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Development of a Practical Synthesis of an Aminoindanol-Derived M1 Agonist†

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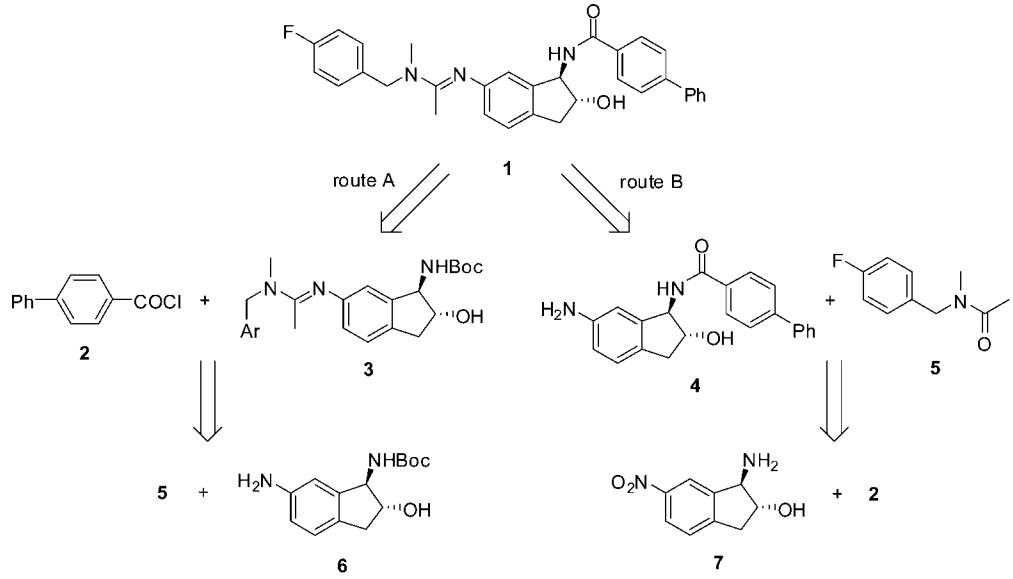
Abstract:

An efficient and scalable synthesis of the clinical candidate 1 is described. The first-generation synthesis built the enantioenriched nitro-aminoindanol core from 6-nitroindanone using a five-step literature route. The second-generation route used a safe aromatic nitration protocol in the presence of the unprotected alcohol to afford the requisite nitro-aminoindanol in one step. Challenges addressed in the remainder of the synthesis include a nitro group reduction to afford ppm levels of unreacted Ar-NO_2 (a mutagen) and a novel amidine formation under mild conditions via DMAP/K_2CO_3-promoted reaction with a thioimidate-activated amide. A convenient protocol for freebasing the API was provided by stirring with solid K_2CO_3 and monitoring disappearance of HI by reverse-phase HPLC.

Introduction

In support of the muscarinic receptor (M1) agonist program at Lilly, we required a practical and scalable synthesis of the aminoindanol-derived clinical candidate **1** (Scheme 1).[1] Two basic routes for assembling the three main subunits were examined. Route A was used to supply the structure−activity relationship (SAR) studies due to facile preparation of a variety of substituted amidines from the Boc-protected aminoindanol **6**, followed by deprotection and coupling with a diverse array of biaryl acid chlorides. Aminoindanol **6** was derived from (1*R*,2*R*)-*trans*-1-amino-6-nitro-indan-2-ol (**7**) via Boc-protection followed by nitro group reduction. Route B was selected for development of a multikilo-scale route in order to avoid the steps required by Boc protection and deprotection. A key component of the synthetic strategy required an improved synthesis of the core aminoindanol subunit **7**. Aminoindanol **7** has found importance as a scaffold in several SAR studies[2] and has also been utilized as a chiral auxiliary for the asymmetric synthesis of ketones and aldehydes through dynamic kinetic resolution of imines.[3] Herein we describe an initial synthesis of candidate **1**, utilizing a standard approach to aminoindanol **7**, and an improved route that delivered key intermediate **7** in one step from commercially available materials.[4]

Scheme 1. **Retrosynthetic options**



† This paper is dedicated to the memory of our friend and former colleague, Dr. Christopher R. Schmid.

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‡ Chemical Product Research and Development Division.

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(1) (a) Allen, J. R.; Hitchcock, S. A.; Liu, B.; Turner, W. W.; Jamison, J. A. PCT Int. Appl. WO 2003027061 A2. (b) Bush, J. K.; Heath, P. C. PCT Int. Appl. WO 2004018411 A1.

(2) (a) Gross, M. F.; Beaudoin, S.; McNaughton-Smith, G.; Amato, G. S.; Castle, N. A.; Huang, C.; Zou, A.; Yu, W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2849–2853. (b) Kozhushkov, S. I.; Yufit, D. S.; De Meijere, A. *Adv. Synth. Catal.* **2005**, *347*, 255–265, references 1−6 cited therein. .

(3) Kosmrlj, J.; Weigel, L. O.; Evans, D. A.; Downey, C. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 3208–3209.

(4) Safety note: All nitro aromatic intermediates were found to be mutagenic. Use appropriate care in handling.

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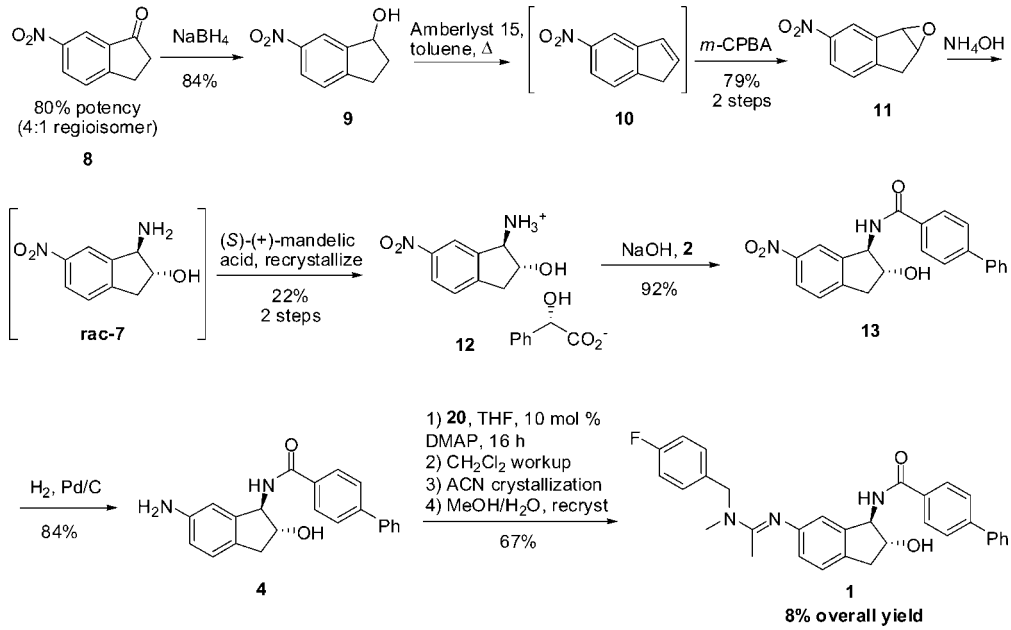
Scheme 2. **Synthesis of 1 via indanone route**



Results and Discussion

Synthesis of Resolved Aminoindanol 7. The synthesis of the key nitro-aminoindanol **7** from 1-indanone has been reported by several groups,[5] and this well precedented route was chosen for an initial kilolab campaign (Scheme 2).[6] The nitration of 1-indanone has been reported to provide a 3−4:1 mixture of 6-nitroindanone **8** to the 4-nitroisomer. The isomers have been separated by chromatography[2a] or by a tedious crystallization in unreported yield. We purchased 50 kg of 6-nitroindanone **8** from Sumikin Chemical Company[7] as a 4:1 mixture of 6-nitro- and 4-nitro-regioisomers. Since separation at this stage was challenging, the ketone was reduced with sodium borohydride to afford the indanol **9**. Crystallization of indanol **9** in the laboratory efficiently rejected the 4-nitro isomer. The process was scaled in the plant in three batches, with the first two batches containing 1.2% of the undesired 4-nitro isomer and the third batch containing 20.1%.

Further investigation was required to understand the failure of this crystallization process and ensure utilization of the third pilot-plant lot. Further recrystallization of the 4:1 mixture of 6- and 4-nitro isomers from a variety of solvents did not remove, and in some cases enriched, the undesired 4-isomer. Solid-state characterization showed that a new cocrystalline phase was present in the 4:1 mixture relative to the batches with low levels of the 4-nitro isomer. Figure 1 (top) shows two views of the hydrogen-bonding network in the crystal structure of the regiopure, racemic, 6-nitro isomer **9**. In Figure 1 (bottom) the hydrogen bonding of the cocrystal obtained by recrystallization of the 4:1 mixture of 6-nitro and 4-nitro isomers (racemic) is shown. The formation of a new cocrystal form from the 4:1 mixture and its apparent higher stability (forms in multiple solvent systems) relative to the pure 6-nitro isomer is analogous to the often reported "disappearing polymorphs" phenomenon.[8]

Having lost our control point for rejection of the 4-nitro isomer, the 4:1 mixture of **9** isomers was evaluated in the downstream chemistry. Elimination of the alcohol with Amberlyst 15 resin in toluene at 100 °C afforded 5-nitroindene (**10**). The alkene was stable toward isomerization under these conditions in a nonpolar solvent, but other conditions lead to isomerization. NMR solutions in polar solvents such as methanol or DMSO gave isomerization on standing. Addition of Et_3N increased the rate of isomerization as expected on the basis of literature studies.[9] In this respect, Amberlyst 15 provided a benefit versus the literature protocol using *p*-toluene sulfonic acid, because aqueous $NaHCO_3$ washes required to remove *p*-toluene sulfonic acid led to variable amounts of alkene isomerization.[2a,5c] Nitroindene **10** was not isolated but was carried forward as a toluene/CH_2Cl_2 solution into an epoxidation with *m*-CPBA. After a base wash to remove *m*-CBA, a solvent exchange to heptane resulted in crystallization of epoxide **11**. This crystallization efficiently purged the 4-nitro isomer carried in with the alcohol substrate. For the batch with a 4:1 mixture of alcohols, the 4-nitro isomer was controlled to <0.4 area % by HPLC. For the two batches containing 1.2% of the undesired isomer, the 4-nitro isomer was <0.1 area % at the stage of epoxide **11**.

