

# A Practical Synthesis of the RAR $\gamma$ Agonist, BMS-270394

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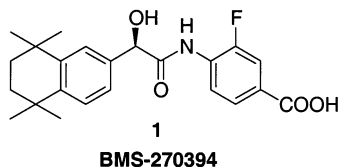
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## Abstract:

A novel synthesis of **1** (BMS-270394), a nuclear retinoic acid receptor (RAR $\gamma$ ) agonist, is reported. The synthesis includes an enantioselective reduction of  $\alpha$ -ketoacid **4** to the corresponding chiral  $\alpha$ -hydroxy acid **7** using a NaBH<sub>4</sub>/L-tartaric acid mixture and a novel coupling between **7** and an electron-deficient aniline **11** which was activated via N-sulfinyl derivative **15** to form chiral  $\alpha$ -hydroxy amide **16**. The synthesis was completed by a racemization-free hydrolysis of **16** to the corresponding  $\alpha$ -hydroxy amidoacid **1** using KOSiMe<sub>3</sub> in acetonitrile.

## 1. Introduction

Retinoids, which are analogues of *all-trans*-retinoic acid, exert their biological effects through two families of nuclear receptors, retinoic acid receptors (RARs) and retinoid X receptors (RXRs). These receptors belong to the superfamily of steroid/thyroid hormone receptors.<sup>1</sup> A number of retinoids are used to treat a variety of diseases including acne, psoriasis, and cancer as well as the repair of photoaging of the skin. BMS-270394 (**1**) belongs to a class of retinobenzoic acids (arotinoids) that specifically activate the RAR $\gamma$  subtype (the other two subtypes of RARs are RAR $\alpha$  and RAR $\beta$ ) and is proposed for use in the oral treatment of acne and in the prevention of the progression of precancerous lesions in organ transplant patients.<sup>2</sup> RAR $\gamma$  agonists apparently lack the hepatic toxicity associated with the systemic use of nonselective retinoids.<sup>2</sup>



## 2. Results and Discussion

**2.1. Previous Work.** BMS 270394 was originally prepared by the route outlined in Scheme 1. Starting from **2**,<sup>2</sup> a

Friedel–Crafts acylation gave the keto ester **3**, which was hydrolyzed and converted to the allyl ester **5**. Enantioselective reduction of the latter with (*R*)-Alpine-Borane followed by ester deprotection gave hydroxy acid **7** with an ee of 93–94%. Crystallization of this material improved the ee to >99%. Reaction of **7** with diphosgene gave **8**. This, in turn, was coupled with the aniline **9** to give the ester **10**. Deprotection of the allyl ester with Pd(PPh<sub>3</sub>)<sub>4</sub>/morpholine provided **1**.

Although this synthesis was suitable for the laboratory-scale preparation of **1**, two major issues associated with the scale-up of this process to supply material required for toxicological and clinical studies emerged:

(a) (*R*)-Alpine-Borane is relatively expensive and requires special handling on a large scale because of its pyrophoric nature.

(b) The published coupling conditions<sup>2</sup> using diphosgene, **7** and the methyl ester of **9** (instead of the allyl ester) gave us variable yields of the product, accompanied by numerous byproducts that were difficult to separate.

An alternate synthesis of **1** was thus desirable to circumvent these issues.

**2.2. New Route.** A retrosynthetic analysis (similar to the published synthesis)<sup>2</sup> of the molecule is summarized in Scheme 2.

