Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 2245–2303

TETRAHEDRON: *ASYMMETRY*

TETRAHEDRON: ASYMMETRY REPORT NUMBER 43

Pyroglutamic acid: a versatile building block in asymmetric synthesis

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Received 21 May 1999; accepted 25 May 1999

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1. Introduction

α-Amino acids are important members of the so-called 'chiral pool' commonly found in nature as the L-forms and have been widely used as versatile building blocks.[1] Glutamic acid is the precursor of pyroglutamic acid, easily prepared by direct dehydration,[2] which is also available in both enantiomeric forms. It can be found as the end group in biologically active peptides such as gonadotrophin-[3] and thyrotropin-releasing[4] hormones, in depsipeptides such as didemnins[5] and in naturally occurring peptides and pseudopeptides.[6]

Pyroglutamic acid 2-oxotetrahydropyrrole-5-carboxylic acid **1** is recognised as an internally protected glutamic acid. The synthetic applications of pyroglutamic acid as chiral building blocks have been previously reviewed.[1] It has been used as starting material for natural products, for example (−)-domoic acid,[7] the neurotoxin anatoxin-a,[8a] *trans*-5-butyl-2-heptylpyrrolidine, a major component of the repellant venom of the ant *Solenopsis fugax*,[8b] (+)-gephyrotoxin,[9] the phenanthroindolizidine alkaloids

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PII: S0957-4166(99)00213-X

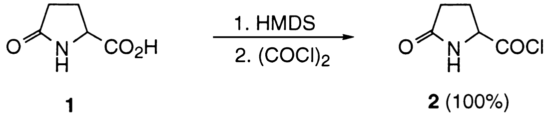
(+)-tylophorine and cryptopleurine,[10] and kainic acid.[11] The well-known chiral auxiliary (*R*)-1-amino-2-methoxymethylpyrrolidine (RAMP) is prepared from (*R*)-pyroglutamic acid.[12]

The aim of this review article is to highlight the increasing use of pyroglutamic acid **1** in the synthesis of enantiomerically pure compounds (EPC synthesis) since 1986,[1] as well as a chiral auxiliary in asymmetric synthesis. According to the structure of pyroglutamic acid, the different functional group modifications at the carboxy group and at the ring, as well as the ring opening reactions, will be considered.

2. Transformations on the carboxylic group

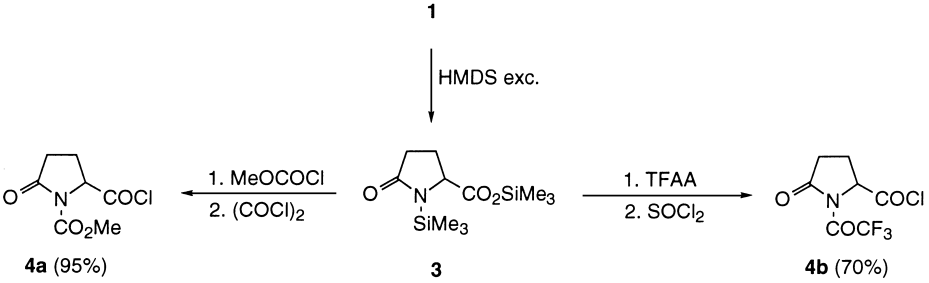
The esterification of pyroglutamic acid **1** takes place during the treatment of glutamic acid with thionyl chloride in methanol or ethanol followed by basification.[13] Pyroglutamic acid can also be esterified under similar reaction conditions.[14]

For the activation of the carboxylic group, the simplest compound is pyroglutamoyl chloride **2**, which has to be prepared in situ due to its instability. Rigo et al.[15] have recently found a more convenient synthesis by silylation of **1** with hexamethyldisilazane (HMDS) to give trimethylsilyl pyroglutamate followed by reaction with oxalyl chloride[16a] (Scheme 1).



Scheme 1.

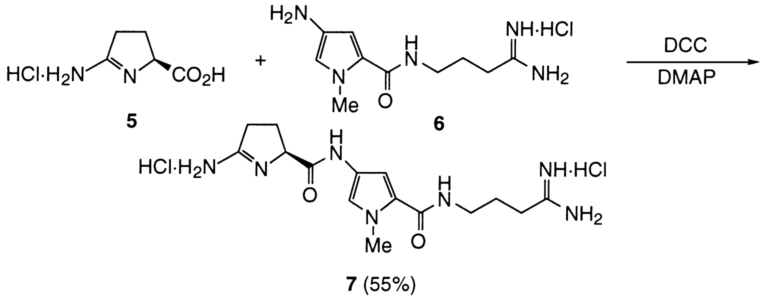
Pyroglutamoyl chlorides *N*-protected by a methoxycarbonyl **4a** or a trifluoroacetyl group **4b** are more stable than compound **2** and can be prepared by reaction of bis(trimethylsilyl)pyroglutamate **3** with methyl chloroformate or trifluoroacetic anhydride (TFAA) followed by reaction with thionyl or oxalyl chloride[16b] (Scheme 2). All these acyl chlorides can be easily transformed into the corresponding esters or amides.



Scheme 2.

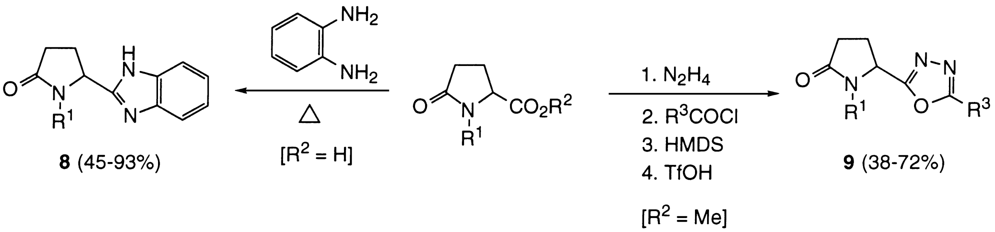
Another method for the activation of **1** in amidation reactions is the use of dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP). This strategy has been used in the preparation of (+)- and (−)-dihydrokikumycin B[17a] and (+)- and (−)-anthelvencin.[17b] For instance, the amino acid **5**—prepared from (*S*)-pyroglutamic acid (see Section 3.4.2)—is coupled with the aminopyrrol **6** to give (−)-dihydrokikumycin B (**7**) in 80% ee[17a] (Scheme 3).

Direct reaction of *o*-phenylenediamine by melting with **1**, or other *N*-allylated pyroglutamic acid derivatives, affords benzimidazoles **8**. Methyl *N*-alkyl pyroglutamates can be transformed into the



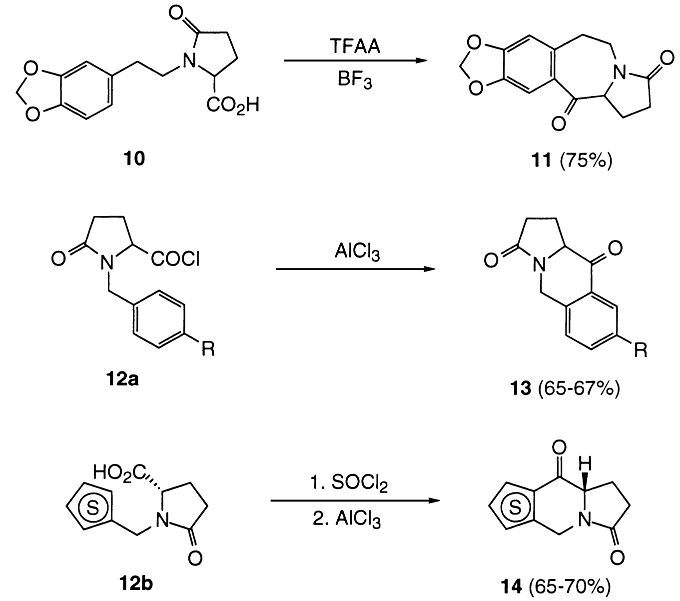
Scheme 3.

corresponding hydrazides by reaction with hydrazine, which are precursors of oxadiazoles **9** (Scheme 4). These racemic heterocyclic derivatives show weak antifungal activity.[18]



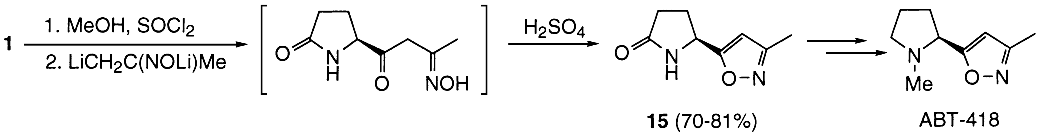
Scheme 4.

In the total synthesis of the antitumour (±)-cephalotoxinamide, the intramolecular Friedel–Crafts acylation of the acid **10** has been carried out with trifluoroacetic anhydride and boron trifluoride etherate under 1,2-dichloroethane reflux to give the corresponding pyrrolobenzazepine **11**[19] (Scheme 5). On the other hand, ketones **13** have also been prepared by an aluminium trichloride promoted intramolecular acylation of in situ generated pyroglutamoyl chlorides **12a**,[20] prepared from *N*,*O*-bis(trimethylsilyl)pyroglutamate (**3**) (Scheme 5). This methodology has been applied to the synthesis of (*S*)-thieno[*f*]indolizinediones **14** from *N*-alkylated (*S*)-pyroglutamic acid **12b**[21] (Scheme 5).



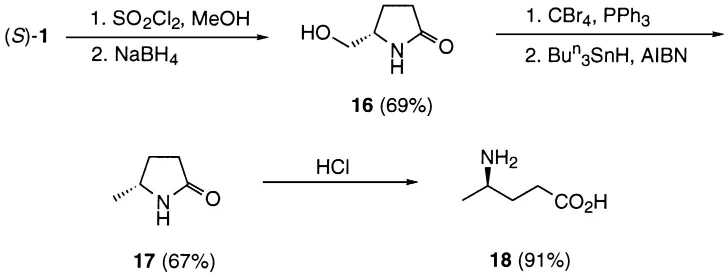
Scheme 5.

(*S*)-3-Methyl-5-(1-methyl-2-pyrrolidinyl)isoxazole (ABT-418), a potent cholinergic channel activator with important cognitive and anxiolytic activities, has been prepared from compound **1**[14] (Scheme 6). The addition of acetone oxime dianion to its methyl ester gave a ketone, isolated as the corresponding isoxazol **15**, which is transformed into the pyrrolidine ABT-418 by reduction of the carbonyl group (see Section 3.4.1) and *N*-methylation.



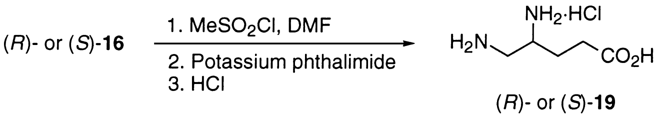
Scheme 6.

The reduction of **1** to pyroglutaminol **16** or 5-(hydroxymethyl)-2-pyrrolidinone is usually carried out by reduction of the corresponding esters with lithium or sodium borohydride without racemisation.[13] The primary alcohol, which is also commercially available, can be transformed into the corresponding halides (chloride or bromide) by reaction with triphenylphosphine and the appropriate carbon tetrahalide. The corresponding fluoride or cyanide are obtained from the bromolactam with silver fluoride in acetonitrile or sodium cyanide impregnated neutral alumina in toluene, respectively.[13a] The bromo derivative can be reduced under radical conditions to the methyl lactam **17**, which gives, after hydrolysis with hydrochloric acid (4*R*)-APA **18**, a moiety of a bleomycin analogue[22] (Scheme 7).



Scheme 7.

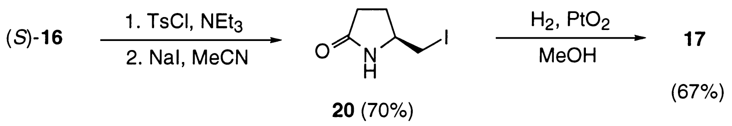
The former chlorinated derivatives can also be obtained by mesylation of (*R*)- or (*S*)-alcohols **16** with methanesulfonyl chloride in dimethylformamide (DMF). These chlorides react with potassium phthalimide giving, after final hydrolysis with hydrochloric acid, the corresponding (*R*)- or (*S*)-4,5-diaminovaleric acids (DAVA) **19**[23] (Scheme 8).



Scheme 8.

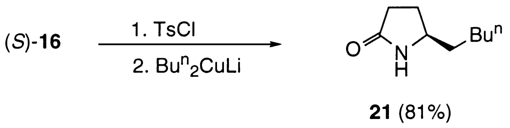
The corresponding tosyl derivative of (*S*)-**16** has been transformed into its iodide **20** with sodium iodide under acetonitrile reflux, which is converted in the lactam **17** by hydrogenolysis[24a] (Scheme 9). Transmetallation with zinc in DMF allows the coupling with propargyl tosylates in the presence of copper(I) salts affording enantiopure allenic lactams.[24b]

The same tosylate intermediate has also been alkylated with an excess of lithium di-*n*-butylcuprate to give the corresponding lactam **21**, which is a precursor of the (−)-indolizidine 209B[25a,b] (Scheme 10). The same strategy has also been used in the synthesis of the indolizidine (+)-monomorine from the (*R*)-tosylate.[25c] However, the alkylation of *N*-Boc-protected (*S*)-pyroglutaminol tosylate with cytosine gives



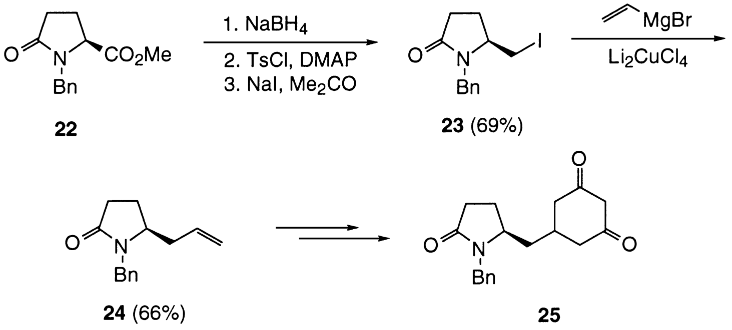
Scheme 9.

better yields than for the corresponding unprotected derivative. The hydrolysis of the lactam ring with lithium hydroxide affords the expected γ,4-diamino-2-oxo-1(2*H*)-pyrimidinepentanoic acid.



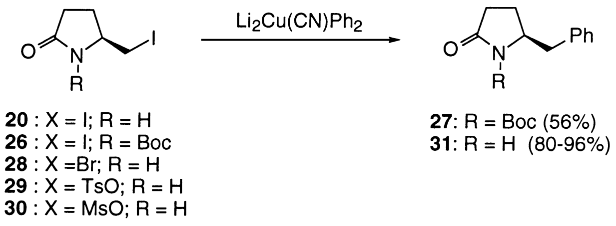
Scheme 10.

A similar coupling has also been carried out in the case of the iodide **23**, derived from methyl *N*-benzylpyroglutamate (**22**), with vinylmagnesium bromide and dilithium tetrachlorocuprate in order to prepare the dione **25**, a precursor of a peptide mimetic of the thyrotropin-releasing hormone[4] (Scheme 11).



Scheme 11.

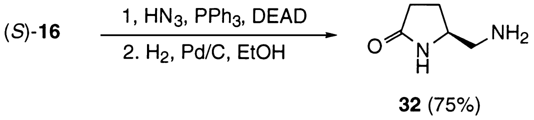
However, when the pyroglutamic acid is *N*-Boc-protected a different behaviour is observed depending on the functional group at the alcohol moiety. Thus, for the corresponding mesylate, tosylate or bromide the reaction with the cuprate $Li_2Cu(CN)Ph_2$ fails and a ring opening occurs (see Section 4). Only in the case of the iodide **26** does the reaction afford the expected product **27** (Scheme 12), the difference being explained by considering the enhanced reactivity of the leaving group.[27a] The unprotected lactams **20**, **28** and **29** react with the same cuprate giving the expected product in good yields, especially in the case of the corresponding tosylate, whereas compound **30** gives a very low yield of the coupling product **31** (Scheme 12).



Scheme 12.

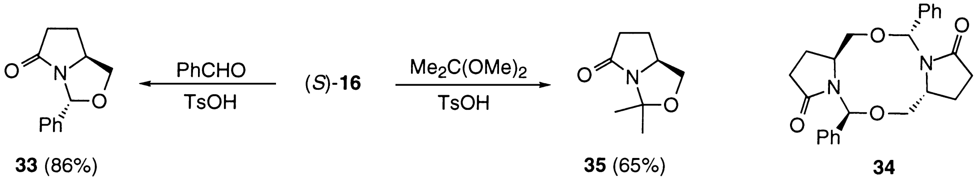
The nucleophilic substitution of iodine by azide in the lactam **20** is greatly accelerated by adding catalytic amounts of sodium hydride before addition of the azide.[27b,c] On the other hand, the mesylate derived from *N*-(*p*-methoxybenzyl)pyroglutaminol can be substituted by sodium cyanide in DMF, this process being considered as a homologation strategy for pyroglutamates.[28]

(*S*)-5-(Hydroxymethyl)pyrrolidone **16** has been transformed into its acetoxy derivative by reaction with acetic anhydride in pyridine[13e] and used in the synthesis of chiral pyrrolidines[29] (see Section 3.4.1). (*S*)-5-Aminomethyl-2-pyrrolidone **32**, a precursor of (*S*)-DAVA **19**, has also been prepared in a two-step synthesis by a Mitsunobu reaction of (*S*)-**16** with hydrazoic acid followed by hydrogenation of the resulting azide[30] (Scheme 13). The obtained amine **32** has been transformed into chiral 1,2,4-triaminobutanes by ring opening with ammonia (see Section 4) and subsequent Hofmann rearrangement.



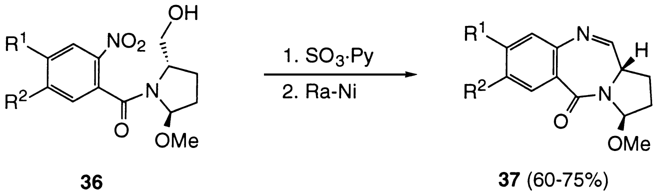
Scheme 13.

The protection of both active hydrogen atoms in (*S*)-**16** can be carried out with benzaldehyde in the presence of an acid catalyst with azeotropic removal of water affording the bicyclic *O*,*N*-acetal **33**[31] (Scheme 14). This acetal has been widely used in the synthesis of chiral prolines (see Section 3.4.1) because the primary alcohol serves as a latent carboxylic acid. However, under the same reaction conditions, racemic **16** gave the *meso*-dimer **34**.[32] The treatment of (*S*)-5-(hydroxymethyl)-2-pyrrolidinone (**16**) with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid affords the acetonide **35**, which has been used in the synthesis of γ-lactam analogues of carbapenems[33] (Scheme 14).



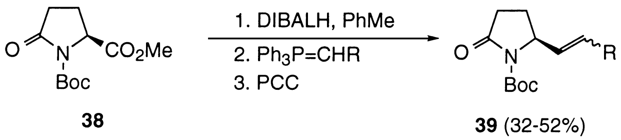
Scheme 14.

The preparation of the 5-carbaldehyde derivative is usually carried out by oxidation of the primary alcohol.[13e] The *N*-benzoylated pyroglutaminol derivatives **36** are oxidised to the corresponding aldehydes by means of SO_3·pyridine and condensed with the amine resulting from the reduction of the nitro group present in the molecule with Raney-Ni giving products **37**, which are finally converted into neothramycins, a family of the antitumoural antibiotics with the pyrrolobenzodiazepine[1,4] structure[34] (Scheme 15).



Scheme 15.

N-Boc-protected methyl pyroglutamate **38** can be reduced with diisobutylaluminium hydride (DIBALH) at −78°C to the corresponding aldehyde, but the carbonyl group of the lactam is also reduced to the hemiacetal (see Section 3.4). Wittig reaction with phosphoranes followed by oxidation with pyridinium chlorochromate (PCC) affords (*S*)-5-alkenyl-2-pyrrolidinones **39**[35] (Scheme 16). The corresponding vinyl derivative gives, after hydrolysis, (*S*)-4-amino-5-hexenoic acid or (*S*)-Vigabatrin®, a highly selective enzyme inhibitor of γ-aminobutyric acid transaminase (GABA-T).[36]



Scheme 16.

Finally, decarboxylation of pyroglutamic acid has been carried out electrochemically in water or methanol to give 5-hydroxy or methoxy pyrrolidinones.[37] By heating different *N*-substituted pyroglutamic acids with a mixture of phosphorus pentoxide and methanesulfonic acid, carbon monoxide evolves and the intermediate aryl iminium salts react in situ with aromatics to give 5-aryl-2-pyrrolidinones.[38] This reaction also takes place with acid chlorides in the presence of aluminium trichloride or tin tetrachloride and trifluoroacetic acid.[39] Obviously, in all these reactions the chirality of the stereogenic centre is lost.

3. Transformations on the ring

3.1. Alkylation or functionalisation reactions

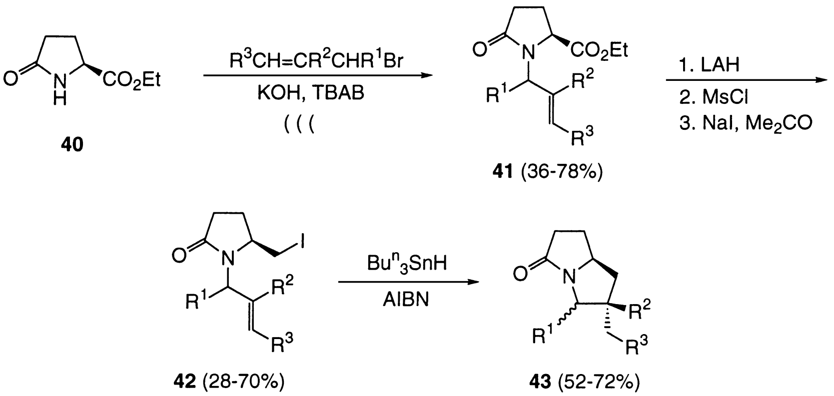
3.1.1. At the nitrogen atom

The acylation of the nitrogen atom can be considered as a protective strategy, methoxycarbonyl, *tert*-butoxycarbonyl (Boc) or benzyloxycarbonyl (Cbz) being the most commonly used groups.[40a] The deprotection can be carried out either under acidic conditions or by hydrogenolysis in the last case. Recently, magnesium methoxide has been reported to be a selective reagent for the deprotection of *N*-alkoxycarbonylpyroglutamates in the presence of other carbamate groups.[40b]

N-Acylpyroglutamate esters have shown bactericide and fungicide properties and can be prepared from the corresponding esters by direct reaction with formic acid, with acetic anhydride and DMAP as catalyst or with acyl chlorides in the presence of triethylamine or pyridine.[41] The best method is the treatment of *N*,*O*-bis(trimethylsilyl)pyroglutamic acid **3** with acid chlorides or diketene.[42] In the case of the carbamoylation, better yields are obtained from the unsubstituted pyroglutamic acid derivatives (toluene, 80°C) rather than starting from the *N*-silyllactam (room temperature).[43] 1-[(*N*-Acetyl-*N*-arylamino)methyl]pyroglutamic acid derivatives can be prepared by using the Mannich reaction from *N*-chloromethylpyroglutamates and *N*-silyl amides or with *N*-silylpyroglutamates and *N*-chloromethylcarboxamides.[44] All these studies have been carried out with racemic pyroglutamic acid.

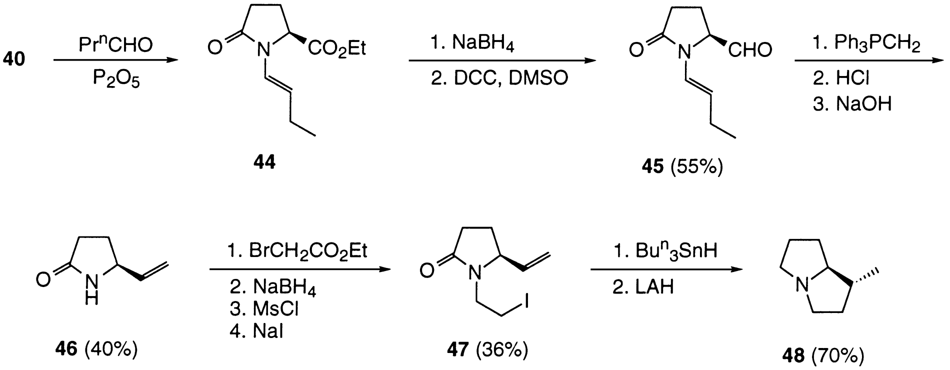
The *N*-protection of pyroglutamic acid with benzyl[20] or benzhydryl bromides has been carried out with *N*-silyl pyroglutamates better than with the corresponding alkali metal salts because in this case a complete racemisation takes place. The deprotection can be performed by hydrogenolysis. This protective strategy allows the carboxylation at the γ-position and has been applied to the synthesis of γ-carboxy-L-glutamic acid (L-Gla)[45] (see Section 3.1.4).

N-Allylation of ethyl pyroglutamate **40** can be carried out without racemisation and in good yields using potassium hydroxide under phase transfer catalysis conditions and ultrasound giving compound **41**. Subsequent reduction of the ester group with lithium aluminium hydride and iodination of the corresponding mesylate yields the iodinated derivative **42**, which by treatment with tri-*n*-butyltin hydride,[46] suffers diastereoselective radical cyclisation to give pyrrolizidin-2-ones **43**[47] (Scheme 17).



Scheme 17.

