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Stereospecific Synthesis of (R)-[2-$^2H_1$]-Glycine by Means of Microbial Reduction and A Determination of It's Absolute Configuration by CD Spectra.

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Summary

A preparation of optically pure (R)-[2-$^2H_1$]-glycine by microbial reduction is detailed. The reduction of [2-^{2}H]-furfural and furfural with S. Cerevisiae in H_2O and in D_2O gave (S)- and (R)-labeled furfuryl alcohol respectively, which could be converted to the labeled glycine in three steps. A new method for the determination of the sense of chirality of the labeled glycine by means of CD spectra and an application of MTPA method for the determination of the optical purity are also described.

Key words: [2-$^2H_1$]-glycine, [2-$^2H_1$]-furfuryl alcohol, Microbial reduction, CD spectra, deuterium.

Introduction

One of the most powerful techniques for the study of biosynthetic pathways is the use of stable isotope labeling of substrates and NMR spectroscopy in defining the structure. We required chiral ^{2}H-labeled aminolevulinic acid(ALA) and porphobilinogen(PBG) for biosynthetic studies of Vitamin B_{12} and

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Chlorophyll and, at first, attempted to prepare chiral [2-$^2H_1$]-glycine derivatives from which labeled ALA and PBG could be obtained.

Several syntheses of chiral glycine have been reported. They involve a chemical method starting from chiral O-benzylserine[1] and an enzymic one starting with serine hydroxymethyl transferase[2]. Optically active benzyl-α-d alcohol has been used extensively to prepare chiral glycine[3-5] and acetic acid[6]. The benzyl-α-d alcohol can be obtained in a number of ways[3-9].

This general approach involves the conversion of a benzene ring into a carboxylic acid. But the benzene ring is not good substrate for oxidation. Recently dimethoxybenzaldehyde is selected to facilitate the final oxidation step[6].

A furan ring is readily convertible to the carboxylic acid compared with the benzene ring, which makes it possible to use the furan ring as a precursor of the carboxylic acid[10].

Recently asymmetric reduction of a carbonyl group by S. Cerevisiae (Baker's yeast) becomes a useful preparative method[11]. It has been reported that the furan derivatives are readily reduced by microorganisms in high yield with high optical purity[10]. Based on these results, [2-^{2}H]-furfural was chosen as the substrate for the stereospecific synthesis of chiral glycine.

It is always helpful for stereochemical work to make both enantiomers of the chiral alcohol available and to prepare them in the complementary fashion. We have recently found that Baker's yeast in D_2O reduced furfural to give the opposite enantiomer (ie., (R)-[2-$^2H_1$]-furfuryl alcohol) of high optical purity. Consequently, we realize the preparation of both enantiomers of labeled furfuryl alcohol by means of yeast reduction.

Another problem accompanied with this synthesis was the determination of the optical purity and the absolute configuration of the chiral glycine. ORD spectrum[4], camphan amide

derivative[1] and L-phenylalanylglycine[4,12] make it possible to establish the chirality of glycine.

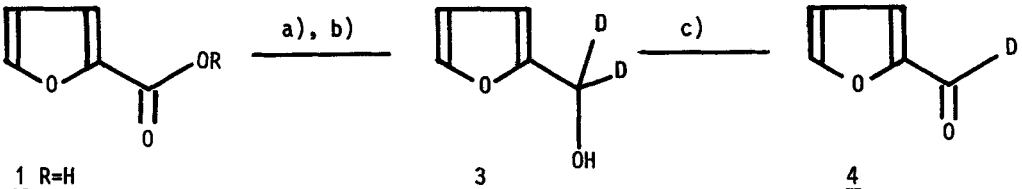
In this paper we describe the synthesis of (R)-[2-$^2H_1$]-glycine by microbial reduction and the application of the CD spectrum to the determination of the chirality of glycine derivatives.

Results and Discussion

Synthesis of chiral glycine

Furfural 4 required for the microbial reduction was obtained in the following way.(see Fig-1)

Esterification of 2-furoic acid with ethanol using p-TsOH gave the corresponding ester 2 in 96% yield. The ester 2 was reduced with $LiAlD_4$ to afford [2-$^2H_2$]-furfuryl alcohol 3, which was subjected to the Swern oxidation[14] to furnish labeled furfural 4 in 67% yield from the ester 2.



