Synthetic Endeavours Towards Oxasqualenoid Natural Products Containing 2,5-Disubstituted Tetrahydrofurans – Eurylene and Teurilene

Journal:	*Natural Product Reports*
Manuscript ID:	NP-HIG-03-2014-000029.R1
Article Type:	Highlight
Date Submitted by the Author:	06-May-2014
Complete List of Authors:	Sheikh, Nadeem; King Faisal University,

Synthetic Endeavours Towards Oxasqualenoid Natural Products Containing 2,5-Disubstituted Tetrahydrofurans – Eurylene and Teurilene

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Keywords: 2,5-Disubstituted tetrahydrofuran; oxasqualenoid natural products; metal oxidants; oxidative cyclisation; epoxidation–ring-opening cascade; eurylene; teurilene.

Covering: up to February 2014

Abstract

2,5-Disubstituted tetrahydrofurans constitute the core skeleton of several natural products and are pivotal synthetic analogues of medicinal importance that exhibit remarkable bioactivities. Oxasqualenoid natural products are implicated as potent biologically active molecules, particularly with regard to demonstrating significant cytotoxicity. Characteristic features of oxasqualenoids containing tetrahydrofuran fragment include the presence of either *cis*- and/or *trans*-2,5-disubstituted pattern in tetrahydrofuran moieties and molecular symmetry is often noticed as well. Given their unique structural features combined with bioactivity, representative examples from this class of natural products, eurylene and teurilene have been reviewed concisely. Eurylene with reported cytotoxicity against lymphocytic leukemia, contains two nonadjacently linked *cis*- and *trans*-2,5-disubstituted tetrahydrofuran rings and a combined total of eight stereogenic centres. It is a chiral molecule due to lack of C_2 axis of symmetry. Teurilene shows a prominent cytotoxicity on KB cells and has three adjacently linked 2,5-disubstituted tetrahydrofurans. A distinctive achiral facet is observed in teurilene despite of having eight stereocentres, due to the presence of *meso* symmetry (C_s). The prime objective of this account is to describe a precise mechanistic insight for both *cis*- and *trans*-2,5-disubstituted tetrahydrofurans present in these natural products and to highlight the exciting challenges encountered during the installation of functionalities or structural motifs en route to their synthetic approaches.

1. Introduction

2,5-Disubstituted tetrahydrofurans[1] (THFs) represent one of the most valuable five-membered ring systems in modern synthetic chemistry because of their widespread prevalence in numerous natural products and biogenetically intriguing polyoxygenated squalene-derived[2] cytotoxic molecules[3] such as glabrescol (**1**),[4] (+)-omaezakianol (**2**),[5] longilene peroxide (**3**),[6] (+)-intricatetraol (**4**),[7] (+)-ekeberin **D4** (**5**),[8] 14-deacetyl eurylene (**6**), eurylene (**7**)[9] and teurilene (**8**,[10] Fig. 1). Thus, these heterocycles have attracted a lot of interest from a synthetic viewpoint. Among various established methodologies towards the synthesis of THFs, oxidative cyclisations involving metal–oxo-promoted process are ubiquitous. A number of metal based oxidants have been explored and reported for the synthesis of 2,5-disubstituted tetrahydrofuran (THF) rings of eurylene and teurilene employing sequential epoxidation–5-*exo*-*tet* cyclisation applied to 5-hydroxyalkenes. Alternate reported strategies for THF units of eurylene include oxidative cyclisation protocol designed for 5,6-dihydroxyalkenes and 1,5-diene precursors, while biomimetic epoxide–ring-opening cascade has been articulately incorporated to provide a succinct route to achieve the synthesis of teurilene.

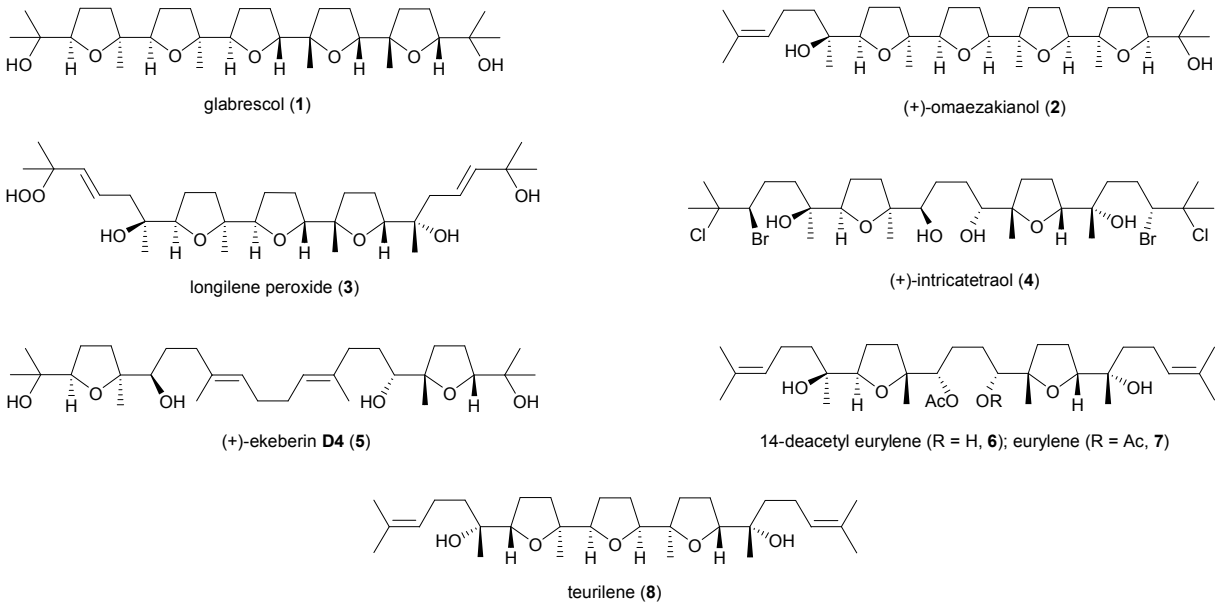


Fig. 1 Structures of representative oxasqualenoids containing 2,5-disubstituted THF rings.

Oxidative cyclisation of 1,5-diene precursors in the presence of $Mn^{(VII)}$[11] or $Os^{(VIII)}$[12] species results in *cis*-THF adducts exclusively (Fig. 2a). The proposed mechanism for this synthetically significant transformation is based on sequential [3+2] cycloadditions,[11b] however Sharpless–type [2+2] cycloadditions sequence is also reported in the literature.[11c] Kinetic isotopic investigations[13a] and spectroscopic determination of intermediate species[13b] reveal that operational mechanism follows [3+2] pathway which was later supported by DFT calculations and labelling studies confirming that concerted [3+2] cycloaddition is favoured by about 40 kcal/mol relative to the stepwise [2+2] counterpart.[13c] In addition to this, $Ru^{(VIII)}$ catalysed oxidative cyclisation of 1,5-diene offers *cis*-stereoselectivity *via* [3+2] cycloaddition along with *trans*-THF compound (*cis*:*trans* up to 95:5).[14] An expedient access to *cis*-stereoselectivity in the incipient disubstituted THF ring is achieved when $Os^{(VI)}$[15] or $Cr^{(VI)}$[16] oxidants are applied to 5,6-dihydroxyalkenes, whereas $Ru^{(VIII)}$[17] species also leads to *cis*-selective THF adducts in a ratio of *cis*:*trans* > 95:5 (Fig. 2b). Like oxidative cyclisation for 1,5-dienes, these transformations are also proposed to follow an intramolecular [3+2] cycloadditions. In addition to this, $Os^{(VI)}$ chemistry has been elegantly extended to 5,7-dihydroxyalkenes to achieve *cis*-2,5-disubstituted THF motifs.[18]

5-Hydroxyalkenes have been subjected to cyclisation using oxorhenium [$Re^{(VII)}$][19] or $Co^{(II)}$[20] oxidants to afford *trans*-2,5-disubstituted THF (Fig. 2c). Mechanistically, $Re^{(VII)}$ mediated oxidative cyclisation goes through an intramolecular [3+2] cycloaddition after the hydroxyalkene coordinates to the metal, whereas $Co^{(II)}$ catalysed cyclisation follows a radical pathway. Epoxidation followed by 5-*exo*-*tet* cyclisation cascade used for 5-hydroxyalkenes furnishes both *cis*- and *trans*-THFs that is determined by the relative stereochemistry of epoxide and hydroxyl group i.e., *syn*-configuration in epoxy alcohol leads to *cis*-selectivity while an *anti*-epoxy alcohol provides *trans*-THF ring (Fig. 2d).[21]

