Oxidative Cyclization of Dienes and Polyenes Mediated by Transition-Metal–Oxo Species

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Abstract: During the last forty years, several groups have reported results concerning the oxidative cyclization of polyenes, mostly dienes, with transition-metal–oxo species such as permanganate, ruthenium tetroxide, perruthenate and osmium tetroxide, but only recently has a systematic study of some of these processes been undertaken. The formation in a single step of tetrahydrofuran, poly-tetrahydrofuran, tetrahydropyran and oxepane products with complete relative stereocontrol, and the unique postulated mechanisms, render these processes very appealing from both the synthetic and theoretical points of view. Recent synthetic applications of these oxidative transformations have highlighted their usefulness. This review summarizes the state of the art in this field, in an attempt to provide a comprehensive view of these processes. Some similarities between the chemistry of ruthenium tetroxide and rhenium(VII)–oxo species are highlighted.

1 Introduction

Saturated ether rings of various sizes are part of the structure of a variety of natural substances from both marine and terrestrial origins, as well as of non-natural substances. In particular, 2,5-disubstituted tetrahydrofurans are structural fragments commonly encountered in natural substances including polyether antibiotics such as monensin A, squalene-derived metabolites such as glabrescol, and annonaceous acetogenins such as goniocin and mucocin (Figure 1), to mention a few representative categories. Some of these molecules possess important biological properties and intriguing structures that have challenged the creativity of synthetic organic chemists. A variety of methods have been developed to produce oxacycles and much work has been carried out for the construction of tetrahydrofuran and tetrahydropyran rings.1

Figure 1 Some representative tetrahydrofuran- and tetrahydropyran-containing natural products

In the mid-1960s, it was discovered that 1,5-dienes were not oxidized to tetroles, but instead to 2,5-bis(hydroxyalkyl)-substituted tetrahydrofurans in a stereoselective manner.2 An impetus toward synthetic applications of this process as well as mechanistic insights followed, though the published results were scattered over more than twenty years. Synthetic interest in this process was motivated by the fact that stereochromically elaborated tetrahydrofuran-diol products embodying four chiral centers could be obtained as single diastereomers, in a stereoselective and stereospecific manner, starting from achiral substances.
Though initial efforts in the field of oxidative cyclization of polyenes were restricted to the reactivity of permanganate with 1,5-dienes, general interest in this area has increased over the last ten years due to some significant, though sporadic, discoveries, mostly concerning ruthenium tetroxide, osmium tetroxide and permanganate itself. Only very recently have systematic studies been undertaken and the general picture of some of these transformations is becoming clearer. On one side, osmium tetroxide, ruthenium tetroxide, and permanganate appear to share a common reactivity toward 1,5-dienes as well as toward 1,6-dienes, as recent results seem to suggest. On the other, ruthenium tetroxide in catalytic amounts, in the presence of a suitable reoxidant, has been shown to be a unique oxygen-transfer reagent able to induce polyenes with a repetitive 1,5-diene structural motif, such as squalene, to undergo oxidative polycyclization to give stereochemically complex poly-tetrahydrofuran products. The efficiency of some of these processes has been proven through the recent synthesis of some tetrahydrofuran-containing natural products belonging to the annonaceous acetogenins class. Notwithstanding these advancements, the chemistry underlying these processes is still rather unexplored and further experimental and theoretical work need to be carried out to confirm mechanistic hypotheses and to increase our understanding of the stereochemistry of some of these cyclizations, as well as to reach the objective of their absolute stereocontrol. This review aims to delineate the state of the art of the oxidative cyclization processes of polyenes mediated by metal–oxo species by providing a working knowledge in the area. Rhodium(VII)- and chromium(VI)-mediated oxidative cyclizations of alk- enols or hydroxypolyenes are processes strictly related to the oxidative cyclizations of polyenes. Therefore, some incursions into their chemistry will be made to the extent required so as to understand some mechanistic hypotheses or stereochemical outcomes, mostly concerning ruthenium-mediated processes. For the sake of completeness, the recently discovered formation of tetrahydrofurans from 5,6-dihydroxylalkenes, and pyrrolidines from vicinal amino alcohols derived from 1,5-dienes, will also be briefly treated.

Biographical Sketch

Vincenzo Piccialli, born in Italy in 1958, obtained his degree in chemistry from the University of Naples ‘Federico II’ in 1983. He received his PhD in Chemistry from the same university in 1988, under the supervision of Prof. D. Sica and Prof. L. Mayol, having worked on the isolation, structure elucidation and synthesis of natural substances from marine organisms. After three years of postdoctoral studies, focused primarily on the synthesis of polyoxygenated steroids, he was appointed Associate Professor of Organic Chemistry in 1992. Since then, his scientific interests have been centered on the discovery of new oxidative processes. Currently his studies address the development of new catalytic oxidative transformations mediated by transition-metal–oxo species.

2 Formation of Tetrahydrofurans

2.1 Permanganate-Mediated Cyclization of 1,5-Dienes

In 1965, Klein and Rojan disclosed the stereostructure of the crystalline product, named oxidohydroxygeranyl acetate, that had been isolated more than forty years before by Kötz and Steche from the permanganate oxidation of geranyl acetate (1). They also demonstrated, through the oxidation of various 1,5-dienes, that the process was stereospecific, and general in scope (Scheme 1). All the oxidations were carried out by using the same amounts of both the 1,5-diene (50 g) and permanganate (60 g) so that a variable amount of oxidant was employed in each process (0.62–1.5 equiv). All the obtained products were cis-2,5-bis(hydroxyalkyl)tetrahydrofurans (tetrahydrofurandiols), and not the tetrals that were expected based on the known reactivity of permanganate toward alkenes. Some years later, Walba and Baldwin independently confirmed the stereospecificity of the process. Baldwin oxidized deuterium-labelled (E,E)- and (Z,Z)-hexa-1,5-dienes under Klein and Rojan’s conditions, but using two molar equivalents of potassium permanganate (yields of tetrahydrofuran-diols = ~30%). NMR studies performed on bicyclic derivatives of the tetrahydrofuran-diol products demonstrated that all the new bonds were formed in a stereospecific manner by suprafacial processes. Walba oxidized the three isomeric octa-2,6-dienes and thereby demonstrated that the process was >97% stereospecific. However, the mechanistic hypotheses put forward by these two research groups differed. Based on Sharpless’s new proposal on the formation of a metallaoxetane intermediate in the reaction of alkenes with high-valent transition-metal reagents, Walba (Scheme 2) discarded classical ideas on the permanganate oxidation of olefins and proposed the intermediacy of a double manganese-oxetane species, formed through a double Sharpless-type [2+2] cycloaddition. This intermediate then evolved into the tetrahydrofuran product through an alkyl migration (from Mn to O) with retention of configuration, followed by a reductive elimination, again with retention of configuration, then finally oxidation at manganese and hydrolysis.
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Scheme 1  Oxidative cyclization of some 1,5-dienes with permanganate performed by Klein and Rojan

