

Oxidative polycyclizations with rhenium(VII) oxides*

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Abstract: The consecutive oxidative polycyclization reaction with rhenium(VII) oxides represents a highly stereoselective synthetic tool by which polyenes that contain a bis-homoallylic alcohol can be transformed into poly-THF products in a single step. On the basis of a detailed study with model substrates, a set of rules is proposed to predict product configurations in the polycyclization reactions with trifluoroacetylperhenate. This methodology is exceptionally useful for the synthesis of polyoxygenated carbon skeletons that contain many stereogenic centers, and for the Annonaceous acetogenins in particular. Many of these potent antitumor agents, including solamin, reticulatacin, asimicin, bullatacin, trilobin, trilobacin, squamotacin, rolliniastatin, uvaricin, rollidecins C and D, mucocin, goniocin, and cyclogoniodenin T, as well as chemical libraries of non-natural analogs, were synthesized using the oxidative polycyclization reaction in combination with the Sharpless AD and AE reactions.

SYNTHETIC TARGET: ANNONACEOUS ACETOGENINS

The Annonaceous acetogenins [1] represent a rapidly growing family of natural products, which are known not only for their antitumor activity, but also for being potent antimalarial, immunosuppressive, pesticidal, and antifeedant agents [2]. More than 350 acetogenins have already been isolated from 37 species in the Annonaceae, a family of tropical trees and shrubs that accommodates over 2300 species [3]. While most of these fatty acid derivatives exhibit remarkable structural diversity, they share very similar carbon skeletons, with the main variations being the relative and absolute configuration of the various stereogenic oxygen functions. On the basis of the number and relative positioning of the tetrahydrofuran moieties within the molecule, these acetogenins have been classified into three subgroups (Fig. 1): the mono-THF (e.g., annonacin), the adjacent bis-THF (e.g., uvaricin), and the nonadjacent bis-THF acetogenins (e.g., trilobalacin). Rare acetogenins having more complex structures, including mucocin and goniocin, have been discovered in recent years.

The Annonaceous acetogenins have attracted intense synthetic activity in recent years [4]. The syntheses of such polyoxygenated structures, which contain numerous asymmetric centers, require synthetic methodologies that create carbinol centers with predictable stereochemistry. Our mostly used synthetic approach to these compounds is the “naked carbon skeleton” strategy [5], where most of the asymmetric centers are produced by selective placement of oxygen functions onto an unsaturated non-functionalized carbon skeleton. The versatility of this approach stems from the flexible choice of the

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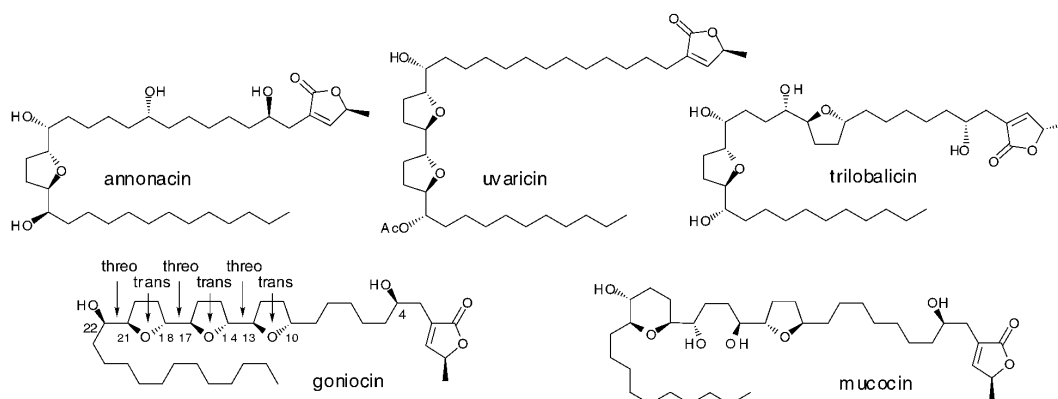
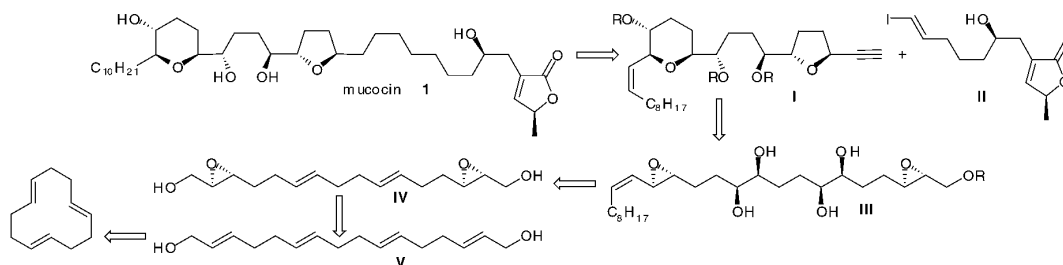


Fig. 1 Representative Annonaceous acetogenins.

appropriate carbon skeleton and from the use of three classes of synthetic tools: (a) methods that introduce new asymmetric centers, such as the Sharpless asymmetric dihydroxylation (AD) [6] and the asymmetric epoxidation (AE) [7] reactions; (b) methods that manipulate carbinol centers, such as the Mitsunobu-type alcohol epimerization reaction [8] and the Williamson etherification/ring closure reaction [9]; and (c) methods that involve chirality transfer, such as the oxidative cyclization [10] and polycyclization [11] with rhenium(VII) oxides. Here, we focus of the latter methodology and on its relevance to the asymmetric total synthesis of acetogenins.

