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Facile synthesis of unsaturated pyroglutaminol derivatives

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ABSTRACT

A novel approach to the synthesis of unsaturated pyroglutaminol derivatives was developed. Condensation of a protected serine derivative with Meldrum's acid followed by decarboxylative cyclization afforded a tetramic acid, which was then converted to a hydroxylactam using sodium borohydride. Iodine displacement of the hydroxyl group induced spontaneous elimination to afford unsaturated pyroglutaminol derivatives in good yields.

Unsaturated pyroglutaminol derivatives **1** and their bicyclic analogues **2** (Fig. 1) are recognized as versatile chiral building blocks for the synthesis of optically active compounds. Their versatility comes about because the olefin functionality can be easily modified in a stereospecific manner by conjugate addition, dihydroxylation, cyclopropanation, epoxidation, cycloaddition, and so on.[1–3] We have often used the unsaturated pyroglutaminols **1** as chiral templates for the stereoselective synthesis of stable isotope-labeled amino acids.[4]

Recently, we and Herdeis et al. independently reported the synthesis of unsaturated pyroglutamate derivatives **3**[5] and **4**,[6] in which the carboxyl function is protected as 5-methyl-2,7,8-trioxabicyclo[3.2.1]octane (ABO ester) or 4-methyl-2,6,7-trioxabicyclo [2.2.2]octane (OBO ester), respectively. These orthopyroglutamates serve as versatile chiral templates for the synthesis of a variety of nonproteinogenic amino acids.

In general, chiral unsaturated γ-lactams as shown in Figure 1 are prepared from optically active glutamic acid via a multistep process which involves the use of a highly toxic organoselenium reagent to introduce the olefin functionality (Scheme 1, route A). Some alternative routes, such as a ring-closing olefin metathesis, to the unsaturated pyroglutaminols can be seen in the literature (route B).[3c,7] However, these methods are only rarely used. We herein describe a novel approach to the synthesis of unsaturated pyroglutaminol derivatives **1**, which is based on a formal dehydration of hydroxypyroglutaminol derived from serine and Meldrum's acid (route C).

The synthetic course of hydroxypyroglutaminol derivatives **8** is outlined in Table 1. Preparation of **8** starting from protected serine and Meldrum's acid was originally reported by Jouin and co-workers in conjunction with statine synthesis.[8] The procedure was modified by Ma and co-workers, who used *N*,*N*′-dicyclohexylcarbodiimide (DCC) instead of currently commercially unavailable isopropenyl chloroformate as a carboxyl activating agent.[9]

Following Ma's method, we carried out the DCC-promoted condensation of *N*-Boc-L-Ser(Bn)-OH (**5a**) with Meldrum's acid in the presence of 4-dimethylaminopyridine (DMAP) to give compound **6a**. An L-form of protected serine was used as a source of chirality for economical reasons. Decarboxylative cyclization of **6a** in refluxing ethyl acetate for 0.5 h produced tetramic acid **7a**, which upon reduction with sodium borohydride, afforded hydroxypyroglutaminol **8a** as a single diastereomer in 53% yield based on **5a**. Compounds **6a** and **7a** seemed to be relatively unstable and were used immediately in the next step without further purification.

As shown in Table 1, other protected L-serine derivatives **5b–d** were similarly converted to the corresponding hydroxypyroglu-

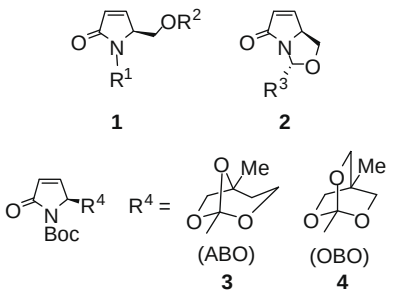

Figure 1. Unsaturated γ-lactam derivatives.

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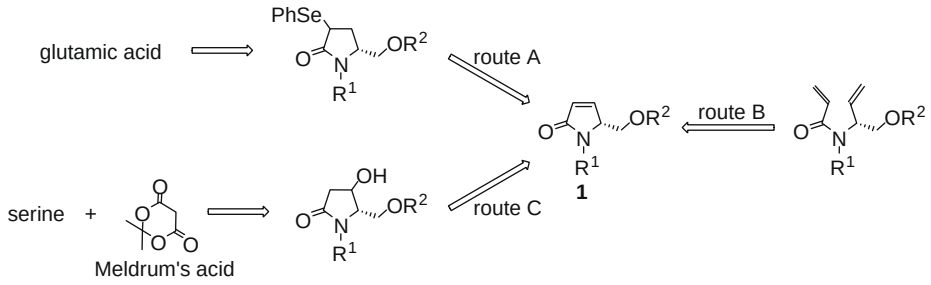
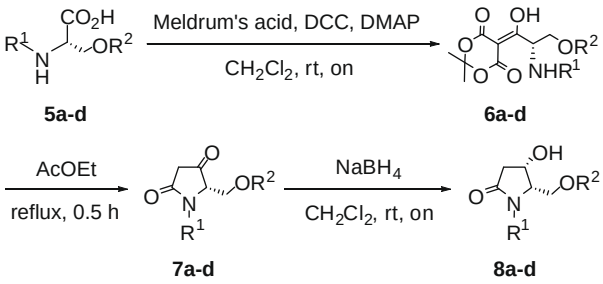


