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Selection and Scale-Up Evaluation of an Alternative Route to (−)-(3*R*,4*R*)-1-Benzyl-4-(benzylamino)piperidin-3-ol

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ABSTRACT: An efficient, scalable synthesis of (−)-(3*R*,4*R*)-1-benzyl-4-(benzylamino)piperidin-3-ol (**4**) is described. Reduction of the pyridinium salt prepared from pyridine and benzyl chloride generated the corresponding tetrahydropyridine derivative. A two-stage epoxidation, followed by ring-opening of the epoxide with $BnNH_2$, established the regiochemistry of the amino alcohol and served to set the *trans*-relationship between the amine and the hydroxyl group. The resulting racemic intermediate was then resolved by salt formation with (*R*)-*O*-acetyl mandelic acid. The process produced the *O*-acetyl mandelic acid salt of (−)-**4** in 27% overall yield from benzyl chloride.

INTRODUCTION

Lung cancer is responsible for over one-third of cancer related deaths in the United States, with the non-small cell variant being a particularly aggressive form. Treatments that prolong the life of those stricken with this disease are of the utmost importance and, as a result, are being actively investigated by the pharmaceutical industry. BMS-690514 (**1**) is a potential therapeutic agent for the treatment of lung and other cancers.[1] From a retrosynthetic perspective, compound **1** can be dissected to protected piperidine **2** and pyrrolotriazine **3**, the union of which is realized by an S_N2 displacement of the activated primary alcohol (Figure 1). Compound **3** is derived from chloro-substituted pyrrolotriazine **6** and *m*-anisidine (**5**); and coupling partner **2** is generated from bis-benzyl derivative (−)-**4**. 3,4-Disubstituted piperidine (−)-**4** is the compound of interest in this communication.

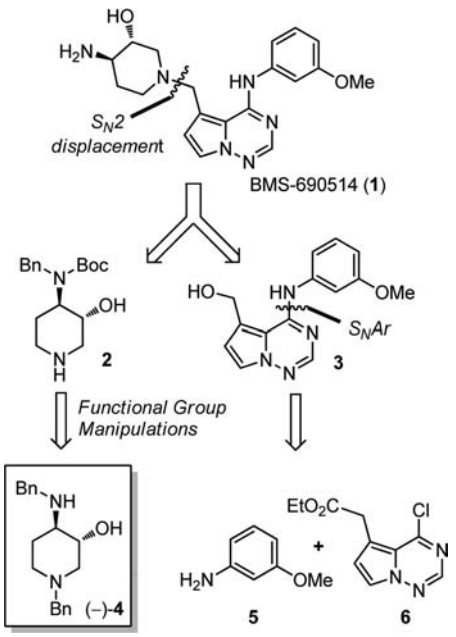

Figure 1. Retrosynthesis of BMS-690514 (**1**) to yield the intermediate of interest (**4**).

The current large scale synthesis of piperidine (−)-**4** features the ring expansion of pyrrolidinol **9**, which is derived from (*R*)-pyroglutamic acid (**7**).[2] The overall process requires seven steps and proceeds in 22% overall yield (Figure 2). Although this strategy has been used to prepare greater than 200 kg of piperidine (−)-**4**, many of the transformations are operationally laborious. The preparation of (−)-**4** requires significant plant time, leading to decreased throughput and increased production costs. Due to the need for large quantities (>100 kg) of **1**, a more efficient synthesis of (−)-**4** was desired.

As previously reported,[3] four alternative syntheses of compound (−)-**4** were accomplished on lab scale (Figure 2). We began to evaluate the metrics/(dis)advantages of each strategy to select a route for further development. The initial sequence considered (*route A*, Figure 2) set the absolute and relative stereochemistry through asymmetric hydrogenation of enolized *β*-ketoester **10**, and a Curtius rearrangement installed the second requisite nitrogen of **11**. This route produced cyclic carbamate **11** in high overall yield (68%) and in short order (3 steps). Carbamate **11** has the potential to serve as an alternative protecting group to those currently used (Boc, Bn) during the coupling,[4] although the API step deprotection would have to be redeveloped. Alternatively, **11** could be converted to **4** by a two step process (hydrolysis of carbamate and subsequent benzylation). While this work was being conducted, the cost and availability of the hydrogenation ligand **12** were of concern.

Route B utilized material from the chiral pool and featured ring expansion[5] of a 2-deoxy-D-ribose derived bis-amine **14**. This strategy was shorter than the current route (5 vs 7 steps) but produced the desired target in only 15% overall yield (>99.9% ee). The key rearrangement to produce (−)-**4** was low yielding and would require substantial optimization. The rearrangement was complicated by the observation that each

