Pergamon

Tetrahedron 55 (1999) 909–918

TETRAHEDRON

CRYSTALLIZATION-INDUCED ASYMMETRIC TRANSFORMATION: STEREOSPECIFIC SYNTHESIS OF L-768,673

Yao-Jun Shi,*† Kenneth M. Wells,* Philip J. Pye,*
Woo-Baeg Choi, Hywyn R.O. Churchill, Joseph E. Lynch, Ashok Maliakal,
Jess W. Sager, Kai Rossen, R. P. Volante, and Paul J. Reider

Department of Process Research, Merck Research Laboratories
P.O. Box 2000, Rahway, New Jersey 07065

Received 2 October 1998; accepted 20 November 1998

Abstract

A highly convergent, asymmetric synthesis of L-768,673, an I_{Ks} Class III antiarrythmic drug candidate, is described. Synthesis of the racemic 1-trifluoroethyl-3-amino-5-phenyl benzodiazepinone [(±)-amine] was achieved by Ru-catalyzed hydrogenation of the corresponding oxime that was derived from commercially available 1-trifluoroethyl-5-phenyl benzodiazepine in 76% overall yield. An efficient one-pot resolution-racemization of (±)-amine provided the desired (+)-amine as its mandelate salt in 92% yield and 99.4% ee. Regioselective ortho-lithiation of 1,3-bis(trifluoromethyl)benzene with n-BuLi in the presence of a catalytic amount of 2,2',6,6'-tetramethylpiperidine afforded its aryl lithium. Subsequent transmetalation and alkylation with allyl bromide produced the corresponding olefin. Ru-catalyzed oxidative cleavage of the terminated double bond of the olefin provided the desired 2,4-bis(trifluoromethyl)phenylacetic acid in 35% overall yield. A modified Schotten-Baumman procedure was developed for coupling of (+)-amine and the acid to produce L-768,673 in 92% yield without racemization. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Asymmetric synthesis; Benzodiazepines; Oximes; Resolution-racemization

Introduction

The potent potassium channel blocker, L-768,673 (**1**), has been identified as an I_{Ks} Class III antiarrythmic agent both in vitro and in vivo.[1] L-768,673 (**1**) exhibits excellent oral activity in dogs and has been selected for extensive preclinical studies for treatment of ventricular arrhythmia and the prevention of Sudden Cardiac Death (SCD). Hence, an efficient process for the preparation of large quantities of L-768,673 (**1**) was required

† Email: y-j_shi@merck.com

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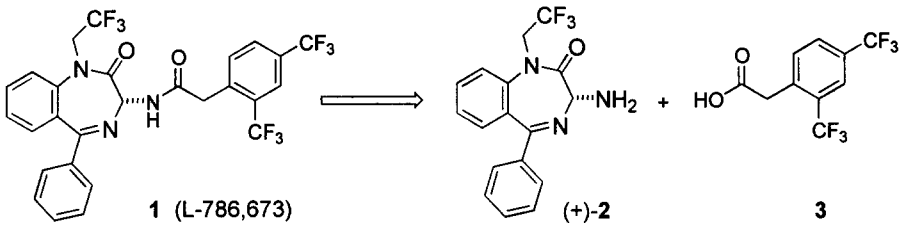
PII: S0040-4020(98)01098-9

to support preclinical evaluation. Structurally, L-768,673 (**1**) consists of a chiral 3-amino-5-phenyl-1,4-benzodiazepin-2-one and a lipophilic bis(trifluoromethyl)phenylacetyl group (Scheme 1). Described herein is a highly efficient synthesis of L-768,673 (**1**) from commercially available materials.

