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Article

A Convenient Preparation of Ambergris Odorants from Copalic Acid

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Descrevemos neste trabalho as sínteses de odoríferos de âmbar gris: *ent*-epi-8-ambracetal (**7**), *ent*-ambrox (**10**) e dois óxidos **13** e **14**, a partir do ácido copálico (**2a**).

The syntheses of the ambergris odorants *ent*-epi-8-ambraketal (**7**), *ent*-ambrox (**10**), and two oxides **13** and **14** starting from copalic acid (**2a**) are described.

Keywords: *copalic acid, ambergris odorant,* ent-*ambrox,* ent-*epi-8-ambraketal*

Introduction

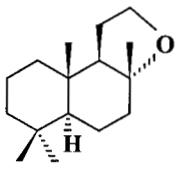
Ambergris is a metabolic product of the sperm whale (*Physeter macrochephallum*) and is considered one of the most valuable animal perfumes besides civet, musk and castoreum[1]. Due to enforced whale protection, the use of ambergris in perfumery has been abolished, thus encouraging chemists to search for new synthetic substitutes. (-)-Tetranorlabdane oxide (**1**) is one of the commercially important products, synthesized for the first time by Stoll and Hinder in 1950[2], which is more commonly known under the trade names Ambrox (Firmenich), Amberlyn (Quest) and Ambroxan (Henkel)[3].

The great interest and importance of ambergris derivatives nowadays can be demonstrated by the increasing number of recent publications on this topic[4].

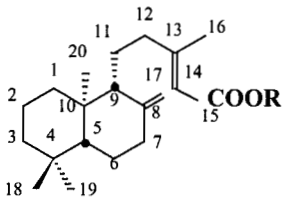
Many of the total syntheses have been developed either in a racemic[5] or optically active form[6], although the most successful asymmetric syntheses have started from naturally occurring sesqui or diterpenes such as (-)-drimmenol[7], (-)-levopimaric acid[8], (-)-labdanolic acid[9], (-)-abietic acid[10], (-)-communic acid[11], (+)-*cis*-abienol[4c], (+)-manool[12], manoyl oxide[13] , and (-)-sclareol[4a,14]. Continuing a program to develop our project, where resinic acid was used as the chiral starting material for stereocontrolled synthesis of the optically active compounds[15], we undertook the synthesis of *ent*-ambrox (**10**), *ent*-epi-8-ambraketal (**7**) and two oxides **13** and **14** starting from copalic acid (**2a**)[16].

Results and Discussion

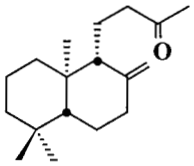
As can be seen in Scheme 1 and Scheme 2, the epoxy-ketone **6** is the key intermediate for the synthesis of **7**, **10**, **13** and **14**. This intermediate could be prepared in two steps following the known procedure, *i.e.*, $KMnO_4$ oxidative degradation of the side chain of **2a**, followed by stereospecific epoxidation of the exocyclic methylene double bond of **3** with *m*CPBA[17]. In our case, the best results obtained



1
(-)-Ambrox



2a R= H
2b R= CH_3



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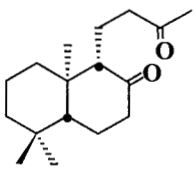
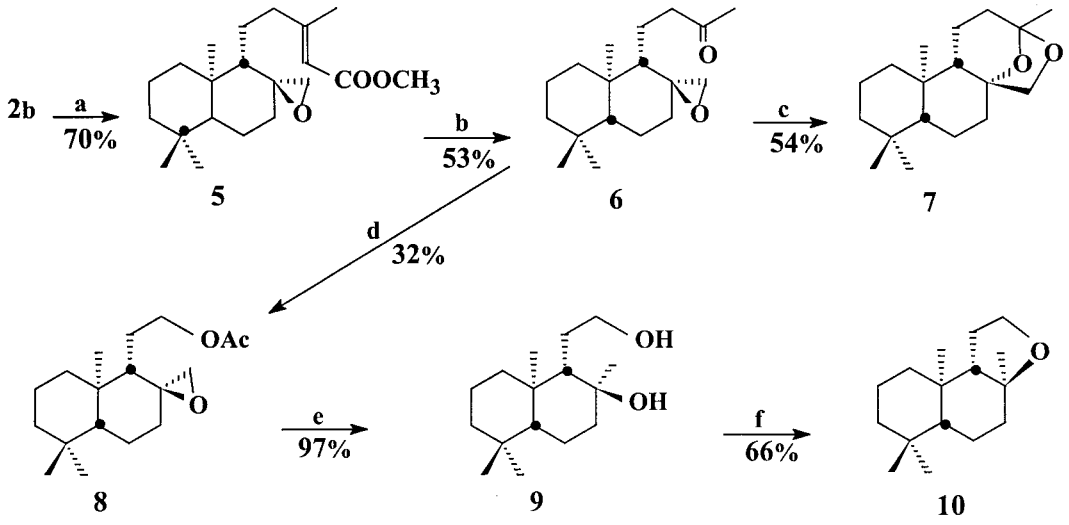


