

# A Practical Synthesis of a Chiral Analogue of FTY720

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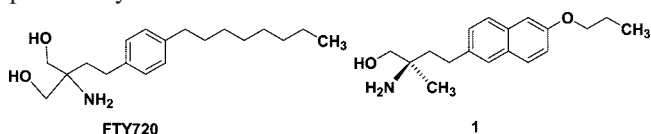
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## Abstract:

A practical synthesis of **1** involving a catalytic enantioselective construction of the quaternary carbon from imine **10** (derived from **13** and **14**) and alkyl iodide **5** using Maruoka's chiral catalyst **11** is described. This asymmetric alkylation followed by hydrolysis to amino acid **9** was accomplished in good yield with high chemical purity (>98%) and chiral purity (>96% ee). The improved synthesis enabled production of **1** in seven chemical steps (six isolations) in an overall yield of 22%.

## Introduction

FTY720 is a novel immunomodulator which acts via S1P-receptor agonism and is highly effective in animal models of organ transplantation and autoimmunity. Chiral derivatives of FTY720 played an important role in the initial understanding of FTY720's mode of action.<sup>1</sup> They are also invaluable tools to clarify further the pharmacology of single S1P-receptors. Compound **1** was selected as an interesting chiral analogue of FTY720 for further development, and in this publication a practical synthesis of **1** is described.



The previous method<sup>2</sup> that had been used for making compound **1** is shown in Scheme 1. The key reaction in this sequence is the generation of the quaternary carbon in compound **7** which is achieved from compound **5** using Val-Ala-derived Schölkopf auxiliary **6**.<sup>3</sup>

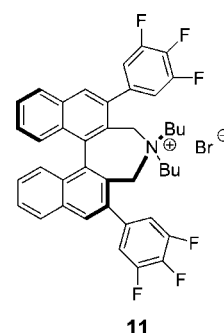
The diastereoselectivity of the C–C bond-forming alkylation step was 90–95%. Although this chemistry is elegant in the academic sense, it is of less preparative value as one needs to use stoichiometric amounts of Schölkopf's reagent, which is expensive and not readily available. In addition, these alkylation conditions needed low temperature (typically –70 °C) and workup was cumbersome. In addition, elimination of HI from **5** occurred to a significant extent as the reaction utilized *n*-butyllithium.

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- (1) (a) Brinkmann, V. *Yonsei Med. J.* **2004**, *45*, 991–997. (b) Chiba, K. *Pharmacol. Ther.* **2005**, *108*, 308–319. (c) Albert, R.; Hinterding, K.; Brinkmann, V.; Guerini, D.; Müller-Hartwig, C.; Knecht, H.; Simeon, C.; Streiff, M.; Wagner, T.; Welzenbach, K.; Zecri, F.; Zollinger, M.; Cooke, N.; Francotte, E. *J. Med. Chem.* **2005**, *48*, 5373–5377.
- (2) (a) Hinterding, K.; Cottens, S.; Albert, R.; Zecri, F.; Buehlmayer, P.; Spanka, C.; Brinkmann, V.; Nussbaumer, P.; Eitmayer, P.; Hoegenauer, K.; Gray, N.; Pan, S. *Synthesis* **2003**, 1667. (b) Buehlmayer, P.; Hinterding, K.; Spanka, C.; Zecri, F., WO 2004/024673, CAN 140: 287164 AN 2004:252472, 2004.
- (3) (a) Schölkopf, U.; Groth, U.; Westphalen, K.-O.; Deng, C. *Synthesis* **1981**, *12*, 969. (b) Schölkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799.

As our aim was to make **1** on multikilogram scale for further study, we evaluated all possible options, trying to improve the research route to **1**. After brief evaluation, we settled on the strategy shown in Scheme 2.

Since the introduction of the term phase transfer catalysis by Starks<sup>4</sup> in 1971, many phase transfer catalysts have been developed and successfully used in organic synthesis to construct many useful molecules for academia and industries.<sup>5</sup> Of particular relevance to our work was the method reported by Maruoka, in which a series of optically enriched disubstituted  $\alpha$ -amino acids were synthesized by alkylation of the alanine-derived imines in the presence of chiral phase transfer catalyst **11**. The enantiomeric excess of the products reported under these conditions varied from 90 to 99%. The final synthesis of compound **1** that we designed based on this approach is shown in Scheme 3.

