TFAA, 0°C, 1 h (**3**: 95%, **5**: 2%); (c) i) NaBH₄, MeOH, rt, 20 min. 83 %, ii) Ac₂O, Py, rt, 20 h. 96 %, iii) UHP, TFAA, 0°C, 30 min. (**4**: 90%, **6**: 6%).

Treatment of **2** with urea-hydrogen peroxide and trifluoroacetic acid (UHP-TFAA) [7] for one hour gives the epoxyacetates **3** and **5** with high stereoselectivity as a result of a Baeyer-Villiger reaction and epoxidation of the double bond. By contrast, the reaction of **2** with *m*-CPBA was slow, gave low yields

and is non-stereoselective. The configurations of the epoxide groups were established by nOe experiments, as shown in Figure 3. While in compound **3** H-1 has an nOe with Me-17 and Me-20, in **5** a nOe can only be observed between H-1 and Me-20.

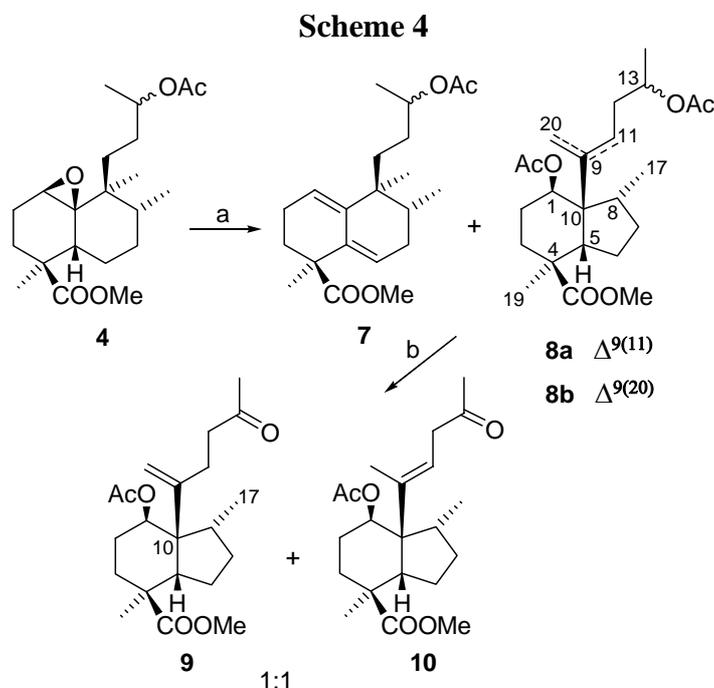
Figure 3. nOe experiments for determination of the configurations of epoxides **3** and **5**.



In order to obtain compound **4** it was necessary to reduce the ketone in **2**, followed by acetylation to give the corresponding acetate, which was treated with UHP-TFAA, under the same conditions as before, to give the corresponding epoxides **4** and **6** in excellent yield and with good stereoselectivity.

Treatment of epoxide **4** with Lewis acids

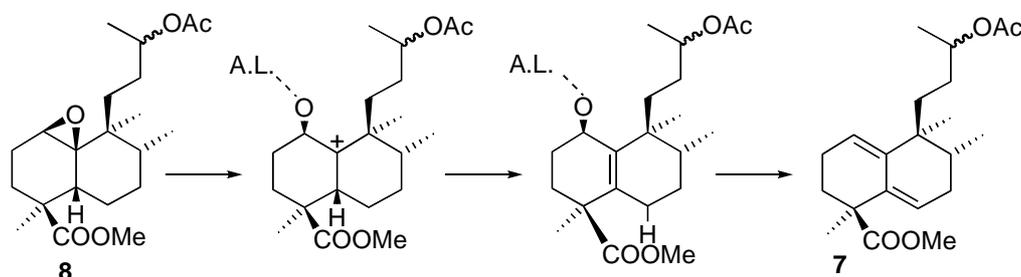
Corey *et al.* studied the rearrangement of epoxides in their synthesis of gicinoelepin A [8] and after using different Lewis acids and reaction conditions, achieved the rearrangement of an angular methyl with $\text{FeCl}_3\text{-Ac}_2\text{O}$. With this precedent in mind we started our study by treatment of epoxide **4** with $\text{FeCl}_3\text{-Ac}_2\text{O}$, and after several minutes a mixture of compounds **7** (20%) and **8** (56%) was obtained (Scheme 4).



Reagents: (a) $\text{FeCl}_3/\text{Ac}_2\text{O}$, rt, 30 min (**7**: 20%, **8**: 56%); (b) i) K_2CO_3 , MeOH, rt, 8 h (74%); ii) TPAP, NMO, rt, 30 min (**9**: 42%, **10**: 45%).

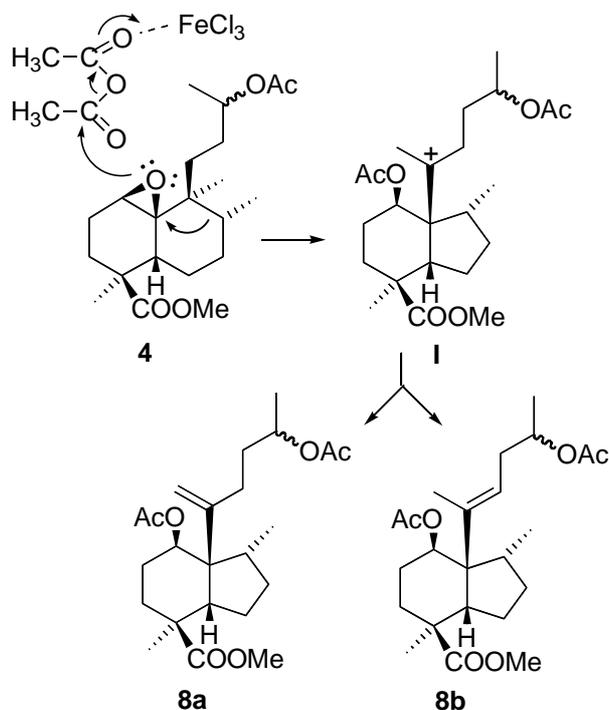
The less polar compound, **7**, was identified as a heteroannular diene (U.V.: 238 nm) that could arise through the mechanism shown in Figure 4.

Figure 4. Proposed mechanism for the formation of **7**.



The more polar compound **8** was a mixture of compounds which proved very difficult to separate by chromatography, so it was decided to simplify the analysis by carrying out the hydrolysis of the acetate group, followed by oxidation with TPAP/NMO [9], to thus obtain compounds **9** and **10** in good yield. The structures of these compounds were established by HMQC and HMBC experiments. The presence of an olefin and a methyl on a methine indicates that a skeletal rearrangement has taken place in the reaction of **4** with the Lewis acid. The observed correlation in the NMR experiments between Me-17 and C-10, tell us that B ring of *ent*-halimane has undergone a contraction to produce a five membered ring, giving a perhydroindene system. The mechanism that explains the formation of these compounds is shown in Figure 5.

