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Biomimetic synthesis via polyepoxide cyclizations*

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Abstract: The biomimetic synthesis of *trans,syn,trans*-fused polycyclic ether natural products involving a cascade of stereospecific and regioselective oxacyclizations of polyepoxide substrates is described as applied to the synthesis of polyoxepane and polypyran structures. In addition, an extension of biomimetic polyene cyclizations to terpenoid natural products is outlined.

Keywords: biomimetic synthesis; polycyclic ethers; polyepoxides; tandem cyclizations; polycyclic terpenes.

INTRODUCTION

Nature has provided a fascinating array of chemical structures and reactivities, particularly for the chemistry of life processes. The fashion in which structurally complex natural products are formed provides inspiration to scientists working in several arenas, ranging from uncovering how natural products are biosynthesized, to mimicking the biosynthetic approach with nonenzymatic reagents and catalysts. As our understanding of the biosynthesis of cholesterol has developed over several decades [1], significant societal benefits have arisen, including the discovery of cholesterol biosynthesis inhibitors ("statin" drugs), as well as efficient chemical syntheses of other condensed terpenoid structures, some of which exhibit pharmacologically interesting and valuable properties.

The marine dinoflagellates *Karenia brevis*, primarily of Atlantic origin, and the Pacific Ocean organism *Gambierdiscus toxicus* have been implicated in production of a family of potent neurotoxins exemplified by compounds **1–4** (Fig. 1) which in the case of *K. brevis* is accompanied by the formation of the "red tide" phenomenon [2]. The toxic principles, such as brevetoxins from *K. brevis* and ciguatoxins from *G. toxicus*, are responsible for a host of maladies, including diarrhea, respiratory distress, and reversal of temperature sensation, with mechanism of action traced to persistent activation of voltage-sensitive sodium ion channels [3]. Several types of brevetoxin and ciguatoxin compounds are known, bearing a common structural feature of *trans,syn,trans*-fused polycyclic ethers, with alternating positions of oxygen atoms in each ring [4]. The severity of toxic effects on fish and marine mammals arising from the Atlantic "red tide" phenomenon varies periodically, seemingly unrelated to the concentration of brevetoxins. In 2004, the isolation and structural characterization of a new polycyclic ether natural product, brevenal (**3**), was implicated as the principle responsible for modulating the severity of "red tide" toxic events [5]. In particular, brevenal is nontoxic at micromolar levels, and has been observed to competitively displace brevetoxin B (**1**) from specific sites of the voltage-sensitive sodium ion channel. Despite the potent toxicity of brevetoxin and ciguatoxin polycyclic ethers, a few compounds with similar structures exhibit potentially useful activity as antifungal agents [6].

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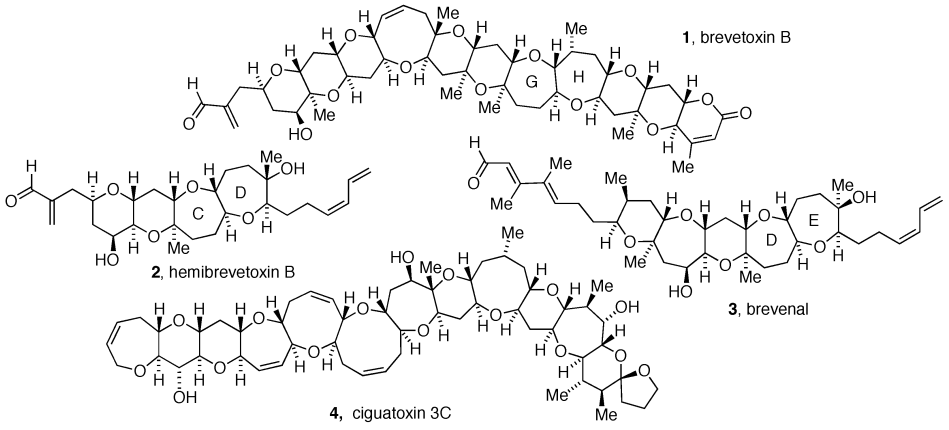


Fig. 1 Representative polycyclic ether natural products.

Nakanishi and Shimizu have independently shown that most carbon atoms arise from a modified polyketide biosynthesis with some methyl substituents from *S*-adenosylmethionine (Fig. 2) [7]. Several reductions and desaturations to polyene **6** and stereoselective epoxidation from the same face of each alkene would provide the stereochemistry required for the *trans,syn,trans*-polycyclic ether structure of brevetoxins (i.e., **1**), assuming inversion of stereochemistry at each site of carbon–oxygen bond formation in oxacyclization of polyepoxide **7**.

