HHS Public Access

Author manuscript

Chem Rev. Author manuscript; available in PMC 2018 September 27.

Published in final edited form as:

Chem Rev. 2017 September 27; 117(18): 11753–11795. doi:10.1021/acs.chemrev.6b00834.

Navigating the Chiral Pool in the Total Synthesis of Complex Terpene Natural Products

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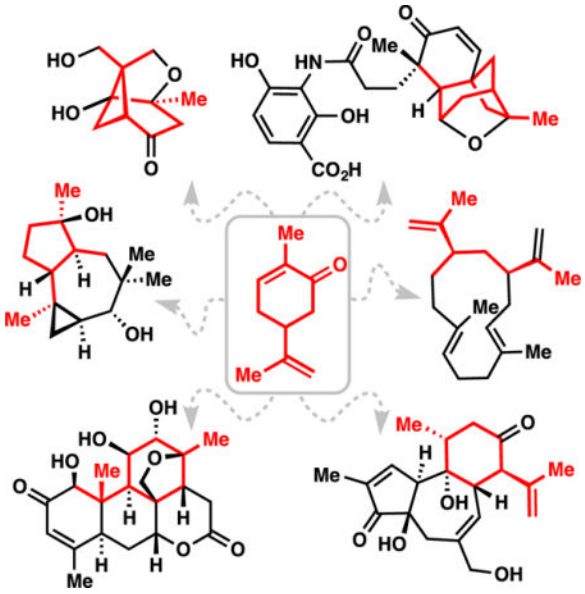
Abstract

The pool of abundant chiral terpene building blocks (i.e. “chiral pool terpenes”) has long served as a starting point for the chemical synthesis of complex natural products, including many terpenes themselves. As inexpensive and versatile starting materials, such compounds continue to influence modern synthetic chemistry. This review highlights 21st century terpene total syntheses which themselves use small, terpene-derived materials as building blocks. An outlook to the future of research in this area is highlighted as well.

Graphical abstract



1. Introduction

Naturally occurring terpenes and their derivatives have profoundly impacted the human experience.[1] As flavors, fragrances, poisons, and medicines, nearly every human on earth has experienced their effects. As potential fuels,[2] monomers for polymer synthesis,[3]

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Notes

The authors declare no competing financial interests.

biochemical signaling agents,[1] sources of chirality for synthetic reagents and catalysts,[4] and starting materials for organic synthesis, terpenes have also impacted virtually every area of modern chemistry. Along with carbohydrates and amino acids, small chiral terpenes collectively form what is commonly referred to as the "chiral pool," that is, the collection of abundant chiral building blocks provided by nature. Owing to their low cost, high abundance, and general renewability, the chiral pool has been extensively utilized by synthetic chemists in the synthesis of both natural products as well as pharmaceutical agents and dozens of reviews, books, and highlights exist on this topic.[5–11] In particular, the ability to convert one terpene into another was recognized long before the biogenetic "isoprene rule" was formally delineated.[12–14] Coupled with advances in spectroscopy and separation techniques, the last 50 years have witnessed an explosion in synthetic terpene research resulting in the total synthesis of many complex terpene natural products, the rise of the semisynthetic steroid field, and the FDA-approval of a variety of terpene-based drugs.[15] Even considering the enormous advances in asymmetric synthesis developed during the 20th century,[16] the use of chiral terpenes as starting materials for terpene synthesis continues unabated today. Multiple recent reviews on the total synthesis of complex terpenes exist.[17–20] This review focuses on complex terpene total syntheses utilizing the chiral pool of terpenes as starting materials and effort has been made to avoid overlap with an excellent 2012 review by Gaich and Mulzer on this topic.[21] In addition, the material discussed herein is limited solely to total syntheses appearing in the 21st century and also largely omits meroterpenes, terpene/alkaloid hybrids, and other compounds of "mixed" biosynthetic origins. The semisynthesis of steroid derivatives, to which multiple books and reviews have been devoted, are also not highlighted herein.[22,23]

2. Starting Points and Historical Perspective

Chiral pool terpene syntheses are influenced by three main factors: (i) the current availability of the starting terpene building blocks, (ii) the current state of the art in synthetic methodology, and (iii) the creativity of the practitioner. With regard to the first point, Figure 1 presents a general depiction of the most frequently utilized chiral pool terpenes in total synthesis. In addition, their current lowest available prices from Sigma-Aldrich are also shown.[24] It should be noted that the enantiomeric purity of many terpene-building blocks are variable depending on the source and this information is not always stated.[10] As many terpenes are liquids or oils, they cannot be crystallized to enantiopurity directly. Moreover, even if a terpene starting material is of high enantiomeric excess, it may be only available as one enantiomer. Sometimes this is not a problem as a convenient asymmetric method exists to prepare the needed enantiomer, or a related terpene can be converted into the scarcer enantiomer. Many of these points will be further discussed below.

(−)-Citronellol (**1**) serves as a common acyclic, chiral pool terpene building block and is easily transformed into both citronellal and citronellic acid, two useful synthetic derivatives, via oxidation. A review on the use of citronellal in synthesis has been reported.[25] While the (+)-enantiomer of **1** is approximately twenty times more expensive, either enantiomer is readily prepared from geraniol via enantioselective reduction.[26] Similarly, linalool (**2**), which is most readily available as the (−) enantiomer, can be easily prepared in either

enantiomeric form though asymmetric epoxidation of geraniol, mesylation, and reductive ring opening.[27]

The monocyclic monoterpenes represent widely utilized building blocks in polycyclic terpene synthesis and many chemical transformations.[10,11] The chiral hydrocarbon limonene (see **3** and **4**) is a commodity chemical, available as both (+) and (−) enantiomers, and is exceedingly inexpensive in either mirror image form. Its allylic oxidation product carvone (see **5**, **6**), however, represent the most useful and versatile building blocks in this series and the most frequently utilized chiral pool terpene employed in this review. A review on the use of carvone in natural product synthesis has also recently appeared.[28] (−)-Isopulegol (**7**), a monoterpene of the menthane subtype, also finds use in total synthesis owing to its altered oxygenation pattern, as does (−)-perillyl alcohol (**9**). Pulegone (**8**), whose reactive enone system is readily functionalized, has found extensive use in terpene synthesis; it is of note that the (−) enantiomer of **8** is prohibitively expensive. Although somewhat less frequently employed in total synthesis, the bicyclic family of monoterpenes (see **10**–**20**) offer unique synthetic possibilities in synthesis owing to the ring strain present in many members.[10,11] α-Pinene (see **10** and **11**) is perhaps the flagship member, and it is also one of the most inexpensive terpenes in general. Its β-isomer (**12**), however, is inexpensive only as the (−) enantiomer. While more costly, verbenone (**13**) and myrtenal (**14**) offer more possibilities in synthesis owing to the presence of increased functionality. (+)-Camphor (**15**), (−)-borneol (**16**), (+)-camphene (**17**), and (−)-fenchone (**18**) represent inexpensive building blocks containing the bicyclo [2.2.1] heptane nucleus. The chemistry of camphor is especially extensive.[29] Notably, oxidation of **16** serves as a way of accessing (−)-camphor. Finally, the carenes (see **19** and **20**), which have proven especially useful in the synthesis of cyclopropane-containing terpenes (*vide infra*), round out this series. Notably, 2-carene can be prepared in either enantiomer from carvone.[30] Bulk 3-carene of unreported optical purity is exceedingly inexpensive ($0.04 USD/gram). Besides steroid systems, which lie outside the scope of this review, several complex, higher-order terpenes have found general use in the synthesis of natural products. Two examples are (−)-α-santonin (**21**) and sclareolide (**22**), the former of which has been utilized extensively in the synthesis of guaianolide natural products.[21,31]

With an abundance of terpene building blocks available for use, where does one start in designing a chiral pool-based terpene synthesis? While there are no general flowcharts for such activities, chiral pool syntheses can be roughly grouped based on the similarity of the terpene building block to the target molecule (Figure 2). In the most common scenario (denoted here as “level 1”), the entire uninterrupted carbon skeleton of the starting terpene can be directly identified within the skeleton of the target. Notably, structural database searching tools (i.e. Reaxys, Scifinder, etc.) can be easily employed for identifying such relationships, in addition to the capable human mind which is adept at pattern recognition.[32] Corey’s landmark 1979 synthesis of picrotoxinin (**23**) from carvone,[33] and the Hoffman La Roche synthesis of artemisinin (**24**) from isopulegol,[34] exemplify level 1 syntheses. It should be noted however, that this classification has no bearing on the actual tools, tactics, and exact starting terpene employed.[35] For instance, the skeleton of a monocyclic monoterpene can be easily identified within the carbon framework of the marine-derived anticancer agent

eleutherobin (**25**), yet the Nicolaou and Danishefsky groups identified different starting terpenes, namely (+)-carvone and (−)-α-phellandrene respectively, and completely different synthetic strategies *en route* to this target.[36,37]

On level 2, one can find a partial, but substantial, structural match between the starting terpene and the target. For instance, while (3*Z*)-cembrene A (**26**) does not directly contain an uninterrupted monocyclic monoterpene unit, it is only one bond removed from doing so. Wender and co-workers exploited this similarity in their pioneering synthesis of **26** from carvone wherein a C–C bond of carvone was ultimately broken.[38] Similarly, jatropholone A (**27**) does not contain the carbon skeleton of (−)-carene, but its dimethylcyclopropane unit is suggestive of this unique monoterpene and this recognition was leveraged by Smith in a concise total synthesis of this compound.[39]

Finally, on level 3, there is a significant disconnect between the structure of the starting terpene and the placement of the carbon atoms in the final target. Moreover, not all of the carbons of the starting terpene may be found in the final structure. Level 3 syntheses are often only possible by having in-depth knowledge of the unique chemistry of a particular terpene family. For instance, the chemistry of camphor and its many fascinating rearrangements have been studied in detail,[29] and such knowledge was utilized by Kishi in a historic synthesis of ophiobolin C (**28**).[40] Taxol (**29**), perhaps the most important synthetic terpene target of the 20th century, is another interesting case study.[41,42] By understanding and exploiting the photochemistry of verbenone and the acid-mediated rearrangement chemistry of patchoulene epoxide respectively, the Wender and Holton groups were able to accomplish innovative total syntheses of this venerable anticancer agent.[43,44] In both the case of ophiobolin C and Taxol, it is not easy to “map” the structures of the starting terpenes onto the final target owing to deep-seated molecular rearrangements.

Throughout this review, which will highlight only selected syntheses from the 21st century, we will see a variety of approaches to complex terpenes on all three previously discussed levels. The efficiency of the syntheses covered depends less on the correct choice of starting terpene, but more on the combination of this material with the synthetic strategy and methods employed. If the correct terpene and strategy are chosen, redox operations can often be minimized leading to short step-counts and minimal use of protecting groups.[45–49]

3. Syntheses from the 21st Century

3.1. Monoterpene Targets

While the ten carbon-containing family of monoterpenes represent important sources of flavors and fragrances,[1] as well as the majority of commercially available terpenes utilized for synthesis, they themselves are the least important group of terpenoids from a human health and medicinal perspective. Accordingly, such targets have received much less synthetic attention than their larger sesquiterpene (C-15) and diterpene (C-20) counterparts. Nevertheless their densely packed structures, which are often highly hydroxylated, make the synthetic construction of such compounds by no means trivial. Two representative works are discussed below. MacMillan’s elegant 2004 synthesis of brasoside and littoralisone,[50] while fitting for this section, was highlighted in Gaich and Mulzer’s 2012 review.[21]

3.1.1. Bermejo's Synthesis of (+)-Paeonisuffrone (2008) (Scheme 1)—The plant family Paeoniaceae produces a variety of highly-oxygenated pinene-derived monoterpenes which have been extensively used in traditional Chinese medicine.[51,52] Isolated from the roots of the chinese peony, paeoniflorigenin (**30**), its β-glucoside paeoniflorin (**31**), and paeonisuffrone (**32**) are representative of this monoterpene class and have proven popular and challenging synthetic targets (Scheme 1). To date, two total syntheses of **31** have been reported by the groups of Corey and Takano,[53,54] and two of **32** by Hatakeyama and Bermejo.[55,56] Bermejo's 10-step, chiral pool-based synthesis of paeonisuffrone will be discussed below.

The synthesis of **32** begins with carvone and in 3 steps arrives at **33** via allylic chlorination of the isopropenyl group with calcium hypochlorite, chloride displacement with potassium acetate, and ester hydrolysis. The allylic alcohol (**33**) was then epoxidized (*m*-CPBA) and protected (PivCl) arriving at epoxide **34**. In the key step of the synthesis, the strained cyclobutane-containing ring system was constructed by a reductive, titanocene-mediated cyclization initiated by homolytic epoxide-opening.[57,58] This transformation afforded **35** in a remarkable 70% isolated yield with 2:1 diastereoselectivity at the newly forged quaternary center (C-8). From a historic perspective, it is of note that the strained cyclobutane unit found in pinene-type monoterpenes is often strategically broken during a total synthesis while in this case, it is constructed.[10,21] With the pinene ring system in hand, only 4 additional transformations were required to complete the target. The two free hydroxyl groups were protected (see **36**), allowing for subsequent chromium-mediated allylic C–H oxidation leading to enone **37**. Upon deprotection of the pivaloyl group with sodium hydroxide, the primary hydroxyl group was found to spontaneously engage the neighboring enone system in a conjugate addition reaction leading to ketone **38**. Finally, hydrogenolysis of **38** (H_2, Pd/C) completed a synthesis of (+)-paeonisuffrone (*ent*-**32**) in only 10 operations and further solidified the power of Ti(III)-mediated radical transformations in natural product synthesis.[59]

3.1.2. Maimone's Synthesis of (+)-Cardamom Peroxide (2014) (Scheme 2)—In 1995 Clardy and co-workers isolated an unusual endoperoxide natural product (see **39**) from *Amomum krervanh* Pierre (Siam Cardamom) (Scheme 2).[60] As with most O–O bond-containing molecules,[61–63] the cardamom peroxide (**39**) was found to possess significant inhibitory activity against *P. falciparum*, the major causative agent of malaria. Given the symmetry of **39** and the observation that it was isolated alongside a variety of monoterpenes, Maimone and co-workers suggested this terpene might arise in nature from the coupling of two pinene fragments and three equivalents of molecular oxygen (Scheme 2). This hypothesis guided a 2014 synthesis of **39** in four steps.[64]

The monoterpene (−)-myrtenal was first dimerized using the venerable McMurray coupling leading to triene **40** in 53% isolated yield. This C_2-symmetric compound was then subjected to singlet oxygen ($^1O_2$), inducing a [4+2] cycloaddition reaction,[65] and after exposure to DBU, a Kornblum-DeLaMare fragmentation ensued. Following Dess-Martin periodinane (DMP) oxidation, enone **41** was obtained. Taking inspiration from the hydroperoxidation reaction of Mukaiyama and Isayama,[66] and the enone conjugate reduction of Magnus,[67] **41**

was treated with catalytic quantities of $Mn(dpm)_3$ in the presence of oxygen and phenylsilane, presumably leading to peroxyradical intermediate **42**. This species underwent an unusual and diastereoselective 7-*endo* peroxyradical cyclization,[68,69] followed by trapping with an additional molecule of oxygen and reduction, ultimately affording hydroperoxide **43**. Addition of triphenylphosphine then led to chemoselective hydroperoxide reduction and formation of the cardmom peroxide (**39**) in 52% isolated yield from **41**. It is notable that the chirality of the pinene nucleus subtlety orchestrates all aspects of selectivity in this tandem process, which also serves to further showcase the power of metal-catalyzed, radical-based hydrofunctionalization chemistry in the rapid assembly of molecular complexity.[70] Moreover, this work highlights the power of biosynthetic planning in the efficient chemical synthesis of terpenes.[71]

3.2 Sesquiterpenes

15-Carbon sesquiterpenes represent a historically popular class of targets for total synthesis and many chiral pool strategies have been documented.[10] A handful of excellent 21st century chiral pool-based sesquiterpene syntheses were disclosed in Gaich and Mulzer's 2012 review and will not be duplicated herein. These include Danishefsky's synthesis of peribysin E,[72] Ward's synthesis of lairdinol,[73] Nicolaou's synthesis of zingiberene and biyouyanagin A,[74] Fürstner's synthesis of α-cubebene,[75] Ley's synthesis of thapsivillosin F,[76] Xu's synthesis of 8-*epi*-grosheimin,[77] Altmann's synthesis of valerenic acid,[78] and Zhai's synthesis of absinthin.[79]

3.2.1. Bachi's Synthesis of (+)-Yingzhaosu A (2005) (Scheme 3)—The sesquiterpene endoperoxide yingzhaosu A (**44**) was isolated in 1979 from the plant *Artabotrys uncinatus*, extracts of which have been used to treat malaria in traditional Chinese medicine (Scheme 3).[80] Two total syntheses of this compact natural product have been reported to date, both of which utilize chiral pool terpenes as starting materials.[81,82] Herein, we discuss Bachi's 2005 synthesis of yingzhaosu A starting from limonene.[82]

To construct the bridging endoperoxide ring system, Bachi and co-workers turned to the classic thiol-oxygen cooxidation (TOCO) reaction, which has found extensive use in the synthesis of peroxides.[68,69] In this reaction, a thiyl radical is generated which adds to an olefin, producing a carbon-centered radical that rapidly reacts with O_2. Thus treatment of (−)-limonene with thiophenol and O_2 led to a cascade peroxidation forming bicyclic hydroperoxide **45** as an approximate 1:1 mixture of inseperable C-4 diastereomers. As in the synthesis of **39**, the hydroperoxide group could be chemoselectively reduced *in situ* with triphenylphosphine leading to endoperoxide **46**. The extraneous tertiary alcohol could then be eliminated ($SOCl_2$/pyridine) leading to **47** as a mixture of $\Delta_{7,8}$ and $\Delta_{8,10}$ alkene isomers. The thiol group was then oxidized to a sulfoxide with *m*-CPBA, which upon treatment with trifluoroacetic anhydride and 2,6-lutidine, underwent Pummerer rearrangement. The thiohemiacetal ester thus formed was then cleaved (morpholine/MeOH), resulting in aldehyde **48**. Notably at this stage in the synthesis, the C-4 diastereomers could be separated. Remarkably, under very careful temperature control, the double bond of **48** could be hydrogenated in the presence of the sensitive peroxide and aldehyde groups. With aldehyde **49** in hand, the authors then installed the final five carbons of the target through a $TiCl_4$-

mediated Mukaiyama aldol reaction with silyl enol ether **50**.[83] With added pyridine, the initial aldol product **51** could be funneled into enone **52**. The final reduction of **52** into protected yingzhaosu A (**44**), however, proved challenging as achiral reducing agents showed little preference for producing a single secondary alcohol diastereomer. Ultimately, the Corey-Bakshi-Shibata reduction was found to impart good stereoselectivity (~9:1 dr) to this process,[84] affording **44** after desilylation with HF. Again, the ability to perform a reduction of this type in the presence of an endoperoxide is notable; moreover, the fact that an endoperoxide was carried through an entire total synthesis speaks to the synthetic acumen of the practitioners.[85] Finally, the conciseness of this route allowed for the procurement of sufficient material to further quantify the antimalarial activity of **44**.

3.2.2. Vosburg's Synthesis of (+)-Artemone (2015) (Scheme 4)—The oil extract of the Indian sage *Artemisia pallens* (Davana oil) contains a multitude of sesquiterpene natural products characterized by a tetrahydrofuran ring system and various members have proven popular synthetic targets.[86] Artemone (**53**) is one such natural product and despite its small size, early syntheses of **53** required up to 20 synthetic steps.[87–89] Vosburg and co-workers have devised two syntheses of this molecule,[86,87] one of which employs the chiral pool monoterpene linalool as starting material (Scheme 4).[87]

Allylic oxidation of (−)-linalool (cat. SeO_2/*t*BuOOH) under microwave heating afforded enal **54** in 52% yield. In the bioinspired key step of the synthesis, **54** was stirred for one week in presence of the catalytic quantities of the Hiyashi-Jørgensen organocatalyst (**55**) and sodium bicarbonate.[90] These conditions promoted *oxy*-Michael addition of the hindered tertiary alcohol to the enal system as well as controlled formation of the α-methyl stereocenter after enolate protonation (3:1 ratio of **56**: the sum of other isomers). In the final step, reverse prenylation of the chiral aldehyde using Ashfield's conditions[91] followed by oxidation led to (+)-artemone (**53**). Incredibly, only 4 steps were required to access this target highlighting the power of chiral pool synthesis in concert with the judicious employment of reagent-controlled methodology.

3.2.3. Romo's Synthesis of (+)-Omphadiol (2011) (Scheme 5)—The sesquiterpene omphadiol (**57**) was isolated from the fungus *Clavicorona pyxidata* and the basidiomycete *Omphalotus illudens*.[92,93] As a member of the biologically active africanane sesquiterpenes, **57** possesses a complex and synthetically challenging 5,7,3-fused tricyclic ring system (Scheme 5).[94] In 2011, the Romo research group reported the inaugural total synthesis of this natural product starting from (−)-carvone.[95]

Utilizing Magnus's formal enone hydration conditions,[67] carvone could be converted into hydroxyl ketone **58** which served as a substrate for a periodic acid-mediated oxidative cleavage reaction affording ketoacid **59**. In a key step of the synthesis, **59** was activated with tosyl chloride and upon addition of the nucleophilic promoter 4-pyrrolidinopyridine and base (DIPEA), pyridinium enolate **60** was presumably generated. Through the chair transition state depicted, this compound underwent a tandem aldol/lactonization cascade, generating β-lactone **61** in high yield and with excellent diastereoselectivity (83%, >19:1 dr).[96] Reduction of this strained compound with DIBAL afforded diol **62**. The primary

hydroxyl group in **62** was converted to the corresponding alkylbromide (TsCl, LiBr) and the tertiary alcohol acylated leading to ester **63**. Treating this compound with strong base (KHMDS) induced intramolecular enolate alkylation, which was then followed by an intermolecular alkylation with added methyl iodide. The lactone product formed (see **64**) was then opened with allyllithium (generated *in situ* from allyltriphenyltin and phenyllithium) leading to ketone **65**. The critical 7-membered ring was then forged in near quantitative yield via ring closing metathesis of **65** catalyzed by Grubbs' second-generation ruthenium catalyst;[97] notably, one of the olefins first isomerizes into conjugation prior to the metathesis event. Stereoselective reduction of **66** with the DIBAL/*t*-BuLi "ate" complex (see **67**) followed by non-directed Simmons-Smith cyclopropanation afforded (+)-**57**. Remarkably only 10 steps were required to reach this complex target, no protecting groups were necessary,[47,48] and all relevant transformations proceeded with high levels of stereocontrol and efficiency, resulting in an impressive 18% overall yield. Moreover, the conversion of a cyclic monoterpene's six-membered ring to that of a cyclopentane is a recurring theme in chiral pool terpene syntheses and will be utilized in several additional syntheses (*vide infra*).[10,11,28]

3.2.4. Liu's Synthesis of (+)-Onoseriolide and (−)-Bolivianine (2013) (Scheme 6)—

The flowering plant family Chloranthaceae has been widely used in traditional Chinese folk medicine and produces an array of complex lindenane-type sesquiterpenes.[94,98,99] In 2007, the architecturally interesting 25-carbon metabolite bolivianine (**68**) was isolated from the Chloranthaceae species *Hedyosmum angustifolium* (Scheme 6).[98] It was initially hypothesized that **68** resulted from the coupling of an oxidized form of the sesquiterpene onoseriolide (**69**) with geranylpyrophosphate followed by an *ene*-type cyclization and hetero Diels-Alder reaction.[98] Owing to the observation that β-(*E*)-ocimene (**70**) is also detected in *Hedyosmum angustifolium*, Liu *et al.* proposed that this diene might be capable of engaging the unsaturated butenolide unit directly in a Diels-Alder cycloaddition reaction. Herein we highlight Liu's successful execution of this idea resulting in a highly concise route to **68** and **69** from verbenone.[99,100]

Stereoselective copper-mediated conjugate addition of a vinyl group to verbenone (see **71**) following by Lewis acid-mediated cyclobutane cleavage afforded enol acetate **72**.[101] This material could be directly converted to ketal **73** (ethylene glycol, acid) allowing for a subsequent allylic oxidation leading to enal **74**. Conversion of **74** to its tosylhydrazone proceeded cleanly, setting the stage for one of several key steps in the synthesis. Decomposition of **75** with base in the presence of $Pd_2(dba)_3$, presumably generating an unusual allylic palladium carbenoid, led to a highly diastereoselective cyclopropanation reaction and the formation of **76** in good yield (65%).[102] More commonly utilized metals in diazo-based cyclopropanation chemistry,[103] such as rhodium and copper, were less effective for this transformation.[99] Following deketalization (cat. TsOH, Me_2CO), the ketone formed engaged the TES-protected pyruvate derivative shown in an aldol condensation, and following treatment with strong acid, furan **77** was formed. DIBAL reduction of the ester and silylation afforded **78**. At this stage the furan was oxidized directly to the unsaturated butenolide system (an alkylidene-*5H*-furan-2-one) with DDQ, and after fluoride-mediated desilylation (+)-onoseriolide (**69**) was obtained. It was discovered that this dienophile was

thermally unreactive toward β-(*E*)-ocimene (**70**) at temperatures up to 150 °C; however, once oxidized to the corresponding aldehyde (IBX, Δ), a smooth cycloaddition took place, presumably through transition state **79** wherein the diene approaches the butenolide from its less hindered α-face. After this initial [4+2] cycloaddition occurs, a facile intramolecular hetero Diels-Alder reaction ensues, affording (−)-bolivianine (**68**) in 52% yield for this pericyclic cascade. In parallel studies, it was found that **80** cyclizes to **68** at ambient temperatures.[99] Overall, only 12 and 14 steps were needed to access **68** and **69** respectively, and the choice of verbenone, along with knowledge of its fragmentation chemistry, were crucial in this regard.[101] Aside from giving credence to a pericyclic-based biogenesis of **68**,[104–106] this work once again shows the unquestionable power of the Diels-Alder reaction in the rapid assembly of complex polycyclic molecules.[107]

3.2.5. Total Syntheses of Jiadifenolide—Since their isolation beginning in the late 1960's, sesquiterpenes from the *Illicium* family of plants have proven popular synthetic targets.[108] Among this large family, jiadifenolide (**81**, Scheme 7) has recently attracted significant synthetic attention owing to its compact and highly oxidized molecular framework coupled with its ability to promote neurite outgrowth at very low concentrations.[109] To date, total syntheses of **81** have been disclosed by the groups of Theodorakis,[110,111] Paterson,[112] Sorensen,[113] Shenvi,[114] and Zhang,[115] in addition to a recent formal synthesis by Gademann.[116] Herein we discuss the three chiral pool-based total syntheses of **81** by Sorensen (2014), Zhang (2015), and Shenvi (2015).

