74. The Absolute Configuration of β-Bisabolol

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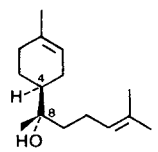
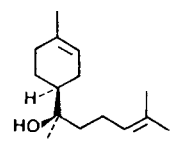
(21.I.86)

From bergamot oil (*Citrus bergamia* RISSO), (−)-(4*S*,8*R*)-8-epi-α-bisabolol (**2**) and (−)-(4*R*, 8*S*)-4-epi-β-bisabolol (**3**) were isolated. The absolute configuration of their stereoisomers **4** and **5** was established by an enantioselective synthesis starting from (−)-(*S*)-*p*-mentha-1,8-dien-4-ol.

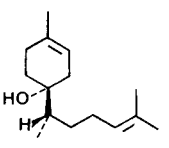
The bisabolols **1**–**3** are encountered relatively frequently in the sesquiterpene fraction of essential oils. (−)-(4*S*, 8*S*)-α-Bisabolol (**1**) in a concentration of up to 45% is contained in the oil of German camomile (*Matricaria chamomilla* L.) [1] where it belongs to the antiphlogistic principle of the blossoms [2]. (+)-(4*R*, 8*R*)-α-Bisabolol



1 4*S*,8*S*



2 4*S*,8*R*



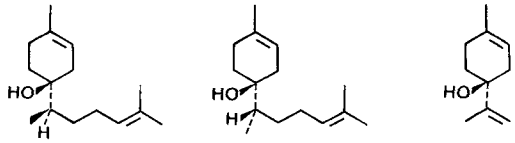
3 4*R*,8*S*

(*ent*-**1**) was isolated from *Atlantia monophylla* DC. [3]. Both diastereoisomers **1** and **2** are found in Brazilian cabreuva oil (*Myrocarpus frondosus; M. fastigiatus* FR. ALLEM) [4]. The racemic equivalent of the diastereoisomers **1**/**2** has been commercialized and is used in a large number of cosmetic products. The absolute configuration of the diastereoisomers **1** and **2** has recently been determined [3].

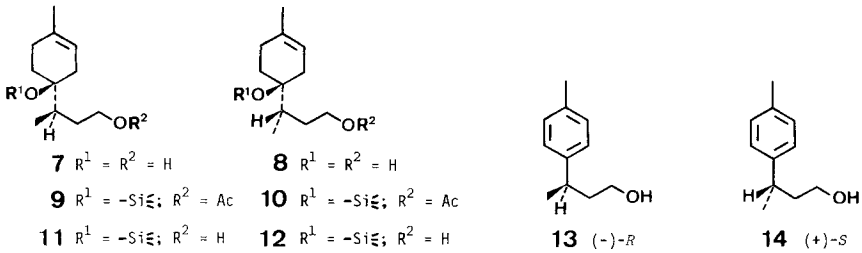
(+)-β-Bisabolol of unknown configuration has an apple-blossom-like odor and was first isolated from the essential oil of cotton buds; (*Gossypium hirsutum* L.); it turned out to be moderately attractive to the boll weevil [5]. Later, β-bisabolol has been identified in camphor oil [6], corn oil [7], vanilla [8], and olibanum oil [9].

In this paper, we describe the isolation of (−)-(4*S*, 8*R*)-8-epi-α-bisabolol (**2**) and (−)-(4*R*, 8*S*)-4-epi-β-bisabolol (**3**) from bergamot oil and the absolute configuration of the stereoisomeric alcohols **4** and **5**. (−)-(*S*)-*p*-Mentha-1,8-dien-4-ol (**6**) [10] served as key compound in the enantioselective synthesis of (+)-(4*S*, 8*R*)-8-epi-β-bisabolol (**4**) and (+)-(4*S*, 8*S*)-β-bisabolol (**5**). In the first step, **6** was converted into the 1:1 mixture of the diastereoisomeric diols **7** and **8** by hydroformylation followed by treatment with $LiAlH_4$. After acetylation and silylation, the diastereoisomers **9** and **10** were separated by flash chromatography [11]. The less polar diastereoisomer **9** was converted into (−)-(*R*)-3-(*p*-tolyl)-1-butanol (**13**) (see *Exper. Part*) which has been linked with (+)-*ar*-turmerone (= (*S*)-2-methyl-6-(*p*-tolyl)hept-2-en-4-one) [12]. (+)-(*S*)-Alcohol **14** arose from the more polar derivative **10** (see *Exper. Part*).