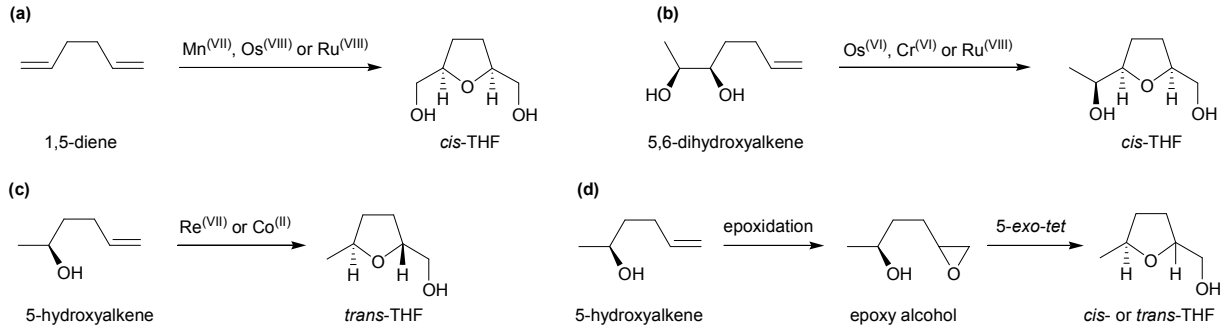


Fig. 2 Metal–oxo species-mediated oxidative cyclisations; 1,5-diene: (a), 5,6-dihydroxyalkene (b), 5-hydroxyalkene (c), and epoxidation–cyclisation tandem sequence (d).

In this commentary, biosynthesis, biological activity and reported fervid endeavours towards the total and formal syntheses of eurylene and teurilene are delineated with respect to the challenges and accomplishments while keeping noteworthy aspects of the routes as equally important considerations.

2. Biogenesis of oxasqualenoids

In general, biosynthesis of polytetrahydrofurans present in oxasqualenoid family of triterpene polyethers is believed to follow sophisticated epoxidation–ring-opening cascade, involving an intramolecular 5-*exo*-*tet* cyclisation *via* spiro transition state to construct THF ring and tetrahydropyran unit of such molecules is the result of 6-*endo*-*tet* cyclisation *via* fused transition state.[22] According to Baldwin's rules, 6-*endo*-*tet* cyclisation is disfavoured however certain directing groups including alkenyl, sulfone, silane and methoxymethyl attached at an appropriate position of an epoxide have a tendency to promote 6-*endo*-*tet* cyclisation either by stabilizing the corresponding transition state or by slowing the 5-*exo*-*tet* cyclisation.[21c,d] Secondary metabolites consist of lipids, terpenoids, oxiranes, flavonoids, polyketides and carbohydrates and these are produced biogenetically as a result of series of enzymatic transformations.[23] The formation of polyether motifs in oxasqualenoid terpenoids is an intricate process and Nature delivers this in highly efficient manner with an excellent stereocontrol, where needed.[24] It is an ongoing quest to fully understand and unveil the streochemical features of natural biosynthetic architecture. Biosynthetic protocol for teurilene as an oxasqualenoid representative illustrates the formation of C_2 symmetric tetraepoxide species derived from the biogenetic squalene precursor,[7a,25] which might be triggered by particular enzymes such as peroxidases or alkene mono-oxygenases (Fig. 3). The resultant stereochemistry in epoxides is exquisitely controlled by the geometry of the double bonds and the presence of methyl branching in the acyclic squalene precursor. Additionally, chiral hydroxyl groups also play a crucial role in directing the stereochemical outcomes during the reaction sequence, if present. Subsequent enzymatic protonation followed by 5-*exo*-*tet* cyclisation cascade produce C_s symmetric *meso* polyether, teurilene (**8**).

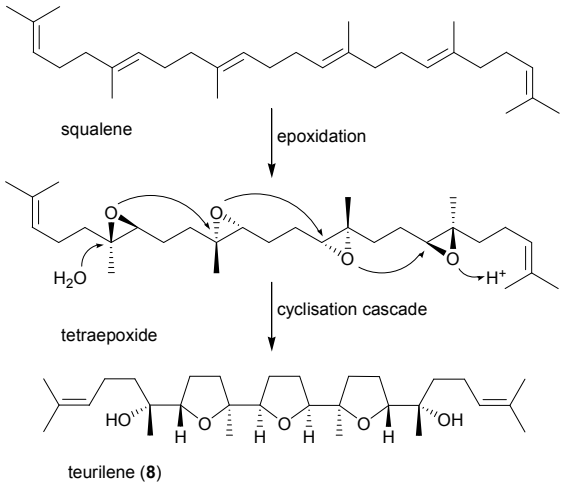


Fig. 3 Representative biosynthesis of THF rings in teurilene (**8**), epoxidation–ring-opening cascade.

3. Structure and biological activities of eurylene and teurilene

Eurylene (**7**), with reported cytotoxicity against lymphocytic leukemia is one of the oxasqualenoid natural products with two nonadjacently linked 2,5-disubstituted THF moieties. It was isolated from the wood of a tropical Asian shrub *Eurycoma longifolia*,[26] which is a tall slender shrub like tree native to Burma, Indochina, Thailand, and Southeast Asia. It belongs to the plant family Simaroubaceae and is commonly found as an under story in the lowland forests at up to 500 m above the sea level. The tree has many local names depending on the regions in which it is found. It is known locally as "Tongkat Ali" in Malaysia, "Pasakbumi" in Indonesia, "Cay Ba Binh" in Vietnam and "Ian-Don" in Thailand. The crude extract of this shrub is popularly used in herbal remedies as a traditional folk medicine.[3b] Spectroscopic data of eurylene was incorporated to assign structural and partial stereochemical features of the molecule and ultimately, the relative and absolute stereostructure was elucidated using X-ray crystallography combined with the analysis of Mosher ester derivatives.[26] The left segment of this bicyclic squalenoid contains an acylated *trans*-THF diol, whereas the other acylated THF diol segment has *cis*-configuration. Both, left and right fragments of eurylene are structurally and functionally similar, but there is a lack of C_2 axis of symmetry due to stereochemical differences between two carbon pairs.

Teurilene (**8**), a rare naturally occurring biologically active polycyclic triterpene consisting of squalene carbon skeleton that was isolated from marine red algae *Laurencia obtusa* by Kurosawa and co-workers[27] and from the wood of terrestrial shrub *Eurycoma longifolia* by Itokawa and colleagues.[3a] It has three adjacently linked *cis*- and *trans*-2,5-disubstituted THF rings and despite of having eight asymmetric centres in the molecule, it is an achiral compound due to the presence of *meso* symmetry (C_s). The entire stereochemical features of teurilene were established unequivocally by X-ray crystallographic studies.[27]

Like structurally related *Annonaceous* acetogenins, polyethers such as eurylene and teurilene are suggested to possess ionophoric nature that provides metal binding tendency with physiologically important metallic cations.[28] This characteristics of oxasqualenoids is postulated to induce cytotoxic potency, which has been observed and a relation between ions transport ability across the liposomal membrane made up of egg phosphatidylcholine and cytotoxicity is reported.[9c] Also, teurilene (**8**) and 14-deacetyl eurylene (**6**) show a remarkable cytotoxic activity against KB cells (IC_{50}: 7.0 μg/mL and 0.52 μg/mL respectively).[3] The presence of both *cis*- and *trans*-2,5-disubstituted THF rings in eurylene (**7**) and teurilene (**8**), expedient manipulations of eurylene to access epimeric compounds, significant ions transport ability and cytotoxic activities make them an interesting synthetic choice for the researchers.

4. Synthetic strategies towards eurylene

First stereoselective synthesis of the *trans*-THF, left fragment of eurylene was achieved in 25 linear steps that involves Sharpless asymmetric epoxidation applied to 5-hydroxyalkene followed by acid-catalysed 5-*exo*-*tet* cyclisation as a key step.[29] However, synthetic efforts towards the total and formal syntheses of 14-deacteyl eurylene (**6**) and eurylene (**7**) are described below.

