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# SYNTHESIS AND STEREOCHEMISTRY OF α-BISABOLOL

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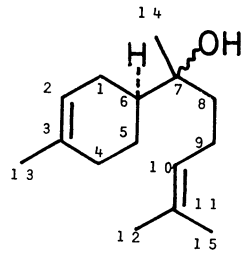
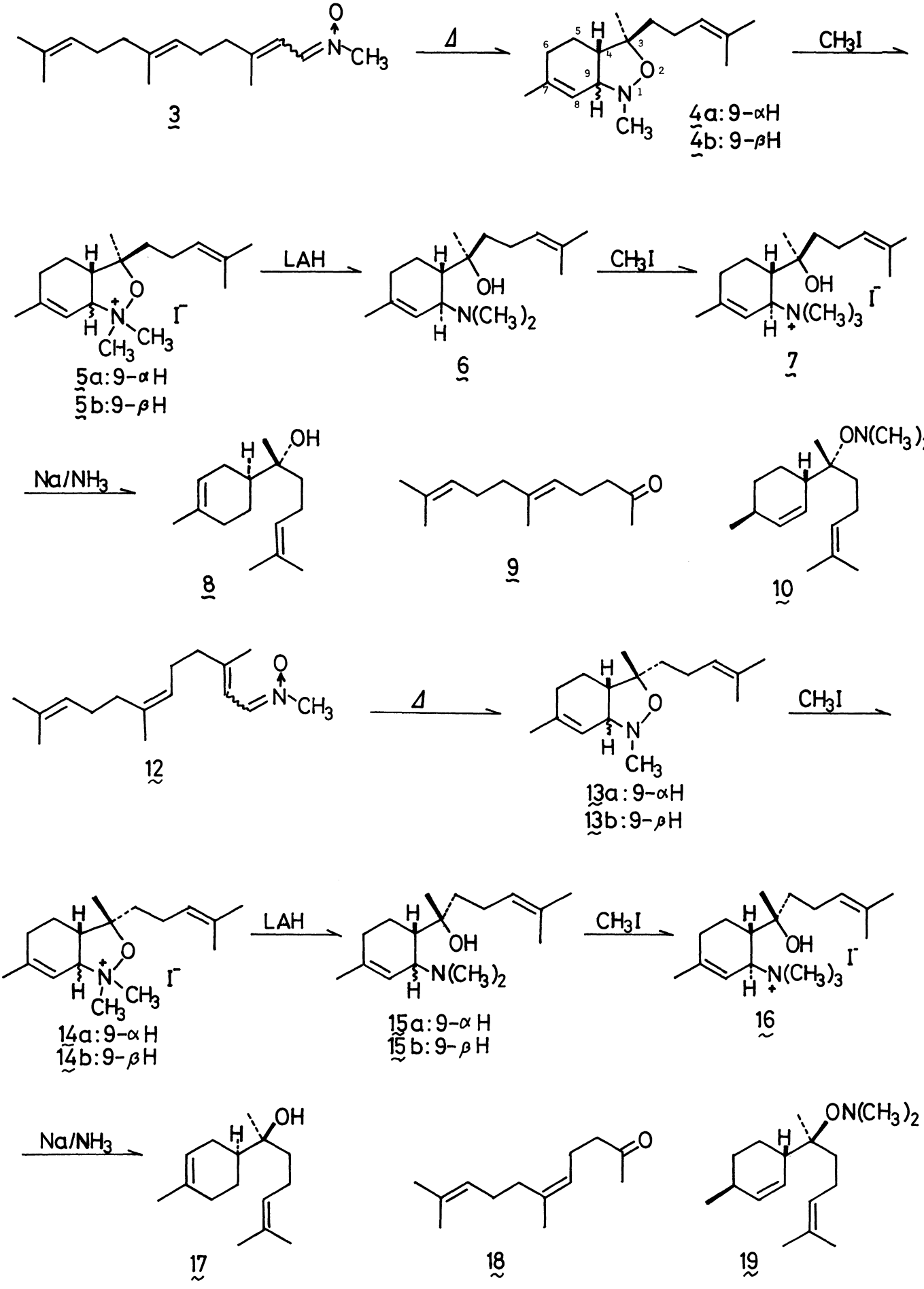
Intramolecular addition reaction of nitrone (3) derived from (6E)-farnesal and N-methylhydroxylamine afforded isoxazolidines (4a, 4b), methyl amino group of which was removed by a series of reactions to obtain the stereoisomer (8) of α-bisabolol. Synthesis from (6Z)-farnesal by the same method afforded α-bisabolol, which established the stereochemistry of (-)-α-bisabolol as (17).

