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Synthesis of sibiricinone A, sibiricinone B and leoheterin

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ABSTRACT

Two labdenolides, sibiricinone A and sibericinone B, and a furo-labdane leoheterin have been synthesized from sclareol, for the first time, establishing in this manner the absolute configuration for these compounds.

1. Introduction

Labdane diterpenes with a highly functionalised ring B that present important biological activities are very commom.[1] Among them, forskolin **1**, is one of the most representative as it has cardioactive, adenylate cyclase stimulant and hypotensive properties.[2]

Recently our group has carried out a study on the synthesis of highly functionalised ring B labdanes[3] introducing a new strategy for the synthesis of α-*cis*, β-*cis* or *trans* diols in that ring. Now we put in practice this methodology for the synthesis of sibiricinone A **2**,[4] sibiricinone B **3**[4] and leoheterin **4**[5] (Fig. 1).

The plants from genus *Leonorus* are widely distributed and medicinally important members of Lamiaceae. Preparations of some of them have been used for the treatment of cardiovascular diseases and for their sedative as well as uterotonic effects. Sibiricinone A **2** and sibiricinone B **3** are two labdanes isolated from *Leonorus sibericus* L., which is commonly referred to as 'motherwort' in the West Indies, where it is utilized as a cough syrup and antipyretic for malaria.[4] The juice of the fresh plant is used to treat haemoptysis, oedema, gout and arthritis. Both compounds show oxygenated functionalities at C-6 and C-7 and a hydroxyl group at C-9, for sibiricinone A **2**, or a double bond in C-8 sibiricinone B **3**. In the side chain appears a γ-hydroxybutenolide for both. The α-hydroxyketone on ring B appears alternatively in one and another molecule, that is, the carbonyl group and the hydroxyl group are in C-6 and C-7 or in C-7 and C-6, respectively.

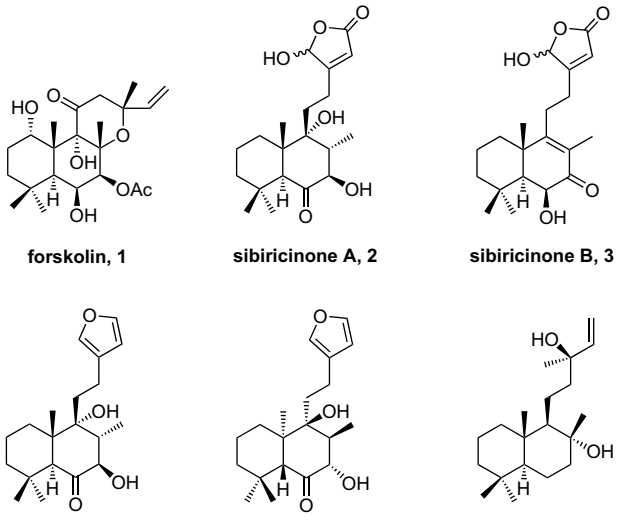

Figure 1.

Leoheterin **4**, $[\alpha]_D^{22}$ +47.7 (*c* 0.65, EtOH), is a furo-labdane isolated from *Leonorus heterophyllus*.[5] These kind of compounds are very abundant in plants of this genus.[6] From *Ballota aucheri* was isolated compound **5**,[7] $[\alpha]_D^{22}$ −48 (*c* 0.78, $CHCl_3$), with the same physical properties as the ones of leoheterin **4** with the only

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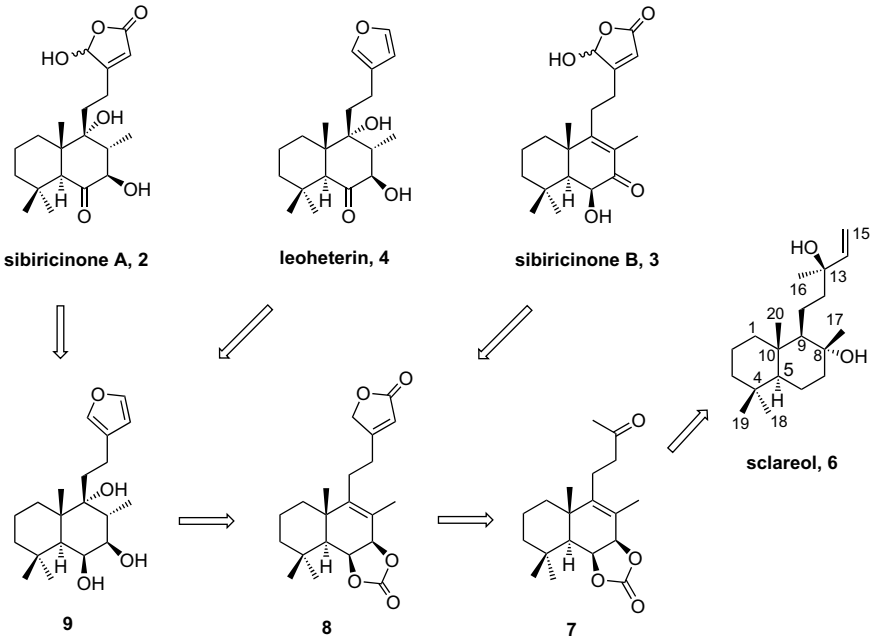


Scheme 1.

difference in the sign of the rotation value. So both compounds are enantiomers, although the absolute configuration for both remains undisclosed. To the best of our knowledge these compounds have not been synthesized until now. The synthesis of **2**, **3** and **4** will corroborate the structure and establish the absolute configuration for all of them.

