Photoinduced Isomerisation of a 5,6-*trans*-Penem to a *cis*-Penem

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5,6-*trans*-Penem compounds were photochemically transformed *via* isomerisation at C(5) to 5,6-*cis*-penems, the structures of which were confirmed by spectroscopic and X-ray crystallographic analysis.

The conformation of β-lactam antibiotics has been widely investigated using X-ray crystallographic analysis, especially focusing on fused five- or six-membered rings.[1] The conformation of the 4-membered β-lactam ring, on the other hand, has not received so much attention may be because of the flat structure of nonfused monocyclic β-lactams.[2] However, recent analysis of the fused β-lactam ring in pencillins (and cephalosporins) revealed a characteristic puckered conformation (*e.g.* distance *r* of the carbonyl oxygen from the N(4)–C(5)–C(6) plane in penicillins varies between 0.14 and 0.83 Å) with a pseudoaxial S(1)–C(5) bond.[3]

In 6-hydroxyethyl substituted penem or carbapenem deriva-

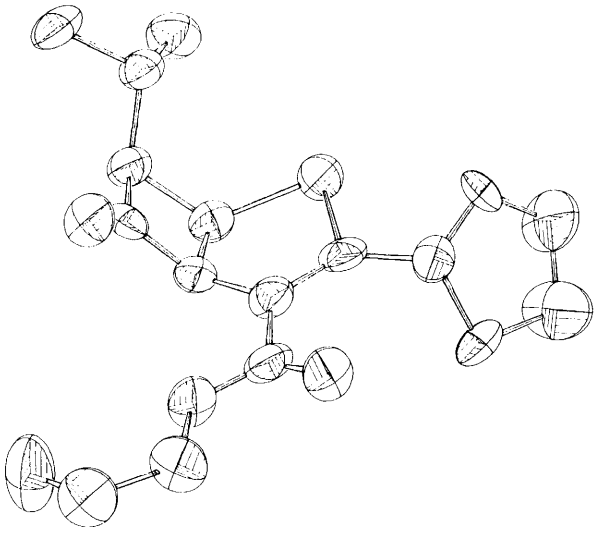

Fig. 1 Perspective view of the *cis*-penem **8**

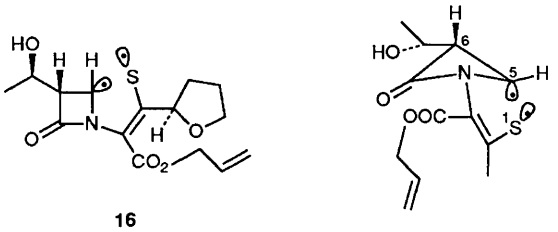

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Fig. 2 Puckered conformation with pseudoequatorially oriented substituent at C(6) for the biradical intermediate

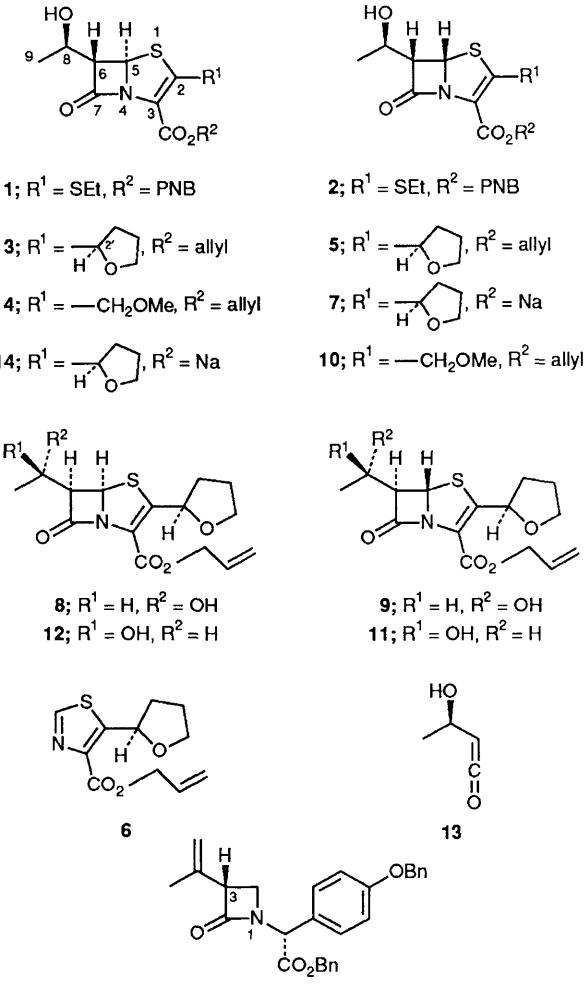
tives, the same puckered conformation (r = 0.23–0.39 Å) has been observed by X-ray crystallographic analysis.[4] In this conformation, the hydroxyethyl group in 5,6-*trans*-penem derivatives occupies a pseudoaxial position, while 5,6-*cis*-derivatives will have a pseudoequatorial orientation at C(6). Thus, on cleavage of the pseudoaxial S(1)–C(5) bond, the resultant monocyclic β-lactam ring would form the puckered conformation with the more stable 1,3-dipseudoequatorial conformation (see Fig. 2).

