# One-pot Synthesis of Optically Active Tetramic Acids from Amino Acids Mediated by 1-Hydroxybenzotriazole

Giorgos Athanasellis, Efstathios Gavrielatos, Olga Igglessi-Markopoulou*

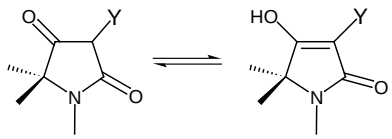
Laboratory of Organic Chemistry, Department of Chemical Engineering, National Technical University of Athens, Zografou Campus, 15773 Athens, Greece
Fax +30(1)7723072; E-mail: ojmark@orfeas.chemeng.ntua.gr

*Received 11 June 2001*

**Abstract:** A novel synthesis of chiral 3-ethoxycarbonyl-5-substituted tetramic acids in moderate yields (45–75%) is reported. HPLC analysis of these tetramic acids shows very good enantiomeric excesses (82–98%).

**Key words:** tetramic acids, 1-hydroxybenzotriazole, natural products, amino acids

The pyrrolidine-2,4-dione ring system containing a 3-acyl substituent is a common skeleton of naturally occurring tetramic acids.[1,2] (Figure)



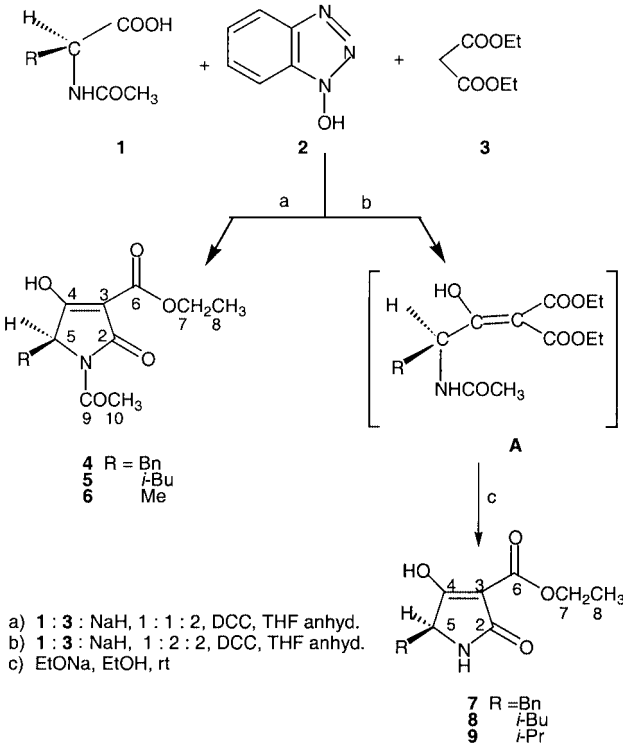
**Figure**

The spectrum of biological activity displayed by these natural products is remarkable in its diversity and it includes potent antibiotic, antiviral and antifungal properties, cytotoxicity and mycotoxicity as well as the inhibition of tumors.[3–6] It has also been reported that tetramic acids have been designed as glycine site *N*-methyl-D-aspartate (NMDA) antagonists, which may be of use in the treatment of neurological diseases.[7] Recently, the total syntheses of reutericyclin,[8] and physarorubinic acid[9] have also been reported.

Studies on the structure-activity relationships of these natural products have revealed that only one of their two enantiomers has been isolated. This shows that the pure enantiomers of tetramic acid display different activity and toxicity profiles and their pronounced pharmacological activity derives from only one single enantiomer.[1] So, it is obvious that the synthesis of optically active tetramic acids is a research field of major importance as it has relevance to virtually all areas of pharmaceutical industries.

During the last 25 years numerous approaches to the synthesis of chiral tetramic acids have been reported. They mainly make use of amino acids derived precursors whose stereochemical integrity remains more or less conserved in the structure of the products. Significant studies on the synthesis of such optically active compounds have been made by Ley et al.[2] who used a series of β-ketoamides as intermediates for the preparation of enantiomerically pure 3-acyl tetramic acids. On the other hand, Moloney et al.[10] provided a *N*-acyloxazolidine derived from L-serine as a suitable precursor for the construction of chiral substituted tetramic acids with high enantiomeric excess. Other methodologies based on the enantioselective Lacey-Dieckmann cyclization, requiring strongly basic conditions[11,12] have also been reported.