1 R=H
2 R=Et

3 4

a) p-TsOH, EtOH. b) $LiAlD_4$, THF. c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2.

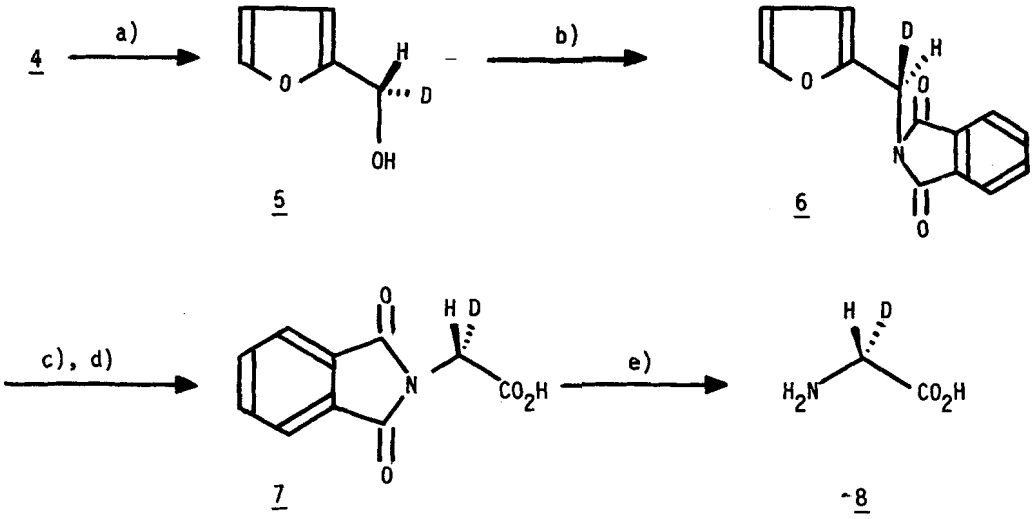
Fig-1

This three-step sequence provided a substantial quantity of the required furfural 4 in a reasonable yield.

Conversion of 4 into the chiral glycine 8 via asymmetric microbial reduction of the furfural 4 was examined.(see Fig-2)

Reduction of the furfural 4 with Baker's yeast in H_2O gave (S)-[2-$^2H_1$]-furfuryl alcohol 5 in 85% yield. The deuterated alcohol 5 was converted to (R)-N-phthaloyl[2-$^2H_1$]-furfuryl amine 6 by using the Mitsunobu's procedure[15], which should proceed with inversion of configuration. Ozonolysis of 6, followed by

oxidation with hydrogen peroxide gave (R)-N-phthaloyl[2-$^2H_1$]-glycine 7 in 80% yield. Treatment of 7 with hydrazine in ethanol afforded (R)-[2-$^2H_1$]-glycine 8 in 98% yield.



a) B. YEAST, H_2O. b) PPh_3, Phthalimide, $(EtO_2CN)_2$, THF.
c) O_3, CH_2Cl_2. d) 30% H_2O_2. e) H_2NNH_2-H_2O, EtOH.

Fig-2

Next we investigated the preparation of the antipodal compound 12 in a similar way. When furfural 11 was subjected to reduction with Baker's yeast in D_2O, (R)-[2-$^2H_1$]-furfuryl alcohol 12 was isolated in 71% yield.(see Fig-3)

