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Synthetic Approaches to Spiroaminals

Marie-Eve Sinibaldi*[a] and Isabelle Canet*[a]

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The 1-oxa-7-azaspiro[5.5]undecane, 1-oxa-6-azaspiro[4.5]-decane, 1-oxa-7-azaspiro[5.4]decane and 1-oxa-6-azaspiro-[4.4]nonane ring systems are found as the cores of natural or synthetic products that possess significant biological activities. Because of their potential applications, together with the novelty of their skeletons, these compounds represent challenging targets for chemical synthesis. In this review we summarize the different strategies developed for the synthesis of these spiroaminals.

1. Introduction

Spiroaminal – also called spiroaminoketal or spiro-N,O-ketal – systems are oxa-aza spirobicyclic frameworks that constitute the prevalent substructures encountered in a number of biologically active compounds such as pandamarilactone (**1**),[1] the herbicide hydantocidin (**2**),[2] the marine phycotoxins the azaspiracids **3**,[3] the immunosuppressant sanglifehrin (**4**),[4] the solanum alkaloids[5] [e.g., tomatidine (**5**), exhibiting activity towards DNA-repair-deficient yeast mutants, the potent glycosidase inhibitor spironucleosides **6**,[6] and the aza-spiropyrans **7**,[7] a well known class of photochromic compounds for practical applications in new technologies (optical switching, nonlinear optics, etc.)], and chlorofusin,[8] a complex p53-MDM2 antagonist (Figure 1).

[a] Laboratoire de Synthèse et Etude de Systèmes à Intérêt Biologique (SEESIB), UMR 6504, Université Blaise Pascal, 63177 Aubière Cedex, France
Fax: +33-4-73407717
E-mail: m-eve.sinibaldi-troin@univ-bpclermont.fr
isabelle.canet@univ-bpclermont.fr

Spiroaminals have received far less attention than their oxygenated analogues the spiroketals, for which a plethora of synthetic strategies are available,[9] in spite of their attractive skeletons, and fewer methods to elaborate these novel and attractive motifs have been reported to date. This Microreview focuses on a compilation of the synthetic approaches described in the literature.

As with the spiroketals, different approaches can be undertaken for the generation of aza-oxa spiro systems (Scheme 1). Strategy A involves the formation of the second cycle by a cycloaddition ring-closure process, starting from a monocyclic N-exocyclic hemiaminal **Ia** (or analogue **Ib**). Strategy B is based upon the elaboration of a monocyclic intermediate **II** on which the second cycle is appended; in this case, and unlike in that of the spiroketals, two pathways can be envisaged, starting from either oxa- or aza-preformed cycles **IIa** or **IIb**. In strategy C, formation of both cycles through a concomitant double cyclization of a linear precursor **III** is achieved.

Marie-Eve Sinibaldi (right) was born in 1962 in Alger. She received her PhD degree, for which she worked in the area of indole alkaloids, more particularly in the Aspidosperma family, from the University of Clermont-Fd. in 1988. She applied the photocyclization of arylenaminoketones to the synthesis of N_a-benzyl-20-deethyl-aspidospermidine, 19-oxo-aspidospermidine and 19-oxo-aspidosfractinine. After post-doctoral training with Prof. L. Ghosez at l'Université Catholique de Louvain, where she participated in a program devoted to the synthesis of γ-lactams, she was appointed CNRS researcher at the University of Clermont-Fd. in 1990. From 1990 to 1997 she developed the photochemical synthesis of carbazoles, azacarbazoles, 3,3′-spiroindolines and piperidines by photocyclization of arylenaminones or arylenamides.
Isabelle Canet (left), born in 1969 in Congis (France), was trained in chemistry at the University of Paris-Sud Orsay, where she obtained her PhD degree in 1994 under the supervision of Prof. J. Courtieu. She investigated a new method of enantiomeric analysis based on the use of deuterium NMR in oriented chiral media. After post-doctoral training at the University of Clermont-Fd., she was appointed as Assistant Professor at the same University in 1995 and started her work on the synthesis of analogues of calcimycin – a spiroketalic ionophore antibiotic – and the study of their biological activities.
Since 2001, M.-E. Sinibaldi and I. Canet have formed a research team involved in the chemistry of spiroheterocycles. Their current interests concern the development of new strategies for the elaboration of spiroketals and spiroaminals, together with their application to the synthesis of natural substrates or analogues that could act as antitumour agents, peptidomimetics or glycosidase inhibitors.