During the last decade, our research group has been investigating the synthesis of nitrogen heterocycles containing the pyrrolidine-2,4-dione nucleus. We have developed a facile and convenient approach to highly functionalized *N*-acyl and *N*-alkoxycarbonyl tetramic acids.[13–15] This methodology has also been proposed for the synthesis of chiral tetramic acids in enantiopure form.[16]




**Scheme**

Synlett 2001, No. 10, 28 09 2001. Article Identifier:
1437-2096,E;2001,0,10,1653,1655,ftx,en;G11301st.pdf.

ISSN 0936-5214

As a continuation of these efforts, we managed recently to synthesize a series of 3-ethoxycarbonyl-5-substituted tetramic acids **4**–**9** using a simple and stereoselective method (Scheme). The one-pot synthesis comprises a C-acylation reaction between the 1-hydroxybenzotriazole ester of the appropriate optically active amino acid **1** and diethyl malonate **3**. When the product was not the corresponding tetramic acid **4**–**6** but the C-acylation compound **A**, a cyclization reaction under basic conditions was performed to afford the corresponding tetramic acid **7**–**9**.[17]

**Table** Optical Rotations, Enantiomeric Ratios and Enantiomeric Excesses of Compounds **4**–**9**

| Compound | Yield (%) | e.r.[b] | e.e. | $[a]_D$ (c1, MeOH)[a] |
|---|---|---|---|---|
| **4** | 43 | 97:3 | 94 | +2.4 |
| **5** | 75 | 91:9 | 82 | +37.6 |
| **6** | 44 | 91:9 | 82 | +45.1 |
| **7** | 45 | 98:2 | 96 | –38.4 |
| **8** | 74 | 93:6 | 87 | –21.3 |
| **9** | 59 | 92:8 | 84 | –4.2 |

[a] Optical rotations were recorded on a Perkin-Elmer 241 polarimeter.
[b] Enantiomeric ratios were determined by HPLC analysis with a CHIRALPAK AS column (4.6 · 250 mm), [254 nm, 0.6 mL/min, ethanol–hexane (1:1)]

The crucial parameter in the synthesis of the N-acylated 3-ethoxycarbonyl tetramic acids **4**–**6** or *N*-*H*-3-ethoxycarbonyl tetramic acids **7**–**9** is the molar ratio between the N-acylated amino acid **1** and diethyl malonate **3**. We observed that when diethyl malonate **3** was used in molar excess (2 equiv) the oily product containing the C-acylation compound **A** and diethyl malonate **3** was obtained. This mixture was stirred under basic conditions to afford the *N*-*H*-3-ethoxycarbonyl tetramic acids **7**–**9**. On the other hand, when diethyl malonate **3** was used in stoichiometric ratio (1 equiv), the *N*-acetyl-3-ethoxycarbonyl tetramic acids **4**–**6** were obtained as white solids. In both circumstances, HPLC analysis showed that the enantiomeric ratio between the two enantiomers of products was satisfactory. (Table)

These results indicate the success of the proposed methodology to maintain the stereochemical integrity of the corresponding α-amino acids. Another advantage of the proposed methodology is that there is no need for isolating the intermediates 1-hydroxybenzotriazole esters of the chiral α-amino acids, in contrast to previously described methodologies.[15,16] This fact reduces the time for the synthesis of the desired products and is beneficial for the overall yield of the reaction (45–75%). Additionally, the reaction is simple, inexpensive, easily scaled up and proceeds with low racemization. The structures of the tetramic acids **4**–**9** have been elucidated by elemental analyses, NMR and FT-IR Spectroscopy.[18]

In conclusion, we have investigated a novel one-pot synthetic route to chiral 3-ethoxycarbonyl tetramic acids **4**–**9** from *N*-acetyl-α-amino acid hydroxybenzotriazole intermediates. The results of this work are very promising and it is clear that the proposed methodology could be applied for the synthesis of highly functionalized tetramic acids as well as other optically active heterocyclic compounds.

