Tetrahedron Vol. 49, No. 42, pp. 9525-9534, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Amber-type Odorants from Communic Acids

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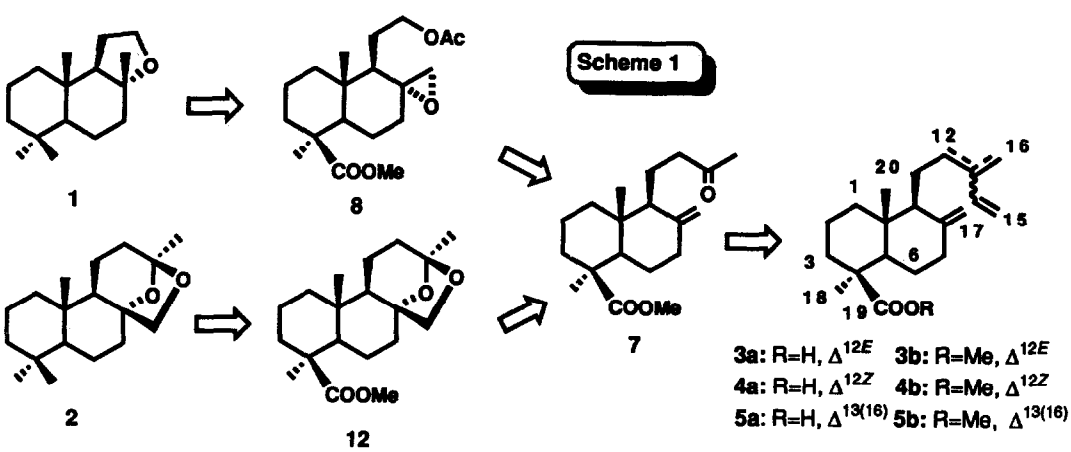
(*Received in UK* 26 *May* 1993; *accepted* 6 *August* 1993)

Abstract: A mixture of the methyl esters of communic acids (**3b**, **4b**, **5b**) was used in the synthesis of the ambergris-type odorants Ambrox® (**1**) and ambracetal (**2**). Both syntheses involve methyl ketone **7** as the key intermediate.

INTRODUCTION

Among the animal perfumes like civet, musk and castoreum, *ambergris* has been particularly prized by perfumers since ancient times for its unique fragrance and fixative properties.[1] It is a concretion formed in the intestinal tract of the blue sperm whale which, after one to three years of aging, can be used in perfumery in the form of an infusion in alcohol. Due to enforced whale protection, *ambergris* is thankfully not used any more, thus encouraging chemists to search for synthetic substitutes. Nowadays, the most important equivalents of this scarce natural source are the norlabadane oxides Ambrox® (**1**) and ambracetal (**2**) which possess a strong and tenacious ambergris-type odour.



Because of its greater demand, most efforts have been concentrated on compound **1**, and several syntheses of the pure (-)-enantiomer from naturally occurring sesquiterpenes or diterpenes such as (-)-drimenol,[2] (-)-sclareol,[3] (-)-manoyl oxide,[4] (-)-abietic acid,[5] (-)-levopimaric acid,[6] (-)-labdanolic acid,[7] have been performed. Furthermore, the total synthesis of the racemate has also been described.[8] With respect to the synthesis of compound **2**, sclareol[3c,9] and the more often, but less abundant manool[10] are the basic starting materials used.

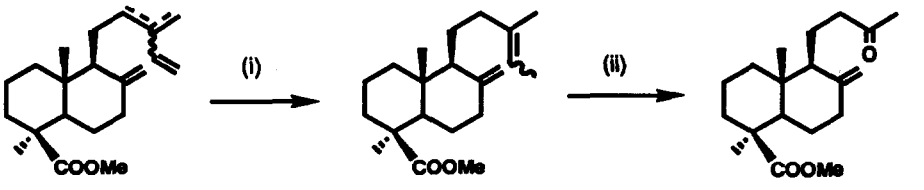
We have recently described two syntheses of (-)-Ambrox® (**1**) from *trans*- and/or *cis*-communic acids (**3a**, **4a**),[11] based on the preferential C_{12}-C_{13} cleavage of their side chains.[12,13] The "communic acids" (**3a**, **4a**, **5a**), usually occurring as mixtures of different proportions, are the main components of non-polar extracts of species of the genus *Juniperus*.[14] However, as a result of the phytochemical studies carried out on the genus *Juniperus* we are in a position to say which is the best source to provide separately each one of these substrates. Thus, for example, *trans*-communic acid (**3a**) can be found as the virtually sole component in both the berries[14] and wood[15] of *Juniperus sabina* L., the *cis*-communic acid (**4a**) in the berries of *Juniperus thurifera* L.,[16] and mirceocommunic acid (**5a**) in the berries of *Juniperus oxycedrus* L.[17] Nevertheless, the most interesting natural source of communic acids, the commercially available berries of *Juniperus communis* L., contains the three acids (**3a**, **4a**, **5a**) in a ratio of *ca.*15:35:50.[18]

Aware of the advantages of using this latter source of communic acids, we report here on the syntheses of both amber-type odorants (-)-Ambrox® (**1**) and (+)-ambracetal (**2**) from such a mixture of communic acids, obtained directly from the berries of *Juniperus communis* L.

