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Tetrazolyl Peptides and the Tetrazole Analogue of 3-Aminonocardicinic Acid

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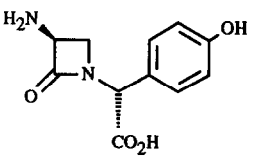
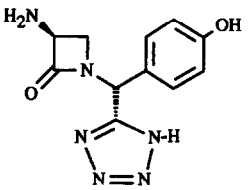
Abstract *The synthesis of the tetrazole analogue of the β-lactam, 3-aminonocardicinic acid, is described. Analogues of seryl p-hydroxy-phenylglycine were also prepared.*

Replacement of the carboxyl group in biologically active compounds by the tetrazole group is undertaken because of the close similarity in pKa values, and the steric and electronic similarities.[1] We therefore report the diastereoselective synthesis of the tetrazole (2), designed to mimic 3-aminonocardicinic acid (1), the nucleus of the nocardicin family of antibiotics.[2] Tetrazole analogues (3) have been reported,[3] but are more remote from the natural skeleton. A complementary study addresses the synthesis of the phosphonate analogues.[4]



1



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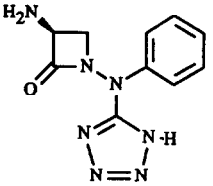
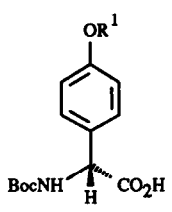


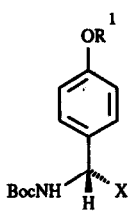
3

The N-Boc derivative of D-p-benzyloxyphenylglycine (4) was converted to tetrazole (8) by the sequence shown. Amide (5) was prepared (91%) from acid (4) ($EtOCOCl,NH_3$ gas), and dehydrated (68%) by $POCl_3$, giving nitrile (6). Formation of the tetrazole (86%) required NaN_3/NH_4Cl. Formic acid removed the Boc group, giving the formate salt which was transposed into the amine hydrochloride salt of (8) (75%). Tetrazole protection was necessary for the projected synthesis, but isomers were invariably produced, as in benzylation ($PhCH_2Br/Et_3N$, 80%) of (7) which gave the isomers (10) and (11) which were readily separable. Either (12) or (13) could be hydrogenolysed to the totally deprotected 'D'-aminotetrazole (9) in 60% yield.

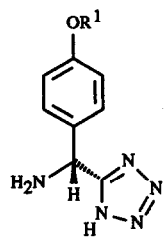
Prior to addressing the 3-amino azetidinone target (2), a model cyclisation study was undertaken. β-Bromopropionic acid was coupled with (13) (DCC, 81%) to give (14). Phase transfer cyclisation gave (15) (KOH, nBu_4NBr, CH_2Cl_2, 81%). Hydrogenolysis gave the deprotected β-lactam (16) (H_2, Pd-C, 92%). Note that in other model studies involving nitriles rather than tetrazoles, complications emerged. For example, (17) gave low yields (14% and 41%) of β-lactam (18) and γ-lactam (19) when treated with $NaH/DMF/CH_2Cl_2$.



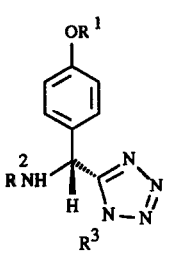
4, R^1=$PhCH_2$



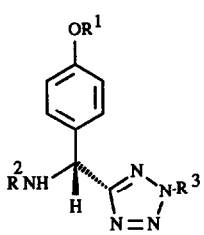
5, X=$CONH_2$, R^1=$PhCH_2$
6, X=CN, R^1=$PhCH_2$
7, X=tetrazole, R^1=$PhCH_2$



8, R^1=$PhCH_2$
9, R^1=H



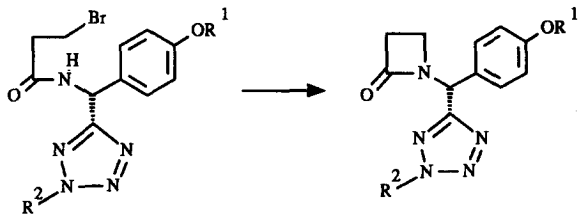
10, R^2=Boc, R^1=R^3=$PhCH_2$
12, R^1=R^3=$PhCH_2$, R^2=H



11, R^2=Boc, R^1=R^2=$PhCH_2$
13, R^1=R^3=$PhCH_2$, R^2=H

DDC coupling procedures gave the dipeptide analogues (20), (21) and (22) which were deprotected, e.g. by catalytic hydrogenolysis of (21) giving the free peptide surrogates (23) and (24), in good yield.

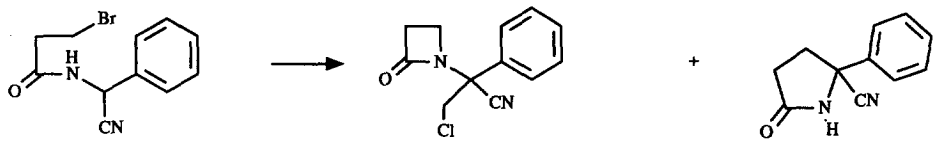
Because of complications encountered in a complementary programme involving cyclisations of aminophosphonate structures closely similar to (20), N-phthaloyl dipeptide (22) was cyclised by the Mitsunobu procedure[5], (DEAD, Ph_3P, 67%) to give the single diastereoisomer (25). Careful hydrazinolysis (Na_2S $9H_2O$, then $MeNHNH_2$, 55%)[6] gave free amine (26) which was completely deprotected (H_2/Pd-C,90%) to give (2). By an identical sequence, the benzyltetrazolyl isomer (11) was also progressed to the target β-lactam (2).



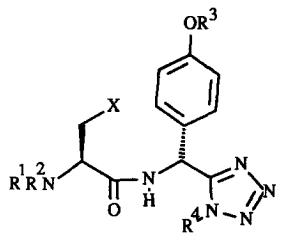
14, R^1=R^2=$PhCH_2$

15, R^1=R^2=$PhCH_2$

16, R^1=R^2=H



17 18 19



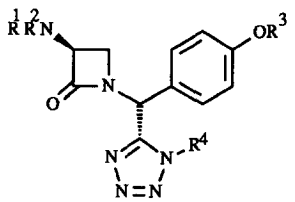
20, X=Cl, R^1=Z, R^2=H, R^3=R^4=$PhCH_2$

21, X=OH, R^1=Z, R^2=H, R^3=R^4=$PhCH_2$

22, R^1R^2=phthalimide, X=OH

23, X=Cl, R^1-R^4=H

24, X=OH, R^1-R^4=H



25, R^1=R^2=phthalimide, R^3=R^4=$PhCH_2$

26, R^1=R^2=H, R^3=R^4=$PhCH_2$

2, R^1-R^4=H

A direct route to the chiral tetrazole analogues of 3-aminocardicinic acids has therefore been established, paralleling our synthesis[4] of the 3-aminophosphonocardicinic acid. In the key cyclisation steps, different tactics were necessary in each case, emphasising the problems inherent in this approach, and extending other related studies[7] in the area.

Acknowledgement

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New compounds gave satisfactory elemental analyses and/or high resolution mass measurement on

homogeneous samples, and polar compounds gave correct FAB -ve ion M-1 ions.

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