Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. ^{1}H NMR spectra were measured on Varian A-60A and JOEL FX-90Q NMR spectrometers. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Solvents were purified by standard methods. Diastereomeric oxaziridines 1–4 were prepared as previously described[10] and were greater than 95 % ee. Sulfides were prepared by standard methods.

Oxidative Kinetic Resolution Procedure. In a 5-mL, single-necked round-bottom flask equipped with magnetic stirring bar and drying tube was placed 0.8 mmol of the appropriate sulfoxide, **6a** or **6b**, in 1 mL of the designated solvent. The chiral oxaziridine, 0.4 mmol, was added as a solid portionwise with stirring to the reaction mixture. After 24 h of stirring at 25 °C, the solvent was removed under vacuum. The residue was taken up in a minimum of $CHCl_3$ and the sulfoxide isolated by preparative TLC (silica gel) using chloroform. Methyl *p*-tolyl sulfoxide (**6a**) required a second purification by TLC, developing with pentane–chloroform (1:1).

Two-Step Kinetic Resolution Procedure. In a 10-mL, round-bottom flask equipped with a magnetic stirring bar and drying tube was placed 38 mg (0.27 mmol) of methyl *p*-tolyl sulfide (**5a**) in 1 mL of chloroform. The reaction mixture was cooled to −50 °C in a dry ice/methanol bath, and 132 mg (0.27 mmol) of oxaziridine (+)-(*R,R*)-**4** in 1 mL of chloroform was added dropwise. After 1 h of stirring at room temperature, an additional 66 mg (0.135 mmol) of oxaziridine (+)-(*R,R*)-**4** was added. The reaction mixture was allowed to stir for 24 h, and methyl *p*-tolyl sulfoxide (**6a**) was isolated as described above. The optical purity of the sulfoxide, 11.4 mg (54%), was determined to be 27.9 % ee by using a chiral shift reagent.

General Procedure for Determining Optical Purities of Sulfoxides. Optical yields were ascertained by comparing the optical rotations of sulfoxides **6a,b** obtained via kinetic resolution using chiral 2-sulfonyloxaziridines **1**, **3**, and **4** with those reported in the literature.[10] The optical yields determined in this manner were verified by comparing a series of 60- and 90-MHz ^{1}H NMR spectra ($CDCl_3$) at increasing concentration of the chiral shift reagent tris[3[(heptafluoropropyl)hydroxymethylene)]-*d*-camphorato]europium(III) derivative [Eu(hfc)$_3$]. When the shift difference of the appropriate absorption was at least 9 Hz, the peak areas were determined by integration. Agreement between the two methods was approximately ±1.0 % ee.

All asymmetric oxidations were carried out at least twice and the results averaged (Table I).

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Registry No. (−)-(*S,S*)-**1**, 81310-08-9; (+)-(*R,R*)-**2**, 81369-89-3; (−)-(*S,S*)-**3**, 81446-77-7; (+)-(*R,R*)-**4**, 81422-07-3; **6a**, 934-72-5; **6b**, 4170-71-2.

1,4-Oxazines via Intramolecular Ring Closure of β-Hydroxydiazoacetamides: Phenylalanine to Tetrahydroindeno[1,2-*b*]-1,4-oxazin-3(2*H*)-ones

D. E. McClure,* P. K. Lumma, B. H. Arison, J. H. Jones, and J. J. Baldwin

Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

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The synthesis of the tetrahydroindeno[1,2-*b*]-1,4-oxazin-3(2*H*)-one system from phenylalanine is described. Conversion of the intermediate vicinal amino alcohol to the 1,4-oxazine was accomplished via BF_3·Et_2O-catalyzed ring closure of a β-hydroxydiazoacetamide. The stereoselectivity and generality of the inter- and intramolecular Friedel–Crafts reactions of protected amino acids including homophenylalanine are presented.

Although α-diazocarbonyl compounds, which serve as precursors to α-keto carbene/carbenoid or α-diazonium carbonyl intermediates, have been used extensively in synthetic organic chemistry, there has been a recent resurgence of their utilization in intramolecular ring closure reactions.[1,2] Elegant and practical examples of this utilization include the syntheses of gibberellin/gibberellic acid[3] and thienamycin.[4] In this paper we report on the novel conversion of vicinal amino alcohols to 1,4-oxazinones through β-hydroxydiazoacetamides, specifically, the overall conversion of phenylalanine ((*R,S*), (*R*), or (*S*)) into 4,4a,5,9b-tetrahydroindeno[1,2-*b*]-1,4-oxazin-3(2*H*)-ones. In addition, further studies into the stereoselectivity and generality of the inter- and intramolecular Friedel–Crafts reactions of protected amino acids are also included.[5]

Initially, a classical conversion[6] of amino alcohols **1** through chloroacetamides **2** to the desired 1,4-oxazin-3-(2*H*)-ones was attempted (Scheme I). Although **2a** formed in good yield, treatment with various bases produced **3a** as a minor component of a complex mixture. Under the best conditions found (NaH, Me_2SO), the overall yield of **3a** from **1a** was in the range of 10–20% after chromatography. A variety of bases was examined on a probe scale, and none appeared to produce satisfactory yields of **3a** as determined by TLC analysis.[7] Use of the corresponding bromoacetamide gave similar results. Therefore, the preparation and decomposition of the related α-diazoacetamides **6** were considered as an alternative approach. Mechanistically, such an intermediate should facilitate the

