Synthesis of [c]-Fused Bicyclic Proline Analogues

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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.

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).

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.

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 structures of a new class of specific inhibi-
tors of the molecular chaperone Hsp90 with in vivo antitu-
mour activity in human melanoma cells (Figure 3).[5] More-
over, 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 relation-
ship 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 PPARδ
agonists (Figure 3), which are considered promising leads
for drugs for the treatment of diabetes, obesity or athero-
sclerosis.[11]

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 appli-
cation in structure–activity relationship studies for the
design of inhibitors of angiotensin-converting enzyme,[13]
hepatitis C virus NS3 protease[14] and rhinovirus 3C prote-
ase,[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

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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 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 dihalogened α-xylene, 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 acid 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 and 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 diisobutylaluminium 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 hydrolysed to furnish isodindole-1-carboxylic acid as the hydrochloride salt. The high yield of each individual step and the easy accessibility of the starting isodindolinone makes this synthetic methodology quite effective. In fact, a substantial number of strategies for the preparation of isodindolinones have been developed;\textsuperscript{[26,27]} they include reductive amination and intramolecular amidation of 2-formylbenzoic acid and amines,\textsuperscript{[26b]} Curtius rearrangement of an acyl azide derived from homophthalic acid,\textsuperscript{[26c]} palladium-catalysed carboxylation of 2-bromobenzaldehyde with a primary amine,\textsuperscript{[26d]} reduction of phthalimide\textsuperscript{[26e,26f]} and dephosphonylation of 3-oxoisodindo1-yl phosphonates obtained through one-pot reactions of 2-formylbenzoic acid, amines and dimethyl phosphate.\textsuperscript{[26a]}

Scheme 3.

In addition, the asymmetric synthesis of isodindoline carbamates 15 (Scheme 3) was successfully achieved through an enzyme-mediated dynamic kinetic resolution of 14.\textsuperscript{[25]} This strategy employed Pseudomonas cepacia lipase (PSL-C I) as biocatalyst and avoided the use of metal or acid-base catalysis for racemization of the substrate. Specifically, optically active carbamates 15 were obtained in good yields and with excellent degrees of enantioselectivity in alkoxy carbonylation 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 dihydroisodindole-1-carboxylic acid derivatives are based on 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 dihydroisodindole-1-carboxylates.\textsuperscript{[17,28]} These proved to be highly sensitive to air, thus requiring isolation as their hydrochloride salts. In particular, isodindoline 14 was obtained by catalytic hydrogenolysis of the N-benzyl derivative 17b, but it was also sensitive to air. Use of phenyldiazene as the nucleophile furnished 17d in only 24% yield, due to concomitant formation of the corresponding isodindole.\textsuperscript{[29]} Conversely, condensation between 16 and tert-butyl carbazate afforded 17e, which was then converted into the corresponding aminoisodindole upon acidic treatment.\textsuperscript{[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.\textsuperscript{[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
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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 either of 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. reported 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 2H-isouquinolin-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 benzynes (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 CuI-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]

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-dienes, such as 42, and acetylene.[37]

2.2. Synthesis of Octahydroisoindole-1-carboxylic Acid Derivatives

A number of strategies have been devised for the preparation of octahydroisoindole-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 octahydroisoindole-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 dispositions of appropriate carboxylic acid and amine substituents (substrates C).

2.2.1. Synthesis from Isoindoline-1-carboxylic Acid Derivatives

Racemic octahydroisoindole-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 through the use of (1S)-(−)-10-camphorsulfonic acid was indicated in a patent,[13] but no details relating to the effi-
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Cacy 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-1H-isoindolin-1-carboxylic Acid Derivatives

The cis-fused octahydroisoindole-1-carboxylic acid system has also been constructed in a straightforward manner from methyl 3-oxo-1H-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 diisobutylaluminium 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.\[^{[40–42]}\] The preparative pathways for such isoindoliones (Scheme 14) include the nucleophilic attack of 3-metallated 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 carbylation of an orthopalladated complex generated from a phenylglycine derivative (Scheme 14, path b).\[^{[40c,40f]}\]

Scheme 14.

In addition, octahydroisoindolinone 48 (Scheme 13) was synthesized through a 5-endotrig 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 proved to be valuable intermediates for the synthesis of analogues of kainic and domoic acids.\[^{[44]}\]

2.2.3. α-Functionalization of Octahydro-1H-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 \emph{Aspergillus niger}) and molecular oxygen for the generation of an intermediate enantiopure Δ1-pyrroline. This compound underwent nucleophilic addition in the presence of cyanide and provided a diastereomeric mixture of α-amino nitriles, which were converted into 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 Δ1-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.

