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Strategies and approaches for constructing 1-oxadecalins

Yu Tang, Jossian Oppenheimer, Zhenlei Song, Lingfeng You, Xuejun Zhang and Richard P. Hsung*

Division of Pharmaceutical Sciences and Department of Chemistry, University of Wisconsin, Rennebohm Hall, 777 Highland Avenue, Madison, WI 53705-2222, USA

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* Corresponding author. E-mail: rphsung@pharmacy.wisc.edu

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1. Introduction

Tetrahydropyrans represent a fundamental structural motif ubiquitous in natural products and prevalent in organic transformations. In particular, 1-oxadecalins, in which the tetrahydropyranyl unit is fused to a six-membered ring, are commonly seen in biologically relevant natural products such as arisugacins,[1–4] cordypyridones,[5] hongoquercins,[6–8] penostatins,[9,10] rhododaurichromanic acids,[11,12] pyripyropenes,[13,14] phomactin A,[15–18] and forskolin [Fig. 1].[19,20] These are just a few representatives.

Given such prevalence, we decided to examine recent strategies and approaches employed in the constructions of 1-oxadecalins. In order to stay focussed on these strategies and approaches, we elected not to include strategies and approaches for constructing chromenes or chromanes related systems such as rhododaurichromanic acids, which have been summarized in other excellent recent reviews.[4a,c]

In this review, we have only selected work reported on 1-oxadecalins in the last 10 years. We intend to summarize these approaches based on their reaction types. As usual, we apologize in advance for any relevant work that is not cited and/or highlighted here, as it is not intended to be comprehensive but a sketch summary for efforts that have been exerted toward this fundamental structural motif.

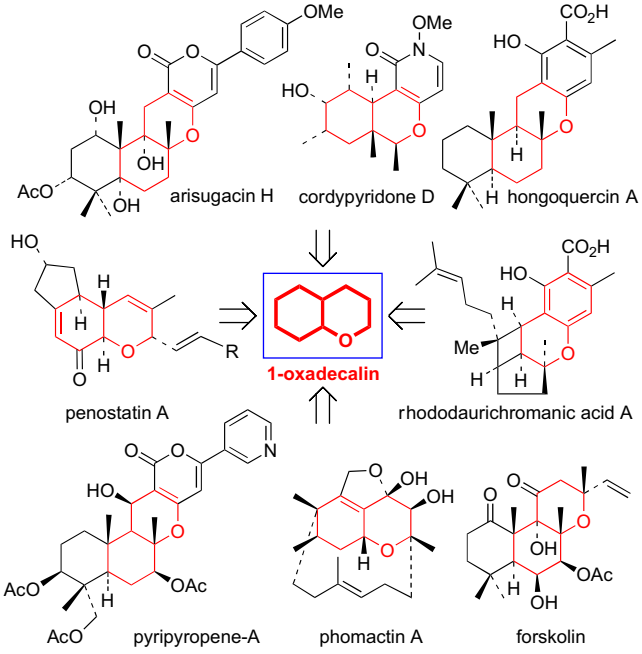
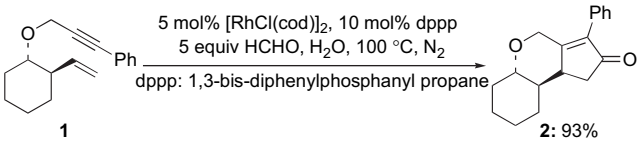


Figure 1.

2. Cycloaddition and annulation reactions

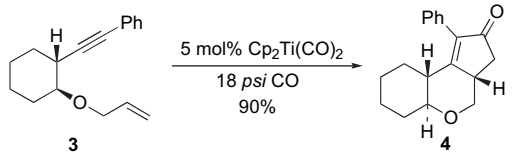
2.1. [2+2+1]

Given that [2+2+1] mathematically implies constructions of a five-membered ring, there are very few examples of [2+2+1] cycloadditions that actually led to 1-oxadecalins. Kakiuchi[21] reported the development of catalytic Pauson–Khand cycloadditions of enynes **1** in aqueous medium employing formaldehyde as a water-soluble source of CO [Scheme 1]. With the oxygen atom being the tether, the cycloaddition gave tricycle **2** that contains a 1-oxadecalin.



Scheme 1.

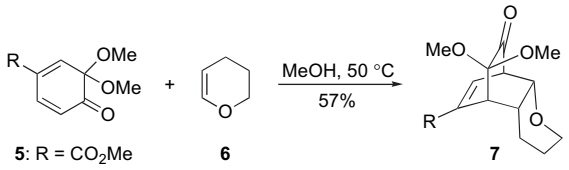
Buchwald[22] showed an interesting intramolecular titanocene-catalyzed Pauson–Khand cycloaddition reaction that led to 1-oxadecalin **4** when using enyne **3** also containing an oxygen atom tether [Scheme 2].



Scheme 2.

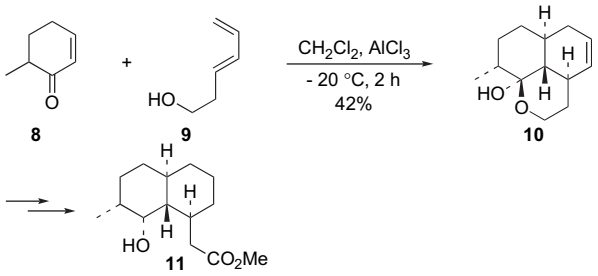
2.2. [4+2]

Including the next section on hetero [4+2] cycloadditions, its very nature implies that Diels–Alder type cycloadditions are quite prevalent as an approach in the synthesis of 1-oxadecalins. Plumet[23] reported that masked *o*-quinones **5** could serve as electron deficient dienes and react in an inverse-demand manner to give *endo*-cycloadduct **7** as a single diastereomer [Scheme 3].



Scheme 3.

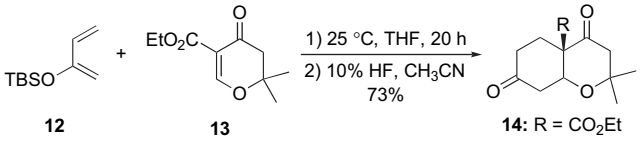
Haynes[24] uncovered a new variation of an $AlCl_3$-catalyzed [$Cu(OTf)_2$ in CH_3CN was also used] highly stereoselective ionic Diels–Alder reaction between enone **8** and diene **9**, which provided racemic hemiacetal **10** [Scheme 4].



Scheme 4.

Totah[25] developed an elegant method for preparations of 1-oxadecalinic frameworks through Diels–Alder reactions of Danishefsky's diene **12** with the 5-carbethoxy

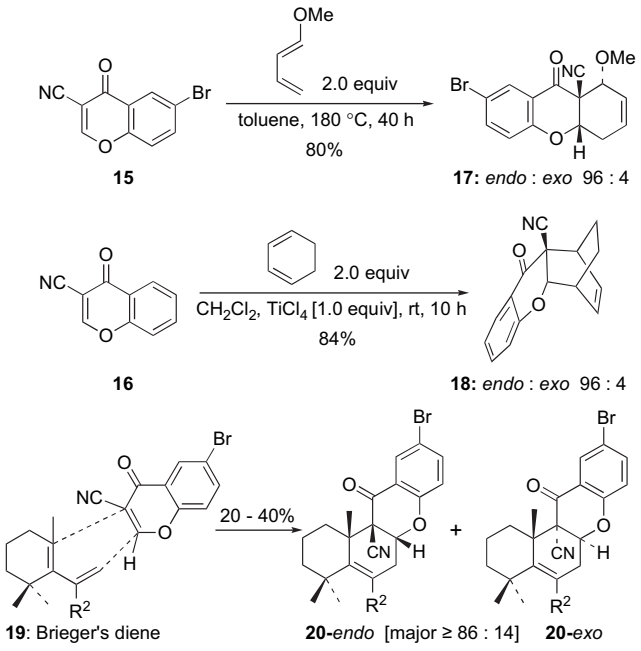
dihydro-γ-pyrone derivatives **13** [Scheme 5]. These cycloadditions can also be catalyzed by Lewis acid such as $ZnCl_2$. This work represents the best example in which γ-pyrones are being utilized as dienophiles and provides an excellent approach toward phomactin A.[15–18]



12 **13** **14:** R = CO_2Et

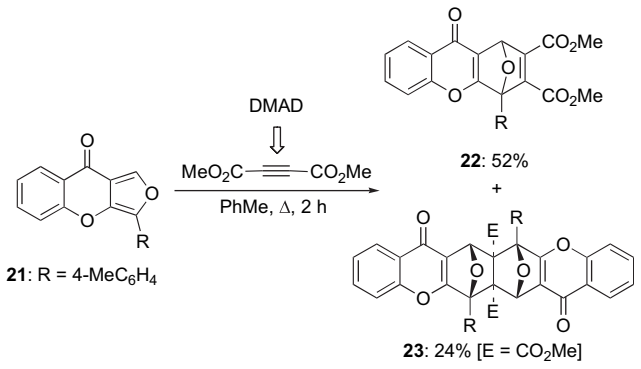
Scheme 5.

Hsung[26] also reported a related Diels–Alder cycloaddition but using 3-cyano-benzopyrones as dienophiles or surrogates of γ-pyrones, leading to the synthesis of xanthones **17** and **18** as well as more elaborate systems such as tetracycle **20** that could be useful for the synthesis of natural product such as hongoquercins[6–8] [Scheme 6].



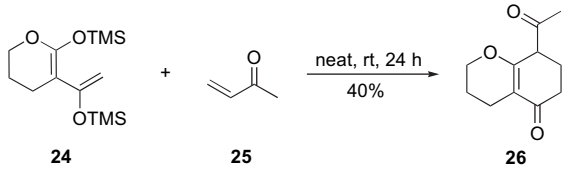
Scheme 6.

Gabbutt[27] found that the reaction of furan **21** with DMAD gave two compounds: cycloadduct **22** in 52% yield and a C_2 symmetric *anti exo–exo* bis-cycloadduct **23** in 24% yield [Scheme 7].



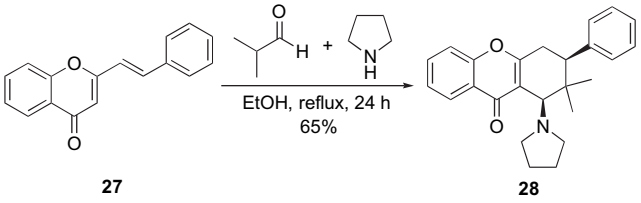
Scheme 7.

Diels–Alder reactions of a novel 'inner-outer-ring' 1,3-silyloxydiene with a variety of dienophiles were reported by Sarandeses [Scheme 8].[28] The reaction with methyl vinyl ketone gave 1-oxadecalin **26** in 40% yield.



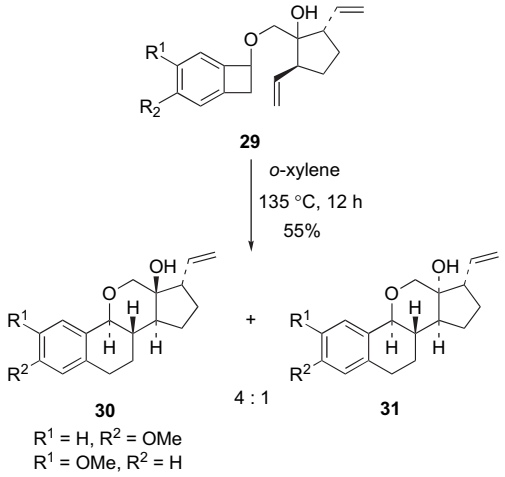
Scheme 8.

Kelkar[29] developed an interesting approach to the synthesis of C-ring substituted xanthones utilizing the [4+2] cycloaddition reactions of vinyl chromones **27** with enamines obtained in situ from the corresponding ketones or aldehydes [Scheme 9].



Scheme 9.

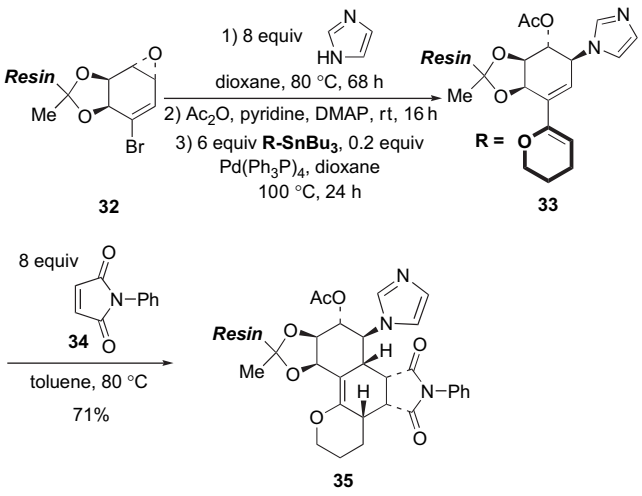
Santelli[30] reported a total synthesis of 11-*oxa*-steroids via an intramolecular Diels–Alder cycloaddition of *ortho*-quinonedimethane derived from ring-opening of benzocyclobutane **29** as the key-step [Scheme 10].



Scheme 10.

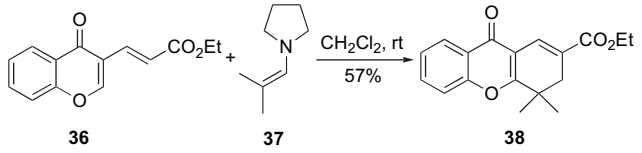
Wendeborn[31] demonstrated a highly efficient sequence of transformations including Stille coupling and *endo*-selective Diels–Alder reactions for the synthesis of highly functionalized polycycles **35** on solid phase [Scheme 11].[31]

In a related manner as Kelkar's work[29] shown in Scheme 9, Bodwell found that the reaction of vinyl chromone **36** with enamine **37** afforded **38** in 57% yield. Elimination of the pyrrolidine group in the initial cycloadduct and isomerizations



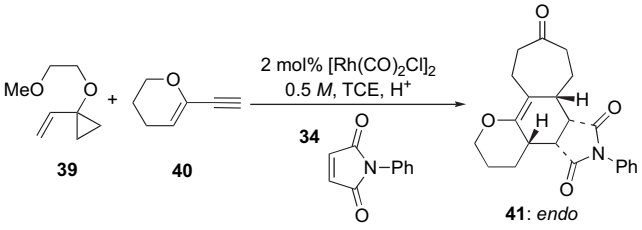
Scheme 11.

of the two olefins occurred to give the conjugation shown in **38** [Scheme 12].[32]



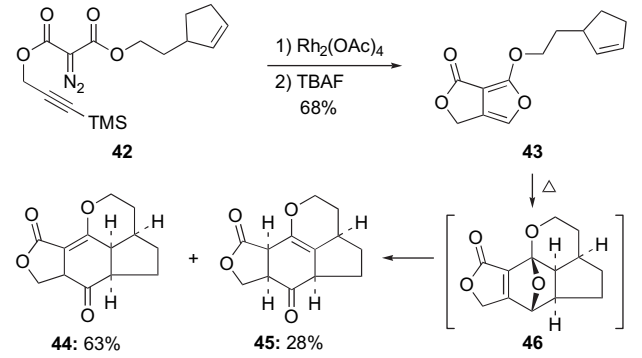
Scheme 12.

Wender[33] developed an impressive three-component tandem [5+2]/[4+2] cycloaddition process to synthesize polycyclic compounds such as **41** [Scheme 13].



Scheme 13.

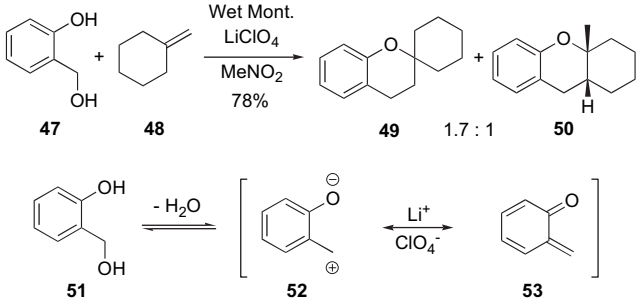
Padwa[34] reported an elegant tandem cyclization/cycloaddition sequence. As shown in Scheme 14, treatment of α-diazo ester **42** with Rh(II) catalyst gave the intramolecular Diels–Alder adduct **46** through furan intermediate **43**. Adduct **46** rearranged to a 2:1 mixture of **44** and **45** in 91% yield.



Scheme 14.

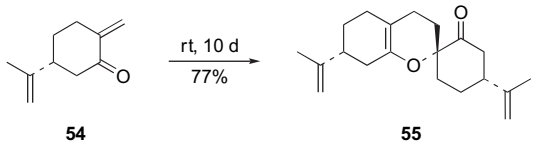
2.3. Hetero [4+2]

Chiba[35] found that intermolecular hetero-Diels–Alder reactions of in situ-generated *o*-quinomethanes **53** [from **47**] and unactivated dienophiles **48** could be accomplished through a wet Montmorillonite catalyst in an $LiClO_4/MeNO_2$ solution to give various chromane skeletons including 1-oxadecalin **50** [Scheme 15].



