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Selective preparative 'oxidase phase' in sesquiterpenoids: the radical approach

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The necessity for highly selective oxidative transformations towards the synthesis of complex natural compounds such as sesquiterpenoids makes total synthesis a rich terrain of development for powerful widely applicable methods. Due to excessive oxidative decoration of sesquiterpenoids, which is traced back to the impressive performance of monooxygenases, synthetic efforts have been recently directed also towards more monooxygenase-like radical approaches to address the synthetic challenge of installing an 'oxidase phase' in their carbocycles. This review collects recent total syntheses of sesquiterpenoids relying mainly on radical reactions for allylic hydroxylations, hydrations and C–H oxidations.

1. Introduction

The impressive machinery of complexity as exemplified by the biosynthesis of terpenoids highlights the ability of Nature to perform highly selective transformations by utilizing enzymes and rather simple common scaffolds.[1] This divergent protocol empowered by the iterative use of primary metabolism reactions (IPP, DMAPP, and cationic reactions) produces carbocyclic frameworks (cyclase phase) that finally become oxidative enzymes (oxidase phase) (Fig. 1). The common motifs of reactivity used by Nature permit, to some extent, the identification and application of selective biosynthetic-like reactions in modern total synthesis. Sesquiterpenoids play a pivotal role as model templates in biomimetic synthesis by sustaining the crucial balance between their observed molecular complexity and the straightforward link of how their selectivity might arise from their natural roots.

Containing more than 50 000 members, sesquiterpenoids represent an active 'X-ray scan' of primitive mechanisms in biosynthesis, retaining their importance as biological probes. Compounds such as parthenolide (**1**), thapsigargin (**2**), picrotoxinin (**4**), and artemisinin (**5**) (Fig. 1, blue frame) are important pharmaceutical leads for anti-cancer, anti-malarial, anti-inflammatory agents *etc.* but most importantly they also serve

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Georgia G. Bagkavou

Georgia G. Bagkavou received her bachelor's degree from Aristotle University of Thessaloniki in 2020, spending the last semester as an exchange student at the University of Florence. In 2022, she obtained her master's degree from Aristotle University of Thessaloniki and currently she is pursuing her doctorate under the supervision of Prof. Christos Stathakis at the same university. Her research is focused on the synthesis of natural products utilizing transition metal catalytic processes.

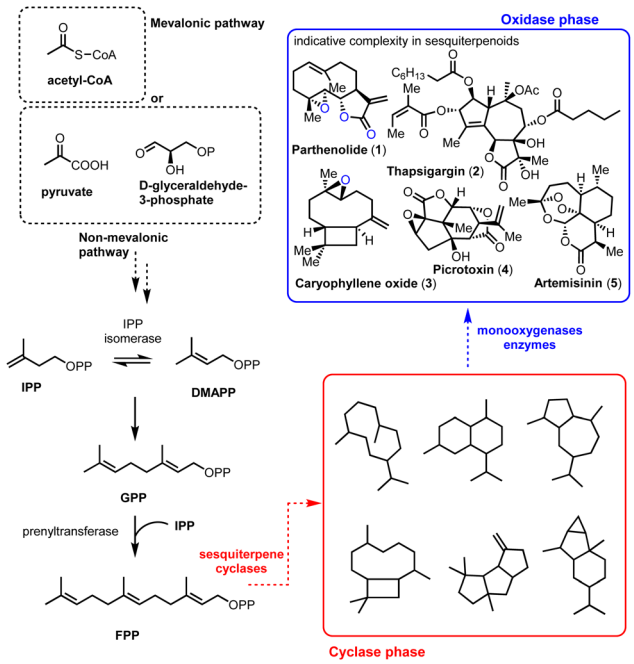

Fig. 1 Schematic representation of sesquiterpenoid biosynthesis.

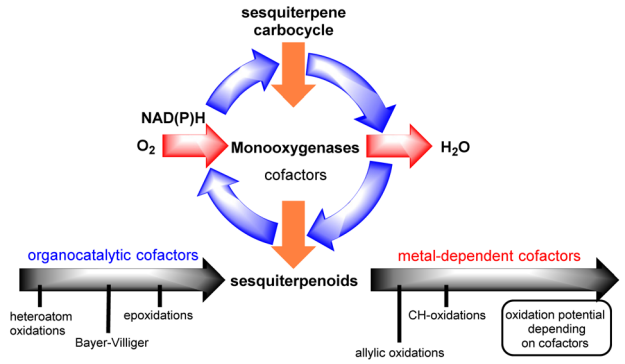

Fig. 2 Monooxygenase catalytic cycle for sesquiterpenoids.

as platforms to test the boundaries of total synthesis. A common molecular characteristic in many of the biologically important sesquiterpenoids is the richness of oxidative decoration that they possess. Methods to achieve selectivity in the oxidase phase, especially by their late-stage functionalization, are constantly gaining attention from the scientific community as powerful wide-scope prototypes for further applications.

Interestingly, successful methods towards this goal are commonly the ones that unlock and harness the biosynthetic information of 'natural-players', namely monooxygenase enzymes (Fig. 2).[2]

Monooxygenases are common enzymes used in the oxidase phase of sesquiterpenoids. They are usually associated with co-reductase enzymes (NADH, NADPH) and co-factors such as hemes, flavins, pterins *etc.* for the activation of dioxygen which is utilized as the terminal oxidant of the process. During this process, depending on the associated co-factors, monooxygenases can achieve the reduction of dioxygen to organo- or alternatively metal-superoxy- and hydroperoxy-species to oxidize alkenes, allylic and/or C–H positions.

Depending on sesquiterpenoid complexity, one can recognize three sites for potential oxidation: (i) alkenes, (ii) allylic positions and (iii) unactivated C–H bonds, including those that are involved in lactone functionality formation. In all cases, Nature seems to follow the same one-electron, radical logic to access them, utilizing monooxygenases with co-factors

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Christos I. Stathakis studied chemistry at Aristotle University of Thessaloniki (AUTH), where he also received his Ph.D. in organic chemistry in 2007. His postdoctoral experience (2008–2012) comprises appointments at the research groups of Prof. Snyder at Columbia University, Dr Vourloumis at NCSR Demokritos, and Prof. Knochel at Ludwig Maximillian University. For the next five years, Dr Stathakis worked as a research scientist at Pharmathen Pharmaceuticals, Greece. In 2018, he was elected as an assistant professor at the chemistry department of AUTH. The main interest of his research focuses on the total synthesis of constructively challenging molecules and the development of novel methodologies that promote structural complexity.

Alexandros L. Zografos

Alexandros L. Zografos graduated as a chemist in 1996 from National University of Athens. After earning his Ph.D. in 2001 at National Technical University of Athens, he pursued postdoctoral studies at The Scripps Research Institute and at Columbia University, before he moved back to Greece to work as a senior researcher first at National University of Athens and then at NCRS Demokritos Institute. In 2009, he began his independent career at Aristotle University of Thessaloniki. His group is working on the exploration of common synthetic strategies towards diverse natural molecular structures.

possessing the appropriate oxidative potential for each purpose. On the other hand, in laboratory synthesis commonly the polar logic prevails for such transformations with those of peroxides being more applied for the epoxidation of alkenes[3] and hydroboration for their hydration,[4] and selenium dioxide metal-allylic activation for allylic oxidations, with only scarce success for selective polar C–H oxidations.[5]

In this review, we focus on methods that harness one-electron potential to achieve 'oxidase' functionalization. The review does not intend to be an exhaustive collection of total syntheses utilizing radicals, but instead a selection of synthetic routes bearing the most selective oxidative pathways on the way to the total synthesis of sesquiterpenoids.[6] In this review no electrochemical methods and singlet oxygen oxidations are included and readers interested in these topics are advised to follow some excellent reviews.[7,8]

1.1. Monooxygenases and biomimetics in practice

Cytochrome P_{450} monooxygenases (CYPs) are mostly involved in the oxidative decoration of sesquiterpenoid carbocyclic cores contributing significantly to their structural diversity. Therefore, a brief introduction of their mechanisms will help underline the evolution of the existing oxidative methods used to access sesquiterpenoids. Their mechanism of action has been extensively studied.[9] It involves the initial binding of the substrate to the enzyme (**6**) followed by a one-electron transfer to the heme metal co-factor (**7**) (most commonly iron) independent of the class of CYPs used. The subsequent reduction of iron(III) to iron(II) initiates the activation of dioxygen to superoxide (**8**), followed by a second electron donation (**9**) and a double addition of protons to produce an iron(V) oxo-heme complex (**11**), responsible for the oxidation of the substrate (**12**) (Fig. 3A). The latter event is considered to involve, in its simplest form, the addition of the high valency metal-oxo PM═O species (**14**) to the alkene (**15**) (epoxidation, compound **16**, Fig. 3C) or the abstraction of a proton (in the cases of allylic oxidation and C–H oxidation) to produce caged radical intermediates (**I** and **II**, Fig. 3B). For H-atom abstraction, the rebound of high valency hydroxyl complexes provides substrate oxidation with retention of the configuration or stereochemical epimerization (**18** or **19**) in the cases where the radical escapes the cage or if the rebound energy is high.

Taking into consideration this biosynthetic knowledge, many groups focused on the development of biomimetic variants harnessing the synthetic potential of radicals in their design.

Thus, the points of interest (alkenes, allylic positions and C–H bonds) were tested in radical reactions for their ability to selectively deliver the 'oxidase phase'. The methods applied so far are not highly diverse and can be roughly divided into four classes: (i) photochemical Hofmann–Loffler–Freytag-type reactions and Suarez-modification; (ii) metal-catalyzed reactions; (iii) Mukaiyama-type hydrations; and (iv) stoichiometric metal oxidations.

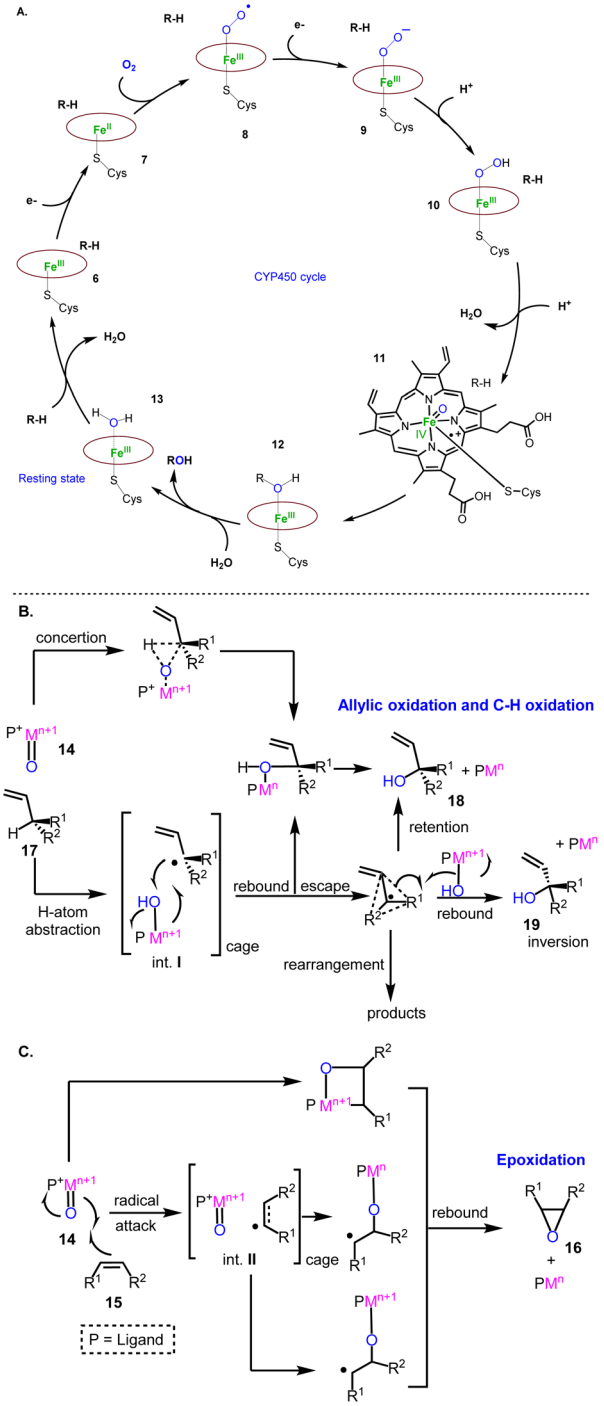


Fig. 3 General proposed mechanisms involved in monooxygenase oxidations. (A) Iron(v) oxo-heme complex; (B) Allylic and C-H oxidation; (C) Epoxidation mechanisms.