Conversion of the epoxide to racemic aminoindanol ***rac*-7** has been reported using NaN_3 followed by reduction[10] or with NH_3.[11] Due to azide safety concerns, the ammonia process was selected for scale-up. Despite the 91% yield reported for this

(5) (a) Wan, P.; Davis, M.-A.; Teo, J. *J. Org. Chem.* **1989**, *54*, 1354–1359. (b) Buckle, D. R.; Arch, J. R. S.; Edge, C.; Foster, K. A.; Houge-Frydrych, C. S. V.; Pinto, I. L.; Smith, D. G.; Taylor, J. F.; Taylor, S. G.; Tedder, J. M.; Webster, R. A. B. *J. Med. Chem.* **1991**, *34*, 919–926. (c) Castle, N. A.; Hollinshead, S. P.; Hughes, P. F.; Mendoza, J. S.; Wilson, J. W. Amato, G.; Beaudoin, S.; Gross, M.; McNaughton-Smith, G. PCT Int. Appl. WO 199904778. (d) See ref 2.

(6) Preparation of resolved salt **12** was completed in the pilot plant, and the remaining steps were completed in the kilolab.

(7) Sumikin is now Air Water Chemical Co., Ltd.

(8) Although not comparing two polymorphs, the current situation shows how formation of a more stable crystal form will make it difficult or impossible to generate the original form, see: (a) Dunitz, J. D.; Bernstein, J. *Acc. Chem. Res.* **1995**, *28*, 193–200.

(9) Friedrich, E. C.; Taggart, D. B. *J. Org. Chem.* **1975**, *40*, 720–723.

(10) See ref 5b.

(11) See refs 2a, 5c, and 5d.

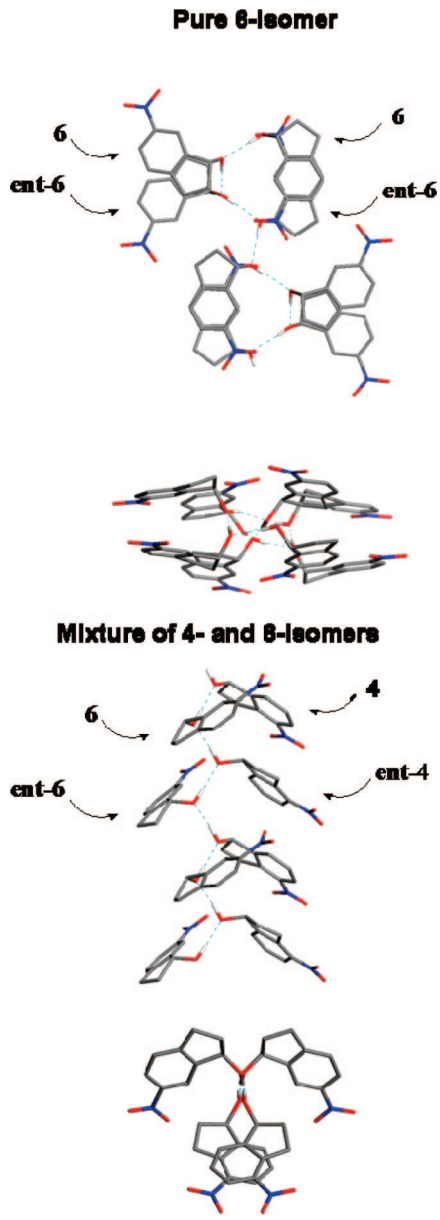
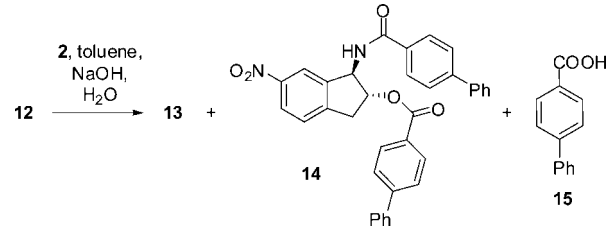


Figure 1. **Hydrogen-bonding networks of 6-nitroindanol 9 and 4-/6-nitroindanol cocrystal of 9.**

transformation, an efficient isolation procedure has not been described. In order to refine the isolation, we developed a telescoped procedure that proceeded to the resolution without isolation of the racemic amine. The ring opening was best achieved using aqueous NH_4OH, despite the low solubility of the epoxide in this medium.[12] Treatment of epoxide **11** with 14 volumes of concentrated NH_4OH and 4 volumes of H_2O at 36 °C for 21 h resulted in consumption of the epoxide via a slurry-to-slurry process.[13] With this large excess of NH_4OH, bis-alkylation was effectively suppressed, but black insoluble material was also formed. Higher temperatures were not utilized due to ammonia off-gasing and increased formation of black byproduct. The crude ***rac*-7** was isolated by a slow pressure filtration (to avoid NH_3 off-gasing) using Celite as a filter aid. To the resulting wet cake, containing product, Celite, and the black byproduct, were added methanol, H_2O and (*S*)-(+)-mandelic acid. The mandelic acid served to dissolve ***rac*-7** such that the Celite and black byproduct could be removed by filtration through a carbon impregnated cartridge in a CUNO Zeta Plus filter. The colorless filtrate was concentrated, and EtOAc was added to crystallize the mandelic acid salt in nearly racemic form (1.1 to 1.5/1 mixture of diastereomers). A recrystallization from aqueous MeOH consistently afforded the resolved mandelic acid salt **12** in high ee (>97%) and 22−25% overall yield from epoxide **11**. The synthesis above was suitable for our initial campaign, especially with the telescoped processes from **9** to **11** and **11** to **12**, but the overall efficiency and *e*-factor[14] were not desirable. These deficiencies were addressed after completion of the initial kilolab campaign (see below).

Synthesis of Aniline 4. With a scaleable synthesis of enantiomerically enriched aminoindanol **7** in hand, we moved to investigation of the side-chain installation (Scheme 2). Typical Schotten−Baumann[15] acylation of the resolved salt **12** was effected using 1.1 equiv of acid chloride **2** in a heterogeneous reaction in toluene and aqueous NaOH. The only significant byproduct on laboratory scale was the hydrolysis product **15** (~5 area %), and this acid was effectively rejected to the mother liquor in the nitro reduction step. However, scale-up in the kilolab gave high levels of the bis-acylated byproduct **14**: approximately 5% each of **14** and acid **15** (Scheme 3). An expedient reslurry process in EtOAc was used to purge the bis-acylated byproduct and provide amide **13** of suitable quality for forward processing (<0.5% **14**).

Scheme 3. **Schotten−Baumann acylation**



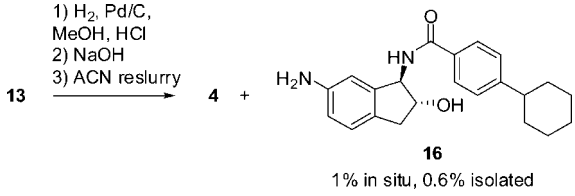
Initially it was speculated that poor agitation could explain the poor results in the kilolab, but subsequent laboratory work showed that a slow filtration versus the laboratory model allowed additional contact time between amide **13** and unreacted acid chloride **2** and increased formation of bis-acylated **14**. Optimization efforts in support of a subsequent pilot-plant campaign showed that the extreme insolubility of amide **13** in toluene or CH_2Cl_2 (solvents appropriate for Schotten−Baumann two-phase conditions) led to crystallization of fine particles and an inherently slow filtration. The best case used CH_2Cl_2 and a slow addition of acid chloride **2**, but further Ostwald ripening[16] was not possible due to low product solubility. Ultimately, a MeOH reaction quench was inserted in order to consume excess acid chloride **2** after an acceptable conversion of **12** was

(12) Other conditions, including NH_3/alcohol mixtures, gave more byproducts.
(13) The particle size of the epoxide and the stir rate had an impact on the reaction rate. In the lab, best results were obtained with epoxide that had been ground with a mortar and pestle, but surprisingly no particle size reaction rate dependence was found on scale-up.
(14) Sheldon, R. A. *Chem. Ind. (London)* **1997**, 12. Sheldon, R. A. *Chem. Ind. (London)* **1992**, 903.
(15) Sonntag, N. O. V. *Chem. Rev.* **1953**, *52*, 237–416 (see p 272). .
(16) Ng, J. D.; Lorber, B.; Witz, J.; Theobald-Dietrich, A.; Kern, D.; Giege, R. *J. Cryst. Growth* **1996**, *168*, 50–62.

achieved. Isolation of the product by filtration afforded amide **13** in 86−95% yield and >98.8 area % purity without the necessity of a reslurry in EtOAc (~0.5% of methyl ester from **2**, <0.5% acid **15**, <0.5% bis-acylated impurity **14**).

