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A Catalytic Asymmetric Route to Carbapenems

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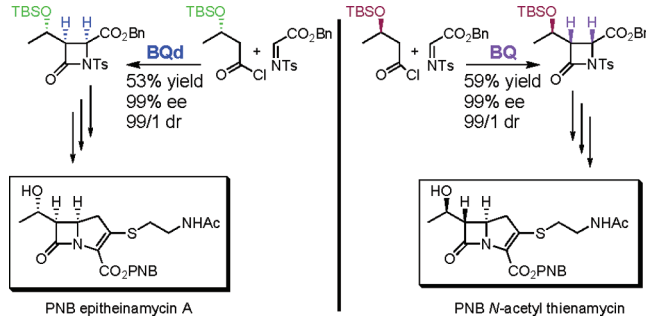
ABSTRACT



Efficient syntheses of *N*-acetyl thienamycin and epithienamycin A in their readily deprotected form are reported where three contiguous stereocenters are established in a single catalytic asymmetric azetidinone-forming reaction. These examples are a template for synthesizing C-5/C-6 *cis* or *trans* carbapenems with independent control of the C-8 stereocenter. A library of oxidatively and sterochemically defined azetidinone precursors to a variety of naturally occurring carbapenems and potential biosynthetic intermediates has been prepared to facilitate studies of carbapenem antibiotic biosynthesis.

Thienamycin and related carbapenem antibiotics show high potency, a broad spectrum of activity, and comparative stability to many clinically encountered β-lactamases that confer resistance to penicillins and cephalosporins. Efficient, scalable routes for the preparation of carbapenems are a valuable, practical goal because they are not available by large scale fermentation and/or semisynthesis. Most carbapenem syntheses proceed through azetidinone intermediates, and the majority of the synthetic effort is expended in establishing properly functionalized stereocenters at C-5, C-6, and C-8 (Figure 1). Previous reports have shown that desired C-5 and C-6 configurations can be derived from chiral precursors.[1a−d] Some common methods of azetidinone formation are ester enolate-imine condensations,[2a−d] [2 + 2] cycloaddition reactions of olefins with isocyanates[3] or ketenes with imines.[4a−c] The stereochemical outcome of the latter is highly dependent upon the substrates and reaction conditions giving C-3 and C-4 *cis* or *trans* diastereoselectively, but not enantioselectively. Optically active material has been obtained in specific cases by using ketenes or imines bearing chiral auxiliaries, but these reactions are not applicable to general carbapenem synthesis.[5a−c] Azetidinones with a carboxylic acid **8**, carboxymethylene **9**, or an equivalent group at C-4 can be converted by several methods to carbapenems.[6a−c]

To carry out biosynthetic studies of the carbapenems, we required syntheses of naturally occurring carbapenams/ems

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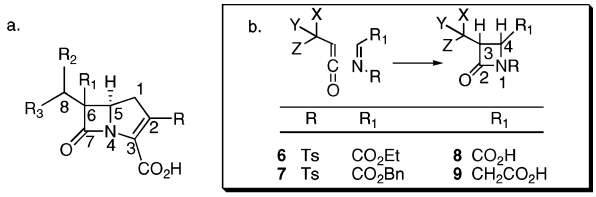


R	R	R_1	R_2	R_3
1 thienamycin	$SCH_2CH_2NH_2$	(*S*) H	(*R*) OH	CH_3
2 epithienamycin A	SCH_2CH_2NAc	(*R*) H	(*S*) OH	CH_3
3 PS-5	SCH_2CH_2NAc	(*S*) H	H	CH_3
4 PS-6	SCH_2CH_2NAc	(*S*) H	CH_3	CH_3
5 deshydroxy northienamycin	$SCH_2CH_2NH_2$	(*S*) H	H	H

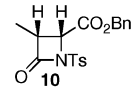
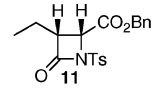
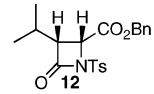
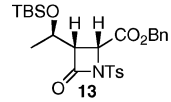
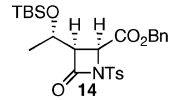
Figure 1. (a) Naturally occurring carbapenems and potential biosynthetic intermediates. (b) Azetidinone forming reactions of ketenes and imines.

and potential pathway intermediates to serve as enzyme substrates and reference standards. The naturally occurring carbapenems number about 50 and constitute a native combinatorial library exhibiting modulated biological activities expressed in substituent and oxidation state variation at C-2 and C-6.[7] Moreover, advanced investigations of the simplest carbapenem, carbapen-2-em-3-carboxylic acid,[8] and thienamycin[9] have established that an epimerization event occurs at C-5 (from *S* to *R*) during the course of biosynthesis. Thus, an approach was needed to establish either the 5*S*- or 5*R*-configuration, establish the relative *cis* or *trans* stereochemistry of the C-6 substituent, and set the historically troublesome C-8 hydroxyl stereocenter.