3.2.5.1. Sorensen's Synthesis of (−)-Jiadifenolide (2014) (Scheme 7): The Sorensen synthesis commenced with dibromination of pulegone (producing **82**), ethoxide-induced Favorskii-type ring contraction leading to ethyl pulegenate (**83**),[117] and finally ozonolysis of the resulting tetrasubstitued alkene.[118] This decades-old sequence gives rise to optically active keto-ester **84** which has seen use in multiple terpene syntheses.[10,118] Subjecting **84** to the venerable Robinson annulation produced enone **85**,[119] a building block employed in the classic 1990 synthesis of the *Illicium* sesquiterpene anisatin by Niwa and co-workers.[120] Thermodynamic enolate formation and double α-alkylation yielded ketone **86**. Protection of the ketone (ethylene glycol, H^+), ester reduction, and reoxidation afforded aldehyde **87**. Utilizing toluenesulfonylmethyl isocyanide (TosMIC), the authors were able to effect an unusual one-carbon Van Leusen-type homologation of an aldehyde,[121] arriving directly at nitrile **88**. Treating this material with acid brought about three transformations: deprotection of the masked ketone, nitrile hydrolysis, and cyclization to the jiadifenolide γ-lactone system. Subsequent oxime formation lead to the production of **89**, setting up a key step in the synthesis. Taking inspiration from the work of Sanford,[122–124] treatment of **89** with catalytic quantities of $Pd(OAc)_2$ and stoichiometric $PhI(OAc)_2$ promoted C–H bond acetoxylation resulting in the formation of acetyl oxime **90** in 22% yield. A lack of differentiation between the two oxidizable methyl groups, combined with the formation of *bis*-acetoxylated material, accounted for the relatively low isolated yield of product. Nevertheless, gram quantities of **90** could be procured through this sequence demonstrating the robustness of this chemistry. The oxime was then reductively cleaved (Fe, TMSCl) and the resulting ketone converted to its corresponding vinyl triflate with Comins' reagent (**91**). A Pd-mediated methoxycarbonylation reaction then afforded ester **92**. Treating **92** with basic

methanol assembled the second lactone ring, and a nucleophilic epoxidation (H_2O_2/NaOH) then arrived at **93**. Iodination of the silyl ketene acetal of γ-lactone **93**, following by oxidation with dimethyldioxirane, afforded an intermediate α-keto lactone (not shown). Treatment of this material with lithium hydroxide completed a total synthesis of jiadifenolide (**81**) by an epoxide-opening/ketalization sequence. This synthesis is a beautiful demonstration of the successful merger of classic, scalable carbonyl-based chemistry combined with cutting-edge C-H activation synthetic methodology.[125–130]

3.2.5.2 Zhang's Synthesis of (−)-Jiadifenolide (2015) (Scheme 8): In 2015, Zhang and co-workers reported a synthesis of jiadifenolide (**81**) (Scheme 8) which also employed the pulegone-derived building block **84**.[115] Diastereoselective alkylation of ketone **84** with allyl bromide, followed by ozonolytic alkene cleavage, afforded aldehyde **94**. The extended boron enolate of butenolide **95** was then coupled with this material via an aldol reaction, and following treatment with acetic anhydride to induce dehydration, compound **96** was produced (a similar disconnection was utilized by Paterson in an earlier 2014 synthesis of **81**).[112] Treating **96** with excess LDA masked both the butenolide and cyclopentenone carbonyl groups as transient enolates, thereby allowing for reduction of the ester group with DIBAL. Following hydrogenation (PtO_2, H_2), alcohol **97** was forged, setting up a key step in the synthesis. Taking inspiration from Paterson and coworkers, the authors closed the central 6-membered ring of the target through a reductive radical cyclization.[112] Thus treating **97** with the powerful reductant SmI_2/H_2O accomplished this transformation,[131–133] producing tricycle **98** in excellent yield (80%) and with good diastereoselectivity (7:1). Swern oxidation of **98** led to aldehyde **99**, thus setting the stage for a second pivotal annulation reaction wherein the authors envisioned formally "inserting" one-carbon to construct the final γ-lactone ring in the target. Thus addition of the anion derived from trimethylsilyldiazomethane to aldehyde **99** led to lithium alkoxide **100**, which underwent Brook rearrangement to form anion **101**. A proton transfer event then led to intermediate **102** which was converted into the product (**103**), possibly via a carbene intermediate. Advanced tetracycle **103** was then subjected to one-pot phenylselenation and oxidative elimination sequence furnishing an intermediate α, β-unsaturated ester, which could be epoxidized with DMDO. The epoxide intermediate thus formed (see **104**) could be converted into jiadifenolide (**81**) in only two additional steps. First **104** was directly oxidized to α-keto lactone **105** with $RuCl_3/NaIO_4$, and finally the bridging lactol motif was constructed via base-mediated epoxide opening as previously demonstrated in Sorensen's synthesis. Overall only 15-steps were needed to access **81**, and the synthesis pathway was devoid of protecting group manipulations.[47,48]

3.2.5.3. Shenvi's Synthesis of (−)-Jiadifenolide (2015) (Scheme 9): In 2015, Shenvi and co-workers reported an exceedingly concise route to **81** utilizing the chiral pool terpene (+)-citronellal (Scheme 9).[114] Dehydration of citronellal was achieved in one step using the activating agent nonafluorobutanesulfonyl fluoride (NfF) and the bulky phosphazine base *tert*-butylimino-tri(pyrrolidino)phosphorane (BTPP).[134] The resulting alkyne substrate (**106**) was then subjected to ozone, resulting in cleavage of the double bond and formation of an aldehyde capable of undergoing a subsequent molybdenum-mediated *hetero* Pauson-Khand reaction. In a separate sequence, diketene acetone adduct **109** was converted into known

butenolide **108** in two steps.[135] In the key step of the synthesis, butenolide **107** was deprotonated with LDA and the resulting enolate reacted with butenolide **108**. This butenolide coupling presumably first formed intermediate **110**, the product of a direct Michael-type addition. When $Ti(O\textit{i}\text{-}Pr)_4$ was added to this intermediate followed by additional LDA, a second Michael-type process ensued leading to tetracyclic lactone **111** in 70% isolated yield (20:1 dr). Thus in a single step sequence, the entire carbocyclic core of the natural product was constructed and only redox manipulations were required to access the target. α-Oxidation of the 1,3-dicarbonyl motif with *m*-CPBA afforded lactone **112** and a subsequent directed reduction of the ketone group gave **113**.[112] To complete the synthesis of **81** the authors first brominated the α-position of the lactone (LDA, CBr_4), which upon further enolate oxidation with Davis' racemic oxaziridine afforded jiadifenolide (**81**). This total synthesis required only 8 linear operations, was devoid of protecting group use,[47,48] and enabled the production of 1 gram of jiadifenolide in a single synthetic pass.[136] Moreover, the Shenvi route to **81** is a model for convergency in complex terpene synthesis.[20]

3.2.6 Total Syntheses of Englerin A—In 2009, Beutler and coworkers isolated the complex guaianane sesquiterpenoid englerin A (**114**) from the East African plant *Phyllanthus engleri*.[137] This natural product immediately attracted the attention of both chemists and biologists due its high potency and selectivity toward renal cancer cell lines (GI_{50} values = 1–87 nM). Not surprisingly, myriad synthetic groups have pursued syntheses of this target,[138] and in the eight years since its isolation, total and formal syntheses have already been reported by the groups of Christmann,[139] Nicolaou,[140] Theodorakis,[141] Ma,[142] Echavarran,[143] Chain,[144] Hatakeyama,[145] Parker,[146] Cook,[147] Metz,[148] Sun and Lin,[149] Shen,[150] Hashimoto and Anada,[151] Iwasawa,[152] and Mascareñas.[153] Among these works, five have utilized chiral pool terpenes: Christmann's synthesis using *cis,trans*-nepetalactone,[139] Ma's synthesis employing citronellal,[142] Chain's synthesis from citronellal,[144] Metz's synthesis from isopulegol,[148] and Shen's carvone-based route.[150] The Christmann and Ma syntheses were recently highlighted in Gaich and Mulzer's 2012 review;[21] herein we will discuss the Chain and Metz routes to englerin A (**114**).

3.2.6.1. Chain's Synthesis of (−)-Englerin A (2011) (Scheme 10): In 2011, Chain and co-workers reported an exceedingly concise route to englerin A (**114**) (Scheme 10).[144] Chiral pool monoterpene (+)-citronellal was converted into cyclopentenal **116** via a previously developed, two-step procedure involving α-methylenation (see **115**) following by ring closing metathesis with Grubbs' second generation catalyst.[154,155] This chiral aldehyde was then ingeniously merged with the lithium enolate of butenolide **117** via a diastereoselective Michael addition which afforded coupling product **118** in 75% yield and with 2:1 selectivity (**118**: sum of other isomers = 2:1). In a second powerful bond-forming step, the authors constructed the central 7-membered ring of the target via a SmI_2-mediated reductive cyclization.[131–133] This transformation was conducted using the diastereomeric mixture of aldehydes containing **118**, and while the isolated yield is moderate (43%), the theoretical maximum yield is only ~66%. Moreover, polycycle **119**, which bears the entire guaianane core, is remarkably assembled in only 4 linear steps. To complete the synthesis of **114**, the cinnamyl ester sidechain was attached using Yamaguchi's protocol,[156] and the ketone group was stereoselectvely reduced with sodium borohydride leading to **120**. Finally, the

secondary alcohol was converted into its corresponding sulfonate imidazole (LHMDS, $(imid)_2SO_2$) and this activated species displaced with cesium hydroxyacetate completing the synthesis of englerin A (**114**). Overall, the Chain synthesis required only 8 steps and was devoid of protecting group use. This work showcases highly creative synthetic planning in the convergent assembly of complex terpenes,[20] and like Shenvi's route to **81**, highlights the timeless power of fundamental carbonyl chemistry in the rapid, assembly of polycyclic ring systems.

3.2.6.2. Metz's Synthesis of (−)-Englerin A (2013) (Scheme 11): In 2013, the group of Metz reported a chiral pool approach to **114** (Scheme 11).[148] As in many guaianane and guaianolide syntheses of the past,[10,21,31,138] the Metz approach relies on the ring contraction of a 6-membered cyclic monoterpene to a stereodefined cyclopentane ring system. Their requisite building block, known aldehyde **122**, was constructed in two-steps from (−)-isopulegol via a novel pathway. Oxidative cleavage of isopulegol with $Pb(OAc)_4$ produced aldehyde **121** which could be reclosed to **122** via palladium-catalyzed allylic alkylation of an *in-situ* formed enamine.[157] A significant quantity of C-2 *epi*-**122** was also produced in this reaction. A Reformatzky reaction between aldehyde **122** and α-bromoester **123** furnished **124** as an inconsequential mixture of diastereomers. This C–C bond-forming step was immediately followed by a high yielding ring-closing metathesis reaction, thus completing the hydroazulene core of the natural product (see **125**) in only 4 steps. A two-step process transformed ethyl ester **125** into methyl ketone **126**, which was then dehydrated to enone **127** via the intermediacy of a mesylate. At this point, several oxygen atoms were stereoselectively installed via nucleophilic epoxidation of the enone group and dihydroxylation of the remaining double bond (see **127** to **128**). The diastereoselectivity of the second step was modest, and various attempts to increase the selectivity were unsuccessful. The first ester side-chain was attached to the free secondary alcohol group via coupling with acid chloride **129**, and the methyl ketone moiety of **130** was converted to an isopropenyl group via Wittig olefination. Treating this material with hydrochloric acid forged the natural product's hallmark bridging ether by nucleophilic opening of the reactive allylic epoxide. With intermediate **131** in hand, the natural product was procured in three additional steps: hydrogenation of the isopropenyl group, cinnamoylation of the secondary alcohol, and acidic deprotection of the primary alcohol. Overall, this synthetic pathway constructed (−)-englerin A (**114**) in only 14 steps from abundant (−)-isopulegol and featured many high-yielding transformations. The ablity to cleave isopulegol and rapidly reforge **122** in only two steps was particularly noteworthy. It should be noted that Shen and co-workers reported a conceptually similar metathesis-based total synthesis of **114**, also employing building block **122**, in 2014.[150]

3.3. Diterpene Targets

Owing to their vast numbers, significant biological activities, and enormous structural diversity, diterpenes have historically been the most heavily investigated group of terpenes from a total synthesis perspective.[1,10,11,21,158] A variety of informative 21st century chiral pool-based diterpene syntheses were disclosed in Gaich and Mulzer's 2012 review and will not be duplicated herein.[21] These include Deslongchamps' synthesis of chatancin,[159] Overman's syntheses of briarellin E and F,[160] Sorensen's synthesis of guanacastepene E,[161]

Ghosh's synthesis of platensimycin,[162] Harrowven's synthesis of colombiasin A,[163] Halcomb's synthesis of phomactin A,[164] Mulzer's synthesis of platencin,[165] Rutjes synthesis of platencin,[166] Molander's synthesis of deacetoxyalcyonine acetate,[167] and Chen's synthesis of nanolobatolide.[168]

3.3.1. Overman's Synthesis of (−)-Aplyviolene (2012) (Scheme 12)—Marine nudibranchs and sponges produce a variety of rearranged spongiane-type diterpenes with interesting biological properties and unique structures, and many members have proven to be attractive synthetic targets.[169] One such natural product is aplyviolene (**133**), isolated in 1986 from the purple encrusting sponge *Chelonaplysilla violacea*.[170] Aplyviolene possesses two complex ring systems linked by a central C–C σ-bond (shown in blue)–such motifs pose unique challenges to the field of stereoselective synthesis (Scheme 12).[171] In 2011, the group of Overman reported the first chemical solution to this highly challenging problem in terpene synthesis,[172] and in 2012, disclosed a second-generation, chiral pool-based strategy which will be discussed below.[173]

The bicyclic monoterpene (+)-fenchone, who carbon atoms are not straightforwardly mapped onto **133**, was converted to its corresponding oxime and then subjected to Beckmann fragmentation affording nitrile **134**.[174] DIBAL reduction of **134** produced an intermediate aldehyde which underwent Wittig olefination and a subsequent deprotection with hydrochloric acid. These three operations required only a single chromatographic event. Primary alcohol **135** was then converted to nitroalkane **136** via an Appel reaction (I_2, PPh_3) followed by iodide displacement with silver nitrite. Dehydration of **136** with phenylisocyanate and base generated a reactive nitrile oxide, which participated in a diastereoselective, intramolecular dipolar cycloaddition. The isoxazoline formed (see **137**), was directly reduced to keto alcohol **138**, which possesses the 5,7-fused ring system found in the western sector of aplyviolene. This material could then be dehydrated (TsOH, Δ), forming an enone which underwent copper-mediated 1,4-addition of a vinyl group producing ketone **139** in good yield. Addition of (trimethylsilyl)methyllithium to this ketone, followed by ozonolysis of the vinyl group and treatment with hydrofluoric acid produced an exomethylene aldehyde product which could be converted into activated ester **140** via Pinnick oxidation and DCC coupling with *N*-hydroxyphthalimide. With activated ester **140** in hand, this material was subjected to a decarboxylative radical coupling with chloroenone **141** under photoredox-mediated conditions.[175] In this transformation, a tertiary radical is generated on fragment **140** which then undergoes diastereoselective radical conjugate addition to **141** forming an α-keto radical which abstracts a hydrogen atom from Hantzsch ester **142**. Considering the steric congestion surrounding the newly formed C–C bond in this process, the 61% isolated yield is quite remarkable. Reductive dehalogenation of **143** with dilithium dimethyl(cyano)cuprate led to the formation of an enolate which could be trapped with *tert*-butyldimethylsilyl chloride to form enol silane **144**. Takai-Lombardo olefination of **144** afforded an intermediate methyl enol ether, which underwent selective hydrolysis with oxalic acid to deliver methyl ketone **145**. The silyl enol ether double bond was selectively cleaved via osmylation (cat. OsO_4/NMO), followed by scission of the resulting crude α-hydroxycyclopentanone with $Pb(OAc)_4$. With aldehyde **146** in hand, the TBS-protected alcohol was then removed with TBAF to provide a hemiacetal, which could

be converted to fluoride **147** upon reaction with diethylaminosulfur trifluoride (DAST). Hydrolysis of the methyl ester (NaOH) produced a carboxylic acid product that underwent lactonization in the presence of $SnCl_2$ thus unveiling the hallmark dioxabicyclo[3.2.1]octan-3-one motif (see **148**). The anomeric fluoride was crucial in this process as it allowed for lactonization to proceed under mild conditions tolerant of the acid sensitive *exo*-methylene group. In a bold final maneuver, the sensitive α-acetoxy acetal functionality was introduced via Baeyer-Villger oxidation thus completing the total synthesis of (−)-aplyviolene (**133**). This work testifies to the power of radical-based coupling strategies in the convergent synthesis of complex terpenes featuring highly sterically congested chiral fragments.[175]

3.3.2. Vanderwal and Alexanian's Synthesis of (+)-Chlorolissoclimide (2015) (Scheme 13)—Owing to their interesting biological profiles, which often include antineoplastic effects,[176] labdane diterpenes have proven popular synthetic targets.[177] In the 1990's, the groups of Malochet-Grivois and Roussakis described an interesting halogenated class of labdanes which included chlorolissoclimide (**149**) (Scheme 13).[178,179] Moreover, **149** and congeners were shown to possess potent cytotoxicity toward a number of tumor cell lines.[178, 179] In 2015, a total synthesis of **149** was reported by a collaborative effort between the groups of Vanderwal and Alexanian.[180] Utilizing (+)-sclareolide as a chiral pool-derived building block, this work represents the first synthesis of a member of this class of labdanes.

The installation of the remote chlorine stereocenter poses an obvious challenge to the synthesis of **149** and this hurdle was cleared in the first step of the synthesis. Visible light irradiation of a solution of sclareolide and bulky *N*-chloroamide **150** promoted radical C-H chlorination leading to 2-chlorosclareolide (**151**). While alkane free radical halogenation is one of the oldest organic reactions, and many conditions are known to effect this process,[181] the use of **150**, which arose from prior work on C–H bromination,[182] was superior to all other reagents examined in terms of yield, scalability, selectivity, and ease of use. The regio- and stereoselectivity in this process is in accordance with previous reports on the C–H oxidation,[183–187] and in particular, C–H halogenation,[188–195] of sclareolide. Weinreb aminolysis of lactone **151** and subsequent tertiary alcohol dehydration then afforded amide **152**. The less hindered allylic position of **152** could be oxidized with selenium dioxide and a subsequent Swern oxidation converted this material into **153**. Treating this material with DIBAL led to both reduction of the Weinreb amide (producing an aldehyde), and stereoselective formation of the C-7 hydroxyl group, which was consequently protected with trimethylsilyl trifluoromethanesulfonate. To install the succinimide portion of the target, previously employed imide **155** was merged with aldehyde **154** using Evans boron-aldol methodology.[196] These conditions also fortuitously removed the trimethylsilyl protecting group. Coupled product **156** could be converted into chlorolissoclimide (**149**) by auxiliary removal with ammonia/MeOH and cyclization to the succinimide with sodium hydride. Overall this 9-step route to **149** proceeded in an impressive 14% overall yield, further demonstrating the power of $C(sp^3)$–H bond oxidation in the synthesis of complex terpenoids.[125–130,184]

3.3.3. Lindel's Synthesis of (+)-Cubitene (2012) (Scheme 14)—Macrocyclic terpenes pose unique synthetic challenges in comparison to many of the rigid polycyclic structures discussed in this review; in many cases, the identification of a suitable chiral pool starting material is less obvious.[197] (+)-Cubitene (**157**),[198] a member of a small family of diterpenes containing a twelve-membered ring (i.e. cubatinoids),[199] exemplifies these challenges (Scheme 14). In addition to its conformational flexibility, **157** is devoid of common functional groups, and a lack of such synthetic handles can complicate terpene syntheses.[200] A non-stereoselective synthesis of **157** was first reported in 1980,[201] followed by a stereoselective, racemic synthesis by Kodama in 1982.[202] To date, two asymmetric routes to (+)-cubitene have been disclosed, both of which utilized chiral pool materials: Kodano's 1996 synthesis from D-mannitol,[203] and Lindel's 2012 synthesis from carvone.[204]

The Lindel route begins with a stereoselective aldol reaction of the lithium enolate of carvone and geraniol-derived aldehyde **158**, producing enone **159** in 85% yield. Protection of the resulting secondary alcohol (TBSCl, imidazole), ester hydrolysis, and phosphate ester formation afforded allylic phosphate **160**, setting the stage for the key macrocyclization. When a solution of **160** was added slowly to a cold solution of SmI_2, 12-membered macrocycle **161** was formed stereoselectively in 77% isolated yield. The presumed organosamarium intermediate showed high preference for 1,4-addition, possibly due to the intramolecular nature of this transformation.[205] After having cleverly used the six-membered ring of carvone to template assembly of the bicyclo[8.2.2] tetradecane ring system, the authors then proceeded to dismantle it as cubitene possesses a single ring. Thus aerobic α-oxidation of ketone **161** (LHMDS, O_2, $P(OEt)_3$) followed by carbonyl reduction afforded diol **162** which could be oxidatively cleaved in the presence of H_5IO_6/EtOH. The crude keto aldehyde formed (see **163**) was immediately subjected to Pinnick oxidation conditions resulting in a 54% isolated yield of **164**. A Wittig olefination converted the methyl ketone into an isopropenyl group and the TBS protecting group was removed under acidic conditions (TsOH, MeOH). Oxidation of **165** under Parikh–Doering conditions ($Pyr{\cdot}SO_3$, $DMSO/NEt_3$) produced keto acid **166**, which was found to undergo smooth decarboxylation when heated, thus unveiling the full cubitene ring system. With **167** in hand, all that remained was the removal of a single oxygen atom. While many conditions can be envisioned to elicit this transformation, the authors obtained the best results via the following sequence: i) reduction of **167** with $LiAlH_4$, ii) silylation of the resulting secondary alcohol (TBSOTf, DIPEA), and iii) careful deoxygenation via titration with $Li/EtNH_2$. Under these conditions, overreduction and double bond migration could be minimized and (+)-cubitene (**157**) was isolated in 49% over three steps. Lindel's synthesis was quite efficient (5.2% overall yield) and like Wender's classic synthesis of (3*Z*)-cembrene A (**26**) (Figure 2), featured a very non-obvious use of carvone.[38] Moreover, this work is an excellent example of Hoffman's "overbred skeleton" concept wherein the skeletal complexity present in synthetic intermediates is greater than that of the final target.[206]

3.3.4. Hoppe's Synthesis of (+)-Vigulariol (2008) (Scheme 15)—In 2005, the polycyclic diterpene (+)-vigulariol (**168**) was isolated from the sea pen *Vigularia juncea*.[207] As a member of the cembrane-derived cladiellin diterpenes, **168** contains a hallmark 6,10-fused carbocyclic ring system.[208,209] Along with the biogenetically related briarellin,

asbestinin, and sarcodictyin diterpenes, members of this large family have proven popular targets for total synthesis and many creative strategies have been described.[210] Of relevance to this review are 21st century chiral pool syntheses of deacetoxyalcyonine acetate (by Molander)[167] and briarellins E and F (by Overman),[160] both of which were highlighted in Gaich and Mulzer's review.[21] Paquette and co-workers first described a synthetic route to **168** during their studies toward the synthesis of related sclerophytin A.[211] Notably this work was reported several years prior to **168** being discovered as a true natural product. Since then, "targeted" syntheses of vigulariol have been reported by the groups of Clarke (2007),[212] Hoppe (2008),[213] and Crimmins (2011).[214]

Hoppe's chiral pool-based route to **168** (Scheme 15) begins with the conversion of cryptone, found in eucalyptus oil or easily prepared by asymmetric synthesis,[215] to carbamate **169** via reduction and carbamoylation. When **169** was treated with *sec*-butyllithium and racemic, *trans N,N,N′,N′*-tetramethyl-1,2-diaminocyclohexane (TMCDA), stereoselective deprotonation occurred, presumably forming anion **170**. Addition of $ClTi(O\textit{i}\text{-}Pr)_3$ to this species resulted in lithium–titanium exchange, and this allylic nucleophile was then added to chiral aldehyde **171** resulting in the formation of **172** in 40% yield (5:1 dr). Enol carbamate **172** was then found to engage acetal **173** in a BF_3-mediated condensation leading to tetrahydrofuran **174** in an excellent 71% yield.[216] From a strategic perspective, this clever two-step protocol allows for both carbons *a* and *b* of **170** (shown in red) to function as nucleophilic sites. The oxacyclononene ring was then constructed using ring closing metathesis with Grubbs' second generation catalyst to afford **175**. The trisubstituted olefin was epoxidized with dimethyldioxirane (DMDO), and following benzyl group removal (H_2, Pd/C), the final tetrahydrofuran ring instantly assembled via transannular epoxide opening. In the final step, **176** was converted into (+)-vigulariol via Wittig olefination. Overall, only 8 linear steps were required to access this complex diterpene, magnificently showcasing the synthetic utility of lithiated carbamates in organic synthesis.[217,218]

3.3.5. Reisman's Synthesis of (+)-Ryanodol (2016) (Scheme 16)—

Polyhydroxylated terpenes present unique challenges and opportunities to synthetic chemists. On the one hand, their highly oxidized structures often represent the ultimate testing ground for new chemoselective chemical transformations and methodologies. On the other, a judiciously chosen synthetic strategy can greatly increase the accessible structural variations of a natural product family, paving the way for future biologically relevant discoveries. The pyrrole ester-containing diterpene ryanodine (**178**),[219,220] and its hydrolysis product ryanodol (**177**),[221] have caught the eye of synthetic chemists for precisely these reasons (Scheme 16). As modulators of the ryanodine receptors (RyRs), these compounds markedly influence intracellular calcium-ion flux.[222,223] As such, **178** and its derivatives represent both potent biochemical tools as well as potential medicinal and former agrochemical agents.[224–226] Three syntheses of ryanodol (**177**) have been reported by the groups of Deslongchamps (1979),[227–231] Inoue (2014),[232] and very recently Reisman (2016).[233] The Deslongchamps route to **177** was a landmark achievement in 20th century terpene synthesis. Of these works, only Inoue's synthesis has proven capable of furnishing synthetic ryanodine (**178**).[234,235] Both Deslongchamps' and Reisman's syntheses utilize

chiral pool terpene starting materials (carvone and pulegone respectively), and both target a degradation product anhydroryanodol (**180**) as a key intermediate en route to ryanodol (**177**).

Reisman's synthesis of ryanodol begins with a noteworthy opening sequence, a double hydroxylation of the monocyclic monoterpene (−)-pulegone in which two oxygen atoms (shown in red) are installed stereoselectively. First, γ-deprotonation of pulegone (KHMDS) forms an extended enolate, which reacts with Davis' oxaziridine electrophile at the α-position. Then, a second enolization/oxidation sequence takes place at the α′-position, furnishing an intermediate diol as a single diastereomer. Straightforward protection of this compound as a bis BOM ether (BOMCl, *i*-Pr_2NEt) afforded ketone **181**. Addition of propynylmagnesium bromide to **181**, followed by ozonolysis of the pendant isopropenyl group led to keto alcohol **182** in high yield. Ethoxyethynylmagnesium bromide addition to this ketone produced a tertiary alcohol that underwent a facile Ag-catalyzed cyclization/elimination cascade to produce lactone **183**.[236] Stereoselective, vinyl cuprate conjugate addition smoothly constructed enyne **184**, which was poised to undergo an intramolecular Pauson-Khand reaction. After optimization, conditions were developed (1 mol% $[RhCl(CO)_2]_2$, CO) to produce cyclopentenone **185** in an impressive 85% yield.[237] With the full ring system of anydroryanodol (**180**) now in hand, subsequent steps focused on tailoring this core to the precise structure of the natural product. A remarkable selenium dioxide-mediated oxidation of **185** installed the remaining hydroxyl groups of anhydroryanodol and generated diosphenol **186** in a single operation. **186** was then triflated (Comins' reagent, *i*-Pr_2NEt) and cross-coupled with tributyl(isopropenyl)stannane under standard Stille conditions to give anhydroryanodol precursor **187**. Two reductions ($LiBH_4$ then H_2, $Pd(OH)_2/C$) – the latter of which also removed the BOM protecting groups – completed the synthesis of anydroryanodol (**180**) in 13 steps. Conversion of this compound to ryanodol (**177**) itself was brought about using a slight modification of Deslongchamps' two-step route featuring epoxidation (CF_3CO_3H) and reductive epoxide opening (Li^0), thereby producing **177** in only 15 steps from pulegone. This work highlights a formidable combination of the strategic use of chiral pool material along with powerful metal-catalyzed C–C bond forming reactions. Moreover, both the strategic and serendipitous finding that five of the eight oxygen atoms of the target could be installed in only two steps was crucial in minimizing protecting group use, step count, and non-strategic redox manipulations.[44–49]

3.3.6. Williams' Synthesis of (+)-Fusicoauritone (2007) (Scheme 17)—The fusicoccanes constitute members of a large family of diterpenes containing 5,8,5-fused tricyclic ring systems, constituents of which includes the cotylenins (see cotylenol, **188**), fusicoccin A (**189**), fusicoplagin A (**191**), and epoxydictymene (**192**) (Figure 3).[238] Fusicoccanes and cotylenins have been shown to promote various biological effects, including activation of plasma membrane H^+-ATPase and interaction with fusicoccin-binding proteins that play key roles in intracellular signal transduction pathways.[239–241] Molecules of this class have proven to be powerful chemical tools for studying plant physiology.[241] Several pioneering chiral pool-based syntheses of 5,8,5-fused diterpenes were accomplished in the 20th century, including Kato and Takeshita's synthesis of **188**,[242,243] and total syntheses of **192** by the groups of Paquette and Schreiber.[244,245] In 2007, Williams and coworkers disclosed a chiral pool-based synthesis of fusicoauritone (**193**),[246] a natural

product isolated in 1994 from the liverwort *Anastrophyllum auritum*.[247] Utilizing biosynthetic logic, the Williams team first targeted a 5,11-fused macrocycle, which is believed to be a biogenetic precursor to **193** by way of a transannular ring closing step.[248]

Starting with limonene oxide, a previously developed five-step sequence was used to construct cyclopentane building block **194**,[249] which has also found use in the synthesis of this class of molecules.[242] A Johnson-Claisen rearrangement ($(EtO)_3CCH_3$, *cat.* $EtCO_2H$, Δ) was used to set one of the key all-carbon quaternary centers in the target and following carbonyl reduction ($LiAlH_4$), alcohol **195** was prepared in 75% yield. The bulky neighboring isopropyl group dictated the stereochemical course of this pericyclic reaction. A protection/hydroboration/oxidation sequence then produced an aldehyde to which (*Z*)-propenyllithium was added furnishing **196**. A second Johnson-Claisen reaction was then cleverly employed, setting a remote methyl stereocenter, and after reduction ($LiBH_4$) alcohol **197** was formed. Dissolving metal conditions (Na^0, HMPA, *t*BuOH) were employed to reduce the lone olefin, which was prone to isomerize under more typical hydrogenation conditions. Tosylation of the free alcohol followed by Finkelstein reaction (NaI, Δ) afforded a primary iodide which could be displaced ($NaSO_2Tol$, Δ) to yield a sulfone. Deprotection of the MEM protecting group and Swern oxidation fashioned intermediate **198**. Wittig olefination, ester reduction (DIBAL), and Swern oxidation produced aldehyde **199**, setting the stage for a critical macrocyclic Julia condensation. Treatment of **199** with sodium *tert*-amylate led to a very efficient (73–82%) ring closure, forming β-hydroxysulfone **200** as a 5:1 mixture of isomers. Swern oxidation then constructed an α-sulfonyl ketone which could be desaturated using an α-selenation/elimination sequence. Carbonyl reduction (DIBAL) led to an allylic alcohol, which could be desulfonylated with sodium naphthalenide. Mild allylic oxidation (MnO_2) then produced (*Z*)-configured enone **201** setting the stage for the critical transannular cyclization event. In line with the authors biomimetic retrosynthesis, treating **201** with *p*-TsOH facilitated a Nazarov-type cyclization constructing 5,8,5-fused tricyclic enone **202** in high yield (92%).[250] Serendipitously, the authors discovered that this material underwent slow air oxidation at C-6 to produce fusicoauritone (**193**) directly. A hypochlorite-mediated oxidation, however, was found to be superior for material throughput purposes, thus resulting in a 40% yield of **193**. Overall, 25 steps were required to construct this complex diterpene from limonene, an exercise which not only further highlights the strength of biomimetic planning in complex molecule synthesis,[251–255] but also showcased the timeless power of the classic Claisen rearrangement in stereocontrolled synthesis.[256–258]

3.3.7 Total Synthesis of Diterpenes from Euphorbiaceae—The “spurge” family of flowering shrubs (Euphorbiaceae) is found throughout the world and contains a wide range of highly complex, bioactive oxygenated terpenes.[259–262] A particularly important class, from both a medicinal and synthetic perspective, are the biosynthetically related lathyrane, daphnane, tigliane, and ingenane diterpenes (Figure 4). Lathyranes possess a 5,11,3-fused tricyclic structure, and are believed to be the biosynthetic precursors to the 5,7,6,3-fused tiglianes by way of transannular C-8–C-9 bond formation.[261] Cleavage of the tigliane cyclopropane (C-14–C-15 bond cleavage) presumably leads to the daphnanes (see **205**),[262] while *1,2*-migration of the C-9–C-11 bond forges the ingenane ring system. Diterpenes from *Euphorbiaceae* possess great medicinal potential, with members exhibiting tumor promoting,

anti-cancer, neurotrophic, anti-inflammatory, and anti-HIV activity among others.[259–262] Most of these effects have been attributed to modulation of protein kinase C (PKC), a family of enzymes involved in myriad cell signaling processes.[263] Esters of the tiglianes phorbol (**203**) and ingenol (**206**) are believed to chemically mimic diacylglycerols (DAG), the natural PKC secondary messengers. While many daphnanes are also believed to modulate PKC,[262] the flagship member resiniferatoxin (**205**) activates the TRPV-1 receptors.[264] These features, combined with their unique and highly complex molecular architectures, made diterpenes from Euphorbiaceae some of the most highly investigated classes of terpenes in the 20th century. Accordingly, completed total syntheses during this period remain landmark accomplishments in the field (*vide infra*).

