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

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Abstract: This review focuses on the methodology used for the construction of tetrahydropyran (THP) rings in the synthesis of natural products over the last seven years. While methods like cyclisation onto oxocarbenium ions, reduction of cyclic hemi-ketals, Michael reactions, hetero-Diels-Alder cycloadditions and cyclisations onto epoxides continue to find application, several other strategies including metal-mediated cyclisations, ring-closing metathesis, radical cyclisations and carbocation cyclisations have also found use. This review is intended to provide an overview 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.

Dr. Paul Clarke began his career at the University of Bath where he obtained his B.Sc(Hons) in 1993. He remained at Bath to study the utility and mechanism of intramolecular dioxirane epoxidation reactions under the supervision of Dr. A. Armstrong. In 1996, he obtained his Ph.D and moved to Florida State University where he spent two years working with Prof. R. A. Holton on the synthesis of taxane ring systems. In 1999, he returned to the UK to work on a carbenoid insertion approach to peptide synthesis with Prof. C. J. Moody at the University of Exeter. In September 1999, he was appointed lecturer in Organic Chemistry at the University of Nottingham and in January 2006, he moved to his current position as a senior lecturer in Organic Chemistry at the University of York. In 2009 he was admitted as a Fellow of the Royal Society of Chemistry.

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Kristaps Ermanis was born in Ventspils, Latvia in 1987. He received his Bachelor of Science in Chemistry from University of Latvia in 2010 before moving to the United Kingdom to pursue his PhD. He is currently working on the total synthesis of phorboxazole B under the supervision of Dr. Clarke in University of York, with support from the Department of Chemistry's Wild Fund.

1. Introduction

Functionalized tetrahydropyran rings are important building blocks in the synthesis of natural products, which include lasonolide A, the phorboxazoles and many other biologically active compounds with potential for use in medicine. In the last seven years many hundreds of valuable and high quality contributions have been published in this area which have described various efficient methods for THP ring construction.

In this review we are focusing on the developments in the synthesis of the THP rings in natural products that have been disclosed since 2006 when our previous review in this area was published.[1] Significant developments in the synthesis of THP rings have been achieved using several important methods, including cyclisations onto oxocarbenium ions, oxy-Michael reactions, transition metal catalysed cyclisations, reduction of cyclic hemi ketals, and hetero-Diels-Alder cycloadditions. Other somewhat less prevalent methods also covered in this article include ring-closing metathesis, cyclisations onto epoxides, radical cyclisations and carbocation cyclisations. While over the last seven years oxy-Michael reactions and oxocarbenium ion cyclisations have seen frequent use, cyclisations onto epoxides have become less popular in the construction of THP rings.

2. Cyclisation onto Oxocarbenium Ions

The Prins cyclisation has been developed into a very powerful method for the formation of functionalized tetrahydropyrans, tetrahydropyranones and dihydropyrans. Most Prins reactions involve the coupling of homoallylic alcohols with simple aldehydes using Brønsted or Lewis acid catalysis under thermodynamic control to generate the 2,6-*cis*-THP. This reaction has been successfully applied to several total syntheses. For example, Rychnovsky has employed a TMSOTf catalyzed silyl Prins reaction of **1** in the total synthesis of cyanolide A to provide the *exo*-olefin dimer **2** in 76% yield (Scheme 1).[2]

Insert Scheme 1 here

Scheme 1. Synthesis of cyanolide A

Furman reported the use of a Prins reaction in the total synthesis of (-)-centrolobine **7**. The cyclisation of **3** with 4-tosyloxybenzaldehyde **4** in the presence of TMSOTf yielded dihydropyran **5** in 87% yield. Reduction of the olefin led to the formation of tetrahydropyran **6** in 78% yield, which was transformed into (-)-centrolobine **7** in 73% over several steps (Scheme 2).[3]

Insert Scheme 2 here

Scheme 2. Synthesis of (-)-centrolobine using TMSOTf

Lee reported that condensation of β-keto ester **8** and alkynal **9** with $In(OTf)_3$ provided the intermediate oxocarbenium ion **10** which underwent Prins cyclisation to form tetrahydropyran-4-one **11**. This was followed by a Conia-ene reaction to give 1-oxadecalin unit of phomactin A **12** as a single diastereomer in 82% yield (Scheme 3).[4]

