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Stereoselective Synthesis of (2*S*,3*S*,4*R*,5*S*)-Proline-3,4,5-d_3

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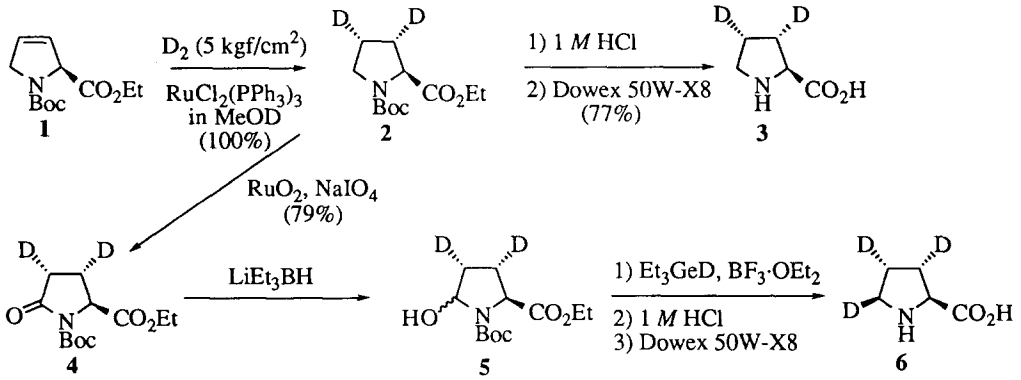
Abstract: A catalytic deuteration of protected 3,4-dehydro-L-proline using $RuCl_2(PPh_3)_3$ followed by RuO_4-oxidation gave a 3,4-dideuterated L-pyroglutamic acid derivative which is considered to be a promising precursor for various deuterated amino acids. The present study demonstrates a stereoselective reduction of the amide carbonyl moiety leading to L-proline derivatives in which all of the ring methylenes are stereoselectively labeled with deuterium. © 1997 Elsevier Science Ltd.

The proline residue is usually located in turn structures of protein due to its unusual conformational preference; hence, it is recognized to be one of the important residues which are responsible for the folding of the polypeptide chain. Furthermore, the proline skeleton can often be seen in antibiotics, pharmaceuticals, and metabolites.[1] Specimens of L-proline chirally labeled with isotopic hydrogen(s) would allow a conformational analysis around the residue of peptide and the stereochemical studies on the enzymatic reaction of the biologically important compounds which contain the proline framework.[2]

Recently, D. W. Young *et al.* developed the synthesis of proline derivatives which are stereospecifically labeled with deuterium on the β-carbon.[3] For stereoselective labeling at the γ-carbon, reductive deuteration of tosylates derived from 4-hydroxyproline with $LiAlD_4$ or $LiEt_3BD$ was reported.[4] However, there have been no reports concerning the selective deuterium incorporation into the δ-position except for an enzymatic method.[5] As a part of our continuing studies on the synthesis of isotopically labeled amino acids,[6] we here wish to report a stereoselective synthesis of (2*S*,3*S*,4*R*,5*S*)-proline-3,4,5-d_3 in which all of the prochiral methylenes are stereoselectively labeled with deuterium.

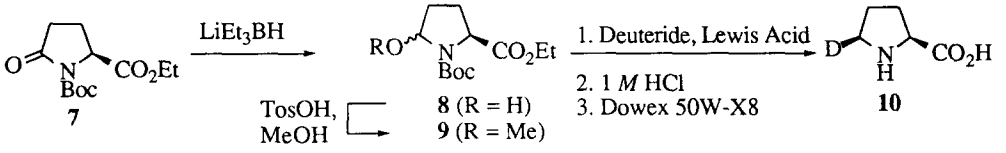
Since a catalytic deuteration of optically active dehydroamino acids has provided an extremely useful approach to stereoselective introduction of deuterium atoms, we employed a protected 3,4-dehydro-L-proline **1**[7] derived from *trans*-4-hydroxy-L-proline as a chiral template for this work (Scheme 1). Hitherto, a few papers concerning a catalytic deuteration[8] or tritiation[9] of 3,4-dehydroproline itself have been published, but no papers concerning the corresponding protected derivatives can be seen in the literature. It was further pointed out that the tritiated samples showed some scrambling of the label.[10] Therefore, we initially examined the regio- and stereoselective deuteration of the dehydroproline **1**. When a catalytic deuteration of compound **1** was carried out using 10% Pd on carbon in MeOD for 24 h under the medium pressure of deuterium gas (5 kgf/cm^2), serious H-D scrambling was observed, probably due to the presence of the electron-attractive Boc group on nitrogen which would make the δ-protons labile to permit the formation of a π-allyl complex with the catalyst. In fact, the extent of the H-D scrambling observed in a similar treatment of the non-protected 3,4-dehydroproline was not so significant. The regio- and stereoselectivities of the deuteration were checked by ^{1}H NMR spectroscopy after being converted to the non-protected proline **3** because the ^{1}H NMR spectrum of the protected product **2** was too complex to be assessed due to the well known *cis-trans* isomerism about the urethane amide bond in *N*-carbamoylproline derivatives.[11]