3.3.7.1 Wood's Synthesis of Ingenol (2004) (Scheme 19): Ingenol (**206**), first isolated in 1968 by Hecker from *Euphorbia ingens*,[265] and its esters have long been studied for their potent biological activity, including anti-cancer and anti-HIV potential.[266–268] Furthermore, Picato® (ingenol mebutate) has recently been approved as a first-in-class treatment for the precancerous skin condition actinic keratosis.[269] Ingenol has long served as a holy grail for total synthesis due to its complex oxygenation pattern and the unique "*in,out*" stereochemistry observed at the bridgehead positions of the bicyclo[4.4.1]undecane motif.[270] While many groups have studied its synthesis,[271] only Winkler (2002),[272] Kuwajima (2003),[273] Kigoshi (2004),[274] Wood (2004),[275] and Baran (2013)[276] have published total or formal synthetic routes to ingenol, the latter two of which utilized the chiral pool of terpenes and will be discussed herein.

The *in,out* stereochemistry of ingenol has been one of the most difficult structural challenges to tackle en route to its synthesis, and was first solved by Funk and co-workers using a ring-contracting Claisen rearrangement strategy.[277] While ultimately not leading to a final synthesis of **206**, this work developed a five step sequence to convert chiral pool-derived (+)-3-carene, which contains the hallmark tigliane dimethylcyclopropane unit, into a suitable cycloheptanone precursor (Scheme 18). Ozonolysis, selective acetalization, and Claisen condensation afforded ester **207**.[30] A Lewis-acid mediated ($TiCl_4$) intramolecular aldol condensation led to **208**, which was transformed into keto ester **209** via diastereoselective methyl cuprate addition.

Wood's synthesis began with conversion of **209** into alcohol **210** via ketalization, ester reduction, and deprotection (Scheme 19). Acetylation of **210** followed by elimination with DBU led to an enone that underwent facile Diels-Alder cycloaddition with cyclopentadiene assembling **211**. Ring-opening metathesis of the [2.2.1] bicycle in **211** in the presence of ethylene, followed by selective olefin cleavage (OsO_4/ $NaIO_4$) and subsequent aldehyde protection generated spirocycle **212**. This material underwent a high-yielding (98%) alkylation with allyl chloride **213**, producing a substrate (see **214**) poised to under a second metathesis event.[278] Thus, treatment of **214** with Hoveyda-Grubbs' second generation catalyst yielded [4.4.1]-bicycle **215**, which possesses the challenging *in,out* stereochemistry, in 76% yield.[97] A four-step sequence consisting of aldehyde deprotection and subsequent reduction, Appel reaction, and elimination converted **215** to **216**. Allylic oxidation (SeO_2/ *t*BuOOH) followed by hydroxyl oxidation formed an enone, which could then be isomerized

to **217** with $RhCl_3$. Two of ingenols key hydroxyl groups were then installed in rapid, diastereoselective fashion via an enolate oxygenation with O_2, followed by hydroxyl-directed epoxidation of the resultant allylic alcohol. The epoxide formed (see **218**) was then taken through a seven-step sequence involving tertiary alcohol protection, ketone reduction, TMS hydrolysis with concomitant acetonide formation, PMB removal, a three-step conversion of the primary hydroxyl group to a sulfone, and double bond isomerization with DBU. Reduction of **220** with sodium amalgam followed by acidic removal of the acetonide group furnished deoxyingenol (**221**), which could be converted into the natural product via allylic oxidation with selenium dioxide. As in Smith's classic synthesis of jatropholone A (**27**) (Figure 2), the identification and exploitation of a dimethylcyclopropane-containing chiral pool terpene was highly simplifying.[39] This work also highlights how judicious retrosynthetic planning, in conjunction with two highly powerful metathesis-based events,[279] can be leveraged in the construction of topologically and thermodynamically challenging polycyclic ring systems.

3.3.7.2 Baran's Synthesis of Ingenol (2013) (Scheme 20): In 2013, Baran and coworkers developed an elegant 14-step route to ingenol (**206**), also utilizing (+)-3-carene as a starting material but with a distinctly different strategy to access the unusual *in,out* bicyclo[4.4.1]undecane ring system.[276,280] The team was inspired by the work of Cha and coworkers who, in 2005,[281] demonstrated that the 5,7,6-fused tigliane core (see **222**) could be converted into the ingenane skeleton (see **223**) via a Lewis acid-mediated rearrangement along plausible biosynthetic lines (Figure 5).

The Baran synthesis begins with allylic chlorination and ozonolysis of (+)-3-carene to furnish α-chloro ketone **224** (Scheme 20). Reductive dechlorination of **224** with lithium naphthalenide produced an enolate that could be stereoselectively alkylated with methyl iodide. In the same pot, the resulting methylated ketone was deprotonated and subjected to an aldol coupling with chiral aldehyde **225** thus forming allene **226** in short order. Addition of ethynylmagnesium bromide to **226** and double protection afforded allene **227** which was primed for an allenic Pauson-Khand reaction.[282] This transformation was realized using catalytic quantities of $[RhCl(CO)_2]_2$ under a carbon monoxide atmosphere, wherein enone **228** was formed in 72% yield. Methyl Grignard addition to this material furnished compound **229** – thus constructing the entire carbon skeleton of the tiglianes in only seven linear steps. After dihydroxylation of the trisubstituted alkene and subsequent carbonate formation, attention turned toward eliciting the key alkyl *1,2*-shift reaction in analogy to Figure 5. Ultimately it was discovered that treating **230** with boron trifluoride diethyl etherate induced ionization of the tertiary alcohol and a subsequent high yielding (80%) ring shift.[280] Ingenane core-containing ketone **231** was then oxidized at an allylic position with selenium dioxide and subsequently acetylated. Treatment of **232** with hydrofluoric acid removed the silyl protecting group, unveiling a secondary alcohol which could be dehydrated with Martin's sulfurane. Ester and carbonate cleavage with sodium hydroxide furnished deoxyingenol (**221**). As in the Wood synthesis, the final step consisted of a selenium-mediated allylic oxidation, albeit under slightly modified conditions. At 14 steps, this work represents the shortest route to ingenol to date by a substantial margin. By using several powerful skeletal bond-forming steps and judicious incorporation of the oxygen

atoms late stage, the authors were able to minimize functional group manipulations, thus resulting in an unusally concise synthesis of this complex terpene.[45–49]

3.3.7.3 Baran's Synthesis of (+)-Phorbol (2016) (Scheme 21): Phorbol (**203**), which was first isolated in 1934 by Bohm and coworkers as one of the principle constituents of croton oil,[283] has been a target of intense synthetic interest for decades, particularly because of the unique biochemical and medicinal properties of the phorbol esters which have remained powerful tools for the study of PKC.[284–287] Despite numerous synthetic studies directed towards phorbol,[260,284] only syntheses by Wender,[288–291] a formal synthesis by Cha,[292] and a recent total synthesis by Baran have reached the final goal.[293] Only the Baran synthesis utilizes the terpene chiral pool, and this work takes inspiration from their ingenol strategy (*vide supra*), which generates the tigliane framework *en route* to rearrangement. However, the presence of significant additional oxidation on the carene-derived C-ring fragment of the tiglianes (which is not found in ingenol) remained a key challenge to address in this synthetic campaign.

With large scale access to intermediate **228** in hand, the authors began with a Mukaiyama hydration of the trisubstituted alkene and subsequent protection affording enone **233**.[70] Impressively, and guided by NMR calculations, treating **233** with methyl(trifluoromethyl)dioxirane (TFDO) introduced a single hydroxyl group onto this complex scaffold in a regio- and stereoselective manner and on gram scale.[294,295] Treating intermediate **234** with ZnI_2/MgI_2 led to ring-opened triene **235** and a second Mukaiyama hydration of the resulting isopropenyl group, followed by ruthenium-catalyzed alkene oxidation, afforded diketone **236**. At this point, the cyclopropane was reassembled through a cascade process. Conversion of the tertiary alcohol to a trifluoroacetate group, followed by zinc-mediated reduction of the dione and acetylation, led to activated intermediate **237**, which underwent a cyclopropane-forming displacement reaction to give **238**. An enone reduction with concomitant alkene transposition, followed by chromium-mediated allylic oxidation, afforded enone **239**. Iodination of this enone followed by methyl Stille coupling gave **240**, which possesses the full tigliane carbon ring system. To complete the synthesis of phorbol, the following sequence was employed. First, selective deprotection of the TBS-protected secondary alcohol was accomplished with HF-pyridine, allowing for subsequent alcohol dehydration with Martin's sulfurane, and allylic oxidation with selenium dioxide. Finally, reductions and global deprotections yielded fully synthetic phorbol (**203**). By incorporating an unactivated methylene oxidation into their retrosynthetic design, the authors did not have to change their starting chiral pool terpene from that used in the previous ingenol work, thus greatly simplifying the overall pathway. The Baran synthesis of phorbol clearly exemplifies the power of remote C–H bond functionalization in influencing the retrosynthesis of complex terpene natural products.[125–129,184]

3.3.7.4 Inoue's Synthesis of (+)-Crotophorbolone (2015) (Scheme 22): Crotophorbolone (**241**) was first isolated in 1934 as a degradation product of phorbol,[296] and was subsequently found to occur naturally in the dried plant roots of *Euphorbia fischeriana*.[297] Though the specific biological activity of this diterpene is unknown, Wender has demonstrated that **241** can be converted in three steps into prostratin (**204**, Figure 4), a C-12

deoxytigliane that has significant potential in the treatment of HIV.[298,299] A structural analysis of **241** identifies a monocyclic monoterpene substructure embedded within its carbon skeleton and in 2015, Inoue and coworkers disclosed the inaugural total synthesis of crotophorbolone starting from (+)-carvone.[300]

Carvone was first subjected to conditions promoting γ-selective deprotonation and silyl enol ether formation ($FeCl_3$, TMSCl, MeMgBr).[301] This sequence was followed by a Lewis acid-mediated Mukaiyama aldol reaction with trimethyl orthoformate (Scheme 22). The acetal formed (**242**) was then taken through a four-step sequence consisting of: *i)* stereoselective hydroxymethylation employing formaldehyde equivalent **243**, *ii)* TIPS protection of the resulting primary alcohol, *iii)* dissolving metal reduction of the enone, and *iv)* reoxidation of the resulting allylic alcohol to form **244**. Addition of the lithiate derived from ethyl vinyl ether followed by acid-mediated cyclization furnished caged compound **245**. The Inoue team then began to assemble selenide **251** which was to function as a radical precursor. This was accomplished by epoxidation and Baeyer-Villiger oxidation of the enol ether, mesylation, and selenation under decarboxylative Barton-McCombie-type conditions. After oxidation of the TIPS-protected primary alcohol, selenide **247** was formed. Through a sequence including addition of vinyl lithiate **248** and acetylation, Pd-catalyzed allylic transposition, and protecting group interconversion, alcohol **249** was constructed. This material was converted to its corresponding allylic chloride, thus allowing for a Stille coupling with stannane **250**. In the key step of the synthesis, a bridgehead radical was formed from selenide **251** using radical initiator **252**. This reactive species then underwent smooth 7-*endo* radical cyclization onto the pendant enone, and after hydrogen atom abstraction from Tris(trimethylsilyl)silane, complex 5,7,6-fused tricyclic intermediate **253** was produced in an impressive 69% yield. It is of note that *cis*-stereochemistry was observed at the 5,7-ring junction in the product which would later need to be corrected. Next, the full crotophorbolone core was constructed by silyl enol ether formation, α-methylenation with Eschenmoser's salt, and thermodynamic olefin isomerization with rhodium(III)chloride. After acidic opening of the bicyclic ketal unit in **254**, hydroxyl group protection, and Pinnick oxidation of the resulting aldehyde, the desired *trans*-configuration at the 5,7-ring fusion could be attained via silyl enol ether formation (TMSOTf, base) and reprotonation. To complete the synthesis, six additional transformations were required. First, the carboxylic acid of **255** was transformed to a Barton ester (**256**, EDCI), which was subsequently irradiated under aerobic conditions leading to decarboxylation and peroxide formation. Following the addition of a reducing agent ($P(OEt)_3$), a secondary alcohol group was formed which was subsequently protected (TESOTf). α-Oxidation of the cyclopentenone unit (NaHMDS, Davis' oxaziradine), forged the critical tertiary alcohol moiety. Through various protecting group and redox manipulations, the synthesis of crotophorbolone (**241**) was then completed. Like the Overman synthesis of aplyviolene (Scheme 12), this work showcases the power of radical-based synthetic methods in the construction of complex, densely functionalized terpene natural products.[302–305]

3.3.8. Corey's Synthesis of (+)-Pseudopteroxazole (2003) (Scheme 23)—The pseudopterosins are marine natural products noted for their diverse biological activities and tricyclic core structures containing a fully-substituted aromatic ring.[306] Accordingly,

members of this family have attracted considerable synthetic attention over the past several decades, culminating in a variety of completed total syntheses.[307–323] Pseudopteroxazole (**257**), isolated by Rodriguez and co-workers in 1999 from the gorgian sea whip *Pseudopteragorgia elisabethae*,[324] presents unique challenges and opportunities (Scheme 23). Its demonstrated *in vitro* inhibition of *Mycobacterium tuberculosis* and highly-substituted benzoxazole core, combined with previous observations that members of this family have been structurally misassigned,[325,326] makes **257** an intriguing synthetic target. To date, total syntheses of **257** have been completed by the groups of Corey,[327] Harmata,[328] Li,[329] and Luo.[330] The Corey and Li routes utilized the terpene chiral pool and will be discussed herein. While a chiral monocyclic monoterpene can be easily identified within the structure of these marine metabolites, the two research groups employed quite distinct chemistry to access the hallmark aromatic sector of the target.

Corey and coworkers disclosed the first total synthesis of pseudopteroxazole (**257**) from (−)-limonene, and in doing so, also managed to demonstrate conclusively the correct stereochemical assignment of the natural product (Scheme 23).[327] In this work, (−)-limonene was converted to ketone **259** via a three-step protocol previously developed by Corey.[317] Notably, the use of a cyclic hydroboration/oxidation strategy (thexylborane/H_2O_2) was key in setting the stereocenter alpha to the future ketone selectively.[331] Chemoselective oxidation of the secondary alcohol (NaOCl) furnished ketone **258**. Owing to lack of diastereoselectivity in the initial hydroboration of the limonene isopropenyl group, a kinetic resolution (isopropenyl acetate/lipase) was required at this stage to separate this mixture and produce **259** in pure form. Double silylation of **259** (TBDPSCl/imid. followed by LDA/TMSCl) produced silyl enol ether **260**, which was a suitable substrate for $SnCl_4$-mediated conjugate addition to enone **261**, thus affording adduct **262** as an inconsequential mixture of diastereomers. Modified Robinson annulation (KOH/EtOH followed by $SOCl_2$/pyr.) then furnished **263**.[119] Oxime formation followed by pivaloylation forged **264** setting up the key aromatization reaction, in which treatment with one equivalent of acetyl chloride induced a mild Semmler-Wolff rearrangement leading to arene **265**.[332] Straightforward protecting group manipulations then gave carbamate **266**, which was smoothly converted to diene **268** via deprotection of the primary hydroxyl group, oxidation to an aldehyde, and Wittig-Vedejs *E*-selective olefination (using phosphonium ylide **267**).[333] Diene **268** then underwent smooth, cationic cyclization to directly generate **269** in a diastereoselective fashion when treated with methanesulfonic acid. During these studies, it was also found that by altering the carbamate protecting group, another epimer could be prepared, thus assisting in confirming the stereochemistry of the natural product. Finally, removal of the carbamate protecting group and condensation of the resulting aminophenol with triethylorthoformate afforded (+)-pseudopteroxazole (**257**) in 19 steps thereby completing the first total synthesis of this molecule and confirming its relative and absolute stereochemistry.

3.3.9. Li's Synthesis of (+)-Ileabethoxazole (Scheme 24), (+)-Pseudopteroxazole (Scheme 25), and (+)-*seco*-Pseudopteroxazole (Scheme 25) (2016)—

Recently Li and coworkers reported a second chiral pool-based total synthesis of pseudopteroxazole (**257**, Scheme 25) as well as syntheses of *seco*-pseudopteroxazole

(**270**, Scheme 25) and ileabethoxazole (**271**, Scheme 24), the latter of which had previously been synthesized by Williams and possesses a fused cyclopentane ring.[322,334]

Whereas the Corey synthesis utilized limonene as the chiral pool building block, Li and co-workers began their studies with (−)-isopulegol (Scheme 24). Once again, stereoselective hydroboration of the isopropenyl group proved troublesome. By preparing epimer **272** via Mitsunobu inversion, however, it was possible for the subsequent hydroboration (BH_3•THF) to be directed by the secondary alcohol, thus favoring the correct face of the alkene.[335] Silylation of this material with functionalized chlorosilane **273** afforded alkyne **274**. Dess-Martin oxidation and triflation (KHMDS, $PhNTf_2$) gave rise to enol triflate **275**. Treating this compound with a catalytic quantity of tetrakis(triphenylphosphine)palladium and stannane **276** elicited an impressive carbopalladation/Stille coupling cascade forging two carbon-carbon bonds and a seven-membered silacycle.[336] The product formed (see **277**) was primed to undergo a 6π-electrocyclization/aromatization sequence and indeed did so when heated to 140 °C followed by oxidation in the presence of air. Thus in two steps, a relatively simple monoterpene derivative was converted into a densely functionalize aromatic precursor. The benzoxazole product (**278**) subsequently served as a key precursor to ileabethoxazole (**271**), pseudopteroxazole (**257**), and *seco*-pseudopteroxazole (**270**).

First, intermediate **278** was advanced to ileabethoxazole (**271**) through a nine-step sequence (Scheme 24). Deprotections and functional group manipulations produced aldehyde **279** in four steps, and a subsequent Gilbert-Seyferth homologation of this aldehyde produced alkyne **280**. Formal alkyne C–H insertion of the carbene derived from ethyl diazoacetate afforded ester **281**.[337] Subjecting this material to reductive radical cyclization conditions (Bu_3SnH/AIBN) promoted a 5-*exo* cyclization process leading to tricycle **282** in high yield (87%). While the product was formed as mixture of olefin isomers, this proved inconsequential as DBU cleanly isomerized the double bond into conjugation. Finally, addition of methyllithium to this conjugated ester (see **283**) succinctly completed the synthesis of (+)-ileabethoxazole (**271**).

Concurrently, key intermediate **278** was also advanced to both pseudopteroxazole (**257**) and *seco*-pseudopteroxazole (**270**) in seven- and six-step sequences, respectively (Scheme 25). Global desilylation of **278** with hydrofluoric acid pyridine complex followed by oxidation of the primary alcohol (DMP) yielded aldehyde **284**. Horner-Wadsworth-Emmons olefination, followed by two-step reduction of the unsaturated ester (H_2, Pd/C *then* DIBAL) then afforded key intermediate **285**. A straightforward Wittig olefination converted **285** into (+)-*seco*-pseudopteroxazole (**270**). To synthesize pseudopteroxazole (**257**) itself, a diastereoselective oxidative α-arylation of **285** was employed using MacMillan's shown chiral imidazolidinone catalyst shown and the iron(III) oxidant $[Fe(phen)_3][(PF_6)_3]$.[338] Finally, analogous Wittig olefination completed the synthesis of (+)-pseudopteroxazole (**257**) in 15 total steps. From a strategic perspective, the ability to use common intermediate **278** in multiple synthesis pathways is a powerful method for accessing diverse natural product family members.

3.3.10. Nicolaou and Chen's Synthesis of (−)-Platensimycin (2008) (Scheme 26)—

In 2006, scientists at Merck reported the structure of the potent antibiotic

platensimycin (**287**), isolated from South African soil samples (Scheme 26).[339,340] Its novel structure, distinctive mechanism of action, and lack of cross-resistance immediately resulted in rarely seen synthetic fervor.[341–346] Within the same year of its isolation, the first total synthesis of platensimycin appeared by the group of Nicolaou.[347] In approximately ten years since this first report, **287** has already seen total and formal syntheses reported by the groups of Nicolaou,[347–351] Mulzer,[352] Snider,[353] Yamamoto,[354] Corey,[355] Nicolaou and Chen,[356] E. Lee,[357] Matsuo,[358] Njardarson,[359] Ghosh,[162,360] D. Lee,[361] Canesi,[362] Magnus,[363] Nakada,[364] Ito,[365] Wright,[366] C.-S. Lee,[367] Nagasawa and Kuwahara,[368] Zhang and Lee,[369] Lear,[370,371] and Wang.[372] Of these impressive works, the chiral pool of terpenes has been utilized by Nicolaou and Chen,[356] Ghosh,[162,360] and D. Lee.[361] The 2012 Gaich and Mulzer review highlighted Ghosh's chiral pool route from carvone as well as Mulzer's and Rutjes's syntheses of the structurally related natural product platencin.[165,166] Herein we will focus on the Nicolaou/Chen and Daesung Lee routes, both of which utilize carvone, but feature markedly different chemical transformations.

In their chiral pool-based synthesis of platensimycin (**287**), the Nicolaou and Chen groups selected carvone as the tactical precursor to the highly substituted cyclohexane core of the natural product (Scheme 26). To begin, cerium-mediated 1,2-addition of Grignard reagent **288** to carvone, and subsequent Dauben oxidation (PCC) of the resulting tertiary alcohol, afforded enone **289** in high yield. In a key sequence, formal allylation of the enone was brought about in two steps. First, oxymercuration ($Hg(OAc)_2/H_2O$) of the isopropenyl group provided a primary alkyl mercury compound. Following reductive work up ($NaBH_4$) of this intermediate, a 5-*exo* cyclization onto the cyclohexenone ensued, presumably through a primary radical intermediate.[373] The tertiary alcohol formed during this step was then dehydrated using Martin's sulfurane to give bicyclic ketone **290**. Conversion of this material to an *exo*-methylene enone was accomplished by silyl enol ether formation followed by a selenation/elimination (TMSI, PhSeCl *then* H_2O_2) sequence. Removal of the cyclic acetal with acetic acid then produced aldehyde **291**. In another key ring-forming step, **291** underwent intramolecular 6-*endo* radical cyclization when subjected to the reductant SmI_2, affording **292** as a single diastereomer. Two-step Mitsunobu inversion of the secondary alcohol, with concomitant epimerization of the ketone, furnished compound **293** as a separable ~1:1 mixture of C-9 isomers (shown in red). Stereoselective reduction of the ketone (L-selectride) gave a secondary alcohol that cyclized onto the isopropenyl group when treated with acid and a PCC oxidation of the remaining secondary alcohol then provided caged ketone **294**. Further processing to enone **295** was achieved by regioselective silyl enol ether formation (TMSI, HMDS), followed by oxidation with either IBX or $Pd(OAc)_2$.[374] Of note, compound **295** serves as the endpoint in most formal syntheses of platensimycin including this work by Nicolaou and Chen. Shown in Scheme 26 is the end game previously developed by Nicolaou to deliver the final natural product.[350] Sequential alkylation of **295** (KHMDS, MeI *then* KHMDS, allyl iodide) led to enone **296** in a stereoselective manner. The allyl group underwent efficient cross metathesis with vinyl boronic acid pinacol ester under the action of Grubbs' second generation catalyst, and following oxidation at boron (Me_3NO) aldehyde **297** was obtained. This somewhat unorthodox two-step sequence was vastly superior to more conventional hydroboration/oxidation sequences in terms of isolated yield. **297** underwent Pinnick oxidation to yield

platensic acid (see **298**), which was then efficiently coupled (HATU, Et_3N) with aniline **299**. After a deprotection sequence (LiOH then HCl), platensimycin (**287**) was unveiled in a total of 21 steps. By leveraging carvone, a route to either enantiomer of **287** has been rendered accessible from simple inexpensive sources.