The starting material for the synthesis was sclareol **6**, a commercial compound that our group has used for the synthesis of natural products as luffolide,[8] subersic acid,[9] hyrtiosal,[10] chrysolic acid,[11] nimbiol[12] and others.[3]

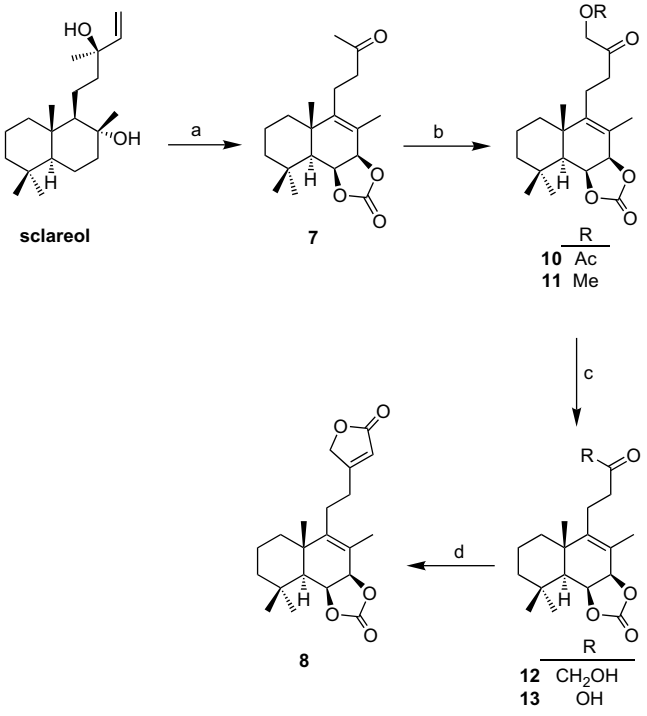
2. Results and discussion

The synthesis of the diterpenes **2**, **3** and **4** was planned according to the following retrosynthetic scheme (Scheme 1). The key compound is ketone **7**,[3] previously obtained by us from sclareol **6**. The methylketone of **7** permit us to have access to the butenolide **8**. This compound could be transformed into a γ-hydroxybutenolide and by control of the functionality at C-6 and C-7 in ring B to obtain sibiricinone B **3**. The synthesis of sibiricinone A **2** and leoheterin **4** will require the use of triol **9** as intermediate, that can be accessible from lactone **8**. Lactone **8** will be obtained from methylketone **7** after C-16 functionalization and the introduction of the two remaining carbons in the side chain.

In summary compound **7** shows a carbonate function that could be transformed into hydroxyketones at C-6 and C-7 or C-7 and C-6, respectively, as well as to a hydroxy group at C-9 in ring B of the labdane skeleton. The methylketone in the side chain of compound **7** is the starting point for the synthesis of furane or γ-hydroxybutenolide, making this compound a reference for the control of the functionality in ring B and functionalization of the side chain for these kind of compounds.

2.1. Synthesis of intermediate 8

As described in Scheme 1, lactone **8** is the key intermediate for the synthesis of **2**, **3** and **4**. The synthesis of **8** from methylketone **7** was carried out according to Scheme 2. First of all C-16 functionalization was achieved and later on the γ-butenolide function of the side chain was installed.



Scheme 2. Reagents and conditions: (a) Ref. 3; (b) $Pb(OAc)_4$, $BF_3{\cdot}Et_2O$, MeOH, C_6H_6, rt, 50 min (**10**, 60%; **11**, 21%); (c) K_2CO_3, MeOH, rt, 20 min (**12**, 81%; **13**, 13% from **10**); (d) $Ph_3P{=}C{=}C{=}O$, C_6H_6, 85 °C, 40 min (84% from **12**).

Reaction of **7** with $Pb(OAc)_4$[13] in presence of $BF_3{\cdot}Et_2O$ gave a mixture of **10** and **11**, **10** being the major compound. Alkaline hydrolysis of **10** gives hydroxyketone **12** and a small proportion of acid **13**. Compound **12** was transformed, in good yield, into **8** by reaction with Bestmann ketene $Ph_3P{=}C{=}C{=}O$.[14]

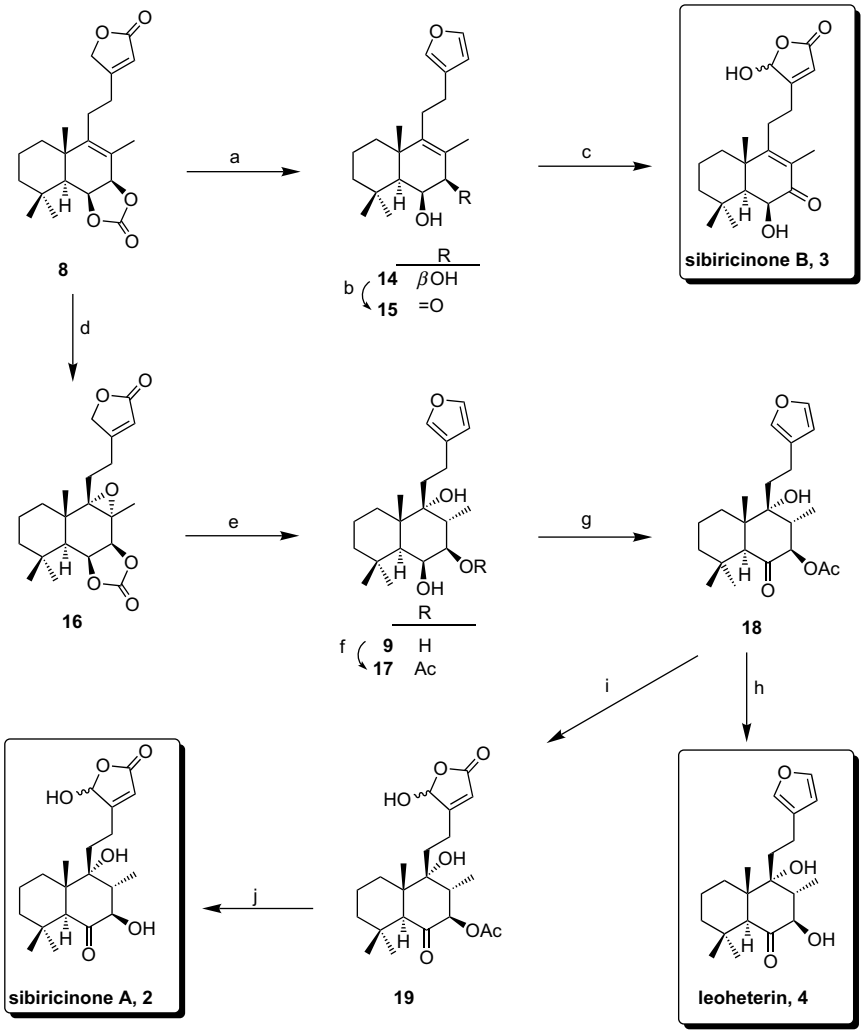
2.2. Synthesis of 2, 3 and 4

The synthesis of sibiricinone A **2** sibiricinone B **3** and leoheterin **4** was achieved according to Scheme 3.

