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ARTICLE

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Mitsunobu Inversion of a Secondary Alcohol with Diphenylphosphoryl azide. Application to the Enantioselective Multikilogram Synthesis of a HCV Polymerase Inhibitor

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ABSTRACT: The development of a practical synthesis of the hepatitis C virus polymerase inhibitor **1** was necessary to support preclinical safety and human clinical studies. Significant challenges face the process chemist in developing a route to **1** that is amenable to multikilogram operation. In particular, an efficient construction of the eight-membered dihydroindolobenzoxazocine ring and enantioselective synthesis of the secondary amine stereocenter are required. This article describes our process development of a Mitsunobu protocol to achieve the latter goal which uses diphenylphosphoryl azide at ambient temperature to invert a scalemic secondary alcohol. The hazard evaluation performed to establish the safety of this protocol and allow pilot-plant introduction at >8.0 kg scale is discussed. Overall, an enantioselective synthesis of **1** by way of seven isolated intermediates in 32% overall yield was developed from commercially available materials. This allowed us to prepare over 3 kg of the targeted drug candidate.

INTRODUCTION

The treatment of hepatitis C virus (HCV) infections represents a major unmet medical need that impacts an estimated 170 million people throughout the world.[1a] It is the leading cause of liver transplantation in the developed world and results in over 10000 deaths annually in the United States. At present there is no marketed vaccine to prevent the disease nor is there a specific antiviral agent effective against HCV infection. The standard of care for chronic hepatitis C patients is based on the combination of subcutaneous pegylated interferon (Peg-IFN) along with the oral nucleoside drug, ribavirin. However, side effects and poor patient response rates, particularly amongst those with genotype 1, render the development of novel anti-HCV therapies as urgent.[1b] As part of a programme within Merck Research Laboratories directed toward the identification of hepatitis C virus NS5B-polymerase allosteric inhibitors,[2] candidate **1** was identified for development, and a scaleable synthetic route was required to support early preclinical and clinical evaluation.

The polymerase inhibitor **1** poses a number of challenges with regard to development of a concise asymmetric synthesis suitable for multikilogram scale up. Most notably, the construction of the eight-membered heterocyclic biaryl-containing ring, as well as the single amine stereocenter were expected to be challenging. Previous investigations from our Medicinal Chemistry laboratories had identified two asymmetric routes to **1** proceeding by way of primary amine **2** (Scheme 1).[2] The first-generation route involved the five-step preparation and use of the bifunctional aziridine reagent **5**. A second-generation approach replaced the aziridine with the commercially available enantiopure epoxide **6**. Both of these bifunctional electrophiles underwent reaction with the commercially available indole fragment **4** to form the eight-membered dihydroindolobenzoxazocine ring in moderate to good yield.[3]

Both of the Medicinal Chemistry approaches allowed for the multigram synthesis of **1**, facilitating early biopharmaceutical, biological, and toxicological evaluation. However, there were issues with these synthetic routes that would prohibit further scale-up. In particular, the thermal instability of aziridine **5** was a concern as was the number of steps required to prepare this intermediate.[4] The stereoselective conversion of secondary alcohol **3** to amine **2** required activation as either mesylate or tosylate derivative and displacement with sodium azide at high temperature (95−100 °C, DMF) to introduce the nitrogen functionality. Concerns with regard to the potential formation of hydrazoic acid in the reactor headspace together with the thermal stability of the product azide formed would require addressing this to scale without risk to equipment and personnel. Both Medicinal Chemistry routes also entailed a relatively long six-step sequence to elaborate the *N*,*N*-ethylenediamine side chain from amine **2** to deliver the candidate **1**, contributing to an overall longest linear sequence of 16 steps in the best case.

A more expedient route to **1** which addressed a number of the issues was rapidly developed within the Process Research group and enabled us to obtain **1** in a total of nine steps on multigram scale from the biaryl core **4** (Scheme 2). Medicinal chemistry intermediate alcohol **3** was oxidized to the ketone **7** under modified

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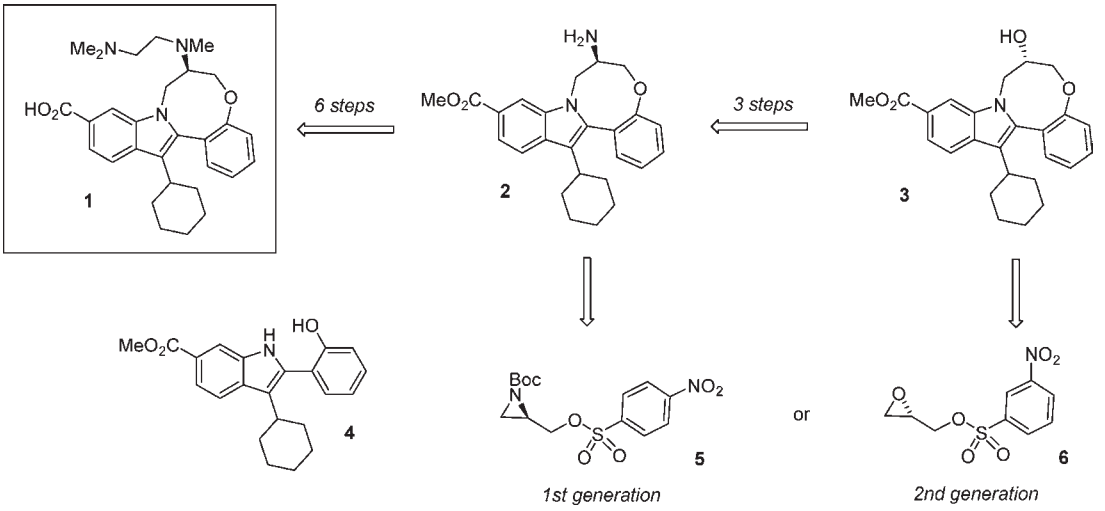
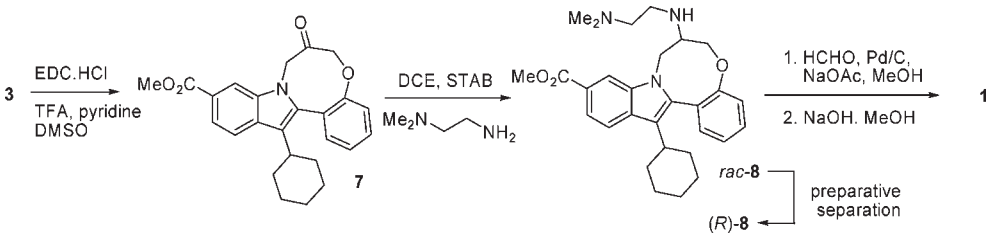
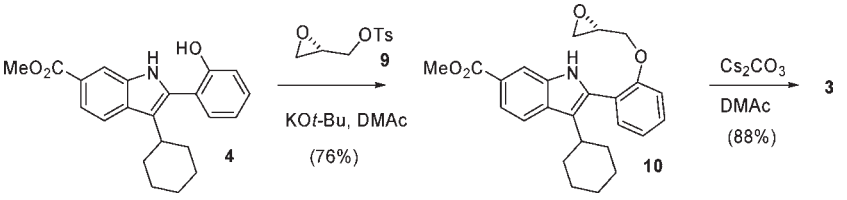
Scheme 1. Medicinal Chemistry retrosyntheses



