# Synthetic Applications of the Carbonyl Generating Grob Fragmentation

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## *1. Introduction*

According to Grob,[1,2] a heterolytic fragmentation is a reaction where a molecule with a certain carbon−heteroatom (N, O, S, P, Si, B, or halogen) combination is cleaved under specific mechanistic principles in three fragments. Fragmentation substrates are typically 1,3-diheterofunctionalized compounds featuring a nucelophilic atom with a negative charge or lone electron pair and a leaving group in a 1,3-relationship.[3−6] We restrict this Review to the synthetically most important constellation given below, where a cyclic or acyclic 1,3-diheterosubstituted substrate **I** breaks up into a carbonyl or carbonate fragment **II** along with an olefin **III** and the leaving group $Y^-$ (Figure 1).

Additionally, substrate **I/IV** can also undergo substitution, cyclization, or elimination (Figure 2). However, fragmentation is the main pathway, if the alternatives are disfavored or excluded by additional effects such as optimum stereoelectronic geometries or ring strain (in cyclic substrates).

### 1.1. History

As early as 1933, a fragmentation was described as a consecutive reaction of a carbocation formation in the dehydration of di-*tert*-butylcarbinol **1** (Scheme 1).[7] Thus, the dehydration of di-*tert*-butylcarbinol **1** at 180 °C yielded 77% of trimethylethylene **2** and isobutylene **6**. At lower temperature, there was additionally a mixture of nonenes. This result can be rationalized by a three-step process: first, the removal of the hydroxyl group of **1** to give a positive charged di-*tert*-carbinyl group **3**, second, methyl migration to the tertiary cation **4**, and, third, the elimination of a *tert*-butyl cation **5** to give trimethylethylene **2** and isobutylene **6**. The generation of the nonenes can be explained by hydrogen loss of one of the intermediate cations **3** or **4**.

In 1945, fragmentation was also observed in the dehydration of di-*tert*-1,3-diols, which resulted in a C−C bond cleavage to ketones and olefins (Scheme 2).[8,9] In analogy to the dehydration of di-*tert*-butylcarbinol **1**, an ionic mechanism is assumed. One hydroxyl group of **7** is transformed into a leaving group by protonation, which after $H_2O$ elimination leads to carbocation **9**. Next, the oxonium ion **11** is cleaved to give the unsaturated fragment **10** and ketone **12**.

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Kathrin Prantz was born in 1981 in Vienna, Austria. She studied Chemistry at the University of Vienna, where she received her master degree in 2005. She completed her Ph.D. in 2009 under the guidance of Professor Mulzer at the University of Vienna on Grob fragmentations used for the generation of trisubstituted double bonds in natural product synthesis.

Johann Mulzer was born in 1944 in Prien, Germany. He completed his Ph.D. in 1974 under the supervision of Rolf Huisgen at Ludwig-Maximilians-Universität in Munich and then joined the research group of E. J. Corey at Harvard University as a postdoctoral fellow. Between 1982 and 1996, he held professorships at the University of Düsseldorf, Freie Universität Berlin, and Frankfurt University. Since 1996, he has been a full professor at the University of Vienna. His main research interests lie in the total synthesis of structurally and physiologically interesting natural products.

Eschenmoser was the first to investigate the behavior of $\beta$-hydroxy ketones under basic conditions and call these

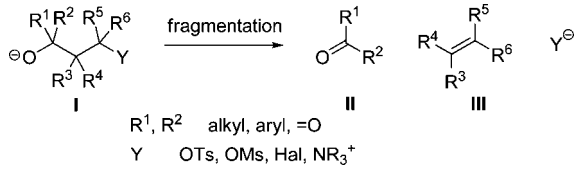



**Figure 1.** Grob fragmentation of a general 1,3-diheterosubstituted substrate.

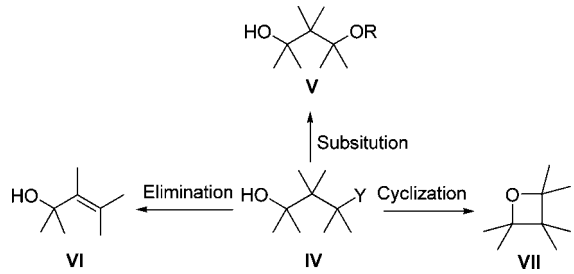
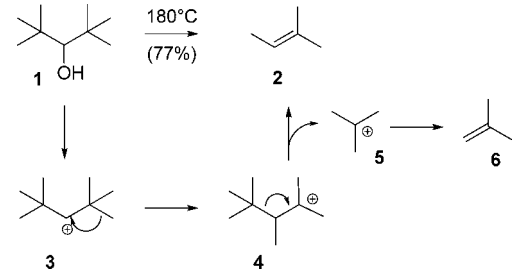
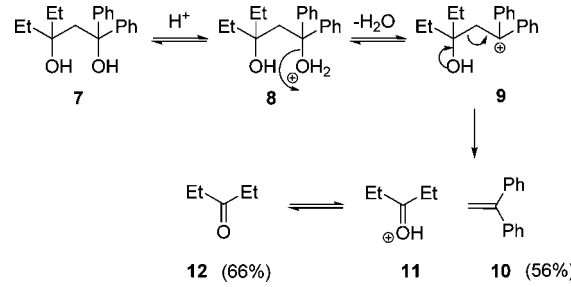



**Figure 2.** Alternative reaction pathways of 1,3-diheterosubstituted compounds.

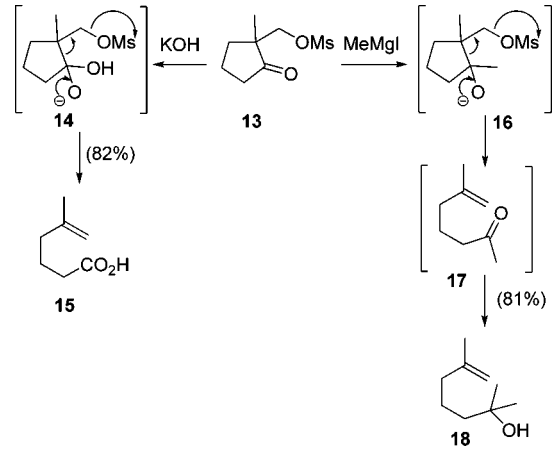
**Scheme 1. Early Fragmentation of Carbocation Observed**



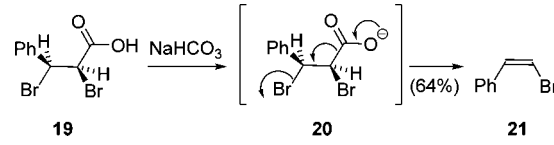

**Scheme 2. Fragmentation of Carbocation into Olefin and Ketone**




**Scheme 3. Eschenmoser's Pioneering Work on Fragmentations**




**Scheme 4. Spontaneous Fragmentation of $\beta$-Bromo Acid 19**



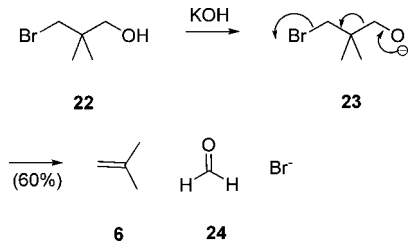

reactions fragmentations (Scheme 3).[10] He observed the formation of *exo*-methylene moieties in **15** and **18** by a fragmentation reaction of **13**, induced by hydroxide or Grignard reagent.

A year later, $\beta$-bromo carboxylic acids were discovered as fragmentation substrates (Scheme 4). The spontaneous decomposition of *trans*-cinnamic acid dibromide **19** that led to *cis*-$\beta$-bromostyrene (**21**) was intensively investigated.[11,12]

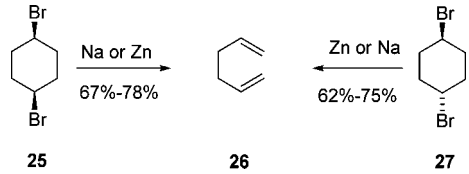
Also, the fragmentation of **22**, another 1,3-diheterosubstituted substrate, was observed by treatment with base (Scheme 5).[13]

In 1955, Grob showed that the treatment of *cis*- or *trans*-1,4-dibromocyclohexanes **25** and **27** with metal led to fragmentation product **26** (Scheme 6).[14] After that time, this

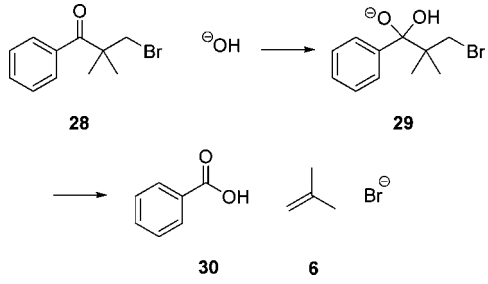
**Scheme 5. Fragmentation of 3-Bromoalcohol 22**



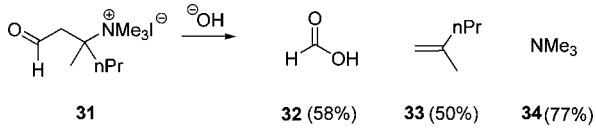

**Scheme 6. Fragmentation of 1,4-Dibromocyclohexane**




**Scheme 7. Mechanistic Investigations of β-Bromo Ketone Fragmentation**



**Scheme 8. β-Amino Aldehyde Fragmentation**



reaction type was named "Grob fragmentation", in more or less glaring disregard of the earlier contributions described above.

First, kinetic investigations were performed with bromopivalophenone **28** (Scheme 7). The fragmentation was found to proceed via a two-step mechanism, both steps being irreversible.[15]

Also, β-amino aldehydes like **31** were used as fragmentation substrate with hydroxide (Scheme 8).[16] The leaving ability of the amino group was increased by transformation into a quaternary ammonium salt.

## 1.2. General Mechanistic Considerations

Mechanistically, fragmentation can proceed via either a one- or a two-step pathway (Figure 3). In the two-step process, the more common possibility is the carbonium ion **X** mechanism, which is similar to an E1 or $S_N1$ reaction. Here, the leaving group is cleaved first to form a carbonium ion **X**, which can then further react via fragmentation, elimination, substitution, or ring-closure. The rate-determining step is the ionization to the carbonium ion **X**. The tendency to ionize is greater when a tertiary and thus stable carbonium ion is formed. Also, the leaving ability of $Y^-$ is important, as the ionization rate increases, for example, from Cl < Br < I. The other possibility is that the electrofugal group **VIII** leaves first to form a carbanion **XI**, which can then eject the leaving group $Y^-$ in the second step. This mechanism is rather rare and can only occur if the carbanion is stabilized by electron-withdrawing substituents and the leaving tendency of $Y^-$ is small. Additionally, fragmentation can occur via free radical intermediates.

In the concerted process, at least five centers contribute to the transition state, which results in strict structural and stereoelectronic requirements for the fragmentation (Figure 4). The lone pair on O, the C1−Y, and C2−C3 σ-bonds must be *anti*-periplanar for maximal orbital overlap in the transition state of the p-orbitals in the newly formed π-bond. In this way, the relative configuration at C1 and C2 is transformed into the *E*/*Z*-geometry of the olefin. The all-*anti*-periplanar arrangement is met in the staggered conformation **IVa** and its rotamers **IVb** and **IVc** around C2−C3, but rotation around C1−C2 leads to unfavorable conformations.[1,2,4,10,17,18]

In the cyclic templates **35**−**39**, the C1−C2−C3-conformations are fixed (Scheme 9), and one can see that the required all-*anti*-periplanar arrangement is present in **36**−**39**, but not in **35**. Consequently, **36**−**39** do undergo Grob fragmentation, and **35** does not.[19]

In a similar way, these stereoelectronic requirements are corroborated by the 3-chlorotropanyl epimers **41** and **43** (Scheme 10).[20] In **41**, the required all-*anti* arrangement is present, and the fragmentation to iminium ion **42** proceeds quantitatively. In contrast, isomer **43** just undergoes substitution and elimination reactions to form products **44** and **45**. Substitution and elimination is also observed exclusively for the carbon analogues **46** and **47**. However, there is a significant difference in reactivity: **41** reacts 13 500 times faster than **46**, whereas **43** and **47** show similar rates. The acceleration of **41** versus **46** is called the "frangomeric effect", and it is considered as a relevant criterion for a concerted fragmentation process.[2]

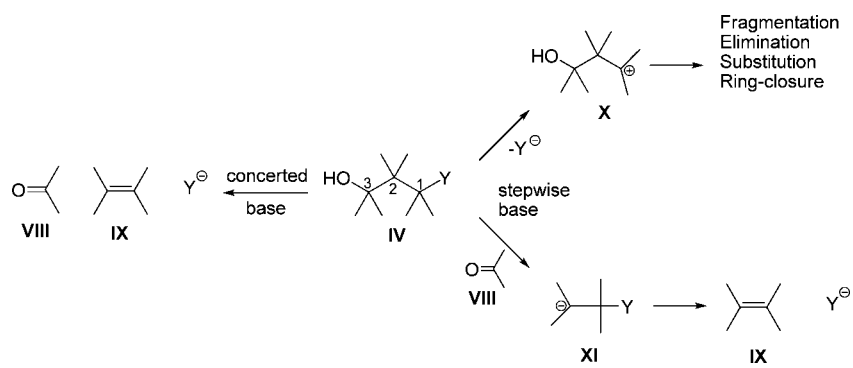



**Figure 3.** Fragmentation of 1,3-diheterosubstituted substrates can proceed via a one- or two-step mechanism.

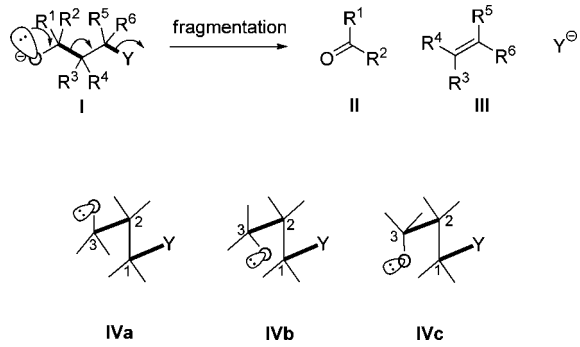
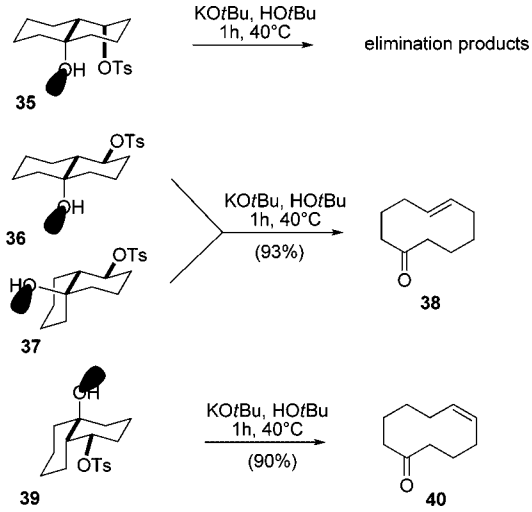
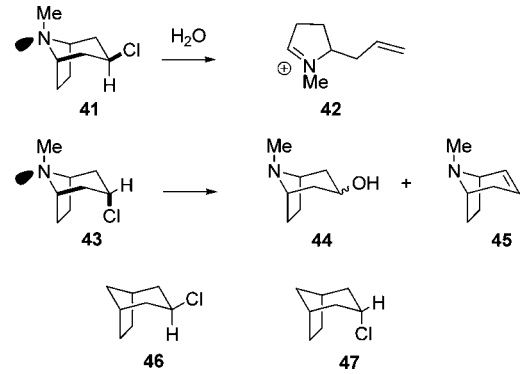



**Figure 4.** Conformational requirements for a concerted Grob fragmentation.

**Scheme 9. Fragmentation on Cyclic Templates**

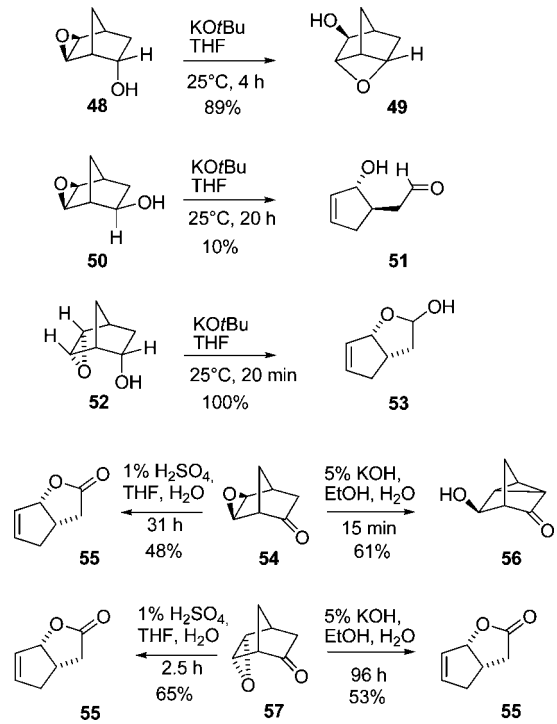



**Scheme 10. Reactivity of Chlorotropanes 41 and 43**

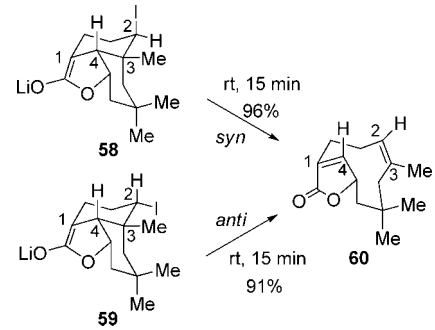



Although the stereoelectronic all-*anti* arrangement appears a general prerequisite of fragmentations, there are, however, a number of examples where syn and anti fragmentations have similar activation parameters. For instance, Holton and Kennedy (Scheme 11) have studied the reaction of the *exo*- and *endo*-[2.2.1-]bicycloheptanyl-epoxy alcohols **48**, **50**, and **52** under basic conditions.[21] Quite surprisingly, they found that despite the *anti*-alignment of the C1−C2 and the C6−O bonds, *exo*-epoxide **48** forms oxetane **49** via $S_N2$-displacement and **50** only reluctantly undergoes fragmentation to generate 10% of cyclopentene **51** among a variety of other products. The *endo*-epoxide **52** however cleanly and rapidly fragments to give the bicyclic acetal **53**. This means that a syn alignment of the C1−C2 and the C6−O bonds (in **52**) is better suited for fragmentation than an anti one (in **48** and **50**). A similar behavior is shown by the corresponding ketones **54** and **57**. The *endo*-derivative **57** fragments much more easily under both basic and acidic conditions than does the *exo*-isomer **54**. The authors interpret their observations with a higher coplanarity of the orbitals involved.

