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Comparative perspective and synthetic applications of transition metal mediated oxidative cyclisation of 1,5-dienes towards *cis*-2,5-disubstituted tetrahydrofurans

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Abstract

Cis-2,5-disubstituted tetrahydrofurans constitute the core of several natural products and synthetic analogues which exhibit a broad and interesting range of biological activities. This review highlights a personal perspective and provides a comparative note on the synthesis of *cis*-2,5-disubstituted tetrahydrofuran rings from 1,5-diene precursors using metal–oxo species. Also, mechanistic insights for these synthetically significant protocols are given and striking examples from the literature are reported, which draw an attention towards the scope and synthetic utility of metal oxidants in the domain of *cis*-2,5-tetrahydrofuran containing bioactive natural product synthesis.

1. Introduction

Substituted tetrahydrofurans[1] (THFs) are considered as one of the most valuable five-membered ring systems in modern synthetic chemistry because of their widespread prevalence in a large number of natural products and biogenetically intriguing polyoxygenated cytotoxic molecules[2] such as salinomycin

(**1**),[3] *cis*-solamin (**2**),[4] *cis*-sylvaticin (**3**),[5] *cis*-uvariamicin I (**4**) and *cis*-reticulatacin (**5**),[6] membranacin (**6**),[7] membrarollin (**7**)[8] and eurylene (**8**,[9] Fig. 1). These compounds are associated with potent cytotoxic activities against cancer cells,[10] multidrug resistant tumors[11] and significant bioactivities including antiparasitic, antimalarial and pesticidal.[12] Thus, these heterocycles have attracted a lot of interest from the synthetic community. The most common biosynthetic route to 2,5-disubstituted THF units involves sophisticated enzyme catalyzed stereospecific epoxidation–ring-opening cascade applied to acyclic squalene precursors[13] and their intrinsic ionophoric nature provides a metal binding tendency with physiologically important metallic cations.[14] This ability to bind metal ions is recognized as one mechanism of action leading to their notable bioactivity.

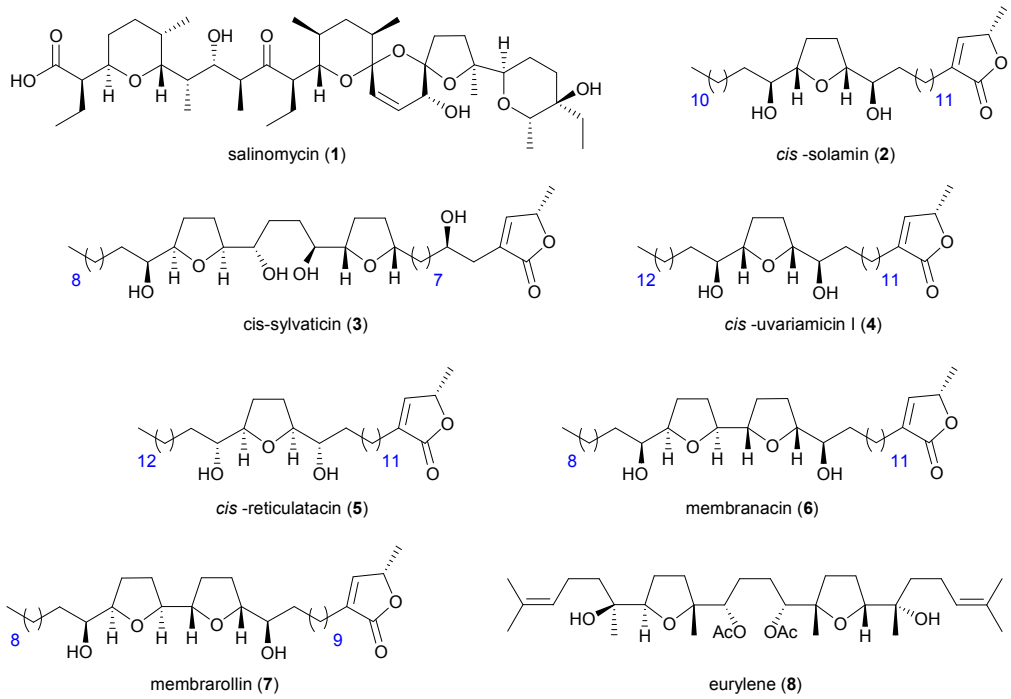


Fig. 1 Structures of representative natural products containing 2,5-disubstituted THFs, directly obtained by metal–oxo-mediated oxidative cyclisation of 1,5-diene precursors.

Among various established methodologies towards the synthesis of tetrahydrofuran (THF) rings, oxidative cyclisations involving metal–oxo-promoted process are one of the most attractive. A number of metal based oxidants have been explored and reported for the synthesis of 2,5-disubstituted THFs involving oxidative cyclisation of 1,5-dienes (Fig. 2a),[15-17] 5,6-dihydroxyalkenes (Fig. 2b),[18-20] 5-hydroxyalkenes (Fig. 2c),[21,22] and sequential epoxidation–5-*exo*-*tet* cyclisation applied to 5-hydroxyalkenes (Fig. 2d),[23] while biomimetic epoxide–ring-opening cascade[24] has been articulately incorporated to provide a succinct route to achieve the synthesis of THF entities of a cytotoxic natural product, teurilene.[24,25] In addition to this, $Os^{(VI)}$ chemistry has been elegantly extended to 5-hydroxy-6-protected aminoalkenes, 5,7- and 5,8-dihydroxyalkenes to synthesise *cis*-2,5-disubstituted THF motifs.[26]

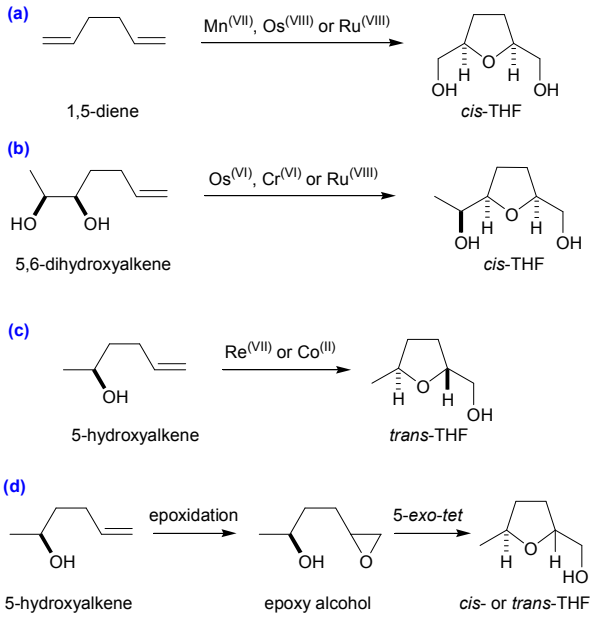


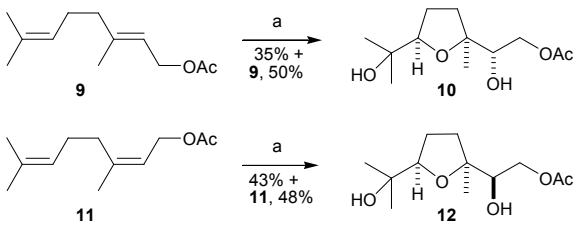
Fig. 2 Metal–oxo species-mediated oxidative cyclisations; (a) 1,5-diene, (b) 5,6-dihydroxyalkene, (c) 5-hydroxyalkene and (d) epoxidation–cyclisation tandem sequence.

The prime focus of this review is to summarise the main synthetic routes to *cis*-2,5-disubstituted THFs directly from 1,5-diene precursors using metal–oxo reagents (Fig. 2a) along with mechanistic insight and synthetic applications. Oxidative cyclisation of 1,5-dienes is a powerful and economical methodology to construct THF rings in one step, which establishes four new carbon–oxygen (C–O) bonds and potentially up to four new chiral centres. Despite of all progressive developments in this area, there are significant concealed aspects to be explored by the scientific community. Potential leading future trends and directions in this field include development of chiral phase-transfer catalysts and reagents for efficient enantioselective variants of oxidative cyclisation, possibility of absolute stereoinduction with $Os^{(VIII)}$ and $Ru^{(VIII)}$ oxidants, polycyclisation using oxomanganese [$Mn^{(VII)}$] and $Os^{(VIII)}$ species as observed for $Ru^{(VIII)}$ chemistry, mechanistic investigations to get further insight about the reactive conformations, and incorporation of oxidative cyclisation in multi-component reactions.

2 Permanganate-mediated oxidative cyclisation

Kötz and Steche attempted to oxidise geranyl acetate **9** with potassium permanganate under mildly basic conditions in 1924.[15a] At that time, the reaction product could not be identified and was described as "oxidodioxygeraniolmonoacetate". In 1965, Klein and Rojahn re-investigated this protocol and elucidated the product as a *cis*-2,5-disubstituted THF diol **10**, obtained in moderate yield (Scheme 1).[15b] Neryl acetate **11** underwent cyclisation as well to afford the *cis*-THF diol **12**, using the same reaction conditions. Both reactions proceeded in a stereospecific fashion with respect to each alkene and only the

cis-isomers were observed, which is highly significant in the context of stereocontrolled synthesis of *cis*-2,5-disubstituted THF rings contained within many cytotoxic natural products.



Scheme 1 Klein and Rojahn's investigations towards permanganate-catalysed oxidative cyclisation.
Reagents and conditions: (a) $KMnO_4$, acetone:H_2O (5:1), CO_2 bubbling, pH = 7.5, 0 ˚C, 30 min.

The structural elucidation of the products of oxidative cyclisation triggered a new direction and two mechanistic proposals were put forward separately by the research groups of Walba[15c] and Baldwin.[15d] In their pioneering study, Walba and colleagues investigated the effect of double bond geometry present in the 1,5-diene on the relative stereochemistry of the resultant alcohol moieties adjacent to the *cis*-THF ring.[15c] Oxidative cyclisation of several 1,5-dienes in a mixture of acetone:H_2O (5:1) followed by CO_2 bubbling led to the formation of the corresponding diols in approximately 97% *cis*-stereoselectivity (Fig. 3).

