Synthesis of (±)-Geosmin. Part 1. On the Synthesis and Epoxidation of 1,4a-Dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one

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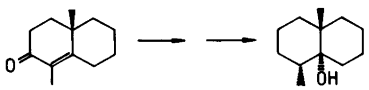
An improved method for the preparation of 1,4a-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one has been developed. This compound has been used as a key intermediate in several previous syntheses of geosmin. The regioselectivity in the alkylation of 2-methylcyclohexanone with ethyl vinyl ketone or 1-chloro-3-pentanone was investigated. The stereoselectivity in the epoxidation of the octalone† by hydrogen peroxide, *t*-butyl hydroperoxide and *m*-chloroperbenzoic acid was also studied. The results obtained were, to some extent, different from previous reports, both with respect to regio- and stereo-selectivity. The isolated yield of the octalone was 81–83 % as a 96:4 mixture with the 1,8-dimethyl isomer. Epoxidation of this material using *m*-chloroperbenzoic acid resulted in a 92:8 (α:β) mixture of epoxides, which also contained 4 % of the epoxide(s) from the 1,8-dimethyloctalone isomer(s). The isolated yield of epoxide mixture was 89 %.

In an on-going study of possible synthetic pathways to (±)-geosmin (**6**), it was necessary to prepare 1,4a-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (**1**) in substantial amounts. This compound has been used as a key intermediate in several previously reported total syntheses of **6**. The bicyclic tertiary alcohol **6** was of interest to us as a reference substance in a study of volatile mold metabolites. The structures of **1** and **6** are shown in Scheme 1.



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Scheme 1.

Initial experiments by us to prepare **1** – according to procedures given in Refs. 1 and 2 – showed that the regioselectivity obtained by these methods seems to have been overestimated, as we found that the isomeric 1,8-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (**2**) was also formed. In order to establish an optimum preparative-scale path to geosmin, we decided to reinvestigate these methods. This paper presents our findings and also some improvements to the procedure. Reported methods that were intially run, were: (a) the acid-catalyzed alkylation of 2-methylcyclohexanone (**3**) with 1-chloro-3-pentanone[1] (**4**) and (b) the alkylation of the imine derived from (**3**) and α-methylbenzylamine with ethyl vinyl ketone (**5**).[2–4] In (a), **1** is obtained after the initial alkylation product undergoes aldol condensation and dehydration under the conditions used. In (b) the alkylated imine has to be hydrolyzed and cyclized in subsequent steps (Scheme 2).

The preparation of **1** via regioselective alkylation of lithium enolates derived from **3** with alkyl 2-ethyl-4-iodo-2-butenoate has also been reported,[5] but the synthesis of the alkylating agent is tedious and made this method of little interest to us. An alkylation of the lithium enolates derived from **3** with **5** was included in our study to gain some insight into the regioselectivity under strongly basic conditions. A method described by Heathcock *et al.*,[6] is analogous to (a), but is described with methyl vinyl ketone as the alkylating agent. This method was also considered to be of interest when the alkylating agent was changed to **5**.

The target molecule **6** was then synthesized via the α-epoxide of **1**. Hence, we also wished to compare the diastereoselectivity of the epoxidation with different reagents: hydrogen peroxide[7] (H_2O_2), *t*-butyl hydroperoxide[8] (TBHP) and *m*-chloroperbenzoic acid (MCPBA).[2,9] The use of MCPBA was reported[2,9] during the course of this work, but our results differ.

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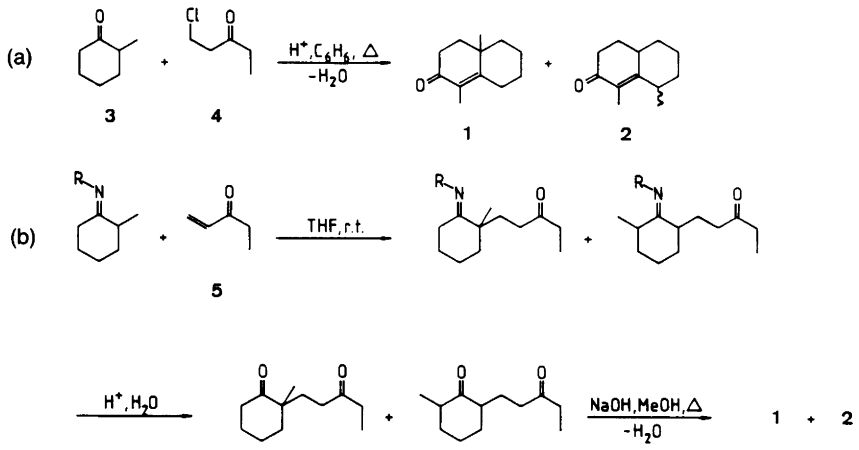
† Hexahydronaphthalenone.