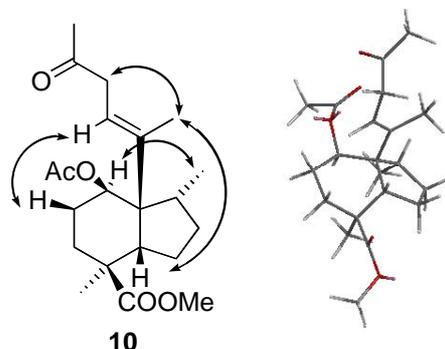
Figure 5. Proposed mechanism for the formation of **8**.



The Lewis acid coordination with acetic anhydride promotes a concerted rearrangement to produce olefins **8a** and **8b**. The stereochemistry for C-1, C-8 and C-10 is proposed in accordance with the

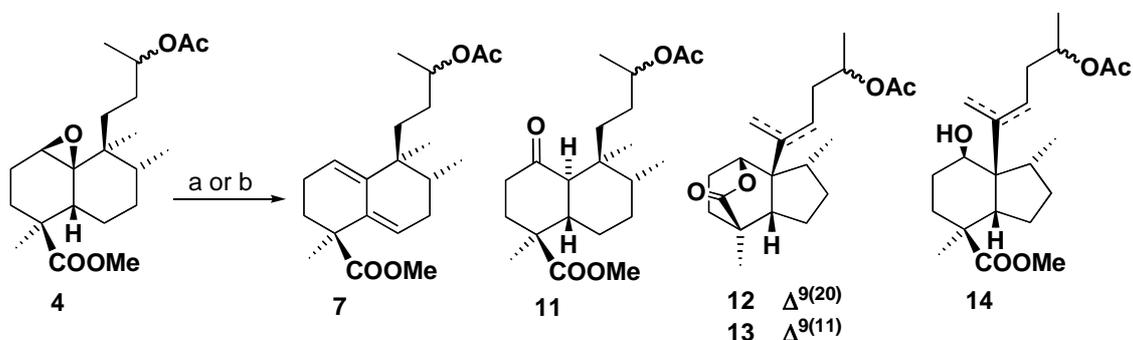
shown mechanism. In a ROESY experiment of **10** (Figure 6) nOes can be observed between H-1 and Me-17, H-5 and Me-20, H-11 and H-2 β and finally H-12 and Me-20, which corroborate the proposed configurations.

Figure 6. nOe experiments for determination of the configuration of **10** and a Chem 3D model to better understand the nOes.



To test other Lewis acids compound **4** was treated with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and TiCl_4 . The best results are shown in Scheme 5. Treatment of **4** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in ether gave a mixture of compounds **7**, **11**, **12** and **13**, with ketone **11** as the major product. The synthesis of this ketone can be rationalized by the opening of the oxirane by the Lewis acid and a subsequent α -face C-1 \rightarrow C10 hydride rearrangement. Compounds **12** and **13** are perhydroindenes, analogues of **9** and **10**, with the hydroxy group of C-1 forming a δ -lactone with the methoxycarbonyl in C-18.

Scheme 5.



Reagents: (a): $\text{BF}_3 \cdot \text{Et}_2\text{O}$, C_6H_6 0°C , 30 min (**7**: 11%, **11**: 47%, **12**: 13% and **13**: 15%); (b) TiCl_4 , CH_2Cl_2 , -44°C , 1 h (**7**: 25%, **11**: 27%, **12**: 4%, **13**: 4% and **14**: 22%).

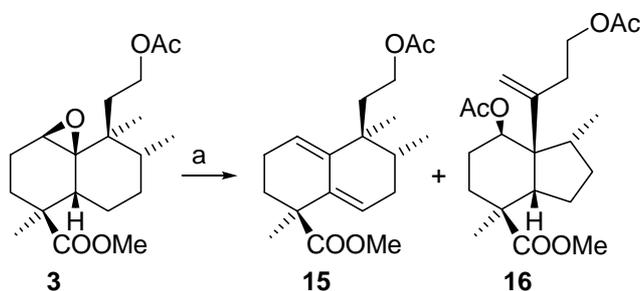
Treatment of **4** with TiCl_4 gave similar results as those obtained with $\text{BF}_3 \cdot \text{Et}_2\text{O}$, but in this case the corresponding hydroxyester **14** was obtained as well. As can be seen, the rearrangement of compound **4** with different Lewis acid did not give us the required results, so we decided to change the starting material to compound **3** which possesses a less demanding side chain.

Treatment of epoxide 3 with Lewis acids

Treatment of epoxide **3** with $\text{FeCl}_3/\text{Ac}_2\text{O}$ takes place to give compounds **15** and **16** that were separated by column chromatography (Scheme 6). The less polar compound **15** corresponds to a diene

similar to **7** obtained by the analogous treatment of **4**. The more polar compound is **16**, which is produced by a skeletal rearrangement similar to that of compounds **8**.

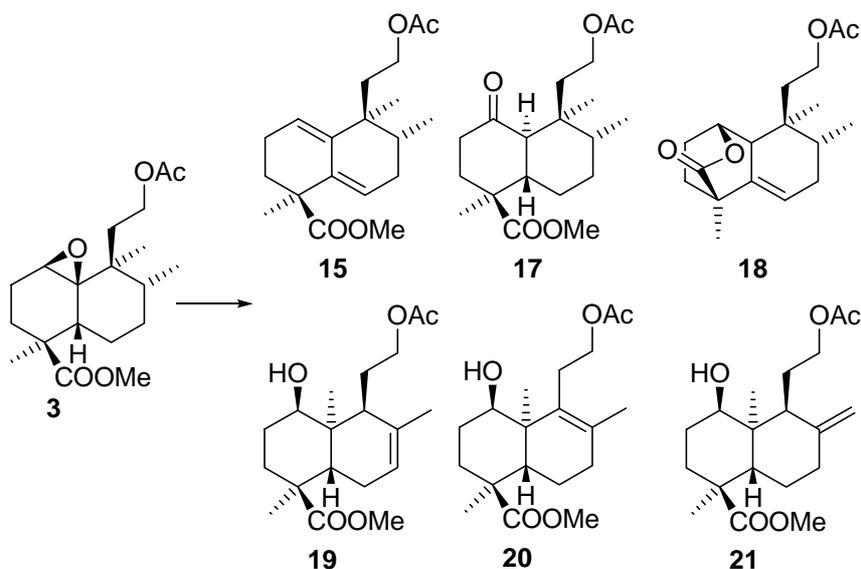
Scheme 6.



