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AN ENANTIOSELECTIVE SYNTHESIS OF *S*-γ-[(4-TRIFLUOROMETHYL)PHENOXY]BENZENEPROPANAMINE-[3-^{14}C] HYDROCHLORIDE, AN IMPORTANT METABOLITE OF FLUOXETINE HYDROCHLORIDE

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SUMMARY

The *S*-enantiomer of γ-[(4-trifluoromethyl)phenoxy]benzenepropanamine-[3-^{14}C] hydrochloride has been prepared in eight steps from acetophenone-[carbonyl-^{14}C]. The key step in the synthesis involved the enantioselective reduction of *R*-2-chloroacetophenone-[1-^{14}C] with (-)-diisopinocampheylchloroborane in an 86.5% yield. The chlorohydrin was converted to *R*-phenyloxirane-[1-^{14}C], which was subsequently converted to the corresponding *R*-cyanohydrin by reaction with TMS-CN/CaO. Borane reduction and arylation, followed by salt formation yielded *S*-γ-[(4-trifluoromethyl)phenoxy]benzenepropanamine-[3-^{14}C] hydrochloride.

Key words: C14, enantioselective reduction, *S*-γ-[(4-trifluoromethyl)phenoxy]benzenepropanamine-[3-^{14}C] hydrochloride.

INTRODUCTION

N-Methyl-γ-[(4-trifluoromethyl)phenoxy]benzenepropanamine hydrochloride (**1**) (fluoxetine hydrochloride), a specific serotonin re-uptake inhibitor which is clinically useful as an antidepressant, is a mixture of enantiomers.[1] Parli and Hicks have shown that one of the principle routes of metabolism of fluoxetine is the cytochrome P_{450}-mediated oxidative N-demethylation to form the primary amines **2a,b**.[2] Robertson *et al.* have recently synthesized the *R*- and *S*-enantiomers of *nor*-fluoxetine and studied the effect of the pure enantiomers on serotonin uptake.[3] The *S*-enantiomer of *nor*-fluoxetine (**2b**, seproxetine) was equipotent with fluoxetine in the inhibition of serotonin uptake, but sixteen times more

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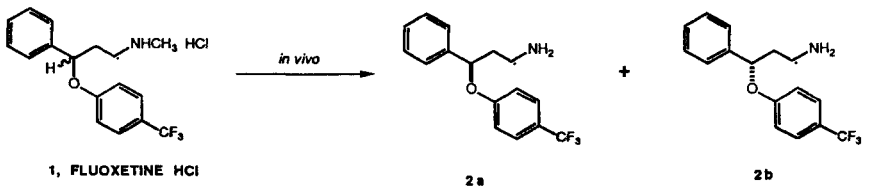
potent than the corresponding *R*-enantiomer (**2a**). Seproxetine was also found to be substantially more potent than *R-nor*-fluoxetine in a number of *in vivo* studies.[4] In order to learn more about the disposition and metabolism of the individual isomers of this major metabolite, the preparation of their ^{14}C-isotopomers was undertaken. Wheeler has previously reported on the preparation of seproxetine-[1-^{14}C];[5] however, 22% of the administered dose was recovered as expired $^{14}CO_2$ after oral administration to rats.[6] Alternatively, an enantioselective synthesis of the seproxetine-[3-^{14}C] (previous studies have shown the 3-position to be a more stable position metabolically) has been completed and hereupon, the results of these efforts are reported .