An inverse radical cyclisation to 7-substituted pyrrolizidinones can be carried out with lactams of the type **47**, prepared from the vinyl lactam **46**. This last compound has been synthesised from ethyl pyroglutamate **40** by condensation with *n*-butanal to give the *N*-vinyl derivative **44**[48] followed by successive reduction and Moffat oxidation to yield the aldehyde **45**, which after Wittig olefination and final hydrolysis of the butenyl protecting group, gives the lactam **46**. The *N*-alkylation of compound **46** is performed with ethyl bromoacetate and further reduction to the corresponding alcohol followed by transformation into the iodide **47**, which is finally stereoselectively cyclised and reduced (see Section 3.4.1) to (−)-heliotridane **48**[49,50] (Scheme 18). Another protection strategy consists of reacting lactams of the type **40** with butanal or phenylacetaldehyde in the presence of *p*-toluenesulfonic acid to give the corresponding *N*-(1-butenyl) or *N*-(1-styryl) derivatives. In the case of ethyl pyroglutamate, the *N*-butenyl derivative **44** can also be deprotected with triethyloxonium tetrafluoroborate.[51]

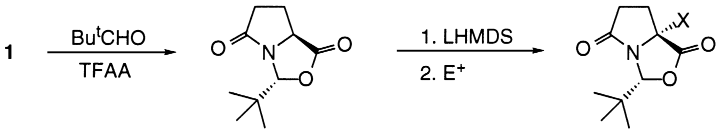


Scheme 18.

The *N*-urethane protection of pyroglutamate esters is very important for the differentiation of the carbonyl group of the lactam moiety and the carboxylate group present in the molecule, during electrophilic and nucleophilic attacks. In the case of pyroglutaminol, it is possible to use *N*-urethane protection or acetalisation.

3.1.2. At the 2-carbon atom

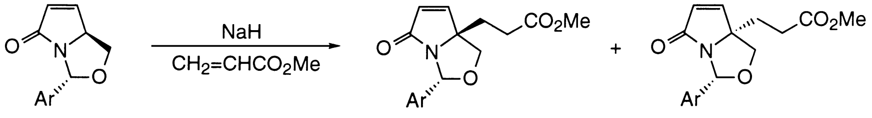
The 2-alkylation of alkyl pyroglutamates can be carried out by deprotonation at the 2-position with LHMDS when the nitrogen is unsubstituted[52] or benzylated,[53] but with subsequent loss of chiral information. However, the bicyclic derivative **51** prepared from pyroglutamic acid and pivalaldehyde, can be deprotonated and alkylated with benzylic bromides or carbonyl compounds with retention of the configuration[54] (Scheme 19). This procedure can be considered as an example of self reproduction of chirality in pyroglutamates.[55]



51 (40%) **52** (44-57%)

Scheme 19.

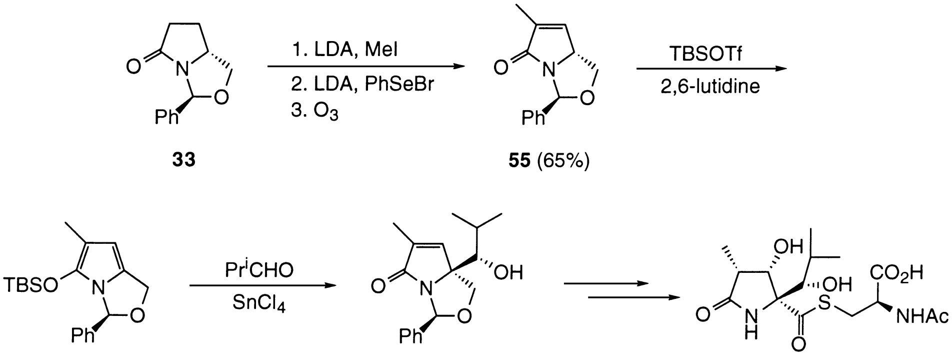
In another strategy, saturated bicyclic lactams of the type **33** are transformed into the corresponding 3,4-didehydro derivatives (see Section 3.1.3) in order to avoid deprotonation at the 4-position. Unsaturated lactam **53**,[56] prepared by phenylsulfenylation of the corresponding saturated lactam enolate followed by thermolysis, undergoes Michael addition to methyl acrylate in the presence of sodium hydride affording a diastereomeric mixture of products **54** (Scheme 20). These compounds can be separated, and after final hydrogenation and hydrolysis, give the corresponding α-substituted pyroglutaminols.[56]



53 **54** (58%)

Scheme 20.

The didehydropyroglutaminol **55**,[31,57] derived from the bicyclic oxazolidinone (*R*)-**33** by sequential methylation and selenenylation at the 4-position (see Section 3.1.4) and final ozonolysis, is transformed into the key silyloxypyrrole **56**.[58] This compound undergoes an aldol reaction at the 2-position with isobutyraldehyde at −78°C in the presence of 2 equivalents of tin tetrachloride to mainly afford the diastereomer **57**, which is an intermediate used in the total synthesis of (+)-lactacystin[58a] (Scheme 21). The influence of the Lewis acid in the Mukaiyama-type aldol reaction of pyrrole **56** with isobutyraldehyde has been studied.[59]



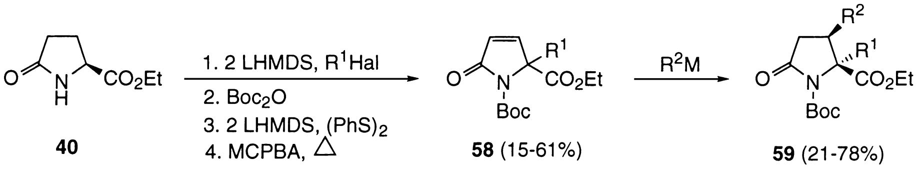
33 **55** (65%)

56 (89%) **57** (55%) (+)-lactacystin

Scheme 21.

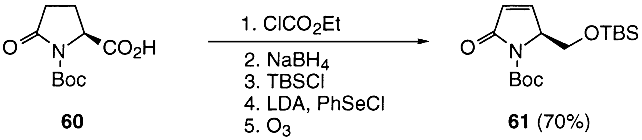
3.1.3. *At the 3-carbon atom*

For alkylation and functionalisation at the 3-position of the lactam ring it is necessary to use the 3,4-didehydroderivative of pyroglutaminol. The conjugation of the double bond with the carbonyl group activates the 3-position for nucleophilic attacks by carbanions or heteronucleophiles. The reduction of the carboxylic group is necessary because it avoids the isomerisation of the double bond to the 2,3-position with consequent racemisation of the stereogenic centre.[60] The only described cases are the Michael addition of cuprates and malonate to racemic 3,4-didehydroglutamates **58** substituted at the 2-position,[52] prepared from ethyl pyroglutamate **40**. This addition gives stereoselectively 2,3-disubstituted pyroglutamates **59** bearing substituents R^1 and R^2 in a *trans* relationship, which after final hydrolysis, give *syn*-2,3-disubstituted glutamic acids[61] (Scheme 22).

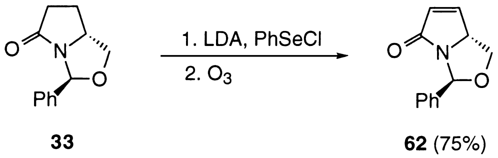


Scheme 22.

The most used didehydroderivatives are the silylated alcohol **61** and related systems, as well as the bicyclic compound **62** or related systems. The lactam **61** can be prepared[7] from *N*-Boc-L-pyroglutamic acid **60** by successive reduction of a mixed anhydride, silylation of the obtained alcohol, selenation at the 4-position and final oxidation in 70% overall yield (Scheme 23). The bicyclic reagent **62**[57b] has also been prepared from compound (*R*)-**33**[57a] by selenation and oxidation with ozone (Scheme 24).

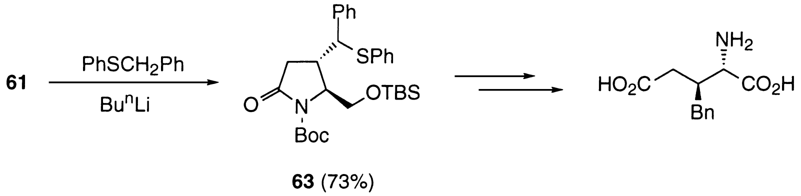


Scheme 23.



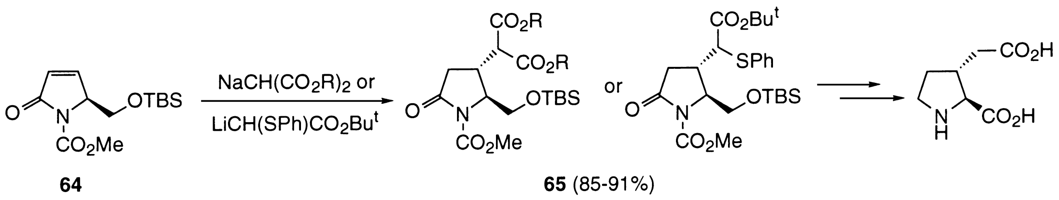
Scheme 24.

Michael addition of lithiated benzyl phenyl thioether to the α,β-unsaturated lactam **61** gives the adduct **63**, which after several steps has been transformed into (2*S*,3*S*)-3-benzylglutamic acid, an acyclic analogue of kainoids, in order to examine its neuroexcitatory activity[62] (Scheme 25). The enantiomer of compound **61** has also been used for the preparation of (2*R*,3*R*)-3-benzylglutamic acid.



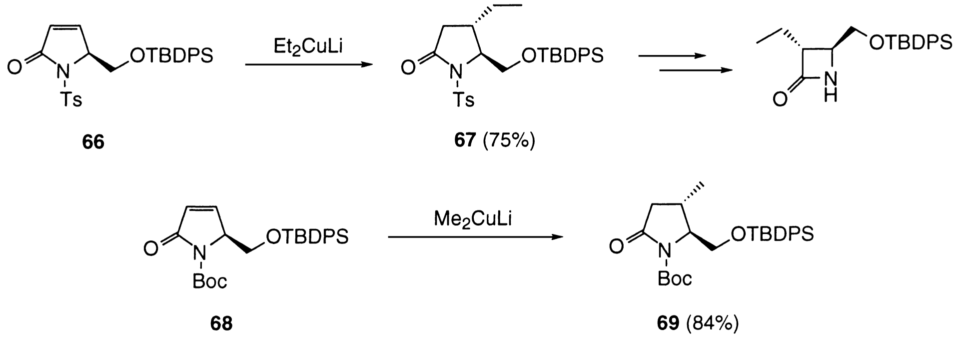
Scheme 25.

The addition of dialkyl sodiomalonates and *tert*-butyl lithiophenylthioacetate to the methoxy derivative **64** takes place stereoselectively at 0 and −78°C, respectively (Scheme 26). The thioether **65** has been transformed into (2*S*,3*R*)-2-carboxy-3-pyrrolidineacetic acid, a kainic acid analogue, by desulfurisation, reduction of the carbonyl group with borane (see Section 3.4.1) and Jones oxidation to give the corresponding acid.[63]



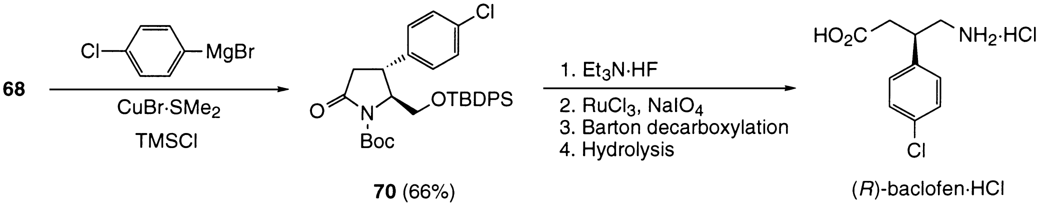
Scheme 26.

A diastereoselective synthesis of the β-lactam nucleus of carbapenems starts with the addition of lithium diethylcuprate to the *O*-silylated *N*-tosyldidehydropyroglutaminol **66** to yield compound **67**.[64] A similar result is obtained with the *N*-Boc compound **68** giving compound **69**[65] (Scheme 27).



Scheme 27.

The last strategy has been used for the preparation of (*R*)-baclofen, a derivative of the inhibitory neurotransmitter GABA.[64] The Michael addition needs an excess of cuprate (5 equivalents) and use of trimethylsilyl chloride in order to avoid the lactam opening (see Section 4). Compound **70** is transformed after oxidation and Barton decarboxylation, into a γ-lactam, which is hydrolysed to (*R*)-baclofen[66] (Scheme 28).

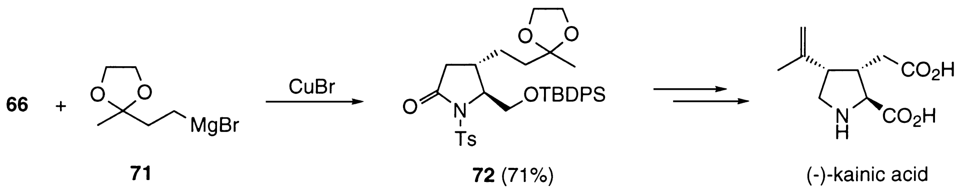


Scheme 28.

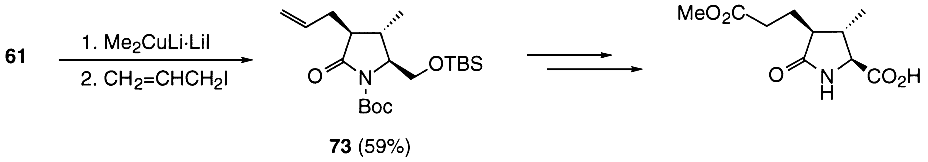
Michael adducts derived from compound **68** related to **70** can be transformed into 3-substituted prolines[67] (see Section 3.4.1).

The cuprate derived from homoenolate **71** has been added to compound **66** providing the adduct **72**, which is an intermediate in the synthesis of (−)-kainic acid[68] (Scheme 29).

The enolate resulting from the Michael addition of lithium dimethylcuprate to compound **61** has been trapped with allyl iodide affording stereoselectively the 3,4-disubstituted pyroglutaminol **73** (Scheme 30), which is a precursor of the pyroglutamate component of the tetrapyrrole compound of the krill fluorescent compound F.[69]

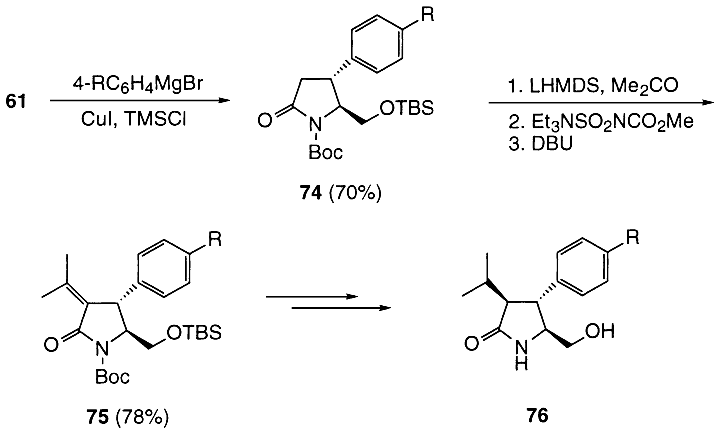


Scheme 29.



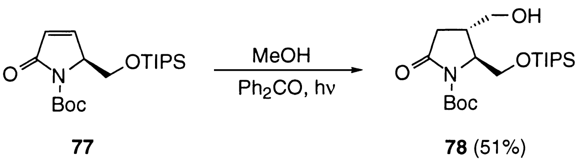
Scheme 30.

Another way to generate the corresponding enolate is the treatment with LHMDS after the Michael addition and final trapping with acetone. This procedure has been applied to the stereoselective synthesis of pyrrolidones of the type **76**, which are very active as protein kinase C (PKC) modulators[70] (Scheme 31).



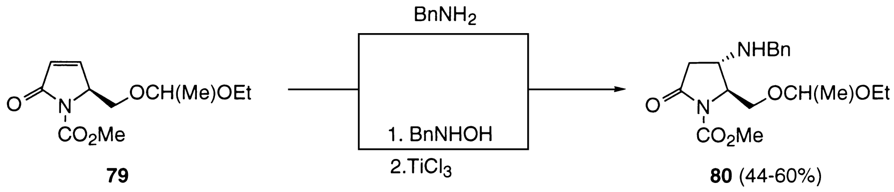
Scheme 31.

Recently, a photoinduced addition of methanol to compound **77**, with benzophenone as photoexcitant, has been carried out with total regio- and diastereomeric control[71] (Scheme 32). The triisopropylsilyl ether derived from pyroglutaminol gives better yields than the *tert*-butyldimethylsilyl derivative. Compound **78** has also been transformed into a fluoromethyl derivative by reaction with diethylaminosulfur trifluoride (DAST) in 56% yield.



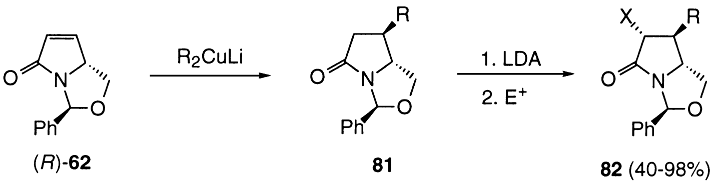
Scheme 32.

Another unsaturated derivative of (*S*)-pyroglutaminol **79**,[72] prepared from the corresponding saturated acetal, reacts stereoselectively with *N*-benzylhydroxylamine or with benzylamine giving substituted 4-aminopyrrolidin-2-one **80**[73] (Scheme 33).



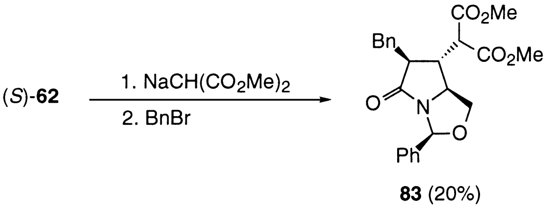
Scheme 33.

The bicyclic derivative **62**[57b] also undergoes a highly stereoselective conjugate addition of lithium dialkylcuprates giving the *trans*-adduct **81** (Scheme 34) in spite of the absence of an electron withdrawing group (*N*-tosyl or *N*-Boc). Hanessian attributes this behaviour to the increased pyramidalisation of the nitrogen atom and the unfavourable stereoelectronic alignment of the lone pair as a consequence of the constrained bicyclic structure.[74] The deprotonation of compound **81** with LDA followed by the addition of alkyl halides or carbonyl compounds allows the alkylation at the 4-position (see Section 3.1.4) with excellent stereochemical control (≥97%) in products **82**. The 3,4-dialkylated products have been reduced to the corresponding pyrrolidines with LAH (see Section 3.4.1). The same authors describe the synthesis of the *C*-terminal D-proline residue of an analogue of *N*-acetylmuramyl dipeptide (MDP) by addition of lithium diallylcuprate to (*R*)-**62**, which takes place in 85% yield.[75]



Scheme 34.

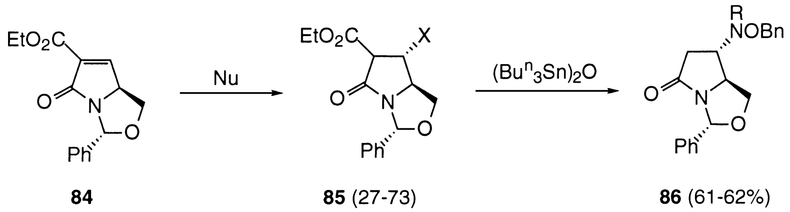
Michael addition of dimethyl malonate to the compound (*S*)-**62** followed by subsequent alkylation with benzyl bromide stereoselectively provides the product **83** in low yield (Scheme 35).[76]



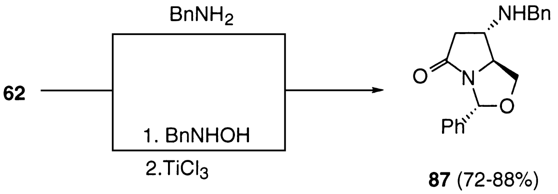
Scheme 35.

The addition of enolates derived from 1,3-dicarbonyl compounds and of Reformatsky reagents also takes place with the more reactive α,β-unsaturated lactam **84**,[77] obtained by reaction of the saturated lactam **33** with ethyl carbonate in the presence of sodium hydride, so the corresponding *trans*-adducts **85** are isolated in good yields and diastereoselectivities[78] (Scheme 36). Nitrogen-containing nucleophiles derived from hydroxylamine and hydrazine also give good yields and diastereoselectivities, producing after final deprotection β-aminopyrrolidinones.[79] The ester group can be decarboxylated by means of tributyltin oxide[80] to yield products **86** in the case of the amino derivatives.[79]

4-Aminopyrrolidin-2-one derivatives **87** can be obtained not only by conjugate addition of *N*-benzylhydroxylamine but also with benzylamine using the α,β-unsaturated lactam **62** as the starting material[73,81] (Scheme 37). Similar results have been described in the case of the compound **79**[73] (see Scheme 33).



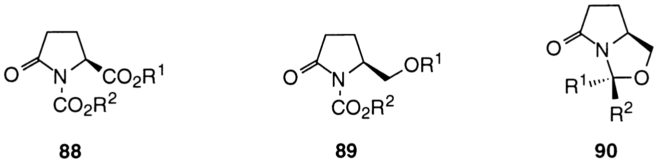
Scheme 36.



Scheme 37.

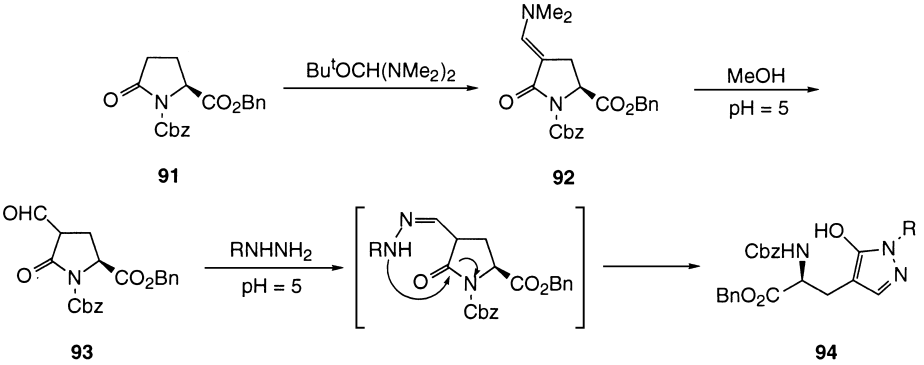
3.1.4. At the 4-carbon atom

Lactam enolates are generally generated from *N*-urethane-protected pyroglutamates **88** or pyroglutaminol derivatives, such as **89** or **90** with strong bases at low temperatures. They usually react diastereoselectively with different electrophiles giving mainly *trans*-4-substituted derivatives (Scheme 38).



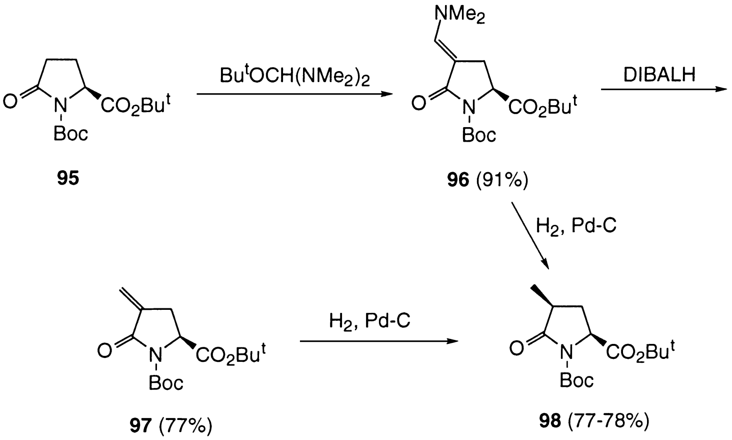
Scheme 38.

Danishefsky et al. have noted that the enolate derived from *N*-(benzyloxycarbonyl)pyroglutamate **91** reacts with the Bredereck reagent [*tert*-butoxybis(dimethylamino)methane] to give the enamine **92**[82] (Scheme 39). The reactivity of this enamine and its application to the synthesis of 4-substituted glutamic acid derivatives have been widely studied by Bowler et al. It can be carefully hydrolysed to the aldehyde **93**, which reacts in situ with nucleophiles to give heterocyclic derivatives, such as **94**, related to (*S*)-glutamic acid through an intramolecular lactam opening (see Section 4)[83] (Scheme 39).



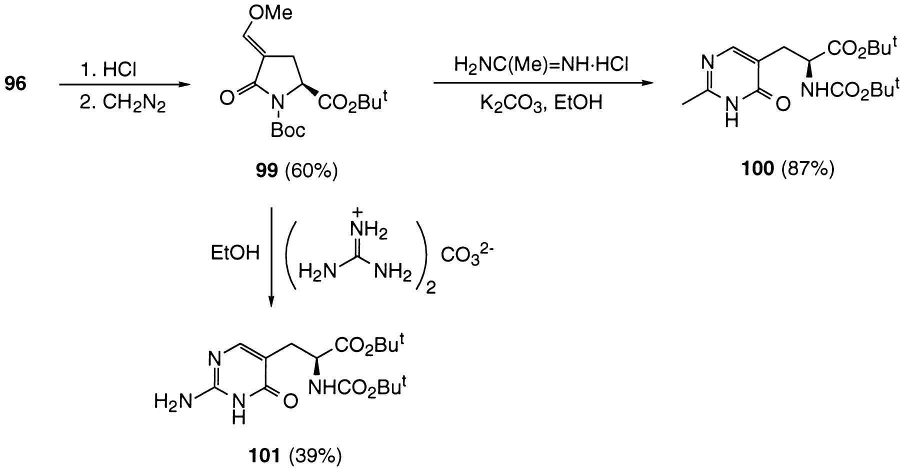
Scheme 39.

