ORGANIC LETTERS

2011
Vol. 13, No. 20
5480–5483

A Concise Synthesis of a β-Lactamase Inhibitor

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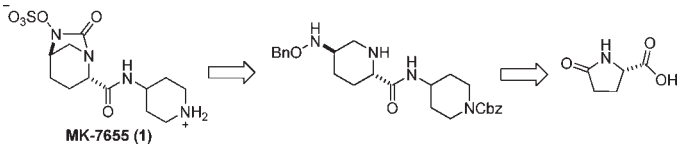
Received August 12, 2011

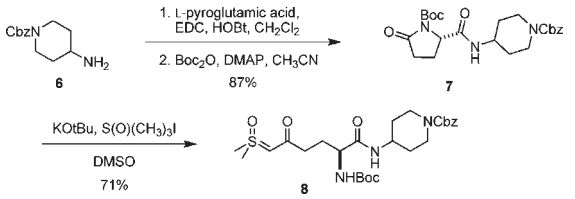
ABSTRACT



MK-7655 (1) is a β-lactamase inhibitor in clinical trials as a combination therapy for the treatment of bacterial infection resistant to β-lactam antibiotics. Its unusual structural challenges have inspired a rapid synthesis featuring an iridium-catalyzed N−H insertion and a series of late stage transformations designed around the reactivity of the labile bicyclo[3.2.1]urea at the core of the target.

The successful development of broad spectrum antibiotics remains a milestone achievement in the history of medicine, credited with having saved millions of human lives.[1] Recently, there has been a significant increase in bacterial resistance to modern antibiotics including the venerable β-lactam class of antibiotics.[2] Production of β-lactamases is a central mode of bacterial resistance,[3] and ongoing research has been directed toward the discovery and synthesis of β-lactamase inhibitors which can be used in conjunction with β-lactam antibiotics to treat otherwise resistant infections.[4] MK-7655 (**1**) is a potent, covalent β-lactamase inhibitor currently in clinical trials for the treatment of bacterial infection.[5] It features an unusual strained bicyclic urea bearing an aminoxy sulfate and has limited stability in the presence of base or nucleophiles. We sought to demonstrate a practical and economical synthesis of **1** suitable for the production of clinical supplies.

Scheme 1. Synthesis of β-Keto Sulfoxonium Ylide **8**



A robust synthesis of **1** requires judicious planning of endgame chemistry, as the lability of the urea toward nucleophiles and the polarity of the zwitterionic sulfate suggest a limited choice of appropriate conditions for synthesis and isolation. It should be noted that it is this same instability that makes MK-7655 a potent β-lactamase inhibitor. We envisioned a late stage introduction of the sulfate and urea, with the nucleophilic hydroxyamide and piperidine concealed with protecting groups as a strategy for overcoming the inherent reactivity present in **1** (**2**, Scheme 1). With that plan in place, two new synthetic challenges emerged: (1) introduction of the hydroxylamine functional group and (2) preparation of the chiral piperidine moiety, which

(1) Fabbretti, A.; Gualerzi, C. O.; Brandi, L. *FEBS Lett.* **2011**, *585*, 1673.

(2) (a) Murray, B. E. *J. Infect. Dis.* **1991**, *63*, 1185. (b) Travis, J. *Science* **1994**, *264*, 360.

(3) (a) Sanders, C. C.; Sanders, W. E. J. *Clin. Infect. Dis.* **1992**, *15*, 824. (b) Davies, J. *Science* **1994**, *264*, 375.

(4) (a) Pérez-Llarena, F. J.; Bou, G. *Curr. Med. Chem.* **2009**, *16*, 3740. (b) Drawz, S. M.; Bonomo, R. A. *Clin. Microbiol. Rev.* **2010**, *23*, 160. (c) Bebrone, C.; Lassaux, P.; Vercheval, L.; Sohier, J.-S.; Jehaes, A.; Sauvage, E.; Galleni, M. *Drugs* **2010**, *70*, 651.

