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# Synthesis of (+)-lagerstronolide from (+)-sclareol

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**Abstract**—The γ-acetoxybutenolide (+)-lagerstronolide was synthesized from (+)-sclareol, with an overall yield of 10%. The absolute stereochemistry for the natural compound (−)-lagerstronolide has been correctly established.


## 1. Introduction

*Lagerstroemia* is an important member of Lythraceae consisting of 31 genera. This genus contains more than 56 species of trees or shrubs with colourful flowers distributed from south-eastern Asia to Australia.[1] (+)-Lagerstronolide is a metabolite isolated from *Lagerstreomia lancasteri*, which contains a unit of γ-hydroxybutenolide.[2] The γ-hydroxybutenolide group is present in several compounds with important biological activities, such as luffolide (which has anti-inflammatory activity),[3] dysidiolide (which is an inhibitor of the cdc25A protein phosphatase)[4] and its analogue (which has antitumoural properties),[5] this biological activities prompted us to the synthesis of (+)-lagerstronolide (Fig. 1).

In the last years our group has been involved in the use of readily available (+)-sclareol, as the substrate for the preparation of scarce natural products with important biological activities.[6]

## 2. Results and discussion

The synthesis of (+)-lagerstronolide from (+)-sclareol needed to dehydrate the tertiary hydroxyl group of the bicyclic system into a terminal double bond and change the functionality of the side chain to the required γ-hydroxybutenolide. The synthesis was planned according to Scheme 1. (+)-Lagerstronolide can be obtained from a γ-butenolide as **9**, which could be synthesized from the ketone **5a**. This last compound could be obtained from (+)-sclareol by dehydration of the hydroxyl group on the decalin and degradation of the side chain of two carbon atoms. So the synthesis will be achieved as follows:

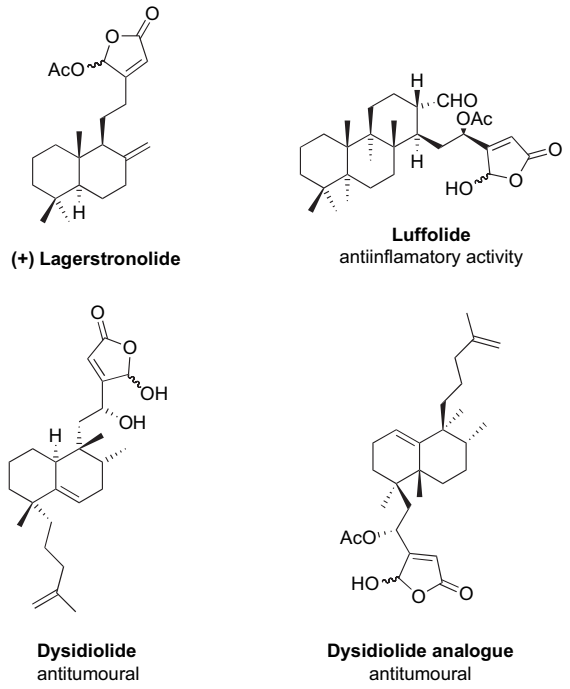


**Figure 1**.

1. Synthesis of intermediate **5a** from (+)-sclareol.
2. Synthesis of the butenolide ring in the side chain.
3. Synthesis of the γ-acetoxybutenolide.

### 2.1. Synthesis of intermediate 5a from (+)-sclareol

Oxidation of sclareol[7] with $KMnO_4$ and ensuing reduction[8] with LAH gave diols **1a/1b**. The elimination of the hydroxyl group to the tetrasubstituted double bond has been achieved by our group.[9] In this case we planned to use the pyrolysis of