3.3.11 Lee's Formal Synthesis of Platensimycin (2009) (Scheme 27)—In 2009, Lee and co-workers reported a distinct route to key intermediate **295** from carvone using an alkylidene carbene C-H insertion strategy (Scheme 27).[361] Carvone was first reduced to *cis*-carveol with lithium aluminum hydride and then subjected to a bromoetherification reaction with NBS, thus forging the tetrahydrofuran ring in the opening sequence. Ether **300** was then converted into enal **301** via two allylic oxidations. In a key C–C bond forming step, a reductive radical cyclization (AIBN, Bu_3SnH) was used to construct caged compound **302** via a 5-*exo* cyclization process.[375] One carbon Wittig-homologation afforded aldehyde **303**, which was converted into methyl ketone **304** via addition of MeMgBr followed by PCC oxidation. In the key step of the synthesis, **304** was treated with the lithium anion of trimethylsilyl diazomethane, presumably forming vinyl carbene **305** by an addition/Brook rearrangement/elimination/nitrogen extrusion cascade. This reactive species underwent insertion into the neighboring tertiary C-H bond. While there are two tertiary C-H bonds that could react in **305**, insertion was observed away from the electronegative oxygen atom due to orbital overlap considerations.[361] The C-H insertion product (**306**) could be advanced efficiently into the platensimycin core (**295**) via oxidative alkene cleavage (OsO_4 *then* $NaIO_4$) and subsequent aldol condensation (39% over 4 steps). Overall, only 12 steps were needed to access **295**, exemplifying the power of alkylidene carbenes in opening up unique and powerful retrosynthetic disconnections.[376–379]

3.4. Sesterterpene Targets

Twenty-five carbon sesterpenes are relatively uncommon, and far fewer syntheses have been completed in comparison to their sesqui- and diterpene brethren. Nevertheless, this family of terpenes possesses an assortment of diverse chemical architectures that have historically challenged the field of chemical synthesis. An excellent recent review by Trauner specifically covers this area of terpene research from a historic perspective.[380]

3.4.1. Ma's Synthesis of (+)-Leucosceptroids A and B (2015) (Scheme 28)—The grandular trichomes of the plant *Leucosceptrum canum*, which is often avoided by herbivores and many pathogens, were found to contain the novel sesterterpenes leucosceptroids A (**307**) and B (**308**).[381] These compounds display significant antifeedant activity as well as antifungal activity, and could serve as excellent tool compounds to better understand and develop novel pesticides for crop protection.[381] Isolated in 2010, leucosceptroids are relative terpene newcomers, yet several groups have already reported creative solutions to their synthetic construction. In 2013, Liu reported a synthesis of leucosceptroid B (**308**),[382] from 2014–2015 the group of Magauer reported the synthesis of eighteen leucosceptroids (including **307** and **308**),[383,384] and in 2015, Ma reported a chiral pool approach to both **307** and **308** which will be discussed herein.[385]

The Ma synthesis utilized (*S*)-citronellol as starting material and after ozonolysis, Wittig reaction, and DMP oxidation, arrived at allylsilane **309** (Scheme 28). Applying MacMillan's organo-SOMO oxidative coupling methodology using amine catalyst **310** then furnished key aldehyde coupling partner **311**.[386,387] Meanwhile, the authors prepared lactone **312** via a seven-step sequence (see inset). The cuprous salt generated from alcohol **313** was coupled with 3-bromopropyne producing a diyne which when treated with a gold catalyst and silver additive cyclized to furan **314** in excellent yield (85%). Addition of the titanium acetylide of **314** to chiral aldehyde **315** (under Felkin-Anh control) yielded an intermediate alcohol which was subjected to alkyne carbomagnesiation (Fe(III), MeMgBr), acetonide deprotection, and selective silylation. Finally, treatment of **316** with PhSeCl facilitated intramolecular selenolactonization producing an intermediate β-phenylseleno alcohol, which was converted to **312** upon treatment with hydrogen peroxide. Key fragments **311** and **312** were then merged via a diastereoselective, boron-mediated aldol reaction which produced **317** in 78% yield. A six-step sequence was then employed to epimerize the resulting alcohol to form trimethylsilyl ether **318**, which was subjected to a samarium iodide-mediated 6-*exo* ketyl olefin cyclization producing **319** after deprotection. The multi-step epimerization sequence proved necessary because, when utilizing the alternative β-disposed alcohol (or TMS ether), the undesired 7-*endo* cyclization pathway predominated. Oxidation of the primary alcohol of **319** and Wittig olefination completed the synthesis of the pendant prenyl chain of the natural product, and a Swern oxidation of the secondary alcohol accomplished the synthesis of leucosceptroid B (**308**). Stereo- and regioselective α-oxidation of the ketone moiety then forged leucosceptroid A (**307**) in a total of 19 steps (longest linear sequence) from alcohol **313**. Overall this synthesis further showcases how several powerful radical-based reactions,[302–305] in conjunction with chiral pool building blocks and asymmetric catalysis, can lead to creative and convergent solutions to complex problems in terpene synthesis.

3.4.2. Trauner's Synthesis of (−)-Nitidasin (2014) (Scheme 29)—The Peruvian infusion "Hercampuri," which has been used as an ancient remedy against hepatitis, diabetes, and hypertension, was shown in 1997 to contain several complex terpenoids, including the synthetically daunting sesterterpene nitidasin (**320**).[388,389] Comprised of a rare 5,8,6,5-fused tetracyclic architecture possessing ten chiral centers, **320** represents a state-of-the-art challenge in complex terpene synthesis. In 2014, Trauner and coworkers accomplished the first total synthesis of this enigmatic sesterterpene, utilizing chiral pool (−)-citronellene as a key building block (Scheme 29).[390]

The Trauner synthesis began with a selective oxidative cleavage of the more substituted olefin of (−)-citronellene (*m*CPBA then HIO_4) to produce **321**, followed by a methylative Corey-Fuchs reaction sequence affording enyne **322**. A zirconium-mediated cycloisomerization of this material,[391] utilizing NIS to quench the intermediate zirconocycle, furnished iodide **323**.[392] The isomeric mixture produced proved inconsequential, as the primary iodide was eliminated with base (DBU) and the resulting olefin subjected to hydroboration/oxidation sequence. A Swern oxidation and Wittig methylenation then afforded key vinyl iodide **324**. The "eastern" sector of nitidasin was then constructed beginning from intermediate **326**, which is ultimately derived from the Hajos-

Parrish ketone (see inset).[393–395] Ketone **326** was protected and then subjected to a palladium-catalyzed enolate allylation forming **327**. Ketone reduction (K-selectride) and oxidative cleavage of the alkene produced a lactol that was subsequently oxidized with PCC. Deprotonation of the resulting lactone (LHMDS) followed by quenching with methyl iodide produced **328** stereoselectively. Reduction of lactone **328** with lithium aluminum hydride, followed by global silylation and chemoselective oxidation under Swern conditions provided an aldehyde that could be converted into transhydrindanone **325** via a three-step protocol consisting of Wittig olefination, chemoselective deprotection, and subsequent oxidation.

With complex fragments **324** and **325** in hand, a key coupling sequence was developed wherein the vinyl lithiate derived from **324** was added to ketone **325**. Following a stereoselective epoxidation of the product, epoxide **329** was constructed. The authors employed a ring closing metathesis reaction using Grubbs' second-generation catalyst to forge the challenging 8-membered ring of nitidasin. This closure was likely aided by the pre-organization imparted by the geometrically defined epoxide. Completion of the total synthesis from **330** relied on a simple sequence including alkene hydrogenation, deprotection, and alcohol oxidation to furnish nitidasin (**320**). In addition to showcasing a masterful use of a variety of stereocontrolled transformations, this work also allowed the authors to establish the absolute configuration of the natural product.

3.4.3 Maimone's Synthesis of (−)-6-*epi*-Ophiobolin N (2016) (Scheme 30)—The ophiobolins are a class of sesterterpenes containing a 5,8,5-fused tricyclic core common to a variety of terpene families including the previously discussed fusiccocanes (see Section 3.3.6).[396] Ophiobolins were the first sesterterpenes ever isolated and are well documented phytotoxins.[396] More recently a variety of ophiobolins have been found to possess fascinating anticancer activity, including the ability to kill the typically drug resistant brain tumor glioblastoma multiforme cells.[397] There have been three total syntheses of members of the ophiobolin family, including the seminal synthesis of ophiobolin C by Kishi in 1989,[398] a synthesis of ophiobolin A by Nakada in 2011,[399,400] and a recent synthesis of 6-*epi*-ophiobolin N by Maimone in 2016 (Scheme 30).[401]

The Maimone synthesis of (−)-6-*epi*-ophiobolin N (**331**) utilized (−)-linalool as a chiral pool building block (Scheme 30). Ring-closing metathesis of this material and *in situ* silylation afforded protected cyclopentenol **332**, which was converted smoothly into enone **333** through direct allylic oxidation ($RuCl_3$, *t*BuOOH). Concurrently, *trans,trans*-farnesol was cyclopropanated according to Charette's enantioselective procedure employing tartrate-derived boronate **334**.[402] The resulting alcohol (see **335**) was then converted into highly sensitive iodide **336** via an Appel-type reaction. In a key 3-component coupling sequence, **336** was treated with *tert*-butyllithium inducing lithium-halogen exchange and anionic cyclopropane opening; after transmetalation with copper iodide, the resulting cuprate formed was added to enone **333**, resulting in a diastereoselective conjugate addition reaction. Finally, this mixture was quenched by the addition of trichloroacetyl chloride, resulting in the formation of **337** in 45% isolated yield along with 15% of the C-2 diasteromer. Cyclopentanone **337** could be stereoselectively reduced and acetylated *in situ* setting up the key step in the synthesis. Exposing this material to reductive radical cyclization conditions

(Et_3B/O_2, $(TMS)_3SiH$) led to a tandem *8-endo*/*5-exo* radical cyclization process (see **339**), forming the remaining two rings of the ophiobolins. Crucial to this process was the radical termination step at the C-15 position, which was accomplished diastereoselectively (dr = 3.4:1) under polarity-reversal conditions using the bulky dibenzothiophene derived TADDOL-based monothiol **338**.[403,404] It is noteworthy that the native selectivity for this reaction, when simple, achiral thiols such as thiophenol were utilized, favored the undesired C-15 diastereomer (dr = 1:1.9). Product **340** then underwent a Corey-Chaykovsky epoxidation and a reductive epoxide opening induced by lithium naphthalenide forging diol **341**. Finally, double Swern oxidation of **341** followed by acidic elimination of the linalool-derived tertiary alcohol afforded **331** in nine steps and as the non-natural enantiomer. This work clearly showcases both the power, as well as current practical challenges, of radical cascade processes in the rapid assembly of complex, stereochemically-rich terpene architectures.[302–305]

3.5. Triterpene-derived Targets

Thirty-carbon triterpenes and their derivatives comprise one of the largest groups of terpenes, with an estimated 20,000 members.[405] Given that many of these compounds are frequently modified steroids, semisynthesis from an abundant steroid precursor is often employed.[22,23] As noted previously, steroid semisynthesis lies outside the scope of this review. The natural products discussed in this section, while not comprising 30 carbons, are all believed to be biosynthetically derived from triterpenes.

3.5.1 Shing's Synthesis of (−)-Samaderine Y (2005) (Scheme 31)—Samaderine Y (**342**) belongs to the quassinoid family of natural products and while containing 20 carbon atoms, **342** – like all quassinoids – is more properly described as a degraded triterpene from a biosynthetic perspective.[406,407] These compounds are often found in the bitter principles of the *Simaroubaceae* family of plants and display high levels of oxidation, intricate ring systems, and potent biological activities.[408,409] Accordingly, many members of this family have inspired creative syntheses, employing a number of diverse strategies.[410,411] Shing's 2005 synthesis of samaderine Y from carvone exemplifies the chiral pool approach to these natural products.[412,413]

The synthesis of samaderine Y (**342**) (Scheme 31) commenced with a double formaldehyde aldol reaction of carvone followed by acetonide formation.[414] Product **343** was then processed through a five-step sequence involving a regioselective allylic oxidation, Luche reduction, protection, epoxidation, and a second Luche reduction to give **344**. Treatment of this material with TFA removed the acetonide group, triggering an intramolecular epoxide opening from one of the free primary hydroxyl groups. Upon addition of 2,2-dimethoxypropane the resulting diol formed a second acetonide. Secondary alcohol protection (TBSOTf), acetonide removal, and double oxidation furnished keto aldehyde **345**. The allylic Grignard reagent shown then added selectively to the aldehyde moiety to furnish secondary alcohol **346**. As is common, γ-attack of the allylic nucleophile was observed. Upon treatment with sodium hydride, an anion accelerated 1,3-sigmatropic rearrangement occurred,[415,416] which was followed by acetylation of the secondary alcohol. The diene product generated then underwent intramolecular thermal Diels-Alder reaction to forge the

6,6-fused ring system of the quassanoids resulting in **347** with 2:1 *trans:cis* selectivity at the ring fusion. Next, a three-step sequence was employed to invert the stereochemistry of secondary acetate to provide diastereomer **348**. Two-step acetate aldol condensation then delivered the final ring of samaderine Y and a subsequent reduction of this unsaturated lactone ($NaBH_4$, Ni^{II}) yielded acetal **349**. With the full ring system in place, the concluding steps of the synthesis focused on installing the final requisite oxidations. Allylic oxidation of **349** ($Mn(OAc)_3$, *t*BuOOH) gave an enone which was α-acetoxylated with additional $Mn(OAc)_3$. Unfortunately, product **350** required another three-step inversion sequence leading to enone **351**. With this material in hand, an acetal deprotection (HCl/H_2O), lactol oxidation (Fétizon's reagent), and global deprotection (HCl/TFA), completed the synthesis of (−)-samederine Y (**342**) in 29 steps, showcasing the power of chiral pool starting materials in concert with pericyclic processes to construct exceedingly compact and stereochemically rich carbocyclic ring systems.

3.5.2 Li's Synthesis of the Proposed Structure of Rubriflordilactone B (2016) (Scheme 32)—

Triterpene derivatives from *Schisandraceae*, like rubriflordilactone B (**352**, Scheme 32) and schilancitrilactones B and C (**364**, **365**, Scheme 33) have attracted great synthetic attention ever since their isolation and characterization.[417–422] Boasting polycyclic structures with a characteristic 7-membered ring and often containing multiple lactone moieties, these natural products are noted for both their structural intricacies and biological potencies – most have strong antiviral properties and many also display antiproliferative effects.[423,424] Rubriflordilactone B (**352**) itself is a bisnortriterpenoid (C-28) that contains a central tetrasubstituted aromatic ring.[425] By anticipating the construction of that motif in at the end of their synthesis, Li and coworkers developed a convergent synthetic strategy involving the late-stage union of two complex building blocks.[422] Of note, a chiral pool terpene building block is not obviously identified within the gross structure of the final target.

As part of this plan, the western portion of the molecule, particularly the cycloheptane ring, was traced back to chiral pool starting material perillyl alcohol (Scheme 32). This material was first converted into a phosphonate ester using Zn(II)iodide and triethylphosphite. Ozonolysis then cleaved the more electron-rich, trisubstituted olefin producing an intermediate keto aldehyde that immediately underwent intramolecular Horner-Wadsworth-Emmons olefination in the presence of base. The enone formed (**353**) was then converted to cyanide **355** via a three-step sequence involving oxidation to a dienone with Mukaiyama's reagent (**354**), regioselective hydride conjugate reduction of the less hindered olefin with L-selectride, and conjugate addition of cyanide. An efficient Mukaiyama hydration of the isopropenyl group produced a tertiary alcohol, which cleanly forged a γ-lactone ring (see **356**) upon basic hydrolysis of the nitrile. At this point, chemoselective α-hydroxylation of the lactone was required in the presence of the more reactive ketone moiety. To address this challenge, the ketone was protected as an *exo*-methylene group using the Wittig olefination ($Ph_3P{=}CH_2$), thereby allowing for lactone α-oxygenation (KHMDS, oxaziridine **357**, then TESOTf), and finally the ketone was revealed through ozonolysis, yielding lactone **358**. Triflation of the ketone (LHMDS, $PhNTf_2$) proceeded smoothly and the triethylsilyl group was exchanged for an acetate, using a procedure particularly suited for hindered tertiary

alcohols ($Sc(OTf)_3$, Ac_2O).[426] Enol triflate **359** was then exposed to LHMDS, promoting an intramolecular acetate aldol condensation which was followed by ionic hydrogenation (Et_3SiH, $BF_3{\bullet}OEt_2$). The tricyclic lactone product then underwent regioselective allylic radical bromination (NBS, $(BzO)_2$), producing bromide **360** as an inconsequential mixture of diastereomers. Unfortunately, direct elimination of this bromide proved unsuccessful; therefore, a two-step protocol was developed wherein the bromide was first displaced by an aryl selenide (*o*-$NO_2C_6H_4SeCN$, $NaBH_4$) and the resulting intermediate was oxidized and eliminated (H_2O_2, pyr.), thus delivering key coupling partner **361**.

At this juncture, **361** was merged with alkyne **362** – itself prepared in 11 steps from a non-chiral pool starting material – by means of a high yielding Sonogashira coupling. **363** was then semi-hydrogenated (H_2, Lindlar's cat.) forming a triene and setting the stage for Li's signature electrocyclization/aromatization cascade sequence.[329,427,428] Thus, heating the intermediate triene at 80°C brought about the desired 6π-electrocyclization and the crude mixture was then successfully oxidized with DDQ to succinctly produce rubriflordilactone B (**352**) in a longest linear sequence of 20 steps from perillyl alcohol. Despite X-ray crystallographic data of both synthetic and natural naturally occurring material, the NMR data of synthetic **352** did not match the reported literature values.[425] Supported by recent calculations by Kaufman and Sarotti,[429] the true structure of rubriflordilactone B is suggested to be a diastereomer of **352**. In addition to highlighting the role of total synthesis in structural confirmation, Li's synthesis of **352**, which employs a late-stage coupling of thirteen and fifteen carbon fragments, is a model for convergency in complex terpene assembly.[20]

3.5.3 Tang's Synthesis of Schilancitrilactones B and C (2015) (Scheme 33)—

Though the schilancitrilactones share some structural similarities to rubriflordilactone B (Section 3.5.2), particularly in the western portion of their structures, their differing carbon skeleton and distinctive oxidation pattern make them unique synthetic challenges.[430] In 2015, the group of Tang reported synthetic solutions to the formidable targets schilancitrilactones B (**364**) and C (**365**) utilizing carvone as a chiral pool building block (Scheme 33).[419]

The Tang synthesis began with substantial degradation of carvone utilizing a sequence previously developed by Deslongchamps (Scheme 33).[431] Carvone was first epoxidized (H_2O_2/NaOH) and the resulting epoxide subjected to hydrolytic ring opening with sulfuric acid. Oxidative C–C bond cleavage with sodium periodate not only ruptured the 6-membered ring, but also carved out two carbon atoms furnishing linear acid **366**. From this point, iodolactonization proceeded uneventfully, producing lactone **367** as an inconsequential mixture of diastereomers. Reduction of the aldehyde ($NaBH_4$) and radical dehalogenation (Bu_3SnH, AIBN) furnished a substrate suitable for an Appel reaction (I_2, PPh_3, imidazole), leading to iodide **368** in three steps from **367**. Concurrently, aldehyde **369** was prepared in ten steps employing a non-chiral pool based route. Straightforward aldol coupling between the lithium enolate of **368** and aldehyde **369** cleanly generated **370** in excellent yield (86%). Alcohol dehydration of **370** ($CuCl_2$, EDC) and subsequent conjugate addition of the alkyl iodide center (CuI/Zn)[432] to the resulting unsaturated system zipped up

the seven-membered ring, affording pentacycle **371** as the major product. Notably, conventional tin-based and modern photoredox-mediated radical cyclizations failed to elicit this seven membered ring-forming process. Treatment of **371** with *m*CPBA gave an epoxide, which underwent facile β-elimination when treated with sodium methoxide. The α, β-unsaturated ester product was then chemoselectively reduced ($NaBH_4$, $NiCl_2$•$6H_2O$), yielding tertiary alcohol **372**. To complete the synthesis it was necessary to append a butenolide motif onto this advanced core structure, yet **372** did not possess obvious "synthetic handles" to do so. Boldly, Tang and co-workers found that treating **372** with iodine monochloride induced formal oxidative C–H iodination delivering secondary iodide **373** as a 1.5:1 mixture of diastereomers. With this material in hand, a daring radical coupling was saved for the very last step. Under alkyl radical generating conditions (Bu_3SnH, AIBN), **373** was found to undergo formal coupling with stannane **374**,[433] affording a diastereomeric mixtures of schilancitrilactones B (**364**) (9%) and C (**365**) (36%). Overall, this concise, 17-step total synthesis elegantly leveraged the known cleavage chemistry of carvone. It is also noteworthy that by utilizing a late stage formal C–H halogenation, the authors did not need to carry a sensitive, and potentially incompatible, secondary halide (or protected precursor) throughout the synthesis.

4. Conclusion

As this review hopefully has made clear, the field of synthetic terpene chemistry is still vibrant with many creative players distributed widely across the globe. Even in an age of advanced analytical techniques, the use of total synthesis in the structural confirmation of terpene natural products is still relevant. Moreover, natural products that several decades earlier seemed nearly impossible to synthesize, many of which ultimately required 30–50 operations to do so, have now been synthesized in a fraction of synthetic steps.[434] Furthermore, some of the syntheses discussed herein are quite efficient in terms not only of step count, but yield and material throughput as well.[46,49,136,435] Some have overall yields approaching 20%,[64,95] and one has produced gram quantities of the target in a single synthetic pass.[114] However, much work remains to be able to accomplish this on a consistent basis, particularly owing to the highly variable structures of terpenes and the lack of a universal synthetic strategy. In addition, modular medicinal chemistry-type routes, while becoming increasinlgy feasible with other highly complex natural product scaffolds,[436,437] are very much still challenging in the terpenoid arena.[438] Moreover, is a chiral pool strategy the best bet for this line of research? And if suitable clinical candidates were to emerge from such studies could they be prepared in kilogram (or more) scales?

Are chiral pool syntheses more efficient than non-chiral pool (i.e. asymmetric synthesis-based) strategies? This question was not addressed in this work and has no simple answer. Many of the syntheses covered in this review are the shortest routes to the given structure. However many chiral pool syntheses have historically been quite lengthy.[10,11,21] In many of the latter cases, extensive protecting group and redox manipulations were often required, thereby nullifying the benefits of starting with a substantial portion of the carbon atoms in place. The synthetic practitioner must always be mindful of these drawbacks when considering a chiral pool-based approach to a complex target (of any type). Finally, as documented numerous times in this review, many convergent terpene syntheses employ both

a chiral pool component and a fragment prepared by asymmetric synthesis thus complicating this direct evaluation.[20]

What might the future of this area look like? It is clear from many of the works showcased that truly efficient syntheses are possible when powerful synthetic methodology is leveraged on a judiciously chosen chiral pool scaffold using an overall sound synthetic strategy. Thus this field evolves with the synthetic methods of the period.[434,439] It is of note that radical chemistry is as alive as ever, as is clear from the many radical-based key steps in the discussed works. Current activities in the methodological areas of both C–H and C–C activation will also feature prominently for the foreseeable future as these methods not only alter the oxidation state of chiral pool materials but can also rearrange their carbon frameworks.[440–446] The methodologic aspect of chiral pool terpene synthesis is highlighted by Reisman's pulegone-based, and Deslongchamps' carvone-based syntheses of ryanodol (the latter of which was not discussed due to the period of the review). While both laboratories likely had access to either of these chiral pool materials in house, the Pauson-Khand reaction[447] was only just starting to "come online" during the 1970's when Deslongchamps' historic campaign toward this target began.[227] Thus, chiral pool terpene syntheses are in a way a product of their times, and the terpene starting material simply represents a blank canvas from which the synthetic practitioner can create from. However, with a greater assortment of starting materials, a wider sampling of finished pieces can be expected. Consider Baran's route to phorbol (Scheme 21). What if modified (+)-3-carene was available with the cyclopropane hydroxyl group already in place? Would these researchers have had to expend the time and steps to deal with breaking and reforming the cyclopropane? How concise could this route become? Would their key remote C–H activation reaction even work with this electronegative substituent already present? What if carene was commercially available with hydroxyl groups at every position? While these questions are left unanswered for now, it's clear that expanding the chiral pool of terpenes fundamentally alters the disconnections and possibilites available to the synthetic practitioner, aiding in both natural and non-natural synthetic designs.[448] Although the field of synthetic biology is actively engaged in this line of research,[449–454] substantial engineering (and fundamental research) hurdles are still present in nearly all cases to translate proof-of-concept experiments to portfolios of products available in kilogram quantities for cents/gram. Nevertheless, these goals, in conjunction with advances in synthetic methodology and strategy, could fundamentally alter how chemists synthesize complex terpenes and their diverse analogs well into the 21st century.

Acknowledgments

Funding

Financial support for this work was provided by the NIH (GM116952). T. J. M. is an Alfred P. Sloan Fellow and Cottrell Scholar. Z. G. B, M. L. C., and C. P. T. thank the NSF for pre-doctoral fellowships (DGE-1106400). Z. G. B. and M. L. C. acknowledge UC-Berkeley for Berkeley graduate fellowships. C. P. T. acknowledges Bristol-Myers Squibb for a pre-doctoral fellowship.

Biographies

Tom Maimone received a B.S. degree in chemistry from UC-Berkeley (2004) where he was introduced to organic chemistry research in the laboratory of Prof. Dirk Trauner. From 2005–2009 he was a member of Prof. Phil Baran's research group at The Scripps Research Institute, and from 2009–2012, an NIH postdoctoral fellow in Prof. Steve Buchwald's lab at MIT. In 2012, he returned to UC-Berkeley as an assistant professor in the area of natural products total synthesis.

Zachary Brill received his B.A. in chemistry (*summa cum laude*) from Columbia University in 2012, where he conducted research in the lab of Prof. Scott Snyder. As an undergraduate, he completed the total synthesis and structural revision of the resveratrol dimer caraphenol B and pursued the synthesis of the unusually strained halogenated sesquiterpenoid aplydactone. In 2012, he began his graduate studies at University of California, Berkeley with Prof. Tom Maimone. Continuing his pursuit of total synthesis, his work at Berkeley on complex polycyclic terpenes has explored the use of tandem radical cyclization cascades in the construction of ophiobolin sesterterpenes.

Matthew Condakes received his AB and AM degrees in chemistry *summa cum laude* from Harvard University in 2014. While an undergraduate there, he conducted research on the synthesis of novel macrolide antibiotic analogs under the guidance of Prof. Andrew Myers. His passion for complex molecules then led him to pursue graduate work with Prof. Tom Maimone at the University of California, Berkeley as an NSF predoctoral fellow. At Berkeley, his work has focused on developing innovative synthetic strategies and methodologies–efforts that recently culminated in an oxidative synthetic strategy toward the *Illicium* sesquiterpenes.

Chi P. Ting was born in Hong Kong, and grew up in Chicago, Illinois. He received a B.S. degree in Chemistry at the University of Illinois at Urbana-Champaign, where he worked under the direction of Prof. Steven Zimmerman. In 2012, he began his PhD studies at the University of California, Berkeley as a founding member of the Maimone research group. His graduate work has explored concise total synthetic routes to podophyllotoxin, hyperforin, berkeleyone A, and garsubellin A.

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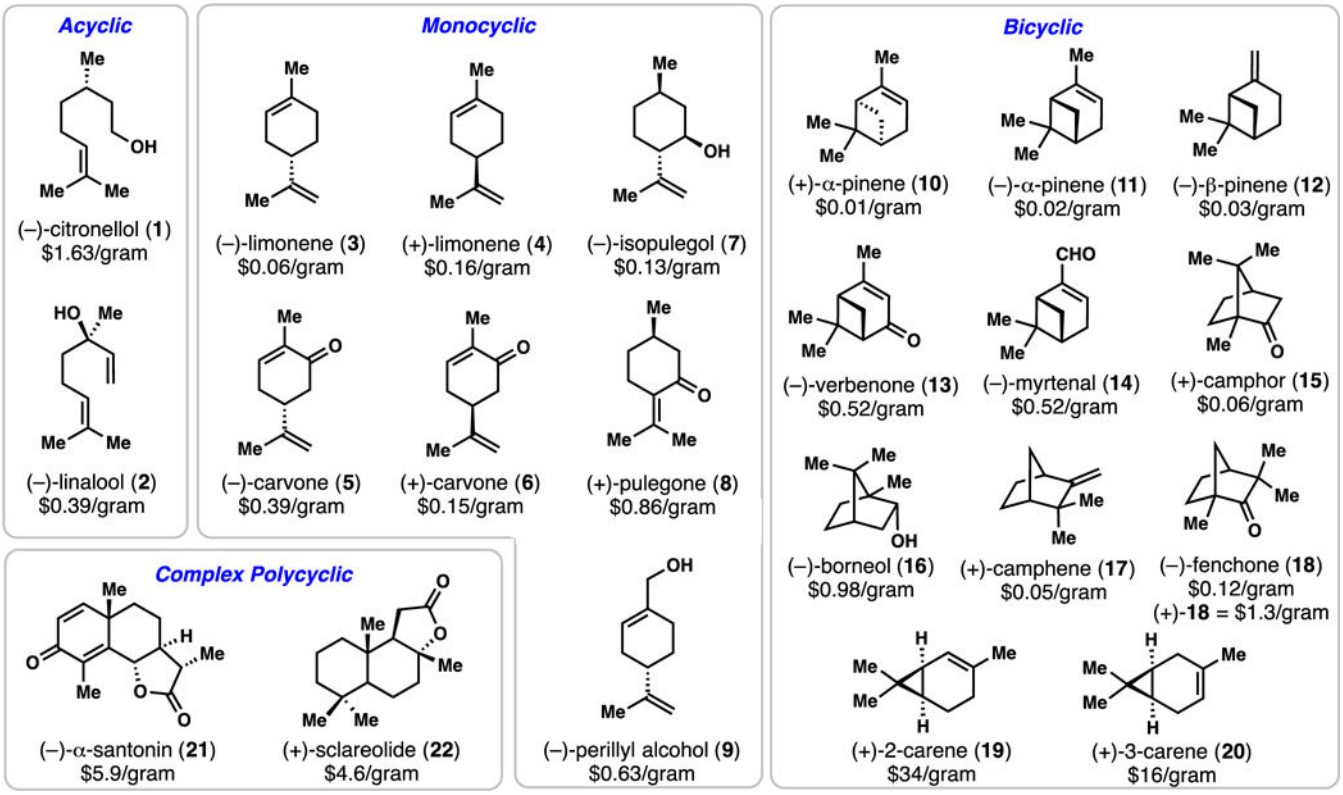


Figure 1.
Chiral pool terpenes of both historical and modern use in natural product synthesis.

