Cationic Cyclopentannelation of Allene Ethers

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ABSTRACT

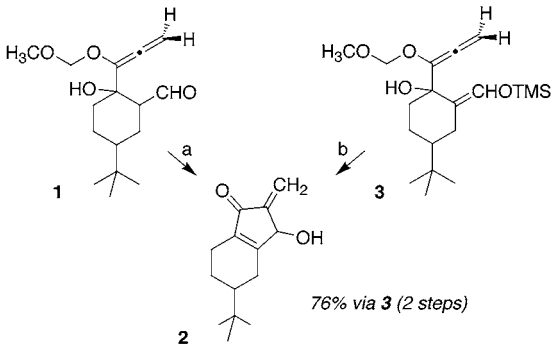
The variant of the Nazarov cyclization that makes use of allenyl ethers is suitable for the preparation of diverse, highly functionalized cyclopentenones. Three variants of the basic reaction, differing in the nature of the electrophile that is combined with the allene to prepare the precursor for the pentadienyl cation, are described. One variant, which utilizes an α,β-unsaturated morpholino amide, has been successfully employed in an enantioselective version of the cyclopentannelation.

Introduction

In the early 1980s, my group was trying to develop a method for preparing *ortho*-quinones. The idea was to epoxidize one of the two carbon−carbon double bonds in **1** to give the corresponding allene oxides, both of which would rearrange to the same oxyallyl zwitterion (eq 1). We hoped that the aldehyde in **1** would intercept the zwitterion in an aldol process. A series of elimination and dehydration reactions would have led to the *ortho*-quinone. However, treatment of **1** with *m*-CPBA in dichloromethane at room temperature led to hydroxycyclopentenone **2**.[1] The same product was formed when aldehyde **1** or silyl enol ether **3** was treated with BF_3•Et_2O in dichloromethane. The conversion of **1** to **2** is not an oxidation and is catalyzed by the *m*-chlorobenzoic acid that is present in untreated commercial samples of *m*-CPBA.[2] Since I thought that the reaction leading to **2** was more interesting than the *ortho*-quinone synthesis and I recognized the close structural homology between **2** and the methylenomycins,[3] I decided to examine this cyclopentannelation more closely.[4]

Variants of the Cyclization

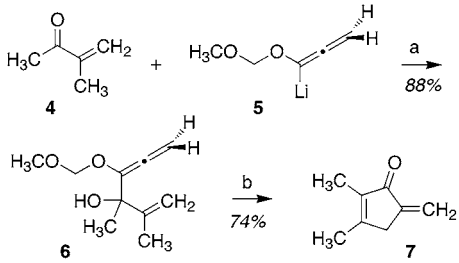
To rationalize the conversion of **3** (or **1**) to **2**, we postulated a 4 π electrocyclization process of a pentadienyl



[1]

(a) CH_2Cl_2, 3-chlorobenzoic acid, 25 °C; (b) CH_2Cl_2, BF_3•Et_2O, 0 °C.

cation.[5] The details of the mechanism will be discussed in a later section of this Account. This hypothesis allowed us to design the three variants of the process that are described below.



[2]

(a) 4 equiv **5**, THF, Et_2O, -78 °C; 88%; (b) 3 equiv TFAA, 5 equiv 2,6-lutidine, CH_2Cl_2, -20 °C; 74%.

The first variant of the cyclopentannelation involves the cyclization of a tertiary alcohol (viz. **3**, **6**). An application of this process to the synthesis of methylenomycin B (**7**) is shown in eq 2. 3-Methyl-3-buten-2-one **4** was treated with 1-lithio-1-(methoxy)methoxyallene **5** to produce tertiary alcohol **6** in 88% yield.[6] Exposure of **6** to 3 equiv of trifluoroacetic anhydride (TFAA) and 5 equiv of 2,6-lutidine in dichloromethane at −20 °C led to the very simple fungal antibiotic **7** in 74% yield. A variety of protic and Lewis acids can be used successfully for the cyclization step, including ferric chloride, conditions developed for the Nazarov reaction by Denmark.[7]

The second variant of the reaction is illustrated by the preparation of prostaglandin analogue **11** and involves the intermediacy of allenyl ketone **10** (eq 3).[8] Addition of lithioallene **9** to Weinreb amide **8** at −78 °C, followed by quenching of the reaction mixture with aq NaH_2PO_4 led to cyclopentenone **11** in 80% yield. Ketone **10**, the presumed reaction intermediate, was not detected. There are at least two features of this reaction that are noteworthy. First, the conditions for the cyclization are extraordinarily mild, and second, there is a marked kinetic

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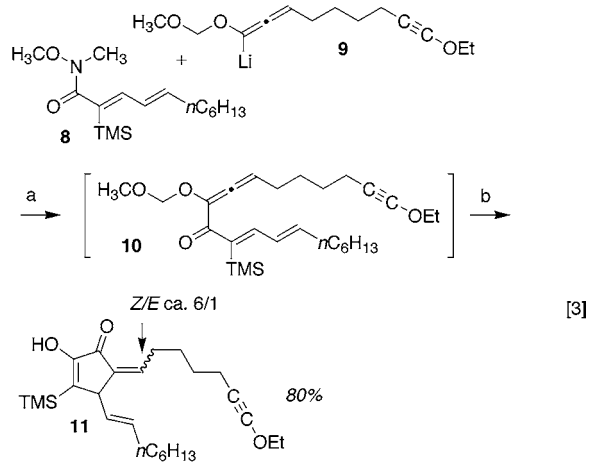
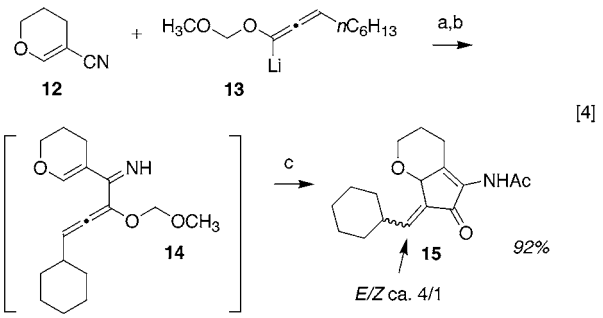


[3]

(a) THF, Et_2O, -78 °C; (b) aq NaH_2PO_4; 80%.

preference for formation of the *Z* isomer of the exocyclic double bond: product **11** was isolated as a 6/1 mixture of *Z* and *E* isomers.



