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Synthesis of (+)-leopersin D

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ABSTRACT

This paper describes the use of (−)-sclareol in the first synthesis of the spirolabdanolide (+)-leopersin D, which also establishes the absolute configuration of the product. The reversibility of conjugate addition/elimination of oxaspirolabdanolide formation is demonstrated.

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1. Introduction

Labdane diterpenes with highly functionalized B rings constitute an interesting class of natural products with important biological activities.[1]

Labdanes bearing a dioxaspiro group with oxygen at C-9 represent a group of natural products that are sufficiently significant from a structural point of view.

Currently, 29 natural spirolabdanes with a highly functionalized B ring are known, some of which are shown in Figure 1. All of these compounds have been isolated from plants of the genus *Leonorus*,[2] *Otostegia*[3] or *Ballota*.[4] The genus *Leonorus* is a widely distributed, medicinally important member of the Lamiaceae family that comprises more than 20 species. Preparations from some of the plants of this genus are utilized in the treatment of cardiovascular diseases, as sedatives, antitumor and for their uterotonic effects.[2b]

(+)-Leopersin D is an example of a natural spirolabdanolide with a highly functionalized B ring. It was first isolated and characterized by Tasdermir and co-workers in 1996 from the aerial parts of *Leonorus persicus*.[2a]

Surprisingly, there are few publications on the synthesis of spirolabdanes. The only example in the literature was the synthesis of prehispanolone reported by Wong,[5] Figure 2. The spirolabdane prehispanolone was found to be unstable under acidic conditions providing the corresponding furolabdane, hispanolone.[5c]

Our group is studying the synthesis of highly functionalized B ring diterpenes, such as labdanes,[6] furolabdanes[7] and labdenolides[7] beginning with (−)-sclareol. In this paper we communicate the first synthesis of the spirolabdanolide (+)-leopersin D, starting from commercial (−)-sclareol. The pivotal step of the synthesis was an intramolecular conjugate addition to make the spirolabdane. As (+)-leopersin D was synthesized from a diterpene of known configuration, its absolute configuration was established, Figure 3.

2. Results and discussion

The syntheses of the spirolabdanolides (+)-leopersin D **1**, and 13-*epi*-leopersin D **2** were planned according to the following retrosynthetic scheme, Scheme 1.

The key intermediate for the elaboration of the target compounds **1** and **2** is the butenolide **7**, which by intramolecular conjugate addition generates the oxaspiro group. The butenolide **7** can be accessed from **4** by functionalization of the side chain and fitting the B ring functionality. The triol **4** obtained from (−)-sclareol **3** has been used before in the synthesis of natural compounds by our group.[6,7]

Initially the synthesis of **7** will be described, followed by that of **1** and **2**.

2.1. Synthesis of intermediate 7

The synthesis of **7** from triol **4** is carried out according to Scheme 2, by protecting the diol at C-6 and C-7 and subsequently altering the side chain.

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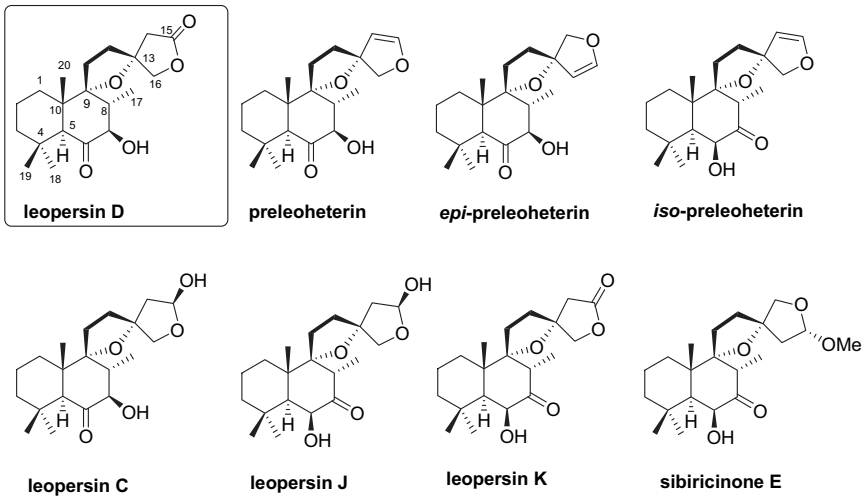


Figure 1.

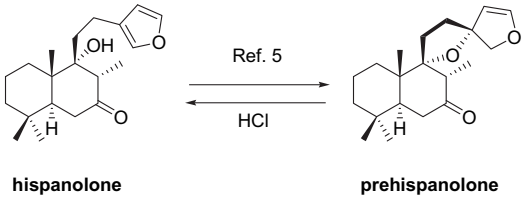


Figure 2.

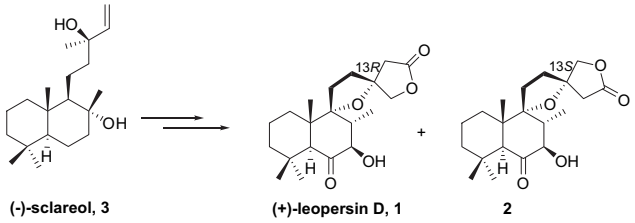


Figure 3.

The reaction of **4** with triphosgene[8] was found to give the carbonate **5** quantitatively. The ulterior oxidation of **5** with $^1O_2$ using Faulkner methodology[9] afforded the γ-hydroxybutenolide **6**. Finally **7** was obtained by the reduction of **6** with $NaBH_4$, with an overall yield from **4** of 54%.

2.2. Synthesis of (+)-leopersin D, 1 and (+)-13-*epi*-leopersin D, 2

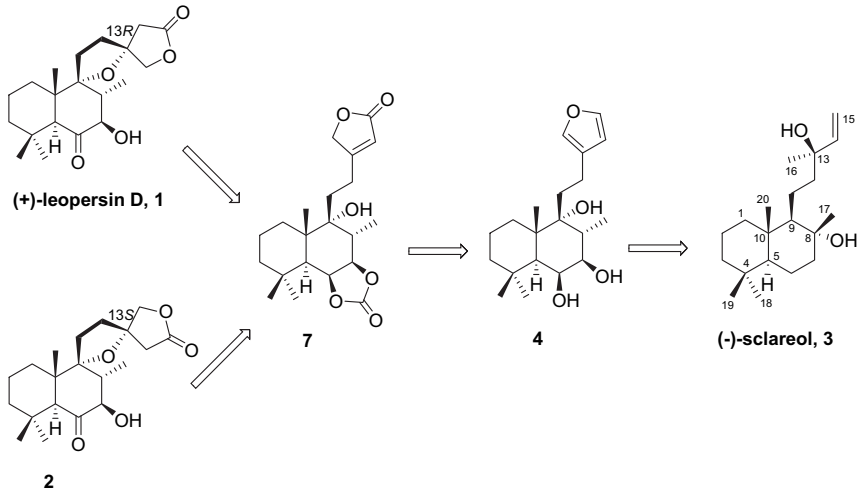
The structures of **1** and **2** differ in the configuration of C-13, being *R* in **1** and *S* in **2**.

The intramolecular conjugate addition of **7**, shown in Scheme 3, provides an inseparable mixture of the spirolabdanolides **8** and **9**. This reaction was carried out in various conditions. When DBU/Et_3N[5] (**a**) was used, a mixture of **8**/**9** (1:1) was obtained and when *R*-(-)-1,1′-binaphthyl-2,2′-diyl hydrogenophosphate[10] (**b**), *S*-(+)-1,1′-binaphthyl-2,2′-diyl hydrogenophosphate[10] (**c**) or *S*-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (**d**) were used, a mixture of **8**/**9** (3:7) was obtained.

