REVIEW

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Modern synthetic efforts toward biologically active terpenes

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Terpenes represent one of the largest and most diverse classes of secondary metabolites, with over 55,000 members isolated to date. The terpene cyclase enzymes used in nature convert simple, linear hydrocarbon phosphates into an exotic array of chiral, carbocyclic skeletons. Further oxidation and rearrangement results in an almost endless number of conceivable structures. The enormous structural diversity presented by this class of natural products ensures a broad range of biological properties—ranging from anti-cancer and anti-malarial activities to tumor promotion and ion-channel binding. The marked structural differences of terpenes also largely thwart the development of any truly general strategies for their synthetic construction. This review focuses on synthetic strategies directed toward some of the most complex, biologically relevant terpenes prepared by total synthesis within the past decade. Of crucial importance are both the obstacles that modern synthetic chemists must confront when trying to construct such natural products and the key chemical transformations and strategies that have been developed to meet these challenges.

With their usage dating as far back as ancient Egypt, terpenes hold a special place in both chemical and world history. Scientists and non-scientists alike can appreciate these truly functional molecules, whose applications range from flavor and fragrance to hormones, medicine and even rubber[1]. Synthetic chemists were drawn to terpenes before their polymeric origins were even clearly delineated (via the "biogenetic isoprene rule") by Ruzicka in 1953 (refs. 2,3 and references therein). The arrival of spectroscopic and chromatographic techniques brought about an explosion in the chemical aspects of terpene research that continues to this day. As a consequence, many highly complex terpenes have been prepared by total synthesis (**Fig. 1**)[4–6]. Although terpenes formally are made from only one biosynthetic unit, in contrast to the 20 proteogenic amino acids that make up proteins, the fact that they can be rearranged and highly oxidized means that the synthetic challenge of constructing them rivals that of many other secondary metabolites in terms of difficulty. In addition, their ubiquity in nature often results in natural products of 'mixed' biosynthetic origins, such as terpene alkaloids and terpene polyketides[7].

Introduction to the synthesis of terpenes

Because the carbon skeleton of a terpene is often its defining structural feature, it is there that synthetic chemists usually begin their planning. Indeed, a plethora of approaches for accessing terpene ring systems are often published before an actual total synthesis. Unfortunately, significant difficulties are often encountered in attempting to translate the results of a model system to one laden with more functionality; in some cases an entirely new strategy must be devised to access the natural product[8]. This highlights the fact that subtle steric and electronic factors, as well as functional-group incompatibilities, are often difficult—or impossible—to predict at the beginning of a total synthesis endeavor[9]. So where does one start when trying to access a complex terpene skeleton? Although there are many useful guidelines that can be followed during the planning stage, there are simply no general rules to apply when synthesizing a terpene. Indeed, successful syntheses of complex terpenes often rely on a mixture of imaginative planning and extensive empirical testing. Part of the charm and appeal of such molecules to synthetic organic chemists is the unpredictable nature that results from their highly rearranged and unprecedented carbon skeletons. Three different approaches can often aid chemists in their synthetic studies, all relying on the principles of retrosynthetic analysis[10]. In the first approach, the standard logic of synthetic planning can be applied, whereby one looks for strategic bond disconnections within the target molecule. This approach largely rests on the available toolbox of known transformations, resulting, after multiple iterations, in the identification of a suitable starting material. A second approach identifies a specific structural motif contained within the terpene skeleton that could be made via a certain synthetic methodology that is either known or newly invented. As a third option, one can try to find a structural match between the target and a smaller, commercially available terpene. The large number of commercially available terpenes (often in either enantiomer) coupled with the abundance of modern asymmetric transformations make the last two methods particularly attractive for asymmetric synthesis[11,12]. As we will see, modern terpene syntheses are an amalgam of classical organic transformations, modern catalytic asymmetric reactions and efficient use of the pool of available chiral terpenes.

The importance of natural products as sources of new drugs has been recently reviewed[13,14]. Although many terpenes do not resemble 'typical' therapeutics (heteroatom-laden aromatics), their structures have presumably been selected to interact with biological targets. In addition, the presence of multiple stereocenters, molecular rings and diverse oxygenation patterns also bodes well for sampling chemical space[15].

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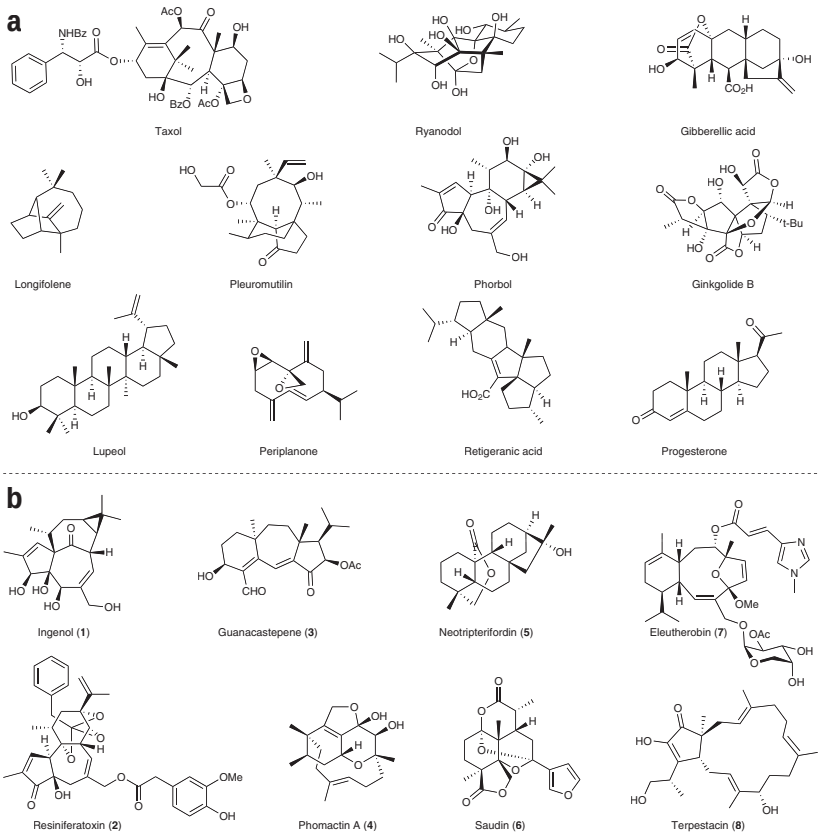

Figure 1 Highly complex terpenes that have been prepared by total synthesis. (**a**) Classic terpene targets of the twentieth century. (**b**) Selected complex, biologically active terpenoids synthesized in the past decade (1997–2007). Ac, acetyl; Bz, benzoyl.

While most of the terpenes discussed in this review may never arrive in your neighborhood pharmacy (although some have), the motifs present in these natural products could very well find their way into future pharmaceuticals. Indeed, terpenes often provide the impetus for the discovery and development of new ring-forming reactions in synthesis. In addition, the synthesis of terpenes can lead to a greater understanding of fundamental chemical reactivity, as well as proving or disproving a structural assignment[16]. Diversification of strategy is also important in modern day chemists' pursuit of efficiency, selectivity and flexibility. Molecules discussed in this review were chosen on the basis of following criteria: (i) their primary carbon skeletons are solely of terpene origin (or believed to be), (ii) they possessed interesting biological profiles at the time of their isolation, (iii) they possess interesting, unusual or unprecedented structures and (iv) solutions to their total chemical synthesis have been reported only within the past decade (1997–2007). Because of space limitations, only the key chemical transformations leading to successful total syntheses can be illustrated. In many cases, the interested reader can find a more comprehensive survey on the approaches to these natural products elsewhere.

