Organic Process Research & Development **2006**, *10,* 1205–1211

# Development of a Manufacturing Process for 1-(1-Pyridin-2-yl methyl-piperidin-4-yl)-1*H*-indole: A Key Intermediate for Protein Kinase C Inhibitor LY317615

Sathish Boini,[†] Kenneth P. Moder,*[,†] Radhe K. Vaid,[†] Micheal Kopach,[‡] and M. Kobierski[‡]

*Chemical Product Research and Development, Eli Lilly and Company, Tippecanoe Laboratories, 1650 Lilly Road Shadeland, Indiana 47909, U.S.A., and Chemical Process Research and Development, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285, U.S.A.*

**Abstract:**

**This contribution describes process development leading to the production of 1-(1-pyridin-2-yl methyl-piperidin-4-yl)-1*H*-indole (11). The title compound 11 was produced via a Leimgruber−Batcho indole synthesis using key intermediates 2-(2,2-dimethoxyethyl)benzenamine (6) and, 1-(2-pyridinylmethyl)-4-piperidinone camphor sulfonate (9). Direct crystallization of 11 from IPA or ethanol−water was developed to provide (11) with <1% impurities and high yield (78%). The combined process leads to a five-step synthesis of 11 that was efficient and reflected Eli Lilly and Company's commitment to implementation of environmental friendly processes whenever feasible.**

## Introduction

Most solid tumors increase in mass though proliferation of malignant and stromal cells leading to formation of tumor vasculatures. LY317615, an investigatory new drug, is an inhibitor for protein kinase C which is presently under evaluation in the clinic for the treatment of glioblastoma. The mode of action of LY317615 is to prevent angiogenesis by cancer cells during tumor growth.[1]

Our goal was to evolve the operative small scale synthesis[2] for the key starting material 1-(1-pyridin-2-yl methyl-piperidin-4-yl)-1*H*-indole (**11**) (Scheme 1) into a scalable, robust manufacturing process capable of producing multiton quantities of high quality **11** in a cost-effective and environment friendly manner where feasible.

## Results and Discussion

Faul et al. developed a synthetic protocol that was sufficient for lab scale and small pilot scale production of 2-(2,2-dimethoxyethyl)benzamine (**6**) from *o*-nitrotoluene **1** (Scheme 1).[2] As the project proceeded towards full scale production, 1-(2-pyridinylmethyl)-4-piperidinone camphor sulfonate (**9**)[3] and subsequent coupling with **6** were identified as key steps which required optimization.[2] As part of the overall process development strategy, each step in the synthesis was examined with respect to optimum conditions and special considerations needed for reagents, reaction conditions, robustness, and minimization of the environmental impact.

**Amino Acetal 6 Synthesis. Enamines 3 and 4.** Generation of enamine (*E*)-1-[2-(2-nitrophenyl)ethenyl]pyrrolidine **3** using DMF−dimethylacetal in DMF and pyrrolidine at 80 °C has been described previously.[2] It was later determined by $^1$H NMR that this reaction results in a mixture of enamines **3** and (*E*)-1-[2-(2-nitrophenyl)ethenyl]dimethylamine **4** in a ratio of 85:15 as shown in Scheme 1. Impediments to full scale production of **3** and **4** were identified to be as follows: (1) purification of **3** and **4** by high vacuum distillation[4] would not be feasible due to thermal instability; (2) conducting the conversion of **2** to **3** and **4** at elevated temperatures bordered on the thermal stability of the reaction mixture;[4] (3) the need for the aqueous extractions so as to remove DMF which impedes conversion of **3** and **4** to 1-(2,2-dimethoxyethyl)-2-nitrobenzene (**5**); and (4) complications encountered during the aqueous extractive workup to remove DMF in the form of tary black-on-black layer separations coupled with the propensity to form stable emulsions. The key to the solution was DMF. Could this solvent be eliminated and the process conducted so as to afford **3** and **4** safely and in a form capable with the next step?

Eliminating the DMF permitted the facile removal, by simple atmospheric distillation, of the methanol at temperatures between 79 and 85 °C. The DMF cosolvent used in the initial protocol impeded the distillation of the MeOH byproduct thus prolonging the reaction time. Removing DMF, permitting ready removal of methanol, resulted in accelerating the conversion rate from 24 to 10 h. Eliminating DMF also eliminated the need for the subsequent problematic extractions. This change translated into several production oriented bonuses. First, the new process required a minimum equipment set. Second, the process cycle time was improved from ∼36 h to ∼15 h. Third, productivity would be improved as the batch size could be increased by 100%. Fourth, by

* To whom correspondence should be addressed. E-mail: moder_kenneth_p@lilly.com.

[†] Chemical Product Research and Development.

[‡] Chemical Process Research and Development.

(1) Graff, J. R.; McNulty, A. M.; Hanna, K. R.; Konicek, B. W.; Lynch, R. L.; Bailey, S. N.; Banks, C.; Capen, A.; Goode, R.; Lewis, J. E.; Sams, L.; Huss, K. L.; Campbell, R. M.; Iversen, P. W.; Neubauer, B. L.; Brown, T. J.; Musib, L.; Geeganage, S.; Thornton, D. *Cancer Res.* **2005**, *65* (16), 7462−9.