4

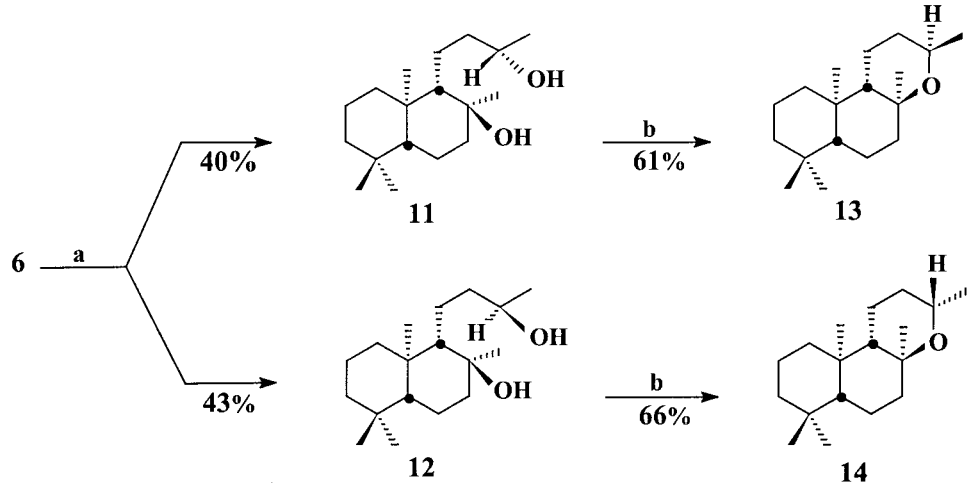
was 25% overall yield, and although it has not been previously mentioned in the literature, the diketone **4** was always isolated in an approximately 15% yield, along with unreacted starting material (10-15%). Thus, to avoid further oxidation of the exocyclic methylene group, methyl copalate (**2b**) was first epoxidized with *m*CPBA (Scheme 1), followed by ozonolysis of the resulting epoxide **5** in methylene chloride at -78 °C, to afford **6** in a ~37% overall yield[18]. In the next step, a benzene solution of **6** was treated with *p*-TsOH affording the expected *ent*-epi-8-ambraketal **7**[19] in a 54% yield.

In order to begin the synthesis of *ent*-ambrox (**10**) (Scheme 1), the epoxy-ketone **6** was submitted to the Baeyer-Villiger reaction with *m*CPBA[11a]. The progress of the reaction was monitored by TLC, and after 7 days, the epoxy-acetate **8** was obtained in a 32% yield along with recovered starting material (30%). Following the sequence, the reduction of **8** with $LiAlH_4$ in THF furnished the diol **9** in a 97% yield, which was treated with MsCl and pyridine in benzene, affording the *ent*-ambrox (**10**)[20] in a 66% yield.

