Novel Synthetic Approach to Carbapenems Utilizing Aza-Cope Mannich Cyclization

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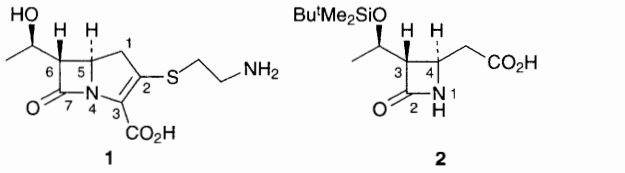
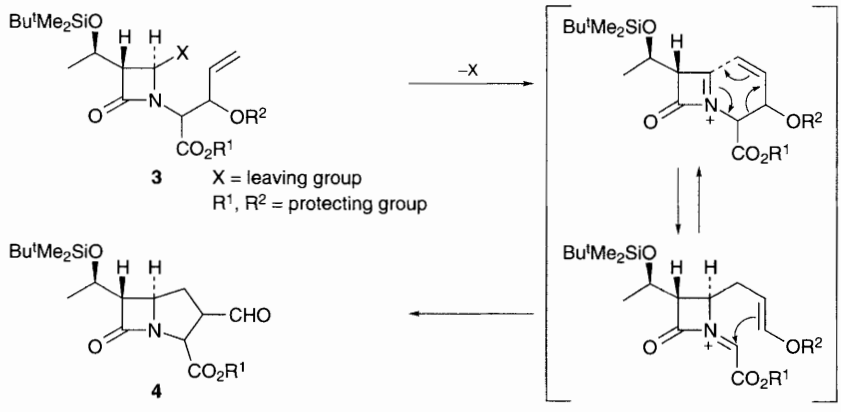
Treatment of chloride **10** with silver tetrafluoroborate afforded aldehyde **11**, which was converted to β-ketoester **12**, *via* tandem C-1–C-5 and C-2–C-3 bond formation.

Since the discovery of thienamycin **1**[1] carbapenems have been fascinating synthetic targets because of their intriguing molecular structure and their potency as antibacterial agents. In most of the syntheses of carbapenems, formation of the azetidinones possessing a carbon side chain at C-4 position (azetidinone numbering),[2] *e.g.* carboxylic acid **2**, is followed by the construction of the fused five membered ring by C-2–C-3 bond[1c,3] or C-3–N bond[4] formation. On the other hand, use of C-1–C-5 bond formation as a key step to construct carbapenem skeletons has hardly been reported to date.[5] This could be for the following reasons: firstly, in the introduction of a carbon nucleophile into the azetidinones with a leaving group at C-4, requisite generation of the acyliminium ion, in which the lactam nitrogen has a substituent, is much more reluctant than that of an acyl imine;[6] secondly, preparation of a suitable carbon nucleophilic moiety in the substituent on the lactam nitrogen for the C-1–C-5 bond formation is difficult and/or troublesome due to the many functionalities which are required for the carbapenem structure. In the course of our synthetic studies on carbapenems, we have been interested in an approach in which the C-1–C-5 bond formation is involved, and report herein a novel synthesis of carbapenems in which aza-Cope Mannich cyclization is utilized as a key step.

Aza-Cope rearrangement reactions[7] have been widely utilized to construct the fused nitrogen-containing ring systems in the syntheses of alkaloids. These reactions are initiated by generation of the iminium ion intermediates for the rearrange-



1 **2**



3 X = leaving group; R^1, R^2 = protecting group

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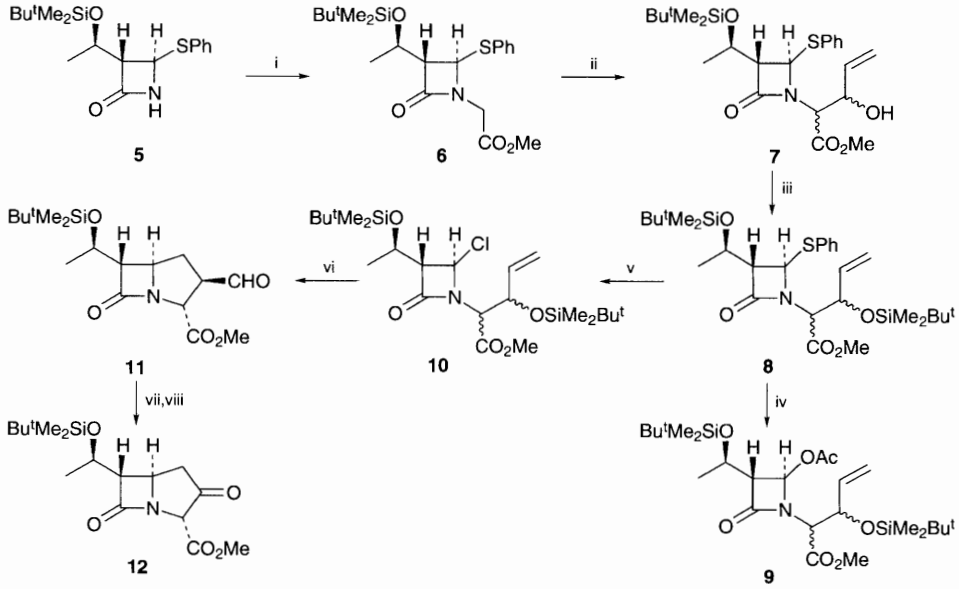
Scheme 1