[4]

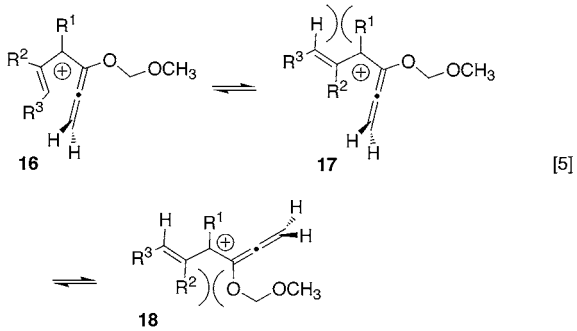
(a) THF, -78 °C; (b) aq $(NH_4)H_2PO_4$; (c) EtOAc, pyr, DMAP (cat.), Ac_2O; 92% (4/1 *E/Z*).

The third variant involves the addition of a lithioallene to an α,β-unsaturated nitrile (eq 4).[9] For example, addition of **13** to nitrile **12**, followed by quenching with aq $(NH_4)H_2PO_4$, led to a cyclic α-amino ketone. *N*-Acetylation led to **15** in 92% overall yield as a 4/1 mixture of *E* and *Z* isomers. Like the second variant, the cyclization in this case is very facile and probably proceeds through the intermediacy of a protonated imine. The α-aminoenones that are the primary reaction products are chromatographically isolable but have a tendency to polymerize on standing, so they are conveniently isolated as acetamides. The ratio of geometrical isomers of the exocyclic double bond reflects isomerization that inevitably takes place during the acetylation.

This appears to be the first example of an imino-Nazarov reaction. The classical imino-Nazarov cyclization is energetically disfavored because the ring-open cation is strongly stabilized through electron pair donation by the nitrogen atom.[10] The reason the cyclization that leads to **14** is successful is because an unfavorable equilibrium for the cyclization can be overcome by irreversible loss of the methoxymethyl cation from the cyclic product.

Limitations

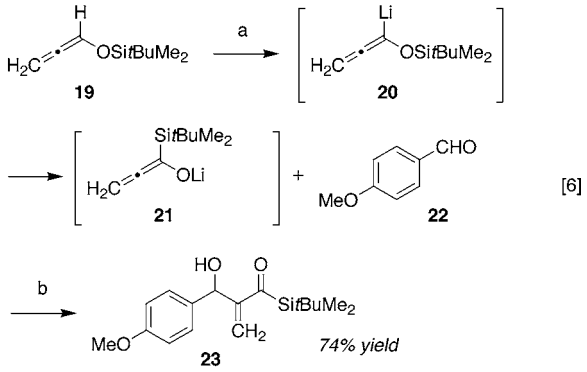
The method appears to be reasonably versatile, and although it can be used to access a wide variety of cyclopentenones, there are some limitations. One limitation, apparently, is that the α,β-unsaturated ketone, amide or nitrile must bear a non-hydrogen α substituent. For example, the allenyl ketone related to **10** having a hydrogen atom in place of the α-trimethylsilyl group underwent cyclization in <10% yield. We are not certain of the origin of this effect, but it may be related to the population of the U-shaped conformer **16** of the pentadienyl cation (eq 5). Since the cyclization of necessity must take place through conformer **16**, any factor that diminishes the proportion of **16** in the equilibrium mixture of conformers of the pentadienyl cation can be expected to adversely affect the cyclization yield. When R^1 or R^2 are larger than a hydrogen atom, conformers **17** and **18** are disfavored relative to **16**.[11] Assuming that the conformational equilibrium is rapidly established, this would result in a mixture enriched in **16**, and a favorable cyclization.[12] We have only encountered one exception to this generalization.[13] This discussion underscores a fundamental difference between the classical Nazarov reaction of a divinyl ketone and the cyclization that takes place through the allenyl ether intermediates (viz. **6**, **10**, and **14**). Whereas the pentadienyl cation may be formed reversibly and may have a long lifetime in the classical Nazarov reaction, in the case of the allenyl ethers, this is probably not the case because of the multiplicity of acid-catalyzed decomposition pathways available. As a corollary, cyclization in the present case must take place rapidly in order to be successful.



[5]

There appear to be some restrictions on the ether substituent of the allene. Although we have consistently obtained the best yields for cyclization in the case of methoxymethyl allenyl ether, 2-tetrahydropyranyl, (2-ethoxy)ethyl and (methylthio)methyl also work.[14] Apparently, in order for the cyclization to succeed, it is necessary that the ether fragment on the allene be lost from the cyclic intermediate as a stable carbocation, and that this process take place rapidly. This suggests that allenyl trialkylsilyl ethers might also be useful for the cyclopentannelation. However, these materials lead to a different reaction manifold. For example, sequential treatment of

a solution of *tert*-butyldimethylsilyl ether **19** in THF with *tert*-BuLi at −78 °C and *p*-methoxybenzaldehyde **22** led to α,*β*-unsaturated acylsilane **23** in 74% isolated yield (eq 6).[15] This reaction presumably takes place through a "reverse-Brook" rearrangement of **20** to give enolate **21**. In our 1994 communication, we stated that **19** can be used successfully for the cyclopentannelation reaction. In light of our more recent results, this statement is probably wrong.