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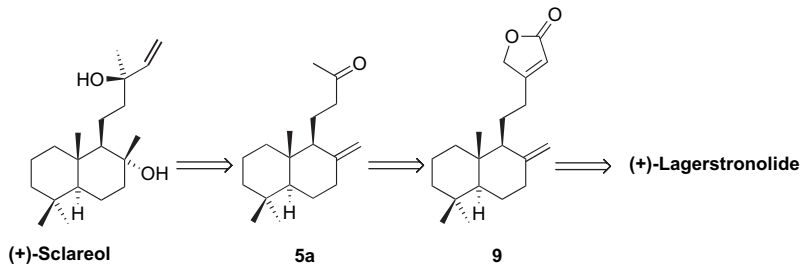
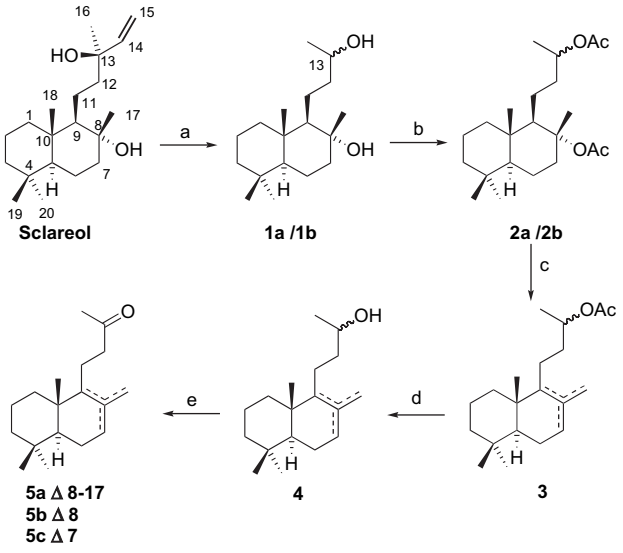



**Scheme 1**. Retrosynthesis of (+)-lagerstronolide from (+)-sclareol.

an acetate. Acetylation of diols **1a/1b** gave the mixture of epimeric acetates at C-13, **2a/2b**. The elimination of the acetoxyl group in the bicyclic system by pyrolysis on silica gel[10] gave a mixture of olefins **3**. As this mixture is very difficult to separate we decided to go on with the synthesis. Hydrolysis of the secondary acetoxyl group with $K_2CO_3$ in MeOH (3%) gave the mixture of inseparable alcohols **4**. TPAP oxidation[11] of **4** gave the mixture of methylketones **5a**–**5c**, the desired **5a** being the major compound (70% by $^1$H NMR of the mixture) (Scheme 2). In order to separate **5a** from the other two isomers it was decided to epoxidize the mixture to obtain epoxides **6a**–**6c** and recovering the unreacted **5a**, due to the less reactivity of the terminal double bond. This compound is now very easy to separate by chromatography in a 61% yield. In this manner we got intermediate **5a** in large quantity, which allows us to continue with the synthesis. The analogue of compound **5a** with a hydroxyl group at C-3 has been synthetized via other routes.[12]



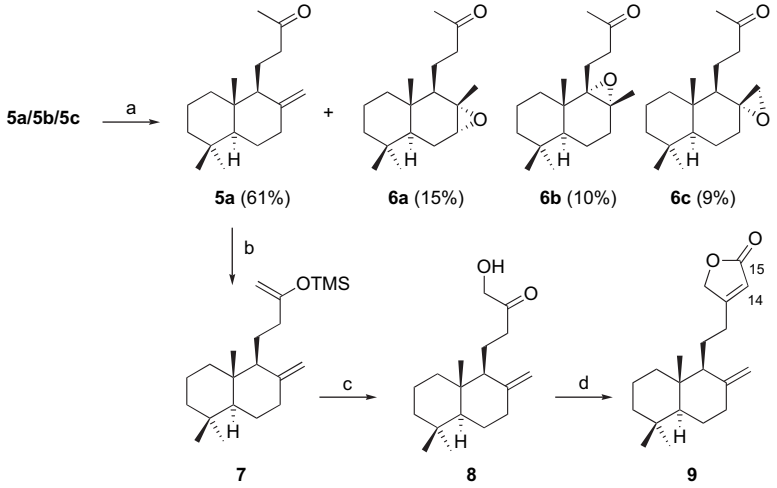

**Scheme 2**. (a) $KMnO_4$, acetone, $MgSO_4$, rt 6 h (80%), see Refs. 7 and 8; (b) AcCl, *N*,*N*-dimethylaniline, DCM (93%); (c) $SiO_2$, 100 °C (90%); (d) $K_2CO_3$/MeOH 3% (90%); (e) TPAP, NMO, DCM, molecular sieves 3 Å (100%).