(1) Smith, A. B., III; Dieter, R. K. *Tetrahedron* **1981**, *37*, 2407.
(2) Burke, S. D.; Grieco, P. A. *Org. React.* **1979**, *26*, 361.
(3) Lombardo, L.; Mander, L. N.; Turner, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6626. Hook, J. M.; Mander, L. N. Urech, R. *Ibid.* **1980**, *102*, 6628.
(4) Melillo, D. G.; Liu, T.; Ryan, K.; Sletzinger, M.; Shinkai, I. *Tetrahedron Lett.* **1981**, *22*, 913. Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Ibid.* **1980**, *21*, 2783. Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.
(5) McClure, D. E.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1981**, *46*, 2431.
(6) Anderson, P. S.; Baldwin, J. J.; McClure, D. E.; Lundell, G. F.; Jones, J. H. *J. Org. Chem.* **1982**, *47*, 2184.
(7) In two instances yields of 40–50% of **3b** were obtained from **1b** by using potassium *tert*-butoxide in THF. However, this yield was not consistent, and in most instances the conversion of **1a** to **3a** proceeded in less than 10% yields.

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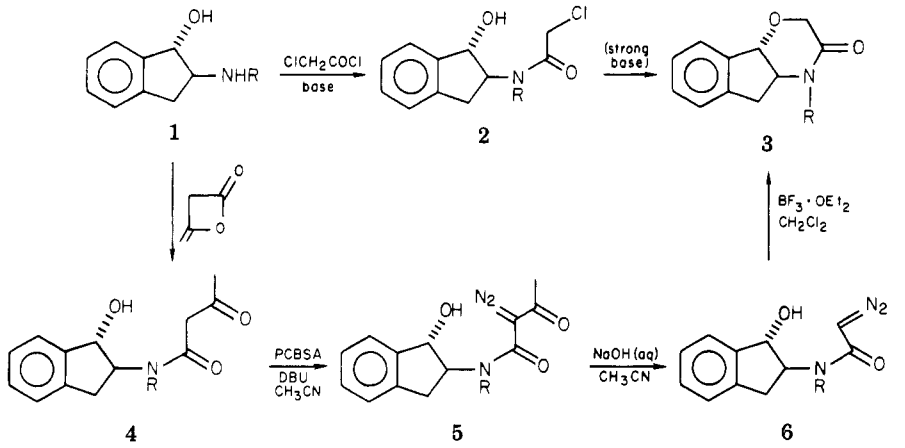
Scheme I[a]



[a] a, R = CH_3; b, R = CH_3CH_2; c, R = $CH_3CH_2CH_2$; d, R = H.

ring closure by substantially improving the leaving group properties.

We examined the sequence shown in Scheme I, since it looked promising as an approach to the desired compounds. Reaction of **1a** with diketene[9] in ethanol gave the acetoacetamide **4a** suitably bisactivated as required for the subsequent diazo-transfer reaction.[8] The extra two carbons introduced in this step should be readily removed, since the diazo compounds derived from 1,3-dicarbonyl compounds are known to hydrolytically deacylate.[8] The standard conditions for diazo transfer with *p*-carboxybenzenesulfonyl azide (PCBSA) and triethylamine in acetonitrile[8] proved unsuccessful. No reaction was apparent, since the triethylamine salt of *p*-carboxybenzenesulfonamide did not precipitate from solution. However, when the stronger base 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) was used, a precipitate formed in seconds, and the reaction to give **5a** was complete in a few hours. Aqueous hydroxide-mediated deacetylation[8] of **5a** produced **6a** in good yield.

In the cyclization of **6a**, the hydroxyl moiety should internally intercept either the α-keto carbenoid or α-diazonium carbonyl species. Treatment of **6a** with rhodium diacetate[4] or boron trifluoride etherate[1,2] in dichloromethane led to immediate gas evolution and gave the desired product. However, the BF_3-catalyzed reaction was somewhat cleaner, and this cyclization catalyst was used in all subsequent reactions. The overall process was an efficient one, giving greater than 50% yields over four steps in cases where R = alkyl (**1a,c**). Purification of the intermediates[10] was not required. In the case of the unsubstituted example **5d**, the intermediates generated in the deacetylation were apparently base sensitive; the reaction failed, producing only decomposition products.[12] This result imposes a limitation to the generality of the sequence.

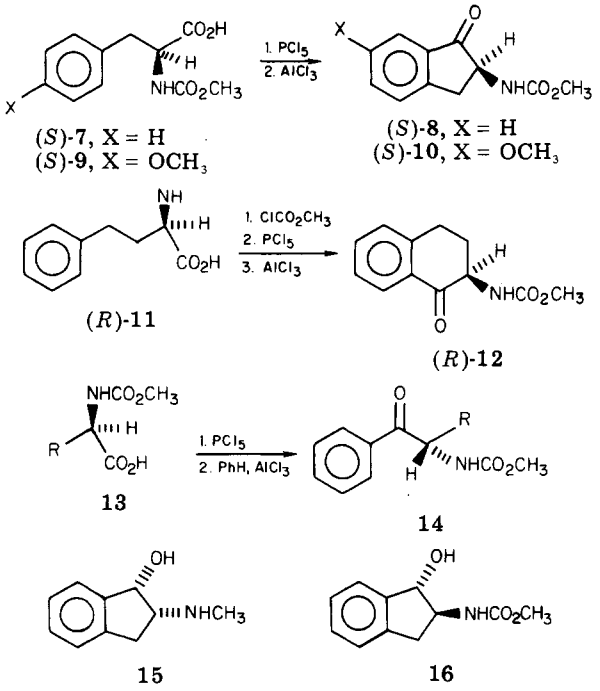
We had earlier reported on the synthesis of **1a** via the conversion of phenylalanine to 2-(methylamino)-1-indanol through the *N*-methoxycarbonyl-protected derivative with complete retention of stereochemistry.[5] Alternatively, racemic compounds **1** were formed from the corresponding azlactones of phenylalanine[5] or from the oximino ketone derived from nitrosation of indanone.[13] Many of the experimental procedures from that paper[5] are included here, since the complete details were not previously published. As a reminder, we note that reduction of chiral **8** to chiral *trans*-2-[(methoxycarbonyl)amino]-1-indanol (**16**) with $NaBH_4$ produced substantial racemization while BH_3·THF gave chiral **16** with complete retention of stereochemistry. The utilization of different anhydrides in the formation of azlactones for use in the Friedel–Crafts cyclization allowed for the synthesis of variously substituted amino alcohols **1**[5] (i.e., **1b** and **1c**). However, the preparation of azlactones is known to produce at least some racemization when chiral amino acids serve as starting materials.[5,14]