4.1 Vanadium-catalysed epoxidation–acid-mediated cyclisation sequence

Ujihara and Shirahama envisaged the utility of vanadium$^{(V)}$ promoted epoxidation followed by cyclisation in an acidic medium to synthesize *cis*-THF ring of eurylene by applying to 5-substituted-4-alken-1-ol *via* *syn*-epoxy alcohol (Fig. 4).[9a] The *trans*-THF adduct of eurylene was constructed by employing the same approach applied to 4-substituted-4-alken-1-ol *via anti*-epoxy alcohol.

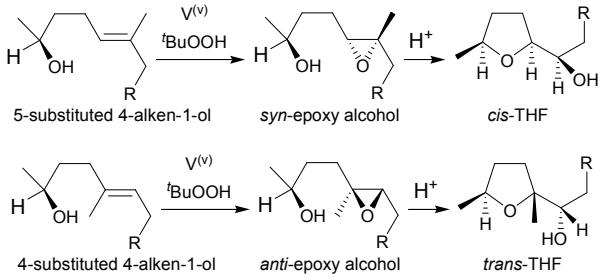
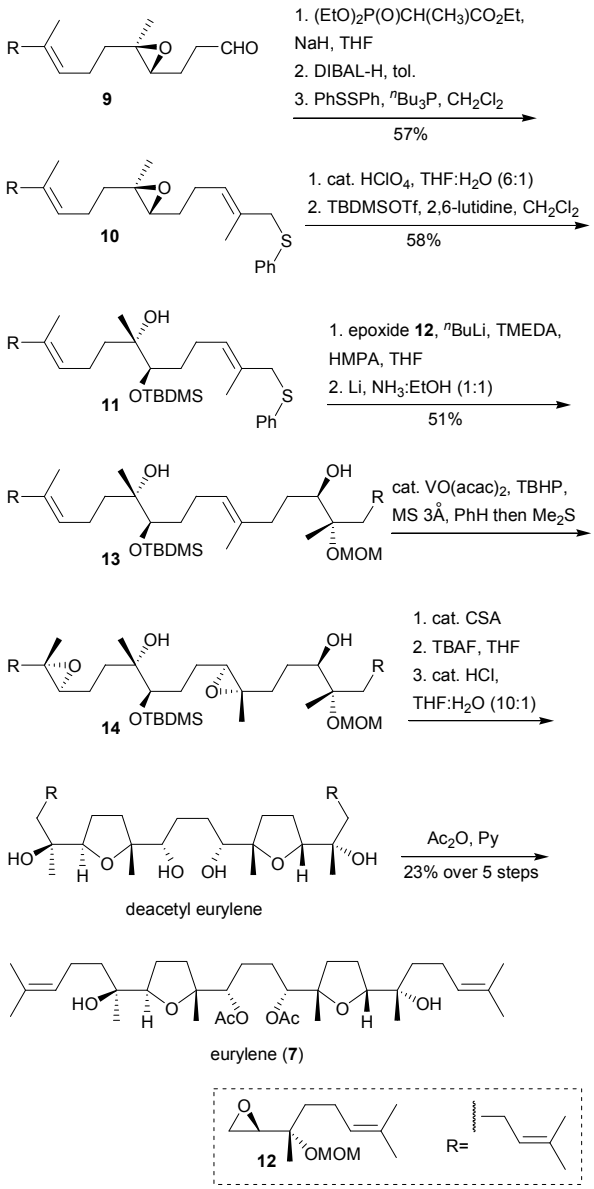


Fig. 4 Proposed strategy for the syntheses of *cis*- and *trans*-THF fragments of eurylene (**7**) using epoxidation–cyclisation protocol.

The reported synthesis commenced with an enantiomerically pure aldehyde **9** which was synthesized according to the literature precedent reported in the paper.[9a] A well-established Horner-Wadsworth-Emmons olefination coupling to the aldehyde **9** afforded an ethyl ester, which was subsequently reduced to alcohol and finally converted to thioether **10** (Scheme 1). Hydrolysis of epoxide moiety in thioether **10** followed by the protection of the resultant secondary alcohol yielded silyl ether **11**. Oxirane **12** was synthesized in 5 steps from commercially available starting material and successfully coupled with lithio-

anion of thioether **11** to offer *bis*-homoallylic alcohol that was desulfurized using Birch conditions to provide the diol **13**, which was subjected to vanadium-catalysed epoxidation to provide *bis*-epoxide **14**. At this juncture, the diastereomeric purity of *bis*-epoxide **14** could not be confirmed, which is reported to be due to the side reactions including deprotection and/or oxidation of terminal double bonds. An acid-catalysed cyclisation of the left side epoxide and deprotection of the silyl group followed by second acid-promoted cyclisation of the right hand epoxide with simultaneous cleavage of the methoxymethyl group afforded deacetyl eurylene. Finally, acetylation of the secondary alcohols led to the first total synthesis of eurylene (**7**) and absolute stereochemistry was explicated by correlating the spectroscopic and optical rotation data of synthetic eurylene with the one reported in the literature.[26]

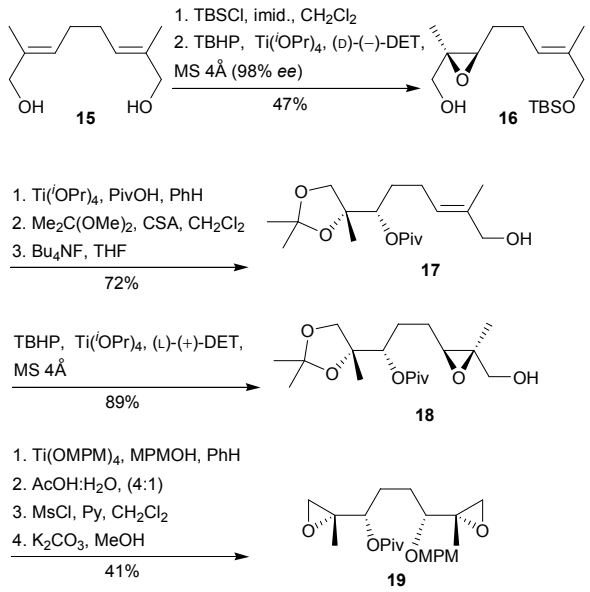


Scheme 1 Total synthesis of eurylene (**7**) by Ujihara and Shirahama; vanadium-catalysed epoxidation–acid-mediated cyclisation sequence.

4.2 Rhenium and chromium-promoted bidirectional oxidative cyclisations

In their pioneering studies towards the total synthesis of eurylene (**7**), Morimoto and his colleagues envisioned an effective bidirectional concept that utilizes the intrinsic molecular symmetry.[9b] They elaborated an application of rhenium$^{(VII)}$ oxidative cyclisation for the construction of the *trans*-THF ring while the *cis*-THF motif of eurylene was synthesised by applying chromium$^{(VI)}$ as an oxidant. Another smart trick was added to the synthesis when two neryl units were introduced to perform regioselective ring opening of the *bis*-epoxide **19**, again in bidirectional manner to establish the side chains on either sides.

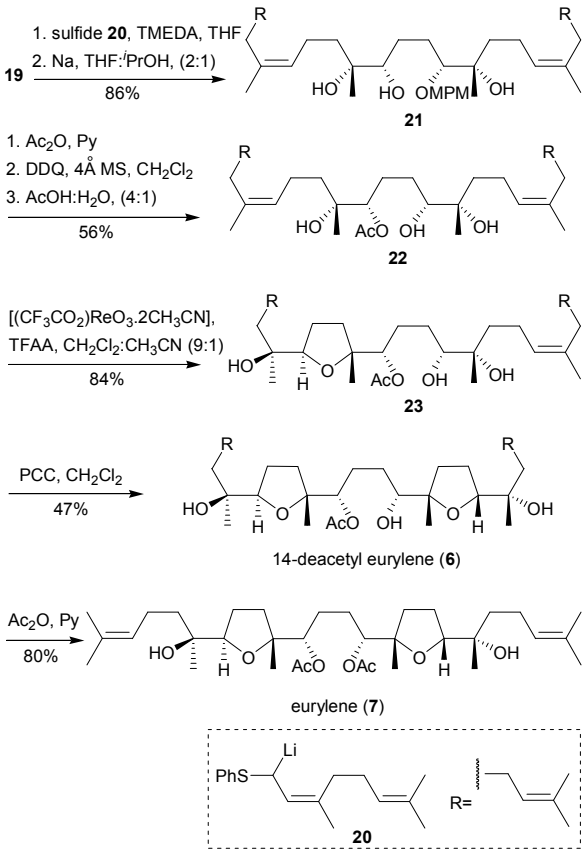
The implementation of this strategy began with the known diol **15**, previously synthesized in 4 steps (overall 31% yield, reference cited in the paper).[9b] This was monoprotected and then subjected to Sharpless asymmetric epoxidation to provide epoxy alcohol **16** in 98% *ee* (Scheme 2). A regioselective introduction of pivalate group yielded the diol as a single diastereoisomer which on subsequent acetonide protection and desilylation furnished the allylic alcohol **17**. Epoxide **18** was generated by second asymmetric epoxidation followed by ring-opening to afford the desired 1,2-diol, along with a by-product, 1,3-diol in a ratio of approximately 3:1, which on cleavage of the acetonide, mesylation of both primary hydroxyl groups and epoxide closure provided the desired *bis*-epoxide **19**.