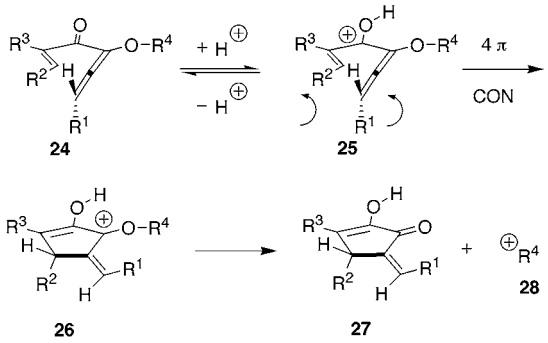


[6]

(a) *t*-BuLi, THF, -78 °C; (b) add **22** at -78 °C; 74%.

Mechanism

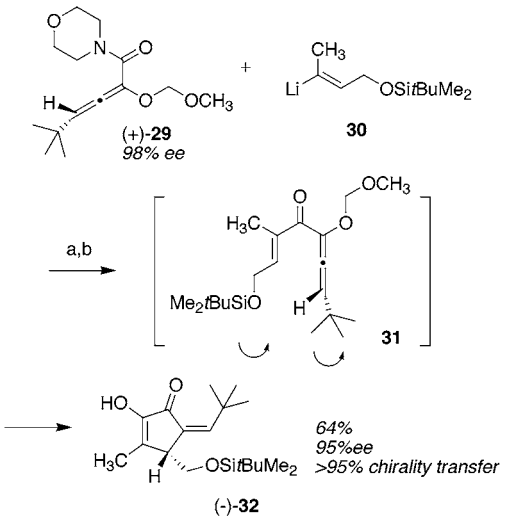
All mechanisms represent oversimplifications. This should be borne in mind during the discussion that follows. Our hypothesis for the mechanism of cyclization of the allenyl ketones (viz. **10**) is summarized in eq 7. Although we have never been able to isolate α-allenyl ketones such as **24**, it is reasonable to postulate these as reaction intermediates. Reversible protonation of **24** leads to pentadienyl cation **25** which can undergo thermally allowed conrotatory ring closure to give **26**. This process is accompanied by relief of strain associated with the allene function. Loss of R^4 as a stable cation leads irreversibly to **27**. This process must take place rapidly; otherwise, decomposition of cation **26** through rearrangements and proton loss will erode the yield of **27**. The stereochemistry determining step is the ring closure of **25** to **26**. The allene function in **24** is stereogenic ($R^1 \neq H$). Although conrotation in both the clockwise and the counterclockwise sense is allowed, for steric reasons **25** will preferentially undergo counterclockwise conrotation as shown. In this way the steric bulk of R^1 moves away from R^2. This has two consequences. First, the exocyclic double bond in **27** will have a preference for the *Z* geometry, as was seen in **11**. Second, the cyclization will be accompanied by transfer of axial asymmetry from the allene to tetrahedral asymmetry of the ring carbon in **27**. It follows from this discussion that transfer of asymmetry during the cyclization will be most efficient when R^1 is a large group, such as *tert*-butyl. It also follows that any *E* to *Z* isomerization of **24** will lead to a nonstereoselective cyclization reaction.



[7]

Asymmetric Cyclopentannelations

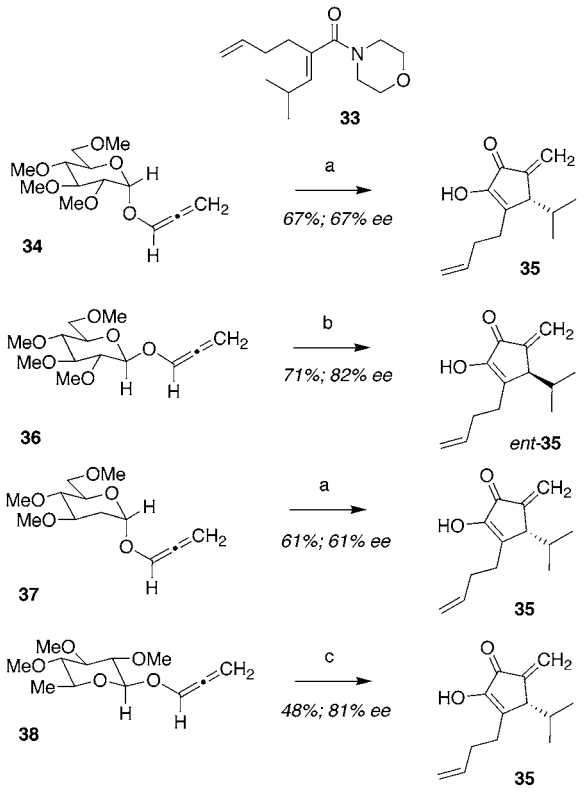
Support for the mechanistic hypothesis was obtained when we examined the cyclization reactions of chiral, nonracemic allene ethers. Methods for the enantioselective synthesis of allene ethers are known, notably those due to Alexakis[16] and Hoppe;[17] however, they are not well-suited for the preparation of alkoxyalkyl allenyl ethers. To get around the problem of enantioselective allene ether synthesis, we decided to resolve allene enantiomers by preparative chiral HPLC. The racemate of **29** was prepared through the carboxylic acid, which was formed by trapping the lithioallene with carbon dioxide (eq 8).[18] The chromatographic resolution of enantiomers was accomplished on a 10 mm × 250 mm Chiralcel OD column. Allenamide (+)-**29** (98% ee) was combined with vinyllithium **30** to produce cyclopentenone (−)-**32** in 64% yield. The putative allenyl ketone intermediate **31** was not isolated but underwent spontaneous cyclization during workup with aqueous NaH_2PO_4. Product (−)-**32** was isolated in 95% ee; therefore, chirality transfer from the allene was >95%. The absolute stereochemistry of (−)-**32** and of (+)-**29** in each case was determined crystallographically. The absolute stereochemistry of (−)-**32** can be understood by postulating a counterclockwise conrotation of **31**. The geometry of the exocyclic alkene and the absolute stereochemistry of (−)-**32** are consistent with the mechanistic hypothesis.



