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# Development of a New Synthesis for the Large-Scale Preparation of Triple Reuptake Inhibitor (−)-GSK1360707

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**Abstract:**

**The triple reuptake inhibitor, GSK1360707, was synthesized via an efficient, scalable route, which features a vinyl triflate Suzuki coupling followed by a single-step, double alkylative cyclopropanation with a dihalomethane. Also, a mechanistic understanding of the Suzuki reaction (as it relates to the control of a polychlorinated biphenyl impurity) is discussed.**

## Introduction

Major depressive disorder (MDD) is the most common form of depression.[1] According to statistics, approximately 10 million U.S. adults are classified as severely depressed.[2] GSK1360707 is a potent serotonin, noradrenaline, and dopamine reuptake (triple reuptake) inhibitor under development at GlaxoSmithKline for the treatment of MDD. In order to fully evaluate the clinical potential of GSK1360707, an efficient, safe, and scalable synthetic route to the desired single enantiomer was required. The original synthesis of GSK1360707[3] was deemed not suitable for scale-up because of the high energy of decomposition of the diazomalonate intermediate, the throughput of the synthesis (13 total steps, 11 longest linear, 5% overall yield), and a laborious, low-yielding resolution[4] of racemic GSK1360707 at the final step (Scheme 1).

## Results and Discussion

Our first attempts at an alternate route to GSK1360707 are shown in Scheme 2. Suzuki coupling[5] of the conjugated vinyl triflate (**1**, *vide infra*)[6] derived from the commercially available $\beta$-ketoester **2** and 3,4-dichlorophenylboronic acid **3** afforded $\alpha,\beta$-unsaturated ester **4a** (see Scheme 4 for details). Unfortunately, all efforts to convert **4a** to the corresponding cyclopropane **5a** by reaction with a variety of sulfur ylides[7] or with basic nitromethane[8] failed. The major outcome in these reactions was migration of the olefin out of conjugation with the ester, likely due to substrate deprotonation at the $\gamma$ position rather than conjugate addition.

Next, we reduced ester **4a** and attempted cyclopropanation of the corresponding allylic alcohol (**4b**) and methyl ether (**4c**) under Simmons−Smith conditions.[9] We found that the Boc protecting group was incompatible with the strongly Lewis acidic conditions and caused substrate decomposition. A dichlorocyclopropane was successfully installed in ∼50% yield by reacting **4c** with $CHCl_3$/NaOH.[10] However, several attempted reaction conditions[11] to selectively remove the cyclopropyl chlorine atoms failed due to substrate decomposition.

Undeterred, we turned our attention to a different cyclopropanation strategy involving the alkylation of a dihydropyridone ring with diiodomethane[12] followed by a second, intramolecular alkylation (Scheme 3). The desired cyclopropanation substrate **8** was prepared in two steps by the Mannich reaction of commercially available 3,4-dichloroacetophenone **6** and benzylamine followed by condensation with ethyl malonyl chloride.[13] In line with our observations for the reactivity of enoate **4a**, the product from this intramolecular condensation was isolated as the thermodynamically more stable olefin isomer in which the olefin is not conjugated with the carbonyl (the corresponding conjugated isomer is presumably destabilized due to $A^{1,3}$ strain). Gratifyingly, treatment of **8** with NaH in THF followed by diiodomethane afforded the product of alkylation $\alpha$ to the ester (compound **9**). This iodide could be isolated by column chromatography in ∼75−80% yield, or preferentially treated with a second equivalent of base to afford the desired cyclopropane **10** in excellent overall yield. Presumably, this second deprotonation occurs $\alpha$ to the nitrogen, and the resulting allylic anion is intramolecularly alkylated with exclusive regi-

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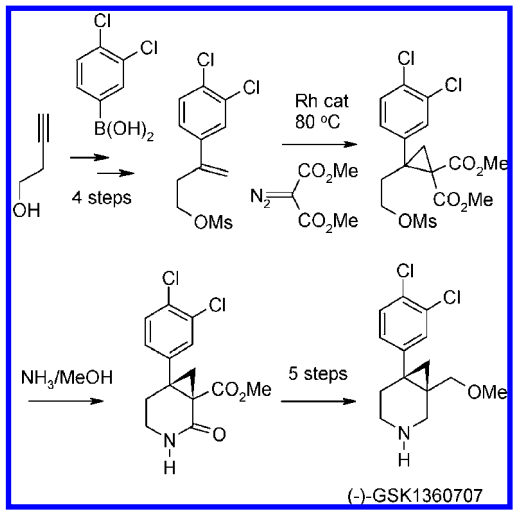
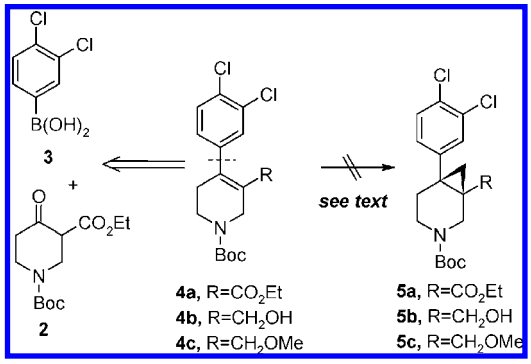
***Scheme 1.*** **Original synthesis of GSK1360707[3]**




