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A Short Synthesis of C-2 Symmetric (2*S*, 5*S*) Pyrrolidine-2,5 Dicarboxylic Acid, a Constituent of Red Alga *Schizymenia dubyi*

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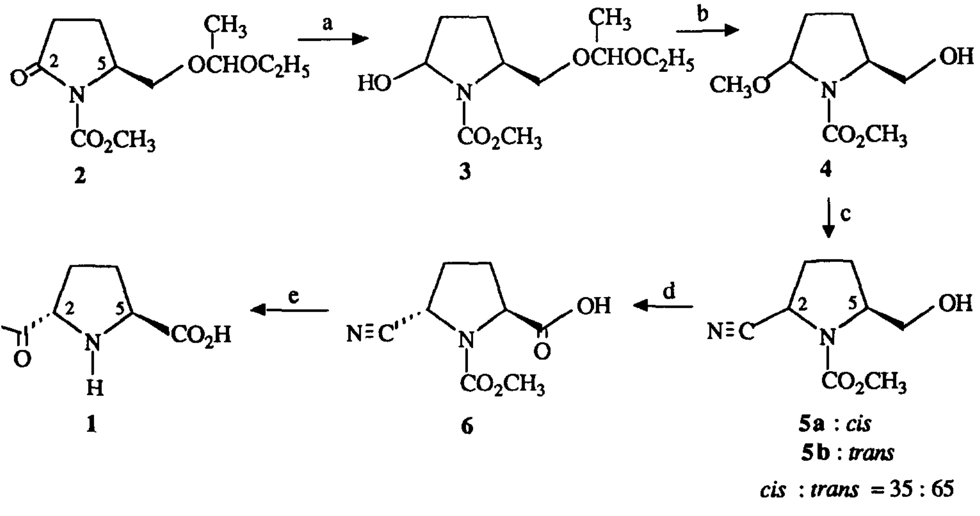
***ABSTRACT** : (2S, 5S) pyrrolidine-2,5-dicarboxylic acid* **1** *was synthesized from (5S) N-methoxycarbonyl-5-ethoxyethoxy-methyl pyrrolidin-2-one* **2** *by a simple and efficient way* [1]

The *trans* diacid **1** is a natural marine product isolated from the red alga *Schizymenia dubyi*.[2] It could be also used as an intermediate in the preparation of C-2 symmetric chiral auxiliaries in asymmetric synthesis.[3] The first synthesis of this amino diacid was developed from a *t*-butylpyroglutamate carbamate.[4] This synthesis involved a two carbon unit addition (CH_2= CHMgBr) to the pyrrolidine carbonyl with opening of the ring, followed by cyclization and elimination of one of these two carbons.[5]

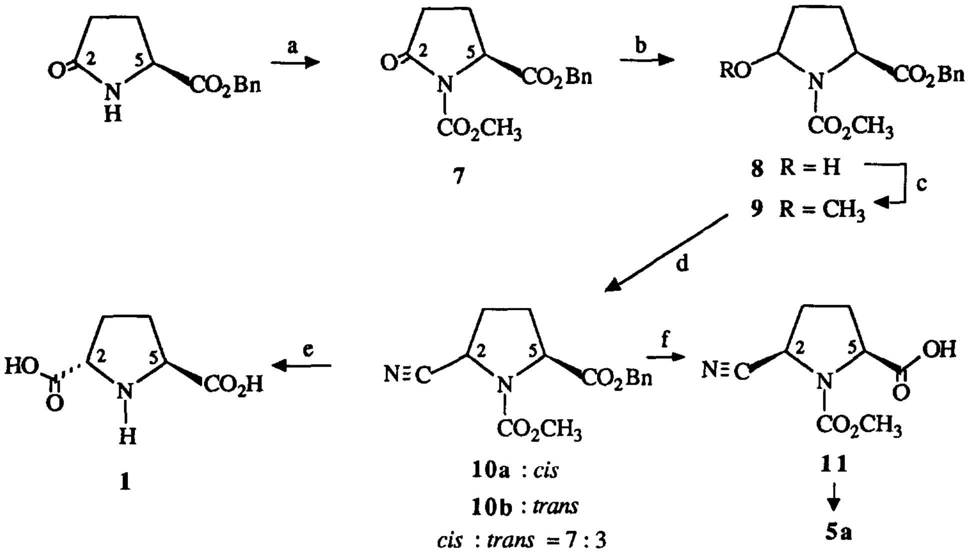
Taking advantage of our previous work in this field,[6] we planned to prepare the *trans* diacid **1** from readily available (5*S*) *N*-methoxycarbonyl-5-ethoxyethoxymethyl pyrrolidin-2-one **2**[6b,7] as outlined in scheme 1.



