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Semisynthesis of (+)-angeloyl-gutierrezianolic acid methyl ester diterpenoid

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ABSTRACT

This paper describes the use of zamoranic acid in the first semisynthesis of the furolabdane (+)-angeloyl-gutierrezianolic acid methyl ester diterpenoid, which also establishes the absolute configuration of the natural product. Direct deconjugation of Δ^7 in zamoranic acid and Bestmann methodology for the furan ring synthesis are the key steps.

1. Introduction

Diterpenes of the labdane-type belong to a class of compounds with increasing pharmacological interest.[1] Antimutagenic, antibacterial, antifungal and blood coagulation influencing effects are reported.[2]

However, as in the case of many other natural products, they are isolated in minute amounts. This fact inhibits their unambiguous structural determination and often precludes the study of biological and chemical reactivity. Therefore, the synthesis of minor components from other abundant natural products is of longstanding interest. As an example angeloyl-gutierrezianolic acid **1**, Fig. 1, is a furolabdane, isolated by Timmermann et al.[3] from *Baccharis pingraea* DC (family Asteraceae, tribe Astereae), popularly known as 'Chilca' and before by Bohlmann et al. from *Gutierrezia espinosae* (Compositae, tribe Astereae).[4] These plants are used in South America in folk medicine due to their antirheumatic, antiinflamatory, antitumoural and antibiotic properties. From the large genus *Baccharis* already more than 50 species have been investigated chemically. From *Baccharis pingraea* a big number of *ent*-labdane glycosides and several labdanes of the normal series have been reported. The absolute configuration of several of them remains undetermined, the one of **1**, Fig. 1, was proposed on the basis to biogenetic and taxonomic considerations, but until now has not been rigorously established.

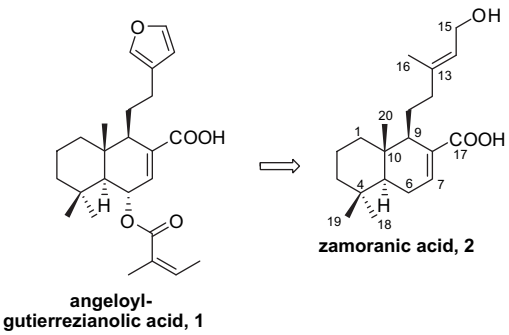

Fig. 1.

As continuation of our studies to the synthesis of furolabdane and labdenolide terpenoids we decided to synthesise angeloyl-gutierrezianolic acid, **1**, for the reasons proposed above and in order to do structure–activity relationship studies. As starting material was chosen zamoranic acid, **2**[5] a diterpene of known configuration, Fig. 1, already used for the synthesis of bioactive natural products as drimanes,[6] (+)-limonidilactone,[7] chrysolic acid,[8] totarol[9] and other tricyclic diterpenes of different skeletons.[10]

In this paper, we describe an easy and direct route for the access to compounds functionalised in C-6 from zamoranic acid. This methodology makes possible the first synthesis of the gutierrezianolic acid and to determine the absolute configuration of the natural product.

2. Results and discussion

The synthesis of the target compound, the methyl ester of the angeloyl-gutierrezianolic acid, **30**, can be carried out attending to

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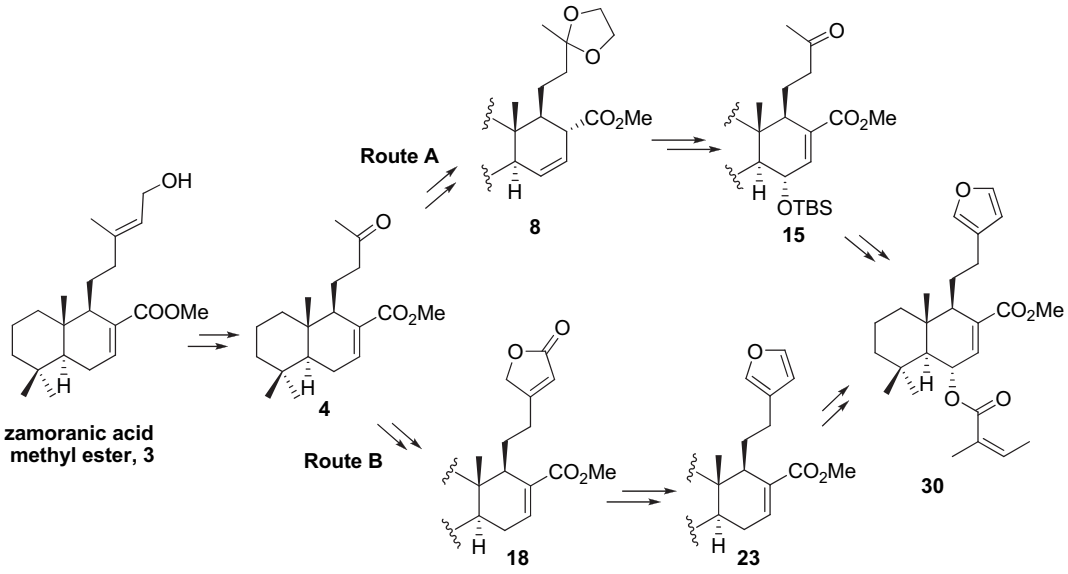
the synthetic proposals shown in Scheme 1. In route A, the first step is the functionalisation of C-6 position with the side chain protected. Further transformations at the side chain will afford the furan ring. In route B, the furan ring will be set up at the side chain in an earlier step with the subsequent C-6 functionalisation. In both cases, methylketone **4** will be the key intermediate. The access to compound **4** by degradation of the side chain of zamoranic acid methyl ester, **3**, has been previously developed by our group.[9–11]

The deconjugation reaction was carried out by treatment of ester **5** under different basic conditions. In all cases, the hydrolysis of the ester took place in forming an inseparable mixture of acids **6**/**7** due to residual water presence (Scheme 2). After esterification of this mixture, a column chromatography was done and methyl esters **5** and **8** were separated. The best results obtained were when NaOMe was used as base for 72 h at 85 °C leading to compound **8** in 66% yield and 28% yield of ester **5**. The stereochemistry of ester **8**



Scheme 1.

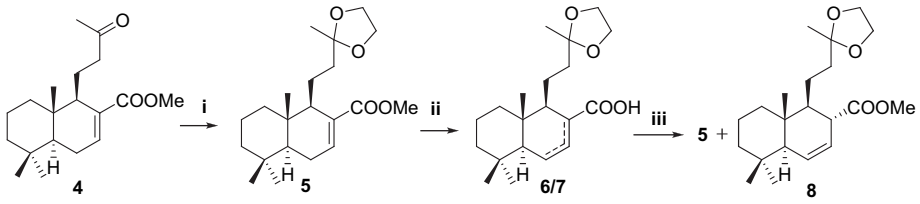
2.1. Route A

Previous experience in our lab, in the allylic oxidation, with labdanes analogues to the ones described here, showed us about the impossibility to oxidise C-6 in one step, without rearrangement of the double bond from Δ^7 to Δ^8.[12] So the challenge is to develop a reaction that gives access to the C-6 position in good yields. The deconjugation reaction of the double bond from Δ^7 to Δ^6 was our choice, taking advantage of the presence of the conjugate ester in the starting material **4**.

The route was started with the protection of methylketone **4** as its dioxolan derivative **5** achieved using ethylene glycol with a catalytic amount of *p*-TsOH (Scheme 2).

can be justified by the mechanism proposed in Fig. 2. Under basic conditions, the abstraction of the most accessible equatorial hydrogen at C-6, lead to the intermediate enolate, that after reprotonation taking place by the beta face of the molecule gives the thermodynamic more stable compound **8**. The coupling constant measured for H_8–H_9 (11.8 Hz) in compound **8** establish the stereochemistry at C-8, being the methoxycarbonyl group equatorial, as can be seen in Fig. 2.

The first attempt to obtain the desired allylic system of gutierrezianolic acid was based on a sequence of two steps: *cis*-dihydroxylation reaction and a subsequent selective elimination of hydroxyl group at C-7 (Scheme 3). Treatment of compound **8** with OsO_4[13] afforded the expected glycol **9** as the only product detected.



Scheme 2. (i) *p*-TsOH, ethylene glycol, reflux 24 h, 98%; (ii) NaOMe, MeOH, 85 °C, 72 h; (iii) $TMSCHN_2$, C_6H_6/MeOH, 66% for the two steps.

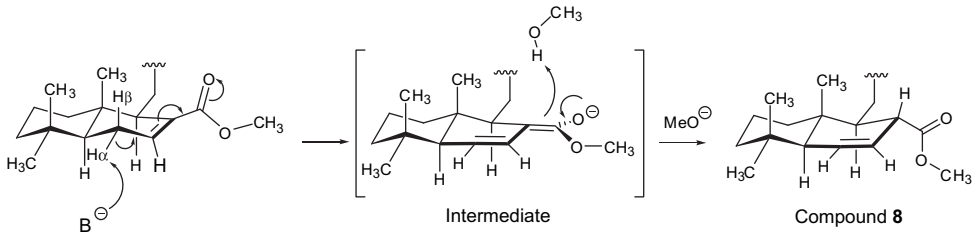
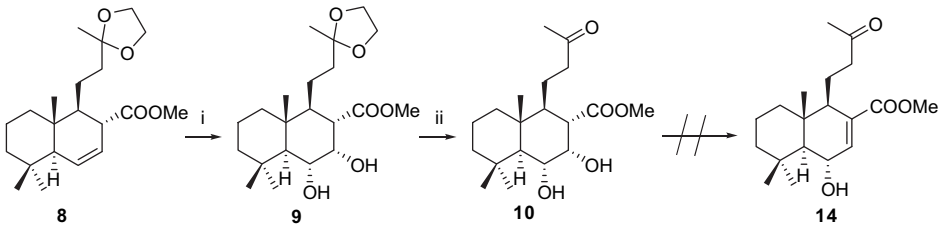


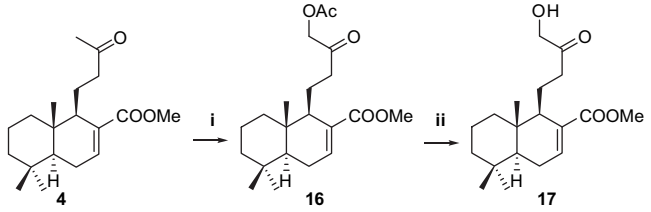
Fig. 2.



