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The enantioselective synthesis of LTD_4 antagonist L-708,738

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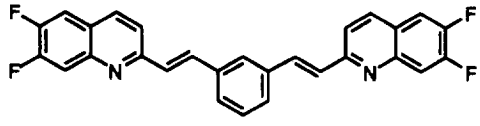
Abstract: An efficient, 9-step synthesis of LTD_4 antagonist L-708,738 is described. The asymmetric center is set via a chiral borane reduction. © 1997, Elsevier Science Ltd. All rights reserved.

In the 1970s several leukotrienes, biological metabolites of arachadonic acid via the arachadonic acid cascade, were identified as the active species of the slow-reacting substances of anaphylaxis (SRS-A), which were first isolated in the 1930s. These leukotrienes, LTB_4, LTC_4, LTD_4, and others, were shown to induce smooth muscle contraction, constriction of airways, vasoconstriction, and mucus secretion among their pharmacological actions.[1] Inhibition of the production of these agents has been the center of intensive research over the past several decades. In particular, LTD_4 has been shown to be one of the most potent causative agents of these biological responses. As a target for the treatment of asthma, LTD_4 antagonists show great promise as a therapy for this seriously debilitating, potentially fatal disease. An efficient synthesis of the LTD_4 antagonist L-708,738, **1**, is described herein.

In an approach similar to the syntheses of MK-0476[2] and L-699,392,[3] the preparation of L-708,738, **1**, began with the condensation of 3,4-difluoroaniline, **2**, and crotonaldehyde, **3**, in a Skraup synthesis[4] to provide 6,7-difluoroquinaldine, **4** (Scheme 1). By employing the use of a quinone oxidant (p-chloranil) in this reaction,[5] **4** was obtained in 65–72% yield as its crystalline hydrochloride salt.

Conversion of **4** to aldehyde **6** was readily effected by refluxing a xylene solution of the free base of **4** with 3 equivalents of isophthalaldehyde, **5**, and acetic anhydride. Aldehyde **6** was crystallized directly from the reaction mixture by addition of hexanes. When the reaction was run using 3 equivalents of isophthalaldehyde, 80–90% yields of **6** containing 4% of bis adduct **7** were obtained. Using less than 3 equivalents of **5** in this reaction led to substantially more **7** being produced, with a concomitant decrease in the yield of **6**. Utilizing more than 3 equivalents of isophthalaldehyde had a negligible effect on the level of **7** produced, and made the isolation of **6** more difficult. Excess **5** was removed by recrystallization of **6** from 1:1 ethyl acetate:hexanes. Removal of bis adduct **7** from **6** proved to be difficult due to their similar solubility properties. Since **7** was inert to the reaction conditions of the next step (vide infra), **7** was carried forward with **6** and removed at a later stage.



