Technology Reports

A Practical Synthesis of the PDE4 Inhibitor, SB-207499, from a Cyclohexanone Precursor

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Abstract:
The synthesis of SB-207499 is described. Investigation and development of new strategies for the homologation of ketone, 4-cyano-4-[3-(cyclopentyloxy)-4-(methoxyphenyl)]-cyclohexan-1-one 2 are described which produce SB-207499. Our ultimate route of synthesis to SB-207499 is robust and operationally simple and produces the final drug substance in good yield and purity.

Introduction

SB-207499 is a potent second-generation inhibitor of PDE4 (phosphodiesterase-4) with decreased side effects versus those of the well-known first-generation inhibitor, (*R*)-rolipram. SB-207499 is in clinical development both for asthma and chronic obstructive pulmonary disease (COPD),[1] Figure 1. At the outset of our work, there were issues associated with the existing preparation from ketone **2** such as cost of goods, necessity for column chromatography, purity of final drug substance, and other operational procedures not amenable to scale-up. These have been addressed and are discussed here in the preparation of this development compound (**1a**).

Results and Discussion

The Medicinal Chemistry synthesis of ketone **2** was six steps.[2] Ketone **2** was then taken four steps to give SB-207499, shown in Scheme 1.

The homologation of ketone **2** was done using a Peterson-type reaction with 2.1 equiv of 2-lithio-2-(trimethylsilyl)-
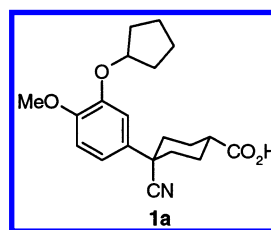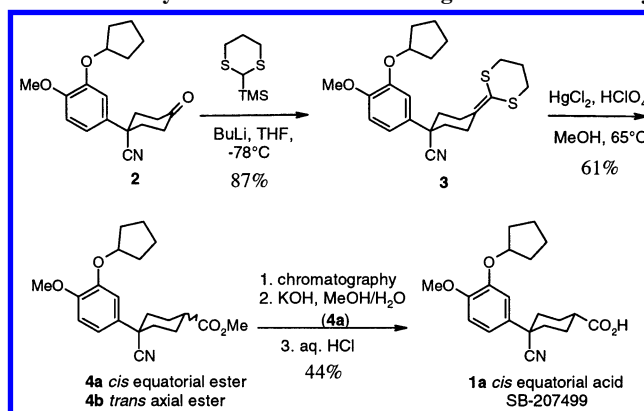
Figure 1. SB-207499.

Scheme 1. Synthesis of SB-207499 using dithiane chemistry

1,3-dithiane[3] at −78 °C in THF to produce ketene dithio-acetal **3** in 87% yield. Mercury (II) chloride-mediated methanolysis[3] of **3** provided an approximately 11:1 mixture of cis and trans esters (**4a:4b** respectively) which were separated by flash chromatography on silica gel. Saponification of ester **4a** with potassium hydroxide in a THF/methanol/water mixture, followed by acidification gave the corresponding acid **1a**[2] in 44% yield. This sequence had drawbacks for scale-up. First, 2-(trimethylsilyl)-1,3-dithiane was expensive (∼$800/kg), was not available in bulk, and required the use of low temperature. Second, the use of mercury (II)

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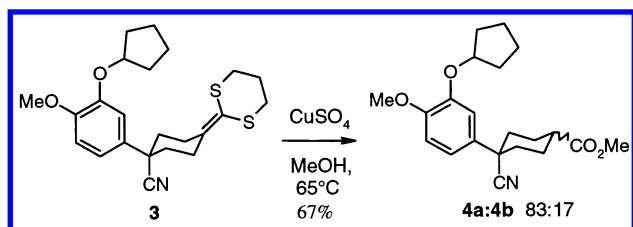|| Current address: Rhodia ChiRex, 383 Phoenixville Pike, Malvern, PA 19355, U.S.A.
⊥ Current address: Genaera Corporation, 5110 Campus Drive, Plymouth Meeting, PA 19462, U.S.A. E-mail: rmills@genaera.com.

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Scheme 2. Hydrolysis of ketene dithiane 3 with copper sulfate

Scheme 3. Equilibration and hydrolysis of methyl esters 4 using KOtBu

Scheme 4. Use of TFA to hydrolyze ketene dithiane 3

chloride and perchloric acid for hydrolysis of **3** was undesirable due to the known dangers associated with perchloric acid (explosive)[4] and the toxicity of the mercury salts. Third, the esters **4** were separated by chromatography to give the desired equatorial ester **4a**, which on hydrolysis gave the desired compound **1a**. Finally after hydrolysis and isolation, acid **1a** still contained high levels of mercury. Our early focus was to replace the mercury salts and the perchloric acid to increase the safety of the synthesis, and to enhance the purity of the final drug substance. Copper (II) salts and silica gel have been used to hydrolyze ketene dithioacetals;[5] a modification of this procedure with the use of copper (II) sulfate in methanol gave the esters **4** (**4a**:**4b**, 83:17), Scheme 2.
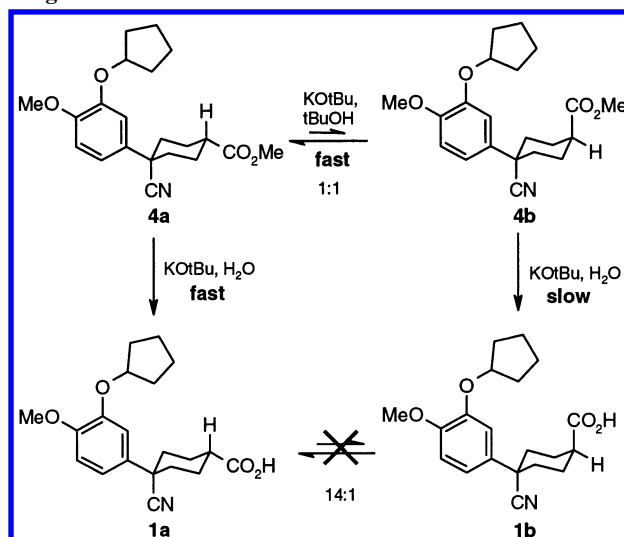
After a solvent exchange to toluene, removal of the residual copper salts was easily achieved by washing the crude reaction mixture with 10% aqueous ammonia. Although this eliminated the use of heavy metals and perchloric acid, the variability and heterogeneous nature of these reactions conditions rendered them difficult to scale.