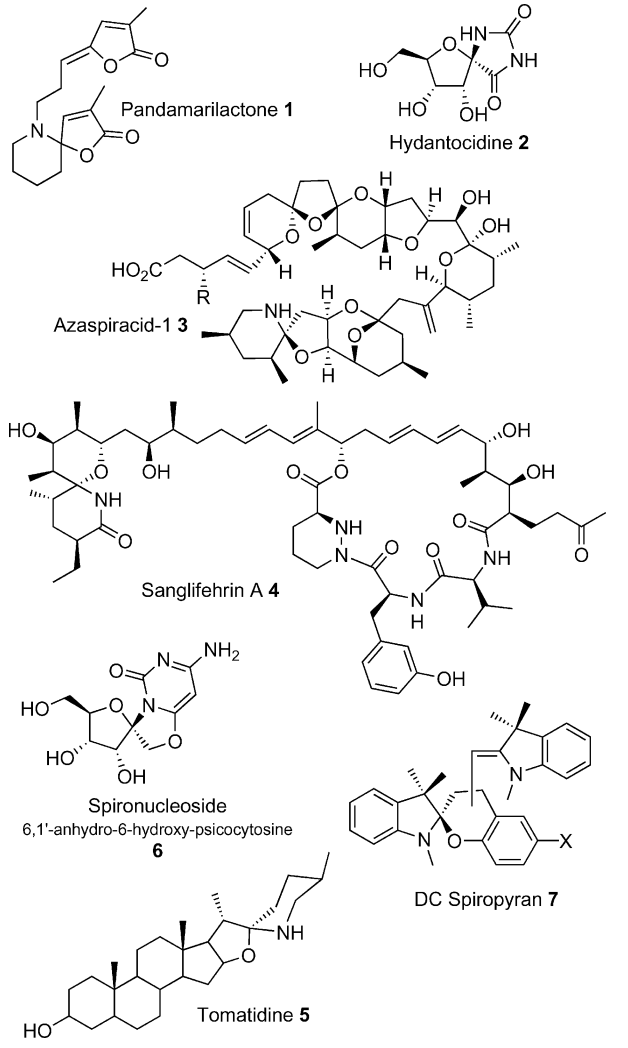
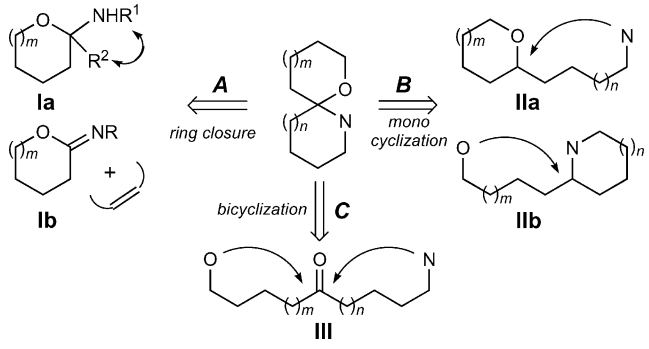


Figure 1. Selected compounds with spiroaminal frameworks.



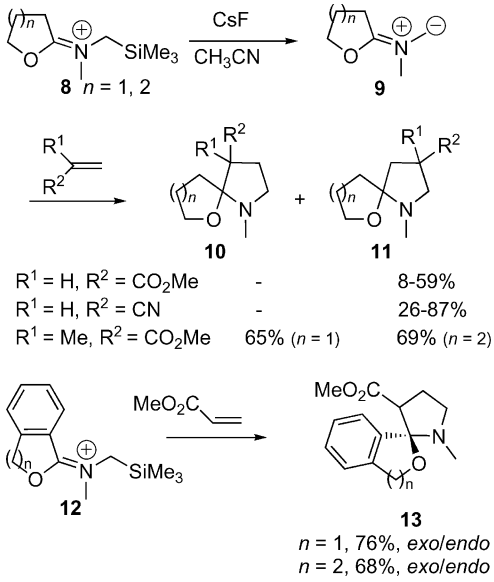
Scheme 1. Strategies used to construct spiroaminal cores.

2. Strategy A – Ring-Closure of Hemiaminals

Some examples of the elaboration of spiroaminal aza-cycles through ring-closure of preformed N-exocyclic hemiaminals or analogues have been described. Most of them require as key step a cycloaddition on the imino group of a cyclic imidate. This approach allows the generation of spiroaminals incorporating small-sized aza-cycles (four- or five-membered rings). More recently, ring-closure by RCM of a conveniently substituted N-exocyclic hemiaminal has been proposed. This method gives access to larger aza-cycles. Nevertheless, in all cases, modulation of the oxa-cycle size can only be envisaged through the synthesis of another hemiaminal precursor.

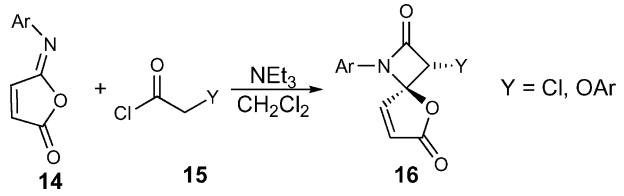
2.1 Cycloadditions on Imidate Structures

Fishwick and co-workers[10] have studied the potential of 1,3-dipolar cycloadditions of azomethine ylides for the construction of spiroaminal cores (Scheme 2). Desilylation of iminium salts **8** with fluoride anion led quantitatively to the (*Z*)-1,3-dipoles **9**, which indeed underwent facile 1,3-dipolar cycloadditions with electron-deficient dipolarophiles. With monosubstituted alkenes, these reactions led to mixtures of regioisomers **10** and **11**, from which only **11** could be isolated, spiropyrrolidines **10** suffering ring-opening to yield the corresponding vinyl ethers. With a *gem*-disubstituted alkene, namely methyl methacrylate, the authors obtained either spiroaminal **10** or **11** regioselectively, depending on the size of the ether ring. In all cases, better diastereoselectivities were obtained when starting from tetrahydrofuran than from tetrahydropyran rings. Finally, when applied to cyclic fused azomethine methylides **12** and an unsymmetrical dipolarophile, this reaction led regiospecifically to isomers **13** with the substituents located near to the spiro centres.[10b]



