Asymmetric Synthesis of the Enkephalinase Inhibitor Thiorphan

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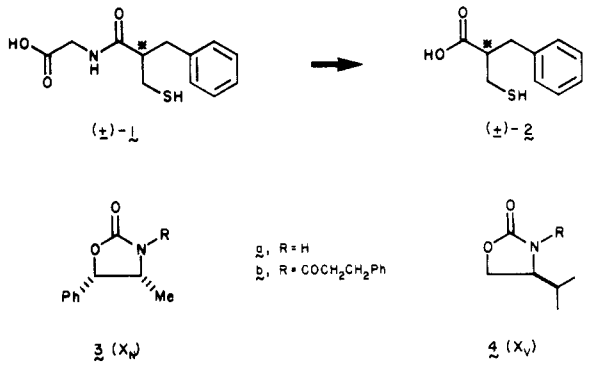
Independent enantioselective synthesis of (*R*)- and (*S*)-thiophan (1) via a six-step sequence has been completed. The pivotal step in the establishment of absolute stereochemistry in the enantiomeric target structures was the alkylation of the oxazolidyl carboximide-derived enolates **6** and **7** with bromomethyl benzyl sulfide (**5b**). The diastereoselection observed in these bond constructions was in excess of 95%.

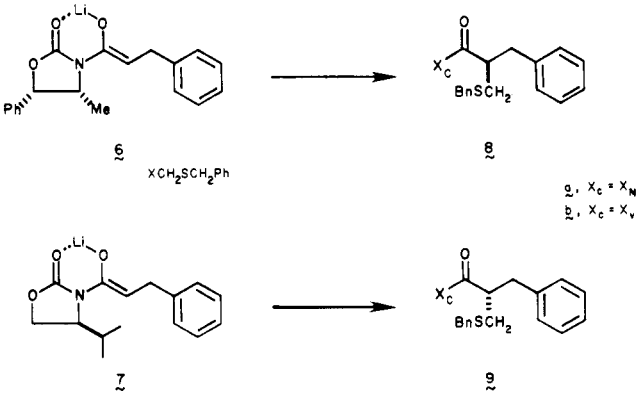
It is now well appreciated that the endogenous opioid pentapeptides, leucine and methionine enkephalin are neutrotransmitters involved with the induction of analgesia.[1] Hydrolysis of the enkephalin Gly^3–Phe^4 bond by a membrane-bound metalloendopeptidase, "enkephalinase", located near the enkephalin and opioid receptors, has been postulated to mediate enkephalin-induced analgesia.[2] Recently, it has been disclosed that racemic thiorphan [(±)-*N*-[1-oxo-2-(mercaptomethyl)-3-phenylpropyl]glycine] (1) inhibits enkephalinase,[3] extends the duration of analgesia induced by enkephalin analogues or noxious stimuli,[4] and is even claimed to induce analgesia.[5] Other recent studies have documented the fact that several other related zinc-containing metallopeptidases, such as angiotensin converting enzyme (ACE), also exhibit inhibition by (±)-1.[5,6] In view of the above observations, it was of considerable interest to us to evaluate the chemotherapeutic potential of each thiorphan enantiomer in enkephalinase and ACE inhibition and to define the absolute stereochemical requirements for thiorphan's role as a potential analgesic agent.[7] Accordingly, we have developed a practical approach to the asymmetric synthesis of both (*R*)- and (*S*)-thiophan which embodies considerable flexibility for the construction of related homochiral analogues.

By inspection, the asymmetric synthesis of thiorphan reduces to the construction of (*R*)- and (*S*)-2-(mercaptmethyl)dihydrocinnamic acid (**2**) in suitably protected form. This α-substituted carboxylic acid was viewed as



being directly accessible via the chiral enolate technology under development in our laboratory.[8] Based upon our prior studies, we projected that the chiral enolates **6** and **7** illustrated in Scheme I would serve as practical precursors to (*R*)- and (*S*)-thiorphan, respectively. Accordingly, the two requisite chiral oxazolidinones **3a** and **4a** were prepared from the respective amino alcohols by derivatization with either diethyl or diphenyl carbonate.[9,10] (1*S*,2*R*)-Norephedrine, commercially available as the hy-

Scheme I



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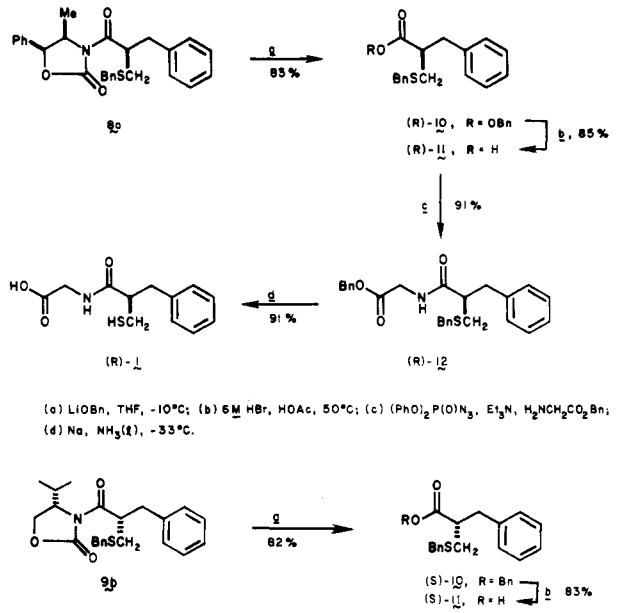
drochloride salt,[11] may be transformed into the chiral auxiliary **3a** with either phosgene[12] or one of a number of phosgene equivalents. In this particular instance, after having evaluated most of the obvious phosgene variants, we have found that the diphenyl carbonate procedure described herein is the most convenient for the laboratory-scale synthesis of **3a** in up to 3-mol-scale reactions. The norephedrine-derived oxazolidone **3a** produced via this procedure is readily purified by direct crystallization, mp 121–122 °C (lit.[12] mp 117 °C), in yields ranging from 82% to 95%. In contrast, we have found that (*S*)-valinol[13] is most conveniently transformed into oxazolidone **4a**[14] with diethyl carbonate. This procedure reliably affords 85–95% yields of nicely crystalline material, mp 69–70 °C (lit.[14] 71.5 °C), which may be purified by direct crystallization. A careful evaluation of the sterochemical homogeneity of both **3a** and **4a** revealed that both chiral auxiliaries were greater than 99% enantiomerically pure.[15]