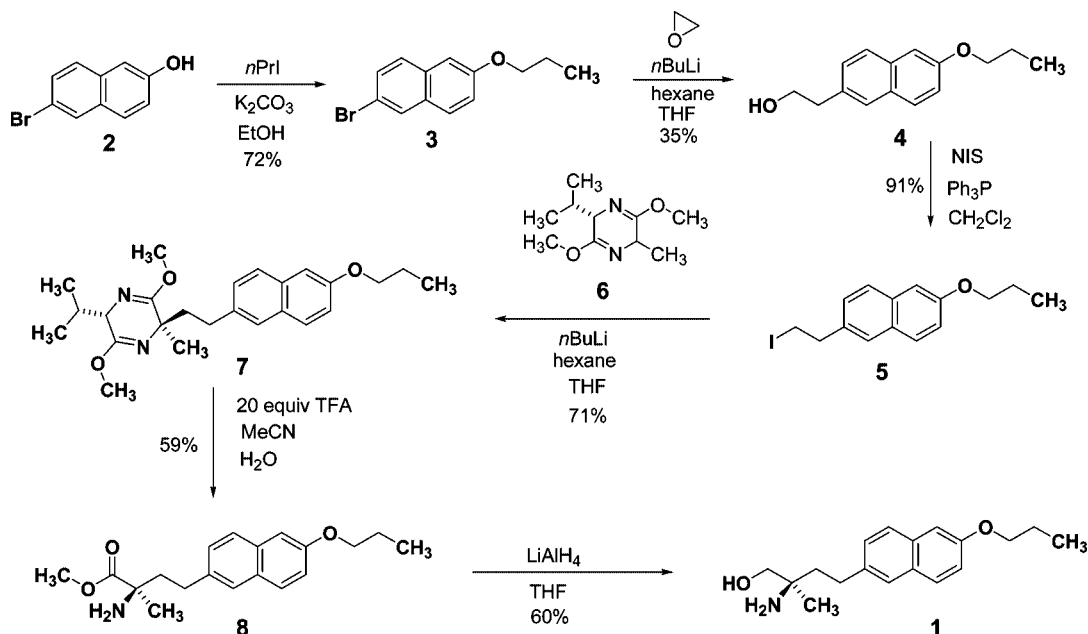


**Synthesis of Iodo Intermediate 5.** Although the synthesis of **5** employed by research was straightforward, we modified their route as ethylene oxide that was used for introducing the hydroxyethyl chain is toxic and has low emission limits. The details are as follows. For converting **2** to **3** in the finalized procedure, acetone was used as the solvent, and alkylation was conducted with 1-iodopropane using potassium carbonate as the base. Product **3** (95% yield and 99% purity by HPLC) was precipitated from the reaction mixture by water addition. The modification involves a palladium-catalyzed C–C bond formation<sup>6</sup> as shown in Scheme 4.

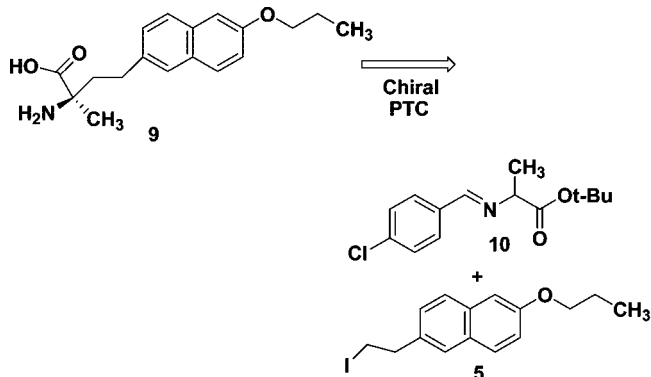
In this two-step process, the reaction mixture containing **3**, ethyl acetoacetate,  $K_3PO_4 \cdot H_2O$ ,  $Pd(OAc)_2$ , and a phosphino ligand in toluene was first heated to 85–90 °C to generate the intermediate shown in Scheme 4, which was then deacylated by heating at 100–104 °C. To minimize the formation of des-bromo byproduct, the first-step reaction temperature should be kept strictly at 85–90

- (4) Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195.
- (5) Maruoka, K. *Asymmetric Phase Transfer Catalysis*; Wiley-VCH Verlag GmbH & Co., KGaA: Weinheim, 2008 and references therein.
- (6) Zeevaert, J. G.; Parkinson, C. J.; de Koning, C. B. *Tetrahedron Lett.* **2004**, *45*, 4261.

**Scheme 1. Research synthesis**



**Scheme 2. Retrosynthesis**



°C. The reaction temperature was then raised to 100–104 °C after HPLC analysis confirmed the complete consumption of starting material **3**. Premature heating of the reaction mixture to 100–104 °C could generate up to 15% of the des-bromo byproduct, which was difficult to remove as **12** is an oil. With the two-staged temperature control approach, the unwanted des-bromo byproduct was minimized to <2%. When anhydrous  $K_3PO_4$  was used as the base, we found that it took more than 24 h to complete the deacylation, whereas a small amount of water accelerated this deacylation. Consequently,  $K_3PO_4$  monohydrate was used as the base, and the deacylation was usually finished within 5 h. We observed light etching of the glassware when using  $K_3PO_4$  monohydrate, and the use of metal reactors is recommended for this purpose.