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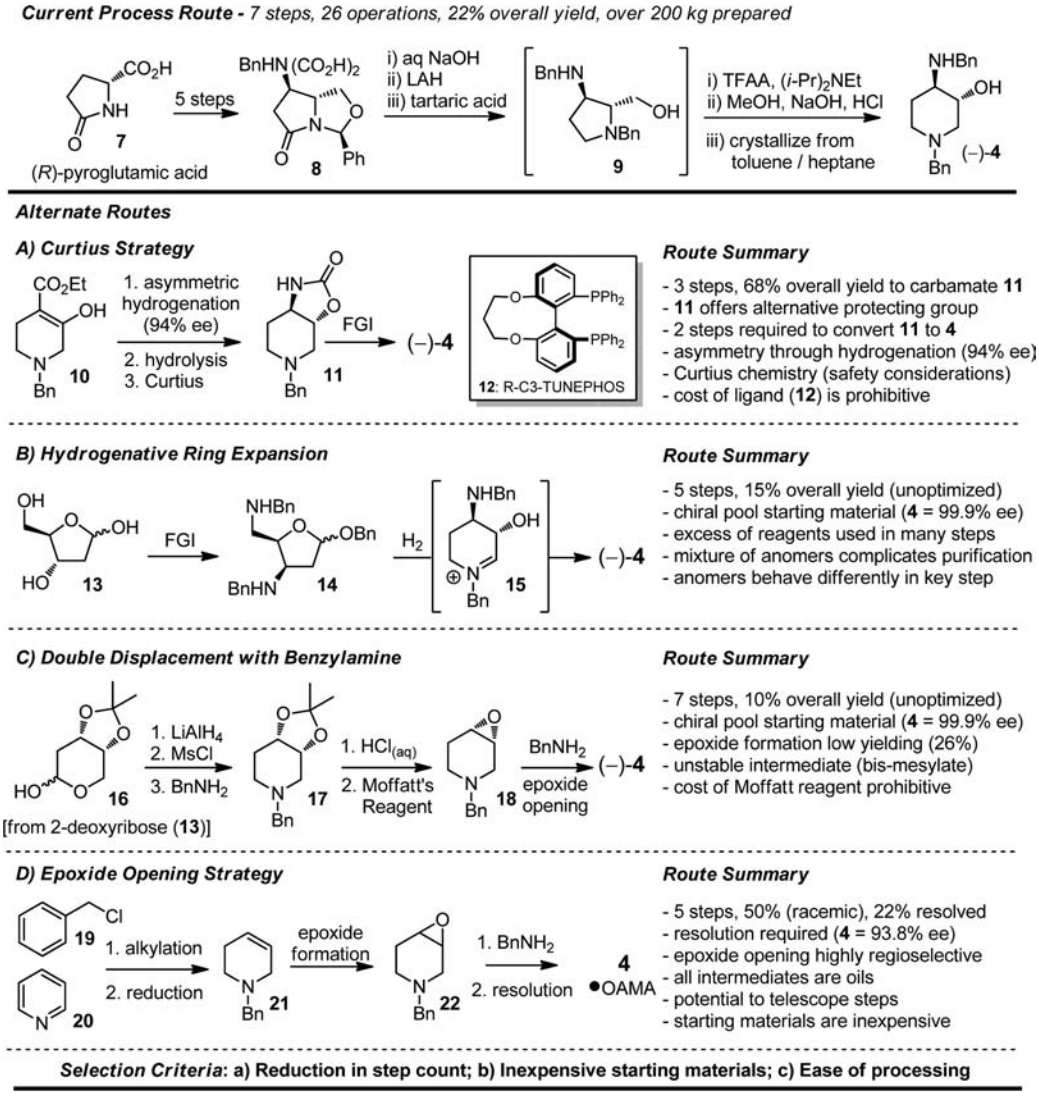

Figure 2. Current route to piperidine (−)-**4** and evaluation of alternative strategies. FGI = functional group interconversion; OAMA = (*R*)-*O*-acetyl mandelic acid.

anomer of **14** displayed differing behavior upon subjection to catalytic hydrogenolysis. One anomer converted to the desired product (**4**) more rapidly (1−2 h), and if this anomer was subjected to the extended reaction times (4.5 h) required to convert the other anomer to **4**, substantial product *N*-debenzylation occurred. To overcome this, the anomers had to be separated prior to rearrangement. Another concern was the necessity to purify the polar intermediates by chromatography, as anomeric mixtures at each stage rendered isolation by crystallization difficult. *Route C* also utilized 2-deoxy-D-ribose (**13**) as a feedstock, from which a bis-mesylate intermediate was prepared. Double displacement of the mesylates with $BnNH_2$ induced closure to piperidine **17**. Further functional group manipulations[6] installed the epoxide of **18**, which was regioselectively opened (>20:1) with $BnNH_2$ in the presence of a lithium salt.[7] Overall, seven steps were required to produce (−)-**4** in 10% yield (>99.9% ee), with inefficient epoxide formation (26%) being the major contributor to the low overall yield. Instability of the bis-mesylate intermediate and difficulties encountered during purifications were also areas of concern.

The final sequence considered (*Route D*) featured an alternative synthesis of the epoxide (**18**) used in *Route C*, albeit in racemic form (**22**).[8] After opening with $BnNH_2$, (±)-**4** was produced in 50% yield (5 steps, unoptimized) from inexpensive and readily available benzyl chloride (**19**) and pyridine (**20**).[9] After resolution with (*R*)-*O*-acetyl mandelic acid (OAMA), the salt of **4** was obtained in 22% overall yield (93.8% ee after salt break).[10] Upon evaluating the scalability of this sequence, we envisioned a reduction in the number of operations through telescoping transformations. Challenges associated with this route were that some intermediates were identified to be oils and salt formation was necessary for crystallization. Additionally, further resolution development would be required to increase enantiomeric excess.

With four sequences available, we defined our criteria for route selection: (a) a reduction in step count compared to the current seven steps; (b) utilization of inexpensive starting materials; and (c) a reduction in the total number of operations. Based on the summaries in Figure 2, we deemed that *Route D* had the greatest potential to meet these requirements. Only five steps were required from inexpensive pyridine and benzyl chloride, and the reactions on lab scale were operationally simple to perform. Areas requiring further study were identified during our lab scale campaign (lack of

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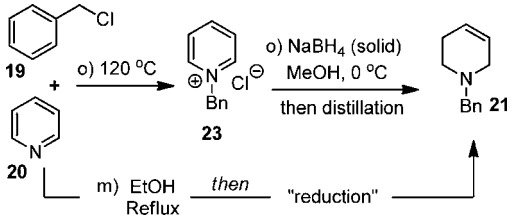
crystalline/isolable intermediates, and the requirement for resolution optimization). Preliminary results during the lab scale development of this route [fumaric acid salt of epoxide **22** for isolation, and (*R*)-*O*-acetyl mandelic acid for the resolution of (±)-**4** (44%, 93.8% ee)][10] served as a starting point for addressing these issues. The following reports our findings and optimizations upon performing this chemistry on scales approaching 1 kg.