Scheme 2 Stereoselective synthesis of *bis*-epoxide **19**.

Alkylation of lithio derivative of neryl phenyl sulfide **20** with *bis*-epoxide **19** provided the bidirectional chain extension, furnishing bisulfide that was desulfurized under Bouvault–Blanc conditions to provide the triol **21** (Scheme 3). Selective acetylation, MPM deprotection with subsequent acidic hydrolysis offered the triol **22**, which was ready to test for key oxidative cyclisations. The end-game was achieved by treating this with oxorhenium$^{(VII)}$ complex in the presence of TFAA to install anticipated *trans*-THF ring **23** of eurylene resulting from a steric control. Treatment of 5,6-dihydroxyalkene unit of *mono*-THF

adduct **23** with oxochromium$^{(VI)}$ complex afforded *cis*-THF ring, thus completing the synthesis of 14-deacetyl eurylene (**6**), which on acetylation accomplished the total synthesis of eurylene (**7**).

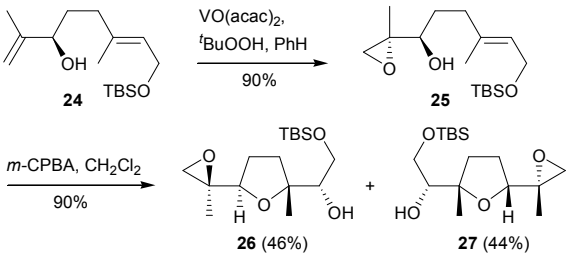


Scheme 3 Morimoto's approach towards 14-deacetyl eurylene (**6**) and eurylene (**7**); rhenium$^{(VII)}$ and chromium$^{(VI)}$ promoted bidirectional oxidative cyclisations.

4.3 *m*-CPBA Epoxidation–cyclisation cascade

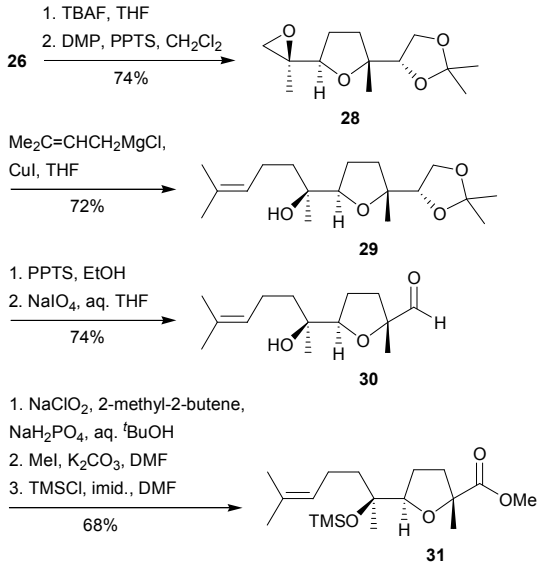
Kodama and collaborators achieved the synthesis of 14-deacetyl eurylene (**6**), eurylene (**7**) and their epimeric derivatives by non-stereoselective THF ring formation.[9c] More importantly, the relation between the ability to transport ions and cytotoxic activity was investigated. It is postulated that the activity is due to the complexation with the metal ion, in particular with K^+ and the stereochemistry at acylated position adjacent to the *trans*-THF ring of eurylene (**7**) plays a crucial role in the cytotoxicity.

The synthetic story started with the Baker's yeast reduction process that was applied to synthesise (*R*)-allylic alcohol **24** in 99% *ee*. The alcohol **24** was converted into epoxide **25** in 86% diastereomeric excess, which on treatment with *m*-CPBA afforded *trans*-THF **26** and *cis*-THF **27** unselectively and in almost equal amounts (Scheme 4). Due to the difference in polarity, the polar *trans*-THF moiety **26** was separated from the *cis*-THF adduct **27** and stereochemistry was determined by NOE experiments.



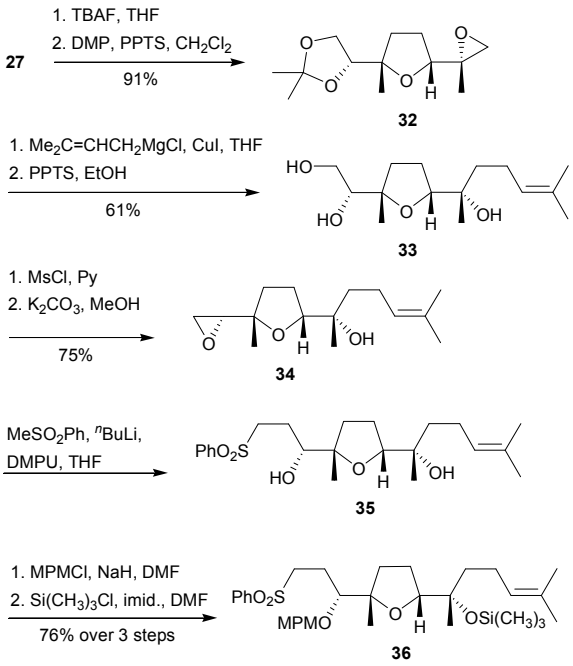
Scheme 4 Non-stereoselective approach to *cis*- and *trans*-2,5-disubstituted THF rings of eurylene (**7**).

To accomplish the synthesis of left segment of eurylene, *trans*-THF product **26** was converted to acetonide **28** by sequential deprotection of silyl ether and protection of the resulting 1,2-diol (Scheme 5). Alkylation of epoxide **28** provided the desired chain length to give alcohol **29**. Subsequent deprotection and oxidative cleavage of the resultant diol furnished the aldehyde **30** that was further oxidized and esterified to set up the methyl ester **31**, the left fragment of eurylene (**7**).



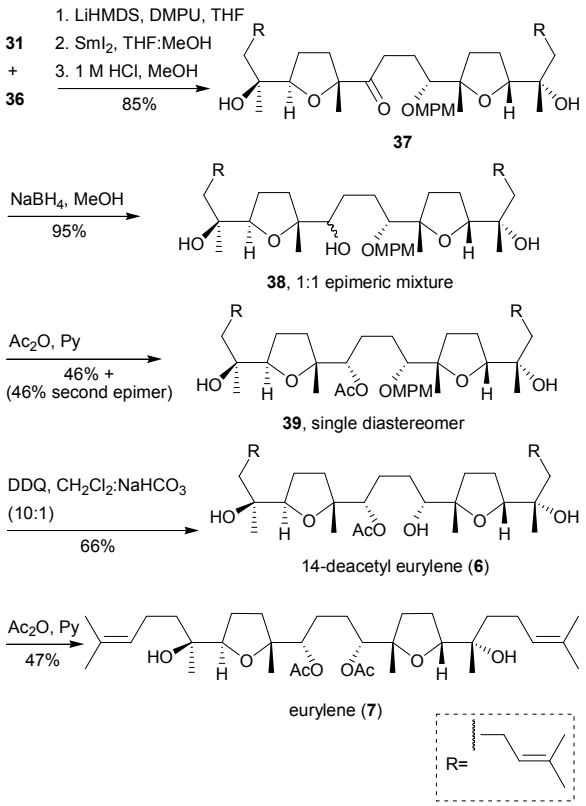
Scheme 5 Synthesis of *trans*-THF fragment **31** of eurylene (**7**).

Similarly, *cis*-THF **27** was transformed into acetonide **32** which was subsequently alkylated and the acetonide functionality was deprotected to afford 1,2-diol **33** (Scheme 6). The primary alcohol was selectively mesylated and treated under basic conditions to afford the epoxide **34**. Alkylation of epoxide **34** with the lithio-anion of methyl phenyl sulfone gave the diol **35**, in which secondary and tertiary hydroxyl groups were protected as MPM and TMS ethers respectively to afford the sulfone **36**, the right fragment of eurylene (**7**).



