Cascading pericyclic reactions: building complex carbon frameworks for natural product synthesis

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Tandem reactions have emerged as powerful strategies to synthesize complex structures, in particular, processes involving pericyclic reactions. This article describes recent advancement by our group in the development of novel tandem pericyclic reactions aimed at constructing diterpene frameworks.

Introduction

The quest to develop methods for the assembly of complex carbon frameworks quickly and efficiently has long been a challenge and goal for synthetic organic chemists. One of the driving forces for the development of these methods is their application to the total synthesis of natural products, the majority of which have a carbon skeleton which forms the backbone of the molecule.

Recent years have seen the emergence of tandem reactions as a powerful tool to construct complicated molecular scaffolds. In the literature there are reports involving the terms tandem, domino or cascade reactions where the reactions were performed separately. In our opinion, these are not tandem processes but rather sequential reactions. Tandem or domino reactions can be defined as two or more distinct chemical transformations that occur in quick succession in the same reaction vessel. If the reactions involve a sequential addition of reagents, part of these reagents must be embedded in the final product in order to be considered a tandem reaction. For instance, the 1,4-addition of an organocuprate to an enone followed by the enolate trapping with an electrophile to give the corresponding α,β-substituted ketone is considered a tandem reaction. Not only can reactions of this sort quickly assemble non-trivial carbon skeletons, they also offer an atom-economy not observed with single-step processes, inherent to this also being a notable minimization of waste produced in the given process.

The use of cascading reactions in organic chemistry, either by chance or design, is not a new concept, and many excellent reviews have been published on the subject.[1] Despite the abundance of reaction combinations, pericyclic reactions occurring in cascade constitute one the most fascinating transformations. One might consider that the concerted nature of pericyclic reactions render them particularly attractive due to the relative ease of predicting the stereochemical outcome of the final product. Undoubtedly, this represents a true advantage when considering the elaboration of complex carbon frameworks bearing multiple stereogenic centers. For example, Nicolaou *et al.*'s synthesis of endiandric acid B (**3**) constitutes probably one of the most spectacular tandem pericyclic reaction transformations reported in the literature (Scheme 1).[2,3] Upon heating, polyene **1** was converted to endiandric B methyl ester **2** in a single operation.

In the past decade, tandem pericyclic reactions have gained in popularity, particularly in the biomimetic synthesis of complex natural diterpenes.[1a] In fact, numerous clever transformations were reported, demonstrating the power and the usefulness of these tandem processes. This account will outline the recent progress in this field, having a focus on our contributions that we have made since 2000 at the University of Ottawa.

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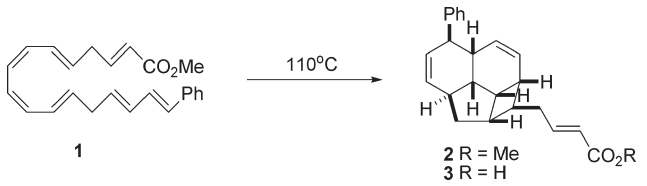
Steve Arns was born in St. John's, Newfoundland, Canada, in 1980 and received his BSc (chemistry) in 2003 at Memorial University of Newfoundland. Since then he has been working under the guidance of Professor Louis Barriault, engaged in the synthesis of several natural products using the oxy-Cope–Claisen–ene reaction. He has been awarded both NSERC PGS-A and PGS-D postgraduate scholarships.

Louis Barriault was born in Armagh, Québec, Canada, in 1970. He received his BSc (chemistry) in 1993 at the University of Sherbrooke. He pursued his PhD studies under the supervision of Professor Pierre Deslongchamps at the same institution. After completing his doctorate in 1997, he joined the group of Professor Leo A. Paquette at the Ohio State University (OSU) as a FCAR postdoctoral fellow where he completed the total synthesis of (−)-polycavernoside A. In May 1999, he accepted a position as Assistant Professor at the University of Ottawa where he has been promoted to Associate Professor (2003). Professor Barriault's research involves the development of novel strategies using tandem pericyclic reactions to construct complex bioactive natural products. Recently, Professor Barriault received the John Polanyi Award in Chemistry (2000), Premier's Research Excellence Award (2002), Ottawa Life Science Michael Smith Award (2002), Boehringer Ingelheim Young Investigator Award (2002), University of Ottawa young researcher of the year (2005), University of Ottawa excellence in education award (2005), Merck Research Laboratory academic development award (2006) and was appointed University Research Chair in Synthetic Organic Chemistry (2006).



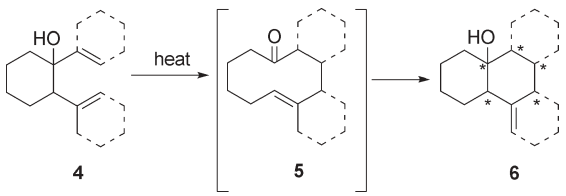
Scheme 1 Synthesis of endiandric acid B.

Results and discussion

Our group has long been interested in using various cascading pericyclic reactions to access complicated carbon frameworks. Our long term goal is to use these processes to fabricate various carbon skeletons which correspond to the cores of various natural products, culminating in their total synthesis. In addition to this, through both experiment and calculation, we strive to understand these reactions on a mechanistic level, enabling us to accurately predict their outcome and explain the formation of the compounds we observe as products.

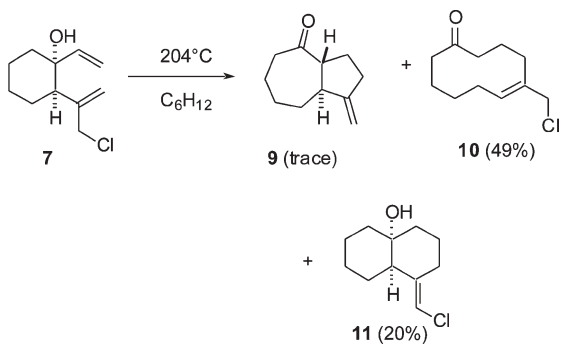
1. Oxy-Cope–transannular ene reaction

Our first foray into investigating tandem pericyclic processes was centered on the oxy-Cope–transannular ene reaction of 1,2-divinylcyclohexanols (eqn (1)).[4] We imagined that alcohol **4**, upon heating, would be transformed into the corresponding decalin framework **6**. We expected that this tandem process would be highly diastereoselective on the basis of preferential conformations of macrocycle **5** at the transition state of the ene reaction. Our exploitation of this process was not without precedent. There are very few examples in the literature of the tandem oxy-Cope–ene reaction.[5] To the best of our knowledge, the first example of this tandem process was reported by Sworin and Lin (Scheme 2).[6]



(1)

During the course of their investigation of tandem oxy-Cope–S_N2' reactions to create hydroazulenoid scaffolds, they observed that heating of **7** at 204 °C gave mainly macrocycle **10** and decalin **11** (from **10**) in 49% and 20% yields respectively.

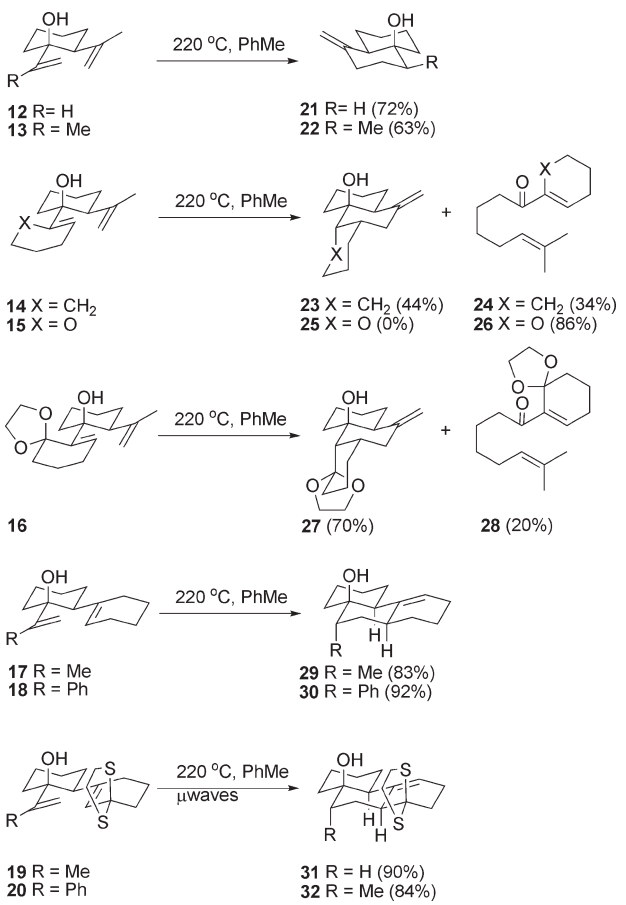


Scheme 2 Attempt to create hydroazulenoid scaffolds.

