20% purity by GLC. This fraction (1.05 g) was subjected to preparative layer chromatography over alumina in $CHCl_3$, alumina in $CHCl_3/Et_2O$ (4:1, 2×), alumina in $CHCl_3$/EtOAc (97:3), and finally alumina in $CHCl_3$ to yield 4-(3-methoxy-4-hydroxyphenyl)-4-[2-(acetylmethylamino)ethyl]cyclohexadienone (**24**) as a solid: mp 107.5 °C; IR 3540 (phenolic OH), 1637 (amide C=O), 1665 (dienone C=O) cm^{-1}; 100-MHz NMR δ 2.97 and 3.01 (2 s, 3 H), 3.82 and 3.86 (2 s, 3 H), 6.35 (d, 2 H, J = 14 Hz), 6.98 (d, 2 H, J = 14 Hz), 6.85–6.93 (m, 3 H); mass spectrum m/e (relative intensity) 315 (20, M^+), 273 (15), 242 (45), 229 (20), 215 (40), 100 (45), 86 (40), 73 (100); molecular ion at 315.1472 (calcd for $C_{18}H_{21}NO_4$, 314.1470).

Acetylation of 4′-*O*-Demethylmesembrenone (29). A mixture of 100 mg of **32**, 3 mL of acetic anhydride, and 10 mg of anhydrous sodium acetate was stirred at room temperature for 4 h. The mixture was diluted with water (100 mL), basified with solid K_2CO_3, and extracted with $CHCl_3$ (2 × 50 mL). The $CHCl_3$ was washed with water and dried over magnesium sulfate. The solvent was removed in vacuo to yield 4-(3-methoxy-4-acetoxyphenyl)-4-[2-(acetylmethylamino)ethyl]cyclohexadienone (**30**) as an oil, pure by GLC and TLC: molecular ion at m/e 357.1573 (calcd for $C_{20}H_{23}NO_5$: 357.1576).

O-Deacetylation of 4-(3-Methoxy-4-acetoxyphenyl)-4-[2-(acetylmethylamino)ethyl]cyclohexadienone (30). A 50-mg sample of **30** was stirred with 3 mL of absolute methanol and anhydrous K_2CO_3 (10 mg) for 6 h at room temperature. The mixture was diluted with 50 mL of water and extracted with $CHCl_3$ (2 × 50 mL). The $CHCl_3$ was washed with water and dried over sodium sulfate. The solvent was removed to give a product exhibiting chromatographic and spectral data identical with those of the natural base **24**.

Acknowledgment. We are indebted to the National Institute of Environmental Health Sciences for a training grant in support of R.R. (Grant No. 5-T32-ES-07031).

Registry No. **1**, 24880-43-1; **3**, 35135-35-4; (-)-**4**, 35722-04-4; **5**, 82545-08-2; (+)-**6**, 82545-10-6; (-)-**10**, 59096-18-3; **13**, 59096-21-8; (-)-**16a**, 23544-42-5; (-)-**16b**, 82545-11-7; (-)-**17**, 82545-14-0; **20**, 82545-07-1; **23**, 82545-09-3; **24**, 82545-13-9; **29**, 82597-44-2; **30**, 82545-12-8; mesembrenone, 25516-12-5; *N*-formyltortuosamine, 59096-17-2; Δ^7-mesembrenone, 59122-98-4.

Synthesis and Absolute Configuration of (*R*)-(+)- and (*S*)-(-)-5-(1,3-Dimethylbutyl)-5-ethylbarbituric Acid

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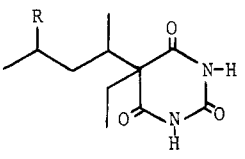
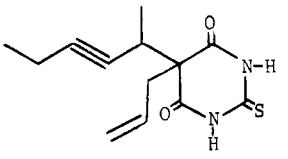
(*R*)-(+)- and (*S*)-(-)-5-(1,3-dimethylbutyl)-5-ethylbarbituric acids, which show excitatory–convulsant and sedative–hypnotic effects in mice, respectively, were synthesized by a sequence of reactions that permitted assignment of the absolute configuration of these enantiomers. Racemic 3,5-dimethylhexanoic acid was prepared in three steps from 4-methyl-2-pentanone by Wittig–Horner reaction with triethyl phosphonoacetate, hydrogenation of the resulting α,β- and β,γ-unsaturated ester mixture, and alkaline hydrolysis of the ethyl ester obtained. An optical resolution of this acid afforded relatively large quantities of the (*R*)-(+) and (*S*)-(-) enantiomers of previously established absolute configuration. Optical purity of >99% was determined for these enantiomers by HPLC analysis of the amides formed with optically pure (*R*)-(+)- or (*S*)-(-)-1-phenylethylamine. Transformation of (*R*)-(+)- and (*S*)-(-)-3,5-dimethylhexanoic acids to the title compounds by a route shown earlier not to involve racemization thus afforded the enantiomeric barbiturates of >99% optical purity and of established absolute configuration.

Racemic 5-(1,3-dimethylbutyl)-5-ethylbarbituric acid [(±)-DMBB, (±)-**1**] was first synthesized[1] and characterized[1,2] as a convulsant many years ago. Subsequent studies[3,4] using partially resolved material revealed that the convulsant action resided in the (+) isomer while the (-) isomer showed the classical sedative–hypnotic actions common to many barbiturates such as pentobarbital [(±)-**2**]. The relationship between mechanism of action of barbiturates and benzodiazepines has recently come under close scrutiny since the discovery that (±)-pentobarbital [(±)-**2**] potentiates the γ-aminobutryic acid (GABA)[5] enhancement of benzodiazepine binding to membrane-bound receptors[6,7] and also enhances benzodiazepine receptor affinity in the absence of GABA as do (±)-**1**, the enantiomers of **2**, and other barbiturates.[7,8] The different pharmacological profiles of (±)-DMBB [(±)-**1**][1-3] and pentobarbital [(±)-**2**][3,9] in vivo and the close structural similarity of these compounds (which differ only by one methyl group at the 3-position in the butyl side chain) suggested that the optically pure enantiomers of **1** could



