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SYNTHESIS OF 2-(5-HYDROXYMETHYL-2-FORMYLPYRROL-1-YL)PROPIONIC ACID LACTONE

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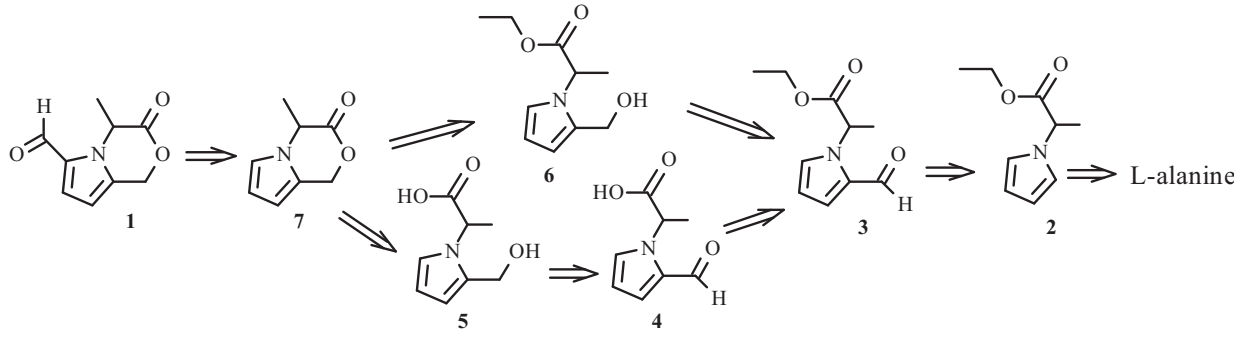
2-(5-Hydroxymethyl-2-formylpyrrol-1-yl)propionic acid lactone was synthesized in six steps with a 17.0% overall yield, starting from L-alanine. The synthetic route involved the Clauson-Kaas reaction, Vilsmeier reaction, and transesterification. The transesterification was the key step in the formation of the target compound.

Keywords: alkaloid, L-alanine, transesterification, lactone.

2-(5-Hydroxymethyl-2-formylpyrrol-1-yl)propionic acid lactone (**1**) was firstly reported by Shigematsu, who obtained compound **1** via roasting DL-alanine and D-glucose at 200–250°C [1]. Subsequently, compound **1** was isolated from flue-cured tobacco and used to improve its flavor and aroma [2–5]. Recently, compound **1** was isolated from mature fruits of *Capparis spinosa* [6, 7], whose extract showed anti-inflammatory and pain-relieving activity. It is necessary that an appropriate synthesis route be found to supply enough sample since there is only 1.5 mg compound **1** per 10 kg dry fruits of *C. spinosa*.

Obviously, it is not easy to get compound **1** by roasting DL-alanine and D-glucose. To the best of our knowledge, no other total synthesis of compound **1** has been reported. In the present research, the retrosynthetic analysis of compound **1** is outlined (Scheme 1). Two strategies for the present purpose were explored: i) synthesize lactone **7** by intramolecular esterification of compound **5** and ii) synthesize lactone **7** by intramolecular transesterification of compound **6**.

Starting from L-alanine, ethyl 2-(2-formyl-1*H*-pyrrol-1-yl)-propionate (**3**) was prepared according to the reference procedure [8]. In pathway i, the ethyl ester protecting group was hydrolyzed by aqueous NaOH to afford compound **4**. During the reduction of compound **4**, a problem appeared. Unfortunately, compound **5** was not obtainable. Compound **5** could be monitored in the reaction solution when compound **4** was reduced by $NaBH_4$. Upon neutralization, the reaction mixture immediately turned to violet, and a red-violet solid was generated from the aqueous phase. The target compound **5** no longer existed. We speculate that polymerization between molecules of compound **5** occurred. Probably, the π-excessive characteristic of the pyrrole ring caused the problem. Therefore the other strategy was carried out.



