base had $[\alpha]_D^{20}$ −4.14° (c 0.125 g, 5 mL of $CHCl_3$)]. Anal. Calcd for $C_{21}H_{27}N_3 \cdot H_2O \cdot 2$ HCl: C, 61.16; H, 7.58; N, 10.19. Found: C, 61.38; H, 7.74; N, 10.09.

The presence of water and its approximate proportion were confirmed by ^1H NMR. A sample converted to base was extracted into chloroform and dried for ^{13}C and ^1H NMR. The dihydrochloride monohydrate appears to lose gas at 200–270 °C and melts with decomposition at 272–278 °C.

The enantiomer, (*R,R*)-**2**, similarly prepared, had $[\alpha]_D^{20}$ −4.22° (c 0.129 g, 5 mL of $CHCl_3$), +4.57 (c 0.1031 g, 5 mL of 0.1 N aqueous HCl).

Acknowledgment. We thank Dr. W. Pendergast who prepared the initial sample of compound **5** for use and advised us on details of earlier parts of this synthetic method and Dr. B. R. Cooper for permission to summarize his animal test results.

Registry No. **2**(*S,S*), 95586-97-3; **2**(*S,S*)·2HCl, 95586-98-4; **2**(*R,R*), 95586-99-5; **4**(*R*), 10009-70-8; **5**(*R*), 51063-99-1; **5**(*S*), 30365-54-9; **7**(*S,S*), 84029-00-5; **7**(*R,R*), 95482-49-8; **7**(*R,S*), 84028-99-9; **8**(*S,S*), 95482-50-1; **8**(*R,R*), 95482-51-2; **8**(*R,S*), 95482-62-5; **9**(*S,S*), 95482-52-3; **9**(*R,R*), 95482-53-4; **10**(*S,S*), 95482-54-5; **10**(*R,R*), 95482-55-6; **11**(*S,S*), 95482-56-7; **11**(*R,R*), 95482-57-8; **12**(*S,S*), 95482-58-9; **12**(*R,R*), 95482-59-0; **13**(*S,S*), 95482-60-3; **13**(*R,R*), 95482-61-4; (*R,R*)-2,2′-iminobis[propionic acid] hydrochloride, 95586-06-4; D-alanine, 338-69-2; L-alanine ethyl ester hydrochloride, 1115-59-9; D-alanine ethyl ester hydrochloride, 6331-09-5; ethyl chloroformate, 541-41-3; *N,N′*-dicyclohexylurea, 2387-23-7; 9-(3-aminopropyl)carbazole, 23690-10-0.

Syntheses of (±)-α- and (±)-β-Eudesmol and Their Diastereomers by Intramolecular Nitrone–Olefin Cycloaddition[1]

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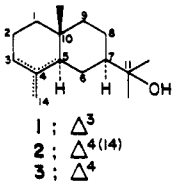
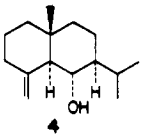
(±)-α-Eudesmol and its three possible diastereomers, 7-epi-, 5-epi-, and 5-epi-7-epi-α-eudesmol, as well as (±)-β-eudesmol and 7-epi-β-eudesmol, have been synthesized from farnesol.

The three isomeric eudesmols, (+)-α- (**1**), (+)-β- (**2**), and (+)-γ-eudesmol (**3**), are among the most widely distributed sesquiterpenes in nature.[2] Considerable effort has been



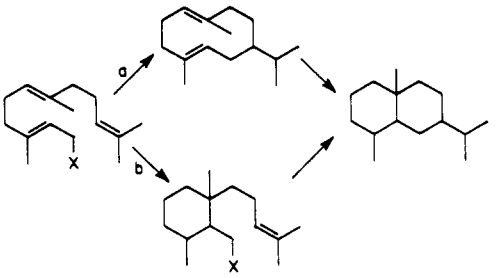
1; Δ^3
2; $\Delta^{4(14)}$
3; Δ^4



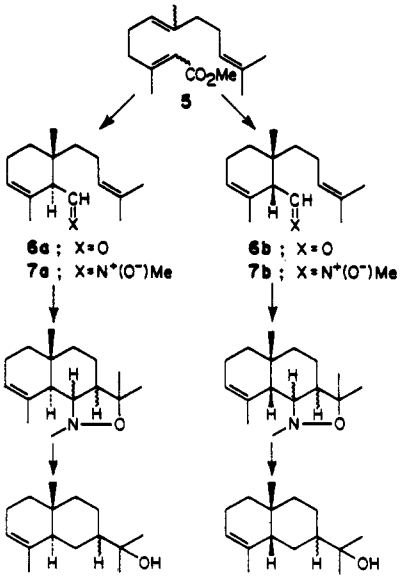
4

directed to the total synthesis[3] of these deceptively simple natural products as well as of some of their diastereomers.[4] Biomimetic syntheses of eudesmols based on the farnesane → germacrane → eudesmane biosynthetic pathway[5] (Scheme I, path a) have also been recorded.[6] We some time ago applied an alternate cyclization-based approach (Scheme I, path b) to the synthesis of the eudesmane sesquiterpene (±)-junenol (**4**).[7] We wish now to describe

Scheme I



Scheme II



5

6a; X=O
7a; X=N⁺(O⁻)Me

6b; X=O
7b; X=N⁺(O⁻)Me

a modification and extension of this approach which allows syntheses of racemic **1** and all three of its diastereomers,

(1) Taken from Willbrand, A. M. Ph.D. Dissertation, The Florida State University, 1981.

(2) For example, the Chemical Abstracts 9th Collective Index lists 17 new sources of β-eudesmol (**2**); eudesmols have been isolated from more than 50 sources.

(3) (a) Marshall, J. A.; Pike, M. T.; Carroll, R. D. *J. Org. Chem.* **1966**, *31*, 2933. (b) Humber, D. C.; Pinder, A. R.; Williams, R. A. *Ibid.* **1967**, *32*, 2335. (c) Heathcock, C. H.; Kelly, T. R. *Tetrahedron* **1968**, *24*, 1801. (d) Huffman, J. W.; Mole, M. L. *J. Org. Chem.* **1972**, *37*, 13. (e) Carlson, R. G.; Zey, E. G. *Ibid.* **1972**, *37*, 2468. (f) Miller, R. B.; Nash, R. D. *Ibid.* **1973**, *38*, 4424. (g) Posner, G. H.; Loomis, G. L. *Ibid.* **1973**, *38*, 4459. (h) Cooper, J. L.; Harding, K. E. *Tetrahedron Lett.* **1977**, 3321.

(4) (a) Marshall, J. A.; Pike, M. T. *J. Org. Chem.* **1968**, *33*, 435. (b) Huffman, J. W.; Miller, C. A.; Pinder, A. R. *Ibid.* **1976**, *41*, 3705. (c) Zalkow, L. H.; Smith, M.; Chetty, G. L.; Shaligram, A. W.; Ingwalson, P. *Ibid.* **1976**, *41*, 3710. (d) Baker, R.; Evans, D. A.; McDowell, P. G. *Tetrahedron Lett.* **1978**, 4073.

(5) Parker, W.; Robberts, J. S.; Ramage, R. *Q. Rev., Chem. Soc.* **1967**, *21*, 331.

(6) (a) Kodama, M.; Yokoo, S.; Matsuki, Y.; Itô, S. *Tetrahedron Lett.* **1979**, 1687 and previous papers in this series. (b) Kodama, M.; Shimada, K.; Itô, S. *Ibid.* **1981**, *22*, 1523.