***Scheme 2.*** **Unsuccessful cyclopropanation reactions**



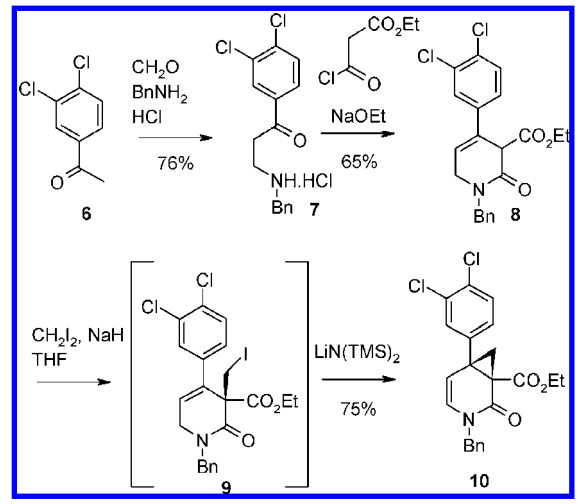

oselectivity.[14] It is noteworthy that the second deprotonation/alkylation sequence was unsuccessful in the absence of the olefin.

Although we had successfully incorporated the cyclopropane ring in the desired position, lactam **10** proved to be a nonviable intermediate for the synthesis of GSK1360707. We found that **10** was unstable, particularly in the presence of even mild acids such as aqueous $NH_4Cl$, or under standard hydrogenation conditions (1 atm $H_2$, Pd/C). Thus, all attempts to convert **10** into GSK1360707 by reduction of the ester, lactam, and/or olefin functional groups resulted in decomposition, presumably *via* cleavage of the cyclopropane ring.

On the basis of these results we turned our attention back to the Suzuki coupling product **4a**. We postulated that this substrate could also undergo the double alkylation sequence with a dihalomethane electrophile and would afford a more stable cyclopropane that could then be converted to GSK1360707. The successful application of this strategy is shown in Scheme 4. As previously alluded to, the commercially available Boc-protected $\beta$-keto ester **2** was treated with triflic anhydride in the presence of Hünig's base to prepare the vinyl triflate **1**. Without isolation, **1** was subjected to the Suzuki coupling conditions with 3,4-dichlorophenylboronic acid **3** to afford the desired coupled product **4a**. Treatment of **4a** with 2.4 equiv of

(14) The same selectivity has been observed in intermolecular alkylations of similar substrates: (a) Werner, J. A.; Cerbone, L R.; Frank, S. A.; Ward, J. A.; Labib, P.; Tharp-Taylor, R. W.; Ryan, C. W. *J. Org. Chem.* **1996**, *61*, 587. (b) Beak, P.; Lee, B. *J. Org. Chem.* **1989**, *54*, 458. (c) Sugg, E. E.; Portoghese, P. S. *J. Med. Chem.* **1986**, *29*, 2028.

***Scheme 3.*** **Cyclopropanation of dihydropyridone 8**




lithium *tert*-butoxide and 3 equiv of chloroiodomethane at 0 °C afforded the desired cyclopropane **12** in 84% yield in a single step. These alternative cyclopropanation conditions were deemed more scalable than the ones described in Scheme 3.[15,16] As expected, compound **12** was found to be much more stable than the corresponding benzyl protected lactam **10**, which allowed subsequent modifications en route to GSK1360707. Thus, treatment of **12** with $LiBH_4$ and MeOH[17] cleanly reduced the ester to the primary alcohol which was in turn methylated[18] to give the corresponding racemic methyl ether **13** in 97% yield. At this stage we evaluated various chiral resolution options in order to obtain the final product as a single enantiomer. We determined that the penultimate intermediate **13** was an excellent candidate for preparative chiral chromatography. An efficient and practical separation was developed using ChiralPak AD and heptane/IPA mobile phase that afforded the desired enantiomer in 46% recovery and 99% ee with a throughput rate of 7.2 kg of racemic **13**/day. Lastly, we found that rapid enamine reduction and subsequent deprotection of the Boc-enamine moiety could be accomplished in 96% yield in a single step by treatment with triethylsilane and 8 equiv of TFA in toluene at room temperature.[19] After a basic aqueous workup, the final product could then be isolated as a crystalline salt by treatment of the free base with either phosphoric or L-(+)-tartaric acid.[20] The absolute stereochemical configuration was confirmed by single-crystal X-ray (Figure 1). This represented a synthesis of enantiomerically pure GSK1360707 from commercially available materials in five steps and 21% overall yield.

(15) $CH_2ClI$ gave a cleaner process than $CH_2I_2$, presumably due to improved stability of the intermediate primary chloride **11**.

(16) Sodium hydride is generally not preferred on scale. For an excellent discussion, see: Fluegeman, C.; Hilton, T.; Moder, K.; Stankovich, R. *Process Saf. Prog.* **2005**, *24* (2), 86.

(17) Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000.

(18) Johnstone, R.; Rose, M. *Tetrahedron* **1979**, *35*, 2169.