RESULTS AND DISCUSSION

The use of one mixture of methyl esters of communic acids (**3b**, **4b**, **5b**) to prepare both **1** and **2** is justified by its suitable conversion into methyl ketone **7** (scheme 1) which is known to be the key intermediate in the synthesis of **2**[3c,9,10] and also a valid substrate for **1**[19] and derivatives.[20] Thus, the stereoselective formation of the ketal system from **7** and the reduction of its methoxycarbonyl group leads to **2**, and *Baeyer-Villiger* reaction on **7**, to afford **8**, is used to prepare **1** (scheme 1).

It is known that conjugated dienes react with sodium in alcohols to afford predominantly 1,4-addition products.[21] Following a known procedure,[22] we have shown how the reaction of methyl mirceocommunate (**5b**) with sodium in *t*-butanol affords the 1,4-hydrogenated compound (80-90%), accompanied by lesser amounts (5-10%) of the Δ^{14}-hydrogenated derivative.[13] As the mixture of methyl communates obtained from the berries of *Juniperus communis* L. is mainly composed of **5b**, we were curious to know the behaviour of the mixture under these conditions. Conveniently (scheme 2), the overnight reaction of the mixture of methyl communates (**3b**, **4b**, **5b**) with sodium/*t*-butanol at room temperature afforded a crude reaction (90% yield) again containing principally dienes **6** (*E*/*Z* 1.5:1; *ca* 80-85% crude yield) and a mixture of 1,2-hydrogenated compounds (*ca* 10-15% crude yield). The reaction of crude **6** with OsO_4-$NaIO_4$ (scheme 2), under conditions described in our earlier studies,[13] afforded a mixture from which methyl ketone **7** was then purified (60-65% overall yield from **3b**-**5b**).

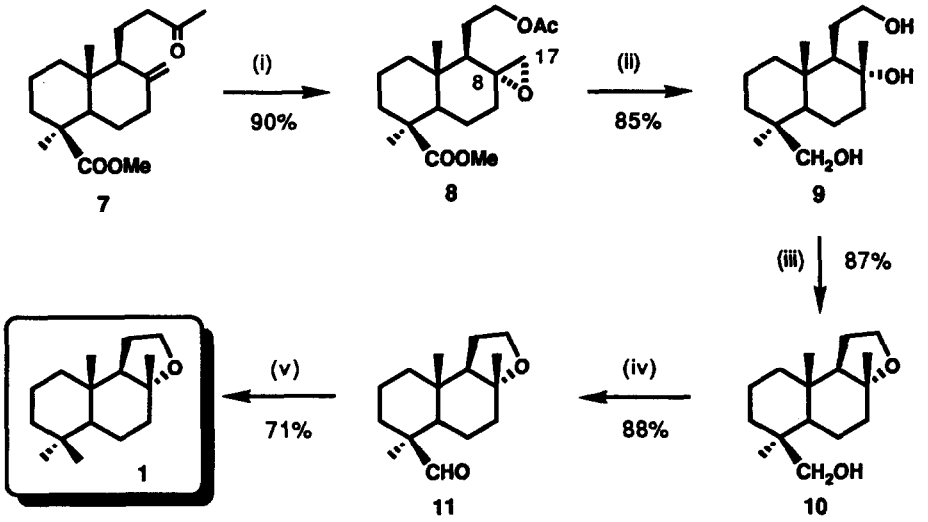


3b/4b/5b — 6 (*E*/*Z* 1.5:1) — 7 (60-65% from 3b-5b)

Scheme 2

(i) *t*-BuOH, Na, r.t., overnight. (ii) $NaIO_4$, 0.2% OsO_4, t-BuOH, H_2O, r.t., 150 h.

