Synthesis of [c]-Fused Bicyclic Proline Analogues

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ABSTRACT

An overview of synthetic methods developed to build [c]-fused bicyclic proline analogues is presented. The focus is on the preparation of azabicycles that bear a carbocyclic ring fused to the [c] face of the pyrrolidine unit. Attention is paid both to procedures that afford the desired compounds in racemic form and to asymmetric strategies. Procedures are organized according to the size of the carbocycle that is fused to the pyrrolidine moiety. Strategies able to provide multigram quantities of enantiopure compounds that have application in the synthesis of marketed drugs are highlighted.

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1. Introduction

In recent years important pharmacological properties have been described for compounds containing bicyclic proline residues that incorporate a carbocyclic ring fused to the [c] face of the pyrrolidine unit (Figure 1).

Figure 1. General structures of [c]-fused bicyclic proline analogues. The positions of chiral carbons are indicated.

Among them, azabicycles **1** and **2**^[1] (Figure 2) have found application in the synthesis of Telaprevir,^[2] and Boceprevir,^[3] respectively; these are drugs in the market for the treatment of hepatitis C virus infection.

Figure 2. Marketed and new experimental hepatitis C protease inhibitors containing a [c]-fused bicyclic proline moieties.

In addition, the isoindoline-1-carboxylic acid scaffold forms part of the structures of compounds with potential applications as inhibitors of coagulation factor Xa.^[4] It is also found in the structure of a new class of specific inhibitors of the molecular chaperone Hsp90 with *in vivo* antitumour activity in human melanoma cells (Figure 3).^[5] Moreover, isoindoline-1-carboxylic acid has been useful in the design of analogues of indapamide, a diuretic agent used in the therapy of hypertension.^[6] Its sterically constrained structure has been valuable in structure-activity relationship studies for the design of inhibitors –or activators –of different receptors for the development of therapeutic approaches targeting hypertension,^[7] inflammation,^[8] or autoimmune^[9] and neurodegenerative diseases.^[10] Furthermore, its use as a surrogate of proline has contributed to enhancement of the selectivity properties of human PPAR δ agonists (Figure 3), which are considered promising leads for drugs for the treatment of diabetes, obesity or atherosclerosis.^[11]

Figure 3. Isoindoline-1-carboxylic acid derivatives with pharmacologically important properties.

More lipophilic bicyclic proline analogues that bear a saturated ring fused to the [c] face of the pyrrolidine make up the core structures of compounds under investigation for potential applications in diseases characterized by joint cartilage damage.^[12] These analogues have also found application in structure-activity relationship studies for the design of inhibitors of angiotensin converting enzyme,^[13] hepatitis C virus NS3 protease,^[14] and rhinovirus 3C protease,^[15] which are associated with hypertension, hepatitis, and human rhinovirus infections, respectively. In addition, *cis*-methano-L-proline is a component of peptidomimetic inhibitors of the transcription factor Stat3, an attractive target for anticancer drug design,^[16] and both stereoisomers of methano-L-proline are growth-inhibitory to bacteria.^[17] Moreover, *cis*-fused methano-L-proline bearing a carboxylic acid moiety attached to the cyclopropane ring is a known blocker of excitatory amino acid transporters that plays a major role in neurotransmission.^[18]

In view of the enormous potential of proline analogues of this type and the growing interest in them, we wish to illustrate available methods for the synthesis of the family of [c]-fused bicyclic proline derivatives depicted in Figure 1. Attention is paid both to procedures that afford the desired compounds in racemic form and to asymmetric strategies. The diverse approaches are arranged according to the size of the carbocycle that is fused to the [c] face of proline and are grouped by synthetic methodologies. Because of the abundant literature in the field, synthetic strategies leading to proline analogues that bear heterocyclic rings fused to the [c] face of the pyrrolidine moiety are not included.

2. Synthesis of six-membered ring [c]-fused proline analogues

2.1. Synthesis of isoindoline-1-carboxylic acid derivatives

Various synthetic procedures for the preparation of isoindoline-1-carboxylic acid have been described in the literature, most of them dealing with the preparation of its racemic form. Some methods involve the α -carboxylation of a nitrogenated bicyclic precursor (Figure 4, type A substrates), either through an electrophilic alkylation or through nucleophilic acylation. Alternatively, a number of strategies involve the construction of the pyrrolidine ring through intramolecular C–N or C–C bond-forming reactions (Figure 4, type B substrates). In addition to those routes, cycloaddition reactions have provided access to polyfunctionalized isoindoline-1-carboxylic acid analogues with high degrees of stereocontrol.

Figure 4. Precursors used for the synthesis of isoindoline-1-carboxylic acid derivatives.

2.1.1. α -Functionalization of isoindoline derivatives

In 1990, Beeley and Rockell reported the preparation of isoindoline-1-carboxylic acid by α -metallation of suitably protected isoindoline **4** (Scheme 1).^[19] In turn, the starting precursor **3** can be synthesized by treating *p*-tolylsulfonamide^[20] or hexamethylene tetramine^[21] with a dihalogenated *o*-xylylene, by reduction of phthalimide with borane tetrahydrofuran complex,^[20] or through cycloaddition reactions.^[22] Treatment of formamidine **4** with *sec*-butyllithium, followed by addition of ethyl chloroformate as the electrophile, afforded **5** in moderate yield. The acylation reaction was reported to require a large excess of the electrophile to minimize the generation of the 1,1-di(ethoxycarbonyl) derivative through deprotonation of the monoalkylated product. In addition, the asymmetric α -deprotonation of isoindoline **3** has been accomplished with chiral oxazoline^[20] or formamide^[21] auxiliaries as precursors. However, only alkyl and benzyl halides have been tested as the electrophiles.

Scheme 1.

Interestingly, lithiation of the doubly benzylic position of the *tert*-butylformamidine generated from racemic **6** (Scheme 1) provided an α -amino carbanion at the bridgehead position that was remarkably stable even at room temperature.^[23] Addition of ethyl chloroformate to this anionic species proceeded smoothly, and subsequent acidic hydrolysis provided amino ester **7**, which can be seen as a bicyclic analogue of isoindoline-1-carboxylic acid. The interest in this type of compounds stems from the fact

that MK-801 (Scheme 1) is a potent and selective ligand for brain phencyclidine (PCP) receptors that possesses both anticonvulsant and neuroprotective properties *in vivo*.^[23b]

More recently, Sato et al. reported the preparation of **9** (Scheme 2) through carboxylation of stannane **8**, which was in turn generated from *N*-Boc-protected isoindoline (*N*-Boc-**3**) by α -lithiation and subsequent electrophilic substitution with tributyltin chloride. The carboxylation of **8** occurred under carbon dioxide in the presence of caesium fluoride as a mild tin activator.^[24]

Scheme 2.

2.1.2. α -Functionalization of isoindolinone derivatives

The utility of isoindolinone **10** as a precursor for the preparation of racemic isoindoline-1-carboxylic acid **13** has recently been demonstrated (Scheme 3).^[25] The procedure involved the reduction of the lactam carbonyl group in **10** with diisobutylaluminum hydride to obtain an intermediate hemiaminal, which was immediately transformed into the corresponding methoxyaminal. Subsequent treatment of **11** with trimethylsilyl cyanide in the presence of boron trifluoride etherate yielded compound **12**, which was hydrolyzed to furnish isoindoline-1-carboxylic acid as the hydrochloride salt. The high yield of each individual step and the easy accessibility to the starting isoindolinone makes this synthetic methodology quite effective. In fact, a substantial number of strategies for the preparation of isoindolinones have been developed;^[26,27] they include reductive amination and intramolecular amidation of 2-carboxybenzaldehyde and amines,^[26b] Curtius rearrangement of an acyl azide derived from homophthalic acid,^[26c] palladium catalysed carbonylative cyclization of 2-bromobenzaldehyde with a primary amine,^[26d] reduction of phthalimide,^[26e,f] and dephosphonylation of 3-oxoisoindolin-1-ylphosphonates obtained by one-pot reaction of 2-formylbenzoic acid with amines and dimethylphosphite.^[26a]

Scheme 3.