For the synthesis of oxides **13** and **14** (Scheme 2) the epoxy-ketone **6** was reduced with $LiAlH_4$ in THF[21], leading to a C-13 epimeric mixture of diols **11** and **12**. The mixture was easily separated by silica-gel column chromatography to furnish **11** and **12** in 40% and 43% yields, respectively. The stereochemistry at C-13 of the diols **11** and **12** was established by the comparison of the physical and spectral data with those reported for their enantiomers[9], and also by analysis of the ^1H- and ^{13}C-NMR data of the oxides **13** and **14**. Finally, using the same conditions employed for the cyclization of **9** to **10**, the diols **11** and **12** were converted separately to the oxides **13** and **14** in 61% and 66% yields, respectively. The physical constants and spectral data of these oxides are in good agreement with



Scheme 1: **(a)** *m*-CPBA, CH_2Cl_2; **(b)** O_3, CH_2Cl_2 then Me_2S; **(c)** TsOH, Bz; **(d)** *m*-CPBA, CH_2Cl_2; **(e)** $LiAlH_4$, THF; **(f)** MsCl, Py, Bz.



Scheme 2: **(a)** $LiAlH_4$, THF; **(b)** MsCl, Py, Bz.

those reported for their respective enantiomes[9]. Taking into account that cyclization of diols **11** and **12** with MsCl-pyridine proceeds through an S_N2 mechanism, the stereochemistry of **13** and **14** at C-13 should be assigned as depicted in the structure.

In summary, we have described a two-step synthesis of the epoxy-ketone **6**, starting from copalic acid (**2a**), an important intermediate for the synthesis of the ambergris odorant derivatives **7**, **10**, **13** and **14**. It is worth mentioning that compounds **7** and **10**, which belong to the *ent*-labdane series, are known to have characteristic olfactory properties[20,22].

Experimental Details

^{1}H- and ^{13}C-NMR spectra were recorded in a $CDCl_3$ solution at 300 MHz and 75.5 MHz, respectively, with a Bruker spectrometer. IR spectra of neat samples were obtained with a Perkin-Elmer 1600 series FT-IR. Elemental analyses were performed with a Perkin-Elmer 2400 CHN analyzer. Melting points were determined on a Reichert-Kofler hot stage and are uncorrected. Optical rotations were measured with a Carl Zeiss photoelectric polarimeter.

Methyl 8β,17-epoxy-copalate (5)

m-Chloroperoxybenzoic acid (50%, 420 mg, 1.21 mmol) was added to a stirred solution of **2b** (320.0 mg, 1.0 mmol) in dry dichloromethane. After the mixture was stirred overnight at room temperature, it was diluted by adding dichloromethane (30 mL), washed with 10% aqueous sodium hydrogen carbonate solution (3 x 30 mL), followed by saturated aqueous sodium chloride, dried with anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica-gel chromatography [n-hexane/ethyl ether (7:3)] to give **5** (237.0 mg, 70%): $[\alpha]_D^{23}$ -101.5 (c 0.8, $CHCl_3$). - IR (film) 1720, 1649, 1224, 1148 cm^{-1}; ^{1}H-NMR δ 0.80 (s, 3H), 0.83 (s, 3H), 0.90 (s, 3H), 2.13 (s, 3H), 2.50 (d, J = 4.32 Hz, 1H), 2.70 (d, J = 4.32 Hz, 1H), 3.68 (s, 3H), 5.65 (s, 1H); ^{13}C-NMR (Table 1).

Table 1. ^{13}C-NMR data of compounds **2b, 5-14** (δ, $CDCl_3$, 75.5 MHz)[a].