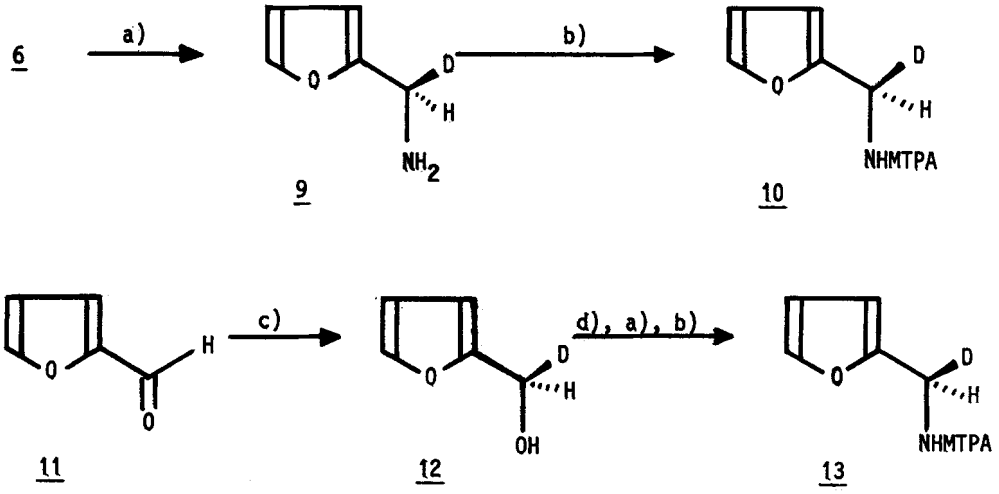
The reduction in D_2O combined with the one in H_2O provided a facile and practical method for the preparation of the (S)- and (R)-isomer.

(R)-furfuryl alcohol 12 could also be obtained by enzymic reduction with horse liver alcohol dehydrogenase and 1-deuterated cyclohexanol in 72% yield.

Determination of the optical purity

The Mosher's method has been widely used for the determination

of the optical purity of the secondary alcohols and amines[13]. Applying this method to our compounds, the deuterated N-phthaloyl furfuryl amine 6 was converted to the MTPA amide 10 in the following way.



a) H_2NNH_2-H_2O. b) MTPACl, Py., CH_2Cl_2. c) B. YEAST, D_2O.
d) PPh_3, Phthalimide, $(EtO_2CN)_2$, THF.

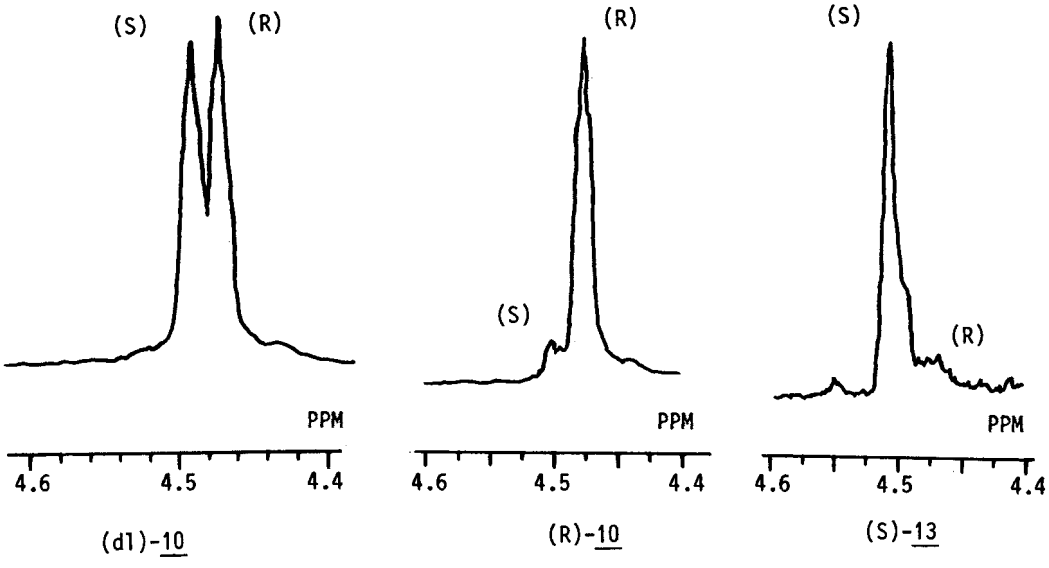
Fig-3

Removal of the phthaloyl group with hydrazine in H_2O gave furfuryl amine 9 in 69% yield, which was treated with the MTPACl in CH_2Cl_2 to afford the corresponding amide 10 in 45% yield. Transformation of the (R)-furfuryl alcohol 12, which was prepared by yeast reduction in D_2O to the MTPA amide 13 was accomplished in the same manner.