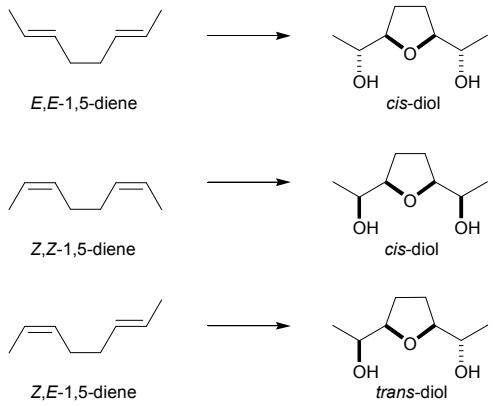


Fig. 3 An effect of alkene geometry on the relative stereochemistry of incipient THF rings and diols.

The Sharpless mechanistic proposal for the oxidation of olefins by oxo–transition metal species[27] was advanced by Walba and co-workers to account for the permanganate-mediated oxidative cyclisations (Fig. 4).[15c] It was proposed that after an initial attack of $Mn^{(VII)}$ on the diene and the formation of bis-π-complex, an octahedral $Mn^{(VII)}$ intermediate is produced *via* two Sharpless–type [2+2] cycloadditions. Alkyl migration from $Mn^{(VII)}$ to one of the oxygen atoms with the retention of configuration provides $Mn^{(V)}$ intermediate, which after a reductive elimination affords $Mn^{(III)}$ diester. Oxidation of $Mn^{(III)}$ ester

followed by the hydrolysis gives MnO_2 and the desired *cis*-THF ring with the observed relative stereochemistry.

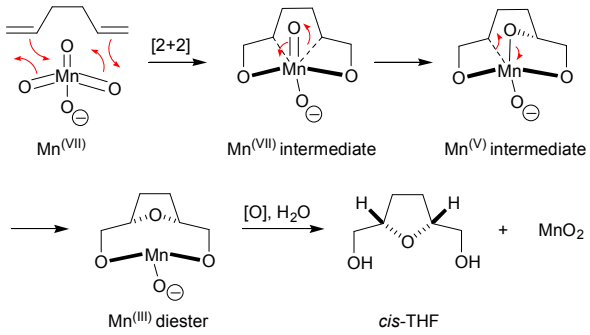


Fig. 4 Sharpless–type [2+2] cycloadditions based mechanistic proposal by Walba and colleagues.

Further investigations to explore the stereoselectivity of the reaction were carried out in the laboratory of Baldwin. For this purpose, deuterated dienes were subjected to permanganate oxidative cyclisation and the *cis*-stereoselectivity of the resultant THF diols was confirmed by NMR analysis.[15d] A different mechanistic route for the cyclisation is presented by Baldwin, which is based on sequential [3+2] cycloadditions (Fig. 5).[15d] According to his proposal, an initial [3+2] cycloaddition of permanganate ion to one of the two double bonds of 1,5-diene takes place, which leads to an intermediate $Mn^{(V)}$ ester. After rapid oxidation of the $Mn^{(V)}$ intermediate to $Mn^{(VI)}$, a second [3+2] intramolecular cycloaddition occurs on the remaining double bond, followed by hydrolysis of the $Mn^{(V)}$ diester to afford the *cis*-THF. Kinetic isotopic investigations[28a] and spectroscopic determination of the intermediate species[28b] reveal that operational mechanism in permanganate-promoted oxidative cyclisation of 1,5-dienes follow a [3+2] pathway. It was later supported by Density Functional Theory (DFT) calculations and labelling studies which confirm that concerted [3+2] cycloaddition is favoured by about 40 kcal/mol relative to the stepwise [2+2] counterpart.[28c] The role of water in the permanganate oxidative cyclisation has been investigated using computational methods and it suggests that water plays a significant role by lowering the activation energies.[28d]

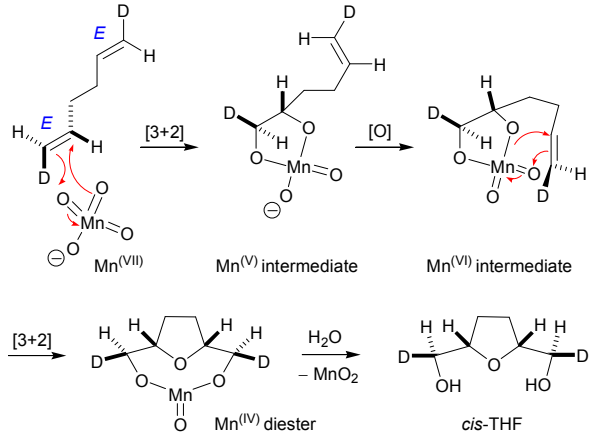
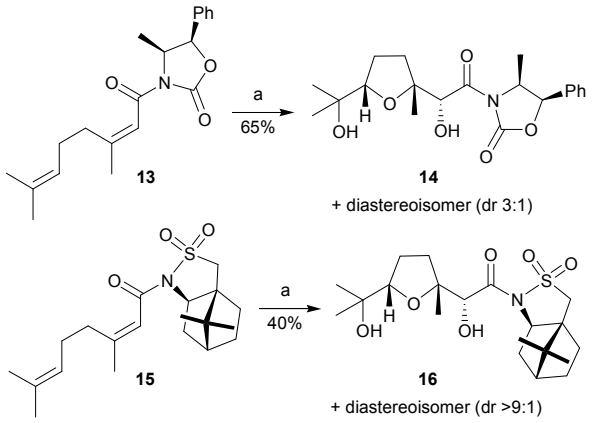


Fig. 5 Mechanistic proposal for cyclisation by Baldwin and co-workers.

An asymmetric version of this reaction was sought based on controlling the initial facial attack of the oxidant. This was achieved by Walba and co-workers by incorporating Evans' oxazolidinone as a chiral auxiliary into the diene substrate **13** (Scheme 2).[29] The expected reaction product, *cis*-THF diol **14** and its minor diastereoisomer were obtained in good yield with moderate diastereoselectivity (dr 3:1). It was postulated that the origin of diastereoselctivity was due to an initial *Re*-face attack on the conjugated double bond, leading to *cis*-THF diol **14** as a major product. The stereoselectivity was enhanced by exchanging Evans' auxiliary with Oppolzer's camphorsultam.[30] Dienoate **15** was subjected to permanganate oxidation and the resultant *cis*-THF diols **16** and its minor diastereoisomer were obtained in moderate yield with an improved diastereoselectivity (dr >9:1). The major diastereoisomer **16** also arose due to an initial attack from the *Re*-face of the enoyl olefin bond and same facial preference was previously reported by Oppolzer and Barras in dihydroxylation reactions.[30*a*]

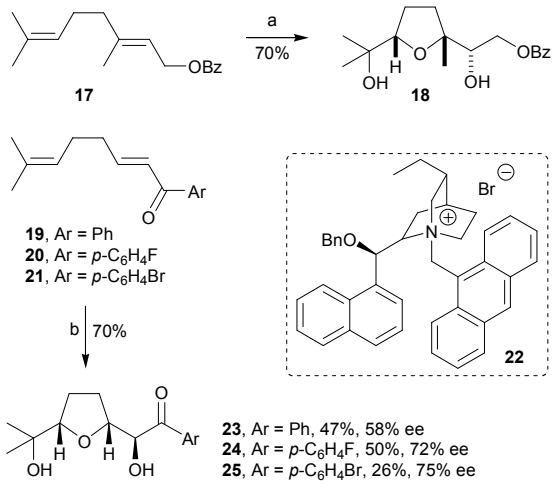


Scheme 2 Asymmetric oxidative cyclisation of 1,5-dienes bearing chiral auxiliary.

Reagents and conditions: (a) $KMnO_4$, acetone:H_2O (10:1), CO_2 bubbling, pH = 7.5, –30 ˚C, 30 min.

Oxidative cyclisation of 1,5-dienes using permanganate has been particularly championed by Brown and co-workers. A considerable modification in this area of research is the use of phase-transfer catalyst

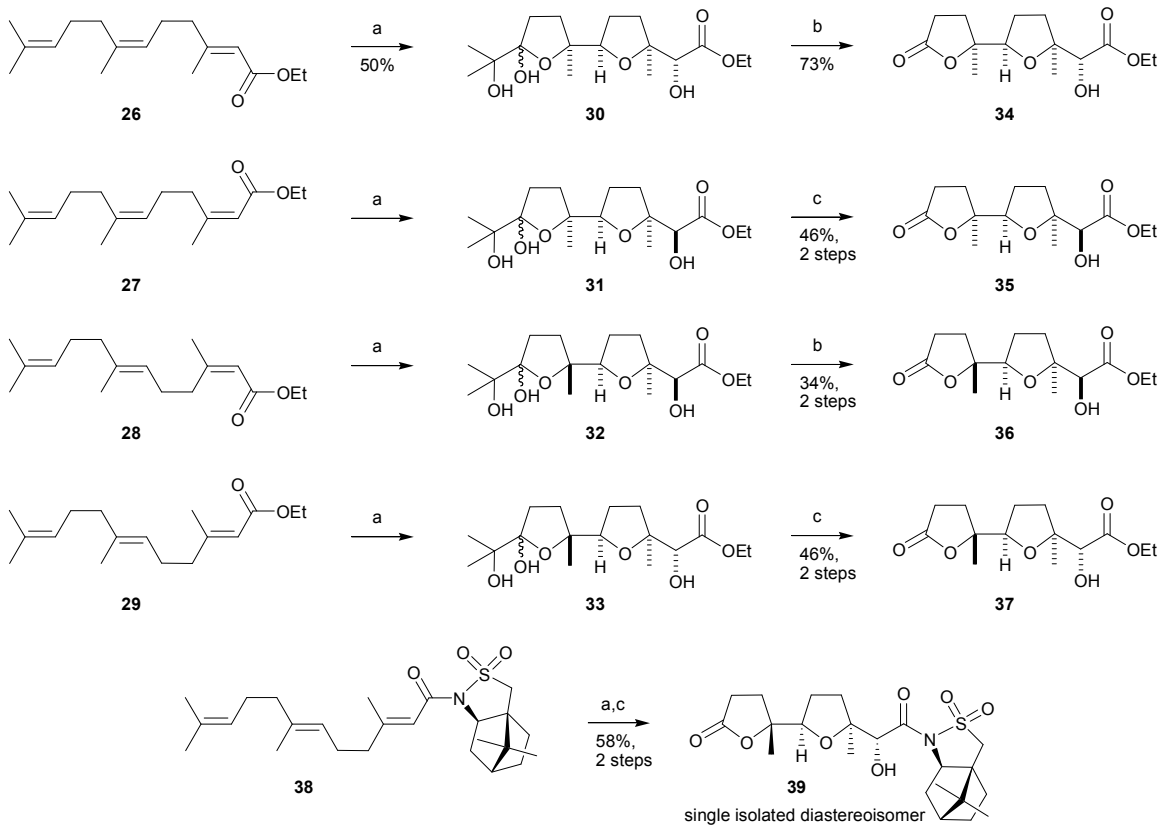
(PTC) for the permanganate-induced oxidative cyclisation of 1,5-dienes. Geranyl benzoate **17** was oxidised using potassium permanganate in the presence of adogen 464 (PTC) to afford the *cis*-THF **18** in good yield (Scheme 3).[15e] Asymmetric oxidation of dienes **19-21** was also attempted using chiral phase-transfer catalyst **22** and corresponding *cis*-THF diols **23-25** were produced in moderate yields with promising enantiomeric ratios.



