Enantiospecific Synthesis of the *trans*-9-[3-(3,5-Dimethyl-1-piperazinyl)propyl]carbazoles

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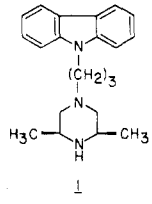
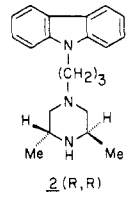
The compounds in the title, (*R,R*)- and (*S,S*)-**2**, are isomers of the *cis*-dimethyl compound **1**, which is in human trials as an antipsychotic. They were made starting with chiral alanine esters (**6**) and the 2-bromopropionic esters made from the alanines of opposite chirality (**5**) and proceeding by cyclization of the ethoxycarbonyl-protected iminodipropionic acids **9**, via anhydride **10**, with 3-(9-carbazolyl)propylamine and subsequent BH_3 reduction of the imides **12** followed by hydrolytic removal of the COOEt. Selection of the reagents necessary to minimize racemization, $[\alpha]_D^{20}$ values at each condensation stage, and the ^1H and ^{13}C NMR absorption data required for structure proof of **2** are given; a ring inversion rate of 5200 s^{-1} is calculated based on low and ambient temperature ^{13}C NMR data.

Animal behavioral studies in our laboratories based on models and theories about differing brain sites responsible for control of emotions and for the side effects caused by conventional neuroleptic drugs suggested that *cis*-9-[3-(3,5-dimethyl-1-piperazinyl)propyl]carbazole (**1**) should have antipsychotic activity without the extrapyramidal side effects ("Parkinson-like" symptoms and involuntary movements) associated with prolonged use of accepted "major tranquilizers".[2] Compound **1** is in clinical trial in humans. Most of a variety of analogues required to study structure–activity relationships could be made by standard procedures; preparation of many of these and their activities in test animals will be submitted for publication elsewhere. The enantiospecific preparation of the *R,R* and *S,S* trans analogues **2** is reported here, as well as aspects of their ^{13}C and ^1H NMR, and a preliminary determination of the biological activity of these substances in rats.



1

cis-9-[3-(3,5-Dimethyl-1-piperazinyl)-propyl]carbazole

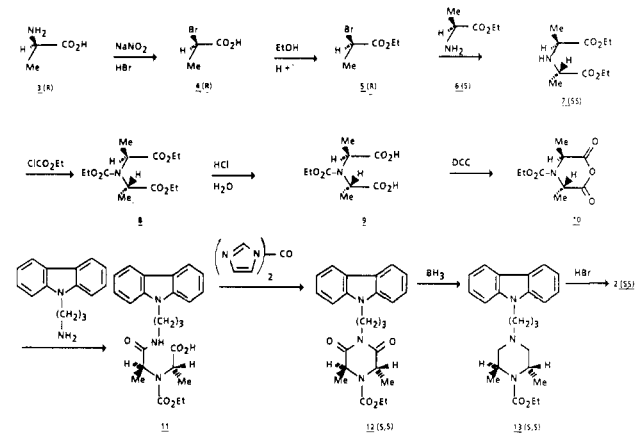


2 (R,R)

(R,R)-trans-9-[3-(3,5-Dimethyl-1-piperazinyl)propyl]carbazole

One report in the literature[3] describes the preparation of racemic *trans*-2,6-dimethylpiperazine. Racemic **2** could be made from this compound. Since biological activity often varies between enantiomers, testing of both enantiomers of **2** seemed desirable. It was thought that enantiospecific synthesis would be a more efficient as well as a more elegant way of obtaining them than resolution. This is especially true since the published route[3] to the piperazine resulted in scrambling both the position of the methyls and their cis–trans relationship at several stages of synthesis. An enantiospecific synthesis would also establish the absolute configuration of each product. The route selected is shown in Scheme I for the *S,S* enantiomer. The route to the *R,R* enantiomer was identical. Both enantiomers of α-alanine are available and can be converted to the α-bromo acids **4** with retention of configuration by the stereospecific nitrosyl bromide route used by Emil Fisher in his classical proof[4] of Walden inversion. Displacement of bromide from either esterified product **5** (*R* or *S*)[5] by attack of the amino group of the alanine ester **6** of opposite configuration should yield the desired enantiomeric disubstituted amine **7** with Walden inversion at the bromine-bearing carbon. Although inversion should be essentially complete, some meso amine diester **7** (meso) was expected to result from the attack by bromide ion formed during the reaction on initially unreacted bromo ester with inversion and subsequent amination of inverted bromo compound. The mixture of predominantly *S,S* (or later of *R,R*) **7** with the *meso*-**7** was carried through to **8**.