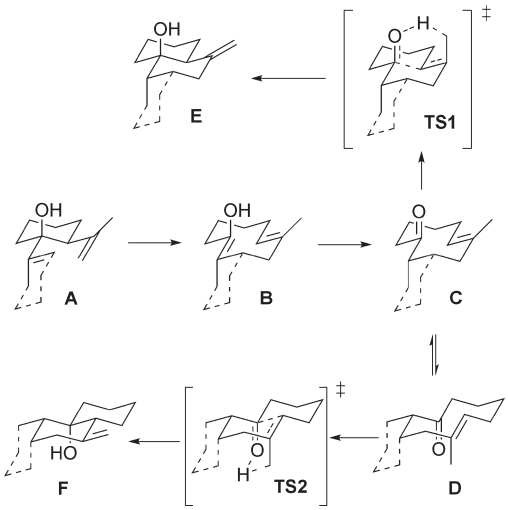
Only a trace of desired compound **9** was isolated. This tandem process leading to **11** was also observed in other cases as an unwanted side reaction in both thermal[7] and anionic oxy-Cope[8] reactions. We thought, using the appropriate starting 1,2-divinylcyclohexanols, that we would be able to take advantage of this process to specifically build decalin systems containing a tertiary alcohol at the ring junction. This type of framework is embedded in various natural sesqui- and diterpenes.

Heating the 1,2-divinylcyclohexanols **12–20**, readily prepared in a few steps from commercially available starting material, in a sealed tube in toluene for 5 h at 220 °C yielded a variety of cyclic compounds in moderate to good yields (Scheme 3). However, in some cases we isolated retroene by-products **24**, **26** and **28**. We found that increasing electron density in the allylic double bond favors the retroene manifold to become the main pathway up to the point where it is the only product observed, such as in the case of 1,2-divinylcyclohexanol **15**. This is in agreement with the results reported by Paquette, Houk *et al*.[9]

In each case where the oxy-Cope–ene product was isolated, only a single diastereomer was observed. This highly selective process can be rationalized by first assuming that the initial thermal oxy-Cope reaction occurs through a chair-like transition state, as in the conversion of **A** to **B** (Scheme 4). The latter then undergoes a stereospecific tautomerization to give **C**. At this point, ketone **C** can undergo a chair-like



Scheme 3 Tandem oxy-Cope–ene reaction of 1,2-divinylcyclohexanols.



Scheme 4 Proposed mechanism for the tandem oxy-Cope–ene reaction.

transannular ene reaction[10] to afford compound **E** or do a ring flip (**D**) followed by an ene reaction to provide **F**.

Assuming a rapid equilibrium between conformers **C** and **D**, the product ratio will be determined by the energy difference between **TS1** and **TS2**.[11] In the case of cyclic allylic alcohols **14** and **16**, **TS1** is favored over **TS2** due to the presence of severe 1,3-diaxial interactions, methylene–methyl, in **TS2**, thereby giving tricycles **23** and **27** as single diastereomers. In the case of the tandem oxy-Cope–ene reaction of 1,2-divinylcyclohexanol **13**, only decalin **22** was isolated after heating at 220 °C for 5 h. This indicates that the transannular ene reaction proceeds through **TS2** where the methyl group is oriented in the pseudo-equatorial position. In the case of a cyclic ene donor such as **17–20**, no macrocyclic ring flip (**C** → **D**) is possible. This ensures the stereoselective formation of tricycles **29–32**. Although the diastereoselectivity of the process was exceptional for generating decalins and tricycles, we were still faced with the problem of the retroene reaction manifold competing with the desired oxy-Cope–ene pathway.

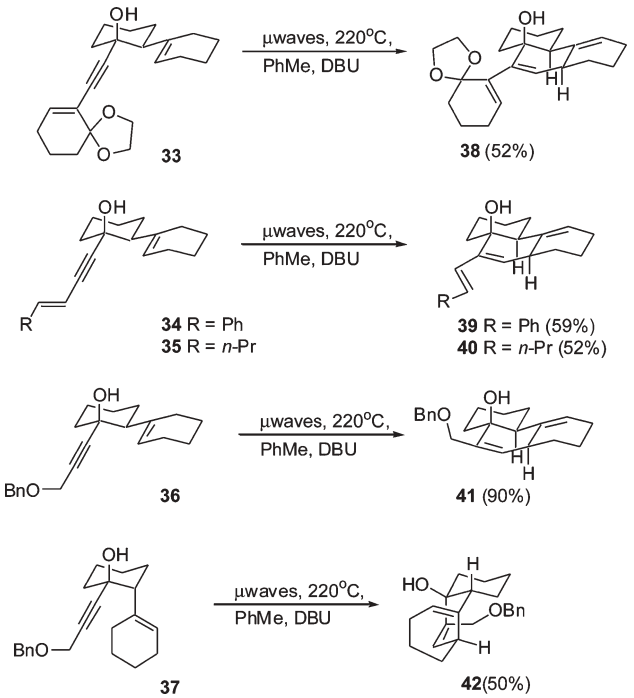
Literature precedent suggested the rate of the oxy-Cope rearrangement can be accelerated by additive solvents.[12] It was postulated that hydrogen bonding of solvent to the hydroxyl proton increases the electron density on the oxygen, allowing for an "electron push" that accelerates the C–C bond breaking in the [3,3] sigmatropic rearrangement. In light of this observation, we scanned various solvent additives hoping to find something that would increase the rate of the oxy-Cope rearrangement sufficiently so as to suppress the retroene reaction. To our delight, we discovered that the use of DBU as an additive suppressed or diminished isolation of retroene reaction products (Table 1).[13]

Finally, we demonstrated that the tandem oxy-Cope–ene reaction can be performed on 1-alkynyl-2-vinylcyclohexanols (Scheme 5). The conversion of **33–37** to their respective dienes **38–42** was accomplished by microwave irradiation in the presence of 5–20 equivalents of DBU in toluene.[14] In all cases, the desired product was isolated as the sole diastereomer in fair to good yield.

Table 1 DBU and NMP assisted oxy-Cope–ene reactions

Entry	Alcohol	Additive (equivalents)	Products	Ratio (yield)
1	**15**	DBU (0.5)	**25**, **26**	1 : 7.9 (80%)
2	**15**	DBU (50)	**25**, **26**	1 : 3 (89%)
3	**15**	NMP (solvent)	**27**, **28**	11 : 1 (18%)
4	**16**	DBU (20)	**27**, **28**	20 : 1 (75%)
5	**16**	DBU (60)[a]	**27**, **28**	>25 : 1 (98%)

[a] Microwave irradiation for 40 min at 220 °C.



Scheme 5 Tandem oxy-Cope–ene reactions of 1-alkynyl-2-vinylcyclohexanols.

2. Oxy-Cope–ene reaction in the synthesis of (+)-arteannuin M (43)

Having developed a reliable and predictable reaction cascade for generating *trans*-decalin ring systems, we then set our sights towards applying this methodology in a total synthesis. Of particular interest were natural products containing a *trans*-decalin ring system with a tertiary alcohol at one of the ring junctions. (+)-Arteannuin M (**43**), a natural product isolated from *Artemisia annua* L (Fig. 1).[15] proved to be the perfect target, containing all the desired structural features we wished to construct using our cascading sequence. It is important to point out that the absolute configuration of the molecule and the stereochemistry at C9 were unknown.

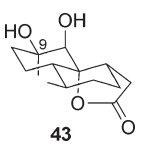
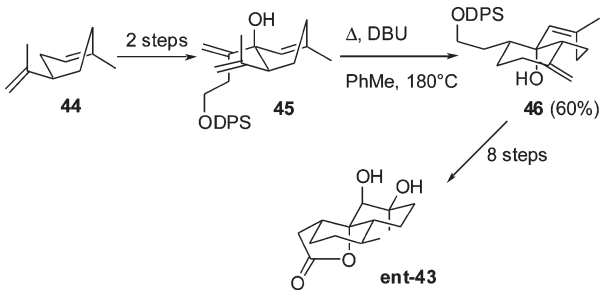


Fig. 1 Structure of (−)-arteannuin M (**43**).