(19) To the best of our knowledge, this tandem process has not been described previously. For examples of $Et_3SiH$/TFA reductions of *N*-acyl enamines, see: (a) Lucarini, S.; Bedini, A.; Spadoni, G.; Piersanti, G. *Org. Biomol. Chem.* **2008**, *6*, 147. (b) Taylor, M.; Tokunaga, N.; Jacobsen, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 6700. (c) Wendeborn, S.; Lamberth, C.; Nebel, K.; Crowley, P. PCT Int. Appl. WO/2006/100038, 2006.

(20) The L-tartrate salt was prepared in analogous fashion by treatment of (−)-GSK1360707 free base with L-(+)-tartaric acid in EtOH—see the Experimental Section. The L-tartrate salt was initially selected for development; however, the phosphate salt was subsequently selected on the basis of its superior solid-state properties.

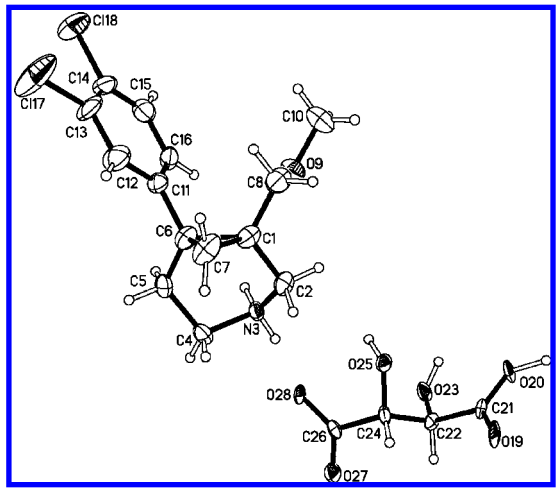
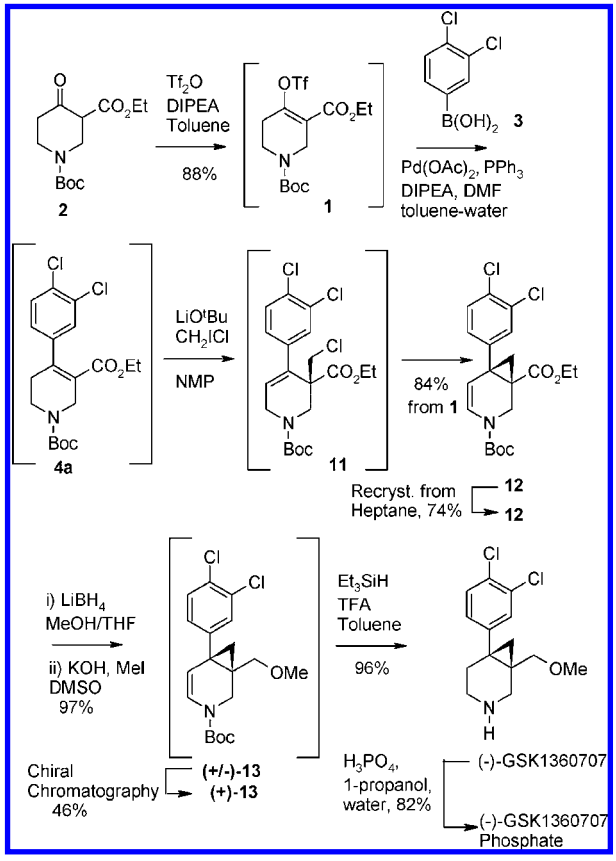


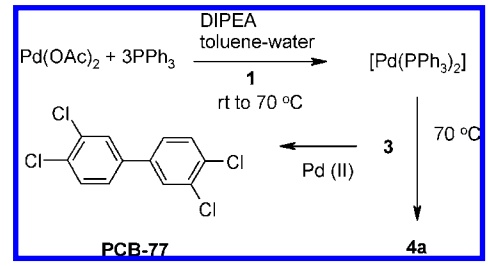

***Figure 1.*** **X-ray structure of GSK1360707 L-tartrate.**

***Scheme 4.*** **Synthesis of GSK1360707**




Before further scaling up this new route we needed to understand and control the formation of a potential polychlorinated biphenyl (3,3′,4,4′-tetrachloro-1,1′-biphenyl, PCB-77) impurity (a highly regulated class of compounds) that could be produced in the Suzuki coupling reaction by dimerization of the 3,4-dichlorophenyl boronic acid. For ease of analysis, we chose to determine the PCB levels in intermediate **12** after the cyclopropanation reaction since this intermediate is readily isolated as a stable crystalline solid. The initial conditions for the Suzuki coupling involved combining the reagents (1:1 vinyl triflate/boronic acid, 2.5 mol % $Pd(OAc)_2$, 7.5 mol % $PPh_3$, Hünig's base, water) in toluene at room temperature and heating the mixture to 70 °C. This resulted in good yields of the product. However, after conversion to cyclopropane **12**, the isolated material was found to contain between 1 and 5% of the PCB impurity by HPLC analysis. We needed to significantly lower the amount of PCB formed in the coupling reaction before scaling up the process and be confident that we could eliminate this impurity from the final product, GSK1360707.