The chiral purity of **1a** could be easily established by examination of the NMR spectra in the presence of the chiral shift reagent, $Eu(hfbc)_3$.[5] Unfortunately, none of the intermediates **3a–6a** was amenable to such analysis. Direct examination of the chiral purities of **3a** via HPLC on an optically active support gave only partial resolution of the racemic mixture into separate peaks.[15] The fact that (*R,R*)- and (*S,S*)-**3a** exhibited approximately equal specific rotations having opposite signs provided support for the retention of stereochemistry through the reaction sequence. The optical rotations of (*R,R*)- and (*S,S*)-**6a** were also approximately equal and opposite in both solvents in which they were examined. Thus, although the sequence from **1** through **4–6** has not been absolutely established to occur with retention of stereochemistry, the indications are very strong that such is the case. In addition, epimerization of only one center to give the geometric cis isomers was not observed.

As mentioned in our previous publication,[5] the *cis*-2-(methylamino)-1-indanols (**15**) related to **1a** were minor products from the $LiAlH_4$ reduction of **8**. Racemic **15** and (*S,R*)-**15** were isolated by chromatography, and their properties are included in the Experimental Section. Comparison of racemic **15** to that previously prepared by a different route[16] showed them to be identical.[5] In addition to our use of *N*-(methoxycarbonyl)phenylalanine (**7**),

(8) Hendrickson, J. B.; Wolf, W. A. *J. Org. Chem.* **1968**, *33*, 3610.
(9) Kato, T. *Acc. Chem. Res.* **1974**, *7*, 265.
(10) The products from the diazo transfer reaction could be purified by flash chromatography[11] or by a water wash to remove any excess DBU.
(11) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978** *43*, 2923.
(12) Other conditions (aqueous K_2CO_3 or excess DBU in the diazo-transfer reaction) also led to decomposition.
(13) Rimek, H.-J.; Yuprophat, T.; Zymalkowski, F. *Justus Liebigs Ann. Chem.* **1969**, *725*, 116.
(14) Carter, H. E. *Org. React.* **1946**, *3*, 198. Goodman, M.; Levine, L. *J. Am. Chem. Soc.* **1964**, *86*, 2918.
(15) Pirkle, W. H.; Finn, J. M.; Schreiner, J. L.; Hamper, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 3964.
(16) Huebner, C. F.; Donoghue, E. M.; Novak, C. J.; Dorfman, L.; Wenkert, E. *J. Org. Chem.* **1970**, *35*, 1149. Huebner, C. F.; Strachan, P. L.; Donoghue, E. M.; Cahoon, N.; Dorfman, L.; Margerison, R.; Wenkert, E. *Ibid.* **1967**, *32*, 1126.

Scheme II



reports have appeared recently on the aminoacylation of aromatic rings using other N-protected derivatives to yield compounds of type **14** with retention of stereochemistry. Rapoport and Buckley[17] have reported on the reactions of the related *N*-ethoxycarbonyl- and *N*-benzenesulfonyl-protected amino acids. In addition, their work also discussed the alternative approach using arylmetallic reagents (M = Li, MgX) in reaction with amino acids or acid chlorides to achieve the same overall aminoacylation process.

We have expanded our investigation of these aminoacylation reactions and found that under the standard Friedel–Crafts conditions (3 equiv of $AlCl_3$, CH_2Cl_2) which gave excellent results with phenylalanine, none of the desired cyclization product was obtained from the methyl ether derived from tyrosine [(S)-**9**]. Even when only 1 equiv of $AlCl_3$[18,19] was used, no **10** could be isolated (see Scheme II).

However, the cyclization proved successful in the conversion of chiral homophenylalanines[20] into N-protected aminotetralones with retention of stereochemistry [e.g., (*R*)-**11** → (*R*)-**12**]. The yields were generally good (80–90% overall), and the products could be purified preferably by chromatography.[21] Examination of these materials as well as the crude products directly from the reaction mixture by chiral shift NMR analysis[5,22] showed the composition of each enantiomer to be at least 95% chirally pure.[21] The tetralones seemed to be more sensitive to epimerization[21] than the corresponding indanones. However, even under these unoptimized conditions, the tetralones were formed with predominant retention of stereochemistry; previous work[5] with the indanones had found them to be formed with complete retention of stereochemistry.

