Organic Process Research & Development

Article

pubs.acs.org/OPRD

Process Development of a Novel Azetidinyl Ketolide Antibiotic

Bryan Li,*[,†] Thomas V. Magee,[†] Richard A. Buzon,[†] Daniel W. Widlicka,[†] Dave R. Bill,[†] Thomas Brandt,[†] Xiaoping Cao,[†] Michael Coutant,[†] Haijian Dou,[‡] Karl Granskog,[†] Mark E. Flanagan,[†] Cheryl M. Hayward,[†] Bin Li,[‡] Fengwei Liu,[‡] Wei Liu,[§] Thuy-Trinh Nguyen,[†] Jeffrey W. Raggon,[†] Peter Rose,[†] Joseph Rainville,[†] Usa Datta Reilly,[†] Yue Shen,[†] Jianmin Sun,[†] and Glenn E. Wilcox[†]

[†]Groton Laboratories, Pfizer Global Research and Development, Groton, Connecticut 06340, United States

[‡]Shanghai ChemPartner Co. Ltd., 720 Cailun Road, Zhangjiang Hi-Tech Park, Shanghai, China

[§]Asymchem Life Science Co. Ltd., No. 71, 7th Street, TEDA, Tianjin, China

ABSTRACT: Process development and the multikilogram synthesis of a novel azetidinyl ketolide antibiotic is described. Starting with clarithromycin, the eight-step synthesis features several telescoped operations and direct isolations, which results in a significant improvement in throughput and a major reduction in solvent usage and waste stream volume over the first scale-up campaign. Particular highlights of this effort include the development of an efficient synthesis of 3-hydroxy-1,5-naphthyridine-4-carbaldehyde via a Skraup process and engineering a robust final API synthesis. We also discovered a crystalline monotosylate salt that addressed significant formulation and degradation issues experienced when using the noncrystalline freebase.

INTRODUCTION

Macrolides are an important class of antibacterial agents.[1] Clarithromycin (**1b**, Figure 1) and azithromycin (**2**) are among the most prescribed medicines for the treatment of community-acquired respiratory tract infections.[2] The emergence of resistant bacterial strains in public health settings has fueled the need for novel antibacterial agents.[3] Telithromycin (**3a**)[4] represents a newer generation of ketolides that targets macrolide-sensitive and -resistant strains. Cethromycin (**3b**) is currently under late-stage development as an oral antibiotic for the treatment of life threatening infections caused by community-acquired bacterial pneumonia (CABP) and bio-defense pathogens.[5] Efforts in our antibacterial research program led to the discovery of azetidinyl ketolide **4** (Figure 1) as a promising drug candidate for the treatment of CABP, acute exacerbations of chronic bronchitis (AECB), sinusitis, and pharyngitis.[6]

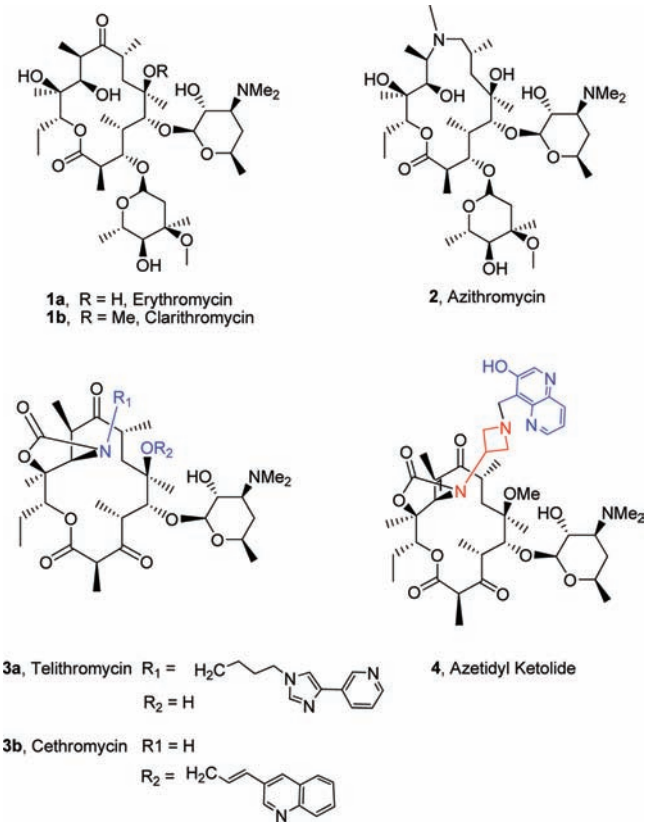


Figure 1. Structures of antibiotic macrolides.

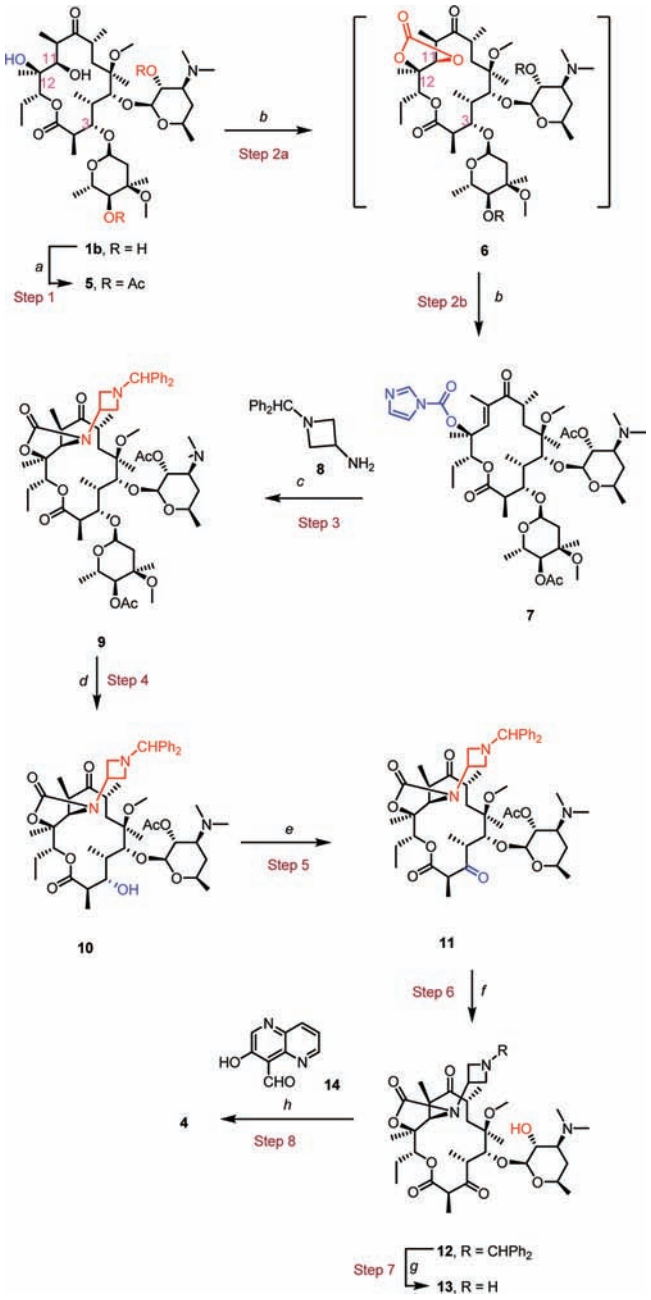
DISCUSSIONS AND RESULTS

1. Initial Route Optimization for the Synthesis of Ketolide (4). In the original synthesis[6] of macrolide **4** (Scheme 1), the azetidine (linker) and the naphthyridine (head piece) are installed sequentially in an eight-step linear sequence from clarithromycin (**1b**). In the first step, bis-acetylation of the hydroxyl groups on the desosamine and cladinose sugars of **1b** gave diacetate **5**.[7] Treatment with carbonyl diimidazole (CDI) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the C-11/C-12 cyclic carbonate **6** which subsequently eliminated to generate the intermediate C10−C11 enone, which reacted with another equivalent of CDI to afford acyl imidazole **7**.[7] Incorporation of the aminoazetidine side chain (**8**) followed by cyclization was promoted by DBU in acetonitrile and provided oxazolidinone 9. Subsequent removal of the 4″-acetylcladinose using aqueous HCl and ethanol provided the C-3 hydroxyl intermediate **10**, which was oxidized to ketone **11** using Corey−Kim oxidation conditions.[8] The penultimate intermediate **13** was generated by removal of the

Received: March 12, 2012
Published: April 30, 2012

   dx.doi.org/10.1021/op300064b | *Org. Process Res. Dev.* 2012, 16, 788−797

Scheme 1. Synthesis of azetidinyl ketolide (4)[a]