These encouraging results prompted us to transform **7** into Ambrox® (**1**) and ambracetal (**2**) as depicted in schemes 3 and 4, respectively. The synthesis of Ambrox® (scheme 3) is based on the stereoselective conversion of **7** to **8** with *m*-CPBA at room temperature (*Baeyer-Villiger*/epoxidation reaction). This compound is attributed the *R* configuration at C-8 based on the δ value at C-17 (50.12 ppm) of the ^{13}C NMR spectrum compared to related 8α,17-epoxide derivatives.[23] Next, **8** was refluxed with $LiAlH_4$ in THF to afford the triol **9** which, without further purification, was cyclized in CH_3NO_2 at room temperature[24] with *p*-TsOH to yield **10**. Finally, the conversion of alcohol **10** into Ambrox® was performed in two steps following the experimental procedure outlined in our previous work (scheme 3).[11]

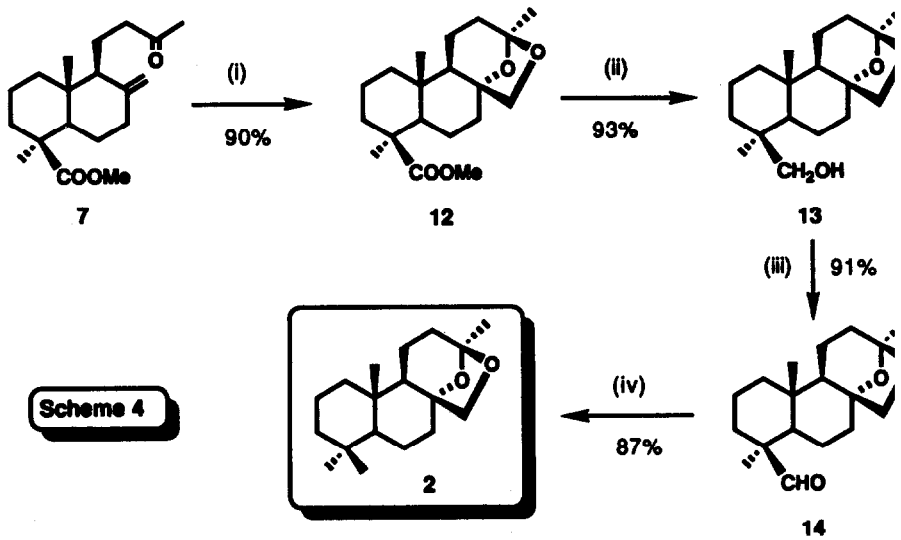


7 — 8 — 9 — 10 — 11

Scheme 3

(i) *m*-CPBA, CH_2Cl_2, r.t., 5 days. (ii) $LiAlH_4$, THF, reflux, 1 h. (iii) *p*-TsOH, CH_3NO_2, r.t., 1 h. (iv) *Jones* reagent, acetone, 0°C. (v) N_2H_4·H_2O, KOH, triethylene glycol, reflux, 1 h.

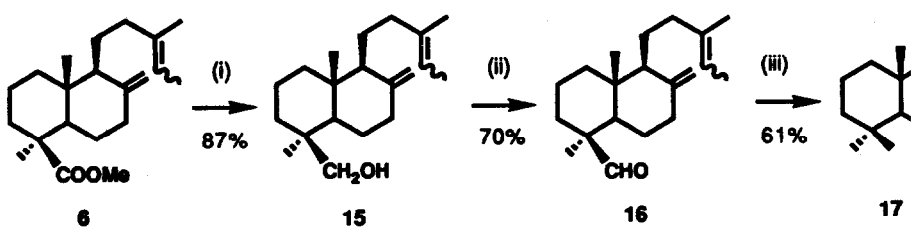
Concerning the synthesis of ambracetal (2) (scheme 4), 7 was first converted to 12 by treat catalytic amount of OsO_4 in refluxing *t*-BuOH/pyridine/H_2O mixtures, with trimethylamine oxidant.[3e] We then proceeded to convert the hindered methoxycarbonyl group into the methyl grou in the Ambrox® approach (scheme 3).[11] Accordingly, reduction with $LiAlH_4$ was followed by oxi resulting alcohol 13 to aldehyde 14 with *Jones* reagent; finally, a *Huang-Minlon* reaction[26] success ambracetal (2) (scheme 4).



Scheme 4

(i) Cat. 0.2% OsO_4, $Me_3NO{\cdot}H_2O$, *t*-BuOH, pyridine, H_2O, reflux, 24 h. (ii) $LiAlH_4$, THF reflux, 1 h. (iii) *Jones* reagent, acetone, 0°C. (iv) $N_2H_4{\cdot}H_2O$, triethylene glycol, reflux, 3 h

For purposes of comparison, transformation of the methoxycarbonyl functionality to a meth also effected at an earlier stage of the synthetic route; the overall yield, however was inferior (schen



Scheme 5

(i) $LiAlH_4$, THF, reflux, 0.5 h. (ii) *Jones* reagent, acetone, 0°C. (iii) $N_2H_4{\cdot}H_2O$, triethylene glycol, reflux, 4 h.

