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TOTAL SYNTHESIS OF THE 1-CARBAPEN-2-EM AND 1-CARBACEPHA-1,3-DIENE SYSTEMS

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Summary: The total synthesis of the 1-carbapen-2-em and 1-carbacepha-1,3- diene systems via an internal aldol condensation of enolisable oxo derivatives of azetidinones is described.

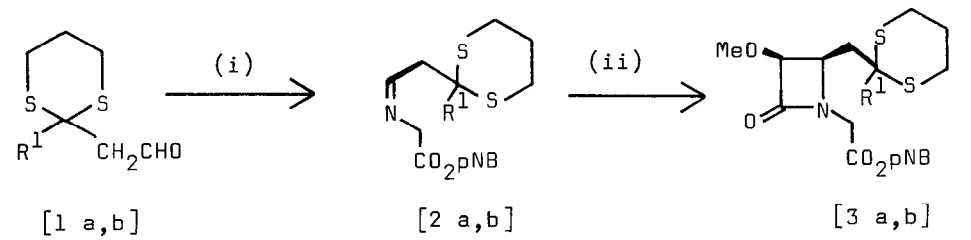
The discovery of the naturally-occurring, broad spectrum antibiotic, thienamycin[1], stimulated an intensive search for means of synthesising the 1-carbapen-2-em ring system[2]. A recent communication[3] detailed construction of this system by an internal aldol condensation using a non-enolisable aldehyde. These workers state "no aldol-type ring closure to produce a carbapenem ring system has been reported, presumably because the reaction would involve competing enolisation of the aldehyde group and high strain of the product". We wish to report the total synthesis of the 1-carbapen-2-em-system utilising the ring closure of such enolisable oxo compounds.

The Schiff's base [2a], (Scheme I), formed quantitatively from the aldehyde [1a][4] and 4-nitrobenzyl glycinate, reacted with methoxyacetyl chloride in the presence of triethylamine to give exclusively the cis-azetidinone [3a] (53%)[5], which was converted into the aldehyde [4a] (62%)[6]. Cyclisation of aldehyde [4a] with lithium hexamethyldisilazide, followed by quenching with acetic acid gave the 2-hydroxy-1-carbapenam [5a, R^2=pNB] (33%)[7], which was dehydrated, via the mesylate[8], to the 1-carbapen-2-em [6a, R^2=pNB] (69%). No identifiable β-lactam was obtained after removal of the 4-nitrobenzyl protecting group from [6a]. However, the biologically-labile ester [6a, R^2=CH_2OMe] was prepared from [5a, R^2=pNB] (20%) [i) H_2-Pd, ii) $KHCO_3$, iii) $MeOCH_2Cl$, iv) $MeSO_2Cl$, Et_3N].

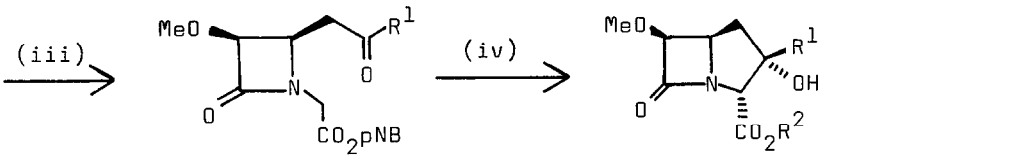
The diethyl acetal of the aldehyde [1a][9] was methylated to give [1b] (55%) which was converted into the 2-hydroxycarbapenam [5b] (12% overall). Treatment of [5b] with thionyl chloride in pyridine at -10° gave the 2-exomethylene carbapenam [7], which was isomerised to the 1-carbapen-2-em [6b]. Ozonolysis of the exomethylene derivative [7] gave the 2-oxo-1-carbapenam [8], as an unstable oil.

The 1-carbacephadiene [13, R^2=pNB][10] was synthesised by a similar reaction sequence (Scheme 2). Thus, the Schiff's base, from trans-cinnamaldehyde and 4-nitrobenzyl glycinate, reacted with methoxyacetyl chloride in dichloromethane at 20° in the presence of

SCHEME 1



[1 a,b] [2 a,b] [3 a,b]

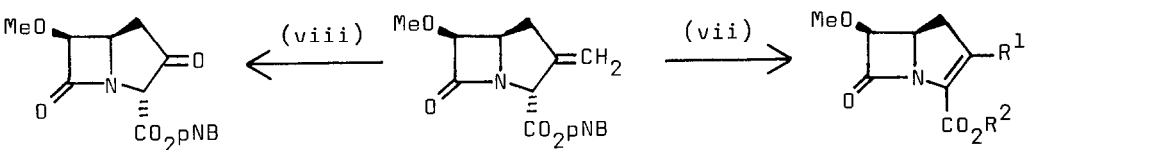


[4 a,b]

