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SYNTHESIS OF *ent*-CROTONADIOL AND COMPOUNDS RELATED TO IT FROM (+)-LARIXOL

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*A new synthesis of 13*E-ent-*crotonadiol and its 13*Z*-isomer from 6α-acetoxy-14,15-bis-norlabd-8(17)-en-13-one is described. A mixture of methyl esters of 13*E*- and 13*Z*-6α-acetoxylabd-8(17),13-dien-15-oic and 13*E*- and 13*Z*-6α-hydroxylabd-8(17),13-dien-15-oic acids was formed by its reaction with trimethylphosphonoacetate. Mixtures of 13*E*- and 13*Z*-6α-hydroxylabd-8(17),13-dien-15-oic acids were formed by hydrolysis of this mixture. These were separated, methylated, and reduced by $LiAlH_4$ to give the pure 13*E*- and 13*Z*-crotonadiols in 64 and 16% yields, respectively. The two known syntheses of crotonadiol from (+)-larixol were reproduced. It was shown that they produced only 13*E*-crotonadiol.*

Keywords: crotonadiols, synthesis, larixol, 6α-acetoxy-14,15-*bis*-norlabd-8(17)-en-13-one, methyl esters of 13*E*- and 13*Z*-6α-hydroxy- and 6α-acetoxylabd-8(17),13-dien-15-oic acids.

The labdane diterpenoid labd-8(17),13*E*-dien-6α,15-diol (**1**) {$[\alpha]_D^{25}$ –28.0° ($CHCl_3$)} was isolated from bark of the medicinal bush *Croton zambesicus* Muell. Arg. growing in central and western Africa. The researchers reported [1] the isolation of a "new labdane diterpenoid" and gave it the common name crotonadiol. *C. zambesicus* is used by the local population to treat dysentery, fever, and malaria. Its extracts also exhibit laxative, antimicrobial, and anticonvulsive activity [2].

The structure, relative configuration, and *trans*-configuration of the C-13 double bond in **1** were established [1] on the basis of spectral data. The absolute configuration of diol **1** was not found.

Later Chinese chemists [3] isolated from bark of the larch *Larix olgensis* Henry var. *koreana* Nakai a compound corresponding to the structure of **1** with mp 154°C and $[\alpha]_D$ +32.57° (MeOH). They also considered this compound to be "new" and proved its structure and relative stereochemistry on the basis of spectral data and an x-ray crystal structure. The absolute configuration of diol **1** in this instance also remained unclear. However, it turned out that a compound with the structure of **1** was described rather long ago [4]. It was synthesized from the natural compound larixol monoacetate (**2**). An allylic rearrangement occurred upon its reaction with PCl_3 to form unstable primary chloride **3**, which was used without purification in a reaction with KOAc to produce isolarixol diacetate (**4**) (Scheme 1). This compound was saponified by KOH in MeOH. The product was chromatographed over a column of SiO_2 to afford crystalline diol **1** in 35% yield, mp 139–140°C. The configuration of the C-13 double bond in the obtained compound and the possible formation of the *cis*-isomer **5** of **1** were not discussed [4]. Compound **1** (mp 146–147°C) was also produced in low yield via oxidation of larixol acetate (**2**) by oxygen in the presence of heteropolyacids [5]. Both syntheses of diol **1** from larixol acetate (**2**) confirmed that it, like larixol (**6**), belonged to the steric type of labdane diterpenoids. Thus, the absolute configuration of **1** was established.

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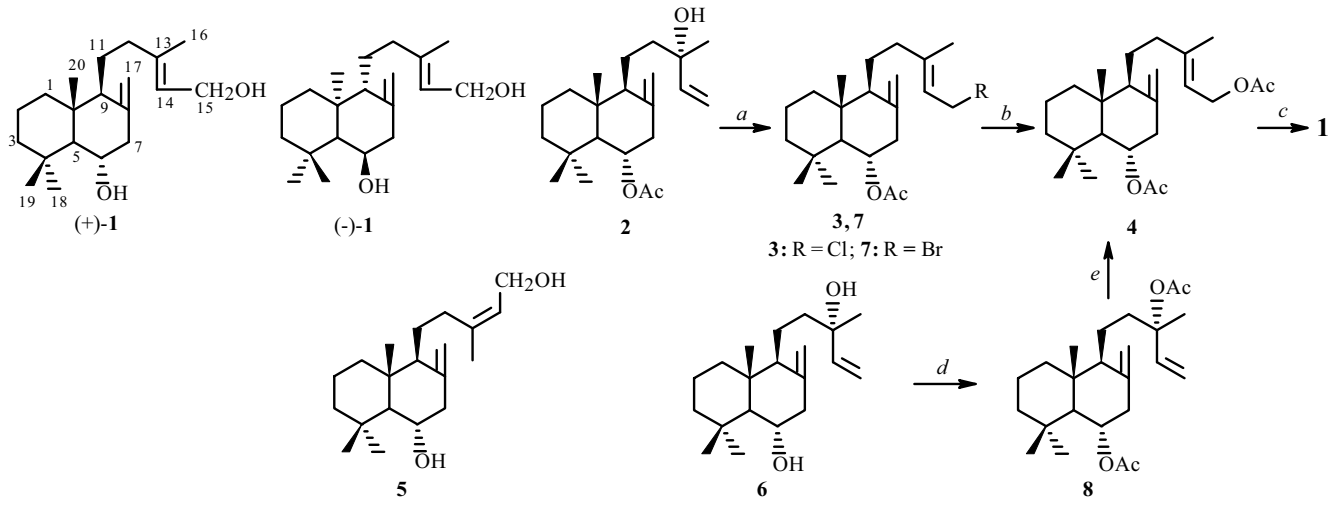


a. PCl_3 or PBr_3, Et_2O, r.t., 12 h; *b*. KOAc, DMF, r.t., 12 h, 39%; *c*. KOH, EtOH, reflux, 2 h, 98%; *d*. AcCl, DMA, 5°C, 12 h, 93%; *e*. $PdCl_2 \cdot (CH_3CN)_2$, THF, Ar, r.t., 12 h, 86%

Scheme 1

It became necessary for us to prepare crotonadiol **1** and its isomer **5** with the *cis*-configuration at C-13 during synthetic studies of labdane diterpenoids. Because the extract of *C. zambesicus* contains a small amount of crotonadiol (+)-**1**, its isolation was problematical. Therefore, we decided to synthesize (+)-**1** and **5** from the available labdane diterpenoid larixol **(6)**.

