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# Synthesis and reactions of a novel 3,4-didehydropyroglutamate derivative

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**Some reactions such as catalytic hydrogenation, Diels–Alder reaction, cyclopropanation, dihydroxylation, and Michael addition of a novel 3,4-didehydropyroglutamate derivative, in which the carboxylic group is protected as an ABO ester, are examined and found to take place in a stereospecific manner giving 3- and/or 4-substituted pyroglutamate derivatives without loss of enantiomeric purity at the α-position.**

L-Pyroglutamic acid, easily prepared by the direct dehydration of L-glutamic acid, is recognized as a versatile building block in asymmetric synthesis.[1] Among a wide variety of chiral synthons derived from pyroglutamic acid, 3,4-didehydropyroglutaminol derivatives are often used to introduce various substituents at the 3- and/or 4-positions *via* dihydroxylation, epoxidation, cycloaddition reaction, Michael addition, and so on. The most employed unsaturated pyroglutaminol derivatives are their silyl ethers or cyclic *N*,*O*-acetals. The reduction of the carboxyl group of the pyroglutamic acid is necessary to perform the above reactions without affecting the integrity of chirality; and after the required modification has been completed, the carboxylate functionality must be regenerated if necessary.

On the other hand, the corresponding 3,4-didehydropyroglutamic esters could not be used as a chiral template due to its tendency to racemize and isomerize to the corresponding 2,3-didehydropyroglutamate or a heteroaromatic pyrrole.[2,3] To our knowledge, there is only one report concerning the reactivity of the 3,4-didehydropyroglutamate where the Diels–Alder adduct of the olefin with cyclopentadiene was obtained only in 50% ee.[4] In this Communication, we describe the synthesis of a stable 3,4-didehydropyroglutamate derivative in which the carboxylate function was masked as a cyclic *ortho* ester to reduce the acidity of the α-proton. Some reactions of the olefin such as catalytic hydrogenation, Diels–Alder reaction, cyclopropanation, dihydroxylation, and Michael addition are also investigated.

Recently, Lajoie and co-workers have developed a new strategy for the synthesis of a variety of amino acids based on the elaboration of a chiral serine aldehyde equivalent in which the carboxylic acid is protected as a 2,6,7-trioxabicyclo[2.2.2]octane (OBO ester).[5,6] In this work, we chose a 2,7,8-trioxabicyclo[3.2.1]octane (ABO ester) as a carboxyl protecting group. The ABO ester is more Brønsted acid-stable and easy to prepare. During the course of our manuscript preparation, synthesis of an unsaturated pyroglutamic OBO ester has been published; however, the reaction of the olefin was limited to Michael additions.[7]

As shown in Scheme 1, the ABO ester of the L-pyroglutamic acid was prepared *via* a zirconocene-catalyzed epoxy ester–*ortho* ester rearrangement reported by Wipf and co-workers.[8] After protection of the amide proton with a *tert*-butoxycarbonyl (Boc) group, the pyroglutamate was converted to a 3,4-didehydropyroglutamate derivative **4**† using a selenenylation–oxidative deselenenylation procedure. The obtained unsaturated orthopyroglutamate **4** is a colorless crystalline solid which is stable at room temperature for several months.

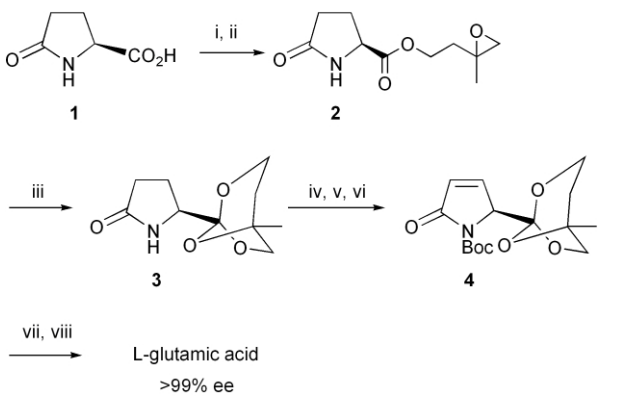
In order to check if the synthesis of the compound **4** had proceeded with complete retention of chiral integrity, the olefin **4** was hydrogenated in the presence of 10% palladium on carbon and the obtained orthopyroglutamate was hydrolyzed in refluxing 1 M HCl for 3 h to give L-glutamic acid in 77% yield. The enantiomeric purity of the obtained L-glutamic acid was found to be > 99% by HPLC analysis using a chiral stationary column (MCIGEL CRS10W), suggesting that no racemization of the stereogenic center occurred during the above reaction sequence.

