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Strategies for the Formation of Tetrahydropyran Rings in the Synthesis of Natural Products

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Keywords: Tetrahydropyran / Total synthesis / Natural products

This microreview surveys the literature over the last five years with regard to construction of functionalised tetrahydropyran (THP) rings in the context of the synthesis of natural products. The overview given is intended to provide a working knowledge of the area for those who are unfamiliar, and to refresh and remind those who do work in the area of the exciting developments in the field. While the construction of the THP rings in a number of natural products has been reviewed, we have attempted to highlight the different strategies by focusing on two natural products, namely phorboxazole and centrolobine as case studies. Over the last five years, these natural products have become a test bed for new methods for the construction of THP rings.

Contents

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1. Introduction

This microreview surveys the literature over the last five years with regard to construction of functionalised tetrahydropyran (THP) rings in the context of the synthesis of

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Soraia Santos was born in Alhos Vedros, Portugal, in 1980. She graduated from the New University of Lisbon (2003) and worked for one year in the laboratory of Organic Synthesis (ITQB, Portugal) as a research assistant for TECNIMEDE. In 2004, she joined the group of Dr. Paul Clarke as a PhD student, at the University of Nottingham. Her research involves the development of an asymmetric Maitland–Japp reaction for application in total syntheses of THP-containing natural products.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

natural products. It is not intended to give an exhaustive account, but rather highlight what we consider to be the most interesting recent advances in the area. Due to the quality and quantity of work in this area it has proved impossible to include all contributions which were made over the last 5 years, and we apologise to those workers whose contributions to this area were not included.

Since the year 2000, a number of reactions have been identified for the efficient construction of THP rings and a number of research groups have concentrated on developing these for the use in natural product synthesis. Those which have made a particularly big impact are the Prins and related cyclisation reactions, the hetero-Diels–Alder cyclisation, and transition metal catalysed cyclisations of hydroxy groups, as well as more venerable methods such as cyclisation onto epoxides, intramolecular oxy-Michael reactions and the manipulation of carbohydrate precursors. In addition to these, the revival of the multi-component Maitland-Japp reaction has also been shown to give rapid access to THP rings present in natural products. While the construction of the THP rings in a number of natural products has been reviewed, we have attempted to highlight the different strategies by focusing on two natural products, namely phorboxazole and centrolobine as case studies. Over the last 5 years, these natural products have become a test bed for new methods for the construction of THP rings.

2. Cyclisations onto Oxocarbenium Ions

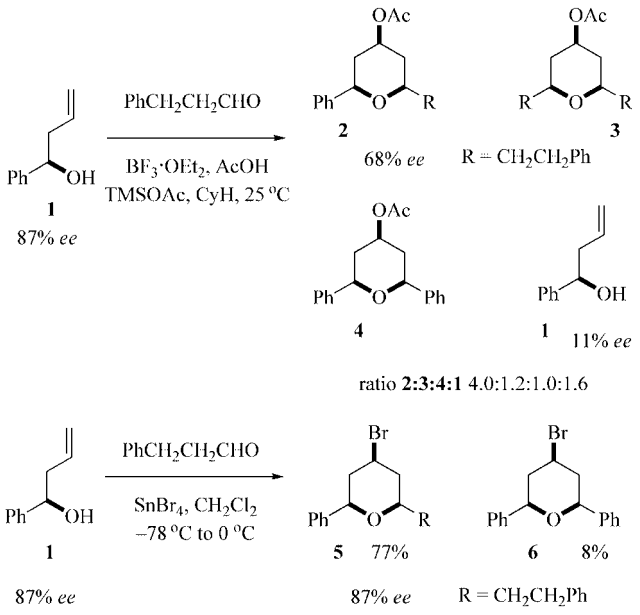
Over the last five years, the application of the Prins reaction to the synthesis of natural products has become commonplace, undoubtedly because of the convergent and efficient nature of the reaction for the formation of THP rings. Until recently, however, the Prins reaction suffered the drawback of the potential for its products to be partially racemised by a symmetric 2-oxonia Cope rearrangement.[1] This led to THP products with lower enantiomeric excesses than the starting homoallylic alcohols. Rychnovsky overcame this problem through the use of $SnBr_4$ instead of $BF_3{\cdot}OEt_2$/AcOH to promote the cyclisation. It would seem that the cyclisation promoted by $SnBr_4$ is much faster than that promoted by $BF_3{\cdot}OEt_2$/AcOH and thus suppresses the competing 2-oxonia Cope process (Scheme 1). The use of $SnBr_4$ to promote the α-acetoxy ether Prins cyclisation was then applied to the synthesis of (–)-centrolobine in 94% *ee* and 31% overall yield (Scheme 2).[2]

Loh and Chan have also addressed the problem of racemisation in the Prins cyclisation and applied it to the synthesis of (–)-centrolobine.[3] In this instance, catalytic $In(OTf)_3$ was used to promote the formation of the oxocarbenium ion with TMSBr as an additive included in the pot to trap the carbocation formed on cyclisation. This strategy furnished the natural product in 84% *ee* and in a 46% overall yield.