Scheme 3 Application of phase-transfer catalysts in $KMnO_4$ oxidative cyclisation by Brown and co-workers.

Reagents and conditions: (a) $KMnO_4$ (2.0 eq.), AcOH, adogen 464 (40 mol %), Et_2O; (b) $KMnO_4$ (1.6 eq.), AcOH, chiral phase-transfer catalyst **22** (10 mol %), CH_2Cl_2.

Permanganate oxidative cyclisation has also been elegantly applied to 1,5,9-triene systems in a regiocontrolled manner to gain an expedient access to synthetically significant adjacent bis-THF architectures. Farnesoate esters **26-29** were synthesised using reported procedures and subjected to cyclisation which provided adjacent bis-THF lactols **30-33** (Scheme 4).[31] Subsequent oxidative cleavage of vicinal diol units in lactols afforded the desired lactones **34-37** and the relative stereochemistry of resultant lactones **35** and **36** correlates with polyether antibiotics such as semduramycin and CP-54883 respectively.[32] Later on, (2*R*)-10,2-camphorsultam was used to carry out the cyclisation in a stereoselective fashion. Oxidation of 1,5,9-triene **38** followed by oxidative cleavage of the resulting lactol afforded the lactone **39** in good yield and diastereoselctivity.



Scheme 4 Regiocontrolled and stereoselective oxidative cyclisation of 1,5,9-trienes.

Reagents and conditions: (a) $KMnO_4$ (3.0 eq.), AcOH, pH = 6.2 buffer, acetone-H_2O; (b) $Pb(OAc)_4$, CH_2Cl_2, Na_2CO_3; (c) $NaIO_4$-SiO_2, CH_2Cl_2.

The mechanism of cyclisation for 1,5,9-triene **29** is in accordance with the one originally proposed by Baldwin and co-workers for 1,5-dienes.[15d] After the formation of *cis*-THF diol **40**, oxidation of the remaining double bond affords the hydroxy ketone **41**, which subsequently undergoes an intramolecular cyclisation to furnish the lactol **33** (Fig. 6). In addition to this, Both racemic and asymmetric approaches to prepare 2,6-disubstituted tetrahydropyrans with an exclusive 2,6-*cis*-selectivity from the permanganate oxidative cyclisation of 1,6-dienes have also been reported, albeit in moderate yields and diastereocontrol.[33]

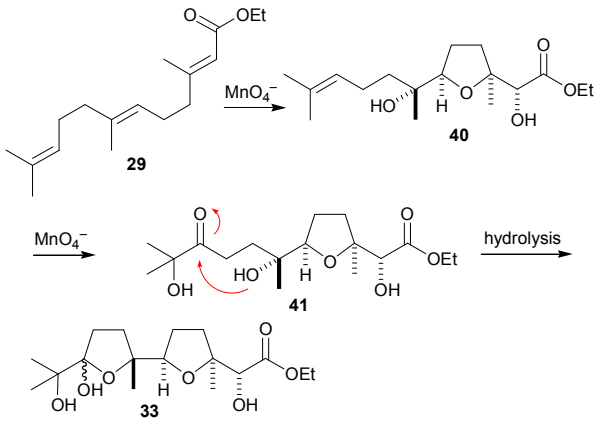
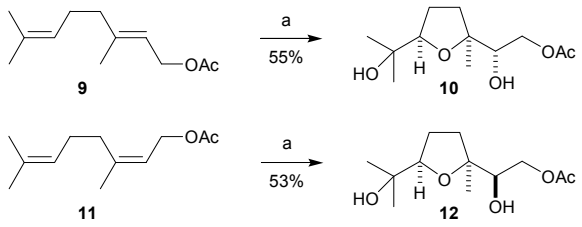


Fig. 6 Brown's proposed mechanism for the formation of adjacent bis-THF lactol **33**.

From cytotoxic natural products to useful synthetic building blocks, permanganate oxidative cyclisation has been successfully employed to construct THF rings in racemic and enantioselective fashions.[34] The asymmetric variant of cyclisation extended the utility of this methodology in total synthesis, and its first application was described by Kocienski and colleagues within a total synthesis of salinomycin (**1**).[3b] Extensive work in this domain has been published from the laboratory of Brown and a wider prospect of permanganate-catalused oxidative cyclisation has been illustrated by completing enantioselective syntheses of a number of members belonging to *Annonaceous* acetogenin and oxasqualenoid families of natural products. These include mono-THF, adjacent bis-THF and non-adjacent bis-THF containing bioactive molecules such as *cis*-solamin (**2**),[4b] *cis*-sylvaticin (**3**),[5b] *cis*-uvariamicin I (**4**) and *cis*-reticulatacin (**5**)[6] obtained from 1,5-diene precursors, membranacin (**6**) using bifuranyl synthetic approach applied to 1,5,9-triene substrate,[7b] membrarollin (**7**) from a dienyne motif,[8] and a formal synthesis of eurylene (**8**) by chemoselective and regiocontrolled monocyclisations of 1,5,9-trienes.[9d] Recently, this chemistry has been applied to an efficient stereoselective synthesis of *trans*-(+)-linalool oxide,[35] which is a monoterpenoid present in essential oils and one of the most commonly used compounds in beverages, foods, and perfumery.

3 Osmium-catalysed oxidative cyclisation

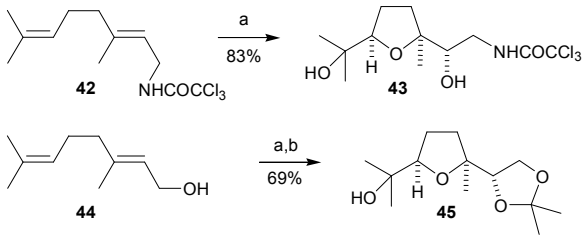
Piccialli and colleagues were the first to report the osmium tetroxide-mediated oxidative cyclisation under catalytic conditions using sodium periodate ($NaIO_4$) as a co-oxidant. Gernayl acetate **9** and neryl acetate **11** were oxidised to the corresponding *cis*-THF diols **10** and **12** respectively in good yields (Scheme 5).[16a] Interestingly, changing the co-oxidant from sodium periodate to *N*-methylmorpholine-*N*-oxide (NMO) failed to yield the desired cyclised products even though NMO is a well-known co-oxidant in the catalytic asymmetric dihydroxylation of olefins.[36]



Scheme 5 First examples of OsO_4 mediated oxidative cyclisation.

Reagents and conditions: (a) OsO_4 (5 mol %), $NaIO_4$ (4.0 eq.), DMF, 16 h.

Intensive work in the field of OsO_4 promoted oxidative cyclisation has been carried out by the research group of Donohoe and synthetic application of an OsO_4/TMEDA combination for the stereoselective oxidative cyclisation of 1,5-functionalised dienes has been explored.[16b] 1,5-Dienes **42** and **44** were oxidised in a regioselective way and it was expected to obtain the corresponding dihydroxylated products, however *cis*-THF diols **43** and **45** were obtained in good yields (Scheme 6). The OsO_4/TMEDA combination provides a hydrogen bond acceptor reagent, which is an efficient way to direct the regioselectivity during the dihydroxylation of allylic alcohols such as **44**.[37]



Scheme 6 Oxidative cyclisation of 1,5-dienes using OsO_4/TMEDA complex by Donohoe and co-workers.

Reagents and conditions: (a) OsO_4 (1.0 eq.), TMEDA (1.0 eq.), CH_2Cl_2, –78 ˚C then MeOH, HCl, rt; (b) $(MeO)_2CMe_2$, TFA.