Scheme 2. Preparative separation approach via *rac*-8



Scheme 3. Construction of the eight-membered ring



Pfitzner−Moffatt conditions and then underwent facile reductive amination with commercially available *N*,*N*-dimethylethylenediamine using sodium triacetoxyborohydride (STAB) to afford *rac*-**8**. Preparative chiral phase separation of **8**[5] followed by reductive methylation with formaldehyde and hydrolysis afforded the desired **1**. Unfortunately, the preparative separation of the enantiomers of **8** or intermediates downstream on multikilogram scale proved infeasible due to low volume productivity, and an alternative route was required to support early-phase kilogram-scale preparation of **1**.

The Mitsunobu reaction is a well-established transformation to stereochemically invert secondary alcohols, facilitating a displacement by activation of the alcohol through the adduct of an azodicarboxylate and a tertiary phosphine.[6] A range of amine nucleophiles can be used in this reaction, and the formation of azides is possible at low temperatures. With this in mind, we envisaged the alcohol **3** as attractive for multikilogram preparation of **1**, and our efforts focused on exploiting this intermediate and developing a means to introduce the required nitrogen side chain to prepare **1** enantioselectively.

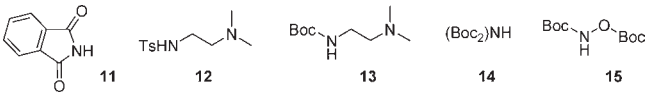


Figure 1. Nucleophiles evaluated for Mitsunobu inversion of alcohol **3**.

RESULTS AND DISCUSSION

O-Alkylation and Cyclisation to Prepare Alcohol 3. (*S*)-Glycidyl tosylate **9** was used as the alkylation agent in preference to the cheaper (*S*)-epichlorohydrin, as the latter resulted in epimerization of the stereocenter under all reaction conditions evaluated (Scheme 3). A slow, reverse addition procedure was developed to minimise the formation of dialkylated and dimeric impurities. Polar, aprotic solvents were optimal and the reaction was carried out in DMAc with potassium *tert*-butoxide as the base of choice. Thus, the preformed phenoxide anion was added as a solution in DMAc over 2 h to the epoxide in DMAc at 65 °C. The reaction was complete in 30 min and with typical assay yields of

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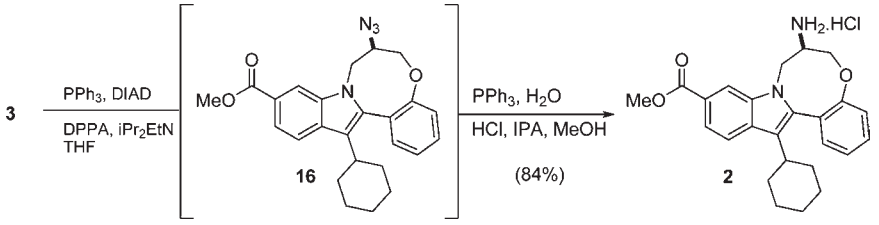
Scheme 4. One-pot Mitsunobu inversion and Staudinger reduction



85%. The reaction mixture was then cooled to 45 °C, and ethyl acetate (1 mL/g of product) was added to avoid gumming during the subsequent direct crystallisation carried out by the addition of water (10 mL/g) at 45 °C. Cooling to ambient temperature and filtration were followed by a purity upgrade of the crude product in MTBE (4 mL/g).[7] Some ring closure to **3** was observed (up to 10 area % (A%)) in this process, and since this was the desired product of the next step, this upgrade was optimised to retain as much of this as possible. The bulk scale reaction afforded epoxide **10** in 76% yield and with 95% ee.

Telescoping of the alkylation and cyclisation steps into a one-pot process was evaluated but resulted in unsatisfactory impurity levels and low overall assay yields. Consequently, the cyclisation to form **3** was developed as a discrete step. A reverse addition protocol was also applied in this step, with slow addition of the epoxide in DMAc to a slurry of cesium carbonate (0.5 equiv) in DMAc at 65 °C. This promoted intramolecular over intermolecular cyclisation by addition of the substrate into the basic solution. The reaction was complete in 30 min and was cooled to 45 °C before the addition of isopropyl acetate to aid the crystallisation. This was preferred to ethyl acetate to minimise formation of the acetate derivative of alcohol **3** which formed by way of transesterification on aging of the reaction mixture at this elevated temperature. Addition of water (10 mL/g) over 1 h with seeding at 40−50% addition ensured smooth crystallisation. Cooling to ambient temperature and aging of the slurry overnight gave mother liquor losses of less than 1%, and alcohol **3** was isolated in 88% yield with a typical 3 A% of the seven-membered ring byproduct present. The optical purity was typically 93% ee.