(±)-**1**: R = CH_3

(±)-**2**: R = H



(±)-**3**

(1) Shonle, H. A.; Waldo, J. H.; Keltch, A. K.; Coles, H. W. *J. Am. Chem. Soc.* **1936**, *58*, 585.
(2) Swanson, E. E.; Chen, K. K. *Q. J. Pharm. Pharmacol.* **1939**, *12*, 657.
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(5) GABA is the major inhibitory neutrotransmitter in the mammalian CNS. For a recent review see: Haefely, W.; Kulcsar, A.; Mohler, H.; Pieri, L.; Polc, P.; Schaffner, R. "Mechanism of Action of Benzodiazepines"; Costa, E., Greengard, P., Eds.; Raven: New York, 1975; p 131.
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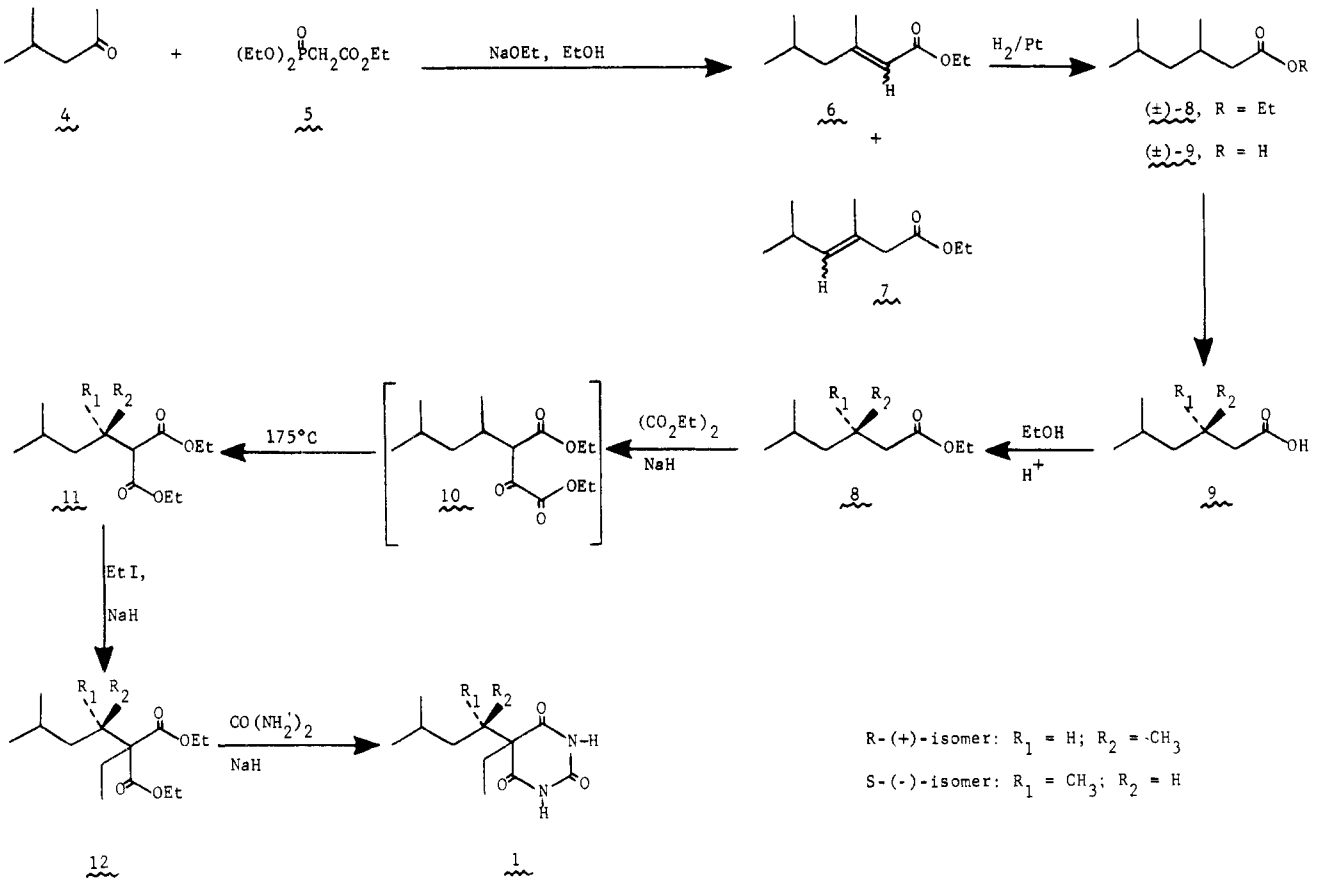
Scheme I



prove to be valuable probes for further elucidation of the fundamental mechanism of action of both barbiturates and benzodiazepines. In this report, synthesis of (*R*)-(+)- and (*S*)-(−)-DMBB (1) of known optical purity is described, with the absolute configuration being proven by the synthetic route utilized.

The absolute configuration of 1 has been designated as (*R*)-(+) and (*S*)-(−) earlier;[10] however, a complete search of the literature revealed no basis for these assignments which apparently have been perpetuated since they were first used. Fortunately, these designations happened to be correct since they are in agreement with the absolute configuration of 1 unequivocally established as described below.

The enantiomers of 1 have previously been obtained by an unspecified route, and characterization was not reported, although differences in the in vivo effects of the two enantiomers were discussed.[11] Incomplete optical resolution of (±)-1 has only afforded the partially resolved enantiomers[3,12] (see below) although one group obtained (*R*)-(+)-1 of constant rotation.[3] In the present study, a synthetic sequence to (*R*)-(+)- and (*S*)-(−)-1 was desired that would provide reasonable quantities of the optically pure enantiomers and permit assignment of absolute configuration to these compounds. An attractive possibility appeared to be the route used by Cook and Tallent[13] for synthesis of (*R*)-(+)-pentobarbital [(*R*)-(+)-2] and by Carroll and Meck[14] for the corresponding *S* isomer from the appropriate enantiomer of 3-methylhexanoic acid. In the latter study, this route was shown to proceed without racemization since the optical rotation observed for (*S*)-(−)-2 obtained by exhaustive resolution was in excellent agreement with that for (*S*)-(−)-2 synthesized from the (*S*)-(−) isomer of 3-methylhexanoic acid obtained by optical resolution. In addition, the magnitude of the optical rotation of (*R*)-(+)-2 synthesized from natural (*R*)-(+)-pulegone via (*R*)-(+)-3-methylhexanoic acid was also in excellent agreement with that of the *S* isomer obtained by the two methods mentioned above.[13,14] Finally, recent work by Carroll,[15] who utilized this route for the synthesis of the enantiomers of 5-allyl-5-(1-methyl-2-pentynyl)-2-thiobarbituric acid [(±)-3] with a chiral side chain very similar to that of 1 and 2, revealed that no racemization occurred as shown by an interesting double-irradiation NMR study which was capable of detecting 2% enantiomeric contamination.