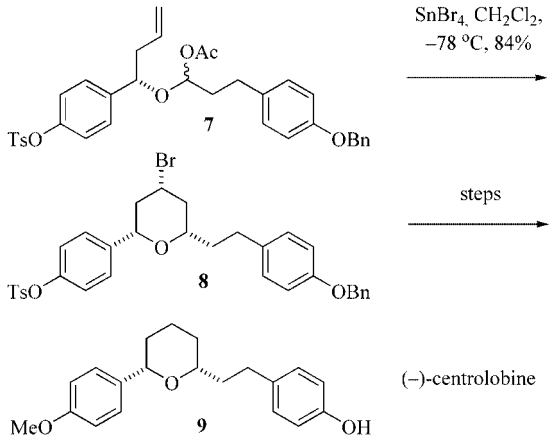
The Prins reaction has been brought to bear successfully on the challenge of the synthesis of three of the four THP rings in the natural products phorboxazole A and B. Rychnovsky has employed his α-acetoxy ether Prins methodology to the synthesis of the penta-substituted THP ring[4] and the bis-THP unit embedded in the structure.[5] The 2-oxonia Cope–Prins cyclisation cascade was employed in the asymmetric synthesis of the C18–C25 segment of Lasonolide A. When α-acetoxy ether **10** was subjected to TMSOTf at –78 °C it was converted into **12** in 74% yield (Scheme 3).[6]

The THP ring in (+)-dactylolide has been synthesised by use of a Sakurai reaction.[7] In this case, the ester function present in the cyclic acetal **13** was subjected to Grignard addition, Lewis acid mediated silanol elimination, and oxocarbenium ion formation was followed by a Prins cyclisation to furnish the THP ring **17** of (+)-dactylolide in 75% yield (Scheme 4).

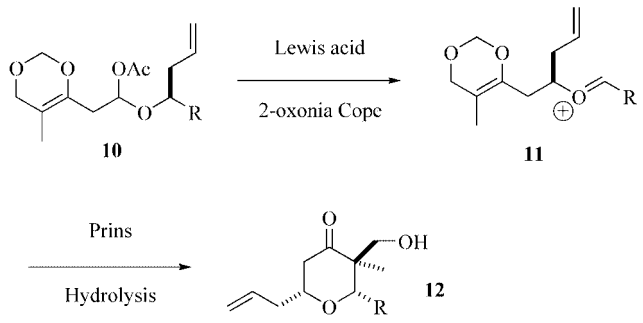
Hoye exploited the Brønsted acid mediated Sakurai cyclisation of an allylsilane onto an oxocarbenium ion in



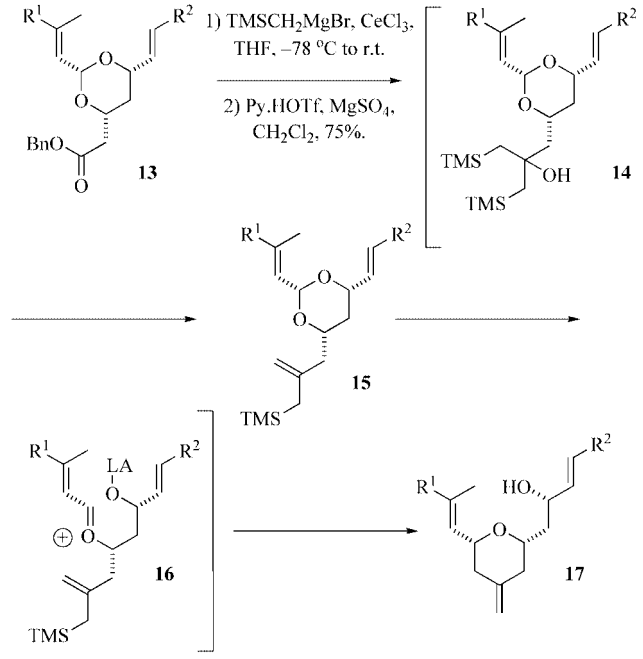
Scheme 1. Racemisation by a symmetric 2-oxonia Cope rearrangement and its suppression with $SnBr_4$.



Scheme 2. Synthesis of (–)-centrolobine through a $SnBr_4$-mediated Prins cyclisation.



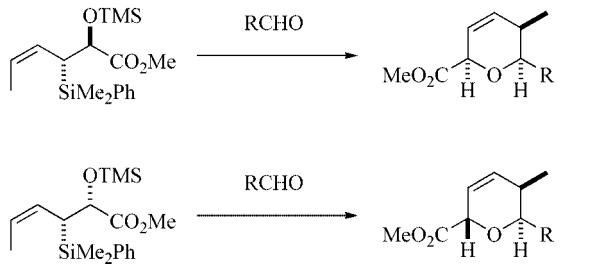
Scheme 3. The C18–C25 fragment of lasonolide A by a 2-oxonia Cope–Prins cyclisation cascade.