Scheme 6 Synthesis of *cis*-THF fragment **36** of eurylene (**7**).

Final fragment assembly was achieved by coupling lithio-anion of *cis*-THF sulfone **36** with the *trans*-THF ester **31**, followed by reductive desulfonylation, deprotection of the silyl ether, and finally the reduction of the resultant ketone **37** to access a mixture of epimeric secondary alcohols **38** (ca. 1:1, Scheme 7). The epimers could not be separated and the mixture was acetylated and then separated to give pure *bis*-THF adduct **39** and it's epimer. Removal of MPM protecting group furnished 14-deacetyl eurylene (**6**), which was acylated to complete the synthesis of eurylene (**7**). The syntheses of epimeric eurylene and 14-deacetyl eurylene were also carried out, utilising the second epimer of *bis*-THF compound **39**.



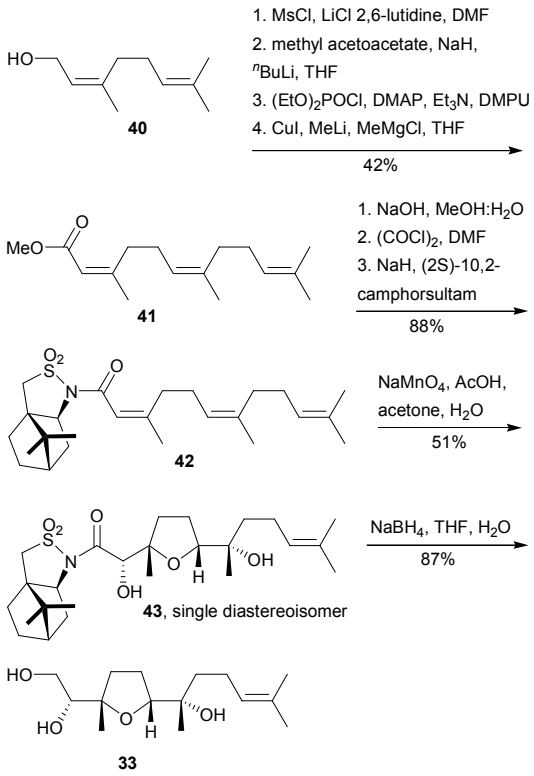
Scheme 7 Total syntheses of 14-deacetyl eurylene (**6**) and eurylene (**7**) by Kodama's group.

4.4 Chemoselective permanganate-mediated oxidative cyclisation

Given the importance of 2,5-disubstituted THF fragments in natural products, an alternate protocol that allows a convenient access to such motifs is particularly championed by Brown and co-workers using chemo- and stereoselective permanganate-promoted oxidative cyclisation. An efficient synthesis of both fragments of eurylene is described, which not only coincides with the key synthetic intermediates of eurylene reported by kodama and colleagues but also inspire to reconnoitre new coupling strategies.[9d] Disconnecting eurylene from the centre led to the *cis*- and *trans*-fragments of eurylene, which are the end products of strategically placed manipulations applied to respective 1,5,9-trienes **42** and **47** respectively. Chirality in the molecule was established using external suitable chirophores and seven out of eight chiral centres were created by applying two oxidative cyclisations.

An expeditious synthetic route is described for the *cis*-THF fragment of eurylene that follows a 9 step linear sequence with 16% overall yield. Methyl ester **41** was prepared from readily available nerol (**40**) in four steps involving chlorination, methyl acetoacetate dianion addition, phosphate formation and stereoselective methylation. Hydrolysis of methyl ester **41** followed by coupling with (2*S*)-camphorsultam afforded trienoyl sultam **42**, which underwent permanganate oxidative monocyclisation in regio- and stereoselective fashion to provide the desired *cis*-THF diol **43** in a 8:1 diastereomeric mixture that were separable by flash column chromatography. An overoxidised by-product was also observed

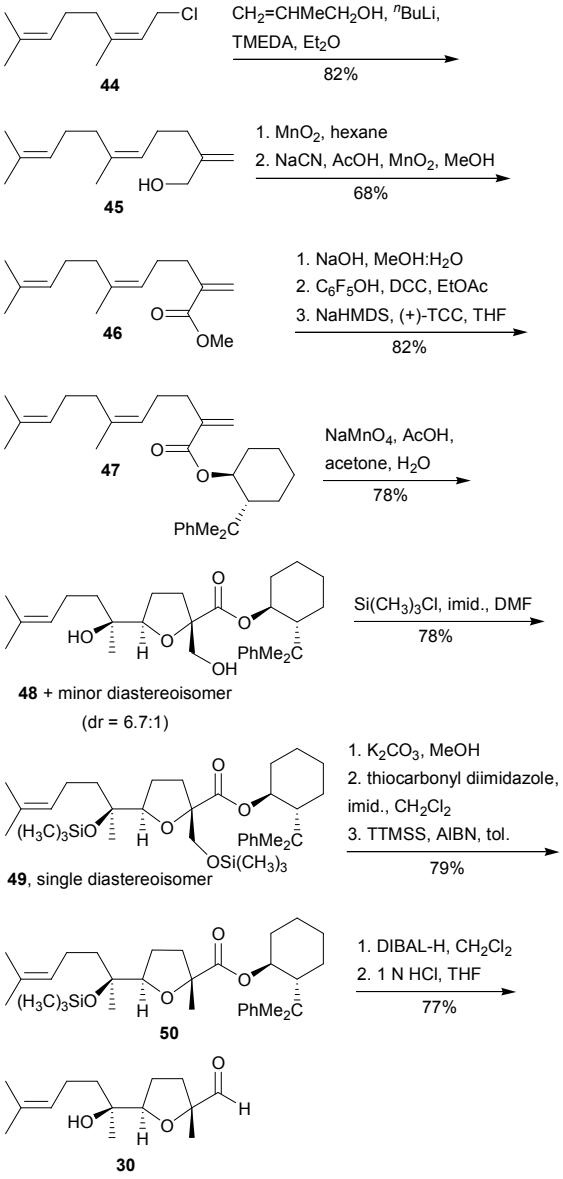
during the cyclisation in 6% yield which is presumably because of using excess of permanganate. Finally, reductive cleavage of the chiral auxiliary led to the formal synthesis of *cis*-THF unit **33** of eurylene that coincided with the reported in the literature.[9c]



Scheme 8 Brown's synthetic strategy for the *cis*-THF ring of eurylene (**7**); permanganate-mediated monocyclisation.

For the synthesis of *trans*-THF unit of eurylene, a different concept was imagined that involved the formation of *cis*-THF diol followed by a subsequent stereospecific transformation into the desired *trans*-THF fragment. This strategically placed manipulation enabled to overcome the lack of permanganate-promoted stereoselective route for the *trans*-selective oxidative cyclisation of 1,5-diene motif. Alkylation of methallyl alcohol dianion with neryl chloride (**44**) and two-step MnO_2-mediated oxidation of the resultant allylic alcohol **45** provided a structurally distinct trienoate methyl ester **46**, which was coupled with various chiral auxiliaries (Scheme 9). The best results for oxidative cyclisation was reported for trienoate **47** bearing (+)-*trans*-2(α-cumyl)cyclohexanol, (+)-TCC in 78% yield to give the monocyclised diol **48** in a diastereomeric ratio of 6.7:1. Notably, the trisubstituted terminal alkene during this key step remains unaffected and oxidative cyclisation triggered successive [3+2] cycloadditions on the electron-deficient part of the triene. The separation of diastereoisomers was successfully achieved chromatographically by protecting diastereomeric mixture of THF diols **48** as their *bis*-TMS ethers and the rest of the synthesis was carried out using diastereomerically pure *cis*-THF diol **49**. In order to obtain the desired *trans*-THF ester **50** of eurylene, selective deprotection of the primary silyl ether followed by

two-steps Barton McCombie radical deoxygenation was performed. Ester **50** is an analogue of methyl ester **31** reported by Kodama and co-workers previously.[9c] However, reductive cleavage of the chiral auxiliary using DIBAL-H and subsequent deprotection of tertiary silyl ether afforded the aldehyde **30** in 13 linear steps (17% overall yield), which was in agreement with the reported synthesis of left segment of eurylene.[9c]



Scheme 9 Synthesis of *trans*-THF ring of eurylene (**7**) by Brown's group.