Reagents: (a) $\text{FeCl}_3/\text{Ac}_2\text{O}$, rt, 1 h (**15**: 20%, **16**: 58%)

The perhydroindene structure for **16** was established spectroscopically by 2D-NMR experiments. Treatment of epoxide **3** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (Scheme 7) produced a mixture of compounds that could be separated by column chromatography.

Scheme 7.



Reagents: (a) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, C_6H_6 , rt, 2h (**15**: 22%, **17**: 20%, **18**: 3%, **19**: 9%, **20**: 34%, **21**: 2%).

Besides diene **15** obtained in the previous treatment (Scheme 6), we obtained ketone **17** (analogous to **11**), lactone **18**, produced by transesterification of the hydroxy group in C-1 with the methoxycarbonyl at C-18 and, as the main component, a more polar mixture constituted by three compounds – **19**, **20** and **21** – all of them *ent*-labdanes, as desired. In the $^1\text{H-NMR}$ spectra of **19** and **20** signals corresponding to a methyl group on a double bond can be observed in ring B instead of the methyl on a methine. In the minor compound, **21** a terminal double bond in ring B is observed instead.

Conclusions

The transformation of *ent*-halimanes to *ent*-labdanes has been achieved for the first time. This methodology opens the way for the use of the available *ent*-halimanes for the synthesis of tri- and tetracyclic compounds of the normal series such as tricyclic diterpenes and degraded triterpenes like quassinoids with a picrasane skeleton. Future work will involve using this kind of rearrangement on tricyclic compounds with similar systems to the tirucalanes and euphanes that are the biological precursors in which this rearrangement takes place.

Experimental

General

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 BOMEM 100 FT-IR or an AVATAR 370 FT-IR Thermo Nicolet spectrophotometers. ^1H - and ^{13}C -NMR spectra were performed in CDCl_3 and referenced to the residual peak of CHCl_3 at δ 7.26 ppm and δ 77.0 ppm, for ^1H - and ^{13}C -, 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, a 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 an Ar atmosphere.

Methyl 12-acetoxy-1 β ,10 β -epoxy-13,14,15,16-tetranor-ent-haliman-18-oate (3) and methyl 12-acetoxy-1 α ,10 α -epoxy-13,14,15,16-tetranor-ent-haliman-18-oate (5).

An ice cooled solution of **2** (1.41 g, 4.59 mmol) and UHP (5.49 mg, 58.35 mmol) in CH_2Cl_2 (55 mL) was treated with TFAA (4.6 mL, 32.57 mmol) under argon. The reaction mixture was stirred at room temperature for 1 h, then a 40% aqueous solution of NaHSO_3 was added and the stirring was continued for an additional 30 min. The mixture was extracted with Et_2O and washed successively with a 6% aqueous solution of NaHCO_3 , water and brine. The organic layer was dried (Na_2SO_4), evaporated and chromatographed on silica gel (95:5 \rightarrow 9:1 hexane/EtOAc) giving **3** (1.34 g, 95%) and **5** (54 mg, 2%).

Compound **3**: a colourless solid; $[\alpha]_{\text{D}}^{22} +52.1$ (c 0.4, CHCl_3); mp 55 °C; IR (film) ν (cm^{-1}) 1736, 1464, 1373, 1246, 1125, 1030; ^1H -NMR (400 MHz): 4.21 and 4.08 (1H, two dt, $J_{\text{AB}} = 11.4, 5.7$ Hz, H-12), 3.62 (3H, s, $-\text{COOMe}$), 2.96 (1H, s, H-1), 2.78-2.72 (1H, m, H-5), 2.40-2.30 (1H, m), 2.22-2.00 (2H, m), 2.03 (3H, s, MeCOO-), 1.82-1.73 (1H, m), 1.71-1.55 (3H, m), 1.45-1.38 (2H, m), 1.23-1.12 (2H, m), 0.95 (3H, s, Me-19), 0.91 (3H, d, $J = 6.8$ Hz, Me-17), 0.72 (3H, s, Me-20); ^{13}C -NMR (100 MHz)

53.6 (C-1), 20.1 (C-2), 23.2 (C-3), 42.4 (C-4), 38.6 (C-5), 21.0 (C-6), 28.3 (C-7), 38.7 (C-8), 39.3 (C-9), 64.4 (C-10), 36.5 (C-11), 61.6 (C-12), 14.9 (C-17), 177.4 (C-18), 25.4 (C-19), 15.5 (C-20), 51.3 (-COOMe), 21.1 (MeCOO-), 170.4 (MeCOO-); EIMS m/z (%) 279 (M^+ - 59, 12), 263 (10), 219 (21), 203 (14), 192 (51), 173 (61), 163 (38), 119 (38), 105 (63), 91 (58), 55 (100).

Compound **5**: a colourless oil; $[\alpha]_D^{22}$ -8.94 (c 0.3, CHCl₃); IR (film) ν (cm⁻¹) 1738, 1462, 1375, 1236, 1125, 1034; ¹H-NMR (400 MHz) 4.12 and 4.07 (1H, two dt, J_{AB} = 10.7, 5.7 Hz, H-12), 3.64 (3H, s, -COOMe), 2.92 (1H, s, H-1), 2.50-2.55 (1H, m, H-5), 2.10-1.55 (8H, m), 2.04 (3H, s, MeCOO), 1.52-1.42 (2H, m), 1.38-1.30 (1H, m), 1.19 (3H, s, Me-19), 0.98 (3H, d, J = 6.8 Hz, Me-17), 0.71 (3H, s, Me-20); ¹³C-NMR (100 MHz) 51.3 (C-1), 20.5 (C-2), 31.5 (C-3), 45.3 (C-4), 36.8 (C-5), 21.0 (C-6), 28.9 (C-7), 38.4 (C-8), 39.3 (C-9), 64.1 (C-10), 36.7 (C-11), 61.5 (C-12), 15.5 (C-17), 178.6 (C-18), 17.5 (C-19), 15.9 (C-20), 52.0 (-COOMe), 21.1 (MeCOO-), 171.0 (MeCOO-); EIMS m/z (%) 279 (M^+ - 59, 9), 220 (18), 203 (12), 193 (54), 173 (48), 163 (38), 105 (63), 91 (100).

Methyl 13-acetoxy-1 β ,10 β -epoxy-14,15-dinor-ent-haliman-18-oate (4) and methyl 13-acetoxy-1 α ,10 α -epoxy-14,15-dinor-ent-haliman-18-oate (6).