Scheme 2.

Methods

The selected reactions were initially run in accordance with the references given in Table 1. In the reaction with enolates, the conditions were as given in Ref. 5, but with **5** as the alkylating agent instead of the alkyl 2-ethyl-4-iodo-2-butenoate. Cyclization of the initial products in the reactions with enolates and imines was carried out according to Ref. 2. The acid-catalyzed reaction, using **5** as the alkylating agent, was optimized with respect to the experimental variables (reaction temperature, amount of catalyst, addition time of **5** and the volume of solvent used for the dilution of **5**) prior to comparison with the other methods. Toluene was used as the solvent in this case to replace the toxic solvent benzene used in Ref. 6. Yields of the reactions were determined gravimetrically on isolated mixtures of **1** and **2**. Yields determined by gas/liquid chromatography (GLC) using internal standard techniques were considered to be less reliable with the multistep reactions. The best system was then further investigated with respect to an alternative optimization criterion, Table 2.

The epoxidation reactions were run as given in Refs. 7–9 (with some minor modifications, see the Experimental) and in Table 4. Conditions for the reactions with MCPBA are only briefly described in Ref. 9 and were hence investigated. The yields in the epoxidation reactions were determined both by isolation of the products and by GLC analyses.

Results

Octalone synthesis. The results summarized in Table 1 show that the conditions of entry 2 gives the highest regioselectivity. From the standpoint of convenience and yield, however, the conditions of entry 4 are to be preferred as this is a one-step procedure. Synthesis of **1** involving entry 2 is actually a four-step sequence. The ratio **1**:**2** in entry 3 was approximately the same as the ratio of the regioisomeric enol acetates used [10] (93:7 as determined by GLC). Considering the fact that **5** is about 20 times more expensive than **3**, calculated on a molar basis (this is also true for **4**), we have optimized the yield of **1** with respect to **5**. This was done by varying the excess of **3** with conditions as in entry 4, Table 1. The results of the optimization experiments are summarized in Table 2.

Table 1. Yield and regioselectivity obtained by different preparative modes.

Entry	Reference	Time/h[a]	Ratio **1**:**2**	Yield (%)[b]	Yield (%)[c]
1	1	18	95:5	54	58
2	2	30+12	98:2[d]	65[e]	67
3	2,5	2+12	92:8	32	–
4	6	20	96:4	62	–
5[f]	1	24	95:5	57	–

[a]The two figures given in entries 2 and 3 refer to the reaction times for the alkylation and the cyclization respectively. [b]Isolated yield of distilled **1**, based on **3**. [c]Reported yield by references. [d]A 94:6 ratio of initial alkylation products was observed prior to distillation. [e]Yield based on imine derived from **3** and α-methylbenzylamine. [f]The reaction was run under the same conditions as in entry 4 (see the Experimental).

Table 2. Yield of octalone when optimized with respect to ethyl vinyl ketone (**5**).

Entry	Equiv. **3**	Time/h	Yield (%)[a,b]
1	1.0	12	57
2	2.0	10	75
3	2.5	8	86
4	3.0	8	82
5[c]	2.5	24	67

[a]Yield determined by GLC with hexadecane as an internal standard. [b]Ratio **1**:**2** was unaffected by the use of an excess of **3**. [c]Experiment with **4**, under the best conditions found for **5**.

When the reaction was run on a 0.2 mol scale (with respect to **5**), an isolated yield of 81–83 % of pure distilled product was obtained. This can be compared with Ref. 1 where a yield of 35–40 % was obtained, based on the more expensive **4** rather than **3**.

