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Stereoselective Synthesis of 2-Aryloxy Esters: An Asymmetric Approach to Fluoxetine, Tomoxetine and Nisoxetine

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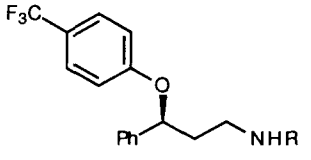
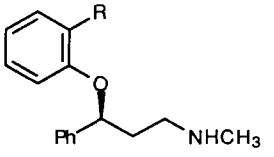
Serotonin and norepinephrine uptake inhibitors have proven to be indispensible for the treatment of psychiatric disorders such as anxiety and clinical depression.[1] In addition, several members of this class have shown promise for the treatment of alcoholism, chronic pain and eating disorders such as obesity and bulimia.[2] Fluoxetine, marketed under the trade name Prozac®, has recently surpassed the $2 billion mark in annual sales. The four most prominent compounds of this class are depicted below and accordingly, several asymmetric syntheses of these compounds have appeared (Figure **1**).





1 R = H (S)-Norfluoxetine

2 R = CH_3 (S)-Fluoxetine

3 R = CH_3 (S)-Tomoxetine

4 R = OCH_3 (S)-Nisoxetine

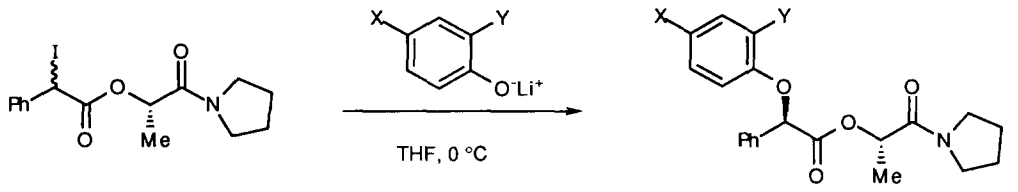
Figure **1**

Chirality has been introduced into these compounds via enantioselective epoxidation followed by stereoselective openings[3] as well as chemical[4] and enzymatic[5] reductions of precursory ketones and esters. All the syntheses thus far reported go through a common 3-phenyl-3-hydroxy substituted propylamine or alcohol intermediate. The most elegant synthesis of fluoxetine has been reported by the Corey group wherein asymmetry was introduced via an oxazaborolidine catalyzed ketone reduction.[6] The trifluoromethylphenyl functionality was introduced through an O-arylation reaction between the sodium salt of the alcohol and the *p*-chloroaryl derivative. The synthesis was completed in 4 steps with an overall yield of 77-82%. The O-arylation reaction proved to be problematic in the synthesis of tomoxetine.[7] The product was formed in moderate chemical yield with accompanying racemization at the chiral center. Tomoxetine and nisoxetine have been synthesized via a

Mitsunobu reaction between the chiral alcohol and the appropriately substituted phenol although the process is not amenable to scale-up.[3a, 4b, 5d]

Recently, we described a highly stereoselective coupling reaction between racemic α-haloacids and aryloxides mediated by a pyrrolidine derived (S)-lactamide auxiliary.[8] The auxiliary utilized is inexpensive and easily prepared in multigram quantities. Diastereoselectivities greater than 95% are routinely obtained at ambient temperature and product is formed in excellent yield. This note describes application of the highly stereoselective coupling reaction to the enantiopure preparation of fluoxetine, tomoxetine and nisoxetine.