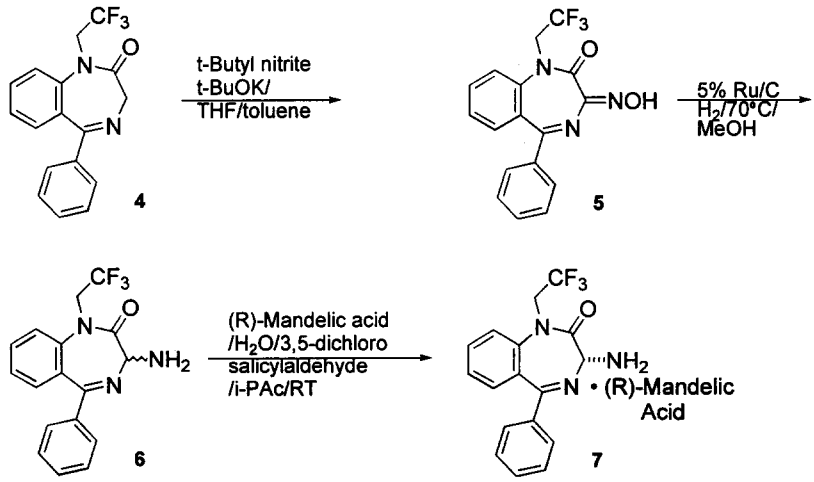
Scheme 1



Results and Discussion

Although there are several asymmetric syntheses of the 3-amino-1,4-benzodiazepin-2-one moiety in the literature,[2] there was a need to develop a practical process that was applicable to the 1-trifluoroethyl 3-amino-5-phenyl benzodiazepinone, such as **6**. Furthermore, since the one-pot resolution-racemization of N-methyl-3-amino-5-phenyl-1,4-benzodiazepin-2-one had already been developed in these laboratories (CCK antagonist L-364,718),[3] we decided to focus our efforts on adopting such a crystallization-induced asymmetric transformation to produce the desired 3-amino-1,4-benzodiazepin-2-one, (+)-**2**.

Scheme 2

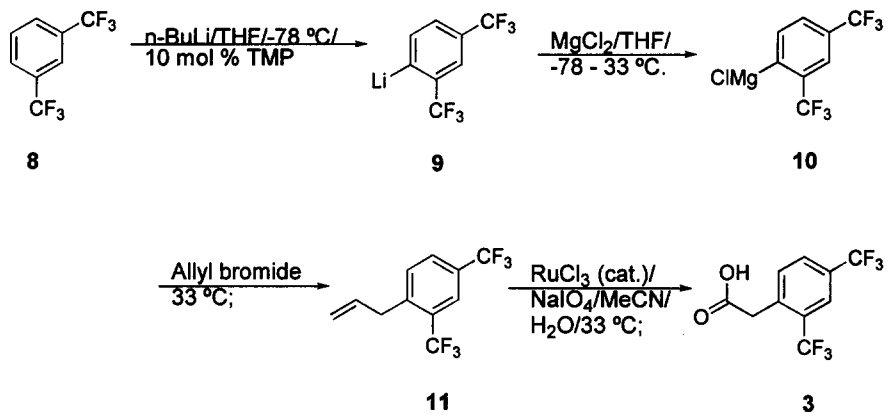


The synthesis of the desired salt **7**, the mandelate salt of (+)-**2**, from commercially available benzodiazepinone **4** is depicted in Scheme 2.[4] Our initial synthesis of oxime **5** was accomplished by the base catalyzed reaction of 5-phenyl-1,4-benzodiazepin-2-one with isoamyl nitrite [$(CH_3)_2(CH_2)_3ONO$].[3] Treatment of **4** with potassium t-butoxide (t-BuOK) and isoamyl nitrite gave the oxime **5** but the yield was typically poor (~55%) and was not reliable. In one experiment we isolated a significant amount of isoamyl carbonate (~30%) which suggested that oxime **5** was suffering attack by the isoamyl alkoxide by-product of the reaction.[5] Indeed, when t-butyl nitrite (t-BuONO) was substituted for isoamyl nitrite, oxime **5** was obtained reproducibly in 85% isolated yield. Subsequent Ru-catalyzed hydrogenation of oxime **5** as previously reported[3] gave the racemic amine **6** in 90% yield. Although the crystalline (±)-**6** could be obtained,[1] it was more efficient to use the solution of the racemic amine directly for the resolution-racemization step without isolation.