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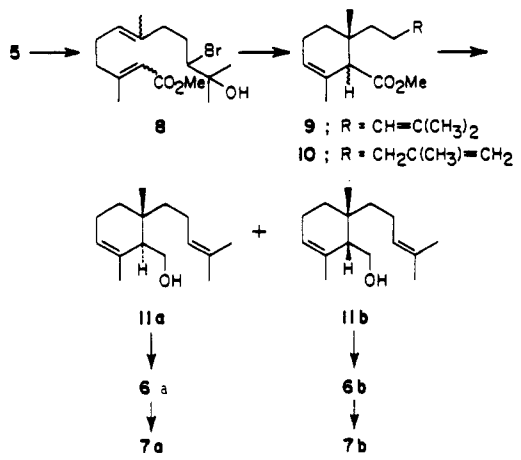
Scheme III



as well as racemic 2 and its C-7 epimer.[8]

In an effort to improve upon the unfavorable stereoselectivity encountered in the second cyclization step of the junenol synthesis, we planned to utilize an intramolecular nitrone–olefin cycloaddition[9] to generate the second ring. Thus, methyl farnesate (**5**) would be converted[7] to the (*SR,RS*)- and (*SS,RR*)-monocyclofarnesals (**6a** and **6b**, respectively, Scheme II). The derived *N*-methylnitrones **7a** and **7b** would undergo 1,3-dipolar cycloaddition to the corresponding tricyclic isoxazolidines, which upon reductive deamination[9a] would yield the α-eudesmols. Based on LeBel's stereochemical studies on intramolecular nitrone cycloadditions,[10] (*SR,RS*)-monocyclofarnesal nitrone **7a** would be expected to give predominately the *trans-anti-trans*-isoxazolidine, with the trans-anti-cis tricycle as a minor product. The isomer ratio might also be expected to vary as a function of reaction temperature,[10] in which case both (±)-α-eudesmol (**1**) and its 7-epimer would be available. The (*SS,RR*)-monocyclofarnesal nitrone **7b** would similarly yield cis-fused α-eudesmol diastereomers (Scheme II).

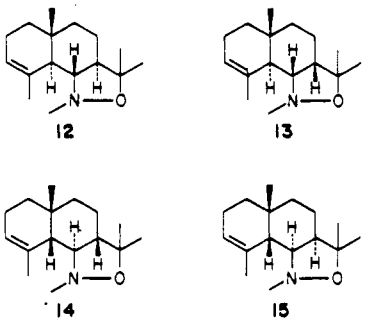
Results

Methyl farnesate (**5**, mixture of all four stereoisomers) was oxidized with *N*-bromosuccinimide in aqueous tetrahydrofuran[11] to the 10,11-bromohydrin **8** (Scheme III) in 68% yield. Cyclization of **8** with 85% phosphoric acid and reduction of the crude product with zinc and acetic acid afforded a 61% yield of the methyl monocyclofarnesates **9**, contaminated by approximately 5% of the side chain double bond isomer **10** (NMR). This method for the cyclization of **5** to **9** was found to be more reproducible and not to require the careful chromatographic separations needed in our previously reported[7] methods.

Lithium aluminum hydride reduction of ester **9** gave a mixture of epimeric alcohols which was separated by preparative HPLC to give (*SR,RS*)-monocyclofarnesol **11a** in 47% yield and (*SS,RR*)-monocyclofarnesol **11b** in 34% yield. The stereochemical assignments for the two alcohols and the derived aldehydes **6a** and **6b** were made initially on the basis of the ^{1}H NMR shifts of the quaternary methyl group. The methyl protons consistently appeared at higher field in the *SS,RR* diastereomers (δ 0.87–0.89) than in the corresponding *SR,RS* isomers (δ 0.96–1.00); the most stable conformation (minimum $A^{1,2}$ strain) of the *SS,RR* compound is the one in which the methyl group must occupy an axial position and thus experience some shielding by the endocyclic double bond. The assignment of stereochemistry to **6a** and **6b** was confirmed by the conversion[7] of monocyclofarnesal **6a** to (±)-junenol (**4**) and (±)-dihydrojunenol.

Treatment of aldehyde **6a** with *N*-methylhydroxylamine in absolute ethanol at 25 °C afforded nitrone **7a** in 92% yield; the corresponding reaction with **6b** gave nitrone **7b** in 76% yield. Both nitrones could be isolated as stable crystalline solids.

(*SR,RS*)-Nitrone **7a** underwent intramolecular cycloaddition upon being heated at 90 °C in toluene for several days to give two isoxazolidines. The major product, isolated in 50% yield, was identified as the trans-anti-trans tricycle **12** by its NMR spectrum; H-6 (eudesmol numbering) appeared as a triplet at δ 3.17, J = 12 Hz, consistent with an axial H coupled to two adjacent axial protons. The minor product (12% yield) exhibited H-6 as a double doublet at δ 3.01, J = 12 and 7.5 Hz, consistent with the trans-anti-cis diasteromer **13**. When the cyclization was carried out at 140 °C in refluxing xylene, isoxazolidines **12** and **13** were isolated in yields of 44% and 20%, respectively.



The analogous cycloaddition of (*SS,RR*)-nitrone **7b** at 90 °C in toluene afforded isoxazolidines **14** and **15** in 9% and 74% yields, respectively. The cis-anti-trans stereochemistry of **14** was assignable on the basis of H-6 appearing as a triplet at δ 2.50, J = 12 Hz. However, tricycle **15** could not be unambiguously identified from its NMR spectrum; the H-6 resonance at δ 2.88 appeared as a triplet, J = 7 Hz, which would be consistent with either the cis-anti-cis or cis-syn-cis stereochemistries. The former seemed more likely on mechanistic grounds because it would be the result of cycloaddition via a twist boat transition state[10] in which C-6 was pseudoaxial to the cyclohexene ring; generation of the cis-syn-cis stereochemistry would require C-6 to be pseudoequatorial in the transition state, with a resulting serious $A^{1,2}$ interaction with the C-4 methyl group. The final assignment of **15** as the cis-anti-cis isomer was made when it was converted to an α-eudesmol diastereomer different from those obtained from isoxazolidines **12**, **13**, or **14** (vide infra); the cis-syn-cis isomer would have given the same α-eudesmol as was obtained from **14**. The isoxazolidine product distribution changed dramatically when the cycloaddition of **7b** was carried out at 140 °C in refluxing xylene, with **14** and **15** being obtained in yields of 34% and 31%, respectively.

(7) (a) Schwartz, M. A.; Crowell, J. D.; Musser, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 4361. (b) Crowell, J. D. Ph.D. Dissertation, The Florida State University, 1972.

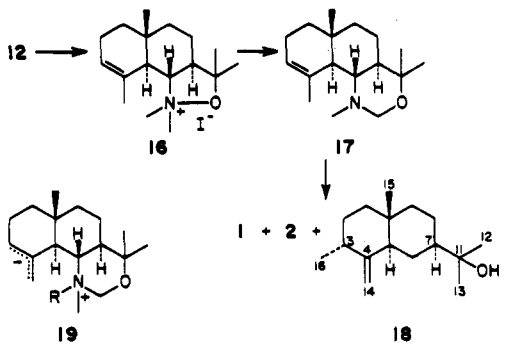
(8) All of the compounds synthesized in this work are racemic. For convenience, however, the structures depict the absolute configuration of the natural (+)-eudesmol, and "epi-" designations for the diastereomers are made relative to the enantiomer with the 10-β configuration in each case.

(9) (a) Schwartz, M. A.; Swanson, G. C. *J. Org. Chem.* **1979**, *44*, 953. (b) For other recent applications of nitrone cycloadditions in synthesis, see: Wovkulich, P. M.; Uskoković, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 3956 and references therein.

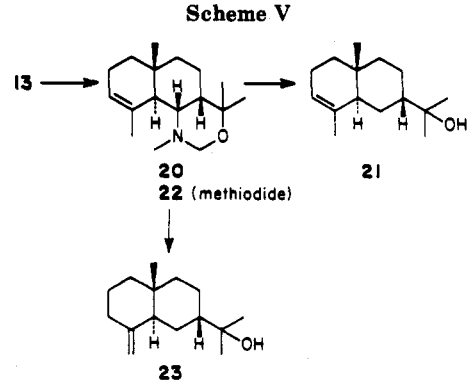
(10) LeBel, N. A.; Banucci, E. G. *J. Org. Chem.* **1971**, *36*, 2440.

