Olivanic Acids and Related Compounds: Total Synthesis of (±)-PS-5 and (±)-6-*Epi* PS-5

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Summary The *trans*- and *cis*-substituted β-lactam isomers of *p*-nitrobenzyl 3-(2-acetamidoethylthio)-6-ethyl-7-oxo-1-azabicyclo[3 2 0]heptane-2-carboxylate can be oxidised with iodobenzene dichloride–pyridine under anhydrous conditions to give the 3,4-unsaturated esters, which after isomerisation and deprotection afford the sodium salts of (±)-PS-5 and (±)-6-*epi* PS-5

In the context of preparing β-lactam systems related to the olivanic acids,[1] we have shown[2] how thiols react readily with C(3)-unsubstituted 1-azabicyclo[3 2 0]hept-2-ene-2-carboxylates to give products resulting from addition of thiol to the 2,3-double bond Such addition products have now been utilised to prepare the racemic form of the β-lactam antibiotic PS-5[3] (**7b**), a naturally occurring relative of the olivanic acids, and also its racemic C(6)-epimer (**7d**)

4-Allylazetidin-2-one[4] (**1a**) was converted by a sequence of *N*-silylation (Bu^tMe_2SiCl,Et_3N,DMF),† alkylation (LICA, THF,EtI, −78 °C to room temp),† and desilylation (KF,MeOH, room temp , 5 min) into the *trans*-substituted β-lactam (**1b**)‡ ($J_{3,4}$ 2 Hz), in 60% overall yield from (**1a**)

Conversion of (**1b**) into the phosphorane (**1c**) was by the standard procedure[5] Subsequent cyclisation[4] (CF_3CO_2H, O_3,Ph_3P,$NaHCO_3$) gave (**2a**) (60% from the phosphorane), ν_{max} ($CHCl_3$) 1775 cm^{-1} (β-lactam carbonyl) ($J_{5,6}$ 3 Hz)

Reaction of (**2a**) in dimethylformamide with an excess of 2-acetamidoethanethiol in the presence of potassium carbonate (20 min, room temp) gave a 70% yield of an inseparable mixture of the isomers (**3a**) (δ 4·76, d, *J* 7 Hz, 2-H), (**4a**) (δ 4 41, d, *J* 5 Hz), and (**5a**) (δ 4·14, d, *J* 8 Hz) in the ratio 5:3:2 On treatment with DBU,† (**5a**) was converted into the more thermodynamically favoured epimer (**4a**) (h p l c and n m r monitoring)

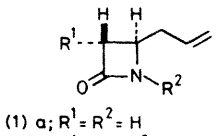
Reintroduction of the double bond was by a method that we have found to have some general application to thiol addition products of type (**3**)—(**5**) Oxidation of a mixture of (**3a**) and (**4a**) under rigorously anhydrous conditions with iodobenzene dichloride ($PhICl_2$) (1 equiv) in dichloromethane containing pyridine (2 equiv) (5 °C, 3 h) gave the 1-azabicyclo[3 2 0]hept-3-ene isomer§ (**6a**) (60%), m p 95—97 °C, without any detection of α-chlorosulphide[6] Treatment of (**6a**) with a catalytic amount of DBU¶ (CH_2Cl_2, room temp , 5 h) followed by rapid fractionation

† DMF = dimethylformamide, LICA = lithium *N*-isopropylcyclohexylamide, THF = tetrahydrofuran, DBU = 1,5-diazabicyclo-[5 4 0]undec-5-ene, HMPA = hexamethylphosphoramide

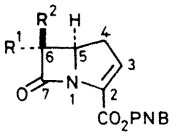
‡ Only one enantiomer is shown for each (±)-mixture

§ With certain other substituents, the 1-azabicyclohept-2-ene isomer was also observed as a minor product, with more soluble substrates reactions were conducted in benzene

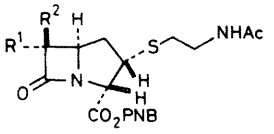
¶ Pyridine was ineffective in establishing this equilibrium



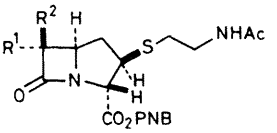
(1) a; $R^1 = R^2 = H$
b; $R^1 = Et$, $R^2 = H$
c; $R^1 = Et$, $R^2 = C(:PPh_3)CO_2PNB$



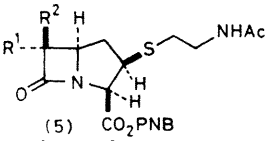
(2) a; $R^1 = Et$, $R^2 = H$
b; $R^1 = H$, $R^2 = CH_2CHO$



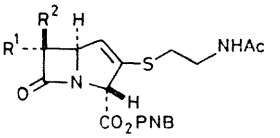
(3)



