Asymmetric Synthesis of (S)- and (R)-[2-$^2H_1$]Glycine via Photolysis of Optically Active Chromium Carbene Complexes: A Comparison of Stereoselectivity between Chromium Ketene Complexes, Ketenes, and Ester Enolates

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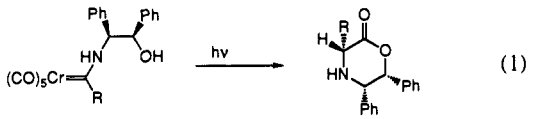
Abstract: (S)- and (R)-[2-$^2H_1$]glycine ("chiral glycine") were synthesized in good yield with high deuterium incorporation and ee's of 82–86% by two different routes. Photolysis of optically active oxazolidine carbene chromium complexes and lithiation–deuteration of optically active α-oxazolidinone acetic esters were carried out. The stereoselectivities of the reactions of ketenes and chromium-bound ketenes with methanol-*d* were compared.

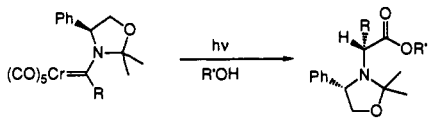
Introduction

We have recently reported two related approaches to the diastereoselective synthesis of optically active α-amino acids (eq 1,[1] eq 2[2]). Both involve photolysis of optically active chromium aminocarbene complexes, and whatever the detailed mechanism, the newly formed stereogenic center must be formed by an asymmetric protonation. Stereoselectively deuterated α-amino acids should be directly available by either procedure by simple substitution of the proton source (R'OH) with a source of deuterium (R'OD). Of particular interest is "chiral glycine", [2-$^2H_1$]glycine, an important substance for the study of biochemical reactions and the target of several recent syntheses.[3-5] The synthesis of chiral glycine using the reactions in eqs 1 and 2 would provide the most stringent test of asymmetric deuteration, since the prochiral center of the intermediate is the least sterically biased toward the incoming deuterium. The results of studies directed toward the synthesis of chiral glycines, as well as studies designed to provide insight into the requirements for asymmetric induction in these systems, are described below.



(1)

70-90% de

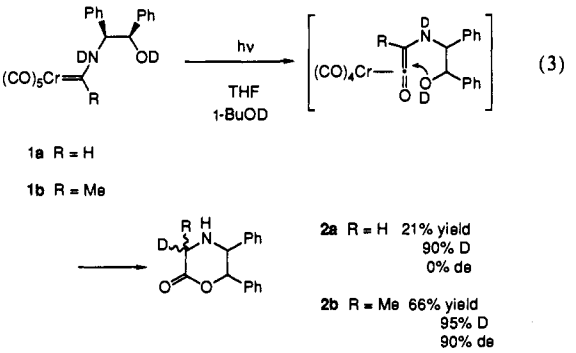


(2)

≥97% de

Results and Discussion

Attempts to prepare deuterated glycines via the chemistry in eq 1 were plagued by a number of difficulties. Although high deuterium incorporation should be readily achieved by simply exchanging the OH and NH protons in carbene complex **1a** for deuterium, this proved remarkably difficult. However, by stirring complex **1** with 10 equiv of methanol-*d*, evaporating the solvent, repeating the cycle once, and carrying out the photolysis in THF as solvent in the presence of 50 equiv of *tert*-butyl alcohol-*d*, deuterium incorporation of >90% was achieved (eq 3). Because



(3)

of chromium residues, the crude reaction mixture could not be directly analyzed. Because unsubstituted oxazinone **2a** is relatively unstable, purified yields of only 25–30% are obtained. Worse yet, the product was a 1:1 mixture of diastereoisomers, the product having been formed with virtually no stereoselectivity. This stands in marked contrast to the high (77–82%) asymmetric induction observed in the catalytic reduction of the related α-bromo-oxazinone,[5] a process involving the same chiral auxiliary but with quite a different mechanism for formation of the new stereogenic center.

This lack of stereoselectivity was unexpected, given the high stereoselectivity observed when R ≠ H.[1] To ascertain whether deuterium transfer could occur stereoselectively in this system, the corresponding deuterated alanine precursor **1b** was prepared and photolyzed (eq 3). The resulting oxazinone **2b** was considerably more stable than **2a** and was obtained in good yield with high deuterium incorporation and high diastereoselectivity. Thus, replacing hydrogen in **1** with a methyl group profoundly influenced the stereochemical outcome of this reaction.