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
Scheme 15.

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 after 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 nitrene intermediate from the si face of the double bond.

Scheme 16.

Alternatively, the octahydroisoindole-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 acid 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 octahydroisoindole-1-carboxylic acid derivatives 63 and 66, cis- and trans-fused bicyclic proline analogues, respectively (Scheme 18).[38] In the synthesis of 63, compound 62 was

Scheme 18.
obtained as a mixture of stereoisomers. The ring junction was set in the disposition depicted in 63 during the alkyla-
tion of 62. Subsequent reduction of the lactam carbonyl
group, followed by treatment of the aminoacetal with a
Lewis acid, afforded an acyl iminium species that under-
went 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 inter-
mediate acyl iminium species. Presumably attack from the
si face is not favoured due to axial interactions with a
methyl group and the hydrogen atom at the ring junction.

Gais et al. described the asymmetric synthesis of bicyclic
proline analogue 74, with a cis relative disposition between
the carboxylic acid ester group and the six-membered ring,
that underwent addition to a sulfonyl imino ester to furnish a mixture of
69 and 70 with high regio- and diastereoselectivity. Activi-
tion 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 substi-
tution of the sulfoxonium group that provided bicyclic proline
analogue 73. Finally, cleavage of the tert-butylsulfonyl pro-
tecting group under acidic conditions furnished 74 in en-
antio- and diastereomerically pure form. Alternatively, all-
ylic 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 deriv-
ate 76 in practically quantitative yield.

2.2.5. Intramolecular Cyclization through C–C Bond
Formation

The preparation of racemic cis-fused octahydroisoindole-1-carboxylic acid derivatives 78 and 79 has been ac-
complished through the reductive intramolecular cycliza-
tion of α-(phenylthio)glycines 77, each bearing a 3-alkenyl
substituent at the nitrogen atom (Scheme 20).[49] Treatment
of 77a with tributyltin hydride and a catalytic amount of
AIBN in toluene solution at 80–90 °C produced a captod-
ative radical that preferentially underwent a 5-exo intra-
molecular 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 com-
plex 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 bicy-
clic octahydroisoindole-1-carboxylic acid skeleton make use
of cycloaddition reactions. Diels–Alder reactions of pyro-
glutaminol or proline derivatives provided access to the bi-
cyclic 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 Danishefsky’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/endo ratio of the methoxy group in the cycloadducts. This mixture was converted into 85, which was isolated with an ee better than 99% after 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 an octahydroisoindole-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 octahydroisoindole-1-carboxylic acid derivatives.[53] For example, silver-catalysed cycloadditions of compounds 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 BF₃·Et₂O in dichloromethane and provided an isomeric mixture of 93 and 94 contaminated with olefin 95. According to the authors, the stereochemical integrity during the Sn2-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 bicyclics, and their stereochemistry was assigned by NMR experiments. The preparation of trans-fused octahydroisoindole-1-carboxylic acid 96 was accomplished by oxidation of silane 93 to the carboxylic acid in two steps, followed by removal of the amino protecting group.

2.2.7. Miscellaneous

An approach to trans-octahydroisoindole derivative 98 through a 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 iso-merically pure form. According to the authors, the stereoselectivity achieved reflects the thermodynamic equilibrium between the two isomers that can be established under the
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Scheme 24.

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 octahydroisoindole-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).\cite{54,55} 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 pyrroline analogues with a three-component Ugi reaction has been recently applied to the highly stereoselective synthesis of substituted prolyl peptides.\cite{56}

Scheme 26.

Previously, a patent\cite{57} by Tanoury et al. had described 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). 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 derivative 110a (Scheme 29). In the same way as described previously for the homologous six-membered-ring 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 derivative 110b.[50]

Scheme 29.

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] Treatment of the silylated allylic acetate 118 with Pd[P(OiPr)3]2, generated in situ with palladium(II) acetate and triisopropyl phosphite, produced trimethylenemethane, which 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.

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 dehydroproline derivative 121 (Scheme 32).[63] A Diels–Alder reaction between 121 and cyclopentadiene afforded 122 as a single stereoisomer. This
Synthesis of c-Fused Bicyclic Proline Analogues

Scheme 31.

cycloadduct was smoothly converted into 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. Contrary to what had previously been observed for the synthesis of octahydroisoindole-1-carboxylic acid (see Scheme 24), the intramolecular formal [3+2] cycloaddition reaction of aziridine-allylsilane 124 (Scheme 33), by treatment with BF₃·Et₂O, gave the bicyclic skeleton with the cis relative disposition of the hydrogen atoms at the ring junction as the major compound. Column chromatography gave diastereomerically pure 125. Its treatment with mercury(II) acetate gave an alcohol derivative that was further oxidized to provide 127.