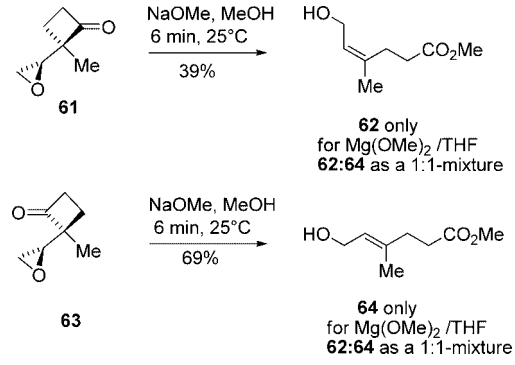
**Scheme 11. Syn Fragmentation Is Favored in *endo*-Epoxides**




**Scheme 12. Syn and Anti Fragmentation via SET Processes**

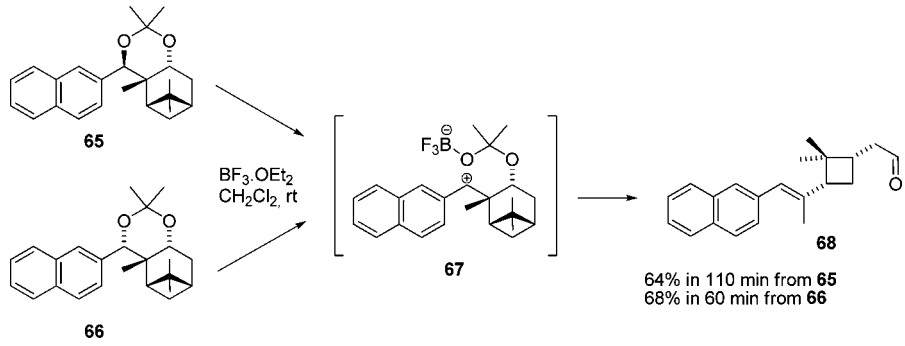



**Scheme 13. Anti Fragmentation of 61 and 63 Is Limited to the NaOMe/MeOH System**

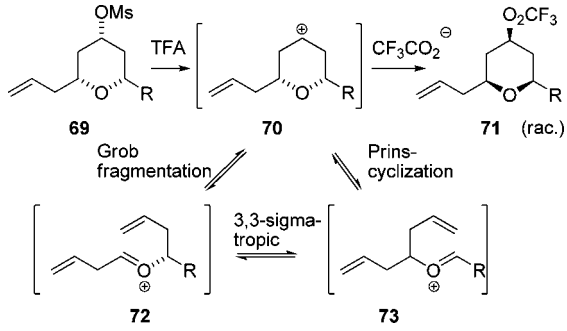



On investigating the epimeric tricyclic enolate iodides **58** and **59**, Wender and Manly found that (*Z*)-olefin **60** is generated independently of the configuration at C2 (Scheme 12).[22] This means that syn and anti fragmentation have similar activation energies, a phenomenon that is explained by assuming an SET free radical mechanism instead of the regular ionic pathway.

**Scheme 14. Under Lewis-Acidic Conditions, Both Syn and Anti Fragmentation Occur**




**Scheme 15. Solvolysis of Mesylate 69**




The epimeric cyclobutanone epoxides **61** and **63** form the corresponding epoxyalcohols **62** and **64** via clean base-induced anti fragmentation (Scheme 13).[23] However, it turned out that this stereoselectivity strongly depends on the conditions. When $Mg(OMe)_2$ in THF is used, from both **61** and **63** 1:1-mixtures of **62** and **64** are generated. The authors claim that chelate formation between the ketone and the epoxide oxygens and magnesium strongly enhances the tendency toward the syn pathway.

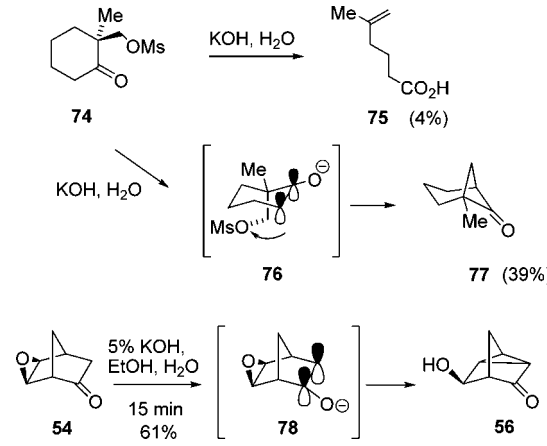
Under acidic conditions, carbenium intermediates may be formed, and the distinction between syn and anti pathways disappears. For example, Barluenga et al. observed that acetonides **65** and **66** both furnish olefin **68** under acidic conditions, probably via the benzylic cation **67**.[24] The *cis*-acetonide **66** reacts faster, presumably due to higher strain relief in forming cation **67** (Scheme 14).

Rychnovsky and Jasti investigated the acid-catalyzed solvolysis of enantioenriched tetrahydropyranyl mesylate **69** (Scheme 15).[25] Racemic trifluoroacetate **71** is formed in 82% yield. The authors postulate a Grob fragmentation of cation **70** to oxonium ion **72**, which racemizes to **73** via a [3.3]-sigmatropic 2-oxonia-Cope rearrangement. Recyclization to **70** is then achieved via Prins reaction.

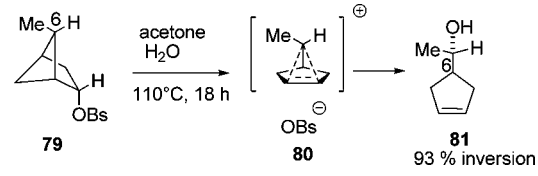
Apart from the syn−anti-dichotomy, the competition of fragmentation versus cyclization in bicyclic ketones implies some interesting stereoelectronic aspects (Scheme 16).[26] Thus, cyclopentanone mesylate **13** under basic conditions cleanly fragments to carboxylic acid **15** as was shown above (Scheme 3). The analogous reaction with cyclohexanone analogue **74**, however, furnishes only 4% of the olefin. The main product is **77**, formed by intramolecular alkylation, which is induced by the favorable orbital interaction in the enolate **76**. A similar situation has already been encountered in enolate **78**, where the $\pi$-orbital of the enolate readily overlaps with the $\sigma^*$-orbital of the epoxide C−O bond.[21]

A more marginal yet interesting aspect of fragmentation stereochemistry is shown in Scheme 17. Kirmse and Zander have shown that the fragmentation of nonracemic brosylate

**Scheme 16. Cyclization versus Fragmentation in Cyclic Ketones**




**Scheme 17. Stereochemical Course of the Fragmentation of 79**



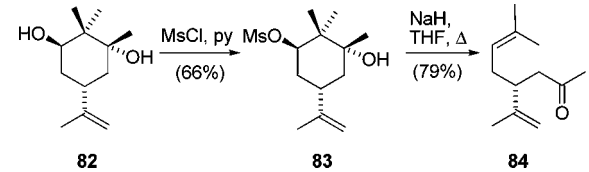

**79** to optically active cyclopentene **81** proceeds via inversion at the electrofugal center C6, presumably via a nonclassical carbenium intermediate **80**.[27]

## 2. Carbonyl Generating Grob Fragmentation via Ring Cleavage

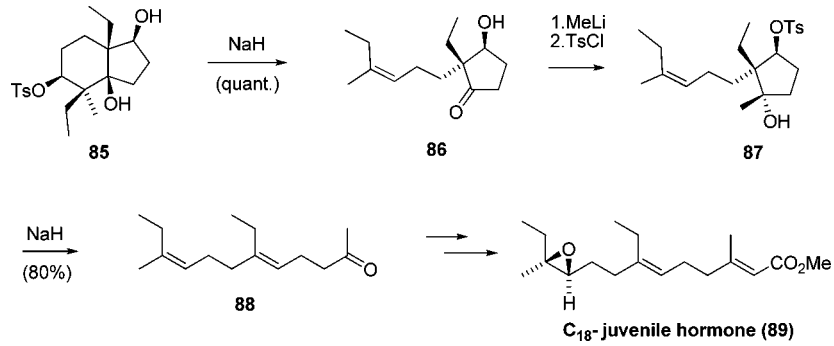
### 2.1. Monosulfated 1,3-Diols

(−)-Carvone was diastereoselectively transformed into diol **82**, which gave $\gamma$-hydroxymesylate **83** as fragmentation precursor after selective mesylation of the secondary alcohol (Scheme 18).[28] Grob fragmentation generated the framework of the lavandulyl system **84**. Fragmentation reactions were used as a convenient method for the stereospecific synthesis of acyclic trisubstituted olefin subunits in cecropia juvenile hormone **89** (Scheme 19).[29] Treatment

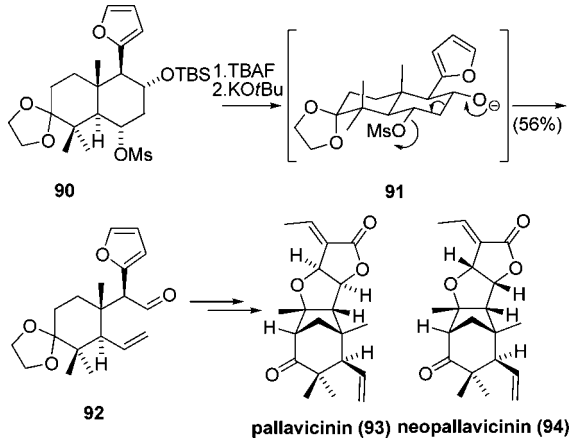
**Scheme 18. The Lavandulyl System by Fragmentation**



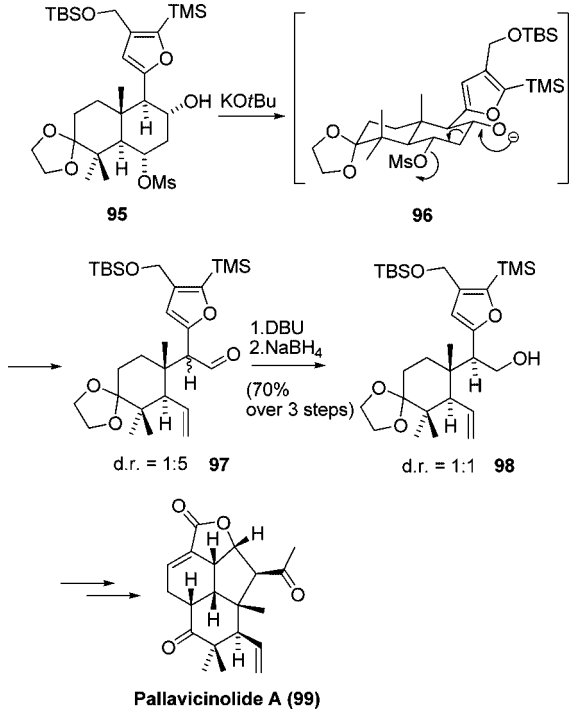
**Scheme 19. Synthesis of Trisubstituted (*Z*)-Olefins in Cecropia Juvenile Hormone**




**Scheme 20. Construction of the Vinyl Moiety in (±)-Pallavicinin (93) and (±)-Neopallavicinin (94)**

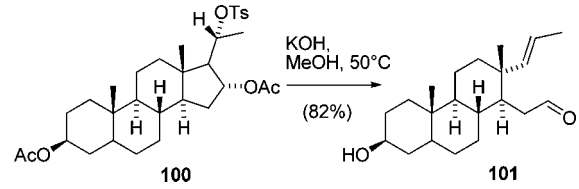



**Scheme 21. Synthesis of the Vinyl Moiety in (±)-Pallavicinolide A (99)**

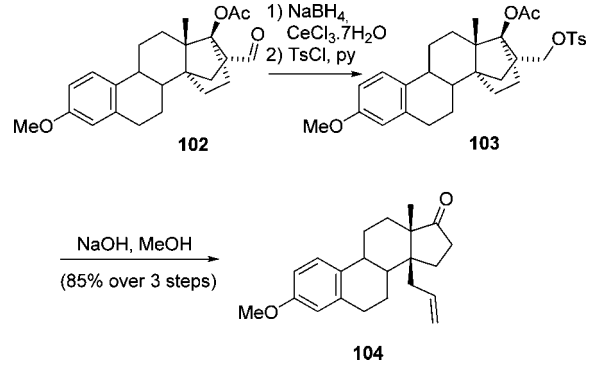



of tosylate **85** with sodium hydride at room temperature gave *cis*-olefin **86** as the desired product. Repetition of the sequence led to hydroxy tosylate **87** and ketone **88**. The total synthesis of (±)-pallavicinin (**93**) and (±)-neopallavicinin (**94**) relied on a Grob fragmentation to generate the vinyl moiety in **92**, which is present in both targets (Scheme 20).[30]

**Scheme 22. Removal of Acetate and Fragmentation in One Pot**



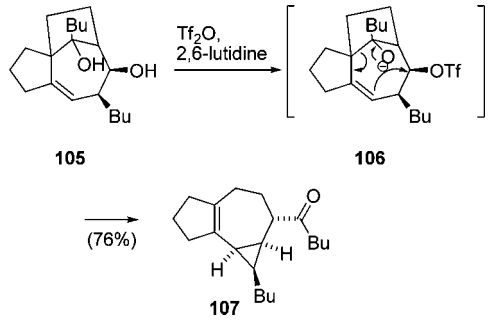

**Scheme 23. Synthesis of Estriol Analogue Featuring an Allyl Moiety**




The cyclic diol **90** contains the *anti*-periplanar arrangement required for the Grob fragmentation of **91** to generate aldehyde **92**.

Three years later, a similar fragmentation was used in the total synthesis of (±)-pallavicinolide A (**99**) (Scheme 21).[31] Here, unfortunately, epimerization of aldehyde **97** occurred during the fragmentation, and thus subsequent epimerization with DBU was needed, which was followed by reduction to alcohol **98**. For the syntheses of D-*seco*-pregnenes, the diol derivative **100** was used (Scheme 22).[32] Deacetylation with an excess of potassium hydroxide led to the corresponding monotosylated 1,3-diol, which gave the Grob fragmentation product **101**. In the synthesis of an estriol analogue, a Grob fragmentation was employed to generate the 14-allyl ketone **104** (Scheme 23).[33] Thus, aldehyde **102** was selectively reduced to the hydroxyl alcohol, which was tosylated to fragmentation substrate **103**. Treatment with sodium hydroxide in methanol gave the desired 14$\beta$-allyl-17-ketone **104**. Treatment of diol **105** with triflic anhydride did not lead to the expected ring expanded Grob fragmentation product but gave **107** as single diastereomer (Scheme 24).[34] This result was interpreted by a vinylogous Grob fragmentation, where the double bond formed a cyclopropane ring under extrusion of the triflate.

**Scheme 24. Vinylogous Grob Fragmentation of in Situ Formed Triflate 106**




## 2.2. β-Hydroxy Ketones

For the synthesis of cyclopentandiol **110**, the fragmentation (Scheme 25)[35] of the 2,7-disubstituted norbornane **108** was used, which gave the five-membered ring by cleavage of the C1−C2 bond.

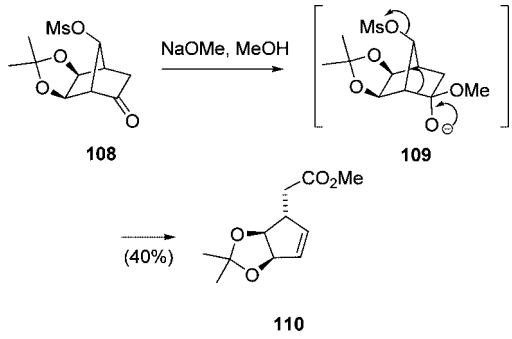
The double bond in *cis*-chrysanthemic acid (**112**) was introduced by Grob fragmentation (Scheme 26).[36] The starting material was gained in enantiomeric pure form by using the symmetry of the corresponding diol in an enzymatic resolution with PLE. Oxidation and mesylation led to the fragmentation precursor **111**, which on treatment with KOH gave the desired acid **112**.

Later, a similar precursor **114** was generated in situ from dibromide **113**, which under the reaction conditions smoothly underwent fragmentation to acid **115** (Scheme 27).[37]

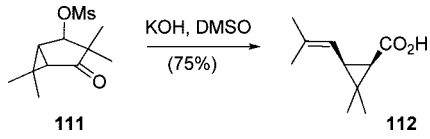
When tosyl ketone **116** was treated with different nucleophiles (NaOH, NaOMe, KO$^t$Bu, $NaNH_2$, and MeLi), fragmentation products **117** were gained (Scheme 28).[38]

The regioisomeric keto tosylate **118** behaved differently (Scheme 29).[39,40] With KO$^t$Bu, an intramolecular cyclization to enol ether **121** was observed instead of fragmentation,

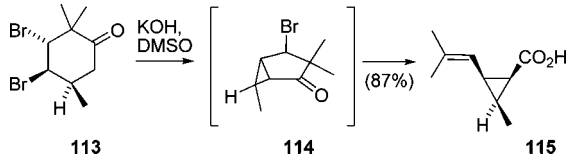
**Scheme 25. Cylopentandiols by Fragmentation of Diels−Alder Products**



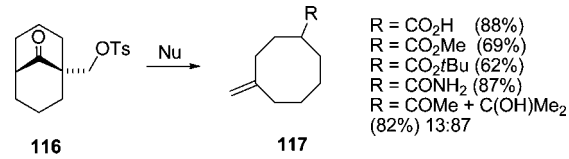

**Scheme 26. Synthesis of *cis*-Chrysanthemic Acid (112)**



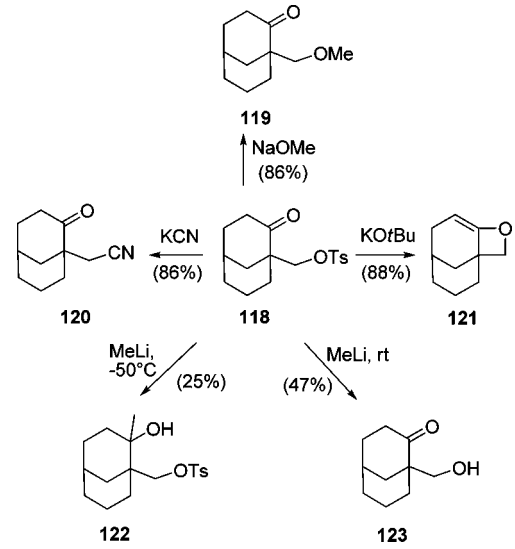

**Scheme 27. Novel Approach to Des-methyl-*cis*-chrysanthemic Acid (115)**



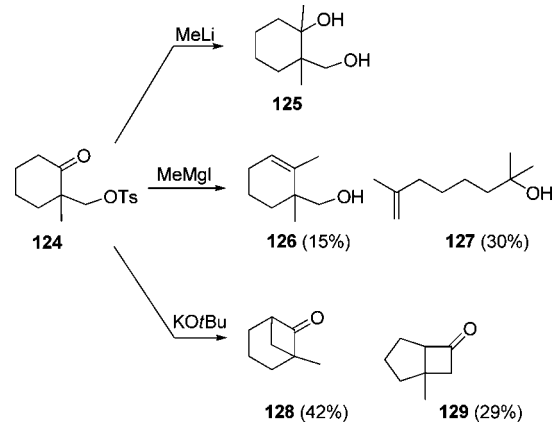

**Scheme 28. Fragmentation Induced by Different Nucleophiles**




**Scheme 29. Reaction of Keto Tosylate 118 with Different Nucleophiles**




**Scheme 30. Reaction of Keto Tosylate 81 with Different Nucleophiles**



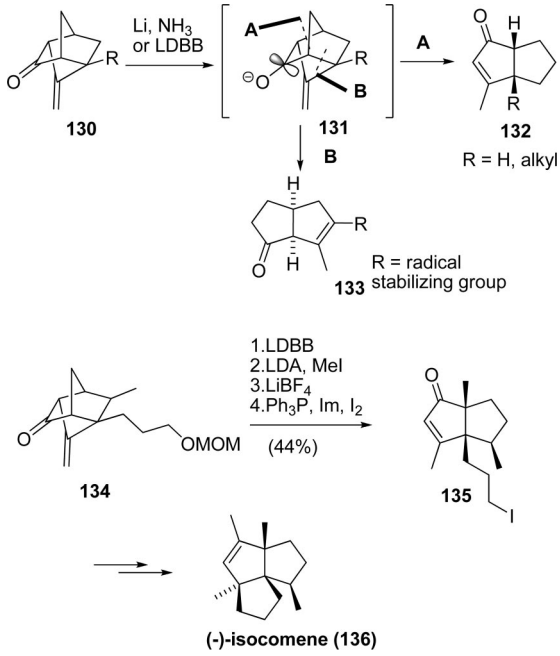

whereas NaOMe or KCN gave the substitution products **119** and **120**. Methyllithium did not induce fragmentation either.