Scheme I



Carbethoxylation of **7** yielded **8**. The carbethoxy group was retained through subsequent hydrolysis of the terminal ester groups. A satisfactory separation of enantiomeric **8** from *meso*-**8** was readily achieved by HPLC.

All subsequent steps in which the anhydride or piperazinedione rings were present were unexpectedly prone to cause racemization. Presumably this is due to a larger 1:3 (axial methyl:axial H) interaction in the trans isomer than we had anticipated; a small effect was predicted since it would not be reenforced by additional 1:3 interactions with the O (anhydride **10**) or N (imide **12**). Thus the standard[6] formation of the anhydride **10** with acetic anhydride (5 min under reflux) gave unacceptable racemization. However, dicyclohexylcarbodiimide (DCC) was successfully em-

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(2) (a) Ferris, R. M.; Harfenist, M.; MacKenzie, G. M.; Cooper, B.; Soroko, F. E.; Maxwell, R. A. *J. Pharm. Pharmacol.* **1982**, *34*, 388. (b) "Drugs of the Future"; 1983; Vol. 8, p 303.

(3) Cignarella, G.; Gallo, G. G. *J. Heterocycl. Chem.* **1974**, *11*, 985.

(4) Fisher, E. *Chem. Ber.* **1907**, *40*, 489.

(5) Amarego, W. L. F.; Milloy, B. A.; Pendergast, W. *J. Chem. Soc., Perkin Trans. 1*, **1976**, 2229.

(6) Henry, D. W. *J. Heterocycl. Chem.* **1966**, *3*, 503.

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Table I. ^{13}C and ^{1}H NMR Assignments for Cis Isomer 1 Aliphatic Resonances[a]

	^{13}C shift[b]	^{1}H shift[b]	couplings, Hz
$CH_2(1')$	40.44	4.37	$J_{1',2'} = 6.6$
$CH_2(2')$	25.84	2.04	$J_{2',3'} = 6.6$
$CH_2(3')$	54.98	2.26	
$CH_2(2,6)$	60.67	2.70 (e)	$J_{gem} = -10.5$, $J_{3,2e} = 2.4$
		1.53 (a)	$J_{3,2a} = 10.0$
CH(3,5)	50.72	2.94	$J_{CH_3} = 6.3$
CH_3	19.92	1.02	

[a] Data is for free bases in a 0.3 M solution in $CDCl_3$ at 29 °C, D_2O exchanged. [b] Shifts given in ppm relative to tetramethylsilane (0).

Table II. ^{13}C and ^{1}H NMR Assignments for Aliphatic Resonances of Trans Isomers 2[a]

	^{13}C shift[b]	^{1}H shift[b]	couplings, Hz
$CH_2(1')$	40.25	4.40	$J_{1',2'} = 6.6$
$CH_2(2')$	25.62	2.01	$J_{2',3'} = 6.6$
$CH_3(3')$	55.13	2.23	
$CH_2(2,6)$	60.00	2.11 (a)	$J_{3,2a} = 5.9$, $J_{gem} = -10.5$
		2.39 (e)	$J_{3,2e} = 3.3$
CH(3,5)	46.13	3.26	$J(CH_3) = 6.5$
CH_3	19.46	1.21	
	Free Base at −75 °C		
C(2)	62.2		
C(6)	57.2		
C(3)	47.9		
C(5)	43.9		
CH_3	19.2		
CH_3	20.6		