The synthesis of sibiricinone B **3** (Scheme 3) was done in three steps from **8**. DIBAL-H[15] reduction of **8** and after filtration on silica gel gave a furo-labdane derivative that without purification was reduced with LAH to give diol **14**, with both hydroxyl groups at C-6 and C-7 β, from which **15** was obtained by allylic oxidation with MnO_2, with the required hydroxyketone functionality in ring B, in a 81% yield from **8**. Compound **15** has been recently synthesized by Davies-Coleman et al. from hispanolone, showing that it is the enantiomer of the natural compound isolated from *Ballota aucheri*.[16] The oxidation of **15** with $^1O_2$ using Faulkner[17] methodology gave sibiricinone B **3**, $[\alpha]_D^{22}$ +7.5 (*c* 0.42, $CHCl_3$), in excellent yield. The physical properties of **3** are coincident with the ones described by Tinto et al.[4] for sibiricinone B, $[\alpha]_D^{20}$ +4.4 (*c* 0.18, $CHCl_3$).

The synthesis of **9** (69%) from **8** was carried out through epoxide **16**. Epoxidation of **8** was achieved quantitatively with total stereoselection from the α side of the molecule, due to the steric hindrance that Me-20 and carbonate at C-6 and C-7 exert on the β side to give **16**. DIBAL-H reduction of the latter compound installed the furane ring in the side chain, as was done for the synthesis of **3**, to give an epoxyfuro-labdane intermediate that without isolation was submitted to LAH reduction in hot THF of the epoxide group, to obtain the desired triol **9**. In this manner, considering the trans-diaxial opening of the epoxide, and entry of the hydride at C-8, the required triol **9** was obtained with a α-hydroxy group at C-9 and Me-17 equatorial as required.

Chemoselective acetylation of **9** gave quantitatively the monoacetyl derivative **17** needed for the synthesis of the α-hydroxyketone at C-6 and C-7 group. TPAP[18] oxidation of **17** gave **18** that by hydrolysis led quantitatively to leoheterin **4**, $[\alpha]_D^{22}$ +46.0 (*c* 0.37, $CHCl_3$). The physical properties of **4** are coincident with the ones of



Scheme 3. Reagents and conditions: (a) (i) DIBAL-H, DCM, −78 °C, 30 min; (ii) LAH, Et_2O, rt, 1 h (91%); (b) MnO_2, DCM, rt, 2.5 h (89%); (c) $^1O_2$, Rose Bengal, DIPEA, DCM, −78 °C, 2.5 h (85%); (d) *m*-CPBA, DCM, rt, 40 h (98%); (e) (i) DIBAL-H, DCM, −78 °C, 30 min; (ii) LAH, THF, 50 °C, 24 h (70%); (f) Ac_2O, Py, rt, 18 h (98%); (g) TPAP, NMO, sieves, DCM, rt, 3 h (86%); (h) K_2CO_3, MeOH, rt, 50 min (99%); (i) $^1O_2$, Rose Bengal, DIPEA, DCM, −78 °C, 5 h (92%); (j) K_2CO_3, MeOH, rt, 1 h (97%).

For the synthesis of sibiricinone A **2** and leoheterin **4** (Scheme 3), besides the adequate functionalization at C-6 and C-7 positions, it was necessary to introduce an hydroxy group in C-9a (symbol) of B ring and finally in the case of **2** to oxidize the side chain and to achieve the γ-hydroxybutenolide function.

the compound described by Wong et al., $[\alpha]_D^{22}$ +47.7 (*c* 0.65, EtOH), so leoheterin has the structure and absolute configuration of **4**. Consequently, the compound described by Zdero et al.,[7] $[\alpha]_D^{24}$ −48 (*c* 0.78, $CHCl_3$), is the enantiomer of **4** and corresponds to the structure of (−)-leoheterin **5**.

Oxidation of **18** with $^1O_2$ gave the γ-hydroxybutenolide **19**, that by alkaline hydrolysis rendered sibiricinone A **2**, $[\alpha]_D^{22}$ +20.2 (*c* 0.27, $CHCl_3$). The physical properties of **2** are coincident with the ones described by Tinto et al.[4] for sibiricinone A, $[\alpha]_D^{20}$ +18.4 (*c* 0.64, $CHCl_3$).

3. Conclusions

Starting from sclareol **6**, has been carried out the synthesis of two natural γ-hydroxybutenolides sibiricinone A **2** and sibiricinone B **3**, and one natural furo-labdane leoheterin **4**, from a very valuable common intermediate **7**. The synthesis of these compounds has permitted us to establish unequivocally the structure and absolute configuration of all of them. Currently these and other dioxygenated labdanes at C-6 and C-7 are being biologically evaluated.