With the simplified keto tosylate **124**, similar results were observed, but with methyl Grignard reagent Grob fragmentation to **127** took place in competition with elimination to **126** (Scheme 30).

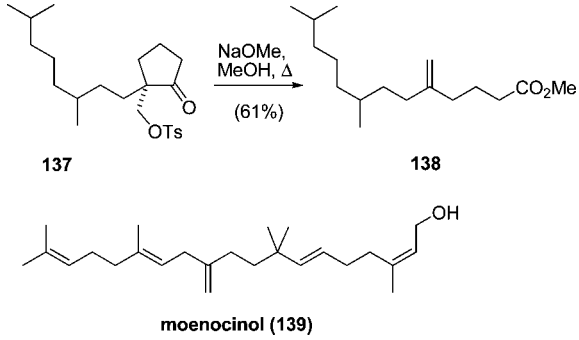
The strained tricyclic structure **130** can fragment to the diquinane system **132** with complete stereoselectivity under reductive conditions (Scheme 31). Depending on the electronic properties of the substituent R, fragmentation proceeds via path **A** or **B**. These findings were used in the asymmetric synthesis of (−)-isocomene (**136**).[41−43] Thus, the tricyclic precursor **134** was fragmented under reductive conditions and further transformed to enone **135**. An intramolecular Michael addition led to the isocomene skeleton, which was further converted to **136**.

In a model system for the synthesis of moenocinol **139**, Grob fragmentation was used to introduce the exomethylene

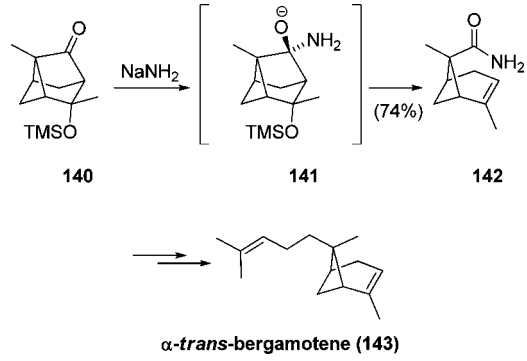
**Scheme 31. Synthesis of (−)-Isocomene (136)**




**Scheme 32. Efforts toward the Synthesis of Moenocinol (139)**




**Scheme 33. Synthesis of *trans*-Bergamotene (143)**

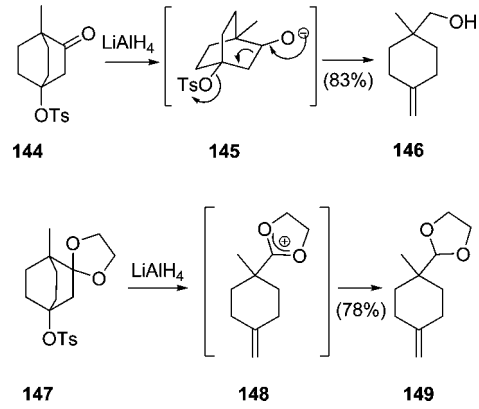



moiety in **138** (Scheme 32).[44] Treatment of $\beta$-tosyloxyketone **137** with sodium methoxide in refluxing methanol smoothly gave olefin **138**.

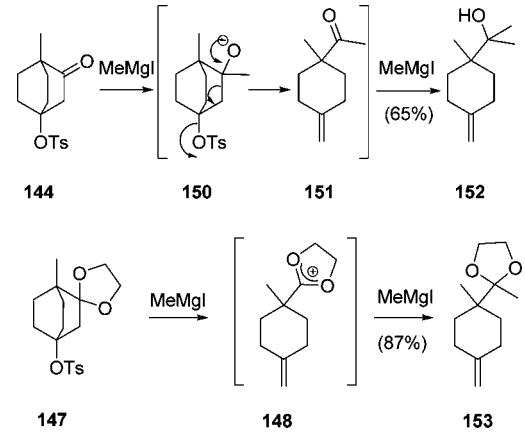
In the synthesis of racemic α-*trans*-bergamotene (**143**), the desired fragmentation of **140** to the bicyclic system **142** took place only if a N-nucleophile was used. O-Nucleophiles failed to give the desired product (Scheme 33).[44]

Reductive fragmentation was observed when bicyclic $\beta$-tosyloxyketone **144** or $\beta$-tosyloxyketal **147** was treated with $LiAlH_4$ to generate the exomethylene group in **146** and **149** (Scheme 34).[45,46]

**Scheme 34. Reductive Fragmentation of Bicyclic $\beta$-Tosyloxyketones**




**Scheme 35. Fragmentation of Bicyclic $\beta$-Tosyloxyketones with Methyl Grignard Reagent**



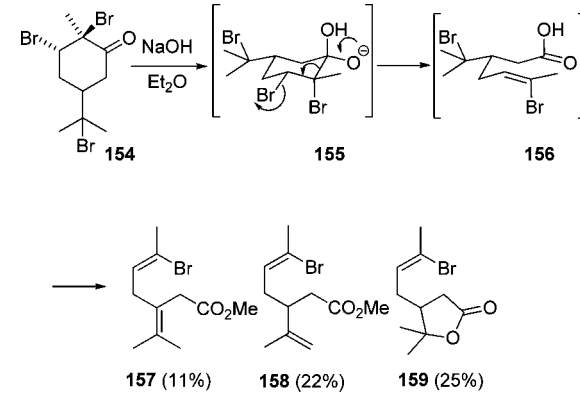

Treatment of bicyclic $\beta$-tosyloxyketone **144** with methylmagnesium bromide in refluxing ether led to the fragmentation product **152** (Scheme 35). Similar results were observed with ketal **147** under the same conditions.[47]

## 2.3. Bromide/Iodide as Leaving Group

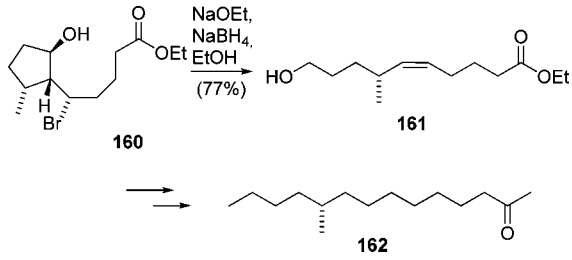
The Grob fragmentation of carvone tribromide **154** occurred by axial attack of hydroxide at the carbonyl group to give carboxylic acid **156**, which was ultimately transformed into **157**−**159** depending on the solvent (Scheme 36).[48]

In the synthesis of linear pheromones with chiral methyl-branching, for instance, **162**, the pheromone of the southern corn rootworm (Scheme 37),[49] the base-induced fragmentation of hydroxy bromide **160** was performed under reductive

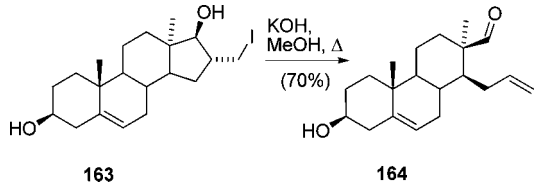
**Scheme 36. Fragmentation of Carvone Tribromide 154**



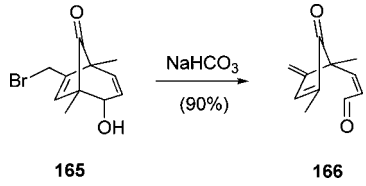
**Scheme 37. Synthesis of Insect Pheromone 162**




**Scheme 38. Fragmentation to *seco*-Steroids Featuring an Allyl Moiety**




**Scheme 39. Vinylogous Grob-type Fragmentation of 165**




conditions to give alcohol **161**, as the aldehyde, which was formed first, was unstable and decomposed.

Halohydrin **163** was treated with KOH in methanol under reflux to give allyl D-*seco*-steroid **164** and, additionally, in small amounts the elimination (11%) and substitution (4%) products (Scheme 38).[50]

The treatment of **165** with aqueous sodium hydrogencarbonate led to aldehyde **166**, which is the result of a base-induced vinylogous Grob-type fragmentation (Scheme 39).[51]

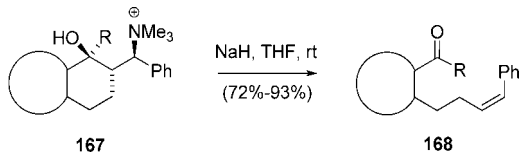
## 2.4. Ammonium as Leaving Group

Grob-type fragmentation of quaternary $\gamma$-amino alcohols **167** gave access to unsaturated aldehydes and ketones **168** with a (*Z*)-double bond (Scheme 40).[52,53] The starting material was easily accessible by Mannich reaction followed by quaternation of the amine with methyl iodide.

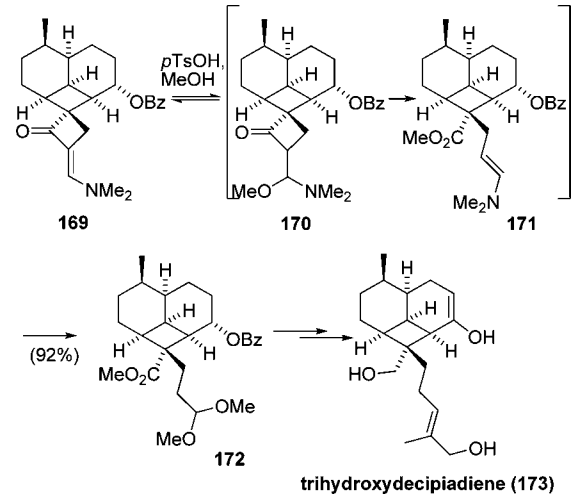
Grob fragmentation of a cyclobutanone was employed in the total synthesis of (±)-trihydroxydecipiadiene (**173**) (Scheme 41).[54] The spirocyclobutanone was first activated by the introduction of a formyl group in form of the vinylogous amide **169**. Heating with *p*TsOH in methanol resulted in ring-opening presumably first to enamine **171**, which was solvolyzed to acetal **172**.

There exists also one example for a nitrate as a leaving group (Scheme 42). When pentaerythritol mononitrate **174** was treated with potassium hydroxide in refluxing ethanol, fragmentation product **176** was isolated. However, the main reaction was substitution, generating oxetane **175**.[55]

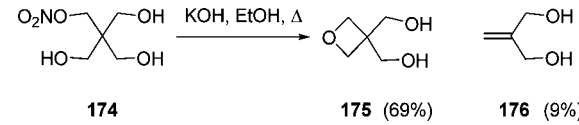
**Scheme 40. $\gamma$-Ammonium Alcohols as Fragmentation Substrates**




**Scheme 41. Synthesis of (±)-Trihydroxydecipiadiene (173)**




**Scheme 42. Nitrate as Leaving Group**

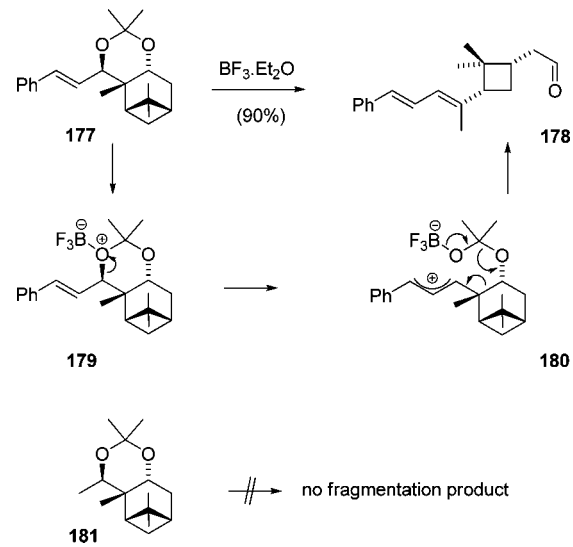



## 2.5. Acetals

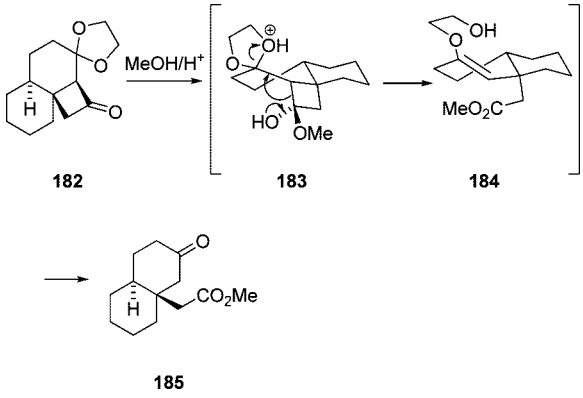
In the acid-catalyzed Grob fragmentation of acetonide **177** (Scheme 43),[24] a concerted mechanism is not possible, due to the rigid structure. The Lewis acid promotes formation of the allylic carbocation **180**, which forms the aldehyde **178** by fragmentation and loss of acetone. This stepwise mechanism was supported by the observation that substrates such as **181**, which cannot form stabilized carbocations, did not undergo fragmentation.

In the fragmentation of 5-dioxolan-bicyclo[4.2.0]octan-2-one **182** to 3-(methoxycarbonylmethyl)cyclohexanone **185**, both the cyclobutane and the dioxolane ring were opened via an *anti*-periplanar arrangement (**183**, Scheme 44).[56] The vinyl ether **184** was then solvolyzed to ketone **185**.

**Scheme 43. Fragmentation of Allylic Acetonide with Lewis Acid**



**Scheme 44. Fragmentation of Acetal 138**




## 2.6. 3,4-Epoxy Alcohols as Fragmentation Substrates

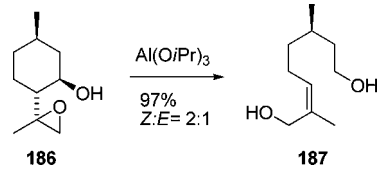
3,4-Epoxy alcohols were used as substrates for fragmentation reactions (Scheme 45).[57] Commercially available isopulegol was epoxidized with *m*CPBA to give isopulegol epoxide **186** as a mixture of diastereomers. Electrophilic attack of $Al(O^iPr)_3$ acid on the epoxide oxygen initiated the fragmentation to yield 8-hydroxycitronellol **187** as a 2:1 *Z*:*E*-olefin mixture.

The synthesis of allylic alcohol **189** was also achieved through Grob fragmentation (Scheme 46).[58] In this case, a 1:1 diastereomeric mixture of epoxide **188** was used, which in a Lewis acid-mediated fragmentation gave the desired (*Z*)-olefin **189** exclusively. This result indicates that the configuration of the epoxide has no effect on the Grob fragmentation. Allylic alcohol **189** was further converted to the ester side chain of disdemnaketal A (**190**), a HIV protease inhibitor.

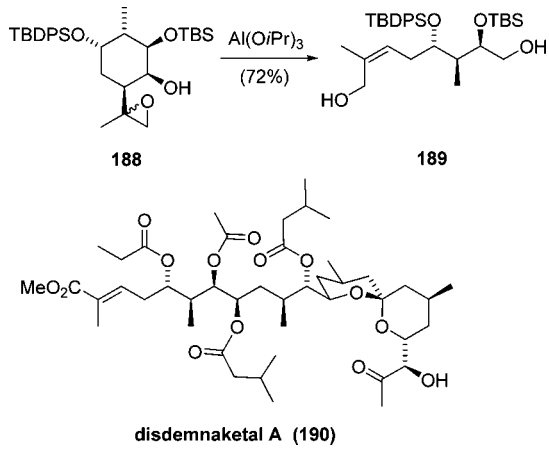
## 2.7. Miscellaneous

A lead(IV) acetate (LTA)-promoted cylopropane fragmentation was described (Scheme 47).[59] The C1−C6 bond

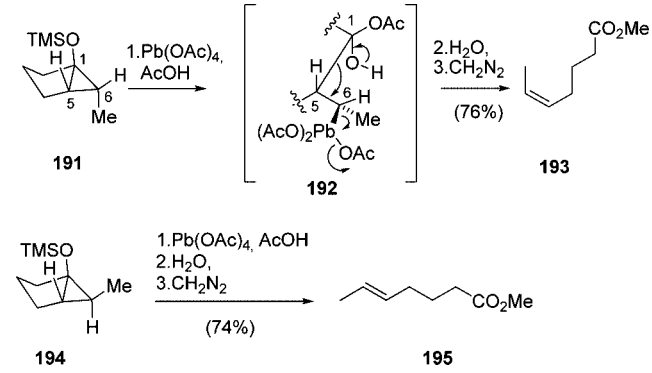
**Scheme 45. Fragmentation of Isopulegol Epoxide 186**



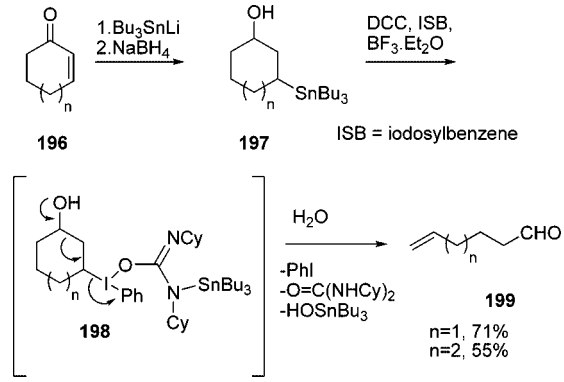

**Scheme 46. Synthesis of the Allylic Alcohol in the Disdemnaketal A (190) Side Chain**




**Scheme 47. Cyclopropane Fragmentation Promoted by Lead(IV) Acetate**




**Scheme 48. Fragmentation of γ-Tributylstannyl Alcohols with ISB, DCC, and $BF_3$**



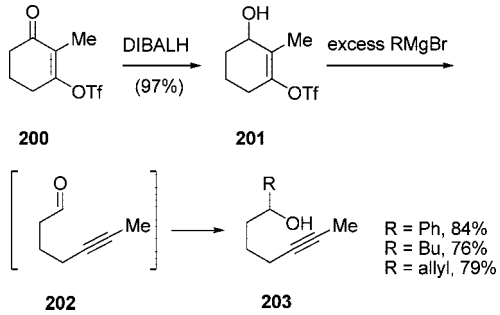

in **191** was cleaved under inversion of configuration at C6 to form intermediate **192**. The *anti*-periplanar arrangement of C1−C5−C6−Pb in **192** was ideal for the Grob fragmentation to give **193**. The olefin geometry depended on the configuration of the starting material: **191** gave (*Z*)-olefin **193**, and **194** (*E*)-olefin **195**.