[8]

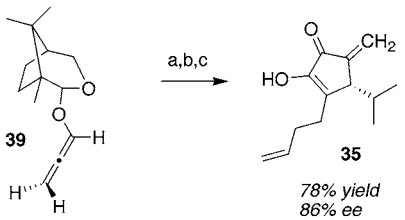
(a) THF, -78 °C, 30 min; (b) aq KH_2PO_4; 64%, 95% ee.

Whether an asymmetric synthesis of five-membered rings based on the reaction that has been discussed in the preceding paragraph can ever become practical will depend on whether a general synthesis of chiral, nonracemic allene ethers such as **29** can be developed. Nevertheless, there is an asymmetric cyclopentannelation reaction that does not depend on the axial chirality of the allene for the transfer of asymmetry, the reaction of γ,γ-unsubstituted allenyl ethers. Our first choice was to examine chiral auxiliaries on the allene.



(a) (i) *n*-BuLi, LiCl, THF, -78°C; (ii) -78°C, 1 h, **33**; (iii) HCl, EtOH, -78°C; (b) (i) *n*-BuLi, LiCl, THF, -78°C; (ii) -78°C, 1 h, **33**; warm to -40°C; cool to -78°C; (iii) HCl, HFIP, 0°C; (c) (i) *n*-BuLi, LiCl, THF, -78°C; (ii) -78°C to -45°C, 1 h, **33**; cool to -78°C; (iii) HCl, HFIP, 0°C.

In order for a chiral auxiliary to be useful, it must be reasonably cheap, and both enantiomeric forms should be commercially available. It may then seem peculiar that we first examined auxiliaries based on D-glucose:L-glucose is not a practical starting material for a chiral auxiliary. A reason to favor a sugar-derived auxiliary is because, like methoxymethyl or tetrahydropyranyl, the ether fragment can be lost from the cyclic intermediate as a stable cation. As will be discussed, both enantiomers of the cyclopentenone products are available from D-glucose derived auxiliaries. That this would turn out to be the case was not obvious to us from the outset. The first chiral auxiliary that we examined was allene **34**, derived from the permethyl ether of α-D-glucose.[19] α-Deprotonation of the allene function took place readily; however, the derived allenyllithium species was not a good nucleophile. In order for addition to morpholino amides to take place, it was necessary to add 4 equiv of LiCl to the reaction mixture. Under these conditions addition to amide **33** took place in good yield. Cyclization of the adduct by exposure to HCl in ethanol led to cyclopentenone **35** in 67% yield and in 67% ee. This was our first example of the asymmetric cyclopentannelation using a chiral auxiliary on the allene. It is worth pointing out that the auxiliary is "traceless"; it is cleaved from the product during the cyclization reaction, and no separate step is needed for its cleavage. Out of curiosity we tried the same process with auxiliary **36**, which differs from **34** only in the stereochemistry of the anomeric carbon atom. To our surprise, the product that was formed in 71% yield and in 82% ee was the enantiomer of **35**. We then tried two more experiments. Auxiliary **37** that was prepared from 2-deoxy-D-glucose gave essentially the same result as **34**. Finally, we examined L-6-deoxyglucose-derived allene **38**, which was prepared from cheap 3,4-di-*O*-acetyl-6-deoxy-L-glucal. Auxiliary **38** is the pseudoenantiomer of **36** and lacks the C6 methoxyl that is present in **36**. Cyclization led to **35** in 48% yield and in 81% ee. One conclusion that can be drawn from this study is that higher enantiomeric excesses of products are observed in the case of β-anomers **36** and **38**. Another conclusion is that neither the methoxyl at C2 nor the one at C6 exerts a strong influence on the optical purity of the product. This latter follows from a comparison of **34** with **37** and of **36** with **38**. What the results with all four auxiliaries show is that the absolute stereochemistry of the product correlates with the absolute stereochemistry of the anomeric carbon atom regardless of whether the allene is α or β. This suggests that an interaction involving the pyran oxygen atom of the auxiliary is critical for determining the product stereochemistry.

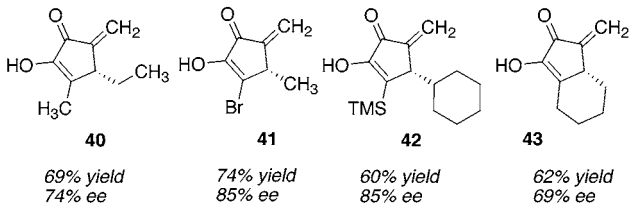


[9]

(a) *n*-BuLi, THF, -78 °C; (b) add **33**; -78 °C to -30 °C, 1 h; (c) HCl, HFIP/TFE (1/1), -78 °C; 78%, 86% ee.