The intermolecular version of the reaction also exhibited a sensitivity to the substituents present. When either proline or leucine (**13**, R = $(CH_3)_2CHCH_2$), protected as its *N*-methoxycarbonyl derivative, reacted with benzene under Friedel–Crafts conditions, the desired aminoacylation product[17] was isolated in 30–35% yield after chromatography. This should be compared to 50–60% yields obtained in the alanine series.[5] However, these products were not completely free of impurities, having aromatic absorptions in their NMR spectra. When either valine (**13**, R = $(CH_3)_2CH$) or isoleucine (**13**, R = $CH_3CH_2CH(CH_3)$) was examined in the sequence, none of the desired product was isolated after chromatography. Thus, the reaction appeared to exhibit an extreme sensitivity to steric influence; i.e., as the R group increased in size near the reacting acyl terminus, decreasing amounts of the aminoacylation products resulted. The chiral purities of the proline- and leucine-derived aminoacylation products were not examined since the yields and purities were of only borderline usefulness in a preparative sense. Due to the sensitivity of this Friedel–Crafts aminoacylation to steric influences and substituent effects, the alternative approach delineated by Rapoport and Buckley[17] should be a most valuable complementary synthetic procedure.

Experimental Section

NMR spectra were determined in the indicated solvent on a Varian EM-390 or Nicolet NT-360 with tetramethylsilane as an internal standard. The NMR studies to determine the chiral purity of various products were conducted on a Varian SC-300 operating in the Fourier transform mode. Optical rotations were determined by using a Perkin-Elmer 141 polarimeter. Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Concentration of solutions was accomplished on a Büchi rotary evaporator at water aspirator pressure (20–25 mm).

(*S*)-2-[(Methoxycarbonyl)amino]-1-indanone [(*S*)-8]. To an ice-cooled solution of L-phenylalanine (16.5 g, 0.1 mol) in 1 N NaOH (100 mL) to which solid Na_2CO_3 (5.3 g, 0.05 mol) had been added was added methyl chloroformate (7.8 mL, 0.1 mol). Stirring was continued for $^1/_2$ h with cooling and $^1/_2$ h without. The mixture was carefully acidified with concentrated HCl to pH ~2–3. After extraction with CH_2Cl_2 and drying (Na_2SO_4) of the extract, concentration of the solvent left (*S*)-*N*-(methoxycarbonyl)phenylalanine [(*S*)-**7**] (21 g, 94%).

To an ice-cooled solution of (*S*)-**7** in ether (300 mL) was added solid PCl_5 (19.4 g, 0.093 mol). Stirring was continued for 1 h with cooling and $^1/_2$ h without. After concentration of the mixture at 30 °C (25 torr), the residue was dissolved in CH_2Cl_2 (250 mL) and added dropwise rapidly to a suspension of $AlCl_3$ (37.2 g, 0.28 mol) in CH_2Cl_2 (150 mL). Stirring was continued for 1–2 h after the addition had been completed. The mixture was poured into ice-cold dilute HCl with vigorous stirring which was continued for 1 h. The layers were separated, and the aqueous phase was extracted several times with CH_2Cl_2. The combined organic phase was dried by adding Na_2SO_4 and silica gel, filtered, and concentrated to give (*S*)-**8**: 13.2 g (64% overall); mp 157–159 °C. A small portion was recrystallized from toluene: mp 164–166 °C; $[\alpha]^{25}_D$ +134.1° (*c* 0.51, $CHCl_3$); NMR ($CDCl_3$) δ 3.0 (1 H, dd, *J* = 6, 18 Hz), 3.7 (1 H, dd, *J* = 9, 18 Hz), 3.7 (3 H, s), 4.4 (1 H, m), 5.7 (1 H, brs), 7.2–7.9 (4 H, m). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.33; H, 5.50; N, 6.86. Chiral shift NMR analysis detected none of the opposite isomer (≥98% *S*).

(*R*)-2-[(Methoxycarbonyl)amino]-1-indanone [(*R*)-8]. Following the procedure above for (*S*)-**8** but substituting D-

(17) Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157.
(18) House, H. O.; Hudson, C. B. *J. Org. Chem.* **1970**, *35*, 647.
(19) Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1980**, *102*, 3056.
(20) Weller, H. N.; Gordon, E. M. *J. Org. Chem.* **1982**, *47*, 4160.
(21) (*R*)-Homophenylalanine [(*R*)-**11**, Chemical Dynamics Corp.] gave (*R*)-**12** which was recrystallized from cyclohexane or chromatographed, and (*S*)-homophenylalanine [(*S*)-**11**, United States Biochemical Corp.] gave (*S*)-**12** which was purified via chromatography. Recrystallization or sublimation of crude samples sometimes led to decreased specific rotations for (*S*)- and/or (*R*)-**12**. Since these products might be sensitive to acidic or basic impurities it is preferable to use chiral **8**, **12**, and **14** (R = CH_3) without purification or to purity them *only* by chromatography. None of the opposite isomer was detected in the analyzed samples of (*S*)-**12**, while ~5% of the *S* isomer was detected in the analyzed samples of (*R*)-**12**.
(22) Baldwin, J. J.;Raab, A. W.; Mensler, K., Arison, B. H.; McClure, D. E. *J. Org. Chem.* **1978**, *43*, 4876. McClure, D. E.; Arison, B. H.; Baldwin, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 3666.

phenylalanine as the starting material, (*R*)-2-[(methoxycarbonyl)amino]-1-indanone (74%; mp 160–163 °C) was obtained. Recrystallization from toluene gave material having the following properties: mp 165–167 °C; $[\alpha]^{25}_D$ -134.5° (*c* 0.51, $CHCl_3$). Anal. Calcd, as above. Found: C, 64.54; H, 5.56; N, 6.70. Chiral shift NMR analysis detected none of the opposite isomer (≥98% *R*).