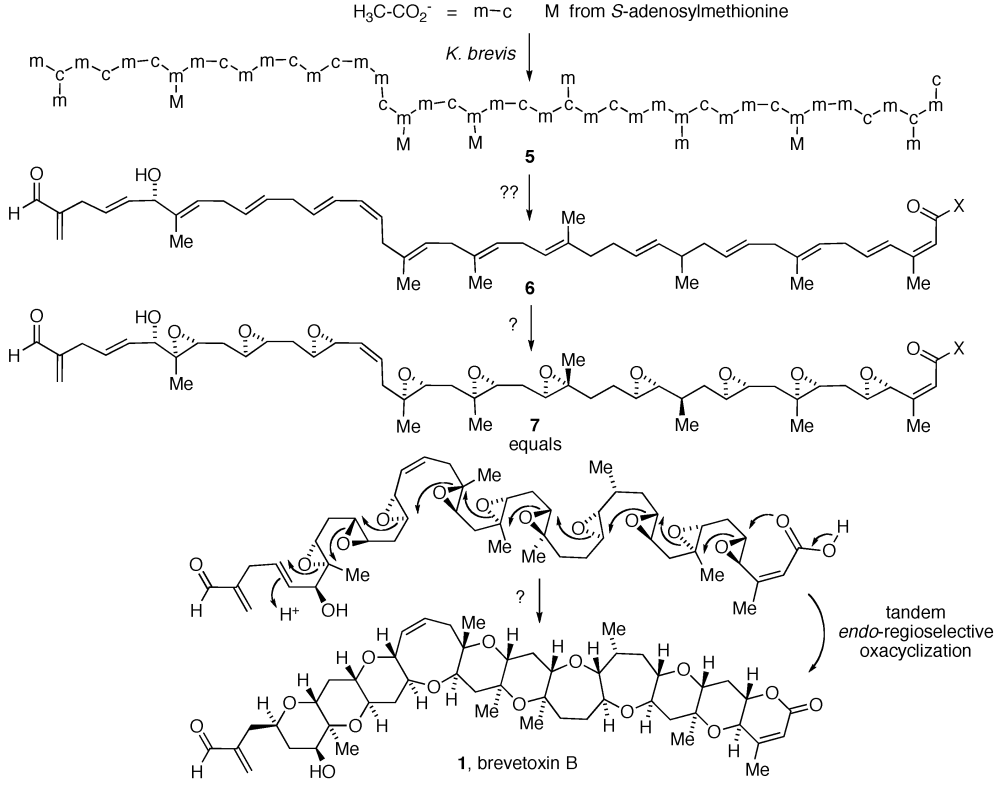


Fig. 2 Proposed biosynthesis of brevetoxin B (**1**).

Although many methods now exist for the chemical synthesis of polyene compounds, which might be applied to the preparation of the proposed biosynthetic precursors, and significant progress toward the stereoselective epoxidation of dialkyl-substituted alkenes and polyenes has also been accomplished over the past decade, the challenge in our opinion was to form the fused rings of brevetoxins, since the kinetically favored process for oxacyclizations of polyepoxides with hydroxylic nucleophiles is generally the exocyclic pathway to chain polycyclic ethers (i.e., **9** to **10**) (Fig. 3) [8].