After we examined numerous chiral acids for resolution of (±)-**6**, we found that (R)-(-)-mandelic acid proved to be optimal.[6] Initially the resolution was conducted in isopropyl acetate (i-PAc) with addition of (R)-(-)-mandelic acid at room temperature to afford the desired crystalline salt **7** in 45% yield and 99.3% ee.[7] Subsequently, based on our previous work, 3,5-dichlorosalicylaldehyde was found to be an effective catalyst for the racemization-resolution of the undesired enantiomer.[3] Thus, the one-pot resolution-racemization of (±)-**6** was in hand. In the presence of 3,5-dichlorosalicylaldehyde (2 mol %) and water (1.5-2.0 mole)[8], the resolution-racemization of (±)-**6** was achieved at room temperature in 24 h to provide the resolved mandelate salt **7** as a hydrate in 92% yield and 99.4% ee. Once again, from a practical point of view, the isolated mandelate salt **7** was directly used as the masked (+)-**2** in the forthcoming coupling reaction.

Next, we needed to develop an efficient process for the synthesis of 2,4-bis(trifluoromethyl)phenylacetic acid (**3**) [the original route[1] suffered from poor availability and high cost of the 2,4-bis(trifluoromethyl)benzyl bromide starting material.[9]] Thus, the readily available, less expensive 1,3-bis(trifluoromethyl)benzene (**8**) appeared to be a very attractive starting material. Regioselective conversion of **8** to aryl lithium **9** had been reported in the literature using a stoichiometric amount of lithium 2,2',6,6'-tetramethylpiperidinium amide (Li-TMP).[10] However, in our hands a deuterium quench (CH_3CO_2D) of this reaction[10] indicated only partial lithiation of starting material **8** (40% deuterium incorporation).[11] Complete lithiation of **8** could be achieved by utilizing n-butyllithium (n-BuLi) in the presence of a catalytic amount of 2,2',6,6'-tetramethylpiperidine (TMP) at -78 °C. This procedure gave the same high regioselectivity as the stoichiometric reaction as determined by carbon dioxide quench and HPLC analysis of the resulting benzoic acids.[10a,12] This newly discovered procedure not only increases the conversion of **8** to aryl lithium **9**, but also the efficiency of the ortho-lithiation by a reduction in the use of expensive TMP.

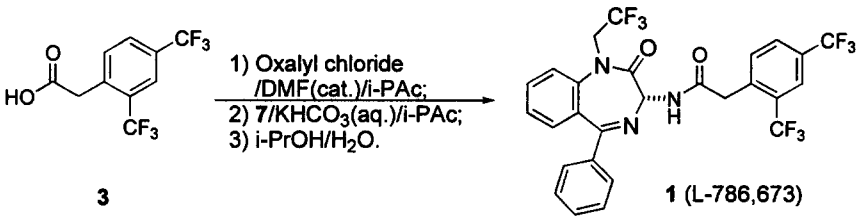
Scheme 3



Attempts to react aryl lithium **9** with a number of suitable electrophiles were unsuccessful due to unsuccessful quenching of the aryl lithium and/or halogen-metal exchange process. In order to circumvent these problems, aryl lithium **9** was converted to the corresponding Grignard reagent **10** through transmetalation with magnesium chloride ($MgCl_2$)[13] in THF at -30 °C. The alkylation of **10** was achieved by treatment with allyl bromide at 33 °C to directly produce the olefin **11**. Finally, Ru-catalyzed oxidative cleavage[14] of the terminal double bond with sodium periodate ($NaIO_4$) as co-oxidant afforded the desired acid subunit **3**. Recrystallization of crude **3** from warm hexanes afforded **3** in an acceptable 35% yield from commercially available 1,3-bis(trifluoromethyl)benzene (**8**).

