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Construction of spiro lactones with concomitant formation of the fused quaternary centre – application to the synthesis of natural products

Alexandra Bartoli, Fabien Rodier, Laurent Commeiras, Jean-Luc Parrain and Gaëlle Chouraqui*

Polycyclic structures fused at a central carbon are of great interest due to their appealing conformational features and their structural implications in biological systems. Although progress in the development of synthetic methodologies towards such structures has been impressive, the stereoselective construction of such quaternary stereocentres remains a significant challenge in the total synthesis of natural products. This review highlights the progress in the formation of 1-oxaspiro[4.*n*]alkan-2-ones ($2 \leq n \leq 7$) with concomitant formation of the quaternary spiro centre.

- 1 Introduction
- 2 Oxidation: dearomatisation of phenol to quinone
 - 2.1 Hypervalent iodine(III)
 - 2.2 CAN oxidative coupling
- 3 Reductive cross-coupling
- 4 Radical-based approaches
- 5 Furanyl dienolate-based cyclisation
 - 5.1 Alkylation
 - 5.2 Addition onto an imine (vinylogous Mannich)
 - 5.3 Vinylogous aldol reaction
- 6 Cationic rearrangement
- 7 Use of organometallic derivatives
 - 7.1 Double acylation
 - 7.2 Reformatsky-type reaction
 - 7.3 Carbonyl insertion
- 8 Halolactonisation
- 9 Pericyclic-type reactions
 - 9.1 Electrocyclisation
 - 9.2 [2 + 1] photocycloaddition
 - 9.3 [2 + 2] cycloaddition
 - 9.4 Diels–Alder reaction
 - 9.5 [3 + 2]-type cyclisation
- 10 Miscellaneous
 - 10.1 1,6-Addition
 - 10.2 Dyotropic rearrangement
- 11 Conclusion
- 12 Acknowledgements
- 13 References

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1 Introduction

Spirolactones containing natural products represent a large class of structurally diverse molecules exhibiting a wide range of biological activities. Key examples include: drospirenone (Fig. 1), a synthetic progestin that is a component of certain birth control formulations such as Yasmin 28[®] (marketed by Bayer Schering Pharma),¹ the world's most popular contraceptive pill, ranked in the top 200 brand-name drugs by retail dollars in 2008;² and abyssomicin C, a potent antibacterial agent against Gram-positive bacteria, including resistant *Staphylococcus aureus* strains (MIC for a methicillin-resistant strain = 4 $\mu\text{g mL}^{-1}$; MIC for a vancomycin-resistant strain = 13 $\mu\text{g mL}^{-1}$).³

The stereoselective synthesis of spiro lactones is a challenging task, requiring control in the construction of the quaternary carbon.⁴ The presence of the sterically constrained spiro structure in various natural products of biological importance also adds to the interest in investigations of spiro compounds. Most of the methods to access spiro lactones involve an intramolecular esterification reaction, which is favoured for entropic reasons. A number of natural products have been obtained by this approach (e.g. arteannuine,⁵ norsecuringine,⁶ secu'amanine,⁷

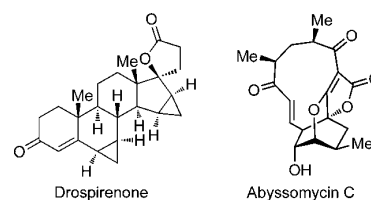


Fig. 1

stemamide⁸). Since this strategy requires the prior installation of the tertiary alcohol, these methods will not be covered within this review. Instead, we will focus on transformations involving the creation of the spiro lactone concomitant to cyclisation with the fused stereocentre – potentially powerful synthetic



Alexandra Bartoli

Alexandra Bartoli was born in Marseille (France) in October 1984. She obtained her BSc in chemistry in 2006 and her MSc in 2008, both from the Université Paul Cézanne in Marseille, where she is currently pursuing her PhD under the supervision of Dr Gaëlle Chouraqui and Dr Jean-Luc Parrain. Her research focuses on the development of new methods to access polycyclic compounds and spiro lactones.



Fabien Rodier

Fabien Rodier was born in Nîmes (France) in June 1984. In 2006, he joined the University of Montpellier (France) where he was awarded his BSc in chemistry. He then moved to the École Nationale Supérieure de Chimie de Montpellier (ENSCM), where he obtained his MSc in chemistry. He is currently pursuing his PhD under the supervision of Dr Gaëlle Chouraqui, Dr Laurent Commeiras and Dr Jean-Luc Parrain at the Université Paul Cézanne in Marseille (France).

His research focuses on the synthesis of spiro lactone moieties using [5 + 2] cycloaddition.



Laurent Commeiras

Laurent Commeiras was born in Marseille (France) in 1975. After studying chemistry at the Université Paul Cézanne in Marseille, he received his PhD degree in 2002 under the supervision of Dr Jean-Luc Parrain, working on the total synthesis of terpenoids isolated from algae of the order Caulerpales. After a postdoctoral position in the laboratory of Professor Sir Jack E. Baldwin at the University of Oxford (UK), he became Lecturer at the University of Marseille. His main research

interests include the total synthesis of natural and biologically active compounds.

transformations allowing the formation of a quaternary stereocentre (still one of the most challenging tasks in organic synthesis).

Herein, we will cover the synthesis of spirobutenolides and more specifically the 1-oxaspiro[4.*n*]alkan-2-ones ($2 \leq n \leq 7$) (Fig. 2).

This review will discuss different methods to create simultaneously the spiro lactone and the quaternary spiro stereocentre and their application to the synthesis of natural products. This will be divided either into categories of reaction or species used: oxidation, reduction, radicals, dienolate, cationic rearrangement, organometallic derivatives, halolactonisation, pericyclic reactions.

Spirocyclic structures have already been the subject of a number of reviews,^{9,10} including those devoted to spiroketals¹¹ and spirocyclic ethers,¹² and the reader is directed to these articles for discussion of these topics.



Jean-Luc Parrain

Jean-Luc Parrain obtained his PhD in Chemistry at the University of Nantes (France) under the supervision of Professor Jean-Paul Quintard. After post-doctoral studies in the laboratory of Professor Steve Davies at the University of Oxford (UK), he joined the CNRS as “chargé de recherche” at the laboratory of Organic Synthesis of the University of Nantes. In 1995, he moved to the University of Marseille and then was appointed a CNRS “directeur de recherches” in 2001. His

research interests include new catalytic reactions toward new synthetic methods, development of new organotin and silicon reagents and total synthesis of natural compounds.



Gaëlle Chouraqui

Gaëlle Chouraqui obtained her PhD in 2003, from the Université Pierre et Marie Curie (Paris, France), where she worked under the guidance of Professor Max Malacria and Dr Corinne Aubert. After a two-year stay as a Postdoctoral Research Fellow with Professor James H. Rigby at Wayne State University (US), she returned to Europe and completed a further year as a Postdoctoral Research Fellow in Professor Ian Paterson’s laboratory at Cambridge University. She was

appointed CNRS Tenured-Researcher in 2007 at Aix-Marseille University (France), and her research interests are centred on new methods for the synthesis of natural products.

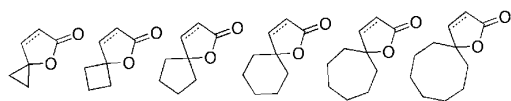


Fig. 2

2 Oxidation: dearomatisation of phenol to quinone

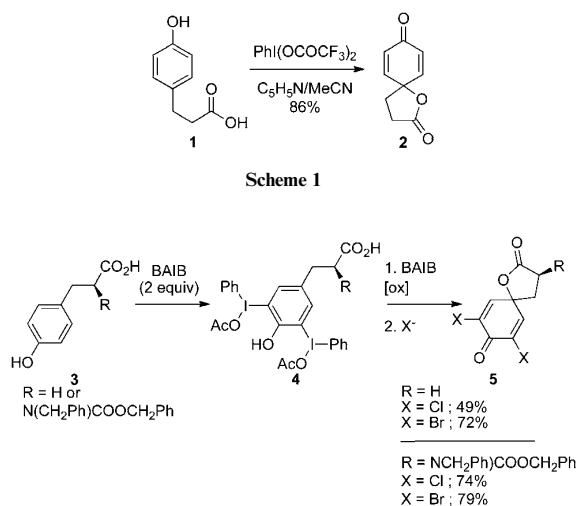
The prevalence of *p*-spiroquinones in natural products, biologically active molecules and ligands underscores the importance of devising general methods for their efficient construction. Quinones are commonly prepared by chemical oxidation,¹³ electrochemical oxidation¹⁴ or monohydrolysis of the corresponding quinone bisacetals. Phenolic oxidation has often been implicated as the pivotal step in the biosynthesis of natural product incorporating a *p*-spiroquinone moiety.

In 1987, Tamura¹⁵ reported an iodine(III)-induced dearomatisation of phenols to quinones. Later on Kobayashi described a novel cerium(IV)-mediated oxidative coupling of 2,6-dibromophenol derivatives.¹⁶ Both these methods have been used extensively in spiro lactone synthesis.

2.1 Hypervalent iodine(III)

In a typical procedure, a solution of *p*-phenol **1** in anhydrous acetonitrile was treated with bis(trifluoroacetoxy)-iodobenzene (BTIB) in presence of pyridine (Scheme 1). After oxidation of this phenol ring to the corresponding quinone, intramolecular *ipso*-trapping by the carboxy nucleophile took place, leading to the spiro compound **2** in 86% yield.

Later on, Hara¹⁷ described a one-pot procedure utilising bis(acetoxy)-iodobenzene (BAIB) followed by an aqueous sodium chloride or bromide quench to access dihalodienone spiro lactone **5** from phenol **3** (Scheme 2). Three equivalents of BAIB were required, but this reagent is much less expensive than the previously used BTIB. This domino process allowed the formation of three new σ -bonds together with a stereogenic quaternary centre.



Scheme 2

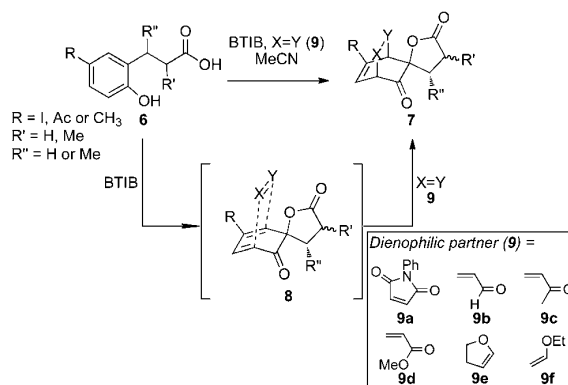
This methodology was next extended to a domino reaction featuring the Wessely-type intramolecular oxidation¹⁸ followed by an intermolecular Diels–Alder reaction (Scheme 3).¹⁹ Unlike previously reported examples, phenol **6** bears the carboxylic acid suitably tethered at the *ortho* position. An additional functional group *para* to the alcohol circumvents any trapping at that position. Treatment of phenol **6** with BTIB provided intermediate diene **8**, which was then set to undergo [4 + 2] cycloaddition with a range of dienophiles **9a–f** present in the reaction mixture.

Alkenes **9a–d** proved to be good dienophiles, and provided the corresponding polycyclic structures **7** (R' = R'' = H) as single diastereomers in yields ranging from 50 to 89%. The diastereoselectivity of the transformation is explained by attack of the dienophile occurring from the less hindered oxygen-bearing face of the diene.

