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Enantioselective synthesis of the carbacephem antibiotic loracarbef via Mitsunobu and Dieckmann cyclization from an unnatural amino acid

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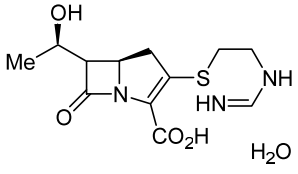
Abstract—The nucleus of the carbacephem antibiotic loracarbef was synthesized in a highly efficient and enantioselective fashion from 2*S*,3*S*-2-amino-3-hydroxy-6-heptenoic acid (AHHA), which was derived from enzyme-catalyzed condensation of glycine and 4-pentenaldehyde. The bicyclic framework of this compound was established through sequential Mitsunobu reaction and aldol condensations.

β-Lactams occupy a unique place in the history of heterocyclic chemistry for their role in combating infectious diseases around the globe. They are still the best selling class of pharmaceuticals by volume in the world after more than seven decades of widespread clinical applications. In the search for a wider antibacterial spectrum and longer systemic effect, the carbon analog of penicillins and cephalosporins, namely carbapenems and carcephems, have emerged as a new generation of β-lactams featuring enhanced chemical and serum stability over their sulfur parents. This culminated in the launch of the first carbapenem and carbacephem antibiotics, imipenem (**1**) and loracarbef (**2**),[1] respectively.

Unlike carbapenem, no naturally occurring carbacephem has been reported, and hence their entire structural activity relationship (SAR) studies were based on compounds of total or semisynthetic origin. The sensitive nature of these densely functionalized chiral compounds make their enantioselective synthesis a challenging task. With the increasing threat of newly discovered infectious pathogens and drug resistant strains of known ones, β-lactams remain a privileged platform for medicinal chemists in search of inhibitors of bacterial cell wall synthesis, and numerous disease related proteases. Reported herein is a new methodology for the synthesis of carbacephems via the Mistunobu cyclization.

2*S*,3*S*-2-Amino-3-hydroxy-6-heptenoic acid (**3**, AHHA) has been demonstrated to be available in large scale from serine hydroxymethyltransferase (SHMT) catalyzed condensation between 4-pentenaldehyde and glycine.[2] This highly functionalized material in essentially enantiopure form appeared as a versatile intermediate for building the loracarbef (**2**) framework.[3] Thus the carboxyl and the α-amino groups were protected as *p*-nitrobenzyl ester (*p*NB-) and phenoxyacetamide (V-), affording compound **4**. Attempts to obtain the β-lactam by cyclizing this compound, however, were met with



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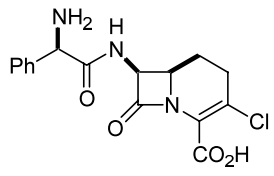

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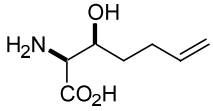

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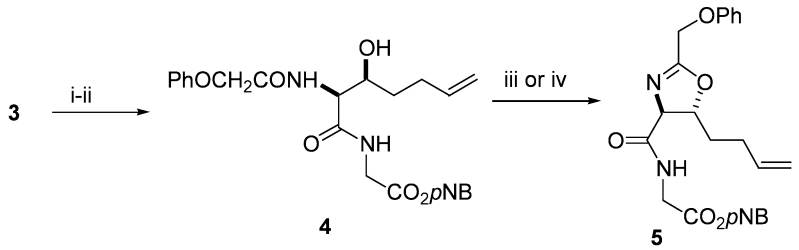


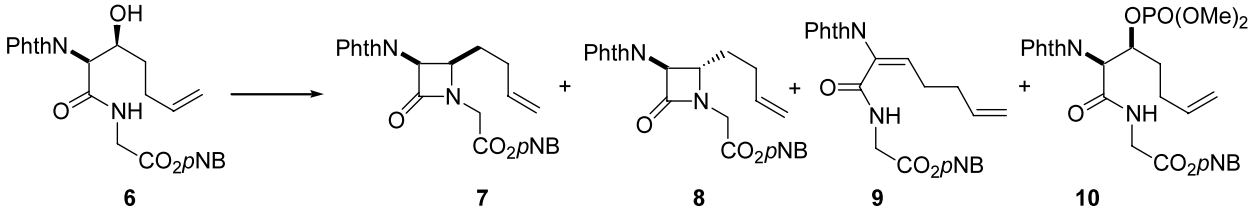
i. $PhOCH_2COCl$; ii. iBuOCOCl, NMM, $H_2NCH_2CO_2pNB$; iii. MsCl, Et_3N; iv. PPh_3, DEAD

predominant formation of oxazoline **5**, either with the alcohol under Mitsunobu conditions or the corresponding mesylate in the presence of various bases.

Replacing the phenoxyacetyl with benzyloxycarbonyl offered little relief in this regard. The insufficient nucleophilicity of the amide nitrogen and the proximity of the α-amido oxygen made the five membered ring formation a favorable process. This problem could be solved by enhancing the nucleophilicy of the nitrogen via conversion into an ionizable sulfonamate, followed by nucleophilic displacement of the mesylate group to form the β-lactam ring.[3] However, this approach necessitates multiple steps of mesylation, amide activation, cyclization, and alkylation of the β-lactam nitrogen for the cephem ring fusion. We chose to focus on the Mitsunobu[4] cyclization for a more direct synthesis of **2**.