Iodoester **5** was synthesized from the α-bromo compound via the Finkelstein reaction. The bromide was in turn synthesized from the commercially available bromoacid and the chiral auxiliary whose synthesis has been reported elsewhere.[9]



5

6 X=H, Y=Me
7 X=H, Y=OMe
8 X=CF_3, Y=H

Entry	X	Y	Time (h)	Yield (%)	DR*
1	H	Me	0.1	85	98:2
2	H	OMe	2	87	97:3
3	CF_3	H	2	83	99:1

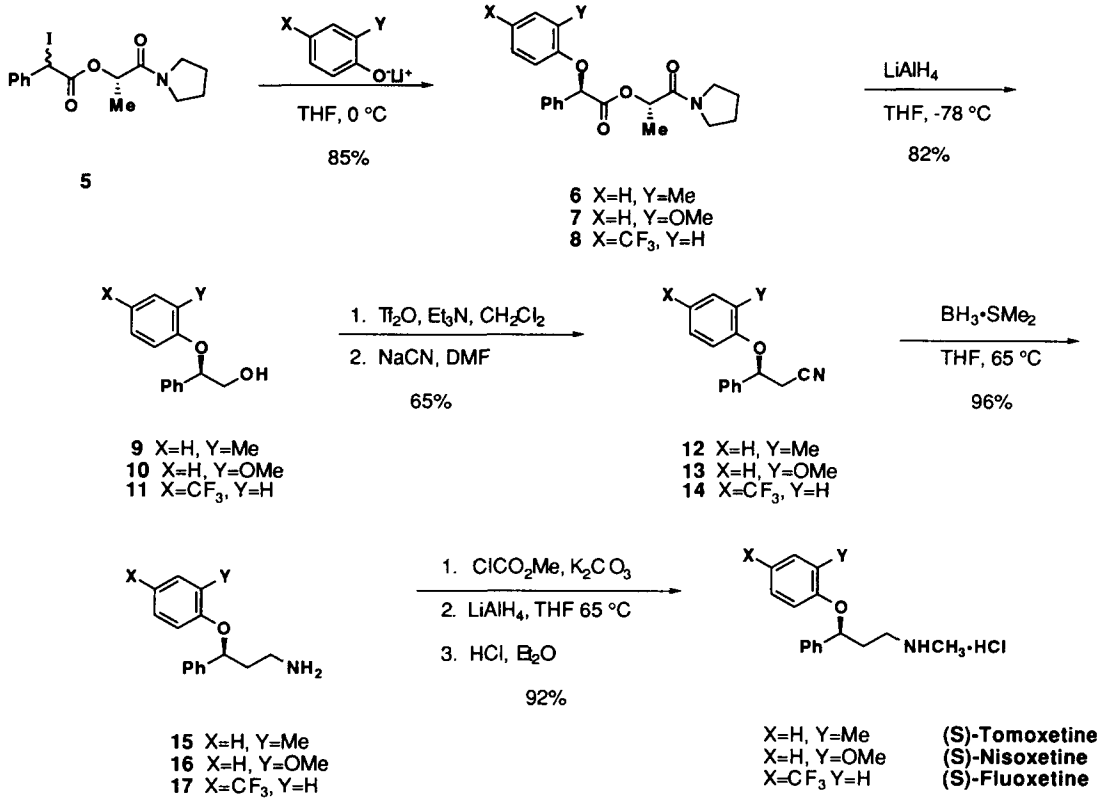
*Diastereomeric ratios determined via HPLC utilizing a Supelcosil LC-CN or Chiracel OD column and via 300 MHz ^{1}H NMR integration of the diastereomeric methine protons of methyl doublets.

Scheme **1**

The iodoester undergoes a highly stereoselective reaction with the lithium salt of *o*-cresol at 0 °C (Entry **1**).[10] The product is isolated in 85% yield as a 98:2 mixture of diastereomers. The absolute configuration about the newly formed stereogenic center has previously been determined to be "R".[8] Electronic effects showed little effect on stereoselectivity as high diastereomeric ratios were obtained with the electron rich phenol, guaiacol (Entry **2**) as well as with the more electron deficient *p*-trifluoromethylphenol (Entry **3**). The diastereomers are readily separated through chromatography, although the crude material was generally carried on to the subsequent steps. It was found that the optical purity of the final compounds could be upgraded through recrystallization of their hydrochloride salts, thus obviating the need for chromatography.