After the clear establishment of the chiral centers at C(4) and C(8) of **9** and **10**, the corresponding monosilylated alcohols **11** and **12** were converted stepwise in separate experiments to (+)-(4*S*, 8*R*)-8-epi-β-bisabolol (**4**) and (+)-(4*S*, 8*S*)-β-bisabolol (**5**), respectively. The spectroscopic properties of the naturally occurring alcohol **3** agree with those of its enantiomer **4**.



4 4*S*,8*R* **5** 4*S*,8*S* **6**



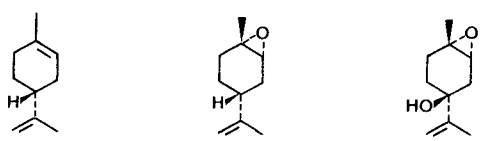
7 $R^1 = R^2 = H$ **8** $R^1 = R^2 = H$

9 $R^1 = -Si\equiv$; $R^2 = Ac$ **10** $R^1 = -Si\equiv$; $R^2 = Ac$

11 $R^1 = -Si\equiv$; $R^2 = H$ **12** $R^1 = -Si\equiv$; $R^2 = H$

13 (-)-*R* **14** (+)-*S*

The preparation of the starting material **6** from (+)-(*R*)-limonene (**15**) by our previously described method [10] gave unexpected difficulties on a larger scale. Therefore, a useful method, for the synthesis of large quantities of **6** was developed starting from (+)-*cis*-1,2-epoxy-*p*-menth-8-ene (**16**) which allowed introduction of the OH group with retention of configuration at C(4) by reaction with *t*-BuOOH in the presence of SeO_2 (→**17**). The oxirane ring was then removed from the crude epoxy alcohol **17** yielding **6** in a 12% overall yield. Direct treatment of optically active limonene with SeO_2 leads to the racemic alcohol **6** [13].



15 **16** **17**

Experimental Part

(with the valuable collaboration of *Beatrice Frei* and *Joël Perrinjaquet*)

General. Prep. column chromatography: silica gel (*Merck 60*, 230 mesh; 5 bar pressure). GC: *Carlo Erba Model 2101 AC*, capillary column *A* (*UCON HB 5100*, 50 m/0.3 mm); *Varian Model 3700*, packed column *B* (*SP 1000* 5% on *Chromosorb W*, 80–100 mesh, acid washed, 3.5 m/3 mm); *Carlo Erba Model Fractovap 2900*, capillary column *C* (*Chrompack CP Wax 57 CP*, 10 m); *Carlo Erba Model Fractovap 4200*, packed glass column *D* (15% *Carbowax* on *Chromosorb*, 60–80 mesh, 3 m) and column *E* (15% *SE 30* on *Chromosorb*, 80–100 mesh, 3 m); *Carlo Erba Model GT 450*, packed column *F* (*SP 1000* on *Chromosorb G*, 80–100 mesh, acid washed, 2.7 mm/4 mm) and column *G* (2.5% *SOMB* on *Chromosorb G*, 80–100 mesh, acid washed, 2.7 m/4 mm). $[\alpha]_D$: *Perkin-Elmer 141* polarimeter. IR: *Perkin-Elmer 297*. ^1H- and ^{13}C-NMR: *Bruker WH 360* and *Bruker HX 90*; solvent $CDCl_3$, with tetramethylsilane as internal standard (= 0.00 ppm). MS: *Finnigan 4023c* or *Varian MAT 112* with *ca.* 70 eV.

