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Stereospecific Syntheses of the Diastereomeric (±)-α-Bisabolols. A Caveat on the Assignment of Stereochemistry to Natural α-Bisabolol

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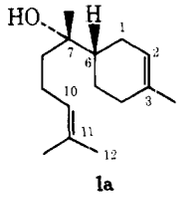
Received August 29, 1978

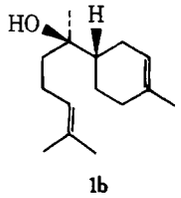
The diastereomeric racemic (6*S*,7*S*–6*R*,7*R*)-α-bisabolol and (6*S*,7*R*–6*R*,7*S*)-α-bisabolol were stereospecifically synthesized from (6*Z*)- and (6*E*)-farnesal, respectively, using intramolecular 1,3-dipolar cycloaddition of the corresponding *N*-methylnitrones as the key ring- and stereochemistry-forming step. A subsequent reductive deamination of a quaternary ammonium salt afforded a mixture of the respective bisabolol and its Δ^1 double-bond isomer in each case. NMR and gas chromatographic comparison of (−)-α-bisabolol isolated from chamomile oil with the two synthetic diastereomers showed the natural material to possess the 6*S*,7*S* stereochemistry, in contrast to a previously reported assignment of 6*S*,7*R* stereochemistry. In initial exploratory work, application of the synthetic sequence to citral smoothly yielded α-terpineol.

The sesquiterpene α-bisabolol (**1**) has been isolated from the essential oils of a wide variety of plants, shrubs, and trees.[1] The (−) enantiomer is the most widespread,[1c-g] but the (+) form has also been reported.[1i,j] Although the assignment of gross structure to synthetic (±)-α-bisabolol was made even prior to isolation of the natural material,[2] the problem of assignment of relative stereochemistry at the two asymmetric centers has been less tractable. None of the various synthetic routes[2,3] to racemic α-bisabolol have been capable of stereospecificity; hence mixtures of (±)-**1a** and (±)-**1b** have always resulted. In only one case was an analysis of the diastereomeric mixture carried out, using capillary column gas chromatography of the corresponding trimethylsilyl ethers.[3b] A tentative assignment of relative stereochemistries was made on the basis of mechanistic considerations, but neither isolation of the diastereomers nor gas chromatographic comparison of the mixture with natural material was reported.[3b]

In more recent work, the 6*S* absolute configuration was assigned to (−)-α-bisabolol by virtue of the levo rotation of a mixture of (6*S*,7*RS*)-α-bisabolols derived by synthesis from (−)-limonene,[4a] but a determination of whether the 6*S*,7*S* (**1a**)



1a

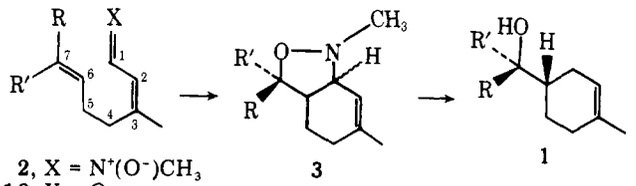


1b

or 6*S*,7*R* (**1b**) stereochemistry represented the natural material was not made. Finally, in a very recent report[4b] of the synthesis of (+)- and (−)-α-bisabolol from (+)- and (−)-limonene, respectively, in which absolute configurations were assigned to intermediate diastereomeric epoxylimonenes, the 6*S*,7*R* stereochemistry (**1b**) was designated for (−)-α-bisabolol.[4c]

As part of a continuing investigation into biogenetically patterned syntheses of terpenes via novel cyclization methods,[5] we sought to develop a stereospecific, cyclization-based synthetic approach to (±)-**1a** and (±)-**1b** that would allow unambiguous assignment of stereochemistry to these compounds. Since the direct biogenetic-type cationic cyclization of farnesol derivatives does not proceed with the required stereospecificity,[3a,b] an alternative approach was sought.

Scheme I



2, X = $N^+(O^-)CH_3$
13, X = O

3

1

a, R = CH_3, R′ = $CH_2CH_2CH{=}C(CH_3)_2$; b, R = CH_2CH_2-$CH{=}C(CH_3)_2$, R′ = CH_3

The work of LeBel et al. on intramolecular 1,3-dipolar cycloadditions of olefinic nitrones[6] suggested a potential solution to this problem (Scheme I). Thus, the nitrone **2** derived from farnesal would be expected to undergo thermal cyclization to give the isoxazolidine **3** as a mixture of isomers at the ring fusion,[6a,7] but with complete retention of the relative configuration of the 6,7 double bond.[7,8] The (6*Z*)-farnesal nitrone **2a** would therefore ultimately yield racemic (*SS*,*RR*)-α-bisabolol (**1a**), and the (6*E*)-farnesal nitrone **2b** would give racemic (*SR*,*RS*)-α-bisabolol (**1b**). Since all four possible 2,3–6,7 double bond isomers of the corresponding farnesols have been prepared and characterized,[9] unambiguous syntheses of (±)-**1a** and (±)-**1b** would be in hand.

Initial studies were carried out in the citral (**4**) series in order to confirm LeBel's assertion[10] that both the (2*Z*)- and (2*E*)-nitrone isomers would ultimately cyclize (the latter by isomerization to the former under the reaction conditions), and to develop a reductive deamination procedure for the conversion

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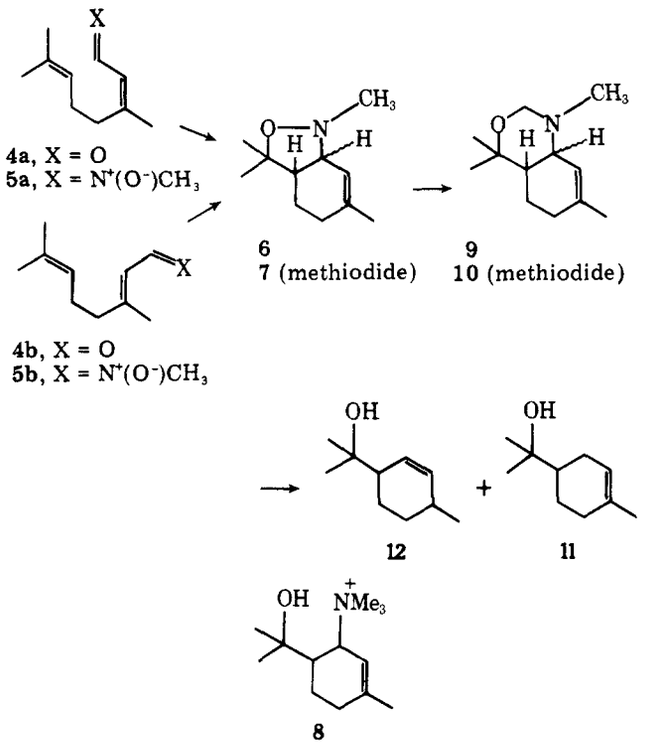
Scheme II

