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A Concise, Asymmetric Synthesis of Tetramic Acid Derivatives

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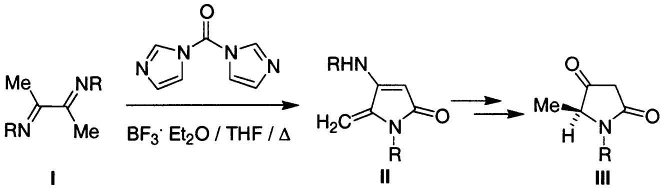
ABSTRACT



A simple, asymmetric synthesis of tetramic acid derivatives is described in this paper. The key step is a carbonyl transfer from carbonyldiimidazole (CDI) to α-diimines (I) to form *N*-alkyl-4-alkylamino-5-methylenepyrrol-2-ones (II). In turn, these compounds can be easily transformed into tetramic acid derivatives (III) in two additional steps.

CDI has been widely used in organic synthesis as a transfer reagent of both the imidazole ring and the carbonyl group.[1] One of the most frequent applications of CDI is as carbonylating agent in processes that imply formation of two carbon−heteroatom bonds.[2] In contrast, CDI has been used much less frequently in the formation of one or two carbon−carbon bonds. To the best of our knowledge, only four examples have been reported related to such processes.[3] In the most recent case,[3d] our research group was able to prepare *β*-enamino esters and thioesters through the reaction of ketimines with CDI, followed by reaction with an alkoxide. In this paper, we are reporting a novel carbonyl transfer from CDI to α-diimines that constitutes the key step for a synthesis of tetramic acid derivatives.

A number of natural products with a wide range of biological activities, which include antiviral, antitumoral, antibiotic, and antimicrobial activities, include the core structure of tetramic acid (**1**, pyrrolidin-2,4-dione). Some examples of these substances are tirandamycine (**2**), disidine (**3**), and magnesidine (**4**).[4]

Natural products that derive from tetramic acid and include an acyl group on C-3 are called 3-acyltetramic acids. Their biological activity is essentially due to the presence of the pyrrolidin-2,4-dione ring, the carbonyl group on C-3, and the stereocenter on C-5, together with the ability to form complexes with metallic ions.[5]

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[‡] X-ray analysis.

(1) (a) Staab, H. A. *Liebigs Ann. Chem.* **1957**, *609*, 75−83. (b) Staab, H. A. *Angew. Chem.* **1962**, *74*, 407−423; *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351−367. (c) Paul, R.; Anderson, G. W. *J. Am. Chem. Soc.* **1960**, *82*, 4596−4600. (d) Knölker, H. J.; El-Ahl, A. A. *Heterocycles* **1993**, *36*, 1381−1385. (e) Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72−74. (f) Armstrong, A. In *Encyclopedia of Reagents for Organic Synthesis*; Paquete, L. A., Ed.; Wiley & Sons: New York, 1995; Vol. 4, p 1006.

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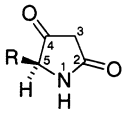
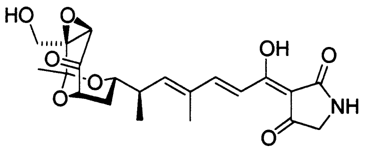
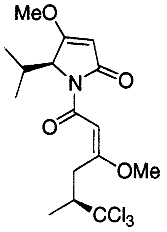