(11) (a) Hessler, E. J. Ph.D. Dissertation, Stanford University, 1965. (b) van Tamelen, E. E.; Storni, A.; Hessler, E. J.; Schwartz, M. A. *Bioorg. Chem.* **1982**, *11*, 133.

Scheme IV



Scheme V



Completion of the synthesis of the diastereomeric eudesmols required removal of the nitrogen function from the four isoxazolidines. Our previously successful reductive deamination sequence,[9a] proceeding via tetrahydro-1,3-oxazine methiodide intermediates, was applied. *trans-anti-trans*-Isoxazolidine **12** reacted smoothly with methyl iodide and the resulting methiodide **16** (Scheme IV) underwent ring expansion to the tetrahydro-1,3-oxazine **17** upon refluxing with aqueous NaOH in a two-phase medium containing hexane, both steps proceeding in high yields.

As might be expected, quaternization of **17** proved to be far more difficult than was alkylation of **12**. The amine was recovered unchanged after being heated in neat methyl iodide at 80 °C (sealed tube) for five days. Alkylation did occur when **17** was heated with methyl iodide in acetonitrile or in sulfolane (tetrahydrothiophene 1,1-dioxide)[12] in the presence of sodium or potassium carbonate in a sealed tube at 80–90 °C for several days; however, the resulting methiodide in each case was obviously a mixture based on its NMR spectrum. When the methiodide mixture from a reaction in acetonitrile was subjected to hydrogenolysis with lithium in liquid ammonia,[9a] an alcohol fraction was isolated (58% yield) which was shown by gas chromatographic analysis to consist of α-eudesmol (**1**), β-eudesmol (**2**), and the subsequently identified 3-methyl-β-eudesmol **18** (Scheme IV) in the ratio of 50:36:14, respectively. β-Eudesmol (**2**) became the major product when the alkylation was carried out in technical grade sulfolane, with alcohols **1**, **2**, and **18** being generated in a 17:65:18 ratio (GC) after hydrogenolysis. The latter product mixture was essentially unchanged when the methylation reaction was carried out in technical sulfolane containing Na_2CO_3 with added Na_2SO_3, or in the dark, or when the alkylating agent was changed to methyl bromide or to dimethyl sulfate. However, when methylation was effected with methyl iodide in anhydrous sulfolane (refluxed and distilled from NaOH), subsequent hydrogenolysis of the methiodides afforded a 67:19:14 ratio (GC) of 1:2:18.

(±)-α-Eudesmol (**1**), mp 78–79 °C,[13] was isolated in 37% overall yield from **17** when the product from methiodide formation in anhydrous sulfolane followed by hydrogenolysis with lithium in liquid ammonia was chromatographed on silver nitrate impregnated silica gel. (±)-β-Eudesmol (**2**) was isolated similarly in 32% overall yield from the technical sulfolane reaction sequence. Each of the racemic sesquiterpenes was spectrally and chromatographically indistinguishable from its respective optically active counterpart (+)-**1** and (+)-**2**.[14]

The third alcohol, isolated in 6% yield from the reaction sequence involving methylation in technical sulfolane containing sodium carbonate was assigned the structure of 3α-methyl-β-eudesmol (**18**) based on its spectral properties, especially in comparison with those of **2**. The ^{13}C NMR spectrum of **18** correlated nicely with that of **2**, except that **18** showed an additional methyl signal at δ 20.18 and had the signals for C-2 and C-4 shifted downfield ca. 5 ppm and the signals for C-1 and C-5 shifted upfield ca. 5 ppm from the corresponding signals in the spectrum of **2**. The assigned stereochemistry at C-3 was confirmed by ^1H NMR spin decoupling studies; H-3 was coupled to the C-3 methyl group (J = 7 Hz), to H-2_{ax} (J = 5 Hz), and to H-2_{eq} (J = 1 Hz), consistent with H-3 being equatorial in a flattened chair ring conformation.

The co-occurrence of double bond isomerization and C-3 alkylation during the course of the quaternization of **17** suggested the intermediacy of an allyl anion in these reactions. The zwitterionic structure **19** (R = H or CH_3) might be unusually accessible because of the steric compression between C-14 and the nitrogen function. When methylation of **17** was carried out in anhydrous sulfolane to which had been added D_2O, subsequent reductive deamination of the product afforded alcohols **1**, **2**, and **18** in a 5:75:20 ratio; the (±)-β-eudesmol (**2**) isolated from this reaction was shown by mass spectrometry to be approximately 50% monodeuterated.

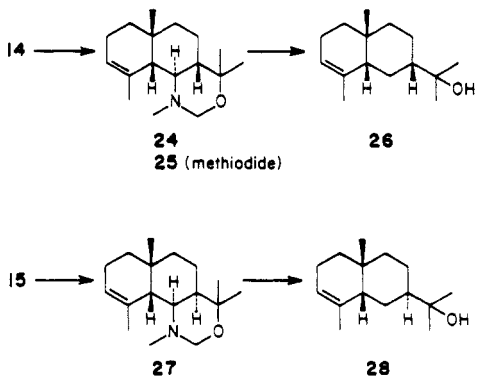
With total syntheses of the two natural eudesmols thus accomplished, attention was turned to generating their diastereomers. *trans-anti-cis*-Isoxazolidine **13** was converted to oxazine **20**, which was smoothly alkylated in neat methyl iodide at 80 °C to give a crystalline methiodide in 87% yield; reduction of the latter with lithium–ammonia afforded the previously unknown 7-epi-α-eudesmol (**21**) in 67% yield (Scheme V). The relative ease of methylation of oxazine **20** as compared to its stereoisomer **17** was probably due to the accessibility of a B ring boat conformation in the transition state for alkylation of **20**, which would relieve the peri interaction between the *N*-methyls and the C-4 methyl; the NMR spectrum of the methiodide **22** showed H-6 as a triplet at δ 4.32, J = 3 Hz, indicative of H-6 being equatorial in such a conformation. When the methylation of **20** was carried out with methyl iodide in technical sulfolane in the presence of potassium carbonate (80–85 °C, 3 days), subsequent hydrogenolysis of the methiodide mixture gave 7-epi-β-eudesmol (**23**)[4c,6b] in 30% overall yield; isomerization, presumably by way of a zwitterion analogous to **19**, once again occurred under these conditions.

cis-anti-trans-Isoxazolidine **14** gave the oxazine **24** in

(12) Coleman, B. D.; Fuoss, R. M. *J. Am. Chem. Soc.* **1955**, *77*, 5472.
(13) We have not been able to find a literature reference to (±)-α-eudesmol having been isolated in crystalline form previously.

(14) We thank Professor A. R. Pinder, Clemson University, for providing us with a sample of authentic (+)-**2** and with a gift of the "commercial eudesmols" mixture from which we isolated (+)-**1**.

Scheme VI



very high yield (Scheme VI). Quaternization of **24** occurred at room temperature in neat methyl iodide to afford a 90% yield of methiodide **25**, but hydrogenolysis of **25** in the usual way gave only an 11% yield of 5-epi-7-epi-α-eudesmol (**26**).[4d] The major hydrogenolysis product proved to be oxazine **24**, isolated in 85% yield; resubmission of the recovered **24** to the alkylation–hydrogenolysis sequence gave the same result, confirming *N*-methyl cleavage to be more facile than the normal N–C-6 cleavage in the case of methiodide **25**. A possible explanation of this behavior is that the cis-anti-trans stereochemistry does not allow a transition-state conformation in which a developing p orbital at C-6 will be parallel to, and thus capable of interacting with, the p orbitals of the Δ^3 double bond; in the absence of this homoallylic participation the *N*-methyl cleavage apparently becomes favored.

cis-anti-cis-Isoxazolidine **15** was converted to the corresponding oxazine **27**, which did not react with methyl iodide at 25 °C but was smoothly methylated (95% yield) in neat methyl iodide at 70 °C (Scheme VI). Hydrogenolysis of the resulting methiodide gave a 62% yield of 5-epi-α-eudesmol (**28**), which was distinguishable spectrally, gas chromatographically, and by melting point from the other three racemic α-eudesmols prepared in this work.

