SYNTHETIC APPROACHES TO HETEROCYCLIC α,α-DISUBSTITUTED AMINO ACIDS

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Abstract. *The incorporation of constrained quaternary amino acids into peptide sequences is one of the most common strategies to induce the folding of a peptide chain into therapeutically relevant secondary structure elements. Although acyclic and carbocyclic analogues have been widely studied, less attention has been paid to heterocyclic amino acids, especially concerning chiral derivatives and their stereoselective synthesis. Interestingly, the side-chain heteroatom in heterocyclic quaternary amino acids represents a useful handle for engineering additional functionalities into the peptides. This review intends to cover the reported synthetic approaches toward α,α-disubstituted heterocyclic amino acids, highlighting their interest in peptidomimetic chemistry and providing a perspective on where future opportunities may lie in this field.*

Contents

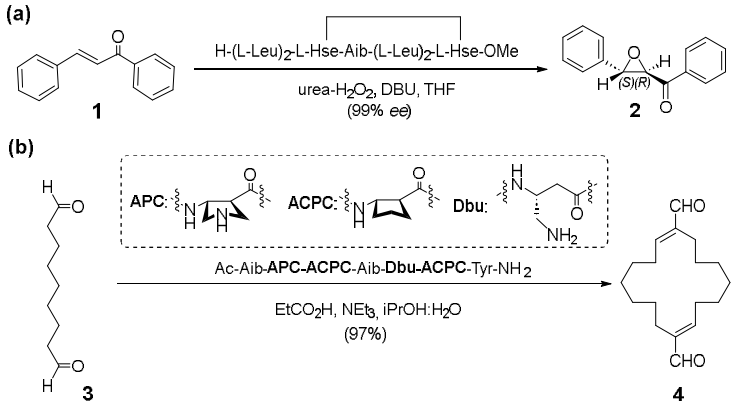
1. Introduction

Peptide secondary structure is a key element in the 3D structure of proteins, therefore essential in the regulation of protein function.[1] In fact, relatively short sequences with a defined secondary structure often contribute to the majority of the binding affinity in protein-protein interactions and protein recognition.[2,3] Regarding that the misregulation of these interactions is often implicated in disease states, there is a great interest in developing methods for the inhibition or stabilization of such protein-protein interactions.[4]

Among the most abundant secondary structure elements, α-helices and β-strands are the main structural features of proteins. Around a third of protein residues are present in α-helical segments and there is a multitude of examples of α-helix-mediated protein-protein and protein-nucleic acid interactions.[5,6] β-Strands are the second most abundance secondary structure, accounting for about 20% of amino acid secondary structure states.[7] 3_{10}-Helices, the third most abundant secondary structure, are considered key intermediates in protein folding, also crucial for the antimicrobial activity of naturally occurring peptaibols.[8]

One of the most promising approaches for modulating protein-protein interactions is the design of small-molecule mimetics or stabilizers of secondary structure elements, which tend to lose the bioactive conformation when they lack the stabilization mediated by favourable interaction with the protein environment.[5,9] The use of constrained quaternary amino acids represents a successful strategy to induce the folding of a peptide chain into secondary structure elements. C_α-tetrasubstitution imposes a significant restriction on the conformation space of a peptide chain by the Thorpe-Ingold effect, bringing the nearby atoms on both sides of the substituted carbon in close proximity.[10] Moreover, constrained peptides able to display a defined secondary structure have also found interesting applications beyond chemical biology and drug discovery. The great interest in efficient metal-free asymmetric reactions prompted the expansion of the field of peptide-based organocatalysis in the last decades. For example, a 3_{10}-helical stapled peptide was successfully used as a chiral catalyst in the enantioselective epoxidation of α,β-unsaturated ketone **1** to access diastereopure epoxide **2** (Scheme 1a).[11] Recently, a catalytic covalent template-directed aldol macrocyclization of linear dialdehyde **3** has been reported (Scheme 1b).[12] The catalytic template is a hybrid

α-/β-peptide foldamer displaying a helical conformation, critical for the formation of the key intermediate in the right conformation for favouring the macrocyclization reaction toward product **4**.



Scheme 1. a) 3_{10}-Helical peptide-based catalysis of asymmetric epoxidation of α,β-unsaturated ketones. b) Catalytic templated macrocyclization of a dialdehyde with a helical foldamer.

Achiral α-aminoisobutyric acid (Aib) is the simplest quaternary amino acid and the focus of extensive studies due to its ability to induce helical conformation in peptides (Figure 1a).[13] Aib homo-oligomers tend to stabilize 3_{10}-helices while inducing a variety of helical arrangements, including 3_{10}-, α- and distorted or mixed 3_{10}-/α-helices, when combined to non-quaternary proteinogenic amino acids (Figure 1b).[10,13]

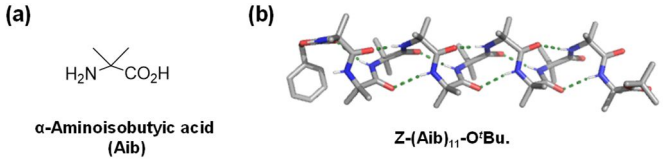


Figure 1. a) Structure of α-aminoisobutyric acid (Aib). b) X-ray structure of Z-$(Aib)_{11}$-O^{t}Bu, the longest Aib homo-oligomer reported at atomic resolution (CCDC 204587).

From the simplest Aib, more complex quaternary amino acids have been studied in the last decades. As illustrated in Figure 2, they can be classified in four categories regarding if they are achiral or chiral as well as if the side chain is linear or cyclic.[10] Figure 2 also includes other non-natural constrained amino acids able to induce peptide secondary structures when incorporated into peptides. β-Amino acids contain an extra carbon atom between the *N*- and *C*-terminal groups, so these residues are able to access the conformational space restricted to glycine residues.[14] They have been classified according to their substitution pattern and the nature of the substituents (acyclic and cyclic). Many foldamers with relevant applications are based on β-peptides and hybrid α-/β-peptides.[15,16] Peptoids are a different class of conformationally restricted amino acids, based on the placement of amino acid side chains in the nitrogen instead of the α-carbon, giving rise to rigid peptidomimetics.[17] The first generation of peptoids is based on an achiral polyglycine backbone while a polyalanine backbone has been also used to access chiral peptidomimetics able to modulate protein-protein interactions of therapeutic relevance.[18] Other peptidomimetic backbones able to induce well-defined secondary structures include γ-peptides, γ-AApeptides, oligoureas and aromatic oligoamides.[19]

In the context of organic synthesis, considerable attention has been paid to the development of efficient synthetic routes toward quaternary amino acids, due to their above-mentioned ability to stabilize peptide secondary elements of interest in chemical biology, catalysis and supramolecular chemistry.[20] Acyclic quaternary amino acids can be considered as Aib analogues showing a similar restriction of the

conformational space promoting helical conformations, with defined screw-sense for the chiral analogues.[10] The synthesis of acyclic quaternary amino acids has been covered in several reviews.[21-23]

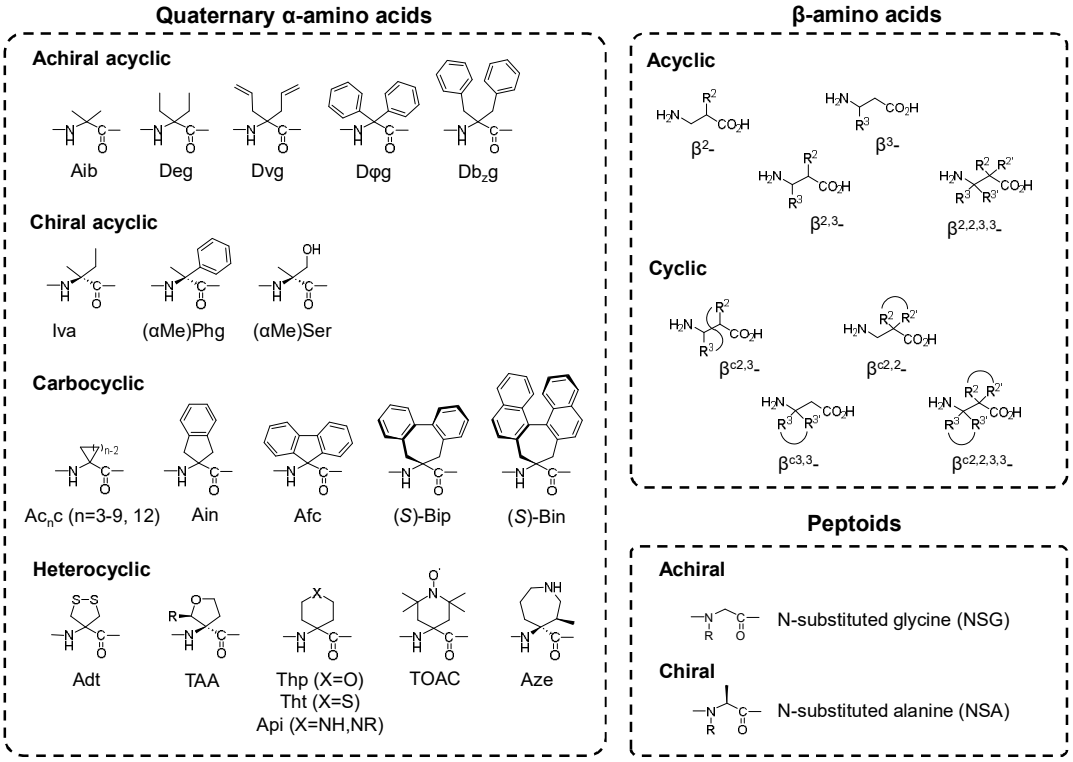


Figure 2. Main types of constrained amino acids.