The proposed mechanism for OsO_4/TMEDA cyclisation is believed to follow the principle of sequential [3+2] cycloadditions reported for the permanganate-mediated oxidative cyclisation of 1,5-dienes.[15d] Initially, one of the double bonds of 1,5-diene substrate undergoes a regioselective osmylation, controlled by hydrogen bonding to form an osmate$^{(VI)}$ ester, which has been characterised in some cases (Fig. 7).[16b] An intramolecular cyclisation takes place involving the reduction of active osmate$^{(VI)}$ to an osmate$^{(IV)}$ ester, which on subsequent acidic hydrolysis affords the *cis*-THF adduct and OsO_2 that is oxidised back to OsO_4. It is proposed that acid either serves to promote the rapid ligand exchange to permit the cyclisation or protonates the oxo–ligand species. In latter situation, the metal would be more electron deficient hence more reactive in the cyclisation. The *cis*-selectivity of the five membered ring is believed to be due to the proposed transition state, in which the intact glycol osmium bonds impose the *cis*-stereochemistry across the incipient THF ring.[16b]

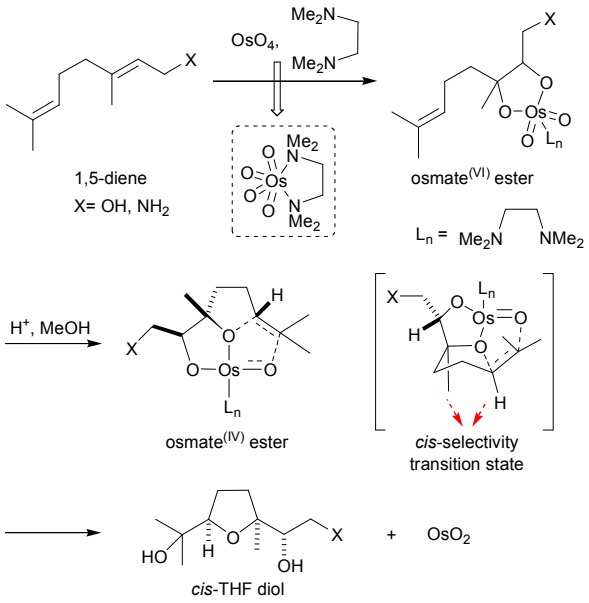
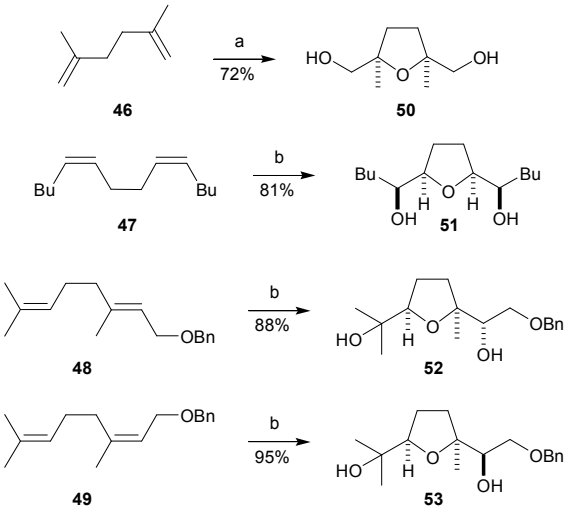


Fig. 7 Donohoe's mechanistic proposal for OsO_4/TMEDA oxidation of 1,5-dienes.

To avoid an unattractive use of stoichiometric OsO_4, Donohoe and co-workers investigated the use of catalytic osmium along with trimethylamine *N*-oxide (TMO) as a co-oxidant under acidic conditions.[16c] Several structurally diverse 1,5-dienes **46-49** were subjected to catalytic OsO_4 promoted oxidative cyclisation to yield *cis*-THF diols **50-53**, in good to excellent yields and as single diastereoisomers (Scheme 7). Notably, the choice of solvent and organic acid plays an influential role.

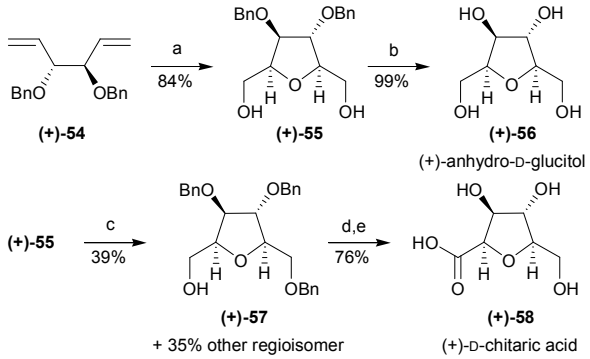


Scheme 7 Catalytic use of OsO_4 under acidic conditions.

Reagents and conditions: (a) OsO_4 (5 mol %), TMO (4.0 eq.), CSA (6.0 eq.), CH_2Cl_2; (b) OsO_4 (5 mol %), TMO (4.0 eq.), TFA (excess), acetone:H_2O (9:1).

To control the facial selectivity of this reaction, an internal stereodirecting substituent on 1,5-diene precursor has been investigated. Facile and effective stereo-controlled syntheses of (+)-anhydro-D-glucitol (**(+)-56**) and (+)-D-chitaric acid (**(+)-58**) illustrate the synthetic utility of catalytic OsO_4 promoted

oxidative cyclisation of 1,5-dienes. Enantiomerically enriched 1,5-diene **(+)-54** was synthesised from D-mannitol in 4 steps, which was subjected to catalytic OsO_4 oxidative cyclisation to offer a single stereoisomeric *cis*-THF diol **(+)-55** in an excellent yield (Scheme 8).[16c] Deprotection of benzyl ethers completed a synthesis of (+)-anhydro-D-glucitol (**(+)-56**) in 6 steps and 42.5% overall yield. Furthermore, selective monoprotection of primary alcohol motif of *cis*-THF diol **(+)-55**, alcohol oxidation and finally deprotection provided (+)-D-chitaric acid (**(+)-58**) in total 8 steps and 12.7% overall yield. Oxidative cyclisation of 1,4-dienes to generate 2,5-disubstituted THFs has also been reported using catalytic OsO_4 with Oxone® as co-oxidant in moderate yields.[38] For this particular transformation, exchanging OsO_4 with $KMnO_4$ and RuO_4 results in comparatively poor yields.

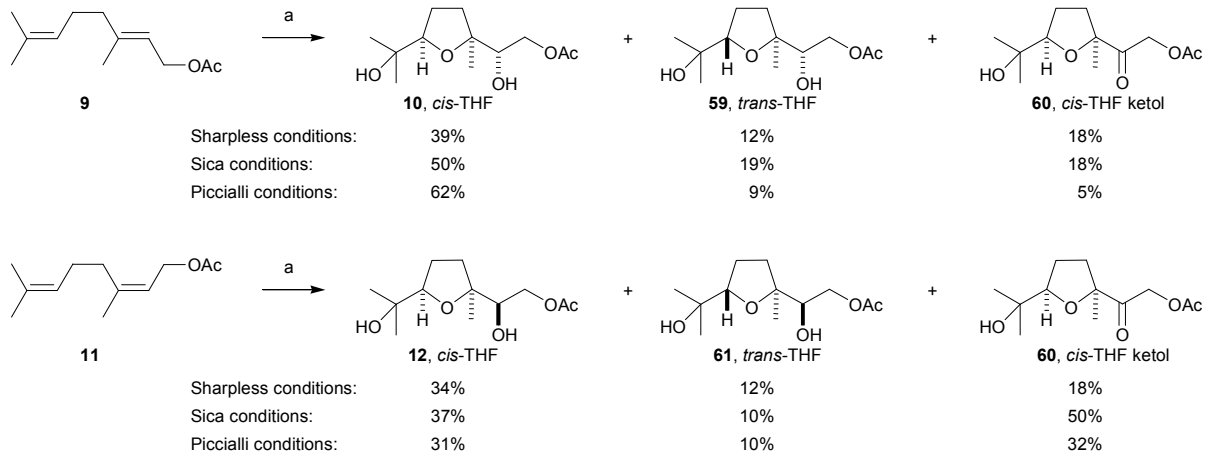


Scheme 8 Role of internal stereodirecting groups and stereoselective synthesis of (+)-anhydro-D-glucitol (**(+)-56**) and (+)-D-chitaric acid (**(+)-58**).

Reagents and conditions: (a) OsO_4 (5 mol %), TMO (4.0 eq.), CSA (6.0 eq.), CH_2Cl_2; (b) H_2, Pd/C, EtOH; (c) BnBr, Ag_2O, toluene; (d) TEMPO (catalytic), $NaClO_2$, NaClO, MeCN; (e) H_2, Pd/C, MeOH.

4 Ruthenium-promoted cyclisation

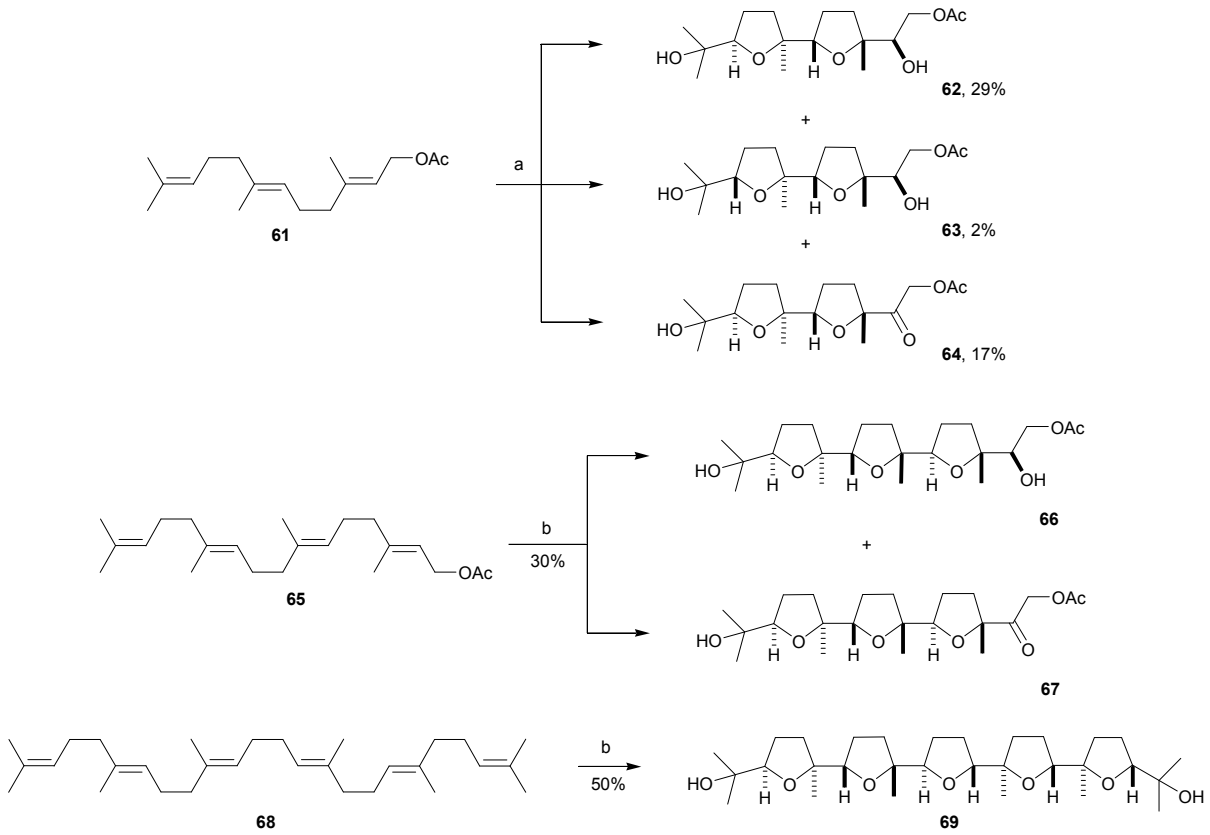
The use of ruthenium in the oxidative cyclisation of 1,5-dienes was first reported by Sharpless and colleagues (Scheme 9).[17a] The focus of the study was to improve the catalytic conversion of primary alcohols to carboxylic acids using ruthenium and it was discovered that the oxidation of geranyl acetate **9** and neryl acetate **11** led to the formation of *cis*-THF adducts **10** and **12** respectively along with their *trans*- isomers **59** and **61** respectively (*cis*:*trans* ratio ~3:1), while *cis*-THF ketol **60** was obtained as a major by-product. Sica and co-workers also investigated the same transformation and attempted to enhance the *cis*-selectivity of the reaction but could not achieve a significant improvement.[17b] The research group of Piccialli had some success with geranyl acetate **9** and their improved method minimised the formation of over oxidised product **60** as well.[17c]