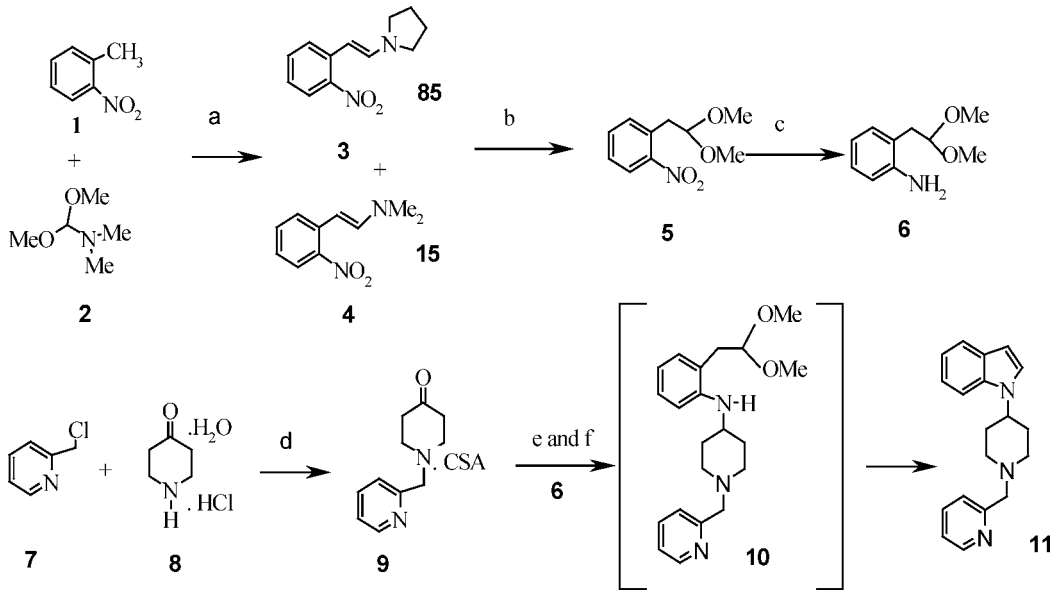
(2) Faul, M. M.; J. L.; Kobierski, M. E.; Kopach, M. E.; Krumrich, C. A.; Staszak, M. A.; Udodong, U.; Vicenzi, J. T.; Sullivan, K. A. *Tetrahedron* **2003**, *59*, 7215−7229.

(3) Faul, M. M.; Kobierski, M. E.; Kopach, M. E. *J. Org. Chem.* **2003**, *68* (14), 5739−5741.

(4) Accelerated rate calorimetry (ARC) data indicated an uncontrolled exotherm starting at 120 to 130 °C that negated higher temperatures as an option.

10.1021/op060068k CCC: $33.50 
Published on Web 10/24/2006

***Scheme 1.*** **Lab and pilot scale route to 11**[a]




[a] Reagents and conditions: (a) (i) DMF, pyrrolidine, 80 °C; (ii) MTBE/water; (iii) brine; (iv) MgSO4; (b) (i) TMSCl, MeOH; (ii) distill MeOH; (iii) EtOAc/water; (iv) concentrate; (v) MgSO4; (vi) heptane/EtOAc, silica gel, concentrate; (c) 5% Pd/C, MeOH, $H_2$, and concentration; (d) (i) $Na_2CO_3$/ACN; (ii) EtOAc, CSA; (e) (i) THF/$C_2H_5CO_2H$, $NaBH(OAc)_3$ $NaBH_4$; (f) (i) TFA/EtOAc; (ii) concentrate; (iii) IPA.

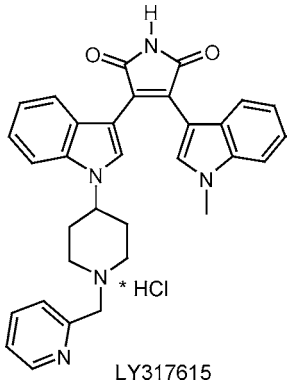



***Figure 1.*** **LY317615.**

eliminating the DMF one eliminated the problematic extractions so that the final product to waste ratio decreased from 1:51 g/mL to 1:1.6 g/mL without sacrificing yield, 95−99%. The final unexpected bonus was ARC data on the new reaction mixture that indicated that the thermal decomposition onset temperature was now 140 vs 120 °C. The temperature safety gap was now ∼60 °C that represents a huge safety improvement for production operations. The resulting MeOH stream could either be recovered or used as primary fuel for a waste incineration unit.

The improvements to the process for **3** and **4** would be for naught if one could not convert the new process material to **5**. Of concern was the impact, on step 2, of the step 1 reaction byproducts, *N*-formylpyrrolidine and corresponding orthoamide,[5] as confirmed by HPLC retention time matching and LC/MS data. Laboratory trials with the new process for **3** and **4** indicated no interference in the conversion to **5**.