(4)



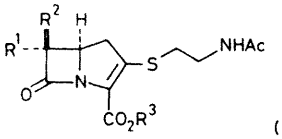
(5)



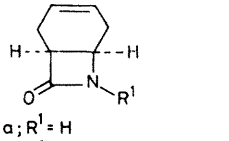
(6)

(3)–(5) a; $R^1 = Et$, $R^2 = H$
b; $R^1 = H$, $R^2 = CH_2CHO$
c; $R^1 = H$, $R^2 = CH_2CH_2OSO_2Me$
d; $R^1 = H$, $R^2 = Et$

a, $R^1 = Et$, $R^2 = H$
b, $R^1 = H$, $R^2 = Et$



(7) a; $R^1 = Et$, $R^2 = H$, $R^3 = PNB$
b; $R^1 = Et$, $R^2 = R^3 = H$
c, $R^1 = H$, $R^2 = Et$, $R^3 = PNB$
d; $R^1 = R^3 = H$, $R^2 = Et$



(8) a; $R^1 = H$
b, $R^1 = C(:PPh_3)CO_2PNB$

PNB = $CH_2C_6H_4NO_2$-*p*

on silica gel gave recovered (**6a**) (45%), and the *p*-nitrobenzyl ester of (±)-PS-5 (**7a**) (30%), m.p. 135—139 °C, λ_{max} (EtOH) 268 and 317 nm; ν_{max} ($CHCl_3$) 1780 (β-lactam carbonyl), 1700 (ester), and 1670 (amide carbonyl) cm^{-1}, having the *trans*-stereochemistry of β-lactam ring protons ($J_{5,6}$ 2·8 Hz). The u.v., i.r., n.m.r., and mass spectral data for ester (**7a**) were identical to those of semi-synthetic material derived[7] from the naturally occurring olivanic acid MM 17880. Hydrogenolysis (i; H_2,Pd–C,dioxan–H_2O; ii; $NaHCO_3$) afforded the sodium salt of (±)-PS-5 (**7b**), which was indistinguishable by u.v. and 250 MHz n.m.r. spectroscopy and h.p.l.c. from authentic material kindly supplied by Sanraku-Ocean Co. Ltd.

Preparation of the corresponding *cis*-substituted β-lactam isomer (**7d**) utilized the β-lactam (**8a**),[8] which was converted into the phosphorane (**8b**), and cyclised by our previously reported[4] method to the aldehyde (**2b**), m.p. 132—133 °C. Addition of 2-acetamidoethanethiol to (**2b**) produced (**3b**), (**4b**) (major component), and (**5b**) (71% total yield). Without separation this mixture was subjected to reduction ($NaBH_4$,THF,H_2O; 0 °C), followed by mesylation ($MeSO_2Cl$,pyridine), to give a separable mixture (81% overall) of (**3c**), (**4c**), m.p. 137—138 °C, and (**5c**), m.p. 148—150 °C. The methanesulphonate isomer (**4c**), on treatment with excess of sodium cyanoborohydride (HMPA; 95 °C; 4 h) gave (**4d**) (74%), m.p. 127—129 °C. Introduction of the double bond into (**4d**) resulted in a 66% yield of (**6b**) m.p. 122—123 °C. Isomerisation as before led to (**7c**) (14%), m.p. 143—144 °C, having the *cis*-arrangement of β-lactam ring protons ($J_{5,6}$ 6 Hz), and unchanged (**6b**) (70%) which could be re-equilibrated. Deprotection gave the sodium salt of (±)-6-*epi* PS-5 (**7d**), λ_{max} (EtOH) 299 nm. The sodium salts of (**7b**) and (**7d**) have also been prepared[7] from MM 17880. All compounds were satisfactorily characterised.

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[1] A. G. Brown, D. F. Corbett, A. J. Eglington, and T. T. Howarth, *J. Antibiotics*, 1979, **32**, 961, and references cited therein.
[2] J. H. Bateson, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1980, 185.
[3] K. Yamamoto, T. Yoshioka, Y. Kato, N. Shibamoto, K. Okamura, Y. Shimauchi, and T. Ishikura, *J. Antibiotics*, 1980, **33**, 796, and references cited therein.
[4] A. J. G. Baxter, K. H. Dickinson, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1979, 236.
[5] R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, *Helv. Chim. Acta.*, 1972, **55**, 408.
[6] K. G. Schreiber and V. P. Fernandez, *J. Org. Chem.*, 1961, **26**, 2910.
[7] D. F. Corbett and A. J. Eglington, *J. Chem. Soc., Chem. Commun.*, 1980, preceding communication.
[8] L. A. Paquette and T. Kakihana, *J. Am. Chem. Soc.*, 1968, **90**, 3897.