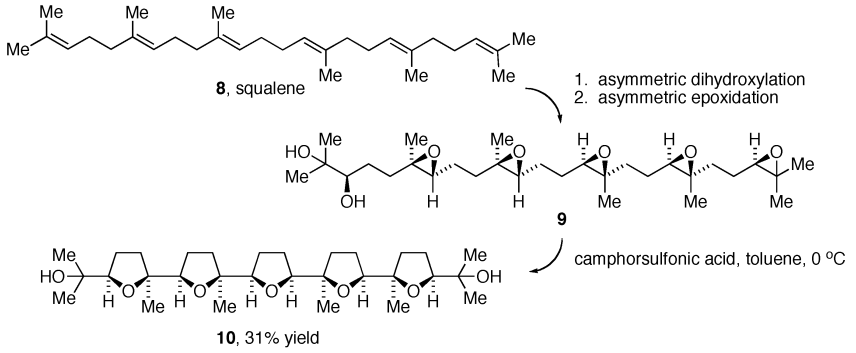
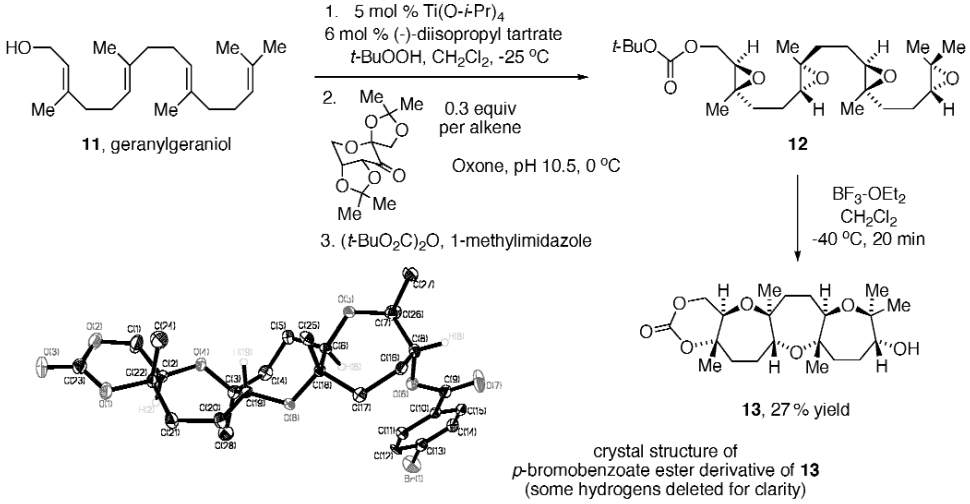


Fig. 3 The challenge: *exo*-cyclizations of polyepoxides are kinetically favored.

SYNTHETIC AND MECHANISTIC ASPECTS OF POLYEPOXIDE CYCLIZATIONS

Our initial studies were conducted with polyene epoxides arising from geraniol, farnesol, and geranylgeraniol. These experiments taught us that (1) polyepoxides from 1,5-dienes, 1,5,9-trienes, and 1,5,9,13-tetraenes underwent stereospecific tandem oxacyclizations upon reaction with aprotic Lewis acids, most generally BF_3-etherate; (2) endocyclization regioselectivity was consistent with Markovnikov addition of each oxygen nucleophile to the more substituted position of each terpene-derived epoxide; and (3) a carbonyl nucleophile was required as the nucleophilic terminator in order to achieve *endo*-mode regioselectivity as the major pathway as observed in the tetracyclization of *tert*-butylcarbonates **12** to **13** (Scheme 1) [9].



Scheme 1 All *endo*-oxacyclization of tetraepoxide substrate from geranylgeraniol.

In addition to *tert*-butylcarbonates, ketones and esters can also serve as carbonyl nucleophiles to terminate oxacyclization cascades. Crystallography was extraordinarily valuable to this research, not only in establishing elements of stereochemistry and even unambiguous confirmation of ring size resulting from *endo*-mode regioselective cyclization, but also providing information regarding mechanism. Specifically, the absolute stereochemistry of the polycyclization products could be obtained with *para*-bromobenzoate derivatives. The absolute stereochemistry of product **13** was consistent with the proposed direction of oxacyclization, initiated by Lewis acid coordination to the epoxide most distant from the *tert*-butylcarbonate nucleophile (i.e., **14**) and terminated by this carbonyl (Fig. 4). An alternative mechanism involving nucleophilic addition of adventitious water or hydroxide to the terminal epoxide (i.e., **16**) and cyclic carbonate formation could now be excluded, as this mechanism would have given the enantiomeric product *ent*-**13** [9].