In addition, the asymmetric synthesis of isoindoline carbamates (Scheme 3, **15**) was successfully achieved through an enzyme-mediated dynamic kinetic resolution process of **14**.^[25] This strategy employed *Pseudomonas cepacia* lipase (PSL-C I) as biocatalyst and avoided the use of metal or acid-base catalysis for the racemization of the substrate. Specifically, optically active carbamates **15** were obtained in good yield and excellent degree of enantioselectivity in alkoxycarbonylation reactions with diallyl or dibenzyl carbonates.

2.1.3. Intramolecular cyclization through C–N bond formation

Some of the methodologies developed for the synthesis of dihydroisoindole-1-carboxylic acid derivatives are based on the construction of the pyrrolidine ring by intramolecular C–N bond formation. Reactions between α -bromophenyl acetates, such as **16** (Scheme 4), and primary amines or hydrazines furnished dihydroisoindole-1-carboxylates.^[7,28] These proved to be highly sensitive to air, thus requiring isolation as their hydrochloride salts. In particular, isoindoline **14** was obtained by catalytic hydrogenolysis of the *N*-benzyl derivative **17b**, but it was also sensitive to air. The use of phenylhydrazine as the nucleophile furnished **17d** in only 24% yield due to concomitant formation of the corresponding isoindole.^[29] Conversely, condensation between **16** and

tert-butyl carbazate afforded **17e**, which was then converted into the corresponding aminoisoindoline upon acidic treatment.^[6]

Scheme 4.

More recently, Scherkenbeck et al. reported the preparation of **20** (Scheme 5) as a simplified analogue of the alkaloid cyclopiazonic acid, which is an attractive lead for the development of antimalarial drugs and plant protection.^[30] The cyclization of isopropenylated phenylglycine **19** was achieved by treatment with triflic acid. The protonation of the double bond generated a benzylic cation that was then attacked by the amino function. Therefore, a strongly electron-withdrawing protecting group was required for the nitrogen atom in order to prevent its protonation during the generation of the cationic species. A subsequent two-step deprotection/reprotection sequence provided access to racemic **20** in gram quantities.

Scheme 5.

2.1.4. Intramolecular cyclization through C–C bond formation

A different cyclization strategy for the synthesis of dihydroisoindole-1-carboxylic acid derivatives was described by Buchwald and Gaertzen (Scheme 6).^[31] The pyrrolidine ring formation was achieved through palladium-catalysed intramolecular α -arylation of α -amino acid esters **21**. The reaction conditions were optimized in terms of base, solvent, metal source and ligand. It was found that catalysts based on biphenyl aminophosphines provided better results than those based on trialkyl- or triarylphosphine ligands with regard to yield and reaction rate. According to the authors, this could be related to the fact that the biphenyl backbone provides a weak coordination site to the metal, either through the amino group or through the arene itself.

Scheme 6.

In a related approach, Solé and Serrano reported palladium-catalysed intramolecular α -arylation reactions of (2-iodobenzyl)amino acid esters **23** that allowed the selective synthesis of either isoindolines **25** or of the corresponding isoindole-1-carboxylates **24** in a very efficient manner (Scheme 7).^[32] In particular, isoindoles **24** were the result of a palladium-catalysed cascade that involved enolate arylation and dehydrogenation of the initially formed isoindoline. Interestingly, analogous aryl bromides or aryl triflates were less efficient than aryl iodides in the α -arylation reaction, being either completely unreactive or unstable, respectively.

Scheme 7.

2.1.5. Cycloaddition reactions

As previously mentioned, cycloaddition reactions have provided access to polyfunctionalized isoindoline-1-carboxylic acid analogues with high degrees of stereocontrol. Durst et al. described that azaallyllithium species **27** (Scheme 8) reacted with benzyne to furnish a 1,3-dihydroisoindole through a [3+2] cycloaddition when the reaction was quenched after a short reaction time at low temperature (3 h, –78 °C).^[33] It was suggested by the authors that the formation of a single stereoisomer of **28** with a *cis* relationship between the ethoxycarbonyl group and the 3-alkyl substituent is consistent with a concerted cycloaddition involving an azaallyllithium species that exhibits lithium complexation to both oxygen and nitrogen atoms. It was also observed that dihydroisoindole **28** rearranged to (2*H*)-isoquinolin-3-one **29** on prolonged exposure of **26** to base at temperatures above 0 °C.^[33]

Scheme 8.

More recently, [4+2] cycloaddition reactions between 1,3-disubstituted isoindoles and alkynes or benzyne (Scheme 9) have provided access to complex dihydroisoindole-1-carboxylic acid derivatives, such as **31** and **32**, in good yields.^[34] These adducts have

proved to be ideal precursors for the preparation of aromatic hydrocarbons through an oxidative deamination process.

Scheme 9.

In this context, several authors have demonstrated the utility of azomethine ylide dipoles for the synthesis of isoindoline-1-carboxylic acid derivatives.^[35] Gong et al. reported the use of ylides generated by activation of azomethines with chiral phosphoric acids (Scheme 10).^[35c] For example, the reaction between quinone and the azomethine ylide generated from *p*-nitrobenzaldehyde and *p*-chlorophenylglycine methyl ester, followed by a base-promoted isomerization, was reported to furnish isoindoline **35** in good yield and with good enantioselectivity. Similarly, Wang et al. described a one-pot approach to enantioenriched isoindolines **38** (Scheme 10), each also containing a quaternary stereogenic centre, through highly efficient Cu(I)-catalysed 1,3-dipolar cycloaddition of azomethine ylides and quinone derivatives, followed by silica-gel-promoted aromatization. The absolute configuration of one adduct was determined by X-ray crystallographic analysis of a single crystal, and those of other adducts were tentatively proposed on the basis of that result.^[35d]

Scheme 10.

Dixneuf and Osipov employed cycloaddition reactions of unsaturated α -trifluoromethyl amino acid esters to assemble the aromatic ring of the isoindoline scaffold (Scheme 11). On one hand, α -alkynyl amino acid ester **39** allowed access to a five-membered ring by enyne metathesis performed with a ruthenium-allenylidene complex.^[36] The resulting α -trifluoromethylated proline derivative containing a diene moiety underwent a Diels-Alder reaction followed by aromatization upon treatment with DDQ. On the other hand, ruthenium-catalysed cyclotrimerizations were achieved with suitable 1,6-diynes, such as **42**, and acetylene.^[37]

Scheme 11.

2.2. Synthesis of octahydroisindole-1-carboxylic acid derivatives

A number of strategies have been devised for the preparation of octahydroisindole-1-carboxylic acid derivatives with either *cis* or *trans* relative dispositions of the hydrogen atoms at the ring junction. Strategies that give access to *cis*-fused octahydroisindole-1-carboxylic acid derivatives involve the hydrogenation of isoindole or isoindolinone precursors, as well as the activation of the C–H bond α to the nitrogen atom in *cis* [*c*]-fused bicyclic pyrrolidines (Figure 5, type A substrates). In addition, intramolecular radical cyclizations of α -(phenylthio)glycine derivatives or cycloaddition reactions of pyroglutamate derivatives (type B substrates) also preferably furnish *cis*-fused bicyclic systems. On the other hand, the *trans* relative disposition of the hydrogen atoms at the ring junction has been accomplished through reductive cyclization of cyclohexane derivatives exhibiting *trans* relative disposition of appropriate carboxylic acid and amine substituents (substrates C).