The transformation of **12** to **4** was accomplished using  $LiBH_4$  in THF at 60 °C. The major byproduct was the olefin formed from elimination. The chemical purity at this stage can be increased to >98% by slurrying the crude product in a mixture of isopropyl acetate and *n*-heptane, and **4** was isolated in 85% yield. Research used NIS and  $Ph_3P$  to convert **4** to **5**. Silica gel column purification was required, as both succinimide and  $Ph_3PO$  were generated as byproducts in large quantities. To

simplify the purification process, a modified procedure utilizing  $Ph_3P$ ,  $I_2$ , and imidazole was adopted.<sup>7</sup> The imidazole hydrogen iodide salt was easily removed by aqueous workup. The majority of  $Ph_3PO$  was removed as an insoluble solid by slurrying the crude product in a 1:1 ratio of MTBE and *n*-heptane followed by filtration. This simple treatment removed more than 90% of  $Ph_3PO$ . The rest was removed by a simple silica gel pad filtration. Iodo intermediate **5** was obtained in 90.6% yield with 98.1% HPLC purity.

**Main-Chain Chemistry.** Aldimine **10** was prepared from alanine *tert*-butyl ester hydrochloride **12** and 4-chlorobenzaldehyde **13** in the presence of  $MgSO_4$  in methanol. Product **10** was isolated in 95% yield and >98% purity by NMR, and it was used as a toluene solution in the next step.

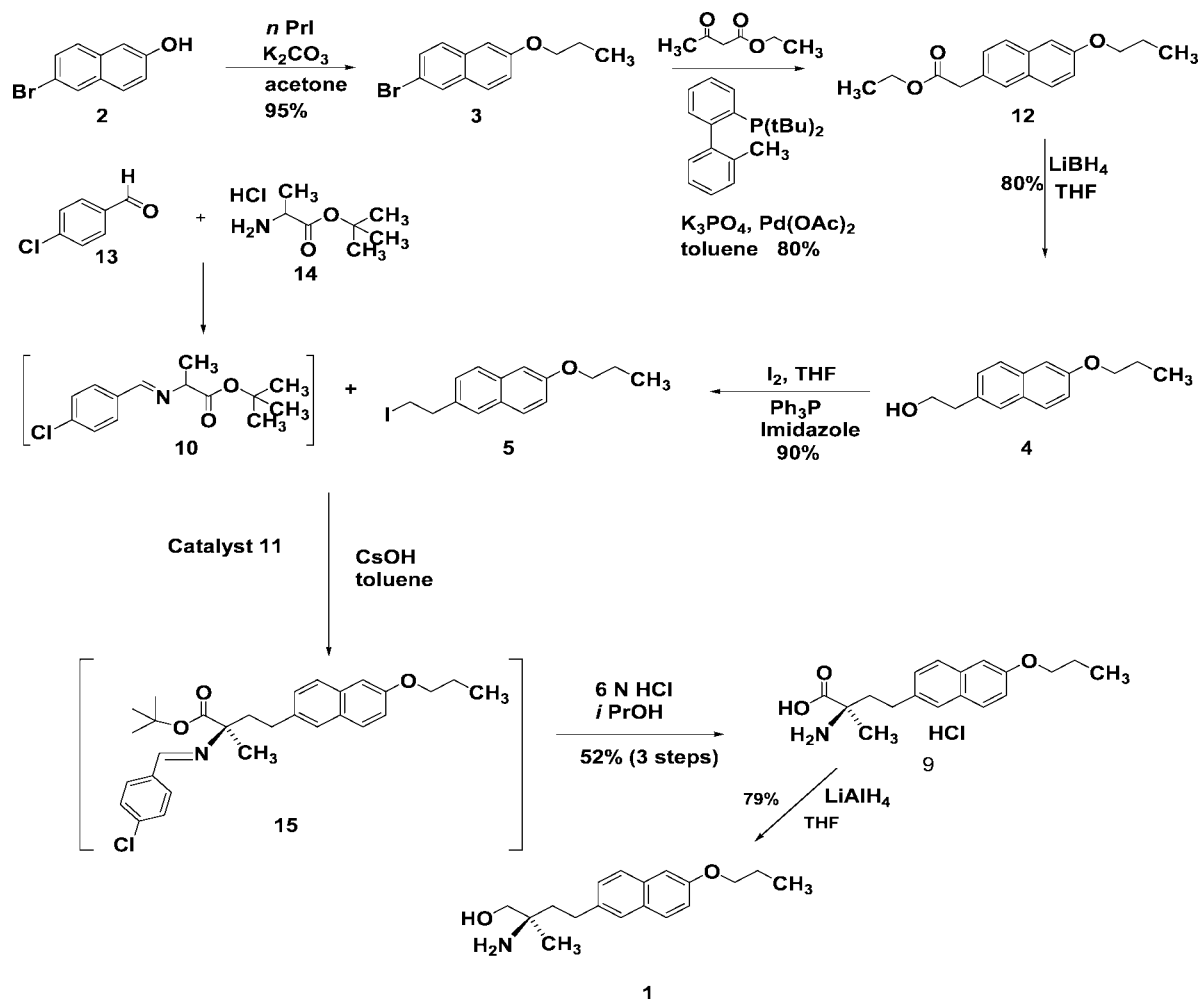
The key step in the present synthesis is the asymmetric alkylation of **10** with **5** using a chiral phase transfer catalyst. As mentioned earlier, our choice in this context was the  $C_2$ -symmetric chiral PTC **11** developed by Maruoka and co-workers.<sup>8</sup> Thus we first investigated the alkylation of **10** with iodide **5** using PTC **11** and  $CsOH \cdot H_2O$  as the base in toluene at 0 °C. Gratifyingly, the result (Table 1, entry 1) was excellent with >94% conversion and 96% ee. We next examined bases such as  $Cs_2CO_3$  and KOH. Alkylation in the presence of  $Cs_2CO_3$  gave a similar result (entry 4) as in entry 1, while with a stronger