Scheme 3. (i) OsO_4 2.5% in *t*-BuOH (8%), NMO, *t*-BuOH/THF/H_2O (7:2:1), rt, 24 h, 92%; (ii) *p*-TsOH, benzene, rt, 6 h, 94%.

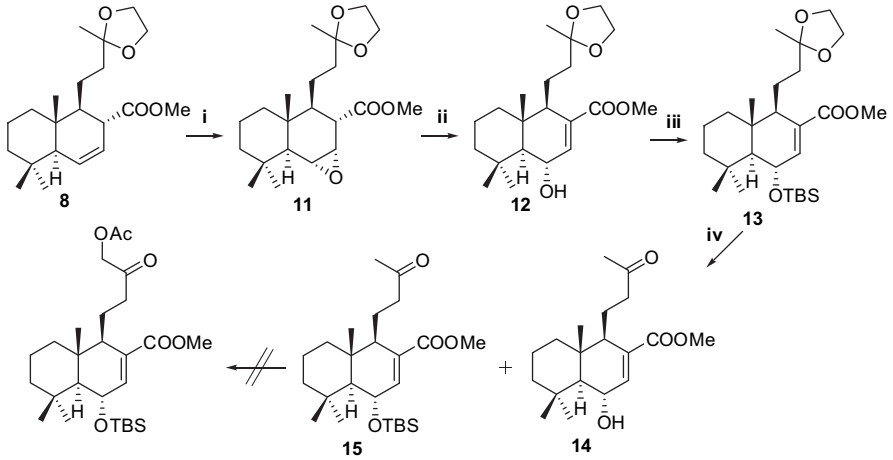
However, all efforts to produce a selective elimination of the hydroxyl group at C-7 in acidic or basic medium were unsuccessful, only being isolated compound **10**, the result of deprotection in acid conditions. No results were obtained when glycol **10** was subjected to the same conditions tested for compound **9**, as well.

Considering the negative results in the previous procedure, we decided to try an alternative route. First of all, we prepared regioselectively epoxide **11** from ester **8** using *m*-CPBA (Scheme 4). Treatment of compound **11** with K_2CO_3 3% as weak base to avoid the ester hydrolysis produces a selective opening of the epoxide **11** in the expected way to lead to the allylic alcohol **12** with the desired stereochemistry on C-6 (Scheme 4). At this point, the protection of the allylic alcohol as its silyl derivative **13** was necessary to prevent unwanted reactions in the followings steps.



Scheme 5. (i) $Pb(OAc)_4$, $BF_3 \cdot Et_2O$, C_6H_6, MeOH, 0 °C to rt, 45 min, 98%; (ii) K_2CO_3, MeOH, rt, 45 min, 97%.

of **18** with an excess of DIBAH gave a mixture of lactols **19a**/**19b**. A solution of this mixture in Et_2O was treated with SiO_2 to give furan **20** in an excellent yield. Oxidation of **20** was carried out using PDC[16] to afford aldehyde **21** (Scheme 6), and subsequent oxidation using



Scheme 4. (i) *m*-CPBA, DCM, rt, 4 h, 82%; (ii) K_2CO_3, MeOH, rt, 3 h, 96%; (iii) 2,6-lutidine, TBSOTf, THF, 45 min, 74%; (iv) *p*-TsOH, acetone, rt, 14 h **14** (42%) and **15** (50%).

Treatment of compound **13** with *p*-TsOH in catalytic amount gave a mixture of hydroxyketone **14** and the desired compound **15** (Scheme 4). When ketone **15** was treated with $BF_3 \cdot Et_2O$ and $Pb(OAc)_4$ to prepare the α-acetoxyl derivative,[14] the reaction did not work and all the subsequent attempts to achieve a hydroxyl group at C-13 led to unknown by-products. This lack of reactivity ended this route and it was decided to start the second one, installing first the furan ring and then functionalisation at C-6.

2.2. Route B

The first goal of this route will be to build the furan ring at the side chain of the methylketone **4** followed by the development of the allylic system at ring B.

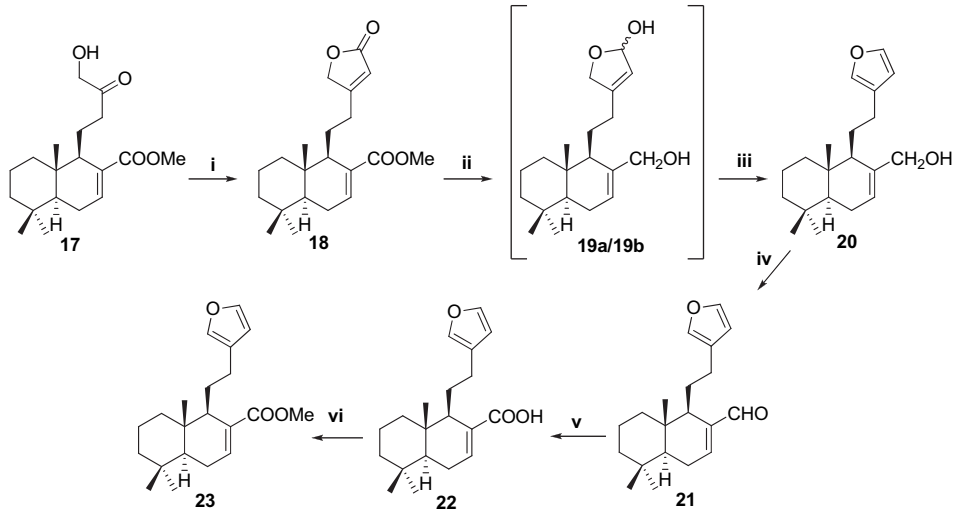
Regioselective acetoxylation of compound **4** was achieved in an excellent yield using $Pb(OAc)_4$ and $BF_3 \cdot Et_2O$ in benzene (Scheme 5).[14] Hydrolysis of **16** gave the 16-hydroxyketone **17**, needed to install the furan ring at the side chain.

Treatment of **17** with Bestmann's[15] ketene under reflux in benzene afforded in one step the lactone **18** (Scheme 6). Reduction $NaClO_2$[17] gave acid **22**, which was esterified to produce the desired ester **23**.

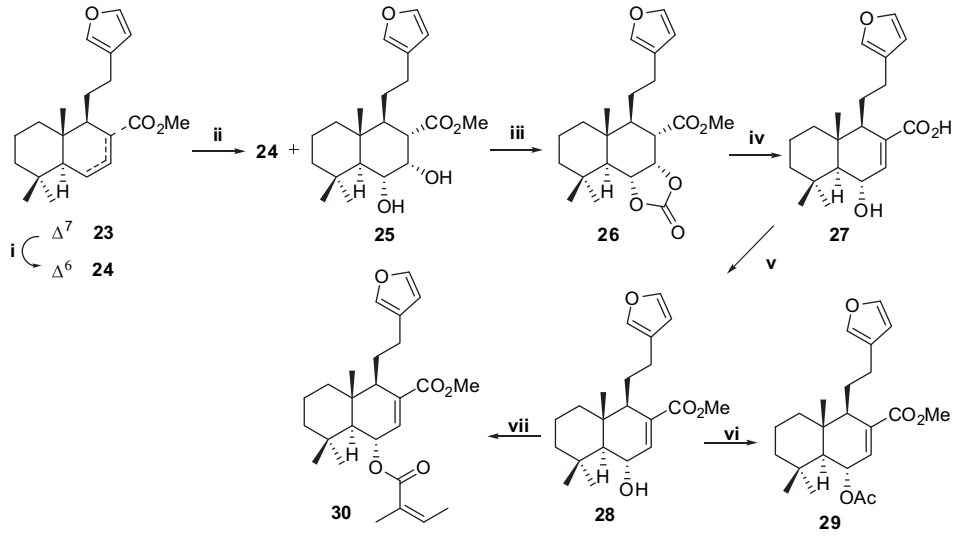
The physical data of compound **22** ($[\alpha]_D^{20}$ −28.0 (*c* 0.1, $CHCl_3$)) are identical to those corresponding to the natural product furolabd-7-en-17-oic acid ($[\alpha]_D^{25}$ −27.0 (*c* 0.9, $CHCl_3$)).[3]

When ester **23** was subjected to the deconjugation conditions previously described, compound **24** was obtained in good yield (Scheme 7). Unlike route A, the inability to use peroxides in the presence of the furan ring forced us to develop an alternative way for the oxidation of the double bond to access at C-6. It was chosen to synthesise a carbonate, which under basic conditions will give a regioselective opening to afford the allylic system. Treatment of **24** with OsO_4 for 16 h at room temperature gave glycol **25**, in moderate yield that can be increased to 68% by recycling the recovered starting material (Scheme 7).

Carbonate **26** was obtained from **25** using triphosgene[18] under basic conditions. The treatment of **26** with NaH under reflux afforded the hydroxyacid **27** (gutierrezianolic acid), which was esterificated in situ to obtain gutierrezianolic methyl ester **28**. In our knowledge, this is the first time that an optical rotation for



Scheme 6. (i) $Ph_3P{=}C{=}C{=}O$, C_6H_6, reflux, 90 min, 97%; (ii) DIBAH, DCM, rt, 10 min, 99%; (iii) SiO_2, Et_2O, 97%; (iv) PDC, DMF, rt, 2 h, 96%; (v) $NaClO_2$, NaH_2PO_4, *t*-BuOH/2-methyl-2-butene/H_2O (2:2:1), rt, 21 h, 87%; (vi) $TMSCHN_2$, C_6H_6/MeOH (1:1), rt, 98%.