[5a]: R^2 = pNB, K, $-CH_2OMe$

[5b]: R^2 = pNB

[5b] (vi) [5a] (v)



[8] [7]

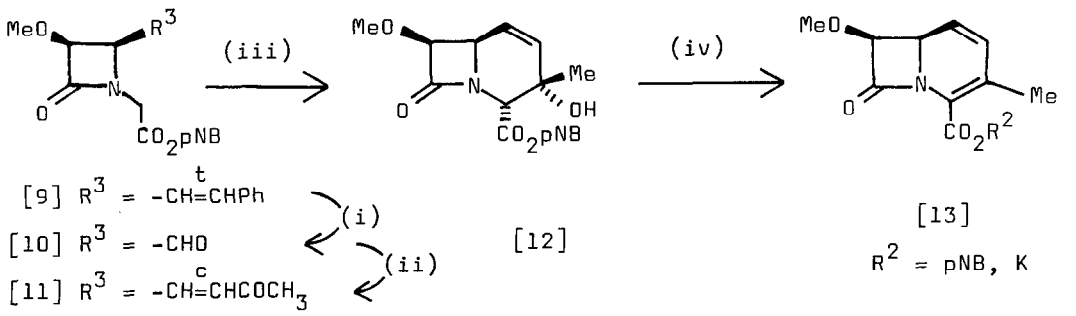
[6a]: R^2 = pNB, $-CH_2OMe$

[6b]: R^2 = pNB

1 - 6 : a, R^1 = H ; b, R^1 = CH_3 ; pNB = 4-Nitrobenzyl

1) $H_2NCH_2CO_2pNB$,EtOAc,$MgSO_4$, 1h, 20°; ii) $MeOCH_2COCl$,Et_3N,CH_2Cl_2, 3h, 20°; iii) $Tl(NO_3)_3$,MeOH-THF, 5 min, 20°, then $HClO_4$, aq. dioxan, 10 min, 20°; iv) $LiN(SiMe_3)_2$, THF, 1 min, -70°; v) $MeSO_2Cl$,Et_3N, 7h, 20°; vi) $SOCl_2$, pyridine, 0.5h, -10°; vii) Et_3N, $CDCl_3$, 1.5h; viii) O_3,CH_2Cl_2, -70°.

SCHEME 2



pNB = 4-Nitrobenzyl

1) O_3, EtOAc -78°, ii) $Ph_3P{=}CHCOCH_3$, CH_2Cl_2, 15h, 20°, iii) $LiN(SiMe_3)_2$, THF, 6 min, -78°; iv) $MeSO_2Cl$, Et_3N, THF, 1h, 0°; to remove pNB: Fe, aq. NH_4Cl, 2.25h, 0°, then aq. $KHCO_3$.

triethylamine to give the cis-azetidinone [9] (31%)[11], which was cleaved to the aldehyde [10] (45%). Reaction of this aldehyde [10] with acetylmethylene-triphenylphosphorane[12] gave [11] as a separable mixture of cis (27%) and trans (35%) isomers. The cis isomer [11] was cyclised to the 1-carbaceph-1-em [12] (35%)[7], which was dehydrated to the 1-carbacephadiene [13, R^2=pNB]. This ester was converted into the corresponding potassium salt [13, R^2=K].

Neither [6a, $R^2=CH_2OMe$] nor [13, R^2=K] possessed significant antibacterial activity or β-lactamase inhibitory properties.

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2. For example: i) D.G. Meilillo, I. Shinkai, T. Liu, K. Ryan and M. Sletzinger, Tetrahedron Letters, 21, 2783, (1980); ii) L. Cama and B.G. Christensen, Tetrahedron Letters, 21, 2013, (1980); iii) R.J. Ponsford and R. Southgate, J. Chem. Soc., Chem. Commun., 1085, (1980); and references cited therein.