## Acknowledgement

We thank Ms V. Skouridou (National Technical University of Athens, Biotechnology Laboratory) for recording the IR spectra. We also thank the National Technical University of Athens for financial support (project "Archimides").

## References and Notes

(1) Royles, B. J. L. *Chem. Rev.* **1995**, *95*, 1981.
(2) Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, *48*, 1145.
(3) (a) DeBoer, C.; Dietz, A.; Silver, W. S.; Savage, G. M.In *Antibiotics Annual*; Welch, H.; Marti-Ibanez, J., Eds.; Medical Encyclopedia, Inc.: New York, **1956**, 886.
(b) Meyer, C. E. *J. Antibiot.* **1971**, *24*, 558.
(4) Terret, N. *DDT* **1998**, *3*, 1998.
(5) Hashidoko, Y.; Nakayama, T.; Homma, Y.; Tahara, S. *Tetrahedron Lett.* **1999**, *40*, 2957.
(6) Sata, N. U.; Matsunaga, S.; Fusetani, N.; Van Soest, R. W. M. *J. Nat. Prod.* **1999**, *62*, 969.
(7) Mawer, I. M.; Kulagowski, J. J.; Leeson, P. D.; Grimwood, S.; Marshall, G. R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2643.
(8) Marquardt, U.; Schmid, D.; Jung, G. *Synlett* **2000**, 1131.
(9) Dixon, D. J.; Ley, S. V.; Longbottom, D. A. *J. Chem. Soc., Perkin Trans 1* **1999**, 2231.
(10) Andrews, M. A.; Brewster, A. G.; Krapnell, K. M.; Ibbett, A. J.; Jones, T.; Moloney, M. G.; Prout, K.; Watkin, D. *J. Chem. Soc., Perkin Trans 1* **1998**, 223.
(11) Paquette, L. A.; MacDonald, D.; Anderson, L. G.; Wright, J. *J. Am. Chem. Soc.* **1989**, *111*, 8037.
(12) Jones, R. C. F.; Tankard, M. *J. Chem. Soc., Perkin Trans 1* **1991**, 240.
(13) Detsi, A.; Markopoulos, J.; Igglessi-Markopoulou, O. *Chem. Commun.* **1996**, 1323.
(14) Detsi, A.; Micha-Screttas, M.; Igglessi-Markopoulou, O. *J. Chem. Soc., Perkin Trans 1* **1998**, 2443.
(15) Petroliagi, M.; Igglessi-Markopoulou, O. *J. Chem. Soc., Perkin Trans 1* **1997**, *23*, 3543.
(16) Petroliagi, M.; Igglessi-Markopoulou, O. *Tetrahedron: Asymmetry* **1999**, *10*, 1873.
(17) General procedure for the synthesis of compounds **4**–**9**: In a typical reaction, 10 mmol of the optically active N-acylated amino acid **1** was treated with 10 mmol of 1-hydroxybenzotriazole **2** and 10 mmol DCC in anhyd THF at 0 °C for 1 h. The resulting mixture was refrigerated at 3–5 °C overnight. The precipitated solid (DCCU) was filtered off and discarded, the THF filtrate was added to a solution of 20 mmol of NaH and 10 or 20 mmol of diethyl malonate **3** in anhyd THF. The resulting mixture was stirred at r.t. for 2.5 h. and then concentrated in vacuo. The obtained gummy solid was diluted with water and washed with diethyl ether. The aq extract was acidified with 10% HCl in an ice water bath to give a white solid (1-hydroxybenzotriazole **2**) which was filtered off. The aq filtrate was extracted with 3 portions of $CH_2Cl_2$ and the combined organic extracts were dried ($Na_2SO_4$) and concentrated in vacuo to afford either

*N*-acetyl-3-ethoxycarbonyl tetramic acid **4**–**6** as a solid, or an oily product. This oily product, a mixture of the C-acylation compound **A** and of diethyl malonate **3**, was stirred in a solution of sodium ethoxide in absolute EtOH (prepared by addition of 12 mmol of sodium in absolute EtOH) at r.t. for 24 h. The resulting solution was concentrated in vacuo and the resulting gummy solid was diluted with water and washed with diethyl ether. The aq extract was acidified with 10% HCl to afford *N*-H-3-ethoxycarbonyl tetramic acid **7**–**9** as a white solid.