Scheme 9 Comparative report on RuO_4 promoted oxidative cyclisation of 1,5-dienes.

Reagents and conditions: (a) *Sharpless conditions*: $RuCl_3•(H_2O)_n$, (2.2 mol %), $NaIO_4$ (3.1 eq.), CCl_4:CH_3CN:H_2O (2:2:3), 0 ˚C, 15 min; *Sica conditions*: $RuO_2•2H_2O$, (5.0 mol %), $NaIO_4$ (2.5 eq.), EtOAc:$(CH_3)_2CO$:H_2O (2:1:1), 0 ˚C, 4 min; *Piccialli conditions*: $RuO_2•2H_2O$, (4 mol %), $NaIO_4$ (4.0 eq.), EtOAc:CH_3CN:H_2O (3:3:1), 0 ˚C, 4 min.

Investigative studies on RuO_4 catalysed polycyclisation of isoprenoid polyenes towards the syntheses of adjacently linked poly-THF rings have been described. Farnesyl acetate **61**,[39a,b] geranylgeranylacetate **65**[39c,d] and squalene **68**[39c,d] underwent polycyclisation to afford bis-, tris- and penta-THF diols **62**, **66** and **69** respectively (Scheme 10). In the case of tris-THF product **66** and penta-THF product **69**, the relative configuration was determined by NMR studies and confirmed by preparing the diols **66** and **69** *via* reported methods. Also, polycyclisation of *meso* symmetric (*Cs*) tetraene, digeranyl has been carried out and the resultant stereochemical outcome is explained by NMR analysis and simulated three dimensional structures of the possible transition states.[39e]



Scheme 10 RuO_4 promoted polycyclisations of isoprenoid polyenes.

Reagents and conditions: (a) RuO_2•$2H_2O$ (20 mol %), $NaIO_4$ (4.0 eq.), EtOAc:CH_3CN:H_2O (3:3:1), 0 ˚C, 30 min; (b) RuO_2•$2H_2O$ (20 mol %), $NaIO_4$ (8.0 eq.), EtOAc:CH_3CN:H_2O (3:3:1), 0 ˚C, 30 min.

It is thought that the mechanism of this reaction is related to the proposal presented by Baldwin for the permanganate oxidative cyclisation of 1,5-dienes.[15d] It is believed that RuO_4 interacts with a double bond to form $Ru^{(VI)}$ diester, followed by an intramolecular [3+2] cycloaddition and subsequent hydrolysis to afford mono-*cis*-THF product (Fig. 8).[39a] In order to achieve an active oxidation level, $Ru^{(V)}$ is oxidised to give $Ru^{(VII)}$ intermediate, which readily undergoes another [3+2] cyclisation to form $Ru^{(V)}$ ester. Hydrolysis of the resultant $Ru^{(V)}$ ester releases the bis-THF diol adduct, while oxidative cleavage leads to bis-THF ketol.

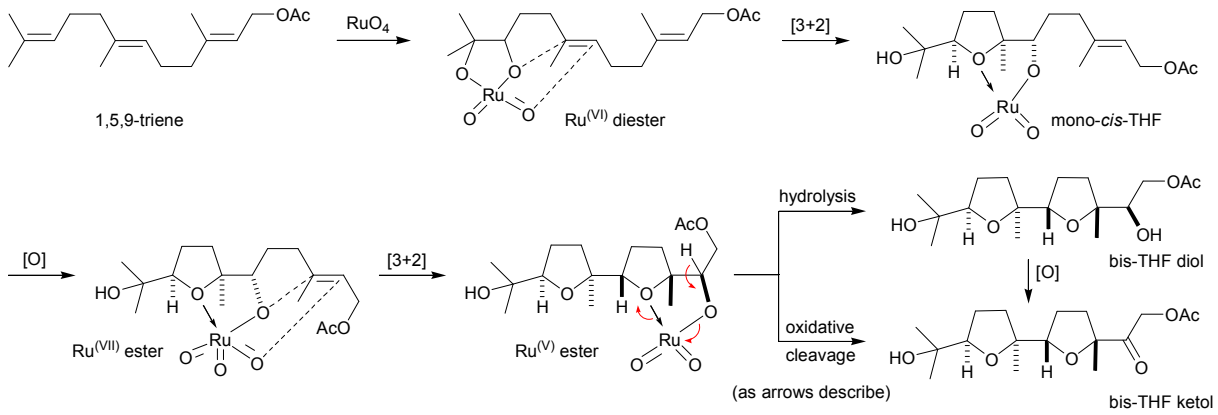


Fig. 8 Piccialli's proposed mechanism for RuO_4 catalysed oxidative cyclisation of 1,5,9-trienes.

Origin of *cis*- and *trans*-selectivity in the incipient THFs resulting from RuO_4 cyclisations is also described with conformational models. After an initial attack of the $Ru^{(VIII)}$ species, diester **70** is formed which adopts a specific stereochemical arrangement **70a** to ensure the correct positioning of the second double bond involved in THF ring formation (Fig. 9).[40] Such a chair-like conformation **70a**, on hydrolysis, leads to *cis*-THF ring **71**. It is also proposed that hydrolysis of C(1)O–Ru bond would afford $Ru^{(VIII)}$ ester **72**. The coordination of C(1)OH with $Ru^{(VIII)}$ would lead to a chair like conformation **70b**, which is analogous to the reactive conformation **70a** and provides *cis*-selectivity in the resulting THF ring **71** through chelation control mechanism.

Alternatively, if no coordination of C(1)OH takes place with $Ru^{(VIII)}$ diester **72**, conformation **72a** would be obtained which provides *trans*-THF product **73**, based on the steric reasons. This form of $Ru^{(VIII)}$ intermediate **72a** is similar to the perrehenate ester involved in the *trans*-diastereoselective oxidative cyclisation of the bishomoallylic alcohols.[41]

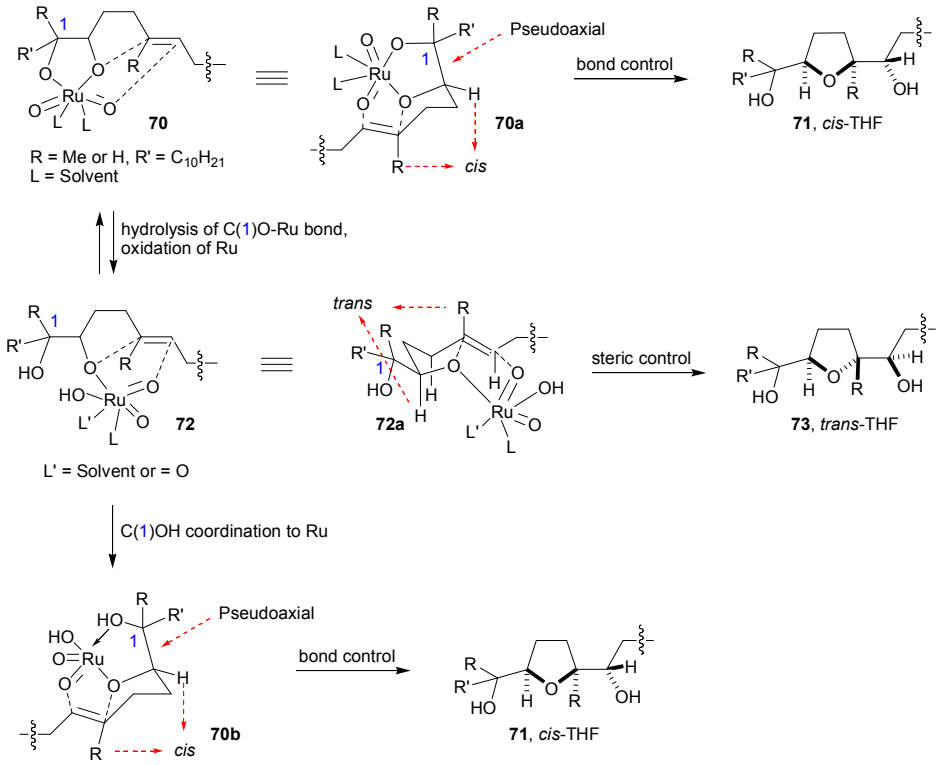
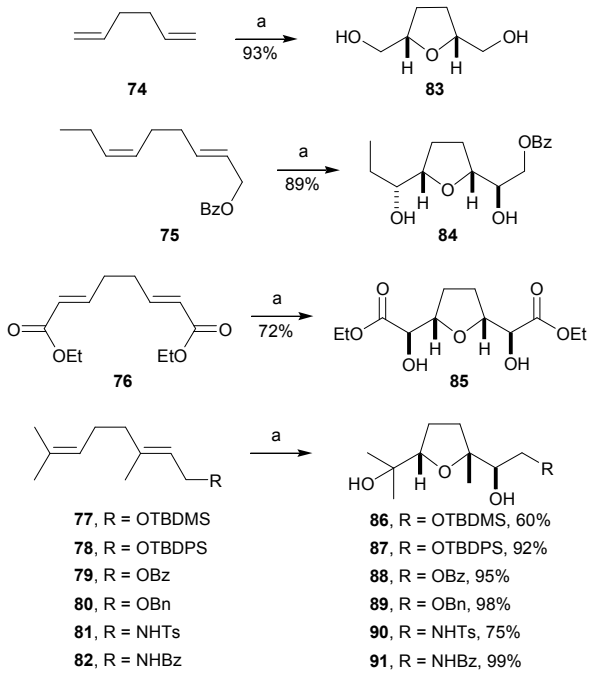