**Acetal 5.** Enamines **3** and **4** were initially converted to **5** via in situ generated anhydrous HCl using TMSCl in methanol. The TMSCl method was sensitive to residual DMF that retarded the conversion of **3** and **4** to **5**. At issue with the original TMSCl method was the need for an extensive extractive workup, silica gel treatment, and finally a trituration with hot heptane to remove impurities. A literature survey revealed that several methods with alternate acids were known[6] to accomplish the desired transformation. Bulk commodity sulfonic acids such as *p*-toluenesulfonic acid monohydrate and sulfuric acid in methanol were found to work well. These sulfonic acids were not sensitive to residual DMF and were compatible with the new process enamines. In our hands, the *p*-TsOH process was more robust than the sulfuric acid modification with respect to reaction rate and impurity formation as confirmed by HPLC (area%). The sulfuric acid option was prone to generation of additional impurities, as detected by HPLC analysis. Our initial concern was whether residual acid could lead to reversion to **3** and **4** as predicted by Gallo et al.[7] Upon extending the distillation time for the removal of methanol postconversion to acetal, reversion was detected by HPLC analysis. Extensive heating resulted in near-complete reversion of **5** to enamines. The portent for reversion would be of concern in a production environment. The excess acid that not neutralized by the displaced pyrollidine was addressed in the original process after removal of the MeOH and dilution with EtOAc. The excess acid and salts were removed using aqueous bicarbonate or carbonate extractions. The need was to introduce a base prior to distillation of the methanol to prevent product reversion.

Potential options included liquid organic bases, deemed too expensive, or introduction of a cost-effective inorganic

(5) Wawer, I.; Osek, J. *J. Chem. Soc., Perkin Trans. II* **1985**, (10), 1669−1671.

(6) (a) Vinogradov, V. M.; Dalinger, I. L.; Starosotnikov, A. M.; Shevelev, S. A. *Mendeleev Commun.* **2000**, (4), 140−141. (b) Todd, M. H. *Org. Letters* **1999**, *1* (8), 1149−1151. (c) *Chem. Pharm. Bull.* **1981**, *29* (3), 726−738. (d) Cornell, L.; Richards, I. C. Schering Agrochemical LTD UK, patent, WO9107385, 1991.

(7) Bianchetti, G.; Pocar, D.; Croce, P. D.; Gallo, G. G.; Vigevani, A. *Tetrahedron Lett.* **1966**, *15*, 1637−1642.

***Table 1.*** **Stability of 5 postdistillation of methanol**

| | | % area[a] (**3** and **4**) | % area[a] impurities | % area[a] (**5**) |
|---|---|---|---|---|
| 1 | initial rxn mixture | <0.1 | 0.7 | 99.3 |
| | Flash Distillation | | | |
| 2 | control 1 (no base added) | 0.5 | 1.3 | 98.7 |
| 3 | control 2 (amb. 24 h stir) | 1.1 | 2.3 | 97.7 |
| 4 | $K_2CO_3$ | 0 | 1.4 | 98.6 |
| 5 | $CaCO_3$ | 0 | 0.9 | 99.1 |
| 6 | $Na_2CO_3$ | 0 | 1.6 | 98.4 |
| | Stressed: 55−60 °C for 30 min | | | |
| 7 | control 3 (no base added) | 3.72 | 52.8 | 47.2 |
| 8 | $K_2CO_3$ | 0 | 54.5 | 45.5 |
| 9 | $CaCO_3$ | 0 | 0.9 | 99.1 |
| 10 | $Na_2CO_3$ | 0 | 1.2 | 98.8 |

[a] Values reflect area percent without the contribution of *p*-TsOH where applicable.

base. The latter option was explored further. Addition of inorganic bases such as $Na_2CO_3$, $K_2CO_3$, and $CaCO_3$, prior to the distillation of methanol, was hoped to be effective at preventing the reversion reaction and other degradation pathways. Solid base was chosen so as not to introduce water and risk product hydrolysis. Solids addition to a flammable solvent mixture in production is not optimum; however the operation was feasible in production. The relatively small molar proportion of solid base did not give rise to concerns about off gassing, as the solids addition would be controlled. Laboratory trials were conducted to mimic the worse case, rapid charging of base. Considering the large heat sink, the volume of chilled MeOH (see experimental), the heat of neutralization should be dissipated quickly. Equally, the small volume of $CO_2$ expected to be released should be soluble in the reaction mixture. These expectations would be confirmed by laboratory and 7.5 L scale trials. The question was which base to use?

Multiple replicate trials were conducted to test the three prospective bases under control and stress conditions. Entry 1 in Table 1 reflected the reaction mixture prior to solvent removal, i.e., $T_o$. Entries 2, 4, 5, and 6 indicated the amount of impurities generated with and without base addition under rapid solvent removal. To test robustness, the sample in entry 1 was allowed to stir for 24 h prior to rapid solvent removal, and that in entry 2 was to test reaction mixture stability. The level of impurities nearly doubled. In a production environment, solvent removal, either atmospheric or under a vacuum, would require heating the vessel and thus subjecting material at the interface to elevated skin temperatures. A worse case production scenario, the entire reaction mixture was subjected to elevated temperatures for a short period of time, entries 7−10, Table 1. With no base added, entry 7, extensive degradation was observed with some product reversion to starting material as determined by HPLC. Addition of $K_2CO_3$, entry 8, prevented the reversion reaction but not the degradation. The potassium salt of *p*-TsOH was soluble under the test conditions. Addition of either $Na_2CO_3$ or $CaCO_3$ afforded excellent product stability, which were further evaluated as options for the production process. Both the sodium and calcium salts of *p*-TsOH were insoluble in the reaction mixture. Granulated or powdered $Na_2CO_3$ was preferred over calcium carbonate because $Na_2CO_3$ reproducibly inhibited reversion and degradation under normal and stressed conditions. The deciding factor was that the sodium *p*-toluenesulfonate byproduct was readily removed by filtration, whereas the calcium salt filtered poorly. The use of *p*-TsOH in this step followed by use of $Na_2CO_3$ prior to the vacuum distillation of methanol afforded **5** in >98% yield and >97% by HPLC (area %). Following an extractive water workup, the product was either isolated as an oil by removal of the extraction solvent toluene or held as a toluene solution. Elimination of the extensive workup protocol of the original process improved the product to waste ratio from 1:84 g/mL to 1:23 g/mL. Ultimately, the use of a toluene solution of **5** may lead directly into the reduction process for **6**. Further optimization of equivalents of acids should further improve the performance of this process.