Ingenol (1)

In 1968 Hecker and co-workers isolated the highly oxygenated diterpene ingenol (**1**) from the roots of *Euphorbia ingens*[17,18]. Though the terpenes are not carcinogenic themselves, esters of several diterpenes derived from this genus—including ingenol and phorbol (**Fig. 1**)—are some of the most potent tumor promoters ever isolated. Accordingly, these molecules have received considerable attention from the biological and medical communities. More recently ingenol has also been shown to possess anti-tumor, anti-leukemic and anti-HIV properties (ref. 19 and references therein). Its structural features have also fascinated synthetic chemists for the past 25 years, owing in large part to a rare form of isomerism displayed in its B and C rings (**Scheme 1a**). 'In-out' isomerism, wherein a bridgehead hydrogen is formally 'inside' the bicycle, provides ingenol with a thermodynamically disfavored configuration[20,21]. Many early synthetic investigations failed to address this feature, although some provided evidence that this isomeric form is required for biological activity[22]. The first synthetic strategy to address this challenging aspect of the molecule was described in 1987 by Winkler and colleagues[23] and later by several other groups[21,24,25]; however—as a true testament to the difficulty ingenol poses—it was not until 2002 that Winkler's group could claim a total synthesis of **1** (**Scheme 1b**)[26]. After Winkler's synthesis, total syntheses were reported by the Kuwajima group in 2003 (**Scheme 1c**) and by the Wood group in 2004 (**Scheme 1d**)[27,28]. In addition, one formal synthesis and many approaches have been published[19,29,30].

Use of the De Mayo reaction en route to the first total synthesis of (±)-1 (Winkler). The Winkler group sought to assemble the in-out system by an intramolecular variant of the venerable De Mayo reaction wherein a vinylygous ester engages an olefin in a 2+2 cycloaddition[26,31,32]. The intermediate cyclobutane then undergoes base-mediated retro-aldol fragmentation (**Scheme 1b**). To give the desired strained bicycle, they began by elaborating enone **9** into key compound **10** by an 11-step procedure. Irradiation of **10** in acetonitrile provided the desired cyclobutane **11**. It is worth noting that the hydrogen atom in the cyclobutane ring will become the 'in' hydrogen in the in-out bicycle, and thus its position in the cycloaddition is critical to its position in the C–B-ring junction. Treatment of **11** with potassium carbonate in methanol led to **13** after loss of acetone and retro-aldol fragmentation. The conversion of **13** into ingenol required 33 steps owing to both the unfunctionalized nature of **13** and the synthetic difficulty associated with the three contiguous asymmetric hydroxyl groups. Capable of being performed in a complex molecular setting, the De Mayo reaction—as demonstrated by Winkler—is an extremely powerful tool for the synthesis of complex ring systems. Another elegant application of this strategy, in the synthesis of saudin, is discussed below.

A total synthesis of (±)-1 featuring Nicholas and pinacol-type chemistry (Kuwajima). The Kuwajima group took a markedly different approach to constructing the ingenane skeleton, in which they envisioned that that C ring could be formed via a Nicholas-type reaction (**16** → **18**) (**Scheme 1c**)[19,27,33]. In this reaction, the presence of the cobalt-carbonyl complex makes the neighboring acetate highly prone to ionization and displacement due to the bridging ability of cobalt.

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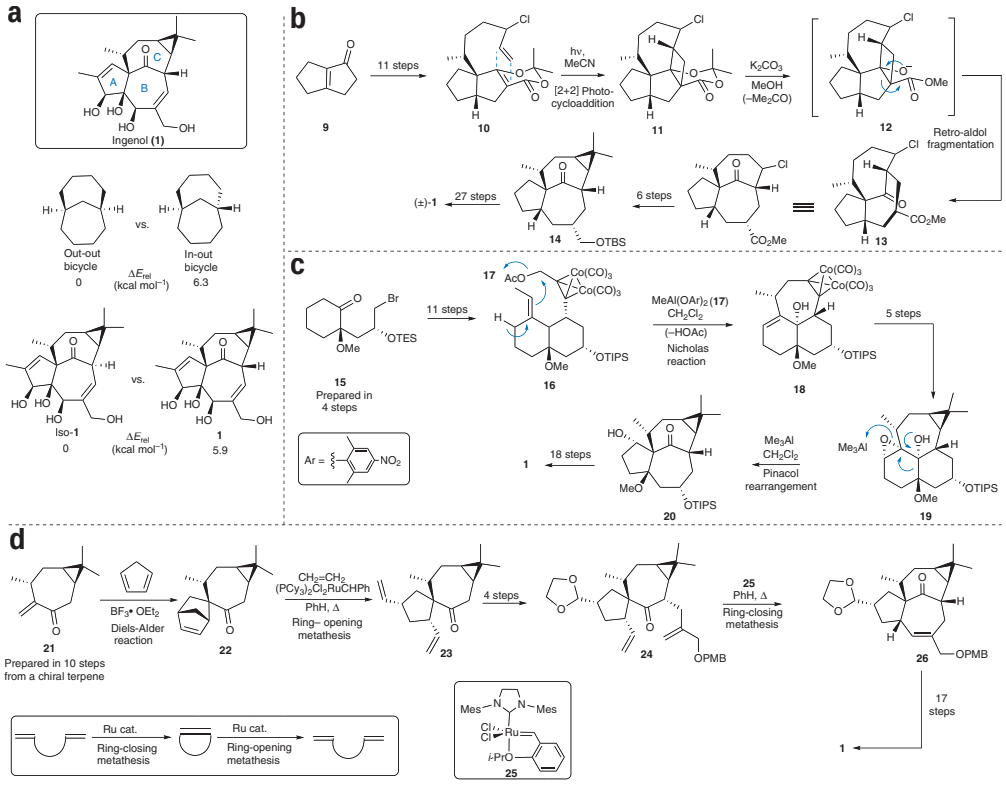
The A and B rings would originate from a pinacol-type rearrangement converting the 6-6 fused ring system into the desired 7-5 system. The synthesis of **16** required 15 steps, and upon treatment with Lewis acid **17**, Kuwajima and colleagues were able to produce tricyclic compound **18**. In a short (five-step) sequence, **18** could be converted into **19**. Treatment of **19** with trimethylaluminum induced the desired bond reorganization to give **20**, which contains the complete ingenane skeleton. Ingenol could then be prepared in 18 steps from compound **20**. This synthesis served to demonstrate how a complex ring system can be prepared by a careful orchestration of favorable known reactions.

A ring-opening and ring-closing metathesis strategy to construct ingenol (Wood). Wood and co-workers began their journey to the synthesis of ingenol with a functionalized C ring possessing the requisite asymmetric methyl and dimethylcyclopropyl groups (**Scheme 1d**)[28]. This key compound (enone **21**) could be constructed from a commercially available terpene in ten steps, closely following a route described by Funk[21]. Enone **21** was then coaxed into participating in a Lewis acid–catalyzed Diels-Alder cycloaddition with cyclopentadiene to produce spirocycle **22**, thus delivering all of the carbons needed for the five-membered A ring. Treatment of ketone **22** with Grubb's catalyst in refluxing toluene opened the bicyclo [2.2.1] ring system (ring-opening metathesis) to spiro-ketone **23**, which in turn could be elaborated into **24** via a four-step procedure. Using Grubbs-Hoveyda catalyst **25**, the Wood group was able to carry out the transformation **24** → **26** (ring-closing metathesis), thus forming the coveted in-out system. Compound **26** could be transformed into ingenol in an additional 17 steps. The olefin metathesis reaction (whose pioneers were awarded the 2005 Nobel Prize in chemistry) has proven to be one of the most reliable and powerful reactions in modern chemistry for the construction of carbocyclic rings[34].

Resiniferatoxin (2)

Isolated from *Euphorbia resinifera*, resiniferatoxin is a powerful analgesic that has been used to treat pain for almost 2,000 years[6]. It belongs to the daphnane family of diterpenes, and its molecular skeleton is biosynthetically related to both the tigliane (phorbol) and ingenane (ingenol) classes (**Scheme 2a**). Although it lacks the in-out ring system of its chemical cousin, it is still an extremely challenging synthetic target owing to its dense, highly oxygenated skeleton. Indeed, Wender's 1997 total synthesis remains the only synthetic route to **2** (ref. 35), although various approaches toward obtaining the A-B-C ring system have been reported (refs. 36,37 and references therein).