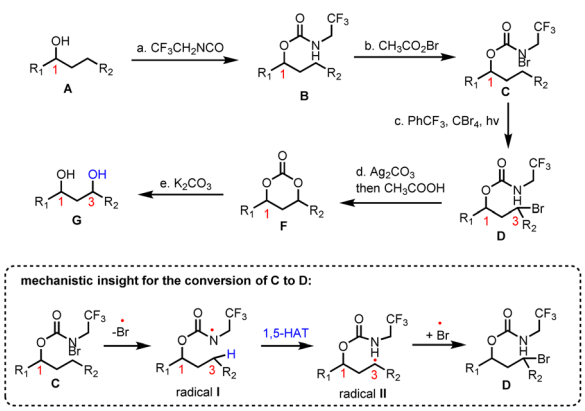
2. Hofmann–Loffler–Freytag (HLF) reaction–Suarez modification

The Hofmann–Loffler–Freytag (HFL) reaction was invented in the late 19th century and involves the photochemical generation of nitrogen-centered radicals from N–X bonds.[10] 1,5-

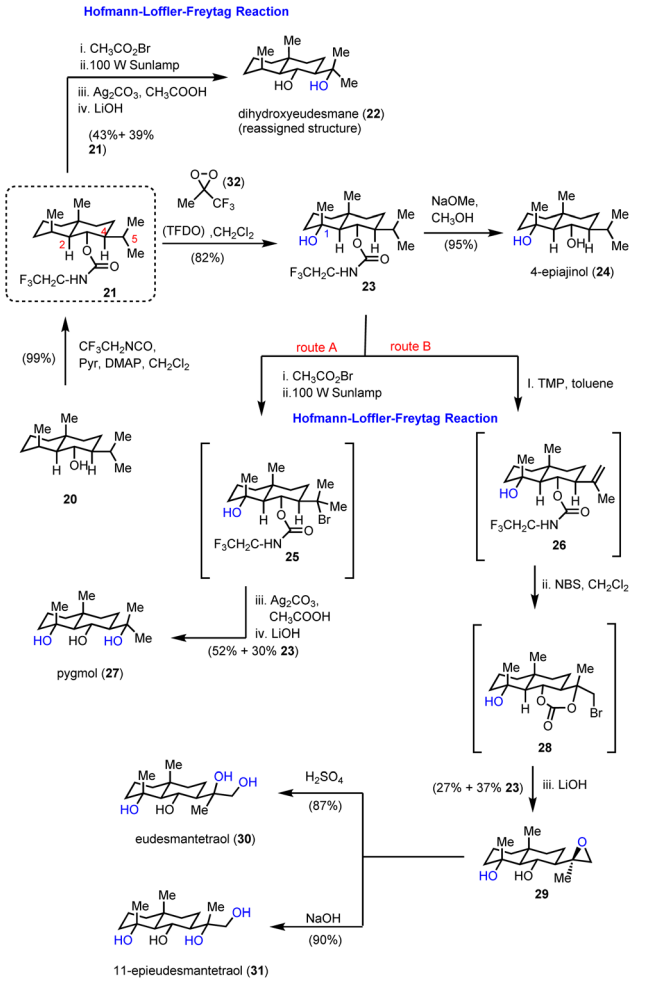
Hydrogen atom transfer (HAT) follows the radical generation to provide the requisite C–H activation for further functionalization. In its classic variant, the HFL reaction is used for the preparation of pyrrolidines and piperidines by the subsequent cyclization of halo-amines. The modification by Suarez enabled the reaction to be extended to O–X bonds by utilizing hypervalent iodine compounds followed by the photochemical cleavage of O–X bonds to deliver mostly ethers. The latter represents a powerful method for the C–H oxidation of sesquiterpenoids.

2.1. Eudesmanes (Baran's group)

Inspired by the HLF reaction, Baran and co-workers developed a method to convert alcohols **A** to 1,3-diols **G** *via* a photochemically initiated intramolecular radical hydrogen atom transfer from an appropriately bromo activated trifluoroethyl-substituted carbamate (**C**) (Scheme 1).[11] The latter allows the formation of iminocarbonates in the presence of Ag_2CO_3, which can be readily hydrolyzed by acetic acid and K_2CO_3 to provide 1,3-diols. This concept has been successfully applied to an impressive highly selective divergent synthesis of eudesmane sesquiterpenoids: 4-epiajanol (**24**), dihydroxyeudesmane (**22**), pygmol (**27**) and eudesmantetraol (**30**) (Scheme 2).[12] Accordingly, dihydrojunenol (**20**), representing the end point of the cyclase phase and the common synthetic intermediate for this divergent synthesis, was accessed in a gram scale quantity *via* a 9 step sequence in 21% yield and was transformed to its trifluoroethyl carbamate counterpart **21** (Scheme 2).[13] The latter, apart from its projected participation in the HFL-type reaction for the installation of hydroxyl moieties, served also the purpose of depleting the electron density from neighbouring carbon atoms (C-2 and C-4) to deactivate them during the electrophilic C–H activation event. The gram scale oxidation of **21** at C-1 to **23** was selectively achieved by Curci oxidation with TFDO in 82% yield.[14] This impressive selectivity between the five electronically similar tertiary positions in this scaffold was explained on the basis of carbon nucleophilicity, steric strain and strain release. In particular, the observed non-expected selectivity between the C-5 position



Scheme 1 Method to achieve 1,3-diols utilizing a modified HFL reaction.



Scheme 2 Divergent synthesis of eudesmanes based on the HLF oxidation protocol (Baran's group).

(more nucleophilic and less sterically strained) which is more prone to electrophilic oxidation and the obtained oxidation product at the C-1 position can be attributed to the high strain energy release of the latter in the transition state formation.[15] The hydrolysis of trifluoroethyl carbamate in **23** allowed the total synthesis of 4-epiajanol (**24**). Demonstrating the power of their radical 1,3-diol protocol in both **21** and **23** allowed them to access dihydroxyeudesmane (**22**) and pigmol (**27**) in 43% and 52% yields, respectively, after photochemical bromination, iminocarbonate formation and hydrolytic cleavage. Additionally, further oxidative manipulations provided the total syntheses of tetraols eudesmanotetraol (**30**) and 11-epieudesmantetraol (**31**).

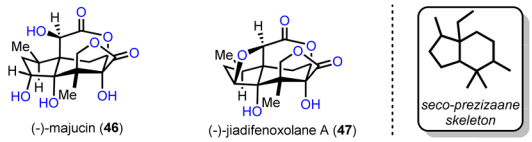
2.2. Asteraceae guaianolides (Zografos' group)

In 2021, Zografos' group demonstrated the ability of a modified Suarez reaction to elaborate the biologically important sesquiterpenoid scaffolds α-methylene-γ-lactones.[16] The group highlighted the efficiency of the method in the synthesis of the common scaffold **36** that served as a multipurpose intermediate for total syntheses and for accessing sesquiterpenoid

core structures (Scheme 3).[17] More specifically, acrylic acid **34** reacts with PIDA and iodine to form intermediate **35**, which can be photochemically cleaved to provide a long-lived carboxyl-radical able to initiate a 1,5-hydrogen atom transfer to the respective iodide (structure not shown). The latter is readily cyclized under the reaction conditions to allow the synthesis of **36** in 45% yield (78% brsm). Interestingly, despite the higher acidity of C-6 than that of C-8, only 8,12-lactone has been observed under these conditions. In contrast, α-ketone halogenation, performed under light or radical initiators, resulted only in the formation of 6,12-lactone, proving the essential participation of the carboxyl moiety in the radical event. Faster hydrogen atom transfer from the allylic position (lower energy of allylic radicals) ensures the chemoselectivity of the process. Compound **36** was then selectively alkylated to **37** followed by Martin's sulfurane dehydration to provide **38** and the sulfur-ylide **39**. Subsequent alkylation of both resulted in **41a and b** and **43** that served as points of divergence to access germacranolides and guaianolides through oxy–Cope reactions[16] and furo sesquiterpenoids by cycloisomerizations.[17] Worth mentioning is the ability of sulfur-ylides to serve as convenient precursors for C-6 oxidation.

2.3. (−)-Majucin and (−)-jiadifenoxolane A (Maimone's group)

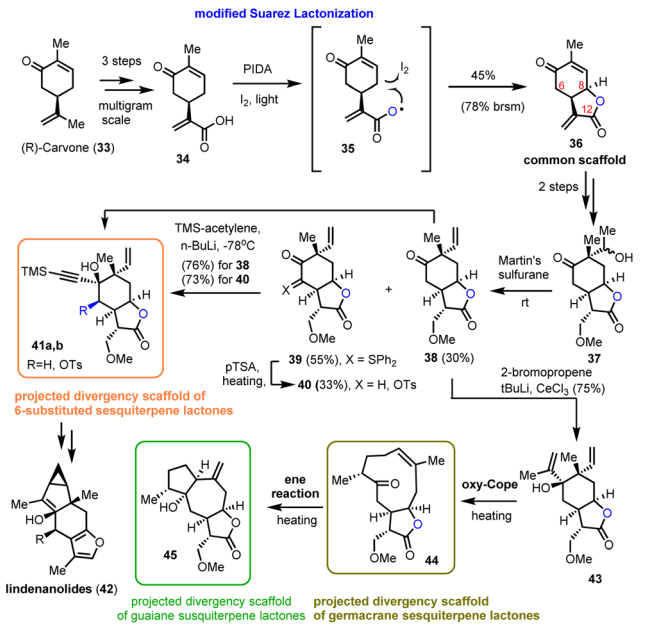
Two distinct Suarez reactions were among the ten net oxidation events involved in the chemical synthesis of (−)-majucin (**46**) and (−)-jiadifenoxolane A (**47**), reported by Maimone's group in 2017.[18] The latter natural products are distinguished members of the seco-prezizaane subtype of *Illicium* sesquiterpene family, the key core of which is presented in Scheme 4. Specifically, (−)-majucin (**46**) is one of the most highly oxidized members,



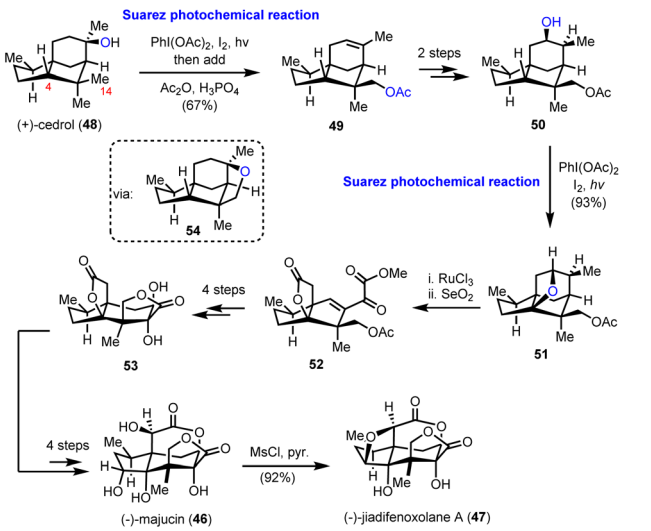
Scheme 4 Seco-prezizaane-type *Illicium* sesquiterpenoids.

and although it was isolated about thirty years ago, its total synthesis had not been achieved before the impressive work by Maimone and his co-workers.[19] Its sophisticated architecture features a bridging δ-lactone and a γ-lactone, in proximity with four other hydroxylated sites.