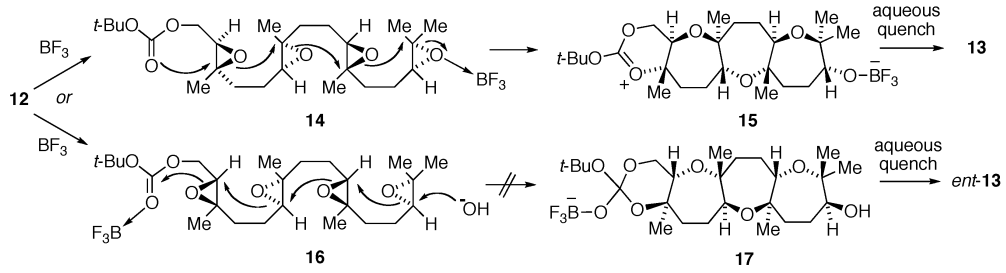
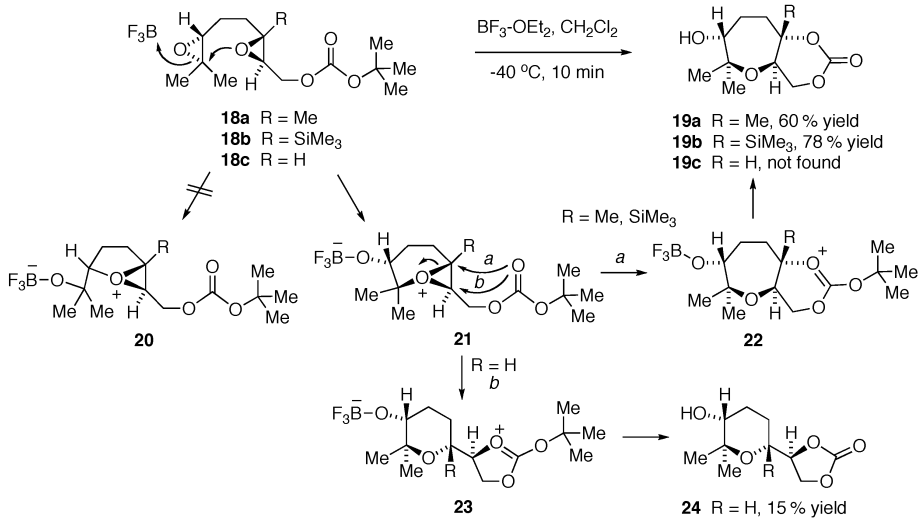


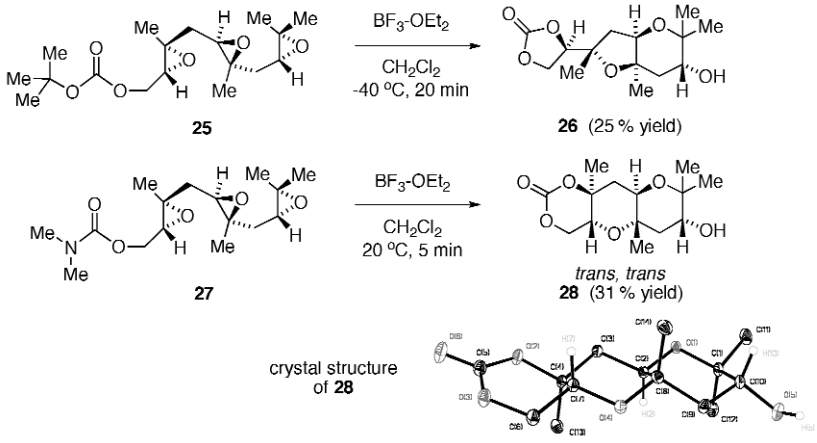
Fig. 4 Absolute stereochemistry of product indicates direction of polyepoxide cyclization.

The explanation for *endo*-mode regioselectivity is based largely on the hypothesis of thermodynamically favored formation of the epoxonium ion intermediate (i.e., **21**) from epoxide oxygen addition to a Lewis acid-activated terminal epoxide (i.e., **18**). The [4.1.0] epoxonium intermediate **21** is likely to be less strained than the [3.1.0] isomer (from initial *exo*-mode oxacyclization). We also established the importance of an alkyl substituent at the remaining epoxide carbon distal to the carbonate nucleophile, which could also be substituted by trimethylsilyl as a temporary regioselectivity directing group **18b** (Scheme 2) [10].



Scheme 2 Methyl or silyl substitution is required for regioselective *endo*-regioselectivity.

We then sought a similar synthetic approach to forming multiple pyran rings from the corresponding 1,4,7-triepoxides. In this case, we were surprised to observe different modes of regio- and stereoselectivity of the cyclization of **25**, evidenced by the formation of a *cis*-fused [4.3.0] bicyclic structure **26** connected to a five-membered cyclic carbonate. Notably, the desired regio- and stereochemical outcome was obtained only when the terminating nucleophile was changed from *tert*-butylcarbonate **25** to the *N*,*N*-dimethylcarbamate **27** (Scheme 3).



Scheme 3 Regioselectivity and stereospecificity of 1,4,7-triepoxide polycyclizations.

