SUPPLEMENTARY MATERIAL

One-pot diastereoselective synthesis of chiral tricyclic L-cysteine and D-penicillamine derivatives: a laboratory experiment

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GENERAL INFORMATION

$^1$H NMR spectra were recorded on an instrument operating at 400 MHz. $^{13}$C NMR spectra were recorded on an instrument operating at 100 MHz. The solvent was deuterochloroform. TMS was used as the internal standard, chemical shifts are given in ppm and coupling constants ($J$) are in Hz. Infrared spectra (IR) were recorded on a Fourier transform spectrometer. Melting points were determined in open glass capillaries and are uncorrected. Optical rotations were measured on an Optical Activity AA-5 electrical polarimeter. Thin-layer chromatography (TLC) was performed using precoated silica gel plates. L-Cysteine, D-penicillamine, 2,5-dimethoxymethyltetrahydrofuran and deuterochloroform are commercially available in Aldrich and Alfa Aesar and have been used without further purification. HCl (aqueous solution, 35%), sodium chloride and sodium sulfate anhydrous were used as received. All organic solvents were dried and distilled before use.

HAZARDS AND SAFETY INFORMATION

Students should use protective clothing, gloves and safety glasses, and perform all the manipulations in a fume-hood. L-cysteine and D-penicillamine are harmful if swallowed. D-penicillamine may cause skin, eye and respiratory irritations. 2,5-Dimethoxymethyltetrahydrofuran is a flammable liquid. It causes skin and eye irritation and is harmful if inhaled. Dichloromethane, diethyl ether, ethyl acetate and hexane are harmful if swallowed or inhaled. Diethyl ether, ethyl acetate and hexane are flammable liquids. Dichloromethane may cause eye and skin irritation. Ethyl acetate causes eye irritation and hexane is a neurotoxin that is irritant in case of skin contact. Hydrochloric acid causes skin burns, eye damage and may cause respiratory irritation. Deuterated chloroform is harmful if swallowed and causes skin and eye irritation. Prolonged exposure may cause cancer and damage to organs. Sodium chloride and sodium sulfate may cause eye irritation. Organic solvents waste should be disposed in appropriate waste collector containers. Neutralized aqueous solutions may be diluted and discarded in the sink. According to our experience, the tricyclic compounds 5 and 9 are harmless under standard safety laboratory manipulation conditions.
EXPERIMENTAL PROCEDURES

(2aS,4aR,6aR)-2a,3,4,4a,6,6a-Hexahydropyrrolo-[1’,2’,5’:3,4,5]thiazolo[3,4-c]oxazol-1-one (5)

First session
In a 100 mL round bottom flask equipped with a magnetic stirring bar and a condenser, a mixture of 2,5-dimethoxytetrahydrofuran (0.33 mL, 2.55 mmol) and HCl aqueous solution (0.1 mol L⁻¹, 10 mL) was heated at 100 °C for 45 min. After this time, the solution was allowed to cool to room temperature and dichloromethane (20 mL) and L-cysteine (0.303 g, 2.5 mmol) were successively added. The reaction mixture was stirred at room temperature for 24 h, under vigorous stirring (Note 1).

Second session
Water (10 mL) was added to the reaction mixture and the organic phase was separated. The aqueous phase was extracted with dichloromethane (3 x 20 mL) and the combined organic extracts were washed with brine (2 x 20 mL). After being dried over anhydrous Na₂SO₄, the organic solvent was evaporated off. Compound 5 was obtained as a white solid.
Figure 1S. TLC of compound 5, using ethyl acetate/hexane (1:1) as eluent and iodine vapors to reveal the spot

Characterization: R_t = 0.38 [ethyl acetate/hexane (1:1)]. m.p. 99.3-100.2 °C (from ethyl acetate/hexane); IR (ATR) ν 833, 1194, 1351 and 1762 cm⁻¹. ^1H NMR (CDCl₃) δH: 2.18-2.31 (m, 2H, H-4), 2.38-2.48 (m, 2H, H-3), 3.43 (dd, 1H, J = 6.1 and 12.2 Hz, H-6), 3.53 (pseudo-d, 1H, J = 12.2 Hz, H-6), 4.10 (pseudo-d, 1H, J = 6.1 Hz, H-6a), 4.92 (dd, 1H, J = 4.0 and 8.0 Hz, H-4a), 5.53 (dd, 1H, J = 5.0 and 5.2 Hz, H-2a). ^13C NMR (CDCl₃) δC: 27.4, 31.6, 39.3, 67.2, 75.0, 98.5, 175.7. HMRS (Cl): calcd. for C₇H₁₀NO₂S, 172.0432 [M+H⁺]; found, 172.0430. [α]_D²⁵ = +30 (c = 1.0, CH₂Cl₂).