Cyclic quaternary amino acids have also received considerable attention in the field of peptidomimetics as they impose higher conformational rigidity compared to their linear analogues.[24] Several reviews were dedicated to the synthesis of carbocyclic α,α-disubstituted amino acids.[25-27] By contrast, little attention has been paid to quaternary heterocyclic amino acids as they are synthetically challenging building blocks, especially concerning chiral derivatives and the development of stereoselective synthetic routes. However, the presence of heteroatoms in the side chains provides anchor points to engineer additional functionalities into the peptides incorporating these constrained amino acids. This review intends to cover the reported synthetic approaches toward α,α-disubstituted heterocyclic amino acids **5** (Figure 3). To the best of our knowledge, this topic has not been specifically covered in any previous review. Each section is dedicated to a particular ring size from 3- to 7-membered ring and larger amino acids, with a final section providing a perspective on where future opportunities may lie in this field.

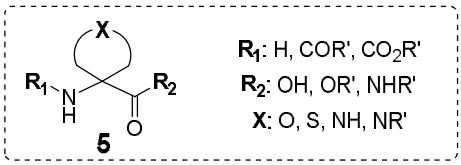
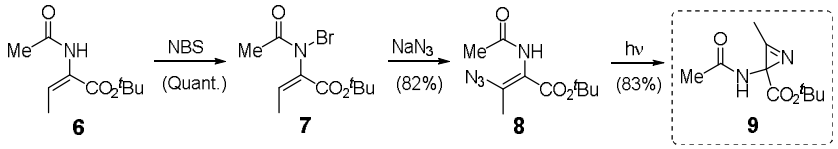


Figure 3. General structure of quaternary heterocyclic amino acids **5** covered in this work.

2. Three-membered ring quaternary heterocyclic amino acids

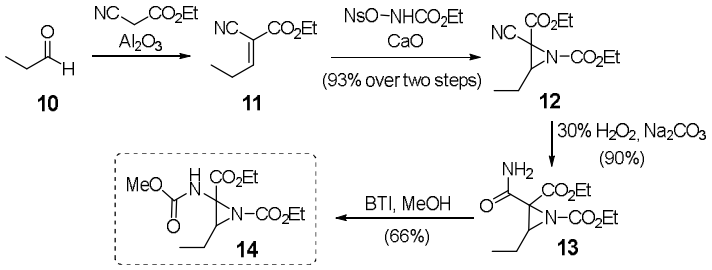
Cyclopropane amino acids (Ac_3c) were proved to inhibit amino acid processing enzymes of therapeutic interest. In the context of peptidomimetics, they promote distorted 3_{10}-/α-helical conformations in linear peptides.[10] Thus, there are several reports regarding methodologies for the preparation of cyclopropane amino acids, including stereoselective methods for substituted analogues.[28] For their heterocyclic counterparts, few methods have been reported as they are challenging building blocks due to the associated high ring strain energy.

Azirine-derived amino acids were prepared more than 40 years ago (Scheme 2).[29] First, the synthetic route involved the bromination of *t*-butyl 2-acetyl-amino-2-alkenoate **6** with *N*-bromosuccinimide to give compound **7**. The reaction of **7** with sodium azide gave access to compound **8** in high yield. Finally, after photochemical reaction of **8** using a high-pressure mercury lamp, 1-*tert*-butoxycarbonyl-1-acetylamino-2-azirine **9** was obtained in good yield.[29,30] The addition of pyrimidine and purine bases to benzyl 2H-azirines, obtained following a similar synthetic methodology, has been also described.[31]



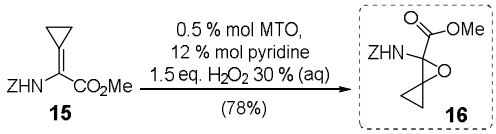
Scheme 2. Synthesis of azirine-derived amino acid **9**.

As shown in Scheme 3, aziridine amino acids have been prepared from simple aliphatic aldehydes, like propionaldehyde **10**, and ethyl cyanoacetate. After Knoevenagel condensation, the obtained α,β-unsaturated nitrile **11** was allowed to react with nosyloxycarbamate giving access to the corresponding 2-cyanoaziridine **12** in excellent yield.[32] After selective hydrolysis of the cyano group to amide group, the product **13** was subjected to Hofmann rearrangement using [bis(trifluoroacetoxy)iodo]benzene (BTI), which provided the corresponding α-carbamoyl α′-carboxyl aziridine **14** in good yield.[33]



Scheme 3. Synthesis of α-carbamoyl α′-carboxyl aziridine **14**.

The synthesis of methyl 2-(benzyloxycarbonylamino)-2-cyclo-propylideneacetate **15**, in several steps from L-serine, as well as its transformation to the corresponding oxaspiropentanecarboxylate **16** was reported by Limbach *et al.* (Scheme 4).[34] Although epoxidation of **15** occurs upon standing in air, the transformation was optimised using H_2O_2 in the presence of methyltrioxorhenium (MTO) and pyridine, a method developed by Sharpless for efficient epoxidation of olefins.[35] Other authors reported a structurally more complex epoxide-derived cyclic amino acid, obtained from enol triflates.[36]

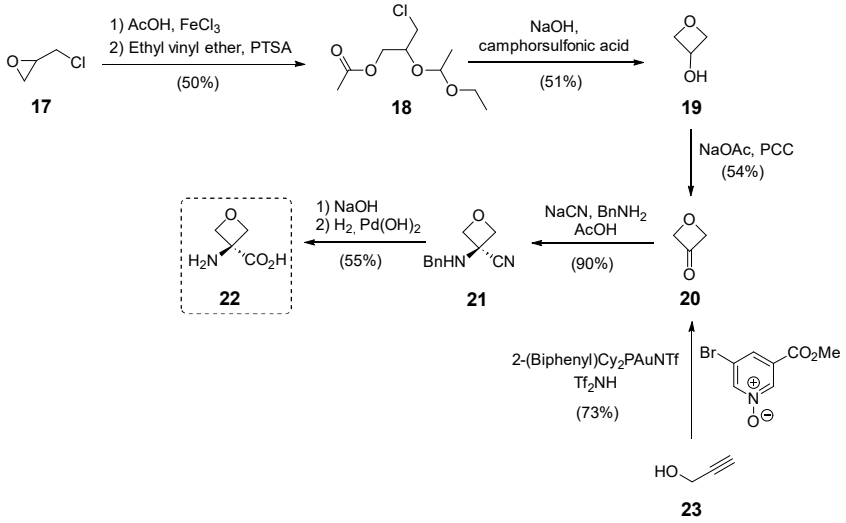


Scheme 4. Synthesis of oxaspiropentanecarboxylate **16**.

