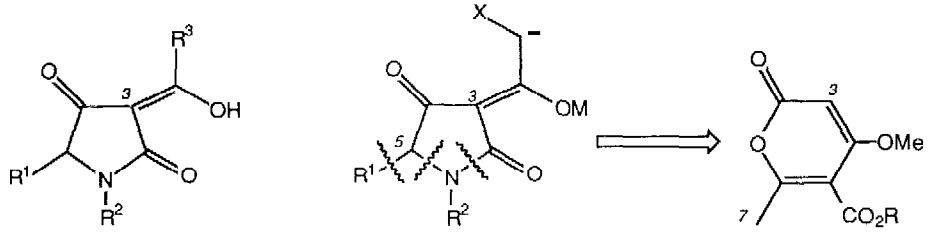
Tetrahedron Letters,Vol.30,No.24,pp 3217-3218,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

A NEW PYRONE STRATEGY FOR THE SYNTHESIS OF 3-ACYLTETRAMIC ACIDS

Raymond C.F. Jones * and Jacqueline M. Patience
(Chemistry Department, Nottingham University, Nottingham NG7 2RD, U.K.)

Summary: The potential of pyrones as precursors to 3-acyltetramic acids has been demonstrated by the conversion of 5-ethoxycarbonyl-4-methoxy-6-methyl-2-pyrone into a 3-acetyltetramic acid.

The 3-acylpyrrolidine-2,4-dione (3-acyltetramic acid) unit (1) is common to a family of microbial metabolites that display a wide variety of biological properties and have attracted much synthetic attention.[1] Problems with manipulation and purification of this highly polar enolic moiety [2] make it advantageous to generate or incorporate the nitrogen heterocycle as late in a sequence as possible. We report here a novel approach using a non-polar building block for acyltetramic acids.



(1) (2) X= H, $P(O)(OEt)_2$ M= Li, K (3)

A popular strategy for elaboration of the 3-(poly)enoyl substituent often present in these molecules has been to generate a nucleophilic site at a 3-acetyl group either directly [3] or with activation (2).[1a,4] Taken with the preparation of methyl tetramates from acetoacetate esters,[5] this suggested an analysis that identified pyrones (3) as potential precursors. The viability of this strategy was demonstrated as follows.

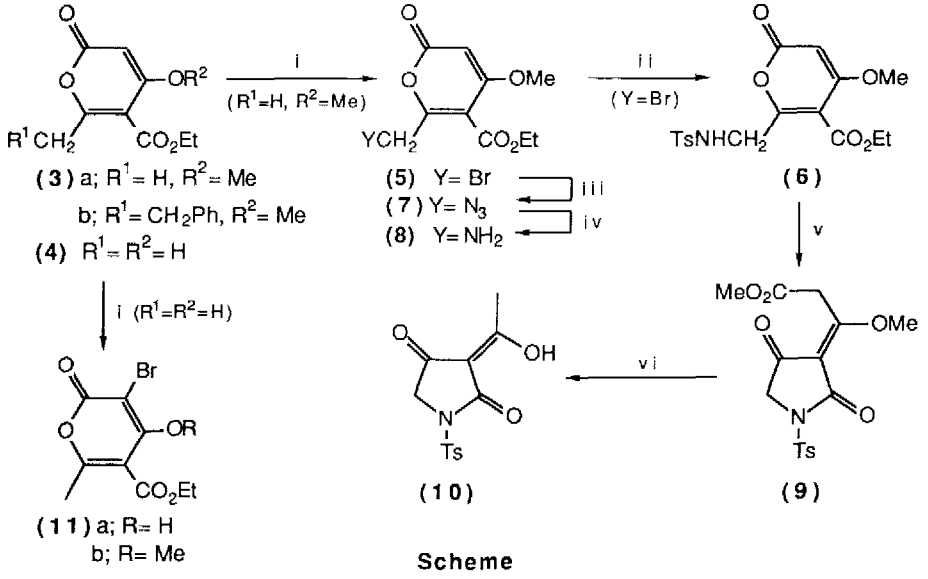
The ethyl ester (3a), m.p. 78-80°C,[6] was prepared (Scheme) by treatment of ethyl acetoacetate with malonyl dichloride (benzene reflux; 40%) [7] and methylation of the 4-hydroxypyrone (4) with dimethyl sulphate (K_2CO_3, acetone; 62%). Regiospecific bromination of (3a) was accomplished either with N-bromosuccinimide [azobis(isobutyronitrile), CCl_4 reflux] or via deprotonation ($LiNPr^i_2$, THF, -78°C; then Br_2) to afford the 6-bromomethyl pyrone (5) (97 and 70% respectively). Treatment of bromide (5) with sodium p-toluene-sulphonamide (THF, 20°C) afforded the sulphonamide (6) (92%), m.p. 106-108°C; a nitrogen atom could also be introduced by treatment of (5) with sodium azide in DMF (20°C) which led to the azidomethyl compound (7) (95%) that could be reduced (H_2, 1atm., Pd-C, MeOH) to the 6-aminomethyl pyrone (8) (81%). Both amide (6) and amine (8) were reluctant to cyclise directly onto the ester function to give the pyrano[2,3-*c*]pyrrole ring system under a variety of conditions.