**Amino Acetal 6.** Alcohol solvents were employed in the low $H_2$ pressure catalytic reduction of **5** to **6**. Use of alcohol solvents resulted in either leaching of the palladium from the carbon support or partial digestion of the carbon support. In either case, the amino acetal **6** was contaminated with black solids after solvent removal. Alternate solvents, MTBE, THF, EtOAc, and toluene, were evaluated with toluene being found superior with regards to lack of impurity generation, ease of catalyst removal, and limited catalyst support digestion or palladium leaching. Using toluene as the reduction solvent, yields > 95% were achieved with assays between 92 and 96% by HPLC (area %). The major impurity was indole.

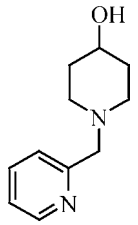
As amino acetal **6** was to be a key intermediate, product quality was paramount. The standard release assay for **6** needed to be >98% by HPLC (area %). The technical material produced by the process described fell just short of this goal. To achieve an assay of >98% by HPLC (area %), the crude product oil was vacuum distilled. The overall yields with distillation were 80 to 85% having assays of >98.5% by HPLC (area %). The major impurity, indole, was confirmed by HPLC retention time match and $^1$H NMR and comprised the bulk of the precut. The product to waste ratio remained consistent at 1:5 g/mL. The above process sequence has been run at a 7.4 L scale achieving the stated yields and assays. The combined product to waste ratio, **2** thru **6**, was 1:30 kg/L for the modified process vs the initial process ratio average of 1:140 kg/L.

**Synthesis of 11.** The parallel piece of the synthesis involved the alkylation of **8** with 2-picolyl chloride[8] **7** and salt formation to generate 1-(2-pyridinylmethyl)-4-piperidinone camphor sulfonate (**9**). The process involved condensation of **6** with **9** followed by reductive amination to **10**, ring closure of **10** under acidic conditions to form **11**, and isolation and purification by crystallization.[2,3] While essentially following Faul's procedure, subtle changes were incorporated to improve process reliability while maintaining the high level of product quality needed for downstream processing.

(8) Picolyl chloride HCl had a isomeric purity of >99% by HPLC (area %).

These subtle, but important, process modifications began with the preparation of **9**. Conducting the alkylation of **8** with **7** under a 2-fold increase in concentration coupled with increasing the temperature of the CSA salt formation step from 55 °C to 70 °C permitted isolation of **9** under controlled crystallization conditions vs precipitation. The original process for conversion of **9** to **10** was accomplished with the reagent[9] $NaBH(OAc)_3$ at 50 °C with yields in the range 50−60%. These conditions, using acetic acid as solvent, caused formation of acid-catalyzed cyclization of **6** to indole and the formation of 1-acetylindole. Reducing the reaction temperature to 20−25 °C improved yields to 80% and suppressed impurity formation. Drawbacks to using the triacetoxy borohydride reagent were instability of the reagent upon storage and solidification of the reagent below 18 °C.

Alternate acyloxborohydrides[10] have been used for similar conversions. Generation of a 1 M solution of $NaBH(OCOC_2H_5)_3$ in THF vs propionic acid performed admirably and exhibited excellent stability for several weeks when refrigerated; see Experimental Section. Using the alternate borohydride reagent with a propionic acid solution of **9** at −20 to −10 °C afforded in situ yields of **10** of 85−90%. Attempts at inverse addition or substitution of propionic acid with EtOAc, THF, MTBE, or toluene resulted in elevated levels (25−77% vs <8%) of the alcohol impurity **12**.




**12**

The original workup of the reduction reaction involved addition of EtOAc followed by pH adjustment to 8.5−10 at 47−55 °C with aq. NaOH to neutralize excess acid. The elevated temperatures were to prevent crystallization of the sodium salts. The subtle change from aq. NaOH to aq. KOH permitted the extractions to be completed at ambient temperature thus avoiding issues with salt crystallization. The potassium acid salt was more soluble than the sodium salt and also avoided potential hydrolysis of EtOAc.

Final conversion of **10** to **11** was accomplished by first concentrating the EtOAc layer followed by acid cyclization. Of the following acids tested, acetic, formic, trifluoroacetic (TFA), and chloroacetic acids, TFA was preferred. Selection of TFA was based upon reaction time, impurity profile by HPLC (area %), and extent of conversion as the desired quality attributes. Initial use of TFA (2.5 equiv) at 45−50 °C afforded clean conversion, 88−93% within 15 to 24 h. Increasing the charge of TFA to 4.9 equiv with temperature-controlled addition (<30 °C) followed by heating to 44−48 °C reduced the cyclization time from 15 to 24 h to 4−5 h without any decrease in yield or product quality.