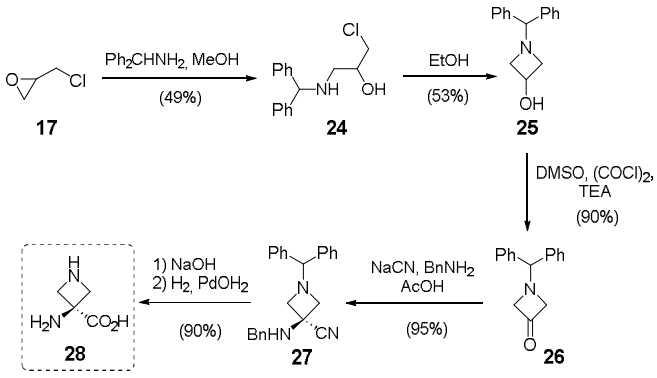
3. Four-membered ring quaternary heterocyclic amino acids

The conformational preferences of peptides containing 1-aminocyclobutanecarboxylic acid (Ac_4c) closely resemble those of Aib-derived peptides, that is the stabilization of type III/III′ β-bends and 3_{10}/α-helices. In addition, the incorporation of Ac_4c residues in polyarginine peptides results in the stabilization of helical structures and enhancement of their cell permeability.[37]

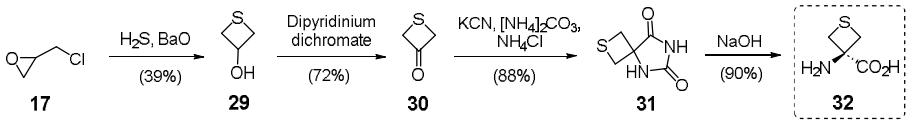
Heterocyclic Ac_4c analogues are synthetically more accessible than 3-membered ring analogues, especially for those achiral derivatives. The most straightforward synthetic pathway to access oxetane-, azetidine- and thietane-derived amino acids starts from 2-(chloromethyl)oxirane **17** (Schemes 5-7), *via* ring opening with acetic acid to give **18**, 1-diphenylmethylamine to provide **24** and hydrogen sulfide to afford **29**, respectively.[38] The corresponding heterocycle was constructed *via* base-induced ring closure and subsequent oxidation of the alcohol **19**, **25**, and **29** to the cyclobutanone derivative **20**, **26**, and **30**. From these derivatives, the amino acid functionality was incorporated *via* Strecker or Bucherer-Bergs amino acid synthesis using sodium or potassium cyanide, providing **21**, **27** and **31**, respectively. Finally, after hydrolysis and removal of the protecting group when needed, the corresponding oxetane-, azetidine- and thietane-derived amino acids **22**, **28** and **32** were obtained in moderate to good yield. In the case of the oxetane amino acid, Ye *et al.* reported the preparation of the oxetan-3-one **20** in one step from propargyl alcohol **23**, assisted by gold catalysis (Scheme 5).[39]



Scheme 5. Synthesis of oxetane α,α-disubstituted amino acid **22**.

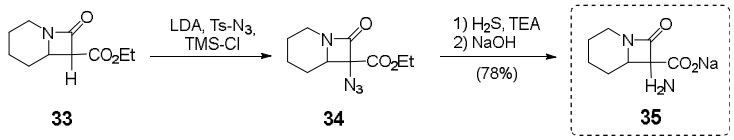


Scheme 6. Synthesis of azetidine α,α-disubstituted amino acid **28**.



Scheme 7. Synthesis of thietane α,α-disubstituted amino acid **32**.

The bicyclic β-lactam amino acid **35** was prepared from racemic derivative **33** through azidation using toluene-*p*-sulphonyl azide followed by reaction with TMS-Cl (Scheme 8).[40] The obtained azide **34** was reduced with hydrogen sulfide to provide the corresponding amino ester, subsequently treated with NaOH to give access to the amino carboxylate derivative **35**. A similar approach was used by Plagge *et al.* to obtain β-sultam-derived azido acid derivatives, a precursor of the corresponding amino acid.[41] In a similar way, Choi *et al.* described the reaction oxetane-2-carboxylic esters with lithium hexamethyldisilazide, generating an anion which can be trapped with carbon tetrabromide. The obtained bromo-derivative was easily converted into the corresponding azidoester.[42] It is also worth mentioning the synthesis of 6α-carboxypenicillins from 6α-formylpenicillins *via* hemiacetal formation followed by oxidation, which allowed the access to penicillin-derived amino acids.[43]

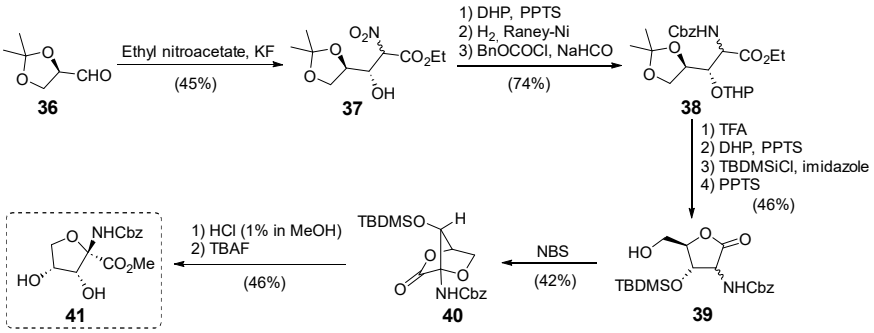


Scheme 8. Synthesis of bicyclic β-lactam amino acid **35**.

4. Five-membered ring quaternary heterocyclic amino acids

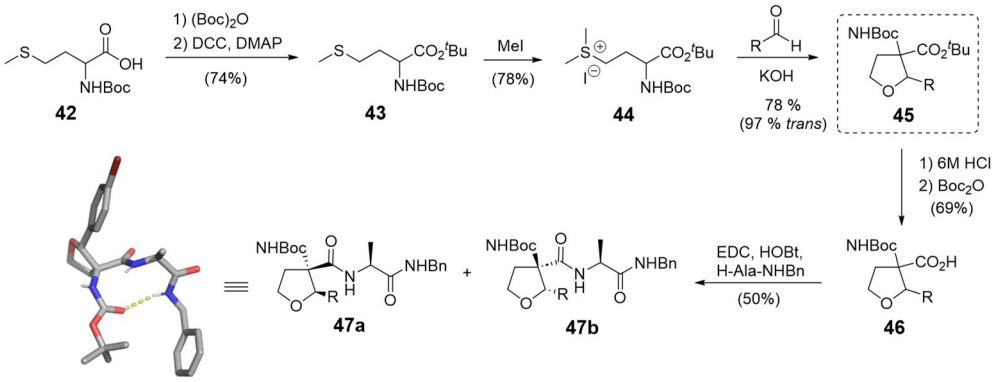
1-Amino-cyclopentane carboxylic acid (Ac_5c) is able to induce β-turns and helical arrangements in peptides, not differing from the conformational restriction provided by Ac_4c or Ac_6c.[10] In addition, it possesses interesting medicinal chemistry properties as antitumoral against different types of carcinomas.[44]

Regarding heterocyclic five-membered ring quaternary amino acids, there are several reports on the synthesis of tetrahydrofuran-derived amino acids. Scheme 9 shows the synthetic route toward amino acid **41** described by Soengas *et al.*[45] Condensation of D-glyceraldehyde **36** with ethyl nitroacetate under Henry reaction conditions gave **37** as a mixture of epimers. After alcohol protection, catalytic hydrogenation and protection of the resulting amino group as benzyloxycarbonyl derivative, compound **38** was isolated as a mixture of epimers. The tetrahydropyran (THP) group was removed with TFA, which promoted the lactonization of the product. The resulting secondary alcohol was protected with a silyl group, needing first the protection and subsequent deprotection of the primary alcohol with dihydropyran to provide compound **39**. Reaction of **39** with NBS in acetonitrile then gave the bicyclic lactone **40**, which was opened with methanol and subjected to removal of the silyl protecting group to give target compound **41**.



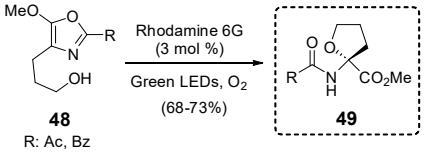
Scheme 9. Synthesis of tetrahydrofuran-derived amino acid **41**.

