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A Practical Large Scale Chemical Synthesis of Chiral Glycines

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SUMMARY: (*R*)- and (*S*)-[2-^{2}H]glycine of high chiral purity were synthesized in large quantities in ≈ 40% overall yield from readily available starting materials *via* a totally chemical procedure. Reduction of either [1-^{2}H]-furfural or [1-^{2}H]-4-methoxybenzaldehyde with either (+) or (-)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane gave chiral arylmethyl alcohols which were converted into their respective phthaloyl amino derivatives of the opposite configuration at the methylene carbon *via* the Mitsunobu reaction. The aromatic groups were oxidatively unmasked to give their corresponding glycine derivatives by either ozone or ruthenium tetraoxide oxidation.

In connection with our interest in and need for synthetic quantities of stereospecific deuterium-labelled glycine, we have developed a practical large-scale chemical synthesis of both isomers of chiral glycine.

Interest in the synthesis of chiral glycine and other regio- and stereospecific deuterium-labelled amino acids stems from the fact that incorporation of these amino acids into various peptides allows for the total assignment of all hydrogen atoms in the peptide, a necessary condition for the use of various one- and two-dimensional ^{1}H-nmr techniques such as measurement of NOE interactions and NOSEY experiments[1] to determine intramolecular distances in peptides. The inter-atomic distances obtained *via* these techniques are utilized as constraints for distance geometry calculations to generate families of 3D solution conformations.[2] These labelled amino acids are equally important probes for the elucidation of biosynthetic pathways and for studying the detailed enzymatic mechanisms for these same transformations.[3]

At least 11 routes for the synthesis of chiral glycine have been reported to date.[4-18] These methods may be roughly divided into four different categories depending on the method used to introduce the chirality: 1. Those that involve a stereoselective exchange of the diastereotopic protons of glycine with ^2H_2O in an inert Co(III) complex.[4,5] 2. Those that use either an enzyme(s) or a microorganism for the introduction of chirality followed (and/or preceded) by chemical elaboration.[6-12] 3. Methods that utilize a complex chiral synthon, not commercially available, prepared in a multistep synthetic procedure which may involve several resolution steps[13,14] The chiral auxiliary may, however, be recyclable. 4. Those in which naturally-occurring chiral compounds such as D-glucose, D-ribose, L-glutamic acid or L-serine have been chemically labelled and then degraded to chiral glycine.[15-18]

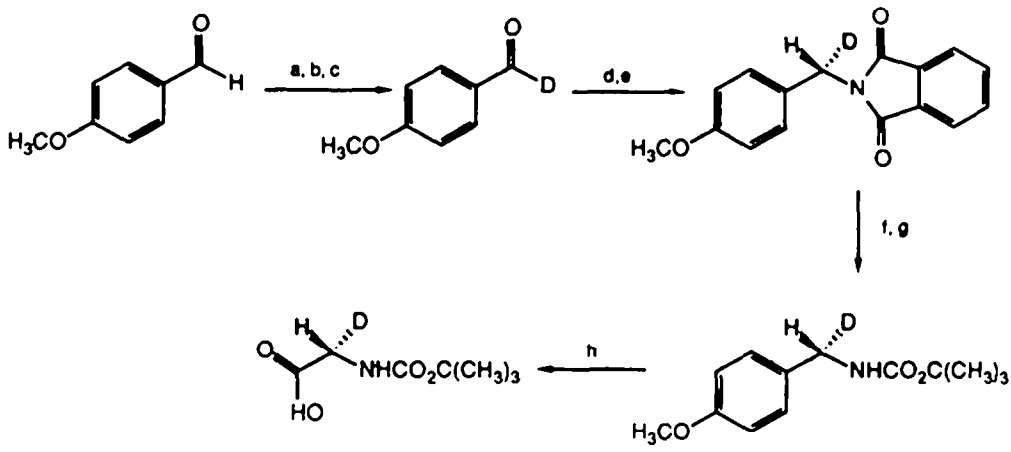
One of the newer approaches reported to synthesize chiral acetic acid[19] involved the asymmetric reduction of a suitable deuteriated substituted benzaldehyde with an asymmetric hydrogen reducing agent (or vice versa) to a chiral substituted benzyl alcohol. Since most of the methods which fall under category 2 involve either the enzymatic or microbial reduction of a deuterated aromatic aldehyde to the corresponding arylmethyl alcohol, it should be relatively simple to combine these two approaches into a suitable method for the synthesis of chiral glycine.