The elegant synthetic endeavor was based on the easily accessible (+)-cedrol (**48**) as the feedstock material, which was subjected to Suarez photochemical conditions to activate selectively the equatorial methyl in the nearby *gem*-dimethyl moiety (intermediate **54**, Scheme 5). The observed selectivity was attributed to the favorable positioning of the C-14 C–H bond with respect to the hydroxyl group, due to the favorable entropic factor of a 1,5-hydrogen atom transfer (1,5-HAT) compared to a 1,6-HAT event that implies the activation of hydrogen at C-4. Opening of the tetrahydrofuranyl ring in **54** led to alkene **49** in 67% combined yield for the two successive transformations. Working on alkene **49**, in another two trivial chemical steps, alcohol **50**, with a stereo-defined hydroxyl substituent on the six-membered ring, was obtained. The latter was a suitable substrate for a second Suarez oxidation event to selectively oxidize the C-4 position with impressive efficiency (93% yield) (Scheme 5). Again, the observed selectivity can be explained by the advantage of the 1,5-HAT event compared to the 1,6 one. To capitalize on this entropic difference between the two hydrogen transfers, the selection of the protection group on the C-14 hydroxyl group proved pivotal. As smoothly illustrated by Maimone's group in a subsequent report,[20] protection of



Scheme 3 Early lactonization with a modified Suarez reaction to access diversity in sesquiterpenoids (Zografos' group).



Scheme 5 Multiple oxidative manipulations to illicium sesquiterpenoids **46** and **47** (Maimone's group).

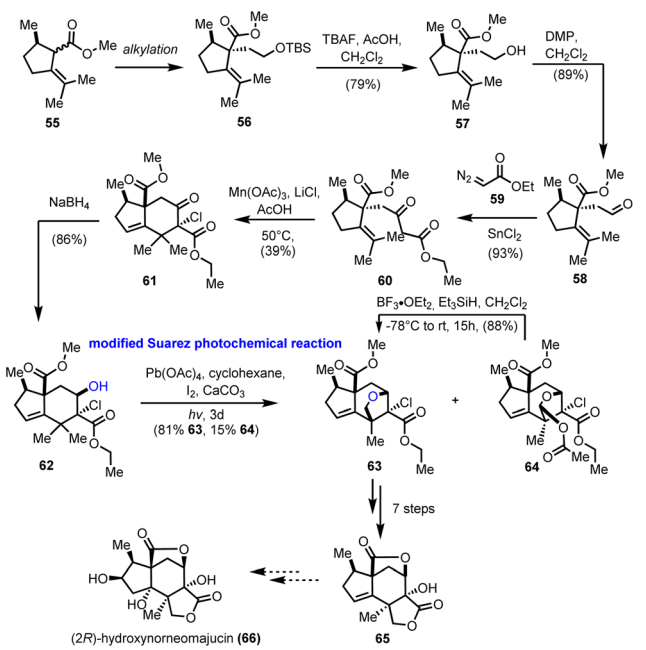
the C-14 hydroxyl group by a methyl ether resulted in a reversal of the preference due to the substantial weakening of the C–H bond in the α-position to an ether, compared to that of an ester. Additional oxidations including a ruthenium catalyzed scission of the six-membered ring led to intermediate **52**, and then to lactone **53**, after selective hydroxylation with DMDO and adjustment of the oxidation state of the molecule. Further delicate manipulations, involving, among others, stereoselective enolate hydroxylation, ruthenium catalyzed free alcohol isomerization and conventional OsO_4 catalyzed dihydroxylation, led to (−)-majucin (**46**). (−)-Jiadifenoxolane A (**47**) was accessed from the latter, after careful activation of the less hindered secondary alcohol and intramolecular displacement by the α-hydroxyl group of *δ*-lactone in 92% yield.

2.4. Seco-prezizaane type sesquiterpenes (Gademann's group)

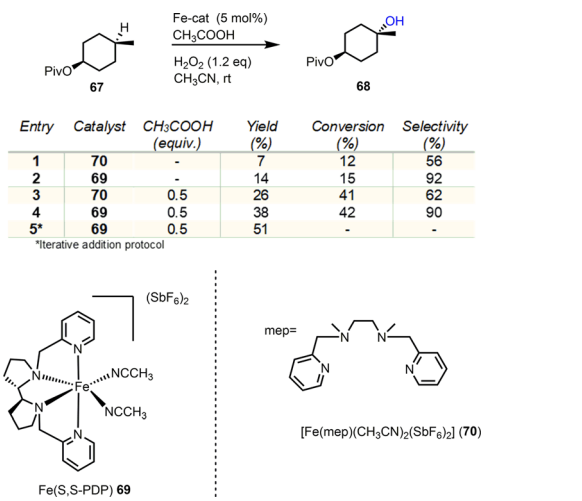
The seco-prezizaane sesquiterpenes have been the center of interest for many other synthetic endeavors. At around the same time as Maimone's group, the work of Gademann and his co-workers on the preparation of the main scaffold of seco-prezizaanes was presented (Scheme 6).[21] Starting from enantiopure (*R*)-pulegone, intermediate **55** was obtained as a mixture of diastereomers by a known procedure.[22] Alkylation of the latter, followed by typical FGI and Roskamp reaction[23] led to enantiopure β-ketoester **60** in a high overall yield. Subsequent free radical cyclization to alkene **61** was realized with moderate efficiency using $Mn(OAc)_3$ in the presence of LiCl. Diastereoselective reduction of the ketone functionality provided the desired stereoisomer of alcohol **62**, bringing the hydroxyl group in proximity to one of the nearby methyl groups on the six-membered ring. At this point, the ground for a successful Suarez oxidation was laid, a transformation that was realized in excellent yield 81%, using modified conditions ($Pb(OAc)_4$) for the generation of the initial O-centered radical.[24] Along with the desired ether **63**, an overoxidized protected acetal **64** was formed in 15% yield, which could, ideally, be converted reductively to ether **63**, thus increasing the overall efficiency of the reaction. Applying conventional chemical transformations, compound **63** was converted to the advanced intermediate **65**, which is regarded as a common precursor to various members of the seco-prezizaane sesquiterpene family. In particular, the authors suggested certain modifications on the five-membered ring of **65** to gain access to (2*R*)-hydroxynorneomajucin (**66**); however, no experimental proof has been provided.

3. Metal catalyzed C–H oxidations

Selective oxidation of C–H bonds is a major challenge in organic synthesis. The multitude of applications and selectivity provided by natural oxygenases, especially in the cyclase phase of terpenoids, has been the determinant for the development of biomimetics. Non-heme iron and manganese catalysts bearing tetradentate N_4 ligands are of exceptional importance as biomimetics allowing the efficient, stereospecific hydroxylation of C–H bonds by utilizing H_2O_2 as the oxidant in the process.[25] The mechanisms of these processes collectively follow the heme-iron mechanism (see Fig. 3A), utilizing high valency metal-oxo species to perform hydrogen abstraction from the hydrocarbon with the incipient alkyl radical to rebound with the nascent Fe–OH moiety to provide the hydroxylated product.[26] In 2007, a seminal report by White's group described the non-heme iron complex **69** of the tetradentate PDP ligand as an efficient, selective and most importantly predictable catalyst for the hydroxylation of hydrocarbons (Scheme 7).[27]



Scheme 6 Synthesis of core structure of seco-prezizaane-type sesquiterpenoids (Gademann's group).



Entry	Catalyst	CH_3COOH (equiv.)	Yield (%)	Conversion (%)	Selectivity (%)
1	70	-	7	12	56
2	69	-	14	15	92
3	70	0.5	26	41	62
4	69	0.5	38	42	90
5*	69	0.5	51	-	-

*Iterative addition protocol

Scheme 7 Seminal report by White's group for the preparative C–H oxidation of alkanes.

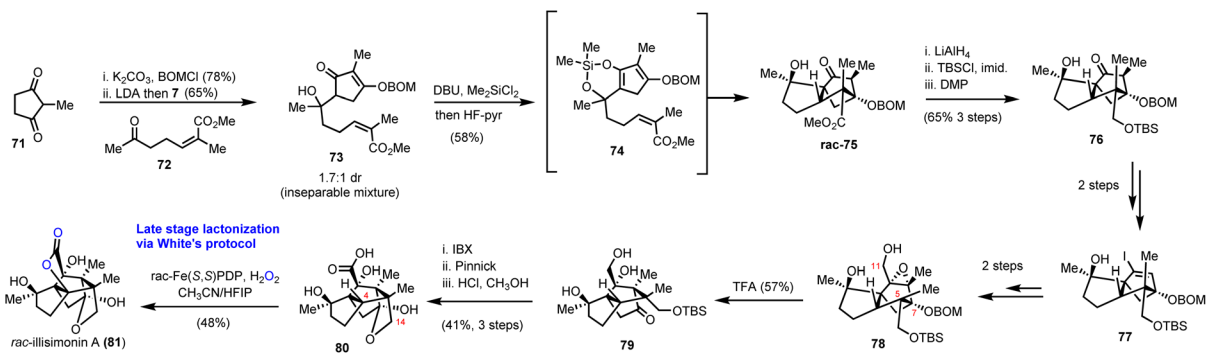
In their report, they demonstrate that the electronic and steric properties of C–H bonds can effectively provide prediction for the sites of oxidation, regarding any directing groups. Later, Baran and Eschenmoser added the strain release in the transition state formation of the C–O bond as an effective factor for C–H oxidation prediction.[15] Additionally, under this catalytic protocol, White's group demonstrated the utilization of carboxyl groups as directing groups to allow the predictable formation of lactones under mild conditions. Based on these findings, several similar catalysts have been developed utilizing the same electrophilicity logic to direct oxidations in more nucleophilic, less sterically hindered positions. In all cases, equatorial hydrogens are more amenable for abstraction and C–H activation due to their enhanced strain release in the transition state formation.