An oxidative Grob fragmentation of γ-tributylstannyl alcohols can be achieved with a combination of iodosylbenzene, dicyclohexylcarbodiimide, and boron trifluoride (Scheme 48).[60] In this reaction, γ-stannyl alcohol **197** was generated via conjugate addition from ketone **196** and then converted into an activated γ-hydroxy iodine(III) species **198**, which underwent Grob fragmentation to olefin aldehyde **199**. This method is highly versatile as a lot of modifications are possible; for instance, by organolithium addition to the carbonyl group ketones are generated after fragmentation of the tertiary alcohol. Also, substitution of the double bond is possible by trapping the enolate after the conjugated addition with an alkyl halide; in this case, fragmentation gave (*E*)-olefins due to the trans arrangement of the substituents.

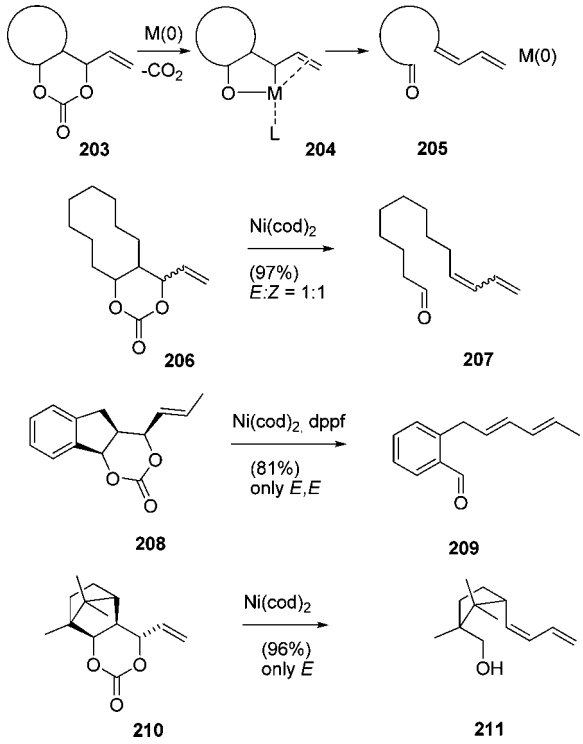
Cyclic vinylogous triflate hemiacetals were used as surrogates for alkynyl aldehydes (Scheme 49).[61,62] Thus, hemiacetal **201** directly generated alkynyl alcohol **203** with excess Grignard reagent presumably via fragmentation to alkynyl aldehyde **202** followed by nucleophilic attack of the Grignard reagent.

In a nickel-catalyzed Grob fragmentation, a $Ni(cod)_2$-phosphane catalyst promoted a Grob-type decarboxylative ring-opening of six-membered carbonates **203** to generate dienyl aldehydes **205**. As an intermediate, Ni-complex **204** was postulated, which underwent fragmentation under reductive elimination of the metal. As shown by examples **208** and **210**, the olefin geometry is controlled by the configuration of the carbonate substrates (Scheme 50).[63]

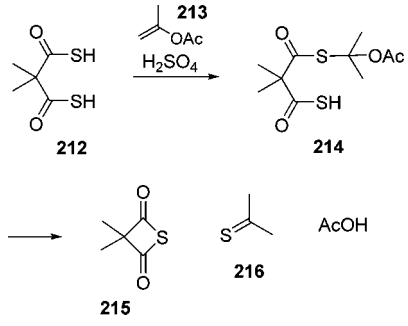
**Scheme 49. Vinylogous Triflate Hemiacetals as Fragmentation Substrates**




**Scheme 50. Nickel-Catalyzed Fragmentation**



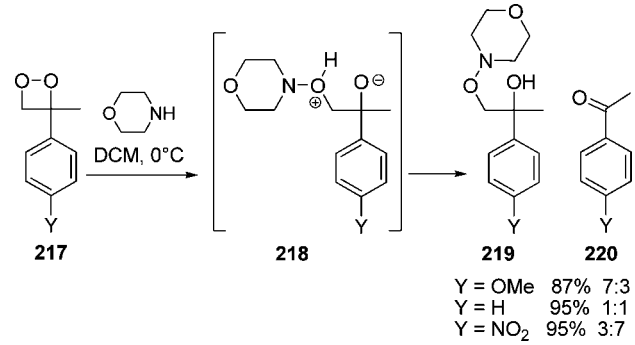

**Scheme 51. Cyclic Thietanedione by Fragmentation**



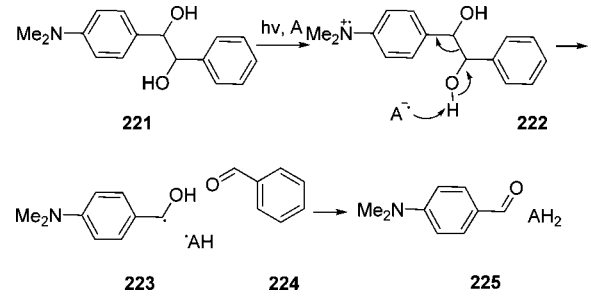

The synthesis of a cyclic thietanedione was achieved by fragmentation (Scheme 51).[64] When bisthiomalonic acid **212** was treated with isopropenyl acetate **213** under acidic conditions, Grob fragmentation occurred to give thietanedione **215** and thioacetone **216**.

The fragmentation of 3,3-disubstituted 1,2-dioxetanes **217** with morpholine was investigated (Scheme 52).[65] Nucleophilic attack on 1,2-dioxetanes **217** occurred on the sterically less hindered site of the peroxide bond. The zwitterionic intermediate **218** can react in two different ways: either by proton transfer to form the stable hydroxyl amine ethers **219**

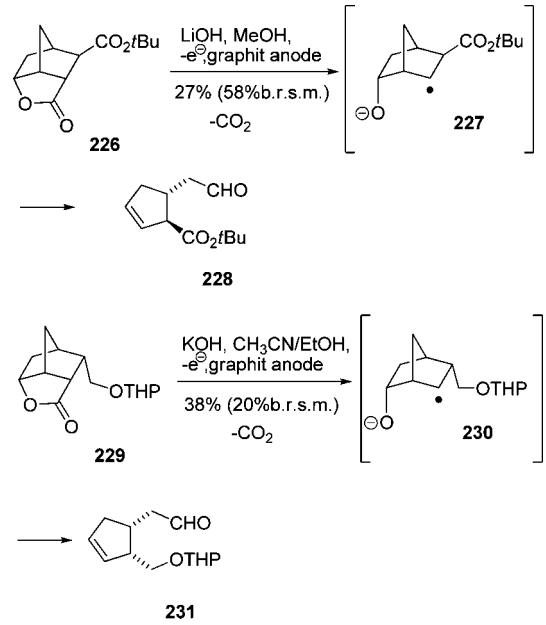
**Scheme 52. Reactivity of 1,2-Dioxetanes with Morpholine**




**Scheme 53. Photofragmentation**




**Scheme 54. Fragmentation by Electrolysis**




or via Grob fragmentation to generate ketones **220**. The product mixture depended on the M-effect of the substituents in 4-position: electron-accepting substituents favored the fragmentation products **220**, whereas the formation of hydroxylamine **219** was enhanced by electron-donating substituents.

The photofragmentation of 1,2-diol **221** (Scheme 53)[66] gave aldehyde **225** via two successive SETs to acceptor A (A = lapachone or fluorescine of thioindigo).

In an anodic Grob fragmentation (Scheme 54),[67] 3-substituted 6-hydroxy-2-norbornanecarboxylic acids **226** and **229** stereospecifically gave 3,4-disubstituted cyclopentenes **228** and **231**. In this Kolbe-type electrolysis, radical anions **227** and **230** presumably serve as intermediates.

## 3. Carbonyl Generating Grob Fragmentation via Ring Expansions

### 3.1. Monosulfated 1,3-Diols

A reliable approach to medium-sized rings is the fragmentation of rigid bicyclic structures, in which the bond to break and the leaving group are fixed in an *anti*-periplanar position.[19]

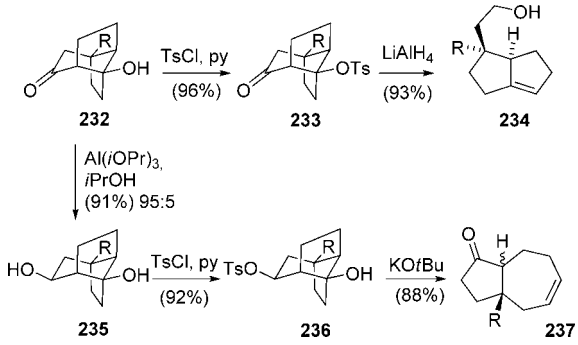
In a fragmentation approach to hydroazulenes (Scheme 55),[68] diol **235** was obtained by Meerwein−Ponndorf−Verley reduction of $\beta$-hydroxy ketone **232**. Regioselective monotosylation of the secondary alcohol in **235** gave **236**. Treatment with KO$^t$Bu induced the Grob fragmentation, which led to **237**. The configuration of the starting material was determined by tosylation of **232** to **233**. Reductive fragmentation of **233** gave **234** whose structure was secured by NMR analysis.

The same strategy worked successfully in the synthesis of the bicyclo[5.4.0]undecenone system **239** from **238** (Scheme 56).[69]

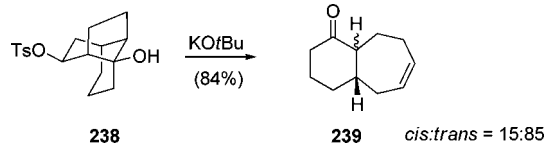
In the synthesis of (±)-parvifoline (**242**), a 5,5-ring system was used to generate the eight-membered ring (Scheme 57).[70] When **240** was treated with sodium methoxide under reflux, Grob fragmentation occurred to form cyclooctenone **241**.

A bridged 5,6-ring system was needed in the synthesis of zizaane sesquiterpenes (Scheme 58).[71] The tetracyclic precursor **201** was generated in a [2 + 2] cycloaddition. Upon treatment with sodium hydroxide, saponification of the acetate was followed by Grob fragmentation to give tricyclic olefin **202**.

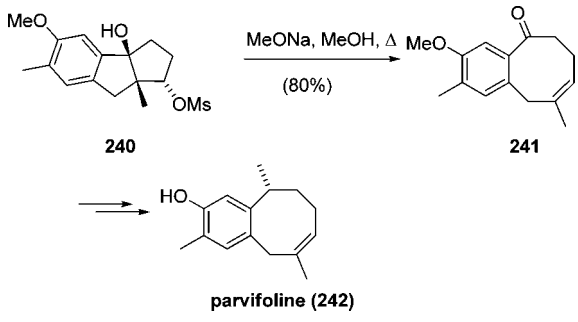
**Scheme 55. Hydroazulenes by Fragmentation**



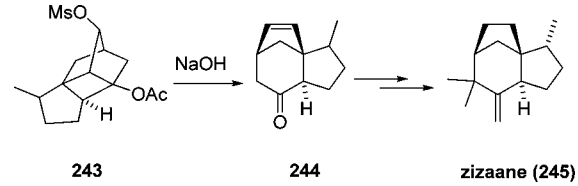

**Scheme 56. Synthesis of Bicyclo[5.4.0]undecenone**



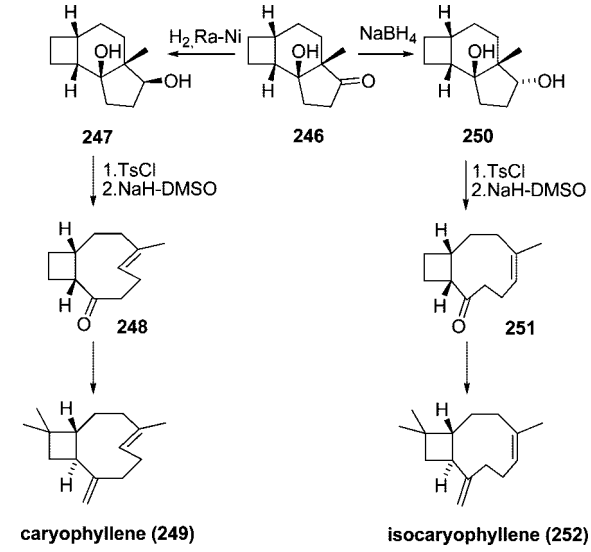

**Scheme 57. Synthesis of (±)-Parvifoline (242)**



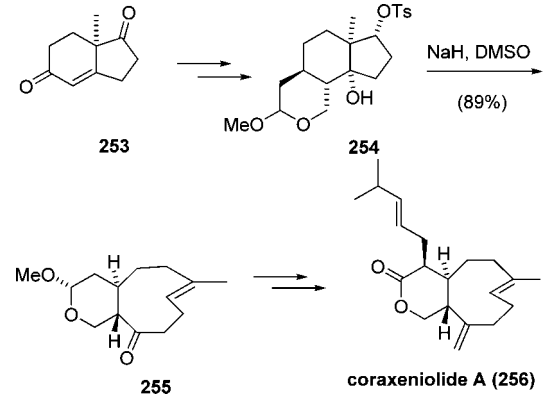

**Scheme 58. Fragmentation in the Synthesis of Zizaane Sesquiterpenes**




**Scheme 59. Synthesis of Caryophyllene (249) and Isocaryophyllene (252)**




**Scheme 60. Fragmentation in the Total Synthesis of Coraxeniolide A (256)**

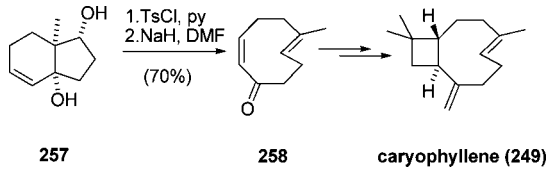



In the synthesis of racemic caryophyllene (**249**) and isocaryophyllene (**252**), a trisubstituted (*E*)- and (*Z*)-double bond, respectively, was installed by ring expansion of a *cis*-fused 5,6-ring system (Scheme 59).[72,73] Thus, from racemic tricyclic hydroxy ketone **246** two diastereomeric diols **247** and **250** were available, which gave fragmentation substrates after regioselective monotosylation. Upon treatment with base, (*E*)- and (*Z*)-olefins **248** and **251** were formed, which were elaborated into caryophyllene (**249**) and isocaryophyllene (**252**), respectively.

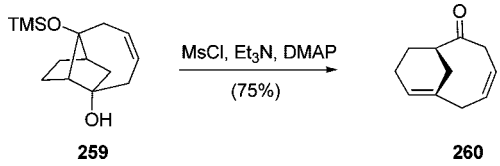
Decades later, in 2000, in the total synthesis of nonracemic coraxeniolide A (**256**), a very similar structural motive was generated by Grob fragmentation (Scheme 60).[74] Hydroxy tosylate **254** was easily accessible from Hajos−Parrish diketone **253**. Treatment with sodium hydride led to the unsaturated nine-membered ring **255**.

In 2008, Corey published an enantioselective synthesis of caryophyllene (**249**) (Scheme 61).[75] Here, the nine-membered

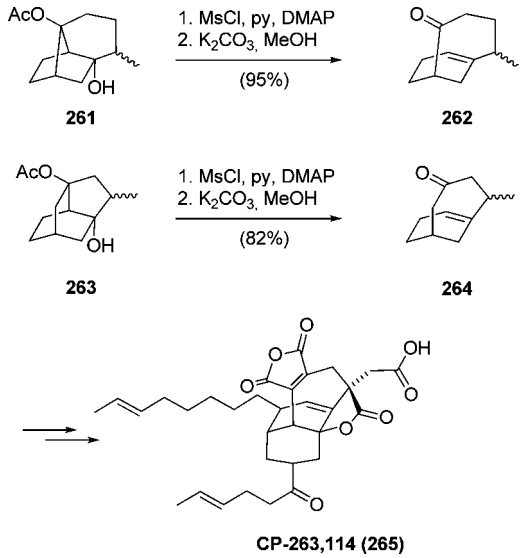
**Scheme 61. Synthesis of Enantiomerically Pure Caryophyllene (249)**




**Scheme 62. *anti*-Bredt Alkenes by Fragmentation**




**Scheme 63. Toward CP-263,114 (265)**




ring was generated by fragmentation of diol **257** to dienone **258**. This reaction is particularly remarkable, as central chirality is converted to helical chirality so that the (*E*)-cyclooctene moiety is generated in optically active form. Dienone **258** was also an intermediate in his synthesis of coraxeniolide A (**256**).

Mehta developed a general approach to *anti*-Bredt alkenes starting from easily available norbornyl precursors (Scheme 62).[76] Precursor **259** was generated by RCM and under mesylation conditions **259** readily underwent fragmentation to **260**.

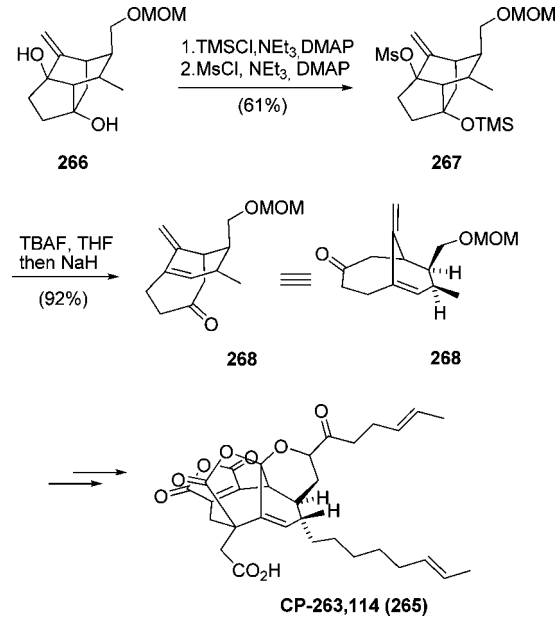
Two different fragmentation approaches to the carbocyclic core of CP-263,114 (**265**) were used to install the quaternary center and the bridgehead olefin in one step (Scheme 63).[77] Therefore, the tertiary alcohol of norbornane **261** and isotwistane **263** was mesylated, and the mesylate was treated with potassium carbonate to remove the acetate and initiate fragmentation. In this way, the desired bicyclic core structures **262** and **264** were generated in high yields.