In contrast, the synthesis of chiral glycine by the chemistry in eq 2 was quite efficient (eq 4). Photolysis of (R) or (S) carbene complex **3** in methanol-*d*/acetonitrile at −20 °C produced deuterated glycine precursors **4** in excellent chemical yield with almost complete monodeuteration and high stereoselectivity. The absolute stereochemistry of **4** was shown to be (R,R) and (S,S), respectively, by removal of the oxazolidine protecting group and conversion of the free amino acid salt to its (−)-camphanyl amide **6**.[6] The diastereomeric excess of **4** correlated well with the enantiomeric excess observed, in this manner, for **6**. Thus, (S)-[2-$^2H_1$]glycine with >97% D incorporation and 84% ee could be synthesized in 74% overall yield from (S) carbene **3**. The (R)

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(2) Hegedus, L. S.; Schwindt, M. A.; DeLombaert, S.; Imwinkelried, R. *J. Am. Chem. Soc.* **1990**, *112*, 2264.
(3) Hamon, D. P. G.; Razzino, P.; Massy-Westropp, R. A. *J. Chem. Soc., Chem. Commun.* **1991**, 332; by reduction of optically active α-bromo amino esters with Bu_3SnD.
(4) Ramalingam, K.; Nanjappan, P.; Kalvin, D. M.; Woodard, R. W. *Tetrahedron* **1988**, *44*, 5597 and references therein; by asymmetric borane reduction of deuterioaldehyde.
(5) Williams, R. M.; Zhai, D.; Sinclair, P. J. *J. Org. Chem.* **1986**, *51*, 5021; by catalytic D_2 reduction of optically active bromooxazinones.
(6) Armarego, W. L. F.; Milloy, B. A.; Pendergast, W. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2229.

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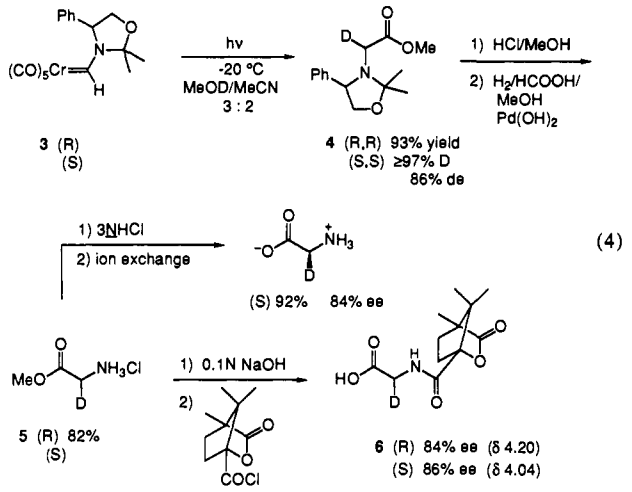
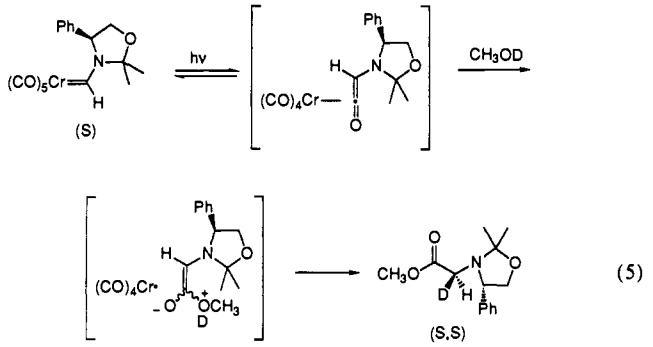
enantiomer was synthesized in an identical manner from (*R*)-**3**.



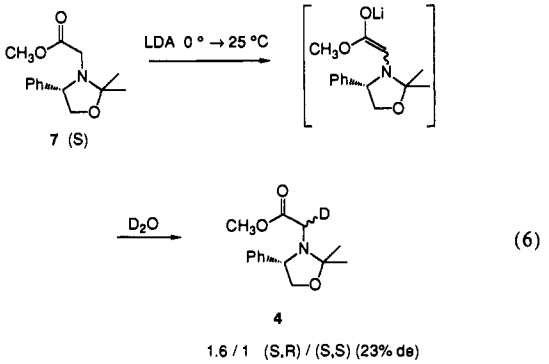
(4)

The reaction in eq 4 is thought to proceed by nucleophilic attack of the alcohol on a photogenerated chromium ketene[1,2] complex, with the new stereogenic center being formed by protonation (deuteration) of the resulting chromium-complexed zwitterion (eq 5). We have previously[7] shown that chromium had no apparent effect on the stereoselectivity of cyclobutanone formation (olefin/ketene), but that it played a major role in the stereoselectivity of β-lactam formation[8] (ketene/imine) by stabilizing the zwitterionic intermediate in this reaction. The role of chromium in the stereoselectivity of this amino acid formation was next addressed.



