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Direct Chain Elongation of N-Carbamoylpyroglutamate. An Efficient Synthesis of (-)-Pyrrolidine-2,5-Dicarboxylic Acid

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(-)-Pyrrolidine-2,5-dicarboxylic acid, an acidic amino acid component of marine red alga *Schizymenia dubyi*, has been synthesized with a direct chain elongation reaction of N-carbamoylpyroglutamates at C-5 and a pyrrolidine ring formation.

The utility of an amino acid as a chiral element in an asymmetric synthesis has been fully recognized as well as that of carbohydrates and terpenoids. (S)-4-Carboxybutan-4-olide can be transformed from the most abundant chiral natural resource, L-glutamic acid, by nitrite and is a well known chiral synthon.[1] However, the application of L-glutamic acid as an asymmetric element in the chiral synthesis of nitrogen containing natural products has been less than that of the above lactone.[2] We designed the reaction scheme of L-pyroglutamate with the concept that it is desirable to use a bifunctional chiron directly without a prior modification.

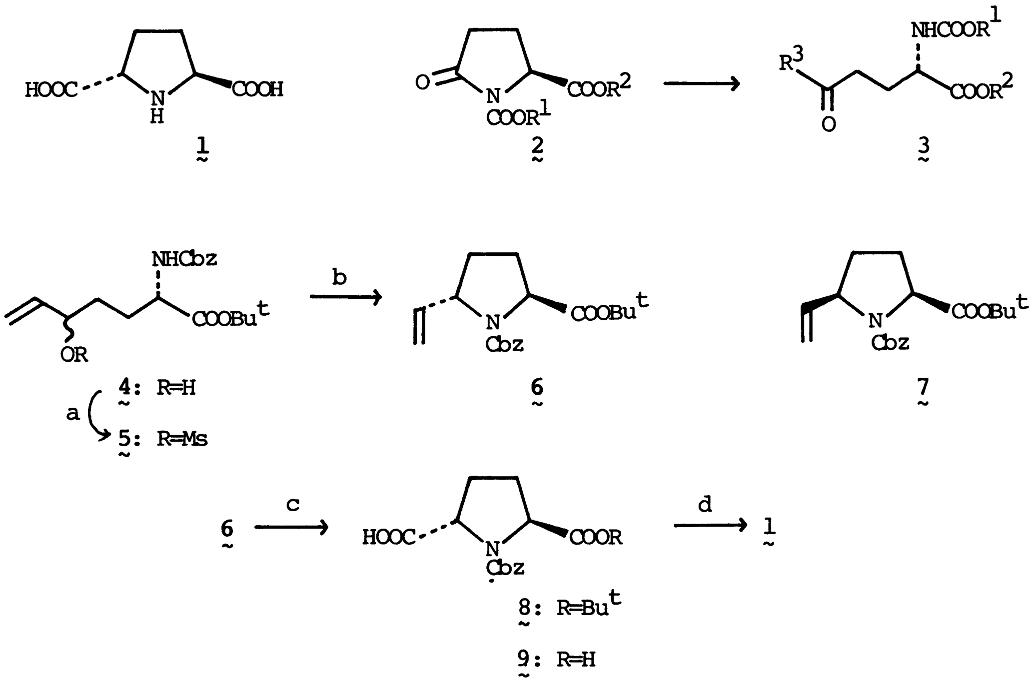
We describe, in this communication, a facile carbon chain elongation reaction at C-5 of L-glutamic acid and a diastereospecific pyrrolidine ring formation which leads to the first synthesis of (2S,5S)-pyrrolidine-2,5-dicarboxylic acid (**1**), the acidic amino acid constituent of the marine red alga *Schizymenia dubyi*.[3] We have found the pyroglutamates (**2**) on.treatment with a Grignard reagent at low temperature, react function-selectively to give exclusively 5-monosubstituted derivatives (**3**).