Scheme 7. (i) NaOMe, MeOH, 85 °C, 72 h, 65%; (ii) OsO_4 2.5% in *t*-BuOH (10%), NMO, *t*-BuOH/THF/H_2O (7:2:1), rt, 16 h, 68%; (iii) $(Cl_3CO)_2CO$, Py, DCM, 75 min, from −78 °C to rt, 98%; (iv) NaH 60%, THF, 45 min, 0 °C to 60 °C, 62%; (v) $TMSCHN_2$, C_6H_6/MeOH (1:1), rt, 98%; (vi) Ac_2O, Py, overnight, rt, 97%; (vii) (1); (2) To a solution of **28** in benzene and K_2CO_3, add the mixed anhydride resulting from mixing of angelic acid, Et_3N, 2,4,6-trichlorobenzoyl chloride at rt for 2 h, and then heat the mixture to 80 °C for 72 h; 47%.

compound **28** has been reported, $[\alpha]_D^{20}$ +12.9 (*c* 0.2, $CHCl_3$). The acetyl derivative **29** was prepared in the usual conditions ($[\alpha]_D^{20}$ +53.1 (*c* 0.3, $CHCl_3$)) in order to compare with the one given by Bolhmann et al. ($[\alpha]_D^{25}$ +59.9 (*c* 1.3, $CHCl_3$)).[19] Both are in agreement, and the absolute configuration of the natural product was corroborated, as shown in Scheme 7.

Finally, to achieve the angeloyl derivative **30**, Yamaguchi[20] conditions were required, due the instability of the angelic acid.[21] This procedure involves a first stage in which a mixed anhydride is formed by adding Et_3N of a mixture of angelic acid and 2,4,6-trichlorobenzoyl chloride. After the mixed anhydride is obtained, a solution of alcohol **28** was added to afford the desired angeloyl ester **30**, in low yield. The yield can be increased to 47% doing an inverse addition, via cannula, over a solution in toluene of **28**, in presence of an equimolar quantity of K_2CO_3, a solution of the mixed anhydride, obtaining **30**. The optical rotation of **30**, $[\alpha]_D^{20}$ +62.0 (*c* 1.0, $CHCl_3$), is identical to the natural product, $[\alpha]_D^{25}$ +72.0 (*c* 1.0, $CHCl_3$),[4] being corroborated the absolute configuration of the natural product.

3. Conclusions

A direct deconjugation reaction of Δ^7 at dinorlabdane derivatives from zamoranic acid has been developed to access at C-6. The use of the best conditions obtained for this reaction made possible to elaborate the allylic system of gutierrezianolic acid regioselectively. Bestmann ketene was used to achieve after reduction of the furan ring at the side chain of the dinorlabdane derivatives. The synthesis of furolabd-7-en-17-oic acid, gutierrezianolic acid methyl ester and angeloyl-gutierrezianolic acid methyl ester made possible to establish the absolute configuration of these natural products.

4. Experimental

4.1. 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. ^{1}H 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 ^{1}H 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 hertz. 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 ionisation (ammonia as gas) or Fast Atom Bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionisation (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 argon atmosphere. Zamoranic acid $[\alpha]_D^{20}$ −46.6 (*c* 0.82, $CHCl_3$) has been isolated from *Halimium viscosum* (Valparaiso) as indicated in Ref. 5.

4.2. Reaction of 4 with ethylene glycol, *p*-TsOH to yield 5

To a solution of compound **4** ($[\alpha]_D^{20}$ −52.0 (*c* 0.7, $CHCl_3$));[5,9–11] (1.6 g, 5.22 mmol) in benzene (52 ml) were added ethylene glycol (4.6 ml, 6.02 mmol) and a catalytic amount of *p*-TsOH (15 mg, 0.16 mmol) and the solution was refluxed in a Dean–Stark apparatus. After 24 h, the mixture was cooled and diluted with Et_2O (300 mL), followed by successive washing (50 mL each) of the organic layer with $NaHCO_3$ 6%, water and brine, dried (Na_2SO_4 anhydrous), filtered and the solvent removed to give **5** (1.8 g, 98%).

*4.2.1. Methyl 13-ethylenedioxy-14,15-dinor-labd-7-en-17-oate (**5**).* R_f 0.28 (*n*-Hex/EtOAc 8:2); $[\alpha]_D^{20}$ −8.2 (*c* 0.2, $CHCl_3$); IR ν_{max} (film): 2955, 1717, 1647, 1462, 1435, 1375, 1317, 1269, 1244, 1211, 1150 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.66–6.60 (1H, m, H-7), 3.89–3.87 (4H, m, $-OC_2H_4O-$), 3.68 (3H, s, $-COOMe$), 2.18–1.13 (14H, m), 1.26 (3H, s, H-16), 0.88, 0.83 and 0.81 (3Me, s each, Me-18, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.8 (C-17), 136.9 (C-7), 135.8 (C-8), 110.2 (C-13), 64.6 ($-OC_2H_4O$), 51.2 ($-COOMe$), 50.6 (C-9), 49.6 (C-5), 42.1 (C-12), 40.1 (C-3), 39.6 (C-1), 37.1 (C-10), 33.2 (C-18), 32.8 (C-4), 24.0 (C-6), 23.6 (C-16), 22.5 (C-11), 22.0 (C-19), 18.6 (C-2), 14.4 (C-20); EIHRMS: calcd for $C_{21}H_{34}O_4Na$ (M+Na$^+$): 373.2345, found: 373.2342.

4.3. Reaction of 5 with NaOMe/MeOH, $TMSCHN_2$ to yield 8

To a solution of NaOMe/MeOH (2 N), prepared by adding carefully sodium (1.2 g, 50.0 mmol) over MeOH (22 mL), a solution of compound **5** (890 mg, 2.54 mmol) in MeOH (3 mL) was added dropwise at 0 °C; the mixture was heated under reflux for 72 h. After this time, the reaction mixture was allowed to reach room temperature and then, quenched by adding 10 mL of a saturated solution of NH_4Cl dropwise; the mixture was extracted with Et_2O (500 mL) and washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude was dissolved in a mixture of C_6H_6/MeOH (1:1, 14 mL) and was esterificated by adding a solution of $TMSCHN_2$ 2 M in *n*-hexane (1.54 mL) at room temperature. When the addition was completed, the reaction mixture was left to stir for 30 min, and the solvent was evaporated. A column chromatography was carried out by eluting with *n*-Hex/EtOAc (9:1) and compounds **5** (231 mg, 26%) and **8** (586 mg, 66%) were separated.

*4.3.1. Methyl (8R)-13-ethylenedioxy-14,15-dinor-labd-6-en-17-oate (**8**).* R_f 0.44 (*n*-Hex/EtOAc 8:2); $[\alpha]_D^{20}$ −90.2 (*c* 1.1, $CHCl_3$); IR ν_{max} (film): 2949, 1726, 1462, 1375, 1204, 1171, 1063, 733 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.74 (1H, dd, *J*=10.0 and 3.5 Hz, H-6), 5.48 (1H, dd, *J*=10.0 and 3.5 Hz, H-7), 3.96–3.84 (4H, m, $-OC_2H_4O-$), 3.61 (3H, s, $-COOMe$), 2.38 (1H, dd, *J*=11.8 and 3.5 Hz, H-8), 2.00–1.98 (2H, m, H-12), 1.90–1.00 (10H, m), 1.23 (3H, s, H-16), 0.80, 0.76 and 0.75 (3Me, s each, Me-18, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 175.9 (C-17), 130.5 (C-7), 124.7 (C-6), 110.3 (C-13), 64.7 ($-OC_2H_4O-$), 54.1 (C-5), 52.1 ($-COOMe$), 50.0 (C-9), 49.4 (C-8), 41.3 (C-3), 39.1 (C-12), 37.2 (C-10), 37.1 (C-1), 32.8 (C-18), 32.4 (C-4), 23.8 (C-11), 22.8 (C-16), 21.8 (C-19), 18.8 (C-2), 13.5 (C-20); EIHRMS: calcd for $C_{21}H_{34}O_4Na$ (M+Na$^+$): 373.2345, found: 373.2340.

4.4. Reaction of 8 with OsO_4 to yield 9

To a solution of compound **8** (64.8 mg, 0.185 mmol) in *t*-BuOH/THF/H_2O (7:2:1, 5 mL), NMO (93 mg, 0.684 mmol) and OsO_4 (2.5% in *t*-BuOH, 0.15 mL, 0.015 mmol) were added. The solution was stirred for 24 h at room temperature, and then, a saturated aqueous solution of Na_2SO_3 (5 mL) was added and the mixture was stirred for 30 min. After that, the reaction mixture was extracted with EtOAc (100 mL) followed by successive washing (10 mL each) of the organic layer with $Na_2S_2O_3$ 10%, HCl 2 M, H_2O and brine. Then, the organic phase was dried over Na_2SO_4 and the solvent was evaporated to afford compound **9** (65 mg, 92%).

