A short synthesis of diastereomeric norambraketals

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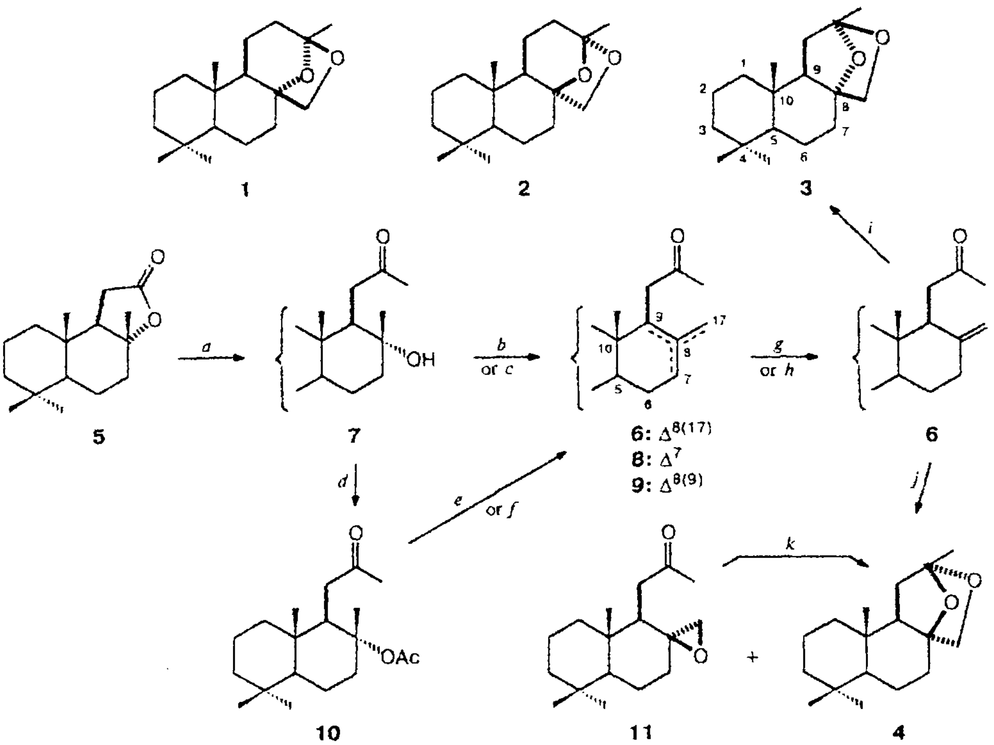
A short synthesis of diastereomeric norambraketals was accomplished starting from norambreinolide. The reaction of norambreinolide with methyllithium followed by dehydration of the obtained 8α-hydroxy-14,15,16-trinorlabdan-12-one gave 14,15,16-trinorlabd-8(17)-en-12-one. Oxidation of the latter with OsO_4 or peracids with subsequent isomerization of the formed epoxy ketone leads, respectively, to (12*R*)-8α,12:12,17- and (12*S*)-8β,12:12,17-diepoxy-14,15,16-trinorlabdans. Only the former is fragrant and possesses ambergris odor.

Key words: norambraketals, norambreinolide, 14,15,16-trinorlabd-8(17)-en-12-one, synthesis, oxidation, ambergris odor.

Ambraketal (**1**) belongs to compounds with the most intense ambergris odor. At the same time, its diastereomer (**2**) has no odor.[1] The norambraketal (**3**) recently synthesized (Scheme 1) also possesses a strong ambergris odor.[2] From the viewpoint of studying the dependence of odor on the structure, it was of interest to synthesize compound **4**, a diastereomer of norambraketal **3**.

Scheme 1



Reagents, conditions, yields: *a.* MeLi, Et_2O, 67%; *b.* $POCl_3$, Py, 76%, **6** : **8** : **9** = 55 : 36 : 9; *c.* $(COCl)_2$, DMSO, 79%, **6** : **8** : **9** = 73 : 20 : 7; *d.* AcOCl, $C_6H_5NMe_2$, 84%; *e.* 200 °C (760 Torr), 1 min, 91%, **6** : **8** : **9** = 52 : 30 : 18; *f.* DMSO, $NaHCO_3$, 150 °C, 12 h, 100%, **6** : **8** : **9** = 85 : 10 : 5; *g.* 1) *o*-$C_6H_4(CO_2H)CO_3H$, $NaHCO_3$, Et_2O, 4 °C, 48 h; 2) column chromatography(CC) on SiO_2; *h.* CC on SiO_2; *i.* OsO_4—$K_3[Fe(CN)_6]$, 40%; *j.* MCPBA, 10.4% **4** + 81% **11**; *k.* catalysts: $ZnCl_2$ (84.7%), SiO_2 (81%), H_3BO_3/SiO_2 (80%), Al_2O_3 (78%), Nafion (H^+) (75%).