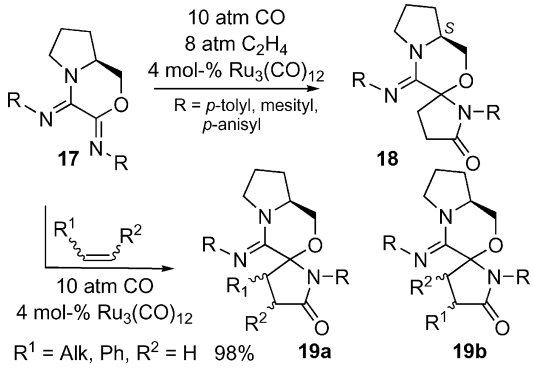
Scheme 2.

In search of new spiro 2-azetidinone structures, Santillan and co-workers[11] have developed an approach based on [2+2] cycloadditions between isomaleimides **14** and acyl chlorides **15** by means of Staudinger reactions (Scheme 3). Whereas the reactions proceeded with good *trans* diastereoselectivities, spirolactams **16** were generally obtained only in moderate yields (27–34%).



Scheme 3.

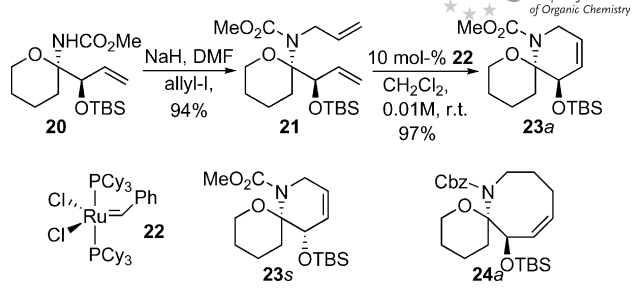
Another approach has been recently proposed by Imhof et al.[12] and involves hetero-Pauson–Khand-type [2+2+1] cycloadditions on ketimines (Scheme 4). Chiral diimines **17** – easily prepared from (*S*)-prolinol – reacted with carbon monoxide and ethylene in the presence of catalytic amounts of $Ru_3(CO)_{12}$ to give the pyrrolidin-2-ones **18** almost quantitatively as mixtures of two diastereomers in 1.5:1 ratio. The [2+2+1] cycloadditions took place only at the C=N double bond next to the oxazine oxygen atom, the second imine group acting as a ligand towards the transition metal atom.[12a] This strategy has been extended to substituted alkenes: with terminal ones the reactions proceeded very efficiently, but mixtures of diastereomers and regioisomers **19a** and **19b** were obtained, whereas with electron-deficient or disubstituted alkenes, compounds **17** remained unchanged.[12b]



Scheme 4.

2.2 Ring-Closure Metathesis of N-Exocyclic Hemiaminals

In 2006, Hsung and co-workers[13] demonstrated that aminal-tethered RCM could be accomplished with efficiency comparable to that of its ketal-tethered counterpart (Scheme 5). Allylation of the anomeric nitrogen atom of hemiaminal **20** furnished **21** (94% yield), which was subjected to RCM conditions to afford the *anti* spiroaminal **23***a* stereospecifically in 97% yield. The C1,2-*syn* spiroaminal **23***s* could be also prepared through RCM of the corresponding cyclic *syn* aminal precursor. The authors illustrated the potential of RCM to generate spiroaminals of a larger aza-cycle size through the synthesis, by the same procedure, of the *anti* 1-oxa-7-azaspiro[5.7]tridecane **24***a*.



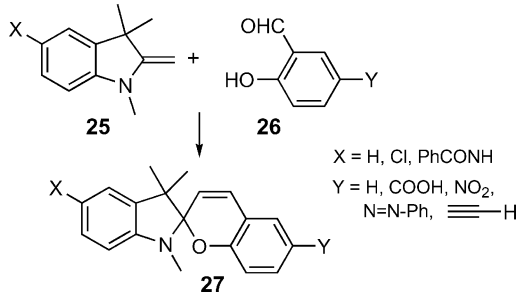
Scheme 5.

3. Strategy B – Monocyclization Processes

In this case, the elaboration of the spiro system is based on the elaboration of a key intermediate consisting of one oxa- or aza-cycle, bearing in its α-position a linear chain ω-functionalized with an aza or oxa group, respectively. This then generates the second cycle of the spiro system through an intramolecular process. From ω-hydroxylated pyrrolidines or piperidines, these strategies are mainly based on enamine and iminium reactivities. In the case of oxa-cyclic precursors, ionic approaches involving nucleophilic displacement of hemiketals by nitrogen are the most usual, although some radical-mediated approaches have also been reported.

