1 [3,3]-Sigmatropic Rearrangements

GENERAL CONSIDERATIONS

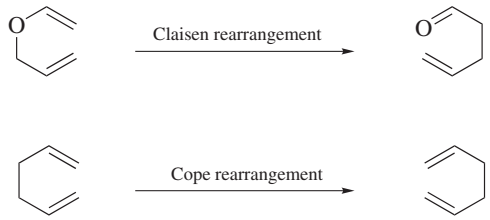
The Claisen and Cope rearrangements are two of the best known sigmatropic rearrangements in organic chemistry[1] (Scheme 1.I). As the rearrangement involves six electrons in a six-atom system, these two reactions serve as excellent examples of the ubiquitous existence of a six-membered transition state in organic chemistry.

In 1912, Ludwig Claisen discovered that the allyl ether **1** of ethyl acetoacetate underwent a reaction to afford **2** upon heating in the presence of ammonium chloride[2] (Scheme 1.II). Similarly, the allyl naphthyl ether **3** transformed into 1-allyl-2-naphthol (**4**) in 82% yield at 210°C. The reaction, now known as the *Claisen rearrangement*, is general for a variety of aliphatic and aromatic ethers and is recognized as one of the most synthetically useful reactions in organic chemistry.[3]

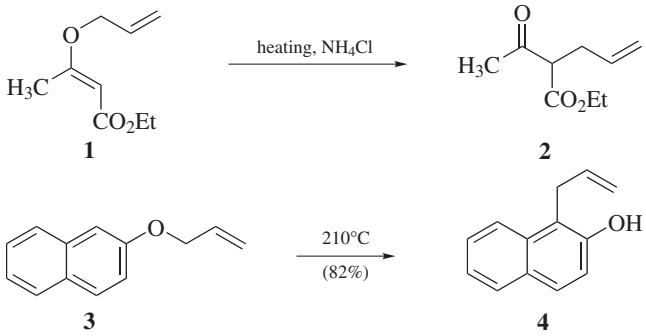
The Claisen rearrangement is a thermally induced [3,3]-sigmatropic rearrangement of allyl vinyl ethers to form γ,δ-unsaturated carbonyl compounds.[4] Due to the concerted nature and synthetic utilities of the Claisen rearrangement, much effort has been devoted to understanding the mechanism of the reaction.[5] Although the extent of delocalization of the six electrons involved in the transition state may depend on the nature of the substrates, it is believed that the rearrangement goes through a six-membered aromatic transition state[6] (Scheme 1.III).

To uncover the transition-state structures for Claisen rearrangement of the parent allyl vinyl ether,[7] Vance et al. performed ab initio quantum mechanical calculations[8] (Scheme 1.IV). When the transition structures were calculated using the 6-31G* basis set, the partially formed C_1-C_6 bond length is 2.26 Å and the partially broken C_4-O bond length is 1.92 Å in chairlike transition structure **A**. These two bond lengths were confirmed by Meyer et al. in a later study employing different-level calculations.[9] Another important finding in Vance et al.'s study is that chairlike transition structure **A** is more stable than boatlike structure **B**, by 6.6 kcal/mol. The conclusion thus supports the proposals of chairlike transition structures for the stereoselectivities observed for the Claisen rearrangement reactions of substituted molecules.

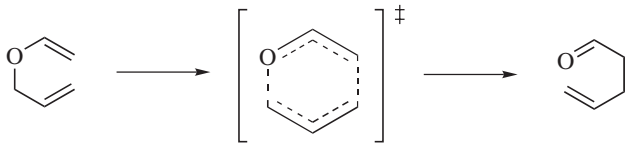
Six-Membered Transition States in Organic Synthesis, By Jaemoon Yang