The technical product was isolated in a similar manner as that described for **10** with the exception that the pH range was lowered to 8−9. Final solvent exchange to IPA followed by slow cooling permitted the controlled crystallization of **11** in 75−80% yield with assays >99.5% by HPLC (area %). Isolated yields could be improved substituting MeOH/water (86%) or EtOH/water (82%) for IPA; however the quality suffered respectively (96% and 98%). As **11** was a key starting material, product quality was paramount and IPA was retained as the isolation solvent.

## Conclusions

The work disclosed here has provided an efficient and reagent frugal process for the manufacture of acetal **6**. The synthesis of **6** involved formation of **3** and **4** under solvent-free conditions. The conversion of **3** and **4** to **5** using *p*-TsOH in methanol followed by carbonate neutralization of excess acid avoided multiple solvent extractions and both a silica gel plug filtration and subsequent heptane trituration. The toluene solution of **5** thus generated was reduced to **6** in using Pd/C with low-pressure hydrogen. Purification of crude **6** by vacuum distillation provided high quality product >98.5% by HPLC (area %). The product to waste ratio from the initial process (1:140 kg/L) was improved to (1:30 kg/L) with improved product quality, reductions in cycle times, and no yield erosion. Modifications were described concerning the synthesis of **9** and improvements to the borohydride reduction reagent, $NaBH(OCOC_2H_5)_3$. Conversion of **10** using a modified TFA cyclization followed by direct recrystallization from IPA provided a facile route to our target 1-(1-pyridin-2-yl methyl-piperidin-4-yl)-1*H*-indole, **11**. Modifications in the conversion of **7** to **11** did not afford any product to waste improvements. However the modifications improved cycle times, process reliability, and, in the case of the synthesis of **9**, batch size enhancement. The revised process route is shown in Scheme 2.

Eli Lilly and Company successfully completed a 7.5 L scale-up of the above-described chemistry with multiple lots at each stage from **2** through **11**. The 7.5 L scale-up mirrored the laboratory results. Eli Lilly and Company chose to use a contracted manufacturer for the supply of **11** and provided all required technical documents. The contract manufacture successfully translated the chemistry as described on laboratory scale and then more recently completed a successful 5−10 lot per step campaign at a greater than 1000 L scale using the described chemistry with the claimed results.

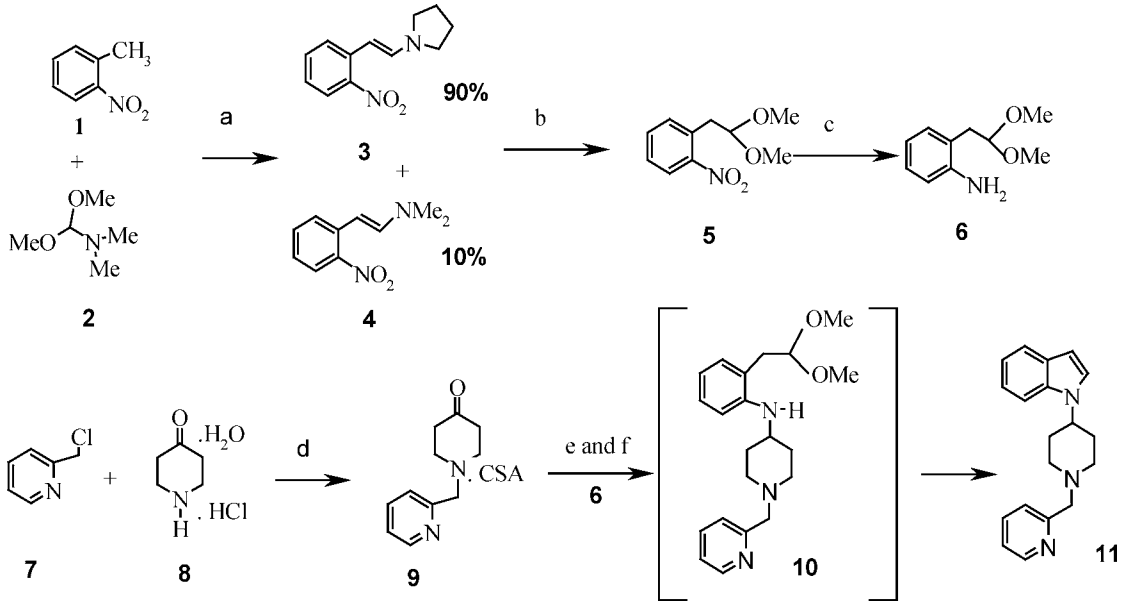
## Experimental Section

**General Methods.** Reaction completion and product purity for all steps were evaluated by HPLC using the following RP-HPLC conditions: **(Initial Route)** Zorbax C-8 25 cm × 4.6 mm, flow 1.0 mL/min; wavelength = 250 nm; temperature 23 °C; injection volume: 20 $\mu$L of a ca. 0.05% solution in ACN/water 1:1 v/v; eluent A = ACN, B = (1.5 mL of $Et_3N$/1.5 mL of $H_3PO_4$/1 L of $H_2O$) pH 3.0; and gradient: (0 min) A = 20%, B = 80%; (1 min) A = 20%,

(9) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

(10) (a) McGill, J. M.; Labell, E. S.; Williams, M. A. *Tetrahedron Lett.* **1996**, *37*, 3977. (b) McGill, J. M.; Burks, J. E.; Espinosa, L.; Labell, E. S.; Ritter, A. R.; Speakman, J. L.; Williams, M. A.; Bradley, D. A.; Haenl, M. G.; Schmid, C. R. *Org. Process Res. Dev.* **1997**, *1*, 198.