Scheme 1. Synthetic route to unsaturated pyroglutaminol derivatives **1**.

Table 1
Preparation of hydroxypyroglutaminol **8a–d**



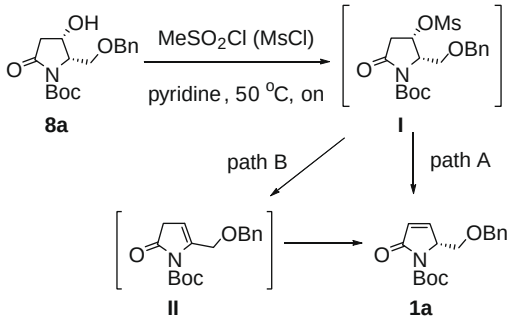
Entry	R^1	R^2		**8**, Yield[a] (%)
1	Boc	Bn	(**a**)	53
2	Boc	TBDMS	(**b**)	55
3	Fmoc	*tert*-Bu	(**c**)	62
4	Cbz	Bn	(**d**)	52

[a] Isolated yield based on the starting protected amino acid.

taminols **8b–d** in acceptable overall yields over three steps. Although Jouin[8a] and Joullié[10] reported that DCC is not a suitable reagent for the initial condensation step, the DCC–DMAP carboxyl activation system worked well in our case.

Preparation of unsaturated pyroglutaminol derivatives **1** is expected to be accomplished by elimination of the hydroxyl group of **8** via the corresponding sulfonate. When a solution of **8a** in pyridine was treated with methanesulfonyl chloride, the mesylate **I** so formed underwent spontaneous elimination to afford the desired olefin **1a** in 57% yield (Scheme 2). However, its specific rotation, $[\alpha]_D^{26}$ +80 (*c* 1.00, $CHCl_3$), is much smaller than that of the optically pure sample ($[\alpha]_D^{24}$ +141 (*c* 1.03, $CHCl_3$)), indicating that partial racemization took place during elimination. Changing the sulfonylating agent to *p*-toluenesulfonyl chloride or trifluoromethanesulfonic anhydride did not improve the outcome.

Figure 2 shows an optimized[11] structure of model mesylate **I′**, where the *tert*-butyl and benzyl groups of **I** are replaced by methyl



Scheme 2. Conversion of **8a** to **1a** using a sulfonylation–elimination procedure.

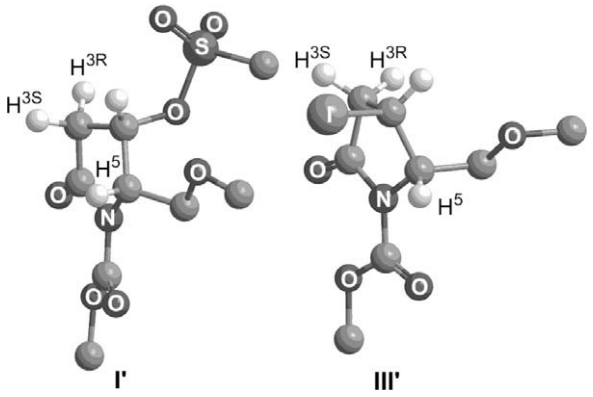


Figure 2. Molecular structures of model compounds **I′** and **III′** for mesylate **I** and iodide **III**, optimized at the B3LYP/6-31G(d,p) and B3LYP/6-31G(d,p)+LANL2DZdp(I) levels of theory, respectively.

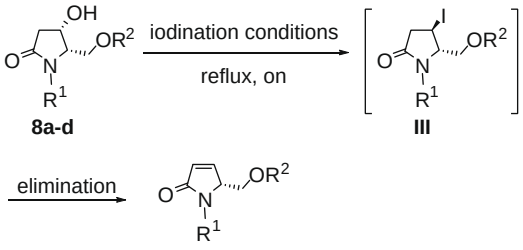
groups. If typical anti-elimination occurs, loss of either of two different anti-periplanar hydrogen atoms, H^{3S} or H^5, leads to the desired product **1a** (path A) or its regioisomer **II** (path B), respectively. The kinetic intermediate **II** immediately isomerizes to thermodynamically more stable **1a** as a racemate. The energy difference between **1a** and **II** is calculated to be 2.38 kcal/mol at the B3LYP/6-31G(d,p) level of theory. We assume that competition between paths A and B accounts for the observed racemization.