The N-acylation of the two chiral oxazolidones **3a** and **3b**, via their lithium conjugates, with 3-phenylpropanoyl chloride afforded the nicely crystalline carboximides **3b** (mp 95–96 °C) and **4b** (mp 63–64 °C) in 89% and 91% yields, respectively.[16] Initial attempts to carry out the illustrated alkylation of lithium enolate **6** (Scheme I) with chloromethyl benzyl sulfide (**5a**)[17] were unsuccessful. Only recovered starting material and/or products derived from enolate decomposition were detected. However, the more reactive bromomethyl benzyl sulfide (**5b**)[18] was found to function admirably. Enolization of carboximide **3b** with lithium diisopropylamide (LDA) and subsequent treatment of lithium enolate **6** with 1.1 equiv of alkyl bromide **5b** (2 h, −25 °C; 2 h, 0 °C) afforded the desired carboximide **8a** along with minor amounts of the diastereomeric alkylation product **9a**. Analysis of the unfractionated product mixture by capillary gas chromatography (GLC) indicated a 98:2 ratio of **8a** to **9a**. In addition to the desired product, both unreacted carboximide **3b** (ca. 8%) and 2-oxazolidone **3a** (5%) were detected. Product isolation by preparative silica gel chromatography (Waters Prep 500) afforded **8a** in 76% yield as a viscous colorless oil (**8a**:**9a** = 98:2). Although the use of excess alkyl halide (2–5 equiv) improved the extent of alkylation, the resulting unreacted electrophile complicated product isolation. In investigating other alkylation conditions, it was found that the sodium enolate derived from **3b** ($NaN(SiMe_3)_2$) afforded comparable yields and reaction diastereoselection. The analogous alkylation of the complementary lithium enolate **7** afforded nearly identical results. Treatment of **7** with alkyl bromide **5b** (1.1 equiv) for 2 h at −20 °C afforded a 97:3 ratio of **9b**:**8b**. Chromatographic product isolation provided an 83% isolated yield of **9b** as a viscous oil (**9b**:**8b** = 98:2).

The completion of the synthesis of (*R*)-thiorphan is illustrated in Scheme II. Based upon prior experience, we

Scheme II



were not surprised that the direct hydrolysis (KOH, EtOH–H_2O) of carboximide **8a** to acid (*R*)-**11** was severely compromised by competing hydroxide attack at the urethane carbonyl. In numerous other studies currently in progress, we have established that the relative rates of nucleophilic attack at either of the two carbonyl functions of these carboxamides are dictated by the subtle interplay of electronic and steric effects. In sterically unencumbered situations (e.g. **3b**, **4b**) selective nucleophilic attack at the exocyclic carboximide carbonyl is strongly preferred. This trend also holds for α-methyl-substituted carboximides as well. However, when the smaller of the two α-substituents exceeds the approximate steric requirements of a methyl group, the regioselectivity of carboximide hydrolysis is compromised as in the case of **8a**.[19] Practical experience with these systems has revealed that carboximide transesterification with lithium benzyloxide under aprotic conditions (THF, ca. 0 °C) is remarkably substrate independent and quite reliable.[8a,21] Accordingly, upon treatment of carboximide **8a** (Scheme II) with lithium benzyloxide (1.5 equiv. THF, −10 to 0 °C), an 83% yield of benzyl ester (*R*)-**10**, $[\alpha]_{589}$ +36.2° (*c* 0.86, CH_2Cl_2), was obtained after chromatography. The accompanying norephedrine-derived oxazolidone **3a** was also recovered in 75% yield. In a similar fashion the enantiomeric benzyl ester (*S*)-**10**, $[\alpha]_{589}$ −34.6° (*c* 2.46, CH_2Cl_2), was obtained from carboximide **9b**. In direct analogy to the racemization-free debenzylation of *S*-benzylcysteine benzyl ester,[20] (*R*)-**10** was transformed to carboxylic acid (*R*)-**11** with anhydrous hydrogen bromide in acetic acid in 85% yield. The peptide bond construction between carboxylic acid (*R*)-**11** and benzyl glycinate was effected with diphenylphosphoryl azide.[22] A solution of (*R*)-**11**, the *p*-toluenesulfonate salt of benzyl glycinate, and triethylamine in DMF was treated with diphenyl phosphoryl azide for 4 h at −10 °C and 18 h at room temperature. After purification

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(15) The enantiomeric purity of the 2-oxazolidinones employed in this study were determined to be greater than 99% by capillary GC analysis of the imides derived from the Mosher acid chloride: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
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by flash chromatography,[17] the benzyl ester of (2R)-S-benzylthiorphan ((R-12)) was obtained as a nicely crystalline solid, mp 72–73 °C, in 91% yield, $[\alpha]_{598}$ + 25.2° (c 1.61, EtOH). When the same reaction was carried out on the carboxylic acid (S)-11, the enantiomeric benzyl ester (S)-12, mp 73.5–74 °C, $[\alpha]_{598}$ −24.5° (c 1.82, EtOH), exhibited the expected physical properties and an optical rotation which was nearly equal in magnitude but opposite in sign to (R)-12.

The completion of the synthesis was effected by the bis-debenzylation of (R)-12 under carefully controlled dissolving metal conditions.[23] A solution of (R)-12 in liquid ammonia–THF (1:1) was treated with 5 equiv of sodium metal over a 15-min period (−33 °C). After the heterogeneous blue solution was maintained at this temperature for 15 min, the reaction was quenched with ammonium chloride. Product isolation afforded (R)-thiorphan ((R)-1) 91%, as a viscous colorless oil which slowly crystallized upon standing: mp 108–110 °C; $[\alpha]_{589}$ −40.1° (c 2.25, EtOH). The same debenzylation, when carried out on the enantiomeric benzyl ester (S)-12, afforded (S)-thiorphan ((S)-1) in 96% yield: mp 110–111 °C; $[\alpha]_{589}$ +39.6° (c 2.78, EtOH). During optimization of this reduction it was noted that when less than 5 equiv of sodium metal were employed a mixture of thiorphan and S-benzylthiorphan was obtained. However, the use of a larger excess of sodium resulted in a significant decrease in the isolated yield of thiorphan. Within experimental error, the complementary specific rotations (−40.1°, +39.6°) for (R)- and (S)-thiorpahn demonstrate a good degree of internal consistency with regard to the overall diastereoselection and racemization (or lack thereof) during the synthesis of each enantiomer. Nonetheless, an unequivocal assessment of enantiomer purity was carried out. The reaction of (±)-thiorphan methyl ester with (R)-1-(1-naphthyl)ethyl isocyanate (13) afforded the diastereomeric thiourethanes 14 and 15, which readily are resolved by HPLC on a Pirkle covalent phenylglycine column (α = 1.52).[24,25] The use of a chiral column in this analysis was necessitated by the lack of resolution of 14 and 15 on more conventional column supports. The same derivatization process and HPLC analysis of both (R)-1 and (S)-1 established a lower limit of ca. 95% optical purity for each enantiomer. Peak broadening in this analysis prevented a more accurate accessement of enantiomeric purity.