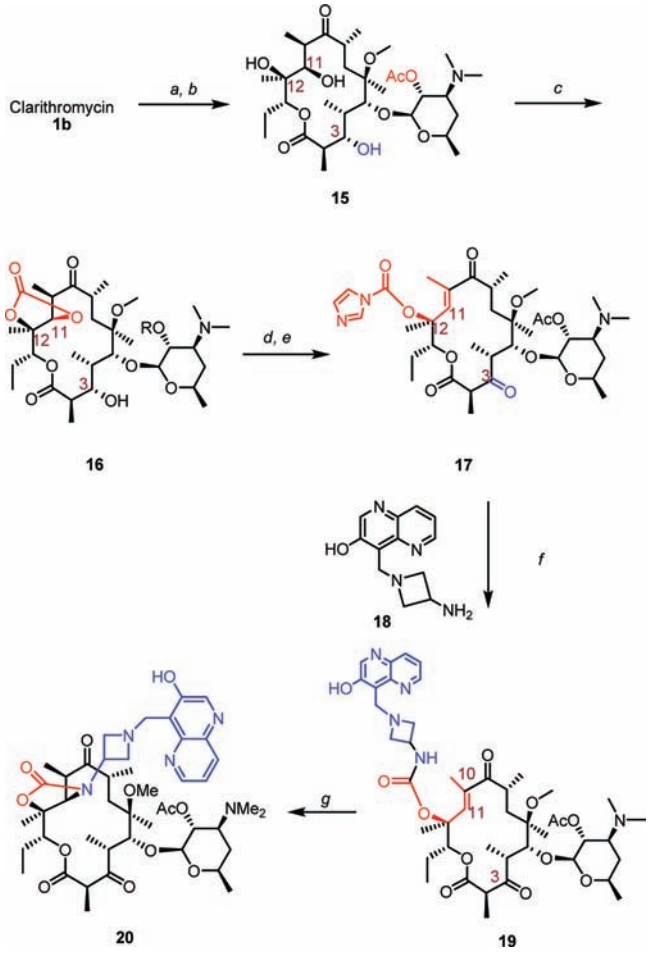


[a]Reagents and conditions used in 10 kg campaign: a) Ac_2O, TEA, DMAP, THF; b) DBU, CDI, THF; 98% overall from **1b**. c) DBU, 1-benzhydryl-azetidine-3-ylamine, MeCN, 50 °C. d) pH 2 (aq HCl), EtOH, 40 °C; 76% overall from 7. e) DMS, NCS, CH_2Cl_2. f) MeOH, 50 °C. g) Pearlman's catalyst, H_2 (50 psi), MeOH, conc. aq HCl, 35 °C; 84% overall from **10**. h) aldehyde **14**, pivalic acid, TEA, $Na(OAc)_3BH$ (STAB); reversed phase chromatography; TsOH, acetone/EtOAc, 44%.

2′-acetyl group on the desosamine sugar by heating in methanol followed by hydrogenolysis of the benzhydryl protecting group using Pearlman's catalyst. A final reductive amination was utilized to couple **13** with the 1,5-naphthyridine aldehyde **14** and afforded the desired product **4** after a tedious workup and purification. Several issues were present in this synthesis: (1) The overall throughput was less than 5%, most notably the final coupling step gave ~20% yield. (2) The final product isolated was below 90% purity (by HPLC) despite repetitive chromatographic purifications. (3) The final form of the active pharmaceutical ingredient (API) was an amorphous solid. (4) The original syntheses of both the azetidine (linker) and the naphthyridine (head piece) were not deemed scalable (vide infra).

In an attempt to obtain higher throughput and process efficiency, a more convergent synthesis was initially explored (Scheme 2). In this approach, the fully assembled azetidyl-

Scheme 2. Attempted convergent synthesis of azetidinyl ketolide 4[a]



[a]Reagents and conditions: a) Ac_2O, TEA, DMAP, DCM; b) 2N HCl, EtOH, 40 °C; c) DBU, CDI, THF, isopropyl ether; d) DMSO, pyridinium trifluoroacetate, EDC; e) DBU, CDI, MeCN; f) DIPEA, MeCN, RT; g) DBU, 80 °C, MeCN or toluene, or KO*t*Bu, THF, RT to 65 °C.

napthyridine moiety was installed after the hydrolytic cleavage of cladinose and oxidation of the resulting C-3 alcohol, therefore shortening the linear sequence. Thus, intermediate **15** was obtained by acetylation of clarithromycin (**1b**) followed by hydrolysis of the cladinose sugar. Treatment of **15** with CDI gave the cyclic carbonate **16**. Oxidation of the C-3 hydroxyl group using Moffatt conditions followed by β-elimination of the carbonate with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and concurrent reaction with CDI afforded C-12 acylimidazoyl ketolide **17**.[9] While reaction of **17** and the azetidinyl naphthyridine **18** occurred readily to give the carbamate (**19**), the subsequent intramolecular Michael addition to the

dx.doi.org/10.1021/op300064b | *Org. Process Res. Dev.* 2012, 16, 788−797

C10−C11 enone required forcing conditions and generated a number of impurities. Consequently, the desired oxazolidinone product **20** was isolated in only low yields (<20%) by chromatography. Poor reactivity in this step was attributed to steric hindrance due to the bulky 1,5-napthyridyl group. We were unable to solve this issue and therefore had to abandon this route.

2. Optimization of the Process for Pilot-Plant Manufacturing. In order to generate sufficient quantities of **4** to fund toxicology studies, the initial synthetic route was quickly enabled for a first scale-up campaign. The primary focus was to ensure the scalability of the chemistry to meet an initial delivery target of approximately 2 kg. Subsequent process development was carried out to facilitate a 10 kg API campaign to support clinical trials. With the larger-scale campaign moving into a pilot plant, it became necessary to develop a streamlined and robust process. An additional challenge was that a stable crystalline final API form had yet to be discovered and was needed to support formulation development.

In the following sections, we describe how these objectives were achieved, with concomitant reduction in solvent usage and process time, and substantially greater throughput.

2.1. Preparation of Acyl Imidazole ***7****.* In the initial scale-up, the preparation of acyl imidazole **7** followed literature conditions[8] in two discrete steps (steps 1 and 2, Scheme 1). The acetylation was accomplished with the use of Ac_2O, DMAP, and TEA in CH_2Cl_2. Formation of the acyl imidazole **7** was driven by employing excess CDI/DBU in THF. The product isolation of both steps used typical extractive workup procedures, followed by crystallization. A second crop recovery was necessary for the isolation of **7**.

By examining the unit operations, we realized that the process time, solvent consumption, and waste streams were mostly from the reaction workup/isolation. The process efficiency could be greatly improved by telescoping the steps. We found THF worked equally well as the reaction solvent for step 1 and thus eliminated the need to exchange the solvent for step 2. Although an aqueous workup for the acetylation step was still needed, the organic phase could be effectively dried by azeotropic distillation to remove a partial amount of the solvent and then be carried to step 2 directly. For the product isolation, a method was developed to precipitate **7** directly by the addition of aqueous NH_4Cl solution to the reaction mixture. The stability of **7** in aqueous THF was studied and showed no sign of decomposition at 60 °C after 4 h. This allowed the isolation of **7** in 98% yield, over two steps, in one crop.

2.2. Azetidine Linker Incorporation and Cladinose Hydrolysis. Reaction screening was performed for the incorporation of the azetidine linker and concomitant intramolecular Michael addition (step 3, Scheme 1). The optimal condition was to employ DBU in MeCN at 50 °C. In the first scale-up, the product (**9**) was isolated in two crops, and the second crop isolation required an aqueous/organic extractive manipulation.[11] For the hydrolysis (2 N HCl) of the cladinose sugar, the reaction was worked up by inverse addition of the reaction mixture to a vessel containing IPE, water, and TEA. The product (**10**) isolation was accomplished with two crops, with the second crop isolation involving extractive workup.

Since **10** is a crystalline intermediate, we recognized that the isolation of **9** could be eliminated to improve the yield. Hence, after step 3 completion, MeCN in the reaction was exchanged with EtOH[12] for the cladinose hydrolysis. We discovered that hydrolysis using a pH 2 buffer solution (using DBU as the base) offered a much cleaner reaction profile than using 2 N HCl in EtOH. The product (**10**) was readily isolated by adjusting the pH to 7.0[13] with triethylamine followed by filtration.

Table 1. Comparison of first and second campaigns for steps 1 and 2

	Campaign 1	Campaign 2	Improvement
Solvents	44 L/kg[10] total Step 1: DCM (10 L/kg) IPE (6 L/kg) Heptanes (6 L/kg) Step 2: THF (10 L/kg) IPE (6 L/kg) Heptanes (6 L/kg)	10 L/kg total Step 1: THF (10 L/kg) Step 2: Use THF carried from step 1	77% ↓
Aqueous workup	27 L/kg total Step 1: Water (8.5 L/kg) Sat. brine (5 L/kg) Step 2: NaH_2PO_4 (4.2 equiv) in water (8.5 L/kg) Sat. brine (5 L/kg)	12.5 L/kg total Step 1: Water (3.5 L/kg) Step 2: NH_4Cl (4 equiv) in water (5 L/kg)	54%↓
Reagent	CDI (5 equiv) DBU(3.5 equiv)	CDI (2.1 equiv) DBU (1.0 equiv)	58%↓ 71% ↓
Yields	74% overall Step 1: 95% Step 2: 70% (first crop) 8% (2nd crop)	98% overall Step 1: not isolated	32%↑

Table 2. Comparison of first and second scale-up runs for steps 3 and 4

	Campaign 1	Campaign 2	Improvement
Solvents	43 L/kg total Step 3: MeCN (10 L/kg) EtOAc (10 L/kg) EtOH (5 L/kg) Step 4: IPE (12 L/kg) EtOH (6 L/kg) 2N HCl (5 L/kg)	16 L/kg total Step 3: MeCN (10 L/kg) Step 4: EtOH (6 L/kg) 2N HCl (2 L/kg)	63% ↓
Aqueous workup	22 L/kg total Step 3: Water (12 L/kg) Step 4: Water (11 L/kg)	11 L/kg total Step 3: None Step 4: Water (11 L/kg)	54%↓
Yields	47% overall Step 3: 50% (first crop); 14%(second crop) Step 2: 56% (first crop); 18% (second crop)	76% overall Step 3 Not isolated	62% ↑