Mitsunobu Inversion. The secondary alcohol **3**, after activation as a tosylate or mesylate, was inert to displacement to a range of primary and secondary nitrogen nucleophiles evaluated ($MeNH_2$, $MeONH_2$, or NH_3) or underwent elimination to an olefinic byproduct when employing sodium phthalimide as nucleophile. Displacement of the secondary alcohol using diphenylphosphorylazide (DPPA) and DBU was investigated in toluene at room temperature; however, no formation of the desired azide was observed.[8] The nucleophiles **11**−**15** were tested under Mitsunobu reaction conditions to generate the chiral amine intermediate (Figure 1). Unfortunately, direct introduction of any imide or amide functionality as nucleophile was unsuccessful, and the generation of an azide intermediate proved unavoidable.

Under Mitsunobu conditions, the alcohol **3** was activated with 1.2 equiv of diisopropylazodicarboxylate (DIAD) and 1.2 equiv of triphenylphosphine in THF (Scheme 4). Following addition of 1.2 equiv of diphenylphosphorylazide (DPPA),[6e] smooth conversion to the azide **16** took place at ambient temperature (20−25 °C) and with typical assay yields of 95%. The DPPA was added after the triphenylphosphine had fully reacted with DIAD; this was critical since triphenylphosphine reacts with DPPA to form the corresponding iminophosphorane with release

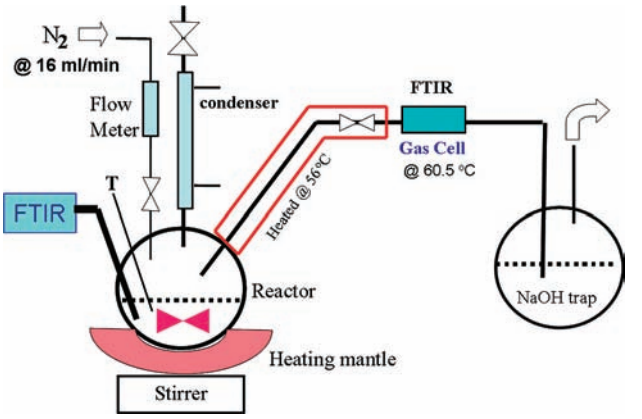


Figure 2. Equipment setup for hydrazoic acid headspace evalution using FT-IR.

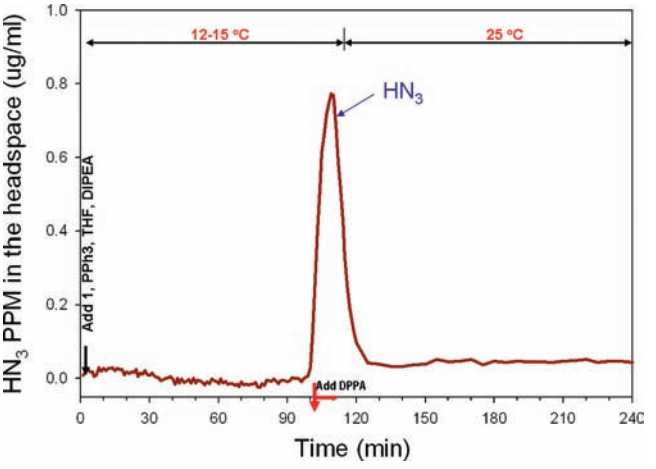


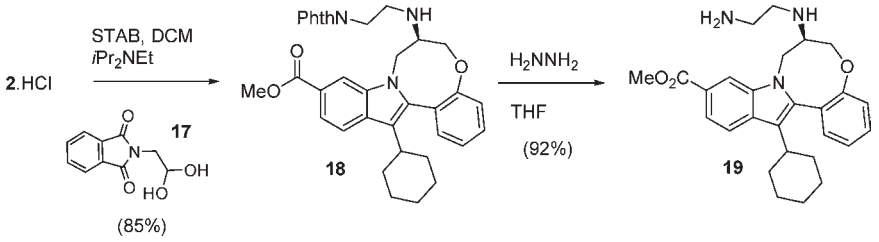
Figure 3. Hydrazoic acid measured in the headspace before and after DPPA addition.

of nitrogen.[10] Diisopropylethylamine (1.0 equiv) was also added at the reaction outset to ensure the pH of the system remained basic and thus avoid the release of hydrazoic acid in the reactor headspace. Staudinger reduction of the intermediate azide to the iminophosphorane was developed as a through-process to avoid any significant handling of the azide intermediate **16**. Thus the addition of further PPh_3 led to complete consumption of the azide **16** within 24 h at 30 °C (nitrogen off-gassing observed). Hydrolysis with water at 50 °C then afforded the primary amine **2** which was isolated as the hydrochloride salt. The 2 molar equiv of triphenylphosphine oxide formed during the reaction was completely rejected to the methanol/isopropanol mother liquors. This process gave the hydrochloride salt of primary amine **2** in

Table 1. RC-1 Calorimetry Data

batch operation	heat of reaction (kJ mol^{-1} of alcohol **3**)	adiabatic temperature rise (°C)	comments
addition of DIAD	−173.1	23.3	addition rate controlled; accumulation <5% (addition over 20 min at 10 °C)
addition of DPPA	−149.3	18.5	70% accumulation (addition over 6 min at 15 °C)
addition of THF solution of Ph_3P	−277.7	30.5	~50% accumulation (addition over 12 min at 25 °C)
addition of water	−11.8	1.3	–

Scheme 5. Reductive amination and hydrazinolysis



84% isolated yield in excellent chemical purity and with minimal erosion of enantiopurity (98 A%, 91% ee).[10]

Safety Evaluation of Mitsunobu Process. The Mitsunobu process engendered the potential formation of the toxic and highly explosive hydrazoic acid[11] as well as the stoichiometric formation of an organic azide intermediate. An explosive gas mixture can be formed with air or nitrogen when hydrazoic acid concentrations exceed 10%.[11b] Extensive safety studies were carried out to mitigate the risks involved with operating this chemical process. Online monitoring of the gas phase by FT-IR was carried out (Figure 2) and indicated that, prior to the addition of water to hydrolyse the iminophosphorane, there is less than 1 ppm HN_3 in the headspace at any point in time. Indeed HN_3 was only observed during the DPPA addition and this is likely due to the above-surface addition mode (Figure 3) and represented the level of HN_3 present in the commercially available DPPA used. After the addition of water and subsequent aging at 50 °C over 24 h, no significant amount of HN_3 is released to the headspace. Apparently, the addition of 1.2 equiv of diisopropylamine ensures any azide remains in the solution phase as the ion. Any risk of potential accumulation of hyrazoic acid in the headspace was further reduced by applying a constant sweep of nitrogen over the head space during plant operation. In addition, to avoid any opportunity for explosive liquid hydrazoic acid condensates to form upstream of the reactor, the reactor condenser system was not used during the process. Any presence of heavy metals which could catalyse azide decomposition was also avoided through ICP analysis for metal residues in the input materials and through diligent cleaning of the reactor.