This paper presents the large scale, totally chemical syntheses of both isomers of chiral glycine from common economical reagents available from the usual sources in which the key step is the introduction of chirallity *via* the use of commercially available *R* or *S*- *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (marketed by the Aldrich Chemical Company under the trade name *R*- and *S*- Alpine borane). Two different deuteriated aldehydes are used to demonstrate the utility of the methodology. In both pathways, the aromatic rings, furyl and 4-methoxyphenyl, serve as masked carboxyl groups and are uncovered *via* two different oxidation protocols, one ozonolysis and the other ruthenium tetraoxide oxidation. Although the deuteriated aldehydes are commercially available (MSD Isotopes, both cost $495/5g), their preparations are also presented since the syntheses of both are

are straightforward (~ 74% overall yield) and involve only three steps, from the undeuteriated aldehyde and utilize ^2H_2O as the source of deuterium.

The preparation of the starting deuteriated aldehydes follows either of two classical procedures.[20,21] The desired [1-^{2}H]-furfural was obtained by mercury(II) salt decomposition of the 2-[^{2}H]-2-(2-furyl)-1,3-dithiane (available from quenching the lithium salt of the 1,3-dithiane derivative of furfural, prepared by standard methods,[20]

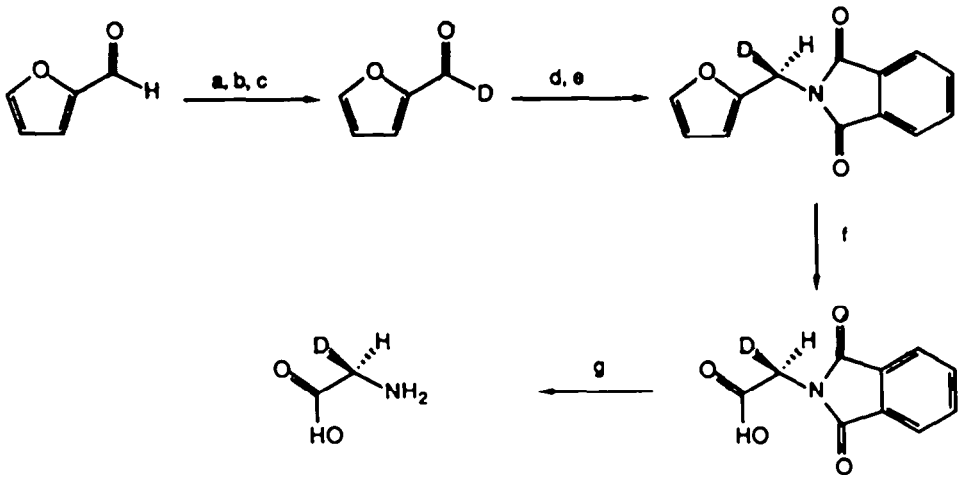
Scheme I [α]



[α] (a) Morpholine•perchlorate, morpholine, 60°C, 1h; NaCN, H_2O, 90°C, 1h; (b) NaH, THF, 50°C, 2h; D_2O; (c) 2N HCl, 100°C, 2h; (d) (*S*)-(-)-Alpine Borane, THF, 25°C, 4h; 75°C, 1h; (e) PPh3, phthalimide, diethylazidodicarboxylate, THF, 0°C, 4h; 25°C, 18h; (f) $NaBH_4$, 2-propanol, water, 25°C, 24h; glacial acetic acid, 80°C, 2h; (g) Di-butyl-dicarbonate, dioxane, water, pH 8.5, 0°C, 4h; 25°C, 18h; (h) $NaIO_4$, $RuCl_3•3H_2O$, CH_3CN, CCl_4, H_2O, 25°C, 20h.