After hydrolysis of **4**, acids **1a** and **1b** could be separated by crystallization from ethyl acetate/hexanes (eliminating the need for chromatography of the esters) to give the desired acid **1a** (>99:1, **1a**:**1b**). To increase the yield of the desired equatorial acid **1a** further, equilibration studies[6] of the cis/trans methyl esters **4** were examined. After equilibration of esters **4**, hydrolysis of the esters was performed in situ to give the acids **1**. It was determined that NaH in methanol epimerized the esters **4** and subsequent hydrolysis gave a cis:trans ratio of acids **1a**:**1b**, 8:1. By changing the base from NaH to KOtBu, the ratio of **1a**:**1b** increased from 8:1 to 14:1[7] (Scheme 3).
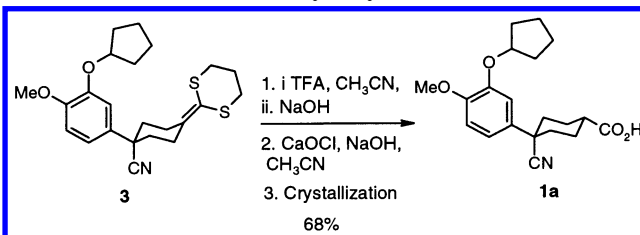
We also confirmed that epimerization of the corresponding acids **1a**:**1b** did not occur under the reaction conditions. These epimerization and hydrolysis results were in agreement with what Caron and Vazquez reported for a similar compound.[8]

It had also been reported that strong acids can hydrolyze ketene dithianes to the acids directly.[9] Various attempts were tried, and it was found that trifluoroacetic acid in aqueous acetonitrile followed by calcium hypochlorite (or hydrogen peroxide) treatment afforded the corresponding acids **1**.[10]

Acids **1a** and **1b** were then crystallized from ethyl acetate/ hexanes to give the desired acid **1a** in 68% yield (>99:1 **1a**:**1b**) The use of hypochlorite also allowed for the oxidation of all the sulfur residues, reducing the odor (Scheme 4).

Although this improved sequence from compound **3** could produce the target acid **1a** without any chromatography, the throughput was still very inefficient using the TFA hydrolysis method, and 2-(trimethylsilyl)-1,3-dithiane was still used to prepare **3**. Other alternatives were sought for an efficient and robust homologation of ketone **2** to give acid **1a**. There are various methodologies in the literature for the homologation of a ketone to a secondary carboxylic acid in two or three steps. Representative methodologies have involved intermediates such as enol ethers,[11] epoxides,[12] cyanohydrins,[13] α,β-unsaturated sulfones,[14] glycidic esters,[15] and nitriles,[16] to add the one-carbon unit. However, most transformations are not amenable to scale-up. We initially focused on the classical way of introducing one carbon by formation of the cyanohydrins **5**[17] (Scheme 5).

Treatment of ketone **2** with sodium cyanide gave the cyanohydrin **5** in 93% yield, which was then dehydrated with thionyl chloride and pyridine in toluene to give the unsaturated nitrile **6** in 92% yield.[13a] Hydrolysis of nitrile **6** with

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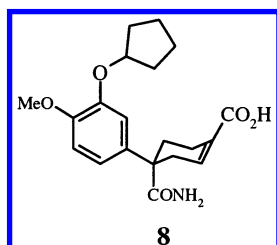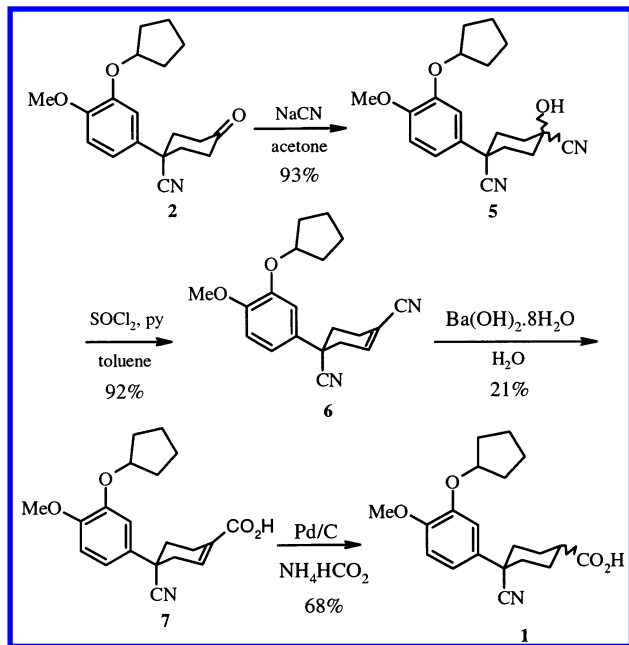(17) Webb, K. S. PCT Int. Appl. WO 0151455, 2001.
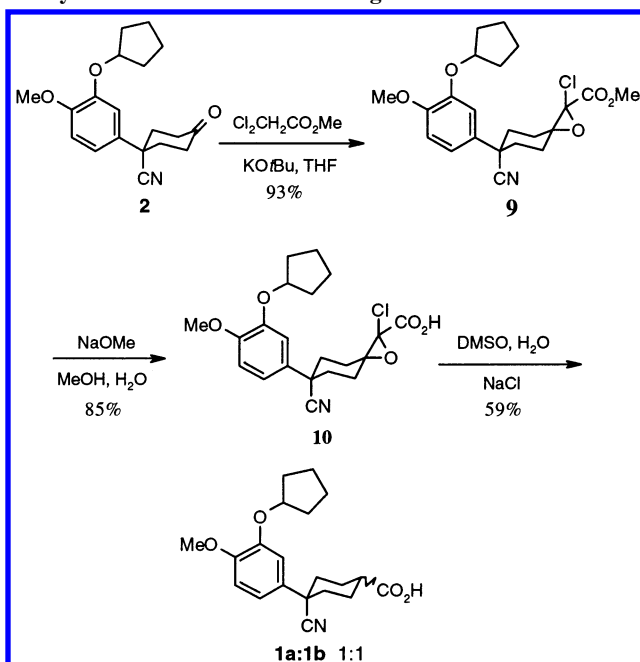
Figure 2. Tertiary amide hydrolysis impurity 8.