**Table 1. Catalytic Asymmetric Phase Transfer Alkylation of 10**

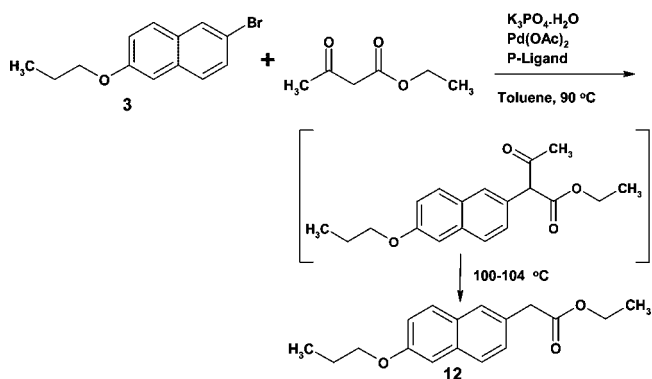
entry	solvent	base	temp (°C)	time (h)	<i>R/S</i>	conversion (%)
1	toluene	$CsOH$	0	10	<b>98/2</b>	>94
2	toluene	$CsOH$	5–10	6	80/20	>94
3	toluene	$CsOH$	20–22	6	65/35	>94
4	toluene	$Cs_2CO_3$	0	10	97/3	>95
5	toluene	50% KOH	0–22	16	NA	13
6	$CH_2Cl_2$	$CsOH$	0	5	52/48	>92
7	THF	$CsOH$	0	6	51/49	>90
8 <sup>a</sup>	TBME	$CsOH$	0	6	53/47	>95

<sup>a</sup> 1 mol % of catalyst **11** was used.

### Scheme 3. Current synthesis



### Scheme 4



base KOH (entry 5), decomposition of **5** to the corresponding styrene became a serious problem. Since the best result was obtained using cesium hydroxide (entry 1), two critical parameters, *i.e.*, solvent and temperature, were varied (entries 2, 3, 6, 7, and 8). Solvents such as THF, dichloromethane and TBME gave almost no enantioselectivity (Table 1, entries 6–8) although the reaction time was dramatically reduced to 5–6 h. The conditions mentioned in entry 1 were found to be best. As cesium hydroxide monohydrate and the chiral catalyst **11** were

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not soluble in toluene, we optimized these conditions further. The final conditions chosen were 1.0 equiv of **10**, 1.3 equiv of **5**, and 5 equiv of cesium hydroxide monohydrate in 17:1 (v/v) toluene/TBME at 0 °C for 10 h.

Since the crude **15** contained impurities, such as excess of **5**, the elimination byproduct of **5**, PTC, and a small amount of **10**, the purification was tedious and not ideal for scale-up. To address this challenging issue, crude **15** was treated with 2 N HCl in acetonitrile to form the hydrochloride salt **9**, during which both the imine and the *tert*-butyl ester group hydrolyzed, in 70% yield (based on **10**) with 96% ee. The enrichment of the chiral purity of **9** could easily be achieved by slurrying **9** in absolute ethanol (200 proof) at 56 °C, followed by addition of toluene and cooling. The optimal ratio was 1 g of **9** in 4.5 mL of ethanol and 50 mL of toluene. The undesired enantiomer could be reduced from 2.5% to 0.3% under these conditions, and the yield was 90%. About 2 kg of **9** were obtained in one batch with >99% ee.

The carboxylic acid **9** was reduced to the corresponding alcohol with lithium aluminum hydride in THF at 56 °C. After quenching the reaction with the minimum amount of water/NaOH, the heterogeneous mixture was filtered, and the product was isolated by precipitation from ethyl

(7) Trost, B. M.; Shen, H. C.; Dong, Li; Surivet, J.-P.; Sylvain, C. *J. Am. Chem. Soc.* **2004**, *126*, 11966.

(8) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028.

acetate and heptane. Under these conditions, 1.2 kg of **1** was obtained in 77% yield with almost 100% ee.