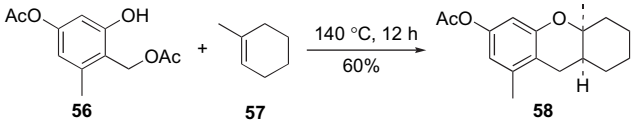
Scheme 15.

Kamat[36] found that the biogenesis of cymbodiacetal involved the key intermediate **55**, which could be prepared by self-dimerization of enone **54** [Scheme 16].



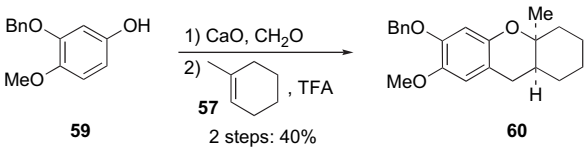
Scheme 16.

Baldwin[37] demonstrated that *o*-quinone methide generated thermally from *o*-methyleneacetoxy-phenol **56** could be employed in the preparation of benzopyrans such as **58** after hetero [4+2] cycloaddition with 1-methylcyclohexene **57** [Scheme 17].



Scheme 17.

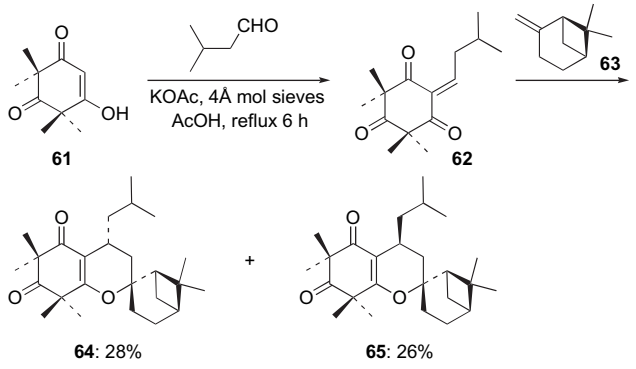
Kraus[38] uncovered a sequence of regioselective hydroxymethylation and hetero-Diels–Alder reaction that constitutes a convenient synthesis of tricyclic analogs of puupehenone [Scheme 18].



Scheme 18.

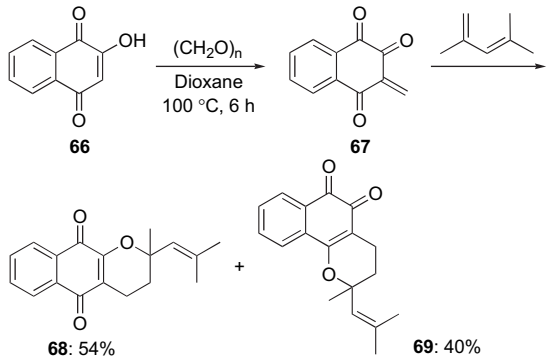
In the structural confirmation of ficifolidione, (1*S*)-β-pinene **63** was reacted with the Knoevenagel condensation product **62** derived in situ from syncarpic acid **61** and

iso-valeraldehyde, leading to the two diastereomers **64** and **65** with **64** being ficifolidione [Scheme 19].[39]



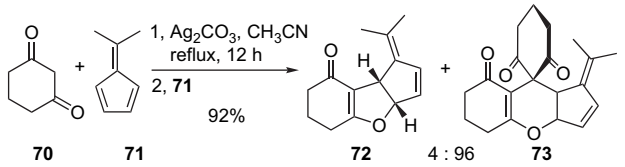
Scheme 19.

Nair[40] reported the generation of *o*-quinone methide **67** from 2-hydroxynaphthoquinone **66** and paraformaldehyde, and its hetero-Diels–Alder reaction as a one-pot synthesis of α- and β-lapachone derivatives [**68** and **69**] [Scheme 20].



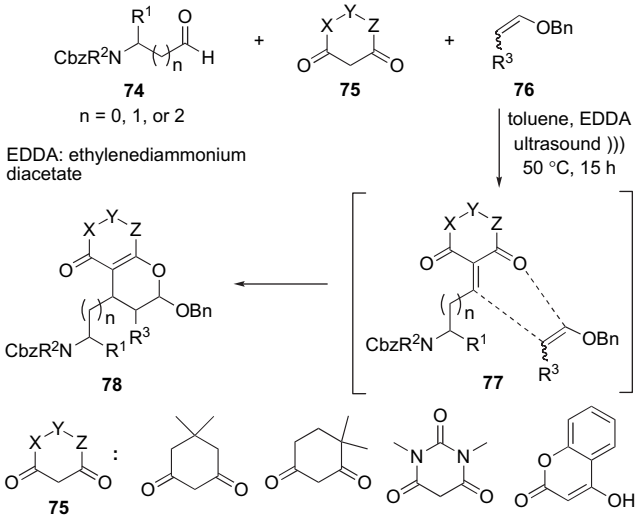
Scheme 20.

Hong[41] cleverly developed a novel sequence of oxidative dimerization/hetero-[3+2] or hetero-Diels–Alder cycloaddition of 1,3-diketones such as **70** with fulvene **71**. This sequence led to polycyclic products such as **72** and **73** [Scheme 21]. When diketone **70** was refluxed with Ag_2CO_3 prior to the addition of fulvene, **73** was almost the sole product [**72**:**73**=4:96]. The process is likely a radical-mediated dimerization.



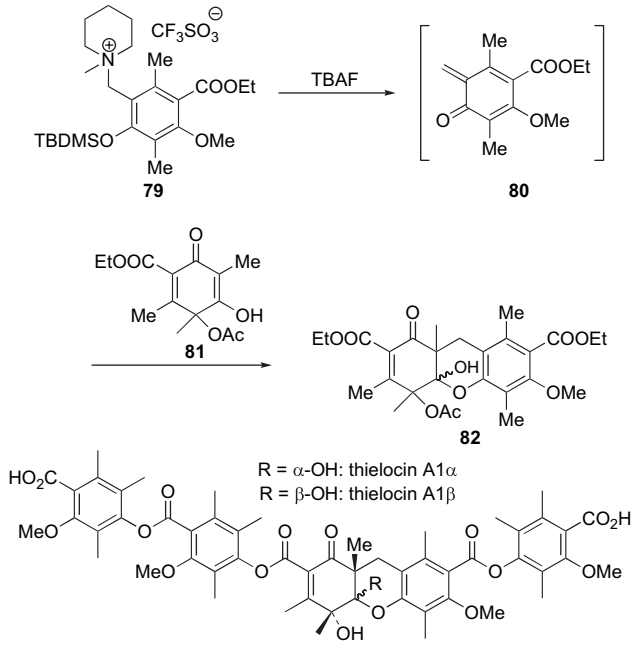
Scheme 21.

Over the last two decades, Tietze[42] has elegantly developed a range of different Knoevenagel condensation/hetero-DA cycloaddition tandem sequences. Specifically here, Knoevenagel condensations of amino aldehydes **74** with 1,3-dicarbonyl components **75** followed by Diels–Alder reactions with enol ethers afforded a range of 1-oxadecalins **78** [Scheme 22].



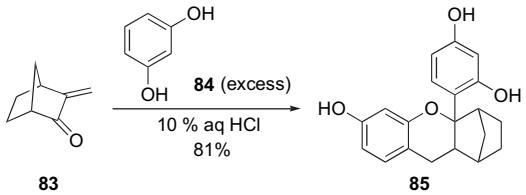
Scheme 22.

In their total synthesis of thielocin A1β, Young[43] used hetero [4+2] cycloaddition of an *o*-quinone methide intermediate **80** with vinylogous acid **81** to construct a 1-oxadecalin moiety **82** [Scheme 23].



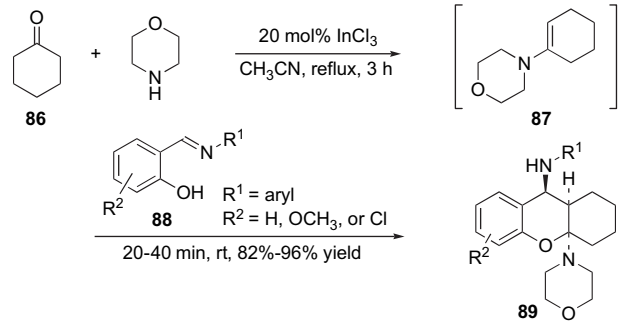
Scheme 23.

An acid-catalyzed reaction of resorcinol **84** with vinyl ketone **83**, which constitutes a formal [4+2] cycloaddition, led to **85** [no stereochemical assignment was given] [Scheme 24].[44]



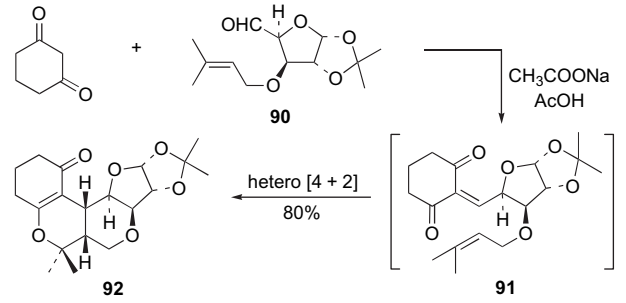
Scheme 24.

In the presence of $InCl_3$ as a catalyst, a one-pot reaction of cyclohexanone **86** and morpholine with salicylaldehyde imines **88** proceeded smoothly to give aminal **89** in good yields [Scheme 25].[45]



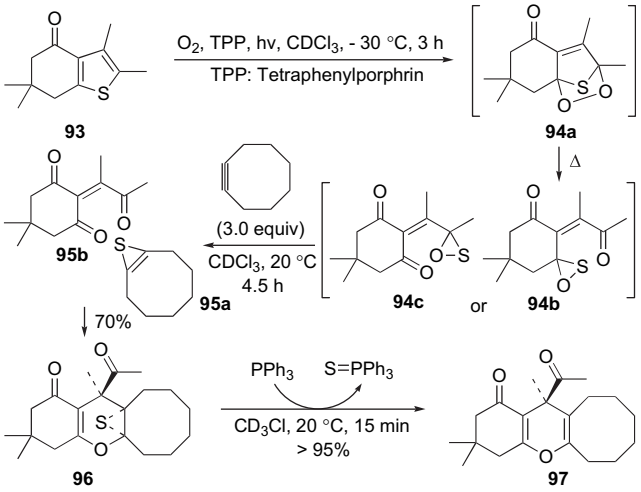
Scheme 25.

Yadav[46] illustrated that the *O*-prenylated sugar derivative **90** derived from D-glucose could undergo an intramolecular domino Knoevenagel condensation/hetero-Diels–Alder reaction with 1,3-cyclohexanediones to afford **92** in a good yield and high diastereoselectivity [Scheme 26].



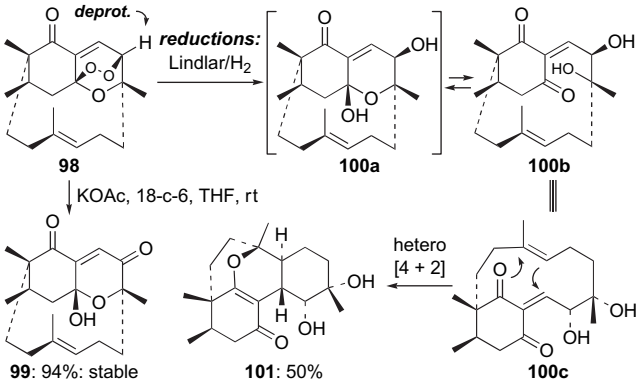
Scheme 26.

Adam[47] reported a very interesting sequence in which 1-oxadecalins **96** and **97** were obtained from thiophene **93** via: (a) a singlet-O_2 Diels–Alder cycloaddition, (b) thermal rearrangements of the resulting *endo*-peroxide **94a**, (c) a sulfur transfer from oxathiiranes **94c** or **94b**, and (d) a hetero [4+2] cycloaddition of the resulting thiirene **95a** with enedione **95b**. Compound **97** was a result of *epi*-sulfide contraction of **96** promoted by triphenylphosphine [Scheme 27].[47]



Scheme 27.

Hsung[48] reported another study also involving *endo*-peroxides [Scheme 28]. In this case, while under basic conditions, ring-opening of *endo*-peroxide **98** occurred to give hydroxy enone **99**, reductive conditions led to a new 1-oxadecalin **101** likely through ene-diol **100a** and an intramolecular hetero-Diels–Alder cycloaddition of **100c**.

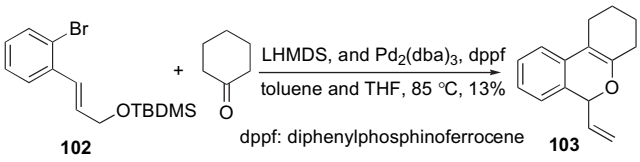


Scheme 28.

2.4. [3+3]

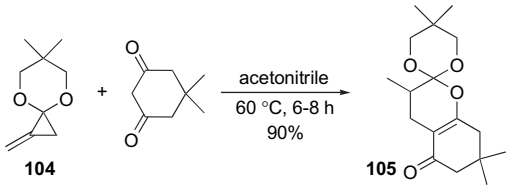
We note here that this section will only highlight some of the recent studies and try not to duplicate those [3+3] cycloaddition or annulations that are already reviewed in two excellent earlier reviews.

Wills[49] discovered a Pd(0)-catalyzed tandem sequence in a formal [3+3] cycloaddition or annulation manner to form 1-vinyl-1*H*-isochromene derivatives such as **103** from lithium enolate generated from cyclohexanone, albeit the yield is not high in this case [Scheme 29].



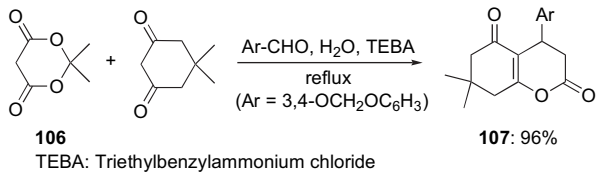
Scheme 29.

Nakamura[50] developed a well-designed [3+3] formal cycloaddition reaction employing ketal protected methylidene cyclopropanone **104** as a trimethylenemethane equivalent, leading to 1-oxadecalin **105** [Scheme 30].



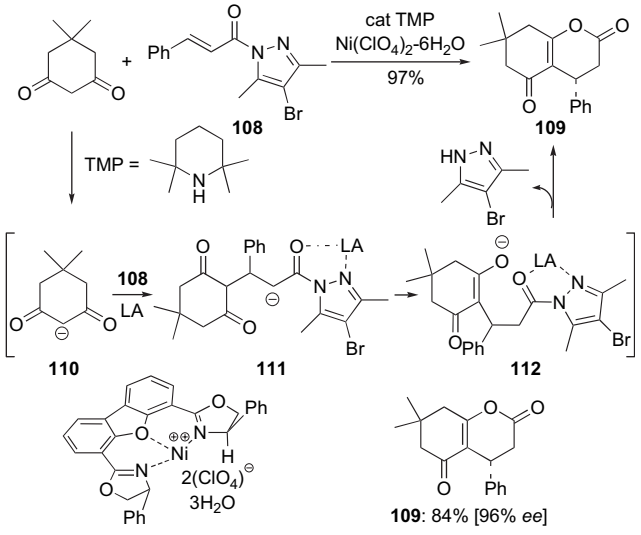
Scheme 30.

A three-component process involving aromatic aldehydes, Meldrum's acid **106**, and 5,5-dimethyl-1,3-cyclohexanedione led to the synthesis of **107** in 96% yield in aqueous media [Scheme 31].[51]



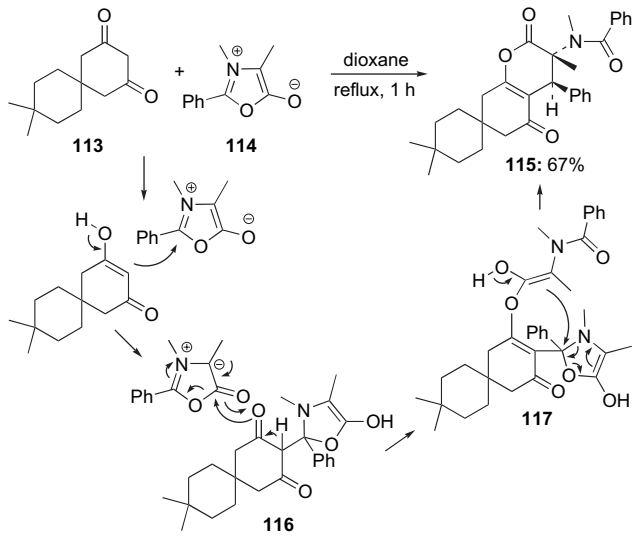
Scheme 31.