Figure 5. Precursors used for the synthesis of octahydroisindole-1-carboxylic acid derivatives

2.2.1. Synthesis from isoindoline-1-carboxylic acid derivatives

Racemic octahydroisindole-1-carboxylate **45a** has been synthesized by hydrogenation of the isoindole precursor (Scheme 12).^[13] The use of rhodium on charcoal as a catalyst provided a single stereoisomer in good yield after recrystallization. It was tentatively presumed by the authors that the hydrogen atoms at the chiral centres have a *cis* relationship as a result of the hydrogenation taking place on the less hindered face of the molecule. Similar hydrogenations provided access to ethyl, and *tert*-butyl ester derivatives. Later, the chemical resolution of the ethyl ester derivative by using (1*S*)-(+)-10-camphorsulfonic acid was indicated in a patent,^[12] but no details regarding the efficacy of the process were provided. In the same way, catalytic hydrogenations of **44b**^[30] and **44c**^[38] led to the exclusive formation of **45b** and **45c** as single stereoisomers.

Scheme 12.

2.2.2. Synthesis from 3-oxo-1*H*-isoindolin-1-carboxylic acid derivatives

The *cis*-fused octahydroisindole-1*H*-carboxylic acid system has also been constructed in a straightforward manner from methyl 3-oxo-1*H*-isoindolin-1-carboxylate **46** (Scheme

13).^[39] The four-step procedure for the stereoselective synthesis of **49** started with the hydrogenation of **46** under hydrogen (atmospheric pressure) in the presence of platinum oxide as a catalyst. This treatment provided a 96:4 ratio of stereoisomers, **47** and **48**. The major stereoisomer was isolated by column chromatography and the relative *cis* orientation of the two bridgehead hydrogen atoms with respect to that at the carbon α position was established by NMR experiments. Subsequent protection of the amino function in isolated **47** improved the electrophilic nature of the lactam carbonyl group and allowed its reduction to a methylene group by sequential treatment with diisobutylaluminum hydride and triethylsilane.

Scheme 13.

This methodology is quite convenient because many approaches to the preparation of isoindolinone precursors have been described in the literature.^[40,41,42] The preparative pathways for such isoindolinones (Scheme 14) include the nucleophilic attack of 3-metalated isoindolines onto carbon dioxide (path a),^[40a] and the addition of nitrogen equivalents to phthalonic acid (path c),^[40b] phthalaldehydic acid (path d)^[40c] or diethyl α -bromohomophthalate (path e).^[40d] Specifically, compound **46** (Scheme 13) was obtained by carbonylation of an orthopalladated complex generated from a phenylglycine derivative (Scheme 14, path b).^[40e,f]

Scheme 14.

In addition, octahydroisoindolinone **48** (Scheme 13) was synthesized through a 5-*endo-trig* dearomatizing anionic intramolecular cyclization of a lithiated benzamide precursor.^[43] Interestingly, stereospecific lithiations of more complex benzamides have provided access to octahydroisoindolinone derivatives that have proven valuable intermediates for the synthesis of analogues of kainic and domoic acids.^[44]

2.2.3. α -Functionalization of octahydro-(1*H*)-isoindole derivatives

Turner et al. described the enantioselective synthesis of **51** (Scheme 15), a useful precursor of octahydroisoindole-1-carboxylic acid, through direct activation of the C–H bond α to the nitrogen atom in pyrrolidine **50**.^[45] The process involved the use of the biocatalyst MAO-N D5 (monoamine oxidase from *Aspergillus niger*) and molecular oxygen for the generation of an intermediate enantiopure Δ^1 -pyrroline. This compound underwent nucleophilic addition in the presence of cyanide and provided a diastereomeric mixture of α -amino nitriles, which were converted to trifluoroacetamides. The diastereoselectivity achieved during the nucleophilic addition was reported to be strongly dependent on the reaction conditions. In buffered aqueous medium the addition of cyanide to the Δ^1 -pyrroline occurred with high diastereoselectivity (*dr* 82:18) and preferentially furnished **51**, with a *trans* relative disposition between the nitrile group and the six-membered cycle. In addition, the authors reported that MAO-N D5 displayed good activity towards a range of substituted pyrrolidines. In general, increasing the pyrrolidine bulk and lipophilicity correlated with higher rates of oxidation.

Scheme 15.

The introduction of the carboxylic acid moiety α to the amine function by means of a chemical oxidative process followed by nitrile addition had previously been reported.^[38,46] In particular, oxidation and α -cyanation of pyrrolidine **52** (Scheme 16) afforded nitrile **53**, which after hydrolysis gave amino acid **54** as the only stereoisomer.^[38] Similarly, pyrrolidine **55** furnished **56** accompanied by trace amounts of the other stereoisomer, which was removed by chromatography following a *N*-methylation.^[38] The structural assignment, based on NMR experiments, determined that in both cases the rigid structure forced the nitrile anion to attack the nitron intermediate from the *si* face of the double bond.

Scheme 16.

Alternatively, the octahydroisindole-1-carboxylic acid system has been assembled through *N*-Boc-directed lithiation of a pyrrolidine followed by carboxylation. In particular, Kotsuki et al. described the preparation of enantiomerically pure anthracene-fused proline analogues, **59** and **60** (Scheme 17).^[47] The lithiation of *N*-Boc protected pyrrolidine **57** gave amino acid **58** as a mixture of *endo*- and *exo*-isomers. Their treatment with (–)-menthol gave a diastereomeric mixture of menthyl esters that underwent isomerization quite smoothly to furnish the more stable *exo* isomers. Removal of the *N*-Boc protecting group gave nearly equal amounts of free amino menthyl esters that were

isolated by column chromatography. Alkaline hydrolysis of the menthyl esters provided enantiopure **59** and **60**, which were used as organocatalysts.^[47] Their stereochemistry was unambiguously established by X-ray crystallographic analysis of the menthyl ester derivative of **60**.

Scheme 17.

2.2.4. Intramolecular cyclization through C–N bond formation

Reductive intramolecular cyclization of **61** and **64** has been employed for the preparation of racemic octahydroisindole-1-carboxylic acid derivatives **63** and **66**, which are *cis*- and *trans*-fused bicyclic prolines, respectively (Scheme 18).^[38] In the synthesis of **63**, compound **62** was obtained as a mixture of stereoisomers. The ring junction was set in the disposition depicted in **63** during the alkylation of **62**. Subsequent reduction of the lactam carbonyl group, and treatment of the aminoacetal with a Lewis acid, afforded an acyl iminium species that underwent attack by the nitrile anion exclusively from the *si* face. Similar elaboration of *gem*-dimethyl-substituted **65**, with a *trans* ring junction, provided **66** as the only isomer. In this case, the nitrile anion attacks from the *re* face of the intermediate acyl iminium species. Presumably, the attack from the *si* face is not favoured due to axial interactions with a methyl group and the hydrogen atom at the ring junction.

Scheme 18.

Gais et al. described the asymmetric synthesis of bicyclic proline **74**, with a *cis* relative disposition between the carboxylic acid ester group and the six-membered ring, by making use of a migratory cyclization procedure (Scheme 19).^[48a] Treatment of enantiomerically pure allylic sulfoximine **67** with $n\text{BuLi}$ and $\text{ClTi}(\text{OiPr})_3$ afforded bis(allylsulfoximine)titanium complex **68**, which underwent addition to a sulfonyl imino ester to furnish a mixture of **69** and **70** with high regio- and diastereoselectivity. Activation of the *N*-methyl sulfoximine group of **70** afforded sulfoxonium salt **71**. The migratory cyclization took place through isomerization of the double bond in **71**. The allylic sulfoxonium salt **72** underwent an intramolecular substitution of the sulfoxonium group that provided bicyclic proline **73**. Finally, cleavage of the *tert*-butylsulfonyl protecting group under acidic conditions furnished **74** in enantio- and diastereomerically

pure form. Alternatively, allylic chloride **75** was obtained from **70** when a chloroformate was used for the activation and migratory substitution.^[48b] Subsequent treatment of **75** with DBU gave proline derivative **76** in practically quantitative yield.

Scheme 19.

