

Kilogram-Lab-Scale Oxindole Synthesis via Palladium-Catalyzed C–H Functionalization

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Supporting Information

ABSTRACT: A scalable method for the preparation of oxindole **8**, a key intermediate en route to a serine palmitoyl transferase inhibitor, compound **1**, is presented. A three-step, chromatography-free route has been designed that takes advantage of Buchwald's palladium-catalyzed C–H functionalization to cyclize an α -chloroacetanilide to form the five-membered ring. This process has been successfully carried out in our kilogram laboratory facility on 10-kg scale in 76% yield.

INTRODUCTION

Compound **1** (Figure 1) is a molecule designed to inhibit the serine palmitoyl transferase (SPT) enzyme.¹ It has been proposed that inhibition of SPT may elevate levels of HDL cholesterol.² This effect is associated with decreased cardiovascular health risk, and therefore, compound **1** represents a potential treatment for heart disease.³

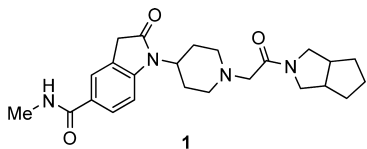


Figure 1. Structure of SPT inhibitor **1**.

MEDICINAL CHEMISTRY ROUTE

The original medicinal chemistry route for synthesizing the target **1** involved a key oxindole intermediate **8** which was accessed through a five-step synthetic process (Scheme 1).^{1a} The synthesis started with the esterification of 3-fluoro-4-nitrobenzoic acid (**2**) in MeOH as solvent and catalytic H₂SO₄ to provide methyl ester **3** in 89% yield. This intermediate then underwent reaction with di-*tert*-butyl malonate and NaH as base to generate intermediate **4** after fluoride displacement via S_NAr in 79% yield.⁴ The nitro group was hydrogenated with Ra–Ni as catalyst to afford aniline **5** in 88% yield,⁵ which underwent reductive amination with 1-benzoyloxycarbonyl-4-piperidone (**6**) to give secondary amine **7** in 82% yield after chromatography.^{4a,5} Indole **8** was produced in 81% yield after treating **7** with *p*-TsOH·H₂O in toluene at reflux followed by chromatography.^{4a} Four additional steps completed the synthesis of **1** from **8**.

Even though this route was satisfactory for the preparation of small batches of **1**, the need for kilo quantities of material to support clinical studies required the development of either an optimized or a new route. We focused our attention on the preparation of oxindole **8** as a key advanced intermediate en route to **1**. The Medicinal Chemistry route provided this material in five steps and 41% overall yield from **2** but required

the use of NaH and two chromatographic purifications. In addition, the high cost of **2** made this starting material undesirable in the long run for large-scale manufacturing. On the basis of a report from Buchwald's group on the preparation of substituted oxindoles from α -chloroacetanilides via palladium-catalyzed C–H functionalization,⁶ we envisioned that this method could provide rapid access to oxindole **8** and streamline the synthesis of compound **1**. The original conditions reported by this group employed Pd(OAc)₂ as catalyst and 2-(di-*tert*-butylphosphino)biphenyl as ligand in the presence of Et₃N and toluene at 80 °C (Scheme 2). This method represents an innovative and direct approach for the preparation of oxindoles that avoids the high temperatures and strongly acidic conditions usually required when a Friedel–Crafts-type of approach is employed with α -halo-⁷ or α -hydroxy⁸ acetanilides to generate similar substrates. In addition, the α -chloroacetanilide precursor can be readily accessed from the corresponding aniline and chloroacetyl chloride.

To the best of our knowledge, only one report on the application of this method for the large-scale preparation of an oxindole has been found in the literature.⁹ Conditions similar to those described by Buchwald et al.⁶ were employed with the only major change being trifluorotoluene in place of toluene as solvent. Encouraged by this precedent on multikilogram scale, we decided to investigate the application of this approach to our substrate.

