Tetrahedron Letters,Vol.30,No.30,pp 4019-4020,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

SYNTHESIS OF A NOVEL BICYCLIC γ-LACTAM ANALOGUE OF THE 1-OXAPENAMS

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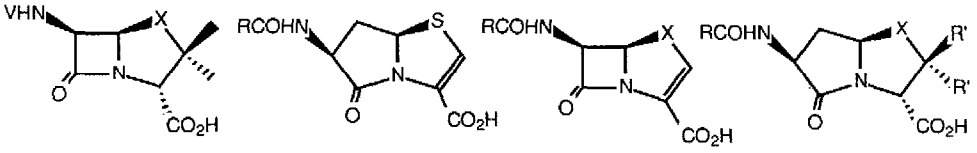
Summary: A succinct synthesis of a new bicyclic γ-lactam designed to possess antibacterial activity containing an oxazolidine ring is described.

In recent years both ourselves[1] and others[2] have attempted the synthesis of biologically active γ-lactams analogue of the β-lactam antibiotics [e.g. penicillin V(1)]. Independently we[3] and the Eli Lilly group [4] published the synthesis of similar γ-lactam analogues (2) of the penems (3), which possessed antibacterial activity and recently bicyclic pyrazolinones have been found to possess high antibacterial activity.[5] In contrast analogues (4a,b) of the penams (e.g. 1) showed no antibacterial activity,[6] possibly because of the relatively unreactive nature of the lactam. In our continuing efforts to obtain potent antibacterials based on γ-lactam structures we now report the synthesis of γ-lactam analogues of the oxa-penams (6).



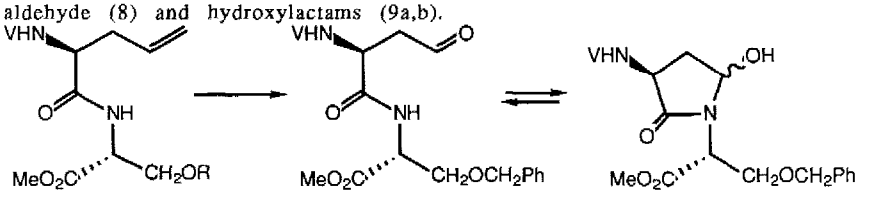
1, V = $PhOCH_2CO$, X = S
6, X = O

2

3, X = S

4a, R' = H, X = S
4b, R' = Me, X = S
5, X = O

Thus, dipeptide (7)[7] was synthesised from L-phenoxyacetyl allylglycine[8] and D-O-benzyl serine [(i)isobutylchloroformate/Et_3N/tetrahyhrofuran, (ii) D-O-benzyl serine/Et_3N][9]. Oxidation of the olefinic linkage of (7) [OsO_4 (cat.), $NaIO_4$, dioxan/water] gave a mixture of aldehyde (8) and hydroxylactams (9a,b).



7, R = CH_2Ph
14, R = H

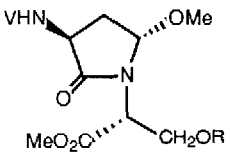
8

9a,b

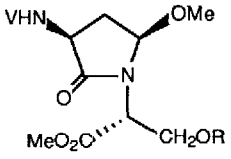
SCHEME 1

Treatment of the crude mixture with acidified methanol gave the methoxy lactams (10a:10b, c.a 3:1) [67%, from (7)] (Scheme 2), which were separated by flash chromatography.[10] Removal of the benzyl protecting group (H_2/Pd/C) gave the alcohols (11a and 11b) which were separately cyclised (p-toluenesulphonic acid, toluene, 20°C) to give the bicyclic lactams (12a) and (12b) respectively, i.e. the intramolecular cyclisation occurred predominantly with inversion of configuration at C-5 [of (12a) and 12b)].[11] Deprotection of the methyl ester (LiOH, tetrahydrofuran/water) gave the lithium salts of the desired analogue (13a), [66% from (10a)] and its diastereomer (13b), [69% from(10b)].

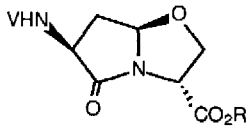
Both of these compounds were tested for antibiotic activity against *Staphylococcus aureus* NCTC-6571 at a concentration of 100μg ml^{-1} and shown to be inactive.



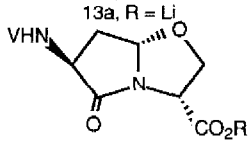
10a, R = CH_2Ph
11a, R = H



10b, R = CH_2Ph
11b, R = H



12a, R = Me
13a, R = Li



12b, R = Me
13b, R = Li

SCHEME 2

Acknowledgement R.T.F. thanks the British Council for support.

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6. J.E. Baldwin, C. Lowe, R.T. Freeman, C.J. Schofield and E. Lee, *Tetrahedron*, in press.

7. All new compounds gave satisfactory analytical and spectroscopic data.

8. Prepared by acylation of L-allyl glycine with phenoxyacetyl chloride with (dioxan, H_2O, K_2CO_3).

9. Purchased from Sigma, Chemical Company, Fancy Road, Poole, Dorset, BH17 7NH, England.

10. Stereochemical assignments were made on the basis of ^1H n.m.r. studies. Selected spectral data: For (12a): $[\alpha]_D^{20}$ +104 ($CHCl_3$, c = 1.4); ν_{max} ($CHCl_3$) 1734s, 1684s; d_H (200MHz, $CDCl_3$) 1.88-2.05(1H, m 6-H), 3.09-3.24(1H, m, 6-H), 3.79(3H, s, CO_2Me), 4.02(1H, dd, *J* 6.5,8Hz, 3-H), 4.46(1H, ca t, *J* 8Hz, 2-H), 4.53(2H, s, CH_2OPh), 4.72(1H, dd, *J* 6.5, 8Hz, 3-H), 4.88-4.97(1H, m, 7-H), 5.25(1H, *J* 4.5, 5.5Hz, 5-H); NOE data: irradiaton at 3.09-3.24(6-αH) showed 35% enhancement to 1.88-2.05 (6-βH), 15% to 4.88-4.97 (7-H), and 20% to 5.25 (5-H). Irradiation at 1.88-2.05 (6-βH) showed 21% enhancement to (6-αH) and <5% to (4-H) and (5-H); m/z (chemical ionisation) 355(MH^+). For (12b):$[\alpha]_D^{20}$ +63.5 ($CHCl_3$, c = 1.4); ν_{max} ($CHCl_3$) 1732s,1685s; NOE data:(α and β refer to the stereochemistry as drawn) irradiaton at (6-βH) showed 26% enhancement to (6-αH) and 15% (5-H). Irradiation at (6-αH) showed 27% enhancement to (6-βH) and <17% to (7-H); m/z (chemical ionisation) 355(MH^+).

11. An attempted 'one pot' synthesis of (12a,b) via treatment of alcohol (14) with (OsO_4(cat)/$NaIO_4$/dioxan/water (ii) p-toluenesulphonic acid/benzene gave only a low yield of the desired bicyclic lactams (12a) and (12b), hence the stepwise procedure reported above was used.

(Received in UK 30 May 1989)