(5)

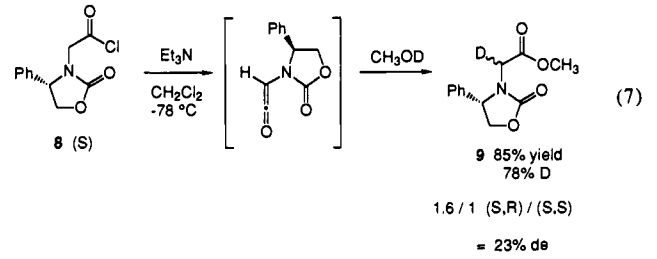
Methyl glycinate **7**, prepared by photolysis of (*S*)-**3** in methanol, was treated with lithium diisopropyl amide (LDA) at 0 °C and was allowed to warm to room temperature to generate the lithium enolate. This solution was cooled to 0 °C and quenched with D_2O to produce the monodeuterated glycine derivative **4** in 60–70% yield, with 60–70% deuterium incorporation (eq 6). The product



(6)

was a 1.6:1 mixture of diastereoisomers with the (*S*,*R*) diastereoisomer being the major one (δ 3.27 vs δ 3.20 for (*S*,*S*)). Thus, protonation of the ester enolate was relatively nonstereoselective and slightly favored the *opposite* diastereoisomer from that favored by the photolytic reaction of complex **3**. This experiment provided little insight into the role of chromium, since protonation of an enolate need not proceed with the same stereoselectivity as nucleophilic addition to a ketene (see below).

It was not possible to generate the "free" oxazolidine ketene corresponding to the chromium-bound analogue in eq 5 for direct assessment of the role of chromium in these reactions. However, comparison in the closely related *oxazolidinone* ketene system was possible and proved instructive (eqs 7–9).



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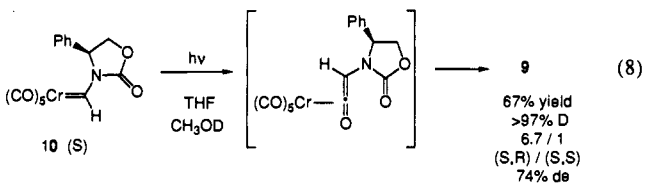

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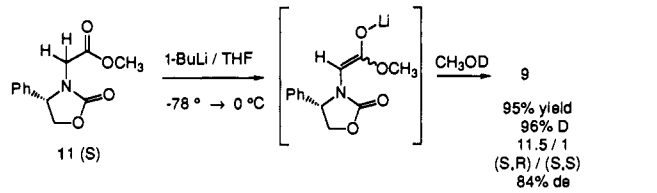

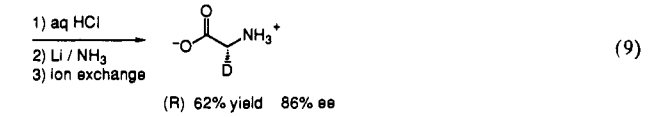

(9)

Treatment of oxazolidinone acid chloride **8**[9] with triethylamine to produce the ketene[10] followed by addition of methanol-*d* produced glycinate derivative **9** in good chemical yield, with reasonably good deuterium incorporation (eq 7). However, the diastereoselectivity was very low and slightly favored the (*S*,*R*) diastereoisomer. (The absolute stereochemistry of the products was determined by hydrolysis of the oxazolidine ring in (*S*,*S*)-**4** to the amino alcohol followed by conversion to the *oxazolidinone* (*S*,*S*)-**9** by treatment with triphosgene. This diastereoisomer was the *minor* component of all reactions involving the *oxazolidinone* auxiliary.) In contrast, photolysis of the (*S*) oxazolidinone carbene complex **10**[8] in the presence of methanol-*d* gave a fair yield of completely deuterated **9** with a very much higher stereoselectivity (74% de vs 23% de) (eq 8). Again, the (*S*,*R*) diastereoisomer was the major product. Remarkably, the most efficient production of **9** was by generating the ester enolate and quenching with methanol-*d* (eq 9). Thus, treatment of (*S*)-**11** with *t*-BuLi followed by quenching with methanol-*d* produced an excellent crude yield of **9**, with 96% D incorporation and a de of 84%, again favoring the (*S*,*R*) diastereoisomer. Hydrolysis of the ester by heating at reflux in 1:1 THF/1 N HCl, followed by reductive cleavage of the oxazolidinone (Li/NH_3),[9] purification by ion-exchange chromatography, and flash chromatography (Si gel, 5:1 95% $EtOH/H_2O$), gave (*R*)-[2-$^2H_1$]glycine in (from **11**) 62% overall yield, with an ee of 85%. (The absolute configuration and the ee were determined as above by conversion to the camphanyl amide and integration of the ^1H NMR methane signals at δ 4.04

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(minor, *S*) and δ 4.20 (major, *R*)).

