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Chemoselective Nucleophilic Attack on *N*-Acyl Derivatives of (*S*)-Ethyl 4,4-Dimethyl Pyroglutamate (DMPG)

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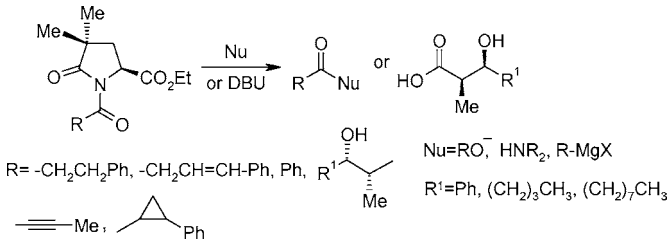
ABSTRACT



Heteronucleophiles and *C*-nucleophiles chemoselectively react with *N*-acyl (*S*)-ethyl 4,4-dimethyl pyroglutamate (DMPG) affording esters, amides, and ketones in high yield. The intramolecular process allows the stereoselective formation of *β*-hydroxy acids likely by formation and ring opening of the corresponding *β*-lactones

Pyroglutamate derivatives, in which the carboxylic moiety is reduced and suitably protected to avoid potential epimerization of the C-2 stereogenic center, have been widely used in enantioselective synthesis. There are also a notable number of reports in which pyroglutamate itself generates the same kind of efficiency. Thus, pyroglutamic acid **1** has been widely used as a chiral building block for natural product synthesis and preparation of designed chiral compounds with biological activity.[1,2]

Another field of emerging interest is the use of pyroglutamic acid derivatives as chiral auxiliaries in asymmetric synthesis. For example, pyroglutamate **2** attached to simple dienes such as those represented by **4** showed good diastereoselectivity in Diels−Alder cycloaddition reactions.[3] Some of us have recently reported that (*S*)-ethyl 4,4-dimethyl pyroglutamate **3** (DMPG)[4] can be a valid chiral auxiliary template, allowing the functionalization of acyl moieties attached to the pyroglutamate nitrogen. By blocking the pyroglutamate C-4 position with a geminal dimethyl group, enolization of the lactam carbonyl group is prevented and it is possible to perform aldol condensation[5] (**5**) or asymmetric Michael addition reactions[6] (**6a**) in high yields and with complete stereocontrol over the newly generated sterogenic centers. Noteworthy, the pyroglutamate stereogenic center

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(1) For reviews see: (a) Nájera, C.; Yus, M. *Tetrahedron*: *Asymmetry* **1999**, 10, 2245−2303. (b) Coppola, G.; Schuster, H. F. In *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*; John Wiley: New York, 1987.

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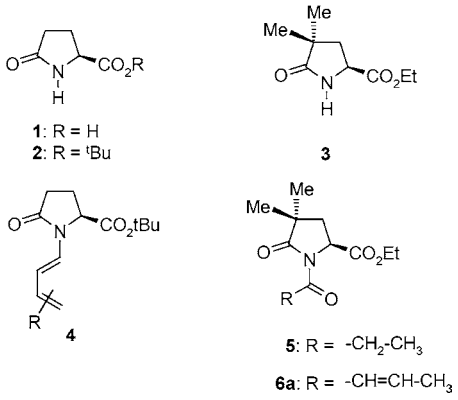


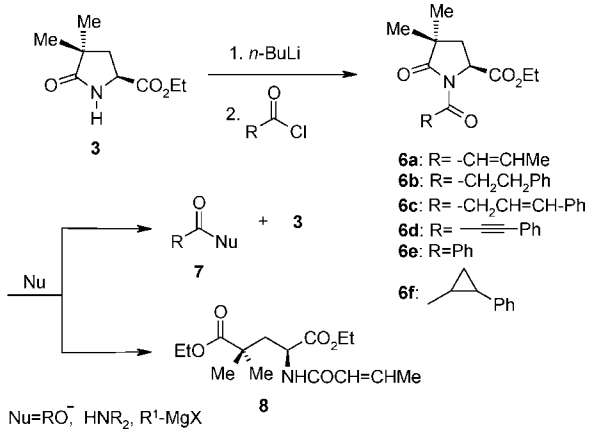
Figure 1. Pyroglutamate derivatives as chiral auxiliaries.

is not affected during the whole asymmetric process. Removal of **2** after the asymmetric Diels−Alder reaction of **4** required hydrogenolysis over Raney-nickel at 40 °C. The recovery of **3** was achieved by treatment of either the Michael adducts or the aldol condensation products with LiOH in a 1:1 mixture of THF/H_2O. Under these basic hydrolytic conditions, the pyroglutamate ester group is saponified, requiring a final re-esterification step with HCl(g)/EtOH to fully recover the chiral auxiliary.