Scheme 4. Synthesis of the THP ring of (+)-dactylolide.

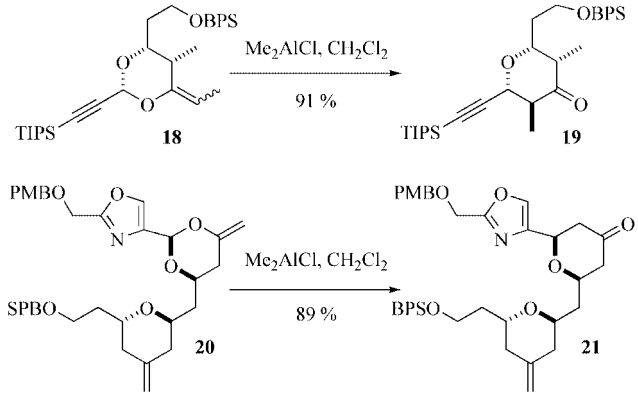
his synthesis of (–)-dactylolide and zampanolide. The key cyclisation yielded only the desired 2,6-*cis*-THP ring in 78% yield, in contrast to when non-Brønsted acids such as TMSOTf were used, which furnished mixtures of both the 2,6-*cis* and 2,6-*trans* diastereomers.[8] Panek has shown that *syn*-(*Z*)- and *anti*-(*Z*)-crotylsilanes react with aldehydes in the presence of Lewis acids to generate the 2,6-*cis*- and 2,6-*trans*-THP ring, respectively (Scheme 5), and went on to utilise this reaction in the synthesis of the C1–C13 fragment of bistramide A.[9]

Smith has utilised the Petasis–Ferrier rearrangement in his syntheses of a number of molecules including (+)-zampanolide,[10] (+)-dactylolide[11] and phorboxazole A.[12] In the case of phorboxazole A, **18** which formed as a 1:1 mixture of double-bond isomers, was cleanly converted into a single diastereomer of the central penta-substituted THP ring of the natural product **19**. Smith rationalises that the *Z*-isomer rearranges via the expected chair-like transition state. However, the formation of **19** from the *E*-isomer implies that the unfavourable 1,3-diaxial interactions, which would be present in the chair-like transition state, forces the



Scheme 5. Chiral crotylsilanes for the synthesis of THP rings.

reaction to occur via an alternative boat-like transition state. The challenging bis-THP unit was constructed through the elegant use of the Petasis–Ferrier rearrangement of **20**, in which one of the THP rings was already in place (Scheme 6).



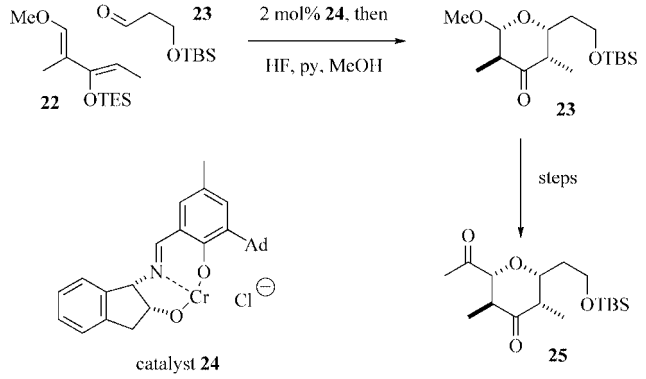
Scheme 6. Use of the Petasis–Ferrier rearrangement in the synthesis of phorboxazole A.

3. Hetero-Diels–Alder Cyclisations

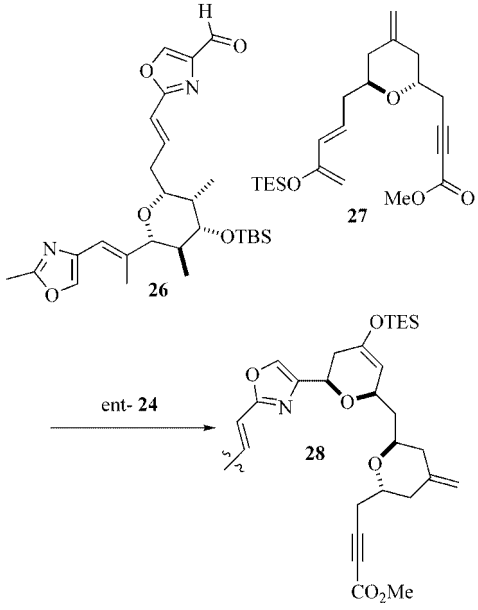
Hetero-Diels–Alder cyclisations have been used by several groups for the construction of the functionalised THP rings in the phorboxazoles. The C20–C32 fragment, which contains the penta-substituted THP ring, was constructed by Burke utilising a hetero-Diels–Alder reaction catalysed by the Jacobsen catalyst (Scheme 7). The silyl enol ether, which was the product of the Diels–Alder reaction of **22** and **23**, was immediately treated with HF and pyridine to furnish **25** in 77% yield and 91% *ee*.[13]