*4.4.1. Methyl (8S)-13-ethylenedioxy-14,15-dinor-6R,7S-dihydroxy-17-oate (**9**).* R_f 0.21 (*n*-Hex/EtOAc 6:4); $[\alpha]_D^{20}$ +20.8 (*c* 0.66, $CHCl_3$); IR ν_{max} (film): 3458 (br), 2933, 1737, 1444, 106, 860; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.02 (1H, m, H-7), 3.94 (1H, m, H-6), 3.91–3.84 (4H, m, $-OC_2H_4O-$), 3.73 (3H, s, $-COOMe$), 2.65–2.58 (1H, dd, *J*=12.0 and 2.6 Hz, H-8), 1.24 (3H, s, Me-16), 1.80–1.44 (12H, m), 1.14, 1.00 and 0.84 (3H, s each, Me-18, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 174.7 (C-17), 108.7 (C-13), 70.5 (C-7), 69.7 (C-6), 63.6 ($-OC_2H_4O-$), 51.1 ($-COOMe$), 50.3 (C-9), 48.6 (C-5), 44.7 (C-8), 42.9 (C-3), 39.2 (C-10), 38.3 (C-1), 37.7 (C-12), 35.5 (C-18), 32.2 (C-4), 22.7 (C-16), 21.8 (C-19), 21.0 (C-11), 17.6 (C-2), 13.5 (C-20); EIHRMS: calcd for $C_{21}H_{36}O_6Na$ (M+Na$^+$): 407.2406, found 407.2404.

4.5. Reaction of 9 with *p*-TsOH to yield 10

To a solution of compound **9** (20 mg, 0.05 mmol) in 1.8 mL of benzene, *p*-TsOH (16 mg, 0.08 mmol) was added at room temperature and the mixture was stirred for 6 h. After this time, the reaction mixture was extracted with EtOAc (100 mL) followed by successive washing (10 mL each) of the organic layer with $NaHCO_3$ 6%, H_2O and brine. Then, the crude was dried over Na_2SO_4 and the solvent was evaporated to afford compound **10** (16 mg, 94%).

*4.5.1. Methyl (8S)-6R,7S-dihydroxy-13-oxo-14,15-dinor-labdan-17-oate (**10**).* R_f 0.51 (*n*-Hex/EtOAc 7:3); IR ν_{max} (film): 3468 (br), 2972, 1718, 1400, 1363, 1169, 1125, 1019, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.04 (1H, c, *J*=2.3 Hz, H-7), 3.79 (1H, dt, *J*=10.7 and 2.3 Hz, H-6), 3.75 (3H, s, $-COOMe$), 3.26 (1H, d, *J*=2.3 Hz, C_7-OH), 2.64 (1H, dd, *J*=12.2 and 2.3 Hz, H-8), 2.46 (1H, ddd, *J*=18.4, 11.1 and 5.6 Hz, H_A-12), 2.37 (1H, ddd, *J*=18.4, 11.12 and 5.6 Hz, H_B-12), 2.09 (3H, s, $MeCO-$), 2.02 (1H, d, *J*=10.7 Hz, C_6-OH), 1.80–0.91 (10H, m), 1.15, 1.01 and 0.85 (3H, s each, Me-18, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 208.8 (C-13), 175.7 (C-17), 71.6 (C-7), 71.0 (C-6), 52.3 ($-COOMe$), 51.5 (C-9), 49.8 (C-5), 45.4 (C-8), 45.2 (C-12), 43.9 (C-3), 39.4 (C-10), 39.0 (C-1), 36.6 (C-18), 33.4 (C-4), 30.1 (C-16), 22.6 (C-11), 22.2 (C-19), 18.7 (C-2), 14.6 (C-20); EIHRMS: calcd for $C_{19}H_{32}O_5Na$ (M+Na$^+$): 363.2142, found 363.2140.

4.6. Reaction of 8 with *m*-CPBA to yield 11

To a solution of compound **8** (102 mg, 0.29 mmol) in DCM (3.0 mL), *m*-CPBA (76 mg, 0.44 mmol) in DCM (1.0 mL) was added at 0 °C and then, the mixture was stirred at room temperature for 4 h. After this time, $NaHSO_3$ 10% (10 mL) was added, the mixture

was extracted with Et_2O (200 mL), followed by successive washing (10 mL each) of the organic layer with $NaHCO_3$ 6%, H_2O and brine. Then, the product was dried over Na_2SO_4, filtered and the solvent was evaporated to afford **11** (87 mg, 82%).

*4.6.1. Methyl (8S)-13-ethylenedioxy-6α,7α-epoxy-14,15-dinor-labdan-17-oate (**11**).* R_f 0.22 (*n*-Hex/EtOAc 8:2); $[\alpha]_D^{20}$ −27.2 (*c* 0.8, $CHCl_3$); IR ν_{max} (film): 3480, 2927, 2252, 1733, 1461, 1368, 1247, 1059, 915, 734 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.92–3.89 (4H, m, $-OC_2H_4O-$), 3.75 (3H, s, $-COOMe$), 3.38 (1H, t, *J*=3.4 Hz, H-7), 3.05 (1H, dd, *J*=3.4 and 2.2 Hz, H-6), 2.67 (1H, dd, *J*=16.5 and 3.4 Hz, H-8), 2.22–1.11 (12H, m), 1.26 (3H, s, Me-16), 1.05, 0.96 and 0.82 (3Me, s each, Me-18, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 173.5 (C-17), 110.0 (C-13), 64.7 ($-OC_2H_4O-$), 54.9 (C-7), 53.2 (C-6), 52.2 ($-COOMe$), 47.3 (C-5), 46.7 (C-9), 45.7 (C-8), 41.6 (C-3), 39.4 (C-12), 37.0 (C-1), 36.5 (C-10), 33.3 (C-18), 32.4 (C-4), 24.0 (C-11), 23.7 (C-16), 22.5 (C-19), 18.6 (C-2), 15.1 (C-20); EIHRMS: calcd for $C_{21}H_{34}O_5Na$ ($M+Na^+$): 389.2298, found: 389.2296.

4.7. Reaction of 11 with K_2CO_3/MeOH to yield 12

To a solution of **11** (120 mg, 0.33 mmol) in MeOH (2 mL), K_2CO_3 (180 mg, 1.30 mmol) was added at room temperature and the mixture was left to stir for 3 h. After this time, water was added and extracted with Et_2O (200 mL), followed by successive washing (15 mL each) of the organic layer with H_2O and brine. Then, the product was dried over Na_2SO_4 anhydride, filtered and the solvent was evaporated to obtain **12** (115 mg, 96%).

*4.7.1. Methyl 13-ethylenedioxy-6α-hydroxy-14,15-dinor-labd-7-en-17-oate (**12**).* R_f 0.47 (*n*-Hex/EtOAc 7:3); $[\alpha]_D^{20}$ −14.2 (*c* 1.8, $CHCl_3$); IR ν_{max} (film): 3446 (br), 3029, 2926, 1738, 1647, 1461, 1434, 1379, 1245, 1061, 855 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 6.42 (1H, t, *J*=2.8 Hz, H-7), 4.38 (1H, dt, *J*=9.4 and 2.8 Hz, H-6), 3.86–3.84 (4H, m, $-OC_2H_4O-$), 3.68 (3H, s, $-COOMe$), 2.18–1.23 (12H, m), 1.24, 1.09, 1.01 and 0.82 (4Me, s each, Me-16, Me-18, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.7 (C-17), 140.7 (C-7), 135.4 (C-8), 110.1 (C-13), 69.0 (C-6), 64.6 ($-OC_2H_4O$), 55.6 (C-9), 51.8 ($-COOMe$), 50.0 (C-5), 43.6 (C-3), 40.2 (C-12), 39.7 (C-1), 39.5 (C-10), 36.4 (C-18), 33.2 (C-4), 23.5 (C-16), 22.8 (C-11), 22.2 (C-19), 18.3 (C-2), 15.5 (C-20); EIHRMS: calcd for $C_{21}H_{34}O_5Na$ ($M+Na^+$): 389.2394, found: 389.2396.

4.8. Reaction of 12 with TBSOTf to yield 13

To a solution of compound **12** (30 mg, 0.08 mmol) in THF (0.6 mL), 2,6-lutidine (70 μL, 0.6 mmol) was added at 0 °C, followed by the addition of TBSOTf (70 μL, 0.3 mmol). The mixture was stirred for 45 min at room temperature. After this time, 10 mL of a $NaHCO_3$ 6% solution was added at 0 °C to quench the reaction and then, the mixture was extracted with EtOAc (100 mL) followed by successive washing (50 mL each) of the organic layer with $NaHCO_3$ 6%, HCl 2 M, H_2O and brine. The mixture was dried over Na_2SO_4 anhydride, filtered and the solvent was evaporated. The crude was chromatographed over silica gel eluting with *n*-Hex/EtOAc (9:1) to separate compound **13** (29 mg, 74%).

*4.8.1. Methyl 13-ethylenedioxy-6α-tert-butyldimethylsilyloxy-14,15-dinor-labd-7-en-17-oate (**13**).* R_f 0.60 (*n*-Hex/EtOAc 8:2); $[\alpha]_D^{20}$ +10.6 (*c* 1.6, $CHCl_3$); IR ν_{max} (film): 2929, 1722, 1653, 1463, 1435, 1255, 1145, 1059, 837, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.44 (1H, d, *J*=2.8 Hz, H-7), 4.46 (1H, dt, *J*=10.0 and 2.8 Hz, H-6), 3.92–3.88 (4H, m, $-OC_2H_4O-$), 3.72 (3H, s, $-COOMe$), 2.12–1.22 (12H, m), 1.27, 1.10 and 1.01 (3Me, s each, Me-16, Me-20 and Me-18), 0.89 (9H, s, $-Me_2Si\text{-}Bu$), 0.85 (3H, s, Me-19), 0.17 and 0.13 (2Me, s each, $-Me_2Si$-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.9 (C-17), 140.5 (C-7), 134.6 (C-8), 110.0 (C-13), 69.6 (C-6), 64.5 ($-OC_2H_4O-$), 55.7 (C-9), 51.4 ($-COOMe$), 49.9 (C-5), 44.0 (C-3), 40.1 (C-12), 39.9 (C-1), 39.4 (C-10), 36.3 (C-18), 32.9 (C-4), 26.0 ($-Me_2SiCMe_3$), 23.5 (C-16), 22.4 (C-19), 22.3 (C-11), 18.2 (C-2), 18.0 ($-Me_2SiCMe_3$), 15.7 (C-20), −3.6 ($-Me_2SiCMe_3$); EIHRMS: calcd for $C_{27}H_{48}O_5SiNa$ ($M+Na^+$): 503.3169, found: 503.3166.