The search for milder reaction conditions for the cleavage step of *N*-acyl pyroglutamates (**5**, **6**) led us to study in more detail the reactivity of the *N*-acyl group attached to the chiral auxiliary with different nucleophiles. In addition to the optimization in the chiral auxiliary removal, a further functionalization opportunity could be opened for this kind of highly congested carbonyl functional group class of molecules, depending on the nature of the nucleophile employed.

In this Letter we report our results on the chemoselective nucleophilic reaction of functionalized pyroglutamates (**6**). This has allowed the use of milder reaction conditions to recover the DMPG. This method also provides a convenient means for further transformation of the acyl moiety into a

Scheme 1



variety of functional groups, including esters, amides, and ketones, rather than solely the carboxylic acids produced by the basic hydrolysis.

(*S*)-*N*-Acyl ethyl 4,4-dimethylpyroglutamate derivatives **6a**−**f**, used in this study, were obtained in moderate yields from **3** by deprotonation with *n*-BuLi followed by reaction with the corresponding acyl chlorides[7] (Scheme 1).

Attempts to remove the chiral moiety with use of NaOEt in ethanol resulted in a clean and selective reaction affording the corresponding ethyl esters (Table 1, entries 1, 5, and 6)

Table 1. Reaction of **6** with Heteronucleophiles

entry	*N*-acyl derivative (**6**)	nucleophile	yield of **7** (%)	yield of **3** (%)
1	**6b**	EtO	76	86
2	**6b**	MeO	94	95
3	**6b**	morpholine	73	81
4	**6c**	MeO	87	88
5	**6d**	EtO	79	86
6	**6e**	EtO	77	85
7	**6e**	morpholine	64	85
8	**6f**	morpholine	73	83

with yields ranging from 73% to 79% and **3** was recovered in yields up to 80%. Similar or better yields were obtained by using NaOMe/MeOH, although in this case extensive transesterification was observed, with the DMPG recovered as the corresponding methyl ester (Table 1, entries 2 and 4). In both cases it is of interest to note that the nucleophilic attack is completely chemoselective not observing ring-opened products as has been shown in the literature on *N*-urethane protected pyroglutamates.[8] Likely, the electron-withdrawing nature of the carbonyl moiety on the pyroglutamate nitrogen is responsible for this chemoselectivity.

The only example in which this regioselective reaction pattern is different was found with *N*-α,*β*-unsaturated acyl pyroglutamate derivative **6a**, where the nucleophile reacts with the pyroglutamate lactam carbonyl moiety, yielding the corresponding ring-opening product **8a** (R = CH=CHMe; Nu = OEt). The effect of the π system close to the acyl carbonyl should account for this reactivity difference. This result resembles that found with *N*-BOC protected ethyl pyroglutamate in which on treatment with alcohols in the presence of catalytic amounts of cyanide or alkoxides produced the ring-opened product.[9]

Other heteronucleophiles such as secondary cyclic amines (morpholine was used as a model) also reacted chemoselectively with the *N*-acyl carbonyl, yielding **3** and the corresponding amide **7**, although lower yields compared with the alkoxides were found (Table 1, entries 3, 7, and 8).[10]

(7) Compounds **6** were obtained following the general procedure previously reported for **5** (ref 5) and **6a** (ref 6). Yields: **6b** (73%); **6c** (55%); **6d** (28%); **6e** (45%); **6f** (70%).

(8) Schoenfelder, A.; Mann, A. *Synth. Commun*. **1990**, *20*, 2585.
(9) Molina, M. T.; del Valle, C.; Escribano, A. M.; Ezquerra, J.; Pedregal, C. *Tetrahedron*, **1993**, *49*, 3801.