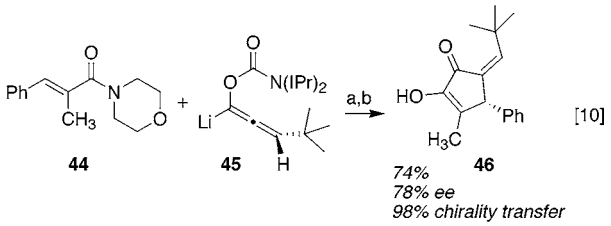
Although the sugar-derived auxiliaries led to preparatively useful results, especially in the case of **36**, there were two shortcomings associated with all of them. First, the nucleophilicity of the derived allenyllithium species was limited. Second, we noted an erosion in the ee of products when we scaled the reactions up from 0.2 mmol to 4 mmol. This led us to explore the camphor-derived auxiliary **39** (eq 9).[20] Camphor is an attractive starting material for chiral auxiliary synthesis, since both enantiomers are

commercially available and cheap. Auxiliary **39** proved to be generally useful for the asymmetric synthesis of cyclopentenones. α-Deprotonation, followed by trapping with amide **33** and acid-mediated cyclization in a mixture of hexafluoro-2-propanol (HFIP) and trifluoroethanol (TFE) led to **35** in 78% yield and in 86% ee. Cyclopentenone **35** was a key intermediate in our recent synthesis of natural roseophilin (*20*).

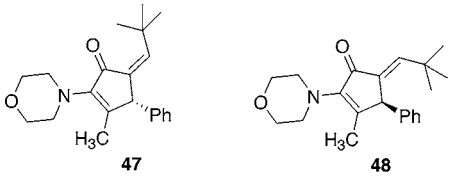


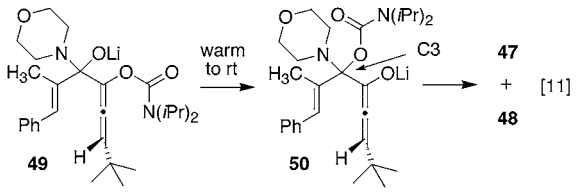
Shown above are some representative examples of cyclopentenones that have been prepared from **39**. The cyclization appears to be tolerant of a variety of substitution patterns and heteroatoms. The absolute stereochemistry has been unambiguously determined in two cases, one of which is **35**, and the other is **32**. The stereochemical assignment in **40**−**43** was done by analogy, an admittedly risky approach. For example, an indication of the mechanistic complexity inherent to this system that might confound stereochemical predictions can be appreciated through the work of Hoppe and co-workers (eq 10).[21] Axially chiral allenyllithium species **45** was added to morpholino amide **44** in toluene at −78 °C. After 2.5 h, the reaction mixture was transferred rapidly via cannula to 5% HCl in ethanol, to produce *Z* cyclopentenone **46** in 74% yield with 98% chirality transfer from **45**. This result is fully consistent with a conrotatory cyclization, the direction being controlled by the steric bulk of the *tert*-butyl group, just as was the case for **31** (eq 8). However, when the addition of **45** to **44** was performed at −78 °C and the reaction mixture warmed to room temperature for 1 h prior to being treated with 2N HCl, two products, **47** and **48**, were isolated in 50% (79% ee) and 24% (80% ee) yield, respectively. In both cases chirality transfer from **45** was >98%. This is surprising because it suggests that the direction of conrotatory ring closure leading to **47** and **48** is controlled not by the axial chirality of the allene, but by the stereochemistry of C3 (eq 11), with the product ratio reflecting the diastereoselection for the addition of **45** to the amide carbonyl group of **44**. Upon warming of **49**, transfer of the carbamoyl group takes place to give allenolate **50** as a mixture of C3 diastereomers. Conrotatory ring closure then takes place according to an allowed anti S_E' substitution of the allylic system. Hoppe and coworkers have demonstrated that the mechanism is not unique to this example. A related example will be discussed later in this Account.

Hoppe uses sparteine-mediated enantioselective deprotonation to prepare **45**.[17] One can also make use of the camphor-derived chiral auxiliary to prepare axially chiral

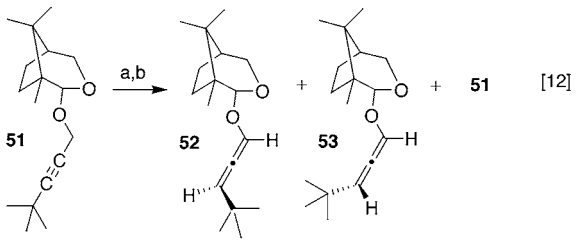


(a) PhMe, 2.5 h, -78 °C; (b) transfer rapidly via cannula into 5% HCl in EtOH.

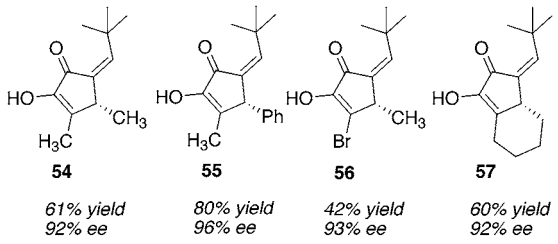




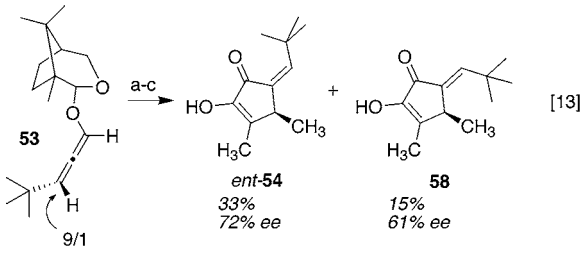
allene ethers. Exposure of propargyl ether **51** to *t*-BuLi at −78 °C, followed by quenching of the anion with *tert*-butyl alcohol, led to a 3/1 mixture of allene diastereomers **52** and **53**, along with recovered **51** (eq 12).[22] Major diastereomer **52** was isolated in 65% yield. For cyclopentannelations making use of **52**, in which the auxiliary as well as the axial chirality of the allene both influence the absolute stereochemistry of the product, one must consider the matched/mismatched issue. As it turned out, allene **52** represents the matched case, and as would be expected, the enantiomeric excesses of the derived cyclopentenone products were very high. Some representative examples are shown below. By neutralizing the acid in the cyclization reaction mixture at low temperature, we were able to isolate the kinetically favored *Z* isomers of the exocyclic alkene.