Scheme 5. Use of cyanohydrins to form SB-207499 from ketone 2

Scheme 6. Classical Darzens reaction using methyldichloroacetate and rearrangement

Ba(OH)$_2$·8H$_2$O gave **7** which had to be purified by reverse phase HPLC in 21% yield. Pure **7** in turn was hydrogenated using Pd/C and ammonium formate[18] as the hydrogen source to give the acids **1** (**1a:1b**, 96:4). Although this approach required four steps, each step was operationally simple which lowered the cost of the synthesis. There was still a problematic step in the synthesis, however. The hydrolysis of the secondary nitrile in the presence of the tertiary one (compound **6**) was very difficult. Under the basic conditions tried, there was always some competing hydrolysis of the tertiary nitrile (Figure 2) to give amide **8** which proved difficult to remove, resulting in purification by reverse phase HPLC and a yield of **7** of 21%.

While this work was proceeding, other approaches were also being considered. It is known that ketones can be treated under classical Darzens conditions to give epoxyesters, which in turn can be rearranged to give homologated secondary aldehydes.[19] For our system we theorized that treatment of the ketone **2** with methyldichloroacetate in place of the more traditional methylchloroacetate would give a chloroepoxyester, which could be rearranged to an acid chloride. This acid chloride could then be used for subsequent traditional transformations, Scheme 6.

Treatment of ketone **2** with methyldichloroacetate and potassium *tert*-butoxide at 0 °C gave the chloroepoxyester in 93% yield.[20] Compound **9** was formed as an approximately 3.5:1 ratio of isomers. Attempted rearrangement of **9** under Krapcho conditions[21] led to several decomposition products and isolation of **1a** in about 30% yield. These steps were reordered so that hydrolysis of ester **9** gave the epoxy acid **10** in 85% yield. Treatment of acid **10** under the Krapcho decarboxylation conditions at 150 °C in a pressure vessel gave acids **1** (**1a:1b**, 1:1) in a crude yield of 59%.[22] This route was shorter than the cyanohydrin route (Scheme 5) and avoided the use low temperatures and expensive reagents; however, this route also suffered from scale-up issues. The biggest issue was that chloroacid **10** was unstable and needed to be used directly in the next step. Also, the rearrangement conditions were harsh (150 °C, pressure vessel). The formation of product **1** also occurred as a 1:1 mixture of cis and trans acids in 59% (i.e., about 29% yield **1a**).

Another strategy along the same lines had been developed by White.[23] This was formation of an epoxynitrile using a Darzens[24] reaction followed by rearrangement to give a secondary carboxylic acid. To this end we prepared epoxynitrile **11** from ketone **2** in 80% yield (Scheme 7) under modified phase-transfer conditions.[25]

Isolation of **11** was achieved from methanol, but the temperature of isolation had to be controlled due to the formation of the methylimidate **12** at higher temperatures (Figure 3).

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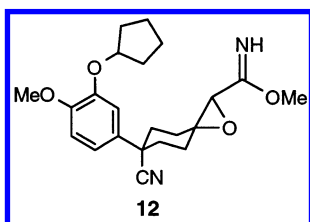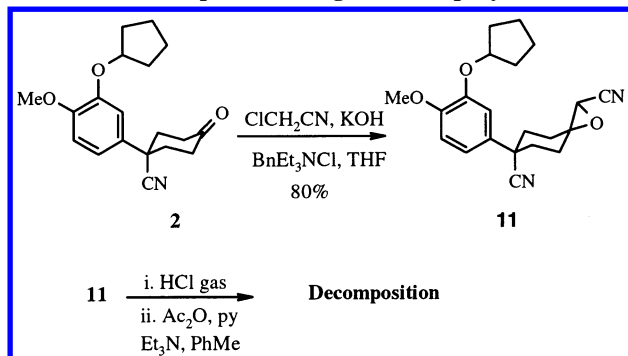
Figure 3. Methyl imidate impurity 12.

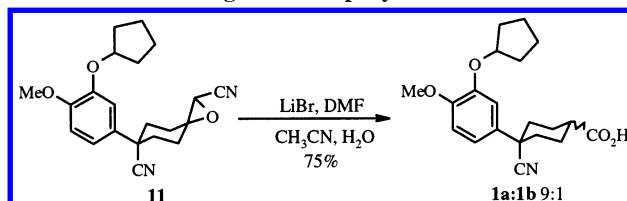**Scheme 7.** Attempted rearrangement of epoxynitrile 11

This methylimidate impurity was shown to carry through and therefore had to be minimized. Alternative non-nucleophilic combinations of solvents or binary solvents were tried which had the same cohesive energy density values as methanol.[26] Ultimately methylcyclohexane/THF, 5:1, was found to be a good alternative solvent mixture for the isolation of **11**, eliminating the formation of the imidate impurity **12**.
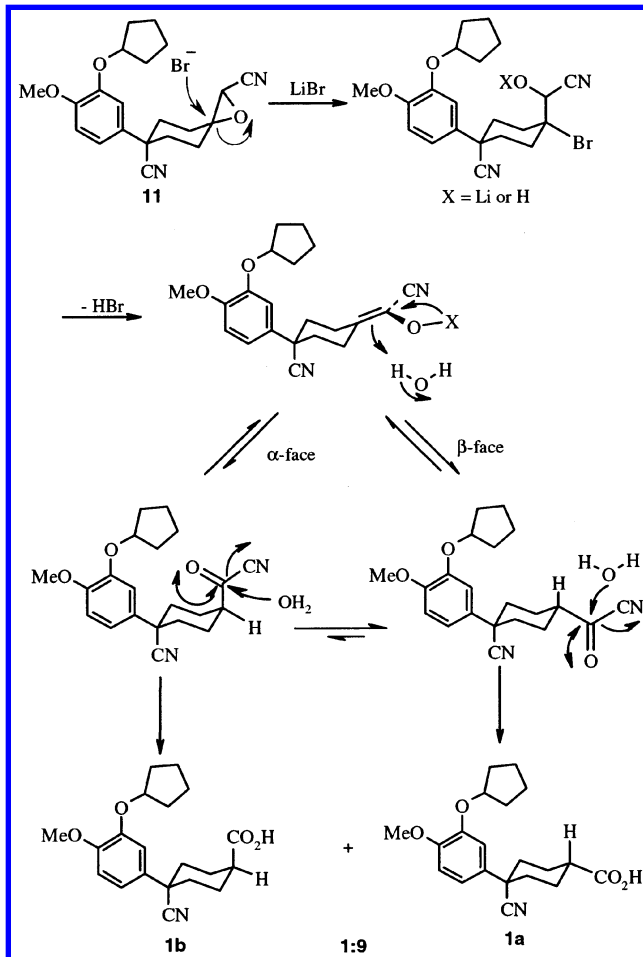
The second stage of the homologation strategy, however, was not successful; treatment of **11** using White's conditions to give the acid **1a** (exposure of **11** to anhydrous HCl) resulted in decomposition of compound **11** without formation of White's disclosed intermediates. Therefore, we tried other conditions for rearrangement of **11** which avoided the use of strong acid. In the same publication, White had reported conditions specific for rearrangement of aryl-substituted epoxynitriles to acids.[23] This synthetic approach looked attractive since it involved a one-pot rearrangement of the aryl precursors. However, application of this methodology to **11**, for example, using White's Lewis acids, $LiClO_4$, $Li(O_2-CCF_3)$, and $KHSO_4$ in toluene or xylene at reflux, resulted in recovery of starting material. We therefore extended our studies to other Lewis acids and solvents with the hope that they could be applied to substrate **11**. Ultimately, we found a set of conditions that worked well for this pivotal transformation. The combination of lithium bromide (or magnesium bromide) in DMF, acetonitrile, and a small amount of water at 90−95 °C efficiently transformed **11** into acids **1**[27] in 75% yield, (**1a:1b**, 9:1, Scheme 8). This ratio reflects a thermodynamic ratio of products. The acid **1a** was also shown to be more stable than **1b** by molecular modelling.