(18) Compound spectroscopic and analytical data:

***N*-Acetyl-3-ethoxycarbonyl-5-(*S*)-benzyl pyrrolidine-2,4-dione (4)**: 43% yield, mp 101–103 °C; IR (KBr) 1737, 1688, 1665, 1614 (C=O) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ (ppm) 1.33 (t, $J$ = 7.1 Hz, 3 H, $COOCH_2CH_3$), 2.52 (s, 3 H, $COCH_3$), 3.26 (dd, $J_1$ = 2.5 Hz, $J_2$ = 14.0 Hz, 1 H, $PhCH_2$), 3.60 (dd, $J_1$ = 6.2 Hz, $J_2$ = 14.0 Hz, 1 H, $PhCH_2$), 4.32 (m, 2 H, $COOCH_2CH_3$), 4.97 (dd, $J_1$ = 2.5 Hz, $J_2$ = 6.2 Hz, 1 H, CH), 6.97–7.01 (m, 2 H, phenyl protons), 7.20–7.26 (m, 3 H, phenyl protons); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ (ppm) 14.0 (C-8), 25.5 (C-10), 34.4 ($PhCH_2$), 58.6 (C-5), 62.0 (C-7), 99.3 (C-3), 127.7, 128.7, 129.7, 133.6 (phenyl carbons), 164.4 (C-9), 167.2 (C-2), 170.7 (C-6), 188.0 (C-4); Anal. calcd for $C_{16}H_{17}NO_5$: C, 63.37; H, 5.61; N, 4.62. Found: C, 63.04; H, 5.61; N, 4.83.

***N*-Acetyl-3-ethoxycarbonyl-5-(*S*)-isobutyl pyrrolidine-2,4-dione (5)**: 75% yield, mp 67–68 °C; IR (KBr) 1746, 1713, 1687, 1599 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ (ppm) 0.90, 0.96 (2d, $J$ = 6.2 Hz, 6 H, 2 × $CH_3$), 1.41 (t, $J$ = 7.0 Hz, 3 H, $COOCH_2CH_3$), 1.82–1.93 [m, 3 H, $(CH_3)_2CHCH_2$], 2.54 (s, 3 H, $COCH_3$), 4.41 (q, $J$ = 7.2 Hz, 2 H, $COOCH_2CH_3$), 4.73–4.76 (m, 1 H, CH); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ (ppm)14.1 (C-8), 22.4, 23.5, 24.3 [$(CH_3)_2CHCH_2$], 25.5 (C-10), 39.0 [$(CH_3)_2CHCH_2$], 57.2 (C-5), 62.1 (C-7), 98.2 (C-3), 164.4 (C-9)167.6 (C-2), 170.3 (C-6), 190.5 (C-4); Anal. calcd for $C_{13}H_{19}NO_5$: C, 57.99; H, 7.06; N, 5.20. Found: C, 57.78; H, 6.92; N, 5.34.

***N*-Acetyl-3-ethoxycarbonyl-5-(*S*)-methyl pyrrolidine-2,4-dione (6)**: 44% yield, mp 89–90 °C; IR (KBr) 1717, 1678, 1630, 1606 (C=O) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ (ppm) 1.41 (t, $J$ = 7.2 Hz, 3 H, $COOCH_2CH_3$), 1.57 (d, $J$ = 6.6 Hz, 3 H, $CH_3$), 2.54 (s, 3 H, $COCH_3$), 4.42 (q, $J$ = 7.2 Hz, 2 H, $COOCH_2CH_3$), 4.69 (q, $J$ = 6.6 Hz, 1 H, CH); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ (ppm)14.0 (C-8), 16.5 ($CH_3$), 25.3 (C-10), 54.2 (C-5), 61.9 (C-7), 100.0 (C-3), 164.3 (C-9), 167.3 (C-2), 170.2 (C-6), 190.0 (C-4); Anal. calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.73; N, 6.17. Found: C, 52.67; H, 5.61; N, 6.01.

