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A SHORT SYNTHESIS OF THE Δ^1-CARBOPENEM RING SYSTEM

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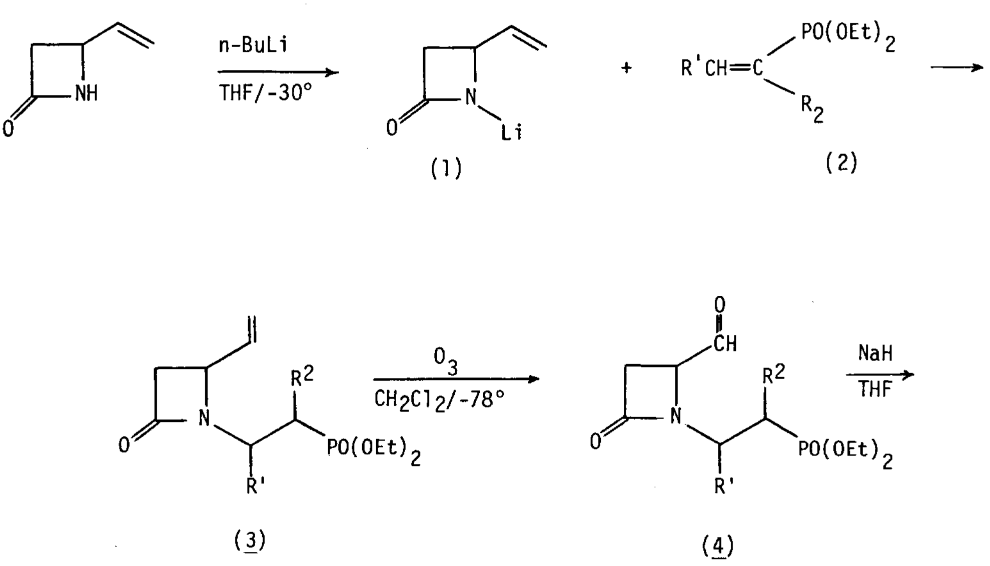
Abstract: Michael addition of N-lithio-4-vinyl-azetidin-2-one to several vinyl phosphonates gave adducts which were converted to Δ-1 carbopenems via ozonolysis and an intramolecular Horner-Wittig reaction.

The discovery of thienamycin[1] has created considerable interest in the synthesis of the carbopenem ring system and a number of imaginative routes to the Δ^2-carbopenem ring system, present in thienamycin, have been described over the past three years[2].

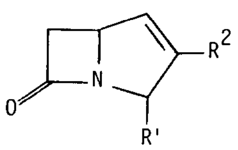
In contrast much less effort has been directed to the Δ^1-carbopenem system. Christensen and coworkers[2a] prepared an example of this system as an intermediate in the first thienamycin synthesis and showed that the Δ^1 double bond was partly isomerized to the Δ^2 position on treatment with diisopropylamine in DMSO. Thus an effective synthesis of Δ^1 - carbopenems could prove to be a valuable approach to the Δ^2 isomers.

We would like to report that Δ^1-carbopenems are readily prepared by the Michael addition of the N-lithio salt of 4-vinyl-azetidin-2-one 1 to a variety of vinyl phosphonates of the type 2 followed by ozonolysis of the adduct 3 in CH_2Cl_2 at -78° and subsequent treatment of the intermediate aldehyde 4 with NaH in THF. Scheme 1.



Scheme 1

Scheme 1 (Continued)

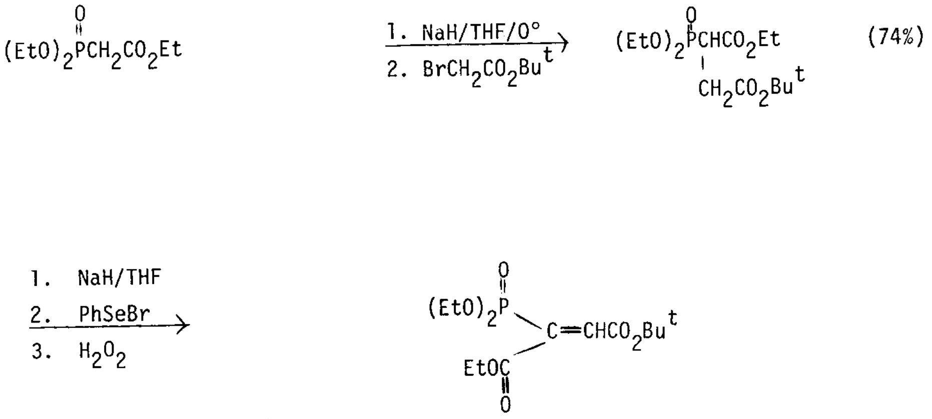


(5)