3.1. Illisimonin A (Rychnovsky's group)

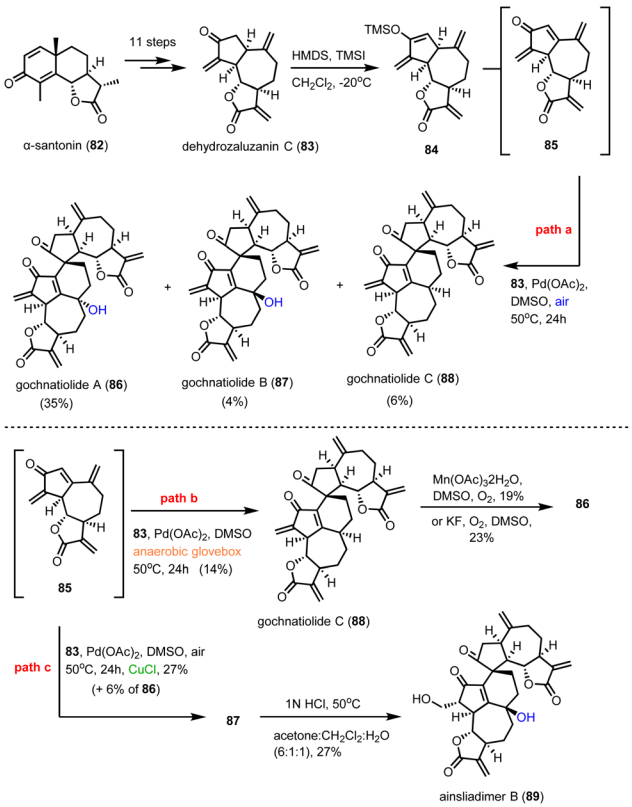
Illicium sesquiterpenoids are common templates in modern organic synthesis and challenge chemists' creativity. Illisimonin A is a member of the class isolated from *Illicium simonsii* with an unprecedented tricyclo[5.2.1.0^{1,6}] decane carbon framework.[28,29] Illisimonin A displays neuroprotective effects against oxygen-glycose deprivation-induced cell injury in SH-SY5Y cells.[28] The first total synthesis of illisimonin A, reported by Rychnovsky's group, relied on a highly diastereoselective intramolecular Diels–Alder (IMDA) reaction for the synthesis of the congested carbocycle **75** from the *in situ* prepared silacycle **74** (Scheme 8).[28] The latter was readily prepared from an aldol reaction between protected **71** and **72** followed by silylation. The silacycle which stabilizes the enol-diene was warmed to 40 °C to initiate the IMDA reaction producing the five stereocenters and two rings of **75** in 58% yield in a single synthetic step. Functional group interconversions (FGI) followed by introduction of C-11 and epoxide formation led to compound **78**. An impressive semipinacol rearrangement follows after acidic deprotection to produce **79** bearing the correct trans-pentalene core for the natural product. Sequential oxidation of the primary alcohol to the acid followed by deprotection led to **80**. At this point, a lactone moiety at C-4 was missing to address the natural complexity. This especially difficult challenge was addressed in 48% yield by late stage functionalization utilizing White's catalyst Fe(S,S)(PDP) **69** with the aid of hydrogen peroxide as the terminal oxidant of the process. The reaction was performed in an acetonitrile/HFIP mixture to avoid the overoxidation to lactol at C-14 through hydrogen bonding deactivation of the alcohol by HFIP.

3.2. Gochnatiolides A–C and ainsliadimer B (Lei's group)

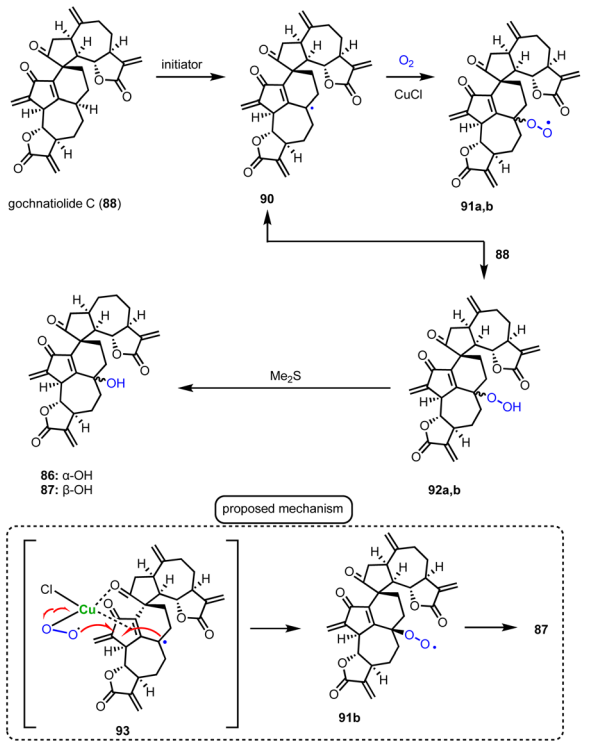
Guainolide dimers represent a highly complex class of sesquiterpenoid natural products. Members of this class exhibit potent biological profiles as anticancer, anti-inflammatory and anti-HIV agents.[30] Gochnatiolide A–C (**86–88**) and ainsliadimer B (**89**) are characteristic natural products of this class and despite the rather obvious Diels–Alder reaction as the origin of their dimerization, significant challenges still exist in exploring their biomimetic routes (Scheme 9). In 2012, Lei's group developed a biomimetic divergent plan for their synthesis starting from the proposed natural monomeric congener **83** (Scheme 9).[31] The monomer was previously synthesized in an 11-step sequence starting from α-santonin.[32] Based on previous studies of the same group demonstrating the BINOL-promoted homodimerization of **83** to (+)-ainsliadimer A,[32] they explored the feasibility of a biomimetic cross-coupling between **83** and its oxidized congener **85**, formed by the Saegusa oxidation. *In situ* preparation of **85** from silyl enol **84** with $Pd(OAc)_2$ in DMSO and air in the presence of an excess of **83** to avoid the homodimerization of **85** was selected, to provide **86–88** in 35%, 4% and 6% yields, respectively. Interestingly, strict exclusion of dioxygen from the reaction mixture resulted only in the formation of **88** in 14% yield, suggesting the participation of dioxygen for the late stage allylic oxidation event. Indeed, when **88** was allowed to react under radical conditions either with $Mn(OAc)_3$ or KF in the presence of dioxygen it led to the selective formation of **86** in 19% and 23% yields, respectively. On the other hand, when the oxidation of **85** was performed in the presence of a catalytic amount of $CuCl_2$, a preference for the formation of gochnatiolide B was observed delivering **87** in 27% yield and reversed ratio of products **86 : 87** from 6.6 : 1 (KF) to 1 : 4.5 ($CuCl_2$). For the latter, a monomeric Cu(II)-peroxo-species was proposed to interact with carbonyl at C-3′ to deliver selectively



Scheme 8 Total synthesis of illisimonin A (Rychnovsky's group).



Scheme 9 Biomimetic synthesis of gochnatiolides (Lei's group).

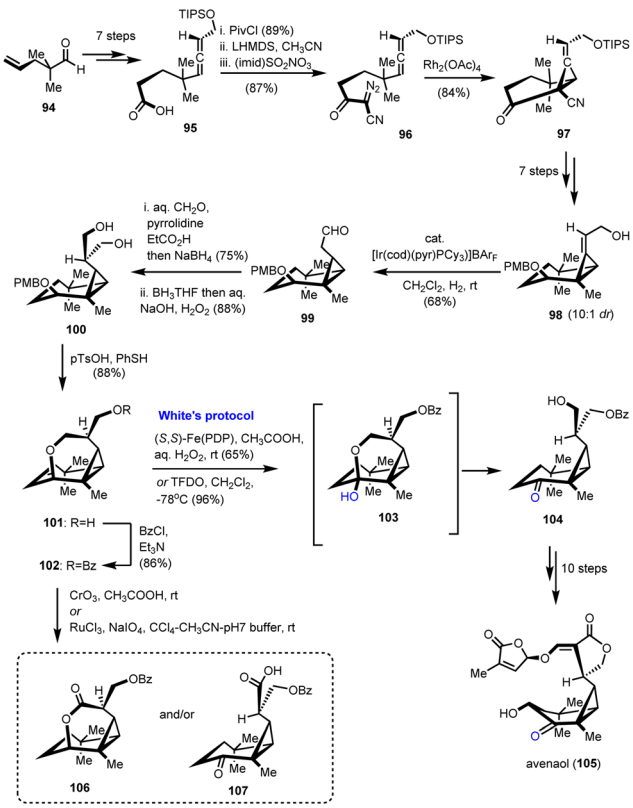


Scheme 10 Postulated mechanism for aerobic oxidation.

the hydroperoxy-group from the β-face (see transition state **93**) (Scheme 10). Finally, hydration of **87** by 1 N HCl in a 6 : 1 : 1 acetone/DCM/H_2O solvent mixture allowed the synthesis of ainsliadimer B (**89**) in 27% yield.

3.3. Total synthesis of avenaol (Takemoto's group)

Strigolactones are sesquiterpenoid plant hormones that play a pivotal role in the response of plants to various biotic and abiotic stresses.[33] Avenaol (**105**) which was isolated from the allelopathic plant black oat is the first C20 germination stimulant that was found to be related to strigolactones (Scheme 11).[34] As part of the extreme synthetic challenge of the target, Takemoto's group utilized C–H oxidation as a way to differentiate similar hydroxyl moieties in their synthetic endeavour.[35] According to them, avenaol possessing a challenging all-*cis*-cyclopropane ring and six stereogenic centers was derived from the substituted diazo-allene compound **96** through rhodium-catalyzed carbene cyclopropanation (Scheme 11). This method was selected on the basis of all-*cis*-cyclopropane sensitivity to decomposition and easy formation of caged-type compounds. Precursor **96** was prepared from **95**, which in turn was delivered in a 7-step sequence from a known aldehyde **94**. Reaction of **95** to the mixed anhydride followed by the nucleophilic attack by acetonitrile resulted in β-cyanoketone amenable for diazo-introduction. The latter was achieved using the imidazole-1-sulfonyl-azide hydrochloride diazo-transfer reagent to provide compound **96**.



Scheme 11 Total synthesis of avenaol by C–H assisted desymmetrization of a diol (Takemoto's group).

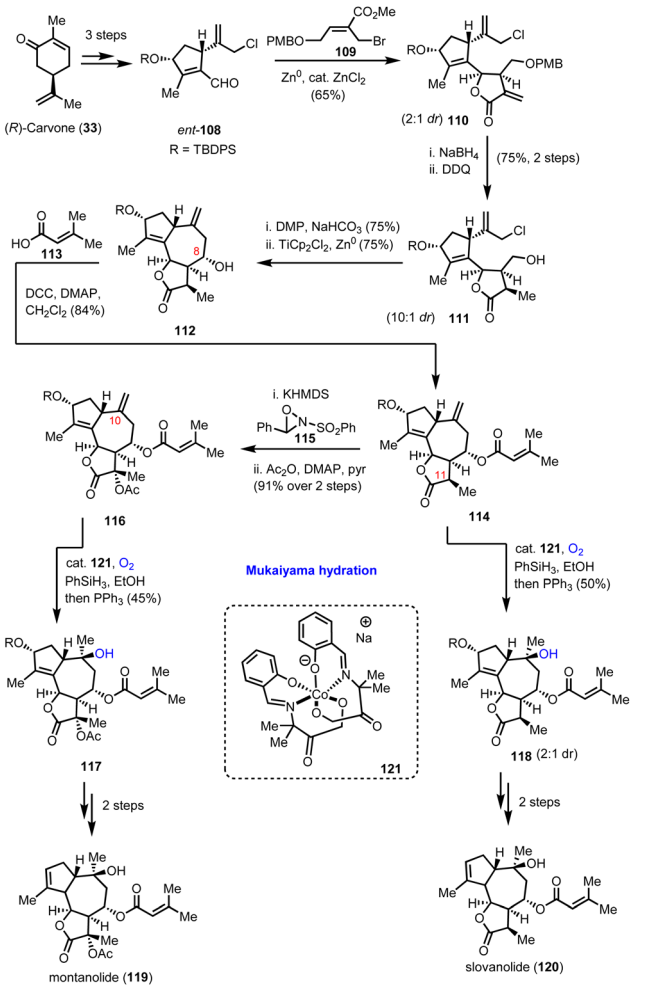
Cyclopropanation with the aid of $Rh_2(OAc)_4$ followed to deliver **97** in 84% yield. Attempts to prepare the all-*cis* cyclopropane by direct reduction of the alkene moiety failed and the authors appropriately transformed **97** to **98** to succeed in their goal by hydroxyl-directed iridium-catalyzed isomerization of cyclopropyl alkene to compound **99**. With all-*cis* cyclopropane in hand, the next challenge was to install the lactone ring. Further FGI led to the introduction of the hydroxymethyl group to the aldehyde to form compound **100**. The diol functionalization using **100** was envisioned to give the ideal precursor of the lactone moiety if the differentiation of the hydroxyl groups were feasible. To address this challenge, the pendant hydroxyl was cyclized to the six-member ring of **101** followed by a subsequent protection of the free hydroxyl to **102**. A C–H oxidation was designed to cleave the pyrane ring back to the free alcohol. Several C–H oxidations were tried to deliver in most cases byproducts **106** and **107**. Interestingly, stoichiometric utilization of White's catalyst in the presence of hydrogen peroxide resulted in the selective formation of **104** in 65% yield. Further improvement of reaction yield using TFDO led to **104** in 96% yield. Ten reactions that followed completed the first total synthesis of avenaol (**105**).