Maity *et al.* synthesized and studied the tetrahydrofuran-derived amino acid TAA **45**, obtained as a racemic mixture from racemic methionine (Scheme 10).[46] First, the methionine-derived sulfonium salt **44** was prepared by treating fully protected methionine **43**, obtained from Boc-Met-OH **42**, with MeI. The aldol-type reaction of **44** presumably takes place through the formation of the corresponding ester enolate and its reaction with the carbonyl group of an aldehyde, with the intermediate alkoxide substituting intramolecularly dimethylsulfide. The tetrahydrofuran amino acids **45** were obtained as a racemic mixture with high diastereoselectivity of the α- and β-stereocenters. The corresponding carboxylic acid derivative **46** was prepared *via* sequential hydrolysis and amine protection, subsequently subjected to a coupling with alanine to give diastereoisomeric tetrapeptide models **47a** and **47b**, separated by column chromatography. Only the *S* diastereoisomer is able to induce β-turns and 3_{10}-helices when incorporated into peptides.[46,47]



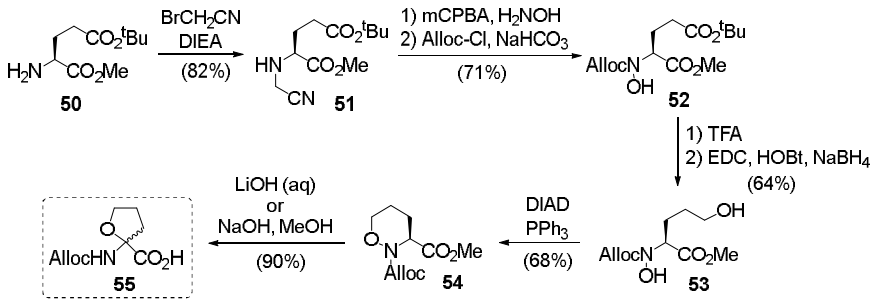
Scheme 10. Synthesis of TAA **45** and β-turn induction by the *S* diastereoisomer, as demonstrated with the X-ray structure of peptide model Boc-(*S*)-TAA-Ala-NHBn (CCDC: 668640). R=*p*-bromophenyl.

Du *et al.* reported the visible-light-mediated synthesis of oxidized amides *via* organic photoredox catalysis.[48] Following this methodology, tetrahydrofuran derivatives **49** with the amino and carboxyl group in position 2 are easily accessible, starting from the oxazole substrate **48** (Scheme 11).



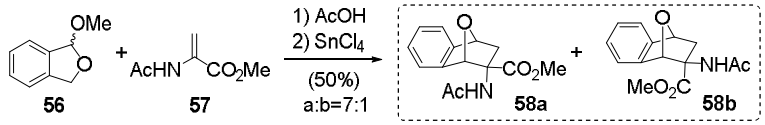
Scheme 11. Synthesis of tetrahydrofuran amino acid **49**.

The synthesis of 2-substituted tetrahydrofuran amino acids can also be accomplished from ε-oxapipecolic acid derivatives.[49] As shown in Scheme 12, monoalkylation of commercially available glutamate derivative **50** with bromoacetonitrile gave **51**, which was subjected to aminolysis of the nitrone and subsequent Alloc-protection. Hydrolysis of the *t*-butyl ester in **52** followed by reduction of the carboxylic acid gave **53**. The ε-oxapipecolic acid derivative **54** containing a tetrahydrooxazine ring was obtained *via* Mitsunobu reaction from **53**. Finally, hydrolysis of the methyl ester also promoted ring opening and subsequent cyclisation of the *N*-acyloxyimine intermediate, providing the corresponding tetrahydrofuran amino acid **55** in excellent yield. It is worth mentioning that **55** was not the target compound in this work, focused on the preparation of ε-oxapipecolic acid derivatives and its employment to access model peptides toward bioactive peptidomimetics. In fact, they described a suitable method for the methyl ester hydrolysis in **54**, allowing to keep the tetrahydrooxazine ring intact by using aqueous hydrochloric acid instead of lithium or sodium hydroxide.



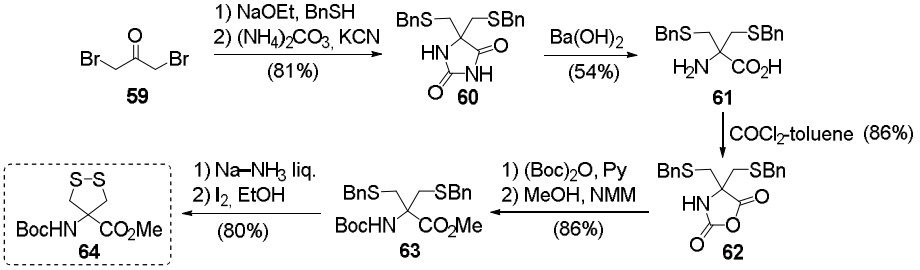
Scheme 12. Synthesis of tetrahydrofuran amino acid **55**.

Related tetrahydrofuran amino acids are 2-aminooxanorbornenes, accessible *via* Diels-Alder reaction between 1-methoxyphtalane **56** and dehydroalanine derivative **57** (Scheme 13).[50] The reaction provided the adducts **58a** and **58b**, which were separated by column chromatography. The formation of the 2-*endo*-acetamido derivative **58a** is favoured over 2-*exo* **58b**, as determined by NMR as well as *via* derivatisation of **58a** to the corresponding oxazoline, which cannot be formed when using **58b** as starting material.



Scheme 13. Synthesis of 2-aminooxanorbornenes **58a** and **58b**.

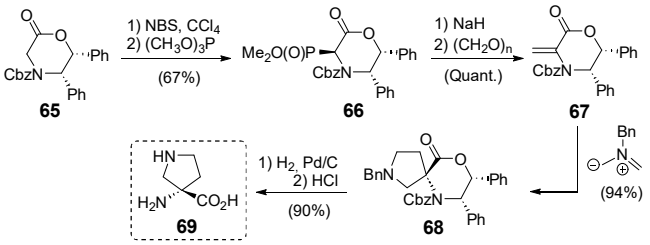
Achiral 5-membered 1,2-dithiolane (Adt) has been the focus of extensive studies regarding its great ability to stabilize β-turns in tetrapeptide models, although the stabilization of 3_{10}-helices in longer systems is prevented due to unfavorable interactions between dithiolane rings.[51,52] As shown in Scheme 14, the hydantoin **60** was prepared from 1,3-dibromoacetone **59**, *via* double S_N2 to incorporate the thioether moiety followed by Bucherer-Bergs reaction on the ketone.[53] The hydrolysis with $Ba(OH)_2$ provided amino acid **61**, which was converted in the corresponding *N*-carboxyanhydride **62**. After Boc-protection, the highly reactive urethane protected *N*-carboxyanhydride was reacted with MeOH affording **63** in good yield. Finally, the deprotection of the two mercapto groups followed by oxidation gave the orthogonally protected Adt derivative **64** in good yield.



Scheme 14. Synthesis of orthogonally protected Adt derivative **64**.

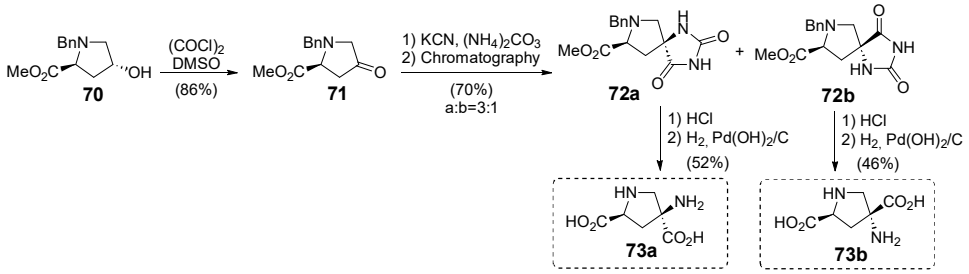
Pyrrolidine-derived amino acids have been prepared in different ways. A efficient method was described by Williams *et al*. in their study on the asymmetric synthesis of (*S*)-(–)-cucurbitine.[54] As shown in Scheme 15, the key step of the synthesis involves the 1,3-dipolar cycloaddition of azomethine ylide to α,β-dehydrolactone **67**, previously synthetized from lactone **65** *via* the preparation of derivative **66**. This

reaction yields pyrrolidine **68** as a single diastereomer in excellent yield. The corresponding amino acid derivative **69** was obtained after removal of protecting groups by hydrogenolysis and hydrolysis.



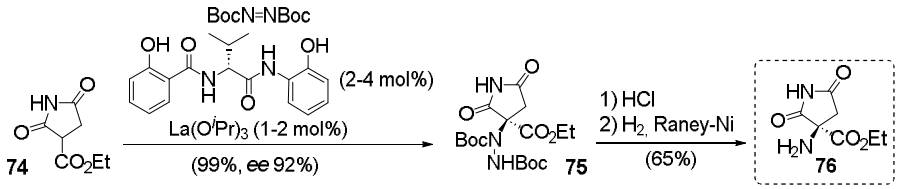
Scheme 15. Synthesis of pyrrolidine amino acid **69**.