## 2.2. Synthesis of the butenolide ring in the side chain

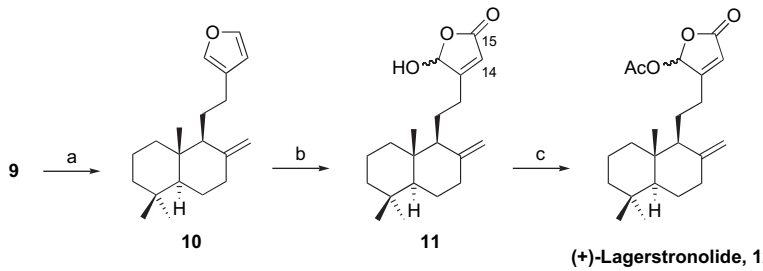
The hydroxylation of **5a** was achieved by treatment with LDA in the presence of TMSCl[13] followed by oxidation[14] of the intermediate silyl enol ether with *m*-CPBA, affording the hydroxyketone **8**. The synthesis of the required γ-butenolide **9** was carried out in high yield, by treatment of **8** with Bestmann ketene.[15] This compound is being tested for biological activity as compounds with this group, such as ajugarin A, have antifeedant activity[16] Scheme 3.

## 2.3. Synthesis of the γ-acetoxybutenolide

The synthesis of the γ-butenolide ring of (+)-lagerstronolide was achieved following Faulkner methodology[17] for the synthesis of γ-hydroxybutenolides that we have previously used.[18] It is necessary to obtain first the furan derivative, which was achieved by DIBAL[19] reduction of **9** and chromatography to give the required furan ring in high yield




**Scheme 3**. (a) *m*-CPBA, DCM; (b) LDA, TMSCl, THF, −78 °C (100%); (c) *m*-CPBA, DCM (90%); (d) $Ph_3P{=}C{=}C{=}O$, benzene, 90 °C (60%).




**Scheme 4**. (a) DIBAL, DCM, −78 °C and then $SiO_2$ (70%); (b) $^1O_2$, Rose Bengal, DCM, −78 °C (86%); (c) $Ac_2O$, pyridine (92%).

(Scheme 4). The furan derivative **10** was transformed into the γ-hydroxybutenolide by photochemical oxidation with singlet oxygen[17] to give **11**. Final acetylation gave compound **12**. This compound showed spectroscopical properties identical to those of (−)-lagerstronolide, but the values of the specific rotation were not coincident (**12** $[\alpha]_D^{22}$ +31.4 and (−)-lagerstronolide $[\alpha]_D^{22}$ −7). The authors who isolated the natural compound only assigned the absolute stereochemistry based in the analogy of the rotation value with similar compounds.[20] In this work we have synthetized compound **12** (+)-lagerstronolide from the known (+)-sclareol, so the absolute stereochemistry of the natural compound as (−)-lagerstronolide has been established.

## 3. Conclusions

The synthesis of (+)-lagerstronolide has been achieved in a 10% global yield starting from (+)-sclareol. The absolute stereochemistry of the natural product has been established. Some of the intermediates and the final product are being tested for biological activity and will be published in due course.

## 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 FTIR or an AVATAR 370 FTIR Thermo Nicolet spectrophotometer. $^1H$ and $^{13}C$ NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at $\delta$ 7.26 ppm and $\delta$ 77.0 ppm for $^1H$ and $^{13}C$, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in $\delta$ ppm and coupling constants ($J$) are given in hertz. HRMS were recorded on a quadruple-time of flight QSTAR XL spectrometer using electrospray (ESI) technique with MeOH as solvent. 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.

**4.1.1. 8α,13 (*R*,*S*)-Diacetoxy-14,15-dinor-labdane: 2a/2b.** To a solution of **1a/1b** (247 mg, 0.9 mmol) in 1 mL of DCM cooled at 0 °C under argon atmosphere *N*,*N*-dimethylaniline (1.1 mL, 8.8 mmol) and AcCl (0.44 mL, 6.1 mmol) were added. The reaction was allowed to stir at room temperature overnight. Then, ice was added and the mixture was stirred to get a homogeneous solution, which was extracted with EtOAc. The combined organic extracts were washed with HCl 2 M, $NaHCO_3$ 10%, water and brine. Then, it was dried over anhydrous $Na_2SO_4$ and filtered. After evaporation of the solvent, 300 mg of **2a/2b** (0.8 mmol, 93%) was obtained. IR ($\nu_{max}$, $cm^{-1}$) 2928, 1739, 1459, 1372, 1199, 1130, 1072, 1020. $^1H$ NMR (200 MHz, $CDCl_3$, ™ ppm) 4.82 (1H, m, H-13), 2.09 (6H, s, *Me*COO), 1.99–0.90 (16H, m), 1.42 (3H, d, $J$=6.2 Hz, Me-17), 1.19 (3H, s, Me-16), 0.83 (3H, s, Me-19), 0.79 (3H, s, Me-18), 0.75 (3H, s, Me-20). $^{13}C$ NMR (200 MHz, $CDCl_3$, ™ ppm) 39.3 (C-1), 18.3 (C-2), 41.9 (C-3), 33.1 (C-4), 55.6 (C-5), 20.0 (C-6), 41.9 (C-7), 87.6 (C-8), 58.4/58.7 (C-9), 39.5 (C-10), 21.3 (C-11), 38.7/39.0 (C-12), 71.1/71.3 (C-13), 19.8 (C-16), 22.7 (C-17), 33.3 (C-18), 21.5 (C-19), 15.7 (C-20), 169.8/170.3 (Me*C*OO), 21.5 (*Me*COO). HRMS $m/z$ [M+Na]: found: 389.2659; calculated for $C_{22}H_{38}O_4Na$: 389.2662.