Racemic 2-[(Methoxycarbonyl)amino]-1-indanone (8). Substituting racemic phenylalanine as the starting material and following the procedure for (*S*)-8, racemic 8 was obtained (65%; mp 141–143 °C). Anal. Calcd, as above. Found: C, 64.47; H, 5.50; N, 6.53.

(*S*)-2-[(Methoxycarbonyl)amino]-1,2,3,4-tetrahydronaphthalen-1-one [(*S*)-12]. By use of the procedure presented for the preparation of (*S*)-8 and substitution of (*S*)-(+)-homophenylalanine as the starting material, (*S*)-12 was obtained in 89% overall yield. Chromatography on silica gel under flash conditions, eluting with 0.5% CH_3OH/CH_2Cl_2, provided pure (*S*)-12: mp 125–127 °C; $[\alpha]^{25}_D$ +67.0° (*c* 0.60, $CHCl_3$); NMR ($CDCl_3$) δ 1.95 (1 H, dq, *J* = 5, 14 Hz), 2.8 (1 H, brm), 3.05 (1 H, ddd, *J* = 3, 5, 16 Hz), 3.25 (1 H, ddd, *J* = 4, 14, 16 Hz), 3.75 (3 H, s), 4.45 (1 H, dt, *J* = 14, 5 Hz), 5.9 (1 H, brs), 7.25 (1 H, d, *J* = 8 Hz), 7.35 (1 H, t, *J* = 8 Hz), 7.5 (1 H, td, *J* = 8, 1 Hz), 8.0 (1 H, dd, *J* = 8, 1 Hz). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39: Found: C, 65.40; H, 6.10; N, 6.41. Chiral shift NMR analysis of crude samples detected none of the opposite isomer (≥98 ± 2% *S*).

(*R*)-2-[(Methoxycarbonyl)amino]-1,2,3,4-tetrahydronaphthalen-1-one [(*R*)-12]. By use of the procedure presented for the preparation of (*S*)-8 and substitution of (*R*)-(−)-homophenylalanine as the starting material, (*R*)-12 was obtained in 88% overall yield. Recrystallization from cyclohexane gave (*R*)-12: mp 121–123 °C; $[\alpha]^{25}_D$ -60.3° (*c* 0.73, $CHCl_3$). Chromatography as given for (*S*)-12 gave (*R*)-12: mp 124–125 °C; $[\alpha]^{25}_D$ -62.6° (*c* 0.58, $CHCl_3$). Anal. Calcd, as above. Found: C, 65.76; H, 6.11; N, 6.07. Chiral shift NMR analysis of crude or recrystallized samples showed ~5% of the opposite isomer (95 ± 2% *R*).

Racemic 2-[(Methoxycarbonyl)amino]-1,2,3,4-tetrahydronaphthalen-1-one (12). By use of the same procedure and racemic homophenylalanine as the starting material, 12 was obtained. Sublimation provided pure 12, mp 119–122 °C. Anal. Calcd, as above. Found: C, 65.49; H, 6.08; N, 6.32.

2-(Acetylamino)-1-indanone. The preparation of this compound is given as an example of the azlactone procedure. The use of other anhydrides obviously allows for the introduction of different acyl groups into the final product.

Phenylalanine (4.95 g, 0.03 mol) was dissolved in acetic anhydride (50 mL), and the mixture was heated on a steam bath for 15 min. Most of the acetic anhydride was removed on a rotary evaporator at 50 °C (2 torr), and the residue was distilled to yield azlactone: 4.1 g (72%); bp 95–104 °C (0.1–0.5 torr); NMR ($CDCl_3$) δ 2.05 (3 H, d, *J* = 2 Hz), 3.0 (1 H, dd, *J* = 6, 14 Hz), 3.2 (1 H, dd, *J* = 5, 14 Hz), 4.4 (1 H, ddq, *J* = 5, 6, 2 Hz), 7.3 (5 H, brs).

The azlactone was dissolved in CH_2Cl_2 (25 mL) and rapidly added to $AlCl_3$ (8.5 g, 0.064 m, 3 equiv) in CH_2Cl_2 (25 mL) dropwise. After the mixture was stirred for 30 min, HCl/ice was added and stirring was continued for 30 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined CH_2Cl_2 phase was dried (Na_2SO_4) and concentrated to give solid 2-(acetylamino)-1-indanone (55%) which was recrystallized from toluene; mp 162–163 °C. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.41. Found: C, 70.10; H, 5.89; N, 7.41.

***trans*-(1*S*,2*S*)-2-(Methylamino)-1-indanol [(*S*,*S*)-1a].** To lithium aluminum hydride (3.20 g, 0.085 mol) in THF (100 mL) was added a suspension of (*S*)-8 (8.72 g, 0.0425 mol) in THF (100 mL) dropwise over $^1/_2$ h. The mixture was refluxed for $^1/_2$ h and then cooled. The saturated aqueous Na_2SO_4 solution was added dropwise to quench the excess $LiAlH_4$. After the mixture was stirred for $^1/_2$ h, CH_2Cl_2 was added along with solid Na_2SO_4 for drying, and the mixture was filtered. Evaporation of the solvent gave the crude product which exhibited the following properties after trituration with and/or recrystallization from hot *n*-butyl chloride: mp 140–142 °C; $[\alpha]^{25}_D$ +39.9° (*c* 0.516, CH_3OH); NMR ($CDCl_3$) δ 2.4 (3 H, s), 2.5 (1 H, m), 3.2 (2 H, m), 3.7 (2 H, brs, exchangeable), 4.9 (1 H, d, *J* = 7 Hz), 7.1–7.5 (4 H, m). Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.29; H, 8.04; N, 8.58. Chiral shift NMR analysis detected none of the opposite isomer (≥98% *S*,*S*).

