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Stereoselective Synthesis of *cis*-5-Alkyl-(S)-prolines from (S)-Pyroglutamic Acid *via* 5-Alkyl-5-hydroxy-(S)-prolines

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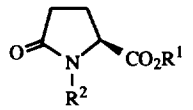
Abstract: Introduction of alkyl groups with trialkylaluminums in the 5-position of the pyroglutamic ring system without ring opening and subsequent hydrogenation over Pt/C lead to exclusively *cis*-5-alkyl-(S)-prolines without epimerization of the chiral centre. © 1997 Elsevier Science Ltd.

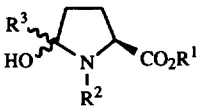
Optically pure 2,5-disubstituted pyrrolidines continue to be of great interest both as chemotherapeutic agents and also function as powerful catalysts in numerous asymmetric reactions.[1] As synthetic precursors of these compounds, N-protected pyroglutamates (**1**) which are obtained stereospecifically from commercially available and inexpensive glutamic acid, are particularly useful because they provide the chiral source and also possess an activated lactam carbonyl group for synthetic manipulation.[1,2]

Generally, reactions of **1** with nucleophiles induce ring opening. Thus, N-*tert*-butoxycarbonyl (Boc) pyroglutamate esters undergo ring opening with Grignard reagents,[3] ester lithium enolates,[4] C-nucleophiles[5] and heteronucleophiles[6] in the presence of KCN as catalyst. However, in the couse of our investigation of **1** with trialkylaluminums (AlR_3: R=Me, Et, *n*-Pr), we have found that benzyl N-methoxycarbonyl- and N-allyloxycarbonyl (Alloc)-pyroglutamates (**1a** and **b**) react with AlR_3 (5 mol eq.) in CH_2Cl_2 at room temperature for 4 ~ 6 h to give the corresponding alkylated hemiaminals (**2**)[7] in 40~92% yield, with no ring opening detected. Similarly, treatment of the benzyloxycarbonyl (Z) derivative (**1c**) with $AlMe_3$ gave the corresponding hemiaminal and benzyl pyroglutamate (**1e**), in yields of 17% and 71%, respectively (Table 1). In the case of the N-Boc derivative (**1d**), $AlMe_3$ functioned only as a Lewis acid to remove the protecting group and the isolated product was **1e** (64%) alone. Recently, it was reported that nonylmagnesium bromide reacted with a 2-pyrrolidinone derivative to give a 2,5-disubstituted 2-hydroxypyrrolidine derivative without ring opening.[8]

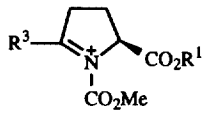
In our initial experiments directed toward stereoselective synthesis of 5-alkyl-(S)-prolines, attempts to reduce **2a** to **4a** with $Et_3SiH/BF_3{\cdot}Et_2O$[9] in THF (-78 °C; 2 h) or excess $NaBH_3CN$[10] in acetic acid (room temperature; 3 h) failed and starting compound (92%) or a ring opened product, **5**[11] (72%) along with small amounts of **4a** (5%) were obtained. Similarly, pyridine-borane reduction[12] in MeOH-10% aq. HCl (1:1) (room temperature; 0.5 h) gave **4a** (45%) and **5** (20%). However, change of solvent from MeOH-10% aq. HCl to trifluoroacetic acid (TFA)[13] brought about smooth reduction to give **4a** *via* **3a** in good yield (66%). 2,6-Lutidine-borane reduction gave the similar result (88%) (Table 2). Separation of the diastereoisomers by silica gel chromatography produced almost equal amounts of the C-5 epimers, although formation of *cis*-isomers became predominant with bulkier alkyl groups than methyl (Table 3).



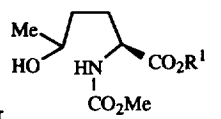
1a: R^1=Bn, R^2=CO_2Me
b: R^1=Bn, R^2=Alloc
c: R^1=Bn, R^2=Z
d: R^1=Bn, R^2=Boc
e: R^1=Bn, R^2=H
f: R^1=Me, R^2=CO_2Me
g: R^1=Me, R^2=Alloc



2a: R^1=Bn, R^2=CO_2Me, R^3=Me
b: R^1=Bn, R^2=CO_2Me, R^3=Et
c: R^1=Bn, R^2=CO_2Me, R^3=*n*-Pr
d: R^1=Bn, R^2=Alloc, R^3=Me
e: R^1=Bn, R^2=Alloc, R^3=Et
f: R^1=Me, R^2=CO_2Me, R^3=Me
g: R^1=Me, R^2=CO_2Me, R^3=Et
h: R^1=Me, R^2=CO_2Me, R^3=*n*-Pr
i: R^1=Me, R^2=Alloc, R^3=Me



