Studies on the Synthesis of Scoparic Acid A and Related Labdane Diterpenoids. Synthesis of (E)-6#-Hydroxylabda-8-(17),13-dien-15-oic Acid

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STUDIES ON THE SYNTHESIS OF SCOPARIC ACID A AND RELATED LABDANE DITERPENOIDS. SYNTHESIS OF (*E*)-6β-HYDROXYLABDA-8-(17),13-DIEN-15-OIC ACID

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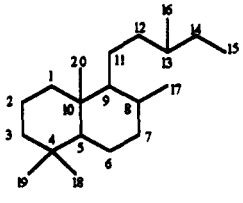
ABSTRACT.—A general strategy for a successful approach to labdanes of the type **3–5** is described. This methodology, which makes use of the known Eschenmoser fragmentation of **9**, 1,3-oxidative rearrangement of allylic tertiary alcohol **14**, and photochemical double bond isomerization of allylic acetate **17** as key synthetic steps, is used to prepare optically pure labdane **5** from readily available (+)-podocarpenone **8**.

A very large number of diterpenoids possessing a labdane skeleton **1** occur in nature 1). Several of them (including some biologically active ones) possess a C-8–C-17 exomethylene group and a β-oriented C-6 oxygenated function as common structural features. These are exemplified by compounds **2–5** (**2–7**).

By far the most interesting compound of this type is scoparic acid A [**2**], a labdane-type diterpenoid isolated from the extract of "Typychá Kuratu" (8), a Paraguayan folk medicine used for the treatment of stomach disease and hepatosis (9). This compound, as recently demonstrated (10), is characterized by an unusual syn stereochemical relationship between the H-9 and 10-Me substituents.

As a part of our preliminary investigations directed toward the synthesis of scoparic acid A, initiated before the configuration of the side chain attached to C-9 was firmly established, we decided to explore the synthesis of **5**, one of the less complex of these molecules (2). No biological activity has been reported for this compound, but the work



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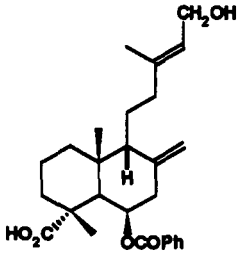

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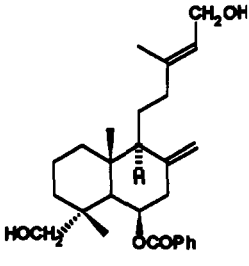

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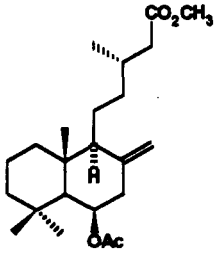

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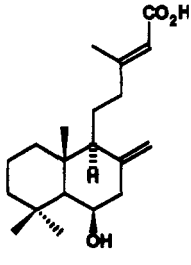


5

made it possible to probe the scope of a series of transformations planned to work out the B-ring substitution pattern.

In this paper we describe the synthesis of this compound, which can be considered as a general synthetic approach to the labdanes of this type and which might serve, with minor modifications, for the preparation of many other related labdanes of the usual 9,10-anti series.

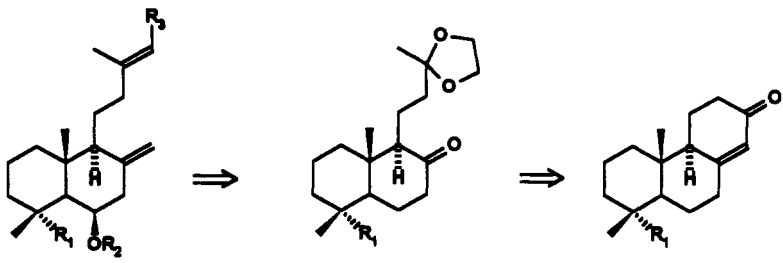
As Scheme 1 shows, retrosynthetic analysis of this class of compounds, via at least one pathway, should ultimately terminate in the structure of a suitably substituted decalone **6** which, in turn, could derive from a podocarpenone such as **7**. Podocarpenones of this type can be easily obtained in optically active form from natural sources (11,12). One advantage of this strategy is that many routes to compounds such as **7** have been already developed (13).

RESULTS AND DISCUSSION

On the basis of retrosynthetic analysis, the synthesis begins with the ring C opening of chiral podocarpenone **8** (12) (Scheme 2) by means of the known Eschenmoser fragmentation of the corresponding α,β-epoxyketone (14,15). Epoxidation of the enone **8** was achieved in high yield using alkaline H_2O_2 to give the α,β-epoxy ketone **9**, which fragmented smoothly when it was treated with *p*-toluenesulfonohydrazide in the presence of Si gel (16) to give the acetylenic ketone **10** (75–85% yield).

First we examined the preparation of the keto ketal **12** from **10** by means of the hydration of the triple bond and subsequent selective ketalization of the initially formed diketone **11**. Thus, mercury-catalyzed hydration of **10** gave the previously known (17) diketone **11** in nearly quantitatively yield, which upon treatment with 1 equiv of ethylene glycol and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in refluxing C_6H_6 afforded a mixture of products from which the required keto ketal **12** was isolated in only 75% yield after careful cc (17). The modest yield obtained for this simple transformation and the difficulties we encountered in the separation of the reaction mixture led us to search for a more efficient method for accomplishing this transformation. It was eventually found that conversion of the acetylenic ketone **10** to **12** could be carried out in a single step (93% yield) by treatment of **10** with ethylene glycol and catalytic amounts of mercuric oxide and camphorsulfonic acid (CSA) in THF at reflux. The only observed side product in this reaction was the diketone **11**.