Kanemasa[52] reported an elegant series of studies on [3+3] annulations employing cyclic 1,3-dicarbonyl compound with acyl pyrrazole **108** under the double catalytic activation conditions consisting of Lewis acid [Ni(II)] and an amine catalyst [TMP] to provide a new synthetic route to enol lactone **109** by a Michael addition/cyclization sequence [Scheme 32]. Most impressively, they were able to render this reaction highly enantioselective [96% ee] using BOX-type ligand.



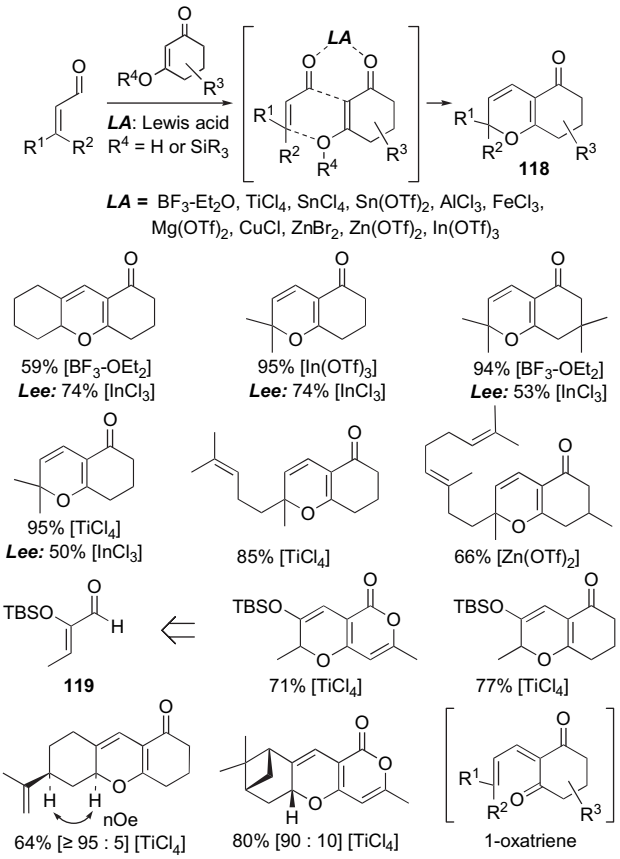
Scheme 32.

Another interesting [3+3] annulation is shown in Scheme 33. Enol lactone **115** was obtained through a one-pot reaction of diketone **113** and **114** [Scheme 33].[53]



Scheme 33.

Both Hsung[54] and Lee[55] [Scheme 34] reported Lewis acid promoted [3+3] annulations employing either diketones or vinylogous silyl esters. In Lee's work,[55] $InCl_3$ was the primary Lewis acid, while Hsung demonstrated that a range of different Lewis acids is feasible. These studies led to an array of 1-oxadecalins. Despite being different from earlier work using amine salts, the Lewis acid promoted version still involves an aldol condensation followed by a 6π-electron electrocyclic ring-closure of 1-oxatriene [see the bracket].



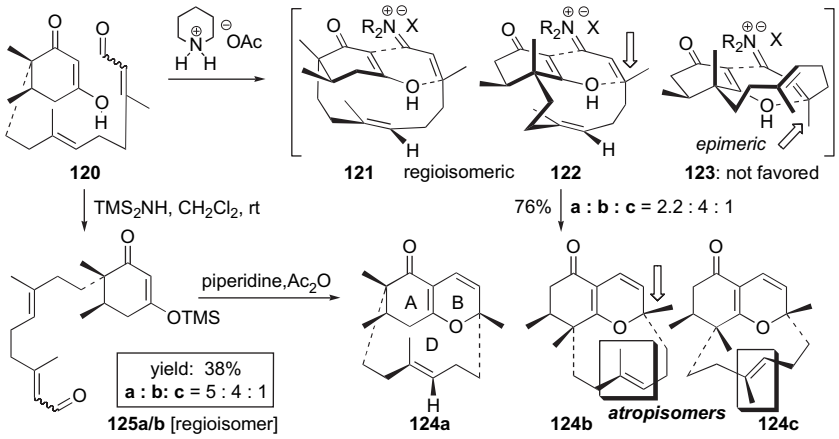
Scheme 34.

Hsung[48,56] reported the first example of an intramolecular *oxa*-[3+3] annulation employing 1,3-diketone **120** and isolated three products **124a–c**. The same three isomers were also found from the annulation of vinylogous TMS-ester **125a/b**, although in different ratios [Scheme 35].

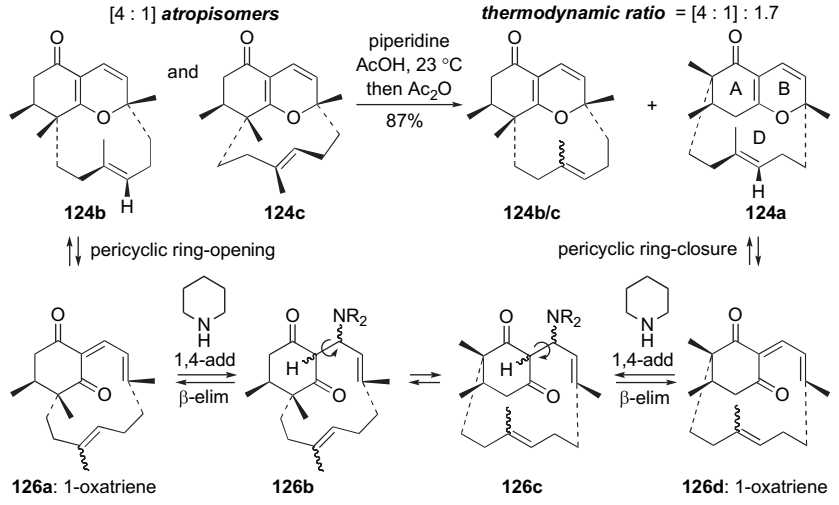
Interestingly, the two regioisomers **124b** and **124c** are actually atropisomers with respect to the orientations of their belt olefins, and thus, both are likely derived from TS-**122**. The respective annulation product derived from TS-**124** was not observed, as TS-**124** is highly strained for the annulation. In addition, the two regioisomers **124b** and **124c** could be equilibrated to give **124a** likely through a sequence of ring-opening and ring-closure sandwiching isomerizations [Scheme 36].

2.5. [3+2] Cycloadditions

Muthusamy[57a,b] discovered a tandem cyclization/hetero [3+2]-cycloaddition of Rh-carbenoids with various carbonyl

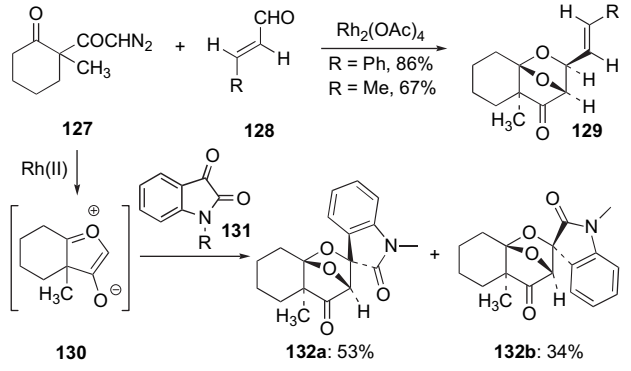


Scheme 35.



Scheme 36.

compounds to give 1-oxadecalins **129** and **132** with high regio- and/or diastereoselectivities [Scheme 37]. Muthusamy[57c,d] also recently used ionic liquids as a convenient and recyclable medium to promote these and related reactions.

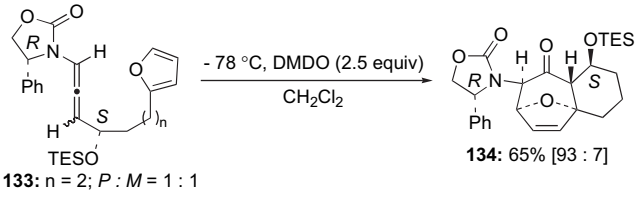


Scheme 37.

2.6. [4+3] Cycloadditions

There are only a few examples of approaches for constructing 1-oxadecalins in which a [4+3] cycloaddition is utilized.

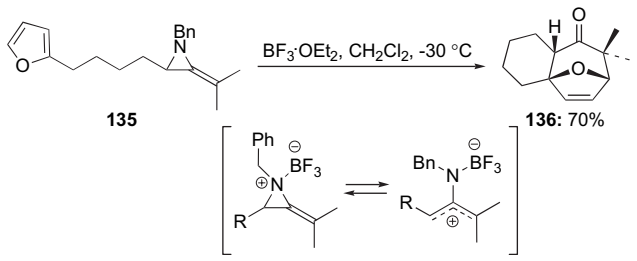
Hsung[58] reported a novel tandem DMDO epoxidation/stereoselective intramolecular [4+3] cycloaddition reaction involving nitrogen-stabilized oxyallyl cations derived from chiral allenamides **133** [Scheme 38].



Scheme 38.

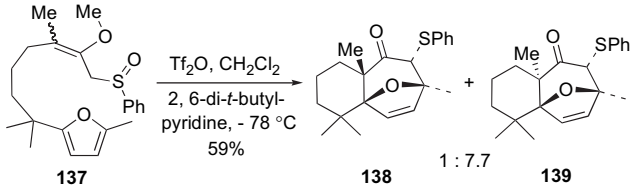
Shipman[59] developed an elegant Lewis acid [$BF_3 \cdot Et_2O$ or $Sc(OTf)_3$]-catalyzed intramolecular [4+3] cycloaddition employing vinyl aziridines such as **135** as a 1,3-dipole precursor [an aza-allyl cation equivalent see the bracket] en route to **136** in good yields [Scheme 39].

In their seminal work on [4+3] cycloadditions, Harmata[60] demonstrated that substituted alkoxyallylic sulfones **137**



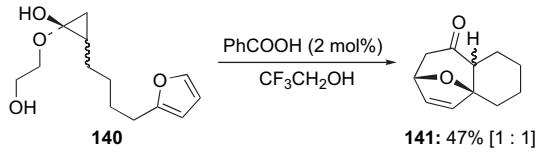
Scheme 39.

could produce vinylthionium ions that when treated with Lewis acids, can undergo intramolecular [4+3] cycloaddition reactions to give adducts **138** and **139** [Scheme 40].



Scheme 40.

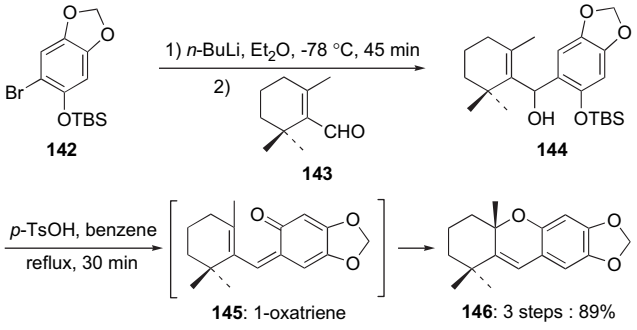
Cha[61] reported that a small amount of benzoic acid could promote intramolecular [4+3] cycloadditions of furan-tethered cyclopropanone hemiacetal **140** giving rise to **141** in 47% yield [Scheme 41].



Scheme 41.

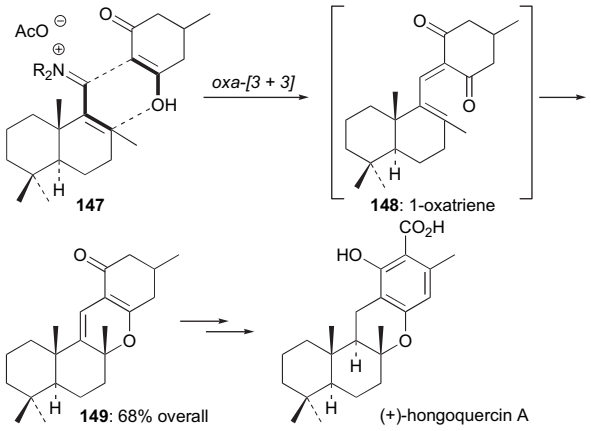
3. Pericyclic ring-closure

To study the structure–biological activity relationship for some activated compounds, Barrero[62] synthesized the cytotoxic benzopyran derivatives **146** from the aryl lithium derived from aryl bromide **142** and β-cyclocitral **143** through a ring-closure of 1-oxatriene **145** [Scheme 42].



Scheme 42.

In Hsung's recent total synthesis of (+)-hongoquercin A,[63] ring-closure of 1-oxatriene **148** occurred en route to the tetracycle **149** in 68% overall yield, thereby completing the oxa-[3+3] annulation sequence [Scheme 43].

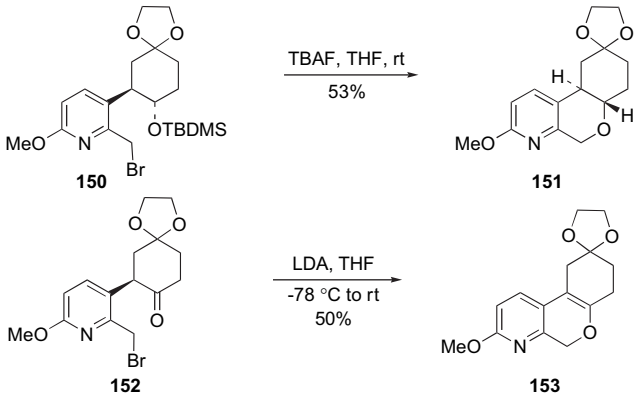


Scheme 43.

4. Cyclization reactions

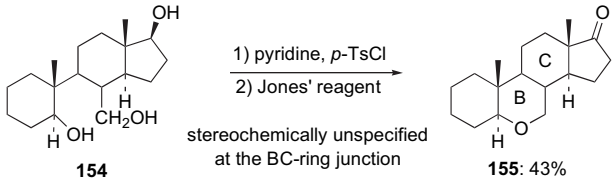
4.1. S_N2 additions

Mann[64] demonstrated that upon removal of the TBDMS group [*n*-Bu_4NF–THF] in compound **150**, a nucleophilic displacement of the bromide occurred concomitantly to produce **151** [Scheme 44]. In addition, lithium enolate derived from ketone **152** and LDA at −78 °C also gave **153** through an S_N2 addition.



Scheme 44.

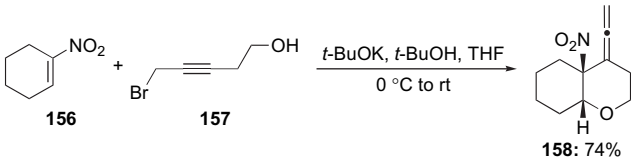
Hanson[65] found that the cyclization of triol **154** through a tosylate intermediate could take place to give tetracyclic ketone **155** after oxidation [Scheme 45].



Scheme 45.

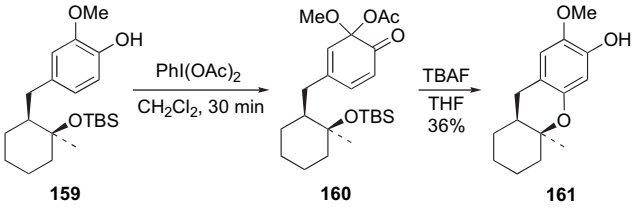
4.2. 1,4- or Oxa-1,4-addition

An oxa-1,4-addition/S_N2' substitution involving nitroalkene **156** and homo-propargyl alcohol derivatives **157** led to the synthesis of 1-oxadecalin **158** [Scheme 46].[66]



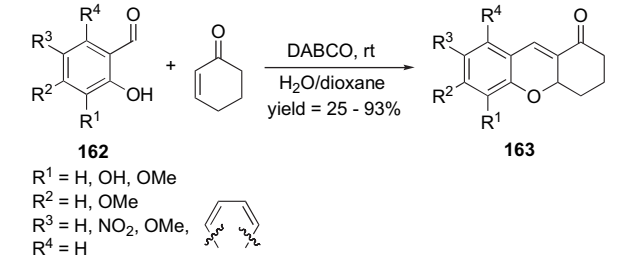
Scheme 46.

Quideau's[67] new preparation of orthoquinol acetates was applied in various O-1,4-addition reactions [Scheme 47]. Specifically, fluoride-mediated desilylation of **160** using TBAF occurred concomitantly with a 6-*exo-trig* cyclization to give **161** after aromatization via elimination of HOAc.



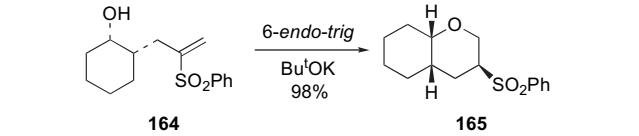
Scheme 47.