The reduction of the Boc-protected derivative **96**, obtained by the same methodology, with DIBALH in THF gives the *exo*-methylenepyroglutamate **97**. Hydrogenation of both compounds **96** or **97** affords the *cis*-4-methylpyroglutamate **98**, which can be transformed into (2*S*,4*S*)-[5,5,5-$^2H_3$]-leucine[84] (Scheme 40).



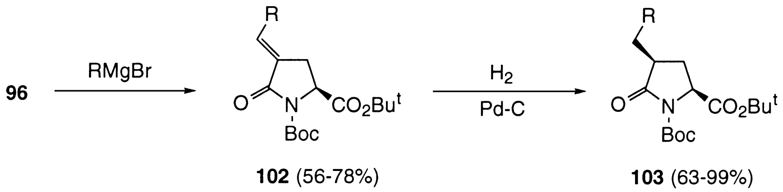
Scheme 40.

The enol ether **99** derived from an aldehyde of type **93**, prepared from the enaminone **96**, has been transformed into different L-alanine derivatives substituted at the β-carbon atom with six-membered heteroaromatic rings. For instance, by reaction of compound **99** with acetamidine hydrochloride the pyrimidin-4-one **100** is obtained, the amino acid form being a glutamate agonist. The amino acid derived from the guanidine derivative **101** has shown weak glutamate antagonist properties[85] (Scheme 41). In this case, an intramolecular lactam opening also takes place (see Section 4), as has been mentioned before in Scheme 39.[83]



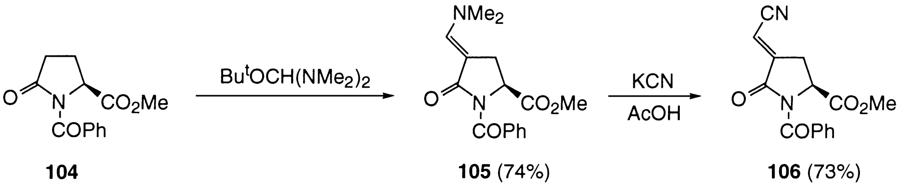
Scheme 41.

The aldehyde resulting from the enamine **96** is reduced by sodium cyanoborohydride to a mixture of *trans* and *cis* alcohols, the former being the precursor of (2*S*,4*S*)-5,5′-dihydroxy[5,5-$^2H_2$]leucine.[86] The enaminone **96** reacts with Grignard reagents affording stereoselectively (*E*)-alkylidene derivatives **102**, which can be hydrolysed to give 4-alkylideneglutamic acids, some of them being natural products.[87,88] Catalytic hydrogenation of compounds **102** gives *cis*-4-alkylpyroglutamates **103** (Scheme 42), which can be hydrolysed to (2*S*,4*S*)-4-alkylglutamic acids and also transformed into (2*S*,4*S*)-4-alkylprolines (see Section 3.4.1).[88,89] Compound **98** has also been transformed into (2*S*,4*S*)-5-fluoroleucine.[90]



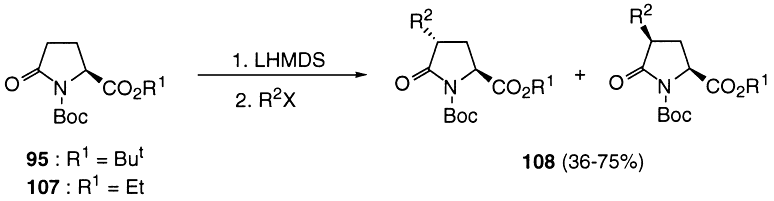
Scheme 42.

Enaminone **105**, prepared by reaction of the *N*-benzoylpyroglutamate **104** with Bredereck's reagent, undergoes nucleophilic vinylic substitution by potassium cyanide at room temperature to give the cyanomethylene derivative **106** (Scheme 43). This compound reacts with different dipoles such as diazomethane, 2,4,6-trimethoxybenzonitrile oxide or benzonitrile imines with low stereoselectivity (see Section 3.3).



Scheme 43.

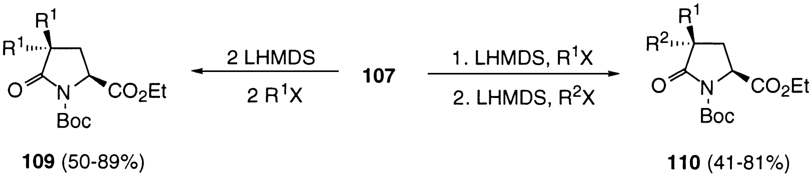
The alkylation of lithium enolates derived from different *N*-protected pyroglutamates was initially studied by Baldwin et al. finding good yields for the aldol reaction, but only benzyl bromide reacts affording the corresponding *trans*-4-benzylated pyroglutamate.[92] Ezquerra et al.[93] obtain good yields in the alkylation with activated halides (benzylic and allylic bromides, ethyl bromoacetate and iodoacetonitrile). The 4-alkylated derivatives **108** are obtained mainly or exclusively, in the case of benzylic derivatives, as the corresponding *trans*-diastereomers (Scheme 44). The benzylated pyroglutamates can be isomerised to the *cis*-diastereomers by treatment with potassium cyanide in DMF at room temperature.



Scheme 44.

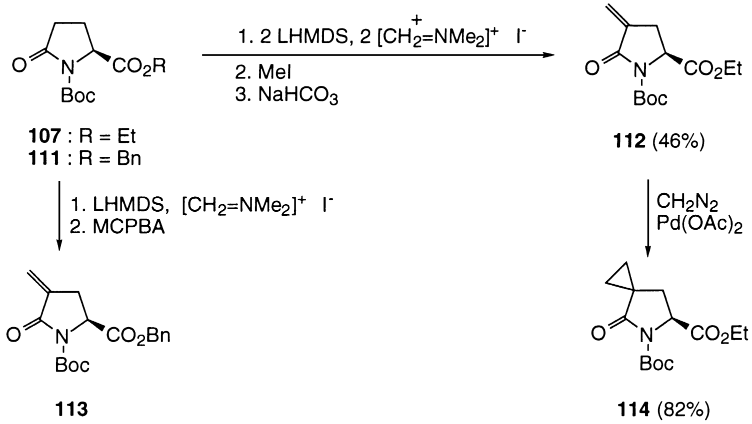
Charrier et al.[94] have again recently studied this alkylation process with compound **95** and found that methyl iodide or triflate give a 5:1 *cis*:*trans* ratio in 67 or 75% yield, respectively. Moreover, *tert*-butyl bromoacetate also gives[92] a 4:1 *cis*:*trans* ratio in 70% yield, whereas Langlois and Rojas[95] obtained a ca. 1:3 ratio and 82% yield for benzyl *N*-methoxycarbonyl pyroglutamate. Charrier et al. proposed that *trans* alkylation takes place with S_N1-type electrophiles, whereas S_N2-type electrophiles give the thermodynamically less stable *cis* products. The use of 2,6-di-*tert*-butylphenol as the bulky proton source in order to quench these reactions yields the corresponding *cis* diastereomers as the only reaction products.[94]

Double dialkylation at the 4-position has been carried out with compound **107** using the same electrophile or by alkylation of 4-monosubstituted pyroglutamates **108**. In the last case, high diastereoselectivity can be achieved when bulky electrophiles (benzylic or cinnamyl) are used[96] (Scheme 45).



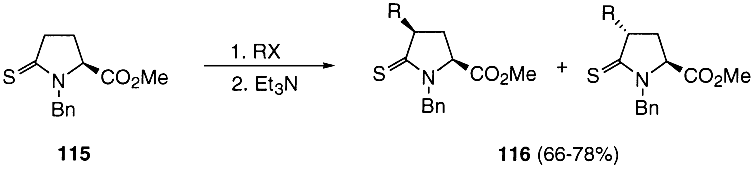
Scheme 45.

The 4-methylene derivatives **112** and **113**, related to compound **97** (see Scheme 40), can be prepared by mono[97] or dialkylation[98] of the lactam enolates with the Eschenmoser salt. In the first case,[97] the Mannich base is submitted to a Cope elimination and in the second case[98] the methylation affords a retro-Mannich type reaction[97] (Scheme 46). The product **112** has been hydrolysed[98] to the natural product 4-methylene-L-glutamic acid which is ten times more active than L-glutamate for NMDA receptors.[99] The cyclopropanation of compound **112** with diazomethane catalysed by palladium(II) acetate provides compound **114** (Scheme 46), which by hydrolysis gives the cyclopropyl analogue[98] of 4-methylene-L-glutamic acid. This methano derivative is twice as potent as L-glutamate as a depolarising agent.[99]



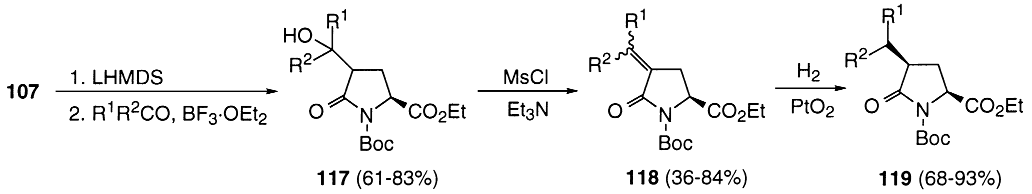
Scheme 46.

Another alkylation strategy is the thio-Claisen rearrangement on the thiopyroglutamate **115**.[8a] It reacts with allylic or propargylic bromides yielding *S*-alkyl thioimminium salts, which on treatment with triethylamine, give the thiopyroglutamates **116** in low diastereoselectivity[100] (Scheme 47).



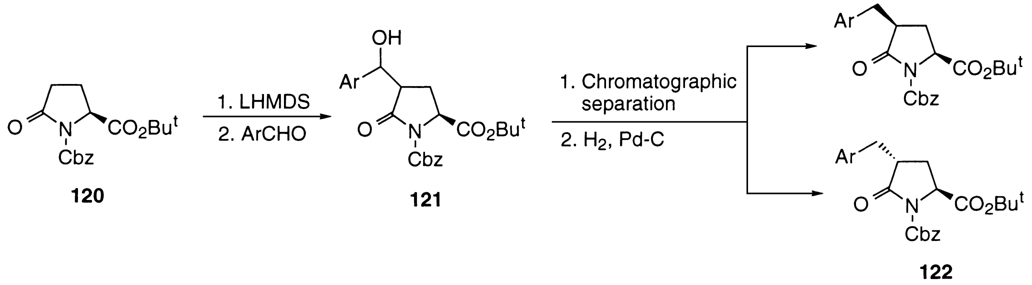
Scheme 47.

Aldehydes react with pyroglutamate lactam enolates, as previously mentioned, in low to good yields.[92,101] The addition of boron trifluoride etherate also promotes the aldol reaction with ketones affording products **117** as a mixture of diastereomers in better yields (Scheme 48). The mesylations of the corresponding alcohols at room temperature furnish 4-alkylidenepyroglutamates **118**, which are hydrogenated, as in the case of compound **102** (see Scheme 42), to give 4-substituted pyroglutamates **119**. They have been hydrolysed to the corresponding 4-alkylated glutamic acids or reduced to prolines (see Section 3.4.1).[102]

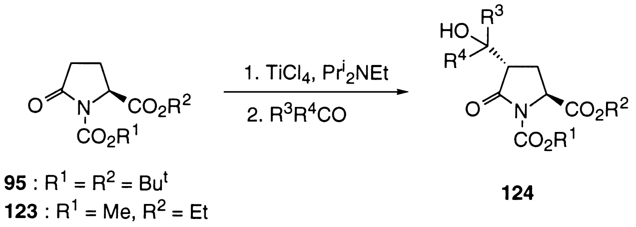


Scheme 48.

Aldols **121**, related to compounds **117**, obtained in a 3:1 *trans*:*cis* ratio from **120**, can be separated and directly transformed into *cis*- or *trans*-4-alkylpyroglutamates **122** by hydrogenolysis[103] (Scheme 49). However, when the titanium trichloroenolates are allowed to react with carbonyl compounds, exclusive formation of *trans*-aldol adducts **124** in good yields is observed[104] (Scheme 50).

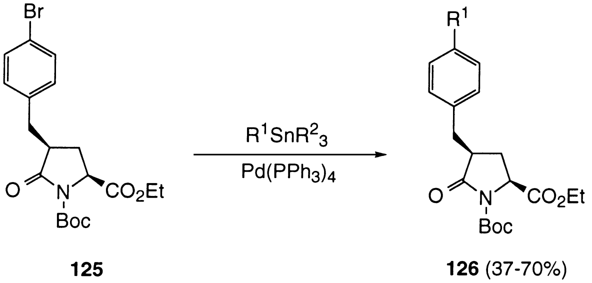


Scheme 49.



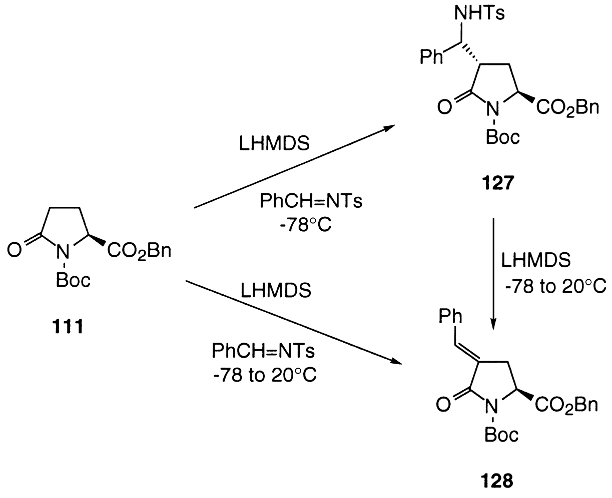
Scheme 50.

Compound **125**, obtained by reaction of the enolate derived from **107** with *p*-chlorobenzaldehyde followed by hydrogenation, has been transformed into different *cis*-4-benzylic derivatives **126** by cross-coupling Stille reaction with organostannanes[105] (Scheme 51).



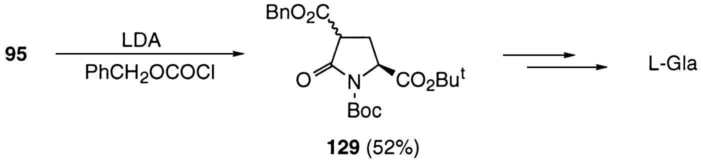
Scheme 51.

Activated imines react with lactam enolates derived from pyroglutamic esters providing two diastereomeric *trans*-products. In the case of *N*-tosylbenzalimine, when the reaction is carried out at −78°C compound **127** is obtained in a 4:1 ratio. However, when the reaction is allowed to warm to room temperature, the benzylidene derivative **128** is isolated, which can also be obtained when compound **127** is treated with one equivalent of LHMDS at −78°C and warmed up to room temperature[106] (Scheme 52).



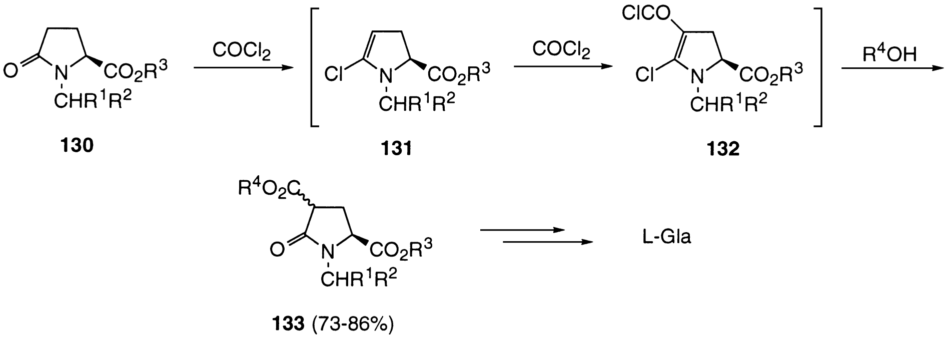
Scheme 52.

Benzyl chloroformate is also a good electrophile in order to introduce the carboxylic functionality at the γ-position of pyroglutamates. Product **129** has been obtained using this procedure (Scheme 53), being transformed into (*S*)-γ-carboxyglutamic acid (Gla) (see Section 4), a constituent of prothrombin and other proteins.[107]



Scheme 53.

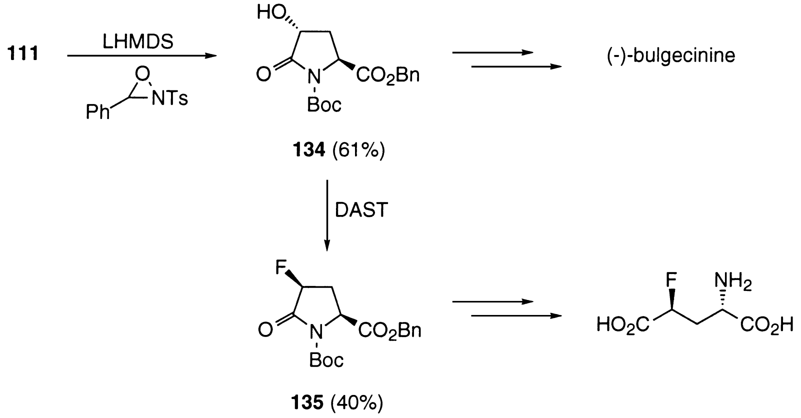
N-Alkylpyroglutamates **130** (see Section 3.1.1) react with phosgene to form the α-chloroenamines **131**, which react further to produce the 4-carboxylated compounds **132**. Alcoholysis of these compounds give esters **133**, precursors of L-Gla[45] (Scheme 54).



Scheme 54.

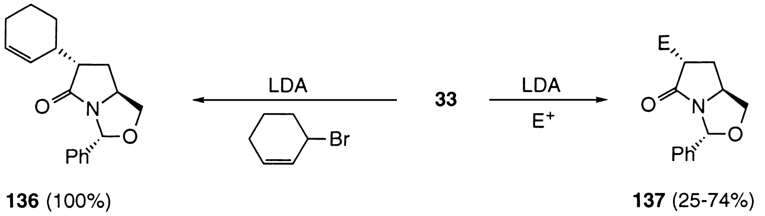
The lactam monoenolate derived from **111** can be stereoselectively oxidised with 2-tosyl-3-phenyloxaziridine to give *trans*-4-hydroxypyroglutamate **134** (Scheme 55), from which (−)-bulgecinine is synthesised[108] (see Section 4). Avent et al. used compound **134** for the preparation of the fluoride

135 by reaction with diethylaminosulfur trifluoride (DAST), which after hydrolysis gives (2*S*,4*S*)-4-fluoroglutamic acid[109] (Scheme 55).



Scheme 55.

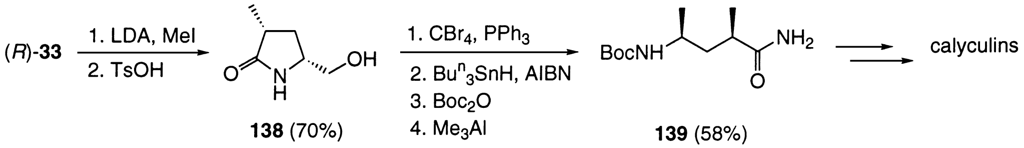
The use of pyroglutaminol derivatives of general structure **89** and **90** for the alkylation or functionalisation of the 4-position in pyroglutamates is a longer route than the use of *N*-protected pyroglutamates, such as **88** (see Scheme 38). Obviously, it is necessary to reduce the carboxylate group to the corresponding alcohol, which has to be finally oxidised again to the acid. The *O*,*N*-acetal **33** was initially used by Thottathill et al. for the generation of lactam enolates, which are alkylated with 3-bromocyclohexene to give compound **136** with a diastereoselectivity >95%[31] (Scheme 56). The alkylation with bromo or iodocyclohexane failed. Compound **136** has been transformed into *trans*-4-cyclohexyl-L-proline (see Section 3.4.1), an intermediate for the synthesis of fosenopril.



Scheme 56.

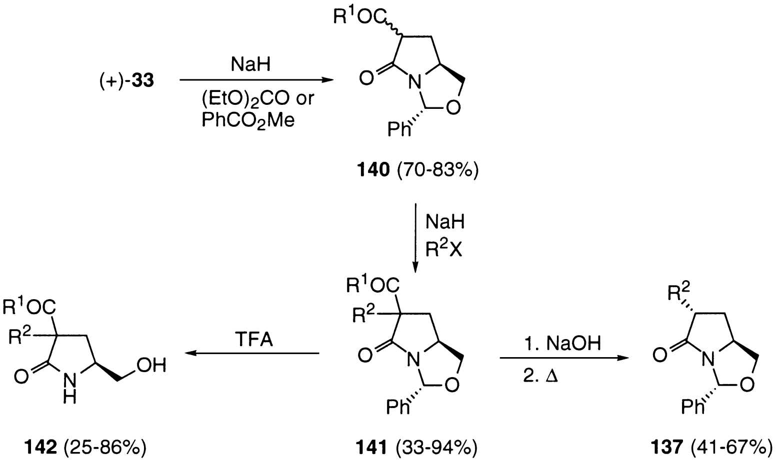
Baldwin et al.[76] have studied the reaction of the enolate derived from compound **33** with benzylic bromides, aromatic aldehydes, phenylselenyl bromide and dimethyl oxalate to give products **137** as a mixture of diastereomers, the major one being the *trans* derivative (Scheme 56). The phenylselenyl derivative has been transformed by ozonolysis into the didehydro compound **62** (see Scheme 24, Section 3.1.3). The methylation has been carried out with methyl iodide to afford a 5:1 ratio of *cis*:*trans* or *endo*:*exo* diastereomers in 90% yield.[110] With other electrophiles, such as benzyl or allyl bromides, the corresponding ratio is 1:2 or 1:1, respectively. Kinetic *endo* selectivity in the alkylation of the enolate derived from compound **33** is preferred when the steric demand of the electrophile is small. The D-pyroglutamic derivative (*R*)-**33** has been methylated and transformed into the amide **139**, which is the C29–C32 fragment of calyculins[110] (Scheme 57).

Moloney et al.[77] have studied the alkylation of (*S*)-**33**, after deprotonation with LDA, as well as the acylation with diethyl carbonate or methyl benzoate in the presence of sodium hydride under toluene reflux. Acylated products **140**, obtained as a mixture of diastereomers, have been alkylated in the presence of sodium hydride with alkyl halides, phenylselenyl bromide and benzaldehyde giving mainly the *exo*-



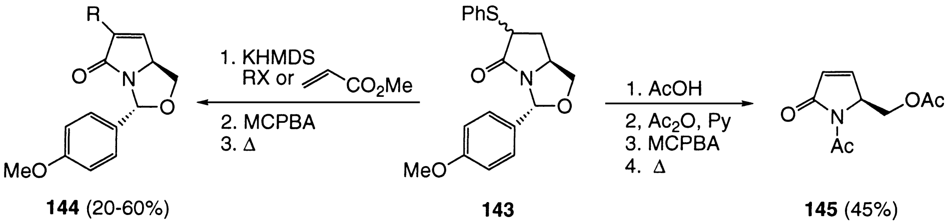
Scheme 57.

adducts **141**. They can be transformed into 4,4-disubstituted pyroglutaminols **142** and by decarboxylation into *trans*-4-substituted acetals **137** (Scheme 58). In the case of the phenylselenyl derivative, it has been converted into the dehydro derivative **84**, after oxidation with hydrogen peroxide (see Scheme 36). In the case of benzaldehyde, a ca. 1:1:1 mixture of diastereomers are obtained in 91% yield.



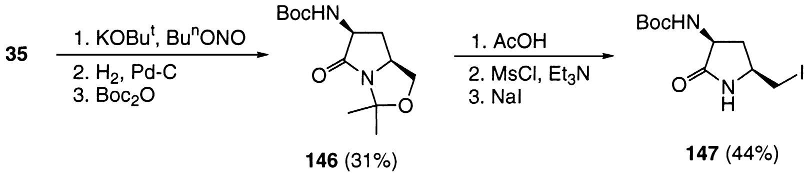
Scheme 58.

The corresponding *N*,*O*-acetal derived from *p*-methoxybenzaldehyde has been used by Nagasaka and Imai[56b] for the functionalisation at the 4-position of pyroglutaminol with methyl iodide, oxaziridines and diphenyl disulfide as electrophiles. The methylation occurs in a similar way as for compound **33**,[110] whereas the hydroxylation affords a 1:1 mixture of hydroxy derivatives as well as the reaction with diphenyl disulfide. The last mixture of isomers **143** has also been deprotonated with LDA, or better with KHMDS, and allowed to react with methyl iodide, methyl bromoacetate or methyl acrylate giving a mixture of isomers, which are transformed into the corresponding didehydro derivatives **144** by oxidation with MCPBA and final heating. Compound **143** has also been converted into the didehydropyroglutaminol acetate **145** (Scheme 59).