The higher nucleophilicity of the carbamate is attributed to react more quickly and in a synchronous manner through the internal epoxide into the activated epoxonium ion to give the *trans*,*syn*,*trans*-fused product **28** (Fig. 5). In the case of the carbonate, we propose that the strained nature of the [3.1.0] epoxonium ion **29** favors some separation in the ion pair **31** in the absence of a more active nucleophile, resulting in the loss of stereospecificity in the epoxide reaction step and giving the thermodynamically favored *cis*-fused intermediate **32** [11]. At this stage, the reaction is terminated by kinetically controlled *exo*-mode cyclization to provide the five-membered cyclic carbonate **26**.

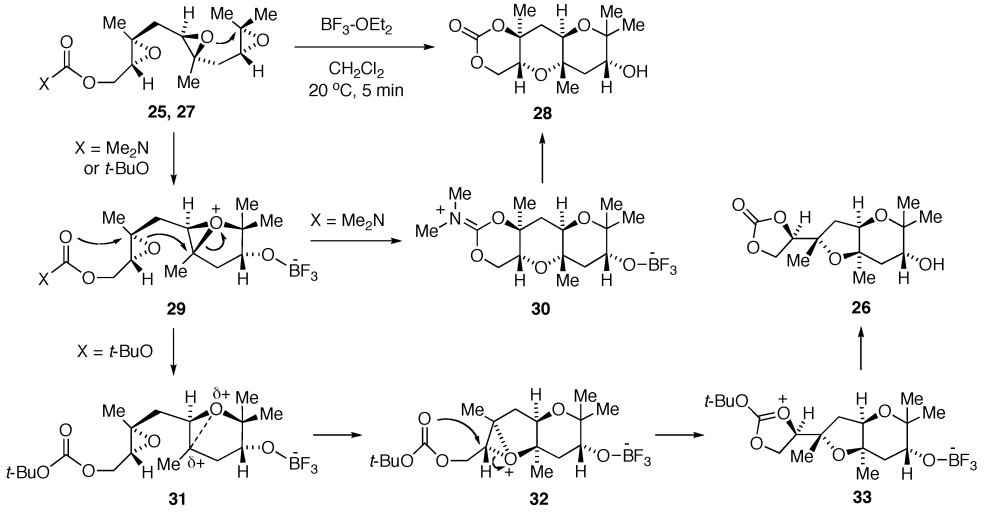
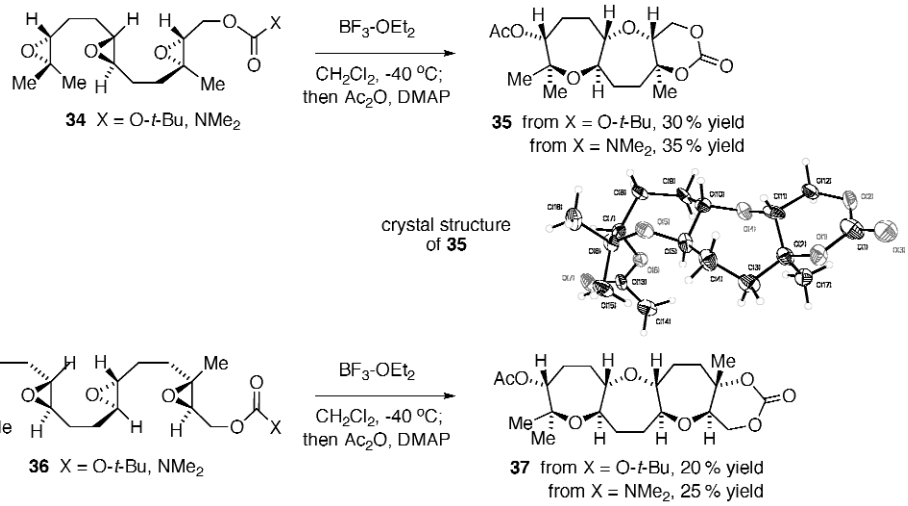


Fig. 5 Proposed mechanisms for stereo- and regioselective *endo*, *endo*, *endo*-oxacyclizations.

Although the yields for both pathways are modest, these products are the only major compounds produced in the tandem cyclization reactions. Furthermore, none of the *trans*,*syn*,*trans*-fused product **28** was observed from the reaction of the *tert*-butylcarbonate-terminated triepoxide **25**, nor was the five-membered cyclic carbonate *cis*-fused product **26** found from the reaction of the *N*,*N*-dimethylcarbamate-terminated substrate **27** [11].