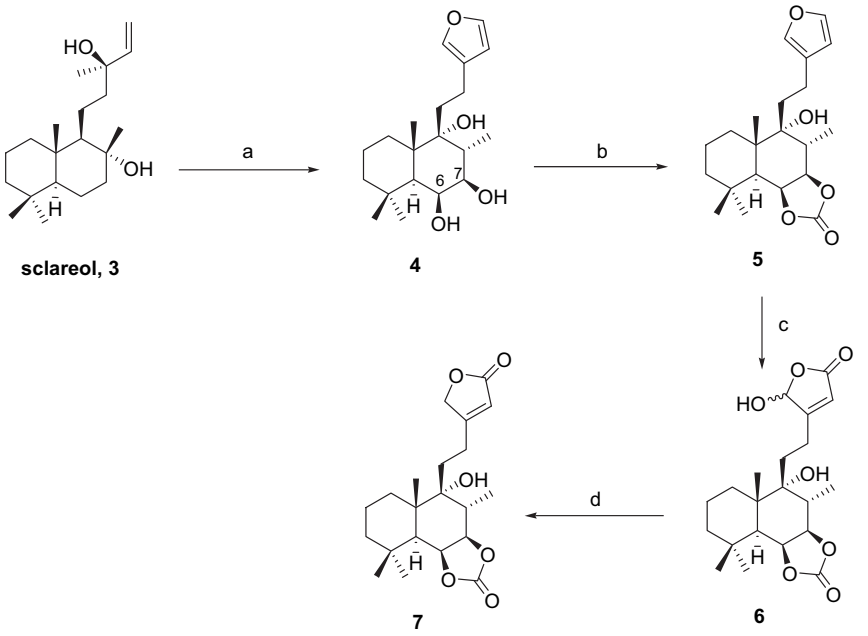
The different proportion of **8** and **9** obtained can be explained as the thermodynamic equilibrium is only reached with DBU/Et_3N; in the other cases the major product **9** obtained, corresponded to the addition of the more stable conformer of **7**, Figure 4.

Hydrolysis with K_2CO_3 in MeOH of the mixture **8**/**9** (1:1) obtained from the reaction using DBU/Et_3N led to another inseparable mixture **10**/**11** (1:1) in quantitatively yield, Scheme 4. The acetylation of this mixture followed by the oxidation with TPAP[11] was shown to afford **12**/**13** (1:1). Finally the hydrolysis of **12**/**13** (1:1) with K_2CO_3 in MeOH provided a mixture (1:1) of compounds **1** and **2**.

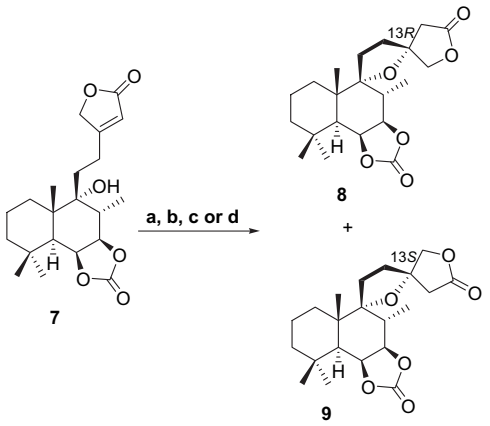
When the mixture **8**/**9** (3:7) was hydrolyzed with K_2CO_3 in the conditions used before, the same mixture as before **10**/**11** (1:1) was

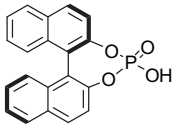
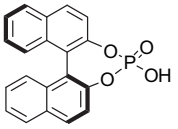
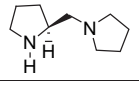


Scheme 1.



Scheme 2. Reagents and conditions: a) 16 steps, 5% global yield,[6,7]; b) $(Cl_3CO)_2CO$, DCM, Py, −78 °C, 40 min, (100%); c) $^1O_2$, Rose Bengal, DIPEA, DCM, −78 °C, 12 h, (95%); d) $NaBH_4$, EtOH, rt, 20 min, (57%).



	Reagent	8/9	Yield (%)
a	DBU	1:1	74
b		3:7	80
c		3:7	83
d		3:7	79

Scheme 3. Reagents and conditions: a) DBU, Et_3N, 90 °C, 1 h, (74%, **8**/**9**: 1/1); b) *R*-(-)-1,1′-binaphthyl-2,2′-diyl hydrogenophosphate, toluene, 80 °C, 72 h, (80%, **8**/**9**: 3/7); c) *S*-(+)-1,1′-binaphthyl-2,2′-diyl hydrogenophosphate, toluene, 80 °C, 82 h, (83%, **8**/**9**: 3/7); d) *S*-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine, toluene, 80 °C, 22 h, (79%, **8**/**9**: 3/7).

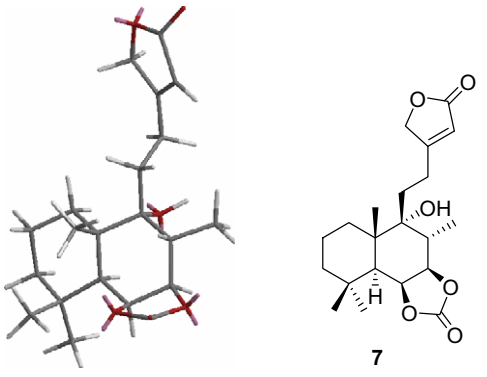
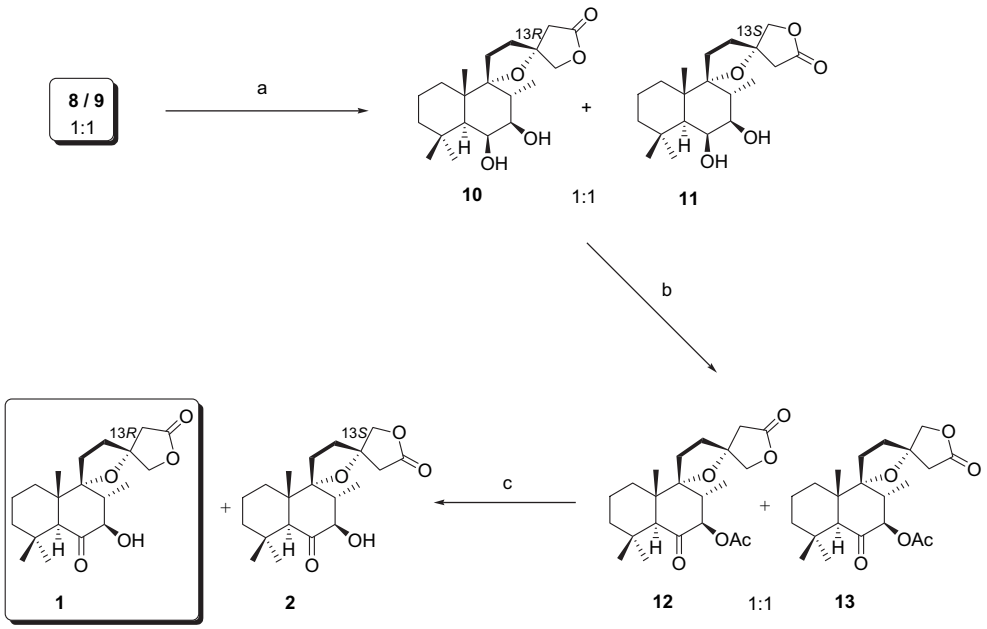


Figure 4. Molecular model made by ChemBioOffice® and is included for better understanding of the structure.