O
3
R
4
5
1
2
O
H
N
H

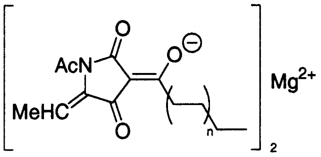
1


HO
O
O
O
O
OH
O
NH
O

2


MeO
N
O
O
OMe
CCl3

3

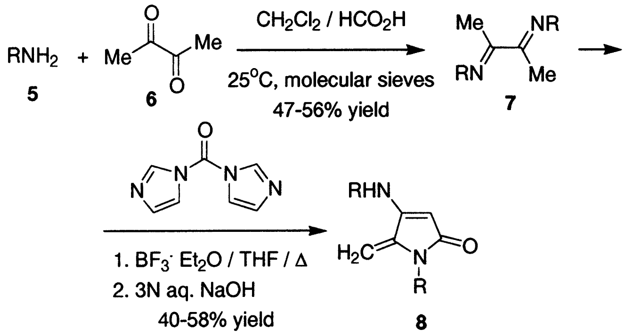

O
AcN
O⊖
Mg2+
MeHC
O
n
2

4

A variety of procedures using either standard solution[4] or solid-phase[6] chemistry have been used to prepare optically pure tetramic acid derivatives. In all of them a chiral α-amino acid source is a useful precursor to induce asymmetry.

Our synthesis of the tetramic acid derivatives begins with the double condensation of a primary amine (**5**) with butanedione (**6**) in dichloromethane at room temperature, in the presence of 98% formic acid and 4 Å molecular sieves.[7] After 7 days, the corresponding α-diimines **7** were obtained in 47−56% yield (Scheme 1).

Scheme 1


RNH2
+
Me
O
Me
O
5
6
CH2Cl2 / HCO2H
25°C, molecular sieves
47-56% yield
Me
NR
RN
Me
7
O
N
N
N
N
1. BF3·Et2O / THF / Δ
2. 3N aq. NaOH
40-58% yield
RHN
H2C
N
R
O
8

The second step consists of a carbonyl transfer from *N,N*′-carbonyldiimidazole (CDI) (2.0 equiv) in the presence of BF$_3$·OEt$_2$ (2,0 equiv)[3d] to the diimines **7a**−**d** (1.0 equiv) to give the cyclic derivatives **8a**−**d** in moderate yields (Scheme 1 and Table 1).

The achiral compound **8a** was obtained in 40% yield (entry 1, Table 1). However, we were mainly interested in exploring the possibility of an asymmetric synthesis through chiral induction of the R group in the subsequent steps. For that reason, a chiral substituent was also introduced (entries 2−4, Table 1) in compounds **7b**−**d** to yield **8b**−**d**. The formation of the condensation compounds **8** might be rationalized

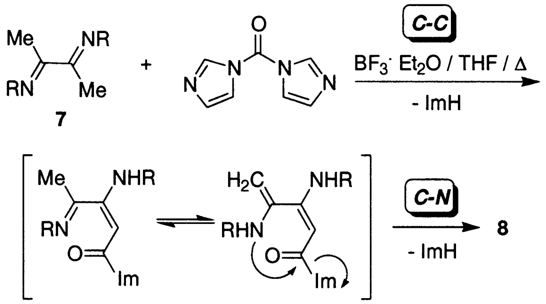
Table 1. Results for the Reaction between α-Diimines **7** and CDI

entry	α-diimine	R	product	yield (%)[a]
1	**7a**	*c*-C_6H_{11}	**8a**	40
2	**7b**	(±)-sec-Bu	**8b**	58
3	**7c**	*R*-(+)-C_6H_5(Me)CH	**8c**	47
4	**7d**	*S*-(−)-C_6H_5(Me)CH	**8d**	51

[a] Isolated yields.

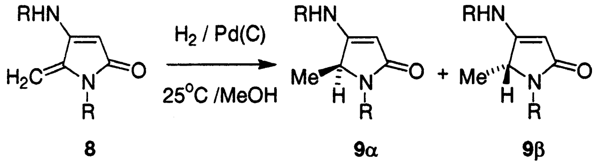
either through the formation of a C−C bond or a C−N bond as a first step. Although the acyclic intermediate has never been isolated, the results obtained in related reactions[3d,8] seem to point to the first hypothesis, as represented in Scheme 2.