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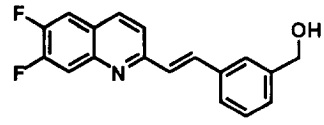
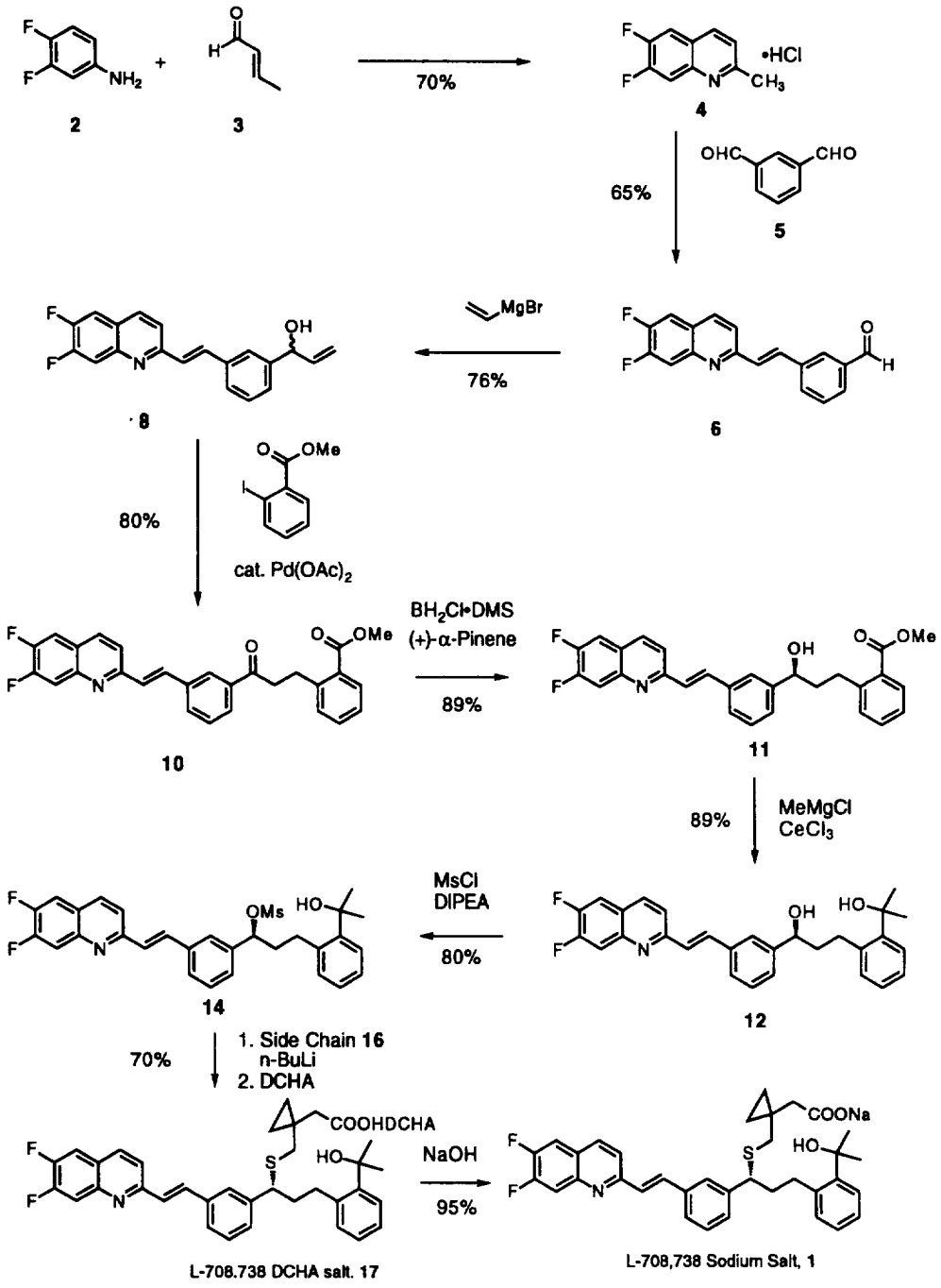


9

Alkylation of aldehyde **6** with vinylmagnesium bromide afforded good yields (70–75%) of allylic alcohol **8**. When a solution of vinylmagnesium bromide in THF was added to a THF solution of aldehyde **6** at 0°C, the reaction afforded 10% of reduction product **9**. However, when the order of addition was reversed and **6** in THF was added to vinylmagnesium bromide, only 1–1.5% **9** was

* Corresponding author.


2
3
70%
4
•HCl
65%
5
6
MgBr
76%
8
80%
cat. Pd(OAc)2
10
BH2Cl•DMS
(+)-α-Pinene
89%
11
89%
MeMgCl
CeCl3
12
MsCl
DIPEA
80%
14
70%
1. Side Chain 16
n-BuLi
2. DCHA
COOHDCHA
NaOH
95%
L-708.738 DCHA salt. 17
L-708,738 Sodium Salt, 1

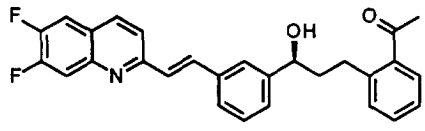
Scheme 1.

formed. Bis adduct **7** was readily removed (to <0.2%) by dissolution of crude **8** in 2-propanol, filtration to remove **7**, followed by crystallization of **8** from toluene/hexanes.