With the unsaturated orthopyroglutamate **4** in hand, we investigated the functionalization at 3- and/or 4-positions of the pyroglutamate skeleton. The results are outlined in Scheme 2.

First of all, we examined the Diels–Alder reaction of the olefin **4**. When a solution of compound **4** and an excess of cyclopentadiene in toluene was heated at 140 °C for 12 h in a sealed tube, the expected *endo*-adduct **5** was obtained in 75% yield as a single diastereomer. The reaction proceeded with high facial selectivity to the less hindered face of the olefin. The structure and the enantiomeric purity ( > 99% ee) of the adduct **5** were confirmed by transforming the ABO ester into the corresponding ethyl ester **6**.[4]

Cyclopropanation of the olefin **4** was carried out by 1,3-dipolar cycloaddition of diazomethane followed by photolysis of the resultant pyrazoline **7** in the presence of benzophenone as a photosensitizer.[6] When $Pd(OAc)_2$-catalyzed cyclopropanation of the olefin **4** with diazomethane was tried, no cycloadduct was produced. Generally, this type of cyclopropanation gives a mixture of diastereomers; however, the bicyclic compound **8** was obtained as a single diastereomer in 61% yield, which could be converted to enantiomerically pure ( > 99% ee) (2*S*,3*S*,4*R*)-(carboxycyclopropyl)glycine (**9**, CCG-III)[9] in a single step by acid hydrolysis in 61% yield.

Stereoselective introduction of the vicinal diol function to the pyroglutamate framework was achieved by catalytic osmylation of the olefin **4** in the presence of *N*-methylmorpholine *N*-oxide (NMO) as a co-oxidant to give the *cis*-diol **10** in 65% yield as a single diastereomer. The stereochemistry was tentatively




**Scheme 1** *Reagents and conditions:* i, $CH_2$=C(Me)$CH_2CH_2OH$, DCC, DMAP, $CH_2Cl_2$; ii, *m*CPBA, $CH_2Cl_2$, 0 °C; iii, $Cp_2ZrCl_2$, $AgClO_4$, $CH_2Cl_2$; iv, (*tert*-$BuOCO)_2O$, DMAP, $CH_3CN$, 60% (4 steps); v, $NaN(SiMe_3)_2$, DMPU, THF, -78 °C, then, PhSeCl; vi, $H_2O_2$, THF, 82% (2 steps); vii, $H_2$, 10% Pd/C, $CH_3OH$; viii, 1 M HCl, reflux, then, Dowex 50W-X8, 77% (2 steps).

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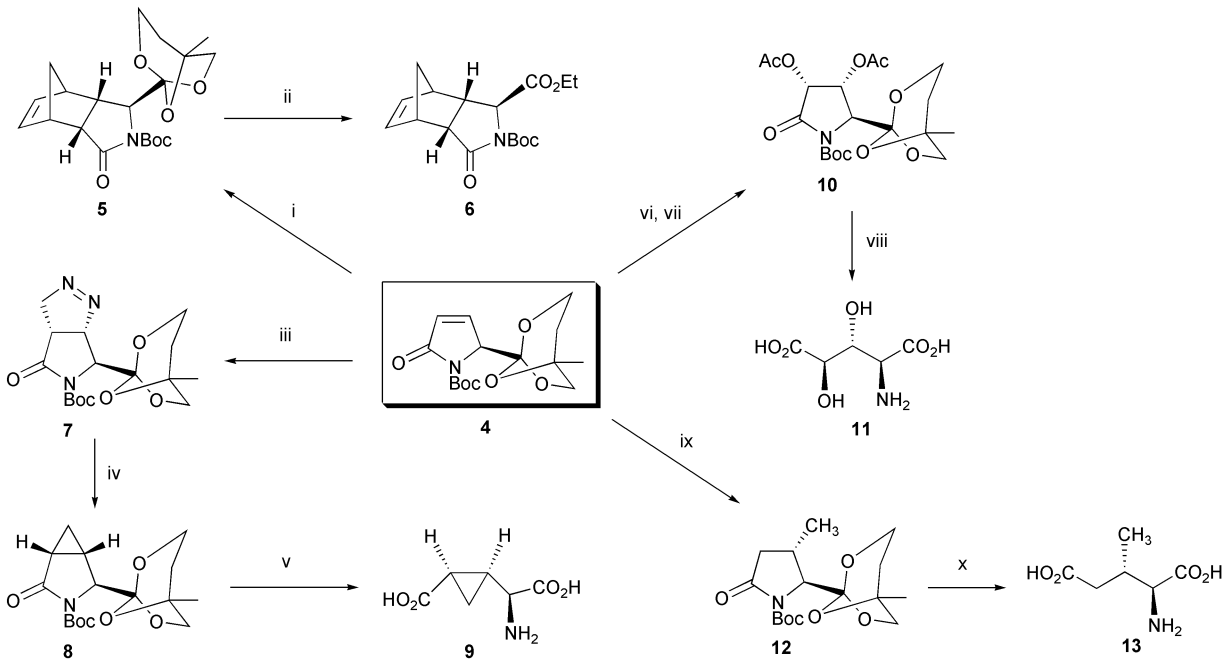