2.3. Oxidation, Methanolysis, and Hydrogenolysis. The Corey−Kim[8] oxidation has been demonstrated to be the most effective method for the oxidation of the C-3 alcohol for the preparation of ketolides.[14] Careful engineering control using a bleach (5%) scrubber system and proper personnel protection equipment (PPE) sufficiently addressed the concern of worker and environmental exposure. Following the standard reaction protocol, the reaction mixture after an extractive workup was treated with methanol at reflux to remove the C-2′ acetate to give **12**. In the second scale-up campaign, we elected to carry the methanol solution of **12** to the hydrogenolysis. In both campaigns we found that the hydrogenolysis stalled regardless whether **12** was isolated prior to step 7. Recrystallization and/or active carbon treatment of **12** did not remedy this issue.[15] In

dx.doi.org/10.1021/op300064b | Org. Process Res. Dev. 2012, 16, 788−797

the end, we resorted to pretreating the methanolic solution of **12** with Pearlman's catalyst, followed by hydrogenolysis. This protocol allowed the reaction to go to completion. Azetidine **13** was isolated in 84% yield overall (three steps) compared to 67% yield overall from the first campaign.

Table 3. Comparison of first and second campaigns for steps 5, 6, and 7

	Campaign 1	Campaign 2	Improvement
Solvents	41 L/kg total Steps 5 and 6: DCM (10 L/kg) MeOH (10 L/kg) Step 7: MeOH (10 L/kg) THF (6 L/kg) MTBE (5 L/kg)	31 L/kg total Steps 5 and 6: DCM (10 L/kg) MeOH (10 L/kg) Step 7: MeOH (10 L/kg) carried from step 6 THF (6 L/kg) MTBE (5 L/kg)	24% ↓
Reagents	NCS (3 equiv) DMS (3 equiv)	NCS (2 equiv) DMS (2 equiv)	33% ↓
Yields	67% overall 70% overall Steps 5 & 6 90% step 7	84% overall Steps 5 & 6 : not isolated	25% ↑

2.4. Reductive Amination and Final Form. The original reductive amination utilized to couple azetidine **13** with naphthyridine aldehyde **14** employed acetic acid, 4 Å powdered molecular sieves, and $NaBH(OAc)_3$ in methylene chloride. The reaction suffered from poor yields (~20%), and even after multiple silica gel chromatographies the highest purity achieved was still well below 90% (HPLC area %). The isolated product was an amorphous, bright yellow, foamy solid that presented significant difficulty for scale-up and isolation.

We examined the reaction and found that the original conditions gave a substantial amount of azetidinyl acetamide byproduct (**13a**, Scheme 6). This was overlooked initially due to the lack of chromophore by HPLC. In fact, when **13** was heated with acetic acid (in the presence of 2 equiv TEA to neutralize the HCl), formation of **13a** was almost quantitative. Simply changing the acid component to pivalic acid effectively blocked azetidine amidation. An additional improvement was realized by concentration of THF to azeotropically remove water,[16] which ensured that iminium intermediate **21** was formed completely. The reaction mixture was then added to a mixture of STAB in EtOAc and acetonitrile. We observed that the presence of acetonitrile consistently gave a cleaner reduction for reasons that are not well understood. The reaction was quenched by the addition of 5% sodium bicarbonate solution followed by a standard extractive workup. During the scale-up, about 30% of the product was retained as borate complex **22** as determined by LC–MS analysis. Thus, the organic solution after extractive workup was concentrated and heated at reflux in methanol for 24 h. This effectively converted **22** to the desired product (**4**) cleanly.

Since **4** was an amorphous, foamy solid, its isolation on scale was problematic. Salt screening led to the identification of the fumarate salt of **4** as a noncrystalline solid form that, while not ideal, was deemed a better alternative than the foamy freebase as it allowed the product isolation by filtration. Thus, **4** was treated with fumaric acid in ethyl acetate, and the resulting precipitate was filtered to give the final API as fumarate salt in 54% yield in ~92% HPLC purity. Further purification was only possible by chromatography, and after preparative-scale reverse-scale chromatography **4** was isolated in ≥97% purity. With cleaner material, a reinvestigation of salts of **4** resulted in identification of a monotosylate salt as a white, crystalline solid. The preparation of this salt proved straightforward on scale; a solution of **4** in acetone was treated with toluenesulfonic acid (1 equiv) at 40–45 °C to give the crystalline product. The final API was isolated in greater than 98% purity. It is noteworthy that preparation of the tosylate salt using ~92% pure **4** (from freebasing the fumarate salt of **4**) was not successful.

3. Synthesis of the Azetidine Linker and the Napthyridine Headpiece. *3.1. Synthesis of 1-Benzhydryl-azetidine-3-ylamine (**8**).* Several preparations of **8** have been reported in the literature from commercially available 1-azetidinol **23**.[17] One method (Scheme 4, steps *a*/*c*/*d*) employing the Gabriel synthesis is inefficient and suffers from the use of hydrazine hydrate (high thermal potential) to deprotect the phthalimide group. Another method (Scheme 4, steps *a*/*h*/*i*) employs azide displacement of the sulfonate followed by reduction[18] This chemistry was not pursued due to the process safety hazard associated with handling azides. The most attractive chemistry in the literature is the direct aminolysis (Scheme 4, steps *a*/*e*) of the mesylate **24**, but the procedure as described gave a poor yield (27%) of **8**.[19]

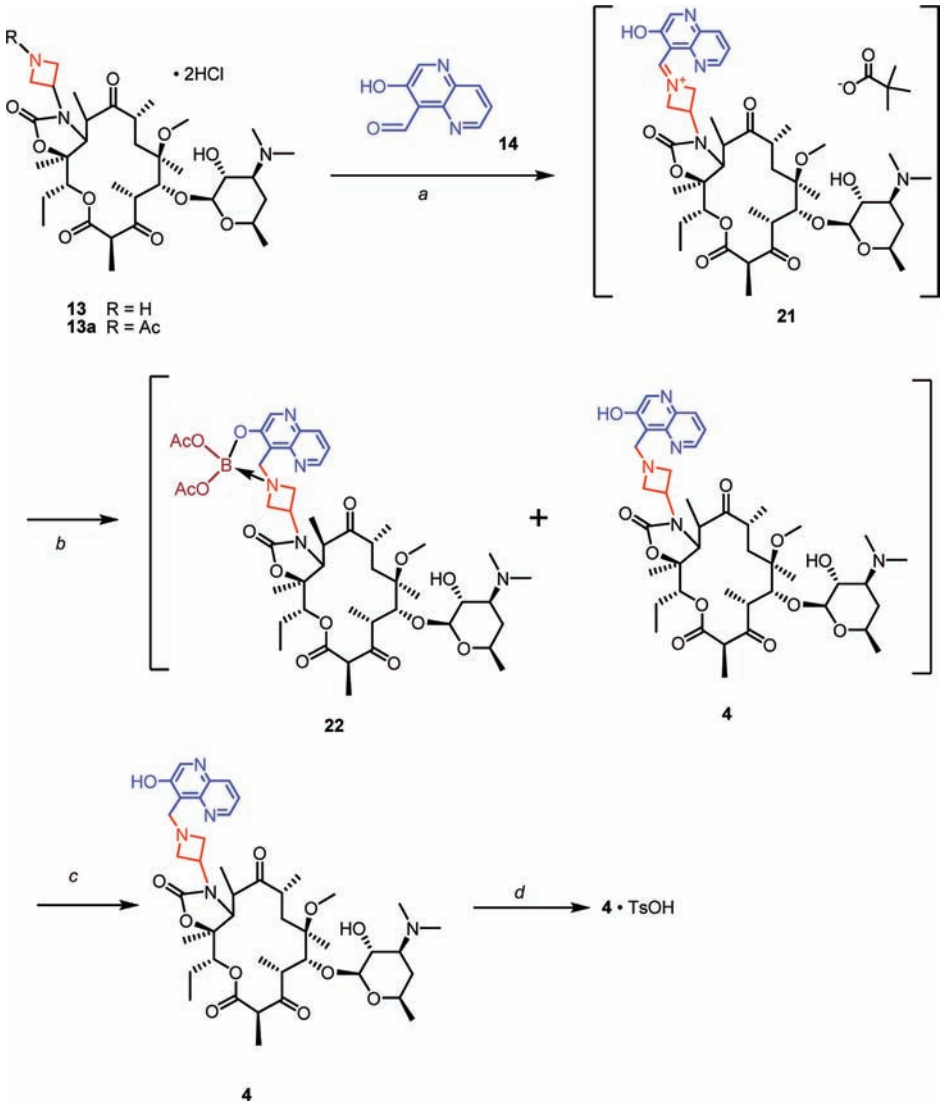
Our initial approach was a three-step sequence going through an oxime intermediate (Scheme 4, steps *g*/*j*/*k*). Swern oxidation of azetidinol **23** provided azetidinone **28** in good yield. Condensation of **28** with hydroxylamine hydrochloride provided oxime **29**, which was reduced to the amine using $LiAlH_4$. This sequence routinely gave **8** in good yields with the product conveniently isolated as the oxalic acid salt. To further streamline the process, the oxime intermediate was taken directly into the LAH reduction without isolation. Several hundred grams of **8** were delivered by this route early in the program, but as material needs increased, we recognized that the low-temperature Swern oxidation and tedious workup of the LAH reduction negatively impacted operational cost and efficiency if they were to be run in the pilot plant.