Heck coupling of allylic alcohol **8** with methyl 2-iodobenzoate in acetonitrile containing triethyl amine afforded ketoester **10**. Reaction concentrations of 1.5–2 M afforded reaction times of 24 hours while more dilute reaction conditions (0.3 M) resulted in elongated reaction times (40–48 hours). Crude **10** crystallized directly from the reaction mixture upon cooling. Residual palladium was removed by hot filtration of an ethyl acetate solution of **10**, followed by product crystallization upon addition of hexanes.

Chiral reduction of ketone **10** was accomplished with (−)-B-chlorodiisopinocampheylborane, freshly prepared from monochloroborane methylsulfide complex and (1R)-(+)-α-pinene. At −20°C, the reduction of **10** was slow, affording only 50% conversion to hydroxyester **11** in 6 hours. The reaction rate was slowed by the limited solubility of **10** in hexanes/THF. When the reaction temperature was increased to 0°C the reaction mixture became homogeneous within 1 hour and the reaction was complete in 4–6 hours. Chiral HPLC assay of **11** prior to crystallization showed 92.4% ee for the reduction. After crystallization, the chiral purity of **11** was upgraded to >99% ee, while the crystallization mother liquors contained a nearly 1:1 ratio of enantiomers.

Conversion of hydroxyester **11** to diol **12** occurred very cleanly using MeMgCl/$CeCl_3$[6]. Hydroxyester **11** monohydrate was first dried by azeotropic distillation with toluene. The resulting solution was then added to a preformed suspension of anhydrous $CeCl_3$ and excess MeMgCl in THF. The use of $CeCl_3$ in this reaction effectively suppressed the production of methyl ketone **13** from 12–15% to <0.8%, while affording 85–90% yields of diol **12**.



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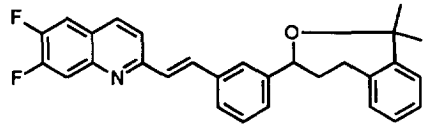
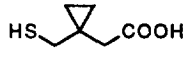


15

Mesylation of diol **12** using 1.2 equivalents of methanesulfonyl chloride and 1.5 equivalents of diisopropylethylamine in acetonitrile/toluene at −15°C occurred selectively at the 2° alcohol to afford mesylate **14** which was crystallized directly from the reaction mixture in 70–75% yield. A major impurity in **14** was unreacted diol **12** (6–10%) which co-crystallized with **14** under the reaction conditions. While the amount of diol **12** which crystallized with **14** could be decreased by increasing the reaction temperature, mesylation selectivity for the 2° alcohol decreased, and more importantly, in the presence of acid (DIPEA·HCl) and at temperatures greater than −10°C decomposition of **14** into cyclic ether **15** became a predominate reaction. To minimize unreacted **12** the reaction solvent was changed to DMF, where diol **12** was quite soluble even at −25°C. Selective mesylation of **12** in DMF proceeded cleanly with **14** being crystallized directly from the reaction mixture in 80–85% yield by addition of acetonitrile. Mesylate **14** prepared in this fashion typically contained <2% diol **12**.



16

Coupling of mesylate **14** with the dianion of **16**[2] afforded L-708,738, **1**. Thiol acid **16** was treated with a slight excess of titrated n-BuLi to afford a thick slurry of **16** dianion. A solution of **14** in THF was then added to the slurry to afford **1**. Crystallization of **1** as its dicyclohexylamine (DCHA) salt **17** afforded a crucial purification. Salt break of **17** with HOAc, followed by sodium salt formation and crystallization using NaOH afforded **1** in high yield.

Experimental

General experimental

Melting points were determined by using the Thomas Hoover capillary melting point apparatus and were uncorrected. IR spectra were obtained as thin films on disposable, polytetrafluoroethylene cards, on a Nicolet Magna-IR spectrometer 550. ^{1}H and ^{13}C spectra were recorded on a Bruker AM-250 NMR spectrometer (operating at 250 MHz and 62.9 MHz, respectively) and the chemical shifts were reported in ppm (δ) downfield from TMS. Elemental analyses were performed by the Quantitative Technologies Inc., Whitehouse, NJ. Water content was determined by Karl Fisher titration on an EM Science AquaStar C2000 Titrator.