Scheme 1

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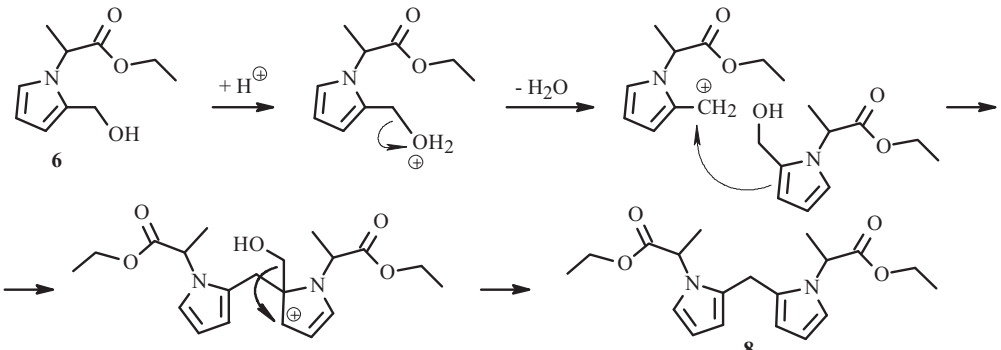
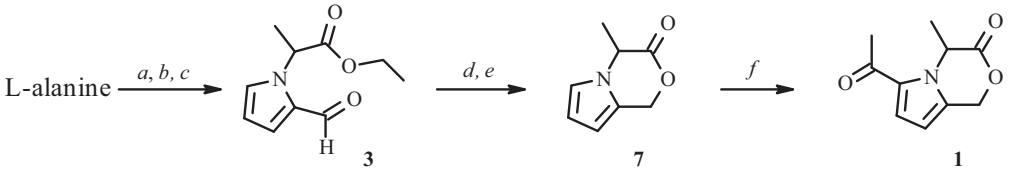


Scheme 2



a. $SOCl_2$, EtOH, –5°C to room temperature to reflux, 7h; *b*. NaOAc, HOAc, 2,5-dimethoxytetrahydrofuran, 1h; *c*. **2**, $POCl_3$, DMF, NaOAc, CH_2Cl_2, –5°C to room temperature to reflux, 8h; *d*. $NaBH_4$, MeOH, –15°C, 2h; *e*. **6**, DBU, toluene, 45°C, 5h; *f*. $POCl_3$, DMF, NaOAc, CH_2Cl_2, –5°C to room temperature to reflux, 8h.

Scheme 3

In pathway ii, compound **3** was reduced by $NaBH_4$ to afford compound **6** [9]. In general, such reaction is conducted at room temperature and the yield is acceptable. However, we did not get the desired compound **6** when the reaction temperature was –5°C. Instead, a compound with $[M + Cl]^-$ 190.1 analyzed by API-ES was generated, which was assumed to be 2-(2-hydroxymethylpyrrol-1-yl)-propan-1-ol. We found that the reaction must be kept at low temperature. Once the temperature was higher than –8°C, ethyl ester would be reduced too. Finally we conducted the reaction at –15°C.

We tried three catalytic conditions to generate compound **7** [10–12].

It has been reported that transesterification occurs when toluene is used as solvent [10]. However, transesterification did not occur under the first conditions. In the second catalytic system using acidic ion-exchange resin Amberlyst-15, polymerization occurred between two molecules of compound **6** to generate compound **8** (Scheme 2), as confirmed by ^1H NMR and ^1H–^1H COSY. This indicated that acidic conditions were not suitable for the system. We speculate that a possible mechanism may be bimolecular polymerization. Finally, DBU in toluene was chosen to catalyze transesterification between ethyl and hydroxymethyl to afford the key intermediate compound **7**. We also needed to concern with the reaction temperature because side reactions occurred when the temperature reached 60°C. Finally, a formyl group was introduced at the 5-position of the pyrrole ring of compound **7** via the Vilsmeier reaction to afford target compound **1**. Pathway ii was successful (Scheme 3).