Insert Scheme 3 here

Scheme 3. Synthesis of 1-oxadecalin catalysed by $In(OTf)_3$

A recent advance in this area has been the development of the oxidative Prins reaction. This modification makes use of enol acetates as stabilizing groups for oxidative carbocation formation. For instance, in Peh and Floreancig's efforts towards clavosolide A they achieved the formation of alkenyl tetrahydropyranones by submitting **13** to DDQ, which provided **14** as a single stereoisomer in 62% yield. Similarly, when exposed to DDQ and elevated temperatures, precursor **15** provided THP **16** in 51% yield (Scheme 4).[5]

Insert Scheme 4 here

Scheme 4. Comparison of oxidative cyclisation substrates

The THP ring in (+)-neopeltolide has been synthesized *via* a [4+2]-allylsilane annulation.[6a] In this reaction, Panek *et al.* combined allylsilane **17** with aldehyde **18** in a triflic acid promoted [4+2] annulation reaction to form dihydropyran **19** in a 75% yield. In this reaction the 2,6-*cis* stereochemistry is set up by the *cis*-nature of the hydroxysilane **17**: for effective σ-p overlap in the cyclisation step the authors suggest a pseudoaxial orientation for the silyl group in a boatlike transition state.[6b] This fragment was further elaborated through a selective oxymercuration reaction on the pyran olefin to yield C5 alcohol **21** as a single stereoisomer (Scheme 5).

Insert Scheme 5 here

Scheme 5. Synthesis of (+)-neopeltolide using [4+2]-allylsilane annulations

Floreancig has applied an electron-transfer-initiated cyclisation (ETIC) method for the synthesis of leucascandrolide A **22**. The C3-C7 portion of **22** can be prepared through the oxidative cleavage of a homobenzylic group. The key ETIC reaction proceeds with **23** being treated with ceric ammonium nitrate at room temperature to form tetrahydropyranone **25** as a single stereoisomer. They state that the reaction proceeds through the oxidative cleavage of the benzylic carbon-carbon bond to form oxocarbenium ion **24**. Excellent diastereoselectivity was achieved, which arose from the chair-like transition state for the *endo*-cyclisation (Scheme 6).[7]

Insert Scheme 6 here

Scheme 6. Use of ETIC reaction method in the synthesis of leucascandrolide A

Mukaiyama aldol-Prins (MAP) and segment-coupling Prins reactions have been successfully used to construct the constituent tetrahydropyrans of SCH 351448. Rychnovsky has employed α-acetoxy ether in a segment-coupling Prins reaction in the synthesis of the C14-C29 fragment of SCH 351448. When α-acetoxy ether **26** was subjected to $SnBr_4$ it was converted into **27** in 55% yield (Scheme 7). In the same synthesis the C1-C13 THP containing fragment of SCH 351448 was constructed using a Mukaiyama aldol-Prins Reaction. The enol ether **28** and aldehyde **29** were subjected to $TiBr_4$ promoted MAP reaction in the presence of 2,6-di-*tert*-butylmethylpyridine to form **30** (Scheme 8).[8]

Insert Scheme 7 here

Scheme 7. Segment-coupling Prins reactions

Insert Scheme 8 here

Scheme 8. Mukaiyama aldol-Prins Reaction

Willis efficiently formed two of the tetrahydropyran rings of (-)-clavosolide D using a stereoselective Prins cyclisation. For the synthesis of fragment **34**, (*S*)-homoallylic alcohol **31** was treated with methyl propiolate **32** and catalytic amounts of quinuclidine to form enol ether **33**. Upon addition of TFA, three new stereocentres were formed in a one-pot process which gave the tetrasubstituted THP **34** in 65% yield (Scheme 9).[9] The same steps were applied to the formation of trisubstituted THP from the (*S*)-homoallylic alcohol **35**. Interestingly, this sequence generated a 4:1 mixture of trisubstituted THP **37** and the epimer **38** (Scheme 10).[9]

Insert Scheme 9 here

Scheme 9. Synthesis of a tetrasubstituted THP of (-)-clavosolide D

Insert Scheme 10 here

Scheme 10. Synthesis of trisubstituted THP of marine metabolite (-)-clavosolide D

3. Reduction of Cyclic Hemi-Ketals

The formation of THP rings in natural products also can also be achieved by reduction of cyclic hemi-ketals. These reactions proceed through a cyclic oxocarbenium ion intermediate which is trapped by the incoming nucleophile. Nucleophilic addition to the cyclic oxocarbenium ion usually occurs from a pseudoaxial orientation for well established stereoelectronic reasons, thus depending on the nucleophile both 2,6-*cis* or 2,6-*trans*-THPs can be accessed.