R = H  
1 R = OAc (geranyl acetate)

\[ \text{KIO}_3 (1.5 \text{ equiv}) \]
\[ 10\% \text{aq acetone} \]
\[ \text{CO}_2 \text{ stream, } 0 \degree \text{C} \]
\[ R = \text{OAc, } 70\% \] (at 50% conversion)

R = OAc, 70%

R = H  
2 R = OAc (neryl acetate)

\[ \text{KIO}_3 (1.5 \text{ equiv}) \]
\[ 10\% \text{aq acetone} \]
\[ \text{CO}_2 \text{ stream, } 0 \degree \text{C} \]
\[ R = \text{OAc, } 68.5\% \] (at ca. 50% conversion)

20%

Scheme 2  Walba’s mechanistic hypothesis for the permanganate-mediated oxidation of 1,5-dienes

Baldwin proposed (Scheme 3) the formation of a manganese(V) intermediate through the [3+2] cycloaddition of permanganate onto one double bond followed by oxidation at manganese and a second [3+2] cycloaddition step of a O–Mn=O moiety onto the remaining double bond and hydrolysis. Thus, in both cases, a combination of two syn-additions of oxygen atoms across the two double bonds and a preferred folding of the molecule during the cycloaddition step account for the observed stereoselectivity of the process. The latter mechanism is usually invoked to explain this process, as well as related processes mediated by osmium tetroxide and ruthenium tetroxide.

In a subsequent study, Wolfe and Ingold11 provided evidence, through oxygen-labelling experiments, for the probable involvement of water in the mechanism. They supposed the intervention of a manganese complex, with coordination number greater than four, incorporating one or two molecules of water. This species would then be responsible for the transfer of one solvent-derived oxygen (O*) to the product (Scheme 4).

Recent density functional theory calculations on the permanganate hydroxylation of alkenes12 predicted that the concerted [3+2] pathway is favored by about 40 kcal/mol relative to the stepwise process involving a [2+2] cycloaddition followed by rearrangement. This result is in line with calculations carried out for the same process mediated by osmium tetroxide13 and ruthenium tetroxide,14 and supports the first step of Baldwin’s proposed sequence. However, as far as we know, no further evidence has been reported that would confirm the rest of the mechanism.

The application of this process to the synthesis of the BC-rings portion (3) of the ionophore monensin (Scheme 5) was carried out by Walba and Edwards.15 A modified work-up procedure, involving reduction of the produced manganese dioxide with sodium bisulfite, was worked out to prevent material losses experienced when simple filtration was required.
tion of the solids was carried out. In this way, the yield was improved from 22% to 45–47%.

Some years later, Spino and Weiler\textsuperscript{16} carried out the synthesis of the terminal cis-tetrahydrofuran ring of ionomycin under the conditions devised by Walba’s research group (Scheme 6), and obtained racemic fragment 4 in a 53% isolated yield. Subsequent resolution of a derivative of 4 with (S)-(+-)O-acetyl mandelic acid, followed by further synthetic manipulations, yielded a tetrahydrofuran-containing fragment, possessing the absolute configuration shown.

Scheme 6 Permanganate-mediated synthesis of the terminal tetrahydrofuran ring of ionomycin

The problem of asymmetric induction in this process was first dealt with by Walba et al.,\textsuperscript{17} who used Oppolzer’s (2S)-bornane-10,2-sultam system\textsuperscript{18} to functionalize the 2,6-dienoate system (Scheme 7). Oxidation of neroic acid derivative 5, under Klein and Rojan’s conditions, gave a >9:1 diastereomeric mixture, from which the major tetrahydrofuran-diol product 6 (with R absolute configuration at C2) was obtained in 38% yield after chromatography; removal of the chiral auxiliary was accomplished with methoxymagnesium bromide. The observed attack of permanganate on the electron-deficient double bond took place from the Re face, in agreement with the facial selectivity previously observed by Oppolzer in the osmylation of sultam-functionalized enoates.\textsuperscript{19} The procedure worked well on two other substituted dienoates, though the yield never exceeded 40%.\textsuperscript{19}

Scheme 7 Permanganate-mediated diastereoselective oxidative cyclization of a chiral neroic acid imide derivative

Kocieski and Brown\textsuperscript{20} employed the same chiral auxiliary to synthesize the C21–C30 fragment (8) of salinomycin (Scheme 8). The cyclization step, however, was accomplished under modified conditions. These authors, assum-
as the sole detectable diastereomer in a satisfactory 58% yield (Scheme 10).

In an application of this strategy, the building of the tetrahydrofuran-diol or bis-tetrahydrofuran-diol cores of some annonaceous acetogenins was accomplished. It should be noted that the stereochemistry of the permanganate-mediated cyclization allows the elegant assembly of the tetrahydrofuran-diol portion of some of these products. For example, in the synthesis of cis-solamin, a three-cis-three mono-tetrahydrofuran acetogenin, the pivotal cyclization step of diene 11 (Scheme 11, top), derivatized with (2S)-10,2-camphorsultam, was accomplished in a 55% yield and 10:1 diastereomeric ratio under phase-transfer conditions (see below), previously set up by the same authors, with ethyl acetate as solvent. This result also demonstrated that new conditions had to be devised in order to induce unbranched 1,5-diienes to cyclize in reasonable yields.

Following the same route, but using the enantiomeric (2R)-10,2-camphorsultam, the tetra-epimeric diastereoisomer 13 of cis-solamin was also synthesized (Scheme 11, bottom). The availability of both stereoisomers 12 (cis-solamin A; also called simply cis-solamin) and 13 (cis-solamin B) led the same authors to recognize that natural cis-solamin is actually made up of a mixture of almost equal quantities of these two products.

In a subsequent paper, Brown and co-workers reported the synthesis of the cis-solamin isomers ent-12 and ent-13 that were to be used for in vitro cytotoxicity studies.

Membranacin (Scheme 12), an erythro-cis-three-cis-three adjacent bis-tetrahydrofuran acetogenin, was also synthesized by the same group. Cyclization of a double (2S)-10,2-camphorsultam-derivatized symmetric triene, followed by further chemistry, gave tetrahydrofuran-γ-lactone 14 in good yield and, after further transformations, membranacin.

