An Approach to Furolabdanes and Their Photooxidation Derivatives from *R*-(+)-Sclareolide

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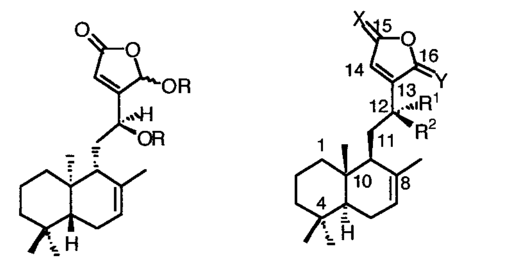
A synthetic route to furolabdanes from commercially available *R*-(+)-sclareolide is reported, with the specific aim of preparing (12*R* and 12*S*,15*ξ*)-12,15-dihydroxylabda-7,13-dien-16,15-olides (**3** and **5**) and (12*R* and 12*S*,16*ξ*)-12,16-dihydroxylabda-7,13-dien-15,16-olides (**4** and **6**). The key points of our approach are the use of Weinreb's amide **11** to join the furan ring to the terpenic unit. Photooxidation of the furan moiety of compounds **15** and **16**, and of their acetates **19** and **20**, has been used to built the hydroxybutenolide fragment. In this way the four possible isomers at the butenolide moiety, compounds **3**−**6**, and their C-12 acetyl derivatives **21**−**24** have been obtained. On the basis of comparison of the spectral data (^{1}H NMR) of the synthetic peracetates **25**−**28** (derived from **21**−**24**) with the reported data for the peracetate **2** (derived from the natural product **1**), the relative configuration at carbon C-12 of the natural product has been corrected. Furthermore, the absolute configuration of the natural product **1**, considered to belong to the *enantio*-series, has to be changed to the *normal*-series on the basis of the optical rotation obtained for the synthetic derivative.

Labdane diterpenoids are among the most common types of diterpenes isolated from higher plants.[1] The interest of this class of compounds resides in their significant antimutagenic,[2] antibacterial, and antifungal activities.[3] However, as in the case of many other natural products, they can be isolated only in minute amounts. This fact inhibits their unambiguous structural determination and often precludes the study of biological and chemical reactivity. Therefore, the hemisynthesis of minor components from other abundant natural products is of longstanding interest. As an example, (12*S*,16*ξ*)-12,16-dihydroxy-*ent*-labda-7,13-dien-15,16-olide, **1**, has been recently isolated from *Alomira myriadenia* (Asteraceae) only in a 0.011% yield with respect to plant material. This compound shows significant cytotoxic activity against human oral epidermoid carcinoma and against colon cancer[4] and is identical to one of the products previously isolated by Bohlmann from *Acritopappus hagei*,[5] since both compounds yielded the same diacetylated derivative **2**. On the basis of biogenetic grounds, Bohlmann suggested an *enantio* absolute configuration for these compounds, although neither the relative stereochemistry at carbon C-12 nor the absolute configuration of compound **2** has been rigorously established.

Continuing with our research directed toward the hemisynthesis of terpenoids,[6] we have been interested in the development of synthetic routes to furolabdane diterpenoids. With this in mind, (12*R*- and 12*S*)-12,15-dihydroxylabda-7,13-dien-16,15-olides **3** and **5**, and their regioisomers (12*R*- and 12*S*)-12,65-dihydroxylabda-7,13-dien-15,16-olides **4** and **6**, were attractive targets, since their synthesis would provide these labdanes in amounts sufficient for biological assay. Additional reward would be the structural determination of **1**. The study of compounds **3**−**6** shows that (+)-sclareolide (**7**) may be a suitable starting material for their synthesis. In fact (+)-sclareolide (**7**) bears the methyl groups at carbons C-4, C-8, and C-10 of the decalin moiety, placed in the appropriate positions. The butenolide fragment present in the synthetic targets **3**−**6** may be derived



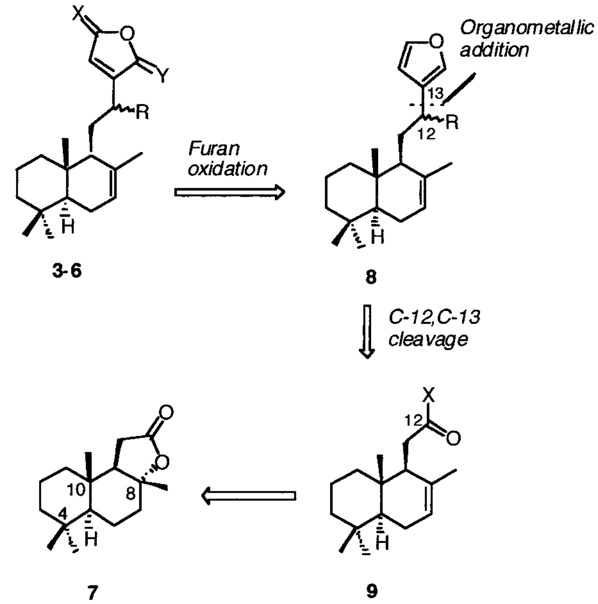
1 R=H
2 R=Ac

3 R¹=OH, R²=H, X=H, OH, Y=O
4 R¹=OH, R²=H X=O, Y=H,OH
5 R¹=H, R²=OH, X=H,OH, Y=O
6 R¹=H, R²=OH, X=O, Y=H, OH

Figure 1.

from the oxidation of a furan ring in an intermediate like **8** (Scheme 1). The furan moiety required for this transfor-

Scheme 1. Retrosynthetic Analysis of Compounds **3**−**6**



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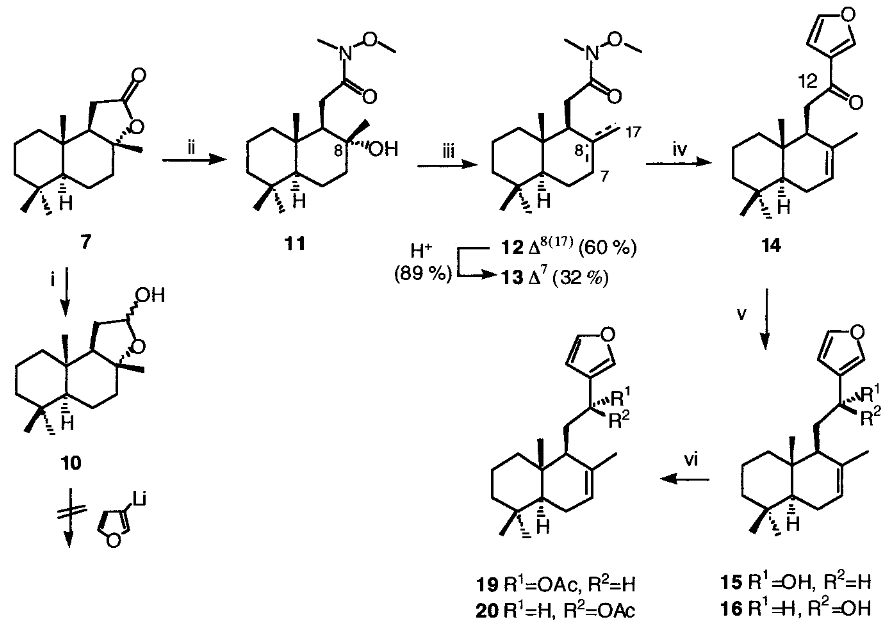
Scheme 2[a]



[a] (i) 1 equiv of DIBAL-H, toluene, −78 °C (94%); (ii) Me_3 Al-MeONHMe-HCl, CH_2Cl_2, 0°C to rt (88%); (iii) $SOCl_2$, py, 0 °C; (iv) 3 equiv of 3-bromofuran, 3 equiv BuLi, THF, −78 °C, 1 h, then 1 equiv of **13**, 2 h (72%); (v) 2 equiv of $CeCl_3 \times 7H_2O$, 8 equiv of $NaBH_4$, MeOH, 0 °C, 30 min (37% for **15**, 33% for **16**); (vi) Ac_2O/py (1:2) 24 h, rt (99% for **19**, 98% for **20**).

mation would be incorporated into the (+)-sclareolide derivative **9**, by reaction of 3-lithiofuran with the electrophillic function at carbon C-12. It should be noted that the proposed synthesis would be effected in a compound having a *normal* configuration instead of the *enantio* proposed for **1**.