Scheme 1

After a survey of various transition metal catalysts such as $RhCl(PPh_3)_3$, $RuCl_2(PPh_3)_3$, Rh/C, Ru/C, PdO, and PtO_2, $RuCl_2(PPh_3)_3$ was found to be effective for the stereoselective deuteration of dehydroproline **1** to afford 3,4-dideuterated proline derivative **2** without significant H-D scrambling. A successive hydrolysis of the compound **2** in refluxing 1 *M* HCl for 3 h gave (*2S,3S,4R*)-proline-3,4-d_2 (**3**) in 77% yield. It was confirmed by ^1H NMR integration that the deuterium content of the *3S*-proton in compound **3** was up to 95%. The relative configuration was determined by ^1H NMR spectrum and the optical purity (98%ee) was checked by HPLC analysis using chiral stationary phase column (MCIGEL CRS10W).

In order to incorporate a deuterium atom into the δ-position, the redox treatment on the δ-position was schemed as follows. Thus, oxidation of the protected proline-3,4-d_2 **2** was carried out using RuO_4, prepared *in situ* from RuO_2 and $NaIO_4$,[12] to afford 3,4-dideuterated pyroglutamic acid derivative **4** in 79% yield. Although several methods for conversion of pyroglutamic acid to proline have been known,[13,14] a procedure which involves a stepwise process of reducing the carbonyl moiety is required to achieve a stereoselective incorporation of deuterium into the δ-position. Therefore, a preliminary examination was carried out using unlabeled ethyl pyroglutamate **7** as a substrate (Scheme 2).



Scheme 2

According to the procedure of C. Pedregal *et al.*,[14] we performed the reduction of the protected pyroglutamic acid **7** to the 5-hydroxyproline **8** with lithium triethylborohydride. Then the crude amino alcohol **8** was directly subjected to a reductive deuteration using Et_3SiD-BF_3·OEt_2 system at -78 ℃ followed by an acidic hydrolysis to give proline-5-*d* (**10**) in 64% yield based on the ethyl pyroglutamate **7** (Table 1, entry 1). The stereoselectivity of the deuteration was determined by ^1H NMR integration of the δ-proton signals, and it was found that the formation of (*2S,5S*)-**10**, the *cis* isomer, was predominant in the ratio of *cis/trans* = 87/13. This was rationalized by the preferential delivery of deuteriosilane from the β-side of the acyl iminium salt opposite to the Boc group which would be located in the α-side due to the steric repulsion between the group and the ester moiety.

A reduction of the amino alcohol **8** using other silanes such as tris(trimethylsilyl)deuteriosilane (TMS_3SiD), Ph_3SiD, or Ph_2SiD_2 with $BF_3{\cdot}OEt_2$ was investigated and the results are listed in Table 1. As shown in the entries 1,3-5, the nature of the deuteriosilane significantly influenced the facial selectivity. The other group 14 metal deuterides were also tested (entries 8-10) and Et_3GeD afforded the best results in our case. The employment of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and trityl perchlorate (Ph_3CClO_4) as a Lewis acid resulted in the same degree of selectivity (entries 6 and 7). Also, an etherification of the aminoalcohol **8** to **9** prior to the reduction did not show any remarkable improvement of the selectivity (entries 2 and 9).