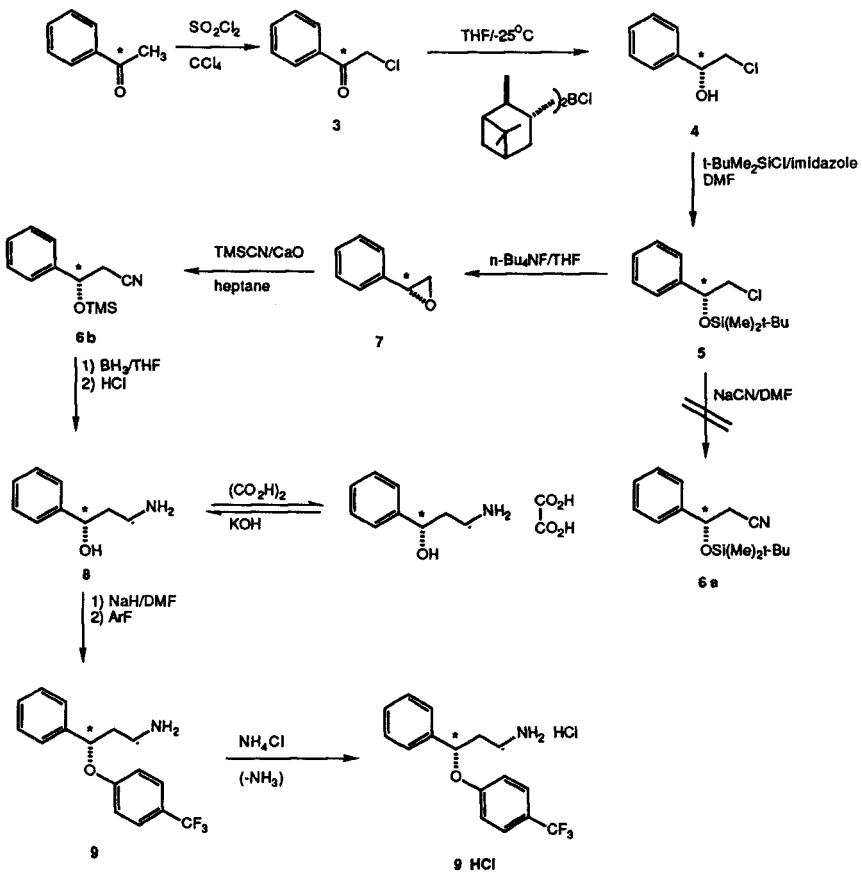
1, FLUOXETINE HCl 2a 2b

DISCUSSION

Acetophenone-[carbonyl-^{14}C] was treated with sulfuryl chloride in refluxing carbon tetrachloride. The resulting 2-chloroacetophenone-1-^{14}C] (**3**) was reduced according to the method of Srebnik *et al* with (-)-diisopinocampheylchloroborane in anhydrous THF at -25°C to yield *R*-chlorohydrin **4**.[7] In hopes of following the method developed for *S*-γ-[(4-trifluoromethyl)phenoxy]benzenepropanamine-[1-^{14}C], **4** was converted to its *tert.*-butyldimethylsilyl ether **5** by reaction with *tert.*-butyldimethylsilyl chloride/imidazole in DMF.[5] Unfortunately, all attempts to convert **5** to nitrile **6a** in reasonable yield were unsuccessful (the major product of this reaction was cinnamonitrile). Alternatively, **5** was converted to *R*-phenyloxirane-[1-^{14}C] (**7**) by reaction with N-Bu$_4$NF/THF. Subsequently, treatment of **7** with trimethylsilylcyanide (TMS-CN) /CaO, according to the method described by Sugita *et al.*,[8] provided silylnitrile **6b** in good yield. Borane reduction of **6b** in THF, yielded *S*-aminoalcohol **8**.

Conversion of **8** to its crystalline oxalate salt resulted in purification; transformation back to *S*-aminoalcohol **8**, followed by reaction with NaH/DMF, and subsequent reaction of the resulting