The synthesis of the enantiomers of 1 by a parallel route (Scheme I) thus required relatively large amounts of the enantiomeric 3,5-dimethylhexanoic acid (9) and demonstration of optical purity (see below) which would ensure the optical purity of the barbiturates. Since the absolute configuration of 9 has been determined and independently checked[16] as (*R*)-(+)- and (*S*)-(−), the synthesis depicted in Scheme I permitted assignment of the absolute configuration of 1 as shown. Partially resolved (*R*)-(+)-9 has been obtained in a difficult resolution using quinine[17] and

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(11) Hupka, A. L.; Williams, J. K.; Karler, R. *J. Pharm. Pharmacol.* **1969**, *21*, 838.
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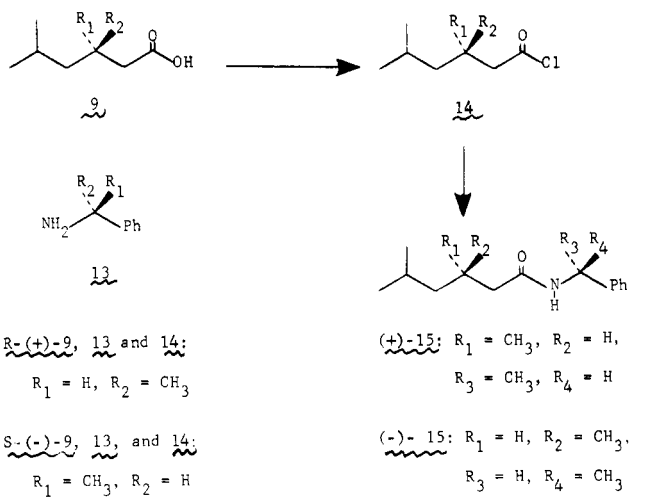
in a state of optical purity, or nearly so, from 3,5-dimethylphenol by a lengthy synthesis requiring optical resolution of an intermediate, which was used to prepare and determine the absolute configuration of the 3,5-dimethylpimelic acids and the corresponding half-methyl esters.[16] Partially resolved (*S*)-(−)-**9** was also obtained in this work by a similar route.[16] Although the enantiomers of **9** could be obtained by using this methodology, the most direct route to (*R*)-(+)- and (*S*)-(−)-**9** appeared to be development of a simplified procedure for resolution of the racemate. A likely starting material for preparation of large quantities of racemic **9** for resolution appeared to be the mixture of *E* and *Z* acrylates **6** which was prepared as follows.

Wittig–Horner reaction[18,19] of 4-methyl-2-pentanone (**4**) with triethyl phosphonoacetate (**5**) on a 1.3-mol scale easily afforded 88% yield of an ester mixture, which appeared, after NMR, IR, and GLC analysis, to consist of predominately (~85%) of the *E* and *Z* α,β-unsaturated esters **6** and ~15% of the β,γ-unsaturated esters **7**. Apparently the β,γ-unsaturated esters **7** were formed by base-catalyzed isomerization of the primary reaction products **6**. Catalytic hydrogenation of the mixture of four esters gave the saturated ester (±)-**8** in 98% yield which was essentially pure by GLC. Alkaline hydrolysis of (±)-**8** then gave the acid (±)-**9** required for optical resolution in 98% yield. The favorable results reported by Levin and Marker,[20] which were later confirmed by Carroll and Meck,[14] for obtaining (*S*)-(−)-3-methylhexanoic acid [the 5-demethyl derivative of (−)-**9**] from the racemate via the (−)-cinchonidine salt suggested initial attempts at resolution of (±)-**9** should be made with this alkaloid. Indeed, (−)-cinchonidine proved to be the most effective base of a number examined for resolution of (±)-**9**, particularly when employed in less than an equivalent amount. Comparison of the literature value[16] for the optical rotation of (*R*)-(+)-**9** with that obtained for (*S*)-(−)-**9** regenerated from the salt after five recrystallizations suggested that optically pure material had been obtained. The optical rotation of the partial resolved (*R*)-(+)-**9** recovered from the filtrate of the initial crystallization of the (−)-cinchonidine salt indicated it to be ~73% optically pure. A number of bases were examined as possible resolving agents for the (+) acid, and (*R*)-(+)-1-phenylethylamine [(*R*)-(+)-**13**] proved most satisfactory. The (*R*)-(+)-**9** recovered from the salt purified by ten recrystallizations from hexane showed an optical rotation consistent with complete resolution. Nevertheless, it seemed desirable to confirm the optical purity of both enantiomers by an independent method. One such method is the use of chiral derivatizing agents (CDA) in conjunction with NMR or chromatographic techniques. As Pirkle has pointed out,[21] this method relies on optically pure CDA, configurationally stable derivatives, and lack of asymmetric induction or fractionation during derivatization. One possible chiral derivative of acid **9** which could meet the requirements appeared to be the amide formed with (*R*)-(+)- or (*S*)-(−)-1-phenylethylamine (**13**). The pure acid chloride (±)-**14** prepared from (±)-**9** in the usual way reacted exothermically with an equimolar amount of a commercial sample of (*R*)-(+)-**13** in dry alcohol-free chloroform containing a moderate excess of dry triethylamine. The resulting diastereoisomers were subjected to high-performance liquid chromatography (HPLC), and base-line

Scheme II



separation was obtained after optimization of conditions. The optically pure samples of (*R*)-(+)- and (*S*)-(−)-**13** then required for optical purity analysis of (*R*)-(+)- and (*S*)-(−)-**9** were obtained via the salts with (−)- and (+)-tartaric acids, respectively.[22] Derivatization of (*S*)-(−)-**9** with this sample of (*R*)-(+)-**13**, via acid chloride (*S*)-(−)-**14** as shown in Scheme II, afforded amide (+)-**15** which was subjected to HPLC analysis as crude material. In order to access the accuracy of the result obtained, incremental amounts (in the range 0–1%) of enantiomeric impurity were added to aliquots of the sample of (*S*)-(−)-**9**. Derivatization as before, HPLC analysis, and construction of a calibration curve which was linear showed that the original sample of (−)-**9** contained about 0.7% enantiomeric impurity.[25] Similar derivatization of (*R*)-(+)-**9** with (*S*)-(−)-**13** via acid chloride (*R*)-(+)-**14** afforded amide (−)-**15**. HPLC analysis of crude (−)-**15** showed about 0.5% optical impurity in the original sample of (*R*)-(+)-**9**. When this derivatization was repeated with (*S*)-(−)-**9** and several commercial samples of (*R*)-(+)-**13** selected at random, HPLC analyses and integration of the chromatogram revealed 2.5–4.8% optical impurity in the samples of (*R*)-(+)-**13**, depending on which sample of (*R*)-(+)-**13** was used for derivatization. Since the optical impurity in the commercial (*R*)-(+)-**13** would appear as optical impurity in the derivatized sample of (*S*)-(−)-**9**, this exercise clearly illustrates the pitfalls which could be encountered unless the optical purity of the commercial CDA is critically evaluated. The enantiomers of **15** were obtained in crystalline condition; however, the diastereoisomers of **15** obtained by derivatization of (*R*)-(+) and (*S*)-(−)-**9** with (*R*)-(+) and (*S*)-(−)-**13**, respectively, resisted crystallization from a variety of solvents. Optical resolution of (±)-**9** via the crystalline amides **15** was investigated but proved less favorable than the salts utilized.