These results with the oxazolidinone chiral auxiliary stand in marked contrast to those observed with the oxazolidine chiral auxiliary, and they illustrate several points made previously.[8] Most notable in the context of this study is that the oxazolidine-derived ketene (eq 4) induces absolute stereochemistry *opposite* to that of the oxazolidinone-derived ketene (eqs 8 and 9), indicating that the primary determinant of the absolute stereochemistry of the new stereogenic center is the precise structure of the chiral auxiliary. Since the oxazolidine and oxazolidinone chiral auxiliaries differ markedly both sterically and electronically, this difference in stereoselectivity is not surprising, although difficult to explain. A comparison of the results in eqs 7 and 8 confirms previous assertions[1,2,7,8] that photolysis of chromium carbene complexes does not generate free ketenes and that complexation to chromium influences the degree but not the sense of stereoselection at the center adjacent to the chiral auxiliary. Finally, protonation of the lithium enolates of protected α-amino acid esters is not a good model for the addition of alcohols to the structurally analogous ketenes, in that both the degree and the absolute sense of asymmetric induction in the two cases can be quite different (e.g., eq 7 vs eq 9; eq 9 vs eq 6).

Without a detailed understanding of the precise mechanisms involved in each of these reactions, rationalization of the differences observed in stereoselectivity is difficult, and arguments based on two-dimensional drawings are hazardous. An examination of three-dimensional, space-filling models is of little use as well, so understanding of stereoselectivity must await further studies.

In summary, two new, efficient syntheses of optically active glycine (eqs 4 and 9) have been developed, and the role of the chiral auxiliary and of the presence or absence of complexation to chromium in the stereoselectivity of the reactions has been clarified.

Experimental Section

General Procedures. Melting points were taken on a Mel-Temp apparatus and are uncorrected. A Bruker IBM-270 NMR spectrometer was used for the 270-MHz ^1H NMR and 68-MHz ^{13}C NMR spectra. A Bruker ACE-300 NMR spectrometer was used for the 300-MHz ^1H NMR and 75-MHz ^{13}C NMR spectra. IR spectra were recorded on a Beckman 4240 spectrophotometer.

Photolysis reactions were carried out in Pyrex test tubes or Pyrex pressure tubes placed at a distance of 10 cm from a Conrad-Hanovia 7825 medium-pressure mercury lamp operating at 450 W, which was placed in a water-cooled immersion well. A Conrad-Hanovia 7830-C power supply was used. Reactions run under CO pressure were saturated with CO (3 cycles to 60 psi of CO) and were photolyzed under 60 psi of CO. Oxidation of reaction mixtures was carried out by saturating a diethyl ether/hexane solution of the crude product with air and oxidizing it in a light box equipped with six 20-W Vitalite fluorescent lamps until most of the chromium residue had turned brown and precipitated (usually overnight).

Materials. Tetrahydrofuran (Fischer, reagent grade) was predried over CaH_2 and distilled from benzophenone ketyl under a nitrogen atmosphere just prior to use. Methylene chloride was distilled over CaH_2. Hexane (technical grade) was distilled at atmospheric pressure. Acetonitrile (Fischer) was distilled over CaH_2 and stored over 4-Å molecular sieves. (1*S*)-(−)-Camphanic chloride, 4-(dimethylamino)pyridine, methyl alcohol-*d* (MeOD, 99.5% D), *tert*-butyl alcohol-*d* (*t*-BuOD, 98% D), triphosgene (Aldrich), and chromium hexacarbonyl (Pressure Chemical) were used without further purification. Carbene complexes **1a**,**b**,[1] **3**,[11] **10**,[8] and [(*S*)-2-oxo-4-phenyl-3-oxazolidinyl]acetyl chloride (**8**)[9] were prepared by literature procedures.