EXPERIMENTAL

For general procedures see reference 11. The mixture of **3b**, **4b** and **5b** was isolated from diazomethane-treated acid fractions of the berries of *Juniperus communis* L.[18]

Methyl labda-8(17),13*E*/*Z*-dien-19-oate (6)

To a stirred solution of the mixture of **3b**, **4b** and **5b** (650 mg, 2.06 mmol) in *t*-BuOH (30 ml), an excess of Na (2.10 g, 91.18 mmol) was slowly added within 2 h at room temperature. The resulting viscous mixture was further stirred overnight at room temperature. After decantation of the solution from the solid sodium, the mixture was fractionated in H_2O-hexane and extracted with hexane (3x50 ml). The dried organic phases finally yielded a crude (590 mg, 90%) principally formed by **6** (*E*/*Z* 1.5:1; 80% crude yield): oil; $[\alpha]_D$ (25°C) +43.5° (*c* 1.00); IR ν (neat) cm^{-1}: 3080, 1642, 888 (C=CH_2), 1724, 1227, 1153 (CO_2Me); ^1H NMR (300 MHz): corresponding to the *E* isomer: δ 0.49 (*s*, Me-10), 1.17 (*s*, Me-4), 1.55 (*d*, 6.7, Me-14), 1.57 (*br s*, Me-13), 3.59 (*s*, MeO-19), 4.51 (*br s*, H-17), 4.83 (*br s*, H'-17), 5.15 (*tq*, 1.1, 6.7, H-14); corresponding to the *Z* isomer: δ 0.49 (*s*, Me-10), 1.17 (*s*, Me-4), 1.50 (*d*, 6.7, Me-14), 1.53 (*br s*, Me-13), 3.59 (*s*, MeO-19), 4.59 (*br s*, H-17), 4.86 (*br s*, H'-17), 5.19 (*br q*, 6.7, H-14); ^{13}C NMR (75 MHz): corresponding to the *E* isomer: δ 39.11 (C-1), 19.96 (C-2), 38.24 (C-3), 44.26 (C-4), 56.34# (C-5), 26.26 (C-6), 38.54* (C-7), 148.10 (C-8), 55.44# (C-9), 40.16 (C-10), 22.20 (C-11), 38.75* (C-12), 136.27 (C-13), 118.03 (C-14), 13.27 (C-15), 15.63 (C-16), 106.28 (C-17), 28.77 (C-18), 177.68 (C-19), 12.58 (C-20), 51.02 (OCH_3); corresponding to the *Z* isomer: δ 39.04 (C-1), 19.96 (C-2), 38.24 (C-3), 44.26 (C-4), 56.34# (C-5), 26.26 (C-6), 38.54 (C-7), 148.19 (C-8), 55.20# (C-9), 40.16 (C-10), 21.49 (C-11), 30.09 (C-12), 136.27 (C-13), 119.23 (C-14), 13.27 (C-15), 23.27 (C-16), 106.21 (C-17), 28.77 (C-18), 177.68 (C-19), 12.58 (C-20), 51.02 (OCH_3). MS *m*/*z* (rel. int.): 318 (M^+, 2%), 303 (8), 259 (5), 258 (5), 243 (7), 189 (14), 161 (6), 147 (5), 133 (9), 121 (57), 107 (21), 91 (28), 79 (30), 67 (30), 55 (36), 41(100).

Methyl 13-oxo-14,15-dinorlabd-8(17)-en-19-oate (7)

A mixture of the latter crude **6** (*E*/*Z*) (480 mg, 1.51 mmol), *t*-BuOH (15 ml), H_2O (5 ml), $NaIO_4$ (770 mg, 3.60 mmol) and a 0.2% aq. OsO_4 solution (1.6 ml, 0.013 mmol) was stirred at room temperature under argon for 150 h. The mixture was fractionated into Et_2O-H_2O and extracted with Et_2O (3x20 ml), and the combined organic layers washed with sat. K_2CO_3 (2x20 ml) and H_2O (20 ml). The organic phase was dried over anh. Na_2SO_4 and the solvent evaporated to afford a mixture (450 mg) which, after column chromatography, yielded **7** (332 mg, 65% from **3b**-**5b**, 96:4 hexane-Et_2O): white crystals; m.p. 60-2°C (MeOH/H_2O); $[\alpha]_D$ (25°C) +38.8° (*c* 1.00); IR ν (neat) cm^{-1}: 3078, 1643, 891 (C=CH_2), 1718 (C=O), 1718, 1229, 1155 (CO_2Me); ^1H NMR (300 MHz): δ 0.48 (3H, *s*, Me-10), 1.14 (3H, *s*, Me-4), 2.06 (3H, *s*, Me-13), 3.57 (3H, *s*, MeO-19), 4.40 (1H, *br s*, H-17), 4.81 (1H, *d*, 0.8, H'-17); ^{13}C NMR (75 MHz): δ 38.89 (C-1), 19.77 (C-2), 38.04 (C-3), 44.10 (C-4), 56.09 (C-5), 26.08 (C-6), 38.70 (C-7), 147.60 (C-8), 55.31 (C-9), 40.19 (C-10), 17.51 (C-11), 42.62 (C-12), 208.92 (C-13), 29.80 (C-16), 106.26 (C-17), 28.65 (C-18),

#,*These assignments are interchangeable.