EXPERIMENTAL

Solvents and chemicals were reagent grade or better and were obtained from commercial sources. The petroleum ether (PE) used was the fraction boiling in the range 60–90°C. Reactions were monitored by TLC on 0.25 mm silica gel plates ($60GF_{254}$) and visualized with ultraviolet light. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AV 400MHz spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C). High-resolution mass spectra (HR-MS) were obtained on a Micromass GCT-TOF mass spectrometer.

Ethyl (2*S*)-2-(1*H*-Pyrrol-1-yl)propionate (2). L-alanine (17.82 g, 0.2 mol) was added to EtOH (200 mL) at r.t. The mixture was stirred at –5°C for 10 min. $SOCl_2$ (35.69 g, 0.3 mol) was added to the above mixture dropwise and stirred at r.t. for 2 h. The mixture was then stirred under reflux for 5 h. The solvent was evaporated under vacuum, and the residue was suspended in a solution of NaOAc (16.41 g, 0.2 mol) and 2,5-dimethoxytetrahydrofuran (26.43 g, 0.2 mol) in AcOH (150 mL).

The mixture was stirred at 80°C for an appropriate time (0.5 h, TLC monitoring). After the AcOH was evaporated, the residue was dissolved in water (200 mL) and extracted with EtOAc (200 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatograph (PE–EtOAc, 6:1) to give **2** (28.0 g, 83.7%) as colorless oil, $[\alpha]_D^{20}$ –15.0° (*c* 5.78, $CHCl_3$). IR (neat, ν, cm^{-1}): 3102, 724 (=C–H), 2985, 2939, 1449, 1376 (CH, CH_2, CH_3), 1740 (C=O), 1550, 1491 (C=C), 1189 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.25 (3H, t, J = 7.2, $OCH_2C\underline{H}_3$), 1.71 (3H, d, J = 7.2, $CHC\underline{H}_3$), 4.17 (2H, q, J = 7.2, $OC\underline{H}_2$), 4.74 (q, 1H, J = 7.2, $C\underline{H}CH_3$), 6.19 (2H, s, H-3′, 4′), 6.76 (2H, s, H-2′, 5′). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm, J/Hz): 171.3 (s, C-1), 119.7 (s, C-2′, 5′), 108.6 (s, C-3′, 4′), 61.6 (s, C-2), 57.1 (s, $O\underline{C}H_2CH_3$), 18.4 (s, C-3), 14.1 (s, $OCH_2\underline{C}H_3$). TOF-MS (EI, *m/z*): 167.0943 (calcd for $C_9H_{13}NO_2$, 167.0946).

Ethyl 2-(2-Formyl-1*H*-pyrrol-1-yl)propionate (3). $POCl_3$ (12.27 g, 80 mmol) was added dropwise to DMF (6.97 g, 80 mmol) in 15 min at –5°C, and the whole was stirred for another 20 min. A solution of compound **2** (13.38 g, 80 mmol) in CH_2Cl_2 (40 mL) was added dropwise to the mixture in 30 min. The mixture was allowed to warm to r.t., stirred for 2 h, and then poured into a solution of NaOAc (26.24 g, 0.32 mol) in water (100 mL). The mixture was heated to reflux for 5 h. Later, the reaction solution was diluted with water (100 mL) and extracted with CH_2Cl_2 (200 mL × 3). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by silica gel chromatograph (PE–EtOAc, 5:1) to give **3** (13.35 g, 85.5%) as colorless oil, $[\alpha]_D^{20}$ –59.1° (*c* 5.78, $CHCl_3$). IR (neat, ν, cm^{-1}): 3116, 778, 755 (=C-H), 2985, 2941, 2810, 1410, 1371 (CH, CH_2, CH_3), 1740, 1655 (C=O), 1529, 1474 (C=C), 1202 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.25 (3H, t, J = 7.2, $OCH_2C\underline{H}_3$), 1.74 (3H, d, J = 7.2, $CHC\underline{H}_3$), 4.19 (2H, q, J = 7.2, $OC\underline{H}_2$), 5.87 (1H, q, J = 7.2, $C\underline{H}CH_3$), 6.31 (1H, t, J = 3.2, H-4′), 6.97–6.99 (1H, m, H-3′), 7.18 (1H, m, H-5′), 9.51 (1H, s, CHO). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm, J/Hz): 179.5 (s, $\underline{C}HO$), 171.0 (s, C-1), 131.6 (s, C-2′), 128.9 (s, C-5′), 125.4 (s, C-3′), 110.1 (s, C-4′), 61.5 (s, C-2), 55.5 (s, $O\underline{C}H_2CH_3$), 17.7 (s, C-3), 14.0 (s, $OCH_2\underline{C}H_3$). TOF-MS (EI, *m/z*): 195.0902 (calcd for $C_{10}H_{13}NO_3$, 195.0895).