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(21) Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1981**, *46*, 3239.

(22) In earlier work, the enantiomers of **13** purified in this manner were converted to the corresponding isocyanates which reacted selectively with the amino function in (*R*)-(+)- and (*S*)-(−)-1-(3-hydroxy-4-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline obtained by optical resolution. Enantiomeric impurity could not be detected in either enantiomer of the tetrahydroisoquinoline or **13** by NMR studies[23] at 220 MHz or by HPLC analysis[24] of the resulting urea derivatives.
(23) Rice, K. C. *J. Org. Chem.* **1980**, *45*, 3135.
(24) Rice, K. C. *Proc. Prob. Drug Dep.* **1981**, 99.
(25) The amount of enantiomeric impurity detected in an analysis such as this actually represents that present only if the conditions[21] discussed above are met as in this case, and the detection–integration system gives the same response to the diasterisomers being separated in the concentration range under investigation. When both the CDA and the enantiomer under investigation are slightly optically impure and the ratio of major to minor diasterisomers observed is >20:1, the amount of diasterisomeric impurity observed closely approximates the sum of optical impurity in the CDA and the enantiomer being analyzed.

Once the optical resolution and demonstration of optical purity in excess of 99% was complete for (*R*)-(+)- and (*S*)-(−)-**9**, their conversion to (*R*)-(+)- and (*S*)-(−)-1, respectively, was easily accomplished by using the standard sequence[13-15] shown in Scheme I. The absolute configuration of the enantiomers of 1 was thus unequivocally established by synthesis. Since no racemization occurs in this sequence, the optical rotations of (*R*)-(+)- and (*S*)-(−)-1 prepared in this study permitted estimation of the optical purity of samples of these barbiturates obtained earlier by other workers. The optical rotations reported by Downs[3] for (*R*)-(+)- and (*S*)-(−)-1 suggest about 85% and 79% optical purity, respectively, for the samples prepared in that study. Similarly, optical purities of 60% and 94% for the corresponding samples appear to have been reached by Sitsen.[4]

As with optical pairs of drugs in other classes, results of pharmological studies involving partially resolved barbiturate enantiomers must be cautiously interpreted until results with the pure enantiomers are available. Pharmacological effects of the enantiomers of 1 prepared in this study have been reported elsewhere,[26] and the electrophysiological study of the actions of the enantiomers is in progress and will be reported in due course.

Experimental Section

Melting points (corrected) were determined in open capillary tubes by using a Thomas-Hoover apparatus. Elemental analyses were performed by the Section on Microanalytical Services and Instrumentation of this laboratory. IR spectra were recorded on a Beckman IR 4230 instrument. Gas–liquid chromatography (GLC) was done with a Hewlett-Packard Model 5880A gas chromatograph (level four) equipped with a 10-m methylsilicone fluid capillary column and a flame-ionization detector at the column temperature (CT) specified. Analytical high-performance liquid chromatography (HPLC) was performed by using a Waters Model 6000 solvent-delivery system, a Waters Model 450 variable-wavelength detector operating at 260 nm, and a 6.25 mm × 25 cm Du Pont Zorbax-Sil column eluted with 3% (v/v) 2-propanol in 2,2,4-trimethylpentane at 1.0 mL/min. A Hewlett-Packard 3390 reporting integrator was used to integrate the HPLC chromatograms. Optical rotations were measured with a Perkin-Elmer Model 241 MC polarimeter with the solvents and concentrations specified. NMR spectra were determined by using a Varian HR-220 spectrometer with $(CH_3)_4Si$ as the internal reference. For nominal mass determination chemical-ionization mass spectra (CI MS) were obtained with a Finnigan 1015D spectrometer with a Model 6000 data collection system, and electron-ionization mass spectra (EI MS) were obtained with a Hitachi Perkin-Elmer RMU 6E spectrometer (70 eV). Accurate mass determinations were made with a VG Micromass Model 7070F spectrometer using either chemical or electron ionization. Short-range Hydrion paper was used for pH determinations. Silica gel GF plates for thin-layer chromatography were purchased from Analtech, Inc., Newark, DE.

(*E*)- and (*Z*)-Ethyl 3,5-Dimethyl-2-hexenoate (6). The following procedure is a modification of that utilized by Ogura[18] for synthesis of a series of methyl acrylates. Triethyl phosphonoacetate (5; 300.0 g, 1.34 mol) was added to a stirred solution of 32.79 g (1.42 mol) of clean Na in 1.0 L of absolute EtOH under argon at ambient temperature. After 5 min, 142.6 g (1.42 mol) of dry redistilled 4-methyl-2-pentanone (4) was added in one portion which resulted in an exothermic reaction (22 → 47 °C) during 40 min. When the temperature began to fall, the mixture was refluxed 1.5 h and then distilled through a short column until the batch temperature reached 90 °C. After being cooled to 15 °C, and addition of 750 mL of petroleum ether (bp 30–60 °C), the mixture was diluted with 500 mL of ice–H_2O. After equilibration of the phases, the aqueous phase was reextracted with petroleum ether (2 × 250 mL). The combined extracts were washed with H_2O (3 × 250 mL), dried with $MgSO_4$, evaporated, and distilled to give 200.6 g (88%) of mixed esters: bp 70–76 °C (5.0 mm) [lit.[27] bp 67–78 °C (6 mm)]; CI MS, *m/e* 171 ($M^+ + 1$); IR (film) 1715 (α,β-ester C=O), 1735 cm^{-1} (sh, β,γ-ester C=O); NMR (neat) δ 5.52 and 5.44 (1:2.2 ratio, 2 s, *Z* and *E* olefinic H of α,β-unsaturated ester **6**), 4.96 and 4.93 (2 overlapping d, $J \approx 8$ Hz, appearing as t, *Z* and *E* olefinic H of β,γ-unsaturated ester **7**), integration of the olefinic absorption showed that the ratio of β,γ- to α,β-unsaturated esters was ~15:85; GLC (CT 85 °C) showed four major components in a ratio 8:7:27:58 and traces of two other unidentified components.