By contrast with other procedures, this method required only inexpensive reagents and very moderate reaction

Scheme 8. Rearrangement of epoxynitrile 11

Scheme 9. Proposed mechanism of rearrangement of 11

conditions. This methodology has been further investigated for its generality.[28] The proposed mechanism of the rearrangement is shown in Scheme 9. The investigation and supporting data for this mechanism are described elsewhere.[27]

During the rearrangement of **11**, hydrogen cyanide was liberated. To eliminate the cyanide, the reaction was treated with base and then with sodium hypochlorite which oxidized the hydrogen cyanide to cyanate[29] and subsequently to ammonia and carbon dioxide (Scheme 10).[30]

Although this method eliminates the need for expensive reagents and low temperature, there were still some scale-up issues to address. The cyanide liberation required ap-

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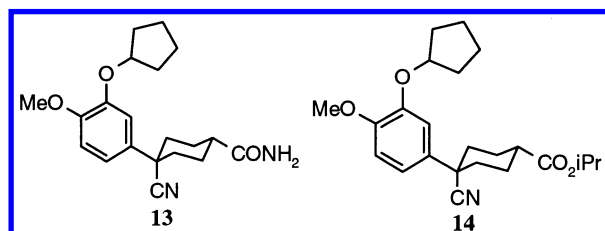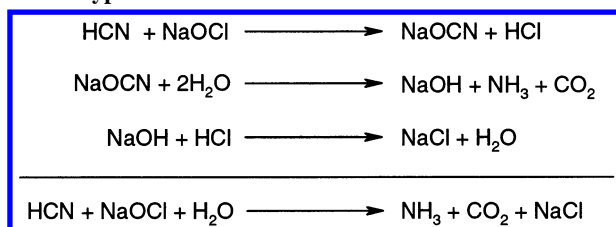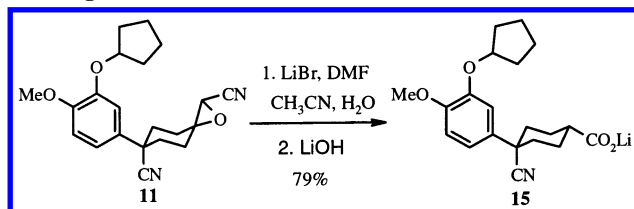
Figure 4. Primary amide 13 and isopropyl ester 14 impurities.

Scheme 10. Oxidation of hydrogen cyanide with basic sodium hypochlorite

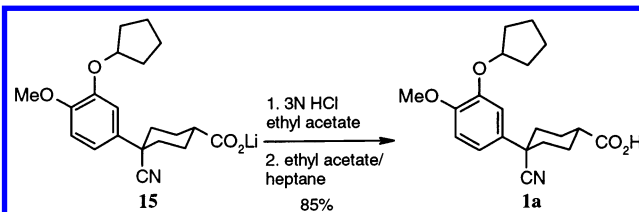**Scheme 11.** Isolation of the lithium salt 15 after rearrangement of 11

propriate safety precautions. The oxidative workup to remove cyanide was very volume-inefficient, and it generated a lot of waste. Also, since the oxidative workup is done in the presence of the product **1a**, small amounts of impurities were produced in the final drug substance (e.g., the primary amide **13**, Figure 4). This facilitated introducing a crystallization from 2-propanol/water to bring the purity of **1a** up to an acceptable level. However, we found on scaling the 2-propanol/water crystallization that care had to be taken to avoid the formation of the isopropyl ester **14** (Figure 4).
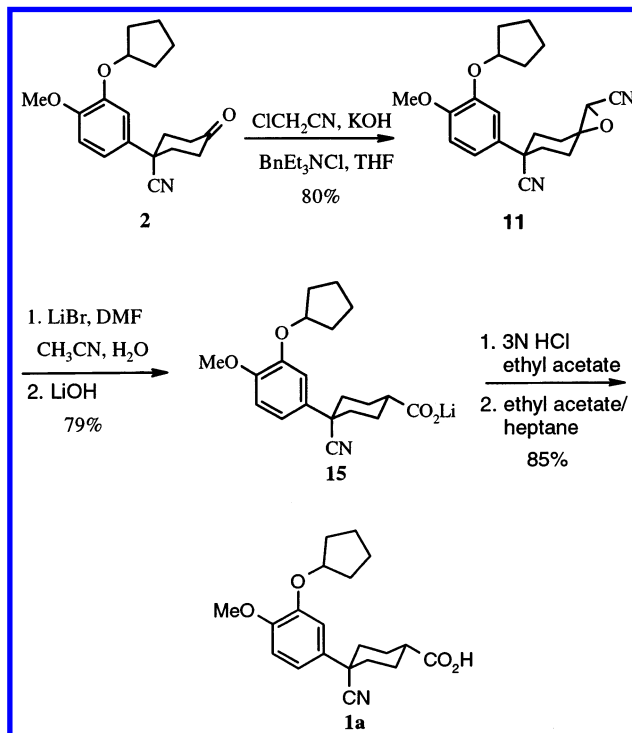
Alternatives were needed to isolate the product from the rearrangement without introducing new impurities in the workup. Isolation of the carboxylate salt of **1a** was investigated.[31] Bases such as sodium hydroxide, lithium hydroxide, and potassium hydroxide were tried to isolate the sodium, lithium, or potassium salt of **1a**. Lithium hydroxide gave the best results, allowing the lithium salt **15** to be isolated as a stable white solid directly from the reaction liquors in 79% yield (Scheme 11).