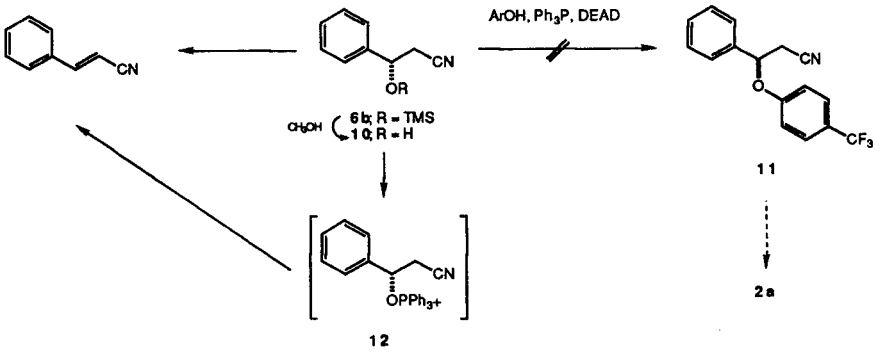
SCHEME 1



alkoxide with α,α,α,4-tetrafluorotoluene yielded *S*-γ-[(4-trifluoromethyl)phenoxy]benzenepropanamine-[3-^{14}C] (**9**) which was converted to its hydrochloride salt by reaction with NH_4Cl/methanol.

The crystalline HCl salt of **9** contained less than 0.3% of the corresponding *R*-enantiomer;[9] the radiochemical purity was >98% by TLC and radio-HPLC.

SCHEME 2

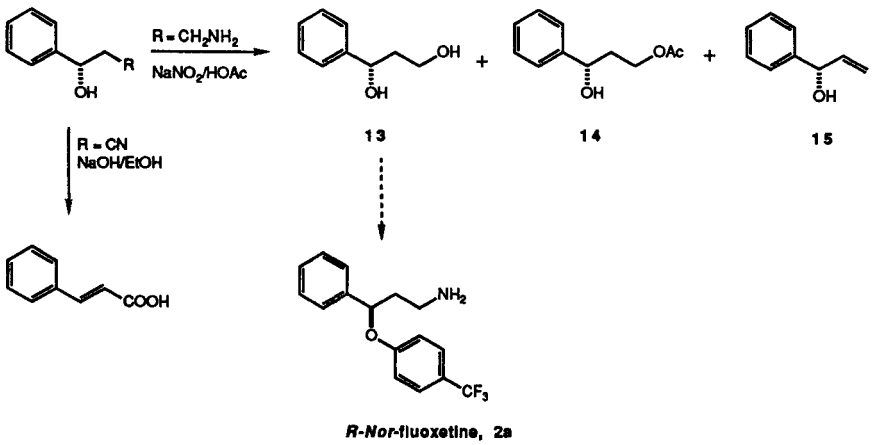


Attempts were made to convert **6b** into *R-nor*-fluoxetine via a series of reactions outlined in **Scheme 2**, thus enabling the preparation of both isomers of *nor*-fluoxetine from a common intermediate. Cleavage of the TMS-protecting group from non-labeled **6b** with methanol, followed by reaction of cyanohydrin **10** with α,α,α-trifluoro-4-cresol in the presence of diethyl azodicarboxylate/triphenylphosphine in THF, yielded not the desired cyanoether **11**, but cinnamonitrile. This presumably resulted from the elimination of triphenylphosphine oxide from the Mitsunobu intermediate **12**,[10] prior to displacement by ArO^-.

An alternative strategy (**Scheme 3**) would provide *R-nor*-fluoxetine from 1,3-glycol **13**, paralleling the work of Gao and Sharpless in their preparation of the pure enantiomers of fluoxetine and tomoxetine;[11] however, attempts to prepare **13** from **11** or **8** (non-labeled) were either unsuccessful or very low yielding reactions. Base hydrolysis of **13** yielded sodium cinnamate. Diazotization of **8** (non-labeled) in acetic acid yielded a complex mixture of 1,3-glycol **13**, its *primary* acetate **14**, and a number of more polar products. It was apparent that the preparation of R-*nor*-fluoxetine-[3-^{14}C]

would be more convenient in a procedure analagous to that shown in **Scheme 1**; that synthesis will not be detailed herein.

