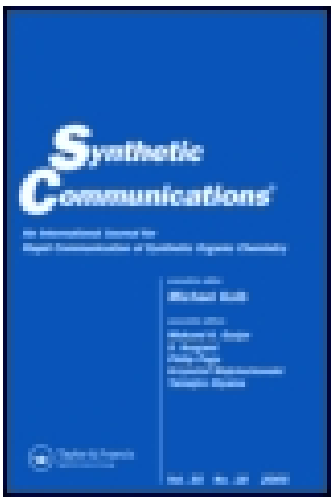


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of New 2-Thiomethyl Penem Derivatives

Danilo Giannotti [a] & Maria Altamura [a]

[a] Chemical Research Department, "A. Menarini" S.r.1. , Via Sette Santi 3, 1-50131, Firenze, Italy

Published online: 23 Sep 2006.

To cite this article: Danilo Giannotti & Maria Altamura (1995) Synthesis of New 2-Thiomethyl Penem Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:10, 1567-1574, DOI: 10.1080/00397919508011770

To link to this article: http://dx.doi.org/10.1080/00397919508011770

SYNTHETIC COMMUNICATIONS, 25(10), 1567-1574 (1995)

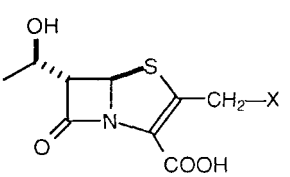
SYNTHESIS OF NEW 2-THIOMETHYL PENEM DERIVATIVES

Danilo Giannotti,* Maria Altamura

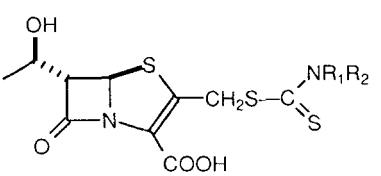
Chemical Research Department, "A. Menarini" S.r. l.,Via Sette Santi 3, I-50131 Firenze (Italy)

ABSTRACT: New penem thiolesters (**4-5**) were synthesized and **5** was hydrolyzed. 2-mercaptomethyl penem **7** is formed *in situ* and transformed into penem monothiocarbamates **9** and **10**.

The penems [1] are a group of synthetic antibiotics displaying potent *in vitro* activity against a broad range of bacteria. Many 2-methyl substituted penems **1** have been synthesized [1b] in recent years: the presence of a heteroatom in the side chain in position 2 has been related [1c] to an enhanced chemical reactivity of the β-lactam linkage and therefore to a higher biological activity. In particular a number of 2-alkylthiomethyl derivatives (**1**, X = S-alkyl) have been reported [2].



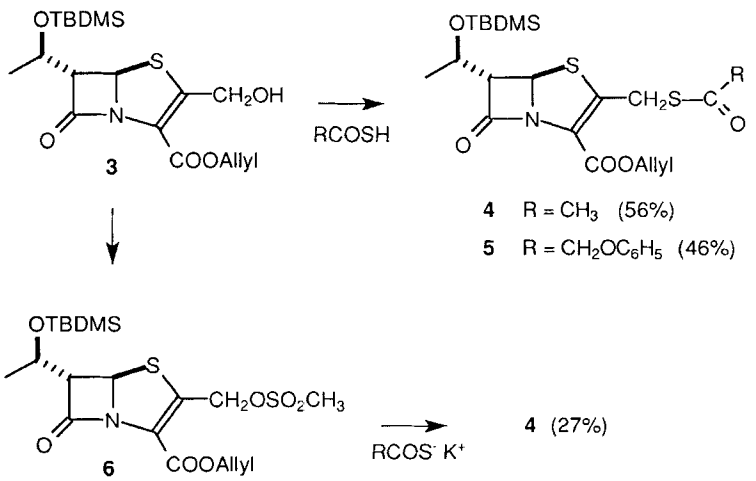
1



2

In a previous paper we described [3] the synthesis of new penem dithiocarbamates **2** with relevant antibacterial activity. In the course of this study, we needed to prepare the hitherto unknown 2-mercaptomethyl penems **7** and evaluate the possibility of derivatizing the mercapto moiety for the preparation of new penem antibiotics.