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. ^1H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^1H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ parts per million and coupling constants (*J*) are given in hertz. MS were performed using 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. α-Acetoxylation of 7 with LTA/$BF_3\cdot Et_2O$ to yield 10 and 11

To a solution of **7** (163 mg, 0.508 mmol) in benzene (6.5 mL) and MeOH (0.025 mL), $Pb(OAc)_4$ (308 mg, 0.712 mmol) was added and this mixture was treated under argon with $BF_3\cdot Et_2O$ (1 mL) and stirred at room temperature for 50 min. Then the solution was diluted with Et_2O and H_2O was added. The mixture was extracted with Et_2O and washed with H_2O and brine, the organic layer was dried over Na_2SO_4, filtered and evaporated to give a crude oil, which was chromatographed on silica gel to afford **7** (22 mg, 14%), **10** (115 mg, 60%) and **11** (37 mg, 21%).

*4.2.1. 16-Acetoxy-6β,7β-carbonyldioxy-14,15-dinor-labd-8-en-13-one (**10**)*

R_f (hexane/OAcEt 1:1)=0.39; $[\alpha]_D^{22}$+43.1 (*c* 1.09, $CHCl_3$); IR (film): 1795, 1740, 1732, 1463, 1417, 1375, 1323, 1233, 1171, 1118, 1077, 1018, 960, 781; ^1H NMR δ: 5.17 (1H, dd, *J*=8.0 and 1.4 Hz, H-6), 4.90 (1H, d, *J*=8.0 Hz, H-7), 4.63 (2H, s, *CH*$_2$OAc), 2.60–0.80 (11H, m), 2.17 (3H, s, –OAc), 1.72 (3H, s, Me-17), 1.23 (3H, s, Me-20), 1.18 (3H, s, Me-19), 1.03 (3H, s, Me-18); ^{13}C NMR δ: 203.0 (C-13), 170.5 (O*C*OMe), 155.3 (O*C*OO), 148.5 (C-9), 122.2 (C-8), 78.8 (C-7), 75.1 (C-6), 68.0 (C-16), 51.9 (C-5), 42.7 (C-3), 39.1 (C-10), 38.8 (C-1), 38.7 (C-12), 34.2 (C-4), 33.0 (C-18), 23.7 (C-19), 22.6 (C-20), 21.0 (C-11), 20.7 (OCO*Me*), 18.8 (C-2), 16.5 (C-17); EIHRMS calcd for $C_{21}H_{30}O_6Na$ (M+Na^+): 401.1935, found: 401.1940.

*4.2.2. 6β,7β-Carbonyldioxy-16-methoxy-14,15-dinor-labd-8-en-13-one (**11**)*

R_f (hexane/OAcEt 4:6)=0.39; $[\alpha]_D^{22}$+32.4 (*c* 0.76, $CHCl_3$); IR (film): 1794, 1718, 1459, 1374, 1319, 1170, 1137, 1117, 1082, 1018; ^1H NMR δ: 5.17 (1H, dd, *J*=8.0 and 1.4 Hz, H-6), 4.90 (1H, d, *J*=8.0 Hz, H-7), 3.98 (2H, s, *CH*$_2$OMe), 3.42 (3H, s, CH$_2$O*Me*), 2.60–0.80 (11H, m), 1.72 (3H, s, Me-17), 1.24 (3H, s, Me-20), 1.19 (3H, s, Me-19), 1.03 (3H, s, Me-18); ^{13}C NMR δ: 208.1 (C-13), 155.4 (O*C*OO), 148.8 (C-9), 122.0 (C-8), 78.9 (C-7), 77.9 (C-16), 75.1 (C-6), 59.6 (OMe), 51.9 (C-5), 42.7 (C-3), 39.1 (C-10), 38.9 (C-1), 38.7 (C-12), 34.2 (C-4), 33.0 (C-18), 23.7 (C-19), 22.5 (C-20), 21.1 (C-11), 18.8 (C-2), 16.5 (C-17); EIHRMS calcd for $C_{20}H_{30}O_5Na$ (M+Na^+): 373.195, found: 373.1958.

4.3. Reaction of 10 with K_2CO_3/MeOH to yield 12 and 13

Compound **10** (110 mg, 0.291 mmol) was treated with K_2CO_3 in MeOH (1%, 6 mL) and the mixture was stirred at room temperature for 20 min. After that time, the reaction mixture was diluted with H_2O and 2 M HCl 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 to give a crude oil, which was chromatographed on silica gel to afford **12** (79 mg, 81%) and **13** (12 mg, 13%).

*4.3.1. 6β,7β-Carbonyldioxy-16-hydroxy-14,15-dinor-labd-8-en-13-one (**12**)*

R_f (hexane/OAcEt 4:6)=0.53; $[\alpha]_D^{22}$+46.5 (*c* 0.97, $CHCl_3$); IR (film): 3447, 1793, 1718, 1458, 1374, 1174, 1118, 1076, 1018; ^1H NMR δ: 5.18 (1H, dd, *J*=8.0 and 1.8 Hz, H-6), 4.90 (1H, d, *J*=8.0 Hz, H-7), 4.25 (2H, s, *CH*$_2$OH), 2.60–0.80 (11H, m), 1.73 (3H, s, Me-17), 1.24 (3H, s, Me-20), 1.19 (3H, s, Me-19), 1.03 (3H, s, Me-18); ^{13}C NMR δ: 208.6 (C-13), 155.3 (O*C*OO), 148.3 (C-9), 122.4 (C-8), 78.8 (C-7), 75.0 (C-6), 68.2 (C-16), 51.9 (C-5), 42.7 (C-3), 39.2 (C-10), 38.8 (C-1), 38.3 (C-12), 34.2 (C-4), 33.0 (C-18), 23.7 (C-19), 22.6 (C-20), 21.3 (C-11), 18.8 (C-2), 16.5 (C-17); EIHRMS calcd for $C_{19}H_{28}O_5Na$ (M+Na^+): 359.1829, found: 359.1815.