Total synthesis of (+)-2 featuring an oxidopyrylium 1,3-dipolar cycloaddition (Wender). As an efficient synthetic entry into both the tigliane and daphnane terpene classes, the Wender group developed an intramolecular variant of the oxidopyrylium 1,3-dipolar cycloaddition (**Schemes 2b**,**c**) (ref. 38 and references therein). This powerful reaction allows for the rapid, stereoselective construction of bridged



Scheme 1 The total synthesis of ingenol. (**a**) 'In-out' isomerism of the C-B rings as a key synthetic challenge posed by ingenol. (**b**) Winkler's approach featuring an intramolecular variant of the De Mayo reaction. (**c**) Kuwajima and Tanino's approach using a Nicholas-type cyclization and pinacol rearrangement to form the in-out system. (**d**) Wood's approach using a ring-opening and ring-closing metathesis strategy. Cy, cyclohexyl; Mes, 2,4,6-trimethylphenyl; PMB, *p*-methoxybenzyl; TBS, *t*-butyldimethylsilyl; TES, triethylsilyl; TIPS, triisopropylsilyl.

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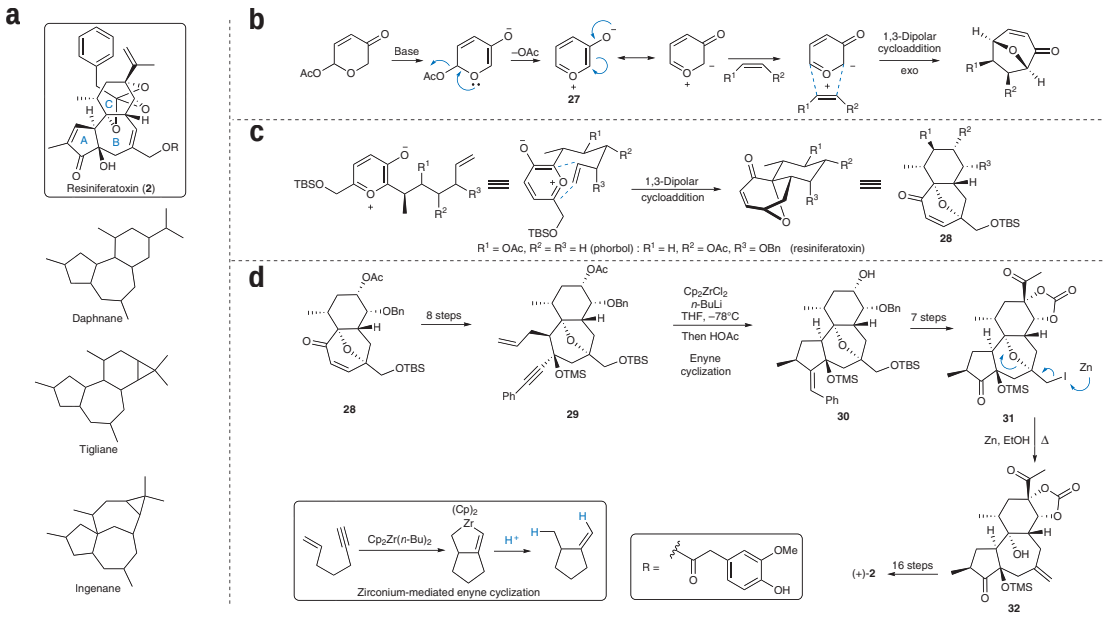

Scheme 2 Synthetic methods used in the construction of resiniferatoxin. (**a**) Resiniferatoxin's daphnane skeleton and its close chemical relatives, also from the plant family Euphoriaceae. (**b**) General method for the generation of a reactive oxidopyrylium (**27**) and its subsequent participation in an *exo*-selective 1,3-dipolar cycloaddition. (**c**) Use of an intramolecular oxidopyrylium cycloaddition as an efficient synthetic entry into the tigliane and daphnane skeletons (Wender and colleagues). (**d**) Key transformations in Wender's pioneering total synthesis of resiniferatoxin. Ac, acetyl; Bn, benzyl; Cp, cyclopentadienyl; TBS, *t*-butyldimethylsilyl; THF, tetrahydrofuran; TMS, trimethylsilyl.

polycyclic architectures such as **28**. Using this methodology, tricycle **28** could be fashioned and transformed into **29** by an eight-step sequence (**Scheme 2d**). Treatment of **29** with butyl lithium and Cp_2ZrCl_2 cleanly formed the desired A ring, via an enyne cyclization. Seven steps were required to convert **30** into **31**, which was heated with zinc in ethanol to induce elimination of the extraneous oxygen bridge. It is worthy of note, however, that having the oxygen bridge present until then served both to rigidify the 6-7 ring system (thus aiding intermediate substrate-controlled reactions) as well as to protect a tertiary hydroxyl group. Compound **32** can be converted into resiniferatoxin in 16 steps. Although the Diels-Alder reaction has typically been the premier cycloaddition reaction in synthesis (leading to six-membered rings)[39], one cannot ignore the power of the 1,3-dipolar cycloaddition to form both five- and seven-membered ring architectures.

Guanacastepenes (3)

In the search for biologically active natural products, fungi have traditionally provided fertile harvesting ground. In 2000, Clardy and coworkers isolated guanacastepene A (**3**) from an unidentified endophytic fungus present on the bark of *Daphnopsis americana* in Costa Rica[40]. A year later, 14 more guanacastepenes were discovered[41]. Biosynthetically, it has been proposed that the guanacastepene skeleton may be related to that of the well-precedented dolabellanes (**Scheme 3a**)[40]. Interest in **3** related initially to its activity against antibiotic-resistant bacteria. Further studies, however, have shown **3** to possess hemolytic activity against human red blood cells, most likely acting by nonspecific membrane lysis[42]. In synthetic circles, the guanacastepenes remain a vibrant proving ground for the development of new synthetic methods. To date, five total syntheses, two formal syntheses and a myriad of approaches have been reported (refs. 42–50; ref. 51 and references therein).

A condensation and β-elimination cascade en route to (±)-guanacastepene A (Danishefsky). The Danishefsky group assembled guanacastepene A (**3**) from the left to the right side, with the A ring originating from 2-methylcyclopentenone (**Scheme 3b**)[42,43]. A vicinal difunctionalization of this simple starting material led to vinyl iodide **33**. Lithium-halogen exchange and intramolecular quenching onto the internal ketone led to **34** after an additional oxidative allylic transposition step (Dauben oxidation). With the A and B rings quickly formed, the Danishefsky team elaborated enone **34** into keto-ester **35** in a ten-step procedure. Their key step involved the base-mediated conversion of **35** to **36**. This cascade sequence probably proceeds via a Knoevenagel condensation with concomitant β-elimination of the epoxide moiety. Conversion of **36** to (±)-**3** required 12 steps. In addition to this work, an asymmetric synthesis was published in 2005 (ref. 44). That the Danishefsky group could arrive at a complex molecular target such as **3** using only simple starting materials and reagents is a testament to their brilliant synthetic design.

Diastereoselective synthesis of (±)-guanacastepene C (43) using cyclopentenone 'masking' (Mehta). Mehta's approach toward guanacastepene C (**43**) followed a choreography of ring construction (A → B → C) similar to that of the Danishefsky group (**Scheme 3c**)[45]. Key building block **39** could be prepared by a selective conjugate addition and alkylation of a norbornene 'masked' cyclopentenone (**37**), followed by mask removal (that is, a retro Diels-Alder reaction; see **38** → **39**). This general strategy has been broadly popularized by Winterfeldt[52]. The stereochemistry of the substituents on **39** are a result of the steric influence of the norbornene, which dictates the face that nucleophiles and electrophiles approach from. Ketone **39** could be elaborated to **40** in two steps by nucleophilic addition and Dauben oxidation. Ring-closing metathesis using Grubbs catalyst smoothly

