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 squa- lene hopene cyclase, which catalyzes the cyclization of squalene (1, Scheme 1A). 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 1B).[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, 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 1C).

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 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). The use of a vinyl-substituted alkene 8 served as a masked carbonyl function and enabled access to the lactone unit of neotripterifordin (9). Further elaboration of this concept has revealed aryl enol ethers as powerful bifunctional modifications. 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) and pimarane with high efficiency.

## Monofunctional Polyenes

In 1987, the Johnson group already identified the synthetic potential of modified isoprene subunits to enhance polyene cascades. Substitution of the methyl group by a vinyl residue significantly improved the cyclization pathway via stabilization of the central cation (Scheme 2A). 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 2B). 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 deamination 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. As illustrated in Scheme 3, Lewis acid-mediated activation (SnCl4) 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 (Na/K alloy and TFA) delivered 24 in 31% yield.

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**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 penta-cyclizations applied in the total synthesis of 24 and 28.
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 polycyde 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 cestroid natural product family, wilforol A (32) was obtained after 13 steps and subsequent redox manipulations (four steps) also provided celastrol (6).

**Bifunctional Polynes**

Synthetic access to oxygenated polycycles such as 10 or 12 via an isoprene-based biomimetic polycycle 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 polycycle cyclizations.

Treatment of epoxide 33 with diethyl aluminum chloride (Et\(_2\)AlCl) led to the formation of ketol 34, which could be isolated in 81% yield. In the presence of ethylaluminum dichloride (EtAlCl\(_2\)), however, opening of the ketol 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 ketol. Another essential feature for the successful promotion of the polycycle 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-
nular exo-termination step. The enol ether propagated the cat-
ionic charge during the polyene cyclization and the aryl group
underwent an intramolecular Friedel–Crafts cyclization via the
thionium intermediate as the terminating step. This re-
vealed the aryl enol ether as a bifunctional modification of the
isoprene pattern. The densely functionalized product 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 pimaranese installed within tetracyclization precursor (Scheme 6). 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. 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-methoxypheno-
fail 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 to 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 in-
duction of the tertiary alcohol and acted as an internal ter-
mating group. In contrast to the synthesis of cyclosmenos-
ponge (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 skele-
ton allowed for the installation of the vinyl group of the natu-
ral product pimara-15-en-3α,8α-diol (12).

Conclusions
Classical polynene cyclizations still represent one of the most
powerful reactions to construct complex molecules. However,
monofunctional polynene 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 polynene cycliza-
tions 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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