*4.3.2. 6β,7β-Carbonyldioxy-14,15-dinor-labd-8-en-13-oic acid (**13**)*

R_f(hexane/OAcEt 4:6)=0.18; $[\alpha]_D^{22}$+37.9 (*c* 0.99, $CHCl_3$); IR (film): 3600–300, 1793, 1716, 1458, 1374, 1171, 1138; ^1H NMR δ: 5.18 (1H, dd, *J*=8.0 and 2.0 Hz, H-6), 4.91 (1H, d, *J*=8.0 Hz, H-7), 2.60–0.80 (11H, m), 1.77 (3H, s, Me-17), 1.25 (3H, s, Me-20), 1.19 (3H, s, Me-19), 1.04 (3H, s, Me-18); ^{13}C NMR δ: 180.6 (C-13), 155.3 (O*C*OO), 148.0 (C-9), 122.5 (C-8), 78.8 (C-7), 75.1 (C-6), 51.9 (C-5), 42.7 (C-3), 39.1 (C-10), 38.7 (C-1), 34.2 (C-4), 33.7 (C-12), 33.0 (C-18), 23.7 (C-19), 23.0 (C-11), 22.5 (C-20), 18.8 (C-2), 16.4 (C-17); EIHRMS (M^+) calcd for $C_{18}H_{26}O_5$: 322.1780, found: 322.1785.

4.4. Reaction of 12 with the Bestmann ketene to yield 8

To a solution of **12** (71 mg, 0.211 mmol) in dry benzene (9 mL), Bestmann ketene ($Ph_3P{=}C{=}C{=}O$)[14] (133 mg, 0.423 mmol) was added and the mixture was stirred 40 min at 85 °C under argon. Then the solution was cooled down to room temperature and AcOEt was added. The resulting organic layer 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 **8** (64 mg, 84%).

*4.4.1. 6β,7β-Carbonyldioxy-labd-8,13-dien-16,15-olide (**8**)*

R_f (hexane/OAcEt 4:6)=0.37; $[\alpha]_D^{22}$+48.7 (*c* 0.75, $CHCl_3$); IR (film): 1791, 1746, 1637, 1458, 1374, 1324, 1171, 1140, 1118, 1081, 1036, 1018; ^1H NMR δ: 5.89 (1H, s, H-14), 5.21 (1H, dd, *J*=8.4 and 1.0 Hz, H-6), 4.92 (1H, d, *J*=8.4 Hz, H-7), 4.75 (2H, br s, H-16), 2.60–0.80 (11H, m), 1.76 (3H, s, Me-17), 1.26 (3H, s, Me-20), 1.20 (3H, s, Me-19), 1.05 (3H, s, Me-18); ^{13}C NMR δ: 173.8 (C-15), 169.3 (C-13), 155.2 (O*C*OO), 147.8 (C-9), 122.8 (C-8), 115.7 (C-14), 78.6 (C-7), 75.0 (C-6),

73.0 (C-16), 51.9 (C-5), 42.6 (C-3), 39.1 (C-10), 38.9 (C-1), 34.3 (C-4), 33.0 (C-18), 28.7 (C-12), 25.5 (C-11), 23.7 (C-19), 22.7 (C-20), 18.8 (C-2), 16.6 (C-17); EIHRMS calcd for $C_{21}H_{28}O_5Na$ ($M+Na^+$): 383.1907, found: 383.1859.

4.5. Reaction of 8 with DIBAL-H and $LiAlH_4$ to yield 14

To a solution of **8** (56 mg, 0.155 mmol) in CH_2Cl_2 (4 mL) at −78 °C, DIBAL-H (0.31 mL of solution 1.5 M in toluene, 0.466 mmol) was added under argon. After 30 min the mixture was warmed up to 0 °C, quenched with wet Et_2O and at room temperature, Et_2O, Na_2SO_4 (1.0 g) and $NaHCO_3$ (0.8 g) were added. The solution was stirred for 1 h, filtered through silica gel eluting with Et_2O and EtOAc, and concentrated to afford a crude oil, which was dissolved in dry Et_2O (5 mL) cooled at 0 °C, treated with $LiAlH_4$ (12 mg, 0.320 mmol) and stirred at room temperature for 1 h. Then, the solution was cooled back to 0 °C, wet EtOAc was added and the mixture was filtered. The resulting organic phase was dried over Na_2SO_4, filtered and evaporated affording **14** (45 mg, 91%).

*4.5.1. 15,16-Epoxy-labd-8,13(16),14-trien-6β,7β-diol (**14**)*

R_f (hexane/OAcEt 6:4)=0.47; $[\alpha]_D^{22}$+13.0 (*c* 0.67, $CHCl_3$); IR (film): 3405, 1465, 1378, 1265, 1121, 1066, 1025, 929, 901, 874, 778, 739; ^{1}H NMR δ: 7.36 (1H, br s, H-15), 7.24 (1H, br s, H-16), 6.30 (1H, br s, H-14), 4.33 (1H, d, *J*=4.4 Hz, H-7), 4.00 (1H, dd, *J*=4.4 and 1.0 Hz, H-6), 2.60–0.80 (11H, m), 1.76 (3H, s, Me-17), 1.36 (3H, s, Me-20), 1.22 (3H, s, Me-19), 0.97 (3H, s, Me-18); ^{13}C NMR δ: 143.9 (C-9), 143.0 (C-15), 138.7 (C-16), 125.8 (C-8), 125.6 (C-13), 111.0 (C-14), 73.5 (C-7), 68.0 (C-6), 53.2 (C-5), 43.0 (C-3), 40.1 (C-1), 40.1 (C-10), 34.0 (C-4), 33.8 (C-18), 28.2 (C-12), 25.3 (C-11), 24.2 (C-19), 22.1 (C-20), 19.2 (C-2), 15.1 (C-17); EIHRMS calcd for $C_{20}H_{30}O_3Na$ ($M+Na^+$): 341.2087, found: 341.2086.

4.6. Reaction of 14 with MnO_2 to yield 15

To a solution of **14** (38 mg, 0.119 mmol) in dry CH_2Cl_2 (3 mL) was added MnO_2 (519 mg, 5.975 mmol). The reaction mixture was stirred at room temperature for 2.5 h and then was filtered through Celite® eluting with CH_2Cl_2 and AcOEt. The solvent was evaporated to afford **15** (34 mg, 89%).