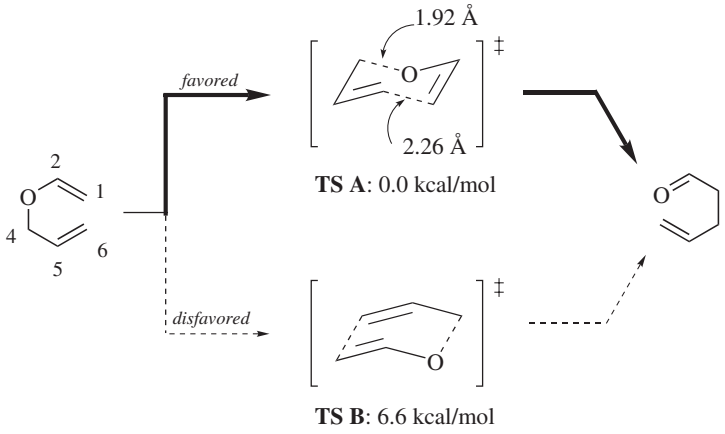
Scheme 1.I



Scheme 1.II

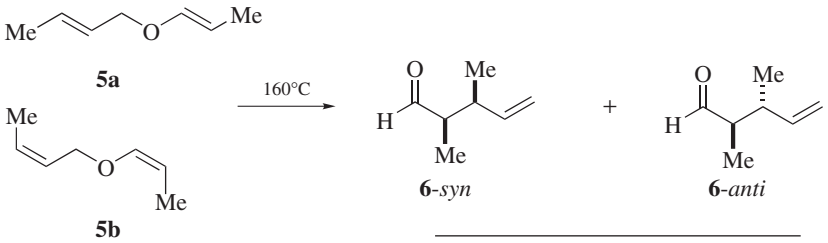


Scheme 1.III



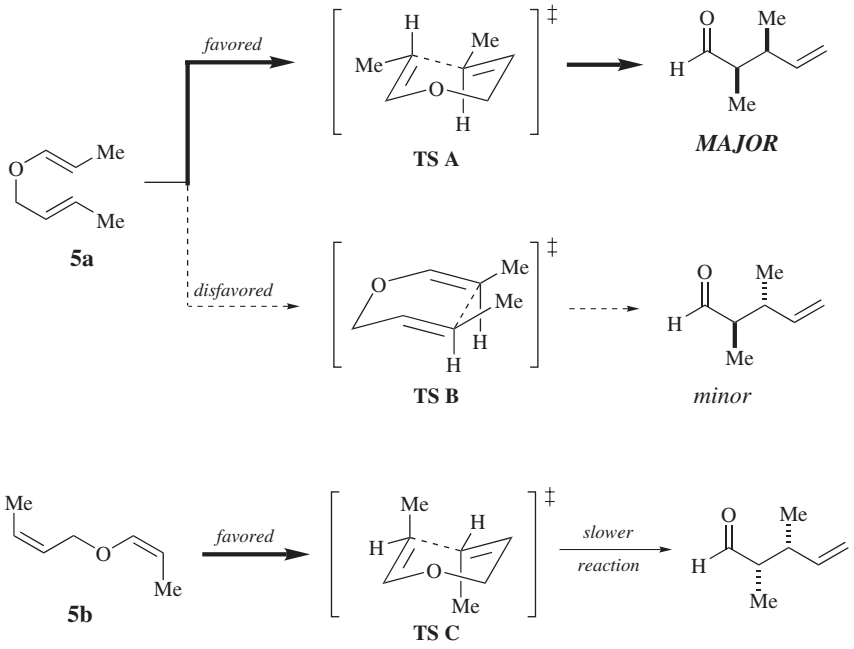
Scheme 1.IV

One classic example that confirms the preference of Claisen rearrangement for a chairlike transition state was provided by Hansen and others. In 1968, they investigated the Claisen rearrangement of the crotyl propenyl ethers **5a** and **5b** to examine the stereochemistry of the rearrangement in the gas phase at 160°C[10] (Scheme 1.V). Both the *E*,*E*- and *Z*,*Z*-isomers rearrange to afford a *syn*-isomer as the major product. The stereochemical outcome of the reaction can be explained



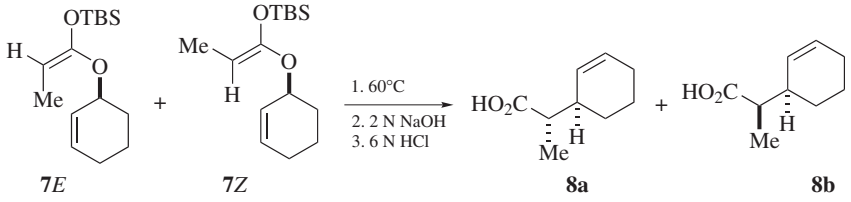
Ether	*syn*/*anti*	Rel. Rate
5a	95.9:4.1	9
5b	94.7:5.3	1