To an ice cooled solution of **2** (0.37 g, 1.21 mmol) in MeOH (12 mL) was added NaBH₄ (47 mg, 1.25 mmol). After being stirred at room temperature for 20 min the reaction mixture was diluted with Et₂O and water, acidified with a few drops of a 2M aqueous solution of HCl, and extracted with Et₂O. The organic layer was washed with H₂O, dried (Na₂SO₄) and evaporated to give a hydroxyester (0.31 g, 83 %), which was used in the next step without further purification. To a solution of this hydroxyester (3.65 g, 11.85 mmol) in dry pyridine (5.5 mL) was added acetic anhydride (5.5 mL). The mixture was stirred at room temperature for 20 h, and then it was poured into ice-water and extracted with EtOAc. The organic layer was washed successively with aqueous 2M HCl, aqueous 6% NaHCO₃, water and brine. The resulting solution was then dried (Na₂SO₄) and evaporated to obtain the desired acetate (3.98 g, 96%). An ice cooled solution of acetate (375 mg, 1.07 mmol), UHP (1.85 g, 19.66 mmol) in CH₂Cl₂ (12 mL) was treated with TFAA (0.8 mL, 5.67 mmol) under argon. The reaction mixture was stirred at room temperature for 30 min. Following the same work-up described above, the residue obtained was purified by column chromatography and **4** (322 mg, 90%) and **6** (54 mg, 6%) were thus obtained.

Compound **4**: a colourless oil; IR (film) ν (cm⁻¹) 1736, 1464, 1373, 1246, 1125 1030; ¹H-NMR (400 MHz) 4.91-4.78 (2H, m, H-13 and H-13'), 3.63 (6H, s, -COOMe), 2.94-2.92 (2H, m, H-1 and H-1'), 2.80-2.68 (2H, m, H-5 and H-5'), 2.30-1.10 (26H, m), 2.03 and 2.01 (3H, two s, MeCOO-), 1.23 and 1.21 (3H, d each, J = 6.2 Hz, Me-16 and Me-16'), 0.96 (6H, s, Me-19 and Me-19'), 0.91 (6H, d, J = 7.0 Hz, Me-17 and Me-17'), 0.65 (6H, s, Me-20 and Me-20'); ¹³C-NMR (100 MHz) 52.8/52.7 (C-1), 20.0 (C-2), 23.1 (C-3), 42.4 (C-4), 38.1/37.8 (C-5), 20.9 (C-6), 28.1 (C-7), 38.6 (C-8), 39.9 (C-9), 64.7 (C-10), 30.2/30.1 (C-11), 33.8/33.2 (C-12), 71.8/71.7 (C-13), 19.9 (C-16), 15.4 (C-17), 177.3 (C-18), 25.4 (C-19), 17.0 (C-20), 51.1/51.0 (-COOMe), 21.2 (MeCOO-), 170.6 (MeCOO-); HRMS (EI): m/z calcd for C₂₁H₃₄O₅ (M^+ + Na): 389.2298, found 389.2304.

Compound **6**: as a colourless oil; IR (film) ν (cm^{-1}) 2948 1732, 1474, 1375, 1249, 1112 1025; $^1\text{H-NMR}$ (400 MHz) 4.91-4.78 (1H, m, H-13), 3.65 (3H, s, -COOMe), 2.93 (1H, d, $J = 3.8$ Hz, H-1), 2.56-2.44 (1H, m, H-5), 2.05 (3H, s, MeCOO-), 2.02-0.90 (13H, m), 1.23 (3H, d, $J = 6.4$ Hz, Me-16), 1.00 (3H, d, $J = 7.0$ Hz, Me-17), 1.20 and 0.65 (3H, s each, Me-19 and Me-20); HRMS (EI) m/z calcd for $\text{C}_{21}\text{H}_{34}\text{O}_5$ ($\text{M}^+ + \text{Na}$): 389.2298, found: 389.2290.

Methyl 13-acetoxy-14,15-dinor-ent-halima-1(10),5-dien-18-oate (7), methyl 1 β ,13R and S-diacetoxy-14,15-dinor-8(9 \rightarrow 10)abeo-ent-halim-9(11)E-en-18-oate (8a) and methyl 1 β ,13R and S-diacetoxy-14,15-dinor-8(9 \rightarrow 10)abeo-ent-halim-9(20)-en-18-oate (8b).

a) To a solution of **4** (86 mg, 0.23 mmol) in EtOAc (0.5 mL) and Ac_2O (0.5 mL), FeCl_3 (9 mg, 0.055 mmol) was added and the mixture was stirred under argon at room temperature for 30 min. The reaction mixture was poured into ice-water and extracted with *n*-Hexane. The organic layer was washed successively with aqueous 6% NaHCO_3 , and water. The resulting solution was then dried (Na_2SO_4) and evaporated, a residue was obtained and purified by column chromatography (95:5 \rightarrow 8:2 hexane/EtOAc), yielding **7** (16 mg, 20%) and **8a/8b** (54 mg, 56%).

b) To a solution of **4** (86 mg, 0.23 mmol) in 10:1 $\text{Ac}_2\text{O}/\text{CH}_2\text{Cl}_2$ (2.3 mL), FeCl_3 (42 mg, 0.26 mmol) in Ac_2O was added. The mixture was stirred under argon at -78°C for 24 h. Following the same procedure described above, column chromatography afforded **7** (15 mg, 19%) and **8a/8b** (56 mg, 58%).

Compound **7**: a colourless oil; UV: 238 nm (EtOH); IR (film) ν (cm^{-1}) 3046, 1738, 1240, 1100, 1032; $^1\text{H-NMR}$ (400 MHz) 5.51-5.42 (4H, m, H-1, H-6, H-1' and H-6'), 4.87-4.78 (2H, m, H-13 and H-13'), 3.60 (6H, s, -COOMe), 2.02 and 2.01 (3H, s each, MeCOO-), 1.31 (6H, s, Me-19 and Me-19'), 1.12 and 1.18 (3H, d each, $J = 6.0$ Hz, Me-16 and Me-16'), 0.92 (6H, s, Me-20 and Me-20'), 0.78 and 0.77 (3H, d each, $J = 7.0$ Hz, Me-17 and Me-17'); HRMS (EI) m/z calcd for $\text{C}_{21}\text{H}_{32}\text{O}_4$ ($\text{M}^+ + \text{Na}$): 371.2193, found 371.2182.

Compound **8a**: a colourless oil; IR (film) ν (cm^{-1}) 2954, 1732, 1458, 1374, 1243, 1135, 1039; $^1\text{H-NMR}$ (400 MHz) 5.79-5.72 (1H, m, H-11), 5.04-4.92 (2H, m, H-1 and H-13), 3.70 (3H, s, -COOMe), 2.79 (1H, t, $J = 10.0$ Hz, H-5), 2.38-1.08 (11H, m), 1.97 (6H, s, MeCOO-), 1.51 (3H, s, Me-20), 1.24 (3H, d, $J = 6.8$ Hz, Me-16), 1.03 (3H, s, Me-19), 0.72 (3H, d, $J = 6.5$ Hz, Me-17); HRMS (EI) m/z calcd for $\text{C}_{23}\text{H}_{36}\text{O}_6$ ($\text{M}^+ + \text{H}$): 409.2590, found 409.2534.