***Scheme 2.*** **Refined process for synthesis of 11**[a]




[a] Reagents and conditions: (a) (i) Pyrrolidine, 80 °C, distill volatiles; (b) (i) *p*-TsOH, MeOH; (ii) $Na_2CO_3$, distill MeOH; (iii) toluene/water; (iv) concentrate; (c) 5% Pd/C, toluene, $H_2$, and concentration; (ii) vac. distill product; (d) (i) $Na_2CO_3$/ACN; (ii) EtOAc, CSA; (e) (i) THF/$C_2H_5CO_2H$, $NaBH_4$; (f) (i) $C_2H_5CO_2H$, solution from (e); (ii) EtOAc, aq. NaOH; (iii) TFA/EtOAc; (iv) water, aq. NaOH; (v) concentrate; (vi) IPA.

B = 80%; (35 min) A = 80%, B = 20%; (36 min) A = 80%, B = 20%; (45 min) A = 20%, B = 80%. **(Production Route)** Zorbax SB-C8 25 cm × 4.6 mm, flow 1.0 mL/min; wavelength = 250 nm; temperature 30 °C; injection volume: 20 $\mu$L of a ca. 0.05% solution in ACN; A = 0.05% trifluoroacetic (v/v) in ACN and B = 0.05% trifluoroacetic (v/v) in Milli-Q water; gradient: (0 min) A = 10%, B = 90%; (25 min) A = 80, B = 20%; (26 min) A = 80%, B = 20%; (27 min) A = 10%, B = 90%; (35 min) A = 40%, B = 60%; (40 min) A = 10%, B = 90%. All reagents were commercially available except where indicated. Melting points were measured in open capillary tubes and are uncorrected. $^1$H NMR spectra were measured in $CDCl_3$ unless otherwise indicated, and IR spectra were taken using a KBr salt pellet.

**(*E*)-1-[2-(2-Nitrophenyl)ethenyl]pyrrolidine, 3, and (*E*)-1-[2-(2-nitrophenyl)ethenyl]dimethylamine, 4.** To a 1 L three-necked flask equipped with a magnetic stir bar, thermocouple, and distillation head was charged 2-nitrotoluene **(**300.0 g, 2.19 mol) followed by pyrrolidine (186.5 g, 2.63 mol) and DMF dimethylacetal (313 g, 2.63 mol). The resulting reddish/orange solution was heated to 80 ± 2 °C for 18−24 h. The reactor was set to provide for distillation of low boiling byproducts while maintaining the reactor set point. During this period the reaction changed color from a reddish/orange solution to dark red. The reaction was monitored by HPLC. The final distillate volume was 294 mL. The crude product oil weighed, 561 g; theoretical, 100%; weight, 477 g. The red oil **3** and **4** was 85% pure by HPLC (area %). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 1.94 (m, 4H), 3.34 (m, 4H), 3.50 (s, 6H, $N(CH_3)_2$), 5.83 (d, $J$ = 13.4 Hz, 1H), 6.93 (m, 1H), 7.23 (d, $J$ = 13.7 Hz, 1H), 7.31 (m, 1H), 7.44 (dd, $J$ = 8.2, 1.2 Hz, 1H), 7.83 (dd, $J$ = 8.2, 1.2 Hz, 1H). The resonance at 3.50 (s, 6H) corresponded to **4**. **Caution:** The product oil contained pyrrolidine byproducts, and attempts to further purify the product oil by distillation may result in detonation of the oil due to thermal instability starting at 120 °C.

**1-(2,2-Dimethoxyethyl)-2-nitrobenzene, 5.** To a 2 L three-necked flask equipped with a dropping funnel, thermocouple, stirrer, condenser, and $N_2$ inlet was charged crude **3** and **4** (150 g, 0.599 mol) followed by methanol (1.0 L). To this solution was added a solution of *p*-toluenesulfonic acid monohydrate (136 g, 0.716 mol) in methanol (1 L). The reaction mixture experienced a mild exotherm during the addition from 23 °C to 31 °C. The reaction mixture lightened after the addition of acid but darkened somewhat during the reaction. The resulting solution was heated to reflux 64−68 °C for 3 h. The solution was cooled to ambient temperature, and solid $Na_2CO_3$ (20 g, 0.189 mol) was carefully added and no exotherm or gas evolution was observed. The slurry was stirred for 15 min at ambient temperature. Excess methanol (1,290 mL) was removed by vacuum distillation. To the resulting slurry after methanol distillation was added agitation water (500 mL) followed by toluene (800 mL). The mixture was agitated for ∼15 min to permit dissolution of the salts. The agitation was ceased, and layers were allowed to separate. The lower aqueous layer was back-extracted with toluene (1 × 400 mL then 1 × 200 mL). The water layer was discarded (805 mL, pH 11.0), and the toluene layers were combined. The combined toluene layers were filtered though a pad (5 cm × 2 cm) of filter aid to remove solids and a small amount of entrained water. The toluene was then removed by vacuum to form an oil. Some toluene remained in the oil. Weight of product: 139 g. % Yield > 98%, based upon HPLC analysis. A sample was purified by placing a sample under a high vacuum (1 Torr) over 64 h at ambient temperature. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 3.25 (d, $J$ = 5.3 Hz, 2H), 3.38 (s, 6H), 4.60 (d, $J$ = 5.3 Hz, 1H), 7.42 (m, 2H), 7.56 (m, 1H), 7.92 (dd, $J$ = 7.9, 1.3 Hz, 1H).