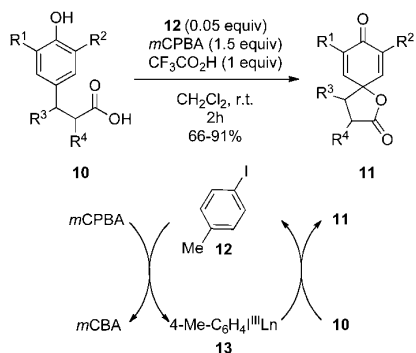
Alkynes are also competent dienophiles but require higher temperatures, and yields are lower than with their olefinic counterparts. Electron-deficient dienes **8** (R = I or Ac and R = R' = H) when reacted with electron-rich alkenes (**9e–f**) gave excellent yields (from 74 to 91% yield) in this inverse-electron-demand Diels–Alder reaction. Single diastereomers were observed here also.

Finally, Wood *et al.* showed that this reaction proceeded with good substrate-based control. Whilst a methyl group α to the carboxylic acid **6** (R = R' = Me and R'' = H) provided little stereo-induction, leading to a mixture of two diastereomers in a 1 : 1 ratio, a methyl group at the β position **6** (R = R'' = Me and R' = H) provided cycloadduct **7** as a single diastereomer. Hypervalent iodine(III) has the advantage of using an environmentally benign organo-oxidant, which is more efficient than DDQ or ferric chloride.

Kita recently made an important breakthrough by perfecting the first Wessely-type reaction using a catalytic amount of iodine(III)²⁰ and subsequently by developing a chiral hypervalent iodine(III) reagent for the enantioselective dearomatisation of phenols.²¹ In the catalytic version the authors demonstrated that hypervalent iodine(III) could be generated *in situ* from 4-iodotoluene (**12**) by using *m*-CPBA as a co-oxidant in presence of triflic acid as an additive (Scheme 4). The intermediate **13** mediated the oxidation of phenols **10** into spiro-quinones **11** with concomitant regeneration of 4-iodotoluene **12** in yields ranging from 66 to 91%. This versatile procedure was performed at room



Scheme 3



Scheme 4

temperature and required only 0.05 equivalents of catalyst **12**. The authors did not mention the diastereoselectivity of the reaction.

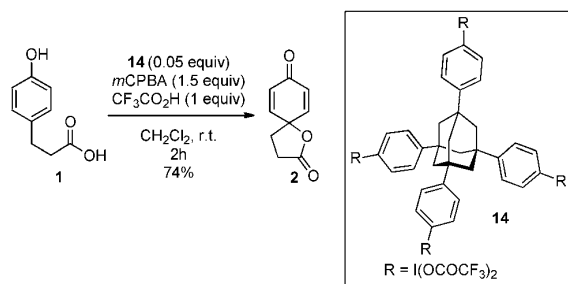
In further experiment, Kita *et al.* designed and synthesised a recyclable catalyst **14** (Scheme 5). Its extraction from the reaction mixture, in nearly quantitative yield, was facilitated by its insolubility in methanol.

In the first example of its kind, Kita and co-workers have designed and implemented a chiral iodine(III) oxidant for the enantioselective formation of spirolactones. Chiral iodine(III) reagent (*R*)-**15**, which has a rigid spirobiindane skeleton (Scheme 6), mediates the formation of *ortho*-spirolactone (+)-**18** in high yield (86%) with a significant level of enantioselectivity (86% *ee*). Early studies also demonstrated that a catalytic version was possible by using 30 mol% of chiral iodoarene (*R*)-**16** and *m*-CPBA as a co-oxidant in the presence of acetic acid; however, the observed enantiomeric excess was significantly lower (69% *ee*).

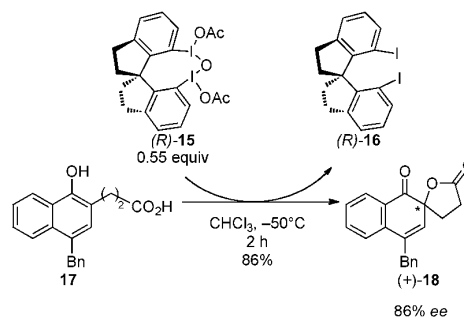
In early 2010, Ishihara *et al.* developed a conformationally flexible C_2 -symmetric chiral iodoarene **19**,²² which, upon reaction with an oxidant, generated *in situ* the effective catalyst iodosylarene **20** (Scheme 7). The authors believed that a structural chiral environment is imparted by either hydrogen-bonding (see **20a**) or $n-\sigma^*$ intramolecular interactions (see **20b**).

Treatment of 1-naphthol derivatives **21** with precatalyst **19** (10 mol%) and *m*-CPBA (1.2–1.5 equiv) at 0 °C in a 2 : 1 mixture of chloroform and nitromethane (Scheme 8) provided *o*-spirolactones in good yield and enantiomeric excess (>83% *ee*).

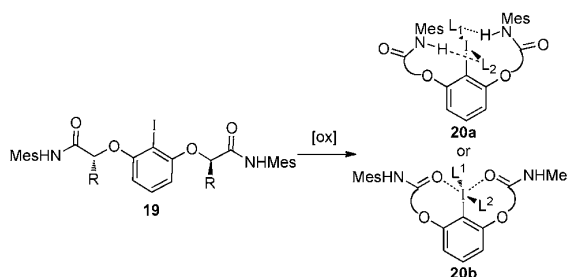
The hypervalent iodine(III) phenolic dearomatisation strategy has been applied with success to the synthesis of a range of natural products including aranorosin (**22a**) (Fig. 3) or



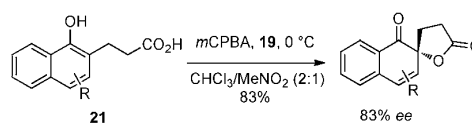
Scheme 5



Scheme 6



Scheme 7



Scheme 8

(+)-scyphostatin (**23**) (*vide infra*), thereby illustrating the scope of the method.

Aranorosin (**22a**) was isolated in 1988 from the fermentation broth of the fungal strain *Pseudoarachniotus roseus* by Fehlhauer, Mukhopadhyay and co-workers.²³ This highly

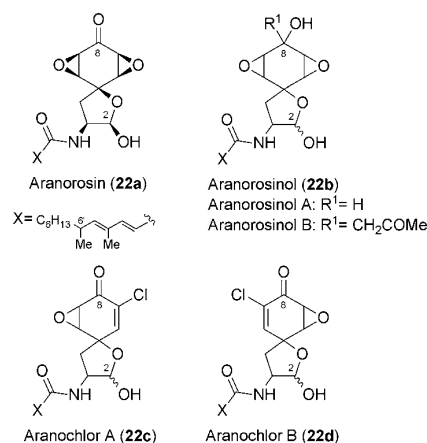


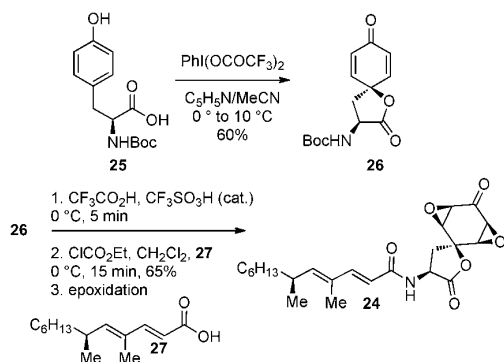
Fig. 3

oxygenated tetracyclic compound incorporates seven stereocentres (five being contiguous) and two epoxides. Whilst the relative stereochemistry for aranososin has been established by extensive NMR spectroscopic analysis together with chemical degradation, the stereochemistry of the remote C-6' stereocentre together with the absolute configuration remained undetermined. Aranososin exhibits antitumour and antifungal properties in addition to antibiotic activity against both Gram-positive and Gram-negative bacteria,^{23a,c} yeast and filamentous fungi (*e.g.* MIC = 1.5 $\mu\text{g mL}^{-1}$ for *Staphylococcus aureus*, *Bacillus subtilis* and *Micrococcus luteus* strains). Subsequently, fermentation of the same fungal strain led to the isolation of four more metabolites: aranorisinols A and B (which were reduced at C-8 and C-2; compare to **22a**)²⁴ and aranochlors A and B (monoepoxides).²⁵ These compounds proved to be less active, therefore suggesting that the bicyclic core plays a crucial role in the antifungal activity of aranososin. Accordingly a structure–activity relationship carried out by Vijayakumar *et al.* concluded that the carbonyl at C-8 and the bisoxirane moiety are essential for the antifungal activity.²⁶ Aranososin has also been reported to inhibit the anti-apoptotic functions regulated by Bcl-2.²⁷

Three total syntheses²⁸ have been reported, each of which has used the same method to install the quaternary spiro stereocentre *i.e.* an oxidative cyclisation. However, Rama Rao was the first to use (in 1991) the phenolic dearomatisation as a key step to reach the spirolactone backbone **24** contained in aranososin (Scheme 9).²⁹ Due to the chemical instability of the lactol natural product, the authors chose to prepare the corresponding lactone **24**. The quaternary stereocentre was set up *via* the Wessely-type oxidation of *N*-trifluoroacetyl-L-tyrosine **25** in the presence of BTIB and pyridine in acetonitrile. Compound **26** was obtained in 60% yield. Deprotection of the Boc group followed by the introduction of the side chain **27** and subsequent epoxidation provided the bis-epoxide **24**. Even though the NMR spectra were similar to that reported for the natural compound **22a**, the stereochemistry at C-6' could not be firmly established due to the lack of optical rotation data for the side chain.

En route to their total synthesis, both Wipf and McKillop prepared the natural product and its C-6' epimer in order to be able to assign its absolute configuration as *R*.

More recently, in a related example, Takagi and co-workers³⁰ were able to take advantage of the diastereoselective formation of the spiro quaternary centre during the phenolic



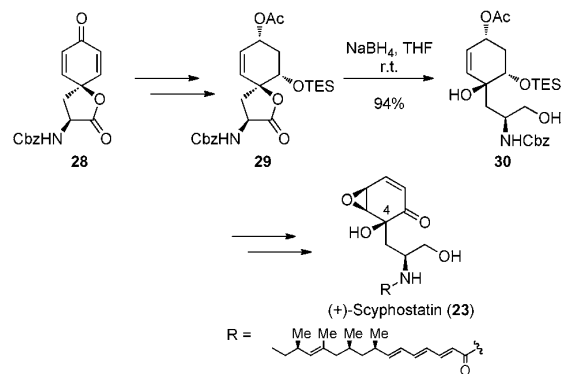
Scheme 9

dearomatisation step leading to **28** in their total synthesis of (+)-scyphostatin (**23**) (Scheme 10). This natural product was isolated from a mycelial extract of *Dasyascyphus mollissimus* SANK-13892, and displays the most potent and specific inhibitory activity to sphingomyelinase (N-SMase) reported to date, with an IC₅₀ of 10 μM .³¹ (+)-Scyphostatin **23** and its analogues quickly attracted the attention of the synthetic community,³² and hold significant potential as drug candidates for the treatment of inflammatory, immunological and neurological disorders.