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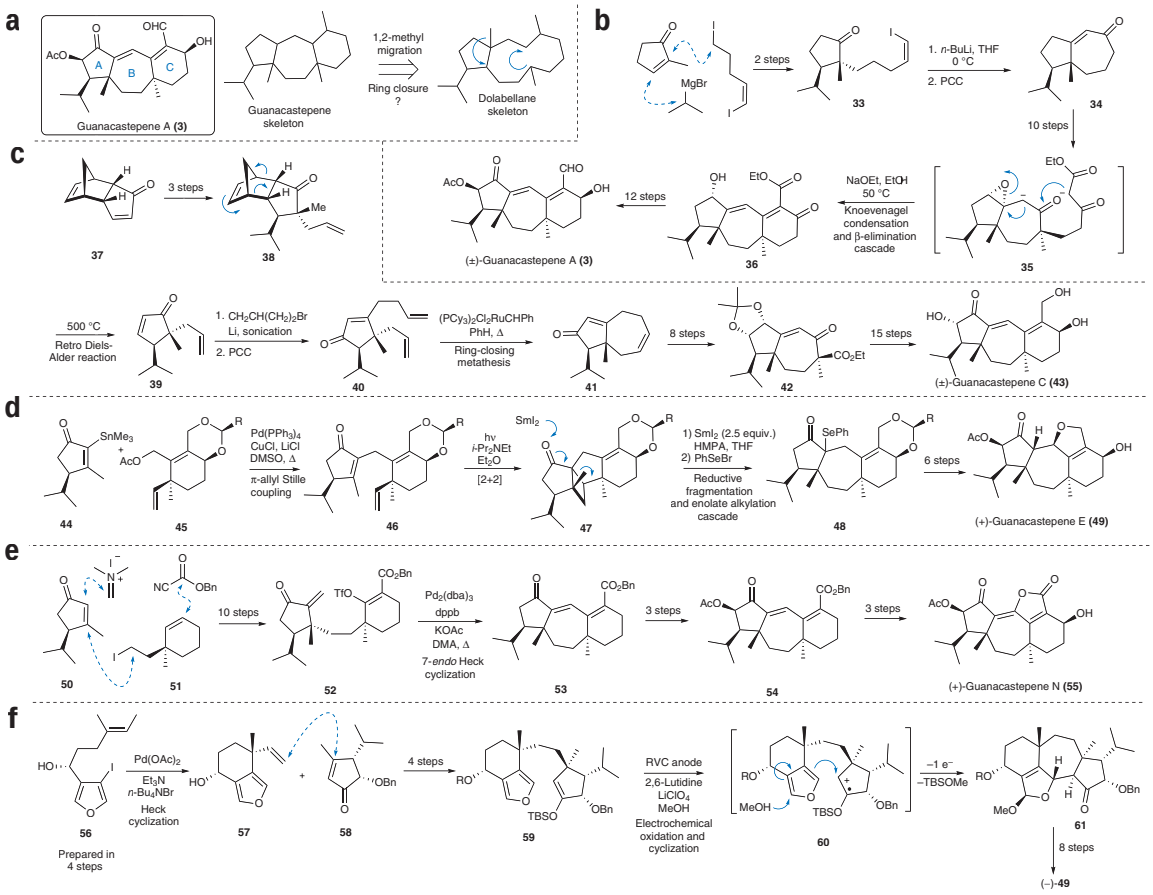

Scheme 3 Synthetic strategies for the construction of the guanacastepenes. (**a**) The biosynthesis of the guanacastepene skeleton may arise from the familiar dolabellanes. (**b**) Key steps in Danishefsky's total synthesis of guanacastepene A. (**c**) Use of a norbornene mask to control the stereocenters of the A rings en route to guanacastepene C (Mehta and colleagues). (**d**) Convergent assembly of guanacastepene E via a π-allyl coupling and selective cyclobutane fragmentation (Sorensen and colleagues)). (**e**) Overman's synthesis of guanacastepene N featuring a unique 7-*endo* Heck cyclization. (**f**) Trauner's convergent synthesis of guanacastepene E featuring an anodic oxidation and cyclization strategy. Ac, acetyl; Bn, benzyl; Cy, cyclohexyl; dba, dibenzylideneacetone; DMA, *N,N*-dimethylacetamide; DMSO, dimethyl sulfoxide; HMPA, hexamethyl-phosphoramide; dppb, 1,4-bis(diphenylphosphino)butane; PCC, pyridinium chlorochromate; Ph, phenyl; RVC, reticulated vitreous carbon; TBDPS, *t*-butyldiphenylsilyl; Tf, trifluoromethane sulfonate; THF, tetrahydrofuran.

produced the B ring (**40** → **41**), and several straightforward manipulations converted **41** into (±)-guanacastepene C. Though not a new idea, the use of an auxiliary to control diastereoselective reactions is still a cornerstone of modern organic synthesis.

A cycloaddition and ring-fragmentation strategy en route to (+)-guanacastepene E (49) (Sorensen). The Sorensen group developed a highly convergent strategy to assemble the guanacastepene skeleton[46]. Their plan involved the union of highly functionalized A and C rings, with the central B ring being formed last. The premier step in their sequence was a daring [2+2] cycloaddition and ring fragmentation strategy to form the B ring (**Scheme 3d**). A palladium-mediated Stille coupling between **44** and **45** led smoothly to **46**, which contains all of the carbon atoms needed for guanacastepene E (**49**)[53]. Irradiation of **46** in the presence of base led to the desired cyclobutane **47**. Addition of the one-electron reducing agent SmI_2 induced the desired cyclobutane fragmentation, presumably through the intermediacy of a ketal radical, and further reduction formed an enolate, which could be trapped by phenylselenium bromide forming **48**. Conversion of **48** into (+)-**49** required six steps. Through a masterful choice of classic reactions, Sorensen's construction of guanacastepene E was a model for the benefits of an extremely convergent synthesis.

Total synthesis of (+)-guanacastepene N (55) using a 7-*endo* Heck cyclization (Overman). Much like Sorensen, Overman and co-workers developed a highly convergent synthesis of the guanacastepene skeleton[47]. The Overman group, which has extensive experience in the use of palladium-mediated reactions in complex molecule synthesis[54], chose to form the B ring via a fascinating 7-*endo* Heck cyclization (**Scheme 3e**). The tendency of the Heck reaction to proceed via an *exo*, and not an *endo*, pathway makes this choice of bond construction rather intriguing. In practice, heating triflate **52** (prepared in ten steps from **50** and **51**) with the correct palladium source and additives produced the desired dienone (**53**), which could be transformed into guanacastepene N (**55**) in six steps. Palladium-mediated reactions are currently one of the premier synthetic tools for C–C bond construction[53], and Overman's guanacastepene N synthesis is a beautiful example of their utility in complex total synthesis.

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Total synthesis of (−)-guanacastepene E (49) featuring an electrochemical strategy (Trauner). The Trauner group also developed a unique and impressive route to access the guanacastepene architecture (**Scheme 3f**)[48]. The key step involved an electrochemical oxidative cyclization. It was envisioned that electrochemical oxidation of silyl enol-ether **59** would produce a radical cation (**60**) that could be trapped by the pendent electron-rich furan, thus forming the B ring. Compound **59** in turn could originate from two pieces of roughly equal size, namely **57** and **58**. To prepare furan **57**, the group turned to the intramolecular Heck cyclization (**56** → **57**). The union of furan **57** and enone **58** proceeded smoothly and provided tetracycle **61** as a single isomer after anodic oxidation of a methanolic solution of **59**. Eight steps were required to convert **61** into guanacastepene E. Electrochemical methods remain underused in organic synthesis, but as Trauner's synthesis demonstrated, these reactions should not be overlooked when approaching challenging bond constructions.