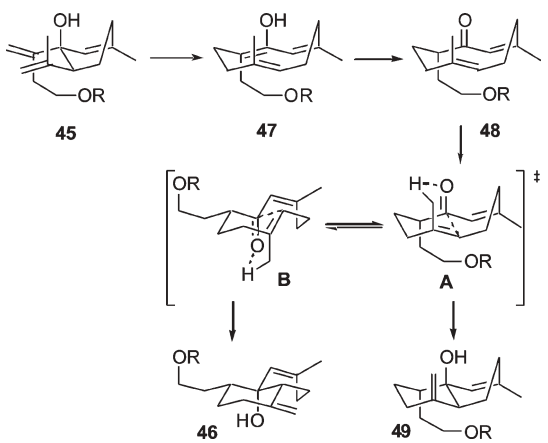


Scheme 6 Synthesis of *ent*-arteannuin M (**43**).

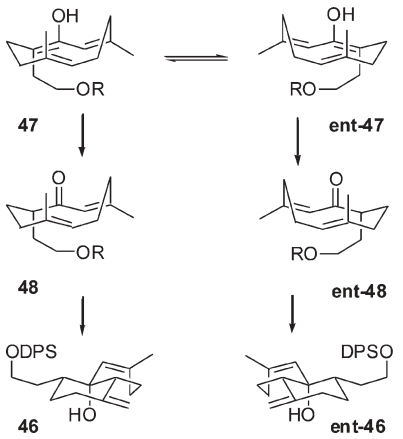
Our synthesis commenced with the conversion of limonene **44** (ee > 98%) to 1,2-divinylcyclohexanol **45** (Scheme 6).[16] Thermal rearrangement of **45** gave **46** in 60% yield as the sole diastereomer with an enantiomeric excess of 78%. The high diastereoselectivity of the process is rationalized using the mechanism depicted in Scheme 7. The process is triggered by a [3,3] sigmatropic rearrangement of **45** to afford enol **47** which after tautomerization led to **48**. The latter is poised to undergo a transannular ene reaction through transition states **A** and **B**.

A close examination of transition states **A** and **B** reveals that the alkyl group in **A** is oriented pseudo-axially, whereas in **B** the alkyl chain occupies a pseudo-equatorial position. On the basis of this observation, transition state **B** is favored over **A**, explaining why we observed **46** as the sole product.

The loss of enantiopurity can be accounted for by a ring flip of **47** to give ***ent*-47** (Scheme 8). We initially proposed that the chirality present in **45** would be transferred, by virtue of the planar chirality[17] of the intermediate macrocyclic enol **47**, through to the final product. We thought that the three double bonds embedded in enol intermediate **47** would create a rigid structure that would prevent the enol moiety from rotating and thereby producing ***ent*-47**. However, we observed in our substrate that such an inversion is feasible, hence accounting for the loss of enantiopurity. Of course, ***ent*-47** leads ultimately to ***ent*-46** *via* the same manifold by which **47** leads to **46**. This synthesis firmly established the use of the oxy-Cope–ene reaction as a viable synthetic method for generating decalin ring systems.



Scheme 7 Proposed mechanism for the tandem oxy-Cope–ene reaction.



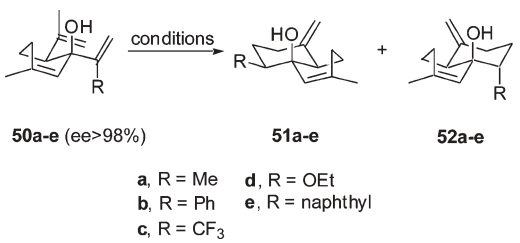
Scheme 8 Planar chirality.

3. Conservation of planar chiral information in the oxy-Cope–ene reaction

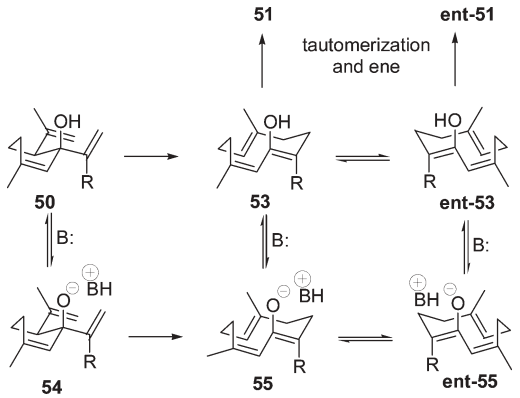
Intrigued by the enantioselectivity leakage in the tandem process, we initiated a more in-depth investigation into the diastereo- and enantioselectivity of the tandem reaction. This began with the preparation of several optically pure 1,2-divinylcyclohexanols **50a–e**, which were then subjected to microwave irradiation[18] at 220 °C for one hour to give decalins **51a–e** and **52a–e** (Scheme 9).[19]

We scanned a variety of basic additives in an effort to evaluate their effects on the enantioselectivity. We found that in the majority of cases we isolated decalins **51** and **52** with ratios ranging from 8.5 : 1 to 25 : 1, regardless of the additive, in moderate to excellent yields. In addition, the majority of the bases used[20] resulted in essentially no erosion of enantiopurity. However, DBU represents an exception. Heating of **50a–e** in the presence of 10 equivalents of DBU gave the corresponding decalins **51a–e** having enantiomeric excesses of 93%, 35%, 70%, 74% and 84% respectively. We discovered that an increase in the DBU proportion was directly related to a lowering of enantiomeric excess. Interestingly, when we performed the anionic oxy-Cope[21] rearrangement this resulted in a complete racemization of the substrate.

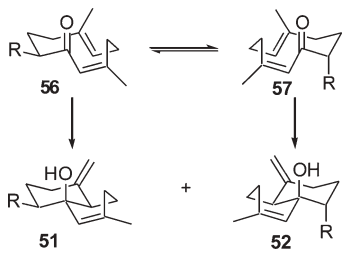
This suggests that enol **53** possesses a high energy barrier to invert to ***ent*-53**, whereas enolate **55** has a lower energy barrier for ring inversion (Scheme 10). The ring inversion can also compete with the tautomerization process which after the transannular ene reaction leads to ***ent*-51**. Therefore, when a weak base or no strong base is present in the reaction mixture, a complete conservation of the planar chirality information through the process is observed. However, when a portion of



Scheme 9 Enantioselective tandem oxy-Cope–ene reaction.



Scheme 10 Proposed mechanism for the tandem oxy-Cope–ene reaction.



Scheme 11 Proposed mechanism for the tandem oxy-Cope–ene reaction.

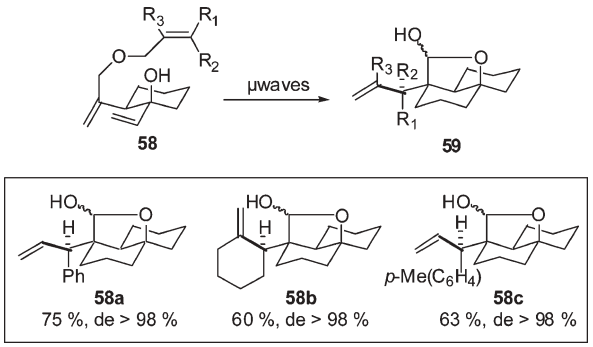
the enol **53** is converted to enolate **55**, we observe a leak in ee. On the basis of the results reported above, this strongly suggests that the pK_a of the proton on the enol **53** combined with the strength of the base used are directly responsible for the loss of chirality.

We also found that the electronic nature of the R group affected the diastereomeric ratio of products **51** and **52**. While most substituents still favor products **51** greatly over type **52**, it was observed that electron-withdrawing substituents lower the ratio of **51** : **52**. For instance, when R = CF_3 (**50c**), the diastereomeric ratio fell to 8.5 : 1 favoring **51c**. However, when R = OEt (**50d**), the formation of **52d** was slightly favored over **51d** in a ratio of 1 : 2.3.