As for smaller and larger counterparts, Bucherer-Bergs amino acid synthesis remains one of the most convenient methods to access quaternary amino acid from readily available ketones. For example, Tanaka *et al.* reported the synthesis of all four isomers of 4-amino-4-carboxyproline as conformationally restricted glutamic acid analogues (Scheme 16).[55] Swern oxidation of the hydroxyproline derivative **70** gave 4-oxoproline **71**, subjected to Bucherer-Bergs reaction with potassium cyanide to give the diastereoisomeric mixture of spirohydantoins **72a** and **72b**, separated *via* flash chromatography. Hydrolysis and hydrogenolysis of the different protecting groups afforded 4-amino-4-carboxyproline analogues **73a** and **73b** in moderate yield. The other pair of diastereoisomers was obtained in an identical fashion from the D-proline starting material. Interestingly, one of the diastereoisomers showed a potent, highly selective, and systemically-active agonist activity for metabotropic glutamate receptors negatively coupled to adenylate cyclase.[56] The same methodology has been employed to access 2-phosphonomethylpyrrolidines.[57]



Scheme 16. Synthesis of 4-amino-4-carboxyprolines **73a** and **73b**.

Mashiko *et al.* reported the synthesis of **76**, a key intermediate in the synthesis of a relevant aldose reductase inhibitor for the treatment of diabetic complications (Scheme 17). The relevant synthetic step in this method involves the catalytic asymmetric amination of succinimide **74** with azodicarboxylate and using a lanthanum-amide catalytic complex.[58] Following this procedure, intermediate **75** was obtained in excellent yield and stereoselectivity, and was subsequently transformed into the amino acid **76**.



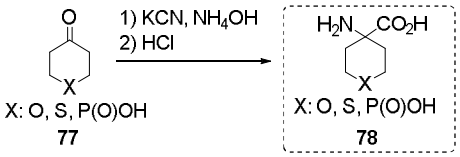
Scheme 17. Synthesis of succinimide amino acid **76**.

5. Six-membered ring quaternary heterocyclic amino acids

1-Aminocyclohexane carboxylic acid (Ac_6c) derivatives have attracted a significant attention in peptidomimetic chemistry due to their high helix promoting effects.[27] In addition, the Ac_6c scaffold served as the basis for the design of potent cathepsin K inhibitors and V2 agonists of arginine vasopressin.[59,60]

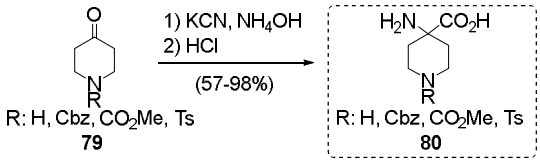
There are many examples on the synthesis and applications of six-membered ring quaternary heterocyclic amino acids, especially those achiral analogues with the amino and carboxyl functionalities in position 4 of the ring. This is mainly due to their easy of synthesis and strong helicogenic properties. In fact, tetrahydropyran (Thp) and tetrahydrothiopyran (Tht) derivatives were studied as reverse turn and 3_{10}-helix inducers in peptide models.[61,62] Piperidine-derived quaternary amino acids (Api) have attracted more attention than oxygen and sulfur counterparts due to their potential to incorporate substituents in the heterocyclic nitrogen.[63,64] Their ability to induce helical conformations in peptide sequences has been reported in combination with Aib or though covalent and non-covalent bonds involving the piperidine ring, either *via* metal chelation, salt bridges or stapling.[63,64]

As described in the previous sections, Strecker and Bucherer-Bergs amino acid synthesis are convenient routes to oxygen-, sulfur- and phosphorus-containing quaternary amino acids of general formula **78**, starting from the corresponding ketones **77** (Scheme 18).[65-67]

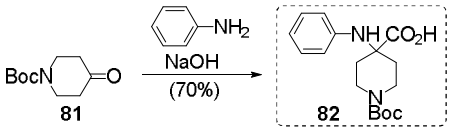


Scheme 18. Synthesis of *O*-, *S*- and *P*-containing six-membered ring quaternary amino acids **78**.

For piperidine-derived amino acids, a range of free and side-chain protected analogues **80** is accessible through Strecker amino acid methodologies from ketones **79** in all the possible positions of the heteroatom regarding the amino and carboxyl groups (Scheme 19).[66,68] Butcher *et al.* reported the synthesis of *N*-*tert*-butoxycarbonyl-protected (Boc) piperidine amino acids **82** using aromatic amines as nucleophiles in the Bargellini reaction of *N*-Boc piperidone **81** (Scheme 20).[69]



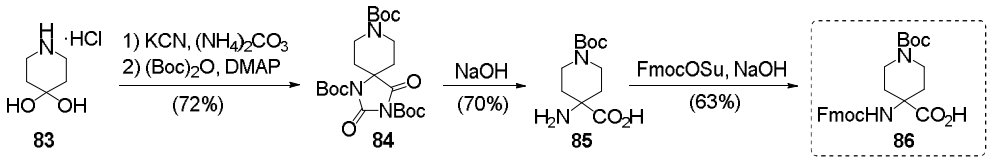
Scheme 19. Synthesis of piperidine-derived amino acids.



Scheme 20. Synthesis of *N*-Boc-piperidine-derived amino acids.

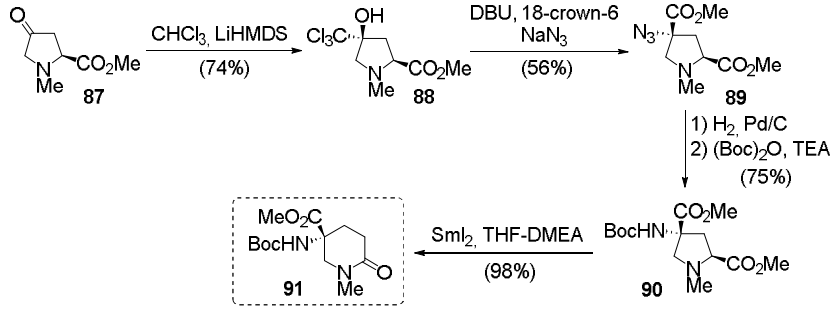
Wysong *et al.* reported the synthesis of 4-aminopiperidine-4-carboxylic acid, bearing compatible protecting groups for standard Fmoc/^{t}Bu solid-phase peptide synthesis.[70] The synthetic procedure depicted in Scheme 21 starts with the formation of hydantoin **84** from piperidine derivative **83** by a Bucherer-Bergs procedure and subsequent Boc-protection of the piperidine nitrogen. After treating with hydroxide, α-amino and α-acid moieties were unmasked providing **85**, followed by Fmoc-protection of the amino group using Fmoc-OSu under basic conditions to yield **86** in good overall yield. Other authors have described the use of amino-azirines as synthons for accessing sterically constrained peptides incorporating Thp, Tht and Api residues, able to adopt rigid helical conformations, as well as the stereoregulated dimerization reaction of

N-(arylmethylene)dehydroalanine derivatives to produce heterocyclic α,α′-diaminodicarboxylic acid derivatives.[61,71,72]



Scheme 21. Synthesis of orthogonally protected piperidine amino acid Fmoc-Pip(Boc)-OH **86**.

Katoh *et al.* reported the synthesis of valerolactam-derived amino acids from 4-oxoproline **87** *via* the stereoselective addition of trichloromethyl function to give **88**, followed by the formation of azido-ester **89** under the modified Corey-Link reaction (Scheme 22).[73] Azide reduction and subsequent amine protection gave methyl ester **90**, which was treated with samarium iodide to give δ-lactam **91** in excellent yield.

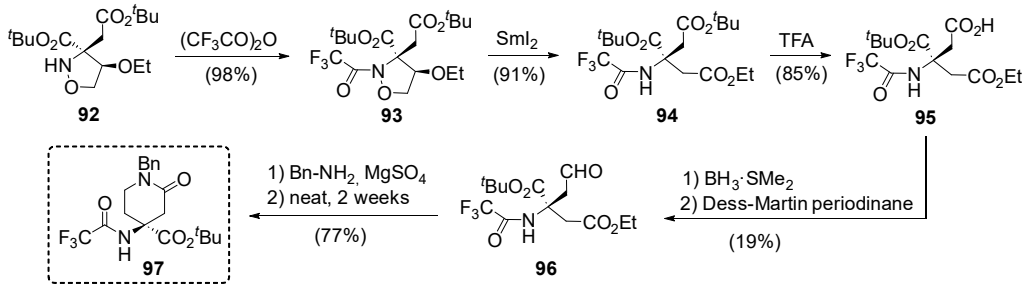


Scheme 22. Synthesis of δ-valerolactamic quaternary amino acid **91**.