6,7-Difluoroquinaldine hydrochloride, 4

A 5 L flask was charged with p-chloroanil (200 g) and 2-butanol (800 mL). Conc. HCl (200 mL), followed by 3,4-difluoroaniline (80 mL) were added then the mixture was heated to reflux. A solution of crotonaldehyde (72 mL) in 2-butanol (128 mL) was added over 45 minutes, followed by a 30 minute age at reflux. Toluene (1000 mL) was added then solvent (1000 mL) was removed by distillation. A second aliquot of toluene (1000 mL) was added and solvent (1000 mL) was removed by distillation. The solution was cooled to 85°C, then THF (1000 mL) was added. The solution was slowly cooled to −10°C. A bronze colored precipitate was isolated by filtration. The filter cake was washed with THF (3×500 mL) then dried at 45°C under vacuum to afford **4** (128g, 74% yield) as a pale brown solid: ^{1}H NMR (DMSO-d_6) δ 8.90 (d, J=8.6, 1H), 8.4 (m, 2H), 7.95 (d, J=8.6, 1H), 2.95 (s, 3H); 13C NMR (DMSO-d_6): 158.5, 152.7, 149.4, 143.0, 136.4, 124.2, 124.0, 115.2, 108.7, 20.8.

Aldehyde 6

A 1 L seperatory funnel was charged with xylenes (300 mL) and 10% aq. Na_2CO_3 (250 mL). 6,7-Difluoroquinaldine hydrochloride, **4**, (20 g) was added (**Caution**: gas evolved). The layers were separated and the organic phase was washed with H_2O (1×250 mL). The organic phase was charged to a 3-neck flask equipped with a distillation head and solvent (100 mL) was removed by distillation (90–137°C). The solution was cooled, the distillation head was replaced with a reflux condensor, and isophthalaldehyde (37.4 g) and acetic anhydride (26 mL) were added. The solution was refluxed for 19 h, then cooled slowly to 20°C. The resulting suspension was filtered, and the product was dried *in vacuo* at 45°C to afford 40.8 g crude **6** (86% yield corrected for wt%) as a yellow solid. The crude solid contained 57.8 wt% **6**, 31.8 wt% isophthalaldehyde, and 3.6 wt% bis adduct **7**. Crude **6** (34.1 g) was dissolved in 1:1 hexanes:EtOAc (200 mL) at reflux. Cooling to 20°C afforded **6** (18.5 g, 73% yield from **4**) as a pale yellow solid: 90.8 wt% **6**, 5.6 wt% isophthalaldehyde, 3.6 wt% **7** by HPLC. mp 148–150°C; IR (neat): 3045 (w), 1698 (s), 1517 (s); ^{1}H NMR ($CDCl_3$): 10.05 (s, 1H), 8.07 (m, 2H), 7.86–7.70 (m, 4H), 7.60–7.33 (m, 4H); ^{13}C NMR ($CDCl_3$): 192.0, 137.3, 136.9, 135.7, 135.6, 133.2, 132.9, 129.9, 129.8, 129.5, 128.0, 124.3, 124.2, 119.9, 115.6, 115.3, 112.9, 112.6.

Allylic alcohol 8

Vinylmagnesium bromide (1 M in THF, 510 mL) and sieve dried THF (300 mL) were charged to a 3-neck flask equipped with a thermocouple, addition funnel, N_2 inlet and overhead mechanical stirrer. The solution was cooled to 0°C. Aldehyde **6** (88.7 g) dissolved in warm THF (700 mL) was added dropwise via addition funnel over 30 min keeping T ≤5°C. The reaction was aged for 1 hour, then cautiously quenched into 2 N HOAc (1000 mL). The mixture was extracted with ethyl acetate (1×1000 mL). The organic phase was washed with 10% Na_2CO_3 (1000 mL) and water (1000 mL).