[a] Data for 0.3 M solutions of free bases in $CDCl_3$ at 29 °C, D_2O exchanged. [b] Shifts given in ppm relative to Me_4Si (0).

ployed to yield unracemized **10**, as shown by hydrolysis of an aliquot of anhydride **10** back to diacid **9** which showed no detectible loss of rotation. Reaction of **10** with 9-(3-aminopropyl)carbazole was uneventful, but closure of **11** to the imide **12** with DCC gave **12** noticeably lower in rotation than that obtained by use of carbonyldiimidazole. That the product of the latter reagent was not racemized was again corroborated by hydrolysis of an aliquot to diacid **9** of unchanged optical rotation.

Reduction of the imide **12** to **13**, the carbethoxylated target, was best done with borane in THF, which gave no detectable reduction of the carbethoxy group or racemization (^{13}C NMR on final product). Removal of the carbamate carbethoxyl to give the target **2** required prolonged heating with aqueous HBr; the conventional[7] two days under reflux with constant boiling (approximately 6 N) aqueous HCl gave little removal of the COOEt group, and basic hydrolysis was extremely slow.

The *R,R* and *S,S* products were approximately equipotent in standard neuroleptic assays (apomorphine-induced aggressive behavior in rats[13]) and about half as potent as **1**.

NMR Data. The proton NMR data for related isomers of 2,6-dimethylpiperidine[8] and for the 2,6-dimethylpiperazines[3] and the 4-benzyl derivatives of the latter have been reported. The earlier reports were that steric interactions in the trans isomer cause dynamic differences compared to the nearly rigid (both methyl groups equatorial) cis isomer. The rapid ring inversion of the *trans*-dimethylpiperazine leads to an averaging of the methine proton chemical shift and of the coupling values. The cis isomer, in contrast, gives proton NMR parameters which are at the extremes of the chemical shifts and coupling constants expected for rigid chair rings. Our ^{13}C and proton NMR data for the dimethylpiperazine portions are shown in Table I for the *cis*-3,5-dimethyl compound **1** and in Table II for the *trans*-3,5-dimethyl compounds **2**. Since protonation (presumably of the secondary nitrogen) obscures the fine structure of the resonances, results are given only for the free bases. Proton and ^{13}C assignments for the carbazole rings are shown in Table III.

Table III. ^{13}C and ^{1}H Assignments for the Carbazole Resonances[a]

	^{13}C shift[b]	^{1}H shift[b]	couplings, Hz
8a,9a	140.53		
2,7	125.48	7.43	$J_{2,3} = 6.87$, $J_{2,4} = 1.25$
4a,4b	122.79		
4,5	118.72	8.08	$J_{4,1} = 0.70$, $J_{4,3} = 7.81$
3,6	120.23	7.21	$J_{3,1} = 1.50$
1,8	108.76	7.47	$J_{1,2} = 8.14$

[a] 0.3 M $CDCl_3$ solutions at 29 °C. [b] Shifts given in ppm relative to Me_4Si (0).

Proton assignments are based on double resonance experiments and spin simulations. Values for the piperazine moieties were in close agreement with the reported[3] analysis for the N-unsubstituted 2,6-dimethylpiperazine isomers.

Carbon 13 assignments were made on the basis of symmetry and of information from attached proton test (APT) experiments.[11] The ^{13}C chemical shift of the methine C(3,5) is seen at a 4.5-ppm higher field for the trans isomer than the cis. This chemical shift difference is understandable since the resonance position in the trans isomer should reflect the average of the conformations with each methyl group axial while the other is equatorial. The compression shift resulting from the axial methyls should lead to an upfield shift for the methine carbons in the trans isomer compared to those in the cis isomer, as observed.[12]

^{13}C NMR data acquired at −75 °C are shown at the bottom of Table II. This allows determination of the ^{13}C chemical shifts of each population of **2**. Analysis of the variable temperature data allowed calculation of the inversion $\Delta H^* = -6.6$ Kcal/mol, which corresponds to a ring inversion rate of 5200/s at 0 °C. As expected, the ^{13}C NMR spectrum of the cis isomer was not perceptibly affected by cooling.