4. Mukaiyama hydration

A common way to circumvent the challenging C–H oxidation in unsaturation-rich substrates such as sesquiterpenoids is by the direct oxidation of alkene moieties. Epoxidations and hydrations are part of the synthetic routine in terpenoid total synthesis. Sharpless epoxidation[3] and Brown hydroboration[4] provide reliable access to oxidized compounds but in some cases, further synthetic steps are needed to introduce the requisite hydroxyl functionality. Direct functionalizations allow for simpler retrosyntheses avoiding the protection–deprotection stages. Toward this end, use and advancement of radical hydrations was recently reconsidered in complex molecular settings. Radical Markovnikov additions, based on the seminal reports of the Mukaiyama hydration protocol,[36] provide a reliable access to the hydroxyl functionality. The method relies on the formation of metal hydrides (usually Co (II)) for initial alkene hydrometallation followed by dioxygen oxidation. The method has inspired several approaches for hydrogen atom transfer-initiated C–C formation,[37] alkene transposition[38] and multi-oxidation processes.

4.1. Montanolide and slovanolide (Maimone's group)

In 2019, Maimone's group reported a series of total synthesis of complex guaianolides from *Apiaceae* and *Asteraceae* families.[39] The divergent synthetic routes heavily relied on radical Mukaiyama-type chemistry for the introduction of their 'oxidase-phase' complexity. Synthesis of highly functionalized cyclopentene **108** and its enantioisomer *ent*-**108** from carvone enantiomers in gram scale quantities in 3 synthetic steps served as the starting point of their divergent plan (Scheme 12). A double reductive allylation protocol was found



Scheme 12 Total syntheses of montanolide and slovanolide guaianolides which relied on Mukaiyama hydration (Maimone's group).

amenable for accessing the rich stereoselectivity possessed by guaianolide cores in both *Asteraceae* and *Apiaceae* families by just altering the allylation conditions between aldehydes **108** and appropriately substituted allylbromides of type-**109**. In *Apiaceae*, Zn^0-mediated allylation was selected followed by $ZnCl_2$ to provide 65% yield of **110** as a 2 : 1 diastereoisomeric mixture favouring the desired stereochemistry for the synthesis of slovanolide (**120**) and montanolide (**119**) natural products (Scheme 12). The presence of catalytic $ZnCl_2$ was found essential to promote cyclization to the requisite lactone. Alkene reduction, followed by deprotection of the PMB group and subsequent oxidation set the stage for the second reductive allylation event which was accomplished by $TiCp_2Cl_2$ and Zn^0 to result in compound **112**. Extensive experimentation was required to develop the appropriate conditions to achieve the correct stereochemistry at C-8 in 75% yield and 10 : 1 diastereoisomeric ratio. Acylation provided the complete carbocycle **114** for both natural products, where the oxidative decoration is partially missing. To address it, the group selected Mukaiyama hydration for the hydroxylation of the C-10 posi-

tion, utilizing catalyst **121** in the presence of $PhSiH_3$ under dioxygen. Compound **118** was delivered in 50% yield and 2 : 1 diastereoisomeric ratio. Subsequent deprotection of the secondary alcohol followed by reductive transposition of the alkene furnished slovanolide (**120**). The more oxidized congener montanolide (**119**) was achieved under similar conditions after the introduction of the acetyl functionality at C-11 with Davis oxaziridine.

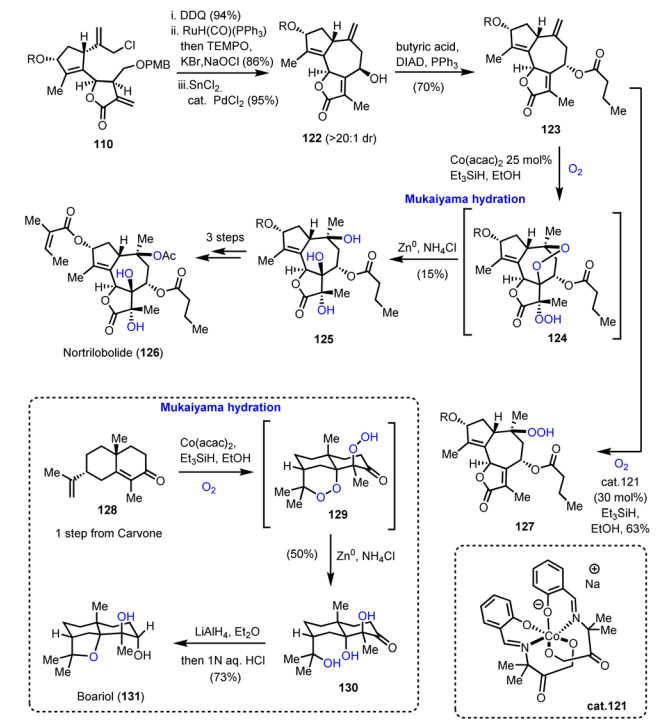
4.2. Notrilobolide, boariol (Maimone's group)

Utilizing the same common scaffold **110**, Maimone's group also succeeded in the synthesis of nortrilobolide **126** (Scheme 13).[39] The exocyclic double bond was isomerized using $RuH(CO)(PPh_3)_3$ following a similar reductive allylation to furnish **122** in high diastereoselectivity. Mitsunobu epimerization and acylation provided compound **123** which served as an ideal template for a multi-oxidation event producing the correct stereochemistry for three tertiary hydroxyls. In accordance with that, when **123** was allowed to react under the classic Mukaiyama conditions, a cascade was initiated to produce a diperoxy-intermediate **124** which was reductively cleaved to produce **125** as a single diastereoisomer. The event invoked the HAT from the [Co–H] complex to initiate a radical at C-10 followed by dioxygen introduction. The formed superoxide cyclized to C-7 to form a peroxy-bridge and a radical that was trapped by dioxygen. Despite its low yield (15%), this impressive transformation unlocks a potential biosynthetic pathway towards these polyoxidized natural products. Screening of different conditions failed to optimize the yield but provided interesting insights on the reaction mechanism. Interestingly, when cobalt complex **121** was used, compound **127** in 63% yield (Scheme 13) was obtained.

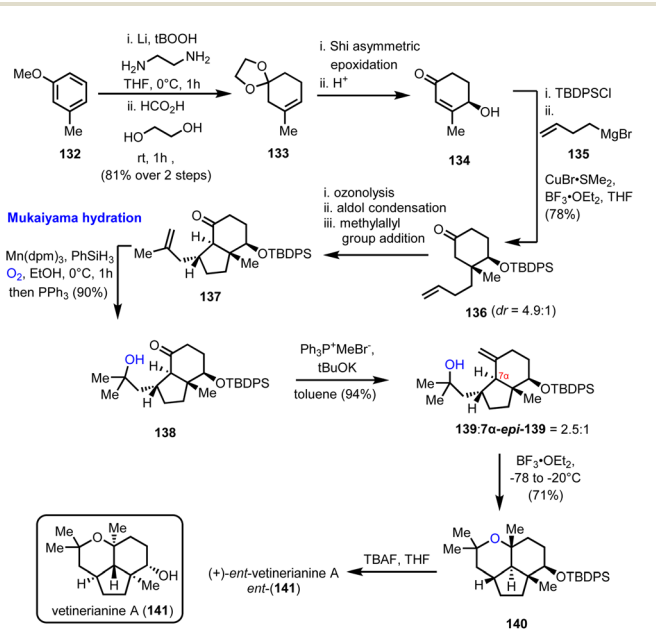
These insights allowed the three-step total synthesis of boariol (**131**) from compound **128**. Mukaiyama hydration at **128** resulted in compound **130**, which after reduction provided the natural product stereoselectively.

4.3. (+)-*ent*-Vetiverianine A (Sugita's group)

Mukaiyama hydration is the protocol of choice for the formation of a critical advanced intermediate *en route* to the 2,2,6,6 tetrasubstituted tetrahydropyrane ring found in vetiverianine A (**141**) (Scheme 14). Vetiverianines are novel sesquiterpenoids isolated in 2016 from vetiver oil, obtained *via* steam distillation of *Vetiveria zizanioides* roots, and exhibit cytotoxic activity against HL-60 cells and their full biological profile is still under investigation.[40] Their distinctive 5/6/6 tricyclic ring system that encompasses a highly congested tetrahydropyrane makes their total synthesis challenging. The first synthesis of the enantiomer of the natural product (*ent*-**141**) to be reported was by Sugita's group in 2022, which made use of the inexpensive 3-methoxytoluene (**132**) as the starting material (Scheme 14).[41] Birch reduction and acetalization led to trisubstituted alkene **133** and from there to enantioenriched cyclohexenone **134**, employing a Shi asymmetric epoxidation and acidic treatment of the resulting epoxide. Steric interactions drove the subsequent conjugated addition of γ-butenyl Grignard reagent stereoselectively from the α-face of the protected enone giving ketone **136**. Ozonolysis and aldol condensation led to the formation of the second ring of the system, while it also set the stage for a second stereo-controlled conjugated addition of the methylallyl group with the correct relative configuration. The product of this sequence of events, inter-



Scheme 13 Mukaiyama-type hydration cascade for the synthesis of notrilobolide and boariol (Maimone's group).



Scheme 14 Total synthesis of *ent*-vetiverianine A (**141**) (Sugita's group).

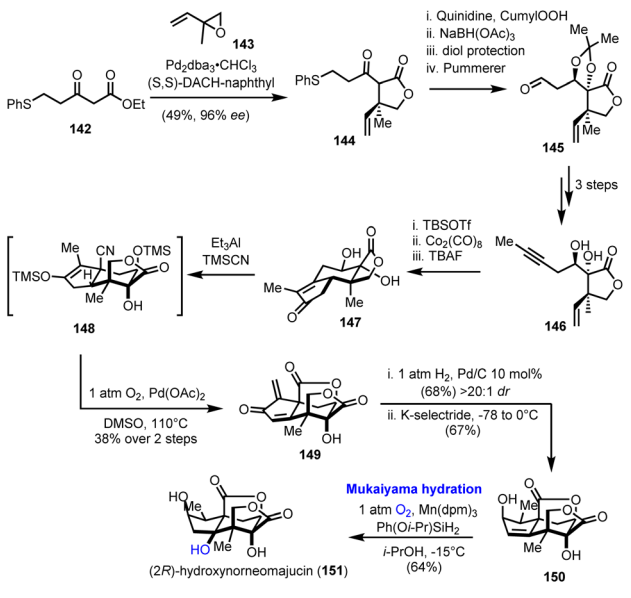
mediate **137**, was the substrate for a Mukaiyama hydration, which was realized in excellent yield (90%), using the sterically hindered $Mn(dpm)_3$ as the catalyst of choice, instead of the conventional $Co(acac)_3$ catalyst, providing access to the tertiary alcohol **139**. The critical cyclization to the tetrasubstituted tetrahydropyranyl ring, which completed the synthesis of the enantiomer of the natural product (after deprotection), was accomplished using $BF_3{\cdot}OEt_2$ at a low temperature.