Bräse[68] described a domino oxa-1,4-addition and aldol condensation between salicylic aldehyde derivatives **162**s and 2-cyclohexenone that led to **163** [Scheme 48].



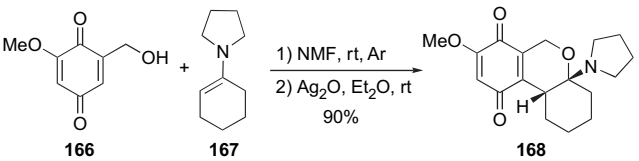
Scheme 48.

Khan[69] investigated the synthesis of *cis* and *trans* [not shown] 1-oxabicyclo[4,4,0]decanes through 6-*endo-trig* cyclization of hydroxy sulfone **164** [Scheme 49].



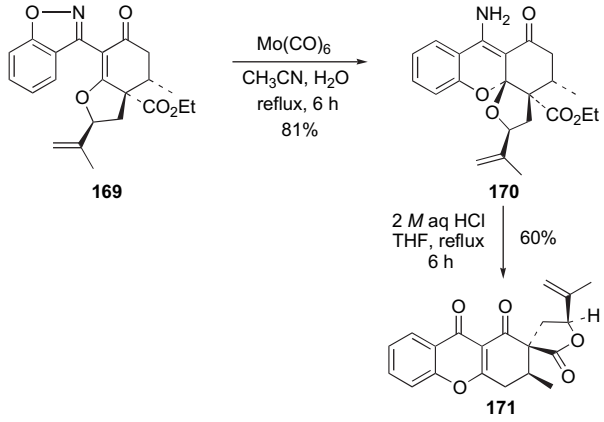
Scheme 49.

An efficient synthesis of the title benzo-pyranodione derivative **168** based on a stereoselective tandem 1,4-addition/cyclization sequence utilizing 2-(1-hydroxyalkyl)-1,4-benzoquinones and enamines was studied by Konishi[70] [Scheme 50].



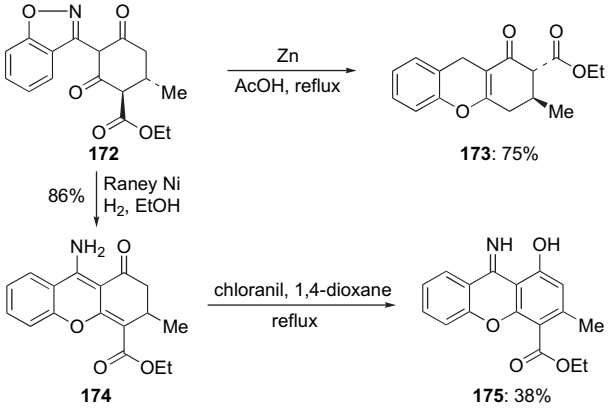
Scheme 50.

Bode and Suzuki[71] reported an interesting reduction of benzisoxazole **169** employing $Mo(CO)_6$ that led to tetracyclic vinylogous amide **170** in 81% yield. The subsequent acid hydrolysis resulted in the formation of **171** via a very unique structural rearrangement that can be an excellent cume question [Scheme 51].



Scheme 51.

Bode and Suzuki[72] also reported by other reductions of benzisoxazole **172** using Zn–AcOH or Raney-Ni led to the formation of 1-oxadecalins **173** or **175**, respectively [Scheme 52].

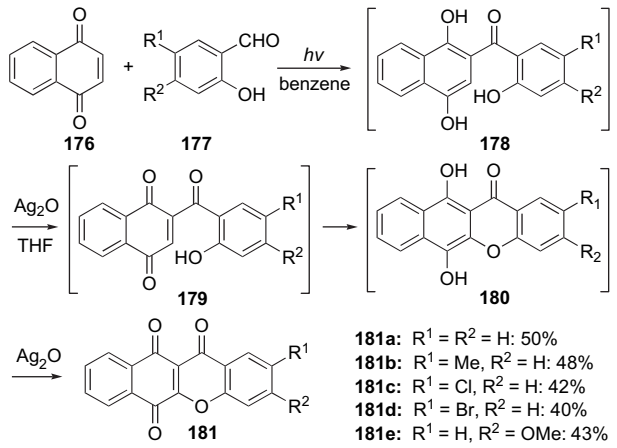


Scheme 52.

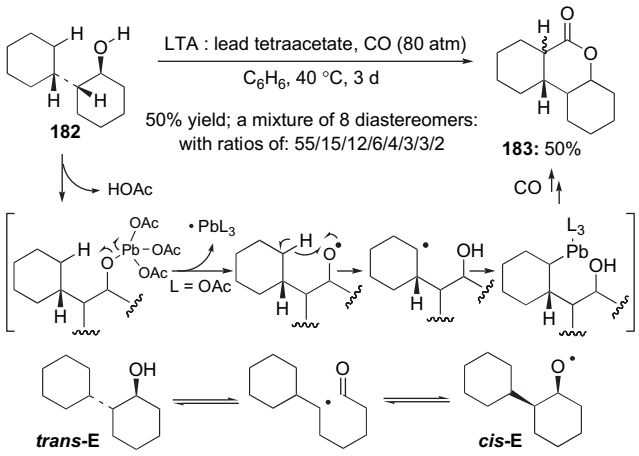
A two-step sequence, involving a photo-induced C-acylation of 1,4-naphthoquinone **176** with 2-hydroxybenzaldehyde **177** followed by O-1,4-addition and Ag_2O oxidations, for the synthesis of the xanthenequinone derivatives **181** was developed by Konishi[73] [Scheme 53].

4.3. Radical cyclizations

Ryu[74] observed an interesting formation of δ-lactones from saturated alcohol **182** in the presence of CO and lead tetraacetate [LTA] [Scheme 54]. The reaction likely proceeds through a 1,6-hydrogen abstraction [or 1,5-shift] by the alkoxyl radical intermediate [see in the bracket] presumably generated by LTA, serving as a one-electron oxidant, followed by carbonylation at the δ-carbon atom [assistance from Pb is a real possibility] and lactonization. Unfortunately, for



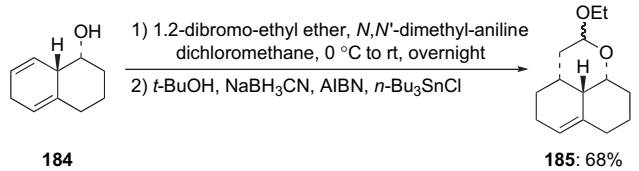
Scheme 53.



Scheme 54.

this specific example, β-bond cleavage occurred leading to scrambling of stereochemistry.

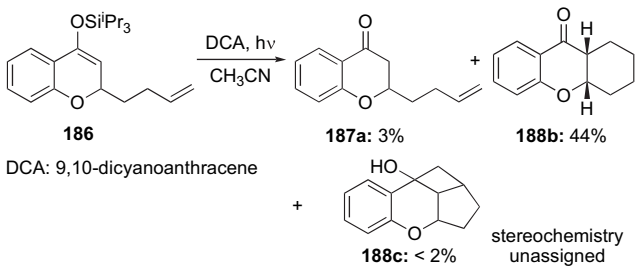
A Stork-type radical cyclization of the bromo-ketal intermediate derived from alcohol **184** and 1,2-dibromo-ethyl ether was revealed to give 1-oxadecalin **185** in a regio- and stereoselective manner [Scheme 55].[75]



Scheme 55.

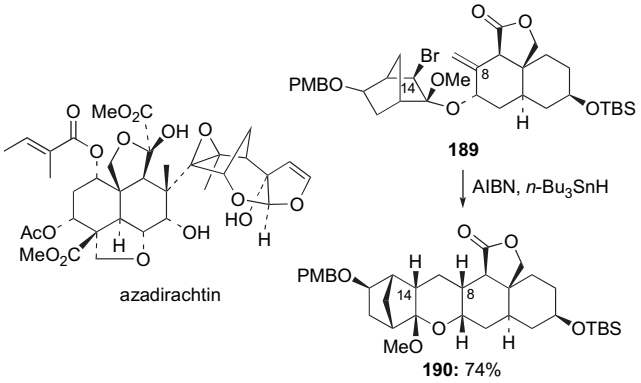
Oxidative photo-induced electron transfer (PET) reactions have been applied to the synthesis of a range of different oxygen heterocycles from silyl enol ethers such as **186** [Scheme 56].[76]

In their synthesis of azadirachtin, Nicolaou[77] attempted a radical-based approach for the construction of its crowded C8–C14 bond. Instead, treatment of the minor product bromo-ketal **189** with *n*-Bu_3SnH and AIBN [0.01 M in



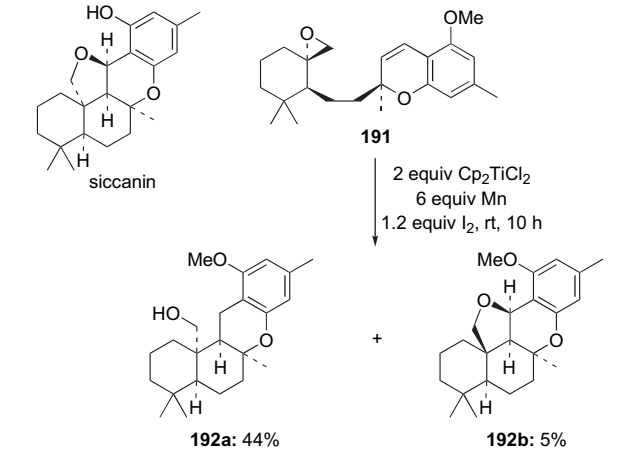
Scheme 56.

toluene, 110 °C] led to a 6-*endo-trig* radical cyclization product **190** in 74% yield [Scheme 57].



Scheme 57.

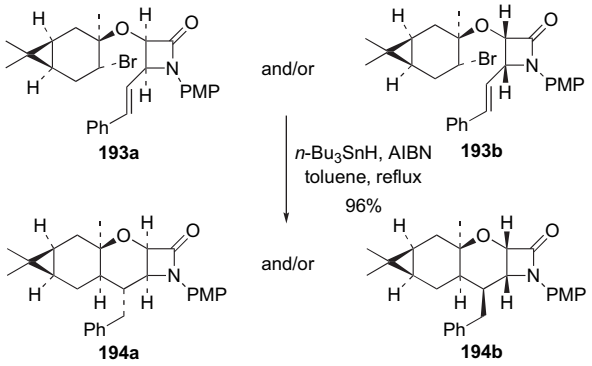
Trost[78] developed a nifty biomimetic enantioselective synthesis of (−)-siccanin that featured the Pd-catalyzed asymmetric allylic alkylation [AAA] and a Ti(III)-mediated 6-*exo-trig* radical cyclization of epoxyolefin **191** [Scheme 58].



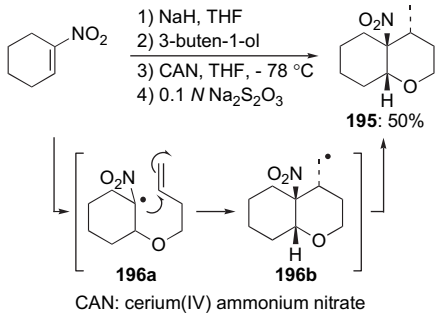
Scheme 58.

An efficient and diastereoselective synthesis of a β-lactam **194a** [or **194b**] has been achieved in high yield via a 6-*exo-trig* radical cyclization employing bromo alkene **193a** [or **193b**] [Scheme 59].[79]

Upon one-electron CAN-oxidation of the nitroanion resulting from an oxa-1,4-addition of homoallylic alcohol to nitroalkene, the radical intermediate **196a** underwent 6-*exo-trig* radical cyclization, leading to 2,3-dialkyl-4-methyl tetrahydropyran **195** stereoselectively [Scheme 60].[80]

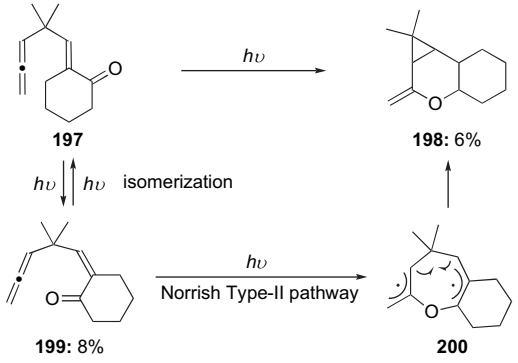


Scheme 59.



Scheme 60.

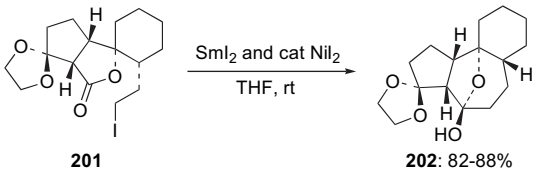
Tsuno[81] reported an interesting 1-oxadelic formation via photochemistry of γ-allenyl-substituted α,β-unsaturated enone derivative. As shown in Scheme 61, irradiation of **197** led to predominantly *E*–*Z* geometric isomerization, but the *Z*-isomer **199** apparently underwent radical cyclization in a Norrish Type-II manner to give **198** [stereochemistry unassigned] in 6% yield. The overall process represents an equivalent of photochemical hetero Diels–Alder reaction [Scheme 61].



Scheme 61.

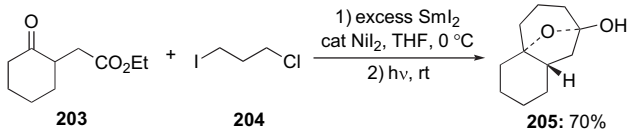
4.4. SmI_2-mediated cyclizations

In their synthetic efforts toward the phorbol ester, Little[82] used an intramolecular reductive cyclization of **201** using SmI_2 [Scheme 62]. The reaction was sluggish, but upon the addition of catalytic amount of NiI_2, the reaction reached completion within 1 h and yields were improved to 82–88%.



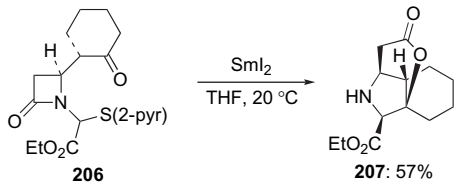
Scheme 62.

Molander[83] developed a beautiful tandem sequence of intermolecular carbonyl addition/intramolecular nucleophilic acyl substitution promoted by SmI_2 [Scheme 63]. They were able to construct bicyclic system **205** in good yields and high diastereoselectivities from simple and readily available ketoester **203** and dihalide **204**. The reducing power of SmI_2 with nickel(II) iodide serving as a catalyst is the key in the first step and irradiation with visible light was more useful in the second step.



Scheme 63.

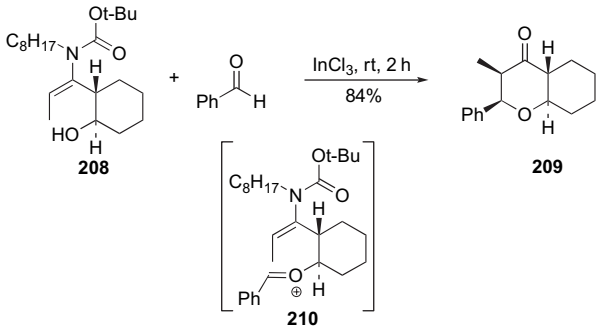
In attempts to promote a Reformasky-type cyclizations of **206** with SmI_2 to construct fused tricyclic β-lactams, Skrydstrup[84] found that the favored pathway is a cyclization pathway followed by a trans-acylation step involving the cleavage of the β-lactam ring to give bridged tricycle **207** [Scheme 64].



Scheme 64.

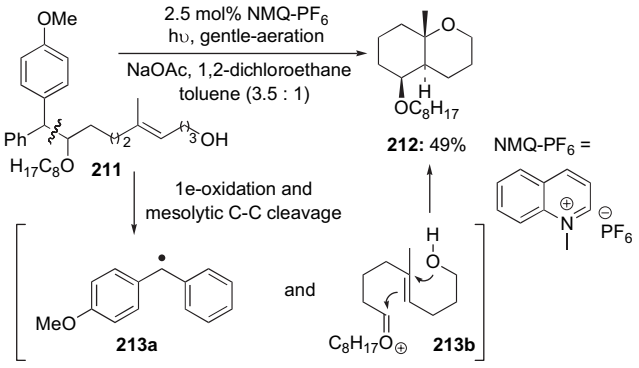
4.5. Prins-type cyclizations

Funk[85] reported an interesting approach to 1-oxadecalin through a diastereoselective Prins cyclization of enecarbamate **208** that was promoted by 0.5 equiv of $InCl_3$ [Scheme 65].