4.9. Reaction of 13 with *p*-TsOH to yield 14 and 15

To a solution of compound **13** (110 mg, 0.23 mmol) in acetone (4 mL), *p*-TsOH (1 mg, 0.05 mmol) was added and the mixture was stirred for 14 h. After this time, 10 mL of EtOAc/water (1:1) was added and extracted with EtOAc (200 mL) followed by successive washing (50 mL each) of the organic layer with $NaHCO_3$ 6%, H_2O and brine. The organic phase was dried over Na_2SO_4 anhydride, filtered and the solvent was evaporated under reduced pressure. Column chromatography over silica gel and eluting with *n*-Hex/EtOAc (9:1), compounds **14** (31 mg, 42%) and **15** (37 mg, 50%) were separated.

*4.9.1. Methyl 6α-hydroxy-13-oxo-14,15-dinor-labd-7-en-17-oate (**14**).* R_f 0.46 (*n*-Hex/EtOAc 7:3); $[\alpha]_D^{20}$ −7.1 (*c* 1.2, $CHCl_3$); IR ν_{max} (film): 3446, 2927, 1721, 1647, 1716, 1653, 1458, 1362, 1241, 1225, 917 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 6.48 (1H, t, *J*=2.3 Hz, H-7), 4.38 (1H, dt, *J*=9.3 and 2.3 Hz, H-6), 3.72 (1H, s, −OH), 3.67 (3H, s, $-COOMe$), 2.85 (1H, ddd, *J*=16.6, 11.4 and 4.8 Hz, H_A-12), 2.37 (1H, ddd, *J*=16.6, 11.4 and 4.8 Hz, H_B-12), 2.07 (3H, s, Me-16), 1.85–1.15 (10H, m), 1.10, 1.02 and 0.82 (3Me, s each, Me-20, Me-19 and Me-18); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 209.3 (C-13), 169.3 (C-17), 140.6 (C-7), 135.2 (C-8), 69.1 (C-6), 57.0 (C-9), 51.9 ($-COOMe$), 50.1 (C-5), 45.9 (C-12), 43.7 (C-3), 39.8 (C-1), 39.5 (C-10), 36.7 (C-18), 33.4 (C-4), 29.9 (C-11), 22.7 (C-16), 22.1 (C-19), 18.5 (C-2), 15.4 (C-20); EIHRMS: calcd for $C_{19}H_{30}O_4Na$ ($M+Na^+$): 345.2041, found: 345.2035.

*4.9.2. Methyl 6α-tert-butyldimethylsilyloxy-13-oxo-14,15-dinor-labd-7-en-17-oate (**15**).* R_f 0.46 (*n*-Hex/EtOAc 8:2); $[\alpha]_D^{20}$ +29.1 (*c* 3.2, $CHCl_3$); IR ν_{max} (film): 2929, 2858, 1721, 1463, 1365, 1240, 1127, 837, 776 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 6.50 (1H, t, *J*=2.2 Hz, H-7), 4.52 (1H, dt, *J*=10.3 and 2.2 Hz, H-6), 3.69 (3H, s, $-COOMe$), 2.86 (1H, ddd, *J*=16.6, 11.0 and 5.0 Hz, H_A-12), 2.39 (1H, ddd, *J*=16.6, 11.0 and 5.0 Hz, H_B-12), 2.09 (3H, s, Me-16), 1.82–1.25 (10H, m), 1.08 and 1.00 (2Me, s each, Me-20 and Me-18), 0.88 (9H, s, $-Me_2Si\text{-}Bu$), 0.83 (3H, s, Me-19), 0.15 and 0.12 (2Me, s each, $-Me_2Si$-Bu); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 209.3 (C-13), 169.3 (C-17), 141.7 (C-7), 134.2 (C-8), 69.8 (C-6), 55.8 (C-9), 51.9 ($-COOMe$), 49.9 (C-5), 45.9 (C-12), 44.2 (C-3), 40.0 (C-1), 39.5 (C-10), 36.6 (C-18), 33.2 (C-4), 26.3 (C-16), 26.0 ($-Me_2SiCMe_3$), 22.7 (C-11), 22.1 (C-19), 18.3 (C-2), 18.0 ($-Me_2SiCMe_3$), 15.7 (C-20), −3.3 ($-Me_2SiCMe_3$); EIHRMS: calcd for $C_{25}H_{44}O_4SiNa$ ($M+Na^+$): 459.2901, found: 459.2897.

4.10. Reaction of 14 with *p*-TsOH to yield 15

To a solution of compound **14** (46 mg, 0.14 mmol) in THF (0.6 mL), 2,6-lutidine (60 μL, 0.54 mmol) and TBSOTf (60 μL, 0.26 mmol) were added at 0 °C. The mixture was left to stir for 1 h 20 min at room temperature. After this time, 5 mL of $NaHCO_3$ 6% solution was added at 0 °C and extracted with EtOAc. The organic layers were combined and washed with $NaHCO_3$ 6%, HCl 2 M, H_2O and brine. After dried over Na_2SO_4 and filtered, the solvent was evaporated under reduced pressure. By column chromatography over silica gel and eluting with *n*-Hex/EtOAc (9:1), compound **15** (57 mg, 92%) was separated.

4.11. Reaction of 4 with $Pb(OAc)_4$ to yield 16

To a solution of compound **4** (161 mg, 0.53 mmol) in benzene (6.27 mL), MeOH (190 μl) and $Pb(OAc)_4$ (233 mg, 0.56 mmol), $BF_3 \cdot Et_2O$ (611 μL, 4.95 mmol) was added dropwise at 0 °C and

under argon atmosphere. The solution was kept at this temperature for 5 min and then to room temperature for 45 min. After this, the solution was diluted with Et_2O (200 mL), washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4. The solvent was evaporated to give compound **16** (188 mg, 98%).

*4.11.1. Methyl 16-acetoxy-13-oxo-14,15-dinor-labd-7-en-17-oate (**16**).* R_f 0.44 (*n*-Hex/EtOAc 7:3); $[\alpha]_D^{20}$ −41.4 (*c* 1.0, $CHCl_3$); IR ν_{max} (film): 2926, 2851, 1716, 1643, 1460, 1435, 1368, 1316, 1245, 1144, 1062, 850 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 6.77 (1H, t, *J*=5.2 and 2.4 Hz, H-7), 4.60 (2H, s, H-16), 3.64 (3H, s, −COO*Me*), 2.87 (1H, ddd, *J*=17.1, 11.1 and 4.6 Hz, H_A-12), 2.40 (1H, ddd, *J*=17.1, 11.1 and 4.6 Hz, H_B-12), 2.11 (3H, s, −OCO*Me*), 2.20–1.42 (12H, m), 0.85 (3H, s, Me-20), 0.82 and 0.76 (2Me, s each, Me-18 and Me-19); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 204.3 (C-13), 170.5 (−OCOMe), 169.4 (C-17), 138.7 (C-7), 134.6 (C-8), 68.1 (C-16), 51.7 (−COO*Me*), 50.5 (C-9), 49.5 (C-5), 42.1 (C-3), 40.8 (C-12), 39.4 (C-1), 37.1 (C-10), 33.3 (C-18), 33.0 (C-4), 24.2 (C-6), 22.1 (C-19), 21.7 (C-11), 20.7 (−OCO*Me*), 18.6 (C-2), 14.2 (C-20). EIHRMS: calcd for $C_{21}H_{32}O_5Na(M+Na^+)$: 387.2148, found: 387.2147.

4.12. Reaction of 16 with K_2CO_3 to yield 17

Compound **16** (270 mg, 0.74 mmol) was treated with K_2CO_3 (450 mg, 3.26 mmol) in MeOH (8.0 mL) and the mixture was stirred at room temperature for 45 min. Then, the reaction mixture was extracted with EtOAc (300 mL) followed by successive washing (15 mL each) of the organic layer with water and brine, dried over Na_2SO_4, filtered and the solvent was evaporated to afford **17** (231 mg, 97%).

*4.12.1. Methyl 16-hydroxy-13-oxo-14,15-dinor-labd-7-en-17-oate (**17**).* R_f 0.29 (*n*-Hex/EtOAc 7:3); $[\alpha]_D^{20}$ −81.5 (*c* 0.2, $CHCl_3$); IR ν_{max} (film): 3477 (br), 2925, 2851, 1714, 1644, 1435, 1396, 1247, 1065, 850, 760 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 6.77 (1H, t, *J*=5.2 and 2.4 Hz, H-7), 4.23 (2H, s, H-16), 3.69 (3H, s, −COO*Me*), 2.84 (1H, ddd, *J*=16.5, 10.9 and 5.3 Hz, H_A-12), 2.40 (1H, ddd, *J*=16.5, 10.9 and 5.3 Hz, H_B-12), 2.20–1.42 (12H, m), 0.90 (3H, s, Me-20), 0.87 and 0.81 (2Me, s each, Me-18 and Me-19); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 210.2 (C-13), 169.4 (C-17), 139.0 (C-7), 134.5 (C-8), 68.2 (C-16), 51.7 (−COO*Me*), 50.6 (C-9), 49.5 (C-5), 42.1 (C-3), 40.5 (C-12), 39.5 (C-1), 37.2 (C-10), 33.3 (C-18), 33.0 (C-4), 24.2 (C-6), 22.1 (C-19), 22.0 (C-11), 18.6 (C-2), 14.3 (C-20); EIHRMS: calcd for $C_{19}H_{31}O_4$ ($M+H^+$): 323.2221, found: 323.2215.