Example 1: Total synthesis of mucocin

The potent antitumor agent, mucocin, **1**, which was isolated from leaves of *Rollinia mucosa* [12], was the first reported acetogenin that bears a hydroxylated THP ring along with a THF ring. As illustrated in our retrosynthetic analysis (Scheme 1), **1** could be constructed from two key building blocks, **I** and **II**. While **II** is relatively easy to synthesize using well-documented precedents, construction of **I**, which contains the THP and THF rings, including seven asymmetric carbon atoms, represents a nontrivial synthetic challenge. Our synthetic design was based on a key step in which two ring closure reactions convert the linear intermediate **III** to the bicyclic intermediate **I**. According to the Baldwin rules, the formation of a 6-membered ring via a 6-*endo* epoxide opening is disfavored in comparison with the alternative formation of a 5-membered ring [13]. Therefore, in our synthetic design we have used an alkenyl epoxide to revert the Baldwin regioselectivity and promote formation of a THP ring rather than a THF product.



Scheme 1 Retrosynthetic analysis of mucocin.

Our synthetic approach to **III** was based on a highly symmetrical starting material and an extensive use of the AD and AE reactions. We envisioned the synthesis of **III** in two major steps from skeleton **V** using first the AE reaction to epoxidize the two peripheral double bonds, affording **IV**, followed by double AD reaction to tetrahydroxylate the remaining two double bonds. The synthesis of **1** was indeed achieved following this plan with 20 steps from cyclododecatriene, thus confirming the proposed structure of this unusual acetogenin [14]. Demonstrating the power of the “naked carbon skeleton” strategy, all seven asymmetric centers in the key fragment of the molecule originated from the double AE and double AD reactions. The simultaneous closure of both THP and THF rings represent the key step of the synthesis.

Example 2: Chemical libraries of Annonaceous acetogenins

Taking into consideration the fact that only 37 out of 2300 Annonaceae species have been screened so far, one may conclude that isolation and full characterization of the entire naturally occurring repertoire of the Annonaceous acetogenins will require a formidable effort. The urgent need for a comprehensive biological screening of such compounds led us to the design of synthetic approaches to chemical libraries of stereoisomeric acetogenins [5,15].

A dominant structural feature that appears in more than 40% of the Annonaceous acetogenins, particularly in those showing the highest antitumor activity, is a linear 10-carbon skeleton that comprises two adjacent THF rings flanked by two hydroxyl groups. Having six stereogenic carbinol centers, this unit alone may appear in the form of as many as 64 stereoisomers. To date, only few diastereomers of this fragment have been identified in naturally occurring bis-THF acetogenins (Fig. 2). We have developed efficient methodologies to produce all possible stereoisomers [15]. One approach to a 32-member library is demonstrated here by the first total synthesis of trilobacin.

Using the advantages of a convergent strategy we started with two fragments, each containing two stereogenic centers; one is a phosphonium salt and the other is an aldehyde. Referring to the structures shown in Fig. 2, the phosphonium salts **3a–d** and aldehydes **5a–d** (Scheme 2) contain stereogenic centers that are destined to become carbons 23–24, and 15–16, respectively, in the target molecules. All of these compounds were prepared in very high ee using the AD reaction with alkenes **2** and **4**, respec-

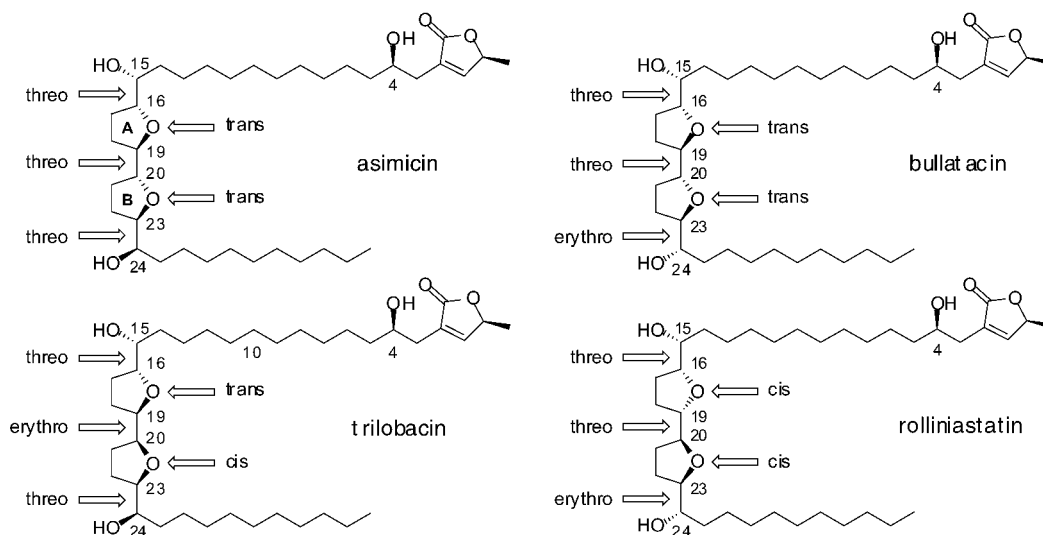
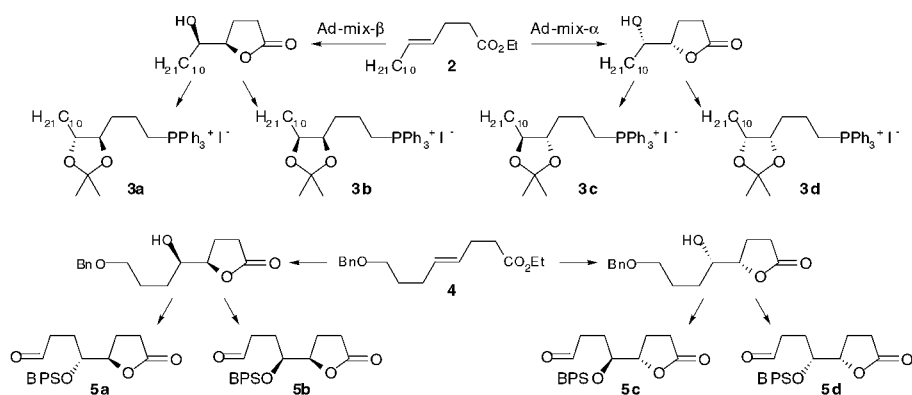