The lithium salt of the undesired isomer, **1b**, was mainly soluble in the mother liquors, allowing an easier separation from **1a**. By isolating the lithium salt, **15**, the vast majority of the cyanide waste was eliminated in the waste stream and thus did not need to be destroyed via an oxidative workup in the presence of **1a**. This greatly reduced the impurities (such as the primary amide **13**) that were produced as a result of the oxidative workup. Another major benefit was that throughput was dramatically increased. Protonation of **15** with mineral acid in organic solvent was then investigated.

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Scheme 12. Protonation of the lithium salt 15

Scheme 13. Final route of synthesis of SB-207499 from ketone 2

We were pleased to find that the lithium salt **15** in ethyl acetate and protonation with 3 N HCl gave **1a**, which could be subsequently crystallized from ethyl acetate/heptane to give pure **1a** in 85% yield (Scheme 12).

The pH of this reaction was found to be critical. A pH <1.5 was needed for subsequent isolation of **1a** with an acceptable ROI. The final route of synthesis of SB-207499 from ketone **2** is shown in Scheme 13.

The overall yield of SB-207499 (**1a**) from ketone **2** by the final route of synthesis was 54%. The original Medicinal Chemistry approach (Scheme 1) produced **1a** from ketone **2** in 23% overall yield.

Conclusions

Various methodologies for homologation of ketone **2** to the preparation of SB-207499, **1a**, have been investigated. The final route of synthesis no longer requires low or high temperatures or chromatography, is operationally simple, and is amenable to multikilogram scale. In summary, methodology was developed for a two-step homologation of ketone **2** to acid **1a** via an epoxynitrile intermediate and rearrangement. Isolation of the lithium salt **15** after the rearrangement allowed for the separation of product **15** from the reaction byproducts and cyanide waste.

Experimental Section

4-Cyano-4-[3-(cyclopentyloxy)-4-(methoxyphenyl)]-1-cyclohexanecarboxylic acid, 1. Method 1: Hydrolysis of Ketene Dithiane 3 Using TFA. To a suspension of ketene dithiane **3** (140 g, 0.34 mol) in acetonitrile (500 mL) and water (140 mL) was added trifluoroacetic acid (136 g, 1.19 mol). The suspension was heated to 65 °C for 1.25 h, followed by the addition of 20% NaOH (420 g, 2.1 mol). The solution was heated to 70−75 °C for an additional 1.25 h and then cooled to 45 °C where water (420 mL) and 3 N HCl (392 mL, 1.18 mol) were added. The suspension was cooled to 5 °C and held for 1 h. The suspension was then filtered, washed with cold water, and dried in vacuo. The crude solid in acetonitrile (425 mL) was heated to 65 °C, and 1 N NaOH (425 mL, 0.425 mol) was added. The solution was cooled to 60 °C where calcium hypochlorite (4.25 g, 0.03 mol) was added and the reaction stirred for 2 h. The reaction was partially concentrated and ethyl acetate added. This was repeated, and at 55 °C, ethyl acetate and 6 N HCl (10:1) were added. The organic layer was isolated and washed three times with water. Ethyl acetate was added and the reaction partially concentrated. The solution was cooled to 65 °C, and hexane was added. The suspension was cooled to 5 °C, held at this temperature for 1 h and then filtered, and the solid washed with cold ethyl acetate/hexane (1:9). The solid was dried in vacuo to give **1a** as a white solid (78.7 g, 68%). The analytical data were consistent with the literature.[2]

Method 2: Equilibration and Hydrolysis of Esters 4. Methyl esters **4** (2.94 g, 8.2 mmol) (**4a**:**4b** 1:1) were dissolved in tBuOH (30 mL). Potassium *tert*-butoxide (1.8 g, 16.5 mmol) was added and the mixture stirred for 5 d at ambient temperature. Ratio (**4a**:**4b**, 14:1) was determined by HPLC.[7] Water (2 drops) was added, the solution stirred for 1 h, and then 5% HCl and TBME were added. The organic layer was separated and concentrated in vacuo. The oil was dissolved in warm ethyl acetate, and the product was precipitated by adding hexanes. The reaction was cooled to 0 °C, and the product **1a** was isolated and dried in vacuo (1.75 g, 62%). The analytical data were consistent with the literature.[2]

Method 3: Hydrogenation of Compound 7. To compound **7** (15 mg, 0.04 mmol) in DMF (0.5 mL) was added ammonium formate (36 mg, 0.6 mmol) and 10% Pd/C (6 mg, 40%w/w). The reaction was stirred at 20 °C for 48 h and then filtered. The product was extracted into ethyl acetate, and the combined organic layers were washed with water and brine. The organics were concentrated in vacuo to give crude **1** (10.3 mg, 68%) (**1a**:**1b**, 96:4). The analytical data were consistent with the literature.[2]

Method 4: Rearrangement of Compound 10. To compound **10** (1.26 g, 2.79 mmol) in DMSO (7.5 mL) and water (0.5 mL) was added sodium chloride (50 mg, 0.85 mmol). The reaction was heated to 150 °C in a pressure vessel for 3.5 h. The solution was then cooled and assayed for **1**. (0.57 g, 59%), (**1a**:**1b**, 1:1).