177.40 (C-19), 12.27 (C-20), 50.91 (OCH_3); MS *m/z* (rel. int.): 306 (M^+, 2%), 288 (5), 246 (9), 235 (2), 229 (6), 213 (8), 188 (15), 173 (8), 161 (10), 121 (100), 107 (27), 91 (25), 84 (75), 49 (66), 43 (65).

Methyl 12-acetoxy-8α,17-epoxy-13,14,15,16-tetranorlabdan-19-oate (8)

m-Chloroperbenzoic acid (70%, 570 mg, 2.30 mmol) was added to a solution of methyl ketone **7** (570 mg, 1.86 mmol) in 25 ml of CH_2Cl_2 and the mixture was left to stand in the dark at room temperature for 5 days. Additional portions of *m*-CPBA (225 mg, 0.91 mmol) were added each 24 h. The mixture was washed with saturated Na_2CO_3 and NaCl solutions, dried over Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography to afford **8** (566 mg, 90%, 85:15 hexane–Et_2O): white crystals; m.p. 85-8°C (MeOH/H_2O); $[\alpha]_D$ (25°C) +32.0° (*c* 1.00); IR ν (neat) cm^{-1}: 1725, 1236, 1158 (CO_2Me), 1725, 1236, 1034 (AcO), 896, 810 (oxirane); ^1H NMR (300 MHz): δ 0.60 (3H, *s*, Me-10), 1.20 (3H, *s*, Me-4), 2.01 (3H, *s*, AcO), 2.52 (1H, *d*, 4.2, H-17), 2.71 (1H, *dd*, 4.2, 2.0, H'-17), 3.63 (3H, *s*, MeO-19), 3.97 (1H, *td*, 11.1, 7.6, H-12), 4.03 (1H, *td*, 11.1, 8.2, H'-12); ^{13}C NMR (75 MHz): δ 39.04 (C-1), 19.29 (C-2), 37.94 (C-3), 44.11 (C-4), 55.67 (C-5), 23.36 (C-6), 36.62 (C-7), 58.56 (C-8), 49.74 (C-9), 40.28 (C-10), 21.67 (C-11), 65.45 (C-12), 50.12 (C-17), 28.80 (C-18), 177.47 (C-19), 12.78 (C-20), 51.28 (OMe), 171.03 (CH_3CO), 21.05 (CH_3CO); MS *m/z* (rel. int.): 338 (M^+, 0.1%), 323 (0.3), 278 (6), 263 (4), 218 (2), 203 (2), 121 (26), 109 (19), 107 (11), 105 (11), 93 (13), 91 (15), 81 (14), 79 (17), 67 (15), 59 (10), 55 (21), 43 (100), 41 (23).

13,14,15,16-tetranorlabdan-8α,12,19-triol (9)

A mixture of **8** (300 mg, 0.88 mmol), THF (12 ml) and $LiAlH_4$ (135 mg, 3.56 mmol) was refluxed for 1 h. The mixture was cooled to room temperature and diluted with Et_2O (10 ml), acidified with a 10% HCl solution and extracted with Et_2O (3x30 ml). The organic phase was washed with 10% $NaHCO_3$ solution, dried over anh. Na_2SO_4 and evaporated to yield **9** (202 mg, 85%): IR ν (neat) cm^{-1}: 3325, 1157, 1126, 1027 (OH); ^1H NMR (300 MHz): δ 0.80 (3H, *s*, Me-10), 0.98 (3H, *s*, Me-4), 1.18 (3H, *s*, Me-8), 3.27-3.95 (2H, *m*, H-12), 3.46 (1H, *da*, 10.5, H-19) , 3.70 (1H, *d*, 10.5, H'-19); MS *m/z* (rel. int.): 270 (M^+, 0.7%), 255 (2), 252 (0.7), 239 (2), 237 (1), 221 (3), 211 (4), 182 (12), 177 (4), 123 (63), 121 (20), 109 (44), 95 (94), 81 (79), 71 (69), 69 (43), 67 (58), 57 (23), 55 (67), 43 (100).