Ethyl 2-(2-Hydroxymethyl-1*H*-pyrrol-1-yl)propionate (6). Compound **3** (2.93 g, 15 mmol) was dissolved in MeOH (60 mL) and chilled in an ice-salt bath. When the temperature was reduced to –15°C, $NaBH_4$ (0.57 g, 15 mmol) was added to the solution. The reaction temperature was kept below –10°C for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (60 mL). The solution was extracted with CH_2Cl_2 (80 mL × 3). The combined extract was dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by silica gel chromatograph (PE–EtOAc, 4:1) to give **6** (2.40 g, 81.0%) as colorless oil, $[\alpha]_D^{20}$ –24.0° (*c* 1.86, $CHCl_3$). IR (neat, ν, cm^{-1}): 3404 (OH), 2985, 2940, 2876, 1429, 1378 (CH, CH_2, CH_3), 1736 (C=O), 1552, 1482 (C=C), 1202 (C-O), 716 (=C-H). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.24 (3H, t, J = 7.2, $OCH_2C\underline{H}_3$), 1.71 (3H, t, J = 7.2, $CHC\underline{H}_3$), 2.14 (1H, s, OH), 4.16 (2H, q, J = 7.2, $OC\underline{H}_2$), 4.52 (2H, s, $C\underline{H}_2OH$), 5.05 (1H, q, J = 7.2, $C\underline{H}CH_3$), 6.08–6.12 (2H, m, H-3′, 4′), 6.81 (1H, t, J = 2.4, H-5′). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 171.9 (s, C-1), 131.8 (s, C-2′), 119.7 (s, C-5′), 109.1 (s, C-4′), 107.8 (s, C-3′), 61.7 (s, C-2), 56.6 (s, $O\underline{C}H_2CH_3$), 53.7 (s, $\underline{C}H_2OH$), 18.1 (s, C-3), 14.1 (s, $OCH_2\underline{C}H_3$). TOF-MS (EI, *m/z*): 197.1056 (calcd for $C_{10}H_{15}NO_3$, 197.1052).

2-(2-Hydroxymethylpyrrol-1-yl)propionic Acid Lactone (7). To a solution of **6** (2.37 g, 12 mmol) in toluene (100 mL), DBU (9.13 g, 60 mmol) was added. The mixture was stirred at 45°C for 5 h. The solution was washed with saturated aqueous NH_4Cl (100 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatograph (PE–acetone, 8:1) to give **7** (1.18 g, 65.3%) as colorless oil, $[\alpha]_D^{20}$ –8.0° (*c* 0.81, $CHCl_3$). IR (neat, ν, cm^{-1}): 3105, 801, 779, 765, 712 (=C-H), 2990, 2941, 1372 (CH, CH_2, CH_3), 1751 (C=O), 1479 (C=C), 1205 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.78 (3H, d, J = 7.2, $CHC\underline{H}_3$), 4.76 (1H, q, J = 7.2, $C\underline{H}CH_3$), 5.36 (1H, d, J = 14.4, $OC\underline{H}_2$), 5.39 (1H, d, J = 14.4, $OC\underline{H}_2$), 6.11 (1H, d, J = 2.8, H-3′), 6.22 (1H, m, H-4′), 6.72 (1H, s, H-5′). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 169.3 (s, C-1), 122.1 (s, C-2′), 117.6 (s, C-5′), 109.6 (s, C-4′), 104.8 (s, C-3′), 64.4 (s, C-2), 53.6 (s, $\underline{C}H_2O$), 17.0 (s, C-3). TOF-MS (EI, *m/z*): 151.0639 (calcd for $C_8H_9NO_2$, 151.0633).