***Scheme 5.*** **Improved Suzuki coupling conditions**




Palladium(II) catalysis has previously been implicated in the dimerization of arylboronic acids.[21] Therefore, we felt that it was important to ensure the complete conversion of $Pd(OAc)_2$ to the desired active Pd(0) catalyst for the Suzuki coupling reaction,[22] ideally in the absence of boronic acid. We further speculated that using a slight excess of vinyl triflate in the reaction should ensure that no free boronic acid would remain and be available for homocoupling at the end of the reaction. On the basis of the above rationale, we modified the conditions by combining 1 equiv of vinyl triflate **1**, 2.5 mol % $Pd(OAc)_2$, 7.5 mol % $PPh_3$, Hünig's base, and water in toluene at room temperature, heating the mixture to 70 °C to preform the active Pd(0) catalyst, and then adding 0.95 equiv of the boronic acid as DMF/toluene solution over 1 h (Scheme 5). Using these conditions lowered the level of PCB in intermediate **12** to <30 ppm. We also found that recrystallizing this intermediate from heptane further lowered the PCB levels to <10 ppm.

## Conclusion

We have developed a practical synthesis of the promising antidepressant GSK1360707. This new route was facilitated by our in-depth understanding of the Suzuki coupling mechanism and its effect on PCB byproduct formation. Other noteworthy transformations include the novel double alkylation-based cyclopropanation method, the efficient enantiomeric separation, and the final single-step reduction−deprotection. The final route as depicted in Scheme 4 was recently scaled in our 200-gal pilot plant to afford over 10 kg of (−)-GSK1360707 as the phosphate salt.

## Experimental Section

Mass spectra were obtained using a ThermoScientific LTQ Orbitrap Discovery mass spectrometer using positive electrospray ionization (ESI). HPLC purity was determined on a Hewlett-Packard series 1100 system using Agilent Eclipse XDB C18 columns (150 mm × 4.6 mm, 3.5 $\mu$m), and a mixture of water and acetonitrile as mobile phase (gradient at a flow rate

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of 1.0 mL/min and UV detector at 220 nm). Preparative Chiral HPLC was conducted on a Chiralpak AD, 20 $\mu$m, 20 cm × 25 cm column at ambient temperature. Processing parameters: Flow: 92 L/h; Detection: 225 and 280 nm; Feed stock: 80 g/L. PCB-77 content was determined by a gradient, reversed-phase HPLC using a polar embedded C14 column. The mobile phase was (A) water with 0.05% v/v TFA and (B) acetonitrile with 0.05% v/v TFA. The gradient runs from 80 to 95% B over 5 min. The detection wavelength was 262 nm. The content of **1** in solution was determined by a gradient, reversed-phase HPLC using a C18 column. The mobile phase is (A) water with 0.05% v/v TFA and (B) acetonitrile with 0.05% v/v TFA. The gradient runs from 0 to 95% B over 8 min. The detection wavelength is 255 nm. The content of **13** in solution was determined by a gradient, reversed-phase HPLC using a C18 column. The mobile phase is (A) water with 0.05% v/v TFA and (B) acetonitrile with 0.05% v/v TFA. The gradient runs from 0 to 95% B over 8 min. The detection wavelength is 220 nm.

**1-(1,1-Dimethylethyl) 3-ethyl 4-{[(trifluoromethyl)sulfonyl]oxy}-5,6-dihydro-1,3(2*H*)-pyridinedicarboxylate (1).** 1-(1,1-Dimethylethyl)-3-ethyl 4-oxo-1,3-piperidinedicarboxylate (41.1 kg, 151.4 mol) dissolved in toluene (320 kg, 3473 mol) was cooled to −5 °C and then treated with *N*,*N*-diisopropylethylamine (29.4 kg, 1.5 equiv, 227 mol) at <5 °C. After 5 min, trifluoromethanesulfonic anhydride (46.9 kg, 1.1 equiv, 167 mol) was added at <5 °C. The reaction mixture was warmed to ∼0 °C. Upon disappearance of starting material **2** as determined by HPLC, the reaction mixture was warmed to ∼20 °C and filtered. The solids were rinsed with toluene (35.6 kg, 387 mol), and the resultant toluene solution of **1** (chemically unstable) was used directly in the next stage. Analytical data obtained on a concentrated sample: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.32−4.27 (m, 4H), 3.61 (t, $J$ = 5.7 Hz, 2H), 2.51−2.49 (m, 2H), 1.47 (s, 9H), 1.33 (t, $J$ = 7.1 Hz, 3H).