2.2.5. Intramolecular cyclization through C–C bond formation

The preparation of racemic *cis*-fused octahydroisindole-1-carboxylic acid derivatives **78** and **79** has been accomplished through the reductive intramolecular cyclization of α -

(phenylthio)glycines **77**, each bearing a 3-alkenyl substituent at the nitrogen atom (Scheme 20).^[49] The treatment of **77a** with tributyltin hydride and a catalytic amount of AIBN in toluene solution at 80–90 °C produced a captodative radical that preferentially underwent a 5-*exo* intramolecular cyclization. Similar results were observed in the copper(I)-catalysed chlorine transfer radical cyclization of α -chloroglycine **77b**.^[50] In this case, the authors suggested the cyclization of an incipient free radical. The copper complex acts as a carrier of the chlorine atom by way of a redox reaction.

Scheme 20.

2.2.6. Cycloaddition reactions

A variety of procedures for the preparation of the bicyclic octahydroisindole-1-carboxylic acid skeleton make use of cycloaddition reactions. Diels-Alder reactions of pyrrolutaminol or proline derivatives provided access to the bicyclic skeleton with *cis* relative disposition of the hydrogen atoms at the ring junction.^[14a,51] For example, treatment of **80** with cyclopentadiene was reported to furnish **81** in 67% yield (Scheme 21). Unfortunately, details relating to the stereochemical outcome of the cycloaddition step, as well as the effectiveness of the subsequent transformations to obtain **82**, were not provided by the authors.^[14a]

Scheme 21.

More recently, Poisson et al. described the high-pressure-promoted Diels-Alder cycloaddition of dehydroproline derivative **83** and Danishesfsky's diene (Scheme 22).^[51] According to the authors, an enormous effect of pressure on the rate of racemization of **83** was observed. As a consequence, it was essential to remove traces of triethylamine contained in the diene in order to preserve the enantiomeric excess of the product. The cycloaddition was face-selective, with the stereochemical outcome governed by the ester group in the α position, and furnished **84** with a 3:1 *endo/exo* ratio of the methoxy group in the cycloadducts. This mixture was converted into **85**, which was isolated with an *ee* better than 99% upon recrystallization. Next, base-induced monodecarboxylation of **85** and exposure of the product to diazomethane produced a nonconjugated ketone that was subsequently converted into conjugated enone **86** by treatment with DBU. The assumption of the *cis* ring fusion in **86**, from the DBU-induced transformation, was shown to be correct through its successful conversion into (–)-kainic acid.

Scheme 22.

In addition, the construction of the octahydroisindole-1-carboxylate scaffold embedded in a fused tricyclic system by means of an intramolecular Diels-Alder reaction has also been reported.^[52]

Alternatively, [3+2]-cycloadditions between azomethine ylides and dipolarophiles such as cyclic α,β -unsaturated ketones, quinones or alkenes have provided access to *cis*-fused polyfunctional octahydroisindole-1-carboxylic acid derivatives.^[53] For example, silver-catalysed cycloadditions of **87** to cyclohexadione lactone **88** in the presence of a chiral

catalyst provided compounds **89** in high yields and with excellent levels of diastereo- and enantioselectivity (Scheme 23).^[53g]

Scheme 23.

On the other hand, aziridine-allylsilane **92** (Scheme 24) underwent an intramolecular formal [3+2] cycloaddition reaction that preferentially gave access to the bicyclic skeleton with *trans* relative disposition of the hydrogen atoms at the ring junction.^[54] This aziridine-allylsilane was synthesized by treatment of **91** with the cuprate derived from iodide **90**. The intramolecular cyclization occurred upon treatment of **92** with a catalytic amount of $BF_3 \cdot Et_2O$ in dichloromethane, and provided an isomeric mixture of **93** and **94** contaminated with olefin **95**. According to the authors, the stereochemical integrity during the S_N2 -type intramolecular displacement of the optically pure aziridine with the allylsilane was very high. Column chromatography of the mixture allowed for the ready separation of the *cis*- and *trans*-fused bicycles and their stereochemistry was assigned by NMR experiments. The preparation of *trans*-fused octahydroisindole-1-carboxylic acid **96** was accomplished by oxidation of silane **93** to carboxylic acid in two steps, followed by removal of the amino protecting group.

Scheme 24.

2.2.7. Miscellaneous

An approach to *trans*-octahydroisindole derivative **98** through Favorskii-type ring contraction of α -chlorinated lactam **97** was described by Henning and Urbach (Scheme 25).^[55] The rearrangement of **97** on treatment with barium hydroxide in aqueous solution afforded **98** in isomerically pure form. According to the authors, the stereoselectivity achieved reflects the thermodynamic equilibrium between the two isomers that can be established under the strongly basic reaction conditions. The *trans* disposition between the carboxylic acid group and the six-membered ring in **98** makes this isomer more stable than the one exhibiting a *cis* relative disposition.

Scheme 25.

3. Synthesis of five-membered ring [c]-fused proline analogues

Nearly all the strategies previously described for the synthesis of *cis*-fused octahydroisindole-1-carboxylic acid derivatives (Figure 5) have also been applied to the preparation of 3-azabicyclo[3.3.0]octane-2-carboxylic acid homologues. In addition, abundant contributions have been made in the field of intramolecular and intermolecular cycloaddition reactions for the stereoselective and asymmetric preparation of polysubstituted *cis*-fused 3-azabicyclo[3.3.0]octane-2-carboxylic acid derivatives.

3.1. Synthesis from 3-azabicyclo[3.3.0]octane derivatives

The strategy based on the enantioselective biocatalytic oxidative desymmetrization of a bicyclic pyrrolidine (see Scheme 15), followed by nucleophilic addition of cyanide, has also been applied to the synthesis of five-membered ring [c]-fused proline derivatives (Scheme 26).^[45,56] Thus, the use of the biocatalyst MAO-N D5 and molecular oxygen for the oxidation of **99** provided the imine **100** in 94% *ee*. Treatment of the organic extracts of the biotransformation with TMSCN/MeOH in dichloromethane afforded a 96:4 diastereomeric mixture of α -amino nitriles with isomer **101** as the major product. Their hydrolysis led, after ion exchange chromatography and recrystallization, to **1** in a *dr* of 150:1 and 98% *ee*. The combination of the biocatalytic desymmetrization of *cis* [c]-fused pyrrolines with a three-component Ugi reaction has been recently applied to the highly stereoselective synthesis of substituted prolyl peptides.^[57]

Scheme 26.

Previously, a patent by Tanoury et al. had described^[58] the preparation of **105** through lithiation and carboxylation of **102**, followed by chemical resolution with (*S*)-1,2,3,4-tetrahydro-1-naphthylamine (Scheme 27). Subsequent processing of **104** gave oxalate salt **105** with an enantiomeric excess of 99%.

Scheme 27.

3.2. Intramolecular cyclization through C–N bond formation

The chiral phase-transfer-catalysed asymmetric conjugate addition of glycine derivative **106** to α,β -unsaturated aldehyde **107** gave an optically enriched α -amino acid ester that underwent intramolecular imine formation after hydrolysis of the amine protecting group (Scheme 28).^[59] Catalytic hydrogenation of the resulting imine **108** provided 3-azabicyclo[3.3.0]octane-2-carboxylate **109** as a single diastereoisomer.

Scheme 28.

3.3. Intramolecular cyclization through C–C bond formation

The preparation of racemic *cis*-fused 3-azabicyclo[3.3.0]octane-2-carboxylic acid derivatives **111a** and **112a** has been accomplished through the reductive intramolecular cyclization of α -(phenylthio)glycine **110a** (Scheme 29).^[49] In the same way as described previously for the homologous six-membered bicyclic proline analogue (see Scheme 20), treatment of **110a** with tributyltin hydride and a catalytic amount of AIBN in toluene solution at 80–90 °C generated a captodative radical that underwent cyclization to produce the *exo* stereoisomer preferentially. Similar results were also observed in the copper(I)-catalysed chlorine transfer radical cyclization of α -chloroglycine **110b**.^[50]

Scheme 29.