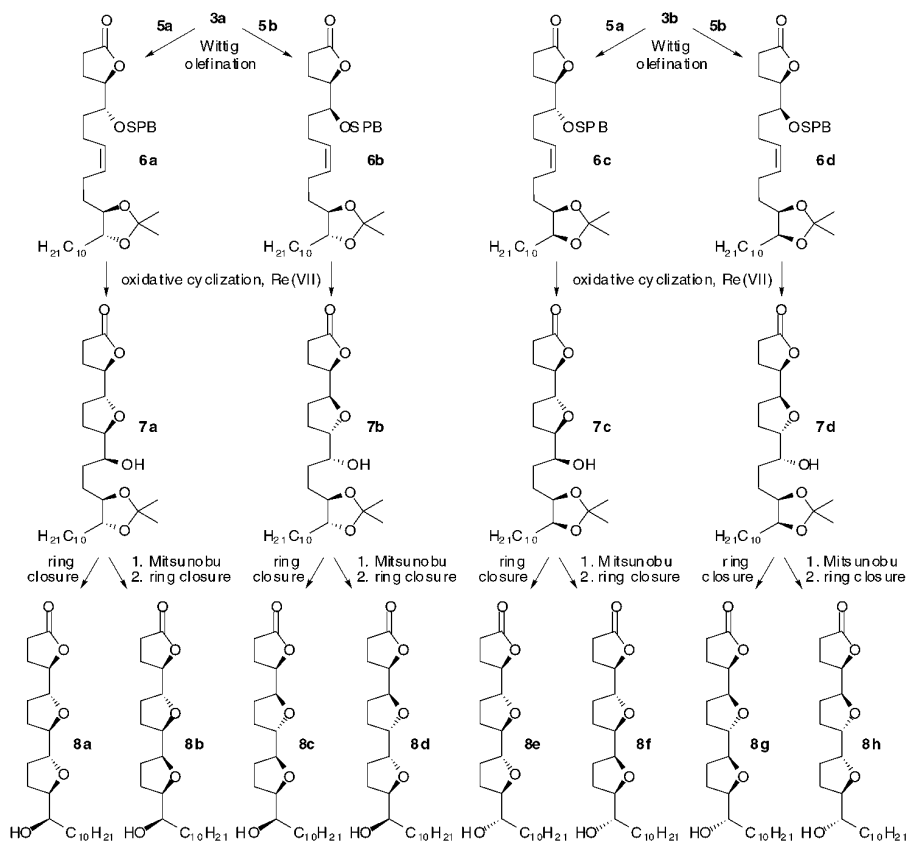
Fig. 2 Adjacent bis-THF acetogenins.



Scheme 2 Building blocks for combinatorial library of adjacent bis-THF acetogenins.

tively. For example, reaction of **2** with AD-mix- β produced the (*R,R*) hydroxylactone in 96% ee (>99.5% ee after recrystallization). The latter was converted to either (*R,R*) phosphonium salt, **3a**, or, using the Mitsunobu inversion, to the (*4R,5S*) diastereomer, **3b**.

Coupling of all four Wittig reagents **3a–d** with the four aldehydes **5a–d** can produce 16 stereoisomeric *Z*-alkenes. We demonstrated this strategy by the synthesis of four alkenes, **6a–d** (Scheme 3).



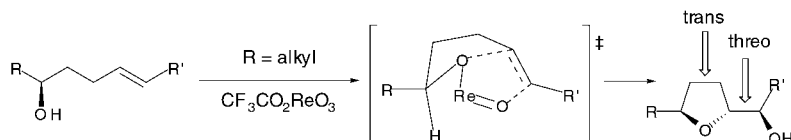
Scheme 3 Synthesis of eight representative bis-THF stereoisomers.

Oxidative cyclization with Re_2O_7 /lutidine afforded the corresponding *trans*-substituted tetrahydrofurans **7a–d**. Conversion of **7a** to the corresponding mesylate followed by acid-catalyzed acetonide-cleavage and ring closure produced the tricyclic lactone **8a**. Alternatively, Mitsunobu inversion of the free alcohol's configuration within **7a**, prior to its mesylation and ring-closure, gave rise to lactone **8b**. All other isomers of **8** were obtained in the same way from the corresponding isomers of **7**.

Altogether, using two diastereomeric Wittig reagents, **3a** and **3b**, and two diastereomeric aldehydes, **5a** and **5b**, we have synthesized eight diastereomers of **8a–h**. Consequently, combinatorial coupling of **3a–d** with **5a–d** should create a library of 32 out of the 64 possible stereoisomeric skeletons, four of which are shown in Fig. 2. For example, compounds **8a**, **8b**, and **8e** represent the precursors of asimicin, trilobacin, and bullatacin, respectively. We have demonstrated this potential by the first total synthesis of trilobacin, which exhibits two unusual features structural: an *erythro* junction between the two adjacent THF rings and a *cis* stereochemistry in the B ring. Trilobacin was easily prepared from lactone **8b**.