with ^2H_2O). The [1-^{2}H]-4-methoxybenzaldehyde was prepared by quenching the sodium salt of 1-(4-methoxy-phenyl)-1-morpholinoacetonitrile, obtained by reacting morpholine perchlorate, 4-methoxybenzaldehyde, and sodium cyanide as previously described,[21] with ^2H_2O. Although the furfural was prepared *via* the dithiane procedure, it could have been prepared by the morpholinoacetonitrile method and the deuteriated anisaldehyde could have been prepared by the dithiane route. Once in hand these aldehydes were reduced with either *R* or *S*- *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane, reagents first described by Midland, et al.,[22] to give the desired chiral deuteriated arylmethyl alcohols. The *S*-Alpine-Borane presently[23] gives (*R*)-alcohols with lower %ee than the (*S*)-alcohols obtained with *R*-Alpine-Borane since the (-)-α-pinene used to prepare *S*-Alpine-Borane is less optically pure. The %ee (uncorrected for % deuteriation or %ee of the starting Alpine-Borane) of the desired alcohols are ~ 76% from the *S*-Alpine-Borane reduction and ~ 82% from the *R*-Alpine-Borane reduction. Both alcohols are converted to the corresponding chiral arylmethyl amino derivatives having the opposite configuration at the arylmethylene carbon atom *via* the procedure of Mitsunobu, et al.[24] The phthaloyl derivative of furfurylamine was subjected to ozonolysis to unmask the carboxyl group and the phthaloyl group of the chiral glycine was removed by hydrazine in ethanol.[12] The strategy for the use of ruthenium tetraoxide oxidation[25] to unmask the carboxyl group is slightly different since glycine is water soluble and the ruthenium oxidation mixture contains water. In order to avoid any solubility problems the phthaloyl group was first removed, *via* sodium borohydride reduction of the succinimide ring followed by acid hydrolysis.[26] The amine was converted to the *tert*-Boc derivative *via* standard methods.[27] The (1*S*)[1-^{2}H] *N*-*t*-Butyloxycarbonyl-4-methoxybenzylamine was subjected to ruthenium oxidation and *N*-*t*-Butyloxycarbonyl glycine was obtained. This derivative is actually preferred for peptide synthesis. The methods presented in this paper are totally interchangeable and the choice of which aldehyde,[28] the choice of which oxidation procedure and the choice of which method for the deprotection of the phthaloyl group should be based on the individual investigator's comfort with each procedure. The choice of which Alpine-Borane to use, of course, is dictated by which chiral glycine one wishes to obtain. If one needs the (*R*)-[2-^{2}H]glycine, one should use *R*-Alpine Borane as the reducing reagent and vice versa.

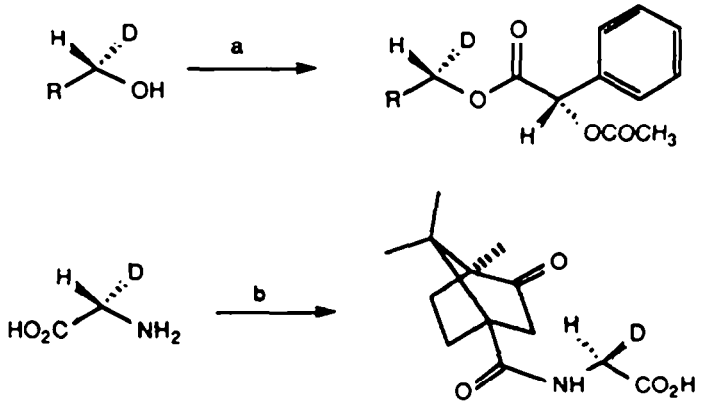
Scheme II [α]



[α] (a) $HS(CH_2)_3SH$, $BF_3 \cdot Et_2O$, CH_2Cl_2, 0°C, 1h; 25°C, 18h; (b) *n*-ButylLi, THF, -78°C, 1h; -50°C, 6h; D_2O; (c) HgO, $HgCl_2$, CH_3OH, H_2O, 80°C, 4h; (d) (*R*)-(+)-Alpine Borane, THF, 25°C, 4h; 75°C, 1h; (e) PPh_3, phthalimide, diethylazidodicarboxylate, THF, 0°C, 4h; 25°C, 18h; (f) O_3, CH_2Cl_2, -78°C, 2h; 30% H_2O_2, 25°C, 18h; (g) $NH_2NH_2 \cdot H_2O$, ethanol, 80°C, 4h.

The optical purity (%ee) of the chiral arylmethyl alcohols may be checked *via* the method described by Parker[29] and the optical purity (%ee) of the glycines may be determined by any of the several published methods.[15] All the methods referenced rely on the coupling of the chiral arylmethyl alcohol or glycine (the methylene protons of both are isochronous and therefore cannot be distinguished by ^{1}H-nmr) with a readily available optically active derivatizing reagent to form a diastereomeric compound in which the now diastereotopic hydrogen atoms of both the arylmethyl alcohol and glycine are anisochronous (chemically shift different in the ^{1}H-nmr). Optical rotation values at various wavelengths for both chiral glycines and several of their derivatives have been reported.[6,7,12]

Scheme III[α]



[α] (a) DMAP(catalyst), 2(*S*)-2-acetoxy-2-phenylethanoic acid, DCC, CH_2Cl_2, 0°C, 4h; 25°C, 18h; (b) (1*R*)-(-)-camphanoyl chloride, NaOH, pH > 7, 0°C, 3h.

Experimental Section

General Methods. All melting points are obtained on a Mel-temp apparatus and are uncorrected. The ^{1}H-nmr spectra are recorded on an IBM WP-270 MHz NMR spectrometer in $CDCl_3$ and D_2O. Samples dissolved in $CDCl_3$ are reported in ppm downfield from tetramethylsilane, while samples in D_2O are reported downfield from 3-(trimethylsilyl)propionic acid sodium salt. All spectral and physical properties of the deuterated compounds are found to be comparable to the non-deuterated compounds.