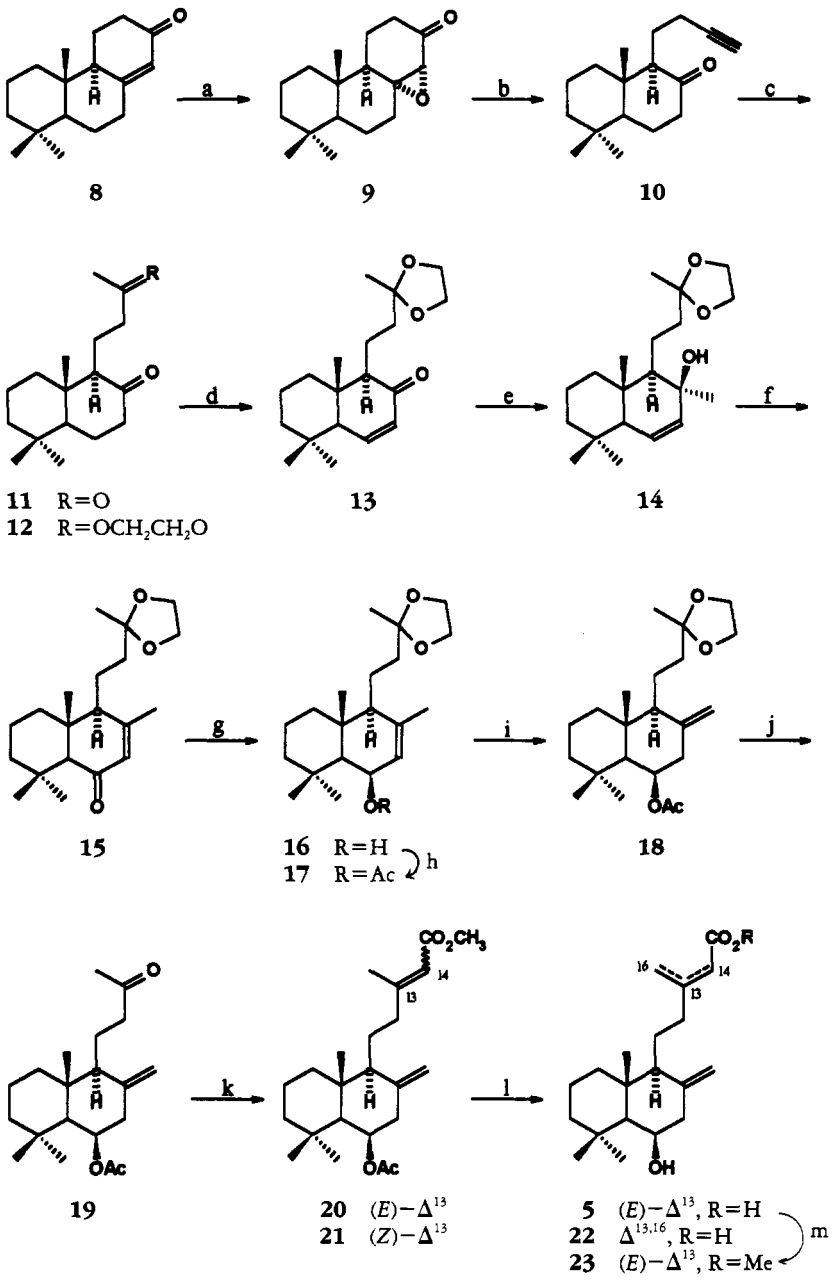
Next, we focused on the elaboration of the B-ring functionality of **12**. Towards this end, a 6(7)-double bond was introduced in **12** by employing standard selenium-based methodology. Thus, treatment of ketone **12** with potassium hexamethyldisilazide (18) (KHMDS) at −78° followed by selenylation with benezeneselenenyl bromide and



R_1=Me, CH_2OH, CO_2H
R_2=H, OAc
R_3=CH_2OH, CO_2H

6 7

SCHEME 1



SCHEME 2. Reagents: (a) H_2O_2, NaOH, MeOH; (b) $TsNHNH_2$, Si gel, CH_2Cl_2; (c) $HOCH_2CH_2OH$, HgO, CSA, THF; (d) i: KHMDS, THF then PhSeBr; ii: H_2O_2, CH_2Cl_2, pyridine; (e) MeLi, THF; (f) DMP.CrO_3, CH_2Cl_2; (g) DIBALH, THF; (h) Ac_2O, pyridine; (i) hν, xylene/iPrOH; (j) PPTS, aqueous Me_2CO; (k) $(EtO)_2P(O)=CHCO_2Me$, THF; (l) KOH, EtOH/toluene; (m) CH_2N_2, Et_2O.

subsequent oxidation with 30% H_2O_2 in aqueous CH_2Cl_2 containing pyridine at room temperature provided, after cc, the enone **13** in 80% yield. The use of KHMDS in the deprotonation step was essential to the realization of high yields, since incomplete consumption of **12** was observed when LDA was employed (unconsumed **12** was recovered in ca. 50% yield). The failure of the Li enolate of **12** to undergo complete

reaction with the electrophilic reagent (PhSeBr) may be due, at least in part, to the presence of the amine derived from the base used to generate the enolate (19).

Introduction of the oxygen at the sterically hindered C-6 position was based on the 1,3-oxidative rearrangement of an allylic tertiary alcohol. Therefore a methyl group at C-8 was introduced at this stage by reacting **13** with methyllithium in Et_2O. Only one isomeric alcohol was isolated from this reaction in 93% yield. The stereochemistry of the product was elucidated by intramolecular nOe studies. In particular, irradiation of the 8-Me signal at δ 1.21 ppm gave nOe enhancements for H-7, H-11, and H-12. This fact, together with the absence of nOe enhancement for the 10-Me, can be explained only by assuming an α disposition of the 8-Me, as indicated in structure **14**.

The 1,3-oxidative rearrangement of carbinol **14** was carried out with a 3,5-dimethylpyrazole complex of chromium trioxide, generated in situ (20), in CH_2Cl_2 at low temperature to give enone **15** in 83% yield. Oxidative rearrangement of **14** using other CrO_3 derivatives (21) gave worse results [e.g., reaction with PDC was extremely slow, giving only 50% conversion after 2–3 days at room temperature].