This alternative cyclization-based approach to the eudesmane sesquiterpenes thus provides stereocontrolled access to all four (±)-α-eudesmol diastereomers and to two of the (±)-β-eudesmols from farnesol. The intramolecular nitrone–olefin cycloaddition proved to be more stereoselective and more controllable than the intramolecular Lewis acid catalyzed ene reaction previously used[7] to form the second ring. The eudesmol synthesis is accomplished in 10 steps and 0.5–3% overall yield (depending on isomer) from methyl farnesate.

Experimental Section

General Methods. Melting points are uncorrected. Unless otherwise specified, IR spectra were measured in $CHCl_3$ and NMR spectra in $CDCl_3$. Column chromatographies were carried out with 60–200 mesh silica gel deactivated with 15% (w/w) water or with neutral alumina, activity III; silica gel–25% $AgNO_3$ was prepared by adding a solution of the appropriate amount of $AgNO_3$ in 15% (w/w) water and mixing thoroughly. Gas chromatographic (GC) analyses were done on a 30-m SE-30 glass capillary column with a flame ionization detector.

All solvents were distilled before use, except that technical grade sulfolane (mp 21–24 °C) was used directly, or was refluxed over NaOH pellets for 12 h and then was distilled (bp 75–80 °C (0.01 torr)) from NaOH and immediately used. Liquid ammonia was distilled from sodium metal directly into the cooled (−78 °C) reaction flask equipped with a dry ice condenser.

The isolation of products via extraction involved extraction of the reaction mixture with the specified solvent at least three times; the combined organic extracts were washed with H_2O and/or the specified aqueous solution followed by saturated aqueous NaCl, then were dried over anhydrous Na_2SO_4, and evaporated under reduced pressure on a rotary evaporator. The residue was dried under high vacuum for at least 0.5 h.

Methyl Farnesate 10,11-Bromohydrin (8).[11] A solution of 10.0 g (40.0 mmol) of methyl farnesate (**5**) in 150 mL of freshly distilled tetrahydrofuran (THF) and 15 mL of water was cooled to 0 °C and 7.83 g (44.0 mmol) of *N*-bromosuccinimide was added. The mixture was allowed to stand in the dark at 25 °C for 4 h with occasional stirring. The solvent was then evaporated and ether and water were added. The ether layer afforded 14.8 g of crude product which was chromatographed on silica gel, eluting with hexane and hexane–5% ether to give 9.46 g (27.3 mmol, 68%) of bromohydrin **8**: IR 3550, 2940, 1720, 1650, 1440, 1380, 1370, 1330, 1280, 1220, 1150 cm^{-1}; NMR (60 MHz) δ 5.66 (br s, 1 H), 5.16 (br s, 1 H), 3.92 (br m, 1 H), 3.66 (s, 3 H), 2.75–1.90 (12 H), 1.66 and 1.60 (3 H), 1.33 (s, 6 H). Anal. Calcd for $C_{16}H_{27}O_3Br$: C, 55.33; H, 7.84; Br, 23.01. Found: C, 55.48; H, 7.91; Br, 23.25.

Methyl Monocyclofarnesates 9. A solution of 5.00 g (14.4 mmol) of bromohydrin **8** in 25 mL of hexane was added to 175 mL of 85% phosphoric acid and the mixture was vigorously stirred with a mechanical stirrer at 25 °C for 6 h. The reaction mixture was diluted with ice water and was extracted with ether to afford 4.80 g of a viscous yellow oil. The crude product was dissolved in 200 mL of ether, 20 mL of glacial acetic acid and 10 g of zinc dust were added, and the mixture was refluxed with stirring under nitrogen for 18 h. The reaction mixture was cooled and filtered, and the filtrate was washed with water and with saturated aqueous $NaHCO_3$. The ether layer afforded a yellow oil which was chromatographed on silica gel with hexane to give 2.19 g (8.75 mmol, 61%) of ester **9**, containing 5% of the side chain double bond isomer **10**: IR 2915, 1725, 1450, 1435, 1380, 1325, 1155 cm^{-1}; NMR (60 MHz) δ 5.58 (br s, 1 H), 5.05 (br t, J = 6 Hz, 0.95 H), 4.67 (br s, 0.1 H), 3.68 (s, 3 H), 2.68 (br s, 1 H), 1.67 and 1.62 (9 H), 0.93 (s, 3 H); MS, *m/e* (relative intensity) 250 (16), 235 (3), 218 (9), 191 (13), 165 (22), 135 (22), 121 (48), 107 (100). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.76; H, 10.47. Found: C, 76.56; H, 10.61.

The ester mixture was used without further purification.

***(SR,RS)*- and *(SS,RR)*-Monocyclofarnesols 11a and 11b.** To a solution of 6.93 g (27.7 mmol) of methyl monocyclofarnesate (**9**) in 100 mL of THF was added excess lithium aluminum hydride and the mixture was refluxed with stirring under nitrogen for 17 h. After cooling, saturated aqueous sodium potassium tartrate was added dropwise to destroy the excess hydride, then 10% aqueous HCl was added to dissolve the salts. Extraction with ether afforded 5.93 g of crude product which was chromatographed on silica gel in hexane to yield 5.73 g of an oil. The alcohol mixture was separated by preparative HPLC (3 × 4 ft, $^3/_8$ in OD columns packed with Porasil B) with heptane–7% ether to give, in order of elution, 2.09 g (9.41 mmol, 34%) of (*SS,RR*)-monocyclofarnesol **11b** [IR 3460, 2915, 1460, 1380, 1065 cm^{-1}; NMR (60 MHz) δ 5.61 (br s, 1 H), 5.12 (br t, J = 7 Hz, 1 H), 3.70 (d, J = 4 Hz, 2 H), 1.76 (s), 1.70 (s), 1.62 (s), 0.89 (s, 3 H)] and 2.89 g (13.0 mmol, 47%) of (*SR,RS*)-monocyclofarnesol **11a** [IR 3450, 2910, 1450, 1380, 1045 cm^{-1}; NMR (60 MHz) δ 5.58 (br s, 1 H), 5.15 (br t, J = 6 Hz, 1 H), 3.73 (d, J = 5 Hz, 2 H), 1.73 (s), 1.67 (s), 1.58 (s), 1.00 (s, 3 H)].

***(SR,RS)*- and *(SS,RR)*-Monocyclofarnesals 6a and 6b.** To a solution of 5.25 mL (65.3 mmol) of pyridine in 25 mL of dichloromethane was added 3.26 g (32.6 mmol) of CrO_3 with rapid stirring in an ice bath.[15] The resulting mixture was stirred at 25 °C for 30 min, then a solution of 1.22 g (5.49 mmol) of *SR,RS* alcohol **11a** in 20 mL of dichloromethane was added dropwise over 30 min, and the resulting slurry was stirred at 25 °C for 1.5 h. The supernatant was decanted and was washed with 10% aqueous NaOH and 10% aqueous HCl. The organic layer gave 1.14 g of a yellow oil, which was filtered through silica gel in hexane to afford 970 mg (4.41 mmol, 80%) of (*SR,RS*)-monocyclofarnesal **6a**: IR 2910, 2725, 1725, 1450, 1360 cm^{-1}; NMR (60 MHz) δ 9.50 (d, J = 5 Hz, 1 H), 5.71 (br s, 1 H), 5.06 (br t, J = 6 Hz, 1 H), 2.43 (d, J = 5 Hz, 1 H), 1.61 and 1.56 (9 H), 0.96 (s, 3 H); MS, *m/e* (relative intensity) 220 (3), 205 (26), 187 (8), 162 (22), 147 (8), 121 (13), 109 (70), 69 (100); molecular ion at 220.1810, calcd for $C_{15}H_{24}O$ 220.1827.

