The Preparation of the First α-Vinylidene-β-lactams

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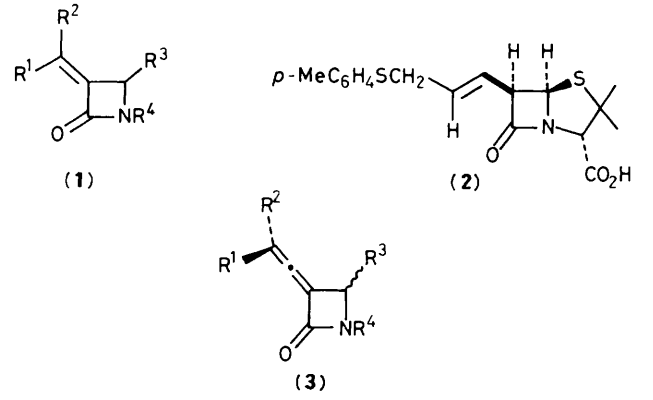
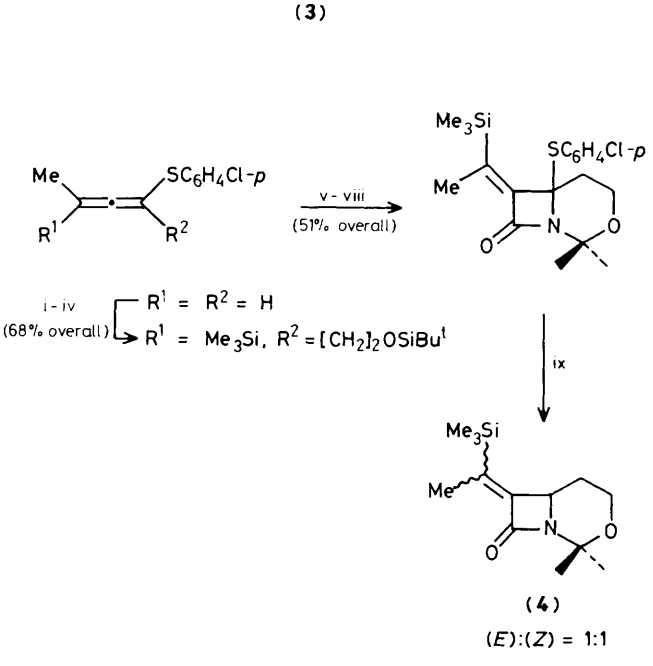
The first examples of β-lactams having a fused exocyclic allene at the α-postion are reported and some of their chemistry is described.

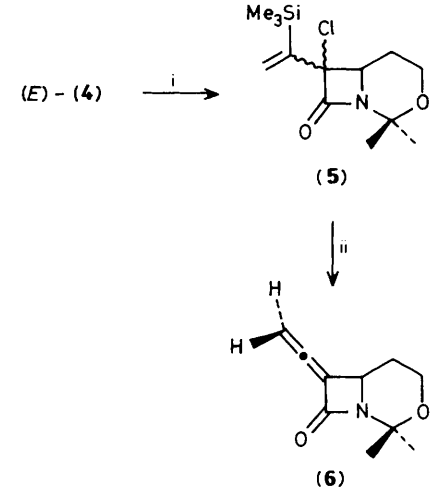
A recent surge in the number of papers and patents involving α-alkylidene-β-lactams (**1**) attests to the synthetic and medicinal value of this subunit.[1] The 6β-vinyl substituent has also been shown to be compatible with biological activity in the penam series [*e.g.*, (**2**)].[2] Some time ago, we considered preparing α-vinylidene-β-lactams (**3**), which would incorporate both these functionalities. Historically, several excellent inhibitors have been generated by incorporating allenes into enzyme substrates. Examples include amino acids,[3] amines[4] (and polyamines[5]), fatty acids,[6] prostaglandins,[7] and steroids.[8] We have recently published a series of articles on the preparation of the α-alkylidene-β-lactam subunit from the addition of chlorosulphonyl isocyanate (CSI) to substituted allenes and explored the usefulness of this functionality in the preparation of the asparenomycins, carpetimycin, and thienamycin.[9] We now report the first synthesis of the novel α-vinylidene-β-lactams and a brief investigation of their chemistry.