The optical purity was determined by 400MHz-^{1}H NMR spectra of the respective MTPA derivatives. Attempts to distinguish the diastereotopic methoxy protons of the dl-MTPA amide were unsuccessful. The signals for the methoxy protons were separated not enough to determine the optical purity. When 94MHz ^{19}F-NMR of the dl-MTPA derivative was examined, the ^{19}F-signal showed no

separation at all. But the protons α to the nitrogen of the MTPA amides could be capable of discreminating the diastereotopic protons. Namely the amide proton was subjected to irradiation, which separated the signals as shown in Fig-4. From the height of the peaks optical purities of (R)- and (S)-isomer are about 92% and 88% respectively. These data exhibit that the Mosher's method can also be applicable to the amine having H, ^{2}H chirality as well as the normal secondary amine[16].

400MHz ^{1}H-NMR spectra of the MTPA derivatives



(dl)-10 (R)-10 (S)-13

* The amide proton was irradiated.

Fig-4

CD spectra of the chiral glycine derivatives

Circular dichroic spectroscopy (CD) is useful to establish the absolute configuration, because of a fact that the positive and negative signals can be obtained. Recently the CD spectra combined with nonempirical methods such as the exciton theory[17] can determine the accurate relationships between the sign of the CD and the absolute configuration.

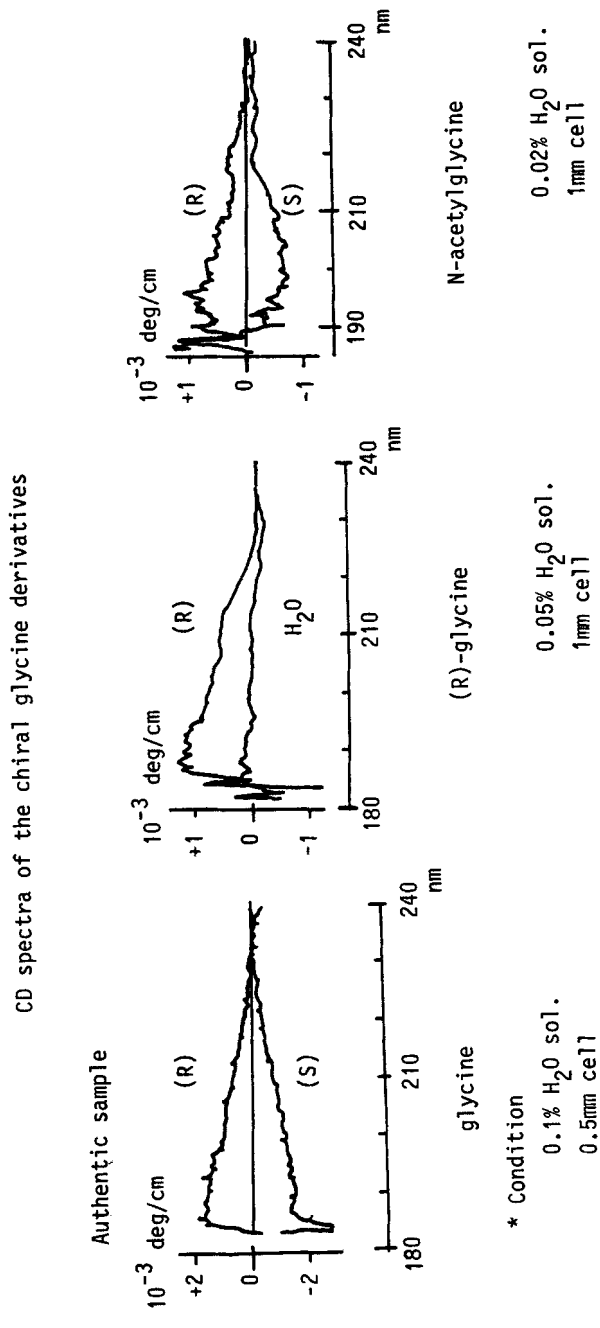

CD spectra of the chiral glycine derivatives
Authentic sample
10^{-3} deg/cm
+2
0
-2
(R)
(S)
180
210
240
nm
glycine
* Condition
0.1% H_2O sol.
0.5mm cell
10^{-3} deg/cm
+1
0
-1
(R)
H_2O
180
210
240
nm
(R)-glycine
0.05% H_2O sol.
1mm cell
10^{-3} deg/cm
+1
0
-1
(R)
(S)
190
210
240
nm
N-acetylglycine
0.02% H_2O sol.
1mm cell