Isolation of (−)-(4S,8R)-8-Epi-α-bisabolol (= (−)-(2R)-6-Methyl-2-[(1S)-4-methylcyclohex-3-enyl]hept-5-en-2-ol; **2**) *and (−)-(4R,8S)-4-Epi-β-bisabolol (= (−)-(1R)-1-[(1S)-1,5-Dimethylhex-4-enyl]-4-methylcyclohex-3-enol;* **3**) *from Bergamot Oil* (Citrus bergamia RISSO). At 10^{-3} Torr, 4 kg of bergamot oil (*Simone GATTO*, Messina, Italy) were distilled. At a bath temp. of 180°, a fraction of 7.42 g distilled at 85–90°. The latter was redistilled using a *Fischer* column at 10^{-3} Torr to give 900 mg (= *Fraction A*) at 82° and 300 mg (= *Fraction*

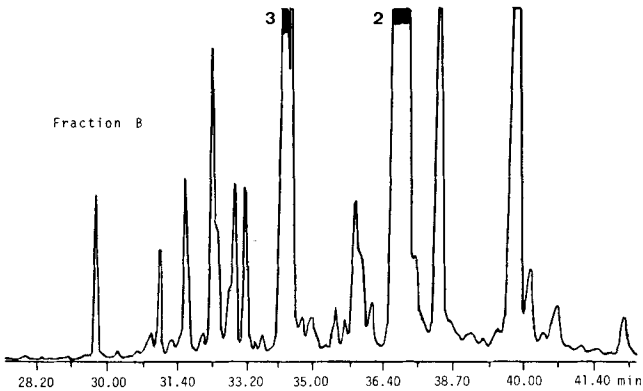


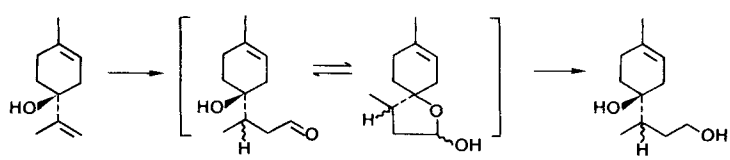
Fig. 1. *GC* (column *A*) *of fraction B*

B, see *Fig. 1*) at 85°. *Fraction A* consisted of a complex mixture of sesquiterpenic alcohols and oxidized linalyl acetates which were separated on silica gel with hexane/Et_2O 7:3. One fraction of 50 mg *(Fraction A-1)* contained *ca.* 10% of α- and 10% of β-bisabolol. *Fraction B* contained 25% of α- and 7% of β-bisabolol. By prep. GC of *Fraction B* on *SOMB* and *Carbowax*, 1.5 mg of pure **2** were obtained. Combining GC of *Fractions A-1* and *B* on *SOMB* and on *Carbowax* with chromatography on silica gel impregnated with $AgNO_3$, 1 mg of 95% pure **3** was isolated. Trapping was performed on column *F* and on column *G*.

2: t_R (column *A*, 120–180°, 3°/min, 1.0 kg/cm^2) 37.05 min; t_R (column *B*, 150–250°, 5°/min, 40 ml He/min) 12.9 min. $[\alpha]_D^{20} = -51°$ (*c* = 0.1%, $CHCl_3$). ^{1}H-NMR: 1.14 (*s*, 3 H); 1.28 (*m*, 1 H); 1.62 (*s*, 3 H); 1.65 (*s*, 3 H); 1.69 (*s*, 3 H); 1.69 (*s*, 3 H); 5.14 (*t*, 1 H); 5.40 (br. *s*, 1 H). MS: 222 (0, M^+), 204 (18), 189 (3), 161 (8), 147 (4), 134 (7), 119 (67), 109 (72), 93 (31), 69 (83), 43 (100) (see [3]).

3: t_R (column *A*, 120–180°, 3°/min, 1.0 kg/cm^2) 34.25 min; t_R (column *B*, 150–250°, 5°/min, 40 ml He/min) 11.8 min. $[\alpha]_D^{20} = -57°$ (*c* = 0.1, $CHCl_3$). ^{1}H-NMR and MS: identical with data for **4.**

