Natural products

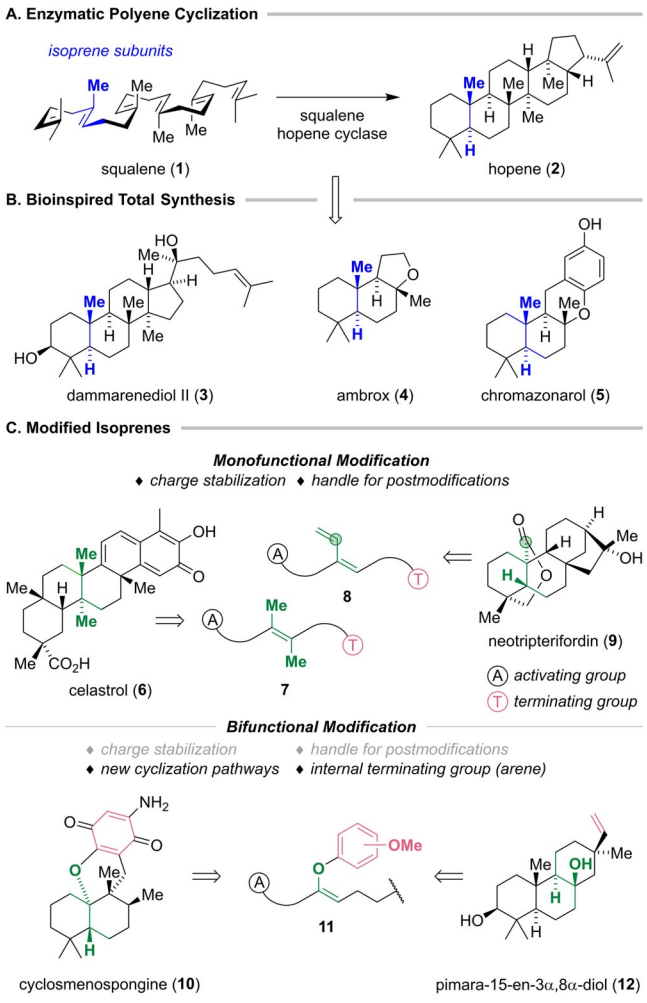
Beyond the Isoprene Pattern: Bifunctional Polyene Cyclizations

Julian M. Feilner[+], Franz-Lucas Haut[+], and Thomas Magauer*[a]

Abstract: Polyene cyclizations are capable of producing molecular complexity in a single step. While classical systems are limited to simple alkyl substitution patterns only, bifunctional polyenes take advantage of the unique reactivity of higher-functionalized alkenes. Here, we highlight the potential of these variants for the synthesis of structurally complex polycycles involving unprecedented termination steps. We also want to provide a stimulus for the development of novel modes of cyclization that involve bifunctional units to enable efficient synthesis of yet inaccessible natural products.

Introduction

The biosynthesis of terpenoid-like molecules is based on the cyclization of linear polyenes that feature a varying number of isoprene subunits. Enabled by cyclase-type enzymes, a high level of molecular complexity arises from these fascinating transformations. The enzymes perform highly selective and efficient cationic cyclization reactions by providing a defined molecular environment in the enzymatic active site and by preorganizing the linear precursor.[1] A prominent example is squalene hopene cyclase, which catalyzes the cyclization of squalene (**1**, Scheme 1 A). In this process, nine stereocenters are set and five carbon–carbon bonds are formed.[2] Synthetic chemists have mimicked these cyclizations with great success and demonstrated their efficiency in a large number of elegant syntheses (Scheme 1 B).[3] This includes the groundbreaking bioinspired total syntheses of dammarenediol II (**3**),[4] ambrox (**4**)[5] or chromazonarol (**5**).[6] For the initiation of the cyclization, a plethora of methods has been developed and various functional groups were shown to be amenable to activate (A) and terminate (T) the overall process.[1b,3,7] However, modifications of the linear polyene are still rare. Trisubstituted alkenes containing a methyl group—as those found in biosynthetic cyclization precursors—dominate the olefin substitution pattern of synthetic polyenes. Modified polyenes leave the traditional substitution pattern by introducing new substituents to the internal double bonds. Surprisingly, the variation of the linear polyene backbone has remained largely unexplored and only few modifications have been reported. Below we will highlight the key contributions (Scheme 1 C).



Scheme 1. Comparison of cyclization precursors: A) Nature's polyene cyclizations are based on the cyclization of isoprene derived substrates. B) Selected natural products synthesized via bioinspired cyclization cascades. C) Mono- and bifunctional modifications for second generation polyene cyclizations.