3.1 Addition of Fischer's Base and Aldehyde

Aromatic spiro compounds featuring steric constraints have been easily prepared by addition of Fischer bases **25** and substituted salicylaldehydes **26** (Scheme 6). These reaction furnished the monocondensed spiropyrans **27**, but also the dicondensed compounds in ratios depending upon solvent, substituents and reaction conditions.[14a] Adaptation of this strategy to solid-phase-supported synthesis has permitted access to a library of spiropyrans in excellent yields and purities.[14b] This method has also been applied to the preparation of symmetric spiropyran dimers of enhanced activity.[14c]

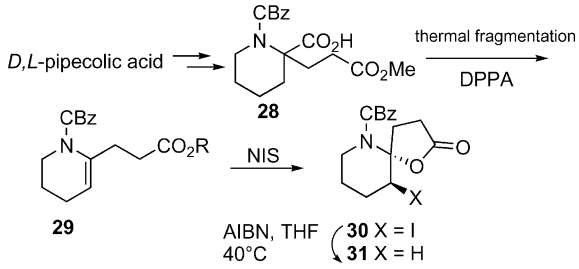


Scheme 6.

3.2 Cyclization on Enamines

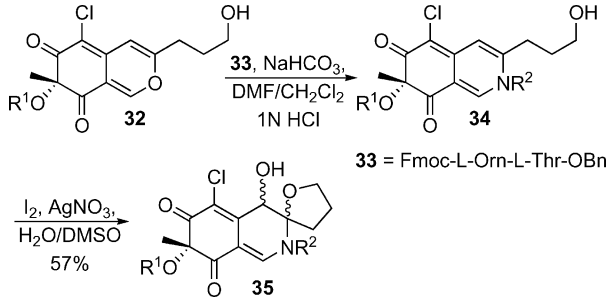
In their study directed towards the synthesis of the spiro part of pandamarilactone (**1**), Bermejo and co-workers[15] set out to obtain spiroaminals through oxidative cyclization

of *N*-substituted tetrahydropyridines. The α,α-disubstituted piperidine **28**, classically prepared in seven steps and 24% overall yield from D,L-pipecolic acid, underwent a diphenylphosphorazidate-promoted (DPPA-promoted) decarbonylation to give the enamine **29**. Saponification, followed by treatment with *N*-iodosuccinimide, afforded the unstable iodolactone **30** through an oxidative cyclization in 75% yield. Reduction with tri-*n*-butyltin hydride in the presence of AIBN finally furnished the azaspiro[4.5]decan-2-one **31** in 72% yield (Scheme 7).



Scheme 7.

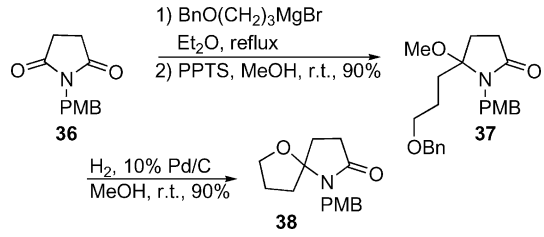
An analogous procedure has been applied to the synthesis of the chromophoric spiroaminal of chlorofusin. Thus, oxidative cyclization (I_2, $AgNO_3$, H_2O/DMSO) of **34**, obtained from condensation of **32** with peptide **33**, provided spiroaminal **35** as a mixture of four stereoisomers (Scheme 8).[16a] Other authors reported the condensation of **32** with, this time, the natural cyclopeptide part of chlorofusin. A similar oxidative process under NBS/Ag_2O conditions led to the natural metabolite as a mixture of isomers in 70% yield.[16b]



Scheme 8.

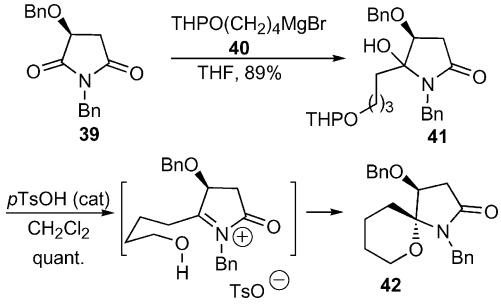
3.3 Acyliminium Cyclization

In their work devoted to the synthesis of stemoamide through *N*-acyliminium chemistry, Kende et al.[17] described the synthesis of the spiro compound **38** (Scheme 9). Addition of (3-benzyloxypropyl)magnesium bromide to *N*-(4-methoxybenzyl)succinimide (**36**) led to a hemiaminal, which was protected as its methoxy derivative **37** in 90% yield (two steps). Hydrogenolysis of the benzyl group with palladium on carbon in methanol then afforded the spiro compound **38** in 90% yield.



Scheme 9.

In a similar way, Huang and co-workers[18] prepared the aza-spiropyran **42** by starting from the addition of the THP-protected 4-hydroxybutylmagnesium bromide **40** to the succinimide **39**. The N,O-acetal intermediate **41**, obtained as an 7:1 epimeric mixture, was then converted into **42** by an acidic cyclization (Scheme 10).

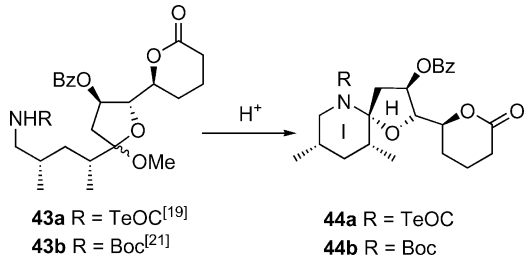


Scheme 10.