α-Bisabolol is distributed in various plants of Compositae[1,2] and other families,[3,4] and the levo rotatory isomer has been found to possess physiological activities.[5] Although the synthesis of this sesquiterpenol was reported,[6] the synthetic substance was seemingly a mixture of diastereomeric isomers. The absolute configuration of one(C-6) of two chiral centers in (-)-α-bisabolol has been determined to be S,[1] but the chirality of the other center(C-8) remained without determination. In previous paper we have reported that the intramolecular cycloaddition reaction of nitrones provides a convenient annelation procedure and the cyclization reaction is more favorable for formation of five and six membered rings than for formation of medium size rings.[7] This reaction is applied for the synthesis of α-bisabolol. We now wish to report the stereospecific synthesis of (±)-α-bisabolol with concomitant determination of the full stereochemistry.[10]




A nitrone(3) derived from (6E)-farnesal (2)[8] and N-methylhydoxylamine on refluxing in xylene was easily cyclized to a mixture of two isoxazolidine derivatives, (4a) and (4b),[9] which were accompanied with norketone (9). The two products (4a) and (4b) have the same stereochemistry about asymmetric centers at C-3 and C-4 because of stereospecific 1,3-dipolar addition of the nitrone to the trans ethylenic double bond, but the different configuration about C-9. The isoxazolidines, (4a) and (4b), were converted into crystalline methiodides,[9] (5a) and (5b), respectively. The stereochemistry of the ring junctions in these compounds were deduced from the nmr patterns of vinyl proton in the cyclohexene rings: coupling constant between protons 8 and 9 in (5a) was observed almost zero, but that in (5b) was 5 Hz. The N-O bond of the methiodide (5a) was smoothly cleaved by reduction with lithium aluminium hydride to afford the amino-alcohol (6).[9] Treatment of the isomeric methiodide (5b) with the same reagent yielded a hydroxylamine (10)[9] as a result of the cleavage of the C-N bond.


3
Δ
CH3I
4a: 9-αH
4b: 9-βH
5a: 9-αH
5b: 9-βH
LAH
6
CH3I
7
Na/NH3
8
9
10
12
Δ
CH3I
13a: 9-αH
13b: 9-βH
LAH
14a: 9-αH
14b: 9-βH
15a: 9-αH
15b: 9-βH
CH3I
16
Na/NH3
17
18
19

The aminoalcohol (6) was further converted into a new methiodide (7),[9] which on reduction with sodium in liquid ammonia released an ammonium group to give an alcohol (8): ir, 3410, 1670, 1440, 1380 $cm^{-1}$;nmr($CCl_4$),δ 1.06(3H,s), 1.58(6H.brs), 4.96(1H,m), 5.20(1H,m);m/e 204($M^+-H_2O$). The synthetic alcohol (8) showed the almost superimposable ir spectrum on that of natural α-bisabolol, and the nmr spectrum also strongly resembled to that of the natural substance except that 14-methyl signal of the synthetic compound appeared at 0.02 ppm lower field than that of natural bisabolol.

The other stereoisomer was obtained from (6Z)-farnesal (11) by the same method as above. A mixture of (6E) and (6Z)- farnesals was converted to the corresponding nitrones,[9] (3) and (12). A mixture of the nitrones was heated in xylene to afford four isoxazolidine derivatives and norketones, (9) and (18), which were separated by chromatography on silicic acid. Two isoxazolidines separated from the mixture were identical with the isoxazolidines (4a) and (4b), respectively, which had been made from the nitrone of (6E)-farnesol. The remaining two isoxazolidines, (13a) and (13b), were derived from the nitrone of (6Z)-farnesol. The stereochemistry around C-3 and C-4 in the isoxazolidines,[9] (13a) and (13b), is same but different from that of (4a) and (4b). The stereochemistry of ring junctions of (13a) and (13b) was assigned trans and cis, respectively, from their nmr spectra. Lithium aluminium hydride reduction of methiodide[9] (14a) derived from (13a) afforded an aminoalcohol[9] (15a), but stereoisomer (14b) gave a mixture of aminoalcohol (15b)[9] and hydroxylamine (19).[9,11] Treatment of (15a) with methyl iodide followed by reduction with sodium in liquid ammonia afforded an expected sesquiterpenol(17): ir, 3420, 1670, 1440, 1380 $cm^{-1}$;nmr($CCl_4$),δ 1.04(3H,s), 1.62(6H,brs), 5.05(1H,brt), 5.27(1H,m);m/e 204($M^+-H_2O$). The gas chromatogram and proton nmr spectrum showed that the product is composed of single component. Spectroscopic properties (ir, nmr, and ms) and chromatographic behaviors of synthetic compound(17) were completely identical with those of natural (-)-α-bisabolol.