In the same way, the trans-cis bis-tetrahydrofuran moiety of 21,22-di-epi-membrarollin was synthesized through two sequential metal–oxo-mediated oxidative cyclizations (Scheme 13). The first, which was cis-stereoselective, was performed with potassium permanganate in acetone–acetic acid; the second, carried out with trifluoroacetyl perrhenate (from ReO₇–TFAA), allowed for the closure of the trans-tetrahydrofuran ring, with the anticipated stereoselectivity based on that displayed in the hydroxyl-directed oxidative cyclization of bishomoallylic alcohols with rhenium(VII) oxides. Brown and Keily were also able to obtain promising levels of asymmetric induction by performing the oxidative
cyclization of aromatic 1,5-dienones 15–17 in the presence of catalytic amounts of the chiral tertiary ammonium salt 18 (Scheme 14). The level of asymmetric induction (58–75% ee) was comparable with the degree of diastereoselectivity (80% de) obtained for the oxidative cyclization of simple 1,5-dienes derivatized with Oppolzer’s chiral auxiliary.17 The observed enantioselection was accounted for by a model previously suggested for the nucleophilic epoxidation of α,β-enones by hypochlorite.30

![Scheme 14](image)

Scheme 14  Asymmetric permanganate-promoted oxidative cyclization of 1,5-dienones under chiral phase-transfer catalysis

A related oxidative transformation of 1,5-dienes was reported to take place with potassium permanganate–copper(II) sulfate pentahydrate under heterogeneous conditions to give 5-substituted butenolides (Scheme 15).31 The presence of a catalytic amount of water was crucial to this process, and a large amount of both potassium permanganate (25 equiv) and copper(II) sulfate pentahydrate (11 equiv) was employed. In some cases, minor amounts (8–10%) of the related δ-lactones were obtained. A plausible route that explains the formation of these substances, closely related to that hypothesized for the formation of tetrahydrofuran-diols by permanganate oxidation of 1,5-dienes (Scheme 3), is shown for geranyl acetate in Scheme 16. According to this proposed mechanism, the manganese(VI) intermediate can undergo cyclization in one of two different conformations, I or II, with the latter being obtained by rotation around the C3–C4 bond in I, to give the tetrahydrofuran or tetrahydropyran intermediates III or IV, respectively. Oxidation at manganese followed by scission of the C6–C7 bond, with concomitant release of acetone, would give a stabilized cation species as a C2 or C3 manganese(V) ester.

Further oxidation at C6 and C2 would then generate the γ-lactone products, while oxidation at C6 and hydrolysis would give the δ-lactones.

The possible involvement of hydroxymethyltetrahydrofurans cannot be ruled out, as suggested by the facile oxidative cleavage of 19 to the corresponding lactone, under the same conditions (Scheme 17).
also obtained. Formation of the ketone was observed along with an increase in the overall yield of cyclization for cis-tetrahydrofurans. The process was generally conducted at 0 °C and required three to four minutes to go to completion. The process could be scaled up to a multigram scale (15 mmol for geranyl acetate) without loss of yield or stereoselectivity. Nerol-derived 1,5-dienes required longer reaction times (18 min) and were conducted at –10 °C. The overall yield of cyclization for cis-tetrahydrofurans was equally improved, but overoxidation at C2 took place to a greater extent, likely because of the prolonged reaction time.

A subsequent study by our group, on a wider range of 1,5-dienes, was carried out in the solvent mixture ethyl acetate–acetone–water (2:1:1). The new conditions proved equally effective, though in some cases the stereoselectivity level was lower and overoxidized products were more abundant (Scheme 20). Worthy of note is the 94% overall cyclization yield for 8-acetoxygeranyl acetate (20) and the absence of the trans-isomer in this transformation. Also notable is the capability of ruthenium tetroxide to induce conversion of (−)-limonene into a bicyclic compound.

Recently, Stark and co-workers reported the oxidation of a wide range of 1,5-dienes with ruthenium tetroxide under further-optimized conditions (Scheme 21). The oxidations were conducted in the unusual solvent mixture tetrahydrofuran–dichloromethane (9:1), wherein ethers are usually oxidized to the corresponding esters, using 2.2 equivalents of sodium periodate supported on wet silica in the presence of 0.2 mol% ruthenium(III) chloride, adding...
The estimated diastereomeric ratio (cis/trans-tetrahydrofuran) was constantly >95:5, yields were generally high, and the overoxidation products were obtained in very low yields except in a few cases (dienes 21 and 22).

The new conditions were tolerated by a wide range of functional groups such as esters, ethers, amines, amides and silyl ether protecting groups. However, once again, a lower yield of tetrahydrofuran-diol was obtained for neryl benzoate (21) compared to geranyl benzoate.

The mechanism proposed for this cis-selective cyclization36 (Scheme 22) was based upon both the mechanism hypothesized for the analogous process with permanganate8 and DFT calculations.13 The reaction is presumed to start with oxidation of the precatalyst (RuO2 or RuCl3) to ruthenium tetroxide, the [3+2] cycloaddition of which to one of the double bonds generates a ruthenium(VI) ester 23. This then participates in a second intramolecular and stereoselective [3+2] cycloaddition where the cis-configuration of the nascent tetrahydrofuran is set. Hydrolysis of the ruthenium(IV) intermediate (24) so-formed delivers the tetrahydrofuran-diol and ruthenium(IV) oxide. Reoxidation of this to ruthenium tetroxide, by means of sodium periodate, completes the catalytic cycle.
Synthetic Application of Ruthenium Tetroxide Catalyzed Oxidative Cyclization of 1,5-Dienes

Synthesis of Neodysiherbaine

Lygo et al.\textsuperscript{40} employed the above-described ruthenium tetroxide mediated oxidative cyclization to generate, in a stereoselective manner, the tetrahydrofuran moiety of neodysiherbaine (Scheme 25), a potent excitatory amino acid isolated from the sponge \textit{Dysidea herbacea}. An examination of all three related oxidants, osmium tetroxide, permanganate and ruthenium tetroxide, revealed that the reagent of choice for the required cyclization was ruthenium tetroxide.

When the reaction was carried out in a 2:1:1 mixture of ethyl acetate–acetone–water, bicyclic tetrahydrofuran-diol \textbf{27} was obtained in a satisfactory 61% isolated yield. Coupling of the process with a lactonization step resulted in tetrahydrofuran-lactone \textbf{28} being obtained in an improved 81% yield (for the two steps). It should be noted that when the same transformation was accomplished with osmium tetroxide, only dihydroxylation products were obtained, and the use of potassium permanganate resulted in bicyclic compound \textbf{27}, but in significantly lower yields. These results offered further evidence for the synthetic potential of the ruthenium-mediated transformation.

