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A NEW STRATEGY FOR THE SYNTHESIS OF CARBAPENEMS. A FORMAL TOTAL SYNTHESIS OF (+)-THIENAMYCIN.

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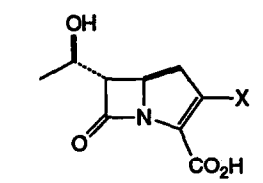
Abstract: *A new approach to formation of the carbapenem ring system is presented. The key step involves the Lewis acid mediated cyclocondensation of a β-lactam nitrogen and the α-keto ester of a suitably disposed side-chain. The preparation of a known and pivotal intermediate in the synthesis of thienamycin serves to demonstrate this strategy.*

The class of β-lactam containing compounds known as carbapenems **1** have been the focus of countless chemical and biological studies since the naturally occurring structural type was reported in 1976.[1] The discovery of thienamycin, with its extraordinarily potent broad-spectrum antibacterial profile, prompted a rigorous search for efficient and general routes to totally and partially synthetic carbapenems.[2,3]

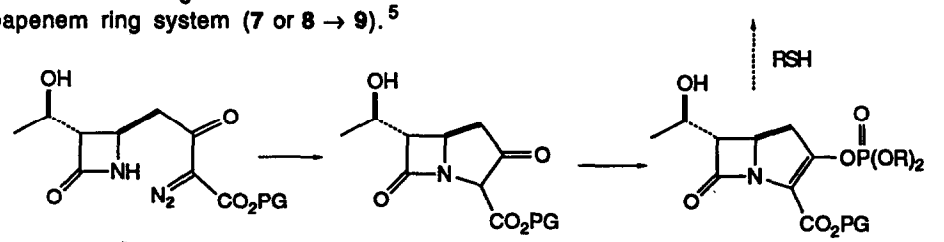
While many strategies for carbapenem construction have been brought to fruition, only two approaches (and conceptually related ones) have emerged with the generality useful for medicinal chemistry endeavors. In fact, they have been applied relentlessly in analogue programs around the world.

The landmark synthesis developed at Merck utilizes a rhodium catalyzed carbene insertion (**3** → **4**) to establish the bicyclic ring system.[4] The resulting β-keto ester, **4**, is transformed into carbapenem **6** via vinyl phosphate **5**. Thiol addition - phosphate elimination (**5** → **6**) occurs readily to incorporate the side-chain X.

The other widely used protocol employs an intramolecular Wittig reaction to form the carbapenem ring system (**7** or **8** → **9**).[5]



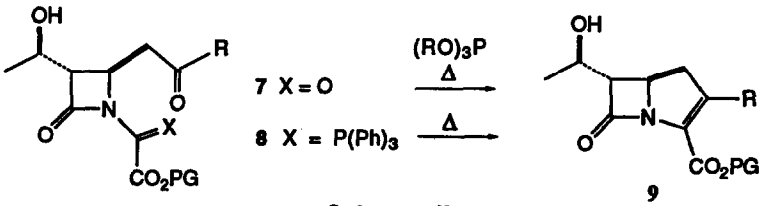
1 Carbapenem
2 Thienamycin, X = $SCH_2CH_2NH_2$
6 X = SR



3 **4** **5**

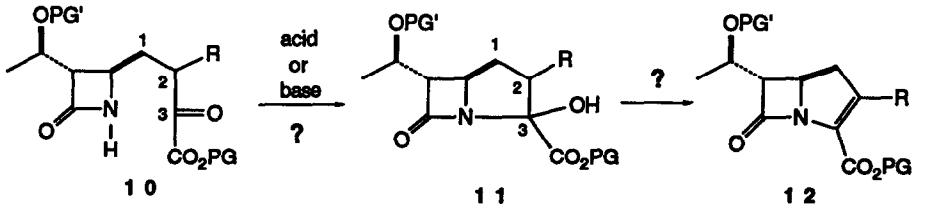
PG = protecting group

Scheme I



Scheme II

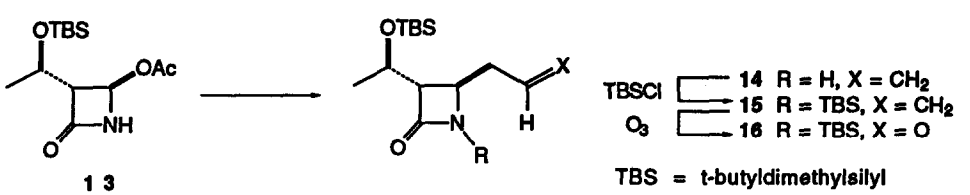
An alternative to the above mentioned routes was sought which was conceptually distinct and had potential for broad application. The strategy outlined in **Scheme III** incorporated the retrosynthetic view that the carbapenem five-membered ring was the product of a cyclocondensation between the β-lactam nitrogen and a suitably disposed α-keto ester.[6] That such a transformation might require strongly acidic or basic conditions was cause for concern. Indeed, convention suggested that the *fragile* carbapenem ring system might not survive its formation under such conditions.



