A Formal Synthesis of (±)-Thienamycin

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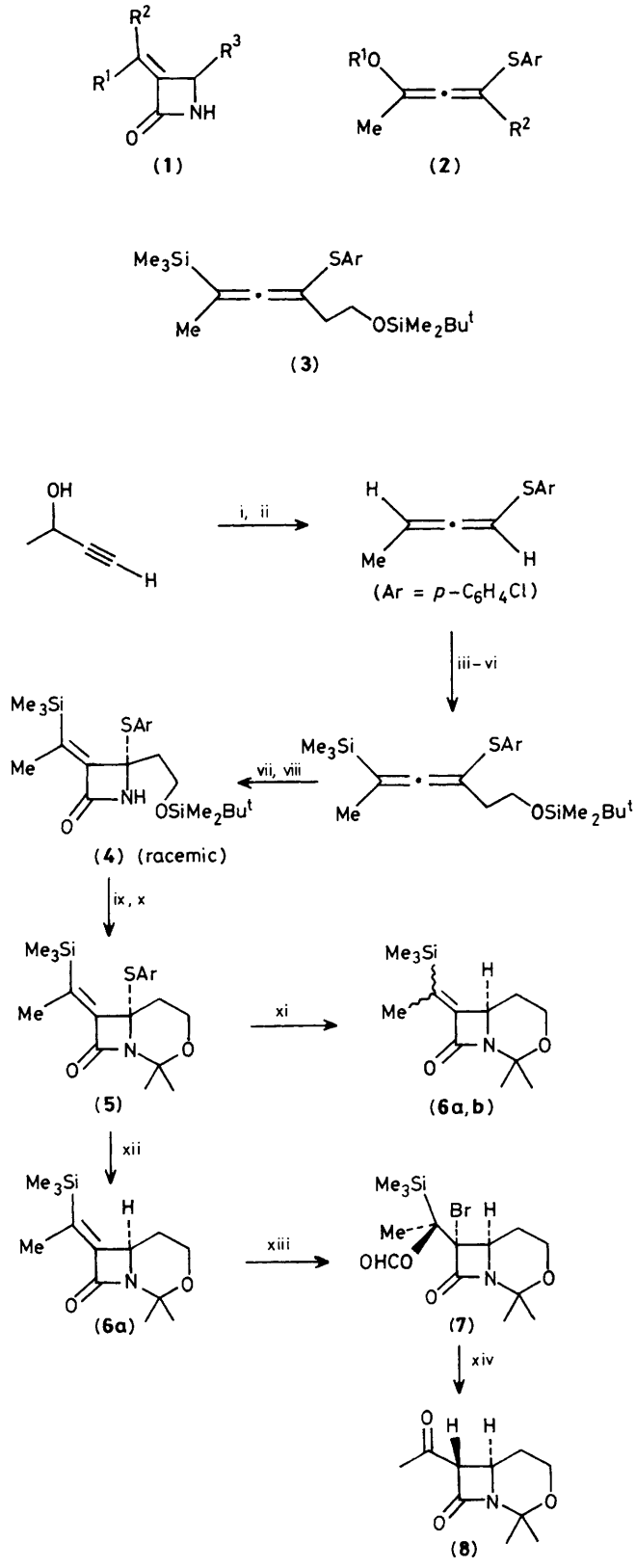
An α-silylethylidene-β-lactam is generated *via* chlorosulphonyl isocyanate (CSI) addition to a silylated allenyl sulphide and converted into a key intermediate for the synthesis of thienamycin.

Through syntheses of asparenomycin[1] and carpetimycin,[2] we have shown that the α-alkylidene-β-lactams (**1**) are readily accessible, synthetically versatile precursors to the carbapenem antibiotics. The α-alkylidene substituent does not appear to introduce unusual instability into the ring. Among the reactions which we have been able to perform in the presence of this functionality are: nucleophilic substitution of 4-position leaving groups, tin hydride reduction of 4-position sulphides, allylic brominations, and *N*-methylation (MeI/KOH) and *N*-silylation (R_3SiCl/Et_3N) of the β-lactam nitrogen. The alkylidene side chain provides a convenient handle for introduction of the hydroxyalkyl side chains common to the carbapenems. These materials are prepared by addition of chlorosulphonyl isocyanate (CSI) to an appropriately functionalized allene. While our initial studies focused on allenyl acetates, more recently[3] we have found allenyl sulphides to be preferable, both in terms of their stability and the ease with which additional substituents can be introduced (*via* alkylation of the allenyl anions) at either terminal carbon. We now report the successful utilization of these materials in the synthesis of a key intermediate for the preparation of thienamycin.