For example, in their efforts towards the C1-C17 fragment of narasin, Brazeau *et al*. employed the reduction of lactone **39** to form the corresponding acetals (**40a** or **40b**) followed by treatment with $TiCl_4$ at -78°C and the addition of ketene silyl acetal **41**, leading to the formation of 2,6-*trans* products **42a** and **42b**. These were then subjected to radical mediated debromination, which gave THP fragment **43** in 91% yield (Scheme 11).[10]

Insert Scheme 11 here

Scheme 11. Synthesis of the THP ring of C1-C17 fragment of narasin

Cossy also used the same strategy in the synthesis THP ring of leucascandrolide A. Lactone **44** was reduced to give ketal **45**, which was then treated with $ZnCl_2$ to generate an oxocarbenium ion which was quenched with silylenol ether **46** to afford *trans*-THP **47** in 89% yield (Scheme 12).[11]

Insert Scheme 12 here

Scheme 12. Leucascandrolide A THP formation through the functionalisation of a hemiacetal

Smith, III employed a similar strategy in his synthesis of (+)-spongistatin 1. Thus, Grignard reagent **49** was added to lactone **48** to give a hemi-ketal, which was in turn reduced to form the *cis*-tetrahydropyran **50** (Scheme 13).[12]

Insert Scheme 13 here

Scheme 13. Synthesis of a THP ring of (+)-spongistatin 1

The total synthesis of kendomycin by Tanaka *et al.* has also employed the reduction of a cyclic hemi-ketal to form the THP ring (Scheme 14). Suzuki-Miyaura coupling of **51** and **52** followed by oxidation to ynone **53** provided the substrate needed for THP ring formation **54**, which was achieved by acetal exchange and reduction with Et_3SiH in 71% yield.[13]

Insert Scheme 14 here

Scheme 14. The reduction of a cyclic hemi-ketal to form the THP ring of kendomycin

Similarly, the Guindon group applied the reduction of a cyclic hemi-ketal in the synthesis of the C1-C13 fragment of zincophorin. The aldehyde **55** was reacted with ketene silyl acetal **56** in presence of catalytic amounts of $BiBr_3$ which affected the cyclisation to yield the *trans* THP ring **57**, which was formed as a 1:1 mixture of C2 epimers 84% yield (Scheme 15).[14]

Insert Scheme 15 here

Scheme 15. Functionalisation of the cyclic hemi-ketal in synthesis of the C1-C13 fragment of zincophorin

The Zakarian group, used an Achmatowicz rearrangement to produce a cyclic hemiketal. Furan **58** underwent an oxidative ring expansion in the presence of NBS and the resulting product was treated with BF_3•OEt_2 and Et_3SiH to produced **59** in 54% yield. A diastereoselective conjugate addition of Me_2CuLi gave ketone **60** which was in turn reduced to alcohol **61** as a single diastereomer in 85% yield (Scheme 16).[15]

Insert Scheme 16 here

Scheme 16. Achmatowicz rearrangement for the formation of THP ring of (+)-brevisamide

4. Michael Reactions

The Michael reaction has gained popularity in recent years as a way to construct THP rings. Lee *et al*. used it in the synthesis of 2,3-*trans*-2,6-*trans*-tetrahydropyran **65** and 2,6-*cis*-tetrahydropyran **68** of leucascandrolide A macrolactone **69**. The tetrahydropyran **63** was formed as the major diastereomer (10:1) from aldehyde **62** using piperidine as the catalyst at -40 °C, however, at 25 °C the undesired 2,6-*cis*-THP was formed. While the authors do not provide an explanation, this likely due to the reaction switching between kinetic and thermodynamic control. The coupling of **65** with **66** set the scene for the key tandem allylic oxidation/ oxy-Michael reaction. The synthesis of **69** was accomplished in 5 steps from **68** and in 96% yield (Scheme 17).[16]