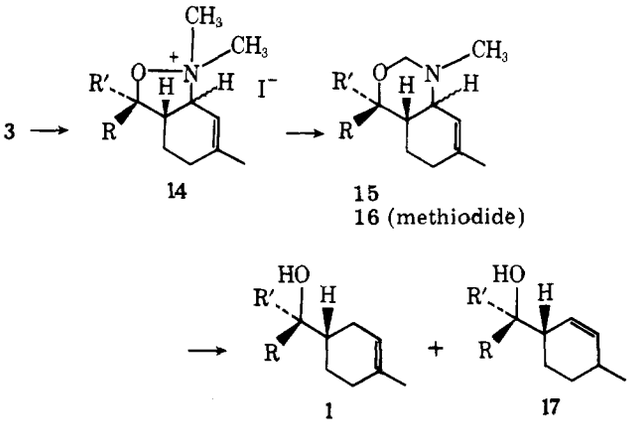


of **3** to **1**. Treatment of neral [(2*Z*)-citral, **4a**] with *N*-methylhydroxylamine in absolute ethanol at room temperature afforded the nitrone **5a** (Scheme II), while the corresponding reaction of geranial [(2*E*)-citral, **4b**] with *N*-methylhydroxylamine gave nitrone **5b**. NMR analysis of the crude nitrones confirmed that no significant equilibration of the 2,3 double bond had occurred at this stage; the C-3 methyl group appeared as a singlet at δ 1.87 in **5a** and at δ 1.78 in **5b**. Refluxing of either nitrone **5a** or **5b** in anhydrous xylene afforded an 80% yield of the isoxazolidine **6** as a 3:1 mixture of isomers, which have been previously assigned[10] the cis- and trans-fused stereochemistries, respectively. The 2,3 double-bond geometry was therefore demonstrated to be of no concern in the subsequent work with farnesal.

Removal of the nitrogen function by reductive cleavage of an appropriate quaternary salt was then explored. While the isoxazolidine mixture **6** was smoothly converted (82% yield) to the methiodide **7**, as a solid that was indicated by NMR to still retain the 3:1 isomer ratio, all attempts to prepare the quaternary salt **8** were stymied by the unreactivity of the corresponding amino alcohol (derived by reduction of **7**) toward N-alkylation. Consequently, methiodide **7** was subjected to base-catalyzed rearrangement[6a] to give the tetrahydro-1,3-oxazine **9** (Scheme II) in 50% yield, as an approximately 1:1 mixture of isomers. Whether the change in isomer ratio was due to selective loss of the cis-fused material in side reactions or due to base-catalyzed equilibration at the ring junction was not ascertained. Amine **9** reacted readily with methyl iodide in ether to afford the required methiodide **10** in 78% yield. Lithium–liquid ammonia reduction of **10** gave a 64% yield of a 4:1 mixture of alcohols which was separated by chromatography on silver nitrate impregnated silicic acid; the major product was identical with authentic α-terpineol (**11**) in GC, NMR, and mass spectral behavior, while the minor product exhibited NMR and mass spectra consistent with the expected double-bond isomer **12**. The procedures necessary for the bisabolol synthesis were thus in hand.

(6*E*)-Farnesal (**13b**, Scheme I) was obtained as a 3:2 mixture of 2*E*:2*Z* isomers by oxidation[11] of natural (2*EZ*,6*E*)-farnesol.[9,12] The corresponding nitrone **2b** was prepared (49% yield after chromatographic purification) and cyclized to isoxazolidine **3b** as in the citral series. Methylation of crude **3b** afforded the quaternary salt **14b** (Scheme III) as a solid (67% yield from **2b**), again indicated by NMR to be a 3:1 mixture of cis- and trans-fused isomers, respectively. Ring expansion to the tetrahydro-1,3-oxazine **15b** was effected in 72% yield by steam distillation of **14b** from aqueous sodium hydroxide. Quaternization of **15b** with methyl iodide in ether gave **16b** as a solid which was indicated by NMR to consist of a 3:2 cis/trans mixture. The trans-fused methiodide could be selectively crystallized from acetone, while a mixture enriched in the cis-fused methiodide was obtained by recrystallization of the original mixture from ethanol–ether; NMR analysis of both of these purified salts confirmed the assigned stereochemistry. Finally, demethylation of *trans*-**16b** by treatment with lithium *n*-propyl mercaptide in hexamethylphosphoramide afforded *trans*-**15b**, the NMR spectrum of which again supported the assignments.

Scheme III



a, R = CH_3, R′ = $CH_2CH_2CH{=}C(CH_3)_2$; b, R = CH_2CH_2-$CH{=}C(CH_3)_2$, R′ = CH_3

The mixed methiodides **16b** (3:2 cis/trans) were subjected to hydrogenolysis with lithium in liquid ammonia to afford, after chromatographic separation, racemic (*SR*,*RS*)-α-bisabolol (**1b**) (41% yield) and its Δ^1 double-bond isomer **17b** (15% yield). All spectral data were consistent with the assigned structures.