**1-(1,1-Dimethylethyl)-3-ethyl 4-(3,4-dichlorophenyl)-5,6-dihydro-1,3(2*H*)-pyridinedicarboxylate (4a).** To the 1-(1,1-dimethylethyl) 3-ethyl 4-{[(trifluoromethyl)sulfonyl]oxy}-5,6-dihydro-1,3(2*H*)-pyridinedicarboxylate (**1**) solution in toluene (51.4 kg, 127 mol, from previous reaction) was added *N*,*N*-diisopropylethylamine (26.3 kg, 203.1 mol, 1.6 equiv), water (34.25 kg, 1901 mol), triphenylphosphine (2.5 kg, 9.52 mol, 0.075 equiv), and palladium(II) acetate trimer (709 g, 1.1 mol, 0.0083 equiv). The reaction was heated to ∼70 °C. To the reaction mixture was added over 1 h a solution of 3,4-dichlorophenylboronic acid (23.3 kg, 122 mol, 0.96 equiv) in *N*,*N*-dimethylformamide (21.3 kg, 291 mol) and toluene (115 kg, 1251 mol). After the complete consumption of **3** as determined by HPLC, the reaction was cooled to ∼0 °C followed by the addition of 1 N sodium hydroxide (308 L, 320 kg) at 0−15 °C. The reaction mixture was warmed to about 20 °C and stirred for ∼1 h. The reaction mixture was filtered, and the aqueous layer was discarded. Next, 20% w/w aqueous sodium bisulfite (401 kg) was added while maintaining the temperature at 15−28 °C. The mixture was heated to ∼60 °C and stirred for ∼1 h. The mixture was cooled to ∼22 °C and filtered, and the aqueous layer was discarded. The organic layer was washed with water (343 L, 343 kg) and used directly in the next stage. Analytical data obtained on a concentrated sample: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.39 (d, $J$ = 8.2 Hz, 1H), 7.23 (d, $J$ = 1.8 Hz, 1H), 6.96 (dd, $J$ = 2.0, 8.24 Hz, 1H), 4.24 (s, 2H), 3.99 (dd, $J$ = 7.1, 14.3 Hz, 2H), 3.59 (t, $J$ = 5.7 Hz, 2H), 2.44 (br s, 2H), 1.49 (s, 9H), 1.00 (br s, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 166.0 (br), 154.5, 144.2, 142.1, 132.2, 131.5, 130.2, 129.1, 126.6, 126.3, 80.3, 60.7, 44 (br), 40.5−39.4 (br), 32.8, 28.5, 13.8; IR (ATR) 2978 (w), 1693 (s), 1468 (m), 1418 (m), 1366 (m), 1294 (w), 1236 (s), 1163 (m), 1135 (m), 1114 (m), 1052 (m), 1030 (m), 996 (w), 899 (w), 820 (w), 764 (w); HRMS *m*/*z* 400.1077 [($M^+$); calcd for $C_{19}H_{24}Cl_2NO_4$: 400.1077].

**(±)-3-(1,1-Dimethylethyl)-1-ethyl 6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]hept-4-ene-1,3-dicarboxylate (12).** Lithium *t*-butoxide (23.4 kg, 292 mol, 2.4 equiv) and 1-methyl-2-pyrrolidinone (240 kg, 234 L) were stirred for ∼1 h at ∼25 °C. The resulting suspension was transferred to a pressure vessel. The reactor was rinsed with 1-methyl-2-pyrrolidinone (4.90 L, 5 kg) into the pressure vessel.

The 1-(1,1-dimethylethyl)-3-ethyl 4-(3,4-dichlorophenyl)-5,6-dihydro-1,3($^2$H)-pyridinedicarboxylate (49 kg, 122 mol, 1 equiv. based on 100% yield in Suzuki and 3,4-dichlorophenylboronic acid as limiting reagent) solution in toluene was distilled under reduced pressure to remove the toluene. 1-Methyl-2-pyrrolidinone (244 L, 250 kg) was added, and the resulting solution was cooled to 20 °C. Chloroiodomethane (64.4 kg, 366 mol, 3 equiv) was charged into the reactor, and the resulting slurry was cooled to ∼0 °C. The lithium *tert*-butoxide suspension prepared above was added at <10 °C. The resulting solution was warmed to ∼20 °C and stirred until the starting material was consumed by HPLC. Acetic acid (11 kg, 183 mol, 1.5 equiv) was added all at once, followed by water (342 kg, 342 L) over ∼30 min. The resulting slurry was cooled to 15 °C and stirred for ∼30 min. The solids were collected by filtration. Water (63.4 kg, 63.4 L) and methanol (147 kg, 186 L) were charged into the reactor to rinse it, and the resulting aqueous methanol solution was used to wash the product cake. The resulting yellow solids were dried to a constant weight in a 55 °C vacuum oven to provide 42.1 kg of (±)-3-(1,1-dimethylethyl)-1-ethyl 6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]hept-4-ene-1,3-dicarboxylate (12) (83.7% crude yield).

**Recrystallization of (±)-3-(1,1-Dimethylethyl)-1-ethyl 6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]hept-4-ene-1,3-dicarboxylate.** (±)-3-(1,1-Dimethylethyl)-1-ethyl 6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]hept-4-ene-1,3-dicarboxylate (41.8 kg, 101.5 mol) was suspended in heptane (209 L, 143 kg). The resulting slurry was heated to ∼80 °C and filtered into a clean reactor. The filter and lines were rinsed with heptane (41.8 L, 28.6 kg) preheated to ∼70 °C, and the rinse was combined with the filtrate. The solution was heated to 80 °C and then cooled to 43−47 °C over 60 min. Seed crystals of (±)-3-(1,1-dimethylethyl) 1-ethyl 6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]-hept-4-ene-1,3-dicarboxylate (21 g, 0.0005 equiv) were added. The slurry was cooled to 22 °C over 60 min. The solids were collected by filtration, the reactor was rinsed with heptane (41.8 L, 28.6 kg), and the rinse was used to wash the filter cake. The solids were dried to a constant weight in a 50−60 °C vacuum oven to provide 31 kg of (±)-3-(1,1-dimethylethyl)-1-ethyl 6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]hept-4-ene-1,3-dicar-