In another synthesis of CP-263,114 (**265**),[78] diol **266** was regioselectively converted into its mono-TMS ether, followed by introduction of the mesylate to give fragmentation precursor **267** (Scheme 64). Removal of the TMS and treatment with NaH induced Grob fragmentation to furnish the bicyclic compound **268**.

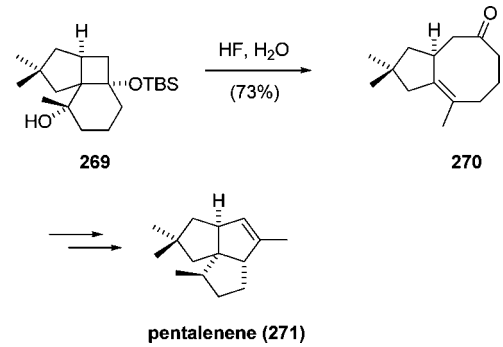
In the total synthesis of (±)-pentalenene (**271**), an eight-membered cyclic ketone was generated by Grob fragmentation (Scheme 65).[79] The tricyclic substrate **269** came from a regioselective intramolecular [2 + 2] cycloaddition. In compound **269**, the free hydroxyl group is quasi-axial to the quasi-equatorial silyl ether residue. Upon treatment of **269** with aqueous hydrofluoric acid, the cleavage of the silyl ether was followed by Grob fragmentation and led smoothly to the 5,8-ring fused enone **270**.

In Baran's ingenious approach to the diterpene vinigrol (**274**), a fragmentation was used to overcome the inherent ring strain of the decahydro-1,5-butanonaphthalene system in intermediate **273** (Scheme 66).[80] The tetracyclic precursor **272** was prepared by two Diels−Alder reactions. Grob fragmentation of monomesylated diol **272** with KHMDS was

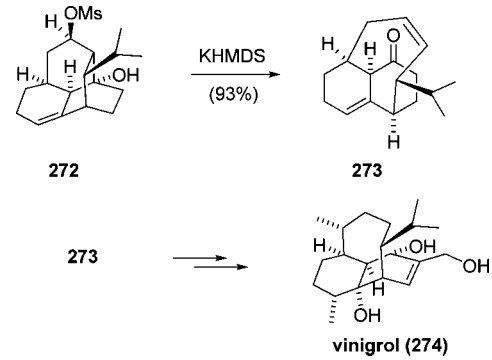
**Scheme 64. Toward the Synthesis of CP-263,114 (265)**



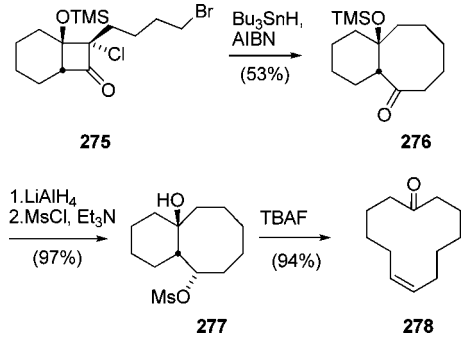

**Scheme 65. Fragmentation in the Synthesis of (±)-Pentalenene (262)**



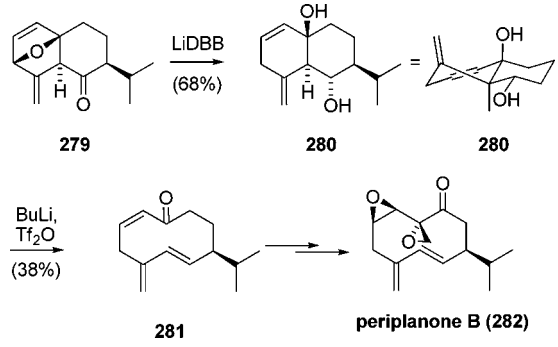

**Scheme 66. Baran's Synthesis of Vinigrol (274)**



**Scheme 67. Large Cyclic Ketones by Fragmentation**




**Scheme 68. Synthesis of Periplanone-B (282)**




used to convert **272** into the tricyclic core **273**. The transformation of **273** into vinigrol (**274**) was published recently.[81]

Grob fragmentation was used as the second step in a double ring expansion to prepare medium and large cyclic ketones (Scheme 67).[82] From cyclobutanone system **275**, free radical ring expansion led to the *cis*-fused ring system **276**. After standard manipulations, fragmentation precursor **277** was reached, which underwent Grob fragmentation to (*Z*)-olefin **278**. The fluoride-induced fragmentation has the advantage to avoid strongly basic conditions.

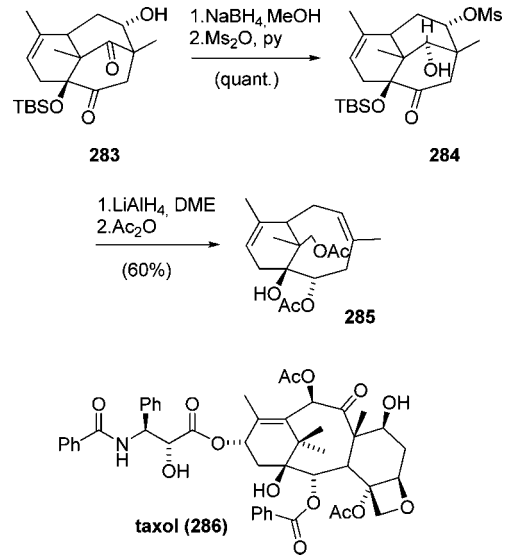
In the synthesis of periplanone-B (**282**), the 10-membered ring was introduced by Grob fragmentation (Scheme 68).[83] As starting material, the tricyclic system **279** was generated by IMDA reaction between a furan and an allene moiety. The reduction of the carbonyl and reductive cleavage of the oxo-bridge with lithium di-*tert*-butylbiphenyl radical anion gave diol **280**, which features the correct *anti*-periplanar arrangement for the fragmentation reaction. Thus, treatment of the dilithium salt of diol **280** with triflic anhydride led to the desired trienone **281**.

The highly strained bridged AB ring system of taxol (**286**) was generated by fragmentation (Scheme 69).[84] Reduction of tricyclic **283** led to a single dihydroxy-ketone, which was mesylated to **284**. Treatment with LAH triggered the fragmentation and reduced the ensuing aldehyde, and after acetylation of the free OH-functions the taxane AB-fragment **285** was obtained.

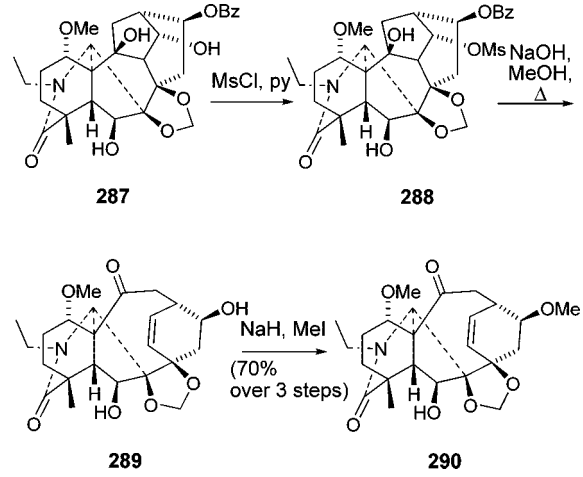
Grob-type fragmentation was also used in an approach to the taxane ABC ring system (Scheme 70).[85,86] Intermediate **287** was converted to **290** in a one-pot procedure *via* selective mesylation of the more accessible secondary alcohol. Treatment with hydroxide both induced Grob fragmentation and saponification of the benzoate to generate the unsaturated six-membered ring **289**. Finally, the free alcohol was methylated to **290**.

Fragmentation was used in a ring-expansion approach to the aquariane ring system of the aquaeriolide diterpenes

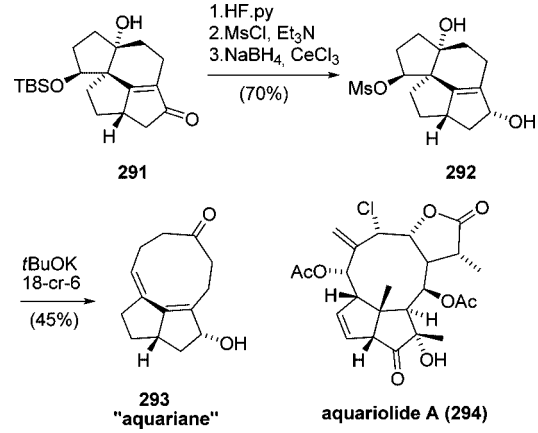
**Scheme 69. Fragmentation To Generate the AB Ring System of Taxol (286)**




**Scheme 70. Synthesis of the Taxane ABC Ring System**



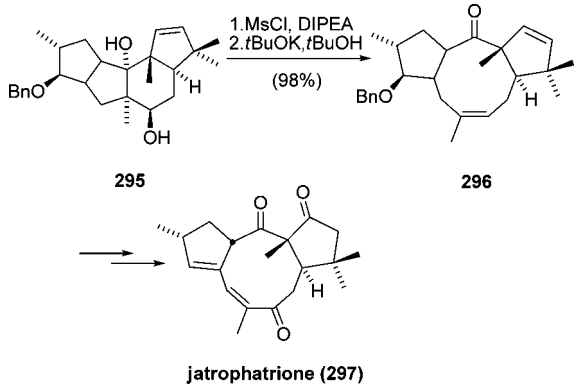

**Scheme 71. Fragmentation To Generate the Aquariane Ring System**



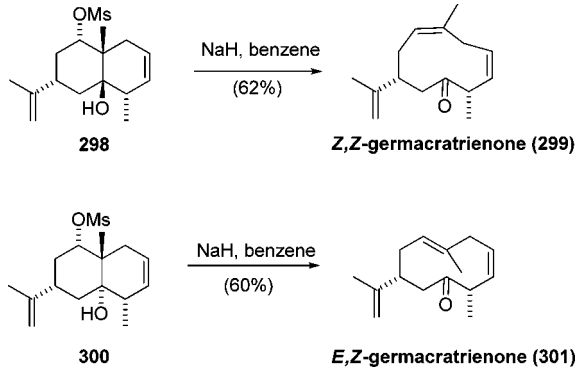

(Scheme 71).[87] Thus, tetracyclic enone **291** was elaborated to precursor **292**, whose Grob fragmentation with $^t$BuOK delivered the nine-membered ring **293**.

Paquette's synthesis of the diterpene jatrophatrione (**297**) employed a Grob fragmentation to generate the nine-membered ring (Scheme 72).[88,89] Monomesylation of tetra-

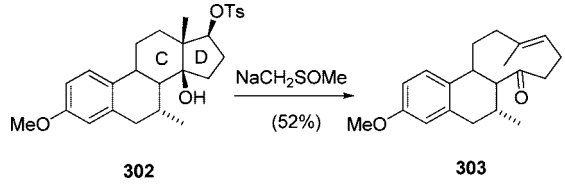
**Scheme 72. Paquette's Jatrophatrione (297) Synthesis**




**Scheme 73. (*Z*)- and (*E*)-Germacrenes by Fragmentation**




**Scheme 74. *seco*-Steroids by Fragmentation**




cyclic **295** was followed by treatment with *t*BuOK to yield nine-membered ketone **296** in quantitative yield.

An expeditious route to (*E*)- and (*Z*)-germacrenes centered on a Grob fragmentation (Scheme 73).[90] Decalins **298** and **300** were prepared from (*R*)-(−)-carvone via RCM, and standard base-induced fragmentation generated the (*Z*)- and (*E*)-cyclodecenones **299** and **301**.

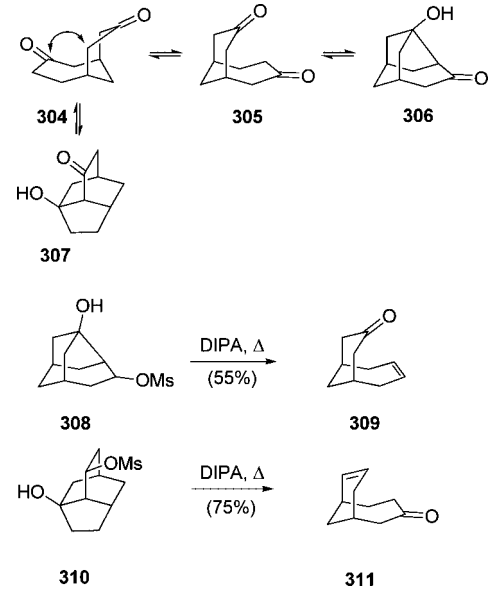
Grob fragmentation was used for C/D-ring cleavage in the synthesis of functionalized 13,14-*seco*-steroids (Scheme 74).[91] The 14$\beta$-hydroxy-17$\beta$-tosylate **302** underwent fragmentation to give *seco*-steroid **303** in 52% yield, although the conformation is not strictly *anti*-periplanar.

An easy access to diastereomeric bicyclo[3.3.1]nonanes was opened by Grob fragmentation (Scheme 75).[92] The fragmentation precursors **308** and **310** were made by aldol cyclization of bicyclo-[4.3.1]decane-3,8-dione **304**. After reduction and conversion into the monomesylates **308** and **310** and treatment with diisopropylamine, the bicyclo-[3.3.1]nonanes **309** and **311** were obtained.

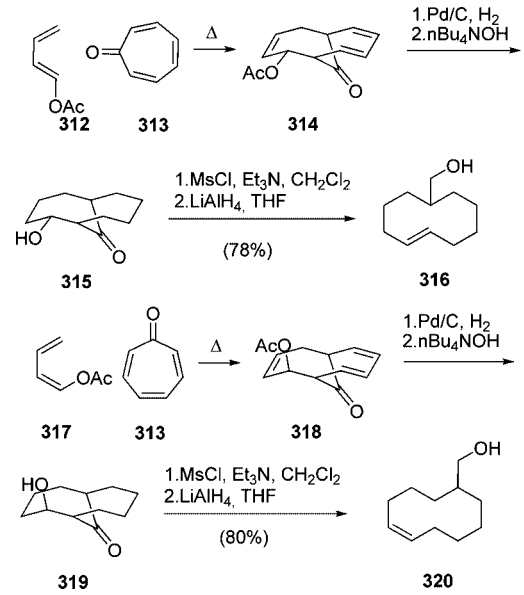
## 3.2. $\beta$-Hydroxy Ketones

The reductive fragmentation of two isomeric bicyclo[4.4.1]-undecanones **315** and **319** led to two isomeric 10-membered rings **316** and **320** (Scheme 76).[93] The one-carbon bridge was cleaved to establish an (*E*)- or (*Z*)-olefin. The starting material came from a [6 + 4] cycloaddition of cycloheptatrienone

**Scheme 75. Fragmentation To Generate Bicyclic Nonanes**




**Scheme 76. Reductive Fragmentation by Cleavage of a Keto-Bridge**




**313** with (*E*)- or (*Z*)-1-acetoxy-1,3-butadiene **312** or **317**, respectively.

In their synthesis of (±)-laurenene (**324**), Wender et al. converted **321** with NBS to the bromomethyl derivative **322**, which underwent Grob fragmentation upon treatment with KOH. Spontaneous lactonization led to **323** (Scheme 77).[94]

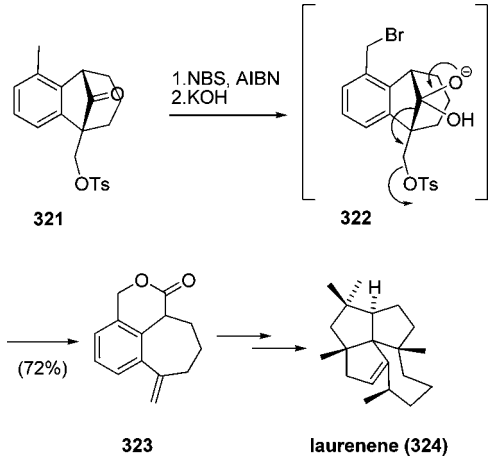
The eight-membered ring in (±)-ceroplastol I (**328**) was introduced via Grob fragmentation of **325**. On treatment with sodium methoxide in refluxing methanol, **327** was generated via intermediate **326** (Scheme 78).[95]

## 3.3. Enolate-Induced Grob Fragmentation

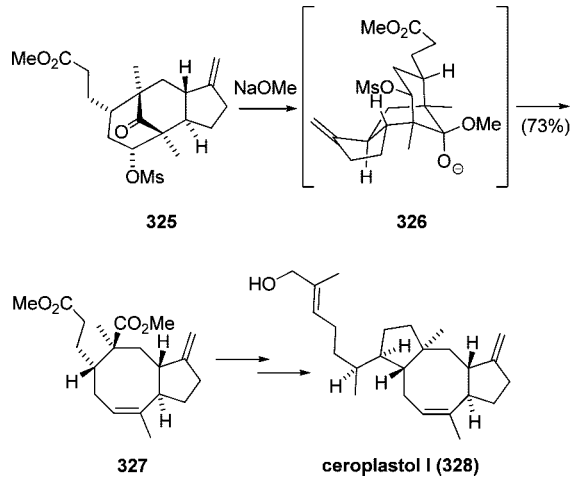
In the synthesis of sericenine (**333**) (Scheme 79),[96] ester **329** was deprotonated to form enolate **330**, which underwent Grob fragmentation to neosericenine **332**. Excess base led to (*E*)/(*Z*)-isomerization to minimize ring strain.

Similarly, the 10-membered ring of the germacrane system **336** present in tulipinolide (**337**) was synthesized by Grob fragmentation (Scheme 80).[97] Precursor **334**, which was

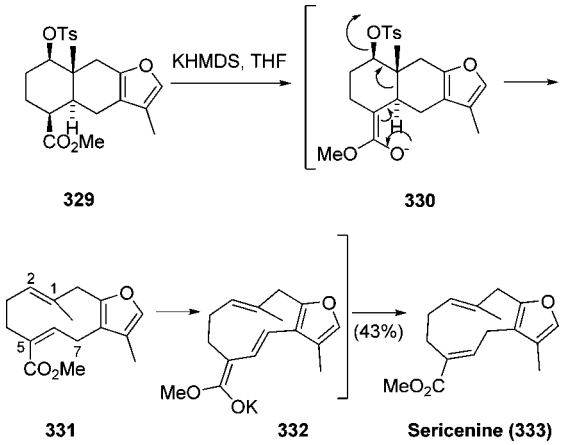
**Scheme 77. Wender's Synthesis of (±)-Laurenene (324)**




**Scheme 78. Synthesis of (±)-Ceroplastol I (328)**




**Scheme 79. Synthesis of Sericenine (333)**

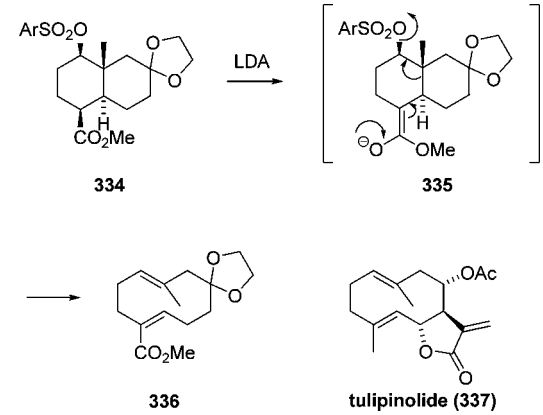



prepared from 5-methoxy-1-tetralone, cleanly gave diene **336** on treatment with LDA at room temperature.