We elected to revisit the direct aminolysis of mesylate **24** and initiated an optimization of the reaction.[20] For the first step (synthesis of mesylate **24**), we first addressed reaction solvent and base, since the literature employed pyridine in both roles. By simply changing the reaction conditions to dichloromethane as the solvent and triethylamine as the base the yield was improved to ~80% after a simple extractive workup. Since mesylate **24** is a crystalline solid with minimal solubility in water, the use of acetonitrile (3 L/kg.) as reaction solvent further streamlined the process by enabling product isolation simply with the addition of water. The precipitated solid product was filtered to give a quantitative yield. Subsequently, we established that the wet cake could be directly used in the subsequent aminolysis reaction without drying.

Attention was then turned to the aminolysis of the mesylate (**24**). In our hands the literature conditions[19] did indeed result in poor yields of **8**. Our initial modification of the procedure used the more readily handled aqueous 28% ammonium hydroxide (10 L/kg) and isopropanol (15 L/kg) at 75 °C in a standard reaction flask open to the atmosphere. Under these conditions the desired product **8** was observed as the major product, but a dimeric byproduct (**27**, Scheme 4) was also formed at high levels (>35% by HPLC). While we anticipated that some **8** would react further with the mesylate (**24**) to give the dimer (**27**), we had hoped that the large excess of ammonia would suppress its formation. To prevent loss of NH_3 during the course of the reaction, the process was next conducted in a Parr reactor using 7 N ammonia in methanol for the aminolysis.

dx.doi.org/10.1021/op300064b | Org. Process Res. Dev. 2012, 16, 788–797

Scheme 3. Endgame synthesis of 4[a]



[a]Reagents and conditions: a) pivalic acid, TEA, THF. b) $Na(OAc)_3BH$ in MeCN/EtOAc. c) MeOH, reflux. d) chromatography; tosylate salt formation.

On heating this reaction to 70−75 °C, the pressure of the vessel rose to 40−50 psi. After 3 h, the reaction was nearly complete with a mixture of **8**:**27** in a 94:6 ratio by HPLC. The product was isolated by evaporation of the volatiles and recrystallized from MTBE to give a 70% yield of **8**. The use of a closed vessel for this process has a dual benefit of retaining the NH_3 and increasing the rate of the reaction, as the rate of S_N2 reactions have been reported to be accelerated by applying pressure to the reaction.[21]

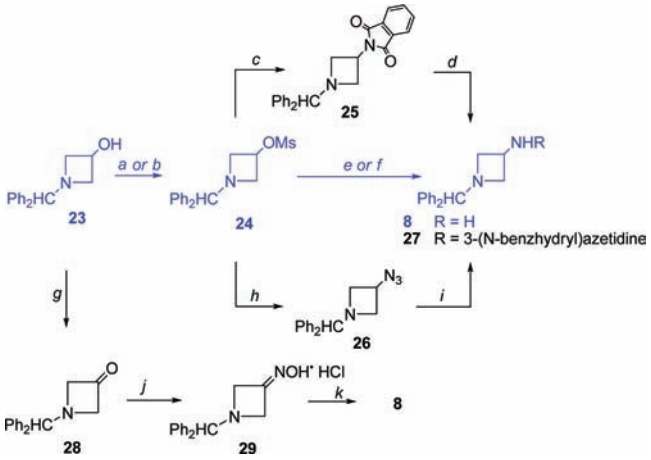
Since 7 N NH_3/MeOH is not readily available on scale, we next employed 28% aqueous NH_4OH. Again we opted to run the same reaction (10 L/kg of 28% NH_4OH and 15 L/kg of isopropanol) in the Parr Reactor and observed the dimer was reduced to approximately 4%. For workup, the reaction mixture was concentrated under reduced pressure to remove the isopropanol and the residue extracted into MTBE. As the free base is difficult to isolate as a solid, the acetate salt was precipitated directly from the organic extracts on addition of 1 equiv of acetic acid. This protocol gave a 72−84% yield of **8** on multihundred gram scale in the lab. The methanolic ammonia and the ammonium hydroxide aminolysis reactions were comparable in yields, and azetidine ring-opening products were not observed in either reactions. Using this protocol, more than 20 kg of 3-amino-1-benzhydryl-azetidine monoacetate (**8**) was prepared in high quality (>99% purity).

*3.2. Synthesis of 3-Hydroxy-1,5-naphthyridine-4-carbaldehyde (**14**).* The synthesis started with 3-bromo-5-methoxypyridine.[22] The initial approach followed a literature precedent[23] by treatment with *tert*-butylcarbamate under palladium-catalyzed conditions to give **30** (Scheme 5). The high cost of the palladium catalyst prompted us to search for more economical alternatives. Consequently, a more cost-effective amination was found using aqueous ammonia under Cu^{2+}-catalyzed conditions at 130 °C.[24] Installation of the methyl group at the 4-position and the subsequent removal of the Boc group proceeded uneventfully to afford **33**.[25]

The naphthyridine was formed via a Skraup reaction (Scheme 6). This process was highly exothermic[26] and was scaled up successfully by carefully controlling the addition rate of glycerol to the heated reaction mixture. Following the

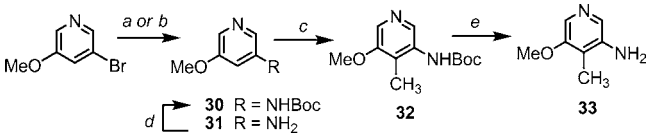
dx.doi.org/10.1021/op300064b | *Org. Process Res. Dev.* 2012, 16, 788−797

Scheme 4. Synthesis of 1-Benzhydryl-azetidine-3-ylamine (8)[a]



[a]Reagents and conditions: a) MsCl, pyridine, −10 °C, 80%; b) MsCl, NEt_3, CH_3CN, −10 °C, 100%; c) potassium phthalimide, $CH_3(CH_2)_{15}P^+Bu^n{}_3Br^-$, PhMe, reflux, 67%; d) $H_2NNH_2{\cdot}H_2O$, MeOH, reflux, 96%; e) NH_3/MeOH, 27%; f), 28% aq NH_3/Pr^iOH, 72−84%. g) Oxalyl chloride, DMSO, −78 °C, 93%. h) NaN_3, 90%. i) LAH, 74%. j) $NH_2OH{\cdot}HCl$, 96%. k) LAH, 71%.

Scheme 5. Synthesis of 5-amino-3-methyl-4-methylpyridine (33)[a]



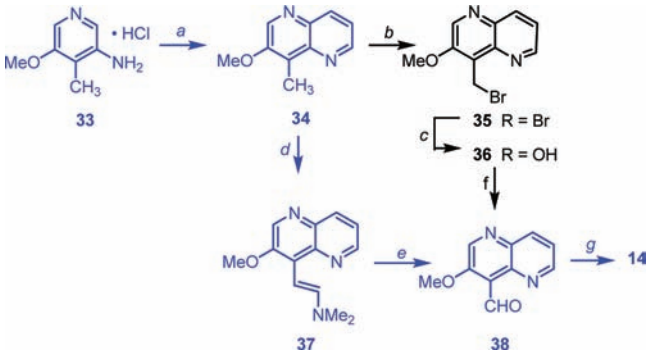
[a]Reagents and conditions: a) $BocNH_2$, $Pd_2(dba)_3$−$CHCl_3$, Xantphos, Cs_2CO_3, dioxane, 100 °C, 84%. b) NH_4OH, $CuSO_4$, 130 °C, 82%. c) n-BuLi, THF; MeI, 80%. d) Boc_2O, THF, 100%. e) 4 N HCl, MeOH; 96%.

reported procedure of a quinoline synthesis,[27] we found the reaction gave the product (**34**) in 3−48% yield using methanesulfonic acid. By switching to 75% aqueous H_2SO_4 the reaction yield was improved to 57−72%. Oxidation of **34** to the corresponding aldehyde proved to be challenging. Direct oxidation using selenium dioxide, or *t*BuI/DMSO (the Vismara[28] method) was not successful. A long sequence that involved bromination with NBS followed by acetate displacement, ester hydrolysis, and Dess−Martin oxidation was initially used to meet preclinical needs. In addition to the process safety concerns of using oxidation conditions (SeO_2, *t*BuI/DMSO or Dess−Martin methods), the approach suffered from the lack of scalability of the free radical bromination, the instability of the benzylic bromide **35**, and the low throughput. Oxidation of the benzylic bromide (**35**) with either modified Swern or Hass−Bender conditions[29] gave aldehyde **38** in poor yields.