Synthesis of a 1,2-Secocladiellane Diterpenoid

Another recent example\textsuperscript{41} of the synthetic application of the ruthenium-mediated process was given in the one-step construction of the tetrahydrofuran-diol substructure of a \textit{seco}-cladiellane diterpenoid (Scheme 26), which is structurally related to eleutherobin, a potent $\beta$-tubulin inhibitor. Cyclization of the geraniol-type side-chain in \textbf{29} gave a 1:1 mixture of diastereomeric tetrahydrofuran-diols \textbf{30} in 40% combined yield. The possibility of accessing such a stereochemically elaborated product in a simple manner, coupled with the short, three-step sequence employed in this synthesis, compensates for the lack of stereoselectivity in the cyclization process.

Synthesis of \textit{cis}-Solamin

Göksel and Stark\textsuperscript{42} used a similar ruthenium-mediated process to build up the \textit{three-cis-three} tetrahydrofuran-diol core of \textit{cis}-solamin. Cyclization of the symmetric diene \textbf{31} (Scheme 27), under their improved conditions, afforded the \textit{meso}-tetrahydrofuran-diol \textbf{32} in a remarkable 83% yield and with a diastereomeric ratio of $>98:2$. Subsequent synthetic work, including enzymatic desymmetrization of \textbf{31}, led to the target molecule.
2.3 Perruthenate-Catalyzed Cyclization of 1,5-Dienes

In another study on the oxidation of 1,5-dienes conducted by our group,43 we discovered that the formation of 2,5-oxygenated tetrahydrofuran products can also be induced in the presence of catalytic amounts of perruthenate ion, from tetrapropylammonium perruthenate (TPAP). While tetrapropylammonium perruthenate alone gave clean, but incomplete, conversion into the tetrahydrofuran-ketol products, the oxidative cyclization could be forced to completion in the presence of a suitable co-oxidant. N-Methylmorpholine N-oxide (NMO) was effective (Scheme 28), but the required amount of 12–25 equivalents was unacceptably high and strongly dependent on the amount of tetrapropylammonium perruthenate used, in an inverted sense – lower tetrapropylammonium perruthenate loadings resulted in higher quantities of N-methylmorpholine N-oxide required. Further, the yield of the process under these conditions was strongly affected by the degree of alkylation on the 1,5-diene, with less alkylated substrates requiring higher amounts of reagents.

The oxidation in the presence of tetrabutylammonium periodate (TBAPI) proved more effective, and allowed for a reduction in the amount of tetrapropylammonium perruthenate to 5 mol%, and for an increase in the cyclization yield (Scheme 29). In some cases, such as for diene 33, 10 mol% of tetrapropylammonium perruthenate was required.

Under acidic conditions, this oxidative cyclization process could be driven toward the formation of tetrahydrofuran-diols; the best results were obtained for geraniol-type dienes (Scheme 30).

Based on previous studies by Lee et al.,44 the mechanism shown in Scheme 31 was proposed. A [3+2] cycloaddition of perruthenate ion onto one of the two double bonds initially gives the ruthenium(V) ester 35 that is then quickly intercepted by the second double bond either directly or via a further-oxidized ruthenium species, with formation of the ring-enlarged ruthenium species 36. This intermediate can undergo hydrolysis to deliver the tetrahydrofuran-diol and a low-valent ruthenium species that is reoxidized to perruthenate itself, or to another ruthenium species capable of maintaining the cycle. The α-ketol could be formed by oxidative cleavage of ester 36 itself, or by overoxidation of the tetrahydrofuran-diol after its release.

The absence of ruthenium tetroxide under the reaction conditions was suggested by the results of a control experiment on trans-7-tetradecene that failed to give any oxidation product, as well as the observations of the very different behavior exhibited by some substrates under the same reaction conditions.
2.4 Osmium Tetroxide Catalyzed Cyclization of 1,4- and 1,5-Dienes

In 1998, we discovered\(^{15}\) that the 1,5-dienes geranyl acetate and neryl acetate could be oxidized with catalytic amounts (5 mol%) of either osmium dioxide or osmium tetroxide, by using sodium periodate (4 equiv) as co-oxidant in both cases, in \(N,N\)-dimethylformamide (Scheme 32) to give the same \(cis\)-tetrahydrofuran-diol products that were previously obtained with permanganate and ruthenium tetroxide. Further investigations from our group were conducted using the pair osmium(III) chloride dihydrate (5 mol%) and sodium periodate,\(^{46}\) in the same solvent, and a range of 1,5-dienes with various substitution patterns. The procedure proved general in scope and allowed for cyclization to take place even on rigid and distal 1,5-dienes such as 4-vinylcyclohexene \(38\) and \((-\)-limonene. We also observed\(^{46}\) that these two dienes did not react with permanganate under Klein and Rojan’s conditions.\(^{2}\) A dimeric osmium(VI) intermediate was isolated from the oxidation of geranyl acetate, and was determined to have the structure \(39\) (Scheme 33). Its transformation into tetrahydrofuran-diol \(37\) was proven by the subjecting of this substance to the same conditions, which caused direct cyclization; in contrast, this substance was recovered unaltered in the absence of co-oxidant, even upon prolonged treatment at 70 °C.\(^{46}\) This suggested

**Scheme 30** Perruthenate-catalyzed oxidative cyclization of 1,5-dienes under acidic conditions

**Scheme 31** Mechanistic proposal and catalytic cycle for the perruthenate-catalyzed oxidative cyclization of 1,5-dienes

**Scheme 32** Selected examples of osmium-mediated oxidative cyclization of 1,5-dienes under Piccialli’s conditions

**Scheme 33** Possible catalytic cycle for the osmium-mediated oxidative cyclization of 1,5-dienes under Piccialli’s conditions
that a further oxidation step must take place at osmium before the cyclization step can occur, and thus the intermediacy of an osmium(VIII) species, such as 40 or a monomeric species at the same oxidation level, was proposed.

From a mechanistic point of view (Scheme 33), based on inspection of molecular models, we hypothesized a [3+2] cycloadition, involving osmate ester 39, for the ring-closing step. In light of our new evidence, a cyclization step involving an osmium(VIII) species can also be envisaged.

A few years later, Donohoe et al. found that stoichiometric amounts of osmium tetroxide, in the presence of tetramethylethylenediamine (TMEDA; 1 equiv), caused the oxidative cyclization of derivatized 1,5-dienes (1-trichloroacetamide 2,6-dienes) to the corresponding tetrahydrofuran-diol products (Scheme 34). The whole process was accomplished by first generating osmate ester 41 (Scheme 35) and then decomposing it with acidic methanol. This protocol was applied to a range of 1,5-dienes and afforded the cyclized products in 44–83% yield. Hydrogen-bond formation between the amide group and the osmium tetroxide–tetramethylethylenediamine adduct caused a regioselective attack of the latter to the proximal double bond. From a mechanistic point of view (Scheme 35), the cyclization step is proposed to involve a [3+2] addition of an O–Os=O moiety across the remote alkene through a chair-like transition state. It is presumed that acid then could protonate the oxo ligands and thereby render the metal a better, and more reactive, electrophile in the cyclization step.