Attempted separation of **1** *and* **2**. The analytical separation was easily achieved on several types of capillary GLC columns, see the Experimental. However, none of the earlier reports recognized the presence of **2** in the products obtained. We made unsuccessful attempt to separate the mixture both by TLC and distillation. By TLC the material appeared homogeneous both on silica and alumina plates with several eluent systems. Careful fractionation on both a 30- and 90-plate column did not alter the ratio of the constituents of the mixture to any significant extent (within the error of the GLC analysis).

Independent synthesis of **2**. So that the structure of **2** could be confirmed by NMR spectroscopy, this compound was prepared by an alternative method. The treatment of the lithium enolate from **3**, generated under conditions of kinetic control, with **5** at 0 °C, followed by cyclization of the initial alkylation product by the method given in Ref. 2, afforded a 91:9 mixture of **2**:**1** (GLC). ^{1}H NMR spectroscopy showed the expected methyl doublet at δ 1.08 (J = 7.4 Hz) and a methyl doublet at δ 1.82 (J = 2.3 Hz) which is consistent with the proposed structure. The spectrum does not contain any olefinic signals, which rules out both of the structures depicted below (Fig. 1) as the correct structure of **2**. Structures of the type given in Fig. 1 are often reported as products of a Robinson annulation.

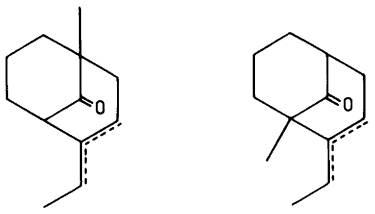


Fig. 1.

Table 3. Yield of octalone epoxides when the excess of MCPBA is varied.

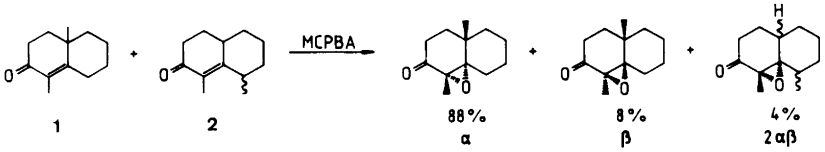
Entry	Equiv. MCPBA	Time/h	Unconv. **1** (%)[a]	Yield (%)[b,c,d]
1	1.20	20	4	85, (83)
2	1.35	15	2	87, (87)
3	1.50	10	–	91, (90)
4	1.65	6	–	84, (83)
5	1.50	10	–	89, (87)
6	1.50	10	–	89, (89)

[a,b]Determined by GLC with hexadecane as an internal standard. [c]Figures within parantheses refer to isolated yields. The isolated products in entries 1 and 2 contained 4 % and 2 % of **1**, respectively. [d]Stereoselectivity was 92:8 (α:β) in all cases and the product always contained 4 % epoxide derived from **2**.

Epoxidation. Epoxidation of the 96:4 mixture of **1**:**2** was carried out, varying the excess of MCPBA. The results are reported in Table 3 and in Scheme 3.

The yields and reaction times given in Table 3 are in agreement with those previously reported. However, the distilled final product was obtained as a 92:8 mixture of the α- and β-epoxides. This also contained 4 % of epoxide(s) derived from **2**. The reaction with MCPBA was further investigated in some buffered systems. This is summarized in Table 4, which also shows the results from the reaction with H_2O_2 and TBHP.

Table 4 confirms that improvement of the stereochemical outcome of the reaction with MCPBA can be accomplished, although at the expense of chemical yield. This result is probably due to a more rapid degradation of the undesired products compared with the degradation of the desired α-epoxide under the conditions used. The difference noted between entries 4 and 5 is an indication of the same phenomenon. In the case of TBHP, no reaction was observed even when the mixture was heated at reflux in methanol for 24 h.



Scheme 3.

Table 4. Yield and stereoselectivity of octalone epoxides with H_2O_2 and TBHP. Reactions with MCPBA in some buffered systems.