Photolysis of Chromium Carbene Complex 1a in the Presence of *t*-BuOD After Proton–Deuterium Exchange. The chiral carbene complex **1a** (87.3 mg, 0.21 mmol) was placed in a predried Pyrex test tube and was taken up in MeOD (0.85 mL, 100 equiv) under argon. After being purged several times with argon, the solution was allowed to stand at room temperature in the dark overnight. The solvent was removed and the residue dried under vacuum for 9 h in the dark. Argon gas was introduced, and MeOD (0.85 mL, 100 equiv) was again added. The above procedure was then repeated. After removal of the solvent, the residue was taken up in freshly distilled THF (10.5 mL), and 4-(dimethylamino)pyridine (41.4 mg, 0.34 mmol) and *t*-BuOD (1.0 mL, 11 mmol, 50 equiv) were added. The solution was purged with argon and irradiated for 13 h. The dark yellow solution was concentrated and quickly chromatographed on silica gel (hexane/EtOAc 2:1 to ~0:1) to give 10.9 mg (21%) of the product as a pale yellow oil. The product was determined to have 91% deuterium incorporation and to be a mixture of two isomers (ca. 1:1 ratio): ^1H NMR (270 MHz, $CDCl_3$) δ 1.89 (br s, 1 H, NH), 4.00 and 4.08 (two br s, 1:1 ratio, 1.09 H, CHD), 4.62 (br d, *J* = 4 Hz, 1 H, C*H*Ph), 5.67 (d, *J* = 4 Hz, 1 H, OC*H*Ph), 6.80 (m, 2 H, Ph), 6.91 (m, 2 H, Ph), 7.19 (m, 6 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$) δ 48.4 (br, CHD), 60.7 (NC), 84.6 (OC), 126.6, 127.4, 127.7, 128.2, 128.3, 129.4, 135.1, 137.3 (ArC), 167.8 (CO); IR (film) ν 1738 cm^{-1}.

Photolysis of Chromium Carbene Complex 1b in the Presence of *t*-BuOD. The above procedure was used to produce 21.8 mg (66%) of oxazinone **2b** from 52.8 mg (0.122 mmol) of chromium carbene complex, 0.5 mL (12 mmol) of MeOD, 6.1 mL of THF, 25.5 mg (0.21 mmol) of 4-(dimethylamino)pyridine, and 0.5 mL (5.3 mmol) of *t*-BuOD. The product was determined to have 95% deuterium incorporation and a diastereomeric excess of 90% by ^1H NMR analysis. The unlabeled material was observed at δ 4.03 (0.05 H) as a broad signal and two methine protons of the anti isomer were detected at δ 4.73 and 5.72 (0.05 H). **2b**: ^1H NMR (270 MHz, $CDCl_3$) δ 1.64 (br s, 3 H, CH_3CD), 1.72 (br, 1 H, NH), 4.68 (br d, *J* = 4 Hz, 1 H, NC*H*Ph), 5.62 (d, *J* = 4 Hz, 1 H, OC*H*Ph), 6.79 (m, 2 H, Ph), 6.90 (m, 2 H, Ph), 7.16 (m, 6 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.1 (Me), 54.4 (t, $J_{(CD)}$ = 19 Hz, CDMe), 61.8 (NC), 84.4 (OC), 127.5, 127.6, 128.1, 128.3, 135.3, 137.8 (ArC), 171.2 (CO); IR (film) ν 1726 cm^{-1}.

Photolysis of Chromium Carbene 3 in the Presence of MeOD. Synthesis of (*S*,*S*)- and (*R*,*R*)-4. The chiral aminocarbene complex **3** (*S* or *R*) (0.2 g, 0.49 mmol) and 30 mL of a 3:1 mixture of CH_3CN/MeOD were placed in an oven-dried pressure tube. The solution was photolyzed for 12 h under CO pressure (60 psi). The solvent was concentrated under reduced pressure, and the crude material was oxidized according to the general procedure. The solution was filtered through Celite (EtOAc wash), and the filtrate was concentrated to yield a colorless oil (118 mg, 98%).

The ^1H NMR of the spectrum sample showed the two diastereoisomers in a ratio of 10:1 (82% de). The major isomer was (*S*,*S*) or (*R*,*R*), depending on whether the (*S*) or (*R*) carbene (**3**) was used. The deuterium incorporation was determined to be >97% by ^1H NMR analysis. When the photolysis reaction was carried out at −20 °C (ethylene glycol bath) and photolyzed for 63 h, the product was obtained in a 93% yield with a de of 86%: ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 3.20 (t, $J_{(HD)}$ = 1.8 Hz, 0.92 H), 3.27 (t, $J_{(HD)}$ = 1.8 Hz, 0.08 H, CHD), 3.44 (s, 3 H, OCH_3), 3.60 (t, *J* = 8 Hz, 1 H, OCH_2), 4.10 (t, *J* = 7 Hz, 1 H, OCH_2), 4.24 (t, *J* = 7 Hz, 1 H, NC*H*Ph), 7.19–7.35 (m, 5 H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2 (CH_3), 27.7 (CH_3), 47.9 (t, $J_{(CD)}$ = 20.6 Hz, *C*HD), 51.4 (CH_3O), 65.5 (CH_2O), 72.0 (*C*HN), 95.2 ($C(CH_3)_2$), 127.8, 127.9, 128.4, 139.5 (Ph), 172.1 (CO); IR (film) ν 1748 (C=O) cm^{-1}.

