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A Short and Efficient Synthesis of (*S*)-4-Methylene Proline Benzyl Ester from (*S*)-Pyroglutamic Acid

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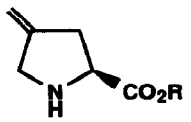
Abstract : (S)-4-methylene proline benzyl ester 2 was synthesized from benzyl N-tert -butoxycarbonyl pyroglutamate through a Mannich and a Cope elimination reactions.

Racemic 4-methylene proline is a natural product which has been isolated from seeds of loquat (*Eriobotrya japonica*).[1] Optically pure (*S*)-**1**, as structurally modified proline, has been described as potential enzyme inhibitor,[2,3] particularly as inhibitor of proline dehydrogenase.[3] It has also been found to be useful as element of peptides and drugs[4] such as tomaymycin analogs.[4a]



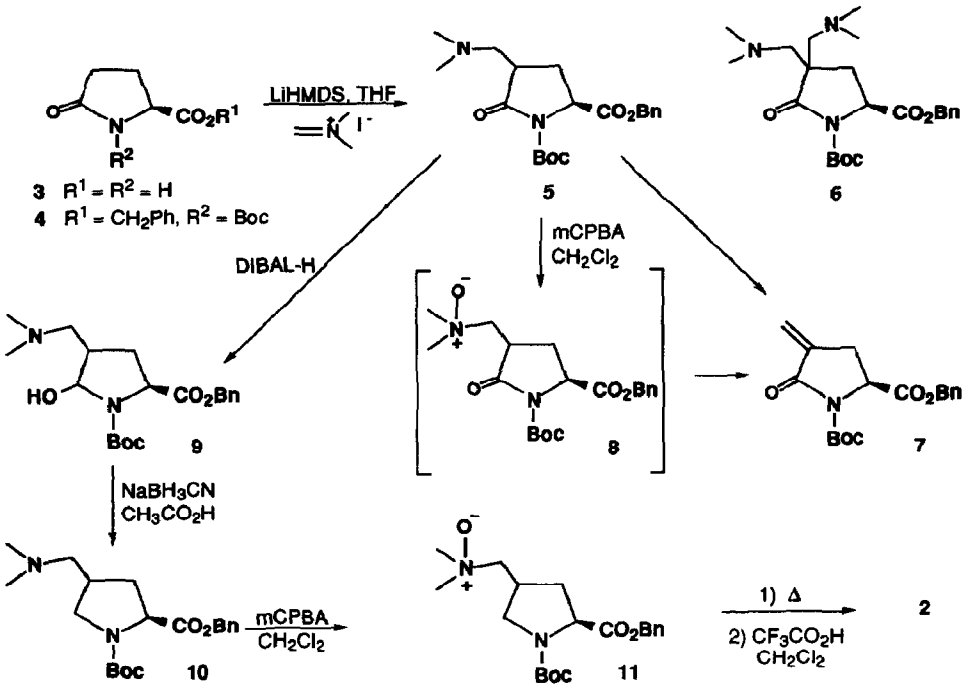
1 R = H
2 R = Bn

The first synthesis of racemic 4-methylene proline was achieved through the condensation of dimethylmalonate and 1,3-dichloroisobutene.[5] Optically pure (*S*)-**1** was synthesized by Wittig reactions of (*S*)-*N*-alkoxycarbonyl-4-oxoproline[6] or methyl *N-tert*-butoxycarbonyl 4-oxoprolinate,[3a] prepared from (2*S*)-*trans*-4-hydroxyproline.[7] Recently, a procedure was reported using radical cyclisation and leading to (*S*)-4-exomethylene proline without racemization.[8] However, the development of a simple alternate route which use very accessible starting material was still demanding.