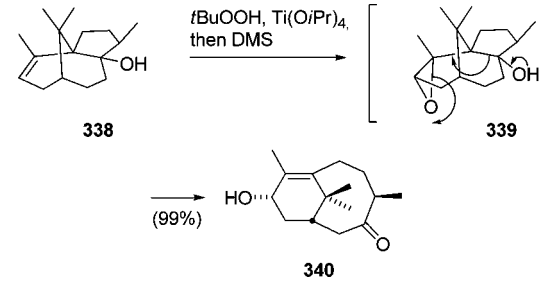
## 3.4. Fragmentation of 3,4-Epoxy Alcohols

In his approach to the taxane ring system, Holton used a Grob fragmentation of epoxide **339** to generate the eight-membered ring (Scheme 81).[98] Therefore, tertiary alcohol **338** was subjected to a hydroxyl-directed epoxidation to generate the unstable epoxide **339**, which underwent fragmentation to hydroxyketone **340**.

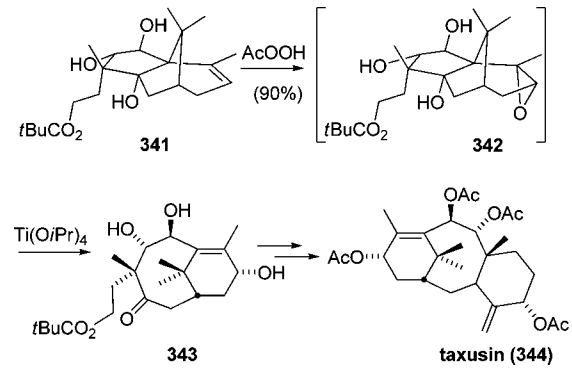
**Scheme 80. Synthesis of the Germacrane System**



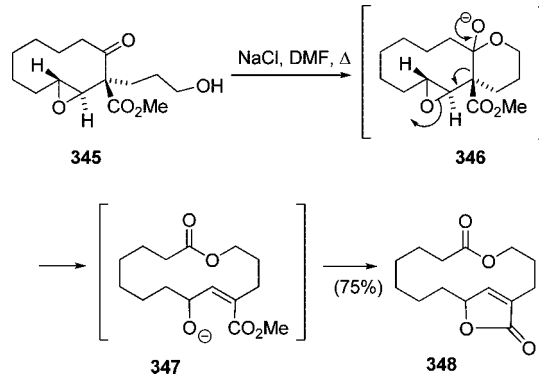

**Scheme 81. Holton's Synthesis of the Taxane Ring System**




**Scheme 82. Holton's Synthesis of Taxusin (344)**



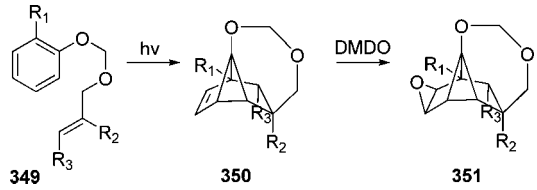

**Scheme 83. Epoxy Hemiketal Fragmentation**



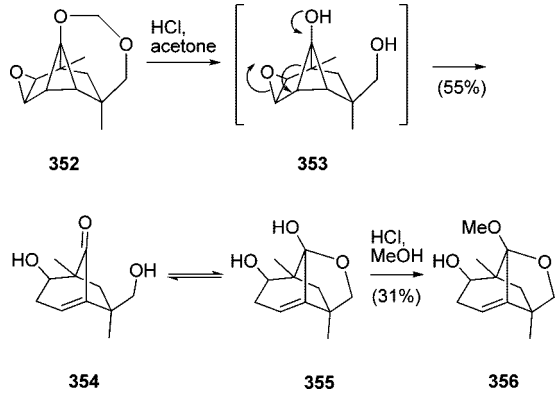

With a similar substrate, Holton applied this strategy to the synthesis of taxusin (**344**) (Scheme 82).[99] As Sharpless epoxidation of **341** failed, a large excess of peracetic acid was used to produce the unstable epoxide **342**, which was directly refluxed with $Ti(OiPr)_4$ to generate triol **343**.

An interesting case is shown in Scheme 83. Here, the fragmentation precursor is hemiketal **346**, which was formed

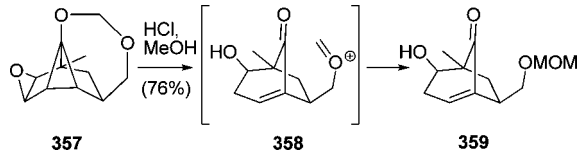
**Scheme 84. Meta-photocycloaddition To Generate Fragmentation Precursors**




**Scheme 85. Fragmentation of Meta-photocycloaddition Products**




**Scheme 86. Alternative Conditions for the Fragmentation of Meta-photocycloaddition Products**




in situ from **345**.[100] Stereospecific ring-enlargement via Grob fragmentation led to **347**, which immediately formed butenolide **348**.

The meta-photocycloaddition reaction (Scheme 84) is a very convenient method to generate fragmentation substrates **351**.[101] Grob fragmentation of epoxide **352** under acidic conditions gave hydroxyketone **354** in equilibrium with hemiketal **355** (Scheme 85). To get a uniform product, the mixture was further converted to methoxy acetal **356**.

When the fragmentation was performed in methanol to obtain the methoxy acetal directly, oxonium ion **358** was generated and trapped with methanol to form MOM ether **359** (Scheme 86).

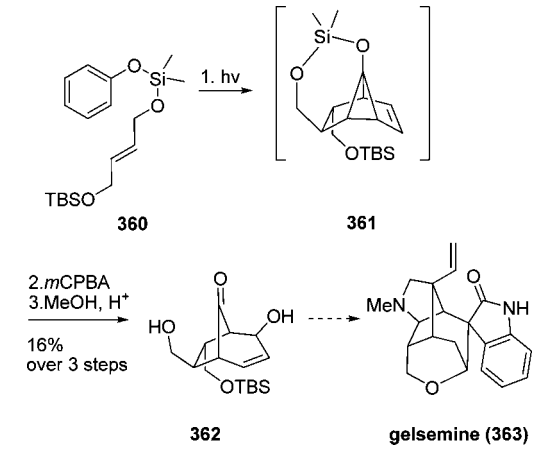
In an approach toward gelsemine (**363**), a silicon tether was used in the meta-photocyclization (Scheme 87). Thus, photosubstrate **360** was irradiated, and the product **361** was epoxidized and desilylated to give keto-diol **362** as the fragmentation product.

## 3.5. Ammonium Ions as Leaving Group

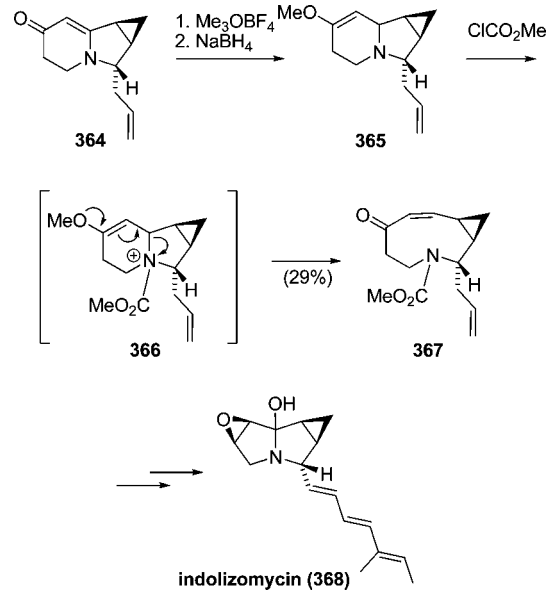
In Danishefsky's synthesis of indolizomycin (**368**) (Scheme 88),[102] vinylogous lactam **364** was O-alkylated, and the resulting iminium species was reduced to **365**. Acylation with chloroformate gave ammonium ion **366**, which underwent fragmentation to **367**.

In an approach to eight-membered cycloolefins, morpholino-ketone **369** was treated with methyl iodide to generate the quaternary amine as leaving group. Addition of hydroxide induced the Wharton fragmentation to **370** (Scheme 89).[103]

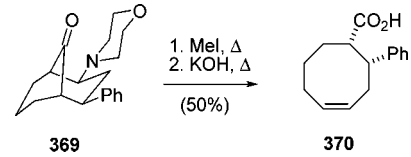
**Scheme 87. Toward the Synthesis of Gelsemine (363)**




**Scheme 88. Danishefsky's Indolizomycin (368) Synthesis**




**Scheme 89. Morpholine as Leaving Group**



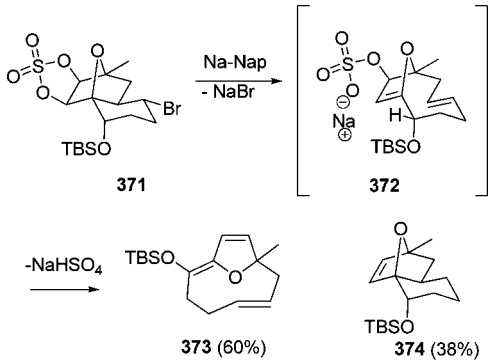

## 3.6. Miscellaneous

Treatment of bromide **371** with sodium napthalenide resulted in a tandem Grob fragmentation-homoallylic elimination to give the bicyclic ether **373** via **372** in 60% yield. Additionally, 38% of the elimination product **374** was formed (Scheme 90).[104]

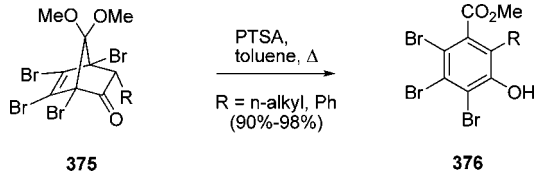
Pentasubstituted phenols were generated by Grob-type fragmentation (Scheme 91).[105,106] The fragmentation of bicyclic ketone **375** was induced with acid to furnish the pentasubstituted tribromophenol **376** in almost quantitative yield.

The Grob fragmentation was also investigated in the tricyclo[2.1.0.$0^{2,5}$]pentan-3-one series (Scheme 92).[107] Treatment of the dichloro derivative **377** with sodium borohydride gave methylene cyclobutene **379** by strain-induced ring-opening. This reaction can formally be envisaged as a homologous Grob fragmentation where the oxyanion **378** uses the leaving group six carbons away for ring-opening.

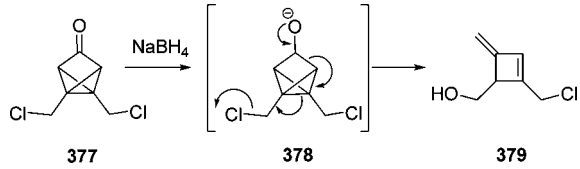
**Scheme 90**



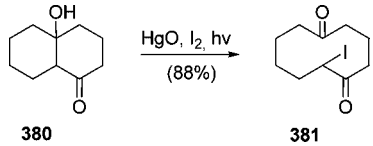

**Scheme 91. Pentasubstituted Phenols by Fragmentation**




**Scheme 92. Fragmentation To Generate an Exo-methylene Cyclobutene**




**Scheme 93. Oxidative Fragmentation**




Free radical-induced fragmentation was used to generate a medium-ring system (Scheme 93).[108] Bicycle **380** was treated with $HgO/I_2$ to induce the fragmentation to the desired α-iodoketone **381**. In this way, various 9- to 11-membered ring iodo-diketones were synthesized. HgO can be replaced by $PhI(OAc)_2$, which gave somewhat lower yields, and also with $Pb(OAc)_4$, which generated the corresponding α-acetoxy diketones.

## 3.7. Miscellaneous without Electrofugal Carbonyl Groups

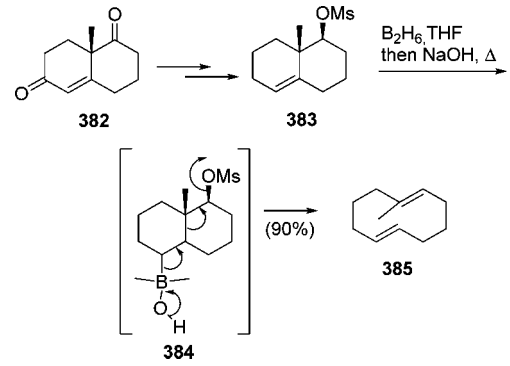
Boronic esters can also be used as electrofugal groups (Scheme 94).[109] Unsaturated *O*-mesylate **383** was prepared as fragmentation substrate from Wieland−Miescher ketone **382**. Treatment with diborane was followed by addition of sodium hydroxide, and after refluxing the mixture for an hour cyclic diolefin **385** was isolated in 90% yield.

This reaction was applied in the synthesis of thapsigargin (**389**) (Scheme 95).[110] Thus, alkyl-monoborane **386** underwent Grob fragmentation upon treatment with sodium methoxide to give cyclodecadiene **388**. The 10-membered ring was further converted into the annulated 5,7-ring system of the target.

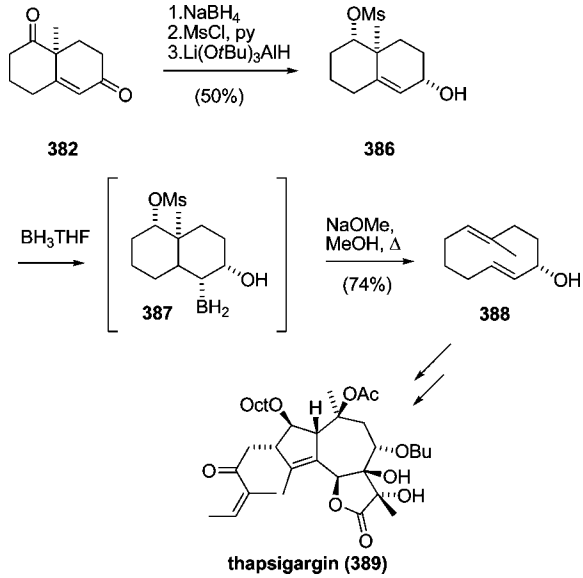
Grob fragmentation was also attempted in the 2,4,6,8-tetracarbomethoxybarbaralane (**391**) synthesis. As base-induced fragmentation failed,[111] $P_2I_4$ was tested to induce the fragmentation (Kuhn−Winterstein reaction) of *exo*,*exo*-diol **390**, which gave the desired product **391** along with two side products **392** and **393** (Scheme 96).

In the total synthesis of (±)-aphidicolin (**398**), the cyclobutanone rearrangement of **394** was used to form the crucial bicyclo[3.2.1]octane core **397**. This reaction can also be considered as an acid-induced Grob fragmentation (Scheme 97).[112]

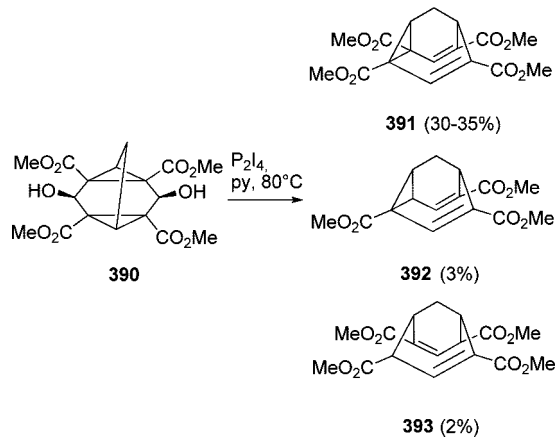
**Scheme 94. Fragmentation of Boronic Esters**



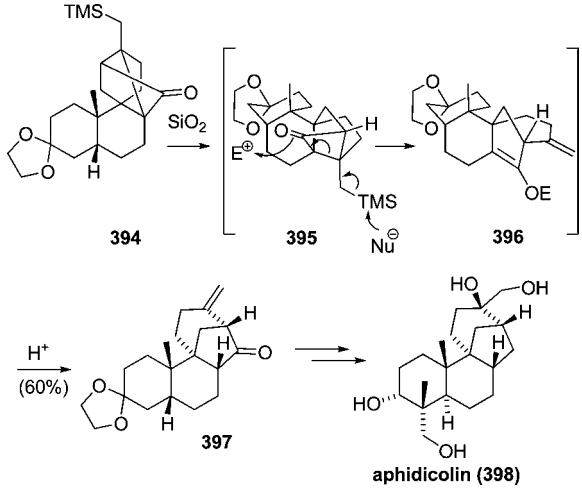

**Scheme 95. Toward the Synthesis of Thapsigargin (389)**




**Scheme 96. $P_2I_4$-Induced Fragmentation**



**Scheme 97. Synthesis of (±)-Aphidicolin (398)**




## 4. Decarboxylative Fragmentations

In an ingenious approach to macrolides, Eschenmoser used a decarboxylative double fragmentation of amidinium salt **399** to generate unsaturated lactone **401** (Scheme 98).[113]

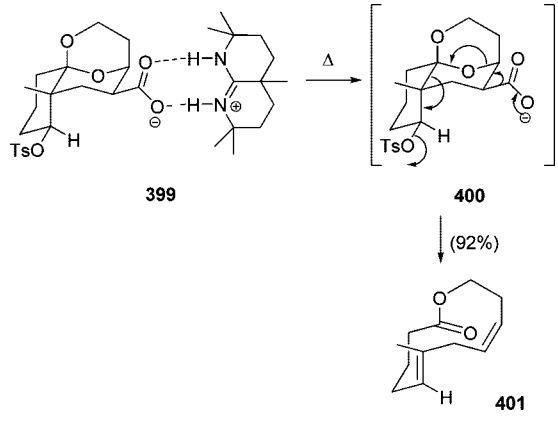
Winkler described a fragmentation approach to the carbon framework of the eleutherobin aglycon (Scheme 99).[114] In the presence of potassium carbonate, tetracyclic fragmentation substrate **402** provided **405** as sole product in 68% yield. Presumably dianion **403** was formed first, which underwent fragmentation under extrusion of carbon dioxide.

The decarboxylative fragmentation of $\beta$-halogen-substituted $\alpha,\beta$-unsaturated acids was investigated (Scheme 100).[115] When heated in aqueous solutions, the potassium salts of these acids formed acetylides. The salt of (*Z*)-**407** gave acetylene **408** only, presumably via a concerted mechanism, whereas the (*E*)-compound also generated substantial amounts of acetophenone **409**. This can be explained by ionization to a carbonium ion, which can either directly eliminate $CO_2$ to give the acetylene or add water to give the $\beta$-keto acid, which is decarboxylated.

