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

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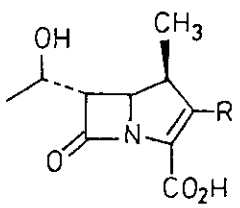
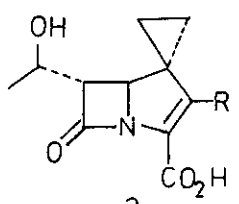
Abstract - The total synthesis of the spirocyclopropane 1,1'-carbapenem 13 has been achieved through the Wittig cyclization of the phosphorane 11. A modified Simmons-Smith reaction on the olefinic ketone 6 gave the key cyclopropane derivative 7 in good yield.

A recent report[1] 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.



1



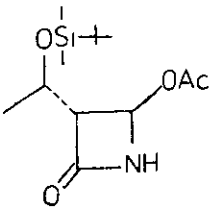
2

The chiral acetoxyazetidinone 3, readily available by several routes[3] was chosen as the starting material for the construction of the cyclopropane intermediate 7. Nucleophilic displacement of the acetoxy group of 3[4] 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/CH_2I_2 (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 ^{1}H 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) palladium[7] 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 cyliza-tion 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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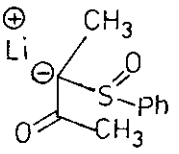

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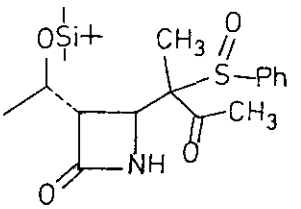

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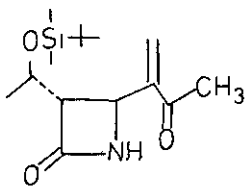

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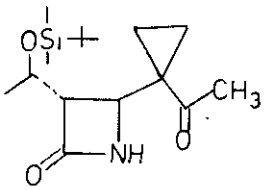

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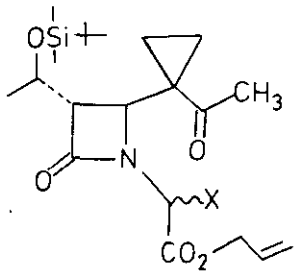
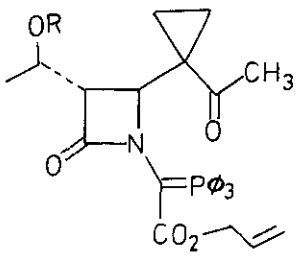


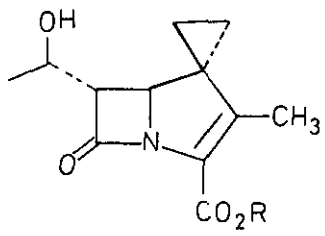
8, X=OH

9, X=Cl



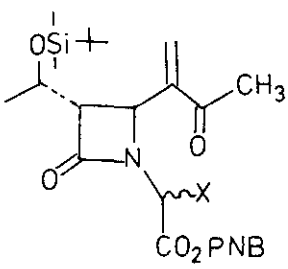
10, R=Si

11, R=H



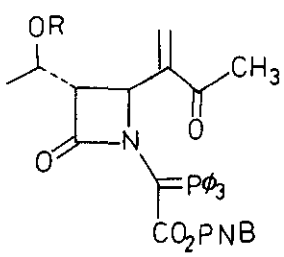
12, R=

13, R=K



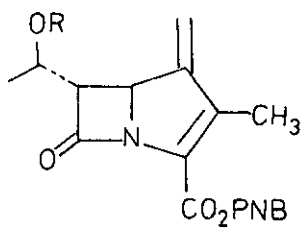
14, X=OH

15, X=Cl



16, R=Si

17, R=H



18, R=Si

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 = CH_3) and 13 will be published elsewhere.

10. Selected NMR Data:

6 ($CDCl_3$-D_2O): 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 ($CDCl_3$): 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 ($CDCl_3$): 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 (D_2O): 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 ($CDCl_3$): 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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