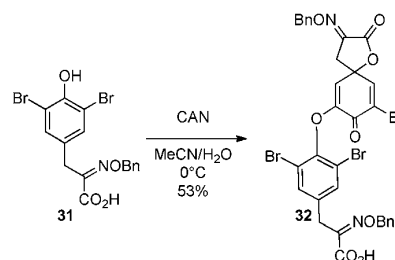
Structurally, (+)-scyphostatin consists of an oxygenated cyclohexenone adorned with an epoxide and an unsaturated fatty acid side chain bearing an amino alcohol. The tertiary alcohol at C-4 was installed in an efficient manner through reductive opening of the spirolactone **29**, to provide the corresponding diol **30** in an excellent yield of 94%. According to Giannis and Pitsinos,^{32b} the epoxy-cyclohexenone appears to be important for the biological activity.

2.2 CAN oxidative coupling

In 2005,¹⁶ a publication featuring a cerium(IV)-mediated oxidative coupling of 2,6-dibromophenol derivatives was reported by Kobayashi. None of the classical oxidants usually used for phenolic oxidation were able to deliver the expected compound **31** – reagents derived from iron(III), thallium(III) or lead(IV) led to the degradation of the starting material. Hypervalent iodine(III) BTIB gave only trace amounts of the desired adduct. However cerium(IV) ammonium nitrate (CAN) in aqueous acetonitrile afforded the desired cyclic carbamate in 53% yield (Scheme 11). This domino reaction allowed the formation of two new C–O



Scheme 10



Scheme 11

single bonds concomitantly with the creation of a stereogenic quaternary centre.

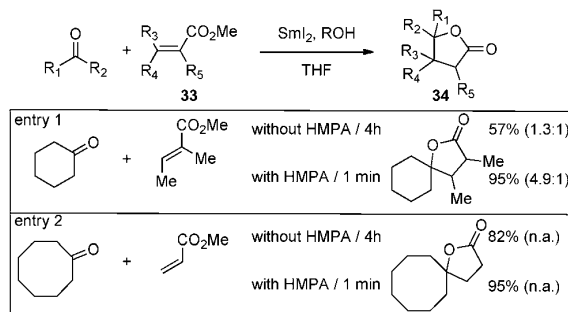
These different approaches illustrate the versatility of phenol ring oxidation to the corresponding quinone in the synthesis of complex molecules. Not only is the diastereoselectivity excellent in many cases, but the conditions for hypervalent iodine(III) are especially mild. Thanks to recent work from Kita, only a catalytic amount of iodotoluene is sufficient to perform the reaction. In addition, chiral hypervalent iodine(III) catalysts reported by Ishihara and Kita are also available for the enantioselective synthesis of these spiro compounds. However, this is only applicable to the chemistry of phenol rings.

3 Reductive cross-coupling

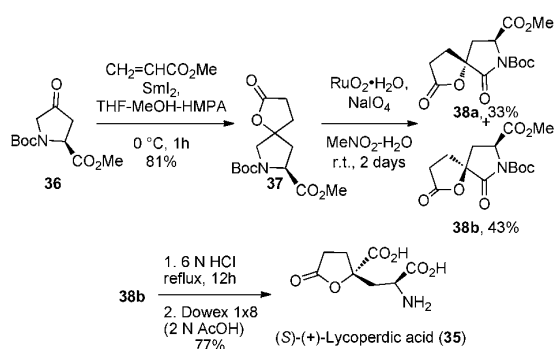
A particularly attractive method for the formation of spirolactones was independently reported by Fukuzawa³³ and Inanaga,³⁴ involving the samarium(II)-mediated reductive cross-coupling of ketones with α,β -unsaturated esters, leading to lactones of type **34** (Scheme 12). This one-pot reaction effected rapid (1 min) formation of two single bonds and the creation of a quaternary stereocentre in high yields (95%), albeit with modest diastereoselectivity. Significant rate enhancement and improved diastereoselectivity was observed with HMPA as co-solvent (entry 1).

This methodology was employed in the first synthesis of lycoperdic acid (**35**) (Scheme 13),³⁵ a non-proteinogenic α -amino acid isolated in 1978 from the mushroom *Lycoperdon perlatum*.³⁶ To date, no biological activity has been reported for this natural product. However it is a glutamate derivative and was therefore considered to be promising in the search for new biologically active compounds targeting neurodegenerative disorders. The structural features of lycoperdic acid were determined by both chemical and spectroscopic methods. This five-membered lactone incorporates a quaternary carbon α to the lactone oxygen, which was introduced by the cross-coupling of ketone **36** with methyl acrylate. The corresponding spirolactone **37** was obtained as a mixture of two diastereomers. Subsequent oxidation provided the amides **38**, which could be separated by flash chromatography on silica gel. The major stereoisomer **38b** underwent a straightforward hydrolysis in acidic conditions to provide the natural product **35**. The quaternary centre thus established corresponds to the fused stereocentre of the previous spiro compound.

The scope of this reductive cross-coupling reaction was further extended when Merlic developed an enantioselective version



Scheme 12



Scheme 13

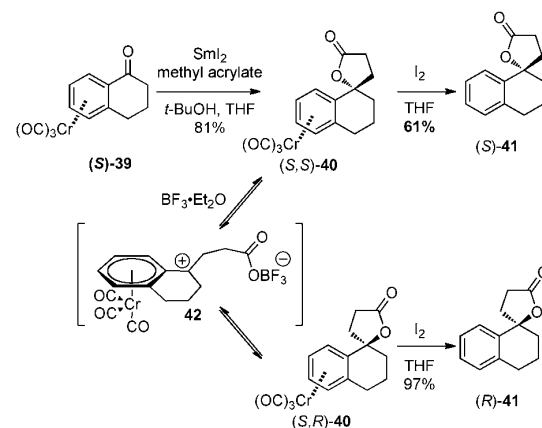
employing enantiopure tricarbonylchromium–arene complexes such as (*S*)-**39**.³⁷ Treatment with 2.5 equivalents of samarium iodide and 5 equivalents of methyl acrylate in the presence of *tert*-butyl alcohol led to the *endo*-lactone complex (*S,S*)-**40** in 81% yield, with 100% *de* and 100% *ee* (Scheme 14). The stereocontrol in this process derives from approach of the ester to the ketyl radical *anti* to chromium. Decomplexation by treatment with iodine provided the enantiopure spiro product (*S*)-**41** in 61% yield.

The authors were then able to access the alternative diastereomer of chromium-spirolactone (*S,R*)-**40** via a Lewis acid-mediated cationic rearrangement. In presence of 0.5 equivalents of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in 1,2-dichloroethane for 1 min, the *endo*-lactone complex underwent a ring-opening–ring-closing sequence via the stabilised carbocation **42**, leading to a mixture of *exo*- and *endo*-lactone (*S,R*)-**40** and (*S,S*)-**40** in an 8 : 1 ratio. Decomplexation of the major diastereomer (*S,R*)-**40** provided the enantiopure spiro product (*R*)-**41** in 97% yield.

Thus, both possible spirolactone enantiomers can be accessed from the same starting material. However, the nature of the substrates is limited due to the requirement for an appended benzene ring.

4 Radical-based approaches

Various radical initiators, *e.g.* TTMSH/AIBN and $(\text{Bu}_3\text{Sn})_2/h\nu$, have been used to synthesise spirolactones. However, all the



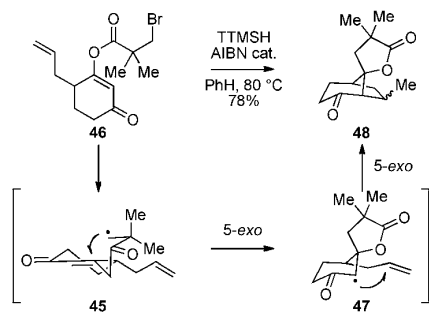
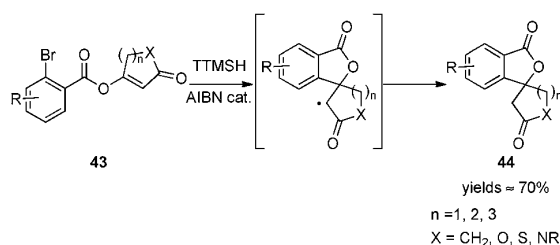
Scheme 14

different methods rely on the same strategy, which consists of radical-promoted formation of the five-membered lactone (the appended ring at the spiro centre being established already).

A radical-mediated Michael addition was developed by Zhang for the formation of benzospirrolactones.³⁸ Tris(trimethylsilyl)silane (TTMSH) and a catalytic amount of 2,2'-azobis(2-methylpropionitrile) (AIBN) as initiator were employed to generate the aryl radical from **43** (X = CH₂), which then underwent a smooth 5-*exo* cyclisation to generate spirrolactones **44** in good yield (Scheme 15). This method is quite versatile and tolerant of different substituents on the aryl moiety; similar results were obtained with electron-withdrawing or electron-donating substituents. However, the diastereoselectivity observed is often poor. This approach was then extended to the formation of spirodilactones (X = O), spirrolactone-lactams (X = NR) and spirrolactone-thiolactones (X = S) in similar yields.³⁹

The methodology was exploited in a domino reaction leading to bridged spirrolactones after a double cyclisation (Scheme 16).⁴⁰ Generation of the alkyl radical **45** from bromide **46** initiated a 5-*exo* cyclisation onto the appended enone to provide a second radical **47**, which could then undergo a second 5-*exo*-trig cyclisation to generate the bridged lactone **48** in 78% yield as a 1 : 2 mixture of diastereomers (Scheme 16). Isolation of compound **48** suggested that the initial radical added onto the enone *anti* to the allylic group **45**. However, due to free rotation around the allylic double bond the second cyclisation is less selective, explaining the poor diastereoselectivity observed during this sequence. Despite this, three new contiguous stereocentres were created, including the spiro carbon along with two single bonds, making it a very powerful process for building molecular complexity.

Larger ring sizes could also be accessed *via* this method. When a methyl group is added to the double bond on the side chain (as



in **49** and **50**), a 6-*endo* process occurred, affording **51** and **52** in 76 and 58% yield (respectively) as single isomers (Scheme 17). 16% of the product **53** arising from a single Michael addition was also isolated.

Another method utilised hexabutylditin as the radical initiator. Curran *et al.* have demonstrated formation of spirrolactones *via* a one-pot atom-transfer addition and annulation of iodo-malonate **54** and methylenecyclohexane (**55**) in the presence of a catalytic amount of hexabutylditin (10 mol%) under irradiation (275 W sun-lamp).⁴¹ The reaction is thought to proceed *via* intermediate **56** to afford the corresponding lactone **57** in 47% yield, together with 25% of eliminated alkenes **58** (8 : 1 *endo:exo*) (Scheme 18). During this process, several bonds were created sequentially with concomitant formation of the fused quaternary carbon.