4.13. Preparation of Bestmann ketene

To a solution of $Ph_3P{=}CH_2COOEt$ (5.0 g, 14.7 mmol) in C_6H_6 (24.0 mL) was added NaHMDS (14.3 mL, 14.3 mmol), under argon, giving an orange solution. After 30 min the solution become turbid, then benzene (200 mL) was added and filtered off. After that the solvent was evaporated and ether (100 mL) was added, then a white precipitate was formed, which was filtered off, giving the Bestmann ketene (3.6 g, 84%) ($Ph_3P{=}C{=}C{=}O$, mp 162–165 °C).

4.14. Reaction of 17 with Bestmann ketene[15] to yield 18

To a solution of **17** (26 mg, 0.08 mmol) in benzene (2.7 mL), $Ph_3P{=}C{=}C{=}O$ (32 mg, 0.1 mmol) was added at room temperature. The mixture was heated at 85 °C for 90 min. After that, the benzene was evaporated and then solved in ether (100 mL), washed with water (10 mL) and dried (Na_2SO_4 anhydrous). Subsequent chromatography on silica gel afforded compound **18** (27 mg, 97%).

*4.14.1. Methyl 15,16-epoxy-15-oxo-labda-7,13-dien-17-oate (**18**).* R_f 0.61 (*n*-Hex/EtOAc 6:4); $[\alpha]_D^{20}$ −36.0 (*c* 0.6, $CHCl_3$); IR ν_{max} (film): 2926, 2866, 1780, 1749, 1712, 1639, 1458, 1267, 1247, 1042, 866, 733 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 6.80 (1H, t, *J*=5.2 and 2.6 Hz, H-7), 5.79 (1H, s, H-14), 4.72 (2H, d, *J*=1.5 Hz, H-16), 3.69 (3H, s, −COO*Me*), 2.85 (1H, ddd, *J*=16.4, 11.1 and 4.8 Hz, H_A-12), 2.37 (1H, ddd, *J*=16.4, 11.1 and 4.8 Hz, H_B-12), 2.28–1.52 (12H, m), 0.90, 0.86 and 0.81 (3Me, s each, Me-18, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 174.5 (C-15), 171.4 (C-13), 169.2 (C-17), 139.4 (C-7), 134.2 (C-8), 115.1 (C-14), 73.3 (C-16), 51.7 (−COO*Me*), 51.1 (C-9), 49.5 (C-5), 42.1 (C-3), 39.6 (C-1), 37.1 (C-10), 33.3 (C-18), 33.0 (C-4), 30.7 (C-12), 26.3 (C-11), 24.3 (C-6), 22.1 (C-19), 18.6 (C-2), 14.4 (C-20); EIHRMS: calcd for $C_{21}H_{31}O_4$ ($M+H^+$): 347.2213, found: 347.2208.

4.15. Reaction of 18 with DIBAL to yield 19a and 19b

Diisobutylaluminium hydride (0.05 mL of a 1.5 M solution in toluene, 0.08 mmol) was added dropwise to a stirred solution of **18** (12 mg, 0.03 mmol) in DCM (1.2 mL), under argon at −78 °C. The solution was stirred for 45 min, quenched with water and allowed to warm to room temperature; upon gelling the slurry was stirred with solid $NaHCO_3/Na_2SO_4$, and diluted with EtOAc. The mixture was stirred vigorously until, upon standing, the solution cleared. The organic phase was decanted and filtered through a pad of Celite. The filtrate was evaporated in vacuo and purified by column chromatography on silica gel to give **19a** and **19b** (12 mg, 99%).

*4.15.1. 15,16-Epoxy-labda-7,13-dien-15,17-diol (**19a**/**19b**).* R_f 0.39 (*n*-Hex/EtOAc 6:4); ^1H NMR (200 MHz, $CDCl_3$) δ: 6.03 (1H, br s, H-7), 5.79–5.76 (1H, m, H-15), 5.53–5.45 (1H, m, H-14), 4.74–4.41 (2H, m, H-16), 4.16–4.01 (2H, m, H-17), 2.88–1.22 (14H, m), 0.89, 0.87 and 0.76 (3Me, s each, Me-18, Me-19 and Me-20).

4.16. Reaction of 19a/19b with SiO_2 to yield 20

The mixture **19a**/**19b** (29 mg, 0.08 mmol) in Et_2O (2 mL) was treated with SiO_2 (300 mg) and stirred for 45 min, after that the mixture was filtered, dried over Na_2SO_4 and the solvent was evaporated to yield **20** (23 mg, 97%).

*4.16.1. 15,16-Epoxy-labda-7,13(16),14-triene-17-ol (**20**).* R_f 0.44 (*n*-Hex/EtOAc 8:2); $[\alpha]_D^{20}$ +7.2 (*c* 3.9, $CHCl_3$); IR ν_{max} (film): 3325 (br), 2922, 2846, 1502, 1458, 1441, 1387, 1163, 1024, 993, 874, 776 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 7.35–7.33 (1H, m, H-15), 7.24–7.23 (1H, m, H-16), 6.29 (1H, s, H-14), 5.78–5.76 (1H, m, H-7), 4.18 (1H, d, *J*=13.3 Hz, H_A-17), 4.03 (1H, d, *J*=13.3 Hz, H_B-17), 2.78 (1H, ddd, *J*=16.4, 11.1 and 4.8 Hz, H_A-12), 2.37 (1H, ddd, *J*=16.4, 11.1 and 4.8 Hz, H_B-12), 2.50–1.34 (12H, m), 0.88, 0.86 and 0.75 (3Me, s each, Me-18, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 142.9 (C-15), 139.4 (C-16), 139.1 (C-8), 126.1 (C-7), 125.5 (C-13), 111.3 (C-14), 66.3 (C-17), 51.5 (C-9), 50.0 (C-5), 42.4 (C-3), 39.3 (C-1), 36.8 (C-10), 33.4 (C-18), 33.2 (C-4), 27.7 (C-12), 26.4 (C-11), 24.0 (C-6), 22.1 (C-19), 19.0 (C-2), 13.8 (C-20); EIHRMS: calcd for $C_{20}H_{31}O_2$ ($M+H^+$): 303.2325, found: 303.2321.

4.17. Reaction of 20 with PDC to yield 21

To a solution of **20** (30 mg, 0.12 mmol) in DMF (1.20 mL) PDC (180 mg, 0.48 mmol) was added and stirred for 2 h under argon. Then the reaction was quenched with water (10 mL) at 0 °C, extracted with ether (100 mL), dried over Na_2SO_4 and the solvent was evaporated to give **21** (34.2 mg, 96%).

*4.17.1. 15,16-Epoxy-labda-7,13(16),14-trien-17-al (**21**).* R_f 0.61 (*n*-Hex/EtOAc 8:2); $[\alpha]_D^{20}$ −12.9 (*c* 1.3, $CHCl_3$); IR ν_{max} (film): 2923, 2850, 1689, 1631, 1459, 1389, 1261, 1161, 1024, 873, 797, 701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 9.41 (1H, s, −C*H*O), 7.34–7.33 (1H, m, H-15), 7.24 (1H, m, H-16), 6.82–6.80 (1H, m, H-7), 6.33 (1H, s, H-14), 2.97–2.82 (2H, m, H-12), 2.40–1.26 (12H, m), 0.93, 0.89 and 0.79

(3Me, s each, Me-18, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 195.3 (C-17), 153.1 (C-7), 144.6 (C-8), 142.7 (C-15), 138.9 (C-16), 126.0 (C-13), 111.5 (C-14), 50.4 (C-9), 49.6 (C-5), 42.2 (C-3), 39.1 (C-1), 36.8 (C-10), 33.3 (C-18), 33.1 (C-4), 28.1 (C-12), 26.9 (C-11), 25.5 (C-6), 22.1 (C-19), 18.7 (C-2), 14.3 (C-20); EIHRMS: calcd for $C_{20}H_{29}O_2$ (M+H$^+$): 301.2065, found: 301.2061.

4.18. Reaction of 21 with $NaClO_2$ to yield 22

To a solution of **21** (35 mg, 0.12 mmol) in *t*-BuOH/2-methyl-2-butene (1:1, 2.4 mL), was added a solution of NaH_2PO_4 (71.0 mg, 0.6 mmol) in water (0.46 mL) and $NaClO_2$ (0.36 mL, 1.2 mmol). The mixture was stirred for 21 h at room temperature. After that, the reaction was quenched with water and HCl 5% (10 mL), extracted with EtOAc (200 mL), followed by successive washing (10 mL each) of the organic layer with water and brine, dried (Na_2SO_4), and the solvent was evaporated to give **22** (33 mg, 87%).

*4.18.1. 15,16-Epoxy-labda-7,13(16),14-trien-17-oic acid (**22**).* R_f 0.43 (*n*-Hex/EtOAc 8:2); $[\alpha]_D^{20}$ −28.0 (*c* 0.1, $CHCl_3$); IR ν_{max} (film): 3000 (br), 2925, 2665, 1699, 1502, 1459, 1277, 1214, 1168, 1025, 974, 874, 780 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.28 (1H, s, H-15), 7.16 (1H, s, H-16), 6.92–6.90 (1H, m, H-7), 6.23 (1H, s, H-14), 2.85 (1H, ddd, *J*=17.0, 11.4 and 4.6 Hz, H_A-12), 2.37 (1H, ddd, *J*=17.0, 11.4 and 4.6 Hz, H_B-12), 2.21–1.46 (12H, m), 0.88, 0.85 and 0.81 (3Me, s each, Me-18, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 174.5 (C-17), 142.7 (C-15), 140.9 (C-7), 138.8 (C-16), 134.6 (C-8), 125.9 (C-13), 111.3 (C-14), 50.8 (C-9), 49.5 (C-5), 42.2 (C-3), 39.6 (C-1), 37.1 (C-10), 33.3 (C-18), 33.0 (C-4), 29.4 (C-11), 26.7 (C-12), 24.4 (C-6), 22.1 (C-19), 18.7 (C-2), 14.4 (C-20); EIHRMS: calcd for $C_{20}H_{28}O_3Na$ (M+Na$^+$): 339.1943, found: 339.1946.