In addition, (S,S)-*N*-methoxycarbonylamino-1-indanol could be substituted for the starting material (S)-8 in this preparation of (S,S)-1a.

***trans*-(1*R*,2*R*)-2-(Methylamino)-1-indanol [(*R*,*R*)-1a].** When (*R*)-8 was used as the starting material in the procedure for (*S*,*S*)-1a, (1*R*,2*R*)-1a was obtained: mp 140–143 °C; $[\alpha]^{25}_D$ −38.9° (*c* 0.51, CH_3OH). Anal. Calcd, as above. Found: C, 73.74; H, 8.23; N, 8.71. Chiral shift NMR analysis detected none of the opposite isomer (≥98% *R*,*R*).

Racemic *trans*-2-(Methylamino)-1-indanol (1a). With racemic 8 as the starting material in the procedure for (*S*,*S*)-1a, racemic 1a (79%; mp 115–116.5 °C) was obtained. Anal. Calcd, as above. Found: C, 73.84; H, 8.43; N, 8.72.

***trans*-(1*S*,2*S*)-2-[(Methoxycarbonyl)amino]-1-indanol [(*S*,*S*)-16].** To a suspension of (*S*)-8 (1.03 g, 5 mmol) in THF (30 mL) was added dropwise a 1 M solution of borane in THF (10 mL, 10 mmol) with ice-bath cooling. After completion of the addition, the mixture was allowed to warm to room temperature with stirring for 2 h. HOAc (5 mL) and MeOH (5 mL) were added, and the mixutre was concentrated on a rotary evaporator. Retreatment with MeOH and reconcentration was repeated twice in order to remove any boron-containing products. The remaining solvent was removed in vacuo to leave the product (85%). Recrystallization of a small amount from chloroform gave (*S*,*S*)-2-[(methoxycarbonyl)amino]-1-indanol having the following properties: mp 176–178 °C; $[\alpha]^{25}_D$ +23.6° (*c* 0.58, CH_3OH); NMR ($CDCl_3$ + Me_2SO-d_6) δ 2.7 (1 H, dd, *J* = 10, 18 Hz), 3.2 (1 H, dd, *J* = 6, 18 Hz), 3.7 (3 H, s), 4.0 (1 H, m), 5.0 (1 H, d, *J* = 7 Hz), 7.0–7.5 (4 H, m). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.73; H, 6.32; N, 6.54. Chiral shift NMR analysis detected none of the opposite isomer (≥98% *S*,*S*).

Racemic *trans*-2-[(Methoxycarbonyl)amino]-1-indanol (16). To racemic 8 (1.03 g, 5 mmol) in EtOH was added a solution of $NaBH_4$ (200 mg, 5 mmol) in EtOH dropwise with ice cooling. After completion of the addition, the mixture was stirred at room temperature for 1 h. MeOH was added, and the mixture was concentrated. The residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The layers were separated, and the EtOAc layer was dried (Na_2SO_4) and concentrated to give the product (82%). Recrystallization from $CHCl_3$ gave material having the following properties: mp 178–180 °C. Anal. Calcd, as above. Found: C, 63.69; H, 6.21; N, 6.46.

Racemic *cis*-2-(Methylamino)-1-indanol (15). This compound was prepared by following the procedures of Huebner et al.[16] Flash chromatography of the product mixture, eluting with 5% MeOH in NH_3-saturated CH_2Cl_2, gave the desired racemic 15: mp 75–77 °C (lit.[20] mp 70–72 °C); NMR ($CDCl_3$) δ 2.5 (3 H, s), 2.9 (2 H, m), 3.2 (1 H, m), 4.9 (1 H, d, *J* = 5 Hz), 7.1–7.6 (4 H, m).

This material was also obtained as the minor product from the $LiAlH_4$ reduction of racemic 2-[(methoxycarbonyl)amino]-1-indanone. After recrystallization of the major product, *trans*-2-(methylamino)-1-indanol (1a), the mother liquors from the crystallization were concentrated, and the residue was flash chromatographed on silica gel 60, eluting with 5% MeOH in NH_3-saturated CH_2Cl_2 to give the desired racemic cis isomer. Conversion to the hydrochloride salt and recrystallization from *n*-BuCl/CH_3CN gave pure 15·HCl: mp 168–171 °C; NMR (D_2O) δ 2.7 (3 H, s), 3.0 (1 H, d of d, *J* = 16, 8 Hz), 3.2 (1 H, d of d, *J* = 16, 8 Hz), 3.7 (1 H, d of t, *J* = 5, 8 Hz), 4.6 (3 H, s), 5.2 (1 H, d, *J* = 5 Hz), 7.3 (4 H, m). Anal. Calcd for $C_{10}H_{13}NO$·HCl: C, 60.15; H, 7.07; N, 7.02. Found: C, 60.25; H, 7.25; N, 6.90.