Biological Studies. Although a detailed biochemical evaluation of (R)- and (S)-thiorphan will be reported elsewhere,[7] the interesting conclusions drawn from this study are noteworthy. First, synthetic (S)-thiorphan is approximately 24-fold more effective as an ACE inhibitor than (R)-thiorphan. Parenthetically, the low levels of ACE inhibition noted for synthetic (R)-thiorphan ((R)-1) could largely, if not exclusively, be derived from enantiomer contamination. In contrast, the two thiorphan enantiomers did not exhibit large differences in the inhibition of enkephalinase A. Finally, the analgesic properties reported for (±)-thiorphan[5] are largely, if not exclusively, associated with the R enantiomer.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded on a Varian Associates EM-390 (90 MHz) or a Bruker WM-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, and b = broad), coupling constant (Hz), integration, and interpretation. ^{13}C NMR were recorded on a JEOL FX-90Q (22.5 MHz) spectrometer and are reported in ppm from tetramethylsilane on the δ scale. Optical rotations were determined with a Jasco DIP-181 digital polarimeter. Data are reported as follows: specific rotation, [α], concentration (c = g/100 mL), and solvent. When chloroform was used as the solvent, it was filtered through activity 1 alumina immediately prior to use. Analytical gas chromatography (GC) was carried out on a Hewlett-Packard 5880A gas chromatograph equipped with a flame ionization detector. Hydrogen was used as the carrier gas. The following wall coated open tubular (WCOT) fused silica capillary columns were employed: 30 m × 0.32 mm DB-1 (J and W Associates) and 30 m × 0.32 mm DB-5 (J and W Associates). Flash chromatography was performed according to the general procedure of Still[26] employing EM Reagents silica gel 60 (40–63 μm). Analytical high performance liquid chromatography (HPLC) was carried out on a Waters Associates ALC 202/401 HPLC using the following columns: Waters Radial Pak (8 mm × 10 cm, 5-μm silica gel) or a Regis (4.6 mm × 25 cm, Pirkle phenylglycine covalently bound to 5-μm aminopropyl silica gel).[25] Preparative HPLC was performed on a Waters Associates PrepLC/System 500 liquid chromatograph equipped with a refractive index detector and using two PrepPak 500 silica gel cartridges (5 × 30 cm). Analytical thin layer chromatography (TLC) was performed with EM Reagents 0.25-mm silica gel 60-F plates.

When necessary, solvents were dried before use. Tetrahydrofuran (THF) and benzene were distilled from sodium benzophenone ketyl. Boron trifluoride-diethyl etherate and diisopropylamine were distilled from calcium hydride. Dimethylformamide (DMF) was distilled from calcium hydride and stored over 4-Å molecular sieves. Unless otherwise noted, all nonaqueous reactions were performed under an oxygen-free atmosphere of argon or nitrogen with rigid exclusion of moisture.

(4R,5S)-4-Methyl-5-phenyl-2-oxazolidinone (3a). A mechanically stirred mixture of 151 g (1.00 mol) of (1S,2R)-norephedrine ($[\alpha]_{589}$ +33.4° (c 7, water), as the hydrochloride salt, Aldrich Chemical Co.), 236 g (1.10 mol) of diphenyl carbonate, and 152 g (1.10 mol) of anhydrous potassium carbonate was heated at 110 °C for 4–6 h. The resultant mixture was cooled to <60 °C. Excess diphenyl carbonate was hydrolyzed by addition of 600 mL of methanol and heating the mixture at reflux for 0.5 h. Sufficient water (400–600 mL) was added to dissolve the potassium carbonate. Methanol was removed in vacuo. The product and phenol were extracted into dichloromethane (3 × 1 L). The combined extracts were washed with 2 M aqueous sodium hydroxide (3 × 1 L) to remove the phenol, 1 M aqueous hydrochloric acid (1 × 1 L), and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 195 g (110% mass balance) of a light-yellow solid. Recrystallization from toluene (600 mL, 3 crops) afforded 145–165 g (82–93%) of oxazolidinone **3a** as a white crystalline solid: mp 121–122 °C (lit.[12] mp 117 °C); IR ($CHCl_3$) 3460, 3400–3200, 3020, 2980, 1760, 1450, 1380, 1350, 1220, 1125, 1000, 960, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$/90 MHz) δ 7.33 (s, 5 H, aromatic H's), 6.3–6.0 (br s, 1 H, NH), 5.67 (d, J = 7.5 Hz, 1 H, C_5-H), 4.17 (qn, J = 7.0 Hz, 1 H, C_4-H), 0.80 (d, J = 7.0 Hz, 3 H, C_4-CH_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 159.9, 135.0, 128.4, 125.9, 81.0, 52.4, 17.4; $[\alpha]_{589}$ +177.2°, $[\alpha]_{577}$ +186.1°, $[\alpha]_{546}$ +212.0°, $[\alpha]_{435}$ +368.6°, $[\alpha]_{365}$ +598.6° (c 2.21, $CHCl_3$) (lit.[12] $[\alpha]_{589}$ +158.4° (c, 0.44, $CHCl_3$)); TLC (ethyl acetate) R_f 0.45.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.62; N, 7.90. Found: C, 67.42; H, 6.19; N, 7.87.