4.19. Reaction of 22 with $TMSCHN_2$ to yield 23

To a solution of acid **22** (100 mg, 0.6 mmol) in MeOH/benzene (1:1, 20 mL) was added $TMSCHN_2$ 2 M in hexane (0.3 mL). After 30 min the solvent was evaporated to give **23** (102 mg, 98%).

*4.19.1. Methyl 15,16-epoxy-labda-7,13(16),14-trien-17-oate (**23**).* R_f 0.78 (*n*-Hex/EtOAc 8:2); $[\alpha]_D^{20}$ −35.3 (*c* 1.0, $CHCl_3$); IR ν_{max} (film): 2925, 2851, 1716, 1646, 1558, 1501, 1458, 1388, 1244, 1214, 1104, 1024, 976, 874, 850 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.33 (1H, s, H-15), 7.20 (1H, s, H-16), 6.69 (1H, s, H-7), 6.26 (1H, s, H-14), 3.72 (3H, s, −COO*Me*), 2.74 (1H, ddd, *J*=17.1, 11.6 and 5.6 Hz, H_A-12), 2.37 (1H, ddd, *J*=17.1, 11.6 and 5.6 Hz, H_B-12), 2.48–1.46 (12H, m), 0.91, 0.87 and 0.83 (3Me, s each, Me-18, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.9 (C-17), 142.8 (C-15), 138.8 (C-7), 137.6 (C-16), 135.4 (C-8), 125.9 (C-13), 111.3 (C-14), 51.6 (−COO*Me*), 51.0 (C-9), 49.6 (C-5), 42.2 (C-3), 39.6 (C-1), 37.1 (C-10), 33.4 (C-18), 33.0 (C-4), 29.3 (C-12), 26.6 (C-11), 24.2 (C-6), 22.2 (C-19), 18.7 (C-2), 14.5 (C-20); EIHRMS: calcd for $C_{21}H_{30}O_3Na$ (M+Na$^+$): 353.2093, found: 353.2091.

4.20. Reaction of 23 with NaOMe/MeOH to yield 24

A solution of NaOMe (2 N) in MeOH was prepared carefully adding sodium metal (166 mg, 0.71 mmol) over MeOH (360 μL) at 0 °C. Then, a solution of compound **23** (280 mg, 0.85 mmol) in MeOH (0.2 mL) was added at room temperature. The solution was left to stir at 85 °C for 72 h. After that, the mixture was diluted with Et_2O (200 mL) followed by successive washing (30 mL each) of the organic layer with saturated NH_4Cl solution, H_2O, brine and dried over Na_2SO_4. The solvent was removed and the crude mixture was chromatographed (Hex/EtOAc 8:2) and compounds **23** (73 mg, 26%) and **24** (174, 62%) were separated.

*4.20.1. Methyl (8R)-15,16-epoxy-labda-6,13(16),14-trien-17-oate (**24**).* R_f 0.69 (*n*-Hex/EtOAc 8:2); $[\alpha]_D^{20}$ −56.9 (*c* 0.3, $CHCl_3$); IR ν_{max} (film): 2925, 2867, 1738, 1501, 1459, 1383, 1270, 1192, 1162, 1104, 1025, 974, 874, 783 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.32 (1H, s, H-15), 7.18 (1H, s, H-16), 6.24 (1H, s, H-14), 5.79 (1H, dt, *J*=5.8 and 2.9 Hz, H-6), 5.59 (1H, dd, *J*=5.8 and 2.9 Hz, H-7), 3.69 (3H, s, −COOMe), 2.88–1.28 (12H, m), 2.84 (1H, dd, *J*=9.5 and 2.9 Hz, H-8), 0.91, 0.87 and 0.83 (3Me, s each, Me-18, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 175.9 (C-17), 142.8 (C-15), 138.8 (C-16), 130.5 (C-7), 125.5 (C-13), 124.6 (C-6), 111.1 (C-14), 54.0 (C-5), 52.2 (−COOMe), 49.1 (C-9), 50.1 (C-8), 41.3 (C-3), 37.3 (C-1), 37.1 (C-10), 33.0 (C-18), 32.8 (C-4), 30.7 (C-12), 25.0 (C-11), 21.8 (C-19), 18.8 (C-2), 13.5 (C-20). EIHRMS: calcd for $C_{21}H_{30}O_3Na$ (M+Na$^+$): 353.2093, found: 353.2091.

4.21. Reaction of 24 with OsO_4 to yield 25

Compound **24** (63 mg, 0.20 mmol) in *t*-BuOH/THF/H_2O (7:2:1, 2 mL) was treated with 4-methylmorpholine *N*-oxide (NMO) (26 mg, 0.19 mmol) and OsO_4 (2.5% in *t*-BuOH, 0.2 mL, 0.02 mmol). The solution was stirred and checked by TLC during 24 h. Then, a saturated aqueous solution of Na_2SO_3 (15 mL) was added and the mixture stirred for 30 min. The resulting solution was diluted with Et_2O (200 mL) followed by successive washing (30 mL each) of the organic layer with HCl 7%, water, brine and dried over Na_2SO_4. After evaporating the solvent a column chromatography (*n*-Hex/EtOAc 8:2) was done to afford **24** (47 mg, 73%) and **25** (15 mg, 20%).

*4.21.1. Methyl (8S)-6α,7α-dihydroxy-15,16-epoxy-labda-13(16),14-dien-17-oate (**25**).* R_f 0.15 (*n*-Hex/EtOAc 7:3); $[\alpha]_D^{20}$ +9.5 (*c* 0.2, $CHCl_3$); IR ν_{max} (film): 3447 (br), 2925, 2869, 1734, 1684, 1556, 1458, 1388, 1244, 1168, 1024, 977, 874, 779 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.32 (1H, br s, H-15), 7.18 (1H, br s, H-16), 6.21 (1H, br s, H-14), 4.04–4.02 (1H, m, H-7), 3.73 (3H, s, −COO*Me*), 3.66–3.64 (1H, m, H-6), 2.65 (1H, dd, *J*=12.0 and 2.6 Hz, H-8), 2.48–1.46 (12H, m), 1.14, 1.01 and 0.84 (3Me, s each, Me-18, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 176.4 (C-17), 143.0 (C-15), 138.7 (C-16), 125.3 (C-13), 111.5 (C-14), 72.1 (C-6), 70.8 (C-7), 54.3 (−COO*Me*), 52.1 (C-5), 50.0 (C-8), 46.2 (C-9), 43.8 (C-3), 38.5 (C-10), 37.5 (C-1), 34.6 (C-18), 32.0 (C-4), 30.8 (C-12), 26.8 (C-11), 22.1 (C-19), 18.9 (C-2), 14.6 (C-20); EIHRMS: calcd for $C_{21}H_{32}O_5Na$ (M+Na$^+$): 387.2138, found: 387.2134.

4.22. Reaction of 25 with $(Cl_3CO)_2CO$ to yield 26

To a solution of pyridine (0.02 mL) in DCM (0.1 mL), $(Cl_3CO)_2CO$ (9.0 mg, 0.03 mmol) was added at −78 °C, under argon and stirred for 5 min, then compound **25** (6.0 mg, 0.02 mmol) in DCM (0.1 mL) was added. The reaction mixture was allowed to warm to room temperature. After 75 min 5 mL of a saturated NH_4Cl solution was added at 0 °C, extracted with EtOAc (100 mL), washed with water (10 mL) and brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated to yield **26** (6 mg, 98%).

*4.22.1. Methyl (8S)-6α,7α-carbonyldioxy-15,16-epoxy-labda-13(16),14-dien-17-oate (**26**).* R_f 0.35 (*n*-Hex/EtOAc 7:3); $[\alpha]_D^{20}$ −2.5 (*c* 0.6, $CHCl_3$); IR ν_{max} (film): 2962, 2925, 2851, 1806, 1738, 1462, 1367, 1261, 1124, 873, 800 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.31 (1H, s, H-15), 7.17 (1H, s, H-16), 6.20 (1H, s, H-14), 4.95 (1H, t, *J*=6.5 Hz, H-7), 4.76 (1H, dd, *J*=10.8 and 6.5 Hz, H-6), 3.75 (3H, s, −COO*Me*), 2.80 (1H, dd, *J*=11.5 and 6.5 Hz, H-8), 2.21–1.26 (12H, m), 1.05, 1.01 and 0.78 (3Me, s each, Me-18, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 170.9 (C-17), 153.9 (−OCOO−), 143.0 (C-15), 138.8 (C-16), 125.2 (C-13), 111.0 (C-14), 77.4 (C-7), 76.1 (C-6), 53.1 (C-5), 52.6 (−COO*Me*), 47.6 (C-8), 46.0 (C-9), 42.8 (C-3), 38.3 (C-1), 37.5 (C-10),

35.1 (C-18), 33.3 (C-4), 31.6 (C-12), 26.3 (C-11), 22.3 (C-19), 18.3 (C-2), 15.1 (C-20); EIHRMS: calcd for $C_{22}H_{30}O_6Na$ (M+Na^+): 413.1921, found: 413.1917.