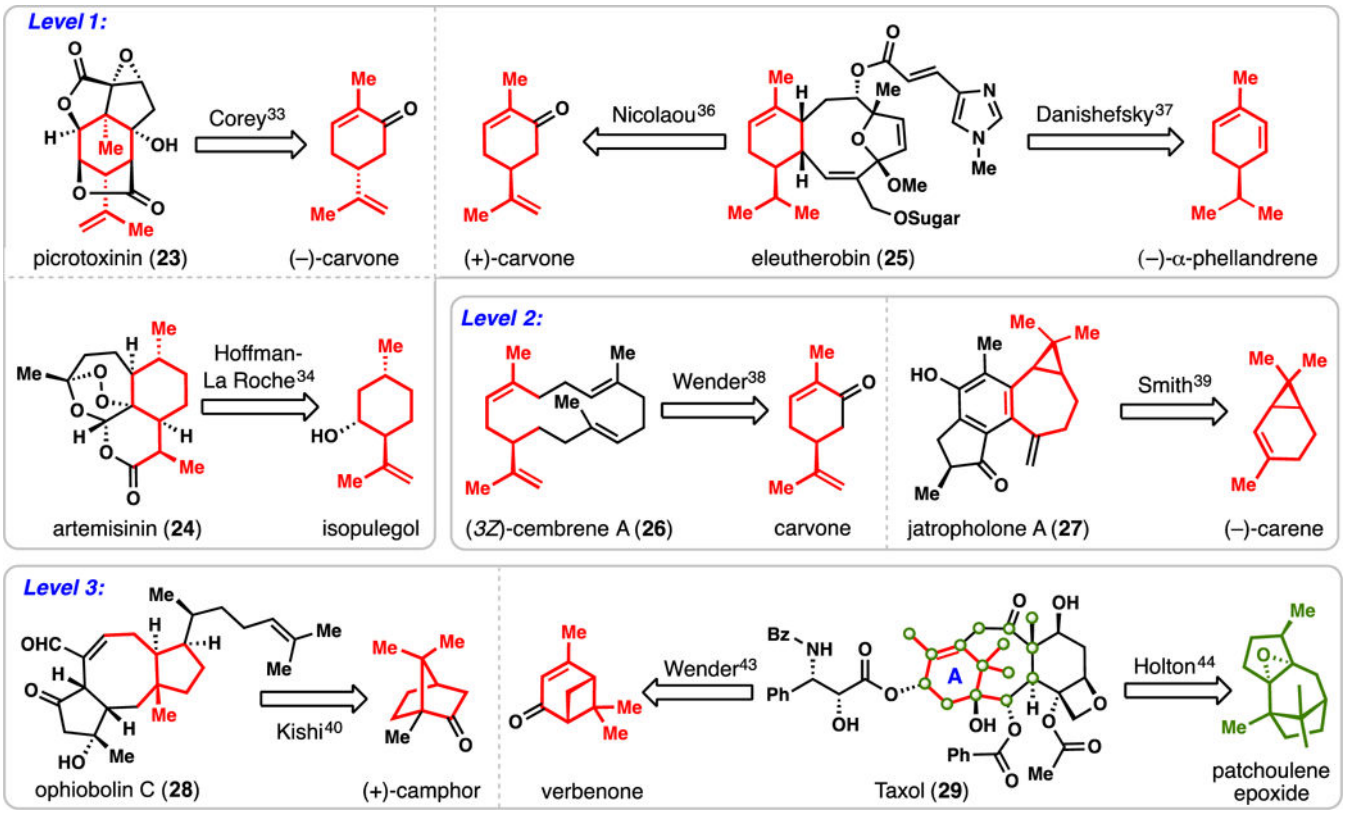


Figure 2.

Selected terpene syntheses of the 20th century. Terpene syntheses can be roughly grouped according to the structural similarity of the starting terpene with that of the final product.

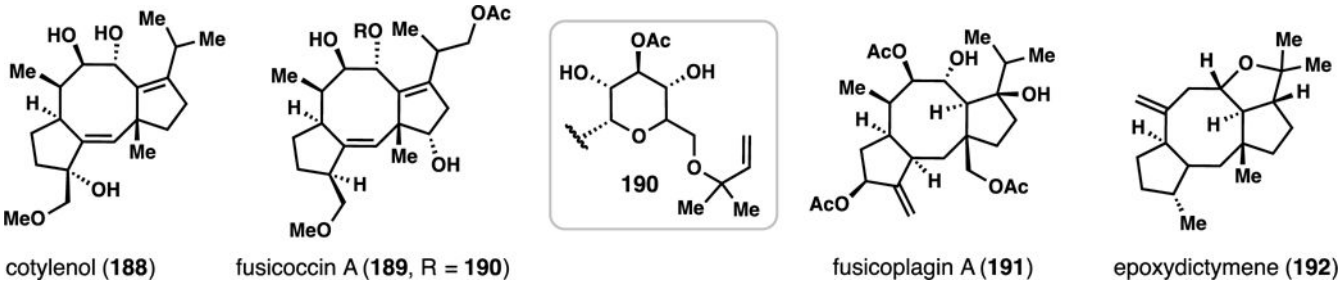


Figure 3.
Various diterpenes containing 5,8,5-fused ring systems.

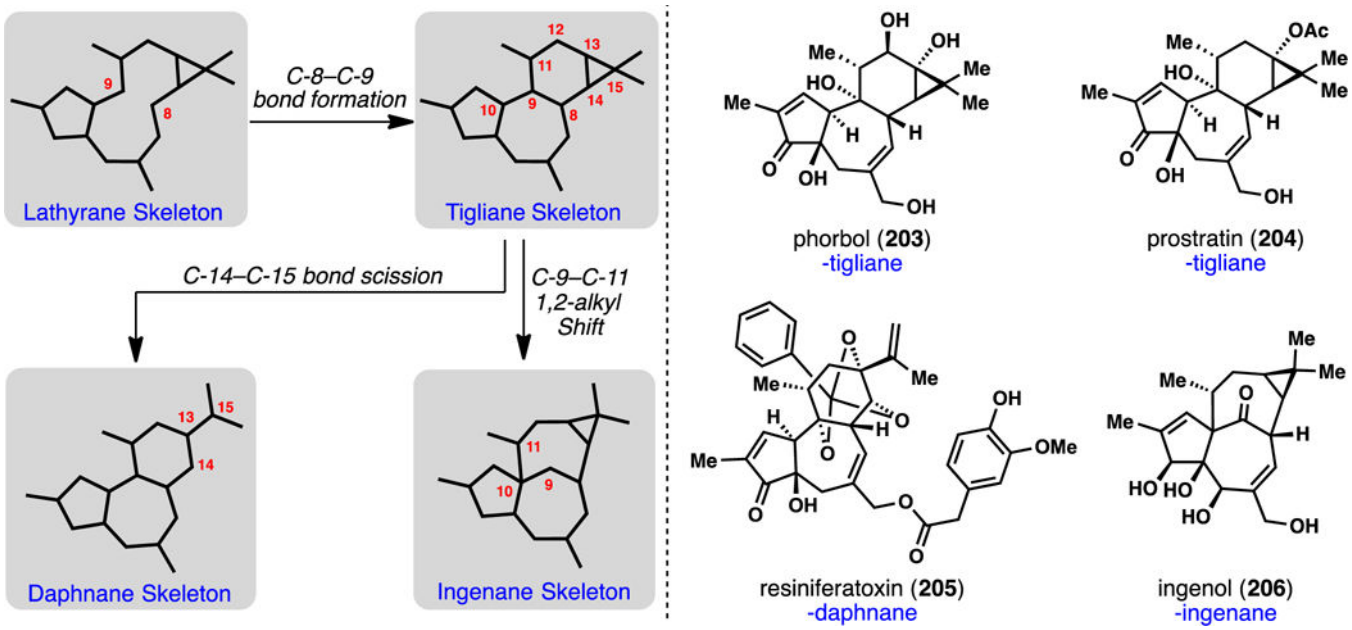
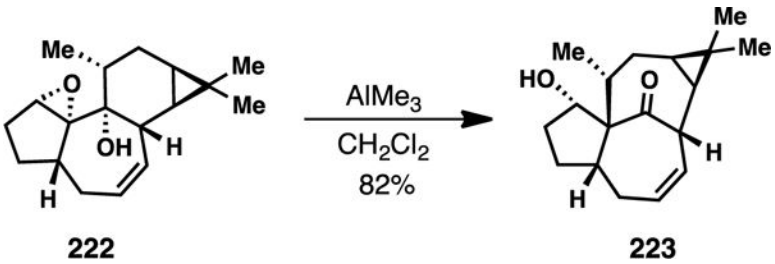
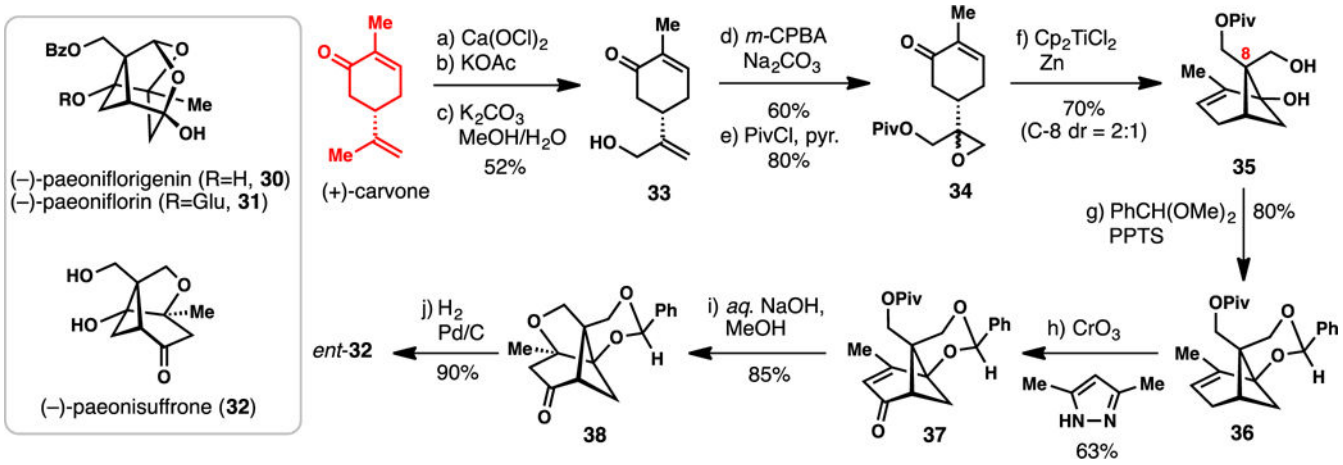


Figure 4.
Complex diterpenes from Euphorbiaceae.



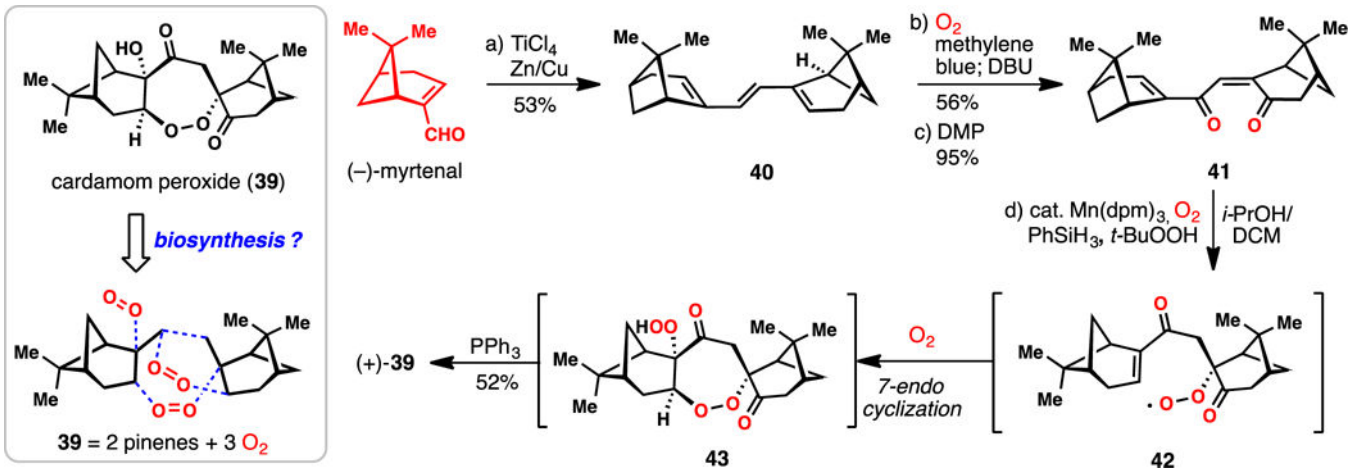
222 223

Figure 5.
Cha's pinacol-type rearrangement to access the ingenane ring system.



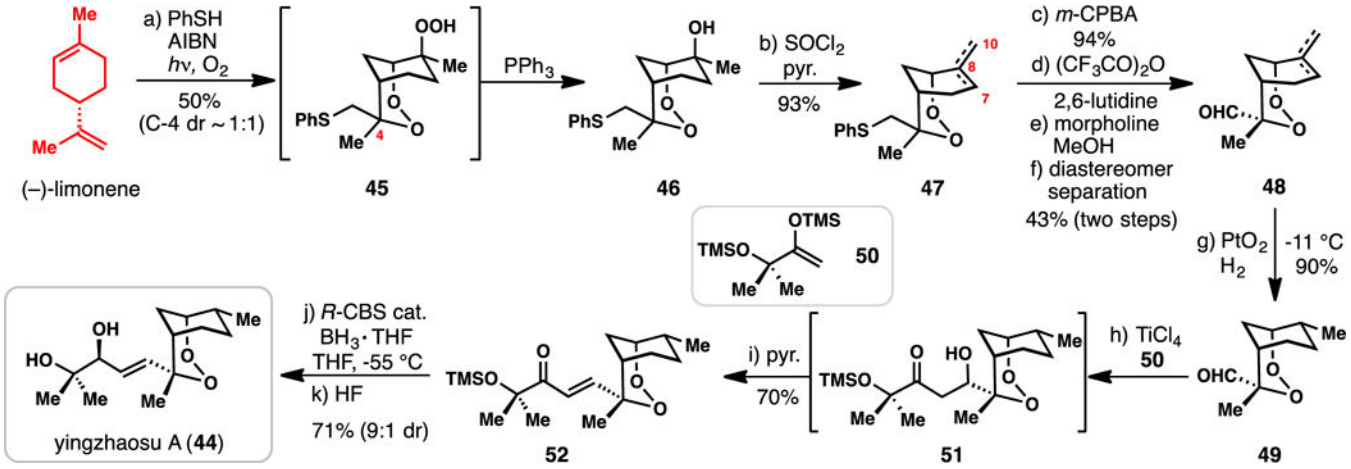
Scheme 1.

Bermejo's Synthesis of (+)-Paeonisuffrone from (+)-Carvone (2008)



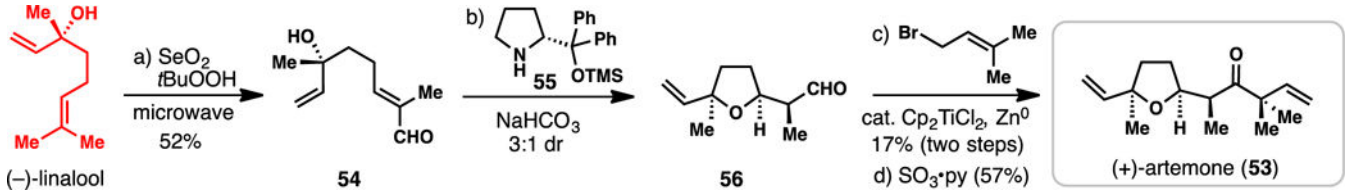
Scheme 2.

Maimone's Synthesis of (+)-Cardamom Peroxide from (−)-Myrtenal (2014)



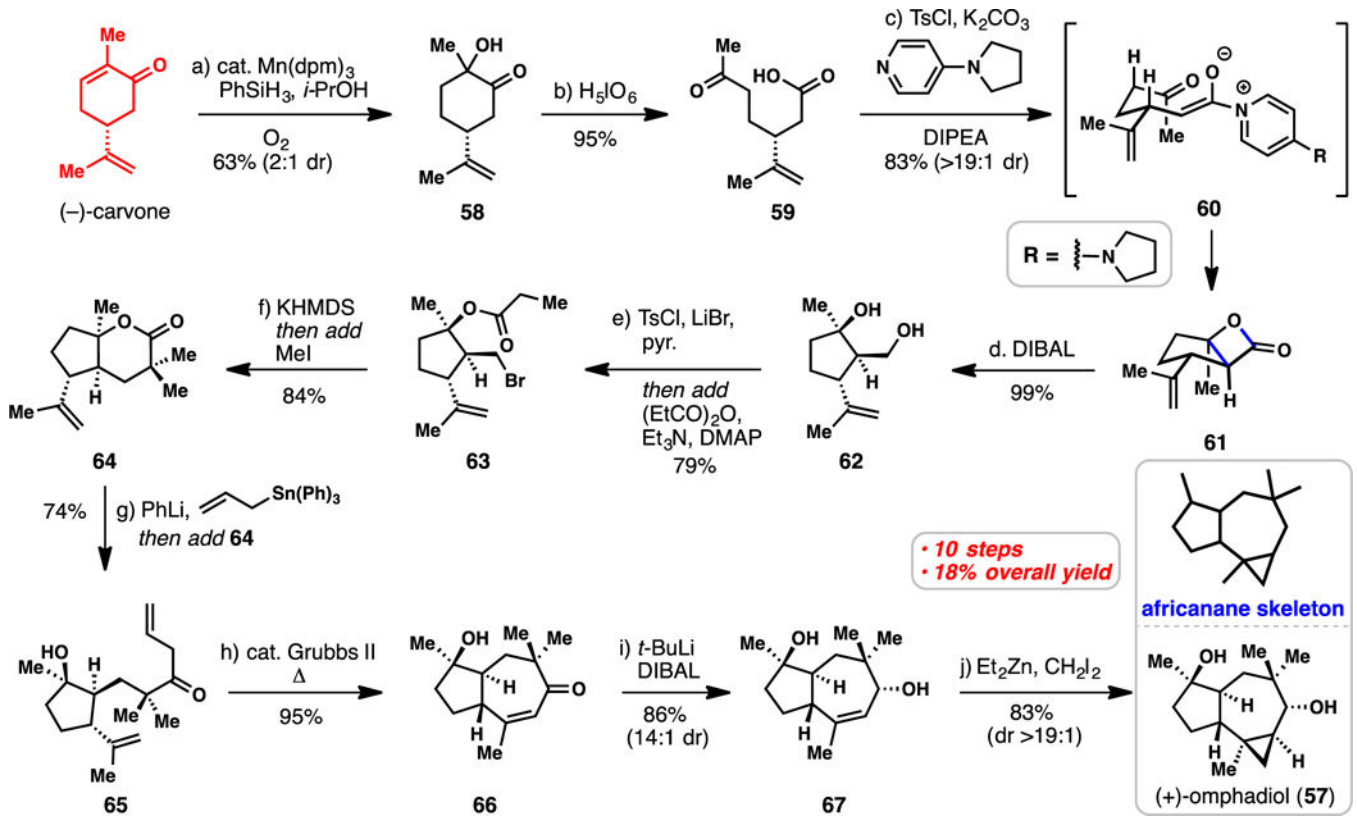
Scheme 3.

Bachi's Synthesis of (+)-Yingzhaosu A from (−)-Limonene (2005)



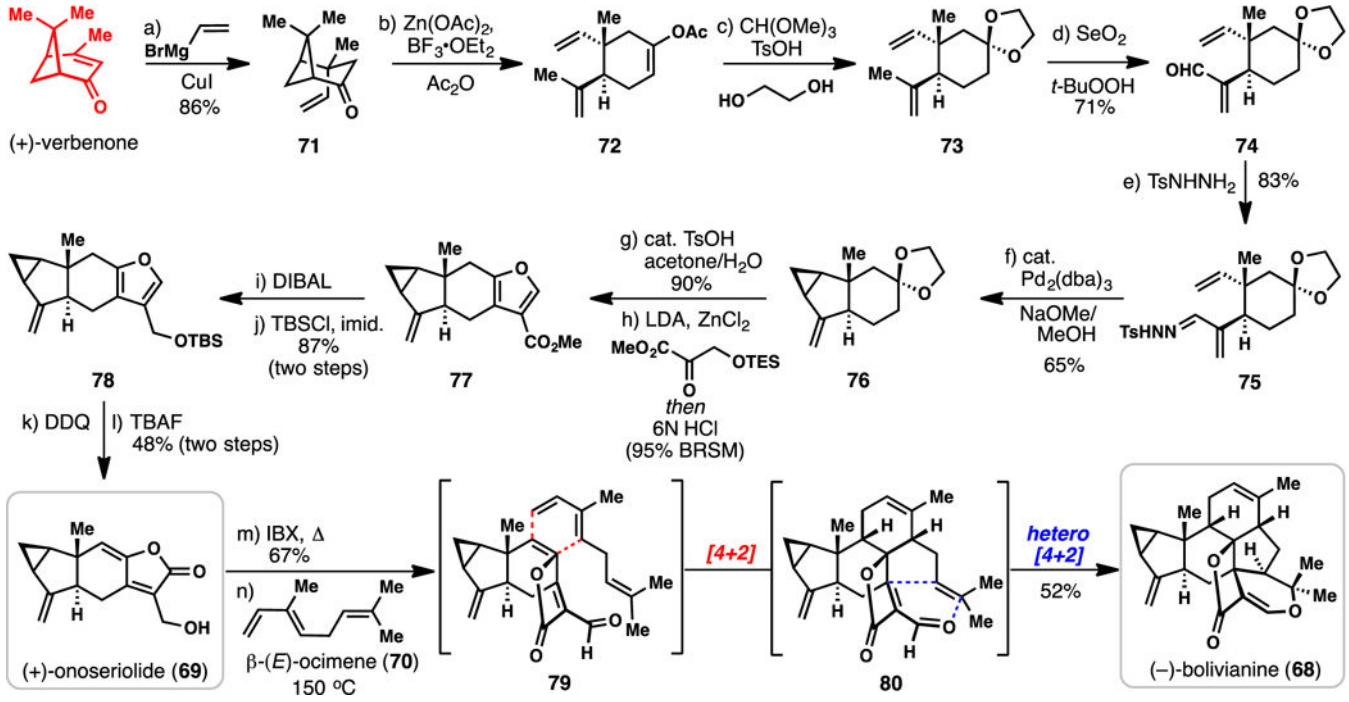
Scheme 4.

Vosburg's 4-step Synthesis of (+)-Artemone from (−)-Linalool (2015)



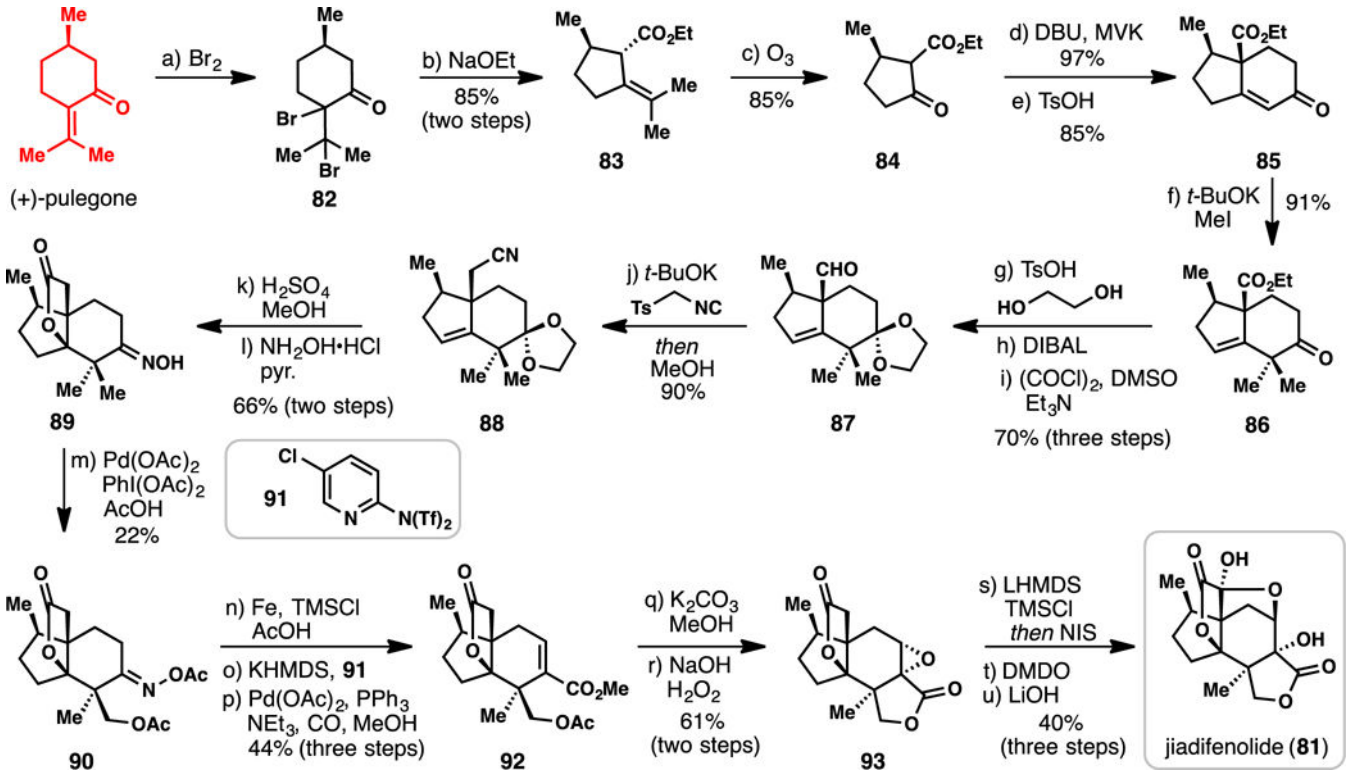
Scheme 5.

Romo's 10-step Synthesis of (+)-Omphadiol from (−)-Carvone (2011)



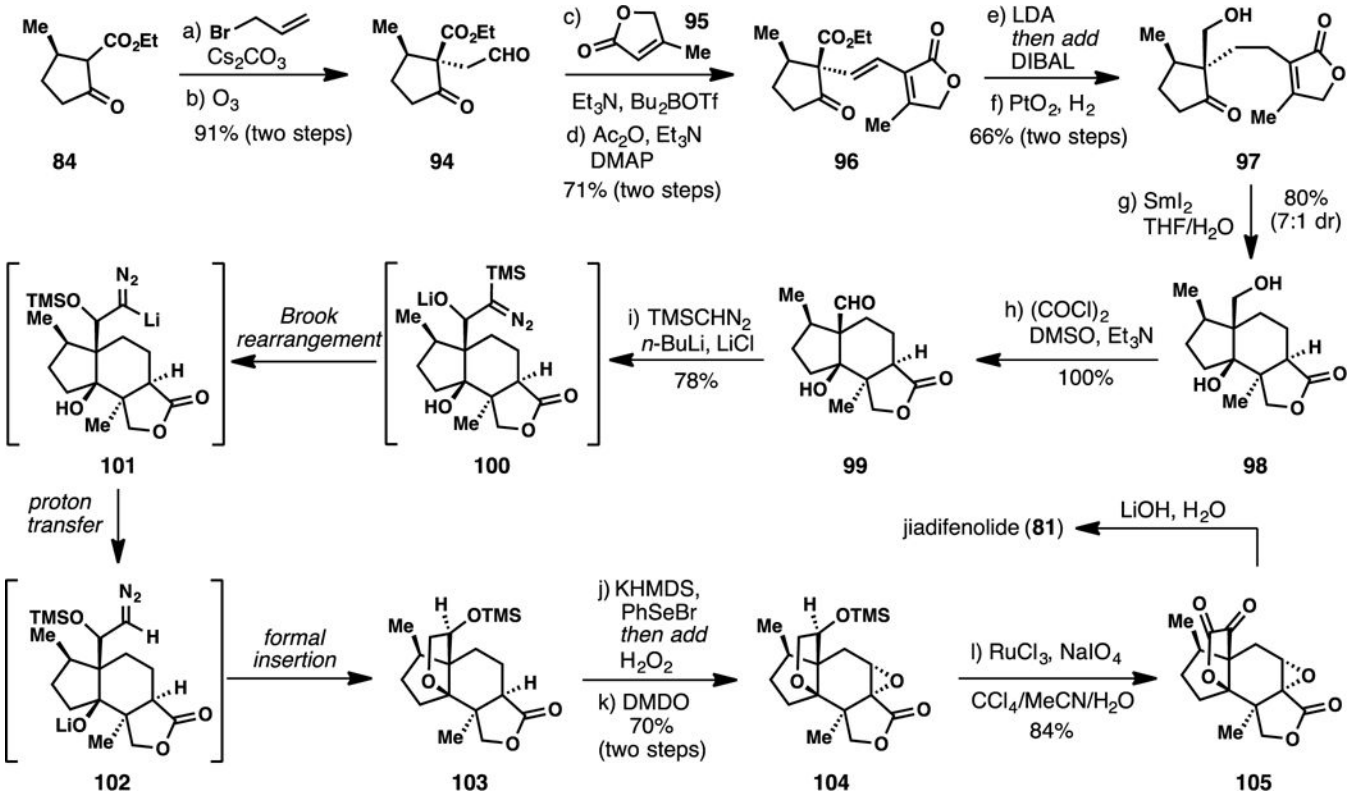
Scheme 6.