The synthesis of leucascandrolide A macrolactone by the Evans group also applied a similar strategy to form the THP rings.[17]

The C20-C32 tetrahydropyran core of the phorboxazoles and the C22 epimer were synthesised in Clarke group using silyl ether deprotection/oxy-Michael cyclisation as the key step. Fuwa[18] speculated that the replacement of α, β-unsaturated ester Michael

acceptor with α, β-unsaturated thioester Michael acceptor may enhance the 2,6-*cis*-selectivities of THP formation. The Clarke group found that using a Michael cyclisation reaction and a thioester electrophile they could generate either the 2,6-*cis*- or 2,6-*trans*-THP unit with excellent selectivities depending on the reaction conditions used. While, AcOH buffered TBAF generated the 2,6-*trans*-THP, a mixture of TFA, water and DCM gave the 2,6-*cis*-THP. The total overall yield of the synthesis of the C20-C32 core **73** of the phorboxazoles was 31% and was accomplished in only 7 steps (Scheme 18).[19]

Insert Scheme 17 here

Scheme 17. Synthesis of the THP rings of leucascandrolide A

Insert Scheme 18 here

Scheme 18. Synthesis of C20-C32 core of the phorboxazoles

The Clarke group also synthesized the C1-C19 *bis*-pyran unit of phorboxazole B by an asymmetric Maitland-Japp reaction in 14 steps and 10.4 % of overall yield (Scheme 19).[20] In another paper by the Clarke group, a highly enantioselective Maitland-Japp reaction was applied to the synthesis of tetrahydropyran-4-ones of (-)-centrolobine **7** and a second generation synthesis of the C9-C19 unit of (+)-phorboxazole **76**.[21]

Insert Scheme 19 here

Scheme 19. Synthesis of tetrahydropyran-4-ones of C1-C19 unit of (+)-phorboxazole B

Paterson also employed a *cis*-selective hetero-Michael "Fuwa" cyclisation in his synthesis of the C1-C11 subunit of madeirolide A **83**. Starting with known (*S*)-ester **78** in 6 steps the α,β-unsaturated thioester was synthesized as precursor for hetero-Michael cyclisation. This reaction formed 2,6-*cis* THP ring **82** in 61% yield, which then after further 2 steps formed **83** in excellent 78% yield (Scheme 20).[22]

Insert Scheme 20 here

Scheme 20. Construction of 2,6-*cis* THP ring of C1-C11 subunit of madeirolide A

Cyanolide A **84** has also been synthesised using an oxy-Michael reaction. The THP ring **87** of cyanolide A was constructed by Hajare *et al.* from (-)-pantolactone **85**. Fragment **86** was constructed in 4 steps which then underwent oxy-Michael cyclisation upon deprotection to provide the *cis*-THP ring **87** in 83% yield (Scheme 21).[23] A similar strategy was also employed by Kim and Hong in their synthesis of cyanolide A,[24] and by Waldeck and Krische in their synthesis of the THP rings of cyanolide A using cross-metathesis/oxy-Michael cyclization.[25]

Insert Scheme 21 here

Scheme 21. Formation of THP ring of cyanolide A

The Harrowven group, synthesised the key tetrahydropyran building block **90** for the syntheses of pysmberin, onnamide and pederin. The precursor **88** was prepared from (*S*)-malic acid in 4 steps. This was then converted to amide bearing *trans*-THP ring **90** in 43% yield and amide bearing *cis*-THP ring **91** in 52% yield (Scheme 22).[26] The Hong group also applied the oxy-conjugate addition reaction to the stereoselective synthesis of 2,6-*trans*-3,3-dimethyl tetrahydropyran found in psymberin.[27]

Insert Scheme 22 here

Scheme 22. The construction of central THP ring of pysmberin, onnamide and pederin

The total synthesis of (+)-neopeltolide **92** has been reported by the Ghosh group. In their route the THP ring of (+)-neopeltolide was constructed by a palladium-catalyzed oxy-Michael reaction. The synthesis began with Horner-Wadsworth-Emmons condensation between ketophosphonate **93** and aldehyde **94** to form enone **95**. This was then subjected to palladium-catalyzed oxy-Michael reaction to form two diastereomers **96a** *cis*-C7 (*R*) and **96b** *trans*-C7 (*S*) in 48% yield and 12% yield respectively (Scheme 23).[28] Ketone **97** was the delivered in a further 2 steps.