Stereoselective reduction of the ketone group in **15** was cleanly achieved with DIBALH in THF at −78°, affording the alcohol **16** in nearly quantitative yield. Only the desired 6β-OH stereoisomer was detected. The axial orientation of the C-6 hydroxyl group in **16** was assigned on the basis of the observed coupling constant between H-5 and H-6 ($J_{5\alpha,6\alpha}$=ca. 4 Hz).

The final stage to complete the elaboration of the B-ring functionality of the target molecule required isomerization of the 7(8) double bond to the thermodynamically less stable 8(17) exocyclic position. This isomerization was attempted photochemically. Unfortunately, irradiation of **16** with a medium-pressure mercury lamp in iPrOH containing xylene as a photosensitizer (22) at room temperature led only to a slow disappearance of starting material, with no detectable isomerization occurring. Since the preparation of the exocyclic olefin through the allylic alcohol **16** did not appear feasible, the photochemical isomerization of its acetate **17** was considered. Transformation of the alcohol **16** into acetate **17** was accomplished in good yield by treatment with Ac_2O in pyridine at 80°. We were delighted to find that irradiation of an iPrOH solution of the allylic acetate **17** and xylene proceeded slowly but efficiently to produce **18** in nearly quantitative yield. Interesting, the endo-exo double bond isomerization could also be carried out with the same effectiveness using the benzoylated derivative of **16** [prepared by treatment of **16** with benzoyl chloride and DMAP at room temperature for 3 days (90% yield)].

With the desired exocyclic olefin **18** in hand, we were ready to introduce the methoxycarbonylmethylene group at C-13. Deprotection of compound **18** with PPTS in aqueous Me_2CO at reflux, followed by Wadsworth-Emmons reaction (23) of the resulting methyl ketone **19**, obtained in 95% yield, with the methyl diethylphosphonoacetate anion in THF provided a ca. 5:1 mixture of (*E*)- and (*Z*)-α,β-unsaturated methyl esters **20** and **21** in excellent yield. Both isomers could be separated, at least partially (see Experimental section), by careful flash chromatography. The ^{13}C-nmr spectra of both isomers showed that the C-12 and C-16 resonances of the major isomer **20** occur at 7 ppm downfield and 6.8 ppm upfield, respectively, relative to the minor isomer **21**, indicating a cis-vicinal relationship of C-16 and C-12 of **20** and **21**, respectively, with the ester function (γ-effect).

The synthesis of the target compound was completed by alkaline hydrolysis of both the acetate and methyl ester moieties of **20**. As expected, the axially oriented acetate group at C-6 was much more resistant to hydrolysis than the unsaturated methyl ester moiety. The main problem in this transformation was the tendency of the 13(14) double

bond of **20** to isomerize, thus always yielding, under the different reaction conditions used, a mixture of the desired alcohol acid **5** and its unconjugated counterpart **22**. It was eventually found that formation of **22** could be reduced to a minimum by treating **20** with KOH in a 4:1 mixture of EtOH and toluene at reflux for 20 h. By this means the acid **5** was obtained in 85% yield, only contaminated by ca. 5% of **22**.

Since natural acid **5** is described in the literature through its methyl ester (2), the synthetic hydroxy acid **5** was transformed into its corresponding methyl ester **23** by treatment with CH_2N_2. The synthetic methyl ester **23** thus obtained had spectral characteristics identical with those previously reported for the natural compound; the only difference was in the sign of the optical rotation, which suggests that the natural and synthetic labdane **5** are antipodal.

The method described here for the synthesis of **5** should be useful for the preparation of other related natural products, using the appropriately substituted podocarpenone as the starting material. Efforts along these lines are underway.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points are uncorrected. Chromatography refers to flash chromatography and was performed on Merck Si gel 60 (230–400 mesh). ^{1}H- and ^{13}C-nmr spectra were recorded on Bruker AC-200 (200 MHz for ^{1}H and 50.32 MHz for ^{13}C), and on Varian XL-300 (300 MHz for ^{1}H and 75.43 MHz for ^{13}C) spectrometers as indicated. Multiplicities of ^{13}C-nmr signals were determined from DEPT spectra; ^{13}C signal assignments were aided by HMQC spectra. Ir spectra were recorded on a Perkin-Elmer 281 spectrometer. Optical rotations were recorded on a Schmidt Haensch polarimeter. Ms spectra were determined at 70 eV on a Perkin Elmer 5988A spectrometer. Elemental analysis was performed by Servicio de Semimicroanálisis del CSIC (Barcelona). Final purification of all products for microanalysis was done by preparative hplc on a μ-Porasil column. Reactions were run in oven-dried glassware under Ar or N_2. Commercially available chemicals were used as obtained without further purification, except for solvents, which were purified and dried before use by standard methods. Anhydrous Na_2SO_4 was used for drying organic solvent extracts. Removal of the solvent was performed with a rotary evaporator under high vacuum.

(+)-8α,14-Epoxypodocarpan-13-one [**9**].—To a solution of podocarpenone **8** (492 mg, 2 mmol) in MeOH (2.4 ml) were added 6 N NaOH (0.1 ml, 0.6 mmol) and 33% H_2O_2 (0.84 ml, 5.4 mmol) at 0°. After stirring for 3.5 h at room temperature, the mixture was diluted with H_2O and extracted with Et_2O. The combined extracts were washed with H_2O, dried, and concentrated to yield chromatographically pure epoxide **9** (559 mg, 96%), which could be used in the next step without further purification or chromatographed on Si gel, using hexane-EtOAc (8:2) as eluent, to afford crystalline **9** (524 g, 90%): mp 106–106.5° (pentane) [lit. (14) 102–103°]; $[\alpha]^{22}$D +55° (*c*=2, $CHCl_3$); ir ν max (KBr) 3020, 3000–2820, 1700, 1450, 1260, 800 cm^{-1}; ^{1}H nmr ($CDCl_3$, 200 MHz) δ 3.13 (1H, s, H-14), 0.89 (3H, s, H-18), 0.82 (3H, s, H-19), 0.79 (3H, s, H-20); ^{13}C nmr ($CDCl_3$, 50.32 MHz) δ 16.07 (C-20), 16.69 (C-11), 18.49 (C-2), 21.33 (C-6), 21.69 (C-19), 33.24 (C-4), 33.65 (C-7), 33.72 (C-18), 35.10 (C-12), 39.74 (C-10), 39.74 (C-1), 41.72 (C-3), 48.30 (C-9), 54.33 (C-5), 63.71 (C-14), 67.21 (C-8), 208.81 (C-13); ms *m/z* (rel. int.) $[M]^+$ 262 (14), 247 (26), 229 (5), 206 (11), 137 (75), 123 (74), 109 (37), 95 (57), 81 (66), 41 (100). *Anal.* calcd for $C_{17}H_{26}O_2$, C 77.82, H 9.99; found C 77.87, H 10.07.