**4.1.2. Compounds 3.** Compounds **2a/2b** of 1.03 g were dissolved in hexane (5 mL) and then silica gel was added (10 g). Hexane was evaporated allowing the compound to be adsorbed on silica. The mixture was heated at 100 °C for 1 h with magnetic stirring under anhydrous conditions. After this time it could be observed by TLC that the starting material has disappeared. The silica was allowed to reach room temperature and then introduced in a chromatographic column eluting directly with hexane/EtOAc 95:5. Compounds **3** of 744 mg (2.4 mmol, 90%) were obtained. IR ($\nu_{max}$, $cm^{-1}$) 2936, 1739, 1458, 1372, 1243. $^1H$ NMR (200 MHz, $CDCl_3$, ™ ppm) 5.39 (1H, br s), 4.84 (1H, m), 4.81 (1H, s), 4.50/4.45 (1H, s), 2.01 (3H, s), 1.90–0.78 (20H, m), 0.86 (3H, s), 0.79 (3H, s), 0.65 (3H, s). HRMS $m/z$ [M+Na]: found: 339.2455; calculated for $C_{20}H_{34}O_2Na$: 339.2451.

**4.1.3. Compounds 4.** To 688 mg of **3** (2.2 mmol) 10 mL of a solution of $K_2CO_3$ in MeOH (3%) was added. The reaction is allowed to stir at room temperature for 6 h controlling the progress by TLC. Then, water was added and MeOH was evaporated. It was extracted with EtOAc and the combined organic extracts were washed with $NaHCO_3$ 10% and water. It was dried over anhydrous $Na_2SO_4$ and filtered. After evaporation of the solvent 536 mg (2.0 mmol, 90%) of **4** was obtained. IR ($\nu_{max}$, $cm^{-1}$) 3345, 2925, 1459, 1387, 1374. $^1H$ NMR (200 MHz, $CDCl_3$, ™ ppm) 5.36 (1H, br s), 4.79 (1H, s), 4.50/4.46 (1H, s), 3.74 (1H, m), 2.40–0.78 (20H, m), 0.84 (3H, s), 0.80 (3H, s), 0.65 (3H, s). HRMS $m/z$ [M+Na]: found: 287.2326; calculated for $C_{18}H_{32}ONa$: 287.2345.

**4.1.4. Compounds 5a/5b/5c.** To a solution of **4** (543 mg, 2.1 mmol) in 40 mL of DCM molecular sieves 3 Å

(210 mg), NMO (850 mg, 6.3 mmol) and a catalytic amount of TPAP (84 mg) were added. The mixture was allowed to stir at room temperature under anhydrous atmosphere for 1 h. Then, the crude was filtered through Celite and silica gel, eluting with EtOAc. After evaporation of the solvent 539 mg of **5a/5b/5c** (2.1 mmol, 100%) was obtained.

**4.1.5. Compounds 5a, 6a–6c.** To a solution of the mixture of ketones **5a/5b/5c** (963 mg, 3.6 mmol) in 45 mL of DCM cooled at 0 °C *m*-CPBA was added (286 mg, 1.5 mmol). The mixture was allowed to stir at room temperature for 1 h. Then, diethyl ether was added and the resulting solution was washed with a saturated solution of $Na_2SO_3$, $NaHCO_3$ 10% and water. It was dried over anhydrous $Na_2SO_4$, filtered and evaporated the solvent. The mixture of compounds obtained was separated by silica chromatography eluting with hexane/EtOAc 98:2 and 95:5. Compound **5a** of 573.5 mg (2.2 mmol, 61%), 153 mg of **6a** (0.32 mmol, 15%), 98 mg of **6b** (0.21 mmol, 10%) and 93 g of **6c** (0.19 mmol, 9%) were obtained.

