Direct versatile route to conformationally constrained glutamate analogues

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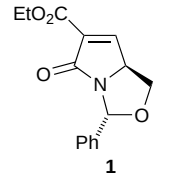
Novel conformationally constrained glutamate analogues are readily available from (*S*)-pyroglutamic acid; using a bicyclic lactam template, diastereocontrolled and sequential modification of the pyrrolidine ring is possible, allowing a versatile access to several glutamate and kainoid analogues; variations in the C(2)H–C(3)H coupling constants were observed depending upon the nature of remote substituents on the heterocyclic ring, consistent with modification of the ring conformation.

Nitrogen heterocycles occur widely in nature, in isolation and as structural subunits in many families of alkaloids, and possess wide ranging biological and pharmacological activities.[1–3] Of particular current interest are conformationally constrained glutamines,[4] which have been shown to possess potent activity at both the ionotropic and metabotropic receptors.[5,6] These receptors are selectively activated by excitatory amino acids, and are known to play an important role in various physiological processes, such as memory and learning, neuroendocrine regulation, and acute and chronic neuronal disfunction.[7] Excessive activation of these receptors can in some cases lead to cell death.[8] The search for selective agonists and antagonists offers the potential for both the structural and physiological characterisation of the receptors, and treatment of a range of physiological disorders, in particular Alzheimer's and Parkinson's diseases. Highly functionalised pyrrolidines have been found to have activity at these receptors,[9] and there has therefore been considerable recent interest in the development of practical and versatile methodology for the preparation of this important class of compound;[10,11] particularly elegant protocols have been developed by Shirahama[12,13] and by Baldwin[14–16] which use 4-hydroxyproline as a chiral starting material, and which offer considerable simplicity and generality for the introduction of the ring substituents. We report here an alternative but equally versatile and simple approach to functionalised pyroglutamates which uses a sequential conjugate addition/alkylation or arylation strategy to a $\Delta^{3,4}$ pyrrolidinone derivative. This method has been applied to the synthesis of a novel class of conformationally restricted glutamates, which possess a similar ring substitution pattern to the kainoid group of amino acids.

We used the recently described and readily available lactam **1** as a template for manipulation to a variety of functionalised pyrrolidinones.[17,18] Thus, conjugate addition of the Reformatsky reagent derived from *tert*-butyl bromoacetate generated in THF and DMPU with ultrasonic irradiation gave the diester **2**, in 77% yield as a mixture of diastereomers at the C(7) position, using our previously reported method;[19] conjugate additions to a related enone have been reported previously, although not with Reformatsky reagents.[19,20] This compound was readily functionalised at C(7) by direct arylation using several aryllead triacetates [$ArPb(OAc)_3$, $CHCl_3$, Py, reflux, 72 h][21,22] to give the aryl derivatives **3a**–**d** in good yield as mixtures of diastereomers at C(7) (Table 1) which could be separated only with some difficulty.[23] In the case of **3a**,**b**, the stereochemistry of the C(7)–Ar *exo*- diasteromer was assigned by a series of NOE experiments. Alternatively, alkylation with benzyl bromide under previously reported conditions (NaH, THF, reflux)[24] gave the derivative **3e** as a separable mixture of diastereomers in very good yield. In all arylations, a diastereomeric mixture was obtained, in which preferential addition of the aryl substituent to the *exo* face of **2** was predominant, although for the alkylation with benzyl bromide, a slight preference for *endo* addition was observed.



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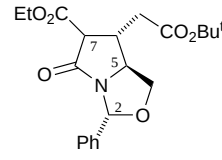

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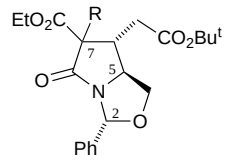
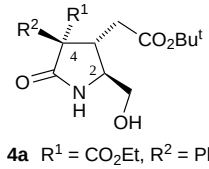
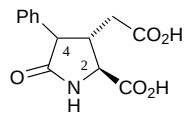


3a R = Ph
b R = *p*-BrC_6H_4
c R = *p*-$MeOC_6H_4$
d R = *o*-$MeOC_6H_4$
e R = Bn



4a R^1 = CO_2Et, R^2 = Ph
b R^1 = Ph, R^2 = CO_2Et
c R^1 = Ph, R^2 = H
d R^1 = H, R^2 = Ph
e R^1 = Ph, R^2 = CO_2H
f R^1 = Bn, R^2 = CO_2Et
g R^1 = CO_2Et, R^2 = Bn
h R^1 = Bn, R^2 = CO_2H
i R^1 = R^2 = H



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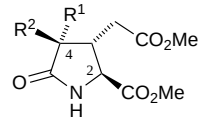
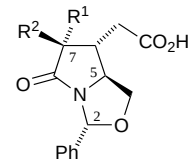


6a R^1 = Ph, R^2 = H
b R^1 = H, R^2 = Ph
c R^1 = Bn, R^2 = H
d R^1 = H, R^2 = Bn
e R^1 = CO_2Et, R^2 = Bn
f R^1 = CO_2Me, R^2 = Bn
h R^1 = R^2 = H