RESULTS AND DISCUSSION[11]

Although not discussed in our original communication,[3] tetrahydropyridine **21** was prepared by the alkylation of pyridine with benzyl chloride and subsequent reduction.[12] The initial lab-scale procedure required slow addition of benzyl chloride to neat pyridine at 120 °C to prevent a delayed exotherm (Scheme 1). The resulting salt **23** was dissolved in

Scheme 1. Preparation of Tetrahydropyridine 21 by Original Lab Scale (o) and Proposed Modified (m) 20 L Procedures

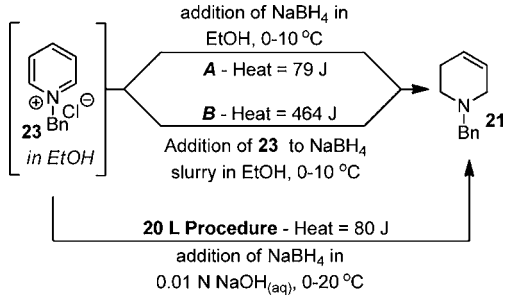


methanol, and solid sodium borohydride was added portionwise to prevent excessive foaming. After workup, tetrahydropyridine **21** was isolated by vacuum distillation. As a means to alleviate the first issue (neat reaction conditions, 120 °C), we evaluated the performance of this alkylation in toluene. Although the precipitated product could be isolated by filtration, the hygroscopicity of **23** limited the practicality of this approach. We then considered the possibility of performing the alkylation reaction in ethanol, as this would allow the reduction to be performed in the same reactor without isolation of salt **23**. Experimentally, the reaction required 8−10 h at reflux for complete consumption of benzyl chloride. A slight excess of pyridine (7%) was utilized, as the presence of residual benzyl chloride during the subsequent reduction led to quaternization of reduction product **21**. With an ethanolic solution of **23** in hand, we began development of a scalable sodium borohydride reduction.

During the original lab scale developments, solid sodium borohydride (1.2 equiv) was added portionwise to a methanol solution of salt **23** to minimize foaming/exotherm. It was estimated that this addition would take 3−4 h on 20 L scale, rendering this addition method impractical. To alleviate the issue, we considered two protocols for reduction: 1) addition of a basic, aqueous solution of sodium borohydride to the alcoholic solution of **23**; and 2) addition of the alcoholic solution of **23** to a slurry of sodium borohydride in ethanol. It was presumed that each of these alternatives would yield a dose controlled reaction rate. Prior to scaling this reaction to 20 L, we initiated a study of the reduction by calorimetry to identify potential thermal events.

Initially, the mode of addition ($NaBH_4$ to **23** vs **23** to $NaBH_4$) was evaluated on the basis of heat evolution. Charging an ethanol solution of sodium borohydride (0.25 mmol, 10 mol %) to a solution of **23** (2.5 mmol) in ethanol at 10 °C (mode A, Scheme 2) generated 79 J over a 6 min reaction time (Figure

Scheme 2. Addition Modes Evaluated by Calorimetry for the Reduction of Pyridinium Salt 23 and the 20 L Procedure[a]



[a]For ***A*** and ***B***, values are for addition of 0.1 equiv of limiting reagent ($NaBH_4$ and **23**, respectively).

3). In the reverse mode of addition [**23** (0.25 mmol in ethanol) to an ethanol solution of $NaBH_4$ (2.5 mmol) (mode B, Scheme

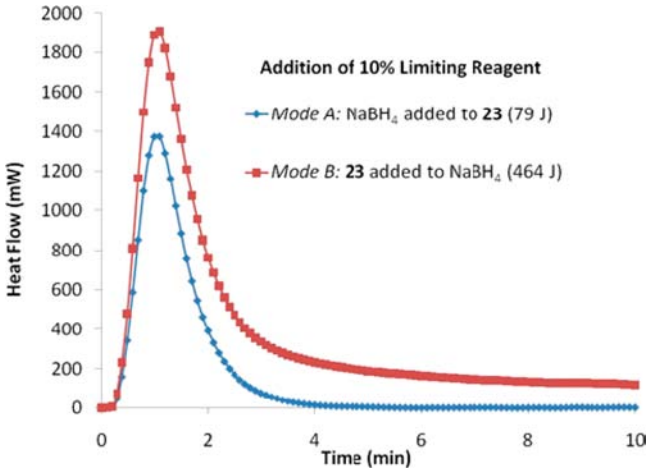


Figure 3. Heat flow versus time detected by isothermal reaction calorimetry.

2)], the total heat detected was 464 J, with the exotherm being self-sustaining for more than 140 min. There was also a substantial increase in pressure within the calorimeter during this mode of addition. The marked difference in heat evolution (79 vs 464 J) resulted from the tertiary amine reduction product[13] (**21**) catalyzing the exothermic decomposition[14] of the remaining sodium borohydride (0.9 equiv). To validate this theory, addition of a catalytic amount of tetrahydroypyridine **21** to a slurry of sodium borohydride in ethanol initiated violent gas evolution, indicating that reverse addition of pyridinium salt **23** to $NaBH_4$ was not feasible. Further lab scale optimization in conjunction with calorimetry studies identified the addition of a solution of $NaBH_4$ (1.15 equiv) in aqueous NaOH (0.01 M)[15] to an ethanol solution of **23** as a viable procedure for scale-up (Scheme 2, 20 L procedure). For this process, the heat detected by reaction calorimetry was 80 J and the adiabatic temperature rise was estimated to be 104 °C. Upon implementation on 20 L scale, addition of the $NaBH_4$ solution over 4 h led to minimal exotherm and allowed the reaction temperature to be maintained below 20 °C.