Compound **8b**: a colourless oil; IR (film) ν (cm^{-1}) 2954, 1732, 1458, 1374, 1243, 1135, 1039; $^1\text{H-NMR}$ (400 MHz) 5.40 and 4.97 (1H, two s, H-20), 5.04-4.92 (2H, m, H-1 and H-13), 3.54 (3H, s, -COOMe), 2.80 (1H, t, $J = 10.0$ Hz, H-5), 2.36-1.08 (13H, m), 2.04 y 2.03 (3H, two s, MeCOO-), 1.23 (3H, d, $J = 6.8$ Hz, Me-16), 1.03 (3H, s, Me-19), 0.75 (3H, d, $J = 6.5$ Hz, Me-17); HRMS (EI) m/z calcd for $\text{C}_{26}\text{H}_{36}\text{O}_6$ ($\text{M}^+ + \text{H}$): 409.2590, found 409.2566.

Methyl 1 β -acetoxy-13-oxo-14,15-dinor-8(9 \rightarrow 10)abeo-ent-halim-9(20)-en-18-oate (**9**) and methyl 1 β -acetoxy-13-oxo-14,15-dinor-8(9 \rightarrow 10)abeo-ent-halim-9(11)*E*-en-18-oate (**10**)

The **8a/8b** mixture (51 mg, 0.13 mmol) was treated with potassium carbonate in MeOH (3%, 4 mL) for 8 h at room temperature. The MeOH was removed and the residue was diluted with water and extracted with Et₂O. The organic fractions were combined and washed with 2M aqueous HCl solution and water. Evaporation of solvent after drying over Na₂SO₄ gave a residue which was chromatographed on silica gel (95:5 hexane/EtOAc) affording the desired hydroxy ester (34 mg, 74%), which was directly used in the next step. To a mixture of hydroxy ester (34 mg, 0.092 mmol), *N*-methylmorpholine *N*-oxide (NMO) (17 mg, 0.13 mmol) and molecular sieves (41 mg, 500 mg/mmol) in dry CH₂Cl₂ (1 mL) under argon, at room temperature was added TPAP (2 mg, 0.004 mmol). The reaction mixture was stirred for 30 min and then was filtered through a short pad of silica gel eluting with EtOAc. The solvent was evaporated and the residue was purified by chromatography on silica gel (99:1 CHCl₃/Me₂CO) yielding **9** (14 mg, 42%) and **10** (15 mg, 45%).

Compound **9**: a colourless oil; $[\alpha]_D^{22} +16.4$ (c 0.5, CHCl₃); IR (film) ν (cm⁻¹) 2942, 1737, 1458, 1359, 1255, 1211, 1145, 1025; ¹H-NMR (400 MHz) 5.41 (1H, s, H-20), 5.03 (1H, s, H-20), 4.98 (1H, dd, *J* = 14.0, 6.0 Hz, H-1), 3.57 (3H, s, -COOMe), 2.85 (1H, t, *J* = 10.0 Hz, H-5), 2.56 (2H, ddd, *J* = 12.0, 8.0, 4.0 Hz, H-12), 2.32-2.28 (1H, m, H-2), 2.32-2.22 (1H, m, H-11), 2.21-2.11 (1H, m, H-8), 2.18 (3H, s, Me-16), 2.10-1.95 (1H, m, H-3), 1.99 (3H, s, MeCOO-), 1.88-1.81 (1H, m, H-7), 1.78-1.72 (1H, m, H-11), 1.75-1.60 (2H, m, H-6), 1.70-1.60 (1H, m, H-2), 1.62-1.48 (1H, m, H-3), 1.47-1.39 (1H, m, H-7), 1.03 (3H, s, Me-19), 0.77 (3H, d, *J* = 7.0 Hz, Me-17); ¹³C-NMR (100 MHz) 71.1 (C-1), 26.3 (C-2), 28.6 (C-3), 43.3 (C-4), 49.6 (C-5), 23.3 (C-6), 29.0 (C-7), 42.1 (C-8), 145.4 (C-9), 55.4 (C-10), 25.5 (C-11), 44.3 (C-12), 208.6 (C-13), 29.9 (C-16), 15.0 (C-17), 177.1 (C-18), 26.2 (C-19), 115.8 (C-20), 51.3 (-COOMe), 21.7 (MeCOO-), 170.6 (MeCOO-); EIMS *m/z* (%) 387 (M⁺ + Na, 360), 382 (173), 365 (50), 305 (90), 245 (50), 227 (57); HRMS (EI) *m/z* calcd for C₂₁H₃₂O₅ (M⁺ + Na): 387.2142, found 387.2137.

Compound **10**: a colourless oil; $[\alpha]_D^{22} +27.7$ (c 0.4, CHCl₃); IR (film) ν (cm⁻¹) 2964, 1721, 1452, 1370, 1255, 1195, 1129, 1030; ¹H-NMR (400 MHz) 6.05 (1H, t, *J* = 6 Hz, H-11), 5.01 (1H, dd, *J* = 14.0, 6.0 Hz, H-1), 3.52 (3H, s, -COOMe), 3.19 (1H, dd, *J* = 16.0, 8.0 Hz, H-12), 3.10 (1H, dd, *J* = 16.0, 8.0 Hz, H-12), 2.80 (1H, t, *J* = 10.0 Hz, H-5), 2.35-2.25 (1H, dd, *J* = 12.0, 4.0 Hz, H-2), 2.24-2.11 (1H, m, H-8), 2.16 (3H, s, Me-16), 2.10-1.40 (4H, m, H-7, H-3), 2.0 (3H, s, MeCOO-), 1.75-1.60 (2H, m, H-6), 1.70-1.62 (1H, m, H-2), 1.55 (3H, s, Me-20), 1.03 (3H, s, Me-19), 0.73 (3H, d, *J* = 7.0 Hz, Me-17); ¹³C NMR (100 MHz) 71.2 (C-1), 26.4 (C-2), 28.4 (C-3), 43.4 (C-4), 48.9 (C-5), 23.2 (C-6), 28.5 (C-7), 42.3 (C-8), 136.2 (C-9), 55.5 (C-10), 121.9 (C-11), 44.7 (C-12), 206.9 (C-13), 29.2 (C-16), 14.7 (C-17), 176.9 (C-18), 26.2 (C-19), 13.3 (C-20), 51.3 (-COOMe), 21.7 (MeCOO-), 170.5 (MeCOO-); EIMS *m/z* (%) 387 (M⁺ + Na, 166), 382 (80), 375 (58), 305 (43), 293 (32), 277 (35), 227 (22), 181 (20); HRMS (EI): *m/z* calcd for C₂₁H₃₂O₅ (M⁺ + Na): 387.2142, found 387.2144.