In a subsequent study carried out by the same group, new conditions were devised to accomplish this transformation and the process was rendered catalytic in osmium. The systematic oxidation of a range of 1,5-dienes demonstrated the new process to be general in scope and high-yielding (Scheme 36) even with mono- and disubstituted alkenes, which tend to give overoxidation products with permanganate and ruthenium tetroxide.

The synthetic effectiveness of this new methodology was proven through a short synthesis of (+)-anhydro-D-glucitol (44) and D-chitaric acid (45) (Scheme 37) starting from the C2-symmetric, enatiomerically pure, 1,5-diene 42.48 The cyclization step gave compound 43 as a single stereoisomer in 84% yield.

2.4.2 Oxidative Cyclization of 1,4-Dienes

Travis and Borhan found that methyl linoleate (46) could undergo oxidative cyclization to a mixture of diastereomeric 2,3,5-trisubstituted tetrahydrofuran-diols in a stereoselective manner (Scheme 38). They proved that the
oxidation could be conducted with all three o xo species – permanganate, ruthenium tetroxide and osmium tetroxide. After a careful examination of experimental parameters, it was found that a 30\% yield of a 1:1 mixture of regioisomers 47 and 48 (2-trans,3-cis relative ring configuration) could be obtained with catalytic amounts of osmium tetroxide (2.5 mol\%) and Oxone\textsuperscript{®} as co-oxidant, in N,N-dimethylformamide. This process also worked well on the trans-methyl linoleate (49), and gave a comparable 30\% yield of the all-cis 2,3,5-tetrahydrofuran-diol products 50 and 51 (dr = 1:1) (Scheme 38).

![Scheme 38](image)

Scheme 38 Osmium-catalyzed oxidative cyclization of 1,4-dienes

The mechanism of this transformation (Scheme 39) was postulated to be analogous to that accepted for the oxidation of 1,5-dienes with osmium tetroxide.

![Scheme 39](image)

Scheme 39 Proposed mechanism for the oxidative cyclization of methyl linoleates; formation of one diastereomer is shown

In particular, the first step, as usual, involves formation of an osmium(VI) ester, in this case 52, which is then oxidized to the osmium(VIII) ester 53. This then undergoes a [3+2] cycloaddition with the remaining olefin bond and an O–Os=O moiety (in bold), as seen for the 1,5-dienes. However, in this case, closure of the tetrahydrofuran ring involves O1 and C4 (the internal olefin carbon). Examination of the molecular model reveals that the approach of the involved portions is difficult, owing to the hindered rotation about the C1–C2 bond that causes an unsatisfactory overlap of the participating atoms. Further oxidation at osmium is hypothesized before the tetrahydrofuran-diol is released by hydrolysis.

This is the sole report that deals with a tetrahydrofuran-forming oxidative cyclization of 1,4-dienes.

3 Osmium Tetroxide Catalyzed Formation of Tetrahydrofurans from Alkenediols

A further advancement in this type of process was obtained very recently by Donohoe\textsuperscript{50} who discovered that vicinal diols derived from 1,5-dienes (5,6-dihydroxylefins) undergo an osmium-catalyzed cyclization to cis-tetrahydrofuran-diols (Scheme 40) when subjected to the conditions that cause the direct oxidative cyclization of 1,5-dienes.

![Scheme 40](image)

Scheme 40 Osmium tetroxide catalyzed oxidative cyclization of 1,2-diols derived from 1,5-dienes. * For diol 54, cyclohexene was used as additive.

Therefore, since the starting diols can be readily obtained from 1,5-dienes in a regio- and enantioselective manner by Sharpless asymmetric dihydroxylation, tetrahydrofuran products can also be accessed in enantiopure form; the enantiomeric purity is completely preserved during the cyclization step. A sacrificial alkene is added to increase the amount of the active osmium(VI) catalyst in the reaction mixture. Formation of an osmate ester intermediate is presumably formed, and then cyclizes as usual. The synthetic value of this transformation was proven by the formal synthesis of (+)-cis-solamin\textsuperscript{50} (Scheme 41) and the total synthesis of (+)-cis-sylvatacin\textsuperscript{51} (Scheme 42), the latter through a remarkable double oxidative cyclization.
4 Osmium Tetroxide Catalyzed Formation of Pyrrolidines

Donohoe et al. demonstrated that N-protected 1,2-amino alcohols that carry a distal alkene in the structure can undergo oxidative cyclization to give cis-pyrrolidines or cis-tetrahydrofurans (Scheme 43), in a stereoselective and stereospecific manner, in good to excellent yields. The process is related to the aforementioned oxidative osmium-catalyzed cyclization of alkene diols. The type of product obtained is governed by the position of the heteroatom in the starting material. Application of the process to enantiopure starting materials was shown to afford both nitrogen- and oxygen-containing heterocycles without loss of enantiomeric purity. The catalyst loading was generally 5 mol%, but it could be reduced to 1 mol%, with a minimal drop in yield, and even as low as 0.2 mol%. Oxidative cyclization of the competition substrate 55, capable of giving either the N- or the O-heterocycle, provided evidence for the preference to form pyrrolidines. A sacrificial alkene was added, as for the analogous process with alkene diols; trans-cinnamic acid proved ideal for this purpose. It is believed that the role of the additive is to participate in forming an osmium(VI) species which is then capable of chelating to the substrate and thus leads to its cyclization.

5 Chromium(VI)-Mediated Formation of Tetrahydrofurans from Alkenediols

For the sake of completeness, the closely related oxidative cyclization of 5,6-dihydroxyalkenes (56) derived from geranyl and neryl acetates, to cis-tetrahydrofuran-diols by chromium(VI)–oxo species (Scheme 44), is mentioned here. The process, discovered by Casida and co-workers and later studied by Walba and Stoudt, appears to be related to the osmium-catalyzed oxidative cyclization of the same substrates. Both Collins reagent and pyridinium
chlorochromate proved effective for this transformation that exhibits a high stereoselectivity level and a >99.5% stereospecificity.