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Monofunctional modifications change the substitution pattern of the alkene to stabilize cationic intermediates or to implement linkers for late-stage transformations. An isoprene modification is considered to be monofunctional if only the alkene, but not its substituent reacts during the polyene cyclization.

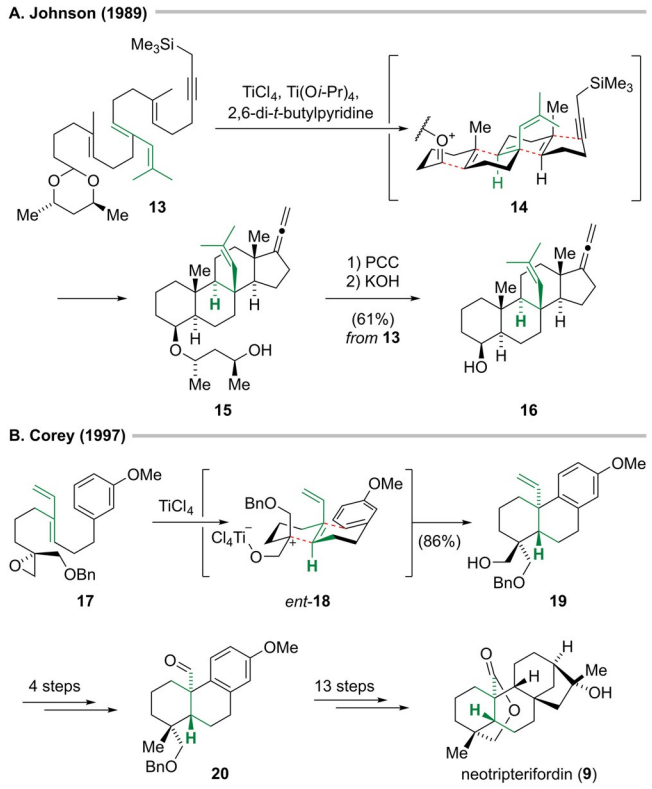
As an example, cyclization of a tetrasubstituted double bond **7** led to the formation of a central *trans*-1,2-dimethyl motif as found in celastrol (**6**).[8] The use of a vinyl-substituted alkene **8** served as a masked carbonyl function and enabled access to the lactone unit of neotripterifordin (**9**).[9] Further elaboration of this concept has revealed aryl enol ethers **11** as a powerful bifunctional modification. The electron-rich arene carried out a dual role: stabilization of the cationic intermediate and termination of the polyene cyclization reaction allowing reposition of the terminating group from the end of the linear polyene to one of the internal alkenes. The introduction of these bifunctional aryl enol ethers enabled unique cyclization modes to access the natural products cyclosmenospongine (**10**)[10] and pimarane **12**[11] with high efficiency.

Monofunctional Polyenes

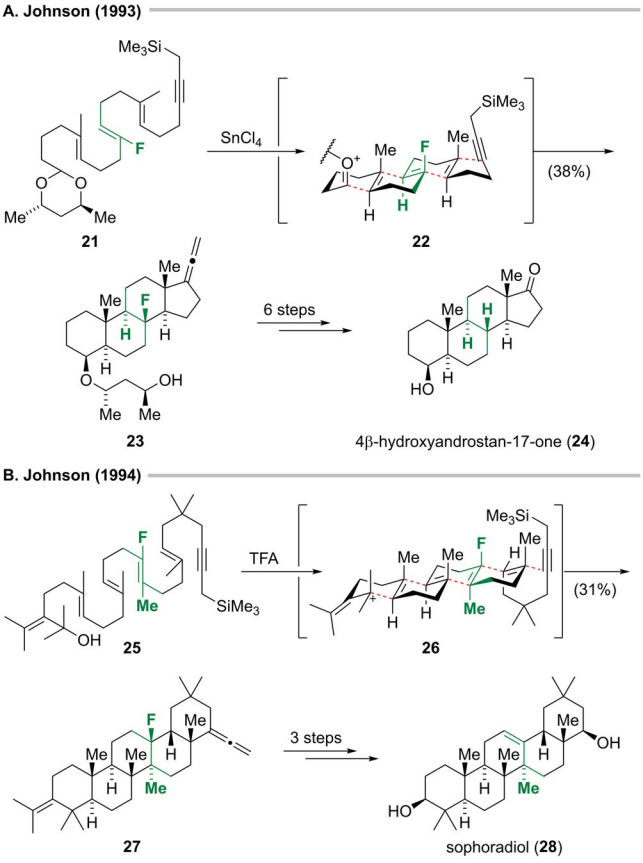
In 1987, the Johnson group already identified the synthetic potential of modified isoprene subunits to enhance polyene cascades.[12] Substitution of the methyl group by a vinyl residue significantly improved the cyclization pathway via stabilization of the central cation (Scheme 2 A). The concept of cation-stabilizing auxiliaries was demonstrated by the efficient assembly of tetracycle **15**. Cation-stabilizing auxiliaries like the isobutenyl group enhance the yield and the rate of polyene cyclization reactions by resonance stabilization.[12,13] Herein, polyene **13** was activated by titanium(IV) reagents to furnish **15** after termination by the propargylic silane. The steroidal framework **16** was then obtained via ether cleavage in 61% over three steps.[12b]