Phomactin A (4)

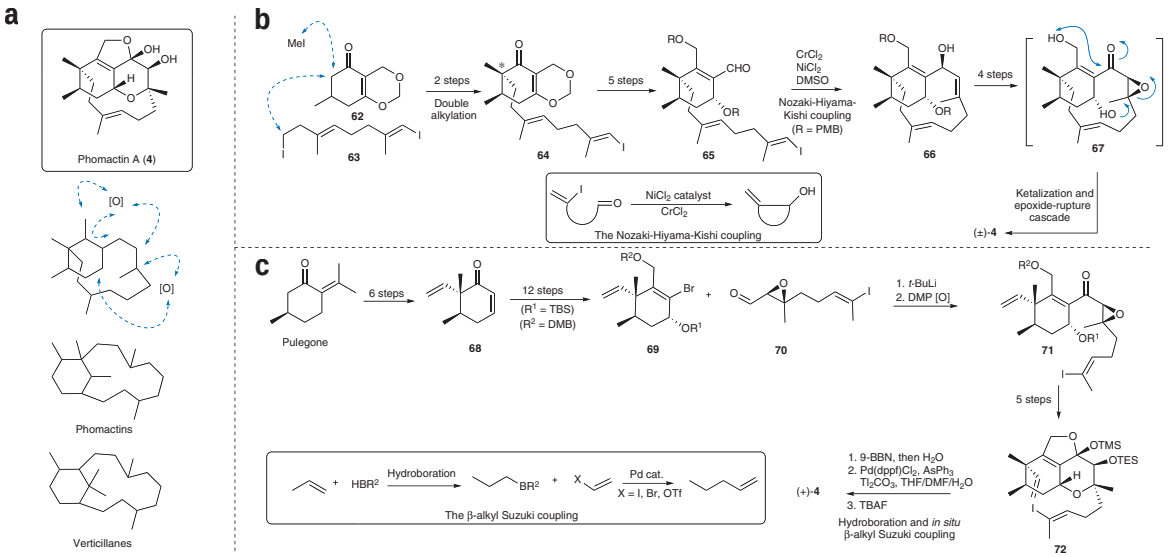
Isolated from marine fungal sources in 1991 by Sugano and co-worker, phomactin A (**4**) represents an unusual platelet-activating factor (PAF) antagonist[55]. Its carbon skeleton is reminiscent of the famous verticillanes (biosynthetic precursors of the taxanes, such as taxol), but the terpene in its final natural form is considerably modified (**Scheme 4a**). The core synthetic challenge posed by the phomactin skeleton is a 12-membered macrocycle with a sensitive hydrated furan. To date, total syntheses have been completed by both the Pattenden (2002) and Halcomb (2003) groups[56,57].

Total synthesis of (±)-4 featuring a Nozaki-Hiyama-Kishi macrocyclization (Pattenden). Pattenden and co-workers quickly established the all-carbon quaternary center (see starred atom, **Scheme 4b**) in phomactin via dialkylation of enone **62** with methyl iodide and then iodide **63** (**Scheme 4b**)[56]. This seemingly simple step attached all the carbons needed for the natural product. Five simple manipulations led to compound **65**, which was poised to undergo a Nozaki-Hiyama-Kishi coupling to form the phomactin macrocycle (**66**)[58]. A four-step sequence arrived at epoxy-ketone **67**, which spontaneously cyclized in the presence of acid to form (±)-**4**, via ketalization of the primary alcohol and epoxide rupture by the neighboring secondary hydroxyl group.

A β-alkyl Suzuki macrocyclization en route to a (+)-4 (Halcomb). Halcomb and Mohr developed an enantiospecific route to (+)-**4** starting with the chiral terpene pulegone (**Scheme 4c**)[57]. Transformation of pulegone into enone **68** required six steps, thus also forming the key all-carbon quaternary center early in the synthesis. Conversion of **68** into vinyl bromide **69** required 12 transformations. Compound **69** underwent clean lithium-halogen exchange with *tert*-butyl lithium and the resulting lithiate was quenched with aldehyde **70** to provide an allylic alcohol that was oxidized with Dess-Martin periodinane. Five steps, similar to Pattenden's, transformed **71** into **72**, thus setting the stage for the key step: an intramolecular *B*-alkyl Suzuki macrocyclization[59]. To this end, hydroboration of **72** and subsequent treatment with catalytic palladium (under modified Johnson conditions) at room temperature provided (+)-**4**, demonstrating both the versatility and the mildness of the Suzuki coupling in a complex setting.

Neotripterifordin (5)

In a search for new anti-HIV agents, Lee and co-workers isolated the unusual kaurane-type diterpene neotripterifordin (**5**) from the roots of *Tripterygium wilfordii* in 1995 (ref. 60). This natural product was found to be a potent inhibitor of HIV replication in H9 human lymphocyte cells (EC_{50} of 25 nM). The structure originally proposed for **5** was found to be incorrect through the synthetic efforts of Corey and Liu, who prepared the correct compound in 1997 (ref. 61). The originally proposed structure was epimeric at the tertiary hydroxyl–bearing stereocenter (**Scheme 5a**).



Scheme 4 Total syntheses of phomactin A. (**a**) Phomactin's unusual diterpene skeleton coupled with its high oxidation render it a formidable synthetic challenge. Also shown for comparison is the verticillane skeleton. (**b**) Pattenden's total synthesis featuring a Nozaki-Hiyama-Kishi macrocyclization. (**c**) *B*-alkyl Suzuki macrocyclization strategy used by Halcomb and co-workers. 9-BBN, 9-borabicyclo[3.3.1]nonane; DMB, 3,4-dimethoxybenzyl; DMSO, dimethylsulfoxide; DMP, Dess-Martin periodinane; PMB, *p*-methoxybenzyl; dppf, 1,1-bis(diphenylphosphino)ferrocene; TBAF, tetrabutylammonium fluoride; TBS, *t*-butyldimethylsilyl; TES, triethylsilyl; Tf, trifluoromethane sulfonate; THF, tetrahydrofuran; TMS, trimethylsilyl.

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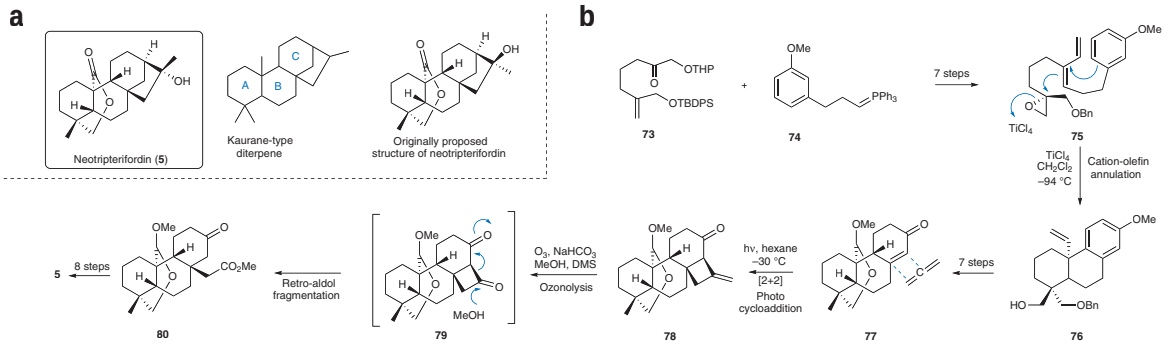
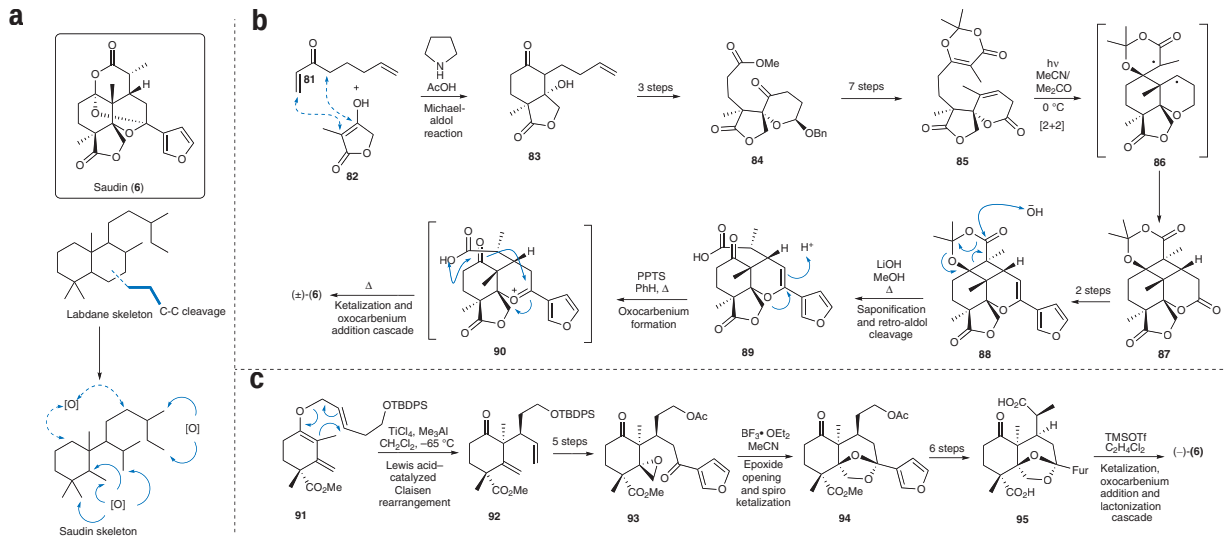


Scheme 5 Total synthesis of neotripterifordin. (**a**) The potent anti-HIV agent neotripterifordin, a member of the kaurane diterpenes. The correct structure was determined through the synthetic efforts of Corey and Liu. (**b**) Key steps in Corey's enantioselective synthesis. A variation of the classical cation-olefin cyclization formed both the A and B rings in a single step. Enone **77** smoothly reacted with allene in a [2+2] photocycloaddition to secure all of the carbon atoms needed for neotripterifordin. DMS, dimethyl sulfide; Ph, phenyl; TBDPS, *t*-butyldiphenylsilyl; THP, tetrahydropyran.