Given the variety of products desired, we were limited by the scope of existing methods. We chose to build upon a recently developed catalytic, asymmetric azetidinone-forming reaction. This robust, scalable method uses the *cinchona* alkaloid derivatives *o*-benzoylquinine (BQ) or its pseudoenantiomer *o*-benzoylquinidine (BQd) as catalysts to give *cis*-substituted azetidinones with excellent enantioselectivity (ee) and diastereoselectivity (dr).[10a−e] We reasoned that if this system could be applied to carbapenem synthesis, catalyst choice would determine the C-5 and C-6 stereocenters and enantiopure ketenes could be employed to establish that at C-8.[11,12] Various ketenes could be used to make *cis* azetidinones, which could be epimerized to *trans,* to afford precursors of *cis* or *trans* carbapenems.

We investigated the azetidinone-forming reaction of simple alkyl ketenes with imine **7** catalyzed by BQ or BQd (Table 1). Ketenes were generated from the corresponding acid chlorides by treatment with triethylamine *in situ*. The reaction produced *cis*-azetidinones with excellent enantioselectivity, and only a trace of the *trans* diastereomer. Propionyl chloride, butyryl chloride and isovaleryl chloride were used to synthesize azetidinone precursors of deshydroxy northienamycin **5**, PS-5 (**3**) and PS-6 (**4**). To synthesize azetidinone precursors of thienamycin (**1**) and epithienamycin A (**2**), ethyl (3*S*)-hydroxybutanoate and ethyl (3*R*)-hydroxybutanoate were silated and saponified to give the corresponding acids, which were converted to the acid chlorides for ketene generation.[13] The expected azetidinones were produced on a multigram scale.

Table 1. Azetidinone Precursors of Carbapenems[a]

compound	catalyst	yield	ee	dr (cis/trans)
 **10**	BQ	64%	99%	6/1
 **11**	BQ	68%	99%	6/1*
 **12**	BQ	70%	99%	24/1*
 **13**	BQ	59%	99%	99/1
 **14**	BQd	53%	99%	99/1

*can be recrystallized to dr 99/1

[a] Reaction conditions: 10 mol % catalyst, 10 mol % $In(OTf)_3$, 1.2 equiv acid chloride, 1.2 equiv Et_3N, 1.0 equiv imine **7**, toluene, −78 °C.

It was postulated that the chiral transition state of the azetidinone-forming reaction might be used to amplify diastereoselection at C-8 from a pool of racemic starting material. This possibility was investigated using silyl-protected 3-hydroxy butyryl chloride as the ketene precursor. The racemic 3-hydroxybutyrate was protected as the *t*-butyldimethyl silyl, *t*-butyldiphenyl silyl, or triisopropyl silyl

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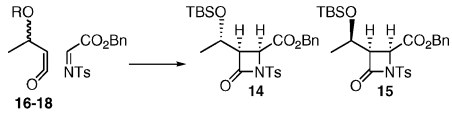
ether in anticipation that steric bulk would accentuate any stereoselection observed resulting from bias in the transition state. One equivalent of each ketene (**16**−**18**) was used under the standard reaction conditions showing only modest selectivity (ca. 2:1) when the bulky triisopropyl silyl group was used (Scheme 1). When the reaction was repeated with

Scheme 1. Effect of C-8 Stereocenter on Catalysis[a]



	R	14	15
16	TBS	1	0.83
17	TBDPS	1	0.77
18	TIPS	1	0.64

[a] Reaction conditions: 10 mol % BQd, 10 mol % $In(OTf)_3$, 1.0 equiv acid chloride, 1.0 equiv Et_3N, 1.0 equiv imine **7**, toluene, −78 °C.