(15) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

Table I. ^{1}H NMR Spectra of Isoxazolidines, Tetrahydro-1,3-oxazines, and Methiodides[a]

	assignment[b]						
compd	H-3	H-6	C-4 Me	C-10 Me	C-11 Me	*N*-Me	*N*-CH_2O
12	5.35	3.17 (t, J = 12)	1.84	0.85	1.07, 1.42	2.62	
13	5.33	3.01 (dd, J = 12, 7.5)	1.81	0.83	1.27, 1.40	2.76	
14	5.59	2.50 (t, J = 11)	1.74	0.93	1.18, 1.27	2.71	
15	5.44	2.88 (t, J = 7)	1.82	1.03	1.30	2.68	
16	5.69	4.87 (t, J = 12)	2.12	1.03	1.47, 1.58	3.53, 4.09	
13·MeI	5.78	5.62 (dd, J = 11,9)	2.08	1.00	1.47, 1.60	3.48, 4.01	
14·MeI	5.73	3.87 (t, J = 12)	1.95	1.07	1.41, 1.57	3.62, 3.79	
15·MeI	5.66	4.38 (dd, J = 8, 5)	2.05	1.14	1.51, 1.64	3.78, 3.88	
17	5.32	2.96 (t, J = 12)	1.87	0.81	1.22, 1.25	2.43	4.20, 4.70 (AB q, J = 10)
20	5.34	2.59 (m)	1.85	0.85	1.27, 1.38	2.61	4.02, 4.77 (AB q, J = 10)
24	5.37	2.88 (t, J = 12	1.90	0.88	1.20, 1.22	2.51	4.22, 4.64 (AB q, J = 11)
27	5.51	2.75 (br t, J = 3)	1.71	1.20[c]	1.23[c], 1.29	2.18	3.78, 4.25 (AB q, J = 9)
22	5.61	4.32 (br t, J = 3)	1.98	0.92	1.36, 1.68	3.29, 3.39	5.25, 5.51 (AB q, J = 9)
25	5.72	4.21 (t, J = 11)	1.98	0.91	1.38, 1.62	3.31, 3.52	4.82, 5.44 (AB q, J = 10)
27·MeI	5.57	3.89 (m)	2.08	1.04	1.34, 1.65	3.29, 3.59	5.16, 5.49 (AB q, J = 9)

[a] At 270 MHz in $CDCl_3$; chemical shifts are in δ units and coupling constants are in hertz. [b] Eudesmol numbering is used—see structure 1. [c] Assignments may be interchanged.

By the same procedure, 3.58 g (16.1 mmol) of *SS,RR* alcohol **11b** afforded 2.89 g (13.1 mmol, 81%) of (*SS,RR*)-monocyclofarnesal **6b**: IR 2910, 2740, 1720, 1450, 1375 cm^{-1}; NMR (60 MHz) δ 9.38 (d, J = 5 Hz, 1 H), 5.70 (br s, 1 H), 5.01 (br t, J = 7 Hz, 1 H), 2.37 (d, J = 5 Hz, 1 H), 1.63 and 1.57 (9 H), 0.87 (s, 3 H); MS, m/e (relative intensity) 220 (0.3), 205 (10), 187 (17), 162 (4), 147 (6), 121 (15), 109 (77), 69 (100); molecular ion at 220.1812, calcd for $C_{15}H_{24}O$ 220.1827.

(*SR,RS*)- and (*SS,RR*)-Monocyclofarnesal *N*-Methylnitrones 7a and 7b. To a solution of 951 mg (4.32 mmol) of *SR,RS* aldehyde **6a** in 50 mL of absolute ethanol were added 397 mg (4.75 mmol) of *N*-methylhydroxylamine hydrochloride and 257 mg (4.76 mmol) of sodium methoxide, and the mixture was stirred at 25 °C for 18 h. The solvent was evaporated under reduced pressure and the residue was triturated with hexane and filtered. The filtrate was evaporated and the residue was chromatographed on a short column of alumina. Elution of the column with hexane removed impurities and subsequent elution with chloroform gave 989 mg (3.97 mmol, 92%) of (*SR,RS*)-nitrone **7a** as a colorless oil which crystallized from cold pentane: mp 63–64 °C; IR 2950, 1600, 1445, 1405, 1395, 1380, 1155, 950, 905 cm^{-1}; NMR (270 MHz) δ 6.48 (d, J = 10 Hz, 1 H), 5.38 (br s, 1 H), 5.08 (br t, J = 5 Hz, 1 H), 3.74 (s, 3 H), 3.62 (d, J = 10 Hz, 1 H), 1.69 (s), 1.62 (s), 1.52 (s), 0.97 (s, 3); MS, m/e (relative intensity) 249 (8), 234 (30), 218 (2), 203 (14), 190 (6), 166 (28), 150 (40), 126 (50), 108 (100). Anal. Calcd for $C_{16}H_{27}NO$: C, 77.06; H, 10.91; N, 5.61. Found: C, 77.02; H, 10.95; N, 5.61.

The same procedure was followed by using 1.16 g (5.27 mmol) of *SS,RR* aldehyde **6b**, 485 mg (5.81 mmol) of *N*-methylhydroxylamine hydrochloride, and 313 mg (5.80 mmol) of sodium methoxide. The crude product (1.32 g) was crystallized from hexane to afford 995 mg (4.00 mmol, 76%) of (*SS,RR*)-nitrone **7b**: mp 92–93 °C; IR 2940, 1600, 1405, 1395, 1380, 1155, 955 cm^{-1}; NMR (270 MHz) δ 6.44 (d, J = 10 Hz, 1 H), 5.48 (br s, 1 H), 5.07 (br t, J = 5 Hz, 1 H), 3.72 (s, 3 H), 3.56 (d, J = 10 Hz, 1 H), 1.68 (s, 6 H), 1.62 (s, 3 H), 1.00 (s, 3 H); MS, m/e (relative intensity) 249 (5), 234 (48), 218 (5), 203 (6), 190 (9), 162 (10), 148 (17), 124 (29), 108 (100). Anal. Calcd for $C_{16}H_{27}NO$: C, 77.06; H, 10.91; N, 5.61. Found: C, 77.13; H, 10.95; N, 5.60.

Nitrone–Olefin Cycloaddition. Isoxazolidines 12, 13, 14, and 15. The nitrone was heated at 85–90 °C (oil bath) in anhydrous toluene (ca. 0.03 M) under nitrogen for 4–6 days or it was refluxed in anhydrous xylene under nitrogen for 15–17 h. The solvent was evaporated under reduced pressure and the residue was dissolved in 10% aqueous HCl and was extracted with ether. The organic layer was discarded and the aqueous layer was basified with 30% aqueous NaOH and was extracted with ether. The oil obtained upon evaporation of the ether was chromatographed on silica gel.