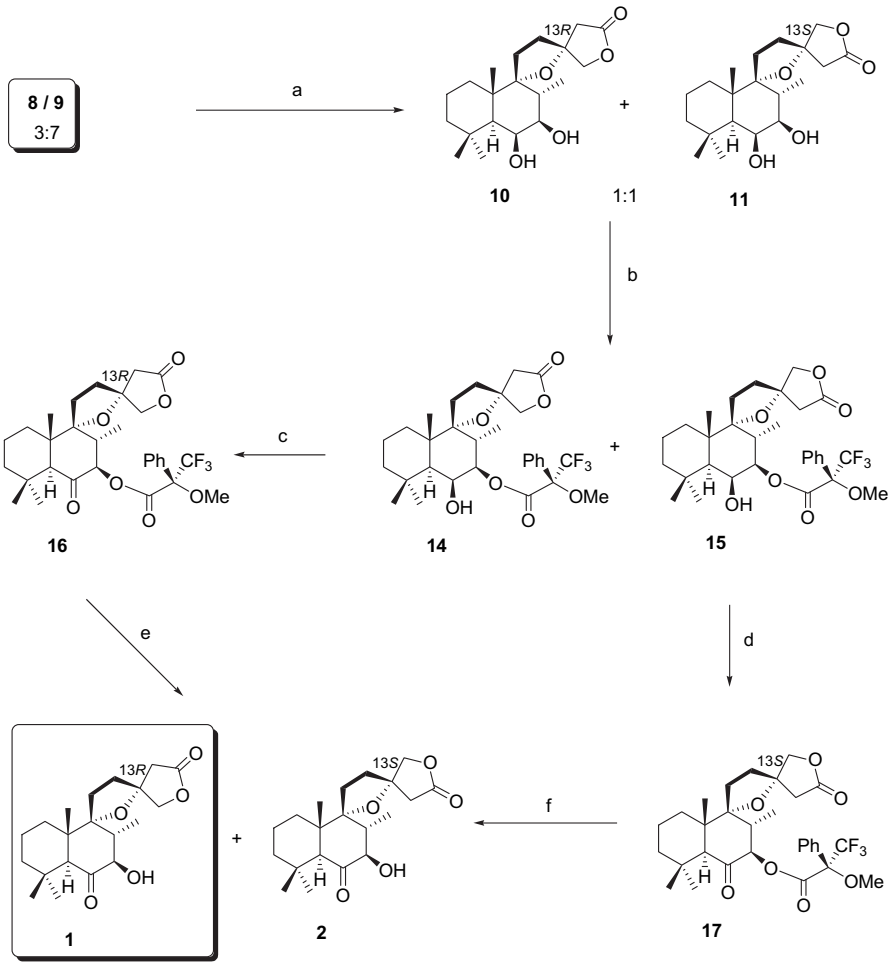
obtained, Scheme 5. This supports the view that the products are in equilibrium. An attempt to separate the C-13 epimers was made, through the preparation of derivatives as shown in Scheme 5.

To separate these epimers, the mixture **10**/**11** was treated with (*R*)-$C_6H_5C(OMe)(CF_3)COOH$[12] and **14**/**15** were obtained. Fortunately these compounds could be separated by column chromatography and the relative configurations of C-13 were established by 2D ROESY, Figure 5. **14** was shown to have 13*R* configuration, as the NOE between Me-17 and H-16 was observed, and **15** was shown to have 13*S* configuration, as the NOE between Me-17 and H-14 was observed.

Once the epimers at C-13 were separated, the synthesis of **1** and **2** was attempted by oxidation of **14** as described previously; this was unsuccessful, presumably due to steric or electronic interactions with the Mosher ester. However the oxidation of **14** with CrO_3/py[13] at 45 °C gives **16** and in the same way **15** is transformed into **17**, as shown in Scheme 5. When **16** was treated with KOH/MeOH a mixture of **1**/**2** was obtained identical to the mixture found when **17** was subjected to the same conditions, and also similar to the mixture when **12**/**13** was hydrolyzed to give **1**/**2**. This corroborates that in basic conditions a retro-Michael reaction occurs and an ulterior cyclisation takes place with both conformers of the open side chain.



Scheme 4. Reagents and conditions: a) K_2CO_3, MeOH, rt, 22 h, (99%; **10**/**11**: 1/1); b) i) Ac_2O, Py, rt, 18 h; ii) TPAP, NMO, sieves, DCM, rt, 4 h, (85%; **12**/**13**: 1:1); c) K_2CO_3, MeOH, rt, 90 min, (**1**, 47%; **2**, 47%).



Scheme 5. Reagents and conditions: a) K_2CO_3, MeOH, rt, 22 h, (99%, **10**/**11**: 1/1); b) $C_6H_5C(OMe)(CF_3)COOH$, DCC, DMAP, DCM, rt, 16 h (**14**, 39%; **15**, 42%); c) CrO_3, Py, DCM, 45 °C, 1 h, (81%); d) CrO_3, Py, DCM, 45 °C, 1 h, (89%); e) K_2CO_3, MeOH, rt, 15 h, (**1**, 47%; **2**, 47%);f) K_2CO_3, MeOH, rt, 15 h, (**1**, 47%; **2**, 47%).

Luckily **1**/**2** could be separated by column chromatography using DCM and Et_2O as solvents. The ROESY experiment shows NOEs between Me-17 and H-16 for **1** (13*R*) and between Me-17 and H-14 for **2** (13*S*), Figure 6. The physical properties of the natural compound, isolated from *Leonorus persicus*, $[\alpha]_D^{22}$ +26.3 (*c* 0.18, $CHCl_3$), are coincident with the ones of **1**, $[\alpha]_D^{22}$ +25.4 (*c* 0.14, $CHCl_3$); so the

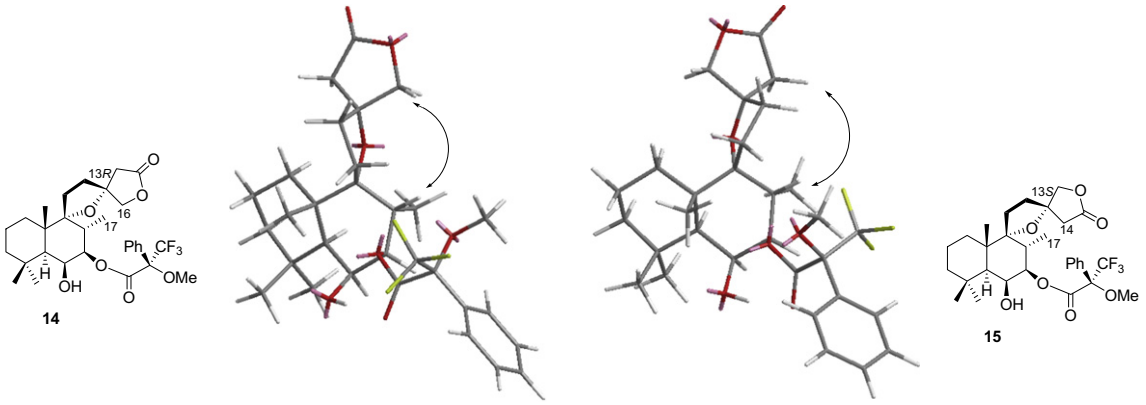


Figure 5. Molecular model made by ChemBioOffice® and is included for better understanding of the structures and the NOEs experiments.

