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Synthesis and enantiomeric excess measurements of optically active *N*-acetyl tetramic acids

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Abstract

A facile route to chiral functionalised tetramic acids through *C*-acylation–cyclisation reactions of active methylene compounds with *N*-hydroxysuccinimide esters of *N*-acetyl-L-amino acids is described. Enantiomeric excesses and physical characteristics of all compounds are reported.

The synthesis of optically active tetramic acids (pyrrolidine-2,4-diones) is a research field of major importance as it has relevance to virtually all areas of pharmaceutical industries. These compounds constitute an important class of natural products possessing significant antiviral, antibiotic and antifungal properties. Studies on their structure–activity relationships have revealed that their pure enantiomers show different activity and toxicity profiles and their pronounced pharmacological activity derives from only one single enantiomer.[1] In the light of this relevance, the development of efficient methods for the construction of such enantiomerically pure compounds has gained increasing interest in organic and medicinal chemistry.

During the last two decades numerous approaches to the synthesis of chiral tetramic acids have been reported, making use of amino acid-derived precursors whose stereochemical integrity remained more or less conserved in the structures of the products. The applied methodologies are modifications of the enantioselective Lacey–Dieckmann cyclisation, requiring strongly alkaline conditions.[2,3] Significant studies on the synthesis of such optically active compounds have been made by Ley et al. who used a series of β-ketoamides as intermediates for the preparation of enantiomerically pure 3-acyl tetramic acids,[4] and Moloney et al. who provided an *N*-acyloxazolidine derived from L-serine,[5] as a suitable precursor, for the construction of chiral substituted tetramic acids with high ee values.

As part of our research programme on the construction of nitrogen heterocycles containing the pyrrolidine-2,4-nucleus,[6–8] we have developed a facile and convenient approach to highly functionalised *N*-acetyl tetramic acids.[9] In this paper we wish to extend this approach to an expeditious synthesis of the tetramic acid nucleus with the additional requirement that the proposed strategy should

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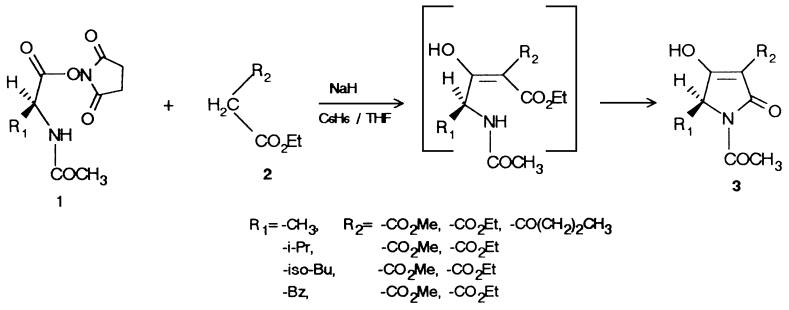
allow for the synthesis of tetramic acids in enantiopure form. The proposed methodology involves the *C*-acylation–cyclisation reaction of active methylene compounds **2** with the optically active *N*-hydroxysuccinimide esters of *N*-acetyl-α-amino acids (L-alanine, L-phenylalanine, L-valine, L-leucine) **1** (Scheme 1).



Scheme 1.

In a typical reaction, 3 equiv. of the active methylene compound were treated with 1 equiv. of *N*-hydroxysuccinimide esters in the presence of 3 equiv. of NaH, in anhydrous THF or C_6H_6, at 0°C, for 3–5 h. The reaction mixture was concentrated in vacuo and the obtained solid was diluted in water and washed with diethyl ether. The aqueous layer was separated, acidified with 10% hydrochloric acid in an ice-water bath giving a solid that was filtered off. The obtained optically active *N*-acetyl tetramic acids **3** were isolated in good yields (Table 1). The structures of the newly prepared tetramic acids **3** have been elucidated with elemental analyses, NMR and IR spectroscopy.