(−)-(1S)-p-Mentha-1,8-dien-4-ol (6) from (+)-cis-1,2-Epoxy-p-menth-8-ene (**16**). A soln. of *t*-BuOOH (150 ml); 40.6% in CH_2Cl_2 [14] was added dropwise to a magnetically stirred suspension of SeO_2 (2 g) in CH_2Cl_2 (20 ml). To the resulting soln. at 25° (water bath), **16** (118 g in 200 ml of CH_2Cl_2) was added dropwise. After 3 days, further *t*-BuOOH soln. (50 ml) was added. After 7 days, no **16** remained, and a soln. of Na_2SO_3 (100 g) in H_2O (1 l) was added dropwise under stirring to destroy the excess of *t*-BuOOH. After 6 h at 25–30°, the org. phase was separated and concentrated. The remaining crude **17** was diluted with AcOH (500 ml), and NaOAc (50 g) and NaI (100 g) were added. Under stirring, Zn dust (100 g) was introduced within 5 h. After 20 h, H_2O (2 l) was added to dissolve the inorg. salts. The aq. phase was extracted with petroleum ether (b.p. 30–50°), and the combined org. phases were washed with H_2O and brine, concentrated, and distilled to give 26 g of crude **6**. Chromatography (SiO_2, cyclohexane/Et_2O 9:1) afforded 6.6 g of pure **6**. $[\alpha]_D^{20} = +16.3°$ ($CHCl_3$), −10.5° (EtOH; [10]: −9.8° (EtOH)).

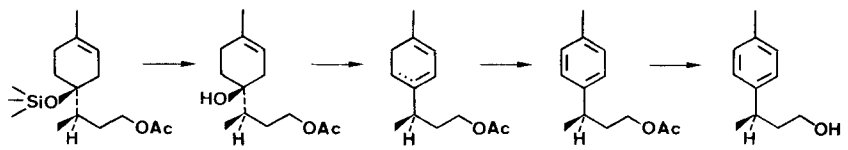


6 **18** **7/8**

3-[(1S)-1-Hydroxy-4-methylcyclohex-3-enyl]butanol (**7/8**). In a stainless steel autoclave were placed **6** (14 g), $RhH(CO)(PPh_3)_3$ (0.3 g), and cyclohexane (250 ml). Under a CO/H_2 pressure of 200 bar, the temp. was raised gradually to 110° with stirring. After 6 h, the mixture was concentrated and the crude **18** directly reduced with $LiAlH_4$ (2 g) in Et_2O (2 h reflux). The stirred mixture was then treated with H_2O (2 ml), 15% NaOH soln. (2 ml), and H_2O (6 ml) [15]. After filtration and concentration, the crude mixture was chromatographed (SiO_2, Et_2O) to afford **7/8** (10.2 g). $[\alpha]_D^{20} = +25.1°$ (EtOH). ^{1}H-NMR: 0.915, 0.955 (2 *d*, *J* = 6).

3-[(1S)-4-Methyl-1-(trimethylsilyloxy)cyclohex-3-enyl]butyl Acetate (**9**/**10**). A soln. of **7**/**8** (10 g), pyridine (100 ml), and Ac_2O (10 ml) was allowed to stand at r.t. during 2 h. The mixture was diluted with Et_2O (300 ml) and washed with cold, dil. H_2SO_4, cold, dil. NaOH soln., and brine. The solvent was evaporated to give the crude monoacetate (12 g), which was redissolved in pyridine (30 ml). After addition of hexamethyldisilazane (25 ml) and chlorotrimethylsilane (1 ml), the mixture was refluxed for 48 h, concentrated *i.v.*, and distilled to afford a pure 1:1 mixture **9**/**10** (13.7 g). Repeated chromatography (SiO_2, cyclohexane) afforded enriched fractions of **9** and **10**.

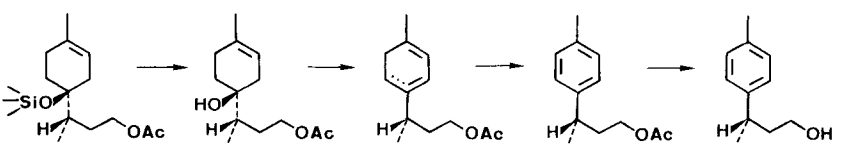
(−)-(R)-3-(p-Tolyl)butanol (**13**) *from* **9**. A soln. of **9**/**10** (63: 37; 400 mg) in MeOH (5 ml) was treated with conc. HCl (2 drops) with stirring. After 1 h, Et_2O (50 ml) was added, and the mixture was washed with dil. $NaHCO_3$ soln. and brine and evaporated to give crude *(3R)-3-[(1S)-1-hydroxy-4-methylcyclohex-3-enyl]butyl acetate* (**19**;