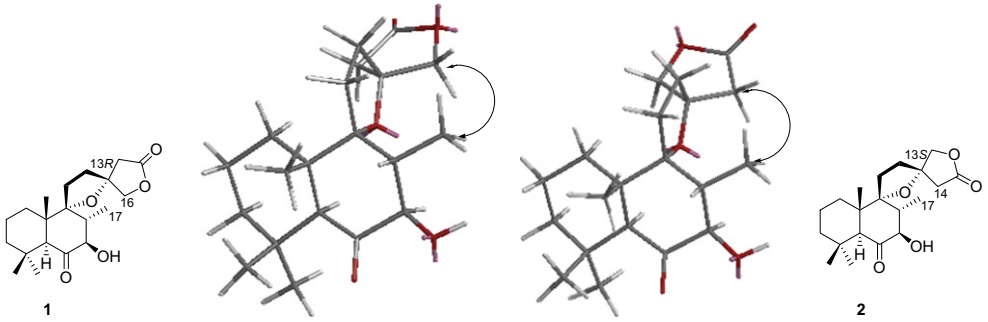


Figure 6. Molecular model made by ChemBioOffice® and is included for better understanding of the structures and the NOEs experiments.

structure and absolute configuration for the natural compound is established, as shown in Figure 6.

3. Conclusions

Starting from (−)-sclareol the syntheses of two spirolabdanolides, **1** and **2**, have been carried out for the first time. Compound **1** has been shown to have identical properties to the natural product (+)-leopersin D, the structure of the natural compound has been corroborated and the absolute configuration established. In addition it has been reported that when the oxo-spirolabdanolides are subjected to basic conditions a retro-Michael/Michael addition occurs, the first case described for this type of compounds.

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 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) or Fast Atom Bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionization (ESI). Optical rotations were determined on a Perkin–Elmer 241 polarimeter in 1 dm cells. Diethyl ether and THF were distilled from sodium, and dichloromethane was distilled from calcium hydride under argon atmosphere.

4.2. Reaction of 4 with triphosgene to yield 5

To a solution of triphosgene (14 mg, 0.048 mmol) in pyridine (0.04 mL) and CH_2Cl_2 (0.2 mL) cooled at −78 °C was added a solution of **4** (16 mg, 0.048 mmol) in CH_2Cl_2 (0.6 mL). The reaction mixture was stirred until it warmed up to room temperature and then saturated NH_4Cl solution (1 mL) was added. The mixture was extracted with Et_2O and washed with 2 M HCl, aqueous 6% $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated to afford **5** (17 mg, 100%).

*4.2.1. (8R)-6β,7β-Carbonyldioxy-15,16-epoxy-labda-13(16),14-dien-9α-ol (**5**).* R_f (Hex/EtOAc 6/4)=0.55; $[\alpha]_D^{22}$ +15.8 (*c* 0.79, $CHCl_3$); IR (film): 3435, 1786, 1459, 1383, 1262, 1149, 1096, 1033, 943, 874, 799, 739; ^{1}H NMR (200 MHz) δ: 7.37 (1H, br s, H-16), 7.24 (1H, br s, H-15), 6.27 (1H, br s, H-14), 4.96 (1H, dd, J=6.2 and 3.0 Hz, H-7), 4.32 (1H, dd, J=9.8 and 6.2 Hz, H-6), 2.80–0.80 (12H, m), 1.25 (3H, s, Me-20), 1.21 (3H, d, J=6.6 Hz, Me-17), 1.18 (3H, s, Me-19), 1.05 (3H, s, Me-18); ^{13}C NMR (50 MHz) δ: 156.0 (OCOO), 143.5 (C-15), 138.9 (C-16), 124.9 (C-13), 110.9 (C-14), 82.1 (C-7), 78.0 (C-9), 77.6 (C-6), 48.5 (C-5), 43.0 (C-3), 42.5 (C-10), 38.8 (C-8), 34.4 (C-4), 33.8 (C-1), 32.8 (C-18), 32.8 (C-12), 24.0 (C-19), 21.4 (C-11), 18.6 (C-2), 18.2 (C-20), 12.7 (C-17); EIHRMS: calcd for $C_{21}H_{30}O_5Na$: 385.1985, found 385.1977.

4.3. Oxidation of 5 with $^{1}O_2$ to yield 6

Rose Bengal (1.1 mg) was added to a solution of **5** (160 mg, 0.442 mmol) and DIPEA (diisopropylethylamine) (0.79 mL) in

CH_2Cl_2 (39 mL) at room temperature. Anhydrous oxygen was bubbled in for 10 min, and after that the solution was placed under oxygen atmosphere at −78 °C and irradiated with a 200 W lamp. After 12 h, irradiation was stopped and the pink solution was allowed to warm to room temperature and saturated oxalic acid solution (50 mL) and H_2O were added. After 30 min of vigorous stirring the mixture was extracted with CH_2Cl_2 and the combined organic extracts were washed with H_2O, dried over Na_2SO_4, filtered and evaporated to afford **6** (166 mg, 95%).

*4.3.1. (8R)-6β,7β-Carbonyldioxy-9α,16-dihydroxy-labd-13-en-15,16-olide (**6**).* R_f (Hex/EtOAc 4/6)=0.40; $[\alpha]_D^{22}$ −93.5 (*c* 0.90, $CHCl_3$); IR (film): 3399, 1786, 1763, 1648, 1461, 1379, 1263, 1112, 1034, 945, 800, 737; ^{1}H NMR (200 MHz) *δ*: 6.02 (1H, br s, H-16), 5.86 (1H, br s, H-14), 4.97 (1H, dd, *J*=6.2 and 3.0 Hz, H-7), 4.32 (1H, dd, *J*=9.4 and 6.2 Hz, H-6), 2.60–0.80 (12H, m), 1.25 (3H, s, Me-20), 1.19 (3H, s, Me-19), 1.17 (3H, d, *J*=6.6 Hz, Me-17), 1.06 (3H, s, Me-18); ^{13}C NMR (50 MHz) *δ*: 171.4 (C-15), 169.7 (C-13), 156.0 (OCOO), 117.6 (C-14), 99.3 (C-16), 82.0 (C-7), 77.9 (C-9), 77.6 (C-6), 45.8 (C-5), 42.9 (C-3), 42.7 (C-10), 38.7 (C-8), 34.5 (C-4), 33.0 (C-18), 32.9 (C-1), 29.9 (C-12), 24.0 (C-19), 23.6 (C-11), 18.6 (C-2), 18.3 (C-20), 12.6 (C-17); EIHRMS: calcd for $C_{21}H_{30}O_7Na$: 417.1884, found 417.1885.

4.4. Reduction of 6 with $NaBH_4$ to yield 7

To a solution of **6** (165 mg, 0.420 mmol) in EtOH (14 mL) cooled at 0 °C was added $NaBH_4$ (25 mg, 0.671 mmol). After stirring for 20 min at room temperature 2 M HCl (6 mL) and H_2O (6 mL) were added. The solution was then extracted with Et_2O and the organic phase was washed with H_2O, dried over Na_2SO_4, filtered and evaporated to give a crude oil, which was chromatographed on silica gel to afford **7** (91 mg, 57%).