Alternatively, Bunch et al. demonstrated the utility of (*S*)-pyroglutaminol as precursor for the enantioselective synthesis of *cis*-fused bicyclic proline **116**, which can also be seen as a conformational restricted (*S*)-glutamic acid analogue (Scheme 30).^[60] The reaction between **80** and the cuprate generated from vinyl bromide **113** set the desired absolute stereochemistry in **114**. Subsequent removal of the *p*-methoxybenzyl group, followed by conversion of the free alcohol to a phenylsulfonic ester, allowed for cyclization into **115**. Hydroboration of the methylidene group in **115** gave a high degree of facial selectivity with use of Wilkinson's catalyst/catecholborane (*dr* 90:10). Further reduction of the lactam carbonyl group, alcohol oxidation and nitrogen deprotection provided the target compound in 99% *ee* after recrystallization of the diastereomeric mixture.

Scheme 30.

3.4. Cycloadditions

Unsaturated lactam **117**, which is derived from (*S*)-pyroglutaminol, proved to be an excellent substrate for a palladium-assisted trimethylenemethane [3+2] cycloaddition reaction (Scheme 31).^[61] The treatment of the silylated allylic acetate **118** with $\text{Pd}[\text{P}(\text{O}i\text{Pr})_3]_4$, generated in situ with palladium(II) acetate and tri(isopropyl)phosphite, produced trimethylenemethane that underwent a totally regioselective and stereoselective cycloaddition with **117**. The resulting tricyclic lactam **119** was subjected to cyclopropanation of the double bond, *N,O*-benzylidene acetal deprotection, lactam

reduction, and protective and oxidative treatment of the nitrogen and alcohol, respectively, thus affording proline analogue **120**.

Scheme 31.

An intramolecular version of this type of cycloaddition was employed by Shirama et al. for the preparation of related 3-azabicyclo[3.3.0]octane-2-carboxylic acid derivatives featuring an exocyclic double bond attached to the carbocyclic ring.^[62]

In 2003, Arawaka et al. described the synthesis of **123** starting from enantiopure dehydropoline **121** (Scheme 32).^[63] A Diels-Alder reaction of **121** with cyclopentadiene afforded **122** as a single stereoisomer. This cycloadduct was smoothly converted to **123** by ruthenium tetroxide oxidation. Although some racemization of the starting material was observed during the synthetic process, the amino acid **123** isolated after recrystallization proved to be optically pure.

Scheme 32.

The bicyclic skeleton of 3-azabicyclo[3.3.0]octane-2-carboxylic acid has also been assembled through intramolecular cycloaddition reactions.^[54,64] Contrary to what had

previously been observed for the synthesis of octahydroisindole-1-carboxylic acid (see Scheme 24), the intramolecular formal [3+2] cycloaddition reaction of aziridine-allylsilane **124** (Scheme 33), by treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$, gave the bicyclic skeleton with the *cis* relative disposition of the hydrogen atoms at the ring junction as the major compound.^[54] Column chromatography gave diastereomerically pure **125**. Its treatment with mercury (II) acetate gave an alcohol derivative that was further oxidized to provide **127**.

Scheme 33.

In addition, azabicyclooctanones **130** have been synthesized through iron-mediated intramolecular cycloadditions (Scheme 34).^[64] The addition of protected amino acids to $(\eta^5\text{-pentadienyl})\text{Fe}(\text{CO})_3$ cations gave $(\eta^4\text{-dienylamine})\text{Fe}(\text{CO})_3$ complexes **128**. These in turn provided azabicyclooctanones **130** upon treatment with LDA at -78°C under carbon monoxide. The authors suggested that the formation of compounds **130** as single diastereoisomers arise from *anti* addition of the α -face of enolate **129** at the internal position of the diene.

Scheme 34.

Intramolecular Pauson-Khand cycloaddition of optically pure enyne amino acid derivatives has provided access to enantiopure 3-azabicyclo[3.3.0]octane-2-carboxylic acid derivatives such as **133** and **135** (Scheme 35).^[65a] It was observed that enynes **131** and **132** both gave **133** as a single isomer; that is, the vinyl part of the starting enyne amino acid ester does not control the configuration of the resulting cycloadduct. The starting amino acid esters were synthesized by Mannich-type reaction of phenylethenylboronic acid, chiral *N*-propargylamines and glyoxylic acid. Interestingly, optically pure lactone **134**, which is easily obtained from (*S*)-*N*-2-propargyl-2-phenylglycinol, underwent the Pauson-Khand cycloaddition in high yield.

Scheme 35.

Subsequently, Brummond et al. studied the Pauson-Khand cycloaddition of allenynes **136** in the presence of molybdenum hexacarbonyl (Scheme 36).^[65b-d] It was found that amino acids with aromatic side chains (Entries a and b) afforded azabicycles with opposite diastereoselectivity in comparison with amino acids with aliphatic side chains (Entries c and e). The reversal in diastereoselectivity was attributed to different complexation models of the substrate with the transition metal (complexation models A and B). In the case of the aromatic side chains, the complexation of the aryl ring with the metal places the ester group in a pseudoequatorial position, whereas aliphatic substituents reside preferentially in such a pseudoequatorial orientation. In all cases the bicyclic compounds **139** were obtained as byproducts. Substrates **137** (entries a-b) and **138** (entries c-e) have found utility for the preparation of tricyclic pyrrole libraries for biological tests.^[65c,d]

^a determined by ¹H NMR

Scheme 36.

In 1994, Monn and Valli reported the stereocontrolled preparation of azabicyclooctanone **144** through cycloaddition between an azomethine ylide and 2-cyclopentenone (Scheme 37).^[66] The required ylide was generated *in situ* from thiazolium

bromide **140** and triethylamine. The cycloaddition reaction provided a diastereomeric mixture of tetracycles that were not separated because the thiotetrahydrofuranyl portion was excised in a later step. The stereochemical outcome of the cycloaddition was attributed to thiazolium ylide **141** reacting in the conformation depicted. The alternative conformation, in which the ester is placed in proximity to the adjacent methyl substituent, is less favourable due to $A^{1,3}$ -strain. The relative stereochemistry of substituents was established by single-crystal X-ray analysis of azabicyclooctanone **144**, obtained by reductive cleavage of the thiazolidine C–S bond in **142** and **143**, followed by hydrolysis of the resulting hemiaminal and protection of the nitrogen atom. A number of selective transformations of the oxo moiety in **144** have afforded access to **145**,^[66] **147**,^[14b,15] and fluorinated **148**.^[14b,15,38]

Scheme 37.

More recently, the application of asymmetric 1,3-dipolar cycloadditions of azomethine ylides derived from iminoesters for the preparation of the 3-azabicyclo[3.3.0]octane-2-carboxylic acid skeleton has been reported. The protocols are based on the use either of

chiral dipolarophiles^[67] (Scheme 38) or of chiral catalysts^[68] (Scheme 39) and give access to *cis*-fused bicyclic proline analogues with high enantiocontrol. In particular, α -sulfinylcyclopentenone **149** reacted with the ylide generated by treatment of **150a** with DBU in the presence of a silver salt in a completely regio and *endo*-selective manner but with low facial selectivity (Scheme 38, entry a).^[67] In contrast, the use of LHMDS as a base afforded **151** in high yield. The authors assumed that this reaction takes place by a nucleophilic/ring closure process in which the lithium acts as a tether between the reagent and the substrate in a way that is essential for achieving complete stereoselectivity. Adducts **151** (entries b-e) were transformed into 6-oxo-3-azabicyclo[3.3.0]octane-2-carboxylic acid derivatives through hydrogenolysis of the C–S bond with Raney nickel.

entry	Ar	R	conditions	yield (%) ^b		
				151	152	152
a	Ph	H	A	52:48 ^a	42	38
b	Ph	H	B	>98:<2 ^a	89	-
c	Ph	Me	B	>98:<2 ^a	91	-
d	2-Naph	H	B	>98:<2 ^a	93	-
e	2-Naph	Me	B	>98:<2 ^a	91	-

^a determined by ¹H NMR from the crude reaction mixture

^b homochiral integrity was supported by comparison of [α]_D values of enantiomers resulting from desulfinylation of **151a** and **152a**

Scheme 38.