Compounds **11**, **12** and **13**

To a solution of **4** (83 mg, 0.23 mmol) in dry C₆H₆ (5 mL), BF₃·Et₂O (0.1 mL, 0.87 mmol) was added under argon at 0°C. After being stirred at room temperature for 30 min, the mixture was poured into ice-water, and extracted with Et₂O. The organic layer was washed successively with aqueous 6% NaHCO₃ and water. The resulting solution was then dried (Na₂SO₄) and evaporated, giving a residue that was purified by column chromatography (95:5→9:1 hexane/EtOAc), yielding **7** (9 mg, 11%), **11** (39 mg, 47%), **12** (10 mg, 13%) and **13** (12 mg, 15%).

Methyl (10R)-14,15-dinor-13-acetoxy-1-oxo-ent-haliman-18-oate (11): a colourless oil; IR (film) ν (cm⁻¹) 1732, 1717, 1456, 1373, 1258, 1138, 1071, 955; ¹H-NMR (400 MHz) 4.87-4.78 (2H, m, H-13 and H-13'), 3.69 (6H, s, -COOMe), 2.04 and 2.02 (3H, two s, MeCOO-), 1.36 (6H, s, Me-19 and Me-19'), 1.22 and 1.21 (3H, two d, *J* = 6.3 Hz, Me-16 and Me-16'), 1.04 (6H, s, Me-20 and Me-20'), 0.86 (6H, d, *J* = 7.1 Hz, Me-17 and Me-17'); HRMS (EI) *m/z* calcd for C₂₁H₃₄O₅ (M⁺ + Na): 389.2298, found 389.2312.

13R and S-acetoxy-14,15-dinor-8(9→10)abeo-ent-halim-9(20)-en-18(1)-olide (12): a colourless oil; IR (film) ν (cm⁻¹) 2926, 1748, 1463, 1375, 1249, 1101, 1025; ¹H-NMR (400 MHz) 5.08 (1H, s, H-20), 5.02-4.86 (1H, m, H-13), 4.97 (1H, s, H-20), 4.82-4.78 (1H, m, H-1), 2.36-1.02 (14H, m), 2.03 (3H, s, MeCOO-), 1.24-1.21 (3H, d, *J* = 6.8 Hz, Me-16), 1.16 (3H, s, Me-19), 0.98-0.95 (3H, d, *J* = 6.8 Hz, Me-17); HRMS (EI) *m/z* calcd for C₂₀H₃₀O₄ (M⁺ + Na): 357.2036, found 357.2025.

13R and S-acetoxy-14,15-dinor-8(9→10)abeo-ent-halim-9(11)E-en-18(1)-olide (13): a colourless oil; [α]_D²² +0.1 (c 0.86, CHCl₃); IR (film) ν (cm⁻¹) 2942, 1737, 1463, 1370, 1255, 1107, 1030; ¹H-NMR (400 MHz) 5.38-5.30 (1H, m, H-11), 4.98-4.93 (1H, m, H-13), 4.80 (1H, t, *J* = 3.8 Hz, H-1), 2.40-2.30 (1H, m, H-12), 2.22-2.10 (1H, m, H-5), 2.10 (3H, s, MeCOO-), 1.98-1.96 (1H, m, H-8), 1.84-1.80 (2H, m, H-6), 1.80-1.78 (2H, m, H-2), 1.62 (3H, s, Me-20), 1.45-1.38 (1H, m, H-12), 1.44-1.34 (2H, m, H-7), 1.42-1.40 (2H, m, H-3), 1.23 (3H, d, *J* = 6.8 Hz, Me-16), 1.15 (3H, s, Me-19), 0.95 (3H, s, Me-17); ¹³C-NMR (100 MHz) 76.5 (C-1), 24.1 (C-2), 23.4 (C-3), 40.6 (C-4), 47.8 (C-5), 26.4 (C-6), 34.6 (C-7), 43.3 (C-8), 138.6 (C-9), 56.5 (C-10), 120.0 (C-11), 34.7 (C-12), 70.6 (C-13), 19.6 (C-16), 12.7 (C-17), 178.1 (C-18), 20.2 (C-19), 14.0 (C-20), 170.7 (MeCOO-), 21.3 (MeCOO-); EIMS *m/z* (%) 335 (M⁺ + H, 335), 275 (140), 229 (55); HRMS (EI) *m/z* calcd for C₂₀H₃₀O₄ (M⁺ + H): 335.2217, found 335.2223.

Methyl 13R and S-acetoxy-1-hydroxy-14,15-dinor-8(9→10)abeo-ent-halim-9(11)E-en-18-oate and methyl 13R and S-acetoxy-1-hydroxy-14,15-dinor-8(9→10)abeo-ent-halim-9(20)-en-18-oate (14)

At -44°C and under argon, a solution of **4** (114 mg, 0.31 mmol) in CH₂Cl₂ (7 mL), was treated with TiCl₄ (0.35 mL, 2.52 mmol) and stirred at room temperature for 1 h. The reaction was quenched by addition of Et₂O/H₂O and extracted with Et₂O. The organic layer was washed successively with aqueous 6% NaHCO₃, and water. The resulting solution was then dried (Na₂SO₄) and evaporated, a residue was obtained and purified by column chromatography (95:5 hexane/EtOAc), yielding **14** (29 mg, 22%), **7** (26 mg, 25%), **11** (30 mg, 27%) and **12/13** (8 mg, 8%).

Compound **14**: a colourless oil; IR (film) ν (cm^{-1}) 3458, 2926, 1732, 1463, 1375, 1244, 1134, 1063, 992; $^1\text{H-NMR}$ (400 MHz) 5.38-5.30 (1H, m, H-11), 5.07 and 4.98 (1H, two s, H-20), 5.00-4.96 (1H, m, H-13), 3.98 (1H, br s, H-1), 3.63 (3H, s, $-\text{COOMe}$), 2.01 (3H, s, MeCOO-), 1.56 (3H, s, Me-20), 1.20 (3H, d, $J = 6.8$ Hz, Me-13), 1.14 (3H, s, Me-19), 0.85 (3H, d, $J = 6.5$ Hz, Me-17); HRMS (EI) m/z calcd for $\text{C}_{21}\text{H}_{34}\text{O}_5$ ($\text{M}^+ + \text{H}$): 367.2406, found 367.2395.