(2*EZ*,6*Z*)-Farnesal **13a** was synthesized from nerol (**18**) as outlined in Scheme IV. The aldehyde so obtained was shown by GC and NMR analyses to be about an 85:15 mixture of the 6*Z* and 6*E* compounds. The same sequence of reactions as described above was carried out with **13a** (Schemes I and III) without purification of the intermediates. NMR spectra (270 MHz) of the crude tetrahydro-1,3-oxazine **15a** and its methiodide **16a** showed C-7 methyl and *N*-methyl resonances, respectively, assignable to the corresponding compounds of the **b** series, and constituting about 15% of the peak heights of the signals due to the **a** series. Hydrogenolysis of crude **16a** as before afforded, after silver nitrate–silicic and chromatography, racemic (*SS*,*RR*)-α-bisabolol (**1a**) (30% yield) and its Δ^1

Scheme IV

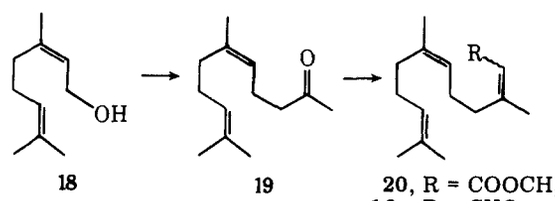


Table I. NMR Comparison[a] of the Diastereomeric (±)-α-Bisabolols with Natural (−)-α-Bisabolol

proton[b]	(±)-1a	(±)-1b	(−)-α-bisabolol
H-2	5.37 (br s)	5.39 (br s)	5.37 (br s)
H-10	5.12 (t, J = 7 Hz)	5.12 (t, J = 7 Hz)	5.12 (t, J = 7 Hz)
H-12	1.68	1.68	1.68
C-3 Me	1.64	1.64	1.64
C-7 Me	1.10	1.13	1.10
C-11 Me	1.62	1.62	1.62

[a] At 270 MHz in $CDCl_3$; values are in δ units. [b] For numbering system, see structure **1a.**

double-bond isomer **17a** (5% yield). NMR analysis of **1a** and **17a** indicated each to be contaminated by approximately 15% of the corresponding **b** series diastereomer, based on the signal for the C-7 methyl group in each case (vide infra).

Natural (−)-α-bisabolol was isolated from chamomile oil[13] as previously described.[1c,h] The natural material was essentially indistinguishable from (±)-**1a** and (±)-**1b** in the infrared and mass spectra, and all three compounds gave the same trichloride, mp 78–80 °C, upon treatment with gaseous hydrogen chloride.[1f] The compounds were readily distinguishable in the NMR, however, by virtue of the signals for the C-7 methyl and C-2 hydrogen (see Table I); it was clear from these data that the natural product corresponded to synthetic (±)-**1a**. The diastereomeric racemic α-bisabolols were also distinguishable by gas chromatography on a 150-ft Carbowax 20M capillary column; coinjection of the natural material with each of the synthetic diastereomers confirmed the correspondence of the former with (±)-**1a.** *Natural (−)-α-bisabolol must therefore be assigned the 6S,7S configuration shown in* ***1a,*** *as opposed to the previous assignment.*[4b]

That the synthetic approach was stereospecific was shown by the fact that both NMR and GC analyses indicated the (±)-**1a** to be contaminated with approximately 15% of (±)-**1b** but the (±)-**1b** to be free of the diastereomeric (±)-**1a,** in direct correspondence to the 6,7 double-bond isomer purity of the starting farnesals **13a** and **13b.** The stereochemistry assigned to the racemic bisabolols thus rests on the well-precedented[7,8] expectation of stereospecific cis addition in intramolecular 1,3-dipolar cycloadditions of olefinic nitrones. We therefore are unable to reconcile the contradiction between our results and those of Kergomard and Veschambre[4b] concerning the stereochemistry of (−)-α-bisabolol. Until the source of this discrepancy can be identified, the stereochemistry of this natural product and related compounds[4b] must be considered an unresolved question.[14,15]

Experimental Section

Melting points were measured on a Kofler microscope hot stage and are uncorrected. NMR spectra were recorded on Varian A-60, Bruker HFX-90, or Bruker HFX-270 spectrometers. The NMR spectra were obtained in $CDCl_3$ unless otherwise noted; chemical shifts are reported in parts per million downfield from tetramethylsilane (δ), and coupling constants are reported in hertz. Mass spectra were obtained using an AEI MS902 instrument. Optical rotations were obtained on a Bendix-Ericsson automatic polarimeter equipped with a Bendix DR-1 digital readout. Gas chromatographic (GC) analyses were carried out using Varian Aerograph 1200 or Tracor MT 220 instruments, and preparative high-pressure liquid chromatography (LC) was accomplished with a Waters Associates ALC 202/401 liquid chromatograph equipped with ⅜-in. stainless steel columns packed with Porasil B (75–125 μm). Combustion analyses were carried out by M-H-W Laboratories, Garden City, Mich.

Neral *N*-Methylnitrone (5a). A solution of 1.14 g (7.40 mmol) of nerol (**18**) (Chemical Samples Co., 95% isomer purity) in 180 mL of hexane was cooled in an ice bath, 19.6 g of activated MnO_2 was added, and the mixture was stirred at 0 °C for 3 h.[16] The slurry was filtered, and the filtrate was evaporated to give 679 mg (62%) of neral (**4a**), homogeneous to GC analysis (15% Carbowax 20M, 125 °C): NMR δ 1.59 (s, 3), 1.67 (s, 3), 1.96 (d, 3, J = 1 Hz), 2.07–2.77 (m, 4), 5.10 (t, 1, J = 7 Hz), 5.86 (d, 1, J = 8 Hz), 9.87 (d, 1, J = 8 Hz).

A solution of 499 mg (5.98 mmol) of $CH_3NHOH{\cdot}HCl$ in 50 mL of absolute ethanol containing a trace of phenolphthalein was cooled in an ice bath and neutralized by the dropwise addition of 1 M ethanolic sodium ethoxide until a faint pink color persisted. The ice bath was removed, a solution of 696 mg (4.58 mmol) of neral (**4a**) in 5 mL of absolute ethanol was added, and the mixture was stirred at 25 °C for 21 h. The solids were removed by filtration, the filtrate was evaporated, and the residue was dried under high vacuum to afford 798 mg (96%) of nitrone **5a** as a pale yellow oil, homogeneous to TLC (alumina, $CHCl_3$): NMR (CCl_4) δ 1.58 (s, 3), 1.65 (s, 3), 1.87 (s, 3), 2.11 and 2.15 (4), 3.58 (s, 3), 5.05 (br t, 1), 6.41 (d, 1, J = 10 Hz), 7.38 (d, 1, J = 10 Hz).