(*S*)-Methyl Glycinate Hydrochloride Salt 5. To a solution of (*S*,*S*)-**4** (316 mg, 1.26 mmol) in 10 mL of methanol was added 9 mL of HCl (0.2 N). The reaction was stirred for 0.5 h at room temperature. The solvent was removed under reduced pressure, yielding 300 mg (97%) of the open-chain amino acid ester: ^1H NMR (300 MHz, D_2O, internal standard HDO, δ 4.85) δ 3.80 (s, 3 H, OCH_3), 3.86 (s br, CHD), 4.08 (m, 2 H, CH_2), 4.53 (m, 1 H, CHPh), 7.54 (s br, Ph).

This product (300 mg, 1.22 mmol) and 20 mL of a formic acid solution (4% in methanol) were placed in a pressure tube. Pearlmans's catalyst (100 mg) was added and a pressure head was attached. The mixture was purged with H_2 (3 cycles) and stirred for 36 h at 40 psi of H_2. The reaction mixture was filtered through a glass frit, and the filtrate was concentrated. The residue was dissolved in 8 mL of HCl (0.1 N) and washed with CH_2Cl_2 (3 × 10 mL). The aqueous phase was concentrated under reduced pressure to give 1.18 mmol (97%) of the white solid, (*S*)-**5**: ^1H NMR (300 MHz, D_2O, internal standard HDO, δ 4.85) δ 3.92 (s, 3 H, OCH_3), 4.02 (s br, 1 H, CHD). (*R*)-**5**: ^1H NMR (300 MHz, D_2O) δ 3.93 (s, 3 H, OCH_3), 4.07 (s br, 1 H, CHD).

Determination of Stereochemistry. Synthesis of 6. (*S*)-Methyl glycinate hydrochloride salt (**5**) (30 mg, 0.24 mmol) was dissolved in 5 mL of 0.1 N sodium hydroxide and was added to a stirred solution of (−)-camphanic chloride (65 mg, 0.3 mmol) in 3 mL of toluene at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then 4.5 h at 25 °C. The reaction mixture was washed with $CHCl_3$ (5 mL), and the aqueous phase was acidified with 1 N HCl. The resulting solution was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were combined and concentrated. The product was analyzed by NMR spectroscopy. ^1H NMR (300 MHz, $CDCl_3$) for the proton of glycine: (*S*) 4.04 (d, *J* = 5 Hz, 0.93 H), (*R*) 4.20 (d, *J* = 5 Hz, 0.07 H), 86% de.

(11) Schwindt, M. A.; Lejon, T.; Hegedus, L. S. *Organometallics* **1990**, *9*, 2814.

Synthesis of (*S*)-[2-$^2H_1$]Glycine. (*S*)-Methyl glycinate hydrochloride salt (**5**) (150 mg, 1.18 mmol) was dissolved in 10 mL of HCl (3 M) and heated at reflux for 2 h. The solution was concentrated to get the hydrochloride salt of glycine. The HCl salt was dissolved in water and eluted with 1 N NH_4OH through an ion-exchange resin (Dowex 50W-X8, 20–50 mesh, in H^+ form after washing with 1 N NaOH and 10% H_2SO_4), yielding 86 mg (92%) of a white solid: ^1H NMR (300 MHz, D_2O) δ 3.59 (t, $J_{(HD)}$ = 2.2 Hz); mp 230 °C dec (lit. mp 234 °C dec).[6]

Synthesis of Methyl Glycinate (7). The (*S*) carbene (**3**) was photolyzed as described for the synthesis of **4**, except nondeuterated methanol was used in the reaction. The product was obtained in 93% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 3.20 (d, J = 16.0 Hz, 1 H, CH_2), 3.29 (d, J = 16.0 Hz, 1 H, CH_2), 3.43 (s, 3 H, OCH_3), 3.59 (t, J = 8 Hz, 1 H), 4.07 (t, J = 7 Hz, 1 H), 4.24 (t, J = 7 Hz, 1 H), 7.18–7.36 (m, 5 H, Ph); IR (film) ν 1741 (s, C=O) cm^{-1}.

Synthesis of (*S*,*R*)- and (*S*,*S*)-4 via Methyl Ester 7. To a solution of lithium diisopropylamine (LDA) (0.25 mmol) (prepared in situ from *n*-BuLi and diisopropylamine) in 10 mL of THF at 0 °C was added a solution of the ester **7** (49 mg, 0.2 mmol) in 5 mL of THF via syringe. The solution was warmed to room temperature and stirred for 2 h. The yellow solution was cooled to 0 °C, and 30 mL of D_2O was added dropwise via syringe. The solution was stirred at room temperature for 0.5 h. THF was removed under reduced pressure, and the aqueous solution was extracted with CH_2Cl_2. The organic layers were collected, dried ($MgSO_4$), filtered, and concentrated to give 30 mg (62%) of a 1.6:1 mixture of diastereoisomers, where (*R*,*S*) or (*S*,*R*) (depending on the starting material) was the major product. The product was determined to have 60–70% deuterium incorporation and a de of 23% by ^1H NMR analysis. The spectroscopic data for this oil was the same as reported previously for **4**. ^1H NMR (270 MHz, $CDCl_3$): δ 3.20 (t, $J_{(HD)}$ = 1.8 Hz, 0.39 H, CHD), 3.27 (t, $J_{(HD)}$ = 1.8 Hz, 0.61 H, CHD).