boxylate (74.2% yield) as an off-white solid. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.35 (m, 2H), 7.11 (m, 1H), 6.65 (br m, 1H), 5.16 (br m, 1H), 4.27 (br m, 1H), 3.79 (br m, 3H), 2.32 (m, 1H), 1.59 (m, 1H), 1.52 (s, 9H), 0.94 (br m, 3H); $^{13}$C NMR (125.7 MHz, $CDCl_3$) $\delta$ 169.1−168.9 (br), 152.6 (br), 140.6, 132, 131.1, 131, 129.9, 128.5, 124.3, 81.5, 60.9, 40.8−39.5 (br), 40.1, 31.6, 28.2, 23.2, 13.8; IR (ATR) 2976 (w), 1699 (s), 1640 (m), 1469 (w), 1356 (s), 1307 (m), 1245 (m), 1238 (m), 1161 (m), 1136 (s), 1045 (w), 946 (w), 873 (m), 771 (w), 737 (w), 678 (w); HRMS *m*/*z* 412.1079 [($M^+$); calcd for $C_{20}H_{24}Cl_2NO_4$: 412.1077]; mp = 111−113 °C.

(±)-3-(1,1-dimethylethyl)-1-ethyl 6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]hept-4-ene-1,3-dicarboxylate (**12**) may be reworked if necessary to reduce amount of PCB No. 77 by slurrying in heptane (3.42 wt) at 50 °C for 1 h. Cooling to room temperature, filtering, and drying affords (±)-3-(1,1-dimethylethyl)-1-ethyl 6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]hept-4-ene-1,3-dicarboxylate as a white solid.

**(±)-1,1-Dimethylethyl-6-(3,4-dichlorophenyl)-1-(hydroxymethyl)-3-azabicyclo[4.1.0]hept-4-ene-3-carboxylate Reduction Product of 12 and Precursor to (±)-13.** (±)-3-(1,1-Dimethylethyl)-1-ethyl 6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]hept-4-ene-1,3-dicarboxylate (41.8 kg, 101 mol) was dissolved in THF (75 kg). A solution of 2 M $LiBH_4$ in THF (62 kg, 1.5 equiv, 155 mol) was added and the resulting solution heated to 40 °C. Methanol (9.7 kg, 3 equiv, 304 mol) was added over ∼60 min (*this reaction is exothermic and releases hydrogen gas*). The reaction was stirred for 40 min until consumption of starting material as determined by HPLC, cooled to 20 °C and heptane (209 L) was added over ∼15 min. Water (84 L) was added over ∼10 min, and the resulting slurry was stirred for 15−20 min (*hydrogen gas is released during this addition*). Aqueous HCl (1 N, 167 L) was added over ∼15 min (*hydrogen gas is released during this addition*), the mixture was stirred for 15 min, and the layers were separated. The organic layer was washed with water (209 L), and filtered. The resulting solution was used directly in the next stage. Analytical data on a concentrated sample: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38 (br m, 2H), 7.15 (br m, 1H), 6.60 (br m, 1H), 5.12 (br m, 1H), 4.24 (br m, 1H), 3.38 (br m, 2H), 3.29 (br m, 1H), 1.51 (br m, 10H), 1.30 (br m, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 153.2 (br), 141.7, 132.6, 131.2, 131.0, 130.5, 128.7, 123.1−122.8 (br), 113.1−112.6 (br), 81.5, 65.7, 42.0−41.0, 37.6−36.8, 32.1, 29.2−28.1, 22.9−22.2, 14.4; IR (ATR) 3430 (w), 2977 (w), 1702 (m), 1646 (m), 1471 (m), 1353 (s), 1237 (m), 1163 (s), 1127 (s), 1029 (m), 912 (w), 864 (w), 766 (m), 731 (m), 676 (w); HRMS *m*/*z* 370.0968 [($M^+$); calcd for $C_{18}H_{22}Cl_2NO_3$: 370.0972].