Alternatively, Carretero et al. reported cycloadditions between azomethine ylides derived from iminoesters **153** (Scheme 39, entries a-d) and cyclopentenone in the presence of Cu^I-Fesulphos complex as a catalyst.^[68a] The reactions between *N*-aryl imines of glycine methyl ester (entries a-d) and 2-cyclopentenone catalysed by the cationic Cu^I complex of **156** afforded the bicyclic adducts with high *endo* selectivity, enantioselectivity and chemical yield. Only the electron rich imine derived from *p*-methoxybenzaldehyde (entry d) showed a lower reactivity and stereochemical control.

entry	Ar	conditions	<i>exo:endo</i>	155		ref.
				yield (%)	<i>ee</i> (%) ^d	
a	Ph	A	10:90 ^{a,b}	70	94	68a
b	2-Naph	A	2:98 ^{a,b}	61	91	68a
c	4-BrC ₆ H ₄	A	2:98 ^{a,b}	68	95	68a
d	4-MeOC ₆ H ₄	A	25:75 ^a	52	85	68a
e	2-ClC ₆ H ₄	B	– ^c	93	>99	68b
f	4-FC ₆ H ₄	B	– ^c	82	>99	68b
g	4-NO ₂ C ₆ H ₄	B	– ^c	82	>99	68b
h	4-MeOC ₆ H ₄	B	– ^c	86	99	68b
i	2-Thienyl	B	– ^c	82	>99	68b
j	2-Naph	B	– ^c	89	>99	68b
k	4-ClC ₆ H ₄	C	– ^c	73	98	68c
l	2-Naph	D	2:98 ^a	72	94	68d

^a determined by ¹H NMR from the crude reaction mixture^b 5–10% of ring-opened Michael addition product was detected in the crude mixture^c only *endo* cycloadduct **155** was obtained^d determined by HPLC on a chiral column

Scheme 39.

More recently, chiral ferrocenyl *P,S* ligands **157** and **158** have been successfully applied in asymmetric 1,3-dipolar cycloadditions between azomethine ylides **153** (Scheme 39, entries e–k) and cyclopentenone.^[68b,c] Both ligands provided copper-complexes that effectively catalysed the cycloaddition to give the *endo* cycloadducts with complete enantiocontrol. In particular, when *P,S* ligand **157** was used, a substrate with an electron-withdrawing substituent (entry g) showed higher reactivity than one with an electron-donating group (entry h). Azomethine ylides derived from 2-thiophenecarbaldehyde (entry i) or 2-naphthalenecarbaldehyde (entry j) also proved to be suitable substrates and gave the *endo* cycloadducts in >99% *ee*.

3.5. Miscellaneous

Sançon and Sweeney reported the stereocontrolled formation of azabicyclooctene **161** through the sigmatropic rearrangement of an ammonium ylide generated from amine **160**

(Scheme 40).^[69] The authors suggested that the remarkably low temperature required for the rearrangement to proceed might be due to the rigidity of **160** that provides a preorganization of the *endo* transition state required for the key [2,3]-rearrangement.

Scheme 40.

4. Synthesis of four-membered ring [c]-fused proline analogues

The stereoselective synthesis of 2-substituted 3-azabicyclo[3.2.0]heptanes has been accomplished by the intramolecular [2+2]-photocycloaddition of vinylglycine derivative **162** (Scheme 41).^[70] The cycloaddition, which makes use of acetophenone as triplet sensitizer, gave a 2:1 mixture of compounds **163** and **164**, each exhibiting a *cis*-relative configuration of the hydrogen atoms at the ring junction. The relative configuration of the major diastereoisomer **163** was explained based on a preferred conformation of **162** that minimizes the 1,3-allyl strains and places the methoxycarbonyl group in a pseudoequatorial position.

Scheme 41.

In addition, the [2+2]-photochemical cycloaddition of ethylene to unsaturated γ -lactams is a straightforward methodology for the preparation of azabicycles that can be useful precursors towards the synthesis of four-membered ring [c]-fused proline derivatives. For example, the cycloaddition between enantiopure **80** and ethylene was reported to afford **165** in a stereoselective manner (Scheme 42).^[71a] Moreover, Aitken et al. described the synthesis of lactams **167** and **168** from enantiopure γ -lactam **166**.^[71b] A subsequent two-step deprotection-reprotection sequence provided access to *N*-Boc protected derivatives **169** and **170**.

Scheme 42.

Alternatively, polysubstituted 3-azabicyclo[3.2.0]heptane 2-carboxylic acids **173** and **176** (Scheme 43) have been synthesized through 1,3-dipolar cycloaddition between münchnone **172** and 1,2-dicyanocyclobutene,^[72] and by metal-promoted alkylation of lactone **174**, respectively.^[73] In the latter case, azalactones **175** were employed as nucleophiles for the ring opening of **174**. According to the authors, this process probably furnishes a carboxylic acid, which appears to undergo rupture of the azalactone moiety followed by cyclization to a lactam. The resulting cycloadducts were obtained with high diastereoselectivity (typically $\leq 10\%$ of the lactam epimeric at the quaternary centre was observed in crude reactions mixtures), thus making feasible the isolation of diastereomerically pure **176** in yields ranging 26-68%.

Scheme 43.

5. Synthesis of three-membered ring [c]-fused proline analogues

5.1. From 3-azabicyclo[3.1.0]hexane derivatives

Several methods for the synthesis of racemic and enantiomerically pure 3,4-methanoproline derivatives have been reported (Figure 6). The most general strategies, which involve the cyclopropanation of pyrrolidine derivatives (type B substrates) and the conversion of cyclopropane derivatives (type C substrates), have been reviewed previously.^[74] In recent years, very efficient procedures that make use of 3-azabicyclo[3.1.0]hexane derivatives (A) or natural products as starting materials have been developed, especially for the manufacture of *trans*-6,6-dimethyl-3,4-methano-L-proline, the key component of medically relevant drugs Boceprevir and Narlaprevir.^[3]

Figure 6. Precursors used for the synthesis of 3,4-methanoproline derivatives

The multigram preparation of enantiomerically pure *N*-Boc protected *cis*- and *trans*-3,4-methanoproline analogues has been accomplished by resolution of the racemates synthesized by lithiation of *N*-Boc protected 3-azabicyclo[3.1.0]hexane (Scheme 44).^[75] Lithiation of **177** in the presence of diamine **178** preferentially afforded **179** (*cis* stereoisomer). On the basis of *ab initio* calculations, the authors suggested that the unexpected *cis* selectivity was due to a more energetically favoured staggered conformation for the *cis* Li-**177**-diamine-**178** complex that was maintained through the CO₂-insertion mechanism. The *trans* stereoisomer was obtained by means of an epimerization process, that is, a double deprotonation of **177** with LDA, which afforded a 1:9 *cis/trans* ratio of stereoisomers. The enantioselective deprotonation of **177** with *sec*-BuLi and (–)-sparteine was tested but it resulted in only a 32% yield of **179** and 73% *ee*. Optical resolution of **179** and **180** was accomplished through diastereomeric salt formation (Scheme 44) or, alternatively, by chromatography of the benzyl ester derivative of the *cis* stereoisomer on a chiral stationary phase. In this case, epimerization of enantiomerically pure **181** gave access to enantiopure **180b** after hydrogenolysis. In order to avoid transformations of large batches of **181**, and to achieve good productivity of **180b**, a flow set-up reactor was employed for the epimerization step.

Scheme 44.

Previously, the synthesis of racemic *cis*- and *trans*-3,4-methanoproline derivatives by a procedure including a Strecker reaction, together with their chemical resolution, had been disclosed in patents.^[76a-c] More recently, an oxidative Strecker reaction that involves a chemoenzymatic process^[76d,e] has been developed for the manufacture of enantiomerically pure **186** (Scheme 45), the key structural feature of Boceprevir and Narlaprevir. The prochiral amine **182** was subjected to an enzymatic oxidative desymmetrization after had been improved the activity and thermal stability of MAON (from *Aspergillus niger*) over four rounds of evolution. An amino sulfonate was generated in the enzymatic reaction stream by sodium bisulfite treatment of the imine generated *in*

situ. In addition, the enzymatic reaction stream was subjected to cyanation and gave only the *trans* stereoisomer **185**, in >99% *ee*. This compound was treated under Pinner conditions for the generation of the methyl ester derivative, and the free amine was crystallized as the hydrochloride salt **186**.