The synthesis of tomoxetine is described below (Scheme **2**). The syntheses of fluoxetine and nisoxetine were accomplished in similar fashion. The crude coupled product **6** was treated with $LiAlH_4$ in THF at -78 °C to

obtain alcohol **9** in 82% yield. The reaction was found to proceed without concommittant loss in stereochemistry at the chiral center as evidenced by chiral HPLC. Initially, alcohol **9** was transformed into the mesylate upon treatment with methanesulfonyl chloride and triethylamine. However, all attempts to displace the mesylate with cyanide anion met with failure.



5

6 X=H, Y=Me
7 X=H, Y=OMe
8 X=CF_3, Y=H

9 X=H, Y=Me
10 X=H, Y=OMe
11 X=CF_3, Y=H

12 X=H, Y=Me
13 X=H, Y=OMe
14 X=CF_3, Y=H

15 X=H, Y=Me
16 X=H, Y=OMe
17 X=CF_3, Y=H

Scheme 2

Conducting the reaction at elevated temperatures led to decomposition of the mesylate. The problem was circumvented by converting the alcohol to the triflate. The alcohol reacted smoothly with triflic anhydride in the presence of triethylamine to give the triflate. This compound was found to be remarkably stable and could be isolated via an aqueous work-up. The crude triflate reacted instantaneously with sodium cyanide in DMF at ambient temperatures giving nitrile **12** in 65% overall yield from alcohol **9**. The nitrile was readily reduced with borane in refluxing THF giving primary amine **15** in 96% isolated yield. N-methylation to give tomoxetine was accomplished by first forming the carbamate under Schotten-Baumann conditions. Chiral HPLC assay of the carbamate indicated that the stereochemical integrity of the asymmetric center was preserved throughout the synthetic sequence.[10] Reduction of the carbamate followed by acidification according to literature precedent afforded tomoxetine hydrochloride as one enantiomer.[7] Measurement of optical rotation indicated the product

formed possessed the "S" stereochemistry. The synthesis of (S)-tomoxetine was completed in eight steps from iodide **5** in 40% overall yield. The syntheses of (S)-fluoxetine and (S)-nisoxetine were accomplished in similar fashion in 37% and 42% overall yield, respectively.

A highly asymmetric synthesis of (S)-tomoxetine, (S)-fluoxetine and (S)-nisoxetine has been achieved. This is the first approach where a key chiral intermediate is not a 3-hydroxy-3-phenyl substituted propylamine or propylalcohol derivative and therefore circumvents problems associated with these syntheses. The auxiliary utilized is inexpensive and readily prepared allowing for the synthesis of multigram quantities of these useful therapeutic agents.

Experimental Section

Proton and ^{13}C spectra were obtained on a Bruker AM-300 spectrometer and recorded at 300 and 75 MHz, respectively. The IR absorption spectra were recorded on a Perkin-Elmer 281B spectrophotometer. Commercially available organic and inorganic compounds were used without further purification. THF, CH_2Cl_2 and Et_2O were dried over 4Å molecular sieves prior to use. The synthesis of tomoxetine is described below. The syntheses of fluoxetine and nisoxetine were accomplished in similar fashion.

General Coupling Methodology: The following coupling procedure is typical for all coupling reactions: To a solution of *o*-cresol (0.33 ml, 3.2 mmol) in THF (5 ml) at 0 °C was added nBuLi (1.2 ml of 2.5 M sol'n in hexanes, 3.0 mmol). The reaction was stirred for 5 min. and then added via cannula to a solution of iodide **5** (1.1 g, 2.9 mmol) also at 0 °C. The reaction was stirred for 10 min and then quenched with aqueous sodium bicarbonate (10 ml). The phases were separated and the aqueous phase was extracted with EtOAc (2x10 ml). The combined organic phases were washed with brine (1x10 ml) and dried ($MgSO_4$). Concentration under reduced pressure gave a viscous yellow oil which was used without further purification. An analytical sample was purified via flash chromatography (2:1 hexanes:EtOAc).