With a process to safely produce tetrahydropyridine **21** on scale, we turned our attention to improving the epoxide formation sequence. For lab scale development, distilled **21** was treated with NCS in the presence of TFA to form the

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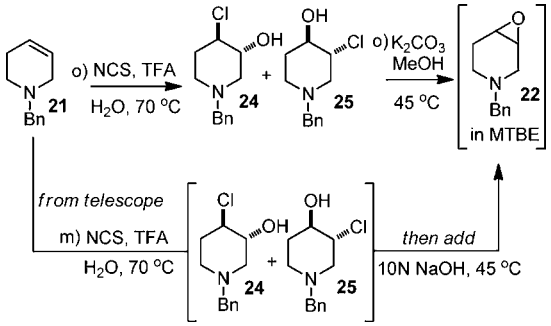
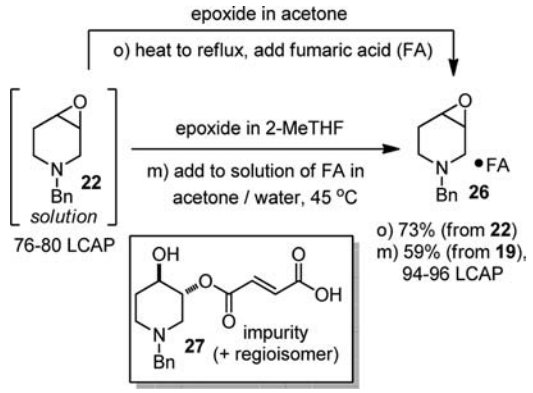
chlorohydrins **24**/**25** (Scheme 3). The crude product was then isolated and subjected to potassium carbonate (2.0 equiv) in methanol to yield epoxide **22**. For the 20 L campaign, the crude tetrahydropyridine stream from reduction of pyridinium **23** was used directly. A similar protocol for epoxide formation was utilized, with the exception of the direct addition of 10 N NaOH to the reactor once chlorohydrins formation was complete. This removed the necessity for workup and isolation of **24**/**25**. It was necessary to charge 4.2 equiv of sodium hydroxide to compensate for the acidic components [TFA (1.25 equiv) and succinimide (1.2 equiv), leaving 1.75 equiv of NaOH for reaction] present from chlorohydrin preparation. After three telescoped steps, the crude epoxide **22** was extracted into an organic solvent in preparation for salt formation/crystallization with fumaric acid.

Scheme 3. Preparation of the Racemic Epoxide by Both Original Lab Scale (o) and Modified 20 L (m) Methods



On lab scale, crude epoxide **22** was extracted into MTBE, concentrated, and then redissolved in acetone. After heating this solution to reflux, solid fumaric acid (1.0 equiv) was added directly to the flask (Scheme 4). This led to rapid precipitation of salt **26**, and the addition of solid to the refluxing solution caused excessive foaming. Due to the uncontrolled crystallization, excess fumaric acid contaminated the isolated product. Nonetheless, this procedure offered the first isolable, solid intermediate in this sequence.

Scheme 4. Preparation of Fumaric Acid Epoxide Salt 26 by Both Original Lab Scale (o) and Modified 20 L (m) Methods[a]

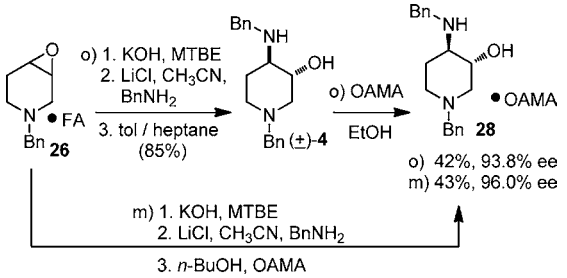


[a]LCAP = liquid chromatography area percent.

Modifications were necessary to make this salt formation amenable to 20 L scale, as better control of both crystallization rate and purity upgrade were required. The foaming observed upon direct addition of fumaric acid to the refluxing epoxide solution also needed to be addressed. Due to the insolubility of fumaric acid in most organic solvents, slow addition of a fumaric acid solution to the epoxide stream was not feasible. After exploring a variety of mixed solvent systems, it was found that fumaric acid was soluble in 11 volumes of 10:1 acetone/water at reflux (higher ratios of water further increased fumaric acid solubility but led to diminished recovery of the salt **26**). After reducing the temperature of the fumaric acid solution to 45 °C (the minimum temperature at which the fumaric acid would remain soluble), seeds of **26** (10 mol %) were added. The crude epoxide solution in 2-MeTHF (used instead of MTBE for extraction of the epoxide) was then dosed at a rate to control the crystallization. Salt **26** was obtained in 59% yield (from benzyl chloride) with a purity of 94−96 LCAP (liquid chromatography area percent, crude LCAP = 76−80). The addition temperature of 45 °C was a key process parameter. If the epoxide solution is added to the fumaric acid solution at temperatures > 50 °C, a significant amount (up to 12%) of byproduct (**27**) from epoxide opening by fumaric acid is observed in the isolated product.