Geranial *N*-Methylnitrone (5b). Geranial was prepared as described for neral. From 1.14 g (7.40 mmol) of geraniol (Chemical Samples Co.) was obtained 547 mg (49%) of geranial (**4b**): NMR δ 1.60 (s, 3), 1.68 (s, 3), 2.14, 2.16, and 2.23 (7), 5.06 (br t, 1), 5.86 (d, 1, J = 8 Hz), 9.95 (d, 1, J = 8 Hz).

The nitrone was prepared as described for **5a** above. From 547 mg (3.59 mmol) of **4b** and 341 mg (4.08 mmol) of $CH_3NHOH{\cdot}HCl$ was obtained 622 mg (96%) of nitrone **5b** as a yellow oil, homogeneous to TLC (alumina, $CHCl_3$): NMR (CCl_4) δ 1.57 (s, 3), 1.63 (s, 3), 1.78 (s, 3), 2.09 and 2.14 (4), 3.58 (s, 3), 5.05 (br t, 1), 6.41 (d, 1, J = 10 Hz), 7.43 (d, 1, J = 10 Hz).

Cyclization of Nitrones 5a and 5b. A solution of 704 mg (3.89 mmol) of the neral nitrone **5a** in 150 mL of anhydrous xylene was refluxed with stirring under nitrogen for 23 h. The xylene was removed by distillation under vacuum. Hexane was added to the residue, the resulting slurry was filtered, and the filtrate was evaporated under reduced pressure to give 560 mg (80%) of the isoxazolidine **6** as an orange oil, homogeneous to TLC (alumina, $CHCl_3$). The NMR spectrum (see Table II) showed signals at δ 1.15 and 1.03 with peak heights in a 3:1 ratio, respectively.

Repetition of the above experiment with 522 mg (2.88 mmol) of the geranial nitrone **5b** afforded 413 mg (79%) of isoxazolidine **6**, again as an orange oil, identical in NMR, TLC, and GC (15% Carbowax 20M, 125 °C) with the product from **5a.**

Column chromatography of a 1.0-g sample of crude isoxazolidine **6** on 30 g of activity III alumina allowed isolation of 295 mg of pure *cis*-**6** (eluted with hexane) and 74 mg of pure *trans*-**6** (eluted with hexane–10% ether). The NMR spectra of each were consistent with the assignments in Table II.

Isoxazolidine Methiodides 7. To a solution of 4.7 g (26 mmol) of mixed isoxazolidines **6** in 100 mL of anhydrous ether was added 10 mL of methyl iodide, and the mixture was stirred at 25 °C for 3 days. The resulting thick yellow suspension was filtered, and the solid was washed with ether and dried under vacuum to give 6.9 g (82%) of methiodide **7** as a light yellow solid: mp 165–171 °C dec; NMR (Table II) indicated a 3:1 mixture of *cis*-**7** and *trans*-**7**, respectively. The melting point was unchanged after recrystallization from $CHCl_3$–ether.

Anal. Calcd for $C_{12}H_{22}ONI$: C, 44.59; H, 6.86; N, 4.33. Found: C, 44.96; H, 6.89; N, 4.13.

Methylation of *trans*-**6** gave *trans*-**7**, mp 169–171 °C dec, from $CHCl_3$–ether.

Anal. Found: C, 44.51; H, 6.76; N, 4.07.

Methylation of *cis*-**6** gave *cis*-**7**, mp 184–186 °C dec, from acetone. The NMR spectra of each of the pure salts were consistent with the assignments in Table II.

Tetrahydro-1,3-oxazine Methiodides 10. A mixture of 6.9 g (21 mmol) of methiodide **7** and 1.7 g of NaOH in 200 mL of water was slowly distilled, with periodic additon of more water to maintain the volume, until 700 mL of distillate was collected. The distillate was extracted thoroughly with ether, and the ether layer was dried over anhydrous Na_2SO_4 and evaporated to give 3.2 g of an orange liquid. Chromatography of the crude product on 100 g of activity III alumina, eluting with hexane to hexane–10% ether, afforded 2.1 g (51%) of the tetrahydro-1,3-oxazine **9** as an oil. GC analysis (12% SE-30, 125 °C) showed two peaks in an area ratio of 43:57; NMR, see Table III.

To a solution of 2.09 g (10.7 mmol) of **9** in 50 mL of anhydrous ether was added 5 mL of CH_3I, and the mixture was stirred at 25 °C for 12 h. The resulting precipitate was filtered, washed with ether, and dried under vacuum to yield 2.18 g (78%) of methiodide **10** as a light yellow solid: mp 186–190 °C; NMR (Table III) was consistent with an approximately 1:1 mixture of cis and trans isomers. Recrystallization from acetone afforded colorless crystals, mp 197–208 °C.

Anal. Calcd for $C_{13}H_{24}ONI$: C, 46.30; H, 7.17. Found: C, 46.32; H, 6.91.

Table II. NMR Spectra of Isoxazolidines and Methiodides[a]

compd	assignment[b] C-3Me	C-7 Me	N-Me	H-1	H-2	H-10	H-12	C-11 Me
cis-**6**[c]	1.70	1.15, 1.20	2.49	~2.7 (m)	5.25 (br)			
trans-**6**[c]	1.69	1.03, 1.24	2.50	~2.7 (m)	5.42 (br)			
cis-**3b**[d]	1.68	1.15	2.54	2.68 (m)	5.21 (br)	5.30 (m)	1.62	1.56
trans-**3b**[d]	1.68	1.03	2.58	2.68 (m)	5.36 (br)	5.03 (m)	1.62	1.56
cis-**3a**[e]	1.68	1.27	2.65		5.22 (m)	5.08 (m)	1.68	1.60
cis-**7**[d]	1.92	1.41, 1.74	3.37, 3.97	5.59 (m)	6.18 (br)			
trans-**7**[d]	1.83	1.47, 1.51	3.55, 3.95	5.00 (d, J = 10)	6.41 (br)			
cis-**14b**	1.95	1.42	3.41, 3.89	5.13 (m)	6.12 (br)	5.13 (m)	1.72	1.64
trans-**14b**	1.87	1.52	3.50, ~3.9	5.13 (m)	6.29 (br)	5.13 (m)	1.72	1.64
cis-**14a**[e]	1.93	1.73	3.38, 3.90		6.02 (m)	5.07 (m)	1.67	1.60

[a] At 60 MHz in $CDCl_3$ unless otherwise noted; chemical shifts are in δ units, and coupling constants are in hertz. [b] See **1a** for numbering system. [c] In CCl_4. [d] At 270 MHz. [e] Crude material; peaks due to the trans isomer could not be assigned.

