

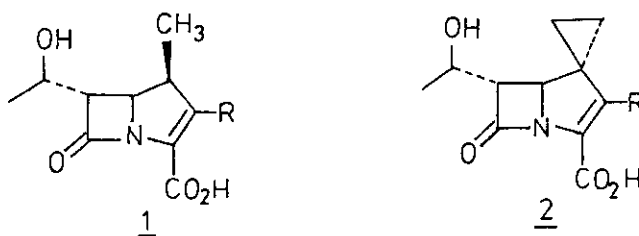
A SYNTHESIS OF A SPIROCYCLOPROPANE-1,1'-CARBAPENEM

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Abstract - The total synthesis of the spirocyclopropane 1,1'-carbapenem 13 has been achieved through the Wittig cyclization of the phosphorane 11. A modified Simmons-Smith reaction on the olefinic ketone 6 gave the key cyclopropane derivative 7 in good yield.

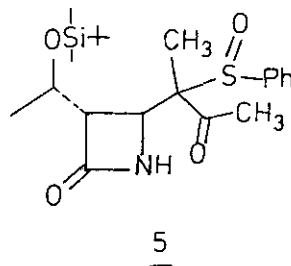
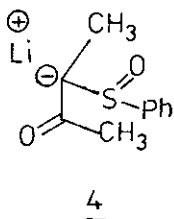
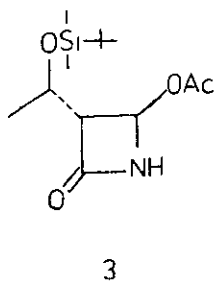
A recent report¹ by Shih and co-workers on the synthesis of 1- β -methylcarbapenems 1 which possess much improved chemical and metabolic stability than 1-unsubstituted carbapenems has created considerable interest in the chemical modification of the carbapenem ring at the C-1 position of carbapenems.² Specifically, this paper describes an efficient synthesis of a new carbapenem derivative having the cyclopropane ring attached at the C-1 position as depicted in the structure 2.

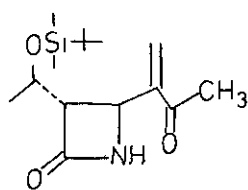


The chiral acetoxызetidinone 3, readily available by several routes³ was chosen as the starting material for the construction of the cyclopropane intermediate 7. Nucleophilic displacement of the acetoxy group of 3⁴ with the lithium anion 4 (THF, -20°, 2h) gave the trans product 5 in 75% yield as a mixture of diastereomers. Thermolysis of 5 (toluene, reflux 4h) generated cleanly the olefinic ketone 6 in 80% yield after chromatographic purification on silica gel. When the enone 6 was treated with Zn-Cu/CH₂I₂ (in situ generation of Zn-Cu from zinc dust and CuCl)⁵ in anhydrous ether, the desired cyclopropane intermediate 7 was obtained in 60-70% yield.

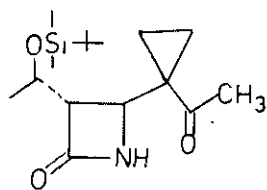
This modified Simmons-Smith procedure was quite reliable for reproducibility and scale up. Assignment of the structure 7 is based upon the presence of four cyclopropane ring protons at 1.0-1.4 in the ^1H NMR.¹⁰ Condensation of 7 with allylglyoxylate (benzene, reflux) gave the hemiaminal 8, which upon treatment with thionyl chloride followed by triphenylphosphine and 2,6-lutidine afforded the phosphorane 10 in 63% overall yield. Exposure of 10 to TFA-anisole (0°, 1h) provided the desilylated product 11 in 85% yield. The phosphorane 11 was transformed into the desired carbapenem 12 in 82% yield by the intramolecular Wittig procedure (xylene, reflux, 14h) developed by Woodward.⁶ Finally removal of the allyl group with tetrakis(triphenylphosphine) palladium⁷ in the presence of potassium 2-ethylhexanoate gave the potassium salt 13 in 35% yield after HP-20 column purification. The product showed a UV absorption maximum at 275 nm (ϵ 6,700) and a β -lactam carbonyl IR absorption at 1780 cm^{-1} characteristic of the bicyclic β -lactam.