With the fumaric acid salt (**26**) in hand we were prepared to evaluate epoxide opening and resolution on scale. For the lab scale synthesis, fumaric acid was removed by basic washes to yield epoxide **22**, and then epoxide opening (LiCl, $BnNH_2$, CH_3CN) proceeded with a high degree of regioselectivity (>20:1)[7c] to yield (±)-**4** (Scheme 5). Racemic **4** was crystallized from toluene/heptane (85%) and then subjected to the unoptimized resolution conditions [ethanol (anhydrous), (*R*)-*O*-acetyl mandelic acid] to yield **28** (42%, 93.8% ee).[10] Upon scaling this sequence to 20 L, our objectives were to eliminate the isolation/crystallization of racemic **4** prior to resolution, and improve both the recovery and enantiomeric excess of isolated **28**.

Scheme 5. Preparation of Racemic 4 and Resolution by Both Original Lab Scale (o) and Modified 20 L (m) Methods[a]



[a]FA = fumaric acid; OAMA = (*R*)-*O*-acetyl mandelic acid.

The epoxide opening conditions (LiCl, $BnNH_2$, CH_3CN) used on lab scale to generate racemic **4** yielded similar results on scales approaching 1 kg and were not modified. Further development of the isolation/resolution of racemic **4** supported the continued use of (*R*)-*O*-acetyl mandelic acid (**29**) in alcoholic solvents. Utilizing previously crystallized (±)-**4**, the greatest enantioenrichment (97.3% ee)[10] was achieved by salt formation in EtOH [SDA-3A, 190 proof (the SDA-3A designation indicates denaturing with 5 parts methanol)], but the recovery was modest (36%). This reduction in yield is presumably due to water present in the ethanol leading to increased solubility of the product salt (Figure 4). The use of anhydrous solvents such as ethanol (200 proof) and *n*-BuOH

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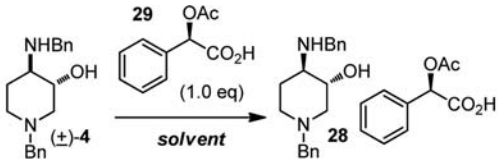

Initial Studies for Solvent Selection

Solvent	%ee	%recovery
EtOH (200 proof)	93.8	42
EtOH SDA-3A (190 proof)	97.3	36
i-PrOH	91.8	49
***n*-BuOH**	***93.5***	***47***

Optimization Using *n*-BuOH

Conditions	%ee	%recovery
Spontaneous	88.9	46
Seeded	91.8	45
Seeded with 1 temp cycle	94.6	44

Figure 4. Optimization of the (*R*)-*O*-acetyl mandelic acid resolution of racemic **4**.

was examined to circumvent this issue, and while both solvents yielded comparable enantiomeric excess (93.8 and 93.5%, respectively), the recovery with *n*-BuOH was superior (47 vs 42%). Further improvements with *n*-BuOH were realized by seeding the crystallization (1% loading) and utilizing a temperature cycle.[16] This process allowed (−)-**4** to be isolated in 94.6% enantiomeric excess and 44% recovery from previously isolated racemic **4**.

With an optimal resolution developed using previously crystallized (±)-**4**, we attempted to use the (*R*)-*O*-acetyl mandelic acid crystallization as a means of both resolution and purification. Upon completion of epoxide opening by $BnNH_2$, water was added to the reaction mixture and crude (±)-**4** was extracted into *n*-BuOH. This aqueous extraction was necessary to remove lithium chloride (its presence leads to uncontrolled precipitation of the racemate during the salt formation), and upon addition of *O*-acetyl mandelic acid, **28** was produced in 43% yield and 96.0% ee (Scheme 5).[10] The chemical purity of (−)-**4** that was isolated after salt break was greater than 99.9 LCAP, indicating that the crystallization effectively rejected the impurities from the epoxide opening sequence.

The enantiomeric excess garnered from the resolution was still insufficient for our purposes; however, the route to coupling partner **2** offered three opportunities for enantioenrichment. Initially we examined crystallization of the material resulting from salt break of **28** (option 1, Figure 5). It was found that either acceptable enantioenrichment or recovery could be achieved by crystallization from varying ratios of toluene/heptane, but both could not be realized simultaneously. The second option (Figure 5) involved conversion of salt **28** to the coupling partner **2** and then crystallization from toluene/heptane. Unfortunately, a similar outcome to the crystallization of (−)-**4** (either good recovery or chiral purity, but not both) was found. The final option investigated (option 3, Figure 5) involved simple recrystallization of salt **28** resulting from the resolution. Since we were now separating diastereomeric salts rather than enantiomers, this enantioenrichment strategy proved to be the most effective. A range of alcoholic solvents were surveyed, and recrystallization from ethanol (SDA-3A 190 proof, 10 vol) yielded **28** in 99.9% ee with an

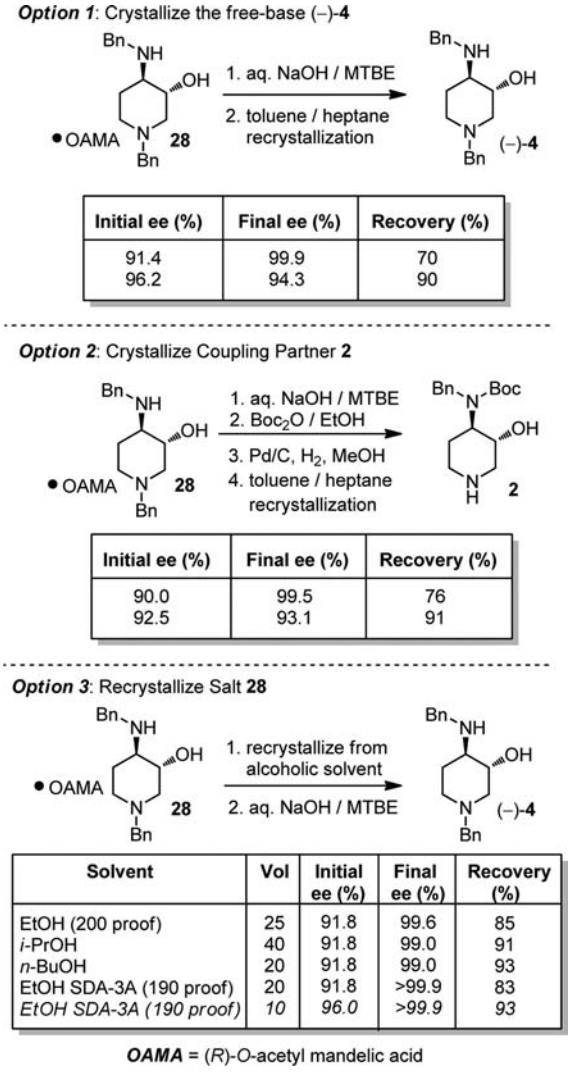

Figure 5. Strategies investigated for enantioenrichment.

