Nuclear analogs of β-lactam antibiotics. XIV. Synthesis of penems via (4-tritylthio-2-azetidinon-1-yl)triphenylphosphoranylideneacetates

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The preparation of (4-tritylthio-2-azetidinon-1-yl)triphenylphosphoranylideneacetates from 4-acetoxyazetidin-2-one is described. They are easily converted to mercuric or silver mercaptides. These mercaptides are acylated with a wide variety of acylating agents and cyclized to 2-substituted penem-3-carboxylates.

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On décrit la préparation des (tritylthio-4 azètidinone-2 yl-1) triphénylphosphoranylidèneacétates à partir de l'acétoxy-4 azétidinone-2. On les transforme facilement en sulfures de mercure ou d'argent. On acyle ces sulfures avec une grande variété d'agents acylants et on les cyclise en pénèmecarboxylates-3 substitués en position 2.

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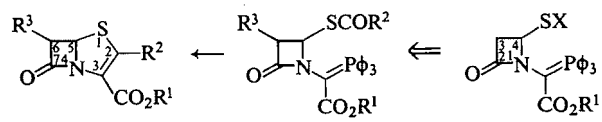
In connection with our continuing effort in modified β-lactam antibiotics (1) the penicillin–cephalosporin hybrid nature of the penem nucleus **1** looked especially attractive to us. The "Wittig route" to the penems, as devised by Woodward (2), was ingenious but too restrictive: the potential substituents on the nucleus must be introduced early in a long sequence, which severely limits the preparation of a series of analogs (3). Consequently we searched for a more versatile modification of the approach.[3] A recent publication by Farmitalia (4) has since described a similar approach to the synthesis of penems.

We considered that a building block such as **3**, with a sulfur protecting group that (a) allows introduction of R^2 through acylation at sulfur, (b) could potentially allow introduction of R^3 (e.g. hydroxyethyl) through anion generation at C(3),[4] and (c) is commercially available and devoid of asymmetric centers, would possess the required versatility. We found that a trityl group fulfilled all the above requirements as a sulfur protecting group.



1 **2** **3**

SCHEME 1

In this paper we describe the preparation of penems substituted in position 2 via (1) synthesis of 4-tritylthioazetidinonylphosphorane carboxylic acids (**8**) protected by two alcohol residues, (2) transformation of **8** to heavy metal mercaptides **9** (M = Ag, Hg), (3) their reaction with various acylating agents, and (4) their cyclization followed by deprotection.

Nucleophilic displacement of the acetoxy group of azetidinone **4** is well known (5). Reaction with sodium triphenylmethyl mercaptide gave a high yield (90%) of crystalline 4-triphenylmethylthio-2-azetidinone (**5**). *N*-substitution with two glyoxylic acid esters (R^1 = *p*-nitrobenzyl and trimethylsilylethyl), reaction with thionyl chloride, and then with triphenylphosphine following well documented procedures[4] afforded the key intermediates **8** (66% and 68% overall from **5** for the respective esters). Whereas both carboxylic acid protecting groups were found suitable for conversion to 2-substituted penems, the trimethylsilylethyl ester

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[3]This work is part of a Bristol-Myers patent filed on September 21, 1979 (see ref. 3*c*); it was also presented at the ACS Annual Meeting held in New York City, August 23–28, 1981.

[4]See ref. 2*c*, and references cited therein.

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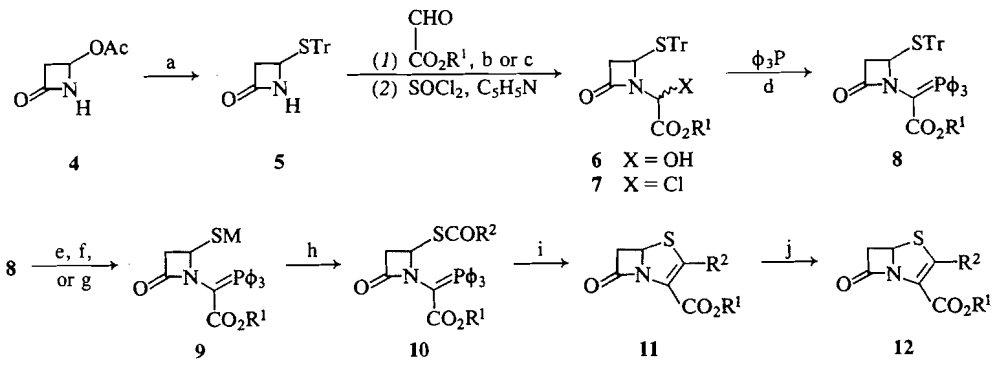

11a R^1 = *p*-nitrobenzyl; R^2 = CH=CHNOMe
11b R^1 = $(CH_2)_2Si(CH_3)_3$; R^2 = $(CH_2)_3CN$
11c R^1 = $(CH_2)_2Si(CH_3)_3$; R^2 = $(CH_2)_3SCN$
11d R^1 = *p*-nitrobenzyl; R^2 = $CH_2OCH{=}NOMe$
11e R^1 = *p*-nitrobenzyl; R^2 = CH_2SCH_3

12a R^1 = Na; R^2 = CH=CHNOMe
12b R^1 = K; R^2 = $(CH_2)_3CN$
12c R^1 = K; R^2 = $(CH_2)_3SCN$
12d R^1 = Na; R^2 = $CH_2OCH{=}NOMe$
12e R^1 = H; R^2 = CH_2SCH_3