Scheme 45.

5.2. From proline derivatives

The addition of carbenes^[77] and titanacyclopropane reagents^[78] to 3,4-dehydroprolinates proceeds diastereoselectively to afford mainly *trans*-3,4-methyleneproline derivatives **188** and **189** in enantioenriched or enantiomerically pure form (Scheme 46). In particular, the aminocyclopropanation of **187** (entry d) involved the generation of a titanacyclopropane intermediate from a Grignard reagent and methyltitanium triisopropoxide. After ligand exchange with **187**, the titanacyclopropane intermediate underwent insertion of the carbonyl group of the formamide into the titanium-carbon bond. The resulting oxatitanacyclopentane underwent ring opening to an iminium-titanium oxide inner salt that cyclized to the cyclopropylamine. The overall transformation gave only one diastereoisomer, in which the *tert*-butoxycarbonyl group, the dibenzylamino group and the two cyclopropane bridgehead protons are *cis*-oriented with respect to each other. According to the authors, the high diastereoselectivity in the transformation was due to the considerable steric bulk of the *tert*-butyl ester group.

Scheme 46.

The same stereoselectivity was observed for the titanium-mediated aminocyclopropanation of 3,4-dehydroprolinol derivative **190** (Scheme 47).^[79] Removal of the silyl-protecting group furnished **191**, which proved to be a suitable starting material for the introduction of different protecting groups. In particular, the *N* γ -Fmoc/*N* α -Boc protected derivative (**193**) was shown to be compatible with solid-phase peptide chemistry.

Scheme 47.

Access to the 3-azabicyclo[3.1.0]hexane system by cyclopropanation of unsaturated lactams **117**, **80** (Scheme 48)^[14a,80,81] and **197** (Scheme 49)^[82] with alkylidene transfer reagents has also been explored. In particular, Madalengoitia et al. reported the stereoselective cyclopropanation of **117** and **80** with different sulfur ylides (Scheme

48)^[80a] and explored the applicability of the resulting azabicycles in the design of poly-L-proline type II peptide mimics.^[80b-f] Furthermore, a procedure of this type was also employed by Masse et al. for the preparation of deuterated derivatives.^[83] The cyclopropanation of **117** and **80** with sulfur ylides afforded the products of addition from the less hindered faces of the bicyclic lactams. The *syn/anti* cyclopropane stereochemistry (Scheme 48, entries d-g) was found to be dependent both on the synthon and on the sulfur ylide. The stereochemical outcome of these reactions was interpreted by the authors on the basis of the *synclinal*-like transition state geometry A which is favoured by steric and electrostatic factors only for small R² substituents (*i.e.* R² = Me). Therefore, for such substituents the *anti* isomer is favoured.

^a*anti* and *syn* denote cyclopropane stereochemistry (only the *anti* product that exhibits R¹=H in *trans* disposition with respect to the hydrogens at the ring junction is represented for entries d-g)

Scheme 48.

Alternatively, Venkatraman et al. reported the stereoselective cyclopropanation of **117** (Scheme 48) with isopropylidenetriphenylphosphorane.^[81] The resulting adduct **194** (R¹, R²=Me) was subsequently transformed into **195** (R¹, R²=Me) by Madalengoitia's procedure^[80b] with some modifications.

Oba and Nishiyama^[82] reported the use of unsaturated pyroglutamate derivatives in which the carboxy functionality is protected as an orthoester for the stereocontrolled synthesis of *cis*- and *trans*-3,4-methano-L-proline derivatives in enantiomerically pure form (Scheme 49). The cyclopropanation of **197** by 1,3-dipolar cycloaddition of diazomethane followed by photolysis of the resultant pirazoline afforded adduct **199**. The authors suggest that the orthoester group limits the approach of diazomethane from the β face of the olefin, thus resulting in the stereospecific cyclopropanation. In addition, the ABO group prevents racemization at the α carbon atom. Acidic hydrolysis of **199** followed by methanolysis of the orthoester and re-protection of the amino function was needed to accomplish the chemoselective reduction of the lactam. Enantiomerically pure **200** was isolated after hydrolysis and deprotection under acidic conditions followed by treatment with an ion-exchange resin.

Scheme 49.

In turn, the *cis*-fused 3,4-methano-L-proline framework was assembled through a four-step sequence that involved carboxycyclopropanation of **197**, ring opening of the lactam, decarboxylation of the resulting acid, and intramolecular cyclization. The carboxycyclopropanation of **197** with *tert*-butyl dimethylsulfuranylideneacetate gave a 67:33 mixture of adducts with opposite configuration of the substituent at the

cyclopropane ring, and these were chromatographically separable. The chemoselective ring-opening of the major isomer **201** afforded **202**, which was subjected to Barton decarboxylation reaction. Subsequent treatment of **203** with dry hydrogen chloride in methanol afforded an intermediate dimethyl ester derivative that was neutralized to effect the intramolecular cyclization reaction. The resulting pyroglutamate derivative was subjected to standard deprotection, reduction and reprotection protocols that provided enantiopure **204**.

Additional procedures for the synthesis of analogous pyroglutamates are disclosed in the literature,^[84] although their suitability for the preparation of 3,4-methanoproline derivatives has not been explored. For example, the preparation of **209** and **210** involved rhodium-catalysed cyclopropanation of **205** with ethyl diazoacetate (Scheme 50).^[84a,b] The cleavage of the acetal group provided a diol that was oxidized to hemiketal **206**. This compound was subjected to Strecker reaction and the resulting amino acids, obtained with poor stereoselectivity, were protected, separated by chromatography and oxidized. The relative configurations of **209** and **210** were assigned on the basis of nOe measurements and coupling constant analysis.

Scheme 50.

5.3. Intramolecular cyclization through C–N bond formation

The synthesis of *N*-Boc protected *cis*-3,4-methano-L-proline in enantiomerically form has been accomplished in an efficient manner through the coupling of two easily accessible enantiopure starting materials, **211** and **212**, followed by the construction of the pyrrolidine ring by intramolecular C–N bond formation (Scheme 51).^[85] The method involved the generation of the dianion of **211**, which reacted with glycidyl triflate **212** to furnish β -epoxy sulfone **213**. The addition of one more equivalent of *n*BuLi generated a carbanion α to the sulfone group that underwent epoxide ring-opening to furnish **214**. Cyclization of the mesylates derived from **214** afforded a mixture of **215** and **216** that were separable by chromatography. *cis*-*N*-Boc-3,4-methanoproline **179a** was finally obtained after removal of the tetrahydropyranyl group from **216**, reductive desulfonylation and Jones oxidation.

Scheme 51.

Nair et al. made an interesting contribution that takes advantage of the inherent chirality of the natural product (+)-3-carene (**217**) for the preparation of enantiomerically pure **222** on a multigram scale (Scheme 52).^[86] The sequence started with the oxidative cleavage of the olefin in (+)-3-carene, esterification of the resulting ketoacid, and Baeyer-Villiger oxidation to produce acetate **218**. Deacetylation of **218** gave a hydroxy ester that cyclized under reflux in the presence of catalytic amounts of base. Introduction of the amine moiety on the carbon α to the carbonyl of **219** was achieved through an oximation/reduction sequence. Reduction of oxime **220** from the less hindered side afforded the amino group with a *trans* relative disposition with respect to the bridgehead hydrogen atoms. Methanolysis of this lactone gave amino ester **221** along with a 20% of its C-2 epimer. This mixture underwent cyclization upon treatment under Mitsunobu conditions. When the epimeric bicyclic methyl ester was hydrolysed with LiOH, thermodynamically favoured **222** was formed exclusively.

Scheme 52.