Scheme III

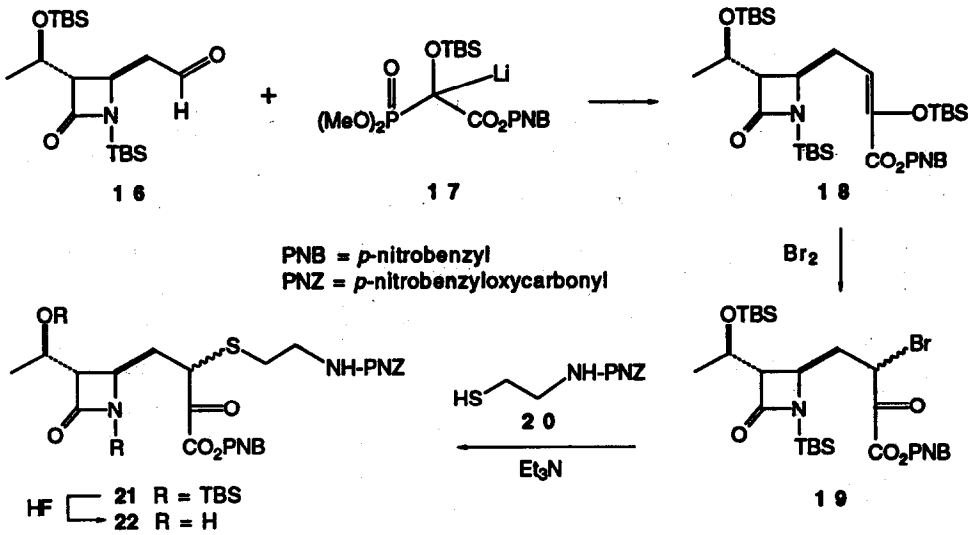
Construction of the requisite α-keto ester bearing β-lactam, **10**, constituted the first challenge. It would remain to find conditions capable of inducing cyclization (**10** → **11**) and determine whether elimination of the angular hydroxyl would occur *in situ* or require a separate step (**11** → **12**).

Assembly of the α-keto ester was initiated by converting commercially available azetidinone **13**[7] into aldehyde **16** via allylation,[8] protection of the β-lactam nitrogen with the *tert*-butyldimethylsilyl group and ozonolysis of the double-bond. Horner-Emmons reaction of phosphonate anion **17**[9] with aldehyde **16** afforded the desired silyl enol ether **18** in greater than 95% yield (E:Z - 82:18). Treatment of compound **18** with bromine unveiled the desired α-keto ester as a mixture of diastereomeric bromides **19**. Bromide displacement with a variety of thiols in the presence of triethylamine was very facile and provided high yields of the desired β-mercapto-α-keto esters. For example, N-[[(p-nitrobenzyl)oxy]carbonyl]cysteamine,[10] **20**, reacted



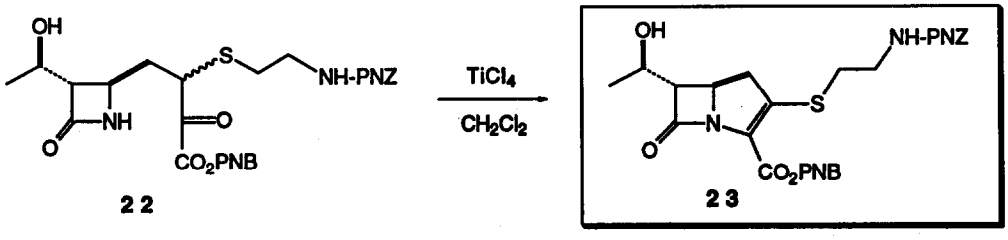
Scheme IV

with bromide **19** to afford 88% of displacement product **21**. Removal of the silyl protecting groups from **21** with 10% HF in acetonitrile[11] provided the key cyclization substrate **22**.