The reaction of tertiary allyl alcohols with PBr_3 and subsequent substitution of the Br atom in allyl bromides by an acetoxy group is known to form a mixture of the *trans*- and *cis*-isomers of primary allyl acetates with the *trans*-isomers predominating [6].

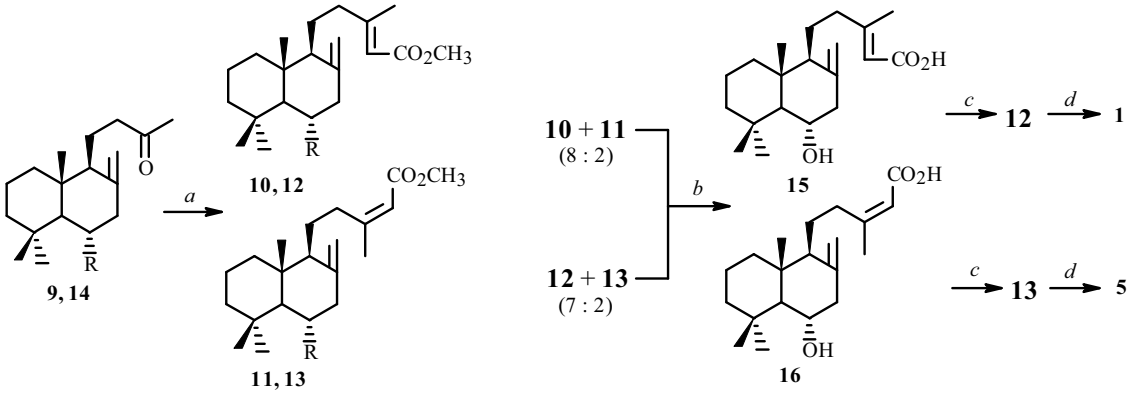
Considering these results, we studied the reaction of larixol monoacetate **(2)** with PBr_3. Product **7** turned out to be unstable. It decomposed during chromatography over a column of SiO_2. Therefore, it was used in the next reaction step with KOAc without purification. Chromatography of the product over a column of SiO_2 isolated isolarixol diacetate **(4)** in 39% yield (Scheme 1). Its structure and stereochemistry were proved on the basis of spectral data and the production of crotonadiol [(+)-**1**] upon saponification by KOH in MeOH.

The PMR spectrum of **4** contained resonances for the C(16) methyl at 1.71 ppm; olefinic proton C(14)-H, 5.32; hydroxymethylene C(15)-H_2, 4.60; and acetate, 2.06. The presence of an $AcOCH_2CH{=}C(CH_3)\text{-}CH_2$ fragment with the *E*-configuration of the double bond was also confirmed by ^{13}C NMR spectra (δ 21.9, 170.1, 61.4, 118.3, 142.6, and 22.4 ppm).

Resonances of C atoms in ^{13}C NMR spectra were assigned based on HSQC-correlation experiments. The relative configuration of **1** was derived on the basis of NOESY correlations between the following atoms: Me(19)↔H-C(6) ↔Me(20); H-C(6) ↔H_β-C(7) ↔H_α-C(17); H-C(9) ↔H-C(5) ↔H_a-C(17); and H_a-C(11) ↔H_b-C(17) ↔H_b-C(12).

The physicochemical and spectral data for crotonadiol [(+)-**1**] agreed with the literature [3, 4]. The 13*Z*-isomer **5** of (+)-**1** was not produced. Therefore, we studied the reaction of larixol diacetate **(8)** with the palladium chloride complex of acetonitrile $PdCl_2 \cdot (CH_3CN)_2$. The reaction with it of tertiary allyl alcohol acetates is known to isomerize them into primary allyl alcohol acetates [7, 8]. Larixol diacetate **(8)** was produced via acetylation of larixol **(6)** by acetylchloride in dimethylaniline (DMA) [9]. The reaction of **8** with $PdCl_2 \cdot (CH_3CN)_2$ formed in high yield (86%) isolarixol diacetate **(4)**. Its *cis*-isomer **5** in this instance also was not produced. Therefore, the Wittig–Horner reaction of 6α-acetoxy-14,15-*bis*-norlabd-8(17)-en-13-one **(9)** with trimethylphosphonoacetate (Scheme 2) was studied next. Acetoxyketone **9** was prepared via oxidation of larixol acetate **(2)** by CrO_3 in acetic acid [10] and by $KMnO_4$ in CH_2Cl_2 in the presence of a phase-transfer catalyst [11, 12].

The Wittig–Horner reaction of **9** gave according to TLC a mixture of two products in ~1:3 ratio. These were separated by chromatography over a column of SiO_2. Although each of these two fractions gave a single spot on TLC under various conditions, NMR spectroscopy indicated that each of these fractions was heterogeneous and contained a mixture of two stereoisomeric compounds. The less polar fraction consisted according to the spectral data of a mixture of 13*E*- and 13*Z*-acetoxyesters **10** and **11** in an 8:2 ratio. The more polar fraction was a mixture of stereoisomeric 13*E*- and 13*Z*-hydroxyesters **12** and **13** in a 7:2 ratio. The formation of **12** and **13** indicated that **9** was partially saponified under the Wittig–Horner reaction conditions, giving hydroxyketone **14**, which then reacted with phosphonoacetate to give a mixture of **12** and **13**.



