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AN EFFICIENT SYNTHESIS OF 4-BENZOYLOXYAZETIDINONE: AN IMPORTANT CARBAPENEM INTERMEDIATE

D.M. Tschaen,* L.M. Fuentes, J.E. Lynch, W.L. Laswell
R.P. Volante and I. Shinkai

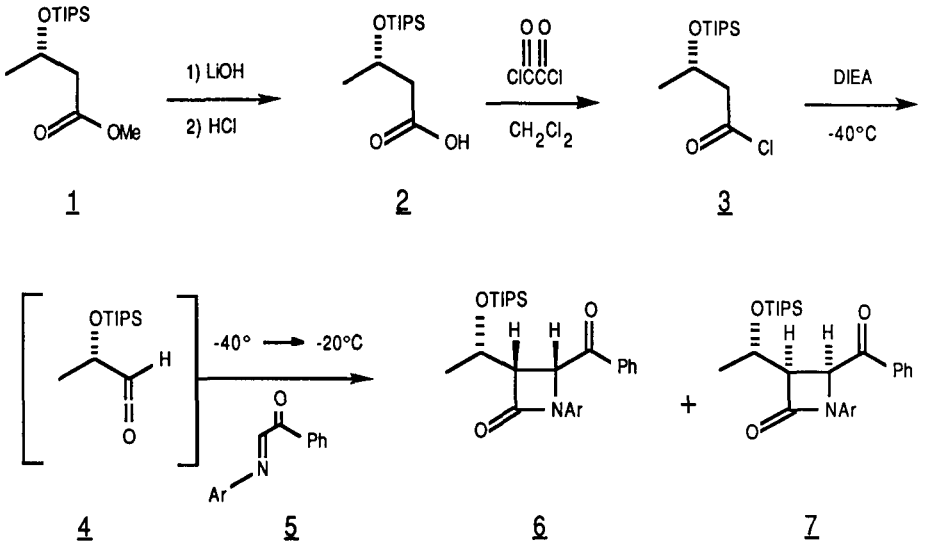
Merck Sharp and Dohme Research Laboratories
Division of Merck & Co., Inc.
P.O. Box 2000
Rahway, New Jersey 07065

Summary: A short, stereoselective synthesis of the key carbapenem intermediate (3R,4R)-3-[(1R)-1-hydroxyethyl]-4-benzoyloxyazetidin-2-one is described.

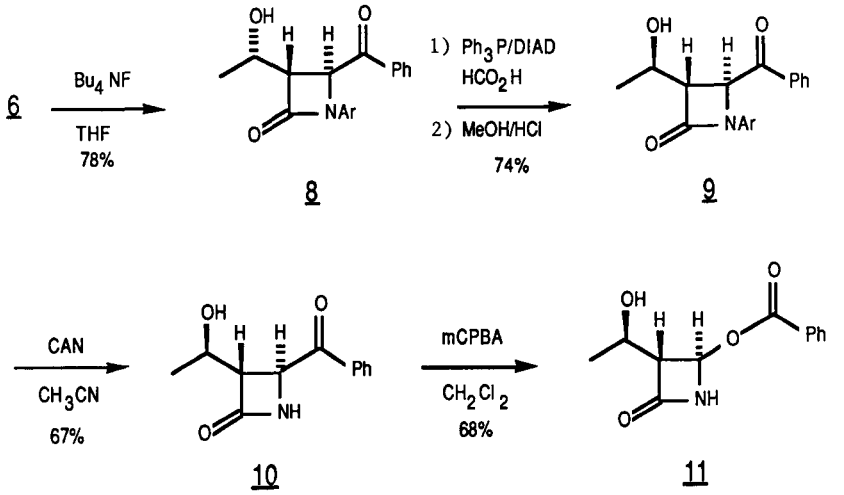
Recently there has been considerable interest in the development of new synthetic approaches to β-lactam antibiotics.[1,2] In searching for an efficient and versatile route to thienamycin[3] and related β-methyl carbapenems[4] we have explored the use of β-hydroxybutyric acid as a readily available, chiral starting material. This reagent has previously been used in enolate condensations with imines to generate β-lactam intermediates; however, these approaches typically provide modest yields of condensation products and require extensive functional group manipulation in order to liberate the desired C-4 acetoxy azetidinone species.[2] Our strategy has focused on the hydroxybutyrate derived ketene-imine cycloaddition for direct generation of the useful C-4 keto-substituted azetidinone. Although ketene-imine cycloadditions have been widely used for the formation of β-lactams, these reactions usually provide moderate yields of azetidinones which lack the functionality necessary for rapid conversion to useful carbapenems.[5]

We wish to report here an efficient, diastereoselective conversion of methyl 3(S)-hydroxybutyrate to (3S,4S)-3-[(1S)-1-hydroxyethyl]-4-benzoylazetidin-2-one (8) and its subsequent transformation to the versatile carbapenem precurser 11.