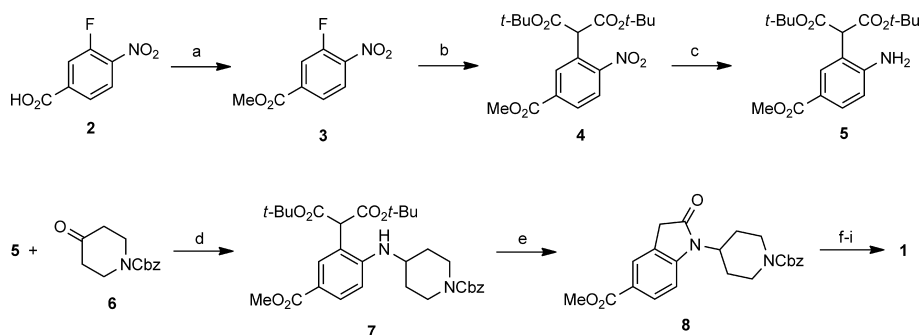
RESULTS AND DISCUSSION

Before we could test Buchwald's C–H activation method⁶ for the preparation of oxindole **8**, we had to access the appropriate α -chloroacetanilide **11**. This was expediently accomplished in two steps from commercially available methyl 4-aminobenzoate (**9**), a considerably cheaper starting material than 3-fluoro-4-nitrobenzoic acid (**2**), and 1-benzoyloxycarbonyl-4-piperidone (**6**) (Scheme 3).

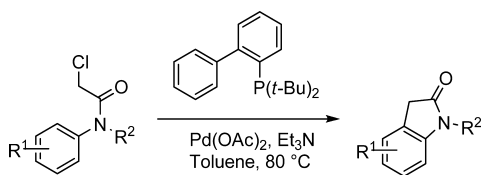
Several conditions were tested for the reductive amination between **6** and **9**. Initially, mixtures of **6**, **9** (1 equiv), and HOAc (1 equiv) were added in a number of solvents (THF,

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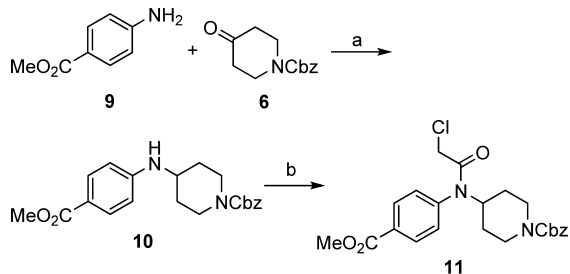
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Scheme 1. Medicinal Chemistry route to oxindole 8^a

^aReagents and conditions: (a) H₂SO₄, MeOH, reflux, 5.5 h, 89%. (b) CH₂(CO₂t-Bu)₂, NaH, THF, 0 °C to rt, 79%. (c) H₂, Ra-Ni, rt, 88%. (d) (i) NaBH(OAc)₃, HOAc, DCE, rt, 72 h; (ii) chromatography, 82%. (e) (i) *p*-TsOH·H₂O, toluene, reflux, 2 h; (ii) chromatography, 81%. (f) 2 N NaOH, MeOH, 80 °C, 2 h, 97%. (g) (i) MeNH₂ (2 M in THF), EDC·HCl, HOBT, CH₂Cl₂, rt, 72 h; (ii) chromatography, 56%. (h) H₂, 10% Pd/C, THF, 10 h, 66%. (i) (3aR,6aS)-2-(chloroacetyl)octahydrocyclopenta[*c*]pyrrole, KHCO₃, MeCN, 72 °C, 1.5 h, 65%.

Scheme 2. Oxindole formation via C–H functionalization by Buchwald's group^{6,a}

^aR¹ = Me, OMe, Cl, CF₃, OTBS, Me₃Si, NO₂; R² = Me, Et, Ph, Bn, *p*-methoxybenzyl, diphenylmethyl.

Scheme 3. Preparation of α -chloroacetanilide 11^a

^aReagents and conditions: (a) NaBH(OAc)₃, HOAc, CH₂Cl₂, 20 °C, 5.5 h, 86%. (b) ClC(O)CH₂Cl, py, EtOAc, 20 °C, 1.5 h, 89%.

1,2-dichloroethane (DCE), CH₂Cl₂) to a suspension of NaBH(OAc)₃ in the same solvent, but incomplete reactions and considerable amounts of alcohol 12 (up to 17%) resulting from the reduction of 6 were observed (Figure 2). Never-

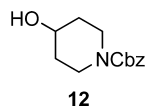


Figure 2. Alcohol byproduct from the reduction of piperidone 6.

theless, higher conversions were obtained in DCE and CH₂Cl₂ (61–65%) compared to that in THF (35%). When the reverse order of addition was implemented¹⁰ (addition of solid NaBH(OAc)₃ in one portion to a solution of 6, 9, and HOAc in either CH₂Cl₂ or DCE), respective yields of 62% and 73% of desired product 10 were obtained. The level of piperidol 12 was 8–12%, and this byproduct could be purged in the filtrates after a final crystallization from heptane/MTBE