In addition, azabicyclooctanones 130 have been synthesized through iron-mediated intramolecular cycloadditions (Scheme 34). The addition of protected amino acids to (η⁵-pentadienyl)Fe(CO)₃ cations gave (η⁴-diynylamine) Fe(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 arises from anti addition of the α-face of enolate 129 at the internal position of the diene.

Scheme 33.

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). 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 reactions 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.

Subsequently, Brummond et al. studied Pauson–Khand cycloaddition of allenynes 136 in the presence of molybdenum hexacarbonyl (Scheme 36). 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–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 pseudo-
M. I. Calaza, F. J. Sayago, P. Laborda, C. Cativiela

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equatorial 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 and b) and 138 (Entries c–e) have found utility for the preparation of tricyclic pyrrole libraries for biological tests.\[65c,65d\]

![Scheme 35](image)

Scheme 35.

In 1994, Monn and Valli reported the stereocontrolled preparation of azabicyclooctanone 144 through cycloaddition between an azomethine ylide and cyclopent-2-enone (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 A1,3-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 36](image)

Scheme 36.

In 1994, Monn and Valli reported the stereocontrolled preparation of azabicyclooctanone 144 through cycloaddition between an azomethine ylide and cyclopent-2-enone (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 A1,3-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.\[14b,15,38\]

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 dipolarephiles\[67\] (Scheme 38) or of chiral catalysts\[68\] (Scheme 39) and give access to cis-fused bicyclic proline analogues with high en-
Synthesis of \([\text{c}]-\)Fused Bicyclic Proline Analogues

antiocntrol. In particular, \(\alpha\)-sulfinylcyclopentenone 149 reacted with the ylide generated by treatment of 150a with DBU in the presence of a silver salt in a completely regios- 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.

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\(^{1}\)-Fesulphos complex as a catalyst \(^{[68a]}\). The reactions between \(N\)-aryl imines of glycine methyl ester (Entries a–d) and cyclopent-2-enone catalysed by the cationic Cu\(^{1}\) 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.

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.\(^{[68b,68c]}\) Both ligands provided copper complexes that effectively catalysed the cycloaddition to give the endo cycloadducts with complete enan- tocontrol. 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-thiopheneacetaldehyde (Entry i) or 2-naphthaleneacetaldehyde (Entry j) also proved to be suitable substrates and gave the endo cycloadducts in >99\% ee.

Scheme 39.

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, which provides preorganization of the endo transition state required for the key [2,3]-rearrangement.

Scheme 40.

4. Synthesis of Four-Membered-Ring \([\text{c}]-\)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
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 on the basis of 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 for 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). Moreover, Aitken et al. described the synthesis of lactams 167 and 168 from enantiopure γ-lactam 166. A subsequent two-step deprotection/reprotection sequence provided access to N-Boc-protected derivatives 169 and 170.

Scheme 42.

Alternatively, polysubstituted 3-azabicyclo[3.1.0]hexane derivatives 173 and 176 (Scheme 43) have been synthesized through 1,3-dipolar cycloaddition between münchnone 172 and 1,2-dicyanocyclobutene and by metal-promoted alkylation of lactone 174, respectively. 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 cycloaducts were obtained with high diastereoselectivity (typically ≤10% of the lactam epimeric at the quaternary centre was observed in crude reaction 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 Analogue

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. 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 medicinally relevant drugs Boceprevir and Narlaprevir.

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). 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-diamine-178 complex that was maintained through the CO₂-insertion mechanism. The trans stereoisomer was ob-
Synthesis of [c]-Fused Bicyclic Proline Analogues

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

tained 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 de-
protonation 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, alter-
atively, 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 em-
ployed for the epimerization step.

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–76c] More recently, an oxida-
tive Strecker reaction that involves a chemoenzymatic
process[76d,76e] has been developed for the manufacture of
enantioomerically pure 186 (Scheme 45), the key structural
feature of Boceprevir and Naranlprevir. The prochiral amine
182 was subjected to an enzymatic oxidative desymmetri-
ization after the activity and thermal stability of MAON
(from Aspergillus niger) had been improved 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 crys-
tallized as the hydrochloride salt 186.

Scheme 45.

5.2. From Proline Derivatives

The addition of carbenes[77] and titanacyclopropane rea-
gents[78] to 3,4-dehydroprolinates proceeds diastereoselec-
tively to afford mainly trans-3,4-methyleneproline deriv-
atives 188 and 189 in enantioenriched or enantiomerically
pure form (Scheme 46). In particular, the aminocyclopro-
panation 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). 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 Nγ-Fmoc/Nα-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–80f]. 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 synthons 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.