It was postulated that the process involves the initial formation of a chromium(VI) diester 57 (Scheme 45). Decomposition of this intermediate was hypothesized to proceed through a second [3+2] cycloaddition and hydrolysis, as proposed by Baldwin for the manganese-mediated oxidation of 1,5-dienes. Alternatively, based on Sharpless’s proposal and Rappé and Goddard’s calculations, formation of the oxametallocyclobutane 58, characterized by a square pyramidal geometry and a chromium–oxo triple bond, can follow, via a [2+2] cycloaddition; reductive elimination would then lead to the same intermediate 59 formed through the alternative route.

Scheme 45  Postulated mechanism for chromium(VI)-mediated oxidative cyclization of 5,6-dihydroxyolefins

Corey and Ha employed this process in the preparation of the chiral tetrahydrofuran-diol fragment 61, for use in the synthesis of venustatriol, by treating alkene diol 60 with pyridinium chlorochromate (Scheme 46).

6  Formation of Tetrahydropyran-Diols

6.1 Ruthenium Tetroxide Catalyzed Cyclization of 1,6-Dienes

In 2000, our group discovered that 1,6-dienes could be cyclized to tetrahydrofuran-diols with the system ruthenium tetroxide (catalytic) with sodium periodate, under the same conditions previously employed for the cyclization of 1,5-dienes (Scheme 47). The process was highly stereoselective with the trans-tetrahydrofuran isomers being the only cyclized products obtained.

Scheme 47  Ruthenium-catalyzed formation of trans-tetrahydropyran-diols from 1,6-dienes

The observed trans stereoselectivity of the process may be accounted for by the initial suprafacial [3+2] cycloaddition of ruthenium tetroxide with the more electron-rich double bond to generate the ruthenium(VI) diester intermediate 62 (Scheme 48). As we previously hypothesized for the 1,5-dienes, a hydrolysis step of the ruthenium–oxygen bond then follows to give the monoester derivative 63 (or 64), where the metal probably is in a higher oxidation state. This open-form intermediate is similar to the perrhenate ester intermediate of the trifluoroacetylperrenate-promoted formation of tetrahydropyran alcohols from trishomoallylic alcohols. Thus, the model proposed by McDonald to explain the trans-selectivity of the latter process was applied. Closure of the tetrahydropyran ring is postulated to occur via a second [3+2] cycloaddition involving the interaction of an O–Ru=O moiety and the second double bond, with the molecule adopting a preferred chair-like conformation as shown in 63, affected by only one gauche interaction (Ru with C7).

The alternative arrangement, 64, which leads to a cis-tetrahydropyran upon cyclization, would be destabilized by two gauche interactions (Ru with C7 and C5). Finally, de-
livery of the trans-tetrahydropyran product occurs by hydrolysis that also generates a ruthenium(IV) species, the reoxidation of which closes the catalytic cycle.

Recently, Roth and Stark\(^\text{3c}\) reinvestigated this process by performing the oxidation of a variety of 1,6-dienes (Scheme 49) with ruthenium(III) chloride (5 mol%; 1% in some cases) and sodium periodate supported on wet silica. The exclusion of water from the medium, the use of a polar solvent mixture (MeCN–EtOAc, 1:1), and dilute reaction conditions (0.03 M) proved crucial for obtaining good yields of tetrahydropyran product. The trans-selectivity of the process was confirmed (dr >95:5). The protocol also proved to be applicable to 1,6-dienes substituted on the trimethylene bridge and to protected diallylamines. However, in contrast to the oxidation of 1,5-dienes, reaction of α,β-unsaturated ester 67 failed to give the cyclized product. In addition, the applicability of the process to disubstituted 1,6-dienes remains to be tested.

Scheme 49  Ruthenium-catalyzed oxidative cyclization of 1,6-dienes under Stark’s conditions

The stereoselectivity of the process was also tested on 1,6-dienes that included a stereogenic center in the C3 bridge (Scheme 50), but no stereoinduction was observed.

Scheme 50  Ruthenium-catalyzed oxidative cyclization of chiral 1,6-dienes

6.2 Permanganate-Mediated Cyclization of 1,6-Dienes

Cecil and Brown\(^\text{3b}\) found that 1,6-dienes could be subjected to the oxidative cyclization in the presence of permanganate to give cis-tetrahydropyran-diols. Specifically, dienones 68 and 69 (Scheme 51) were cyclized to 2,6-cis-disubstituted tetrahydropyran-diols in moderate (30–38%) yields, while the dienoyl sultams 70 and 71 gave the tetrahydropyran-diols in low yield, but with good diastereoselectivity.

The mechanism of this process (Scheme 52) was proposed to be analogous to the oxidative cyclization of 1,5-dienes. The initial [3+2] cycloaddition of permanganate with the more electron-deficient olefin gives the manganese peroxide. The oxidation of the diene gives the diol and the manganese(IV) species, which can be reduced to give the diol and regenerate the manganese(II) species. This process can then be repeated to give the diol and regenerate the manganese(II) species.

Scheme 51  Permanganate-promoted formation of cis-tetrahydropyran-diols from 1,6-dienes

Scheme 52  Mechanistic proposal for the permanganate-mediated oxidative cyclization of 1,6-dienes
nese(V) diester intermediate 74 that is oxidized to 75, a manganese(VI) species. The cyclization step occurs via a second diastereoselective [3+2] cycloaddition through a chair-like transition state, and affords the manganese(IV) diester 76, the hydrolysis of which leads to the tetrahydro-pyran-diol product.

7 Ruthenium Tetroxide Catalyzed Formation of Oxepanes from 1,7-Dienes

Recent studies from our group have led to the discovery that the aforementioned ruthenium-mediated oxidative cyclization of 1,5- and 1,6-dienes can also be employed for the closure of oxepane rings, starting from 1,7-dienes (Scheme 53).58 The process is highly stereoselective (dr >95:5), with the trans isomer being obtained as the sole cyclized product. Currently, the process is applicable only to tetrasubstituted 1,7-dienes, with the less substituted substrates giving other open-chain oxidation products. Compared to the analogous processes with 1,5 and 1,6-dienes, the application to 1,7-dienes requires higher amounts (7 equiv) of reoxidant in order to go to completion.

From a mechanistic point of view, we presume a pathway (Scheme 54) similar to that proposed by Baldwin et al.5 for the analogous permanganate-mediated oxidative cyclization of 1,5-dienes. It is probable that both the increased conformational freedom and the stability of the ruthenium(VI) diester intermediate, formed in the first [3+2] cycloaddition step, play a role in determining the success of the cyclization step.