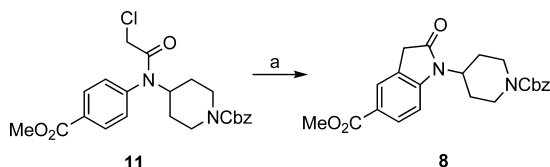
(1:1). Further improvements were the discovery that adding NaBH(OAc)₃ in several portions and the use of 1.2 equiv of piperidone 6 gave complete consumption of 9, an acceptable level (10–12%) of piperidol byproduct 12, and a substantial increase in yield in either halogenated solvent (86–87%). DCE (class 1 solvent) was initially used as the solvent in this reaction; however, CH₂Cl₂ (class 2 solvent) was preferred during large-scale operations due to its lower toxicity.¹¹ The optimal conditions involved dissolving the two substrates in CH₂Cl₂ with 1 equiv of acetic acid and adding NaBH(OAc)₃ in several portions over a few hours. Upon reaction completion, the mixture was quenched into 2 N NaOH, the layers were separated, and the organic layer was washed with water to ensure boron byproducts removal. Concentration of the organic phase and crystallization from a mixture of heptane and MTBE afforded the product in 85–90% yield and >98% purity (HPLC area %) on laboratory-scale (25 g). Two runs were carried out in our kilo lab facility (4.2 and 6.0 kg) in 76% and 86% yield, respectively (HPLC purities >98 area %).

The original method for carrying out the subsequent acylation step to produce α -chloroacetanilide 11 employed CH₂Cl₂ as solvent and solid K₂CO₃ as base. These conditions tended to give variable reaction rates, often resulting in incomplete conversion most likely due to the biphasic nature of the mixture. Schotten–Baumann conditions (CH₂Cl₂ or EtOAc and aqueous K₂CO₃) were also investigated, but low conversion was observed due to hydrolysis of the acid chloride before it had a chance to react with poorly nucleophilic amine 10. Better results were obtained when the reaction was performed by treating an EtOAc solution of 10 with chloroacetyl chloride in the presence of pyridine. Excesses of both reagents (1.5 equiv) were required to drive the reaction to completion. Et₃N as a less toxic alternative than pyridine was found to afford intermediate 11 with a yellow color that could not be removed via crystallization from MTBE (vide infra). The workup involved quenching the reaction with water, separating the layers, and washing the organic layer with half-saturated brine to ensure removal of chloroacetic acid and pyridine hydrochloride byproducts and prevent emulsion formation. α -Chloroacetanilide 11 was isolated by concentration of the organic layer and crystallization of the residue from MTBE. This optimized protocol using pyridine in EtOAc was implemented in the laboratory on 100-g scale in >85% yield and >98% HPLC purity (area %). Yields and purities were

reproducible during two campaigns in our kilogram laboratory facility on 7.8- and 12.5-kg scale.

With **11** in hand, we focused our attention on the oxindole-forming step. Initial efforts at applying Buchwald's method⁶ toward cyclizing compound **11** (Scheme 4) gave incomplete

Scheme 4. Preparation of 8 via C–H functionalization^a



^aReagents and conditions: (a) Pd(OAc)₂ (10 mol %), 2-(di-*tert*-butylphosphino)biphenyl (20 mol %), TEA, MeTHF–IPA (4:1 v/v), 70–75 °C, 2.5 h, 76%.