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 pyrazoline afforded adduct 199. The authors suggest that the ortho-
ester 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 reprotection 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.

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 dimethylsulfurylideneacetate 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. 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,[84a,84b] 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).
5.3. Intramolecular Cyclization through C–N Bond Formation

The synthesis of N-Boc-protected cis-3,4-methano-L-proline in enantiomerically pure form has been accomplished in an efficient manner through the coupling of two easily accessible enantipure 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 nBuLi 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-methano-L-proline (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 group 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. Methanalysis of this lactone gave amino acid ester 221 along with a 20% yield 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 Cα–N bond formation, instead of the Cδ–N closure described by Nair, and make use of natural products as the starting materials 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 diisobutylaluminium 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 cyclopentadiene unit into a C–H bond adjacent to a nitrogen atom (Scheme 54). The required precursor 231 was synthesized from enantiomerically pure dibromocyclopropane 230 in several steps. Subsequent treatment of 231 with methylthioketal furnished an intermediate cyclopentadiene that cyclized to afford 232 as the major isomer. Selective debenzylation 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, which was obtained in 40% overall yield from the corresponding R-configured dibromocyclopropane carboxylic acid.

Alternatively, cis- and trans-3,4-methano-l-proline derivatives were synthesized by use of carbene insertion as the key step (Scheme 55). Compound 234 was N-nitrosilated, and the crude material rearranged in the presence of pyrrolidine to an α-diazoketone. 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 and 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). It was shown that the process involves a ruthenium-catalysed tandem addition of a diazoalkane followed by cyclopropanation. The se-
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 chains, 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.

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 a β-amino acid derivative.

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 of this type 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 refinement of the procedures and on 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. Abbreviations and acronyms used in this article.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2'-azobisisobutyronitrile</td>
</tr>
<tr>
<td>Bn</td>
<td>benzy1</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>BOP</td>
<td>(benzotriazol-1-yl-oxo)tris(dimethylamino)phosphonium hexafluorophosphate</td>
</tr>
<tr>
<td>bpy</td>
<td>2,2'-bipyridine</td>
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<td>DAST</td>
<td>(diethylamino)sulfur trifluoride</td>
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<td>dicyclohexylcarbodiimide</td>
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<td>DCE</td>
<td>dichloroethane</td>
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<td>DPBP</td>
<td>3,7-dipropyl-3,7-diazabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>Hsp90</td>
<td>heat shock protein 90</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>LTMP</td>
<td>lithium tetramethylpiperide</td>
</tr>
<tr>
<td>mCPBA</td>
<td>m-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Ms</td>
<td>methylsulfonyl</td>
</tr>
<tr>
<td>MTBE</td>
<td>tert-butyl methyl ether</td>
</tr>
<tr>
<td>Naph</td>
<td>naphthyl</td>
</tr>
<tr>
<td>NMM</td>
<td>N-methylmorpholine</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>PMB</td>
<td>p-methoxybenzyl</td>
</tr>
<tr>
<td>PPARδ</td>
<td>peroxime proliferator-activated receptor δ</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>SES</td>
<td>2-(trimethylsilyl)ethanesulfonyl</td>
</tr>
<tr>
<td>Stat</td>
<td>signal transducer and activator of transcription</td>
</tr>
<tr>
<td>Su</td>
<td>succinimide</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBAT</td>
<td>tetrabutylammonium difluorotriphenylsilicate</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-butylmethylsilyl</td>
</tr>
<tr>
<td>TDBPS</td>
<td>tert-butylphenylsilyle</td>
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<tr>
<td>TCE</td>
<td>trichloroethane</td>
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<tr>
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<td>trifluoroacetic anhydride</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<tr>
<td>THNA</td>
<td>1,2,3,4-tetrahydro-1-naphthylamine</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydroprpyranyl</td>
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<tr>
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<td>trimethylsilyl</td>
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<td>Ts</td>
<td>p-tolylsulfonyl</td>
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</table>

Acknowledgments

Financial support from the Ministerio de Economía y Competitividad (MINECO) – FEDER (grant numbers CTQ2010-17436, CTQ2013-40855-R; predoctoral fellowship to P. L.) and from the Gobierno de Aragón – FSE (research group E40) is gratefully acknowledged.

[1] Compound 1 is more frequently referred to as (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylic acid rather than (1S,2S,5R)-3-azabicyclo[3.3.0]octane-2-carboxylic acid. On the other hand, both (1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid and trans-6,6-dimethyl-3,4-methanoproline 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.