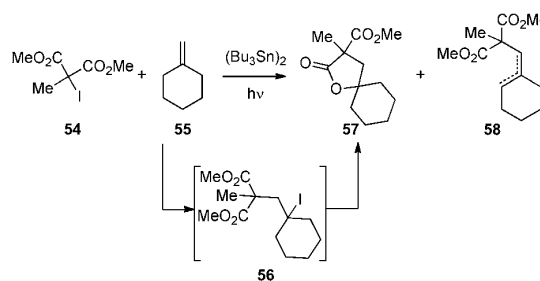
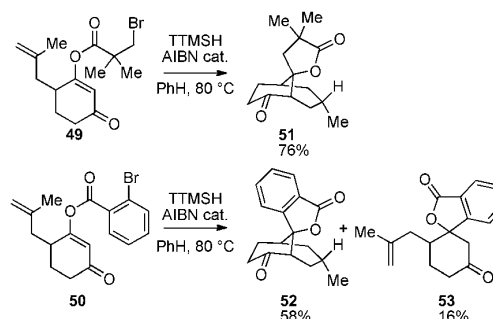
5 Furanyl dienolate-based cyclisation

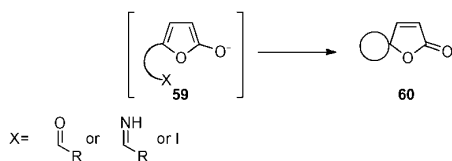
Access to spirrolactones has also been achieved *via* the intramolecular alkylation (X = I) or acylation (X = imines or aldehydes) of furanyl dienolates of type **59** (Scheme 19). Once again, this allows simultaneous generation of the quaternary spiro centre and the ring appended to the lactone.

Unlike the classical esterification strategy to form spirrolactones bicyclic compounds, in Suginome's approach, the cycle appended to the lactone ring was formed last.⁴²

5.1 Alkylation

γ -Deprotonation of benzylic lactone **61** with LDA in HMPA/THF generated the corresponding lithium anion, which





Scheme 19

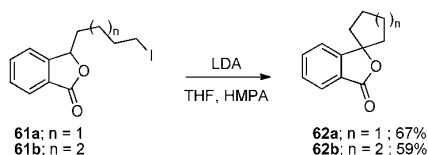
underwent rapid 5- or 6-*exo*-tet alkylation to provide the spiro products **62a** and **62b** in 67 and 59% respectively (Scheme 20).

This process has been extended by Markó to an intermolecular, two-step approach to spirocyclic butenolides.⁴³ First, a ZnCl_2 -mediated condensation of 2-(trimethylsilyloxy)furan (**63**) and orthoester iodides **64** gave the lactones **65** in 95 and 83% yield respectively (Scheme 21). Further treatment with a base produced the corresponding dienolate, which then underwent the previously described intramolecular alkylation reaction to afford the spirocyclic moieties **66** in good yield, whether the extra ring was five- or six-membered. 2-(Trimethylsilyloxy)furan is thus exploited as a dianion equivalent in this short and efficient sequence.

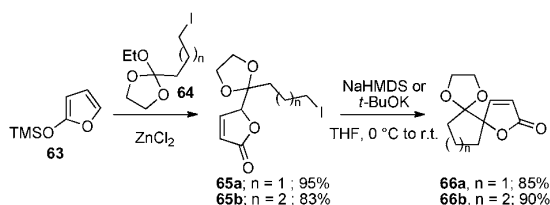
5.2 Addition onto an imine (vinylogous Mannich)

The study of the vinylogous Mannich reaction for the formation of spiroactones has been ably illustrated by the total synthesis of rugulovasines A (**67a**) and B (**67b**), and croomine (**68**).

Isolation of rugulovasines A and B was first reported from strains of *Penicillium concavo-rugulosum*⁴⁴ and subsequently from *Penicillium islandicum*,⁴⁵ *Penicillium bifforme*⁴⁶ and *Penicillium variable* 1912.⁴⁷ Rugulovasines A and B are members of the ergot indole alkaloid family,⁴⁸ which are characterised by the unique spiroactone they contain (Scheme 22). The tetracyclic structure of rugulovasine was proposed on the basis of chemical evidence and crystallographic analysis.⁴⁹ Interestingly, rugulovasines A and B were isolated as racemates which interconverted upon warming, presumably *via* a retro-vinylogous Mannich–vinylogous Mannich process. This provided the inspiration for Martin's total synthesis.⁵⁰ The furyl stannane **69** and the bromo-



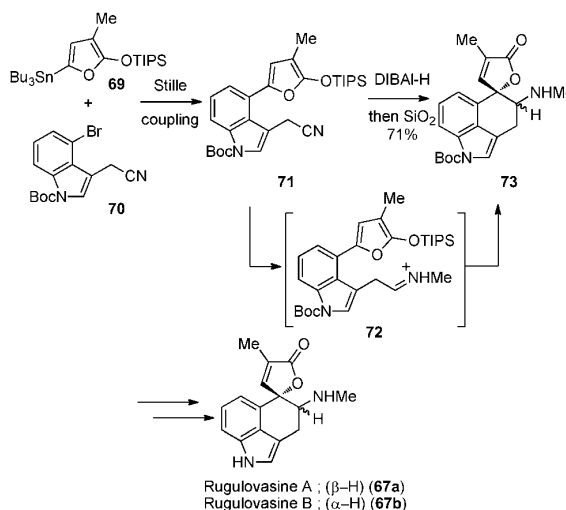
Scheme 20



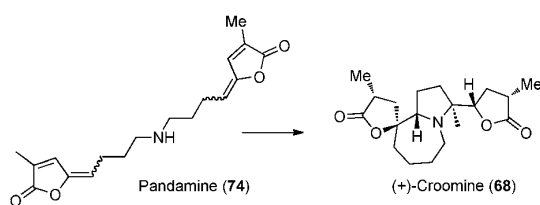
Scheme 21

indole **70** were coupled and advanced to the key cyclisation precursor **71**. Reduction of the nitrile group of **71** with DIBAL-H afforded the intermediate imine **72**, which upon treatment with silica underwent the vinylogous intramolecular Mannich reaction and provided the tetracyclic core of the rugulovasines, **73**.

In a very similar fashion, the vinylogous Mannich strategy was applied to the synthesis of (+)-croomine and allowed the formation of the seven-membered aza ring.⁵¹ (+)-Croomine, which belongs to the *Stemona* alkaloid family, was isolated from the roots and rhizomes of *Croomia heterosepala* in 1979,⁵² and subsequently from *Stemona tuberosa*,⁵³ *Stemona japonica*,⁵⁴ and *Stichoneuros calcicola*⁵⁵ (Scheme 23). These plants have been applied in traditional Chinese medicine for centuries for the treatment of various respiratory diseases (bronchitis, pertussis and tuberculosis), and to prevent attack by human and cattle parasites, agricultural pests and domestic insects.⁵⁶ The antitussive profile of (+)-croomine was highlighted in 2008, and the natural product was reported to exhibit dose-dependent inhibition of coughing ($\text{ID}_{50} = 0.18 \text{ mmol kg}^{-1}$).⁵⁷ Its structure and relative and absolute stereochemistry was elucidated unambiguously on the basis of X-ray crystallographic analysis, and chemical and spectral evidence.⁵² More recently, a biogenetic origin of croomine was suggested and supported by the co-isolation of pandanamine from *Stichoneuros calcicola*.⁵⁵ (+)-Croomine is presumably formed by cyclisation of pandanamine (**74**).



Scheme 22



Scheme 23

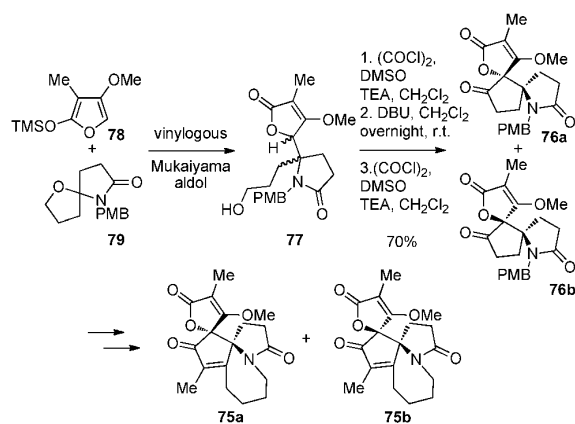
5.3 Vinylogous aldol reaction

As part of the total synthesis of molecules from the family of the stemonamides and the lambertellols, a vinylogous aldol reaction was employed to form the quaternary spiro centre.

(a) Synthesis of (±)-stemonamide and (±)-isostemonamide. (±)-Stemonamide (**75a**) and (±)-isostemonamide (**75b**), members of the aforementioned structurally related family of *Stemona* alkaloids, were isolated from the roots of *Stemona japonica* by Xu and co-workers (Scheme 24).⁵⁸ The densely functionalised pyrrolo[1,2-*a*]azepine structure of these natural products was elucidated by means of X-ray analysis and extensive NMR spectroscopic analysis. In 2010, two stemonamide analogues were identified that inhibited Pim-3 kinase activities ($IC_{50} = 78 \mu\text{M}$ for T-2/ $IC_{50} = 92 \mu\text{M}$ for T-5). In addition, they inhibited the cell proliferation of various cancer cell lines (human pancreatic, hepatocellular and colon cancer) *in vitro*,⁵⁹ and induced the apoptosis of human pancreatic cancer cell lines *in vitro* (Fig. 4)⁶⁰ These molecules could therefore be potential potent anticancer drugs with apoptosis-inducing ability.

In 2001, Kende and co-workers reported the synthesis of stemonamide (**75a**) and its epimer isostemonamide (**75b**).⁶¹ Their strategy suggested reaching the spirobicyclic butenolide **76** via an intramolecular vinylogous aldol reaction from **77**. The bicyclic starting material necessary for this transformation comes from an intermolecular vinylogous Mukaiyama aldol-type reaction between the key subunits **78** and **79**.

Oxidation of the primary alcohol **77** into aldehyde was performed under Swern conditions. Next, treatment with DBU in dichloromethane at room temperature overnight resulted in the formation of the spiro quaternary centre as a 1 : 1 mixture of diastereomers **76**. Finally, the azepine ring **75** was formed *via* an



Scheme 24

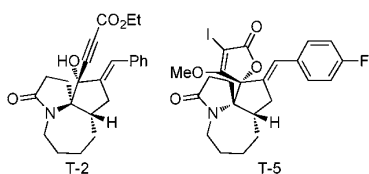


Fig. 4

intramolecular nucleophilic displacement of mesylate in 70% yield over three steps. Notably, the lack of diastereoselectivity observed during the key spirocyclisation was advantageous, as both epimers were required for the total synthesis of (±)-stemonamide (**75a**) and (±)-isostemonamide (**75b**).

(b) Synthesis of lambertellols. The tricyclic spirobutenolides lambertellols A, B⁶² and C⁶³ were isolated from the culture broth of a congeneric fungus, *Lambertella* sp. 1346 (Fig. 5), and are responsible for mycoparasitism on apple fruits.⁶⁴ Structurally, these three molecules present a spiro-1-furan-2-(5*H*) skeleton which was established by extensive NMR spectroscopic methods. The absolute stereochemistry of lambertellols A and B were determined on the basis of CD spectra after chemical derivatization. In contrast, lambertellol C was found to exist as a racemate. A biosynthetic pathway was suggested and supported by the co-isolation of lambertellin and chrysophanol.^{63,64b} From a biological point of view, lambertellols A and B demonstrated growth inhibition of spores of *Cochlibolus miyabeanus* ($IC_{50} = 0.5 \mu\text{g L}^{-1}$) and were found to possess weak cytotoxicity against P388 murine leukemia ($IC_{50} = 12$ and $15 \mu\text{g L}^{-1}$ respectively).⁶⁵

Hashimoto *et al.* exploited an intramolecular vinylogous aldol reaction to form the spirobutenolide moiety.⁶⁵ Accordingly, methacrylation of **81** followed by ring-closing metathesis (RCM) with Grubbs II catalyst conveniently provided the requisite butenolide **82** (Scheme 25). The crucial aldol reaction ensued upon treatment of aldehyde **82** with NaHMDS in DMF at -40°C , forming the lambertellol ring within **83a** and its diastereomer **83b** in 77 and 13% yield respectively. Once again, both diastereomers could be advanced to their respective natural products lambertellol B and A after late-stage chemoselective oxidations. Lambertellol C was obtained by simple oxidation of the corresponding diol.