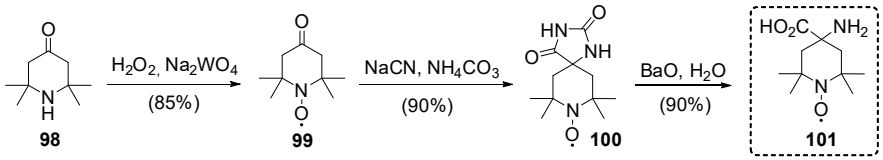
Closely related δ-valerolactamic quaternary amino acid **97** has been obtained in a series of reactions from a 5-membered heterocycle, in this case enantiopure isoxazolidine **92** (Scheme 23).[74] After *N*-substitution to incorporate a trifluoroacetyl group in **93**, SmI_2-promoted reductive opening gave ester **94**. Selective acidolysis of the less hindered *tert*-butyl ester followed by chemoselective reduction of acid **95** and subsequent oxidation of the primary alcohol led to aldehyde **96**. After reductive amination, the obtained amino diester underwent spontaneous cyclization upon storage, yielding δ-valerolactam **97** with complete regioselectivity and in good yield.

The amino acid TOAC **101** (Scheme 24) contains a piperidine *N*-oxide ring and provides conformational restriction to peptide chains in similar fashion as its piperidine analogue Api.[75,76] Interestingly, it is a paramagnetic residue enabling the use of electron paramagnetic resonance (EPR). This technique allows the quantitative measure of distances between paramagnetic residues and can be used to distinguish between closely related 3_{10}- and α-helix structures in peptides incorporating at least two TOAC residues.[75,76] As shown in Scheme 24, it has been prepared by from 2,2,6,6-tetramethyl-4-oxo-piperidine **98** *via* oxidation using sodium tungstate and hydrogen peroxide. *N*-oxide **99** was subjected to Bucherer-Bergs amino acid synthesis affording hydantoin **100**, which was hydrolysed to yield TOAC amino acid **101** with good overall yield.[77]

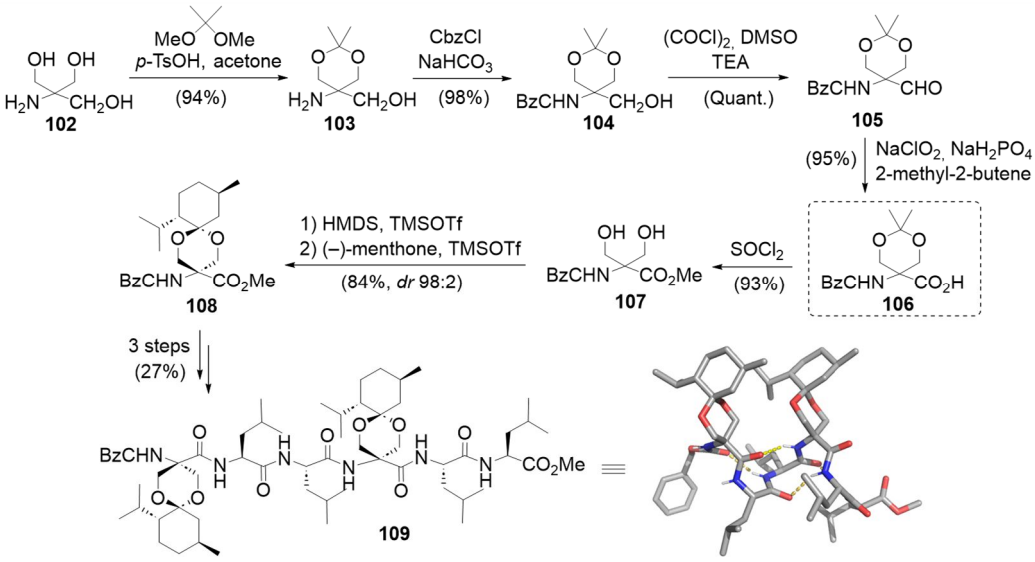
Another interesting example of six-membered ring quaternary heterocyclic amino acid is Hms **106** (Scheme 25), a *O,O*-isopropylidene-α-(hydroxymethyl)serine derivative. Furukawa *et al.* reported the synthesis of Hms from 2-amino-2-hydroxymethyl-1,3-propanediol **102**, first *via* reaction with 2,2-dimethoxypropane and *p*TsOH to give **103**, followed by Cbz protection of the amino group.[78] Swern oxidation of the resulting alcohol **104** provided **105**, then subjected to Pinnick oxidation to afford Cbz-Hms(Ipr)-OH **106** in excellent overall yield. Additionally, in this work, **106** was converted into diol **107** by acidic hydrolysis.



Scheme 23. Synthesis of δ-valerolactamic quaternary amino acid **97**.



Scheme 24. Synthesis of TOAC amino acid **101**.

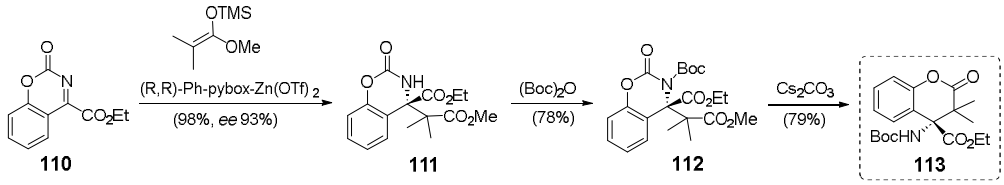


Scheme 25. Synthesis of Hms amino acid **106** and induction of 3_{10}-helices when incorporated in peptide sequences (X-ray structure of heteropeptide **109** is shown, CCDC 1453021).

Acetalization of the side-chain in **107** with (–)-menthone gave access to the chiral Hms analogue Hms[(–)-Men] **108** in good yield and an excellent diastereomeric ratio. Using standard peptide synthesis protocols, these authors reported Hms[(–)-Men] homopeptides and heteropeptides with alternating L-Leu and Hms[(–)-Men] residues, such as compound **109** shown in Scheme 25. Conformational analysis of both types of peptide derivatives suggests the adoption of 3_{10}-helical structures, although the side-chain chirality has little effect on helical-screw control in the case of L-Leu heteropeptides.

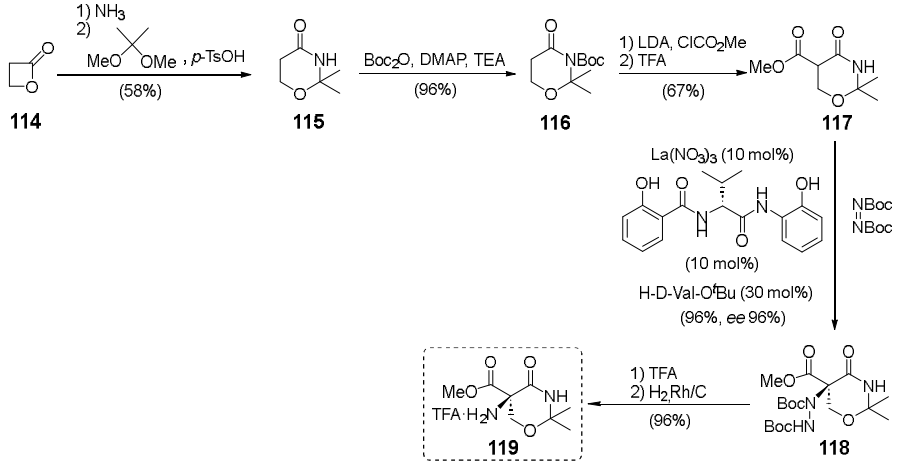
Saaby *et al.* developed a novel approach to an optically active lactone-derived quaternary α-amino acids (Scheme 26).[79] The reaction of a ketimine electrophile **110** with silylketene acetals in the presence of a chiral zinc(II) catalyst afforded the corresponding Mannich base **111** in high yield and optical purity. After

Boc-protection giving compound **112**, quaternary α-amino acid **113** was obtained after spontaneous cyclization.



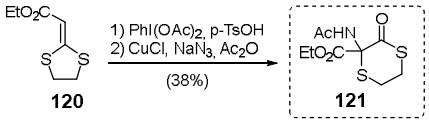
Scheme 26. Synthesis of optically active lactone-derived quaternary α-amino acids **113**.