SCHEME 3



***R-Nor*-fluoxetine, 2a**

EXPERIMENTAL

The acetophenone-[^{14}C] was purchased from Sigma Radiochemicals. The NMR spectra were obtained on a General Electric QE-300 nuclear magnetic resonance spectrometer at 300 MHz. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Direct chemical ionization mass spectra (DCI-MS) and Electron Impact mass spectra (EI-MS) were recorded on a Nermag R30-10 triple stage quadrapole mass spectrometer. High resolution FAB mass spectra were recorded on a VG Analytical VG-ZAB 3F mass spectrometer.[12] Microanalytical, IR, and UV data were provided by the Physical Chemistry Research Department of the Lilly Research Laboratories.

Flash chromatography was performed as described by Still *et al.*, using E.M. Science silica gel 60 (230-400 mesh).[13] Unless otherwise noted, the organic extracts were dried over anhydrous sodium sulfate.

Radiochemical purity (RCP) was assessed by autoradiography employing E. Merck silica gel F-254 TLC plates and Kodak BB-5 x-ray film. The radioactive lane was divided, suspended in methanol, and after sonication, the mixture was diluted with Aquassure™ scintillation cocktail (DuPont NEN) and counted. As a further check of the radiochemical purity, the sample was subjected to radio-HPLC; 30 s samples of the eluent were collected, diluted with Aquassure™ and counted. Enantiomeric purity was determined by HPLC after derivatization with (*R*)-(-)-1-(1-naphthyl)ethylisocyanate (Aldrich Chemicals).[9]

The dimethylformamide (DMF) was stired over 4A-molecular sieves; the tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone.

2-Chloroacetophenone-[1-^{14}C], 3: Acetophenone-[1-^{14}C] (1000 mCi, sp. act. 21.1 mCi/mmol, 47.39 mmol) was dissolved in CCl_4 (125 mL), and treated with SO_2Cl_2 (31.98g, 19 mL, 236.97 mmol) under argon. The mixture was stirred under gentle reflux. After 20 hr, TLC (toluene) showed a substantial amount of unreacted acetophenone-[1-^{14}C] (R_f = 0.247), as well as the desired product (R_f = 0.455), and a higher R_f spot (0.675) which is presumably 2,2-dichloroacetophenenone-[1-^{14}C]. Refluxing was continued for an additional 20 hr; *ca.* 10% unreacted acetophenone-[1-^{14}C] remained. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (toluene in 20 mL fractions). Fractions 20-34 contained **3**. Fractions 16-19 were rechromatographed and combined to yield **3** (5.978 g, 81.9%); 0.35356 g of unreacted acetophenone-[1-^{14}C] was recovered. TLC (toluene) of **3** showed a single spot, co-eluting with authentic 2-chloroacetophenenone.

***R*-(-)-α-(Chloromethyl)benzenemethanol-[1-^{14}C], 4:** (-)-Diisopinocampheylchloroborane (13.975 g, 43.57 mmol) was transferred in a glovebag under argon and dissolved in THF (15 mL). The mixture was chilled to -30 to -35°C and a THF (15 mL) solution of **3** (5.978 g, 38.82 mmol) was added dropwise with stirring. The mixture was then stored at -25°C. After for 68 hr, a small aliquot was removed from the reaction mixture and quenched with methanol. TLC (4:1 hexanes/Et_2O) showed that the reaction was complete (>97% of the radioactivity was associated with the main spot, which co-eluted with authentic *R*-(-)-α-(chloromethyl)benzenemethanol). The THF was removed *in vacuo*; the residue was placed under high vacuum to remove the α-pinene.

The pale yellow residual oil was dissolved in Et_2O (155 mL) and treated with diethanolamine (8.97 g, 8.17 mL, 85.40 mmol, 2.2 eq). A white precipitate formed; the resulting

mixture was stirred for 2 hr and filtered. The filter cake was washed with Et_2O (3 x 25 mL). The filtrate was concentrated and the residue was purified by flash chromatography (eluted with 4:1 hexanes/Et_2O in 10 mL fractions). Fractions 21-46 were combined to yield **4** (5.272 g, 87%); TLC (4:1 hexanes/Et_2O) showed one major spot co-eluting with authentic material (there were also some minor UV transparent spots which stained with iodine); $[\alpha]_D$ (cyclohexane, c = 1.62) = -65.43°.

