Pergamon

Tetrahedron Letters 42 (2001) 5335–5338

TETRAHEDRON LETTERS

A convenient and high yield method to prepare 4-hydroxypyroglutamic acids

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Received 23 May 2001; accepted 8 June 2001

Abstract—$RuO_2/NaIO_4$ oxidation of *N*-Boc-4-silyloxy and 4-acetoxy proline methyl esters under ethyl acetate/water biphase condition gave *N*-Boc-4-silyloxy and 4-acetoxy pyroglutamic acid derivatives in high yields. Desilylation with TBAF afforded both *cis*- and *trans*-*N*-Boc-methyl-4-hydroxy pyroglutamates.

Functionalized pyroglutamic acid derivatives are of great interest because they have been employed as key intermediates in syntheses of many biologically interesting heterocycles.[1,2] One of the most studied methods to obtain these functionalized pyrogluta-mates is alkylation of the lithium enolate derived from *N*-protected pyro-glutamic esters to give 4-substituted derivatives.[3–7] This method is particularly good for reactive electrophiles such as allylic halides and aryl aldehydes, with moderate to good yields and stereoselectivity. However, there still does not exist a practical and stereoselective synthesis of differentially protected derivatives of 4-hydroxy pyroglutamic acids. Nozoe et al. has reported a hydroxylation of the lithium enolate derived from benzyl *N*-Boc-(L)-pyroglutamate with 2-toluenesulfonyl-3-phenyl oxaziridine to give *trans*-4-hydroxy pyroglutamate in moderate yield and good stereocontrol.[8] However, inconsistent yields with this procedure have been reported, presumably due to further reaction of the enolate with the imine liberated from the oxaziridine.[9] An efficient synthesis of racemic *cis*- and *trans*-4-hydroxy pyroglutamic acids has been reported.[10] More recently, Merino et al. reported an asymmetric synthesis of 4-hydroxyl pyroglutamic acids, involving 1,3-dipolar cycloaddition of furfuryl nitrone with acrylamide derived from Oppolzer's chiral sultam.[11] Post transformations of the 1,3-dipolar cycloadduct are necessary to yield the desired product.

In a medicinal chemistry program that required multigram scale synthesis of optically pure methyl *N*-Boc-4-hydroxy pyroglutamates **1a** and **1b** as synthetic precursors, we discovered a highly efficient method to obtain both diastereomers and their derivatives from cheap, commercially available (4*R*)-hydroxy proline **2**. The key reaction is a $RuO_2/NaIO_4$ oxidation of properly protected 4-hydroxy proline derivatives under an ethyl acetate/water biphase condition. This two-phase oxidation was reported some years ago by Yoshifuji et al. for the conversion of cyclic α-aminoacids to α-aminodicarboxylic acids.[12–15] Application of this protocol to the *N*-Boc-4-silyoxy and 4-acetoxy protected proline derivatives (**4a**,**b** and **6a**,**b**) has led us to a high yielding preparation of **1a**,**b** and **8a**,**b**.

(4*R*)-Hydroxy proline **2** was *N*- and *C*-protected as *N*-Boc-(4*R*)-hydroxy proline methyl ester **3a** in a quantitative yield (Scheme 1).[16] The hydroxyl group in **3a** was further protected as TBDMS ether **4a** in 98% yield. Oxidation of **4a** with RuO_2 (20% mol) and $NaIO_4$ (250% mol) in ethyl acetate/water at room temperature gave pyroglutamate **5a** in near quantitative yield.[17,18] ^1H and ^{13}C NMR indicated that **5a**, obtained by simple extraction work-up, was practically pure. This oxidation can be carried out on a 15 g scale of **4a** without loss of yield. The TBDMS protecting group was removed with TBAF to give methyl (4*R*)-*trans*-*N*-Boc-4-hydroxyl pyroglutamate **1a** in 80% yield. The final deprotection could be further improved to 90% yield with 2 equiv. of acetic acid present to minimize base hydrolysis of the pyroglutamate.

