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4-TETRAHYDROPYRANTHIOAZETIDINYL PHOSPHORANES: VERSATILE INTERMEDIATES IN THE SYNTHESIS OF 2-PENEMS

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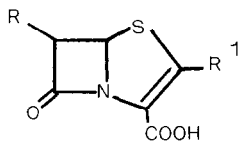
Summary: The total synthesis of four racemic trans-6-ethyl-2-penems has been developed using the 4-tetrahydropyranthioazetidinyl phosphorane 10 as a common precursor.

2-Penem-3-carboxylic acids 1 constitute a class of synthetic β-lactam compounds which show promising biological activity.[1a,b] Woodward and his coworkers[2a-d] were the first to synthesize penems by using an intramolecular Wittig reaction of 4-acylthioazetidinyl phosphoranes 2 for the construction of the thiazoline ring.



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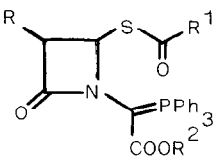

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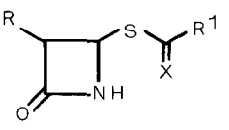


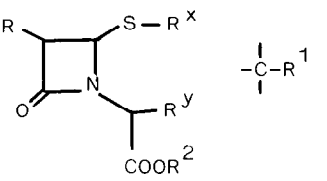
3 X = O
4 X = CH-R^3

While this step is still the most efficient to perform the desired annulation,[3] the synthetic sequence for the obtaining of the intermediates 2 suffers, from our experience, of two main disadvantages: (a) lack of flexibility, because for each substituent R^1 to be introduced in the final product 1 is required the repetition of the whole sequence; (b) lack of productivity, because the very first step of the sequence, consisting in the displacement of a nucleofuge leaving group by a thiolacid[2a] in basic medium to give 4-acylthioazetidinones 3, frequently proceeds with poor yields.

The trick of exploiting the good nucleophility of thioenols[2c,d][4c] to obtain azetidinylthioenolethers 4 in high yields is limited by the availability of the correct thioenol and by the oxidative cleavage of the olefinic bond required to

restore the acylthio functionality in 2. Moreover, the presence of base labile and/or oxidation sensitive moieties in the grouping R^1 may create additional problems.

In order to expand our programs directed towards the synthesis of the so called "non classical" β-lactam compounds, which started few years ago,[4a-f] we were triggered to find a flexible synthetic access to structures possessing the 2-penem nucleus. We reckoned that a common synthon 5 could be built which, by coupling with $-\overset{|}{\underset{|}{C}}-R^1$ units, might feasibly furnish a wide choice of 2-penems.



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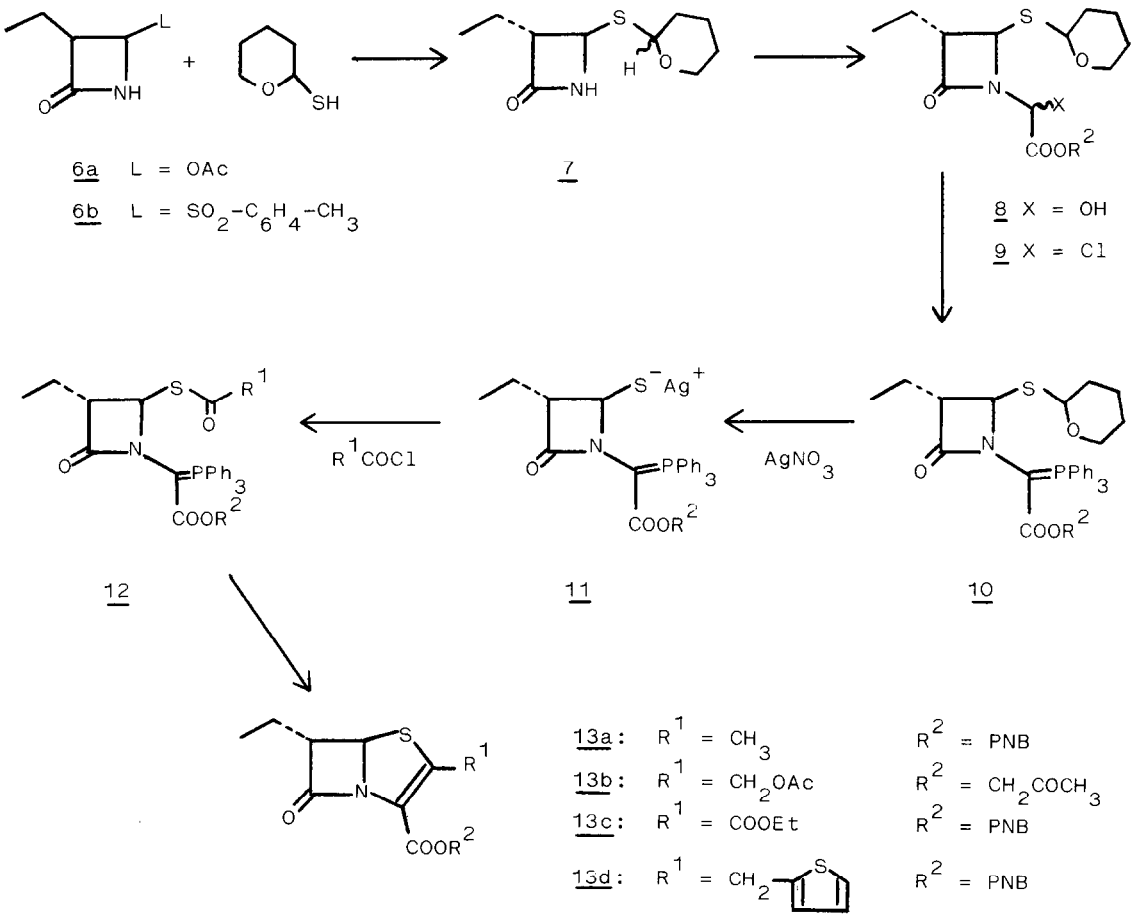
The reaction between 3-ethyl-4-acetoxy-azetidinone 6a[5] (cis/trans mixture 7:3) or 3-ethyl-4-p-toluenesulphonylazetidinone 6b[6] (cis/trans mixture 1:9) with 2-tetrahydropyranthiol[7] (1.1 eq. NaOH, H_2O-Me_2CO, RT, 97%) led to the adduct 7[8] (two diastereoisomers, trans ⩾ 95%) which was condensed with a glyoxylate $CHOCOOR^2$ (Et_3N, THF, RT[9]) to give the crude carbinols 8 which, upon subsequent chlorination ($SOCl_2$, pyridine, THF, -30-0°C) afforded the chlorides 9. Without purification, they were transformed (PPh_3, CH_2Cl_2, RT overnight) into the phosphorane 10 in 60 - 70% yield based on 7, after filtration on silica gel.

