SYNTHESIS OF OPTICALLY ACTIVE 6-HYDROXYETHYL PENEMS

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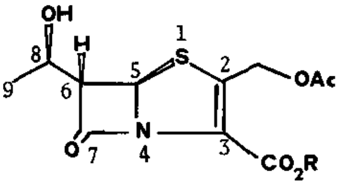
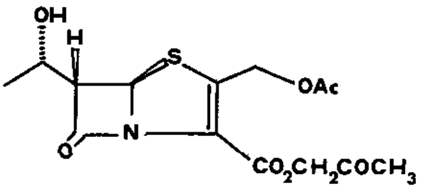
Abstract - The synthesis of optically active 6-hydroxyethyl penems introducing the side chain by an aldol condensation on methyl penicillanate S-oxide is described.

Very recently several papers have been appearing on the synthesis of C-6 substituted penems.[1] As part of our continuing interest[2] in this noteworthy class of antibacterial agents, we wish here to describe the first synthesis of optically active penems bearing at once the thienamycin and cephalosporin functionalities:[3]

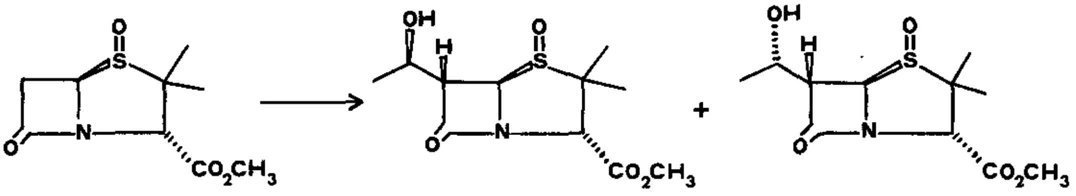


1 (5R,6S,8R)



2 (5R,6S,8S)

Methyl penicillanate S-oxide (3)[4] was chosen as a new substrate for the introduction of the hydroxyethyl side chain by means of an aldol condensation.



3

4 (8R)

5 (8S)

Treatment of compound 3 enolate (LDA, -78°C) with acetaldehyde showed a complete stereoselectivity for the C-6 configuration affording (60% yield) a mixture (2:3) of the *trans* diastereoisomers 4 (8R) and 5 (8S).[5] The separation was performed by preparative HPLC. 4: P.M.R. ($CDCl_3$), δ (ppm): 1.25 (s, 3H, αCH_3); 1.36 (d, J = 6.5 Hz, 3H, CH_3CH); 1.70 (s, 3H, βCH_3); 3.56 (dd, J = 2.0, 6.5 Hz, 1H, H-6); 3.72 (s, 3H, $COOCH_3$); 4.35 (dq, J = 6.5, 6.5 Hz, 1H, CHOH); 4.49 (s, 1H, H-3); 5.00 (d, J = 2.0 Hz, 1H, H-5). 5: P.M.R. ($CDCl_3$), δ (ppm): 1.28 (s, 3H, αCH_3); 1.45 (d, J = 6.0 Hz, 3H, CH_3CH); 1.72 (s, 3H, βCH_3); 3.72 (dd, J = 2.0, 4.0 Hz, 1H, H-6); 3.80 (s, 3H, $COOCH_3$); 4.27 (dq, J = 4.0, 6.0 Hz, 1H, CHOH); 4.48 (s, 1H, H-3); 5.05 (d, J = 2.0 Hz, 1H, H-5).

The stereochemistry of the side chain was assigned by comparison of 4 and 5 with authentic samples[6] obtained following the procedure[7] described for the synthesis of 6-hydroxyethyl penams. Furthermore, shift reagent studies on P.M.R. spectra confirmed this attribution. We began performing the synthesis (scheme) of 1 (natural stereochemistry) starting from 4 knowing[1a] that 8R-hydroxyethyl penems are biologically much more active than the corresponding 8S-isomers.