In an alternative approach, we took inspiration from a two-step process approach involving conversion of 4-methyl pyridines to their corresponding aldehydes via an enamine intermediate. In this approach, Bredereck's reagent[30] or *N*,*N*-dimethylformamide dimethylacetal (DMF−DMA) was employed to form the *N*,*N*-dimethylenamine which,[31] on treatment with sodium periodate, could be readily transformed to the corresponding aldehyde. When **34** was treated with DMF−DMA (3.0 equiv) in DMF at 130 °C only 30% conversion was observed after 36 h. With the addition of one equivalent of Bredereck's reagent, however, complete conversion to enamine **37** was observed. We reasoned that $HC(NMe_2)_3$, a super base generated from disproportionation of Bredereck's reagent,[32] acted as the catalyst in the reaction. However, when $HC(NMe_2)_3$ was used directly as a base in the reaction, the reaction could not be driven to completion (~60% conversion). More conveniently KO*t*Bu or LiOH proved competent catalysts and their use resulted in the enamine formation being complete in 16 h at 120 °C.[33] Enamine **37** was easily isolated and purified after removing volatile materials and triturating the residue in MTBE. Nevertheless, we found that no benefit was gained through isolation of the intermediate for scale-up. Thus, the reaction mixture was carried directly into the oxidative cleavage. Ozonolysis of **37** was attempted but failed to produce the desired aldehyde. Oxidation was effected with sodium periodate uneventfully.[34]

Deprotection of the methyl ether was not straightforward. The matter was further complicated by the poor solubility of **14**.[35] Typical conditions (BBr_3, TMSI, and Me_2BBr)[36] to cleave pyridine or quinoline methyl ethers did not offer satisfactory results. Warm aqueous HCl gave the best results in the preliminary screening. However, the product obtained was of low potency (~60%). Further investigation led to the use of LiCl in DMF (110−120 °C).[37,38] In this method, the lithium salt of **14** was isolated from stirring in methanol after evaporation of DMF. The lithium salt, dissolved in hot water, was then purified by treatment with active carbon to remove color. The hot aqueous solution was then acidified to pH 5−6. Desired product **14** crystallized from the aqueous solution, and was isolated in 56% yield with high purity (>99%) (see Scheme 6).

Scheme 6. Final synthesis of 3-hydroxy-1,5-naphthyridine-4-carbaldehyde (14)[a]



[a]Reagents and conditions: a) sodium 3-nitrobenzenesulfonate, 75% H_2SO_4, $FeSO_4{\cdot}7H_2O$, boric acid, glycerol, 125−130 °C; 57−72%. b) NBS, dibenzoyl peroxide, CCl_4, 72%. c) KOAc, DMF; then MeOH, K_2CO_3; 63%. d) DMF−DMA, LiOH, DMF, 120 °C. e) $NaIO_4$, MeOH, 79% overall last two steps. f) IBX, EtOAc. g) LiCl, DMF, then aq HCl; 56%.

CONCLUSION

We have described a scale-up process for the synthesis of ketolide **4**. For the synthesis leading to the penultimate intermediate (**13**), the throughput was improved to 62% overall in seven steps in the 10 kg API campaign, as compared to 23% from the initial 2 kg scale-up. Solvent usage and waste streams were reduced by nearly 80 L/kg. With telescoped operations

dx.doi.org/10.1021/op300064b | Org. Process Res. Dev. 2012, 16, 788−797

and direct isolations implemented, the overall process became much more streamlined and efficient. The coupling of the penultimate intermediate (**13**) with the naphthyridine aldehyde (**14**) was enabled to provide a robust synthesis of the API. A crystalline monotosylate salt was discovered, which cleared a big hurdle in formulation development.

The preparations of both the amino azetidine (**8**) and the naphthyridine aldehyde (**14**) in multikilogram scales were also discussed. Aminolysis of mesylate **24** using either 7 N methanolic ammonia or 28% aqueous ammonium hydroxide under pressure was found to be more process efficient and friendly than the traditional Gabriel method or the azide/reduction approach. The process development and execution of a seven-step synthetic sequence for the synthesis of naphthyridine aldehyde (**14**) presented significant challenges. We were pleased with the successful scale-up of the highly energetic Skraup reaction and the identification of a convenient and effective oxidation of 4-methylnaphthyridine using DMF−DMA in the presence of catalytic amount of LiOH.

It is recognized that substantial development work remains necessary should the demand arise for a much larger API campaign. The convergent route (Scheme 2) is worthy of reinvestigation by exploring in situ the 3-keto protection and/or reordering oxidation step. Future considerations also include the need to replace the Corey−Kim oxidation with a more worker and environmentally friendly method, substitution of the benzhydryl group with a more readily removed protecting group, and elimination the chromatographic purification of the API.

EXPERIMENTAL SECTION

General. Achiral HPLC analyses were carried out using Agilent SB-CN columns (4.6 mm × 250 mm) with acetonitrile/0.2% perchloric acid aqueous buffer (20/80 or 40/60) as mobile phase (2 mL/min) and detection at 210 nm wavelength. HPLC purity is reported by area %.

10,11-Didehydro-11-deoxy-6-*O*-methyl-2′,4″-diacetate-12-(1*H*-imidazole-1-carboxylate)-erythromycin (7). To a glass-lined reactor was charged clarithromycin (50 kg, 66.89 mol), followed by THF (500 L). After stirring for 20 min, TEA (20.3 kg, 200.7 mol) and DMAP (408 g, 3.35 mol) were added. This was followed by addition of Ac_2O (20.5 kg, 200.7 mol). The reaction was stirred at 20−25 °C for ∼30 h. Water (150 L) was added, and the mixture was stirred for 30 min. The aqueous layer was removed. The organic phase was concentrated under atmospheric pressure (∼250 L of THF was removed). A KF analysis confirmed water at ≤0.1%. The reactor was replenished with the addition of 150 L of anhydrous THF. CDI (22.8 kg, 140 mol) was added in one portion, followed by the addition of DBU (10.2 kg, 66.89 mol) at 20−25 °C. The reaction was heated to 50 °C for 2 h until complete conversion to **7** was noted by HPLC. The reaction was cooled, and 3.5 wt % aq NH_4Cl solution (200 L) was added. The resulting mixture was stirred for 1 h and filtered. The filter cake was rinsed with water (25 L) and pulled dry under nitrogen for 2 h. The product collected was further vacuum oven-dried (45 °C, 60 mmHg) to give **7** as a white solid (59.5 kg, 98%). Analytical data of the product were identical to those reported.[8]

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-12,11-(oxycarbonyl-(1-benzhydryl-azetidin-3-yl)-imino)-erythromycin (10). To a glass-lined reactor was charged acyl imidazole **7** (47.80 kg, 52.6 mol), 3-amino azetidine **8** (16.78 kg, 55.2 mol), and acetonitrile (240 L). After stirring for 15 min, DBU (24.0 kg, 155.5 mol) was added. The reaction was heated at 50 °C for 18 h. HPLC analysis confirmed reaction completion. The reaction was concentrated by vacuum distillation to a lowest stirrable volume, the residual acetonitrile was solvent-exchanged with ethanol under vacuum until acetonitrile was below 0.5% by GC. Water (287 L) was added, followed by slow addition of conc HCl (∼38 L) until pH of 2.0 was reached. The reaction was heated at 38 °C for 16−18 h. The reaction completion was confirmed by HPLC analysis. The reaction was cooled to 20−25 °C, and water (240 L) was added. The pH of the reaction was adjusted up by slow addition of triethylamine with a target range of 7−7.5. The resulting slurry was stirred for 2 h at 15−20 °C and filtered. The filter cake was rinsed with water (240 L) and vacuum oven-dried (45 °C, 50 mmHg). This gave the desired product **10** (35.1 kg, 76%) as a white solid: MS (API-ES) 878.5 $(M + 1)^+$, 712.3, 679.3, 596. ^1H NMR ($CDCl_3$) δ 0.82 (t, 3H, J = 7.3 Hz), 0.91 (d, 3H, J = 7.4 Hz), 0.98 (d, 3H, J = 6.6 Hz), 1.05 (d, 3H, J = 7.5), 1.09 −1.88 (m, 10H), 2.05 (s, 3H), 2.13−2.15 (m, 2H), 2.17−2.30 (m, 6H), 2.38 −2.55 (m, 2H), 2.64−2.85 (m, 6H), 2.90 −3.01 (m, 2H), 3.24−3.65 (m, 6H), 3.68−3.79 (m, 3H), 4.25−4.78 (m, 6H), 5.02 (br s, 1H), 5.29 (s, 1H), 5.57 (dd, 1H, J = 6.0, 1.9 Hz) 7.05−7.58 9 (m, 10 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(azetidin-3-yl)-imino)-erythromycin A Dihydrochloride (13). To glass-lined reactor A was charged NCS (4.57 kg, 34.2 mol) and anhydrous DCM (75 L). After stirring for 15 min, the solution was cooled to −10 °C, and dimethyl sulfide (2.23 kg, 35.9 mol) was added, while keeping the temperature under −10 °C. In a separate glass-lined reactor B was charged 10 (15 kg, 17.1 mol) and then anhydrous DCM (75 L). The resulting solution was cooled to −10 °C and then transferred to reactor A slowly, while maintaining the reaction temperature below −10 °C. After the transfer was complete, triethylamine (1.9 kg, 18.8 mol) was added, while keeping the reaction below −10 °C. The reaction was stirred for 1 h under −10 °C. HPLC analysis indicated reaction completion. The reaction was allowed to warm to 10−15 °C, and saturated sodium bicarbonate solution (90 L) was added. The organic phase was separated and washed with saturated sodium bicarbonate solution (90 L) and saturated brine solution (75 L) successively. The organic phase was concentrated to a small stirrable volume, and MeOH (150 L) was added. The resulting solution was heated at reflux (66 °C) for 12 h. The reaction was cooled. Concentrated HCl (approximately 2 kg) was added to adjust the pH to a target range of 3.8−4.2. The resulting solution was then added to a nitrogen-purged vessel containing 3 kg of 20% $Pd(OH)_2$ on carbon (50% wet). The resulting mixture was stirred at 50 °C for 2 h and filtered. The filtrate was then subjected to hydrogenolysis conditions under 50 psi H_2 in the presence of 1.5 kg 20% $Pd(OH)_2$ on carbon (50% wet) at 50 °C for 2 h. Upon reaction completion, the reaction was cooled to RT and then purged with nitrogen three times and filtered. Concentrated HCl (approximately 200 mL) was added to readjust the pH to a range of 3.8−4.2. The resulting solution was concentrated under partial vacuum. The residual water was azeotropically removed by addition of THF (∼90 L total). MTBE (75 L) was added, and the resulting mixture was granulated for 2 h. The batch was filtered, and the solids were dried under vacuum to afford the desired product **13** (10.6 kg, 84% overall three steps) as a white solid: MS (ESI^+) for m/z 668.4 $(M + H)^+$. ^1H NMR (CD_3OD) δ 0.78 (t, 3H, J = 7.46