Results and Discussion

The synthesis of the key furolabdanes, of general structure **8**, was initially addressed by sequential reduction of the (+)-sclareolide (**7**) to the lactol **10**, followed by coupling with 3-lithiofuran (Scheme 2). Lactol **10** was obtained quantitatively by treatment of (+)-sclareolide with DIBAL-H. In the next step, reaction of 3-lithiofuran with **10** must be performed below 40 °C, to avoid isomerization of the reagent to 2-lithiofuran.[7] Unfortunately, lactol **10** was unreactive at this temperature. A change of strategy was required, and we devised Weinreb's amides as suitable candidates to react with 3-lithiofuran at the required temperature. Weinreb's amide **11** was prepared in 88% yield by aminolysis of (+)-sclareolide (**7**) with the dimethylaluminum amide derived from *N*-methoxy-*N*-methylamine.[8] To prevent waste of organometallic reagent as well as undesired side-reactions, the tertiary alcohol at C-8 was dehydrated prior to the furane addition. Treatment of alcohol **11** with $SOCl_2$ at 0 °C yielded the undesired $\Delta^{8(17)}$ unsaturated derivative **12**, as the major reaction product (60%), together with the desired Δ^7-unsaturated isomer **13** (32% yield). However, the *exo* double bond of compound **12** quantitatively rearranged to the desired *endo*-isomer **13**, under acid treatment. Reaction of alkene **13** with 3-lithiofuran at −78 °C yielded 12-ketolabdane **14** in excellent yield. Reduction of the ketone at C-12 with $NaBH_4$ and excess $CeCl_3 \times 7H_2O$[9] yielded the epimeric 12-hydroxyfurolabdanes **15** and **16** in a 1:1 ratio. These alcohols were separated by column chromatography, and their absolute configuration at carbon C-12 was established by using Mosher's methodology.[10]

Accordingly, the reaction of the alcohols **15** and **16** with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid

Table 1. Chemical Shifts of H-14, H-15, H-16, and OMe for **17** and **18** and Δδ Values ($\delta_{17}-\delta_{18}$)[a]

H	17	18	Δδ
14	6.43	6.27	+0.16
15	7.47	7.42	+0.05
16	7.37	7.36	+0.01
OMe	3.43	3.51	+0.08

[a] At 300 MHz in $CDCl_3$.

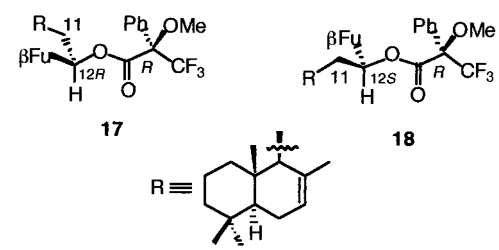


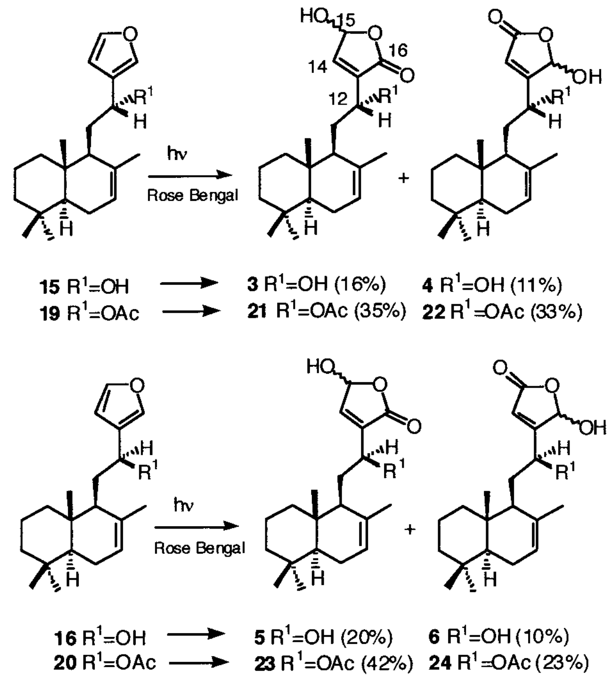
Figure 2. Ideal conformations for the Mosher's esters **17** and **18**.

(MTPA) yielded esters **17** and **18**, respectively. The modified Mosher's[10] method is based on the diamagnetic effect caused by the benzene ring of the MTPA moieties on the β-protons of the alcohol. In the case of α-aromatic secondary carbinols, an anisotropic effect due to the aromatic ring produces negligible Δδ values for these β-protons, which may preclude the use of this method to establish absolute configurations. In addition, the β-protons (H-11) on esters **17** and **18** overlapped with the decalin protons, preventing their analysis. Nevertheless, Isobe[11] has established that, for secondary alcohols bearing an α-furyl substituent, the analysis of the protons attached to the furan ring may be applied to determine the absolute configuration. As shown in Table 1, the furan protons H-14, H-15, and H-16 of ester **18** are shielded with respect to its epimer **17**. This result is fully consistent with the ideal conformation for ester **18** represented in Figure 2, in which the furan ring is eclipsed with the benzene ring of the MTPA group. Therefore, ester **18** and subsequently alcohol **16** must have a C-12*S* absolute configuration. In agreement with these results, the −OMe protons of the MTPA moiety in ester **17** are shielded by the diamagnetic effect caused by the furan [Δδ(**17**−**18**) = − 0.08], and therefore ester **17** and hence alcohol **15** must have a 12*R* absolute configuration.

With alcohols **15** and **16** in hand, we pursued the oxidation of the furan ring to obtain the desired hydroxybutenolides. Among the number of methods that have been developed for the synthesis of 5-hydroxy-2(5*H*)-furanones,[12] the one involving oxidation of furan by $^1O_2$ appears to be the most efficient.[13] In general, the photooxidation of 3-substituted furans is not regiospecific, yielding both the 2-alkyl-4-hydroxy- and the 3-alkyl-4-hydroxybutenolide regioisomers.[14] This fact may be advantageous for us, since we were interested in obtaining both regioisomeric hydroxybutenolides to compare with the natural labdane **1**.[13,14] Irradiation of alcohol **15** in THF (220 W, tungsten lamp, Pyrex well) in the presence of air and a catalytic amount of Rose Bengal for 5 h yielded the regioisomeric hydroxybutenolides **3** and **4**. Both lactones were separated by column chromatography as a mixture of epimers in a 16% and 11% yield, respectively. The ^{1}H NMR spectrum of **3**, obtained in $CDCl_3$, is consistent with an α-alkyl-substituted-15-hydroxybutenolide. Specially relevant are the signals at δ 7.04, which must be assigned to proton H-14, placed at the β-position of an α,β-unsaturated butenolide, and the signal at δ 6.12 attributable to H-15.[15] With respect to the regioisomeric lactone derivative **4**, the most deshielded signal in the ^{1}H NMR spectrum appeared at δ 6.20, and therefore the structure of α,β-alkyl-substituted-16-hydroxybutenolide has been asigned to this compound.[15] Therefore, we established the structure of (12*R*)-12,15-dihydroxylabda-7,13-dien-16,15-olide for compound **3** and the structure of (12*R*)-12,16-dyhydroxylabda-7,13-dien-15,16-olide for compound **4**. Alcohol **16**, having a 12*S* configuration, was submitted to analogous photooxidation conditions, yielding compounds **5** and **6** in 20% and 10% yields, respectively. The ^{1}H NMR of product **5** showed signals at δ 7.08 and 7.04 attributable to H-14, and at δ 6.14 for proton H-15. Compound **6** showed a signal at δ 6.23 that could be assigned to proton H-16 in a 16-hydroxy-15,16-butenolide. In addition, the olefinic proton (H-14) of **6** appears at δ 6.07, 1 ppm shielded with respect to its regioisomer **5**. Consequently, we established a structure of (12*S*)-12,15-dihydroxylabda-7,13-dien-16,15-olide for compound **5** and (12*S*)-12,16-dihydroxylabda-7,-13-dien-15,16-olide for compound **6**.