***R*-(-)-α-(chloromethyl)benzenemethanol, *tert.*-Butyldimethylsilyl Ether, 5a:** A DMF (100 mL) solution of *R*-(-)-α-(chloromethyl)benzenemethanol (2.4 g, 15.4 mmol), imidazole (1.21 g, 17.7 mmol), and *tert.*-butyldimethylsilyl chloride (2.67 g, 17.7 mmol) was stirred at room temperature overnight. The DMF was evaporated *in vacuo* and the residue was triturated with Et_2O (3 x 25 mL), decanted, and then re-concentrated. The crude material was purified by flash chromatography (hexanes in 20 mL fractions). Fractions 23-50 were combined and concentrated to yield **5a** (2.658 g, 64%): NMR ($CDCl_3$) δ -0.07 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.87 (9H, s, $C(CH_3)_3$), 3.57 (2H, m, CH_2Cl), 4.82 (1H, m, CH), and 7.31 (5H, m, aromatic); $(M + H)^+$ 271; $[\alpha]_D$ (cyclohexane, c = 1.54) = -64.94°; TLC (hexanes) R_f = 0.40. HRMS (EI): [M - *tert.*-Bu]$^+$ calc'd for $C_{10}H_{14}ClOSi$: 213.050246. Found: 213.049500.

***R*-(-)-α-(chloromethyl)benzenemethanol-[1-^{14}C], *tert.*-Butyldimethylsilyl Ether, 5b:** A mixture of **4** (5.272 g, 33.79 mmol), imidazole (2.64 g, 38.8 mmol), and *tert.*-butyl-dimethylsilyl chloride (5.85 g, 38.8 mmol) in DMF (200 mL) was stirred overnight at room temperature under argon and then worked up as described for **5a** to yield after flash chromatography **5b** (5.757 g, 63%): $[\alpha]_D$ (cyclohexane, c = 2.36) = -59.32°; TLC single spot with same R_f as **5a** (4:1 pentane/Et_2O and 9:1 pentane/Et_2O).

***R*-(+)-Phenyloxirane-[1-^{14}C], 7:** A THF (80 mL) solution of **5b** (5.757 g, 21.32 mmol) under argon was treated dropwise with *tetra-n*-butylammonium fluoride (1M in THF, 32 mL, 32 mmol); then stirred at room temperature. After 1 hr, 10% of the starting material remained by TLC (9:1 pentane/Et_2O; *ca.* 57% of the total radioactivity was due to **6**). After 3 hr, <0.2% of the starting material remained; the product was still only 57%, so the reaction was worked up. The THF was evaporated and the residue was redissolved in Et_2O (50 mL) and washed with H_2O. The Et_2O solution was dried and concentrated; the residue was purified by flash chromatography (eluted with 20 mL fractions of 9:1 hexanes/Et_2O). Fractions 14-16 were combined to yield **7** (1.0355 g, 40%), which co-eluted with authentic *R*-(+)-phenyloxirane on TLC (9:1 pentane/Et_2O). Fractions 17-19

yielded an additional 0.12869 g of material which was an 83:17 mixture of **7** and a lower R_f contaminant.(This material was retained and converted to **6b** separately from fractions 14-16 and purified at that stage).