3a: R^1=Bn, R^3=Me
b: R^1=Me, R^3=H



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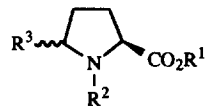


4a: R^1=Bn, R^2=CO_2Me, R^3=Me
b: R^1=Bn, R^2=CO_2Me, R^3=Et
c: R^1=Bn, R^2=CO_2Me, R^3=*n*-Pr
d: R^1=Bn, R^2=Alloc, R^3=Me
e: R^1=Bn, R^2=Alloc, R^3=Et
f: R^1=Me, R^2=CO_2Me, R^3=Me
g: R^1=Me, R^2=CO_2Me, R^3=Et
h: R^1=Me, R^2=CO_2Me, R^3=*n*-Pr
i: R^1=Me, R^2=Alloc, R^3=Me

Table 1. Alkylation of **1** with AlR_3 (R=Me, Et and *n*-Pr)

Compd	Product	Yield (%)	Compd	Product	Yield (%)	Compd	Product	Yield (%)
1a	**2a**	92	**1b**	**2d**	81	**1f**	**2g**	76
1a	**2b**	79	**1b**	**2e**	72	**1f**	**2h**	40
1a	**2c**	29	**1f**	**2f**	82	**1g**	**2i**	75

Table 2. Reduction of **2** with 2,6-lutidine-borane in TFA

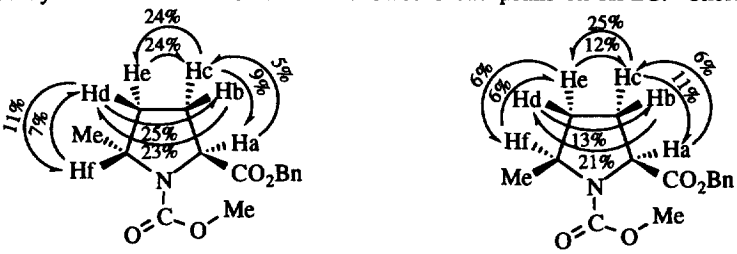
Compd	Product	Yield (%)	Compd	Product	Yield (%)	Compd	Product	Yield (%)
2a	**4a**	88	**2d**	**4d**	71	**2g**	**4g**	73
2b	**4b**	95	**2e**	**4e**	93	**2h**	**4h**	79
2c	**4c**	80	**2f**	**4f**	81	**2i**	**4i**	71

Stereochemical assignments for *cis*- and *trans*-**4a** were made on the basis of NOE measurements.[14] In the *trans* isomer, the proton Ha (0.55H, 4.35 ppm, dd, J_{ab}=9.0 Hz, J_{ac}=1.2 Hz; 0.45H, 4.44 ppm, dd, J_{ab}=9.0 Hz, J_{ac}=1.2 Hz) exhibits two sets of two coupling constants with a different order of magnitude due to the presence of two rotamers.[15] This suggests that Hb is *trans* and Hc *cis* with respect to Ha. When Hb was irradiated, Hd gave a significant NOE. When Hc was irradiated, Ha and He gave significant NOEs. When Hd was irradiated, Hf gave a significant NOE. Results from NOE experiments indicated the expected 2,5-*trans* configuration. For the assignment of the *cis* isomer, proton Ha was taken as the starting point. The observed NOE effects are shown in Figure 1, indicating the 2,5 *cis* configuration.

The highly diastereoselective addition of alkylcopper reagents to the N-acyliminium ion (**3b**) has been reported to produce *trans*-5-alkyl-(S)-prolines.[16] On the other hand, the *cis* isomers were synthesized from protected (S)-glutamic acid[17] and also from (S)-pyroglutamic acid[18] through multistep reaction sequences. Based on 5-alkyl-5-hydroxy-(S)-prolines as intermediate, we have developed a short stereoselective synthesis of the *cis*-isomers.

Initially, we tried to dehydrate **2f** with TFA[19], TsOH[20], NH_4Cl[21] and HMPA[22] in order to carry out catalytic reduction of the double bond. However, we were unable to obtain the dehydrated compound. Fortunately, direct catalytic hydrogenation of **2f** over 5% Pt/C in TFA-chloroform at room temperature for 14 h gave **4f** in high yield, although the use of 10% Pd/C[23] failed. For **4f**, *cis* and *trans* diastereomeric ratio was

determined by ^{1}H-NMR measurement and found to be 95:5. For **4g** and **4h**, the *cis* and *trans* isomers could not be determined by ^{1}H-NMR measurement and showed broad peaks on HPLC. Therefore, they were



4a-*trans* **Figure 1** **4a**-*cis*

converted to the corresponding benzyl esters (**4b** and **4c**)[24] and HPLC analysis revealed the *cis* and *trans* ratios to be 99:1 and 99:1, respectively (Table 4). Enantiometric purity was established by the preparation of (R)-**4a** and the subsequent HPLC characterization of (R)-*cis* and *trans* compounds and (S)-*cis* and *trans* compounds.[25] This experiment clearly demonstrates the absence of epimerization at C-2 during this reaction sequence.