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In this report, we describe the synthesis of ketals **3** and **4** from norambreinolide (**5**), which is an accessible product of decomposition of many labdan diterpenoids[3] (see Scheme 1). It is noteworthy that the direct precursor of norambraketal 3, 14,15,16-trinorlabd-8(17)-en-12-one (**6**), has been previously synthesized from lactone **5** along a rather complex route involving eight steps.[2]

Synthesis of norambraketal (3). We obtained ketone **6** from norambreinolide **5** in two steps. Lactone **5** was transformed into hydroxyketone **7** by the action of MeLi.[4] Hydroxyketone **7** was dehydrated to Py by the action of either $POCl_3$ or Swern's reagent.[5] Mixtures of isomeric olefins **6**, **8**, and **9** were formed in which isomer **6** with the exocyclic double bond was predominant. However, the content of unsaturated ketone **6** in these mixture was, according to the data of NMR spectroscopy, only 42 and 58%, respectively. Therefore, we also studied an indirect method of the transformation of hydroxyketone **7** into unsaturated ketone **6** by the pyrolytic elimination of acetic acid from acetoxyketone **10** obtained in a high yield by the acetylation of hydroxyketone **7** with AcCl in $PhNMe_2$. However, during the pyrolysis of acetoxyketone **10**, the content of isomer **6** in the mixture of ketones **6**, **8**, and **9** was low (52% according to the data of GLC and ^1H NMR spectrum). When acetic acid was eliminated from acetoxyketone **10** by heating it in a solution of DMSO[6] in the presence of sodium bicarbonate,[7] the yield of the desired ketone **6** and its content in the mixture of isomeric ketones reached 85%.

However, to simplify the chromatographic separation, we used a method similar to that described previously.[2] The treatment of the mixture of ketones **6**, **8**, and **9** with *o*-monoperoxyphthalic acid resulted in selective epoxidation of more substituted olefins **8** and **9**. The target ketone **6** was easily isolated in the individual state by chromatography of the reaction mixture on silica gel. Ketone **6** can be also isolated directly from a mixture containing less polar isomers **8** and **9** by column chromatography (CC) on silica gel.

The known norambraketal (**3**) was obtained by the oxidation of ketone **6** with a catalytic amount of OsO_4 in the presence of potassium ferricyanide as the co-oxidant. Unfortunately, its yield is half that for the oxidation of ketone **6** with OsO_4 and trimethylamine *N*-oxide.[2] This is most likely rationalized assuming that under conditions of oxidation by the $OsO_4-K_3[Fe(CN)_6]$ system, a portion of the intermediate osmate remains uncleaved. In fact, the reaction product contained, along with ketal **3**, another compound, whose ^1H NMR spectrum showed that it contained the methylketone group and no double bonds.

Synthesis of 8,12-diepinorambraketal (4). Epoxyketone **11** was needed for the synthesis of diastereomeric norambraketal **4**. This compound turned out to be very unstable and readily underwent subsequent transformations. For example, the epoxidation of unsaturated ketone **6** by *m*-chloroperoxybenzoic acid (MCPBA) in the presence of $NaHCO_3$ at room temperature gave a complex mixture of substances, whereas the lower-temperature epoxidation (4 °C) gave a mixture of the target epoxyketone **11** and a minor amount of the product of its isomerization, norambraketal **4**. The structure of epoxyketone **11** followed from the data of elemental analysis, IR and NMR spectra. The position of the signal of the $C(10)-CH_3$ group in the ^1H NMR spectrum indicates that it is deshielded by the epoxide oxygen atom at C(8) and, hence, the epoxide group of compound **11** has the β-configuration. This agrees with the fact of the exclusive formation of norambraketal **4** during the further isomerization of epoxyketone **11** under the action of various reagents. Lability of epoxyketone **11** explains the fact that the attempts to obtain it by the oxidation of ketone **6** by the urea complex with hydrogen peroxide[9] under different conditions always resulted in the formation of complicated mixtures of compounds, one of which was norambraketal **4**.