Keywords: 4-hydroxyl pyroglutamic acid; ruthenium dioxide; oxidation; Mitsunobu reaction; *N*-acyliminium ion.

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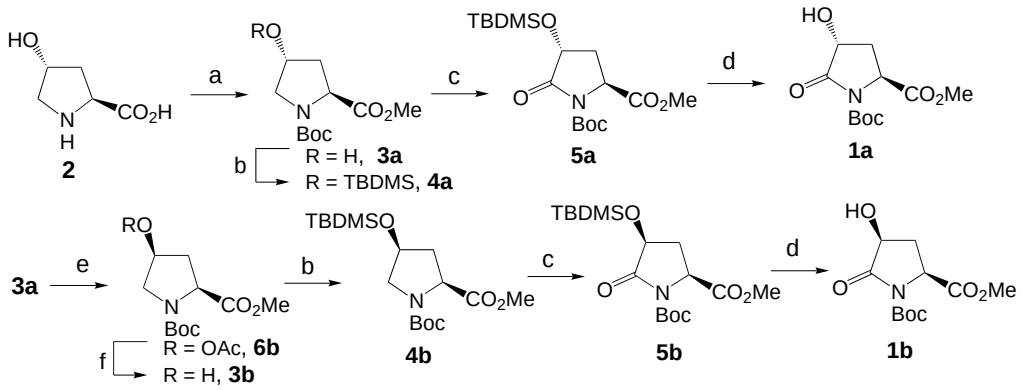
PII: S0040-4039(01)01030-9



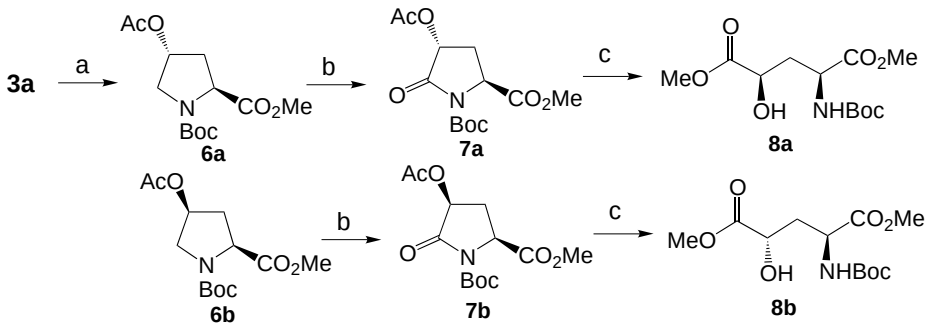
Scheme 1. Preparation of *cis* and *trans*-*N*-Boc-4-hydroxyl pyroglutamates **1a** and **1b**. (a) 1. MeOH, HCl, reflux, 2. $(Boc)_2O$, Et_3N, CH_2Cl_2, 100% for 2 steps; (b) TBDMSCl, imidazole, DMF, 98%; (c) RuO_2(cat), $NaIO_4$, EtOAc/H_2O, >95%; (d) TBAF, HOAc, THF, 80–90%; (e) PPh_3, DEAD, HOAc, THF, >95%; (f) K_2CO_3, MeOH, >95%.

To prepare methyl (4*S*)-*cis*-*N*-Boc-4-hydroxyl pyroglutamate **1b,** compound **3a** was subjected to a Mitsunobu reaction to give the *N*-Boc-4-acetoxy proline **6b**. Acetoxy proline **6b** was hydrolyzed to (4*S*)-*cis*-hydroxy proline **3b** with K_2CO_3 in methanol. The yield of the two-step Mitsunobu inversion and deprotection was near quantitative. With no event, protection of **3b** as the sily ether **4b**, oxidation of **4b** with $RuO_2/NaIO_4$, and deptotection of **5b** with TBAF gave rise to methyl (4*S*)-*cis*-*N*-Boc-4-hydroxyl pyroglutamate **1b** in high yield.