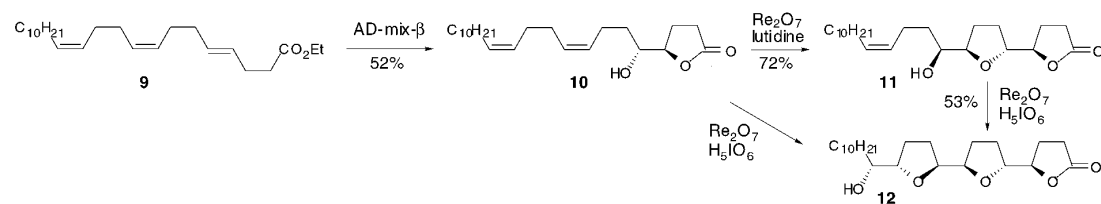
Discovery of the tandem oxidative cyclization with Re(VII)

Early work by Kennedy on the oxidative mono-cyclization reaction with bis-homoallylic alcohols and Re(VII) reagents has suggested that the stereochemical course of this reaction leads consistently to *trans*-THF products [10]. This stereochemistry could reflect a mechanism that involves initial coordination of the metal to the hydroxyl group followed by 3+2 addition via a 5-membered transition state (Scheme 4) in which the alkyl group R has a high preference to take a less sterically demanding pseudo-equatorial position, leading to a *trans*-THF ring. We have confirmed this general rule in our early studies [11,15,17] and similar results were also reported by McDonald [18]. This ligand-assisted oxidative cyclization with Re_2O_7 , features two major advantages: high effective molarity of the oxidant and high regio- and stereochemical control.



Scheme 4

We reasoned that the functional similarity between the starting material and the product (both having one free hydroxyl group) could provide an attractive opportunity to generate many asymmetric centers in a single step via tandem oxidative cyclizations of polyolefins. To check this idea we synthesized the *Z,Z,E* triene **9** and treated it with AD-mix- β to produce the hydroxylactone **10**. Indeed, reaction of **10** with a mixture of Re_2O_7 and 2,6-lutidine afforded the monocyclized product, **11** (Scheme 5). Treatment of the latter with the more reactive mixture, Re_2O_7 (2 equiv) and H_5IO_6 (3 equiv) in dry dichloromethane for 1 h affected the second oxidative cyclization, producing compound **12** in 53% yield. Both cyclizations could be carried out in a single step by treatment of dienol **10** under the latter conditions for 2 h, to produce the bis-THF product, **12**, in 25% yield. Even under these conditions the



Scheme 5 The first demonstration of oxidative polycyclization with Re(VII).

first cyclization was approximately one order of magnitude faster than the subsequent one, offering a synthetic advantage of stopping the reaction after the first step if desired. This differential activity could mirror inhibition by the polyoxygenated product, which, by functioning as a polydentate ligand could inhibit further coordination of rhenium to the next olefinic bond. 2,6-Lutidine also inhibits the reaction, probably by occupying several coordination sites on the metal.

Apparently, this oxidation with Re(VII) is far more selective than with Cr (VI) oxides, which is incompatible with primary and secondary alcohols either in the starting material or in the product, and may even degrade the carbon skeleton [19]. Both reagents originally used by Kennedy, i.e., Re_2O_7 /lutidine and $\text{Re}_2\text{O}_7/\text{H}_5\text{IO}_6$ in dichloromethane, are useful for monocyclization with simple substrates possessing one double bond. However, for double cyclization with substrates containing two double bonds, only the more reactive mixture, $\text{Re}_2\text{O}_7/\text{H}_5\text{IO}_6$, was found to be effective.

This preliminary study had shown that merging the excellent enantioselectivity of the osmium-based AD reaction with the high relative stereoselectivity of the Kennedy's rhenium-based oxidative cyclization technique creates a powerful methodology for asymmetric synthesis of polyoxygenated aliphatic structures, with immediate applications in the Annonaceous acetogenin family. In fact, both compounds **9** and **10** are useful intermediates for synthesis of naturally occurring acetogenins, and bis-tetrahydrofuranoid ones in particular. Our attempts to use this approach for the synthesis of goniocin are described below.

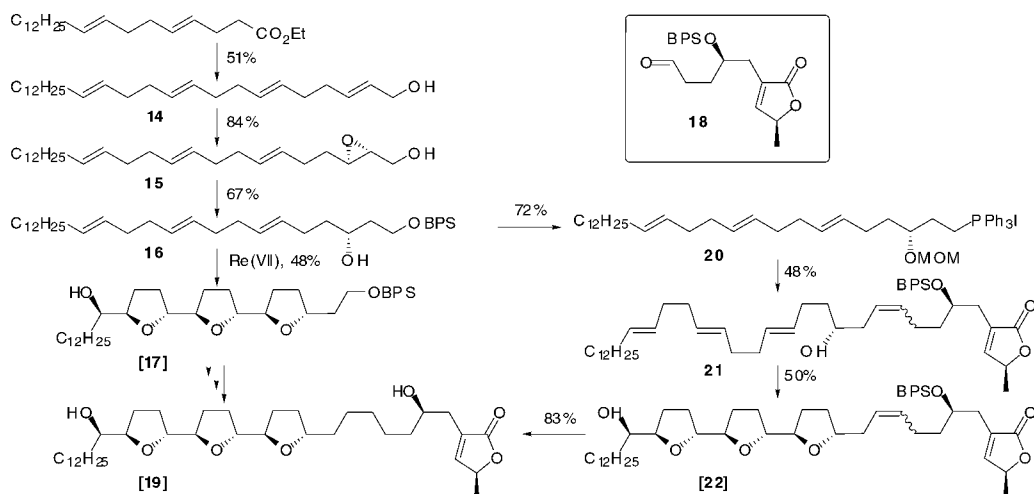
Stereochemistry puzzles in the tandem oxidative cyclization

Goniocin, **13** (Fig. 3), which has been recently isolated from *Goniothalamus giganteus* [20], possesses three adjacent THF rings and, therefore, represents the first example of a new subclass of Annonaceous acetogenins. Structure **13** was proposed on the basis of its MS and ^1H and ^{13}C NMR data [20]. Clearly, construction of the tris-*trans*-THF fragment I with the appropriate configuration of the seven stereogenic carbinol centers represents the main challenge in the synthesis of the molecule. Our previous findings that two consecutive oxidative cyclizations with 4,8-dienols can be carried out in a single step to produce bis-THF derivatives suggested that the tris-THF acetogenin goniocin could be synthesized from a 4,8,12-trienol substrate using the tandem oxidative cyclization methodology. Thus, we planned to use the single stereogenic center in **16** as the only source of chirality at the tris-THF fragment and achieve the other six stereogenic carbinol centers by a tandem oxidative cyclization reaction using a Re(VII) reagent [21].

