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Practical and Cost-Effective Manufacturing Route for the Synthesis of a β-Lactamase Inhibitor

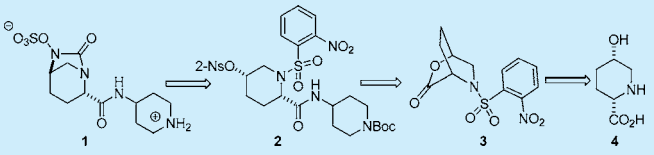
Steven P. Miller,*[,†] Yong-Li Zhong,*[,†] Zhijian Liu,[†] Michael Simeone,[‡] Nobuyoshi Yasuda,[†] John Limanto,[†] Zheng Chen,[‡] Joseph Lynch,[†] and Vincent Capodanno[‡]

[†]Process Chemistry, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065, United States

[‡]Chemical Process Development and Commercialization, Merck Manufacturing Division, P.O. Box 2000, Rahway, New Jersey 07065, United States

Supporting Information

ABSTRACT: Compound **1**, a potent and irreversible inhibitor of β-lactamases, is in clinical trials with β-lactam antibiotics for the treatment of serious and antibiotic-resistant bacterial infections. A short, scalable, and cost-effective route for the production of this densely functionalized polycyclic molecule is described.



The emergence of multidrug resistant Gram-negative bacteria has created an increasingly unmet medical need for new therapies to combat infectious diseases.[1] Not only are these bacteria associated with severe morbidity and mortality,[2] treatment of such infections has also become more difficult as resistance strengthens.[3] That being said, β-lactamase inhibitors have been demonstrated to restore the efficacy of antibacterials against pathogens that have evolved immunity to treatment over time by disrupting the central mode of bacterial resistance, namely the production of β-lactamases.[4] In this regard, MK-7655[5] (**1**), a potent and irreversible inhibitor of β-lactamases, is being clinically evaluated in conjunction with β-lactam antibiotics against severe bacterial infections. Although syntheses of this compound have been reported previously by our laboratories,[6] a short, cost-effective, safe, and scalable manufacturing route to support the late-stage drug-development program is desired.

In order to develop a desired commercial manufacturing route, we identified key aspects of the prior synthetic route that we sought to address (Figure 1). First, the conversion of **5** to **6** required optimization (Figure 1, eq 1).[7] Second, we needed to access intermediate **5** with the desired nitrogen protecting group in a more expedient and efficient manner (Figure 1, eq 2). Third, the final deprotection step involves a hazardous solvent and generated a significant amount of inorganic byproducts that afforded only a moderate yield of desired product (Figure 1, eq 3).[8]

Toward this end, we envisioned a synthetic process that continued to leverage the formation of the bicyclic urea **9** at a late stage but installed the desired Boc protecting group at the beginning (Figure 2). This would avoid the need for a cumbersome protecting group switch during the hydrogenative removal of the benzyl protecting group. Intermediate **10** would be derived from displacement of activated alcohol **2** with an appropriately functionalized hydroxyamine, where **2** would originate from the nucleophilic opening of protected lactone **3**

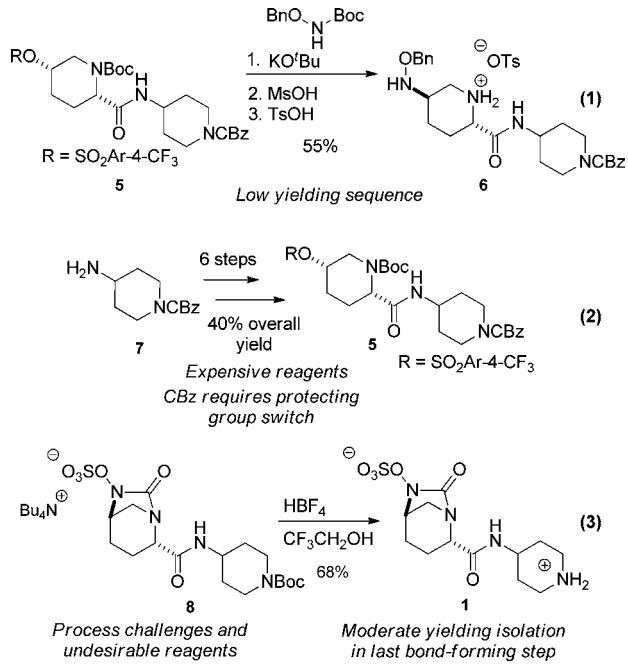


Figure 1. Issues to address in the synthesis of **1**.

with the inexpensive, commercially available amine **11**. Lactone **3** can be prepared in a straightforward manner by taking advantage of the recent availability of optically pure *cis*-5-hydroxypipecolic acid **4** from enzymatic oxidation of pipecolic acid.[9]