*Methyl 12-acetoxy-13,14,15,16-tetranor-ent-halima-1(10),5-dien-18-oate (15) and methyl 1 β ,12-diacetoxy-13,14,15,16-tetranor-8(9 \rightarrow 10)abeo-ent-halim-9(20)*E-en*-18-oate (16).*

To a solution of **3** (137 mg, 0.41 mmol) in EtOAc (0.85 mL) and Ac_2O (0.85 mL) was added FeCl_3 (16 mg, 0.096 mmol). The reaction mixture was stirred under argon at room temperature for 1 h. Then ice-water was added and extracted with *n*-hexane. The organic layer was washed successively with aqueous 6% NaHCO_3 , and water. The resulting solution was dried (Na_2SO_4) and evaporated, a residue was obtained and purified by column chromatography (95:5 \rightarrow 9:1 \rightarrow 8:2 hexane/EtOAc), yielding **15** (26 mg, 20%) and **16** (74 mg, 58%).

Compound **15**: a colourless oil; $[\alpha]_{\text{D}}^{22} +38.9$ (c 1.2, CHCl_3); UV: 238 nm (EtOH); IR (film) ν (cm^{-1}) 3046, 1738, 1454, 1371, 1254, 1109, 1034; $^1\text{H-NMR}$ (400 MHz) 5.58-5.42 (2H, m, H-1, H-6), 4.14 (1H, dt, $J = 10.4, 6.1$ Hz, H-12), 3.91 (1H, dt, $J = 10.4, 6.1$ Hz, H-12), 3.60 (3H, s, $-\text{COOMe}$), 2.60-2.43 (1H, m, H-5), 2.35-1.40 (8H, m), 2.02 (3H, s, MeCOO-), 1.33 (3H, s, Me-19), 1.00 (3H, s, Me-20), 0.80 (3H, d, $J = 6.8$ Hz, Me-17); $^{13}\text{C-NMR}$ (100 MHz) 122.0 (C-1), 23.4 (C-2), 33.5 (C-3), 46.3 (C-4), 135.1 (C-5), 119.6 (C-6), 31.1 (C-7), 36.0 (C-8), 39.4 (C-9), 137.6 (C-10), 36.2 (C-11), 62.0 (C-12), 15.9 (C-17), 176.8 (C-18), 20.9 (C-19), 23.8 (C-20), 51.6 ($-\text{COOMe}$), 21.8 (MeCOO-), 171.0 (MeCOO-); EIMS m/z (%) 320 (M^+ , 1), 305 (1), 290 (1), 260 (1), 245 (1), 233 (5), 217 (1), 201(18), 185 (5), 173 (69), 159 (16), 145 (24), 131 (38), 119 (22), 105 (54), 91 (18), 84 (15), 59 (7), 43 (100); HRMS (EI) m/z calcd for $\text{C}_{19}\text{H}_{28}\text{O}_4$ ($\text{M}^+ + \text{Na}$): 343.1879, found 343.1862.

Compound **16**: a colourless oil ; $[\alpha]_{\text{D}}^{22} +0.01$ (c 0.8, CHCl_3); IR (film) ν (cm^{-1}) 2953, 1726, 1468, 1370, 1244, 1030; $^1\text{H-NMR}$ (400 MHz) 5.5 (1H, s, H-20), 5.12 (1H, s, H-20), 5.05-4.92 (1H, dd, $J = 12.4, 4.8$ Hz, H-1), 4.21-4.05 (2H, m, H-12), 3.59 (3H, s, $-\text{COOMe}$), 2.82-2.70 (1H, t, $J = 8.9$ Hz, H-5), 2.25 (2H, t, $J = 6.8$ Hz, H-11), 2.25-1.15 (1H, m, H-2), 2.10-2.02 (1H, m, H-3), 2.08-2.01 (1H, m, H-8), 2.05 (3H, s, MeCOO-), 1.99 (3H, s, MeCOO-), 1.92-1.40 (2H, m, H-6), 1.70-1.60 (1H, m, H-2), 1.62-1.50 (1H, m, H-3), 1.28-1.22 (2H, m, H-7), 1.05 (3H, s, Me-19), 0.35-0.20 (3H, d, $J = 6.5$ Hz, Me-17); $^{13}\text{C-NMR}$ (100 MHz) 71.0 (C-1), 26.2 (C-2), 28.2 (C-3), 43.3 (C-4), 49.9 (C-5), 23.3 (C-6), 28.7 (C-7), 42.0 (C-8), 142.4 (C-9), 55.1 (C-10), 30.9 (C-11), 65.3 (C-12), 15.2 (C-17), 177.1 (C-18), 26.3 (C-19), 118.1 (C-20), 171.0 (MeCOO-), 170.6 (MeCOO-), 51.3 ($-\text{COOMe}$), 21.7 (MeCOO-), 21.0 (MeCOO-); EIMS m/z (%) 403 ($\text{M}^+ + \text{Na}$, 473), 321 (130), 261 (105), 201 (70); HRMS (EI) m/z calcd for $\text{C}_{21}\text{H}_{32}\text{O}_6$ ($\text{M}^+ + \text{Na}$): 403.2091, found 403.2116.

Compounds 17, 18, 19, 20 and 21.

A solution of **3** (403 mg, 1.19 mmol) in dry C₆H₆ (13 mL) was treated under argon with BF₃·Et₂O (0.33 mL), and the reaction mixture was stirred at room temperature for 2 h. Following the same procedure described above, the residue was obtained and purified by chromatography on silica gel (95:5→9:1→85:15 *n*-hexane/EtOAc), affording **15** (90 mg, 22%), **17** (82 mg, 20%), **18** (8 mg, 3%), **19** (36 mg, 9%), **20** (138 mg, 34%) and **21** (9 mg, 2%).

Methyl (10R)-12-acetoxy-1-oxo-13,14,15,16-tetranor-ent-haliman-18-oate (17): a colourless oil; $[\alpha]_{\text{D}}^{22}$ -4.5 (c 0.5, CHCl₃); IR (film) ν (cm⁻¹) 1734, 1238; ¹H-NMR (400 MHz) 4.16 (1H, dt, *J* = 10.4, 6.4 Hz, H-12_A), 3.91 (1H, dt, *J* = 10.4, 6.1 Hz, H-12_B), 3.70 (3H, s, -COOMe), 2.50-2.18 (6H, m, H-2, H-3_A, H-5, H-10, H-11_A), 2.15-1.90 (2H, m, H-3_B, H-11_B), 2.04 (3H, s, MeCOO-), 1.80-1.58 (2H, m, H-6), 1.55-1.41 (2H, m, H-7_A, H-8), 1.40 (3H, s, Me-19), 1.33-1.15 (1H, m, H-7_B), 1.15 (3H, s, Me-20), 0.90 (3H, d, *J* = 6.8 Hz, Me-17); ¹³C-NMR (100 MHz) 209.9 (C-1), 39.3 (C-2), 31.1 (C-3), 46.5 (C-4), 43.1 (C-5), 22.3 (C-6), 27.2 (C-7), 35.3 (C-8), 37.3 (C-9), 52.5 (C-10), 36.6 (C-11), 61.5 (C-12), 14.2 (C-17), 177.2 (C-18), 18.1 (C-19), 24.7 (C-20), 52.1 (-COOMe), 21.0 (MeCOO-), 171.1 (MeCOO-); EIMS *m/z* (%) 278 (M⁺ - 60, 20), 263 (16), 219 (22), 201 (12), 178 (82), 163 (34), 123 (100), 107 (14), 55 (90); HRMS (EI) *m/z* calcd for C₁₉H₃₀O₅ (M⁺ + Na): 361.1985, found 361.1970.

