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Expedient Synthesis of (-)-(1*S*, 2*R*)-Allonorcoronamic Acid

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Abstract: The title amino acid was synthesized in enantiomerically pure form, starting from (*S*)-(+)-1,2-propanediol **2** in three steps, by condensation of cyclic sulfate **3** with methyl benzylideneglycinate.

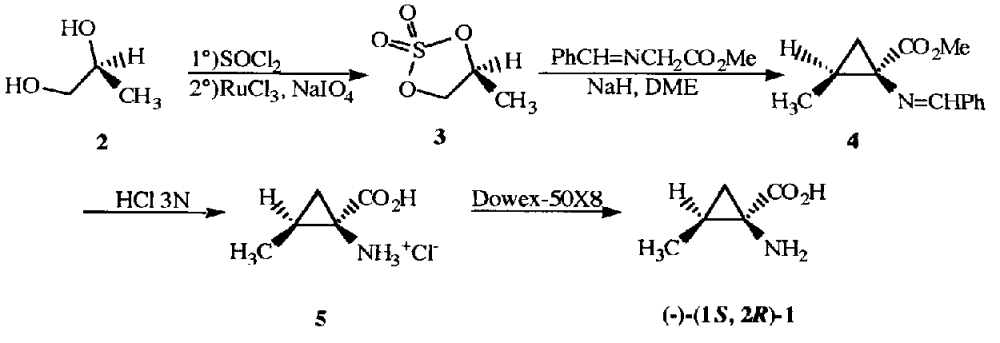
1-Aminocyclopropanecarboxylic acids (ACC derivatives) constitute an important class of nonproteinogenic amino acids because of their conformationally constrained structure, providing them particularly interesting biological properties.[1] Nevertheless, the lack of convenient access to easily available optically pure precursors explain that research progress has been limited. In this area, Cativiela and *al.*[2] reported recently the synthesis of allonorcoronamic acid **1**, the strongest known inhibitor of the ethylene forming enzyme in some plants[3], using *D*-mannitol as chiral source.

We now report a new and expedient synthesis of allonorcoronamic acid **1**, one that can provide multigram quantities of enantiomerically pure material (Scheme 1).

The synthesis of cyclic sulfate **3**[4] from (*S*)-(+)-1,2-propanediol **2** was achieved by the one pot procedure reported by Scharpless and Gao[5] in 95% overall yield.

The next step involved the condensation of **3** with methyl benzylideneglycinate in DME at 50°C in the presence of two equivalents of sodium hydride, to give the alkylated imine **4** in nearly quantitative yield. This reaction is diastereospecific and give the Z isomer, no trace of the E isomer was observed in the crude product.

Scheme 1



2 **3** **4**

5 **(-)-(1*S*, 2*R*)-1**

After hydrolysis with 3N HCl, the amino acid hydrochloride **5** was obtained in 70% from diol **2**. The amino acid **1** was then obtained quantitatively using Dowex-50X8.

No chromatography was required for any of the steps shown in Scheme 1, the amino acid hydrochloride **5** was purified by washing the crystalline product with acetone. To the best of our knowledge, this synthesis constitute the first example of a cyclisation between cyclic sulfate and glycinate anion. The generalisation of this procedure to other α-amino acids is in progress in our laboratory.

EXPERIMENTAL

Apparatus and chemicals: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker AC 300 spectrometer, in deuteriochloroform or deuterium oxide, using the solvent signal as internal reference. Chemicals shifts are expressed in ppm. Optical rotations were recorded on a Perkin Elmer 241 MC polarimeter at 20°C. Melting points were determined on a Kofler hot stage apparatus. DME was distilled over NaH prior to use, (*S*)-(+)-1,2-propanediol was obtain from Acros Organics. Methyl benzylideneglycinate was prepared according to the literature procedure.[6]

4-methyl-2,2-dioxo-1,3,2-dioxathiolane 3

Cyclic sulfate **3** was prepared in 95% yield according to the described procedure.[5]

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (d, J = 6.3 Hz, 3H), 4.24-4.30 (m, 1H), 4.68-4.73 (m, 1H), 5.04-5.15 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.6, 74.3, 80.1.

Alkylation Procedure

A 250 mL three-necked round bottomed flask equipped with reflux condenser, $CaCl_2$ drying tube, nitrogen inlet and rubber septum was charged with NaH (63 mmol, 2.52 g of a 60% suspension in mineral oil) and dry DME (100 mL). Cyclic sulfate **3** (30 mmol, 4.14 g) and methyl benzylideneglycinate (30 mmol, 5.31 g) in dry DME (50 mL) were added in one portion via syringe. The resulting mixture was stirred at 25 °C for 1h and heated at 50°C for 4h. The reaction mixture was cooled, poured in saturated NH_4Cl and chloroform (90 mL) was added. The two phases were separated, the aqueous layer extracted with chloroform (90mL), the organic layer dried over $MgSO_4$, and the solvents evaporated to give the crude alkylated imine **4** in nearly quantitative yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78-0.92 (m, 1H), 1.07 (d, J = 6.2 Hz, 3H), 1;64-1.74 (m, 1H), 1.88-2.00 (m, 1H), 3;71 (s, 3H), 7.40-7.44 (m, 3H), 7.78-7.82 (m, 2H), 8.45 (s, 1H).

(-)-(1*S*, 2*R*)-Allonorcoronamic Acid 1.

The crude imine **4** (29.7 mmol, 6.45 g) was heated at 100 °C with 3N HCl (30 mL) overnight. The aqueous layer was washed with ethyl acetate (3 x 30 mL) and evaporated. The resulting crystalline product was washed with acetone (2 x 20 mL) and dried under vacum to give hydrochloride **5** (22.2 mmol, 3.36 g, 74%)). ^{1}H NMR (300 MHz, D_2O) δ 1.12 (dd, J = 6.4 Hz, J = 7.8 Hz, 1H), 1.22 (d, J = 6.4 Hz, 3H), 1.68 (dd, J = 6.4 Hz, J = 9.9 Hz, 1H), 1.82-1.88 (m, 1H). ^{13}C NMR (75.5 MHz, D_2O) δ 13.7, 22.8, 23.1, 40.6, 175.8.

The amino acid hydrochloride **5** was stirred with an aqueous suspension of Dowex-50X8, filtered, and the solid washed with water until total removing of Cl^-. After a second washing with 2M NH_4OH and evaporation, zwitterion **1** was obtained in quantitative yield. M.p. 270°C (dec) (Lit.[2] M.p. 215°C (dec)), $[\alpha]_D^{20}$ = -74 (c = 0.3, H_2O) (Lit.[7] $[\alpha]_D^{20}$ = -69 (c= 0.3 , H_2O), ^{1}H NMR (300 MHz, D_2O) δ 0.82-0.86 (m, 1H), 1.16 (d, J = 6.5 Hz, 3H), 1.43 (dd, J = 5.9 Hz, J = 9.6 Hz, 1H), 1.58-1.63 (m, 1H). ^{13}C NMR (75.5 MHz, D_2O) δ 14.2, 20.9 , 21.6, 42.3, 178.7.

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