We describe here a short synthesis of benzyl (*S*)-4-methylene pyrrolidine-2-carboxylate **2** starting from inexpensive (*S*)-pyroglutamic acid **3**. The scheme took advantage of the possibility, for conveniently protected pyroglutamates to be regiospecifically deprotonated at C-4.[9] Thus, the lithium enolate obtained from benzyl *N-tert*-butoxycarbonyl pyroglutamate **4** and LiHMDS, was alkylated in good yield at -78°C with Eschenmoser's salt[10] to give the 4-dimethylaminomethyl derivative **5** as a mixture of diastereomers (Scheme 1).[11-13] In this Mannich reaction, the amounts of base (1.05 equiv.) and Eschenmoser's salt (1.1 equiv.) were carefully controlled to avoid the formation of the bis-alkylated product **6**[14], which was obtained in 65% yield by stirring the reaction mixture at - 78° C for 40 min. with twofold excess of base and electrophile.[13]

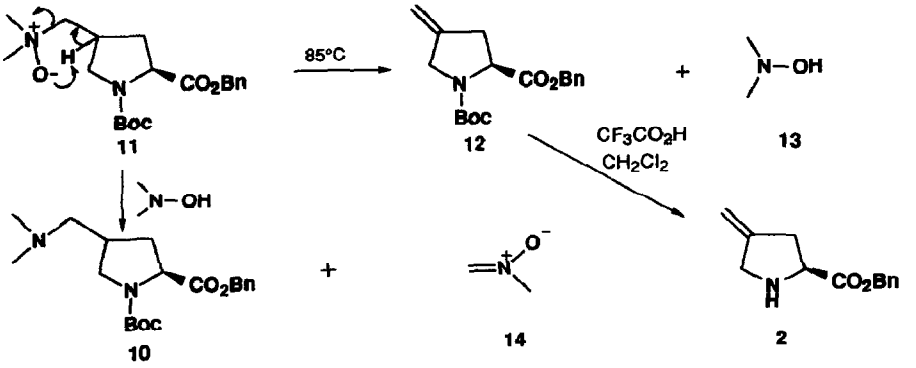
The compound **5** is sensitive to elimination of dimethylamine[15] and led "spontaneously" and specially in the presence of silicagel to small amounts of benzyl *N*-BOC-4-methylene pyroglutamate **7**. This derivative could be obtained by an easy Cope elimination at room temperature of the corresponding N-oxides **8** (mCPBA, Scheme 1).[16]

Attempts for the selective partial reduction of the conjugated carbonyl group of **7** in THF with DIBAL-H (in hexane) were not encouraging owing to the reactivity of the conjugated double bond and the formation of complex mixtures of products.



Scheme 1

Thus, the pyrrolidone carbonyl group of the Mannich product **5** was reduced into methylene according to our two step procedure.[9b] The intermediate α-hydroxy-carbamates **9** were quantitatively obtained by DIBAL-H reduction. They were directly treated with an excess of sodium cyanoborohydride in acetic acid to afford compound **10** without deprotection of the pyrrolidine nitrogen.[17] *N*-oxidation of **10** with mCPBA (1.1 equiv., 98%) and subsequent heating of **11** at 85°C in a THF/toluene mixture (1:1) gave rise to the anticipated elimination product **12** along with compound **10** (Scheme 2).



Scheme 2

The formation of **10** during Cope elimination could be the result of an oxido-reductive pathway between the starting N-oxide **11** and the produced dimethylhydroxylamine **13**, which could be oxidized into methyl nitrone **14**. A dilute solution of **11** was used in this reaction to favour the intramolecular *cis* Cope elimination *versus* the oxido reduction process but the formation of **10** could not be avoided, and the elimination product **12** was isolated in 60% yield.[18] Deprotection of the nitrogen by classical method afforded benzyl (*S*)-4-methylene prolinate **2**. The accessibility of the starting compound and the possibility to realizing this synthesis without separation of diastereoisomers are advantages of this route.