Liu's Synthesis of (+)-Onoseriolide and (−)-Bolivianine from (+)-Verbenone (2013)



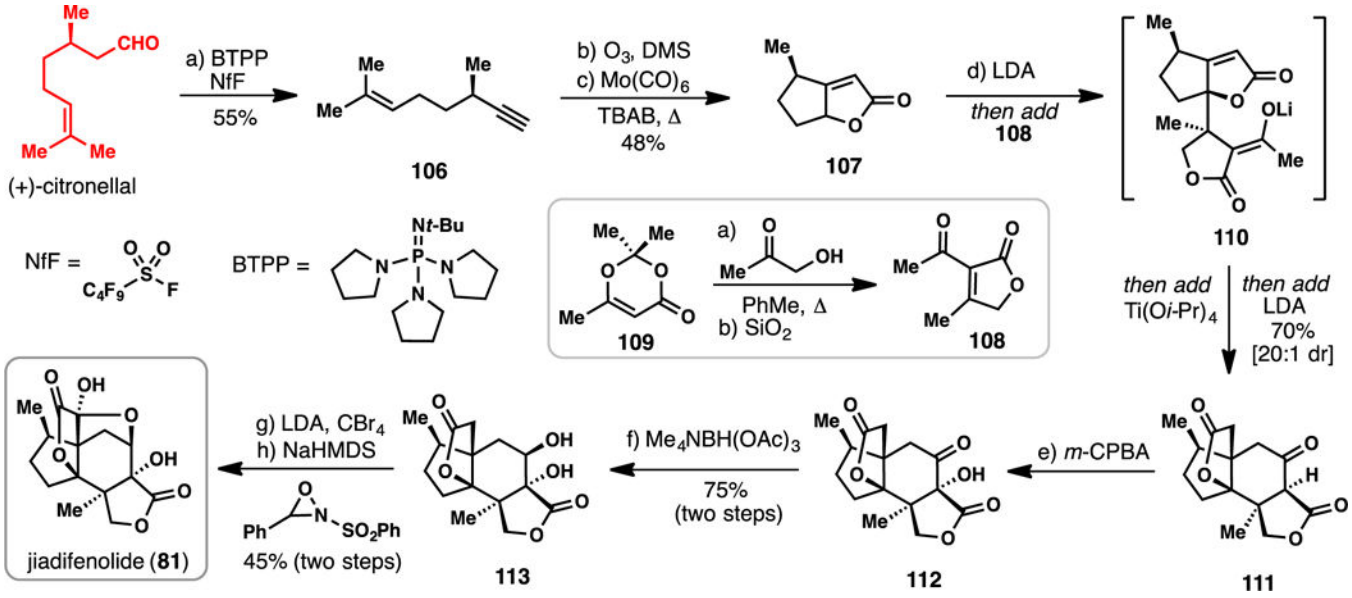
Scheme 7.

Sorensen's Synthesis of (−)-Jiadifenolide Employing (+)-Pulegone (2014)



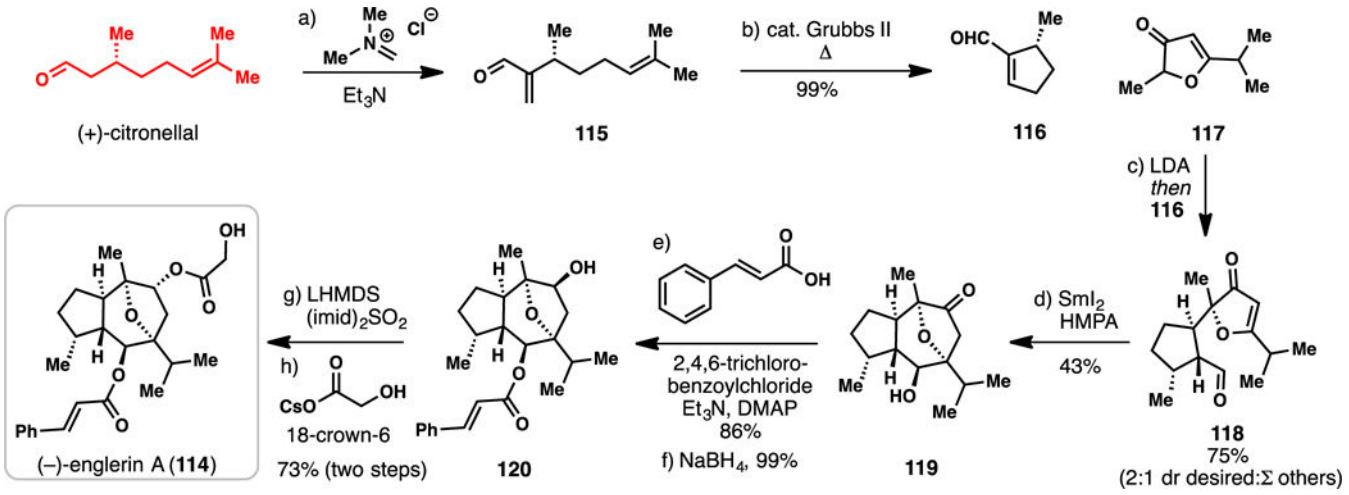
Scheme 8.

Zhang's Synthesis of (−)-Jiadifenolide from Pulegone-derived Building Block 84 (2015)



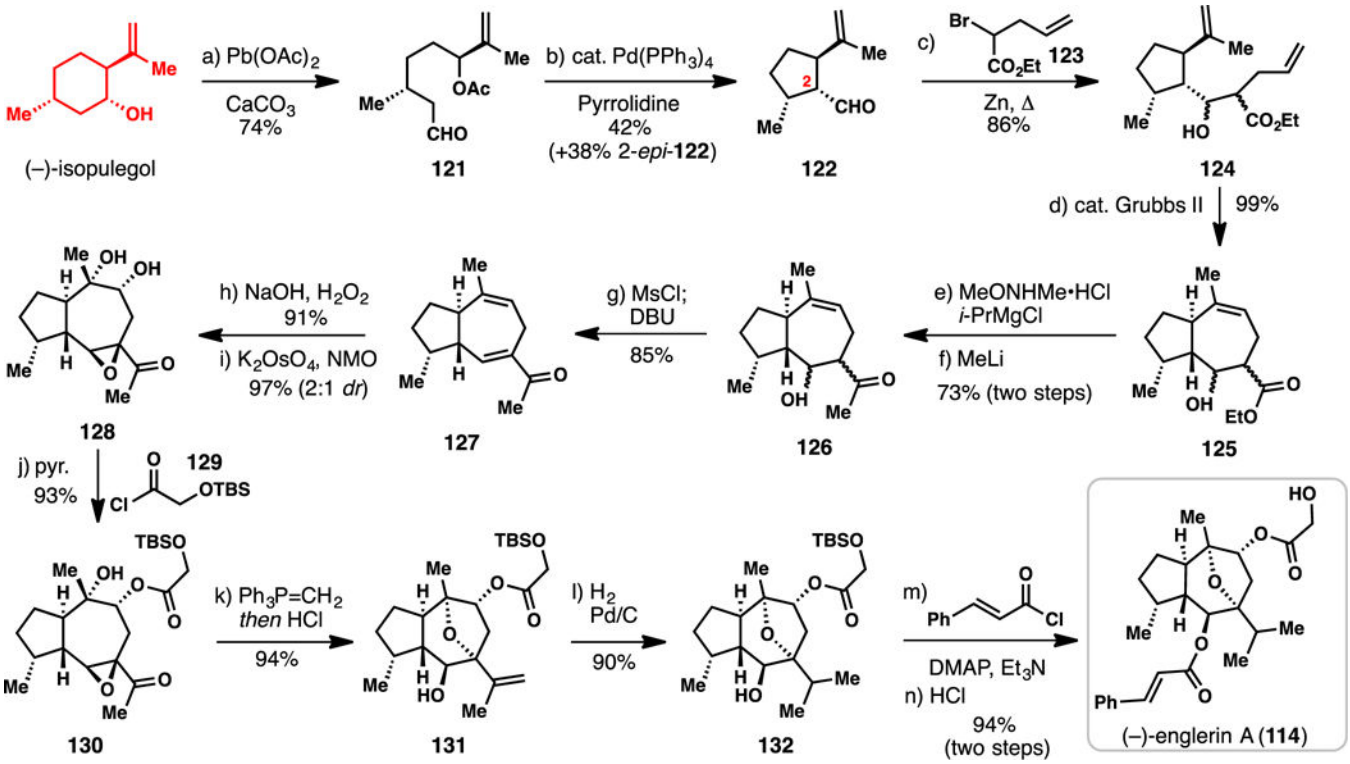
Scheme 9.

Shenvi's 8-step Synthesis of (−)-Jiadifenolide from (+)-Citronellal (2015)



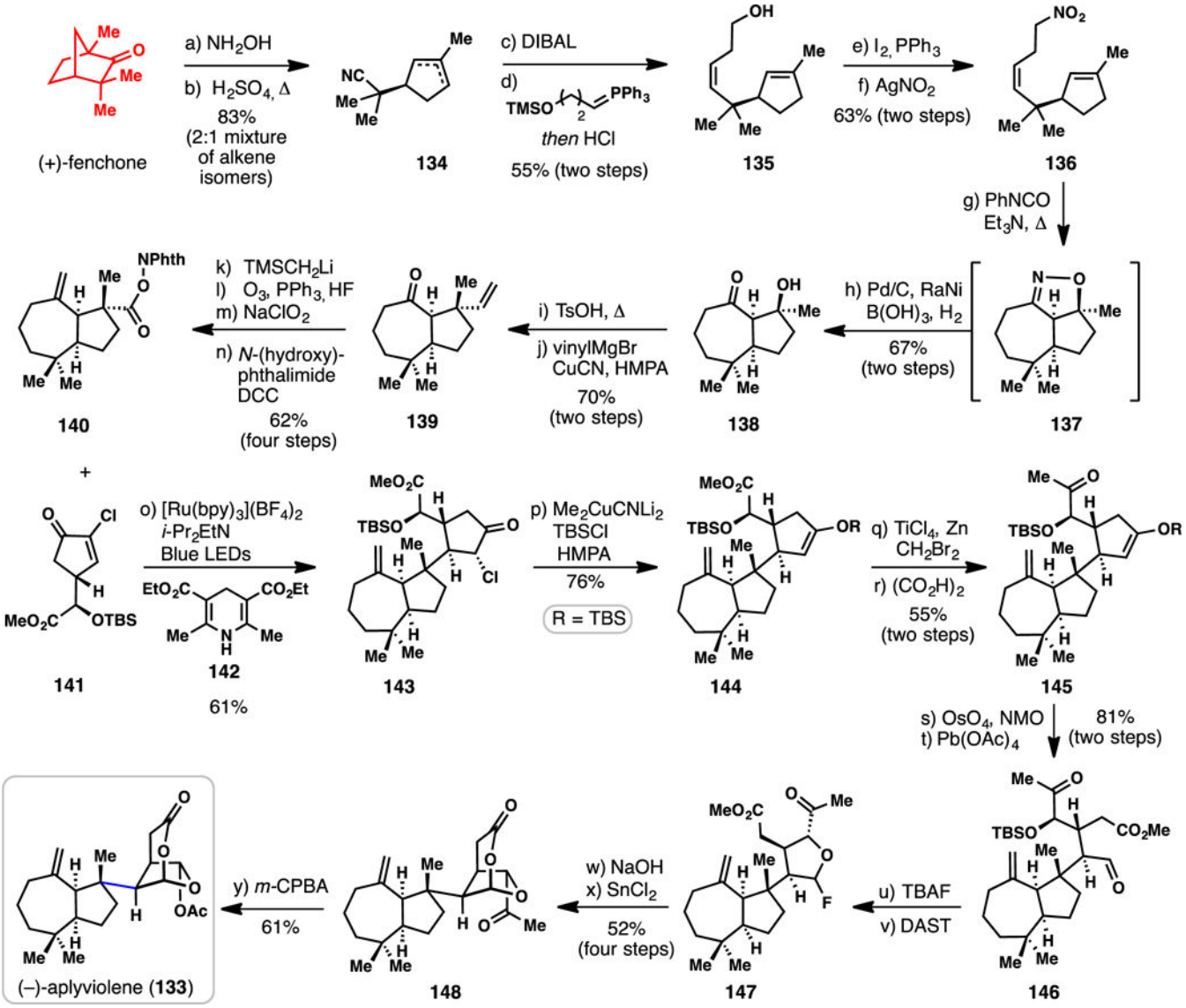
Scheme 10.

Chain's 8-step Total Synthesis of (−)-Englerin A (2011)



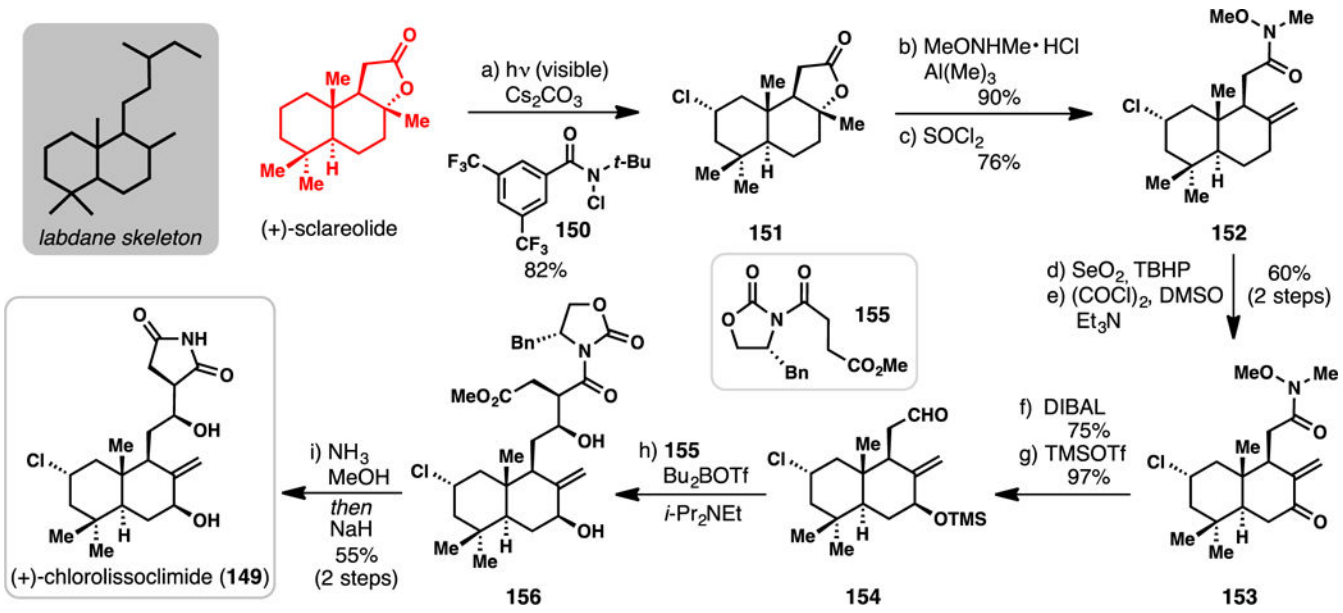
Scheme 11.

Metz's Total Synthesis of (−)-Englerin A from (−)-isopulegol (2013)



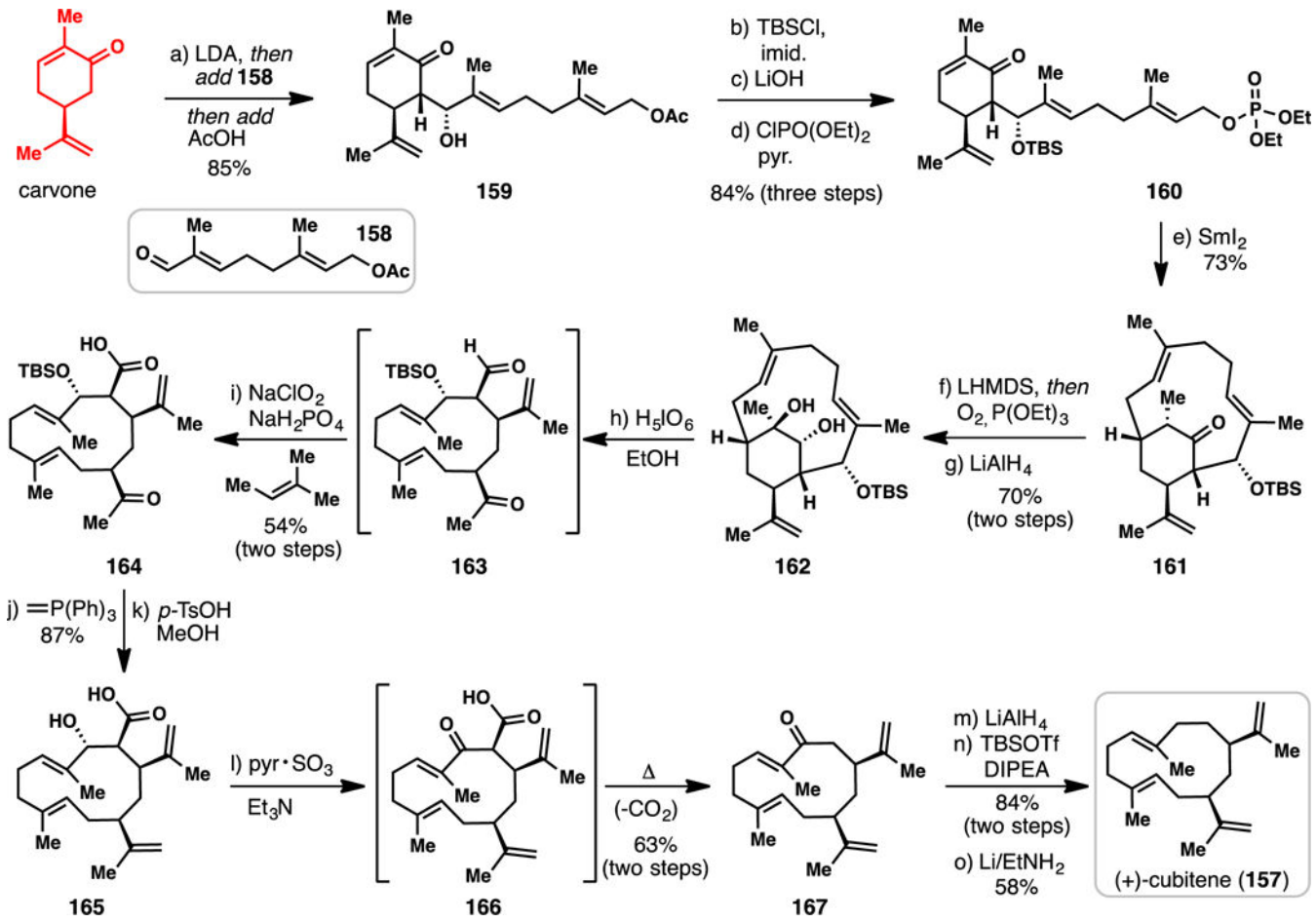
Scheme 12.

Overman's Chiral Pool-based Synthesis of (−)-Aplyviolene from (+)-Fenchone (2012)



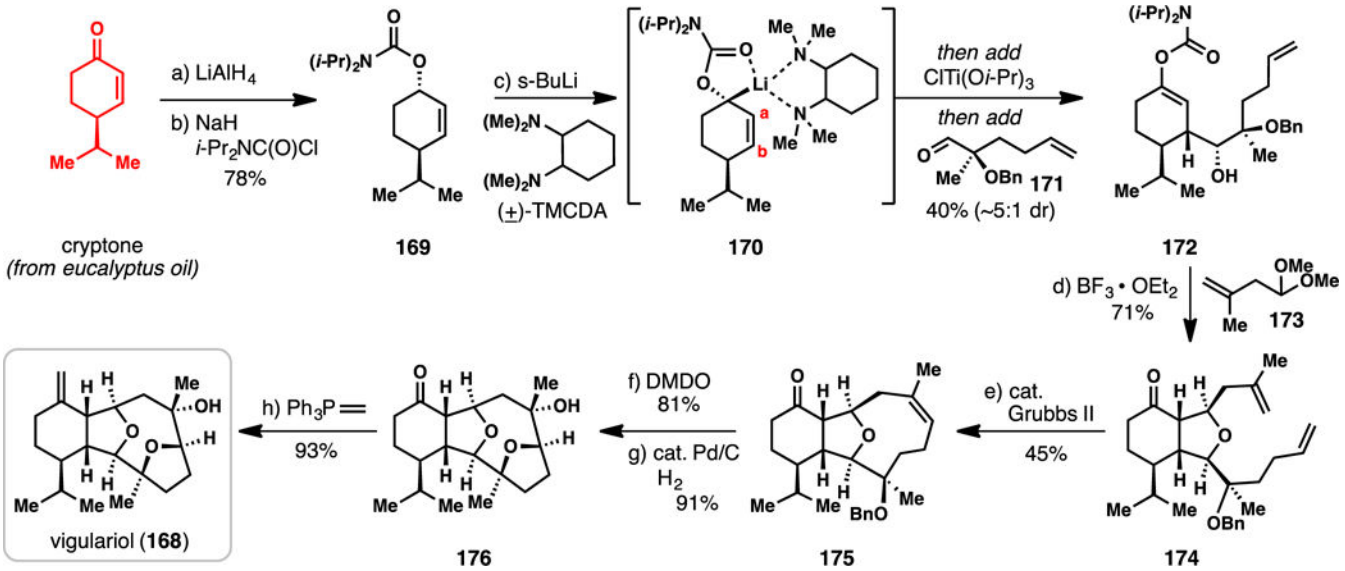
Scheme 13.

Vanderwal and Alexanian's Synthesis of (+)-Chlorolissoclimide from (+)-Sclareolide (2015).



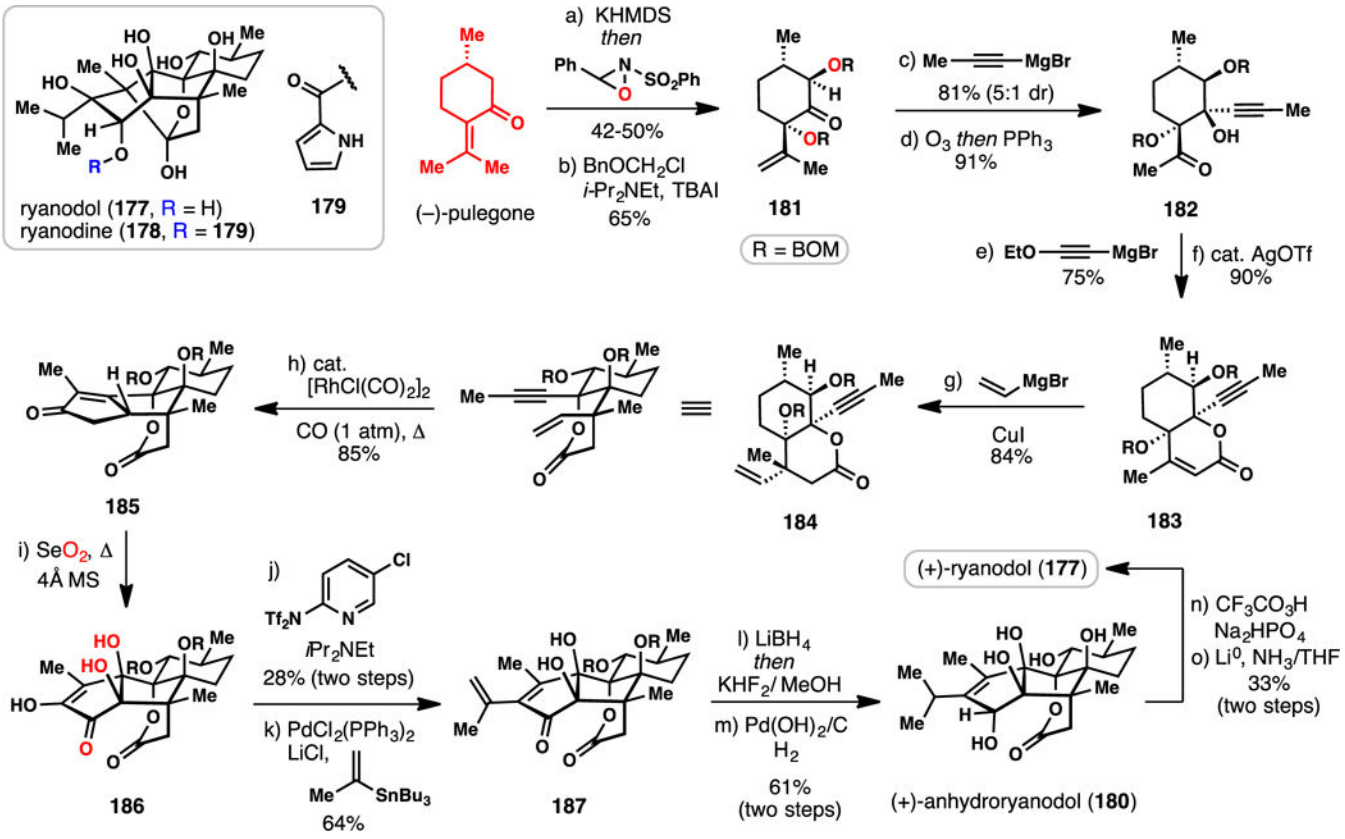
Scheme 14.

Lindel's Total Synthesis of (+)-Cubitene from (+)-Carvone (2012)



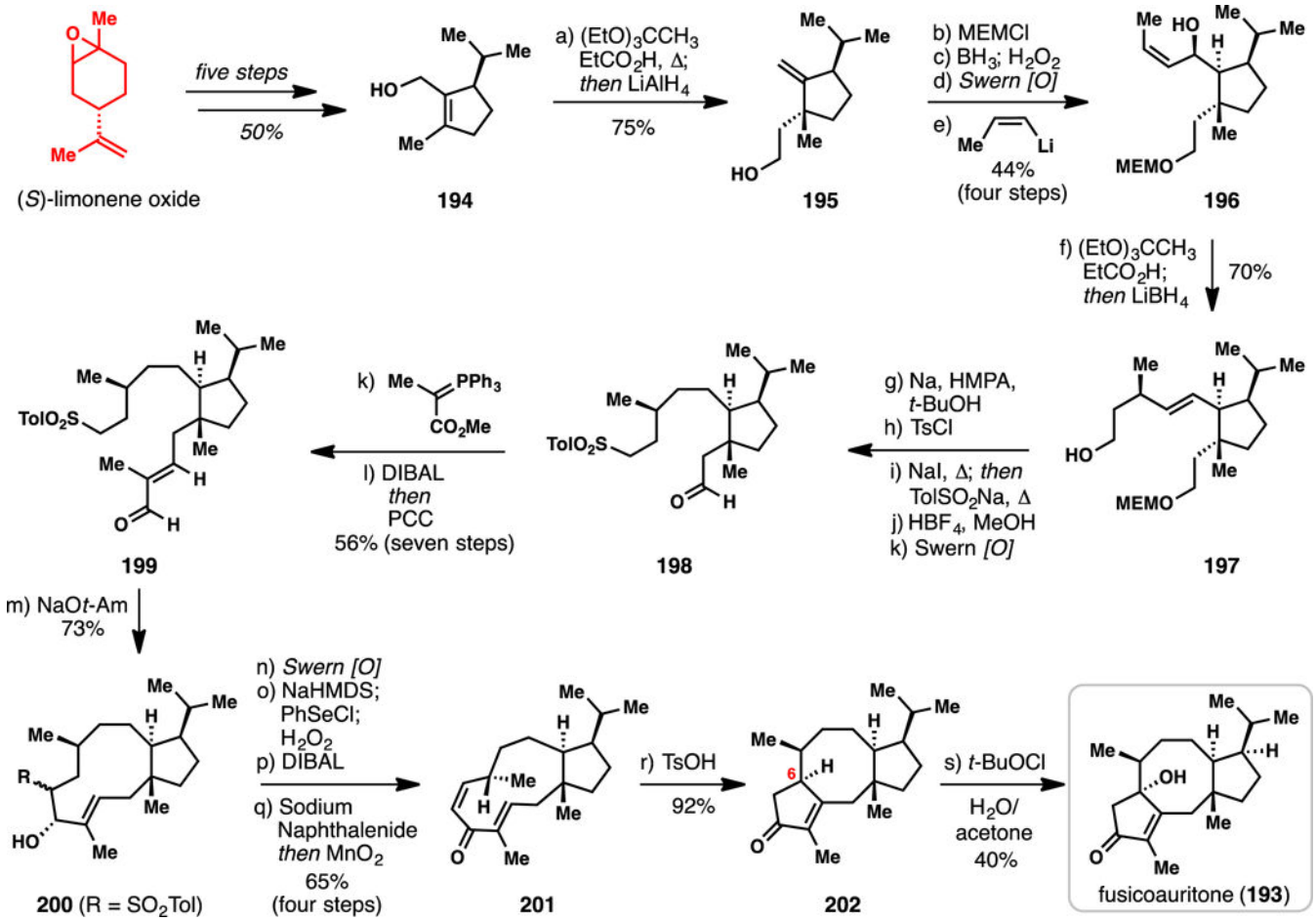
Scheme 15.