(±)-Ethyl 3,5-Dimethylhexanoate [(±)-8]. A mixture of 2.0 g of 10% Pt/C and 95.0 g (0.56 mol) of the ester mixture from above was hydrogenated (exothermic) at an initial pressure of 52.5 psig until uptake ceased (~45 min) at 98.5% of the theoretical amount. The catalyst was filtered and washed with Et_2O (2 × 50 mL). Evaporation of the filtrate and washings afforded an oil that was distilled to afford 94.35 g (98%) of (±)-**8**: EI MS, *m/e* 172 (M^+); bp 64–66 °C (5.5 mm) [lit.[17] bp (for partially resolved (*R*)-(+)-**8**, "dextro-ethyl ester of 2-isobutyl buyric acid-4") 85 °C (20 mm)]; IR (film) 1738 (C=O) cm^{-1}; GLC (CT 85 °C) showed this material to be >99% pure.

(±)-3,5-Dimethylhexanoic Acid [(±)-9]. A mixture of 103.2 g (0.6 mol) of (±)-**8**, 52.7 g (0.8 mol) of 85% KOH in 80 mL of H_2O, and 300 mL of EtOH was refluxed 1.0 h and then distilled at atmospheric pressure until the batch temperature reached 90 °C. The residue was cooled, diluted with 200 mL of H_2O, treated with 100 mL of 37% HCl, and extracted with Et_2O (3 × 100 mL). The combined Et_2O extracts were washed with 100 mL of H_2O, dried ($MgSO_4$), and evaporated. Distillation of the residue gave 84.81 g (98%) of (±)-**9**: bp 106–109 °C (4 mm) [lit.[28] bp 119–120 °C (14 mm)]; IR (film) 1711 (C=O) cm^{-1}.

Optical Resolution of (±)-3,5-Dimethylhexanoic Acid [(±)-9]. (A) (*S*)-(−)-9. A mixture of 225 mL of acetone, 123.85 g (0.86 mol) of (±)-**9**, and 139.25 g (0.473 mol, 0.55 equiv) of *l*-cinchonidine was heated nearly to solution and treated with 45.0 mL of H_2O which soon afforded a homogenous solution. Addition of 500 mL of hexane gave a cloudy solution which afforded much crystalline material after cooling to 25 °C. When crystallization seemed complete, the slurry was diluted with 500 mL of hexane, cooled to 10 °C, and filtered, and the solid was washed well with 1:5 acetone–hexane (4 × 250 mL) to give 157.20 g of hydrated, partially resolved salt after air-drying. The filtrate and washings from this crystallization were processed as described as below for the (*R*)-(+) isomer. A 1.0-g portion of this salt was suspended in 20 mL of hexane and 20 mL of H_2O and treated with 1.0 mL of 37% HCl. The hexane was separated, washed with 20 mL of H_2O, and dried ($MgSO_4$). Evaporation of the solvent and distillation of the residue gave 290 mg of optically impure acid **9**: bp 84–86 °C (1.4 mm); $[\alpha]^{23}_D$ −8.9° (*c* 6.25, $CHCl_3$). The remaining 156.20 g of salt from above was recrystallized four times by heating to solution in a mixture of 350 mL of acetone and 200 mL of H_2O, cooling to 0 °C, and washing the solid with a mixture of 350 mL of acetone and 200 mL of H_2O at 0 °C. The final crystallization afforded 82.54 g of (*S*)-(−)-**9**-cinchonidine–H_2O, partially melting a 78–110 °C, resolidifying, and remelting at 143–160 °C. A sample placed in an oil bath preheated to 120 °C melted completely (froth); $[\alpha]^{23}_D$ −92.0° (*c* 1.0, MeOH).

Anal. Calcd for $C_{27}H_{38}N_2O_3 \cdot H_2O$: C, 71.01; H, 8.83; N, 6.13. Found: C, 70.98; H, 9.15; N, 6.01.

A suspension of 79.0 g (0.17 mol) of the salt in 500 mL of H_2O was treated with 43 mL of 37% HCl and 200 mL of Et_2O and equilibrated to give two homogenous phases. The Et_2O was separated, and the aqueous phase was reextracted with Et_2O (2 × 200 mL). The combined Et_2O solution was washed with 100 mL of brine, dried ($MgSO_4$), evaporated, and distilled to give 24.70 g [99% recovery, 40% from (±)-**9**] of (*S*)-(−)-**9** (shown to be 99.3% optically pure as described below): bp 84–87 °C (1.8 mm); $[\alpha]^{23}_D$ −13.21° (*c* 6.38, $CHCl_3$) [lit.[16] bp (for (+) isomer) 120–130 °C (15 mm); $[\alpha]^{24}_D$ +12.8° (*c* 5.21, $CHCl_3$)].

(B) (*R*)-(+)-9. The filtrate and washings from the initial crystallization of the (−)-cinchonidine salt from above were

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evaporated to a syrup which was shaken well with 500 mL of H_2O, 500 mL of hexane, and 50 mL of 37% HCl. The hexane layer was washed with 500 mL of H_2O, dried ($MgSO_4$), and evaporated, and the residue was distilled to afford 72.80 g of optically impure (*R*)-(+)-**9**: 84–87 °C (1.6 mm); $[\alpha]^{23}_D$ +6.02 (*c* 6.45, $CHCl_3$). A mixture of 60.77 g (0.42 mol) of this acid and 54.45 g (0.45 mol) of optically pure (*R*)-(+)-1-phenylethylamine [(*R*)-(+)-**13**] from below in 400 mL of hexane was allowed to crystallize at 20 °C. The solid was filtered and washed well with 300 mL of hexane to afford 81.15 g of diasterisomeric salts. Nine additional crystallizations from 6 volumes of hexane (cooling to 20 °C and washing with 6 volumes of hexane at 20 °C) gave 38.30 g of (*R*)-(+)-**9**·(*R*)-(+)-**13**: mp 96.5–98 °C; $[\alpha]^{23}_D$ +14.9° (*c* 1.02, MeOH).

Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.26; N, 5.28. Found: C, 72.34; H, 10.19; N, 5.20.

A mixture of 37.64 g (0.14 mol) of this salt and 75 mL of H_2O was treated with 15 mL of 37% HCl and extracted with 300 mL of Et_2O. The aqueous phase was reextracted with Et_2O (2 × 100 mL), and the combined Et_2O extracts were washed with 50 mL of H_2O, dried ($MgSO_4$), and distilled to afford 20.30 g [98% recovery, 33% from (±)-**9**] of (*R*)-(+)-**9**, shown to be 99.5% optically pure as described below: bp 85–88 °C (1.5 mm); $[\alpha]^{23}_D$ +13.28° (*c* 6.07, $CHCl_3$) [lit.[16] bp 120–130 °C (15 mm); $[\alpha]^{24}_D$ +12.8° (*c* 5.21, $CHCl_3$)].

(*R*)-(+)-1-Phenylethylamine [(*R*)-(+)-13]. A commercial sample of (*R*)-(+)-**13** was found to contain ~3.8% of the enantiomer by HPLC analysis of the amides formed with (*S*)-(−)-**9** as described below. The resolution was completed as follows. A mixture of 150.1 g (1.0 mol) of (−)-tartaric acid was heated to solution in 1 L of DMF, treated with 121.2 g (1.0 mol) of the commercial (*R*)-(+)-**13**, and cooled to 20 °C. When crystallization was complete, the salt was filtered, washed thoroughly with cold DMF (3 × 500 mL) and Et_2O (3 × 500 mL), and dried at 50 °C (120 mm) to afford 220.1 g of salt. This material was heated to solution in 660 mL of DMF (<120 °C), cooled, and filtered, and the salt was washed with DMF (2 × 500 mL) and Et_2O (2 × 500 mL) and dried as above to give 180.25 g of salt. Addition of a cold solution of 102.0 g (2.55 mol) of NaOH in 600 mL of H_2O to 175.0 g (0.65 mol) of this salt gave an oil that was extracted with Et_2O (200, and 100 mL). The combined extracts were dried with 3.0 g of $MgSO_4$ and distilled twice to give 69.90 g (58%) of (*R*)-(+)-**13**:[22] bp 83–85 °C (23 mm); $[\alpha]^{23}_D$ +39.3° (neat, *d* = 0.9528) [lit.[29] bp 85–86 °C (21 mm); $[\alpha]^{29}_D$ +39.7° (neat, *d* = 0.9528)].

(*S*)-(−)-1-Phenylethylamine [(*S*)-(−)-13]. A commercial sample of 12.1 g (0.1 mol) of (*S*)-(−)-**13** containing ~3% optical impurity was purified as above via the salt with (+)-tartaric acid to afford 9.3 g (76%) of (*S*)-(−)-**13**:[22] bp 83–85 °C (23 mm); $[\alpha]^{24}_D$ −39.7° (neat, *d* = 0.9528) [lit.[29] bp 94–95 °C (38 mm); $[\alpha]^{29}_D$ −39.4° (neat, *d* = 0.9528)].

(±)-3,5-Dimethylhexanoyl Chloride [(±)-14]. A mixture of 2.88 g (20.0 mmol) of (±)-**9**, 15 μL of DMF, and 4.89 g (41.1 mmol) of $SOCl_2$ was stirred at ambient temperature until gas evolution slowed and then cautiously heated to reflux. After 1.0 h of refluxing, the mixture was cooled, distilled, and redistilled to afford 2.98 g (92%) of (±)-**14**: bp 78–79 °C (28 mm); IR (film) 1802 (C=O) cm^{-1}. This material was further characterized by accurate mass determination of the syrupy, diastereoisomeric amides formed with (*R*)-(+)-**13** (see below).

(*R*)-(+)-3,5-Dimethylhexanoyl Chloride [(*R*)-(+)-14]. Treatment of 1.0 g (6.94 mmol) of (*R*)-(+)-**9** as described for (±)-**9** gave (*R*)-(+)-**14** [characterized further as the crystalline amide (−)-**15**]: 87% yield; bp 78–80 °C (28 mm); IR (film) 1802 (C=O) cm^{-1}; $[\alpha]^{23}_D$ +7.38° (*c* 2.9, dry CH_3Ph).

(*S*)-(−)-3,5-Dimethylhexanoyl Chloride [(*S*)-(−)-14]. Treatment of 1.0 g (6.94 mmol) of (*S*)-(−)-**9** as described above for (±)-**9** gave (*S*)-(−)-**14** [characterized further as the crystalline amide (+)-**15**]: 93% yield; bp 77–80 °C (28 mm); IR (film) 1802 (C=O) cm^{-1}; $[\alpha]^{23}_D$ −7.42° (*c* 2.9, dry CH_3Ph).

***N*-[(*R*)-1-Phenylethyl]-(*S*)-3,5-dimethylhexanamide [(+)-15] and Optical Purity of (*S*)-(−)-9.** To a stirred solution of 242.4 mg (2.0 mmol) of (*R*)-(+)-**13** from above and 303 mg (3.0 mmol) of dry Et_3N in 10 mL of dry alcohol-free $CHCl_3$ was added dropwise 325.3 mg (2.0 mmol) of (*S*)-(−)-**14**. After 30 min, the solution was diluted with 15 mL of $CHCl_3$ and washed with 1 mL of 37% HCl in 25 mL of H_2O and then with 25 mL of H_2O. The $CHCl_3$ solution was dried ($MgSO_4$) and a small portion removed for HPLC analysis. HPLC analysis and integration of the chromatogram showed 0.7% of the diastereoisomeric amide derived from (*R*)-(+)-**13** and (*R*)-(+)-**9**, indicating about 99.3% optical purity of the sample of (*S*)-(−)-**9**. Evaporation of the remainder and drying the residue at 60 °C for 2 h under high vacuum left 445 mg (90%) of essentially pure [TLC, Et_2O–hexane (2:3); HPLC] (+)-**15**. Recrystallization from 4.0 mL of 2,2,4-trimethylpentane afforded an analytical sample: mp 62.5–64 °C; $[\alpha]^{24}_D$ +82.3° (*c* 1.75, $CHCl_3$); EI MS, *m/e* 247 (M^+); IR ($CHCl_3$) 1660 (C=O) cm^{-1}.

Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.66; H, 10.20; N, 5.66.