In the typical procedure, 1 M vinylmagnesium bromide in THF (1.2 ml, 1.2 mmol) was added to the lactam (**2a**, 319 mg, 1.0 mmol) in dry THF (6 ml) at -40 °C under argon atmosphere. After 2 h of stirring, the reaction mixture was quenched with HOAc-MeOH (1:1, 0.5 ml) and diluted with Et_2O. The organic layer was washed with

Table 1. Direct Chain Elongation of Lactam 2

Lactam	R^1	R^2	Nucleophile	Yield/% of ketone 3
2a	Bu^t	Bzl	$CH_2=CHMgBr$	82
2b	Bzl	Bu^t	$CH_2=CHMgBr$	55
2c	Bzl	Bzl	$CH_2=CHMgBr$	52
2d	Bu^t	PNB	$CH_2=CHMgBr$	78
2e	Bu^t	Bzl	CH_3MgI	78[a)]
2f	Bu^t	Bzl	$CH_2=CHCH_2MgBr$	70[a)]
2g	Bu^t	Bzl	$CH_3(CH_2)_3C\equiv CMgBr$	92

a) The reaction was quenched with NH_4Cl aq.



a) MsCl, Et_3N, CH_2Cl_2, 0 °C. b) Et_3N, CH_2Cl_2, rt. c) O_3, MeOH, -78 °C; PDC, DMF, rt. d) TFA, PhOMe, 0 °C; H_2/Pd-C, MeOH.

water, dried and evaporated. Silica gel chromatography [hexane-EtOAc (4:1) elution] gave the enone (**3a**) as an oil. The existence of an enone was shown by the IR absorption at 1680 and 1620 cm^{-1}, and the ^1H NMR signals at δ 5.70, 6.15, and 6.18. No racemization was detected by ^1H NMR using chiral shift reagent, $Eu(tfc)_3$.[4] The enone (**3a**) was crystallized from Et_2O-hexane to give colorless needles (286 mg, 82%).[5] Table 1 shows the generality of this reaction.

This carbon elongation reaction was successfully applied to the synthesis of (2*S*,5*S*)-(-)-pyrrolidine-2,5-dicarboxylic acid (**1**).[3] The enone (**3b**) was reduced with $NaBH_4$-$CeCl_4$[6] at -15 °C and the resulting alcohol (**4**, 91%) was transformed to the mesylate (**5**). The mesylate was somewhat unstable and rearranged gradually to pyrrolidines **6** and **7** on stirring with Et_3N in CH_2Cl_2, at an ambient temperature. Two diastereomers were separated on silica gel giving 2,5-*trans*- (**6**, 46%) and *cis* isomers (**7**, 9%).[7] 5-Vinylprolinate (**6**) was successively oxidized to the carboxylic acid (**8**, mp 120-122 °C, 82%) which on deprotection gave (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid (**1**, 82.6%),[8] $[\alpha]_D^{20}$ -107° (c 1.0, H_2O) [Lit.,[3] $[\alpha]_D^{20}$ -112° (c 1, H_2O)]. Overall yield from pyroglutamate **2b** was 15.5%. Thus the amino acid (**1**) obtained was identical with the natural acid with respect to its physical properties.

Further application of the efficient carbon chain elongation reaction will be reported elsewhere.

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4) ^{1}H-NMR spectra were recorded in $CDCl_3$ at 500 MHz. 7-70 mol% of (+)- or (±)-Eu(tfc)$_3$ was added to the 0.05 mol dm^{-3} solution of the enone (**3a**).

5) **3a**: mp 64-66 °C; $[\alpha]_D^{20}$ -15° (c 1.39, $CHCl_3$); ν^{KBr} 3300, 1740, 1720, 1680, 1620 cm^{-1}; δ_H($CDCl_3$) 1.40 (9H, s), 4.02-4.66 (1H, m), 5.10 (2H, s), 5.15 (1H, bs), 5.70 (1H, dd, J=4.0, 8.0 Hz), 6.15 (1H, d, J=4.0 Hz), 6.18 (1H, d, J=8.0 Hz), 7.26 (5H, s); *m*/*z* 347 (M^+).

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7) The conformation of the allylic cation derived from mesylate **5** may be responsible for the production ratio of two diastereomers **6** and **7**.

8) **1**: mp >300 °C; ν^{KBr} 1680, 1560 cm^{-1}; δ_H(D_2O) 2.00-2.40 (4H, m), 4.30 (2 x 1H's, dd's, J=2.0, 5.0 Hz); δ_C(D_2O) 28.5 (t), 61.1 (d), 172.8 (s); *m*/*z* 160 (M^++1).

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