NMR spectra were taken with a Varian CFT-20 spectrometer. Temperature control accuracy is ±3 °C.

Experimental Section

(*R*)-2-Bromopropionic Acid (4). D-Alanine (50 g, 0.56 mol) was dissolved in a mixture of 580 mL of 48% aqueous HBr and 1 L of water, and cracked ice added to give a total volume of 3 L. $NaNO_2$ (104.3 g, 1.51 mol) was added in small portions with stirring, followed by 700 g of Na_2SO_4. When the stirred reaction had warmed to 15 °C, it was decanted from solids and extracted with five 500-mL portions of Et_2O. Drying over Na_2SO_4 and then $CaCl_2$ and concentration in vacuo gave 65 g of oil as residue. This was distilled collecting a forerun from 40–70 °C (25 torr) and three fractions distilling at 104–108 °C (25 torr) totalling 51.3 g with $[\alpha]_D^{20}$ 45.6° (neat) [lit.[9] for the *S* enantiomer $[\alpha]^{20}_D$ −45.6°) (neat)].

Ethyl (*R*)-2-Bromopropionate (5). Azeotropic esterification of 102.5 g of 4 (0.67 mol) with 100 mL of ethanol, 400 mL of toluene, and Dowex 1-X8 H^+ resin using a Dean–Stark trap gave

(7) Harfenist, M.; Magnien, E. *J. Am. Chem. Soc.* **1957**, *79*, 2215.
(8) Booth, H.; Little, J. H.; Feeney, J. *Tetrahedron* **1968**, *24*, 279.
(9) Fisher, E.; Raske, K. *Chem. Ber.* **1906**, *39*, 3981.
(10) Karrer, P.; Appenzeller, R. *Helv. Chim. Acta* **1942**, *25*, 595.
(11) Patt, S. L.; Shoolery, J. N. *J. Magn. Reson.* **1982**, *46*, 535.
(12) Dalling, D. K.; Grant, D. M. *J. Am. Chem. Soc.* **1972**, *94*, 5318.
(13) McKenzie, G. M. *Brain Res.* **1971**, *34*, 323.

93.4 g of oil after distillation at 51–75 °C (22 torr), showing 3% of toluene (NMR). Correcting the observed $[\alpha]_D^{20}$ for this gave a value of 44.5° (neat).

Diethyl (*S,S*)-2,2′-Iminobis[propionate] (7). The ethyl ester·HCl of L-alanine **6** (73.73 g, 0.48 mol) was dissolved in 800 mL of MeCN and stirred under N_2 with 89 g (1.06 mol) of $NaHCO_3$. After 1 h, 94 g (0.52 mol) of (*R*)-ethyl 2-bromopropionate **5** was added dropwise. Reaction was not complete after 3 days at room temperature, so the reaction was heated under reflux for a day, after which TLC showed 3 spots (silica gel, Et_2O–Petroleum ether (35–60 °C) 1:1 v/v) with R_f 0.42, 0.30, and 0 (visualized with iodoplatinate). GLC (OV-17, 80–150 °C) showed no starting bromo compound **5**. Filtration to remove solids was followed by evaporation of MeCN at a bath temperature below 35 °C, and partitioning the residual oil between Et_2O and 1 N HCl. The HCl layer was basified with $NaHCO_3$, then NaOH, and immediately extracted with Et_2O three times. Removal of Et_2O (rotovac, <35 °C) left 65.7 g of oil after drying (63%), $[\alpha]_D^{20}$ −34.4° (neat), with appropriate IR and ^1H NMR. The *R,R* enantiomer prepared similarly had $[\alpha]_D^{20}$ + 32.9° (neat).

(*S,S*)-Diethyl 2,2′-[(Ethoxycarbonyl)imino]bis[propionate] (8). The 65.7 g of largely **7** (nominally 0.30 mol) in 475 mL of THF was treated with 66.8 mL of 2,6-lutidine (0.57 mol) and chilled in ice under N_2 while 41.4 mL (0.43 mol) of ethyl chloroformate was added dropwise with stirring. The reaction was left for one day and then filtered and the solid washed with Et_2O. The combined solutions were concentrated to leave 100 g of an oil. This was taken up in Et_2O, washed with 3 × 75 mL of 1 N HCl and then water, and then dried over Na_2SO_4. Distillation of solvent left 67.4 g of an oil.