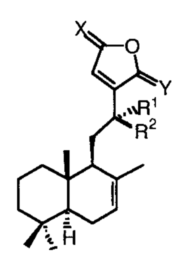
In an attempt to increase the yield of the photooxidation reaction, we checked the oxidation of the 12-acetylderivatives **19** and **20**, quantitatively obtained from alcohols **15** and **16**, respectively, by treatment with Ac_2O−Pyr. Acetate **19** yielded upon sun light irradiation, under the above conditions, the regioisomeric hydroxybutenolides **21** and **22** (35% and 33% yield, respectively). Both compounds were obtained as mixtures of epimers at carbons C-15 and C-16. Again the 15-hydroxy-16,15-butenolide isomer **21** showed signals for protons H-14 and H-15 at δ 6.94 and 6.09, respectively. On the contrary, the ^{1}H NMR of derivative **22** showed a signal for δ H-14, at 5.97, shielded with respect to **21**, while H-16 appeared at δ 6.20 and 6.03. Thus, compound **22** must be the 16-hydroxy-15,16-butenolide. In turn, 12*S*-acetylderivative **20** yielded lactones **23** (42%) and **24** (23%) under analogous reaction conditions. As before, lactone **23** showed signals at δ 7.02−7.01 for H-14 and at 6.13−6.10 for H-15, and therefore it was assigned the structure of (12*S*)-12-acetoxy-15-hydroxylabda-7,13-dien-16,15-olide, derivative **24** being the 16-hydroxy-15,16-butenolide isomer. From these results it is clear that

Scheme 3



although both free alcohols **15** and **16** and their acetates **19** and **20** are suitable substrates for the photooxidation reaction, clearly the presence of the free alcohol group considerably decreases the reaction yields.

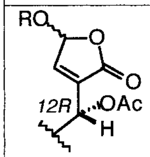
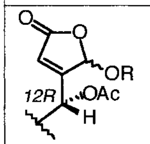
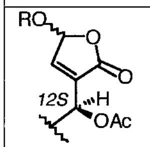
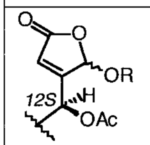
Despite the reported data,[4] 12-hydroxybutenolides **3**−**6** were very unstable and their ^{1}H NMR spectra could not be obtained in py-d_5. This instability thwarted the direct comparison with the literature data for **1**.[4] Thus, the diacetates **25**−**28** were prepared as mixtures of epimers at the hemiacetalic carbon, by Ac_2O−py treatment of lactones **21**−**24**, to compare their ^{1}H NMR data with those reported in the literature for **2**.[4] Comparison of the ^{1}H NMR spectra for the 15-acetoxy-16,15-butenolides **25** and **27** (C12*R* and C-12*S*, respectively) with the ^{1}H NMR spectra for the corresponding 15-hydroxy analogues **21** and **23** (Table 2) showed a strong downfield shift of the signal attributed to H-15, confirming the acetylation of its geminal hydroxyl group (Δδ ≅ 0.9 ppm). Similarly, the ^{1}H NMR of the 16-acetoxy-15,16-butenolides **26** and **28** showed the signals for H-16 deshielded (Δδ ≅ 0.9 ppm), with respect to the 16-hydroxy derivatives **22** and **24**, while the signal for the olefinic proton H-14 remained unchanged upon acetylation. Thus, the structures of (12*R* and 12*S*)-12,15-diacetoxylabda-7,13-dien-16,15-olide (**25** and **27**) and of (12*R* and 12*S*)-12,16-diacetoxylabda-7,13-dien-15,16-olide (**26** and **28**) have been unambiguously established.



25 R^1= OAc, R^2= H, X= H,OAc, Y= O (from **21** 80%)
26 R^1= OAc, R^2= H, X=O, Y= H,OAc (from **22** 90%)
27 R^1= H, R^2= OAc, X= H,OAc, Y= O (from **23** 90%)
28 R^1= H, R^2= OAc, X= O, Y= H,OAc (from **24** 85%)

Figure 3.

Table 2. Chemical Shifts of H-14, H-15, H-16, and H-12 of Compounds **21**−**28** and **2**

	Compound	H-14	H-15	H-16	H-12
	**21** R=H	6.94 m	6.09 m	---------	5.70 dd (6.7, 3.8)
	25 R=25	6.97 m, 6.87 t (1.6)	6.89, 6.97 m	---------	5.76 td (7.8, 1.6)
	**22** R=H	5.97 m	----------	6.20, 6.03 m	5.56 d (10.6)
	26 R=Ac	6.12 dd (1.6, 1.1), 6.04 t (1.1)	----------	7.02 d (1.0), 6.94 d (0.9)	5.81 dt (11.7, 1.1), 5.62 d (13.5)
	**23** R=H	7.01, 7.00 m	6.12, 6.09 m	----------	5.57 t (6.5)
	27 R=Ac	7.05 m	6.92, 6.98 d (1.1)	----------	5.46 t (7.1), 5.62 t (7.3)
	**24** R=H	6.02 m	----------	6.24, 6.05 m	5.36 t (7.7)
	28 R=Ac	6.16, 6.07 t (1.1)	----------	7.04 m,6.97 d (1.0)	5.68 td (8.1, 1.2), 5.46 (overlapped)
	2[a]	6.99, 7.05 dd (0.8, 1.0)	---------	6.09, 6.18 dd (1.1, 0.8)	5.70, 5.10 dt (7.5, 1.2)

[a] Taken from ref 4.

Comparison of the ^{1}H NMR data reported for **2**[4] with the ^{1}H NMR of diacetates **25**−**28** clearly shows that derivatives **2** and **28** have identical ^{1}H NMR spectra. According to this, diacetate **2** and hence the natural product **1** have in fact a 15,16-butenolide moiety. Therefore, the assignment of H-14 and H-16 protons given in the literature for the diacetate **2** must be changed, while the stereochemistry at C-12 in **2** must be the reverse. Consequently, overlooking the absolute stereochemistry, the structure of the reported natural product should be amended to **6**.

Regarding the absolute configuration of compound **1** (isolated from *A. myriadenia*), the sign of the specific rotation reported for its diacetate **2** is negative, like our synthetic diacetate **28** obtained from **24**. Assuming that the ratio of anomeric acetates obtained from **1** and **24** are the same, we conclude that **1** and **28** possess the same absolute configuration. Therefore, diterpene **1** should belong to the *normal* labdane series.

Experimental Section

General Experimental Procedures. Melting points were determined on a Kofler block. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. IR spectra were obtained on a Perkin-Elmer 681 spectrophotometer. ^{1}H NMR spectra were recorded using a Bruker AM 200 apparatus at 200 MHz or a Varian INOVA-300 spectrometer at 300 MHz. ^{13}C NMR spectra were recorded at 50.3 or 75 MHz. Chemical shifts for ^{1}H NMR are reported with respect to residual $CHCl_3$ (δ 7.25) and with respect to $CDCl_3$ (δ 77.00) for ^{13}C NMR spectra. MS were recorded in the positive EI mode on a Hewlett-Packard HP 5989A instrument (70 eV). Elemental analyses were made with a Carlo Erba EA 1108 apparatus. *R*-(+)-Sclareolide was from Aldrich, and it was used as received. All reagents were used as obtained from commercial sources. Methylene chloride (CH_2Cl_2), toluene ($C_6H_5-CH_3$), and tetrahydrofuran (THF) were distilled under positive pressure of argon from CaH_2 or Na-benzophenone. Other solvents were HPLC grade and were used without purification. Na_2SO_4 was used to remove water from the organic layer in reaction workups. Silica gel 60 F_{254} plates were used for TLC. Flash column chromatography was performed using silica gel (Merck, no. 9385, 230−400 mesh) and mixtures of AcOEt−*n*-hexane as eluents.