**4.1.6. 14,15-Dinor-labd-8(17)-en-13-one: 5a.** $[\alpha]_D^{22}$ 35 (*c* 2.5, $CHCl_3$). IR ($\nu_{max}$, $cm^{-1}$) 2926, 1717, 1459, 1388, 1363, 1160. $^1H$ NMR (200 MHz, $CDCl_3$, ™ ppm) 4.81 (1H, m, $H_A$-17), 4.42 (1H, s, $H_B$-17), 2.09 (3H, s, Me-16), 3.61–0.90 (16H, m), 0.85 (3H, s, Me-19), 0.79 (3H, s, Me-18), 0.67 (3H, s, Me-20). $^{13}C$ NMR (200 MHz, $CDCl_3$, ™ ppm) 38.5 (C-1), 19.5 (C-2), 42.3 (C-3), 33.9 (C-4), 55.7 (C-5), 21.9 (C-6), 39.1 (C-7), 148.5 (C-8), 56.4 (C-9), 39.9 (C-10), 24.6 (C-11), 43.1 (C-12), 209.6 (C-13), 30.2 (C-16), 106.5 (C-17), 33.7 (C-18), 21.9 (C-19), 14.5 (C-20). HRMS *m/z* [M+Na]: found: 285.2173; calculated for $C_{18}H_{30}ONa$: 285.2189.

**4.1.7. 7,8-Epoxy-14,15-dinor-labdan-13-one: 6a.** $[\alpha]_D^{22}$ 30 (*c* 1.0, $CHCl_3$). IR ($\nu_{max}$, $cm^{-1}$) 2926, 1717, 1462, 1388, 1365, 1162. $^1H$ NMR (200 MHz, $CDCl_3$, ™ ppm) 2.92 (1H, s, H-7), 2.11 (3H, s, Me-16), 2.78–0.90 (14H, m), 1.25 (3H, s, Me-17), 0.81 (3H, s, Me-19), 0.79 (3H, s, Me-18), 0.71 (3H, s, Me-20). $^{13}C$ NMR (200 MHz, $CDCl_3$, ™ ppm) 38.9 (C-1), 18.8 (C-2), 42.2 (C-3), 33.2 (C-4), 55.2 (C-5), 23.0 (C-6), 61.0 (C-7), 58.5 (C-8), 46.2 (C-9), 36.2 (C-10), 19.5 (C-11), 45.6 (C-12), 208.4 (C-13), 30.3 (C-16), 22.8 (C-17), 32.8 (C-18), 22.1 (C-19), 14.3 (C-20). HRMS *m/z* [M+Na]: found: 301.2140; calculated for $C_{18}H_{30}O_2Na$: 301.2138.

**4.1.8. 8,9-Epoxy-14,15-dinor-labdan-13-one: 6b.** $[\alpha]_D^{22}$ 47 (*c* 0.5, $CHCl_3$). IR ($\nu_{max}$, $cm^{-1}$) 2924, 1717, 1462, 1438, 1365, 1160. $^1H$ NMR (200 MHz, $CDCl_3$, ™ ppm) 2.10 (3H, s, Me-16), 2.51–0.90 (15H, m), 1.12 (3H, s, Me-17), 0.98 (3H, s, Me-19), 0.79 (3H, s, Me-18), 0.77 (3H, s, Me-20). $^{13}C$ NMR (200 MHz, $CDCl_3$, ™ ppm) 34.8 (C-1), 17.3 (C-2), 41.6 (C-3), 33.1 (C-4), 42.5 (C-5), 18.6 (C-6), 29.2 (C-7), 63.2 (C-8), 71.1 (C-9), 38.8 (C-10), 29.2 (C-11), 40.8 (C-12), 208.9 (C-13), 30.3 (C-16), 22.1 (C-17), 33.7 (C-18), 21.6 (C-19), 17.3 (C-20). HRMS *m/e* [M+Na]: found: 301.2140; calculated for $C_{18}H_{30}O_2Na$: 301.2138.