All organic and inorganic reagents are purchased from the usual sources and are used without further purification. Organic solvents are dried by the standard methods. Analytical TLC plates (silica) are purchased from Analtech. The plates are visualized by ultraviolet irradiation from a Mineralight® short wave UV lamp, spraying with ninhydrin or spraying with an aqueous methanolic sulfuric acid solution (20%) followed by charring. Medium grade silica gel (Merck, 70-230 mesh) is used for column chromatography. All organic solvent extracts are dried with Na_2SO_4 and removed *in vacuo* by using a rotary evaporator (water aspirator vacuum) at 40°C unless otherwise stated.

1-(4-Methoxyphenyl)-1-morpholinoacetonitrile.

Morpholine perchlorate [prepared by the dropwise addition of perchloric acid (70%, 9.48 mL, 0.11 mol) to morpholine (9.57 g, 0.11 mol) at -15°C] in morpholine (10 mL) and 4-methoxybenzaldehyde (13.6 g, 0.10 mol) are stirred at 60°C for 1h. Sodium cyanide (5.30 g, 0.11 mol) in water (5 mL) is then added and the reaction mixture heated at 90°C for an additional 1h. The reaction mixture is cooled, poured onto ice with stirring and the colorless solid that forms is collected by suction, washed profusely with water and dried to yield 22.60 g (97.4%) of the acetonitrile derivative; mp 80-82°C [Lit.[21] mp 81-82°C]. ^{1}H-nmr $CDCl_3$ δ 2.58 (t, J = 7.0 Hz, 4H, morpholine *ortho H*), 3.68 (t, J = 7.0 Hz, 4H, morpholine *meta H*), 3.78 (s, 3H, OCH_3), 4.75 (s, 1H, benzylic *H*), 6.88 (d, J = 10.0 Hz, 2H, aromatic *ortho-H*), 7.45 (d, J = 10.0 Hz, 2H, aromatic *meta-H*).

1-[^{2}H]-1-(4-Methoxyphenyl)-1-morpholinoacetonitrile.

To a solution of 1-(4-methoxyphenyl)-1-morpholinoacetonitrile (22.60 g, 0.097 mol) in dry THF (75 mL) stirred at 25°C under nitrogen is added NaH (80%, 3.27 g, 0.109 mol) in small portions over a period of 30 min. After the addition is complete, the reaction mixture is first heated, *via* an oil bath, at 50°C for 2 h and then cooled to 0°C with an ice-salt bath at which time ^2H_2O (60 mL) is added slowly, dropwise, while maintaining the temperature at 0°C. The reaction mixture is stirred for an additional 10 min, thionyl chloride is added carefully until the solution becomes slightly acidic, and the whole mixture is poured onto ice with stirring. The colorless solid that forms is filtered, washed with water and dried to yield 20.2 g (89%) of the deuteriated analogue; mp 80-81°C [Lit.[21] mp 81-82°C for the undeuteriated compound] {>98% $^2H_2$ by ^{1}H-nmr} ^{1}H-nmr $CDCl_3$ δ 2.57 (t, J = 7.5 Hz, 4H, morpholine *ortho H*), 3.68 (t, J = 7.0 Hz, 4H, morpholine *meta H*), 3.78 (s, 3H, $OCH3$), 6.88 (d, J = 10.0 Hz, 2H, aromatic *ortho-H*), 7.45 (d, J = 10.0 Hz, 2H, aromatic *meta-H*).

[1-^{2}H]-4-Methoxybenzaldehyde.

1-[^{2}H]-1-(4-Methoxyphenyl)-1-morpholinoacetonitrile (20.2 g, 0.087 mol) is heated to reflux with 2N HCl (200 mL), *via* an oil bath, for 2 h. After cooling to 25°C, the solution is extracted with $CHCl_3$ (3 x 50 mL) and the $CHCl_3$ layer is washed with saturated aqueous $NaHCO_3$ (2 x 50 mL), water (2 x 50 mL) and dried ($MgSO_4$). After filtering, the chloroform is removed under reduced pressure to give a reddish brown oil which is vacuum-distilled (88-90°C (2.5 torr)) to afford 10.25 g (86.3%) as a colorless liquid. ^{1}H-nmr $CDCl_3$ δ 3.85 (s, 3H, OCH_3), 6.95 (d, J = 10.0 Hz, 2H, aromatic *ortho-H*), 7.78 (d, J = 10.0 Hz, 2H, aromatic *meta-H*).

2-(2-Furyl)-1,3-dithiane.