(4S)-4-(1-Methylethyl)-2-oxazolidinone (4a). Into a 500-mL flask equipped with a 20-cm Vigreux column was introduced 103 g (1.00 mol) of (S)-valinol,[13] 133 mL (130 g, 1.10 mol) of diethyl carbonate, and 14 g (0.10 mol) of anhydrous potassium carbonate. The magnetically stirred mixture was heated at 125–126 °C (internal reaction temperature) until 117 mL (92 g, 2.0 mol) of ethanol distilled (ca. 4–6 h). The resultant mixture was cooled to room temperature and dissolved in diethyl ether (3 L), and the solution was filtered through a 2-cm pad of Celite to remove the potassium carbonate. The etheral solution was concentrated to a volume

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of ca. 1 L and slowly cooled to 0 °C, and product was allowed to crystallize. Concentration of the mother liquors provided two additional crops of crystals. The total yield of oxazolidinone **4a** was 110–123 g (85–95%) as white needles: mp 69–70 °C (lit.[14] mp 71.5 °C); IR (CH_2Cl_2) 3480, 3340–3240, 3060, 2980, 1760, 1400, 1240 cm^{-1}; ^1H NMR ($CDCl_3$/90 MHz) δ 6.7 (br s, 1 H, NH), 4.42 (t, J = 8.6 Hz, 1 H, C_5-H), 4.07 (d of d, J = 8.5, 6.5 Hz, 1 H, C_5-H), 3.58 (d of t, J = 8.6, 6.5 Hz, 1 H, C_4-H), 1.9-1.6 (m, 1 H, C_4-CH), 0.95 (overlapping d's, J = 6.0 Hz, 6 H, $CH(CH_3)_2$); $[\alpha]_{589}$ −16.6°, $[\alpha]_{577}$ −17.3°, $[\alpha]_{546}$ −20.2°, $[\alpha]_{435}$ −37.3°, $[\alpha]_{365}$ −63.7° (*c* 5.81, EtOH); TLC (6:4 hexanes/ethyl acetate) R_f 0.19.

Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58. Found: C, 55.63; H, 8.53.

Benzyl Chloromethyl Sulfide (5a). Anhydrous hydrogen chloride was bubbled through a magnetically stirred, cooled (−10 °C) solution of 25.0 g (0.278 mol) of *s*-trioxane in 100 g (0.805 mol) of benzyl mercaptan until saturated (ca. 1 h). After an additional period of 12 h at room temperature, the reaction mixture was dried over anhydrous calcium chloride. The product was decanted from the calcium chloride and distilled through a 5-cm Vigreux column to afford 101 g (73%) of **5a** as a colorless liquid: bp 74–76 °C (0.01 mmHg) (lit.[17] bp 102 °C, 2 mmHg); ^1H NMR (CCl_4/90 MHz) δ 7.2 (s, 5 H, Ar H), 4.40 (s, 2 H, SCH_2Cl), 3.80 (s, 2 H, $PhCH_2S$).

Benzyl Bromomethyl Sulfide (5b). The title compound was prepared following the procedure of Hollowood et al.[18] The product was purified by molecular distillation (Kugelrohr, 140 °C, 0.01 mmHg) to afford **5b** (92%) as a colorless liquid, which solidified below −10 °C: ^1H NMR (CCl_4/90 MHz) δ 7.27 (s, 5 H, Ar H), 4.33 (s, 2 H, SCH_2Br), 3.82 (s, 2 H, $PhCH_2S$).

(4*R*,5*S*)-3-(1-Oxo-3-phenylpropyl)-4-methyl-5-phenyl-2-oxazolidinone (3b). A mechanically stirred, cooled (−78 °C) solution of 44.3 g (250 mmol) of oxazolidinone **3a** (0.5 M in THF) was metalated with 150 mL (1.70 M in hexane, 255 mmol) of *n*-butyllithium (until the orange-red color of the dianion just persisted) and acylated immediately with 39.0 mL (44.3 g, 263 mmol) of freshly distilled 3-phenylpropanoyl chloride. The reaction mixture was warmed to 0 °C and stirred for 0.5 h. Excess acid chloride was hydrolyzed with 100 mL of 1 M aqueous potassium carbonate by stirring the resultant two-phase mixture for 1 h at room temperature. Volatiles were removed in vacuo and the product was extracted into dichloromethane (3×). The combined organic extracts were successively washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 83.2 g of a yellow solid. Recrystallization from hexanes/ethyl acetate (3 crops) afforded 69.1 g (89%) of **3b** as a white crystalline solid, which was found to be homogeneous by both capillary GC and HPLC analysis: mp 95–96 °C; IR (CH_2Cl_2) 3060, 3000, 1785, 1700, 1370, 1350, 1250 cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ 7.44–7.19 (m, 10 H, Ar H), 5.63 (d, J = 7.5 Hz, 1 H, C_5-H), 4.75 (qn, J = 6.9 Hz, 1 H, C_4-H), 3.34 (m, 2 H, $C_{2'}$-H_2), 3.06–3.00 (m, 2 H, $C_{3'}$-H_2), 0.89 (d, J = 6.8 Hz, 3 H, C_4-CH_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 172.1, 152.9, 140.4, 133.4, 128.7, 126.2, 125.6, 79.0, 54.7, 37.2, 30.3, 14.5; $[\alpha]_{589}$ +28.7° (*c* 0.45, CH_2Cl_2); TLC (7:3 hexanes/ethyl acetate) R_f 0.42.

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19. Found: C, 73.85; H, 6.28.

(4*S*)-3-(1-Oxo-3-phenylpropyl)-4-(1-methylethyl)-2-oxazolidinone (4b). A mechanically stirred, cooled (−78 °C) solution of 20.0 g (155 mmol) of oxazolidinone **4a** (0.3 M in THF) was metalated with 95 mL (1.70 M in hexane, 162 mmol) of *n*-butyllithium and treated with 28.4 (168 mmol) of freshly distilled 3-phenylpropanoyl chloride. The reaction mixture was warmed to 0 °C and stirred for 0.5 h. Excess acid chloride was hydrolyzed by the addition of 100 mL of 1 M aqueous potassium carbonate followed by stirring the resultant two-phase mixture for 1 h at room temperature. Volatiles were removed in vacuo and the product was extracted into dichloromethane (3×). The combined organic extracts were successively washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 41.5 g of a pale-yellow solid. Recrystallization from hexanes afforded 37.0 g (91%) of **4b** as a white crystalline solid, which was found to be homogeneous by capillary GC and HPLC analysis: mp 63–64 °C; IR (CH_2Cl_2) 3060, 2970, 1780, 1700, 1385, 1210 cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ 7.3–7.17 (m, 5 H, Ar H), 4.41 (d of d of d, J = 8.5, 4.0, 3.2 Hz, 1 H, C_4-H), 4.24 (d of d, J = 9.3, 8.4 Hz, 1 H, C_5-H), 4.19 (d of d, J = 9.3, 3.2 Hz, 1 H, C_5-H), 3.30 (d of d of d, J = 17.5, 8.7, 6.9 Hz, 1 H, $C_{2'}$-H), 3.22 (d of d of d, J = 17.5, 8.5, 7.2 Hz, 1 H, $C_{2'}$-H), 3.1–2.9 (m, 2 H, $C_{3'}$-H_2), 2.4-2.3 (m, 1 H, C_4-CH), 0.90 (d, J = 7.4 Hz, 3 H, $CH(CH_3)$), 0.84 (d, J = 7.4 Hz, 3 H, $CH(CH_3)$); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 172.3, 154.0, 140.5, 128.5, 126.1, 63.4, 58.4, 37.0, 30.4, 28.4, 17.9, 14.6; $[\alpha]_{589}$ +71.0° (*c* 4.61, CH_2Cl_2); TLC (8:2 hexanes/ethyl acetate) R_f 0.47.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33. Found: C, 69.17; H, 7.42.