Carbon	5	6	7	8	9	10	11	12	13	14
1	39.0	39.1	40.2	39.0	39.4	39.8	39.9	39.7	39.2	39.2
2	18.7	18.7	18.5	18.7	18.5	18.4	18.4	18.4	18.6[b]	18.6
3	41.9	42.0	42.1	42.0	42.0	42.5	42.0	42.1	42.1	42.1
4	33.5	33.5	33.3	33.5	33.3	33.1	33.2	33.3	33.3	33.3
5	55.1	55.1	55.0	55.2	56.1	57.3	56.2	56.1	56.5	56.6
6	21.9	21.9	19.3	21.9[b]	20.5	20.7	20.6[b]	20.6	20.0	20.1
7	36.5	36.7	33.8	36.4	44.2	40.0	40.7	42.3	42.2	43.3
8	58.9	59.6	81.9	58.8	73.1	79.9	74.6	74.8	74.8	74.9
9	53.4	53.3	50.5	50.6	59.4	60.2	58.2	61.6	57.4	53.1
10	40.4	40.4	38.6	40.1	39.0	36.2	39.2	39.2	36.8	37.2
11	20.0	16.1	17.0	21.6[b]	27.9	22.7	20.0[b]	22.2	18.7[b]	15.4
12	42.5	45.2	35.4	65.7	64.1	65.0	44.2	44.2	35.4	30.4
13	160.9	209.5	108.7	-	-	-	65.3	69.9	65.5	66.3
14	115.0	-	-	-	-	-	-	-	-	-
15	167.3	-	-	-	-	-	-	-	-	-
16	19.0	29.9	25.1	-	-	-	24.7	24.3	20.8	26.3
17	50.7	50.9	76.3	50.7	24.6	21.2	23.2	23.9	22.7	23.5
18	33.5	33.6	33.9	33.6	33.5	33.6	33.4	33.4	33.5	33.5
19	21.7	21.7	21.9	21.7	21.5	21.2	21.5	21.5	21.4	21.5
20	14.6	14.6	16.5	14.7	15.4	15.1	15.3	15.3	15.6	15.5
-OCH_3	50.7	-	-	-	-	-	-	-	-	-
-C=O				171.3						
-CH_3				21.1						

a) Assignments were supported by DEPT NMR experiments.
b) Assignments within a column may be interchanged.

Ent-14,15-dinor-8α,17-epoxy-labdane (6)

A stirred solution of **5** (82.0 mg, 0.24 mmol) in dry dichloromethane (20.0 mL) was slowly bubbled with a O_3/O_2 mixture at -78 °C until the solution became light blue. The excess of ozone was eliminated by bubbling nitrogen and the ozonide was reduced by adding an excess of dimethylsulfide (0.2 mL, 2.7 mmol), and the mixture was being stirred at room temperature for 3 h. The mixture was diluted with dichloromethane (20 mL) and washed with saturated aqueous sodium chloride solution (3 x 30 mL), dried with anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica-gel chromatography [n-hexane/ethyl ether (93:7)] to afford epoxy-ketone **6** (36.8 mg, 54%): $[\alpha]_D^{23}$ -19.5 (c 4.4, $CHCl_3$), {lit.[23] for enantiomer $[\alpha]_D$ +9.0}; IR (film) 1716, 967, 893, 833 cm^{-1}; ^{1}H-NMR δ 0.82 (s, 3H), 0.83 (s, 3H), 0.89 (s, 3H), 2.09 (s, 3H), 2.49 (d, J = 4.5 Hz, 1H), 2.82 (d, J = 4.5 Hz, 1H); ^{13}C-NMR (see Table 1); MS m/z (rel.int.) 278 (M^+, 4), 137(31), 175(32), 218(58), 43(100). Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: 77.66; H, 10.46.

Ent-14,15-dinor-13(R),8β,13,13,17-dioxido-labdane (ent-epi-8-ambra-ketal) (7)

A catalytic amount of *p*-toluenesulfonic acid (1.3 mg) was added to a stirred solution of **6** (21.1 mg, 0.08 mmol) in dry benzene (3 mL), at room temperature. After the reaction mixture was stirred for 5 h, it was diluted with dichloromethane (30 mL) and washed with 10% aqueous sodium bicarbonate solution (3 x 30 mL), followed by saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica-gel chromatography [n-hexane/ethyl ether (7:3)] to give **7** (11.3 mg, 54%) as a colorless crystal: m.p. 103-105°C; $[\alpha]_D^{23}$ +3.7 (c 2.3, $CHCl_3$), {lit.[22a] m.p. 123-124 °C; $[\alpha]_D^{20}$ +5.7}; IR (KBr) 1385, 1364, 1231, 1213, 1145, 1113, 1035, 1025 cm^{-1}; ^{1}H-NMR δ 0.87 (s, 3H), 0.88 (s, 3H), 1.09 (s, 3H), 1.42 (s, 3H), 3.32 (d, J = 6.90 Hz, 1H), 3.77 (d, J = 6.90 Hz, 1H); ^{13}C-NMR (Table 1). Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.67; H, 10.70.