## Conclusions

In summary, an improved synthesis of **1** was developed. The new synthetic route featured a practical asymmetric alkylation using the  $C_2$ -symmetric chiral catalyst **11** of Maruoka. This particular step combined with hydrolysis to **9** achieved an 80% yield and >96% ee. Finally, we demonstrated that the enantiopurity of **9** could be enhanced to >98% ee through crystallization, and the drug substance itself was isolated in >99% ee in an overall yield of 22% based on **2**.

## Experimental Section

**General.** Melting points were measured on a MEL-TEMP 3.0 melting point apparatus and were uncorrected.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on Bruker AVANCE 400 or Bruker AVANCE 500 instruments. Chemical shifts are given on a  $\delta$  (ppm) scale. Enantiomeric purity of compounds was determined by area % using chiral HPLC. For compound **9**, a Chiralpak WH 4.6 mm  $\times$  250 mm column was used. The mobile phase A was 0.25 mM  $\text{CuSO}_4$ , and B was acetonitrile. The chiral method conditions were isocratic for 60 min, column temperature 50  $^\circ\text{C}$ , flow rate 2.0 mL/min, wavelength 230 nm. For compound **1**, a Chiralpak AS-H 4.6 mm  $\times$  250 mm column was used. The mobile phase was hexanes/2-propanol/diethylamine (83:17:0.1). The chiral method conditions were isocratic for 30 min, column temperature 20  $\pm$  5  $^\circ\text{C}$ , flow rate 0.7 mL/min, wavelength 230 nm.

**2-Bromo-6-propoxynaphthalene (3).** A stirred suspension of 6-bromo-2-naphthol, **2**, (10 kg, 44.8 mol) and potassium carbonate (9.3 kg, 67.2 mol) in acetone (50 L) was treated at room temperature with 1-iodopropane (9.1 kg, 53.8 mol). The reaction mixture was heated to reflux (59  $^\circ\text{C}$ ) and held for 48 h. Water (75 L) was added at such a rate as to maintain an internal temperature of  $\geq 50$   $^\circ\text{C}$ . The resulting mixture was cooled to 32  $^\circ\text{C}$ , seeded with **3**, and held for 3 h. The resulting suspension was cooled to 25  $^\circ\text{C}$ , held for 16 h, further cooled to 0  $^\circ\text{C}$ , and held for 1 h. The solids were filtered, washed with cold (0  $^\circ\text{C}$ ) 2:1 (v/v) water/acetone solution (18.75 L), and dried in vacuo at 45  $^\circ\text{C}$  for 16 h to afford **3** [11.0 kg, 95.4% (corrected)] as a white crystalline solid, 99.1% pure by HPLC; mp 59–60  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  8.07 (s, 1 H), 7.80 (d,  $J$  = 9 Hz, 1 H), 7.74 (d,  $J$  = 9 Hz, 1 H), 7.53 (dd,  $J$  = 9 Hz, 2 Hz, 1 H), 7.31 (s, 1 H), 7.19 (dd,  $J$  = 9 Hz, 2 Hz, 1 H), 4.00 (t,  $J$  = 7 Hz, 2 H), 1.77 (m, 2 H), 0.99 (t,  $J$  = 7 Hz, 3 H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  156.97, 132.90, 129.55, 129.29, 129.10, 128.80, 128.48, 119.86, 116.12, 106.55, 69.02, 21.97, 10.38.

**6-Propoxy-2-naphthalene Acetic Acid Ethyl Ester (12).** A stirred suspension of 2-bromo-6-propoxynaphthalene **3** (12.8 kg, 48.2 mol), potassium phosphate monohydrate (36.1 kg, 170.0 mol), 2-(di-*tert*-butylphosphino)-2'-methylbiphenyl (0.30 kg, 0.96 mol), and palladium(II) acetate (0.11 kg, 0.48 mol) in toluene (92 L) was treated at room temperature with ethyl acetoacetate (8.2 kg, 63.1 mol). The reaction mixture was heated to 90  $^\circ\text{C}$  over 30 min and held for 2 h. The reaction mixture was further heated to 100  $^\circ\text{C}$ , held for 5 h, and finally cooled