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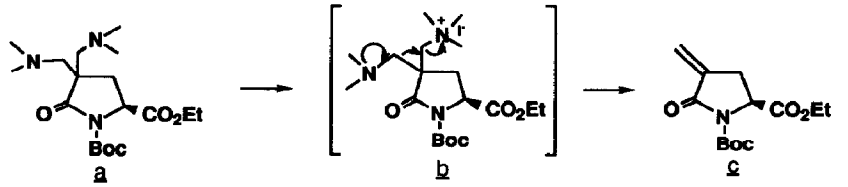
11. The crude product **5** of Mannich reaction (100%) was pure enough to perform directly subsequent steps; it could be purified by fast chromatography on silicagel and isolated in 75% yield with small amounts of **6** and **7** ; in the ^{1}H NMR spectrum of **5** the presence of two signals related to H-2 with different coupling constants (see below) is compatible with the presence of two diastereomers (in a ratio of about 7:3).[12] This observation differs from the very recently published results of C. Pedregal, C. Nájera and al. with the ethyl ester,[13] which prompt us to disclose our own work.
12. **5** : IR ($CHCl_3$, υ cm^{-1}) : 2980, 1790, 1758, 1718 ; ^{1}H NMR [300 MHz, $CDCl_3$, δ = 0 : TMS, *J* (Hz)] : 7.36 (bs, 5H, ArH), 5.20 (m, 2H, OCH_2), 4.62 (dd, 0.7 H, *J* = 9.3, *J'* = 1.9, H-2 major), 4.57 (dd, 0.3H, *J* = 9.2, *J'* = 6.1, H-2 minor), 2.85-2.32 (m, H-4, NCH_2, H-3), 2.20 and 2.17 (2s + m, 2 NCH_3, H-3), 1.96 (m, H-3 min), 1.43 (split s, 9H, 3 CH_3); ^{13}C (75 MHz, $CDCl_3$) : 174.1 (CO), 171.3 (CO), 149.3 (NCO_2), 135.2 (Ar, C*), 128.7 and 128.5 (Ar, CH), 83.7 ($O\underline{C}(CH_3)_3$), 67.4 (OCH_2), 60.2 (min)-60.0 (CH_2N), 57.7 (min)-57.3 (C-2), 45.7-45.5 (NCH_3), 41.7 (min)-40.7(C-4), 28.0-26.2 (C-3), 27.8 (CH_3) ; MS (m/z) : 376 ($M^{+\cdot}$), 275, 185, 91 (100%), 58, 57.
13. Ezquerra, J.; Pedregal, C.; Micó, I.; Nájera, C. *Tetrahedron Asymmetry*. **1994**, *5*, 921-926. The data given in this article for the ethyl ester analog of **5** agree with those of our dialkylated product **6** and could be

related to a. This compound a could give rise to c by a retro-Mannich type reaction of a mono ammonium iodide b (rather than classical Hofmann type elimination) :



Indeed, we treated compound **6** by an excess of methyl iodide in methanol at R.T. and we obtained **7** in 60% isolated yield.