dx.doi.org/10.1021/op300064b | Org. Process Res. Dev. 2012, 16, 788−797

Hz), 0.91 (d, 3H, J = 6.64 Hz), 1.06 (d, 3H, J = 6.64 Hz), 1.08−1.30 (m, 11H), 1.32−1.79 (m, 2H), 1.95 (m, 1H), 2.38−2.54 (m, 1H), 2.59 (s, 3H), 2.68 (s, 3H). 2.77 (s, 3H), 3.02−3.39 (m, 6H), 3.52−3.65 (m, 3H), 3.94 (q, 1H, J = 7.46 Hz), 4.03−4.30 (m, 5H), 4.42 (t, 2H, J = 6.64 Hz), 4.51−4.63 (m, 2H), 4.78−4.93 (m, 2H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-((3-hydroxy-[1,5]-naphthyridin-4-yl)-methyl)-azetidin-3-yl)-imino)-erythromycin A Tosylate Salt (4). The 3-hydroxy-1,5-naphthyridine-4-carbaldehyde 14 (2.0 kg, 11.6 mol) and 3-descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(azetidin-3-yl)-imino)-erythromycin A dihydrochloride 13 (8.28 kg, 11.18 mol) were combined in THF (50 L). TEA (1.98 kg, 19.6 mol) was added. The mixture was stirred for 30 min, followed by the addition of pivalic acid (2.67 kg, 26.1 mol). The mixture was heated to reflux, and approximately 30 L of solvent was removed by concentration under atmospheric pressure to ensure complete removal of water (50 L additional amount of anhydrous THF was added during the concentration). The mixture was then cooled to 20−25 °C and transferred to another reactor that contained sodium triacetoxyborohydride (5.56 kg, 27.6 mol), acetonitrile (25 L), and ethyl acetate (50 L) at 20−25 °C under agitation. After stirring for 30 min, 5% aq sodium bicarbonate (50 L) was added. The layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 50 L). The combined organic phase was treated with anhydrous $MgSO_4$, and then active carbon (2.0 kg) was added. The mixture was filtered and concentrated to ∼10 L volume. The concentrate was purified by preparative reverse-phase chromatography using conditions as follows: Column: Kromasil C-18 100 Å; Column size: 8 in. I.D.; Temperature: 20 °C; Mobile phase: Mobile phase A = 90:10:0.06% acetonitrile/water/phosphoric acid, Mobile phase B = acetonitrile; Gradient: 15% acetonitrile 0−2 min, to 90% acetonitrile over 30 min, hold 90% acetonitrile 3 min, return to 10% acetonitrile and hold 5 min; Flow rate: 1.95 L/min, UV Detection Wavelength: 254 nm; Feed Concentration: 127 g/kg of 33% v/v acetonitrile in water; Feed Amount: ∼125 mL each injection.

Desired fractions were combined, and the acetonitrile was removed by concentration in vacuo under 20 °C. The remaining aqueous mixture was pH adjusted to 8.4 using 4% aq $NaHCO_3$ solution and then was extracted with EtOAc (3 × 90 L). The combined organic phase was washed with saturated brine solution and then concentrated under partial vacuum (100 mmHg, 45 °C) to ∼20 L. The reductive amination and purification processes were repeated at the same scale.

The combined ethyl acetate concentrate obtained above was further reduced in volume to ∼15 L by vacuum distillation. Acetone (15 L) was added, followed by dropwise addition of a solution of $TsOH{\cdot}H_2O$ (2.39 kg, 12.4 mol) in acetone (40 L). After the addition was complete, the mixture was stirred for 2 h at 20−25 °C. The product crystallized out, was filtered, rinsed with cold acetone (10 L), and dried under vacuum to give the desired product (9.82 kg, 44%) as an off-white solid: mp 198.0 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.80 (t, J = 7.42 Hz, 3H), 0.89 (d, J = 6.66 Hz, 3H), 1.10 (d, J = 7.17 Hz, 3H), 1.18−1.24 (m, 12H), 1.36 (dd, J = 12.29, 10.75 Hz, 1H), 1.48 (s, 3H), 1.55−1.60 (m, 1H), 1.60−1.64 (m, 1H), 1.65−1.71 (m, 1H), 1.71−1.77 (m, 1H), 1.90 (dd, J = 10.24, 3.07 Hz, 1H), 2.29 (s, 3H), 2.44 (dd, J = 7.17, 2.56 Hz, 1H), 2.51 (s, 3H), 2.61 (s, 6H), 3.05−3.12 (m, 2H), 3.16−3.26 (m, 1H), 3.29 (dd, J = 10.75, 7.68 Hz, 1H), 3.46 (s, 1H), 3.60−3.66 (m, 1H), 3.69 (dd, J = 6.61 Hz, 1H), 3.83 (dd, J = 6.62 Hz, 1H), 3.96−4.00 (m, 1H), 4.00−4.05 (m, 2H), 4.06 (q, J = 6.66 Hz, 1H), 4.12 (d, J = 8.19 Hz, 1H), 4.27 (d, J = 7.17 Hz, 1H), 4.65 (s, 2H), 4.79 (dd, J = 10.24, 0.66 Hz, 1H), 5.97 (br. s, 1H), 7.07−7.14 (m, 2H), 7.44−7.52 (m, 2H), 7.56 (dd, J = 8.19, 4.35 Hz, 1H), 8.29 (dd, J = 8.19, 1.54 Hz, 1H), 8.64 (s, 1 H), 8.88 (dd, J = 4.35, 1.79 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 10.20, 13.45, 13.60, 13.93, 15.35, 17.62, 19.48, 20.74, 21.66, 29.80, 37.78, 38.11, 40.05, 44.63, 45.33, 46.43, 49.11, 50.07, 52.19, 57.36, 58.90, 61.74, 64.38, 67.74, 68.76, 75.76, 77.69, 77.78, 82.61, 102.60, 120.48, 121.26, 125.47, 127.99, 136.84, 136.85, 137.53, 142.83, 144.73, 145.76, 150.57, 153.66, 155.13, 169.61, 204.18, 216.04. HRMS: calcd for $C_{43}H_{64}N_5O_{11}$: 826.45969; found: 826.45985.

1-Benzhydryl-azetidin-3-yl methanesulfonate (24). To a reaction flask was charged 632 g (2.64 mol) of 1-benzhydryl-azetidin-3-ol, acetonitrile (1.9 L), and triethylamine (601 g, 1.5 equiv). The mixture was cooled in an ice−acetone bath (−5 °C). Methanesulfonyl chloride (436 g, 1.20 equiv) was added via a drop funnel while keeping the reaction temperature at <5 °C. HPLC showed reaction completion after 15 min. Water (6.3 L) was added, and the reaction mixture was stirred for 2 h at room temperature and filtered. The filter cake was rinsed with water (2 × 1 L), pulled dry under vacuum, and directly subjected to the amination reaction in the next step.

1-Benzhydryl-azetidine-3-ylamine (8). The mesylate wet cake (838 g dry weight expected, 2.64 mol) was dissolved in isopropanol at 50 °C. The solution was charged to a 2 gal Parr reactor, followed by the addition of 28 wt % ammonium hydroxide under vacuum. The Parr reactor was sealed and heated to 71 °C for 3 h (38−40 psi pressure observed). The reaction was assayed by HPLC and showed reaction completion. The reaction mixture was cooled to room temperature, discharged from the Parr reactor, and concentrated under vacuum. The product was extracted with isopropyl ether (8.4 L). The organic extract was concentrated to ∼4 L under atmospheric pressure, and 159 g (1 equiv) of acetic acid was added; the mixture was stirred for 2 h, and the product (monoacetate salt) was collected by filtration. The solids were dried at 40 °C under vacuum to give the desired product as a white solid (662 g, 84%). ^{1}H NMR (CD_3OD, 400 MHz) 7.42−7.04 (m, 10 H), 4.44 (s, 1H), 3.78−3.62 (m, 1H), 3.43−2.36 (m, 2H), 3.03−2.99 (m, 2H), 1.93 (s, 3H). ^{13}C NMR (CD_3OD, 100 MHz) 176.2, 141.4, 128.3, 127.3, 127.2, 77.5, 58.3, 41.2, 22.2.