(2aR,4aS,6aS)-6,6-Dimethyl-2a,3,4,4a,6,6a-hexahydropyrrolo[1’’,2’,5’:3,4,5]thiazolo[3,4-c]oxazol-1-one (9)

*First session*

In a 100 mL round bottom flask equipped with a magnetic stirring bar and a condenser, a mixture of 2,5-dimethoxytetrahydrofuran (0.33 mL, 2.55 mmol) and HCl aqueous solution (0.1 mol L⁻¹, 10 mL) was heated at 100 °C for 45 min. After this time, the solution was allowed to cool to room temperature and dichloromethane (20 mL) and 0-
penicillamine (0.373 g, 2.5 mmol) were successively added. The reaction mixture was stirred at room temperature for 24 h, under vigorous stirring (Note 1).

Second session

Water (10 mL) was added to the reaction mixture and the organic phase was separated. The aqueous phase was extracted with dichloromethane (3 x 20 mL) and the combined organic extracts were washed with brine (2 x 20 mL). After been dried over anhydrous Na₂SO₄, the organic solvent was evaporated off. Compound 9 was obtained as a beige solid (Note 2).

![Figure 2S. TLC of compound 9, using ethyl acetate/hexane (1:1) as eluent and iodine vapors to reveal the spot](image)

Characterization: Rᵣ = 0.53 [ethyl acetate/hexane (1:1)]. m.p. 43.2-44.5 °C (from ethyl acetate/hexane). IR (ATR) ν 1138, 1185 and 1768 cm⁻¹. ¹H NMR (CDCl₃) δH: 1.65 (s, 3H, H-7), 1.68 (s, 3H, H-8), 2.15-2.21 (m, 1H), 2.31-2.50 (m, 3H), 3.59 (s, 1H, H-6a), 5.10-5.13 (m, 1H, H-4a), 5.47 (dd, 1H, J = 2.0 and 4.0 Hz, H-2a). ¹³C NMR (CDCl₃) δC: 22.5, 29.1, 32.1, 32.5, 59.5, 71.9, 74.3, 97.7, 173.6. HMRS (Cl+): calcd. for C₉H₁₄NO₂S, 200.0745 [M+H⁺]; found, 200.0747. [α]D²⁵ = −75 (c = 1.0, CH₂Cl₂).

Note 1. Since the reaction of the unprotected succindialdehyde with the amino acids is carried out using a biphasic solvent system it is crucial to have a vigorous stirring. After 24 h stirring, the reaction mixtures are stored in the freezer until the next session and removed 2 h before the beginning of the second class.
Note 2. In the experimental procedures, ethyl acetate may be used as an alternative to dichloromethane.

Note 3. Due to the low melting point of compound 9, it can be obtained as an oil. However, upon addition of diethyl ether the oil becomes a white solid.

OPTICAL ACTIVITY MEASUREMENTS

For the optical activity measurements a solution of compounds 5 or 9 (20 mg) in 2 mL of dichloromethane was prepared using a volumetric flask (Figure 3S A). The solution must be perfectly clear and free of suspended particles otherwise the dispersion of the polarimeter beam will prevent an accurate reading. This solution was transferred to the polarimeter cell until it was completely filled. It is important to avoid any air bubbles (Figure 3S B).

The specific rotation of the sample was calculated by the following formula:

$$[\alpha]_D^2 = \frac{\alpha}{c.l} \times 100$$

where $\alpha$ is the observed angle (Figure 3S C), $c$ is the concentration of the solution (g/100 mL) and $l$ is the length of the polarimeter sample cell (dm).

**Figure 3S.** Automatic polarimeter. A) Volumetric flak; B) Polarimeter cell; C) Display with the observed angle ($\alpha$)
Figure 4S. $^1$H NMR spectrum of compound 5 (400 MHz, CDCl$_3$)

Figure 5S. $^{13}$C NMR spectrum of compound 5 (100 MHz, CDCl$_3$)
Figure 6S. COSY spectrum of compound 5 (400 MHz, CDCl₃)

Figure 7S. Infrared spectrum of compound 5 (ATR)
Figure 8S. $^1$H NMR spectrum of compound 9 (400 MHz, CDCl$_3$)

Figure 9S. $^{13}$C NMR spectrum of compound 9 (100 MHz, CDCl$_3$)
**Figure 10S.** COSY spectrum of compound 9 (400 MHz, CDCl₃)

**Figure 11S.** Infrared spectrum of compound 9 (ATR)
STUDENT REPORT

The report should be written like a scientific paper with a title, abstract, introduction, discussion of results, conclusion, experimental and references. A template from a journal of organic chemistry (e.g. J. Org. Chem.) is given (downloaded) as guide.

HINTS FOR STUDENTS’ DISCUSSION

1. Explain why it is necessary to reflux 2,5-dimethoxytetrahydrofuran in a HCl aqueous solution as the first step of the experimental procedure.
2. Carry out the spectral analysis using the data provided for compounds 5 and 9.
3. Discuss the mechanism involved in the formation of the tricyclic compounds.
4. Comment on the stereoselectivity outcome of the reaction of L-cysteine and D-penicillamine derived thiazolidines leading to the corresponding iminium cation intermediates.
5. Discuss the mechanism of the synthesis of tetrahydro-thiazolo[2,3-b]isoindole 2 outlined in Scheme 2.