Ten years later, the Corey group applied this strategy to the total synthesis of the anti-HIV agent neotripterifordin (**9**, Scheme 2 B).[9] Their synthesis commenced with the rapid assembly of linear precursor **17** bearing a central vinyl-substituted olefin. Activation of the epoxide in the presence of titanium(IV) chloride initiated the polyene cyclization to deliver tricycle **19** in excellent yield of 86%. Reduction of the primary alcohol and ozonolytic cleavage of the vinyl residue unmasked aldehyde **20** in four steps. Subsequent dearomatization as well as installation of the lactone and cyclopentane moieties finally furnished neotripterifordin (**9**) in additional 13 steps.

Ongoing research in this field revealed vinyl fluorides as a second group of cation-stabilizing auxiliaries for polyene cascade reactions.[13] As illustrated in Scheme 3, Lewis acid-mediated activation ($SnCl_4$) of ketal **21** formed intermediate **22**, which efficiently participated in a tetracyclization to access the steroidal scaffold of **23** (38%). Ether cleavage, reductive defluorination using the Ohsawa–Oishi reagent[14] (Na/K alloy and



Scheme 2. Vinyl-substituted olefins as cation-stabilizing auxiliaries established by the groups of: A) Johnson and B) Corey.



Scheme 3. Vinyl fluorides as cation-stabilizing auxiliaries in tetra- and pentacyclizations applied in the total synthesis of **24** and **28**.

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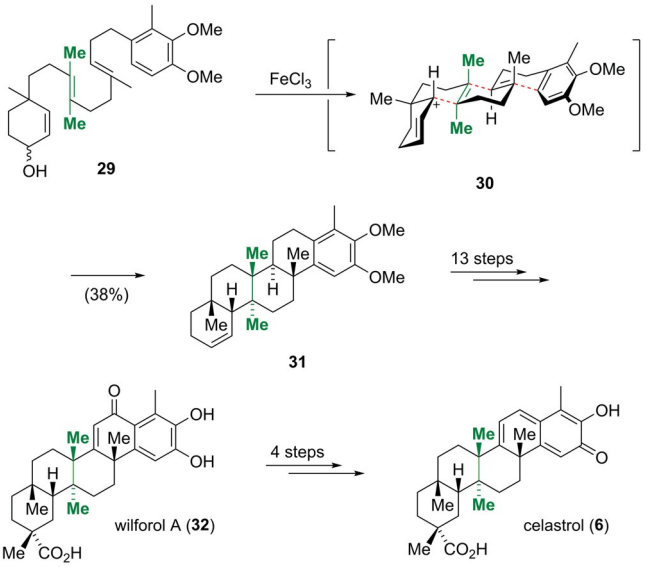
crown ether in toluene) and oxidative degradation of the allene culminated in the synthesis of steroid **24.**[13b]

The feasibility of this concept was further demonstrated by the pentacyclization of tetrasubstituted vinyl fluoride **25**.[15] The cationic cascade reaction was initiated via elimination of the allylic alcohol in the presence of trifluoroacetic acid (TFA). From pentacycle **27**, three additional steps, including regioselective dehydrofluorination ($SnCl_4$) to reveal the alkene, furnished the natural product sophoradiol (**28**). A similar polyene cascade reaction was also applied to the total synthesis of dammarenediol II (**3**).[16]

Next to heteroatom-substituted alkenes, the Johnson group also investigated tetrasubstituted alkenes bearing all-carbon residues.[17] Based on these initial results, the Siegel group accomplished the total synthesis of triterpenoid natural products.[8] As illustrated in Scheme 4, their synthetic route commenced with the iron(III) chloride triggered tricyclization of allylic alcohol **29**. Having installed the pentacyclic skeleton **31** of the celastroid natural product family, wilforol A (**32**) was obtained after 13 steps and subsequent redox manipulations (four steps) also provided celastrol (**6**).