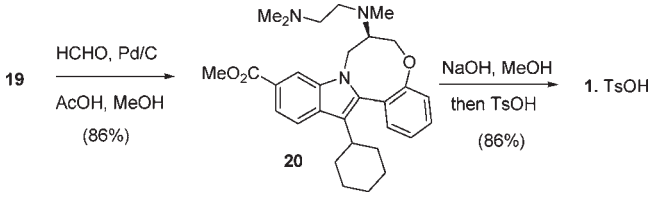
Density scanning calorimetry (DSC), advanced reactive system screening tool (ARSST) experiments as well as RC-1 calorimetry were performed to evaluate potential pressurisation and thermal properties of this chemical process (Table 1). Small exotherms are observed upon the additions of DIAD, DPPA, PPh_3 and water. When DIAD is added, the exotherm is addition-rate controlled, whilst nonproblematic accumulation of reagent occurs during the DPPA and PPh_3 additions based on the charging timecycles employed. A further safety precaution introduced for the reaction workup was to assay the residual azide content of the THF layer of the amine **2** prior to acidification. The level was typically less than 10 ppm based on ion chromatographic analysis indicating acidification could proceed without incident.

***N,N′*-Trimethylethylenediamine side-chain installation.** The elaboration of amine **2** to the desired candidate **1** required six steps using the original medicinal chemistry synthetic routes; consequently, it was desirable to shorten this. A four-step route to achieve this goal was developed.

Reductive Amination and Hydrazinolysis. Phthalimidohydrate **17** was envisaged to undergo a reductive amination with primary amine **2** as the first step to installing the ethylenediamine side chain (Scheme 5). Commercially available phthalimidoacetaldehyde diethylacetal was hydrolysed to the hydrate **17** in a procedure developed to avoid any risk of uncontrolled exothermicity. Thus, a reverse addition protocol, whereby the diethylacetal in THF (2 mL/g) was added to 6 M HCl heated to 40 °C and led to complete acetal cleavage after a 1-h age, and **17** was crystallized directly in 71% isolated yield from the reaction mixture by addition of further water.

The reductive amination of the hydrate **17** with the free base of amine **2** was initially optimized with STAB in isopropylacetate as solvent, but retention of boron residues in the product were undesirable for the subsequent chemical step (Scheme 5). Switching to dichloromethane combined with a pH-controlled workup procedure removed the boron residues successfully. The STAB was added portionwise as a solid to a solution of the hydrate **17**, amine hydrochloride **2**, and *i*-Pr_2EtN in DCM. This allowed for control of the reaction exothermicity given STAB is relatively insoluble in dichloromethane and could not therefore be added as a solution. Crystallisation of **18** from MTBE (9 mL/g) at 40 °C led to rapid crystallisation with initially small particle size, and a heat cycle (aging of batch at 50 °C for 4 h, then cooling to ambient) was used to increase the particle size to give a more rapid filtration. The isolated yield was 85%, and fortuitously, the optical purity of the isolated solids were upgraded to 98% ee at this point.

Scheme 6. Triple methylation and ester hydrolysis



The phthalimide group was removed by hydrazinolysis to form diamine **19** (Scheme 5). Optimisation of this procedure led to the use of 3 equiv of hydrazine to minimize formation of dimeric impurities. Tetrahydrofuran was the solvent of choice, and the reaction proceeded to completion in a typical 12−14 h at 30 °C with assay yields of 81−91%. The reaction workup was developed to remove the stoichiometric phthalohydrazide byproduct as the sodium salt through a wash with NaOH. Water and brine washes of the organic layer of **19** reduced the residual hydrazine levels to 2−3 ppm, ensuring distillation of the batch could then take place safely.[13] Concentration to ~4 mL/g total volume was followed by a controlled crystallisation by solvent switching to heptane via feed-and-distill, giving the product in 92% isolated yield.

Triple Reductive Methylation and Final Hydrolysis. Formation of the penultimate intermediate **20** was completed efficiently from diamine **19** in a single step by triple reductive methylation using aqueous acetic acid, formaldehyde, and Pd-catalysed hydrogenation (Scheme 6). A significant increase of conversion was observed moving from 30 to 80 psi of hydrogen, and 4 equiv of formaldehyde were required to drive the reaction to complete formation of the trimethylated amine. Heating the reaction mixture above ambient temperature led to inferior purity profiles. The catalyst of choice was Pd/C JM paste 91, and a typical 18 mol % was required to obtain complete conversion. MeOH proved to be the best solvent for the transformation with ethanol resulting in slower conversion, and the reaction profile was poor in THF or ethyl acetate. A simple direct crystallization of **20** in 86% yield was achieved following filtration of the catalyst and addition of 10 M NaOH (0.9 mL/g) to adjust the pH to 14.

Hydrolysis of penultimate **20** was achieved using 2 M NaOH in MeOH. Other solvents such as THF afforded slower conversion, although nonalcoholic solvents were preferred to mitigate any potential risk of formation of the known genetoxic toluenesulfonic acid methyl ester.[14] The hydrolysis was complete in 3 h at 70 °C, and salt formation was telescoped into the process. DCM was used to extract the zwitterionic form of **1** after neutralization with HCl. After washing with water, addition of toluenesulfonic acid hydrate as a solution in acetonitrile to the dichloromethane layer formed the tosylate salt. Impurity rejection on batch concentration and isolation was excellent, routinely giving >99 A% tosylate salt of **1** which was isolated in 86% yield and with >99% ee.