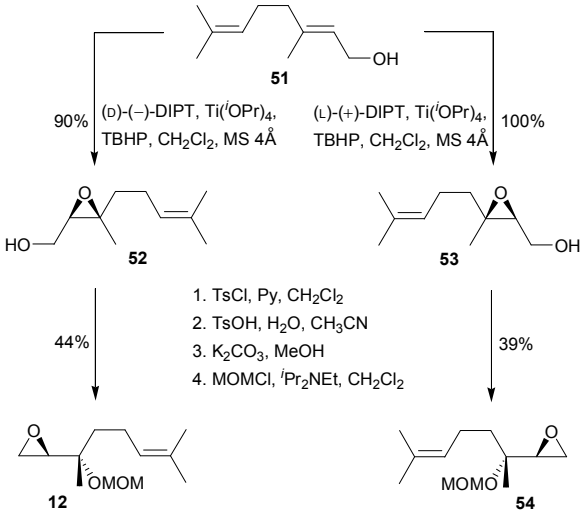
5. Teurilene – a cytotoxic oxasqualenoid

Reported syntheses of teurilene (**8**) not only disclose interesting aspects of synthesis but also stimulate to simulate Nature's synthetic designs for these natural products. These include oxidative cyclisation and epoxide–ring-opening transformations which have been creatively visualised and implemented.

5.1 Vanadium-catalysed tandem epoxidation–ring-opening protocol

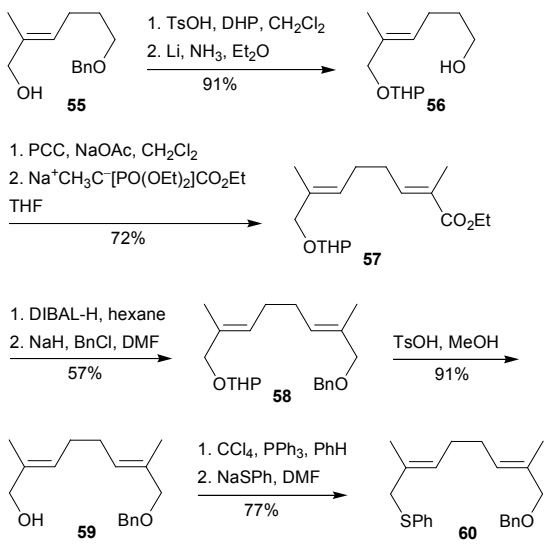
First total synthesis of teurilene (**8**) was reported by Shirahama and co-workers, which was based on vanadium$^{(V)}$ promoted epoxidation–ring-opening sequence applied to substituted alkenols.[10a,b] The methodology was previously established for the synthesis of thyrsiferol, another oxasqualenoid and exquisitely extended to teurilene. Initial investigations were planned on the basis of stepwise THF rings construction,[10a] however, an improved route was described involving simultaneous double oxidation–cyclisation.[10b]

Sharpless asymmetric epoxidation applied to geraniol (**51**) provided epoxide **52** which was subjected to stereospecific nucleophilic transformations and conventional protection procedure to produce (–)-linalool derivative **12** (Scheme 10). The same strategy was used to synthesize (+)-linalool derivative **54** *via* epoxide **53**.



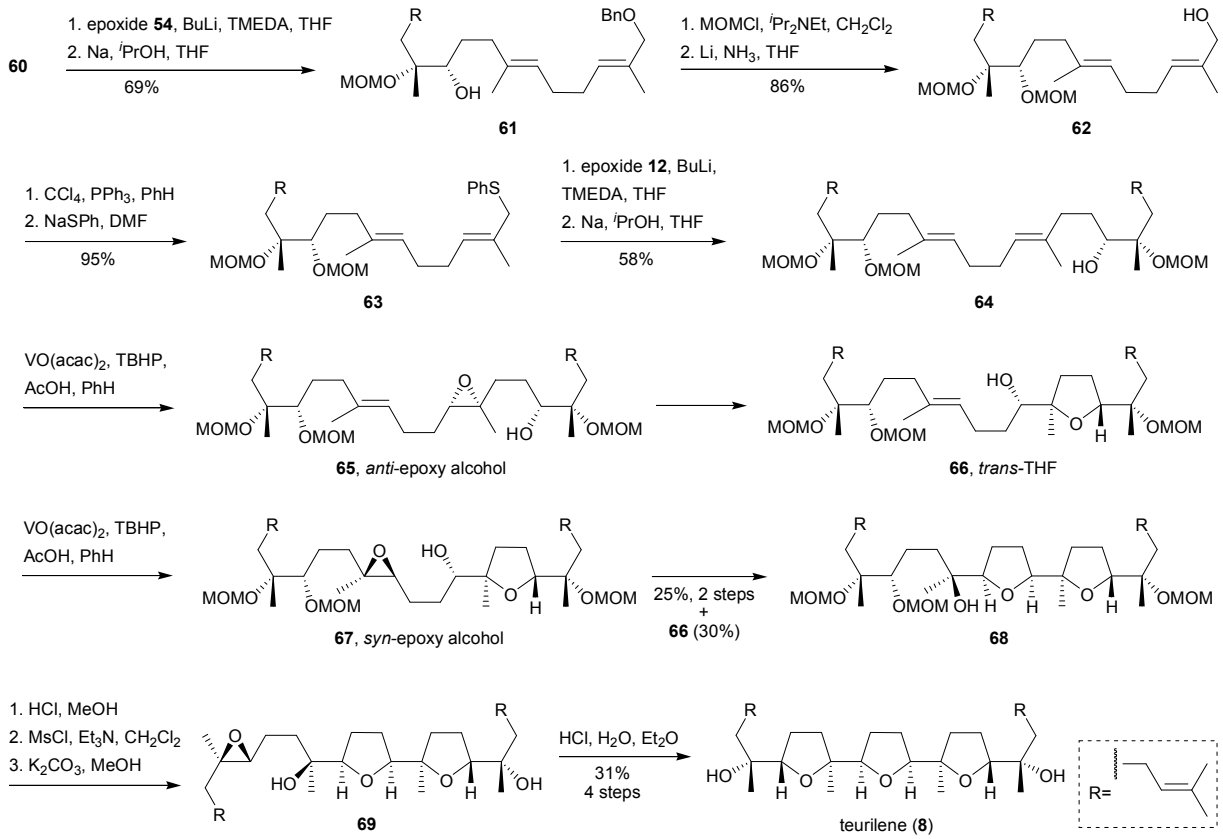
Scheme 10: Asymmetric syntheses of (–)- and (+)-linalool derivatives **12** and **54** respectively.

Allylic sulfide fragment **60** to couple with epoxide **54** was prepared from allylic alcohol **55** according to the reported procedure. Protection of alcohol functionality and removal of benzyl group under dissolving metal conditions provided alcohol **56** (Scheme 11). PCC oxidation to aldehyde followed by Horner–Emmons reaction gave α,β-unsaturated ester **57**, which was reduced to alcohol and subsequently protected as benzyl ether **58**. Tetrahydropyranyl group was cleaved from ether **58** and the resultant alcohol **59** was subsequently converted to allylic sulfide **60** through chlorination and nucleophilic displacement by thiophenoxide anion.



Scheme 11: Synthesis of allylic sulfide **60**.

Treatment of allylic sulfide **60** with (+)-linalool derivative **54** furnished secondary alcohol **61** (Scheme 12). A protection-deprotection strategy was introduced to achieve the desired primary alcohol **62** that was converted to allylic sulfide **63**. Coupling of (–)-linalool derivative **12** with sulfide **63**, followed by desulfurization provided the desired alcohol **64** that was ready to test simultaneous double epoxidation–cyclisation sequence. Vanadium$^{(V)}$ catalysed epoxidation–cyclisation led to an initial formation of *trans*-THF ring **66** *via anti*-epoxy alcohol **65** that was subjected to another cascade to construct the *cis*-THF unit of *bis*-THF adduct **68** *via syn*-epoxy alcohol **67**. At this stage, the starting *mono*-THF **66** was also obtained, which was utilised to prepare additional quantities of *bis*-THF compound **68**. Synthesis of teurilene (**8**) was achieved by installing third THF ring using acid-catalysed cyclisation of epoxide **69** that was the end product of *bis*-THF motif **68** after removal of methoxymethyl groups, selective mesylation and stereospecific epoxidation.