Epoxyketone **11** was isomerized under the action of various catalysts: $ZnCl_2$, silica gel impregnated with boric acid, Al_2O_3, and superacidic cation-exchange resin Nafion (H^+). In all cases, the reaction afforded (12*S*)-8β,12:12,17-diepoxy-14,15,16-trinorlabdan (**4**) in a high yield. Diastereomeric ketal **3** was not observed. Organoleptic testing showed that norambraketal **4** had no odor.

Thus, we accomplished a relatively simple and short synthesis of diastereomeric norambraketals **3** and **4** from norambreinolide (**5**) and established that their organoleptic properties were approximately the same as those for their higher analogs: diastereomeric ambraketals **1** and **2**, namely, the stereoisomer with the α-directed oxymethylene bridge had no odor.

Experimental

Melting points were determined on a Boetius heating table. IR spectra were recorded on a Specord 71 IR instrument in CCl_4. ^1H NMR spectra were recorded on Bruker AC-80 and Varian GMM 300 spectrometers in $CDCl_3$ using $SiMe_4$ as the internal standard. Silica gels (SiO_2, brands L (40/100 and 100/160 μm) and Across (60/200 μm)) and neutral alumina (II degree activity according to Brockmann) were used for column chromatography. To prepare silica gel impregnated with H_3BO_3, a solution of H_3BO_3 (50 mg) in distilled water (1 mL) was added to SiO_2 (1 g, Across brand, 60/200 μm); the mixture was stirred at ~20 °C for 5 min; water was evaporated on a water bath in the vacuum of a rotary evaporator. Impregnated SiO_2 was activated at 110 °C for 5 h. Home-made plates with SiO_2 (LS brand, 5/40 μm) containing 13% gypsum were used for TLC. GLC analysis was carried out on a Chrom-5 chromatograph (flame-ionization detector, glass column 3500×3 mm, 3% Apieson-L on Chromaton H-AW-HMDS (0.16—0.2 mm), helium as the carrier gas). Solutions of substances in organic solvents were dried using anhydrous Na_2SO_4. Solvents were evaporated *in vacuo*.

8α-Acetoxy-14,15,16-trinorlabdan-12-one (10). AcCl (118 mg, 0.107 mL, 1.5 mmol) was added dropwise with stirring to a solution of hydroxyketone **7** (0.4 g, 1.5 mmol) in anhydrous $PhNMe_2$ (1.2 mL) cooled to 5 °C. The mixture was stirred at

18 °C for 96 h, H_2O (5 mL) was added, and the mixture was extracted with Et_2O (3×5 mL). The ethereal extract was washed with a 10% solution of H_2SO_4 (5 mL) and water (2×5 mL), dried, and evaporated. The reaction product obtained (430 mg) was chromatographed on a column with SiO_2 (12 g). 8α-Acetoxy-14,15,16-trinorlabdan-12-one (**10**) was obtained in a 84% yield (398 mg) and eluted with a hexane—Et_2O (9 : 1) mixture; b.p. 73—74°C (from hexane). Found (%): C, 74.10; H, 10.52. $C_{19}H_{32}O_3$. Calculated (%): C, 74.03; H, 10.39. IR, ν/cm^{-1}: 1243 (OAc); 1728 (OAc + —C(=O)CH_3); 1363, 1384 (C$(CH_3)_2$). ^{1}H NMR, δ: 0.78 (s, 3 H, C(10)—CH_3); 0.83 and 0.88 (both s, 2×3 H, C(4)$(CH_3)_2$); 1.50 (s, 3 H, C(8)—CH_3); 1.86 (s, 3 H, OAc); 2.19 (s, 3 H, —C(=O)CH_3).

Oxidation of a mixture of ketones 6, 8, and 9 with *o*-monoperoxyphthalic acid. A solution of *o*-monoperoxyphthalic acid (1.32 mL, 0.97 mmol) in Et_2O was poured in a solution (cooled to 4 °C) of a mixture of ketones **6**, **8**, and **9** (400 mg, 1.61 mmol) obtained by the dehydration of hydroxyketone **7** with $POCl_3$ in Py [5] (the content of isomer **6** with the exocyclic double bond was ~55%), $NaHCO_3$ (16 mg, 2 mmol) was added, and the mixture was kept for 48 h at the same temperature. Then the mixture was diluted with water (5 mL) and extracted with Et_2O (3×5 mL). The ethereal extract was washed with a 1% solution of $NaHCO_3$ (5 mL) and water (5 mL), dried, and evaporated. The residue (450 mg) was chromatographed on a column with SiO_2 (14 g), eluting with a petroleum ether—Et_2O (49 : 1) mixture. 14,15,16-Trinorlabd-8(17)-en-12-one (**6**) (colorless liquid) was obtained (208 mg, 52%). IR, ν/cm^{-1}: 880, 1635, 3080 (C=CH_2); 1705 (C=O). ^{1}H NMR, δ: 0.70 (s, 3 H, C(10)—CH_3); 0.81 and 0.89 (both s, 2×3 H, C(4)$(CH_3)_2$); 2.15 (s, 3 H, C(=O)CH_3); 4.33 and 4.74 (both s, 2×1 H, >C=CH_2).