After cooling a solution of 1,3-propane dithiol (16.25 g, 0.15 mol) and furfural (14.41 g, 0.15 mol) in CH_2Cl_2 (100 mL) to 0°C, with stirring and under a nitrogen atmosphere, for 0.5h, BF_3•Et_2O (2.13 g, 0.15 mol) is added slowly. The temperature of the reaction mixture is allowed to slowly warm to 25°C and the mixture stirred for 18h. The solution is washed with a saturated $NaHCO_3$ solution (2 x 50 mL) and the organic layer dried over Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the solid which formed is recrystallized from hexanes:benzene (85:15) to furnish the title compound as colourless crystals (20.9 g, 75%), mp

42-43°C [Lit.[31] mp.43°C]; ^{1}H-nmr ($CDCl_3$) δ 2.05 (m, 2H, $SCH_2CH_2CH_2S$), 3.00 (m, 4H, $SCH_2CH_2CH_2S$), 5.20 (s, 1H, $HC(S)_2$), 6.40 (m, 2H, furyl 3*H* and 4*H*), 7.40 (m, 1H, furyl 5*H*).

2-[^{2}H]-2-(2-Furyl)-1,3-dithiane.

To a stirred solution of 2-(2-furyl)-1,3-dithiane (10 g, 0.054 mol) in anhydrous THF (220 mL), under a nitrogen atmosphere and cooled to -78°C, is added, over a period of 1h, a solution of *n*-butyllithium in hexane (1.4 M, 43 mL, 59.2 mmol). After standing for a period ≈ 6h at < -50°C, deuterium oxide (>99.8%, 20 mL) is added and the temperature of the mixture is allowed to slowly warm to 25°C. After removing the LiOD salt by decantation, the THF is removed under reduced pressure. The residue is dissolved in diethyl ether (350 mL) and washed with an aqueous solution of NH_4OH/NH_4Cl (pH = 7.0, 2 x 50 mL), water (100 mL) and dried ($MgSO_4$). The ether is then removed under reduced pressure to afford a reddish oil which solidified after standing overnight under high vacuum. The solid is dissolved in acetone treated with charcoal, filtered, and the solvent removed to give white needles (8.45 g, 84%), mp 43-44°C [Lit.[31] mp 43°C for the undeuteriated compound]; {98% $^2H_2$ by ^{1}H-nmr} ^{1}H-nmr ($CDCl_3$) δ 2.05 (m, 2H, $SCH_2CH_2CH_2S$), 3.00 (m, 4H, $SCH_2CH_2CH_2S$), 6.50 (m, 2H, furyl 3*H* and 4*H*), 7.50 (m, 1H, furyl 5*H*).

[1-^{2}H]Furfural.

To a stirred solution of 2-[^{2}H]-2-(2-furyl)-1,3-dithiane (8.45 g, 0.0452 mol) in methanol-water [9:1 (vol/vol), 250 mL), under a nitrogen atmosphere, is added solid mercuric oxide (8.81 g, 40.7 mmol) and a solution of mercuric chloride (24.54 g, 90.4 mmol) in the solvent mixture (50 mL). A voluminous white precipitate forms immediately and the mixture is heated to reflux for 4h, still under a nitrogen atmosphere, and then cooled to 25°C. The solid is removed by suction and the filtrate, after concentration to ≈ 50 mL by distillation, is extracted with dichloromethane (3 x 100 mL). The organic layer is washed consecutively with first a saturated aqueous ammonium acetate solution (2 x 100 mL) and then a saturated brine solution (2 x 50 mL). After drying over Na_2SO_4, filtration and removal of the solvent under reduced pressure, vacuum distillation afforded the deuteriated aldehyde as a colourless liquid (3.11 g, 71%); bp 103-105°C (50 torr) [Lit.[32] bp 70°C (12 torr)]; ^{1}H-nmr ($CDCl_3$) δ 6.80 (m, 1H, furyl 5*H*), 7.40 (m, 1H, furyl 4*H*), 7.80 (m, 1H, furyl 3*H*).

General Procedure for Alpine-Borane Reduction: (1*R*)-[1-^{2}H]-4-Methoxybenzylalcohol.

To a flame-dried 500 mL round-bottom flask, sealed with a rubber septum and equipped for a nitrogen atmosphere, *S*-(-)Alpine borane solution in THF (0.5 M, 250 mL, 0.125 mol) and [1-^{2}H]-4-methoxybenzaldehyde (10.25 g, 0.075 mol) are added. The mixture is stirred for 4 h at 25°C and then heated at reflux for 1 h. After cooling to 25°C, acetaldehyde (10 mL) is added and the mixture stirred for 15 min after which the solvent is removed with a rotary evaporator at 40°C with a water aspirator. The pinene is removed *in vacuo* at 0.1 torr at 50°C. The residue is dissolved in diethyl ether (100 mL) and 2-aminoethanol (7.72 g, 0.125 mol) is added while cooling at <5°C. The mixture is stirred at 25°C for 0.5 h. The precipitate which forms is removed *via* filtration, washed with anhydrous diethyl ether, and the combined ether solutions are washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The oil thus obtained is purified by silica-gel chromatography (200 g) eluting with hexanes-ethyl acetate (8:2) to yield 7.8 g (75%) of the title compound. ^{1}H-nmr ($CDCl_3$) δ 1.94 (s, 1H, -O*H*), 3.79 (s, 3H, OCH_3), 4.65 (s, 1H, $C^2H_RH_S$-OH), 6.81 (d, J = 10.0 Hz, 2H, aromatic *ortho-H*), 7.22 (d, J = 10.0 Hz, 2H, aromatic *meta-H*).