As demonstrated above, the diastereoselectivity of the transannular ene reaction is usually governed by the Curtin–Hammett principle. This is true when electron-donating or neutral groups (R) are adjacent to the carbonyl moiety on **56** (Scheme 11). On the other hand, it seems unlikely that the ene reaction is controlled by the Curtin–Hammett principle when R is an electron-withdrawing group. One might propose that the ring inversion (**56** → **57**) competes with the ene reaction since the latter reaction is accelerated by electron-withdrawing groups such as R = CF_3 and OEt.[22]

4. The oxy-Cope–ene–Claisen cascade

One obvious limitation of the oxy-Cope–ene sequence resides in the inability to install all-carbon quaternary centers on a decalin system. To remedy this problem, we imagined that the addition of an allyloxy ether fragment to the isopropenyl unit would result in the addition of a third pericyclic reaction, a

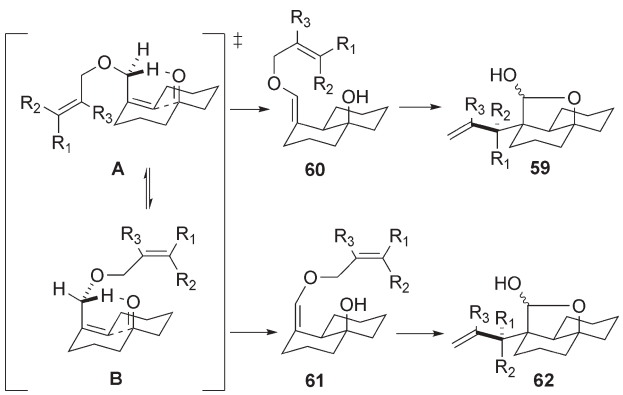


Scheme 12 Tandem oxy-Cope–ene–Claisen.

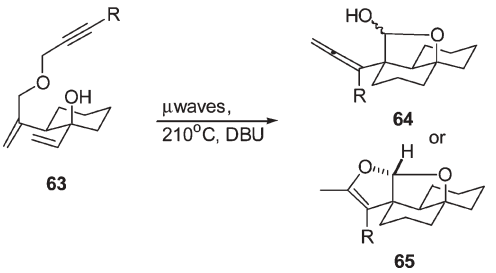
Claisen rearrangement, to the sequence (Scheme 12). This would give access to one or more quaternary carbon centers in the final product, depending on the substitution pattern of the allyl ether moiety. Acting on this possibility, we constructed a variety of simple allyl-1,2-divinylcyclohexanols **58** which reacted through a highly diastereoselective oxy-Cope–ene–Claisen cascade. This gives products of type **59** with an all-carbon quaternary center now embedded in the decalin system.[23] As shown in Scheme 12, thermal rearrangement of an allyl ether monosubstituted at the terminus position afforded the corresponding lactol with high diastereoselectivity.

After the oxy-Cope rearrangement and tautomerization of **58**, the ketone intermediate can undergo a transannular ene reaction through two transition states **A** or **B** (Scheme 13). A closer examination of transition state **B** reveals the presence of a pseudo 1,3-diaxial interaction between the allyl ether group and the macrocyclic ring. Consequently, this favors transition state **A** over **B** as the reactive conformer to provide enol ether **60**. Finally, the latter undergoes a Claisen rearrangement on the opposite side of the tertiary alcohol to afford **59** as the sole isomer. The stereoselectivity of the process is thus explained.

We also found that propargyl ethers **63** were ideal substrates for the tandem oxy-Cope–ene–Claisen rearrangement, giving products **64** or **65** in excellent yields and with high diastereoselectivity, as illustrated in Scheme 14. Allene products **64** were favored in the cases where R was an alkyl group or a proton; whereas cyclic ethers **65** were favored when R was an electron-withdrawing or aryl substituent. Compound **65** arises from a 5-*exo*-dig cyclization onto the previously generated allene **64**.



Scheme 13 Mechanism of the tandem oxy-Cope–ene–Claisen.



Scheme 14 Tandem oxy-Cope–ene–Claisen reaction of propargyl ethers.

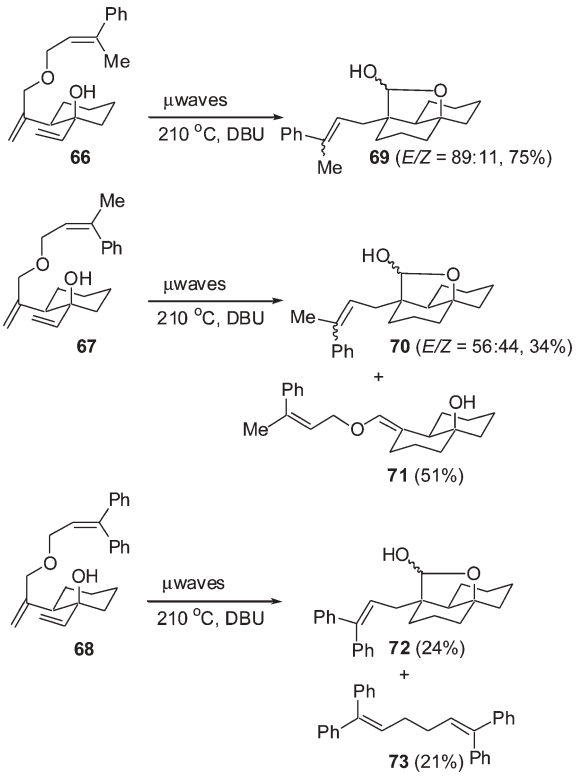
This is the result of a thermodynamically controlled cyclization where the least strained 5-membered-ring acetal is formed.

Having realized the potential of this tandem sequence, we sought to install two contiguous quaternary carbon centers in the molecule. This could be achieved by thermal rearrangement of **58** possessing an allyl ether disubstituted at the distal end of the alkene (where R_1 and $R_2 \neq H$). Much to our surprise, submitting compound **66** to the standard conditions did not give the expected oxy-Cope–ene–Claisen product, but compound **69** in 75% yield with an $E : Z$ ratio of the newly formed olefin of 89 : 11 (Scheme 15).[24] Microwave irradiation of compounds **67** and **68** resulted in the formation of structurally related products **70** and **72** respectively. We also isolated unreacted *E* olefin **71** in the reaction of **67**, and dimer **73** in the reaction of **68**.

These results suggest that there is a radical [1,3]-shift in competition with the [3,3] Claisen rearrangement. Incidentally, the isolation of the *E* olefin **71** serves to confirm the high selectivity of the transannular ene portion of the reaction cascade (*vide supra*).

It has been previously suggested that the Claisen rearrangement could proceed through the formation of an oxallyl–allyl radical pair instead of the concerted mechanism, especially when there are radical-stabilizing substituents present.[25] In our situation, the intermediate after the oxy-Cope–ene portion of the cascade **60** undergoes homolytic C–O bond cleavage to afford **74** and **75** (Scheme 16). Allyl radical **74** can undergo an olefin isomerization to afford **76**, both of which can recombine with rearranged alkyl radical **77** to give the formal [1,3]-shift product **78**.

The scrambling of the geometry in **78** is accounted for by the isomerization of **74** to **76** where the rate of isomerization



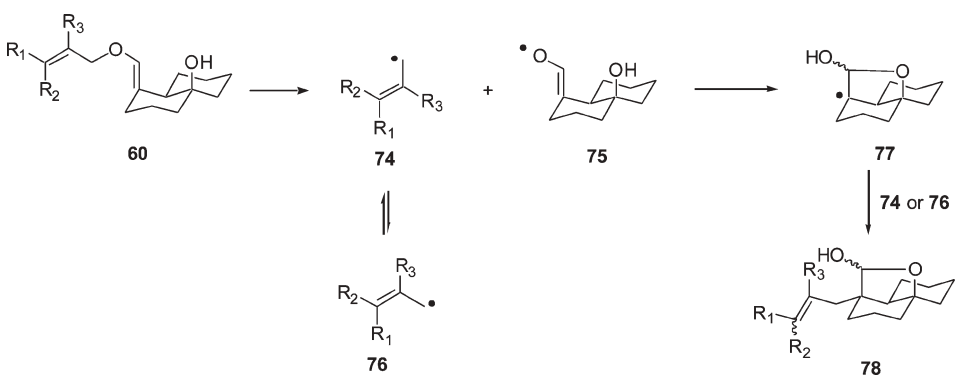
Scheme 15 Tandem oxy-Cope–ene–Claisen reaction of allyl ethers.

competes with the rate of recombination. This is evident by the fact that different $E : Z$ ratios are obtained for **69** and **70** which should have the same allyl radical intermediate. Moreover, the combination of two of the allyl radicals **74** or **76** explains the formation of dimer **73**.