Method 5: Rearrangement of Compound 11. *WARNING: Hydrogen Cyanide is liberated during the rearrange-*

ment. Appropriate safety precautions need to be taken. A solution of DMF (580 g), acetonitrile (480 g), lithium bromide (72 g, 830 mmol), and water (20 g, 1.1 mol) was stirred at 25−30 °C to give a homogeneous mixture. To this was added compound **3** (180 g, 510 mmol). The reaction was stirred at 90−95 °C for 16 h. The reaction was cooled to 20 °C, followed by addition of sodium hydroxide solution (92 g NaOH, 2.3 mol, dissolved in 200 mL water). The suspension was stirred at 20 °C for 30 min and treated with sodium hypochlorite (600 mL, 460 mmol). The contents were stirred for an additional 90 min, followed by addition of TBME and 6 N HCl (644 mL, 3.86 mol). The bottom aqueous layer was separated and back-extracted with TBME; the combined organic layers were washed four times with water. The organic layer was concentrated to a residue, and then ethyl acetate was added and heated to reflux. The solution was cooled to 50 °C; hexanes were added, and the solution was then cooled to 0 °C. After 1 h, the solid was collected, washed with hexanes:ethyl acetate (9:1), and dried in vacuo to give **1a** as an off-white powder (125 g, 69%). A small portion was recrystallized for characterization purposes. The other product, **1b**, remained in the crystallization mother liquors. A small portion of the crude solid from the mother liquors was recrystallized for characterization purposes. The analytical data were consistent with the literature.[2]

Method 6: Protonation of Compound 15. Compound **15** (58.5 g, 0.167 mol) was stirred in ethyl acetate (500 mL). To this was added 3 N HCl (70 mL, 0.21 mol) and the reaction stirred for 10 min. The organic layer was isolated and washed with water. The solution was partially distilled to remove about 40% of the ethyl acetate and cooled to 60 °C where heptane was added (ethyl acetate:heptane, about 1:1). The suspension was cooled to 5 °C and held at this temperature for 2 h. The solid was filtered, washed with cold heptane (5 °C), and dried in vacuo to give **1a** (50.0 g, 85%). The analytical data were consistent with the literature.[2]

***cis*-4-Cyano-4-[3-(cyclopentyloxy)-4-(methoxyphenyl)]-*r*-1-cyclohexanecarboxylic acid (1a):** mp 148−150 °C; IR (KBr pellet) cm^{-1} 3300−2400, 2231, 1707, 1694; ^{1}H (400 MHz, CDCl$_3$) δ 11.75 (1H, br s), 7.02 (1H, d, $J = 2.3$ Hz), 6.98 (1H, dd, $J = 2.3, 8.4$ Hz), 6.87 (1H, d, $J = 8.4$ Hz), 4.82 (1H, m), 3.86 (3H, s), 2.43 (1H, tt, $J = 3.7, 12.2$ Hz), 2.29 (2H, br d, $J = 15.6$ Hz), 2.25 (2H, br d, $J = 16.4$ Hz), 2.05 (2H, m), 1.94 (4H, m), 1.86 (2H, m), 1.82 (2H, m), 1.64 (2H, m); ^{13}C (100 MHz, CDCl$_3$) δ 180.5, 149.8, 147.8, 132.8, 122.2, 117.3, 112.9, 111.9, 80.7, 56.1, 43.0, 41.7, 36.4, 32.8, 25.9, 24.0.

***trans*-4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclohexanecarboxylic acid (1b):** mp 157−158 °C; IR (KBr pellet) cm^{-1} 3427, 2229, 1701, 1262; ^{1}H (400 MHz, CDCl$_3$) δ 11.24 (1H, br s), 7.00 (1H, d, $J = 2.3$ Hz), 6.95 (1H, dd, $J = 2.3, 8.4$ Hz), 6.85 (1H, d, $J = 8.4$ Hz), 4.80 (1H, m), 3.85 (3H, s), 2.87 (1H, m), 2.28 (2H, m); 2.08 (6H, m), 1.90 (4H, m), 1.85 (2H, m), 1.61 (2H, m); ^{13}C (100 MHz, CDCl$_3$) δ 180.7, 149.8, 147.8, 132.8, 122.6, 117.5, 113.2, 111.9, 80.8, 56.1, 42.7, 37.7, 33.6, 32.8, 24.3, 24.1.

Methyl 4-Cyano-4-[3-(cyclopentyloxy)-4-(methoxyphenyl)]cyclohexane-*r*-1-carboxylate (4). Ketene dithiane **3** (0.5

g, 1.2 mmol), copper sulfate heptahydrate (0.62 g, 2.5 mmol), and MeOH (12 mL) were heated at 65 °C for 2 h. The reaction was then concentrated in vacuo and partitioned between toluene/10% aqueous ammonia. The organic layer was separated and washed twice with 10% aqueous ammonia. Concentration in vacuo gave crude **4** (0.29 g, 67%)-(**4a**:**4b**, 83:17). Chromatography on silica gel (85:15 hexane:ethyl acetate) provided pure samples of **4a** and **4b**. The analytical data were consistent with the literature.[2]

***cis*-Methyl 4-Cyano-4-[3-(cyclopentyloxy)-4-(methoxyphenyl)]cyclohexane-*r*-1-carboxylate (4a):** mp 118−119 °C; IR (KBr pellet) 2230, 1734, 1254 cm^{-1}; ^{1}H (400 MHz, CDCl$_3$) δ 7.00 (1H, d, $J = 2.3$ Hz), 6.97 (1H, dd, $J = 2.3$, 8.4 Hz), 6.87 (1H, d, $J = 8.4$ Hz), 4.82 (1H, m), 3.85 (3H, s), 3.72 (3H, s), 2.37 (1H, tt, $J = 3.7$, 12.2 Hz), 2.27−1.78 (14H, m), 1.62 (2H, m); ^{13}C (100 MHz, CDCl$_3$) δ 174.8, 149.8, 147.8, 132.9, 122.3, 117.4, 113.0, 112.0, 80.8, 56.1, 51.8, 43.0, 42.0, 36.6, 32.8, 26.1, 24.0. Calcd C$_{21}$H$_{27}$NO$_4$, C 70.56, H 7.61, N 3.92. Found C 70.63, H 7.54, N 3.88.

***trans*-Methyl 4-cyano-4-[3-(cyclopentyloxy)-4-(methoxyphenyl)]cyclohexane-*r*-1-carboxylate (4b):** mp 50−51 °C; IR (KBr pellet) 2235, 1729, 1257 cm^{-1}; ^{1}H (400 MHz, CDCl$_3$) δ 7.00 (1H, d, $J = 2.3$ Hz), 6.99 (1H, dd, $J = 2.3$, 8.4 Hz), 6.86 (1H, d, $J = 8.4$ Hz), 4.80 (1H, m), 3.85 (3H, s), 3.72 (3H, s), 2.81 (1H, m), 2.28−1.79 (14H, m), 1.63 (2H, m); ^{13}C (100 MHz, CDCl$_3$) δ 174.9, 149.7, 147.8, 133.0, 122.8, 117.6, 113.2, 112.0, 80.8, 56.1, 51.8, 42.9, 37.7, 33.7, 32.8, 24.6, 24.1. Calcd C$_{21}$H$_{27}$NO$_4$, C 70.56, H 7.61, N 3.92. Found C 70.47, H 7.67, N 3.85.