**4.1.9. 8,17-Epoxy-14,15-dinor-labdan-13-one: 6c.** $[\alpha]_D^{22}$ 8 (*c* 0.5, $CHCl_3$). IR ($\nu_{max}$, $cm^{-1}$) 2944, 1716, 1461, 1338, 1365, 1162. $^1H$ NMR (200 MHz, $CDCl_3$, ™ ppm) 2.79 (2H, s, H-17), 2.07 (3H, s, Me-16), 2.60–0.90 (16H, m), 0.87 (3H, s, Me-19), 0.80 (3H, s, Me-18), 0.79 (3H, s, Me-20). $^{13}C$ NMR (200 MHz, $CDCl_3$, ™ ppm) 39.2 (C-1), 18.9 (C-2), 42.1 (C-3), 33.6 (C-4), 53.4 (C-5), 22.0 (C-6), 36.8 (C-7), 59.7 (C-8), 55.2 (C-9), 40.5 (C-10), 16.2 (C-11), 45.4 (C-12), 209.6 (C-13), 30.1 (C-16), 42.1 (C-17), 33.6 (C-18), 21.9 (C-19), 14.7 (C-20). HRMS *m/z* [M+Na]: found: 301.2140; calculated for $C_{18}H_{30}O_2Na$: 301.2138.

**4.1.10. 13-Trimethylsilyloxy-14,15-dinor-labda-8(17),13(16)-diene: 7.** To a solution of *i*-$Pr_2NH$ (2.3 mL, 15 mmol) in 20 mL of THF under argon atmosphere cooled at −78 °C *n*-BuLi 1.6 M in hexane was added (9.4 mL, 15 mmol) and allowed to stir for 30 min. Then, freshly distilled TMSCl was added (4.5 mL, 30 mmol) and allowed to stir for 15 min more. After this time, a solution of **5a** (799 mg, 3 mmol) in 20 mL of THF was added dropwise and the resulting mixture was stirred at −78 °C for 3 h. Then, 1 mL of $Et_3N$ was added, and after 30 min the mixture was warmed to room temperature and $NaHCO_3$ 10% was added (3 mL). It was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried over anhydrous $Na_2SO_4$ and filtered. After evaporation of the solvent 998 mg (3 mmol, 100%) of **7** was obtained. $[\alpha]_D^{22}$ 18 (*c* 0.2, $CHCl_3$). IR ($\nu_{max}$, $cm^{-1}$) 2960, 1636, 1459, 1388, 1294. $^1H$ NMR (200 MHz, $CDCl_3$, ™ ppm) 4.81 (1H, m, $H_A$-17), 4.51 (1H, s, $H_B$-17), 4.01 (2H, d, *J*=1.8 Hz, H-16), 2.40–0.90 (16H, m), 0.86 (3H, s, Me-19), 0.79 (3H, s, Me-18), 0.67 (3H, s, Me-20), 0.19 (9H, s, $Me_3Si$). $^{13}C$ NMR (200 MHz, $CDCl_3$, ™ ppm) 38.5 (C-1), 19.6 (C-2), 42.4 (C-3), 33.7 (C-4), 55.7 (C-5), 21.9 (C-6), 39.2 (C-7), 148.7 (C-8), 56.2 (C-9), 39.8 (C-10), 24.6 (C-11), 35.7 (C-12), 160.2 (C-13), 90.0 (C-16), 106.5 (C-17), 33.8 (C-18), 22.0 (C-19), 14.6 (C-20). HRMS *m/z* [M+Na]: found: 357.2585; calculated for $C_{21}H_{38}OSiNa$: 357.2590.

**4.1.11. 16-Hydroxy-14,15-dinor-labd-8(17)-en-13-one: 8.** To a solution of **7** (998 mg, 3 mmol) in 40 mL of DCM cooled at 0 °C *m*-CPBA was added (540 mg, 3 mmol) and the mixture was allowed to stir at room temperature for 2 h. Then diethyl ether was added and washed with a saturated solution of $Na_2SO_3$, $NaHCO_3$ 10% and water. It was dried over $Na_2SO_4$ and filtered. The resulting crude mixture after removing the solvent was purified by silica gel chromatography eluting with hexane/EtOAc 9:1, to yield 750 mg of **8** (2.7 mmol, 90%). $[\alpha]_D^{22}$ 23 (*c* 0.4, $CHCl_3$). IR ($\nu_{max}$, $cm^{-1}$) 3430, 2926, 1717, 1459, 1388, 1365. $^1H$ NMR (200 MHz, $CDCl_3$, ™ ppm) 4.84 (1H, m, $H_A$-17), 4.43 (1H, s, $H_B$-17), 4.19 (2H, s, H-16), 2.61–0.90 (17H, m), 0.87 (3H, s, Me-19), 0.80 (3H, s, Me-18), 0.69 (3H, s, Me-20). $^{13}C$ NMR (200 MHz, $CDCl_3$, ™ ppm) 38.4 (C-1), 19.5 (C-2), 42.3 (C-3), 33.3 (C-4), 55.6 (C-5), 17.7 (C-6), 39.2 (C-7), 148.2 (C-8), 56.5 (C-9), 39.9 (C-10), 24.6 (C-11), 42.3 (C-12), 210.4 (C-13), 68.3 (C-16), 106.6 (C-17), 33.8 (C-18), 21.9 (C-19), 14.5 (C-20). HRMS *m/z* [M+Na]: found: 301.2128; calculated for $C_{18}H_{30}O_2Na$: 301.2138.