The final stage of the synthesis was the formation of an amide bond between 3R-(+)-3-aminobenzodiazepinone **2** and acid **3** (Scheme 4). Although there are many options for this operation,[15] for example the EDC/HOBT mediated coupling of (+)-**2** and acid **3** used by Selnick, et al.[1], we have found that a modified Schotten-Baumann procedure was the method of the choice.[16]

Scheme 4



The acid chloride from 3,5-bis(trifluoromethyl)phenylacetic acid (**3**) was prepared using oxalyl chloride in the presence of a catalytic amount of DMF in dry i-PAc at 20 °C,[17] and was then used directly without isolation.

The modified Schotten-Baumann reaction was carried out by addition of the above acid chloride solution to a two-phase system (aqueous $KHCO_3$/i-PAc) which contained mandelate salt **7** at 22-25 °C. The desired coupling product **1** (L-768,673) was generated in 92% yield without any significant racemization (> 99% ee). Subsequently, L-768,673 (**1**) was readily obtained in 87% isolated yield and very high purity after recrystallization from i-PrOH/H_2O.

Conclusion

A practical, highly convergent synthesis of L-768,673 (**1**) has been achieved. The desired 2,4-bis(trifluoromethyl)phenylacetic acid (**3**) was made from commercially available 1,3-bis(trifluoromethyl)benzene (**8**) in two steps. The synthesis features an efficient one-pot resolution-racemization to provide 3R-(+)-3-aminobenzodiazepinone **2** in 92% yield and 99.4% ee. The coupling of (+)-**2** as its mandelate salt **7** with acid **3** by the modified Schotten-Baumman procedure produces L-768,673 (**1**) in excellent yield without racemization. The process is free of chromatography, and affords a 61% overall yield of the desired L-786,673 (**1**) with 99.8 A % purity and 99.4% ee from commercial 2,3-dihydro-1-(2,2,2-trifluoroethyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepine (**4**). We have demonstrated the process in our Laboratories to provide several kilograms of pure drug in support of preclinical studies.

Experimental Section

General Procedure. Melting points were determined in capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were measured at 300 MHz and 75 MHz, respectively. All chemicals were used as received unless otherwise noted. Molecular sieves were used to remove water from solvents, and the water content was measured by Karl Fischer titration prior to use.

Synthesis of 3-oximino-5-phenyl-1-(2,2,2-trifluoroethyl)-1H-benzo[e] [1,4]diazepine (5). To a solution of trifluoroethylbenzodiazepinone **4** (3.2 kg, 10.1 moles) in toluene (20 L) and THF (5 L) in a four-neck 50 L round bottom flask was added neat t-butyl nitrite (1.44 L, 12.1 moles) at -40 °C. Next the addition of potassium t-butoxide solution was made (7.4 L, 20 wt. % in THF, 12.0 moles) over 1.5 h to maintain the batch temperature less than -30 °C. The mixture was stirred at -40 °C for 5 h. LC assay after the 5 h age of an aliquot showed a 95% conversion. The reaction mixture was poured to a phosphate buffer (KH_2PO_4 2.02 kg, Na_2HPO_4 1.14 kg in 50 L water) and then extracted with EtOAc (24 L). The organic layer was separated and washed with water (2 x 25 L). The volume of the organic layer was reduced to 10 L by vacuum distillation and then flushed with toluene (12.5 L). Slurry was formed after the first 5 L of toluene was introduced. The slurry (10 L volume) was then stirred at room temperature overnight. The slurry was filtered and washed with toluene. The white crystalline solid was dried at 60 °C in a vacuum-oven until a constant weight was achieved. An 84% yield of oxime **5** was obtained (3.03 kg, 97.3 wt. % pure, mp 125 - 127 °C). ^1H NMR ($CDCl_3$) ∂ 7.78 (dd, J =7.3, 1.5 Hz, 2H), 7.63 - 7.26 (m, 7H), 5.34 (m, 1H), 4.20 (m, 1H), 1.76 (s, 1H). ^{13}C NMR (DMSO-d_6/$CDCl_3$ 1:9) ∂ 168.0, 165.2, 149.3, 139.5, 136.6, 132.1, 131.8, 131.6, 130.3, 130.0, 128.4, 125.7, 123.7 (q, J = 281 Hz), 46.7

(q, J = 34 Hz). Anal. Calcd for $C_{17}H_{12}F_3N_3O_3$ (347.30): C, 58.79; H, 3.48; N, 12.10. Found: C, 58.88; H, 3.45; N, 12.02.

