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SYNTHESIS OF THE CARBAPENAM RING SYSTEM VIA CARBENE MEDIATED REARRANGEMENT OF AN N-BENZYLOXY-β-LACTAM

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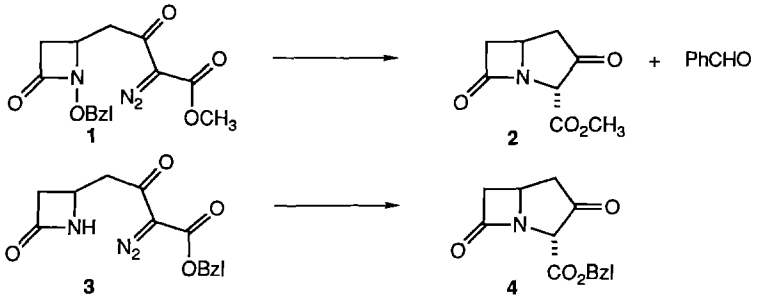
Abstract: The α-diazoester **1** in the presence of catalytic $Rh_2(OAc)_4$ was converted to the carbapenam **2**. The synthesis of **1** and a proposed mechanism are described.

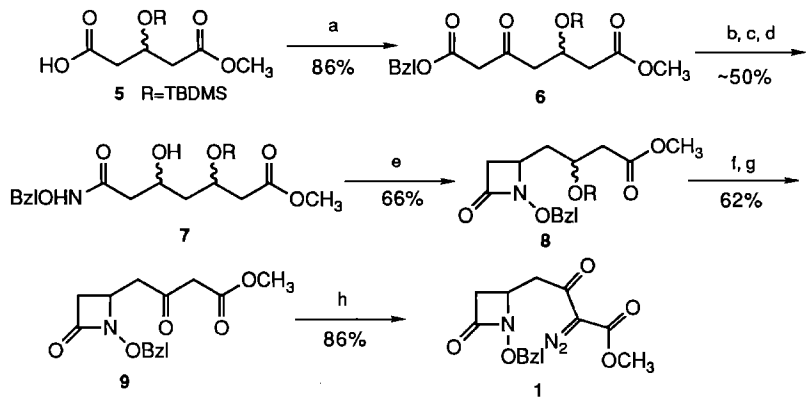
A variety of strategies currently exists in the literature for the synthesis of bicyclic β-lactams. A commonality in most of these synthetic methods is the formation of a bicyclic ring system from an appropriately functionalized azetidinone ring. Of the methodologies utilized, one of the most efficient involves the treatment of an α-diazo-β-ketoester substituted azetidinone **3** with a catalytic amount of $Rh_2(OAc)_4$. The resulting carbenoid species undergoes N-H bond insertion, thereby providing the carbapenam ring system **4**.[2] This process has also been applied to the synthesis of carbacephems.[3] Herein, we describe an unprecedented ring closure of the N-benzyloxy-β-lactam **1** to provide the carbapenam **2**.



The preparation of the key diazo compound **1** is shown in Scheme 1. The known acid-ester **5** [4] was homologated to the β-ketoester **6** via the Masamune[5] procedure. Reduction of the

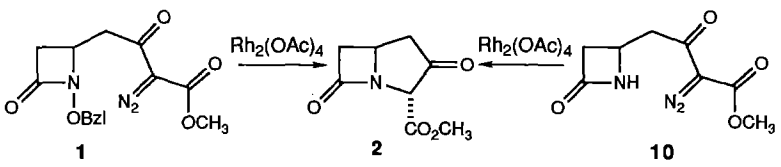
β-keto group and hydrogenolysis of the benzyl ester followed by DCC mediated coupling of the acid with O-benzylhydroxylamine, provided the hydroxamate **7**. Cyclization of this β-hydroxy-hydroxamate using the established variant of the Mitsunobu reaction,[6] gave the β-lactam **8** as a mixture of diastereomers. Deprotection of the silyl ether[7] and subsequent modified Collins oxidation[8] of the alcohol provided the corresponding ketone **9**. Diazo transfer using p-carboxybenzenesulfonyl azide[9] required careful control of temperature (-5 °C, 14 h.) and the amount of base used (1.2 eq.) to afford the α-diazo-β-ketoester **1**.

