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A CONCISE APPROACH TO FUNCTIONALISED, HOMOCHIRAL TETRAMIC ACIDS

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Abstract: Dieckmann cyclisation of homochiral N-acyloxazolidines derived from serine gives good to excellent yields of α,α-disubstituted tetramic acid derivatives.

Because of their range of biological activity, the preparation of tetramic acids has been extensively investigated. This class of compound has been prepared by Dieckmann cyclisation, and recent work has shown that such cyclisations using substrates derived from homochiral amino acids can be performed under carefully controlled conditions, using mild base[1, 2] or fluoride,[3] to give homochiral products. We report here an alternative approach, in which a substrate prepared from serine, designed using the principles of Seebach's "Self Regeneration of Chirality",[4] can be cyclised under basic conditions, to give homochiral tetramic acid derivatives.

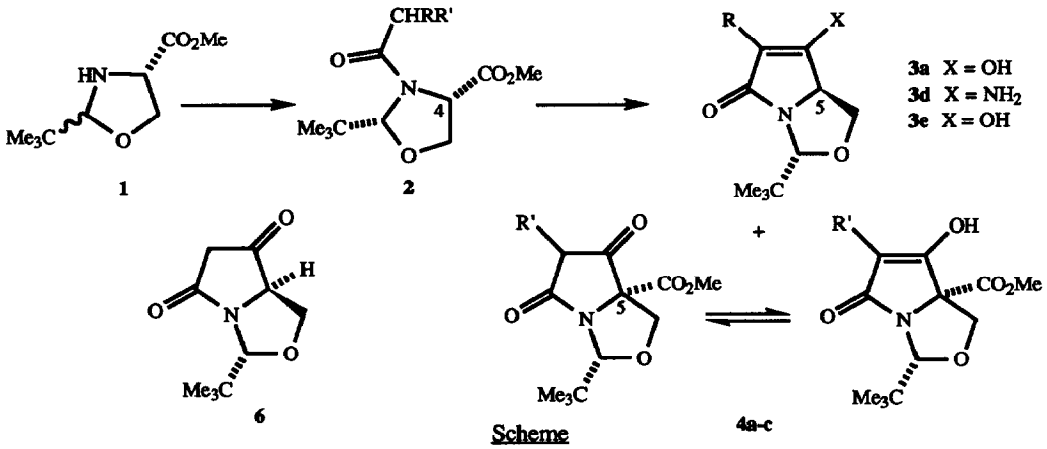
Oxazolidine **1**, readily prepared from L-serine and pivaldehyde according to the Seebach protocol,[5,6] was acylated by DCC coupling with the acid, or by reaction with the corresponding acid chloride, to give **2a-f** in yields ranging from 53-87%. These compounds have been shown by n.O.e. spectroscopic studies to possess exclusively the *cis*- relative stereochemistry indicated, as has been observed in related systems;[4] this result has been confirmed in the case of **2f** by X-ray crystallographic studies.[7] Cyclisation of derivatives **2a-e**, under basic conditions (KOtBu/toluene, NaOMe/MeOH, or KOtBu/tBuOH), gave the products indicated in the Table and Scheme. Although the products **3a, d, e** were obtained exclusively as the enolic tautomers, the compounds **4** were obtained as either the keto (**4a**), enol (**4c**), or mixture of both (**4b**), tautomers. The major products **4a-c** arose by deprotonation at C-4 of oxazolidine **2**, followed by closure to the side-chain ester; the product **3a**, derived from the alternative mode of cyclisation (deprotonation at the N-acyl side chain and subsequent closure to the C-4 ester) was obtained as a minor product, but **3b,c** were not formed. Derivative **2d** cyclised, with concomitant hydrolysis and decarboxylation, to the enamine **3d**. Both **3a** and **3d** could be easily converted, by heating in acetonitrile or aqueous sodium bicarbonate respectively, to dicarbonyl **6**, the relative stereochemistry of which was readily determined by n.O.e. measurement. This was shown to correspond to inversion of stereochemistry of C-5, relative to the C-4 stereochemistry of the starting material **2**. Significantly, in those cases where both of the cyclisation modes were not possible (**2e,f**), either a low yield of product **3e** (22%) was obtained, or for **2f**, neither **3** nor **4** were obtained; rather, β-elimination to the dehydroalanine derivative[5, 6] led to collapse of the starting material.

The distribution of products **3-4** is probably arising as follows: the expected mode of cyclisation, arising by deprotonation of the most acidic site of the substrates **2** followed by direct closure to the C-4 ester, is not possible, since cyclisation puts the bulky t-butyl group on the sterically congested *endo*- face of the bicyclic product. Cyclisation does become possible, however, if epimerisation at C-4 to the *trans*- oxazolidine occurs, but this is not a favoured process given the preference of such systems for the *cis*- arrangement[4]; thus compounds **3** are generally obtained only as a minor product. The preferred mode of cyclisation, therefore, arises by C-4 deprotonation followed by cyclisation, leading to the products **4**.

Conversion of the products **3e** and **4b** to the corresponding Mosher's derivatives[8] and analysis of the product mixture by 500MHz ^1H nmr spectroscopy, has indicated that the ring closure occurs with an e.e. of 69% and 96% respectively.

Table: Yields of intermediates **2**, **3** and **4**.

Compound	R	R'	Yield 2 (%)	Yield 3 (%)	Yield 4 (%)
(a)	EtO_2C-	H	86	12	64
(b)	EtO_2C-	Me	78	-	96
(c)	EtO_2C-	Ph	65	-	73
(d)	H	NC-	82	71	-
(e)	Ph-	H	87	22	-
(f)	Ph-	Ph-	53	-	-



Scheme

These Dieckmann cyclisations provide a rapid entry to α-substituted pyroglutamates **4**, a class of compounds which includes important natural products, such as the neurotrophic growth factor lactacystin,[9-11] and the antitumour and antibiotic agents, oxazolomycin[12] and triedimycin A and B.[13] The minor products **3** are substituted pyroglutaminols, and could be useful synthetic precursors to the kainoid group of amino acids.[14] The application of this approach to the construction of such compounds and their analogues is under investigation.

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