The organic layer was transferred to a flask and solvent (1000 mL) was removed by distillation. 2-Propanol (1000 mL) was added and solvent (1000 mL) was removed by distillation. The procedure was repeated once more, then the solution was cooled to 20°C. The resulting solid, **7**, was removed by filtration. 2-Propanol was removed by distillation and replaced with toluene. The solution was cooled to 70°C and seeded. After cooling to 0°C, the product was isolated by filtration and dried *in vacuo*

at 45°C to afford 68 g (77% yield) of **8**: mp 131–134°C; IR (neat): 3276 (w), 3032 (w), 1604 (m), 1515 (s); ^{1}H NMR ($CDCl_3$): 8.00 (d, J=8.5, 1H), 7.78 (dd, J=11.4, 7.7, 1H), 7.60 (m, 3H), 7.47 (m, 2H), 7.33 (m, 3H), 6.07 (m, 1H), 5.38 (dt, J=17.1, 1.3, 1H), 5.23 (m, 2H), 2,85 (br s, 1H); ^{13}C NMR ($CDCl_3$): 156.2, 143.3, 140.2, 136.5, 135.6, 135.5, 134.8, 129.0, 128.3, 126.9, 126.7, 125.1, 124.1, 124.0, 119.5, 115.4, 115.2, 112.9, 112.6, 75.1. Anal. Calcd. for $C_{20}H_{15}NOF_2 \cdot 0.2C_3H_8O$: C, 73.78; H, 4.99; N, 4.18. Found: C, 73.54; H, 4.80; N, 4.12.

*Ketoester **10***

A 12 L 3-neck flask fitted with a mechanical stirrer and reflux condensor, under a N_2 atmosphere, was charged with CH_3CN (1275 mL), allylic alcohol **8** (640 g, 1.92 mol) methyl 2-iodobenzoate (565 g, 2.16 mol), Et_3N (415 mL, 2.98 mol), and $Pd(OAc)_2$ (13.0 g, 0.6 mol). The reaction mixture was heated at reflux for 26 hours. The dark black reaction mixture was diluted with CH_3CN (5100 mL) and reheated to dissolve the solids. The hot solution was filtered through a pad of Solka-Floc to remove palladium, with the filtrate being collected in a 12 L 3-neck flask. The filter cake was washed with hot CH_3CN (500 mL). The solution was cooled slowly to 0°C to crystallize **10**. The product was isolated by filtration, the cake was washed successively with CH_3CN (750 mL), H_2O (1500 mL), and CH_3CN (500 mL) then dried *in vacuo* at 45°C to afford **10** (728 g, 80% yield) as an off-white solid: mp 143–144°C; IR (neat): 3065 (w), 3032 (w), 2953 (w), 1716 (vs), 1683 (s), 1600 (s), 1264 (s); ^{1}H NMR ($CDCl_3$): 8.26 (s, 1H), 8.04 (d, J=8.6, 1H), 7.94 (m, 2H), 7.78 (m, 3H), 7.61 (d, J=8.6, 1H), 7.53–7.26 (m, 6H), 3.91 (s, 3H), 3.39 (s, 4H); ^{13}C NMR ($CDCl_3$): 199.1, 167.8, 155.8, 143.3, 137.4, 136.7, 135.6, 133.8, 132.3, 131.5, 131.4, 130.9, 129.4, 129.1, 128.2, 126.8, 126.4, 124.2, 124.1, 119.8, 115.6, 115.3, 112.9, 112.6, 52.0, 40.8, 29.5. Anal. Calcd. for $C_{28}H_{21}NO_3F_2$: C, 73.51; H, 4.63; N, 3.06. Found: C, 73.18; H, 4.74; N, 3.00.

*(S)-Hydroxy-ester **11***

In a 3 L flask equipped with an overhead stirrer, N_2 inlet, and temperature probe, a solution of (R)-(+)-α-pinene (445 mL, 2.87 mol) in hexanes (350 mL) was cooled to 0°C. To this solution, $BH_2Cl \cdot DMS$ (147 mL, 1.415 mol) was added slowly over 30 minutes, maintaining T ≤3°C. When the addition was complete, the borane solution was aged at 0°C for 30 minutes, then at 40°C for 30 minutes.