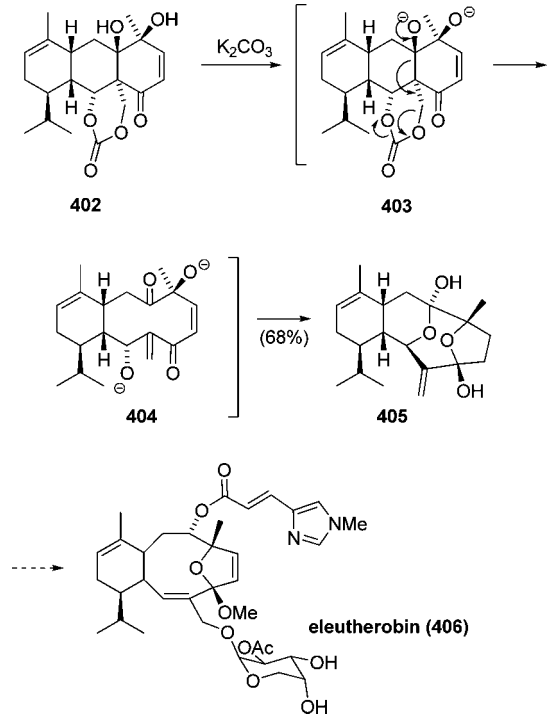
Enol brosylate **410** was also used for fragmentation (Scheme 101).[116] Treatment with 4 equiv of sodium hydroxide in an aqueous dioxane solution at room temperature gave the phenylpropynoic acid **411** by decarboxylative elimination.

Mulzer et al. used decarboxylative dehydration of hydroxyl acid **414** with formamide acetal **415** as a mild method for the synthesis of sensitive 1,3-dienes **416** (Scheme 102).[117,118] Wittig methylenation of **412** failed, and dehydration of tertiary alcohol **414** and **417** led to isomerization, dimerization, and polymerization.

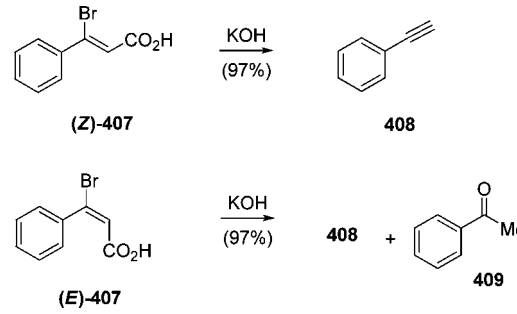
**Scheme 98. Eschenmoser's Decarboxylative Double Fragmentation**



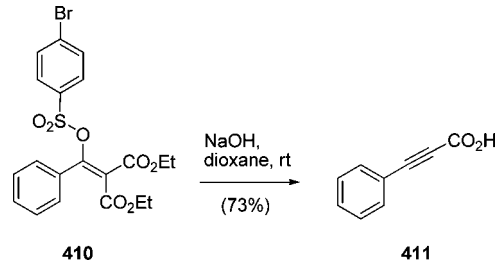

**Scheme 99. Winkler's Eleutherobin Aglycon Synthesis**




**Scheme 100. Fragmentation To Generate Terminal Alkines**



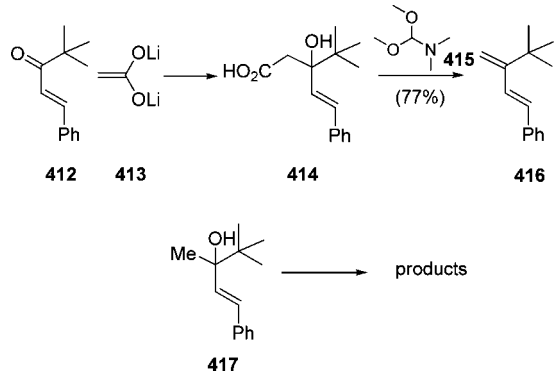

**Scheme 101. Fragmentation for the Synthesis of Acetylenic Acids**



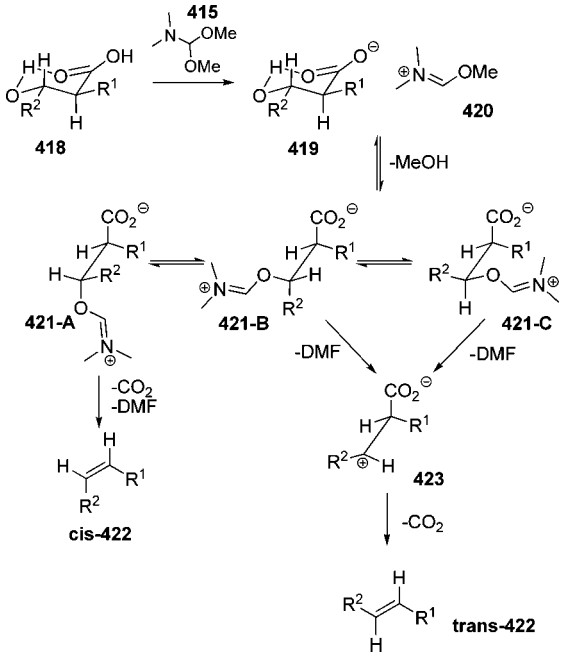

Closer mechanistic investigations of the decarboxylative dehydration of diastereomerically pure $\beta$-hydroxycarboxylic acids **418** with **415** revealed evidence (Scheme 103)[118,119] for an E1/E2-type fragmentation of zwitterionic intermediate **421**. An E2-type concerted fragmentation can only occur from **421-A** where the nucleo- and electrofugal groups are in *anti*-periplanar position. In contrast, **421-B** and **421-C** are suitable for E1 fragmentation via **423**.

Another approach to olefins from $\beta$-hydroxycarboxylic acids ***ent*-418** used the $PPh_3$/DEAD adduct (Scheme 104).[120,121] For *anti*-configurated acids ***ent*-418**, the *E*:*Z* olefin ratio depended on the nature of $R^1$ and $R^2$. Presumably, zwitterion

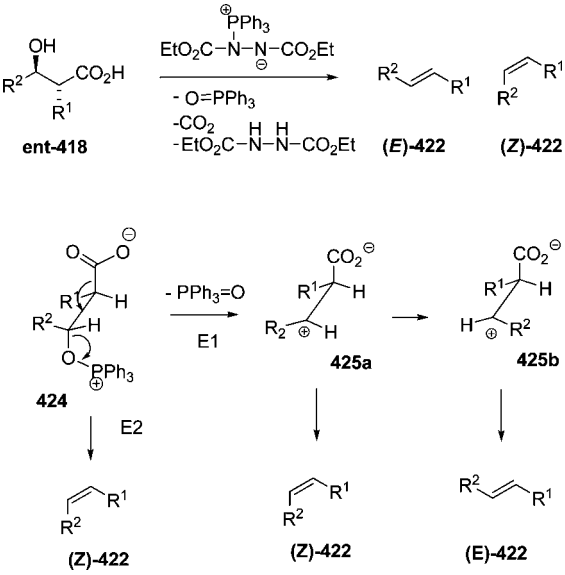
**Scheme 102. Mulzer's Mild Decarboxylative Dehydration Using Dimethylformamide Dimethylacetal**




**Scheme 103. Mechanistic Considerations of Mulzer's Mild Decarboxylative Dehydration**

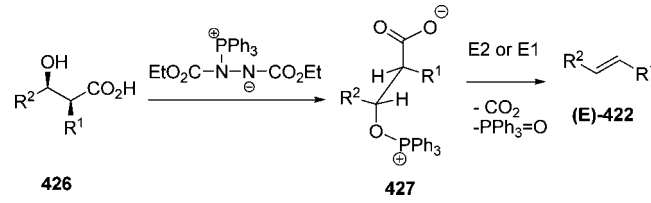



**Scheme 104. Fragmentation of 418 Induced by a $PPh_3$/DEAD Adduct**

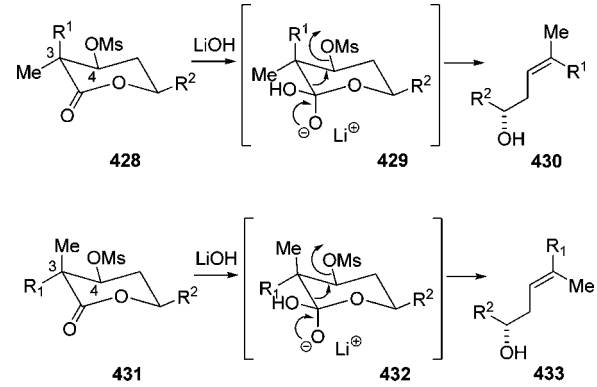



**424** was formed first, which either underwent direct E2-type fragmentation to (*Z*)-**422**, or an E1-elimination to **425a**, which under the steric pressure of R1/R2 quickly rotated to the less strained conformer **425b** and then eliminated $CO_2$ to give (*E*)-**422**. With increasing +M-effect of substituent $R^2$, the E1-pathway and hence the formation of **425b** prevailed, and increasing amounts of (*E*)-**422** were produced.

**Scheme 105. Fragmentation of 426 Induced by the $PPh_3$/DEAD Adduct**




**Scheme 106. Decarboxylative Fragmentation To Generate Trisubstituted (*Z*)-Double Bonds**




In the syn series **426**, the *anti*-conformation **427** is energetically favored for both pathways so that the (*E*)-olefin was generated exclusively (Scheme 105).

(*E*)- and (*Z*)-trisubstituted olefins were also generated stereoselectively by decarboxylative Grob fragmentation (Scheme 106).[122] In this case, $\beta$-mesyloxy-$\delta$-lactones **428** and **431** were used as fragmentation substrates, and hydroxide was the base to induce the fragmentation. The stereochemical outcome of the reaction and hence the formation of the (*Z*)- or the (*E*)-olefin depended on the relative configuration of the stereogenic centers at C3 and C4.

This methodology was used in the stereoselective synthesis of the trisubstituted (*Z*)-olefin moieties in epothilone D (**437**) (Scheme 107), discodermolide (**441**) (Scheme 108), and peloruside A (**445**) (Scheme 109).

When the fragmentation substrate did not feature the *anti*-periplanar arrangement of the nucleo- and electrofugal groups like in **446**, the fragmentation occurred via the open-chain carboxylic acid **449** to give olefin **450** and $\beta$-lactone **451** as the result of competing E2 and $S_N2$ reactions (Scheme 110).

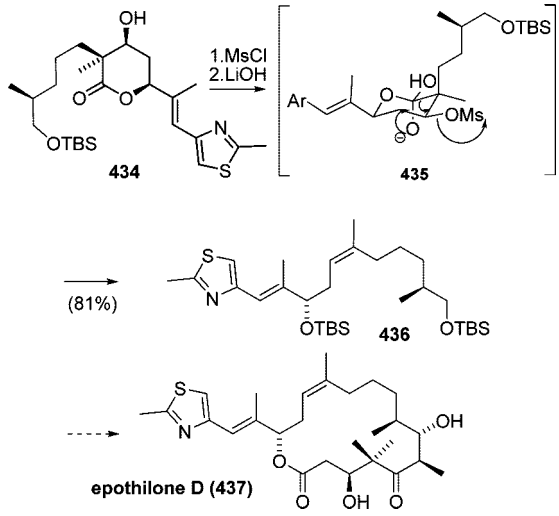
Also, open-chain fragmentation precursors such as **452** were successfully used for the hydroxide-induced decarboxylative Grob-type fragmentation (Scheme 111).[123]

## 5. Tandem Reactions

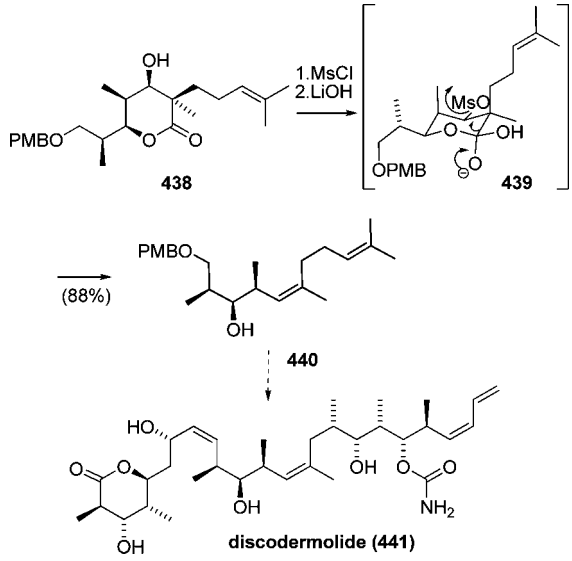
### 5.1. Tandem Aldol−Grob Fragmentation Sequence[124,125]

The tandem Aldol−Grob fragmentation sequence involved the reaction of ketones **455** with aromatic aldehydes **454** in nonnucleophilic solvents, which gave, in the presence of boron trifluoride, the (*E*)-arylalkene **456** (Scheme 112). The first step was the LA-mediated aldol addition between

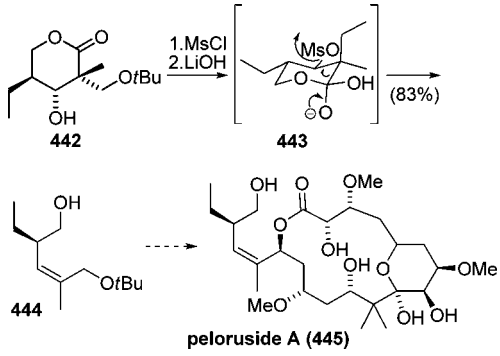
**Scheme 107. Formal Synthesis of Epothilone D (437)**




**Scheme 108. Formal Synthesis of Discodermolide (441)**




**Scheme 109. Formal Synthesis of Peloruside A (445)**

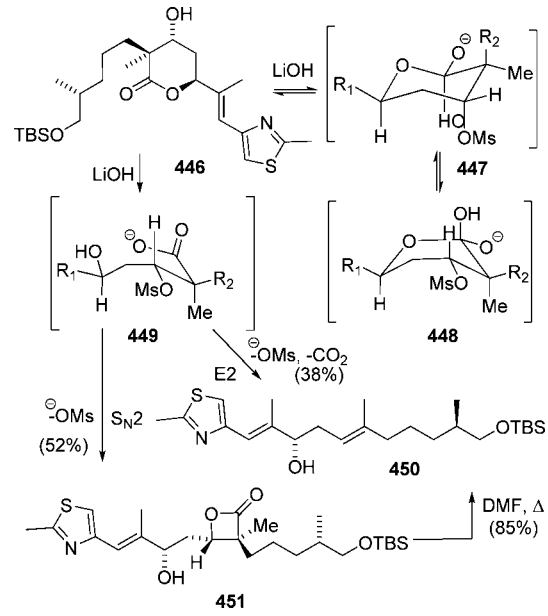



aldehyde **454** and ketone **455**. Next, the newly formed hydroxyl group attacked the activated carbonyl to generate **459**, whose fragmentation led to olefin **456**.

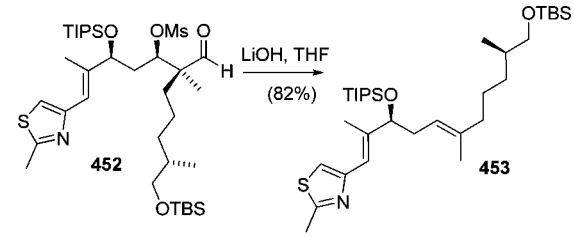
## 5.2. Sequential Semipinacol Rearrangement/Grob Fragmentation of Allylic Alcohols[126]

A one-pot semipinacol rearrangement/Grob fragmentation of allylic alcohols **461** and **464** was reported, consisting of a NBS promoted semipinacol rearrangement to the $\beta$-bromo aldehydes **462** and **465** and subsequent sodium hydroxide-

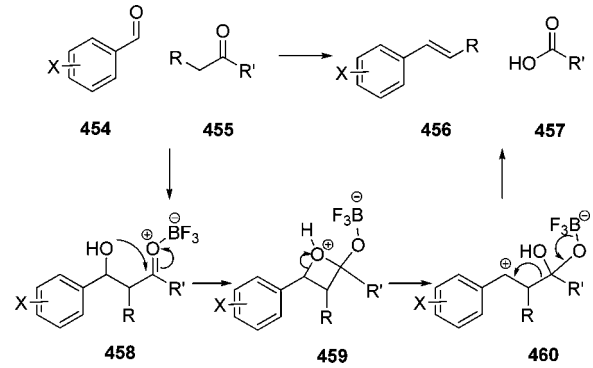
**Scheme 110. Decarboxylative Fragmentation via E2 Mechanism**



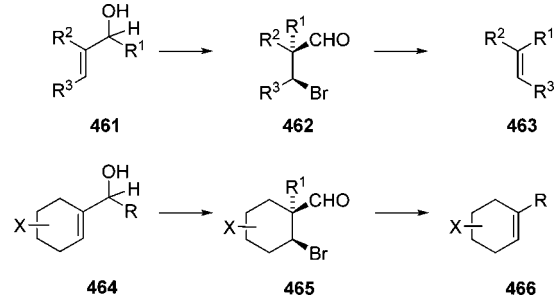

**Scheme 111. Decarboxylative Fragmentation of Open-Chain Precursor 452**




**Scheme 112. Tandem Aldol−Grob Reaction**




**Scheme 113. Tandem Semipinacol Rearrangement/Grob Fragmentation**




mediated Grob fragmentation (Scheme 113). For acyclic substrates, the fragmentation was a one-step *anti*-periplanar

fragmentation, whereas fragmentation of cyclic substrates proceeded via a two-step *syn*-fragmentation.

## 5.3. Intramolecular Barbier Cyclization/Grob Fragmentation[127]

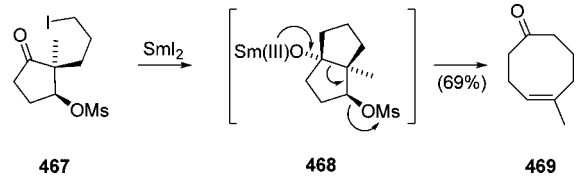
The intramolecular Barbier-type coupling of **467** led to bicyclic alkoxide **468**, which underwent Grob fragmentation to the eight-membered ring **469** (Scheme 114). The major restriction was the length of the iodoalkyl chain, which limited the method to 8-, 9-, or 10-membered rings.

## 5.4. Grob Fragmentation/Michael Addition[128]

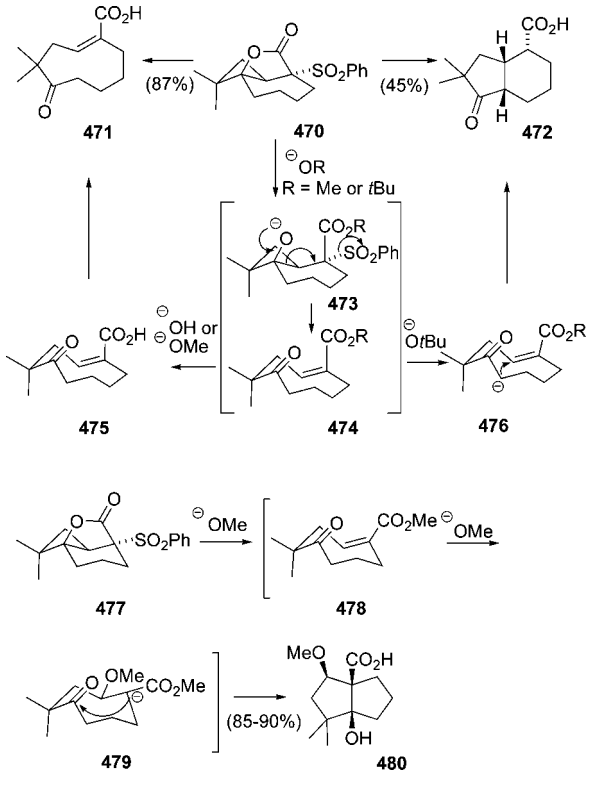
When **470** was treated with KOH in methanol, the Grob fragmentation product **471** was isolated as sole product, giving only the (*E*)-isomer (Scheme 115). When KO$^t$Bu was used as base, mainly **472** was found. Here, deprotonation of the keto group in the fragmentation product **474** took place, and the resulting enolate **476** attacked the newly formed Michael acceptor in a 1,4 addition.