4-[3-(Cyclopentyloxy)-4-(methoxyphenyl)]-1,4-dicarbonitrile-cyclohexan-1-ol (5). To ketone **2** (1.00 g, 3.2 mmol) in water (5 mL) was added sodium cyanide (0.325 g, 6.6 mmol). The reaction was cooled to 0−5 °C, and an aqueous solution of sodium bisulfite (0.625 g, in 2.5 mL water) was then added. After the addition the temperature reached 8 °C. The reaction was cooled and after 30 min set solid. The reaction was warmed to 8−10 °C and acetone (2 mL) added. The reaction was continued at 20 °C for an additional 90 min. The reaction was then partitioned between water and ethyl acetate (1:2), and the organic layer was washed with water and brine and then dried. Filtration and evaporation of the organic layer gave a white solid **5**, which was dried in vacuo (1.01 g, 93%). A small sample was recrystallized for characterization.

^{1}H (400 MHz, CDCl$_3$) δ 7.0 (2H, m), 6.85 (1H, d, $J = 8$ Hz), 4.80 (1H, m), 3.85 (3H, s), 2.90 (1H, s), 2.1−2.48 (7H, m), 2.20 (1H, s), 1.75−2.0 (6H, m), 1.59−1.62 (2H, m); m/z (neg ion/DCI methane) 375 [M + Cl]$^-$ (88%), 348 [M + Cl − HCN]$^-$ (100%), 339 [M − H]$^-$ (100%). Calcd C$_{20}$H$_{24}$N$_2$O$_3$, C 70.58, H 7.11, N 8.23. Found C 70.66, H 7.03, N 8.47.

4-[3-(Cyclopentyloxy)-4-(methoxyphenyl)]-1-cyclohexene-1,4-dicarbonitrile (6). Cyanohydrins **5** (0.50 g, 1.46 mmol) were added to toluene (1.5 mL) and pyridine (0.60 mL, 7.4 mmol), and the reaction was cooled to 0 °C. To this was added a solution of thionyl chloride (0.35 g, 2.95 mmol) in toluene (0.5 mL). A precipitate formed after 1−2 min, and then the reaction was heated to 80 °C for 1 h and

then at reflux and held for an additional 2 h. The solution was cooled and poured into a mixture of aqueous HCl and ice. The reaction was extracted with ethyl acetate. The organic phase was washed three times with 0.6 N HCl, 5% sodium carbonate, and brine, respectively. The organic layer was dried, filtered, and evaporated to give a white solid **6** (0.44 g, 92%).

mp 133.5−134.5°C; ^{1}H (400 MHz, CDCl$_3$) δ 6.83−6.95 (3H, m), 6.67 (1H, m), 4.80 (1H, m), 3.84 (3H, s), 2.6−2.9 (2H, m), 2.2−2.5 (2H, m), 2.05−2.18 (2H, m), 1.80−2.0 (3H, m), 1.55−1.67 (3H, m). Calcd C$_{20}$H$_{22}$N$_2$O$_2$, C 74.51, H 6.88, N 8.69. Found C 74.23, H 6.98, N 8.64.

4-Cyano-4-[3-(cyclopentyloxy)-4-(methoxyphenyl)]-1-cyclohexene-1-carboxylic acid (7). Compound **6** (2.00 g, 6.16 mmol) was heated at reflux in absolute ethanol (25 mL) to give a clear solution. To this was added a suspension of Ba(OH)$_2$·8H$_2$O in water (6.00 g, 19 mmol, in 25 mL water). The solution was then heated at reflux for 3.5 h and then cooled to ambient temperature. The reaction was acidified with 3 N HCl and extracted with ethyl acetate, then TBME. The organic layers were combined and washed with water and brine. After drying, the unsaturated acid **7** was isolated as an oil by concentration in vacuo. The crude reaction was purified by preparative reverse phase liquid chromatography to give **7** (450 mg, 21%).

IR (KBr pellet) 3305, 2235, 1689, 1650 cm^{-1}; ^{1}H (360 MHz, C$_6$D$_6$) δ 7.1 (1H, d, $J = 2.0$ Hz), 7.0 (1H, s), 6.82 (1H, dd, $J = 2.0$, 8.4 Hz), 6.63 (1H, d, $J = 8.4$ Hz), 4.72 (1H, m), 3.50 (3H, s), 2.80 (1H, m), 2.15−2.52 (3H, m), 1.41−2.09 (10H, m); ^{13}C (90 MHz, CDCl$_3$) δ 170.7, 149.9, 147.9, 137.4, 131.5, 129.7, 122.3, 117.5, 112.7, 111.9, 80.7, 56.1, 39.7, 33.0, 32.8, 32.6, 24.1, 22.3.

Methyl 2-Chloro-6-cyano-6-[3-(cyclopentyloxy)-4-(methoxyphenyl)]-1-oxospiro[2.5]octane-2-carboxylate (9). Ketone **2** (4.0 g, 12.8 mmol) and methyldichloroacetate (2.74 g, 19.1 mmol) were added to THF (40 mL). The solution was cooled to 0 °C, and potassium *tert*-butoxide (19.1 mL, 19.1 mmol, 1 M in THF) was added while maintaining the temperature below 5 °C. The reaction was then stirred at this temperature for 30 min and then poured in ethyl acetate and 5% HCl. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with 5% sodium bicarbonate and then brine. The organic layer was concentrated in vacuo to give an oil. Purification through a plug of silica gel (hexanes:ethyl acetate, 3:1) gave **9** as a colorless oil (5.00 g, 93%) (ratio of isomers 3.5:1). The major isomer is shown below.