Table 1. Transformation of Pyroglutamic Acid 7 into Proline-5-*d* (10)

Entry	R	Lewis Acid (2 equiv.)	Deuteride (2 equiv.)	**10**	
				%[a]	*5S* / *5R*[b]
1	H	$BF_3{\cdot}Et_2O$	Et_3SiD	64	87 / 13
2	Me	$BF_3{\cdot}Et_2O$	Et_3SiD	64	89 / 11
3	H	$BF_3{\cdot}Et_2O$	TMS_3SiD	74	74 / 26
4	H	$BF_3{\cdot}Et_2O$	Ph_3SiD	55	55 / 45
5	H	$BF_3{\cdot}Et_2O$	Ph_2SiD_2	87	59 / 41
6	H	TMSOTf	Et_3SiD	87	87 / 13
7	H	Ph_3CClO_4	Et_3SiD	52	88 / 12
8	H	$BF_3{\cdot}Et_2O$	Et_3GeD	81	92 / 8
9	Me	$BF_3{\cdot}Et_2O$	Et_3GeD	64	90 / 10
10	H	$BF_3{\cdot}Et_2O$	Bu_3SnD	88	91 / 9

a) Based on the starting pyroglutamic acid derivative **7**.

b) Determined by 400 MHz ^{1}H NMR.

Consequently, the reaction conditions shown in entry 8 were applied to the reduction of deuterated ethyl pyroglutamate **4** to give a mixture of (*2S,3S,4R,5S*)- and (*2S,3S,4R,5R*)-proline-3,4,5-d_3 (**6**) in 55% yield in a ratio of 89:11. The optical purity at the C-2 position was determined by HPLC analysis to be 97%ee.

The regio- and stereoselectivity of the deuterium incorporation was confirmed by 400 MHz ^{1}H NMR spectrum of L-proline-3,4,5-d_3 (**6**) comparing with that of unlabeled L-proline (Figure 1). Although the deuterium content of the *4R*-proton can not be estimated due to the signal overlapping, the signal intensity of the *3S*-proton corresponds only to the 0.08 proton and the ratio of *5S*- and *5R*-proton signals is 11:89, indicating a stereoselective formation of (*2S,3S,4R,5S*)-isomer.

In conclusion, we realized a stereoselective synthesis of L-proline-3,4,5-d_3 in which all of the prochiral methylenes are stereoselectively labeled with deuterium; in addition, proline-3,4-d_2 and proline-5-*d* are also accessible upon request. Although we have not prepared the corresponding antipode, we can see no reason why a similar process should not be applied to 3,4-dehydro-D-proline or its racemate. An additional advantage of this protocol was the employment of deuterated ethyl pyroglutamate as the key intermediate which can be converted to various amino acids, and hence, the present procedure would provide a new synthetic route to the hitherto unknown deuterium-labeled amino acids.

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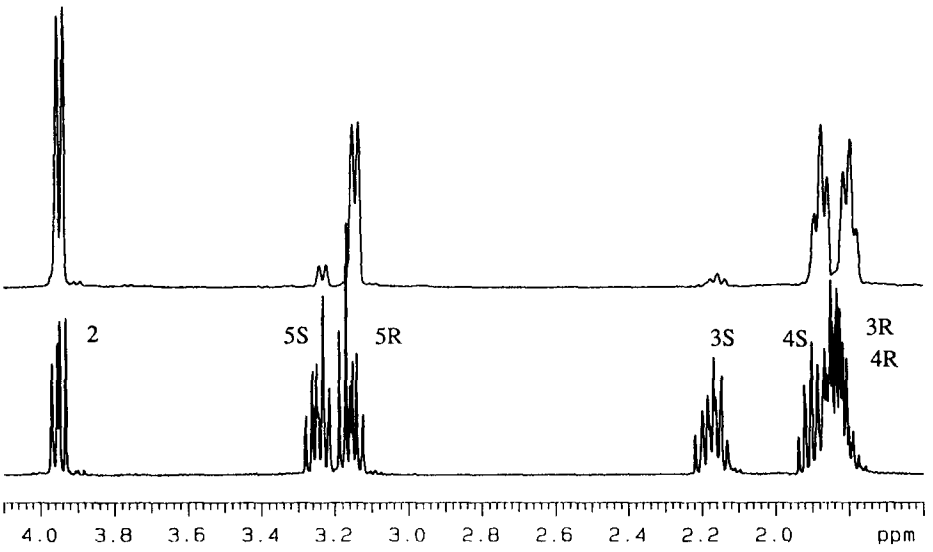

Fig. 1. 400 MHz ^{1}H NMR Spectra of (*2S,3S,4R,5S*)-Proline-3,4,5-d_3 (upper) and Unlabeled Proline (lower) in D_2O at pH 6.0.

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