Pyrolysis of 8α-acetoxy-14,15,16-trinorlabdan-12-one (10). *A.* Ketoacetate **10** (121 mg, 0.39 mmol) was heated in a round-bottomed flask on a metallic bath at 200 °C (760 Torr) for 1 min, and the reaction product (95 mg) was chromatographed on a column with SiO_2 (3 g). A mixture of unsaturated ketones **8** and **9** (43.1 g, 44.1%) and then ketone **6** (45.9 mg, 47%) identical to the sample described above were eluted with a hexane—Et_2O (99 : 1) mixture. The overall yield of a mixture of ketones **6**, **8**, and **9** was 91.2%, and their ratio was 52 : 30 : 18 (GLC and NMR spectroscopy data).

B. $NaHCO_3$ (10 mg, 0.12 mmol) was added to a solution of ketoacetate **10** (36 mg, 0.12 mmol) in DMSO (1.4 mL, 21 mmol), and the mixture was heated at 150 °C for 12 h. The reaction mixture was diluted with water (5 mL) and extracted with Et_2O (3×3 mL). The extract was washed with 10% H_2SO_4 (2 mL) and water (2×2 mL), dried, and concentrated. A mixture of ketones **6**, **8**, and **9** was obtained (29 mg, 100%) in a ratio of 85 : 10 : 5 (according to the GLC data).

(12*R*)-8α,12:12,17-Diepoxy-14,15,16-trinorlabdane (3). OsO_4 (15.4 mg, 0.061 mmol), $K_3[Fe(CN)_6]$ (1.25 g, 3.8 mmol), and K_2CO_3 (0.525 g, 3.8 mmol) were added to a solution of ketone **6** (300 mg, 1.21 mmol) in a mixture of Bu^{t}OH (4 mL), Py (1 mL), and water (5 mL). The mixture was stirred at 40 °C for 48 h. Then Na_2SO_3 (0.107 g, 0.85 mmol) was added, and the mixture was stirred at 60 °C for 2 h. The reaction mass was diluted with water (10 mL) and extracted with Et_2O (3×10 mL). The ethereal extract was washed with 10% H_2SO_4 (10 mL) and water (2×10 mL), dried, and concentrated. The residue (0.225 g) was chromatographed on a column with SiO_2 (7 g). Crystalline ketal **3** (128 mg, 40%) was eluted with a hexane—Et_2O (99 : 1) mixture; m.p. 81—83 °C (from hexane). IR, ν/cm^{-1}: 845, 859, 1005, 1051, 1099 (C—O—C—O—C). ^{1}H NMR, δ: 0.82 (s, 3 H, C(10)—CH_3); 0.89 and 0.98 (both s, 2 3 H, C(4)$(CH_3)_2$); 1.61 (s, 3 H, C(12)—CH_3); 3.34 (d.d, 1 H, *J* = 7.2 and 1.9 Hz) and 4.30 (d, 1 H, *J* = 7.2 Hz) (C(17)—CH_2). These spectral data coincide with those published[2] for compound **3**. A compound (50 mg) was washed with a hexane—Et_2O (49 : 1) mixture. This compound was not studied but, according to the spectral data, it is an undecomposed osmate formed as an intermediate product during the oxidation of ketone **6** by osmic acid.