2-(2-Formylpyrrol-1-yl)propionic Acid (4). To a stirred solution of compound **3** (1.95 g, 10 mmol) in methanol (20 mL), a solution of NaOH (0.80 g, 20 mmol) in water (10 mL) was added dropwise. The reaction mixture was stirred for 3 h at r.t. (TLC monitoring). The reaction mixture was then diluted with water (10 mL) and acidified with HCl (5%) to pH 3–4. The product was extracted with EtOAc (30 mL × 2). The combined organic extracts were dried over Na_2SO_4. The EtOAc was removed in vacumm to give **4** (1.5 9 g, 95.1%) as light pink solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.74 (3H, d, J = 7.6, $CH\underline{CH}_3$), 5.79 (1H, d, J = 7.6, $\underline{CH}CH_3$), 6.31 (1H, t, J = 2.8, H-4′), 6.99–7.00 (1H, m, H-3′), 7.18 (1H, s, H-5′), 9.45 (1H, s, CHO).

2-(5-Hydroxymethyl-2-formylpyrrol-1-yl)propionic Acid Lactone (1). $POCl_3$ (0.35 g, 2.3 mmol) was added dropwise to DMF (0.30 g, 3.5 mmol) in 15 min at –5°C and stirred for another 20 min. A solution of compound **7** (0.35 g, 2.3 mmol) in CH_2Cl_2 (8 mL) was added dropwise to the mixture in 30 min. The mixture was allowed to warm to r.t. and stirred

for 2 h. Then the reaction mixture was poured into a solution of NaOAc (0.75 g, 9.2 mmol) in water (10 mL). The mixture was heated to reflux for 5 h, then diluted with water (10 mL) and extracted with CH_2Cl_2 (20mL × 3). The combined extracts were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by silica gel chromatograph (PE–EtOAc, 6:1) to give **1** (0.19 g, 45.0%) as white solid, $[\alpha]_D^{20}$ 0° (*c* 0.57, $CHCl_3$). IR (neat, ν, cm^{-1}): 3101, 830, 785, 746, 718 (=C-H), 2995, 2977, 1401, 1386 (CH, CH_2, CH_3), 1751, 1650 (C=O), 1501, 1466 (C=C), 1196 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.72 (3H, d, J = 7.2, CHC$\underline{H}_3$), 5.39 (1H, d, J = 14.8, OC$\underline{H}_2$), 5.48 (1H, d, J = 14.8, OC$\underline{H}_2$), 5.85 (1H, q, J = 7.2, C$\underline{H}$CH$_3$), 6.21 (2H, d, J = 4.0, H-4′), 6.97 (2H, d, J = 4.0, H-3′), 9.54 (1H, s, CHO). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 179.2 (s, $\underline{C}$HO), 168.2 (s, C-1), 130.8 (s, C-5′), 130.3 (s, C-2′), 124.5 (s, C-4′), 106.5 (s, C-3′), 63.3 (s, C-2), 53.8 (s, $\underline{C}H_2O$), 19.1 (s, C-3). TOF-MS (EI, *m/z*): 179.0591 (calcd for $C_9H_9NO_3$, 179.0582).

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