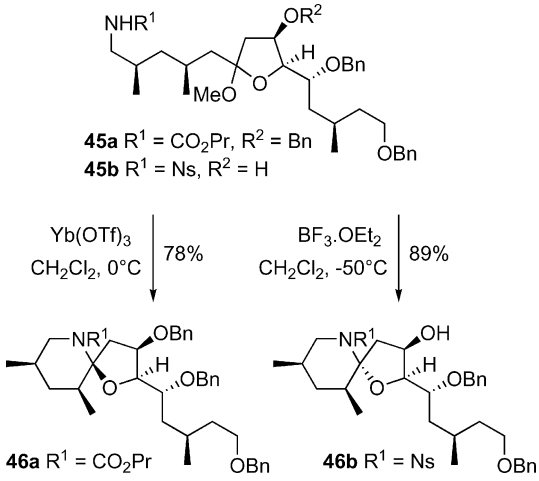
3.4 Cyclizations on Hemiketals

Synthesis of the "HI rings" fragment of azaspiracids by acid-promoted cyclization of chiral amino-acetals **43** (Scheme 11) has received particular attention.[19–23] Although this ring-closure process seemed straightforward, it finally proved nontrivial and needed extensive screening of a variety of acids and solvents. Initial attempts to employ protic acids such as *p*-TsOH, CSA or TfOH failed, leading only to several unidentified products or to decomposition of the starting material.[20] In contrast, exposure to a catalytic amount of $BF_3{\cdot}Et_2O$ at 0 °C rapidly afforded the spiro compound **44a** in 60% yield.[19] Improved results were then obtained by use of the Lewis acid $Yb(OTf)_3$ in CH_3CN over 3 min, which afforded access to **44b** in 72% yield.[21a] Further experimentation finally led to the use of $Nd(OTf)_3$ in the same solvent for a longer time (15 min), giving **44b** in 81% yield. The spiroaminals **44** were obtained in all cases as single diastereoisomers possessing the natural stereogenic centre configuration.

In the same way, spiroaminal **46a**, a precursor of azaspiracid-1, has been stereoselectively prepared from **45a** through the use of a propyl carbamate protecting group and $Yb(OTf)_3$ as acid catalyst (78% yield); the unnatural isomer **46b** was prepared from the (2-nitrophenyl)sulfonylamine **45b** in 89% yield with $BF_3{\cdot}OEt_2$ at lower temperature (Scheme 12).[21b]

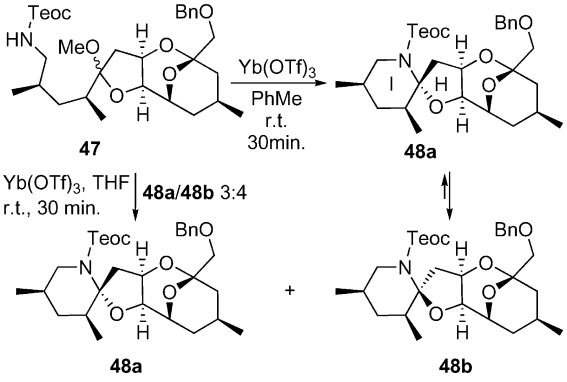


Scheme 11.



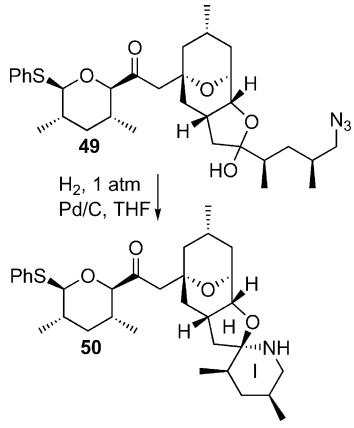
Scheme 12.

Control of the stereoselectivity in the cyclization process has been achieved by Carter and co-workers,[22] who started from **47** and used the acid catalyst $Yb(OTf)_3$ in different solvents (Scheme 13). Thus, with a short reaction time (30 min), the use of toluene at room temperature led to the exclusive formation of the kinetic unnatural azaspiroketal **48a**, whereas in THF the thermodynamic spiro compound **48b** was isolated as the major product (**48a**/**48b** = 3:4, 74% yield). Treatment of pure **48a** in PhMe for a longer time in the same acidic medium led to the formation of the same "thermodynamic" ratio of **48a**/**48b** as observed in THF. These results were attributed by the authors to the steric interaction between the *N*-Teoc group and the fused ring system in precursor **47**.



Scheme 13.

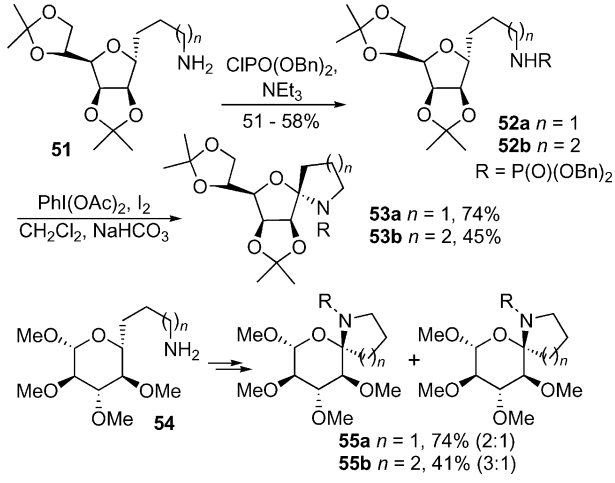
The "HI rings" part of (+)-azaspiracid-1 was elegantly prepared from lactol **49** by Evans and co-workers.[23] In this case, azide reduction of **49** furnished the corresponding amine, which spontaneously cyclised to give the unprotected spiroaminal **50** as a single diastereomer in very good yield. This compound possessed the natural stereochemistry at the spiro centre, as shown by NOE experiments (Scheme 14).