On the other hand, treatment of the sulphonamide (6) with sodium methoxide (1 mol. equiv.) in methanol at reflux led to the sodium salt of an acidic product that on acidification proved to be the 3-substituted tetramic acid

(9) (72%), m.p. 164-166°C. Pyrone ring opening had thus accompanied nitrogen heterocycle formation. Removal of the methoxycarbonyl group and hydrolysis of the enol ether were simply achieved in a single operation (1M NaOH aq., 25°C) [8] to reveal the 3-acetyltetramic acid (10) (82%), m.p. 156-158°C.[9]

Elaboration at C-7 and at C-3 of the pyrone (3a) would provide substituents at C-5 and C-3(acetyl) of a tetramic acid.[10] The former reactivity was demonstrated by alkylation ($LiNPr^i_2$, THF, -78°C, $PhCH_2Br$) to afford (3b) (72%). The potential for functionalisation at C-3 was shown by bromination of 4-hydroxypyrone (4) [N-bromosuccinimide, azobis(isobutyronitrile), CCl_4 reflux; 96%] to afford (11a) and subsequent O-methylation (dimethyl sulphate, K_2CO_3, acetone; 71%) to give the 3-bromo-derivative (11b). Lithium-halogen exchange (BuLi, THF, -78°C) was successful, aqueous work-up regenerating the pyrone (3a).[11]

Further investigations to apply this pyrone strategy are in progress. We thank SERC and Roussel Laboratories for a CASE studentship and Drs. P. Kennewell and J. Golec for helpful discussions.



Scheme

Reagents: (i) NBS, AIBN, CCl_4 reflux; or (R^1=H, R^2=Me) $LiNPr^i_2$, THF, -78°C, Br_2; (ii) NaNHTs, THF, 20°C; (iii) NaN_3, DMF, 20°C; (iv) H_2, Pd-C, MeOH; (v) NaOMe, MeOH reflux; (vi) NaOH aq., 25°C

References and Notes

1. For example: (a) Tirandamycin: R.K. Boeckman, J.E. Starrett, D.G. Nickell, and P.-E. Sum, *J. Am. Chem. Soc.*, 1986, **108**, 5549, and refs. cited therein; (b) Ikarugamycin: L.A. Paquette, J.L. Romine, and H.-S. Lin, *Tetrahedron Lett.*, 1987, **28**, 31,and refs. cited therein
2. See for example: R.K. Boeckman and R.B. Perni, *J. Org. Chem.*, 1986, **51**, 5486, footnote 21.
3. R.C.F. Jones and A.D. Bates, *Tetrahedron Lett.*, 1987, **28**, 1565.
4. R.K. Boeckman and A.J. Thomas, *J. Org. Chem.*, 1982, **47**, 2823; R.H. Schlessinger and G.R. Bebernitz, *J. Org. Chem.*, 1985, **50**, 1344; P. DeShong, J.A. Cipollina, and N.K. Lowmaster, *J. Org. Chem.*, 1988, **53**, 1356.
5. R.C.F. Jones and A.D. Bates, *Tetrahedron Lett.*, 1986, **27**, 5285.
6. All new compounds gave spectra (n.m.r., i.r., u.v., m.s.) consistent with their assigned structure and satisfactory accurate mass measurement or combustion analysis; purity was also assessed by t.l.c. examination.
7. Cf. *Chem. Abstr.*, 1981, **94**, 15568. The by product 4,6-dimethyl-5-ethoxycarbonyl-2-pyrone (from self condensation of ethyl acetoacetate) was removed by base extraction of (4) and acidification.
8. Cf. R.C.F. Jones and G.E. Peterson, *Tetrahedron Lett.*, 1983, **27**, 4751.
9. Removal of the p-toluenesulphonyl group using acidic conditions (e.g. HBr-HOAc; cf. S. Searles and S. Nukina, *Chem. Rev.*, 1959, **59**, 1077) to which acyltetramic acids are stable (cf. ref 1a), and experiments with other nitrogen nucleophiles in this sequence, are underway.
10. An alternative, of course, is to elaborate separately the two precursors to the pyrone ring.
11. Reaction of a 3-metallopyrone (e.g. the 3-lithio derivative) with carbon electrophiles is being pursued.

(Received in UK 4 May 1989)