CONCLUSION

A concise enantioselective synthesis of the hepatitis C polymerase inhibitor **1** was achieved in seven isolated intermediates with 32% overall yield from commercially available indole **4**. The key issues that prohibited scale up of the medicinal chemistry route were addressed, most notably by way of the development of a one-pot Mitsunobu inversion and Staudinger reduction procedure to substitute for the hazardous utilization of sodium azide at high temperature. In addition, a more expedient elaboration of the ethylenediamine side chain was developed. Implementation on scale allowed for the preparation of >3 kg of **1** at >99 A% chemical and >99% optical purity.

EXPERIMENTAL SECTION

General. Melting points were determined by closed-cell DSC. HPLC assays were carried out using a C-18 reversed-phase column eluted with 0.1% H_3PO_4 (aq) and acetonitrile. Assay yields were obtained by HPLC using pure compounds as standards. Isolated yields refer to yields corrected for purity on the basis of HPLC assays using purified standards. All reagents and solvents were used as received without further purification. The ^{1}H and ^{13}C NMR spectra of compounds containing the dihydroindolobenzoxazocine ring are complicated by the presence of atropisomerism, and only the signals observed at 25 °C are reported.

3-Cyclohexyl-2-(2-oxiranylmethoxy-phenyl)-1*H*-indole-6-carboxylic Acid Methyl Ester (10). Methyl ester **4** (9.808 kg) was dissolved in DMAc (74.7 kg) at room temperature and potassium *tert*-butoxide (3.315 kg) added portionwise, maintaining a temperature of 20−25 °C. Separately (2*S*)-glycidyl tosylate (9.60 kg) was dissolved in DMAc (18.6 kg) and the solution heated to 65 °C. Slow addition of the phenol anion solution was then made to the (2*S*)-glycidyl tosylate solution, held at 65 °C, over 2 h. The reaction was aged 30 min, ethyl acetate (9 kg) was added, and the temperature was adjusted to 45 °C. Water (105 kg) was added slowly over 30 min, maintaining the batch temperature at 45 °C. The batch was allowed to cool to ambient temperature, filtered, and washed with DMAc/water (1:3; 7:22.5 kg) and water (30 kg) and dried in vacuo at 60 °C. The solid (11.717 kg) was then swished in MTBE (34.7 kg) overnight at ambient temperature, filtered, and washed with MTBE (6.7 kg) and dried overnight at 40 °C to give 8.647 kg (76% yield) of **10** as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.33 (1H, br s), 7.98 (1H, d, J = 1.3 Hz), 7.80 (1H, d, J = 8.5 Hz), 7.59 (1H, dd, J = 8.5 Hz, J = 1.5 Hz), 7.47−7.42 (1H, m), 7.32 (1H, dd, J = 7.5 Hz, J = 1.6 Hz), 7.20 (d, 1H, J = 8.2 Hz), 7.11 (1H, t, J = 7.4 Hz), 4.34 (1H, dd, J = 11.5 Hz, J = 2.7 Hz), 3.94−3.89 (1H, m), 3.86 (3H, s), 3.25−3.21 (1H, m), 2.79−2.76 (1H, m), 2.63−2.57 (2H, m), 1.94−1.84 (2H, m), 1.75−1.66 (5H, m), 1.38−1.16 (3H, m); ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.8, 156.6, 135.9, 134.9, 132.3, 130.5, 130.4, 122.2, 121.8, 121.3, 120.1, 119.1, 199.0, 115.5, 113.4, 69.9, 52.1, 50.1, 44.2, 36.6, 33.1, 27.2, 26.2; mp 184−186 °C. Chiracel AS-H 250 mm × 4.6 mm, 5 μm; isocratic 97:3 hexane/ethanol, flow 1.5 mL/min, 254 nm, R_t (min) 24.1 (undesired), 27.6 (desired). Enantiomeric excess 95%. HRMS (ES) Calcd for $C_{25}H_{28}NO_4$ (MH^+) 406.2018. Found 406.2019.

Methyl(7)-14-cyclohexyl-7-hydroxy-7,8-dihydro-6*H*-indolo-[1,2-*e*][1,5]benzoxazocine-11-carboxylate (3). A solution of methyl ester **10** (8.6 kg) in DMAc (24.4 kg) was added to a slurry of cesium carbonate (3.48 kg) in DMAc (56.7 kg) at 65 °C over 2 h and the resulting slurry heated at 65 °C for 30 min. The batch was then cooled to 45 °C and isopropyl acetate (7.5 kg) added. Slow addition of water (86.5 L) was then made to the batch over 30 min, maintaining the temperature at 45 °C. The batch was allowed to cool to ambient temperature (21 °C), aged for 30 min, and then filtered. The cake was washed with DMAc/water (1:3; 12 kg), water (12 kg) and dried in vacuo at 60 °C to give a pale-yellow solid (8.3 kg, 92.7% ee, 88% yield). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.22−8.20 (1H, m) 7.90−7.83 (1H, m), 7.69−7.60

(1H, m), 7.54−7.44 (1H, m) 7.32−7.17 (3H, m), 5.67 (0.7H, s br), 5.26 (0.3H, s br), 4.60−4.56 (0.3H, m), 4.42−4.38 (0.7H, m), 4.35−4.31 (0.7H, m), 4.02 (1H, s br), 3.89−3.84 (4H, m), 3.79−3.61 (2H, m), 2.75−2.64 (1H, m), 2.05−1.10 (10 H, m); ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.8, 167.7, 159.8, 158.5, 138.0, 137.8, 137.5, 135.9, 132.9, 132.1, 131.7, 131.4, 129.9, 129.8, 124.0, 123.1, 122.8, 122.7, 122.6, 122.1, 122.07, 121.0, 120.6, 120.1, 119.9, 119.3, 118.8, 118.3, 114.3, 111.8, 76.7, 75.3, 67.6, 67.2, 52.3, 52.2, 48.5, 46.7, 36.8, 36.6, 33.3, 33.2, 33.0, 27.1, 26.0, 22.1; mp 225−226 °C. Chiracel OJ-H 5 μm 250 mm × 4.6 mm, 5 μm; isocratic 95:5:0.1 hexane/ethanol/diethylamine, flow 1.5 mL/min, 55 °C, 254 nm; R_t (min) 11.5 (undesired), 15.6 (desired). Enantiomeric excess 93%. HRMS (ES) Calcd for $C_{25}H_{28}NO_4$ (MH^+) 406.2018. Found 406.2033.