Protection of the hydroxyl group of 4 as its p-nitrobenzylcarbonate and subsequent treatment with 1,4-diacetyloxybut-2-yne (refluxing toluene, 70% yield) gave compound 6 as a mixture of diastereoisomeric sulphoxides with *cis* stereochemistry in the butenyl moiety.[2a] *Major* isomer, P.M.R. ($CDCl_3$), δ (ppm): 1.40 (d, J = 6.0 Hz, 3H, CH_3CH); 1.97, 2.05, 2.10 (s, 9H, 2 $OCOCH_3$, $-\!\!<^{CH_2}_{CH_3}$); 3.64 (m, 1H, H-6); 3.75 (s, 3H, $COOCH_3$); 4.75 (d, J = 7.0 Hz, 2H, $\diagdown\!\diagup CH_2OCO$); 4.77 (s, 2H, CH_2OCO); 4.97 (s, 2H, $-\!\!<^{CH_2}_{CH_3}$); 5.20 (s, 2H, CH_2Ph); 4.8-5.2 (m, 3H, H-5, CH-CH_3, $CHCOOCH_3$); 6.43 (t, J = 7.0 Hz, 1H, $\diagdown\!\diagup H$); 7.4-8.4 (m, 4H, $PhNO_2$).

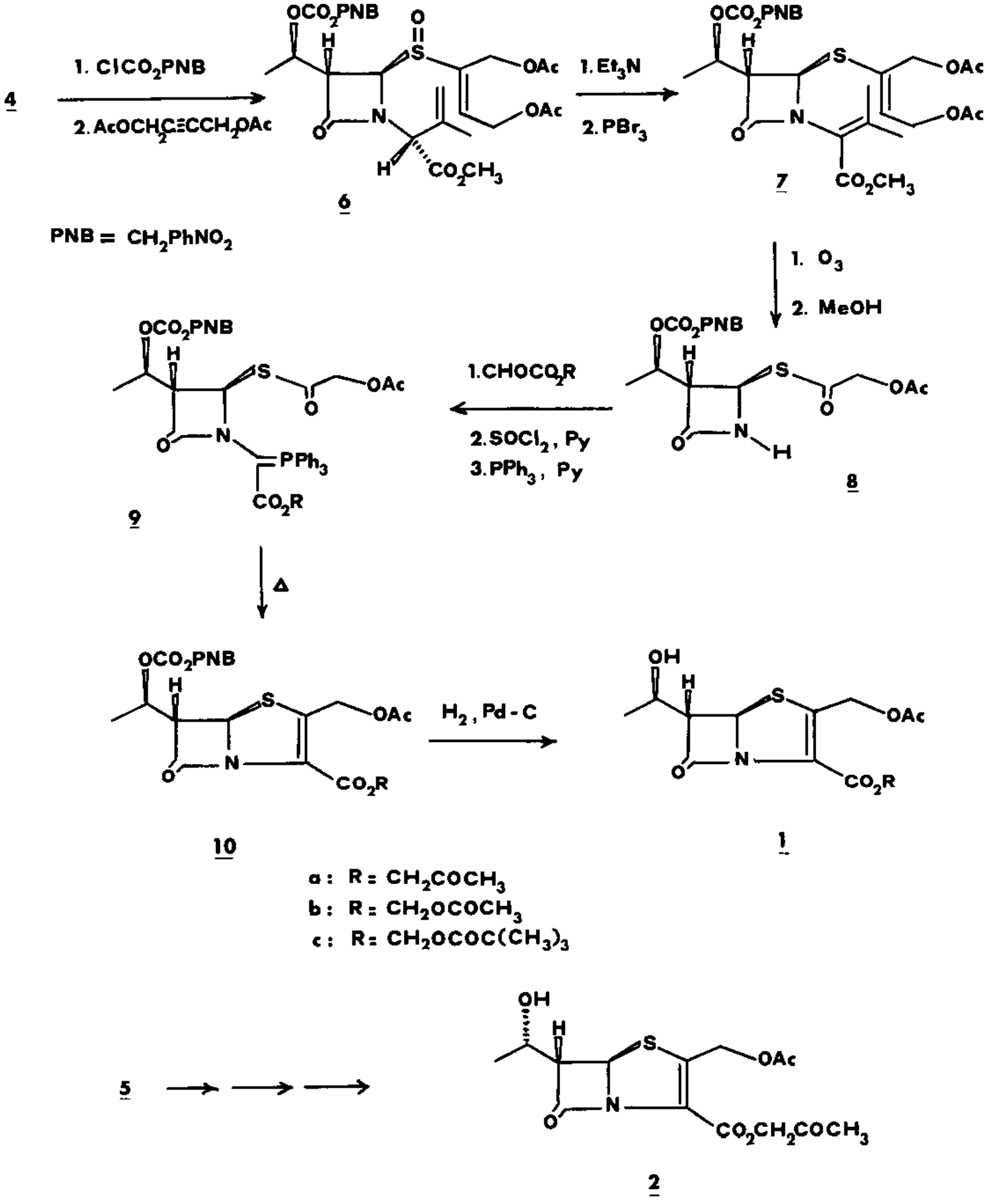
Isomerization of the isopropenyl double bond (Et_3N) and reduction of the sulphoxides (PBr_3, DMF, -20°C) afforded the sulphide 7 in 85% overall yield from 6. Ozonolysis on both double bonds and cleavage of the oxamide moiety (methanol on silica gel) gave 8 in 80% yield over the two steps. P.M.R. ($CDCl_3$), δ (ppm): 1.43 (d, J = 6.0 Hz, 3H, CH_3CH); 2.17 (s, 3H, $OCOCH_3$); 3.39 (dd, J = 2.0, 7.0 Hz, 1H, H-6); 4.72 (s, 2H, CH_2OCO); 5.2-5.4 (m, 1H, $CHCH_3$); 5.24 (s, 2H, CH_2Ph); 5.32 (d, J = 2.0 Hz, 1H, H-5); 6.80 (bs, 1H, NH); 7.4-8.4 (m, 4H, $PhNO_2$).