(−)-15,16,17-Trinorlabd-13-yn-8-one [**10**].—To a suspension of Si gel 60 (70–230 mesh, previously activated at 320° overnight) (524 mg) in CH_2Cl_2 (6.9 ml) at 0°, epoxide **9** (500 mg, 1.9 mmol) in CH_2Cl_2 (2.5 ml) and *p*-toluenesulfonohydrazide (355 mg, 1.9 mmol) in CH_2Cl_2 (2.5 ml) were added. The mixture was stirred at 5° during 24 h and then allowed to warm to room temperature and stirred for 3–4 h. The reaction mixture was diluted with Et_2O and filtered off, and the filtrate was washed with saturated $NaHCO_3$ solution and brine. Drying, removal of the solvent, and chromatography, using hexane-EtOAc (98:2) as eluent, afforded the acetylenic compound **10** (386 μg, 82%), as a low melting point solid: mp 38–39° (pentane) [lit. (14) an oil]; $[\alpha]^{20}$D −26° (*c*=0.7, $CHCl_3$); ir ν max (KBr) 3300, 3000–2820, 1715, 1450, 1200 cm^{-1}; ^{1}H nmr ($CDCl_3$, 200 MHz) δ 0.94 (3H, s, H-18), 0.82 (3H, s, H-19), 0.69 (3H, s, H-20); ^{13}C nmr ($CDCl_3$, 50.32 MHz) δ 14.85 (C-20), 17.58 (C-12), 18.95 (C-2), 20.80 (C-11), 21.65 (C-19), 23.91 (C-6), 33.45 (C-18), 33.66 (C-4), 39.09 (C-1), 41.83 (C-3), 42.34 (C-10), 42.41 (C-7), 54.05 (C-5), 62.31 (C-9), 68.47 (C-14), 84.65 (C-13) 211.79 (C-8); ms *m/z* (rel. int.) $[M]^+$ 246 (3), $[M-Me]^+$ 231 (4), 218 (1), 179 (46), 137 (27), 109 (37), 95 (25), 83 (100), 79 (32), 55 (45). *Anal.* calcd for $C_{17}H_{26}O$, C 82.87, H 10.64; found C 82.86, H 10.88.

(−)-13,13-Ethylenedioxy-15,16,17-trinorlabd-8-one [**12**].—To a stirred mixture of **10** (370 mg, 1.5 mmol), HgO (16 mg, 0.075 mmol), and THF (5 ml) was added a solution of dry ethylene glycol (115.6 mg, 1.84 mmol) and CSA (11.4 mg, 0.045 mmol) in THF (3 ml). The mixture was stirred and heated under reflux (bath temperature 80°) for 1.5 h. The reaction mixture was cooled, diluted with hexane, and filtered. The filtrate was washed with H_2O and brine, dried, and concentrated to give crude crystalline product, which was purified by chromatography, using hexane-EtOAc (9:1) as eluent, to afford the ketone ketal **12** (430 mg, 93%) as an oil [lit. (17) also an oil]; $[\alpha]^{20}D$ −31.6° (c=6.7, $CHCl_3$); ir ν max (film) 3000–2800, 1705, 1450, 1380, 1060–1040 cm^{-1}; ^1H nmr ($CDCl_3$, 200 MHz) δ 3.90 (4H, m, OCH), 1.29 (3H, s, H-14), 0.93 (3H, s, H-18), 0.82 (3H, s, H-19), 0.69 (3H, s, H-20); ^{13}C nmr ($CDCl_3$, 50.32 MHz) δ 14.31 (C-20), 16.14 (C-11), 18.78 (C-2), 21.44 (C-19), 23.30 (C-14), 23.84 (C-6), 33.27 (C-18), 33.43 (C-4), 37.76 (C-12), 38.99 (C-1), 41.74 (C-3), 42.39 (C-7), 42.48 (C-10), 54.08 (C-5), 63.87 (C-9), 64.15 (OCH_2), 64.25 (OCH_2), 109.91 (C-13), 211.69 (C-8). *Anal.* calcd for $C_{19}H_{32}O_3$, C 73.98, H 10.46; found C 74.20, H 10.44.

Further elution with the same eluent gave diketone **11** (15.3 mg, 5%), whose physical and spectral properties agreed with literature values (17).