(a) 2 equiv *t*-BuLi, -78 °C, 2 h; (b) *t*-BuOH; 65% of **52**.



An obvious question to ask is whether the auxiliary or the axially chiral allene exerts the dominant influence on the absolute stereochemical course of the reaction. A 9/1 mixture enriched in allene **53** was subjected to the cyclopentannelation reaction conditions (eq 13).[22] This led to two products, *ent*-**54** and **58** in 33% (72% ee) and 15% (61% ee) yield, respectively. The absolute stereochemistry in both products is the opposite of that of the cyclopentenones derived from **52**, and the enantiomeric excesses of both products are lower. This shows that **53** represents the mismatched case, and that the effect due to the *tert*-butyl group in **53** completely overwhelms the chiral auxiliary.



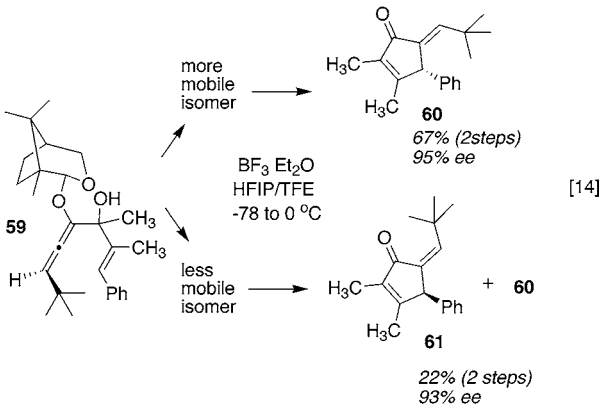
[13]

(a) *n*-BuLi, THF, -78 °C; (b) add 2-methyl-1-morpholin-4-yl-but-2-en-1-one; -20 °C; -78 °C; (c) HCl, HFIP/TFE, -78 °C.

It is clear from the enantiomeric excesses of **54**−**57** that allene **52** is potentially very useful for the enantioselective synthesis of cyclopentenones. The question we had was whether similarly high levels of enantioselection could be realized from the reaction of **52** with α,β-unsaturated ketones. The diastereomeric tertiary alcohols **59** that were prepared from **52** were separated by flash column chromatography and were cyclized independently.[22] The chromatographically less mobile diastereomer gave a 1/1 mixture of **60** and **61**, whereas the more mobile diastereomer produced **60** with <5% of a *Z* diastereomer of unknown absolute configuration. These results bear similarity to Hoppe's results (eq 11).[21] In the case of tertiary alcohols such as **59**, the sense of conrotation is strongly influenced by the stereochemistry of the tertiary alcohol. This seems to indicate that formation of the C−C bond takes place in part as the tertiary alcohol starts to ionize. All of this suggests that at the present state of development, the asymmetric cyclopentannelation will be most useful for the synthesis of α-hydroxy cyclopentenones.

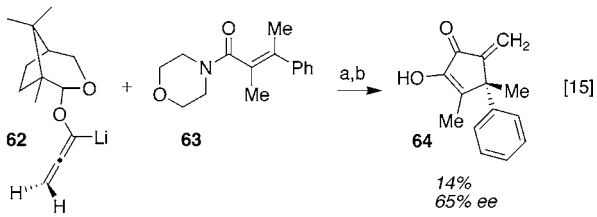
Conclusions

In this Account I have tried to present an overview of a type of Nazarov reaction that we discovered accidentally. The structures shown at the end of this section give some indication of the scope of the reaction. The enantioselective versions of the cyclization have been described in five papers.[18,19,20(a),21,22]



[14]

Although this aspect of our work has enjoyed some early success,

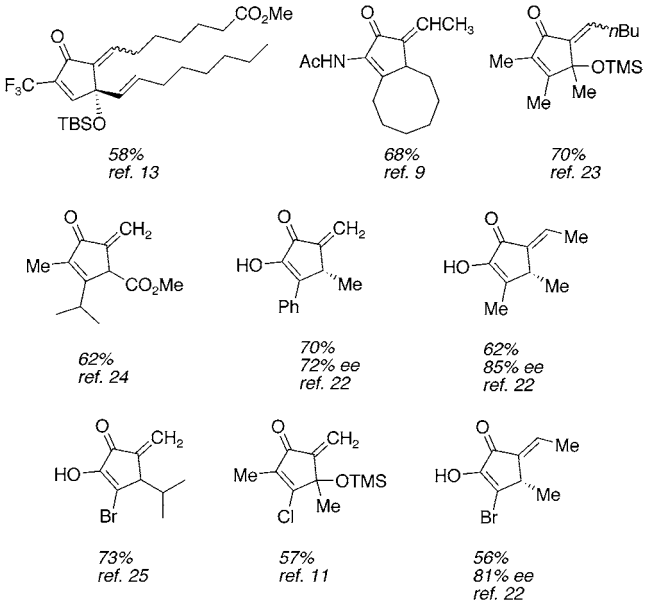


[15]

(a) THF, -78 °C; warm to -30 °C; 1 h; (b) HCl, HFIP/TFE (1/1), -78 °C.