Fig-5

We applied the CD spectra to the determination of the H, ^2H chirality of the glycine derivatives. (R)- and (S)-[2-$^2H_1$]-glycine which were prepared by the known procedure[3] and their chirality and optical purity(>96%) were already established, were used as standard samples. 0.1% H_2O solution of these samples was subjected to the CD measurement. The CD spectra are shown in Fig-5, where (R)-glycine and (S)-glycine show the positive curve and negative curve respectively. From these spectra, the CD can distinguish the deuterated glycine and be applied to the determination of the absolute configuration.

Next we turned our attention to the CD spectra of N-acetyl and N-phthaloylglycine, which were prepared from the authentic glycine. It was impossible to establish the chirality of [2-$^2H_1$]-N-phthaloylglycine due to the absorption of the aromatic ring.

The CD spectra of [2-$^2H_1$]-N-acetylglycine exhibited similar results as shown in Fig-5, where the positive curve could be assigned to (R)-[2-$^2H_1$]-N-acetylglycine and the negative curve corresponds to (S)-acetylglycine. These data also indicate the applicability of the CD spectrum for the determination of the chiral labeled N-acetylglycine.

[2-$^2H_1$]-glycine, previously prepared by the microbial reduction, was subjected to the CD measurement. The CD spectrum showed the positive curve, and we confirmed that glycine synthesized had R-configuration with 92% optical purity.

In summary, the synthesis described is highly stereospecific and particularly useful for preparing chiral [2-$^2H_1$]-glycine. The CD provides the convenient method to establish the sense of chirality of the deuterated glycine derivatives. Since only a small amount of the sample (<1 mg) is required for the measurement of the CD spectrum, this method combined with a degradation experiment offers the powerful technique to study the biosynthetic pathway. For example, [11-$^2H_1$]-labeled PBG can be

converted to [2-$^2H_1$]-glycine[18], so the chirality of PBG is easily established by the CD spectrum. The use of these samples now easily available for the biosynthetic study of porphyrinoid and corrinoid is under investigation.

Experimental Section

General Methods

Tetrahydrofuran was distilled from sodium/ benzophenone immediately prior to use. Methylene chloride, demethylsulfoxide and triethylamine were distilled from calcium hydride. Melting points were determined on a Yazawa micro melting point apparatus (Type BY-I) and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 215 or a JASCO DS-701G spectrophotometer. ^1H NMR spectra were measured with either a Hitachi R-24B (60 MHz) or a JEOL GX-400 (400MHz) instrument. Chemical shifts are given in δ units (parts per million) relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broad). Circular dichroic (CD) spectra were recorded on a JASCO J-500C spectrometer. Mass spectra were obtained with a JEOL JMS-01SG-2 spectrometer. Thin layer chromatography (TLC) was performed with Merk Kieselgel $60F_{254}$ sheet. Flash chromatography was carried out with Wako gel C-300.

2-furoic acid ethyl ester 2

To a solution of 2-furoic acid (12.75 g) in 250 mL of ethanol was added a catalytic amount of p-toluenesulfonic acid and the solution refluxed for 2 days. After evaporation of a half of the solvent, the mixture was poured into sodium bicarbonate solution and extracted with ether five times. The combined extracts were washed with brine and dried over magnesium sulfate. Removal of the solvent gave the ethyl ester 2 (15.3 g, 96%): mp 32-34 ℃ ; IR (neat) 1720 (C=O) cm^{-1} ; ^1H NMR (CCl_4) δ 1.38(t,3,J=7Hz,Me),

4.33(q,2,J=7Hz,CH_2),6.45(dd,1,J=2, 3.4Hz,furan),7.07(d,1,J=3.4Hz, furan),7.52(br d,1,J=2Hz,furan).