As part of an enantioselective synthetic route for Mycesterin F and G, a lactam-type 6-membered ring was obtained.[80] As shown in Scheme 27, the ring opening of β-propiolactone **114** followed by intramolecular protection/cyclization using 2,2-dimethoxypropane gave **115**, subsequently subjected to the installation of the *N*-Boc protecting group. The following step involved first the methoxycarbonylation of the lithium enolate of **116** and then the Boc protecting group removal to provide **117**, in turn subjected to catalytic asymmetric amination using a lanthanum-based ternary asymmetric catalyst. The di-Boc hydrazine **118** was obtained in excellent yield and enantiomeric excess and was easily converted into the amino ester **199** in a two-step sequence comprising Boc removal and hydrogenative cleavage of the N–N bond.

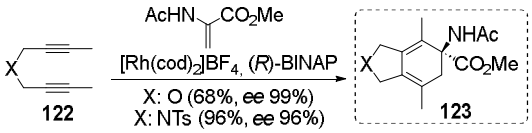


Scheme 27. Synthesis of lactam quaternary amino ester **119**.

The thiolactone-derived amino ester **121** is accessible *via* copper(I)-catalyzed, [PhI(OAc)$_2$]-mediated ring-expansion/thiolactonization of α-oxo ketene dithioacetal **120**, which takes place *via* azidation of the internal olefinic C−H bond with sodium azide (Scheme 28).[81] Another interesting protocol is the Rh-catalyzed [2+2+2]-cycloaddition of 1,6-diynes **122** (Scheme 29) with a protected dehydroamino acid, enabling the synthesis of heterocyclic α,α-disubstituted α-amino acids **123** in high yield and enantioselectivity.[82]



Scheme 28. Synthesis of thiolactone-derived amino ester **121**.

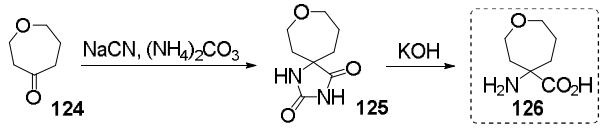


Scheme 29. Synthesis of heterocyclic amino acid **123**.

6. Seven-membered ring and larger quaternary heterocyclic amino acids

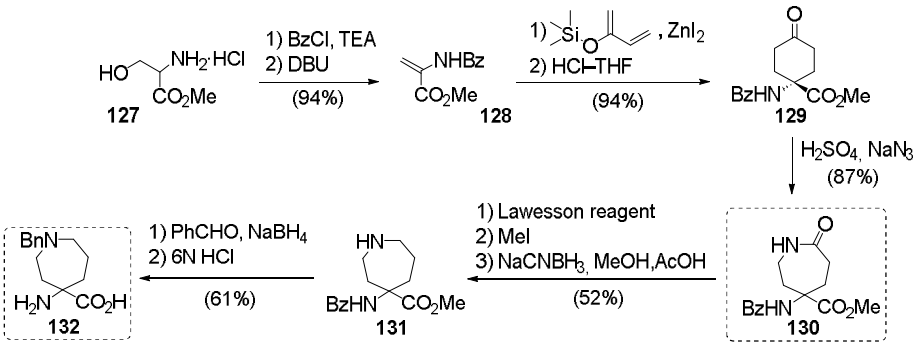
Carbocyclic quaternary amino acids (Ac$_n$c) containing 7- to 12-membered rings have been studied in the context of secondary structure induction when incorporated into peptide sequences. As for smaller counterparts (except for n=3), they tend to facilitate the folding of peptide chains into regular 3_{10}/α-helices as well as β-turns.[10] By contrast, studies on the ability of heterocyclic seven-membered and longer quaternary amino acids to constrain peptide conformations, without the synergistic effect of additional restricted amino acids such as Aib, are scarce in comparison to 5- and 6-membered ring analogues.

As discussed earlier, Bucherer-Bergs amino acid synthesis represents a suitable method to access a range of large heterocyclic amino acids. As an example, Scheme 30 shows the synthetic route to 4-disubstituted oxepane-derived amino acids **126** from ketone **124**, *via* the formation of hydantoin **125**. Analogously, the synthesis 2- and 3-disubstituted analogues have been described following the same procedure.[83,84]



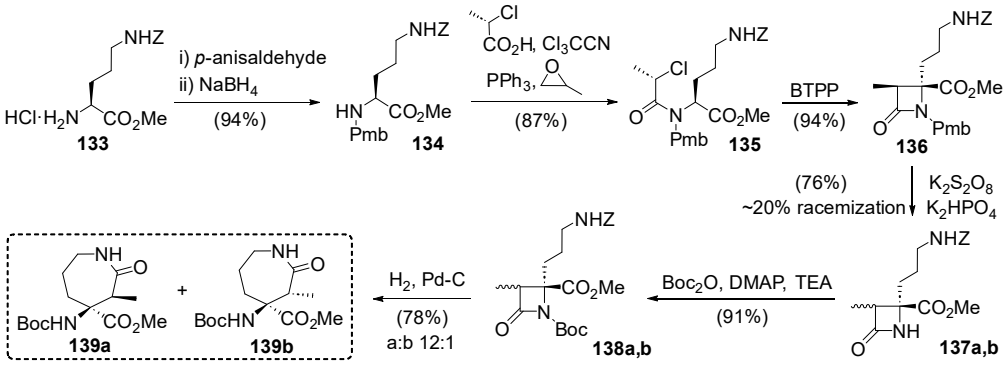
Scheme 30. Synthesis of 4-disubstituted oxepane-derived amino acid **126**.

Azepane- and oxoazepane-derived amino acids have attracted more attention than oxepane analogues. Pellegrino *et al.* reported the synthesis of racemic azepane amino acid **132** in several steps from racemic H-Ser-OMe **127** (Scheme 31).[85] *N*- and *O*-benzoylation of this ester followed by elimination of the benzoyl moiety gave dienophile **128**. Reaction of **128** with 2-trimethylsilyloxy-1,3-butadiene in the presence of ZnI_2 and further treatment of the reaction with HCl in THF provided ketone **129**.[86] The *N*- and *C*-terminal protected amino acid **130** was obtained by a modified Schmidt procedure using sodium azide. Selective transformation of lactam **130** into the corresponding thiolactam using the Lawesson reagent followed by reduction gave *N*-benzylamine **131**. This compound was transformed into the side-chain protected racemic free amino acid **132** *via* reductive amination and subsequent hydrolysis of the *N*-terminal capping group. After incorporation of an Fmoc-L-Ala residue at the *N*-terminal end, the two diastereoisomers were separated by flash column chromatography.



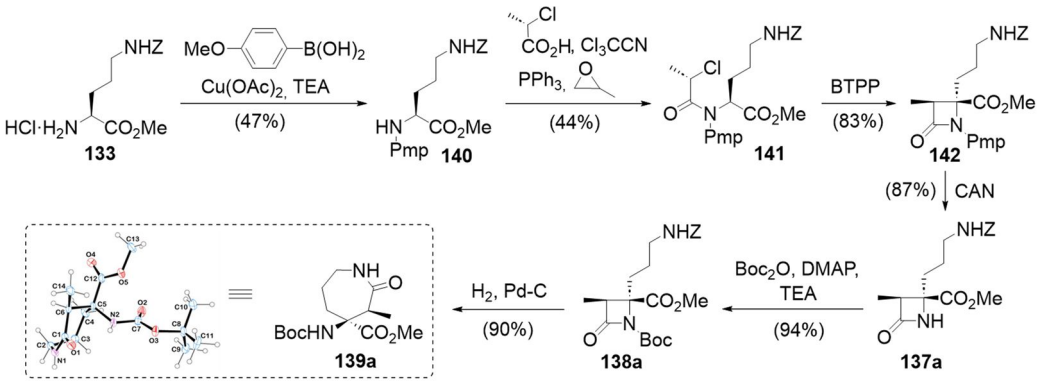
Scheme 31. Synthesis of racemic azepane amino acid **132**.

Earlier, Núñez-Villanueva *et al.* reported a stereoselective route to access 4-amino-4-carboxyl-3-methyl-2-oxoazepane amino acids (Scheme 32).[87] Using commercial H-Orn(Z)-OMe **133** as starting material, the synthetic route involves the Pmb-protection of the free amino group providing **134**, followed by coupling of (*S*)-2-chloropropionic acid under neutral conditions to avoid racemization. Cyclization of the resulting chloropropionyl-derived ornithine **135** using a phosphazene base afforded β-lactam **136** as a single diastereoisomer. In this reaction, the stereochemical control is exclusively directed by the configuration of the *N*-2-chloropropionyl group.[88] However, a partial epimerization in position 3 was observed upon the removal of the *p*-methoxybenzyl group by oxidation. After activation of the β-lactam ring with a Boc group providing **138** and removal of the Cbz side-chain protecting group, the intramolecular nucleophilic attack of the free amino group to the azetidinone ring resulted in the 7-exotrig closure to 3-methyl-2-oxoazepane derivatives **139a** and **139b**, which were separated by column chromatography.