acceptable 93% recovery.[10] With an enantioenrichment strategy in place, it appeared that we could efficiently execute the sequence on 20 L scale. This material (**28**) could then be converted to coupling partner **2** using the current chemistry or be used to explore alternative protecting strategies for coupling. However, at this point we obtained occupational toxicology data that necessitated modification to our isolation strategy.

A local lymph node assay (LLNA) identified the epoxide fumaric acid salt (**26**) as a dermal sensitizer.[17] This introduced material handling restrictions, and we sought to eliminate the formation/isolation of the fumaric acid salt entirely. This would stress our resolution crystallization, which would now afford the only opportunity for purification from benzyl chloride/pyridine. Progression through the sequence yielded epoxide **22**, which was not isolated, but instead carried directly into the epoxide opening process. Reaction of crude **22** with $BnNH_2$ behaved similarly to when isolated epoxide salt **26** was used, and with the dark brown stream of (±)-**4** in hand (60 LCAP), we were now ready to test the limits of our resolution in terms of impurity purge. Using the previously developed conditions (*n*-BuOH, 1% seeding, 1 temperature cycle), target salt **28** was isolated as a white crystalline solid (29% yield from BnCl; 97 LCAP, 95.0% ee) on a 20 L scale. This material was then recrystallized from ethanol (SDA-3A, 190 proof) for

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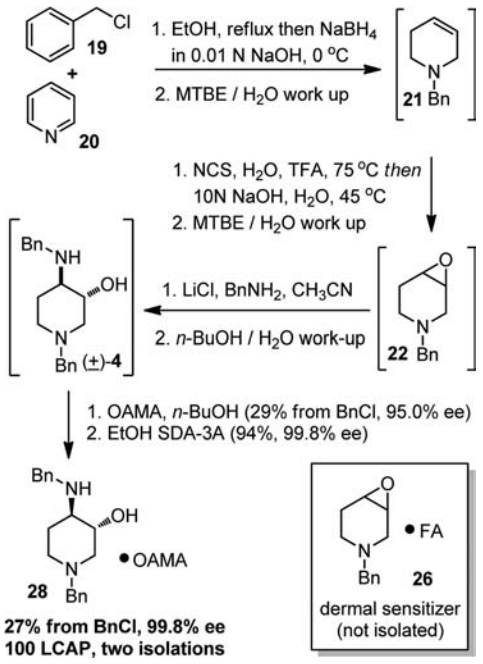
enantioenrichment and chemical purification (94% recovery, 100 LCAP, 99.8% ee) to produce **28** in 27% overall yield from benzyl chloride (Scheme 6). More importantly, this outcome demonstrated that formation/isolation of dermal sensitizer **26** is not necessary.

Scheme 6. Optimized Sequence to 28[a]



[a]FA = fumaric acid; OAMA = (*R*)-*O*-acetyl mandelic acid.

■ SUMMARY

A strategy toward (−)-**4** based on regioselective epoxide opening with $BnNH_2$ was selected for further development. The optimized sequence produced *O*-acetyl mandelic salt **28** in 27% (100 LCAP, 99.8% ee)[10] overall yield from benzyl chloride in five steps and two isolations (see Figure 6 for route metric comparison). This compares favorably with the original lab scale route, which required five steps, a reduced pressure distillation, and two crystallizations to obtain **28** in 21% yield (100 LCAP, 93.8% ee). Calorimetry studies determined that the product (**21**) from reduction of pyridinium salt **23** catalyzes the exothermic decomposition of sodium borohydride. This precluded the use of a reverse addition protocol, and further analysis allowed us to develop a process that removed the potential for an uncontrolled exotherm on scale. The first generation 20 L route required five steps and three crystallizations to obtain *O*-acetyl mandelic salt **28** in 23% overall yield (100 LCAP and 99.9% ee). At this point, epoxide salt **26** was identified as a dermal sensitizer, and the process was modified to eliminate formation/isolation of this compound. This further streamlined the route to **28** and allowed us to arrive at our current process. It was estimated that this route would offer a cost reduction of 60% when compared to the current strategy utilizing pyroglutamic acid [for the multikilogram production of intermediate (−)-**4**]. This potential savings is remarkable, when one considers that more than half of the material is removed during the resolution. A full account reporting the development work toward the preparation of BMS-690514 (**1**) on scale will be forthcoming.

Criteria	Original	Lab Scale	20 L 1st Gen.	20 L 2nd Gen.
# of steps	7	5	5	5
# of isolations	3	3	3	2
LCAP of product	100	100	100	100
enantiomer excess	>99.9	93.8	99.9	99.8
overall yield (%)	22	21	23	27

Figure 6. Route metric comparison.