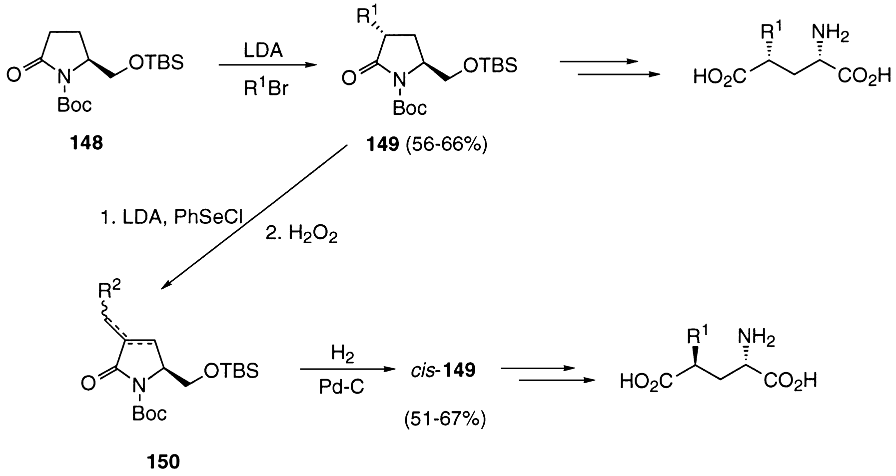
Scheme 59.

The amino group has been introduced at the 4-position of acetonide **35** by reaction with potassium *tert*-butoxide and *n*-butyl nitrite followed by hydrogenolysis and carbamate protection affording the carbamate **146** exclusively. Product **146** has been transformed into the iodide **147**, which after deprotonation has been coupled with 2-phenylsulfinyl maleate to give a γ-lactam analogue to β-lactam antibacterial agents[33,111] (Scheme 60).



Scheme 60.

N-Boc-protected pyroglutaminol **148** gives, by deprotonation with LDA and alkylation of the corresponding enolate with allyl or benzyl bromide, alkylated products **149** in a 15:1 *trans*:*cis* molar ratio, which have been transformed into (2*S*,4*R*)-4-substituted L-glutamic acids[112] (Scheme 61). Compounds **149** give, by a tandem selenation–oxidation process dehydro derivatives **150**, which after hydrogenation afford *cis*-isomers **149**. Final hydrolysis and oxidation leads to (2*S*,4*S*)-4-substituted glutamic acids. The enolate **152** from the homologous *tert*-butyldiphenylsilyl derivative **151** has been methylated to give the intermediate **153** as a 6:1 *trans*:*cis* mixture of isomers. The selenation of this anion **152** followed by oxidation affords compound **68**, whereas the oxidation with MoOPH provides the alcohol **154**[65] (Scheme 62). The reaction of the enantiomer of **152** with benzyl chloroformate provides the corresponding acylated product in 93% yield[113] and by reaction with carbon dioxide yields the corresponding carboxylic acid, which has been used in the synthesis of iricinal A, a related manzamine alkaloid[114] (see Section 3.3).

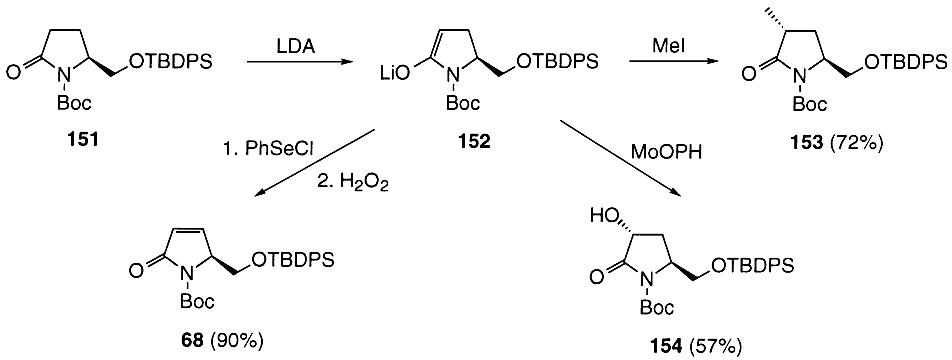


Scheme 61.

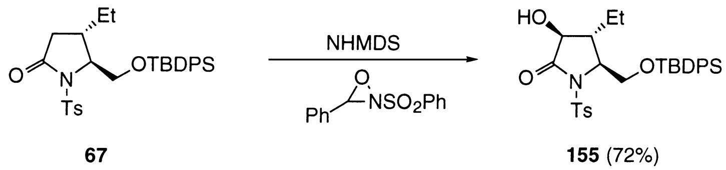
The aldol reaction of the enolate derived from compound **74** has been used in the synthesis of PKC modulators **76**[70] (see Scheme 31, Section 3.1.3). The oxidation of the sodium enolate derived from compound **67** (see Scheme 27) has been carried out with 2-(phenylsulfonyl)-3-phenyloxaziridine to give stereoselectively compound **155** (Scheme 63), a precursor of a carbapenem.[64]

In the synthesis of a 5-substituted-2-formylpyrrolidine derivative **159**, the key D-ring of quinocarcin, the pyroglutaminol derivative **156** reacts with the Bredereck reagent to give the enaminone **157** (Scheme 64). This compound is transformed into the alcohol **158**, a precursor of compound **159**[115] (see Section 3.4.2).

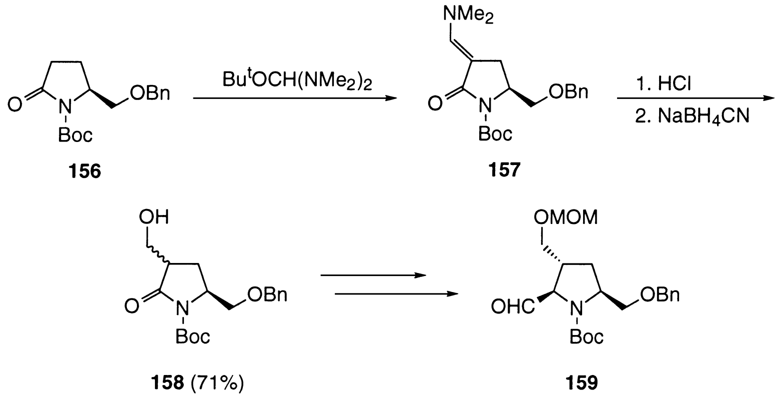
Good diastereoselection has been found in the alkylation of enolates derived from *N*-benzylpyroglutaminol **160** with different halides providing mainly *trans* products **161** (Scheme 65).



Scheme 62.

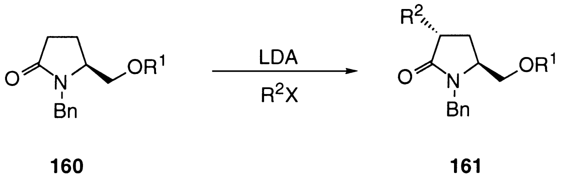


Scheme 63.



Scheme 64.

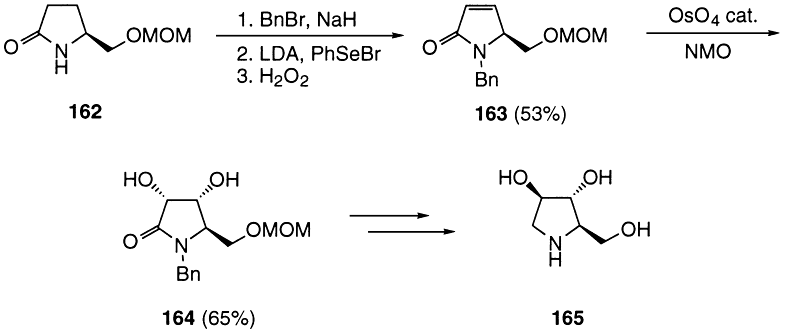
When alkyl iodides are used as electrophiles, alkylation at the benzylic position relative to the nitrogen atom is also observed.[116]



Scheme 65.

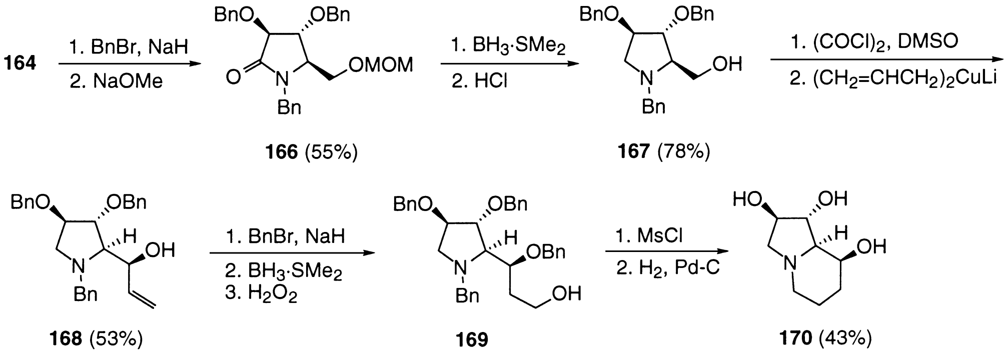
3.2. Dihydroxylation reactions on didehydropyroglutamic acid derivatives

3,4-Didehydropyroglutaminol derivatives are the appropriate systems for carrying out dihydroxylation reactions. The most important application of this reaction is the synthesis of polyhydroxylated alkaloids such as trihydroxypyrrolidines, which are potent α-galactosidase or α-glucosidase inhibitors, and indolizidines. Ikota et al.[117] have applied this strategy for the synthesis of many natural products. For instance, methoxymethylpyroglutaminol **162** gives, after *N*-benzylation (see Section 3.1.1) followed by a selenenylation–deselenenylation procedure, the unsaturated lactam **163**. *cis*-Dihydroxylation of compound **163** with a catalytic amount of osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO) in aqueous acetone affords stereoselectively the diol **164**, which has been transformed into 3,4-dihydroxy-2-hydroxymethylpyrrolidine **165** after epimerisation of the hydroxy group at the 4-position and final reduction of the corresponding carbonyl group[117] (Scheme 66). The MOM-protected compound **163** gives better diastereomeric excess than the corresponding *O*-benzyl system.[118]



Scheme 66.

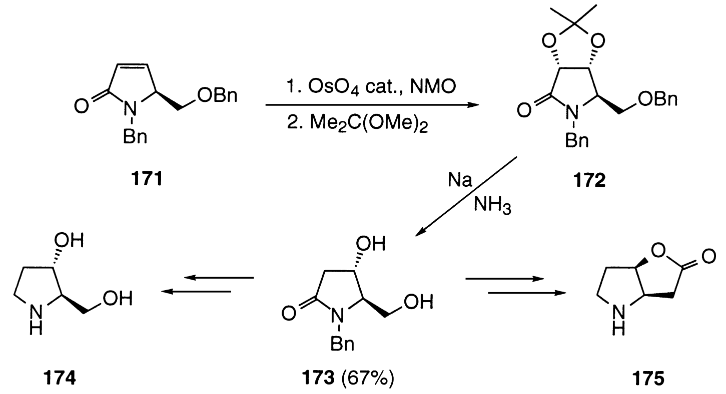
For the synthesis of (−)-1-*epi*- and (+)-1,8-di-*epi*-swainsonine, compound **166**[117] is reduced to the pyrrolidine **167** (see Section 3.4.1). Swern oxidation and reaction with lithium diallylcuprate mainly yields the product **168**, which has been transformed into (+)-1,8-di-*epi*-swainsonine **170** (Scheme 67). The epimer of compound **168** has been transformed into (−)-1-*epi*-swainsonine using the same methodology.[119,120]



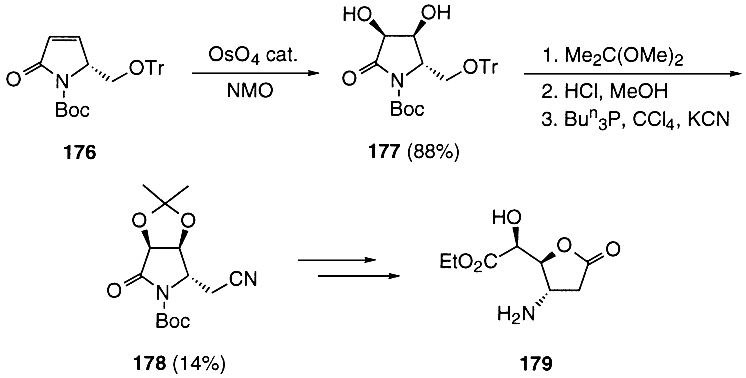
Scheme 67.

The dibenzyl-protected didehydroglutaminol **171** has been dihydroxylated to give the compound **172**. This product has been transformed into the lactam **173** by reduction with sodium in liquid ammonia. Product **173** is converted into (2*R*,3*S*)-3-hydroxy-2-hydroxymethylpyrrolidine **174** as well as the Geisman–Waiss lactone **175**[121] (Scheme 68).

The (*R*)-pyroglutaminol derivative **176**[122] has been used for the synthesis of compound **179**, a precursor of (2*S*,3*S*,4*S*)-4-amino-2,3-dihydroxyhexanedioic acid, a component of the gastroprotective substance AI-77-B.[123] *cis*-Hydroxylation of compound **176** gives **177**, as a single diastereomer, which has also been transformed into the polyhydroxylated pyrrolizidine alkaloids 1,7a-di-*epi*-alexine (1-*epi*-australine), 1,7,7a-tri*epi*-alexine, 1-*epi*-alexine and 1,7-di-*epi*-alexine (Scheme 69).[124]

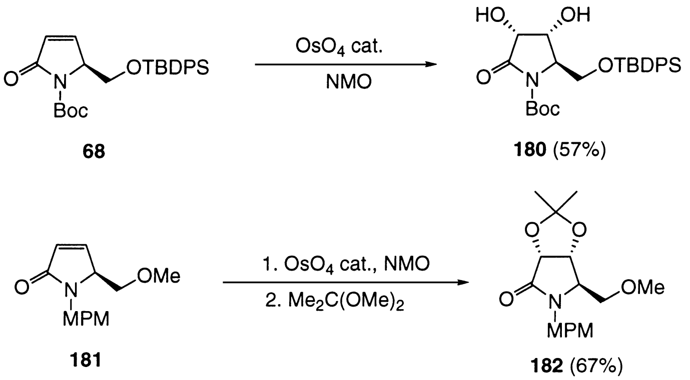


Scheme 68.



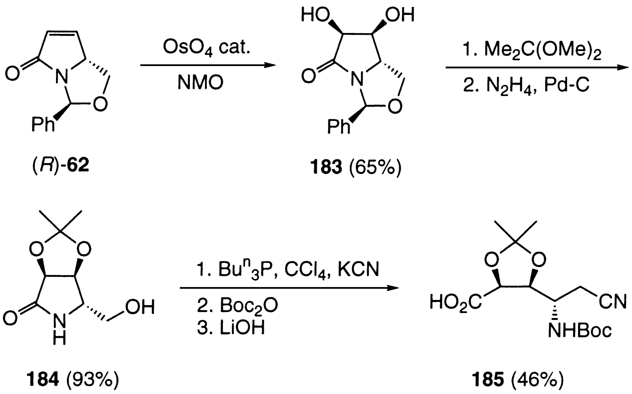
Scheme 69.

The *O*-silyl derivative **68** has been osmylated giving the *cis*-diol **180** as a single diastereomer[65] (Scheme 70). In a similar process, *N*-*p*-methoxybenzyl-*O*-methyl-didehydropyroglutaminol **181** is hydroxylated followed by acetonide formation affording the product **182** also as a single diastereomer[125] (Scheme 70). Compound **182** has been used in the synthesis of (2*R*,3*R*,4*R*)-2,3-dihydroxy-4-dimethylamino-5-methoxypentanoic acid, the antipode fragment of calyculins.[125]



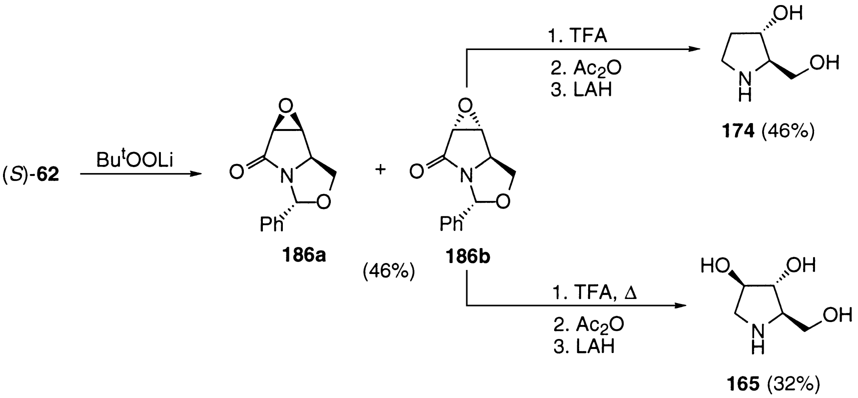
Scheme 70.

The bicyclic unsaturated lactam **62** derived from D-pyroglutaminol has been stereoselectively osmylated on the less hindered side to give the corresponding diol **183** in 96.8% d.e.[57b,126] (Scheme 71). Compound **183** has been transformed into the pyroglutaminol **184** by successive protection of the diol moiety and deprotection of the *N*,*O*-acetal. The primary alcohol is converted into a nitrile, which by *N*-Boc-deprotection of the lactam and final ring opening gives compound **185**, which is, as in the case of compound **179**, also a precursor of the hydroxyamino acid moiety of AI-77-B.[123]



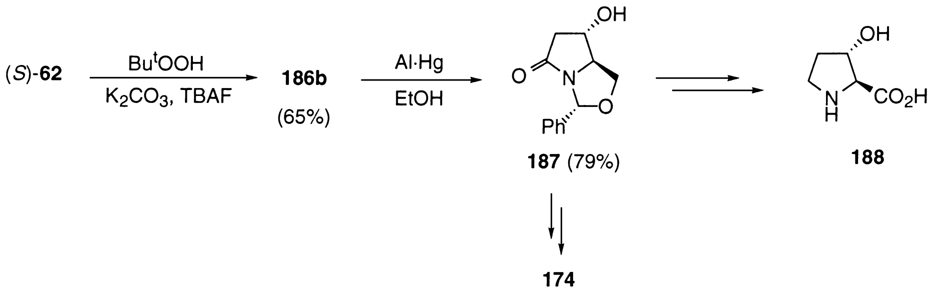
Scheme 71.

The epoxidation of (*S*)-**62** has been carried out with lithium *tert*-butylhydroperoxide giving chromatographically separable epoxides **186** in an 87:13 diastereomer ratio.[127] The major diastereomer **186b** has been transformed by reduction with LAH into the pyrrolidine castanodiol **174**, a natural product isolated from *Castanospermum australe*. Hydrolysis and reduction (see Section 3.4.1) of this epoxylactam **186b** affords the trihydroxylated proline 1,4-dideoxy-1,4-imino-D-arabinitol (**165**)[128] (Scheme 72).



Scheme 72.

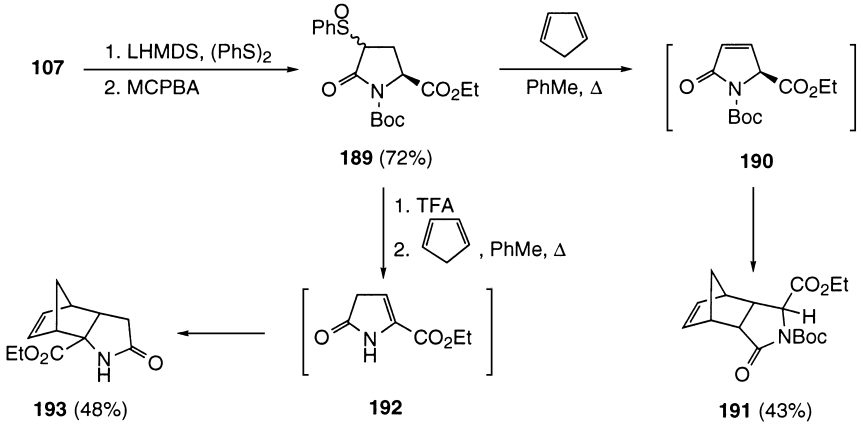
At the same time, Herdeis et al.[129] found better diastereoselectivity in the epoxidation step by using *tert*-butyl hydroperoxide under PTC conditions in DMF with potassium carbonate as base and tetra-*n*-butylammonium fluoride as catalyst. The epoxide **186b** is obtained in 65% yield and characterised by X-ray diffraction analysis. The reduction has been carried out with aluminium amalgam affording the product **187**, which has been transformed into castanodiol **174** and (2*S*,3*S*)-3-hydroxyproline **188**, found in naturally occurring peptides, namely mucrorin-D, telomycin and in bovine Achilles tendon collagen[129] (Scheme 73). The epoxide **186b** has also been reduced to proline (see Section 3.4.1) and converted into 3,4-epoxyproline and aziridinoproline.[130]



Scheme 73.

3.3. Cycloaddition reactions on didehydropyroglutamic acid derivatives

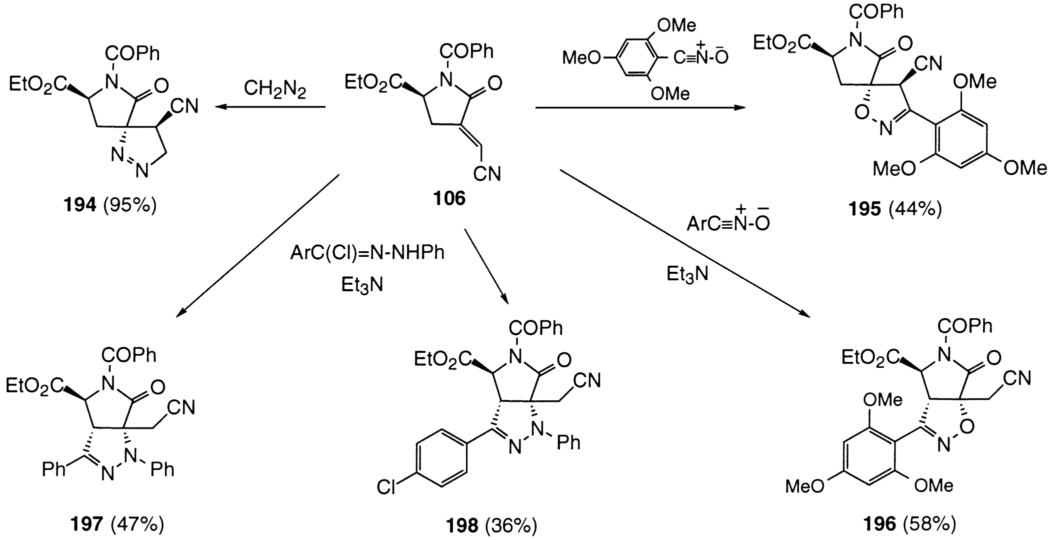
The 3,4-didehydroglutamate **190**, prepared from the sulfoxide **189** via the phenylthio derivative of ethyl (*S*)-*N*-Boc-pyroglutamate **107** is treated with cyclopentadiene to give the *endo*-adduct **191** in 50% e.e. due to the rapid racemisation of the intermediate **190**[60] (Scheme 74). When the same reaction is carried out with the *N*-unprotected derivative, the *exo*-adduct **193**, resulting from an isomerisation of 3,4- to 2,3-didehydropyroglutamate **192**, is exclusively obtained (Scheme 74).



Scheme 74.

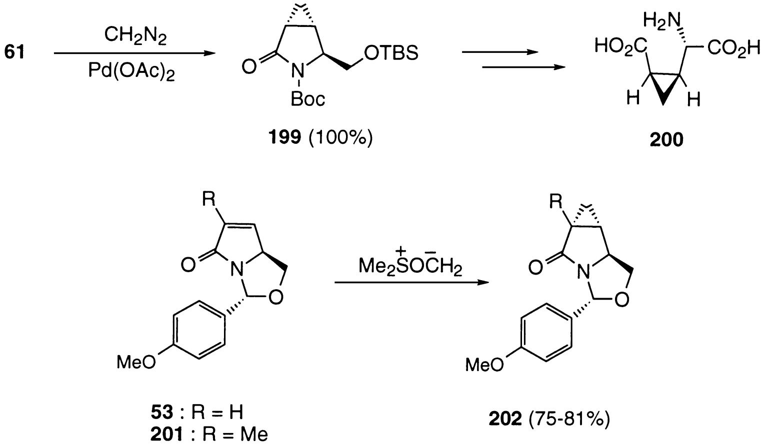
1,3-Dipolar cycloaddition reactions at the *exo*-cyclic carbon–carbon double bond on the nitrile **106**[91] (see Scheme 43) with diazomethane or 2,4,6-trimethoxybenzonitrile oxide afford the corresponding adducts **194** or **195**, respectively. However, in the case of 2,4,6-trimethoxybenzonitrile oxide in the presence of triethylamine or *N*-phenylbenzonitrile and *N*-phenyl-4-chlorobenzonitrile imines the addition to products **196**–**198** takes place at the 3,4-position of pyroglutamate with racemisation, due to the isomerisation of the double bond to the 3,4-position of the pyroglutamate (Scheme 75).

In the case of didehydropyroglutaminol derivatives, cyclopropanation, Diels–Alder, 1,3-dipolar and [2+2] photolytic reactions have been studied. Cyclopropanation of compound **61** has been carried out with diazomethane catalysed by palladium(II) acetate by Ohfune et al.[131] yielding quantitatively the expected product in a 9:1 isomeric ratio, the major isomer **199** being transformed into 2-(carboxycyclopropyl)glycine (L-CCG-III) **200**, a potent inhibitor of glutamate transporters[132] (Scheme 76). Bicyclic lactams **53** and **201** have been cyclopropanated with Corey's ylide to give products **202** in a highly stereoselective manner[56c] (Scheme 76). When substituted ylides derived from sulfonium salts are used in the cyclopropanation of compound **61** or **62**, compounds **203** or **204** are obtained as a mixture of *syn*/*anti* diastereomers. Chromatographic separation of these isomers works



Scheme 75.