5-Methoxy-4-methylpyridin-3-amine Hydrochloride (33). A solution of *tert*-butyl 5-methoxypyridin-3-ylcarbamate (10.1 kg; 45 mol) in THF (125 L) was cooled to −70 °C. *n*-BuLi (2.5 M; 45.0 L; 112.5 mol; 2.5 equiv) was added dropwise, keeping T_{int} < −60 °C. The resulting mixture was warmed to −25 °C and stirred at that temperature for 1 h. The resulting solution was cooled to −70 °C, and a 2.0 M solution of MeI in MTBE (40 L, 67.5 mol, 1.5 equiv) was added dropwise, keeping T_{int} < −65 °C. The resulting mixture was stirred for 1 h at −65 °C and subsequently quenched by addition of water (50 L), allowing the reaction to warm up to 10 °C. The layers were separated, and the organic layer was washed with sat. NaCl, and concentrated to approximately 60 L volume. MeOH (10 L) was added, followed by addition of 4 N HCl (25 L, 100 mol). The resulting mixture was heated at 45 °C for 4 h and then concentrated to ∼35 L. The remaining aqueous phase was basified to pH 10.5 using 4 N NaOH solution. The precipitated product was collected by filtration.

dx.doi.org/10.1021/op300064b | Org. Process Res. Dev. 2012, 16, 788−797

The filter cake was sent back to the reactor, and dissolved in EtOAc (50 L). Gaseous HCl (1.8 kg, 49.5 mol) was introduced to the resulting solution slowly, while keeping the reaction 20−25 °C. The resulting slurry was stirred for 2 h and filtered. The filter cake was rinsed with EtOAc (5 L) and dried to give **33** hydrochloride salt as a light-yellow solid (5.8 kg, 74%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.03 (s, 3H), 3.61 (bs, 2H), 3.87 g (s, 3H), 7.71 (s, 1H), 7.76 (s, 1H).

3-Methoxy-4-methyl-1,5-naphthyridine (34). To a glass-lined reactor was charged conc. H_2SO_4 (49 kg) and sodium 3-nitrobenzene sulfonate (20.9 kg, 95.5 mol) in portions. $FeSO_4{\cdot}7H_2O$ (1.66 kg, 5.98 mol) and boric acid (2.86 kg, 46.2 mol) were added in one portion, below 40 °C. Water (13.3 kg) was then added slowly below 40 °C, followed by addition of hydrochloride salt of **33** (10 kg, 57.3 mol). The reaction mixture was heated to 135−140 °C. Glycerol (14.7 kg, 16.0 mol) was added at the rate of 50 ± 10 mL/min, while keeping the reaction at 135−145 °C. The reaction was heated for 6 h and then cooled to 80−90 °C. The reaction mixture was transferred into a vessel containing water (30 kg) and ice (100 kg); the pH was then adjusted to 8−9 with 20% aq NaOH. Additional water (220 kg) was added to dissolve the inorganic salts. The mixture was then extracted with EtOAc (3 × 200 kg). The combined organic phase was stirred with Na_2SO_4 (5 kg) and active carbon (1 kg) for 4 h. After filtration, the filtrate was concentrated under reduced pressure until black solid appeared as precipitate. DCM (54 kg) was added, the resulting mixture was stirred into complete solution with heat (40 °C), cooled, and washed with 10% aq NaOH (3 × 15 kg), followed by water (15 kg). The organic phase was filtered to remove any insoluble material and concentrated to dryness to give the desired product as a yellow solid (6.79 kg, 68%): mp 100−101 °C (MeCN). LCMS m/z (M + 1) 175.1. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.71 (s, 3H), 4.11 (s, 3H), 7.50 (dd, J = 4.1/8.5 Hz, 1H), 8.32 (dd, J = 1.8/8.5 Hz, 1H), 8.81 (s, 1H), 8.95 (dd, J = 1.8/4.1 Hz, 1H).

3-Methoxy-1,5-naphthyridine-4-carbaldehyde (38). To a glass-lined reactor was charged DMF (113 kg) and **34** (12 kg, 68.9 mol). After stirring into a complete solution, LiOH (0.33 kg, 13.8 mol) and DMF−DMA (16.4 kg, 137.6 mol) were added sequentially. The reaction was heated to 120−130 °C for 24 h and then cooled to RT. The reaction mixture was filtered and the filtrate concentrated under reduced pressure until 105 ± 5 kg of distillate was collected. The resulting residue was cooled to RT, and methanol (115 kg) was added. The resulting enamine solution in methanol was split into four identical batches for the sodium periodate oxidation. Thus, to one-fourth of the batch was added water (4.4 kg) followed by sodium periodate (7.45 kg, 34.8 mol) in portions, while keeping the reaction temperature at 30−40 °C. The reaction mixture was stirred at 30−40 °C for 16 h. $NaHCO_3$ (1.45 kg, 17.3 mol) was added to adjust the pH to 7−8. The reaction mixture was filtered, and the filter cake rinsed with methanol. The filtrate was concentrated until the residue volume was 31−47 L. Then 47.2 kg water was added, and vacuum concentration was continued until the residue was 31−47 L. To this was added 31 kg of water, and the resulting mixture was stirred for 1 h at RT. The mixture was filtered and the filter cake rinsed with water. The filter cake was dried at 50 °C under vacuum to give the product as the first crop. The mother liquor was extracted with DCM (3 × 50 L), and the combined organic phase was concentrated to a minimum stir volume. The mixture was then filtered. The filter cake was dried to give the product as the second crop. Both crops from all four batches were combined to give **38** as a yellow solid (10.2 kg, 79%): mp 170−172 °C (MeCN). ^{1}H NMR ($CDCl_3$ 400 MHz) δ 11.35 (1H, s), 9.09 (1H, s), 9.05 (1H, dd, J = 4.36, 1.86 Hz), 8.425 (1H, dd, J = 8.41, 1.55 Hz), 7.61 (1H, dd, J = 8.41, 4.05 Hz), 4.246 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.0, 57.9, 122.6, 137.4, 141.4, 152.6, 191.9.

3-Hydroxy-1,5-naphthyridine-4-carbaldehyde (14). LiCl (6.38 kg, 150 mol) was added to DMF (26.4 kg). The resulting mixture was heated to 110 −120 °C. To a second reactor, was charged DMF (44.2 kg) and **38** (9.4 kg, 50 mol), and the mixture was heated to 110−120 °C. The LiCl in DMF prepared above was transferred to the second reactor. The mixture was stirred for 30 min at 110−120 °C and then cooled to 30−40 °C. The mixture was concentrated at 60−70 °C under vacuum until the residue was 20−30 L. The material was transferred to a rotovap and continued to concentrate to dryness at 60−70 °C under vacuum (5−10 mmHg). Methanol (22.4 kg) was added, and the resulting mixture was transferred to a reactor and cooled to 0−5 °C. After stirring for 5 h, the mixture was filtered using a centrifuge filter, and the filter cake was rinsed with MeOH (7.4 kg, precooled to 0−5 °C). The filter cake was dried at 40−50 °C under vacuum to obtain the lithium salt of **1**. This was combined with water (140 kg) and active carbon (0.93 kg). The mixture was heated at 90−100 °C for 3 h. The mixture was filtered hot at 80−90 °C. To the filtrate was added 6 N HCl solution (5.31 kg) until the pH was 5−6. The reaction mixture was then stirred for 10 h at 0−5 °C and filtered. The filter cake was rinsed with water and dried at 40−50 °C under vacuum until KF ≤0.5%. This gave the product as a yellow solid (4.87 kg, 56%): mp 238−240 °C (MeOH). MS (ESI$^+$) for m/z 175 $(M + H)^+$. ^{1}H NMR (D_2O, 400 MHz) δ 10.04 (1H, s), 8.54−8.46 (1H, m), 8.46−8.40 (1H, m), 8.32 (1H, s), 7.56−7.46 (1H, m).

AUTHOR INFORMATION

Corresponding Author

*Telephone: (860) 715-1448. E-mail: bryan.li@pfizer.com.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are indebted to Mr. Michael St. Pierre, Mr. John Draper, and Mr. James Long for their manufacturing support in the Pfizer Groton Kilo Lab and the Sandwich Pilot Plant in the UK. We thank Dr. Martin A. Berliner and Mr. Michael Fichtner for their valuable inputs during the preparation of the manuscript.

REFERENCES

(1) Kaneko, T.; Dougherty, T. J.; Magee, T. V. Macrolide Antibiotics. Therapeutic Areas II: Cancer, Infectious Diseases, Inflammation & Immunology and Dermatology. *Comprehensive Medicinal Chemistry II*; Taylor, J. B.; Triggle, D. J., Eds.; Elsevier Ltd.: Oxford, UK, 2007; Vol. 7, pp 519−566.

(2) (a) Kanatani, M. S.; Guglielmo, B. J. *West J. Med.* **1994**, *160*, 31. (b) Pai, M. P.; Graci, D. M; Amsden, G. W. *Ann. Pharmacol. Ther.* **2000**, *34*, 495.