8α,12-epoxy-13,14,15,16-tetranorlabdan-19-ol (10)

A stirred solution of **9** (120 mg, 0.44 mmol), *p*-TsOH (120 mg, 0.70 mmol) and CH_3NO_2 (6 ml) was kept at room temperature for 1 h. It was diluted with Et_2O (10 ml), washed with 15% $NaHCO_3$ solution, dried over anh. Na_2SO_4 and evaporated to afford a residue, which was crystallized from hexane to yield **10** (96 mg, 87%): data in reference 11.

8α,12-epoxy-13,14,15,16-tetranorlabdane (Ambrox®) (1)

Compound **1** was prepared from **10** by oxidation with *Jones* reagent and subsequent *Huang-Minlon* treatment of the resulting aldehyde **11**, according to our previous work.[11]

Methyl (13*S*)-8α,13:13,17-diepoxy-14,15-dinorlabdan-19-oate (12)

A 0.2% aq. OsO_4 solution (2.9 ml) in 25 ml of *t*-BuOH was added to a mixture of **7** (1.47 g, 4.82 mmol), Me_3NO (1.75 g, 23.26 mmol), pyridine (7 ml), H_2O (35 ml) and t-BuOH (75 ml). The solution was refluxed for 12 h under argon. The addition of a portion of Me_3NO (2 g, 26.66 mmol) and 0.2% aq. OsO_4 solution (2 ml) and further refluxing for 12 h were required to complete the reaction. The mixture was cooled, treated with 50 ml of 20% $NaHSO_3$ solution, concentrated under vacuum to remove *t*-BuOH, saturated with NaCl, and extracted with Et_2O (3x50 ml). Organic layers were dried over anh. Na_2SO_4 and evaporated to yield **12** (1.40 g, 90%): white crystals; m.p. 89-92°C (MeOH/H_2O); $[\alpha]_D$ (25°C) +47.8° (*c* 1.00); IR (KBr): ν 1721, 1234, 1161 (COOMe), 1031, 978, 860, 815 (ketal); ^{1}H NMR (300 MHz): δ 0.67 (3H, *s*, Me-10), 1.17 (3H, *s*, Me-4), 1.38 (3H, *s*, Me-13), 3.37 (1H, *dd*, 7.1, 1.1, H-17), 3.60 (3H, *s*, MeO-19), 4.23 (1H, *d*, 7.1, H'-17); ^{13}C NMR (75 MHz): δ 39.13 (C-1), 18.84 (C-2), 37.83 (C-3), 43.68 (C-4), 56.26 (C-5), 21.64 (C-6), 36.42* (C-7), 82.28 (C-8), 52.62 (C-9), 37.76 (C-10), 17.67 (C-11), 35.96* (C-12), 106.08 (C-13), 24.17 (C-16), 73.25 (C-17), 28.73 (C-18), 177.57 (C-19), 12.73 (C-20), 51.22 (OCH_3); MS *m/z* (rel. int.): 322 (M^+, 2%), 307 (1), 292 (3), 263 (8), 262 (16), 247 (4), 234 (9), 203 (13), 202 (21), 174 (25), 159 (16), 149 (14), 121 (52), 105 (21), 86 (66), 84 (100), 49 (51), 43 (34).

(13*S*)-8α,13:13,17-diepoxy-14,15-dinorlabdan-19-ol (13)

A stirred mixture of **12** (1.20 g, 3.73 mmol), THF (10 ml) and $LiAlH_4$ (420 mg, 11.07 mmol) was refluxed for 1 h. Following the same work-up used to prepare **9**, alcohol **13** (1.02 g, 93%) was obtained: oil; $[\alpha]_D$ (25°C) +16.7° (*c* 1.00); IR (neat): ν 3440, 1027 (primary OH), 1027, 865 (ketal); ^{1}H NMR (300 MHz): δ 0.84 (3H, *s*, Me-10), 0.96 (3H, *s*, Me-4), 1.37 (3H, *s*, Me-13), 3.31 (1H, *dd*, 7.1, 1.1, H-17), 3.37 (1H, *da*, 10.9, H-19), 3.66 (1H, *d*, 10.9, H'-19), 4.23 (1H, *d*, 7.1, H'-17); ^{13}C NMR (75 MHz): δ 38.73 (C-1), 17.89 (C-2), 35.45* (C-3), 38.35 (C-4), 56.18 (C-5), 20.18 (C-6), 36.48* (C-7), 82.37 (C-8), 53.33 (C-9), 37.17 (C-10), 17.51 (C-11), 35.77* (C-12), 106.05 (C-13), 24.16 (C-16), 73.23 (C-17), 27.13 (C-18), 65.31 (C-19), 15.02 (C-20); MS *m/z* (rel. int.): 294 (M^+, 0.7%), 264 (0.7), 263 (0.9), 234 (2), 203 (7), 175 (11), 163 (11), 121 (8), 109 (9), 107 (9), 91 (14), 79 (18), 67 (15), 55 (24), 43 (100).