Synthesis of 9 via Acid Chloride 8. Triethylamine (2.0 equiv) was added to a −78 °C solution of the (*S*) acid chloride **8**[9] (50 mg, 0.20 mmol) in CH_2Cl_2 (3 mL). The reaction was stirred at −78 °C for 15 min under an argon atmosphere, and then MeOD (32 μL, 0.80 mmol) was added via syringe. The solution was stirred for 1 h at −78 °C and then for 2 h at 0 °C. The solution was filtered through a short pad of silica gel and washed through with ethyl acetate. The reaction mixture was concentrated, and an ^1H NMR spectrum was obtained. The product was determined to have 78% deuterium incorporation and a diastereomeric excess (de) of 23% by ^1H NMR analysis. The major isomer had the (*S*,*R*) configuration: ^1H NMR (300 MHz, $CDCl_3$) δ 3.38 (s br, 0.48 H, CHD), 3.71 (s, 3 H, OCH_3), 4.15 (t, J = 8.3 Hz, 1 H, CH_2O), 4.27 (s br, 0.30 H, CHD), 4.72 (t, J = 8.8 Hz, 1 H, CH_2O), 5.07 (t, J = 8.4 Hz, 1 H, NCHPh), 7.30 (m, 2 H, Ph), 7.41 (m, 3 H, Ph), absorptions from nondeuterated material appeared at δ 3.40 (d, J = 17.9 Hz, 0.22 H, CH_2) and 4.29 (d, J = 17.9 Hz, 0.22 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.7 (t, $J_{(CD)}$ = 21.5 Hz, CHD), 52.2 (OCH_3), 59.9 (CH_2O), 70.1 (CHN), 127.1, 129.2, 129.3, 136.6, 158.3 (Ph), 168.7 (C=O); IR (film) ν 1740 (s, C=O), 1762 (s, C=O) cm^{-1}.

Conversion of (*S*,*S*)-4 to (*S*,*S*)-9. Hydrochloric acid (9 mL, 0.2 N) was added to a solution of (*S*,*S*)-**4** (316 mg, 1.26 mmol) in 10 mL of methyl alcohol. The solution was stirred for 0.5 h at room temperature. The solution was concentrated under reduced pressure to give 300 mg (98%) of the ring-opened amino alcohol. This compound was subsequently used without further purification. Diisopropylethylamine (5.0 equiv) was added to a 0 °C solution of the ring-opened amino alcohol (29 mg, 0.14 mmol) in 2 mL of CH_2Cl_2 under an argon atmosphere. A solution of triphosgene (41 mg, 0.138 mmol) in CH_2Cl_2 (2 mL) was added via syringe, and the solution was stirred for 2 h at 0 °C and 14 h at room temperature. The reaction mixture was then passed through a short pad of silica gel and washed through with EtOAc. The solution was concentrated to give 0.025 g (0.10 mmol, 77%) of **9** as a golden oil. The product was determined to have 92% deuterium incorporation and a de of ~74%. The major isomer had the (*S*,*S*) configuration: ^1H NMR (300 MHz, $CDCl_3$) δ 3.38 (s br, 0.13 H, CHD), 4.27 (s br, 0.87 H, CHD).

Synthesis of 9 from Carbene Complex 10. The (*S*) complex **10** (100 mg, 0.27 mmol) was added directly to a degassed solution of MeOD (1 mL, 25 mmol) in dry THF (10 mL). The solution was irradiated under 80 psi of CO at room temperature for 1 h. The solution was concentrated, and the crude material was oxidized as described in the general procedure. This solution was then filtered through Celite (EtOAc wash) and concentrated. The product was purified by preparative TLC (2:1 hexane/EtOAc) to give 0.043 g (0.18 mmol, 67%) of the colorless oil. The product was determined to have >97% deuterium incorporation and a de of 74% by ^1H NMR analysis. The major isomer had the (*S*,*R*) configuration: ^1H NMR (300 MHz, $CDCl_3$) δ 3.38 (s br, 0.87 H, CHD), 4.27 (s br, 0.13 H, CHD).