(4*R*,5*S*)-3-[(2*R*)-1-Oxo-2-[[(phenylmethyl)thio]methyl]-3-phenylpropyl]-4-methyl-5-phenyl-2-oxazolidinone (8a). A magnetically stirred, cooled (−78 °C) solution of lithium diisopropylamide (LDA, prepared from 9.5 mL (6.9 g, 67.8 mmol) of diisopropylamine and 40 mL (1.69 M in hexane, 67.6 mmol) of *n*-butyllithium) (0.5 M in THF) was used to enolize 20.0 g (64.6 mmol) of **3b**. After stirring for 0.5 h at −78 °C, the resultant lithium enolate was treated with 10.6 mL (15.5 g, 71.3 mmol) of benzyl bromomethyl sulfide (**5b**) for 2 h at −25 °C and 2 h at 0 °C. The reaction was quenched by addition of half-saturated aqueous ammonium chloride. Volatiles were removed in vacuo and the product was extracted into dichloromethane (3×). The combined organic extracts were successively washed with 1 M aqueous sodium bisulfate (2×), 1 M aqueous potassium bicarbonate (2×), and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 31.3 g of a yellow oil. Analysis by GC (30-m DB-1, 200 °C for 10 min, 25°/min to 275 °C) afforded a 98:2 ratio of **8a** (t_r = 17.92 min) to **9a** (t_r = 18.12 min) and indicated the presence of both **3a** (t_r = 1.19 min, ca. 5%) and **3b** (t_r = 8.60 min, ca. 8%). The title compound was isolated by liquid chromatography (Waters Prep-500, two 5 × 30 cm silica gel columns, ca. 9:1 hexanes/ethyl acetate (adjusted to TLC R_f 0.09), 250 mL/min) in three portions to afford 21.8 g (76%) of **8a** as a colorless oil (**8a**:**9a** = 98:2): IR (neat) 3030, 2920, 1780, 1700, 1490, 1450, 1380, 1340, 1190, 1120 cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ 7.42–7.20 (m, 15 H, Ar H), 5.18 (d, J = 7.0 Hz, 1 H, C_5-H), 4.61–4.52 (m, 2 H, C_4-H, $C_{2'}$-H), 3.77 (d, J = 13.5 Hz, 1 H, $SCH(H)Ph$), 3.72 (d, J = 13.5 Hz, 1 H, $SCH(H)Ph$), 2.91 (d of d, J = 13.0, 8.8 Hz, 1 H, $C_{3'}$-H), 2.86 (d of d, J = 13.0, 7.3 Hz, 1 H, $C_{3'}$-H), 2.83 (d of d, J = 13.8, 9.9 Hz, 1 H, $C_{2'}$-$CH(H)S$), 2.53 (d of d, J = 13.7, 5.0 Hz, 1 H, $C_{2'}$-$CH(H)S$), 0.8. (d, J = 6.5 Hz, 3 H, C_4-CH_3); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 174.5, 152.6, 138.2, 138.0, 133.1, 129.1, 128.9, 128.6, 128.4, 126.9, 126.6, 125.5, 78.7, 55.0, 44.6, 39.0, 35.9, 32.2, 14.4; $[\alpha]_{589}$ +70.6° (*c* 1.42, CH_2Cl_2); TLC (7:3 hexanes/ethyl acetate) R_f 0.44.

Anal. Calcd for $C_{27}H_{27}NO_3S$: C, 72.78; H, 6.11. Found: C, 73.03; H, 6.07.

(4*S*)-3-[(2*S*)-1-Oxo-2-[[(phenylmethyl)thio]methyl]-3-phenylpropyl]-4-(1-methylethyl)-2-oxazolidinone (9b). A magnetically stirred, cooled (−78 °C) solution of LDA (prepared from 15.4 mL (11.1 g, 110 mmol) of diisopropylamine and 65 mL (1.69 M in hexane, 110 mmol) of *n*-butyllithium) (0.75 M in THF) was employed to enolize 26.1 (100 mmol) of **4b**. After stirring for 0.5 h at −78 °C, the resultant lithium enolate was treated with 23.9 g (110 mmol) of benzyl bromomethyl sulfide (**5b**) for 2 h at −20 °C. The reaction was quenched by the addition of half-saturated aqueous ammonium chloride. Volatiles were removed in vacuo and the product was extracted into dichloromethane (3×). The combined organic extracts were successively washed with 1 M aqueous sodium bisulfate (2×), 1 M aqueous potassium bicarbonate (2×), and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 53.0 g of a yellow oil. Analysis by GC (30-m DB-1, 175 °C for 5 min, 20°/min to 250 °C) afforded a 3:97 ratio of **8b** (t_r = 11.74 min) to **9b** (t_r = 11.53 min) and indicated the presence of **4b** (t_r = 4.17 min, ca. 10%). The title compound was isolated by liquid chromatography (Waters Prep-500, two 5 × 30 cm silica gel columns, 87:13 hexanes/ethyl acetate, 250 mL/min) in two portions to afford 33.1 g (83%) of **9b** as a viscous colorless liquid (**8b**:**9b** = 2:98): IR (neat) 3040, 2980, 2940, 1780, 1700, 1495, 1455, 1390, 1300, 1250, 1200, 1100, 700 cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ 7.30–7.16 (m, 10 H, Ar H), 4.60 (m, 1 H, $C_{2'}$-H), 4.27 (d of d of d, J = 8.5, 3.8, 2.5, 1 H, C_4-H), 4.09 (d of d, J = 9.3, 2.7 Hz, 1 H, C_5-H), 3.92 (d of d, J = 9.3, 8.7 Hz, 1 H, C_5-H), 3.76 (d, J = 14.0 Hz, 1 H, $SCH(H)Ph$), 3.70 (d, J = 14.0 Hz, 1 H, $SCH(H)Ph$), 2.90 (d of d, J = 13.0, 8.0 Hz, 1 H, $C_{3'}$-H), 2.80 (d of d, J = 13.5, 10.0 Hz, 1 H, $C_{2'}$-$CH(H)S$), 2.78 (d of d, J = 13.0, 7.5 Hz, 1 H, $C_{3'}$-H), 2.50 (d

