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β-LACTAMS FROM CHIRALLY-ENRICHED (ALLENYLMETHYL)SILANES

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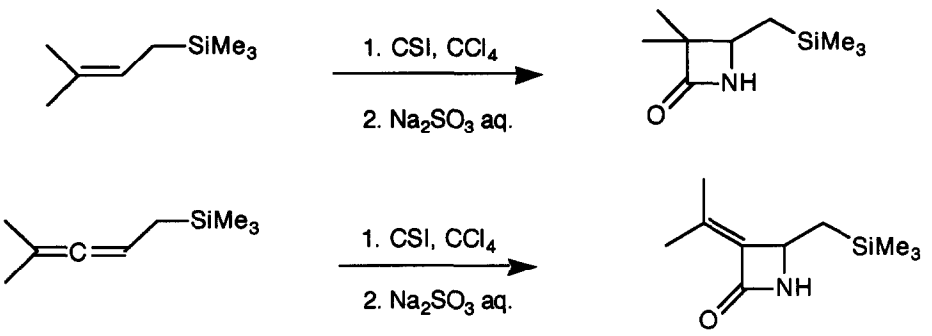
Abstract: Functionalised (allenylmethyl)silanes react with chlorosulphonyl isocyanate in a highly regioselective manner to provide β-lactams with the side-chain functionality of the asparenomycins. Chirally enriched (allenylmethyl)silanes transfer their axial chirality to the carbon-centred chirality in the product β-lactams.

We have recently reported[1] a new route to β-lactams, involving formal cycloaddition of chlorosulphonyl isocyanate (CSI) with allyl- and (allenylmethyl)trimethylsilanes, as exemplified in Scheme 1.

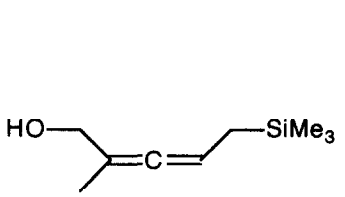
Scheme 1



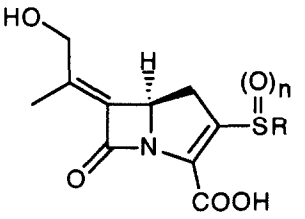
The regiochemistry of these cyclisation processes must be under the control of the β-effect, silicon encouraging the development of carbonium ions or partially-developed ions β to it. Unusually, the silyl group is not lost; electrophilic attack on allylsilanes normally leads to silyl loss with the formation of substituted products with a net double bond shift.[2]

Other investigators, in particular Buynak and co-workers,[3] have demonstrated similar regiocontrol using acetoxy- and thio-substituted allenes.

We now wish to report on the use of functionalised (allenylmethyl)silanes, in particular of hydroxymethylallene (**1**) as a means of accessing the side chain of the asparenomycins (**2**), a class of β-lactamase inhibitors.[4] Further, use of chirally enriched (**1**) results in the formation of chirally-enriched β-lactams.



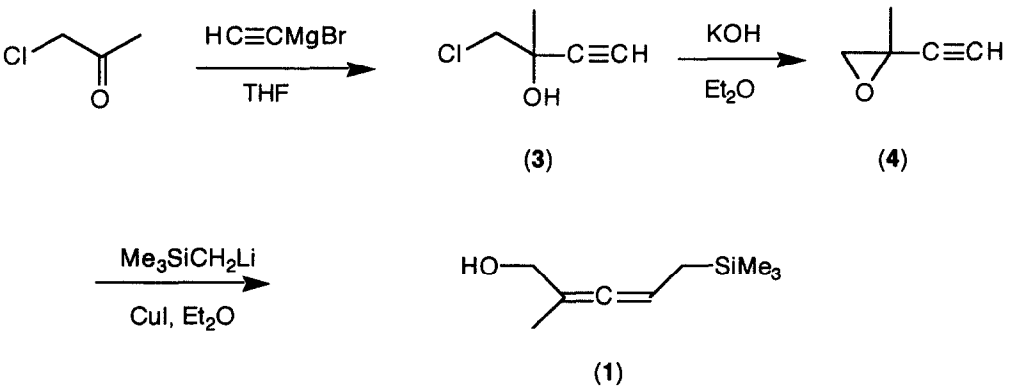
(**1**)



(**2**)

Reaction of chloroacetone with ethynylmagnesium bromide, followed by treatment of the chlorohydrin (**3**) with powdered KOH in ether, provided[5] the epoxybutyne (**4**). Reaction of this with the cuprate[6] derived from trimethylsilylmethyllithium and copper(1) iodide gave the desired hydroxymethylallene (**1**) (Scheme 2).