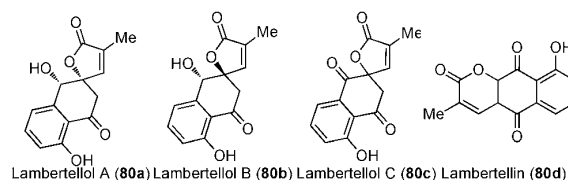
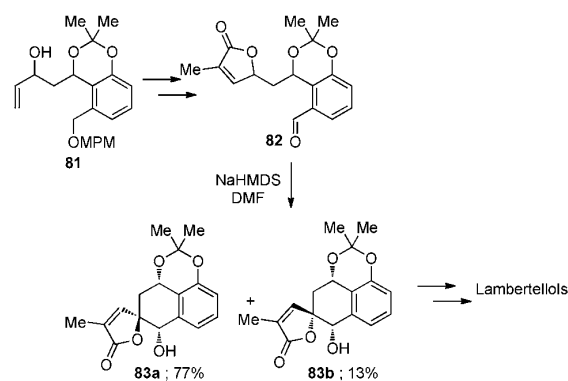


Fig. 5



Scheme 25

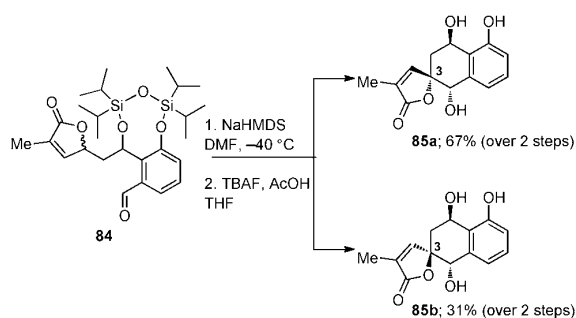
Interestingly, employing the sterically congested butenolide **84** allowed adjustment of the diastereoselectivity of the reaction in favour of diastereomer **85a** (2.2 : 1 *dr*) (Scheme 26).

6 Cationic rearrangement

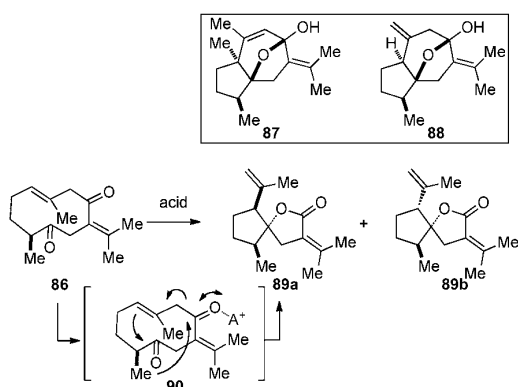
During the course of studies to delineate the biomimetic pathway from dehydrocurdione **86** to curcumenol **87** and isocurcumenol **88**, Kodama and Fukazawa showed that, whilst dehydrocurdione afforded curcumenol upon treatment with potassium carbonate or alumina in benzene, when dehydrocurdione was treated under acidic conditions, a 1 : 1 diastereomeric mixture of spiroactone **89** was obtained quantitatively (Scheme 27).⁶⁶ This interesting transformation presumably proceeds *via* the described cationic intermediate **90** rather than the pericyclic (Alder-ene) pathway to **87** and **88**.

Another cationic rearrangement, this time involving an aryl-nitrenium ion, has been highlighted. A solution of β -(4-azidophenyl)propanoic acid in trifluoroacetic acid at 0 °C was treated with trifluoromethanesulfonic acid and allowed to stir at room temperature for 25 h (Scheme 28).⁶⁷ The spirodienone **92** resulted from *ipso*-attack by the carboxy group *para* to the nitrenium ion, but **92** was produced in a low yield of 20%.

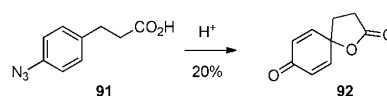
Another method utilising allylic cations has also been employed to generate spiroactones. Treatment of allylic alcohol **93** with hydrochloric acid provided the stabilised allylic carbocation **94** (Scheme 29),⁶⁸ which was trapped by the tethered



Scheme 26



Scheme 27



Scheme 28

carbonyl group to provide the allylic spiroactone **95** in good yield (67%).

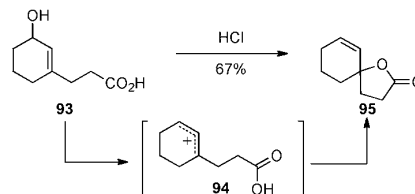
7 Use of organometallic derivatives

In the following section, we provide an inventory of the reactions that use organometallic species to access spiroactones. Three main reactions have been reported in the literature: double acylation using bis-metallated species, metal-mediated Reformatsky reaction, and processes involving carbonyl insertion.

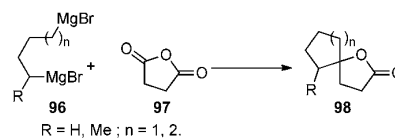
7.1 Double acylation

Bis-metallated species have been exploited to form spirocyclic molecules in a single step through annulation to a carbonyl substrate. This is exemplified by Canonne strategy, which consists of adding a bis-Grignard reagent **96** to a cyclic carbonyl **97**.⁶⁹ A double acylation took place on the same carbonyl of an anhydride derivative, and afforded the corresponding spiroactones **98** (Scheme 30). This strategy has the advantage of flexibility over the bonds formed during the annulation process, as exemplified by addition of lithium 3-lithiopropanoate to cyclic ketone **99** (Scheme 31).

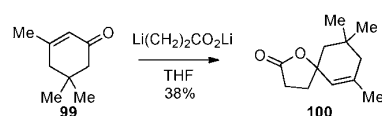
A related strategy reported by Santelli and co-workers⁷⁰ involves the double Sakurai addition of 1,8-bis(trimethylsilyl)octa-1,6-diene **101** with succinic anhydride (Scheme 32), to generate spiroactone **102** in good yield (80%). However, this



Scheme 29



Scheme 30



Scheme 31

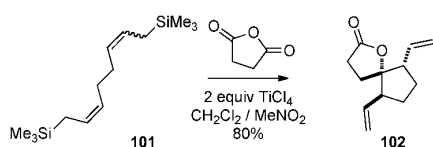
procedure is less efficient with α,β -unsaturated anhydrides like maleic or itaconic anhydride. Divinylspirolactones **102** have proven to be useful in the synthesis of a number of natural and non-natural steroids.⁷⁰

7.2 Reformatsky-type reaction

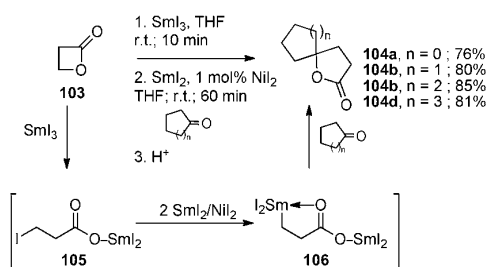
A coupling reaction catalysed by $\text{SmI}_2/\text{NiI}_2$ and using β -propiolactone (**103**) as the reactant has been described to provide spirolactones of different size **104** ($0 \leq n \leq 3$) in good yields (from 76 to 85% yield) (Scheme 33).⁷¹ During the course of this reaction, samarium mediated the formation of a homoenolate equivalent **106**, which then reacted with a cycloalkanone. A samarium-mediated spirocyclisation of cycloalkanones with methyl 3-bromopropionate had already been reported by Csuk seven years earlier,⁷² but the spirolactone product was isolated only as a minor product of the reaction. Since then, several groups have shown their interest in this transformation, and it has been the subject of extensive publications: metallic Zn,⁷³ Sn,⁷⁴ and In⁷⁵ derivatives have been reported to mediate reductive cyclisation of bromomethyl acrylate derivatives **107** and cyclic ketones **108** (Scheme 34). This Reformatsky-type reaction provided spirolactones **109** exhibiting an *exo* double bond in moderate (40% for SnCl_2)⁷⁴ to good yield (82% for electro-generated Zn⁷³).

Stereoselective spirolactone formation has been observed in some cases. For example, addition of deoxyuloside **110** to (*Z*)-ethyl 2-(bromomethyl)but-2-enoate and zinc-silver/graphite at -30°C for seven hours provided the spiro compound **111** in 74% yield as a single diastereomer (Scheme 35).⁷⁶ This could be explained by the highly ordered chair-like transition state **112**, in which the *re*-face of the organozinc intermediate attacks the *re*-face of the carbonyl moiety. The preference for equatorial attack at the *re*-face of the carbonyl group over axial attack may be explained by steric hindrance to *si*-face approach by the axial-oriented anomeric methoxy group.

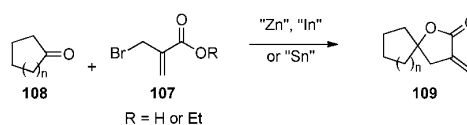
In a similar fashion, Trivedi has utilised α -hydroxy ketones to effect a highly diastereoselective Reformatsky-type reaction



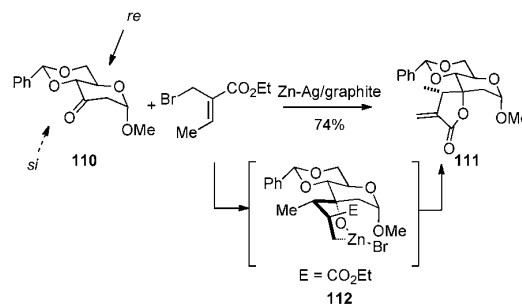
Scheme 32



Scheme 33



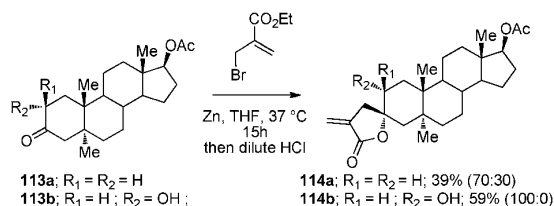
Scheme 34



Scheme 35

leading to spiro- α -methylene- γ -butyrolactones (Scheme 36).⁷⁷ Keto steroids incorporating an α -hydroxy substituent **113b** afforded the corresponding spirocyclic molecule **114b** as a single diastereomer, whereas the same experiment onto a precursor lacking this secondary alcohol function **113a** led to a 70 : 30 diastereomeric mixture at the spirocentre of **114a**. This observation was rationalised by a chelated transition state (Fig. 6) in which the developing carbanion of the Reformatsky reagent attacks from the *re*-face, the *si*-face being disfavoured due to repulsion with the lone-pair of the oxygen of the hydroxyl group.