**Scheme 2** *Reagents and conditions:* i, cyclopentadiene, toluene, 140 °C in sealed tube, 75%; ii, HCl, EtOH, then, (*tert*-BuOCO)$_2$O, DMAP, $CH_3CN$, 50% (2 steps); iii, $CH_2N_2$, ether, quant.; iv, *hν*, benzophenone, $CH_3CN$, 61%; v, 1 M HCl, reflux, then, Dowex 50W-X8, 61%; vi, $OsO_4$, NMO, acetone–$H_2O$ (3:1), 65%; vii, $Ac_2O$, pyridine, 94%; viii, as in v, 42%; ix, $Me_2CuLi$, ether; x, as in v, 75% (2 steps).

assigned on the basis of osmylation from the less hindered face. The obtained diol **10** was then hydrolyzed in refluxing 1 M HCl for 1 h to afford novel (2*S*,3*R*,4*R*)-3,4-dihydroxyglutamic acid **11** in 42% yield. Prolonged reaction time or the use of 6 M HCl as a reaction medium resulted in extensive decomposition along with a formation of the α-epimer. The $^1$H NMR spectrum of the α-epimer, the (2*R*,3*R*,4*R*)-form, was identical with that of (2*S*,3*S*,4*S*)-3,4-dihydroxyglutamic acid reported by Dodd and co-workers.[10]

In order to test if the olefin **4** could be used as a Michael acceptor, we carried out 1,4-addition of lithium dimethylcuprate to the unsaturated lactam system. As anticipated, acidic hydrolysis of the Michael adduct **12** afforded (2*S*,3*S*)-3-methylglutamic acid **13** ( > 99% ee) as the sole product, suggesting that stereospecific cupurate addition to the olefin **4** occurred.

In summary, we have demonstrated the synthesis of 3,4-didehydropyroglutamate **4** in which the carboxyl function was protected as an ABO ester. Some reactions, such as catalytic hydrogenation, Diels–Alder reaction, cyclopropanation, dihydroxylation, and Michael addition, were found to proceed without loss of enantiomeric purity at the α-position. In all cases, excellent π-facial diastereoselectivity to the olefin was observed due to the steric repulsion between the reagent and the bulky ABO ester group. We conclude that the unsaturated orthopyroglutamate **4** obtained in this work will be a versatile chiral template in asymmetric synthesis. A full account of the asymmetric synthesis of non-proteinogenic amino acids using the 3,4-didehydropyroglutamate **4** will be published in due course.

## Notes and references

† Physical and spectral data for new compound **4**: colorless solid, mp 110–112 °C. $^1$H NMR ($CDCl_3$) $\delta$ 1.34 and 1.35 (2 s, 3 H), 1.43–1.48 (m, 1 H), 1.52 (s, 9 H), 1.99 and 2.08 (2 m, 1 H), 3.45 and 3.47 (2 d, $J$ = 2 Hz, 1 H), 3.84–4.10 (m, 3 H), 4.97 and 5.03 (2 dd, $J$ = 2 and 2 Hz, 1 H), 6.11 (m, 1 H), 7.19 (m, 1 H). $^{13}$C NMR ($CDCl_3$) $\delta$ 21.6 and 21.7, 27.7 and 27.8, 33.6, 59.4 and 59.5, 63.3 and 63.9, 73.4 and 73.5, 79.1 and 79.5, 82.6 and 82.7, 117.9 and 118.0, 127.28 and 127.34, 146.1, 149.1, 169.8. HRMS (EI, 30 eV) *m/z* 312.1447 [(M + H)$^+$, calcd for $C_{15}H_{22}O_6N$ 312.1485].


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