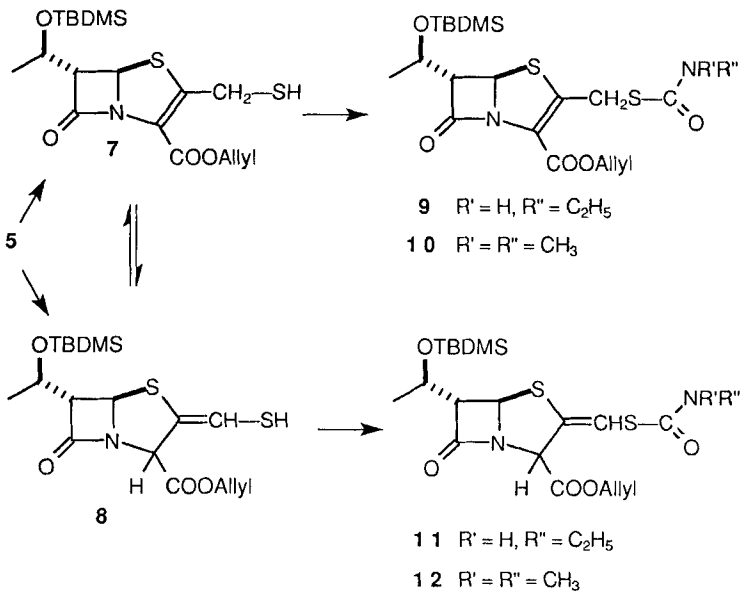
We reasoned that the synthesis of new penem thiolesters **4-5** could afford useful intermediates in the route to thiol derivatives. In facts, thiolesters have been considered in many cases [4] as protected thiol moieties. Therefore we obtained thiolesters **4-5** by the Mitsunobu-Volante[5] procedure [6], starting from the known 2-hydroxymethyl penem **3** [7]. Alternatively, treating the alcohol mesylate **6** [8] with potassium thiolcarboxylates (DMSO, 20°C, 1h), in analogy with our procedure [3] for the synthesis of penem dithiocarbamates, compound **4** could be obtained in lower yields.



TBDMS = $Si(CH_3)_2C(CH_3)_3$

Cleavage of thiolesters **4-5** to obtain 2-mercaptomethyl penems could not be done following standard procedures [4,5], due to the extreme sensitivity of the penem structure to basic or acidic reagents.

However we realized the cleavage of penem thiolester **5** under basic conditions, according to a procedure described for the more stable penicillin and cephalosporin thiolesters [9]. Under these conditions compound **4** did not react. Methanolysis of **5** gave a mixture of unstable thiols **7-8.**



The crude reaction mixture was treated with ethyl isocyanate to give penem N-ethyl monothiocarbamate **9** and penam N-ethyl monothiocarbamate **11** and with dimethylcarbamyl chloride and triethylamine to give penem N,N-dimethyl monothiocarbamate **10** and penam N,N-dimethyl monothiocarbamate **12.**

Although thiols **7-8** could not be identified in the reaction mixture, we suppose that methanolysis of penem thiolester **5** gives a mixture of two isomeric

structures, the thiomethyl penem **7** and the thiomethylene penam **8** [10]. In facts, the two subsequent reactions gave both penem/penam structures in the same ratio 3/2 for **9**:**11** and **10**:**12**. In conclusion we have reported that penem thiolesters can be utilized to generate 2-mercaptomethyl penem **7**, which can be considered an useful intermediate to the synthesis of 2-thiomethyl derivatives. In this case we have synthesized [11] monothiocarbamates that can be deprotected according to known procedures [12] giving antibiotic substances. It is possible, however, to transform the 2-mercaptomethyl penem intermediates into other compounds and after deprotection finally obtain new antibiotics.

Methanolysis of Allyl (5R,6S)-2-(phenoxyacetylthiomethyl)-6-[(1R)-1-tert-butyldimethylsilyloxyethyl]-penem-3-carboxylate (5)

Sodium methoxide (1 mM) in anhydrous methanol (25 mL) was added dropwise at -40°C over 15 min to a stirred solution of thiolester **5** (1mM) in anhydrous methanol (50 mL). After the addition the temperature was allowed to rise to - 25°C until the reaction was complete (about 30 min as determined by TLC). Acetic acid (0.4 mL) and then methylene dichloride were added and the solution washed with 5% $NaHCO_3$ and with water and dried. Distillation of the solvent under reduced pressure gave a crude oil containing thiols **7**-**8** and methyl phenoxyacetate. The mixture was rapidly solubilized in methylene dichloride (20 mL) and treated with triethylamine (1.5 mM) and dimethylcarbamyl chloride (1.5 mM) at -10°C, then was allowed to warm to room temperature with continuous stirring. The reaction was complete in about 2 h (determinated by TLC). The reaction mixture was washed with 5% $NaHCO_3$ and water, and dried; the solvent was evaporated to give a viscous oil which was chromatographed on silica gel (diethyl ether/hexane 1/1) to give allyl (5R,6S)-2-(N,N-dimethylaminocarbonylthiomethyl)-6-[(1R)-1-tert-butyldimethylsilyloxyethyl]-

penem-3-carboxylate **10** (yellow oil, yield: 75 mg, 15.4%) and allyl (5R,6S)-2-(N,N-dimethylaminocarbonylthiomethylene)-6-[(1R)-1-tert-butyldimethylsilyloxyethyl]penam-3-carboxylate **12** (yellow oil, yield: 50 mg, 10.3%) [13].