Scheme 2


Me
NR
RN
Me
7
+
O
N
N
N
N
C-C
BF3·Et2O / THF / Δ
- ImH
Me
NHR
RN
O
Im
H2C
NHR
RHN
O
Im
C-N
- ImH
8

The preparation of the desired tetramic acid derivatives implies two steps: reduction of the exocyclic double bond and hydrolysis of the *N*-protected enamine to a carbonyl group. In principle, either of these two reactions could be done first. However, hydrolysis of the derivatives **8a**−**d** in aqueous acidic conditions yielded complex reaction mixtures, from which isolation of the desired products was not possible. In contrast, the alternative route (reduction followed by hydrolysis) was successful. Thus, catalytic hydrogenation of compounds **8a**−**d** in MeOH solution under atmospheric pressure with hydrogen and 10% Pd/C as catalyst at room temperature gave derivatives **9a**−**d** in good yields (Scheme 3 and Table 2).

Scheme 3


RHN
H2C
N
R
O
8
H2 / Pd(C)
25°C /MeOH
RHN
Me
H
N
R
O
9α
+
RHN
Me
H
N
R
O
9β

While for compound **8a** a single product was obtained (**9a**), in the case of **8b**−**d** a mixture of diastereomers resulted

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(6) (a) Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1998**, *63*, 4808−4810 and literature cited therein. (b) Romoff, T. T.; Ma, L.; Wang, Y.; Campbell, A. *Synlett* **1998**, *12*, 1341−1342.

Table 2. Results for the Reduction of Compounds **8**

entry	R	product	d.r. (α/β)	yield[a] (%)
1	*c*-C_6H_{11}	**9a**		84
2	(±)-sec-Bu	**9b**	16 (58:42)[b]	86
3	*R*-(+)-C_6H_5(Me)CH	**9c**	76 (12:88)[b]	84 (60)[c]
4	*S*-(−)-C_6H_5(Me)CH	**9d**	80 (90:10)[b]	98 (60)[c]

[a] Yield for the purified product or diastereomeric mixture. [b] Diastereomeric ratio as determined through ^{1}H NMR of the reaction crude. [c] The yield of the major reaction product after purification appears in parentheses.

(Table 2). As expected, the *sec*-butyl group in compound **8b** did not cause a significant asymmetric induction (only 16% d.e.). However, in enantiomers **8c** and **8d**, where R is the phenylethyl group in configurations *R* and *S*, respectively, the asymmetric induction worked well, yielding the mixture of diastereomers **9cα** + **9c*β***, and **9dα** + **9d*β*** with diastereomeric ratios of ca. 80%. The corresponding diastereomers were easily separated by means of column chromatography, and their structures secured through extensive spectroscopic analysis and X-ray crystallographic analysis of compound **9c*β***. As a result, the absolute configuration of **9c*β*** was shown to be (*R*,*R*,*R*)[9] (Figure 1).

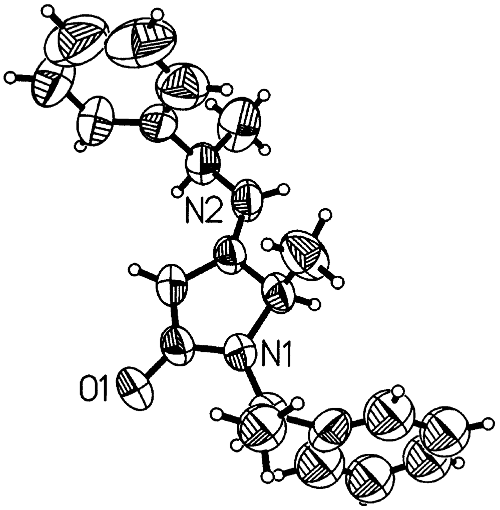
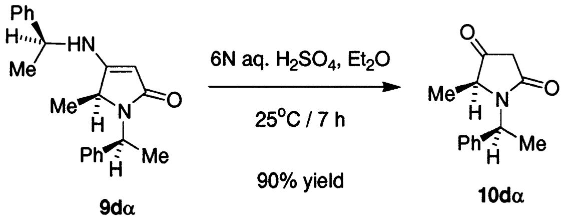


Figure 1. Thermal ellipsoid plot of (*R*,*R*,*R*)-**9c*β***.