***S*-(-)-3-Phenyl-3[(trimethylsilyl)oxy]propanenitrile-[3-^{14}C], 6b:**[14] Calcium oxide (1.726 g) was placed under vacuum and heated with a Bunsen burner until H_2O evolution ceased. The solid was allowed to cool and bled with argon. Heptane (20 mL) was added, followed by **7** (1.0355g, 8.63 mmol); the resulting mixture was treated dropwise with trimethylsilylcyanide (1.71 g, 2.30 mL, 17.26 mmol). After stirring for 1.5 hr (TLC 9:1 pentane/Et_2O showed no remaining **7**), the mixture was filtered. The filter cake was re-suspended in heptane (2 x 50 mL) and filtered. The combined filtrates were evaporated *in vacuo*, to yield **6b** (1.82746 g, 97%): TLC (9:1 pentane/Et_2O) showed a single spot co-eluting with authentic material;[5] $[\alpha]_D$ (toluene, c = 1.41) = -63.83°.

***S*-α-(2-Aminoethyl)benzenemethanol-[1-^{14}C] Oxalate Salt, 8:** Into a flame dried flask was placed **6b** (1.82747 g, 8.34 mmol) in THF (100 mL). The mixture was stirred under argon and treated dropwise with borane-THF (1M, 33.36 mL, 33.36 mmol) at room temperature; stirring was continued overnight. The excess borane was carefully decomposed by the dropwise addition of MeOH (80 mL). The mixture was concentrated *in vacuo*; the residue was redissolved in MeOH and then treated dropwise with HCl (1N, 27 mL). After stirring for 3 hr, the mixture was washed with Et_2O (2 x 25 mL) and then made basic by the portionwise addition of NaOH (1N,27 mL). The solution was saturated with NaCl and exhaustively extracted with Et_2O (7 x 75 mL). The combined extracts were dried and concentrated *in vacuo* to yield **8** as a slightly yellow oil (0.98820 g, 6.56 mmol).

The amino alcohol **8** was dissolved in EtOAc (25 mL) and treated at room temperature with a methanolic (3 mL) solution of oxalic acid (0.602 g, 6.69 mmol). A white precipitate formed immediately; stirring was continued for 2 hr. After chilling to 0-5°C, the solid was collected by filtration, washed with EtOAc, and dried (1.30103 g); $[\alpha]_D$ (MeOH, c = 1.11) = -34.23° (non-labeled **8**, $[\alpha]_D$ (MeOH, c = 2.21) = -41.63°). TLC (CH_2Cl_2/MeOH/ conc. NH_4OH 100:30:1) showed a single spot that co-migrated with authentic *S*-α-(2-aminoethyl)benzenemethanol.

***S*-(-)-γ-[4-(Trifluoromethyl)phenoxy]benzenepropanamine-[3-^{14}C], Hydrochloride Salt, 9:** An aqueous (20 mL) suspension of **8**-oxalate salt (1.30103 g, 5.398 mmol) was treated with KOH (3 eq, 5N, 3.2 mL) and extracted with Et_2O (5 x 75

mL). The combined extracts were washed with saturated brine, dried, and concentrated *in vacuo*. The residue was redissolved in toluene (10 mL) and concentrated, to azeotrope any residual water (this procedure was repeated three times) yielding **8** (0.76978 g). The amino alcohol **8** was redissolved in DMSO (4 mL) and stirred under argon. Sodium hydride (0.2258 g, 60% mineral oil dispersion, 5.65 mmol) was added portionwise at such a rate that hydrogen evolution did not become too vigorous. The mixture was heated at 60°C for 20 min and α,α,α,4-tetrafluorotoluene (1.77 g, 1.30 mL, 10.26 mmol) was added ; the temperature was raised to 90-95°C and stirring was continued for 1 hr.