Coupling Product 6: IR ($CHCl_3$) 2980, 2875, 1750, 1640, 1455 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.33(d, J=6.7Hz, 3H), 1.85(m, 4H), 2.34(s, 3H), 3.27(m,1H), 3.44(m, 3H), 5.22(q, J= 6.7Hz, 1H), 5.75(s, 1H), 6.81(d, J=8.0Hz,1H), 6.87(m, 1H), 7.13(m, 2H), 7.40(m, 3H),7.64(m, 2H). ^{13}C NMR ($CDCl_3$) δ 16.3, 16.50, 23.9, 26.1, 46.0, 46.2, 69.3, 78.0, 112.3, 121.5, 126.9, 127.06, 127.5, 128.73, 128.9, 130.9, 135.7, 155.4, 167.9, 169.7. Anal. Calc'd. for $C_{22}H_{25}NO_4$: C, 71.84; H, 6.86; N, 3.81. Found: C, 71.41; H, 7.11; N, 3.56.

Coupling Product 7: IR (film) 2970, 2875, 1755, 1660, 1590, 1500, 1455 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.33(d, J=6.8Hz, 3H), 1.84 (m, 4H), 3.26 (m, 1H) 3.47(m, 3H) 3.86(s, 3H), 5.26(m, 1H), 5.75 (s, 1H), 6.8-6.9 (m, 4H), 7.3-7.4 (m, 3H), 7.62(m, 2H). ^{13}C NMR ($CDCl_3$) δ 16.4, 23.9, 26.16, 46.0, 46.2, 56.1, 69.2,

79.6, 112.6, 117.6, 120.9, 123.1, 127.3, 128.7, 128.9, 135.7, 146.7, 150.4, 167.9, 169.7. HRMS (CI^+) Calc'd for $C_{22}H_{25}NO_5$, 383.1733, found 383.1738.

Coupling Product 8: mp= 68-69°C. IR ($CHCl_3$) 2980, 1753, 1649, 1615, 1445, 1329 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.375(d, J= 6.8Hz, 3H), 1.81-1.97(m, 4H), 3.25-3.33(m, 1H), 3.39-3.48(m, 1H), 3.5-3.57(m, 2H), 5.19(q, J=6.7Hz, 1H), 5.78(s, 1H), 7.07(m, 2H), 7.38-7.45(m, 3H), 7.55(m, 2H), 7.58-7.62(m, 2H). ^{13}C NMR ($CDCl_3$) δ 16.3, 23.9, 26.1, 46.0, 46.2, 69.5, 78.0, 115.5, 123.8 (q, J_{CF}=32.7Hz), 124.4 (q, J_{CF}=271.3), 127.1 (q, J_{CF}=3.6Hz), 127.3, 128.9, 129.3, 134.6, 159.5, 168.0, 169.0. Anal. Calc'd. for $C_{22}H_{22}F_3NO_4$: C, 62.69; H, 5.27. Found C, 62.63; H, 5.39.

Alcohol Formation: To a solution of ester **6** (1.1 g, 2.9 mmol) in THF (20 ml) at -78 °C was added $LiAlH_4$(10 ml of a 1.0 M sol'n in THF, 10 mmol). The reaction was stirred for 0.5 h and was quenched by the careful addition of MeOH. The reaction was allowed to warm to RT and was partitioned between EtOAc and 1 N HCl. The phases were separated and the aqueous phase was extracted with EtOAc (2 x 20 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give 0.61 g (92%) of a pale yellow oil. The material thus formed was suitable for further use. An analytical sample was purified via flash chromatography (4:1 Hexanes:EtOAc).

Alcohol 9: Chiral HPLC (R,R) Whelk-O column , Hexane:IPA (98:2), Flow rate=1mL/min. Major isomer Rt= 16.46 min. Minor isomer Rt= 18.32 min.