to 0  $^\circ\text{C}$ . Water (50 L) was added at such a rate as to maintain an internal temperature of  $\leq 10$   $^\circ\text{C}$ . The resulting solution was warmed to 20  $^\circ\text{C}$  and held for 1 h. The organic layer was separated, washed twice with 5% aqueous sodium chloride solution (25 kg per wash) and once with saturated aqueous sodium chloride solution (25 kg). The organic layer was filtered through Celite, the filter cake was washed with toluene (8 kg), and the wash was combined with the filtrate. The solution was concentrated under reduced pressure (maximum jacket temperature = 60  $^\circ\text{C}$ ) to afford **12** [14.2 kg, 81.8% (corrected)] as a brown oil, 95.2% pure by HPLC (excluding solvent). The product contained 13% toluene as determined by  $^1\text{H}$  NMR.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.78 (d,  $J$  = 3 Hz, 1 H), 7.76 (d,  $J$  = 2 Hz, 1H), 7.73 (s, 1 H), 7.46 (dd,  $J$  = 9 Hz, 2 Hz, 1 H), 7.34 (m, 1 H), 7.19 (d,  $J$  = 3 Hz, 1 H), 4.25 (q,  $J$  = 7 Hz, 2 H), 4.11 (t,  $J$  = 7 Hz, 2 H), 3.82 (s, 2 H), 1.96 (m, 2 H), 1.34 (t,  $J$  = 7 Hz, 3 H), 1.16 (t,  $J$  = 7 Hz, 3 H).

**6-Propoxy-2-naphthalene Ethanol (4).** A stirred solution of 6-propoxy-2-naphthalene acetic acid ethyl ester **12** (12.8 kg as a concentrate, 47 mol) in dry tetrahydrofuran (47 L) was treated at  $-15$   $^\circ\text{C}$  with lithium borohydride (2.0 N solution in tetrahydrofuran, 18.8 L, 37.6 mol) over 1 h at such a rate as to maintain an internal temperature  $\leq 0$   $^\circ\text{C}$ . The reaction mixture was heated to reflux (65  $^\circ\text{C}$ ) and held for 4 h. The reaction mixture was cooled to  $-15$   $^\circ\text{C}$  and carefully quenched with 2 N hydrochloric acid solution (0  $^\circ\text{C}$ , 18.8 L) at such a rate as to maintain an internal temperature  $\leq 0$   $^\circ\text{C}$ . The resulting solution was warmed to 30  $^\circ\text{C}$  and concentrated under reduced pressure (maximum jacket temperature = 30  $^\circ\text{C}$ ). The concentrate was diluted with water (4.7 L) and isopropyl acetate (75 L), and the reaction mixture was stirred at room temperature for 30 min. The aqueous layer was separated. The organic layer was washed four times with 5% aqueous sodium chloride solution (8 kg per wash) and twice with saturated aqueous sodium chloride solution (8 kg per wash). The organic phase was filtered through Celite, the filter cake was washed with isopropyl acetate (8 L), and the wash was combined with the filtrate. The resulting solution was concentrated under reduced pressure (maximum jacket temperature = 50  $^\circ\text{C}$ ). The resulting brown solid was slurried in isopropyl acetate (5 L) at 40  $^\circ\text{C}$ , stirred 15 min and diluted with *n*-heptane (treated with antistatic agent, 65 L). The mixture was cooled to room temperature and held for 16 h. The slurry was cooled to 10  $^\circ\text{C}$ , held 30 min, and filtered. The filter cake was washed with a cold (10  $^\circ\text{C}$ ) mixture of *n*-heptane (7.6 L) and isopropyl acetate (0.5 L) and dried in vacuo at 50  $^\circ\text{C}$  for 16 h to afford **4** [8.6 kg, 80.2% (corrected)] as a tan, crystalline solid, 96% pure by HPLC; mp 100–101  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.72 (m, 2 H), 7.62 (s, 1 H), 7.33 (d,  $J$  = 8 Hz, 1 H), 7.24 (d,  $J$  = 2 Hz, 1 H), 7.12 (dd,  $J$  = 9 Hz, 3 Hz, 1 H), 4.70 (t,  $J$  = 5 Hz, 1 H), 4.00 (t,  $J$  = 7 Hz, 2 H), 3.69 (m, 2 H), 2.85 (t,  $J$  = 7 Hz, 2 H), 1.77 (m, 2 H), 1.00 (t,  $J$  = 7 Hz, 3 H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  156.12, 134.61, 132.86, 128.76, 128.52, 128.19, 126.72, 126.47, 118.64, 106.38, 68.93, 62.26, 39.05, 22.09, 10.48.

