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 <u>Schizymenia</u> <u>dubyi</u>, 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 $(2\underline{S},5\underline{S})$ -pyrrolidine-2,5-dicarboxylic acid (1), the acidic amino acid constituent of the marine red alga <u>Schizymenia dubyi</u>.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

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 				Yield/% of	
Lactam	R ¹	R^2	Nucleophile	ketone 3 ~	
2a	But	Bzl	CH ₂ =CHMgBr	82	
2b	Bzl	\mathtt{Bu}^{t}	CH2=CHMgBr	55	
2c	Bzl	Bzl	CH2=CHMgBr	52	
2d	\mathtt{Bu}^{t}	PNB	CH ₂ =CHMgBr	78	
2e	\mathtt{Bu}^{t}	Bzl	CH ₃ MgI	78 ^{a)}	
2f	\mathtt{Bu}^{t}	Bzl	CH2=CHCH2MgBr	70 ^{a)}	
2g ~~	Bu^t	Bzl	Сн ₃ (Сн ₂) ₃ С≡СмдВ	r 92	

Table 1. Direct Chain Elongation of Lactam 2

a) The reaction was quenched with ${\tt NH}_4{\tt Cl}$ 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, O °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 Et₂O-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 $(2\underline{S},5\underline{S})-(-)$ -pyrrolidine-2,5-dicarboxylic acid (1,).³⁾ The enone $(3\underline{b})$ was reduced with NaBH₄-CeCl₄⁶⁾ 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 Et₃N in CH₂Cl₂, at an ambient temperature. Two diastereomers were separated on silica gel giving 2,5-<u>trans</u>- (6, 46\$) and <u>cis</u> isomers (7, 9\$).⁷⁾ 5-Vinylprolinate (6) was successively oxidized to the carboxylic acid (8, mp 120-122 °C, 82\$) which on deprotection gave $(2\underline{S},5\underline{S})$ -pyrrolidine-2,5-dicarboxylic acid (1, 82.6\$),⁸⁾ $[\alpha]_D^{20}$ -107° (c 1.0, H₂O) [Lit.,³⁾ $[\alpha]_D^{20}$ -112° (c 1, H₂O)]. 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) ¹H-NMR spectra were recorded in CDCl₃ 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) <u>3a</u>: mp 64-66 °C; $[\alpha]_D^{20}$ -15° (c 1.39, CHCl₃); v^{KBr} 3300, 1740, 1720, 1680, 1620 cm⁻¹; $\delta_{\text{H}}(\text{CDCl}_3)$ 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); $\underline{m}/\underline{z}$ 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; v^{KBr} 1680, 1560 cm⁻¹; $\delta_{\text{H}}(\text{D}_2\text{O})$ 2.00-2.40 (4H, m), 4.30 (2 x 1H's, dd's, J=2.0, 5.0 Hz); $\delta_{\text{C}}(\text{D}_2\text{O})$ 28.5 (t), 61.1 (d), 172.8 (s); $\underline{\text{m}}/\underline{z}$ 160 (M⁺+1).

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