IR (film) 3380 (br), 3030, 3015, 2920, 1605, 1115 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.28 (dd, J=3.7, 9.1 Hz , 1H (OH)), 2.37(s, 3H), 3.90(m, 2H), 5.31(dd, J=3.7, 8.1 Hz, 1H), 6.67(d, J=8.2 Hz, 1H), 6.83 (m, 1H) 7.00(m, 1H), 7.15(m, 1H), 7.2-7.4(m, 5H). ^{13}C NMR ($CDCl_3$) δ 16.7, 67.7, 80.9, 113.1, 120.9, 126.3, 126.8, 127.0, 128.2, 128.8, 130.9, 138.1, 155.7. Anal. Calc'd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.07; H, 7.22.

Alcohol 10: Chiral HPLC (R,R) Whelk-O column, Hexane: IPA (95:5), Flow Rate =1.0ml/min, Major isomer Rt=17.07 min , Minor Rt=23.36 min.

IR(film) 3480(br), 3060, 3025, 2930, 1585, 1495 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.80(m, 1H), 3.89(s, 3H), 4.00(m, 1H), 5.17(dd, J=2.9, 8.4Hz, 1H), 6.76(m, 2H), 6.93(m, 2H), 7.3-7.4(m, 3H), 7.44(m, 2H). ^{13}C NMR ($CDCl_3$) δ 55.9, 67.5, 84.5, 112.0, 117.6, 121.0, 122.5, 126.5, 128.2, 128.7, 138.5, 147.8, 150.3. HRMS (CI^+) Cacl'd for $C_{15}H_{16}O_3$, 244.1099, found 244.1102.

Alcohol 11: IR (film) 3420 (br), 3070, 3030, 1713, 1614, 1512, 1160, 1110 cm^{-1}. ^1H NMR($CDCl_3$) δ 3.83-3.88(m, 1H), 3.09-4.01(m, 1H), 5.32(dd, J= 3.6,8.1Hz, 1H), 6.94(m, 2H), 7.29-7.43(m, 5H), 7.459(m, 2H). ^{13}C NMR ($CDCl_3$) δ 67.4, 81.4, 115.8, 123.4 (q, J_{CF}=32.4Hz), 124.3(q, J_{CF}=271.4Hz), 126.3, 126.9(q, J_{CF}=3.5Hz), 128.6, 129.0, 136.9, 160.2.
Anal. Calc'd. for $C_{15}H_{13}F_3O_2$: C, 63.83; H, 4.64. Found C, 63.63; H, 4.55.

Nitrile Formation: To a solution of alcohol **9** (0.29 g, 1.27 mmol) in CH_2Cl_2 (10 ml) at 0 °C was added triflic anhydride (0.28 ml, 1.65 mmol) followed by Et_3N (0.27 ml, 1.91 mmol). The reaction was stirred 15 min and was quenched with $NaHCO_3$(aq) (10 ml). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude triflate thus obtained was dissolved in DMF (3 ml). NaCN (0.12 g, 2.54 mmol) was added and the reaction was stirred 15 min and then was partitioned between Et_2O and H_2O. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with H_2O (3 x 10 ml), dried ($MgSO_4$) and then concentrated under reduced pressure. The crude material was pure enough for further use but can be purified via flash chromatography (8:1 Hexanes:EtOAc) to give 0.2 g (66%) of a colorless oil.

Nitrile 12: IR (film) 3025, 2920, 2245, 1600, 1115 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.39 (s, 3H), 2.97 (m, 2H), 5.43 (t, J=6.1 Hz, 1H), 6.60(d, J=8.1Hz, 1H), 6.87(m, 1H), 7.01(m, 1H), 7.18 (d, J=7.3Hz, 1H), 7.2-7.4 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 16.5, 27.5, 75.2, 113.0, 116.7, 121.5, 125.7, 126.7, 127.6, 128.9, 129.2, 131.1, 138.6, 155.0. Anal. Calc'd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.78; H, 6.35; N, 5.90.