Enantioselective synthesis of neotripterifordin featuring a cation-olefin cyclization (Corey). The Corey group used a blend of modern catalytic asymmetric reactions and classical organic transformations to arrive at neotripterifordin (**Scheme 5b**)[61]. Beginning with ketone **73** and phosphorus ylide **74**, epoxide **75** could be obtained in seven straightforward manipulations. It is worth mentioning that the lone asymmetric center in **75** will serve to construct a compound containing seven stereocenters, five of which are contiguous. The chirality of **75** stems from a highly enantioselective Katsuki-Sharpless epoxidation[62]. Treatment of **75** with $TiCl_4$ induced a cation-olefin cyclization, stereoselectively forming both the A and B rings in a single operation. The origins of this powerful reaction lie heavily in both the synthetic and biosynthetic steroid field, the history of which has recently been reviewed[63]. Compound **76** could be transformed into **77** in seven operations. Irradiation of **77** in the presence of allene produced cyclobutane **78**, which after olefin scission (via ozonolysis) participated smoothly in a retro-aldol fragmentation producing **80**. Eight manipulations from **80** were required to prepare enantiopure **5**. Corey's elegant synthesis served to demonstrate the way in which classic diastereoselective reactions, coupled with a single asymmetric transformation, can efficiently lead to complex enantiopure terpenes.

Saudin (6)

Leaves from the Saudi Arabian plant *Clutia richardiana* produce the highly complex, labdane-derived diterpene saudin (**6**). Isolated in 1985 by Mossa and Cassidy, this compound was found to be a highly potent inducer of hypoglycemia in mice[64]. From the synthetic vantage point, its highly oxygenated, caged structure poses an especially daunting challenge (**Scheme 6a**). To date, saudin has been prepared by total synthesis only twice, first by the Winkler group[65] and then more recently by the Boeckman group[66]. In addition, several approaches to the core have been published[67–69].



Scheme 6 Total syntheses of the diterpene saudin. (**a**) Saudin's highly complex structure is presumably formed in nature by C-C bond cleavage of the common labdane framework and subsequent oxidations. (**b**) Winkler's approach to (+)-saudin, featuring an impressive intramolecular De Mayo reaction. (**c**) Boeckman's total synthesis of (–)-saudin using a Lewis acid–catalyzed Claisen rearrangement to form the core structure. Ac, acetyl; Bn, benzyl; Fur, furan; Ph, phenyl; PPTS, pyridinium *p*-toluenesulfonate; TBDPS, *t*-butyldiphenylsilyl; TMSOTf, trimethylsilyl trifluoromethane sulfonate.

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An efficient total synthesis of (±)-6 using the De Mayo reaction (Winkler). The Winkler group again turned to the powerful De Mayo reaction to construct the saudin core (**Scheme 6b**)[65]. The key precursor to the De Mayo cascade, namely **85**, could be prepared in ten steps from simple starting materials **81** and **82**. Irradiation of an acetone/acetonitrile solution of **85** led smoothly to cyclobutane **87**, presumably through the intermediacy of diradical **86**. After a two-step procedure to attach the furan, the cyclobutane moiety present in **88** was ruptured by a base-mediated retro-aldol reaction to produce acid **89**. Amazingly, treatment of this compound with acid directly furnished (±)-**6** in a single reaction. Although several mechanistic pathways could be posited, one can imagine that this cascade proceeds via ketalization of the ketone with the neighboring acid group, followed by hemiketal addition into the oxocarbenium ion (see intermediate **90**). In terms of synthetic design, one would be hard pressed to find a more efficient method of constructing saudin (only 15 steps from simple materials were required). In addition, as with ingenol, this synthesis validates the power of the De Mayo reaction in the construction of complex carbocyclic ring systems.

Total synthesis of (−)-6 using a Lewis acid–catalyzed Claisen rearrangement (Boeckman). The Boeckman group used a Claisen rearrangement to forge saudin's central, all-carbon quaternary center (**Scheme 6c**)[66,70]. Treatment of enantioenriched **91** with $TiCl_4$ and Me_3Al led to compound **92** with the desired stereochemistry. The use of a Lewis acid catalyst was essential to override the thermal Claisen reaction's preference for proceeding via a chair transition state, thus leading to an undesired diastereomer. A five-step sequence converted ketone **92** into furan containing compound **93**. Treatment of **93** with boron trifluoride diethyl etherate led smoothly to compound **94** via an epoxide opening and ketalization sequence. In six steps, the Boeckman group was able to produce diacid **95**, which cyclized to form (−)-saudin in the presence of acid, reminiscent of Winkler's final cascade (with an additional lactonization). In addition to establishing the absolute configuration of **6**, the Boeckman synthesis highlights the power of the Claisen rearrangement to construct highly congested quaternary centers.

Eleutherobin (7)

Isolated in 1995, by Fenical and co-workers, from soft corals in the Indian Ocean, eleutherobin (**7**) was one of the most potent anti-cancer agents isolated from natural sources in recent years[71]. As an extremely powerful inhibitor of microtubule disassembly, **7** was immediately placed into the upper echelon of promising cancer therapeutics alongside the likes of taxol, discodermolide and the epothilones. The difficulty associated with its isolation from a rare alcyonacean (*Eleutherobia* sp.), combined with its extremely promising initial bioactivity, made **7** an extremely compelling target for total synthesis. The already complex diterpene skeleton of eleutherobin, which presumably stems from the cembranes (**Scheme 7a**), is further complicated by the attachment of an arabinose sugar moiety. Not long after its isolation, two total syntheses of **7** appeared in the literature, the first by the Nicolaou group and the second, shortly thereafter, by Danishefsky and co-workers[72–77]. In addition, one formal synthesis and a myriad of approaches have been reported (ref. 78 and references therein).

An acetylide addition macrocyclization en route to the total synthesis of (−)-7 (Nicolaou). Upon inspection of **7**, one can immediately envision the A ring arising from a commercially available monoterpene possessing a six-membered ring. The Nicolaou group called carvone to the task and, using reliable reactions, were able to prepare compound **96** in large quantities (**Scheme 7b**)[72–74]. Johnson-Claisen rearrangement smoothly produced ester **98**, which has a complete A ring to which the remaining rings can be appended. Conversion of **98** into highly functionalized acetylene **99** required 15 manipulations. Deprotonation of **99**, followed by internal quenching with the nearby aldehyde and subsequent oxidation, produced the rigid ten-membered macrocycle (**100**). Subsequent reduction of the triple bond greatly reduced the rigidity of the macrocycle, thus allowing the proximal tertiary hydroxyl group to ketalize with the enone (**101** → **102**) and form both the B and the C rings in a single operation. Attachment of the sugar moiety and imidazole-containing side chain completed the first total synthesis of this complex diterpene. As demonstrated, creative synthetic strategies that efficiently incorporate chiral pool materials can provide excellent solutions for molecules that would ordinarily be difficult to obtain by other means.