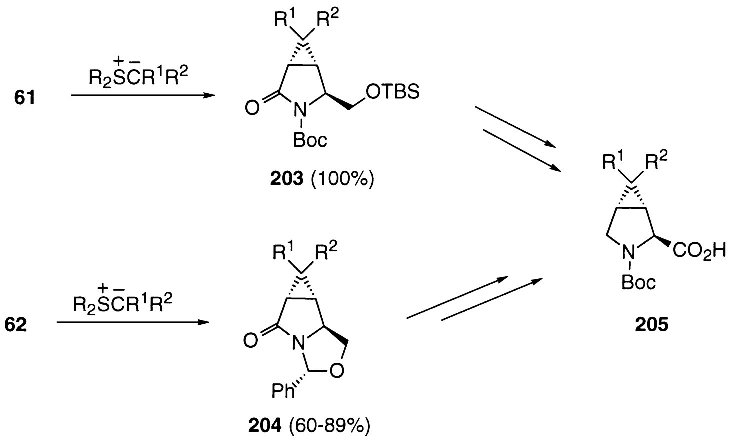
better for compound **204**, which can be transformed into 3,4-cyclopropyl substituted prolines **205**[132] (see Section 3.4.1) (Scheme 77).



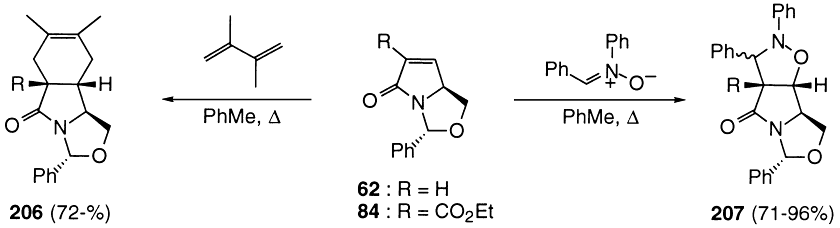
Scheme 76.

Several dienes react with the unsaturated lactams **62**[77] and **84**[27a,77] affording Diels–Alder cycloadducts. For instance, products **206** are obtained in the case of 2,3-dimethylbutadiene resulting from an *exo*-attack.[77] On the other hand, the *N*-α-diphenylnitrone dipole gives a mixture of diastereomers **207**[77b] (Scheme 78). The activated enone **84** is more reactive due to the additional electron withdrawing ester substituent. *N*-Methyl and *N*-benzyl nitrones react with the bicyclic lactam **62** to give cycloadducts of the type **187**. In the case of acetals **79**[72] and **208**, a mixture of regioisomers **209** and **210** in an 8:1–10:1 ratio is formed, respectively[134] (Scheme 79).

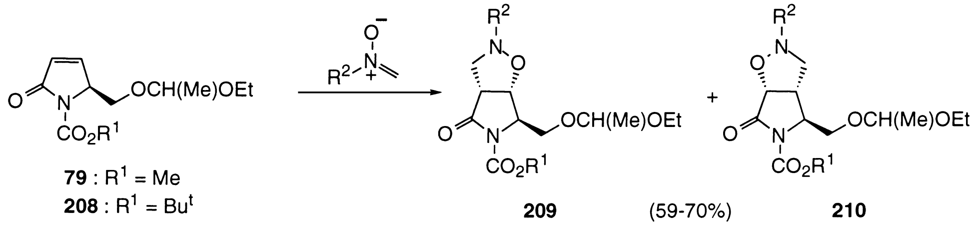
A [2+2] photoaddition of unsaturated lactam **61** and ethylene in acetone has been recently described. This lactam gives the adduct **212** with better diastereoselectivity (91%) than the bicyclic lactam **211**,[135] which affords compound **213** in 75% d.e.[136] (Scheme 80). These reactions proceed smoothly at the less hindered β-face. The major isomer **212** has been transformed into (3*S*,1′*S*,2′*S*)-2-(2-



Scheme 77.

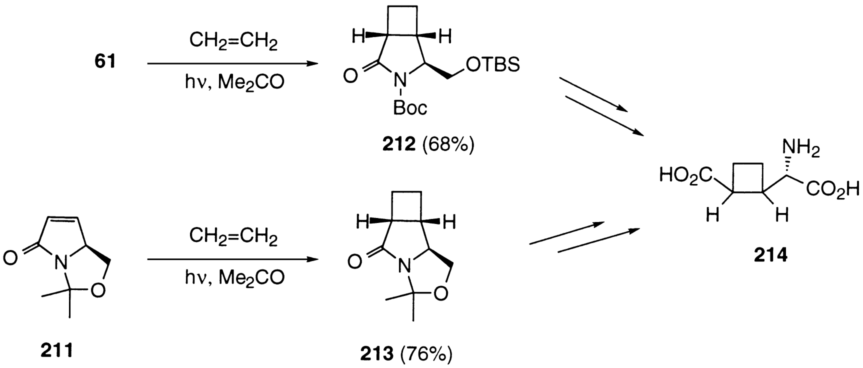


Scheme 78.



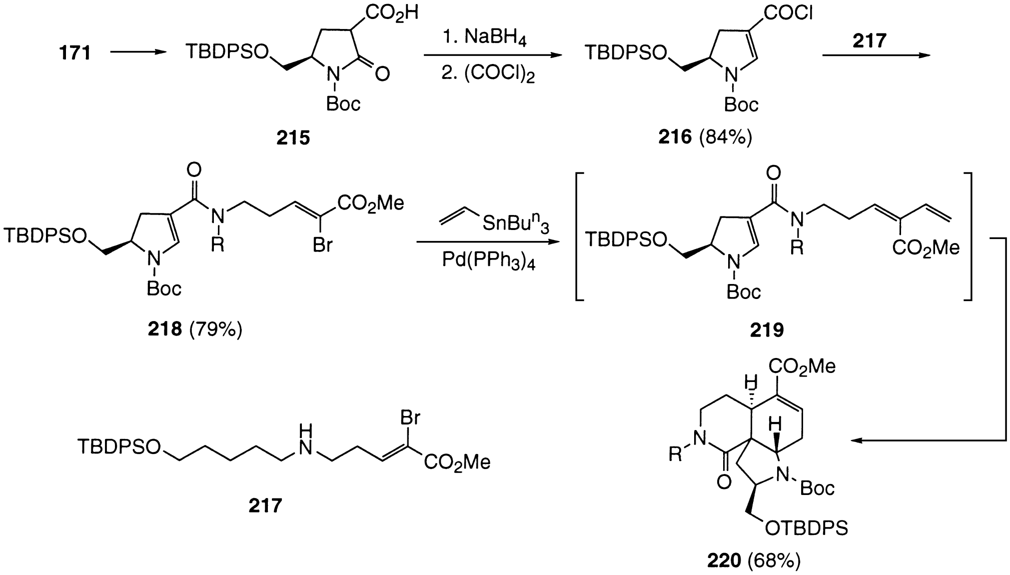
Scheme 79.

carboxycyclobutyl)glycine CBG-III **214**, a homologue of CCG-III **200**,[131,132] which shows a weak activity on group II metabotropic glutamate receptors (mGluR2) of rat brain.



Scheme 80.

An intramolecular Diels–Alder reaction of 4,5-didehydropyroglutaminol **218** is the key step in the total synthesis of ircinal A and related manzamine alkaloids.[113,114] By reduction of the carbonyl group (see Section 3.4.1) of the acid **215**, obtained by carboxylation of pyroglutaminol **171** followed by reaction with oxalyl chloride, the corresponding acyl chloride **216** is obtained. It reacts with the amine **217** to give the amide **218**, which is coupled with vinyl tri-*n*-butylstannane giving a diene **219**. Finally, the corresponding Diels–Alder reaction takes place spontaneously giving solely the intermediate product **220**[114] (Scheme 81).



Scheme 81.

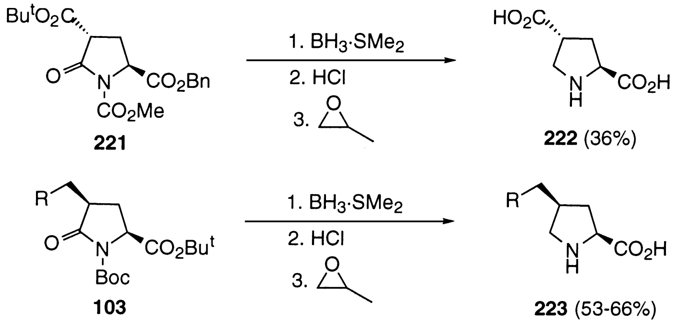
3.4. Transformations on the carbonyl group of the lactam

3.4.1. Reduction reactions

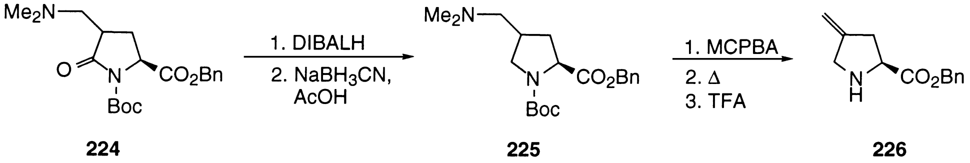
The total reduction of pyroglutamates is a useful strategy for the preparation of proline and its analogues. Borane achieves the reduction of unprotected as well as *N*-Boc-protected pyroglutamates in a one-step process. Compound **15**[14] (see Scheme 6, Section 2) has been transformed into ABT-418 in 59% yield by reduction with borane in THF followed by reaction with formaldehyde in formic acid. 4-Alkylated pyroglutamates such as compound **221**[95] or **103**[87–89,137] (see Scheme 42, Section 3.1.4) have been reduced with the borane–dimethyl sulfide complex to give the corresponding prolines **222** or **223**, respectively (Scheme 82).

Stepwise methods can also be used for the preparation of prolines. In the case of compound **221**, the reduction has been carried out with DIBALH to give the corresponding α-hydroxycarbamate (86%), which is converted into its methoxy derivative (76%) and finally reduced with sodium cyanoborohydride in acetic acid to give the expected protected proline (90%).[95] In other cases, such as the aminomethyl derivative **224**,[97] obtained by reaction of the corresponding enolate with Eschenmoser salt, the hydroxycarbamate can be reduced to compound **225**, which is finally transformed into (*S*)-4-methyleneprolinate **226** by a tandem Cope elimination–deprotection (Scheme 83).

The two-step reduction can also be carried out with lithium triethylborohydride followed by reduction of the hemiaminal intermediate with triethylsilane and boron trifluoride etherate.[138] This methodology has been widely used for the synthesis of *trans*-4-substituted[102] and 4,4-disubstituted prolines.[96] 4-

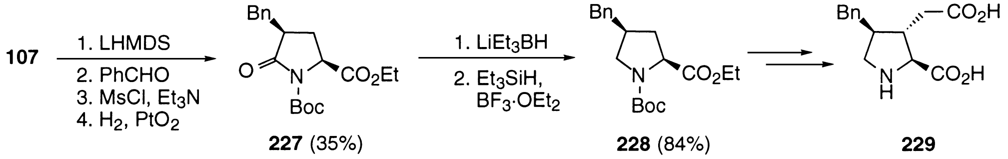


Scheme 82.



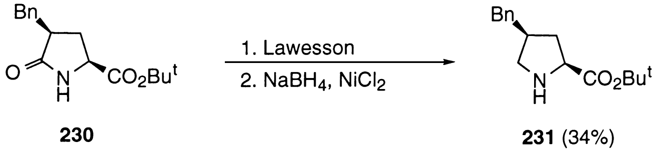
Scheme 83.

Substituted pyroglutamates *trans*-**108**[138] (see Scheme 44, Section 3.1.4) and 4-dialkylpyroglutamates **110**[96] (see Scheme 45, Section 3.1.4) have been transformed in good yields into the corresponding prolines. The *cis*-4-benzylproline **228** has been prepared from ethyl *N*-Boc-pyroglutamate **107** by an aldol reaction with benzaldehyde followed by mesylation and elimination to give the corresponding 4-benzylidenepyroglutamate, which after hydrogenation affords the *cis*-derivative **227**. Final reduction with lithium diethylborohydride and triethylsilane allows the preparation of the protected proline **228**, which has been used for the synthesis of the α-allokainoid **229** (Scheme 84). Starting from the *trans*-benzylated pyroglutamate **227**, the expected enantiomer of compound **229** is also prepared.[139,140]



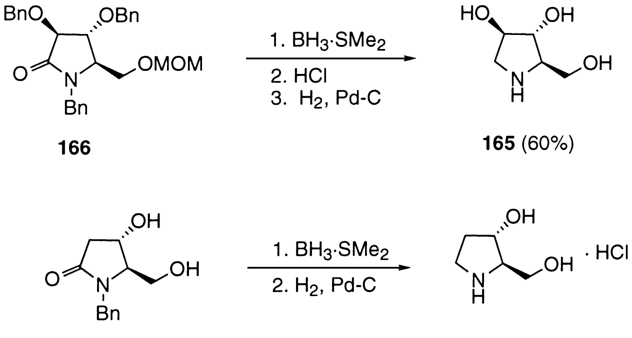
Scheme 84.

Deprotected pyroglutamates can also be transformed into their thioamides with Lawesson's reagent followed by reduction with nickel boride. As an example, the prolinate **231** is obtained from the corresponding pyroglutamate **230** following this methodology[103] (Scheme 85).



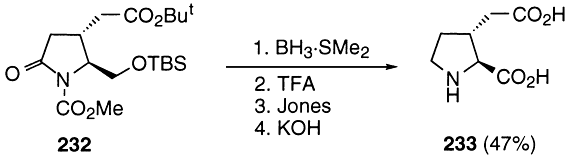
Scheme 85.

O-Protected pyroglutaminols can be reduced to 2-(hydroxymethyl)pyrrolidines by the borane–dimethyl sulfide complex independently of the substitution at the nitrogen atom. Further oxidation of the hydroxymethyl group also allows the preparation of prolines. Ikota et al. have applied this reduction to the synthesis of (−)-swainsonine[117] and its derivatives[118–120] (see Scheme 67, Section 3.2). 1,4-Dideoxy-1,4-imino-D-arabinitol (**165**) is prepared from compound **166** (via compound **144**, Scheme 67) by reduction with diborane and final deprotection[117] (Scheme 86). Castanodiol hydrochloride **174** and the Geisman–Waiss lactone **175** are obtained from compound **173**[121] (see Scheme 68, Section 3.2) by reaction with borane followed by hydrogenation[121] (Scheme 86).



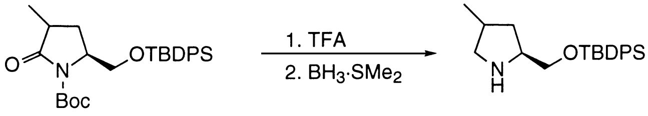
Scheme 86.

N-Methoxycarbonylpyroglutaminol **232**,[63] obtained from compound **64** (see Scheme 26), has also been transformed by reduction with the borane–dimethyl sulfide complex followed by deprotection and oxidation into (2*S*,3*R*)-2-carboxy-3-pyrrolidine acetic acid (CPAA, **233**) (Scheme 87). (2*S*,3*S*)-3-Methyl- and 3-phenylproline have also been obtained following a similar methodology, by a reduction–oxidation sequence from compound **69** (see Scheme 27) and the corresponding phenyl derivative, respectively.[67]



Scheme 87.

In the case of the 4-methylpyroglutaminol derivative **234**, deprotection of the Boc group followed by reduction with borane affords the pyrrolidine **235**[65] (Scheme 88).

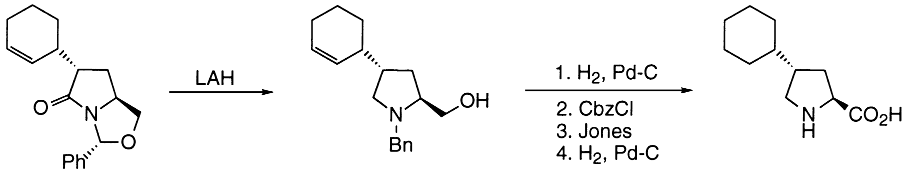


Scheme 88.

trans-4-Alkyl substituted L-prolines have also been obtained by reduction with lithium aluminium hydride of *O*,*N*-acetals derived from pyroglutaminols alkylated at the 4-position. *trans*-4-Cyclohexyl-L-proline **237**, an intermediate for the preparation of certain ACE inhibitors, has been prepared from compound **136** (see Scheme 56, Section 3.1.4) by reduction with lithium aluminium hydride to the pyrrolidine **236** followed by several transformations[31] (Scheme 89).

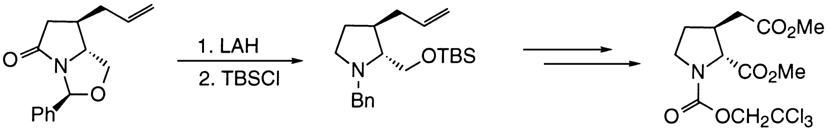
Hanessian et al. have prepared the prolinate **240**, which is the D-propyl moiety of an analogue of *N*-acetylmuramyl dipeptide, from compound **238**, obtained by conjugate addition to the compound (*R*)-**62** (see Scheme 34, Section 3.1.4), by reduction with lithium aluminium hydride and silylation of the resulting alcohol to give the pyrrolidine **239**,[75] the precursor of the final product **240** (Scheme 90).

3,4-Disubstituted derivatives **82** (see Scheme 34, Section 3.1.3) have also been reduced with lithium aluminium hydride to all-*trans* α,β,γ-substituted pyrrolidines.[74]



136 **236** (100%) **237** (78%)

Scheme 89.

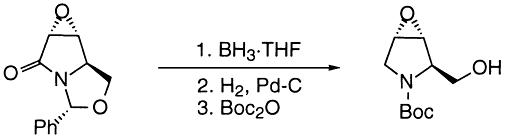


238 **239** (77%) **240**

Scheme 90.

In the preparation of polyhydroxylated pyrrolidines **165**[128] and **174**[127] the reduction of the carbonyl group is carried out with lithium aluminium hydride starting from the epoxide **186b**[127] (see Scheme 72, Section 3.2). Compound **87** (see Scheme 37, Section 3.1.3) is also reduced quantitatively with lithium aluminium hydride to the corresponding *N*-benzylpyrrolidine.[81] 3,4-Cyclopropylprolines **205** are prepared from compounds **204** (see Scheme 77, Section 3.3) by reduction of the carbonyl group with lithium aluminium hydride and further oxidation of the hydroxymethyl group.[133]

Borane–dimethyl sulfide can also be used for the reduction of the carbonyl group of bicyclic lactams derived from pyroglutaminol. Herdeis et al. have synthesised prolines of type **174** and **188** from the 3-hydroxy derivative **186a** (see Scheme 73, Section 3.2). In the reduction of the epoxide **186b** with borane in THF the amide and the acetal groups are reduced to yield the *N*-benzyl epoxyprolinol, which has been used to prepare different L-prolines after *N*-Boc-protection[130] (Scheme 91).



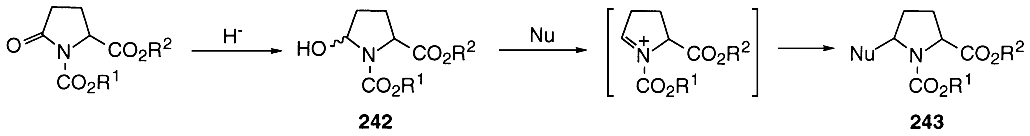
186b **241** (39%)

Scheme 91.

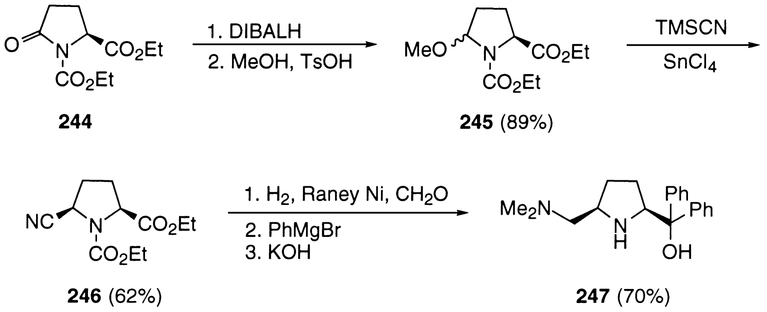
3.4.2. Alkylation reactions

Partial reduction of the lactam carbonyl group in pyroglutamates affords the corresponding hemiaminals **242**, precursors of *N*-acyliminium ions (Scheme 92). The corresponding *O*-methyl aminals can be alternatively obtained by anodic methoxylation[141,142] of proline. Wistrand et al.[143] have reported that the alkylation with alkylcopper reagents occurs with a high degree of *trans*-selectivity. In the case of compounds **242**, they can react with nucleophiles usually in the presence of Brønsted or Lewis acids to give the corresponding 5-substituted prolinates **243**, which can also be transformed into important enantiomerically pure 2,5-disubstituted pyrrolidines.[144]

Corey et al.[145] have prepared the pyrrolidine **247**, a catalyst for the enantioselective addition of dialkylzinc reagents to aldehydes, starting from the pyroglutamate **244**. The reduction of the carbonyl group with DIBALH followed by reaction with methanol affords the compound **245**, which reacts with trimethylsilyl cyanide in the presence of tin(IV) chloride to give a mixture of diastereoisomers. The *cis*-nitrile **246** is further transformed into compound **247** (Scheme 93).

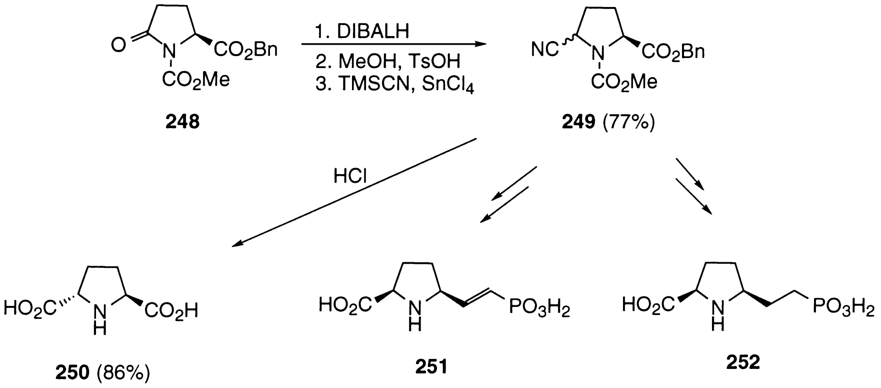


Scheme 92.



Scheme 93.

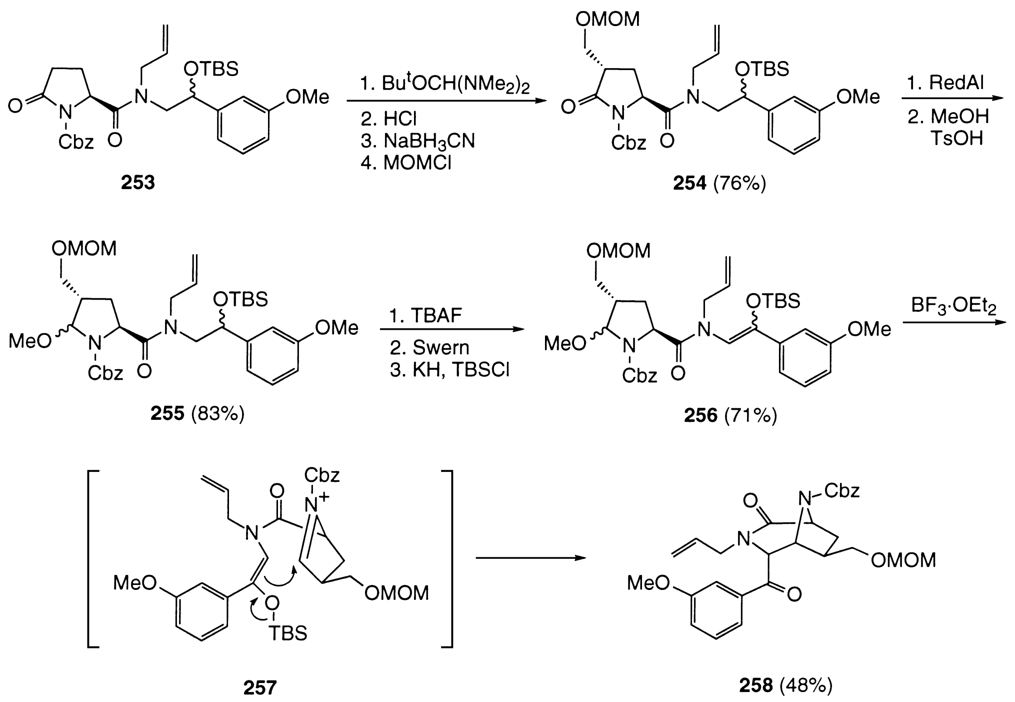
The same strategy has been used for the synthesis of (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid **250**,[146] the epimer of a natural marine product isolated from the red algae *Schizymenia dubyi*[147] and also for the preparation of the phosphonic amino acids **251** and **252**,[148] conformationally constrained analogues of (*R*)-2-amino-7-phosphonoheptanoic acid (AP7)[149] (Scheme 94).



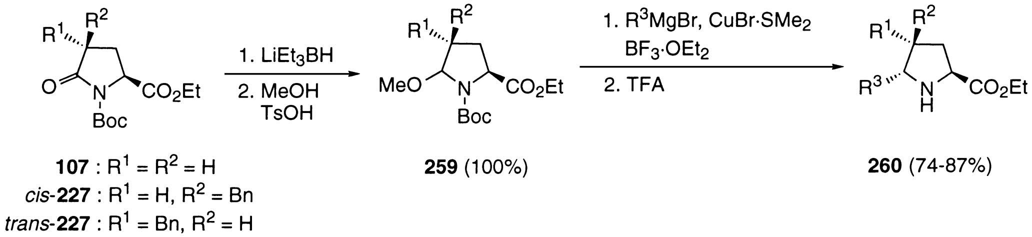
Scheme 94.

