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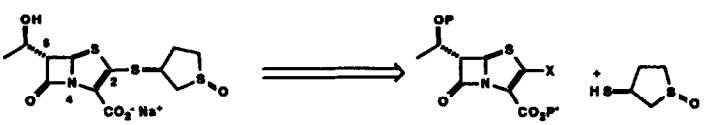
A Convergent Process to C-2 Substituted Penems via Addition of Thiols and Organocuprates to an O-Triflylthioketene Acetal

*Douglas Phillips and Brian T. O'Neill **
Process R & D, Pfizer Inc.; Groton, Connecticut 06340

Abstract: *The synthesis of fully protected penem derivatives has been achieved by addition of thiols and both higher and lower order cuprates to a novel 2-O-triflylpenem.*

Considerable interest in the penem ring system during the preceding decade has led to the discovery of several potent antibacterials. The 2-alkyl series, represented by Farmatalia's FCE 22101[1] (Scheme 1), are analogues of the earliest members of the penem class to be synthesized[2] and contain acyloxymethyl or simple alkyl substituents, reminiscent of the cephalosporins. In the 2-thio series, structure-activity relationships (SAR) have advanced through initial leads such as Schering's SCH 29482[3] and SCH 34343[4] into more functionalized variations such as represented by CP-70,429, developed at Pfizer.[5] Although advanced methodology for penem construction exists,[6,7] the efficient late stage incorporation of functionalized thiols in a convergent fashion has been addressed in only one report.[8] Furthermore, the attachment of alkyl substituents to penem templates using this methodology has not been addressed to our knowledge. For access to these 2-thio or alkyl substituted penems on preparative scale and for reasons of economy, we decided on a strategy that would delay introduction of homochiral mercaptan 2 (or suitable organometallic) until the final stages of the synthesis by utilization of activated penem 1 as the electrophile. Once joined, the resultant "bis-protected penem" (P, P' = protecting groups) need only suffer straightforward deprotection[9] and thus avoid exposure of the sensitive functionality of the side chain towards a variety of reagents currently used in penem cyclization.[6] In addition, this approach allows for further investigation of SAR in this series without requiring cyclization of each penem substrate.

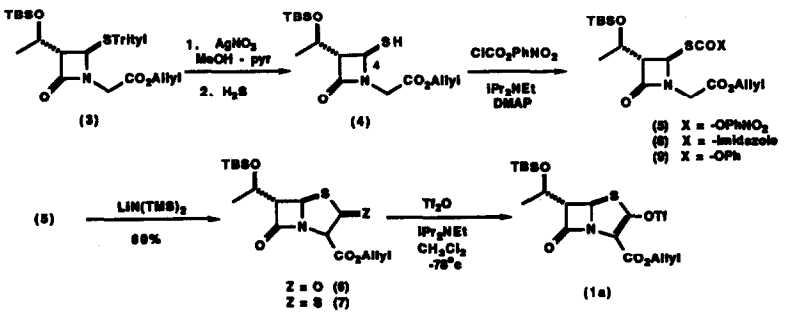
Scheme 1



Although the synthesis of penem antibacterials has been achieved through numerous ring closure and side chain incorporation protocols, the related carbapenem class is marked by at least one common theme in that thiol incorporation at C-2 is always completed by

activation of a β-ketoester moiety through the formation of an enol-ester. Enol-phosphates,[10] tosylates[11] and triflates[12] have all been used as activated precursors towards the addition of functionalized thiols. The situation in the sulfur containing penems is expected to be somewhat different due to the reactivity of the thiazolidine ring. Often side chain incorporation is achieved as part of the ring closure step[6] or by alkylation of dithiolactone 7.[7a] In the former case, these protocols are most general for unfunctionalized side chains which can survive the conditions for cyclization. Late stage incorporation of free thiols at C-2 in the penem class has been possible only through one method in which a sulfinate is the leaving group.[8] The latter approach has been extremely successful in the preparation of a wide variety of penems for biological evaluation; however, because the leaving group, a sulfenic acid, also reacts with free thiols and thiolates an excess of side chain must be employed. We wish to report an alternative penem synthesis which uses novel activated penem 1a as the substrate and which produces an innocuous triflate salt as the only by-product.