***cis*-(1*S*,2*R*)-2-(Methylamino)-1-indanol [(*S*,*R*)-15].** The residue from the mother liquors after recrystallization of the major product [(*R*,*R*)-1a] from the $LiAlH_4$ reduction of (*R*)-2-[(methoxycarbonyl)amino]-1-indanone was flash chromatographed on silica gel 60, eluting with 5% CH_3OH in NH_3-saturated CH_2Cl_2, to give the desired *cis*-(*S*,*R*)-15. Conversion to the HCl salt and recrystallization from 2-propanol gave pure (*S*,*R*)-15·HCl: mp 206–208.5 °C; $[\alpha]^{25}_D$ - 16.5° (*c* 0.50, CH_3OH). Anal. Calcd, as above. Found: C, 60.36; H, 7.31; N, 7.39.

Comparison of the NMR spectrum of the *S*,*R* isomer with that of the racemate in the presence of Eu(hfbc)$_3$ showed that none of the corresponding *R*,*S* isomer could be detected; the chiral

purity of (*S,R*)-**15** was therefore assessed as ≥98%.

***trans*-(1*S*,2*S*)-2-(Acetoacetylmethylamino)-1-indanol [(*S,S*)-4a].** To (1*S*,2*S*)-**1a** (5.0 g, 0.03 mol) in EtOH (100 mL) was added diketene (2.9 g, 0.034 mol) all at once. A mild exothermic reaction ensued. After being stirred 0.5–1 h, the mixture was concentrated. CH_3CN was added, and the mixture was reconcentrated to leave an oil which was suitable for direct use in the next step.

Flash chromatography on silica, eluting with 2% CH_3OH in CH_2Cl_2, gave a viscous oil (*S,S*)-**4a** having the following properties: $[\alpha]^{25}_D$ −15.5° (*c* 0.51, $CHCl_3$). The NMR spectrum of the compound exhibits the presence of a mixture of isomers (~1:1) apparently due to hindered rotation about the amide bond: NMR ($CDCl_3$) δ 2.25 (3 H, s), 2.3 (3 H, s), 2.95 (3 H, s), 2.95 (3 H, s), 3.1 (2 × 2 H, m), 3.6 (2 H, s), 3.7 (1 H, d, *J* = 16 Hz), 3.85 (1 H, d, *J* = 16 Hz), 4.3 (1 H, q, *J* = 8 Hz), 5.0 (1 H, q, *J* = 8 Hz), 5.2 (1 H, d, *J* = 8 Hz), 5.25 (1 H, d, *J* = 8 Hz), 7.2 (1 H, m), 7.3 (2 H, m), 7.4 (1 H, m). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.67. Found: C, 67.48; H, 7.26; N, 5.68.

***trans*-(1*R*,2*R*)-2-(Acetoacetylmethylamino)-1-indanol [(*R,R*)-4a].** Substitution of (1*R*,2*R*)-**1a** in the procedure given for the 1*S*,2*S* isomer gave (1*R*,2*R*)-**4a** as an oil.

Flash chromatography on a small quantity gave a viscous oil (*R,R*)-**4a**: $[\alpha]^{25}_D$ +11.7° (*c* 0.47, $CHCl_3$). Anal. Calcd, as above. Found: C, 67.66; H, 7.30; N, 5.66.

Racemic *trans*-2-(Acetoacetylmethylamino)-1-indanol (4a). Substitution of racemic **1a** in the procedure given for the 1*S*,2*S* isomer gave racemic **4a**. Flash chromatography of a small quantity gave racemic **4a** as a viscous oil. Anal. Calcd, as above. Found: C, 67.87; H, 7.08; N, 5.65.

***trans*-(1*S*,2*S*)-2-[(Diazoacetyl)methylamino]-1-indanol [(*S,S*)-6a].** To (1*S*,2*S*)-**4a** (~0.03 mol) from above in CH_3CN (100 mL) was added *p*-carboxybenzenesulfonyl azide (7.0 g, 0.03 mol), and the mixture was cooled in an ice bath before the addition of 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU; 9.0 mL, 0.06 mol). The mixture became homogeneous, and a precipitate formed within seconds. The cooling bath was removed, and stirring was continued for 3 h. H_2O was added, and the mixture was extracted with CH_2Cl_2 (3×). The combined CH_2Cl_2 phase was washed with H_2O (2×). After the mixture was dried (Na_2SO_4), concentration provided crude product which was sufficiently pure for use in the next conversion. Flash chromatography on silica, eluting with 2% MeOH/CH_2Cl_2, removed the last traces of DBU to yield (1*S*,2*S*)-**5a**: $[\alpha]^{25}_D$ +24.6° (*c* 0.525, $CHCl_3$); NMR ($CDCl_3$) δ 2.1 (3 H, s), 2.8 (3 H, s), 2.9 (1 H, d of d, *J* = 16, 8 Hz), 3.2 (1 H, d of d, *J* = 16, 8 Hz), 5.0 (1 H, m), 6.4 (1 H, d, *J* = 7 Hz), 7.3 (4 H, brs).

The product from the diazo-transfer reaction was redissolved in CH_3CN (100 mL), and 5% aqueous NaOH (50 mL) was added. The mixture was stirred for 5 h. Additional H_2O and CH_2Cl_2 were added, and the layers were separated. Further extraction with CH_2Cl_2 was performed, and the combined organic phase was dried (Na_2SO_4) and concentrated to yield analytically pure (*S,S*)-**6a** (91%) which was recrystallized from CH_2Cl_2 to give (1*S*,2*S*)-**6a**: mp 165–167 °C; $[\alpha]^{25}_D$ −60.9° (*c* 0.525, $CHCl_3$); $[\alpha]^{25}_D$ +35.2° (*c* 0.61, MeOH); NMR ($CDCl_3$ + Me_2SO-d_6) δ 2.9 (3 H, s), 3.0 (2 H, m), 5.1 (1 H, d, *J* = 7 Hz), 5.4 (1 H, s), 7.2–7.5 (4 H, m). Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.46; H, 5.89; N, 18.31.