Starting with the keto acid **4** (see Scheme 2), our first goal was to find an alternative to the (*R*)-Alpine-Borane reduction. It is known that a mixture of sodium borohydride/tartaric acid is efficient in enantioselective reductions of ketones that have a chelating group, such as an ester, alpha to the keto functionality.<sup>3</sup> Using this reduction protocol, **4** gave the desired hydroxy acid **7** in 75% yield with an (*R/S*) ratio of 84:16, as determined by chiral HPLC. The enantiopurity of **7** was improved by crystallization as a diamine salt. Of a variety of chiral bases (~20) evaluated, (1*R*, 2*R*)-(–)-*N,N'*-dimethylcyclohexane-1,2-diamine was found to be the most suitable. Thus, treatment of crude **7** with this amine gave the desired (*R*)-hydroxy acid in high yield (81% after liberation from the amine salt **12**) with ee >99% (Scheme 3). Recycling the (*S*)-enantiomer salt could be achieved by racemization of the mother liquor (enantiomeric ratio 22:78 (*R/S*)) with 5 equiv of TMSCl and 3 equiv of DBU in dichloroethane at 50 °C for 2 h.

With the (*R*)-acid-**7** in hand, we turned our attention to the coupling of this compound to aniline **11**<sup>2a</sup> (Scheme 2).

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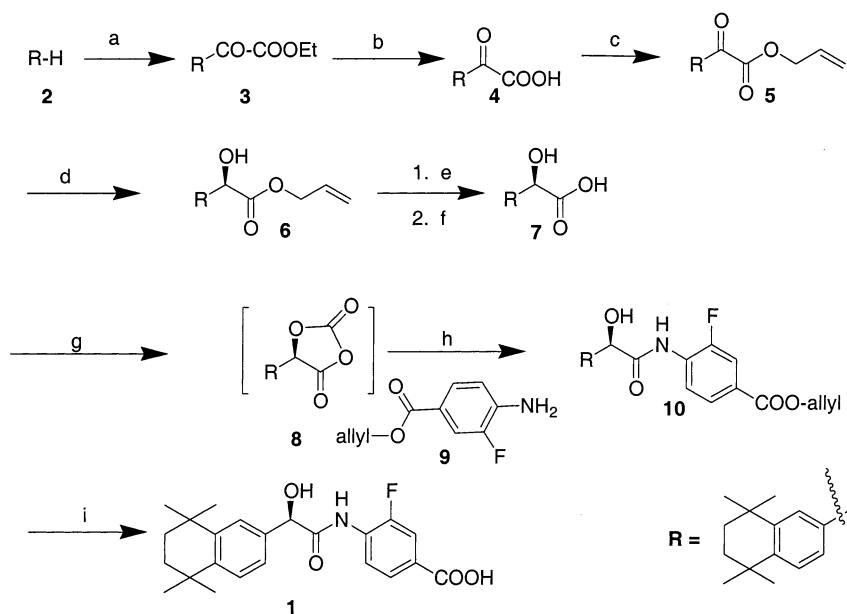
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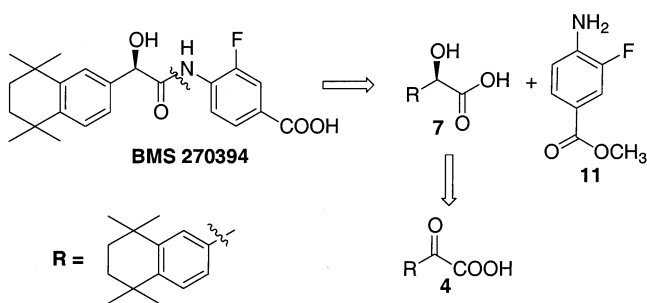
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Scheme 1<sup>a</sup>

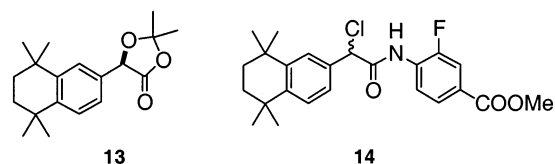
<sup>a</sup> Reagents and Conditions: a) Cl-CO-COOEt, AlCl<sub>3</sub>, 1 h, rt, 79%. b) NaOH, 1 h, rt. c) K<sub>2</sub>CO<sub>3</sub>, allyl bromide, rt, 95% yield from **3**. d) (*R*)-Alpine-Borane, 15 °C, 4 h. e) Pd(PPh<sub>3</sub>)<sub>4</sub>/morpholine, rt, 50 min, 67% yield from **5**, 93–94% ee. f) Two crystallizations from ethyl acetate/hexanes, 68% recovery, 99% ee. g) Diphosgene, 63 °C, 5 h. h) **9**, 16 h, rt, 77%. i) Pd(PPh<sub>3</sub>)<sub>4</sub>/morpholine, 20 min, 88%.