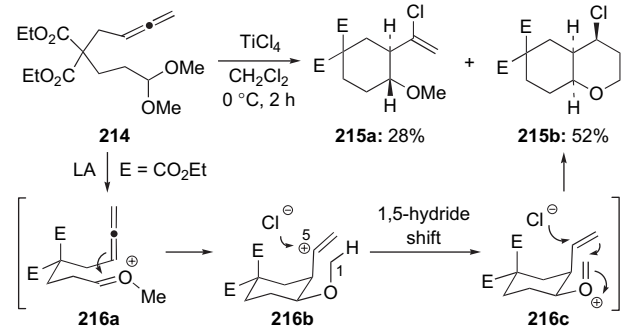
Scheme 65.

Floreancig[86] beautifully demonstrated that organic radical cations can be derived from single-electron oxidation under photochemical conditions and can further undergo the mesolytic C–C σ-bond cleavage to form benzyl radical **213a** and oxocarbenium ion **213b**, which can proceed through a Prins-type cyclization to give 1-oxadecalin **212** [Scheme 66].



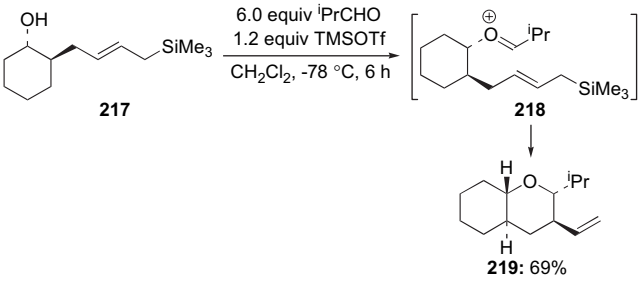
Scheme 66.

Treatment of allenyl-aldehyde dimethyl acetal **214** with $TiCl_4$ afforded the bicyclic pyran **215b** in 52% yield [Scheme 67].[87] The proposed reaction mechanism is a sequence [see the bracket] of an intramolecular allenyl-Prins-cyclization followed by 1,5-hydride shift of vinyl cation **216b**, which itself would lead to **215a** if trapped by the chloride anion. A second Prins cyclization from the resulting oxocarbenium ion **216c** should give **215b**.



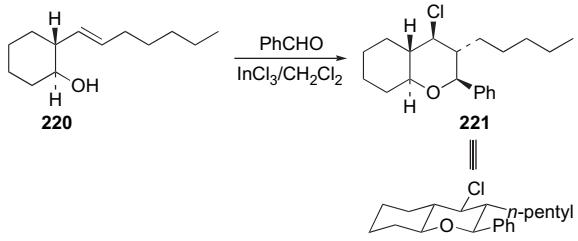
Scheme 67.

Another example of Prins cyclization would involve allyl silane **217** and *iso*-butyrlaldehyde in the presence of TMSOTf to afford 2,3-substituted octahydrochromanes **219** with excellent diastereoselectivity [Scheme 68].[88]



Scheme 68.

Li documented an elegant synthesis of poly-substituted tetrahydropyran **221** with excellent diastereoselectivity via an $InCl_3$-mediated Prins cyclization of alcohol **220** and benzaldehyde [Scheme 69].[89]

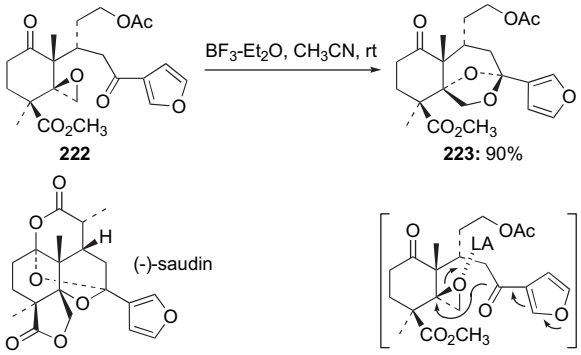


Scheme 69.

4.6. Acid-mediated cyclizations

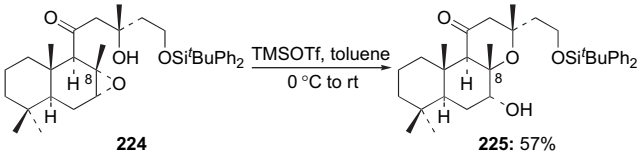
This is the most common approach for constructing 1-oxadecalins, and the section is further divided into four subsections: (1) those involving ring-opening of epoxides, (2) those involving additions onto an olefin, (3) those involving polyene-type cyclizations, and (4) other miscellaneous cyclizations.

4.6.1. Epoxide ring-opening. Boeckman[90] used a Lewis acid promoted ring-opening of epoxide **222** via nucleophilic participation of the side chain ketone carbonyl [see the bracket] followed by cyclization to bicyclic ketal **223** [Scheme 70]. The ring-opening of the epoxide occurred with complete inversion. This was a key-step toward their enantioselective total synthesis of (+)- and (−)-saudin.



Scheme 70.

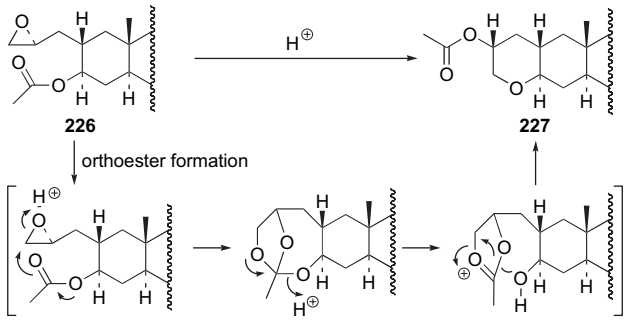
In a study aimed at the synthesis of forskolin [Fig. 1], Welzel[91] found that epoxide **224**, upon treatment with TMSOTf in toluene gave the cyclization product **225** in 57% yield with retention of configuration at C-8 [Scheme 71].



Scheme 71.

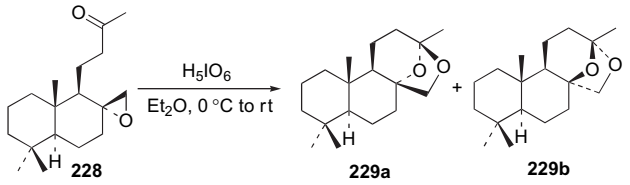
An acid-catalyzed epoxy-ester rearrangement of **226** was reported by Giner[92] to give **227** [Scheme 72]. This study

provides support for the hypothesis that epoxy-ester–orthoester–cyclic ether rearrangement could be involved in the biosynthesis of marine polyether toxins.



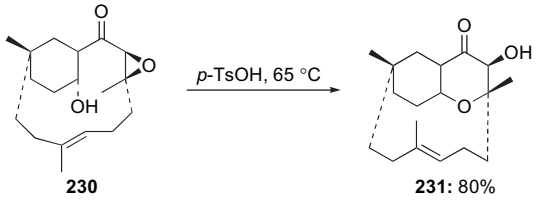
Scheme 72.

Davies-Coleman[93] concisely synthesized ambraketal [**229a**] and 8-*epi*-ambraketal [**229b**] that featured an acid-mediated cyclization of **228** [Scheme 73].



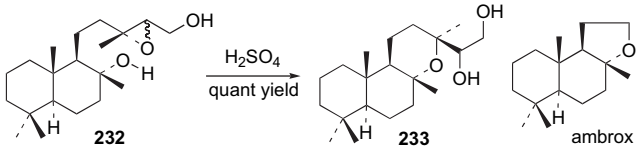
Scheme 73.

In their elegant approach toward phomactins [Fig. 1], Maleczka[94] used an intramolecular acid-mediated epoxide-ring-opening of **230** [Scheme 74].



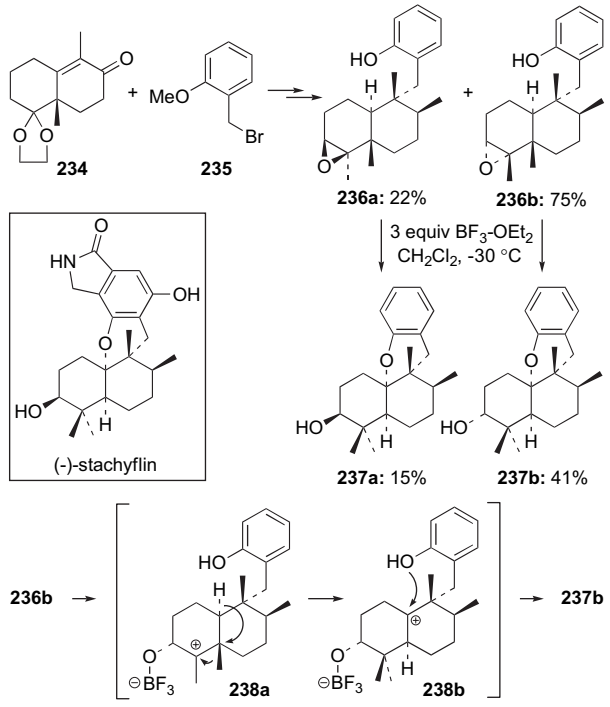
Scheme 74.

Moulines[95] used a key acid-mediated ring-opening of epoxide **232** to afford diol **233** in their synthesis of ambrox, an ambergris-type compound sought after by the perfume industries [Scheme 75].



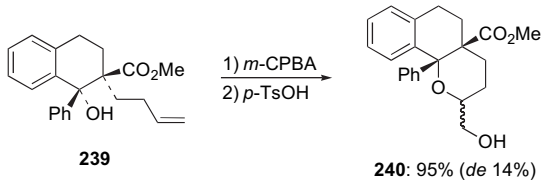
Scheme 75.

Katoh[96] reported in their elegant total synthesis of stachyflin a $BF_3 \cdot Et_2O$-induced domino sequence of epoxide-ring-opening, a double Meerwin rearrangement, and cyclization of **236a** and **236b**, thereby providing a concise route to the tetracyclic core of stachyflin [Scheme 76].



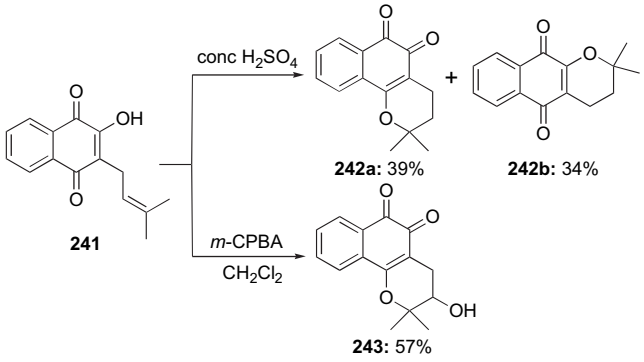
Scheme 76.

Compernolle[97] employed an acid promoted cyclization of alcohol **239** after an initial *m*-CPBA epoxidation [Scheme 77].

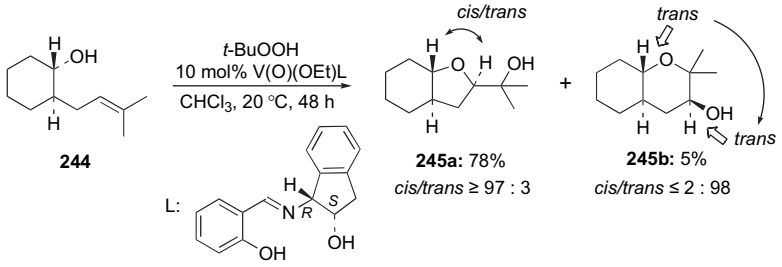


Scheme 77.

In an effort to study the inhibitory effect of lapachol derivatives on Epstein-Barr virus, Pérez Sacau[98] employed an acid-mediated cyclization of naphthoquinone lapachol **241** to obtain lapachol derivatives **242a** and **242b** and **243**, which involved an initial *m*-CPBA epoxidation [Scheme 78].



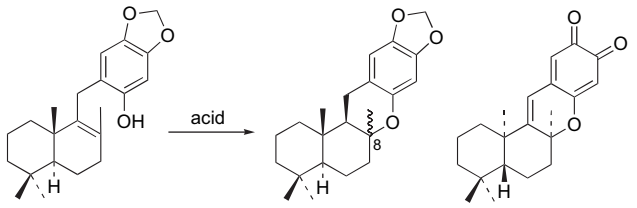
Scheme 78.



Scheme 79.

By using Schiff-based vanadium(V) complex, Hartung[99] efficiently synthesized the functionalized tetrahydrofuran **245a** and tetrahydropyran **245b** [Scheme 79].

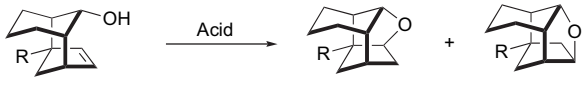
4.6.2. Additions to olefins. In their efforts toward the synthesis of puupehedione, Barrero[100] studied the acid-mediated cyclization of **246** under different conditions and the most significant results are depicted in Scheme 80.



acids	solvents	temp	time	ratios (yields%)
BF_3-Et_2O	CH_2Cl_2	0 °C	15 min	only **b** (85)
2-Naphthalenesulph	CH_2Cl_2	reflux	2 h	**a** : **b** (1 : 2.4) (76)
p-TsOH	benzene	reflux	50 h	**a** : **b** (1 : 4) (90)
conc H_2SO_4	nitropropane	0-10 °C	30 min	**a** : **b** (1 : 9) (93)

Scheme 80.

Ramos-Tombo and Ganter[101] used bridgehead-alkylated *endo*-cyclic olefin **248** to give a mixture of acid-mediated cyclized products **249a** and **249b** [Scheme 81].

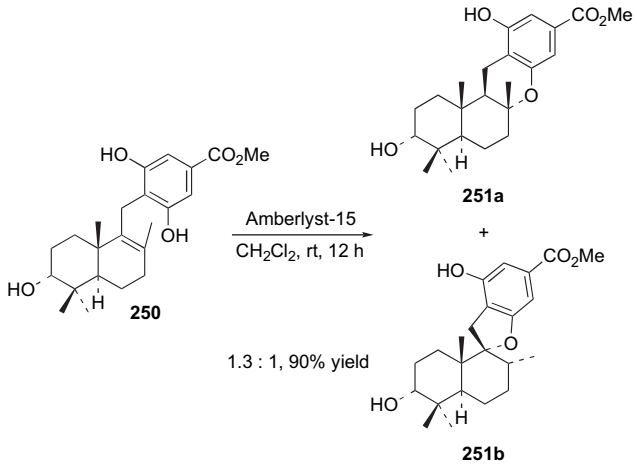


reactant	acid	temp	time (h)	ratio (**a** : **b**)	yield (%)
R = Me	HCl/$CHCl_3$	rt	24	65 : 35	quant
R = Et	HCl/Et_2O	rt	25	80 : 20	87
R = *i*-Pr	HCl/Et_2O	rt	16	95 : 5	90

Scheme 81.

Kende's[102] enantioselective total syntheses of various lactams containing natural products isolated from *Stachybotrys* sp. [not shown here] cleverly featured the Amberlyst-15-mediated cyclization of **250** to give a mixture of **251a** and **251b** in a 1.3:1 ratio [Scheme 82].

Katoh[103] reported an efficient synthesis of the tetracyclic ABCD ring system of the natural products kampanols [see A in Scheme 83], featuring an interesting cyclization of **252** to give both the trans-fused product **253a** using $BF_3 \cdot Et_2O$ and the cis-fused product **253b** using *N*-phenylseleno phthalimide in the presence of $SnCl_4$.



Scheme 82.

In an effort to study the mechanism of abietadiene synthase catalysis, Coates[104] synthesized **255** via an acid-catalyzed dehydrative cyclization of **254** [Scheme 84].

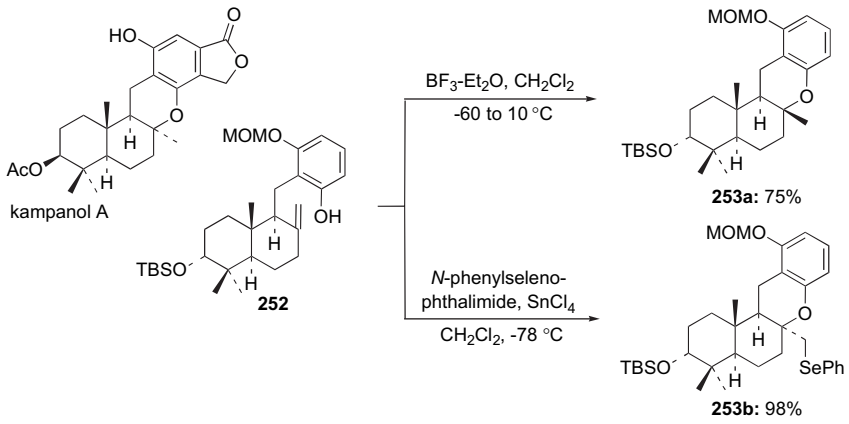
In the synthesis of 3-deoxyschweinfurthin B, Weimer[105] used an acid-catalyzed cationic cyclization of **256** to afford the advanced precursor **257** [Scheme 85].