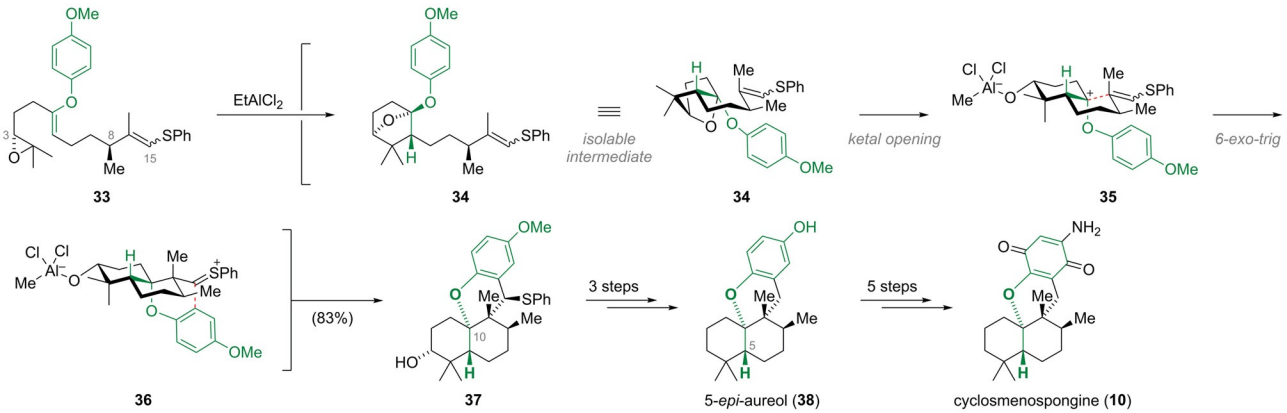
Scheme 4. Rapid assembly of celastroid natural products **6** and **32** via polyene cyclization of tetrasubstituted alkene **29**.

Bifunctional Polyenes

Synthetic access to oxygenated polycycles such as **10** or **12** via an isoprene-based biomimetic polyene cyclization would require additional steps such as late-stage oxidations or rearrangements. Modification of the linear cyclization precursor allowed for the early-stage adjustment of the oxidation pattern. As demonstrated in the synthesis of cyclosmenospongine (**10**), aryl enol ethers represent a synthetically valuable bifunctional modification to introduce an oxygen atom into the cyclization precursor (Scheme 5).[10] This allows for the implementation of new retrosynthetic strategies for the synthesis of oxygenated polycycles, which would not be directly accessible via conventional isoprene-based polyene cyclizations.

Treatment of epoxide **33** with diethyl aluminum chloride (Et_2AlCl) led to the formation of ketal **34**, which could be isolated in 81% yield. In the presence of ethylaluminum dichloride ($EtAlCl_2$), however, opening of the ketal initiated rapid cyclization to deliver tetracycle **37** in high yield (83%) via the transient species **35** and **36**. This extraordinary transformation led to the formation of three carbon–carbon bonds, installation of four stereocenters and was found to proceed in a stepwise fashion. Noteworthy, the cyclized product **37** was obtained as a single diastereomer. The stereocenters at C3/C8 and the double-bond geometry of the enol ether fully controlled the stereochemical outcome of the reaction. Changing the stereochemistry at C3 or C8 prevented further tricyclization of the ketal. Another essential feature for the successful promotion of the polyene cyclization was the vinyl sulfide. Substrates lacking this functional group would generate an energetically unfavorable primary carbocation at C15 and proved to be unreactive.[10b]

The aryl enol ether function of **33** served to position the tertiary alcohol at C10, thereby acting as a cation-stabilizing auxiliary. It also acted as an internal terminating group, which placed the aromatic core of the natural product by a transan-



Scheme 5. Aryl enol ether **33** as a bifunctional modification allowed a unique tricyclization to rapidly construct the cyclosmenospongine skeleton **37**.