Table III. NMR Spectra of Tetrahydro-1,3-oxazines and Methiodides[a]

compd	assignment[b] C-3 Me	C-7 Me	N-Me	O–CH_2–N	H-1	H-2	H-10	H-12	C-11 Me
cis-**9**[c]	1.68	1.20, 1.31[d]	2.18	3.92, 4.12 (AB q, J = 8.5)	2.85 (m)	5.48 (d, J = 5)			
trans-**9**[c]	1.68	1.14,[d] 1.20	2.33	4.13, 4.57 (AB q, J = 10)	3.38 (d, J = 10)	5.23 (br)			
cis-**15b**	1.67	1.13	2.20	3.87, 4.08 (AB q, J = 8.5)	2.89 (t, J = 4.5)	5.51 (d, J = 4.5)	5.12 (t, J = 7)	1.67	1.60
trans-**15b**	1.67	1.16	2.34	4.17, 4.59 AB q, J = 10)	3.42 (d, J = 10)	5.29 (br)	5.12 (t, J = 7)	1.67	1.60
cis-**15a**[c]	1.68	1.20[d]	2.19	3.92, 4.11 (AB q, J = 8.5)	2.7–3.5 (m)	5.52 (d, J = 5)	5.11 (m)	1.68	1.61
trans-**15a**[c]	1.68	1.29[d]	2.35	4.12, 4.58 (AB q, J = 10)	2.7–3.5 (m)	5.24 (br)	5.11 (m)	1.68	1.61
cis-**10**	1.88	1.36, 1.70	3.06,[d] 3.49	5.04, 5.17[d] (AB q, J = 9.5)	4.18 (t, J = 4.5)	5.70 (d, J = 4.5)			
trans-**10**	1.81	1.39, 1.48	3.10,[d] 3.56	5.04, 5.23[d] (AB q, J = 9)	4.66 (d, J = 10.5)	5.66			
cis-**16b**[c]	1.87	1.30	3.03, 3.45	4.9–5.3 (m)	.3–4.8 (m)	5.60 (m)		1.66	1.60
trans-**16b**[c]	1.80	1.47	3.03, 3.55	4.9–5.3 (m)	4.3–4.8 (m)	5.60 (m)		1.66	1.60
cis-**16a**	1.87	1.36[d]	3.04, 3.48	4.9–5.3 (m)	4.4–4.8 (m)	5.6–5.7 (m)		1.67	1.60
trans-**16a**	1.81	1.44[d]	3.10, 3.53	4.9–5.3 (m)	4.4–4.8 (m)	5.6–5.7 (m)		1.67	1.60

[a] At 270 MHz in $CDCl_3$ unless otherwise noted; chemical shifts are in δ units, and coupling constants are in hertz. [b] See **1a** for numbering system. [c] At 60 MHz. [d] Assignments of these signals to the cis and trans isomers may be interchanged.

Hydrogenolysis of 10 to α-Terpineol (11). A dried 25-mL, three-neck flask equipped with a gas inlet tube and a dry ice condenser was charged with 74 mg (0.22 mmol) of the methiodide **10**. The flask was immersed in a dry ice–acetone bath, and ~20 mL of liquid ammonia (distilled from sodium) was allowed to condense. To the mixture was added 41 mg (5.9 mmol) of lithium metal, and the resulting blue solution was stirred at −78 °C for 2 h. The bath was removed and the ammonia allowed to evaporate. Ether was added, and the excess lithium was decomposed with methanol. The ether solution was washed with water, dried over anhydrous Na_2SO_4, and evaporated to yield 22 mg of a colorless oil. GC analysis (15% Carbowax 20M, 120 °C) showed two peaks in an area ratio of 16:84 in order of increasing retention time; the later peak had the same retention time as authentic α-terpineol.

The combined product from several such reactions (176 mg, 1:4 ratio of the two peaks in GC) was chromatographed on 8 g of silicic acid 25% silver nitrate. Elution with hexane–10% acetone afforded 107 mg of (±)-α-terpineol (**11**) as a colorless liquid: NMR δ 1.17 (s, 6), 1.67 (s, 3), 5.43 (m, 1); mass spectrum, *m/e* 154 (tr.), 136 (56), 121 (56), 93 (79), 81 (47), 59 (100); indistinguishable from authentic α-terpineol (Eastman Chemical Co.) in its NMR and mass spectra, and in GC behavior on two columns (Carbowax 20M and SE-30). Additional elution of the column with hexane–10% acetone gave 27 mg of the minor component **12**: NMR δ 0.95 (d, 3, J = 6.5 Hz), 1.16 and 1.19 (6), 5.69 (m, 2); mass spectrum, *m/e* 136 (4), 96 (18), 81 (21), 59 (100).

(6*E*)-Farnesal *N*-Methylnitrone (2b). To a solution of 110 mL of anhydrous pyridine in 500 mL of anhydrous CH_2Cl_2 was added 67 g (0.67 mol) of CrO_3[11] with stirring under nitrogen in an ice bath. The bath was removed, and stirring was continued for 45 min; then 25.0 g (0.113 mol) of (6*E*)-farnesol[12] (a 3:2 mixture of 2*E* and 2*Z* isomers by GC analysis on 12% SE-30 at 150–220 °C) was added. The resulting black mixture was stirred at 25 °C for 1.5 h and then the solution was decanted and the residue washed with 300 mL of ether. The combined solutions were evaporated, ether was added, and the solids were removed by filtration. The filtrate was extracted with dilute HCl, saturated Na_2CO_3 solution, and saturated NaCl solution and then was dried over anhydrous Na_2SO_4 and evaporated to yield 23.7 g (96%) of (6*E*)-farnesal (**13b**): IR ($CHCl_3$) 1675 cm^{-1}; NMR (CCl_4) δ 1.58 (s, 6), 1.66 (s, 3), 1.96, 2.12, 2.15, 2.22, 5.01 (m, 2), 5.72 (d, 1, J = 8 Hz), 9.72 and 9.80 (d, 1, J = 8 Hz); the doublets at δ 9.72 and 9.80 were in an ~2:3 ratio, respectively.