## Scheme 2



Activation of acid **7** via the dioxolanedione **8** made by an alternate procedure<sup>4</sup> or acetonide<sup>5</sup> **13** and subsequent treatment with aniline **11** afforded the desired amide **15** in low yield. Activation<sup>6</sup> with isobutylchloroformate or pivaloyl chloride also resulted in low yields of **15**. The low conversion was presumably due to the poor nucleophilicity of the aniline **11**. Standard coupling procedures using carbodiimides in conjunction with 1-hydroxybenzotriazole (HOBT)<sup>7</sup> and DMAP afforded only trace amounts of the product. Employment of carbonyldiimidazole,<sup>8</sup> benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP),<sup>9</sup> or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ)<sup>10</sup> as coupling agents was also unsuccessful. In another approach, the hydroxy acid was converted to the bis-trimethylsilyl derivative followed by conversion to the acid chloride using oxalyl chloride and then treated with aniline **11**.<sup>11</sup>

However, in our hands, under a variety of conditions, the major product from this protocol was the  $\alpha$ -chloro-amide **14**.



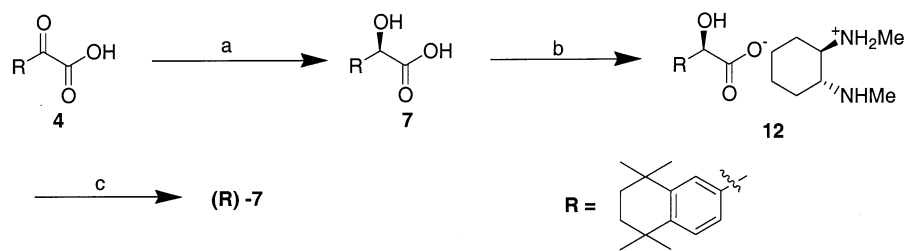
We ultimately developed a practical procedure to prepare enantiomerically pure  $\alpha$ -hydroxy amides from chiral  $\alpha$ -hydroxy acids and electron-deficient anilines via *N*-sulfinyl-aniline derivatives. This procedure has been reported elsewhere.<sup>12</sup> Thus, aniline **11** was converted to its *N*-sulfinyl derivative **15** (see Scheme 4) in 99% yield which was then coupled with the chiral  $\alpha$ -hydroxy acid (*R*)-**7** to give the desired chiral  $\alpha$ -hydroxy amide **16** (77% yield; ee 99%).

Our efforts were then directed towards identifying a procedure for the hydrolysis of the methyl ester **16** without racemization. A variety of conditions were then evaluated [LiOH, NaOH, K<sub>2</sub>CO<sub>3</sub>, *n*-Bu<sub>4</sub>N<sup>+</sup>OH<sup>-</sup> in CH<sub>2</sub>Cl<sub>2</sub>, THF, acetone, IPA, ethanol, methyl *tert*-butyl ether (MTBE) and acetonitrile]. In alcoholic solvents LiOH, NaOH and *n*-Bu<sub>4</sub>NOH gave extensive racemization (10–15%). In other solvents, racemization (1–3%) of **1** was still observed. Attempts to improve the ee via crystallization were not successful. Using potassium trimethylsilyanoate<sup>13</sup> in THF and alcoholic solvents, racemization (1–3%) of **1** was still