8 Ruthenium Tetroxide and Permanganate-Mediated Formation of Oxiranes from 1,3-Dienes

Some years ago, during our studies aimed at the oxygenation of the steroid nucleus, we examined the reactivity of some conjugated-diene steroids with stoichiometric amounts of ruthenium tetroxide. Reaction of 5α-cholesta-8,14-dien-3β-yl acetate (77, Scheme 55) with a stoichiometric amount of ruthenium tetroxide in acetone–water, gave epoxysters 78–80 (overall yield 61%), along with the Δ8,13,14-ketol products (not shown, 32%).59 Both the epoxide pattern and relative configuration in 78 strongly suggest that its formation could parallel the route leading to cis-tetrahydrofuran-diols with the same reagent (see also Scheme 22). Formation of related steroidal epoxydiols 79 and 80 cannot be easily explained, though their derivation can be hypothesized to occur from the initially formed 78.

Scheme 53 Oxidative cyclization of 1,7-dienes catalyzed by ruthenium

Scheme 54 Mechanistic proposal for the ruthenium-mediated oxidative cyclization of 1,7-dienes

Scheme 55 Ruthenium tetroxide promoted formation of steroidal epoxydiols from an 8,14-diene sterol.

Similarly, oxidation of 5α-cholesta-7,14-dien-3β-yl acetate (81), under the same conditions, afforded epoxysters 82–84 (Scheme 56).59 The reasoning used above for the Δ8,14-steroid could also explain the formation of epoxides 82 and 83.

Oxidation of 5α-cholesta-7,9(11)-dien-3β-yl acetate (85) also gave similar epoxydiols in an overall 46% yield (Scheme 57).60 It is worth noting that Δ9,11(15)-steroids with 5α-OH,6α-OAc, 5α-OH,6β-OAc or 6α-OAc substitution patterns only gave 9α,11α-diol and 9α,11-ketosteroids in good combined yields.
The type of reactivity described here had previously been observed for the permanganate-mediated oxidation of cyclic 1,3-dienes such as occidentalol (Scheme 58).\textsuperscript{61} Comparison of this oxidative process with the oxidation of levopimaric acid (Scheme 59), performed with aqueous permanganate under basic conditions,\textsuperscript{62} is instructive. This substrate, which can be seen as either a 1,3- or a 1,5-diene, reacted with permanganate to give the tetrahydrofuran-diol product 86, and not the isomeric epoxydiol 87, probably for steric reasons.

In contrast, reaction of cyclopentadiene\textsuperscript{63} and 1,3-cyclohexadiene\textsuperscript{63} with permanganate under neutral or alkaline conditions gave only the epoxy-1,2-diols 88 and 89, respectively, in fair yields, in addition to ‘normal products’ (Scheme 60). Similarly, cholesta-5,7-dien-3β-ol\textsuperscript{64,65} gave epoxytriol 90 as the main product. The observed oxygenation pattern in 88–90 is the same as that found in steroids 79, 80 and 84 (see Schemes 55 and 56), and raises the question of whether they could derive from initially formed 1,4-epoxydiols. The above-described results further highlight the closely related reactivity of permanganate and ruthenium tetroxide with 1,n-dienes, and the matter is certainly worthy of further investigation.

It should be noted that the reported cases all refer to the oxidation of cyclic or steroidal conjugated dienes, while no case on the generation of 2,3-epoxy-1,4-diols from acyclic 1,3-dienes is yet known.
9 Ruthenium Tetroxide Catalyzed Oxidative Polycyclization

We have explored the reactivity of some all-trans isoprenoid polyenes, such as farnesyl acetate, geranylgeranyl acetate and squalene, under the conditions that induce the oxidative cyclization of 1,5-dienes. A novel oxidative polycyclization process was discovered; it allows for the preparation of all-threo, adjacent, poly-tetrahydrofuran products in a single step and a stereoselective manner (Scheme 61). The process is highly productive from a stereochemical point of view because many chiral centers are created in a single step from an achiral polyene (ten chiral centers in the penta-tetrahydrofuran 91, and, in principle, twelve in an unsymmetrical esaene). The amount of reoxidant necessary in the process was calculated according to the number of double bonds of the substrate, on the basis that four equivalents of sodium periodate are necessary for the oxidative cyclization of a 1,5-diene to go to completion, and that one more equivalent is required per additional double bond. For example, the polycyclization of squalene required eight equivalents of sodium periodate to go to completion, with lesser amounts giving incomplete substrate consumption. The threo-relationship between all the adjacent oxygen-carrying carbon pairs was rigorously proven through extensive chemical work.

Scheme 61 Oxidative polycyclization of isoprenoid polyenes catalyzed by ruthenium tetroxide. After one recycling of the related ketol. Reagents and conditions: RuO₂·H₂O (20 mol%), NaIO₄ (4–8 equiv), MeCN–EtOAc–H₂O (3:3:1), 0 °C, 30 min.

Further studies in our group were conducted on linear all-trans polyenes such as 92 (Scheme 62) and 93 (Scheme 63). Our goal was to probe the synthetic utility of the oxidative polycyclization process in the synthesis of threo-cis-threo-cis-threo(erythro) bis-tetrahydrofuran compounds to be used in the synthesis of the bis-tetrahydrofuran-diol core of some biologically active cis-cis adjacent bis-tetrahydrofuran annonaceous acetogenins such as rolliniastatin-1 or membranacin. Ruthenium tetroxide oxidation of both of these polyenes gave similar overall cyclization yields (42–47%) of bis-tetrahydrofuran products.

Scheme 62 Ruthenium tetroxide mediated oxidative bis-cyclization of an all-trans 1,5,9-triene. Reagents and conditions: RuO₂·H₂O (20 mol%), NaIO₄ (4 equiv), MeCN–EtOAc–H₂O (3:3:1), 0 °C, 30 min.

Scheme 63 Ruthenium tetroxide mediated oxidative bis-cyclization of an all-trans 1,5,9,14-tetraene. Reagents and conditions: RuO₂·H₂O (20 mol%), NaIO₄ (5 equiv), MeCN–EtOAc–H₂O (3:3:1), 0 °C, 30 min.

The ruthenium-mediated oxidative polycyclization process appears to be closely related to the oxidative polycyclization of polyenic bis-homoallylic alcohols carried out with the rhenium(VII)-oxo species that allows for the formation of either bis- or tris-tetrahydrofuran products, either in one step or in a sequential manner (Scheme 64). Some differences between the two systems should, however, be highlighted. While the rhenium(VII)-mediated process consistently gives a trans-tetrahydrofuran in the first cyclization, cis-tetrahydrofurans are invariably obtained from the first two cyclizations in the ruthenium-mediated transformation. The two processes also differ in their requirements for the initial step. While the rhenium(VII)-mediated process needs a hydroxyl group in the structure to give the initially formed rhenium(VII) ester intermediate (RO–ReO₃), the ruthenium-mediated oxidation does not, and the [3+2] cycloaddition of ruthenium tetroxide and a carbon–carbon double bond can be envisaged to give, as usual, a ruthenium(VI) diester intermediate. In
addition, a poly-tetrahydrofuran-diol product is obtained with ruthenium tetroxide, while a mono-, di- or tris-tetrahydrofuran alcohol is obtained when a rhenium(VII)–oxo species is used.