9, 10, 11: R = OAc; **12, 13, 14:** R = OH

a. $NaOCH_3$, $(CH_3O)_2P(O)CH_2CO_2CH_3$, C_6H_6, reflux, 2 h, 23% **10**/**11** and 76% **12**/**13**; *b*. KOH, EtOH, reflux, 1 h, 77% and 79% **15**, 19% and 22 **16**; *c*. $TMSCHN_2$ (2M), THF, MeOH, r.t., 0.5 h, 97% **12** and 98% **13**; *d*. $LiAlH_4$, Et_2O, Ar, 0°C, 3 h, 86% (+)-**1** and 80% **5**

Scheme 2

High-resolution mass spectra of acetoxyesters **10** and **11** did not show peaks for the molecular ions. They did have strong peaks with *m*/*z* 316 $[M - 60]^+$ that were formed upon cleavage from them of acetic acid. Such fragmentation provided evidence of an acetoxy group in **10** and **11** and confirmed their structures. The PMR spectrum of the predominant isomer **10** contained resonances of methyl Me(16) at 2.13 ppm; methoxyl, 3.67; H-C(6), 5.01, and H-C(14), 5.62. The ^{13}C NMR spectrum of **10** showed resonances for C atoms of a triply substituted double bond at 160.7 ppm [C(13)] and 115.2 [C(14)]; a carboxyl, 167.3 [C(15)]; and methyl, 18.9 [C(16)]. These chemical shifts indicated that the C(13) double bond had the *trans*-configuration. These data together confirmed the structure of **10**. The PMR spectrum of the minor isomer **11** exhibited a resonance for the C(16) methyl at 1.87 ppm. It appeared at 25.3 ppm in the ^{13}C NMR spectrum, indicating that the C-13 double bond had the *Z*-configuration.

IR spectra of **12** and **13** contained bands characteristic of hydroxyl at 3519, 3430, 1154, and 1160 cm^{-1} and of ester at 1735, 1265, and 1240. The molecular formula $C_{21}H_{34}O_3$ for **12** and **13** was established on the basis of high-resolution mass spectral data, according to which molecular ions with *m*/*z* 334.2507 and 334.2502 appeared in mass spectra of **12** and **13**. PMR and ^{13}C NMR spectra of **12** and **13** were similar to those of **10** and **11** and confirmed their structures.

Because the mixtures of esters **10**/**11** and **12**/**13** could not be separated, they were saponified separately by alcoholic base (Scheme 2). Mixtures of the same stereoisomeric hydroxyacids **15** and **16** were produced in both instances. These were separated by chromatography over columns of SiO_2.

IR spectra of **15** and **16** contained absorption bands characteristic of hydroxyls at 3452, 3406, 1163, and 1066 cm^{-1}; carbonyl, 1712 and 1694; and exomethylene, 1644, 1648, 893, and 897. The molecular formula $C_{20}H_{32}O_3$ for hydroxyacids 13*E*-**15** and 13*Z*-**16** were established by high-resolution mass spectral data. Peaks for molecular ions $[M]^+$ appeared at *m*/*z* 320.2349 and 320.2356. PMR and ^{13}C NMR spectra of **15** and **16** confirmed their structures.

Separate methylation of hydroxyacids 13*E*-**15** and 13*Z*-**16** by trimethylsilyldiazomethane ($TMSCHN_2$) produced in almost quantitative yield the pure hydroxyesters 13*E*-**12** and 13*Z*-**13**. Reduction of them by $LiAlH_4$ produced in high yield crotonadiols (+)-**1** and **5**, respectively (Scheme 2). Their structures were confirmed by spectral data.

The literature contains contradictory information about crotonadiol (**1**). It has been described as a liquid with $[\alpha]_D$ –28° ($CHCl_3$) [1] and as a crystalline compound with mp 154°C and $[\alpha]_D$ +32.57° (MeOH) [3]. Haeuser [4], in discussing his results, noted that larixol acetate **(2)** isomerized with PBr_3 but used PCl_3 in the Experimental part [4]. This same researcher gave the following properties for (+)-**1**: mp 139–140°C and $[\alpha]_D$ +36.3° (EtOH). Others [5] also described (+)-**1** as a crystalline compound with mp 146–147°C.

Keeping in mind the physicochemical and spectral properties of (+)-**1** and (–)-**1**, it can be concluded that the crotonadiol obtained in one instance [1] was an *ent*-labdane series diterpenoid and its structure and absolute configuration were given by (–)-**1**. It is difficult to explain why (–)-**1** is a liquid whereas its isomer has such a high melting point. The physicochemical properties of isomers, with the exception of the specific rotation, are known to coincide. Thus, the analysis of the physicochemical and spectral data for crotonadiol (+)-**1** and its isomer **5** indicated that both these compounds were normal labdane diterpenoids.

EXPERIMENTAL

Melting points were determined in a capillary on a Buchi B-540 instrument. Specific rotation was recorded in $CHCl_3$ on a JASCO DIP-181 polarimeter. IR spectra were recorded on a PYE UNICAM SP3-200S spectrophotometer; PMR and ^{13}C NMR spectra, on Bruker AM 400 and Bruker Avance DRX 400 spectrometers (both 400.13 and 100.61 MHz) from 2–3% solutions in $CDCl_3$ with TMS internal standard. High-resolution mass spectra were measured in a KRATOS MS spectrometer. Reaction mixtures were worked up by extracting with Et_2O, washing the extract with H_2O until neutral, drying over Na_2SO_4, filtering, and vacuum distilling solvent. TLC used Silica gel 60 F_{254} (Merck) or RP-18 F_{254} (Merck) plates with detection by $Ce(SO_4)_2$ solution in aqueous H_2SO_4 (2 N) with subsequent heating at 80°C for 5 min. Column chromatography used silica gel grade 70–230 μm (Merck).