**(+)-1,1-Dimethylethyl-6-(3,4-dichlorophenyl)-1-[(methyloxy)methyl]-3-azabicyclo[4.1.0]hept-4-ene-3-carboxylate: (+)-13.** (±)-1,1-Dimethylethyl 6-(3,4-dichlorophenyl)-1-(hydroxymethyl)-3-azabicyclo[4.1.0]hept-4-ene-3-carboxylate (estimated 37.6 kg, 101 mol, amount based on 100% yield in reduction) in heptane was dissolved in DMSO (290 kg, 263 L). After the heptane was removed by distillation, the remaining solution was cooled to ∼20 °C, treated with powdered potassium hydroxide (22.8 kg, 4 equiv, 406 mol), and stirred for 15 min. Iodomethane (28.8 kg, 2 equiv, 203 mol) was added over 15 min, and the reaction was stirred for 2 h at 20 °C until the remaining starting material was <2% as determined by HPLC. Water (150 kg) was added over 30 min, followed by heptane (257 kg), and the mixture stirred for 1 h. The phases were separated, and the top (organic) layer was washed with water (150 kg) and partially concentrated under vacuum. The heptane solution of (±)-1,1-dimethylethyl 6-(3,4-dichlorophenyl)-1-[(methyloxy)methyl]-3-azabicyclo[4.1.0]hept-4-ene-3-carboxylate thus prepared was used directly in preparative chiral chromatography next. (±)-1,1-Dimethylethyl-6-(3,4-dichlorophenyl)-1-[methyloxy)methyl]-3-azabicyclo[4.1.0]hept-4-ene-3-carboxylate ((±)-**13**), 36.9 kg, 96 mol) was dissolved in 380 L (95/5 (v/v) heptane/IPA), and the two enantiomers were separated by preparative chiral HPLC on a Hipersep 200 Preparative HPLC system. The feed solution was transferred to the Hipersep 200 feed vessel via a 1 $\mu$m filter. Heptane was charged to solvent vessel A, and IPA was charged to solvent vessel B. The Hipersep instrument was used to mix the mobile phase, 95/5 heptane/IPA, by pumping 95% from vessel A, and 5% from vessel B to elute the desired enantiomer as the first eluting peak. A column containing Chiralpak AD (20 $\mu$m particle size, 20 cm inner diameter ×25 cm length) was equilibrated by passing mobile phase through the column at a flow rate of 100 L/h for 30 min. Chromatography was run under the following conditions, and fractions were collected until all of the feed had been processed.

Mobile phase: 95/5 heptane/IPA for 15 min, followed by 50/50 heptane/IPA for 7 min, and equilibration of the column with 95/5 heptane/IPA for 4 min. Flow rates: 92 L/h. Detection: 290 nm. Temperature: 25 °C. Run time: 26 min. Column: Chiralpak AD (20 $\mu$m), column dimensions: 20 cm ×25 cm. Loading amount per injection: 100 g.

Fractions of the desired enantiomer (containing <1% of the undesired enantiomer by chiral HPLC) were concentrated under vacuum to ∼40 L. Toluene (200 L) was added, and the volume was reduced under vacuum to ∼40 L. This concentrated toluene solution of (+)-1,1-dimethylethyl (1*S*,6*R*)-6-(3,4-dichlorophenyl)-1-[(methyloxy)methyl]-3-azabicyclo[4.1.0]hept-4-ene-3-carboxylate (**(+)-13**, 16.5 kg, 42.9 mol, 46% yield, 92% recovery) was used directly in the next step. Analytical data obtained on a concentrated sample: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40 (d, $J$ = 4 Hz, 1H), 7.37 (d, $J$ = 8 Hz, 1H), 7.15 (dd, $J$ = 8, 4 Hz, 1H), 6.55 (br m, 1H), 5.08 (br m, 1H), 4.19 (br m, 1H), 3.27 (br m, 1H), 3.10 (br s, 3H), 3.04 (br m, 1H), 2.96 (br m, 1H), 1.49 (br s, 9H), 1.42 (d, $J$ = 4 Hz, 1H), 1.28 (br m, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 153.1 (br), 141.8, 132.3, 131.5, 130.8, 130.2, 129.1, 122.9 (br), 113.1 (br), 81.4, 75.3 (br), 59.0, 42.3−41.3, 35.6−35.0, 28.5, 28.3−27.8, 22.7; IR (ATR) 2978 (w), 1700 (s), 1472 (m), 1367 (s), 1354 (s), 1239 (m), 1163 (s), 1102 (s), 1030 (m), 962 (w), 865 (w), 822 (w), 767 (m), 714 (w), 676 (w); HRMS *m*/*z* 384.1126 [($M^+$); calcd for $C_{19}H_{24}Cl_2NO_3$: 384.1128]; $[\alpha]^{25}_D$ = +119.5 ($c$ = 1.90, MeOH).

**(−)-GSK1360707.** 1,1-Dimethylethyl (1*S*,6*R*)-6-(3,4-dichlorophenyl)-1-[(methyloxy)methyl]-3-azabicyclo[4.1.0]hept-4-ene-3-carboxylate (**(+)-13**, 8.25 kg, 20.3 mol) was dissolved in toluene (47.4 kg). The solution was treated with triethylsilane (2.6 kg, 1.1 equiv, 22.5 mol), followed by the addition of

trifluoroacetic acid (18.6 kg, 8 equiv, 163 mol) over 1 h at <30 °C (*Caution: this reaction is exothermic and releases gas!*). The reaction was stirred at 20 °C for 3 h until the starting material was consumed as determined by HPLC, then quenched with 5 N sodium hydroxide (38.5 kg, 32.6 L, 8 equiv), heated to 50 °C, and stirred for 30 min. The pH of the mixture was approximately 13−14. The phases were separated, the toluene layer was treated with 1 N sodium hydroxide (16.3 kg), and the mixture was stirred for 10 min. The phases were separated, the toluene layer was treated with water (15.7 kg), and the mixture was cooled to 20 °C. The aqueous layer was removed and the toluene layer was concentrated to ∼15 L. The solution was used directly in the next stage. Analytical data on a concentrated sample: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.43 (d, $J$ = 4 Hz, 1H), 7.36 (d, $J$ = 8 Hz, 1H), 7.18 (dd, $J$ = 8, 4 Hz, 1H), 3.31 (d, $J$ = 12 Hz, 1H), 3.13 (s, 3H), 3.09 (d, $J$ = 12 Hz, 1H), 2.95 (d, $J$ = 8 Hz, 1H), 2.83 (d, $J$ = 8 Hz, 1H), 2.76 (m, 1H), 2.68 (m, 1H), 1.95 (m, 1H), 1.82 (m, 1H), 1.03 (d, $J$ = 8 Hz, 1H), 1.00 (d, $J$ = 8 Hz, 1H); $[\alpha]^{25}_D$ = −5.7 ($c$ = 0.07, $CCl_4$).