■ EXPERIMENTAL SECTION

General. Reactions were performed under an atmosphere of nitrogen unless otherwise noted. Reagents were used as received unless otherwise noted. Reported yields are for isolated materials or calculated solution yields and are corrected for potency. NMR spectra were recorded on a Bruker DRX-500 instrument and are referenced to residual undeuterated solvent. The following abbreviations are used to explain multiplicities: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on a Thermo Orbi-trap Discovery instrument. Reaction calorimetry was studied using an Omnical Insight RT-10 isothermal reaction calorimeter.

Synthesis of Tetrahydropyridine 21. Caution: Compound **21** was found to catalyze the exothermic decomposition of sodium borohydride. As a result, sodium borohydride should be added to a solution of the pyridinium salt, instead of adding the pyridinium salt solution to a slurry of sodium borohydride. For further discussion, see text.

EtOH (SDA-3A, anhydrous, 2 L) was charged to a 20 L glass reactor equipped with a reflux condenser. Benzyl chloride (800 g, 6.32 mol, 1.0 equiv) and pyridine (533 g, 6.74 mol, 1.07 equiv) were charged into the reactor, and the heating jacket was set to 85 °C. The reaction was refluxed until HPLC analysis (210 nm) indicated that benzyl chloride had been consumed [<0.2 RLCAP (relative liquid chromatography area percent), typically 8−10 h]. Upon reaction completion, the jacket was set to −10 °C and water (2 L) was added once the internal temperature reached −5 °C. A freshly prepared solution of sodium borohydride (288 g, 7.61 mol, 1.20 equiv) in 0.01 N aqueous NaOH (4 L) was charged over 4 h at a rate to maintain the internal temperature below 20 °C. Proper venting of the vessel and control of reaction rate should be used to maintain the hydrogen gas concentration below the lower explosion limit of 4%. After complete addition of the sodium borohydride solution, the chiller was set to 0 °C and the reaction held for 30 min. Upon reaction completion (<1 RLCAP of pyridinium **23**), water (8 L) was added, and the aqueous layer was extracted with MTBE (2 × 4 L). The combined organics were washed with 15% brine (2 L), and the tetrahydropyridine **21** present in the crude stream was quantified by HPLC (930 g, 5.37 mol, 85%).

Synthesis of Epoxide 22. To a 20 L glass reactor containing the MTBE stream from above was added water (5.6 kg). The MTBE was removed by distillation under reduced pressure until the internal temperature reached 47 °C at 180 Torr. The resulting emulsion was cooled to 20 °C, and

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trifluoroacetic acid (765 g, 6.71 mol, 1.25 equiv) was added over a period of 10 min (slight exotherm 20−30.4 °C). The reaction was stirred for 20 min to obtain a slightly hazy solution, and then *N*-chlorosuccinimide (861 g, 6.45 mol, 1.20 equiv) was added in one portion. The reaction was heated to 70 °C and held at this temperature for 4 h. Upon reaction completion (<2 RLCAP of tetrahydropyridine **21**), the reactor contents were cooled to 10 °C over 1 h. To this solution was added aqueous sodium hydroxide (2.3 L of 10 M, 23.0 mol, 4.28 equiv) over 15 min (exotherm from 10 to 26 °C), followed by heating to 45 °C for 4 h, then cooling to 20 °C. The reactor contents were extracted with MTBE (2 × 3 L), and the combined organics were washed with water (1 L) and 1:1 water/brine (1 L). Quantitation of the reaction stream determined that 817 g (4.32 mol, 68% overall from benzyl chloride) of epoxide was present in solution. This material was telescoped directly to the next step.

Optional Crystallization of Epoxide 22 as the Fumaric Acid Salt (26). Caution: Compound **26** was identified as a dermal sensitizer. In order to perform this crystallization, 2-MeTHF (2 × 2 L) should be substituted for MTBE in the above extraction. Based on HPLC quantification, the crude 2-MeTHF stream used in this example contained 1028 g (5.43 mol) of epoxide **22**.

Acetone (4.95 kg), water (0.62 kg), and fumaric acid (624 g, 5.38 mol) were combined in a 20 L glass reactor; the slurry was then heated to reflux and held for 1 h to dissolve the fumaric acid. The solution was cooled to an internal temperature of 45 °C and stirred for 1 h. The fumaric acid solution was seeded with 100 g of previously prepared epoxide salt **26**, and the reaction stream (epoxide solution in 2-MeTHF) was added at a rate of 300 mL/min (total addition time, ∼15 min). The slurry was cooled to −5 °C over 2 h, and then held for an additional 12 h at this temperature. The product was filtered, the cake washed with acetone (2 × 1.5 L), and then dried in a vacuum oven (45 °C). The epoxide salt **26** (962 g, 3.15 mol, 58% from benzyl chloride) was obtained as a beige solid. mp = 161−163 °C; IR (film): ν_{max} = 3412, 3029, 2589, 1712, 1654, 1526 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ = 7.29 (m, 5 H), 6.61 (s, 2 H), 3.46 (d, J = 1.5 Hz, 2 H), 3.19 (m, 2 H), 2.96 (ddd, J = 13.5, 4.0, 1.5 Hz, 1 H), 2.55 (d, J = 13.5 Hz, 1 H), 2.31 (ddt, J = 11.5, 5.0, 1.5 Hz, 1 H), 2.13 (ddd, J = 6.0, 5.0, 2.5 Hz, 1 H), 1.91 (m, 2 H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 166.6, 136.4, 134.3, 129.2, 128.3, 127.5, 60.7, 51.1, 49.9, 49.6, 45.2, 24.4 ppm; HRMS calcd for $C_{12}H_{15}NOH^+$ [M + H^+] 190.1232, found 190.1221.