Scheme 1.V



Scheme 1.VI

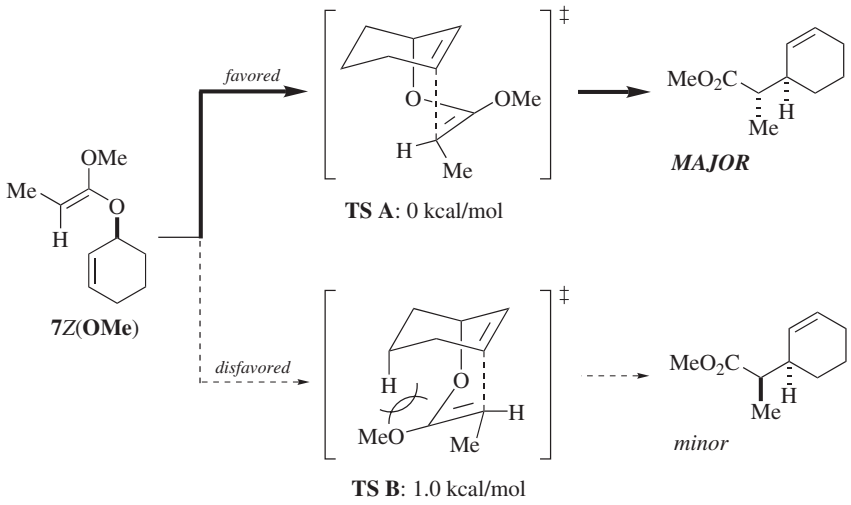
in terms of a six-membered transition state[10] (Scheme 1.VI). Between the two transition states for **5a**, chairlike transition state **A** is favored over boatlike state **B** to afford a *syn*-isomer as the major product. Chairlike transition state **C** can explain the formation of the *syn*-isomer that is enantiomeric to **6**-*syn*. Other indirect evidence for the existence of a chairlike transition state is the fact that the *E*,*E*-isomer **5a** reacts nine times faster than the *Z*,*Z*-isomer **5b**. This difference in the reaction rate can be understood by examining transition states **A** and **C**: Transition state **C** for **5b** is of higher energy than transition state **A** for **5a**, due presumably to the 1,3-diaxial interactions arising from the axial methyl groups in transition state **C**.



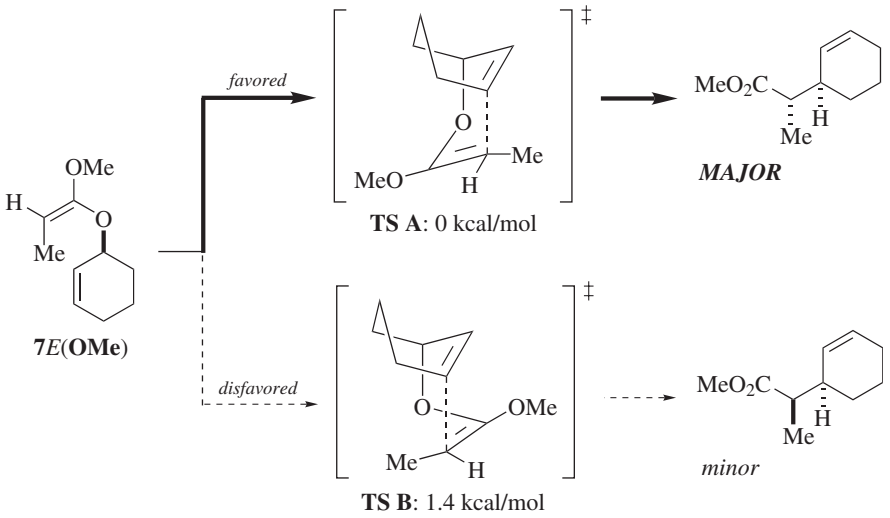
7*E* **7***Z* **8a** **8b**

7*E*/**7***Z*	**8a/8b**	Yield, %
83:17	84:16	79
4:96	72:28	91

Scheme 1.VII



Scheme 1.VIII



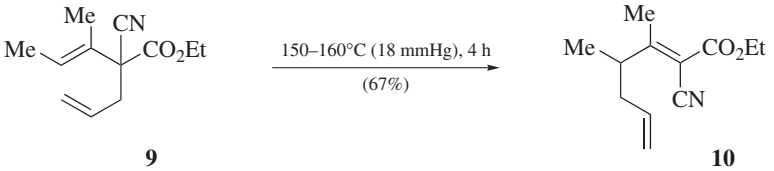
Scheme 1.IX

Although a chairlike transition state is favored for the Claisen rearrangement reactions of acyclic substrates, this is not always the case with cyclic systems. For example, Bartlett and Ireland independently studied the rearrangement reactions of cyclohexenyl silylketeneacetals and found that there was competition between the chairlike and boatlike transition states[11] (Scheme 1.VII). Clearly, the *E*-isomer **7***E* gives **8a** via a chairlike transition state, whereas the *Z*-isomer **7***Z* affords the same product (**8a**) via a boatlike transition state.