(5) (a) Blizzard, T. A.; Chen, H.; Gude, C.; Hermes, J. D.; Imbriglio, J.; Kim, S.; Wu, J. Y.; Ha, S.; Mortko, C. J.; Mangion, I.; Rivera, N.; Ruck, R. T.; Shevlin, M. WO 2009091856, 2009. (b) Butterton, J. R.; Jumes, P. A.; Calder, N. A.; Rizk, M.; Nefliu, M.; Sun, P.; Schwartz, M. S.; Mangin, E. C.; Warrington, S.; Stoch, S. A.; Wagner, J. A. 50th Interscience Conference on Antimicrobial Agents and Chemotherapy, Boston, 2010, abstract F1-1967.

10.1021/ol202195n
Published on Web 09/15/2011

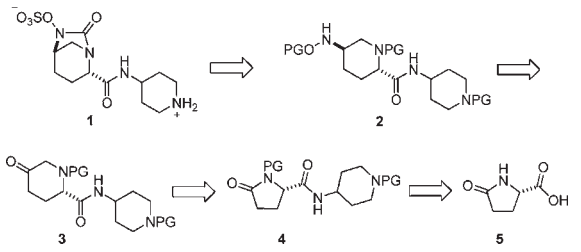


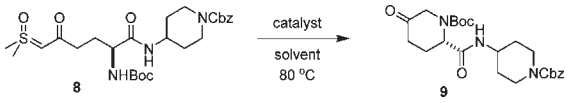
Figure 1. Retrosynthesis of **1**. PG = protecting group.

ultimately required development of novel catalytic chemistry. In our retrosynthetic analysis, the chiral hydroxylamine could derive from the net reductive amination of a ketone (**3**), which is then only a one carbon ring expansion away from amide **4**. We selected compound **4** as the initial target for our synthetic strategy, as it is a simple derivative of L-pyroglutamic acid (**5**) which can be obtained inexpensively on a multikilogram scale.

To investigate this synthetic approach, we sought to establish a strategy employing orthogonal protecting groups that would be compatible with the variety of projected reaction conditions. L-Pyroglutamic acid was coupled with Cbz-protected aminopiperidine **6** and then protected as its *tert*-butyl carbamate (**7**) in 87% yield over two steps (Figure 1). We then evaluated methods to carry out a net ring expansion of intermediate **7** to access the planned 3-piperidinone ring system. A related strategy was recently demonstrated in which a lactam was converted to its corresponding α-diazo ketone by ring opening with diazomethane; subsequent rhodium-catalyzed intramolecular N−H insertion provided the desired 3-piperidinone.[6] Bearing in mind that our route might ultimately be adapted for use on a manufacturing scale, we decided that using a similar approach represented a potential safety hazard due to the thermal or shock sensitivities of diazo compounds.[7] Instead, we drew upon chemistry first disclosed by Baldwin et al. and later developed in our laboratories using *β*-keto sulfoxonium ylides as an alternative carbene source for N−H insertions.[8] In contrast to diazo ketones, these ylides are typically crystalline and bench stable, making them well-suited for large scale processing.[9] *β*-Keto sulfoxonium ylide **8** was easily accessed in 71% yield from lactam **7** following treatment with a premixed slurry of trimethylsulfoxonium iodide and potassium *tert*-butoxide and subsequent direct crystallization by addition of water to the reaction mixture.

The proposed intramolecular N−H insertion of ylide **8** to provide ketone **9** was surveyed with a variety of metal catalysts with demonstrated reactivity toward *β*-keto sulfoxonium ylides (Table 1).[8b,c] Although some rhodium, ruthenium, and platinum catalysts demonstrated competent reactivity (entries 1−5, Table 1), it was found that $[Ir(COD)Cl]_2$ provided the highest overall yield and fastest reaction rate (entries 7−11).[10] The N−H insertion reaction proved amenable to a range of solvents (entries 7−10), but optimal results were obtained using toluene (78% yield, entry 10). The yield was further improved by changing the reaction protocol from a single charge of catalyst and substrate to a slow addition of ylide **8** to a heated mixture of $[Ir(COD)Cl]_2$ in toluene, helping to suppress dimerization of the ylide (87% yield, entry 11), the principal side reaction in this chemistry.[8b] This work represents the first practical application of the N−H insertion of a sulfoxonium ylide in a complex synthesis.[11]