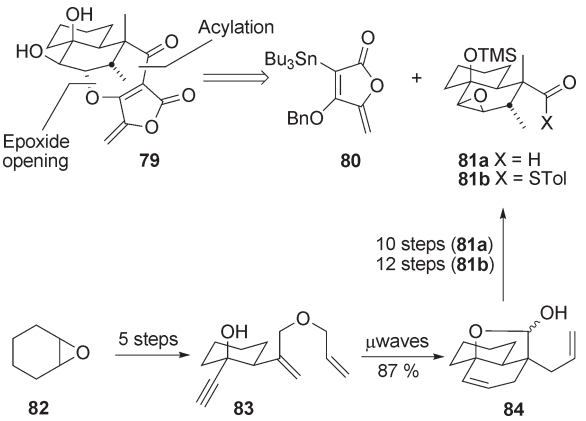
In summary, we have observed that disubstituted allyl ether starting materials in the oxy-Cope–ene–Claisen rearrangement proceed through the expected reaction pathway. However, a different pathway is manifested in the case of more sterically demanding trisubstituted allyl ethers for the Claisen step of the cascade. In this case, a [1,3]-shift radical pathway is favored over the congested [3,3] rearrangement.

5. Oxy-Cope–ene–Claisen in total synthesis

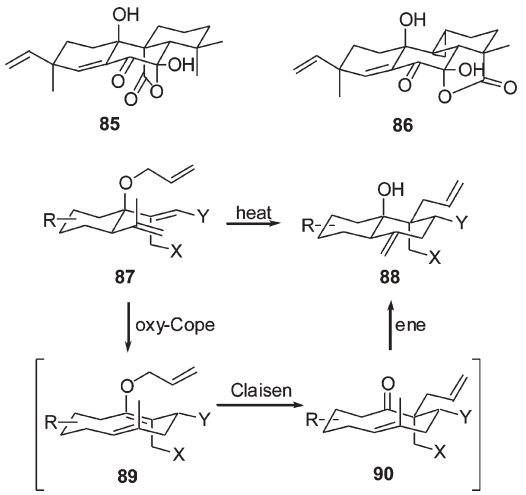
Having undertaken an extensive study of the oxy-Cope–ene–Claisen rearrangement and having devised a predictable



Scheme 16 Mechanism of the 1,3-radical shift.



Scheme 17 Synthesis of tetrodecamycin.



Scheme 18 Tandem oxy-Cope–Claisen–ene.

method for the generation of decalin systems containing a quaternary carbon, we sought to apply our method in total synthesis.

Tetrodecamycin **79**, an antibiotic isolated from *Streptomyces nashvillensis* MJ885-mF8,[26] is a structurally intriguing natural product containing a *trans*-decalin and a tetronic acid moiety as its major structural features (Scheme 17). Its biological activity against several Gram-positive bacteria has resulted in multiple synthetic pursuits, but no total synthesis has yet been reported.[27] Our approach to this compound involved the two disconnections superimposed on **79**, revealing decalin **81** and tetronic acid residue **80** as the major constituents we needed to construct.[28]

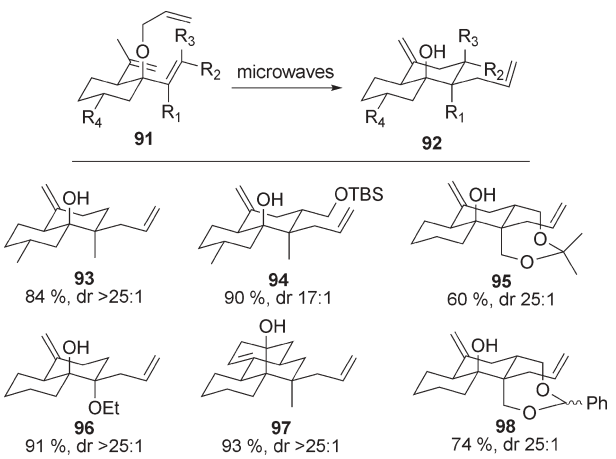
From cyclohexene oxide **82**, the precursor for the pivotal oxy-Cope–ene–Claisen rearrangement **83** was readily available in five steps. As expected, decalin **84**, containing the quaternary center found in the natural product, was isolated after treatment of **83** with microwaves at 220 °C. This was then elaborated to several precursors that we deemed appropriate as intermediates for the coupling with tetronic acid residues of type **80**. Whilst we have yet to complete the total synthesis, we have been successful in synthesizing the decalin cores **81a** and **81b** of tetrodecamycin along with coupling partner **80**. Efforts are ongoing towards the completion of the synthesis.

6. The oxy-Cope–Claisen–ene reaction

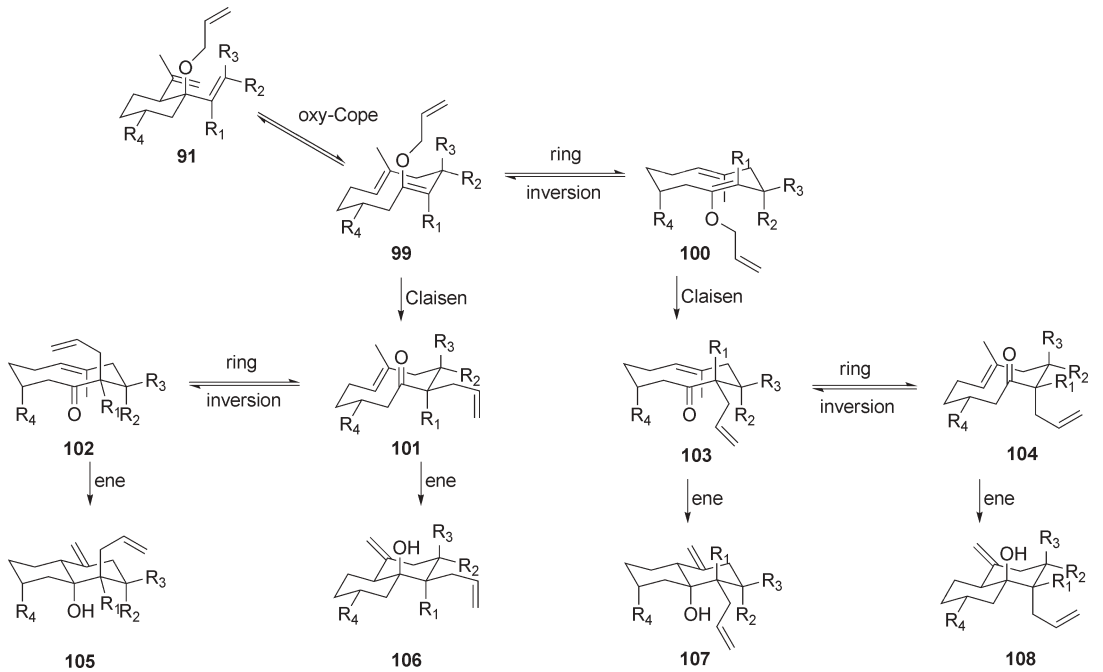
One of the problems encountered in the synthesis of polycyclic compounds is the stereoselective formation of quaternary carbon centers.[29] As an example, bioactive natural diterpenes such as LL-S491β (**85**)[30] and myrocin C (**86**)[31] possess a quaternary center at C9 and a tertiary alcohol at C10 (Scheme 18). The retrosynthetic analysis of these particular molecules reveals that the main framework can be generated from a common decalin intermediate **88**, which bears the requisite quaternary carbon center at C9 adjacent to a tertiary alcohol at C10. We envisaged the formation of **88** *via* a thermal cyclization of the allylic ether **87**. Heating of the allyl ether **87** produces the enol intermediate **89** *via* an oxy-Cope reaction. The latter is transformed into ketone **90** through a Claisen rearrangement. The resulting macrocyclic ketone can undergo a transannular ene reaction to give **88**. It is important to notice that the stereochemical outcome of the final product **88** will depend on the conformational preferences of the macrocyclic intermediates **89** and **90** at the transition states.