***N*-[(*S*)-1-Phenylethyl)]-(*R*)-3,5-dimethylhexanamide [(−)-15] and Optical Purity of (*R*)-(+)-9.** Preparation of this material from (*S*)-(−)-**13** and (*R*)-(+)-**14** as described for the enantiomer above afforded 424 mg (86%) of essentially pure (−)-**15** [TLC, Et_2O–hexane (2:3); HPLC] after removal of a portion of the $CHCl_3$ solution for HPLC analysis and evaporation of the solvent. HPLC analysis and integration of the chromatogram showed 0.5% of the diastereoisomeric amide derived from (*S*)-(−)-**13** and (*S*)-(−)-**9**, indicating the original sample of (*R*)-(+)-**9** was about 99.5% optically pure. Recrystallization as above gave the analytical sample: mp 63–64.5 °C; $[\alpha]^{24}_D$ −81.6° (*c* 1.74, $CHCl_3$); EI MS, *m/e* 247 (M^+); IR ($CHCl_3$) 1600 (C=O) cm^{-1}.

Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.94; H, 9.84; N, 5.68.

***N*-[(*R*)-1-Phenylethyl]-(*R*,*S*)-3,5-dimethylhexanamides.** This mixture of diastereoisomers was prepared from (*R*)-(+)-**13** and (±)-**14** as described above for (+)-**15**. In this manner, 484 mg (98%) of syrupy diastereoisomers was obtained: EI MS, *m/e* 247 (M^+); IR (film) 1640 (C=O) cm^{-1}; high-resolution EI MS, *m/e* 247.1943 (M^+; calcd for $C_{16}H_{25}NO$ 247.1936). The diastereoisomers were not separated on TLC (Et_2O–hexane, 2:3) and appeared essentially pure in this system and on HPLC. In a typical HPLC run, the two diastereoisomers showed retention times of 28.3 and 30.8 min.

(*R*)-(+)-Ethyl 3,5-Dimethylhexanoate [(*R*)-(+)-8]. In a modification of the procedure of Levene and Marker,[17] 15.8 g (0.11 mol) of (*R*)-(+)-**9**, 35 mL of absolute EtOH, and 1.5 mL of 98% H_2SO_4 was refluxed 3 h and then distilled until the vapor temperature reacted 83 °C. The distillate was diluted with 80 mL of H_2O and extracted with 50 mL of Et_2O. This extract and 100 mL of additional Et_2O was added to the cooled pot residue. This mixture was washed successively with H_2O (2 × 20 mL), 10% aqueous K_2CO_3 (4 × 25 mL), 25 mL of H_2O, and 35 mL of brine. Drying ($MgSO_4$) and distillation afforded 17.26 g (91%) of (*R*)-(+)-**8** shown to be >99% pure by GLC (CT 85 °C): EI MS, *m/e* 172 (M^+); bp 68–70 °C (9 mm); $[\alpha]^{23}_{obsd}$ +6.59° (neat, *l* = 1); $[\alpha]^{23}_D$ +8.76° (*c* 5.84, $CHCl_3$) [lit.[17] bp ("dextro-ethyl ester of 2-isobutyric acid-4") 85 °C (20 mm); $[\alpha]^{30}_D$ +1.13° (neat)].

(*S*)-(−)-Ethyl 3,5-Dimethylhexanoate [(*S*)-(−)-8]. Treatment of 18.09 g (0.125 mol) of (*S*)-(−)-**9** as described above for the enantiomer afforded 20.00 g (93%) of (*S*)-(−)-**8** shown to be >99% pure by GLC (CT 85 °C): EI MS, *m/e* 172 (M^+); bp 68–70 °C (9 mm); $[\alpha]^{23}_{obsd}$ −6.54° (neat, *l* = 1); $[\alpha]^{23}_D$ −8.69° (*c* 6.55, $CHCl_3$) [lit.[17] bp for (*R*)-(+)-**8** ("dextro-ethyl ester of 2-isobutyl butyric acid-4") 85 °C (20 mm); $[\alpha]^{30}_D$ +1.13° (neat, *d* = 0.856)].

(*R*)-(+)-Diethyl (1,3-Dimethylbutyl)malonate [(*R*)-(+)-11]. The procedure of Cook and Tallent[13] as modified by Carroll[14] for preparation of (*S*)-(−)-diethyl (2-pentyl)malonate was altered as follows. A stirred mixture of 15.48 g (90 mmol) of (*R*)-(+)-**8**, 70 mL of diethyl oxalate (redistilled and dried over 4-Å molecular sieves), 48 mL of dry benzene, and 7.40 g of 60% NaH in mineral oil was refluxed 1 h during which time the NaH reacted completely. The resulting dark red solution was cooled and treated successively with 18 mL (314 mmol) of AcOH, 300 mL of Et_2O, and 100 mL of H_2O. The H_2O layer was separated and the Et_2O extracted with H_2O (2 × 50 mL). The combined H_2O wash was extracted with 50 mL of Et_2O, and the combined Et_2O extracts were washed with 50 mL of brine, dried ($MgSO_4$), evaporated, and fractionated through a short column to remove all material with a boiling point bp <80 °C (20 mm). The residue was heated

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2 h at 175–180 °C (120 mm) until GLC (CT 140 °C) shown the reaction was complete. **Caution**: Highly toxic CO is produced. The residue was then fractionated to give 14.53 g (65%) of (*R*)-(+)-11 of >98% purity by GLC (CT 120 °C): bp 125–128 °C (8–9 mm); $[\alpha]^{23}_{obsd}$ +8.66° (neat, *l* = 1); $[\alpha]^{23}_{D}$ +12.21° (*c* 5.59, $CHCl_3$); IR (film) 1735 and 1751 (C=O) cm^{-1}; high-resolution CI MS, *m/e* 245.1742 (M^+ + 1; calcd for $C_{13}H_{25}O_4^+$ 245.1753). (*R*)-(+)-11 was easily separated from the mineral oil (originating from the NaH dispersion) which did not distill under these conditions.

(*S*)-(−)-Diethyl (1,3-Dimethylbutyl)malonate [(*S*)-(−)-11]. Treatment of 8.82 g (51.2 mmol) of (*S*)-(−)-8 as described above for the enantiomer gave 6.68 g (53%) of (*S*)-(−)-11 of >98% purity by GLC (CT 120 °C): bp 125–127 °C (8–9 mm); $[\alpha]^{23}_{obsd}$ −8.74° (neat, *l* = 1); $[\alpha]^{23}_{D}$ −12.10° (*c* 5.27, $CHCl_3$); IR (film) 1735 and 1751 (C=O) cm^{-1}; high-resolution CI MS, *m/e* 245.1753 (M^+ + 1; calcd for $C_{13}H_{25}O_4^+$ 245.1753).