4.4. (2*R*)-Hydroxynorneomajucin (Rychnovsky's group)

A regio- and stereoselective Mukaiyama hydration was the final step in the first total synthesis of (2*R*)-hydroxynorneomajucin (**151**), reported by Rychnovsky's research team in 2022 (Scheme 15).[42] The latter sesquiterpene belongs to the seco-prezizaane family of terpenes derived from the *Illicium* genus of flowering plants. Among other interesting highly oxidized natural products of the same origin, many of which are presented in the context of this review, (2*R*)-hydroxynorneomajucin holds a special position as its structure remained resistant to chemical synthesis although it had been known for more than ten years.[43] Some early studies from Gademann and his co-workers on the seco-prezizaane scaffold, analysed in Section 2.4 of this manuscript, remained incomplete.[21]

In Rychnovsky's asymmetric synthesis, which assumes prominent importance for the introduction of chirality, a palladium catalyzed asymmetric allylation of β-ketoester **142** afforded γ-lactone **144** in excellent enantioselectivity (96% ee), using Trost's ligand (Scheme 15).[44] A sequence of stereoselective hydroxylation and reduction of ketone, protection and a Pummerer rearrangement led to aldehyde **145** and eventually to alkyne **146**, after a Seyferth–Gilbert homologation of aldehyde to alkyne, methylation and acetal cleavage. A Pauson–Khand reaction on protected **146** formulated the tricyclic enone **147**. Stereochemical considerations on the manipulation of the five-membered carbocycle in **147** proved quite interesting.

Direct hydrocyanation on the enone moiety resulted in the wrong configuration of the α-methyl group, an issue that was elegantly addressed employing a Segusha–Ito oxidation to exo-methylenic ketone **149** and subsequent catalytic hydrogenation to install the methyl group from the desired face of the ring. Stereoselective 1,2-reduction of the produced enone generated the corresponding alcohol leaving behind trisubstituted alkene **150**. Despite the increased complexity of the latter, the anticipated Markovnikov hydration of the double bond was performed in satisfactory yield, 64%, and with excellent regio- and stereoselectivity applying $Mn(dpm)_3$/$Ph(Oi\text{-}Pr)SiH_2$ as the catalytic system. The role of the selected reductant was essential for the successful outcome of the conversion and the completion of the synthesis.



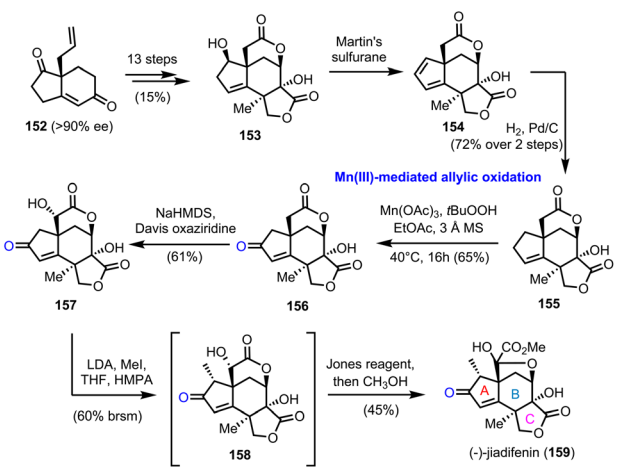
Scheme 15 Total synthesis of (2*R*)-hydroxynorneomajucin (**141**) (Rychnovsky's group).

5. Stoichiometric metal oxidants

The ability of certain non-precious metals to trigger radical generation upon organic molecules has offered valuable solutions for the synthetic community, especially, those involved in the synthesis of terpene natural products. Mn and Cr, in various oxidation states, hold a special position, and their reagents have proved to be unique in succeeding where other protocols have failed. Despite their high toxicity, mainly of the Cr(VI) based oxidants, their stoichiometric use in various synthetic endeavors appeared indispensable, as it is clearly demonstrated in the following examples.

5.1. (−)-Jiadifenine (Theodorakis' group)

In 2011 Theodorakis' group reported the first enantioselective route to (−)-jiadifenin (**159**) (Scheme 16), a potent neurotrophic agent isolated from *Illicium jiadifengpi*.[45] Their syn-



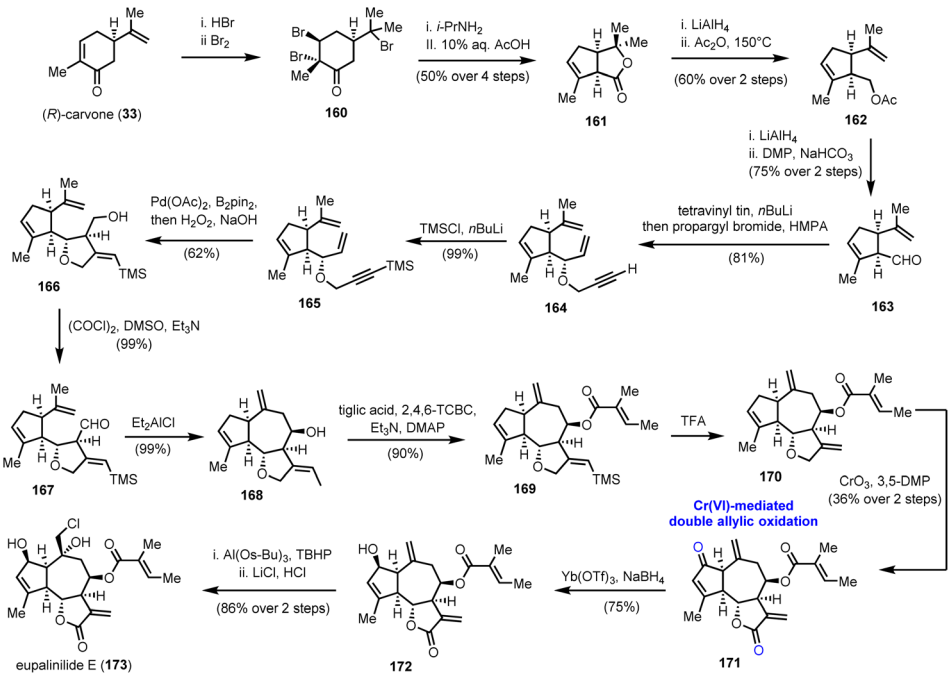
Scheme 16 First asymmetric synthesis of (−)-jiadifenin (**159**) (Theodorakis' group). The unique action of Mn(III) based reagents for the allylic oxidation of the A ring.

thetic approach was based on an advanced intermediate, tetracyclic lactone **153**, which was prepared in the context of jiadifenolide's (not shown) asymmetric synthesis, especially designed to offer diversification to other members of the family.[46] Compound **153** was prepared in 13 steps and 15% overall yield from bicyclic "*Hajos-Parrish-like*" diketone **152**, accessed by an asymmetric Robinson annulation in 90% ee (Scheme 16). Martin's sulfurane dehydration and selective hydrogenation of the more accessible double bond of the resulting diene afforded lactone **155**, the allylic oxidation of which was critical for the appropriate decoration of the A ring of the natural product. Several conditions were tested, including SeO_2, Cr(VI) based oxidants, hypervalent iodine reagents or transition metal catalysis (Pd and Rh), all of which were unable to bring about the desired oxidation. Gratefully, Mn(III) acetate proved to be unique for the selective activation of the allylic position and oxidized it in the presence of TBHP, providing enone **156** in 65% yield. The latter was converted to **159** after a regio- and stereoselective hydroxylation of the α-lactone position, which is more prone to enolization, methylation of the α-enone and Jones oxidation.

5.2. Eupalinilide E (Siegel's group)

A double allylic oxidation event using the CrO_3/3,5-DMP (3,5-dimethylpyrazole) combination was among the key transformations in the enantioselective synthesis of eupalinilide E (**173**) (Scheme 17), a sesquiterpenoid lactone isolated from *Eupatorium lindleyanum*.[47] The special attention paid to this natural product is attributed to its unique ability to expand hematopoietic stem and progenitor cells (HSPCs) and inhibit differentiation. In fact, eupalinilide E was found to be the most potent agent, among 704 pure natural products of variable origin from Novartis' natural product collection, screened for that purpose.[48] Despite its complex oxidative decoration, its elegant synthesis was accomplished by Siegel and coworkers in 2016,[49] providing access to material (>400 mg) for further biological investigations.

Chemistry wise, the enantioselective construction of the basic guaianolide framework was accomplished in 13 steps from (*R*)-carvone (**33**) and 11% overall yield, providing 12 g of the advanced intermediate **168** (Scheme 17). Noteworthy features of this array of transformations are a Favorskii ring contraction, to access substituted cyclopentene **161**, and a Pd catalyzed cycloisomerization event on 1,6-enyne **165**, followed by transmetallation to boron and oxidation to formulate the five-membered ring that serves as a precursor to the γ-lactone ring of the natural product. Alcohol **166**, thus produced, was oxidized to aldehyde **167**, which was subjected to a reductive allylation protocol to generate the seven-membered ring and complete the guaianolide skeleton. We have witnessed a similar strategy in Maimone's syntheses of montanolide and slovanolide, discussed earlier in this review.[39] With an adequate amount of compound **168** in hand, and after a Yamaguchi esterification and TMS group removal, intermediate **170**, the substrate for the highly anticipated double oxidation was prepared (Scheme 17). A thorough investigation of conditions to bring about the said transformation led to the CrO_3/3,5-DMP combination as the one to provide an optimal yield (36% over two steps) of enone **171**. Importantly, the authors highlight that this late-stage manipulation was crucial for the success of the synthesis due to the incompatibility of the chemistry of the early stages with the carbonyl groups. A separate report by the

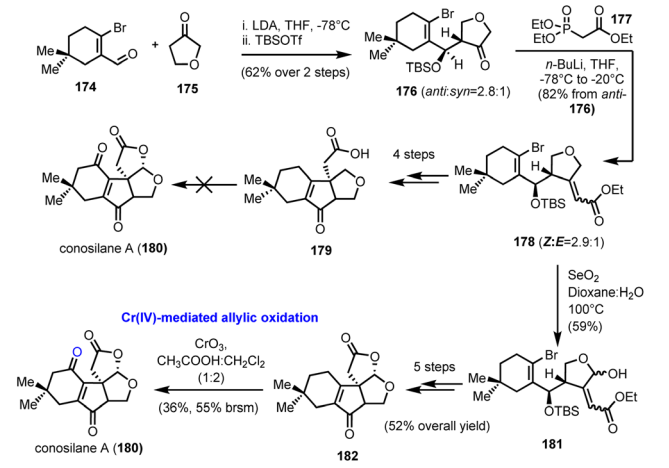


Scheme 17 Double allylic oxidation of the guaianolide skeleton *en route* to eupalinilide E (**173**) (Siege's group).

same team sheds light on previous unsuccessful efforts performed on pre-oxidized substrates.[50] From the remaining steps to the completion of the synthesis, it is worthy to comment that the site-selectivity in the epoxidation of **172**, where the desired product, is not thermodynamically favoured. The use of a bulky aluminium based Lewis acid was critical to achieve high levels of selectivity in favour of the exomethylenic double bond against the more reactive trisubstituted double bond.