We began our studies by optimizing the hydroxyamine nucleophile (Table 1). When this partner bore a Boc group, as it had in the previous route, high conversion was observed but

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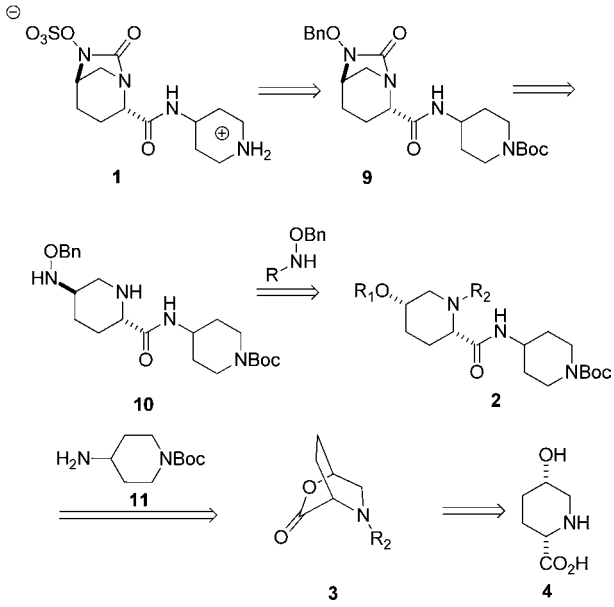
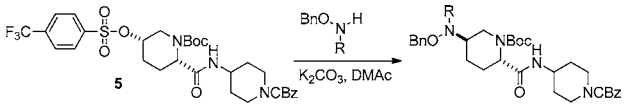


Figure 2. Retrosynthesis of **1**.

Table 1. Optimization of Sulfonate Group on the Nucleophile

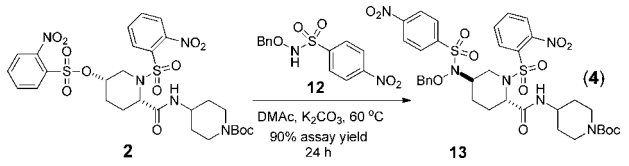


entry[a]	R	time (h)	temp (°C)	conversion (%)	yield[b]
1	Boc	6	40	>98	70
2	Ts	24	40	>98	68
3	2-Ns	72	60	63	55
4	4-Ns	72	60	>98	88

[a]Unless otherwise noted, reactions carried out with 1.2 molar equiv of base and nucleophile and a reaction concentration of 0.35 M. [b]Yields determined by HPLC.

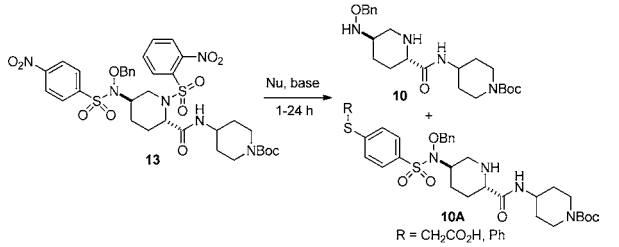
only marginal formation of the desired material (entry 1) was observed, as a significant amount of an elimination byproduct was formed. The tosyl group provided similar results (entry 2). We postulated that using an electron-poor group like 2-nitrobenzene-1-sulfonyl (2-Ns) could reduce the basicity of the nucleophile, and indeed, a more selective, albeit slower, reaction was observed in this case (entry 3). Reducing the steric bulk of the nucleophile by choosing the 4-nitrobenzene-1-sulfonyl (4-Ns) group provided the optimal balance between reactivity and basicity, as the desired product was obtained in 88% assay yield, although the reaction required 72 h to complete (entry 4).

Given the success of the 2-Ns and 4-Ns groups[10] on the nucleophile used in the displacement reaction, we hypothesized that sulfonate groups of this type might also be beneficial as both the leaving group and nitrogen protecting group on the piperidine in the displacement reaction. This strategy would hopefully enhance the speed of the reaction and unify the protecting group strategy for a potential one-step deprotection downstream. Pleasingly, compound **2** underwent the desired nucleophilic displacement in 90% HPLC assay yield in 24 h (eq 4).