13*E*-6α-Acetoxy-15-bromolabda-8(17),13-diene (7). A solution of larixol acetate (**2**, 200 mg, 0.58 mmol) in a mixture of anhydrous Et_2O (2 mL) and Py (0.06 mL) was cooled in an ice bath, treated with a solution of PBr_3 (0.06 mL, 0.58 mmol) in Et_2O (0.23 mL), and stirred at –6°C for 1 h and overnight at room temperature. The usual work up gave unstable bromide **7** (248 mg) that was used without further purification in further reactions.

13*E*-6α,15-Diacetoxylabda-8(17),13-diene (4). A solution of bromide **7** (200 mg, 0.49 mmol) in DMF (3 mL) was treated with KOAc (96 mg, 0.98 mmol) and stirred overnight. The usual work up gave a product (210 mg) that was chromatographed over a column of SiO_2 (21 g) with elution by hexane:EtOAc (4:1). Yield 74 mg (39%) of liquid diacetate **4**. IR spectrum (CCl_4, ν, cm^{-1}): 3083, 2928, 1737, 1647, 1443, 1366, 1239, 1023, 969, 894.

PMR spectrum (δ, ppm, J/Hz): 0.76 (3H, s, CH_3-20), 0.89 (3H, s, CH_3-19), 1.03 (3H, s, CH_3-18), 1.71 (3H, s, CH_3-16), 1.00-2.22 (12H, m), 2.04 (1H, m, H_α-7), 2.06 (3H, s, MeO), 2.07 (3H, s, MeO), 2.70 (1H, dd, J = 4.0, 12.0, H_β-7), 4.60 (2H, d, J = 7.2, H_2-15), 4.64 (1H, d, J = 0.8, H_b-17), 4.95 (1H, d, J = 0.8, H_a-17), 5.05 (1H, td, J = 5.2, 11.2, H-6), 5.32 (1H, td, J = 1.2, 7.2, H-14).

^{13}C NMR spectrum (δ, ppm): 16.1 (C-20), 16.5 (C-16), 19.0 (C-2), 21.0 ($CO\underline{C}H_3$), 21.8 (C-11), 21.9 ($CO\underline{C}H_3$), 22.4 (C-19), 33.5 (C-4), 36.1 (C-18), 38.3 (C-12), 39.2 (C-1), 39.6 (C-10), 43.5 (C-3), 44.2 (C-7), 55.3 (C-9), 57.6 (C-5), 61.4 (C-15), 73.3 (C-6), 109.3 (C-17), 118.3 (C-14), 142.6 (C-13), 144.2 (C-8), 170.1 ($\underline{C}OCH_3$), 171.1 ($\underline{C}OCH_3$).

13*E*-Labda-8(17),13-dien-6α,15-diol; [(+)-1] (crotonadiol). A solution of allyl diacetate **4** (50 mg, 0.13 mmol) in EtOH (2 mL) was treated with a solution of KOH (36 mg, 0.65 mmol) in EtOH (1 mL) and refluxed for 2 h. The usual work up and vacuum distillation of solvent gave a solid (62 mg) that was chromatographed over a column of SiO_2 (6 g) with elution by hexane:EtOAc (7:3) to afford crystalline crotonadiol (38.0 mg, 98%), mp 145–146°C (EtOH), $[\alpha]_D^{16}$ +25.2° (*c* 0.01). IR spectrum (film, ν, cm^{-1}): 3465, 2953, 1645, 1466, 1387, 1210, 1016, 942, 895, 859.

PMR spectrum (δ, ppm, J/Hz): 0.68 (3H, s, CH_3-20), 0.99 (3H, s, CH_3-19), 1.09 (1H, d, J = 10.7, H-5), 1.15 (3H, s, CH_3-18), 1.59 (1H, br.d, J = 10.0, H-9), 1.65 (3H, br.s, CH_3-16), 1.82 (1H, br.ddd, J = 6.5, 10.0, 14.0, H_a-12), 2.02 [1H, br.dd, J = 12.2, 10.7, H_α-C(7)], 2.15 [br.ddd, J = 14.0, 10.0, 4.0, H_b-12], 1.00–1.63 (8H, m), 2.66 (dd, J = 4.9, 12.2, H_β-7), 3.81 (1H, ddd, J = 4.9, 10.7, 10.7, H-6), 4.14 (2H, d, J = 6.9, H_2-15), 4.57 (1H, dd, J = 1.4, H_b-17), 4.88 (1H, dd, J = 1.4, H_a-17), 5.37 (1H, tdq, J = 1.3, 1.3, 6.9, H-14).

^{13}C NMR spectrum (δ, ppm): 16.1 (C-20), 16.4 (C-16), 19.2 (C-2), 22.1 (C-11), 22.4 (C-19), 33.9 (C-4), 36.6 (C-18), 38.4 (C-12), 39.3 (C-1), 39.4 (C-10), 43.7 (C-3), 49.1 (C-7), 55.5 (C-9), 59.4 (C-15), 60.5 (C-5), 71.7 (C-6), 108.2 (C-17), 123.2 (C-14), 140.3 (C-13), 145.5 (C-8).

Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 306.2558 ± 0.0022, $[M]^+$, $C_{20}H_{34}O_2$; calcd 306.2559.

6α,13-Diacetoxylabda-8(17),14-diene (8). A cooled (5°C) solution of **6** (250 mg, 0.82 mmol) in DMA (8 mL) was treated dropwise with AcCl (3.22 g, 2.92 mL, 49 mmol) over 50 min at the same temperature. The mixture was stirred overnight at room temperature. The usual work up gave a solid (315 mg) that was purified by chromatography over a column of SiO_2 (31 g) with elution by hexane:EtOAc (4:1) to afford crystalline **8** (296 mg, 93%) [11, 13], mp 116–117°C (EtOH) (lit. mp 115–116.5°C [11], 114–116.5°C [13]). IR spectrum (CCl_4, ν, cm^{-1}): 3091, 2938, 1726, 1644, 1443, 1365, 1240, 1117, 1021, 969, 914, 865.