In their synthesis of hongoquercin A [Fig. 1], Mori[106] cleverly employed an acid-mediated cyclization of **258** to form the ABCD ring system **259** [Scheme 86].

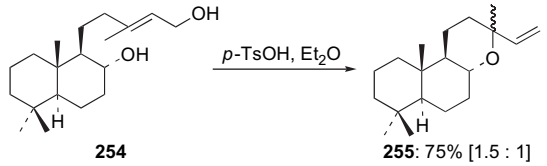
Starting from the appropriate *o*-quinones **260**, Nicolaides[107] used an acid-mediated cyclization to construct 3,4-dihydro-2*H*-benzo[*f*]pyrano[2,3-*h*]chromen-6-one derivatives **261** and **262** [Scheme 87].

Jansen and de Groot[108] were able to transform (+)-larixol to ambra oxides **264** featuring the acid-mediated cyclization of **263** [Scheme 88].

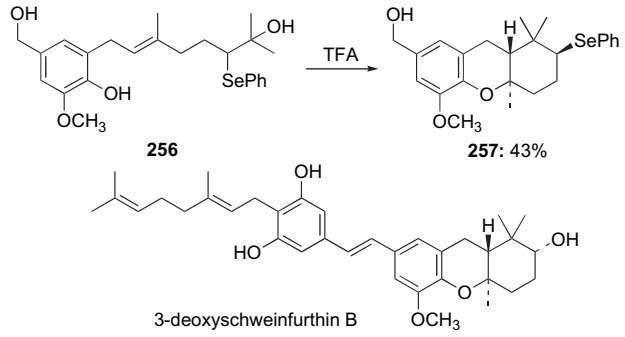
In their concise and elegant stereoselective synthesis of the AB-ring moiety of trichothecene sesquiterpene (+)-calonectrin, Tomioka[109] employed a Lewis acid-mediated cyclization of **265** to afford the cis-fused tetrahedrochromane **266** in good yields [Scheme 89].



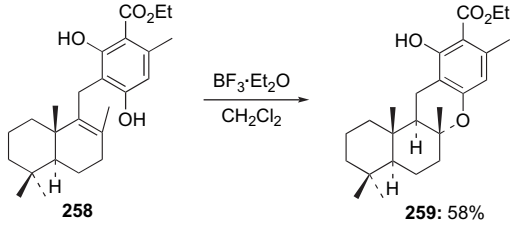
Scheme 83.



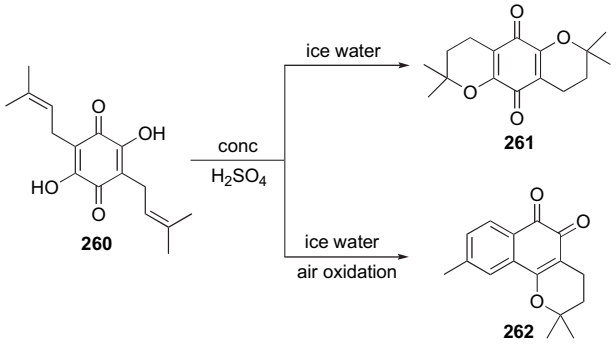
Scheme 84.



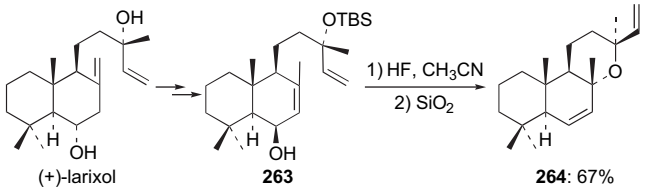
Scheme 85.



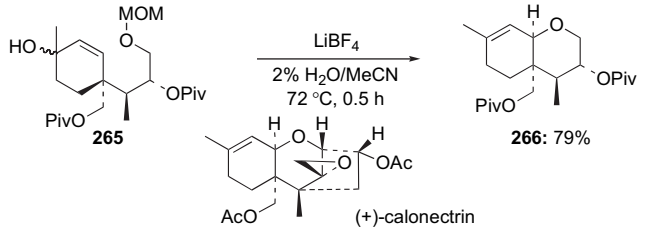
Scheme 86.



Scheme 87.

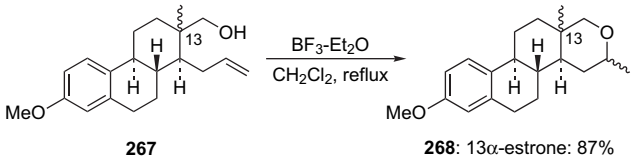


Scheme 88.



Scheme 89.

Schneider[110] reported a stereoselective approach to new oxa-D-homoestrone derivatives that showcased a key stereoselective Lewis acid-mediated cyclization of alkenol **267** to afford 13α-estrone **268** as the only product [Scheme 90].

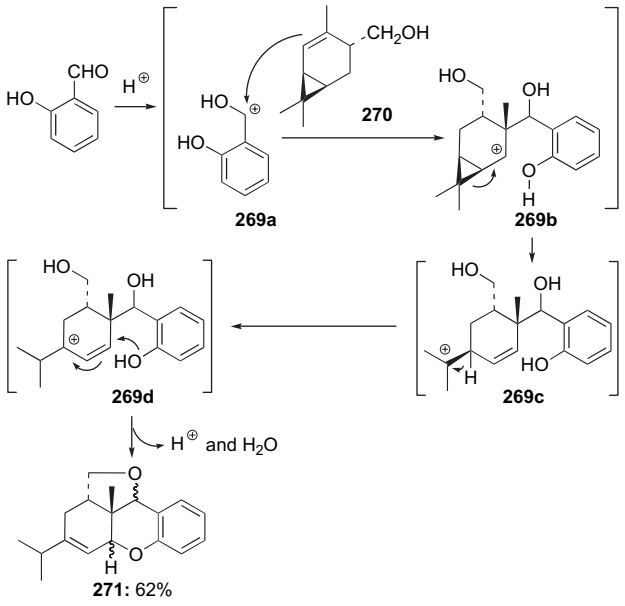


Scheme 90.

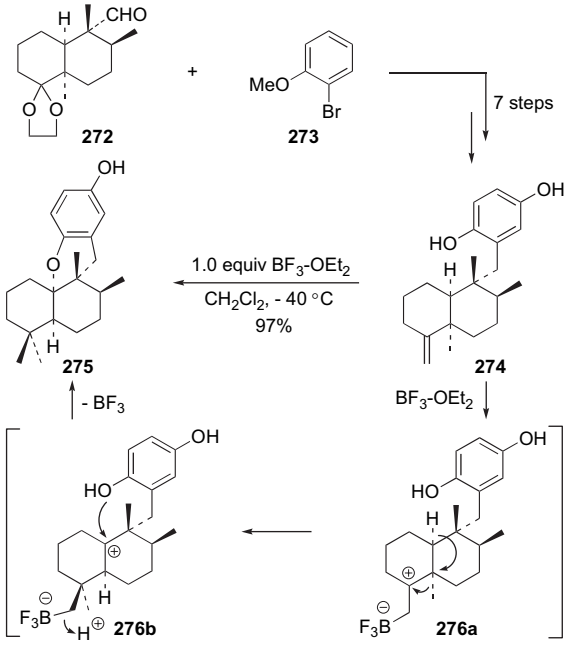
A xanthene skeleton bridged to a tetrahydrofuran ring as shown in **271** was synthesized in 62% yield when carene derivative **270** reacted with *o*-hydroxy aldehyde over the askanite–bentonite clay at room temperature [Scheme 91].[111]

Another interesting $BF_3 \cdot Et_2O$-promoted double Meerwin rearrangement/cyclization reaction employing (+)-arenarol **274** in an efficient synthesis of (+)-aureol **275** was reported by Katoh [Scheme 92].[112]

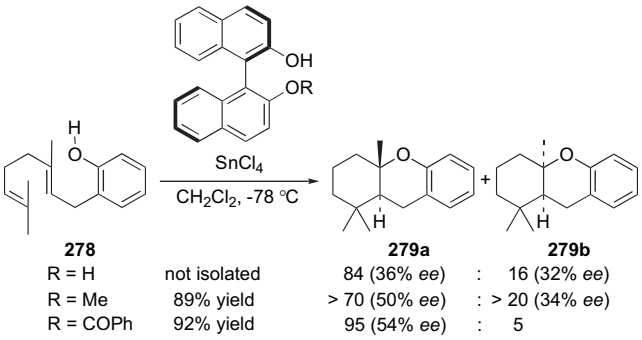
4.6.3. Polyene-type cyclizations. In their development of an enantioselective polyene cyclization, Ishihara and



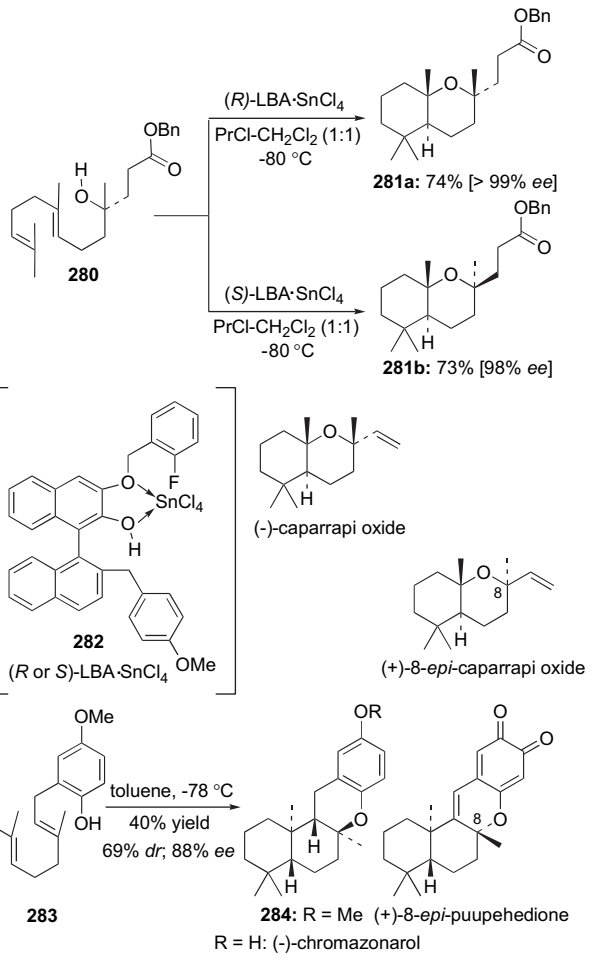
Scheme 91.



Scheme 92.



Scheme 93.



Scheme 94.

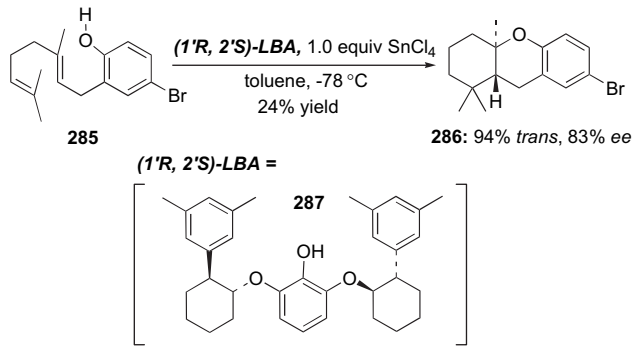
Yamamoto[113] employed Lewis acid-assisted chiral Brønsted acids [LBA] to cyclize various isoprenoids such as **278** into **279** in modest to excellent ees [Schemes 93 and 94].

In their recent asymmetric total synthesis of acid-sensitive (−)-caparrapi- and (+)-8-*epi*-caparrapi oxide, Ishihara[114] demonstrated an excellent application of their Lewis acid-assisted chiral Brønsted acid [LBA]-induced polyene cyclization of **280** [Scheme 94]. In addition, en route to elegant total syntheses of natural products such as (−)-chromazonarol and (+)-8-*epi*-puupehedione, polyene cyclization of **283**[115] employing LBA-**282** gave tetracycle **284** in good dr and ee.

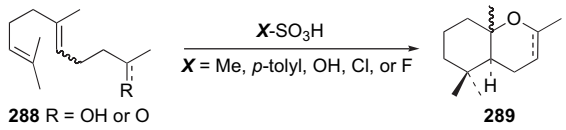
In addition, Ishihara[116] recently reported another novel Lewis acid-assisted chiral Brønsted that constitutes an artificial cyclase for biomimetic cyclization [Scheme 95].

Linares-Palomino[117] demonstrated that chlorosulfonic acid could also promote electrophilic olefin cyclization of substrates **288** to give cyclized products **289** [Scheme 96].

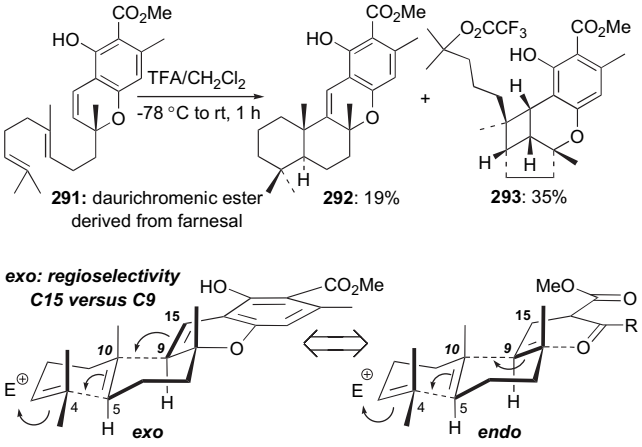
Hsung[63] reported an unusual polyene cyclization pathway that led to a divergent total synthesis of hongoquercin A and rhododaurichromanic acid A [Scheme 97]. This work uncovered a novel cationic cyclobutane formation that could be relevant to the biosynthetic pathway for the formation of



Scheme 95.



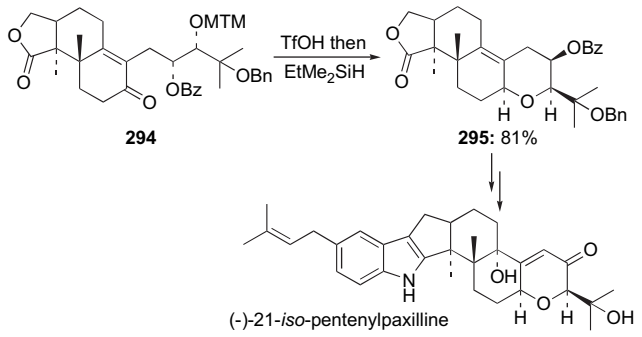
Scheme 96.



Scheme 97.

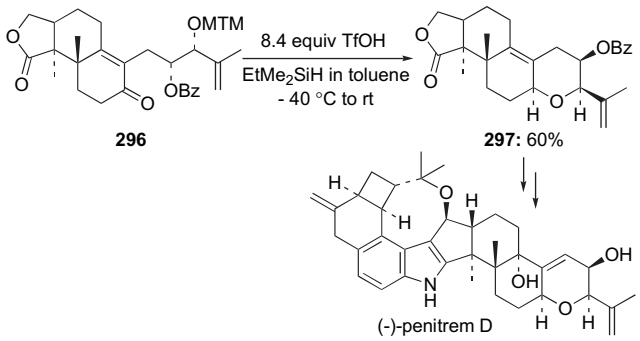
cyclobutane containing terpenoids in addition to rhododaurichromanic acids.

4.6.4. Miscellaneous acid promoted cyclizations. In their elegant total synthesis of (−)-21-isopentenylpaxilline, Smith[118] reported generation of the tetrahydropyran ring in **295** through a cascade process starting from the cleavage of the $MeSCH_2$ (MTM) protecting group to a $EtMe_2Si$-H reduction of the cyclized hemiacetal intermediate [Scheme 98].



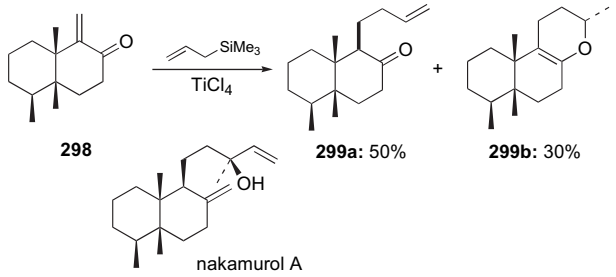
Scheme 98.