Insert Scheme 23 here

Scheme 23. Synthesis of the THP ring of (+)-neopeltolide by a Pd-catalyzed oxy-Michael reaction

The diastereoselective construction of the 2,6-*cis*-2-(4-oxo-2-butenyl)tetrahydropyran subunit **100** in (+)-dactylolide was achieved by the Lee group using an oxy-Michael reaction promoted by pyrrolidine catalyst **99**. This method provided **100** in excellent yield of 98% (d.r.> 20:1), (Scheme 24).[29]

Insert Scheme 24 here

Scheme 24. Synthesis of the THP ring of (+)-dactylolide by organocatalytic oxy-Michael reaction

Fuwa *et al.* have constructed the THP ring subunit of aspergilides A and B by exposing cyclisation precursor **101** to *t*-BuOK to give 2,6-*trans*-tetrahydropyran *trans*-**102** in 96% yield (dr = 17:1). Conversely, when **101** was treated with DBU in toluene at 135°C, 2,6-*cis*-tetrahydropyran *cis*-**103** was formed in 81% yield (dr = 11:1) (Scheme 25).[30] The formation of *trans*-**102** has led to the synthesis of aspergilide B **104** in 94% yield while *cis*-**103** was used to achieve the synthesis of aspergilide A **105** in 84% yield. This switch in reaction selectivity is most likely due to a change from a kinetically controlled cyclisation to a thermodynamically controlled one.

In contrast, the Trost group[31] synthesized the THP ring of aspergilides B by using ruthenium-catalyzed *trans*-hydrosilylation. Trost used hydrosilylation/protodesilylation to chemoselectively reduce the alkyne **109** and form an *E*-double bond. This was followed by a deprotection/oxy-Michael reaction to form 2,6-*anti* tetrahydropyran **110** in 38% yield, which was transformed into aspergilide B **111** in 3 further steps (Scheme 26).

Insert Scheme 25 here

Scheme 25. Synthesis of the *trans*- and *cis*-THP rings of aspergilides A and B

Insert Scheme 26 here

Scheme 26. Synthesis of aspergilides B

5. Hetero-Diels-Alder Cyclisation

Another reaction used to construct functionalised tetrahydropyran rings in the synthesis of natural products is the hetero-Diels-Alder cyclisation. The Sasaki group in their synthesis of (-)-polycavernoside A formed the THP ring *via* catalytic asymmetric hetero-Diels-Alder cyclisation between silyloxy diene **113** and aldehyde **114**, mediated by **115**. This gave the desired product **116**. Subsequent removal of TMS group produced a ketone as a 6:1 mixture of diastereomers **117a** and **117b**. This was followed by reduction of **117a** to form the tetrahydropyran **118** in 94% yield (Scheme 27).[32] Ghosh and Gong also applied a hetero-Diels-Alder reaction to the formation of THP ring of the synthesis of (-)-lasonolide A.[33]

Insert Scheme 27 here

Scheme 27. The hetero-Diels-Alder cyclisation for the construction of the THP ring of (-)-polycavernoside A

The Raghavan group has employed an asymmetric hetero-Diels-Alder reaction using Jacobsen's catalyst to construct the THP ring in the macrolactone core of (+)-neopeltolide **122**. The THP ring was constructed in a reaction between aldehyde **119** and siloxy diene **120** in presence of (*S, S*)-Cr(III)-salen-BF_4^+ **123** to form **121**. A further 8 steps produced the macrolactone core **122** in overall yield of 3.8% (Scheme 28).[34]

Insert Scheme 28 here

Scheme 28. Catalytic construction of the THP ring of the macrolactone core of (+)-neopeltolide

The synthesis of pederin by the Rawal group also utilised a hetero-Diels-Alder reaction. Pyranone **126** was synthesised in a reaction between **124** and **125** in presence of Al(2,6-diphenylphenol)$_2$Me and TMSOTf. Dihydropyranone **126** was then treated with silyl ketene acetal **127** to produce ester **128** in excellent diastereoselectivity (d.r = 20:1). Reduction with L-selectride gave the THP ring **129** in 92% yield (d.r = 12:1) (Scheme 29).[35]