(−)-13,13-Ethylenedioxy-15,16,17-trinorlabd-6-en-8-one [**13**].—To a THF solution of KHMDS [prepared from hexamethyldisilazane (0.267 ml, 209 mg, 1.3 mmol), KH (55 mg, 1.35 mmol), and THF (12 ml)] (18) was added dropwise, over a period of 30 min at −78°, a solution of **12** (308 mg, 1 mmol) in THF (12 ml). The solution was stirred at −78° for 1 h and then warmed to −40°, where stirring was continued for an additional 5 min. After the solution was again cooled to −78°, PhSeBr (378 mg, 1.6 mmol) in THF (1 ml) was added, and the mixture was stirred for 20 min and then quenched by the addition of H_2O. The mixture was extracted with hexane. The combined extracts were washed successively with H_2O, cold 2% HCl, saturated $NaHCO_3$ solution, and brine, dried, and concentrated to give a crude product (528 mg), which was subsequently dissolved in CH_2Cl_2 (7 ml). This solution was chilled to 0° and mixed with pyridine (0.61 ml, 9 mmol), H_2O (0.61 ml), and 30% H_2O_2 (2.1 ml, 18 mmol). After 30 min the vigorously stirred mixture was allowed to warm to room temperature and was stirred for a further hour. The mixture was extracted with CH_2Cl_2. Workup as above afforded an oily residue which was purified by chromatography with hexane-EtOAc (85:15) as eluent to give the enone **13** (245 mg, 80%) as a colorless oil: $[\alpha]^{29}D$ −92° (c=5.6, C_6H_6); ir ν max (film) 3040, 3000–2800, 1675, 1450, 1380, 1060–1040 cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ 6.88 (1H, dd, J=10.3, 2.2 Hz, H-6), 6.02 (1H, dd, J=10.3, 3.4 Hz, H-7), 3.93 (4H, m, OCH), 2.22 (1H, dd, J=3.4, 2.2 Hz, H-5), 2.03 (1H, dd, J=8.1, 2.45 Hz, H-9), 1.34 (3H, s, H-14), 1.02 (3H, s, H-18), 0.89 (3H, s, H-19), 0.79 (3H, s, H-20); ^{13}C nmr ($CDCl_3$, 75.43 MHz) δ 13.63 (C-20), 16.96 (C-11), 18.46 (C-2), 22.29 (C-19), 23.58 (C-14), 32.47 (C-18), 32.79 (C-4), 37.66 (C-12), 38.84 (C-1), 40.96 (C-3), 44.38 (C-10), 56.75 (C-5) 63.26 (C-9), 64.43 (OCH_2), 64.51 (OCH_2), 110.19 (C-13), 130.21 (C-7), 148.70 (C-6), 201.49 (C-8); ms *m/z* (rel. int.) $[M]^+$ 306 (1), 291 (2), 205 (1), 115 (4), 99 (26), 87 (100), 55 (14), 49 (14), 43 (34). *Anal.* calcd for $C_{19}H_{30}O_3$, C 74.47, H 9.87; found C 74.55, H 9.69.

(−)-13,13-Ethylenedioxy-15,16-dinorlabd-6-en-8β-ol [**14**].—A solution of enone **13** (200 mg, 0.65 mmol) in THF (4.5 ml) was cooled to −78°, and ca. 0.45 ml of a 1.6 M solution of MeLi in Et_2O (ca. 0.72 mmol) was slowly added. The reaction mixture was allowed to warm to −15° (1 h) and the excess of MeLi was destroyed by careful addition of H_2O. The resulting mixture was diluted with H_2O and extracted with Et_2O. The combined organic layers were washed with brine, dried, and concentrated to give the crude product, which was chromatographed using hexane-EtOAc (8:2) as eluent to afford carbinol **14** (195 mg, 93%) as a foam: $[\alpha]^{20}D$ −11.3° (c=3.7, C_6H_6); ir ν max (film) 3500, 3020, 3000–2800, 1460, 1380, 1150, 1060–1040 cm^{-1}; ^1H nmr (C_6D_6, 300 MHz) δ 5.57 (1H, dd, J=10, 2.4 Hz, H-7), 5.55 (1H, dd, J=10, 1 Hz, H-6), 3.55 (4H, m, OCH), 2.07 (1H, dddd, J=17.1, 12.9, 4.9, 3.2 Hz, H-11), 1.88 (1H, ddd, J=13.4, 13.4, 4.8 Hz, H_a-12), 1.78 (1H, ddd, J=13.4, 13.4, 4.8 Hz, H_b-12), 1.68 (1H, m, H-1), 1.48 (1H, dd, J=2.4, 1 Hz, H-5), 1.35 (3H, s, H-14), 1.21 (3H, s, H-17), 0.98 (1H, dd, J=4.6, 3.2 Hz, H-9), 0.81 (6H, s, H-18 and H-20), 0.75 (3H, s, H-19); ^{13}C nmr (C_6D_6, 75.43 MHz) δ 14.38 (C-20), 18.52 (C-2), 18.52 (C-11), 21.96 (C-19), 24.05 (C-14), 30.07 (C-17), 32.69 (C-18), 32.86 (C-4), 37.15 (C-1), 38.19 (C-10), 41.58 (C-3), 43.37 (C-12), 55.31 (C-5), 58.39 (C-9), 64.71 (OCH_2), 64.71 (OCH_2), 70.55 (C-8), 110.29 (C-13), 126.68 (C-6), 135.37 (C-7); ms *m/z* (rel. int.) $[M]^+$ 322 (0.3), 307 (2), 235 (0.2), 217 (1), 189 (1), 164 (10), 87 (100), 59 (7), 55 (12), 49 (45), 43 (52).

(+)-13,13-Ethylenedioxy-15,16-dinorlabd-7-en-6-one [**15**].—A suspension of finely powdered CrO_3 (dried over P_2O_5 under vacuum overnight) (372 mg, 3.72 mmol) in CH_2Cl_2 (3 ml) was stirred at −40° for 15 min, and then a solution of 3,5-dimethylpyrazole (358 mg, 3.72 mmol) in CH_2Cl_2 (3 ml) was added in one portion. The brown black suspension obtained was stirred at this temperature for 15 min and then allowed to warm to −30° over ca. 1 h, after which a solution of **14** (150 mg, 0.46 mmol) in CH_2Cl_2 (4.6 ml) was slowly added. The mixture was kept with stirring for 4 h while the temperature was allowed to rise to −10°. NaOH solution (1.5 ml, 5 N) was then added and the mixture was stirred for 1 h at 0°. The resulting deep green reaction mixture was mixed with Celite and filtered through a glass wool plug. After washing