Scheme V

Treatment of crude α-keto ester **22** with excess $TiCl_4$ in methylene chloride afforded, in less than 10 minutes (at room temperature), the desired carbapenem **23** in 52% yield[12] (two steps, **21** → **23**). Under the cyclization conditions, dehydration was apparently very facile as none of the 3-hydroxy bearing intermediate corresponding to **11** was detected. The resulting carbapenem, a protected form of (+)-thienamycin **2**, has been reported previously and shown to



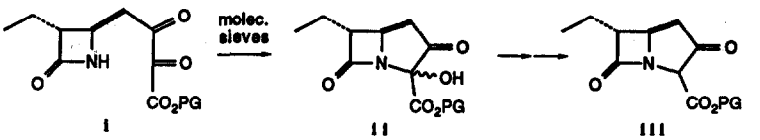
Scheme VI

afford the natural product upon hydrogenolysis.[4a] Spectroscopic data obtained for carbapenem **23**[13] was consistent with data available in the literature.[14]

Thus, a new sequence for constructing the carbapenem ring system has been demonstrated. Instrumental in reaching this goal was efficient formation of β-bromo-α-keto ester **19** from silyl enol ether **18**. Bromide displacement with a variety of nucleophiles gives this approach potential for considerable generality. As exemplified in the formal total synthesis of thienamycin, the crucial cyclization and dehydration occur readily in the presence of a Lewis acid. Extensions of this strategy are presently being evaluated.

References and Notes

1. (a) Kahan, J. S.; Kahan, F. M., Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiot.* **1979**, *32*, 1. (b) Albers-Shonberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhones, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491.
2. For recent reviews see: (a) Palomo, C. Recent Advances in the Synthesis of PS-5 and PS-6 Antibiotics and Related Compounds. In *Recent Progress in the Chemical Synthesis of Antibiotics;* Lukacs, G.; Ohno, M. Eds.; Springer-Verlag: Berlin, 1990; pp. 565-614. (b) Nagahara, T.; Kametani, T. *Heterocycles*, **1987**, *25*, 729. (c) Kametani, T. *Heterocycles*, **1982**, *17*, 463.
3. For recent approaches see (a) Ziegler, C. B.; Curran, W. V.; Feigelson, G. US patent 5,068,232 (1991) (b) Hanessian, S.; Desilets, D.; Bennani, Y. L. *J. Org. Chem.* **1990**, *55*, 3098 and references cited therein.
4. (a) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161. (b) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G.; *Tetrahedron Lett.* **1980**, *21*, 31.
5. For example: (a) Battistini, C.; Scarafile, F.; Foglio, M.; Franceschi, G. *Tetrahedron Lett.* **1984**, *25*, 2395. (b) Guthikonda, R. N.; Cama, L. D.; Quesada, M.; Woods, M. F.; Salzmann, T. N.; Christensen, B. G. *J. Med. Chem.* **1987**, *30*, 871.
6. The closest analogy to this approach, I → III, was reported in Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3747. It is chemically distinct in that the central carbonyl of the tricarbonyl system in I is much more electrophilic than the corresponding ketone of an α-keto ester. Furthermore, the cyclization does not give a carbapenem directly, rather, hydroxy bearing intermediate II. Compound II is converted in two steps into the β-keto ester intermediate of the Merck synthesis III (see compound 4):



I II III

PG = protecting group

It is also worth noting that glyoxylic esters react at the β-lactam nitrogen: Ernest, I.; Gosteli, J.; Greengrass, C. W.; Holick, W.; Jackman, D. E.; Pfaendler, H. R.; Woodward, R. B. *J. Am. Chem. Soc.*, **1978**, *100*, 8214.
7. Commercially available from Kaneka America Corp., NY.
8. (a) Hanessian, S.; Desilets, D.; Bennani, Y. L. *J. Org. Chem.* **1990**, *55*, 3098, (b) Fujimoto, K.; Iwano,Y.; Hirai, K., *Tetrahedron Lett.* **1985**, *26*, 89.
9. Prepared and utilized in analogy to the reagents described in Nakamura, E. *Tetrahedron Lett.* **1981**, *22*, 663.
10. Shinkai, I.; Liu, T.; Reamer, R.; Sletzinger, M. *Synthesis*, **1980**, 924.
11. Newton, R. F.; Reynolds, D. P. *Tetrahedron Lett.* **1979**, *41*, 3981.
12. Unoptimized yield
13. IR (KBr) 1775, 1696, 1642 cm^{-1}; ^1H NMR (Acetone-d_6, 300 MHz) d 8.24 (br d, 4H), 7.81, 7.64 (d, 2H), 6.94 (br s, 1H), 5.41 (midpoint of ABq, 2H, J = 14 Hz), 5.25 (s, 2H), 4.27 (ddd, 1H, J = 10 Hz, 10 Hz, 2.8 Hz), 4.10 (dq, 1H), 3.55-3.28 (m, 5H), 3.17-2.95 (m, 2H), 1.27 (d, 3H, J = 6.1 Hz).
14. See ref. 8a and Schmitt, S. M.; Johnston, D. B. R.; Christensen, B. G. *J. Org. Chem.* **1980**, *45*, 1142.

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