We next investigated the preparation of unsaturated pyroglutaminols **1** via a halogenation–dehydrohalogenation sequence. Considering the leaving aptitude of the halogen atoms, we adopted iodination conditions (Table 2). In general, iodination of alcohols proceeds through inversion of the configuration. The structure of model iodide **III′** optimized at the B3LYP/6-31G(d,p)+LANL2DZdp(I)[12] level of theory is shown in Figure 2. In this case, there is only one anti-periplanar hydrogen, H^{3R}, with respect to the iodine atom. Therefore, its elimination is expected to produce **1** exclusively without affecting the chiral center.

Iodination of **8a** was performed using the I_2–Ph_3P complex in the presence of imidazole.[13] The reaction was accompanied by spontaneous elimination of hydrogen iodide to give **1a** in 83% yield (entry 3). For the sake of simple workup, similar treatment of **8a** on polymer-supported triphenylphosphine (ps-Ph_3P)[14] was carried out and found to be effective in giving **1a** in 80% yield (entry 4). However, iodination of **8a** under the standard Mitsunobu conditions resulted in unsatisfactory yields (entries 1 and 2). A combination of iodine, ps-Ph_3P, and imidazole in refluxing CH_2Cl_2 works well with other hydroxypyroglutaminol derivatives **8b–d**, giving the corresponding unsaturated pyroglutaminols **1b–d** in good yields (entries 5, 6, and 7).

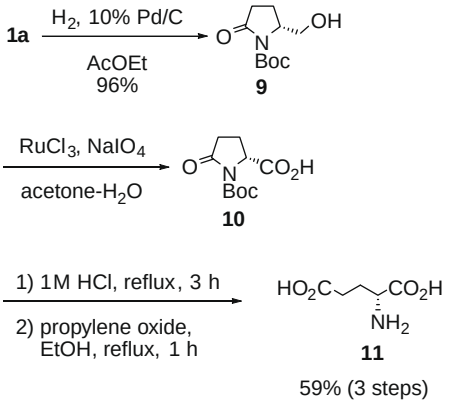
To determine whether the synthesis of the olefin **1a** proceeded with complete retention of chiral integrity, **1a** was converted to D-glutamic acid (**11**). As shown in Scheme 3, **1a** was hydrogenated

Table 2
Preparation of unsaturated pyroglutaminol **1a–d** via a halogenation–dehydrohalogenation sequence



Entry	R^1	R^2		Conditions	Yield[a] (%)
1	Boc	Bn	(**a**)	MeI, Ph_3P, DEAD, THF	36
2	Boc	Bn	(**a**)	MeI, Ph_3P, DMAD, THF	61
3	Boc	Bn	(**a**)	I_2, Ph_3P, imidazole, CH_2Cl_2	83
4	Boc	Bn	(**a**)	I_2, ps-Ph_3P, imidazole, CH_2Cl_2	80
5	Boc	TBDMS	(**b**)	I_2, ps-Ph_3P, imidazole, CH_2Cl_2	90
6	Fmoc	*tert*-Bu	(**c**)	I_2, ps-Ph_3P, imidazole, CH_2Cl_2	78
7	Cbz	Bn	(**d**)	I_2, ps-Ph_3P, imidazole, CH_2Cl_2	81

[a] Isolated yield.



Scheme 3. Conversion of **1a** to D-glutamic acid (**11**).

in the presence of 10% palladium on carbon and the liberated hydroxymethyl group of pyroglutaminol **9** was oxidized with RuO_4 prepared in situ from $RuCl_3$ and $NaIO_4$.[15] The obtained crude pyroglutamic acid **10** was hydrolyzed in refluxing 1 M HCl for 3 h to give glutamic acid hydrochloride which upon treatment with propylene oxide in refluxing ethanol gave free D-glutamic acid (**11**) in 59% yield over three steps. As expected, the enantiomeric purity of **11** was found to be >99% by HPLC analysis using a chiral stationary column (MCIGEL CRS10W).

In conclusion, we developed a novel and concise approach to the synthesis of unsaturated pyroglutaminol derivatives, versatile chiral building blocks for the synthesis of optically active compounds. Reduction of tetramic acid, obtained from the protected serine and Meldrum's acid, with $NaBH_4$ followed by iodination of the hydroxyl group directly affords the unsaturated pyroglutaminol derivatives in good yields over four steps without affecting chiral integrity.

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