(1*S*)-[1-^{2}H]Furfurylalcohol.

The title compound is prepared from [1-^{2}H]furfural (5.0 g, 51.5 mmol), *R*- (+)Alpine borane in THF (0.5 M, 154.5 mL, 77.3 mmol) in 81.1% yield (4.1 g) following the standard procedure described above with the exception that the diethyl ether layer is not washed with water; bp 170°C ^{1}H-nmr ($CDCl_3$) δ 1.72 (d, J = 3.4 Hz, -O*H*), 3.61 (m, 1H, $C^2H_SH_R$-OH), 6.30 (m, 1H, 4 arom *H*), 6.35 (m, 1H, 3 arom *H*), 7.41 (m, 1H, 5 arom *H*).

General Procedure for the Determination of the %ee for Arylmethyl alcohols: [(1*R*)-[1-^{2}H]-4-Methoxybenzyl] (2*S*)-2-acetoxy-2-phenylethanoate.

To a solution of DMAP (0.01 g, 0.082 mmol) and (1*R*)-[1-^{2}H]-4-methoxybenzylalcohol (0.100 g, 0.719 mmol) at 0°C (2*S*)-2-acetoxy-2-phenylethanoic acid (0.140 g, 0.721 mmol) and DCC (0.149 g, 0.722 mmol) in methylene chloride (5 mL) are added and the reaction mixture stirred for 4h at 0°C. After stirring for 18h at 25°C,

the DCU which forms is removed by suction and the solvent is removed on a rotary evaporator. The oil thus obtained is taken up in diethyl ether (25 mL), chilled, and the residual DCU is removed by suction. Silica gel (5 g) is added to the ether solution and the solvent removed. The dry impregnated silica gel containing the crude reaction product is loaded onto a chromatographic column containing silica gel (10 g). On elution with hexanes:ethyl acetate (85:15), a colourless paste is obtained in 88.3% yield (0.20 g); ^{1}H-nmr ($CDCl_3$) δ 2.18 (s, 3H, $-O_2CCH_3$), 3.79 (s, 3H, OCH_3), 5.03 (s, 0.24 H, $C^2H_SH_R$-O-), 5.12 (s, 0.76 H, $C^2H_RH_S$-O-), 5.94 (s, 1H, $-O_2CH$-O_2CCH_3)), 6.70-7.52 (m, 9H, aromatic *H*).

[(1*S*)-[1-^{2}H]-2-Furfuryl] (2*S*)-2-acetoxy-2-phenylethanoate.

A solution of DMAP (0.01 g, 0.082 mmol), (1*S*)-[1-2H]-2-furfurylalcohol (0.071 g, 0.721 mmol), 2(*S*)-2-acetoxy-2-phenylethanoic acid (0.140 g, 0.721 mmol) and DCC (0.149 g, 0.722 mmol) are reacted in methylene chloride as described above to give the desired diastereomeric derivative in 81.2% yield (0.16 g) as a colorless oil. ^{1}H-nmr ($CDCl_3$) δ 2.18 (s, 3H, $-O_2CCH_3$), 5.02 (s, 0.82 H, $C^2H_SH_R$-O-), 5.14 (s, 0.16 H, $C^2H_RH_S$-O-), 5.91 (s, 1H, $-O_2CH$-O_2CCH_3)), 6.32 (m, 2H, 3 and 4 furyl *H*), 7.39 (m, 6H, 5-furyl-*H* and C_6H_5).

General Procedure For Phthalimidation: *N*- Phthaloyl (1*S*)-[1-^{2}H]-4-methoxybenzylamine.