Condensation of 8 with acetonyl glyoxylate and chlorination of the resulting diastereoisomeric carbinolamides were followed by the transformation into the phosphorane 9a (40°C, tetrahydrofuran, PPh_3, pyridine) with 80% yield from 8. Cyclization to the penem derivative 10a occurred by simple heating 9a (refluxing toluene, 30') in the presence of a catalytic amount of hydroquinone (80% yield). Final deprotection of the hydroxyl group (H_2, 10% Pd-C) afforded the (5R, 6S, 8R) penem 1a in 60% yield. $[\alpha]_D^{20}$+ 134° (c 1.04, $CHCl_3$).

P.M.R. ($CDCl_3$), δ (ppm): 1.32 (d, J = 6.5 Hz, 3H, CH_3CH); 2.10 (s, 3H, $OCOCH_3$); 2.20 (s, 3H, $COCH_3$); 3.06 (bs, 1H, OH); 3.74 (dd, J = 2.0, 7.0 Hz, 1H, H-6); 4.23 (m, 1H, CHOH); 4.77 (s, 2H, CH_2CO); 5.12, 5.38 (d, J = 16.0 Hz, 2H, CH_2OCO); 5.63 (d, J = 2.0 Hz, 1H, H-5). IR ($CHCl_3$) ν (cm^{-1}) 1795, 1750, 1720.