This Reformatsky-type methodology has been utilised for the synthesis of sugar moieties substituted with an α -methylene- γ -lactone,⁷⁸ and as a key step, in the total synthesis of stemospironine (**115**) by Rauter and co-workers (Scheme 37).⁷⁹ Stemospironine is another *Stemona* alkaloid that exhibits anti-insecticidal properties, and was isolated from *Stemona japonica* by Murakoshi and coworkers.⁸⁰ Structurally, the 1-azabicyclo[5.3.0]decane nucleus is embedded in a complex tetracyclic



Scheme 36

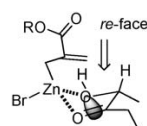


Fig. 6

scaffold. The relative and absolute configuration were established unambiguously by X-ray crystallographic analysis and spectroscopic methods.

The spiro lactone **117** was obtained in 86% yield with complete facial selectivity after treatment of bicyclic compound **116** with ethyl bromomethylacrylate and zinc dust in THF.

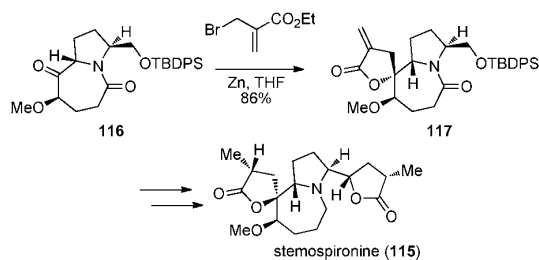
7.3 Carbonyl insertion

(a) **Mg–CO₂**. Rieke and co-workers have utilised a one-pot sequence in which magnesium metalocycle **119** reacted with ketones at $-78\text{ }^{\circ}\text{C}$ (Scheme 38). The corresponding 1,2-addition adduct **120** then reacted with carbon dioxide, leading to the introduction of the carbonyl group contained in the final lactone. The subsequent lactonisation provided the desired spirocyclic molecule **122** in good yields (from 59 to 68% depending on the nature of the ketone).⁸¹

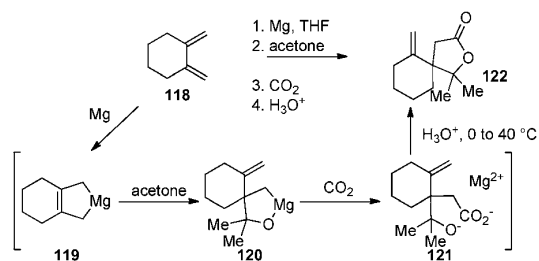
(b) **Nickel-catalysed alkoxy carbonylation**. Ogoshi and co-workers have exploited the formation of a [4.3]spiro lactone starting from a nickel complex.⁸² Oxidative cyclisation of 1,3-butadiene and cyclobutanone mediated by a nickel catalyst led to the formation of an $\eta^3:\eta^1$ -allylalkoxynickel complex **125** (Scheme 39). The latter, upon treatment with carbon monoxide, provided the spiro molecule **126** in 38% yield.

8 Halolactonisation

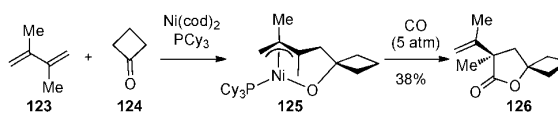
Spiro- γ -butyrolactones may also be obtained in excellent yield *via* halolactonisation of enol lactones such as **127** (Scheme 40).⁸³ This transformation presumably proceeds *via* the intermediate bromonium ion **129** and bromo acid **130**.



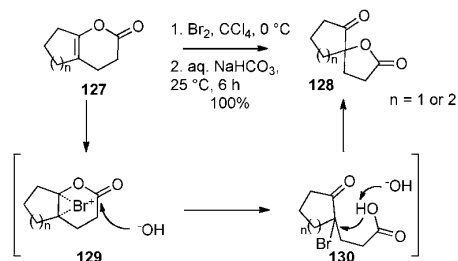
Scheme 37



Scheme 38



Scheme 39



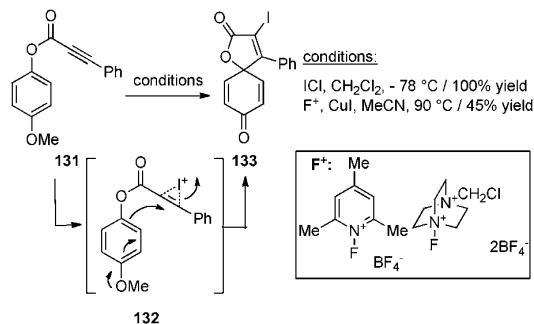
Scheme 40

A similar strategy was adopted by Wawrzęczyk, who used iodine and *N*-bromosuccinimide on limonene and carane systems respectively.⁸⁴ Larock *et al.* formed the iodonium **132** on a triple bond with ICl and therefore obtained the corresponding butenolide **133** in a quantitative manner *via* an *ipso*-halocyclisation (Scheme 41).⁸⁵ This same reaction may also be promoted by CuX (X = I, Br, SCN) and a source of electrophilic fluoride, which produced the spirobutenolide in 45% yield.⁸⁶

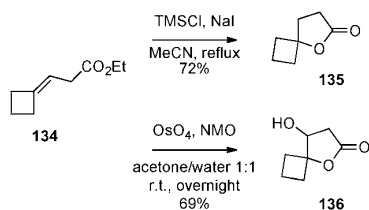
Finally, Piva *et al.* obtained the butyrolactone **135** in 69% yield through treatment of ethyl 3-cyclobutylprop-2-enoate **134** with *in situ*-generated TMSI (Scheme 42).⁸⁷ Dihydroxylation of **134** also provided directly the parent β -hydroxylactone **136** in 69% yield.

9 Pericyclic-type reactions

Pericyclic reactions are without doubt amongst the most powerful of synthetic tools and often offer a high degree of selectivity in both their inter- or intramolecular versions. A further advantage they offer is often providing access to significant complexity from relatively simple precursors. As will be discussed, pericyclic reactions have allowed a convergent, stereoselective and efficient approaches to the spirocyclic molecules, compounds targeted in this review. Here the term pericyclic is



Scheme 41



Scheme 42

used loosely to describe those reactions which appear to have arisen through a formal pericyclic process, although mechanistically this may not always be the case.

9.1 Electrocyclisation

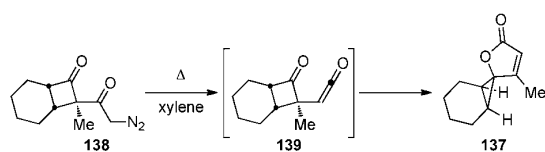
Access to [4.2]spirolactone **137** was achieved by thermal rearrangement of diazo ketone **138**.⁸⁸ Upon brief heating in refluxing benzene, a Wolff rearrangement occurred, leading to the intermediate ketene **139** (Scheme 43). This stereoselectively provided the spiro compound **137** as a single diastereomer in 50% yield via a hypothetical ordered dipolar cyclic transition state. This is a rare example of the formation of [4.2]spirolactones.

9.2 [2 + 1] photocycloaddition

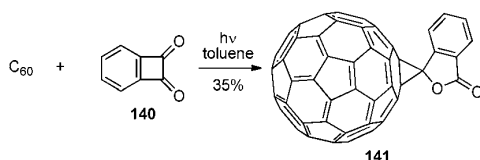
In 1995, Tomioka reported another route to this rare [4.2]spirolactone structure.⁸⁹ Irradiation of a solution of benzocyclobutenedione with C₆₀ in toluene provided spiro C₆₀ monoadduct in 35% yield, along with multiadducts and C₆₀ starting material (55%) (Scheme 44).

9.3 [2 + 2] cycloaddition

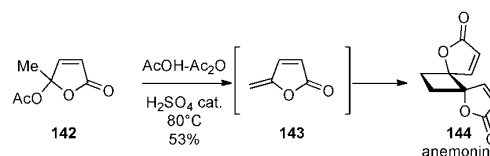
Several cases of dimerisation of alkylidenebutenolides have been reported in the literature, either under photolytic⁹⁰ or thermal conditions.⁹¹ When acetoxy furanone **142** was heated in a mixture of acetic acid and anhydride acetic with a catalytic amount of sulfuric acid, the corresponding methylene furanone protoanemonin (**143**) was formed, which immediately dimerised to the natural product anemonin **144**⁹² in 53% yield (Scheme 45).⁹¹



Scheme 43



Scheme 44



Scheme 45

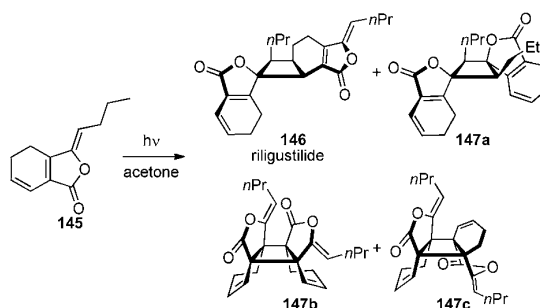
Upon irradiation with a mercury lamp, the bioactive secondary metabolite (*Z*)-ligustilide **145** underwent dimerisation, leading to four different products. The natural product riligustilide **146** and three other phthalides **147a–c** were isolated in 7, 18, 11 and 7% yields, respectively (Scheme 46).

More recently, Sulikowski *et al.* reported the utilisation of the intramolecular [2 + 2] photocycloaddition in their studies directed towards the total synthesis of bielschowskysin (**148**) (Scheme 47).^{90b} This natural product was isolated in 2004 from *Pseudopterogorgia kallos* and exhibits valuable biological activities, including strong *in vitro* cytotoxicity against the EKVX non-small-cell lung cancer (GI₅₀ < 0.01 μM) and CAK-1 renal cancer cell lines (GI₅₀ = 0.51 μM), as well as antiplasmodial activity against drug-resistant strains of the malaria-causing protozoan parasite, *Plasmodium falciparum* (IC₅₀ = 10 μg mL⁻¹).⁹³ This highly oxygenated hexacyclic diterpene contains eleven stereocentres and an unusual [4.3]spirolactol moiety. Irradiation of a solution of **149a** in acetone first led to the isomerisation of **149a**, therefore providing a mixture of geometric isomers of the starting material **149a** and **149b**. Further irradiation resulted in the conversion of both isomers, providing the tetracyclic core **150** of the target compound in 50% yield as a mixture of two diastereomers in a 5 : 1 ratio.

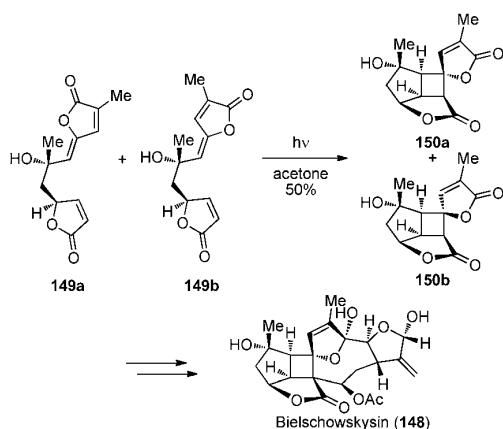
9.4 Diels–Alder reaction

The Diels–Alder reaction has been used as a powerful tool to generate quaternary stereogenic centres, and in this regard spirolactones are no exception.