**2-(2-Iodoethyl)-6-propoxynaphthalene (5).** A stirred solution of 6-propoxy-2-naphthalene ethanol **4** (8.6 kg, 37.3 mol), triphenylphosphine (12.7 kg, 48.5 mol) and imidazole (3.81 kg, 56 mol) in tetrahydrofuran (43 L) was treated at  $-20\text{ }^{\circ}\text{C}$  with a solution of iodine (14.1 kg, 56 mol) in tetrahydrofuran (13 L). The iodine solution was added at such a rate as to maintain an internal temperature  $\leq 10\text{ }^{\circ}\text{C}$ . The reaction mixture was warmed to room temperature, held 15 min, and cooled to  $0\text{ }^{\circ}\text{C}$ . The reaction mixture was quenched with 1.8 M aqueous sodium thiosulfate solution (10.3 kg) at such a rate as to maintain an internal temperature  $10\text{ }^{\circ}\text{C}$ . The resulting solution was concentrated under reduced pressure (maximum jacket temperature =  $25\text{ }^{\circ}\text{C}$ ) with water (21 kg) being added approximately halfway through the concentration. The concentrate was diluted with ethyl acetate (68 L) and stirred, and the aqueous layer was separated. The organic layer was washed twice with 5% aqueous sodium chloride solution (25 kg per wash) and once with saturated aqueous sodium chloride solution (25 kg). The organic layer was concentrated under reduced pressure (maximum jacket temperature =  $25\text{ }^{\circ}\text{C}$ ) to an oil. The concentrate was diluted with *tert*-butyl methyl ether (17 L), warmed to  $60\text{ }^{\circ}\text{C}$ , and held for 15 min. The resulting solution was diluted with *n*-heptane (treated with antistatic agent, 17 L), cooled to  $20\text{ }^{\circ}\text{C}$ , and held for 16 h. The solids (triphenylphosphine oxide) were filtered and washed with a 1:1 (v/v) *tert*-butyl methyl ether and *n*-heptane solution (17 L), and the wash was combined with the filtrate. The filtrate was passed through silica gel (230–400 mesh, 36 kg). The silica gel pad was washed with a 1:1 (v/v) *tert*-butyl methyl ether and *n*-heptane solution (72 L) and the wash combined with the eluant. The eluant/wash was concentrated to a thick slurry and held at  $20\text{ }^{\circ}\text{C}$  for 16 h. The solids were filtered, washed with cold ( $0\text{ }^{\circ}\text{C}$ ) *n*-heptane (10 kg), and dried in vacuo at  $50\text{ }^{\circ}\text{C}$  for 16 h to afford **5** (9.6 kg) as a tan, crystalline solid, 99% pure by HPLC; mp  $56\text{--}57\text{ }^{\circ}\text{C}$ . The mother liquors were concentrated, and the resulting solids were filtered to obtain a second crop of **5** (1.65 kg) as a low-melting solid, 93.3% pure by HPLC. Overall, 11.25 kg (90.6%, corrected) of **5** was produced.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.74 (dd,  $J = 9\text{ Hz, } 4\text{ Hz, } 2\text{ Hz}$ ), 7.66 (s, 1 H), 7.36 (d,  $J = 9\text{ Hz, } 1\text{ Hz}$ ), 7.27 (d,  $J = 2\text{ Hz, } 1\text{ Hz}$ ), 7.13 (dd,  $J = 9\text{ Hz, } 3\text{ Hz, } 1\text{ Hz}$ ), 4.02 (t,  $J = 6\text{ Hz, } 2\text{ Hz}$ ), 3.54 (t,  $J = 7\text{ Hz, } 2\text{ Hz}$ ), 3.23 (t,  $J = 7\text{ Hz, } 2\text{ Hz}$ ), 1.79 (m, 2 H), 1.01 (t,  $J = 7\text{ Hz, } 3\text{ Hz}$ );  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  156.36, 135.61, 133.15, 128.90, 128.35, 127.22, 126.78, 126.55, 118.86, 106.44, 68.94, 39.19, 22.05, 10.47, 8.28.

**2-[[1-(4-Chlorophenyl)methylidene]amino]propionic Acid *tert*-Butyl Ester (10).** To a stirred solution of **13** (6 kg, 33 mol) in 48 L of methanol was added triethylamine (5.05 L, 46 mol), and the mixture was stirred for 30 min followed by the addition of 4.64 kg (33 mol) of **14**. To this solution anhydrous magnesium sulfate (6.1 kg) was added, and the mixture was stirred for 16 h at rt, filtered, and the residue was washed with 6 L of methanol. The combined filtrates were evaporated to dryness, and the

residue was dissolved in *tert*-butyl methyl ether (70 L) washed successively with 5%  $\text{NaHCO}_3$  solution (6 L), water (10 L), and brine solution (10 L). The organic phase was dried with  $\text{MgSO}_4$ , filtered, and concentrated to dryness under vacuum at  $<50\text{ }^{\circ}\text{C}$  to give 8.3 kg of **10** in 93.8% yield as a liquid. It became a solid after being stored in a refrigerator.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.47 (s, 9 H), 1.48 (d,  $J = 5.0\text{ Hz, } 3\text{ H}$ ), 4.04 (q,  $J = 5.0\text{ Hz, } 1\text{ H}$ ), 7.38 (d,  $J = 10\text{ Hz, } 2\text{ H}$ ), 7.72 (d,  $J = 10\text{ Hz, } 2\text{ H}$ ), 8.25 (s, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.38, 28.02, 68.38, 81.18, 128.81, 129.61, 134.42, 136.87, 161.09, 171.61; mp  $25\text{--}27\text{ }^{\circ}\text{C}$ .