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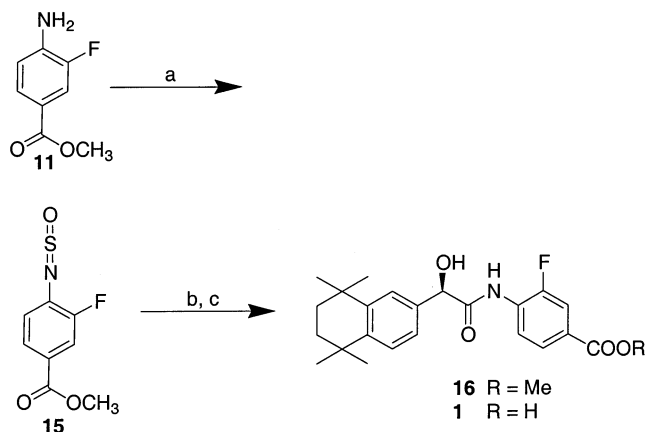
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### Scheme 3<sup>a</sup>



<sup>a</sup> Reagents and Conditions: a) NaBH<sub>4</sub>/L-tartaric acid, -45 °C, 48 h, 75%. b) (1*R*),(2*R*)-*trans*-Dimethylaminomethyl cyclohexane, 60 °C, 3 h, 83%. c) NaOH, 0 °C, 97%.

### Scheme 4<sup>a</sup>



<sup>a</sup> Reagents and conditions: a) SOCl<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 99%. b) (*R*)-**7**, CH<sub>2</sub>Cl<sub>2</sub>, 1,2,4-triazole, 0 °C, 3 h. c) KOSiMe<sub>3</sub>, CH<sub>3</sub>CN, 5 h, 84%.

observed, but when this reaction was carried out in acetonitrile, the potassium salt of **1** precipitated from the reaction mixture, thus protecting the product from racemization (see Scheme 4). Workup included acidification with acetic acid followed by extraction with ethyl acetate. Crystallization from ethyl acetate/heptane gave the desired compound **1** in 84% yield with high ee (98.4%).

## 3. Conclusions

A practical asymmetric reduction of the  $\alpha$ -keto acid **4** using a sodium borohydride/L-tartaric acid mixture was developed and implemented in the synthesis of BMS 270394. Also, an alternative to the phosgene-mediated coupling of the chiral acid **7** with the aniline **9** that involved the formation of an *N*-sulfinyl aniline **15** was developed. Finally, a racemization-free process for the hydrolysis of the  $\alpha$ -hydroxy amidoester **16** to the  $\alpha$ -hydroxy amidoacid **1** was also developed.

## 4. Experimental Section

**General Methods.** THF and CH<sub>2</sub>Cl<sub>2</sub> used in the reactions were purchased from Aldrich in sure-seal bottles and were used without further purification. Acetonitrile and ethyl acetate were purchased from EM Science. All reagents were purchased from Aldrich and used without any further purification. Melting points were measured on a Thomas-Hoover capillary melting point apparatus. IR spectra (KBr) were obtained on a Perkin-Elmer System 2000 FTIR instrument. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a JEOL 400 MHz Eclipse, a Varian 500 MHz Unity Inova, or a

Bruker DRX 500 MHz instrument. Chemical shifts are given on a  $\delta$  (ppm) scale. HRMS (high-resolution mass spectrometry) data were obtained with a Micromass LCT with ESI. HPLC purity of samples were determined using a YMC ODS AQ, 4.6 mm  $\times$  100 mm i.d. column, 3  $\mu$ m particle size diameter. Enantiomeric purity of compounds was determined by chiral HPLC: ChiralpakAD, 4.6 mm  $\times$  250 mm i.d., 10  $\mu$ m particle size diameter for chiral hydroxy acid **7**; Chiralcel OD, 4.6 mm  $\times$  250 mm i.d., 10  $\mu$ m particle size diameter for chiral hydroxy ester **16** and Chiralpak AS, 4.6 mm  $\times$  250 mm i.d., 10  $\mu$ m particle size diameter for the free acid **1**.