An impressive Achmatowicz rearrangement en route to a total synthesis of (−)-7 (Danishefsky). The Danishefsky group turned to the commercially available terpene α-phellandrene as the basis for the A ring in the hope that they could selectively functionalize the disubstituted olefin (**Scheme 7c**)[75–77]. Indeed, this olefin readily participated in a [2+2] cycloaddition with dichloroketene (generated *in situ* from trichloroacetyl chloride), thereby affording compound **103** as the major isomer[79]. An eight-step procedure was developed to cleave the cyclobutane and append the requisite functionality present in compound **104**. Bromofuran **104** took part in an intramolecular Nozaki-Hiyama-Kishi reaction to form the B ring–containing tricycle **105**, after two protecting group manipulations. Epoxidation of the electron-rich furan, followed by rearrangement, led to compound **107** (Achmatowicz reaction), which could be further reacted with methyl lithium to produce **108**. The key ring contraction (**108** → **110**) could be achieved by treating **108** with acetic anhydride and *N*,*N*-dimethylaminopyridine. Compound **110**, which already contains much of the complexity of **7**, could be transformed into the natural product in 11 steps, thereby completing the synthesis of eleutherobin. As with the Nicolaou synthesis, masterful manipulation of chiral terpene building blocks allowed for a rational route to the target structure.

Terpestacin (8)

In 1993, Oka and co-workers isolated the macrocyclic diterpene terpestacin (**8**) from the fungal strain *Arthrinium* sp. Collaborative efforts with Bristol-Myers Squibb subsequently revealed that **8** inhibits the formation of syncytia[80]. These large, multinucleated cells arise from expression of gp120 on cell surfaces during HIV infection. The defining structural feature of this terpene is its 15-membered macrocycle containing a remote chiral alcohol (**Scheme 8a**). This natural product has attracted significant attention from the synthetic community, with total syntheses already reported by four groups[81–86]. In addition to providing a proving ground for new synthetic methodology, the Myers and Jamison syntheses put to rest some inconsistent published data regarding the absolute configuration of **8** and related compounds[83–85].

Total synthesis of (±)-8 featuring a Horner-Wadsworth-Emmons macrocyclization (Tatsuta). Tatsuta reported the first total synthesis of terpestacin in racemic form in 1998 and in optically active form later that year (**Scheme 8b**)[81,82]. Ketone **111**, which could be prepared in five steps from simple materials, underwent a one-ring homologation in six steps to produce keto-ester **112**. Alkylation of **112** with allylic chloride **113** (derived from farnesol) provided compound **114**, which was converted into aldehyde **115** in a short (three-step) sequence. Tatsuta's key macrocyclization employed an intramolecular variant of the reliable Horner-Wadsworth-Emmons (HWE) olefination (**115** → **116**)[87]. It is important to note, however, that the complexity present in **115**,

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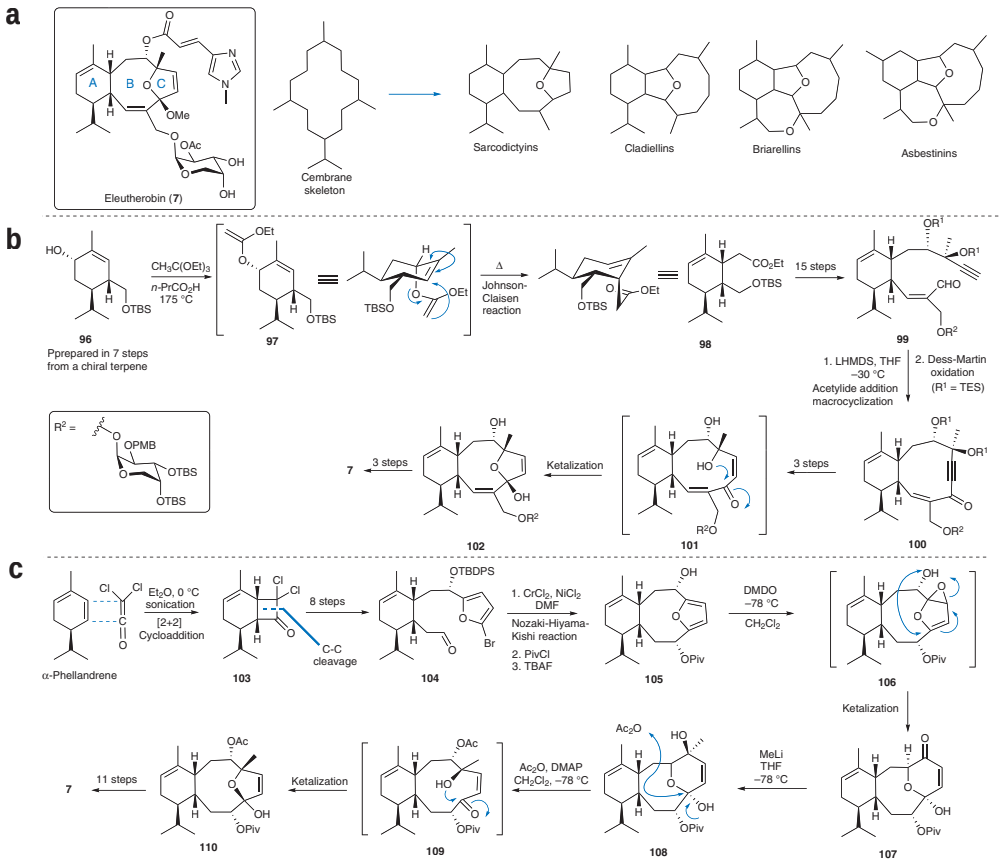

Scheme 7 Total synthesis of eleutherobin. (**a**) Eleutherobin's cembrane-derived skeleton makes it a member of the sarcodictyin family, and it is presumably related to several other large classes of diterpenes. (**b**) Key steps in Nicolaou's synthetic route to eleutherobin. The A ring was derived from a commercially available terpene and the macrocycle was formed by an intramolecular acetylide addition. (**c**) Key steps in Danishefsky's total synthesis of eleutherobin. An intramolecular Nozaki-Hiyama-Kishi coupling was used to construct the B ring. Furan **106** underwent an Achmatowicz ring expansion and ketalization ring contraction to forge the core structure (**110**). Ac, acetyl; DMAP, *N,N*-dimethylaminopyridine; DMDO, 2,2 dimethyldioxirane; LHMDS, lithium hexamethyldisilazide; PMB, *p*-methoxybenzyl; Piv, pivaloyl; TBAF, tetrabutylammoniun fluoride; TBDPS, *t*-butyldiphenylsilyl; TBS, *t*-butyldimethylsilyl; TES, triethylsilyl.

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coupled with the formation of a 15-membered ring, makes this transformation anything but routine. Seven steps were necessary to convert **116** into (±)-**8**.

Total synthesis of (−)-8 featuring stereoselective enolate alkylations (Myers). The Myers group envisioned that alkylations could efficiently both set the key quaternary center in **8** and close the 15-membered macrocycle (**Scheme 8c**)[83]. In practice, deprotonation of lactone **118** with lithium hexamethyldisilazide (LHMDS), and subsequent enolate trapping with allylic bromide **117** (prepared from farnesol), formed ester **119** with high diastereomeric control. A six-step sequence could transform lactone **119** into enone **120**, setting the stage for a second diastereoselective alkylation to furnish key intermediate **121**. This macrocycle (**121**) could be transformed into (−)-**8** in seven additional steps, thus serving to highlight the power of modern enolate chemistry in the synthesis of complex molecules.

A nickel-catalyzed reductive coupling approach to construct (−)-8 (Jamison). To prepare the A ring in enantiomerically pure form, the Jamison group turned to the Pauson-Khand reaction between chiral dihydrofuran **123** and cobalt complex **122** (**Scheme 8d**)[84,85,88]. This powerful reaction could form **124** as essentially a single diastereomer. In five steps, enone **124** could be elaborated into alkyne **125**. The Jamison group used recently developed nickel-catalyzed coupling methodology for the union of **125** and the necessary subunit needed to produce the macrocyclic B ring, namely aldehyde **126** (ref. 82 and references therein). Thus, treatment of **125** and **126** with catalytic Ni(0), phosphine ligand **127** and triethylborane produced key allylic alcohol **128** with both good regiocontrol and good diastereocontrol. Compound **128** could be carried on to (−)-**8** in ten steps, with the macrocycle being formed via an alkylation, reminiscent of the Myers synthesis. The Jamison synthesis of **8** was a striking example of how synthetically useful metal-mediated reactions have permeated modern synthetic chemistry.