5 **6** **7** **8** **9** **10** **11** **12**

Scheme 2 *Reagents and conditions*: i, $LiN(Me_3Si)_2$, $BrCH_2CO_2Me$, THF, −78 °C–room temp. (86%); ii, $LiN(Me_3Si)_2$, acrolein, THF, −78 °C (91%); iii, $Bu^tMe_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, ice cooling (88%); iv, $Hg(OAc)_2$, AcOH, room temp. (49%); v, Cl_2, CH_2Cl_2, −78 °C, then aq. $Na_2S_2O_3$ (85%); vi, $AgBF_4$, CH_2Cl_2, −78 °C (33%); vii, $Bu^tMe_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, ice cooling; viii, O_3, MeOH, −78 °C, then Me_2S (90% from **11**)

ments. We therefore thought that the acyliminium ion intermediate generated from azetidinone **3** would undergo [3,3] sigmatropic rearrangement to form the enol ether, which could cyclize to give carbapenam **4** (Scheme 1).

Our synthetic studies began with an efficient preparation of the rearrangement precursor (Scheme 2). Sulfide **5**[8] was first alkylated at the nitrogen with methyl bromoacetate to afford ester **6**.[3h] Aldol reaction of the lithium enolate of **6** with acrolein produced aldols **7** in a good yield as an inseparable diastereoisomeric mixture. The secondary alcohol of **7** was then protected by a *tert*-butyldimethylsilyl group[9] to give silyl ether **8**.

Our next task was conversion of the phenylthio group to other leaving groups that were suitable for generation of the acyliminium intermediate. We first attempted to obtain acetate **9** since the azetidinones that have an acetoxy group at C-4 were extensively employed in the syntheses of azetidinones with a carbon substituent at C-4. Hg-assisted displacement[10] of the phenylthio group by an acetoxy group proceeded smoothly to give **9**. With the desired precursor in hand, our key reaction, aza-Cope Mannich cyclization, was attempted. Several trials to activate the acetoxy group ($Me_3SiOSO_2CF_3$, $Bu^tMe_2SiO\text{-}SO_2CF_3$, $BF_3{\cdot}OEt_2$), however, ended without yielding any of the desired carbapenam **11**. Then, another way in which chloride ion acts as a leaving group[6,11] was pursued. Chloride **10** was obtained in a good yield by careful treatment of **8** with chlorine[12] followed by aqueous $Na_2S_2O_3$ workup without addition of the resultant sulphenyl chloride to the vinyl group. After testing several silver salts with non-nucleophilic counter anions to generate the iminium ion for aza-Cope rearrangement, we found silver tetrafluoroborate ($AgBF_4$)[11] was suitable. Thus, treatment of chloride **10** with $AgBF_4$ in CH_2Cl_2 at −78°C furnished carbapenam **11**† in 33% yield as a single isomer. The stereochemistry of **11** at C-2, C-3 and C-5 were rigorously determined by NOE measurements (7.8% between H-1–α and H-5, 9.6% between H-1–β and H-6, 10.4% between H-1–α and H-2, and 2.3% between H-1–β and H-3).

Finally, our remaining work was to transform carbapenam **11** to β-ketoester **12** which could be transformed to carbapenems by a sequential process of enol-phosphorylation and addition–elimination with mercaptans.[4a] Aldehyde **11** was converted to the corresponding Bu^tMe_2Si-enol ether,[13] which was subjected to ozonolysis in methanol followed by Me_2S workup to afford **12**‡ cleanly.

We are grateful to Dr A. Kinumaki and his coworkers in our company for the NOE measurements.

Received, 21st August 1995; Com 5/05558J

Footnotes

† *Selected spectroscopic data* for **11**: $[\alpha]_D^{27}$ = + 41.6 (*c* 1.0, $CHCl_3$); IR (neat), ν/cm^{-1} 1772, 1743, 1732; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (6 H, s), 0.88 (9 H, s), 1.22 (3 H, d, *J* 6.2 Hz), 1.8–2.1 (1 H, m), 2.3–2.7 (1 H, m) 2.92 (1 H, dd, *J* 5.4, 2.2 Hz), 3.6–3.8 (1 H, m), 3.76 (3 H, s), 3.9–4.0 (1 H, m), 4.1–4.3 (1 H, m), 4.72 (1 H, d, *J* 6.5 Hz), 9.77 (1 H, d, *J* 1.1 Hz).

‡ *Selected spectroscopic data* for **12**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.10 (6 H, s), 0.93 (9 H, s), 1.28 (3 H, d, *J* 6.3 Hz), 2.3–2.6 (1 H, m), 2.7–3.0 (1 H, m), 3.12 (1 H, dd, *J* 5.0, 2.0 Hz), 3.77 (3 H, s), 4.1–4.5 (2 H, m), 4.67 (1 H, s).

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