of d, J = 13.5, 4.5 Hz, 1 H, C_2-CH(H)S), 2.37 (d of septet, J = 3.8, 7.1 Hz, 1 H, C_4-CH(CH_3)$_2$), 0.91 (d, J = 7.1 Hz, 3 H, CH(CH_3)), 0.89 (d, J = 7.1 Hz, 3 H, CH(CH_3)); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 174.6, 153,7, 138.2, 138.0, 129.1, 128.9, 128.4, 126.8, 126.5, 63.2, 58.7, 44.4, 38.7, 35.7, 32.3, 28.5, 17.9, 14.8; $[\alpha]_{589}$ −29.1° (c 2.34, CH_2Cl_2); TLC (7:3 hexanes/ethyl acetate) R_f 0.54.

Anal. Calcd for $C_{23}H_{27}NO_3S$: C, 69.49; H, 6.85. Found: C, 69.62; H, 6.85.

(2*R*)-2-[[(Phenylmethyl)thio]methyl]-3-phenylpropanoic Acid Benzyl Ester ((*R*)-10). To a magnetically stirred, cooled (−10 °C) solution of lithium benzyloxide prepared from 3.7 mL (3.87 g, 35.8 mmol) of benzyl alcohol and 15.6 mL (1.69 M in hexane, 26.4 mmol) of *n*-butyllithium (0.5 M in THF) was added a solution of 7.86 g (17.6 mmol) of **8a** in 20 mL of THF over a 0.5-h period. The reaction mixture was warmed to 0 °C, stirred for 1.5 h, and then quenched by addition of half-saturated aqueous ammonium chloride. Volatiles were removed in vacuo and the product was extracted into dichloromethane (3×). The combined organic extracts were successively washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 11.2 g of a yellow oil. The title compound was isolated by flash chromatography (5 × 30 cm silica gel column, 9:1 hexanes/ethyl acetate) to afford 5.5 g (83%) of (2*R*)-benzyl ester (*R*)-**10** as a colorless liquid. Further elution of the column with ethyl acetate afforded 2.3 g (75%) of oxazolidinone **3a**. The desired benzyl ester (*R*)-**10**, which was homogeneous by both capillary GC and HPLC analysis, exhibited the following spectral properties: IR (neat) 3070, 3040, 1735, 1600, 1490, 1450, 1210, 1160, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$/90 MHz) δ 7.3–6.9 (m, 15 H, Ar H), 5.0 (s, 2 H, OCH_2Ph), 3.6 (s, 2 H, SCH_2Ph), 3.0–2.3 (m, 5 H, C_2-CH_2S, C_3-H_2); $[\alpha]_{589}$ +36.2° (c 0.856, CH_2Cl_2); TLC (8:2 hexanes/ethyl acetate) R_f 0.50.

Anal. Calcd for $C_{24}H_{24}O_2S$: C, 76.56; H, 6.42. Found: C, 76.52; H, 6.37.

(2*S*)-2-[[(Phenylmethyl)thio]methyl]-3-phenylpropanoic Acid Benzyl Ester ((*S*)-10). The title compound was prepared as above from 19.8 g (49.7 mmol) of **9b**. Isolation of the product by liquid chromatography (Waters Prep-500, two 5 × 30 cm silica gel columns, 95:5 hexanes/ethyl acetate, 250 mL/min) afforded 15.3 g (82%) of (2*S*)-benzyl ester (*S*)-**10** as a colorless liquid. Further elution with ethyl acetate afforded 4.8 g (75%) of oxazolidinone **4a**. Other than the specific rotation, $[\alpha]_{589}$ −34.6° (c 2.46, CH_2Cl_2), the desired benzyl ester (*S*)-**10** exhibited physical and spectral properties identical with (*R*)-**10**.

Anal. Calcd for $C_{24}H_{24}O_2S$: C, 76.56; H, 6.42. Found: C, 76.82; H, 6.51.

(2*R*)-2-[[(Phenylmethyl)thio]methyl]-3-phenylpropanoic Acid ((*R*)-11). A magnetically stirred solution of 2.01 g (5.35 mmol) of (2*R*)-benzyl ester (*R*)-**10** in 9 mL of 6 M anhydrous hydrogen bromide in glacial acetic acid was stirred at 50 °C for 15 min. The reaction mixture was diluted with 20 mL of water and extracted with dichloromethane (4 × 20 mL). The combined organic extracts were concentrated in vacuo. The residue was diluted with toluene (50 mL) and concentrated in vacuo 3 times to remove acetic acid. The residue was dissolved in 1 M aqueous potassium hydroxide, washed with dichloromethane, acidified to pH 1 with concentrated aqueous hydrochloric acid, and extracted with dichloromethane. The combined organic extracts were concentrated in vacuo to afford 1.31 g (85%) of the title compound (*R*)-11 as a colorless oil. An analytical sample was purified by molecular distillation (Kugelrohr, 140 °C (0.01 mm)): IR (neat) 3400–2400, 1710, 1600, 1490, 1450, 1235, 690 cm^{-1}; ^{1}H NMR (CCl_4/90 MHz) δ 11.4 (br s, 1 H, CO_2H), 7.1 (m, 10 H, Ar H), 3.6 (s, 2 H, SCH_2Ph), 3.0–2.3 (m, 5 H, C_2-H, C_2-CH_2S, C_3-H_2); $[\alpha]_{589}$ +54.1° (c 1.54, absolute EtOH).

Anal. Calcd for $C_{17}H_{18}O_2S$: C, 71.30; H, 6.34. Found: C, 71.58; H, 6.52.

(2*S*)-2-[[(Phenylmethyl)thio]methyl]-3-phenylpropanoic Acid ((*S*)-11). The title compound was prepared as above from 9.13 g (24.2 mmol) of (2*S*)-benzyl ester (*S*)-**10** to afford 5.77 g (83%) of (2*S*)-*S*-benzyl acid (*S*)-**11** as a pale-yellow oil. Other than the specific rotation ($[\alpha]_{589}$ −50.6° (c 1.57, absolute EtOH)), the desired acid (*S*)-**11** exhibited physical and spectral properties identical with (*R*)-**11**.