Paterson has also employed the Jacobsen catalyst for the formation of the bis-THP unit present in the phorboxazoles. In this synthesis; both of the rings were formed using a hetero-Diels–Alder reaction. However, the ring which would contain the C13 hydroxy function (**28**) was formed by coupling two units, **26** and **27**, each of which contained a THP ring (Scheme 8).[14,15]

Jacobsen himself has used the catalyst **24** to synthesise the THP ring present in the *anti*-fungal natural product (+)-ambruticin. The key hetero-Diels–Alder step furnished the THP ring in 64% yield and 97% *ee*.[16] The hetero-Diels–Alder reaction has also been used for the synthesis of the B ring **31** in the northern C1–C16 section of bryostatin 1

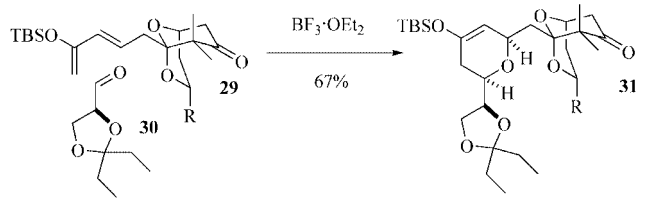


Scheme 7. The hetero-Diels–Alder reaction for the construction of the penta-substituted THP ring of the phorboxazoles.



Scheme 8. Construction of the bis-THP unit of the phorboxazoles by a hetero-Diels–Alder reaction.

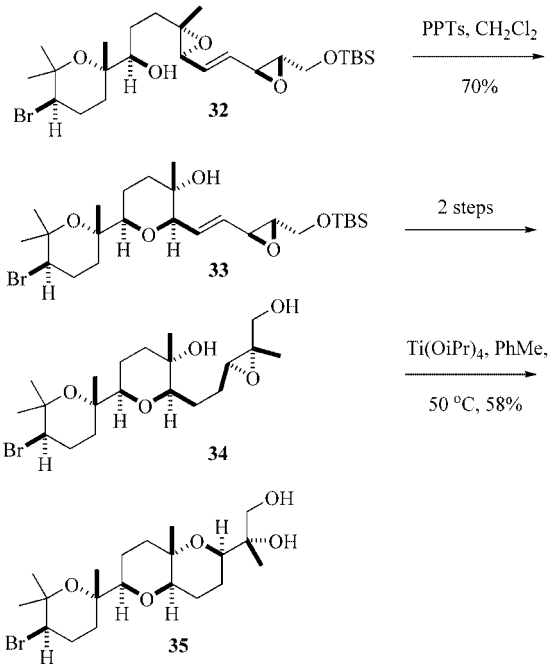
(Scheme 9).[17] In this case a 15:4:1 mixture of diastereomers resulted which were readily separated to provide the major isomer which was assigned as the isomer needed for continuation of the synthesis.



Scheme 9. Construction of the B ring of bryostatin 1.

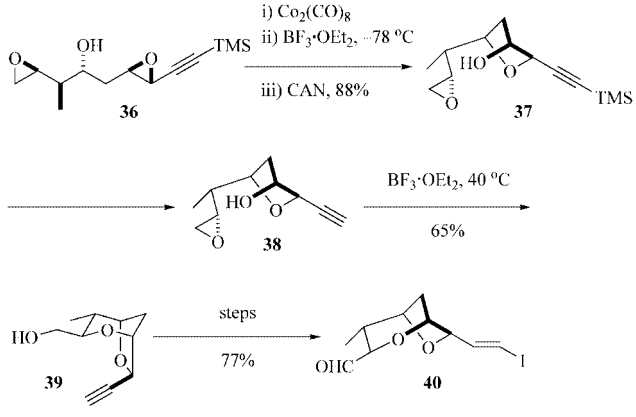
4. Cyclisations onto Epoxides

The cyclisation of hydroxy groups onto epoxides continues to be a useful method for the construction of functionalised THP rings within the context of natural product synthesis. The ABC rings of thyrisferol and venustatriol **35** have been synthesised by McDonald and Wei using this strategy.[18] Acid-catalysed cyclisation of **32** proceeded with excellent *endo* selectivity to form the B ring of both natural products. The selectivity seen was rationalised by the cation-stabilising presence of the adjacent alkene unit. Reduction of the alkene and removal of the silyl protecting group yielded **34**, which was cyclised in the presence of $Ti(OiPr)_4$ to give the desired ABC rings in 58% yield (Scheme 10).



Scheme 10. Construction of the ABC rings of thyrisferol and venustatriol.