*4.6.1. 6β-Hydroxy-15,16-epoxy-labd-8,13(16),14-trien-7-one (**15**)*

R_f (hexane/OAcEt 6:4)=0.62; $[\alpha]_D^{22}$+16.3 (*c* 0.91, $CHCl_3$); IR (film): 3406, 1651, 1604, 1462, 1378, 1157, 1121, 1067, 1026, 872, 784; ^{1}H NMR δ: 7.38 (1H, br s, H-15), 7.28 (1H, br s, H-16), 6.32 (1H, br s, H-14), 4.33 (1H, br s, H-6), 2.70–0.70 (11H, m), 1.86 (3H, s, Me-17), 1.39 (3H, s, Me-20), 1.30 (3H, s, Me-19), 1.06 (3H, s, Me-18); ^{13}C NMR δ: 199.6 (C-7), 170.0 (C-9), 143.3 (C-15), 138.9 (C-16), 128.7 (C-8), 124.7 (C-13), 110.8 (C-14), 71.3 (C-6), 53.4 (C-5), 43.6 (C-3), 41.3 (C-10), 37.7 (C-1), 34.4 (C-4), 32.6 (C-18), 30.9 (C-12), 24.6 (C-11), 24.2 (C-19), 22.4 (C-20), 19.0 (C-2), 11.9 (C-17); EIHRMS calcd for $C_{20}H_{28}O_3Na$ ($M+Na^+$): 339.1931, found: 339.1931.

4.7. Oxidation of 15 with $^1O_2$ to yield 3

Rose Begal (1.5 mg) was added to a solution of **15** (14 mg, 0.044 mmol) and DIPEA (0.085 mL, 0.488 mmol) in CH_2Cl_2 (4.5 mL) at room temperature. Anhydrous oxygen was bubbled in for 2 min, and after that the solution was placed under oxygen atmosphere at −78 °C and irradiated with a 200 W lamp. After 2.5 h irradiation was stopped, the pink solution was allowed to warm to room temperature, and saturated oxalic acid solution (7 mL) and H_2O were added. After 30 min of vigorous stirring the mixture was extracted with CH_2Cl_2 and the combined organics extracts were 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 **3** (13 mg, 85%).

*4.7.1. Sibiricinone B (**3**)*

R_f (hexane/OAcEt 6/4)=0.17; $[\alpha]_D^{22}$ +7.5 (*c* 0.42, $CHCl_3$); IR (film): 3384, 1753, 1736, 1648, 1624, 1604, 1459, 1378, 1332, 1121, 1038, 948, 755; ^{1}H NMR δ: 6.06 (1H, s, H-16), 6.05 (1H, s, H′-16), 5.95 (1H, s, H-14), 4.34 (1H, d, *J*=3.6 Hz, H-6), 2.70–0.80 (11H, m), 1.84 (3H, s, Me-17), 1.41 (3H, s, Me-20), 1.31 (3H, s, Me-19), 1.06 (3H, s, Me-18); ^{13}C NMR δ: 199.1 (C-7), 170.2 (C-15), 167.6 (C-13), 167.5 (C-9), 129.0 (C-8), 118.0 (C-14), 98.3 (C-16), 70.9 (C-6), 53.3 (C-5), 43.2 (C-3), 41.1 (C-10), 37.5 (C-1), 34.1 (C-4), 32.4 (C-18), 26.8 (C-12), 26.7 (C-11), 23.9 (C-19), 22.1 (C-20), 18.6 (C-2), 11.7 (C-17); EIHRMS calcd for $C_{20}H_{28}O_5Na$ ($M+Na^+$): 371.1829, found: 371.1840.

4.8. Epoxidation of 8 with *m*-CPBA to yield 16

To a solution of **8** (42 mg, 0.117 mmol) in dry CH_2Cl_2 (1 mL) cooled at 0 °C was added another solution of *m*-CPBA (31 mg, 0.175 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at room temperature for 40 h and then aqueous 10% $NaHSO_3$ was added. The mixture was extracted with EtOAc, washed with aqueous 6% $NaHCO_3$ and brine, and the organic layer was dried over Na_2SO_4, filtered and evaporated to afford **16** (43 mg, 98%).

*4.8.1. 6β,7β-Carbonyldioxy-8α,9α-epoxy-labd-13-en-16,15-olide (**16**)*

R_f (hexane/OAcEt 4:6)=0.51; $[\alpha]_D^{22}$+28.8 (*c* 0.94, $CHCl_3$); IR (film): 1802, 1736, 1636, 1449, 1375, 1325, 1260, 1167, 1130, 1077, 1044, 894, 851, 776; ^{1}H NMR δ: 5.85 (1H, s, H-14), 5.02 (1H, dd, *J*=8.8 and 2.2 Hz, H-6), 4.78 (1H, d, *J*=8.8 Hz, H-7), 4.73 (2H, br s, H-16), 2.50–0.80 (11H, m), 1.41 (3H, s, Me-17), 1.28 (3H, s, Me-20), 1.18 (3H, s, Me-19), 1.02 (3H, s, Me-18); ^{13}C NMR δ: 173.9 (C-15), 169.3 (C-13), 154.2 (OCOO), 115.7 (C-14), 75.8 (C-7), 74.4 (C-6), 73.2 (C-16), 70.6 (C-9), 60.8 (C-8), 42.9 (C-5), 42.8 (C-3), 37.8 (C-10), 36.8 (C-1), 34.0 (C-4), 33.1 (C-18), 25.5 (C-12), 24.0 (C-19), 23.5 (C-11), 20.1 (C-20), 18.3 (C-2), 17.3 (C-17); EIHRMS calcd for $C_{21}H_{28}O_6Na$ ($M+Na^+$): 399.1778, found: 399.1766.