Synthesis of 3-amino-5-phenyl-1-(2,2,2-trifluoroethyl)-1H-benzo[e] [1,4]diazepine (±)-(6). Oxime **5** (300 g, 0.863 moles) was dissolved in MeOH (3.0 L) in a steel hydrogenation can (7.5 L) and the catalyst was charged (75 g of 5% Ru/carbon). The vessel was heated to 70 °C, and shaken under 40 psi hydrogen. After the theoretical hydrogen uptake was achieved, the hydrogenation was shown by LC to be complete (~3 h). The batch was cooled to room temperature and filtered through a small bed of solka floc with a rinse of MeOH (1.0 L). The combined MeOH solution was concentrated to an oil residue and the residue was redissolved in isopropyl acetate (i-PAc) (12 volume) for direct use in the resolution-racemization step. LC assay yield of i-PAc solution gave 259 g of racemic amine **6** (90% yield). A small amount of analytically pure **6** was obtained by recrystallization from EtOAc/hexane. mp 145-147 °C (lit.[1] mp 141-143 °C). ^{1}H NMR ($CDCl_3$) ∂ 7.61 - 7.24 (m, 9H), 5.21 (dq, J = 15.2, 8.7 Hz, 1H), 4.57 (s, 1H), 4.18 (dq, J = 15.2, 7.7 Hz, 1H), 2.56 (s, 2H). ^{13}C NMR ($CDCl_3$) ∂ 170.6, 166.6, 140.6, 138.1, 131.9, 131.3, 130.6, 130.2, 129.4, 128.4, 125.7, 123.9 (q, J = 281 Hz), 122.1, 70.1, 47.2 (q, J = 34 Hz).

Synthesis of 3R-(+)-3-amino-5-phenyl-1-(2,2,2-trifluoroethyl)-1H-benzo[e][1,4]diazepine-(R)-(-)-mandelate (7). To the aforementioned solution of (±)-**6** in i-PAc (22.87 g, 0.0686 moles, 300 ml) was added 3,5-dichlorosalicylaldehyde (0.262 g, 0.0014 moles), water (2.47 ml, 0.137 moles). Solid R-(-)-mandelic acid (10.41 g, 0.0683 moles) was added portion wise over 5.5 h at room temperature. The mixture was stirred at room temperature for 20 h. The slurry was filtered, and the cake was washed with i-PAc. The crystalline solid **7** was dried at 50 °C in a vacuum-oven for 12 h to provide mandelate salt **7** as a hydrate (34.54 g, 92%) with a 99.4% ee as measured by HPLC assays[7] mp 115 - 120 °C (dec). $[\alpha]^{25}_D$ = +15.3° (c 1.0, MeOH). ^{1}H NMR (DMSO-d_6) ∂ 7.85 (d, J = 8.3 Hz, 2H), 7.72 (t, J = 7.2 Hz, 2H), 7.55 - 7.21 (m, 10H), 5.22 - 5.08 (m, 2H), 4.87 (s, 2H), 4.84 - 4.76 (m, 2H), 4.63 (s, 2H). ^{13}C NMR (DMSO-d_6) ∂ 174.7, 168.9, 166.2, 141.6, 140.1, 137.4, 132.2, 130.7, 129.9, 129.3, 128.9, 128.4, 127.7, 126.9, 126.5, 125.8, 124.2 (q, J = 281 Hz), 123.1, 72.8, 69.2, 46.0 (q, J = 33 Hz). Anal. Calcd for $C_{25}H_{22}F_3N_3O_4$-H_2O (503.47): C, 59.64; H, 4.41; N, 8.35. Found: C, 59.49; H, 4.56; N, 8.17.