5.3. Conosilane A (Liu's group)

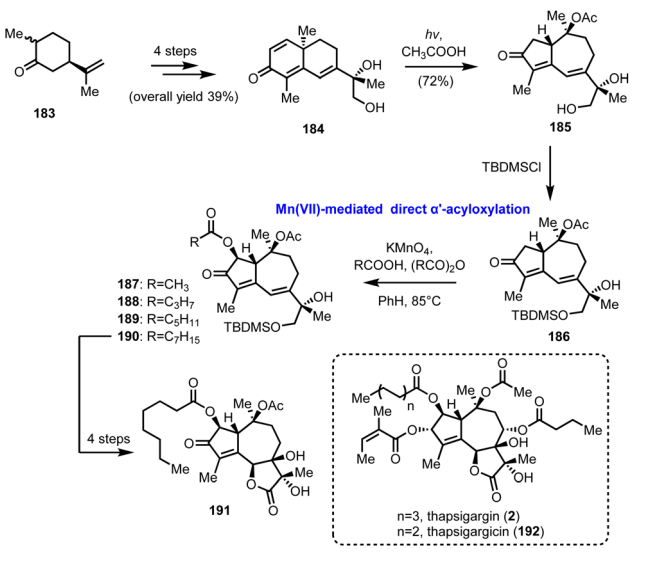
Another success story for the chromium based stoichiometric oxidation of allylic C–H bonds is demonstrated in the racemic synthesis of nonisoprenoid tremulane-type sesquiterpene conosilane A (**180**, Scheme 18), from the culture of mushroom *C. siliginea*, reported by Liu and co-workers in 2018.[51] In fact, the authors described a preliminary unsuccessful study that relied largely on a final stage lactonization by the activation of a C–H bond in the α-position to an oxygen heteroatom (in Scheme 18, conversion of **179** to **180**). Although such a tactic has been effectively applied to numerous cases, including some described previously in this review,[16,28] on substrate **179** it did not deliver the desired product. As an alternative, Liu's team selected to facilitate the lactonization step by converting the tetrahydrofuranyl ring into the respective hemiacetal (SeO_2 oxidation of common intermediate **178** to hemiacetal **181**). After some typical chemical transformations, the natural product precursor **182** was afforded in a good overall yield of 52%. The concluding allylic oxidation of the cyclohexene ring was realized in a moderate yield (36%), using CrO_3 in a 1 : 2 $CH_3COOH : CH_2Cl_2$ mixture at ambient temperature. Although the conversion seems ineffective, it was the only one that could deliver productive amounts of the natural product, among several other tested, including the "privileged" combination of CrO_3 with 3,5-DMP. Transition metal catalysis, as well as direct electrophilic oxidation by DMDO, afforded only a trace amount of conosilane A.



Scheme 18 Total synthesis of conosilane A (**180**) which relied on CrO_3/AcOH oxidation (Liu's group).

5.4. $KMnO_4$ direct α′-acyloxylation of enones in guaianolides (Moreno-Dorado's and Guerra's groups)

In 1989 Watt and his co-workers reported the $Mn(OAc)_3$ mediated oxidative acyloxylation of enones at the α′-position in the presence of an appropriate carboxylic acid.[52] Despite the increased interest in such a transformation, due to the direct access to a structural motif profusely found in biologically important compounds, its establishment as a routinely used synthetic tool never materialized, due, mainly, to reproducibility and practicality issues. Subsequent improvements by Demir *et al.*, where $KMnO_4$ was used for the *in situ* generation of $Mn(OAc)_3$, showed the way for more controllable and predictable reactivity.[53] In 2014 Moreno-Dorado and Guerra published their thorough study on the optimization of the reaction conditions using a computationally aimed design of experiment (DoE) approach, which attests the robustness of the methodology.[54] Several experimental variables have been fine-tuned and the optimum reaction conditions were tested on various substrates, including guaianes and guaianolides, the structural precursors of thapsigargin (**2**) and thapsigargicin (**192**), the structures of which are shown in Scheme 19. In particular, compound **186** was synthesized in 6 steps and 28% overall yield from partially hydrogenated (*R*)-carvone **183**, utilizing the photochemical rearrangement of "santonine-like" intermediate **184** to guaiane derivative **185** as the key transformation (Scheme 19). Next, the critical α′-acyloxylation was performed achieving good yields (56–98%) with an array of linear carboxylic acids, compounds **187–190**, demonstrating the reliability of the method. Finally, advanced intermediate **190** was converted to thapsigargin analogue (**191**) in 3 additional manipulations, involving silyl group removal, site- and stereo selective dihydroxylation and oxidation of primary alcohol to carboxylic acid followed by spontaneous lactonization.



Scheme 19 Direct α′-acyloxylation of a guaianolide type enone based on the $KMnO_4/CH_3COOH$ oxidation system (Moreno-Dorado's and Guerra's groups).

6. Multi oxidation processes

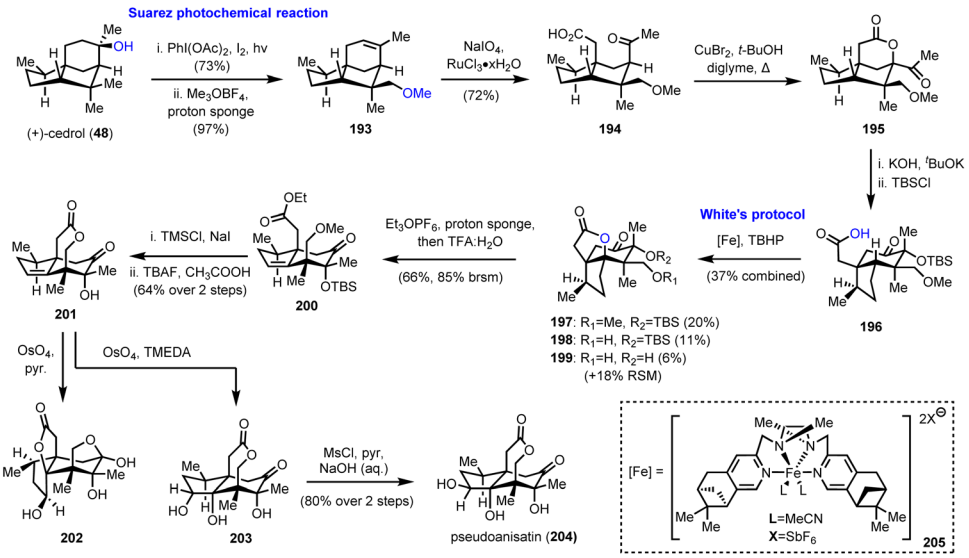
6.1. (+)-Pseudoanisatin (Maimone's group)

As has been easily understood so far, polyhydroxylated seco-prezizaane sesquiterpenoids represent a fertile ground for the exploration of the limits of C–H bond oxidation to act as a direct means to introduce substituent complexity. The case was magnificently demonstrated by Maimone and his group, by the first chemical synthesis of (+)-pseudoanisatin (**204**, Scheme 20),[55] a sesquiterpene of the *Illicium* family, known since 1968,[56] yet never previously synthesized in the lab. His elegant synthetic studies relied largely on radical-based C–H oxidation methods, properly designed to bring about important structural arrangements.

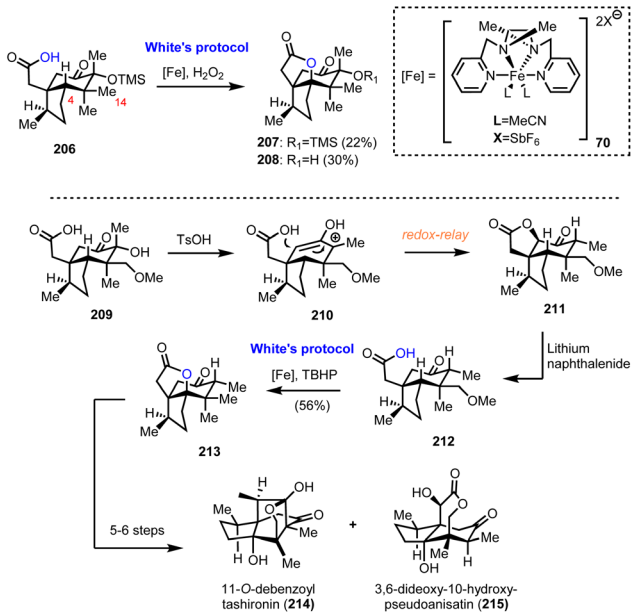
In the same vein as the synthesis of (−)-majucin (**46**), reported by the same team and discussed earlier in Section 2.3 of this review,[18] (+)-cedrol (**48**) was subjected to a Suarez photochemical reaction to selectively oxidize the nearby equatorial methyl group (Scheme 20). Indicative of the power and the robustness of the method is the scale of the reaction that was as large as 50 mmol. Thus, the produced alkene **193** was further elaborated to intermediate **195** by ruthenium catalyzed eruption of the double bond and $CuBr_2$ mediated lactonization at the α-position of methyl ketone **194**. A sophisticated base-induced α-ketol rearrangement was used to convert the 5/5 bicyclic system found in cedrol to the desired 5/6 ring system of the *Illicium* sesquiterpenes; thus carboxylic acid **196** was afforded after silicon-based protection of the hydroxyl group. Preparation of the latter set the stage for the decisive C–H activation of the adjacent tertiary methine group at the bridgehead position. Selectivity issues impose a tremendous challenge in the specific structural setup, and Maimone and his team took up the gauntlet employing nonheme iron catalysis. Building upon existing knowledge from White's[57] and other groups' observations,[58] they discovered that a complex of iron with pinene-based *mepp* ligands (**205** see the inset of Scheme 20) could attain decent levels of selectivity, essentially capitalizing on the directing ability of the carboxylic group. Due to partial deprotection of either the silyl or the methyl ether a mixture of usable products **197–199** was obtained in 37% combined yield, along with 18% recovered starting material. Working with the fully protected lactone **197**, treatment with Meerwein's type salt and then acidic conditions, alkene **200** was produced whereas unsaturated lactone **201** was afforded after two deprotections and spontaneous lactonization. Interestingly, the attempted dihydroxylation of the latter using OsO_4 and pyridine as the base took place from the undesired face of the trisubstituted double bond (compound **202**, Scheme 20), revealing certain facial preference. Fortunately, by switching the base selection from pyridine to TMEDA, a strong directing effect of the homoallylic hydroxyl group was operative and capable of overcoming the stereochemical bias, leading to triol **203**. Inversion of the stereochemistry of the secondary hydroxyl group by selective mesylation and NaOH hydrolysis completed the synthesis of (+)-pseudoanisatine (**204**).

6.2. Collective synthesis of Illicum sesquiterpenoids (Maimone's group)

Numerous interesting observations have emerged during the synthetic studies of pseudoanisatin and related natural products by Maimone's group (Scheme 21). A quite enlightening account, offering fascinating details of C–H oxidation in complex organic settings, have been reported recently.[20] In this saga in the field of effective terpene oxidations, (+)-cedrol (**48**) was the protagonist and Maimone explored all the possible transformations of its framework to access a plethora of scaffolds found within the illicium sesquiterpene family. This effort has provided a wealth of substrates where radical C–H oxidation has been tested. On the way to (+)-pseudoanisatin (**204**), compounds **206** and **212** were explored as suitable sub-



Scheme 20 Total synthesis of (+)-pseudoanisatin (**204**) (Maimone's group).