(13*S*)-8α,13:13,17-diepoxy-14,15-dinorlabdan-19-al (14)

To a stirred solution of **13** (900 mg, 3.06 mmol) in acetone (10 ml), a 2.67 M solution of *Jones* reagent was added dropwise at 0°C till starting material was consumed. The mixture was filtered, evaporated and extracted with Et_2O (3x20 ml). Organic layers were dried over anh. Na_2SO_4 and evaporated to yield **14** (813 mg, 91%): white crystals; m.p. 65-7°C (MeOH/H_2O); $[\alpha]_D$ (25°C) +23.1° (*c* 1.00); IR (KBr): ν 2705, 1714 (aldehyde), 1020, 866 (ketal); ^{1}H NMR (300 MHz): δ 0.73 (3H, *s*, Me-10), 1.01 (3H, *s*, Me-4), 1.39 (3H, *s*, Me-13), 3.38 (1H, *dd*, 7.1, 1.2, H-17), 4.25 (1H, *d*, 7.1, H'-17), 9.68 (1H, *d*, 1.4, H-19); ^{13}C NMR (75 MHz): δ 38.20 (C-1), 18.08 (C-2), 34.21 (C-3), 48.14 (C-4), 55.87 (C-5), 19.70 (C-6), 36.21* (C-7), 82.08 (C-8), 52.23 (C-9), 37.59 (C-10), 17.78 (C-11), 35.92* (C-12), 106.20 (C-13), 24.13 (C-16), 77.33 (C-17), 24.33 (C-18), 205.21 (C-19), 13.70 (C-20); MS *m/z* (rel. int.): 292 (M^+, 3%), 264 (3), 263 (2), 232 (28), 217

* These assignments are interchangeable.

(23), 204 (33), 203 (34), 189 (24), 175 (44), 161 (60), 147 (32), 133 (45), 121 (43), 119 (47), 105 (57), 93 (45), 91 (53), 79 (61), 67 (42), 55 (45), 43 (100).

(13*S*)-8α,13:13,17-diepoxy-14,15-dinorlabdane (2)

A mixture of **14** (700 mg, 2.40 mmol), $N_2H_4 \cdot H_2O$ (1.53 g, 30.60 mmol), powdered KOH (2.33 g, 41.61 mmol) and triethylene glycol (40 g) was refluxed under argon for 3 h. The mixture was acidified with 10% HCl solution, extracted with Et_2O (3x20 ml) and the combined extracts were washed with brine, dried over anh. Na_2SO_4 and evaporated to yield a crude reaction (667 mg) which was crystallized from hexane to afford **2** (580 mg, 87%): white crystals; m.p. 116-119°C (hexane); $[\alpha]_D$ (25°C) +23.4° (*c* 1.00); IR (KBr): ν 1020, 866 (ketal); ^{1}H NMR (300 MHz): δ 0.76 (3H, *s*, Meβ-4), 0.85 (6H, *s*, Me-10, Meα-4), 1.37 (3H, *s*, Me-13), 3.32 (1H, *dd*, 7.0, 0.8, H-17), 4.27 (1H, *d*, 7.0, H'-17); ^{13}C NMR (75 MHz): δ 38.68 (C-1), 18.24 (C-2), 41.76 (C-3), 33.03 (C-4), 55.59 (C-5), 19.98 (C-6), 36.09* (C-7), 82.55 (C-8), 53.26 (C-9), 37.25 (C-10), 17.39 (C-11), 35.86* (C-12), 105.96 (C-13), 24.21 (C-16), 73.40 (C-17), 33.58 (C-18), 21.69 (C-19), 14.54 (C-20); MS *m/z* (rel. int.): 278 (M^+, 1%), 263 (1), 248 (1), 236 (2), 233 (2), 218 (14), 203 (8), 190 (21), 175 (18), 147 (10), 137 (12), 121 (18), 109 (23), 91 (22), 79 (31), 69 (29), 55 (37), 43 (100).

