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First Asymmetric Synthesis of (-)-(2*S*, 3*R*)-Methanoproline

Alain Hercouet*, Bernard Bessières and Maurice Le Corre.

Laboratoire de Synthèse Organique, Associé au CNRS. Université de Rennes I.
Avenue du Général Leclerc, 35042 Rennes Cedex, France.

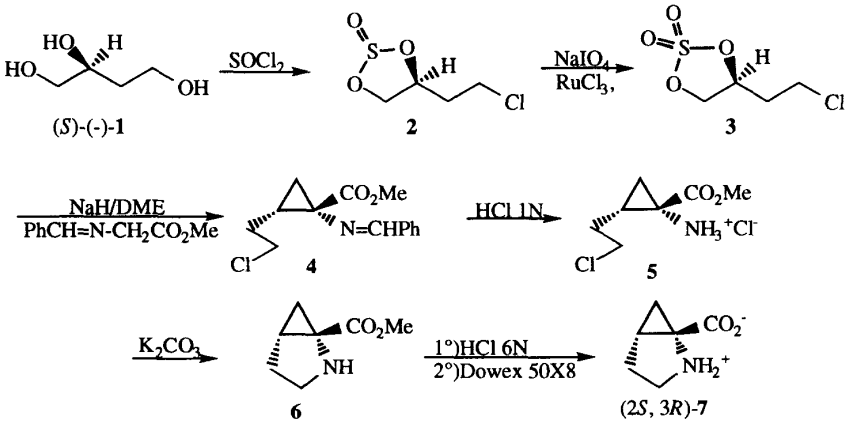
Abstract: The title amino acid was synthesized in enantiomerically pure form, starting from (*S*)-(-)-butanetriol **1**, by condensation of cyclic sulfate **3** with methyl benzylideneglycinate. Copyright © 1996 Elsevier Science Ltd

The potential value of 2,3-methanoaminoacids as enzyme inhibitors or in the synthesis of conformationally constrained peptidomimetics was recognized some years ago[1]. During the course of our studies toward the synthesis of cyclopropane aminoacids[2,3], we recently reported the synthesis of (-)-(1*S*, 2*R*)-allonorcoronamic acid using a chiral cyclic sulfate as precursor[3].

We now wish to report the first asymmetric synthesis of (-)-(2*S*, 3*R*)-methanoproline **7**, a known ethylene biosynthesis inhibitor which has already been prepared by Stammer[4] in the racemic form, and then resolved a few years later[5].

Thus (*S*)-(-)-butanetriol[6] **1** was converted to chlorosulfite **2**[7] which was purified by flash chromatography (Scheme 1). The following oxidation, using the Sharpless procedure[8], gave sulfate **3**.

Scheme 1



Condensation of this sulfate on methyl benzylideneglycinate[9], at room temperature in DME in the presence of two equivalents of sodium hydride, was achieved following the procedure recently reported[3], to give the alkylated imine **4** in quantitative yield. This reaction is diastereospecific, only the Z isomer is obtained.

Hydrolysis of the amino protective group by 1 N HCl gave the hydrochloride **5**[10] in 80% yield, that cyclized to the desired aminoester **6** when treated with K_2CO_3. Hydrolysis of the ester group was realized by refluxing in 6 N HCl. The aminoacid zwitterion **7**[11] was then quantitatively obtained using Dowex 50X8. This new synthesis can be perform on a multigram scale with 43% overall yield from **2** and without purification of intermediates.

Spectral data and specific rotation of aminoacid **7** are in accordance with those obtained by Stammer[5].

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7. 4-chloroethyl-2-oxo-1,3,2-dioxathiolane **2**. $SOCl_2$ (21.3 mL, 300 mmol) is added dropwise to a solution of **1** (10.61 g, 100 mmol) in CCl_4 (100 mL) and the solution is refluxed for 3h. The solvent is evaporated and the resulting oil is chromatographied over SiO_2, eluting with Et_2O to yield the two diastereomers (50:50) of **2** (11.76 g, 69 mmol, 69%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.06-2.48 (m, 4H); 3.65- 3.76 (m, 4H); 4.05-4.07 (m, 1H), 4.38-4.44 (m, 1H), 4.53-4.58 (m, 1H); 4.76-4.81 (m, 2H) and 5.12-5.21 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 35.45 and 36.61; 40.25 and 40.77; 70.43 and 71.26; 77.48 and 80.42.
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10. NMR of crude **5** : ^1H (300 MHz, $CDCl_3$) δ 1.62-1.74 (m, 2H), 1.98-2.05 (m, 1H), 2.19-2.26 (m, 1H), 2.41-2.46 (m, 1H), 3.67-3.82 (m, 2H), 3.78 (s, 3H) and 9.14 (br s, 3H). ^{13}C (75.5 MHz, $CDCl_3$) δ 19.26, 24.19, 30.03, 38.40, 44.05, 53.38 and 169.73.
11. (-)-(2*S*, 3*R*)-Methanoproline **7** : M.p. 217°C (dec) (Litt.[5] M.p. 215°C (dec)), $[\alpha]_D^{20}$ -51.2 (c 1, MeOH) (Litt.[5] $[\alpha]_D^{20}$ -48.2 (c 1, MeOH). ^1H NMR (300 MHz, D_2O) δ 1.27-1.31 (m, 1H), 1.44-1.49 (m, 1H), 2.03-2.21 (m, 3H), 2.86-2.91 (m, 1H) and 3.39-3.46 (m, 1H). ^{13}C NMR (75.5 MHz, D_2O) δ 15.57, 27.28, 27.31, 45.40, 51.16 and 176.81.

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