***trans*-(1*R*,2*R*)-2-[(Diazoacetyl)methylamino]-1-indanol [(*R,R*)-6a].** Substitution of (1*R*,2*R*)-**4a** for (1*S*,2*S*)-**4a** in the preparation of (1*S*,2*S*)-**6a** above gave (1*R*,2*R*)-**6a**: mp 168–170 °C; $[\alpha]^{25}_D$ +60.9° (*c* 0.52, $CHCl_3$); $[\alpha]^{25}_D$ −37.2° (*c* 0.55, MeOH). Anal. Calcd, as above. Found: C, 62.48; H, 5.94; N, 18.41.

Racemic *trans*-2-[(Diazoacetyl)methylamino]-1-indanol (6a). Substitution of racemic **4a** for (1*S*,2*S*)-**4a** in the preparation of (1*S*,2*S*)-**6a** above gave racemic **6a**, mp 142–145 °C. Anal. Calcd, as above. Found: C, 62.09; H, 5.80; N, 17.83.

***trans*-(4a*S*,9b*S*)-4-Methyl-4,4a,5,9b-tetrahydroindeno[1,2-*b*]-1,4-oxazin-3(2*H*)-one [(*S,S*)-3a].** To (1*S*,2*S*)-**6a** (4.5 g, 0.019 mol) in CH_2Cl_2 (200 mL) cooled in an ice bath was added dropwise boron trifluoride etherate (3.4 g, 2.9 mL, 0.023 mol). Gas evolution began immediately. The reaction was stirred for 15–30 min, and 1 N HCl (100 mL) was added. The mixture was stirred for 30 min and additional CH_2Cl_2 used for extraction. The combined organic phase was washed with saturated aqueous $NaHCO_3$ and then H_2O. After drying and concentration, (4a*S*,9b*S*)-**3a** (84%) was obtained. Purification was usually unnecessary but flash chromatography on silica, eluting with 1% MeOH/CH_2Cl_2, gave pure (*S,S*)-**3a**: mp 146–149 °C; $[\alpha]^{25}_D$ +83.5° (*c* 0.51, $CHCl_3$); NMR ($CDCl_3$) δ 2.7 (1 H, d of d, *J* = 11, 14 Hz), 3.0 (3 H, s), 3.1 (1 H, d of d, *J* = 7, 14 Hz), 3.8 (1 H, m), 4.5 (2 H, s), 4.9 (1 H, d, *J* = 9 Hz), 7.3 (4 H, m). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.79; H, 6.67; N, 6.88.

***trans*-(4a*R*,9b*R*)-4-Methyl-4,4a,5,9b-tetrahydroindeno[1,2-*b*]-1,4-oxazin-3(2*H*)-one [(*R,R*)-3a].** Substitution of (1*R*,2*R*)-**6a** for (1*S*,2*S*)-**6a** in the preparation of (*S,S*)-**3a** above gave (4a*R*,9b*R*)-**3a**: mp 146–148 °C; $[\alpha]^{25}_D$ −86.4° (*c* 0.87, $CHCl_3$). Anal. Calcd, as above. Found: C, 70.51; H, 6.55; N, 6.90.

Racemic *trans*-4-Methyl-4,4a,5,9b-tetrahydroindeno[1,2-*b*]-1,4-oxazin-3(2*H*)-one (3a). Substitution of racemic **6a** for (1*S*,2*S*)-**6a** in the preparation of (*S,S*)-**3a** above gave racemic **3a**, mp 154–162 °C. Anal. Calcd, as above. Found: C, 71.12; H, 6.76; N, 6.85.

General Procedure. Reaction of Benzene with the *N*-Methoxycarbonyl Amino Acid Chlorides. The *N*-methoxycarbonyl amino acids were prepared from the corresponding amino acid (1 molar equiv) and methyl chloroformate (1 molar equiv) in H_2O in the presence of NaOH (1 molar equiv) and Na_2CO_3 (0.5 molar equiv) as given for (*S*)-**7**. Larger quantities of the lower molecular weight derivatives could be isolated by saturating the acidic aqueous phase with NaCl prior to extraction with CH_2Cl_2 during the workup. These intermediates were converted directly through their acid chlorides to the desired aminoacylation products via reaction with benzene in CH_2Cl_2 in the presence of $AlCl_3$. Chromatography on silica gel under flash conditions provided relatively pure products.

2-[(Methoxycarbonyl)amino]-1-phenylpropanone (14, R = CH_3). The yield of **14** as an oil after chromatography was 58%: NMR ($CDCl_3$) δ 1.4 (3 H, d, *J* = 7 Hz), 3.7 (3 H, s), 5.4 (1 H, p, *J* = 7 Hz), 5.9 (1 H, brs), 7.3–8.1 (5 H, m); high-resolution mass spectrum, calcd m/e 207.0895; found *m/e* 207.0887.

(*S*)-2-[(Methoxycarbonyl)amino]-1-phenylpropanone [(*S*)-14, R = CH_3]. The yield of (*S*)-**14** as an oil after chromatography was 52%: $[\alpha]^{25}_D$ −11.5° (*c* 1.08, $CHCl_3$); high-resolution mass spectrum, calcd m/e 207.0895, found m/e 207.0887. Slight amounts of the *R* enantiomer (3–5%) were detected by chiral shift NMR analysis, indicating a chiral purity of 95–97%.

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