Reduction of the nitro amide **13** to the aniline **4** was complicated by the insolubility of amide **13** and by the necessity to drive the reaction to ppm levels of unreacted **13**. Genotoxicity testing showed that amide **13** was mutagenic in the AMES assay, and the Lilly toxicology group set a limit of <400 ppm of **13** in the API (kilolab campaign). Initial reaction development showed that, although aniline **4** was soluble in DMF, if too much 10% Pd/C catalyst was used, the product adhered to the carbon. The yield using 5 wt % of 10% Pd/C was 87%, decreasing to 83% with 10 wt % of Pd/C and 31% with 20 wt % of Pd/C. Due to insolubility, it was not possible to reject even ppm levels of unreacted **13** through crystallization from DMF/H_2O or several other solvents. A standard hydrogenation with 5 wt % of 10% Pd/C met the 400 ppm limit, but for the subsequent pilot-plant campaign, the toxicology limit was lowered to 10 ppm. Due to problems with residual DMF in the kilolab campaign, the solvent mixture was changed to MeOH/aqueous HCl for the pilot plant. The acid served to solubilize the aniline product for catalyst removal, and base was then added to crystallize the product. Using 30 wt % of 10% Pd/C (40% H_2O wet),[17] the reaction was scaled up in the pilot plant using *in situ* HPLC monitoring to ensure complete conversion. Unfortunately, the sample dip tube became contaminated after the first sample due to incomplete reaction. Further samples from the dip tube always showed residual amide **13**, so samples were pulled from the bottom valve. Due to delays in getting meaningful analytical samples, the reduction was continued for 3 days. As a result, a new byproduct **16** from reduction of the distal benzene ring was formed (Scheme 4). Partial rejection of impurity **16** was achieved by a reslurry in CH_3CN, and additional purging in the API isolation gave an acceptable level of the over-reduced API analogous to **16**.

Scheme 4. **Over-reduction byproduct**



Synthesis of Thioimidate 20. With aniline **4** in hand, synthesis of a suitably activated form of amide **5** was required for the amidine bond formation (Scheme 1). Amide **5** was initially prepared by alkylation of benzyl bromide **17** with *N*-methylacetamide (**18**) and was purchased for the pilot-plant campaign from Clariant. Amidine formation[18] by amide activation, typically under Vilsmeier conditions,[19] and coupling with aniline **4** gave poor yields of API **1**. A screen of known amidine coupling reagents[20] gave poor results, perhaps due to low solubility of aniline **4** in solvents that were compatible with the activating/dehydrating reagents. After some experimentation it was found that the relatively unreactive thioimidate **20**,[21] derived from the thioamide, was an appropriately activated intermediate. The requisite thioamide **19** was initially prepared using Lawesson's reagent,[22] but silica gel chromatography was required to remove excess reagent and reagent-derived byproduct. Phosphorus pentasulfide (exists as the dimer P_4S_{10}) was selected for scale-up.[23] For the kilolab campaign, a solution of amide **5** in THF was treated with 0.6 equiv (6 equiv if all 10 sulfurs react) of P_4S_{10} at reflux for 5 h. Laboratory screening in preparation for the pilot-plant campaign showed a tendency for the reaction mixture to aggregate into a sticky mass. To suppress this tendency, diatomaceous earth (50 mass % relative to P_4S_{10}) was added to the solution prior to addition of P_4S_{10}, and no aggregation tendency was observed in the laboratory or in the pilot plant. If the reaction was not complete (>3% amide **5**) after 16 h, an additional charge of 0.15 equiv of P_4S_{10} was added along with 50 mass % of diatomaceous earth. For one pilot-plant batch, a third charge of 0.10 equiv of P_4S_{10} was required to reach completion.

Deactivation of P_4S_{10} appears to be accelerated by an activation with various nucleophiles.[24] After initial formation of a more reactive/soluble form, a gelatinous/unreactive solid is produced. Fortunately, each additional charge of reagent provided additional conversion prior to eventual stalling. We propose that adventitious water acts as a nucleophile to break the P−S bond and liberate phosphate-thiol groups. Breaking the adamantane-like structure[25] of P_4S_{10} initially increases solubility, but intermolecular reaction of the liberated phosphate-thiol with more P_4S_{10} could give rise to an insoluble and unreactive polymer. In support of this proposal, we found that stirring a slurry of P_4S_{10} in THF for 1−2 h prior to addition of the substrate led to lower reactivity. Maintaining the reaction temperature at room temperature lowered the reaction rate, but more importantly, increased the period of reactivity prior to formation of the unreactive form.[26]

Thioamide **19** was activated as the thioimidate **20** (mixture of *E*and *Z* isomers) by reaction with 1.5 equiv of MeI (Scheme 5).[27] The thioimidate is reasonably stable to moisture but

(17) Loss of product to the Pd/C catalyst at this high loading was not observed in MeOH/HCl as it was in DMF.

(18) (a) Patai, S., Ed. *The Chemistry of Amidines and Imidates*; John Wiley and Sons: London, 1975. (b) Patai, S., Ed. *The Chemistry of Amidines and Imidates*; John Wiley and Sons: New York, 1991; Vol. 2.

(19) (a) Jones, G.; Stanforth, S. P. *Org. React.* **1997**, *49*, 1–330.

(20) Cai, L.; Han, Y.; Ren, S.; Huang, L. *Tetrahedron* **2000**, *56*, 8253–8262 and references therein. .

(21) (a) Gil, M. J.; Reliquet, A.; Reliquet, F.; Meslin, J. C. *Phosphorus, Sulfur Silicon Relat. Elements* **1994**, *97*, 89–94. (b) Shearer, B. G.; Oplinger, J. A.; Lee, S. *Tetrahedron Lett.* **1997**, *38*, 179–182. (c) See ref 18.

(22) Ozturk, T.; Ertas, E.; Mert, O. *Chem. Rev.* **2007**, *107*, 5210–5278.

(23) (a) Brillon, D. *Synth. Commun.* **1990**, *20*, 3085–3095. (b) Brillon, D. *Sulfur Rep.* **1992**, *12*, 297–338. (c) Polshettiwar, V. *Synlett* **2004**, 2245–2246.

(24) Activation of the insoluble P_4S_{10} with various nucleophiles provides a soluble and more reactive form of the reagent. However, as reported in ref 23a, these soluble forms are metastable and form an unreactive gelatinous mass over time.

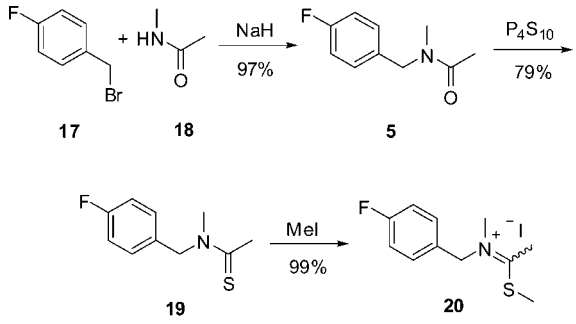
(25) See refs 22 and 23c.

(26) Yields were routinely in the 75−80% range, and the additional mass appeared to be trapped in the P_4S_{10}/diatomaceous earth cake. Extensive washing of the cake did not lead to recovery of additional material. Dissolution of the cake with NH_4OH and extraction afforded some additional product and several byproducts, see: Stahly, B. C. U.S. Patent 4,935,510, 1990.

(27) (a) Peak, D. A.; Stansfield, F. *J. Chem. Soc.* **1952**, 4067–4075. (b) Gompper, R.; Elser, W. *Organic Syntheses*; John Wiley and Sons; New York, 1973; Collect. Vol. V, p 780.

afforded 7% of *N*-4-fluorobenzyl-*N*-methylamine-HI after storage at 5 °C for one year. Material of this quality can still be used in the amidine formation reaction. Hydrolysis or reaction afforded a stoichiometric amount of methane thiol; thus, handling in a hood or use of a bleach scrubber during reaction is a necessity.