The addition of one eq. amount of aqueous $AgNO_3$ to a methanolic solution of the synthon 10 yielded[7] the expected silver salt 11 almost quantitatively. The exposure[10] of 11 to an acyl chloride R^1COCl (1.5 eq., CH_3CN, 5 min. RT) furnished, after filtration (celite) of the precipitated AgCl and alkaline aqueous work up, the desired phosphoranes 12 (60% yield after purification).

Following Woodward's procedure, the ylids 12 were heated in toluene and afforded the trans-6-ethyl-2-penems 13a-d in variable yields. The corresponding acids (R^2 = H) obtained either by hydrogenolysis (R^2 = PNB, p-nitrobenzyl) or phosphate buffer 7.5 hydrolysis (R^2 = CH_2COCH_3) were tested in vitro and their comparative activities as minimal inhibitory concentration (MIC) against a choice of microorganisms are reported.



	NMR, 90-MHz, $CDCl_3$, δ	IR, $CHCl_3$, cm^{-1}	UV, EtOH, nm
13a	1.07 (3H,t,J=7Hz); 1.91 (2H,m,J=7Hz,J_1=7Hz); 2.36 (3H,s); 3.69 (1H,m,J_1=7Hz,J_{vic}=2Hz); 5.34 (2H,dd,J_{gem}=14Hz; 5.36 (1H,d,J_{vic}=2 Hz); 7.63 (2H,d,J_2=8Hz); 8.22 (2H,d,J_2=8Hz).	1790, 1710	264 310
13b	1.03 (3H,t,J=7Hz); 1.94 (2H,m,J=7Hz,J_1=8Hz); 2.06 (3H,s); 2.16 (3H,s); 3.67 (1H,dt,J_1=8Hz,J_{vic}=2Hz); 4.67 (2H,s); 5.17 (2H,cent. of ABq,J_{gem}= 15Hz); 5.30 (1H,d,J_{vic}=2Hz).	1790, 1745, 1715	323
13c	1.09 (3H,t,J=8Hz); 1.27 (3H,t,J_1=7Hz); 1.93 (2H,m,J=8Hz,J_2=7Hz); 3.92 (1H,dt,J_2=7Hz,J_{vic}=2Hz); 4.27(2H,q,J_1=7Hz); 5.38 (2H,ABq,J_g =1Hz); 5.44 (1H,d,J_{vic}=2Hz); 7.93 (4H,cen. of ABq,J_3=8Hz).	1790, 1735, 1725	264 336
13d	1.04(3H,t,J=7Hz); 1.89(2H,m,J=7Hz,J_1=8Hz); 3.82(1H,dt,J_1=8Hz,J_{vic} =1.8Hz); 4.38(2H,cen.of ABq,J_{gem}=17Hz); 5.33(1H,d,J_{vic}=1.8Hz); 5.40(2H,c. of ABq,J_{gem}=14Hz); 6.95, 7.24(3H,m) 7.95(4H,ABq,J_g=9Hz)	1785, 1710 1605, 1580 1520	241 264 381

Spectral data for compounds 13a, 13b, 13c and 13d.

	Staphylococcus aureus Smith	Staphylococcus aureus 39/2	Streptococcus pyogenes C 203	Escherichia coli TEM	Salmonella typhi Watson	Klebsiella pneumoniae ATCC 10031
13a	2	4	1	32	16	32
13b	0.5	1	0.25	64	16	8
13c	>128	>128	>128	>128	>128	>128
13d	0.25	0.24	0.12	64	64	8

Comparative in vitro activities (MIC, μg/ml) of racemic trans-6-ethyl-2-penems 13a, 13b, 13c and 13d (R^2 = H).

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8. δ 1.04 (3H,t,J=7Hz); 1.60-1.90 (8H,br); 3.14 (1H,br m); 3.58 (1H,br m); 4.14 (1H,br m); 4.63 and 4.74 (1H,d,J_{vic}=2Hz); 5.10 (1H,br m); 6.47 and 6.60 (1H,br, exchange with D_2O). ν_{max}: 3330, 2930, 2860, 1760 cm^{-1}
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