Table 1. Optimization of the N−H Insertion of **8**



entry[a]	catalyst	mol %[b]	solvent	yield (%)[c]
1	$Rh_2(OAc)_4$	5	DCE	22
2	$Rh_2(TFA)_4$	5	DCE	35
3	$RuCl_2(DMSO)_4$	3	DCE	57
4	$Pt(COD)Cl_2$	5	DCE	20
5	$AuCl(SMe_2)$	5	DCE	3
6	$[Ir(Cp^*)Cl_2]_2$	1	DCE	64
7	$[Ir(COD)Cl]_2$	1	DCE	72
8	$[Ir(COD)Cl]_2$	1	THF	69[d]
9	$[Ir(COD)Cl]_2$	1	DMF	71
10	$[Ir(COD)Cl]_2$	1	Toluene	78
11	$[Ir(COD)Cl]_2$	1	Toluene	87[e]

[a] All reactions were conducted at 80 °C with degassed solvent under nitrogen at 0.05 M concentration unless otherwise noted. [b] Catalyst loading. [c] Isolated yield. [d] Reaction conducted at 65 °C. [e] **8** added slowly over 1 h to solution of $[Ir(COD)Cl]_2$ at 80 °C.

With ketone **9** in hand, we sought to effect a net diastereoselective reductive amination to access hydroxylamine **12** (Scheme 2). However, conditions to effect *in situ*

(6) Letavic, M. A.; Axt, M. Z.; Barberia, J. T.; Carty, T. J.; Danley, D. E.; Geoghean, K. F.; Alim, N. S.; Roth, L. R.; Kamath, A. V.; Liard, E. R.; Lopresti-Morrow, L.; McClure, F.; Mitchell, P. G.; Natarajan, V.; Noe, M. C.; Pandit, J.; Reeves, L.; Schulte, G. K.; Snow, S. L.; Sweeney, F. J.; Tan, D. H.; Yu, C. H. *Biorg. Med. Chem. Lett.* **2002**, *12*, 1387.

(7) (a) Moore, J. A.; Reed, D. E. *Org. Synth.* **1973**, *41*, 1961. (b) Bio, M. M.; Javadi, G.; Song, Z. J. *Synthesis* **2005**, 19.

(8) (a) Baldwin, J. E.; Adlington, R. M.; Godfrey, C. R. A.; Gollins, D. W.; Vaughan, J. G. *J. Chem. Soc., Chem. Commun.* **1993**, 1434–1435. (b) Mangion, I. K.; Nwamba, I. K.; Shevlin, M.; Huffman, M. A. *Org. Lett.* **2009**, *11*, 3566. (c) Mangion, I. K.; Weisel, M. *Tetrahedron Lett.* **2010**, *51*, 5490.

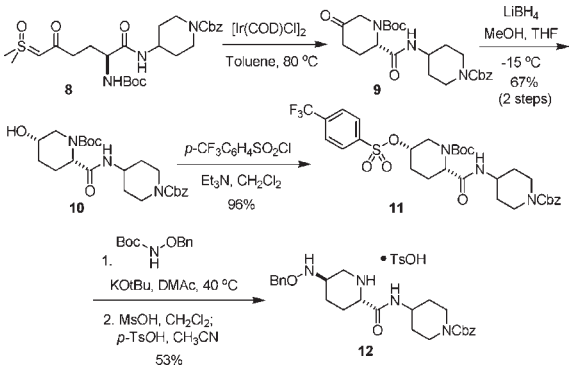
(9) Diazo compounds stabilized by two carbonyl groups have been used in manufacturing processes; see for example: (a) Salzmann, T. N.; Ratcliff, R.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161. (b) Reider, P. J.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 2293.

(10) In the absence of catalyst, no product formation is observed.

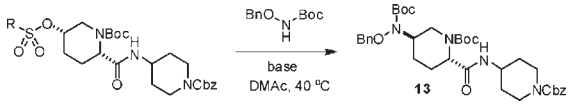
(11) We also investigated conversion of the sulfoxonium ylide to a chloro-ketone to pursue intramolecular S_N2 ring closure. However, the S_N2 was unsuccessful in either the presence or absence of the Boc protecting group on nitrogen. For a method on the conversion of sulfoxonium ylides to chloro-ketones, see: Wang, D.; Schwinden, M. D.; Radesca, L.; Patel, B.; Kronenthal, D.; Huang, M.-H.; Nugent, W. A. *J. Org. Chem.* **2004**, *69*, 1629.