Scheme 5. **Synthesis of thioimidate for coupling**



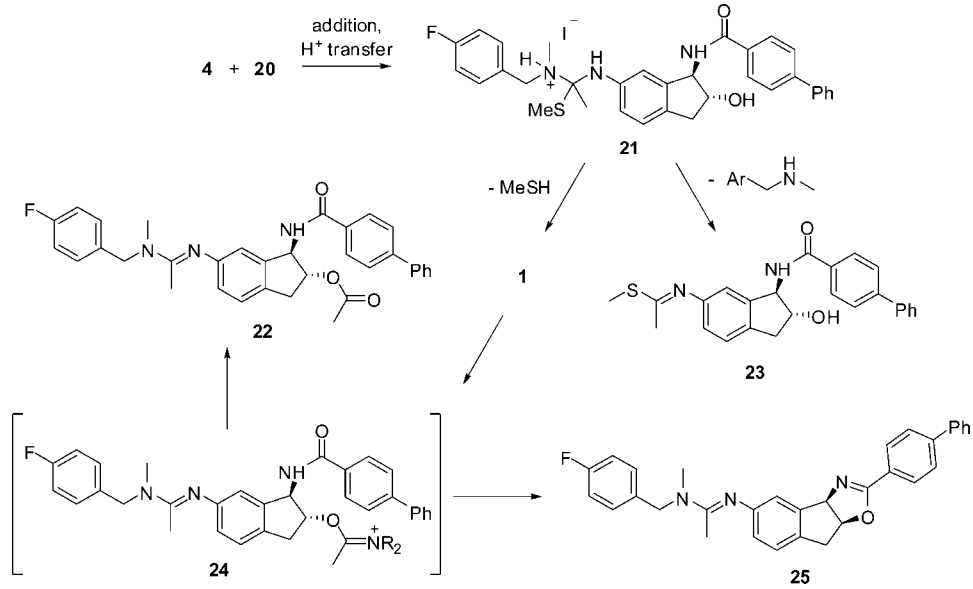
Synthesis of Amidine 1. An initial screen of reaction conditions for coupling of aniline **4** with thioimidate **20** showed that THF and 10 mol % DMAP gave the best conversion and impurity profile (Scheme 2). Due to poor solubility of **1**, CH_2Cl_2 was required for an aqueous base workup to remove HI, and then the solvent was changed to CH_3CN in order crystallize **1** as a partial CH_3CN solvate. The preferred final form was identified as a hemihydrate,[28] but many water miscible solvents tended to form organic solvates. Methanol was optimal among the alcohols in providing the desired hemihydrate with no evidence for formation of a solvate. Due to formation of long, thin, needle-shaped crystals that cracked and produced fines during filtration, slow filtrations were an inherent problem. Attempts to grow larger crystals through Ostwald ripening[29] were thwarted by hydrolysis of the amidine after prolonged heating. Despite these constraints, a suitable process for hemihydrate formation was successfully implemented for the kilolab API delivery.

Further screening was initiated to understand the role of DMAP and provide a more facile and/or higher-yielding amidine formation. The main impurities formed in the reaction were identified, and a proposed mechanism for formation of these impurities is shown (Scheme 6). Addition of aniline **4** to the iminium double bond and proton transfer to the more basic nitrogen would afford tetrahedral intermediate **21**. Loss of the benzyl amine fragment would afford the main byproduct observed by *in situ* HPLC, iminothioether **23**. The presence of a base should suppress formation of the iminothioether by forming a neutral tetrahedral intermediate that would have an increased proclivity to eliminate methane thiol. Excess thioimidate **20** can react with the alcohol of the desired product **1** to activate for ring closure to oxazoline **25** or hydrolysis to acetate **22**. The latter byproducts were suppressed by fixing the **4**:**20** stoichiometry at 1:1. Further screening of bases and acylation catalysts like DMAP[30] is summarized in Table 1. Three general conclusions are clear: (1) base-suppressed formation of the iminothioether **23**, (2) high levels of base (except DMAP)-suppressed conversion, and (3) DMAP counterbalanced the reaction rate suppression seen with other bases. Entries 1−4 show that DMAP increased the reaction rate and suppressed

Table 1. **Base and acylation catalyst impact on amidine formation**

entry number	additive(s), equiv	% conversion, 16 h	% thioether **23**
1	none	99.9	4.6
2	DMAP, 0.01	98.7	5.1
3	DMAP, 0.1	99.5	1.8
4	DMAP, 1	99.9	0
5	Bu_3P, 0.1	99.3	5.2
6	Bu_3P, 1	99.6	2.2
7	DBU, 0.1	99.3	5.5
8	DBU, 1	61.4	0
9	Et_3N, 1	85.6	0.3
10	Et_3N, 0.2	97	3.4
11	Et_3N, 0.2 + DMAP, 0.1	99.6	0.5
12	K_2CO_3, 0.1	98.2	3.7
13	K_2CO_3, 0.5	95	0.9
14	K_2CO_3, 4	50	0.2
15	K_2CO_3, 0.5 + DMAP, 0.1	99.7	0.6

Scheme 6. **Amidine formation byproducts**

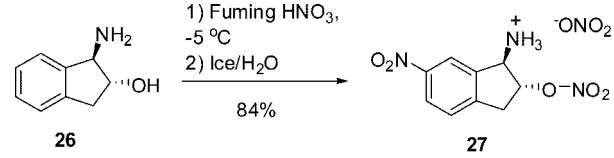


formation of **23** if 1 equiv was used. Due to toxicity and cost, using 1 equiv of DMAP in the final step was not desirable. DBU and tri-*n*-butylphosphine showed little impact at low levels and suppression of both **23** and conversion at high levels (entries 5−8). Et_3N and K_2CO_3 suppressed formation of **23** even at low levels, but gave unacceptable conversion when enough base was used to keep **23** below 1% (entries 9−10, 12−14). In both cases, a mixture of base and 0.1 equiv of DMAP provided a reasonable compromise between conversion and formation of **23** (entries 11 and 15). K_2CO_3 was chosen for the optimal process due to its use in a streamlined workup discussed below. In addition to serving as an auxiliary base, DMAP is presumably serving its typical role as an acylation catalyst.[31]

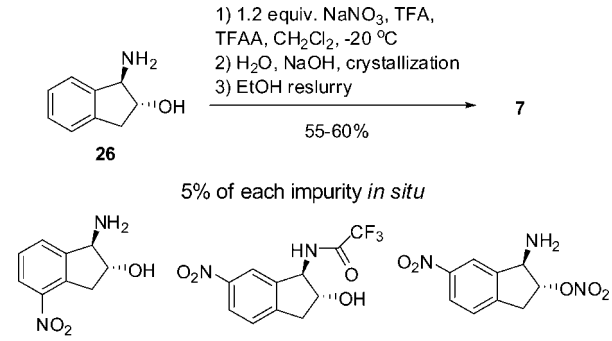
As described above, an aqueous workup with the undesirable solvent CH_2Cl_2 was utilized for the initial API delivery. Solubility constraints limited options for finding a better workup solvent, but it was recognized that the only workup needed was freebasing to remove HI. A novel solution to the freebasing problem was found by stirring the reaction mixture with 3.5 equiv of solid K_2CO_3. A practical problem arose in that it was not possible to determine the necessary stir time to ensure complete freebasing. This problem was solved by noting that iodide gave a significant peak by reverse-phase HPLC at 227 nm. The extent of freebasing was monitored by sampling the mother liquor and stirring until the iodide peak was no longer visible by HPLC (1 h). The final process used 0.5 equiv of K_2CO_3 plus DMAP during the reaction and 3.5 equiv of K_2CO_3 for freebasing after conversion to amidine **1** was complete. Simple filtration followed by solvent exchange into CH_3CN allowed for crystallization of amidine **1** as the partial CH_3CN solvate.

Improved Synthesis of Nitro-aminoindanol 7. Synthesis of clinical trial quantities of amidine **1** was enabled by the chemistry shown in Scheme 2, but the synthesis was long, and a resolution in the middle of the synthesis was highly undesirable. Several asymmetric approaches were considered. An obvious solution was an asymmetric epoxidation of 5-nitroindene (**10**). Good literature precedent is available for Jacobsen epoxidation[32] and enzymatic epoxidation,[33] and the Jacobsen route was demonstrated by the Lilly/Icagen discovery group.[34] However, an asymmetric synthesis analogous to Scheme 2 was still lengthy, and the epoxide opening provided an isolation challenge (mandelic acid was used to aid the isolation). Based on the literature precedent for selective meta-nitration of 1-aminoindan[35] an initial attempt to nitrate commercially available (1*R*,2*R*)-1-amino-2-indanol (**26**)[36] using standard nitration conditions[37] afforded the nitrate ester **27**, isolated as the nitrate salt (Scheme 7). This result was satisfying given the regiocontrol observed, but isolation of an intermediate with three nitro groups represented an unacceptable scale-up hazard.[38] In addition, nitrate esters are not readily hydrolyzed,[39] and reduction in the presence of the aromatic nitro group would provide a challenge.

Scheme 7. **Classical nitration-produced nitrate ester**



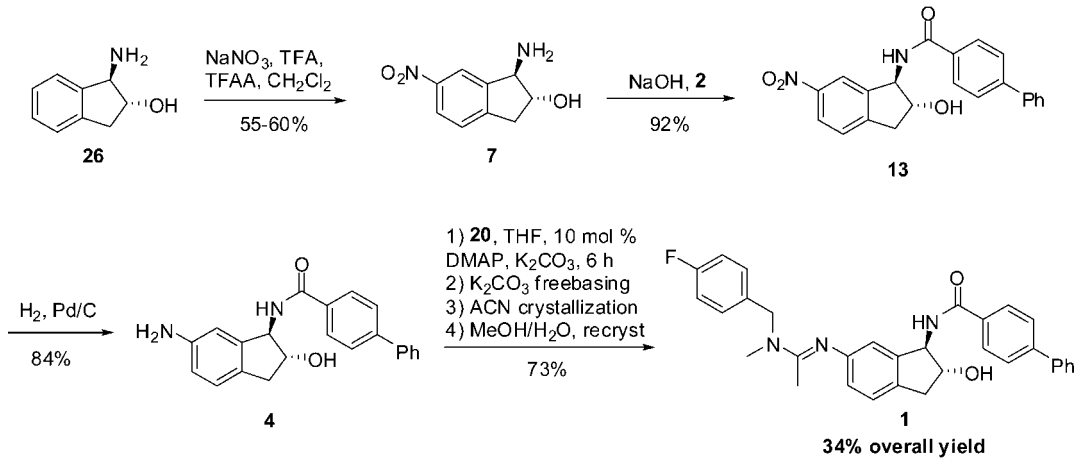
Scheme 8. **Scaleable synthesis of nitro-aminoindanol 7**