Methyl (7)-7-Amino-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-][1,5]benzoxazocine-11-carboxylate hydrochloride (2·HCl). Carboxylate **3** (8.44 kg) and PPh_3 (6.55 kg, 25.0 mol) were slurried in THF (74.1 kg), diisopropylethylamine (2.69 kg, 20.8 mol) was added and the mixture cooled to 10 °C. DIAD (5.05 kg, 25.0 mol) was then added slowly over 15 min at $T \leq +15$ °C and the reaction mixture stirred for 10 min. DPPA (6.87 kg, 25.0 mol) was then added dropwise over 10 min at 15 °C, and the reaction mixture was warmed to 25 °C over a period of 30 min and the reaction mixture aged for at least 2 h. A second batch of PPh_3 (7.10 kg, 27.0 mol) dissolved in THF (6.3 kg) was added over 30 min at $T \leq +30$ °C. *[CAUTION: evolution of nitrogen gas!]* The reaction mixture was stirred for at least 8 h at 25 °C. Water (4.22 kg) was then added, and the batch was heated to 50 °C and stirred overnight for 18 h. NaOH (2 M, 200 mL) was added, the mixture stirred for 5 min, and the phases were settled and cut. Ion chromatographic analysis of the organic layer at this point indicates <4−5 ppm of residual azide (N_3^-). MeOH (59.3 kg) was added to the organic layer and a solution of concentrated HCl (4.70 kg) in IPA (96.5 kg) added dropwise, maintaining the temperature 20−25 °C; the batch aged at 20 °C for 19 h. The solid was filtered, washed with IPA twice (21.3 and 25 kg), and dried at 50 °C in vacuo for 18 h to give 6.64 kg (91% ee, 84% yield) of a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.90 (2H, br s), 8.44 (1H, s), 7.91 (1H, d, J = 8.4 Hz), 7.71 (1H, dd, J = 8.4 Hz, J = 1.2 Hz), 7.58−7.54 (1H, m), 7.35−7.28 (3H, m), 4.75−4.68 (1H, m), 4.52−4.48 (1H, m), 4.15−4.10 (1H, m), 4.02−3.93 (1H, m), 3.88 (3 H, s), 3.61−3.56 (1H, m), 2.71−2.65 (1H, m), 2.01−1.93 (3H, m), 1.84−1.82 (1H, m), 1.76−1.67 (2H, m), 1.54−1.52 (1H, m), 1.37−1.25 (2H, m), 1.18−1.08 (1H, m); ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.7, 159.1, 137.1, 135.9, 132.7, 132.0, 130.1, 124.8, 124.0, 123.2, 122.3, 122.1, 120.7, 120.0, 119.3, 112.4, 52.4, 48.7, 43.8, 36.9, 36.3, 33.2, 33.0, 27.1, 26.0, 25.6; mp >250 °C. Chiracel OD-H 250 mm × 4.6 mm, 5 μm; isocratic 98:2 hexane/ethanol +0.1% isobutylamine, flow 1.2 mL/min, 254 nm, R_t (min) 24.9 (undesired), 29.3 (desired). Enantiomeric excess 91%. HRMS (ES) Calcd for $C_{25}H_{29}N_2O_3$ (MH^+) 405.2178. Found 405.2196.

2-(2,2-Dihydroxyethyl)-isoindole-1,3-dione (17). Concentrated HCl (14.96 L, 12.68 kg) was added slowly to water (13.84 L) to form 6 M HCl that was aged for 15 min and then heated to 40 °C. A solution of phthalimidoacetaldehyde diethylacetal dissolved in THF (9.60 kg) was added slowly to the 6 M HCl over 0.5 h, maintaining the temperature at ≤+41 °C. Water (36 L) was added to the reaction mixture slowly at 40 °C, over 1 h. After cooling and aging overnight at 17 °C, the batch was filtered and washed with water (28.8 kg). Drying the batch in vacuo at 40 °C gave 4.037 kg (98.5 GC A%, 75% corrected yield) of a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.91−7.75 (4H, m), 6.32 (1H, d, J = 8.0 Hz), 5.12 (1H, dd, J = 5.6, 13.2 Hz), 3.58 (1H, dd, J = 5.6, 13.6 Hz), 3.50 (1H, dd, J = 6.0, 14.0 Hz); ^{13}C NMR (100 MHz, d_6-DMSO) δ 168.1, 134.8, 132.1, 123.5, 89.2, 43.0; GC method: RTX5 amine 30 mm × 320 mm, 1 μm; helium at 2 mL/min, constant flow, gradient 100 to 250 °C @ 20 deg min^{-1}, hold 5 min, FID, injector temperature: 50 °C, split 10:1 detector temperature 250 °C. Diluent as an internal standard was prepared by making a 0.5 mg/mL solution of benzophenone in acetonitrile. R_t (min) 17.2.