Our next task was to determine the best way to remove both the 2-Ns and 4-Ns protecting groups from compound **13** (Table 2). Initially, we attempted a global deprotection using

Table 2. Optimization of Global Deprotection Conditions



entry	Nu	base	solvent	temp (°C)	**10**:**10A**[a]
1	$HSCH_2CO_2H$	LiOH	DMF	20	1.6:1
2	PhSH	K_2CO_3	DMF	50	1.8:1
3	PhSH	LiOH	DMF	20	1:4.3
4	$HSCH_2CO_2H$	LiOH	THF	50	1.6:1
5[b]	$HSCH_2CO_2H$	LiOH	MeCN	20	
6	$HSCH_2CO_2H$	LiOH	MeOH	50	10:1
7	$HSCH_2CO_2H$	K_2CO_3	MeOH	50	97:3
8	$HSCH_2CO_2H$	Cs_2CO_3	MeOH	50	97:3
9	$HSCH_2CO_2H$	DBU	MeOH	50	4:1
10	$HSCH_2CO_2H$	K_2CO_3	MeOH	20	99:1

[a]The ratio was measured by HPLC at 210 nm wavelength. [b]No desired product was detected.

conditions reported by Fukuyama[11] (entry 1) and Maligres (entry 2).[12] Unfortunately, significant amounts of a byproduct (**10A**, Table 2)[13] formed from displacement of the 4-nitro group with the thiol were observed, which was consistent with Wuts' prior observation.[14] A small survey of solvent, base, nucleophile, and temperature showed no improvement with regards to byproduct formation (entries 3–5). However, when methanol was used as the solvent in combination with LiOH and thioglycolic acid, we achieved a much improved ratio of desired product to byproduct (entry 6). A subsequent screen of bases and temperature (entries 7–10) identified the optimal reaction conditions that provided a 99:1 ratio of desired product to byproduct with very clean HPLC profile (entry 10). An important observation from the new protocol is that it requires anhydrous conditions as contamination with water generated significant amount of byproduct **10A**.

The scope of this new protocol was investigated and cleavage of 4-nitrobenzenesulfonamides under the described conditions was found to be both chemoselective and high yielding (Table 3). Sulfonamides of acyclic secondary amines (entries 1 and 2, Table 3), cyclic secondary amines (entries 3–6, Table 3), and a primary amine (entry 7, Table 3) performed well, yielding the corresponding amines in greater than 95% isolated yield and greater than 97:3 selectivity versus the byproduct. These results are notable given the reported observation that cyclic amines are prone to give the thiolate addition byproduct in up to 34.5% yield and the reported amount of byproduct for entries 1 and 2 were 3.4% and 7.5%, respectively.[14]

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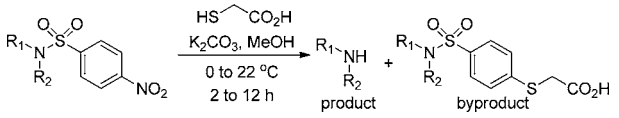
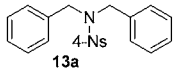
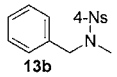
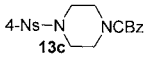
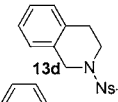
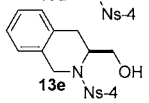
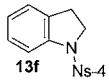
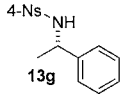
Table 3. Deprotection of 4-Nitrobenzenesulfonamides



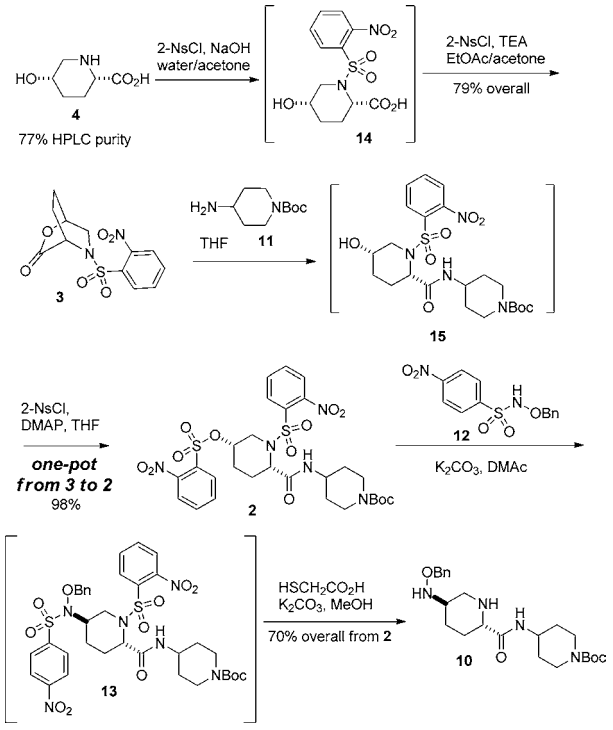
entry	substrate	product:byproduct[a,b]	yield[c] (%)
1	 13a	> 99:1	> 99
2	 13b	> 99:1	98
3	 13c	> 99:1	> 99
4	 13d	> 99:1	98
5	 13e	> 99:1	97
6	 13f	> 97:3	96
7	 13g	> 99:1	95

[a]The ratio was measured by HPLC at 210 nm wavelength. [b]Byproduct is thiolate addition to the nitro carbon of 4-nosylate. [c]Isolated yields based on an average of at least two experiments.