Asymmetric allylic alkylation and Claisen rearrangements en route to (−)-8 (Trost). The Trost group recognized that both the key all-carbon quaternary stereocenter and the chiral methyl group appended to the A ring could be prepared via the time-tested Claisen rearrangement (**Scheme 8e**)[86]. This classical strategy is particularly attractive because stereogenic carbon atoms attached to oxygen (which are often easy to create) can be readily translated into stereogenic carbon-carbon centers. In addition, this approach was also highly desirable in that the

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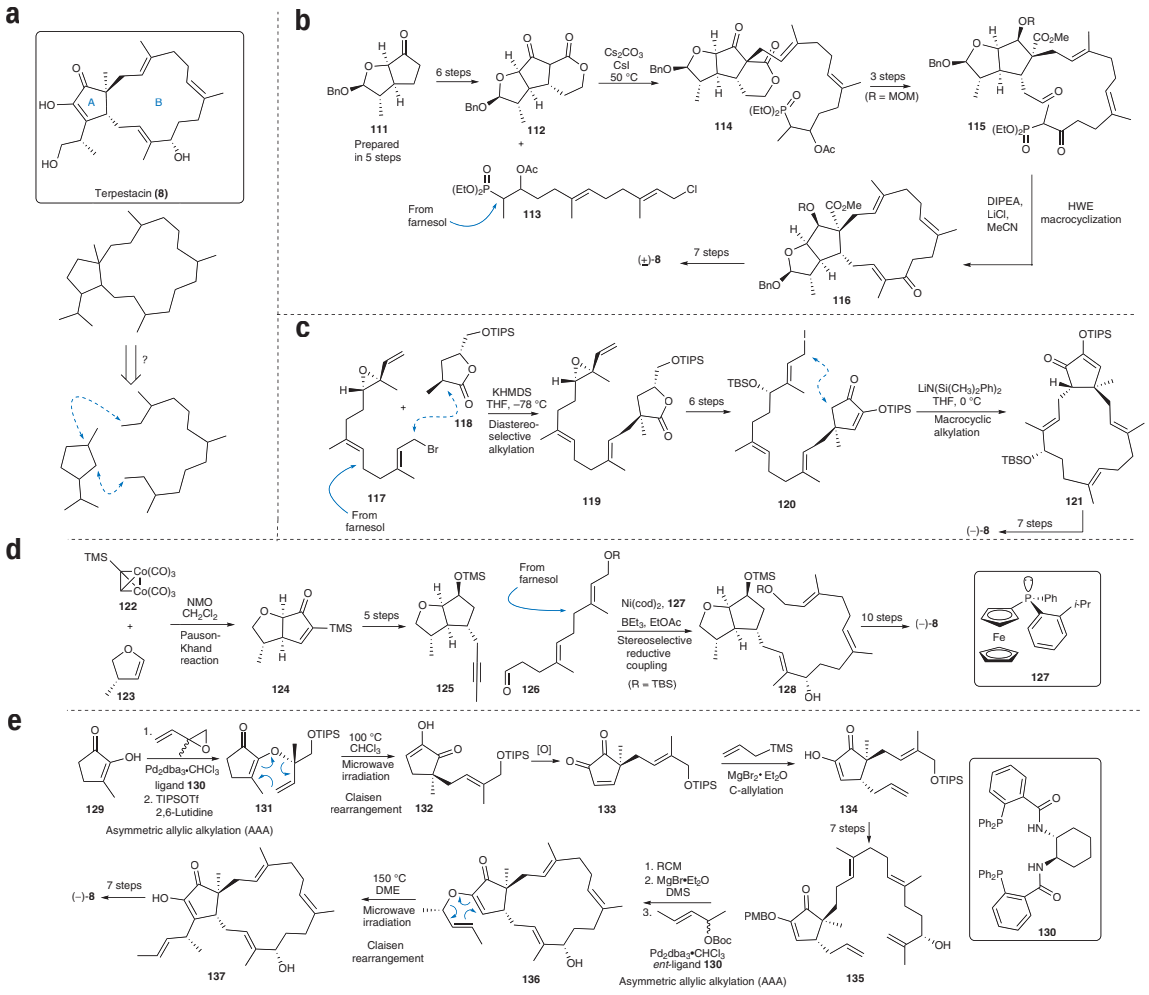
requisite chiral allylic ethers (see **131** and **136**) could be prepared by the palladium-catalyzed asymmetric allylic alkylation reaction (AAA), a methodology pioneered by the Trost group. Thus treatment of cyclopentanedione **129** with isoprene monoepoxide, a palladium(0) source and chiral ligand **130** smoothly formed allylic ether **131** after alcohol protection. Thermal Claisen rearrangement of **131** (using microwave irradiation) cleanly afforded compound **132**, which was then oxidized to enedione **133** and reacted with allyltrimethylsilane in the presence of a Lewis acid to produce cyclopentanedione **134**. A seven-step procedure converted compound **134** into **135**, which underwent *E*-selective ring-closing metathesis (RCM), deprotection and a second palladium-catalyzed AAA step. Compound **136** again participated in thermal Claisen rearrangement to produce compound **137**, which could be transformed into (−)-**8** in seven additional steps. Trost's terpestacin synthesis clearly demonstrated the power of catalyst-controlled palladium-mediated transformations in modern synthetic organic chemistry.

Future directions

The chemical synthesis of terpenes has come astonishingly far since the synthesis of terpineol and camphor over a century ago. Although the syntheses of many highly complex terpenes have been completed in the past century, numerous structures with unusual structural features and promising bioactivities remain to be synthesized. Such accomplishments will continue to enrich the science of synthesis and propel the field to even higher levels of sophistication. Indeed, many historically significant chemical concepts and principles have emerged from the study of terpenes, such as the principles of retrosynthetic analysis (developed en route to the synthesis of longifolene



Scheme 8 Total syntheses of terpestacin. (**a**) Macrocyclization as a key synthetic challenge posed by the anti-HIV agent terpestacin. (**b**) A Horner-Wadsworth-Emmons (HWE) macrocyclic olefination en route to terpestacin (Tatsuta). (**c**) Use of an easily prepared chiral lactone to control the stereochemistry of the critical quaternary center en route to (–)-terpestacin (Myers). (**d**) Use of a stereoselective, regioselective nickel-catalyzed reductive coupling between an aldehyde and alkyne en route to terpestacin (Jamison). (**e**) Trost's synthesis of terpestacin. Two of the four stereocenters were constructed using an asymmetric allylic alkylation (AAA) and Claisen rearrangement protocol. Ac, acetyl; Bn, benzyl; Boc, *t*-butoxycarbonyl; cod, cyclooctadiene; dba, dibenzylideneacetone; DIPEA, diisopropylethylamine; DME, 1,2-dimethoxyethane; DMS, dimethyl sulfide; KHMDS, potassium hexamethyldisilazide; LDA, lithium diisopropylamide; MOM, methoxymethylene; NMO, *N*-methylmorpholine *N*-oxide; [O], oxidation; PMB, *p*-methoxybenzy; RCM, ring-closing metathesis; TBS, *t*-butyldimethylsilyl; TIPS, triisopropylsilyl; TMS, trimethylsilyl.

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(**Fig. 1a**))[89] and the foundations of conformational analysis (as applied to steroidal ring systems)[90], as well as numerous synthetic transformations.

As we hope this review has made clear, chemists have become rather adept at synthesizing molecular skeletons. But if we recall terpene biosynthesis, wherein the carbon skeleton is first assembled by cyclase enzymes and then oxidized afterward by specialized oxidases, one can make the claim that our synthetic efficiency still has a lot of room for improvement. The field of organic synthesis will inevitably have to develop its own 'second step'—hydrocarbon oxidation chemistry—more fully if it is ever to compete with the efficiency of biosynthetic machinery. Fortunately, progress is currently being made in this burgeoning field dubbed "C-H activation" chemistry[91]. Hopefully, and most likely, a plethora of new methods will transform the field of terpene synthesis to unprecedented levels of sophistication.

COMPETING INTERESTS STATEMENT
The authors declare no competing financial interests.

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