

SYNTHESIS OF RACEMIC, 2-(ALKYLTHIO)-6-(1-HYDROXYETHYL) PENEMS;
ATTEMPTED PENEM SYNTHESIS VIA COPPER (I) - PROMOTED CYCLISATIONS

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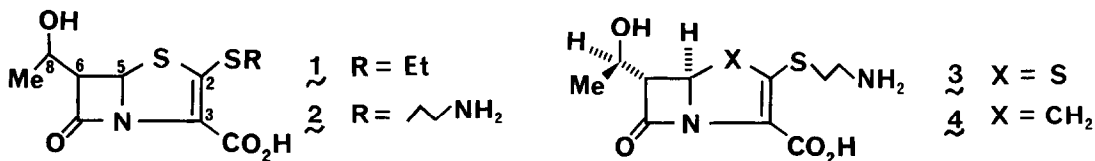
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Abstract: Stereocontrolled syntheses of the diastereoisomeric 6-(1-hydroxyethyl)-2-ethylthio and 2-(2-aminoethylthio)-penem-3-carboxylates from a common monocyclic azetidinone precursor are described. Cu (I)-promoted cyclisation of suitable N/C-3 secopenems is shown to yield "isopenems" (7-oxo-2-thia-1-azabicyclo[3.2.0]-hept-3-enes) as the sole bicyclic product.

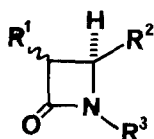
In the accompanying paper¹ we have described the synthesis of several enantiomerically pure forms of the penem (1) and have established the requirement of 5R stereochemistry for antibacterial activity.



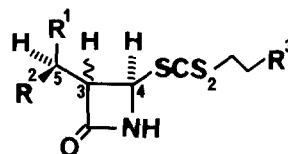
Here, we describe syntheses of the four racemates represented by (1) and three of the racemates (2), including the 5R, 6S, 8R² compound (3), isosteric with the carbapenem antibiotic thienamycin³ (4). In addition, a process for the preparation of (3) described in a patent⁴ is shown to be inoperable.

4-Ethylthioazetidinone⁵ (5) was silylated ($\text{Et}_3\text{N}, \text{ButSiMe}_2\text{Cl}$) to (6) and the isomer mixture (7) prepared ($n\text{-BuLi}, -70^\circ; \text{MeCHO}$). Hydroxyl protection ($\text{CCl}_3\text{CH}_2\text{OCOC1}, \text{py}$) followed by acidic desilylation then gave (8), which was chlorinated (1.1 eq $\text{Cl}_2, -20^\circ$). Addition of the product to excess EtSCS_2K^+ (aq. $\text{EtOH}, 0^\circ$) followed by HPLC separation of isomers then gave the trans trithiocarbonates (9)⁶ and (10).⁶ The stereochemistry of (9), mp $112\text{-}113^\circ$ was established as 3S, 4R, 5S² by single crystal X-ray analysis.⁷ Analogously, trithiocarbonates (11) and (12) were prepared using $\text{K}^+\text{SCS}_2\text{CH}_2\text{CH}_2\text{NHCO}_2\text{CH}_2\text{CH}=\text{CH}_2$ ⁸ in the final step, and the structures correlated⁹ with (9).

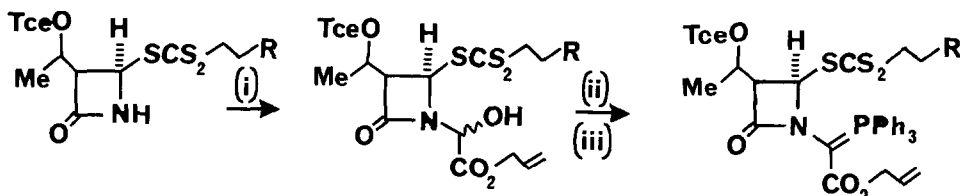
By experimentation with simple C-3-alkyl analogs, a route to cis trithiocarbonates was established. Although the NH compounds gave predominantly trans products, chlorination-



- (5) $R^1=R^3=H$, $R^2=SEt$
 (6) $R^1=H$, $R^2=SEt$, $R^3=TBDMS$
 (7) $R^1=MeCHOH$, $R^2=SEt$, $R^3=TBDMS$
 (8) $R^1=MeCHOTce$, $R^2=SEt$, $R^3=H$
 (13) $R^1=MeCHOH$, $R^2=SCS_2Et$, $R^3=TBDMS$
 (14) $R^1=MeCHOTce$, $R^2=SCS_2Et$, $R^3=TBDMS$