thoroughly with CH_2Cl_2, the filtrate was carefully washed with H_2O, cold 2% HCl, saturated $NaHCO_3$ solution, and brine. After drying, the solvent was evaporated and the crude product was purified by chromatography, using hexane-EtOAc (8:2) as eluent, to yield the enone **15** (124 mg, 83%) as a colorless oil:$[\alpha]^{20}D$ +22.2 (c=1.4, C_6H_6); ir ν max (film) 3020, 3000–2800, 1665, 1450, 1380, 1060–1040 cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ 5.74 (1H, br s, H-7), 3.93 (4H, m, OCH), 2.02 (1H, s, H-5), 2.01 (1H, m, H-9), 1.90 (3H, br s, H-17), 1.31 (3H, s, H-14), 1.13 (3H, s, H-18), 1.10 (3H, s, H-19), 0.82 (3H, s, H-20); ^{13}C nmr ($CDCl_3$, 75.43 MHz) δ 14.61 (C-20), 18.18 (C-2), 21.29 (C-11), 21.51 (C-17), 21.97 (C-19), 23.72 (C-14), 32.27 (C-4), 33.45 (C-18), 38.77 (C-1), 41.41 (C-3), 43.19 (C-12), 43.31 (C-10), 56.32 (C-9), 63.64 (C-5), 64.69 (OCH_2), 64.69 (OCH_2), 109.74 (C-13), 128.57 (C-7), 158.65 (C-8), 200.15 (C-6); ms m/z (rel. int.) $[M]^+$ 320 (6), 305 (2), 233 (0.3), 205 (0.4), 115 (7), 87 (100). *Anal.* calcd for $C_{20}H_{32}O_3$, C 74.96, H 10.06; found C 75.06, H 10.09.

(−)-13,13-Ethylenedioxy-15,16-dinorlabd-7-en-6β-ol [**16**].—To a solution of **15** (100 mg, 0.31 mmol) in THF (2 ml) at −78° was added DIBALH (1 M solution in hexane, 0.77 ml, 0.77 mmol) dropwise. After 30 min, the reaction was quenched by the dropwise addition of H_2O and warmed to 25°. The mixture was extracted with hexane/C_6H_6, and the combined organic phases were washed with H_2O and brine, dried, and concentrated to give a colorless oil of spectroscopically pure allylic alcohol **16** (98.6 mg, 98%), which was used in the next step without further purification. A small sample was purified by chromatography [hexane-EtOAc (8:2)] for analytical purposes: $[\alpha]^{20}D$ −36.7° (c=0.6, C_6H_6); ir ν max (film) 3480, 3020, 2980–2800, 1460, 1380, 1150, 1060–1040 cm^{-1}; ^1H nmr (C_6D_6, 200 MHz) δ 5.42 (1H, m, H-7), 4.28 (1H, m, H-6), 3.54 (4H, br s, OCH), 1.72 (3H, br s, H-17), 1.47 (3H, s, H-19), 1.32 (3H, s, H-14), 1.07 (3H, s, H-18), 1.05 (3H, s, H-20), 0.95 (1H, d, J=4.1, H-5); ^{13}C nmr (C_6D_6, 50.32 MHz) δ 16.33 (C-20), 19.45 (C-2), 22.02 (C-11), 22.17 (C-19), 23.99 (C-14), 25.00 (C-17), 32.92 (C-18), 34.39 (C-4), 37.05 (C-10), 41.60 (C-1), 42.19 (C-12), 45.07 (C-3), 54.57 (C-5), 55.82 (C-9), 64.69 (OCH_2), 64.69 (OCH_2), 65.94 (C-6), 110.17 (C-13), 126.35 (C-7), 137.64 (C-8); ms m/z (rel. int.) $[M]^+$ 322 (19), 304 (1), 235 (0.5), 205 (15), 189 (4), 177 (2), 115 (9), 87 (100), 84 (20), 69 (16), 56 (5), 49 (33), 43 (77).

(−)-6β-Acetyloxy-13,13-ethylenedioxy-15,16-dinorlabd-7-ene [**17**].—A solution of crude **16** (97.8 mg, 0.3 mmol) in anhydrous pyridine (1.5 ml) and Ac_2O (0.37 ml) was stirred at 70° overnight and then at 80° for 3–4 h. The reaction mixture was cooled and diluted with hexane. The resulting mixture was successively washed with H_2O, cold 2% HCl, saturated $NaHCO_3$ solution, and brine, and dried. Evaporation of the solvent followed by chromatography of the residue using hexane-EtOAc (8:2) as eluent afforded the allylic acetate **17** (86 mg, 75% from **15**); as an oil: $[\alpha]^{20}D$ −136.8° (c=5.4, C_6H_6); ir ν max (film) 3010–2800, 1730, 1245, 1050 cm^{-1}; ^1H nmr (C_6D_6, 300 MHz) δ 5.75 (1H, s, H-7), 5.75 (1H, s, H-6), 3.53 (4H, br s, OCH), 1.71 (3H, s, OAc), 1.67 (3H, br s, H-17), 1.31 (3H, s, H-14), 1.152 and 1.147 (each 3H, s, H-19 and H-20), 0.98 (3H, s, H-18); ^{13}C nmr (C_6D_6, 75.43 MHz) δ 15.80 (C-20), 19.25 (C-2), 21.35 (CH_3CO), 21.95 (C-11), 22.02 (C-19), 23.97 (C-14), 24.63 (C-17), 32.71 (C-18), 33.91 (C-4), 37.27 (C-10), 41.01 (C-1), 42.13 (C-12), 45.11 (C-3), 53.14 (C-5), 55.52 (C-9), 64.68 (OCH_2), 64.68 (OCH_2), 67.80 (C-6), 110.08 (C-13), 121.86 (C-7), 140.31 (C-8), 169.68 (CH_3CO); ms m/z (rel. int.) $[M]^+$ 364 (0.7), 305 (0.7), 277 (1), 248 (1), 109 (13), 87 (41), 84 (100), 59 (6), 51 (35), 49 (98), 44 (55).