Scheme 14.

3.5 Intramolecular Hydrogen Abstraction

The preparation of different sized aza-oxaspirocycles through a radical-mediated approach was envisaged by Suárez and co-workers,[24] who used an intramolecular hydrogen abstraction as key step in the promotion of the cyclization. Starting from D-mannose, a multistep synthesis afforded amines **51**. The dibenzyl phosphoramidates **52**, generated by treatment of the corresponding amines **51** with dibenzyl chlorophosphate in the presence of triethylamine, were engaged in reactions with diacetoxyiodobenzene/iodine to give the phosphoramidyl radical intermediates; 1,5- or 1,6-hydrogen atom transfers (HATs) then proceeded with reasonable yields, furnishing the spiro compounds **53a**



Scheme 15.

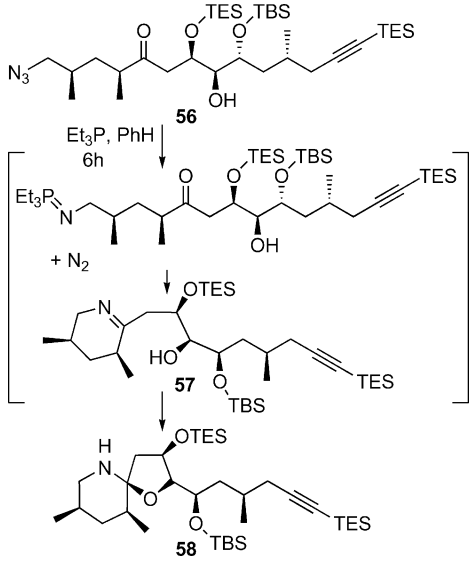
and **53b** as single isomers. From starting amines **54**, derived from D-glucose, application of the same two-step procedure led to spiroaminals **55a** and **55b**, this time as mixtures of C-6 epimers (Scheme 15).

4. Strategy C – Bicyclization of Linear Precursors

In this last approach, obtention of the spiroaminal system proceeds through the concomitant cyclization of an ω-aza-ω′-oxa-functionalized linear key intermediate. Most methods for these double ring-closures are based on nucleophilic addition, with variations in the strategy originating from the nature of the unsaturated function undergoing the nucleophilic attack.

4.1 Staudinger Reduction/aza-Wittig Process

The synthesis of the spiroaminal part of an azaspiracid through a one-pot Staudinger reduction/intramolecular aza-Wittig imine capture sequence starting from the δ-azido γ′-hydroxy ketone **56** was envisaged by Forsyth and coworkers[25] (Scheme 16). The reaction between triethylphosphane and the azide function of **56** generated an iminophosphorane that underwent an intramolecular aza-Wittig reaction with the keto group to form the six-membered cyclic imine **57** in situ. Addition of the hydroxy group to the imine finally furnished the spiroaminal **58** in 75% yield as a 4:1 mixture of spiro epimers, the thermodynamically favoured (*S*) isomer being the major one (established by ^{1}H NMR spectroscopy).

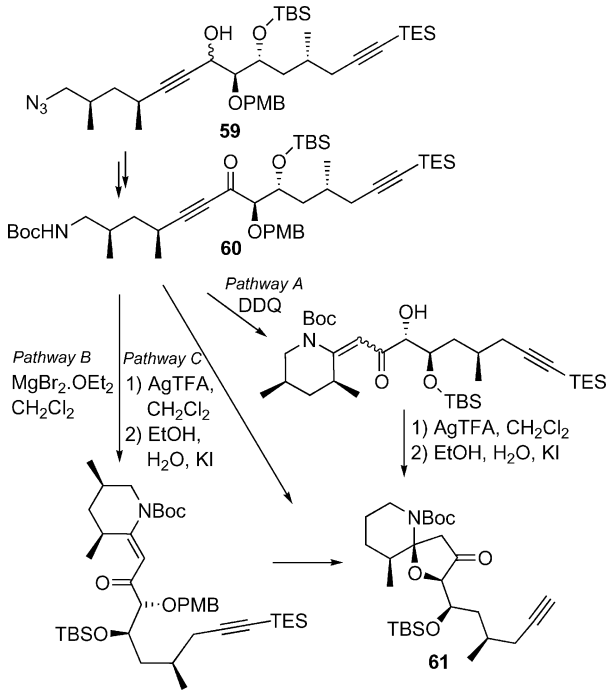


Scheme 16.