The intriguing results regarding the possibility of synchronous polycyclizations of intermediates **29** to **30** suggested that there might be more flexibility in substituent effects than we had previously surmised, at least for internal epoxides if not either terminal epoxide. To this end, the tri- and tetraepoxides **34** and **36** were subjected to our cyclization protocol. We were pleased to observe that the triepoxide **34** gave reasonably good yield of a single cyclization product **35**, containing the fused bis-oxepane rings with only hydrogen substituents at both carbons of this ring fusion (Scheme 4), similar to the CD and DE rings of hemibrevetoxin and brevenal, respectively. This structural assignment was confirmed by crystallography of **35**. Likewise, the tetraepoxide **36** underwent cyclization to the tris-oxepane product **37**. The ^{1}H and ^{13}C NMR spectra of compound **37** were similar to those observed for the geranylgeraniol-derived product **13** with the exception of the additional hydrogens on the internal ether carbons and missing methyls. We observed the same products arising from *tert*-butylcarbonate and *N*,*N*-dimethylcarbamate polyepoxides, with slightly better isolated yields in the case of carbamate substrates [10].



Scheme 4 All *endo*-polycyclizations with disubstituted epoxides.

BIOMIMETIC SYNTHESIS OF TERPENOID NATURAL PRODUCTS

Along with our continuing work on polycyclic ethers and applications of the described methodology to fused polycyclic ether natural products hemibrevetoxin B (**2**) and brevenal (**3**), we have recently expanded our program to include terpenoid natural products which may arise from tandem cyclizations of polyepoxides including carbocyclization of alkene nucleophiles. A class of natural products which has attracted our attention are the abudinols A and B (**38** and **39**, Fig. 6), which were isolated from the Red Sea marine sponge *Ptilocaulis spiculifer*, indigenous to the Dahlak archipelago of Eritrea [12]. The abudinols were characterized in part by studying the products of ozonolysis of the tetrasubstituted alkenes, and the tricyclic compound nakorone (**41**), also found as a natural product from the same source, was also produced by ozonolysis of both abudinols A and B. The bicyclic ozonolysis product from abudinol A, durgamone (**40**), was also found as a natural product, but the oxepane-containing iso-

mer **42** from abudinol B was not reported as a naturally occurring compound. Norte has proposed that the biosynthesis of abudinol B from squalene tetraepoxide (**43**) may first involve formation of the tricyclic nakorone section by tandem reaction of both alkenes with two adjacent epoxides, giving 1,1-disubstituted alkene **44** from deprotonation of the methyl group in the course of cationic carbocyclization (Fig. 7). The bicyclic sector of **39** would then arise from tandem oxacyclization of the remaining two epoxides in **44**, terminated by alkene addition and deprotonation to form the tetrasubstituted alkene of **39** [13].

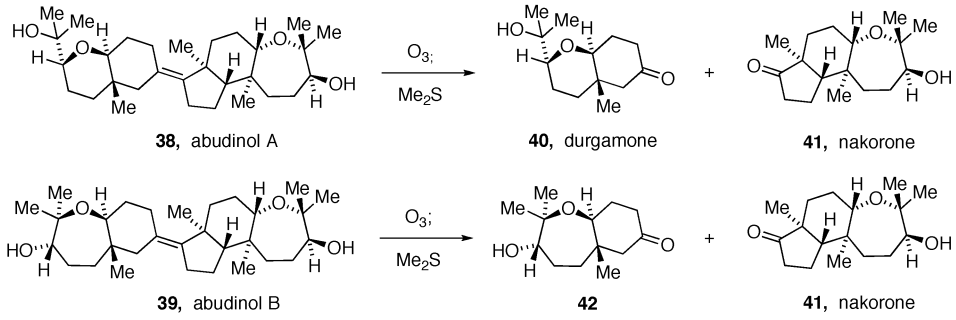


Fig. 6 Oxepanol-containing triterpene natural products.