In pursuit of making this cascading reaction viable, a variety of precursors were synthesized through several routes, giving a series of structurally related compounds designated **91**, with variation throughout R_1, R_2, R_3 and R_4. As we expected, subjection of the majority of these compounds to thermal rearrangement conditions resulted in the formation of decalin products **92** in very good yields and excellent diastereoselectivity, as indicated with the several illustrative examples shown in Scheme 19.[32]

The excellent diastereoselectivity of this process can be explained by taking a closer look at the reaction mechanism, where we find the diastereoselection is ultimately dictated by the conformational preferences of intermediates **99** and **101** (Scheme 20).[33] The oxy-Cope rearrangement of **91** through a chair-like transition state affords intermediate **99**. At this point, two things can happen: it can undergo a ring inversion to **100**, or rearrange to **101** *via* the Claisen reaction. We found that the rate of the ring inversion is slow compared to that of the Claisen rearrangement, leading to exclusive formation of



Scheme 19 Synthesis of decalin frameworks.



Scheme 20 Proposed mechanism for the tandem oxy-Cope–Claisen–ene reaction.

macrocycle **101**. As a result, diastereomeric products **107** and **108** are never observed.

From intermediate **101**, the ene product **106** can be produced directly, or **101** can undergo a ring inversion to **102**, which after transannular cyclization gives **105**. At this stage of the reaction, one might consider a fast equilibrium between conformers. Consequently, the product ratio **105** : **106** is governed by the Curtin–Hammett principle. For the majority of our substrates, we observed compounds structurally related to **106** as the major product of the reaction, although there are exceptions.

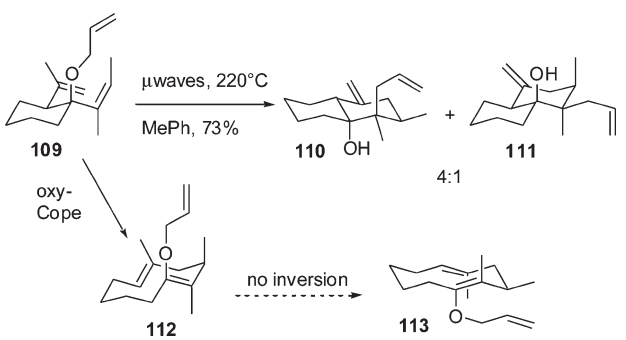
Much circumstantial evidence has been collected to confirm the aforementioned mechanism is what is actually occurring in this tandem sequence.[34] A general survey of our results clearly shows that products **107** and **108** were never observed in any case. This strongly supports the conclusion that the ring inversion of **99** to **100** is a much slower process than the Claisen rearrangement of **99** to **101**.

This is exemplified in the tandem reaction of **109** to give **110** and **111** in a 4 : 1 ratio (Scheme 21). Initial oxy-Cope rearrangement of **109** gives directly **112**, which is analogous to compound **99**. One might propose that conformer **112** should have a higher energy transition state for the Claisen rearrangement than conformer **113**. If the inversion process of **112** to **113** was possible, we should have observed products of type **107/108**. Since we did not observe any of these products, one can suggest that the rotation barrier of the tetrasubstituted enol ether in **112** (or **99**) is a high energy process.

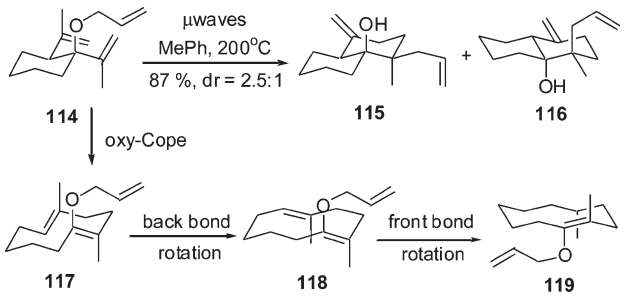
The product distribution of **110** and **111** can be rationalized by Curtin–Hammett control of the ene reaction. The transition state leading to **111** (**106**, R_1 and R_3 = Me) in this case requires that both methyl groups be situated axially, whereas that leading to **110** (**105**, R_1 and R_3 = Me) has the two methyl groups situated equatorially. As a consequence of this, the formation of compound **110** (**105**) is favored over **111** (**106**) thus explaining the diastereoselectivity of the tandem process.

All other examples of this tandem sequence illustrate Curtin–Hammett control in the ene reaction as well. While we cannot discuss all the results in this account, we can state generally that the favored diastereomer observed is the one arising from the ene reaction where the most sterically demanding substituents are in equatorial conformations.

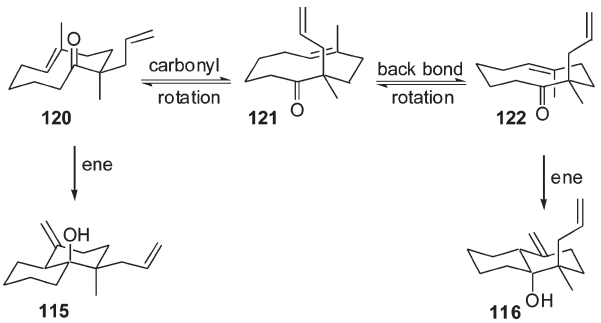
In order to confirm that the Claisen rearrangement is faster than the ring inversion, we performed the tandem reaction using enantiomerically enriched compounds **91** ($R_1 \neq H$; R_2, R_3, R_4 = H; ee = 98%).[35] In these cases, intermediates **99** and **100** are enantiomers, rather than diastereomers, by virtue of planar chirality. Therefore, ring inversion of **99** will result in a complete racemization of the final products **105** and **106**. For every substrate investigated, there was no loss of ee in any case, proving, without a shadow of a doubt, that the ring inversion of **99** to **100** is a higher energy process than the Claisen rearrangement (**99** → **101**).



Scheme 21 Tandem oxy-Cope–Claisen–ene reaction of allyl ether **109**.



Scheme 22 Proposed mechanism for the tandem oxy-Cope–Claisen–ene reaction of allyl ether **114**.



Scheme 23 Ring inversion.

7. Theoretical evidence supporting the oxy-Cope–Claisen–ene mechanism

While there was ample experimental evidence supporting the proposed oxy-Cope–Claisen–ene mechanism, we felt it necessary to provide theoretical proof that the possible ring inversion before the Claisen rearrangement is a high energy process, and that the ene reaction is under Curtin–Hammett control. Furthermore, a theoretical investigation of this process would constitute a quantitative assessment of the energy barriers associated with the processes in our proposed reaction mechanism above and beyond the general conclusions that we have drawn through rationalization of the reaction outcomes.[35]

We decided to model the reaction of **114**, which we had previously examined experimentally (Scheme 22). When considering the ring inversion of the initial oxy-Cope reaction product **117**, we must take into account that it is a two-step process where each double bond rotates through the 10-membered ring separately (**117** → **118** → **119**). Therefore, two transition states must be examined to evaluate the transformation.

DFT calculations at the B3LYP level of theory using the 6-31G(d,p) basis set showed a barrier for the rotation of **117** to **118** of 17.3 kcal mol^{-1}, which, as we would expect, is an allowed process at 200 °C. The second rotation of **118** to **119** was found, however, to have an enormous barrier of rotation of 160.5 kcal mol^{-1}, thereby making it an unfeasible conformational change. While we expected one of the two olefin rotations to have a high barrier of inversion based on experimental evidence that supports no ring inversion, we were surprised to find a barrier of such magnitude for a tetrasubstituted olefin. In addition, we found that the transition state energy of the Claisen rearrangement step itself is 24.1 kcal mol^{-1}, which is just one seventh that of the inversion of **118** to **119**; hence, it is predicted to be the favored process over ring inversion. This is in agreement with our experimental findings.