Ent-13,14,15,16-tetranor-12-acetoxy-8α,17-epoxy-labdane (8)

$NaHCO_3$ (316 mg, 3.76 mmol) and *m*CPBA (60%, 316 mg, 3.76 mmol) was added to a solution of **6** (522.5 mg, 1.48 mmol) in dry dichloromethane (10 mL), and the reaction was left to stand in the dark at room temperature. The reaction was monitored by TLC and progress was stabilized after seven days. The reaction mixture was then diluted with dichloromethane (30 mL), washed with 10% aqueous sodium bicarbonate solution (3 x 30 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica-gel chromatography [n-hexane/ethyl ether (7:3)] to recover the starting material (158 mg, 30%) and to afford **8** (122 mg, 32% based on reacted material): $[\alpha]_D^{23}$ -3.0 (c 2.8, $CHCl_3$); IR (film) 1736, 1246, 1038 cm^{-1}; ^{1}H-NMR δ 0.81 (s, 3H), 0.83 (s, 3H), 0.90 (s, 3H), 2.03 (s, 3H), 2.51 (d, J = 4.50 Hz, 1H), 2.75 (d, J = 4.50 Hz, 1H), 4.02 (m, 2H); ^{13}C-NMR (Table 1). Anal. Calcd. for $C_{18}H_{30}O_3$: C, 73.43; H,10.27. Found: C, 73.55; H, 9.87

Ent-13,14,15,16-tetranor-8α,12-labdanediol (9)

A solution of **8** (60.5 mg, 0.2 mmol) in dry tetrahydrofuran (3 mL) was added by drops to a stirred suspension of $LiAlH_4$ (16.0 mg, 0.4 mmol) in dry tetrahydrofuran (5 mL), at room temperature under argon. The reaction was then refluxed for 12 h, and after cooling at room temperature, the excess of hydride was destroyed by the careful addition of 15% aqueous sodium hydroxide solution. The solid was removed by filtration through a Celite pad, the organic phase was dried with anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica-gel chromatography [n-hexane/ethyl acetate (7:3)] to give diol **9** (47.4 mg, 97%): m.p. 112-113 °C, $[\alpha]_D^{23}$ +5.1 (c 3.3, $CHCl_3$), {lit.[17] for enantiomer m.p. 130-131 °C; $[\alpha]_D^{20}$ -17.0}; IR (KBr) 3242, 1386, 1083, 1053 cm^{-1}; ^{1}H-NMR δ 0.79 (s, 6H), 0.87 (s, 3H), 1.19 (s, 3H), 3.47 (m, 1H), 3.74-3.79 (m, 1H); ^{13}C-NMR (Table 1).Anal. Calcd. for $C_{16}H_{30}O_2$: C, 75.54, H, 11.89. Found: C, 75.93, H, 11.51.

Ent-13,14,15,16-tetranor-8α,12-epoxy-labdane (ent-ambrox) (10)

Methanesulfonyl chloride (0.05 mL) was added to a stirred solution of **9** (68.6 mg, 0.29 mmol) in dry benzene (1.4 mL) and pyridine (0.3 mL) under argon. The reaction mixture was refluxed for 12 h, and after cooling it was poured into water (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic phase was washed with 2 N aqueous hydrochloric solution (3 x 30 mL), followed by saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica-gel chromatography [n-hexane/ethyl acetate (9:1)] to give *ent*-ambrox (**10**) (45.3 mg, 66%). m.p. 69-70°C; $[\alpha]_D^{23}$ +8.5 (c 2.0, $CHCl_3$), {lit.[20] $[\alpha]_D^{20}$ +21.7; lit.[7a] for enantiomer m.p. 75-76°C; $[\alpha]_D^{22}$ -26.0}; IR (KBr) 1458, 1380, 1129, 1007, 978 cm^{-1}; ^{1}H-NMR δ 0.83 (s, 3H), 0.84 (s, 3H), 0.87 (s, 3H), 1.08 (s, 3H), 3.78-3.95 (m, 2H); ^{13}C-NMR (Table 1); Anal. Calcd. for $C_{16}H_{28}O_2$: C, 81.29, H, 11.94. Found: C, 81.24, H, 11.65.