Synthesis of 2,4-Bis(trifluoromethyl)phenylacetic acid (3). (a) A solution of 1,3-bis(trifluoromethyl)benzene (**8**) (5.02 kg, 23.47 moles) and 2,2',6,6'-tetramethylpiperidine (348.8 g, 2.47 moles) in THF (20.0 L) was cooled to -78 °C. 1.67 M n-butyl lithium (15.5 L, 25.89 moles) was added over 3.5 h maintaining the temperature at -70 °C. The mixture was kept at -78 °C for 1.5 h. This solution of aryl lithium **9** was transferred via cannula to a slurry of $MgCl_2$ (3.00 kg, 31.51 moles) in THF (20.0 L), which had been pretreated with 1.67 M n-butyl lithium (440 mL, 0.73 moles) at -78 °C to remove water and then was allowed to warm to 30 °C. To this solution of Grignard **10** was added allyl bromide (2.03 L, 23.47 moles), and the reaction mixture was maintained at 30 °C until an HPLC assay of an aliquot showed completion of the reaction (ca. 4 h). The reaction mixture was cooled to 5 °C and quenched with water (9.0 L), followed by addition of 2N HCl (5.0 L). This mixture was then extracted with EtOAc (24 L) and the organic layer was separated, washed with 2N HCl (4.0 L), followed by two water washes (4.0 L and 7.0 L). The solution of olefin **11** was dried over magnesium

sulfate, and then concentrated to give 4.47 kg of **11** (75% yield) as an off-yellow oil. ^{1}H NMR ($CDCl_3$) ∂ 7.90 (s, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 6.02 - 5.85 (m, 1H), 5.20 - 5.05 (m, 2H), 3.62 (d, J = 8.2 Hz, 1H). (b) To a 10 °C solution of olefin **11** (1.5 kg, 5.91 moles) in water (16.0 L), MeCN (16.0 L) and NaIO4 (2.44 kg, 11.43 moles) was added $RuCl_3$ hydrate (26.25 g, 0.13 moles). An exothermic reaction was observed and the internal temperature rose to 24 °C at which time a ice water bath was used to maintain temperature. Additional $NaIO_4$ was added in portions over 2 h while maintaining the temperature at 10 - 20 °C. After addition of the $NaIO_4$ (a total of 4.57 kg, 21.38 moles), the reaction mixture was stirred for 1.0 h (HPLC showed complete reaction). The reaction mixture was then diluted with EtOAc (28 L) and hexane (4.0 L) and then filtered through a bed of solka floc. The organic layer was separated, washed with water (4.0 L) and extracted with 1 N KOH (2 x 10 L). The combined KOH layers were acidified with concentrated HCl (1.5 L) to bring pH = 1, and followed by extraction with EtOAc (20 L). The EtOAc layer was separated and washed with brine (10 L), dried over MgSO4 (0.8 kg) and filtered. The resulting solution was treated with activated charcoal (70 g) at room temperature for 2.0 h, filtered through a pad of silica gel (0.5 kg) and washed with EtOAc. The filtrate was evaporated under vacuum, toluene (2.0 L) was added and evaporated (to remove residual HOAc) and the mixture was solvent switched to methyl cyclohexane (2.0 L). The resulting precipitate was recrystallized from hexane (3.4 L) afforded 697 g of **3** as an off-white solid[1] (43% yield). mp 85-87 °C. ^{1}H NMR ($CDCl_3$) ∂ 7.94 (s, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 3.94 (s, 2H). ^{13}C NMR ($CDCl_3$) ∂ 176.1, 135.8, 133.5, 130.2 (q, J = 5 Hz), 130.1 (q, J = 5 Hz), 128.8 (q, J = 3 Hz), 123.5 (q, J = 32 Hz), 123.4 (qq, J = 5 Hz), 123.4 (q, J = 32 Hz), 37.8 Anal. Calcd for $C_{10}H_6F_6O_2$ (272.15): C, 44.13; H, 2.22. Found: C, 44.34; H, 2.22.