Preparation of 10 from (+)-Sclareolide (7). To a solution of (+)-sclareolide (**7**, 400 mg, 1.6 mmol) in 60 mL of toluene, at −78 °C, was added DIBAL-H (1.7 mL, 1.7 mmol, 1.0 M in toluene) dropwise. After 45 min of stirring 10 mL of H_2SO_4 aqueous solution (10%) was added, the reaction mixture was allowed to reach room temperature, and it was stirred for an additional 15 min. The mixture was extracted with $CHCl_3$ (3 × 30 mL), and the combined organic phases were dried and solvents removed under reduced pressure. The residue, chromatographed with hexanes−AcOEt (1:4), yielded 380 mg (94%) of pure **10** as a syrup: IR (film) ν_{max} 3314, 2925, 2854, 1460, 1379, 1333, 1205, 1153, 1131, 1074, 965, 888 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.42 (1H, dd, J = 6.1, 5.3 Hz, H-12), 2.02 (1H, ddd, J = 18.5, 12.30, 6.3 Hz, H_B-11), 1.93−1.88 (2H, m, H_A-11 and H-9), 1.75−1.65 (3H, m), 1.22 (3H, s,), 1.47−0.96 (8H, m), 0.85 (2 × 3H, s), 0.81 (3H, s); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 101.8 (d, C-12), 81.2 (s, C-8), 60.2 (d, C-9), 57.0 (d, C-5), 42.4 (t, C-3), 40.0 39.8 (t, C-1), 39.7 (t, C-7), 36.1 (s, C-10), 33.5 (q, C-18), 33.1 (s, C-4), 30.8 (t, C-11), 23.5 (q, C-17), 21.0 (q, C-19), 20.8 (t, C-6), 18.4 (t, C-2), 15.2 y 15.3 (q, C-20); EIMS *m/z* 252 [M]$^{+}$ (5), 237 [M − 15]$^{+}$ (100), 219 (8), 201 (16), 177 (24), 137 (33), 125 (40), 109 (30), 95 (37), 81 (34), 69 (39), 43 (43); *anal.* C 76.05%, H 11.12%, calcd for $C_{16}H_{28}O_2$, C 76.14%, H 11.18%.

Preparation of (1*S*,2*S*,4a*S*,8aS)-*N*-Methoxy-*N*-methyl 1-(2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalenyl)acetamide (11) from (*R*)-(+)-Sclareolide (7). To a stirred suspension of *N,O*-dimethylhydroxylamine hydrochloride (1.5 g, 15.4 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added Me_3Al (8 mL, 16.0 mmol, 2 M in toluene). The mixture was warmed to room temperature and stirred for 2 h until a clear solution was obtained. Sclareolide (**7**, 2.0 g, 8.0 mmol) was added in CH_2Cl_2 (20 mL) and the mixture stirred for another 2 h. After cooling to 0 °C, 15 mL of 10% aqueous H_2SO_4 was added slowly.

The reaction mixture was allowed to reach room temperature, and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic extracts were dried and concentrated under reduced pressure. The residue was purified over silica gel using hexanes−AcOEt (2:3) as eluent to give **11** (2.2 g, 88%) as an amorphous solid: mp 107−109 °C; $[\alpha]^{20}_D$ +26.8°(*c* 0.112, $CHCl_3$); IR (KBr) ν_{max} 3439, 2934, 1643, 1645, 1387, 1167, 1107, 1010, 942 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.71 (3H, s), 3.18 (3H, s), 2.57 (1H, dd, J = 6.5, 16.6 Hz, H_B-11), 1.93 (1H, dt, J = 14.3, 2.9 Hz, H_A-11), 1.94 (1H, s, OH), 1.72−0.92 (10H, m), 1.15 (3H, s), 0.87 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 176.1 (s, C-12), 72.9 (s, C-8), 61.2 (q, OMe), 56.32 (d, C-9), 55.91 (d, C-5), 44.57 (t, C-3), 41.78 (t, C-7), 39.20 (t, C-1), 38.72 (s, C10), 33.4 (q, NMe and C-18), 33.3 (s, C-4), 26.9 (t, C-11), 23.3 (q, C-17), 21.4 (q, C-19), 20.6 (t, C-6), 18.5 (t,C-2), 15.8 (t, C-20); EIMS *m/z* 311 $[M]^+$ (1), 278 $[M - Me - H_2O]^+$ (2), 251 $[M - N(Me)OMe]^+$ (13), 191 (18), 137 (34), 116 (100), 109 (35), 95 (24), 61 (47), 55 (27), 43 (34), 41 (28); *anal.* C 69.22%, H 10.77%, N 4.41%, calcd for $C_{18}H_{33}NO_3$, C 69.41%, H 10.68%, N 4.50%.

Preparation of (1*S*,4a*S*,8a*S*)-*N*-Methoxy-*N*-methyl 1-(5,5,8a-trimethyl-2-methylenedecahydronaphthalenyl)-acetamide (12) and (1*S*,4a*S*,8a*S*)-*N*-methoxy-*N*-methyl 1-(2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8-octahydronaphthalenyl)acetamide (13) from 11. To a solution of **11** (0.5 g, 1.6 mmol) in pyridine (10.0 mL) at 0 °C was added dropwise 1.2 mL (16.0 mmol) of $SOCl_2$ in pyridine (5 mL). The reaction mixture was stirred for 30 min, poured into an ice−water mixture (30 mL), and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried and concentrated under vacuum. The residue was chromatographed with hexanes−AcOEt (95:5) as eluent, yielding **12** (280 mg, 60%) and **13** (150 mg, 32%).

Compound 12: amorphous white solid, mp 90−93 °C; $[\alpha]^{20}_D$ +45.7° (*c* 0.094, $CHCl_3$); IR (KBr) ν_{max} 2960, 2926, 1662, 1645, 1459, 1383, 1364, 1174, 1000, 904 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (1H, s, H_B-17), 4.40 (1H, s, H_A-17), 3.69 (3H, s, OMe), 3.13 (3H, s, NMe), 2.67 (1H, dd, J = 15.8, 9.9 H_B-11), 2.47 (1H, broad d, J = 10.3 Hz, H-9α), 2.36 (1H, dd, J = 15.7, 3.7 Hz, H_A-11), 2.42−2.30 (2H, m), 2.11 (1H, td, J = 12.8, 5.5 Hz, H-7a), 1.76−1.08 (9H, m), 0.86 (3H, s), 0.79 (3H, s), 0.71 (3H, s); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.7 (s, C-12), 149.7 (s, C-8), 105.8 (t, C-17), 61.3 (q, OMe), 55.1 (d, C-9), 51.7 (d, C-5), 42.1 (t, C-3), 39.0 (s, C-10), 38.9 (t, C-1), 37.63 (t, C-7), 33.6 (q, C-18), 33.5 (s, C-4), 32.6 (q, NMe), 27.3 (t, C-11), 24.1 (t, C-6), 21.8 (q, C-19), 19.4 (q, C-19), 19.3 (t, C-2), 14.7 (q, C-20); EIMS *m/z* 293 $[M]^+$ (22), 278 $[M - 15]^+$ (43), 262 $[M - OMe]^+$ (13), 233 (25), 215 (18), 205 (18), 190 (20), 175 (28), 158 (56), 149 (330, 137 (46), 123 (45), 121 (59), 109 (79), 95 (66), 81 (69), 69 (91), 61 (100), 55 (58), 41 (71); *anal.* C 73.79%, H 10.43%, N 4.52%, calcd for $C_{18}H_{31}NO_2$, C 73.67%, H 10.65%, N 4.77%.