4.23. Reaction of with NaH to yield 27

NaH 60% (60 mg, 1.0 mmol) was washed three times with THF in order to remove the oil, then a solution of **26** (27 mg, 0.07 mmol) in THF (1.0 mL) was added at 0 °C. The reaction mixture was heated at 60 °C for 45 min. After this time the reaction mixture was cooled at 0 °C, then a saturated solution of NH_4Cl (10 mL) was added and extracted with EtOAc (100 mL) followed by successive washing (30 mL each) with water and brine. After removing the solvent, compound **27** (14 mg, 62%) was obtained.

*4.23.1. 6α-Hydroxy-15,16-epoxy-labda-7,13(16),14-trien-17-oic acid (**27**).* IR ν_{max} (film): 3370 (br), 2925, 1712, 1688, 1070 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 7.32 (1H, br s, H-15), 7.18 (1H, br s, H-16), 6.67–6.64 (1H, m, H-7), 6.24 (1H, br s, H-14), 4.42–4.38 (1H, m, H-6), 2.41–2.28 (2H, m, H-12), 2.22–1.22 (10H, m), 1.14, 1.07 and 0.87 (3Me, s each, Me-18, Me-19 and Me-20).

4.24. Reaction of 27 with $TMSCHN_2$ to yield 28

To a solution of acid **27** (14 mg, 0.04 mmol) in MeOH/benzene (1:1, 1 mL) was added $TMSCHN_2$ 2 M in hexane (0.03 mL). After 30 min the solvent was evaporated to afford **28** (13 mg, 98%).

*4.24.1. Methyl 6α-hydroxy-15,16-epoxy-labda-7,13(16),14-trien-17-oate (**28**).* R_f 0.24 (*n*-Hex/EtOAc 8:2); $[\alpha]_D^{20}$ +12.9 (*c* 0.2, $CHCl_3$); IR ν_{max} (film): 3583, 3411, 2926, 2854, 1718, 1651, 1501, 1461, 1435, 1384, 1240, 1214, 1123, 1023, 977, 873, 786 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.33 (1H, t, *J*=1.6 Hz, H-15), 7.20 (1H, br s, H-16), 6.48 (1H, t, *J*=2.4 Hz, H-7), 6.24 (1H, br s, H-14), 4.39 (1H, dt, *J*=10.7 and 2.4 Hz, H-6), 3.75 (3H, s, −COO*Me*), 2.74 (1H, ddd, *J*=16.0, 11.2 and 4.3 Hz, H_A-12), 2.38 (1H, ddd, *J*=16.0, 11.2 and 4.3 Hz, H_B-12), 2.20–2.17 (1H, m, H-9), 1.90–1.85 (1H, m, H-1), 1.78–1.70 (1H, m, H-11), 1.60–1.40 (2H, m, H-2), 1.48–1.20 (2H, m, H-3), 1.25–1.23 (1H, m, H-11), 1.18 (1H, d, *J*=10.7 Hz, H-5), 1.12–1.02 (1H, m, H-1), 1.15, 1.07 and 0.87 (3Me, s each, Me-19, Me-18 and Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.2 (C-17), 142.6 (C-15), 139.5 (C-7), 138.6 (C-16), 135.6 (C-8), 125.3 (C-13), 110.9 (C-14), 68.9 (C-6), 56.9 (C-5), 51.6 (−COO*Me*), 50.4 (C-9), 43.4 (C-3), 39.5 (C-10), 39.3 (C-1), 36.4 (C-18), 33.1 (C-4), 28.9 (C-12), 26.4 (C-11), 22.4 (C-19), 18.3 (C-2), 15.2 (C-20); EIHRMS: calcd for $C_{21}H_{30}O_4Na$ (M+Na^+): 369.2042, found: 369.2048.

4.25. Reaction of 28 with Ac_2O to yield 29

A solution of compound **28** (12 mg, 0.03 mmol) in pyridine (0.2 mL) and Ac_2O (0.2 mL) was stirred at room temperature for 14 h. Then, ice was added and the solution was stirred for 30 min and diluted with EtOAc (100 mL) followed by successive washing (20 mL each) of the organic layer with HCl 10% and water, dried over Na_2SO_4 and the solvent was evaporated. Purification by chromatography on silica gel gave the monoacetyl derivative **29** in a quantitative yield.

*4.25.1. Methyl 6α-acetoxy-15,16-epoxy-labda-7,13(16),14-trien-17-oate (**29**).* R_f 0.58 (*n*-Hex/EtOAc 8:2); $[\alpha]_D^{20}$ +53.1 (*c* 0.3, $CHCl_3$); IR ν_{max} (film): 2925, 2858, 1723, 1657, 1461, 1371, 1230, 1126, 1022, 967, 873, 797 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 7.33 (1H, t, *J*=1.6 Hz, H-15), 7.20 (1H, br s, H-16), 6.30 (1H, t, *J*=2.4 Hz, H-7), 6.24 (1H, br s, H-14), 5.59 (1H, ddd, *J*=10.8, 3.2 and 2.4 Hz, H-6), 3.73 (3H, s, −COO*Me*), 2.74 (1H, ddd, *J*=16.0, 11.2 and 4.3 Hz, H_A-12), 2.38 (1H, ddd, *J*=16.0, 11.2 and 4.3 Hz, H_B-12), 2.21–2.18 (1H, m, H-9), 2.07 (3H, s, −OCO*Me*), 1.88–1.06 (6H, m), 1.78–1.72 (1H, m, H-11), 1.54 (1H, d, *J*=10.8 Hz, H-5), 1.28–1.22 (1H, m, H-11), 0.98, 0.96 and 0.92 (3Me, s each, Me-18, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 170.4 (−O*C*OMe), 168.8 (C-17), 142.6 (C-15), 138.6 (C-16), 137.0 (C-7), 135.0 (C-8), 125.2 (C-13), 110.9 (C-14), 71.0 (C-6), 53.0 (C-5), 51.6 (−COO*Me*), 50.2 (C-9), 43.1 (C-3), 39.6 (C-10), 39.1 (C-1), 35.6 (C-18), 33.0 (C-4), 29.0 (C-12), 26.4 (C-11), 22.6 (C-19), 21.6 (−OCO*Me*), 18.2 (C-2), 15.2 (C-20); EIHRMS: calcd for $C_{23}H_{32}O_5Na$ (M+Na^+): 411.2128, found: 411.2130.

4.26. Reaction of 29 with angeloyl-2,4,6-trichlorobenzoyl anhydride to yield 30

To a solution of angelic acid (25 mg, 0.25 mmol) in toluene (0.50 mL), 2,4,6-trichlorobenzoyl chloride (40 μL, 0.25 mmol) and Et_3N (30 μL, 0.25 mmol) were added and the mixture stirred for 2 h at room temperature under argon atmosphere. In a different flask, a solution of compound **29** (24 mg, 0.07 mmol) in toluene (0.5 mL) and solid K_2CO_3 (29 mg, 0.36 mmol) was prepared. The solution of the mixed anhydride obtained before was added to this one via *cannula* and the reaction mixture was heated for 72 h at 80 °C. After that, the mixture was filtered, washing with EtOAc (100 mL) followed by successive washing (20 mL each) of the organic layer with aqueous 2 M HCl, aqueous 6% $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and the solvent was evaporated to give a crude oil. A column chromatography on silica gel was done to separate **29** (11 mg, 44%) and **30** (12 mg, 47%).

*4.26.1. Methyl 6α-angeloyloxy-15,16-epoxy-labda-7,13(16),14-trien-17-oate (**30**).* R_f 0.60 (*n*-Hex/EtOAc 8:2); $[\alpha]_D^{20}$ +62.0 (*c* 1.0, $CHCl_3$); IR ν_{max} (film): 2928, 2869, 1720, 1722, 1651, 1578, 1459, 1436, 1368, 1242, 1154, 1083 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.33 (1H, t, *J*=1.6 Hz, H-15), 7.20 (1H, br s, H-16), 6.26 (1H, t, *J*=2.5 Hz, H-7), 6.24 (1H, br s, H-14), 6.08 (1H, qq, *J*=7.0 and 1.5 Hz, H-3′), 5.69 (1H, ddd, *J*=10.7, 3.2 and 2.5 Hz, H-6), 3.73 (3H, s, −COO*Me*), 2.74 (1H, ddd, *J*=16.0, 11.2 and 4.3 Hz, H_A-12), 2.38 (1H, ddd, *J*=16.0, 11.2 and 4.3 Hz, H_B-12), 2.20–2.17 (1H, m, H-9), 2.00 (3H, dq, *J*=7.0 and 1.5 Hz, H-4′), 1.90–1.02 (6H, m), 1.87 (3H, dq, *J*=1.5 and 1.5 Hz, H-5′), 1.80–1.70 (1H, m, H-11), 1.57 (1H, d, *J*=10.7 Hz, H-5), 1.30–1.20 (1H, m, H-11), 0.99, 0.96 and 0.93 (3Me, s each, Me-18, Me-19 and Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.1 (C-17), 167.0 (C-1′), 142.6 (C-15), 138.8 (C-3′), 138.6 (C-16), 137.1 (C-7), 134.9 (C-8), 128.3 (C-2′), 125.4 (C-13), 111.0 (C-14), 70.4 (C-6), 53.1 (C-5), 51.5 (−COO*Me*), 50.5 (C-9), 43.2 (C-3), 39.8 (C-10), 39.3 (C-1), 35.7 (C-18), 33.0 (C-4), 29.1 (C-12), 26.5 (C-11), 22.6 (C-19), 20.5 (C-5′), 18.3 (C-2), 15.8 (C-4′), 15.4 (C-20); EIHRMS: calcd for $C_{26}H_{36}O_5Na$ (M+Na^+): 451.2461, found: 451.2468.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.09.051. These data include MOL files and InChiKeys of the most important compounds described in this article.

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