Fig. 9 Origin of *cis*- and *trans*-selectivity in THFs resulting from RuO_4 catalysed oxidative cyclisation.

Stark and co-workers have reported a catalytic RuO_4 mediated oxidative cyclisation of several substituted 1,5-dienes **74-82** to afford THF diols **83-91** in good to excellent yields with high *cis*-stereoselectivity (dr >95:5, Scheme 11).[17e,f] The corresponding *trans*-THF diols were not observed except in the case of THF diols **86** and **89**. Sodium periodate on wet silica was used as co-oxidant in a solvent mixture of THF and CH_2Cl_2 (9:1). The generality of this approach is described, in which a range of functional and protecting groups are tolerant to the reaction conditions and the cyclisation proceeds efficiently.



Scheme 11 Catalytic RuO_4 mediated cyclisation of 1,5-dienes by Stark and co-workers.
Reagents and conditions: (a) $RuCl_3$ (0.2 mol %), $NaIO_4$ on wet silica (3.0 eq.), THF:CH_2Cl_2 (9:1).

The mechanism proposed by Stark for the catalytic RuO_4 cyclisation is analogous to the $KMnO_4$[15d] and OsO_4[16b] mediated oxidative cyclisations. It is proposed that after the oxidation of pre-catalyst, an initial [3+2] cycloaddition takes place between RuO_4 and one of the double bond of 1,5-diene to afford $Ru^{(VI)}$ intermediate (Fig. 10).[17e,f] The intermediate undergoes another [3+2] intramolecular cyclisation to give $Ru^{(IV)}$ diester, which on subsequent hydrolysis furnishes a *cis*-THF diol and RuO_2, which is oxidised back to RuO_4. Computational studies based on density functional theory have also been conducted to understand the mechanistic pathway of the reaction and theoretical calculations are found to be in good agreement with the experimental results.[42] The transition state during the formation of *cis*-THF product is reported to have about 40 KJ/mol more stability than the corresponding *trans*-THF ring.

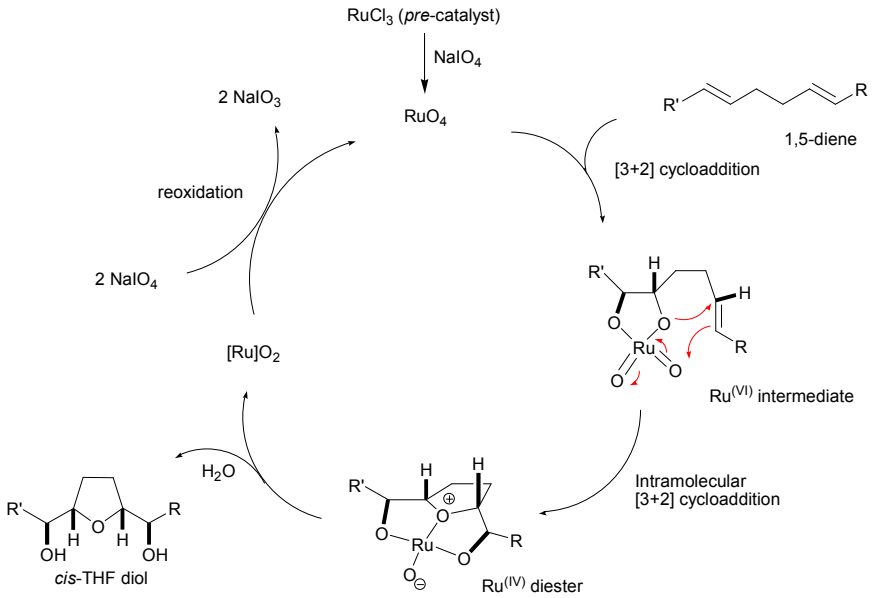
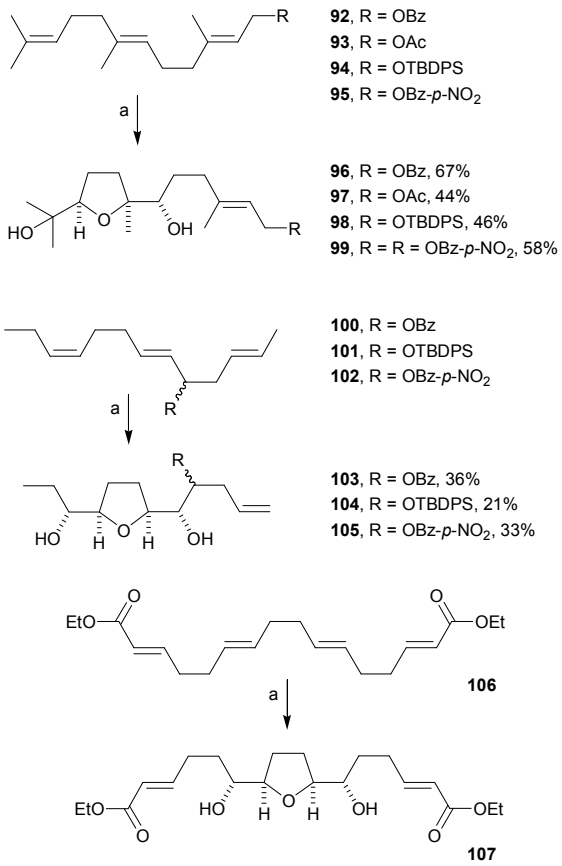


Fig. 10 Stark's proposed mechanism for catalytic RuO_4 promoted cyclisation of 1,5-dienes.

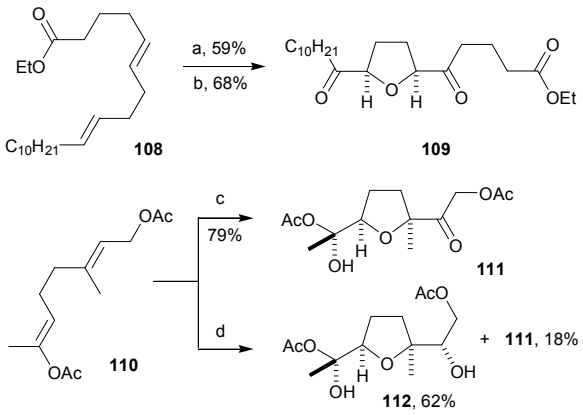
RuO_4 catalysed monocyclisation of 1,5,9-trienes and polyenes has also been performed, and shows good diastereoselectivity and regiocontrol. Farnesol derivatives **92-95**, bearing several protecting groups, were oxidised to corresponding *cis*-THF diols **96-99** in good yields with high diastereoselectivity (dr >95:5, Scheme 12).[17g] Similarly, non-terpenoid 1,5,9-trienes **100-102** were oxidised to *cis*-THF diols **103-105** in moderate yields and with the same level of diastereoselectivity. The methodology was extended to various polyenes including diester **106** and a good level of regiocontrol and diastereoselectivity was observed along with moderate yield of the resultant *cis*-THF diol **107**. Interestingly, the cyclisation of polyenes did not go to complete conversion using previously reported optimised conditions for 1,5-diene substrates.[17e] Changing the solvent from THF:CH_2Cl_2 (9:1) mixture to pure THF increased the reaction rates and yields. This may be due to faster hydrolysis in a more polar solvent.



Scheme 12 Catalytic RuO_4 cyclisation of polyenes.

Reagents and conditions: (a) $RuCl_3$ (1 mol %), $NaIO_4$ on wet silica (3.0 eq.), THF.

Another discovery in the field of ruthenium based cyclisation is the use of perruthenate ion from tetrapropylammonium perruthenate (TPAP). In the presence of NMO as a co-oxidant and excess of TPAP (2.0 eq.), 1,5-diene **108** was cyclised to *cis*-THF diketone **109** in a good yield (Scheme 13).[17d] When TPAP was used alone as an oxidising agent in the absence of NMO, incomplete conversion to the desired THF compound was observed. The reaction was carried out under catalytic conditions of TPAP by changing the co-oxidant from NMO to tetrabutylammonium periodate (TBAPI) and the yield also increased from 59 to 68%. Oxidative cyclisation of diacetate **110** using catalytic TPAP with TBAPI afforded the THF ketol **111** in good yield. When the reaction was performed under acidic conditions using NMO, a mixture of *cis*-THF diol **112** and THF ketol **111** was obtained. By changing the co-oxidant and reaction conditions, the major product of the oxidative cyclisation can be controlled which is of significant synthetic importance.



Scheme 13 Perruthenate-promoted oxidative cyclisation of 1,5-dienes.