The key intermediate in our synthesis (Scheme 6) was the "naked" carbon skeleton, **14**, which was easily prepared from (*E,E*)-ethyl heneicosa-4,8-dienoate [22]. Asymmetric epoxidation using $\text{Ti}(\text{OPr})_4$ and (-)-DIPT produced epoxy alcohol **15** in more than 95% ee. Reductive cleavage of the epoxide ring using Red-Al affords the 1,3-diol, which was then monoprotected at the primary position to give the silyl ether **16**.

Initially, we used the $\text{Re}_2\text{O}_7/\text{H}_5\text{IO}_6$ mixture for the triple cyclization with **16**. Yet, although this reagent did produce some tris-THF product, the reaction conditions were probably too acidic to be compatible with the silyl protecting group. Therefore, we examined various alternative perrhenate reagents, including the Wilkinson's mononuclear perrhenate complex [23] trifluoroacetylperhenate ($\text{CF}_3\text{CO}_2\text{ReO}_3$), which has been used by McDonald for oxidative cyclization [18]. Thus, when trienol **16** was treated with a mixture of $\text{CF}_3\text{CO}_2\text{ReO}_3$ and trifluoroacetic anhydride, a stereochemically pure tris-THF product, **17**, was isolated in 48% yield. However, to our surprise the ^1H and ^{13}C NMR data of this product did not match the expected characteristics of the *trans-threo-trans-threo-trans-threo* goniocin. Compound **17** was converted to the corresponding phosphonium salt in a four-step sequence and then coupled via a Wittig reaction with aldehyde **18**, leading to the final compound **19**. Again, the spectral properties of **19** did not match completely those of the naturally occurring goniocin, **13**.

In the above-described synthesis of **19**, we placed the triple-cyclization step at an early stage of the synthetic scheme, before the attachment of the butenolide fragment. Alternatively, since the tandem



Scheme 6 Total synthesis of **19**. The square brackets indicate incorrect structure.

oxidative cyclization reaction is compatible with many functional groups, it could be carried out in a much later stage, after the completion of the molecular carbon skeleton. To check this possibility, we converted trienol **16** to the phosphonium salt **20** and then coupled it with aldehyde **18** to produce compound **21**. The latter tetraenol represented an interesting substrate for the tandem oxidative cyclization reaction because it was far more complex than substrate **16** in terms of both molecular size and number of functional groups that could potentially bind the rhenium metal. Moreover, substrate **21** provided an interesting opportunity to examine the relative reactivity of the rhenium reagent toward homoallylic and bis-homoallylic alcohols, as the secondary carbinol center in **21** is both homoallylic and bis-homoallylic. Nevertheless, cyclization with trifluoroacetyl perrhenate and trifluoroacetic anhydride took place exclusively at the bis homoallylic site, producing the tris-THF intermediate **22** in 50% yield. This was a remarkable observation, considering the fact that six new stereogenic centers were formed in a single transformation with very high diastereoselectivity, to produce a compound that was only two steps away from the final target molecule. Indeed, hydrogenation and deprotection of **22** afforded **19**. Again, although the samples of **19** obtained by the two synthetic routes were identical with one another they did not match the spectral data of natural goniocin, **13**.

Solving two puzzles: Synthesis of goniocin, cyclogoniocin T, and 17,18-bisepi-goniocin

The observation that our synthetic product, **19**, did not match the spectral data of the naturally occurring goniocin, **13**, was not the only puzzle related to this compound. From a biosynthetic standpoint, the assigned structure of goniocin was remarkable, due to the fact that in almost all of the other structurally related acetogenins isolated from *Goniohalamus giganteus* to date, C-10 was assigned an (*R*) configuration [24]. This biogenetic issue recently became even more intriguing when goniocin, **23**, was isolated from the same plant (Fig. 3) [25]. The structure of **23** was found to be closely related to that of goniocin. In fact, nonstereoselective epoxidation of **23** with *m*-CPBA followed by acid-catalyzed ring closure afforded two new stereoisomers of goniocin [25]. One of them, **24**, containing an all-*trans* tris-THF structure, was named cyclogoniocin T and the other cyclogoniocin C, **25**. It has been reported that goniocin and **24** were different from one another on the basis of the ¹H and ¹⁹F NMR spectra of their Mosher's esters. Yet, their biological activity was found to be similar. Hence, before drawing any further conclusions from a seemingly extraordinary biogenetic event, where two struc-