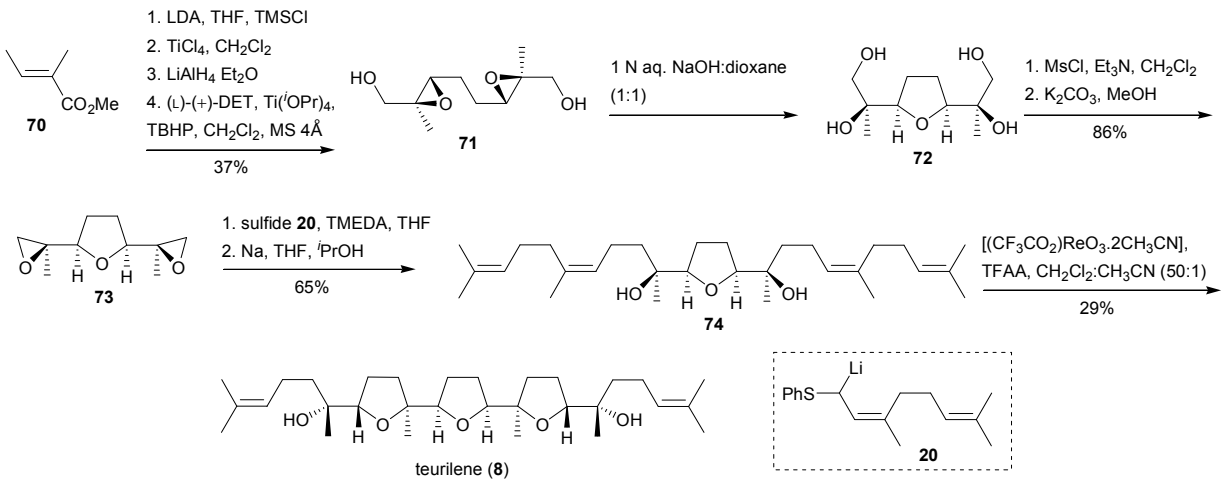


Scheme 12: First total synthesis of teurilene (**8**) using simultaneous double epoxidation–cyclisation sequence by Shirahama and co-workers.

5.2 Rhenium mediated bidirectional oxidative cyclisation

An expedient approach to the synthesis of teurilene (**8**) has been appealingly reported by Morimoto and co-workers, which relies on $Re^{(VII)}$ mediated bidirectional oxidative cyclisation applied to 5-hydroxy alkenes.[10c,d] It is a succinct reported route starting from readily available methyl tiglate (**70**). *Bis*-glycidic alcohol **71** was obtained in stereoselective manner by applying silylation, titanium induced γ-dimerization, reduction to *bis*-allylic alcohol and finally double Sharpless asymmetric epoxidation (Scheme 13). Treatment of *bis*-epoxide **71** with aq. NaOH:dioxane mixture gave *cis*-THF *meso* tetraol **72** through sequential transformations involving base-catalysed Payne rearrangement, intramolecular 5-*exo*-*tet* cyclisation and terminal epoxide opening by hydroxide ion. Selective mesylation of tetraol **72** followed by epoxide formation gave *bis*-epoxide **73**, which was subsequently coupled with lithio derivative of neryl sulfide **20** and desulfurized using Bouvault–Blanc conditions to give the diol **74** that contains complete carbon framework of teurilene. Two-directional $Re^{(VII)}$ catalysed oxidative cyclisation was carried out to afford teurilene (**8**) along with a by-product, monocyclised alcohol in 15% yield that was converted to teurilene by re-subjecting it to oxidative cyclisation. In this case, double cyclisation proceeds *via* steric controlled transition state delivering the desired *trans*-*syn* diastereoselectivity present

in teurilene, however *cis-syn* diastereoselectivity is also discussed in the article that is believed to follow a chelation control mechanism.



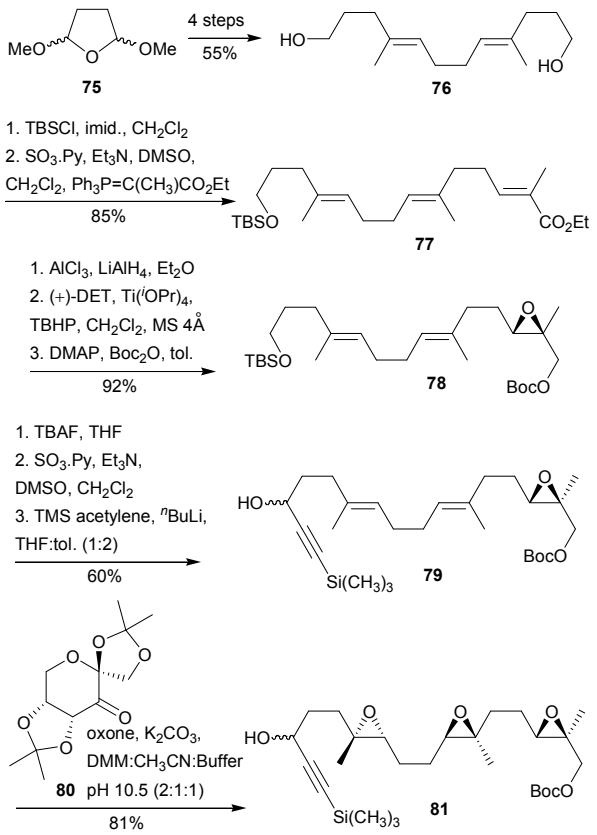
Scheme 13: Morimoto's succinct route to teurilene (**8**); rhenium$^{(VII)}$ catalysed bidirectional oxidative cyclisation approach.

5.3 Epoxide–ring-opening cascade

Year 2013 launched a new direction to the synthesis of teurilene and related cytotoxic compounds. Both Martin and Morimoto have separately and elgantly incorporated an idea of epoxide–ring-opening cascade to the synthesis of teurilene, which seems an inspiration from biomimetic synthesis of oxasqualenoids.[2]

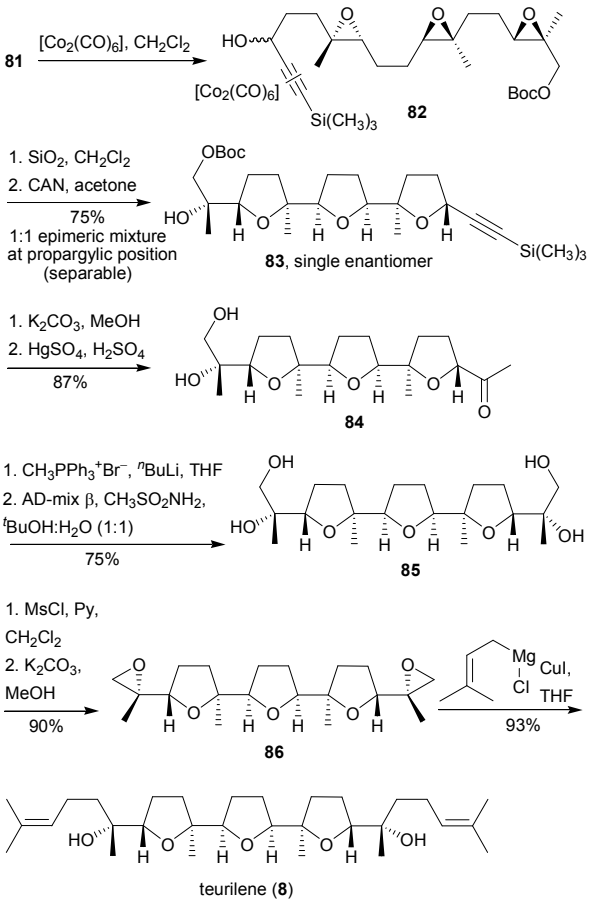
5.3.1 Nicholas reaction in epoxide-opening cascade

Immitating Nature, Martin and co-workers established an effective synthetic protocol to construct 2,5-disubstituted THF rings *via exo* cyclisation applied to polyepoxides.[10e] The process is markedly extended to gain a rapid access into polycyclic compounds in a single step and represents an intramolecular nucleophilic attack on a dicobalt hexacarbonyl stabilized propargylic cation by an epoxide. Their synthetic strategy begins with the conversion of 2,5-dimethoxy THF **75** into isomerically pure diol **76** using a reported procedure which involves the formation of succinic dialdehyde, alkenyl addition, stereoselective Claisen rearrangement and reduction (Scheme 14). Monoprotection of diol **76** as silyl ether followed by single-step homologation involving oxidation and Wittig olefination gave α,β-unsaturaded ester **77**. Reduction of the ester to allylic alcohol, Katsuki–Sharpless epoxidation and protection of primary alcohol afforded the *bis*-protected diol **78**. Synthesis of propargylic alcohol **79** was carried out by employing desilylation, Parikh–Doering oxidation to aldehyde and coupling to lithium TMS acetylide. Finally, Shi asymmetric epoxidation using ketone **80** was carried out to access polyepoxide **81**.