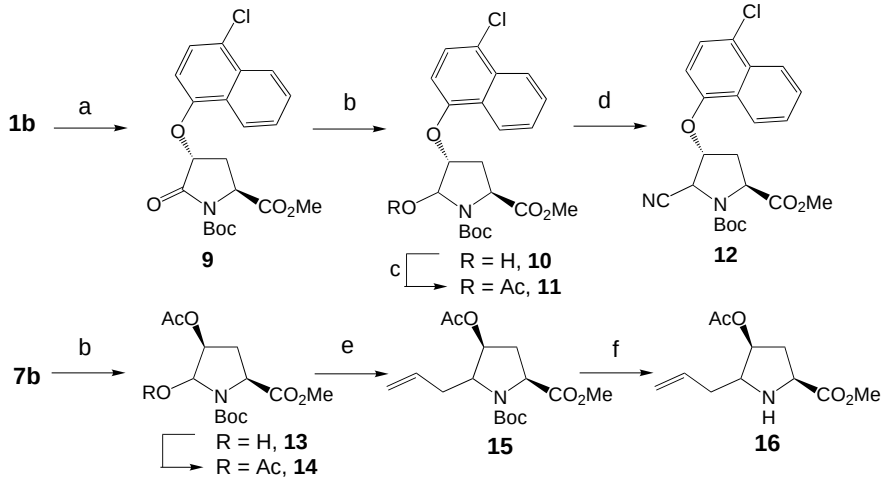
The oxidation could also be carried out on the acetate **6a** and **6b** to give *N*-Boc-4-acetoxy pyroglutamic acid derivatives **7a** and **7b** in high yield (Scheme 2). However, the reaction rate is slower than that of sily ethers **4a** and **4b**, presumably because the acetate is more electron-withdrawing than the sily ether, thus making them less prone to oxidation. Attempts to deprotect the acetate with even a catalytic amount of K_2CO_3 in methanol resulted in attack of methoxide on the pyroglutamate ring carbonyl to give γ-hydroxyl glutamic esters **8a** and **8b**. This result indicated a higher reactivity of the ring carbonyl towards nucleophilic addition.

N-Boc-4-hydroxyl pyroglutamic acid derivatives are useful chiral intermediates. For example, **1b** underwent Mitsunobu reaction with 4-chloro-1-naphthol to give *trans*-*N*-Boc-4-aryloxy pyroglutamate **9** in 78% yield. Reduction of **9** with $LiBEt_3H$ gave a hemiaminal **10,** which was further activated to acetate **11**. Treatment of **11** with TMSCN under Lewis acid conditions afforded *N*-Boc-aminonitrile **12** in 90% yield through an *N*-acyliminium ion intermediate.[19] Similarly, reduction of 4-acetoxy pyroglutamate **7b** gave a hemiaminal **13**. Conversion of **13** to diacetate **14**, and displacement of the 5-acetoxy group in **14** with allyl trimethylsilane gave 5-allyl-4-acetoxy pyrrolidine **15** as a 3:1 mixture of two diastereomers. Deprotection of the Boc group afforded a separable mixture of amines **16**. Both **12** and **16** are important intermediates for the synthesis of bicyclic dipeptide mimetics (Scheme 3).

In summary, we have discovered a highly efficient preparation of either *cis*- or *trans*-*N*-Boc-4-hydroxy pyroglutamic acid derivatives by $RuO_2/NaIO_4$ oxidation starting from a common precursor, (4*R*)-hydroxy proline **2**. These 4-hydroxy pyroglutamic acid derivatives are useful intermediates for the synthesis of other nitrogen containing heterocycles.



Scheme 2. Preparation of γ-hydroxyl glutamic ester **8a** and **8b**. (a) Ac_2O, pyridine, 100%; (b) RuO_2(cat), $NaIO_4$, EtOAc/H_2O, >95%; (c) K_2CO_3, MeOH, >95%.



Scheme 3. Chemical transformation of *N*-Boc-hydroxy pyroglutamate derivatives. (a) 4-Chloro-1-naphthol, PPh_3, DEAD, THF, 0°C–rt, 78%; (b) $LiBEt_3H$, THF, −78°C; (c) Ac_2O, pyridine, 90% for two steps; (d) TMSCN, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −60°C, 80%; (e) allyl trimethylsilane, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −60°C, 70%; (f) TFA, CH_2Cl_2, 90%.