(12) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199. (b) Wu, Y.-D.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 5560.

Scheme 2. Synthesis of Hydroxylamine **12**



reductive aminations of ketone **9** to afford hydroxylamine **12** directly were found to favor the undesired, *cis* diastereomer in accord with steric models and torsional steering.[12] The oxime initially formed on treament of **9** with *O*-benzyl hydroxylamine was formed as a 1:1 mixture of geometries, rendering a catalyst-driven diastereoselective reduction impractical. Therefore, we pursued a stepwise strategy of reduction of **9** to alcohol **10** followed by activation and inversion with an appropriate hydroxylamine source. In accordance with previous observations on the reduction of cyclohexanones,[13] sterically undemanding hydride reagents such as $LiBH_4$ provided the best selectivity for axial attack yielding *cis* alcohol **10** in 12:1 dr.[14]



After substantial experimentation to implement an activation−displacement strategy to access diamine **12** from alcohol **10**, it was found that the judicious choice of a sulfonate leaving group was crucial to the success of the displacement (Table 2). The desired S_N2 displacement was often hampered by competing base-mediated elimination of the sulfonate. Use of potassium *tert*-butoxide as a base improved the yield but without suppressing elimination (entries 1−4, Table 2). A variety of aryl sulfonates were evaluated (entries 4−10), and the *p*-trifluoromethylbenzene sulfonate provided the displacement product in 89% yield (entry 10) whereas more electron-rich aryl sulfonates afforded diminished yields. It was also observed that the chloromethyl sulfonate provided excellent results in the displacement (90% yield, entry 11); however, the *p*-trifluoromethylbenzene sulfonate **11** proved crystalline and easily purified, rendering it the preferred electrophile for use in the synthesis. In the event, activation of alcohol **10** as the trifluoromethylbenzene sulfonate (**11**) was achieved in 96% isolated yield. Displacement with *N*-Boc-*O*-benzyl hydroxylamine under the optimized conditions furnished hydroxylamine **12** after Boc deprotection and crystallization as its tosylate salt.

Table 2. Optimization of the Sulfonate Leaving Group

entry[a]	R	base	yield (%)[b]
1	Ph	K_3PO_4	24[c]
2	Ph	Cs_2CO_3	55[c]
3	Ph	Cs_2CO_3	61
4	Ph	KOtBu	64
5	CH_3	KOtBu	40
6	*p*-$CH_3C_6H_4$	KOtBu	57
7	*p*-FC_6H_4	KOtBu	71
8	*p*-$MeOC_6H_4$	KOtBu	44
9	*p*-BrC_6H_4	KOtBu	75
10	*p*-$CF_3C_6H_4$	KOtBu	89
11	CH_2Cl	KOtBu	90

[a] All reactions conducted at 40 °C in a 1 M dimethylacetamide solution with 1.0 equivalents of base unless otherwise noted. [b] Yield determined by HPLC. [c] Reaction conducted in CH_3CN.

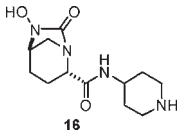
With diamine **12** in hand, we sought to identify a strategy for preparation and manipulation of the functionally reactive bicyclo[3.2.1]urea. Reaction of the diamine free base with carbonyl sources, such as carbonyldiimidazole or *p*-nitrophenylchloroformate, occurred preferentially at the piperidine nitrogen, but this intermediate failed to cyclize to the desired urea. Employment of substoichiometric triphosgene in the presence of excess Hünig's base initially led to a diverse mixture of products, consisting of only a small amount of the bicyclic urea **14**. Interestingly, subsequent addition of a dilute aqueous phosphoric acid solution led to the complete conversion of the mixture to **14**, most likely due to hydrolysis of the trichloromethylcarbamate to the amidoyl chloride or isocyanate. Urea **14** was then crystallized from the reaction in 87% isolated yield to allow entry into the sensitive end-game chemistry with high purity starting material.

Urea **14** was then deprotected to afford Boc-amine **15**, featuring the highly nucleophilic, unprotected *N*-hydroxylamine functional group in the presence of the highly electrophilic bicyclic urea. It was rapidly evident that the

(13) (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (b) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908.