Insert Scheme 29 here

Scheme 29. Synthesis of the THP core of pederin

One of the THP rings in (+)-azaspiracid was prepared using the hetero-Diels-Alder reaction. The THP E-ring **134** was formed from dihydropyran **133** which was in turn prepared by a hetero-Diels-Alder reaction between **130** and **131** catalysed by copper box-complex **132**. This gave mixture of *cis* and *trans* diastereomers (dr 94:6) in a combined yield of 84% (Scheme 30).[36]

Insert Scheme 30 here

Scheme 30. Synthesis of THP E-ring of (+)-azaspiracid

6. Metal-Mediated Cyclisations

Metal-mediated cyclisations have proved to be a useful tool for the construction of the THP rings in natural products. The group of Uenishi, constructed the THP ring of (-)-apicularen A *via* a $PdCl_2$ catalyzed S_N2' type reaction. The cyclisation of **135** proceeded in THF at room temperature in presence of catalytic amount of $PdCl_2(CH_3CN)_2$ and provided the 2,6-*trans*-disubstituted dihydropyran **136** as single diastereomer. After 2 further steps, dihydropyran **137** was subjected to an oxymercuration reaction to form alcohol **138** in 80% yield (Scheme 31).[37] The MacMillan group also applied the same Pd(II) catalyzed formation of a THP ring subunit in their synthesis of callipeltoside C in 75% yield.[38]

Insert Scheme 31 here

Scheme 31. Construction of the THP ring in (-)-apicularen A

Yang *et al*. also employed a palladium-catalyzed reaction in their construction of the THP ring of (+)-neopeltolide. Diol **140** was prepared from propane-1, 3-diol **139** with an iridium-catalyzed allylation. Diol **140** was then submitted to a palladium-catalyzed intramolecular alkoxycarbonylation reaction to give tetrahydropyran **141** in 83% yields (Scheme 32).[39]

The total synthesis of (-)-dactylolide has been achieved by the group of Lee. They used a ruthenium-catalyzed Alder-ene reaction to construct the precursor **144**, which was followed by treatment with palladium-catalyst in the presence of Trost's chiral (+)-DPPBA ligand which in turn afforded 2,6-*cis* tetrahydropyran **145** in 72% yield.(Scheme 33).[40]

Insert Scheme 32 here

Scheme 32. Synthesis of the THP ring in (+)-neopeltolide

Insert Scheme 33 here

Scheme 33. Construction of THP ring in synthesis of (-)-dactylolide

The Roulland group has synthesized the THP subunit of (-)-exiguolide in three different variations of a ruthenium complex-catalysed reaction to construct the key THP ring. The general method employed an ene-yne coupling/oxa-Michael cascade between alkyne **146** and alkene **147** in the presence of ruthenium-catalyst **148** and produced tetrahydropyran **149** in 78% yield in a dr > 9:1. (Scheme 34).[41]

Insert Scheme 34 here

Scheme 34. Synthesis of THP subunit of (-)-exiguolide by ruthenium-catalysis

Other metallic and semi-metallic elements can be used for the construction of THP rings. The group of Tae constructed the THP ring of (-)-apicularen A **151** by use of selenium-mediated cyclisation in 89% yield (Scheme 35).[42] The Clark group used a copper catalyst to form the THP ring of neoliacinic acid.[43] The diazo ketone **152** was treated with Cu(hfacac)$_2$ to form **153** after a metal carbenoid oxonium ylide rearrangement. In a further 2 steps epoxyketone **154** was formed, which was followed by methylenation of the ketone carbonyl give the alkene **155** in an excellent 81% yield (Scheme 36).