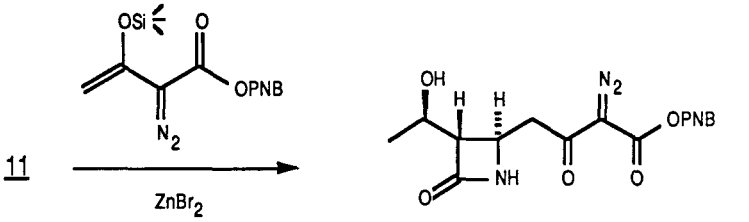
3(S)-Triisopropylsilyloxybutyric acid (2) was treated with oxalyl chloride at room temperature to produce acid chloride 3 in quantitative yield. Ketene 4 was generated *in situ* using diisopropylethylamine[6] and reacted with imine 5[7] (Ar=p-methoxyphenyl) to afford a 7:1 mixture[8] of cis β-lactams 6 and 7 in 90% overall yield.[9,10]



It is important to note that the major isomer 6 posseses the C-3 stereochemistry required for thienamycin.[11] Also, the use of the keto-imine 5 is crucial as it provides direct access to a useful C-4 keto-substituted β-lactam[12] which is not readily available via standard enolate chemistry.[2] Treatment of 6 with tetrabutylammonium fluoride in THF led to desilylation as well as epimerization of C-4 to form trans β-lactam 8 in 78% yield. Under the standard Mitsunobu conditions,[13] (S)hydroxylethyl 8 was inverted to the desired (R)hydroxyethyl β-lactam 9 in 74% yield.



Removal of the p-methoxyphenyl group was achieved by cerric ammonium nitrate oxidation to provide unprotected β-lactam 10 in 67% yield.[14] Baeyer-Villiger oxidation with m-chloroperoxybenzoic acid[12] at room temperature led to benzoyloxy azetidinone 11 which was subsequently chain extended under the conditions of Reider and Grabowski[15] to form the known carbapenem intermediate 12.[16]



12 PNB = p - nitrobenzyl

It is also interesting to note that an intermediate such as 11 has been utilized for the stereoselective synthesis of 1-β-Me-carbapenems.[17]

Thus we have demonstrated a short and efficient synthesis of important carbapenem intermediates using the β-hydroxybutyrate derived ketene-imine cycloaddition.

Acknowledgement: We thank Mr. R. Reamer for valuable NMR assistance.

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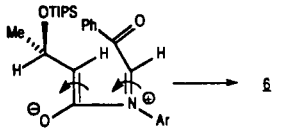
6. FTIR studies indicate that ketene 4 is indeed the reactive species. Manuscript in preparation.
7. Imine 5 was produced by condensation of anisidine with phenyl glyoxal.
8. The best ratio of 6:7 was achieved using DMF as the solvent.
9. Our studies show that the ratio of 6:7 improves as the steric bulk of the hydroxyethyl protecting group increased. Conrotatory cyclization as shown below for the iminium ion A, in its preferred conformation, would be expected to minimize steric interaction of the bulky hydroxyethyl group and the incipient C-4 substituent. See also reference 18.



A

10. The use of (R)hydroxybutyrate also led to a mixture of cis β-lactams. Unfortunately the major product possessed the undesired C-3 stereochemistry.
11. Data for selected intermediates: 6: ^{1}H NMR ($CDCl_3$,300 MHz) δ 0.90 (18H,s), 0.90(3H,m) 1.34(3H,d,J=6.4 Hz), 3.77(3H,s), 3.93(1H,dd, J=3.8,6.3 Hz), 4.31(1H,m), 5.40(1H,d,J=6.3 Hz), 6.83(2H,m), 7.24 (2H,m), 7.52(2H,m), 7.63(1H,m), 8.01(2H,m).
   9: ^{1}H NMR ($CDCl_3$,300 MHz) δ 1.39(3H,d,J=6.3 MHz), 3.23(1H,dd,J=2.4, 6.5 Hz), 4.38(1H,m), 5.52(1H,d,J=2.4 Hz), 6.82(2H,m), 7.20(2H,m), 7.55(2H,m), 7.67(1H,m), 8.20(2H,m).
   10: ^{1}H NMR (CD_3OD,300 MHz) δ 1.27(3H,d,J=6.4 Hz), 3.10(1H,dd,J=2.4, 6.9 Hz), 4.20(1H,m), 5.14(1H,d,J=2.3 Hz), 7.52(2H,m), 7.65(1H,m), 8.15(2H,m).
   11: ^{1}H NMR (CD_3CN,300 MHz) δ 1.27(3H,d,J=6.4 Hz), 3.34(1H,dd,J=1.3, 5.8 Hz), 4.11(1H,m), 6.05(1H,d,J=2.0 Hz), 7.42(1H,bs), 7.51(2H,m), 7.66(1H,m), 8.40(2H,m).
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