If the fumaric acid salt of the epoxide **26** is formed, washing with aqueous base is required prior to the epoxide opening step. To a 20 L glass reactor was charged epoxide salt **26** (975 g, 3.19 mol, 1.0 equiv) and 2 N NaOH (3.69 kg, 7.09 mol, 2.22 equiv) to afford a slurry which was stirred for 10 min. MTBE (4.31 kg) and brine (3.43 kg) were charged to the reactor, and the contents were mixed for 10 min. The layers were allowed to separate, and the aqueous layer was removed. The organic layer was again washed with a combination of brine (0.75 L) and 2 N NaOH (0.75 L). After removal of the aqueous layer, the MTBE solution of the epoxide is used in the opening/crystallization sequence as described below.

Epoxide Opening and Crystallization/Resolution To Prepare 28. The solution of crude epoxide **22** (∼817 g, 4.32 mol, 1.0 equiv) in MTBE (6 L) was placed in a 20 L glass reactor and then distilled under reduced pressure (60 °C, 100 Torr) to an approximate volume of 4.5 L. Acetonitrile (5.65 kg) was then added at a rate to maintain a constant volume of 4.5 L. Distillation was continued until the distillate contained less than 5% MTBE (^1H NMR). The reactor contents were cooled to 20 °C (internal), and an additional 3.5 L of acetonitrile was added to bring the total reactor volume to 8 L. Benzylamine (559 g, 5.22 mol, 1.2 equiv) and lithium chloride (184 g, 4.34 mol, 1.0 equiv) were added, and the reaction was stirred at 20 °C for 16 h and then heated to 50 °C for an additional 2 h (<1 RLCAP of **22**). *n*-Butanol (8 L) was charged and the acetonitrile was removed by reduced pressure distillation until the distillate contained less than 5% acetonitrile (^1H NMR), and then the total volume was reduced to 8 L. The internal temperature was reduced to 35 °C, and the organic layer was washed with water (5 L, then 1.5 L). The water that remained in the organic layer was removed by constant volume azeotropic distillation, until the distillation reached a constant temperature of 56 °C at 44 Torr. *n*-Butanol was then added to bring the total volume to 10.5 L. The solution yield of (±)-**4** was determined to be 90% at this stage, and the charge of (*R*)-*O*-acetyl mandelic acid (**29**, 1.0 equiv based on **4**) was adjusted accordingly. The temperature was increased to 78 °C, and **29** (377 g, 1.94 mol, 0.50 equiv based on in-process **4**) was added as a solution in *n*-butanol (0.75 L). The temperature was reduced to 70 °C, **28** (9 g, 0.018 mol, 1 wt %) was added as seeds, and then **29** (377 g, 1.94 mol, 0.50 equiv based on in-process **4**) was added as a solution in *n*-butanol (0.75 L). The slurry was held at 70 °C for 20 min, cooled to 20 °C over 2 h, and held at this temperature for 12 h. The slurry was then heated to 60 °C and held for 1 h, after which the temperature was reduced to 20 °C over 3 h and held for an additional 2 h. The solids were collected by vacuum filtration, and the cake was washed with *n*-butanol (4 × 1 L) until the washes became colorless. The solid was dried for 48 h in a vacuum oven (50 °C, 25 Torr) to yield **28** (903 g, 1.84 mol, 95% ee, 29% overall yield from benzyl chloride) as a white crystalline solid.

Optional Recrystallization of 28 for Upgrade of Enantiomeric Excess. Salt **28** (725 g, 1.48 mol, 95% ee) was charged to a 20 L glass reactor, followed by ethanol (SDA-3A 190 proof, 5.8 kg). The slurry was stirred for 10 min and then heated to reflux until a solution resulted. The solution was cooled to 65 °C over 1 h, seeded with **28** (7.0 g, 99.9% ee), and stirred at this temperature for 30 min. The slurry was cooled to 0 °C over 2 h and then held for an additional 30 min. The product was collected by vacuum filtration, and the cake was washed with isopropanol (3 × 1.2 L). The solids were dried in a vacuum oven (45 °C) for 12 h to yield **28** (682 g, 94% recovery, 99.8% ee) as a white crystalline solid. mp (DSC) (10 °C/min) = onset 171 °C, peak 173 °C; $[\alpha]_D^{25}$ = −63.9 (c = 1.0, MeOH); IR (film): ν_{max} = 3123, 3024, 2972, 2438, 1730, 1637, 1583, 1374, 1250 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz): δ = 7.54−7.40 (m, 7 H), 7.35−7.25 (m, 8 H), 5.77 (s, 1 H), 4.25 (d, J = 13.5 Hz, 1 H), 4.22 (d, J = 13.5 Hz, 1 H), 3.75 (dt, J = 9.5, 4.5 Hz, 1 H), 3.63 (d, J = 13.0 Hz, 1 H), 3.56 (d, J = 13.0 Hz, 1 H), 3.08 (ddd, J = 11.0, 5.0, 2.0 Hz, 1 H), 2.96 (m, 1 H), 2.82 (m, 1 H), 2.13 (s, 3 H), 2.15−2.04 (m, 2 H), 1.95 (t, J = 10.0 Hz, 1 H), 1.68 (ddd, J = 13.5, 12.0, 4.5 Hz, 1 H) ppm; ^{13}C NMR (CD_3OD, 125 MHz): δ = 176.10, 172.58, 138.74, 138.19, 133.83, 130.92, 130.67, 130.42, 130.35, 129.61, 129.41, 129.25, 128.98, 128.85, 78.98, 69.16, 63.01, 61.80, 59.87, 52.27, 50.23, 27.38, 21.23 ppm; HRMS calcd for $C_{19}H_{24}N_2OH^+$ [M + H^+] 297.1967, found 297.1956.

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Notes

The authors declare no competing financial interest.

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DEDICATION

†This paper is dedicated to the memory of our friend and colleague, Eric Sortore.

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