By the same procedure and treating the crude thiols **7-8** with an excess of ethyl isocyanate, allyl (5R,6S)-2-(N-ethylaminocarbonylthiomethyl)-6-[(1R)-1-tert-butyldimethylsilyloxyethyl]-penem-3-carboxylate **9** (yellow oil, yield: 78 mg, 16%) and allyl (5R,6S)-2-(N-ethylaminocarbonylthiomethylene)-6-[(1R)-1-tert-butyldimethylsilyloxyethyl]-penam-3-carboxylate **11** (yellow oil, yield: 52 mg, 10.7%) were obtained [14].

Acknowledgements: Thanks are due to Prof. F. M. Arcamone and Dr. V. Pestellini for helpful suggestions. We also thank Dr. A. Triolo for mass spectra. This work was supported by Grant 53529 from Istituto Mobiliare Italiano.

Notes and References

(1) (a) Perrone, E.; Franceschi, G. "Synthesis of Penems. In Recent Progress in the Chemical Synthesis of Antibiotics"; Lukacs, G.; Ohno, M., Eds.; Springer Verlag: Berlin-Heidelberg, 1990; pp 613-704.

(b) Perrone, E., Il Farmaco, 1988, 43, 1075.

(c) McCombie, S.W.; Ganguly, A.K., Medicinal Research Review, 1988, 8, 393.

(2) (a) Alpegiani, M.; Bedeschi, A.; Perrone, E.; Zarini, F.; Franceschi, G., Heterocycles, 1985, 23, 2255.

(b) Alfonso, A.; Hon, F.; Weinstein, J.; Gentles, M.; Shapiro, E.S.; Ganguly, A.K.; Naples, L.; Hare, R.S.; Miller, G.H., Bioorganic and Medicinal Chemistry Letters, 1993, 3, 2177.

(3) Altamura, M.; Giannotti, D.; Perrotta, E.; Sbraci, P.; Pestellini, V.; Arcamone, F.M.; Satta, G., Bioorganic and Medicinal Chemistry Letters, 1993, 3, 2159.

(4) Greene, T.W.; Wuts, P.G.M. "Protective Groups in Organic Synthesis"; Wiley: New York, 1991; p 298.

(5) Volante, R. P., Tetrahedron Lett., 1981, 22, 3119.

(6) Procedure for the synthesis of **5**: **3** (5 mM) and phenoxythiolacetic acid (10 mM) in tetrahydrofuran (13 ml) were added dropwise at the PPh_3-DIAD complex (10 mM) in tetrahydrofuran (25 ml) at 0°C. The mixture was kept 1 h at 0°Cand 1 h at r.t.and, after solvent evaporation, the residue oil was chromatographed on silica gel (ether/hexane 2/8) to give **5** (46% yield).

NMR data ($CDCl_3$, ppm): ^1H: 0.03 (6H, s), 0.84 (9H, s), 1.19 (3H, d, J=6.2 Hz), 3.65 (1H, dd, J=1.6, 4.6 Hz), 4.12-4.30 (1H, m), 4.23 and 4.44 (2H, ABq, J=14.3 Hz), 4.60-4.72 (2H, m), 4.70 (2H, s), 5.15-5.43 (2H, m), 5.51 (1H, d, J=1.4 Hz), 5.78-6.02 (1H, m), 6.82-7.35 (5H, m). ^{13}C: -5.1, -4.2, 18.1, 22.5, 25.0 (CH_2S), 25.8, 63.0, 65.4, 66.1, 72.2, 73.0 ($\underline{CH_2}OC_6H_5$), 115.3, 119.0, 122.7, 130.2, 132.0.

By the same procedure and treating **3** and thiolacetic acid with the PPh_3-DIAD complex, thiolester **4** (yield: 56%) was obtained.

NMR data ($CDCl_3$, ppm): ^{1} H: 0.026 (6H, s), 0.83 (9H, s), 1.18 (3H, d, J = 6.3 Hz), 2.34 (3H, s), 3.64 (1H, dd, J = 1.8, 4.6 Hz), 4.12-4.25 (1 H, m), 4.18 and 4.35 (2 H, ABq, J = 14.5 Hz), 4.63-4.70 (1 H, m), 5.17-5.42 (2 H, m), 5.51 (1 H, d, J = 1.6 Hz), 5.80-6.00 (1H, m). ^{13}C: -5.0, -4.3, 18.1, 22.5, 25.8, 26.2 (CH_2S), 30.2 (CH_3CO), 62.9, 65.5, 66.0, 72.3, 118.9, 132.1, 152.9, 159.9, 173.1, 194.5.