**(−)-GSK1360707 Phosphate.** (1*S*,6*R*)-6-(3,4-Dichlorophenyl)-1-[(methyloxy)methyl]-3-azabicyclo[4.1.0]heptane (5.81 kg, 20.3 mol, based on 100% yield in the previous step) was dissolved in 1-propanol (31.5 kg), and the solution was heated to 70 °C. Phosphoric acid (∼85.5 wt %, 2.33 kg, 1 equivalent, 20.3 mol) was added over ∼20 min. The resulting slurry was cooled to 20 °C over 60 min and stirred for 30 min. The slurry was cooled to 0 °C over 20 min, stirred for ∼60 min, filtered, and washed with 1-propanol (6.3 kg). The solid was dried at 50 °C under vacuum for 18 h to give 6.4 kg of (−)-GSK1360707 phosphate as a white solid (82% yield). $^1$H NMR (500.0 MHz, $D_2O$) $\delta$ 7.43 (d, $J$ = 2 Hz, 1H), 7.36 (d, $J$ = 8.3 Hz, 1H), 7.18 (dd, $J$ = 8.4, 2.2 Hz, 1H), 3.58 (d, $J$ = 13.7 Hz, 1H), 3.20 (d, $J$ = 13.9 Hz, 1H), 3.22−3.16 (m, 1H), 3.01 (s, 3H), 3.01 (d, $J$ = 9.7 Hz, 1H), 2.82−2.76 (m, 1H), 2.72 (d, $J$ = 10.4 Hz, 1H), 2.13−2.11 (m, 2H), 1.27 (d, $J$ = 6.4 Hz, 1H), 1.13 (d, $J$ = 6.2 Hz, 1H); $^{13}$C NMR (125.7 MHz, $D_2O$) $\delta$ 142, 131.6, 131.1, 130.41, 130.37, 129, 76.4, 58.1, 44.7, 39.2, 28.4, 27.7, 21.9, 19.4; IR (ATR) 3059 (w), 2977 (m), 2942 (m), 2890 (m), 2649 (b), 1634 (m), 1591 (w), 1555 (w), 1456 (m), 1095 (s), 1071 (s), 959 (s), 831 (m), 678 (m); $[\alpha]^{25}_D$ = −25.8 ($c$ = 0.970, $H_2O$); HRMS $m/z$ 286.0754 [($M^+$); calcd for $C_{14}H_{18}Cl_2NO$: 286.0760]; mp =210 °C.

**GSK1360707 L-tartrate.** (1*S*,6*R*)-6-(3,4-Dichlorophenyl)-1-[(methyloxy)methyl]-3-azabicyclo[4.1.0]heptane (3.7 g, 12.9 mmol) was dissolved in 2-propanol (60 mL), to the solution was added L-(+)-tartaric acid (2.7 g, 18.1 mmol, 1.4 equiv) and the solution was heated to 80 °C. Water (12 mL) was added and the solution stirred for 10 min. The resulting solution was cooled to 0 °C at a rate of 0.2 °C/min, and then held at 0 °C for 7 h. The resulting slurry was filtered and washed with 2-propanol (2 × 10 mL). The solid then dried under vacuum for 5 h at 50 °C to give GSK1360707 L-tartrate of an off-white solid (3.7 g, 65% yield). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.68 (d, $J$ = 2.01 Hz, 1 H), 7.60−7.56 (m, 1 H), 7.39−7.33 (m, 1 H), 3.85 (s, 2 H), 3.43 (d, $J$ = 13.55 Hz, 1 H), 3.11 (d, $J$ = 13.19 Hz, 1 H), 3.04 (s, 4 H), 2.90−2.83 (m, 1 H), 2.79−2.67 (m, 2 H), 2.03 (t, $J$ = 5.26 Hz, 2 H), 1.22 (s, 2 H); $^{13}$C NMR (125.7 MHz, DMSO-$d_6$) $\delta$ 174.7, 143.7, 131.3, 130.7, 130.3, 129.6, 129.2, 76.2, 71.8, 57.9, 43.7, 38.4, 29, 27.1, 22.4, 18.9; IR (ATR) 3434 (m), 3338 (m), 3034 (m), 2977 (m), 2876 (m), 2671 (w), 1657 (s), 1606 (s), 1563 (w), 1471 (s), 1394 (s), 1133 (s), 823 (m), 679 (s) $cm^{-1}$; mp = 193 °C.


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## Supporting Information Available

$^1$H- and $^{13}$C NMR spectra for compounds **4a**, **12**, and (−)-GSK1360707 phosphate; X-ray crystal structure of GSK1360707 L-tartrate.This material is available free of charge via the Internet at http://pubs.acs.org.


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