Entry	Conditions[a]	Time/h	Unconv. **1** (%)	Yield (%)[b]	α:β:2αβ[c]
1	Buffer A, MCPBA	20	34	61	84:11:5
2	Buffer B, MCPBA	10	7	77	90:7:3
3	Buffer C, MCPBA	10	–	48	95:3:2
4	MeOH, NaOH, H_2O_2	24	–	91	59:38:3
5	MeOH, NaOH, H_2O_2	24	–	70	70:28:2
6	MeOH, NaOH, TBHP	24	100	–	–
7	MeOH, NaOH, TBHP	24	100	–	–

[a]Buffer A: 50 ml 1 M $NaHCO_3$, B: 50 ml 1 M Na_2HPO_4, C: 25 ml 1 M NaH_2PO_4 and 25 ml 1 M Na_2HPO_4. The buffered reactions were run in the aqueous buffer and 25 ml dichloromethane at room temperature with 1.5 equiv. of MCPBA and with 5 mmol of **1**. Conditions in entries 4–7 are given in the Experimental section. [b]Entries 1–3: yield determined by GLC with hexadecane as an internal standard. 4–5: isolated yield (see the Experimental). [c]α,β and 2αβ refer to the α- and β-epoxide of **1** and the epoxide(s) derived from **2** respectively.

Discussion

Although the synthesis of **1** has been reported by several authors,[1,2,5,11] in no case was the formation of **2** mentioned. We have found upon re-examination that **2** was formed in all cases. The method given in Ref. 5 was not checked according to the original procedure. It is possible that the crystalline intermediates obtained by the original method could be purified by recrystallization, finally to give pure **1**. The unsuccessful attempts to separate **1** and **2** by TLC and distillation indicate that what was reported as pure **1** was most likely a mixture of **1** and **2**. The regioisomeric product composition is constant, regardless of the variation in the excess of **3** under acidic conditions (Table 2). This is to be noted since the use of an excess of **3** in the alkylation with methyl acrylate under basic conditions has been reported to give a significantly lowered regioselectivity.[12–14]

Our results of the epoxidation of the octalones with MCPBA are in conflict with those in Ref. 9. In our work we obtained a mixture of three compounds with a ratio of 88:8:4 (α:β:2αβ), whereas a mixture of two compounds in the ratio 96:4 (α:β) was reported in Ref. 9.

Conclusions

None of the methods investigated was found to be completely regioselective. A novel, rapid and economical procedure for the preparation of **1** could be established by optimization of the yield with respect to the more expensive component **5**. This method might be of use in other cases when cheap ketones are to be alkylated by expensive alkylating agents.

Experimental

General techniques. NMR spectra (^1H and ^{13}C) were recorded on a Bruker AC80 or a AC250 instrument, using deuteriochloroform as the solvent. Shift values are reported in ppm relative to Me_4Si. Mass spectra were obtained using an HP GS/MSD 5830/5970 system or a Finnigan 4500 instrument at 70 eV, and are reported as *m/z* (% relative intensity) [assignment]. IR spectra were recorded on a Perkin–Elmer 681 or a Philips PU 9706 spectrometer, and are reported in cm^{-1} (intensity s, m, w). GLC analyses were carried out on a Carlo-Erba Fractovap 4160 equipped with an FID. Capillary columns (30 m, 0.53 mm i.d.) coated with DB-5 (J&W), SPB-20 (Suppelco) or Supelcowax (Suppelco) were used. Peak areas were measured with a Milton Roy CI-10 or a Spectra Physics integrator. The columns used in the attempted fractionation of **1** and **2** were a Büchi spinning band column (30 plates) and a Fischer HMS 500 Spaltrohr column (90 plates). The number of plates refers to tests with mixtures of hydrocarbons in the boiling point range 98–102 °C and are given by the manufacturers.

Chemicals. All solvents (Merck) were of AR grade and were used without further treatment with the exception of tetrahydrofuran, which was dried by distillation from sodium–benzophenone under an argon atmosphere. Diisopropylamine (Merck) was distilled from calcium hydride. Butyllithium, 1.6 M and methyllithium, 1.6 M (Aldrich) were used as received. 2-Methylcyclohexanone (**3**) 98 % (Janssen), 1-chloro-3-pentanone (**4**) techn. > 95 % (GC) (Aldrich), ethyl vinyl ketone (**5**) 98 % (Fluka), 30 % hydrogen peroxide (H_2O_2) (Merck), 70 % *t*-butyl hydroperoxide (TBHP) (Janssen) and 70–75 % *m*-chloroperbenzoic acid (MCPBA) (Janssen) were also used as received. The MCPBA was assumed to have a 70 % content of oxidant.