Hoppe's Total Synthesis of (+)-Vigulariol from Cryptone (2008)

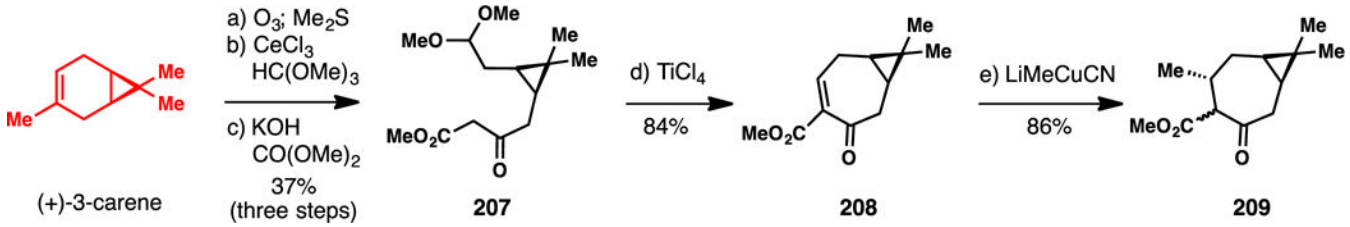


Scheme 16.

Reisman's Synthesis of (+)-Ryanodol from (−)-Pulegone (2016)

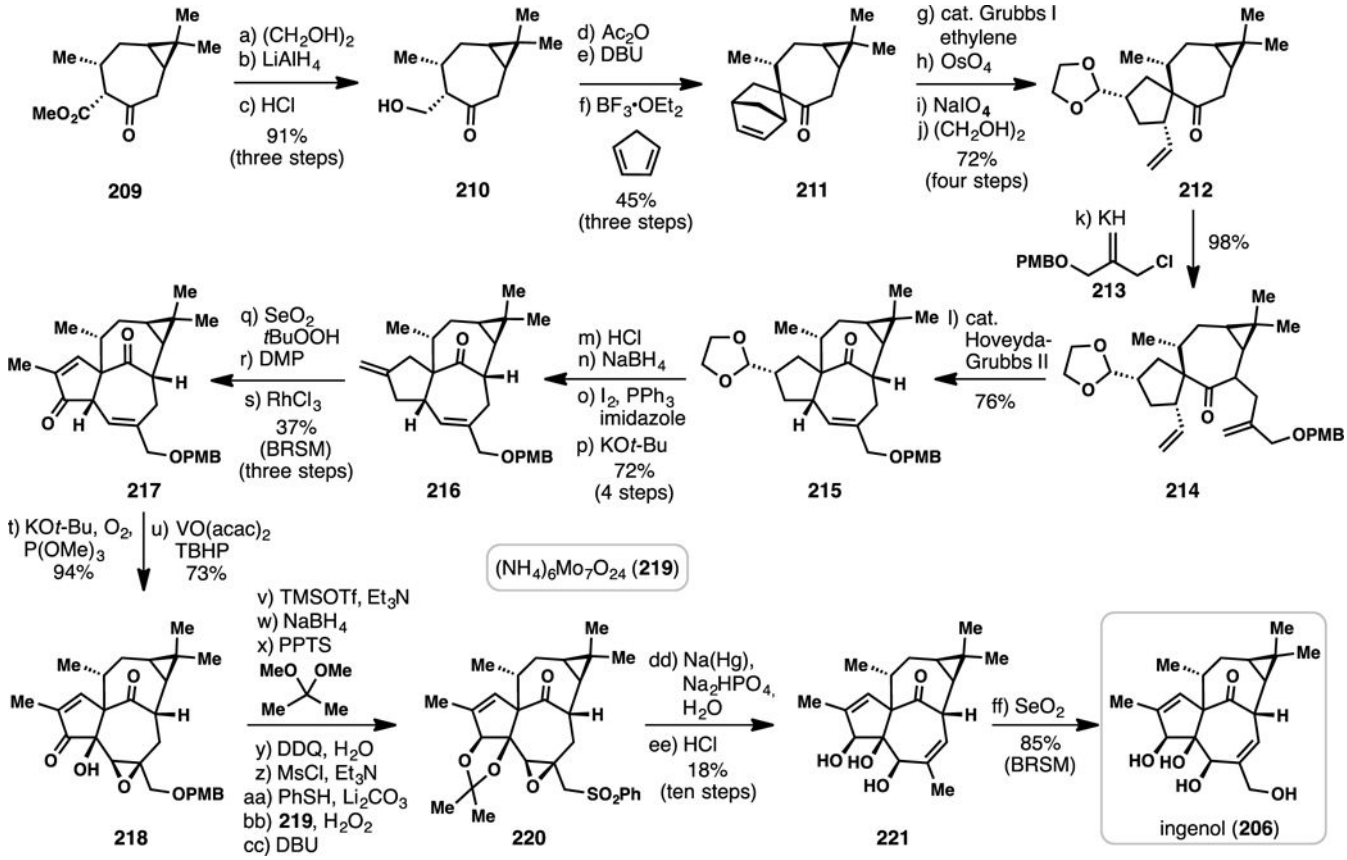


Scheme 17.
Williams' Chiral Pool-based Synthesis of (+)-Fusicoauritone (2007)

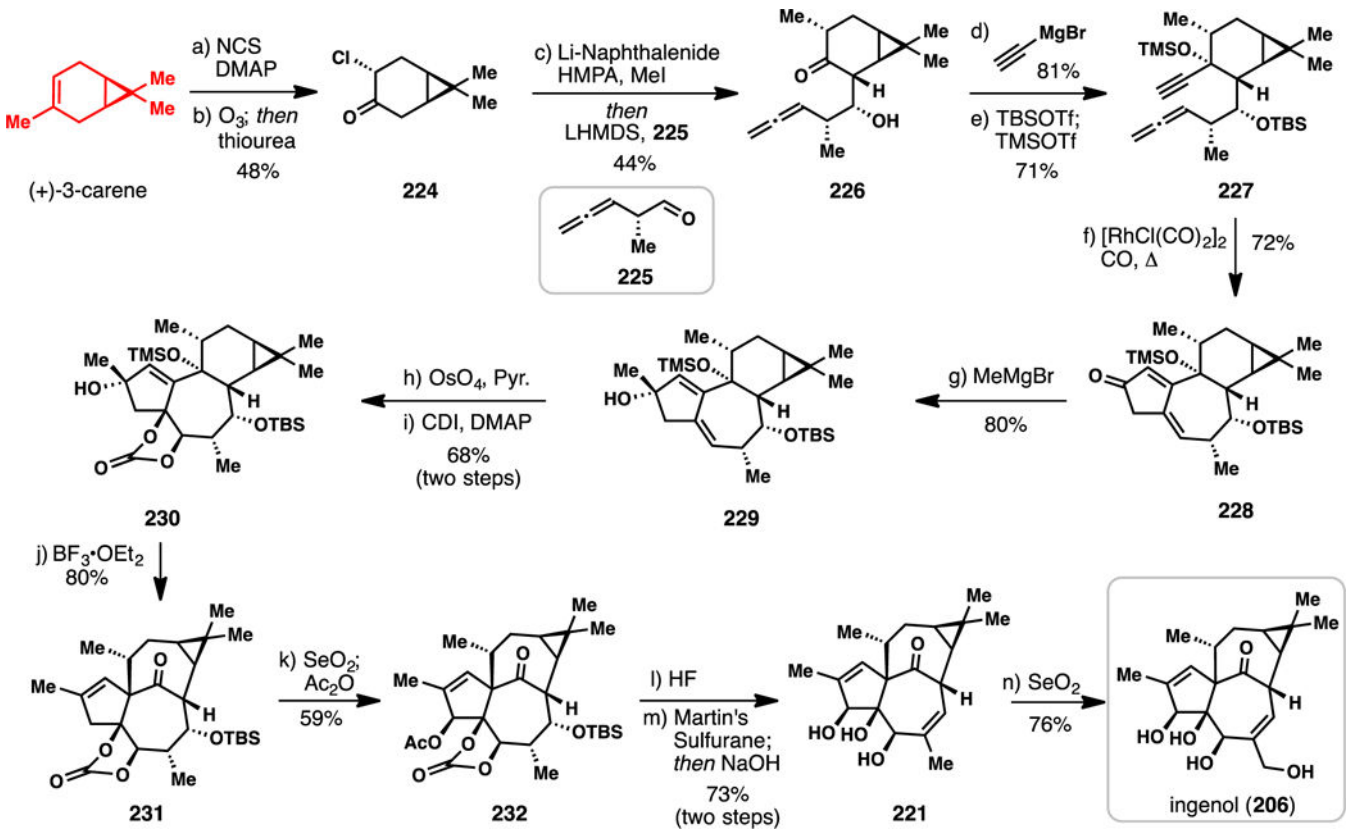


Scheme 18.

Conversion of (+)-3-Carene into Funk's Keto Ester (209).

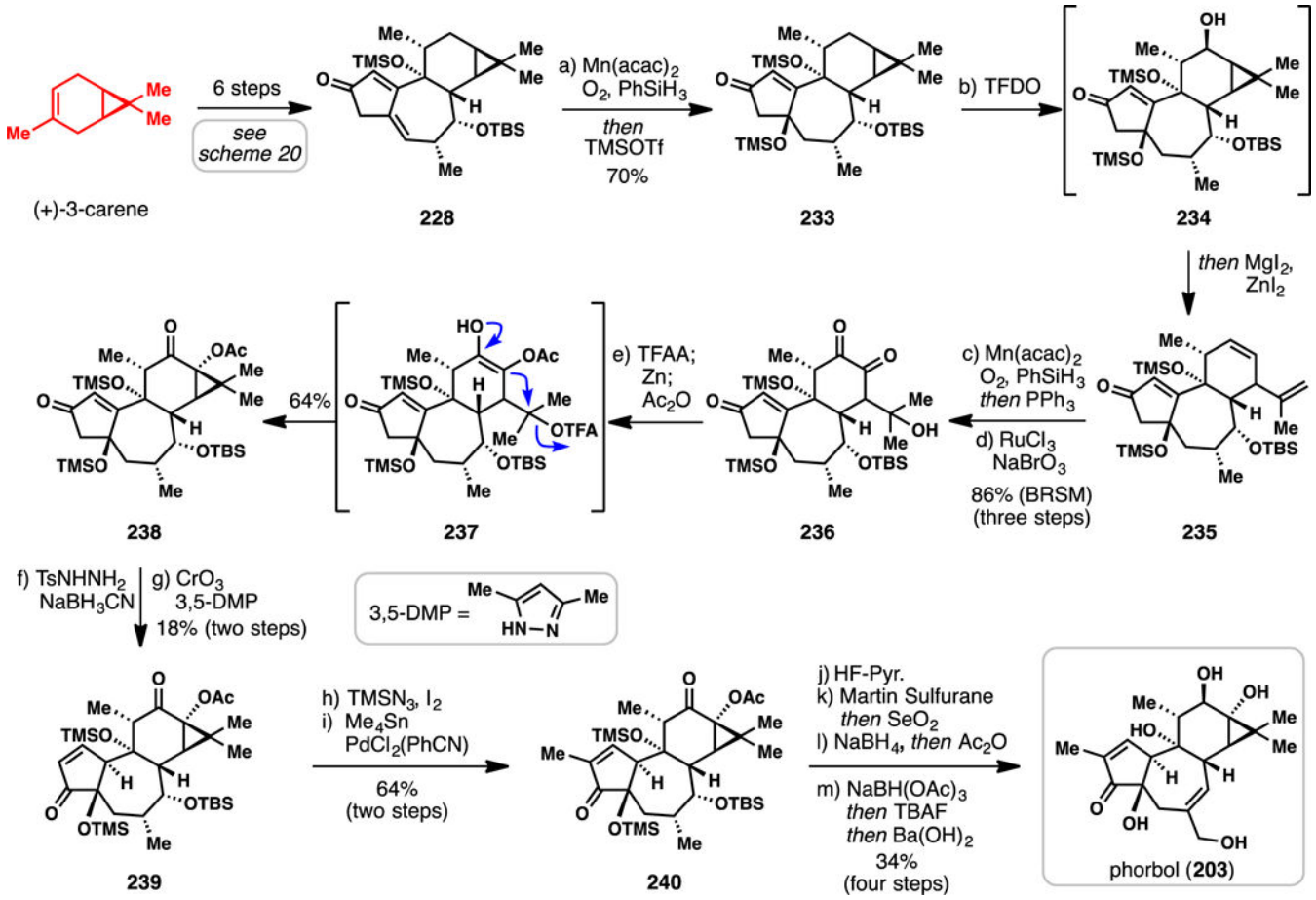


Scheme 19.
Wood's Total Synthesis of Ingenol (2004)



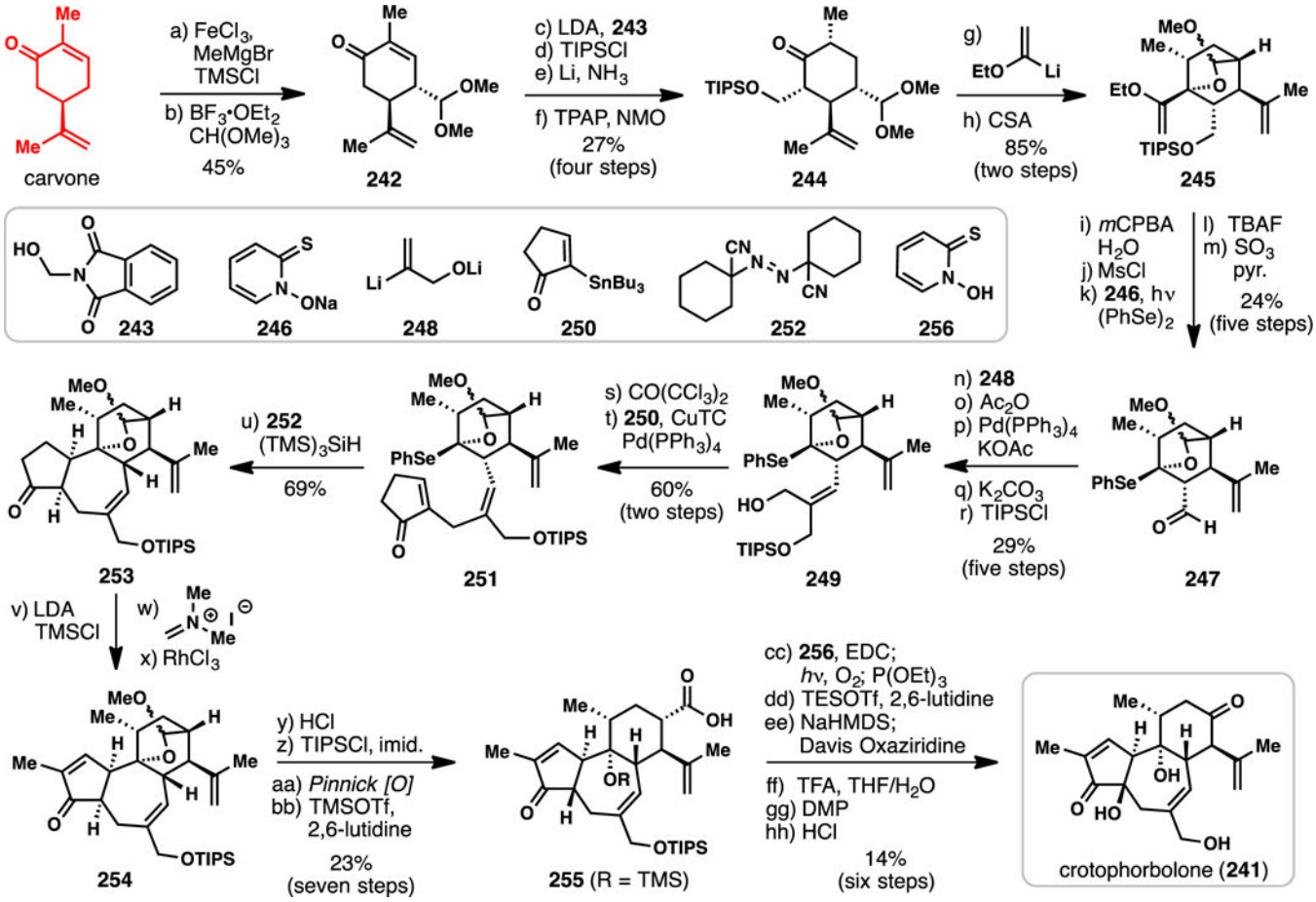
Scheme 20.

Baran's Synthesis of Ingenol from (+)-3-Carene (2013)



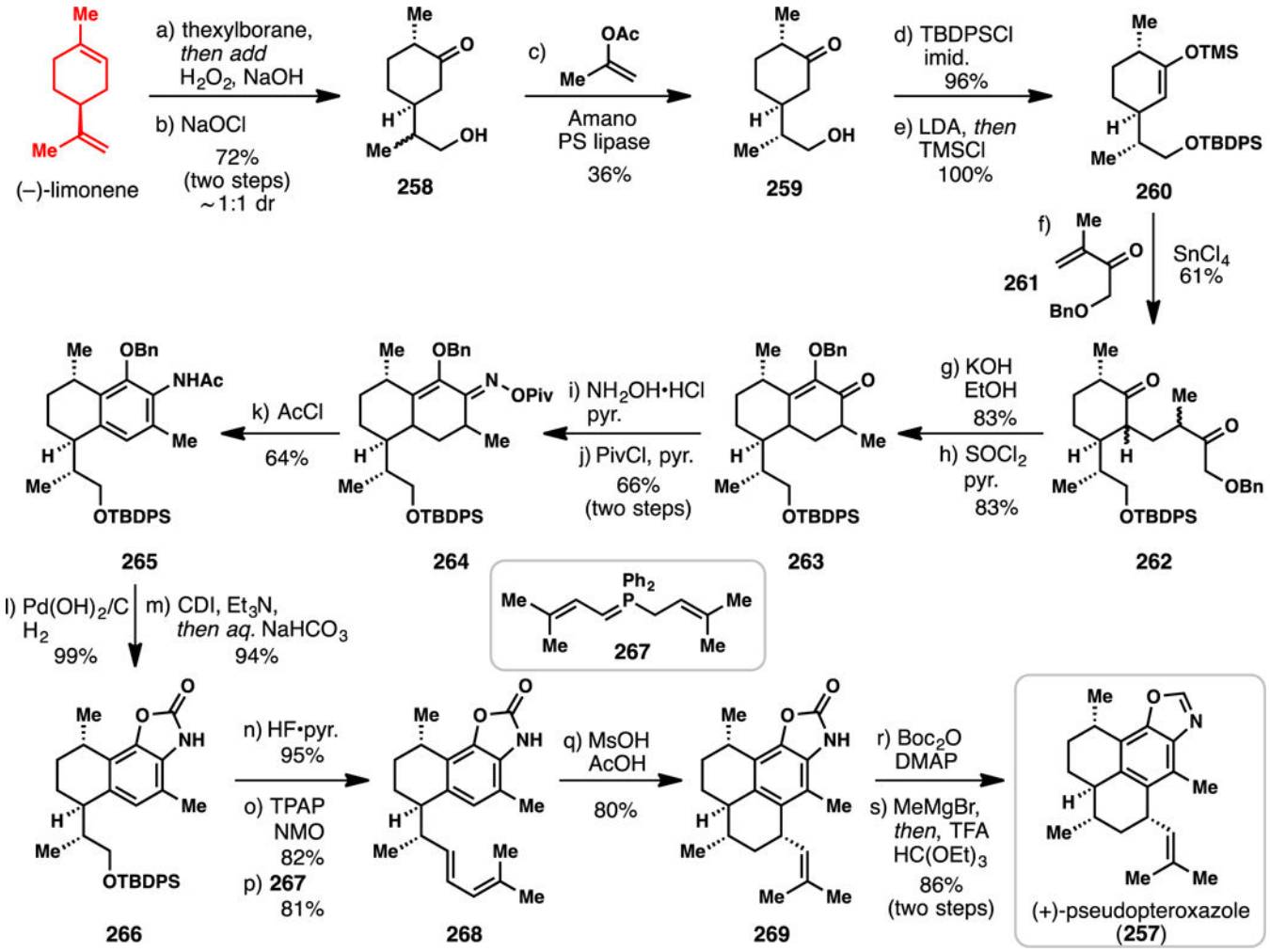
Scheme 21.

Baran's Chiral Pool-based Synthesis of (+)-Phorbol (2016)



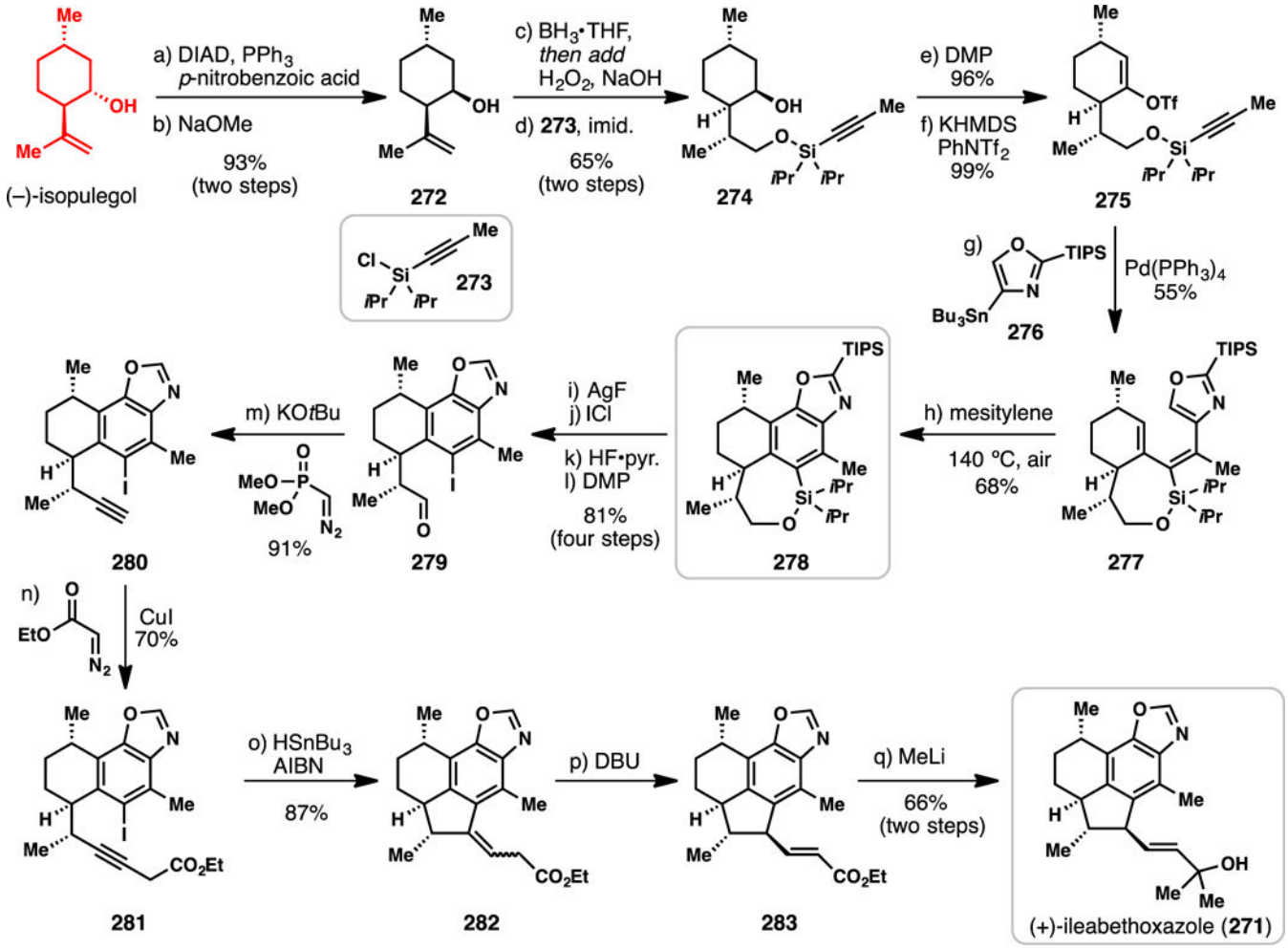
Scheme 22.

Inoue's Synthesis of (+)-Crotophorbolone (214) from (−)-Carvone (2015)



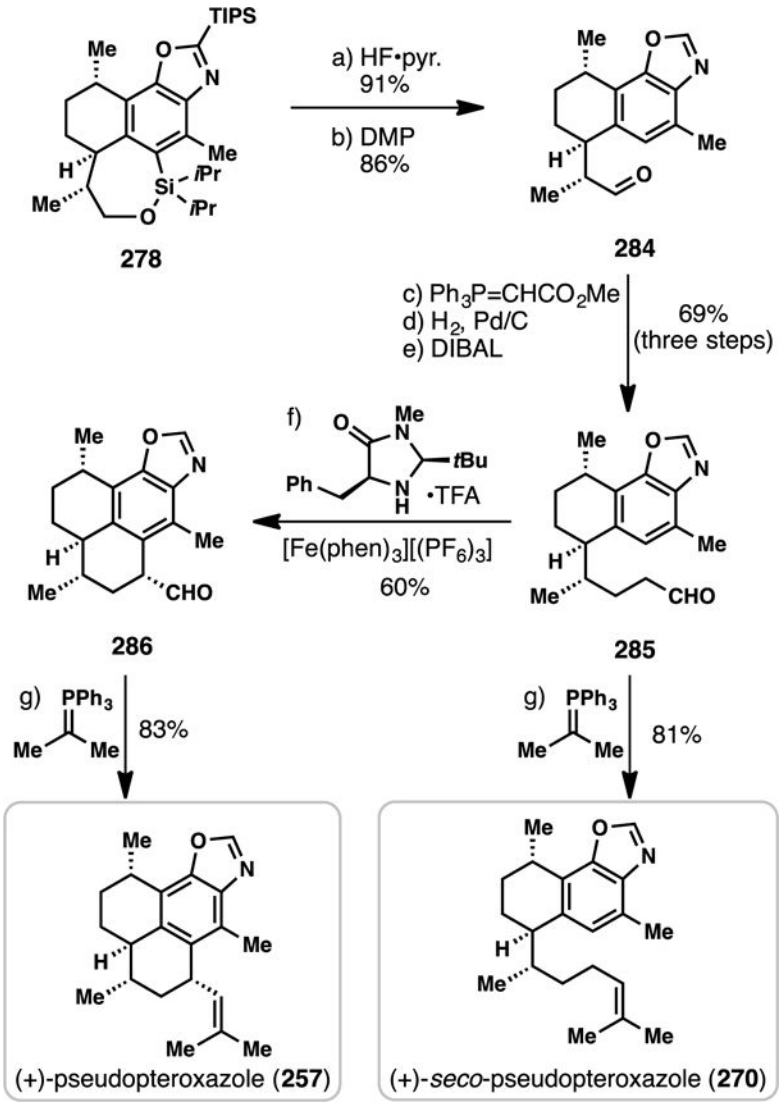
Scheme 23.