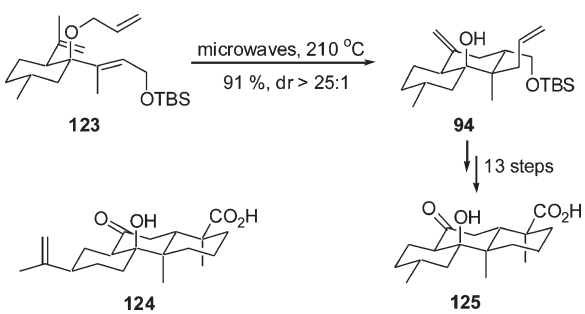
We also examined the energies of the second ring inversion *versus* the two possible transannular ene reactions in the second half of this tandem reaction. The ring inversion is again a two-step process, with both an outside rotation of the carbonyl **120** to **121**, which has a negligible energy cost, and a rotation of the trisubstituted olefin **121** to **122** (Scheme 23). The latter represents the rate determining step of the overall ring flip. We calculated the barrier of the ring inversion of **121** to **122** to be 14.0 kcal mol^{-1}, whereas the energy of both transannular ene reactions **120** → **115** and **122** → **116** has a higher energetic cost at 34.0 kcal mol^{-1} and 34.6 kcal mol^{-1} respectively. This points to a rapid ring inversion that does not compete with the ene reactions.

We ultimately determined from our computational results that the ene reaction is under Curtin–Hammett control, and that the ratio of diastereomers arising from the ene portion of the reaction mechanism can be calculated from the relative transition state energies of the ene reactions with reasonable precision.[35] These calculations reinforce our original mechanism as the correct depiction of the reaction manifold that is followed in the oxy-Cope–Claisen–ene cascade.

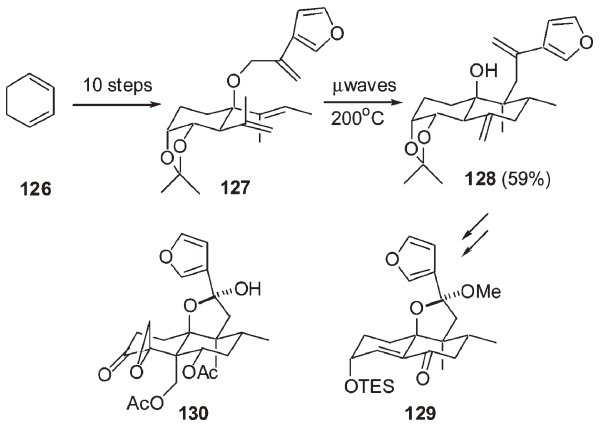
8. Oxy-Cope–Claisen–ene in total synthesis

Having developed an in-depth understanding of the oxy-Cope–Claisen–ene reaction, we sought to apply this powerful sequence to the synthesis of several structurally challenging natural products. Our first target was the natural product wiedemannic acid (**124**), an abietane diterpene isolated from *Salvia wiedemannii* (Scheme 24).[36] A cursory analysis of the molecule reveals five contiguous stereogenic centers based around a *trans*-decalin core, making this the apparent major synthetic challenge. Reviewing our previous studies of the oxy-Cope–Claisen–ene reaction, we found that we had previously prepared compound **94** from **123**, which possesses several architectural features of wiedemannic acid (**124**). Taking advantage of this, we could quickly elaborate an analog of the natural product (**125**).[37]

Unfortunately, despite the close resemblance of our analog **125** to the reported structure of wiedemannic acid (**124**), the ^{1}H and ^{13}C NMR data of **125** were significantly different from those reported for **124**. In particular, the portion of **125** that is



Scheme 24 Synthesis of wiedemannic acid analog.



Scheme 25 Approach toward the synthesis of teucrolivin A.

close to the equatorial methyl group possesses different chemical shifts and coupling constants. The structure of **125** was confirmed by X-ray crystallography, we compared our data to other natural abietane diterpenes and we concluded that the initial structural assignment for wiedemannic acid (**124**) was probably incorrect, prompting us to abandon the total synthesis at that point.

Our most recent synthetic pursuit using the oxy-Cope–Claisen–ene cascade is directed towards the synthesis of teucrolivin A **130**,[38] a neoclerodane diterpenoid isolated from *Teucrium oliverianum*, a plant whose genus is a rich source of such compounds (Scheme 25). While this compound is not known to exhibit any notable biological activity, the highly oxygenated core, coupled with an additional all-carbon quaternary center at the decalin ring junction not accessible with the pericyclic cascade, presents a significant synthetic challenge.

We prepared the cascade precursor **127** in just 10 steps from 1,3-cyclohexadiene **126**. We were successful in implementing the cascade reaction to access the decalin core **128** of the natural product, albeit in a moderate yield due to the instability of the 3-substituted furan to the reaction conditions.[39] To date, we have achieved the synthesis of the advanced intermediate **129** and we are currently investigating the installation of the last remaining all-carbon quaternary center at the ring junction. Significant progress has been made and will be reported in due course.

Conclusions

Over the past several years we have developed numerous pericyclic reaction cascades that constitute efficient and reliable methods for the generation of various carbocyclic ring systems with high diastereoselectivity at one or more stereogenic centers. Accompanying these methodological developments we have invested significant effort to gain a deep mechanistic understanding of these processes and have used this knowledge in application to the total synthesis of various natural targets. Undoubtedly we, and chemists as a whole, will continue to develop cascading reactions in the interest of greater reaction efficiency and facile access to more and more complicated systems in a single transformation.

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References

1 (*a*) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134; (*b*) L. F. Tietze, G. Brasche and K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2006; (*c*) H. Pellisier, *Tetrahedron*, 2006, **62**, 1619; (*d*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*e*) P. J. Parsons, C. S. Penkett and A. J. Shell, *Chem. Rev.*, 1996, **96**, 195; (*f*) T.-L. Ho, *Tandem Organic Reactions*, Wiley, New York, 1992.
2 For a biomimetic approach, see: (*a*) W. M. Bandaranayake, J. E. Banfield, D. St. C. Black, G. D. Fallon and B. M. Gatehouse, *J. Chem. Soc., Chem. Commun.*, 1980, 162; (*b*) W. M. Bandaranayake, J. E. Banfield and D. St. C. Black, *J. Chem. Soc., Chem. Commun.*, 1980, 902.
3 (*a*) K. C. Nicolaou, N. A. Petasis, R. E. Zipkin and J. Uenishi, *J. Am. Chem. Soc.*, 1982, **104**, 5555; (*b*) K. C. Nicolaou, N. A. Petasis, J. Uenishi and R. E. Zipkin, *J. Am. Chem. Soc.*, 1982, **104**, 5557; (*c*) K. C. Nicolaou, R. E. Zipkin and N. A. Petasis, *J. Am. Chem. Soc.*, 1982, **104**, 5558; (*d*) K. C. Nicolaou, N. A. Petasis and R. E. Zipkin, *J. Am. Chem. Soc.*, 1982, **104**, 5560.
4 J. M. Warrington, G. P. A. Yap and L. Barriault, *Org. Lett.*, 2000, **2**, 663.
5 (*a*) K. Rajagopalan and R. Srinivasan, *Tetrahedron Lett.*, 1998, **39**, 4133; (*b*) P. Shanmugam, B. Devan, R. Srinivasan and K. Rajagopalan, *Tetrahedron*, 1997, **53**, 12637; (*c*) K. Rajagopalan and P. Shanmugam, *Tetrahedron*, 1996, **52**, 7737.
6 M. Sworin and K.-C. Lin, *J. Am. Chem. Soc.*, 1989, **111**, 1815.
7 A. P. Chorlton, G. A. Morris and J. K. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1205.
8 (*a*) L. A. Paquette, S. Nakatani, T. M. Zydowsky, S. D. Edmondson, Q.-L. Sun and R. Skerlj, *J. Org. Chem.*, 1999, **64**, 3244; (*b*) K. Rajagopalan, S. Janardhanam and A. Balakumar, *J. Org. Chem.*, 1993, **58**, 5482 and references therein.
9 They observed that electron-rich double bonds cause the anionic oxy-Cope reaction to decelerate, see: F. Haeffner, Y. R. Reddy, K. N. Houk and L. A. Paquette, *J. Am. Chem. Soc.*, 1999, **121**, 11880.
10 T. Terada and S. Yamamura, *Tetrahedron Lett.*, 1979, **20**, 1623.
11 (*a*) D. Y. Curtin, *Rec. Chem. Prog.*, 1954, **15**, 111; (*b*) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, 1955, **77**, 5562; (*c*) E. L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962; (*d*) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, New York, 1970, ch. 5; (*e*) J. I. Seeman, *Chem. Rev.*, 1983, **83**, 83; (*f*) J. I. Seeman, *J. Chem. Educ.*, 1986, **63**, 42.
12 (*a*) Y. Fujita, T. Onishi and T. Nishida, *J. Chem. Soc., Chem. Commun.*, 1978, 651; (*b*) Y. Fujita, T. Onishi and T. Nishida, *Synthesis*, 1978, 934; (*c*) A. Utagawa, H. Hirota, S. Ohno and T. Takahashi, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 1207.
13 D. Deon, MSc thesis, University of Ottawa, 2001.
14 P. R. MacLean, MSc thesis, University of Ottawa, 2003.
15 G. D. Brown, L.-K. Sy and R. Haynes, *Tetrahedron*, 1998, **54**, 4345. The natural enantiomer is actually (−)-arteannuin M, whose absolute configuration we assigned through its total synthesis.
16 L. Barriault and D. Deon, *Org. Lett.*, 2001, **3**, 1925.
17 (*a*) M. Nakazaki, K. Yamamoto and K. Naemura, *Top. Curr. Chem.*, 1984, **125**, 1; (*b*) E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, 1994.