**(R)-2-Amino-2-methyl-4-(6-propoxynaphthalen-2-yl)butyric Acid·HCL Salt (9).** To a 5-L round-bottomed flask were charged **10** (267.8 g, 1.0 mol), **5** (452 g, 1.33 mol), toluene 2.35 L, *tert*-butyl methyl ether (140 mL), and phase transfer catalyst **11** (10 g), and the mixture was stirred until the dissolution of solids. The reaction mixture was cooled to  $-3$  to  $-6\text{ }^{\circ}\text{C}$  followed by the addition of cesium hydroxide monohydrate (840 g, 5.60 mol) in one portion. The reaction mixture was warmed to  $-1$  to  $1\text{ }^{\circ}\text{C}$ , and stirred vigorously for 7 h. The reaction was monitored by HPLC and quenched with water (1.0 L). The separated organic phase was washed successively with water (1 L) and brine (1 L) and was concentrated to a 500-mL volume followed by the addition of 6 N HCl in isopropyl alcohol (670 mL) and water (21 mL). The mixture was heated to  $56\text{ }^{\circ}\text{C}$  for 3–4 h. The reaction was monitored by HPLC followed by the addition of toluene (1.5 L). The resulting solids were filtered and washed with toluene (500 mL), until the disappearance of brown color, and dried at  $25\text{ }^{\circ}\text{C}$  for 16 h to give 230 g of crude **9** in 68% yield.

**Recrystallization of 9.** To a 120 L flask were charged crude **9** (2337 g) and ethanol (9 L, 200 proof), and the suspension was heated at  $56\text{ }^{\circ}\text{C}$  for 45 min followed by the slow addition of toluene (106 L) while maintaining the temperature at  $50\text{--}56\text{ }^{\circ}\text{C}$ . The suspension was stirred for another 40 min. The reaction mixture was cooled to  $16\text{ }^{\circ}\text{C}$  and maintained at this temperature for 1 h. The solids were filtered, washed with 4 L of toluene, and dried at  $20\text{ }^{\circ}\text{C}$  for 16 h to give 1920 g of pure **9**; mp  $> 200\text{ }^{\circ}\text{C}$ , dec;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.02 (t,  $J = 5\text{ Hz, } 3\text{ H}$ ), 1.55 (s, 3 H), 1.79 (m, 2 H), 2.18 (m, 2 H), 2.63 (m, 1 H), 2.92 (m, 1 H), 4.03 (t,  $J = 5\text{ Hz, } 2\text{ H}$ ), 7.13 (m, 1 H), 7.27 (m, 1 H), 7.33 (m, 1 H), 7.61 (s, 1 H), 7.75 (m, 2 H), 8.96 (br s, 3 H), 13.96 (br s, 1 H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  10.42, 22.02, 22.06, 29.22, 38.62, 58.84, 68.96, 106.52, 118.81, 125.82, 126.90, 127.33, 128.48, 128.76, 132.88, 135.46, 156.25, 172.59.

**(R)-2-Amino-2-methyl-4-(6-propoxynaphthalen-2-yl)butan-1-ol (1).** To a 5-L flask were charged **9** (90 g, 0.266 mol) and tetrahydrofuran (1.8 L, anhydrous), and the mixture was cooled to  $5 \pm 5\text{ }^{\circ}\text{C}$  followed by the slow addition of lithium aluminum hydride (1 M in THF, 1.07 L, 1.07 mol). The mixture was heated to  $56\text{ }^{\circ}\text{C}$  and held at this temperature for 4–5 h. After the completion of the reaction, the suspension was cooled to  $-3 \pm 3\text{ }^{\circ}\text{C}$  followed by the slow addition of water (41 g), NaOH (41 g of 15% solution), and water (123 g). The mixture was

stirred at this temperature for 2 h, filtered, and the residue was washed with tetrahydrofuran (200 mL). The combined filtrates were concentrated to a 200 mL volume under vacuum at 40 °C followed by the addition of ethyl acetate (800 mL). The resulting solution was concentrated to a 200 mL volume under vacuum at 40 °C. The mixture was diluted with heptane (2.4 L). The resulting solids were filtered and washed with heptane (200 mL) followed by 3% EtOH in heptanes (100 mL, v/v), dried under vacuum at 45 °C for 16 h to give 61 g of **1** in 79% yield; mp 101 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.00 (s, 3 H), 1.03 (t, *J* = 5 Hz, 3 H), 1.39 (br s, 2 H), 1.61 (m, 2 H), 1.80 (m, 2 H), 2.73 (m, 2 H), 3.20 (s, 2 H), 4.03 (t, *J* = 5 Hz, 2 H), 4.59

(br s, 1 H), 7.11 (m, 1 H), 7.25 (s, 1 H), 7.31 (m, 1 H), 7.59 (s, 1 H), 7.74 (m, 2 H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 10.44, 22.03, 24.59, 29.63, 41.36, 52.47, 68.92, 70.29, 106.49, 118.55, 125.55, 126.52, 127.81, 128.60, 128.63, 132.55, 138.29, 155.97.

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