In a similar manner as described above the olefinic ketone 6 was converted into the phosphorane 16 via the intermediates 14 and 15. Wittig cyclization of 16 was achieved by heating in refluxing toluene (24h) to give the 1-methylene carbapenem 18 in 79% yield. Unfortunately, when the desilylated phosphonate 17 was subjected to the Wittig conditions, only decomposed material was obtained. Thus, it appears that decomposition of 19 is faster than the cyclization of 17 in this case. Several other attempts to obtain the unprotected 1-methylene carbapenem free acid have not been successful so far. Recently the synthesis of Δ^3 -1-methylene-1-carbacephems has been achieved by the similar chemistry described above.⁸ The new carbapenem 13 showed a broad activity against gram positive and negative bacteria. However, to our surprise, compound 13 was hydrolyzed in vitro by dehydropeptidase-I about 100 times faster than the corresponding 1- β -methylcarbapenem analog.⁹

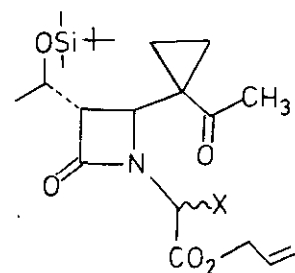




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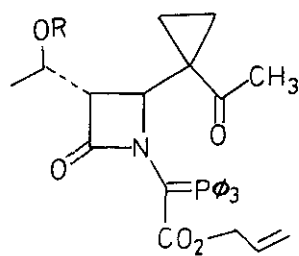


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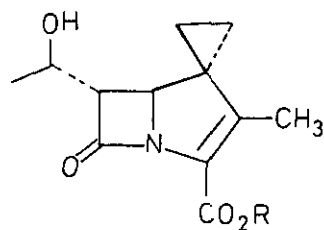
8, X=OH

9, X=Cl



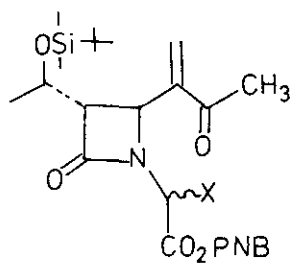
10, R=Si(t-Bu)Me2

11, R=H



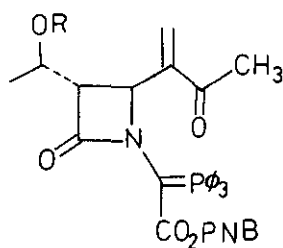
12, R=CH=CH2

13, R=K



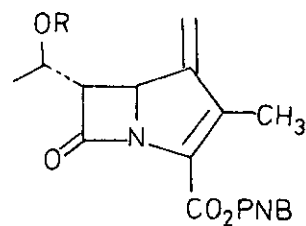
14, X=OH

15, X=Cl



16, R=Si(t-Bu)Me2

17, R=H



18, R=Si(t-Bu)Me2

19, R=H

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8. P. Herdewijn, P. J. Claes, and H. Vanderhaeghe, J. Med. Chem., 1986, 29, 661.
9. We are indebted to Dr. M. Hitchcock of the Screening and Bio-chemical Research Department of Bristol-Myers Company for this test. The full biological activity of 1 (R = CH₃) and 13 will be published elsewhere.
10. Selected NMR Data:
6 (CDCl₃-D₂O): δ 2.41 (s, 3H), 2.94 (dd, J = 2.5, 8.6 Hz, 1H), 4.26 (m, 1H), 4.61 (d, J = 2.5 Hz, 1H), 6.14 (s, 1H), 6.22 (s, 1H).
7 (CDCl₃): δ 1.0-1.38 (m, 4H), 1.21 (d, J = 6.5 Hz, 3H), 1.89 (s, 3H), 2.26 (d, J = 2.1 Hz, 1H), 4.08 (m, 1H), 4.32 (d, J = 2.1 Hz, 1H).
12 (CDCl₃): δ 1.0-1.40 (m, 4H), 1.32 (d, J = 6.2 Hz, 3H), 1.70 (s, 3H), 2.95 (dd, J = 3.0, 7.8 Hz), 3.92 (d, J = 3.0 Hz), 4.10 (m, 1H).
13 (D₂O): δ 1.1-1.5 (m, 4H), 1.22 (d, J = 6.2 Hz, 3H), 1.77 (s, 3H), 3.31 (dd, J = 3.3, 7.8 Hz), 4.06 (d, J = 3.3 Hz, 1H), 4.21 (m, 1H).
18 (CDCl₃): δ 2.15 (s, 3H), 3.14 (dd, J = 2.4, 7.5 Hz, 1H), 4.28 (m, 1H), 4.59 (d, J = 2.4 Hz, 1H), 5.21 (d, J = 2.0 Hz, 1H), 5.28 (d, J = 11.9 Hz, 1H), 5.39 (d, J = 2.0 Hz, 1H), 5.43 (d, J = 11.9 Hz, 1H). All other spectra data were in agreement with the proposed structure.

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