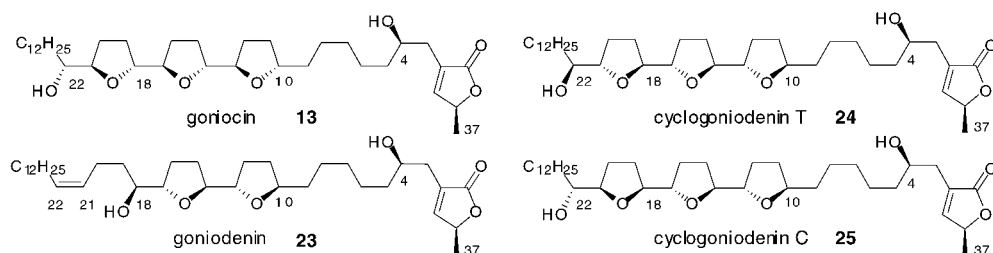
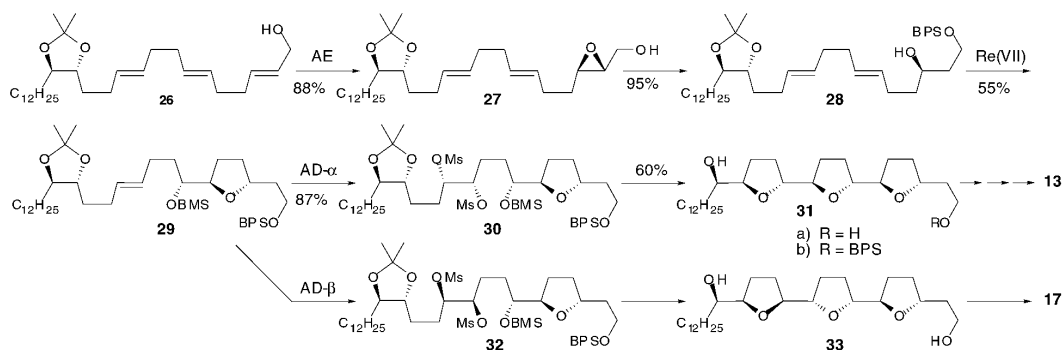


Fig. 3 Acetogenins of *Goniothalamus giganteus*.

naturally similar but stereochemically very different natural products, **13** and **23**, coexist in the same plant, it became necessary to verify their absolute configuration by total synthesis. We decided to synthesize both isomers **13** and **24**.

Clearly, the main challenge in the synthesis of **13** and **24** is the construction of the *trans*-tris-THF fragment with the appropriate configuration of the seven stereogenic carbinol centers. Since the stereochemistry of the oxidative cyclization reaction with trienols was in question we employed alternative synthetic methods, including the AD and AE reactions as well as the Williamson etherification reaction (Scheme 7).

We started the synthesis of **13** with trienol **26** which was obtained from ethyl heptadec-4-enoate using AD- β followed by a sequence of reactions similar to those described above [21]. Asymmetric epoxidation of **4** using (–)-DET produced epoxide **27** in more than 95% ee. Reductive cleavage and mono-silylation afforded **28**. Oxidative cyclization of the latter with CF₃CO₂ReO₃ and lutidine produced the *trans*-THF derivative, whose spectral characteristics were found to be very similar to those of other *trans*-THF analogs. Protection of the free hydroxyl group as a *tert*-butyldimethylsilyl (BMS) ether afforded **29**. Asymmetric dihydroxylation of **29** using AD-mix- α followed by double mesylation produced **30**. Acidic cleavage of the acetonide and the silyl ethers followed by heating of the resultant tetrol in pyridine produced the desired all-*trans* tris-THF diol **31**. The primary alcohol was protected in the form of a BPS ether and the secondary alcohol in the form of a MOM ether. The silyl ether was then hydrolyzed, and the resultant primary alcohol was converted to an iodide and then to a phosphonium salt. The latter was converted to the corresponding Wittig reagent and then reacted with aldehyde **18** to produce an alkene. Finally, catalytic hydrogenation and deprotection of both MOM and BPS groups afforded goniocin, which was found to be identical with the naturally occurring compound, **13**.

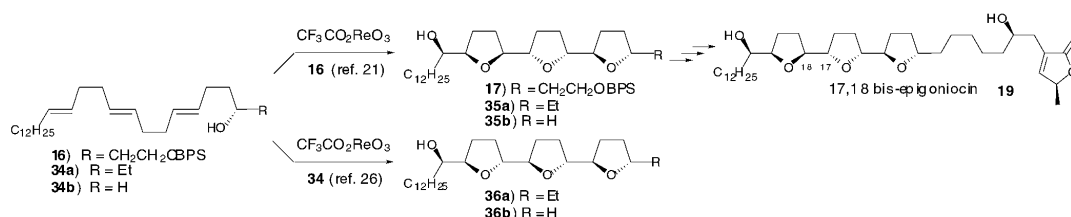


Scheme 7 Total synthesis of goniocin, **13**.

Cyclogonioidenin-T, **24**, was synthesized using the same scheme used for the synthesis of **13**, except enantiomeric reagents were employed for the AE and AD reactions, producing the enan-

tiomeric form of **31**. The synthesis was completed as described in Scheme 7 to give **24**. As both the ^1H and ^{13}C NMR spectra of **13** and **24** are virtually indistinguishable from one other, the absolute stereochemistry of these synthetic compounds were proven by comparison of the ^1H NMR spectra of their (*R*) and (*S*) bis Mosher esters with the original spectra of the esters of the naturally occurring **13** and the semisynthetic **24**. Thus, the first total syntheses of these compounds confirmed their proposed absolute configurations. It is remarkable that the two nearly enantiomeric natural products, **13** and **23**, occur in the same plant. Although the coexistence of both enantiomers of simple natural products having one or two asymmetric centers have been reported, there are very few such cases with more complex structures.

With this biosynthetic puzzle being resolved, we turned our attention to the questionable stereochemistry of compound, **19**, the product of the oxidative tricyclization with Re(VII). The unprecedented possibility that oxidative cyclization reactions did not produce all *trans*-THF products was quite surprising. Furthermore, what we discovered was inconsistent with the findings of an independent study by McDonald who reported that the reaction of very similar trienol substrates, **34a** and **34b**, with the same oxidant, $\text{CF}_3\text{CO}_2\text{ReO}_3$, afforded the all-*trans* products, **35a** and **35b**, respectively [26]. Considering the immense synthetic importance of the tandem oxidative polycyclization reaction, we felt that the discrepancy between McDonald's results and ours had to be resolved.