[2-$^2H_2$]-furfuryl alcohol 3

To a stirring solution of 5.30 g of 2-furoic acid ethyl ester in dry tetrahydrofuran at 0 ℃ was added dropwise lithium aluminum deuteride (1.07 g) and mixture stirred for 10 min. 10% potassium hydroxide solution was added dropwise until the solution became solid. The mixture was filtered on celite and the filtrate was evaporated under reduced pressure to afford the alcohol 3 (3.50 g, 92%): IR (neat) 3350 (OH) cm^{-1}; ^1H NMR (CCl_4) δ 4.06(br s,1,OH),6.1-6.35(m,2,furan),7.27(d,1,J=2Hz,furan).

[2-^2H]-furfural 4

To a solution of oxalyl chloride (4.9 mL) in methylene chloride (150 mL) was added dropwise dimethylsulfoxide (4.8 mL) and the mixture stirred at -78 ℃ for 15 min. To this solution was added dropwise the deuterated furfuryl alcohol 3 (3.76 g) in methylene chloride (100 mL) and the mixture kept stirring for 15 min. 26 mL of triethylamine was added and the stirring was continued at room temperature for 1 hr. The reaction mixture was poured into water and extracted with methylene chloride. The combined organic solutions were washed with sodium bicarbonate solution, brine, dried over magnesium sulfate and evaporated. Chromatography of the crude product on alumina and elution with 1:1 hexane-methylene chloride gave 2.10 g (57%) of the furfural 4: IR (neat) 1670(C=O) cm^{-1}; ^1H NMR (CCl_4) δ 6.54(dd,1,J=2, 3.4Hz,furan), 7.14(d,1,J=3.4Hz,furan),7.63(br s,1,furan).

(S)-[2-$^2H_1$]-furfuryl alcohol 5

A suspension of 15 g of commercial baker's yeast in 200 mL tap water was added to the deuterated furfural 4 (2.10 g) and stirred at 37 ℃ for 2 days. The mixture was centrifuged at 12000G for 15 min. The supernatant solution was extracted with ether four times and the combined extracts were washed with brine and dried over

magnesium sulfate. Removal of the solvent afforded the (S)-furfuryl alcohol **5** (1.66 g, 77%): IR (neat) 3425(OH) cm^{-1}; ^{1}H NMR (CCl_4) δ 3.90(br s,1,OH),4.43(br s,1,CDH),6.2-6.4(m,2,furan),7.35 (d,1,J=2.0Hz,furan); MS m/z 100(6.2),99(M+,90.4),98(100).

(R)-[2-^{2}H$_1$]-**furfuryl alcohol 12**

Treatment of 0.96 g of furfural **11** with 14 g of Baker's yeast in deuterium oxide (40 mL) as in the above preparation of **5** afforded 0.70 g (71%) of the (R)-furfuryl alcohol **12**: IR(neat) 3420 (OH) cm^{-1}; ^{1}H NMR($CDCl_3$) δ 3.10(br s,1,OH),4.50(br s,1,CDH),6.05-6.20(m,2,furan),7.35(m,1,furan); MS m/z 100(8.3),99(M+,85.4),98(100).

(R)-N-**phthaloyl**-[2-^{2}H$_1$]-**furfurylamine 6**

To a mixture of 1.07 g of the (S)-furfuryl alcohol **5**, 3.14 g of triphenylphosphine and 1.78 g of phthalimide in dry tetrahydrofuran (30 mL) was added dropwise diethyl azodicarboxylate (2 mL) at 0 ℃. The stirring was continued at room temperature overnight. After evaporation of the solvent, the mixture was subjected to column chromatography on silica gel and elution with 5:1 hexane-ether afforded 1.69 g (69%) of the (R)-furfurylamine **6**: mp 111-115 ℃; IR (KBr) 1710(C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.8(br s,1,CDH),6.3(m,2,furan),7.32(m,1,furan),7.5-8.0 (m,4,aromatic); MS m/z 229(15.3),228(M+,100),227(5.0)

(S)-N-**phthaloyl**-[2-^{2}H$_1$]-**furfurylamine**

Treatment of the furfuryl alcohol **12** (0.49 g) with triphenylphosphine (1.57 g), phthalimide (0.81 g) and diethyl azodicarboxylate (1.31 g) as in the above preparation of **6** gave the crude product. Purification by column chromatography on silica gel with eluent of 5:1 hexane-ether afforded 0.498 g (44%) of the (S)-fulfurylamine: mp 107-108 ℃; ^{1}H NMR ($CDCl_3$) δ 4.84(br s,1,CDH),6.3(m,2,furan),7.3(m,1,furan),7.5-8.0 (m,4,aromatic); MS m/z 229(18.3),228(M+,100),200(25.2),199(32.4).