(−)-6β-Acetyloxy-13,13-ethylenedioxy-15,16-dinorlabd-8(17)-ene [**18**].—A solution of allylic acetate **17** (50 mg, 0.137 mmol) and xylene (166 μl, commercial mixture of *o-*, *m-*, and *p*-isomers) in iPrOH (8.5 ml) contained in a quartz tube was irradiated at room temperature using a 125-W OSRAM medium-pressure mercury lamp and an H_2O-cooled quartz immersion well. An atmosphere of dry N_2 was maintained during the irradiation. After the reaction was completed (5–6 h), the reaction mixture was distilled, affording an oily residue which was chromatographed, using hexane-EtOAc (8:2) as eluent, to give the exocyclic olefin **18** (46.5 mg, 93%): $[\alpha]^{20}D$ −47.1° (c=3.4, C_6H_6); ir ν max (film) 3000–2800, 1730, 1240, 1050, 1020 cm^{-1}; ^1H nmr (C_6D_6, 200 MHz) δ 5.55 (1H, m, H-6), 4.91 (2H, br s, H-17), 3.57 (4H, br s, OCH), 2.57 (1H, dd, J=14, 3 Hz, H-7), 1.71 (3H, s, OAc), 1.34 (3H, s, H-14), 1.07 (3H, s, H-20), 0.99 (3H, s, H-19), 0.92 (3H, s, H-18); ^{13}C nmr (C_6D_6, 50.32 MHz) δ 16.64 (C-20), 18.36 (C-11), 19.78 (C-2), 21.25 (CH_3CO), 23.52 (C-19), 24.10 (C-14), 33.46 (C-18), 34.29 (C-4), 38.54 (C-12), 41.12 (C-10), 41.31 (C-1), 43.75 (C-7), 44.31 (C-3), 56.22 (C-5), 57.34 (C-9), 64.69 (OCH_2), 64.69 (OCH_2), 71.20 (C-6), 109.84 (C-7), 110.45 (C-13), 144.17 (C-8), 169.57 (MeCO). *Anal.* calcd for $C_{22}H_{36}O_4$, C 72.49, H 9.95; found C 72.54, H 9.87.

(−)-6β-Acetyloxy-15,16-dinorlabd-8(17)-en-13-one [**19**].—A mixture of ketal **18** (26 mg, 0.07 mmol), PPTS (18 mg, 0.07 mmol), H_2O (40 μl), and Me_2CO (1 ml) was stirred and heated under reflux for 6 h. Usual workup afforded an oil which was purified by chromatography, using hexane-EtOAc (9:1) as eluent, to give the methyl ketone **19** (21.7 mg, 95%): $[\alpha]^{20}D$ −46.7° (c=3.7, C_6H_6); ir ν max (film) 3080, 3000–2800, 1730, 1715, 1640, 1365, 1240, 1200, 1025, 885 cm^{-1}; ^1H nmr (C_6D_6, 300 MHz) δ 5.54 (1H, dd, J=5.8, 2.7 Hz, H-6), 4.80 (1H, br s, H_a-17), 4.56 (1H, br s, H_b-17), 2.53 (1H, dd, J=14, 2.8 Hz, H-7), 1.70 (3H, s, OAc), 1.67 (3H, br s, H-14), 1.03 (3H, s, H-20), 0.99 (3H, s, H-19), 0.91 (3H, s, H-18);

^{13}C nmr (C_6D_6, 75.43 MHz) δ 16.47 (C-20), 17.70 (C-11), 19.70 (C-2), 21.22 (*C*H_3CO), 23.50 (C-19), 29.50 (C-14), 33.43 (C-18), 34.26 (C-4), 41.15 (C-10), 41.15 (C-3), 42.17 (C-12), 43.64 (C-7), 44.21 (C-3), 56.13 (C-5), 56.52 (C-9), 71.11 (C-6), 109.40 (C-17), 144.03 (C-8), 169.47 (*C*H_3*C*O), 206.38 (C-13); ms *m/z* (rel. int.) $[M]^+$ 320 (0.2), 305 (0.2), 260 (5), 251 (0.2), 245 (3), 153 (23), 123 (15), 119 (12), 83 (19), 43 (100).

Methyl (E)-6β-*acetyloxylabda-8(17),13-dien-15-oate* [**20**].—Methyl diethylphosphonoacetate (48.4 mg, 0.26 mmol) was added to a suspension of oil-free NaH (10.9 mg, 0.25 mmol) in THF (0.5 ml) and allowed to react at room temperature until the hydrogen evolution ceased (ca. 1 h). A solution of the methyl ketone **19** (20.5 mg, 0.064 mmol) in THF (0.26 ml) was then added, and the mixture stirred at room temperature for 20 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with diluted HCl, saturated aqueous $NaHCO_3$, and brine, and dried. The crude product obtained after evaporation of the solvent was dissolved in CH_2Cl_2 and chromatographed, using hexane-Et_2O (9:1) as eluent, to give a 5:1 mixture (^{1}H nmr analysis) of the (*E*)- and (*Z*)-α,β-unsaturated esters **20** and **21** (21.23 mg, 85%). Careful chromatography of this mixture, using hexane-EtOAc (97:3) as eluent, gave a ca. 1:1 mixture of **20** and **21** (6.8 mg) and pure ester **20** (14.1 mg). Ester **20** (less mobile isomer): an oil; ir ν max (film) 3070, 3020–2800, 1730, 1715, 1640, 1395, 1240, 1215, 1145, 1050 cm^{-1}; ^{1}H nmr ($CDCl_3$, 300 MHz) δ 5.62 (1H, br s, H-14), 5.40 (1H, m H-6), 4.84 (1H, br s, H_a-17), 4.65 (1H, br s, H_b-17), 3.67 (3H, s, OMe), 2.45 (1H, dd, *J*=14, 3 Hz, H-7β), 2.14 (3H, br d, *J*=1 Hz, H-16), 1.99 (3H, s, OAc), 0.93, 0.96 and 0.97 (each 3H, s, H-18, H-19 and H-20); ^{13}C nmr ($CDCl_3$, 75.43 MHz) δ 16.39 (C-20), 18.51 (C-16), 19.38 (C-2), 21.50 (C-11), 21.67 (*C*H_3CO), 23.28 (C-19), 33.41 (C-18), 34.20 (C-4), 39.53 (C-12), 40.89 (C-10), 41.23 (C-1), 43.33 (C-7), 44.06 (C-3), 50.46 (OMe), 56.28 and 56.42 (C-5 and C-9), 71.35 (C-6), 109.17 (C-17), 115.08 (C-14), 143.33 (C-8), 160.77 (C-13),167.25 (C-15), 170.43 (MeCO); ms *m/z* (rel. int.) $[M]^+$ 376 (0.1), 317 (0.6), 301 (0.6), 269 (2), 249 (0.2), 113 (2), 119 (11), 43 (100).