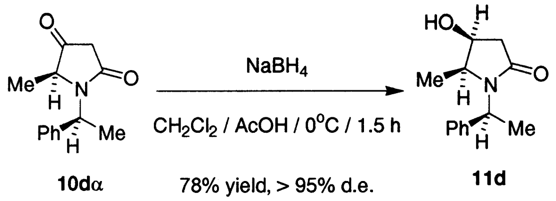
Finally, the preparation of compound **10dα** was achieved by means of treatment of a solution of compound **9dα** in diethyl ether[10] with aqueous 6 N H_2SO_4 at room temperature for 7 h. This procedure gave enantiomerically pure tetramic acid **10dα** in 90% yield (Scheme 4). This method would also allow the preparation of the enantiomer of this compound by simply using **9c*β*** instead of **9dα** as starting material for this reaction.

Scheme 4



Aside from their own interest, chiral *N*-protected tetramic acid derivatives are important precursors of *β*-hydroxy-*γ*-amino acids, which in turn constitute useful building blocks in the synthesis of different classes of biologically active molecules.[11] Thus, compound **11d** was easily prepared in 78% yield and diastereomeric excess of >95% (Scheme 5) when a CH_2Cl_2:AcOH (9:1) solution of **10dα** was treated with 2.0 equiv of $NaBH_4$ at 0 °C for 1.5 h. The structure of **11d** was ascertained by means of spectroscopic analysis and agreed with the results of NOE experiments. These results coincided with others previously reported for the reduction of chiral tetramic acid derivatives.[11a]

Scheme 5



In summary, we have presented a simple, asymmetric synthesis of tetramic acid derivatives that can easily furnish both enantiomers in only four steps from easily available, inexpensive materials and in which the key step is a carbonyl transfer from CDI to an α-ketodiimine.

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(7) Dieck, H. T.; Dietrich, J. *Chem. Ber.* **1984**, *117*, 694−701.

(8) García de la Torre, M. Ph.D. Dissertation, Universidad de Valencia, Burjassot (Valencia), Spain, 1999.

(9) Crystal data for **9c***β*: $C_{21}H_{24}N_2O$; crystals from *n*-hexane/$CHCl_3$ (1:1). Colorless block of dimensions 0.62 × 0.46 × 0.42 mm^3 size, monoclinic, $P2_1$, $a = 8.656(1)$ Å, $b = 6.843(1)$ Å, $c = 16.820(2)$ Å, $\beta = 93.19(1)°$, $V = 994.8(2)$ Å^3, $Z = 2$, $D_c = 1.070$ g cm^{-3}, $2\theta_{max} = 55°$, diffractometer Siemens P4, Mo Kα $\lambda = 0.71073$ Å, ω-scan, $T = 291(2)$ K, 9000 reflections collected of which 4525 were independent ($R_{int} = 0.087$), direct primary solution and refinement on F^2 (SHELXL-97, G. M. Sheldrick, University of Göttingen, 1997), 208 refined parameters, amino hydrogen atom located in a difference Fourier synthesis and refined with restrained N−H bond length, other hydrogen atoms riding, R1[$I > 2\sigma(I)$] = 0.0608, wR2(all data) = 0.2382, residual electron density 0.158 (−0.196) eÅ^{-3}, both the C9 methyl group and the C21−C26 phenyl group are disordered over two sites, absolute structure could not be determined.

(10) Interestingly, when THF was used as solvent, the reaction gave only ill-defined products, and the desired product **10dα** was not detected.

(11) See, for example: (a) Galeotti, N.; Poncet, J.; Chiche, L.; Jouin, P. *J. Org. Chem.* **1993**, *58*, 5370−5376. (b) Palomo, C.; Cossio, F.; Rubiales, G.; Aparicio, D. *Tetrahedron Lett.* **1991**, *32*, 3115−3118. (c) Ma, D.; Ma, J.; Ding, W.; Dai, L. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2365−2370. (d) Bänziger, M.; McGarrity, J. F.; Meul, T. *J. Org. Chem.* **1993**, *58*, 4010−4012.

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Supporting Information Available: Spectroscopic data, experimental details for **8**, **9**, **10**, and **11** and crystal data for compound **9c*β*** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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