In the process of preparing intermediates suitable for the synthesis of thienamycin, we prepared the interesting

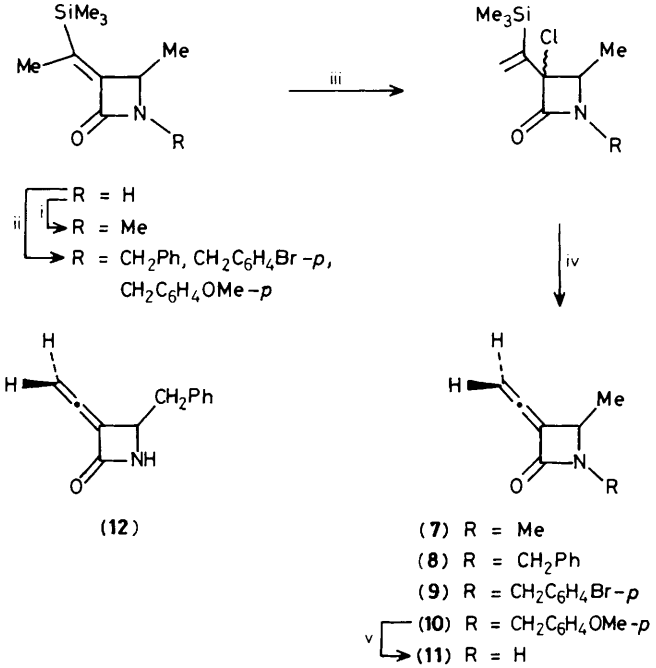




Scheme 1. i, Bu^{n}Li; ii, I[CH$_2$]$_2$OSiBu^t; iii, Bu^{n}Li; iv, Me$_3$SiCl; v, CSI; vi, Na$_2$SO$_3$; vii, HF–MeCN; viii, (MeO)$_2$CMe$_2$, BF$_3$–OEt$_2$; ix, Bu$^n_3$SnH, azoisobutyronitrile, 95%.



Scheme 2. i, Ca(OCl)$_2$–HOAc, 64%; ii, KF, DMSO, 80 °C, 60%.



Scheme 3. i, RI, KOH, or ii, RBr, CH_2Cl_2–4 M NaOH, Et_4NBr, 85—95%; iii, Bu^{t}OCl, THF, 60—80%; iv, KF, DMSO, 70—90%; v, $(NH_4)_2Ce(NO_3)_6$ (2 equiv.), MeCN–H_2O, 92%.

α-(silylalkylidene)-β-lactam (**4**) *via* our usual methodology[9,10] (Scheme 1). We found that (*E*)-(**4**) reacted with hypochlorous acid[11] [*i.e.* $Ca(OCl)_2$–HOAc] to generate the α-chloro-β,γ-unsaturated compound (**5**). While this result was unexpected, we realized the potential value of (**5**) in the generation of the vinylidene derivatives (**3**) *via* fluoride-ion-induced dehalogenosilylation. Indeed, when (**5**) was treated with KF in dimethyl sulphoxide (DMSO), allene (**6**) was isolated in 66% yield (Scheme 2).† Compound (**6**) was surprisingly stable, being readily purified by flash chromatography on silica gel. It showed no detectable signs of decomposition (by ^1H n.m.r. spectroscopy) when stored in solution ($CDCl_3$) at −10 °C for three months.

Several other such allenes could be easily prepared, (**7**)—(**10**) (Scheme 3).‡ In the case of these α-alkylidene-β-lactams, phase-transfer alkylation of the β-lactam nitrogen proved convenient and high yielding. Chlorination with t-butyl hypochlorite [in tetrahydrofuran (THF)] produced more consistent yields of the desired chloride [although this reaction could not be used in the case of (**4**) presumedly owing to traces of HCl which may be formed during the reaction]. These reactions are usually performed in the dark at 0 to −15 °C, although the effect of light has not been investigated. Fluoride-induced desilylchlorination proceeded in good (70—90%) yield in these cases. The *p*-methoxybenzyl group was readily removed[12] to produce the corresponding free NH β-lactam (**11**). In a similar fashion, (**12**) was prepared (by alkylating the allenyl sulphide with benzyl bromide, then trimethylsilyl chloride, and proceeding as usual) and an *X*-ray crystal structure obtained as shown in Figure 1.§

The allene (**8**) was easily hydrogenated to produce a 4:1 mixture of *cis*- and *trans*-4-methyl-3-ethylazetidin-2-one (**13a,b**) (Scheme 4). Bromination yielded predominantly the (*Z*)-dibromide (**14**). In an effort to evaluate the ability of the double bond to serve as a Michael acceptor toward nucleophilic amino acids, treatment of (**8**) with refluxing diethylamine produced a mixture of enamines (**15**) which were hydrolysed to give the corresponding ketone (**16**) on silica gel. Treatment with phenylmethanethiol, however, produced a mixture of the nonconjugated vinyl sulphides (**17**) which could be isomerized to give the corresponding α-alkylidene-β-lactams (**18**) on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF.[13]