To a stirred solution of (1*R*)-[1-^{2}H]-4-methoxybenzylalcohol (2.0 g, 14.37 mmol), triphenylphosphine (4.16 g, 15.86 mmol) and phthalimide (2.33 g, 15.84 mmol) in dry THF (100 mL) at 0°C, under a nitrogen atmosphere, is added diethylazidocarboxylate (2.76 g, 15.84 mmol). The reaction mixture is stirred for 4h at 0°C. After stirring for 18h at 25°C, solid silica gel (20 g) is added and the solvent is removed. The dry impregnated silica gel is loaded onto a chromatography column containing silica gel (300 g). The column is eluted with hexanes: ethylacetate (85 : 15) and the fractions containing the phthalimidated product are combined to give 2.8 g (73%) of the title compound with a mp of 133-134°C; ^{1}H-nmr ($CDCl_3$) δ 3.75 (s, 3H, OCH_3), 4.78 (s, 1H, $C^2H_SH_RN$), 6.83 (d, J = 10.0 Hz, 2H, anisyl aromatic *ortho-H*), 7.40 (d, J = 10.0 Hz, 2H, anisyl aromatic *meta-H*), 7.68 (d, J = 8.0 Hz, 2H, phthaloyl aromatic *ortho-H*), 7.82 (d, J = 8.0 Hz, 2H, phthaloyl aromatic *meta-H*).

***N*- Phthaloyl (1*R*)-1-[^{2}H]-furfurylamine.**

The title compound is prepared in 80% yield (3.68 g) as a colourless solid from (*S*)-1-[2H]-furfurylalcohol (2.0 g, 20.2 mmol), triphenylphosphine (5.869 g, 22.3 mmol), phthalimide (3.3 g, 22.6 mmol) and diethylazidodicarboxylate (3.94 g, 22.6 mmol) in THF (60 mL) as described above for the synthesis of the anisyl derivative; mp 112-114°C [Lit.[12] mp 111-115°C];. ^{1}H-nmr ($CDCl_3$) δ 4.74 (s, 1H, $C^2H_RH_S$-N), 6.3 (m, 1H, 4 arom *H*), 6.42 (m, 1H, 3 arom *H*), 7.41 (m, 1H, 5 arom *H*), 7.7 and 7.88 (m, 4H, arom phth *H*).

General Procedure For The Deprotection of Phthalimides *via* Sodium Borohydride Reduction.
(1*S*)-[1-^{2}H] *N*-*t*-Butyloxycarbonyl 4-methoxybenzylamine.

To a solution of *N*- Phthaloyl (1*S*)-[1-^{2}H]-4-methoxybenzylamine (2.0 g, 7.44 mmol) in propanol (80 mL) and water (13 mL) is added sodium borohydride (1.4 g, 37.24 mmol). After stirring for 24h at 25°C, glacial acetic acid (8 mL) is carefully added. When the foaming subsides, the reaction mixture is heated to 80°C for 2h and then cooled to 25°C. The solvent is removed under vacuum to give a colourless paste which is taken up in dioxane-water (2:1, 20 mL). The solution is cooled to 0°C and the pH is adjusted to ~ 8.5 (as determined by pH paper) by the addition of Na_2CO_3 (3.4 g). Di-*t*-butyl-dicarbonate (2.68 g, 13.24 mmol) in dioxane-water (2 :1, 20 mL) is added and the mixture stirred at 0°C for 4h. After stirring at 25°C for an additional 18h, the dioxane is removed on a rotary evaporator (water aspirator/ 30°C) and the pH of the remaining aqueous solution is adjusted to ~ 2 by the addition of 1N HCl. The mixture is extracted with ethyl acetate (3 x 100 mL) and the organic layer dried (Na_2SO_4). Filtration and evaporation of the ethyl acetate affords a colorless viscous oil which is subjected to silica-gel chromatography (50 g silica gel) using hexanes: ethyl acetate (9:1) as eluant. The title compound is obtained as a colourless oil in 77% yield (1.36 g). ^{1}H-nmr ($CDCl_3$) δ 1.48 (s, 9H, t-C_4H_9), 3.20 (s, 3H, OCH_3), 4.18 (bs, 1H,$C^2H_SH_R$-N), 4.68 (bs, 1H, N*H*), 6.28 (d, J = 10.0 Hz, 2H, aromatic *ortho-H*), 7.18 (d, J = 10.0 Hz, 2H, aromatic *meta-H*).

***N*-*t*-Butyloxycarbonyl (2*S*)-[2-^{2}H]Glycine.**

To a stirred solution of (1*S*)[1-^{2}H] N-*t*-Butyloxycarbonyl 4-methoxybenzylamine (1.36 g, 5.71 mmol) in acetonitrile (7 mL), carbon tetrachloride (7 mL) and water (14 mL) at 25°C is added sodium metaperiodate (22.04 g, 103.04 mmol) and $RuCl_3 \cdot 3H_2O$ (33.6 mg, 0.1284 mmol). The pasty reaction mixture is stirred at 25°C for 20h.