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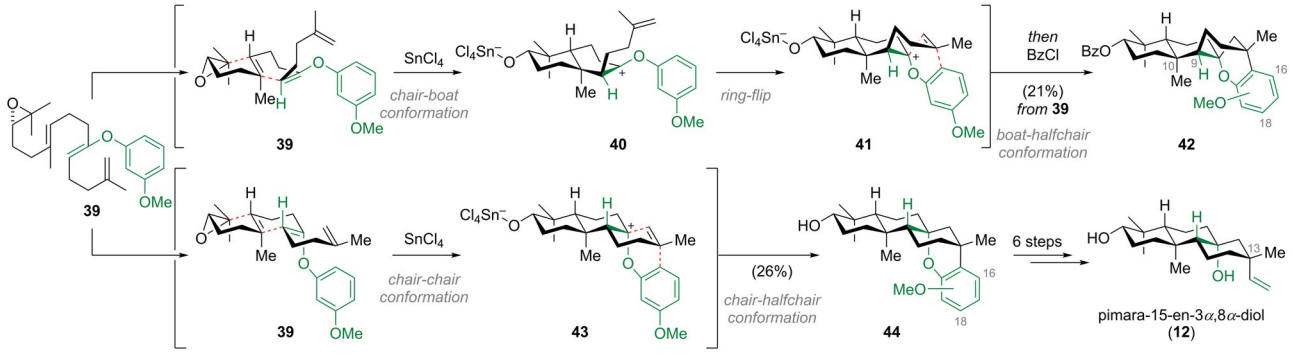

Scheme 6. Tetracyclization of aryl enol ether **39** enabled the total synthesis of pimara-15-en-3α-8α-diol (**12**).

nular *exo*-termination step. The enol ether propagated the cationic charge during the polyene cyclization and the aryl group underwent an intramolecular Friedel–Crafts cyclization via the thionium intermediate **36** as the terminating step. This revealed the aryl enol ether as a bifunctional modification of the isoprene pattern. The densely functionalized product **37** was transformed into 5-*epi*-aureol (**38**) by removing the thioether as well as the secondary alcohol and final deprotection of the phenol. Functionalization of the aromatic core in five steps gave access to more than 400 mg of cyclosmenospongine (**10**).

For the total synthesis of pimarane **12**, an aryl enol ether was installed within tetracyclization precursor **39** (Scheme 6).[11] It was found that due to a low π-facial selectivity at the enol ether involved in the closure of the second ring, the cyclization reaction underwent two different pathways.[18] The formation of product **42** was explained by a chair-boat conformation of the first two rings at the beginning of the cyclization reaction. This set the *syn*-relation between the methyl group at C10 and the hydrogen atom at C9 and led to the formation of oxocarbenium ion **40**. A ring-flip resulted in a chair-chair conformation (**41**) and enabled the cyclization of the third and fourth ring via a boat-halfchair conformation and a transannular *endo*-termination step. Benzoylation allowed purification by flash-column chromatography and provided **42** in 21% yield over two steps. Due do the non-symmetrical *m*-methoxyphenol derived aromatic core, which gave the best yield compared to other substitution patterns, the product was obtained as an inconsequential mixture (1.0:1.3) of regioisomers in respect to the methoxy group (C16:C18).

For the formation of product **44**, no ring-flip was necessary. The cyclization of the first two rings proceeded via a chair–chair conformation resulting in the formation of oxocarbenium ion **43**. The third and fourth ring were formed via a chair-halfchair conformation. Thereby, the transannular *endo*-termination step installed the remaining quaternary stereocenter at C13, resulting in the formation of **44** in 26% yield as an inconsequential mixture (1.0:1.6) of regioisomers in respect to the methoxy group (C16:C18). During the polyene cyclization, five stereocenters, two of which are quaternary, four six-membered rings and four carbon–carbon bonds were formed. The aryl enol ether served as a cation-stabilizing auxiliary, allowed for the introduction of the tertiary alcohol and acted as an internal terminating group. In contrast to the synthesis of cyclosmenospongine (**10**), the aromatic core of the aryl enol ether was not retained in the natural product. Instead, four of its carbon atoms were oxidatively cleaved off. The remaining carbon skeleton allowed for the installation of the vinyl group of the natural product pimara-15-en-3α-8α-diol (**12**).

Conclusions

Classical polyene cyclizations still represent one of the most powerful reactions to construct complex molecules. However, monofunctional polyene systems are restricted to a highly linear mode of cyclizations and simple heteroatom-containing structures. The development of bifunctional double bond modifications addresses these limitations and allows for rapid generation of structural diversity. Bifunctional polyene cyclizations were shown to provide efficient access to natural product families that have previously eluded their synthesis. The design and investigation of new modifications should allow for the unlocking of yet unknown cyclization modes.

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Conflict of interest

The authors declare no conflict of interest.

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