A similar strategy was also used in Smith's total synthesis of (−)-penitrem D [Scheme 99].[119]



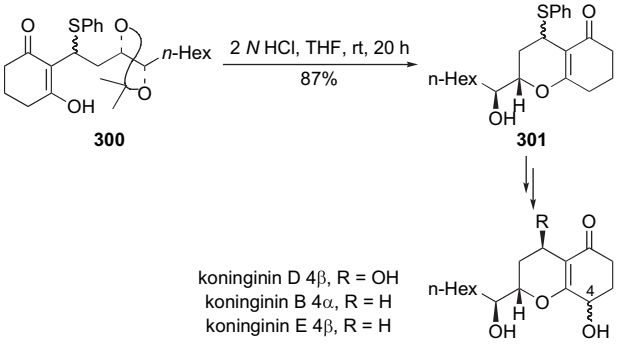
Scheme 99.

In their total synthesis of (±)-nakamurol-A, Bonjoch[120] found that when a slight excess of $TiCl_4$ was used, α-methylene ketone **298** could be transformed to the ketone **299b** via a desired Sakurai reaction, but another product **299b** was also found, which was likely derived from a hetero-Diels–Alder reaction or an acid-mediated cyclization from **299a** [Scheme 100].



Scheme 100.

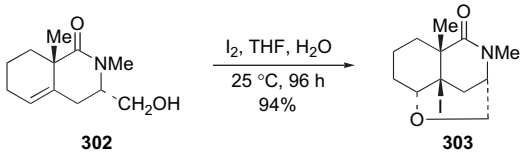
In the total synthesis of koninginins D, B, and E, the deprotection of ketal **300** by treatment with dilute HCl in acetone furnished 1-oxadecalin **301** [Scheme 101].[121]



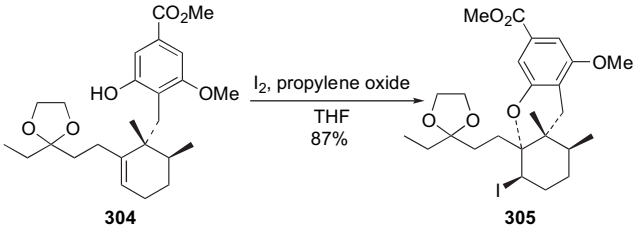
Scheme 101.

4.6.5. Electrophilic etherifications. Schultz[122] reported that treatment of olefinic alcohol **302** with I_2 in THF and H_2O under conditions of thermodynamic control gave iodopyran **303** in 94% yield [Scheme 102].

Mori's[123] total synthesis of (±)-stachyflin [see Scheme 76] showcased the construction of cis-fused 1-oxadecalin via an iodo-etherification [Scheme 103].

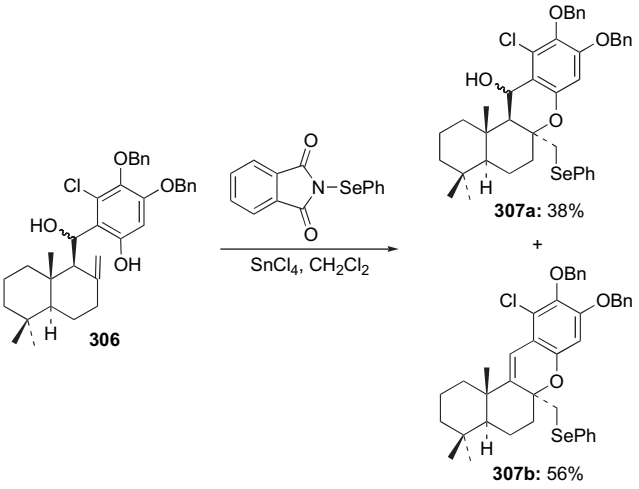


Scheme 102.



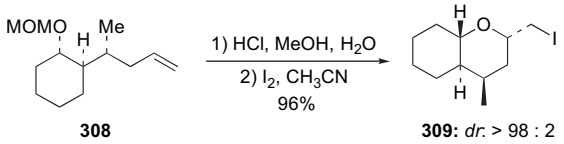
Scheme 103.

Hua[124a] and Katoh[124b] reported that oxy-selenylation of diol **306** with 1.1 equiv of *N*-phenylseleno phthalimide and 0.1 equiv of tin tetrachloride gave selenyl pyran **307a** in 38% yield and unsaturated pyran **307b** in 56% yield, which was formed from the dehydration of **307a** catalyzed by either $SnCl_4$ or HCl [Scheme 104].



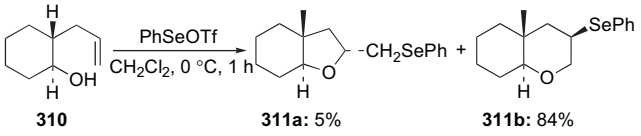
Scheme 104.

Chemla[125] reported the transformation of **308** into the substituted pyran **309** via hydrolysis of the MOM moiety followed by iodo-etherification of the resulting alcohol [Scheme 105].



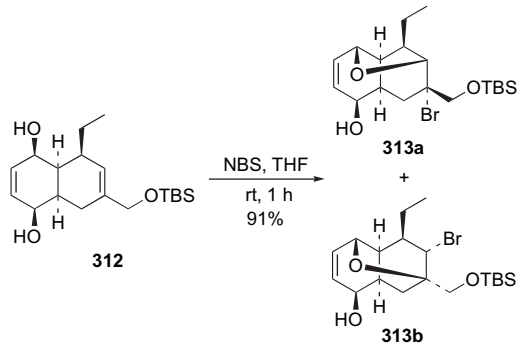
Scheme 105.

Murata[126] studied the selective intramolecular oxy-selennylation of olefinic alcohols and carboxylic acids by using organic cyano selenides in the presence of metal triflates to generate PhSeOTf. Depending on the conditions, reactions of *trans*-2-allylcyclohexanol **310** can selectively afford *exo*-cyclized tetrahydrofuran **311a** or *endo*-cyclized tetrahydropyran **311b** [Scheme 106].



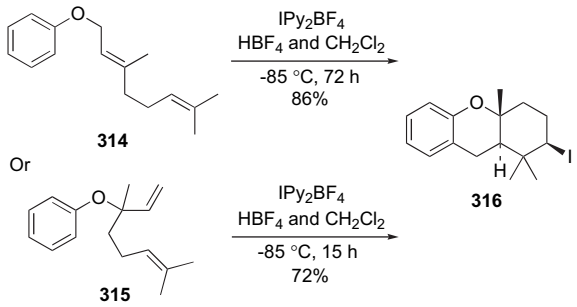
Scheme 106.

White[127] found that when *cis*-diol **312** was treated with *N*-bromosuccinimide [NBS], a mixture of inseparable bromoepoxy alcohols 5-*exo* product **313a** and 6-*endo* product **313b** were obtained [Scheme 107].



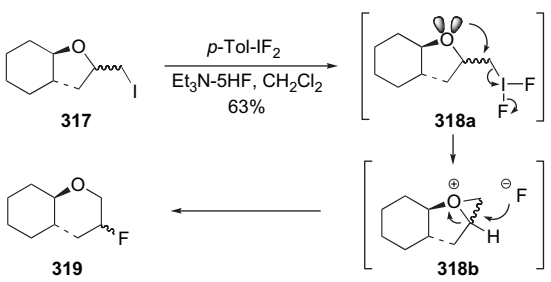
Scheme 107.

Barluenga[128] reported a flexible approach to chromane and tetrahydroquinoline derivatives by using intramolecular arylation reactions of alkenes employing IPy_2BF_4 as the source of iodonium ion [Scheme 108].



Scheme 108.

Interestingly, the fluorinated six-membered cyclic ether **319** was stereoselectively synthesized from furan **317** via a fluorinative ring-expansion reaction using *p*-iodo-toluene difluoride [Scheme 109].[129]

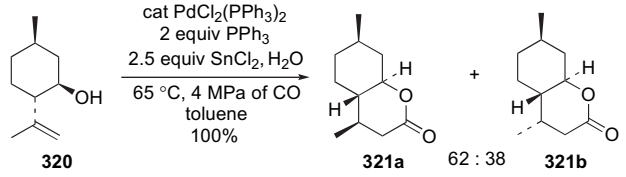


Scheme 109.

5. Transition metal-mediated cyclizations

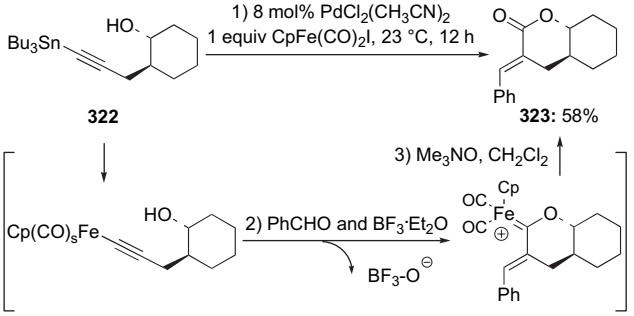
5.1. Palladium

Kalck[130] found that the cyclocarbonylation of isopulegol catalyzed by $PdCl_2(PPh_3)_2$ led to the desired lactone **321** in 60% de [Scheme 110]. A hydride intermediate [PdH–$SnCl_3L_2$] was proposed as the active species that hydro-palladated [likely directed by the hydroxy group] the terminal olefin in an anti-Markovnikov manner prior to carbonylation.



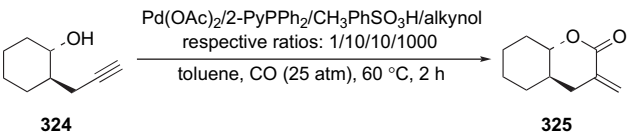
Scheme 110.

Liu[131] observed that in the presence of 1 equiv of $CpFe(CO)_2I$ and 8 mol % of $PdCl_2(CH_3CN)_2$, hydroxyalkynyl stannane **322** underwent Pd(0)-catalyzed transmetalation to give rise to a reactive iron–alkynyl complex, which was condensed in situ with $PhCHO/BF_3{\cdot}Et_2O$ to yield a cationic iron styryl carbene complex that underwent Me_3NO-oxidation to give lactone **323** [Scheme 111].



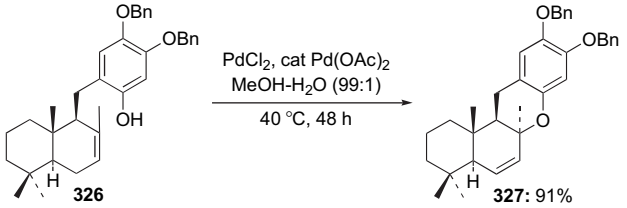
Scheme 111.

Dupont[132] reported that the cyclocarbonylation of alkynol **324** catalyzed by $Pd(OAc)_2$ in either organic solvents or ionic liquids led to *exo*-α-methylene δ-lactones **325** quantitatively in a highly regioselective manner [Scheme 112].



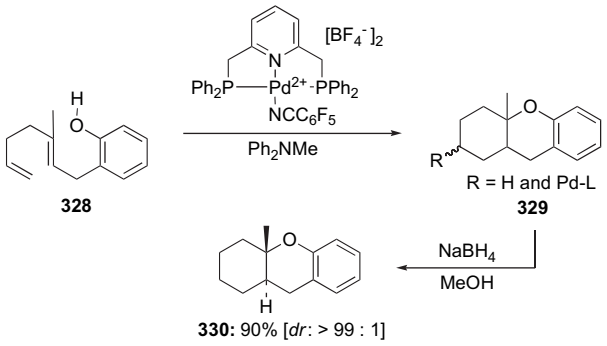
Scheme 112.

In an efficient enantioselective synthesis of the natural product (−)-15-oxopuupehenol [for a related structure see Scheme 80],[100] Alvarez-Manzaneda[133] found that Pd(II)-induced cyclization of **326** in a Wacker-type oxidative manner to give the desired tetracycle **327** as a single isomer [Scheme 113].



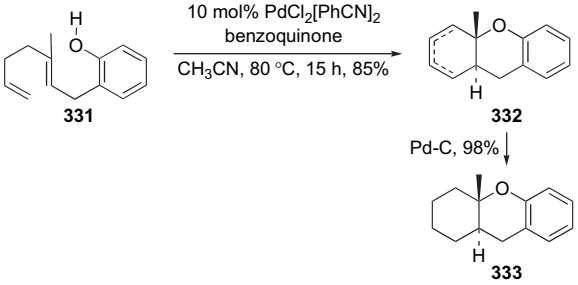
Scheme 113.

Gagne[134] reported an interesting Pd^{II}-mediated oxidative [Wacker-type] poly-cyclization reaction of 1,5-dienes **328** that led to tricycle **329** [Scheme 114].



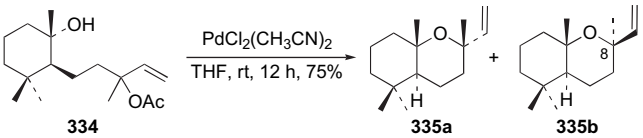
Scheme 114.

Gagne[135] also reported another related Pd^{II}-catalyzed oxidative polyoxa-ene cyclization reaction initiated by carbocyclization of 1,5-dienes **331**. These studies suggest the presence of carbocation-like intermediates that can ultimately be trapped by suitable nucleophiles such as phenols [Scheme 115].



Scheme 115.

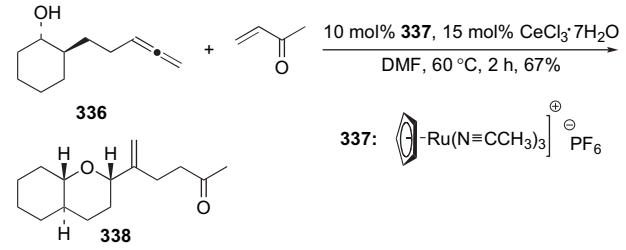
Barrero[136] illustrated that when treating allyl acetate **334** with $PdCl_2(CH_3CN)_2$, mono-carbocyclic terpenoids (−)-caparrapi **335a** and its C8-epimer **335b** [ratio 2:1] were isolated in 75% yield [Scheme 116].



Scheme 116.

5.2. Ruthenium

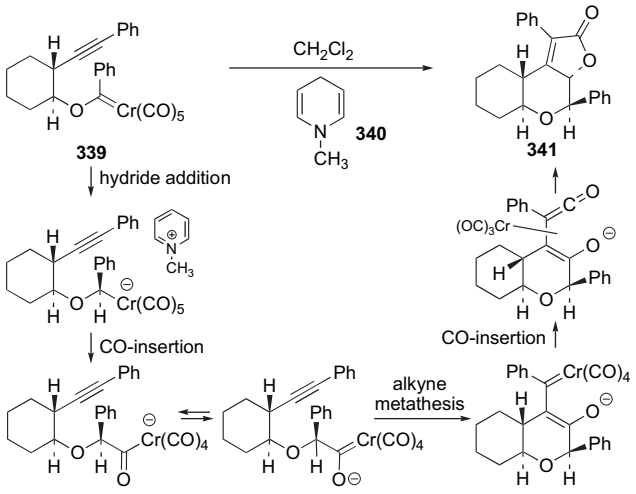
Trost[137] reported a ruthenium-catalyzed alkylative cycloetherification reaction that provided cyclic ethers such as **338** in 67% yield from alcohol **336** and methyl vinyl ketone [Scheme 117].



Scheme 117.

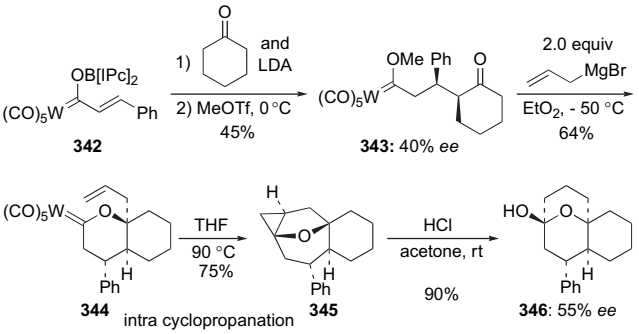
5.3. Chromium and tungsten

Rudler[138] reported a very interesting synthesis of tricyclic butenolide **341** from Fisher Cr(0)-carbene complex **339** through a unique sequence as shown in Scheme 118. The key steps are an initial reduction of the carbene carbon and the two CO insertions.



Scheme 118.

Barluenga[139] reported an interesting synthetic sequence leading to an enantioselective formation of bridged tricycle **346** from chiral alkenyl Fisher Cr(0)-carbene complex **342** and lithium enolate of cyclohexanone [Scheme 119].



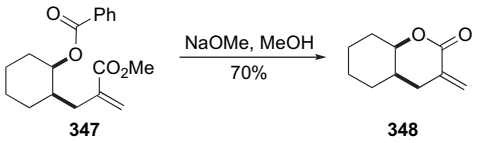
Scheme 119.

6. Simple lactone and lactol formations

This section presents another common and perhaps the most straightforward strategy for constructing 1-oxadecalins.