9 **19** **20** **21** **13**

320 mg). The latter was diluted with pyridine (2 ml) and treated at −70° with $POCl_3$ (0.5 ml) with stirring. The mixture was allowed to reach r.t. overnight. After dilution with Et_2O, the mixture was washed with 5% aq. HCl, 5% $NaHCO_3$ soln., and brine and concentrated to give *(R)-(4-methylcyclohexa-1,3(and 1,4)-dienyl)butyl acetate* (**20**; 196 mg), which was then refluxed in THF (5 ml) with 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ; 215 mg) during 1 h [16]. After cooling to r.t., petroleum ether (b.p. 30–50°, 50 ml) was added, and filtration followed by evaporation of the filtrate gave crude *(R)-3-(p-tolyl)butyl acetate* (**21**; 200 mg). Reduction with $LiAlH_4$ (reflux for 1 h) and the usual workup gave **13** (170 mg). An anal. sample was obtained by prep. GC *(Carbowax)*. $[\alpha]_D^{20} = -5.9°$ ($c = 0.88$, $CHCl_3$).

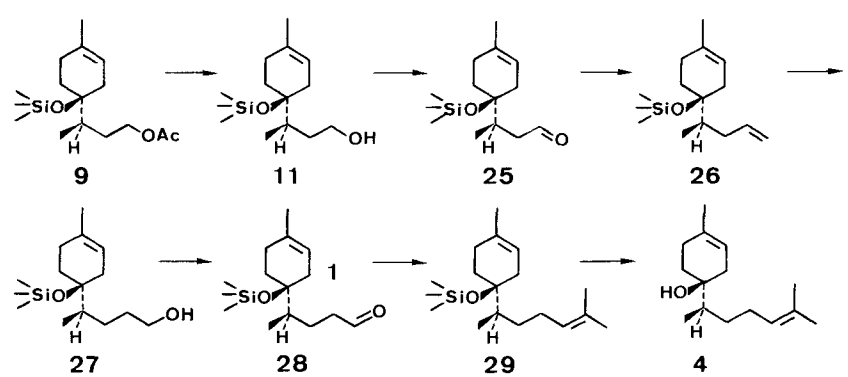
(+)-(S)-3-(p-Tolyl)butanol (**14**) *from* **10**. A mixture **9**/**10** (2:3; 500 mg) was transformed as above (see **9**→→**13**) to 174 mg of crude **14**, which was purified by prep. GC. $[\alpha]_D^{20} = +6.2°$ ($c = 0.8$, $CHCl_3$; [12]: +33°



10 **22** **23** **24** **14**

($CHCl_3$)). ^{1}H-NMR: 1.25 (*d*, $J = 7$, 3 H); 2.32 (*s*, 3 H); 2.85 (*sext.*, $J = 7$, 1 H); 3.55 (*m*, 2 H); 7.1 (*s*, 4 H). MS: 164 (13, M^+), 146 (3), 131 (25), 119 (100), 105 (18), 91 (23), 77 (9).

(+)-(4S, 8R)-8-Epi-β-bisabolol (= (+)-(1*S*)-1-[(1*R*)-1,5-Dimethylhex-4-enyl]-4-methylcyclohex-3-enol; **4**). To a cold suspension of $LiAlH_4$ (100 mg) in Et_2O (15 ml) was added a soln. of **9**/**10** (82:18; 820 mg) in Et_2O (10 ml)



9 **11** **25** **26**

27 **28** **29** **4**

and refluxed for 1 h. The mixture was then cooled in an ice-bath and hydrolyzed with H_2O (0.1 ml), 10% NaOH soln. (0.1 ml), and H_2O (0.3 ml). The org. phase was filtered and concentrated to give crude *(3R)-3-[(1S)-4-methyl-1-(trimethylsilyloxy)cyclohex-3-enyl)]butanol* (**11**; 738 mg). $[\alpha]_D^{20} = -2.4°$, (c = 1.6, $CHCl_3$). ^{1}H-NMR: 0.1 (*s*, 9 H); 0.93 (*d*, J = 7, 3 H); 1.65 (br. *s*, 3 H); 3.6 (*m*, 2 H); 5.2 (br. *s*, 1 H).