(a) Methodology. Participation of the exocyclic double bond of an alkylidene butenolide as a 2π partner in an intermolecular Diels–Alder reaction was initially reported by Font in 1986 (Scheme 48).⁹⁴ Upon heating for 20 h at 210 °C in the presence of hydroquinone and a large excess of butadiene, compound **151** cyclised to the fused six-membered ring **152** in 53% yield but



Scheme 46



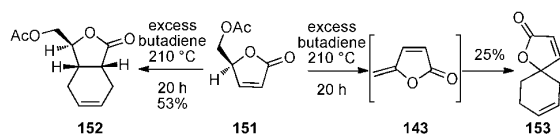
Scheme 47

a side reaction was also noticed. Under the conditions of the reaction, butenolide **151** first eliminated to the corresponding protoanemonin **143**. The latter then underwent the [4 + 2] reaction at the exocyclic double bond, leading to spiro adduct **153** in 25% yield.

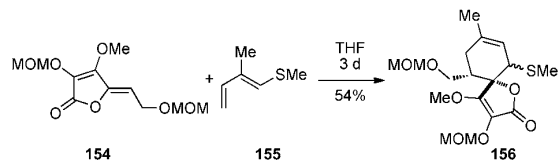
Subsequently, Poss *et al.* prepared dienophile **154** from L-ascorbic acid, and found that in the presence of various dienes Diels–Alder reactions occurred chemoselectively on the exocyclic double bond of the butenolide (Scheme 49).⁹⁵ After stirring the two partners **154** and **155** in THF at 125 °C for three days the spirocyclic adduct **156** was isolated in 54% yield as a single regioisomer. However no *exolendo* preference was observed, as evidenced by the diastereomers being isolated in a 1 : 1 ratio. Similar conclusions were independently reached by Yoshii.⁹⁶

From 1990 to 1997 Font and Ortuño carried out extensive research in order to highlight and understand the factors governing the regio-, chemo- and stereoselectivity of this reaction.⁹⁷ The nature of the diene (open-chain C-substituted, hetero-substituted, cyclic and asymmetric dienes), dienophile and reaction conditions were studied and theoretical calculations and mechanism investigations were performed.

The dienophile alkylidene butenolide, being a conjugated lactone but also an enol lactone, is a complex captodative system



Scheme 48



Scheme 49

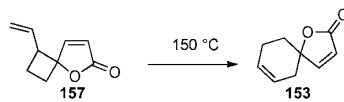
of activation. Theoretical calculations using MNDO and AM1 semi-empirical methods concluded that the frontier orbital theory failed to predict the chemoselectivity of the transformation, and the authors therefore suggested an asynchronous pathway through a biradicaloid transition state.^{97a} Cyclobutane derivatives, detected at the initial stage of the reaction, supported this biradical mechanism (Scheme 50).^{97c} The authors synthesised cyclobutane **157** under photochemical conditions, and this, upon heating to 150 °C, furnished the corresponding [4 + 2] cycloadduct **153**, thus demonstrating that cyclobutane species were intermediates in the formation of the six-membered ring spiro-lactones.

The synthesis of optically active spiro[4,5]decanes **159** (which are building blocks found in many products of biological importance) *via* chiral-auxiliary-mediated [4 + 2] reactions has been demonstrated.⁹⁸ Three different dienes bearing optically active auxiliary groups **158** ($R^* = (-)$ -menthyl, $(-)$ -bornyl or $(+)$ -isocampheyl) were reacted with protoanemonin **143** in a sealed tube between 120 and 140 °C for 14 to 18 h in dichloromethane (Scheme 51). Asymmetric induction was observed but, in all cases, four different diastereomers were obtained. However, the diastereofacial selectivity, especially for the $(-)$ -bornyl substituted diene, was reasonable (*endo:exo* = 28 : 72).

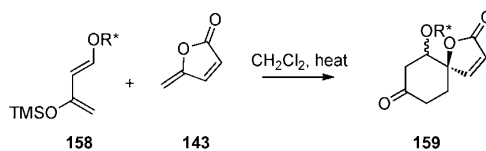
(b) **Synthesis of ircinianin.** $(-)$ -Ircinianin (**160**)⁹⁹ and its cyclic isomer $(+)$ -wistarin (**161**)¹⁰⁰ are unique cyclic furanosesterpenetetrone acids (Fig. 7) isolated from the marine sponge *Ircinia wistarii*. The structures of these unique molecules were elucidated by X-ray crystallographic analysis (for $(-)$ -ircinianin only) and NMR spectroscopic analysis, although the absolute configurations remained unclear at the time. Uenishi has demonstrated that perchloric acid promoted the cyclisation of $(-)$ -ircinianin to $(+)$ -wistarin, therefore highlighting the possible biomimetic pathway to $(+)$ -wistarin.¹⁰¹

Yoshii achieved the first total synthesis of racemic ircinianin in 1986.¹⁰² The key step to form the (5,6,5) core including the spiro quaternary stereocentre involved a biomimetic thermal intramolecular [4 + 2] reaction (Scheme 52). Accordingly, tetraene **162** was heated in boiling benzene and afforded (\pm) -ircinianin in 71% yield as a single diastereomer.

A decade later, as part of a project devoted to the determination of the absolute configuration of these interesting natural



Scheme 50



Scheme 51

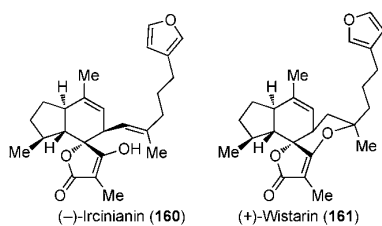
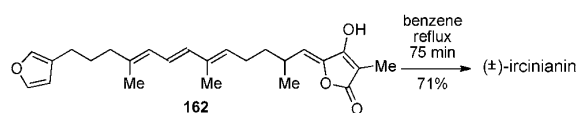


Fig. 7

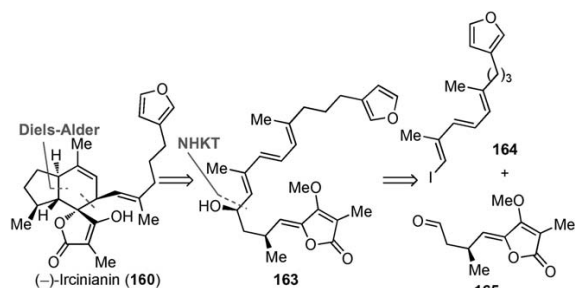


Scheme 52

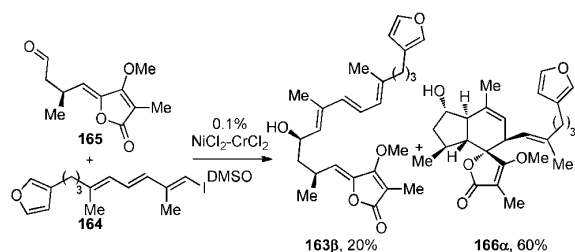
products, Uenishi *et al.* developed an enantioselective approach and achieved the first asymmetric total synthesis of (–)-ircinianin.¹⁰³ Their synthetic strategy is outlined in Scheme 53 and relies on the same biomimetic intramolecular Diels–Alder key step as Yoshii. They envisaged that the fully elaborated precursor **163** might be formed by means of a Nozaki–Hiyama–Kishi–Takai reaction (NHKT) between the two subunits **164** and **165**.

Surprisingly, when a solution of compounds **164** and **165** in DMSO were treated with NiCl₂/CrCl₂ for 18 h, the isomer **163β** (OH = β) resulting from the NHKT coupling was obtained in 20% yield, along with 60% of the cycloadduct resulting from the Diels–Alder reaction, **166α** (Scheme 54). It is noteworthy that the tricyclic structure **166α** was obtained as a single diastereomer.

From these experimental results, several conclusions could be made. The chromium(II) chloride probably acts as a Lewis acid catalysing the [4 + 2] reaction and the Ni/Cr-mediated coupling



Scheme 53



Scheme 54

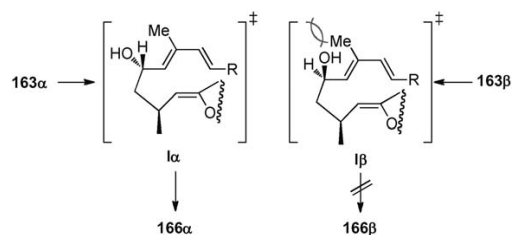
certainly occurred prior to cyclisation. In addition, the fact that the *trans*-fused product **163α** was preferred over the *cis*-fused product indicates that **Iα** is the most likely transition-state (Scheme 55). This last observation might explain why **163β** failed to give the Diels–Alder cycloadduct **166β** under the mild reaction conditions. If we assume, by analogy with **163α**, that **Iβ** is the most likely transition state, to overcome the steric interaction between the Me group of the diene and the hydroxyl group harsher reaction conditions are required.

In conclusion, the first enantioselective synthesis of (–)-ircinianin and (+)-wistarin has been accomplished featuring the construction of the quaternary spiro centre by a domino reaction involving a metal-mediated coupling followed by a Diels–Alder reaction. The absolute configuration of ircinianin and wistarin has therefore unambiguously been assigned.

(c) Synthesis of abyssomicin.

Abyssomicin C (**167a**), isolated by Süssmuth in 2004³ from a marine actinomycete, *Verrucosipora* strain AB18-032, and found to possess significant levels of antimicrobial activity against a variety of Gram-positive bacteria, especially against *Staphylococcus aureus* strains (MIC against methicillin-resistant *S. aureus* = 4 μg mL⁻¹) and drug-resistant strains (MIC against vancomycin-resistant *S. aureus* = 13 μg mL⁻¹) (Fig. 8). Its antibiotic activity is mediated through inhibition of the *p*-aminobenzoic acid pathway. Its chemical structure was determined by comprehensive NMR and MS spectroscopic analysis, and revealed a unique oxabicyclo[2.2.2]octane subunit, a tetronate moiety and an 11-membered ring bearing an enone with an *E*-configured alkene. The stereochemistry of abyssomicin C was assigned as shown in structure **167a**. The co-isolation of inactive compounds abyssomicin B (**167b**) and D (**167c**), lacking the *E*-olefin, with abyssomicin C suggested that the enone might serve as a Michael acceptor in both the mechanism of action and the biogenesis of abyssomicin B and D.

Because of its intriguing and unusual structural features combined with unique biological activities, abyssomicin C



Scheme 55

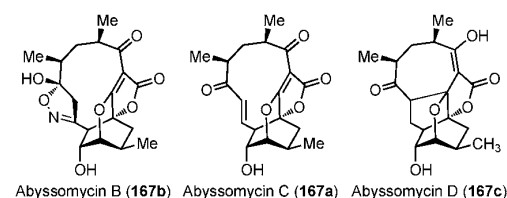


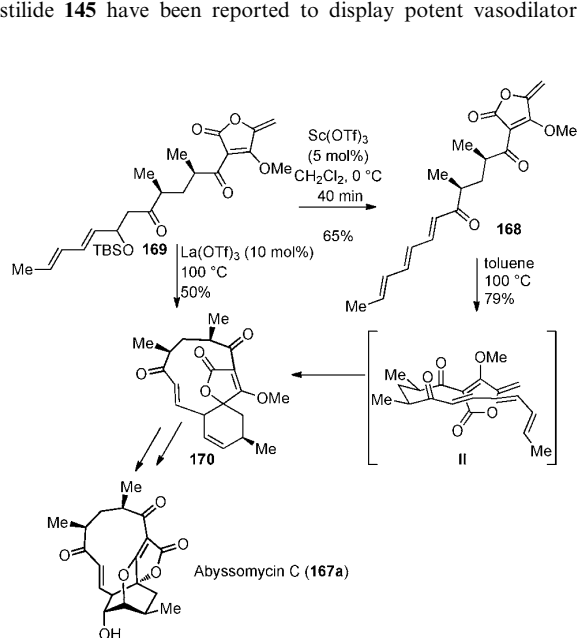
Fig. 8

quickly became an attractive challenge for the worldwide synthetic community.¹⁰⁴ To date, only two total syntheses¹⁰⁵ and two formal ones have been published.¹⁰⁶ The first total synthesis of abyssomicin was reported in 2005 by Sorensen and his co-workers.^{105a} Their strategy is based on a biomimetic intramolecular Diels–Alder reaction of linear precursor **168**.

