D-β-Chlorolactic Acid: A Chemical Synthesis

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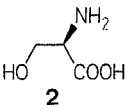
Nitrous deamination of serine-derived β-chloroalanine proceeds without significant racemization, thus opening a chemical route to optically active β-chlorolactic acid.

β-Chlorolactic acid is a useful building block,[1-5] especially since it belongs to the rather restricted group of 3-carbon chirons incorporating three different functionalities.[6-8] Quite recently, efficient laboratory-scale enzymatic preparations of optically active **1** (or its enantiomer) were disclosed;[9-11] as an alternate possibility, a chemical route to pure **1**, and hence to glycidic acid,[9] applicable to both enantiomeric forms is now presented.

Commercially available D-serine **2** appeared to be the starting material of choice. However, it has been shown that, despite some recent improvements,[12,13] nitrous deamination of serine itself does not yield an optically pure glyceric acid, due to some racemization[14] in this critical step. Therefore, modification in this approach were necessary if **2** was still to be considered as a viable source.



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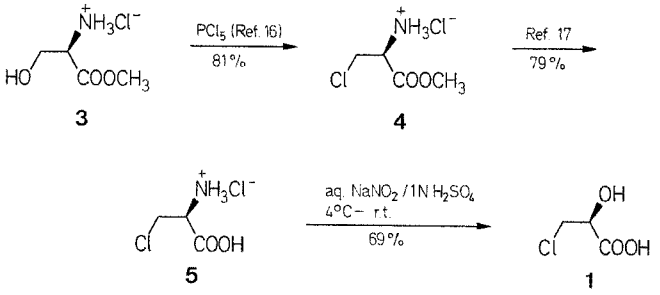
Thus, D-serine methyl ester hydrochloride **3**[15] was converted to the corresponding chloro derivative by literature methods, namely chlorination with phosphorus pentachloride to obtain **4**,[16] followed by hydrolysis to **5**.[17] Some necessary improvements in the purification of **4** and **5** are described in the experimental section because it turned out that back conversion of **5** to **4** occurred easily during its isolation when traces of acid were present, and because it was found necessary to avoid contamination of **5** with the intermediate ester **4**, since the latter does not undergo deamination with full retention of configuration.

With regard to the key deamination step, it was found that sulfuric acid was superior to acetic acid[18] as the reaction medium. However, when following similar literature procedures,[19,20] a number of factors had to be observed to obtain maximum yield. Thus, temperature, addition time of the nitrite, molar ratio of the reactants, stirring time and, last but not least, molarity of the reaction mixture proved critical. The best conditions found were a 12-h addition time of a dilute sodium nitrite solution to a 1 normal aqueous sulfuric acid solution of **5**, at 4 °C, followed by overnight stirring at room temperature. This resulted in a 69% isolated yield of crystalline **1** of excellent optical purity. That no significant racemization had occurred was revealed by comparison of the observed optical rotation (−4.3°) with the literature value[9] (−3.97°),[21] optical purity having been demonstrated in the latter case.



3 **4** **5** **1**

Melting points were obtained with a Kofler hot plate or Reichert microscope. Optical rotations were determined using a Perkin Elmer 141 polarimeter. IR spectra were obtained with a Perkin-Elmer 157 G spectrophotometer. NMR spectra were recorded on a Bruker WP-80 spectrometer:

D-β-Chloroalanine Methyl Ester Hydrochloride (4):
Following the literature procedure,[16] D-serine methyl ester hydrochloride[15] (9 g, 57.35 mmol) is converted into **4** in 81% yield with the following modification: at the end of the reaction, the precipitate is washed once with chloroform (75 ml), then abundantly with cyclohexane until no "acid smell" could be noted.

The crude product is recrystallized from dry methanol (distilled from magnesium and stored over 3 A molecular sieves) and ether (stored over 4 A molecular sieves) in a 1 to 3 ratio (ca. 80 ml).
M.p. = 149–152 °C (dec.) (Lit.[25] m.p. 153 °C).

IR (KBr): ν = 3000–2800 (br NH_3^+), 1745 cm^{-1} (CO).

^{1}H-NMR (DMSO-d_6): δ = 3.81 (s, 3 H, CH_3); 4.17 (d, 2 H, J = 3.4 Hz, CH_2); 4.70 (t, 1 H, J = 3.4 Hz, CH); 9.1 ppm (br, NH_3^+).

D-β-Chloroalanine Hydrochloride (5):
Compound **5** is obtained from **4** (1.2 g, 6.9 mmol), following Ref. 17, in 79% yield with the following modification: after completion of the reaction and evaporation, the residue is dissolved in the minimum amount of water and toluene is added. Coevaporation of these solvents

is performed, and this procedure is repeated twice. The residue is dissolved in 2-propanol (2 × 10 ml), filtered and concentrated to ca. 7 ml. Ether (30 ml) is added slowly, and after standing at 4 °C, crystallization occurred. M.p.: 168–171 °C (dec.) (Lit. m.p. 170 °C,[17] 172–4 °C (dec.)[16]).

IR (KBr): ν = 2970–2850 (NH_3^+); 1740 cm^{-1} (CO).

^{1}H-NMR (DMSO-d_6): δ = 4.13 (d, 2H, J = 3.4 Hz, CH_2); 4.49 (t, 1H, J = 3.4 Hz, CH); 8.8 ppm (very br, NH_3^+).

D-β-Chlorolactic Acid (1):

The preceding amino acid (**5**; 28.58 g, 178.8 mmol) is dissolved in ca. 1 normal aqueous sulfuric acid (30 g of conc. sulfuric acid in 570 ml of water, 0.3 mol), and this solution is stirred at 4 °C. A freshly prepared solution of sodium nitrite (39.00 g, 565.2 mmol) in water (600 ml) is SLOWLY added, dropwise, over a 12-h period, the temperature being maintained at 4 °C. Then, after stirring overnight at room temperature, solid sodium hydrogen carbonate is added in order to bring the pH above 2. The solution is then concentrated under vacuum (without heat) to ca. 200 ml). The now colorless solution is saturated with sodium chloride and extracted with ethyl acetate (6 × 200 ml), maintaining (1 normal sulfuric acid, pH meter) the pH between 2 and 3. After drying with sodium sulfate, the organic layer is evaporated, and the crude product (over 20 g) is dissolved in benzene (100 ml). Toluene (10 ml) is added, and the solution placed at 4 °C. White crystals are isolated from two batches (12.56 g and 2.86 g) to give pure **1**; yield: 15.42 g (69%); m.p. 88 °C (Lit.[5] m.p. 88–9 °C); $[\alpha]^7_D$: −4.3° (c = 9.0, H_2O) [Lit.[9,21] $[\alpha]_D$: 3.97°, 4.14° (c = 9.05, H_2O].

IR (KBr): ν = 3440 (OH), 1715 cm^{-1} (CO).

^{1}H-NMR (acetone-d_6): δ = 3.85 (d, 2H, J = 4.1 Hz, CH_2); 4.5 (t, 1H, J = 4.1 Hz, CH); 5.3 (br, 2H, exchangeable OH's).

This investigation received financial support from the International Organization for Chemical Sciences in Development (IOCD),[22–24] which is gratefully acknowledged. Prof. J. Fried (University of Chicago) is thanked as well for suggesting this approach.

Received: 8 September 1986
(Revised form: 28 October 1986)

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