*4.4.1. (8S)-6β,7β-Carbonyldioxy-9α-hydroxy-labd-13-en-15,16-olide (**7**).* R_f (Hex/EtOAc 4/6)=0.41; $[\alpha]_D^{22}$ +28.4 (*c* 0.32, $CHCl_3$); IR (film): 3468, 1783, 1745, 1461, 1446, 1378, 1172, 1149, 1112, 1034, 781; ^{1}H NMR (200 MHz) *δ*: 5.86 (1H, s, H-14), 4.98 (1H, dd, *J*=6.2 and 3.4 Hz, H-7), 4.76 (2H, s, H-16), 4.32 (1H, dd, *J*=10.0 and 6.2 Hz, H-6), 2.60–0.80 (12H, m), 1.21 (3H, s, Me-20), 1.20 (3H, s, Me-19), 1.17 (3H, d, *J*=6.6 Hz, Me-17), 1.07 (3H, s, Me-18); ^{13}C NMR (50 MHz) *δ*: 173.9 (C-15), 170.0 (C-13), 155.7 (OCOO), 115.6 (C-14), 81.7 (C-7), 77.9 (C-9), 77.6 (C-6), 73.2 (C-16), 45.9 (C-5), 42.9 (C-3), 42.6 (C-10), 38.7 (C-8), 34.5 (C-4), 33.0 (C-18), 32.9 (C-1), 31.0 (C-12), 25.3 (C-11), 24.0 (C-19), 18.6 (C-2), 18.3 (C-20), 12.6 (C-17); EIHRMS: calcd for $C_{21}H_{30}O_6Na$: 401.1935, found 401.1947.

4.5. Reactions of 7 to yield 8/9

a) To a solution of **7** (69 mg, 0.183 mmol) in Et_3N (15 mL) was added DBU (0.054 mL, 0.366 mmol). After heating at 90 °C for 1 h the solvent was removed to give a crude oil, which was chromatographed on silica gel to afford **8**/**9** (1:1) (51 mg, 74%).
b) To a solution of **7** (6 mg, 0.017 mmol) in toluene (0.5 mL) is added *R*-(-)-1,1′-binaphthyl-2,2′-diyl hydrogenophosphate (6 mg, 0.017 mmol) and the mixture is heated at 80 °C for 72 h. After that time, H_2O (1 mL) is added, the mixture is extracted with EtOAc and the organic layer washed successively with 2 M HCl, aqueous 6% $NaHCO_3$ and H_2O, dried over Na_2SO_4 filtered and concentrated to give a crude oil, which was chromatographed on silica gel to afford **8**/**9** (3:7) (4 mg, 80%).
c) To a solution of **7** (5 mg, 0.014 mmol) in toluene (0.5 mL) is added *S*-(+)-1,1′-binaphthyl-2,2′-diyl hydrogenophosphate (5 mg, 0.014 mmol) and the mixture is heated at 80 °C for 82 h. After that time, H_2O (1 mL) is added, the mixture is extracted with EtOAc and the organic layer washed successively with 2 M HCl, aqueous 6% $NaHCO_3$ and H_2O, dried over Na_2SO_4 filtered and concentrated to give a crude oil, which was chromatographed on silica gel to afford **8**/**9** (3:7) (4 mg, 83%).
d) To a solution of **7** (5 mg, 0.015 mmol) in toluene (0.5 mL) is added *S*-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (4 mg, 0.029 mmol) and the mixture is heated at 80 °C for 22 h. After that time, H_2O (1 mL) is added, the mixture is extracted with EtOAc and the organic layer washed successively with 2 M HCl, aqueous 6% $NaHCO_3$ and H_2O, dried over Na_2SO_4 filtered and concentrated to give a crude oil, which was chromatographed on silica gel to afford **8**/**9** (3:7) (4 mg, 79%).

*4.5.1. (8R)-6β,7β-Carbonyldioxy-9R,13R/S-epoxy-labdan-15,16-olide (**8**/**9**).* **8**/**9** (1:1): R_f (Hex/EtOAc 4/6)=0.57; $[\alpha]_D^{22}$ +13.9 (*c* 0.54, $CHCl_3$); IR (film): 3399, 1792, 1716, 1459, 1377, 1167, 1096, 1031, 1020; EIHRMS: calcd for $C_{21}H_{30}O_6Na$: 401.1935, found 401.1946.

8: ^{1}H NMR (200 MHz) *δ*: 4.95 (1H, dd, *J*=6.2 and 3.2 Hz, H-7), 4.33 (1H, d, *J*=9.2 Hz, H-16), 4.21 (1H, d, *J*=9.2 Hz, H-16), 4.20 (1H, dd, *J*=10.0 and 6.2 Hz, H-6), 2.86 (1H, d, *J*=17.4 Hz, H-14), 2.55 (1H, d, *J*=17.2 Hz, H-14), 2.40–0.80 (12H, m), 1.18 (3H, s, Me-20), 1.15 (3H, s, Me-19), 1.11 (3H, d, *J*=6.6 Hz, Me-17), 1.06 (3H, s, Me-18); ^{13}C NMR (50 MHz) *δ*: 174.3 (C-15), 155.6 (OCOO), 94.0 (C-9), 87.0 (C-13), 81.7 (C-7), 78.4 (C-16), 77.9 (C-6), 46.7 (C-5), 43.3 (C-3), 42.7 (C-14), 41.9 (C-10), 37.9 (C-8), 37.3 (C-12), 34.7 (C-4), 33.7 (C-1), 32.6 (C-18), 28.7 (C-11), 23.9 (C-19), 19.8 (C-20), 18.7 (C-2), 13.3 (C-17).

9: ^{1}H NMR (200 MHz) *δ*: 4.95 (1H, dd, *J*=6.2 and 3.2 Hz, H-7), 4.29 (1H, d, *J*=8.0 Hz, H-16), 4.20 (1H, dd, *J*=10.0 and 6.2 Hz, H-6), 4.11 (1H, d, *J*=9.0 Hz, H-16), 2.89 (1H, d, *J*=17.2 Hz, H-14), 2.59 (1H, d, *J*=17.2 Hz, H-14), 2.40–0.80 (12H, m), 1.18 (3H, s, Me-20), 1.15 (3H, s, Me-19), 1.11 (3H, d, *J*=6.6 Hz, Me-17), 1.06 (3H, s, Me-18); ^{13}C NMR (50 MHz) *δ*: 174.2 (C-15), 155.6 (OCOO), 93.9 (C-9), 87.0 (C-13), 81.7 (C-7), 78.2 (C-16), 77.9 (C-6), 46.8 (C-5), 43.3 (C-3), 42.3 (C-14), 42.0 (C-10), 38.0 (C-8), 37.3 (C-12), 34.7 (C-4), 33.4 (C-1), 32.6 (C-18), 28.7 (C-11), 23.9 (C-19), 19.8 (C-20), 18.7 (C-2), 13.3 (C-17).

4.6. Reaction of 8/9 with K_2CO_3/MeOH to yield 10/11

Compounds **8**/**9** (38 mg, 0.100 mmol) were treated with K_2CO_3 in MeOH (4%, 5 mL) and the mixture was stirred at room temperature for 22 h. After that time, the reaction mixture was diluted with H_2O (5 mL) and 2 M HCl (5 mL) was added. The solution was then extracted with EtOAc and the organic phase was washed with H_2O and brine, dried over Na_2SO_4, filtered and evaporated affording **10**/**11** (1:1) (35 mg, 99%).

*4.6.1. (8R)-6β,7β-Dihydroxy-9R,13R/S-epoxy-labdan-15,16-olide (**10**/**11**).* R_f (Hex/EtOAc 3/7)=0.54; $[\alpha]_D^{22}$ +18.1 (*c* 0.37, $CHCl_3$); IR (film): 3453, 1784, 1716, 1465, 1384, 1365, 1266, 1169, 1098, 1023, 737; EIHRMS: calcd for $C_{20}H_{32}O_5Na$: 375.2142, found 375.2153.