The precipitated iodate salts are removed by suction and washed with ethyl acetate (200 mL). The ethyl acetate layer is separated from the aqueous phase, dried and silica gel (2 g) is added. The ethyl acetate is removed *via* evaporation and the product-laden silica gel added to the top of a column containing 50 g of silica gel. The column is eluted with hexanes:ethyl acetate (85:15) and the fractions containing product are combined and evaporated to give 0.68 g (68%) of the title compound as an oil which solidifies on standing, mp 85-87°C. ^{1}H-nmr ($CDCl_3$) δ 1.52 (s, 9H, *t*-C_4H.), 3.95 (d, J = 5Hz, 1H, $C^2H_SH_R$-N), 4.40 (bs, 1H, N*H*), 9.80(bs, 1H, CO_2H).

(*S*)-[2-^{2}H]Glycine.

A solution of *N*-*t*-butyloxycarbonyl (2*S*)-[2-^{2}H]glycine (10 mg, 0.057 mmol) in trifluoroacetic acid and methylene chloride [0.4 mL, 1:1 (vol/vol)] is stirred at 25°C for 10min. The solvent is removed by evaporation. Chloroform (5 mL) is added and the solution evaporated. This procedure is repeated twice more to give (*S*)-[2-^{2}H] glycine•TFA as a colourless solid (8.5 mg, 79%). ^{1}H-nmr (^2H_2O) δ 3.75 (bs, 1H, $C^2H_SH_R$-N). [α]$_{250}$= -20° c 2.0 in H_2O] lit.[18] [α]$_{250}$= -25° c 2.0 in H_2O]

N-Phthaloyl (*R*)-[2-^{2}H]Glycine.

To a solution of *N*- phthaloyl furfurylamine (2.0 g, 8.80 mmol) dissolved in 120 mL of methylene chloride and cooled to -78°C is bubbled a slow stream of ozone until no starting material is left, as monitored by TLC (silica gel, hexanes-diethyl ether 5:1), in the reaction mixture (ca. 2h). After the addition of 2 mL of 30% hydrogen peroxide, the reaction mixture is stirred at room temperature for 18h. The mixture is washed with water, dried (Na_2SO_4) and the methylene chloride is evaporated to give a gummy white solid (1.8 g) which is used for the next step without further purification. ^{1}H-nmr ($CDCl_3$) δ 4.5 (bs, 1H, $C^2H_RH_S$-N), 7.7 and 7.85 (m, 4H, Ar*H*).

Deprotection of Phthaloyl glycine *via* Hydrazine: (*R*)-[2-^{2}H]Glycine.

A mixture of phthaloyl glycine (1.8 g, 8.73 mmol) and hydrazine monohydrate (0.68 g, 13.58 mmol) in 25 mL of ethanol is heated at reflux for 4h. The white solid which forms is filtered and the ethanol is removed on a rotary evaporator. The residue is chromatographed on a silica gel column (35 g) and eluted with propanol-water (7:3). Ninhydrin positive fractions are combined and the solvent is evaporated to give *R*-glycine in 80% yield (620 mg) based on the *N*-phthaloyl furfurylamine. ^{1}H-nmr (^2H_2O) δ 3.38 (bs, 1H, $C^2H_RH_S$-N).

Procedure For Determining the % ee of Chiral Glycine: Camphanoyl (*R*)-[2-^{2}H]glycine.

Freshly sublimed camphanoyl chloride (23.8 mg, 0.11 mmol) is dissolved in toluene (1 ml) and the solution is cooled to 0°C. To this solution glycine (7.6 mg, 0.1 mmol) is added followed by 3N NaOH (0.2 mL). The reaction mixture is stirred for 3h while maintaining the pH above 7.0 by the addition of 1N NaOH. The mixture is extracted with $CHCl_3$ and the organic layer discarded. The aqueous layer is acidified with 1N HCl and stirred at room temperature for 1h. The aqueous solution is evaporated on a rotary evaporator equipped with a vacuum pump, and the oily residue which is obtained is treated with a few drops of water to give 15.6 mg (62%) of the crystalline camphanoyl (*R*)-[2-^{2}H]glycine. ^{1}H-nmr $CDCl_3$ δ 4.08 (d, J = 3.6 Hz, 0.18 H, $C^2H_SH_R$-N), 4.22 (d, J = 3.6 Hz, 0.82 H, $C^2H_RH_S$-N), 6.98 (d, J = 3.7 Hz, N*H*).

Camphanoyl (*S*)-[2-^{2}H]glycine.

^{1}H-nmr $CDCl_3$ δ 4.08 (d, J = 3.6 Hz, 0.76 H, $C^2H_SH_R$-N), 4.22 (d, J = 3.6 Hz, 0.24 H, $C^2H_RH_S$-N), 6.98 (d, J = 3.7 Hz, N*H*).

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