4.9. Reduction of 16 with DIBAL-H and $LiAlH_4$ to yield 9

To a solution of **16** (39 mg, 0.104 mmol) in CH_2Cl_2 (3.8 mL) at −78 °C, DIBAL-H (0.21 mL of solution 1.5 M in toluene, 0.32 mmol) was added under argon. After 30 min the mixture was warm up to 0 °C, quenched with wet Et_2O and at room temperature, Et_2O, Na_2SO_4 (1.0 g) and $NaHCO_3$ (1.0 g) were added and the solution was stirred for 1 h, filtered through silica gel eluting with Et_2O and EtOAc, and concentrated to afford a crude oil, which was dissolved in dry THF (2 mL) cooled at 0 °C and treated with $LiAlH_4$ (8 mg, 0.250 mmol) and stirred at 50 °C for 24 h under argon. Then, the solution was cooled back to 0 °C, wet EtOAc was added and the mixture filtered. The resulting organic phase was dried over Na_2SO_4, filtered and evaporated affording **9** (24 mg, 70%).

*4.9.1. 15,16-Epoxy-labda-13(16),14-dieno-6β,7β,9α-triol (**9**)*

R_f (hexane/OAcEt 4:6)=0.59; $[\alpha]_D^{22}$+7.4 (*c* 0.50, $CHCl_3$); IR (film): 3405, 1459, 1383, 1239, 1156, 1126, 1025, 938, 874, 777; ^{1}H NMR δ: 7.34 (1H, br s, H-15), 7.22 (1H, br s, H-16), 6.27 (1H, br s, H-14), 4.23 (1H, br s, H-6), 3.46 (1H, d, *J*=10.6 and 3.6 Hz, H-7), 2.60–0.80 (12H, m), 1.26 (3H, s, Me-20), 1.12 (3H, d, *J*=7.0 Hz, Me-17), 0.99 (3H, s, Me-19), 0.99 (3H, s, Me-18); ^{13}C NMR δ: 143.2 (C-15), 138.7 (C-16), 125.5 (C-13), 111.0 (C-14), 78.8 (C-9), 74.2 (C-7), 70.6 (C-6), 47.6 (C-5), 43.7 (C-3), 43.4 (C-10), 38.3 (C-8), 35.3 (C-1), 34.4 (C-4), 34.0 (C-18), 30.0 (C-12), 25.0 (C-19), 21.7 (C-11), 19.9 (C-20), 18.9 (C-2), 11.5 (C-17); EIHRMS calcd for $C_{20}H_{32}O_4Na$ ($M+Na^+$): 359.2193, found: 359.2186.

4.10. Acetylation of 9 to yield 17

To a solution of **9** (24 mg, 0.071 mmol) in dry pyridine (0.70 mL), acetic anhydride (0.70 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 **17** (27 mg, 69%).

*4.10.1. 7β-Acetoxy-15,16-epoxy-labda-13(16),14-diene-6β,9α-diol (**17**)*

R_f (hexane/OAcEt 6:4)=0.74; $[\alpha]_D^{22}$; IR (film): 3539, 1737, 1462, 1368, 1237, 1129, 1025, 971, 873, 775; ^{1}H NMR δ: 7.35 (1H, br s, H-15), 7.22 (1H, br s, H-16), 6.27 (1H, br s, H-14), 4.92 (1H, dd, J=11.2 and 3.4 Hz, H-7), 4.29 (1H, br s, H-6), 2.60–0.80 (12H, m), 2.12 (3H, s, *Me*COO), 1.29 (3H, s, Me-20), 1.25 (3H, s, Me-19), 0.97 (3H, d, J=6.2 Hz, Me-17), 0.97 (3H, s, Me-18); EIHRMS calcd for $C_{22}H_{34}O_5Na$ (M+Na^+): 401.2298, found: 401.2288.

4.11. Oxidation of 17 with TPAP to yield 18

To a mixture of **17** (33 mg, 0.087 mmol), *N*-methylmorpholine *N*-oxide (NMO) (50 mg, 0.370 mmol) and molecular sieves (120 mg) in dry CH_2Cl_2 (2 mL) was added TPAP (3 mg, 0.009 mmol). The reaction mixture was stirred at room temperature for 3 h under argon and then was filtered through silica gel and Celite® eluting with AcOEt. The solvent was evaporated to give a crude oil, which was chromatographed on silica gel to afford **18** (28 mg, 86%).

*4.11.1. 7β-Acetoxy-9α-hydroxy-15,16-epoxy-labda-13(16),14-dien-6-one (**18**)*

R_f (hexane/OAcEt 8:2)=0.55; $[\alpha]_D^{22}$+71.3 (*c* 0.64, $CHCl_3$); IR (film): 3531, 1740, 1710, 1461, 1370, 1241, 1158, 1103, 1042, 1025, 966, 908, 782; ^{1}H NMR δ: 7.38 (1H, br s, H-15), 7.26 (1H, br s, H-16), 6.28 (1H, br s, H-14), 5.05 (1H, d, J=11.6 Hz, H-7), 2.91 (1H, s, H-5), 2.60–0.80 (11H, m), 2.18 (3H, s, *Me*COO), 1.27 (3H, s, Me-18), 1.12 (3H, d, J=6.6 Hz, Me-17), 0.96 (3H, s, Me-19), 0.93 (3H, s, Me-20); ^{13}C NMR δ: 205.2 (C-6), 170.6 (*Me*COO), 143.5 (C-15), 138.9 (C-16), 124.8 (C-13), 110.9 (C-14), 79.5 (C-7), 77.6 (C-9), 56.5 (C-5), 48.6 (C-10), 43.9 (C-8), 42.4 (C-3), 34.6 (C-1), 32.8 (C-18), 32.5 (C-4), 31.8 (C-12), 22.4 (C-19), 21.6 (C-11), 21.0 (*Me*COO), 18.4 (C-2), 18.2 (C-20), 12.4 (C-17); EIHRMS calcd for $C_{22}H_{32}O_5Na$ (M+Na^+): 399.2142, found: 399.2160.