While the borane complex was forming, a 12 L flask fitted with a mechanical stirrer, N_2 inlet, and thermocouple was charged with **10** (350 g, 0.77 mol) and sieve dried THF (3.5 L). The slurry was cooled to 0°C and diisopropylethylamine (52.5 mL, 0.30 mol) was added. The borane solution was added to the slurry of **10** over 30 minutes, maintaining T ≤3°C. The reaction was complete in 5 hours. Excess reducing agent was quenched by addition of acetone (175 mL), followed by the addition of 10% aq. Na_2CO_3 (1.75 L) and H_2O (1.75 L). The biphasic mixture was stirred for 1.5 hours at 20°C. The layers were separated and the organic phase was washed with H_2O (1.75 L). An equal volume of IPAc was added to the organic phase and the solution was concentrated to 3.75 L by distillation at atmospheric pressure. Another volume of IPAc was added and the concentration was repeated. The 60°C solution was transferred to a 12 L flask where H_2O (70 mL) was added followed by hexanes (3.5 L). The batch was seeded and cooled to 0°C. The product was isolated by filtration, washed with cold 1:1 IPAc:hexanes (1.0 L) and dried *in vacuo* at 20°C to afford the hydrate of **11** (325 g, 89% yield) as a white solid: mp 85–88°C; $[\alpha]^{25}_{589}$ (c 1.0, MeOH)=−5.7. IR (neat): 3347 (br,w), 3165 (br,w), 3067 (w), 2954 (w), 1712 (vs), 1516 (vs); ^{1}H NMR ($CDCl_3$): 7.99 (d, J=8.6, 1H), 7.89 (dd, J=8.1, 1.5, 1H), 7.78 (dd, J=11.4, 7.7, 1H), 7.62 (m, 3H), 7.45 (m, 3H), 7.29 (m, 5H), 4.73 (t, J=4.6, 1H), 3.87 (s, 3H), 3.46 (d, J=3.1, 1H), 3.10 (t, J=7.7, 2H), 2.10 (m, 3H); ^{13}C NMR ($CDCl_3$): 168.4, 156.3, 152.5 (d, J=254), 149.8 (d, J=252), 145.4, 143.8, 136.3, 135.5, 135.0, 132.2, 131.1, 130.8, 129.2, 128.8, 128.2, 126.4, 126.1, 124.7, 124.0, 119.5, 115.4, 115.2, 112.9, 112.6, 73.1, 52.1, 41.3, 30.4. Anal. Calcd. for $C_{28}H_{23}NO_3F_2 \cdot 1.8\ H_2O$: C, 68.37; H, 5.45; N, 2.85. Found: C, 68.38; H, 5.33; N, 2.81.

*(S)-Diol **12***

In a 22 L flask fitted with mechanical stirrer and distillation head, a suspension of hydroxy-ester hydrate **11** (976 g, 2.05 mol) in toluene (15 L) was heated to reflux. Toluene–H_2O azeotrope (5 L) was removed by distillation at atmospheric pressure (temp. 84–110°C). Toluene (5 L) was charged and additional toluene–H_2O azeotrope (5 L) was removed by distillation. The clear solution was cooled to 20°C.

A 4-neck 50 L flask fitted with a mechanical stirrer and reflux condenser was charged with THF (6.5 L) and anhydrous $CeCl_3$ (518 g, 2.10 mol). The gray suspension was heated at reflux for 5 minutes, then the ivory white suspension was cooled to 0°C. A solution of MeMgCl (3M in THF, 3.41 L, 10.25 mol) was added dropwise over 30 min to the $CeCl_3$ suspension, keeping T=0±5°C. The solution was aged at 0°C for 1 hour. The solution of hydroxy-ester **11** in toluene was added dropwise over 2.0 h keeping T=0±5°C. The solution was aged for 0.5 h after addition was complete then quenched by cautious addition to 2M HOAc (16 L). EtOAc (16 L) was then added and the pale yellow solution was stirred at 20–25°C for 10 min, then the layers were separated. The organic layer was washed with 1×16 L 10% Na_2CO_3 followed by 1×16 L H_2O. The organic layer was concentrated by distillation. Toluene (20 L) was added and concentrated to approximately 6 L by distillation [*in vacuo*, 100 mbar, 40°C; or 1 atm, 110°C]. Added toluene (10 L) and concentrated to approximately 6 L by distillation to afford a yellow solution of diol in toluene. The temperature was adjusted to 70°C and 2 L of heptanes were added. The solution was seeded with crystalline diol **12**, then 2 L of heptanes were added every 10 minutes for a total of 12 L heptanes. The suspension was then cooled slowly to 20°C. The suspension was filtered via centrifugation and the cake was rinsed with 2 L of 2:1 heptanes:toluene. The cake was vacuum dried at 40–45°C to afford crystalline diol **12** (867 g) as a white solid in 92% yield. Mp 148–150°C; $[\alpha]^{25}_{589}$ (c 1.0, MeOH)=−8.2. IR (neat): 3326 (w), 2975 (w), 2933 (w), 1607 (m), 1516 (s); ^{1}H NMR ($CDCl_3$): 7.97 (d, J=8.6, 1H), 7.75 (dd, J=11.4, 7.7, 1H), 7.56 (m, 3H), 7.47–7.00 (m, 9H), 4.67 (t, J=6.5, 1H), 4.10 (br s, 1H), 3.22 (m, 3H), 2.12 (m, 2H), 1.66 (s, 3H), 1.63 (s, 3H); ^{13}C NMR ($CDCl_3$): 156.3, 152.6 (d, J=254), 149.9 (d, J=252), 145.5, 145.3, 145.1, 140.2, 136.2, 135.5, 135.0, 131.4, 128.7, 128.2, 127.2, 126.3, 125.6, 124.7, 124.0, 119.5, 115.4, 115.1, 112.9, 112.6, 74.1, 72.9, 41.9, 32.1, 32.9, 29.6. Anal. Calcd. for $C_{29}H_{27}NO_2F_2$: C, 75.80; H, 5.92; N, 3.05. Found: C, 76.12; H, 5.95; N, 2.98.