Reagents and conditions: (a) TPAP (2.0 eq.), NMO (25 eq.), 4 Å MS, CH_2Cl_2; (b) TPAP (10 mol %), TBAPI (5.0 eq.), CH_2Cl_2; (c) TPAP (5 mol %), TBAPI (5.0 eq.), CH_2Cl_2; (d) TPAP (2.0 eq.), NMO (3.0 eq.), AcOH, 4 Å MS, CH_2Cl_2.

Synthetic applications of catalytic RuO_4 mediated oxidative cyclisation has been investigated, which provide an elegant synthesis of *cis*-solamin (**2**)[4d] and neodysiherbaine.[43] In addition to this, catalytic RuO_4 mediated oxidative cyclisation applied to 1,6- and 1,7-dienes provide a succinct route to *trans*-2,6-disubstituted tetrahydropyrans[44] and *trans*-2,7-disubstituted oxepanes[45] respectively, in good yield with high *trans*-diastereoselectivity (dr >95:5).

5 Conclusion

Natural products containing *cis*-2,5-disusbstituted THF rings show remarkably wide range of pharmacological potential, particularly with regard to exhibiting potent cytotoxic activities against cancer cells, multidrug resistant tumors and significant bioactivities including antiparasitic, antimalarial and pesticidal. Given their distinctive structural features combined with remarkable cytotoxicity, these have attracted an unusually high level of interest from the synthetic community, spending a lot of time and efforts to establish new synthetic protocols and to obtain adequate quantities for expediting their biological evaluations. Several metal-oxo species have been reported to affect the oxidative cyclisation of 1,5-dienes towards *cis*-2,5-disubstitued THF moieties. Permanganate-induced cyclisation generally proceeds in a good yield and it is considered as an environmentally benign protocol in comparison with other counterpart metal–oxo species. In particular, chiral phase transfer catalyst and chiral auxiliaries have been incorporated to provide an effective control of absolute stereoselectivity. However, such a type of oxidative cyclisation of 1,5-dienes requires a stoichiometric amount of the transition metal oxidant. Osmium tetroxide, ruthenium tetroxide and perruthenate-mediated cyclisations can be achieved under catalytic conditions, though excesses of co-oxidants such as TMEDA, TMO, NMO, $NaIO_4$ and TBAPI are often required. Osmium tetroxide provides an efficient route, however does not allow direct

asymmetric oxidative cyclisation of 1,5-dienes. Application of internal stereodirecting to induce indirect enantioselective oxidative cyclisation has been devised. Ruthenium–oxo catalyst results in polycyclisation of multiple double bonds in an efficient manner. The synthetic protocols delineated in this review have been applied to numerous bioactive natural products with profound structural complexity and will continue the irresistible allure of fascinating natural products.

6 Abbreviations

Ac	Acetyl
Ar	aromatic
Bn	benzyl
Bu	butyl
Bz	benzoyl
CSA	camphorsulfonic acid
DFT	density functional theory
DMF	*N,N′*-dimethylformamide
dr	diastereomeric ratio
eq.	equivalent
Et	ethyl
h	hour
Me	methyl
min	minutes
mmol	millimole
MS	molecular sieves
NMO	*N*-methylmorpholine-*N*-oxide
Ph	phenyl
PTC	phase-transfer catalyst
rt	room temperature
TBAPI	tetrabutylammunium periodate
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEMPO	(2,2,6,6,-tetramethylpiperidin-1-yl)oxyl
TFA	triflouroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TMEDA	*N,N,N′, N′*-tetramethylethylenediamine
TMO	trimethylamine *N*-oxide
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*p*-toluenesulfonyl

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8 References

1 (*a*) T. L. B. Boivin, *Tetrahedron*, 1987, **43**, 3309–3362; (*b*) J.-C. Harmange and B. Figadére, *Tetrahedron: Asymmetry*, 1993, **4**, 1711–1754; (*c*) E. Keinan and S. C. Sinha, *Pure Appl. Chem.*, 2002, **74**, 93–105; (*d*) J. Hartung and M. Greb, *J. Organomet. Chem.*, 2002, **661**, 67–84; (*e*) J. P. Wolfe and M. B. Hay, *Tetrahedron*, 2007, **63**, 261–290; (*f*) V. Piccialli, *Synthesis*, 2007, **17**, 2585–2607; (*g*) G. Jalce, X. Franck and B. Figadére, *Tetrahedron: Asymmetry*, 2009, **20**, 2537–2581; (*h*) B. S. Pilgrim and T. J. Donohoe, *J. Org. Chem.*, 2013, **78**, 2149–2167; (*i*) V. Piccialli, *Molecules*, 2014, **19**, 6534–6582; (*j*) N. S. Sheikh, *Nat. Prod. Rep.*, 2014, **31**, 1088–1100.

2 (*a*) H. Morita, E. Kishi, K. Takeya, H. Itokawa and Y. Iitaka, *Phytochemistry*, 1993, **34**, 765–771; (*b*) P.-C. Kuo, A. G. Damu, K.-H. Lee and T.-S. Wu, *Bioorg. Med. Chem.*, 2004, **12**, 537–544.

3 Salinomycin: (*a*) K. Horita, Y. Oikawa, S. Nagato and O. Yonemitsu, *Chem. Pharm. Bull.*, 1989, **37**, 1717–1725; (*b*) P. J. Kocienski, R. C. D. Brown, A. Pommier, M. Procter and B. Schmidt, *J. Chem. Soc. Perkin Trans. 1: Org. Bioorg. Chem.*, 1998, 9–39.

4 *Cis*-solamin: (*a*) H. Makabe, Y. Hattori, A. Tanaka and T. Oritani, *Org. Lett.*, 2002, **4**, 1083–1085; (*b*) A. R. L. Cecil and R. C. D. Brown, *Org. Lett.*, 2002, **4**, 3715–3718; (*c*) T. J. Donohoe and S. Butterworth, *Angew. Chem. Int. Ed.*, 2005, **44**, 4766–4768; (*d*) H. Goskel and C. B. W. Stark, *Org. Lett.*, 2006, **8**, 3433–3436.

5 *Cis*-sylvaticin: (*a*) T. J. Donohoe, R. M. Harris, J. Burrows and J. Parker, *J. Am. Chem. Soc.*, 2006, **128**, 13704–13705; (*b*) L. J. Brown, I. B. Spurr, S. C. Kemp, N. P. Camp, K. R. Gibson and R. C. D. Brown, *Org. Lett.*, 2008, **10**, 2489–2492.

6 *Cis*-uvariamicin I and *cis*-reticulatacin: S. B. Abdel Ghani, J. M. Chapman, B. Figadère, J. M. Herniman, G. J. Langley, S. Niemann and R. C. D. Brown, *J. Org. Chem.*, 2009, **74**, 6924–6928.

7 Membranacin: (*a*) G. D. Head, W. G. Whittingham and R. C. D. Brown, *Synlett*, 2004, 1437–1439; (*b*) G. Keum, C. H. Hwang, S. B. Kang, Y. Kim and E. Lee, *J. Am. Chem. Soc.*, 2005, **127**, 10396–10399.

8 Membrarollin: C. L. Morris, Y. Hu, G. D. Head, L. J. Brown, W. G. Whittingham and R. C. D. Brown, *J. Org. Chem.*, 2009, **74**, 981–988.

9 Eurylene: (*a*) K. Ujihara and H. Shirahama, *Tetrahedron Lett.*, 1996, **37**, 2039–2042; (*b*) Y. Morimoto, K. Muragaki, T. Iwai, Y. Morishita and T. Kinoshita, *Angew. Chem. Int. Ed.*, 2000, **39**, 4082–4084; (*c*) H. Hioki, S. Yoshio, M. Motosue, Y. Oshita, Y. Nakamura, D. Mishima, Y. Fukuyama, M. Kodoma, K. Ueda and T. Katsu, *Org. Lett.*, 2004, **6**, 961–964; (*d*) N. S. Sheikh, C. J. Bataille, T. J. Luker and R. C. D. Brown, *Org. Lett.*, 2010, **12**, 2468–2471.

10 N. H. Oberlies, J. L. Jones, T. H. Corbett, S. S. Fotopoulos and J. L. McLaughlin, *Caner Lett.*, 1995, **96**, 55–62.

11 N. H. Oberlies, V. L. Croy, M. L. Harrison and J. L. McLaughlin, *Caner Lett.*, 1997, **115**, 73–79.

12 H. Makabe, *Biosci. Biotechnol Biochem.*, 2007, **71**, 2367–2374.

13 (*a*) D. E. Cane, W. D. Celmer and J. W. Westley, *J. Am. Chem. Soc.*, 1983, **105**, 3594–3600; (*b*) J. J. Fernández, M. L. Souto and M. Norte, *Nat. Prod. Rep.*, 2000, **17**, 235–246; (*c*) Y. Kashman and A. Rudi, *Phytochem. Rev.*, 2004, **3**, 309–323; (*d*) A. R. Gallimore, *Nat. Prod. Rep.*, 2009, **26**, 266–280.

14 (*a*) W. J. Schultz, M. C. Etter, A. V. Pocius and S. Smith, *J. Am. Chem. Soc.*, 1980, **102**, 7981–7982; (*b*) H. Tsukube, K. Takagi, T. Higashiyama, T. Iwachido and N. Hayama, *Inorg. Chem.*, 1994, **33**, 2984–2987; (*c*) Y. Morimoto, T. Iwai, T. Yoshimura and T. Kinoshita, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2005–2010.

15 (*a*) A. Kötz and T. Steche, *J. Parkt. Chem.*, 1924, **107**, 193–195; (*b*) E. Klein and W. Rojahn *Tetrahedron*, 1965, **21**, 2353–2358; (*c*) D. M. Walba, M. Wand and M. Wilkes, *J. Am. Chem. Soc.*, 1979, **101**, 4396–4397; (*d*) J. E. Baldwin, M. J. Crossley and E. M. M. Lehtonen, *J. Chem. Soc. Chem. Comm.*, 1979, 918–920; (*e*) R. C. D. Brown and J. F. Keily, *Angew. Chem. Int. Ed.*, 2001, **40**, 4496–4498.