12-acetoxy-13,14,15,16-tetranor-ent-halim-5-en-18(1)-olide (18): a colourless oil; IR (film) ν (cm⁻¹) 3403, 2926, 1737, 1463, 1370, 1249, 1107, 1036; ¹H-NMR (400 MHz) 5.49 (1H, m, H-6), 4.82 (1H, s, H-1), 4.15 (2H, m, H-12), 2.68 (1H, br s, H-12), 2.06 (3H, s, MeCOO-), 2.05-0.95 (9H, m), 1.31 (3H, s, Me-19), 0.86 (3H, d, *J* = 6.8 Hz, Me-17), 0.80 (3H, s, Me-20); ¹³C-NMR (100 MHz) 76.9 (C-1), 23.8 (C-2), 33.9 (C-3), 44.4 (C-4), 136.3 (C-5), 117.1 (C-6), 32.4 (C-7), 34.6 (C-8), 35.7 (C-9), 49.5 (C-10), 34.4 (C-11), 60.1 (C-12), 14.3 (C-17), 176.3 (C-18), 17.0 (C-19), 15.2 (C-20), 21.0 (MeCOO-), 171.1 (MeCOO-); HRMS (EI) *m/z* calcd for C₁₈H₂₆O₄ (M⁺ + Na): 329.1831, found 329.1720.

Methyl 12-acetoxy-1β-hydroxy-13,14,15,16-tetranor-ent-labd-7-en-18-oate (19): a colourless oil; $[\alpha]_{\text{D}}^{22}$ -19.0 (c 0.7, CHCl₃); IR (film) ν (cm⁻¹) 3419, 2921, 1742, 1468, 1364, 1238, 1041; ¹H-NMR (400 MHz) 5.34 (1H, s, H-7), 4.35-4.05 (2H, m, H-12), 3.80 (1H, s, H-1), 3.64 (3H, s, -COOMe), 2.55 (1H, br s, H-9), 2.45-2.30 (1H, m, H-5), 2.30-2.20 (1H, m, H-3), 2.10 (3H, s, MeCOO-), 2.00-1.15 (6H, m, H-2, H-6, H-11), 1.70 (3H, s, Me-17), 1.33-1.20 (1H, m, H-3), 1.24 (3H, s, Me-19), 0.75 (3H, s, Me-20); ¹³C-NMR (100 MHz) 69.8 (C-1), 24.7 (C-2), 29.4 (C-3), 46.2 (C-4), 38.7 (C-5), 24.8 (C-6), 121.5 (C-7), 134.1 (C-8), 42.3 (C-9), 40.1 (C-10), 25.5 (C-11), 66.0 (C-12), 21.8 (C-17), 17.0 (C-19), 13.8 (C-20), 170.8 (MeCOO-), 20.9 (MeCOO-), 178.7 (-COOMe), 51.9 (-COOMe); EIMS *m/z* (%) 361 (M⁺ + Na, 325), 339 (180), 329 (140), 324 (160), 307 (145), 261 (260), 247 (112), 201 (208), 159 (38); HRMS (EI) *m/z* calcd for C₁₉H₃₀O₅ (M⁺ + Na): 361.1985, found 361.1975.

Methyl 12-acetoxy-1β-hydroxy-13,14,15,16-tetranor-ent-labd-8-en-18-oate (20): a colourless oil; $[\alpha]_{\text{D}}^{22}$ -51.2 (c 0.8, CHCl₃); IR (film) ν (cm⁻¹) 3438, 2932, 1732, 1468, 1375, 1238, 1118, 1041;

¹H-NMR (400 MHz) 4.29 (1H, ddd, $J = 10.8, 8.7, 7.6$ Hz, H_A-12), 4.09 (1H, ddd, $J = 10.8, 8.6, 7.4$ Hz, H_B-12), 4.01 (1H, br s, H-1), 3.67 (3H, s, -COOMe), 2.40-1.05 (11H, m), 2.05 (3H, s, MeCOO-), 1.66 (3H, s, Me-17), 1.21 (3H, s, Me-19), 1.01 (3H, s, Me-20); ¹³C-NMR (100 MHz) 70.5 (C-1), 26.5 (C-2), 29.5 (C-3), 43.6 (C-4), 39.2 (C-5), 21.1 (C-6), 33.2 (C-7), 132.3 (C-8), 133.1 (C-9), 47.4 (C-10), 24.9 (C-11), 63.9 (C-12), 20.9 (C-17), 178.9 (C-18), 20.3 (C-19), 16.4 (C-20), 51.9 (-COOMe), 21.0 (MeCOO-), 171.1 (MeCOO-); EIMS m/z (%) 278 (M⁺ - 60, 8), 207 (15), 149 (100), 121 (9), 91 (14), 73 (44); HRMS (EI) m/z calcd for C₁₉H₃₀O₅ (M⁺ + Na): 361.1985, found 361.1994.

Methyl 12-acetoxy-1β-hydroxy-13,14,15,16-tetranor-ent-labd-8(17)-en-18-oate (21): a colourless oil; IR (film) ν (cm⁻¹) 3438, 2932, 1732, 1468, 1375, 1238, 1118, 1041; ¹H-NMR (400 MHz) 4.90 and 4.59 (1H, s each, Me-17), 4.36-4.05 (2H, m, H-12), 4.01 (1H, s br, H-1), 3.68 (3H, s, -COOMe), 2.40-1.05 (12H, m), 2.06 (3H, s, MeCOO-), 1.16 (3H, s, Me-19), 0.70 (3H, s, Me-20); HRMS (EI) m/z calcd for C₁₉H₃₀O₅ (M⁺ + Na): 361.1985, found 361.1991.

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Sample Availability: Samples of compounds **1**, **2**, **7**, **9**, **10**, **11**, **15**, **16**, **17**, **19** and **20** are available from the authors

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