**3-Ethoxycarbonyl-5-(*S*)-benzyl pyrrolidine-2,4-dione (7)**: 45% yield, mp 110–112 °C; IR (KBr) 3205 (NH), 1721, 1657, 1639 (C=O) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ (ppm) 1.39 (t, $J$ = 6.9 Hz, 3 H, $COOCH_2CH_3$), 2.70 (dd, $J_1$ = 9.6 Hz, $J_2$ = 13.5 Hz, 1 H, $PhCH_2$), 3.31 (dd, $J_1$ = 9.6 Hz, $J_2$ = 13.5 Hz, 1 H, $PhCH_2$), 4.31 (m, 1 H, CH), 4.40 (q, $J$ = 6.9 Hz, 2 H, $COOCH_2CH_3$), 5.60 (br s, 1 H, NH), 7.20–7.35 (m, 5 H, phenyl protons); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ (ppm) 14.1 (C-8), 38.0, 38.3 ($PhCH_2$), 58.4 (C-5), 61.6 (C-7), 98.0 (C-3), 127.5, 127.6, 129.0, 129.2, 129.2, 129.4, 135.3, 135.8 (phenyl carbons), 167.8 (C-2), 170.7 (C-6), 187.8 (C-4); Anal. calcd for $C_{14}H_{15}NO_4$: C, 64.37; H, 5.75; N, 5.36. Found: C, 63.99; H, 6.01; N, 5.54.

**3-Ethoxycarbonyl-5-(*S*)-isobutyl pyrrolidine-2,4-dione (8)**: 74% yield, mp 156–158 °C; IR (KBr) 3192 (NH), 1720, 1677, 1644 (C=O) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ (ppm) 0.97 (d, $J$ = 6.1 Hz, 6 H, 2 × $CH_3$), 1.38 (t, $J$ = 6.9 Hz, 3 H, $COOCH_2CH_3$), 1.43–1.50 [m, 1 H, $(CH_3)_2CHCH_2$], 1.69–1.84 [m, 2 H, $(CH_3)_2CHCH_2$], 4.16 (br d, $J$ = 6.0 Hz, 1 H, CH), 4.39 (q, $J$ = 6.9 Hz, 2 H, $COOCH_2CH_3$), 6.00 (br s, 1 H, NH); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ (ppm) 14.3 (C-8), 21.9, 23.3, 25.4 [$(CH_3)_2CHCH_2$], 41.0 ($(CH_3)_2CHCH_2$), 54.7 (C-5), 61.6 (C-7), 98.6 (C-3), 168.0 (C-2), 168.7 (C-6), 189.7 (C- 4); Anal. calcd for $C_{11}H_{17}NO_4$: C, 58.15; H, 7.49; N, 6.17. Found: C, 58.41; H, 7.65; N, 6.18.

**3-Ethoxycarbonyl-5-(*S*)-isopropyl pyrrolidine-2,4-dione (9)**: 59% yield, mp 132–133 °C; IR (KBr) 3175 (NH), 1707, 1660, 1618 (C=O) $cm^{-1}$; $^1H$ NMR (300 MHZ, $CDCl_3$) δ (ppm) 0.88 (d, $J$ = 6.9 Hz, 3 H, $CH_3$), 1.04 (d, $J$ = 6.9 Hz, 3 H, $CH_3$), 1.39 (t, $J$ = 7.1 Hz, 3 H, $COOCH_2CH_3$), 2.18–2.24 [m, 1 H, $(CH_3)_2CH$], 4.08 (d, $J$ = 2.4 Hz, 1 H, CH), 4.40 (q, $J$ = 7.1 Hz, 2 H, $COOCH_2CH_3$), 6.00 (br s, 1 H, NH); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ (ppm) 14.1 (C-8), 15.7, 18.8 [$(CH_3)_2CH$], 29.7 [$(CH_3)_2CH$], 41.4 (C-5), 61.2 (C-7), 99.4 (C-3), 167.8 (C-2), 169.1 (C-6), 188.5 (C-4); Anal. calcd for $C_{10}H_{15}NO_4$: C, 56.34; H, 7.04; N, 6.57. Found: C, 56.58; H, 7.00; N, 6.49.