As it was reported that a variety of *C*-nucleophiles including Grignard reagents,[11] methyl sulfinyl organolithium anions,[12] ester lithium enolates, and 1,3-lithio-dithianes[13] reacted regioselectively with *N*-BOC protected ethyl pyroglutamate leading to open-chain products, it was of great interest to investigate the reaction of some *C*-nucleophiles with compounds **6**. We have found that nonstabilized carbanions such as organolithium reagents reacted with **6** leading to complex mixtures of products under different reaction conditions. However, the reaction of Grignard reagents with **6b**−**f** resulted in a clean transformation leading to the corresponding ketones in good yields.[14]

Except for **6a**, the reaction seems to be general since a complete chemoselectivity is observed regardless of the nature of the *N*-acyl group attached to the pyroglutamate (Table 2). For **6a**, the reaction with PhMgBr afforded

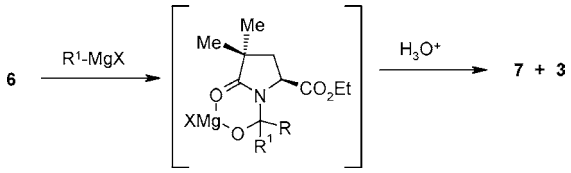
Table 2. Reaction of *6* with Grignard Reagents

entry	*N*-acyl derivative (**6**)	R^1	yield of **7** (%)	yield of **3** (%)
1	**6a**	C_6H_5	22	50
2	**6b**	C_6H_5	85	87
3	**6d**	C_6H_5	88	90
4	**6e**	C_6H_5	85	85
5	**6f**	C_6H_5	77	81
6	**6f**	C_2H_5	76	83
7	**6f**	n-C_3H_7	64	77
8	**6f**	CH_2=CH	65	77
9	**6f**	CH_2=$CHCH_2$	63	80

complex mixtures from which the expected ketone could be isolated in only 22% yield (Table 2, entry 1).

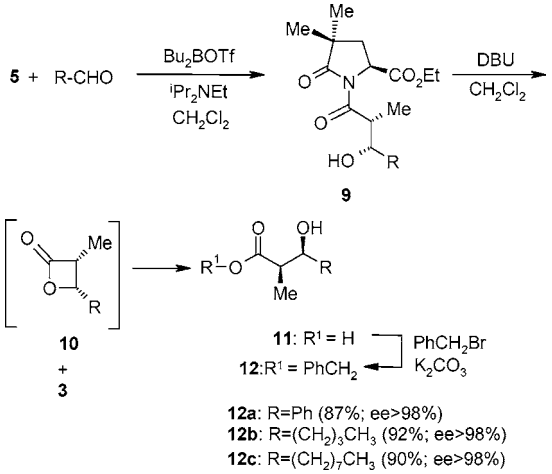
These results demonstrate not only the highly selective removal of the chiral moiety in **6** with heteronucleophiles and *C*-nucleophiles, but also the efficiency of the whole process, allowing the conversion of the *N*-acyl groups into a ketone functional group. In this context the *N*-acyl pyroglutamates can be viewed as acylating compounds affording ketones in excellent yields likely by formation of stable intermediates such as **10**, similar to those described for well-known acylating reagents such as Weinreb amides[15] and related compounds[16] (Scheme 2).

Scheme 2



In light of the results with heteronucleophiles and those previously reported in aldol condensation,[5] it was of interest to test the chemoselective reaction of **6** toward *O*-nucleophiles in an intramolecular fashion to achieve a diastereoselective and efficient preparation of β-hydroxy acids. Scheme 3 illustrates the method, based upon the stereo-

Scheme 3



selective aldol reaction between **5** and aldehydes, followed by intramolecular hydroxy group attack in the presence of DBU. Formation of the β-hydroxy acids **11** involves removal of DMPG and likely formation of the intermediate β-lactone **10**, which could not be isolated under reaction conditions[17] (Scheme 3). The acids, without isolation, were converted into the benzyl esters **12**[18] for an accurate ee determination (chiral-HPLC).

(10) General procedure for heteronucleophiles: To a solution of **6** (0.15 mmol) in the appropriate solvent (THF for morpholine and the corresponding alcohol for alkoxides) was added the heteronucleophile (0.165 mmol of morpholine and 0.15 mmol of the alkoxide) and the reaction mixture was refluxed for 24 h (morpholine) or stirred at room temperature for 1 h (alkoxides). Then the solvent was evaporated and the residue treated with CH_2Cl_2. The organic phase was washed with HCl (morpholine) or NaCl (alkoxydes), the solvent was evaporated, and the residue was chomatographed on silica gel with hexane/EtOAc as eluent (1:1 allowed isolation of amides and 7:3 of esters). Pyroglutamate **3** was recovered with a 3:7 mixture of solvents.