Reagents : a) : DIBAL-H (98%) ; b) : TsOH, MeOH (98%) ; c) : Me_3SiCN, $SnCl_4$ (89%) ; d) : Jones reagent (78%) ; e) : HCl 6N, 100°, 24h, propylene oxide, EtOH (87%).

Scheme 1

Partial regioselective reduction of compound **2** with DIBAL-H in toluene at -78°C afforded the α-hydroxy carbamates **3** (80%)[6b]. The yield was significantly improved by the addition of hexane solution of hydride to a THF solution of **2** and this procedure led nearly quantitatively to **3**. The difference could be explained by the decreased reactivity of the alkylaluminium hydride complexed by THF [8]. Acidic hydrolysis of **3** in methanol gave the two diastereomeric α-methoxy carbamates **4** (98%) and these precursors of the reactive *N*-methoxycarbonyl iminium ion were submitted to nucleophilic addition of cyanide. Reaction of the derivatives **4** with trimethylsilylcyanide and a catalytic amount of Lewis acid ($SnCl_4$, 0.3 equiv.) led to α-cyano carbamates **5** (89% yield). The two cyano diastereomers **5a** and **5b** were isolated in the ratio 35:65. Their relative configurations were ascertained by chemical correlation following scheme 2.

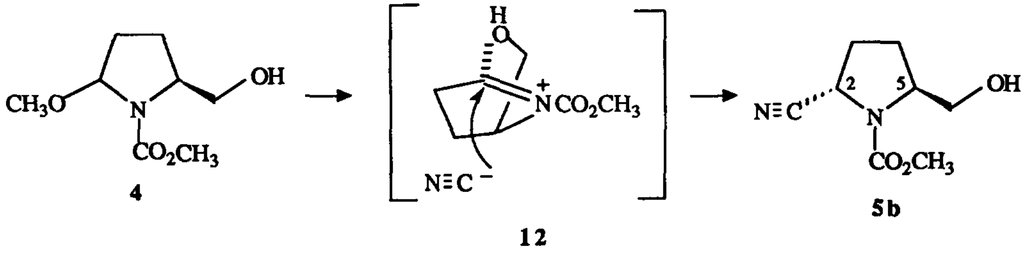


Reagents : a) : MeOCOCl (80%), b) : DIBAL-H (90%) ; c) : TsOH, MeOH (99%) ; d) : Me_3SiCN, $SnCl_4$ (86%) ; e) : HCl 6N, 24h, propylene oxide, EtOH, (86%) ; f): H_2 - Pd/C, BH_3-Me_2S (75%).

Scheme 2

The carbamate **7** was prepared from (*S*) benzylpyroglutamate[9] in a mixture Et_2O-DMF-Et_3N [10] to avoid racemization[11], and reduced with DIBAL-H in hexane to the derivative **8** (90%). The α-methoxy carbamates **8** were treated with trimethylsilylcyanide in the same conditions as **4**, affording the 2,5 cis diastereomer **10a** as major cyanation product [12](86%, **10a** : **10b** = 7 : 3). Hydrogenolysis conditions were used to remove the benzyl group of **10a** and the carboxy group of the acid **11** was reduced with a solution of BH_3-Me_2S in THF, to give the primary alcohol **5a** in 75% yield from **10a**.

This reversed diastereoselectivity of the nucleophilic addition of cyanide, starting from **4** and **9**, could be explained by an interaction of the hydroxymethyl group oxygen of **4** with the *N*-methoxycarbonyl iminium carbon of an intermediate such as **12**, thus favouring a nucleophilic attack of cyanide on the opposite face [13] (scheme 3).