In the synthesis of an intermediate of the antitumour antibiotic quinocarcin,[150] the amide **253** is combined with Bredereck's reagent and, after hydrolysis to the corresponding aldehyde followed by reduction and protection, gives the product **254**. The lactam is then reduced with RedAl, and after reaction with methanol, the methoxy derivative **255** is transformed into the silyl enol ether **256**, which is the nucleophile for the *N*-acyliminium intermediate **257**. The final cyclisation gives the product **258** as a 2:1 epimeric mixture (Scheme 95).

The lactam group in pyroglutamates **107** and **227** can also be reduced with lithium triethylborohydride[138] and transformed into the aminals **259**. The reaction of compounds **259** with organocopper reagents, generated in situ from Grignard reagents and the copper(I) bromide–dimethyl sulfide complex, in the presence of boron trifluoride etherate gives the corresponding prolinates **260** with a high degree of *trans* diastereoselectivity[151] (85–97% d.e.) (Scheme 96). The stereochemistry is probably controlled by the formation of a π-complex between the organocopper reagent, the *N*-acyliminium cation and the carbonyl group of the ester.

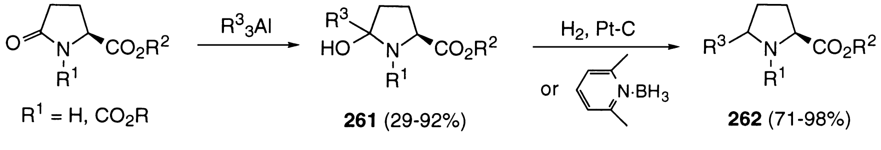


Scheme 95.



Scheme 96.

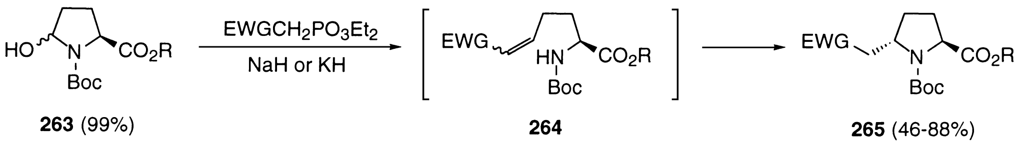
The addition of carbo- and hetero-nucleophiles to pyroglutamates takes place with ring opening (see Section 4). However, trialkylaluminiums add to the carbonyl group of the lactam to yield alkylated hemiaminals **261**. 2,6-Lutidine–borane reduction affords 5-substituted prolinates **262** as a mixture of *cis*:*trans* isomers in 1:1 to 3:1 molar ratio. However, catalytic hydrogenation of compounds **261** over 5% Pt–C in trifluoroacetic acid provides only the corresponding *cis*-diastereomers **262** in high yield and d.e. (90–98%)[152] (Scheme 97).



Scheme 97.

Hemiaminals **263**, obtained quantitatively by lithium triethylborohydride reduction of pyroglutamates,[138] undergo tandem Horner/Wadsworth/Emmons–Michael reaction with stabilised phosphonates giving mainly *trans*-prolinates **265**[153] (Scheme 98). The best diastereoselectivity is obtained with the corresponding acetyl derivative (EWG=MeCO) and potassium hydride as the base.

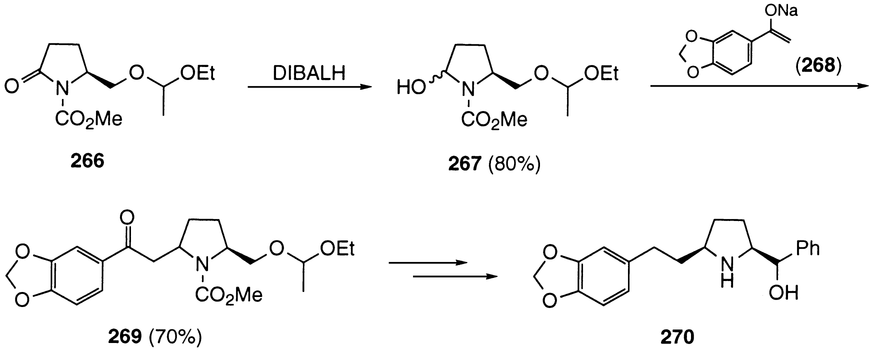
The intermediacy of the unsaturated aminoester **264** has been demonstrated by ^{1}H NMR analysis of the crude reaction mixture, when the process is performed at 0°C for 1 h.



263 (99%) **264** **265** (46-88%)

Scheme 98.

The partial reduction of the lactam carbonyl group in pyroglutaminol derivatives has also been used for the preparation of 2,5-disubstituted pyrrolidines. The lactam **266** has been reduced with DIBALH to the hemiaminal **267**, which reacts with the sodium enolate of 3′,4′-(methylenedioxy)phenyl methyl ketone (**268**) providing the compound **269** as a *cis/trans* mixture of diastereomers. The *cis*-product **269** has been transformed into antihypertensive pyrrolidine **270**[154] (Scheme 99).

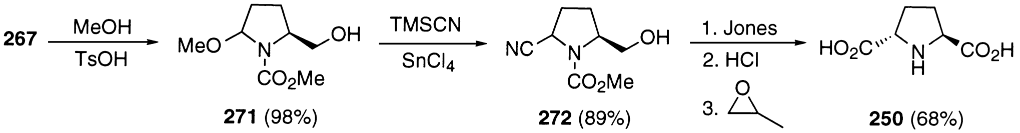


266 **267** (80%)

269 (70%) **270**

Scheme 99.

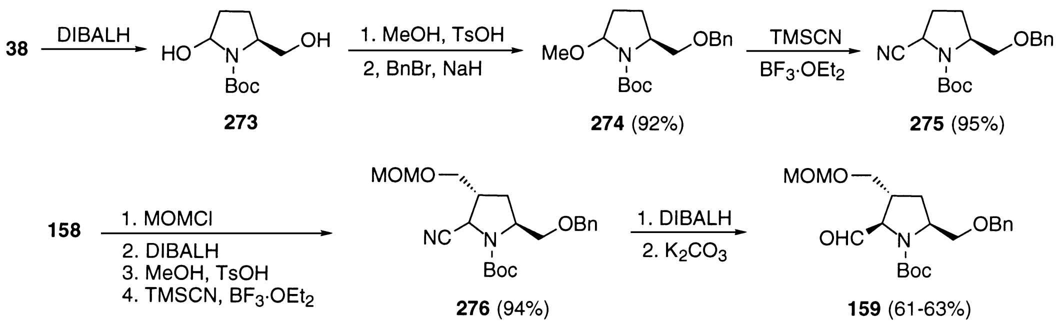
Compound **271**, obtained by reaction of compound **267** with methanol and *p*-toluenesulfonic acid, has been coupled with trimethylsilyl cyanide in the presence of tin tetrachloride to give a 35:65 *cis*:*trans* mixture of the corresponding nitriles **272**. The corresponding *trans*-isomer has been transformed into the diacid **250**, a marine natural product[146] (Scheme 100). This diastereoselectivity is the opposite of that in the case of the pyroglutamate derivative **249**, when the *cis*-isomer is the major one[146] (see Scheme 94).



271 (98%) **272** (89%) **250** (68%)

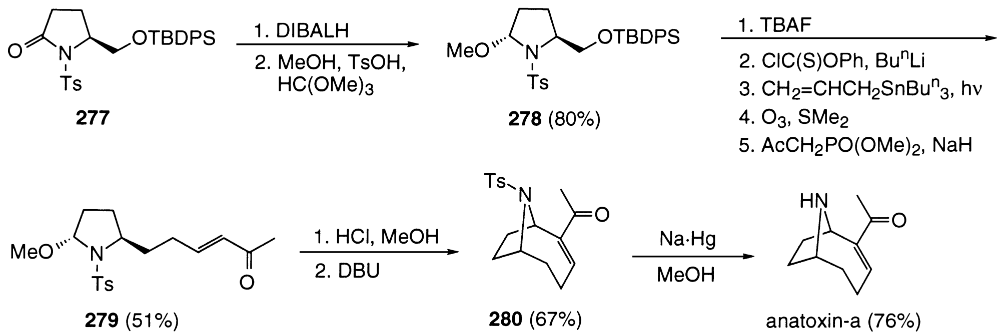
Scheme 100.

The nitrile **275** has been prepared as a 31:69 *cis*:*trans* diastereomeric mixture by: (a) direct reduction of the pyroglutamate **38** with DIBALH to give the diol **273**; (b) treatment of this compound with methanol and *p*-toluenesulfonic acid; (c) benzylation with benzyl bromide to yield the aminal **274**; and (d) final reaction with trimethylsilyl cyanide[115] (Scheme 101). On the other hand, the nitrile **276** has also been prepared in a 27:73 *cis*:*trans* ratio by reduction of the lactam **158** (see Scheme 64, Section 3.1.4) followed by cyanation. Treatment of compound **276** with DIBALH yields the aldehyde **159** (Scheme 101). Both mentioned nitriles **275** and **276** are key fragments of (−)-10-decarboxyquinocarcin and (−)-quinocarcin, respectively.[115] Compound **273** has also been used in the synthesis of 3,5-disubstituted indolizidine toxins 223AB and 239AB, extracted from the Colombian poison frog *Dendrobates histrionicus*, and the pyrrolizidine alkaloids (+)- and (−)-xenovenine.[155]

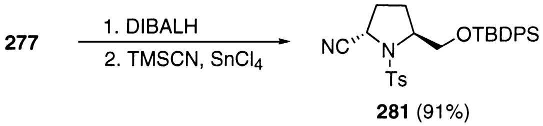


Scheme 101.

Intramo- lecular alkylations of iminium ions derived from *N*-tosylpyroglutaminols have been used for the synthesis of (+)-anatoxin-a, a powerful neurotoxic alkaloid isolated from the fresh-water blue-green algae *Anabaena* flos-aqua.[156a] The reduction of compound **277** with DIBALH followed by reaction with methanol furnishes the compound **278** in 95% d.e., which is further transformed by functionalisation of the primary alcohol into the unsaturated ketone **279**.[156a] This enone is cyclised under Hiemstra and Speckamp conditions[157] to give, after final desulfonylation, (+)-anatoxin-a (Scheme 102). The hemiaminal resulting from compound **277** has also been transformed stereoselectively into the nitrile **281**, as the single *trans*-isomer[156b] (Scheme 103).



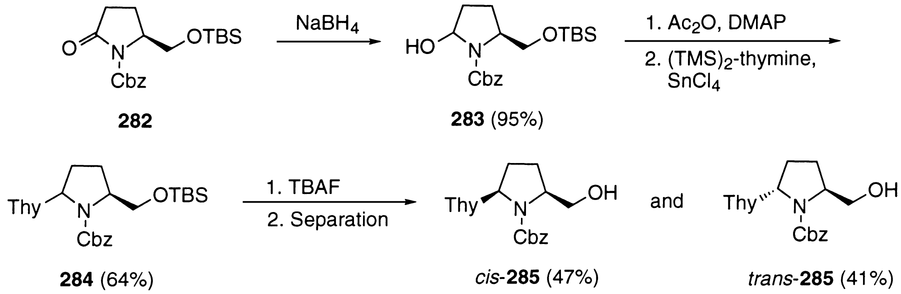
Scheme 102.



Scheme 103.

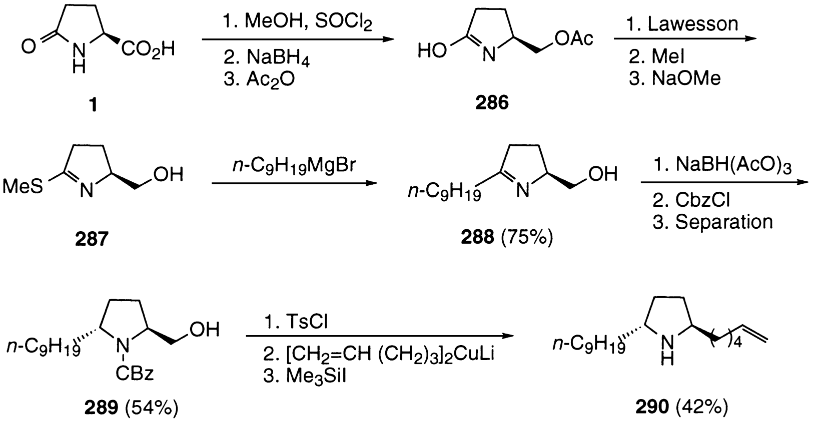
Pyrrolidine-based analogues of 3′-deoxythymidine have been prepared via *N*-acyliminium ion intermediates derived from the pyroglutaminol **282**. In this case, the hemiaminal **283** has been transformed into its acetate and coupled with the bis-trimethylsilyl derivative of thymine in the presence of tin tetrachloride to furnish compound **284** as a mixture of diastereomers. Final desilylation affords, after separation of the isomers, the target molecules *cis*- and *trans*-**285**[158] (Scheme 104).

When *N*-unprotected pyroglutaminols are used, the reduction of the carbonyl group affords pyrrolines, which can be alkylated by means of Grignard reagents through the corresponding thioimidates. The reduction of methyl pyroglutamate with sodium borohydride affords the acetate **286** after acylation of the



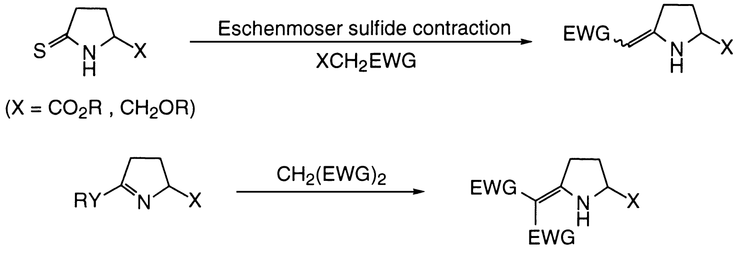
Scheme 104.

hydroxymethyl group. This compound is transformed into the thioimidate **287**,[27] which is alkylated with nonylmagnesium bromide to lead to the (*S*)-imino alcohol **288**. The reduction of this imine using sodium triacetoxyborohydride yields a mixture of *trans*:*cis*-hydroxymethylpyrrolidines in 70:30 ratio, which could be chromatographically separated after *N*-Cbz protection. The corresponding *trans*-isomer **289** is transformed into the pyrrolidine **290**, which is a component of *Monomorium minutum* ant venom[159] (Scheme 105).



Scheme 105.

Another group of alkylation reactions are condensations of: (a) thiopyroglutamates or thiopyroglutaminols with, e.g. α-bromoesters via the Eschenmoser sulfide contraction;[160] and (b) lactim ether or thioether derivatives with active methylene compounds (Scheme 106). In both cases β-enaminoesters of pyroglutamates or pyroglutaminols are obtained.

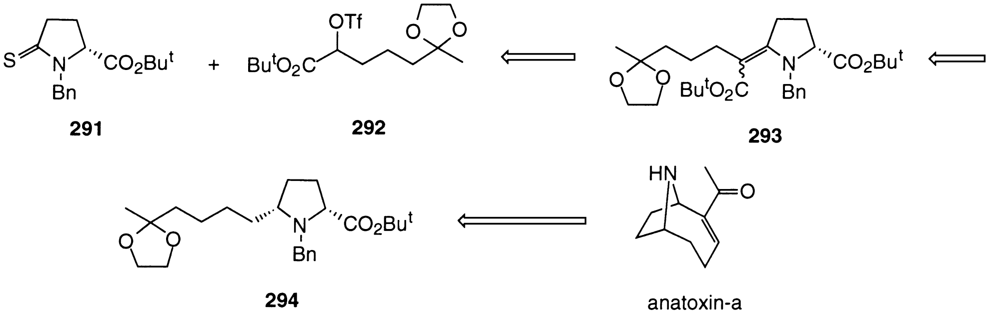


Scheme 106.

The first condensation reaction has been previously used by Fujimoto and Kishi[9] in the synthesis of gephyrotoxin as well as by Rapoport et al. in the case of (−)-anatoxin-a[8a] and 5-butyl-2-

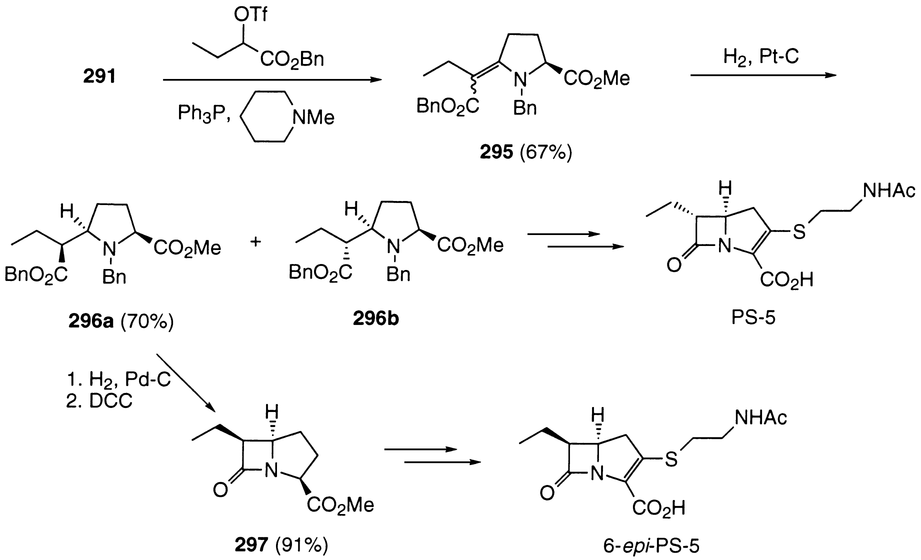
heptylpyrrolidines.[8b] The starting thiolactams can be prepared by reaction of the corresponding lactams with Lawesson reagent in 1,2-dimethoxyethane at room temperature.[161]

Improvements in the synthesis of (+)-anatoxin-a and modified analogues as probes as nicotinic agents have been carried out by Rapoport et al.,[162,163] their basic strategy being summarised in Scheme 107. The thiolactam **291** is alkylated with the triflate **292** followed by sulfur extrusion to give the vinylogous amide **293**. Hydrogenolysis of compound **293** affords the *cis*-disubstituted pyrrolidine **294**, which is submitted to a decarboxylative cyclisation through the corresponding iminium ion giving finally the bicyclic anatoxin-a.



Scheme 107.

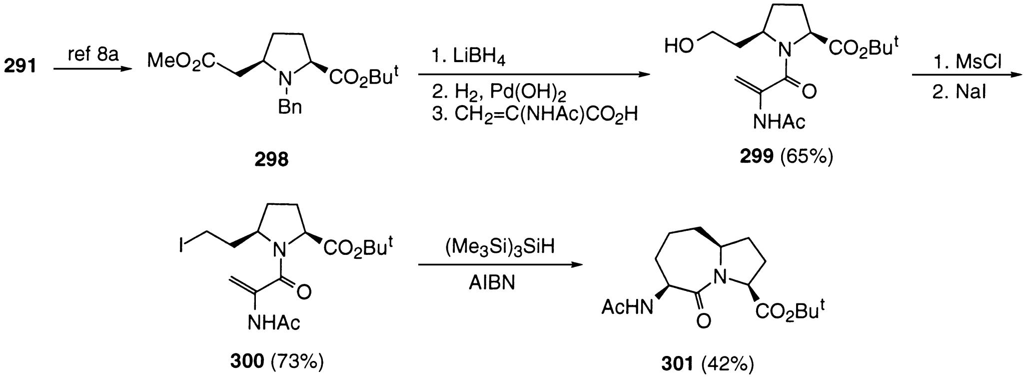
The synthesis of the carbapenem antibiotics 6-*epi*-PS-5 and PS-5 starts with the thiolactam **291**, which after reaction with the triflate derived from α-hydroxybutyric benzyl ester gives the vinylogous compound **295** as a 4.5:1 diastereomeric mixture. Hydrogenation without debenzylation followed by chromatographic separation affords the desired (5*R*,6*S*)-isomer **296a**, which is debenzylated and cyclised with DCC to the corresponding bicycle **297**, precursor of 6-*epi*-PS-5. The minor isomer **296b** has also been converted into PS-5[164] (Scheme 108).



Scheme 108.

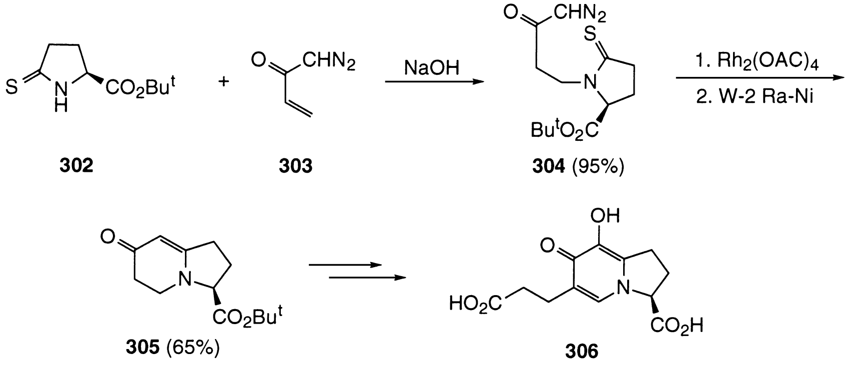
The pyrrolidine **298**, prepared from the thiolactam **291** by an Eschenmoser reaction,[8a] has been used as starting material for the preparation of the hydroxy compound **299**. After conversion of this compound into the iodide **300**, it is submitted to a radical cyclisation with tris(trimethylsilyl)silane giving, through a

7-*endo-trig* process, the fused bicyclic lactam **301** in >95% d.e.[165a] (Scheme 109). This type of 7,5- and 6,5-fused lactams are peptidomimetics as potential serino protease inhibitors.[166] The 5,6-fused derivatives have been prepared by means of a phenylselenyl derivative also by a radical cyclisation.[165b]



Scheme 109.

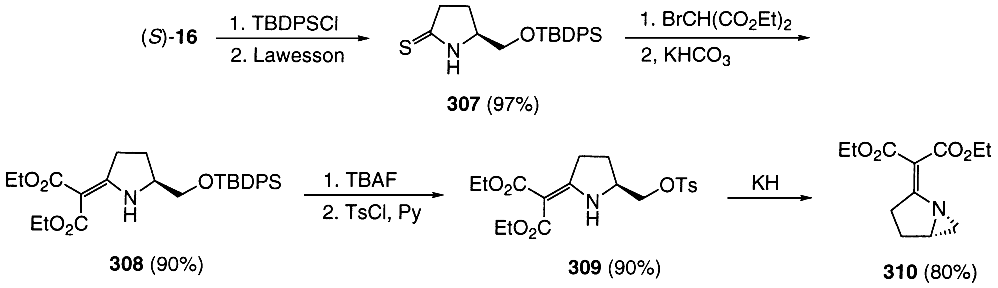
The olefination of the thiolactam **302** by a diazo–thioamide coupling reaction has been used by Danishefsky et al. for the synthesis of the angiotensin converting enzyme (ACE) inhibitor A58365A **306**. Diazoketone **303** is coupled with thiopyroglutamate **302** at room temperature in the presence of a catalytic amount of solid sodium hydroxide to afford the Michael adduct **304**, which cyclises in the presence of rhodium(II) acetate. Subsequent treatment with W-2 Raney nickel provides the indolizidine **305**, which is further transformed into the mentioned compound **306**[167] (Scheme 110).



Scheme 110.

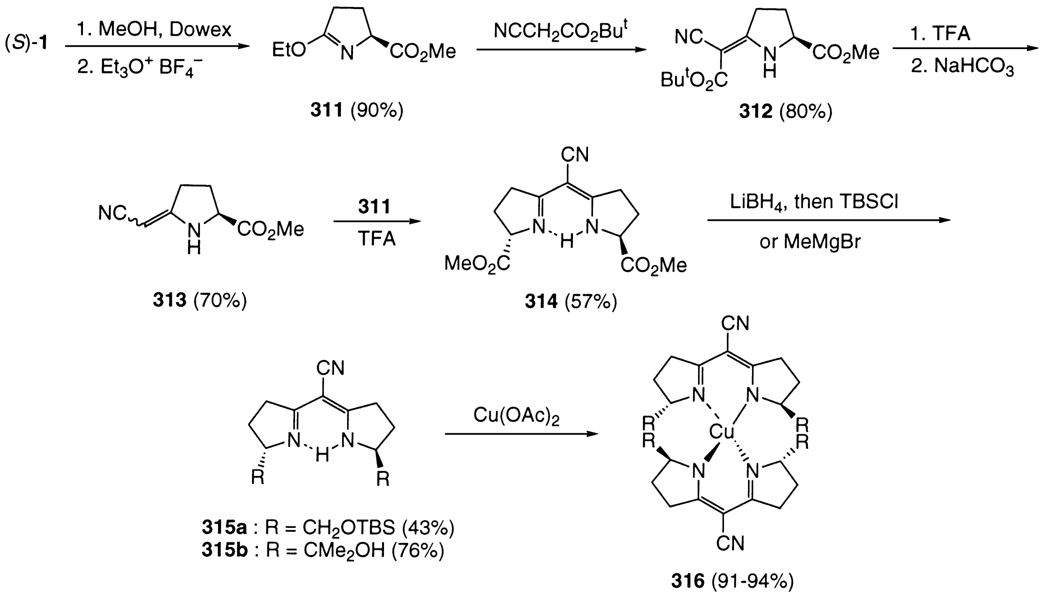
The bicyclic compound **310** and its enantiomer, related to the tumour antibiotic carzinophilin A, have been prepared starting from (*S*)- and (*R*)-pyroglutaminol **16**, which are transformed into thiolactams. The (*S*)-derivative **307** reacts with diethyl bromomalonate and then with aqueous potassium bicarbonate to afford the alkylidenepyrrolidine **308**, which is converted into the corresponding tosylate **309**. Intramolecular cyclisation of compound **309** by treatment with potassium hydride provides the aziridine ring of **310** (Scheme 111). This aziridine shows very weak in vitro cytotoxicity in assays against P388 murine leukemia.[168]

The use of lactim ether derivatives for the preparation of β-enaminoesters by reaction with active methylene compounds was also studied by Pfaltz et al.[169] (see Scheme 106). The iminoether **311**, prepared from pyroglutamic acid **1** has been used by Pfaltz et al. for the synthesis of semicorrin metal complexes, which are useful catalysts for the cyclopropanation of olefins, in conjugate reduction of α,β-unsaturated esters and amides and for allylic nucleophilic substitutions.[170] Compound **311** is heated



Scheme 111.