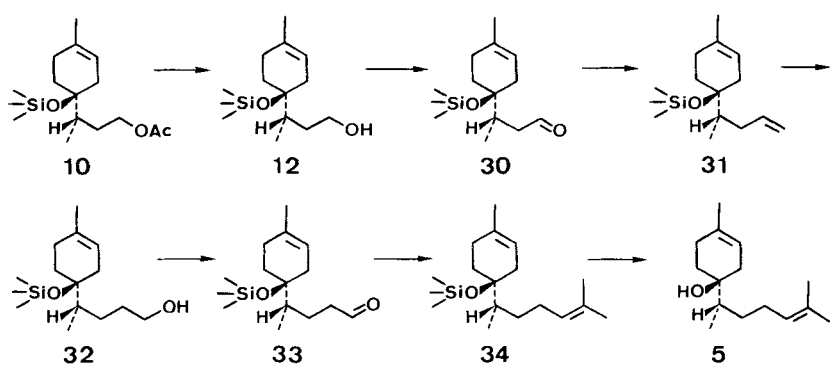
The foregoing **11** was oxidized with 2.7 g of pyridinium dichromate (PDC) in the presence of NaOAc (0.6 g) [17] in CH_2Cl_2 (20 ml) with stirring at r.t. After 2 h, the mixture was diluted with Et_2O (100 ml) and filtered. After concentration, the crude *(3R)-3-[(1S)-4-methyl-1-(trimethylsilyloxy)cyclohex-3-enyl]butanal* (**25**; 743 mg) was used for the next step without further purification.

To a stirred suspension of Ph_3PMeI (1.7 g) in Et_2O (25 ml) was added dropwise a soln. of BuLi (2 ml; 15% in hexane). After 4 h at r.t., a soln. of **25** in Et_2O (20 ml) was added. After reflux for 5 h, petroleum ether (b.p. 30–50°; 100 ml) was added to the cooled mixture, and the liquid phase was filtered and concentrated. The crude product was purified by filtration through SiO_2 (30 g) with cyclohexane to give *(4R)-4-[(1S)-4-methyl-1-(trimethylsilyloxy)cyclohex-3-enyl]pent-1-en* (**26**; 379 mg). $[\alpha]_D^{20} = +4.0°$ (c = 2, $CHCl_3$). ^{1}H-NMR: 0.1 (*s*, 9 H); 0.87 (*d*, J = 7, 3 H); 1.66 (br. *s*, 3 H); 4.8–5.8 (*m*, 3 H).

To a soln. of **26** (250 mg) in THF (1 ml) was added a soln. of 9-borabicyclo[3.3.1]nonane (BBN, 1.5 ml; 0.5M in THF) [18] at 0° with stirring under Ar. After 5 h, more BBN (1 ml) was added and the mixture allowed to attain r.t. After 18 h, the transformation was complete. The mixture was cooled in an ice-bath, and NaOH soln. (10%; 0.5 ml) and H_2O_2 (30%; 0.5 ml) were added. After 1 h, Et_2O (50 ml) was added and the mixture washed with brine. Filtration over SiO_2 (15 g) afforded *(4R)-4-[(1S)-4-methyl-1-(trimethylsilyloxy)cyclohex-3-enyl]pentanol* (**27**; 247 mg). $[\alpha]_D^{20} = +11.4°$ (c = 2, $CHCl_3$). ^{1}H-NMR: 0.1 (*s*, 9 H); 0.89 (*d*, J = 7, 3 H); 1.65 (br. *s*, 3 H); 3.6 (*m*, 2 H); 5.2 (br. *s*, 1 H).

Using the same procedure as before (*cf.* **11**→**25**), **27** (240 mg) was oxidized with PDC/NaOAc in CH_2Cl_2 to afford *(4R)-4-[(1S)-4-methyl-1-(trimethylsilyloxy)cyclohex-3-enyl]pentanal* (**28**). ^{1}H-NMR: 0.1 (*s*, 9 H); 0.9 (*d*, J = 7, 3 H); 1.65 (br. *s*, 3 H); 5.2 (br. *s*, 1 H); 9.78 (br. *s*, 1 H).