Isomerisation at the C(5) position of penems and penams occurs in a hydrolytic degradation of the β-lactam ring *via* heterolytic S(1)–C(5) bond cleavage.[5,6] Similarly, the 2-alkylthiopenem derivative **1** thermally equilibrates at the C(5) position to give a 1 : 4 mixture of 5,6-*cis*- and *trans*-diastereoisomers, with the thermodynamically more stable *trans*-isomer predominating.[7,8] This thermal isomerisation seems to require assistance by the C(2) sulphur, since no such isomerisation has been observed for the 2-alkylpenem derivatives such as compounds **3** and **4** under the same or more vigorous conditions (>130 °C), indicating that *cis*-penems are not usually generated thermally.

Here we report a more generally applicable photochemical bond cleavage of S(1)–C(5) leading to the isomerisation of 5,6-*trans*- to 5,6-*cis*-products. This is useful for the preparation of biologically active *cis*-penems with various side chains at C(2).

Irradiation through a Pyrex filter of a solution of compound **3**[9] in ethylacetate (2 mmol dm^{-3}) at room temperature for 50 min using a medium pressure UV lamp (Hanovia) gave a mixture of *cis*- and *trans*-penems **5** and **3** and thiazole **6**† in 11 : 3 : 1 ratio. The *cis*-penem **5** was separated in 67% yield and deprotected to the sodium salt **7** by treatment with $(PPh_3)_4Pd$ and sodium 2-ethylhexanoate in ethyl acetate.

† All new compounds exhibited satisfactory spectra (^{1}H and ^{13}C NMR, IR, and mass spectroscopy).



1; R^1 = SEt, R^2 = PNB
2; R^1 = SEt, R^2 = PNB
3; R^1 = , R^2 = allyl
5; R^1 = , R^2 = allyl
4; R^1 = —CH_2OMe, R^2 = allyl
7; R^1 = , R^2 = Na
14; R^1 = , R^2 = Na
10; R^1 = —CH_2OMe, R^2 = allyl
8; R^1 = H, R^2 = OH
12; R^1 = OH, R^2 = H
9; R^1 = H, R^2 = OH
11; R^1 = OH, R^2 = H

6 **13**

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Scheme 1 (PNB = *p*-nitrobenzyl)

The *cis*-penem **5** showed characteristic IR (ν_{max} 1763 and 1604 cm^{-1}) and UV (λ_{max} 302 nm) spectra for a penem structure, and the 5,6-*cis*-stereochemistry was confirmed by the characteristic coupling constant (J 4 Hz) between the C(5) and C(6) protons in the ^{1}H NMR spectra. Although a negative Cotton effect at λ_{max} 251 nm ($\theta = 4.70 \times 10^5$) in the circular dichroism spectrum of the compound **5** suggested isomerisation at C(5) to the (*S*) configuration, further confirmation of the isomerisation at C(5) was made by X-ray crystallographic analysis of the *cis*-penem **8**‡, as depicted in Fig. 2, which was derived from (5*S*)-*trans*-penem **9** by photoinduced isomerisation. This isomerisation was observed not only in C(2)-alkyl penems such as **3** and **4**, but also in the C(2)-alkylthio penem **1**. Thus, compound **1** was converted to its (5*S*)-isomer **2** in 58% in isolated yield. Photoirradiation of 5,6-*cis*-penem **5** in ethyl acetate for 2 h produced the degraded thiazole compound **6** and the ketene derivative **13** quantitatively and the corresponding 5,6-*trans*-penem was detected as a minor product by HPLC analysis during this reaction. Since photoisomerisation of the (5*S*)-*trans*-penem **11** afforded only the (5*R*)-*cis*-penem

‡ *Crystal data* for **8**: $C_{15}H_{19}O_5NS$, M = 325.39, monoclinic, a = 10.427(1), b = 17.149(1), c = 4.591(1) Å, β = 101.11(1)°, U = 805.6 Å^3, space group $P2_1$, Z = 2, D_c = 1.342 g cm^{-3}. Crystal dimensions 0.2 × 0.1 × 0.4 mm. 1333 independent reflections (sin θ/λ < 0.58 Å^{-1}) were collected on Rigaku automatic four-circle diffractometer, using graphite-monochromated Cu-Kα radiation. The R factor is 0.065 for 1333 observed reflections. The structure was solved by the direct method (MULTAN84) and refined by block-diagonal least-squares analysis. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

12 and not the (5*S*)-*cis*-penem **5**, it is evident that the [2 + 2] fragmentation at C(5)–C(6) and N(4)–C(7) which gives the same compounds(**6** and **13**) from **3** and **11**, is not the route for the isomerisation at C(5) but only the route for degradation to the thiazole compound **6** and the hydroxyethylketene derivative **13**.

The same photoisomerisation occurred with the sodium salt **14** in aqueous solution to give the *cis*-penem in a similar yield. Thus, the photoinduced isomerisation, which is not dependent on the substituents at C(2), the configuration of C(8), or solvents offers a new versatile route to *cis*-penem derivatives, since either (8*S* or 8*R*, 5*S* or 5*R*)-5,6-*trans*-penem derivatives can be readily prepared by established methods.[10–12] In this context, (5*R*)-*cis*-penems (**8** and **12**) have been prepared from (5*S*)-*trans*-penems (**9** and **11**) respectively in good yield.

The preference for the thermally unfavoured *cis*-product in this reaction may be due to the stability of the puckered conformation (Fig. 2) of the biradical intermediate **16** since pseudequatorial orientation of hydroxyethyl side chain will be favoured as seen in the crystal structure of 1,3-substituted azetidinone **15**.[13]

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