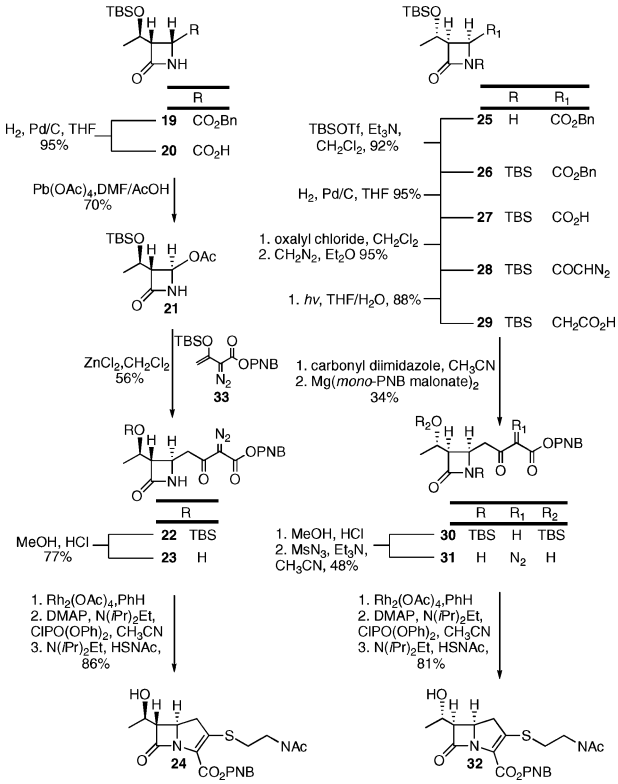
two and three equivalents of ketene, selectivity did not improve and yields decreased. This observation further implied that the catalyst has minimal bias for (*S*) or (*R*) 3-hydroxy butyrates and efficiently catalyzed *cis*-azetidinone formation with either enantiomer.

Having made azetidinones with absolute configurational control of three contiguous stereocenters, we synthesized *p*-nitrobenzyl (PNB) *N*-acetyl thienamycin (**24**) and PNB epithienamycin A (**32**). Initially the C-4 acids of azetidinones **13** and **14** were accessed by hydrogenolysis of the benzyl esters, but the relatively reactive *N*-tosyl azetidnones were not compatible with downstream reactions. We resolved to remove the tosyl group early in the synthesis. After smooth detosylation with samarium(II) diiodide[14a,b] the resulting β-lactams were amenable to efficient completion of carbapenem synthesis (Scheme 2).

For the preparation of **24** and C-5/C-6 *trans* carbapenems, the benzyl ester of **19** was removed by hydrogenation. The resulting acid **20** was oxidatively decarboxylated with lead tetraacetate to epimerize the C-5 stereocenter and produce a known thienamycin precursor, acetoxy azetidinone **21**.[15] This can be readily coupled with TBS enol **33** and desilylated to give diazo azetidinone **23**. The final stages of carbapenem synthesis were achieved by cyclization of **23** to the 2-oxocarbapenam with rhodium acetate. After filtration of the rhodium catalyst, the 2-oxocarbapenam was activated as its enolphosphate, which underwent heteroconjugate addition with *N*-acetylcysteamine (HSNAc) to give PNB *N*-acetyl thienamycin (**24**). The PNB ester, conventionally used in carbapenem syntheses can be readily removed by hydrogenolysis to afford the natural product.[16]

Syntheses of **32** and C-5/C-6 *cis* carbapenems start with TBS protection of the azetidinone nitrogen followed by

Scheme 2. Syntheses of Protected *N*-Acetyl Thienamycin and Epithienamycin A



hydrogenolysis of the C-5 benzyl ester to the acid **27**. In this case the Arndt-Eistert homologation was employed to introduce a methylene and preserve the *cis* stereochemistry. Azetidinone carboxylic acid **27** was activated as the acid chloride, and this was substituted with diazomethane to give diazoketone **28**. The diazoketone was unstable to silica gel chromatography and was subjected directly to light-promoted Wolff rearrangement to give homologated acid **29**.[17] This intermediate was activated with carbonyldiimidazole and the final acetate unit was added by the method of Masamune.[18] The silyl protecting groups were removed followed by the introduction of the diazo moiety to give **31**, directly analogous to **23**. Compound **31** was converted to PNB epithienamycin A (**32**) in the same manner as **23** was cyclized to PNB *N*-acetyl thienamycin (**24**) and similarly can be deprotected by hydrogenation.[19a,b]

Here we demonstrate an efficient approach to carbapenem synthesis with control of the three contiguous stereocenters C-5, C-6, and C-8. Azetidinone precursors of deshydroxy northienamycin (**5**), PS-5 (**3**), and PS-6 (**4**) have been produced on a multigram scale with excellent dr and ee. The

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ease of stereocontrolled azetidinone formation simplified syntheses of protected *N*-acetyl thienamycin (**24**) and epithienamycin A (**32**) as well as provided a general route to carbapenems possessing C-5/C-6 *cis* or *trans* configurations with independent control of C-8 hydroxyl stereochemistry. These efficient and flexible approaches allow access to the many naturally occurring carbapenems and will enable investigation of their biosynthetic relationships.

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Supporting Information Available: Experimental procedures and characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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