(R)-N-phthaloyl-[2-$^2H_1$]-glycine 7

To a solution of the N-phthaloyl furfurylamine 7 (804 mg) in methylene chloride (50 mL) was bubbled ozone at -78 ℃ until no starting material was observed on TLC. 30% hydrogen peroxide was added and stirred overnight at room temperature. The mixture was extracted with methylene chloride. The organic solution was washed with brine, dried and evaporated at reduced pressure. Recrystallization of the crude product from water gave 640 mg (80%) of the N-phthaloyl glycine 7: mp 182-185 ℃; IR (KBr) 3500(OH),1720(C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.50(br s,1,CDH),7.6-7.9(m,4,aromatic); MS m/z 207(1.9),206(M+,6.0),162(100).

(R)-[2-$^2H_1$]-glycine 8

A mixture of the N-phthaloyl glycine 7 (253 mg) and hydrazine monohydrate (0.1 mL) in ethanol (6 mL) was refluxed for 2 hr. The reaction mixture was evaporated at reduced pressure and then the residue dissolved in hot methanol. The resulting suspension was centrifuged at 3000 rpm for 10 min. The precipitate was washed with hot methanol twice and recentrifuged for 10 min. The supernatant solution was removed to give the deutrated glycine 8 (81 mg, 98%): mp 243-247 ℃; IR (KBr) 3100(OH),1600(C=O) cm^{-1}; ^1H NMR (D_2O) δ 3.35(s,1,CDH); MS m/z 77(1.3),76(M+,10.3),31(100).

(R)-[2-$^2H_1$]-furfurylamine 9

A mixture of the N-phthaloyl furfurylamine 6 (114 mg) and hydrazine monohydrate (2 mL) was stirred at 60 ℃ for 10 min. Water was added and the mixture extracted with ether four times. The combined extracts were dried over magnesium sulfate. Careful evaporation of the solvent gave the (R)-furfurylamine 9 (32 mg, 65%): ^1H NMR (CCl_4) δ 3.60-3.85(m,1,CDH),4.55-4.95(m,2,NH_2),5.96 (d,1,J=3Hz,furan),6.14(dd,1,J=2,3Hz,furan),7.16(br d,1,J=2Hz, furan).

(R)-N-α-methoxy-α-trifluoromethyl-phenylacetyl-(R)-[2-^{2}H$_1$]-furfurylamine 10

The MTPACl was prepared by refluxing (R)-2-methoxy-2-trifluoromethyl-phenyl acetic acid (76 mg) in thionyl chloride (1 mL) in the presence of small amount of sodium chloride for 50 hr under nitrogen, followed by evaporation of excess thionyl chloride. To a mixture of (R)-furfurylamine (30.4 mg) and pyridine (53 μL) in methylene chloride (1.5 mL) was added the crude MTPACl. The mixture was stirred at room temperature for 3 hr and then poured into cold 1N-hydrochloric acid. The aqueous solution was extracted with methylene chloride three times. The combined extracts were washed with sodium bicarbonate solution,brine and dried over magnesium sulfate. Removal of the solvent gave an oil which was subjected to column chromatography on silica gel with eluent of 5:1 hexane-ether to afforded 43.7 mg (45%) of the MTPA amide 10: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39(d,3,J=1.2Hz,OMe),4.48(br d,1,J=2.7Hz 7.06(s,1,NH),7.3-7.6(m,6,aromatic, furan).

(R)-N-α-methoxy-α-trifluoromethyl-phenylacetyl-(S)-[2-^{2}H$_1$]-furfurylamine 13

The MTPA-furfurylamine 13 was synthesized by the same procedure as in the above preparation of the MTPA-(R)-furfuylamine 10: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39(d,3,J=1.2Hz,OMe),4.52(d,1,J=5.5Hz,CDH), 6.24(d,1,J=3.4Hz,furan),6.33(dd,1,J=1.9, 3.4Hz,furan), 7.06(s,1,NH),7.3-7.6(m,6,aromatic, furan).

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