- (9) $R^1=Me$, $R^2=OTce$, $R^3=H$, $3\beta-H$
 (10) $R^1=OTce$, $R^2=Me$, $R^3=H$, $3\beta-H$
 (11) $R^1=Me$, $R^2=OTce$, $R^3=NHCO_2A1ly1$, $3\beta-H$
 (12) $R^1=OTce$, $R^2=Me$, $R^3=NHCO_2A1ly1$, $3\beta-H$
 (15) $R^1=Me$, $R^2=OTce$, $R^3=H$, $3\alpha-H$
 (16) $R^1=OTce$, $R^2=Me$, $R^3=H$, $3\alpha-H$

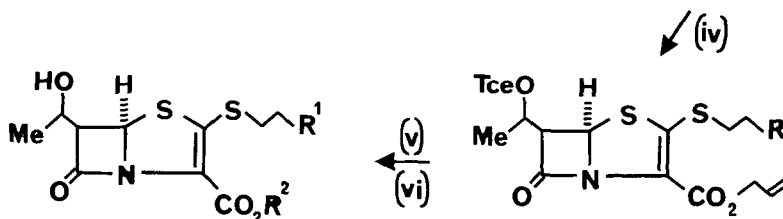


(17) $R=H$

(18) $R=NHCO_2A1ly1$

(19) $R=H$

(20) $R=NHCO_2A1ly1$



(23) $R^1=H$, $R^2=K$

(24) $R^1=NH_2$, $R^2=H$

(25) $R^1=H$, $R^2=A1ly1$

(21) $R=H$

(22) $R=NHCO_2A1ly1$

(a) $5R,6S,8R^2$ (b) $5R,6S,8S^2$ (c) $5R,6R,8R^2$ (d) $5R,6R,8S^2$

(i) $A1ly1OCOCH(OH)_2$, C_6H_6 , 80° . (ii) $MeSO_2Cl, NEt_3$ (iii) PPh_3 , DMF (iv)

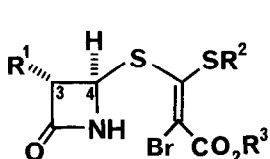
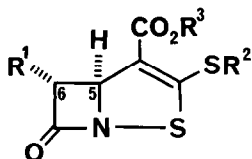
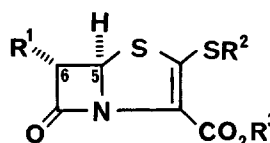
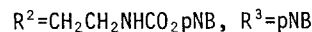
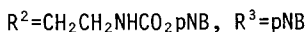
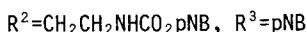
$Toluene$, 110° . (v) $Zn-HOAc$, $aq THF$ (vi) catalytic $Pd(PPh_3)_4$, with

$K-2-Et-hexanoate$ (for 21) or $2-Et-hexanoic acid$ (for 22).

displacement on *N*-TBDMS lactams resulted in increasing amounts of *cis* product as the size of the C-3 substituent was increased.¹⁰ Thus, treatment of mixture (7) with Cl₂ then K⁺-SCS₂Et gave mixture (13) with *cis*:*trans* ≈ 2:1. HPLC separation on the fully blocked mixture (14) followed by desilylation then gave the *cis* isomers⁹ (15)⁶ and (16).⁶

Each trithiocarbonate was transformed to penem using the sequence shown in the Scheme; the crucial intramolecular thiocarbonyl Wittig reaction was developed independently by several groups,¹¹ and the allylic ester and carbamate protecting groups were chosen so as to allow final deprotection under the mild exchange conditions recently developed in our laboratories.¹² During cyclisation, isomerisation of each product generated a second isomer, as observed for the pure enantiomers.¹ The stereochemical consequences of this process were established by single crystal X-ray analysis⁷ on products from (19a). The major product was analysed as the corresponding alcohol, and proved to be the expected 5*R*, 6*S*, 8*R*² compound, (25a). The minor, *cis* product was directly crystalline, and was the 5*S*, 6*S*, 8*R*² compound (21d), identical with material obtained from cyclisation of (19d).

During the course of this work, a new route to 2-(alkylthio) penems was described¹³ and subsequently shown to be in error;¹⁴ cyclisation (LDA, CuBr·SMe₂) of (26) gave (27) rather than (28). We have independently obtained similar results from cyclisation of (29) with Cu (I) complexes; use of a wide variety of bases gave (30) as the sole bicyclic product,¹⁵ with no detectable amounts of (31). A related patent⁴ reports the use of this cyclisation in the preparation of (3) via (32). Upon repetition of this sequence, we obtained a cyclised product with [α]_D²⁶-36.2°, PMR δ5.22 for H-5 (reported⁴ [α]_D²²-41.3°, δ5.22), to which we assign the "isopenem" structure (33). An authentic sample of the true penem (34; [α]_D²⁶+67.6°, δ5.48 for H-5) was prepared by the route described in the accompanying paper,¹ and was found to be absent from the Cu (I) cyclisation reaction.