The unusual C(30–38) dioxabicyclo[3.2.1]octane unit of (+)-sorangicine A, was prepared by two epoxide cyclisations.[19] The bis-epoxide **36** was treated with $Co_2(CO)_8$ and $BF_3{\cdot}OEt_2$, and then with CAN to yield **37**. The cyclisation occurred exclusively at the activated propargylic epoxide and, as anticipated, with retention of the stereochemis-

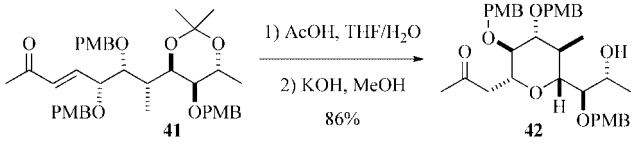


Scheme 11. Synthesis of the dioxabicyclo[3.2.1]octane unit of (+)-sorangicine A.

try.[20,21] Removal of the TMS group and treatment with $BF_3{\cdot}OEt_2$ resulted in the desired regioisomer **39** being formed in 65% yield. The remainder of the mass balance was the undesired seven-membered heterocycle. Installation of the vinyl iodide by treatment with AIBN and I_2 followed by oxidation gave **40** in 77% yield (Scheme 11).

5. Michael Reactions

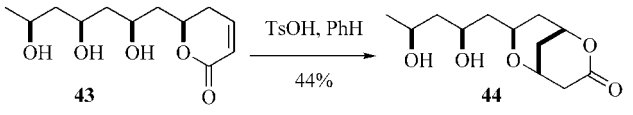
The cyclisation of an alcohol onto an alkene activated by a carbonyl group, the oxy-Michael reaction, has been used to great effect for the construction of functionalised THP units. Pattenden constructed the bis-THP oxazole fragment of phorboxazole A by cyclising a hydroxy group onto an α,β-unsaturated ester.[22] The F ring of spongistatin 1 has also been constructed by an oxy-Michael reaction. In this case, the cyclisation of **41** was promoted under basic conditions and generated the desired isomer **42** in a 95:5 ratio (Scheme 12).[23] A similar strategy was also employed by Roush in his synthesis of the C(29)–C(45) segment of spongistatin 1.[24]



Scheme 12. Synthesis of the F ring of spongistatin 1.

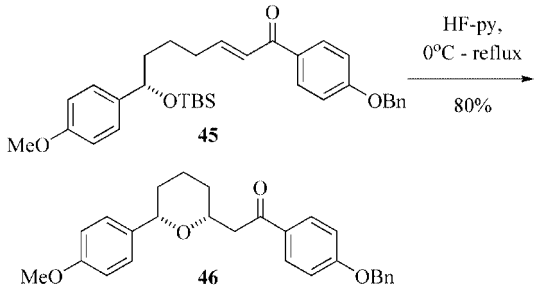
The pyran ring of (–)-apicularen has succumbed to synthesis by an oxy-Michael reaction promoted by amberlyst-15 resin in $CHCl_3$ under reflux. These conditions employed by Rizzacasa furnished the THP ring in 90% yield and as a 10:1 mixture of diastereomers in favour of the desired *trans*-isomer.[25] It was necessary to use elevated temperatures for this cyclisation, as at lower temperatures the undesired *cis*-diastereomer was formed in 67% yield.[26]

The A ring of (+)-ambruticin S was formed under a base-promoted thermodynamic cyclisation of a hydroxy group onto an α,β-unsaturated ester.[27] The bicyclic core of cryptocaryolone has been synthesised by a Brønsted acid mediated oxy-Michael cyclisation (Scheme 13).[28]



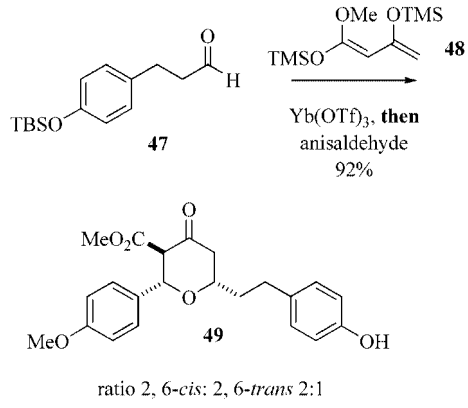
Scheme 13. Synthesis of cryptocaryolone.

(–)-Centrolobine (**9**) has been synthesised by the use of an oxy-Michael reaction. The enone **45** was constructed by a Keck allylation,[29] olefin metathesis and a Horner–Wittig reaction, then cyclised by treatment with HF–pyridine under reflux to yield the thermodynamically more favourable 2,6-*cis*-THP ring **46** (Scheme 14). The carbonyl group and the benzyl ether were removed by the action of Pd/C, H_2 and HCl. This provided (–)-centrolobine in 11 steps.[30]



Scheme 14. Construction of the THP ring of (–)-centrolobine through an oxy-Michael reaction.