10: ^{1}H NMR (200 MHz) *δ*: 4.36 (1H, d, *J*=8.8 Hz, H-16), 4.23 (1H, br s, H-6), 4.21 (1H, d, *J*=8.8 Hz, H-16), 3.40 (1H, dd, *J*=9.2 and 2.6 Hz, H-7), 2.86 (1H, d, *J*=17.0 Hz, H-14), 2.49 (1H, d, *J*=17.0 Hz, H-14), 2.20–0.80 (12H, m), 1.24 (6H, s, Me-20 and Me-19), 1.23 (3H, d, *J*=6.6 Hz, Me-17), 1.00 (3H, s, Me-18); ^{13}C NMR (50 MHz) *δ*: 174.1 (C-15), 95.5 (C-9), 86.4 (C-13), 78.7 (C-16), 74.3 (C-6), 70.7 (C-7), 48.7 (C-5), 44.0 (C-3), 43.1 (C-14), 42.7 (C-10), 37.9 (C-8), 37.8 (C-12), 34.8 (C-4), 34.8 (C-1), 33.5 (C-18), 29.9 (C-11), 25.1 (C-19), 20.2 (C-20), 18.9 (C-2), 12.3 (C-17).

11: ^{1}H NMR (200 MHz) *δ*: 4.28 (1H, d, *J*=8.8 Hz, H-16), 4.23 (1H, br s, H-6), 4.06 (1H, d, *J*=8.8 Hz, H-16), 3.40 (1H, dd, *J*=9.2 and 2.6 Hz, H-7), 2.92 (1H, d, *J*=17.0 Hz, H-14), 2.58 (1H, d, *J*=17.0 Hz, H-14), 2.20–0.80 (12H, m), 1.24 (6H, s, Me-20 and Me-19), 1.23 (3H, d, *J*=6.6 Hz, Me-17), 1.00 (3H, s, Me-18); ^{13}C NMR (50 MHz) *δ*: 174.0 (C-15), 94.0 (C-9), 86.4 (C-13), 78.5 (C-16), 74.3 (C-6), 70.7 (C-7), 48.7 (C-5), 44.0 (C-3), 42.7 (C-10), 42.6 (C-14), 38.0 (C-8), 37.8

(C-12), 34.8 (C-4), 34.3 (C-1), 33.5 (C-18), 29.9 (C-11), 25.1 (C-19), 20.2 (C-20), 18.9 (C-2), 12.3 (C-17).

4.7. Acetylation and oxidation of 10/11 to yield 12/13

To a solution of **10**/**11** (1:1) (9 mg, 0.026 mmol) in dry pyridine (0.50 mL), acetic anhydride (0.50 mL) was added and the mixture was stirred at room temperature for 18 h. The reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed successively with aqueous 2 M HCl, aqueous 6% $NaHCO_3$ and water. The resulting solution was then dried over Na_2SO_4 and evaporated to afford a crude oil that together with *N*-methylmorpholine *N*-oxide (NMO) (11 mg, 0.078 mmol) and molecular sieves (100 mg) were dissolved in dry DCM (1 mL) and then TPAP (1 mg, 0.003 mmol) was added. The reaction mixture was stirred at room temperature for 4 h under argon and then was filtered through silica gel and celite eluting with EtOAc and DCM. The solvent was evaporated to give a crude oil, which was chromatographed on silica gel to afford **12**/**13** (1:1) (8 mg, 85%).

*4.7.1. (8R)-7β-Acetoxy-9R,13R/S-epoxy-6-oxo-labdan-15,16-olide (**12**/**13**).* R_f (Hex/EtOAc 1/1)=0.38; $[\alpha]_D^{22}$ +26.4 (*c* 0.69, $CHCl_3$); IR (film): 1788, 1745, 1727, 1462, 1383, 1229, 1166, 1092, 1031; EIHRMS: calcd for $C_{22}H_{32}O_6Na$: 415.2091, found 415.2102.

12: ^{1}H NMR (200 MHz) δ: 4.94 (1H, d, *J*=12.0 Hz, H-7), 4.42 (1H, d, *J*=8.8 Hz, H-16), 4.24 (1H, d, *J*=8.8 Hz, H-16), 2.99 (1H, d, *J*=16.8 Hz, H-14), 2.63 (1H, s, H-5), 2.61 (1H, d, *J*=16.8 Hz, H-14), 2.30–0.70 (12H, m), 2.18 (3H, s, MeCOO), 1.24 (3H, s, Me-18), 1.00 (3H, d, *J*=7.0 Hz, Me-17), 0.97 (3H, s, Me-19), 0.91 (3H, s, Me-20); ^{13}C NMR (50 MHz) δ: 204.4 (C-6), 174.0 (C-15), 170.4 (OCO), 93.8 (C-9), 87.2 (C-13), 79.5 (C-7), 78.3 (C-16), 57.4 (C-5), 47.8 (C-10), 47.7 (C-8), 43.2 (C-14), 42.5 (C-3), 38.3 (C-12), 32.7 (C-1), 32.4 (C-4), 32.1 (C-18), 29.6 (C-11), 22.3 (C-19), 20.9 (*Me*COO), 19.7 (C-20), 18.4 (C-2), 14.3 (C-17).

13: ^{1}H NMR (200 MHz) δ: 4.94 (1H, d, *J*=12.0 Hz, H-7), 4.37 (1H, d, *J*=8.8 Hz, H-16), 4.20 (1H, d, *J*=8.8 Hz, H-16), 3.04 (1H, d, *J*=16.8 Hz, H-14), 2.65 (1H, s, H-5), 2.64 (1H, d, *J*=16.8 Hz, H-14), 2.30–0.70 (12H, m), 2.18 (3H, s, MeCOO), 1.24 (3H, s, Me-18), 1.04 (3H, d, *J*=7.0 Hz, Me-17), 0.97 (3H, s, Me-19), 0.91 (3H, s, Me-20); ^{13}C NMR (50 MHz) δ: 204.4 (C-6), 174.2 (C-15), 170.4 (OCO), 93.8 (C-9), 87.2 (C-13), 79.5 (C-7), 78.3 (C-16), 57.5 (C-5), 47.8 (C-10), 47.7 (C-8), 43.0 (C-14), 42.5 (C-3), 38.3 (C-12), 32.7 (C-1), 32.4 (C-4), 32.1 (C-18), 29.6 (C-11), 22.3 (C-19), 20.9 (*Me*COO), 19.7 (C-20), 18.4 (C-2), 14.3 (C-17).

4.8. Reaction of 12/13 with K_2CO_3/MeOH to yield 1 and 2

Compounds **12**/**13** (5 mg, 0.013 mmol) were treated with K_2CO_3 in MeOH (2%, 1 mL) and the mixture was stirred at room temperature for 90 min. After that time, the reaction mixture was diluted with H_2O (1 mL) and 2 M HCl (1 mL) was added. The solution was then extracted with EtOAc and the organic phase was washed with water and brine, dried over Na_2SO_4, filtered and evaporated to give a crude oil, which was chromatographed on silica gel eluting with DCM/Et_2O (95/5) to afford **1** (2.3 mg, 47%) and **2** (2.3 mg, 47%).