16 (*a*) M. de Champdoré, M. Lasalvia and V. Piccialli, *Tetrahedron Lett.*, 1998, **39**, 9781–9784; (*b*) T. J. Donohoe, J. J. G. Winter, M. Helliwell and G. Stemp, *Tetrahedron Lett.*, 2001, **42**, 971–974; (*c*) T. J. Donohoe and S. Butterworth, *Angew. Chem. Int. Ed.*, 2003, **42**, 948–951.

17 (*a*) P. H. J. Carlsen, T. Katsuki, V. S. Martin and K. B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3937–3938; (*b*) L. Albarella, D. Musumeci and D. Sica, *Eur. J. Org. Chem.*, 2001, 997–1003; (*c*) V. Piccialli and N. Cavallo, *Tetrahedron Lett.*, 2001, **42**, 4695–4699; (*d*) V. Piccialli and T. Caserta, *Tetrahedron Lett.*, 2004, **45**, 303–308; (*e*) S. Roth, S. Göhler, H. Cheng and C. B. W. Stark, *Eur. J. Org. Chem.*, 2005, **19**, 4109–4118; (*f*) S. Göhler, S. Roth, H. Cheng, H. Goksel, A. Rupp, L. O. Haustedt and C. B. W. Stark, *Synthesis*, 2007, **17**, 2751–2754; (*g*) S. Göhler and C. B. W. Stark, *Org. Biomol. Chem.*, 2007, **5**, 1605–1614.

18 (*a*) T. J. Donohoe and S. Butterworth, *Angew. Chem. Int. Ed.*, 2005, **44**, 4766–4768; (*b*) T. J. Donohoe, P. C. M. Winship and D. S. J. Walter, *J. Org. Chem.*, 2009, **74**, 6394–6397.

19 (*a*) B. D. Hammock, S. S. Gill and J. E. Casida, *J. Agric. Food Chem.*, 1974, **22**, 379-385; (*b*) D. M. Walba and G. S. Stoudt, *Tetrahedron Lett.*, 1982, **23**, 727–730.

20 H. Chang and C. B. W. Stark, *Angew. Chem. Int. Ed.*, 2010, **49**, 1587–1590.

21 (*a*) R. M. Kennedy and S. Tang, *Tetrahedron Lett.*, 1992, **33**, 3729–3732; (*b*) S. Tang and R. M. Kennedy, *Tetrahedron Lett.*, 1992, **33**, 5299–5302; (*c*) S. Tang and R. M. Kennedy, *Tetrahedron Lett.*, 1992, **33**, 5303–5306; (*d*) R. S. Boyce and R. M. Kennedy, *Tetrahedron Lett.*, 1994, **35**, 5133–5136; (*e*) F. E. McDonald and T. B. Towne, *J. Org. Chem.*, 1995, **60**, 5750–5751; (*f*) T. B. Towne and F. E. McDonald, *J. Am. Chem. Soc.*, 1997, **119**, 6022–6028; (*g*) Y. Morimoto and T. Iwai, *J. Am. Chem. Soc.*, 1998, **120**, 1633–1634.

22 S. Inoki and T. Mukaiyama, *Chem. Lett.*, 1990, **19**, 67–70.

23 (*a*) T. Fukuyama, B. Vranesic, D. P. Negri and Y. Kishi, *Tetrahedron Lett.*, 1978, **31**, 2741–2744; (*b*) P. C. Ting and P. A. Bartlett, *J. Am. Chem. Soc.*, 1984, **106**, 2668–2671; (*c*) I. Vilotijevic and T. F. Jamison, *Angew. Chem. Int. Ed.*, 2009, **48**, 5250–5281; (*d*) I. Vilotijevic and T. F. Jamison, *Mar. Drugs*, 2010, **8**, 763–809.

24 (*a*) J. Rodríguez-López, F. P. Crisóstomo, N. Ortega, M. L. López-Rodríguez, V. S. Martín and T. Martín, *Angew. Chem. Int. Ed.*, 2013, **52**, 3659–3662; (*b*) Y. Morimoto, T. Takeuchi, H. Kambara, T. Kodama, Y. Tachi and K. Nishikawa, *Org. Lett.*, 2013, **15**, 2966–2969.

25 Teurilene: (*a*) M. Hashimoto, H. Harigaya, M. Yanagiya and H. Shirahama, *Tetrahedron Lett.*, 1988, **29**, 5947–5948; (*b*) M. Hashimoto, H. Harigaya, M. Yanagiya and H. Shirahama, *J. Org. Chem.*, 1991, **56**, 2299–2311; (*c*) Y. Morimoto, T. Iwai and T. Kinoshita, *J. Am. Chem. Soc.*, 1999, **121**, 6792–6797; (*d*) Y. Morimoto, T. Kinoshita and T. Iwai, *Chirality*, 2002, **14**, 578–586.

26 T. J. Donohoe, K. M. P. Wheelhouse, P. J. Lindsay-Scott, G. H. Churchill, M. J. Connolly and P. A. Glossop, *Chem.–Asian J.*, 2009, **4**, 1237–1247.

27 K. B. Sharpless, A. Y. Teranishi and J. E. Backvall, *J. Am. Chem. Soc.*, 1977, **99**, 3120–3128.

28 (*a*) D. G. Lee and J. R. Brownridge, *J. Am. Chem. Soc.*, 1973, **95**, 3033–3034; (*b*) S. Wolfe, C. F. Ingold and R. U. Lemieux, *J. Am. Chem. Soc.*, 1981, **103**, 938–939; (*c*) K. N. Houk and T. Strassner, *J. Org. Chem.*, 1999, **64**, 800–802; (*d*) A. Poethig and T. Strassner, *Collect. Czech. Chem. Commun.*, 2007, **72**, 715–727.

29 (*a*) D. M. Walba, C. A. Przybyla and C. B. Walker, *J. Am. Chem. Soc.*, 1990, **112**, 5624–5625; (*b*) D. A. Evans, J. Bartroli and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127–2129.

30 (*a*) W. Oppolzer and J. P. Barras, *Helv. Chim. Acta*, 1987, **70**, 1666–1675; (*b*) W. Oppolzer, C. Darcel, P. Rochet, S. Rosset, and J. DeBrabander, J. *Helv. Chim. Acta*, 1997, **80**, 1319–1337.

31 (*a*) R. C. D. Brown, R. M. Hughes, J. Keily and A. Kenney, *Chem. Commun.*, 2000, 1735–1736; (*b*) R. C. D. Brown, C. J. Battaille, R. M. Hughes, A. Kenney and T. J. Luker, *J. Org. Chem.*, 2002, **67**, 8079–8085.

32 C. J. Dutton, J. B. Banks, and C. B. Cooper, *Nat. Prod. Rep.*, 1995, **12**, 165–181.

33 A. R. L. Cecil and R. C. D. Brown, *Tetrahedron Lett.*, 2004, **45**, 7269–7271.

34 (*a*) D. M. Walba and P. D. Edwards, *Tetrahedron Lett.*, 1980, **21**, 3531–3534; (*b*) J. B. Gale, J. G. Yu, X. F. E. Hu, A. Khare, D. K. Ho and J. M. Cassady, *Tetrahedron Lett.*, 1993, **34**, 5847–5850.

35 A. M. Al Hazmi, N. S. Sheikh, C. J. R. Bataille, A. A. M. Al-Hadedi, S. V. Watkin, T. J. Luker, N. P. Camp and R. C. D. Brown, *Org. Lett.*, 2014, DOI: 10.1021/ol502454r.

36 B. D. Hammock, S. S. Gill and J. E. Casida, *J. Org. Food Chem.*, 1974, **22**, 379–385.

37 T. J. Donohoe, P. R. Moore, M. J. Waring and N. J. Newcombe, *Tetrahedron Lett.*, 1997, **38**, 5027–5030.

38 B. Travis and B. Borhan, *Tetrahedron Lett.*, 2001, **42**, 7741–7745.

39 (*a*) G. Bifulco, T. Caserta, L. Gomez-Paloma and V. Piccialli, *Tetrahedron Lett.*, 2002, **43**, 9265–9269; (*b*) G. Bifulco, T. Caserta, L. Gomez-Paloma and V. Piccialli, *Tetrahedron Lett.*, 2003, **44**, 3429; (*c*) G. Bifulco, T. Caserta, L. Gomez-Paloma and V. Piccialli, *Tetrahedron Lett.*, 2003, **44**, 5499–5503; (*d*) T. Caserta, V. Piccialli, L. Gomez-Paloma and G. Bifulco, *Tetrahedron*, 2005, **61**, 927–939; (*e*) V. Piccialli, N. Borbone and G. Oliviero, *Tetrahedron*, 2008, **64**, 11185–11192.

40 V. Piccialli, T. Caserta, L. Caruso, L. Gomez-Paloma and G. Bifulco, *Tetrahedron*, 2006, **62**, 10989–11007.

41 (*a*) T. B. Towne and F. E. McDonald, *J. Am. Chem. Soc.*, 1997, **119**, 6022–6028; (*b*) Y. Morimoto, T. Kinoshiya and T. Toshiyuki, *Chirality*, 2002, **14**, 578–586.

42 P. J. di Dio, S. Zahn, C. B. W. Stark and B. Kirchner, *Z. Naturforsch.*, 2010, **65b**, 367–375.

43 B. Lygo, D. Slack and C. Wilson, *Tetrahedron Lett.*, 2005, **46**, 6629–6632.

44 (*a*) V. Piccialli, *Tetrahedron Lett.*, 2000, **41**, 3731–3733; (*b*) S. Roth and C. B. W. Stark, *Angew. Chem. Int. Ed.*, 2006, **45**, 6218–6221.

45 (*a*) V. Piccialli, N. Borbone and G. Oliviero, *Tetrahedron Lett.*, 2007, **48**, 5131–5135; (*b*) R. Centore, V. Picciallia and A. Tuzi *Acta Cryst.*, 2007, **E63**, o2907–o2908.