**2-(2,2-Dimethoxyethyl)benzamine, 6.** To an inerted 1 L Parr bomb was charged wetted 5% Pd/C (6 g on a dry

basis) followed by a solution of **5** (139 g) in toluene (600 mL). The Parr bomb was inerted 3× using a vacuum/nitrogen procedure. The resulting inerted slurry was hydrogenated at 20 to 30 °C and 30 to 40 psi of $H_2$ pressure for 4 to 8 h or until hydrogen uptake ceased. The system was purged of hydrogen, repeating the vacuum/nitrogen procedure 3 times. The reaction mixture was filtered across a (5 cm × 2 cm) filter aid pad, and the reactor and filter pad were washed with toluene (400 mL) followed by water (50 mL). The water layer was separated and discarded. The toluene was removed under a vacuum to afford an amber colored oil. Weight of product: 120 g. The technical product **6** (120 g) was purified by vacuum distillation. The oil was heated 120 to 130 °C at 1 to 5 mbar of pressure. A precut was taken at a vapor temperature of 104 to 108 °C that was indole. The main cut was then taken from 108 to 110 °C. Weight: 112.3 g. (93.6%) Assay: 98.9 by HPLC (area %) analysis of a clear colorless oil. Alternately, one may decant the Parr reactor's contents through a (5 cm × 2 cm) filter aid pad, and the filtrate is worked up as above. The Pd/C catalyst adhered to the walls of the reactor due to the water generated via reduction of the nitro group. The Parr reaction may then be recharged with a toluene solution of **6**, inerted, and subjected to hydrogenation without any loss of catalytic activity.

**1-(2-Pyridinylmethyl)-4-piperidinone Camphor Sulfonate, 9.** To a 2 gal glass reactor equipped with an overhead stirrer, a condenser, and a nitrogen purge was charged 2-picolyl chloride hydrochloride (300 g, 1.83 mol), 4-piperidone monohydrate hydrochloride (294.96 g, 1.92 mol), powdered sodium carbonate (775.32 g, 7.32 mol), followed by ACN (1.62 L). The contents were carefully heated to 70 to 72 °C over a period of about 2 h to minimize foaming due to off gassing. The reaction mixture changed from an off-white slurry to light orange. The reaction mixture was maintained at 70 to 72 °C for 5 h. The reaction mixture was cooled to ambient temperature and filtered, and the solids were rinsed with EtOAc (2 × 1.20 L). The filtrate was reduced in volume to ~1 L under reduced pressure at 50 to 55 °C. The solution was cooled to 30 to 35 °C and held for the next step. To a second 2 gal reaction vessel equipped with an overhead stirrer and a nitrogen purge was charged camphor sulfonic acid (425 g, 1.83 mol) followed by EtOAc (3.3 L). The contents were heated 68 to 72 °C and stirred until the CSA dissolved. To the warm solution of CSA at 68 to 72 °C was charged the solution from the previous reaction above over a period of 20 to 30 min. The first reactor was rinsed with EtOAc (100 mL), and the rinse was added to the reactor containing CSA. The reactor contents were maintained at 68 to 72 °C for about 30 min to permit crystallization to begin. Once crystals were observed, the reactor was cooled to 58 to 62 °C over 2 h. The thickening crystal slurry was held at 58 to 62 °C for 1 h. The crystal slurry was cooled to ambient temperature over 4 h and stirred for 3 h. The crystals were filtered and washed with EtOAc (0.9 L). The crystals were dried in a 45 to 55 °C vacuum oven overnight to afford 700 g of **9**. (90.5%)

**Preparation of 1.0 M $NaBH(OCOC_2H_5)_3$ THF Solution. Caution:** This reaction generates hydrogen. Into a 2 L four-necked round bottom flask equipped with a mechanical agitator, thermometer, and nitrogen purge was charged sodium borohydride 119 (30 g, 0.793 mol) and THF (0.745 L, 21.5 vol). The suspension was cooled in an ice bath to 10 °C. Propionic acid [0.195 L, (193.44 g) 2.61 mol] was added via syringe drive over 2 h 40 min at a rate of 4.0 mL/min. That exhibited an exotherm. The maximum temperature reached during this exotherm was about 25 °C. At the end of the addition, some solids remained so the reactor contents were allowed to warmed to 25 °C with agitation overnight. A homogeneous to slightly hazy solution was obtained. The 1.0 M $NaBH(OCOC_2H_5)_3$ obtained was stored in a refrigerator for future use.