**(*R*)-2-Hydroxy-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)acetic Acid (**7**).** To a 5-L, three-necked, round-bottom flask equipped with a mechanical stirrer, reflux condenser, addition funnel, and nitrogen inlet adapter were charged L-tartaric acid (111 g, 739.4 mmol) and 2 L of anhydrous THF. NaBH<sub>4</sub> (25.4 g, 672.2 mmol) was added to the flask via an addition funnel, and the reaction mixture was heated at reflux for 5 h. The mixture was slowly cooled to -45 °C. A solution of compound **4** (50 g, 192 mmol) in 500 mL of THF was added dropwise to the reaction mixture while maintaining the temperature at -45 °C. The mixture was warmed slowly to 0–10 °C, stirred for 48 h, and treated dropwise with water (225 mL) at 0 °C. The mixture was warmed to room temperature, and the THF was removed under reduced pressure until the total volume in the flask was about 250 mL. To the mixture was charged 300 mL of methyl *tert*-butyl ether (MTBE) and 30 mL of 1 N HCl (pH 1–2), the organic layer was separated, and the aqueous layer was extracted with MTBE (2  $\times$  150 mL). The combined organic layers were washed with 100 mL of water and 100 mL of brine and then dried over anhydrous MgSO<sub>4</sub>. Removal of the solvents gave 51.5 g of crude product, which was dissolved in 50 mL of ethyl acetate at 50 °C, and to the solution was added dropwise at this temperature 650 mL of hexanes. The mixture was cooled to room temperature and stirred overnight. Filtration gave 37.8 g (75% yield, (*R/S*) = 84:16) of **7** as a white solid.

To a 500-mL, three-necked flask equipped with a mechanical stirrer and an addition funnel were charged the hydroxy acid **7** (37.8 g, 144 mmol), (1*R*,2*R*)-(-)-*N,N'*-dimethylcyclohexane-1,2-diamine (24.7 g, 173 mmol), and 300 mL of 2-propanol. The mixture was heated to 60 °C and held at this temperature until a clear solution was obtained. It was then cooled to 40 °C at which point crystallization occurred. After 3 h, the mixture was cooled

to room temperature, and the crystals were collected by filtration. The filter cake was washed with cold 2-propanol (0 °C) followed by 3 × 40 mL of hexanes to give 40.7 g of the chiral  $\alpha$ -hydroxy acid as a salt (83% yield, (*R/S*) > 99:1).

To a slurry of 40.5 g of the preceding salt in 300 mL of water cooled to 2 °C was added dropwise 150 mL of a 1 N solution of NaOH (1.5 mol equiv) while the temperature was maintained between 0 and 5 °C. The mixture was stirred until it became clear and then extracted with 3 × 80 mL of MTBE. The aqueous layer was acidified to pH of 2–3 with 6 N HCl and extracted with 3 × 150 mL of ethyl acetate. The combined organics were washed with water and brine and then dried over anhydrous MgSO<sub>4</sub>. Removal of the solvents under reduced pressure gave 25.4 g (97% yield from the amine salt, (*R/S*) = 100:0) of **7** as a white solid, mp 145–147 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.27 (s, 12 H), 1.68 (s, 4 H), 5.21 (s, 1 H), 7.18 (dd, *J* = 8.4, 1.6 Hz; 1 H), 7.31 (d, *J* = 8.4 Hz, 1 H), 7.37 (d, *J* = 1.6 Hz, 1 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  31.7, 34.1, 34.3, 34.8, 34.9, 72.7, 123.5, 124.9, 127.1, 134.3, 145.5, 145.7, 178.4. Anal. Calcd for C<sub>16</sub>H<sub>22</sub>O<sub>3</sub>: C, 73.25; H, 8.45. Found: C, 73.05; H, 8.36.