The crude **28** (248 mg) was immediately added to (isopropylidene)triphenylphosphorane, which was prepared from (isopropyl)triphenylphosphonium iodide (1.81 g) and BuLi (2 ml; 15% in hexane) in Et_2O (30 ml). After 1 h reflux and usual workup, the crude **29** (140 mg) was chromatographed on SiO_2 *(Merck 60)* to give pure *(6R)-2-methyl-6-[(1S)-4-methyl-1-(trimethylsilyloxy)cyclohex-3-enyl]hept-2-ene* (**29**; 29 mg), which was hydrolyzed with MeOH (1 ml) and HCl (1 drop) for 1 h. After usual workup and chromatography, pure **4** (5.8 mg) was obtained. $[\alpha]_D^{20} = +49°$ (c = 0.49, $CHCl_3$). ^{1}H-NMR: see *Fig. 2*. MS: 222 (0, M^+), 204 (11), 179 (1), 161 (3), 140 (6), 121 (33), 111 (38), 93 (63), 82 (100), 72 (32), 69 (45), 55 (37), 41 (43).



(+)-(4S,8S)-β-Bisabolol (= (+)-(1*S*)-1-[(1*S*)-1,5-Dimethylhex-4-enyl]-4-methylcyclohex-3-enol; **5**). An enriched mixture of **10** was transformed to **5** following the above procedure (**9**→→**4**). Repeated chromatography of the silyl ether **34** gave, after hydrolysis, pure **5**. $[\alpha]_D^{20} = +7.16°$ (c = 0.28, $CHCl_3$). ^{1}H-NMR: see *Fig. 2*. MS: 222 (0, M^+), 204 (8), 161 (3), 119 (29), 111 (31), 93 (52), 82 (100), 72 (32), 69 (43), 55 (28), 41 (42).

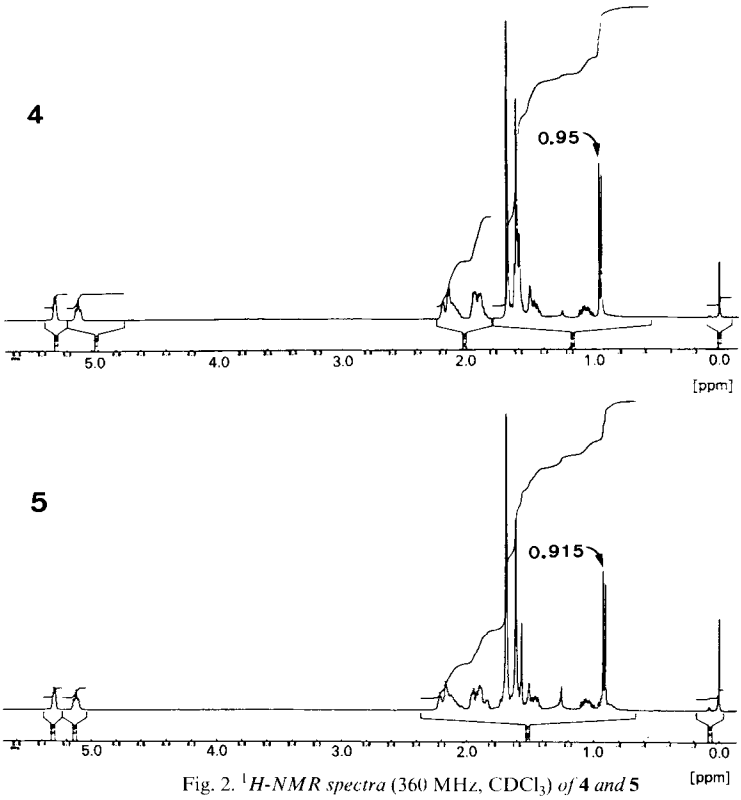


Fig. 2. ^{1}*H-NMR spectra* (360 MHz, $CDCl_3$) *of* **4** *and* **5**

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