The procedure described for the preparation of **5a** was applied to 20.0 g (0.091 mol) of (6*E*)-farnesal to give 20.2 g (89%) of crude *N*-methylnitrone **2b** as a red oil which showed one major and several minor spots on TLC (alumina, $CHCl_3$). The material was chromatographed twice on 600 g of activity III alumina, eluting with hexane–ether, to afford 11.1 g (49%) of (6*E*)-farnesal *N*-methylnitrone (**2b**), homogeneous to TLC: IR ($CHCl_3$) 1625, 1560, 1430, 1400, 1370, 1155, 946 cm^{-1}; NMR (CCl_4) δ 1.57 and 1.65 (9), 1.80, 1.90, 1.95, 2.13, and 2.18 (11), 3.58 (s, 3), 5.03 (br m, 2), 6.41 (d, 1, J = 10 Hz), 7.25 (d, 1, J = 10 Hz); mass spectrum, *m/e* 249, 234, 224, 204, 180, 164, 161, 113, 98, 81, 69 (100).

(*SR,RS*)-Tetrahydro-1,3-oxazine Methiodides 16b. The procedure described for the cyclization of nitrones **5a** and **5b** was applied to 11.1 g (44.4 mmol) of (6*E*)-farnesal *N*-methylnitrone (**2b**) to yield 11.6 g (100+%, contaminated with xylene) of the crude isoxazolidines **3b**: NMR, see Table II; mass spectrum, *m/e* 249, 234, 164 (100), 98, 97, 69.

A sample of 972 mg of this crude **3b** was quaternized as described for the preparation of **7** to give 974 mg (67%) of the isoxazolidine methiodides **14b** as a light yellow solid: mp 113–128 °C; NMR (Table II) indicated a 3:1 mixture of *cis*-**14b** and *trans*-**14b**, respectively, based on the heights of the signals at 1.95 and 1.87, 1.42 and 1.52, and 3.41 and 3.50.

The 974-mg (2.49-mmol) sample of **14b** was subjected to ring expansion as described for **7**, yielding 462 mg (72%) of tetrahydro-1,3-oxazine **15b** as a light yellow oil after steam distillation and extraction: NMR, see Table III.

A solution of 372 mg (1.41 mmol) of crude **15b** in 15 mL of anhydrous ether and 1 mL of CH_3I was stirred at 25 °C for 12 h. The resulting precipitate was isolated as before to give 362 mg (63%) of methiodide **16b** as a yellow solid: mp 135–160 °C; NMR (Table III) indicated a 3:2 mixture of *cis*-**16b** and *trans*-**16b**, respectively, based on the heights of the signals at δ 1.87 and 1.80 and 3.45 and 3 55. Recrystallization of a sample of this mixture from ethanol–ether gave a yellow solid, mp 170–195 °C, shown by NMR to be a 3:1 mixture in favor of *cis*-**16b**: mass spectrum, *m/e* 278.2484 (calcd for $C_{18}H_{32}ON$, 278.2484). Recrystallization of a sample of the original mixture from acetone afforded colorless crystals, mp 198–202 °C, of pure (NMR) *trans*-**16b**.

Anal. Calcd for $C_{18}H_{32}ONI$: C, 53.33; H, 7.96; N, 3.46. Found: C, 53.09; H, 8.18; N, 3.37.

A solution of 11 mg (0.027 mmol) of the *trans*-**16b** in 0.7 mL of hexamethylphosphoramide containing lithium *n*-propyl mercaptide[17] was heated at 110 °C under nitrogen for 24 h.[18] The mixture was partitioned between water and hexane. The hexane layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to yield 6 mg (84%) of *trans*-**15b**, homogeneous to GC (15% Carbowax 20M, 175 °C) and NMR (Table III) analyses.

Hydrogenolysis of 16b to (*SR,RS*)-α-Bisabolol (1b). The procedure described for the hydrogenolysis of **10** was followed. From 214 mg (0.528 mmol) of **16b** (3:2 mixture of cis/trans) was obtained 140 mg of a colorless oil which was chromatographed on 12 g of silicic acid–25% silver nitrate. Elution with hexane–8% acetone afforded 48 mg (41%) of (*SR,RS*)-α-bisabolol (**1b**), 99.5% pure by GC (15% Carbowax 20M, 170 °C): NMR, see Table I; mass spectrum, *m/e* 222.1990 (calcd for $C_{15}H_{26}O$, 222.1983), 204, 161, 121, 119, 109 (100), 95, 93, 79, 69.

Elution of the column with hexane–10% acetone gave 17 mg (15%) of **17b**, 98% pure by GC: NMR (270 MHz) δ 0.95 (d, 3, *J* = 7 Hz), 1.09 (s, 3), 1.62 (s, 3), 1.68 (s, 3), 5.13 (t, 1, *J* = 7 Hz), 5.63 and 5.73 (AB q, 2, *J* = 11 Hz); mass spectrum, *m/e* 222.1976 (calcd for $C_{15}H_{26}O$, 222.1983), 204, 135, 127, 109 (100), 95, 93, 86, 84, 69.

A solution of 26 mg (0.117 mmol) of **1b** in 5 mL of anhydrous ether was cooled with stirring in an ice bath, and anhydrous HCl was introduced via a gas dispersion tube until the solution was saturated.[1f] The mixture was then left at −20 °C for 12 h. The solvent was evaporated, and the solid residue was recrystallized twice from 95% ethanol to afford 15 mg of α-bisabolyl trichloride[1f] as white crystals, mp 78–80 °C. A mixture with the trichloride from authentic (−)-α-bisabolol (vide infra) had mp 78–80 °C.

(6*Z*)-Farnesal (13a). A solution of 29.3 g (0.190 mol) of nerol (**18**) (95% isomer purity) in 150 mL of hexane was cooled with stirring in an ice bath, and 16.2 g (0.118 mol) of PCl_3 was added dropwise over a period of several minutes; stirring was continued for an additional 0.5 h, and then 6 mL of methanol was added. The reaction mixture was extracted with water, saturated aqueous $NaHCO_3$, and saturated brine and then was dried over anhydrous Na_2SO_4 and evaporated to give 28.7 g (87%) of crude neryl chloride.