The trienone **168** was generated from the β -elimination of **169** upon exposure to scandium(III) triflate (Scheme 56). The resulting Diels–Alder precursor **168** proved to be unstable, but succeeded in giving the desired cycloadduct **170** when a solution of the trienone **168** in toluene was heated to 100 °C for four hours. The authors elegantly managed to overcome this problem of stability by developing a one-pot domino process (elimination and [4 + 2] cycloaddition) starting from compound **169**. Accordingly, the tricyclic structure **170** was generated in one step from diene **169** in presence of the Lewis acid lanthanum(III) triflate. Both methods were highly diastereoselective and allowed them to build the spiro quaternary stereocentre. No other regioisomeric cycloadducts were detected. This excellent diastereoselectivity has been rationalised by the authors after calculation of the energies of the different possible transition states. It was concluded that the lowest-energy transition-state conformation resembled **II**, where the two carbonyl groups adopt an *anti* relationship.

This asymmetric synthesis of abyssomicin proceeded in fifteen steps (for the longest linear sequence). Notably, the biomimetic intramolecular diastereoselective Diels–Alder step was also used by Snider^{106a} and Coulaodoros^{106b} as a part of their formal syntheses of abyssomicin.

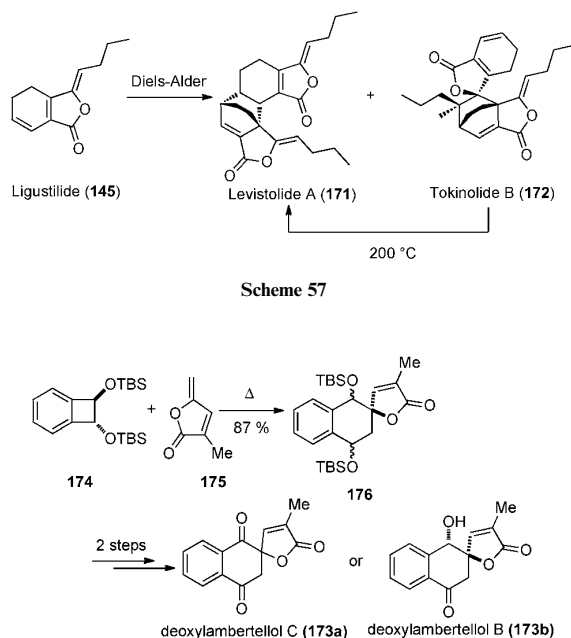
(d) Synthesis of tokinolide B. Levistolide A (**171**) and tokinolide B (**172**), which were isolated from the rhizome of *Ligusticum* and *Cnidium* species, are active constituents of traditional Chinese herbal medicine (Scheme 57).¹⁰⁷ These dimers of ligustilide **145** have been reported to display potent vasodilatory



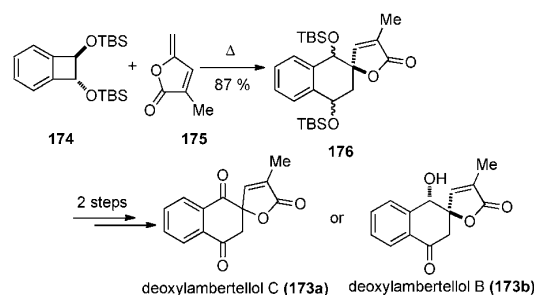
Scheme 56

activity depending predominantly on their Ca²⁺-channel blocker properties.^{107e} In addition, levistolide A has been shown to overcome P-glycoprotein-mediated drug resistance in human breast carcinoma cells.¹⁰⁸ From a structural point of view, these two pentacyclic structures have four stereocentres each and are found as racemates in Nature. To date, only one total synthesis of these two natural products has been reported.¹⁰⁹ Wakamatsu *et al.* strategy employed a Diels–Alder reaction to access both dimers **171** and **172**. Accordingly, a solution of ligustilide **145**¹¹⁰ in benzene was heated to reflux and afforded 2 and 4% of *endo* adducts **171** and **172** respectively, along with 56% of the starting material. Despite the use of Lewis acids or high-pressure conditions, the reaction still proceeded in low yield. When the temperature of the reaction mixture was raised to 200 °C, 23% of dimer **171** along with 60% of starting material were obtained. From these results, it was deduced that the high recovery of starting material was the result of the competing retro-Diels–Alder reaction, that the *endo* approach was preferred due to secondary orbital interactions, and finally that **172** was converted to the thermodynamically more stable compound **171**.

(e) Synthesis of deoxy-lambertellols. Very recently, Commeiras and Parrain¹¹¹ have reported an efficient synthesis of deoxy-lambertellols **173** via a highly chemo- and diastereoselective intermolecular Diels–Alder cycloaddition between *trans*-1,2-disiloxybenzocyclobutenes **174** and 2-methylprotoanemone **175** (Scheme 58). At 50 °C in degassed benzene, [4 + 2] cycloaddition of **174** and **175** occurred within four hours, affording chemoselectively the desired spiro lactone **176** with complete *endo*-stereoselectivity in 87% yield. With the carbon skeleton of lambertellols in hand, the authors carried on the synthesis to the simplified deoxy-lambertellols C and B **173**.



Scheme 58



9.5 [3 + 2]-type cyclisation

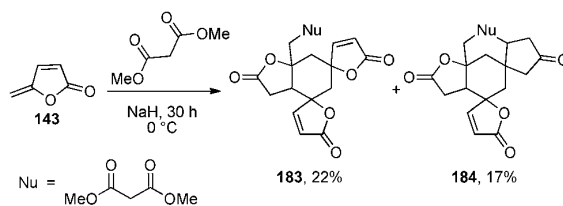
In 1997, Nair reported a new route to spirolactones *via* a triphenylphosphine-mediated-[3 + 2] cyclisation between dimethylacetylene dicarboxylate and either 1,2- or 1,4-benzoquinone **177** (Scheme 59).¹¹² During the course of this reaction, a catalytic amount of phosphine (50 mol%) first adds to the alkyne in a 1,4-fashion. The resulting zwitterionic species **178** then adds onto one of the two ketones present on **177**. Finally, cyclisation of intermediate **179** followed by elimination of the phosphine provides the spirolactone incorporating a ketone α (or γ if 1,4-benzoquinone is used) to the fused quaternary carbon **182**. Only one step was required to access bicyclic compound starting from readily available and simple starting materials. However, the limitation of the method lies in the exclusive use of DMAD. A few years later, Esmaili and Bodaghi used the same procedure for the addition of dimethylacetylene dicarboxylate to istatin derivatives.¹¹³

The cycloaddition strategy allows rapid access to complex polycyclic structures, especially in the intramolecular version of the Diels–Alder reaction. One limitation of this approach can be the instability of the diene employed. On the other hand, if these dienes are easily accessible, the chemist has at their disposal a powerful synthetic tool for the synthesis of the corresponding spiro compounds.

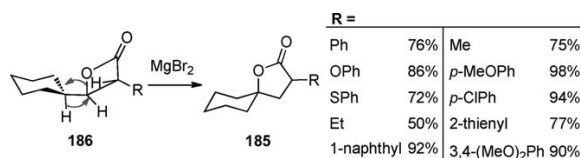
10 Miscellaneous

10.1 1,6-Addition

Reaction of protoanemonin **143** and a dimethyl malonate anion led to the formation of two spiro molecules **183** and **184** in 22 and 17% respectively *via* consecutive 1,6-additions (Scheme 60).¹¹⁴



Scheme 60



Scheme 61

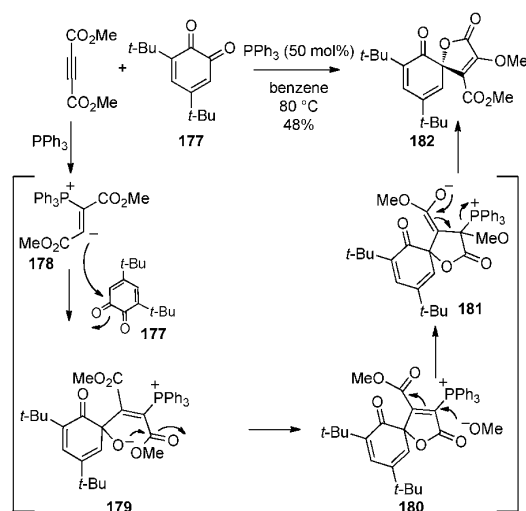
point of view. Black *et al.* reported a sequence in only three steps starting from readily available starting materials to reach efficiently α -substituted spiro butyrolactone **185** (Scheme 61).¹¹⁵ This methodology is based on a stereoselective dyotropic rearrangement. During this process, two σ -bonds simultaneously migrate intramolecularly. The concerted nature of this transformation requires an antiperiplanar alignment of the migrating bonds and hydride migrate preferentially compared to carbon.

In a typical procedure a solution of propiolactone derivative **186** in diethyl ether was treated with one equivalent of magnesium bromide etherate for six hours and the corresponding bicyclic molecule fused at a central carbon was obtained in excellent yield and with complete retention of the stereochemistry.

This expedient hydride transformation in which a ring expansion of β -lactone was accompanied by migration provides easy access to α -substituted spiro butyrolactones. However, this method is limited to appended six-membered rings. The migratory aptitude is also dependent on energetic factors, such as the release of strain in a pendant cycloalkyl ring, and no spiro compound was detected with a five-membered ring; instead, the fused spirobutyrolactone was isolated.

11 Conclusion

Various methods for the synthesis of spirolactones concomitantly with the quaternary stereocentre have been discussed. They provide rapid entry into a diverse range of highly relevant (natural and/or biologically defined targets) and sterically constrained architectures, and ones for which the quaternary centre is often implicated in the bioactivity of the natural product. These methods are also often accompanied by high diastereoselectivities, especially in their intramolecular versions. However, a lack of general enantioselective approaches remains, and this area is still in its infancy. This has been partly solved in the case of phenolic oxidation to quinones by the development of an asymmetric catalyst by Kita and Ishihara, although this method is unfortunately limited to this type of substrate. The development of a suitable chiral catalyst for the cycloaddition reactions could lead to general enantioselective approaches to



Scheme 59

spirolactones. Finally, it would be interesting, from a structure–activity relationship point of view, to understand the role played by the strained spiro-structure when compared to the corresponding tertiary alcohol.

12 Acknowledgements

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