14. **6** : $[\alpha]_D^{25}$ = - 35 (c = 1.0, $CHCl_3$); IR : 2975, 1782, 1742, 1722 sh., 1460 ; ^1H NMR : 7.33 (5H, ArH), 5.17 (s, 2H, OCH_2), 4.66 (dd, 1H, J = 9.7, J' = 5.7, H-2), 2.56-2.23 (m, 6H, 2 NCH_2, 2 H-3), 2.22 (s, 6H, $N(CH_3)_2$), 2.12 (s, 6H, 2 NCH_3), 1.41 (s, 9H, 3 CH_3); ^{13}C: 177.20 (CO), 171.46 (CO), 149.48 (NCO_2), 135.35 (Ar, C*), 128.64 and 128.53 (Ar, CH), 83.25 ($O\underline{C}(CH_3)_3$, 67.06 (OCH_2), 65.05 (NCH_2), 63.19 (NCH_2), 57.33 (C-2), 52.08 (C-4), 47.96 (NCH_3), 47.38 (NCH_3), 28.28 (C-3), 27.88 (CH_3) ; MS : 433 ($M^{+\cdot}$), 389, 375, 319, 275, 197, 139, 91 (100%), 58, 57.
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16. **7** : mp :63-4°C ; $[\alpha]_D^{26}$ = -24 (c = 0.96, $CHCl_3$) ; IR : 3040, 1777, 1750, 1715 ; ^1H NMR : 7.34 (ArH), 6.23 and 5.50 (2dd, 2H, $=CH_2$), 5.19 (2H, OCH_2), 4.66 (dd, 1H, J = 10.4, J' = 3.4, H-2), 3.06 and 2.71 (2m, 2H, J_{AB} = 18, 2 H-3), 1.45 (s, 9H, 3 CH_3); ^{13}C: 170.87 (CO), 165.43 (CO), 149.83 (NCO_2), 136.54 and 135.09 (Ar, C* and C-4), 128.69, 128.64, 128.50 (Ar, CH), 120.93 ($=CH_2$), 83.85 ($O\underline{C}(CH_3)_3$), 67.41 (OCH_2), 55.80 (C-2), 27.87 (CH_3), 27.84 (C-3) ; MS : 332 (M+1$^{+\cdot}$,very weak), 275, 232, 231, 196, 96, 91 (100%). This compound exhibits cytostatic activity against KB cells ; IC50 (7.5 10^{-6} M) was evaluated by C. Tempête and G. Werner), see also : Dembélé, Y.A.; Belaud, C.; Villieras, J. *Tetrahedron Asymmetry* **1992**, *3*, 511-514 and references cited therein.
17. **10** : IR : 1748, 1702 ; ^1H NMR : 7.35 (5H, ArH), 5.15 (2H, OCH_2), 4.45-4.25 (m, 1H, H-2), 3.73 (m, 1H, H-5), 3.1 (m, 1H, H-5), 2.20 (s+m, 2 NCH_3), 1.46 and 1.34 (2s, 3 CH_3) ; HRMS : ($M^{+\cdot}$) calcd for $C_{20}H_{30}N_2O_4$: 362.2205, obsd: 362.2177.
18. **12** : $[\alpha]_D^{26}$ = -23 (c = 1.7, $CHCl_3$) ; IR : 1742, 1696 ; ^1H NMR : 7.34 (bs, 5H, ArH), 5.15 (2H, OCH_2), 4.99 (2H, $=CH_2$), 4.56 and 4.44 (2dd, 1H, J = 9.5, J' = 3.2, H-2), 4.08 (2H, 2 H-5), 2.97 (m, 1H, H-3), 2.63 (m, 1H, J_{AB} = 16, H-3), 1.46 and 1.35 (2s, 9H, 3 CH_3); ^{13}C : 172.6 (CO), 142.5 (C-4), 135.7 (Ar, C*), 108.1-107.9 ($=CH_2$), 80.3 ($O\underline{C}(CH_3)_3$), 66.8 (OCH_2), 59.3-58.8 (C-2), 50.9 (C-5), 36.9-36.2 (C-3), 28.5-28.3 (CH_3) ; MS : 318 (M + 1)$^{+\cdot}$, 262, 261, 182, 126, 91 (100%), 82, 57. Acid hydrolysis of **12** (HCl 5N, 60° C, 100%) led to (*S*)-1, $[\alpha]_D^{27}$ = -50 (c = 0.74, H_2O), lit : $[\alpha]_D^{25}$ = -50.9 (c = 0.44, H_2O).[3a]
19. **2** : $[\alpha]_D^{27}$ = -26 (c = 0.85, $CHCl_3$) ; IR : 1736, 1663 ; ^1H NMR : 7.37 (5H, ArH), 5.18 (s, 2H, OCH_2), 4.95 (2H, $=CH_2$), 3.95(m, 1H, H-2), 3.71 and 3.55 (2d, 2H, J_{AB} = 14, 2 H-5), 2.82 (dd, 1H, J = 16, J' = 8, H-3), 2.62 (1H, J_{AB} = 16, H-3) ; MS : 218 (M + 1)$^{+\cdot}$, 126, 91 (100%), 82.

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