there are many interesting problems in this area that beg to be explored. For example, an important problem in synthesis is the enantioselective construction of quaternary carbon atoms. Orbital symmetry controlled reactions, such as the 4 π electrocyclization that has been the focus of this Account, offer some of the most attractive solutions, in no small part because of the ability to make powerful stereochemical predictions based on the mechanism. Our single foray into this area is summarized in eq 15.[22] The low product yield may be due to deprotonation of the β-methyl group of **63**, which takes place competitively with nucleophilic addition to the carbonyl group. There are many remedies for this problem, and while the ee of the product is modest, a new generation of chiral auxiliaries or catalyzed versions of the cyclopentannelation may offer improvements. A challenge for the future of this research is to render the cyclizations of allene **52** synthetically useful. Although the enantiomeric excesses of products **54**−**57** are excellent, the obligatory presence of the *tert*-butyl group diminishes their appeal. It may be possible to cleave the *tert*-butylmethylene group from such products by means of a retro aldol process; however, it remains to be seen whether this can be accomplished without racemization. Alternatively, a trialkylsilyl group in place of a *tert*-butyl group in **52** may lead to products of high optical purity. This would produce cyclic products bearing a trialkylsilyl group on the exocyclic double bond. The trialkylsilyl group could either be removed through protiodesilylation, or it could be used for subsequent functionalization of the product. We hope to explore some of these issues in the future. The part of our research effort

that examines the allene ether Nazarov chemistry has been intellectually interesting. I hope that the reader has derived some enjoyment from reading this brief Account.



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References

(1) Tius, M. A.; Astrab, D. P. A Cationic Cyclopentannelation. *Tetrahedron Lett.* **1984**, *25*, 1539−1542.

(2) This begs the question: "What happens to **1** if the *m*-CPBA is buffered?" For the answer, the reader is directed to: Tius, M. A.; Cullingham, J. M.; Ali, S. Hydroxyquinone Annelation. *J. Chem. Soc., Chem. Commun.* **1989**, 867−869.

(3) Tius, M. A.; Trehan, S. A Concise Synthesis of D,L-Methylenomycin A and D,L-*epi*-Methylenomycin A. *J. Org. Chem.* **1989**, *54*, 46−51.

(4) Interesting related work has been reported by others: (a) Browder, C. C.; Marmsaeter, F. P.; West, F. G. Highly Efficient Trapping of the Nazarov Intermediate with Substituted Arenes. *Org. Lett.* **2001**, *3*, 3033−3035. (b) Giese, S.; West, F. G. Ionic Hydrogenation of Oxyallyl Intermediates: The Reductive Nazarov Cyclization. *Tetrahedron* **2000**, *56*, 10221−10228. (c) Bender, J. A.; Arif, A. M.; West, F. G. Nazarov-Initiated Diastereoselective Cascade Polycyclization of Aryltrienones. *J. Am. Chem. Soc.* **1999**, *121*, 7443−7444. (d) Hashmi, A. S. K.; Bats, J. W.; Choi, J.-H.; Schwarz, L. Isomerizations on Silica Gel: Synthesis of Allenyl Ketones and the First Nazarov Cyclizations of Vinyl Allenyl Ketones. *Tetrahedron Lett.* **1998**, *39*, 7491−7494. (e) Jacobi, P. A.; Armacost, L. M.; Brielmann, H. L.; Cann, R. O.; Kravitz, J. I.; Martinelli, M. J. Enynones in Organic Synthesis. 6. Synthesis of Spirocyclic Methylenecyclopentenones and Analogues of the Methylenomycin Class of Antibiotics. Mechanism of Phenol Catalysis. *J. Org. Chem.* **1994**, *59*, 5292−5304. (f) Jacobi, P. A.; Cann, R. O.; Skibbie, D. F. A Convenient Synthesis of Methylenomycin B. Further Mechanistic Studies on the SET Catalyzed Electrocyclization of Enynones. *Tetrahedron Lett.* **1992**, *33*, 2265−2268. (g) Denmark, S. E.; Wallace, M. A.; Walker, C. B., Jr. Silicon-Directed Nazarov Cyclizations. 8. Stereoelectronic Control of Torquoselectivity. *J. Org. Chem.* **1990**, *55*, 5543−5545. (h) Jacobi, P. A.; Armacost, L. M.; Kravitz, J. I.; Martinelli, M. J.; Selnick, H. G. Enynones in Organic Synthesis. I. Spiroannulation by Tandem oxy-Cope Rearrangement-Electrocyclic Ring Closure. *Tetrahedron Lett.* **1988**, *29*, 6865−6868, et seq.

(5) Habermas, K. L.; Denmark, S.; Jones, T. K. The Nazarov Cyclization. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1994; Vol. 45, pp 1−158.

(6) (a) Tius, M. A.; Patterson, G. M. L.; Astrab, D. P. Synthesis and in vitro Activity of some Methylenomycin Analogues. *J. Antibiotics* **1985**, *38*, 1061−1067. (b) Tius, M. A.; Astrab, D. P.; Fauq, A. H.; Ousset, J.-B.; Trehan, S. An Efficient Methylenomycin Synthesis. *J. Am. Chem. Soc.* **1986**, *108*, 3438−3442.

(7) (a) Jones, T. K.; Denmark, S. E. Silicon-directed Nazarov reactions. II. Preparation and Cyclization of β-Silyl-Substituted Divinyl Ketones. *Helv. Chim. Acta* **1983**, *66*, 2377−2396. (b) Jones, T. K.; Denmark, S. E. Silicon-directed Nazarov Reactions. III. Stereochemical and Mechanistic Considerations. *Helv. Chim. Acta* **1983**, *66*, 2397−2411.