4.2 Double Intramolecular Hetero-Michael Additions (DIHMAs)

An alternative approach to the spiroaminal domain of azaspiracid has been reported by the same authors, who this time started from an α′-hydroxy-protected ynone **60** and used a double intramolecular hetero-Michael addition to generate the spiro core.[25]

The ketone **60** was first prepared in three steps and 62% overall yield from its corresponding alcohol **59** through a Staudinger reduction of the azide in water, followed by protection of the primary amine as its carbamate derivative and oxidation of the free hydroxy group. At this stage, three pathways were successfully applied for the transformation of the key intermediate **60** into the spiroaminal **61** (Scheme 17). In the first one (pathway A), PMB ether cleavage by DDQ was concomitant with the conjugate addition of the carbamate nitrogen atom at the ynone, leading to a hydroxy enaminone. This, subjected to the action of AgTFA and subsequent addition of ethanolic KI, cyclized to give **61** in two steps. Pathway B was based on the prior addition of the carbamate nitrogen atom at the ynone system by treatment with the Lewis acid $MgBr_2{\cdot}OEt_2$. After PMB ether cleavage, a second conjugate addition, conducted as in pathway A, led to the spiroaminal **61**. Finally, the use only of an AgTFA/ethanolic KI system on **60** allowed its direct conversion into **61** (pathway C) in a 56% one-step yield, through a process of simultaneous cleavage of alkyne and secondary alcohol protecting groups and double hetero-Michael addition.

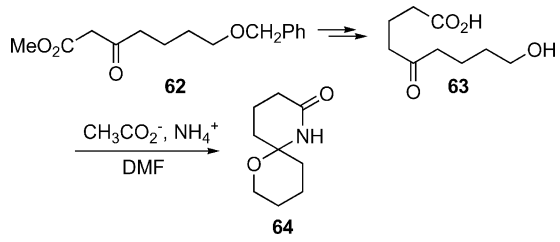


Scheme 17.

4.3 Acid-Catalyzed Spirocyclizations

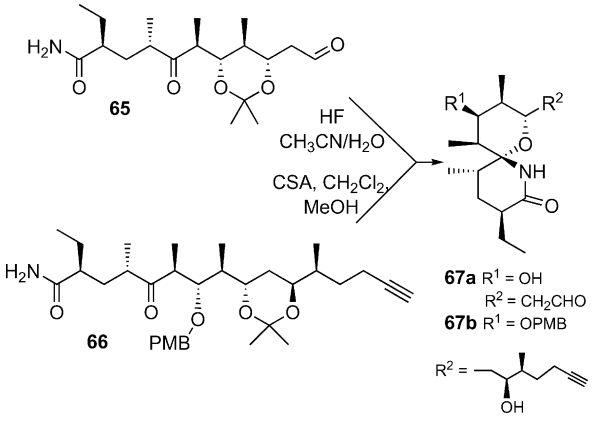
In cases of spiroaminals in which the nitrogen atom forms part of a lactam function, the formation of the spirocyclic system through a double acid-catalyzed cyclization of a linear ketone bearing an alcohol function at one end and an amido group at the other can be envisaged.

Cohen et al.[26] first synthesized the simplest 2-oxo-1-oxa-7-azaspiro[5.5]undecane **64** from the linear ketone **63**. A Michael addition between β-keto ester **62** and methyl acrylate delivered, after basic treatment, decarboxylation and hydrogenolysis, the hydroxy keto acid **63**. Subsequent addition of ammonium acetate in DMF afforded the spirolactam **64** in 62% yield (Scheme 18).



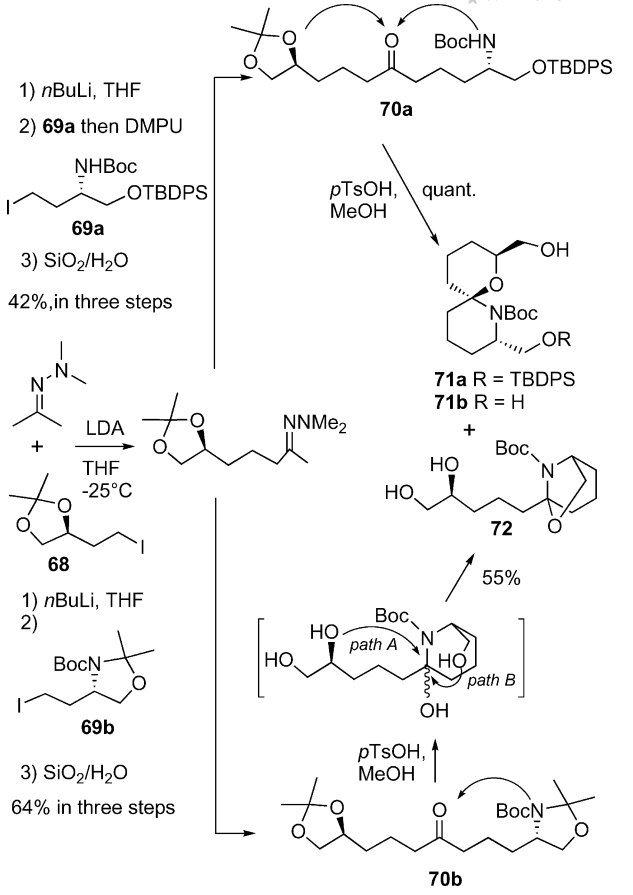
Scheme 18.