reaction and significant side products. It was soon recognized that the problem was the use of toluene as solvent, since the reaction mixture was heterogeneous and tended to produce sticky solids that prevented good agitation as the reaction proceeded. As a result, several solvent and base combinations were tested to find a system capable of providing a more homogeneous mixture. Thus, 2-MeTHF with TEA gave complete conversion at 80 °C but still produced tarry and somewhat sticky solids, whereas that with (*n*-Bu)₃N gave low conversion to the desired product and higher level of impurities due to the prolonged reaction time (overnight at 80 °C). MeCN/TEA showed very low conversion and some decomposition after 4 h at 80 °C, whereas complete consumption of **11** was observed at the same temperature in DMF/TEA to afford a complex mixture with a small amount of oxindole **8**. The small improvement observed with 2-MeTHF led us to investigate this system further. A major breakthrough came when the reaction was performed in a 2-MeTHF/2-propanol mixture. Initially, the reaction was carried out with a 1:1 (v/v) ratio to provide oxindole **8** in 49% yield after 1.5 h at 80 °C. However, when a 4:1 (v/v) mixture of 2-MeTHF and 2-propanol was tested, complete cyclization occurred in less than 1 h at 70–80 °C to afford **8** in 70% yield on gram scale. Tarry solids were still present in the reaction, but the addition of 2-propanol resulted in a more homogeneous and stirrable mixture. The ideal amounts of palladium catalyst and ligand were found to be 10 mol % and 20 mol %, respectively. The use of half of these loadings of catalyst and ligand resulted in the reaction stalling out at 80–85% conversion as well as the formation of higher levels of impurities.¹² The 1:2 ratio of metal to ligand was also found to be important; an attempt with the reverse ratio (2:1) gave little or none of oxindole **8**.¹³ Due to the relatively low solubility of **8** at ambient temperature, attempts at a conventional aqueous workup were abandoned, as the compound had a tendency to precipitate unexpectedly from solution. In addition, the postreaction mixture contained insoluble black, tarry solids (TEA·HCl and metal/ligand residues)¹⁴ which caused intractable emulsions if partitioning with water was attempted. These workup issues were eradicated by filtering the hot reaction mixture through diatomaceous earth. The filtrate was then concentrated and the crude oxindole **8** recrystallized from 2-propanol. The product could also be precipitated directly from the reaction filtrate by cooling; however, yields were lower due to the modest solubility of **8** in 2-MeTHF. Attempts to increase this yield

by adding heptane or MTBE as antisolvent resulted in the coprecipitation of TEA·HCl, which necessitated multiple aqueous washes of the filter cake to be removed and longer product drying times. The 2-propanol purification gave product of high quality (>98 area % by HPLC) in 70–80% overall yield. Residual palladium levels varied between 100–800 ppm.¹⁵ The optimized process was carried out multiple times on 25–50-g scale, and it was subsequently scaled up in our kilo laboratory facility twice on 5-kg and once on 10-kg scale with yields in the 76–84% range. The application of this chemistry to our substrate (bearing a Cbz-protecting group) also represents an extension of the type of protecting group that can be employed on the nitrogen of **11** with respect to the original article.⁶

Even though Buchwald stated in his original article that, after testing several ligands, only 2-(di-*tert*-butylphosphino)biphenyl afforded the desired oxindole,⁶ we decided to investigate the use of 5-(di-*tert*-butylphosphino)-1',3',5'-triphenyl-1'H-[1,4']-bipyrazole (Bippypfos, **13**, Figure 3) in this type of coupling.

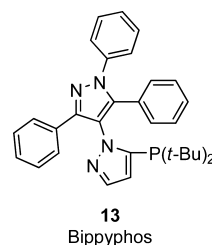


Figure 3. Structure of Bippypfos ligand.

This nonproprietary ligand was originally developed at Pfizer,¹⁶ became available to us shortly after the work described in this article had been implemented, and is currently commercially available from several sources. When α -chloroacetanilide **11** was subjected to the same reaction conditions described in Scheme 4 in the presence of Pd(OAc)₂ (10 mol %) and Bippypfos (20 mol %), complete conversion was observed to oxindole **8** after 2 h and this material was isolated in 84% yield on 25 g-scale. Following the successful application of this catalytic system, we have further expanded the use of this technology for the preparation of other oxindoles in our laboratories.

In summary, we have developed a high-yielding, chromatography-free, scalable process for producing kilogram quantities of oxindole **8** utilizing Buchwald's⁶ C–H functionalization chemistry. The application of this methodology allowed us to remove two processing steps from the original route to compound **8** and eliminated the need for NaH and two chromatographic purifications. The original stirring issues associated with the use of toluene have been overcome by replacing this solvent with a 4:1 2-MeTHF/2-propanol mixture to provide a more homogeneous reaction mixture. We have also demonstrated the applicability of Bippypfos as an alternative ligand to 2-(di-*tert*-butylphosphino)biphenyl in this type of coupling. Even though this technology was suitable for early development campaigns, further optimization would be required to decrease the amount of catalyst and ligand to turn it into a more cost-effective process. On the basis of some additional work carried out in our laboratories for the generation of other oxindoles on gram-scale, we believe that this methodology can become a general and scalable approach for the manufacture of this type of materials.