With this precedent in hand, an extensive screen of safe and scaleable nitration conditions that would avoid nitrate ester formation was initiated.[40] The mild conditions whereby $NaNO_3$ is activated with TFAA at low temperature proved optimal.[41] The reaction was conducted in a mixture of CH_2Cl_2 and TFA (to prevent reaction at the amine) at −20 °C and afforded about 5% of each byproduct shown, along with 5% starting aminoindanol **26** (Scheme 8). Attempts to drive the conversion increased the level of the nitrate ester. The safety of the reaction was

(28) Water is removed upon drying under vacuum, but equilibration in air restores the stable hemihydrate form. There is no change in the XRPD pattern for the dried form relative to the hemihydrate.
(29) See ref 16.
(30) (a) Murugan, R.; Scriven, E. F. V. *Aldrichimica Acta* **2003**, *36*, 21–27. (b) Scriven, E. F. *Chem. Soc. Rev.* **1983**, *12*, 129–162. (c) Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569–583. (d) Vedejs, E.; Bennett, N. S.; Conn, L. M.; Diver, S. T.; Gingras, M.; Lin, S.; Oliver, P. A.; Peterson, M. J. *J. Org. Chem.* **1993**, *58*, 7286–7288.
(31) Addition of DMAP to thioimidate **20** in an NMR reaction provided a complex mixture, showing the potential for DMAP to activate the thioimidate for addition of the aniline. See ref 22.
(32) Pospisil, P. J.; Carsten, D. H.; Jacobsen, E. N. *Chem. Eur. J.* **1996**, *2*, 974–980.
(33) (a) Schmid, A.; Hofstetter, K.; Feiten, H.-J.; Hollman, F.; Witholt, B. *Adv. Synth. Catal.* **2001**, *343*, 732–737. (b) Bernasconi, A.; Orsini, F.; Sello, G.; Colmenga, A.; Galli, E.; Bestetti, G. *Tetrahedron Lett.* **2000**, *41*, 9157–9162.
(34) Castle, N. A.; Hollinshead, S. P.; Hughes, P. F.; Mendoza, J. S.; Wilson, J. W. Amato, G.; Beaudoin, S.; Gross, M.; McNaughton-Smith, G. PCT Int. Appl. WO 199804521, 1998. and ref 2a.
(35) (a) Ingold, C. K.; Piggot, H. A. *J. Chem. Soc.* **1923**, *123*, 1469–1509. (b) Borne, R. F.; Forrester, M. L.; Waters, I. W. *J. Med. Chem.* **1977**, *20*, 771–776. (c) Initial experiments on *cis*-aminoindanol by Tianwei Ma were also promising.
(36) Both enantiomers are available from Aldrich and several other suppliers. (1*R*,2*R*)-1-amino-2-indanol (**26**) was purchased on kilo scale from Arran Chemical Company.
(37) (a) Olah, G. A.; Narang, S. C.; Olah, J. A.; Lammertsma, K. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 4487–4494. (b) *Nitration: Recent Laboratory and Industrial Developments*; Albright, L. F.; Carr, R. V. C.; Schmitt, R. J. ACS Symposium Series 623; American Chemical Society: Washington, DC, 1996, 1. (c) Moodie, R. B.; Schofield, K. *Acc. Chem. Res.* **1976**, *9*, 287–292. (d) Milligan, B. *J. Org. Chem.* **1983**, *48*, 1495–1500. (e) Ridd, J. H. *Acta Chem. Scand.* **1998**, *52*, 11. (f) Adams, J. P.; Box, D. S. *Contemp. Org. Synth.* **1997**, *4*, 415.
(38) Calculated heat of decomposition = 1.22 kcal/g.
(39) For a review of nitrate ester chemistry see: (a) Boschan, R.; Merrow, R. T.; van Dolah, R. W. *Chem. Rev.* **1955**, *55*, 485–510.

Scheme 9. **Synthesis API 1 via aminoindanol route**



augmented by the limited amount of nitrating agent available and the slow dissolution of $NaNO_3$ under these conditions. A standard workup under basic conditions and a reslurry in EtOH afford nitro-aminoindanol **7** in 55−60% yield and high purity (>99 area % by HPLC).

Conclusion

Two different synthetic routes to M1 agonist candidate **1** were described. The initial indanone route suffered from a late resolution and required eight steps to produce API **1** in 8% overall yield. The second-generation route started with the commercial, enantioenriched aminoindanol **26** and provided API **1** in four steps and 34% overall yield (Scheme 9). Challenges addressed in the synthesis include a nitro group reduction to afford ppm levels of unreacted Ar-NO_2 and a novel amidine formation under mild conditions via a DMAP/K_2CO_3 promoted reaction with the thioimidate **20**. A convenient protocol for freebasing the API was provided by stirring with solid K_2CO_3 and monitoring disappearance of HI by reverse-phase HPLC.

Experimental Section

^{1}H NMR spectra were obtained at 300, 400 or 500 MHz and ^{13}C NMR at 75, 100 or 125 MHz. Chemical shifts are in ppm downfield from internal tetramethylsilane. ^{1}H NMR data are tabulated in order: multiplicity, number of protons, coupling constant(s) in hertz. HPLC data was collected using a Zorbax SB-Phenyl column, 25 cm × 4.6 mm, size 5 microns, MeOH or CH_3CN with 0.1% TFA in H_2O, gradient from 60−90% aqueous through 95% organic, 265 nm (227 nm to monitor disappearance of iodide). GC data was collected using a DB-1 column, 30 m × 0.25 mm × 0.25 μm, 1 mL/min He carrier, FID detection, 1.0 μL injection volume, 280 °C injector, (1) 60 °C initial temperature, hold 2 min, (2) increase at 18 °C/min to 300 °C, (3) hold at 300 °C for 15 min.

Experimental Procedures

6-Nitro-1-indanol (9). To 17.4 kg (98.2 mol) of 6-nitro-1-indanone (**8**),[42] that contained approximately 20% of the 4-nitro isomer, was added 35 L of THF. In a separate tank, 155 L of 2B-3 EtOH (denatured with toluene) was cooled to −15 °C, and 1.02 kg (27.0 mol, 1.1 equiv) of $NaBH_4$ was added. The nitroindanone/THF solution was added over 30 min to the cold $NaBH_4$/EtOH slurry. The nitroindanone tank was rinsed with 25 L of THF. After 1 h, acetone (3.5 L) was added to quench excess $NaBH_4$, followed by 4.0 kg of concentrated HCl as necessary to adjust the pH to 3. The solvent was removed by distillation under vacuum down to 35 L. The mixture was filtered, and the tank and filter were rinsed with 140 L of MTBE. The filtrate was washed with 175 L of H_2O (3×). The organic layer was treated with 7 kg of Darco (carbon) and filtered, and the Darco was rinsed with 65 L of MTBE. Water was removed by azeotropic distillation under vacuum, molecular sieves (5 kg, 4Å powdered) were added, and the mixture was stirred for 6 h. The mixture was filtered, and the sieves were rinsed with 35 L of MTBE. The solvent was removed by distillation under vacuum down to 50 L of solution. Heptane (100 L) was added over 6 h. The resulting slurry was stirred for 6 days, and the solid was collected by filtration and rinsed with a cold mixture of 25 L of heptane and 15 L of MTBE. The solid was dried *in vacuo* at 45 °C for 16 h to afford 14.6 kg (84%) of alcohol **9** as a 4:1 mixture of 6-nitro and 4-nitro isomers (79.8% potency for 6-nitro isomer).[43]

1,2-Epoxy-6-nitroindane (11). To 7.25 kg (40.5 mol) of indanol **9** (79.8% potency, ∼20% of the 4-nitro isomer) was added 22 L of toluene and 0.73 kg of Amberlyst 15 resin. The mixture was heated at reflux for 3 h, cooled to rt, and filtered. The resin was rinsed with 75 L of CH_2Cl_2. This solution of 5-nitroindene (**10**)[44] was cooled to 0 °C, and 12.4 kg (70.3% potency, 50.5 mol, 1.2 equiv) of 3-chloroperoxybenzoic acid was added. The mixture was heated to 25 °C over 1 h and stirred for 23 h. The mixture was cooled to 0 °C and filtered, and the cake was rinsed with 110 L of CH_2Cl_2. The filtrate was washed

(40) For selective aromatic ring nitration with an electron-rich aryl, see: Grenier, J. *Synth. Commun.* **1999**, *29*, 1201.

(41) (a) Suri, S.; Chapman, R. D. *Synthesis* **1988**, 743. (b) Kowalcyk, B. A.; Roberts, P. N.; McEwen, G. K.; Robinson, J. *Org. Process Res. Dev.* **1997**, *1*, 355–358. (c) Boschan, R. *J. Org. Chem.* **1960**, *25*, 1450–1451. (d) Crivello, J. V. *J. Org. Chem.* **1981**, *46*, 3056–3060. (e) Romea, P.; Aragones, M.; Garcia, J.; Vilarrasa, J. *J. Org. Chem.* **1991**, *56*, 7038–7042. (f) After our work was completed, ref 2b described a related nitration approach. Protection of the alcohol via the sulfate ester prevented nitrate ester formation, but these classic nitration conditions in concentrated sulfuric acid present safety issues and a scale-up challenge to control the reaction and quench exotherm. In addition, four unit operations are required to afford the freebase nitro-aminoindanol **7**.