Synthesis of (-)-2-[2,4-bis(trifluoromethyl)phenyl]-N-[3R-2,3-dihydro-2-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)-1H-benzo[e][1,4]diazepin-3-yl]acetamide (1). *CAUTION: This compound (L-768,673) is classified as a Performance Based Exposure Control Limit (PB-ECL)[18] level-4 compound and should be handled with extreme caution!* (a) Acid **3** (1.736 kg, 6.378 moles) was dissolved in dry i-PAc (3.52 L, KF 18 µl/ml) at 20 °C. A catalytic amount of DMF (7.55 ml, 0.0974 moles) was added, followed by addition of oxalyl chloride (560.4 ml, 6.425 moles) over 45 min at 20-22 °C. The mixture was stirred at 20 °C for 1.5 h, and was used directly in the next reaction. For the corresponding acid chloride: ^{1}H NMR ($CDCl_3$) ∂ 7.95 (s, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 4.42 (s, 2H). (b) To a 100 L vertical reactor equipped with over-head stirrer, addition funnel and N_2 inlet was added i-PAc (30 L) followed by addition of mandelate salt **7** (3.0 kg, 6.181 moles) at room temperature. To the resulting slurry was added a solution of $KHCO_3$ (3.30 kg) / H_2O (25.0 L) at 23 °C. The slurry was stirred vigorously for 5 min and at which time the above acid chloride solution was introduced over 15 min. The stirring was continued for 1.0 h at 23 °C and LC assay showed the conversion was >99.5%. The organic layer was separated and then washed with 50% saturated $NaHCO_3$ (3x15 L) followed by H_2O (2x20 L). The organic layer was separated and assayed to give 3.33 kg of L-768,673 (**1**) (91.7% yield, >99% ee[7]). The batch was concentrated under vacuum (internal temperature 10-20 °C), and flushed with i-PrOH (20 L). The concentrated i-PrOH solution was diluted with i-PrOH to obtain a concentration of 0.20 g / ml (total 16.6 L of i-PrOH) and heated to 44-45 °C. Water was added until a cloudy suspension was observed (~ 8.0 L water). Seed (**1**, 57.4 g, 1.7 w/w %) was then added at 44 °C and the

resulting slurry was stirred for 2.0 h. Additional H_2O (8.0 L) was added, and the mixture was allowed to cool to 22 °C for 3.0 h. After the HPLC assay showed a supernatant concentration of 7.26 mg/ml (KF 51.7 v/v % H_2O) the slurry was filtered and washed with a mixed solvent (2x4 L, i-PrOH : H_2O 1:1). The filter cake was dried in the filter funnel under N_2 and then further dried in a vacuum oven at 50 °C/25 mm for 12 h to give 2.88 kg of L-768,673 (**1**) (87% isolated yield, 99.8 A %, 99.2% ee[7]). mp 131-133 °C (lit.[1] mp 132-134 °C). $[\alpha]^{25}_{405\ nm}$ = -54.7° (c 1.0, MeOH) {$[\alpha]^{25}_{D}$ = -20.4° (c 0.8, MeOH)}[1]. ^{1}H NMR ($CDCl_3$) ∂ 7.94 (s, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.65 - 7.28 (m, 10H), 5.61 (d, J = 8.0 Hz, 1H), 5.22 (dq, J = 15.2, 8.7 Hz, 1H), 4.16 (dq, J = 15.2, 7.7 Hz, 1H), 3.97 (s, 2H). ^{13}C NMR ($CDCl_3$) ∂ 169.0, 168.6, 168.1, 140.1, 137.7, 133.4, 132.3, 131.1, 131.0, 130.6, 130.3, 130.2, 129.5, 128.7 (q, J =3 Hz), 128.5, 126.2, 123.9 (q, J = 281 Hz), 123.5 (q, J = 32 Hz), 123.4 (qq, J = 5 Hz), 123.4 (q, J = 32 Hz), 122.4, 67.5, 47.3 (q, J = 34 Hz), 39.7.