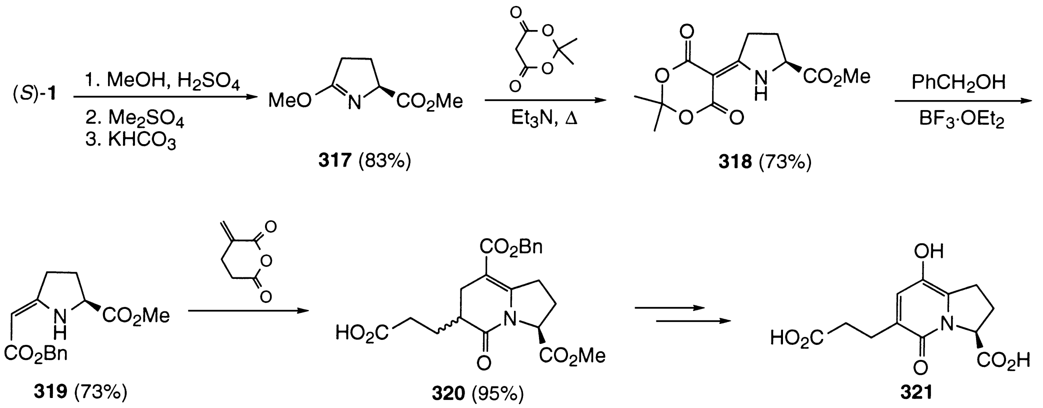
with *tert*-butyl cyanoacetate to give compound **312**, which is transformed after decarboxylation into cyanoenamines **313** as a mixture of diastereomers. Condensation of compounds **313** with the iminoether **311** in the presence of trifluoroacetic acid gives the diester **314** and further reduction or addition of methylmagnesium bromide to the ester groups affords compound **315a** or **315b**, respectively, which after final treatment with copper(II) acetate yield the complexes **316**[171] (Scheme 112).



Scheme 112.

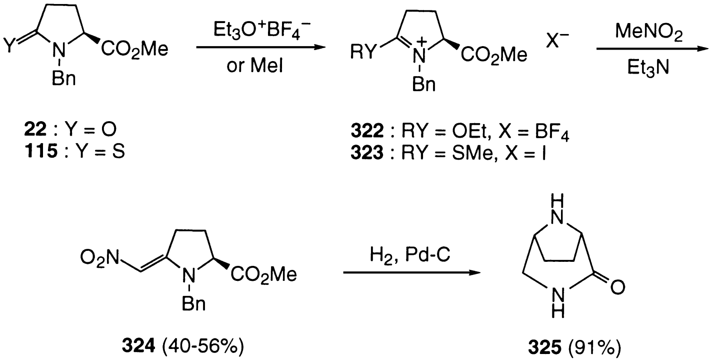
The iminoether **317** has been prepared by reaction of (*S*)-pyroglutamic acid methyl ester with dimethyl sulfate and then with potassium bicarbonate. It reacts with Meldrum's acid to yield the ester **318**, which is stereoselectively transformed into the *Z*-enamine **319** by reaction with benzyl alcohol in the presence of boron trifluoride etherate. The synthesis of compound (±)-**319** was previously carried out in racemic form by Nagasaka et al.[172] for the synthesis of 3,5-*trans*-3-methoxycarbonyl-1-carbapenam. Compound **319** is annulated with α-methyleneglutaric anhydride to form the hexahydroindolizidine **320**, which is transformed into the indolizidine A58365A (**321**), an inhibitor of angiotensin-converting enzyme (ACE) for the treatment of hypertension[173] (Scheme 113). Fang et al. have used the diazo–thiamide coupling reaction[167] for the synthesis of the related compound A58365A (**306**) (see Scheme 110).

Fasseur et al. have studied the condensation reactions of racemic iminoethers of pyroglutamates with different active methylene reagents, usually 1,3-dicarbonyl compounds or related systems.[174] The condensation with nitromethane can be carried out with more activated alkoxyiminium or thioalkyliminium



Scheme 113.

salts. The *N*-benzylpyroglutamate **22** or thiopyroglutamate **115** are transformed into compounds **322** or **323**, respectively, by reaction with Meerwein's salt or methyl iodide. The reaction of these compounds **322** and **323** with nitromethane in the presence of triethylamine yields the nitroenamine **324**. Catalytic hydrogenation of compound **324** at 45 psi gives stereoselectively and directly the bicyclic piperazinone **325** as a single product[175] (Scheme 114).

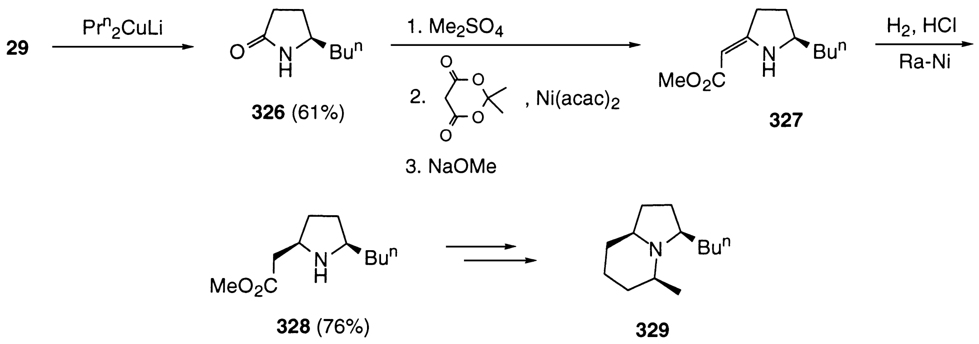


Scheme 114.

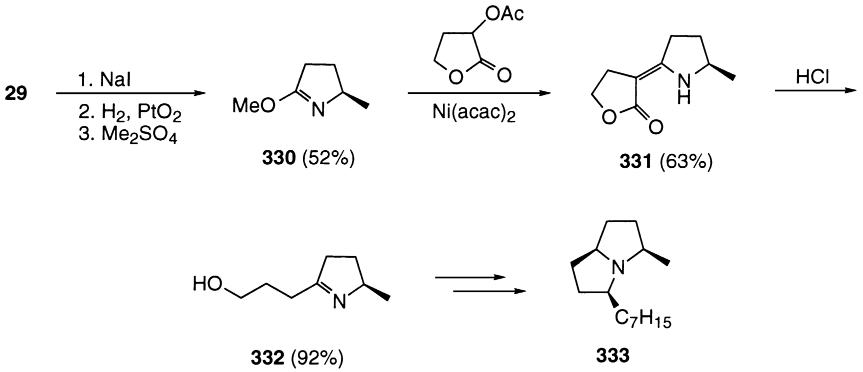
In the case of iminoethers derived from pyroglutaminol, the condensation with active methylene reagents is carried out in the presence of nickel(II) acetylacetonate, which is a better catalyst than triethylamine.[176] This methodology has been used by Célérier et al. in the synthesis of optically active 2,5-disubstituted pyrrolidines and indolizidine or pyrrolizidine derivatives. The lactam **326**, obtained from the (*R*)-pyroglutaminol tosylate **29** (see Scheme 12) has been transformed into its iminoether, which is coupled with Meldrum's acid to give the enamine **327**. Hydrogenation over Raney nickel gives a 96:4 mixture of *cis*:*trans*-pyrrolidines **328**, which is further converted into (+)-monomorine I (**329**)[26] (Scheme 115). A similar strategy has been employed for the synthesis of *cis*/*trans*-(2*S*,5*R*)-(5-hexenyl)-5-nonylpyrrolidine, the *trans*-isomer being a component of *Monomorium minutum* ant venom[159] (see Scheme 105).

The iminoether **330**, derived from the tosylate **29**, has been coupled with 2-acetylbutyrolactone in the presence of nickel acetylacetonate to give stereoselectively the product **331**. Hydrolysis of this compound takes place with decarboxylation providing an iminoalcohol **332**, which is finally transformed into the pyrrolizidine **333**, a bicyclic alkaloidic component of *Solenopsis* ant venom[24] (Scheme 116).

In the synthesis of the carzinophilin unit **338** from (*R*)- and (*S*)-pyroglutaminol carried out by

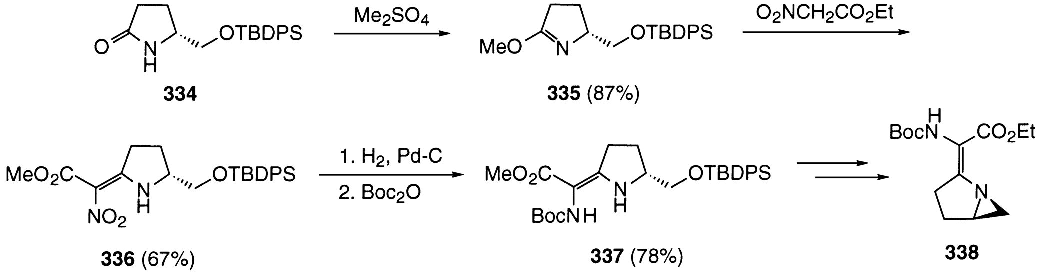


Scheme 115.



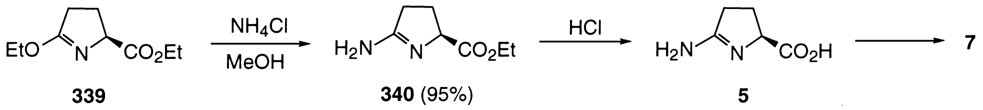
Scheme 116.

Hashimoto et al., a condensation between the iminoether **335**, prepared from the corresponding material **334**, and ethyl nitroacetate is used affording the expected product **336**, which is hydrogenated and protected to give the amino ester **337**, a precursor of compound **338**[177] (Scheme 117).

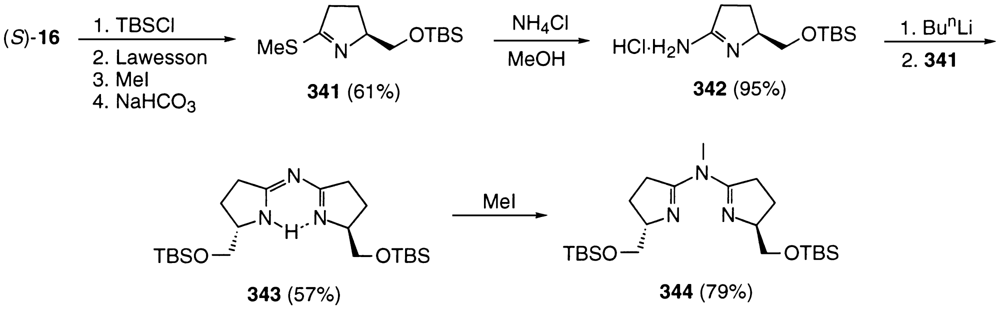


Scheme 117.

Iminoethers derived from pyroglutamates can react with ammonium chloride to give the corresponding amidines. This transformation has been carried out for the synthesis of (+)- and (−)-dihydrokikumycin B.[7] Thus, compound **339** gives the amidine **340** and, after hydrolysis, affords the acid **5** in 80% e.e. (Scheme 118), which is amidated yielding compound (+)-**7** (see Scheme 3)[17a] and also (+)-anthelvencin A.[17b] Leutenegger et al. have used a similar reaction with the iminothioether **341**, derived from pyroglutaminol, in the synthesis of 5-aza-semicorrins.[178] Thus, the reaction of compound **341**, prepared from the corresponding material (*S*)-**16**, with ammonium chloride in methanol gives the amidine hydrochloride **342**, which is deprotonated and coupled again with the iminothioether **341** finally affording the product **344**, after methylation of the intermediate **343** (Scheme 119).



Scheme 118.

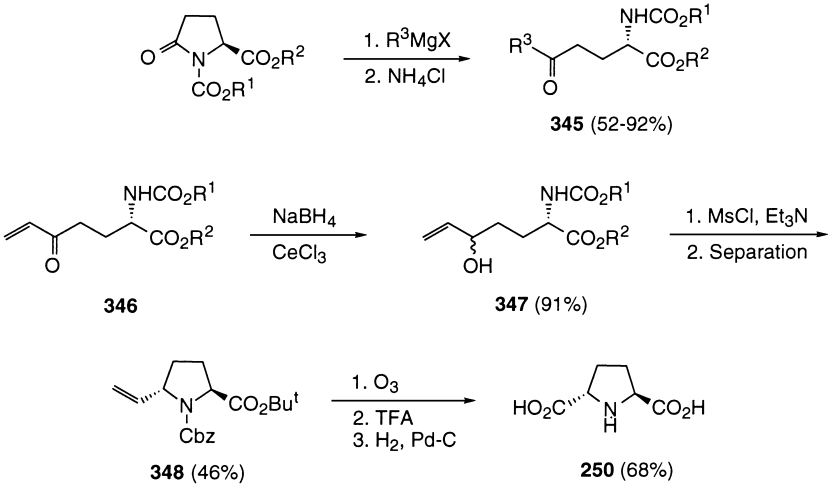


Scheme 119.

4. Ring opening reactions

In this review we have seen that the hydrolysis of pyroglutamate derivatives has been widely used for the preparation of glutamic acid derivatives. This conversion into acyclic series without loss of stereochemical integrity consists of the treatment of *N*-acylated or *N*-urethane pyroglutamates, usually with 1 N aqueous lithium hydroxide in THF.[84a]

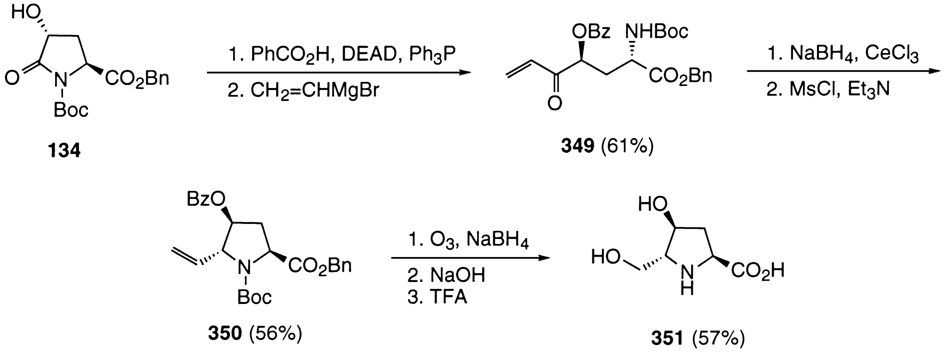
The ring opening of *N*-protected pyroglutamates can be carried out easily with different carbo- or hetero-nucleophiles. Ohta et al. described for the first time the carbon chain elongation reaction at the C-5 of L-glutamic acid by reaction of *N*-urethane pyroglutamates with Grignard reagents to give the corresponding ketones **345**[179] (Scheme 120). This reaction is applied to the synthesis of the natural product (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid **250** by means of the enone **346**, obtained in 55% yield by addition of vinylmagnesium bromide to compound **120**. Chemoselective reduction of this enone to the corresponding alcohol **347** followed by mesylation affords the prolinate **348**. The major diastereomer is separated and oxidised by ozonolysis giving, after final deprotection, the expected acid **250**.



Scheme 120.

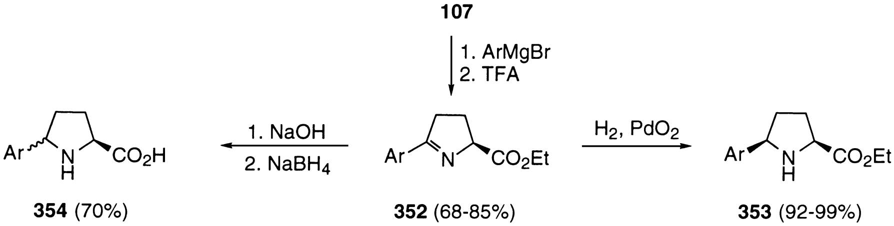
The same strategy has been used in the synthesis of (−)-bulgecinine **351**.[108] Thus, the (4*R*)-4-

hydroxypyroglutamate **134** (see Scheme 55, Section 3.1.4) is converted by a Mitsunobu reaction into its benzoate, which is opened by addition of vinylmagnesium bromide to give the enone **349**. This enone is stereoselectively transformed into the prolinate **350** and finally oxidised and deprotected to give (−)-bulgecinine **351** (Scheme 121).



Scheme 121.

When arylmagnesium bromides are used as nucleophiles, Δ^1-pyrroline derivatives **352** are obtained after treatment of the corresponding phenones with trifluoroacetic acid.[180] These compounds can be transformed either into *cis*-5-arylprolinates **353** by hydrogenation or into a mixture of *cis*/*trans*-prolines **354** by reduction with sodium borohydride[181] (Scheme 122).



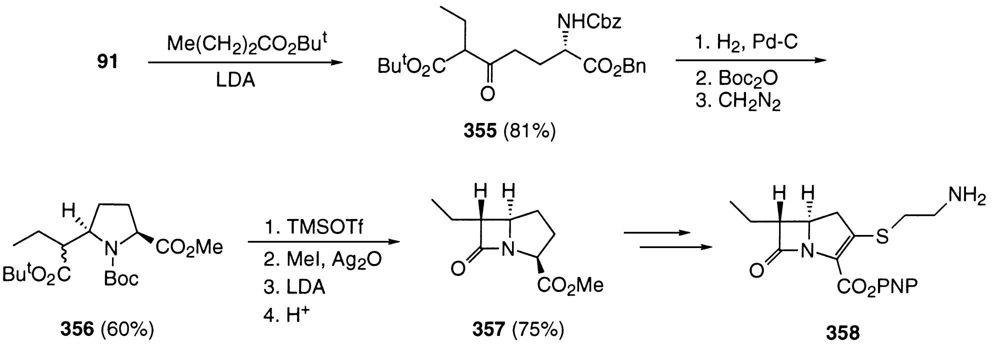
Scheme 122.

Mercaptoacyl dipeptides containing a glycine linked to 5-arylprolines are inhibitors of neutral endopeptidase and angiotensin-converting enzyme (ACE) with a long duration of action.[181]

Lithium diphenylcyanocuprate[27a] and phenyllithium[182] are also adequate nucleophiles for the ring opening of *N*-Boc-pyroglutamates, so making possible the transformation of the resulting ketones into *cis*-5-phenylprolines.[182]

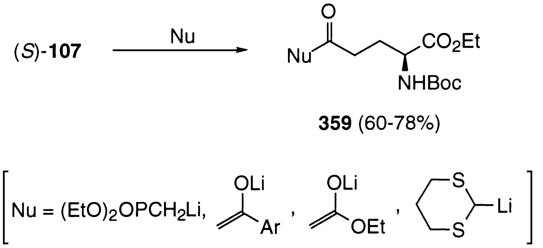
Stabilised carbanions, such as enolates, are efficiently added to *N*-carbamoylpyroglutamates affording 5-oxoaminoester derivatives with preservation of the configuration at C-2.[183] This reaction has been applied as the key step to the synthesis of carbapenam **357** (epimer of compound **297**; see Scheme 108, Section 3.4.2), from which (+)-PS-5 *p*-nitrobenzyl ester **358** has been prepared.[184] Compound **355**, obtained by reaction of pyroglutamate **91** with the enolate of *tert*-butyl butanoate, is stereoselectively hydrogenated affording the 2,5-*cis*-5-substituted proline **356**. The deprotection of the *tert*-butyl ester with trimethylsilyl triflate and cyclisation gives the carbapenam **357**, after diastereoselective enolisation–protonation at C-6 in 85% d.e. (Scheme 123).

Ketone enolates and other stabilised carbanions derived from 1,3-dithiane and diethyl methanephosphonate have also been used as carbon nucleophiles in the ring opening of ethyl L- and D-*N*-Boc-pyroglutamate (**107**).[185a] The reaction takes place in THF at low temperatures and the e.e.s are >95% in all cases. Compounds **359**, derived from ketones, are obtained mainly as enals (Scheme 124). Lithium



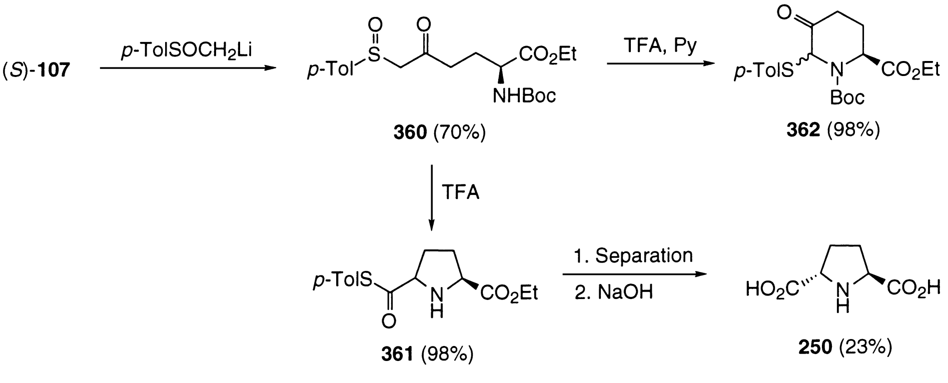
Scheme 123.

trimethylsilyldiazomethane gives good yields of the corresponding substituted 6-diazo-5-oxonorleucine esters.[186]



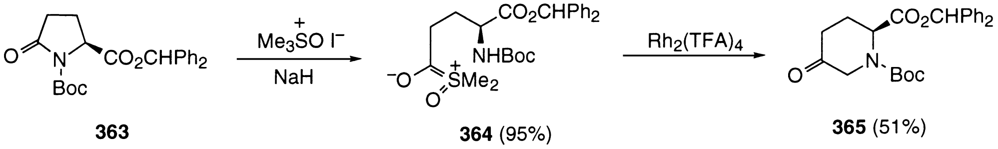
Scheme 124.

Lithiomethyl *p*-tolyl sulfoxide also gives the product **360**. This product is transformed into a 7:3 mixture of *trans*:*cis*-prolinates **361**, which can be separated and hydrolysed to give *cis*- and *trans*-2,5-dicarboxylic acids **250**.[147] When compound **360** is submitted to Pummerer reaction conditions, the 5-oxopipecolic acid derivative **362** is obtained[185b] (Scheme 125). Similar results have been observed in the reaction of the pyroglutamate **363** with Corey's ylide. In this case, when the ylide **364** is treated with rhodium(II) trifluoroacetate it undergoes intramolecular N–H insertion to form the protected 5-oxopipecolic acid **365**[187] (Scheme 126).



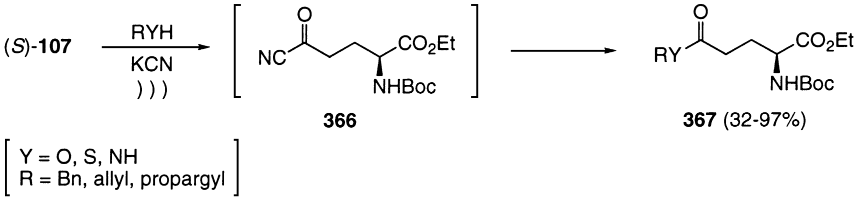
Scheme 125.

Concerning the use of heteronucleophiles for the cleavage of the lactam, alcoholysis is a good strategy for the preparation of disymmetrical diesters of *N*-urethane-protected glutamic acid in order to achieve differentiation between the carboxylic groups.[188] Schoenfelder and Mann have reported the reaction of different *N*-carbamoylpyroglutamates with alcohols in the presence of potassium cyanide as catalyst.



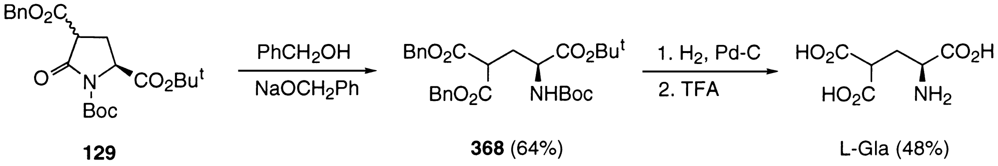
Scheme 126.

However, no mention is made regarding the enantiomeric excess of the corresponding diesters.[189] Molina et al.[190] have studied the heteronucleophilic ring opening of L- and D-*N*-Boc-pyroglutamates **107** catalysed by potassium cyanide under ultrasonic irradiation in order to shorten reaction times. The reaction proceeds by nucleophilic attack of the cyanide anion followed by displacement of the cyanide by the nucleophile in the highly reactive acyl cyanide intermediate **366**, delivering acyclic products **367** (Scheme 127). Alternatively, the reaction can be carried out over shorter time periods using sodium alkoxides.



Scheme 127.

Attwood et al. have used benzyl alcohol containing traces of sodium benzoxide in the preparation of compound L-Gla[107] (see Scheme 53, Section 3.1.4) from compound **129** (Scheme 128).