Nitrile 13: IR (film) 3060, 2960, 2950, 2240, 1590, 1500, 1455, 1250, 1225 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.00 (m, J=6.3, 16.5Hz, 2H), 3.89 (s, 3H), 5.4 (t, J=6.3, 1H) 6.77(m, 2H), 6.95 (m, 2H), 7.36 (m, 3H), 7.46 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 27.0, 56.1, 112.7, 116.9, 118.5, 120.9, 123.4, 126.3, 128.9, 138.6, 146.3, 150.8. HRMS (CI^+) Calc'd for $C_{16}H_{15}NO_2$, 253.1103, found 253.1094.

Nitrile 14: mp= 82-83°C. IR ($CHCl_3$) 3015, 2255, 1614, 1510, 1327, 1163, 1112 cm^{-1}. ^1H NMR($CDCl_3$) δ 2.98(m, 2H), 5.46(dd, J=5.6, 6.6Hz, 1H), 6.93(m, 2H), 7.32-5.1(m, 5H), 7.49(m, 2H). ^{13}C NMR ($CDCl_3$) δ 27.5, 75.6, 116.0, 116.3, 124.0(q, J_{CF}=32.9Hz), 124.2(q, J_{CF}=271.3Hz), 125.76, 127.0(q, J_{CF}=3.6Hz), 129.3, 129.4, 137.5, 159.3.
Anal. Calc'd. for $C_{16}H_{12}F_3NO$: C, 65.97; H, 4.16. Found C, 65.49; H, 4.19.

Amine Formation: To a solution of nitrile **12**(0.92 g, 3.88 mmol) in THF (20 ml) was added BH_3•SMe_2 (0.58 ml, 5.82 mmol). The reaction was heated at reflux for 5h and then cooled to RT. MeOH (5 ml) followed by 6 N HCl (5 ml) were added and the reaction was heated to reflux for an additional 0.5 h and was then concentrated under reduced pressure. The residue was partitioned between Et_2O and 1 N HCl. The phases were separated and the aqueous phase was basified with 5 N NaOH and extracted with CH_2Cl_2 (5 x 10 ml). The combined organic phases were dried (K_2CO_3) and concentrated under reduced pressure.

Amine 15: IR (film) 3300, 3020, 2920, 1600, 1585, 1490, 1235 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.10(m, 1H), 2.21(m, 1H), 2.35(s, 3H), 2.95(m, 2H), 3.51(broad s, 2H), 5.29(dd, J=4.4, 8.24 Hz, 1H), 6.63(d, J=8.1Hz, 1H), 6.80(m, 1H), 6.97(m, 1H), 7.14 (d, J=7.3Hz, 1H), 7.2-7.4 (m, 5H). ^{13}C NMR ($CDCl_3$) δ16.7, 38.4, 41.5, 77.6, 112.8, 120.4, 125.8, 126.7, 127.0, 127.6, 128.7, 130.7, 141.9, 155.9. HRMS (CI^+) Calc'd for $C_{16}H_{19}NO$, 241.1467, found 241.1479.

Amine 16: IR (film) 3360, 2930, 1590, 1500, 1455, 1250, 1220, 1120 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.00 (m, 1H), 2.24 (m, 1H), 2.96 (m , 2H), 3.89(s, 3H), 5.21(dd, J= 4.4, 8.7 Hz, 1H), 6.68(m, 2H), 6.86(m, 2H), 7.2-7.4 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 39.1, 41.9, 56.0, 80.6, 112.0, 116.4, 120.7, 121.6, 126.0, 127.6, 128.6, 141.9, 147.6, 150.1. HRMS (CI^+) Calc'd for $C_{16}H_{19}NO_2$, 257.1416, found 257.1398.