The oxy-Michael reaction is also the final step in the recently revived one-pot, multi-component Maitland–Japp reaction,[31,32] which has been used to synthesise (±)-centrolobine (Scheme 15).[33,34] The aldehyde **47** was subjected to a Lewis acid catalysed aldol reaction with Chan's diene **48**, to yield the expected aldol product, which underwent a Knoevenagel reaction in situ with an equivalent of anisaldehyde, which was added to the reaction vessel. The Knoevenagel reaction was immediately followed by an oxy-Michael cyclisation to yield a 2:1 mixture of 2,6-*cis*/2,6-*trans*-THP rings in 92% yield. Fortunately, the undesired *trans* isomer could be re-equilibrated to a 2:1 *cis*/*trans* mixture, and thus the yield of the desired 2,6-*cis* isomer raised to 82%. At the time, this presented the shortest and highest yielding route to centrolobine.

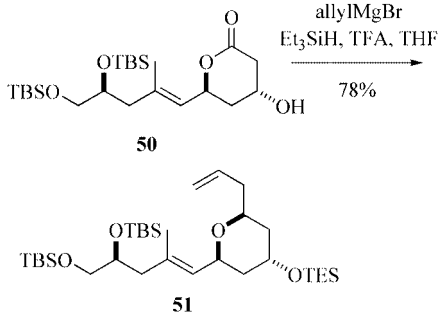


Scheme 15. Use of the Maitland–Japp reaction in the synthesis of (±)-centrolobine.

6. Reduction of Cyclic Hemi-Ketals

Reductive cyclisations have also proved to be a reliable method for the formation of THP rings present in a number of natural products. In general, there are two common strategies: those which involve addition to a lactone precursor, and those which involve the formation of a cyclic hemiketal. Jennings constructed the THP ring **51** in (–)-dactylolide and (–)-zampanolide by the addition of allyl Grignard to the lactone **50** and then treatment of with Et_3SiH and TFA (Scheme 16).[35] The desired *cis*-isomer is set up by the pseudo-axial attack of the reducing agent on the oxocar-

benium ion intermediate. Cossy employed a similar strategy in her synthesis of (–)-centrolobine.[36] In this case, 4-methoxyphenyl Grignard was added to the appropriate lactone and the resultant hemi-ketal reduced with $BF_3{\cdot}OEt_2$ and Et_3SiH.

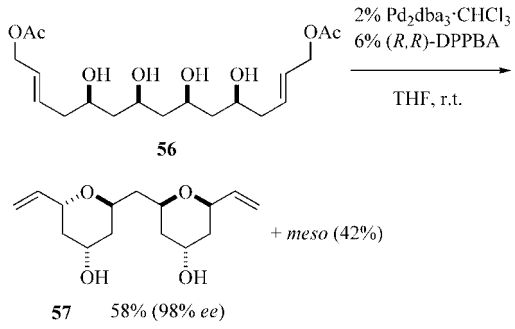


Scheme 16. Synthesis of the THP ring of (–)-dactylolide and (–)-zampanolide.

Two other syntheses of (–)-centrolobine have also employed the reduction of cyclic hemi-ketals as the key ring forming step. Evans used catalytic $BiBr_3$ and Et_3SiH to cyclise and reduce the silyl ether **52**. Removal of the TBS group with TBAF furnished (–)-centrolobine in 93% yield (Scheme 17).[37] The stereochemistry of the key hydroxy group was once again set up by a Keck allylation. Colobert reported the cyclisation and reduction of the hydroxyl-sulfinyl ketone **54** to yield the THP **55**, which was then converted to (–)-centrolobine in a further 5 steps (Scheme 17).[38,39] In Colobert's synthesis, the stereochemistry of the hydroxy group was set up by a diastereoselective reduction of an enantiomerically pure α-sulfinyl ketone.

7. Cyclisation onto Unactivated Carbon–Carbon Double Bonds

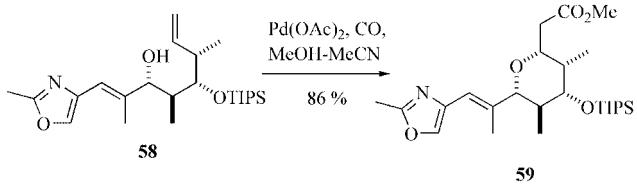
The bis-THP unit of phorboxazole A and B has been constructed by the tandem simultaneous two-directional palladium(0) catalysed cyclisation of hydroxy groups onto allylic acetates (Scheme 18).[40,41] The *meso*-tetraol **56** was prepared by simultaneous chain extension and then treated with Trost's catalyst system,[42] which resulted in cyclisation to give the desired bis-THP **57** in 58% yield and in 98% *ee*, and the undesired *meso*-product in 42% yield. The product distribution is explained by an argument based on the rates of matched and mis-matched cyclisations between the substrate and the catalyst.