To quantitatively understand the preference for the chairlike and boatlike transition states of the Claisen rearrangement, Houk et al. carried out a computational study[12] (Scheme 1.VIII). In the theoretical treatment two methyl acetals, **7***Z*(**OMe**) and **7***E*(**OMe**), were used as a model system instead of the *tert*-butyldimethylsilyl (TBS) ketene acetal. Calculations locate four transition states for the rearrangement of **7***Z*(**OMe**), among which boatlike transition state **A** is of the lowest energy that leads to the formation of the major isomer observed experimentally. Chairlike transition state **B** is disfavored, due to steric repulsion between the axial hydrogen of the cyclohexenyl unit and the methoxy substituent of the alkene.

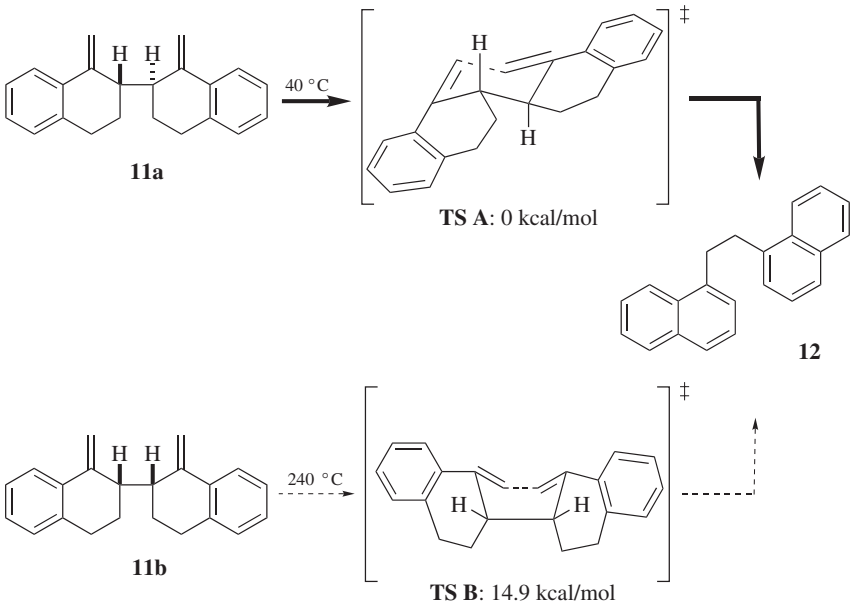
For the reaction of **7***E*(**OMe**), chairlike transition state **A** is favored over boatlike transition state **B**[12] (Scheme 1.IX). These computational results provide a solid theoretical rationalization of the original proposal by Bartlett and Ireland that the boatlike transition state is favored for the Claisen rearrangement of **7***Z*, and the chairlike transition state is preferred for **7***E*.

Another important [3,3]-sigmatropic rearrangement is the *Cope rearrangement*, a carbon analog of the Claisen rearrangement. At the eighth National Organic Chemistry Symposium in 1939, Arthur C. Cope and Elizabeth M. Hardy presented their exciting discovery of this new reaction in which an allyl group