*Mesylate **14***

A 22L flask fitted with a mechanical stirrer, thermocouple, and a 250 mL addition funnel was purged with N_2. The flask was charged with diol **12** (1023 g), DMF (2.56 L), and diisopropylethylamine (503 mL). The solution was cooled to T=−15°C in an ice–methanol bath. Methanesulfonyl chloride (206 mL) was added dropwise over 2.5 h, keeping the $-15 \leq T \leq -10$°C.

Caution: It is imperative that the reaction temperature be maintained at $-15 \leq T \leq -10$°C. Failure to observe this reaction parameter will result in extensive decomposition of the mesylate.

The homogeneous reaction mixture was aged for 1 h at T=−12°C, then the reaction was seeded and cold CH_3CN (10 L, 0°C) was added. The product was crystallized for 1 hour, then filtered. The filter cake was washed with CH_3CN (2×2 L) followed by hexanes (1×4 L). The cake was dried at 4°C by pulling N_2 through the cake for 12 hours. The reaction afforded 1031 g of crude mesylate **14** (887 g corrected for residual solvents).

*L708,738 DCHA salt, **17***

A 50 L flask fitted with a mechanical stirrer, thermocouple, N_2 inlet and a 5 L addition funnel was purged with N_2. The flask was charged with thiol acid **16** (445 g) and THF (12 L). The solution was cooled to T=−15°C in an ice–methanol bath. A solution of n-BuLi in hexanes (3.23 L) was added dropwise over 4.5 h while maintaining T<−4°C to afford a thick creamy-white slurry of thiol acid **16** dianion.

A 12 L flask equipped with a thermocouple probe, N_2 inlet and mechanical stirrer was charged