(a) TrSNa (0.85 equiv.), MeOH/H_2O 1:1, 20°C, 4H; (b) refluxing benzene; (c) benzene, 20°C, triethylamine; (d) refluxing benzene, 2,6-lutidine; (e) $AgNO_3$ (1.1 equiv., 0.15 *M* in MeOH), pyridine (1.1 equiv.), CH_3OH, 20°C, 2h and 5°C, 1h; (f) $Hg(OAc)_2$ (1 equiv.), MeOH/CH_2Cl_2 1:1, 5°C, 2h; (g) $AgNO_3$ (4 equiv.), diethyl ether/water 1:1, tri-*n*-butylamine (1.3 equiv.) 20°C, 20 min; (h) R^2COX, pyridine, CH_2Cl_2, 0°C, 15–20 min; (i) refluxing benzene or toluene; (j) H_2, 30% Pd/Celite, THF, diethyl ether, $NaHCO_3$ (1.1 equiv.), H_2O (R^1 = *p*-nitrobenzyl) and tetrabutylammonium fluoride, THF, 0°C, (R^1 = trimethylsilylethyl), potassium ethylhexanoate.

TABLE 1. Spectral data and yields[a]

Compound	^{1}Hmr, 80 MHz, δ[b]	Infrared,[c] cm^{-1}	Ultraviolet,[d] nm (ε)	Yields
12a	8.01, (1H, d, *J* = 9.0), 7.72 (1H, d, *J* = 15.7), 6.36 (1H, dd, *J* = 9.9, 15.7), 5.76 (1H, dd, *J* = 3.6, 2.9), 3.93 (>3H, m), 3.78 (<1H, d, *J* = 3.6), 3.56 (1H, dd, *J* = 16.9, 2.0), (D_2O)	1750 1600	357 (8325) 300 (9200) 275 (10300)	7.5%
12b	5.72 (1H, dd, *J* = 3.6, 1.7), 3.83 (1H, dd, *J* = 16.7, 3.6), 3.47 (1H, dd, *J* = 16.7, 1.7), 3.30–1.79 (6H, m), (D_2O)	2250 1765 1610	306 (6875) 258 (4810)	46%
12c	5.75 (H, dd, *J* = 3.6, 1.8), 3.87 (1H, dd, *J* = 16.8, 3.6), 3.48 (1H, dd, *J* = 16.8, 1.8) 3.31–2.50 (4H, m), 2.22 (2H, m), (D_2O)	2150 1765	306 (6875) 254 (3786)	34%
12d	7.63 (0.55 H, t, *J* = 5.3), 7.06 (0.45 H, t, *J* = 4.0), 5.78 (1H, dd, *J* = 3.6, 1.8), 5.07, 3.90, 4.53 (1H, part of ABq, *J* = 15.2), 4.44 (0.9 H, d, *J* = 4.0), 4.25 (1.1 H, d, *J* = 5.3), 3.91 (3H, s), 3.88 (1H, dd, *J* = 16.8, 3.6), 3.55 (1H, dd, *J* = 16.8, 1.8), (D_2O)	1765 1620	307 (5500) 253 (3674)	21%
12e	5.33 (1H, dd, *J* = 2.0, 3.8), 3.58 (2H, ABq, *J* = 13.5), 3.48 (1H, dd, *J* = 16.1, 3.8), 3.10 (1H, dd, *J* = 16.1, 2.0), 2.63 (bs), 1.75 (3H, s), (DMSO-d_6)	1780 1657	315 (5600) 260 (3600)	5.8%

[a] Yields (**11** to **12**).
[b] Chemical shifts, δ, in ppm relative to internal TMS. Coupling constants, *J*, in Hz.
[c] Recorded in Nujol.
[d] Recorded in H_2O.

of **8** was the candidate of choice particularly for 6-substitution.[5]

Acylation of the key intermediate at sulfur was achieved through its conversion to metal mercaptides. Reaction of **8** with silver nitrate (6) or mercuric acetate (7) precipitated the corresponding silver (85%, R^1 = *p*-nitrobenzyl; 100%, R^1 = trimethylsilylethyl) or mercuric (91%, R^1 = *p*-nitrobenzyl) mercaptides **9** in high yield.[6] These mercaptides were found to be stable solids that could be stored for months without any sign of alteration; they are soluble in some organic solvents and readily acylated.

Acylation of the mercaptides **9** was found to be a simple process that can be carried out under a wide variety of conditions depending on the nature and stability of the substituents on the acylating moiety. The acylating species can vary from simple acid chlorides (8) to anhydrides, mixed anhydrides (R^2CO_2OCOR, $R^2CO_2SO_2CH_3$), or Vilsmeier complexes ($R^2CO_2CH{=}\overset{+}{N}Me_2\bar{Cl}$), thus making possible the synthesis of penems **11** with a wide variety of functional groups in the substituent at position 2. The phosphoranes **10***a–e*, so obtained, were thermally cyclized to penems (**11***a–e*) (2) in refluxing toluene (R^1 = *p*-nitrobenzyl) or benzene (R^1 = trimethylsilylethyl). The acid protecting groups were finally cleaved with appropriate reagents (R^1 = *p*-nitrobenzyl: H_2/30% Pd/Celite or sodium dithionite; R^1 = trimethylsilylethyl: tetrabutylammonium fluoride) and gave penems **12** (R^1 = H, K, or Na) in reasonable yields (see Table 1).

[5]The methodology for the preparation of 2,6-disubstituted penems from intermediates **8** will be the subject of a following paper.

[6]The mercaptide **9** (M = Ag, R^1 = *p*-nitrobenzyl) can also be obtained in high yield (78% to 93%) by treatment (in MeOH) of the corresponding 4-acetylthio-2-azetidinonephosphorane **10** (R^2 = CH_3) with $AgNO_3$ under basic (DBU, Na_2CO_3) or nucleophilic basic (pyrrolidine) conditions (for preparation of **10** see ref. 2*d*).

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