With the previously developed models for the rhenium(VII)-mediated oxidative cyclization of hydroxy-polyenes as well as precedents from the oxidative cyclization of 1,5-dienes taken into account, a plausible mechanistic hypothesis was formulated (Scheme 65) that envisages a cascade of ring-closing steps. Specifically, in the first step, a ruthenium(VI) diester is formed by interaction of ruthenium tetroxide and the terminal double bond of the polyene. The first cis-stereoselective ring-closing step proceeds through the [3+2] cycloaddition of an O–Ru=O moiety on the next carbon–carbon double bond, with the molecule adopting arrangement in the transition state.

Ruthenium oxidation would, at this stage, need to bring the ruthenium atom to an ‘active’ oxidation level (as in 96), thereby allowing for the second ring-closing step to take place. This well explains the observed need for an increase in the amount of sodium periodate when the number of double bonds of the polyene is increased. The experimental data can be explained through considering that each oxidation step at ruthenium requires one equivalent of sodium periodate. The second tetrahydrofuran ring would be formed through another [3+2] cycloaddition step, wherein the molecule would have adopted arrangement 97. Finally, hydrolysis, which would deliver the bis-tetrahydrofuran-diol product, or further cyclization steps, would follow.

It should be noted that the same stereochemical outcome would be obtained if the ruthenium–(C2)–oxygen bond were to be cleaved and if the molecule were to adopt arrangement 98 (Scheme 66) where the initially formed tetrahydrofuran is, nonetheless, coordinated to the metal. Thus, the observed cis-selectivity for the second cyclization step can be explained through chelation control or through bond control [Ru–(C2)O bond], depending on which species, 97 or 98, is involved. An alternative, non-chelated, structure (99), wherein the tetrahydrofuran ring is pseudoaxial and not coordinated to the metal, would lead to a trans-tetrahydrofuran (not formed) in the second cyclization through steric control (see also Schemes 23 and 24).

The above discussion illustrates that the coordination ability of the tetrahydrofuran rings formed in the previous steps play a pivotal role in determining the stereochemical outcome of each subsequent ring-closing step, as already postulated for the rhenium(VII)-mediated polycyclizations. For example, the third, trans-selective, cyclization step for both geranylgeranyl acetate and squalene (Figure 2, left), appears to be under steric control. Formation of the trans-tetrahydrofuran can be explained through the assumption that the molecule adopts the energetically preferred arrangement 100, where the B-tetrahydrofuran...
is pushed away from the metal, and is hence not coordinated to it, because of its pseudoequatorial disposition. This arrangement is also compatible with the coordination of both the A-tetrahydrofuran and the (C2)OH group to ruthenium, as models show.

The trans selectivity for the fourth ring-closing step in the squalene cyclization can be explained through the steric control model as well (Figure 2, right), with the molecule adopting arrangement 101. In fact, the trans configuration of the C-tetrahydrofuran ring pushes both rings B and C away from the metal, thereby excluding a chelation control model. This is true for the fifth cyclization step as well (not shown), allowing for the closure of a cis-tetrahydrofuran, would be possible for the fourth cyclization, but is disfavored by steric interactions. Therefore, the formation of the first trans-tetrahydrofuran (the C-tetrahydrofuran) in the growing poly-tetrahydrofuran chain appears to impose a trans-selectivity on all subsequent cyclization steps in an all-trans isoprenoid polyene such as squalene.

The influence on the bis cyclization process of a Z-configured carbon–carbon double bond, belonging to both a linear and an isoprenoid triene, was evaluated.66 Oxidation of (E,Z)-farnesyl acetate (Scheme 67) stopped after the first cyclization step, and thus indicated that the presence of a cis carbon–carbon double bond, immediately following a trans carbon–carbon double bond, is a disturbing structural feature for the second ring-closing step. A good yield of the mono-tetrahydrofuran-ketol 102 was obtained when the process was conducted in acetonitrile–acetone–water (3:3:1) as the solvent mixture. Similar results were obtained for the oxidation of triene 103, which included a central Z-configured carbon–carbon double bond (Scheme 67).

To explain the failure of the second cyclization step in both (E,Z)-farnesyl acetate and triene 103, the same type of reasoning given above for the second cyclization step of the all-E polyenes can be applied. Thus, after the formation of the first tetrahydrofuran ring, the molecule adopts the spatial arrangement shown by 104 (Figure 3), wherein the C2-oxygen is in some way linked to the metal (chelated or bonded). Indeed, if this were the case, an erythro relationship would arise from the syn addition of two oxygens to the cis double bond during the first cyclization, and a sterically disfavored endo transition state, leading to a cis-tetrahydrofuran, would be required for the second cyclization step to take place. On the other hand, this chelated arrangement is incompatible with the closure of a trans tetrahydrofuran since the alignment of the alkene cannot take place at all. This explanation agrees with, and is further support for, the model proposed for the cis-selectivity of the second cyclization step of an all-E polyene.

10 Conclusions

Since the discovery of the oxidation of geranyl acetate with permanganate more than forty years ago, the oxidative cyclization of 1,5-dienes with various transition-metal–oxo species has received a great deal of attention, mostly in recent years. Thanks to the efforts of a few research groups, this process has been satisfactorily improved and is now being used in syntheses. In the meantime, new related processes have been discovered – the cyclizations of steroidal 1,3-dienes to epoxydiols, the oxidative cyclizations of 1,6- and 1,7-dienes to six- and seven-membered oxacycles, respectively, and the oxidative polycyclization of polyenes catalyzed by ruthenium. Evidence from the ruthenium-mediated oxidative cyclizations suggest a similarity to rhenium(VII) chemistry.

Figure 2 Arrangements that help to explain the trans-selective third and fourth cyclizations in squalene

Scheme 67 Ruthenium-catalyzed oxidation of (E,Z)-farnesyl acetate and (E,Z,E)-dodeca-2,6,10-trien-1,12-diol acetate
The recent finding that pyrrolidine rings can be obtained from 1,2-aminoalcohols, in turn derived from 1,5-dienes in enantiopure form, discloses new scenarios in the area of heterocyclic synthesis. The important question of how to render the cyclization of underivatized 1,n-dienes enantioselective is, however, still a major problem to be solved in this research area. The difference in the stereochemical course of oxidative cyclization of 1,6-dienes with permanganate and ruthenium tetroxide is also worthy of further investigation, from both theoretical and experimental standpoints.

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