Acknowledgements

We thank Dr. Carl Decicco for his support of this work and Dr. David Nugiel for his critical reading of the manuscript.

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17. A representative procedure for preparation of **1a**: To a solution of $NaIO_4$ (7.43 g, 34.75 mmol) in water (107 mL) was added $RuO_2{\cdot}{\times}H_2O$ (0.37 g, 2.7 mmol) under the protection of nitrogen. The resulting green–yellow solution was stirred for 5 min followed by addition of **4a** (5.0 g, 13.9 mmol) in EtOAc (60 mL) in one portion. The reaction was stirred at rt for 18 h. The solution remained yellowish during the reaction. The resulting mixture was then diluted with EtOAc and filtered through a pad of Celite. The organic layer was washed with saturated $NaHSO_3$, which resulted in precipitation of Ru black. The precipitate was filtered off through a pad of Celite. The EtOAc layer was then washed with brine and dried with $MgSO_4$. Evaporation of solvent gave **5a** as a colorless liquid (4.95 g, 95%). To a solution of **5a** (3.28 g, 8.78 mmol) in THF (6.0 mL) was added TBAF (1.0 M in THF, 14.0 mL, 14.0 mmol) at 0°C. The solution was allowed to warm and stirred at rt for 4 h. Evaporation of THF and a column chromatography (hexane:EtOAc = 1:1) gave compound **1a** (1.90 g, 80%) as a white solid. Spectroscopic data: **5a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.60 (dd, J = 1.44, 9.2 Hz, 1H), 4.42 (dd, J = 8.4, 10.0 Hz, 1H), 3.80 (s, 3H), 2.40–2.20 (m, 2H), 1.50 (s, 9H), 0.89 (s, 9H), 0.18 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.90, 171.73, 149.50, 83.85, 69.66, 54.99, 52.63, 31.86, 27.88, 25.66, 18.18, −4.47. Compound **1a**: mp 90.6°C, $[\alpha]$ = +35.3 (*c* 0.264 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.65 (dd, J = 0.7, 9.8 Hz, 1H), 4.46 (dd, J = 8.5, 10.6 HZ, 1H), 3.80 (s, 3H), 2.49 (m, 1H), 2.29 (m, 1H), 1.51 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.25, 171.29, 148.87, 84.32, 68.68, 55.43, 52.80, 30.57, 27.82.
18. Selected spectroscopic data: **1b**: mp 107.9°C, $[\alpha]$ = −155.7 (*c* 0.264 in $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.48 (t, J = 8.1 Hz, 1H), 4.36 (t, J = 8.1 Hz, 1H), 2.72 (dt, J = 8.1, 13.2 Hz, 1H), 1.95 (dt, J = 8.4, 13.2 Hz, 1H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.51, 171.24, 148.83, 84.36, 69.39, 55.55, 52.70, 30.37, 20.77. Com-

pound **5b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.47 (t, $J=7.7$ Hz, 1H), 4.26 (t, $J=7.7$ Hz, 1H), 3.77 (s, 3H), 2.59 (dt, $J=8.1$, 13.5 Hz, 1H), 2.00 (dt, $J=7.5$, 13.2 Hz, 1H), 1.50 (s, 9H), 0.88 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H). Compound **7a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.46 (t, $J=8.8$ Hz, 1H), 4.67 (dd, $J=1.1$, 9.9 Hz, 1H), 3.81 (s, 3H), 2.60 (m, 1H), 2.29 (m, 1H), 2.15 (s, 3H), 1.51 (s, 9H). Compound **7b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.38 (t, $J=8.1$ Hz, 1H), 4.51 (t, $J=8.1$ Hz, 1H), 3.80 (s, 3H), 2.80 (dt, $J=7.2$, 12.9 Hz, 1H), 2.14 (s, 3H), 2.00 (dt, $J=7.2$, 12.9 Hz, 1H), 1.51 (s, 9H).

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