Compound 13: syrup, $[\alpha]^{24}_D$ +15.2° (*c* 0.250, $CHCl_3$); IR (KBr) ν_{max} 2924, 2847, 2862, 1776, 1668, 1444, 1383, 1173, 1100, 1007 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41 (1H, br s, H-7), 3.70 (3H, s), 3.19 (3H, s), 2.80−1.00 (11H, m), 1.53 (3H, br s), 0.89 (3H, s), 0.87 (3H, s), 0.80 (3H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 175.4 (s, C-12), 134. 1 (s, C-8), 122.1 (d, C-7), 61.1 (q, OMe), 49.7 (d, C-9), 48.9 (d, C-5), 42.0 (t, C-3), 38.8 (t, C-1), 35.8 (s, C-10), 33.0 (q, C-18), 32.8 (s, C-4), 32.7 (q, NMe), 29.1 (t, C-11), 23.6 (t, C-6), 21.7 (q, C-17), 21.3 (q, C-19), 18.7 (t, C-2), 14.2 (q, C-20); EIMS *m/z* 293 $[M]^+$ (56), 278 (25), 262 (15), 233 (20), 215 (38), 190 (53), 175 (27), 137 (33), 119 (88), 109 (94), 103 (100), 95 (47), 81 (55), 69 (44), 61 (53), 41 (30); *anal.* C 73.89%, H 10.56%, N 4.89%, calcd for $C_{18}H_{31}NO_2$, C 73.67%, H 10.65%, N 4.77%.

Preparation of (1*S*,4a*S*,8a*S*)-*N*-Methoxy-*N*-methyl 1-(2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8-octahydronaphthalenyl)acetamide (13) from 12. A mixture of **12** (250 mg, 0.85 mmol) and *p*-TsOH (25 mg) in toluene (25 mL) was heated at 50 °C for 2 h. The reaction mixture was cooled at room temperature and diluted with AcOEt (30 mL). The mixture was washed with $NaHCO_3$ (saturated solution, 3 × 50 mL). The organic layer was dried, and the solvents were evaporated. Chromatography of the residue using hexanes−AcOEt (95:5) yielded 223 mg (89%) of pure **13**.

Preparation of 15,16-Epoxy-12-oxolabda-7,13(16),14-triene (14) from 13. 3-Bromofuran (0.23 mL, 2.5 mmol) was added dropwise to a solution of *n*-butyllithium (1.2 M in hexanes, 2.5 mL, 3.0 mmol) in dry THF (2.5 mL), at −78 °C under argon. The mixture was stirred for 1 h and then transferred via cannula into a solution of amide **13** (0.3 g, 1.0 mmol) in dry THF (40 mL) cooled at −78 °C. After 2 h the substrate was consumed and the reaction was quenched by adding 50 mL of NH_4Cl (saturated solution). The aqueous phase was extracted with AcOEt (3 × 50 mL), the combined organic layers were dried, and the solvent was evaporated. The residue was chromatographed using hexanes−CH_2Cl_2 (4:1) as eluent. Thus, 220 mg of pure ketone **14** (72%) was obtained: spontaneous white crystals mp 70−73 °C; $[\alpha]^{27}_D$ +42.9° (*c* 0.219, $CHCl_3$); IR (KBr) ν_{max} 2963, 2926, 2847, 1668, 1560, 1512, 1385, 1158, 873 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (1H, d, J = 0.9 Hz, H-16), 7.43 (1H, t, J = 1.8 Hz, H-15), 6.78 (1H, dd, J = 1.8, 0.9 Hz, H-14), 5.41 (1H, br s, H-7), 2.80 (1H, m), 2.77 (1H, d J = 16.5 Hz, H_B-11), 2.67 (1H, dd, J = 16.5, 14.3 Hz, H_A-11), 2.04 (1H, m), 1.86 (1H, m), 1.64 (1H, br d, J = 12.6 Hz), 1.45 (3H, br s, Me-17), 1.50−1.00 (7H, m), 0.88 (3H, s), 0.87 (3H, s), 0.81 (3H, s); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 194.9 (s, C-12), 145.6 (d, C-15), 144.0 (d, C-16), 133.8 (s, C-8), 127.8 (s, C-13), 122.4 (d, C-7), 108.7 (d, C-14), 45.6 (d, C-5), 48.2 (d, C-9), 42.0 (t, C-3), 39.1 (t, C-1), 38.3 (t, C-11), 35.7 (s, C-10), 33.0 (q, C-18), 32.8 (s, C-4), 23.6 (t, C-6), 21.9 (q, C-17)*, 21.7 (q, C-19)*, 18.7 (t, C-2), 14.3 (q, C-20), assignments marked with an asterisk may be interchanged; EIMS *m/z* 300 $[M]^+$ (12), 285 (2), 215 (2), 190 (100), 175 (39), 119 (35), 109 (61), 105 (30), 95 (99); *anal.* C 79.56%, H 9.52%, calcd for $C_{20}H_{28}O_2$, C 79.96%, H 9.39%.

Preparation of (12*R*)- and (12*S*)-15,16-Epoxy-12-hydroxylabda-7,13(16),14-triene (15 and 16) from 14. To a solution of ketone **14** (820 mg, 2.7 mmol) in MeOH (53 mL) at room temperature was added 2.0 g of $CeCl_3 \times 7H_2O$ (5.5 mmol), and the mixture was stirred for 30 min. The resulting slurry was cooled until 0 °C, and $NaBH_4$ (625 mg, 16.4 mmol) was added in portions. The mixture was allowed to reach room temperature and stirred for 24 h. After this time, H_2O (50 mL) was added and the mixture stirred for an additional 1 h. The resulting solution was concentrated under vacuum, and the aqueous phase was extracted with AcOEt (3 × 50 mL). The combined organic layers were dried and evaporated under reduced pressure. Chromatography of the residue using hexanes−AcOEt (1:1) yielded in increasing order of polarity unreacted ketone **14** (150 mg), alcohol **15** (250 mg, 37%), and alcohol **16** (220 mg, 33%).

Compound 15: oil; $[\alpha]^{21}_D$ +25.6° (*c* 0.340, $CHCl_3$); IR (film) ν_{max} 3400, 2922, 2847, 1502, 1455, 1387, 1159, 1024, 874 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (2H, m, H-16 and H-15), 6.41 (H, dd, J = 1.5, 0.8 Hz, H-14), 5.43 (1H, br s, H-7), 4.72 (1H, dd, J = 8.4, 1.6 Hz, H-12), 2.20−0.90 (12 H, m), 1.66 (3H, br s), 0.89 (3H, s), 0.87 (3H, s), 0.76 (3H, s); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 143.3 (d, C-15), 138.5 (d, C-16), 134.6 (s, C-8), 130.1 (s, C-13), 123.0 (d, C-7), 108.5 (d, C-14), 67.6 (d, C-12), 50.5 (d,C-9)*, 50.4 (d, C-5)*, 42.3 (t, C-3), 39.4 (t, C-1), 36.3 (t, C-11), 36.3 (s, C-10)*, 33.1 (q, C-18), 33.0 (s, C-4)*, 23.9 (t, C-6), 22.3 (q, C-17)*, 21.8 (q, C-19)*, 18.8 (t, C-2), 13.6 (q, C-20), assignments marked with an asterisk may be interchanged; EIMS *m/z* 302 $[M]^+$ (absent), 284 $[M - 18]^+$ (11), 205 (32), 190 (40), 175 (29), 160 (82), 119 (31), 109 (72), 97 (100), 82 (54), 69 (48), 41 (54); *anal.* C 79.60%, H 9.59%, calcd for $C_{20}H_{30}O_2$, C 79.42%, H 10.00%.