The reaction mixture was allowed to cool to room temperature, then poured into NaOH (1N, 33 mL) and extracted with Et_2O (5 x 25 mL). The combined extracts were washed with H_2O, dried, and concentrated *in vacuo*. The crude product was purified by flash chromatography (eluted with 10 mL fractions of CH_2Cl_2/MeOH/ conc. NH_4OH 100:30:1). Fractions 25-35 were combined and concentrated *in vacuo* (0.6008 g). This purified material was redissolved in MeOH (3 mL), treated with NH_4Cl (0.1187 g, 2.24 mmol) and heated at 50°C for 20 min. The mixture was concentrated to an amorphous foam which was triturated with toluene/heptane (2:3, 4.5 mL) and stirred until crystalline, then an additional 1.5 hr. The solid was collected by filtration and recrystallized from hot toluene/heptane (1:3, 11 mL) to yield **9** HCl (0.37320 g, 55.3%); sp.act. = 65.7 μCi/mg (21.8 mCi/mmol); DCI-MS $(M + H)^+$ 296; enantiomeric purity 99.7% *S*;[9] radiochemical purity by TLC-autoradiography 98.27% and 98.42% ($CHCl_3$/MeOH/HOAc 70:30:1 and CH_2Cl_2/MeOH/ conc. NH_4OH 100:30:1 respectively); radio-HPLC (Zorbax RX-C8, 25 cm x 4.6 mm, eluted isocratically with acetonitrile/aqueous triethylamine buffer,[15] 40:60 at 1 mL/min) showed a radiochemical purity of 98.1%.

Attempted Synthesis of *R*-3-Phenyl-3-[(4-trifluoromethylphenyl)oxy]propanenitrile, 11: A mixture of **10** (0.610 g, 4.15 mmol), triphenylphosphine (1.09 g, 4.15 mmol), and α,α,α-trifluoro-4-cresol (0.672 g, 4.15 mmol) were dissolved in THF (15 mL) and chilled to 0°C. A THF (5 mL) of diethyl azodicarboxylate (0.653 mL, 4.15 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirring was continued overnight. The mixture was concentrated *in vacuo* and the residue was triturated with 6 x 10 mL of pentane and decanted. The pentane was evaporated and the residue was purified by flash chromatography (9:1 pentane/Et_2O). Fractions 13-18 were combined to yield material identical to cinnamonitrile by TLC and ^{1}H-NMR. Fractions 20-40 yielded unreacted α,α,α-trifluoro-4-cresol.

Attempted Synthesis of *R*-3-Phenyl-3-hydroxypropionic Acid: An EtOH (20 mL) solution of **10** (0.765 g, 5.2 mmol) and aqueous NaOH (2.3 mL x 5N, 4.45 mmol) were stirred at room temperature. After 48 hrs, no reaction had taken place, so the mixture was refluxed for 24 hrs. The mixture was allowed to cool, whereupon a white solid crystallized which was collected by filtration. The solid was dissolved in water and acidified with 1N HCl. The resulting solid was collected by filtration, washed with water, and dried to yield cinnamic acid (TLC, ^{1}H-NMR).

Synthesis of *S*-3-Phenyl-1,3-propanediol, 13: An aqueous (50 mL) solution of 8 (non-labeled, 1.51 g, 10 mmol) and HOAc (1.2 g, 20 mmol) was cooled to 0°C, and treated dropwise with $NaNO_2$ (1.38 g, 20 mmol) in water (20 mL). The mixture was allowed to warm to room temperature and was extracted with 5 x 20 mL of EtOAc. The combined extracts were washed with H_2O and dried. Concentration yielded a yellow oil which was shown to be a complex mixture by TLC ($CHCl_3/CH_3OH$ 10:1 and pentane/Et_2O 7:3. DCI-MS showed ions at m/z 135, 153, and 195 (among others) which correspond to $(M + H)^+$ for **15**, **13**, and **14** respectively. The mixture was separated by flash chromatography ($CHCl_3/CH_3OH$ 10:1) to yield 0.047 g (3.1%) of **14** (fractions 15-20) which was identical in all respects to authentic material.[11]

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14. The change from *R* to *S* in this preparation is a consequence of the Cahn-Ingold-Prelog convention rather than an inversion of stereochemistry in the reaction.
15. The triethylamine buffer was prepared as a 99:1 water/triethylamine solution, adjusted to pH 6 with phosphoric acid.