Comments to the experiments given in Tables 1–4. Table 1. All reactions were run with 100 mmol of **3** or the corresponding imine or enol acetate. In entries 2 and 3 the intermediate alkylation products were isolated by fractional distillation (b.p. 120 °C/8 mmHg) prior to the cyclization step. The final product was isolated by removal of the methanol by evaporation under reduced pressure, extraction of the residue with hexane, washing with water and drying ($MgSO_4$). After removal of the volatiles, the prod-

uct was distilled under reduced pressure. Entries 4 and 5 were run as follows. 100 mmol of **3** (11.2 g) and 3 mmol of *p*-toluenesulfonic acid (0.57 g) in toluene (15 ml) were heated under reflux. To this mixture was added 125 mmol of **4** or **5** in toluene (20 ml) over an 8 h period. The heating was continued for 12–16 h. The isolation of the product is given in the Preparative section.

Table 2. Entries 1–5 were all run with 10 mmol of substrate. It was found that a shorter addition time of **5** could be allowed when a large excess of **3** was used. Thus, entries 2–5 were run with a 3 h addition time while entry 1 was run with an 8 h addition time. Control experiments, where all of the **5** was added on one amount Yielded only 48 % of the product.

Table 3. All reactions were performed with 5 mmol of substrate in 25 ml of dichloromethane at ambient temperature. Isolation of the product is given in the Preparative section.

Table 4. Entry 4 is identical with the experiment given in the Preparative section. Entry 5 was run in 100 ml of methanol but was otherwise identical with entry 4. Entry 6 was run with 10 mmol of **1** and 25 mmol of TBHP in 40 ml of methanol at room temperature. Entry 7 used the same conditions except that it was run at reflux temperature.

Preparative-scale procedures

1,8-Dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (**2**). To a stirred solution of 50 mmol of lithium diisopropylamide in dry tetrahydrofuran (50 ml) at 0 °C were added 49 mmol of **3** (5.5 g). After 30 min, 50 mmol of **5** (4.2 g) were added. The mixture was allowed to reach room temperature over a 2 h period. The reaction mixture was then hydrolyzed by the addition of 100 ml of saturated sodium hydrogencarbonate solution. The aqueous solution was extracted with several portions of diethyl ether. The ether extract was washed with three portions of water and then dried ($MgSO_4$). The diethyl ether was removed under reduced pressure. The residue was chromatographed on a silica column (hexane/ethyl acetate 95:5) and was further purified by Kugelrohr distillation, b.p. 120 °C/8 mmHg. This material was dissolved in methanol (50 ml) and 2 ml 5 M NaOH and refluxed for 12 h. The product was isolated as described above. Kugelrohr distillation afforded a 35 % yield (3.05 g) as a 91:9 mixture of **2** and **1**, b.p. 125–130 °C/8 mmHg.

1,4a-Dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (**1**). In a 250 ml round-bottomed flask equipped with a reflux condenser, a dropping funnel and a magnetic stirrer, were placed 500 mmol of **3** (56 g) and 10 mmol of *p*-toluenesulfonic acid (1.9 g) in toluene (50 ml). The mixture was heated to reflux and 200 mmol of **5** (17.1 g 98 %) in toluene (20 ml) were added dropwise over a 3 h period. The mixture was heated for an additional 5–6 h (the reaction was easily followed by GLC). After being cooled, the mixture was diluted with hexane (100 ml), washed with 5 M aqueous NaOH (100 ml) and water (100 ml). The volatiles were removed under reduced pressure (drying was not necessary because of the azeotropic removal of water during this step). The residual oil was distilled under reduced pressure through an efficient column. A forerun of **3** (23–25 g), b.p. 46–48 °C/8 mmHg, was collected after which **1** (28.8–29.5 g), b.p. 131–132 °C/8 mmHg, was collected as a colorless oil. The yield based on **5** was 81–83 %. The purity of **1** was 96 % by GLC with **2** as the only observed impurity.