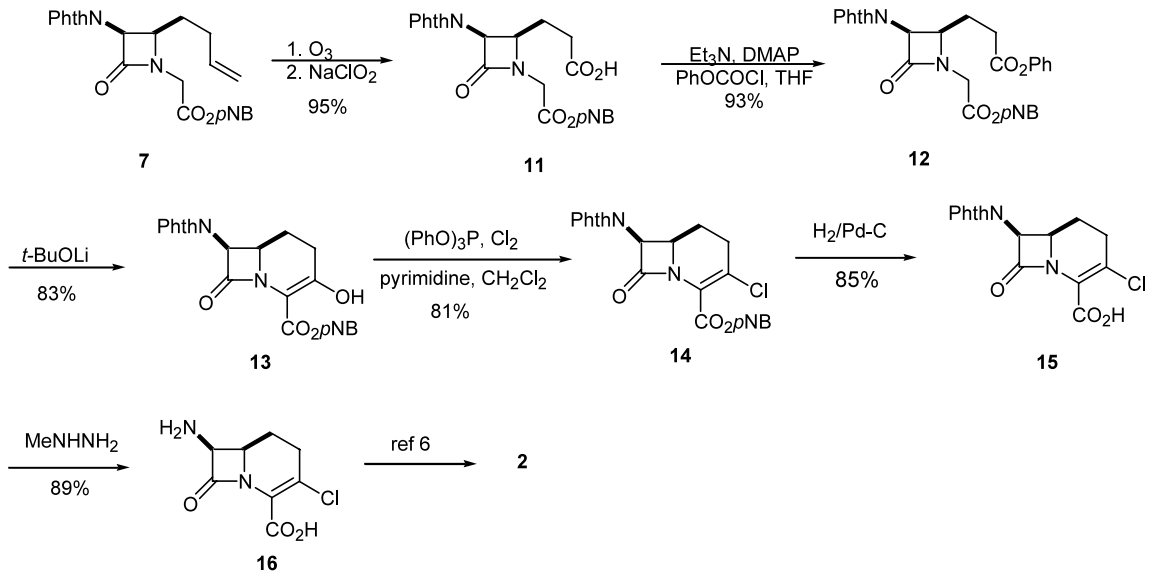
Formation of β-lactams via the Mitsunobu reaction has been demonstrated first by Bose and Miller on various systems.[5] To avoid complication associated with the deleterious α-amido nitrogen participation, the amino group of **3** was protected as a phthalimido group to afford **6** in 87% yield. The corresponding mesylate of **6** proved susceptible to elimination, yielding compound **9** (50%) even in the absence of a base standing at room temperature. Initial tests under the standard Mitsunobu conditions, however, afforded β-lactam **7** in good yield (Scheme 1). Several issues had to be addressed in the context of scaling up this reaction. First, the hallmark problem associated with the traditional Mitsunobu reaction, (i.e. removal of phosphine oxide byproduct from the reaction stream), proved difficult too without resorting to chromatography. Secondly, the reaction was found to be not stereospecific, generating various amounts of epimeric lactam **8**. Towards these ends phosphites were evaluated as a substitute for phosphines for their lower cost and easier byproduct separation. Early screening of phosphites quickly ruled out $(MeO)_3P$ due to mixed phosphite (**10**) formation. Triethyl phosphite was as effective as PPh_3 albeit a larger excess was required. Both $(iPrO)_3P$ and $(PhO)_3P$ resulted in slow rates and poor conversions. The solvent factor was also investigated. Acetonitrile and methylene chloride generally required more reagents to complete the reaction, concomitant with a large extent of α-epimer (**8**) formation, as compared to THF and toluene. Reaction temperature played a critical role governing the selectivity. Lower temperature not only led to slower rate, but also a greater proportion of compound **8**. Poor solubility of **6** in aromatic solvent at lower temperature also points toward a higher reaction temperature. It is important to note that it is essential to have all **6** dissolved in the reaction media or risk higher impurity content, and it is preferable to add DIAD to a mixture of all other ingredients due to the instability of $(EtO)_3P$ /DIAD adduct. After an extensive screening of various reaction conditions, we found a combination of triethyl phosphite, diisopropylazodicarboxylate (DIAD) and toluene as a solvent at higher temperature afforded the best overall yield and selectivity of the desired β-lactam **7**. As an interesting side note, the *threo* (2*S*,3*R*) isomer of **6** gave exclusively elimination product **9** under virtually all of these conditions, providing an unexpected but useful pathway for impurity control.

With compound **7** in hand, elaboration of the terminal alkene took the facility of ozonlysis to afford carboyxlic acid **11** in 95% yield with in situ oxidation (Scheme 2). Conversion to the phenyl ester was accomplished using phenyl chloroformate as both a phenol donor and carboxylate activator, setting the stage for Dieckmann cyclization. The cyclization is best performed using 3.3



$(MeO)_3P$, DEAD	50%		50%
PPh_3, DIAD, THF, 25 °C	80%		
$(EtO)_3P$, DIAD, toluene, 70°C	84%	2%	
$(EtO)_3P$, DIAD, toluene, 80°C	87%	0.6%	
$(EtO)_3P$, DIAD, toluene, 90°C	97%	0%	

Scheme 1.



Scheme 2.

equiv. of *t*-BuOLi between −8 and −15°C, affording enol **13** in 83% yield. Alternatively, the two steps from **11** to **13** can be carried out in a one-pot fashion in slightly higher yield (89%), furnishing the carbacephem skeleton. Chlorination of the enol and deprotection of the ester went uneventfully to afford compound **15**.

Removal of the phthalimido protecting required considerable optimization due to the sensitive nature of the molecule. Deprotection could be achieved either by enzyme catalyzed hydrolysis or assisted cleavage using methylhydrazine to give the loracarbef nucleus **16**.[6] This established an efficient formal total synthesis of the novel antibiotic **2**.

In summary, we have demonstrated the utilization of the Mitsunobu reaction and Dieckmann condensation for the enantioselective synthesis of loracabef, starting from an unnatural aminoacid. All of the synthetic steps are high yielding and no chromatographic separation, or expensive chiral auxiliaries were required.

Acknowledgements

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