(*R*)-(+)-Diethyl (1,3-Dimethylbutyl)ethylmalonate [(*R*)-(+)-12]. The procedure of Beres[30] for the preparation of diethyl *tert*-butylethylmalonate was modified as follows. A stirred slurry of 1.20 g (30 mmol) of 60% NaH–oil in 15.0 mL of dry DMF and 3.0 mL of Et_2O (to prevent foaming) maintained at 25–30 °C was treated dropwise with 6.11 g (25.0 mmol of (*R*)-(+)-11. When H_2 evolution ceased, 6.0 mL (11.7 g, 75.0 mmol) of EtI was added in one portion which resulted in an exothermic reaction and formation of a thick slurry. After being stirred 1 h at 25–30 °C, the mixture was treated with 1.0 mL of AcOH and 200 mL of Et_2O, was washed sucessively with H_2O (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 25 mL), and 25 mL of brine, and was dried ($MgSO_4$). Distillation and redistillation afforded 6.02 g (89%) of (*R*)-(+)-12 of >98% purity by GLC (oven temperature 140 °C): CI MS, *m/e* 273 (M^+ + 1); bp 131–134 °C (7 mm); $[\alpha]^{23}_{obsd}$ +19.84° (neat, *l* = 1); $[\alpha]^{23}_{D}$ +18.24° (*c* 5.30, $CHCl_3$); IR (film) 1723 (br, C=O) cm^{-1} [lit.[1] bp (for racemate) 98–99 °C (3 mm)]. (*R*)-(+)-12 was easily separated from the mineral oil (originating from the NaH dispersion) which did not distill under these conditions.

(*S*)-(−)-Dimethyl (1,3-Dimethylbutyl)ethylmalonate [(*S*)-(−)-12]. Treatment of 5.63 g (23.0 mmol) of (*S*)-(−)-11 as described above for the enantiomer gave 5.54 g (89%) of (*S*)-(−)-12 of >98% purity by GLC (oven temperature 140 °C): CI MS, *m/e* 273 (M^+ + 1); bp 132–135 °C (7 mm); $[\alpha]^{23}_{obsd}$ −19.81° (neat, *l* = 1); $[\alpha]^{23}_{D}$ −18.29° (*c* 4.88, $CHCl_3$); IR (film) 1723 (br, C=O) cm^{-1} [lit.[1] bp (for racemate) 98–99 °C (3 mm)].

(*R*)-(+)-5-(1,3-Dimethylbutyl)-5-ethylbarbituric Acid [(*R*)-(+)-1]. The procedure of Cook and Tallent[13] for preparation of the corresponding isomer of pentobarbital was utilized. From 2.72 g (10 mmol) of (*R*)-(+)-12 was obtained 2.02 g of crude (*R*)-(+)-1. Two recrystallizations from toluene gave 1.72 g (72%) of pure (*R*)-(+)-1: EI MS, *m/e* 240 (M^+); mp 173–175 °C; $[\alpha]^{23}_{D}$ +29.9° (*c* 1.08, $CHCl_3$), +24.41° (*c* 1.575, absolute EtOH) [lit. mp 174–175 °C,[12] $[\alpha]^{21}_{D}$ +4.9° (*c* 1.5, absolute EtOH);[12] $[\alpha]^{22}_{D}$ +16.4° (*c* 1.0, $CHCl_3$)[3]]. (*R*)-(+)-1 prepared in this study was identical with an authentic sample of racemic 1 by IR ($CHCl_3$), NMR ($CDCl_3$), MS, TLC ($CHCl_3$–acetone, 9:1), and GLC (CT 175 °C).

Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 60.15; H, 8.54; N, 11.40.

(*S*)-(−)-5-(1,3-Dimethylbutyl)-5-ethylbarbituric Acid [(*S*)-(−)-1]. The procedure[13] utilized above for the enantiomer afforded 2.10 g of crude (*S*)-(−)-1 from 2.72 g (10 mmol) of (*S*)-(−)-12. Purification as above for the enantiomer gave 1.89 g (79%) of (*S*)-(−)-1: EI MS, *m/e* 240 (M^+); mp 173–175 °C; $[\alpha]^{23}_{D}$ −29.72° (*c* 1.1, $CHCl_3$), −24.32° (*c* 1.55, absolute EtOH) [lit. mp 174–175 °C;[12] $[\alpha]^{23}_{D}$ −21.4° (*c* 1.5, absolute EtOH);[12] $[\alpha]^{24}_{D}$ −13.9° (*c* 1, $CHCl_3$)[3]]. This sample of (*S*)-(−)-1 was identical with an authentic sample of the racemate by the same criteria used above for comparison of the enantiomer to the racemate.

Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 60.26; H, 8.51; N, 11.54.

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Registry No. (*R*)-(+)-1, 24016-63-5; (*S*)-(−)-1, 24016-64-6; 4, 108-10-1; 5, 867-13-0; (*E*)-6, 16812-83-2; (*Z*)-6, 82351-62-0; (*E*)-7, 82351-63-1; (*Z*)-7, 82351-64-2; (±)-8, 82351-65-3; (*S*)-(−)-8, 82398-48-9; (*R*)-(+)-8, 82398-51-4; (±)-9, 82351-66-4; (*S*)-(−)-9, 82398-46-7; (*S*)-(−)-9 cinchonidine, 82398-47-8; (*R*)-(+)-9, 82398-49-0; (*R*)-(+)-9 (*R*)-(+)-1-phenylethylamine, 82398-50-3; (*R*)-(+)-11, 82351-67-5; (*S*)-(−)-11, 82351-68-6; (*R*)-(+)-12, 82351-69-7; (*S*)-(−)-12, 82351-70-0; (*R*)-(+)-13, 3886-69-9; (*S*)-(−)-13, 2627-86-3; (±)-14, 82351-71-1; (*R*)-(+)-14, 82398-52-5; (*S*)-(−)-14, 82398-53-6; (+)-15, 82351-72-2; (−)-15, 82351-73-3; $CO(NH_2)_2$, 57-13-6; diethyl oxalate, 95-92-1; *N*-[(*R*)-1-phenylethyl)-(*R*)-3,5-dimethylhexanamide, 82351-74-4.

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