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(12) Ezquerra, J.; Rubio, C.; Pedregal, C.; Sanz, G.; Rodriguez, J. H.; García Ruano, J. L. *Tetrahedron Lett.* **1993**, *34*, 4989.

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(14) General procedure for *C*-nucleophiles: To a solution of **6** (0.15 mmol) in THF at −40 °C was added the Grignard reagent (0.15 mmol) and the reaction mixture was stirred for 5 h, then treated with NH_4Cl solution and extracted with CH_2Cl_2. The residue obtained after evaporation of the solvent was chomatographed on silica gel with hexane/EtOAc as eluent (9:1) for isolation of ketones. Auxilar **3** was recovered as indicated in ref 10.

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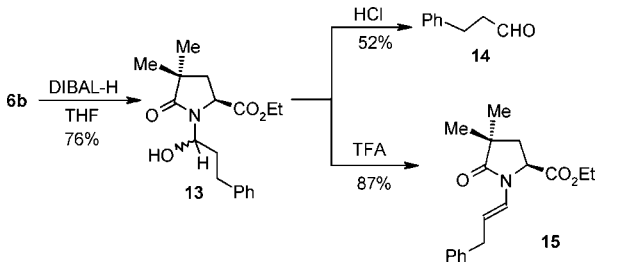
Since reduction of the carboxylic, ester, and lactame carbonyl groups in **1**−**3** has been well established[1,19] it was also of interest to test the conversion of **6** into aldehydes by using typical reducing agents. Results obtained with **6b** show that only DIBAL-H allowed a selective reduction of the acyl group affording the highly stable acetal **13** (76%) (Scheme 4). Treatment of **13** with hydrochloric acid gave the expected

Scheme 4



aldehyde **14** albeit in only 52% yield while **15** (87%) was the resulting compound obtained by treatment with trifluoroacetic acid.

(17) Although lactones **10** are described as stable compounds (Romo, D.; Harrison, P. H. M.; Jenkins, S. I.; Riddoch, R. W.; Park, K.; Yang, H. W.; Zhao, C.; Eright, G. D. *Bioorg. Med. Chem*. **1998**, *6*, 1255) they seem to be prone to hydrolysis under these reaction conditions. Thus the reaction of **9c** carried out in a NMR tube generates the corresponding hydroxy acid **11c** in the reaction medium as we proved by following by NMR this conversion (see Supporting Information) discarding its formation in the workup.

In summary the use of (*S*)-*N*-acyl ethyl 4,4-dimethylpyroglutamate (DMPG) as chiral auxiliary offers the stability of the stereogenic center under different conditions for its removal, using heteronucleophiles and *C*-nucleophiles. Moreover, aldol products formed in the highly diastereoselective condensation of *N*-acyl pyroglutamatesand aldehydes can be easily converted into β-hydroxy acids by intramolecular removal of DMPG and hydrolysis of the corresponding intermediate β-lactones.

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Supporting Information Available: Full experimental procedures, analytical data for all new compounds, and copies of NMR spectra and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) General procedure for **12**: Aldols **9**, obtained following the procedure described for **9a** (R = Ph; ref 5), were stirred in CH_2Cl_2 in the presence of DBU (1.1 mmol) for 12 h at room temperature. Then, a K_2CO_3 solution was added and chiral auxiliary was isolated by extraction with CH_2Cl_2. The aqueous phase was acidified with 1 N HCl and extracted with EtOAc, and the solvent removed under reduced pressure. The residue containing the hydroxy acid **11** was dissolved in DMF and K_2CO_3 (1.1 equiv) and benzyl bromide (1.1 equiv) were added. The solution was stirred for 4 h at rt. Then, EtOAc was added and the organic phase was washed with a NaCl solution. After removal of the solvent the esters **12a**−**c** were isolated by column chromatography with hexane/EtOAc (9:1) as eluent. **12a**: $[\alpha]^{21}_D$ −10 (*c* 0.02, CH_2Cl_2). **12b**: $[\alpha]^{21}_D$ −6 (*c* 0.04, CH_2Cl_2). **12c**: $[\alpha]^{21}_D$ −9 (*c* 0.05, CH_2Cl_2).

(19) Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron Lett.* **1994**, *35*, 2053−2056. Collado, I.; Ezquerra, J.; Vaquero, J. J.; Pedregal, C. *Tetrahedron Lett.* **1994**, *35*, 8037