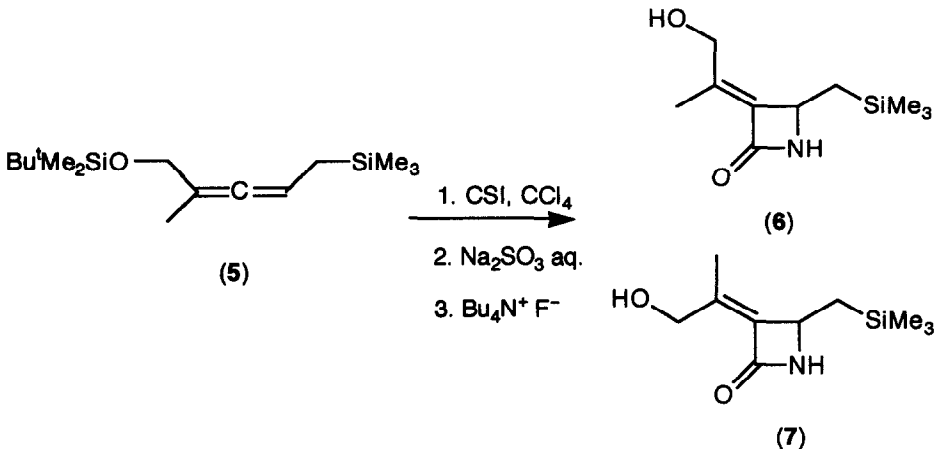
Scheme 2



(**3**) (**4**) (**1**)

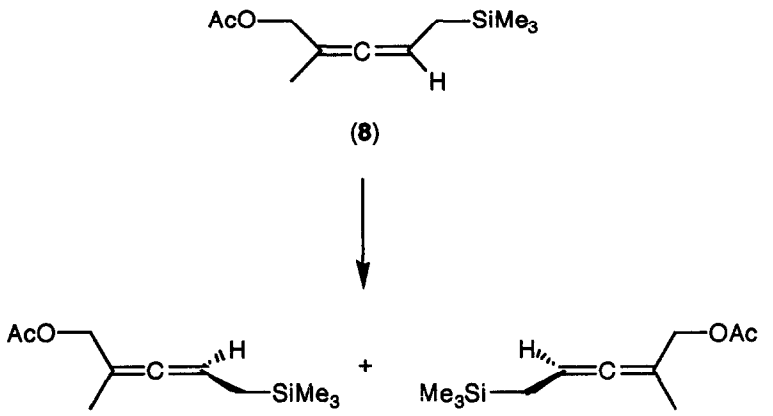
Alcohol (**1**) was converted into the corresponding t-butyldimethylsilyl ether (**5**) using t-butyldimethylsilyl chloride/4,4-dimethylaminopyridine/triethylamine. The course of the reaction of (**5**) with CSI in CCl_4 was conveniently monitored by ^1H NMR spectroscopy, by observing the disappearance of the allene proton multiplet at δ 5. On complete disappearance of this signal, the reaction mixture was quenched with aqueous Na_2SO_3 to effect reduction[7] of the chlorosulphonyl group. After deprotection, the β-lactams (**6**) and (**7**) were obtained in 31% yield as a crystalline 7:1 (*E*):(*Z*) mixture[8] (Scheme 3), with the major isomer (**6**) possessing the correct C-3 alkylidene functionality of the asparenomycins.

Scheme 3



Allene (**1**) is, of course, racemic. Its resolution was attempted, both by Sharpless kinetic resolution[9] and *via* diastereoisomeric esters, with very limited success. Recently, a chromatographic method for the enantioseparation of functionalised allenes was described[10]. For successful separation, the allene must carry a carbonyl group. Allene (**1**) was therefore converted into its acetate (**8**). Reverse phase chromatography using cellulose triacetate (Merck 16363, 25-40 micron) as stationary phase and ethanol as eluant resulted in the partial resolution of (**8**) (Scheme 4).

Scheme 4



This provided two fractions of $[\alpha]_D^{22}$ + 35° and - 29.5°, corresponding to enantiomeric excesses[11] of 82.4% and 67%, respectively. Ester cleavage (K_2CO_3/MeOH) was followed by silylation using t-butyldimethylsilyl chloride.[12] Separate cycloaddition of these allenes gave, after reductive cleavage, the t-butyldimethylsilyl ethers of β-lactam (**6**) with enantiomeric excesses of 48.5% and 42%, respectively. In each case, there has been transfer of the axial chirality of the allene to the C-4 carbon-centred chirality of the product β-lactams with approximately 60% efficiency.

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References and Notes

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8. Selected spectral data for (**6**): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.97 (s, 3H), 4.06 (d, 1H, J = 14.3 Hz), 4.16 (d, 1H, J = 14.3 Hz); for (**7**): δ 1.76 (s, 3H), 4.44 (d, 1H, J = 12.4 Hz), 4.57 (d, 1H, J = 12.4 Hz.
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11. Enantiomeric excesses were determined by capillary g.c. analysis using modified cyclodextrin stationary phases.
12. Earlier studies had indicated that acetoxymethylallenes were unsatisfactory substrates for reaction with CSI.