Anal. Calcd for $C_{17}H_{18}O_2S$: C, 71.30; H, 6.34. Found: C, 71.12; H, 6.29.

***N*-[(2*R*)-2-[[(Phenylmethyl)thio]methyl]-3-phenylpropanoyl]glycine Benzyl Ester ((2*R*)-*S*-Benzylthiorphan Benzyl Ester ((*R*)-12)).** To a magnetically stirred, cooled (−30 °C) solution of 1.66 g (5.79 mmol) of (2*R*)-*S*-benzyl acid (*R*)-**11** and 2.15 g (6.37 mmol) of glycine benzyl ester *p*-toluenesulfonate in 15 mL of anhydrous dimethylformamide was added 1.37 mL (1.75 g, 6.36 mmol) of diphenyl phosphoryl azide followed by 1.77 mL (1.29 g, 12.7 mmol) of triethylamine. The reaction mixture was stirred for 4 h at −10 °C and then overnight at room temperature. The resultant mixture was diluted with 1,1,1-trichloroethane (100 mL) and successively washed with water (3×), 1 M aqueous potassium hydroxide (3×), 1 M aqueous sodium bisulfate (2×), and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 3.5 g of a pale yellow oil. The title compound was isolated by flash chromatography (5 × 20 cm silica gel column, 7:3 hexane/ethyl acetate) to afford 2.28 g (91%) of benzyl ester (*R*)-**12** as a white solid, which was found to be homogeneous by both capillary GC and HPLC analysis. An analytical sample was recrystallized from hexanes/ethyl acetate: mp 72–73 °C; IR (CH_2Cl_2) 3440, 3050, 2990, 1750, 1680, 1720, 1250 cm^{-1}; ^{1}H NMR (CCl_4/90 MHz) δ 7.3–6.9 (m, 15 H, Ar H), 6.0 (br t, J = 6 Hz, 1 H, N-H), 5.0 (s, 2 H, OCH_2Ph), 3.8 (m, 2 H, NCH_2CO), 3.5 (s, 2 H, SCH_2Ph), 2.9–2.2 (m, 5 H, C_2-H, C_2-CH_2S, C_3-H_2); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 173.6, 169.5, 138.9, 138.5, 135.1, 128.9, 128.5, 127.5, 126.4, 67.1, 49.7, 41.3, 38.3, 37.0, 33.3; $[\alpha]_{589}$ +25.2° (c 1.61, absolute EtOH); TLC (7:3 hexanes/ethyl acetate) R_f 0.25.

Anal. Calcd for $C_{26}H_{27}NO_3S$: C, 72.03; H, 6.28. Found: C, 72.14; H, 6.35.

***N*-[(2*S*)-2-[[(Phenylmethyl)thio]methyl]-3-phenylpropanoyl]glycine Benzyl Ester ((2*S*)-*S*-Benzylthiorphan Benzyl Ester ((*S*)-12)).** The title compound was prepared as above from 5.70 g (19.9 mmol) of (2*S*)-*S*-benzyl acid (*S*)-**11** to afford after isolation by liquid chromatography (Waters Prep-500, two 5 × 30 cm silica gel columns, 9:1 hexanes/ethyl acetate, 250 mL/min) 7.34 g (85%) of (2*S*)-*S*-benzylthiorphan benzyl ester (*S*)-**12** as a white solid. Other than the specific rotation, $[\alpha]_{589}$ −24.5° (c 1.82, absolute EtOH), the desired benzyl ester (*S*)-**12** exhibited physical and spectral properties identical with (*R*)-**12**.

Anal. Calcd for $C_{26}H_{27}NO_3S$: C, 72.03; H, 6.28. Found: C, 72.23; H, 6.35.

***N*-[(2*R*)-1-Oxo-2-(mercaptomethyl)-3-phenylpropyl]glycine ((2*R*)-Thiorphan ((*R*)-1)).** To a magnetically stirred, cooled (−33 °C) solution of 0.462 g (1.07 mmol) of (2*R*)-*S*-benzylthiorphan benzyl ester (*R*)-**12** in 20 mL of THF and 30 mL of anhydrous ammonia (distilled from sodium) was added 0.13 g (5.8 mmol) of sodium in six portions over a 0.5-h period. After the reaction mixture had remained dark-blue for 10–15 min, the reaction was quenched by the addition of 0.37 g (6.9 mmol) of ammonium chloride. The ammonia was evaporated under a stream of nitrogen and the THF was removed in vacuo. The residue was dissolved in 5 mL of 1 M aqueous potassium hydroxde and washed with diethyl ether to remove toluene and dibenzyl. The aqueous solution was cooled to 0 °C and acidified to pH 1 with concentrated aqueous hydrochloric acid, and the product was extracted into diethyl ether. The etheral solution was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford 0.246 g (91%) of (2*R*)-thiorphan (*R*)-**1** as a colorless oil which slowly solidified upon standing: mp 108–110 °C; ^{1}H NMR ($CDCl_3$/500 MHz) δ 7.16–7.09 (m, 5 H, Ar H), 6.72 (br s, 1 H, NH), 4.05 (d of d, J = 15, 5 Hz, 1 H, NCH(H)CO), 3.85 (d of d, J = 15, 5 Hz, 1 H, NCH(H)CO), 2.95–2.50 (m, 5 H, C_2-H, C_2-CH_2S, C_3-H_2), 1.67 (br t, J = 7 Hz, 1 H, S-H); ^{13}C NMR ($CDCl_3$/22.5 MHz) δ 147.7, 172.6, 138.2, 128.8, 128.5, 126.7, 52.8, 41.4, 38.0, 26.0; $[\alpha]_{589}$ −40.1° (c 2.25, absolute EtOH); TLC (98:2 ethyl acetate/acetic acid) R_f 0.31.

Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.79; S, 12.66. Found: C, 56.71; H, 6.19; S, 12.88.

***N*-[(2*S*)-1-Oxo-2-(mercaptomethyl)-3-phenylpropyl]glycine ((2*S*)-Thiorphan ((*S*)-1)).** The title compound was prepared as above from 4.33 g (10.0 mmol) of (2*S*)-*S*-benzylthiorphan benzyl ester (*S*)-**12** to afford 2.43 g (96%) of (2*S*)-thiorphan (*S*)-**1** as a colorless oil, which slowly solidified; mp 110–111 °C. Other than the specific rotation, $[\alpha]_{589}$ +39.6° (c 2.78, absolute EtOH), (*S*)-thiorphan (*S*)-**1** exhibited physical and spectral properties identical with (*R*)-**1**.

Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.79; S, 12.66. Found: C, 56.79; H, 6.00; S, 12.53.

Determination of the Enantiomeric Purity of (*R*)- and (*S*)-Thiorphan. A magnetically stirred solution of 89.5 mg (353 μmol) of (±)-thiorphan, 44 μL (51 mg, 360 μmol) of boron trifluoride–diethyl etherate in 5 mL of anhydrous methanol was heated at 50 °C for 4 h (until no starting material remained by TLC analysis). The mixture was diluted with dichloromethane, washed with 1 M aqueous potassium carbonate, water, and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 102 mg (108% mass balance) of (±)-thiorphan methyl ester as a pale yellow oil.

A mixture of 27 mg (100 μmol) of (±)-thiorphan methyl ester, 20 mg (100 μmol) of (*R*)-1-[(1-naphthyl)ethyl]isocyanate (**13**), and 10 mg of anhydrous potassium carbonate in 2 mL of benzene was heated at 80 °C for 4 h (until no starting material remained by TLC analysis). The mixture was diluted with dichloromethane, washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 50 mg (106% mass balance) of a mixture of thiourethane diastereomers **14** and **15**. The unfractionated product was analyzed by HPLC (Regis, 4.6 mm × 25 cm, Pirkle chiral phase covalently bound to 5-μm aminopropyl silica gel; 84:16 isooctane/isopropyl alcohol; 4.0 mL/min; k'(**14**) = 8.16, k'(**15**) = 11.91; α = 1.46).

The reactions were repeated separately with (2*R*)- and (2*S*)-thiorphan. HPLC analysis of the unfractionated product obtained from (2*R*)-thiorphan (*R*)-**1** showed a ≥95:5 ratio of **14** to **15**. Likewise, HPLC analysis of the unfractionated product obtained from (2*S*)-thiorphan (*S*)-**1** showed a ≤5:95 ratio of **14** to **15**. Therefore, the enantiomeric ratio of both (2*R*)- and (2*S*)-thiorphan is ≥95:5.

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Registry No. (*R*)-**1**, 95908-99-9; (*S*)-**1**, 95909-00-5; (±)-**1**, 76721-89-6; (±)-**1** methyl ester, 83960-22-9; **3a**, 77943-39-6; **3b**, 95841-14-8; **4a**, 17016-83-0; **4b**, 95798-31-5; **5a**, 3970-13-6; **5b**, 15960-81-3; **8a**, 95798-32-6; **8b**, 95798-33-7; **9a**, 95798-34-8; **9b**, 95798-35-9; (*R*)-**10**, 95841-15-9; (*S*)-**10**, 95798-36-0; (*R*)-**11**, 95798-37-1; (*S*)-**11**, 95798-38-2; (*R*)-**12**, 95841-16-0; (*S*)-**12**, 95841-17-1; (*R*)-**13**, 42340-98-7; **14** (isomer 1), 95864-07-6; **14** (isomer 2), 95864-08-7; (1*S*,2*R*)-norephedrine hydrochloride, 40626-29-7; diphenyl carbonate, 102-09-0; (*S*)-valinol, 2026-48-4; diethyl carbonate, 105-58-8; benzyl mercaptan, 100-53-8; *s*-trioxane, 110-88-3; 3-phenylpropanoyl chloride, 645-45-4; glycine benzyl ester *p*-toluenesulfonate, 1738-76-7; enkephalinase, 70025-49-9.

Stereoselective Synthesis and Solvolytic Behavior of the Isomeric 7-Dehydrocholesterol 5,6-Oxides

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Cholesterol oxide hydrolase is a recently described mammalian enzyme which catalyzes the hydration of Δ^5-sterol oxides to 5,6-glycols in the liver. As the isomeric 7-dehydrocholesterol 5,6-oxides represent useful mechanistic probes of the action of the enzyme, synthetic procedures were sought for the stereoselective preparation of these unstable epoxides. Direct epoxidation of 7-dehydrocholesterol with peracid in the presence of aqueous buffer stereoselectively provided the α-oxide **2b** in good yield. Synthesis of the β-oxide **12** proved more difficult in that attempted formation of an intermediate bromohydrin with appropriate stereochemistry proved unsatisfactory. The finding that 7α-bromocholesteryl benzoate undergoes selective β-epoxidation and that the desired Δ^7-double bond could be formed by treatment with potassium *tert*-butoxide resulted in the successful synthesis of the β-oxide **12**. Both epoxides undergo cis addition of benzoic acid in chloroform at the allylic carbon and trans addition of 2-mercaptoethanol in base at the same position. Hydrolytic reactions prove to be more complex. Aqueous acid hydrolysis of the α-oxide **2b** produced triol **5a** and dienediol **6**, which can further dehydrate to the trienol **7**. Under identical conditions the β-oxide **12** hydrolyzes to a single product. Both epoxides, particularly the β-oxide **12**, proved to be effective inhibitors of cholesterol oxide hydrolase.

Recently, a new rat liver microsomal epoxide hydrolase capable of catalyzing the metabolism of cholestrol 5,6-oxide and other Δ^5-sterol oxides to 5,6-glycols was reported.[1,2] This newly described cholesterol oxide hydrolase is antigenically distinct from the microsomal epoxide hydrolase (EC 3.3.2.3) that catalyzes the hydrolysis of arene oxides[3,4] to *trans*-dihydrodiols and has none of this catalytic activity. In an investigation[5] of the properties of cholesterol oxide hydrolase, the need for the title compounds arose since these unsaturated epoxides have the potential (1) to be used for a spectrophotometric assay of the enzyme; (2) to determine how changes in the geometry and reactivity of these substrates affect the catalytic activity; and (3) to provide information as to whether the mechanism of hydrolysis proceeds by way of a carbocation intermediate or via nucleophilic displacement by hydroxide.

The direct epoxidation of $\Delta^{5,7}$-steroids has produced varying results (Scheme I). In an attempt to determine the number of double bonds in ergosterol (**1a**), Windaus and Luttringhaus[6] treated the sterol with perbenzoic acid. With excess reagent, exactly 3 mol of peracid were consumed by the $\Delta^{5,7,22}$ double bonds. However, when only 1 mol of the peracid was used, triol monobenzoate **4a** was obtained rather than the expected monooxide **2a**. Reaction

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