PMR spectrum (δ, ppm, J/Hz): 0.75 (3H, s, CH_3-20), 0.89 (3H, s, CH_3-19), 1.03 (3H, s, CH_3-18), 1.54 (3H, s, CH_3-16), 1.06–1.75 (12H, m), 2.02 (1H, m, H_α-7), 2.03 (3H, s, $COCH_3$), 2.05 (3H, s, $COCH_3$), 2.70 (1H, dd, J = 6.0, 12.0, H_β-7), 4.64 (1H, s, H_b-17), 4.94 (1H, s, H_a-17), 5.04 (1H, td, J = 5.2, 11.0, H-6), 5.13 (1H, d, J = 11.0, H-C15), 5.14 (1H, d, J = 17.4, H-15), 5.97 (1H, dd, J = 11.0, 17.4, H-14).

^{13}C NMR spectrum (δ, ppm): 16.0 (C-20), 17.7 (C-2), 19.1 (C-11), 21.9 (CO<u>C</u>H$_3$), 22.2 (CO<u>C</u>H$_3$), 22.4 (C-19), 23.6 (C-16), 33.5 (C-4), 36.2 (C-18), 39.0 (C-1), 39.2 (C-12), 39.8 (C-10), 43.5 (C-3), 44.2 (C-7), 56.3 (C-9), 57.6 (C-5), 73.2 (C-6), 83.3 (C-13), 109.4 (C-17), 113.2 (C-15), 14.18 (C-14), 144.3 (C-8), 169.9 (<u>C</u>OCH$_3$), 170.1 (<u>C</u>OCH$_3$).

13*E*-6α,15-Diacetoxylabda-8(17),13-dene (4). A solution of **8** (250 mg, 0.64 mmol) in anhydrous THF (7 mL) under Ar was treated with $PdCl_2(CH_3CN)_2$ (6.3 mg, 0.024 mmol), The mixture was stirred overnight at room temperature. The usual work up gave a solid (287 mg) that was chromatographed over a column of SiO_2 (28 g) with elution by hexane:EtOAc (4:1) to afford **4** (215 mg, 86%). The PMR and ^{13}C NMR spectra of this compound were identical with those reported earlier.

13*E*-Labda-8(17),13-dien-6α,15-diol [(+)-1] (crotonadiol). A solution of **4** (200 mg, 0.51 mmol) in EtOH (6 mL) was treated with a solution of KOH (143 mg, 2.55 mmol) in EtOH (4 mL) and refluxed for 2 h. The usual work up gave a solid (168 mg) that was chromatographed over a column of SiO_2 (10 g) with elution by hexane:EtOAc (7:3) to afford crystalline crotonadiol (151.0 mg, 96%), mp 145-146°C (EtOH), $[\alpha]_D^{16}$ +23.4° (*c* 0.007). The PMR and ^{13}C NMR spectra of this compound agreed with those obtained by us earlier.

Methyl Esters of 13*E*- and 13*Z*-6α-Acetoxylabda-8(17),13-dien-15-oic Acids 10 and 11 and 13*E*- and 13*Z*-6α-Hydroxylabda-8(17),13-dien-15-oic Acids 12 and 13. A solution of sodium methoxide that was produced by the reaction of metallic Na (8.6 mg, 0.358 g·atom) with MeOH (2.2 mL) was added dropwise to a refluxing solution of trimethylphosphonoacetate (680.0 mg, 3.74 mmol) and acetoxyketone **9** (400.0 mg, 1.25 mmol) in anhydrous benzene (29.0 mL). The resulting mixture was refluxed for 2 h. The usual work up gave a solid (469 mg) that was chromatographed over a column of SiO_2 (45 g) with elution by hexane:EtOAc (95:5) to afford a mixture of liquid acetoxyesters **10** and **11** (108.0 mg, 23%, *E–Z* ratio 8:2). IR spectrum (CCl_4, ν, cm^{-1}): 3106, 3079, 2979, 2872, 1745, 1664, 1443, 1373, 1246, 1157, 1032, 973, 901, 893. Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 316.24000 ± 0.0010, $[M - 60]^+$, $C_{21}H_{32}O_2$; calcd 316.2402.

PMR spectrum of **10** (δ, ppm, J/Hz): 0.72 (3H, s, CH_3-20), 0.85 (3H, s, CH_3-19), 0.99 (3H, s, CH_3-18), 1.40 (1H, d, J = 11.4, H-5), 1.61 (1H, br.d, J = 11.6, H-9), 1.00-1.70 (8H, m), 1.96 (1H, m, H_a-12), 2.00 (1H, m, H_α-7), 2.02 (3H, s, MeO), 2.13 (3H, d, J = 1.3, CH_3-16), 2.28 (1H, m, H_b-12), 2.67 (1H, dd, J = 5.2, 12.1, H_β-7), 3.67 (3H, s, MeO), 4.59 (1H, ddd, J = 1.4, H_b-17), 4.94 (1H, ddd, J = 1.4, H_a-17), 5.01 (1H, ddd, J = 5.1, 11.0, 11.0, H-6), 5.62 (1H, m, H-14).

^{13}C NMR spectrum (δ, ppm): 16.0 (C-20), 18.9 (C-16), 19.0 (C-2), 21.7 (CO<u>C</u>H$_3$), 21.9 (C-11), 22.5 (C-19), 33.5 (C-4), 36.1 (C-18), 39.1 (C-1), 39.6 (C-10), 39.7 (C-12), 43.4 (C-3), 44.1 (C-7), 50.8 (CO_2<u>C</u>H$_3$), 55.2 (C-9), 57.5 (C-5), 73.2 (C-6), 109.4 (C-17), 115.2 (C-14), 143.9 (C-8), 160.7 (C-13), 167.3 (<u>C</u>OCH$_3$), 170.1 (<u>C</u>O$_2$CH$_3$).