■ EXPERIMENTAL SECTION

Reaction completion and product purity were evaluated by HPLC using the following conditions: column: YMC PackPro C18, 150 mm × 4.6 mm, 5 μ m; flow rate: 1.0 mL/min; wavelength: 215 nm; temperature: 30 °C; injection volume: 5 μ L after diluting the sample with 9:1 CH₃CN/water to a concentration of approximately 0.5 mg/mL of analyte; eluent A: water (0.2% HClO₄); B: CH₃CN; gradient: 30% B to 95% B over 10 min; hold 95% B for 5 min; return to 30% B over 1 min. HPLC purities are given in area %.

Synthesis of Benzyl 4-(4-(methoxycarbonyl)-phenylamino)piperidine-1-carboxylate (10). A solution of methyl 4-aminobenzoate (9, 6.00 kg, 39.7 mol) and 1-benzoyloxycarbonyl-4-piperidone (6, 11.14 kg, 47.8 mol) in CH₂Cl₂ (60 L) and glacial HOAc (2.38 kg, 39.6 mol) was treated with NaBH(OAc)₃ (12.60 kg, 59.4 mol) in 5 portions over 4 h at 15–25 °C. The reaction mixture was stirred until HPLC analysis indicated complete reaction (5.5 h). The reaction was transferred into a solution of sodium hydroxide (50 wt %, 4.76 kg, 59.5 mol) in water (30 L) followed by a CH₂Cl₂ rinse (6 L). The reaction mixture was stirred for 1 h at 20 °C, and the layers were separated. The organic layer was washed with water (2 × 30 L), concentrated at atmospheric pressure to a volume of 30 L, and diluted with methyl *tert*-butyl ether (MTBE, 30 L). The mixture was concentrated to a volume of 30 L, and this solvent displacement operation was repeated twice more. The residue was diluted with MTBE (60 L), and to the resulting slurry was added heptane (60 L). The suspension was stirred for 3 h at 20 °C, and the solids were filtered and washed with 1:1 MTBE/heptane (24 L). The solid was dried under vacuum at 50 °C for 24 h to give 12.54 kg (86%) of amine 10 as a white solid. Mp: 94 °C (DSC). HPLC retention time: 8.4 min. HPLC purity: 98.7% (area %). ¹H NMR (400 MHz, CDCl₃) δ 1.41 (d, *J* = 10.04 Hz, 2 H), 2.07 (d, *J* = 11.67 Hz, 2 H), 3.04 (t, *J* = 11.73 Hz, 2 H), 3.47–3.60 (m, 1 H), 3.87 (s, 3 H), 4.17 (br s, 3 H), 5.12–5.20 (m, 2 H), 6.57 (d, *J* = 8.78 Hz, 2 H), 7.30–7.46 (m, 5 H), 7.88 (d, *J* = 8.78 Hz, 2 H). ¹³C NMR (100 MHz, CDCl₃) δ 32.01, 42.76, 49.62, 51.58, 67.23, 111.92, 118.61, 127.91, 128.08, 128.54, 131.67, 136.70, 150.40, 155.21, 167.20. HRMS (EI) Calcd for C₂₁H₂₅N₂O₄ (M + H) 369.18088, found 369.18100.

Synthesis of Benzyl 4-(2-Chloro-*N*-(4-(methoxycarbonyl)phenyl)acetamido)piperidine-1-carboxylate (11). A solution of amine 10 (12.46 kg, 33.8 mol) and pyridine (4.04 kg, 51.1 mol) in EtOAc (119 L) was treated with chloroacetyl chloride (5.77 kg, 51.1 mol) over 40 min at 15–25 °C. The reaction was stirred until HPLC analysis indicated complete consumption of 10 (1.5 h), and water (62.7 L) was added. The resulting mixture was stirred for 1 h at 20 °C, and the layers were separated. The organic layer was washed with a solution of NaCl (8.15 kg) in water (62.7 L). The layers were separated, and the organic phase was concentrated at reduced pressure to 20 L. EtOAc (37.6 L) was charged to the reactor, and the mixture was concentrated again to a volume of 20 L. The product was then fully dissolved by the addition of EtOAc (157 L), and the resulting solution was filtered through an inline polishing filter (0.2 μ m) to remove insoluble material. The reactor and filter were rinsed with EtOAc (12.5 L), and the solution was concentrated at reduced pressure to a volume of 20 L. MTBE (75.2 L) was added, and the mixture was heated at reflux for 30 min and cooled to 25 °C over 3 h. The resulting slurry was stirred for 6 h