Methyl-14-cyclohexyl-7-{[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]amino}-7,8-dihydro-6*H*-indolo[1,2-*e*]-[1,5]benzoxazocine-11-carboxylate (18). Hydrochloride salt of amine **2** (6.6 kg) and 2-(2,2-dihydroxyethyl)isoindole-1,3-dione **17** (3.22 kg) were slurried in dichloromethane (87.5 kg), and the mixture was cooled to 15 °C. Disopropylethylamine (1.93 kg) was then added in one portion over 5 min and the batch aged a further 25 min to give a thin, yellow slurry. Sodium triacetoxyborohydride (4.22 kg) was then added in four equal portions (1.3 kg total) at 15-min intervals at 15 °C and the batch aged a further 80 min. The batch was cooled to 15 °C and quenched by addition of 1 M HCl (1.83 kg 37% HCl in 16.4 kg water) over 30 min. NaOH (6 M [10.2 kg, 10 M NaOH in 4.8 kg water]) was then added while maintaining T < +20 °C, the phases were separated, and the lower organic layer was washed with water (9.3 kg), and the phases were cut. The organic layer was then solvent switched to MTBE to a final volume of 53 L (9 mL/g based on starting material input) at final temperature of 40 °C to give a slurry which was cooled to 20 °C and aged overnight. Filtration, washing with MTBE (7.3 kg), and drying in vacuo at 55 °C for 16 h overnight under a nitrogen sweep gave 7.453 kg (85% yield, 97.6% ee) of a white solid. ^{1}H NMR (400 MHz, d_6-DMSO, 4:1 mixture of atropisomers) δ 8.22−8.18 (1H, m), 7.95−7.65 (6H, m), 7.43−7.31 (1H, m), 7.28−7.05 (3H, m), 4.68 (0.2H, m), 4.50−4.43 (0.8H, m), 4.23−4.18 (0.2H, m), 3.98−3.57 (8H, m), 3.18−2.95 (3H, m), 2.80−2.76 (1H, m), 2.10−1.85 (4H, m), 1.80−1.50 (5H, m) 1.45−1.30 (3H. m); ^{13}C NMR (100 MHz, d_6-DMSO) δ 137.9, 137.6, 137.4, 135.6, 134.0, 133.8, 133.7, 133.3, 132.2, 132.0, 130.7, 130.5, 130.4, 130.0, 123.4, 123.2, 123.0, 122.7, 122.5, 121.6, 121.5, 120.4, 120.4, 120.2, 120.0, 119.7, 117.9, 112.7, 111.672.5, 68.3, 56.3, 56.1, 52.0, 45.2, 45.1, 44.8, 38.9, 36.8, 36.8, 36.7, 33.3, 33.2, 33.1, 27.0, 27.0; mp 143−145 °C. Chiracel OD-H 250 mm × 4.6 mm, 5 μm, isocratic 95:5 hexane/propan-2-ol, flow 1.0 mL/min, 254 nm, R_t (min) 31.9 (undesired), 34.8 (desired). Enantiomeric excess 98%. HRMS (ES) Calcd for $C_{35}H_{36}N_3O_5$ (MH^+) 578.2655. Found 578.2648.

Methyl-7-[(2-aminoethyl)amino]-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (19). The phthalimide derivative **18** (7.35 kg) was dissolved in tetrahydrofuran (65.3 kg) and hydrazine hydrate (3.45 kg) added. The mixture was heated to 30 °C and aged overnight. The reaction mixture was cooled to ambient temperature and diluted with isopropyl acetate (64 kg), followed by addition of 2 M sodium hydroxide (88 L) and water (44 L), and this mixture was thoroughly stirred. The phases were cut, and then the organic layer was washed with distilled water (60 L), and phases were cut again and washed with 50% saturated brine solution (60 L). The batch was concentrated to low bulk (26.5 L) by distillation and flushed with isopropyl acetate (44 kg). The batch was seeded

(5 g), and a slurry formed. Heptane (38.3 kg) was added slowly over 30 min and aged overnight. The batch was concentrated to ~26 L and flushed twice with heptane (2 × 56 L) and then diluted with heptane (56 L). The solid was filtered, washed with heptane (12.3 kg), and dried in vacuo at 45 °C to give 5.36 kg (92% yield and 97.9% ee). ^{1}H NMR (400 MHz, d_6-DMSO, 4:1 mixture of atropisomers) δ 8.28 (0.2H, s), 8.13 (0.8H, s), 7.88−7.82 (1H, m), 7.70−7.55 (1H, m), 7.55−7.40 (1H, m), 7.33 − 7.15 (3H, m), 4.70−4.55 (0.2H, m), 4.55−4.45 (0.8H, m), 4.32−4.25 (0.8H, m), 4.10−4.02 (0.2H, m), 3.98−3.65 (4H, m), 3.55−3.45 (1H, m), 3.05−2.55 (6H, m), 2.05−1.05 (13 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.7, 167.6, 159.8, 158.6, 138.0, 137.8, 135.7, 133.3, 132.1, 131.6, 131.4, 129.9, 129.7, 123.7, 122.8, 122.6, 122.4, 122.0, 121.9, 120.5, 120.2, 120.1, 119.7, 119.4, 118.6, 118.5, 114.2, 111.6, 75.6, 72.4, 57.0, 56.9, 52.3, 52.2, 50.6, 50.5, 46.4, 45.4, 42.4, 42.1, 36.8, 36.6, 33.3, 33.1, 27.1, 20.1, 26.0, 22.1; mp 136−138 °C. Chiralpak AD-H 4.6 mm × 250 mm, 5 μm, isocratic 75:25 hexane/ethanol +0.1% isobutylamine, flow: 1 mL/min, 40 °C, 254 nm, R_t (min) 12 (undesired), 15 (desired). HRMS (ES) Calcd for $C_{27}H_{34}N_3O_3$ (MH^+) 448.2618. Found 448.2600.

(7*R*)-Methyl 14-cyclohexyl-7-[[2-(dimethylamino)ethyl]-(methyl)amino]-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (20). Formaldehyde (3.79 kg) and acetic acid (2.81 kg) were added to a slurry of **19** (5.23 kg) in MeOH (105 L). A slurry of Pd/C (2.53 kg) in MeOH (15 L) in an inert container was then added. and the batch was flushed with nitrogen (twice) and set under a hydrogen atmosphere (flushed three times, 80 psi, ~5.5 barg). The reaction was aged under a constant hydrogen atmosphere of 80 psi for 15 h, maintaining $T \approx 28$ °C. The reaction mixture was then filtered through Celite and washed with MeOH (2 × 20 L). NaOH (10 M ,4.70 L) was added dropwise at ambient temperature (23 °C) to the reaction filtrate over 20 min and then aged for 15 h. Water (2 × 21 kg) was then added. The solid was then filtered, washed with water (20 L), and dried at 50 °C in vacuo for 16 h to give 4.96 kg (86% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO, 4:1 mixture of atropisomers) δ 8.27 (0.2H, s), 8.14 (0.8H, s), 7.93−7.83 (1H, m), 7.72−7.58 (1H, m), 7.55−7.42 (1H, m), 7.33−7.14 (3H, m), 4.71−4.63 (0.2H, m), 4.53−4.45 (0.8H, m), 4.31−4.22 (0.8H, m), 4.10−4.02 (0.2H, m), 3.97−3.55 (3.2H, m), 3.53 (3.45 (1H, m), 3.06−3.00 (0.2H, m), 2.98−2.88 (0.8H, m), 2.86−2.75 (1H, m), 2.75−2.55 (4H, m), 2.48 (3H, br s), 2.01−1.05 (14 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.7, 167.6, 159.8, 158.6, 138.0, 137.8, 137.7, 135.7, 133.3, 132.1, 131.6, 131.4, 129.9, 129.7, 123.7, 122.8, 122.6, 122.6, 122.4, 122.0, 121.9, 120.6, 120.2, 120.1, 119.7, 119.4, 118.6, 118.5, 114.2, 111.6, 75.6, 72.3, 57.0, 56.8, 52.3, 52.2, 50.6, 50.5, 46.4, 45.4, 42.4, 42.1, 36.8, 36.6, 33.3, 33.1, 33.1, 27.1, 27.1, 26.0, 22.1; mp 139−141 °C. HRMS (ES) Calcd for $C_{30}H_{39}N_3O_3$ (MH^+) 490.3070. Found 490.3077.