Scheme 3

The *trans* (2*S*, 5*S*) N-methoxycarbonyl-2-cyano-5-hydroxymethyl pyrrolidine **5b** was oxidized to the cyano acid **6** by Jones reagent (78% yield). Hydrolysis of the cyano group and deprotection of the nitrogen in compound **6** were performed in the same non racemizing step [14]. Heating in 6N aqueous hydrochloric acid gave the *trans* diacid **1** hydrochloride which was treated with propylene oxide as acid scavenger [15] to obtain **1** (87%). In the same experimental conditions, the cyano benzyl ester **10b** was directly converted to **1**, but the overall yield of the synthetic route described in scheme 1 was significantly higher (32% from (*S*) pyroglutamic acid).

Thus, this work constitutes a simple and efficient way to prepare this C-2 symmetric 2,5-disubstituted pyrrolidine diacid which is a precursor of optically pure *trans* 2,5 dialkoxymethyl pyrrolidines, useful as chiral auxiliaries in several enantioselective reactions[3].

EXPERIMENTAL SECTION

Melting points was taken on a Kofler apparatus and was corrected. Optical rotations were measured on a Perkin-Elmer 241 ($CHCl_3$, solution g/100 ml). IR spectra were recorded on a Nicolet 205 (FT)(ν cm^{-1}, $CHCl_3$). NMR spectra were obtained ($CDCl_3$, Me_4Si, $\delta = 0$ ppm) from Bruker AC200 or AC250, coupling constants *J* are given in Hertz (s, d, t, dd and m indicate singlet, doublet, triplet, doublet of doublets and multiplet respectively). Mass spectra were measured on an AEI MS50. Flash chromatography was performed on silica gel (SDS 230-400 mesh) and preparative thin layer chromatography on silica gel (Merck HF 254 + 366).

(S) N-methoxycarbonyl-5-ethoxyethoxymethylpyrrolidin-2-one (2)

Potassium iodide (6.26 g, 37.7 mmol) was added under argon to a suspension of NaH (50% in oil, 1.68 g, 35.0 mmol) in dry THF (28 ml). To this mixture, at 0°C was added a solution of (*S*) 5-ethoxyethoxymethylpyrrolidin-2-one (5.61 g, 30.0 mmol) in THF (28 ml). After being stirred 1.5 h at room temperature, the mixture was cooled again to 0°C and a solution of methylchloroformiate (3.92 g, 41.5 mmol) in THF (28 ml) was added dropwise. The mixture was stirred for 20 min. at room temperature before treating with a saturated aqueous solution of $Na_2S_2O_3$ (5% W/V). After usual work up, compound **2** (oil) was purified by flash chromatography (Et_2O) : 6.98 g (95%). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.86 ; H, 7.81 ; N, 5.71. Found: C, 53.77 ; H, 7.62 ; N, 5.64.

IR : 2980, 1790, 1754, 1720, 1440, 1306. ^{1}H NMR (200 MHz) : 4.68 (m, 1H; OCHO), 4.34 (m, 1H, C-5-H), 3.87 (s, 3H, CO_2CH_3), 3.80-3.36 (m, 4H, $2OCH_2$), 2.78 (m, 1H), 2.42 (m, 1H) and 2.14 (m, 2H) : C-3-H_2 and C-4-H_2, 1.27 and 1.18 (2m, 6H, $CHCH_3$ and CH_2CH_3). FAB MS : 268 (M + 23), 246 (M + H), 200, 174, 156.

(5S) N-methoxycarbonyl-2-hydroxy-5-ethoxyethoxymethylpyrrolidines (3)

To a stirred solution of the pyrrolidone 2 (1.04 g, 4.24 mmol) in dry THF (10 ml) at -78°C was added a solution of DiBAL-H in hexane (1M, 5.1 ml). After 15 min, the reaction was quenched by successive additions of a saturated aqueous solution of NH_4Cl (15 ml) and an aqueous solution of Na_2CO_3 (10% W/V, 10 ml). The mixture was extracted with CH_2Cl_2. After usual work up the crude product was eluted on silica gel (Et_2O) to afford 3 (1.03 g, 98%).