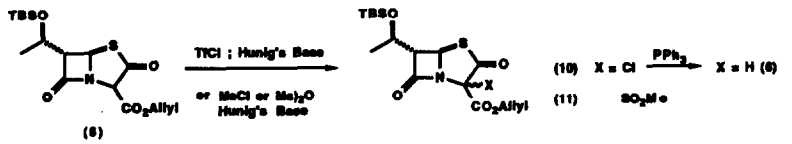
Scheme 2



Our preparation of 6[13] (Scheme 2) follows standard chemistry developed for the synthesis of the related dithiolactone 7,[7] although some modification was required. The known S-trityl-N-substituted azetidinone 3, available in two steps from commercially available starting materials,[7a] was deprotected under standard conditions ($AgNO_3$; methanol-pyridine 0°C 1 hr, then H_2S gas) to afford the thiol 4 in excellent yield. This material was not generally isolated although it was stable for some time under refrigeration. Thiol 4 was identified in part through observation of the 9 Hz coupling between -SH and the C-4 proton in the nmr spectrum. A deuterium exchange experiment confirmed that this was indeed an interaction between the C-4 methine and an acidic hydrogen. Additionally, we found that 4 was transformed into a symmetrical disulfide by copper (I) catalyzed air oxidation.[14] A variety of acylating agents were used to functionalize this thiol in good yield as the required thiocarbonate; nevertheless, reaction with carbonyl diimidazole or phenyl chloroformate afforded adducts 8 and 9 which were later found to be unreactive toward ring closure with base. Fortunately, the use of p-nitrophenylchloroformate provided a characterizable adduct (5) which was easily cyclized to thiolactone 6 in 60% overall yield from 3 [THF soln. of 4 added to the chloroformate in THF / iPr_2NEt (cat. DMAP); 0°C 5 min then via cannula (with in line filter) added 5 to a 1M solution of LiHMDS / THF; -78°C, 1 hr; quench HOAc.] Formation of the activated penem 1a was completed by treatment of a methylene chloride solution of 6 with triflic anhydride and base at low temperature.[15] The triflate 1a was stable at room temperature for a few hours after isolation. [SiO_2 chromatography (8/2; hexanes-ethyl acetate) followed by cryst. from pentane at -40 °C.] Attempts to prepare the corresponding O-phosphate, tosylate or mesylate through use of related methodology were unsuccessful. Treatment of 6 with diphenylphosphoryl chloride did not appear from nmr spectroscopy to form 1b [X = $OP(O)(OPh)_2$] nor was there observed significant amounts of 2-thiosubstituted penem upon subsequent introduction of free thiol [sulfide (h) Table 1] to the reaction mixture. Interestingly, the substitution of triflic chloride for triflic anhydride resulted exclusively in chlorination at the 3-position [compound 10, (Scheme 3)] in accord with the precedent of Just[16] (ir λ 1805, 1778, 1735 cm^{-1}). Attempted O-mesylation likewise led unexpectedly to

the 3-methylsulfone **11** (ir λ 1800, 1760, 1730 cm^{-1}). The halogen substituted thiolactone **10** could be reconverted to **6** by simple treatment with triphenylphosphine.[17]