Scheme 14: Synthesis of triepoxide precursor **81** by Martin's research group.

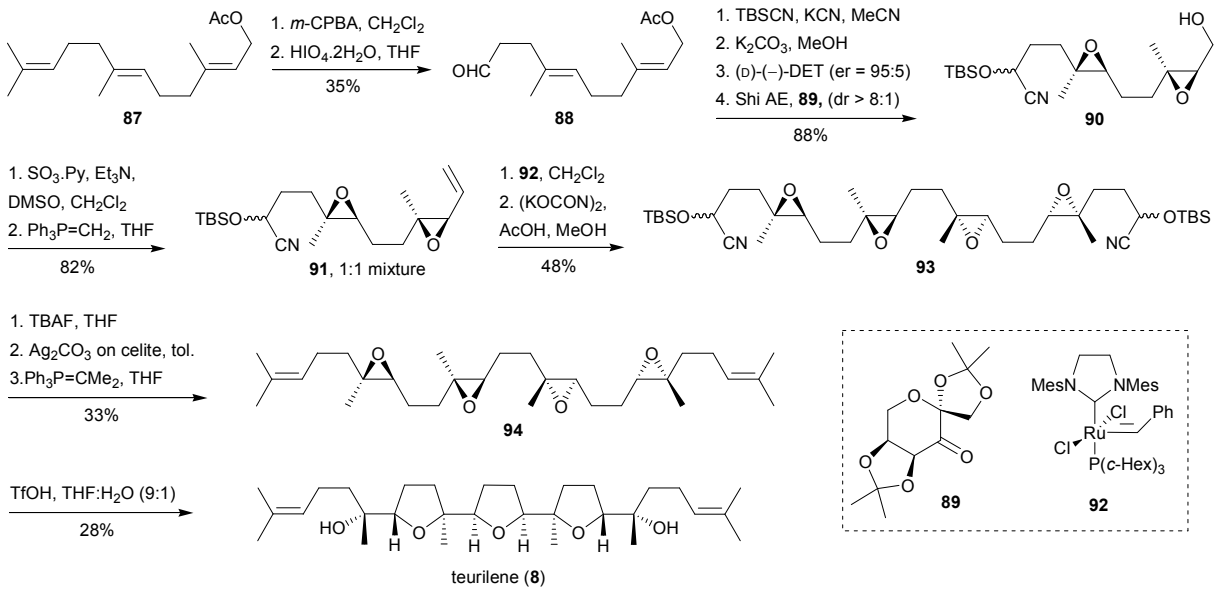
Polyepoxide **81** was converted to hexacarbonyl dicobalt complex **82** and subsequently subjected to the optimised cyclisation cascades that created three THF rings in an excellend yield as 1:1 epimeric mixture at the allylic position (Scheme 15). Epimers were separable by column chromatography and the required THF adduct **83** was converted to methyl ketone **84** after the removal of trimethylsilyl and Boc groups followed by hydration of the terminal alkyne moiety. The undesired epimer of THF adduct **83** was also converted to methyl ketone and subjected to epimerization, giving 1:1 epimeric mixture that was separated to obtain additional quantity of the required methyl ketone **84**. Wittig olefination and Sharpless asymmetric dihydroxylation provided correponding *meso*-tetraol **85**, which was converted to *bis*-epoxide **86** in a bidirectional manner. The end-game was achieved by the addition of bidirectional Grignard reagent to furnsih teurilene (**8**).



Scheme 15: Martin's synthesis of teurilene (**8**); cobalt-mediated epoxide-opening cascade.

5.3.2 Hydrolysis in epoxide-opening cascade

Another interesting idea, which is triggered by Brønsted acid-promoted hydrolysis of terminal epoxide leading to 5-*exo* cyclisation cascade to achieve strategically remarkable synthesis of teurilene has been reported by Morimoto and co-workers.[10f] The methodology was also extended towards the syntheses of glabrescol (**1**) and (+)-omaezakianol (**2**). The synthesis commences with readily available triene **87** which was treated with *m*-CPBA to affect epoxidation and later oxidative cleavage to aldehyde **88** (Scheme 16). Protection of aldehyde moiety as TBS ether of cyanohydrin, deacetylation, Sharpless asymmetric epoxidation followed by Shi asymmetric epoxidation using ketone **89** provided *bis*-epoxy alcohol **90**. Combination of oxidation and Witting methylenation gave alkene **91**, which was dimerized using Grubb's catalyst **92** and the resultant double bond was reduced to tetraepoxide **93**. Standard desilylation procedure, treatment with Fétizon's reagent and finally Wittig olefination furnished the desired C_2 symmetric tetraepoxide **94**, which on treatment with Brønsted acid in the presence of water entered into cyclisation cascade after the hydrolysis of terminal epoxide to accomplish the total synthesis of teurilene (**8**).



Scheme 18: Morimoto's biomimetic epoxide-opening cascade to synthesize teurilene (**8**).

6 Conclusions

Oxasqualenoid natural products show remarkably wide range of pharmacological potential, particularly with regard to exhibiting cytotoxic activities against KB cells (IC_{50}: 7.0 μg/mL and 0.52 μg/mL for teurilene and 14-deacetyl eurylene respectively). Salient features of these potent natural products include the presence of 2,5-disubstituted THF rings and molecular symmetry is also observed very often. 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. This *highlight* provides a concise insight and fervent endeavours towards the total and formal syntheses of eurylene and teurilene, which are representative oxasqualenoids bearing a combined total of eight stereogenic centres and characterised by the presence of both *cis*- and *trans*-2,5-disubstituted THF rings. Both compounds exquisitely represent chiral and achiral facets of squalene-derived natural products containing THFs, as eurylene is a chiral molecule due to lack of C_2 axis of symmetry while teurilene has a *meso* symmetry (C_s) thus making it an achiral compound. The synthetic protocols delineated in this *highlight* have also been applied to numerous other natural products with profound structural complexity and will continue prompting an irresistible allure to fascinating natural products.

7 Abbreviations

Ac	acetyl
AD	asymmetric dihydroxylation
AE	asymmetric epoxidation
AIBN	2,2′-azobis(isobutyro)nitrile
Bn	benzyl
Bu	butyl

cat.	catalytic
CAN	ceric ammonium nitrate
CSA	camphorsulfonic acid or (7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-methanesulfonic acid
DCC	*N,N′*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartrate
DHP	dihydropyran
DIBAL-H	diisobutylaluminium hydride
DIPT	diisopropyl tartrate
DMAP	4-(dimethylamino)pyridine
DMF	*N,N′*-dimethylformamide
DMM	dimethyl maleate
DMP	2,2-Dimethoxypropoane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
er	enantiomeric ratio
Et	ethyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
imid.	imidazole
Pr	propyl
LDA	lithium diisopropylamide
m-CPBA	3-chloroperoxybenzoic acid
M	molar
Me	methyl
MeCN	acetonitrile
Mes	mesityl
MPM	4-methoxybenzyl
Ms	methanesulfonyl (mesyl)
N	normal
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
Ph	phenyl
Piv	pivaloyl
PMBM	*p*-methoxybenzylmethoxy
PMP	*p*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
Py	pyridine
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBS	*tert*-butyldimethylsilyl
TBHP	tetrabutyl hydroperoxide
TCC	*trans*-2(α-cumyl)cyclohexanol
Tf	triflyl or trifluoromethanesulfonyl
TFA	triflouroacetic acid
TFAA	triflouroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TMEDA	*N,N,N′, N′*-tetramethylethylenediamine
TMS	trimethylsilyl
tol.	toluene

Ts	tosyl or *p*-toluenesulfonyl
TTMSS	*tris*-trimethylsilylsilane

8 Acknowledgements

The author would like to gratefully acknowledge an invaluable guidance and encouragement offered by his mentor, Prof. Richard C. D. Brown (University of Southampton, UK). Also, thanks to Prof. Iain Coldham (University of Sheffield, UK) for his continuous support and to the King Faisal University, Saudi Arabia for the financial support.

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