(42) Purchased from Sumikin. See ref 5a for preparation.

with a solution of 20.5 kg of Na_2SO_3 in 105 L of H_2O. The layers were separated, and the organic layer was washed with a solution of 3.4 kg of $NaHCO_3$ in 100 L of H_2O, followed by a solution of 1.0 kg of NaCl in 100 L of H_2O (2×). The solvent was distilled *in vacuo* down to about 30 L, and 70 L of heptane was added to afford a slurry. The solid was collected by filtration and washed with 30 L of heptane. The cake was dried *in vacuo* at 40 °C for 15 h to afford 4.53 kg (79% potency adjusted yield) of epoxide **11** as a white solid (99.78 area %, 0.22 area % 4-nitro isomer by GC). ^{1}H NMR (CD_2Cl_2) δ 3.07 (m, 1), 3.29 (d, 1), 4.20 (t, 1, J = 2.9), 4.35 (m, 1), 7.41 (m, 1), 8.15 (dd, 1, J = 8.4, 2.1), 8.32 (dd, 1, J = 2.2, 1.1). ^{13}C NMR (CD_2Cl_2) δ 35.00, 57.89, 58.08, 120.31, 124.18, 126.84, 143.14, 151.79.[45]

***rac-trans*-1-Amino-6-nitroindan-2-ol (ra-7). Laboratory-Scale Isolation.** To a flask equipped with a N_2 inlet and a magnetic stir bar were charged 20.0 g of mortar-and-pestle-ground epoxide **11** (0.113 mol, 1.0 equiv) and 335 mL of concd NH_4OH (14.5 N, 4.86 mol, 43 equiv). The purple slurry was stirred and heated at 35 °C for 16 h. The resulting dark slurry was transferred to a 1-L flask and agitated at ~10 Torr and 40 °C on the rotary evaporator in which the 1-L receiving flask was charged with 500 mL of ice H_2O. The ammonia was readily transferred from the warmed distillation flask to the cold H_2O of the receiving flask. After 15 min the receiving flask H_2O was recharged with another 500 mL of ice cold H_2O. After 30 min no odor of NH_3 could be detected in the distillation flask. The aqueous slurry was filtered on a pad of diatomaceous earth. The filter cake of product and diatomaceous earth was cut from the filter and slurried in 500 mL of hot methanol. The mixture was treated with 20 g of decolorizing carbon and stirred hot for 5 min. The warm suspension was filtered, and 500 mL of hot methanol was used as a rinse. Evaporation of the methanol under reduced pressure at 40 °C and drying in a vacuum oven afforded 14.6 g (67%) of ***rac*-7**. MS: m/z = 195 (M + 1). ^{1}H NMR (CD_3OD) δ 2.82 (dd, 1, J = 9, 7), 3.29 (dd, 1, J = 9, 7), 4.11 (d, 1, J = 6), 4.18 (m, 1), 7.40 (d, 1, J = 8), 8.10 (dd, 1, J = 8, 2), 8.24 (s, 1).[46]

(1*R*,2*R*)-1-Amino-6-nitroindan-2-ol, (*S*)-(+)-Mandelic Acid Salt (12). Kilo-Scale Telescoped Process. To 6.20 kg (35.0 mol) of epoxide **11** were added 85 L of concd NH_4OH and 28 L of H_2O. The mixture was heated at 36 °C for 21 h and then allowed to cool to rt. The reaction mixture was pressure filtered over a bed of H_2O wet Celite (Hyflo Super Cel, 10 kg) in a Zwag filter, and the cake was rinsed with H_2O. To the wet cake were added 155 L of methanol, 1.3 L of H_2O, and 5.80 kg (38.1 mol, 1.09 equiv) of (*S*)-(+)-mandelic acid. The mixture was heated for 2 h at 55 °C and filtered through a carbon-impregnated filter cartridge. The cake and filter were rinsed with 20 L of methanol. The filtrate volume was reduced by vacuum distillation to 35 L, and 130 L of EtOAc was added. The volume was reduced by vacuum distillation to 65 L. The mixture was cooled to −8 °C and stirred for 8 h. The slurry was filtered, and the cake was rinsed with 30 L of cold EtOAc. The filter cake was dried *in vacuo* at 40 °C for 10 h to afford 7.6 kg of solid. This solid was slurried in 30 L of methanol and 0.3 L of H_2O, and the mixture was heated at reflux for 0.5 h. The mixture was cooled to 45 °C over 0.5 h and stirred for 12 h, followed by cooling to 22 °C and stirring for 10 h. The solid was collected by filtration and rinsed with 5 kg of methanol. The cake was dried *in vacuo* at 40 °C for 8 h to afford 2.7 kg (22%) of resolved salt **12** (97.7% ee, 99.0 wt/wt % assay). $[\alpha]_D$ +48.1 (MeOH, c = 1.0). ^{1}H NMR (DMSO-d_6): δ 2.80 (dd, 1, J = 15, 8), 3.31 (dd, 1, J = 15, 8), 4.37 (m, 2), 4.70 (s, 1), 6.7−7.6 (br m, 8), 7.37 (d, 2, J = 9), 7.50 (d, 1, J = 9), 8.15 (dd, 1, J = 9, 2), 8.37 (s, 1). ^{13}C NMR (DMSO): δ 38.7, 61.7, 73.3, 77.0, 119.9, 123.8, 126.0, 126.3, 126.5, 126.6, 127.2, 127.5, 141.5, 142.6, 146.8, 148.9, 175.5. HRMS calcd for $C_9H_{10}N_2O_3$: 194.0691, Found: 194.0691. IR ($CHCl_3$) 1347, 1074 cm^{-1}. EA calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.57; H, 5.21; N, 8.04.

***N*-[(1*R*,2*R*)-2,3-Dihydro-2-hydroxy-6-nitro-1H-inden-1-yl]-[1,1′-biphenyl]-4-carboxamide (13).** To a biphasic mixture of toluene (9.6 L) and aqueous NaOH (4.8 L, 1 N, 4.8 mol, 2.6 equiv) was added resolved salt **12** (0.64 kg, 1.85 mol). After 1 h, 4-biphenylcarbonyl chloride (**2**) (0.44 kg, 2.0 mol, 1.1 equiv) was added in portions over 20−30 min. After 22 h, the solids were filtered under vacuum and rinsed sequentially with 0.5 L of toluene, 2 L of H_2O, and 2 L of toluene. The wet cake was dried *in vacuo* at 50 °C for 2 days to afford 0.74 kg (107% uncorrected yield) of amide **13** (~5 area % acid from **2** and 5 area % bis-acylated impurity). To 1.914 kg of amide **13** prepared in a similar manner was added 38.2 L of EtOAc. The slurry was stirred for 18 h, and the solid was collected by filtration and washed with 4 L of EtOAc. The solid was dried for 4 d at 45 °C under vacuum to afford 1.76 kg (92%) of amide **13** as a white solid (94.3 area %, 0.4 area % bis-acylated impurity, 4.7 area % acid; the acid was rejected to the filtrate in the next step). IR (KBr, cm^{-1}): 3293, 1640, 1549, 1528, 1345, 1329, 1086, 739; ^{1}H NMR (DMSO-d_6): δ 8.95 (d, 1, J = 7.8), 8.12 (dd, 1, J = 8.1, 1.8), 8.02−8.05 (m, 2), 7.81 (br s, 1), 7.72−7.82 (m, 3), 7.46−7.53 (m, 2), 7.37−7.42 (m, 1), 5.58 (d, 1, J = 5.7), 5.34 (t, 1, J = 7.5), 4.50−4.59 (m, 1), 3.33 (dd, 1, J = 16.5, 6.9), 2.86 (dd, 1, J = 16.5, 6.9); ^{13}C NMR (DMSO-d_6): δ 38.9, 61.3, 77.3, 118.8, 123.1, 125.9, 126.5, 126.8, 128.0, 128.1, 129.0, 129.9, 139.1, 142.9, 144.1, 146.9, 148.5, 166.5. HRMS calcd for $C_{22}H_{18}N_2O_4$: 374.1267, Found: 374.1266. EA calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.61; H, 4.86; N, 7.51. For the pilot-plant campaign, the following general procedure was developed: Nitro-aminoindanol **7** was slurried in 9 mL/g of CH_2Cl_2 and 17 mL/g of H_2O, and 1.6 equiv of 50% aqueous NaOH was added. A slurry of 1.15 equiv of acid chloride **2** in 12 mL/g of CH_2Cl_2 was added over 3−4 h. The slurry was stirred for 2 h, and 12 mL/g of MeOH was added to quench excess acid chloride. After stirring for 10 min, the agitation was stopped to allow layer separation, and the solid was collected by filtration. The cake was washed with 5 mL/g of H_2O followed by 10 mL/g of MeOH. The solid was dried to afford 86−95% yield of amide **13** (>98.8 area %,

(43) Characterization: see ref 5a for ^{1}H NMR. For a batch that gave predominantly the 6-nitro isomer: IR ($CHCl_3$): 3597, 1522 cm^{-1}. EA Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.11; H, 4.87; N, 7.72.

(44) See ref 5a for ^{1}H NMR and mp. EA Calcd for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69 Found: C, 67.01; H, 4.47; N, 8.74.