Compound 16: oil; $[\alpha]^{21}_D$ −18.6° (*c* 0.200, $CHCl_3$); IR (film) ν_{max} 3367, 2922, 2847, 1503, 1456, 1387, 1155, 1022, 874, 790 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (1H, m, H-16), 7.36 (1H, m, H-15), 6.44 (1H, dd, J = 1.6, 1.0 Hz, H-14), 5.42 (1H, br s, H-7), 4.75 (1H, dd, J = 9.4, 5.4 Hz, H-12), 2.20−0.40 (12H, m), 1.76 (3H, br s, Me-17), 0.84 (3H, s), 0.81 (3H, s), 0.74 (3H, s); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 143.4 (d, C-15), 139.7 (d, C-16), 134.6 (s, C-8), 128.5 (s, C-13), 122.9 (d, C-7), 108.7 (d, C-14), 68.0 (d, C-12), 50.4 (d, C-5)*, 50.0 (d, C-9)*, 42.2 (t, C-3), 39.1 (t, C-1), 36.7 (s, C-10), 35.5 (t, C-11), 33.1 (q, C-18), 32.9

(s, C-4), 23.9 (t, C-6), 22.7 (q, C-17), 21.8 (q, C-19), 18.7 (t, C-2), 13.6 (q, C-20), assignments marked with an asterisk may be interchanged; EIMS *m/z* 302 $[M]^+$ (absent), 284 $[M - 18]^+$ (9), 205 (28), 190 (25), 160 (78), 119 (24), 109 (61), 97 (100), 82 (47), 69 (44), 41 (52); *anal.* C 79.67%, H 9.68%, calcd for $C_{20}H_{30}O_2$, C 79.42%, H 10.00%.

Preparation of Mosher's Ester 17 from Alcohol 15. Alcohol **15** (8 mg, 0.025 mmol) in CH_2Cl_2 (1.0 mL) and a catalytic amount of 4-(dimethylamino)pyridine were added to a solution of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (16.0 mg, 0.07 mmol) and 1,3-dicyclohexylcarbodiimide (14.0 mg, 0.07 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. The mixture was stirred for 2 h until complete consumption of alcohol. Then, the reaction mixture was filtered through a pad of Celite and evaporated under vacuum. Chromatography of the residue with hexanes−AcOEt (99:1) yielded 11 mg of pure **17** (89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.31 (7H, m, Ph, H-15, H-16), 6.44 (1H, m, H-14), 6.11 (1H, dd *J* = 11.3, 1.7 Hz, H-12), 5.39 (1H, br s, H-7), 3.44 (3H, br s, OMe), 3.19 (1H, m), 2.07 (1H, dd *J* = 13.9, 11.5 Hz, H_B-11), 1.70 (3H, br s, Me-17), 2.11−1.13 (11 H, m, decalin protons), 0.81 (3H, s), 0.80 (3H, s), 0.64 (3H, s).

Preparation of Mosher's Ester 18 from Alcohol 16. Alcohol **16** (13 mg, 0.043 mmol) in CH_2Cl_2 (2.0 mL) and a catalytic amount of 4-(dimethylamino)pyridine were added to a solution of (*R*)-(+)-α-methoxy-α-(trifluoromethy)phenylacetic acid (26.0 mg, 0.13 mmol) and 1,3-dicyclohexylcarbodiimide (22.0 mg, 0.13 mmol), in CH_2Cl_2 (1 mL) at room temperature. Working as above, 21 mg (93%) of pure **18** was obtained: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63−7.27 (7H, m, Ph, H-15, H-16), 6.28 (1H, m, H-14), 6.06 (1H, dd *J* = 10.0, 5.7 Hz, H-12), 5.44 (1H, m, H-7), 3.52 (3H, br s, OMe), 2.03−1.05 (12H, m,), 1.77 (3H, br s, Me-17), 0.85 (3H, s), 0.82 (3H, s), 0.74 (3H, s).

General Procedure for Irradiation of 15 and 16. A solution of alcohol (100 mg) in THF (10 mL), containing ca. 1 mg of Rose Bengal, was irradiated with a 220 W tungsten lamp for 5 h. The solvent was removed under reduced pressure, and the residue was submitted to column chromatography, yielding pure compounds.

Preparation of (12*R*,15ζ)-12,15-dihydroxylabda-7,14-dien-16,15-olide (3) and (12*R*,16ζ)-12,16-dihydroxylabda-7,14-dien-15,16-olide (4). Photooxidation of 15. Irradiation of alcohol **15** yielded, after chromatographic separation with hexanes−AcOEt (3:1), 18 mg (16%) of lactone **3** and 12 mg (11%) of lactone **4**. Compounds **3** and **4** were unstable, and correct analytical data could not be obtained.

Compound 3: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (1H, m, H-14), 6.12 (1H, m, H-15), 5.42 (1H, m, H-7), 4.56 (1H, m, H-12), 1.73 (3H, s, Me-17), 0.87 (3H, s), 0.86 (3H, s), 0.73 (3H, s). Due to the instability of **3** IR and MS data could not be obtained.

Compound 4: IR (KBr) ν_{max} 3434, 2925, 1752, 1631, 1009 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (1H, s, H-16), 6.12 (1H, br s, H-14), 5.44 (1H, br s, H-7), 4.67 and 4.55 (1H, m, H-12), 1.73 and 1.69 (3H, br s, Me-17), 2.08−1.01 (12H, m), 0.87 (3H, s Me-18), 0.86 (3H, s, Me-19), 0.74 and 0.73 (3H, s, Me-20); EIMS *m/z* 334 $[M]^+$ (absent), 205 (14), 189 (10), 175 (7), 124 (36), 109 (100), 91 (22), 81 (50), 69 (26), 55 (32), 41 (27).

Preparation of (12*S*,15ζ)-12,15-dihydroxylabda-7,14-dien-16,15-olide (5) and (12*S*,16ζ)-12,16-Dihydroxylabda-7,14-dien-15,16-olide (6). Photooxidation of 16. Irradiation of alcohol **15** yielded, after chromatography with hexanes−AcOEt (3:1), 22 mg (20%) of lactone **5** and 15 mg (10%) of lactone **6**. Compounds **5** and **6** were unstable, and correct analytical data could not be obtained.

Compound 5: IR (KBr) ν_{max} 3455, 2924, 2847, 1749, 1634, 1129 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 and 7.05 (1H, s, H-14), 6.15 (1H, br s, H-15), 5.45 (1H, br s, H-7), 4.55 (1H, t, *J* = 6.7 Hz, H-12), 1.95−1.12 (12H, m), 1.70 (3H, br s, Me-17), 0.87 (3H, s, Me-18), 0.84 (3H, s, H-19), 0.76 (3H, s, Me-20); EIMS *m/z* 334 $[M]^+$ (absent), 316 $[M - 18]^+$ (1), 298 $[M - 36]^+$ (1), 205 (50), 149 (17), 124 (25), 109 (100), 81 (59), 55 (27), 41 (21).

Compound 6: IR (KBr) ν_{max} 3435, 2920, 1754, 1631, 112 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (1H, m, H-16), 6.07 (1H, m, H-14), 5.46 (1H, br s, H-7), 4.68 (1H, t, *J* = 6.2 Hz, H-12), 1.73 (3H, br s, Me-17), 2.05−1.11 (12H, m), 0.88 (3H, s, Me-18), 0.86 (3H, s, H-19), 0.79 (3H, s, Me-20); EIMS *m/z* 334 $[M]^+$ (absent), 205 (10), 190 (80), 175 (7), 124 (40), 109 (100), 91 (18), 81 (46), 69 (20), 55 (27), 41 (21).