Corey's (−)-Limonene-derived Synthesis of (+)-Pseudopteroxazole (2003)



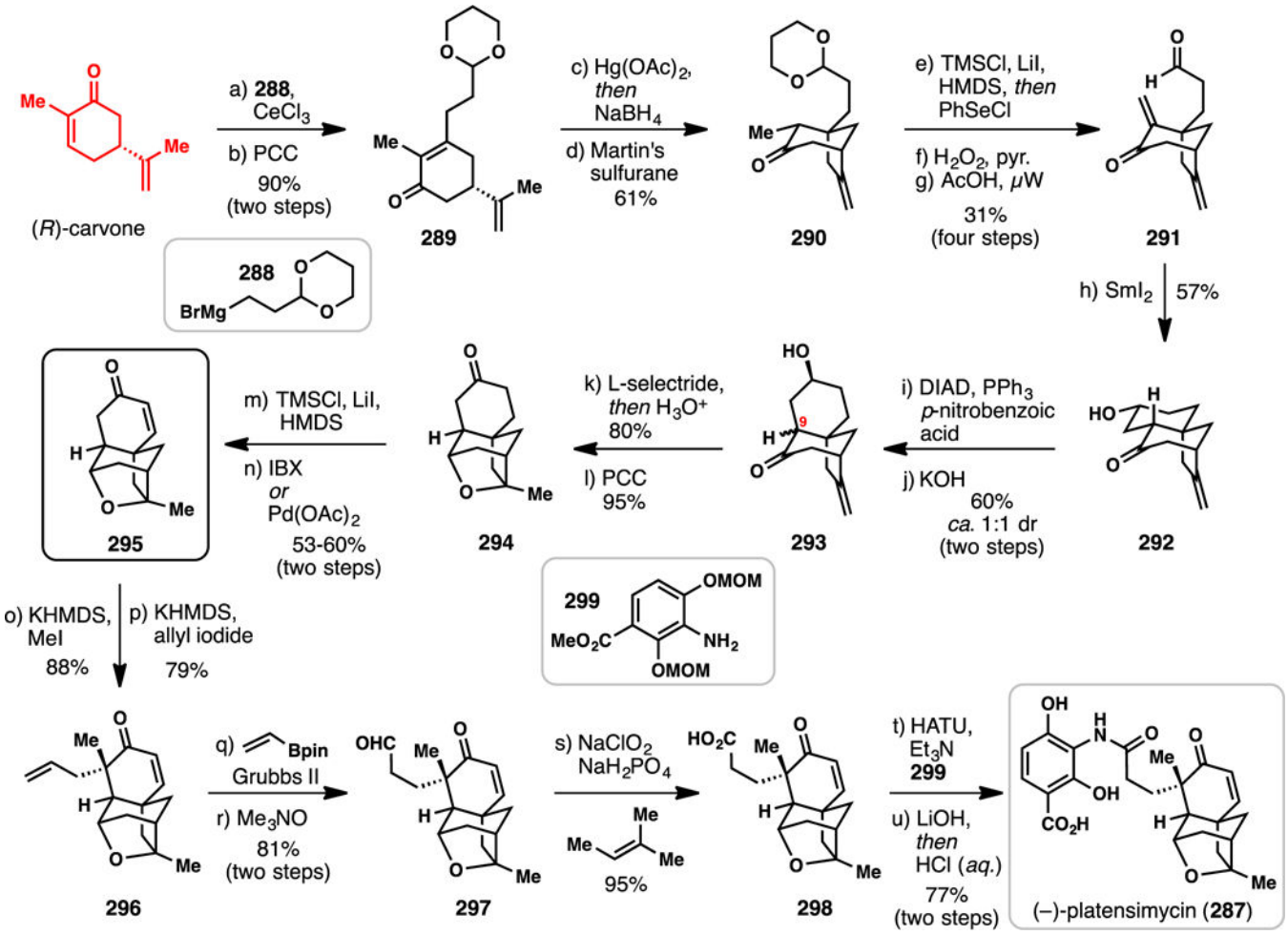
Scheme 24.

Li's Isopulegol-based Synthesis of (+)-Ileabethoxazole (2016)



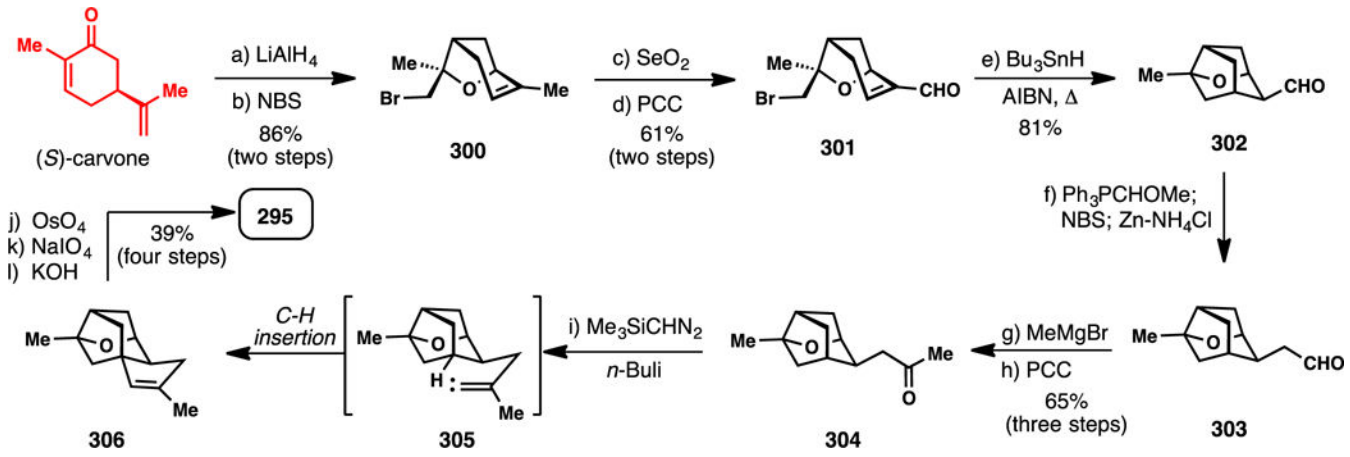
Scheme 25.

Li's Syntheses of (+)-Pseudopteroxazole and (+)-*seco*-Pseudopteroxazole from Intermediate 278 (2016)



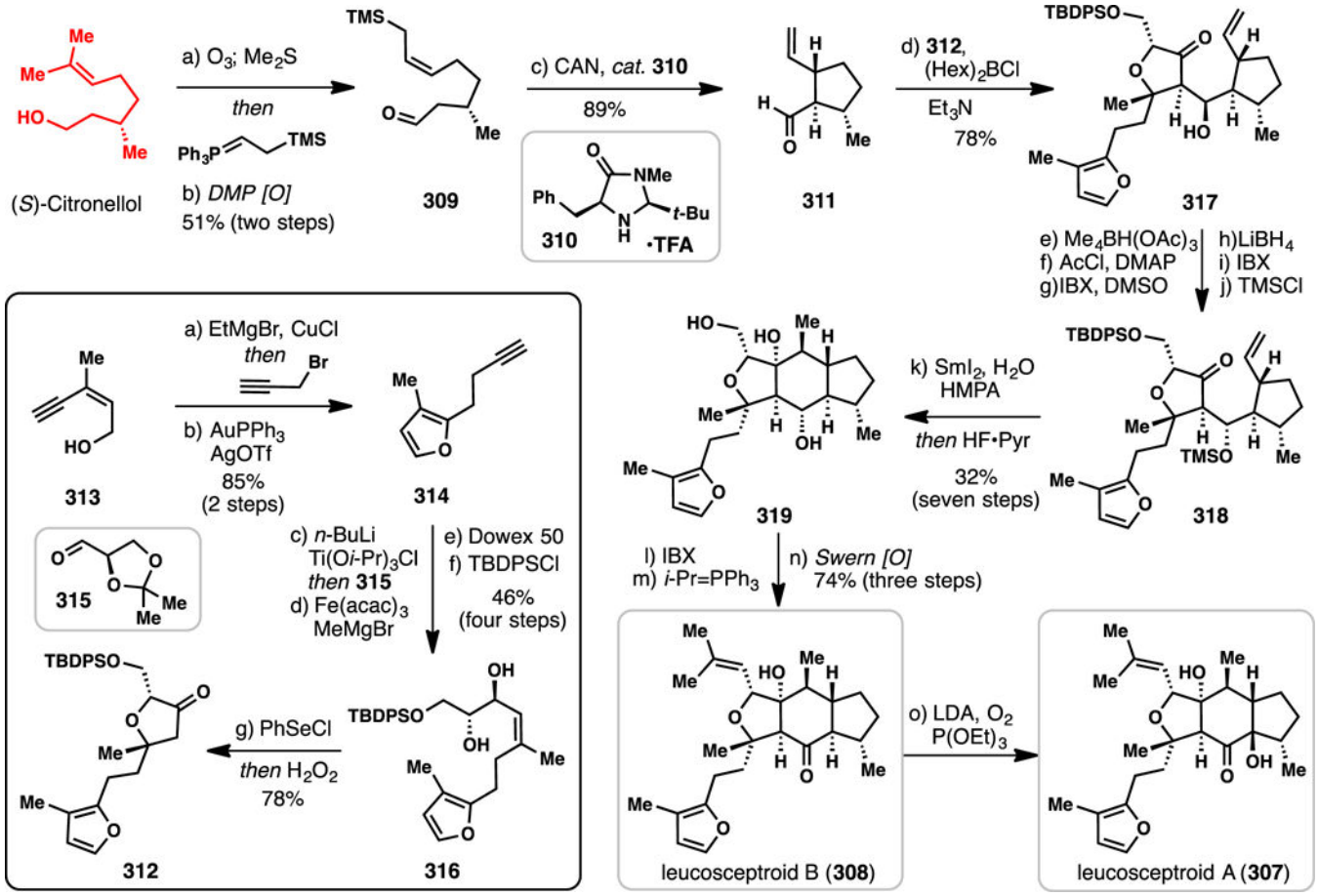
Scheme 26.

Nicolaou and Chen's Chiral Pool-based Synthesis of (−)-Platensimycin (2008)



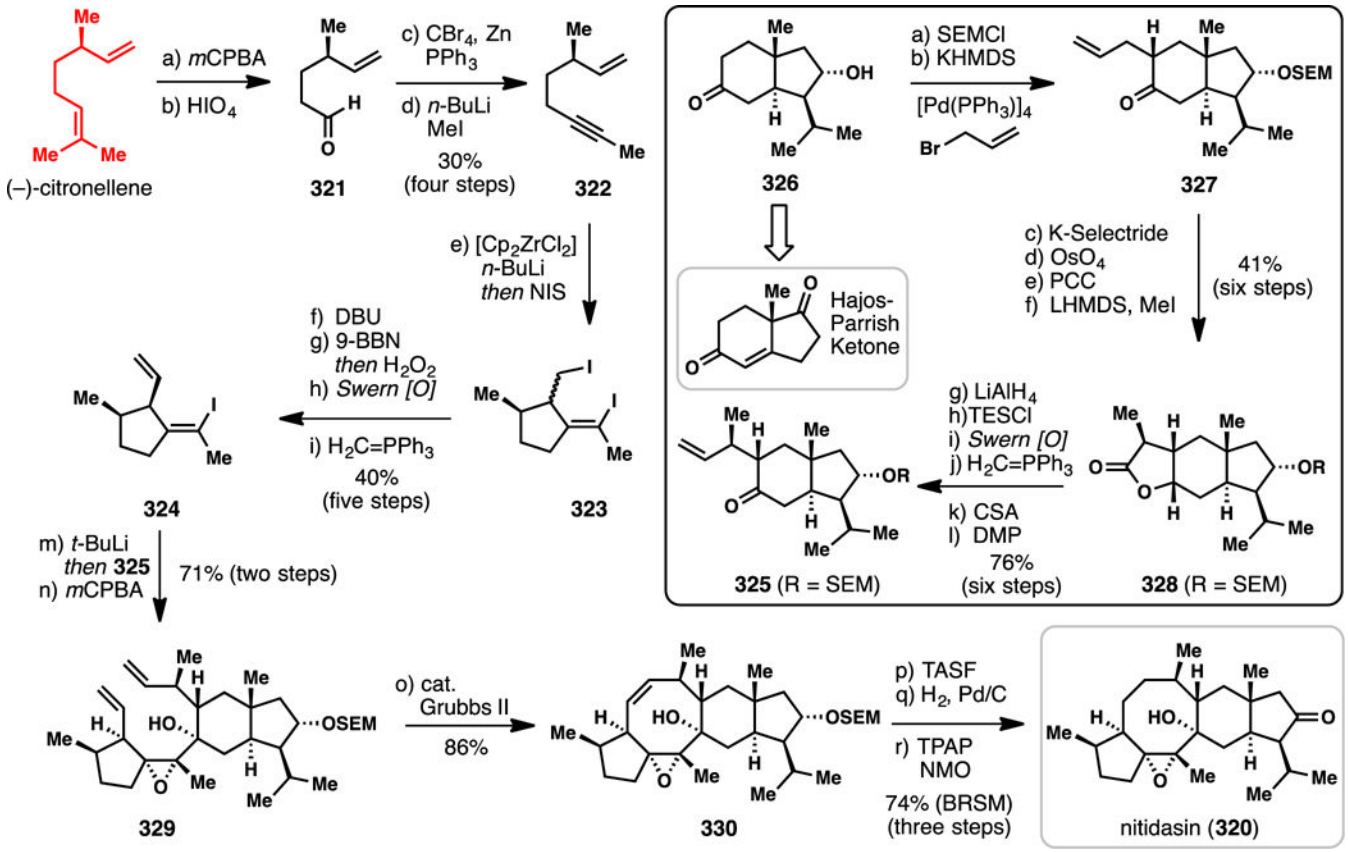
Scheme 27.

Lee's Formal Synthesis of Platensimycin from (+)-Carvone (2009)



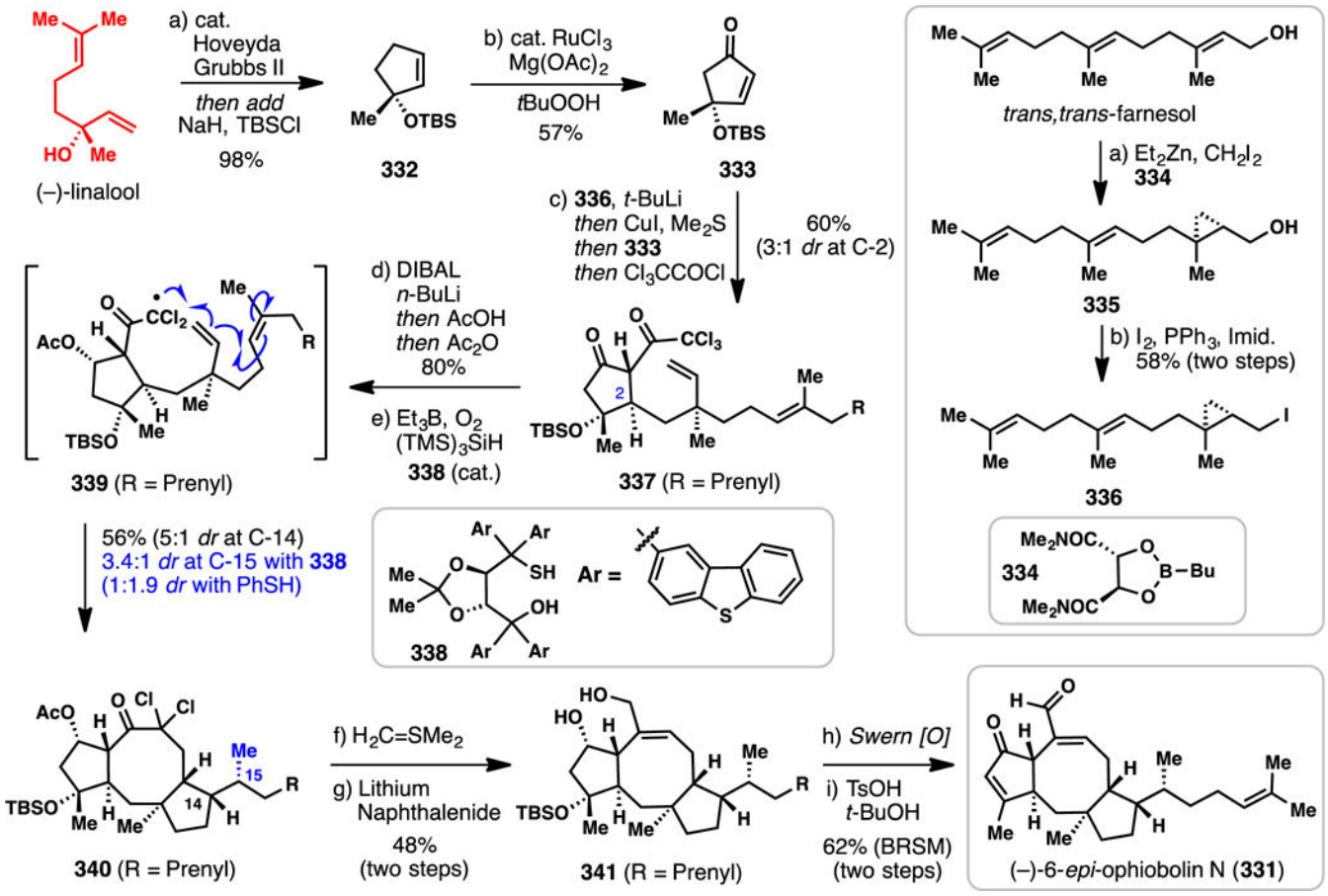
Scheme 28.

Ma's Syntheses of (+)-leucosceptroids A and B from (−)-Citronellol (2015)



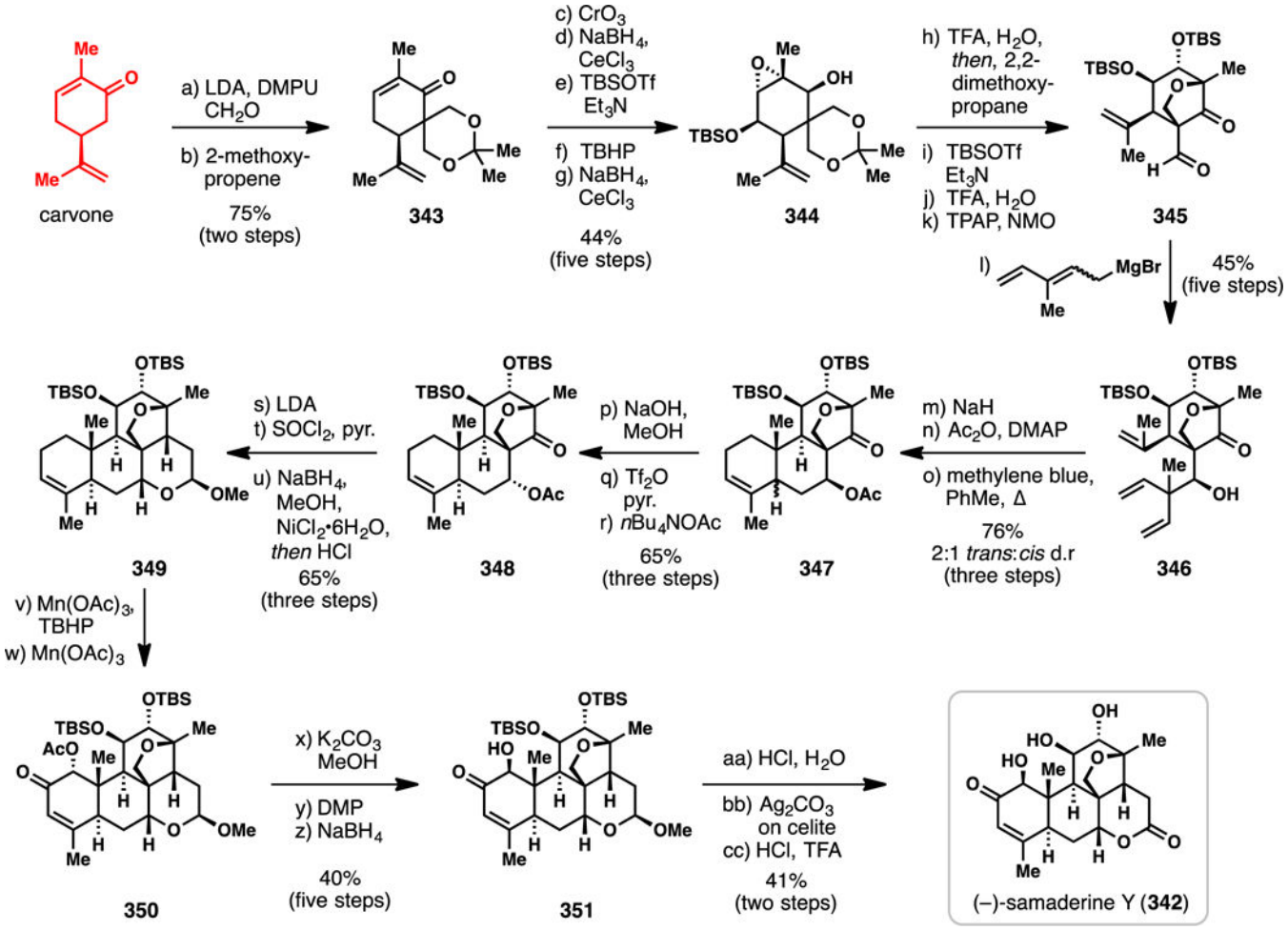
Scheme 29.

Trauner's Total Synthesis of (−)-Nitidasin Employing (−)-Citronellene (2014)



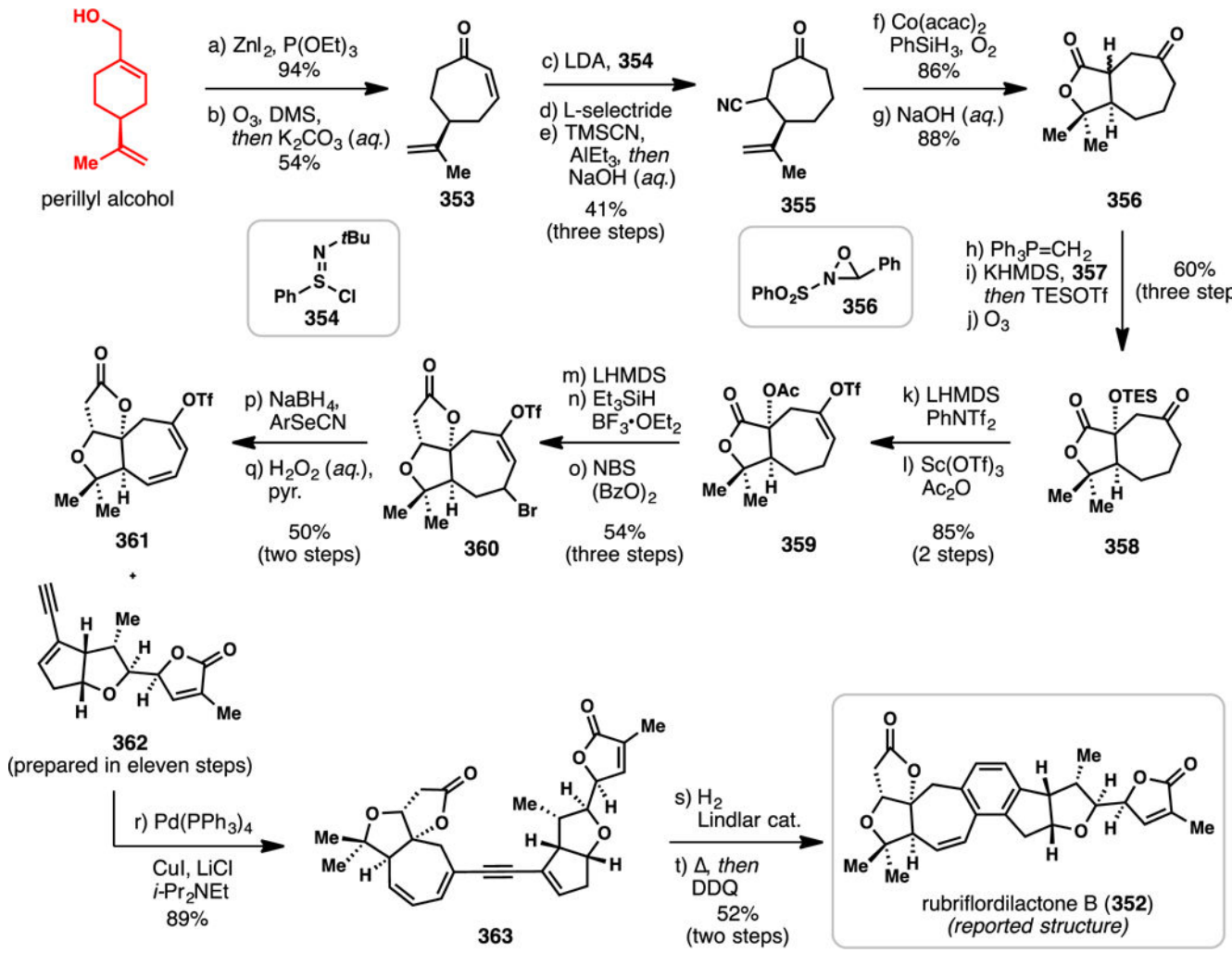
Scheme 30.

Maimone's (−)-Linalool-based Synthesis of (−)-6-*epi*-ophiobolin N (2016)



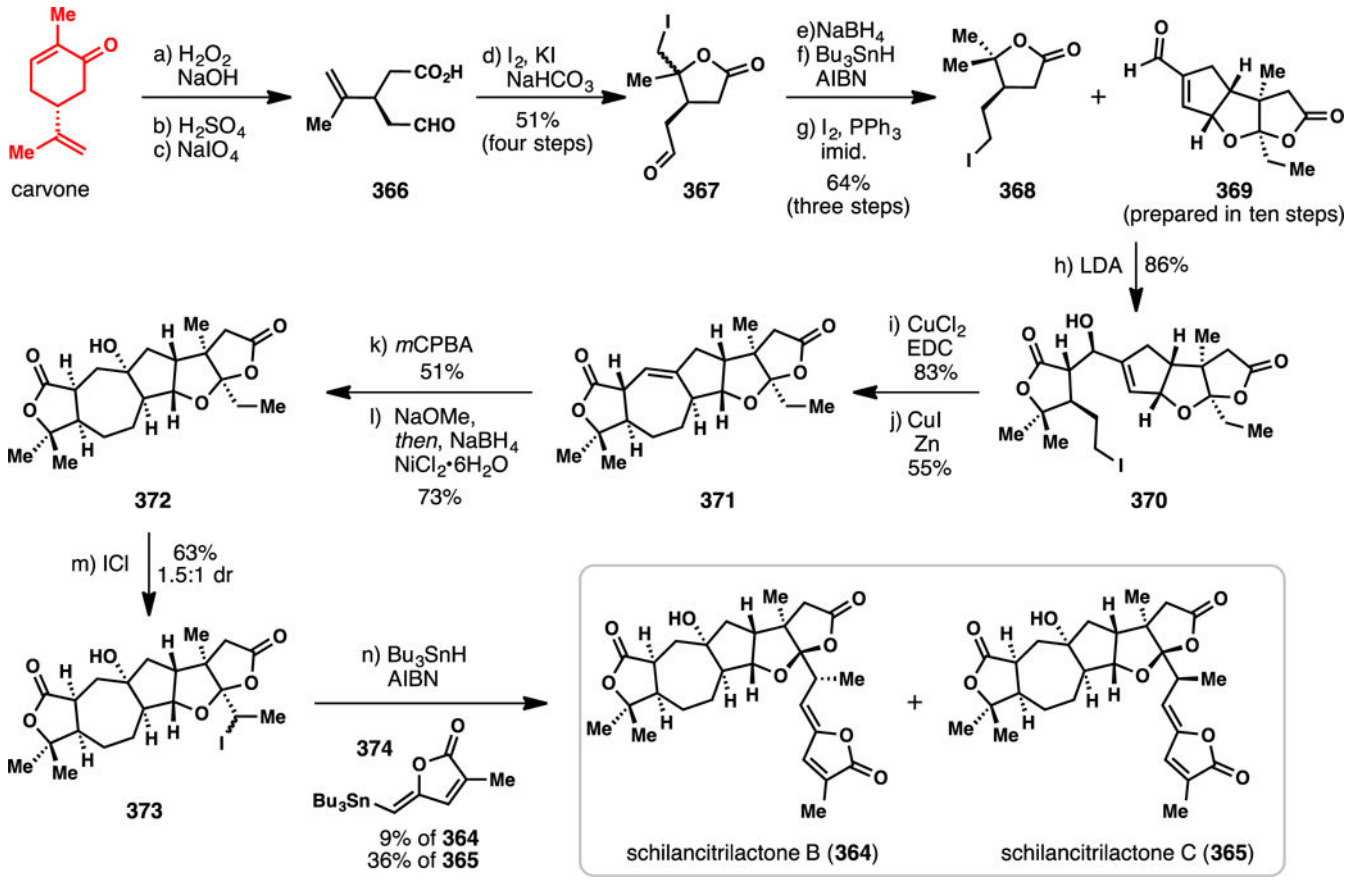
Scheme 31.

Shing's (+)-Carvone-based Synthesis of (−)-Samaderine Y (2005)



Scheme 32.

Li's Total Synthesis of the Reported Structure of Rubriflordilactone B (2016)



Scheme 33.

Tang's Synthesis of Schilancitrilactones B and C from (−)-Carvone (2015)