IR (neat) 2233, 1755, 1259 cm^{-1}; ^{1}H (400 MHz, CDCl$_3$) δ 10.35 (1H, br s), δ 7.01 (1H, d, $J = 2.3$ Hz), 6.96 (1H, dd, $J = 2.3$, 8.4 Hz), 6.88 (1H, d, $J = 8.4$ Hz), 4.81 (1H, m), 3.89 (3H, s), 3.85 (3H, s), 1.75−2.54 (14H, m), 1.46−1.68 (2H, m); ^{13}C (100 MHz, CDCl$_3$) δ 164.6, 150.1, 148.0, 131.1, 121.7, 117.5, 113.2, 112.0, 80.9, 79.1, 67.3, 56.6, 53.6, 42.5, 36.1, 35.8, 32.8, 28.1, 27.2, 24.0; m/z (CH$_4$/Cl) [M + H]$^+$ 420 (44%), [M − H]$^+$ 418 (75%), [MH − HCN]$^+$ 393 (100%), 325 (44%).

2-Chloro-6-cyano-6-[3-(cyclopentyloxy)-4-(methoxyphenyl)]-1-oxospiro[2.5]octane-2-carboxylic acid (10). To

chloroepoxyester **9** (221 mg, 0.53 mmol) in methanol (2.2 mL) was added sodium methoxide (0.6 mL, 2.62 mmol, 25% w/w solution in methanol) and water (90 mL, 5.0 mmol). The solution was stirred for 15 min, and then 1% HCl and TBME (1:1) were added. The organic layer was washed with water and then with brine and was concentrated in vacuo to give a white foam **10** (185 mg, 85%). (Ratio of isomers 3.5:1).The major isomer is shown below.

IR (neat) 3481, 2237, 1727, 1259 cm^{-1}; ^{1}H (400 MHz, CDCl$_3$) δ 10.35 (1H, br s), δ 7.01 (1H, d, $J = 2.3$ Hz), 6.96 (1H, dd, $J = 2.3, 8.4$ Hz), 6.88 (1H, d, $J = 8.4$ Hz), 4.81 (1H, m), 3.85 (3H, s), 1.75−2.56 (14H, m), 1.58−1.72 (2H, m); ^{13}C (100 MHz, CDCl$_3$) δ 166.0, 149.9, 147.8, 131.2, 121.6, 117.5, 113.0, 112.1, 81.0, 79.0, 67.4, 56.1, 42.6, 36.0, 35.8, 32.7, 28.0, 27.3, 24.0; m/z (CH$_4$/Cl) [M + H]$^+$ 406 (8%), [MH − HCN]$^+$ 379 (100%), 345 (61%), 311 (37%).

***cis*-6-[3-(Cyclopentyloxy)-4-(methoxyphenyl)]-1-oxospiro-[2.5]octane-2,6-dicarbonitrile (11).** To 50% potassium hydroxide in water (22 g) and THF (55 mL) was added benzyltriethylammonium chloride (0.81 g, 3.5 mmol) and the solution cooled to 0 °C. A separate solution was made by dissolving the ketone **2** (23.0 g, 73 mmol) and chloro-acetonitrile (5.9 g, 78 mmol) in THF (55 mL) at room temperature. While the base solution was stirred at 0 °C, the ketone solution was added in small portions over 15 min. The temperature during the addition was maintained between 0 and 5 °C and the reaction stirred for 1 h. The reaction was warmed to 25 °C and diluted with water:ethyl acetate (1:1). The layers were separated, and the organic layer was concentrated in vacuo. Methycyclohexane/THF (5:1) was added, and the residue was heated to 60 °C then cooled to 20 °C over 90 min; the product began to crystallize at 40 °C. Cooling was continued to 0 °C and held at 0 °C-5 °C for 2 h. The product was collected and washed with a methanol mixture (0 °C). The product was dried to afford **11** (20.69 g, 80%). The analytical data were consistent with the literature.[28]

IR (KBr pellet) 2242, 2233, 1257 cm^{-1}; ^{1}H (400 MHz, CDCl$_3$) δ 7.00 (1H, d, $J = 2.4$ Hz), 6.98 (1H, dd, $J = 2.4$, 8.3 Hz), 6.87 (1H, d, $J = 8.3$ Hz), 4.82 (1H, m), 3.85 (3H, s), 3.32 (1H, s), 2.54 (2H, m), 2.39 (2H, m), 2.07 (4H, m), 1.90 (4H, m), 1.62 (2H, m), 1.50 (2H, m); ^{13}C (100 MHz, CDCl$_3$) δ 150.21, 140.01, 130.96, 121.50, 117.49, 115.75, 113.05, 112.12, 80.88, 63.90, 56.10, 47.19, 42.33, 36.27, 35.88, 32.79, 30.25, 28.17, 24.03.

Lithium *c*-4-Cyano-4-[3-(cyclopentyloxy)-4-(methoxy-phenyl)]-*r*-1-cyclohexanecarboxylate (15). *WARNING: Hydrogen cyanide is liberated during the rearrangement. Appropriate safety precautions need to be taken!* A suspension of DMF (200 mL), acetonitrile (200 mL), lithium bromide (32.4 g, 0.37 mol), and water (5.6 g, 0.31 mol) was stirred until homogeneous. To this was added epoxynitrile **11** (90.0 g, 0.25 mol). The reaction was heated to 90−95 °C for 8−12 h. The reaction was cooled to 60 °C, where DMF (270 mL) was added. To this was then added an aqueous solution of lithium hydroxide (21.65 g, 0.51 mol in 112.5 mL of water). The suspension was stirred at 60 °C for 1 h, then cooled to 5 °C, and held at this temperature for 1 h. The suspension was filtered and washed with ethyl acetate and dried to give **15** (70.5 g, 79%). To obtain a pure sample of the salt, **15** was slurried in wet acetonitrile, filtered, then dried.

IR (KBr pellet) 3319, 3208, 2230, 1647 cm^{-1}; ^{1}H (400 MHz, CDCl$_3$) δ 7.00 (1H, d, $J = 2.3$ Hz), 6.99 (1H, dd, $J = 2.3, 9.2$ Hz), 6.93 (1H, $J = 9.2$ Hz), 4.81 (1H, m), 3.72 (3H, s), 2.06 (2H, m), 2.01 (2H, m), 1.96 (1H, m), 1.87 (2H, m), 1.76 (2H, m), 1.69 (4H, m), 1.63 (2H, m), 1.56 (2H, m); ^{13}C (100 MHz, CDCl$_3$) δ 178.9, 149.2, 147.0, 133.7, 123.1, 117.5, 112.7, 112.2, 79.6, 55.6, 44.5, 43.0, 36.5, 32.2, 27.5, 23.6. Calcd C$_{21}$H$_{24}$N$_4$Li·H$_2$O, C 65.38, H 7.15, N 3.81. Found C 65.10, H 7.08, N 3.68.