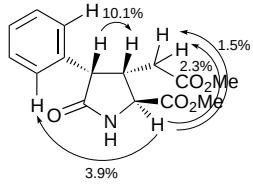


7a R^1 = Ph, R^2 = H
7b R^1 = H, R^2 = Ph

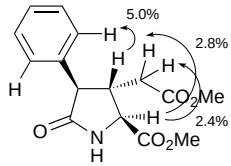
Table 1 Yields of C(7) functionalised products of **3**

Compound	R	Isolated yield (%)	Diastereomer ratio[a] *exo*:*endo*
3a	Ph	86	2.4:1
3b	*p*-BrC_6H_4	76	2.25:1
3c	*p*-$MeOC_6H_4$	38[b]	2.3:1
3d	*o*-$MeOC_6H_4$	72	1.7:1
3e	Bn	75	1:1.2

[a] Determined by ^1H NMR analysis of the crude reaction mixture. [b] Contains starting material, in the ratio **2**:**3c** = 1:1.3.



6a



6b

Fig. 1 NOE enhancements for **6a** and **6b**

In the case of the arylated derivative **3a**, acidic deprotection of the hemiaminal ether function gave the separable diastereomeric alcohols **4a**,**b** in 28 and 52% yield, respectively. Treatment of **4b** with 1 M NaOH in EtOH gave the hydrolysed and decarboxylated products **4c**,**d** on extraction of the basic mixture with EtOAc, and a mixture of the acid **4e** and product **4c**,**d** on extraction of the aqueous mixture after acidification with 2 M HCl. Heating of this mixture at 135 °C at 0.8 mBar for 30 min gave the product **4c**,**d** as a 1 : 1 mixture of diastereomers, in a combined yield of 82%. Acidic deprotection (TFA–CH_2Cl_2) of the *tert*-butyl ester function of **4c**,**d** and then oxidation (RuO_2, $NaIO_4$, MeCN, CCl_4, H_2O) afforded the acid **5** [as a mixture of diastereomers at C(4)] which was partially purified using base wash and then treated with MeOH–H_2SO_4 (catalytic) giving the diesters **6a** and **6b** each in 33% yield (from **4c**,**d**), whose relative stereochemistry was determined by NOE experiments (Fig. 1). An alternative route to **6a**,**b**, which involved treatment of **3a** with 2 M NaOH–EtOH at 50 °C for 5 h to give concomitant ethyl ester hydrolysis, decarboxylation and *tert*-butyl ester hydrolysis, was limited by incomplete and variable hydrolysis of the ester functions, leading to impure **7a**,**b**.

The benzyl derivative **3e** was also amenable to similar manipulation. Thus, hemiaminal ether cleavage of each of the benzyl diastereomers of **3e** (TFA in CH_2Cl_2) afforded the products **4f**,**g**. Hydrolysis (NaOH–EtOH) of **4f** gave **4h** in 99% crude yield, which after heating to effect decarboxylation, and then *tert*-butyl ester removal, oxidation (RuO_2, $NaIO_4$, MeCN, CCl_4, H_2O) and esterification (CH_2N_2) provided the separable diastereomeric benzyl derivatives **6c**,**d** in a ratio of 1 : 4.4 and 38% overall yield. An alternative path, involving hydrolysis of **4g**, followed by direct *tert*-butyl ester removal, oxidation, and esterification using the above conditions gave a 1 : 1 mixture of products **6e**,**f**, indicating that the initial hydrolyis was incomplete.

Pyrrolidinones which were unfunctionalised at C(4) were also available by this route. Thus, direct decarboxylation of the starting lactam **2**, by treatment with ethanolic NaOH followed by thermolysis and deprotection with TFA, afforded **4i** in 33% yield, a compound which has been previously reported in the literature.[25] Conversion to lactam **6h** was achieved by *tert*-butyl ester removal, oxidation as before and esterification (CH_2N_2) in 53% yield over the three steps.

Noteworthy was variation of the C(2)–H/C(3)–H vicinal proton coupling constants for each of the substituted pyroglutamates **6** (Table 2); molecular modelling studies of each of these compounds[27] indicated that the dihedral angle of the energy minimised structures also varied with the nature of the C(4) substituent, particularly for the more sterically congested C(4)–aryl series of compounds **6a**,**b**. Thus, it would appear that analogues of well-defined glutamate conformers could be available by variation in the C(4) substituent of compounds of type **6**.

Table 2 Proton–proton C(2)–H/C(3)–H coupling constant data and corresponding dihedral angles

Compound	*J*/Hz[a]	Dihedral angle (°)[b]
6h	5.5 (5.5)	117
6a	6.5 (6.5)	121
6b	8.0 (8.0)	153
6c	2.5 (2.5)	125
6d	6.0 (6.5)	118

[a] In $CDCl_3$ (in C_6D_6). [b] Ref. 27.

This route represents a novel and simple, but potentially generalisable, approach to highly functionalised pyrrolidinones, and is complementary to existing literature protocols. It in particular provides access to novel pyroglutamate analogues of the kainoid group of amino acids possessing substituents with π-electron density at C(4).

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Note and References

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