**1-(1-Pyridin-2-yl methyl-piperidin-4-yl)-1*H*-indole, 11.** To a 2 gal glass reactor equipped with an agitator, a thermocouple, a condenser, and a $N_2$ inlet was charged propionic acid (0.61 L) followed by addition of **9** (213.12 g, 0.504 mol) and **6** (91.52 g, 0.504 mol). The mixture was agitated at 20 to 25 °C until the contents dissolved (approximately 15 to 30 min). Once the solids dissolved, the reaction mixture was cooled to −12 to −8 °C. To the chilled solution at −12 to −8 °C was charged, over 2.5 h, the 1.0 M $NaBH(OCOC_2H_5)_3$ solution previously prepared. Once the addition of the reducing agent was complete, the reaction was monitored by HPLC for reaction completeness (<1% starting materials or intermediate). The reaction mixture was maintained at −12 to −8 °C. Once the reaction met the reaction completeness criteria, the reaction mixture was warmed to 8 to 10 °C, and EtOAc (1.28 L) was added. Using 40% w/v aq. NaOH, the pH of the reaction mixture was adjusted to 9.8 to 10.5. The reaction mixture was allowed to warm during the pH adjustment to 48 to 53 °C. Once the pH range of 9.8 to 10.5 was achieved, the mixture was agitated for 5 to 15 min, after which agitation was stopped to allow the phases to separate while maintaining a solution temperature of 48 to 53 °C. (Note: if the solution temperature drops to below 45 °C, sodium salts will begin to crystallize.) The lower aqueous phase was separated to a second reactor. The aqueous phase was back-extracted with EtOAc (0.64 L) at 48 to 53 °C. The organic layers were combined and washed with a 20% aq. brine solution (0.96 L) at 48 to 53 °C. The lower brine phase was discarded. The organic phase was then placed under a vacuum, and EtOAc was distilled, 1.07 to 1.17 L (target volume: 1.12 L) with a maximum jacket temperature of 55 °C. Once the distillation was complete, the reactor contents were cooled to 20 to 25 °C and returned to atmospheric pressure. To the reactor contents at ambient temperature, trifluoroacetic (0.192 L, 2.58 mol) was charged over 45 min keeping the maximum temperature below 30 °C. Once the addition of trifluoroacetic was complete, the reactor contents were warmed to 46 °C and maintained at this temperature ±1 °C for 6 h. Progress of the cyclization was monitored by HPLC. When the condensation product from the above protocol was <1% relative to **11**, the reactor contents were cooled to ambient temperature. To the reactor was charged EtOAc (0.96 L) and water (0.16 L). The pH of the reactor contents was carefully adjusted to 8.3 to 8.8 with 40% w/v NaOH solution, while

allowing the contents to warm to 48 to 53 °C. To the reactor contents was added 20% w/v aq. brine while maintaining a temperature range of 48 to 53 °C to prevent crystallization of salts. The layers were allowed to settle for 10 to 20 min before separation. The lower aqueous layer was then back-extracted with EtOAc (0.64 L) at 48 to 53 °C, the lower aqueous layer was discarded, and the organic layers were combined. With a jacket set point of not more than 40−44 °C solvent was removed by distillation until the reaction mixture was a thick paste.

**Crystallization of 11 from EtOH/Water.** Ethanol (2.6 L) was charged to the reactor to dissolve the solids. With a jacket set point of NMT 55 °C, the volume of the reaction was reduced by ∼1.25 L to yield a slurry. The mixture was heated to reflux to effect dissolution of the solids and was then cooled to 55 °C ± 2 °C. The solution temperature was maintained at 55 °C ± 2 °C while adding water (3 L) over 2.5 h. Once the water addition was complete, the resulting slurry was maintained at 55 °C ± 2 °C for 1 h. The slurry was then cooled to 20 to 24 °C over 4 h followed by further cooling to −7 to −4 °C over 2.5 h. The agitated slurry was maintained at −5 ± 2 °C for 2.5 h. The resulting slurry was filtered, and the reactor and cake were washed with chilled 40% aq. EtOH (0.16 L). The cake was dried under a vacuum at 70 to 77 °C for at least 16 h to yield 124.4 g, 84.6% yield. NMR and HRMS data compared to literature.[2]

**Crystallization of 11 from IPA.** Isopropanol (1.91 L) was charged to the reactor contents, and ∼1.1 L of solvent was removed via vacuum distillation with a temperature range of 40−50 °C. To the slurry was added IPA (0.638 L), and the vacuum distillation was continued at a temperature range of 40−50 °C until ∼630 mL were removed. The slurry was held at 43−45 °C for 3 h and was then cooled to −5 °C over 3−4 h. The slurry was filtered and washed with cold, 0−5 °C, IPA (2 × 0.25 L). The product was dried under a vacuum at 50 °C to a constant weight. The weight of the product was 114.7 g (78%).


## Acknowledgment

The authors are thankful to Curtis Miller, Cindy Hammill, Cindy McCurry, Dave Myers, and John Stafford for their invaluable assistance with chemical analysis. We wish to acknowledge the efforts of Ron Stockberger and Bill Henning for their assistance in carrying out 2 gal experiments. We wish to thank Jim Hermiller for physical characterizations and Prof. William Roush for helpful suggestions and discussions.


## Supporting Information Available

Table of cosolvent effects on reductive amination with $NaBH(OCOC_2H_5)_3$ and optimization of cyclization reaction table. This material is available free of charge via the Internet at http://pubs.acs.org.


Received for Review March 23, 2006.

OP060068K