(7*R*)-14-Cyclohexyl-7-[(2-dimethylamino)ethyl](methylamino)-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxacine-11-carboxylic Acid 4-Methylbenzenesulfonate (1). To a slurry of methyl ester **20** (4.94 kg) in MeOH (24.7 L, 19.5 kg) was added 2 M NaOH (aq) (10.1 L) and the reaction heated to ~72 °C for 3 h. The reaction mixture was then cooled to 20 °C and CH_2Cl_2 (52.3 kg) added, followed by 2 M HCl (aq) (10.1 L), maintaining $T < 25$ °C. The phases were then separated, and the organic layer was washed with water (8.9 kg). A slurry of TsOH monohydrate (1.864 kg) in acetonitrile (10.3 kg) was then added to the organic layer. The batch was then flushed twice with acetonitrile (2 × 36.2 kg) and the batch concentrated to ~46 L maintaining $T < 45$ °C. After cooling to ambient temperature, and aging for 1 h, the slurry was filtered and the solid washed with acetonitrile (15.4 kg). Drying in vacuo at 65 °C for 16 h gave 5.346 kg (98.0 A%, >99% ee) of **1** as a white solid in 86% yield. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.62 (1H, br s), 8.95 (1H, br s), 8.17 (1H, s), 7.88 (1H, d, J = 8.4 Hz), 7.69 (1H, d, J = 8.4 Hz), 7.59−7.7.47 (3H, m), 7.35−7.26 (3H, m), 7.09 (1H, d, 7.6 Hz), 4.66−4.53 (1H, m), 4.36−4.30 (1H, m), 4.10−4.00 (1H, m), 3.85−3.75 (1H, m), 3.33−3.25 (1H, m), 3.20−3.03 (3H, m), 2.93−2.75 (7H, m), 2.70−2.65 (1H, m), 2.33 (3H, s), 2.26 (3H, s), 2.05−1.75 (5H, m), 1.75−1.63 (2H, m), 1.55−1.45 (1H, m), 1.38−1.25 (2H, m), 1.18−1.08 (1H, m); ^{13}C NMR (100 MHz, d_6-DMSO) δ 138.2, 137.1, 135.6, 132.0, 131.8, 129.8, 128.5, 125.9, 124.2, 123.7, 123.4, 122.8, 120.5, 120.1, 118.8, 112.0, 61.9, 54.0, 49.2, 44.5, 43.0, 33.7, 33.1, 27.1, 26.0, 21.2; mp 193.6 °C. Chiracel AD-H 250 mm × 4.6 mm, 5 μm, isocratic 95:5 hexane/ethanol +0.1% isobutylamine, flow 1.2 mL/min, 254 nm, R_t (min) 19 (undesired), 29 (desired). Enantiomeric excess >99%. HRMS (ES) Calcd for $C_{29}H_{37}N_3O_3$ (MH^+) 476.2913. Found 476.2911.

FT-IR Hydrazoic acid Headspace Measurements. An FT-IR analyzer (React-IR 4000) equipped with an online gas cell (30 mL) was connected to a 250-mL jacketed resin kettle (Figure 2). The gas phase during the reaction was examined continuously by purging dry nitrogen gas through the headspace at a rate of 16 mL/min. The tubing connecting the headspace of the reactor to the IR gas-cell was heat-traced with a set temperature at 56 or 68 °C, thus preventing the condensation of HN_3 (bp 37 °C) in the tubing. In addition, another FT-IR analyzer equipped with an in situ Dicomp probe was inserted in the reaction mixture to monitor the reaction progress in the liquid phase. The typical absorption bands of HN_3 in the vapour phase are at 2126 and 2154 cm^{-1} and are the linear stretches of HN_3. In a calibration experiment, 0.05 mol NaN_3 was driven out of the aqueous phase by HCl over a period of time and purged through the IR gas-cell by nitrogen gas at 12 mL/min.

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(4) Storage of aziridine 5 at −20 °C was necessary to avoid degradation.

(5) Conditions for sCO_2 preparative separation: Chiralpak OD-H, 150 mm × 4.6 mm, 15% methanol + 25 mM isobutyl amine/CO_2, 200 bar, 35 °C, 2.5 mL/min, 6 min run time. R_t (min) 3.9 (undesired), 4.3 (desired).

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(7) This purity upgrade is primarily to remove unreacted (*S*)-glycidol tosylate **9** which is detrimental to the impurity profile of the subsequent ring closure.

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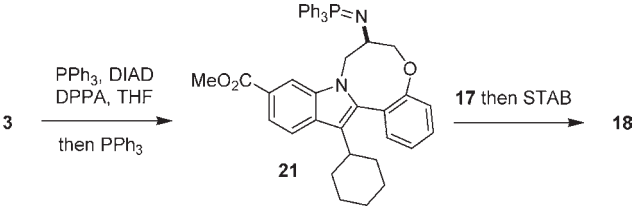

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