Scheme 8 Contradicting reports on stereochemistry in the oxidative triple cyclization reaction.

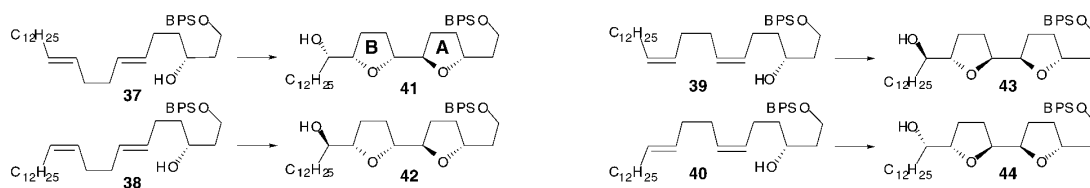
On the basis of a systematic study we discovered that the correct relative stereochemistry of the only isolatable triple cyclization product **17** was *trans-threo-cis-threo-cis-threo* and not the one that was intuitively expected, *trans-threo-trans-threo-trans-threo*. The relative and absolute stereochemistry of **17** were elucidated by carrying out the reaction in a stepwise manner, isolating the mono- and bis-THF products, so the configuration of each intermediate could be determined independently. Their structure was determined on the basis of their ^1H NMR spectral data as well as the spectra of their (*R*) and (*S*) Mosher's esters. The structure of **17** was further corroborated by 2D ^1H - ^1H COSY, TOCSY, and ROESY experiments with the bis-benzoate ester of **17**. Finally, we prepared both compounds **17** and **31a** by independent asymmetric synthesis using the AD reaction [27]. These experiments confirmed unequivocally that the tris-THF product obtained by the tandem oxidative cyclization of **16** was **17** and not **31a**. This finding suggested that compound **19** described in Scheme 6 was in fact 17,18-*bisepigoniocin* (Scheme 8). We also prepared compounds **36a** and **36b** by independent synthesis and compared their spectral properties with the original spectra kindly provided by McDonald. This comparison revealed that the correct structures of the compounds reported in ref. 26 was also **35a** and **35b**, respectively, and not **36a** and **36b**.

Establishing stereoselectivity rules for the tandem oxidative polycyclization reaction

The above-described observation that *trans,trans,trans*-trienols **16** and its analogs underwent stereoselective triple cyclization to give a *trans,cis,cis*-tris-THF product was quite intriguing considering our previously reported observations with a *cis,cis* (4,8)-dienol substrate that afforded *trans,trans*-bis-THF product [11]. Apparently, the relative configuration of the resultant THF rings strongly depends on the

configuration of the vicinal oxygen functions formed in previous cyclizations, which arises from the geometry of the double bonds in the polyenol substrate.

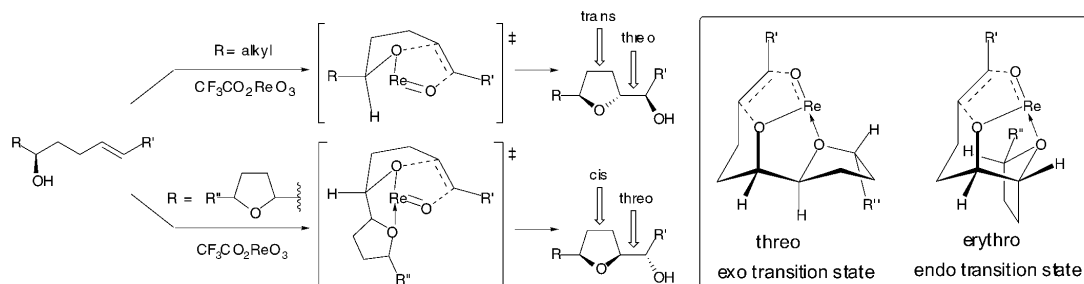
To further understand the stereochemical relationship between the polyenol substrates and the poly-THF products of this reaction and to allow its use in a predictable way we carried out a systematic study with several substrates. Four dienol substrates **37–40** were prepared and subjected to the tandem oxidative bis-cyclization reaction with trifluoroacetyl perrhenate ($\text{CF}_3\text{CO}_2\text{ReO}_3$). The only isolatable products were **41–44** (Scheme 9), which were obtained in 40–48% yield. We used both NMR spectroscopy and independent asymmetric synthesis to determine the stereochemistry of products. For example, the structure of compounds **41–43** was determined on the basis of 2D 1H-1H COSY, TOCSY, and ROESY of their bis-nitrobenzoate derivatives. This analysis clearly indicated that the B-ring is *cis* in **41** and **42** and is *trans* in **43**. The structure of **44** was determined by an independent synthesis starting with compound **37**. Compound **43** was converted to **44** in two steps, reinforcing our NMR structure determination of **43**.



Scheme 9 Tandem oxidative dicyclization reactions with $\text{CF}_3\text{CO}_2\text{ReO}_3$.

On the basis of the stereochemical relationships between **37–40** and **41–44** as well as our previously reported results we proposed a set of stereochemical rules for the tandem oxidative cyclization reaction with $\text{CF}_3\text{CO}_2\text{ReO}_3$. While the first THF ring is always produced with *trans* configuration, the subsequent rings are stereoselectively formed with either *trans* or *cis* configuration, depending on the relative configuration of the two vicinal oxygen functions formed in the first cyclization. With a *threo* relationship (formed from an *E*-alkene in the first cyclization), the next cyclization produces a *cis* THF ring and with an *erythro* relationship (formed from a *Z*-alkene in the first cyclization), the next cyclization produces a *trans* THF ring.