IR : 3425, 2925, 1690. ^{1}H NMR (250 MHz) : 5.47 (m, 1H, C-2-H), 4.72 (m, 1H, OCHO), 4.11 and 3.94 (2m, C-5-H), 3.72 (s, CO_2CH_3), 3.62 and 3.47 (2m, $2CH_2O$), 1.98 (m, C-3-H_2 and C-4-H_2), 1.30 (bd, $CHCH_3$), 1.20 (t, CH_2CH_3). MS (m/z) : 230 $(M - 17)^{+\cdot}$ (100%), 184, 158, 144, 73.

(5S) N-methoxycarbonyl-2-methoxy-5-hydroxymethylpyrrolidines (4)

A solution of *p*-toluenesulfonic acid in methanol (0.10 g, 100 ml, 60 ml) was added to the compounds 3 (1.93 g, 7.81 mmol) under argon at room temperature and the mixture was stirred for 10 min. before the addition of an aqueous solution of Na_2CO_3 (10%, 6 ml). The mixture was extracted with CH_2Cl_2 (3 x 150 ml) and the organic layers were washed with brine, dried with anhydrous $MgSO_4$ and concentrated to give 4 (1.44 g, 97.5%). Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78 ; H, 7.99 ; N, 7.40. Found: C, 50.70 ; H, 7.65 ; N, 7.34. The two diastereomers (4a:4b~85:15) could be separated by chromatography on silica gel (heptane-ether-methanol 1:5:0.1).

Major (less polar) diastereomer 4a.

Oil, $[\alpha]_D$= -49° (c = 1.06). IR : 3422, 2964, 1690. ^{1}H NMR (250 MHz) : 5.19 (m (sh.), C-2-H), 4.05 (m, 1H, C-5-H), 3.95 (ex. with D_2O, OH), 3.76 (s + m, 4H, CO_2CH_3 and C-6-Ha), 3.60 (dd, 1H, C-6-Hb), 3.34 (s, 3H, OCH_3), 2.03, 1.93 and 1.80 (3m, 4H, C-3-H_2 and C-4-H_2). MS (m/z) : 189 $(M^{+\cdot})$, 158 (100%), 126, 98, 82, 68.

Minor (more polar) diastereomer 4b

Oil, $[\alpha]_D$= -31° (c = 0.86). IR : 3410, 2957, 1690. ^{1}H NMR (250 MHz) : 5.02 (bd, *J* ~ 3, C-2-H), 4.09 (m, C-5-H), 3.76 (s, 3H, CO_2CH_3), 3.65 (m, 2H, C-6-H_2), 3.32 (s, 3H, OCH_3), 2.25 (m, 1H), 1.87 (m, 2H) and 1.70 (m, 1H) : C-3-H_2 and C-4-H_2.

(5S) N-methoxycarbonyl-2-cyano-5-hydroxymethylpyrrolidines (5)

To α-methoxy carbamates 4 (1.579 g, 8.35 mmol) at -40°C under argon was added a solution of $SnCl_4$ in dry CH_2Cl_2 (5% V/V, 5.86 ml, 2.5 mmol) and Me_3SiCN (2.23 ml, 16.7 mmol) under stirring. The reaction was monitored by TLC (Et_2O). After 20 min., a solution of aqueous Na_2CO_3 (10%, 10 ml) and then water (5 ml) were added to the reaction mixture before extraction with CH_2Cl_2. The crude product obtained by usual workup was purified by flash column chromatography on silica gel (P = 2 bars, CH_2Cl_2-MeOH 98:2) to afford the diastereomers **5a** (0.49g, 32%) and **5b** (0.88 g, 57%) as oils.