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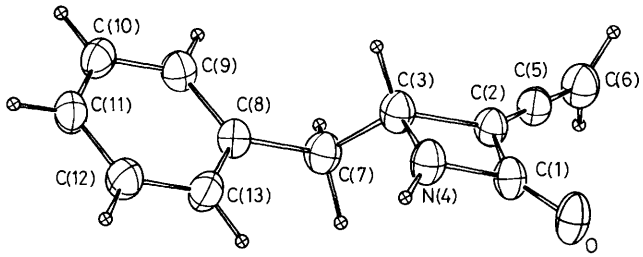
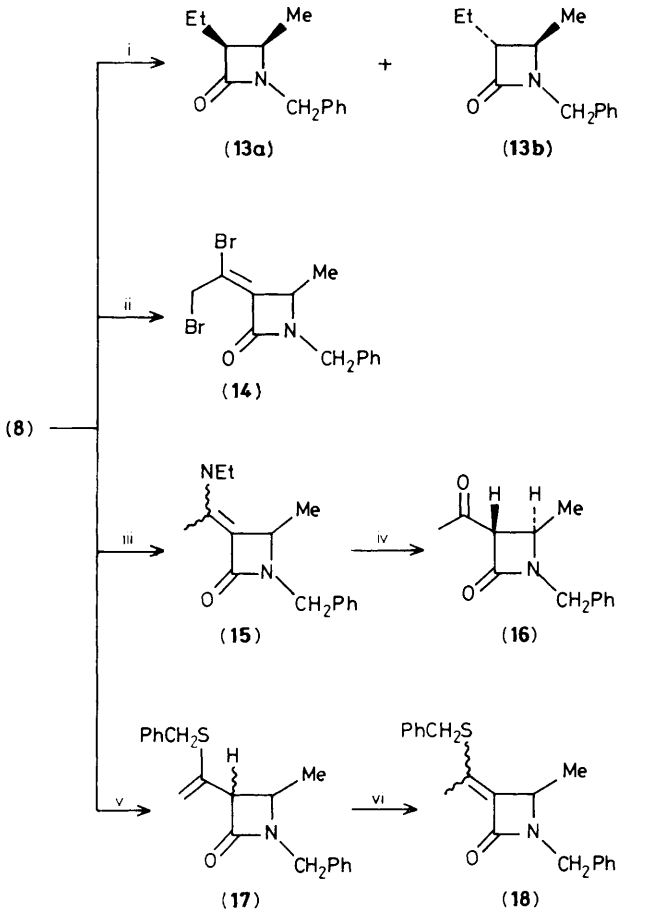


Figure 1. The *X*-ray crystal structure of (**12**).



Scheme 4. i, 1 atm H_2/Pd, 30 min, 72%; ii, Br_2 (1 equiv.), pyridine, 80%; iii, Et_2NH, reflux; iv, silica gel, 45%; v, $PhCH_2SH$, heat, 74%; vi, DBU, THF, 85%.

† *Spectral data* for (**6**): ^1H n.m.r. δ 5.33 (s, 1H), 5.32 (s, 1H), 4.29—4.20 (m, 1H), 3.93—3.86 (m, 2H), 2.00—1.75 (m, 2H), 1.80 (s, 3H), 1.46 (s, 3H); ^{13}C n.m.r. δ 197.1, 159.5, 108.2, 83.9, 79.0, 58.3, 51.7, 29.6, 26.6, 23.1; i.r. (neat) 3050, 2980, 2860, 1960, 1740, 1370, 1325, 1300, 1240, 1200, 1170, 1055 cm^{-1}; high resolution mass spectrum: calc. for $C_{10}H_{13}NO_2$: 179.0947, found: 179.0950.

‡ The structures of compounds (**7**)—(**10**) were verified by ^{13}C n.m.r., ^1H n.m.r., i.r., and high resolution mass spectroscopy.

§ *Crystal data* for (**12**): $C_{12}H_{11}NO$, M = 189.29, monoclinic, space group $P2_1/n$, a = 7.239(2), b = 6.984(2), c = 19.996(5) Å, β = 93.84(2)°, U = 1002.84(45) Å^3, Z = 4, D_x = 1.23 g cm^{-3}, λ(Mo-K_α) = 0.71069 Å, μ(Mo-K_α) = 0.44 cm^{-1}. Data were collected on a Syntex $P2_1$ diffractometer. A total of 1326 independent reflections was measured in the range $3 < 2\theta < 45°$ (θ—2θ scan type, graphite monochromatized Mo-K_α radiation). The crystal (0.56 × 0.41 × 0.23 mm) did not show any significant decay during the data collection. The data were corrected for decay, Lorentz–polarisation effects, but not for absorption. Only 1030 observed reflections with $I > 3\sigma(I)$ were used subsequently. The structure was solved by direct methods MULTAN 78 (Main, Hull, Lessinger, Germain, Declercq, and Woolfson, 1978) and difference Fourier methods. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located in difference Fourier maps and refined isotropically. Full-matrix least squares were used (SHELX76, G. M. Sheldrick, 1976, Program for crystal structure determination, Cambridge, U.K.). The function minimized being $\Sigma w(|F_o|-|F_o|)^2$. Final refinement converged to R = 0.040 and R_w = 0.042, the weights used being $w^{-1} = \sigma^2F + 0.000053(F^2)$. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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