To generate successfully the crucial hydroxyethyl side chain of thienamycin, a judicious choice of allene was deemed essential. We had already demonstrated that tetra-alkylated allenes give the best yields of addition products. Although a directly oxygenated allenyl sulphide of general structure (**2**) was a potential precursor, we recognised that sulphur (not oxygen) was needed to direct the cycloaddition and that CSI can initiate the decomposition of the vinyl ether moiety.[4] We thus decided to utilize silylated allene (**3**) in the hope that the trimethylsilyl group might eventually be converted into an appropriate oxygen-containing substituent.

The desired allene was readily generated from racemic but-3-yn-2-ol by established methodology. CSI addition produced only the (*Z*)-isomer of (**4**). (All compounds are racemic but only one enantiomer is depicted.) We used the Merck[5] methodology to prepare bicyclic acetal (**5**). Surprisingly,



Scheme 1. *Reagents:* i, ArSCl, Et_3N; ii, NaI, $Cl_2(CO)_2$, Et_3N (77%); iii, Bu^nLi; iv, $I[CH_2]_2OSiMe_2Bu^t$; v, Bu^nLi; vi, Me_3SiCl (68% for iii—vi); vii, CSI; viii, Na_2SO_3 (68%); ix, HF/MeCN; x, $Me_2C(OMe)_2$, $BF_3{\cdot}OEt_2$ (75%); xi, Bu^n_3SnH, cat. azoisobutyronitrile, 90 °C (95%); xii, Raney-Ni, EtOH (73%); xiii, NBS, wet DMF (82%); xiv, KF, MeCN, room temp. (64%).

removal of the thioaryl group by tin hydride reduction at 90 °C produced a 1 : 1 mixture of (*E*)- and (*Z*)-α-(α′-silylalkylidene)-β-lactams (**6**). Walling and Thaler[6] have clearly demonstrated the existence of geometrical isomers of substituted allylic radicals, which do not rapidly interconvert at 40 °C. The current example is particularly impressive in view of the additional strain which is imposed on the system by incorporating yet another planar atom in the four-membered ring.† The potential difficulty of dealing with such a mixture was circumvented by performing the reduction with Raney-nickel at room temperature. These conditions cleanly produce the (*Z*)-isomer in 70% yield.

Removal of the silicon and the introduction of an oxygen substituent proved more difficult than initially expected. The vinyl silane was resistant to fluoride treatment, even under vigourous conditions. We then attempted to activate the silicon by introducing the oxygen first. Unfortunately, addition of HOBr [*N*-bromosuccinimide (NBS) in wet Me_2SO] resulted in substantial destruction of the compound. This was also surprising, since we had shown, during our carpetimycin synthesis, that the corresponding α-methylethylidene derivative readily undergoes such an addition. A potential explanation is that, in this case, the initially formed bromohydrin undergoes rapid loss of Me_3SiBr, hence generating HBr. The reaction does become markedly acidic after approximately one hour. Unfortunately, the inclusion of buffers (*e.g.* pyridine, NaO_2CMe, $NaHCO_3$) completely inhibited the addition. After prolonged experimentation, it was found that treatment of (**6a**) with NBS in wet dimethylformamide (DMF)[7] cleanly produces bromoformate (**7**) in 82% yield. This material appears to be present as a single diastereoisomer as witnessed by ^{13}C and ^1H n.m.r. spectroscopy. When (**7**) was subjected to KF in dry acetonitrile, ketone (**8**) was produced directly. This is formed presumably *via* the enol formate, but despite repeated attempts, we were unable to observe this intermediate. Its rapid destruction may be caued by the fluoride itself. Compound (**8**) has been previously generated by the Merck group[8] and they have shown that a highly stereospecific reduction of the carbonyl group can be accomplished leading to an important intermediate for thienamycin synthesis.

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† *Note added in proof:* We have since discovered that the desulphurized β-lactams (**6a,b**) are themselves equilibrated upon treatment with Bu^n_3SnH–azoisobutyronitrile.