and filtered. The solids were washed with MTBE (37.6 L) and dried under vacuum at 50 °C for 25 h to afford 13.53 kg (89%) of acetanilide 11 as a white solid. Mp: 107 °C (DSC). HPLC retention time: 8.1 min. HPLC purity: 99.3% (area %). ¹H NMR (400 MHz, CDCl₃) δ 1.15–1.35 (m, 2 H), 1.85 (d, *J* = 11.67 Hz, 2 H), 2.89 (m, 2 H), 3.70 (s, 2 H), 3.98 (s, 3 H), 4.24 (br s, 2 H), 4.72–4.85 (m, 1 H), 5.06 (br s, 2 H), 7.24 (m, *J* = 8.28 Hz, 2 H), 7.27–7.38 (m, 5 H), 8.14 (d, *J* = 8.66 Hz, 2 H). ¹³C NMR (100 MHz, CDCl₃) δ 30.22, 42.12, 43.32, 52.55, 53.47, 67.20, 127.92, 128.04, 128.47, 130.24, 131.10, 131.22, 136.54, 141.23, 154.92, 165.52, 165.80. HRMS (EI) Calcd for C₂₃H₂₆ClN₂O₅ (M + H) 445.15248, found 445.15246.

Synthesis of Methyl 1-(1-(Benzoyloxycarbonyl)-piperidin-4-yl)-2-oxoindoline-5-carboxylate (8). A solution of α -chloroacetanilide 11 (10.95 kg, 24.6 mol), Pd(OAc)₂ (0.553 kg, 2.46 mol), and 2-(di-*tert*-butylphosphino)biphenyl (1.47 kg, 4.93 mol) in 2-MeTHF (71.2 L) and 2-propanol (17.7 L) was sparged subsurface with nitrogen for 30 min. Triethylamine (3.74 kg, 37.0 mol) was added and the reaction was heated to 71 °C and stirred until HPLC analysis indicated complete consumption of 11 (2.5 h). Without cooling, the reaction mixture was filtered through Celite followed by a second in-line polishing filter (0.2 μ m). The reactor and filters were rinsed with hot (70 °C) 2-MeTHF (11 L), and the combined filtrates were cooled to 51 °C and concentrated at reduced pressure to 20 L. The slurry was diluted with 2-propanol (153 L) and heated to reflux until all the solids dissolved (30 min). The mixture was cooled to 25 °C over 3 h, and the resulting slurry was stirred for 5 h. The solids were filtered, washed with 2-propanol (32.9 L), and dried under vacuum at 35 °C for 72 h to give 7.70 kg (76%) of oxindole 8 as a white solid. Mp: 154 °C (DSC). HPLC retention time: 7.90 min. HPLC purity: 98.4% (area %). ¹H NMR (400 MHz, CDCl₃) δ 1.66 (d, *J* = 11.80 Hz, 2 H), 2.26 (dd, *J* = 12.61, 3.83 Hz, 2 H), 2.84 (br s, 2 H), 3.48 (s, 2 H), 3.83 (s, 3 H), 4.21–4.46 (m, 3 H), 5.10 (s, 2 H), 6.89 (d, *J* = 8.41 Hz, 1 H), 7.23–7.36 (m, 5 H), 7.84 (s, 1 H), 7.88 (d, *J* = 8.28 Hz, 1 H). ¹³C NMR (100 MHz, CDCl₃) δ 28.08, 35.49, 43.72, 50.18, 52.09, 67.40, 109.13, 124.03, 124.59, 125.88, 128.06, 128.17, 128.57, 130.30, 136.62, 147.60, 155.14, 166.70, 174.96. HRMS (EI) Calcd for C₂₃H₂₅N₂O₅ (M + H) 409.17580, found 409.17582.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ¹H and ¹³C NMR spectra for compounds 8, 10, and 11. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (13) The Supporting Information in reference 6 erroneously tells the reader to use this reverse ratio.
- (14) These solids were actually the impetus behind using 2-propanol as a cosolvent in the reaction. Without the added alcohol, the black, tarry solids would build up into a sticky material that would prevent efficient stirring and mixing. We envisioned that this problem would worsen on scale. The addition of 20% alcohol to the solvent avoided this issue. Interestingly, 2-propanol also had a tendency to kick-start the reaction at room temperature; however, without additional heat, it would stop at only fractional conversion. The exact role of the alcohol as a reaction mediator was not determined.
- (15) No attempts were made to remove residual palladium from **8** since a subsequent step also employed this metal (Cbz-protecting group removal via catalytic hydrogenation in the presence of Pd/C). Pd was purged downstream in the synthesis.
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