4.12. Reaction of 18 with K_2CO_3/MeOH to yield 4

Compound **18** (4.2 mg, 0.011 mmol) was treated with K_2CO_3 in MeOH (2%, 0.7 mL) and the mixture was stirred at room temperature for 50 min. After that time, the reaction mixture was diluted with H_2O and 2 M HCl 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 afford **4** (3.7 mg, 99%).

*4.12.1. Leoheterin (**4**)*

R_f (hexane/OAcEt 8:2)=0.47; $[\alpha]_D^{22}$ +46.0 (*c* 0.37, $CHCl_3$); IR (film): 3464, 1706, 1461, 1384, 1258, 1161, 1126, 1096, 1046, 967, 906, 873; ^{1}H NMR δ: 7.37 (1H, br s, H-15), 7.26 (1H, br s, H-16), 6.28 (1H, br s, H-14), 3.89 (1H, d, J=10.6 Hz, H-7), 2.95 (1H, s, H-5), 2.60–0.80 (11H, m), 1.31 (3H, s, Me-18), 1.26 (3H, d, J=6.4 Hz, Me-17), 0.97 (3H, s, Me-19), 0.90 (3H, s, Me-20); ^{13}C NMR δ: 211.9 (C-6), 143.2 (C-15), 138.6 (C-16), 124.8 (C-13), 110.6 (C-14), 77.2 (C-9), 77.0 (C-7), 55.9 (C-5), 49.0 (C-10), 47.6 (C-8), 42.0 (C-3), 34.3 (C-1), 32.6 (C-18), 32.1 (C-4), 31.6 (C-12), 22.2 (C-19), 21.3 (C-11), 18.1 (C-2), 18.0 (C-20), 12.4 (C-17); EIHRMS calcd for $C_{20}H_{30}O_4Na$ (M+Na^+): 357.2036, found: 357.2052.

4.13. Oxidation of 18 with $^1O_2$ to yield 19

Rose Bengal (1.1 mg) was added to a solution of **18** (8.8 mg, 0.023 mmol) and DIPEA (0.042 mL, 0.241 mmol) in CH_2Cl_2 (2.2 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 tungsten incandescent lamp. After 5 h irradiation was stopped, the pink solution was allowed to warm to room temperature, and saturated oxalic acid solution (5 mL) and H_2O were added. After 30 min of vigorous stirring the mixture was extracted with CH_2Cl_2 and the combined organics extracts were washed with H_2O, dried over Na_2SO_4, filtered and evaporated to afford **19** (8.6 mg, 92%).

*4.13.1. 7β-Acetoxy-9α,16-dihydroxy-6-oxo-labd-13-en-16,15-olide (**19**)*

R_f (hexane/OAcEt 4:6)=0.48; $[\alpha]_D^{22}$+55.3 (*c* 0.39, $CHCl_3$); IR (film): 3398, 1736, 1648, 1460, 1373, 1259, 1128, 1042, 949, 910, 742; ^{1}H NMR δ: 6.04 (1H, br s, H-16), 5.88 (1H, br s, H-14), 5.04 (1H, d, J=11.4 Hz, H-7), 2.89 (1H, s, H-5), 2.60–0.80 (11H, m), 2.18 (3H, s, *Me*COO), 1.25 (3H, s, Me-18), 1.09 (3H, d, J=6.6 Hz, Me-17), 0.96 (3H, s, Me-19), 0.94 (3H, s, Me-20); ^{13}C NMR δ: 204.9 (C-6), 171.3 (C-15), 170.9 (MeCOO), 169.3 (C-13), 117.8 (C-14), 99.2 (C-16), 79.4 (C-7), 77.3 (C-9), 56.4 (C-5), 48.7 (C-10), 47.6 (C-8), 42.3 (C-3), 32.8 (C-18), 32.6 (C-4), 31.8 (C-1), 31.1 (C-11), 24.4 (C-12), 22.4 (C-19), 21.0 (*Me*COO), 18.3 (C-2), 18.2 (C-20), 12.4 (C-17); EIHRMS calcd for $C_{22}H_{32}O_7Na$ (M+Na^+): 431.2040, found: 431.2036.

4.14. Reaction of 19 with K_2CO_3/MeOH to yield 2

Compound **19** (6.0 mg, 0.015 mmol) was treated with K_2CO_3 in MeOH (2%, 1.5 mL) and the mixture was stirred at room temperature for 1 h. After that time, the reaction mixture was diluted with H_2O and 2 M HCl 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 to afford **2** (6 mg, 97%).

*4.14.1. Sibiricinone A (**2**)*

R_f (hexane/OAcEt 4:6)=0.30; $[\alpha]_D^{22}$ +20.2 (*c* 0.27, $CHCl_3$); IR (film): 3406, 1740, 1647, 1461, 1384, 1263, 1127, 1042, 951, 907, 737; ^{1}H NMR δ: 6.03 (1H, br s, H-16), 5.90 (1H, br s, H-14), 3.86 (1H, d, J=11.4 Hz, H-7), 2.91 (1H, s, H-5), 2.70–0.80 (11H, m), 1.30 (3H, s, Me-18), 1.24 (3H, d, J=6.6 Hz, Me-17), 0.98 (3H, s, Me-19), 0.91 (3H, s, Me-20); ^{13}C NMR δ: 211.5 (C-6), 170.5 (C-15), 169.3 (C-13), 118.2 (C-14), 98.7 (C-16), 77.4 (C-9), 77.2 (C-7), 56.5 (C-5), 49.3 (C-10), 47.7 (C-8), 42.1 (C-3), 32.9 (C-18), 32.5 (C-4), 31.9 (C-1), 31.2 (C-11), 22.5 (C-19), 21.7 (C-12), 18.3 (C-20), 18.2 (C-2), 12.7 (C-17); EIHRMS calcd for $C_{20}H_{30}O_6Na$ (M+Na^+): 389.1935, found: 389.1950.

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