These rules reflect a dramatic change in the stereochemical course of the tandem oxidative cyclization reaction when proceeding from the first cyclization to the subsequent ones. A plausible explanation for this phenomenon arises from the ability of the newly formed THF ring to chelate the Re atom during the next oxidative cyclization. As illustrated in Scheme 10 (top), in the first cyclization step, the noncoordinating alkyl group has a high preference to take a less sterically demanding pseudoequatorial position in the proposed 3+2 transition state (**I**) [16], leading to a *trans*-THF ring.

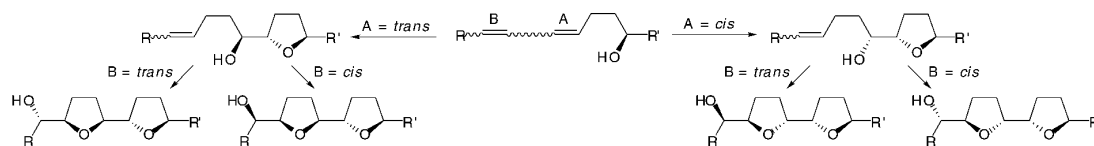


Scheme 10 Plausible transition states for the oxidative cyclization with Re(VII) .

However, in cases where the group R possesses a potential coordination site, the substrate may become a bidentate ligand to rhenium. In that case a pseudoaxial position would be energetically preferred in the transition state (**II**), leading to a *cis*-THF ring. Nevertheless, the coordinating efficiency of this bidentate ligand depends on the relative configuration of the two oxygen functions. With a *threo* relative configuration the reaction proceeds via a sterically favored *exo*-type transition state, **II-T**. By contrast, the *erythro* configuration requires a sterically disfavored *endo*-type transition state, **II-E**, rendering the nonchelated structure, **I**, energetically more favorable.

Applying the stereoselectivity rules in the total synthesis of Rollidecins C and D

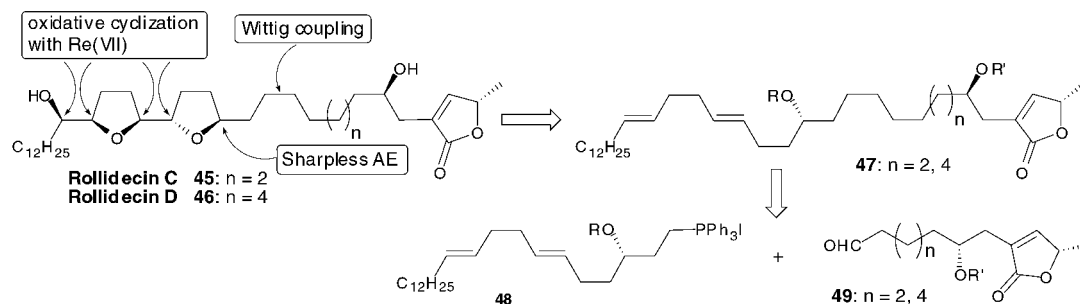
The above-described rules of predicting the product configuration in the oxidative polycyclization reactions with trifluoroacetylperhenate are illustrated graphically in Scheme 11. Since the two oxygen atoms add to the double bond in a *syn* fashion, the relative configuration of the resultant pair of vicinal carbinol centers depends on the double bond geometry: a *cis* double bond leads to an *erythro* diol and a *trans* double bond leads to a *threo* diol. Therefore, any desired absolute stereochemistry can be achieved by the appropriate choice of a double bond geometry and absolute configuration of the bis-homoallylic alcohol in the substrate.



Scheme 11 Rules for predicting the stereochemistry in oxidative polycyclization with trifluoroacetylperhenate.

These rules have been applied in the total synthesis of two homologous acetogenins, rollidecin C, **45**, and rollidecin D, **46**, which were discovered in the bioactive leaf extracts of *Rollinia mucosa* [28]. Both compounds have exhibited cytotoxicity against six human tumor cell lines with some selectivity toward the colon cell line HT-29. Their structure was assigned mainly on the basis of ¹H (1D and 2D) and ¹³C NMR spectroscopy and MS analysis [28]. These are typical adjacent bis-THF acetogenins with an exception that they have only one hydroxyl group flanking the bis-THF moiety.

Our retrosynthetic analysis of **45** and **46** (Scheme 12) dissects the target molecules into two major fragments, the butenolide portion, which contains two asymmetric carbinol centers, and the bis-THF fragment, which contains additional five asymmetric centers. We designed a general synthetic approach that is suitable not only for the two target compounds, but also for many of their stereoisomers. We anticipated that the introduction of both THF rings could be achieved in a single step at the final stages



Scheme 12 Retrosynthetic analysis of rollidecin C and D.

of the synthesis by a Re(VII)-mediated oxidative cyclization of a bis homoallylic dienol, **47**. The expected product could be only two simple steps (hydrogenation and deprotection) away from the target molecule. Intermediate **47** could be obtained by Wittig olefination using the phosphonium salt **48** and aldehyde **49**. Compound **48** could be prepared by the Sharpless AE reaction followed by reductive cleavage of the resultant epoxide [21]. The rules of stereoselectivity in the tandem oxidative polycyclization with $\text{CF}_3\text{CO}_2\text{ReO}_3$ have been applied here and the total syntheses of **45** and **46** were achieved in 13 steps with 5.2% overall yield; and in 12 steps with 2.9% yield, respectively [4].

CONCLUSION

The stereoselectivity rules for the oxidative polycyclization with Re(VII) together with the predictable stereoselectivity of the AD and AE reactions enabled the total syntheses of many acetogenins, including solamin, reticulatacin, asimicin, bullatacin, trilobacin, trilobin, uvaricin, squamotacin, rolliniastatin, rollidecins C and D, goniocin, 17,18-bis-epigoniocin, cyclogniodenin T, and mucocin, as well as chemical libraries of non-natural acetogenins [5a,14,15,17,22,29].

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