Insert Scheme 35 here

Scheme 35. Construction of THP ring by selenium-mediated cyclisation

Insert Scheme 36 here

Scheme 36. Synthesis of neoliacinic acid

7. Other Methods

Ring-Closing Metathesis

Ring-closing metathesis has been commonly used for the construction of THP rings in natural products. Lee used ring-closing metathesis to form the THP ring in a total synthesis of dysiherbaine **156** and neodysiherbaine A **157**.[44] Compound **158** was reacted with vinyl acetate in a ring opening-ring closing metathesis reaction using Hoveyda-Grubbs II catalyst to produce dihydropyran **159**, in which the enol acetate group was expected to provide a distinct electronic environment for selective functionalisation reactions. Compound **159** was converted into **160** in three steps (Scheme 37).[44] Crimmins employed the same strategy for the construction of the *bis*-THP core of amphidinol 3.[45] Fuwa has used a ring-closing metathesis strategy to construct the THP unit for his synthesis of (+)-neopeltolide. In this case the ring-closing metathesis reaction was followed with the stereoselective hydrogenation of **162** to afford THP ring **163** (Scheme 38).[46]

Insert Scheme 37 here

Scheme 37. Ring-opening-ring closing metathesis approach to the synthesis of dysiherbaine and neodysiherbaine

Insert Scheme 38 here

Scheme 38. Synthesis of the THP ring of (+)-neopeltolide

Cyclisations onto Epoxides

Compared to our previous review,[1] the cyclisation of hydroxyl groups onto epoxides has become less prominent the past seven years for the construction of THP rings in natural products. However, in 2013 the group of Smith, III used this strategy to construct a 2,6-*trans*-tetrahydropyran in the total synthesis of (+)-irciniastatin A. According to Baldwin's rules, the desired 6-*exo-tet* and undesired 7-*endo-tet* cyclisation pathways could complete, however under Lewis acidic conditions the desired 6-*exo-tet* cyclisation occurred which provided the THP ring **165** in excellent 92% yield (Scheme 39).[47]

Insert Scheme 39 here

Scheme 39. Construction of the THP ring of (+)-irciniastatin A

A report in 2009 by Oishi demonstrated the use of the cyclisation of a hydroxyl group onto an epoxide for the synthesis of the C31-C40/C43-C52 unit of amphidinol 3. In this example a cross metathesis reaction between terminal olefin **169** with 2 or 4 equiv of *Z*-olefin **170** afford diene **171** which was converted into **172** in three additional steps. Methanolic K_2CO_3 was then used to remove the acetate and provided the epoxy alcohol **173** as the cyclisation precursor. Treatment with PPTS affected 6-*endo-tet* cyclisation to afford the THP ring **174** in 60% yield (Scheme 40).[48]

Insert Scheme 40 here

Scheme 40. Synthesis of the C31-C40/C43-C52 Unit of amphidinol 3

Radical Cyclisations

A radical cyclisation has been used by the Taylor group to construct the THP ring of neopeltolide macrolactone (Scheme 41). Tetrahydropyran core **176** was constructed via a radical cyclisation in 95% yield as essentially a single diastereomer.[49]

Insert Scheme 41 here

Scheme 41. Radical formation of a THP ring in the synthesis of neopeltolide macrolactone

Carbocation Cyclisations

Cyclisation onto a carbocation has been used to construct the THP ring of kendomycin (Scheme 42). Reduction of ketone **177** with $NaBH_4$ produced an alcohol as mixture of diastereomers. This was followed by the removal of the acetonide and loss of water to produce a benzylic carbocation which was trapped by the liberated pendant hydroxyl in a proposed S_N1 cyclisation, to form benzofuran **178** as precursor of kendomycin.[50]

Insert Scheme 42 here

Scheme 42. Carbocationic cyclisation in the formation of THP ring of kendomycin

Summary

The purpose of this review is to provide an overview of the types of reactions used in the construction of the THP rings in natural products in the last seven years. Over this time many hundreds of papers have been published in this area and this review has only been able to scratch the surface of the many strategies which have been successfully used to construct these important units. It is evident from the literature that certain methods of THP formation still remain popular, such as cyclisations onto oxocarbenium ions, others have gained in prominence e.g. the use of ring closing metathesis, while others appear to have fallen out of favour, such as cyclisations onto epoxides. Many exciting developments have been made in the synthesis of THP rings over the last seven years, yet it is clear that many challenges still remain. We hope that this overview provides the opportunity to gain a working knowledge of the field for those unfamiliar with it, and to refresh and remind those who do work in the field of the exciting advances that have been made. In either case it is hoped that the challenge of THP construction in the context of natural product synthesis will continue to inspire new methods to be developed in the coming years.

Notes and references

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