(45) See ref 5b for ^{1}H NMR and mp. EA Calcd for $C_9H_7NO_3$: C, 61.02; H, 3.98; N, 7.91 Found: C, 61.02; H, 4.04; N, 7.82.

(46) See refs 2b and 5b.

~0.5% of methyl ester from **2**, <0.5% bis-acylated impurity, >97.5% wt/wt % assay).

***N*-[(1*R*,2*R*)-6-Amino-2,3-dihydro-2-hydroxy-1H-inden-1-yl]-[1,1′-biphenyl]-4-carboxamide (4). Kilolab Procedure.** Pd/C 10 wt % (50% H_2O wet, 0.176 kg) was wetted with DMF (4 L), and the slurry was charged to a 10-gal autoclave. Amide **13** (1.7 kg) was added, followed by DMF (13.6 L). The autoclave was sealed, purged with nitrogen, and then pressurized to 50 psi of H_2. After 19 h, the mixture was filtered; 5 L of the DMF solution was added to H_2O (10 L), and the slurry stirred for 2 h. This operation was repeated twice to work up the entire reaction volume. The slurries were filtered together, and the resulting filter cake was washed with H_2O (3 × 7 L). The filter cake was dried *in vacuo* to afford aniline **4** (1.42 kg, 87.7%) as a white solid (97.2 wt/wt % assay). IR (KBr, cm^{-1}): 3584, 3364, 3277, 1632, 1543, 1326, 1073, 743. ^1H NMR (DMSO-d_6): δ 8.72 (d, 1, J = 9.0), 8.03−8.05 (m, 2), 7.72−7.79 (m, 4), 7.46−7.51 (m, 2), 7.39 (t, 1, J = 7.5), 6.82 (d, 1, J = 8.4), 6.39 (d, 1, J = 8.1), 6.34 (s, 1), 5.19−5.26 (m, 2), 4.88 (br s, 2), 4.32−4.42 (m, 1), 2.97 (dd, 1, J = 14.7, 7.2), 2.57 (dd, 1, J = 14.7, 8.1); ^{13}C NMR (DMSO-d_6): δ 20.8, 61.5, 77.8, 109.1, 113.4, 124.6, 126.0, 126.2, 126.8, 127.9, 128.0, 128.9, 133.3, 139.1, 142.5, 147.6, 166.0. HRMS calcd for $C_{22}H_{20}N_2O_2$: 344.1525; Found: 344.1525. EA calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.51; H, 5.84; N, 8.10.

Pilot-Plant Procedure. To 205 L of MeOH were added 15 kg of amide **13**, 5.4 kg of concd HCl, and 4.5 kg of 10% Pd/C (40% H_2O wet) slurried in 20 L of MeOH. The catalyst portable tank was rinsed with 10 L of MeOH (2×). After purging with nitrogen, the reaction mixture was subjected to 60 psi of H_2 at 30 °C for 3 d. The catalyst was removed by filtration over diatomaceous earth, and the cake was rinsed with 150 L of MeOH. The mixture was concentrated to 300 L by vacuum distillation, and 300 L of 0.2 N NaOH was added at 50−60 °C. After cooling to rt, the solid was collected by filtration and washed with 110 L of 1:1 H_2O/MeOH followed by 110 L of H_2O. The solid was dried at 50 °C under vacuum to afford 12.9 kg (93%) of aniline **4**. To 25 kg of aniline **4** prepared in this manner was added 1000 L of CH_3CN, and the slurry was heated at 70 °C for 24 h. After cooling to room temperature, the solids were collected by filtration and rinsed with 75 L of CH_3CN. The solid was dried at 50 °C under vacuum to afford 22.3 kg (90% recovery) of aniline **4** (98.8 area %, 100.4 wt/wt % assay).

***N*-[(1*R*,2*R*)-6-[[1-[[(4-Fluorophenyl)methyl]methylamino]-ethylidene]amino]-2,3-dihydro-2-hydroxy-1H-inden-1-yl]-[1,1′-biphenyl]-4-carboxamide, Hemihydrate (1). Kilolab Procedure.** To a slurry of aniline **4** (0.969 kg, 2.8 mol) in THF (9.7 L) at rt was added thioimidate **20** (0.954 kg, 2.8 mol) and DMAP (34.5 g, 0.28 mol). When HPLC indicated that thioimidate **20** was <2 area % (20−24 h), the mixture was transferred to a rotary evaporator, and the solvent was removed *in vacuo*. The resulting foam was dissolved in CH_2Cl_2 (12.5 L), and the organic phase was washed with 1.0 N $HCl_{(aq)}$ (1 × 4 and 1 × 3 L), 1.0 M $NaOH_{(aq)}$ (1 × 2.44 L) and sat. $NaCl_{(aq)}$ (1 × 4 L). The organic phase was separated, dried (Na_2SO_4, 2.5 kg), and filtered, and the solvent was removed *in vacuo* to yield crude amidine **1** as a solid (1.8 kg, 93.5 area % by HPLC). The solid was dissolved in acetonitrile (9 L) while heating to 35−40 °C. After 1/2 h, seed crystals were added, and a thick, white slurry formed. The mixture was cooled to −10 to −15 °C in an ice/acetone bath and stirred for 1−2 h. The slurry was filtered, and the resulting solid was rinsed with cold acetonitrile (2 × 0.5 L) and dried *in vacuo* to provide amidine **1** as a partial CH_3CN solvate (1.10 kg, 77%, 98.6 area % by HPLC). Three CH_3CN solvate lots (2.86 kg) were combined and dissolved in 21.8 L of methanol. The solution was passed through a 0.45 μm carbon impregnated filter, and the tank and filter were rinsed with 24 L of methanol. To the solution was added 5.7 kg of H_2O over 35 min followed by 15 g of seed crystals. After 20 min, 1.15 kg of H_2O was added followed by 15 g of seed crystals. After 1 h, 1.15 kg of H_2O was added over 30 min followed by 15 g of seed crystals. After 10 min, 3.4 kg of H_2O was added over 1 h, and the slurry was stirred at rt for 1 h and at 0 °C for 45 min. The solid was collected by filtration, rinsed with a cold solution of 11.4 L of methanol and 2.9 L of H_2O, and dried under vacuum at 50 °C for 24 h. The solid was equilibrated in air for 4 h to afford amidine **1** as a white solid (hemihydrate), 2.19 kg, 76% recovery (typical laboratory recovery is 87%, but the wash of the carbon impregnated filter was inadequate on scale), 99.3 area % by HPLC, 99.5 wt/wt % assay. $[\alpha]_D$ +105.2 (MeOH, c = 1.0). IR ($CHCl_3$, cm^{-1}): 3489, 1643, 1606, 1600, 1509, 1482. ^1H NMR ($CDCl_3$): δ 7.90 (d, 2, J = 8.6), 7.69 (d, 2, J = 8.6), 7.63 (d, 2, J = 8.2), 7.48 (t, 2, J = 8.2, 7,6), 7.41 (d, 1, J = 7.3), 7.24 (dd, 2, J = 8.5, 5.2), 7.14 (d, 1, J = 7.9), 7.04, (t, 2, J = 8.7), 6.72−6.63 (m, 3), 5.31 (t, 1, J = 5.6), 4.84 (br s, 1), 4.64 (dd, 2, J = 21.4, 15.6), 4.54 (dd, 1, J = 14.0, 7.9), 3.32 (dd, 1, J = 15.6, 7.9), 3.01 (s, 3), 2.95 (dd, 1, J = 15.7, 8.0), 1.97 (s, 3). ^{13}C NMR ($CDCl_3$): δ 15.3, 36.2, 38.3, 52.6, 65.2, 82.7, 115.7, 115.8, 116.7, 123.2, 125.9, 127.5, 127.6, 127.9, 128.4, 128.9, 129.2, 132.2, 133.8, 134.2, 139.7, 140.0, 145.1, 151.8, 157.6, 163.2, 169.7. MS (m/z): 508.2 (M + 1). EA calcd for $C_{32}H_{30}N_3O_2 \cdot {}^1/_2 H_2O$: C, 74.40; H, 6.05; N, 8.13. Found: C, 74.50; H, 5.93; N, 8.17.

Amidine 1. Improved Process Laboratory Procedure. To a slurry of aniline **4** (10.04 g, 29.2 mmol), K_2CO_3 (2.01 g, 14.6 mmol, 0.5 equiv), and DMAP (0.356 g, 2.92 mmol, 0.1 equiv) in THF (100 mL) under nitrogen at ambient temperature was added thioimidate **20** (9.89 g, 29.2 mmol, 1.0 equiv). After stirring overnight, K_2CO_3 (14 g, 101 mmol, 3.5 equiv) was added. After 6 h, the solids were removed by filtration and the filtrate was concentrated *in vacuo*. The resulting tan foam (18 g) was dissolved in CH_3CN (100 mL), and a thick, white slurry resulted within 10 min. The slurry was stirred 2 h at ambient temperature, then 2 h in an ice/H_2O bath. The crystals were collected by filtration, washed with cold CH_3CN (2 × 10 mL), and dried overnight *in vacuo* at 50 °C to afford 12.47 g (84%) of amidine **1** as a partial CH_3CN solvate (99.1 area % by HPLC). The hemihydrate was formed using the procedure above.