With the optimized nucleophilic displacement and deprotection conditions in hand, we began our synthetic route with the protection of amine **4**, which is commercially available on large scale[15] (Scheme 1). Utilizing 2-NsCl, the desired *N*-protection, subsequent lactonization via activation of the carboxylic acid with 2-NsCl, and crystallization from ethyl acetate proceeded in 79% isolated yield to provide lactone **3** in >99% purity. Given that input starting material **4** was only 77% pure,[16] this upgrade in purity was an important achievement. The choice of **4** as the starting material obviated the need to use an expensive iridium catalyst to cyclize the piperidine ring, as in the previously reported synthesis,[6] and avoided the multiple resin purifications and recrystallizations needed on scale to reduce residual iridium to pharmaceutically acceptable levels.[17] Lactone **3** was then treated with the commercially available Boc-protected aminopiperidine **11** in THF, followed by reaction with 2-NsCl and DMAP in one-pot. By choosing to pass through intermediate lactone **3** to form the amide bond, we did not need to use typical coupling reagents (e.g., EDC, CDI, T_3P, etc.), allowing for a cleaner reaction profile and a more cost-effective and environmentally benign process. Crystallization from methanol and water gave desired sulfonate ester **2** in 98% overall isolated yield from **3**.

This process constitutes a two-step synthesis of **2** from commercially available inputs in high yield and purity, while the manufacture of the respective intermediate in the previous route required six isolated steps. Combination of the subsequent displacement and deprotection steps afforded a through process from which crystalline OBn-hydroxyamine **10** was isolated in 70% yield with >97.5% HPLC purity. Completion of the synthesis involved triphosgene-mediated

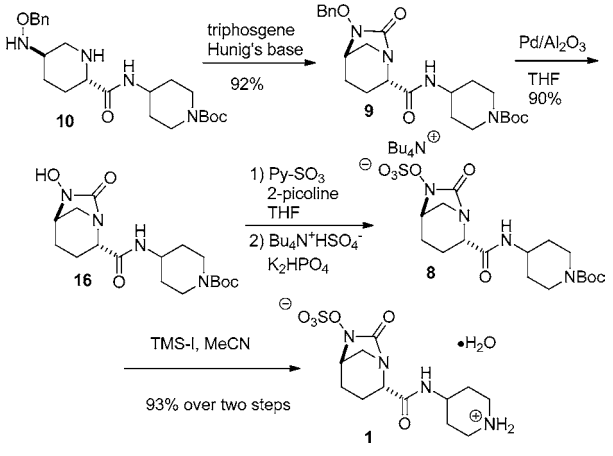
Scheme 1. Synthesis of Intermediate 10



cyclization to form urea **9** in 92% yield followed by hydrogenative removal of the benzyl group in 90% yield. Previously, the Boc removal with HBF_4 required aqueous treatment for isolation of **1** due to the significant amount of inorganic byproducts formed. To avoid this tedious handling and troublesome isolation, TMS-I was used for the removal of the Boc group following sulfation of **16**. All byproducts and impurities were soluble in the organic phase and **1** was crystallized as the monohydrate upon direct addition of 3 equivalents of water to the reaction and isolated in 93% yield over two steps.

In summary, we have developed a highly efficient and scalable manufacturing route to the β-lactamase inhibitor MK-7655 (**1**) and a practical protocol for the highly selective removal of 4-nitrobenzenesulfonamide groups. This route provides pure, crystalline **1** in 8 steps and 42% overall yield, allowing for a more cost-effective and productive manufacture

Scheme 2. Completion of the Synthesis of 1



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of the desired compound. In fact, aspects of this route have already been successfully demonstrated on multikilogram scale allowing for the continued support of the development of **1** as a cotherapy in the treatment of antibacterial resistant infections.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: steven.miller@merck.com.
*E-mail: yongli_zhong@merck.com.

Notes

The authors declare no competing financial interest.

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(7) Significant yield loss due to elimination.
(8) Trifluoroethanol posed an industrial hygiene issue and required special handling on scale. Reaction conditions led to NaF contamination and HF formation.
(9) Klein, C.; Hüttel, W. *Adv. Synth. Catal.* **2011**, *353*, 1375.
(10) Bulk cost of 2-NsCl or 4-NsCl is ~$7/kg.
(11) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. (b) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353.
(12) Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253.
(13) Compound **10A** was observed spectroscopically (HPLC, LCMS, and NMR) but was not isolated.
(14) Wuts, P. G.; Northuis, J. M. *Tetrahedron Lett.* **1998**, *39*, 3889.
(15) The projected long-term cost of **4** is $800 to $1000/kg.
(16) Much of the mass balance was various amino acids.
(17) In our case, the level required was <10 ppm.