(14) With DIBAL it was possible to drive equatorial attack favoring the *trans* diastereomer in a 2:1 ratio.

(15) Intermediate **16** was identified by LCMS as the following structure, which was not stable to isolation:

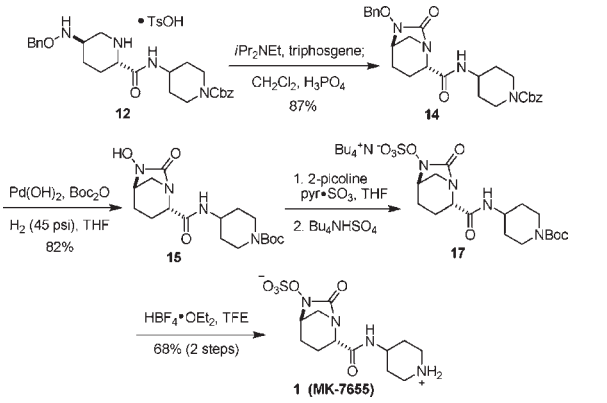


(16) $SO_3 \cdot DMF$ led to no reaction and decomposition at a rate comparable to that in the absence of any sulfating reagent. $SO_3 \cdot$trimethylamine led to rapid decomposition, presumably due to reaction of trimethylamine with the reactive urea. Chlorosulfonic acid led to Boc deprotection and subsequent decomposition.

required hydrogenolysis could not be conducted in traditional alcohol solvents due to the overwhelming presence of reactive nucleophiles; at the same time, the use of more nonpolar solvents led to deposition of fully deprotected intermediate **16** on the catalyst,[15] leading to incomplete reaction and product decomposition. Optimization efforts identified THF as the preferred solvent for this hydrogenolysis–Boc protection sequence, as it provided satisfactory solubility of intermediate **16** to afford rapid Boc protection and crystallization of free *N*-hydroxylamine **15** in 82% yield.

Completion of the synthesis of MK-7655 via a sulfation–Boc deprotection sequence required manipulation of highly reactive compound **15** and the final active pharmaceutical ingredient (API). While crystalline **15** proved bench stable for extended periods, extensive decomposition was rapidly observed in solution. Among commercially available sulfating reagents, only $SO_3 \cdot$pyridine furnished the desired product **17**, albeit at a rate that still led to significant decomposition (Scheme 3).[16] Addition of 2-picoline to the reaction mixture led to a 3-fold rate enhancement and clean conversion to sulfate **17**, worked up as the tetrabutylammonium salt to confer organic solubility on the molecule. The Boc deprotection was examined with the knowledge that MK-7655 was only stable in an aqueous pH range of 4–8. Use of acids traditionally employed for large scale Boc deprotection (e.g., HCl, MSA, *p*TsOH) led to decomposition through ring-opening hydrolysis or desulfation to a combination of intermediates **15** and **16**. Trifluoroacetic acid (TFA) allowed clean conversion to MK-7655 but required the use of 25 equiv of reagent, and it proved impossible to remove all of the TFA or its corresponding metal salts from the API. An extensive screening effort identified that 1.4 equiv of $HBF_4 \cdot OEt_2$ in 2,2,2-trifluoroethanol (TFE) was optimal for this Boc deprotection. MK-7655 was subsequently crystallized from an isopropanol/water mixture to afford β-lactamase inhibitor **1** in 68% yield over two steps.

Scheme 3. Completion of β-Lactamase Inhibitor **1**



We have described a scalable synthesis of a novel β-lactamase inhibitor, MK-7655, in 12 steps and 10% overall yield. The synthesis starts from inexpensive and readily available starting material, L-pyroglutamic acid. A net ring expansion via sulfoxonium ylide formation and a novel iridium-catalyzed N–H insertion afforded the core chiral 3-piperidinone moiety. Diastereoselective ketone reduction, alcohol activation, and displacement furnished the necessary hydroxylamine functional group. Triphosgene-mediated urea formation provided the reactive bicyclo-[3.2.1]urea that was successfully navigated through the manipulations necessary to access MK-7655. This synthesis has since been carried out on a multikilogram scale, supporting the development of this compound as a potent combination therapy with antibiotics in the treatment of bacterial infection.

Supporting Information Available. 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.