Acknowledgments: The authors wish to thank Robert Reamer for his help with interpretation of NMR spectra.

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7. The HPLC conditions for chiral assays of **7** and **1**: Column - ChiralCel OD-R (4.6 x 250 mm); Elute - CH_3CN:H_2O (0.1% H_3PO_4) = 65:35; Flow Rate = 0.5 ml/min; UV = 220 nm; Rt (min): for **7** (as its hydrocinnamoyl amide made from the modified Schotten-Baumman procedure): 14.9 (R-isomer), 18.1 (S-isomer); For **1**: 16.1 (R-isomer), 19.7 (S-isomer).

8. Addition of water (1.5 - 2.0 mol) is critical for success in the resolution-racemization process. The isolated mandelate salt **7** was shown to be a hydrate and without the addition of water the process is much slower and the yield is lower.

9. For recent reviews on the trifluoromethylation see: (a) Kiselyov, A. S.; Strekowski, L. *Org. Prep. and Proc. Int.*, **1996**, *289*, 291318; (b) McClinton, M. A.; McClinton, D. A. *Tetrahedron*, **1992**, *48*, 6555-6666; (c) Burton, D. J.; Yang, Z.-Y. *Tetrahedron*, **1992**, *48*, 189-275.

10. For regioselective ortho-lithiation of 1,3-bis(trifluoromethyl)benzene under various conditions see: (a) Masciadri, R. *US Patent*, US 5,162,577, **1992**; (b) Castaldi, G.; Borsotti, G. *European Patent*, EP 0 491 326 A2, **1992**; (c) Schlosser, M.; Katsoulos, G.; Takagishi, S. *Synlett*, **1990**, 747-748.

11. Partially deuterium incorporation after CH_3CO_2D quench leads us to speculate that there is an equilibrium between aryl lithium **9** and TMP when a stoichiometric amount of base (Li-TMP) is used. In the catalytic reaction conditions, the proton transport vehicle (TMP) for the equilibrium is eliminated by addition of excess n-BuLi to insure the complete conversion. We believed that highly selective ortho-lithiation of 1,3-bis(trifluoromethyl)benzene (**8**) in both stoichiometric and catalytic conditions are attributed to the formation of Li-TMP. Use of n-BuLi in the absence of TMP afforded only 3:1 selectivity.

12. When the ortho-lithiation of **8** is carried out using BuLi in the presence of 10% TMP, a mixture of regioisomers (2,4-, 2,6-, 3,5-) of aryl lithium **9** are obtained. After the mixture is quenched into solid carbon dioxide (CO_2), a ratio of 24/3/1 mixture of the corresponding regioisomeric carboxylic acids was observed.

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15. Bodanszky, M.; Bodanszky, A. *The Practice of peptide Synthesis*, Springer-Verlag: Berlin Heidelberg New York, **1994**, 2nd, Revised Edition, pp 75-126.

16. For reviews, see Beckwith in Zabicky *The Chemistry of Amides*, Wiley: New York, **1970**, pp 73-185.

17. (a) Bosshard, H. H.; Mory, R.; Schmid, M.; Zolinger, H. *Helv. Chim. Acta*, **1959**, *42*, 1653-1659; (b) Burgstahler, A. W.; Weigel, L. O.; Schaefer, C. G. *Synthesis*, **1976**, 767-771; (c) Stadler, P. A. *Helv. Chim. Acta*, **1978**, *61*, 1675-1685.

18. Performance-based exposure control limit(s) (PB-ECL) – An assigned health hazard category by Merck, within five category classification system of increasing hazard potential, which also defines the level of containment required to control exposure to an acceptable level based upon the inherent pharmacological and toxicological properties of the compound. A level-4 compound, such as **1**, is restricted to glove box handling due to its potency.