			Overall Yield (%) from 1 or 2
(a)	R^1=H,	R^2=CO_2Et	(25)
(b)	R^1=H,	R^2=CO_2Bu^t	(18)
(c)	R^1=Ph,	R^2=CO_2Et	(22)
(d)	R^1=CO_2Bu^t,	R^2=CO_2Et	(20)
(e)	R^1=Ph,	R^2=S(O)Me	(25)
(f)	R^1=Ph,	R^2=SO_2Me	(30)

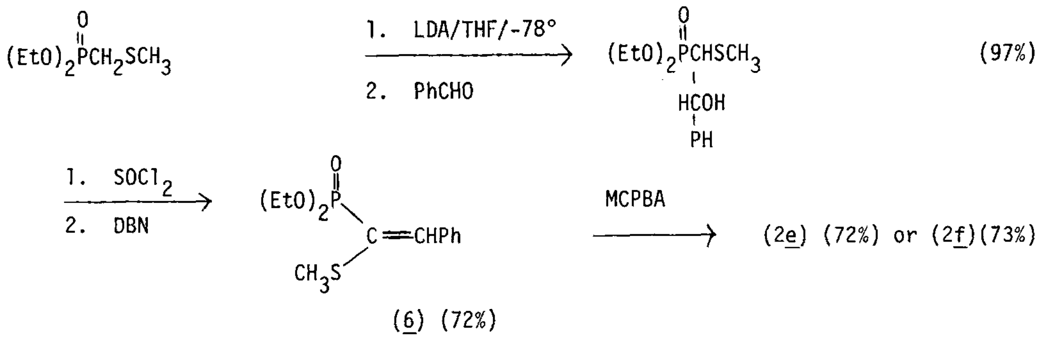
Typically the sequence in Scheme 1 is carried out without purification of the intermediates 3 and 4. The overall yield of the bicyclic lactams 5 based on 2 or 3 was of the order of 20-30%. In instances where the Michael adducts were purified, ozonolysis and subsequent cyclization afforded 5[3] in yields approaching 50%.

The required vinyl phosphonates 2[4] were prepared by several different routes. Compounds 2a and 2b were available in 60 and 38% yield respectively via the reaction of $(EtO)_2P(O)CH_2CO_2Et$ with paraformaldehyde in refluxing methanol containing piperidine as catalyst[5]. The phenyl substituted phosphonate 2c was similarly prepared. Diester 2d[4], [clear oil, b.p. 130-135°, nmr; δ = 6.71 (J_{PCCH} = 23 Hz)] was obtained via the sequence outlined in Scheme 2 and the ethylenic sulfoxide 2e[4], mp 71-73° and ethylenic sulfone 2f[4], colorless oil, according to Scheme 3. In these cases only one isomer, which showed a 23 Hz coupling constant between the remaining H and the phosphonate function, was obtained[6].



(2d)

Scheme 2



Scheme 3

The Δ^1-penems were characterized by their elemental analyses, infrared, ^{1}H and ^{13}C spectra. Thus compound 5b, colorless oil after chromatography showed strong infrared absorption at 1780 and 1715 cm^{-1} due to the β-lactam and conjugated ester linkages respectively. Its proton nmr showed peaks at 1.47 (s, 9H) 2.92 (dd, J=14, 2.5 Hz, 1H), 3.4-3.8 (m, 2H), 4.4-4.7 (m, 2H) and 6.68 (broadened singlet, 1H). The diester lactam 5d was obtained in 20% yield as a single isomer, mp 76-77° (ether-pentane); ^{1}H nmr: 1.30 (t, J-7 Hz, 3H), 1.47 (s, 9H), 2.98 (dd, J=14, 3 Hz,1H), 3.45 (dd, J=14, 6 Hz), 4.23 (q, J=7 Hz, 2H), 4.5-4.8 (m, 1H); ^{13}C: 14.1 (q), 27.8 (q), 44.7 (t), 59.4, (d), 61.2 (t), 66.9 (d), 82.3 (s), 138.7 (s), 141.9 (d), 162.1 (s), 167.5 (s), 177.2(s).