Preparative HPLC was run (Waters Prep 500), injecting the oil neat and eluting with 1:4 ethyl acetate–hexanes (v/v). The separation was followed by TLC (silica gel, Et_2O–petroleum ether 1:1). Three column passes were required, taking second peaks; to yield two single TLC spot fractions, totalling 12.6 g. These had $[\alpha]_D^{20}$ values of −81.75° and −81.3° (neat). An additional 3.5-g fraction with $[\alpha]_D^{20}$ −84.2° (neat) was obtained by again rechromatographing intermediate fractions. First peaks were single spot material, with $[\alpha]_D^{20}$ essentially zero. These totaled 22.5 g, presumably *R,S* material carried through from the preparation of **5** (see the Results and Discussion section). Additional material in the acidic extract was not examined for chirality but was not substantially starting amino diester. The yield of **8** was adequate for our purposes, but a better isolation route (less contact with aqueous bases and acids) might have improved the yield.

(*S,S*)-2,2′-[(Ethoxycarbonyl)imino]bis[propionic Acid] (9). 6 N HCl (250 mL) precooled to 0 °C was added to 34.2 g (0.119 mol) of chiral triester **8**, mixed, and stirred at 4 °C for 22 h. Extraction with four 75-mL portions of $CHCl_3$, filtration, drying (Na_2SO_4), and removal of solvent left 29.8 g of a yellow oil. As the NMR indicated incomplete reaction, the oil was taken into Et_2O, and crystals were induced to form by addition of petroleum ether and slow cooling. The crystals of diacid **9** were separated and the oil obtained by concentration of the filtrate was put through two more repetitions of the same hydrolysis to give 4.8 g of **9** the second time and 1.83 g the third time. One intermediate chromatographing of the oil after removing 4.5 g of diacid crystals gave an incremental additional 0.4 g of solid from 19.1 g of oil (100 g of silica gel, 800 mL of EtOAc to elute oil, 800 mL of EtOAc to recover the diacid **9**). The rotation of **9** varied markedly with concentration, values in ethanol of $[\alpha]_D^{20}$ −58.5° (*c* 0.022 g/mL) and −68.2° (*c* 0.010 g/mL) being typical; mp 162–164 °C; TLC (silica gel, 2-PrOH–NH_4OH 7:3, v/v) R_f 0.19. Anal. Calcd for $C_9H_{15}NO_6$: C, 46.35; H, 6.48; N, 6.01. Found: C, 46.30; H, 6.46; N, 6.23.

(*R,R*)-2,2′-Iminobis[propionic Acid·HCl]. From a run of nearly twice the above scale of *R,R* enantiomer there was obtained from the initial $CHCl_3$-insoluble material 8.4 g of white solid consisting of decarbethoxylated as well as deesterified (*R,R*)-2,2′-iminobis[propionic acid hydrochloride]: mp 180–182 °C; $[\alpha]_D^{20}$ −20.4° (*c* 0.54% 6 N HCl). The base is known.[10] Anal. Calcd for $C_6H_{12}NO_4Cl$: C, 36.46; H, 6.12; N, 7.09. Found: C, 36.21; H, 6.15; N, 7.33.

(*S,S*)-2,2′-[(Ethoxycarbonyl)imino]bis[propionic Anhydride] (10). A solution of 4.2 g (0.0173 mol) of **9** in 50 mL of dried peroxide-free THF was stirred under N_2 with 3.60 g (0.0173 mol) of dicyclohexylcarbodiimide suspended in 50 mL of THF. The reaction became nearly homogeneous, but then a white solid formed. After an hour, the precipitated urea was removed by filtration and washed with Et_2O. Removal of solvent by vacuum distillation left 5.5 g of oil and solid, which were separated by washing wtih 50 mL of Et_2O. Removal of Et_2O left 4.50 g of oil, $[\alpha]_D^{20}$ −20.1° (*c* 0.042 g/mL, $CHCl_3$). Dicyclohexylurea isolated was 95% of theory: mp 231–232 °C (lit. mp 232–233 °C). Hydrolysis of 0.30 g of anhydride (1 h with 25 mL of H_2O on a steam bath) gave diacid **9** with $[\alpha]_D^{20}$ −57.30 (*c* 0.0208 g/mL, EtOH).