Amine 17: IR (film) 3370, 3065, 3035, 2935, 2870, 1900, 1615, 1590, 1515, 1152, 1065 cm^{-1}. ^1H NMR($CDCl_3$) δ 1.38(broad s, 2H), 1.97(m, 1H), 2.18(m, 1H), 2.89(m, 2H), 5.32(dd, J=4.7, 8.3Hz, 1H), 6.91(m, 2H), 7.2-7.39(m, 5H), 7.42(m, 2H). ^{13}C NMR($CDCl_3$) δ 38.6, 42.3, 78.4, 115.8, 122.8(q, J_{CF}=32.6Hz), 124.4(q, J_{CF}=271.3Hz), 125.8, 126.8(q, J_{CF}=3.8Hz), 127.9, 128.8, 141.1, 160.6.

Carbamate Formation: To a solution of amine **15** (0.55 g, 2.28 mmol) and chloroformate (0.26 ml, 2.73 mmol) in CH_2Cl_2 (10 ml) was added an aqueous solution of K_2CO_3 (1.6 g, 11.4 mmol dissolved in 20 ml H_2O). The reaction was rapidly stirred for 10 min. and was diluted with H_2O. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (1 x 10 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give 0.71 g (99%) of a pale yellow oil.

Carbamate 18: IR (film) 3420, 3325, 3020, 2975, 2920, 1700, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.25 (t, J=7.1Hz, 3H), 2.18(m, 2H), 2.38 (s, 3H), 3.41(m, 2H), 4.12 (q, J=7.1Hz, 2H), 5.10(br s, 1H), 5.28(dd, J=4.7, 7.4 Hz, 1H), 6.60(d, J=8.2Hz, 1H), 6.81(m, 1H), 6.95 (m, 1H), 7.15 (d, J=7.2Hz, 1H), 7.26(m, 1H), 7.349(m, 4H). ^{13}C NMR ($CDCl_3$) δ 14.7, 16.7, 38.2, 38.7, 60.8, 78.1, 112.7, 120.5, 125.7, 126.7, 126.9,

127.7, 128.8, 130.8, 141.4, 155.7, 156.8. Anal. Calc'd. for $C_{19}H_{23}NO_3$: C, 72.75; H, 7.40; N, 4.47. Found C, 72.36; H, 7.41; N, 4.28.

Carbamate 19: IR (film) 3380, 3060, 2900, 1710, 1595, 1500, 1455, 1250, 1220 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.29 (t, J=7.1Hz, 3H), 2.13(m, 2H), 3.30(m, 1H), 3.60(m, 1H), 3.96(s, 3H), 4.15 (q, J=7.1Hz, 2H), 5.16 (dd, J=6.1, 6.1Hz, 1H), 6.50(brs, 1H), 6.56(d, J=7.7Hz, 1H), 6.69(m, 1H), 6.89(m, 2H), 7.25-7.35(m, 5H). ^{13}C NMR ($CDCl_3$) δ 14.9, 38.7, 38.9, 55.6, 60.5, 82.3, 111.3, 115.4, 120.7, 121.6, 125.7, 127.8, 128.7, 141.4, 147.3, 149.6, 157.0.

Carbamate 20: IR (film) 3420, 3030, 2980, 1610, 1590, 1513, 1328, 1036 cm^{-1}. ^1H NMR($CDCl_3$) δ 1.23(t, J=7.1Hz, 3H), 2.17(m, 2H), 3.38(m, 2H), 4.1(q, J=7.1Hz, 2H), 4.87(br s, 1H), 5.23(dd, J=4.5,8.3Hz, 1H), 6.89(m, 2H), 7.24-7.40(m, 5H), 7.44(m, 2H). ^{13}C NMR($CDCl_3$) δ 14.6, 38.0, 38.9, 60.9, 78.6, 115.8, 123.1(q, J_{CF}=32.4Hz), 124.4(q, J_{CF}=271.5Hz), 125.7, 126.8(q, J_{CF}=3.6Hz), 128.1, 128.9, 140.5, 156.7, 160.3.

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10. The HPLC conditions were as follows: Chiracel OD column, hexane:2-propanol 80:20 isocratic elution, flow rate = 1.0 ml/min., UV detection at 220 nm. Major enantiomer t_R=8.87 min., minor enantiomer t_R=10.90 min.

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