Preparation of (12*R*)-12-Acetoxy-15,16-epoxylabda-7,13(16),14-triene (19) from 15. Alcohol **15** (50 mg), was treated with Ac_2O−Pyr (12.0 mL, 1:2) for 24 h. Solvents were removed under reduced pressure, and the residue was filtered through a short pad of silica gel using AcOEt as solvent, yielding 55 mg (99%) of pure **19**: amorphous solid; mp 64−67 °C; $[\alpha]^{21}_D$ + 15.7° (*c* 0.070, $CHCl_3$); IR (KBr) ν_{max} 2923, 2847, 1725, 1361, 1240, 1020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (1H, d, *J* = 0.6 Hz, H-16), 7.36 (1H, t, *J* = 1.8 Hz, H-15), 6.38 (1H, dd, *J* = 1.8, 0.6 Hz, H-14), 5.93 (1H, dd, *J* = 10.9, 2.7 Hz, H-12), 5.41 (1H, br s, H-7), 2.06 (3H, s, OAc), 1.70 (3H, br s, Me-17), 0.88 (3H, Me-18), 0.86 (3H, s, Me-19), 0.76 (3H, s, Me-20); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.7 (s, OAc), 143.2 (d, C15), 139.8 (d, C-16), 134.2 (s, C-8), 125.7 (s, C-13), 123.1 (d, C-7), 108.8 (d, C-14), 69.0 (d, C-12), 50.4 (d, C-5)*, 49.9 (d, C-9)*, 42.3 (t, C-3), 39.3 (t, C-1), 36.3 (s, C-10), 33.2 (q, C-18), 33.1 (t, C-11), 33.0 (s, C-4), 23.2 (q, C-17)*, 21.9 (q, C-19)*, 21.3 (q, OAc)*, 18.8 (t, C-2), 13.6 (q, C-20); EIMS *m/z* 344 $[M]^+$ (absent), 284 $[M - 60]^+$ (11), 190 (38), 175 (16), 160 (100), 145 (14), 119 (40), 109 (39), 97 (36), 81 (31), 43 (56); *anal.* C 76.53%, H 9.52%, calcd for $C_{22}H_{32}O_3$, C 76.70%, H 9.36%.

Preparation of (12*S*)-12-Acetoxy-15,16-epoxylabda-7,13(16),14-triene (20) from 16. Alcohol **16 (**150 mg) was treated with Ac_2O−Pyr (18.0 mL, 1:2) for 24 h at room temperature. Solvents were removed under reduced pressure. The residue, filtered through a short pad of silica gel using AcOEt solvent, yielded 160 mg (98%) of pure **20** as a syrup: $[\alpha]^{22}_D$ −32.8° (*c* 0.090, $CHCl_3$); IR (film) ν_{max} 2925, 1739, 1369, 1239, 1022 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42 (1H, m, H-16), 7.39 (1H, t, *J* = 1.5 Hz, H-15), 6.41 (1H, dd, *J* = 1.7, 0.7 Hz, H-14), 5.87 (1H, dd, *J* = 8.8, 6.59 Hz, H-12), 5.42 (1H, br s, H-7), 2.02 (3H, OAc), 1.90−1.40 (12H, m), 1.80 (3H, s, Me-17), 0.84 (3H, Me-18), 0.80 (3H, s, Me-19), 0.73 (3H, s, Me-20); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.3 (s, OAc), 143.2 (d, C-15), 140.9 (d, C-16), 134.3 (s, C-8), 124.5 (s, C-13), 123.0 (d, C-7), 109.2 (d, C-14), 69.9 (d, C-12), 50.2 (d, C-5), 49.9 (d, C-9), 42.1 (t, C-3), 39.2 (t, C-1), 36.8 (s, C-10), 33.0 (q, C-18), 33.0 (s, C-4), 32.3 (t, C-11), 23.8 (t, C-6), 22.7 (q, C-17), 21.8 (q, C-19), 21.3 (q, OAc), 18.7 (t, C-2), 13.6 (q, C-20); EIMS *m/z* 344 $[M]^+$ (absent), 284 $[M - 60]^+$ (11), 269 (3), 190 (26), 160 (100), 140 (25), 119 (36), 109 (48), 105 (23), 97 (50), 81 (38), 43 (74); *anal.* C 76.48%, H 9.60%, calcd for $C_{22}H_{32}O_3$, C 76.70%, H 9.36%.

General Procedure for Irradiation of 19 and 20. A THF solution of the corresponding acetate, containing a catalytic amount of Rose Bengal, was irradiated under direct sunlight until TLC analysis showed complete transformation of the starting material. The solvent was removed under reduced pressure, and the residue was submitted to column chromatography to yield analytically pure compounds.

Preparation of (12*R*)-12-Acetoxy-15-hydroxylabda-7,14-dien-16,15-olide (21) and (12*R*)-12-Acetoxy-16-hydroxylabda-7,14-dien-15,16-olide (22) from 19. Irradiation of **19** (75 mg) in THF (15 mL) yielded, after chromatographic separation with hexanes−AcOEt (4:1), 29 mg of the hydroxybutenolide **21** (35%) and 23 mg (33%) of its isomer **22**.

Compound 21: syrup; IR (film) ν_{max} 3429, 2925, 2847, 1747, 1456, 1373, 1230, 1131, 1042 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (1H, m, H-14), 6.09 (1H, m, H-15), 5.70 (1H, dd, *J* = 6.7, 3.8 Hz, H-12), 5.42 (1H, br s, H-7), 2.13 (3H, s, OAc), 1.75 (3H, br s, Me-17), 2.00−1.15 (12H, m), 0.87 (3H, s, Me-19), 0.72 (3H, s, Me-20); EIMS *m/z* 376 $[M]^+$ (absent), 316 $[M - 60]^+$ (23), 301 (5), 205 (9), 190 (30), 147 (28), 119 (54), 109 (100), 105 (26), 91 (28), 81 (36), 69 (27), 55 (27), 43 (52); *anal* C 69.84%, H 8.35%, calcd for $C_{22}H_{32}O_5$ C 70.18%, H 8.57%.

Compound 22: syrup; IR (film) ν_{max} 3430, 2924, 2827, 1749, 1373, 1235, 1011 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 6.03 (1H, m, H-16), 5.97 (1H, m, H-14), 5.56 (1H, br d, *J* = 10.6

Hz, H-12), 5.46 (1H, br s, H-7), 2.14 (3H, s, OAc), 1.71 (3H, br s, Me-17), 2.00−1.20 (12H, m), 0.88 (3H, s, Me-18), 0.86 (3H, s, Me-19), 0.75 (3H, s H-20); EIMS *m*/*z* 376 $[M]^+$ (absent), 298 $[M - 60 - 18]^+$ (1), 205 (5), 190 (43), 175 (14), 124 (39), 119 (28), 109 (100), 81 (27), 69 (21), 43 (36); *anal* C 69.93%, H 8.38%, calcd for $C_{22}H_{32}O_5$ C 70.18%, H 8.57%.

Preparation of (12*S*)-12-Acetoxy-15-hydroxylabda-7,14-dien-16,15-olide (23) and (12*S*)-12-Acetoxy-16-hydroxylabda-7,14-dien-15,16-olide (24) from 20. Irradiation of **20** (120 mg), in THF (25 mL), yielded, upon chromatography with hexanes−AcOEt (4:1), 55 mg of pure hydroxybutenolide **23** (42%) and 30 mg (23%) of its isomer **24**.