These results indicate the success of the proposed methodology to generate chiral products of good enantiomeric excess, although partial racemisation occurred under the described experimental conditions. An important feature of this synthetic route is the use of *N*-hydroxysuccinimide esters of chiral α-amino acids as optically active starting materials. These acylating agents are easily prepared and partially maintain the stereochemical integrity of their corresponding starting *N*-acetyl-L-amino acids. In addition, the synthesis is performed under mild conditions and with short reaction times, and provides the desired compounds in satisfactory yields. The absence of strongly alkaline or thermal conditions did not promote

Table 1
Physical properties of *N*-acetyl tetramic acids **3**

R_1	R_2	Enant. ratio(t, min)[a]	$[\alpha]_D$ [b]	mp (°C)	Yield(%)	e.e.
Me	CO_2Me	86(6.65):14(8.00)	+75.6 (c3, MeOH)	117-120	39	72
Me	CO_2Et	>88.3(6.48)	+56.6 (c3, MeOH)	69-73	50	>76
iso-Pr	CO_2Me	93(5.98):7(7.27)	+3.16 (c1.2, $CHCl_3$)	92-97	32	86
iso-Pr	CO_2Et	88(6.00):12(7.27)	+44.55 (c1.2, $CHCl_3$)	98-100	30	76
iso-Bu	CO_2Me	93(5.88):7(7.37)	+3.4 (c4, MeOH)	89-93	36	86
iso-Bu	CO_2Et	91(5.83):9(7.23)	+7.45 (c2, MeOH)	71-73	32	82
Bz	CO_2Me	94(5.85):6(7.38)	+14 (c3, MeOH)	140-143	50	88
Bz	CO_2Et	77(6.45):23(8.13)	+40.9 (c2, MeOH)	93-97	48	54
Me	COPr	77(6.55):23(7.48)	-1.2 (c0.99, MeOH)	53-55	44	54

[a]The enantiomeric ratios were determined by HPLC analysis with a CHIRALPAK AS column (4.6x250mm), [245nm, 0.55 ml/min, ethanol-hexane (90:10)]
[b] Optical rotations were recorded on a Perkin-Elmer 241 polarimeter

removal of the acidic α-proton (H-5) in these products and as a result the epimerisation of the stereogenic center at C-5 was minimised although not completely avoided.

During the determination of the enantiomeric excesses of the cyclised compounds **3** by chiral HPLC techniques, it was noticed that when the desired products were dissolved in *i*-propanol or ethanol racemisation occurred after 2–3 h. Thus, the samples were dissolved in *n*-hexane and ethanol was added only when necessary to ensure solubility. The enantiomeric excesses determined for the *N*-acetyl-3-substituted tetramic acids show that the stereochemical integrity of the starting materials is largely retained during the synthesis.

In conclusion, we have investigated a simple, short, efficient and versatile synthetic route for the construction of a new class of optically active functionalised 2,4-pyrrolidinones. The reported work relates not only to the investigation of suitable conditions for the synthesis of optically active compounds, but also to the determination of their enantiomeric excesses.

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References

1. Royles, J. L. *Chem. Rev*. **1995**, *95*, 1981.
2. Paquette, L. A.; Macdonald, D.; Anderson, L. G.; Wright, J. *J. Am. Chem. Soc*. **1989**, *111*, 8037.
3. Jones, R. C. F.; Tankard, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 240.
4. Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, *48*, 1145.
5. Andrews, M. A.; Brewster, A. G.; Crapnell, K. M.; Ibbett, A. J.; Jones, T.; Moloney, M. G.; Prout, K.; Watkin, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 223.
6. Barkley, J. V.; Markopoulos, J.; Markopoulou, O. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1271.
7. Detsi, A.; Markopoulos, J.; Igglessi-Markopoulou, O. *Chem. Commun*. **1996**, 1323.
8. Detsi, A.; Micha-Screttas, M.; Igglessi-Markopoulou, O. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2443.
9. Petroliagi, M.; Igglessi-Markopoulou, O. *J. Chem. Soc., Perkin Trans. 1* **1997**, *23*, 3543.