**Preparation of *N*-Sulfinyl derivative (**15**).** To a 500-mL, three-necked flask equipped with a mechanical stirrer, gas inlet adapter, addition funnel, and a temperature probe were charged imidazole (17.7 g, 260 mmol) and 250 mL of anhydrous methylene chloride. The mixture was cooled to –10 °C, and SOCl<sub>2</sub> (4.75 mL, 65 mmol) was added dropwise while the internal temperature was maintained at ca. –10 °C. The mixture was then warmed to 15 °C, stirred for 10 min, and filtered through an oven-dried glass funnel. The solids were washed with 30 mL of dichloromethane, and the filtrate was transferred to a 500-mL, three-necked flask equipped with a mechanical stirrer, gas inlet adapter, addition funnel, and a temperature probe, and cooled to ca. –10 °C. Additional SOCl<sub>2</sub> (4.75 mL, 65 mmol) was added dropwise to the mixture, which was warmed to 15 °C and stirred for an additional 10 min. This solution was transferred to an addition funnel and added dropwise to a solution of the aniline **11** in 130 mL of anhydrous dichloromethane and 30 mL of anhydrous THF cooled to –30 °C and contained in a 500-mL three-necked flask equipped with a mechanical stirrer, gas inlet adapter, and a temperature probe while the temperature was maintained between –15 and –25 °C. The mixture was then warmed to 15 °C and stirred for an hour. The solids were removed by filtration and washed with 2 × 40 mL of dichloromethane. Argon was bubbled through the filtrate for about a minute. The solvent was removed under reduced pressure, and methylene chloride was distillatively replaced with heptane, which was removed under reduced pressure; the residual yellowish solid was dried to give 27.8 g (99% yield) of **20**. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.93 (s, 1 H), 7.80–7.90 (m, 2 H), 8.14 (dd, *J* = 7.9, 7.9 Hz, 1 H). HRMS: Calcd for C<sub>8</sub>H<sub>6</sub>FNO<sub>3</sub>S: 215.0052. Found: 215.0052

**3-Fluoro-4-[2-hydroxy-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)acetylamino]benzoic Acid Methyl Ester (**16**).** To a 500-mL, three-necked flask equipped with a mechanical stirrer, gas inlet adapter, and

temperature probe and flushed with argon was charged the chiral  $\alpha$ -hydroxy acid **7** (20 g, 76.3 mmol, >99% ee), 1,2,4-triazole (7.4 g, 106.8 mmol), and 150 mL of dichloromethane in that order. The mixture was stirred at room temperature until it became clear, and then it was cooled to 0 °C. The *N*-sulfinyl compound **15** (23 g, 106.8 mmol) was charged in one portion, and the mixture was stirred at 0 °C for 3 h; the dichloromethane was distillatively replaced with heptane at 35 °C. At this point solids precipitated from the solution. The heptane was removed under reduced pressure, and the residue was dissolved in a 2:1 mixture of heptane/MTBE, washed with 5 × 70 mL of 3 N HCl, 2 × 50 mL of saturated NaHCO<sub>3</sub>, and 1 × 50 mL of brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvents were removed under reduced pressure to give 31 g of crude **16**. This was crystallized as follows.