Compound 23: syrup; IR (film) ν_{max} 3434, 2926, 2847, 1768, 1749, 1635, 1458, 1370, 1236, 1014 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01, 7.00 (1H, br s, H-14), 6.12, 6.09 (1H, br s, H-15), 5.57 (1H, t, J = 6.5 Hz, H-12), 5.43 (1H, br s, H-7), 2.10, 2.01 (3H, s, OAc), 1.73 (3H, br s, Me-17), 2.06−0.89 (12H, m), 0.85 (3H, s, Me-18), 0.82 (3H, s, Me-19), 0.75 (3H, s, Me-20); EIMS *m*/*z* 376 $[M]^+$ (absent), 316 $[M - 60]^+$ (25), 301 (6), 215 (5), 190 (27), 133 (14), 119 (48), 109 (100), 105 (26), 91 (29), 81 (36), 69 (26), 55 (27), 43 (57); *anal* C 69.90%, H 8.46%, calcd for $C_{22}H_{32}O_5$ C 70.18%, H 8.57%.

Compound 24: syrup; IR (film) ν_{max} 3430, 2926, 2862, 2847, 1747, 1638, 1458, 1367, 1232 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24, 6.05 (1H, br s, H-16), 6.02 (1H, br s, H-14), 5.47 (1H, br s, H-7), 5.36 (1H, t, J = 7.7 H-12), 2.12, 2.09 (3H, s, OAc), 2.00−2.70 (12H, m), 1.71 (3H, s, Me-17), 0.86 (3H, s, Me-17), 0.84 (3H, s, Me-19), 0.76 (3H, s, Me-20); *anal* C 70.25%, H 8.50%, calcd for $C_{22}H_{32}O_5$ C 70.18%, H 8.57%.

Preparation of (12*R*)-12,15-Diacetoxylabda-7,14-dien-16,15-olide (25), (12*R*)-12,16-Diacetoxylabda-7,14-dien-15,16-olide (26), (12*S*)-12,15-Diacetoxylabda-7,14-dien-16,15-olide (27), and (12*S*)-12,16-Diacetoxylabda-7,14-dien-15,16-olide (28) from 21 to 24. Compounds **21**−**24** were treated with the mixture Ac_2O−Pyr (2 mL, 1:2) for 24 h at room temperature. Solvents were removed under reduced pressure, and the residues were purified by chromatography, using hexanes−AcOEt (9:1).

Compound 25. Following the general procedure, 24 mg (0.064 mml) of **21** yielded 23 mg (86%) of an epimeric mixture of **25** as a syrup: $[\alpha]^{23}_D$ +30.9°(*c* 0.330 $CHCl_3$); IR (film) ν_{max} 2925, 2862, 1780, 1743, 1456, 1373, 1226, 1022, 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (1H, m, H-15 minor), 6.87 (1H, t, J = 1.6 Hz, H-14 minor), 6.97 (2H, m, H-14 and H-15 major), 5.76 (1H, tdd, J = 7.8, 1.6 Hz, H-12 minor and major), 5.42 (1H, br s, H-7), 2.14 (6H, 2 × OAc major), 2.13 (3H, s, OAc, minor), 2.15 (3H, s, OAc, minor), 1.80 (3H, s, Me-17), 0.86 (6H, 2 × Me, minor), 0.85 (6H, 2 × Me, major), 0.73 (3H, Me-20, major), 0.72 (3H, Me-20 minor); EIMS *m*/*z* 418 $[M^+]$ (1), 358 $[M^+ - 60]$ (19), 298 (8), 205 (10), 190 (36), 174 (43), 119 (53), 109 (88), 105 (24), 91 (26), 81 (36), 69 (31), 43 (100); *anal.* C 68.59%, H 7.95%, calcd for $C_{24}H_{34}O_6$, C 68.87%, H 8.19%.

Compound 26. Following the general procedure, 19 mg (0.051 mml) of **22** yielded 18 mg (84%) of an epimeric mixture of **26** as a syrup: $[\alpha]^{24}_D$ +14.7° (*c* 0.660, $CHCl_3$); IR (film) ν_{max} 2962, 2920, 2847, 1800, 1747, 1653, 1455, 1373, 1261, 1226, 1026, 866 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (1H, d, J = 1.0 Hz, H-16 minor), 6.94 (1H, d, J = 0.9 Hz, H-16 major), 6.12 (1H, dd, J = 1.6, 1.1 Hz, H-14 minor), 6.04 (1H, t, J = 1.1 Hz, H-14 major), 5.81 (1H, dt, J = 11.7, 1.7 Hz, H-12 major), 5.62 (1H, br d, J = 13.5 Hz, H-12 minor), 5.45 (1H, br s, H-7), 2.17 and 2.16 (3H each, s, 2 × OAc major), 2.14 and 2.10 (3H each, s, 2 × OAc minor), 1.55 (3H, s, Me-17), 2.03−1.10 (12H, m), 0.87 (3H, s, Me minor), 0.85 (3H, s, Me major), 0.85 (3H, s, Me), 0.75 (3H, s, Me minor), 0.73 (3H, s, Me major); EIMS *m*/*z* 298 $[M^+ - 60 - 60]$ (3), 283 (2), 255 (1), 189 (24), 175 (12), 124 (30), 119 (35), 109 (100), 81 (30), 69 (26), 55 (25), 43 (79); *anal.* C 69.03%, H 7.88%, calcd for $C_{24}H_{34}O_6$, C 68.87%, H 8.19%.

Compound 27. Following the general procedure, 50 mg (0.133 mmol) of **23** yielded 51 mg (92%) of an epimeric mixture of **27** as a syrup: $[\alpha]^{23}_D$ −29.1° (*c* 0.500, $CHCl_3$); IR (film) ν_{max} 2925, 2847, 2862, 1780, 1746, 1458, 1372, 1335, 1227, 1022, 966, 797, 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (1H, m, H-15 or H-14), 6.92 and 6.89 (1H, d, J = 1.1 Hz, H-14 or H-15), 5.64 (1H, t J = 7.1 Hz, H-12 major), 5.62 (1H, t, J = 7.3 Hz, H-12 minor), 5.43 (1H, br s, H-7), 2.15, 2.14, 2.11 and 2.10 (3H each, s, OAc), 1.74 (3H, br s, Me-17), 2.03−1.13 (12H, m), 0.85 (3h, s, Me), 0.83 (3H, s, Me), 0.75 (3H, s, Me); EIMS *m*/*z* 358 $[M^+ - 60]$ (25), 316 (8), 298 (10), 205 (13), 190 (40), 174 (48), 119 (49), 109 (90), 91 (27), 81 (34), 69 (27), 55 (23), 43 (100); *anal.* C 68.63%, H 8.22%, calcd for $C_{24}H_{34}O_6$, C 68.87%, H 8.19%.

Compound 28. Following the general procedure, 25 mg (0.06 mmol) of **24** yielded 20 mg (80%) of an epimeric mixture of **28** as a syrup: $[\alpha]^{24}_D$ −5.8° (*c* 2.170, $CHCl_3$); IR (film) ν_{max} 2962, 2920, 2850, 1797, 1744, 1455, 1372, 1260, 1024, 865, 799 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (1H, m, H-16 minor), 6.97 (1H, d, J = 1.0 Hz, H-16 major), 6.16 and 6.07 (1H each, t, J = 1.1 Hz, H-14), 5.68 (1H, td, J = 8.1, 1.20 Hz, H-12 major), 5.46 (2H, br s, and td H-7 and H12 minor), 2.18 and 2.12 (3H each, s, 2 × OAc, major), 2.15 and 2.07 (3H, each, s 2 × OAc minor), 2.02 (12H, m), 1.69 (3H, me-17), 0.86 (3H, s, Me), 0.84 (3H, s, Me), 0.77 and 0.75 (3H, s, Me-20); IEMS *m*/*z* 358 $[M^+ - 60]$ (1), 343 (1), 298 (7), 283 (5), 189 (43), 175 (17), 124 (34), 119 (34), 109 (100), 91 (17), 81 (26), 69 (19), 55 (17), 43 (53); *anal.* C 69.12%, H 7.84%, calcd for $C_{24}H_{34}O_6$, C 68.87%, H 8.19%.

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