With 4.03 g (16.2 mmol) of (*SR,RS*)-nitrone **7a** as starting material and after 6 days of heating in toluene, elution of the chromatography column with hexane–10% chloroform afforded 482 mg (1.94 mmol, 12%) of *trans-anti-cis*-isoxazolidine **13** which crystallized from pentane: mp 71.5–73 °C; IR 2960, 1460, 1380, 1370, 1240, 1160, 1120, 1040 cm^{-1}; NMR, see Table I; MS, m/e (relative intensity) 249 (12), 234 (100), 126 (12), 109 (26). Anal. Calcd for $C_{16}H_{27}NO$: C, 77.06; H, 10.91; N, 5.61. Found: C, 77.13; H, 10.92; N, 5.60. Further elution of the column with hexane–10% chloroform gave 2.03 g (8.15 mmol, 50%) of *trans-anti-trans*-isoxazolidine **12** which crystallized from pentane: mp 53–54 °C; IR 2910, 1455, 1440, 1380, 1360, 1265, 1165, 1080, 945, 845, 830 cm^{-1}; NMR, see Table I; MS, m/e (relative intensity) 249 (12), 234 (100), 126 (24), 109 (82). Anal. Calcd for $C_{16}H_{27}NO$: C, 77.06; H, 10.91; N, 5.61. Found: C, 77.04; H, 10.94; N, 5.62.

From 240 mg (0.964 mmol) of (*SR,RS*)-nitrone **7a** refluxed in xylene for 15 h was obtained 47 mg (0.189 mmol, 20%) of isoxazolidine **13** and 106 mg (0.426 mmol, 44%) of isoxazolidine **12**.

With 2.00 g (8.03 mmol) of (*SS,RR*)-nitrone **7b** as starting material and after 4 days of heating in toluene, elution of the chromatography column with hexane afforded 1.48 g (5.94 mmol, 74%) of *cis-anti-cis*-isoxazolidine **15** as a colorless oil: IR 2910, 1455, 1440, 1380, 1370, 1215, 1208 cm^{-1}; NMR, see Table I; MS, m/e (relative intensity) 249 (12), 234 (100), 170 (9), 126 (13), 109 (30). Anal. Calcd for $C_{16}H_{27}NO$: C, 77.06; H, 10.91; N, 5.61. Found: C, 77.22; H, 10.92; N, 5.57. Further elution of the column with hexane–10% ether gave 186 mg (0.747 mmol, 9%) of *cis-anti-trans*-isoxazolidine **14** which crystallized from pentane at −20 °C: mp 47–48 °C; NMR, see Table I; MS, m/e (relative intensity) 249 (14), 234 (100), 191 (9), 176 (16), 148 (10), 126 (13), 108 (32); molecular ion at 249.2089, calcd for $C_{16}H_{27}NO$, 249.2092.

The crude nitrone generated from 2.88 g (13.1 mmol) of (*SS,RR*)-monocyclofarnesal (**6b**) was refluxed in xylene for 17 h, to give 1.01 g (4.06 mmol, 31% overall) of isoxazolidine **15** and 1.10 g (4.42 mmol, 34% overall) of isoxazolidine **14**.

Isoxazolidine Methiodides. A solution of the isoxazolidine in freshly distilled methyl iodide was left standing at 25 °C for the specified time, then the excess methyl iodide was evaporated, and the residue was crystallized from the specified solvent.

From 224 mg (0.899 mmol) of *trans-anti-trans*-isoxazolidine **12** in 3 mL of methyl iodide (overnight) was obtained 330 mg (0.844 mmol, 94%) of methiodide **16**: mp 166–168 °C dec (methanol–ether); NMR, Table I.

From 312 mg (1.25 mmol) of *trans-anti-cis*-isoxazolidine **13** in 2 mL of methyl iodide (7 days) was obtained 347 mg (0.887 mmol, 71%) of **13**·methiodide: mp 182–183 °C dec (acetonitrile–ethyl acetate); NMR, Table I.

From 166 mg (0.667 mmol) of *cis-anti-trans*-isoxazolidine **14** in 2 mL of methyl iodide (30 min) was obtained 239 mg (0.611 mmol, 91%) of **14**·methiodide: mp 174–175 °C dec; NMR, Table I.

A solution of 1.00 g (4.02 mmol) of *cis-anti-cis*-isoxazolidine **15** in 5 mL of methyl iodide still contained unreacted **15** after 12 days (TLC analysis); 5 mL of acetonitrile was added and the solution was left at 25 °C for another 2 days. The residue was crystallized from acetonitrile–ether and recrystallized from methanol–ether to give 1.46 g (3.74 mmol, 93%) of **15**·methiodide: mp 168–170 °C dec; NMR, Table I.

Tetrahydro-1,3-oxazines. To a solution of the isoxazolidine

Table II. ^{1}H NMR Spectra[a] and GC Relative Retention Times[b] of Eudesmols

	NMR assignments					
compd	H-3	H-14	C-4 Me	C-10 Me	C-11 Me	GC[b]
(±)-1	5.32		1.63	0.78	1.22, 1.21	1.00
(±)-2		4.70, 4.43		0.71	1.21	0.98
(±)-21	5.30		1.65	0.87	1.25	1.02
(±)-23		4.72, 4.46		0.76	1.27, 1.26	0.96
(±)-26	5.24		1.69	0.87	1.18	0.85
(±)-28	5.44		1.66	1.00	1.18, 1.17	0.95

[a] At 270 MHz in $CDCl_3$; chemical shifts are in δ units. [b] GC on a 30-m glass capillary SE-30 column at 150 °C; retention time of the compound divided by that of α-eudesmol (1).

methiodide in 5 mL of methanol was added 5 mL of 10% aqueous NaOH and 5 mL of hexane, and the mixture was refluxed for 3 h. After cooling, the mixture was extracted with hexane to give the crude product which was crystallized from acetonitrile.

From 330 mg (0.844 mmol) of methiodide **16** was obtained 202 mg (0.768 mmol, 91%) of *trans-anti-trans*-oxazine **17**: mp 97–97.5 °C; IR 2930, 1460, 1445, 1380, 1370, 1240, 1190, 1060, 985 cm^{-1}; NMR, Table I; MS, *m/e* (relative intensity) 263 (44), 248 (96), 190 (10), 147 (26), 140 (100), 110 (40). Anal. Calcd for $C_{17}H_{29}NO$: C, 77.51; H, 11.10; N, 5.32. Found: C, 77.49; H, 11.10; N, 5.32.

From 250 mg (0.639 mmol) of **13**-methiodide was obtained 138 mg (0.525 mmol, 82%) of *trans-anti-cis*-oxazine **20**: mp 47–48 °C (crystallized at −20 °C); IR 2920, 1470, 1445, 1385, 1370, 1245, 1060, 995 cm^{-1}; NMR, Table I; MS, *m/e* (relative intensity) 263 (38), 248 (100), 190 (12), 162 (13), 147 (26), 140 (84), 110 (48). Anal. Found: C, 77.63; H, 11.13; N, 5.25.

From 235 mg (0.601 mmol) of **14**-methiodide was obtained 156 mg (0.593 mmol, 99%) of *cis-anti-trans*-oxazine **24**: mp 88–89 °C (crystallized at −20 °C); IR 2925, 1460, 1380, 1370, 1180, 1150, 1045, 1015, 980 cm^{-1}; NMR, Table I; MS, *m/e* (relative intensity) 263 (50), 248 (100), 140 (94); molecular ion at 263.2229, calcd for $C_{17}H_{29}NO$ 263.2248.

From 200 mg (0.512 mmol) of **15**-methiodide was obtained 112 mg (0.425 mmol, 83%) of *cis-anti-cis*-oxazine **27**: mp 71–73 °C; IR 2910, 1450, 1370, 1220, 1175, 1160, 1090, 1070, 990, 975 cm^{-1}; NMR, Table I; MS, *m/e* (relative intensity) 263 (44), 248 (100), 202 (40), 187 (22), 162 (14), 140 (14), 121 (32), 110 (12). Anal. Found: C, 77.52; H, 11.10; N, 5.30.