Table 3. Ratios of *cis*- and *trans*-**4a**, **b** and **c** by 2,6-lutidine-borane reduction

Compd	Temp.	*cis*:*trans*	Compd	Temp.	*cis*:*trans*
4a	r.t.	47:53	**4b**	r.t.	73:27
4a	0 °C	47:53[a]	**4c**	r.t.	76:24
4a	-78 °C	54:46[b]	**4f**	r.t.	59:41

Table 4. Hydrogenation of **2f, g** and **h** over 5% Pt/C in TFA-$CHCl_3$

Product	Yield (%)	*cis*:*trans*
4f	88	>95:5
4g	85	99:1
4h	98	99:1

[a]Chemical yield, 70%. [b]Chemical yield, 49%.

In summary, a short synthesis of *cis*-5-alkyl-(S)-prolines (**4f, g** and **h**) from the N-protected pyroglutamate (**1f**) *via* the key intermediates *cis*-5-alkyl-5-hydroxy-(S)-prolines (**2f, g** and **h**) was performed, without epimerization of the chiral centre.

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7. All compounds were identified by IR, ^{1}H NMR and mass spectra. Selected spectral data for compounds **2**. **2a**: mp = 34-36 °C (pet. ether); IR (KBr): ν = 3350, 2960, 1720 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.89-1.96 (m, 1H), 2.07-2.22 (m, 1H), 2.09 (s, 3H), 2.41-2.57 (m, 2H), 3.67 (s, 3H), 4.34-4.40 (m, 1H), 5.15 and 5.17 (d, d, AB, *J* = 12.2, 2H), 5.35 (br s, 1H), 7.33-7.39 (m, 5H); FAB-MS m/z: 316 ($M+Na^+$, 100). Anal. calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found:

C, 61.28; H, 6.46; N, 4.67. In the case of **2c** and **2h**, considerable amounts of unidentifiable side products (origin on tlc) were obtained.

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11. Compound **5**: IR (neat): ν = 3325, 2975, 1730, 1720 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 1.8, 1.5H), 1.15 (d, *J* = 2.2, 1.5H), 1.35-1.50 (m, 2H), 1.70-2.08 (m, 3H), 3.67 (s, 3H), 3.67-3.83 (m, 1H), 4.38-4.48 (m, 1H), 5.15 and 5.21 (d, d, AB, *J* = 12.1, 2H), 5.44 (br s, 1H), 7.36 (s, 5H); FAB-MS m/z: 296 ($M+Na^+$, 34.32), 154 (100).
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14. Compounds *cis*- and *trans*-**4a** are 55:45 rotameric mixtures, respectively. *Cis*-**4a**: IR (neat): ν = 2975, 1750, 1710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.1, 1.35H), 1.32 (d, *J* = 6.1, 1.65H), 1.52-1.70 (m, 1H), 1.95-2.10 (m, 2H), 2.15-2.20 (m, 1H), 3.57 (s, 1.65H), 3.73 (s, 1.35H), 3.94-4.02 (m, 0.45H), 4.02-4.13 (m, 0.55H), 4.34 (t, *J* = 6.1, 0.55H), 4.42 (t, *J* = 6.1, 0.45H), 5.14-5.21 (m, 2H), 7.33-7.38 (m, 5H); GC-MS m/z: 277 (M^+, 1.48), 142 (100). *Trans*-**4a**: IR (neat): ν = 2975, 1750, 1710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 6.1, 1.35H), 1.21 (d, *J* = 6.1, 1.65H), 1.52-1.58 (m, 1H), 1.90-1.98 (m, 1H), 2.01-2.13 (m, 1H), 2.22-2.32 (m, 1H), 3.52 (s, 1.65H), 3.73 (s, 1.35H), 4.01-4.13 (m, 0.45H), 4.18-4.21 (m, 0.55H), 4.35 (dd, *J* = 9.0, 1.2, 0.55H), 4.44 (dd, *J* = 9.0, 1.2, 0.45H), 5.11-5.22 (m, 2H), 7.33-7.38 (m, 5H); EI-MS m/z: 277 (M^+, 1.92), 142 (100).
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25. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 5/5, flow rate = 0.3 mL/min) compound, t_R (min): (S)-*cis*-**4a**, 17.5; (S)-*trans*-**4a**, 16.7; (R)-*cis*-**4a**, 20.7; (R)-*trans*-**4a**, 20.0; (S)-*cis*-**4b**, 17.0; (S)-*trans*-**4b**, 15.9; (S)-*cis*-**4c**, 16.4; (S)-*trans*-**4c**, 17.0.

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