When the homologous 6-fused $\gamma$-lactone **477** was used as substrate, treatment with potassium methoxide led to **480**. Here, methoxide was small enough to react as the nucleophile in a Michael addition to the fragmentation product **478**. Ester enolate **479** was generated and underwent an aldol cyclization to form **480**.

**Scheme 114. Tandem Barbier Cyclization/Grob Fragmentation**




**Scheme 115. Tandem Grob Fragmentation/Michael Addition**



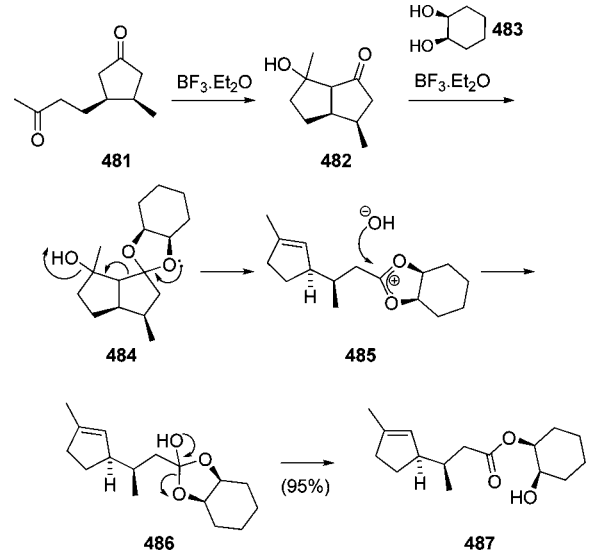

## 5.5. Intramolecular Aldol Reaction/Acetalization/Grob Fragmentation[129]

The first step was the intramolecular $BF_3$-mediated aldol reaction of **481** (Scheme 116). Acetal formation with 1,2-diol **483** and Lewis acid gave acetal **484**, which fragmented to dioxolenium cation **485**. Formation of the ortho hemiacetal **486** finally led to ester **487**. *cis*-Diols afforded better yields in the ring transformation, which might be due to the rigid *anti*-periplanar arrangement of an oxygen lone pair to the C−C bond after dioxolane ring formation.

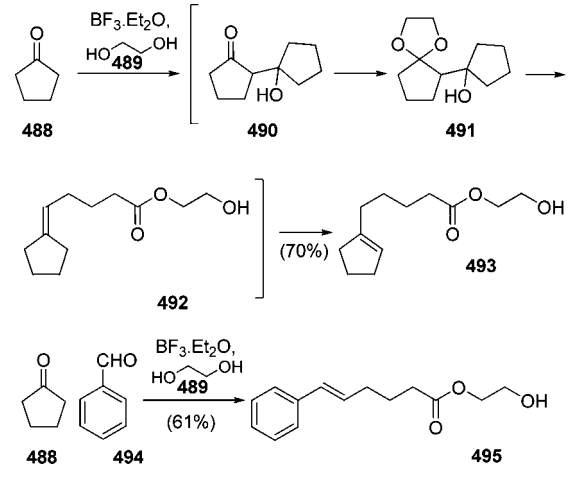
## 5.6. Intermolecular Aldol Reaction/Acetalization/Grob Fragmentation[130]

The aldol reaction/acetalization/Grob fragmentation sequence also worked with an intermolecular aldol reaction in the first step as was shown with several cycloalkanones (Scheme 117). The isomerization of the double bond in the last step was confirmed by chemical conversion into the corresponding aldehyde by oxidative cleavage of the olefin. Treatment of cyclopentanone **488** with $BF_3$ and ethandiol (**489**) led first to the aldol adduct **490**, which underwent acetalization to **491**. Grob fragmentation of acetal **491** gave ester **492**, which isomerized to **493**. Also, crossed aldol

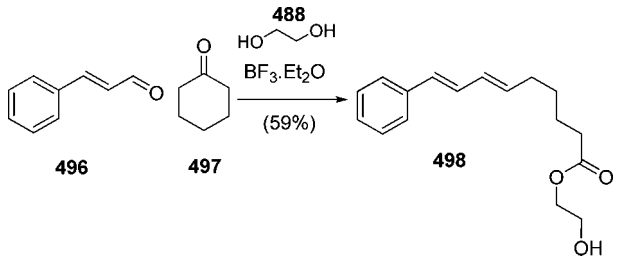
**Scheme 116. Intramolecular Aldol Reaction/Acetalization/Grob Fragmentation**




**Scheme 117. Intermolecular Aldol Reaction/Acetalization/Grob Fragmentation**



**Scheme 118. Intermolecular Aldol Reaction/Acetalization/Grob Fragmentation**




additions (**489** + **494**) were employed using aromatic aldehydes to generate the aromatic conjugated ester derivatives **495**.

The aldol reaction/acetalization/Grob fragmentation was further extended to cinnamaldehyde **496** and cyclohexanone **497** (Scheme 118), which gave ester **498**, used in natural products synthesis.[131,132]

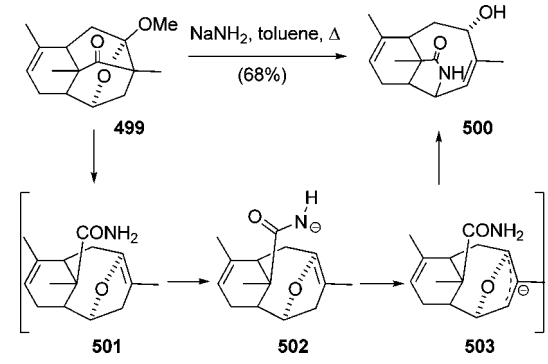
## 5.7. Haller/Bauer-Scission/Grob Fragmentation[133]

The regioselectivity of the fragmentation of **499** was due to the nucleofugal group OMe in $\beta$-position to the ketone (Scheme 119), even though product **501** is an *anti*-Bredt olefin. Under the basic conditions, amide **501** was deprotonated to **502**. Reprotonation and intramolecular $S_N2$ substitution gave the tricyclic lactam **500**.

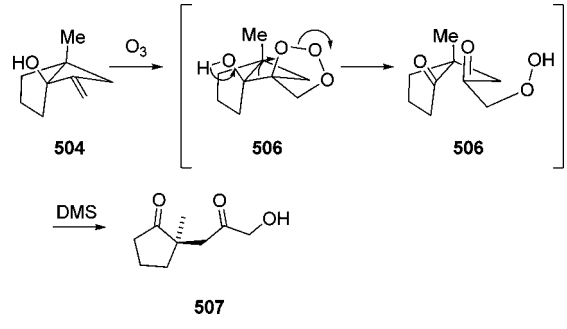
## 5.8. Trapping of Primary Ozonides[134]

After ozonolysis, strained bicyclic allylic alcohols gave hydroxymethyl ketones due to a Grob-like fragmentation of the primary ozonide (Scheme 120). Thus, treatment of olefin **504** with ozone led to ozonide **505**, which gave peroxide **506** after fragmentation. Finally, **506** was reduced to hydroxyketone **507** with dimethylsulfide.

**Scheme 119. Haller/Bauer-Scission/Grob Fragmentation**




**Scheme 120. Fragmentation of Primary Ozonide**




## 5.9. Construction of the Core of Zaragozic Acids

A new synthesis for the core of zaragozic acid A (**511**) was reported (Scheme 121).[135] Base-induced Grob fragmentation of $\gamma$-hydroxymesylate **508** furnished the labile exocyclic enol ether **509**. Reduction of the aldehyde followed by iodo cyclization gave acetal **510**.

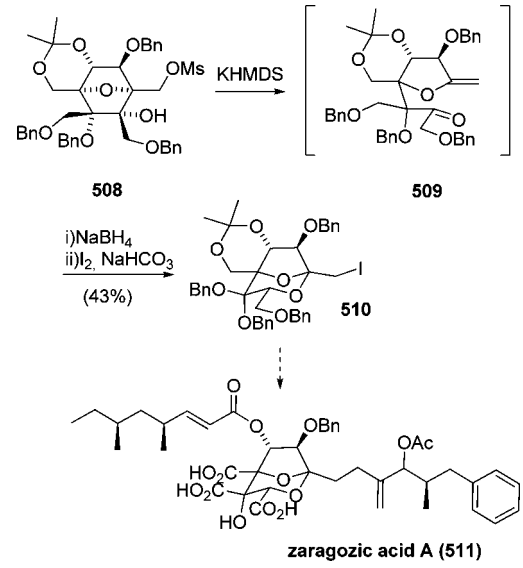
## 5.10. Grob Fragmentation Followed by a Transannular Ketene [2 + 2] Cycloaddition Reaction[136]

Treatment of **512** with excess triethylamine gave the pyroglutamic acid derivative **516** in quantitative yield. This result can be rationalized by a base-induced Grob fragmentation of hydroxyamide **512** to ketene **514**. Transannular ketene-ketone [2 + 2] cycloaddition generated the highly strained $\beta$-lactone **515**, which was hydrolyzed to hydroxy acid **516** (Scheme 122).

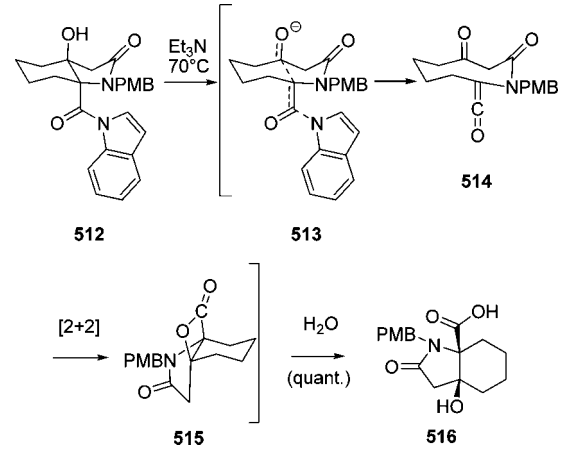
## 5.11. Grob Fragmentation and Stereocontrolled $SmI_2$-Mediated Cyclization[137,138]

Carbohydrates were converted into the corresponding stereodefined cyclopentanols by treating a methyl 6-deoxy-6-iodoglycoside such as **517** with $SmI_2$. This initiated a

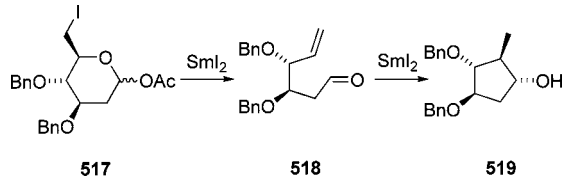
**Scheme 121. Toward the Synthesis of Zaragozic Acid A (511)**



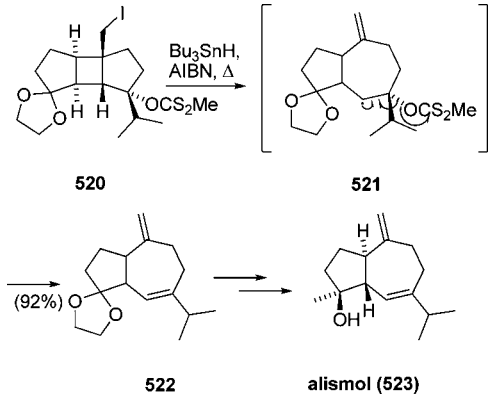

**Scheme 122. Grob Fragmentation/Transannular Ketene [2 + 2] Cycloaddition**



**Scheme 123. Grob Fragmentation/$SmI_2$-Mediated Cyclization**




**Scheme 124. Radical Fragmentation/Elimination**




reductive Grob fragmentation to **518**, which was followed by $SmI_2$-mediated cyclization to **519** (Scheme 123).

## 5.12. Free Radical Fragmentation/Elimination Sequence[139]

A synthesis of alismol (**523**) was reported using a fragmentation/elimination sequence (Scheme 124). Free radical fragmentation of tricyclic **520** gave radical **521** with a leaving group on the adjacent carbon. This triggered an elimination and regioselectively introduced a second double bond in **522**.

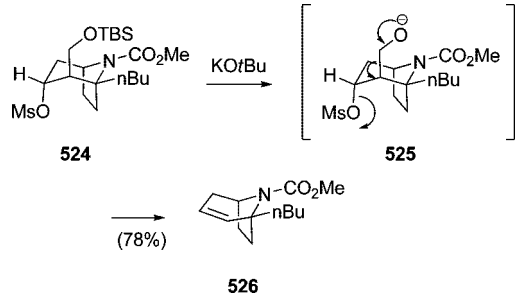
# 6. Fragmentation as Unexpected Side Reaction

In an attempt to eliminate the mesyloxy group of 8-azabicyclo[3.2.1]octane **524** with KO$^t$Bu, a silyl ether cleavage followed by Grob fragmentation took place to generate olefin **526** (Scheme 125).[140]

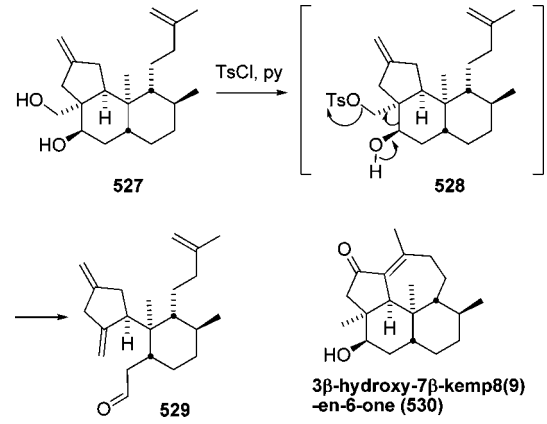
## 6.1. Kempane Diterpenes[141]

In the synthesis toward hydroxykempenones like 3$\beta$-hydroxy-7 $\beta$-kemp8(9)-en-6-one (**530**), Grob fragmentation occurred as an undesired reaction during tosylation of precursor **527** under standard conditions (Scheme 126). The envisaged reduction of **528** to an angular methyl group could not be performed, as spontaneous Grob fragmentation to aldehyde **529** was observed.

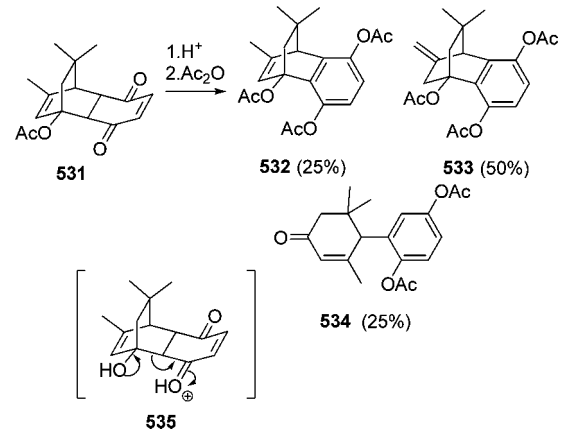
**Scheme 125. Unexpected Fragmentation of the Mesylated Diol 524**




**Scheme 126. Unexpected Fragmentation during Tosylate Formation**




**Scheme 127. Fragmentation as Side Reaction during Acid-Induced Aromatization**




## 6.2. Diels−Alder Adducts of Acetoxy-1,3-dienes and *p*-Benzoquinone[142]

Acid-induced aromatization of the Diels−Alder adduct **531** led to a mixture of **532**, **533**, and **534** (Scheme 127). The formation of **534** involved a Grob fragmentation of intermediate **535**.

# 7. Summary and Conclusions

Since the early 1950s, Grob fragmentations have been employed in the synthesis of double bonds. Especially in the recent past, highly complex fragmentation precursors were developed for double bonds that would be hard to generate otherwise. The approaches toward paclitaxel or vinigrol are striking examples. In general, Grob fragmentations are fast, high yielding, and require simple conditions (base or catalytic amounts of acid). Therefore, they are a useful and reliable synthetic tool, especially when all stereochemical requirements for the concerted mechanism are met. In this case, the stereochemical outcome is easily predictable, and no side reactions are observed. Also, a number of tandem reactions are known, which lead to useful building blocks.

# 8. Abbreviations

| | |
|---|---|
| Ac | acetyl |
| AIBN | 2,2′-azobisisobutyronitrile |
| Bn | benzyl |
| Bu | butyl |

| | |
|---|---|
| Bz | benzoate |
| cod | cyclooctadiene |
| CSA | camphorsulfonic acid |
| Cy | cyclohexyl |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | *N*,*N*′-dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| DEAD | diethyl azodicarboxylate |
| DIBALH | diisobutylaluminium hydride |
| DIC | *N*,*N*′-diisopropylcarbodiimide |
| DIPA | *N*,*N*-diisopropylamine |
| DMAP | 4-(dimethylamino)pyridine |
| DMDO | dimethyldioxirane |
| DMF | *N*,*N*-dimethylformamide |
| DMP | Dess−Martin periodinane |
| DMS | dimethylsulfide |
| DMSO | dimethylsulfoxide |
| IBX | *o*-iodoxybenzoic acid |
| IMDA | intramolecular Diels−Alder reaction |
| ISB | iodosylbenzene |
| KHMDS | potassium hexamethylsilylazide |
| LA | Lewis acid |
| LAH | lithium aluminiumhydride |
| LDA | lithium diisopropylamide |
| LDBB | lithium di-*tert*-butyl biphenylide |
| LG | leaving group |
| LiHMDS | lithium hexamethylsilylazide |
| LTA | lead(IV) acetate |
| *m*CPBA | *meta*-chloroperbenzoic acid |
| MOM | methoxymethyl |
| Ms | methansulfonyl |
| NBS | *N*-bromosuccinimide |
| $NEt_3$ | triethylamine |
| Ph | phenyl |
| PLE | pig liver esterase |
| PMB | *para*-methoxybenzyl |
| Pr | propyl |
| py | pyridine |
| $R_{(1,2,...n)}$ | any substituent |
| Ra−Ni | Raney−Nickel |
| RCM | ring-closing metathesis |
| RT | room temperature |
| SET | single electron transfer |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBDPS | *tert*-butyldiphenylsilyl |
| TBS | *tert*-butyldimethylsilyl |
| TEA | triethylamine |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| Tf | trifluoromethanesulfonate |
| TMS | trimethylsilyl |
| Ts | tosylate |
| *p*TsOHorPTSA | *para*-toluene-4-sulfonic acid |

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