(3) (a) Metlay, J. P.; Fishman, N. O.; Joffe, M. M.; Kallan, M. J.; Chittams, J. L.; Edelstein, P. H. *Emerging Infect. Dis.* **2006**, *12*, 1223. (b) Lonks, J. R.; Garau, J.; Gomez, L.; Xercavins, M.; de Echaguen, A. O.; Gareen, I. F.; Reiss, P. T.; Medeiros, A. A. *Clin. Infect. Dis.* **2002**, *35*, 556. (c) Lynch, J. P., III; Martinez, F. J. *Clin. Infect. Dis.* **2002**, *34*, S27. (d) Hyde, T. B.; Gay, K.; Stephens, D. S.; Vugia, D. J.; Pass, M.;

Johnson, S.; Barrett, N. L.; Schaffner, W.; Cieslak, P. R.; Maupin, P. S.; Zell, E. R.; Jorgensen, J. H.; Facklam, R. R.; Whitney, C. G. *J. Am. Med. Assoc.* **2001**, *286*, 1857. (e) Waterer, G. W.; Jones, C. B. *Chest* **2000**, *118*, 1839.
(4) Zuckerman, J. M. *Infect. Dis. Clin. N. Am* **2004**, *18*, 621.
(5) Hammerschlag, M. R.; Sharma, R. *Expert Opin. Investig. Drugs* **2008**, *17*, 387.
(6) Magee, T. V.; Ripp, S. L.; Li, B.; Buzon, R. A.; Chupak, L.; Dougherty, T. J.; Finegan, S. M.; Girard, D.; Hagen, A. E.; Falcone, M. J.; Farley, K. A.; Granskog, K.; Hardink, J. R.; Huband, M. D.; Kamicker, B. J.; Kaneko, T.; Knickerbocker, M. J.; Liras, J. L.; Marra, A.; Medina, I.; Nguyen, T.-T.; Noe, M. C.; Obach, R. S.; O'Donnell, J. P.; Penzien, J. B.; Reilly, U. D.; Schafer, J. R.; Shen, Y.; Stone, G. G.; Strelevitz, T. J.; Sun, J.; Tait-Kamradt, A.; Vaz, A. D. N.; Whipple, D. A.; Widlicka, D. W.; Wishka, D. G.; Wolkowski, J. P.; Flanagan, M. E. *J. Med. Chem.* **2009**, *52*, 7446.
(7) (a) Asaka, T.; Kashimura, M.; Matsuura, A.; Sugimoto, T.; Tanikawa, T.; Ishii, T. PCT Int. Appl. WO9921869, 1999; *Chem. Abstr.* **1999**, *130*, 296955. (b) Esteban, J.; Costa, A. M.; Cruzado, M. C.; Faja, M.; Garcia, P.; Vilarrasa, J. *Tetrahedron Lett.* **2006**, *47*, 1919. (c) Kashimura, M.; Asaka, T.; Misawa, Y.; Matsumoto, K.; Morimoto, S. *J. Antibiot.* **2001**, *54*, 664. (d) Baker, W. R.; Clark, J. D.; Stephens, R. L.; Kim, K. H. *J. Org. Chem.* **1988**, *53*, 2340.
(8) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586.
(9) (a) Agouridas, C; Denis, A.; Auger, J.-M.; Benedetti, Y.; Bonnefoy, A.; Bretin, F.; Chantot, J.-F.; Dussarat, A.; Fromentin, C.; D'Ambrieres, S. G.; Lachaud, S.; Laurin, P.; Martret, O. L.; Loyau, V.; Tessot, N. *J. Med. Chem.* **1998**, *41*, 4080. (b) Kaneko, T.; McMillen, W.; Lynch, M. K. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5013.
(10) L/kg is defined as liters per kilogram of the limiting reactant in the reaction.
(11) The second crop isolation was done by subjecting the filtrate to an aqueous workup, which involved the removal of MeCN, followed by addition of EtOAc (10 L/kg) and water (10 L/kg), layer separation, solvent exchanged with EtOH (5 L/kg), and finally recrystallization from EtOH.
(12) By vacuum distillation of acetonitrile to a minimum stirrable tank volume, followed by addition of ethanol, and further azeotrope to remove residual acetonitrile.
(13) We observed that at lower pH a substantial amount of product was lost in the mother liquor, and at higher pH some impurities were not excluded from the precipitated product.
(14) (a) Xu, G.; Tang, D.; Gai, Y.; Wang, G.; Kim, H.; Chen, Z.; Phan, L. T.; Or, Y. S.; Wang, Z. *Org. Process Res. Dev.* **2010**, *14*, 504. (b) Cink, R. D.; Chambournier, G.; Surjono, H.; Xiao, Z.; Richter, S.; Naris, M.; Bhatia, A. V. *Org. Process Res. Dev.* **2007**, *11*, 270.
(15) Residual DMS or DMSO was suspected to be the scapegoat, though they were detected at ppm levels.
(16) A reliable method was to add a reaction aliquot to a vial containing STAB in EtOAc/MeCN. The sample was analyzed by HPLC−MS.
(17) Nisato, D.; Frigerio, M. Fr. Demande, FR 2560194, 1985. *Chem. Abstr.* **1986**, 533737.
(18) Okada, T.; Ezumi, K.; Yamakawa, M.; Sato, H.; Tsuji, T. *Chem. Pharm. Bull.* **1993**, *41*, 126.
(19) Arimoto, M.; Hayano, T.; Soga, T.; Yoshioka, T.; Tagawa, H.; Furukawa, M. J. *Antibiotics* **1986**, *39*, 1243.
(20) Jung, M. E.; Choi, Y. M. *J. Org. Chem.* **1991**, *56*, 6729.
(21) (a) Brower, K. R.; Chen, J. S. *J. Am. Chem. Soc.* **1965**, *87*, 3396. (b) Weale, K. E. *Discuss. Faraday Soc.* **1955**, *20*, 83. (c) Lee, K. I.; Okamoto, Y. *J. Org. Chem.* **1976**, *41*, 1552. (d) Evans, M. G.; Polanyi, M. *Trans. Faraday Soc.* **1935**, *31*, 875.
(22) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1990**, *55*, 69.
(23) Dishington, A. P.; Johnson, P. D.; Kettle, J. G. *Tetrahedron Lett.* **2004**, *45*, 3733.
(24) Hauser, C. R.; Reynolds, G. A. *J. Org. Chem.* **1950**, *15*, 1224.
(25) (a) Tamura, Y.; Fujita, M.; Chen, L.-C.; Kiyokawa, H.; Ueno, K.; Kita, Y. *Heterocycles* **1981**, *15*, 871. (b) Tamura, Y.; Fujita, M.; Chen, L-C; Inoue, M.; Kita, Y. *J. Org. Chem.* **1981**, *46*, 3564.
(26) It is commonly believed acrolein is generated by dehydration of glycerol in the reaction. This is supported by the observation of tars in the Skraup reaction from the polymerization of acrolein.
(27) Conlon, D. A.; Drahus-Paone, A.; Ho, G.-J.; Pipik, B.; Helmy, R.; McNamara, J. M.; Shi, Y.-J.; Williams, J. M.; Macdonald, D.; Deschenes, D.; Gallant, M.; Mastracchio, A.; Roy, B.; Scheigetz, J. *Org. Process Res. Dev.* **2006**, *10*, 36.
(28) Vismara, E.; Fontana, F.; Minisci, F. *Gazz. Chim. Ital.* **1987**, *117*, 135.
(29) Hass, H. B.; Bender, M. L. *Org. Synth.* **1963**, *4*, 932.
(30) Kantlehner, W.; Wagner, F.; Bredereck, H. *Liebigs Ann. Chem.* **1980**, 344.
(31) (a) Kantlehner, W.; Mergen, W. W.; Haug, E. *Liebigs Ann. Chem.* **1983**, *2*, 290. (b) Vaiu, L.; Sénéchal, K.; Maury, O.; Guégan, J.; Dupau, P.; Toupet, L.; Le Bozec, H. *Synthesis* **2003**, *4*, 577. (c) Ragan, J. A.; Jones, B. P.; Meltz, C. N.; Teixeira, J. J., Jr. *Synthesis* **2002**, *4*, 483. (d) Coe, J. W.; Vetelino, M. G. *Tetrahedron Lett.* **1994**, *35*, 219.
(32) Csihony, S.; Beaudette, T. T.; Sentman, A. C.; Nyce, G. W.; Waymouth, R. M.; Hedrick, J. L. *Adv. Synth. Catal.* **2004**, *346*, 1081.
(33) While there was no evidence a benzylic anion was involved in the reaction, it was possible that transient deprotonation of the methyl group occurred in the reaction. Thus, a strong base was needed in the reaction.
(34) The use of aqueous methanolic solution effectively addressed the process safety concerns in handling $NaIO_4$.
(35) In all solvents tried that included DMSO, MeOH, H_2O, DMF, THF, DCM, MeCN, PhMe, and acetone, the solubility was <0.3 mg/mL. The solubility was marginally better in hot DMSO (120 °C) at 1.2 mg/mL.
(36) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed., John Wiley & Sons, 1999 and references cited therein.
(37) Bernard, A. M.; Ghiani, M. R.; Piras, P. P.; Rivoldini, A. *Synthesis* **1989**, *4*, 287.
(38) One equivalent of chloromethane was generated from the demethylation reaction. During the scale-up, the off-gas was scrubbed with pyrrolidine.