PMR spectrum of **11** (δ, ppm, J/Hz): 0.72 (3H, s, CH_3-20), 0.85 (3H, s, CH_3-19), 0.99 (3H, s, CH_3-18), 1.43 (1H, d, J = 10.9, H-5), 1.69 (1H, br.d, H-9), 1.10-1.75 (8H, m), 2.02 (3H, s, MeO), 1.87 (3H, d, J = 1.3, CH_3-16), 2.00 (1H, m, H_α-7), 2.55 (2H, m, H_2-12), 2.68 (1H, dd, J = 5.2, 12.1, H_β-7), 3.64 (3H, s, MeO), 4.77 (1H, ddd, J = 1.4, H_b-17), 4.96 (1H, ddd, J = 1.4, H_a-17), 5.02 (1H, ddd, J = 5.2, 11.0, 11.0, H-6), 5.62 (1H, m, H-14).

^{13}C NMR spectrum (δ, ppm): 16.0 (C-20), 19.1 (C-2), 21.7 (CO<u>C</u>H$_3$), 21.9 (C-11), 22.5 (C-19), 25.3 (C-16), 32.7 (C-12), 33.5 (C-4), 36.1 (C-18), 38.9 (C-1), 39.8 (C-10), 43.4 (C-3), 44.2 (C-7), 50.8 (CO_2<u>C</u>H$_3$), 56.2 (C-9), 57.5 (C-5), 73.4 (C-6), 109.4 (C-17), 144.1 (C-8), 115.8 (C-14), 160.7 (C-13), 166.7 (<u>C</u>O$_2$CH$_3$), 170.2 (<u>C</u>OCH$_3$).

The same solvent mixture eluted from the column mixtures of liquid hydroxyesters **12** and **13** (320.0 mg, 76%, *E–Z* ratio 7:2). Their spetral data are given below.

13*E*-6α-Hydroxylabda-8(17),13-dien-15-oic Acid (15) and 13*Z*-6α-Hydroxylabda-8(17),13-dien-15-oic Acid (16).

A. A solution of the mixture of **10** and **11** (80.0 mg, 0.21 mmol) in EtOH (20 mL) was treated with a solution of KOH (95.0 mg, 1.69 mmol) in EtOH (3.0 mL). The resulting mixture was refluxed for 1 h. The usual work up gave a solid (72 mg) that was chromatographed over a column of SiO_2 (7 g) with elution by hexane:EtOAc (85:15) to afford crystalline **15** (54.0 mg, 79%), mp 134–135°C (hexane:EtOAc 4:1), $[\alpha]_D^{25}$ +50.1° (*c* 0.35). IR spectrum (CCl_4, ν, cm^{-1}): 3406, 3089, 2931, 2857, 1694, 1644, 1444, 1381, 1252, 1163, 1052, 1012, 978, 893.

PMR spectrum (δ, ppm, J/Hz): 0.68 (3H, s, CH_3-20), 0.99 (3H, s, CH_3-19), 1.15 (3H, s, CH_3-18), 1.09 (1H, d, J = 11.0, H-5), 1.59 (1H, br.d, J = 11.0, H-9), 1.99 (1H, dddd, J = 1.0, 6.0, 10.0, 14.0, H_a-12), 2.03 (1H, br.dd, J = 1.4, 11.0, 12.0, H_α-7), 1.01-1.70 (8H, m), 2.15 (3H, d, J = 1.2, CH_3-16), 2.32 (1H, dddd, J = 1.0, 4.0, 10.0, 14.0, H_b-12), 2.67 (1H, dd, J = 5.0, 12.0, H_β-7), 3.82 (1H, ddd, J = 5.0, 11.0, 11.0, H-6), 4.56 (1H, ddd, J = 1.4, H_b-17), 4.91 (1H, ddd, J = 1.4, H_a-17), 5.66 (1H, br.s, H-14).

^{13}C NMR spectrum (δ, ppm): 16.1 (C-20), 19.1 (C-2), 19.2 (C-16), 21.8 (C-11), 22.4 (C-19), 33.9 (C-4), 36.6 (C-18), 39.3 (C-1), 3.94 (C-10), 40.0 (C-12), 43.7 (C-3), 49.1 (C-7), 55.4 (C-9), 60.5 (C-5), 71.7 (C-6), 108.3 (C-17), 114.9 (C-14), 145.2 (C-8), 163.6 (C-13), 171.5 (CO_2H).

Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 320.2349 ± 0.0017, $[M]^+$, $C_{20}H_{32}O_3$; calcd 320.2351.

Next the same solvent mixture eluted liquid hydroxyacid **16** (13.0 mg, 19%), $[\alpha]_D^{22}$ +20.8° (*c* 0.25). IR spectrum (film, ν, cm^{-1}): 3452, 3089, 2931, 2857, 1712, 1648, 1453, 1390, 1066, 897, 758.

PMR spectrum (δ, ppm, J/Hz): 0.67 (3H, s, CH_3-20), 0.99 (3H, s, CH_3-19), 1.15 (3H, s, CH_3-18), 1.11 (1H, d, J = 11.0, H-5), 1.67 (1H, m, H-9), 1.91 (3H, d, J = 1.3, CH_3-16), 2.04 (1H, br.dd, J = 1.4, 11.0, 12.0, H_α-7), 1.00-1.70 (8H, m), 2.64–2.50 (2H, m, H_2-12), 2.67 (1H, dd, J = 5.0, 12.0, H_β-7), 3.82 (1H, ddd, J = 5.0, 11.0, 11.0, H-6), 4.72 (1H, ddd, J = 1.4, H_b-17), 4.91 (1H, ddd, J = 1.4, H_a-17), 5.66 (1H, br.s, H-14).