**4.1.12. Labda-8(17),13-dien-15,16-olide: 9.** To a solution of **8** in 4 mL of benzene Bestmann ketene ($Ph_3P$=C=C=O) was added (91 mg, 0.36 mmol) and then heated at 90 °C for 1 h. Solvent was evaporated and the crude was

directly purified by chromatography eluting with hexane/EtOAc 9:1 to yield 44 mg of **9** (0.2 mmol, 60%). $[\alpha]_D^{22}$ 42 (*c* 0.14, $CHCl_3$). IR ($\nu_{max}$, $cm^{-1}$) 2928, 1750, 1459, 1438, 1195. $^1H$ NMR (200 MHz, $CDCl_3$, ™ ppm) 5.85 (1H, s, H-14), 4.87 (1H, m, $H_A$-17), 4.71 (2H, s, H-16), 4.45 (1H, s, $H_B$-17), 2.62–0.90 (16H, m), 0.88 (3H, s, Me-19), 0.80 (3H, s, Me-18), 0.70 (3H, s, Me-20). $^{13}C$ NMR (200 MHz, $CDCl_3$, ™ ppm) 38.4 (C-1), 19.5 (C-2), 42.2 (C-3), 33.8 (C-4), 55.7 (C-5), 21.4 (C-6), 39.4 (C-7), 148.5 (C-8), 56.3 (C-9), 40.0 (C-10), 24.6 (C-11), 27.7 (C-12), 171.4 (C-13), 115.3 (C-14), 174.4 (C-15), 73.4 (C-16), 106.7 (C-17), 33.3 (C-18), 21.9 (C-19), 14.7 (C-20). HRMS *m/z* [M+Na]: found: 325.2148; calculated for $C_{20}H_{30}O_2Na$: 325.2138.

**4.1.13. 15,16-Epoxy-labda-8(17),13(16),14-triene: 10.** To a solution of **9** (20 mg, 0.06 mmol) in 2 mL of DCM under argon atmosphere and cooled at −78 °C DIBAL was added (0.08 mL, 0.12 mmol) and the mixture was allowed to stir at −78 °C controlling the reaction progress by TLC. When the starting material disappeared MeOH was added and it was allowed to reach room temperature. Then a saturated solution of sodium and potassium tartrate was added and the resulting mixture was allowed to stir overnight. It was extracted with EtOAc and the combined organic extracts were washed with $NaHCO_3$ 10% and brine. It was dried over anhydrous $Na_2SO_4$ and filtered. The residue obtained after removing the solvent was purified by silica chromatography eluting with hexane to yield 12 mg of **10** (0.04 mmol, 70%). $[\alpha]_D^{22}$ 16 (*c* 0.23, $CHCl_3$). IR ($\nu_{max}$, $cm^{-1}$) 2925, 1643, 1461. $^1H$ NMR (400 MHz, $CDCl_3$, ™ ppm) 7.35 (1H, s, H-16), 7.20 (1H, s, H-15), 6.26 (1H, s, H-14), 4.86 (1H, m, $H_A$-17), 4.56 (1H, s, $H_B$-17), 2.55–0.90 (16H, m), 0.86 (3H, s, Me-19), 0.80 (3H, s, Me-18), 0.78 (3H, s, Me-20). $^{13}C$ NMR (400 MHz, $CDCl_3$, ™ ppm) 38.3 (C-1), 19.3 (C-2), 42.1 (C-3), 33.6 (C-4), 55.4 (C-5), 23.6 (C-6), 37.0 (C-7), 148.5 (C-8), 56.0 (C-9), 39.5 (C-10), 24.4 (C-11), 42.2 (C-12), 125.6 (C-13), 111.0 (C-14), 146.6 (C-15), 138.6 (C-16), 106.2 (C-17), 33.6 (C-18), 21.6 (C-19), 14.5 (C-20). HRMS *m/z* [M+Na]: found: 309.2189; calculated for $C_{20}H_{30}ONa$: 309.2194.