*4.8.1. Leopersin D (**1**).* R_f (DCM/Et_2O 9/1)=0.38; $[\alpha]_D^{22}$ +25.4 (*c* 0.14, $CHCl_3$); IR (film): 3465, 1788, 1707, 1463, 1385, 1364, 1264, 1166, 1127, 1092, 1028; ^{1}H NMR (400 MHz) δ: 4.44 (1H, d, *J*=9.1 Hz, H-16), 4.27 (1H, d, *J*=9.1 Hz, H-16), 3.81 (1H, dd, *J*=11.1 and 3.6 Hz, H-7), 3.71 (1H, d, *J*=3.6 Hz, OH-7), 2.98 (1H, d, *J*=17.0 Hz, H-14), 2.67 (1H, s, H-5), 2.62 (1H, d, *J*=17.0 Hz, H-14), 2.25–2.15 (1H, m, H-11), 2.20–2.10 (2H, m, H-12), 1.90–1.80 (2H, m, H-8 and H-11), 1.60–1.45 (2H, m, H-2), 1.50–1.35 (2H, m, H-1), 1.40–1.30 (1H, m, H-3), 1.28 (3H, s, Me-19), 1.14 (3H, d, *J*=6.5 Hz, Me-17), 1.15–0.95 (1H, m, H-3), 0.98 (3H, s, Me-18), 0.87 (3H, s, Me-20); ^{13}C NMR (100 MHz) δ: 211.2 (C-6), 174.0 (C-15), 93.6 (C-9), 86.9 (C-13), 78.0 (C-16), 77.3 (C-7), 56.9 (C-5), 48.1 (C-10), 46.6 (C-8), 42.6 (C-14), 42.3 (C-3), 37.8 (C-12), 32.5 (C-1), 32.4 (C-4), 32.3 (C-18), 29.1 (C-11). 22.1 (C-19), 19.6 (C-20), 18.1 (C-2), 13.2 (C-17); EIHRMS: calcd for $C_{20}H_{30}O_5Na$: 373.1985, found 373.1967.

*4.8.2. 13-Epi-leopersin D (**2**).* R_f (DCM/Et_2O 9/1)=0.32; $[\alpha]_D^{22}$ +27.5 (*c* 0.33, $CHCl_3$); IR (film): 3465, 1788, 1707, 1463, 1385, 1364, 1264 1166, 1127, 1092, 1028; ^{1}H NMR (400 MHz) δ: 4.38 (1H, d, *J*=8.9 Hz, H-16), 4.18 (1H, d, *J*=8.9 Hz, H-16), 3.81 (1H, dd, *J*=11.0 and 3.6 Hz, H-7), 3.70 (1H, d, *J*=3.6 Hz, OH-7), 3.02 (1H, d, *J*=17.1 Hz, H-14), 2.66 (1H, d, *J*=17.1 Hz, H-14), 2.65 (1H, s, H-5), 2.25–2.15 (1H, m, H-11), 2.20–2.10 (2H, m, H-12), 1.90–1.80 (2H, m, H-8 and H-11), 1.60–1.45 (2H, m, H-2), 1.50–1.35 (2H, m, H-1), 1.40–1.30 (1H, m, H-3), 1.28 (3H, s, Me-19), 1.17 (3H, d, *J*=6.5 Hz, Me-17), 1.15–0.95 (1H, m, H-3), 0.98 (3H, s, Me-18), 0.87 (3H, s, Me-20); ^{13}C NMR (100 MHz) δ: 211.2 (C-6), 174.1 (C-15), 93.5 (C-9), 86.9 (C-13), 78.0 (C-16), 77.3 (C-7), 57.0 (C-5), 48.0 (C-10), 46.9 (C-8), 42.2 (C-14), 42.2 (C-3), 37.7 (C-12), 32.4 (C-18), 32.3 (C-4), 32.2 (C-1), 29.1 (C-11). 22.2 (C-19), 19.6 (C-20), 18.1 (C-2), 13.3 (C-17); EIHRMS: calcd for $C_{20}H_{30}O_5Na$: 373.1985, found 373.1967.

4.9. Reaction of 10/11 with (*R*)-$C_6H_5C(OMe)(CF_3)COOH$ to yield 14 and 15

To a mixture of **10**/**11** (36 mg, 0.102 mmol), DCC 1 M in DCM (0.2 mL, 0.2 mmol) and DMAP (0.5 mg, 0.005 mmol) in DCM (010 mL) at 0 °C and under inert atmosphere, was added (*R*)-$C_6H_5C(OMe)(CF_3)COOH$ (48 mg, 0.204 mmol) and the solution was stirred for 16 h at room temperature. Then the white solid was filtered, the solution was extracted with EtOAc and the organic layer was washed successively with 2 M HCl, aqueous 6% $NaHCO_3$ and H_2O, dried over Na_2SO_4 filtered and concentrated to give a crude oil, which was chromatographed on silica gel to afford **14** (23 mg, 39%) and **15** (25 mg, 42%).

*4.9.1. (8R)-6β-Hydroxy-7β-[R-(3,3,3-trifluoro-2-methoxy-2-phenyl)-propionoxy]-9R,13R-epoxy-labdan-15,16-olide (**14**).* R_f (Hex/EtOAc 7/3)=0.43; $[\alpha]_D^{22}$ +46.5 (*c* 0.38, $CHCl_3$); IR (film): 3546, 1785, 1744, 1464, 1452, 1365, 1270, 1169, 1123, 1022, 993, 873, 737; ^{1}H NMR (400 MHz) δ: 7.56–7.52 (2H, m, Ph), 7.45–7.40 (3H, m, Ph), 5.02 (1H, dd, *J*=11.6 and 3.0 Hz, H-7), 4.43 (1H, d, *J*=9.1, H-16), 4.34 (1H, br s, H-6), 4.20 (1H, d, *J*=9.1 Hz, H-16), 3.55 (3H, s, MeO), 2.90 (1H, d, *J*=17.0 Hz, H-14), 2.54 (1H, d, *J*=17.0 Hz, H-14), 2.50–0.70 (12H, m), 1.24 (3H, s, Me-20), 1.22 (3H, s, Me-19), 1.00 (3H, s, Me-18), 0.74 (3H, d, *J*=6.8 Hz, Me-17); ^{13}C NMR (50 MHz) δ: 174.7 (C-15), 166.0 (OCO), 132.2 (C-1′), 130.1 (C-4′), 128.8 (C-3′ and C-5′), 127.5 (C-2′ and C-6′), 123.6 (q, *J*=287.5 Hz, CF_3), 95.3 (C-9), 86.6 (C-13), 84.3 (q, *J*=27.5 Hz, *C*CF_3), 80.9 (C-7), 78.5 (C-16), 68.8 (C-6), 55.7 (MeO), 48.6 (C-5), 43.8 (C-3), 43.1 (C-14), 42.8 (C-10), 38.1 (C-8), 38.1 (C-12), 34.7 (C-1), 34.7 (C-4), 33.4 (C-18), 29.8 (C-11). 24.7 (C-19), 20.1 (C-20), 18.8 (C-2), 11.7 (C-17); EIHRMS: calcd for $C_{30}H_{39}O_7F_3Na$: 591.2540, found 591.2550.

*4.9.2. (8R)-6β-Hydroxy-7β-[R-(3,3,3-trifluoro-2-methoxy-2-phenyl)-propionoxy]-9R,13S-epoxy-labdan-15,16-olide (**15**).* R_f (Hex/EtOAc 7/3)=0.46; $[\alpha]_D^{22}$ +51.9 (*c* 0.48, $CHCl_3$); IR (film): 3545, 1786, 1743, 1663, 1452, 1364, 1262, 1168, 1122, 1022, 929, 873, 801, 736; ^{1}H NMR (400 MHz) δ: 7.55–7.53 (2H, m, Ph), 7.45–7.41 (3H, m, Ph), 5.01 (1H, dd, *J*=11.6 and 3.0 Hz, H-7), 4.35 (1H, br s, H-6), 4.28 (1H, d, *J*=8.8 Hz, H-16), 4.05 (1H, d, *J*=8.8 Hz, H-16), 3.55 (3H, s, MeO), 3.02 (1H, d, *J*=17.1 Hz, H-14), 2.54 (1H, d, *J*=17.1 Hz, H-14), 2.50–0.70 (12H, m), 1.26 (3H, s, Me-20), 1.23 (3H, s, Me-19), 1.00 (3H, s, Me-18), 0.75 (3H, d, *J*=6.7 Hz, Me-17); ^{13}C NMR (50 MHz) δ: 174.5 (C-15), 166.0 (OCO), 132.2 (C-1′), 130.1 (C-4′), 128.8 (C-3′ and C-5′),127.5 (C-2′ and C-6′), 123.6 (q, *J*=287.5 Hz, CF_3), 95.2 (C-9), 86.6 (C-13), 84.3 (q, *J*=27.5 Hz, *C*CF_3), 80.9 (C-7), 78.3 (C-16), 68.7 (C-6), 55.7 (MeO), 48.7 (C-5), 43.8 (C-3), 42.7 (C-10), 42.2 (C-14), 38.0 (C-8), 38.0 (C-12), 34.7 (C-4), 34.3 (C-1), 33.4 (C-18), 29.8 (C-11). 24.7 (C-19), 20.1

(C-20), 18.8 (C-2), 11.7 (C-17); EIHRMS: calcd for $C_{30}H_{39}O_7F_3Na$: 591.2540, found 591.2550.