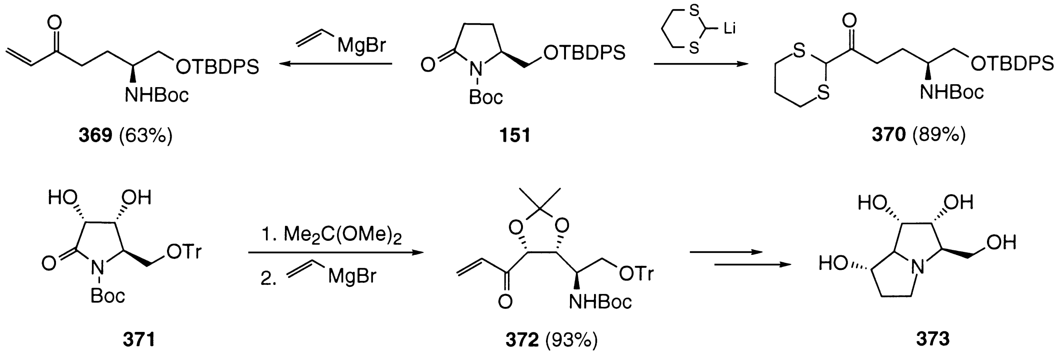


Scheme 128.

Methyl *N*-methoxycarbonylpyroglutamate has been opened in methanol containing *p*-toluenesulfonic acid at room temperature to yield the corresponding methyl glutamate in 65% yield.[191]

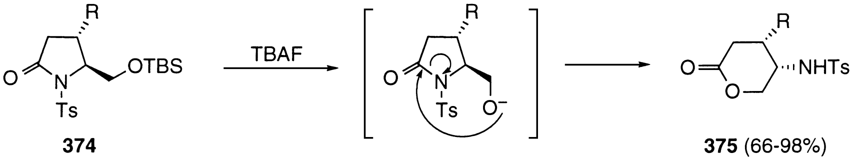
In the condensation reaction of the aldehyde **93**[83] with different nitrogen-containing nucleophiles, such as hydrazines or hydroxylamine, an intramolecular ring opening of the lactam ring has also been observed giving products **94** (see Scheme 39, Section 3.1.4). In the case of the enol ether **99**, derived from compound **93**, the reaction with amidines or guanidines also affords the heterocyclic systems **100** or **101**, resulting from the intramolecular ring opening of the pyroglutamate system[85] (see Scheme 41, Section 3.1.4).

N-Urethane-protected pyroglutaminol derivatives can be hydrolysed by means of 1 M sodium hydroxide in methanol,[62a] lithium hydroxide in THF,[112] or aqueous lithium hydroperoxide in THF,[192] to yield the corresponding γ-amino acids. The lactam functionality in compound **151** can be cleaved by Grignard reagents (e.g. vinylmagnesium bromide) or the anion derived from 1,3-dithiane giving the corresponding ketones **369** and **370**[65] (Scheme 129). The 3,4-dihydroxylated pyroglutaminol **371**[124] (see Scheme 70, Section 3.2), after protection as acetonide, is treated with vinylmagnesium bromide providing the ketone **372**, which has been finally transformed into the polyhydroxylated pyrrolizidine alkaloid 1,7-di-*epi*-alexine **373**[124] (Scheme 129).



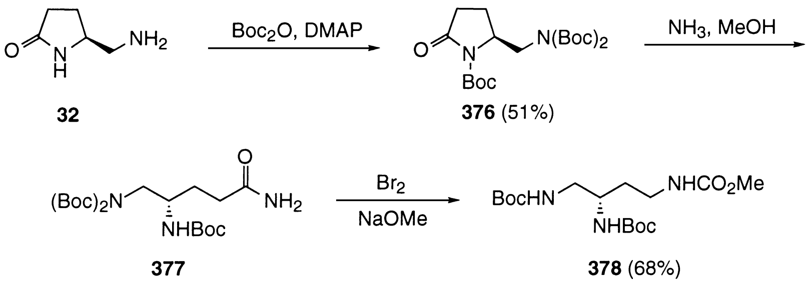
Scheme 129.

Substituted *N*-Boc-aminopyranones of the type **375**, precursors of acyclic analogues of kainoids,[62] have been prepared in a one-step process by intramolecular alcoholate attack to the lactam moiety in *N*-tosylpyroglutaminols.[62] When compounds **374** are desilylated with tetra-*n*-butylammonium fluoride, compounds **375** are obtained in good to excellent yields[193] (Scheme 130).



Scheme 130.

In the synthesis of chiral 1,2,4-triaminobutanes from pyroglutaminol, its aminoderivative **32** (see Scheme 13, Section 2) is transformed, after *N*-Boc-protection, into the compound **376**. This lactam can be opened by ammonia in methanol to lead to the formation of the amide **377**, which after Hofmann rearrangement affords the protected 1,2,4-triaminobutane **378**[30] (Scheme 131).

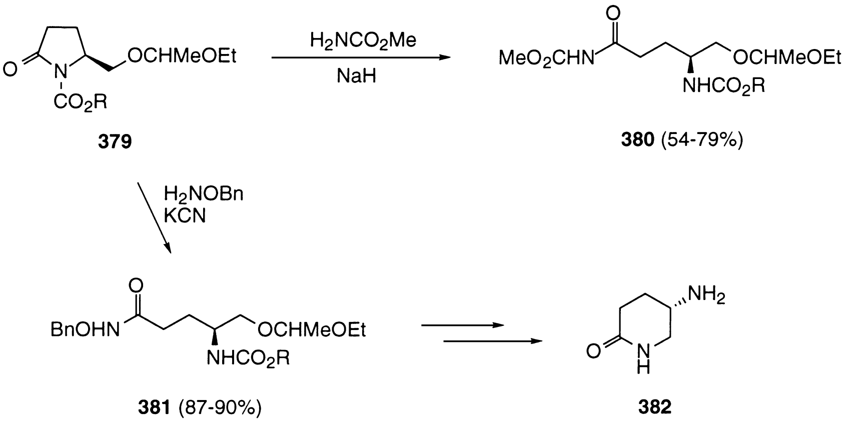


Scheme 131.

Methyl carbamate and *O*-benzylhydroxylamine can open pyroglutaminol derivatives **379** to afford products **380** and **381**, respectively[194] (Scheme 132). The last compound **381** (R=Bu^t) has been used for the synthesis of (*S*)-5-aminopiperidin-2-one **382**, a component of bacterial quinolones and a ligand of antitumour *cis*-platinum complexes.[194]

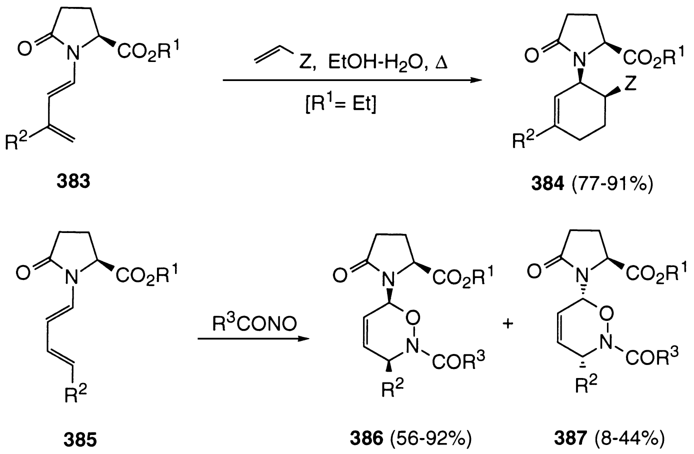
5. Uses as chiral auxiliaries

There are not many examples for the use of pyroglutamate derivatives as chiral auxiliaries. Ethyl *N*-dienylpyroglutamates **383** have been used as chiral dienes in Diels–Alder reactions.[195] These dienes



Scheme 132.

are prepared by reaction of ethyl pyroglutamate **40** with α,β-unsaturated aldehydes.[196] Compounds **383** show excellent diastereoselectivity in the Diels–Alder reaction with electron deficient alkenes and in good *endo* and *ortho* selectivities. The corresponding *cis*-adducts **384** are isolated in 91–97% d.e. (Scheme 133).

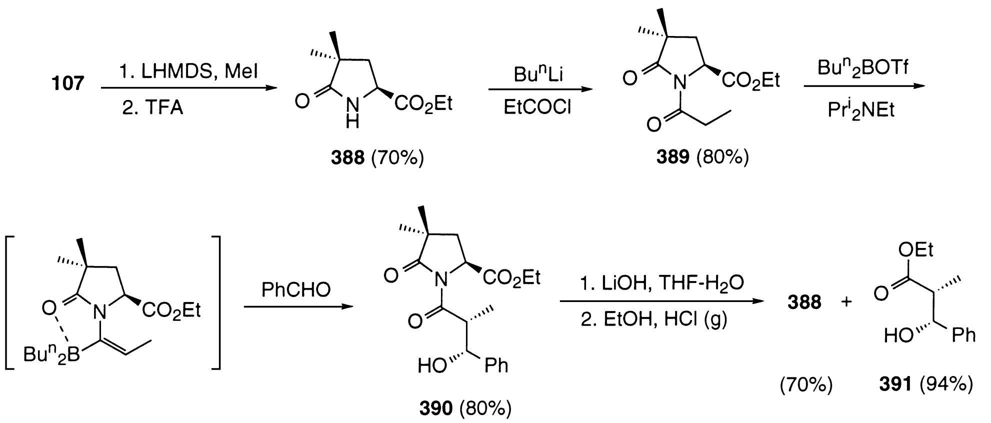


Scheme 133.

The reaction of dienes **385** with nitrosodienophiles, generated in situ, takes place in a regioselective manner leading to cycloadducts **386** and **387**.[197] These products can be separated in most cases, the major diastereomer being compound **386**, resulting from the approach of the dienophile *anti* with respect to the ester moiety of the chiral pyroglutamate auxiliary. The *s-trans* configuration between the amide and the butadiene moieties is postulated in the transition state, so that π-orbital interactions are optimal (Scheme 133).

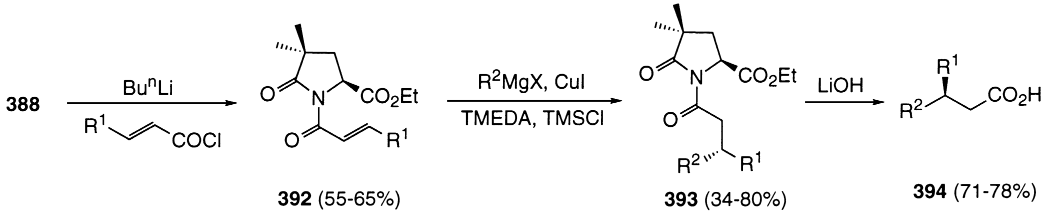
Ethyl (*S*)-4,4-dimethylpyroglutamate **388**,[198] prepared by dimethylation of ethyl *N*-Boc pyroglutamate **107** enolate[96] (see Scheme 45, Section 3.1.4), has been used as 'quat' chiral auxiliaries in aldol condensations[198] and in Michael addition reactions.[199] Compound **388** is acylated with propanoyl chloride to give the imide **389**, which is allowed to react with benzaldehyde by means of its (*Z*)-boron enolate forming the *syn* product **390** in >98% d.e. (Scheme 134). After hydrolysis, the ester **391** is obtained, the chiral auxiliary **388** then being recovered.

In the Michael addition of cuprates to crotonoyl or cinnamoyl derivatives **392**, products **393** are



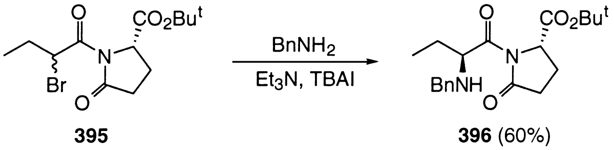
Scheme 134.

obtained in >95% d.e. when TMEDA and trimethylchlorosilane are used as additives[199] (Scheme 135). Hydrolysis of Michael adducts **393** gives β-branched carboxylic acids **394** and the chiral auxiliary after esterification with ethanol–hydrogen chloride.



Scheme 135.

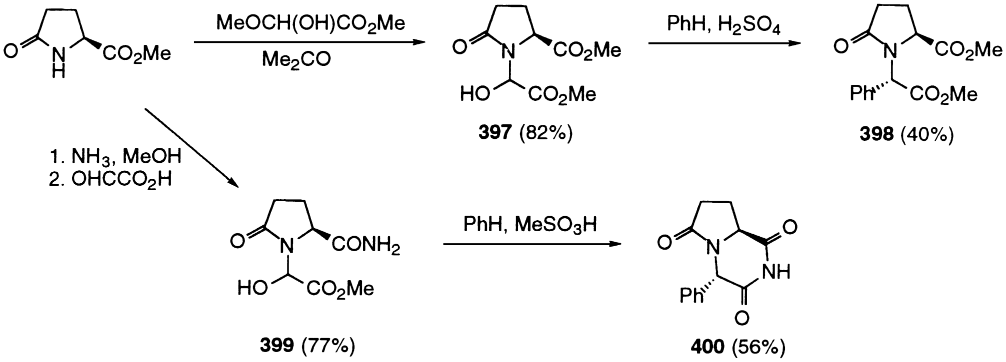
tert-Butyl pyroglutamate has been used in the dynamic kinetic resolution of racemic α-bromobutanoyl derivative **395** by nucleophilic displacement with benzylamine in the presence of triethylamine and tetrabutylammonium iodide to give compound **396** in 94% d.e. but in moderate yield due to a competing acyl transfer process (40%)[200] (Scheme 136).



Scheme 136.

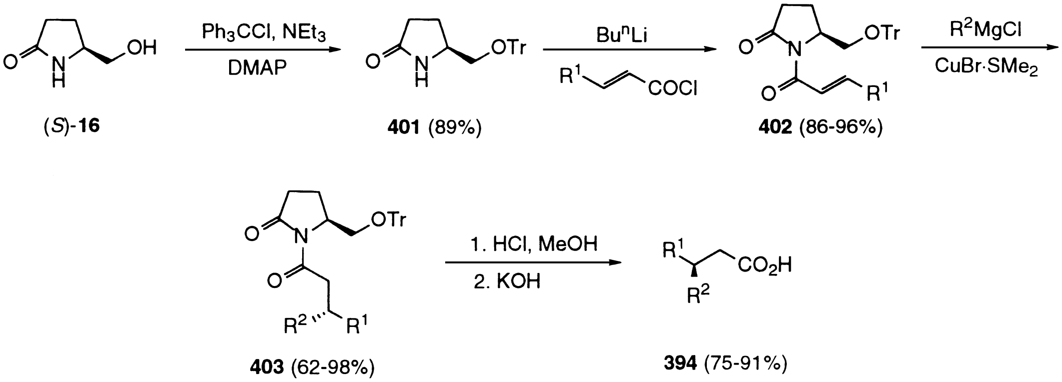
Glyoxylic acid γ-lactam adducts of pyroglutamate have been used in intermolecular electrophilic substitution reactions giving nitrogen substituted phenylglycine derivatives.[201] Methyl (*S*)-pyroglutamate reacts with methyl methoxyglyoxalate in boiling acetone leading to the ester adduct **397**, which after reaction with benzene in sulfuric acid affords, through the corresponding *N*-iminium cation, the product **398** in 93.4% d.e. (Scheme 137). When this reaction is carried out with the amide adduct **399**, piperazine diones **400** are obtained, these systems being part of brevianamides.

The *O*-trityl pyroglutaminol derivative **401** has been used as a chiral auxiliary in Michael addition and Diels–Alder cycloaddition reactions. It can be prepared by tritylation of (*S*)-pyroglutaminol **16** in 89% yield.[202] The α,β-unsaturated imides **402** react with organocuprates affording adducts **403** in 81–95% d.e., which are converted into the corresponding acids **394** in very good yields with recovery of the auxiliary **401**[202] (Scheme 138). The *syn* conformation in compounds **402**, predominant in the presence



Scheme 137.

of magnesium, has been studied by NMR as well as by theoretical calculations.[203] This conformation predicts the observed diastereoselectivity. Thiophenol in the presence of lithium thiophenolate and magnesium perchlorate adds to imides **402** in good yields (64–91%) and stereoselectivity[204] (70–98% d.e.).

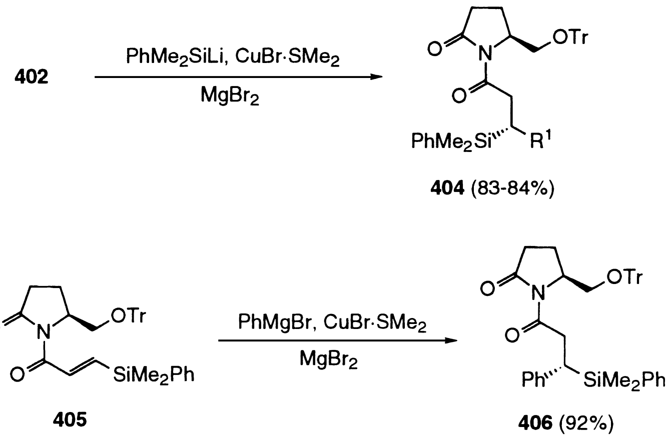


Scheme 138.

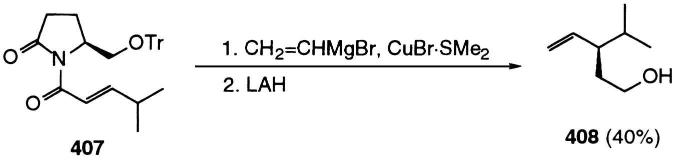
Fleming and Kindon have studied the preparation of β-silyl esters by two routes. Starting from imides **402** by addition of phenyldimethylsilylcuprate in the presence of magnesium bromide, the corresponding adducts **404** are obtained in 78% d.e. If alkyl or phenylmagnesium bromide and the copper(I) bromide–dimethyl sulfide complex are used as the nucleophilic mixture, the addition to the β-silyl imide **405** leads to product **406** with the opposite configuration at the newly created stereocentre (compared to products **404**) and 92% d.e.[205] (Scheme 139).

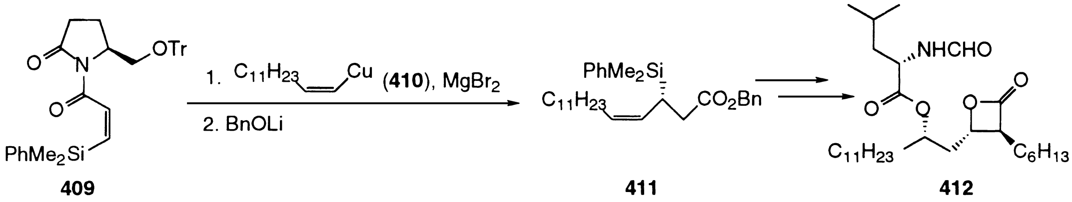
This methodology has been used in the synthesis of the chiral bis-homoallylic alcohol **408** from the imide **407**. The corresponding conjugate addition product is obtained with >95% diastereoselection[206] (Scheme 140). The β-silyl substituted imide **409** reacts with the vinyl cuprate **410** in the presence of magnesium bromide to give the corresponding Michael adduct in 90% e.e. This product is transformed into the ester **411**, a precursor of the esterase inhibitor tetrahydrolipstatin **412**[207] (Scheme 140).

The imides **413**, prepared from the chiral auxiliary **401**, are good dienophiles in asymmetric Diels–Alder reactions giving, for instance with cyclopentadiene, the adduct **414**, in general with good *endo*-approach (>99%) and very high diastereoselection (up to 99%), in the presence of Lewis acids. Final reaction of compound **414** with lithium benzylate gives the bicyclic ester **415** and the auxiliary **401**[208] (Scheme 141).

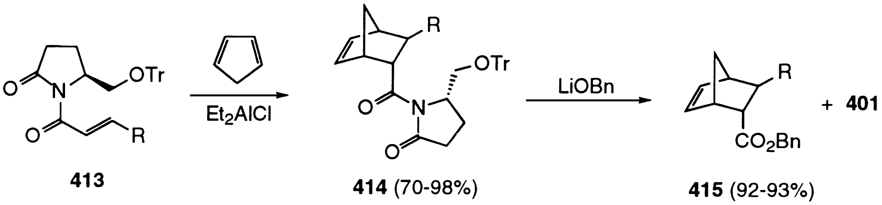


Scheme 139.



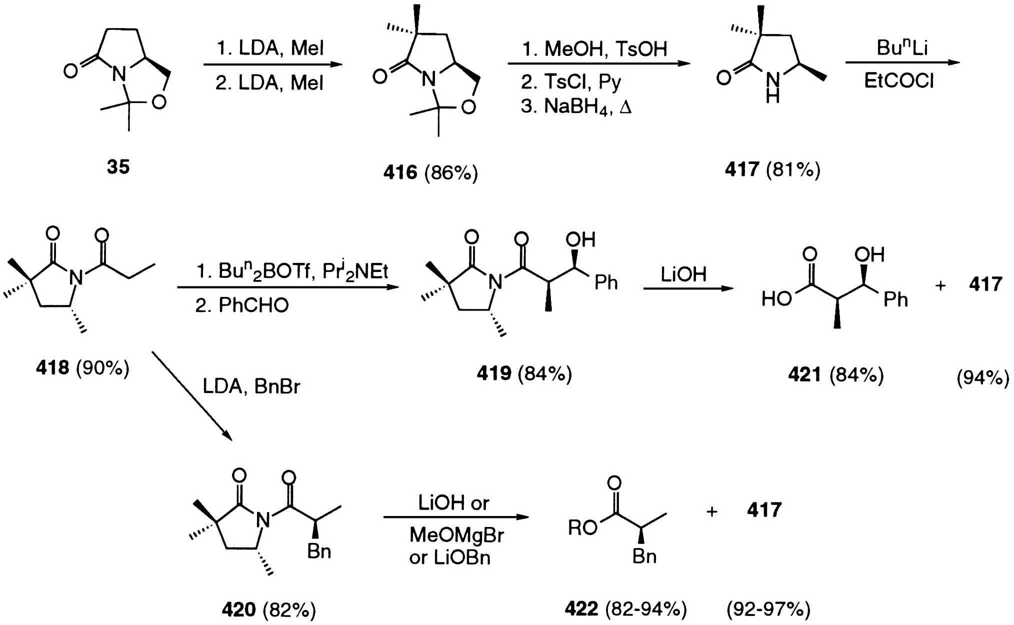


Scheme 140.



Scheme 141.

(*R*)-3,3,5-Trimethyl-2-pyrrolidine **417**,[209] a 'quat' auxiliary, has been developed by Davies et al. and used in asymmetric aldol and alkylation reactions.[210] This reagent is prepared from L-pyroglutaminol by dialkylation of compound **35**[33] (see Scheme 14, Section 2) to yield product **416**. This dimethylated product is hydrolysed to an alcohol, which is reduced through its tosylate by means of sodium borohydride in DMSO[209] (Scheme 142). Other 'quat' derivatives have been prepared from compound **416**, with compound **417** being the best chiral auxiliary because it can be acylated and hydrolysed with excellent results. Aldol and alkylation reactions are studied with the propanoyl imide **418**.[210] A representative aldol reaction with benzaldehyde under Evans conditions gives the *syn*-aldol **419** in >97% d.e. The alkylation of **418** enolate with benzyl bromide affords the product **420** in 96% d.e. Final hydrolysis of compounds **419** and **420** allows the almost quantitative recovery of the chiral auxiliary **417** and the isolation of the 3-hydroxypropionic acid **421** and the alkylated ester or acid **422**, respectively, in good yields (Scheme 142). Alternatively, compound **420** can be treated with lithium aluminium hydride to furnish the corresponding alcohol (84% yield) and the 'quat' **417** quantitatively.



Scheme 142.

6. Conclusions

This review of the use of pyroglutamic acid and its derivatives in asymmetric synthesis has shown how extensive the applications of this simple but highly functionalised molecule are. The possibility of modification and functionalisation of the carboxylic group and the lactam ring allows the preparation of many types of chiral natural products as well as biologically active molecules. One of the most important applications of this molecule is the synthesis of glutamic and kainic acid derivatives, useful tools in neuroscience research due to their extremely potent excitatory activity in the vertebrate and invertebrate glutamatergic system. In the amino acids field, differently substituted prolines as well as γ-amino acid derivatives can be prepared. Chiral saturated heterocyclic compounds such as pyrrolidines, pyrrolizidines, indolizidines and fused lactams have also been prepared. Antitumourals, such as neothramycins and quinocarcin, carbapenems, PKC modulators, ACE and esterase inhibitors, and gastroprotective substances such as AI-77-B are representative examples prepared using pyroglutamic acid derivatives. Other interesting natural products such as dihydrokikumycin B, anthelvencin, heliotridane, several alexines, swainsonine derivatives, manzamine alkaloids, calyculins, bulgecinine and carzinophin A are representative examples synthesised by means of pyroglutamic acid. Chiral catalysts such as semicorrin metal complexes and 2,5-disubstituted pyrrolidines have been prepared from the same starting material. Derivatives of the mentioned acid have also been used as chiral auxiliaries in Diels–Alder reactions, alkylation or aldol reactions of chiral enolates, kinetic resolution of amino acids and Michael addition processes. It can be concluded that pyroglutamic acid occupies an important place as a member of the chiral pool in the field of asymmetric synthesis.

Acknowledgements

The authors acknowledge the Dirección General de Investigación Científica y Técnica (DGICYT) of the Spanish Ministerio de Educación y Cultura (MEC) and Lilly S.A. (Spain) for generous and continuous financial support.

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