Epoxidation of 14,15,16-trinorlabd-8(17)en-12-one (6). *A.* 60% *m*-Chloroperoxybenzoic acid (0.3 mmol) and $NaHCO_3$ (84 mg, 1 mmol) were added at 4 °C to a solution of ketone **6** (90 mg) in CH_2Cl_2 (3 mL), and the mixture was stirred at the same temperature for 5 h. Water (10 mL) was added to the reaction mixture, and the mixture was extracted with CH_2Cl_2 (3×5 mL). The extract was washed with a 3% NaOH (5 mL) and water (3×5 mL), dried, and concentrated. The residue (95 mg) was chromatographed on a column with SiO_2 (3 g). Crystalline (12*S*)-8β,12:12,17-diepoxy-14,15,16-trinorlabdane (**4**) (10 mg, 10.4%) was eluted with hexane; m.p. 86—88 °C (from hexane). Found (%): C, 76.92; H, 10.80. $C_{17}H_{28}O_2$. Calculated (%): C, 77.27; H, 10.61. IR, ν/cm^{-1}: 869, 1013, 1096, 1178 (C—O—C—O—C). ^{1}H NMR, δ: 0.88 (s, 6 H, C(10) and C(4)—CH_3); 0.90 (s, 3 H, C(4)—CH_3); 1.58 (s, 3 H, C(12)—CH_3); 3.25 and 3.41 (both d, AB-system, 2 H, C(20)—CH_2, *J* = 6.4 Hz).

Liquid unstable 8α,17-epoxy-14,15,16-trinorlabdan-12-one (**11**) (77.6 mg, 81%) was subsequently eluted with hexane. Found (%): C, 76.81; H, 10.79. $C_{17}H_{28}O_2$. Calculated (%): C, 77.27; H, 10.61. IR, ν/cm^{-1}: 848, 896, 1032, 1155 (C—O—C), 1717 (C=O). ^{1}H NMR, δ: 0.83 (s, 6 H, C(10)— and C(4)—CH_3); 0.91 (s, 3 H, C(4)—CH_3); 2.13 (s, 3 H); 2.52 (d, 1 H, *J* = 4) and 2.66 (dd, 1 H, *J* = 4 and 1.5 Hz) (C(17)—CH_2).

B. Complex $H_2O_2 \cdot CO(NH_2)_2$[8] (12 mg, 0.2 mmol), Na_2HPO_4 (50 mg, 0.35 mmol), and Ac_2O (0.01 mL, 0.1 mmol) were added to a solution of ketone **6** (10 mg, 0.04 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at 20 °C for 48 h. Then water (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3×5 mL). The extract was washed with water (5 mL), 1% NaOH (3 mL), and water (3 mL), dried, and evaporated. The residue (16 mg) was a complex mixture of substances. The reaction does not occur at 4 °C or at 1 :1 substrate : reagent ratio. The replacement of Na_2HPO_4 with $NaHCO_3$ and Ac_2O with $(CF_3CO)_2O$ did not change the reaction course.

C. 85% HCOOH (0.08 mL) and 30% H_2O_2 (0.32 mL) were added with stirring to a solution of ketone **6** (100 mg, 0.4 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at 22 °C for 48 h and treated as indicated above (*B*). According to TLC, the product was a mixture of at least four substances. It was chromatographed on a column with SiO_2 (13 g). Ketal **4** (20 mg, 18.9%) was eluted with a hexane—Et_2O mixture. No other individual products were isolated. A similar complex mixture of substances is obtained when the oxidation product is saponified by refluxing with 10% alcoholic solution of NaOH.

Isomerization of epoxyketone 11 under the action of various reagents. *A.* $ZnCl_2$ (8.5 mg, 0.062 mmol) was added to a solution of epoxyketone **11** (165 mg, 0.62 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred at 12 °C for 0.5 h and filtered. The solvent was distilled off *in vacuo*. The residue (161 mg) was chromatographed on a column with SiO_2 (3 g) using a hexane—Et_2O (49 : 1) mixture to elute ketal **4** (139.7 mg, 84.7%).

B. SiO_2 (Across brand, 60/200 μm, 0.5 mg) was added to a solution of epoxyketone **11** (24.3 mg) in hexane (0.5 mL). The mixture was stirred at 20 °C for 12 h and worked up as usual to obtain ketal **4** (19.6 mg, 81%).

C. A solution of epoxyketone **11** (30 mg) in hexane (0.5 mL) was stirred at −20 °C for 6 h with SiO_2 (6 mg) impregnated with 5% H_3BO_3. The workup similar to that indicated afforded ketal **4** (24 mg, 80%).

D. A solution of epoxyketone **11** (30 mg) in hexane (0.5 mL) was stirred at 20 °C for 24 h with 11 mg of neutral Al_2O_3 (II degree of activity) to obtain ketal **4** (23.4 mg, 78%).

E. The cation-exchange resin Nafion (H^+) (5 mg) was added to a solution of epoxyketone **11** (47.8 mg) in hexane (1 mL). The mixture was stirred at 20 °C for 24 h to obtain ketal **4** (35.8 mg, 75%).

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