(2R,5S) N-methoxycarbonyl-2-cyano-5-hydroxymethylpyrrolidine* (5a) *(less polar)

$[\alpha]_D$ = +54° (c = 0.93). IR : 3415, 2950, 2220 (very weak), 1689, 1443. ^1H NMR (250 MHz): 4.65 (m, 1H, C-2-H), 3.99 (m, 1H, C-5-H), 3.80 (s, CO_2CH_3), 3.74 (m, C-6-H_2), 2.4-1.8 (m, C-3-H_2 and C-4-H_2). ^{13}C NMR : 155.1 (CO), 118.7 (CN), 63.6 (CH_2O), 60.6-59.5 (C-5), 52.9 (OCH_3), 48.0 (C-2), 29.5 and 26.9 (C-3 and C-4). MS (m/z) : 184 ($M^{+\cdot}$), 153, 109, 82, 68 (100%). HRMS calcd for $C_8H_{12}N_2O_3$: 184.0848; obsd: 184.0829 ; $C_7H_9N_2O_2$: 153.0664; obsd: 153.0630 ; C_4H_6N: 68.0500 ; obsd: 68.0484.

(2S,5S) N-methoxycarbonyl-2-cyano-5-hydroxymethylpyrrolidine* (5b) *(more polar)

$[\alpha]_D$ = -129° (c = 1.2). Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.16 ; H, 6.57 ; N, 15.21. Found: C, 51.81 ; H, 6.39 ; N, 15.28. IR : 3428, 2964, 2233 (very weak), 1702, 1443. ^1H NMR (250 MHz) : 4.57 (d, 1H, *J* = 6.5, C-2-H), 4.09 and 3.96 (2m, 1H, C-5-H), 3.80 (s, 3H, CO_2CH_3), 3.66 (m, 2H, C-6-H_2), 3.15 (ex. with D_2O, OH), 2.33, 2.20 and 2.00 (C-3-H_2 and C-4-H_2). ^{13}C NMR : 154.9 (CO), 118.7 (CN), 63.7 (CH_2O), 59.7-58.7 (C-5), 53.1 (OCH_3), 48.2 (C-2), 29.7-28.9 and 27.7-26.9 (C-3 and C-4). MS (m/z) : 184 ($M^{+\cdot}$, weak), 153 (100%), 109, 82, 68 (100%).

***(2S,5S) N-methoxycarbonyl-2-cyanopyrrolidine-5-carboxylic acid* (6) *and dicarboxylic acid* (1)**

The compound **5b** (0.355 g, 1.9 mmol) in acetone (8 ml) was oxidized by Jones reagent (3.4 ml) at 0°C. The mixture was stirred for 50 min. at 0°C before the addition of isopropanol (20 ml) and water (20 ml). The crude product was extracted with ethyl acetate. The carboxylic acid **6** was isolated by extraction with KOH 0.1N followed by acidification of the aqueous layers with HCl and extraction with ethyl acetate (oil, 0.297 g, 78%).

$[\alpha]_D$ = -114° (c = 0.95). IR : 3700-2400, 2960, 1722, 1450, 1376. ^1H NMR (250 MHz) : 5.8 (OH), 4.70 and 4.50 (2m, C-2-H and C-5-H), 3.82 and 3.75 (CO_2CH_3), 2.30 (m, C-3-H_2 and C-4-H_2). ^{13}C NMR : 175.2 (CO_2H), 154.3 (NCO), 118.1 (CN), 53.6 (OCH_3), 58.8-58.5 (C-5), 48.0-47.5 (C-2), 29.8-29.6 and 28.6-28.3 (C-3 and C-4). MS (m/z) : 198 ($M^{+\cdot}$), 153 (100%), 139, 127, 109, 82, 68. HRMS : calcd for $C_8H_{10}N_2O_4$: 198.0640, obsd: 198.0633 ; $C_7H_{10}NO_4$: 172.0607, obsd: 172.0628 ; $C_7H_9N_2O_2$: 153.0664; obsd: 153.0656 ; $C_6H_7N_2O_2$: 139.0508; obsd: 139.0503.

A solution of the compound **6** (160 mg, 0.8 mmol) in HCl 6N (8 ml) was heated under reflux for 24 h to afford the diacid hydrochloride after evaporation to dryness. This product was treated with propylene oxide[11] and crystallized in EtOH to give the diacid **1** (112.7mg, 87%) : F>280°C, $[\alpha]_D$= -104° (c = 0,93, H2O), [Litt. : $[\alpha]_D$= - 112° (c ~ 1, H2O)[2], $[\alpha]_D$= - 102° (c = 0.983, H2O)[3f]].

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