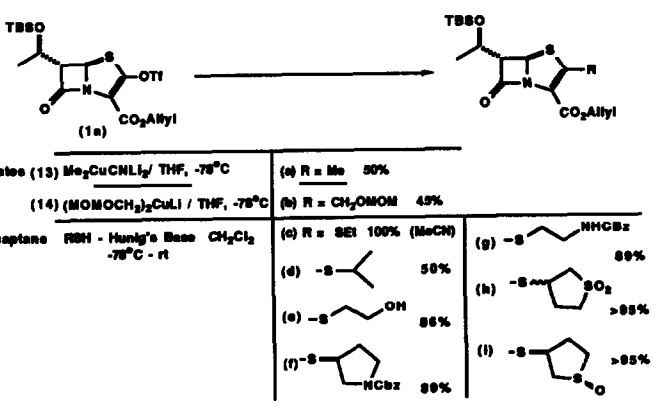
Scheme 3



Enol-triflate **1a** proved to be a convenient intermediate for the synthesis of C-2 thiosubstituted penems [entries (c)-(i);[18] Table 1]. The Michael addition-elimination of substituted thiols was straightforward and was generally completed without isolation of **1a** [entries d-i; RSH + **1a** 1:1 mole equiv.; iPr_2NEt, CH_2Cl_2 and / or CH_3CN; -78°C to rt.] The highest yield for the addition of ethanethiol was achieved with an excess (5 equiv) of the free thiol in acetonitrile solution. The synthesis of CP-70,429 (entry i) began with the hydroxide mediated hydrolysis of the thioacetate derivative of **2**.[19] The resulting crude thiol was found to add quantitatively when mixed with a preformed solution of **1a** in methylene chloride at -78°C. The penem was then liberated under standard conditions [TBAF, HOAc, 0°C, 8 hrs; $(PPh_3)_4Pd$, $NaO_2CCH(Et)n\text{-}Bu$, CH_2Cl_2][9] to afford CP-70,429-sodium salt which was identical with material previously prepared.[20] The yields of most bis-protected addition products were between 85 and 95% with the exception of entry d. The corresponding thiolates (RS^- Na^+, sulfide i) were generally less effective in the addition-elimination process than were thiols. Reaction mixtures from the thiolate addition contained substantial amounts of **6**, indicative of nucleophilic attack on the triflate S-O bond.

In a brief investigation, we determined that cuprate addition to activated penem **1a** can be performed with reagents **13**[21] and **14**.[22] In these cases, it was necessary to isolate **1a** and to then dissolve it in freshly distilled THF before adding the triflate as a substrate to preparations of the cuprate (2-3 equiv.) already at low temperature. The reaction was then allowed to stir for one hour before aqueous quench. In this way modest yields of the C-2 alkyl and alkoxyalkylpenem could be obtained.

Table 1



In conclusion, we have demonstrated that easily available triflate **1a** provides convenient access to a variety of interesting penems under mild conditions and generally in good yield.

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References and Notes.

1 Franceschi, G.; Foglio, M.; Alpegiani, M.; Battistini, C.; Bedeschi, A.; Perrone, E.; Zarini, F.; Arcamone, F. *J. Antibiot.* **1983**,*36*, 938.

2 Ernest, I.; Gosteli, J.; Woodward, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 6301.

3 (a) Girijavallabhan, V. M.; Ganguly, A. K.; McCombie, S. W.; Pinto, P.; Rizvi, R. *Interscience Conference on Antimicrobial Agents and Chemotherapy*; Abstract No. 829, **1981**, Chicago, Ill. (b) Ganguly, A. K.; Girijavallabhan, V. M.; McCombie, S. W.; Pinto, P.; Rizvi, R.; Jeffery, P. D.; Lin, S. *J. Antimicrob. Chemother., Suppl. C*, **1982**, *9*, 1. (c) Girijavallabhan, V. M.; Ganguly, A. K.; McCombie, S. W.; Pinto, P.; Rizvi, R. *Tetrahedron Lett.* **1981**, *22*, 3485.

4 Lin, C-C.; Lim, J.; Radwanski, E.; Kim, H-K.; Marco, A.; Lapiguera, A.; DiGiore, C.; Symchowicz, S. *Antimicrob. Agents Chemther.* **1987**, *31*, 84.

5 Bordner, J.; English, A.; Foulds, G.; Girard, A.; Girard, D.; Gootz, T.; Jasys, J.; Kelbaugh, P.; Kellogg, M.; Hamanaka, E.; Nason, D.; Retsema, J.; Volkmann, R. A.; Campbell, B. *Interscience Conference on Antimicrobial Agents and Chemotherapy*; Abstract No. 220, Oct. 23-26, **1988**; Los Angeles, CA.

6 (a) 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. (b) Afonso, A.; Hon, F.; Weinstein, J.; Ganguly, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6138. (c) Yoshida, A.; Hayashi, T.; Takeda, N.; Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1983**, *31*, 768. (d) McCombie, S.W.; Ganguly, A. K.; Girijavallabhan, V. M.; Jeffery, P.D.; Lin, S.; Pinto, P.; McPhail, A. T. *Tetrahedron Lett.* **1981**, *22*, 3489. (e) Girijavallabhan, V. M.; Ganguly, A. K.; Pinto, P.; Versace, R. *Tetrahedron Lett.* **1983**, *24*, 3179.