Nerylacetone (**19**) was prepared from the crude chloride by application of the ethyl acetoacetate procedure of Dauben and Bradlow.[19] The resulting ketone (75% yield) was shown by GC (15% Carbowax 20M, 125 °C) to be a mixture of 86% **19**, 10% geranylacetone, and 4% unidentified material: NMR δ 1.61 and 1.68 (s, 9), 2.08 (s, 3), 5.07 (br t, 2).

To a solution of 38.0 g (0.209 mol) of trimethyl phosphonoacetate in 175 mL of anhydrous ether stirred under nitrogen was added, simultaneously via pressure-equalizing dropping funnels, solutions of 6.11 g (0.266 mol) of Na in 175 mL of anhydrous methanol and 33.0 g (0.170 mmol) of nerylacetone (**19**) in 175 mL of anhydrous ether over a period of about 0.5 h.[20] The reaction mixture was stirred for an additional 0.5 h and then was poured into 1 L of water and extracted with ether. The combined extracts were washed with saturated brine, dried over anhydrous Na_2SO_4, and evaporated to give 37.2 g (88%) of methyl farnesate (**20**); GC analysis (15% Carbowax 20M, 175 °C) showed the composition to be (in order of increasing retention time) 26% 2*Z*,6*Z*, 4% 2*Z*,6*E*, 55% 2*E*,6*Z*, 9% 2*E*,6*E*, and 7% unidentified.

A solution of 35.2 g (0.141 mol) of **20** in 260 mL of anhydrous benzene was cooled in an ice bath, and 150 mL of a 20% solution of diisobutylaluminum hydride in hexane was added dropwise over 0.5 h. The mixture was stirred in the ice bath for 1 h and then was quenched in 400 mL of cold methanol. The solvents were evaporated under vacuum, hexane was added, and the suspension was filtered through a Millipore filter. The filtrate was evaporated under vacuum to yield 27.3 g (87%) of (6*Z*)-farnesol. The latter was oxidized using the procedure of Ratcliffe and Roderhorst[11] as described for the preparation of **13b** to give (6*Z*)-farnesal (**13a**): GC analysis (15% Carbowax 20M, 175 °C) showed an isomer distribution of approximately 88% 2*EZ*,6*Z* (**13a**) and 12% 2*EZ*,6*E* (**13b**); NMR δ 1.61 (s, ~3), 1.68 (s, ~6), 1.19–2.25 (m, 11), 5.10 (br t, 2), 5.87 (d, 1, *J* = 8 Hz), 9.88 and 9.97 (d, 1, *J* = 8 Hz); the doublets at δ 9.88 and 9.97 were in a 1:2 ratio, respectively.

(*SS,RR*)-α-Bisabolol (1a). The procedures described for the **b** series were followed in each case, but without purification of the intermediates. From 25.1 g (0.114 mol) of (2*EZ*,6*Z*)-farnesal (**13a**) was obtained 25.1 g (88%) of crude (6*Z*)-nitrone **2a**: IR ($CHCl_3$) 1630, 1560, 1440, 1400, 1370, 1150, 945 cm^{-1}; NMR δ 1.60, 1.67, 1.84–2.19, 3.68, 5.09 (br t), 6.57 (d, *J* = 10 Hz), 7.30 (d, *J* = 10 Hz). From 25.1 g (0.101 mol) of crude **2a** was obtained 24.9 g (99%) of isoxazolidine **3a**: NMR, see Table II. The latter was treated with CH_3I in acetonitrile to give 31.8 g (81%) of crude methiodide **14a** as a brown gum: NMR, see Table II.

Steam distillation of 31.7 g (0.081 mol) of crude **14a** from aqueous NaOH as before afforded 15.9 g of crude product, which was extracted into 10% aqueous HCl and then basicified and extracted back into hexane to give 7.44 g (35%) of tetrahydro-1,3-oxazine **15a** as a yellow oil: NMR, see Table III. The latter, upon treatment with CH_3I in ether, yielded 10.8 g (94%) of the methiodide **16a** as an orange glass: NMR, see Table III; mass spectrum, *m/e* 278.2487 (calcd for $C_{18}H_{32}ON$, 278.2484).

A 1.03-g (2.54-mmol) sample of crude **16a** was subjected to hydrogenolysis as before to afford 430 mg of crude product. A 195-mg portion of the latter was chromatographed on 12 g of silicic acid–25% silver nitrate. Elution with hexane–8% acetone yielded 77 mg (30%) of (*SS,RR*)-α-bisabolol (**1a**), 96% pure by GC (15% Carbowax 20M, 180 °C): NMR, see Table I, showed a signal at δ 1.13, ~15% of the height of the δ 1.10 peak; mass spectrum, *m/e* 222.1988 (calcd for $C_{15}H_{26}O$, 222.1983), 204, 161, 121, 119, 109 (100), 95, 93, 86, 84, 69.

Elution of the column with hexane–9% acetone gave 14 mg (5%) of **17a**, 94% pure by GC: NMR (270 MHz) δ 0.96 (d, *J* = 7 Hz), 1.16, 1.63, 1.68, 5.12, 5.63 (s); a signal also appeared at δ 1.09, ~14% of the height of the δ 1.16 peak; mass spectrum, *m/e* 222.1981 (calcd for $C_{15}H_{26}O$, 222.1983), 204, 135, 127, 109 (100), 95, 93, 86, 84, 69.

A sample of 13 mg (0.059 mmol) of **1a** was converted to the trichloride as described for **1b**, giving 10 mg (54%) of white crystals, mp 78–81 °C, after recrystallization from 95% ethanol. A mixture with the trichloride from authentic (−)-α-bisabolol (vide infra) had mp 78–80 °C.

Natural (−)-α-Bisabolol. A 5.53-g sample of chamomile oil[13] was chromatographed on 200 g of Florisil, with monitoring of the composition of the fractions by GC (15% Carbowax 20M, 175 °C). Elution with pentane–4 and 5% ether afforded 2.29 g of oil containing ~60% α-bisabolol by GC. A 412-mg portion of this material was subjected to LC on a 12-ft column, using hexane–5% ether at a flow rate of 4.0 mL/min and differential refractive index detection, to yield 148 mg of (−)-α-bisabolol, 97% pure by GC: $[\alpha]^{25}_{Hg}$ −63.0°, $[\alpha]^{24}_{D}$ −68.4° (*c* 1.16, EtOH) (lit. $[\alpha]^{26}_{D}$ −60.2°,[1f] $[\alpha]_{D}$ −55.7°,[1c] $[\alpha]^{20}_{D}$ −67.6°[1d]); NMR, see Table I; mass spectrum, *m/e* 222.1981 (calcd for $C_{15}H_{26}O$, 222.1983), 204, 161, 121, 119, 109, 95, 93, 79, 69 (100).