Synthesis of (*S*)-11. This compound was prepared directly from a literature procedure by replacing methyl bromoacetate for ethyl bromoacetate.[9] The product was purified by flash chromatography on silica gel (2:1 hexane/EtOAc) to give 92% of the clear oil: ^1H NMR (270 MHz, $CDCl_3$) δ 3.39 (d, J = 18.0 Hz, 1 H, CH_2), 3.72 (s, 3 H, CH_3), 4.15 (t, J = 8.3 Hz, 1 H, CH_2O), 4.30 (d, J = 18.0 Hz, 1 H, CH_2), 4.72 (t, J = 8.7 Hz, 1 H, CH_2O), 5.06 (t, J = 8.3 Hz, 1 H, NCH), 7.30 (m, 2 H, Ph), 7.41 (m, 3 H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.9 (CH_2CO), 52.2 (OCH_3), 60.0 (OCH_2), 70.2 (CHN), 127.2, 129.3, 129.4, 136.7, 158.4 (Ph), 168.8 (C=O); IR (film) ν 1746 (s, C=O) cm^{-1}; $[\alpha]_D$ +153.7 (c = 2.04, $CHCl_3$).

Synthesis of 9 via (*S*) Methyl Ester 11. A solution of (*S*) methyl ester **11** (545 mg, 2.32 mmol) in THF (24 mL) was cooled to −78 °C under an argon atmosphere. *t*-BuLi (1.47 M, 1.6 mL) was added dropwise followed by the addition of methanol-*d* (943 μL, 23.2 mmol). The solution was stirred for 15 min at −78 °C and then for 10 min in a −20 °C bath. A saturated solution of NH_4Cl (4 mL) was added, and the solution was warmed to room temperature. The solution was diluted with 25 mL of H_2O and extracted with EtOAc (3 × 20 mL). The organic layers were collected, dried ($MgSO_4$), filtered, and concentrated to give 500 mg (2.11 mmol, 91%) of a slightly golden oil. The product was determined to have 96% deuterium incorporation and a de of 84% by ^1H NMR analysis. The major isomer had the (*S*,*R*) configuration: ^1H NMR (300 MHz, $CDCl_3$) δ 3.38 (t, $J_{(HD)}$ = 2.3 Hz, 0.92 H, CHD), 4.27 (s br, 0.08 H, CHD).

Synthesis of (*R*)-[2-$^2H_1$]Glycine from (*S*,*R*)-9.[9] A solution of (*S*,*R*)-**9** (500 mg, 2.1 mmol) in 20 mL of 1:1 THF/1 N HCl was heated to reflux temperature for 16 h. The solution was cooled to room temperature and extracted with EtOAc (3 × 20 mL). The organic layers were collected, dried ($MgSO_4$), filtered, and concentrated to give a tacky tan oil. ^1H NMR analysis confirmed complete conversion of the methyl ester to the carboxylic acid. This compound was subsequently used without further purification. A solution of the carboxylic acid (2.1 mmol) in THF (10 mL) and *tert*-butyl alcohol (970 μL, 10.5 mmol) was added by syringe to a −78 °C solution of lithium (87 mg, 12.6 mmol) dissolved in distilled liquid ammonia (~30 mL). After stirring for 10 min at −78 °C, the reaction was quenched by the addition of powdered ammonium chloride (674 mg, 12.6 mmol). Ammonia was allowed to distill from the reaction mixture, and THF was removed under reduced pressure. The concentrate was dissolved in 10 mL of H_2O and acidified with 1 N HCl. The aqueous solution was washed with Et_2O (2 × 10 mL) and then concentrated under reduced pressure. The free amino acid was isolated by ion-exchange chromatography and further purified by flash chromatography on silica gel (5:1 95% EtOH/H_2O) to obtain 107 mg (1.41 mmol, 67% from **9**) as a white solid: mp 230 °C dec (lit.[6] mp 234 °C dec); ^1H NMR (300 MHz, D_2O, internal standard HDO, δ 4.85) δ 3.58 (t, J = 2.2 Hz, CHD); ^{13}C NMR (75 MHz, D_2O, MeOH internal standard δ 50.2) 42.5 (t, $J_{(CD)}$ = 21.7 Hz, CHD), 173.8 (C=O).

The product was determined to have an enantiomeric excess (ee) of 85% by conversion to the camphanyl amide **6** (as above) and analysis by ^1H NMR spectroscopy (the free amino acid was converted to **6** using the same procedure as above for **5** to **6**).

Acknowledgment. Support for this research under Grant 2 RO1 GM26178-12 from the National Institutes of General Medical Sciences (Public Health Service) is gratefully acknowledged. Dr. E. Lastra wishes to thank the Spanish M. E. C. and the Fulbright Foundation for support in the form of a fellowship. Dr. Y. Narukawa thanks Shionogi & Co., Ltd. for support.