Alternative procedures that involve the construction of the pyrrolidine ring of the desired 3,4-methanoproline through intramolecular C α –N bond formation, instead of the C δ –N closure described by Nair, and make use of a natural product as the starting material have been reported.^[87,88] As one example, Berranger and Demonchaux^[87] reported the multigram preparation of enantiomerically pure **229** starting from (–)-biocartol (**223**), which is also derived from (+)-3-carene (**217**) (Scheme 53). (–)-Biocartol furnished the bicyclic lactone **224** in good yield through ester hydrolysis, concomitant aldehyde reduction and subsequent condensation reaction. Treatment of **224** with thionyl chloride provided **225**, which underwent a substitution reaction with ammonia to afford **226**. After protection of the amino function, the procedure involved reduction of the lactam carbonyl group with diisobutylaluminum hydride to obtain an intermediate hemiaminal, which was transformed into methoxyaminal **227**. Subsequent treatment of **227** with trimethylsilyl cyanide in the presence of trimethylsilyl triflate stereoselectively yielded compound **228**, which was hydrolysed to furnish **229**.

Scheme 53.

5.4. Intramolecular cyclization through C–C bond formation

Baird et al. reported the construction of azabicyclo[3.1.0]hexane derivatives through formal insertion of a cyclopropylidene unit into a C–H bond adjacent to a nitrogen atom (Scheme 54).^[89] The required precursor **231** was synthesized from enantiomerically pure dibromocyclopropane **230** in several steps. Subsequent treatment of **231** with methyllithium furnished an intermediate cyclopropylidene that cyclized to afford **232** as the major isomer. Selective debenzoylation of **232**, followed by trifluoroacetylation of the nitrogen atom, oxidation of the phenyl group and nitrogen deprotection afforded *cis*-3,4-methanoproline derivative **233**. This methodology was also applied to the synthesis of enantiomerically pure *cis*-3,4-methano-L-proline that was obtained in 40% overall yield from the corresponding *R*-configured dibromocyclopropane carboxylic acid.

Scheme 54.

Alternatively, *cis*- and *trans*-3,4-methano-L-proline derivatives were synthesized by use of a carbene insertion as the key step (Scheme 55).^[90] Compound **234** was *N*-nitrosilated and the crude material rearranged in the presence of pyrrolidine to an α -diazoketone. The treatment of this with palladium acetate produced a carbene that underwent intramolecular addition to the olefin group. Interestingly, compounds with methyl- or ethyl-disubstituted olefin groups led exclusively to the cycloaddition adducts **235** (entries a,b), possibly due to more favourable steric and electronic interactions in the *exo*-form of the carbene generated. Conversely, a cyclopropyl-substituted olefin (entry c) led to a 1:1 separable mixture of pyrrolidones that, in turn, afforded access to proline derivatives such as **237** upon deprotection and reduction of the lactam moiety. The structure of **236** was confirmed by single crystal X-ray analysis of the lactam obtained after removal of the *N,O*-dimethyl acetal.

Scheme 55.

5.5. Miscellaneous

Dixneuf et al. explored the transformation of fluorinated mixed propargyl allyl amides into azabicyclo[3.1.0]hexane derivatives (Scheme 56, entries a-d).^[91] It was shown that the process involves a ruthenium-catalysed tandem addition of a diazoalkane followed by cyclopropanation. The sequential carbene addition and cyclopropanation reactions of enynes took place under very mild conditions and with high stereoselectivity. Enynes **238a** and **238b** reacted with N₂CHSiMe₃ in diethyl ether to give the diastereoisomers with the *Z* configuration of the alkenyl group. Conversely, the catalytic transformation of enynes **238c** and **238d** with ethyl diazoacetate led preferentially to products with *E*-configured alkenyl side-chain, probably due to thermal factors because the reaction took place at 100 °C. In each case, the major diastereoisomer **240** exhibited a *trans* relative disposition of the ester and the alkenyl group. In addition, the presence of a substituent on the double bond of the starting enyne (Scheme 56, entries e-g) induced the predominant formation of one diastereoisomer with the *Z* configuration of the vinylsilane moiety. The relative stereochemistry of **239d-g** was established on the basis of NMR experiments.

Scheme 56.

Recently, the synthesis of azabicyclo[3.1.0]hexane derivatives, such as **247** and **248**, has been accomplished by means of a tandem process initiated by the conjugate addition of an allylic amine to a vinylsulfonium salt generated *in situ* from a bromoethylsulfonium salt (Scheme 57).^[92] The resulting sulfur ylide underwent intramolecular addition to the Michael acceptor to give a sulfonium enolate that ring-closed to the cyclopropane. In this manner, enantioenriched **244** and **246** were obtained with high diastereoselectivity. The relative stereochemistry of **246** was determined by X-ray analysis and related compounds were assigned by analogy. Deprotection and oxidation of **244** gave **247**, which can be seen as a conformationally locked glutamic acid analogue. On the other hand, oxidative cleavage of the phenyl group in **246** gave pyrrolidine **248**, which is both an α - and β -amino acid derivative.

Scheme 57.

6. Concluding remarks

In this review, we have collected the methods available for the synthesis of bicyclic proline analogues incorporating a carbocyclic ring fused to the [c] face of the pyrrolidine moiety. Procedures that provide the target compounds in racemic form and those that afford enantioenriched products have both been considered. Although a number of strategies have been effectively applied to the large-scale synthesis of enantiopure 3-azabicyclo[3.3.0]octane- and 3-azabicyclo[3.1.0]hexane-2-carboxylic acid derivatives, which are component units of important drugs on the market, many other approaches for the stereoselective and asymmetric construction of [c]-fused bicyclic proline analogues have also been established. In this context, those methods that make use of cycloaddition reactions proved to be mainly suited for the preparation of polysubstituted [c]-fused bicyclic proline analogues. The different methods described should encourage further investigations focusing on the refinement of the procedures and catalytic processes for providing the target molecules in enantiomerically pure form.

7. Abbreviations and acronyms

Abbreviations and acronyms used in this article are summarized in Table 1.

Table 1.

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BOP	(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
bpy	2,2'-bipyridine
Bz	benzoyl
Cbz	benzyloxycarbonyl
cod	cycloocta-1,5-diene
Cp*	pentamethylcyclopentadienyl
CPME	cyclopentylmethyl ether
DAST	(diethylamino)sulfur trifluoride
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DPBP	3,7-dipropyl-3,7-diazabicyclo[3.3.1]nonane
Hsp90	heat shock protein 90
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LTMP	lithium tetramethylpiperidide
mCPBA	<i>m</i> -chloroperoxybenzoic acid
Ms	methylsulfonyl
MS	molecular sieves
MTBE	<i>tert</i> -butyl methyl ether
Naph	naphthyl
NMM	<i>N</i> -methylmorpholine
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
PDC	pyridinium dichromate
PMB	<i>p</i> -methoxybenzyl
PPAR δ	peroxime proliferator-activated receptor δ
PPTS	pyridinium <i>p</i> -toluenesulfonate
Py	pyridine
SES	2-(trimethylsilyl)ethanesulfonyl
Stat	signal transducer and activator of transcription
Su	succinimide

TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TCE	trichloroethane
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
Tf	trifluoromethylsulfonyl
THF	tetrahydrofuran
THNA	1,2,3,4-tetrahydro-1-naphthylamine
THP	tetrahydropyranyl
TMS	trimethylsilyl
<i>p</i> Tol	<i>p</i> -tolyl
Ts	<i>p</i> -tolylsulfonyl

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- [1] Compound **1** is more frequently referred to as (1*S*,3*aR*,6*aS*)-octahydrocyclopenta[*c*]pyrrole-1-carboxylic acid rather than (1*S*,2*S*,5*R*)-3-azabicyclo[3.3.0]octane-2-carboxylic acid. On the other hand, both (1*R*,2*S*,5*S*)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid, and *trans*-6,6-dimethyl-3,4-methano-L-proline are commonly employed to refer to compound **2**. In Figure 2, the positions of chiral carbons are indicated with numerical locants that relate to the nomenclature system more commonly employed to refer to each compound.
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