(8) Tius, M. A.; Busch-Petersen, J.; Yamashita, M. Cross-Conjugated Cyclopentenone Prostaglandins. Synthesis of Δ^7-10-Chloro-15-deoxy PGA_1 Ethyl Ester. *Tetrahedron Lett.* **1998**, *39*, 4219−4222.

(9) Tius, M. A.; Chu, C. C.; Nieves-Colberg, R. An Imino Nazarov Cyclization. *Tetrahedron Lett.* **2001**, *42*, 2419−2422.

(10) Smith, D. A.; Ulmer, C. W., II Effects of Substituents in the 3-Position on the [2 + 2] Pentadienyl Cation Electrocyclization. *J. Org. Chem.* **1997**, *62*, 5110−5115.

(11) Tius, M. A.; Kwok, C.-K.; Gu, X.-q.; Zhao, C. Cyclopentannelation Reaction for Rapid Assembly of Multifunctional Products. (D,L)-Desepoxymethylenomycin A Methyl Ester. *Synthetic Commun.* **1994**, *24*, 871−885.

(12) (a) Shoppee, C. W.; Cooke, B. J. A. Electrocyclic Reactions. Part III. Some Reactions of 2,4-Dimethyl-1,5-diphenylpenta-1,4-dien-3-one (αα′-Dimethylbenzylideneacetone). *J. Chem. Soc., Perkin Trans. 1* **1973**, 1026−1032. (b) Asokan, C. V.; Ila, H.; Junjappa, H. Ketendithioacetals 39. Novel Solvolytic Rearrangements of 1,1-bis-(Methylthio)-2,4-dimethyl-5-aryl (or Styryl)-1,4-pentadien-3-ols to Cyclopentanone Derivatives. *Tetrahedron Lett.* **1985**, *26*, 1087−1091. (c) Asokan, C. V.; Bhattacharji, S.; Ila, H.; Junjappa, H. Polarized ketene S,S- and S,N-acetals. Part 64. Synthesis of Methyl 5-Aryl-3-oxo-4-pentenoates and Novel Substituted Cyclopentenones. *Synthesis* **1988**, 281−283.

(13) Tius, M. A.; Hu, H.; Kawakami, J. K.; Busch-Petersen, J. Synthesis of 15-Deoxy-12-Hydroxy-10-trifluoromethyl-Δ^7-PGA_1 Methyl Ester. *J. Org. Chem.* **1998**, *63*, 5971−5976.

(14) Tius, M. A.; Ousset, J.-B.; Astrab, D. P.; Fauq, A. H.; Trehan, S. Allene Ethers for Cationic Cyclopentannelation. *Tetrahedron Lett.* **1989**, *30*, 923−924.

(15) (a) Stergiades, I. A.; Tius, M. A. α,β-Unsaturated Acyl Silanes. *J. Org. Chem.* **1999**, *64*, 7547−7551. (b) Tius, M. A.; Hu, H. Synthesis of α-Substituted α,β-Unsaturated Acylsilanes. *Tetrahedron Lett.* **1998**, *39*, 5937−5940.

(16) Alexakis, A.; Mangeney, P.; Normant, J. F. Diastereoselective β-elimination. Synthesis of Chiral Alkoxy-Allenes. *Tetrahedron Lett.* **1985**, *26*, 4197−4200.

(17) Schultz-Fademrecht, C.; Wibbeling, B.; Fröhlich, R.; Hoppe, D. Synthesis of Enantiomerically Enriched Allenes by (−)-Sparteine-Mediated Lithiation of Alkynyl Carbamates. *Org. Lett.* **2001**, *3*, 1221−1224.

(18) Hu, H.; Smith, D.; Cramer, R. E.; Tius, M. A. Asymmetric Cyclopentannelation. Axial to Tetrahedral Chirality Transfer. *J. Am. Chem. Soc.* **1999**, *121*, 9895−9896.

(19) Harrington, P. E.; Tius, M. A. Asymmetric Cyclopentannelation. Chiral Auxiliary on the Allene. *Org. Lett.* **2000**, *2*, 2447−2450.

(20) (a) Harrington, P. E.; Tius, M. A. Synthesis and Absolute Stereochemistry of Roseophilin. *J. Am. Chem. Soc.* **2001**, *123*, 8509−8514. (b) Harrington, P. E.; Tius, M. A. A Formal Total Synthesis of Roseophilin: Cyclopentannelation Approach to the Macrocyclic Core. *Org. Lett.* **1999**, *1*, 649−651.

(21) Schultz-Fademrecht, C.; Tius, M. A.; Grimme, S.; Wibbeling, B.; Hoppe, D. Synthesis of Enantioenriched 5-Alkylidene-2-cyclopentenones from Chiral Allenyl Carbamates: Generation of a Chiral Lithium Allenolate and Allylic Activation for a Conrotatory 4-Electrocyclization. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1532−1535.

(22) Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. Asymmetric Cyclopentannelation. Camphor-Derived Auxiliary. *J. Am. Chem Soc.* **2002**, *124*, 10091−10100.

(23) Tius, M. A.; Zhou, X.-M. Densely Functionalized Cyclopentenones. *Tetrahedron Lett.* **1989**, *30*, 4629−4632.

(24) Tius, M. A.; Drake, D. J. Rapid Assembly of Multifunctional Five-Membered Rings. Application to the Synthesis of (±)-Xanthocidin. *Tetrahedron* **1996**, *52*, 14651−14660.

(25) Nakazaki, A.; Sharma, U.; Tius, M. A. Synthesis of the Hydroazulene Portion of Guanacastepene A from the Cyclopentannelation Reaction. *Org. Lett.* **2002**, *14*, 3363−3366.

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