(*R,R*)-DPPBA is *(R,R)-N*-[2-(2'-diphenylphosphanyl)benzamido cyclohexyl] (2'-diphenylphosphanyl)benzamide

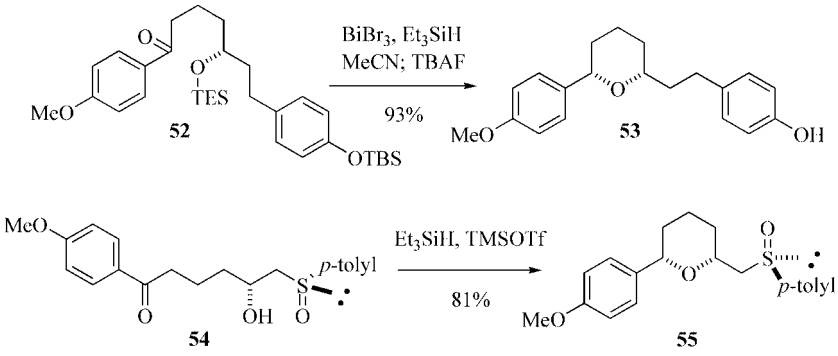
Scheme 18. Simultaneous two-directional approach to the bis-THP unit of the Phorboxazoles.

White has also used a palladium(II) catalysed cyclisation in his construction of the C-ring of phorboxazole A. After much experimentation he found that the optimal conditions were to use $Pd(OAc)_2$ in a MeOH/MeCN solvent mix, which furnished a 70% yield of the C-ring THP **59** (Scheme 19).[43] A similar strategy has also been employed by Kitching in his synthesis of one of the THP rings in the bistramide series of marine metabolites.[44]



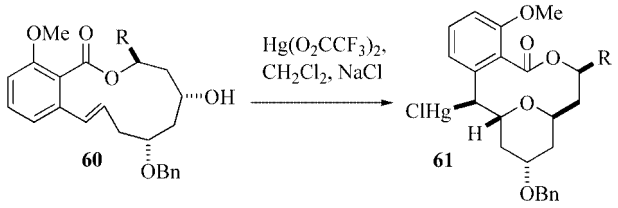
Scheme 19. Formation of the C-ring of phorboxazole by Pd^{II}-mediated alkoxy-carbonylation.

Other elements such as mercury and selenium have also been used to promote the formation of THP rings through the cyclisation of hydroxy- and double-bond-containing precursors. The C-ring of phorboxazole was constructed by use of a $Hg(OAc)_2$-mediated cyclisation. The resultant primary organomercury-containing C-ring was treated with $NaBH_4$ and O_2 to generate the primary alcohol.[45] The



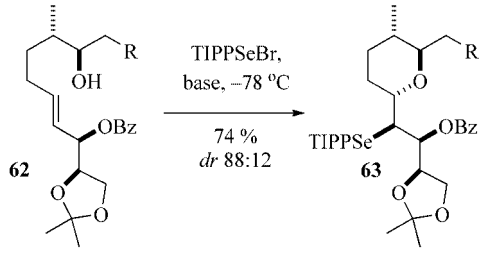
Scheme 17. Reductive cyclisation strategies for the synthesis of (–)-centrolobine.

THP ring of apicularen A was synthesised by the use of a $Hg(O_2CCF_3)_2$-promoted transannular cyclisation across a 12-membered lactone ring **60** (Scheme 20).[46] This process gave a single THP isomer as the product, although the origin of this selectivity was not fully explained by the authors.

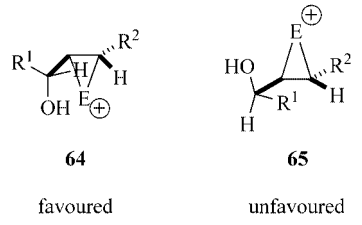


Scheme 20. Transannulation strategy for the synthesis of apicularen A.

Maier and Kuhnert also used a transannular seleno-cyclisation to construct the same ring system in another synthesis of the core of apicularen A.[47] A seleno-cyclisation was also used by Carreira in his synthesis of leucascandrolide A, which furnished the 2,6-*trans*-substituted THP ring in 65% yield (Scheme 21).[48,49] The formation of the 2,6-*trans*-substituted THP ring was rationalised by the preferential cyclisation through the intermediate selenonium ion **64**, as compared to **65**, an attractive interaction between the lone pairs on the hydroxy group and the selenonium ion and a minimisation of $A_{1,3}$ strain (Scheme 21).

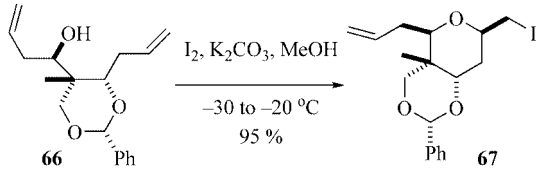


TIPPSeBr = 2,4,6-triisopropylphenylselenyl bromide



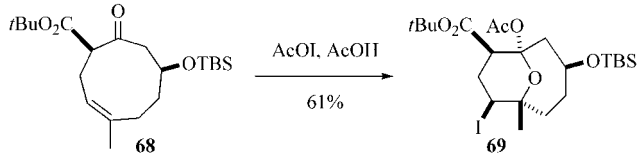
Scheme 21. Seleno-cyclisation in the synthesis of leucascandrolide A.