7 (a) Leanza, W. J.; DiNinno, F.; Muthard, D. A.; Wilkening, R. R.; Wildonger, K.J.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahderon* **1983**, *39*, 2505. (b) Girijavallabhan, V. M.; Ganguly, A. K.; Pinto, P.; Versace, R. *J. Chem. Soc., Chem. Commun.* **1983**, 908.

8 DiNinno, F.; Muthard, D. A.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1982**, *23*, 3535.

9 Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**,*94*, 6190.

10 (a) Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783. (b) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.

11 Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31.

12 Sletzinger, M.; Liu, T.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett. 1980, 21*, 4221.

13 For an earlier synthesis of (6) as the PNB ester see: Hirai, K.; Iwano, Y.; Fujimoto, K. *Heterocycles* **1982**, *17*, 201.

14 This disulfide formation has also been achieved independantly and in fact earlier than our own observations by workers at Schering Corp. Hou, D. T-C.; Wong, Y-S.; Gala, D.; Steinman, M. *Eur. Pat. Appl.* 255,278, 1988.

15 The following procedure is representative: A solution of 101.7 mg (0.264 mmol) of the oxo-penam 6 at 0^0 C in 5 ml of methylene chloride was treated with 184 µl (1.06 mmol) diisopropylethylamine. The clear solution was cooled to -78°C and freshly distilled trifluoromethanesulfonic anhydride (49 µl, 0.290 mmol) was added. The solution that resulted was stirred for 1 hr. Once formation of the enol triflate (1a)was complete by thin layer analysis (8/2, hexanes-ethyl acetate), the cold solution was for characterization purposes passed rapidly down a small plug of silica gel and concentrated in vacuo. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.96 - 5.82 (1H, ddd, J = 18 Hz, J = 12 Hz, J = 6 Hz), 5.71 (1H, d, J = 2 Hz), 5.34 (1H, d, J = 18 Hz), 5.23 (1H, d, J = 12 Hz), 4.71 (2H, d, J = 6 Hz), 4.22 (1H, dq, J = 6 Hz, J = 6 Hz), 3.85 (1H, dd, J = 6 Hz, J = 2 Hz), 1.22 (3H,d, J = 6 Hz), 0.86 (9H, s), 0.06 (6H, s); IR ($CHCl_3$) λ 1800, 1715, 1435, 1215 cm^{-1}; UV (dioxane) γ 273, 322 nm; HRMS calc'd for $C_{14}H_{17}NO_7S_2SiF_3$ 460.0163 (M^+-C_4H_9) found 460.0246

16 Hakimelahi, G. H.; Just, G. *Tetrahedron Lett.* **1979**, *20*, 3643.

17 Girijavallabhan, V. M.; McCombie, S. W.; Pinto, P.; Lin, S.; Versace, R. *J. Chem. Soc., Chem. Commun.* **1987**, 691.

18 Thiols not commercially available were prepared by literature routes; entry f, Shibata, T.; Iino, K.; Sugimura, Y. *Heterocycles* **1986**, *24*, 1331. entry g, Shinkai, I.; Liu, T.; Reamer, R.; Sletzinger, M.*Synthesis* **1980**, 924. entry h, Bezmenova, T. E.; Varshavets, T. N.; Matyash, L. P. *Khim. Geterotsikl. Soedin.* **1975**, *2*, 188, C.A. **1975**, 170558y.

19 Kindly supplied by R. Volkmann and J. Jasys of these laboratories.

20 (a) Our CP-70,429 sodium salt was identical by ^{1}H nmr with material generated by another method[5] and for which an x-ray structure determination has been completed. Further correlation (tlc, ir, nmr, hrms) with the allyl ester of CP-70,429 prepared by this method also verifies our approach. (b) All other structures are in accord with ir, nmr, hrms, uv and rotation data.

21 Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928.

22 Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4930. The required stannane for this procedure was generated as described in the following paper: Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806.

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