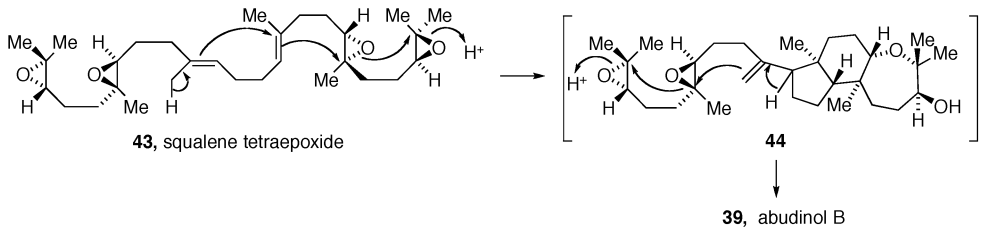


Fig. 7 Proposed biosynthesis of abudinol B (**39**).

Insightful studies on biomimetic polyene polycyclizations over several decades by the Johnson laboratory culminated in tandem cyclization of **45** to **46** (Fig. 8) in a synthesis of amyrin, wherein the optimal electrophile was cyclopentenyl cation, a fluorine substituent served as a temporary regioselectivity-guiding element, and the propargylic silane was demonstrated to be a superb nucleophilic terminator [14]. More recently, the Corey laboratory has demonstrated that enol silyl ethers can also serve as effective terminating nucleophiles for monoepoxide-initiated tandem carbocyclizations of **47** to **48**, as applied in the synthesis of scalarenedial [15].

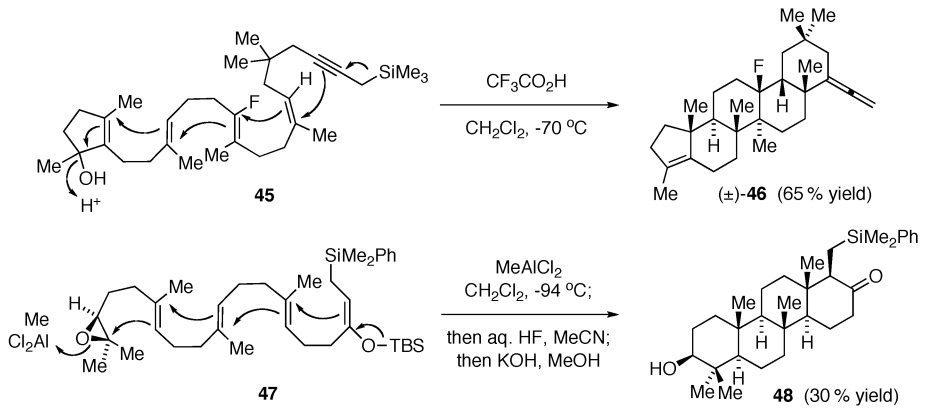
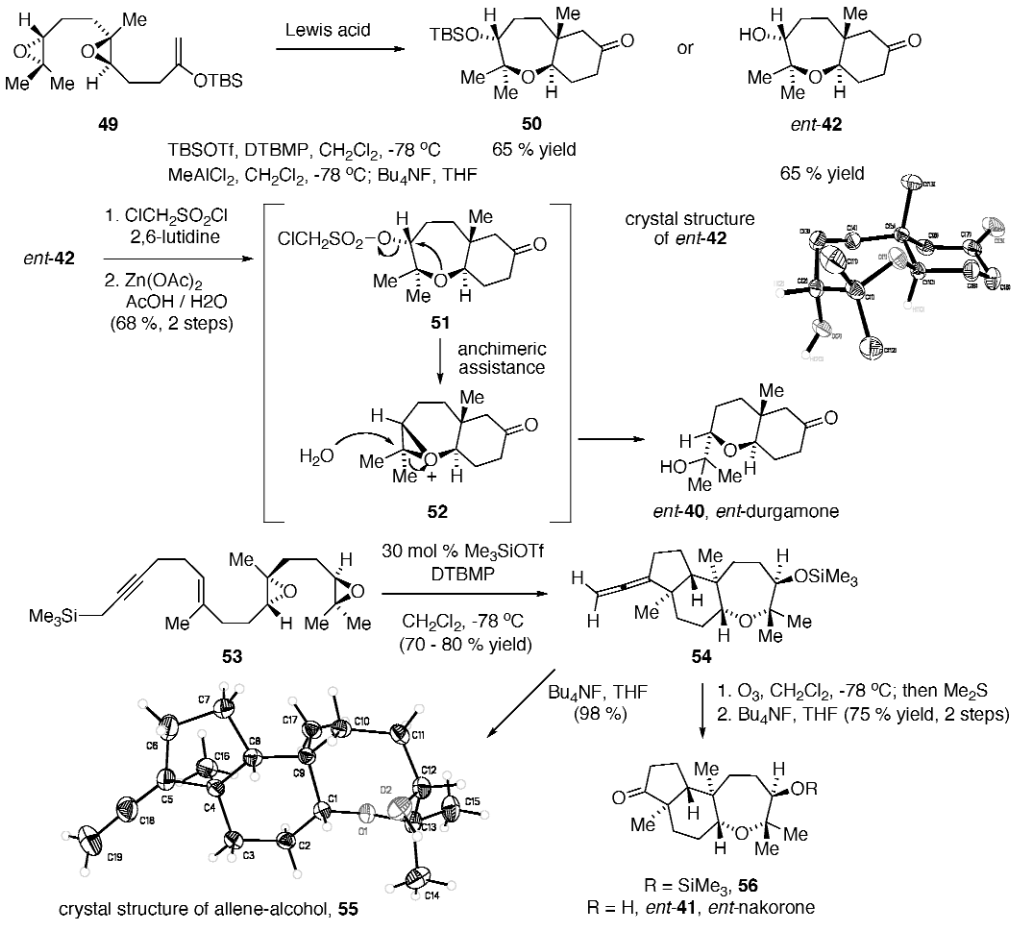