No reaction was observed between 1 and 6. In contrast, Michael addition of 1 to the vinyl sulfoxide 2e and vinyl sulfone 2f occurred in 80 and 61% isolated yields respectively. The Michael adduct 3f was ozonolyzed and cyclized as above to give 5f (49%) as a 2:1 mixture of isomers. Both the major isomer, mp 115-120°, and minor isomers, mp 144-146°, showed strong infrared absorption at 1780, 1310 and 1150 cm^{-1}. The exo vs endo phenyl group structure in these isomers cannot as yet be assigned with certainty.

Ozonolysis and subsequent NaH treatment of the sulfoxide 3e furnished in 31% yield the sulfoxide 5e, accompanied by 10% of the sulfone 5f due to the inadvertent oxidation of the sulfoxide during the ozonolysis reaction. Oxidation of 5e with MCPBA in CH_2Cl_2 gave cleanly 5f.

The above examples demonstrate a new and very short approach to Δ^1-penems. Further examples of such syntheses and their isomerization to Δ^2-penems are being investigated.

A typical experimental procedure is illustrated by the preparation of 5d. To a solution of 1, prepared from 582 mg (6 mmole) of 4-vinyl-azetidin-2-one and n-BuLi (6 mmole), dissolved in 10 ml of THF at -30° was added 2.02 g (6 mmole) of phosphonate 2d. The reaction mixture was stirred for 30 min, quenched with 10 ml of aqueous NH_4Cl and extracted with 30 ml of CH_2Cl_2. The organic phase was dried and evaporated to yield 2.22 g of pale yellow oil. This was redissolved in 20 ml of CH_2Cl_2 and ozonized at -78° until excess ozone was detected (blue colour). The excess ozone was decomposed with dimethyl sulfide, and the crude product, a viscous oil, was dissolved in 20 ml of THF, cooled to -30° and stirred with 6 mmole of NaH for 30 min and then at room temperature for a further 7 h. The reaction mixture was quenched with aqueous NH_4Cl and extracted with CH_2Cl_2. The crude product (1.5 g) was purified on prepa-rative silica gel plates to yield 350 mg (20% from 1 or 2d) or 5d as a colourless solid, mp. 76-77°.

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References

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2. (a) S.M. Schmitt, D.R.B. Johnston and B.G. Christensen J. Org. Chem. **45**, 1142, 1980;
   (b) R.W. Ratcliffe, T.N. Salzmann, and B.G. Christensen, Tetrahedron Letters, **21**, 1 1980;
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3. All bicyclic β-lactam had correct elemental analysis. The proton and carbon 13-spectra were compatible with the assigned structures. Their β-lactam carbonyl band occurred in the 1775-1780 cm^{-1} range.
4. These vinyl phosphonates were characterized by their proton spectra. Their structure follows from the method of synthesis.
5. M.F. Semmelhack, J.C. Tonesch, M. Czarny and Boettger, J. Org. Chem., **43**, 1259, 1978.
6. M.P. Williamson, S. Castellano and C.D. Griffin, J. Phys. Chem.**72**, 175, 1968; the PC=CH coupling constants vary considerably with the geometry about the double bond and the nature of the remaining substituent on the sp^2 carbons. Thus the stereochemistry of 2 d,e,f, cannot be rigorously assigned.
7. The isomers were separated by silica gel column chromatography using ethylacetate-hexane as eluent. The major isomer had nmr absorption at 2.36 (s, 3H), 3.1-3.6(m, 2H) 4.5-4.7 (m, 1H), 5.38 (q, J=2 Hz, 1H) and 7.2-7.5 (m, 6H). Nmr peaks for the minor isomer occurred at 2.36 (s, 3H), 3.10 (dd, J=16, 3 Hz, 1H), 3.56 (dd, J=16, 6 Hz, 1H), 4.8-4.9 (m, 1H) 5.90 (q, J=2 Hz), 1H).

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