4.10. Oxidation of 14 with CrO_3/py to yield 16

To a solution of CrO_3 (40 mg, 0.400 mmol) in DCM (0.2 mL) and pyridine (0.066 mL) was added **14** (6 mg, 0.010 mmol) in DCM (0.4 mL) and the solution was heated at 45 °C for 1 h. After that, the mixture was filtered eluting with EtOAc and then, the organic phase obtained was washed successively with 2 M HCl, aqueous 6% $NaHCO_3$ and brine, dried over Na_2SO_4 filtered and concentrated to give a crude oil, which was chromatographed on silica gel to afford **16** (5 mg, 89%).

*4.10.1. (8R)-6β-Oxo-7β-[R-(3,3,3-trifluoro-2-methoxy-2-phenyl)-propionoxy]-9R,13R-epoxy-labdan-15,16-olide (**16**).* R_f (Hex/EtOAc 6/4)=0.38; $[\alpha]_D^{22}$ +56.0 (*c* 0.49, $CHCl_3$); IR (film): 1787, 1755, 1728, 1463, 1452, 1365, 1267, 1169, 1111, 1028, 737; ^{1}H NMR (200 MHz) δ: 7.75–7.68 (2H, m, Ph), 7.44–7.40 (3H, m, Ph), 5.03 (1H, d, *J*=11.8 Hz, H-7), 4.43 (1H, d, *J*=9.0 Hz, H-16), 4.21 (1H, d, *J*=9.0 Hz, H-16), 3.75 (3H, s, MeO), 3.00 (1H, d, *J*=16.9 Hz, H-14), 2.68 (1H, s, H-5), 2.63 (1H, d, *J*=16.9 Hz, H-14), 2.30–0.70 (12H, m), 1.26 (3H, s, Me-19), 1.01 (3H, s, Me-18), 0.90 (3H, s, Me-20), 0.75 (3H, d, *J*=6.2 Hz, Me-17); ^{13}C NMR (50 MHz) δ: 202.6 (C-6), 174.0 (C-15), 166.1 (OCO), 132.7 (C-1′), 129.8 (C-4′), 128.5 (C-3′ and C-5′).127.7 (C-2′ and C-6′), 123.2 (q, *J*=316.5 Hz, CF_3), 93.8 (C-9), 87.4 (C-13), 84.7 (q, *J*=27,1 Hz, *C*CF_3), 81.3 (C-7), 78.2 (C-16), 57.4 (C-5), 56.3 (MeO), 47.8 (C-10), 47.7 (C-8), 43.2 (C-14), 42.6 (C-3), 38.2 (C-12), 32.8 (C-1), 32.5 (C-4), 33.5 (C-18), 29.6 (C-11). 22.4 (C-19), 19.7 (C-20), 18.3 (C-2), 12.8 (C-17); EIHRMS: calcd for $C_{30}H_{37}O_7F_3Na$: 589.2384, found 589.2393.

4.11. Oxidation of 15 with CrO_3/py to yield 17

To a solution of CrO_3 (40 mg, 0.400 mmol) in DCM (0.2 mL) and pyridine (0.066 mL) was added **15** (7 mg, 0.012 mmol) in DCM (0.4 mL) and the solution was heated at 45 °C for 1 h. After that, the mixture was filtered eluting with EtOAc and then, the organic phase obtained was washed successively with 2 M HCl, aqueous 6% $NaHCO_3$ and brine, dried over Na_2SO_4 filtered and concentrated to give a crude oil, which was chromatographed on silica gel to afford **17** (6 mg, 81%).

*4.11.1. (8R)-6β-Oxo-7β-[R-(3,3,3-trifluoro-2-methoxy-2-phenyl)-propionoxy]-9R,13S-epoxy-labdan-15,16-olide (**17**).* R_f (Hex/EtOAc 6/4)=0.39; $[\alpha]_D^{22}$ +58.4 (*c* 0.64, $CHCl_3$); IR (film): 1788, 1755, 1728, 1451, 1364, 1262, 1230, 1169, 1109, 1028, 803; ^{1}H NMR (200 MHz) δ: 7.75–7.68 (2H, m, Ph), 7.45–7.40 (3H, m, Ph), 5.03 (1H, d, *J*=12.2 Hz, H-7), 4.39 (1H, d, *J*=8.8 Hz, H-16), 4.19 (1H, d, *J*=8.8 Hz, H-16), 3.76 (3H, s, MeO), 3.05 (1H, d, *J*=17.1 Hz, H-14), 2.67 (1H, s, H-5), 2.61 (1H, d, *J*=17.1 Hz, H-14), 2.30–0.70 (12H, m), 1.26 (3H, s, Me-19), 1.00 (3H, s, Me-18), 0.89 (3H, s, Me-20), 0.76 (3H, d, *J*=6.2 Hz, Me-17); ^{13}C NMR (50 MHz) δ: 202.6 (C-6), 174.0 (C-15), 166.1 (OCO), 132.7 (C-1′), 129.8 (C-4′), 128.5 (C-3′ and C-5′).127.7 (C-2′and C-6′), 123.2 (q, *J*=316.5 Hz, CF_3), 93.8 (C-9), 87.4 (C-13), 84.7 (q, *J*=27,1 Hz, *C*CF_3), 81.3 (C-7), 78.3 (C-16), 57.5 (C-5), 56.3 (MeO), 47.8 (C-10), 47.7 (C-8), 42.9 (C-14), 42.6 (C-3), 38.2 (C-12), 32.7 (C-1), 33.5 (C-18), 32.5 (C-4), 29.6 (C-11). 22.4 (C-19), 19.7 (C-20), 18.3 (C-2), 12.9 (C-17); EIHRMS: calcd for $C_{30}H_{37}O_7F_3Na$: 589.2384, found 589.2393.

4.12. Reaction of 16 or 17 with KOH/MeOH to yield 1 and 2

a) Compound **16** (5 mg, 0.010 mmol) was treated with KOH in MeOH (10%, 0.5 mL) and the mixture was stirred at room temperature for 15 h. After that time, the reaction mixture was diluted with H_2O (1 mL) and 2 M HCl (1 mL) was added. The solution was then extracted with EtOAc and the organic phase was washed successively with aqueous 6% $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated to afford **1**/**2** (3.7 mg, 99%).

b) Compound **17** (7 mg, 0.012 mmol) was treated with KOH in MeOH (10%, 0.5 mL) and the mixture was stirred at room temperature for 15 h. After that time, the reaction mixture was diluted with H_2O (1 mL) and 2 M HCl (1 mL) was added. The solution was then extracted with EtOAc and the organic phase was washed successively with aqueous 6% $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated to afford **1**/**2** (4.4 mg, 99%).

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