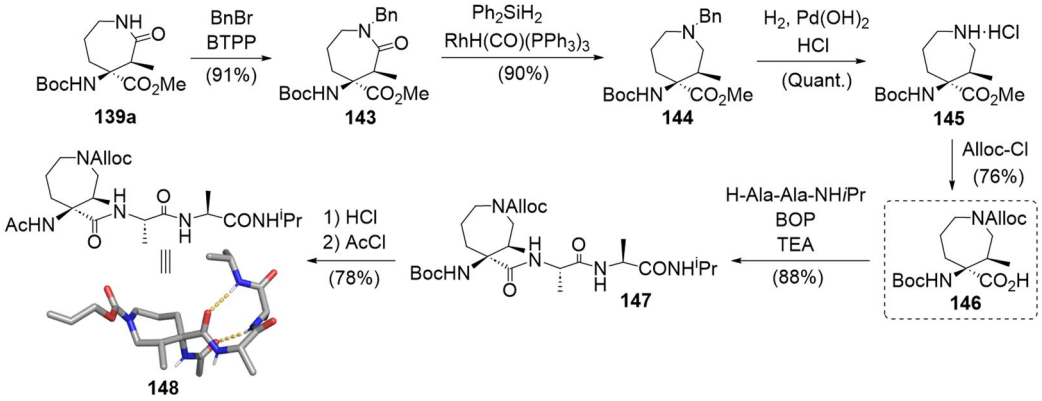
Scheme 32. Synthesis of 4-amino-4-carboxyl-3-methyl-2-oxoazepane derivatives **139a** and **139b** *via* the stereoselective formation of ornithine-derived β-lactams.

Núñez-Villanueva *et al.* also reported a completely stereoselective synthesis of **139a**, based on the replacement of the *p*-methoxybenzyl (Pmb) protecting group for a *p*-methoxyphenyl (Pmp) group in the starting ornithine substrate **133**.[89] Thus, as shown in Scheme 33, the chloropropionil derivative **141** was obtained from *N*-Pmp amino acid **140**, then subjected to cyclisation to give the azetidinone **142** following the same protocol as for *N*-Pmb analogues. In this case, the removal of the Pmp group in **142** under mild conditions proceeded without racemization, providing exclusive **137a** which were converted into **138a** and then **139a** following the same steps as previously described. The formation of the 2-oxoazepane ring and the configuration of the chiral centers in **139a** was confirmed with the X-ray structure.



Scheme 33. Stereoselective synthesis of 4-amino-4-carboxyl-3-methyl-2-oxoazepane derivative **139a**. The X-ray structure of **139a** is shown (CCDC 811795).

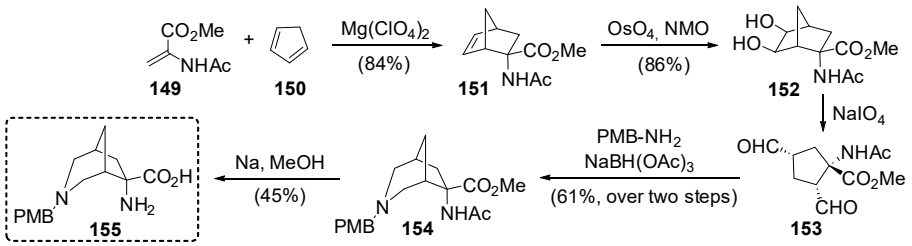
Núñez-Villanueva *et al.* described the reduction of the 2-oxoazepane ring to the azepane amino acid (Scheme 34).[90] The *N*-benzyl derivative **143**, obtained from **139a**, was reduced with diphenylsilane and a rhodium catalyst to provide *N*-benzyl azepane **144**. Removal of the benzyl group provided azepane **145**, then protected with Alloc to give rise to orthogonally protected azepane amino acid **146** in good overall yield. Compound **146** was incorporated into peptide sequences using standard solution phase peptide synthesis protocols. Scheme 34 shows two examples of pentapeptide models, **147** and **148**, incorporating the azepane moiety at the *i*+1 position and displaying a 3_{10}-helical structure both in solution and in the solid state. This amino acid is also an effective β-turn inducer when incorporated into tetrapeptides models and, interestingly, shows a tendency to form a supramolecular helical arrangement in the solid state while maintaining the β-turn structure.[91]



Scheme 34. Synthesis of azepane quaternary amino acid **146** and its incorporation in peptide sequences. The X-ray structure of a model pentapeptide incorporating **146** is shown (CCDC 887956).

In a different study, Núñez-Villanueva *et al.* described the spontaneous rearrangement of the 4-carboxy-2-oxoazepane quaternary amino acid **139a** upon hydrolysis of the ester moiety, leading to 2'-oxopiperidine-containing $\beta^{2,3,3}$-amino acids.[92] Theoretical and experimental data suggest that the rearrangement process occurs through a concerted mechanism, intramolecularly catalysed by the carboxylic acid in position 4.

Caputo *et al.* reported the synthesis of two diastereomeric 6-amino-3-azabicyclo[3.2.1]octane-6-carboxylic acids using *exo*- and *endo*-norbornene amino acids as chiral building blocks.[93] Scheme 35 shows the synthetic route for the *exo*-derivatives. Norbornene derivative **151** was prepared by Diels-Alder reaction starting from 2-aminoacrylate **149** and cyclopentadiene **150**. Diol **152** was prepared by reacting **151** with *N*-methylmorpholine-*N*-oxide (NMO) in the presence of a catalytic amount of osmium tetroxide. Subsequent oxidative cleavage of **152** with sodium periodate gave bis-aldehyde **153**, which was directly transform into the corresponding 3-azabicyclo[3.2.1]octane **154** by reductive amination. Final hydrolysis of the *N*- and *C*-capping groups yielded bicyclic quaternary amino acid **155** in moderate yield.



Scheme 35. Synthesis of -amino-3-azabicyclo[3.2.1]octane-6-carboxylic acid **155**.

7. Conclusions and future perspectives

In the last decades, the ability of constrained amino acids, in particular α,α-disubstituted amino acids, to promote the folding of peptide chains into specific secondary structures has been exploited in the development of peptidomimetics of interest in medicinal chemistry and chemical biology. While the focus has been positioned on acyclic and carbocyclic analogues, little attention has been paid to heterocyclic counterparts. This is mainly due to the lack of efficient synthetic methods for their preparation, in particular regarding chiral analogues and stereoselective methods to access them. This review covers the reported synthetic approaches to α,α-disubstituted heterocyclic amino acids of any ring size, and should serve as a guide to design novel synthetic routes toward these scaffolds.

The interest on heterocyclic quaternary amino acids relies on the plethora of properties that they can confer to a peptide derivative. Apart from imposing conformational restriction, the heteroatom in the ring is likely to have a positive impact on the overall physicochemical properties of peptides, in particular in their solubility, but also can serve as an anchor point to engineer enhanced functionalities. These features make these quaternary derivatives a privileged scaffold with implications beyond fundamental research in peptidomimetics. In the last decade, we have witnessed a revolution in drug discovery with the development of novel therapeutic modalities such as mRNA-based therapeutics or antibody- and peptide-based drugs. In the latter, the use of non-natural amino acids has been key to overcome the inherent metabolic instability of peptides. For example, semaglutide has become a blockbuster drug to treat obesity and type II diabetes. The replacement of a single alanine residue from the natural peptide sequence by a quaternary amino acid (Aib) is key to prevent its degradation by dipeptidyl peptidase-4, increasing significantly the drug half-life in the organism.[94] We envisage that heterocyclic quaternary amino acids have the potential to become a key element in future drug design and development processes.

In this sense, the development of efficient and stereoselective synthetic methods to access a variety of heterocyclic quaternary amino acids is still needed, benefiting from emerging research directions in organic synthesis comprising enzyme catalysis, photocatalysis, electrochemistry and green chemistry. This review intends to put the spotlight on the current available methodologies, aiming to encourage synthetic chemists to pursue this endeavour.

Acknowledgements

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