Ent-14,15-dinor-8α,13(S,R)-labdanediols (11 and 12)

A solution of **6** (408.4 mg, 1.46 mmol) in dry tetrahydrofuran (10 mL) was added by drops to a stirred suspension of $LiAlH_4$ (111.4 mg, 2.94 mmol) in dry tetrahydrofuran (40 mL) at room temperature under argon. The mixture was refluxed for 12 h, and after cooling at room temperature, the excess of hydride was destroyed by the careful addition of 15% aqueous sodium hydroxide solution. The solid was removed by filtration through a Celite pad, and the ether solution was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give **11** [165.8 mg, 40%, n-hexane/ethyl acetate (7:3)] and **12** [179.7 mg, 43%, n-hexane/ethyl acetate (1:1)]. *Ent*-14,15-dinor-8α,13(R)-labdanediol **11**. m.p. 118-119°C; [α] +11.0 (c 2.3, $CHCl_3$), {lit.[9] for enantiomer m.p. 102-103°C; $[\alpha]_D$ -38.6}; IR (film) 3319, 1385, 1133, 1088, 939, 912, 740 cm^{-1}; ^{1}H-NMR δ 0.79 (s, 3H), 0.81 (s, 3H), 0.87 (s, 3H), 1.16 (s, 3H), 1.18 (d, J = 6.30 Hz, 3H), 2.56 (bs, 2H), 3.92 (m, 1H); ^{13}C-NMR (see Table 1); *ent*-14,15-dinor-8α,13(S)-labdanediol **12**. m.p. 123-124°C; $[\alpha]_D^{23}$ -3.4 (c 2.5, $CHCl_3$), {lit.[9] for enantiomer m.p. 112-113°C; $[\alpha]_D$ +6.4}; IR (film) 3355, 1459, 1388, 1130, 1082, 938, 740 cm^{-1}; ^{1}H-NMR δ 0.78 (s, 6H), 0.86 (s, 3H), 1.15 (s, 3H), 1.16 (d, J = 6.0 Hz, 3H), 3.05 (bs, 2H), 3.78 (m, 1H); ^{13}C-NMR (Table 1).

Ent-14,15-dinor-8α,13(S)-epoxy-labdane (13)

Diol **11** (93.5 mg, 0.33 mmol) was cyclized according to the previous experiment for *ent*-ambrox, to give oxide **13** (53.1 mg, 61%). m.p. 56-58 °C; $[\alpha]_D^{23}$ +3.4 (c 2.5, $CHCl_3$), {lit.[24] for enantiomer m.p. 78-79 °C; $[\alpha]_D^{20}$ -9.0; lit.[9] $[\alpha]_D$ -9.5}; IR (KBr) 1456, 1384, 1098, 958 cm^{-1}; ^{1}H-NMR δ 0.74 (s, 3H), 0.80 (s, 3H), 0.86 (s, 3H), 1.08 (d, J = 6.30 Hz, 3H), 1.24 (s, 3H), 3.72 (m, 1H); ^{13}C-NMR (Table 1); Anal. Calcd. for $C_{18}H_{32}O$: C, 81.75; H, 12.20. Found: C, 81.92, H, 12.33.

Ent-14,15-dinor-8α,13(R)-epoxy-labdane (14)

Following the same procedure, diol **12** (134.8 mg, 0.48 mmol) was cyclized to give oxide **14** (57.4 mg, 66%). $[\alpha]_D^{23}$ -7.4 (c 2.1, $CHCl_3$), {lit.[24] for enantiomer $[\alpha]_D^{20}$ +19.0; lit.[9] $[\alpha]_D$ +18.0}; IR (film) 1458, 1376, 1075, 975 cm^{-1}; ^{1}H-NMR δ 0.80(s, 6H), 0.86(s, 3H), 1.14(d, J = 6.60 Hz, 3H), 1.22(s, 3H), 3.97(m, 1H); ^{13}C-NMR (Table 1); Anal. Calcd. for $C_{18}H_{32}O$: C, 81.75; H, 12.20. Found: C, 81.95; H, 12.31.

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