(7) (a) Franceschi, G.; Perrone, E.; Alpegiani, M.; Bedeschi, A.; Zarini, F.; Della Bruna, C., J. Antimicrob. Chemother., 1989, 23, Suppl. C, 1. (b)

Corraz, A.J.; Dax, S.L.; Dunlap, N.K.; Georgopapadakou, N.H.; Keith, D.D.; Pruess, D.L.; Rossman, P.L.; Then, R.; Unowsky, J.; Wei, C., J. Med. Chem., 1992, 35, 1828.

(8) Altamura, M.; Perrotta, E., J. Org. Chem., 1993, 58, 8214.

(9) Sheehan, J.C.; Commons, T.J.; Lo, Y.S., J. Org. Chem., 1977, 42, 2224.

(10) The shift of the double bond between the endo and the exo position following base treatment has been well reported in thiomethyl penems; the ratio between penem and penam structure depends on kinetic and thermodynamic factors: see references 2 and 3.

(11) Mass spectra (Electron Impact, 15 eV) of all compounds showed a $M^{\cdot+}$ in accordance with the proposed structures.

(12) Georg, G. I. "The Organic Chemistry of β-Lactams"; VCH: New York, 1992.

(13) NMR data ($CDCl_3$, ppm) **10**: ^1H: 0.06 (6H, s), 0.96 (9H, s), 1.20 (3H, d, J=6.5 Hz), 3.02 (6H, s, $(CH_3)_2N$), 3.67 (1H, dd, J=1.5, 4.6 Hz), 4.14-4.32 (1H, m), 4.27 and 4.43 (2H, ABq, J=14.8 Hz), 4.58-4.72 (2H, m), 5.20-5.45 (2H, m), 5.52 (1H, d, J=1.4 Hz), 5.78-6.02 (1H, m). ^{13}C: -3.1, -2.3, 19.9, 24.4, 27.6, 29.4 (CH2S), 38.9 ($(CH_3)_2N$), 64.4, 67.0, 73.7, 121.1, 133.1.
NMR data ($CDCl_3$, ppm) **12**: ^1H: 0.06 (6H, s), 0.96 (9H, s), 1.24 (3H, d, J=6.5 Hz), 3.02 (6H, s, $(CH_3)_2N$), 3.36 (1H, dd, J=1.5, 4.6 Hz), 4.14-4.32 (1H, m), 4.58-4.72 (2H, m), 5.20-5.45 (2H and 1H, m, overlapped), 5.78-6.02 (1H, m), 6.82 (1H, s). ^{13}C: -3.1, -2.3, 19.9, 24.5, 27.8, 39.0 ($(CH_3)_2N$), 66.3, 67.1, 72.3, 112.9 (=CH-S), 120.4, 133.6.

(14) NMR data ($CDCl_3$, ppm.) **9**: ^1H: 0.03 (6H, s), 0.84 (9H, s), 1.10-1.25 (3H and 3H, m, overlapped), 3.24-3.41 (2H, m), 3.65 (1H, dd, J=1.8, 4.6 Hz), 4.12-4.27 (1H, m), 4.24 and 4.38 (2H, ABq, J=14.6 Hz), 4.58-4.70 (2H, m), 5.17-5.45 (2H, m), 5.51 (1H, d, J=1.6 Hz), 5.78-6.02 (1H, m). ^{13}C: -5.0,

-4.2, 15.1 ($\underline{C}H_3CH_2NHCO$),18.1, 22.5, 25.8, 27.0 (CH_2S), 37.0 ($CH_3\underline{C}H_2NHCO$), 62.8, 65.4, 66.0, 72.1, 118.9, 132.1.

NMR data ($CDCl_3$, ppm) **11**: ^1H: 0.03 (6H, s), 0.83 (9H, s), 1.10-1.26 (3H and 3H, m, overlapped), 3.20-3.45 (2H and 1H, m, overlapped), 4.15-4.30 (1H, m), 4.60 (2H, d, J=5.9), 5.20-5.52 (2H and 1H, m, overlapped), 5.75-5.98 (1H, m), 6.66 (1H, s). ^{13}C: -5.0, -4.2, 15.0 ($\underline{C}H_3CH_2NHCO$), 19.1, 22.7, 25.8, 37.0 ($CH_3\underline{C}H_2NHCO$), 64.5, 65.6, 66.8, 70.6, 109.9 (=CH-S), 119.7, 131.6.

(Received in The Netherlands 05 September 1994)