(26) R¹=H, R²=Me, R³=pNB(27) R¹=H, R²=Me, R³=pNB(28) R¹=H, R²=Me, R³=pNB(29) R¹=H, R²=Et, R³=Allyl(30) R¹=H, R²=Et, R³=Allyl(31) R¹=H, R²=Et, R³=Allyl(32) R¹=5*R*-CH(OCO₂pNB)Me,(33) R¹=8*R*-CH(OCO₂pNB)Me,(34) R¹=8*R*-CH(OCO₂pNB)Me,

From the blocked penems (21a-d) and (22a, b and c),¹⁶ the corresponding deprotected compounds were prepared by initial OH unmasking (Zn, aq. HOAc, THF, 0°). After recrystallisation, the alcohols were converted either to potassium salt (for the 2-SEt series) or to the free zwitterions by the Pd-catalysed exchange process (see Scheme), the products⁶ precipitating directly from the reaction mixture. All of these racemic penems were evaluated in vitro vs a wide range of bacteria, and proved to be broad-spectrum agents with good resistance to cleavage by β-lactamases. Maximum potency was found for

the 5R, 6S, 8R² isomers (3) and (23a). Detailed microbiological evaluation of these and other 2,6-disubstituted penems will be presented elsewhere.

ACKNOWLEDGEMENTS The authors are grateful to Dr. G. Miller and his staff for microbiology and to the Chemical Development group for support.

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2. An equal amount of the corresponding enantiomer is present.
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6. All new compounds gave satisfactory spectroscopic and analytical data. Selected PMR values (CDCl₃, δ): (9) 3.58 (dd, 1H, J = 4.5, 2.5 c/s, H-3), 5.30 (m, 1H, H-5) and 5.57 (d, 1H, J = 2.5 c/s, H-4). (10) 3.45 (dd, 1H, J = 7.5, 2.5 c/s, H-3), 5.31 (m, 1H, H-5) and 5.68 (d, 1H, J = 2.5 c/s, H-4). (15) 3.90 (ddd, 1H, J = 11.5, 1.5* c/s, H-3), 5.17 (m, 1H, H-5) and 5.85 (d, 1H, J = 5 c/s, H-4). (16) 3.85 (ddd, 1H, J = 7.5, 1.5* c/s, H-3), 5.17 (m, 1H, H-5) and 6.00 (d, 1H, J = 5 c/s, H-4). *Coupling removed by D₂O exchange of N-H. (3) (D₂O): δ 1.34 (d, 3H, J = 7 Hz), 3.30 (m, 4H), 3.90 (dd, 1H, J = 7 and 1.5 Hz), 4.30 (quintet, 1H, J = 7 Hz, and 5.75 (d, 1H, J = 1.5 Hz).
7. These results will be published in detail in a separate publication.
8. HSCH₂CH₂NH₂ + N-(allyloxycarbonyloxy)succinimide, followed by 1 eq. KOH; excess CS₂ on the resulting thiol.
9. Correlation was achieved by treatment with PhSH-NET₃, which gave clean elimination-addition to yield the appropriate *trans*-4-phenylthio compound. The two isomers could be distinguished by PMR, TLC and HPLC.
10. This may involve the bulky TBDMS group in an out-of-plane orientation and/or charge stabilisation in an S_N1-type process by the silicon atom.
11. (a) S.W. McCombie, European Patent Application EP-13,662. (b) M. Lang, K. Prasad, J. Gosteli and R.B. Woodward, *Helv. Chim. Acta*, **63**, 1093 (1980). (c) S. Oida, A. Yoshida, T. Payashi, N. Takeda and E. Ohki, *Chem. Pharm. Bull. Jpn.*, **38**, 3232 (1980).
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13. F. DeNinno, E. Linek and B.G. Christensen, *J. Amer. Chem. Soc.*, **101**, 2210 (1979).
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15. The free acid corresponding to (30) was also prepared; in contrast with its penem counterpart,¹¹ this acid was devoid of antibacterial activity.
16. Cyclisation of (20a) gave both (22a) and (22d), whereas (20b) gave (22b) with only traces of (22c).

(Received in USA 4 May 1981)