***N*-(4-Fluorobenzyl)-*N*-methylacetamide (5).** To 224 g (134 g corrected for mineral oil, 5.55 mol, 1.2 equiv)

of sodium hydride (60% dispersion in mineral oil) as a slurry in THF (8.75 L) was slowly added a solution of 375 g (5.13 mol, 1.12 equiv) of *N*-methylacetamide (**18**) in THF (1.76 L). After 30 min about 25% of the solution had been added, and the temperature had increased from 19 to 29 °C. At this point, addition of 875 g (4.63 mol, 1 equiv) of 4-fluorobenzylbromide (**17**) was started, and the remaining **18** and **17** solutions were added concurrently over 3 h. A H_2O bath was used to maintain the temperature below 40 °C. The resulting mixture was stirred overnight and then poured into a mixture of 20% NH_4Cl (2.5 L), H_2O (6.5 L), and EtOAc (9 L). The layers were separated, and the aqueous layer was back-extracted with EtOAc (4.5 L, then 2 L). The organic layers were combined and washed with H_2O (4 L) and then brine (7 L). The organic layer was dried (Na_2SO_4), and the solvent was removed to afford a residue. The residue was dissolved in CH_3CN (7 L) and heptane (1.75 L). The layers were separated, and the CH_3CN layer was washed again with heptane (1.75 L). The heptane layers were combined and back-extracted with CH_3CN (0.5 L). The CH_3CN layers were combined and evaporated to afford 0.814 kg (97%) of amide **5** (96 wt/wt % assay by GC). Mp = 48−54 °C. ^{1}H NMR ($CDCl_3$): δ 7.27−6.93 (m, 4), 4.5 (d, 2), 2.91 (s, 3), 2.14 (s, 3). ^{13}C NMR (rotamers, F-coupling, DMSO-d_6): δ 21.2, 21.4, 32.9, 35.2, 48.9, 52.5, 114.9, 115.2, 115.3, 115.5, 128.5, 128.6, 128.9, 129.4, 129.5, 133.59, 133.63, 134.0, 134.1, 159.6, 159.7, 162.9, 163.0, 169.7, 169.8. EA calcd for $C_{10}H_{12}FNO$: C, 66.28; H, 6.68; N, 7.73. Found: C, 66.57; H, 6.92; N, 7.52. For the pilot-plant campaign, amide **5** was purchased from Clariant.

***N*-(4-Fluorobenzyl)-*N*-methylthioacetamide (19).** Amide **5** (0.500 kg, 2.76 mol) was dissolved in THF (11.5 L). Phosphorus pentasulfide[47] (P_4S_{10}, 0.737 kg, 1.65 mol, 0.6 equiv) was added, and the mixture was heated at reflux. After 5 h, the mixture was allowed to cool to rt, and the solids were filtered and washed with 12.5 L of THF. The filtrate was combined with an identical filtrate from a separate reaction and concentrated *in vacuo* to 0.978 kg of residue. The residue was dissolved in CH_2Cl_2 (4 L) and applied to silica gel 60 (2.7 kg) that was preconditioned with CH_2Cl_2. Elution with CH_2Cl_2 (27 L) and concentration of the product containing fractions afforded 1.01 kg of solid. The solid was slurried with CH_2Cl_2 (1 L) for 15−30 min. Heptane (5 L) was added, and the mixture was cooled to 0−5 °C and stirred for 2 h. The solid was collected, rinsed with heptane (1.5 L), and dried at 50 °C *in vacuo* to afford 0.814 kg (75%) of thioamide **19** (100.7 wt/wt % assay by GC). Mp = 99−104 °C. IR ($CHCl_3$, cm^{-1}): 2974, 1607, 1511, 1407. ^{1}H NMR (partial protons due to rotamers, $CDCl_3$): δ 7.35−7.26 (m, 1), 7.14−6.96 (m, 3), 5.28 (s, 1.2) and 4.79 (s, 0.8), 3.42 (s, 1.2) and 3.15 (s, 1.8), 2.72 (s, 1.2) and 2.69 (s, 1.8). ^{13}C NMR (rotamers, F-coupling, DMSO-d_6): δ 32.23, 32.71, 42.24, 56.40, 56.43, 115.06, 115.34, 115.51, 115.80, 128.61, 128.72, 129.50, 129.61, 131.92, 131.95, 132.09, 132.13, 159.83, 159.87, 163.05, 163.10, 199.42, 200.00. EA calcd for $C_{10}H_{12}FNS$: C, 60.88; H, 6.13; N, 7.10. Found: C, 60.92; H, 6.17; N, 7.17. For the pilot-plant campaign, diatomaceous earth (50 mass % relative to P_4S_{10}) was added prior to addition of P_4S_{10}, and the reaction temperature was changed to rt. If the reaction was not complete (>3% amide **5**) after 16 h, an additional 0.15 equiv of P_4S_{10} was added along with diatomaceous earth. For one batch, a third charge of 0.10 equiv of P_4S_{10} was required to reach completion. Filtration, silica gel treatment and crystallization from CH_2Cl_2 and heptane as described above afforded thioamide **19** as expected (79% yield).

(*E*,*Z*)-4-Fluoro-*N*-methyl-*N*-[1-(methylthio)ethylidene]benzenemethanaminium, iodide (20). To 2.30 kg (11.6 mol) of thioamide **19** were added 11.5 L of CH_3CN and 2.52 kg (17.7 mol, 1.5 equiv) of MeI. The mixture was heated at 35 °C for 21 h. The volume was reduced by half on a rotary evaporator, and 14 L of MTBE was added (repeat 2×). The resulting slurry was cooled to 0 °C, and the solid was collected by filtration. The solid was rinsed with 6 L of MTBE and dried in a vacuum oven at rt for 4 d to afford 3.92 kg (99%) of thioimidate **20** as a white solid (99.7 area %). Mp 142−150 °C. MS: theoretical for iminium $C_{11}H_{15}FNS$: 212; Found: 212. IR ($CHCl_3$, cm^{-1}): 2944, 1604, 1588, 1513, 1235, 1161. ^{1}H NMR (DMSO-d_6): δ 7.44−7.51 (m, 4), 7.25−7.32 (m, 4), 5.27 (s, 2, isomer 1), 5.16 (s, 2, isomer 2), 3.62 (s, 3, isomer 1), 3.47 (s, 3, isomer 2), 2.92 (s, 3, isomer 1), 2.89 (s, 3, isomer 1), 2.88 (s, 3, isomer 2), 2.81 (s, 3, isomer 2); ^{13}C NMR (peaks grouped for isomers, DMSO-d_6): δ (17.1, 17.0), (22.5, 22.0), (44.4, 44.1), (59.6, 59.3), (115.74, 115.66), (116.03, 115.95), (127.94, 127.90), (129.10, 129.06), (130.2, 130.1), (160.47, 160.42), (163.72, 163.67), (193.8, 193.6). EA calcd for $C_{11}H_{16}FINS$: C, 38.72; H, 5.02; N, 4.10. Found: C, 38.33; H, 4.29; N, 4.07.

(1*R*,*R*)-1-Amino-6-nitroindan-2-ol (7). Nitration Procedure. To 160 L of CH_2Cl_2 were added 15.8 kg of aminoindanol **26** (0.105 mol) and 10.6 kg (0.125 mol, 1.18 equiv) of $NaNO_3$. The slurry was cooled to −15 °C, and 98.7 kg (0.87 mol, 8.2 equiv) of TFA was added over 90 min, maintaining the temperature at −20 °C. Following the acid addition, 60.8 kg (0.29 mol, 2.75 equiv) of TFAA was added over 90 min at −20 °C and rinsed in with 15 L of CH_2Cl_2. The slurry was stirred at −20 °C for approximately 5 h until aminoindanol **26** was <1 area % by HPLC. The reaction mixture was added to 95 L of H_2O at 0−5 °C over 60 min to quench excess TFAA. The reaction vessel was rinsed with 150 L of CH_2Cl_2 which was transferred into the quench vessel. To the quenched reaction mixture was added 260 L of 5 N NaOH at 0−5 °C. Additional 5 N NaOH was added in 6 L increments until pH = 13, and the mixture was stirred for 60 min.

(47) P_4S_{10} (aka phosphorus pentasulfide, P_2S_5) has a noxious odor and liberates the toxic and flammable gas hydrogen sulfide on exposure to moisture. All kilo-scale reaction mixtures should be vented to an NaOCl/NaOH scrubber, and lab-scale experiments should be in a fume hood.

The product was collected by filtration and washed with 210 L of cold H_2O. The product was dried in a vacuum oven at 35−40 °C to afford 12.3 kg (60%) of **7** as an off-white solid: 98.4 area %, 95.8 wt/wt % assay, 0.23% H_2O (KF). These results were similar to the laboratory results, but the isolation/cake rinse protocol proved to be nonrobust with three additional lots providing **7** with purity as low as 91.8 area % and wt/wt % assay as low as 66%. Inefficient rejection of sodium trifluoroacetate, aminoindanol **26**, and the nitrate ester explained the low potency. For these three lots, a reslurry in 8 mL/g of 3A EtOH (contains 5% MeOH) at 50 °C followed by rt filtration and a 3 mL/g H_2O rinse afforded **7** in 85−90% recovery with purity >99.2 area % and >98.6 wt/wt % assay.

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Supporting Information Available

X-ray crystallographic data for the structures in Figure 1 (6-nitro isomer **9** and the 6-nitro/4-nitro isomeric mixture). This material is available free of charge via the Internet at http://pubs.acs.org.

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