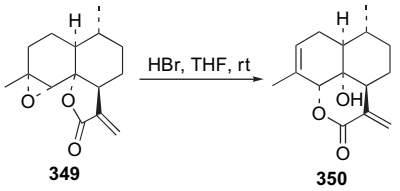
6.1. Lactones

A common way to form 1-oxadecalin containing compounds is esterification. Both Hon[140a] and Rigby[140b] reported that when benzoates such as **347** was subjected to basic condition, lactone **348** could be obtained in 70% yield [Scheme 120].



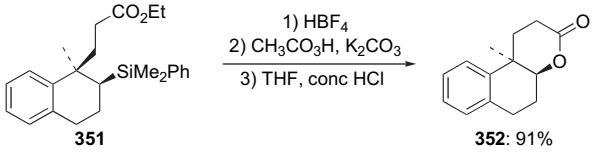
Scheme 120.

When epoxy lactone **349** was subjected to acidic condition, the resulting alcohol underwent trans-esterification in a ring-expansion manner to give the more stable lactone **350** [Scheme 121].[141]



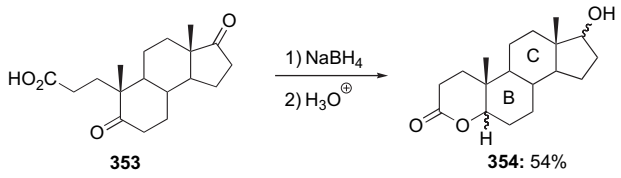
Scheme 121.

Meyers[142] showed an interesting example of employing the silyl substituent as an oxygen surrogate through Tamao–Fleming oxidation en route to lactone **352** [Scheme 122].



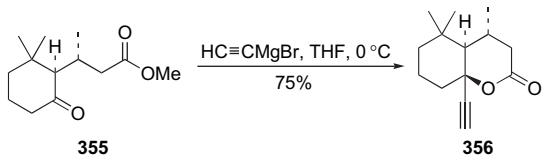
Scheme 122.

Fukazawa[143] illustrated that when diketone **353** was reduced to an alcohol intermediate, it cyclized under acidic condition to give lactone **354** [stereochemistry at its BC-ring junction was not defined] [Scheme 123].



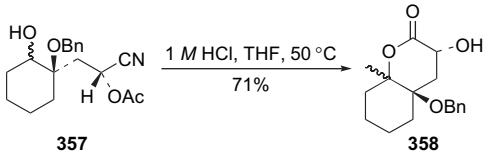
Scheme 123.

In Frater's work,[144] the addition of ethynyl magnesium bromide to ketoester **355** resulted in a tertiary alcohol intermediate that cyclized to give lactone **356** [Scheme 124].



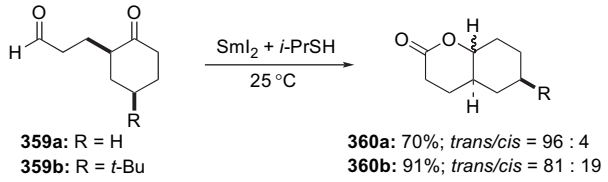
Scheme 124.

Cyanohydrin **357** was hydrolyzed under acidic conditions to give a carboxylic acid intermediate, which underwent lactone formation to give **358** in 71% yield [Scheme 125].[145]



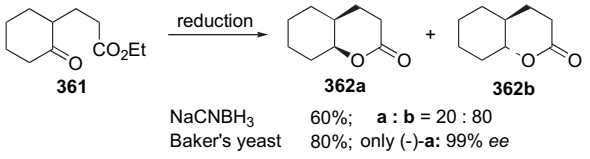
Scheme 125.

Fang[146] reported an interesting SmI_2/*i*-PrSH-mediated formation of 1-oxa-2-decalones **360a** and **360b** from ketone aldehydes **359a** and **359b**, respectively, through an Evans–Tischenko reductive pathway [Scheme 126].



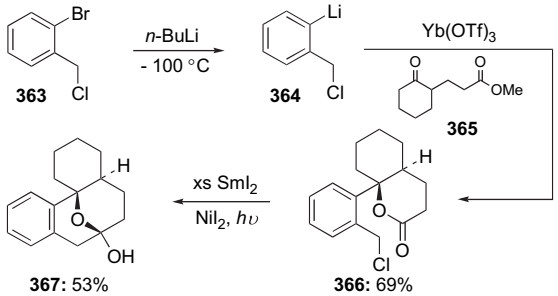
Scheme 126.

Valentin[147] cleverly obtained enantiomerically pure *cis* 1-oxa-2-decalone **362a** from reduction of δ-ketoester **361** using raw Baker's yeast. In comparison, using $NaCNBH_3$ as reducing agent provided a mixture of *trans* and *cis* decalones **362a** and **362b** [Scheme 127].



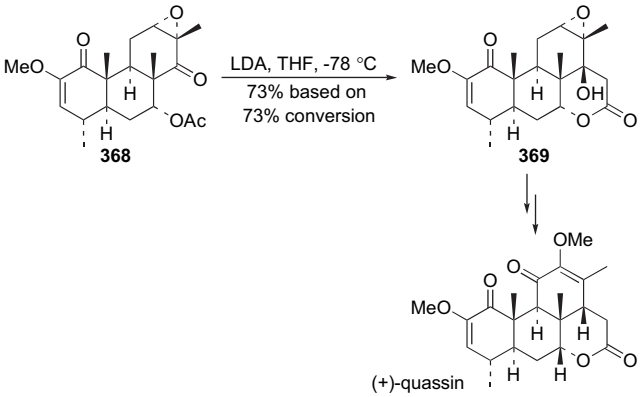
Scheme 127.

Molander[148] reported a sequence leading to lactone **366** via nucleophilic addition of the aryl lithium **364** to ketoester **365**. Subjecting the resulting chloro lactone **366** to intramolecular reductive coupling using SmI_2 and cat NiI_2 led to **367** [Scheme 128].



Scheme 128.

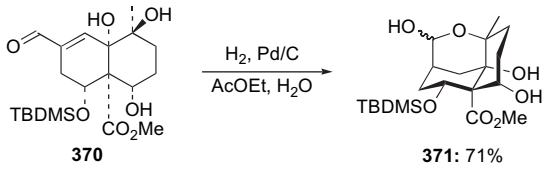
In their beautiful total synthesis of (+)-quassin, Shing[149] found that upon treating acetate **368** with LDA, intramolecular aldol occurred to give lactone **369** as a single diastereomer in good yield [Scheme 129].



Scheme 129.

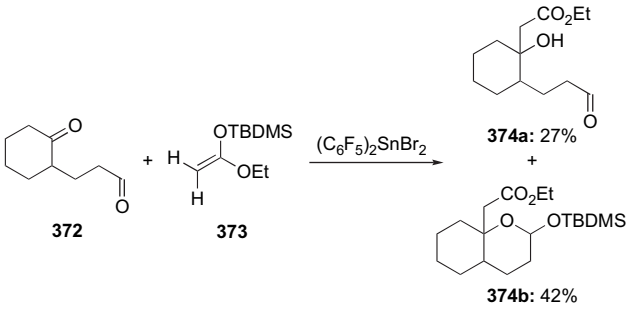
6.2. Lactols

Another commonly used way to form a 1-oxadecalins would involve an alcohol and an aldehyde moiety in the formation of acetal or hemiacetals. In the synthesis of agarofuran antifeedants, catalytic hydrogenation of the double bond of **370** occurred from α-face and resulted in the lactol formation to give hemiacetal **371** [Scheme 130].[150]



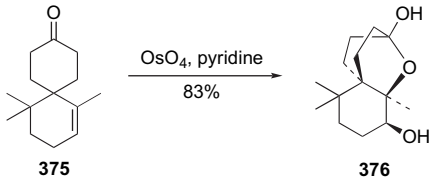
Scheme 130.

Otera[151] observed a very interesting reversal of chemoselectivity in $(C_6F_5)_2SnBr_2$-catalyzed aldol reaction of silyl ketene acetal **373** and ketoaldehyde **372**. The unusual preference for the ketone resulted in the formation of aldehyde **374a**, which was partially converted to 1-oxadecalin **374b** in the presence of Lewis acid [stereochemistry was unassigned] [Scheme 131].



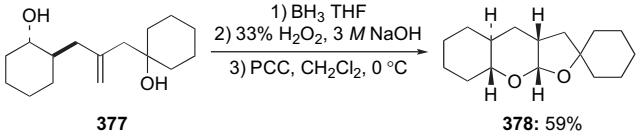
Scheme 131.

In Iwata's synthesis of laurencial [not shown],[152] dihydroxylation of the alkene moiety of enone **375** gave lactol **376** in 83% yield [Scheme 132].



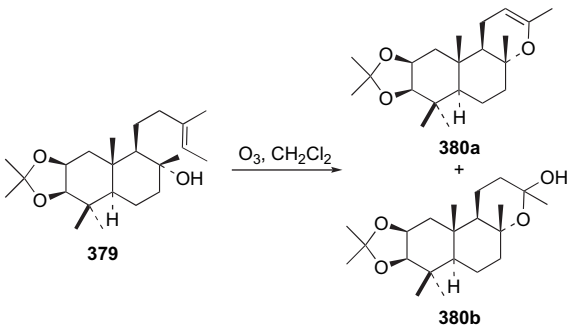
Scheme 132.

Pyran **378** containing 1-oxadecalin was synthesized from diol **377** through a sequence of hydroboration/oxidation developed by Yus[153] [Scheme 133].



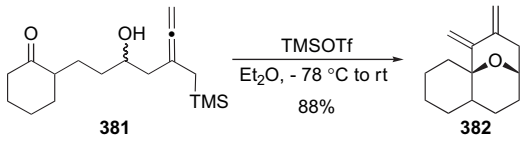
Scheme 133.

Ozonolysis of alkene **379** generated a ketone intermediate that subsequently reacted with the tertiary alcohol to give arise to a mixture of enol ether **380a** and hemiacetal **380b** [Scheme 134].[154]



Scheme 134.

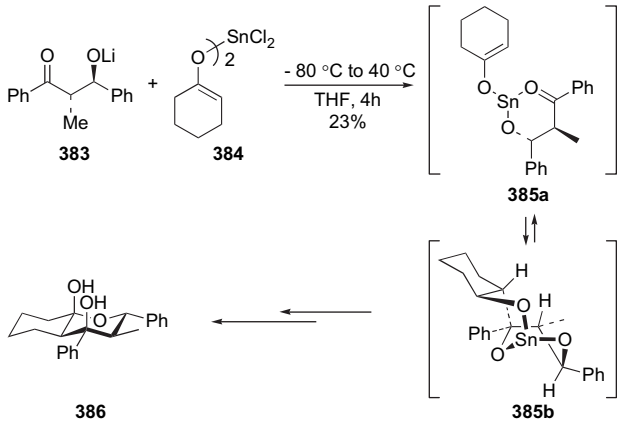
In the presence of TMSOTf, allenol **381** underwent lactol formation followed by addition of allyl silane to the oxocarbenium intermediate to give oxa-bicycle **382** [Scheme 135].[155]



Scheme 135.

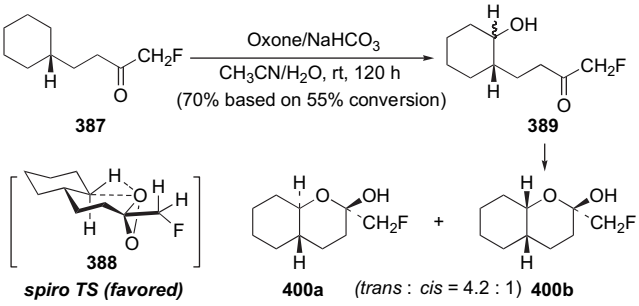
The addition of stannyl enolate **384** to ketone **383** was reported to give lactol **386** [Scheme 136].[156]

Last but not the least, Yang reported an elegant regioselective (δ-selective) intramolecular oxidation of unactivated C–H bonds by dioxiranes with a favored spiro-TS



Scheme 136.

[see **388** in bracket], in which oxidation of the equatorial δ C–H bond is strain-free, leading to the observed diastereoselectivity in 1-oxadecalins **400a** and **400b** after the lactol formation [Scheme 137].[157]



Scheme 137.

7. Conclusion

In conclusion, we have presented here a sample of various strategies and approaches that have been employed in constructing 1-oxadecalins for a diverse array of purposes. Given the prevalence of this structural motif among a diverse array of natural products, we hope this review could serve as a springboard that may help bringing forth future innovative approaches.

Acknowledgements

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References and notes

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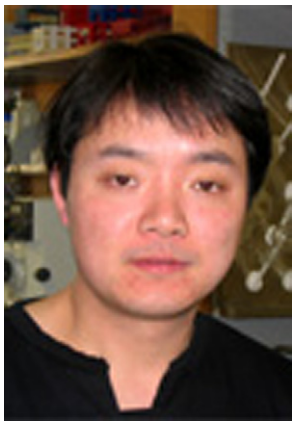
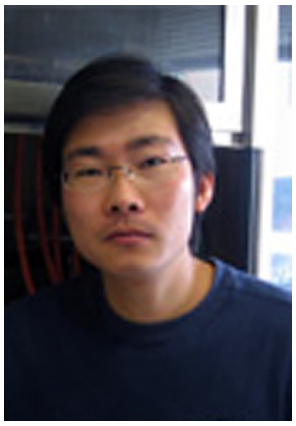
Biographical sketch



Yu Tang was born and raised in Mianyang, China. He received his B.S. from Lanzou University in 1998. He then worked in Diao Gp. from 1998 to 2000 as a research assistant. In 2005, he received his Ph.D. from Shanghai Institute of Organic Chemistry under the guidance of Professor Chaozhong Li, where he worked on amidyl radical cyclizations. In 2005, he joined Professor Richard Hsung's research group as a post-doctoral research associate. His current research interests entail total synthesis of natural products employing intramolecular oxa-[3+3] annulations.



Zhenlei Song obtained his B.S. degree from Lanzhou University in 2000. In 2005, he received his Ph.D. from Lanzhou University with Professor Yongqiang Tu and pursued total syntheses of alkaloids via pinacol-type rearrangements. He is currently a post-doctoral research associate in Professor Hsung's group and his research entails applications of inverse-demand hetero [4+2] cycloadditions of chiral allenamides in natural product syntheses.

Jossian Oppenheimer received his B.S. in Industrial Chemistry from the University of Puerto Rico in 1998, where he worked with Professor Margarita Ortiz on asymmetric reductions of oximes. He received, in 2001, his M.S. in Bio-Organic Chemistry from The Ohio State University under the direction of Professor Rob Coleman, and in 2005, his Ph.D. in Organic Chemistry also with Professor Coleman where he pursued asymmetric total syntheses of oximidines. Currently, he is a post-doctoral research associate in Professor Hsung's research laboratories pursuing cycloadditions of ynamides.

Lingfeng You obtained his B.S. from University of Science and Technology of China in 1998. From 1998 to 2005, he studied in West Virginia University and University of Pittsburgh under the supervision of Professor Kay Brummond, and obtained his Ph.D. in 2005. He is currently a post-doctoral research associate in Professor Hsung's group pursuing 1,3-dipolar cycloadditions of ynamides and syntheses of benzimidazoles in a joint project with Emeritus R. F. Hirschmann Professor Dan Rich.

Xuejun Zhang received his B.S. from University of Science and Technology of China in 2002 and worked with Professor Guan-Wu Wang. Since 2002, he has been pursuing Ph.D. degree in Organic Chemistry under the supervision of Professor Hsung at the University of Minnesota and then University of Wisconsin at Madison. His thesis focuses on syntheses and reactions of ynamides as well as intramolecular aza-[3+3] annulations.

Richard P. Hsung enrolled at Calvin College in Grand Rapid, MI, obtaining his B.S. in Chemistry and Mathematics in 1988, and worked on electrochemistry in Professors Ron Blankespoor and Kenneth Piers' laboratories. He then attended The University of Chicago and received his M.S. and Ph.D. degrees in Organic Chemistry in 1990 and 1994, respectively, under supervisions of Professors Jeff Winkler and Bill Wulff. After pursuing a brief post-doctoral stay at Chicago with Professor Larry Sita in 1995, he completed his training as an NIH post-doctoral fellow in Professor Gilbert Stork's laboratory at Columbia University. In 1997, he moved to University of Minnesota as an Assistant Professor, and was promoted to Associate Professor in 2002. He was promoted to Professor and moved to University of Wisconsin at Madison in 2006. He is a recipient of Johnson and Johnson Focused Giving Award, McKnight Young Faculty Award, Camille Dreyfus Teacher-Scholar Award, and National Science Foundation Career Award. He has co-authored over 150 publications and his research interests involve developing cycloaddition and annulation approaches to natural product syntheses and stereoselective methods using allenamides, ynamides, and cyclic ketals.