The synthetic results showed that α-bisabolol has the configurations either 6S,7S or 6R,7R. Since the absolute configuration at C-6 of (-)-α-bisabolol had been assigned as S, the absolute configuration at the remaining C-7 was determined S as shown in the structure(17).

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9) Satisfactory analytical data were obtained for each synthetic intermediates.

10) After this synthesis had completed, synthesis of α-bisabolol was reproted by M.A.Schwartz and G.C.Swanson in J.Org.Chem., 44, 953 (1979). The cyclization of farnesal was essentially same as the present report, but the precise course after the cyclization to the isoxazole derivative was different.

11) The physical properties of the intermediates in the synthesis were as follows:

4a; ν 1660, 1450, 1380 $cm^{-1}$; δ($CCl_4$) 1.02(3H,s), 1.66(9H,brs), 2.50(3H,s), 5.05(1H,brt), 5.35(1H,brs,W=6Hz).

4b; δ($CCl_4$) 1.14(3H,s), 1.66(9H,brs), 2.50(3H,s), 5.05(1H,brt), 5.16(1H,brs, W=9Hz).

5a; mp 146.5°C; ν(KBr) 1650,1450 $cm^{-1}$; δ($CDCl_3$) 1.50(3H,s), 1.60(3H,brs), 1.68 (3H,brs), 1.84(3H,brs), 3.49(3H,s), 3.92(3H,s), 5.10(2H,m), 6.35(1H,brs,W= 4Hz).

5b; mp 127°C; δ($CDCl_3$) 1.40(3H,s), 1.61(3H,brs), 1.68(3H,brs), 1.93(3H,brs), 3.41(3H,s), 3.90(3H,s), 5.16(2H,m), 6.14(1H,brs,W=8Hz).

6; ν 3170, 1675, 1450, 1380 $cm^{-1}$; δ($CCl_4$) 1.05(3H,s), 1.62 and 1.66(9H,s), 2.27(6H,s), 3.38(1H,brd,J=10Hz), 5.08(1H,brt), 5.34(1H,brs).

7; ν 3400, 1670, 1450, 1380 $cm^{-1}$; δ($CDCl_3$) 1.09(3H,s), 1.63 and 1.67(6H,brs), 1.87(3H,brs), 3.32(9H,s), 4.62(1H,m), 5.10(1H,m), 5.70(1H,m).

10; ν 1450, 1370 $cm^{-1}$; δ($CDCl_3$) 0.94(3H,d,J=7Hz), 1.05(3H,s), 1.60(3H,brs), 1.68(3H,brs), 2.50(6H,s), 5.05(1H,m), 5.48(1H,brd,J=11Hz), 5.71(1H,brd,J= 11Hz).

13a;ν 1650, 1440,1375 $cm^{-1}$; δ($CCl_4$) 1.23(3H,s), 1.60 and 1.66(9H), 2.52(3H,s), 2.70(1H,m), 5.03(1H,brt,J=7Hz), 5.34(1H,brs,W=4.5Hz).

13b;ν 1670, 1440, 1380 $cm^{-1}$; δ($CCl_4$) 1.20(3H,s), 1.60, 1.67, 1.72(9H), 2.52(3H,s), 2.73(1H,m), 5.09(1H,m), 5.20(1H,d,J=4Hz, W=8Hz).

14a;mp 152.5°C; ν(KBr) 1655, 1445 $cm^{-1}$; δ($CDCl_3$) 1.53(3H,s), 1.62(3H,brs), 1.68 (3H,brs), 1.82(3H,brs), 3.58(3H,s), 3.87(3H,s), 4.93(2H,m), 6.34(1H,brs,W= 4.5Hz).

14b;mp 129°C; ν(KBr) 1670, 1450 $cm^{-1}$; δ($CDCl_3$) 1.61(3H,brs), 1.68(3H,brs), 1.74 (3H,s), 1.91(3H,brs), 3.36(3H,s), 3.93(3H,s), 5.02(1H,m), 5.60(1H,m), 6.12 (1H,brs,W=9Hz).

15a;ν 3170, 1450, 1380, 1210 $cm^{-1}$; δ($CCl_4$) 1.05(3H,s), 1.63(9H,brs), 2.27(6H,s), 3.38(1H,m), 5.06(1H,brt), 5.28(1H,brs).

15b;ν 3230, 1670, 1460, 1380, 1160, 980 $cm^{-1}$; δ($CCl_4$) 1.20(3H,s), 1.60 and 1.65 (9H), 2.32(6H,s), 5.05(1H,brt), 5.44(1H,m).

16; δ($CDCl_3$) 1.40(3H,s), 1.61(6H,brs), 1.88(3H,brs), 3.33(9H,s), 4.45(1H,m), 5.03(1H,m), 5.69(1H,m).

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