The enzymatically labile esters 1b[8] and 1c[9] were analogously prepared. The same reaction pattern was then repeated for the synthesis of (5R, 6S, 8S) hydroxyethyl penem 2 from 5. 2: P.M.R. ($CDCl_3$), δ (ppm): 1.38 (d, J = 6.5 Hz, 3H, CH_3CH); 2.09 (s, 3H, $OCOCH_3$); 2.20 (s, 3H, $COCH_3$); 3.86 (dd, J = 2.0, 4.0 Hz, 1H, H-6); 4.22 (dq, J = 6.5, 4.0 Hz, 1H, CHOH); 4.72 (s, 2H, CH_2CO); 5.12, 5.42 (d, J = 15.5 Hz, 2H, CH_2OCO); 5.58 (d, J = 2.0 Hz, 1H, H-5). The high antibacterial activity of the sodium salt of 1 will be reported.[10]

SCHEME



PNB = CH_2PhNO_2

a: R = CH_2COCH_3
b: R = CH_2OCOCH_3
c: R = $CH_2OCOC(CH_3)_3$

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   b) V.M. Girijavallabhan, A.K. Ganguly, S.W. McCombie, P. Pinto and R. Rizvi, *Tetrahedron Letters*, 1981, *22*, 3485.
   c) S.W. McCombie, A.K. Ganguly, V.M. Girijavallabhan, P.D. Jeffrey, S. Lin, P. Pinto and A.T. McPhail, *Tetrahedron Letters*, 1981, *22*, 3489.
2. a) M. Foglio, G. Franceschi, C. Scarafile and F. Arcamone, *J.C.S. Chem. Commun.*, 1980, 70.
   b) A. Longo, P. Lombardi, C. Gandolfi and G. Franceschi, *Tetrahedron Letters*, 1981, *22*, 355.
   c) M. Foglio, G. Franceschi, C. Scarafile and P. Zini, *Heterocycles*, in press.
3. This work was presented at the 8th International Congress of Heterocyclic Chemistry, August 1981, Graz (Austria).
4. J.P. Clayton, *J. Chem. Soc. C*, 1969, 2123 and subsequent oxidation with m-chloroperbenzoic acid.
5. Only traces of the *cis* isomer were detected.
6. We are indebted to Dr. A. Bedeschi for having accomplished the synthesis of these products, allowing a direct and unambigous comparison on the stereochemistry.
7. F. Di Ninno, T.R. Beattie and B.G. Christensen, *J. Org. Chem.*, 1977, *42*, 2960.
8. $\underline{1b}$. UV (EtOH): λ_{max} 327 nm (ε 8000). P.M.R. ($CDCl_3$), δ(ppm): 1.35 (d, J = 6.5 Hz, 3H, $\underline{CH}_3CH$); 2.12 (s, 6H, $OCO\underline{CH}_3$, $CH_2OCO\underline{CH}_3$); 2.87 (bs, 1H, $\underline{OH}$); 3.75 (dd, J = 1.5, 6.0 Hz, 1H, $\underline{H\text{-}6}$); 4.21 (m, 1H, $\underline{CH}OH$); 5.10, 5.42 (two d, J = 16.0 Hz, 2H, $\underline{CH}_2OCO$); 5.65 (d, J = 1.5 Hz, 1H, $\underline{H\text{-}5}$); 5.84 (s, 2H, $COO\underline{CH}_2$). F.D. Mass Spectrum m/z 359 ($M^{+\cdot}$).
9. $\underline{1c}$. UV (EtOH): λ_{max} 328 nm (ε 6000). P.M.R. ($CDCl_3$), δ(ppm): 1.22 (s, 9H, $C(\underline{CH}_3)_3$); 1.33 (d, J=6.5 Hz, 3H, $\underline{CH}_3CH$); 2.48 (bs, 1H, $\underline{OH}$); 3.74 (dd, J = 1.5, 6.5 Hz, 1H, $\underline{H\text{-}6}$); 4.23 (m, 1H, $\underline{CH}OH$); 5.06, 5.38 (two d, J = 15.5 Hz, 2H, $\underline{CH}_2OCO$); 5.62 (d, J = 1.5 Hz, 1H, $\underline{H\text{-}5}$); 5.86 (dd, 2H, $COO\underline{CH}_2$). I.R. (CH_2Cl_2) ν(cm^{-1}): 1795, 1750, 1720 (sh).
10. Submitted to J. Antibiotics for publication.

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