Labda-8(17),13*E*/*Z*-dien-19-ol (15)

A stirred mixture of **6** (2.98 g, 9.36 mmol), THF (35 ml) and $LiAlH_4$ (530 mg, 13.98 mmol) was refluxed for 0.5 h. Following the same work-up used to prepared **9**, the residue was purified by column chromatography to afford **15** (2.36 g, 87%, 8:2 *E*/*Z* ratio, 95:5 hexane-Et_2O): oil; $[\alpha]_D$ (25°C) +26.0° (*c* 1.00); IR ν (neat) cm^{-1}: 3078, 1641, 888 (C=CH_2), 3346, 1024 (primary OH) ; ^{1}H NMR (300 MHz): corresponding to the *E* isomer: δ 0.63 (*s*, Me-10), 0.96 (*s*, Me-4), 1.55 (*d*, 6.5, Me-14), 1.58 (*br s*, Me-13), 3.37 (*d*, 10.9, H-19), 3.73 (*d*, 10.9, H'-19), 4.52 (*d*, 0.9, H-17), 4.80 (*d*, 1.5, H'-17), 5.15 (*br q*, 6.5, H-14); corresponding to the *Z* isomer: δ 0.63 (*s*, Me-10), 0.96 (*s*, Me-4), 1.55 (*d*, 6.5, Me-14), 1.58 (*br s*, Me-13), 3.38 (*d*, 10.8, H-19), 3.74 (*d*, 10.8, H'-19), 4.58 (*br s*, H-17), 4.83 (*d*, 1.5, H'-17), 5.16 (*br q*, 6.5, H-14); ^{13}C NMR (75 MHz): corresponding to the *E* isomer: δ 38.96* (C-1), 18.99 (C-2), 35.42 (C-3), 38.83 (C-4), 56.29# (C-5), 24.44 (C-6), 38.49*(C-7), 148.19 (C-8), 56.33# (C-9), 39.47 (C-10), 22.13 (C-11), 38.63* (C-12), 136.39 (C-13), 118.00 (C-14), 13.30 (C-15), 15.67 (C-16), 106.47 (C-17), 27.04 (C-18), 65.02 (C-19), 15.30 (C-20); corresponding to the Z isomer: δ 38.96* (C-1), 18.99 (C-2), 35.42 (C-3), 38.83 (C-4), 56.29# (C-5), 24.26 (C-6), 38.49*(C-7), 148.21 (C-8), 56.25# (C-9), 39.47 (C-10), 21.43 (C-11), 30.07 (C-12), 136.39 (C-13), 119.25 (C-14), 12.43 (C-15), 23.32 (C-16), 107.61 (C-17), 27.04 (C-18), 65.02 (C-19), 15.24 (C-20); MS *m/z* (rel. int.): 290 (M^+, 0.8%), 275 (4), 259 (10), 203 (1), 189 (4), 177 (6), 163 (5), 135 (10), 121 (12), 107 (20), 95 (28), 91 (24), 81 (27), 79 (27), 69 (25), 67 (28), 55 (46), 41(100).

Labda-8(17),13*E*/*Z*-dien-19-al (16)

To a stirred solution of **15** (396 mg, 1.37 mmol) in acetone (5 ml), a 2.67 M solution of *Jones* reagent was added dropwise at 0°C till starting material was consumed. The mixture was filtered, evaporated and extracted with Et_2O (3x20 ml). Organic layers were dried over anh. Na_2SO_4 and evaporated to yield a crude

*,#These assignments are interchangeable.

(370 mg; **16** represents 75% of the crude). ^{1}H NMR (80 MHz): corresponding to the *E* isomer: δ 0.57 (3H, *s*, Me-10), 1.01 (3H, *s*, Me-4), 1.55 (3H, *d* , 6.0, Me-14), 1.58 (3H, *br s*, Me-13), 4.56 (1H, *br s*, H-17), 4.87 (1H, *br s*, H'-17), 5.15 (1H, *br q*, 6.0, H-14), 9.72 (1H, *br s*, H-19).

Labda-8(17),13*E/Z*-diene (17)

A mixture of crude **16** (290 mg, 1.00 mmol), $N_2H_4 \cdot H_2O$ (440 mg, 8.80 mmol), powdered KOH (580 mg, 10.36 mmol) and triethylene glycol (15 g) was refluxed under argon for 4 h. Following the same work-up used to prepare **2**, the resulting crude was purified by column chromatography to afford **17** (167 mg, 61%, hexane): oil; IR (neat): ν 3079, 1640, 888 (C=CH_2); ^{1}H NMR (80 MHz): corresponding to the *E* isomer: δ 0.65 (3H, *s*, Me-10), 0.77 (3H, *s*, Meβ-4), 0.85 (3H, *s*, Meα-4), 1.55 (3H, *d*, 6.0, Me-14), 1.58 (3H, *br s*, Me-13), 4.52 (1H, *br s*, H-17), 4.81 (1H, *br s*, H'-17), 5.12 (1H, *br q*, 6.0, H-14); MS *m/z* (rel. int.): 274 (M^+, 3%), 259 (11), 204 (1), 189 (3), 163 (5), 149 (5), 137 (12), 121 (10), 109 (14), 95 (30), 81 (33), 69 (36), 55 (42), 41 (100).

ACKNOWLEDGMENTS

We thank the *Junta de Andalucía* for their financial support.

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