(*S,S*)-2-[*N*-[1-[*N*-[3-(Carbazol-9-yl)prop-1-yl]carbamoyl]ethyl]-*N*-(ethoxycarbonyl)amino]propionic Acid (11). A solution of 3.7 g (16.5 mmol) of anhydride **10** in 50 mL of $CHCl_3$ was stirred overnight with 4.0 g (16.5 mmol) of 9-(3-aminopropyl)carbazole suspended in a mixture of 50 mL of toluene and 30 mL of THF. The reaction mixture was then extracted in turn with 70 mL of H_2O, 60 mL of 1 N HCl (an oil produced at the interface was discarded with the HCl), and H_2O, then dried (Na_2SO_4), and concentrated to give 5.42 g of a thick oil. This was impure, showing 5 spots on TLC (silica gel, $CHCl_3$–MeOH 19:1, v/v) detectable by UV or bromocresol green, the major one at R_f 0.08 and the others faint. The nominal $[\alpha]_D^{20}$ was −26.° (*c* 0.0692 g/mL, $CHCl_3$). Impurities included a trace of dicyclohexylurea, but no attempt to identify other impurities seemed required as purification was readily accomplished after the next reaction. The *R,R* enantiomer showed $[\alpha]_D^{20}$ + 21.85° (*c* 0.303 g/mL, $CHCl_3$).

(*S,S*)-1-[3-(Carbazol-9-yl)propyl]-3,5-dimethyl-4-(ethoxycarbonyl)piperazine-2,6-dione (12). A solution of 9.5 g of the acid amide **11** (21.6 mmol) in 200 mL of THF was treated with 4.55 g of carbonyldiimidazole (28.1 mmol) in 50 mL of THF under N_2, then heated under reflux for 45 min, and left to stir overnight. Removal of THF at water aspirator pressure, dissolution of the remaining oil in $CHCl_3$, extraction with 1 N HCl followed by H_2O, drying, and concentration left 9.4 g of an oil showing 3 spots on TLC. Preparative HPLC in CH_2Cl_2 on silica gel gave 4.2 g of a single spot combined fractions as an oil: $[\alpha]_D^{20}$ −41.9° (*c* 0.0226 g/mL, $CHCl_3$) with R_f 0.73 (silica gel, 19:1 $CHCl_3$–MeOH) and R_f 0.21 (silica gel, CH_2Cl_2) (UV detection). Anal. Calcd for $C_{24}H_{27}N_3O_4$: C, 68.38; H, 6.46; N, 9.97. Found: C, 68.35; H, 6.44; N, 9.99.

(*S,S*)-1-[3-(Carbazol-9-yl)propyl]-3,5-dimethyl-4-(ethoxycarbonyl)piperazine (13). Reduction of **12** was accomplished by heating a mixture of 2.8 g of **12** (6.7 mmol) in 50 mL of THF and 22 mL of 1 M BH_3 in THF under reflux (N_2) for 30 min. Dropwise addition of Me_2CO was followed by slow addition (frothing!) of 15 mL of 4 N HCl and brief heating. The reaction was concentrated to ca. 15 mL to remove THF, then 50 mL of $CHCl_3$ and an additional 30 mL of water were added, and the mixture was made basic with excess K_2CO_3. The separated $CHCl_3$ layer with three further $CHCl_3$ extracts was dried (Na_2SO_4) and concentrated to constant weight at aspirator pressure on a hot water bath. Two grams of oil remained, $[\alpha]_D^{20}$ 31.8° (*c* 0.012 g/mL, $CHCl_3$).