Fig. 8 Biomimetic polyene polycyclizations in synthetic chemistry.

With these encouraging precedents in mind, we sought to extend the biomimetic tandem cyclizations to diepoxides **49** and **53**, leading to the terminal oxepanol rings in *ent*-**42** and *ent*-**41** of abudinol B. Since the best currently available method for enantioselective epoxidation of alkyl-substituted alkenes utilizes a chiral ketone catalyst derived from D-fructose [16], we have initially chosen to prepare the enantiomers of the natural products nakorone and durgamone. The cascade of diepoxide oxacyclization terminated by carbocyclization with the enol silyl ether **49** (prepared in four steps from geranylacetone) provided compound **50** resulting from silyl group transfer, which could be deprotected to the secondary alcohol *ent*-**42**, whose structure was confirmed by crystallography (Scheme 5). The use of methylaluminum dichloride as the Lewis acid promoter gave mostly *ent*-**42** arising from direct loss of the silyl group, whereas TBSOTf in the presence of a bulky pyridine base afforded the silyl ether product **50** [17]. The secondary alcohol-oxepane moiety of *ent*-**42** could also be converted into *ent*-durgamone (*ent*-**40**), utilizing a ring-contraction variant of the Nakata rearrangement [18] of the secondary chloromesylate **51**. In similar fashion, the diepoxide-alkene **53** (prepared in five steps from farnesol), bearing Johnson's propargylic silane [14] as a nucleophilic terminator, underwent high-yield stereo- and regioselective tricyclization with silyl group transfer to provide the tricyclic allene **54**, which after desilylation to **55** was characterized by crystallography. Ozonolysis of the allene of **54** and desilylation of intermediate **56** provided the enantiomer of nakorone (*ent*-**41**) [17].



Scheme 5 Biomimetic synthesis of bicyclic substructure *ent*-**42** of *ent*-abudinol B, isomerization to *ent*-durgamone (*ent*-**40**), and synthesis of ent-nakorone (*ent*-**41**).

CONCLUSIONS

We have demonstrated that *trans*,*syn*,*trans*-fused polyoxepanes and polypyrans can be prepared by regioselective polyepoxide oxacyclizations. *Endo*-regioselectivity in the polyepoxide oxacyclizations generally requires alkyl (or trimethylsilyl) substitution at both terminal epoxides, and a carbonyl group as a terminating nucleophile, ideally carbamate, carbonate, or ester. The potential extension of this methodology to natural product synthesis is greatly enhanced by the observation that 1,2-disubstituted epoxides at internal positions are compatible with regioselective tandem cyclizations. Polyepoxide cyclizations can also be coupled with alkene reactants for potentially biomimetic carba- and oxacyclizations, featuring propargylic silanes and enol silyl ethers as terminating nucleophiles. We are currently engaged in completing the synthesis of abudinol B by cross-coupling methods to achieve the synthetic equivalent of "retroozonolysis" of the tetrasubstituted alkene.

Although these synthetic routes mimic reasonable biosynthetic hypotheses for these natural products, we emphasize that these hypothesis remains untested. However, our syntheses of polyene and polyepoxide precursors might be exploited to uncover biosynthetic pathways by feeding experiments with the natural product-producing organisms.

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