with THF (10 L) and cooled to 10°C. Mesylate **14** (1440 g) was added and the solution was cooled to 0°C. The mesylate solution was transferred quickly (5 minutes) into the dianion slurry and the mixture was stirred at 0°C overnight. Assay of the reaction mixture showed no remaining mesylate, so the solution was transferred into a vessel containing EtOAc (20 L). An additional charge of EtOAc (3 L) was used to rinse the reaction vessel. The organic solution was successively washed with 10% brine (20 L), 1M tartaric acid (10.2 L), then H_2O (15 L). The organic solution was concentrated to approximately 10 L, flushed with EtOAc (15 L) and reconcentrated to an oil (2–3 L). The oil was dissolved in EtOAc (12 L) and DCHA (809 mL) was charged followed by hexanes (15 L). The batch was heated to 45°C and an additional aliquot of hexanes (15 L) was added in portions. The solution was seeded and the temperature was cycled between 45°C and 65°C several times over 3.5 days. The suspension was cooled to 22°C and filtered. The cake was washed with 2:1 hexanes:EtOAc (18 L) and vacuum dried at 45°C to afford 1513 g of L-708,738 DCHA salt, **17** (94.8 wt% pure). mp 122–124°C; $[\alpha]^{25}_{589}$ (c 1.0, MeOH)=+78.8. ^{1}H NMR (DMSO-d_6): 8.35 (d, J=8.7, 1H), 7.95 (m, 4H), 7.52 (m, 6H), 7.07 (m, 3H), 4.00 (m, 1H), 3.04 (m, 1H), 2.74 (m, 3H), 2.51 (m, 2H), 2.17 (m, 4H), 1.84 (d, J=10.0, 1H), 1.65 (m, 3H), 1.53 (d, J=10.0, 2H), 1.42 (s, 6H), 1.17 (m, 9H), 0.36 (m, 4H); ^{13}C NMR (DMSO-d_6): 173.7, 156.2, 146.6, 143.7, 139.7, 135.9, 134.7, 130.9, 128.8, 128.2, 128.1, 126.7, 126.2, 125.6, 125.2, 125.1, 124.0, 120.2, 114.9, 114.6, 113.6, 113.3, 71.5, 51.8, 49.4, 40.9, 31.8, 31.5, 31.4, 26.2, 25.4, 24.3, 17.1, 12.1, 11.8. Anal. Calcd. for $C_{47}H_{58}N_2O_3SF_2 \cdot 0.5H_2O$: C, 72.55; H, 7.64; N, 3.60. Found: C, 72.62; H, 7.50; N, 3.25.

L-708,738 sodium salt, 1

A 12 L flask fitted with a mechanical stirrer, thermocouple, and N_2 inlet was purged with N_2. The flask was charged with ethanol (8 L), H_2O (80 mL) and NaOH (160 g). The suspension was heated to 60°C to afford a slightly cloudy solution. The solution was cooled to 22°C overnight. Immediately prior to use the solution was filtered through Solka Floc and the resulting clear solution was titrated.

A 100 L extractor was charged with toluene (30 L) and H_2O (20 L). DCHA salt **17** (1550 g) was added followed by 2 M HOAc (1.6 L). The solution was mixed vigorously, then the aqueous layer was removed. The organic layer was washed with H_2O (2×20 L), then transferred to a 72 L flask, followed by 0.48 M NaOH solution (4.122 L). The solution was concentrated *in vacuo* to approximately 11 L at T=10±5°C. Acetonitrile (22 L) was charged and the temperature was raised to 30°C. The solution was seeded and aged at 30°C to afford a suspension of amorphous solid. Additional CH_3CN (11 L) was added and the temperature was cycled between 40°C and 60°C over 2 days with a portion of the batch being removed, crystallized, and returned to the main batch. The crystalline suspension was cooled to 22°C and filtered under an N_2 atmosphere. The product was vacuum dried at 40°C to afford 1174 g of L-708,738 Na salt, **1**. Mp 118–120°C. $[\alpha]^{25}_{589}$ (c 1.0, MeOH)=+99.9. ^{1}H NMR (DMSO-d_6): 8.34 (d, J=8.7, 1H), 7.94 (m, 4H), 7.71 s, 1H), 7.59 (d, J=5.5, 1H), 7.39 (m, 4H), 7.09 (m, 3H), 4.01 (t, J=7.4, 1H), 3.54 (br s, 1H), 3.06 (m, 1H), 2.56 (m, 3H), 2.12 (m, 4H), 1.43 (s, 6H), 0.39 (m, 2H), 0.24 (m, 2H); ^{13}C NMR (DMSO-d_6): 175.8, 156.2, 146.7, 144.9, 144.0, 139.8, 136.0, 135.9, 134.7, 130.9, 128.8, 128.2, 128.1, 126.7, 126.2, 125.5, 125.2, 125.0, 123.9, 120.2, 114.9, 114.6, 113.6, 113.3, 71.5, 49.4, 43.7, 31.9, 31.6, 31.5, 17.9, 12.3, 11.9. Anal. Calcd. for $C_{35}H_{34}NO_3SF_2Na \cdot 0.3H_2O$: C, 68.34; H, 5.67; N, 2.28. Found: C, 68.42; H, 5.88; N, 2.20.

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