The corresponding (*R,R*)-**13**, prepared by reduction by 100 mL of 1 M BH_3 in THF of 13.8 g of the *R,R* isomer of **12**, was 12.1 g of oil: $[\alpha]_D^{20}$ −28.8° (*c* 0.34 g/mL, $CHCl_3$); TLC (silica gel $CHCl_3$–MeOH 19:1) R_f 0.70 and trace spots at 0.36, 0.08, 0.

(*S,S*)-*trans*-9-[3-(3,5-Dimethyl-1-piperazinyl)propyl]-carbazole (2). A total of 3.6 g (9.15 mmol) of **13** was heated on the steam bath with 36 mL of 48% aqueous HBr overnight and then was poured into 4 mL of 10 N NaOH in 100 g of ice, extracting the resulting oil with three 75-mL portions of ether. The ethereal solution was dried (Na_2SO_4) and concentrated to yield 2.5 g of oil. The $[\alpha]_D^{20}$ in $CHCl_3$ was 4.1° (0.0145 g/mL) and 3.9° (0.0110 g/mL). TLC (silica gel, 85:10:5 ethyl acetate–CH_3CN–Et_2NH) showed a major spot at R_f 0.25 and trace spots at R_f 0.04 and the origin. The oil was taken up in 75 mL of ether, filtered to remove an insoluble residue, and treated with anhydrous HCl. The pale blue solid so produced was recrystallized by dissolving it in 50 mL of EtOH and adding 250 mL of EtOAc–Et_2O to turbidity at the boiling point. A total of three crops of crystals was obtained by filtration, rewarming the filtrate, and adding more ether to incipient turbidity. These totaled 2.4 g. TLC showed a single spot (silica gel, 8.5:10:5 EtOAc–MeCN–Et_2NH) R_f 0.33; $[\alpha]_D^{20}$ for the *S,S* base 3.76° (*c* 0.127 g, 5 mL of $CHCl_3$) [the *R,R*

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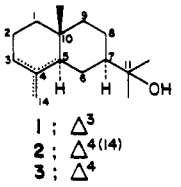
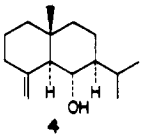
(±)-α-Eudesmol and its three possible diastereomers, 7-epi-, 5-epi-, and 5-epi-7-epi-α-eudesmol, as well as (±)-β-eudesmol and 7-epi-β-eudesmol, have been synthesized from farnesol.

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



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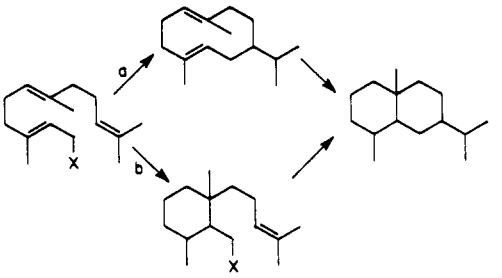
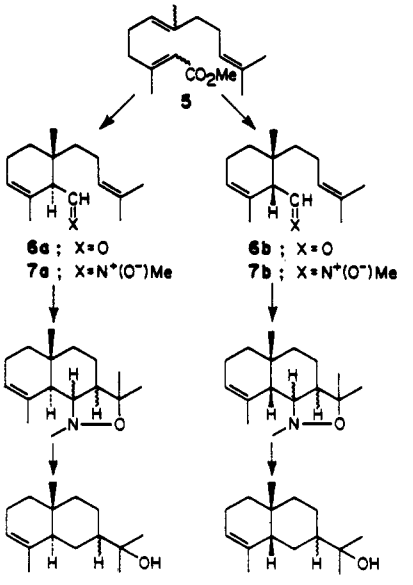
directed to the total synthesis[3] of these deceptively simple natural products as well as of some of their diastereomers.[4] Biomimetic syntheses of eudesmols based on the farnesane → germacrane → eudesmane biosynthetic pathway[5] (Scheme I, path a) have also been recorded.[6] We some time ago applied 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



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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.

0022-3263/85/1950-1359$01.50/0