18 Microwave heating was found to be more desirable compared to conventional heating methods, with our cascading reaction sequences occurring with a 10–300 fold increase in rate under these conditions. For reviews on the use of microwaves in organic synthesis, see: (*a*) A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault and D. Mathé, *Synthesis*, 1998, 1213; (*b*) G. Majetich and R. J. Hichs, *Journal of Microwave Power and Electromagnetic Energy*, 1995, **30**, 27; (*c*) A. Loupy and L. Perreux, *Tetrahedron*, 2001, **57**, 9199; (*d*) P. Lidström, J. Tierny, B. Wathey and J. Westman, *Tetrahedron*, 2001, **57**, 9225; (*e*) A. Loupy, *Microwaves in Organic Synthesis*, Wiley-VCH, Weinheim, 2006.
19 All reactions were performed in toluene, using different additives as noted above depending on the purpose of the experiment.
20 Bases used: DBU, TMEDA, Et_3N, pyridine, 2,6-di-*tert*-butylpyridine, DMAP, sparteine and 2-*tert*-butyl-1,1,3,3-tetramethylguanidine.
21 Conditions: KHMDS, DME, 110 °C. Quench with AcOH to isolate the macrocyclic ketone, the precursor for the ene reaction in the thermal sequence.
22 (*a*) B. B. Snider, in *Comprehensive Organic Synthesis, Combining C–C π Bonds*, ed. L. A. Paquette, Pergamon Press, Oxford, 1991, vol. 5, ch. 1.1; (*b*) B. B. Snider, in *Comprehensive Organic Synthesis, Addition To C–X π Bonds*, ed. C. H. Heathcock, Pergamon Press, Oxford, 1991, vol. 2, ch. 2.1.
23 L. Barriault and I. Denissova, *Org. Lett.*, 2002, **4**, 1371.
24 L. Barriault, J. A. Farand and I. Denissova, *Heterocycles*, 2004, **62**, 735.
25 (*a*) J. J. Gajewski and N. D. Conrad, *J. Am. Chem. Soc.*, 1979, **101**, 2747; (*b*) F. Barluenga, A. R. Liz and M. Bayod, *J. Org. Chem.*, 1987, **52**, 5190; (*c*) J. J. Gajewski, *Acc. Chem. Res.*, 1997, **30**, 219.
26 (*a*) T. Tsuchida, H. Iinuma, C. Nishida, N. Kinoshita, T. Sawa, M. Hamada and T. Takeuchi, *J. Antibiot.*, 1995, **48**, 1104; (*b*) T. Tsuchida, H. Iinuma, R. Sawa, T. Takahashi, H. Nakamura, K. T. Nakamura, T. Sawa, H. Naganawa and T. Takeuchi, *J. Antibiot.*, 1995, **48**, 1110.
27 (*a*) F. F. Paintner and G. Bauschke, *Tetrahedron Lett.*, 2003, **44**, 2549; (*b*) F. F. Paintner, L. Allmendinger, G. Bauschke, C. Berns and P. Heisig, *Bioorg. Med. Chem.*, 2003, **11**, 2823; (*c*) F. F. Paintner, L. Allmendinger, G. Bauschke and K. Polborn, *Synlett*, 2002, 1308; (*d*) F. F. Paintner, G. Bauschke and M. Kestel, *Tetrahedron Lett.*, 2000, **41**, 9977.
28 J. M. Warrington and L. Barriault, *Org. Lett.*, 2005, **7**, 4589.
29 For recent reviews, see: (*a*) B. M. Trost and C. Jiang, *Synthesis*, 2006, 369; (*b*) J. Christoffers and A. Baro, *Adv. Synth. Catal.*, 2005, **347**, 1473; (*c*) *Quaternary Stereocentres: Challenges and Solutions for Organic Synthesis*, ed. J. Christoffers and A. Baro, Wiley-VCH, Weinheim, 2005; (*d*) D. J. Ramon and M. Yus, *Curr. Org. Chem.*, 2004, **8**, 149; (*e*) C. J. Douglas and L. E. Overman, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5363; (*f*) L. Barriault and I. Denissova, *Tetrahedron*, 2003, **59**, 10105; (*g*) J. Christoffers and A. Baro, *Angew. Chem., Int. Ed.*, 2003, **42**, 1688; (*h*) J. Christoffers and A. Mann, *Angew. Chem., Int. Ed.*, 2001, **40**, 4591; (*i*) E. J. Corey and A. Guzman-Perez, *Angew. Chem.*, 1998, **110**, 402.
30 G. A. Ellestad, M. P. Kunstmann, P. Mirando and G. O. Morton, *J. Am. Chem. Soc.*, 1972, **94**, 6206.
31 (*a*) M. Nakagawa, Y.-H. Hsu, A. Hirota, S. Shima and M. Nakayama, *J. Antibiot.*, 1989, **42**, 218; (*b*) M. Nakagawa, Y.-H. Hsu, A. Hirota, S. Shima, M. J. Nakayama, T. Adachi and H. Nozaki, *J. Antibiot.*, 1989, **42**, 223.
32 E. L. O. Sauer and L. Barriault, *J. Am. Chem. Soc.*, 2004, **126**, 8569.
33 Seminal work in the field of diastereoselective control through macrocyclic conformation was performed by W. C. Still *et al.*, see: (*a*) W. C. Still and I. Galynker, *Tetrahedron*, 1981, **37**, 3981; (*b*) W. C. Still, *J. Am. Chem. Soc.*, 1977, **99**, 4186; (*c*) W. C. Still, *J. Am. Chem. Soc.*, 1979, **101**, 2493; (*d*) W. C. Still, *Curr. Trends Org. Synth., Proc. Int. Conf. 4th 1982 (1983)*, 233; (*e*) W. C. Still, S. Murata, G. Revial and K. Yoshihara, *J. Am. Chem. Soc.*, 1983, **105**, 625; (*f*) W. C. Still and V. J. Novack, *J. Am. Chem. Soc.*, 1984, **106**, 1148; (*g*) W. C. Still and A. G. Romero, *J. Am. Chem. Soc.*, 1986, **108**, 2105.
34 There is a wealth of experimental evidence supporting this mechanism; however it is impossible to include all results in a review: key ideas have therefore been presented. A full account of the results leading to these conclusions can be found in ref. 32 and 35.
35 E. L. O. Sauer, J. H. Hooper, T. Woo and L. Barriault, *J. Am. Chem. Soc.*, 2007, **129**, 2112.
36 (*a*) A. Ulubelen, G. Topcu and B. Terem, *Phytochemistry*, 1987, **26**, 1534; (*b*) A. Ulubelen and G. Topcu, *Phytochemistry*, 1990, **29**, 2346.
37 E. L. O. Sauer and L. Barriault, *Org. Lett.*, 2004, **6**, 3329.
38 M. Bruno, A. A. Omar, A. Perales, F. Piozzi, B. Rodriguez, G. Savona and M. C. De la Torre, *Phytochemistry*, 1991, **30**, 275.
39 S. Arns and L. Barriault, *J. Org. Chem.*, 2006, **71**, 1809.