Alkylation–Deamination of Tetrahydro-1,3-oxazine 17. (±)-α-Eudesmol (1) and (±)-β-Eudesmol (2). To 300 μL of distilled sulfolane in a dried 3.5-mm ID glass tube was added a solution of 93 mg (0.35 mmol) of oxazine **17** in 200 μL of distilled methyl iodide. The tube was immersed in a dry ice–isopropyl alcohol bath, was evacuated and filled with nitrogen three times, and then was sealed under reduced pressure (water aspirator). The reaction mixture was heated at 80–85 °C (oil bath) for 6 days. After cooling, the tube was opened and the yellow solution was transferred in chloroform to a dry two-neck round-bottom flask and the volatile components were evaporated under reduced pressure. Lithium wire (150 mg, 21.4 mmol) was added and ca. 15 mL of liquid ammonia was condensed in the flask; the deep blue solution was stirred at −78 °C for 6 h. The ammonia was evaporated by warming to room temperature under a stream of nitrogen, methanol and water were added, and the mixture was extracted with ether. The residue from evaporation of the ether was dissolved in hexane and was extracted with 10% aqueous HCl. Evaporation of the hexane gave 55 mg of a neutral fraction; the aqueous acid layer was basified with 10% aqueous NaOH and was extracted with ether to give 23 mg of an amine fraction. Chromatography of the amine fraction on silica gel and elution with hexane afforded 20 mg (0.076 mmol, 22% recovery) of oxazine **17**. GC analysis (150 °C) of the neutral fraction showed three peaks in area ratio 19:67:14 in order of increasing retention time; the first two peaks coeluted with authentic β-eudesmol and α-eudesmol, respectively. The mixture was chromatographed on silica gel–25% $AgNO_3$. Elution of the column with hexane–30% benzene afforded 30 mg of an off-white solid which was filtered through alumina in hexane–10% benzene and was crystallized from pentane at −20 °C to give 29 mg (0.13 mmol, 37%) of (±)-α-eudesmol (**1**) as waxy needles: mp 78–79 °C; IR 3600, 3460, 2910, 1450, 1375, 1325, 1240, 1155, 1115, 1085, 1000, 900, 845 cm^{-1}; NMR, Table II; MS, *m/e* (relative intensity) 222 (4), 204 (50), 189 (66), 175 (13), 161 (68), 149 (70), 133 (34), 122 (25), 107 (52), 91 (39), 81 (51), 59 (100); molecular ion at 222.1967, calcd for $C_{15}H_{26}O$, 222.1983. The IR, NMR, MS, and GC retention time were identical with those of authentic[14] (+)-α-eudesmol.

Table III. ^{13}C NMR Spectra of 3α-Methyl-β-eudesmol (18) and β-Eudesmol (2)[a]

	compd	
C[b]	18	2[c]
1	36.31 (t)	41.90 (t)
2	28.84 (t)	23.42 (t)
3	38.81 (d)	36.81 (t)
4	155.36 (s)	150.90 (s)
5	44.23 (d)	49.36 (d)
6[d]	25.00 (t)	24.94 (t)
7	49.57 (d)	49.73 (d)
8[d]	22.50 (t)	22.30 (t)
9	41.23 (t)	41.10 (t)
10	36.15 (s)	35.76 (s)
11	72.79 (s)	72.65 (s)
12, 13	27.23 (q), 27.01 (q)	27.02 (q)
14	105.26 (t)	105.22 (t)
15	15.87 (q)	16.20 (q)
16	20.18 (q)	

[a] In $CDCl_3$; shifts in parts per million downfield from Me_4Si. [b] For numbering, see structures **2** and **18**. [c] Authentic[14] (+)-β-eudesmol. [d] Assignments may be interchanged.

To a 3.5-mm ID glass tube containing 300 μL of technical sulfolane were added 50 mg of Na_2CO_3 and a solution of 52 mg (0.20 mmol) of oxazine **17** in 200 μL of methyl iodide. The tube was degassed, sealed, and heated at 80–90 °C for 5 days. The lithium/liquid ammonia reduction and isolation procedure as above gave 2 mg of amine fraction and 23 mg of a neutral fraction; GC analysis (150 °C) of the latter showed three peaks in area ratio 65:17:18 in order of increasing retention time. Chromatography of the neutral fraction on silica gel–25% $AgNO_3$ eluting with hexane–30% benzene gave 3 mg (0.014 mmol, 7%) of (±)-α-eudesmol (**1**). Further elution with the same solvent afforded 3 mg (0.013 mmol, 6%) of (±)-3α-methyl-β-eudesmol (**18**) which crystallized from pentane at −20 °C as waxy needles: mp 72.5–74 °C; IR 3600, 3450, 2910, 1640, 1380, 1260, 1150, 1080, 1010, 890 cm^{-1}; ^{1}H NMR (270 MHz) δ 4.77 (d, J = 2.5 Hz, H-14), 4.41 (d, J = 2.5 Hz, H-14), 2.55 (ddq, H-3, $J_{3,16}$ = 7 Hz, $J_{3,2\,ax}$ = 5 Hz, $J_{3,2\,eq}$ = 1 Hz), 2.02 (br d, J = 12 Hz, H-5), 1.84 (tdd, H-2 ax, $J_{2\,ax,2\,eq}$ = 13 Hz, $J_{2\,ax,1\,ax}$ = 13 Hz, $J_{2\,ax,1\,eq}$ = 4 Hz, $J_{2\,ax,3}$ = 5 Hz), 1.22 (s, 6 H, H-12, 13), 1.11 (d, J = 7 Hz, 3H, H-16), 0.71 (s, 3 H, H-15), the coupling constants for H-2ax, H-3, and H-16 were determined by spin-decoupling; ^{13}C NMR, see Table III; MS, *m/e* (relative intensity) 236 (1), 218 (4), 203 (6), 178 (22), 163 (34), 149 (22), 135 (14), 121 (22), 107 (36), 93 (39), 81 (42), 59 (100); molecular ion at 236.2133, calcd for $C_{16}H_{28}O$, 236.2139. Elution of the chromatography column with benzene gave 14 mg (0.063 mmol, 32%) of (±)-β-eudesmol (**2**) which crystallized from pentane at −20 °C as waxy needles: mp 66.5–68 °C (lit.[3a] mp 68.5–69.5 °C, lit.[3c] mp 69–71.5 °C); IR 3600, 3450, 2920, 1640, 1470, 1450, 1380, 1265, 1085, 880 cm^{-1}; NMR, Table II; MS, *m/e* (relative intensity) 222 (2), 204 (6), 189 (7), 164 (22), 149 (36), 123 (15), 122 (15), 109 (26), 95 (20), 81 (24), 59 (100); molecular ion at 222.1984, calcd for $C_{15}H_{26}O$ 222.1983. The IR, NMR, MS, and GC retention time were identical with those of authentic[14] (+)-β-eudesmol.

Methylation of 40 mg (0.15 mmol) of oxazine **17** was carried out as above, but in distilled sulfolane to which was added 5 μL of D_2O. After reduction there was isolated 11 mg of amine fraction and 19 mg of the eudesmol mixture in ratio 75:5:20 (GC, 150 °C) in order of increasing retention time. Chromatography of the alcohols on alumina with hexane–10% benzene gave 8 mg of a 50:9:41 mixture (GC) of eudesmols, and 4 mg of 94% pure (±)-β-eudesmol (**2**). The latter crystallized from pentane at −20 °C: mp 61–64 °C; MS, *m/e* (relative intensity) 223 (0.57), 222 (0.44), 205 (2.2), 204 (2), 190 (4), 189 (3), 165 (10), 164 (8), 150 (22), 149 (19), 122 (18), 109 (21), 95 (17), 81 (22), 59 (100).

Alkylation–Deamination of 20. (±)-7-Epi-α-eudesmol (21) and (±)-7-Epi-β-eudesmol (23). A solution 69 mg (0.26 mmol) of oxazine **20** in 500 μL of distilled methyl iodide was heated at

80 °C in a sealed tube for 17 h. Evaporation of the methyl iodide left 100 mg of a yellow solid which was recrystallized from acetonitrile–ethyl acetate to give 92 mg (0.23 mmol, 87%) of methiodide **22**: mp 258–260 °C; NMR, Table I.