^{13}C NMR spectrum (δ, ppm): 16.1 (C-20), 19.1 (C-2), 22.4 (C-19), 22.7 (C-11), 25.7 (C-16), 32.9 (C-12), 33.9 (C-4), 36.6 (C-18), 39.2 (C-1), 39.5 (C-10), 43.7 (C-3), 49.1 (C-7), 56.3 (C-9), 60.5 (C-5), 71.7 (C-6), 108.3 (C-17), 115.5 (C-14), 145.3 (C-8), 163.9 (C-13), 171.0 (CO_2H).

Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 320.2356 ± 0.0016, $[M]^+$, $C_{20}H_{32}O_3$; calcd 320.2351.

B. A solution of the mixture of hydroxyacids **12** and **13** (290.0 mg, 0.87 mmol) in EtOH (9.0 mL) was treated with a solution of KOH (392.0 mg, 6.99 mmol) in EtOH (11.0 mL). The resulting mixture was refluxed for 1 h. The usual work up gave a solid (282.0 mg) that was chromatographed over a column of SiO_2 (28 g) with elution by hexane:EtOAc (85:15) to afford crystalline **15** (214.0 mg, 77%) and **16** (60.0 mg, 22%). The PMR and ^{13}C NMR spectra of **15** and **16** agreed with those obtained above.

Methyl Ester of 13*E*-6α-Hydroxylabda-8(17),13-dien-15-oic Acid (12). A solution of **15** (200.0 mg, 0.63 mmol) in THF (2.7 mL) was stirred, treated with a solution of $TMSCHN_2$ (2.0 M in hexane, 1.3 mL), and stirred for 30 min. The solvent was vacuum distilled. The product (226.0 mg) was chromatographed over a column of SiO_2 (22 g) with elution by hexane:EtOAc (9:1) to afford liquid **12** (202.0 mg, 97%), $[\alpha]_D^{25}$ +54.5° (*c* 0.30). Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 334.2507 ± 0.0018, $[M]^+$, $C_{21}H_{34}O_3$; calcd 334.2508.

PMR spectrum (δ, ppm, J/Hz): 0.68 (3H, s, CH_3-20), 0.99 (3H, s, CH_3-19), 1.08 (1H, d, J = 11.0, H-5), 1.15 (3H, s, CH_3-18), 1.58 (1H, br.d, J = 11.0, H-9), 1.00–1.70 (8H, m), 1.96 (1H, dddd, J = 1.0, 4.0, 10.0, 14.0, H_a-12), 2.02 (br.dd, J = 1.0, 11.0, 12.0, H_α-7), 2.14 (3H, d, J = 1.4, CH_3-16), 2.28 (1H, dddd, J = 1.0, 6.0, 10.0, 14.0, H_b-12), 2.66 (1H, dd, J = 5.0, 11.0, 11.0, H_β-7), 3.67 (3H, s, MeO), 3.82 (1H, br.ddd, J = 5.0, 11.0, 11.0, H-6), 4.55 (1H, ddd, J = 1.4, H_b-17), 4.90 (1H, ddd, J = 1.4, H_a-17), 5.62 (1H, m, H-14).

^{13}C NMR spectrum (δ, ppm); 16.1 (C-20), 18.9 (C-16), 19.1 (C-2), 21.8 (C-11), 22.4 (C-19), 33.9 (C-4), 36.6 (C-18), 39.3 (C-1), 39.4 (C-10), 39.8 (C-12), 43.7 (C-3), 49.1 (C-7), 50.8 ($CO_2\underline{C}H_3$), 55.3 (C-9), 60.5 (C-5), 71.7 (C-6), 108.3 (C-17), 115.1 (C-14), 145.2 (C-8), 160.8 (C-13), 167.3 ($\underline{C}O_2CH_3$).

Methyl Ester of 13*Z*-6α-Hydroxylabda-8(17),13-dien-15-oic Acid (13). A solution of **16** (120.0 mg, 0.38 mmol) in THF (1.6 mL) was stirred, treated with a solution of $TMSCHN_2$ (2.0 M in hexane, 0.76 mL), and stirred for 30 min. The solvent was vacuum distilled. The product (127.0 mg) was chromatographed over a column of SiO_2 (12 g) with elution by hexane:EtOAc (9:1) to afford liquid **13** (122.0 mg, 98%), $[\alpha]_D^{21}$ +63.0° (*c* 0.94). IR spectrum (film, ν, cm^{-1}): 3430, 2930, 1735, 1647, 1438, 1265, 1160, 1021, 896. Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 334.2502 ± 0.0025, $[M]^+$, $C_{21}H_{34}O_3$; calcd 334.2508.

PMR spectrum (400 MHz, δ, ppm, J/Hz): 0.68 (3H, s, CH_3-20), 0.99 (3H, s, CH_3-19), 1.11 (1H, d, J = 11.0, H-5), 1.15 (3H, s, CH_3-18), 1.68 (1H, m, H-9), 1.00–1.70 (8H, m), 1.87 (3H, d, J = 1.4, CH_3-16), 2.04 (1H, br.dd, J = 1.0, 11.0, 12.0, H_α-7), 2.48–2.62 (2H, m, H_2-12), 2.68 (1H, dd, J = 5.0, 12.0, H_β-7), 3.65 (3H, s, MeO), 3.82 (1H, br.ddd, J = 5.0, 11.0, 11.0, H-6), 4.74 (1H, ddd, J = 1.4, H_b-17), 4.93 (1H, ddd, J = 1.4, H_a-17), 5.62 (1H, m, H-14).