Iodocyclisations have also been used to construct the THP units in a number of natural products. For example, the A-ring of (+)-lasonolide was formed by treatment of the acetal **66** with I_2 and K_2CO_3. This cyclisation provided both the 2,6-*cis*-**67** and 2,6-*trans* diastereomers in a ratio of 27:1. The desired 2,6-*cis*-THP **67** was taken forward in the total synthesis of (+)-lasonolide (Scheme 22).[50] The C-ring of phorboxazole has also succumbed to synthesis by an iodocyclisation strategy, which was then coupled to the vinyl bromide containing tail fragment.[51]



Scheme 22. Iodocyclisation approach to the A-ring of (+)-lasonolide.

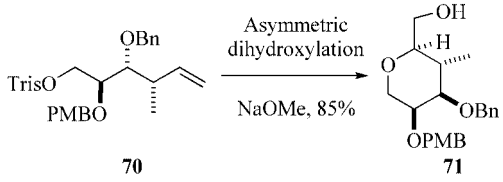
A transannular-iodocyclisation approach has been applied successfully to the synthesis of a DEF-ring system of hexacyclinic acid.[52,53] The transannular attack of the ketone carbonyl group on the double bond was initiated by treatment of **68** with AcOI. This provided the DF-ring system **69** in 61% yield (Scheme 23). Compound **69** was converted in a few more steps into a DEF-ring system of the natural product. Interestingly, the cyclisation only occurred through the carbonyl group when the reaction was performed in AcOH. Other solvents such as $CHCl_3$ and Et_2O led to cyclisation through either the ester carbonyl group or the oxygen of the silyl ether. This was explained by the intermediate iodonium ion adopting different reacting conformations in different solvents.



Scheme 23. Transannulation approach to a DF-ring system of hexacyclinic acid.

8. Other Methods

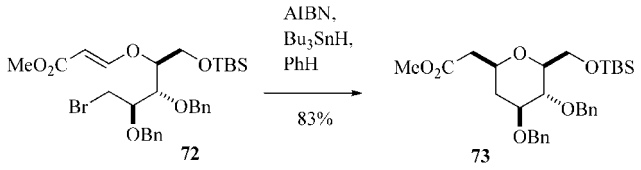
The venerable Williamson ether synthesis has also seen use for the construction of THP units in natural products. Smith closed one of the THP rings in his synthesis of (+)-spongistatin 1, by the displacement of an OTris moiety (Scheme 24).[54] Both Pattenden[55] and Williams[56] have used the displacement of a mesylate with a pendant hydroxy group in their syntheses of phorboxazole A. Pattenden employed this strategy for the construction of the bis-THP fragment, while Williams used it for the construction of the penta-substituted C-ring.



Scheme 24. Williamson ether synthesis for the construction of a THP ring in (+)-spongistatin 1.

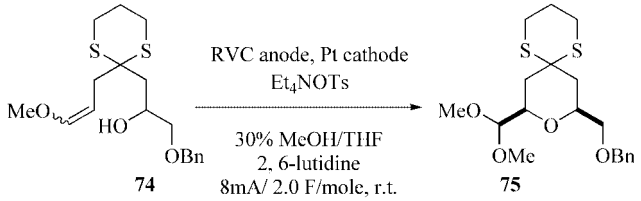
The group of Lee has used radical cyclisations to close the THP rings in both (+)-ambruticin[57] and lasonolide A.[58] In the case of (+)-ambruticin, the THP ring **73** was

closed by the conjugate addition of a primary radical to vinylogous carbonate **72** (Scheme 25).



Scheme 25. Radical ring closure of a THP in the synthesis of (+)-ambruticin.

An anodic cyclisation has been used to construct THP rings (Scheme 26). Although this method has yet to be used in the synthesis of a natural product, it does furnish substituted THP rings which may be useful in their construction.[59] It is proposed that the initial oxidation occurs at the sulfur atom to generate a radical cation which would transfer to the enol ether and then "decompose" by an intermolecular trapping reaction involving the methanol solvent. Indeed, when conditions had been optimised, the desired product **75** could be isolated in 70% yield.



Scheme 26. Anodic cyclisation for the formation of THP rings.

9. Summary

The elucidation of the structures of new natural products and the desire to synthesise them provides an impetus for the synthetic chemist to devise new and more efficient methods for the construction of their constituent parts. Of all of the natural products characterised, those containing substituted THP rings attract more than their fair share of attention. Over the last five years, many hundreds of papers have been published on the synthesis of THP natural product fragments, and this review has only been able to scratch the surface of the methods, approaches and strategies which have been used successfully for the synthesis of these important structural units. The overview given is intended to provide a working knowledge of the area for those who are unfamiliar, and to refresh and remind those who do work in the area of the exciting developments in the field. In either case, it is hoped that challenge of THP construction in the context of the synthesis of natural products will inspire new and exciting methods and strategies to be developed in the coming years.

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