1,4a-Dimethyl-1,8a-epoxyperhydronaphthalen-2-one. In a 500 ml Erlenmeyer flask with magnetic stirring were placed 56 mmol of **1** (9.97 g) in dichloromethane (0200 ml). To the stirred solution were added 84 mmol of solid MCPBA (20.7 g, 70 %), in portions over 15 min. The flask was stoppered and the solution stirred for 10 h, after which the reaction ws complete (as indicated by either GLC or TLC). A 5 M aqueous NaOH solution (100 ml) was then added to the flask, with continued stirring for 5 min. The dichloromethane layer was separated, washed with water (50 ml) and then returned to the flask. Another portion of 5 M NaOH (200 ml) was then added and the mixture was stirred for 15 h. The dichloromethane layer was separated, washed with water (50 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield an colorless oil 10.4 g (95 %). The crude oil was purified by Kugelrohr distillation, b.p. 125 °C/8 mmHg. An 89 % yield (9.72 g) of epoxide mixture was obtained (see the text). The purity was > 99 % by GLC. Distillation at 69 °C/0.15 mmHg by means of a 5 cm Vigreux column offered no advantage and no change in the isomeric ratio of the epoxide mixture was observed.

Epoxidation using H_2O_2. In a 500 ml Erlenmeyer flask were placed 50 mmol of **1** (8.90 g) and 5 M NaOH (10 ml) in methanol (200 ml). To the stirred mixture were added 175 mmol H_2O_2 (20 ml 30 %) over 30 min. The solution was stirred at ambient temperature for 24 h. The volatiles were removed under reduced pressure, the residue taken up in hexane (100 ml) and washed with water (050 ml). After drying ($MgSO_4$) and removal of the solvent, the crude product was distilled with a Kugelrohr apparatus, to yield 8.84 g (91 %) of a mixture of α- and β-epoxides as a colorless oil, b.p. 95 °C/2 mmHg or 125 °C/8 mmHg. The purity of the isomeric mixture was >95 % by GLC.

Physical properties of compounds

1,4a-Dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (**1**). B.p. 131–132 °C/8 mmHg ^{1}H NMR: δ 2.71 (m, 1 H), 2.45 (m, 2 H), 1.75 (d, J = 1.2 Hz, 3 H), 1.36 (m, 2 H), 1.22 (s, 3H) ^{13}H NMR: δ 199.2, 163.0, 129.3, 42.1, 37.7, 36.2, 33.8, 27.7, 26.6, 22.4, 21.4, 10.8 MS: 178 (100) [M^+],

163 (39), 136 (43), 122 (62), 121 (42), 107 (28), 79 (34) IR(neat): 2930(s), 2860(s), 1670(s), 1610(s), 1450(m), 1315(m).

1,8-Dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (**2**). B.p. 125–130 °C/8 mmHg. ^{1}H NMR: δ 3.08 (m, 1 H), 1.82 (d, J = 2.3 Hz, 3 H), 1.08 (d, J = 7.4 Hz, 3 H) ^{13}C NMR: δ 199.4, 163.5, 128.2, 36.4, 34.6, 34.1, 32.3, 31.9, 29.0, 19.5, 18.4, 9.8 MS: 178 (100) [M^+], 122 (92), 121 (55), 107 (56), 93 (59), 79 (76) IR(neat): 2930(s), 2860(s), 1670(s), 1610(m), 1455(m), 1330(m).

1,4a-Dimethyl-1α,8aα-epoxyperhydronaphthalen-2-one. B.p. 69 °C/0.15 mmHg 95 °C/2 mmHg or 125 °C/8 mmHg. ^{1}H NMR: δ 1.31 (s, 3 H), 1.00 (s, 3 H) ^{13}C NMR: 207.7, 71.7, 65.2, 38.0, 34.1, 33.2, 31.9, 26.2, 23.9, 20.8, 20.4, 11.1 MS(CI): 195 (55) [M^++1], 177 (100) EI: 194 (0.5) [M^+], 176 (14) [M^+-H_2O], 133 (16), 109 (100), 81 (25), 67 (49), 55 (24) IR(neat): 2940(s)m, 2870(m), 1705(s), 1450(m).

1,4a-Dimethyl-1β,8aβ-epoxyperhydronaphthalen-2-one. B.p. as the α-isomer above. ^{1}H NMR: 1.39 (s, 3 H), 1.15 (s, 3 H) MS(CI): 195 (27) [M^++1], 177 (100) 179 (85) EI: 176 (23) [M^+-H_2O], 151 (18), 133 (27), 109 (100), 81 (27), 67 (47).

1,8-Dimethyl-1,8a-epoxyperhydronaphthalen-2-one. B.p. as above isomers. MS(CI): 195 (7) [M^++1], 177 (100) EI: 194 (38) [M^+], 109 (71), 108 (87), 95 (57), 81 (93), 67 (92), 55 (100).

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