A similar approach was developed to afford access to the complex spiroaminal part of the natural sanglifehrin (Scheme 19). Elaboration of the spirocycles **67a** and **67b** through intramolecular lactamization of acetonide keto amides **65**[27] or **66**[28] in acidic medium was envisaged. Under these conditions, acetonide hydrolysis releases the alcohol functions, allowing in situ spirocyclization. This transformation was accomplished by use either of hydrofluoric acid in aqueous acetonitrile or of camphorsulfonic acid in a mixture of CH_2Cl_2 and MeOH, and led to **67a** or **67b** in 95% or 78% yields, respectively. These spiro compounds were isolated as single diastereomers possessing the natural spiro centre configuration.



Scheme 19.

For our part, we have envisaged the use of this acid-catalyzed spirocyclization strategy for the preparation of non-lactam spiroaminals. We have disclosed a practical and rapid synthesis of the spiroaminal **71** by using, as key step, an acidic catalysis to achieve concomitant deprotection of the acetonide moiety and ring-closure on the central keto function of **70a** (Scheme 20).[29]

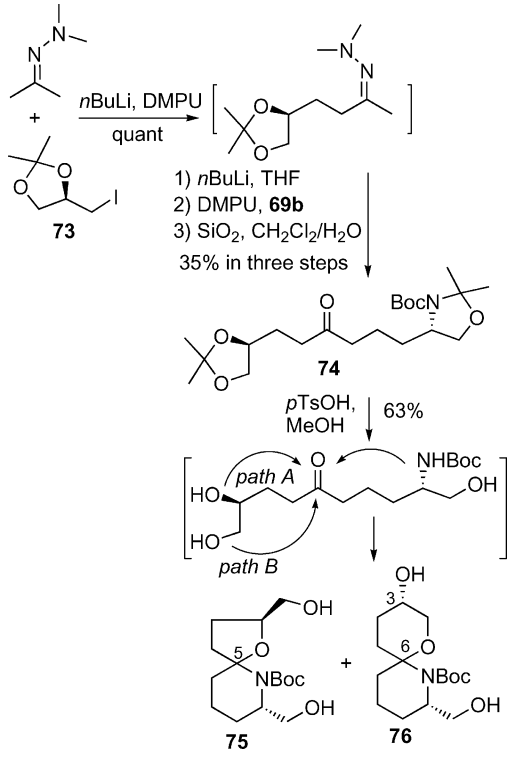


Scheme 20.

Preparation of the polyfunctionalized ketone **70a** was achieved in three steps with only one last purification, by iterative alkylation of the acetone *N*,*N*-dimethylhydrazone with chiral iodides **68** and then **69a**, followed by SiO_2/H_2O hydrolysis of the hydrazone.[29a] The limiting stage of this approach was the second alkylation step, which in fact led to complex mixtures (mono- and dialkylated compounds) and, to be efficient, required the use of DMPU as additive (Scheme 20). In this way, and after final exposure of **70a** to a catalytic amount of *p*-TsOH in methanol, spiro compound **71a** was obtained almost quantitatively as a single stereoisomer with a spiro centre configuration corresponding to those of the spiroaminal parts of azaspiracids or sanglifehrin.

Improvement of the ketone yield (64% instead of 42%) was achieved by use of oxazolidine iodide **69b**.[29b] However, the last step – simultaneous cleavage of oxazolidine and acetonide moieties together with spiroannelation through acid catalysis – afforded the spiroaminal **71b** only in a moderate yield of 47%. This result could be explained by the possible competition of two cyclization pathways, A and B, allowing the formation of the expected spiroaminal **71b** (path A) together with a polar bicyclic oxazolidine **72** (path B), which we were unable, however, to isolate in a pure state.[29b]

To validate the flexibility of our approach, we also prepared the homologue of **71** possessing a five-membered oxygenated ring: namely the spiroaminal **75** (Scheme 21). Alkylation of acetone *N*,*N*-dimethylhydrazone with iodide **73** in the presence of *n*BuLi/DMPU, followed by a second alkylation with *n*BuLi/**69b**/DMPU, afforded – after SiO_2 cleavage – ketone **74** in an overall three-step yield of 35%. Treatment of **74** with *p*-TsOH in methanol led, as expected, to deprotection of both dioxolane and oxazolidine moieties and promoted the spiroketalization in 63% yield. As we had observed in the spiroketal series,[30] two isomers **75** and **76** – resulting from a cyclization according to path B – were detected in a 8:17 ratio, each existing as a mixture of C-5 or C-6 epimers. However, in this aza series, the spiro[5.5]-undecanes **76** existed in equilibrium with the spiro[4.5]decanes **75**, and their separation could not be achieved.[29b]



Scheme 21.

3. Conclusion

The occurrence of spiroaminal frameworks in natural products of pharmacological importance constitutes an interesting challenge for the development of original and efficient synthetic methods to access these skeletons.

While this review demonstrates the existence of various pathways for the elaboration of simplest spiroaminals, it also shows the difficulty remaining in the establishment of a general strategy for rapid access to more complex compounds. Although work in this domain has experienced a significant increase these last years, this research area is still at its beginning, and chemistry of spiroaminals need to be – and certainly will be – developed in the next years.

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