**4.1.14. 16-Hydroxylabda-8(17),13-dien-15,16-olide: 11.** Rose Bengal (2 mg) was added to a solution of **10** (12 mg, 0.04 mmol) and DIPEA (0.9 mL, 0.4 mmol) in 3 mL of DCM 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 6 h irradiation was stopped, the pink solution was allowed to warm to room temperature and aqueous oxalic acid (1 mL) was added. After 30 min of vigorous stirring, the mixture was diluted with water and extracted with DCM. The combined organic extracts were washed with water and dried over anhydrous $Na_2SO_4$. After filtration, the solvent was evaporated to give a residue, which was purified by silica gel column chromatography (hexane/EtOAc 9:1 and 8:2) to yield **11** (11 mg, 0.035 mmol, 86%). $[\alpha]_D^{22}$ 46 (*c* 0.12, $CHCl_3$). IR ($\nu_{max}$, $cm^{-1}$) 3303, 2928, 1720, 1459, 1442, 1194. $^1H$ NMR (400 MHz, $CDCl_3$, ™ ppm) 5.99/5.96 (1H, s, H-16), 5.86 (1H, s, H-14), 4.88 (1H, m, $H_A$-17), 4.48 (1H, s, $H_B$-17), 2.70–0.95 (17H, m), 0.88 (3H, s, Me-19), 0.80 (3H, s, Me-18), 0.70 (3H, s, Me-20). $^{13}C$ NMR (400 MHz, $CDCl_3$, ™ ppm) 38.2 (C-1), 19.3 (C-2), 42.0 (C-3), 33.5 (C-4), 55.5 (C-5), 20.8 (C-6), 39.1 (C-7), 147.9 (C-8), 56.2/56.4 (C-9), 39.8 (C-10), 24.7 (C-11), 26.7 (C-12), 169.9 (C-13), 117.2/117.4 (C-14), 170.9 (C-15), 98.2/98.4 (C-16), 106.4/106.5 (C-17), 33.5 (C-18), 21.6 (C-19), 14.4 (C-20). HRMS *m/z* [M+Na]: found: 341.2084; calculated for $C_{20}H_{30}O_3Na$: 341.2087.

**4.1.15. 16-Acetoxylabda-8(17),13-dien-15,16-olide: 12.** To a solution of **11** (6.8 mg, 0.02 mmol) in pyridine (0.5 mL) $Ac_2O$ (0.5 mL) was added and the mixture was allowed to stir at room temperature overnight. Then, ice was added and it was extracted with EtOAc. The combined organic extracts were washed with HCl 2 M, $NaHCO_3$ 10% and dried over anhydrous $Na_2SO_4$. After filtering, the solvent was removed to yield **12** (6.6 mg, 0.018 mmol, 92%). $[\alpha]_D^{22}$ 31 (*c* 0.21, $CHCl_3$). IR ($\nu_{max}$, $cm^{-1}$) 2927, 1799, 1782, 1460, 1460, 1164. $^1H$ NMR (400 MHz, $CDCl_3$, ™ ppm) 6.83/6.80 (1H, s, H-16), 5.95 (1H, s, H-14), 4.87 (1H, m, $H_A$-17), 4.45/4.42 (1H, s, $H_B$-17), 2.70–0.95 (16H, m), 2.16 (3H, s, *Me*COO), 0.88 (3H, s, Me-19), 0.81 (3H, s, Me-18), 0.70 (3H, s, Me-20). $^{13}C$ NMR (400 MHz, $CDCl_3$, ™ ppm) 38.2 (C-1), 19.3 (C-2), 42.0 (C-3), 33.5 (C-4), 55.5 (C-5), 20.7 (C-6), 39.1 (C-7), 149.7 (C-8), 56.1/56.3 (C-9), 39.8 (C-10), 24.3 (C-11), 26.5 (C-12), 167.9 (C-13), 118.0/118.1 (C-14), 170.9 (C-15), 93.7/94.2 (C-16), 106.3/106.4 (C-17), 33.5 (C-18), 21.6 (C-19), 14.4 (C-20), 33.5 (*Me*CO), 170.9 (Me*C*O). HRMS *m/z* [M+Na]: found: 383.2185; calculated for $C_{20}H_{32}O_4Na$: 383.2193.

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