3. M. Shibuya and S. Kabuta, Tetrahedron Letters, 21, 4009, (1980).

4. B.M. Trost and R.A. Kunz, J. Amer. Chem. Soc., 97, 7152, (1975).

5. All the synthetic β-lactams are racemic mixtures, but only one enantiomer is depicted for convenience. All new compounds had satisfactory microanalytical and/or mass spectral dat

and their infrared and proton magnetic resonance spectra fitted the assigned structures. Selected physical data includes:-

[4a]: m.p. 90.0°; ν($CHBr_3$) 1764, 1750, 1720 cm^{-1}; τ($CDCl_3$) 0.17 (s,1,CHO), 5.37 (d,1,J=5, H3), 5.63 (dd,1,J=5 and 6, H4), 7.06 (d,2,J=6, CH_2CO); [4b]: m.p. 101.5°; ν($CHBr_3$) 1766, 1752, 1714 cm^{-1}; τ($CDCl_3$) 5.40 (d,1,J=5, H3), 5.70 (m,1,H4), 7.09 (d,2,J=6, CH_2CO), 7.88 (s,3,CH_3); [5a: R^2=pNB]: m.p. 167.2°; ν(Nujol) 3420, 1753, 1742 cm^{-1}; τ(DMSO-d6) 4.28 (broad s,1,OH) 5.0-5.2 (m,2,H2+H6), 5.48 (d,1,J=5, H3), 5.80 (m,1,H5), 7.9-8.3 (m,2,H1); [5a, R^2=K]: ν(Nujol) 3400, 1770, 1596 cm^{-1}; τ(D_2O) 5.05 (d,1,J=5, H6), 5.24 (m,1,H2), 5.64 (d,1,J=5, H3), 5.74 (m,1,H5), 6.52 (s,3,OMe), 7.85 and 8.19 (m,2,H1); [5b]: m.p. 115.8°; ν($CHBr_3$) 3580, 1770, 1740 cm^{-1}; τ($CDCl_3$) 5.32 (d,1,J=4.5,H6), 5.78 (s,1,H3), 5.7-6.0 (m,1,H5), 7.68 (broad s,1,OH), 7.8-8.2 (m,2,H1), 8.40 (s,3,Me); [6a, R^2=pNB]: ν($CHBr_3$) 1784, 1728 cm^{-1}; τ($CDCl_3$) 3.30 (t,1,J=3,H2), 5.14 (d,1,J=5,H6), 5.60 (m,1,H5), 6.47 (s,3,OMe), 6.89 and 7.36 (m,2,H1); [6a, R^2=CH_2OMe] ν($CDCl_3$) 1772, 1718 cm^{-1}; τ(Me_2CO-d6) 3.29 (t,1,J=3,H2), 5.04 (d,1,J=5,H6), 5.57 (m,1,H5), 6.9-7.3 (m,2,H1); λ_{max}(pH7 buffer) 270 nm (ε 2500); [6b]: ν ($CDCl_3$) 1770, 1725 cm^{-1}; τ(C_6D_6) 5.86 (d,1,J=5,H6), 6.44 (m,1,H5), 6.87 (s,3,OMe), 7.23 and 8.28 (m,2,H1), 8.18 (s,3,Me); [7]: τ($CDCl_3$) 4.72 and 5.04 (two m,2=CH_2), 5.22 (d + s,2,J=5, H3 + H6), 5.82 (m,1,H5), 6.48 (s,3,OMe), 7.28 (m,2,H1); [8]: ν($CDCl_3$) 1774, 1750 cm^{-1}; τ($CDCl_3$) 5.07 (d,1,J=5,H6), 5.31 (s,1,H3), 5.66 (m,1,H5), 6.43 (s,3,OMe), 7.12 and 7.40 (m,2,H1); [12]: ν($CHBr_3$) 3560, 1766, 1746 cm^{-1}; τ($CDCl_3$), 4.13 (s,2,H1+H2), 5.28 (s,1,H4), 5.38 (d,1,J=4,H7), 5.74 (d,1,J=4,H6), 8.55 (s,3,Me); [13, R^2=pNB]: m.p. 108-109°; ν($CHBr_3$) 1764, 1712 cm^{-1}; τ($CDCl_3$) 3.90 (s,2,H1+H2) 4.92 (d,1,J=4,H7), 5.54 (d,1,J=4,H6), 6.40 (s,3,OMe), 7.78 (s,3,Me); [13, R^2=K]: ν(Nujol) 1746, 1590 cm^{-1}; τ(D_2O) 3.86 (s,2,H1+H2), 4.80 (d,1,J=4,H7), 5.44 (d,1,J=4,H6), 6.44 (s,3,OMe), 7.97 (s,3,Me); λ_{max}(pH6 buffer) 303 nm.

6. The intermediate dimethyl acetal could be isolated, and was fully characterised.

7. The relative stereochemistry of compounds [5] and [12] has not been definitely assigned, but p.m.r. spectral evidence strongly supports the structures as shown.

8. Work-up of the reaction mixture after ca. 5 min. gave the intermediate mesylate, which was fully characterised.

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10. This ring system has been synthesised by two alternative strategies:-
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11. Performing the reaction in refluxing benzene gave a 1:1 mixture of cis and trans azetidinones.

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