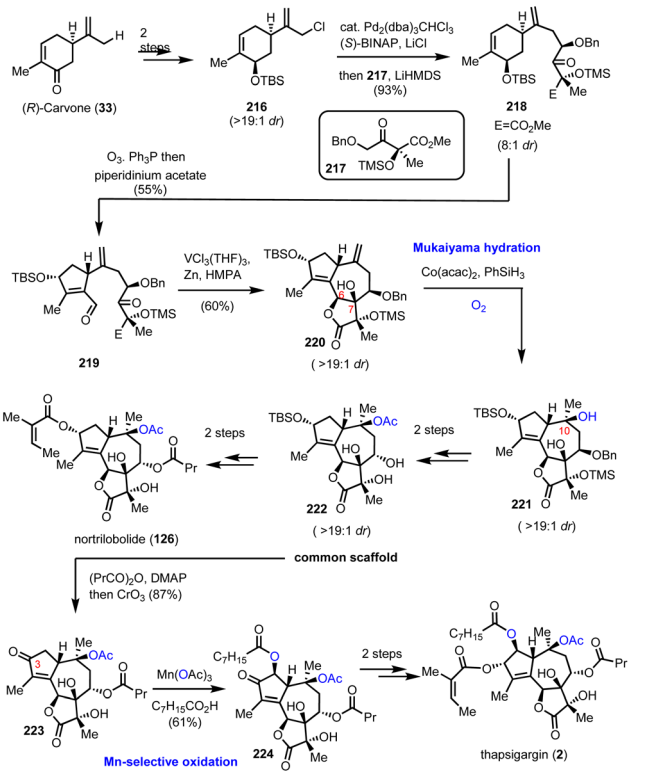


Scheme 21 Substrates for successful implementation of non-heme iron catalysis (Maimone's group).

strates for C–H activation induced lactonization during initial studies (Scheme 21). The former was explored in the context of a C-14 late-stage oxidation strategy and represented the first breakthrough of non-heme iron success in C-4 methine selective C–H activation. Furthermore, while working with the C-14 oxidized substrate **209**, a TsOH induced redox-relay cascade was discovered that led to lactone **211** and then to carboxylic acid **212** after lithium naphthalenide reduction. Once again, iron catalysis was effective and provided the respective lactone in 56% yield, thus allowing the access to sesquiterpenes **214** and **215**, through a reported sequence.[59]

6.3. Nortrilobolide and thapsigargin (Evans' group)

Thapsigargin (**2**) is among the most prominent structures for potent new anticancer agents. The high level of selectivity as an inhibitor of intracellular calcium ion transport enzymes[60] and the high induction of cell apoptosis due to calcium signals[61] has led to the development of novel cancer theurapeutics.[62] In 2007, Evans' group reported a concise total synthesis of thapsigargin (**2**) and nortrilobolide (**126**) by utilizing the common synthetic scaffold **222** (Scheme 22).[63] The divergent plan of Evans' group was based on bioinspired retrosynthesis to form the C-6–C-7 bond as the last step for the synthesis of the guaianolide core. The synthesis started by the asymmetric alkylation of carvone derivative **216**, readily available from (*R*)-carvone in 2 steps, and derivative **217** available from methylerythritol under $Pd_2(dba)_3CHCl_3$ and (*S*)-BINAP catalysis to furnish **218** in 93% yield (Scheme 22). Selective ozonolysis of the cyclohexene moiety followed by organocatalytic aldol reaction provided compound **219** in gram scale quantity and 55% yield. A pinacol coupling/lactonization cascade resulted from the reaction of **219** with the $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$

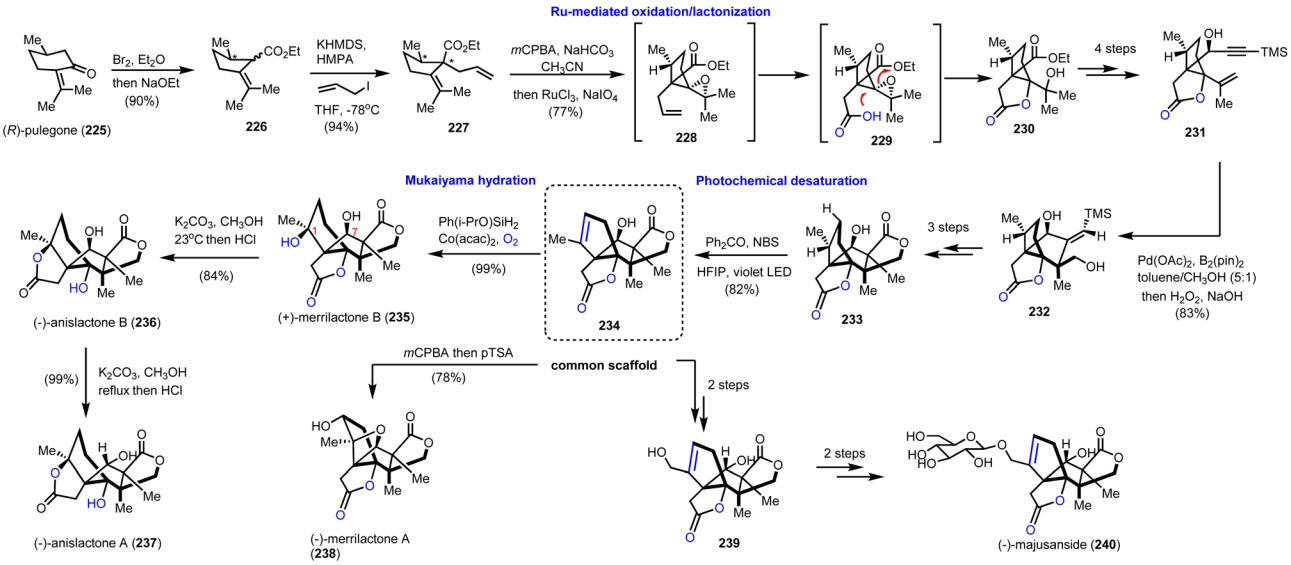


Scheme 22 Total synthesis of the thapsigargin and nortrilobolide oxidase phase relying on Mukaiyama hydration (Evans' group).

complex, prepared *in situ* in the presence of hexamethylphosphoramide (HMPA). The sequence allowed the concise synthesis of the complete carbocyclic core of the guaianolide in a high overall yield and diastereoselectivity (19 : 1). From this point, the quest to introduce the rest of the oxidase phase began. A Mukaiyama hydration with the aid of $Co(acac)_2$ and $PhSiH_3$ was selected for C-10 hydroxylation to provide **221** in 79% yield and high diastereoselectivity (19 : 1). FGI for the introduction of the requisite acyl groups followed for the synthesis of nortrilobolide (**126**), and with subsequent oxidation of C-3 to ketone for the synthesis of thapsigargin (Scheme 22). The latter was used as a handle for α-hydroxylation with the aid of $Mn(OAc)_3$ and octanoic acid to provide compound **224**, which was readily reduced and acylated to furnish thapsigargin (**2**).

6.4. Merrilactone B, anislactone A, B and majusanside (Zhang's and Zhang's groups)

To take advantage of the synthetic potential of alkenes in stereoselective oxidations, Zhang's and Zhang's groups developed a novel aliphatic desaturation protocol able to work under complex molecular settings.[64] To reach *Illicium* complexity authors realized that they can use the appropriately substituted alkene **234** (Scheme 23, dashed frame) as a common synthetic scaffold for the divergent total synthesis of merrilactone A (**238**) and B (**235**), anislactone A (**237**) and B (**236**) and majusanside (**240**). The synthesis began with the transformation of



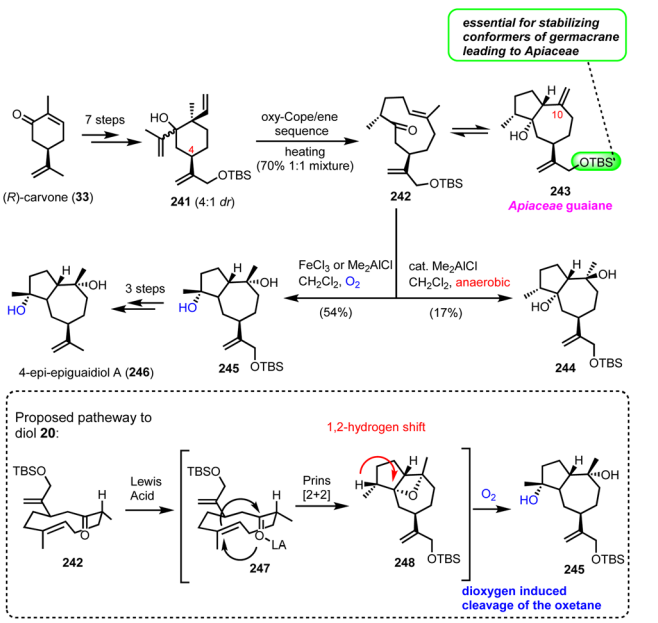
Scheme 23 Divergent synthesis of merrilactone B, anislactone A, B and majusanside based on a 'desaturation' protocol (Zhang's and Zhang's groups).

(*R*)-pulegone (**225**) to **226** through dibromination and Favorskii rearrangement. Stereoselective introduction of an allyl chain followed by mCPBA epoxidation and ruthenium chloride, sodium hypoiodide alkene cleavage/oxidation furnished lactone **230**. FGI and subsequent introduction of the acetylene moiety allowed a palladium(II)-promoted cyclization-borylation of enyne to **232**, which was three steps away from precursor **233**. At this point, the authors explored the possibility of an unsaturation event to **234**. To achieve it a photochemical bromination was considered. Molecular calculations on BDE values of the C–H cleavage on **233** revealed C-1 and C-7 as more prone positions for an electrophilic cleavage. Bromination with the aid of benzophenone under violet light in HFIP resulted in alkene **234** in 82% yield. HFIP served as an efficient hydrogen donor to the hydroxyl moiety altering the BDE value at the C-7 position and masking it. Having in hand compound **234** in multigram quantities allowed them to complete the total synthesis of merrilactone A (**238**) by *m*-CPBA epoxidation followed by intramolecular epoxide opening (Scheme 23). Mukaiyama hydration of **234** provided stereoselectively merrilactone B (**235**) in 99% yield by using $Co(acac)_2$ and $Ph(i\text{-}PrO)SiH_2$ under dioxygen. Translactonization of the latter with potassium methoxide formed anislactone B (**236**) and anislactone A (**237**) after epimerization. Finally, epimerization of C-7 followed by selenium dioxide allylic oxidation completed the total synthesis of the aglycon of (–)-majusanside (**240**).

7. Miscellaneous

7.1. *epi*-Epiguaianol A (Zografos' group)

Recently, Zografos' group reported an interesting dioxygen-induced C–H oxidation for the synthesis of *epi*-epiguaianol (**246**).[65] Based on earlier findings of the group, non-natural elemane-type sesquiterpenoids can serve as ideal precursors to access germacranolides and guaianolides through an oxy–Cope-(ene) reaction (cascades).[17] Applying an oxy–Cope/ene sequence to a diasteroisomeric mixture of **241** (*anti* : *syn* = 4 : 1), readily accessible from (*R*)-carvone (**33**) in 7 steps, led to germacrane **242** and guaiane **243** as a 50 : 50 mixture in 70% yield (Scheme 24). Interestingly, the isopropenyloxy-TBS substituent at the 4-position was found essential to lock the desired



Scheme 24 Stereoselective oxidation for the synthesis of 4-*epi*-epiguaianol based on dioxygen induced oxetane cleavage (Zografos' group).

chair conformations for the oxy–Cope event to deliver only the correct stereochemistry for *Apiaceae* guaiane sesquiterpenoids (Scheme 24). The evidence of a thermal equilibrium between **242** and **243** allowed further elaboration of germacrane **242** to oxidized members of the family. Thus, when **242** was treated with Lewis acids in the presence of dioxygen ($FeCl_3$ or Me_2AlCl), an impressive highly stereoselective oxidation was realized to produce **245** in 54% yield. On the other hand, treating **242** with catalytic Me_2AlCl in the absence of dioxygen provided diol **244**, possessing the diastereomeric alcohol at C-10 in 17% yield. Based on the different behaviour of **242** when dioxygen was absent, the authors proposed a Prins-[2 + 2]-type reaction for the formation of the congested oxetane ring **248**, during the Lewis-acid reaction, followed by dioxygen mediated cleavage of the oxetane ring and hydroxyl migration for compound **245**. FGI that followed provided the synthesis of *epi*-epiguaianol A (**246**).

8. Conclusions

The impressive transformations highlighted in this review underline the power of selected radical reactions to achieve selectivity where polar reactions may fail. The uniqueness of the Hoffmann–Loffler–Freytag variants and P450-like metal oxidations paves the way for further development of the field, indicating the possibility of achieving highly selective transformations in a non-enzyme environment. We strongly believe that, in the future, further development will be achieved in organocatalytic radical reactions that will manage to harness the inherent activity of sesquiterpenoid scaffolds for oxidation.

Conflicts of interest

There are no conflicts to declare.

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