Scheme 1



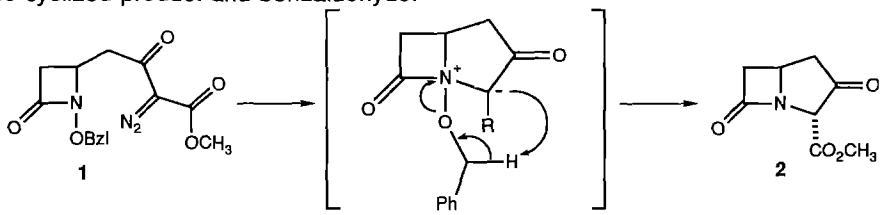
a) carbonyldiimidazole , $Mg^{2+}(^{-}O_2CCH_2CO_2Bzl)_2$ **b**) $NaBH_4$ **c**) H_2 , Pd / C **d**) DCC , H_2NOBzl
e) DEAD , Ph_3P **f**) $Bu_4N^+F^-$ **g**) CrO_3 , pyridine **h**) p-carboxybenzenesulfonyl azide , iPr_2NEt

With this substrate in hand, we were interested in exploring the reactivity of the generated carbenoid with respect to benzylic C-H insertion or oxonium ion formation followed by rearrangement, thereby providing an entry into novel bicyclic β-lactam systems. Treating **1** with $Rh_2(OAc)_4$ (5 mol%) in refluxing CH_2Cl_2, however, gave the carbapenam **2** in approximately 40% unoptimized yield after purification on silica. In addition to the cyclized product, benzaldehyde was produced as verified by TLC, HPLC, and Purpald®(4-amino-3-hydrazino-5-mercapto-1,2,4-triazole)[10] test of the crude reaction mixture. The product **2** was confirmed by comparison to spectral data from a previous synthesis.[11] In addition, an authentic sample of the carbapenam **2** was prepared by rhodium-catalyzed cyclization of **10** and proved identical, with respect to NMR, IR, and TLC, to the product obtained from the treatment of **1** with $Rh_2(OAc)_4$.[12]



1 2 10

The low isolated yield in the conversion of **1** to **2** may be partially attributed to decomposition during purification on silica, since the cyclization of **10** to **2**, which appeared clean and complete by TLC analysis, was also isolated in low yield.[13] A mechanism consistent with the observed products is presented below. The initially generated carbenoid may first interact electrophilically with the N-alkoxylactam electron lone pair to give intermediate **11**. Abstraction of a proton from the benzylic position by this ylide intermediate, followed by N-O bond heterolysis yields the cyclized product and benzaldehyde.



1 2

11 R=CO_2CH_3

This unique rearrangement conveniently circumvents the well documented procedure for the debenzylation and N-O bond reduction of N-benzyloxy-β-lactams.[14] Application of this reduction to **9**, followed by diazo transfer would then afford a substrate compatible for cyclization employing the Merck protocol.[2] Further studies of this unique cyclization are in progress.

Acknowledgements We gratefully acknowledge the financial support of this research by the N.I.H. and Eli Lilly and Company. We also thank Dr. C.- N. Hsiao for the preparation of compound **10.**

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12. Compound **10** was synthesized by Dr. C.- N. Hsiao from 4-Acetoxy-2-azetidinone and the bis-trimethylsilylated dianion of methylacetoacetate in the presence of trimethylsilyltriflate, followed by diazo transfer. Cyclization was effected with $Rh_2(OAc)_4$ in refluxing benzene.
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15. Selected Characterization Data. ^1H NMR and ^{13}C NMR data were recorded at 300 and 75 MHz respectively in $CDCl_3$ with TMS as an internal reference. **9**: oil; IR ($CHCl_3$) 3010, 2960, 1770(broad), 1720 cm^{-1}; ^1H NMR δ 7.38 (m, 5H), 4.91 (d, 1H, J=10.9 Hz), 4.85 (d, 1H, J=10.9 Hz), 4.02 (m, 1H), 3.69 (s, 3H), 3.41 (s, 1H), 3.40 (s, 1H), 2.84 (dd, 1H, J=2.4, 13.9 Hz); ^{13}C NMR δ 199.86, 167.07, 164.07, 135.16, 129.41, 128.97, 128.61, 77.86, 52.49, 52.37, 49.06, 45.05, 38.11; high resolution MS calcd for $C_{15}H_{17}NO_5$ 291.1107, found 291.1110. **1**: oil; IR (thin film) 3040, 2960, 2140, 1775, 1720, 1650 cm^{-1}; ^1H NMR δ 7.38 (m, 5H), 4.96 (1H, J=6.7, 17.5 Hz), 2.88 (dd, 1H, J=5.2, 13.9 Hz), 2.42 (dd, 1H, J=2.4, 13.9 Hz); ^{13}C NMR δ 189.02, 163.98, 161.35, 135.12, 129.31, 128.89, 128.55, 77.99, 76.23, 53.02, 52.37, 42.86, 38.16. **2**: oil; IR (CCl_4) 2960, 1785, 1775, 1750 cm^{-1}; ^1H NMR δ 4.71 (s, 1H), 3.81 (s, 3H), 3.67 (dd, 1H, J=5.1, 16.3 Hz), 2.97 (dd, 1H, J=2.0, 16.4 Hz), overlaps with 2.92 (ddd, 1H, J=.63, 6.8, 18.8 Hz), 2.41 (dd, 1H, J=7.8, 18.8 Hz); MS (CI) m/e 184 (M+1).

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