A 60-mg (0.15 mmol) sample of methiodide **22** was reduced with 20 mg (2.8 mmol) of lithium in liquid ammonia as before to give 30 mg of crude product which was filtered through silica gel in hexane–5% ether to yield 27 mg of a pale yellow oil. Chromatography on alumina eluting with hexane–10% benzene afforded 22 mg (0.099 mmol, 66%) of (±)-7-epi-α-eudesmol (**21**) as a colorless oil which showed a single peak on GC (150 °C) but would not crystallize: IR 3600, 3465, 2910, 1460, 1435, 1375, 1125, 1100, 940 cm^{-1}; NMR, Table II; MS, *m/e* (relative intensity) 222 (0.17), 204 (17), 189 (15), 161 (100), 149 (15), 133 (13), 122 (80), 107 (52), 93 (22), 79 (56), 59 (44); molecular ion at 222.1981, calcd for $C_{16}H_{26}O$ 222.1983.

To a 3.5-mm ID glass tube containing 150 μL of technical sulfolane were added 50 mg of K_2CO_3 and a solution of 61 mg (0.23 mmol) of oxazine **20** in 300 μL of methyl iodide. The tube was degassed, sealed, and heated at 80–85 °C for 3 days. The lithium/liquid ammonia reduction and isolation procedure as for **17** gave 3 mg of amine fraction and 30 mg of neutral fraction. Chromatography of the latter on silica gel–25% $AgNO_3$ gave 4 mg (0.018 mmol, 8%) of 7-epi-α-eudesmol (**21**), and 15 mg (0.068 mmol, 30%) of 7-epi-β-eudesmol (**23**) as a waxy solid: mp 62–64 °C; IR 3625, 3525, 2920, 1640, 1465, 1450, 1390, 1380, 1260, 890 cm^{-1}; NMR Table II, in agreement with lit.[4c,6b] values; MS, *m/e* (relative intensity) 222 (0.18), 204 (36), 189 (42), 176 (16), 161 (68), 149 (30), 133 (56), 122 (26), 107 (48), 91 (80), 79 (72), 59 (100); molecular ion at 222.1988, calcd for $C_{15}H_{26}O$ 222.1983.

Alkylation–Deamination of Oxazines 24 and 27. (±)-5-Epi-7-epi-α-eudesmol (26) and (±)-5-Epi-α-eudesmol (28). A solution of 709 mg (2.70 mmol) of oxazine **24** in 25 mL of methyl iodide was left at 25 °C for 2 days. Evaporation of the methyl iodide and recrystallization of the residue from acetonitrile–ethyl acetate gave 945 mg (2.33 mmol, 86%) of methiodide **25**: mp (sealed tube) 248–250 °C dec; NMR, Table I. A sample of 700 mg (1.73 mmol) of **25** was reduced with 120 mg (17.3 mmol) of lithium wire in 100 mL of liquid ammonia for 3 h. Isolation as before afforded 387 mg (1.47 mmol, 85%) of oxazine **24** and 68 mg of a neutral fraction. Chromatography of the latter on alumina eluting with hexane–10% benzene gave 43 mg (0.19 mmol, 11%) of (±)-5-epi-7-epi-α-eudesmol (**26**) as an oil which crystallized from pentane at −20 °C: mp 45–47 °C; IR 3620, 3450, 2910, 1455, 1440, 1370, 1260, 1100 cm^{-1}; NMR, Table II; MS, *m/e* (relative intensity) 222 (0.9), 204 (21), 189 (18), 161 (16), 149 (35), 135 (11), 121 (10), 109 (55), 93 (26), 81 (21), 59 (100); molecular ion at 222.1983, calcd for $C_{15}H_{26}O$ 222.1983.

A solution of 100 mg (0.38 mmol) of oxazine **27** in 2 mL of methyl iodide was heated at 70 °C in a sealed tube for 4 days. The solvent was evaporated and the residue was recrystallized from acetonitrile–ethyl acetate to give 144 mg (0.36 mmol, 95%) of **27**·MeI: mp (sealed tube) 239–245 °C dec; NMR, Table I. A sample of 104 mg (0.257 mmol) of this methiodide was reduced with 20 mg (2.9 mmol) of lithium in liquid ammonia as above to give 49 mg of crude product which did not contain any oxazine **27** (TLC). Chromatography of the oil on alumina eluting with hexane–10% benzene afforded 36 mg (0.16 mmol, 62%) of (±)-5-epi-α-eudesmol (**28**) which crystallized from pentane at −20 °C: mp 68–69 °C; IR 3600, 3450, 2920, 1450, 1370, 900 cm^{-1}; NMR, Table II; MS, *m/e* (relative intensity) 222 (0.1), 204 (18), 161 (64), 149 (19), 122 (32), 109 (32), 93 (22), 81 (17), 59 (100); molecular ion at 222.1981, calcd for $C_{15}H_{26}O$ 222.1983.

Registry No. (±)-**1**, 69686-15-3; (±)-**2**, 3287-59-0; **5**, 10485-70-8; (±)-**6a**, 95421-18-4; (±)-**6b**, 95421-19-5; (±)-**7a**, 95421-20-8; (±)-**7b**, 95421-21-9; **8**, 70038-03-8; **9**, 38142-31-3; **9** (bromohydrin), 95421-27-5; **10**, 38142-32-4; (±)-**11a**, 95421-16-2; (±)-**11b**, 95421-17-3; (±)-**12**, 95530-47-5; (±)-**13**, 95421-22-0; (±)-**13**·CH_3I, 95529-61-6; (±)-**14**, 95529-59-2; (±)-**14**·CH_3I, 95529-62-7; (±)-**15**, 95529-60-5; (±)-**15**·CH_3I, 95529-63-8; (±)-**16**, 95421-23-1; (±)-**17**, 95421-24-2; (±)-**18**, 95421-25-3; (±)-**20**, 95529-64-9; (±)-**21**, 95529-68-3; (±)-**22**, 95421-26-4; (±)-**23**, 95529-67-2; (±)-**24**, 95529-65-0; (±)-**25**, 95585-28-7; (±)-**26**, 69686-18-6; (±)-**27**, 95529-66-1; (±)-**27**·CH_3I, 95529-69-4; (±)-**28**, 69686-16-4; CH_3N-HOH·HCl, 4229-44-1.

Ruthenium Complex Catalyzed N-Heterocyclization. Syntheses of N-Substituted Piperidines, Morpholines, and Piperazines from Amines and 1,5-Diols

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1,5-Pentanediol reacts with aliphatic and aromatic primary amines in the presence of a ruthenium catalyst modified with phosphine ligands to give N-substituted piperidines in fair to goods yields. The reactions were carried out at 150–180 °C for 5 h in dioxane. The nature of the phosphorus ligands has a remarkable effect on the catalytic activity. For the reaction of aromatic amines, triphenylphosphine is effective, while for aliphatic amines more basic tributyl- or triethylphosphine is preferable. Amines also react with diethylene glycol and N-substituted diethanolamines in the presence of the ruthenium catalyst to give N-substituted morpholines and piperazines in good yields, respectively.

A large variety of methods are known for building up piperidine,[1] morpholine,[2] and piperazine[3] rings. In these methods, substrates such as 1,5-dihalogenopentanes, 1,5-halogenoamines, diethanolamines, *N*-(2-hydroxyethyl)-ethylenediamine, and diethylenetriamines are used as the starting materials, and the hetero rings are usually closed intramolecularly at the nitrogen or oxygen atom.

We have reported the syntheses of N-substituted piperidines from glutaraldehyde and primary amines with $KHFe(CO)_4$ as a reductant.[4] This reaction, however, required a stoichiometric amount of $KHFe(CO)_4$. We have recently developed organic syntheses involving dehydrogenation of an alcohol by a ruthenium catalyst as a key step.[5-7] One possible feature of homogeneous ruthenium

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