Ester **21** could not be obtained analytically pure. However, subtraction of the signals for the *E* isomer **20** from the spectrum of the mixture of **20** and **21** allowed the major signals of the minor *Z* isomer **21** to be identified: ^{1}H nmr ($CDCl_3$ 300 MHz) δ 5.62 (1H, br s, H-14), 5.40 (1H, m, H-6), 4.84 (1H, br s, H_a-17), 4.82 (1H, br s, H_b-17), 3.64 (3H, s, OMe), 2.55 (2H, m, H-12), 2.45 (1H, dd, *J*=14, 3 Hz H-7β), 1.99 (3H, s, OAc), 1.87 (3H, s, H-16), 0.93, 0.96 and 0.97 (each 3H, s, H-18, H-19 and H-20); ^{13}C nmr ($CDCl_3$, 75.43 MHz) δ 16.39 (C-20), 19.38 (C-2), 21.54 (C-11), 21.67 (*C*H_3CO), 23.28 (C-19), 25.32 (C-16), 32.51 (C-12), 33.41 (C-18), 34.20 (C-4), 40.97 (C-10), 41.11 (C-1), 43.38 (C-7), 44.10 (C-3), 50.46 (OMe), 56.31 and 56.50 (C-5 and C-9), 71.46 (C-6), 108.86 (C-17), 115.48 (C-14), 143.44 (C-8), 160.39 (C-13), 166.88 (C-15), 170.43 (Me*C*O).

(E)-6β-*Hydroxylabda-8(17),13-dien-15-oic acid* [**5**] *and its methyl ester* [**23**].—A mixture of 0.4 ml of 15% ethanolic KOH, 0.1 ml of toluene, and 9 mg (0.024 mmol) of ester **20** was heated under Ar in a sealed tube for 20 h at 78°. The mixture was successively treated with H_2O and cold 5% HCl and extracted with C_6H_6. The combined organic extracts were washed with H_2O and brine and dried. Removal of solvent gave a residue which was filtered through Celite using CH_2Cl_2 to afford an amorphous solid (7 mg, 85%), which ^{1}H-nmr analysis showed to be a mixture of ca. 95% of **5** and 5% of **22** [identified by the signals observed at δ 3.1 ppm (br s, H-14), 4.93 and 4.97 (each s, both H-16)]: ^{1}H nmr ($CDCl^3$, 300 MHz) δ 5.65 (1H, br s, H-14), 5.02 (1H, m, H_a-17), 4.76 (1H, br s, H_b-17), 4.35 (1H, m, H-6), 2.15 (3H, d, *J*≈1.2 Hz, H-16), 1.18 (3H, s, H-19), 0.98 and 0.97 (each 3H, s, H-18 and H-20); ^{13}C nmr ($CDCl_3$, 75.43 MHz) δ 17.13 (C-20), 19.14 (C-16), 19.49 (C-2), 21.48 (C-19), 23.59 (C-11), 33.63 (C-18), 34.43 (C-4), 39.70 (C-12), 40.90 (C-10), 41.95 (C-1), 43.85 (C-3), 47.62 (C-7), 56.65 and 57.39 (C-5 and C-9), 69.34 (C-6), 110.34 (C-17), 114.79 (C-14), 143.85 (C-8), 163.68 (C-13), 171.18 (C-15).

Treatment of the above product with an ethereal solution of CH_2N_2 followed by chromatography [hexane-ether (8:2) as eluent] afforded (+)-methyl (*E*)-6β-hydroxylabda-8(17),13-dien-15-oate [**23**] as a white solid (5.8 mg, 74% from **20**): mp 82–84° (pentane); $[\alpha]^{20}$D +18° (*c*=0.66, $CHCl_3$) [lit. (2) −11°]; ir ν max (film) 3550, 1718, 1641 cm^{-1}; ^{1}H nmr ($CDCl_3$, 300 MHz) δ 5.63 (1H, br s, H-14), 5.00 (1H, m, H_a-17), 4.75 (1H, br s, H_b-17), 4.34 (1H, m, H-6), 3.67 (3H, s, OMe), 2.14 (3H, d, *J*=1.5 Hz, H-16), 1.18 (3H, s, H-19), 0.98 and 0.97 (each 3H, s, H-18 and H-20); ^{13}C nmr ($CDCl_3$, 75.43 MHz) δ 17.14 (C-20), 18.83 (C-16), 19.51 (C-2), 21.50 (C-19), 23.59 (C-11), 33.64 (C-18), 34.44 (C-4), 39.44 (C-12), 40.90 (C-10), 41.94 (C-1), 43.86 (C-3), 47.64 (C-7), 50.81 (OMe), 56.64 and 57.39 (C-5 and C-9), 69.34 (C-6), 110.31 (C-17), 115.10 (C-14), 143.90 (C-8), 160.76 (C-13), 167.25 (C-15); ms *m/z* (rel. int.) $[M]^+$ 334 (0.4), 319 (0.6), 317 (0.4), 301 (2), 221 (0.4), 41 (100).

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