To a 500-mL three-necked flask equipped with a mechanical stirrer, gas inlet adapter, and temperature probe were charged the crude ester (31 g) and 360 mL of cyclohexane. The mixture was heated to 75 °C at which point it turned clear; it was then cooled slowly to 35 °C and seeded with an authentic sample of the ester **16**. Crystallization commenced at this point. The reaction mixture was held at 37 °C for 3 h and then at room temperature (22 °C) for 10 h. The crystals were collected by filtration, washed with cyclohexane, and dried at 40 °C under reduced pressure for 3 h to give 24.2 g of **16** (77% yield, 99.7 area % pure, 99% ee). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  1.25–1.30 (overlapping singlets, 12 H), 1.68 (s, 4 H), 3.51 (bd, *J* = 2.6 Hz, 1 H), 3.89 (s, 3 H), 5.17 (bd, *J* = 2.1 Hz, 1 H), 7.22 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.33 (d, *J* = 8.4 Hz, 1 H), 7.40 (d, *J* = 1.6 Hz, 1 H), 7.75 (dd, *J* = 11, 1.6 Hz, 1 H), 7.80 (d, *J* = 11 Hz, 1 H), 8.44 (m, 1 H), 8.86 (bd, *J* = 2.1 Hz, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  26.8, 31.6, 31.7, 31.8, 34.1, 34.3, 34.8, 34.9, 52.3, 75.0, 115.9 (d, *J* = 20.3 Hz), 120.3, 123.5, 125.1, 126.0, 126.1, 126.5, 127.4, 130.2 (d, *J* = 10.1 Hz), 135.5, 145.8 (d, *J* = 26.3 Hz), 151.7 (d, *J* = 242.9 Hz), 165.8, 170.7; HRMS: Calcd for C<sub>24</sub>H<sub>28</sub>FNO<sub>4</sub>: 414.2081 (M + H); Found: 414.2066

**BMS-270394 (**1**).** To a 1-L, three-necked flask equipped with a mechanical stirrer, nitrogen inlet adapter, and temperature probe was charged the ester **16** (15 g, 36.3 mmol, 99% ee). The flask was flushed thoroughly with nitrogen and charged with 225 mL of acetonitrile (HPLC grade, Karl Fisher  $\leq$  0.1), and the mixture was stirred at room temperature (22 °C) until a solution was obtained. Potassium trimethylsilylanolate (18.1 g, 126.29 mmol) was added in one portion. After 5 h, the reaction mixture was cooled to 0–5 °C and quenched with a solution of acetic acid (15.3 mL, 253.9 mmol) in 15.3 mL of water, while the temperature was maintained between 1 and 5 °C. Ethyl acetate (225 mL) was then added, and the mixture was warmed to room temperature. The organic layer was collected and washed with 2 × 100 mL of water and 1 × 100 mL of brine, and dried over sodium sulfate. Removal of the solvents under reduced pressure gave 15 g of the crude product **1** which was then crystallized.

To a 1-L three-necked flask equipped with a mechanical stirrer, temperature probe, nitrogen inlet adapter, and an addition funnel was charged the crude acid (15 g) followed by 45 mL of ethyl acetate. The mixture was heated to 50 °C at which point the compound dissolved. Heptane (45 mL) was then added dropwise while the temperature was maintained at 50 °C. The reaction mixture turned cloudy and was seeded at 50 °C at which point crystallization of **1** commenced. The mixture was then stirred at 50 °C for 2 h. Additional heptane (225 mL) was added, and stirring continued at 50 °C for 2 h; and the reaction mixture was cooled to room temperature and stirred for an additional 16 h. Filtration gave 12.2 g of **1** (84% yield, 99.6 HPLC purity, 98.4% ee) as a white solid, mp 195–200 °C. IR: 3400–3300 br, 3100–2850 br, 2600, 1720, 1686, 1674, 1526 cm<sup>-1</sup>.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.20–1.23 (overlapping singlets, 12 H), 1.61 (s, 4 H), 5.16 (apparent d, *J* = 3.2 Hz, 1 H), 6.60 (apparent d, *J* = 3.7 Hz, 1 H), 7.21 (d, *J* = 8.4 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 1 H), 7.45 (s, 1 H), 7.70–7.77 (m, 2 H), 8.07–8.12 (m, 1 H), 9.80 (s, 1 H), 13.15 (s, 1 H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 31.7, 33.8, 34.0, 34.6, 73.7, 116.0, 122.3, 124.9, 126.0, 126.3, 127.4, 130.0, 137.4, 144.0, 144.1, 152.0, 166.0, 171.6. Anal. Calcd for C<sub>23</sub>H<sub>26</sub>FNO<sub>4</sub>: C, 69.16; H, 6.56; N, 3.51; F, 4.76. Found: C, 69.17; H, 6.58; N, 3.39; F, 4.82

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