A sample of the (−)-α-bisabolol was converted to the trichloride as described for **1b** to yield white crystals, mp 78–80 °C, after three recrystallizations from 95% ethanol (lit. mp 79–80,[1c-2b] 77–79,[1b] 79,[1i] and 77.5–78 °C[4a]).

Anal. Calcd for $C_{15}H_{27}Cl_3$: C, 57.42; H, 8.67; Cl, 33.90. Found: C, 57.13; H, 8.93; Cl, 33.77.

GC analysis (150 ft × 0.01 in capillary column coated with Carbowax 20M, 170 °C) of a mixture of the (−)-α-bisabolol with **1b** showed two peaks, retention times 80.2 and 80.8 min; a mixture of the former with **1a** gave one peak, retention time 79.6 min.

Registry No.—(±)-**1a**, 67375-41-1; (±)-**1b**, 25428-43-7; **1b** trichloride, 68813-47-8; **2a**, 68813-48-9; **2b**, 68813-49-0; *cis*-**3a**, 68852-

74-4; *cis*-**3b**, 68889-59-8; *trans*-**3b**, 68813-37-6; **4a**, 106-26-3; **4b**, 141-27-5; **5a**, 68813-50-3; **5b**, 68813-51-4; *cis*-**6**, 68813-35-4; *trans*-**6**, 68813-36-5; *cis*-**7**, 68813-38-7; *trans*-**7**, 68813-39-8; *cis*-**9**, 68813-41-2; *trans*-**9**, 68813-42-3; *cis*-**10**, 68813-44-5; *trans*-**10**, 68813-45-6; **11**, 2438-12-2; **12**, 19651-06-0; **13a**, 3790-68-9; **13b**, 4380-32-9; *cis*-**14a**, 68852-76-6; *cis*-**14b**, 68813-40-1; *trans*-**14b**, 68852-75-5; *cis*-**15a**, 68852-78-8; *trans*-**15a**, 68852-79-9; *cis*-**15b**, 68813-43-4; *trans*-**15**, 68852-77-7; *cis*-**16a**, 68852-81-3; *trans*-**16a**, 68852-82-4; *cis*-**16b**, 68813-46-7; *trans*-**16b**, 68852-80-2; **17a**, 68813-52-5; **17b**, 68852-83-5; **18**, 106-25-2; **19**, 3879-26-3; (2*Z*,6*Z*)-**20**, 4176-78-7; (2*Z*,6*E*)-**20**, 4176-77-6; (2*E*,6*Z*)-**20**, 4176-79-8; (2*E*,6*E*)-**20**, 3675-00-1; (6*E*)-farnesol, 3790-71-4; (6*Z*)-farnesol 16106-95-9; neryl chloride, 20536-36-1; geranial, 106-24-1; (−)-α-bisabolol, 23089-26-1.

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(13) Chamomile oil, "German Extra" from Fritzsche Bros., New York, N.Y.; we thank Dr. P. A. Hedin of the USDA Boll Weevil Research Laboratory, State College, Miss., for a generous sample of this oil.

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Total Synthesis of an Estrajervatetraene[1]

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Received August 31, 1978

The benzdecalone **2a** was converted to the benzindanone **7a** by peroxide cleavage of the furfurylidene derivative **3** and subsequent base-catalyzed cyclization of the corresponding diester **5b**. Michael addition of the keto ester **7a** to methyl vinyl ketone followed by anhydrous lithium iodide–collidine cyclization of the adduct **8b** gave the desired etiojervane **9b** in good yield.

The veratrum alkaloids have long been recognized as potent vasoactive agents.[2] More recently we have described simpler (C_{19}) analogues which contain the same jervane skeleton found in the veratrum alkaloids and which possess similar stereochemistry.[3] These derivatives have shown significant antimineralocorticoid activity.[3,4] Because of this pharmacological activity, it became important to explore alternate synthetic routes in this series in ways which would allow preparation of compounds not readily obtained from natural sources. One such route involves the total synthesis of the etiojervane **9**.

Since the inception of this work, a great deal of effort has been expended in the partial and total syntheses of various etio- and pregnajervanes.[5] However none of these efforts readily provided etiojervanes possessing a cis C/D ring juncture, a feature important to the antimineralocorticoid activity of these compounds.[6]

The initial strategy to obtain a C/D *cis*-estrajervatriene was to find a route which would lead by relatively certain steps to the estrajervatetraene **9**. Simpler, more efficient or more elegant routes would be developed as the need arose. Accordingly an AB → C → D sequence was chosen in which a benzindanone of fixed stereochemistry (B/C trans) would be prepared at an early stage.

The desired benzindanone **4a** was unknown, but work by Juday[7] indicated that a direct reduction of a C ring unsaturated benzindanone would be unlikely to give the desired trans isomer. To circumvent this problem, the corresponding phenanthrone **1** was chosen as a starting material since the B/C *trans*-phenanthrones could be prepared from it by a known route.[8] Direct reduction of the unsaturated ketone **1** with lithium–ammonia gave a 2:3 mixture of *trans*-/*cis*-ketones; moreover, separation of the desired isomer from the mixture was difficult. Catalytic reduction of ketone **1** was remarkably slow, leading to mixtures containing extensive amounts of material containing hydroxyl group absorption but no ketone.

Potassium–ammonia reduction of the ethylenedioxy ketal of **1** afforded a 4:1 ratio of *trans*-/*cis*-ketones which were readily separated by fractional crystallization. Hydrolysis gave the known *trans*-ketone **2a**.[8]

Conversion of the benzdecalone **2a** to the benzindanone **4a** was accomplished by well-established methodology.[9] The furfurylidene ketone **3** was prepared in 87% yield by treatment of the ketone **2a** with furfural in methanolic base. Cleavage of the ketone with basic peroxide provided a crystalline diacid **5a** in 68% yield.

Cyclization of the diacid **5a** to the desired ketone (**4a**) was

0022-3263/79/1944-0958$01.00/0