^{13}C NMR spectrum (δ, ppm): 16.1 (C-20), 19.1 (C-2), 21.8 (C-11), 22.4 (C-19), 25.3 (C-16), 32.8 (C-12), 33.9 (C-4), 36.6 (C-18), 39.3 (C-1), 39.4 (C-10), 43.7 (C-3), 49.1 (C-7), 50.8 ($CO_2\underline{C}H_3$), 56.3 (C-9), 60.5 (C-5), 71.7 (C-6), 108.3 (C-17), 115.8 (C-14), 145.2 (C-8), 160.8 (C-13), 166.7 ($\underline{C}O_2CH_3$).

13*E*-Labda-8(17),13-dien-6α,15-diol [(+)-1] (crotonadiol). A solution of $LiAlH_4$ (23.0 mg, 0.6 mmol) in dry Et_2O (3.0 mL) under Ar at 0°C was stirred, treated dropwise with a solution of **12** (192.0 mg, 0.58 mmol) in anhydrous Et_2O (7.0 mL), stirred at the same temperature for 3 h, and worked up. Distillation of solvent gave a solid (175.0 mg) that was chromatographed over a column of SiO_2 (10 g) with elution by hexane:EtOAc (7:3) to afford crystalline (+)-**1** (151.0 mg, 86%), mp 144–145°C (EtOH), $[\alpha]_D^{16}$ +19.3° (*c* 0.012).

The PMR and ^{13}C NMR spectra of this compound were identical to those obtained above.

13*Z*-Labda-8(17),13-dien-6α,15-diol (5). A solution of $LiAlH_4$ (16.0 mg, 0.41 mmol) in dry Et_2O (3.0 mL) under Ar at 0°C was stirred, treated dropwise with a solution of **13** (133.0 mg, 0.39 mmol) in anhydrous Et_2O (4.0 mL), stirred at the same temperature for 3 h, and worked up. Distillation of solvent gave a solid (119.0 mg) that was chromatographed over a

column of SiO_2 (8 g) with elution by hexane:EtOAc (7:3) to afford diol **5** (97.0 mg, 80%), liquid, $[\alpha]_D^{16}$ +41.35° (*c* 0.014). IR spectrum ($CHCl_3$, ν, cm^{-1}): 3360, 2920, 1638, 1440, 1372, 1215, 1043, 888, 870, 756.

PMR spectrum (400 MHz, δ, ppm, J/Hz): 0.72 (3H, s, CH_3-20), 1.01 (3H, s, CH_3-19), 1.17 (3H, s, CH_3-18), 1.13 (1H, d, J = 10.4, H-5), 1.55 (1H, br.d, J = 10.0, H-9), 1.00-1.67 (8H, m), 1.69 (3H, br.s, CH_3-16), 2.07 (1H, t, J = 10.4, 12.0, H_α-7), 2.28–2.38 (2H, m, H_2-12), 2.68 (1H, dd, J = 4.8, 12.0, H_β-7), 3.70 (2H, t, J = 6.0, H_2-15), 3.84 (1H, ddd, J = 4.8, 10.4, 10.4, H-6), 4.56 (1H, s, H_b-17), 4.90 (1H, s, H_a-17), 5.27 (1H, t, J = 6.0, H-14).

^{13}C NMR spectrum (δ, ppm): 16.0 (C-20), 19.1 (C-2), 22.8 (C-11), 22.4 (C-19), 23.3 (C-16), 33.9 (C-4), 35.3 (C-12), 36.7 (C-18), 39.5 (C-1), 39.4 (C-10), 43.8 (C-3), 49.0 (C-7), 56.7 (C-9), 60.5 (C-15), 60.6 (C-5), 71.6 (C-6), 109.2 (C-17), 128.7 (C-14), 130.7 (C-13), 145.6 (C-8).

Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 306.2557 ± 0.0021, $[M]^+$, $C_{20}H_{34}O_2$; calcd 306.2559.

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REFERENCES

1. B. T. Ngadjui, G. G. Folefoc, F. Keumedjio, E. Dengo, B. L. Sodengam, and J. D. Connolly, *Phytochemistry*, **51**, 171 (1999).
2. A. Salatino, M. L. F. Salatino, and G. Negri, *J. Braz. Chem. Soc.*, **18**, 11 (2007).
3. B. H. Yang, W. D. Zhang, Z. B. Gu, T. Z. Li, C. Zhang, and Y. Zhou, *Chin. Chem. Lett.*, **15**, 919 (2004)
4. J. Haeuser, *Bull. Soc. Chim. Fr.*, **9**, 2645 (1965).
5. M. A. Golikova, T. V. Romanchenko, V. I. Bolshakova, E. N. Shmidt, V. A. Pentegova, G. M. Maksimov, and C. I. Matveev, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim.*, **3**, 109 (1988).
6. V. Kulcitki, N. Ungur, and P. F. Vlad, *Tetrahedron*, **54**, 11925 (1988).
7. P. Martes, P. Perfetti, J. P. Zahra, and B. Waegell, *Tetrahedron Lett.*, **32**, 765 (1991).
8. J. P. Zahra, F. Chauvet, I. Coste-Maniere, P. Martres, P. Perfetti, and B. Waegell, *Bull. Soc. Chim. Fr.*, **134**, 1001 (1997).
9. W. Sandermann and K. Bruns, *Chem. Ber.*, **99**, 2835 (1966).
10. C. Morin and N. Nedjar, *Tetrahedron Lett.*, **37**, 4705 (1996).
11. M. G. Bolster, B. J. M. Jansen, and A. de Groot, *Tetrahedron*, **57**, 5663 (2001).
12. M. G. Bolster, B. M. F. Lagnel, B. J. M. Jansen, C. Morin, and A. de Groot, *Tetrahedron*, **57**, 8369 (2001).
13. W. Sandermann and K. Bruns, *Naturwissenschaften*, **52**, 560 (1965).