9 **10**

Scheme 1.X

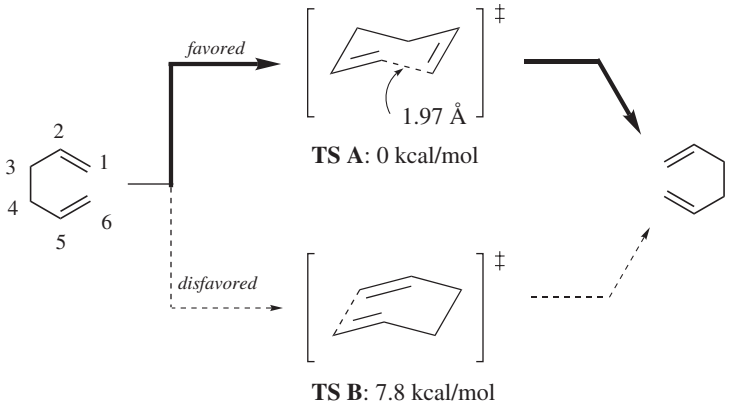


11a **11b**

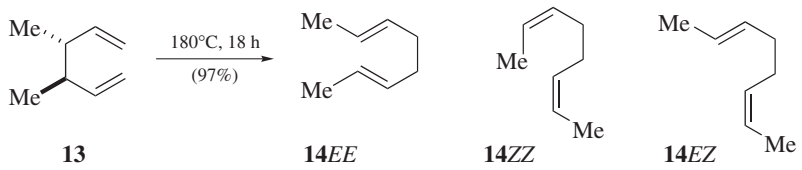
Scheme 1.XI

migrated in a three-carbon system[13] (Scheme 1.X). The discovery of the reaction was made possible by careful analysis of the product (**10**) that formed during vacuum distillation of the diene **9**.

The Cope rearrangement, which is the conversion of a 1,5-hexadiene derivative to an isomeric 1,5-hexadiene by the [3,3]-sigmatropic mechanism, has been studied extensively.[14] As is the case for the Claisen rearrangement, the Cope rearrangement prefers to go through a six-membered chairlike transition state. Shea et al. demonstrated elegantly the preference for the chairlike over the boat-like transition state by carrying out Cope rearrangements of racemic (**11a**) and meso (**11b**) naphthalenes[15] (Scheme 1.XI). It was determined that the racemic 1,5-diene **11a** underwent Cope rearrangement 7 million times faster than the meso diene **11b**. The energy difference between transition states **A** and **B** is calculated to be 14.9 kcal/mol.

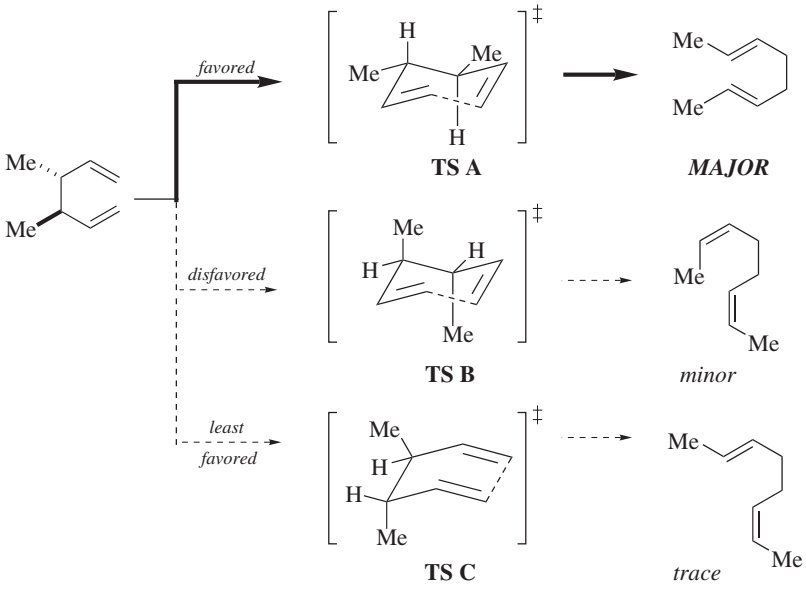


Scheme 1.XII



14*EE*/**14***ZZ*/**14***EZ* = 90:9:<1

Scheme 1.XIII



Scheme 1.XIV

A number of theoretical studies have been conducted to understand the mechanism of the Cope rearrangement.[16] According to calculations by Houk and co-workers, the chairlike transition state is more stable than the boatlike transition state by 7.8 kcal/mol (Scheme 1.XII). When Schleyer and colleagues performed calculations to compute the magnetic properties of the transition-state structures, transition states **A** and **B** had a magnetic susceptibility of −55.0 and −56.6, respectively. These values are comparable to that of benezene (−62.9), confirming the existence of an aromatic transition state in the Cope rearrangement.

One classic example is an experiment reported by Doering and Roth in 1962[17] (Scheme 1.XIII). Upon heating, racemic 3,4-dimethylhexa-1,5-diene (**13**) rearranged to a mixture of (2*E*,6*E*)-octa-2,6-diene (90%), (2*Z*,6*Z*)-octa-2,6-diene (9%), and a trace amount of (2*E*,6*Z*)-isomer. The experimental results are explained in terms of a six-membered transition state[17] (Scheme 1.XIV). Chairlike transition state **A** is favored over transition state **B** based on the conformational analysis of 1,2-dimethylcyclohexane, in which the methyl substituents prefer to be in an equatorial position. The observation that **14***EZ* was formed in only trace amounts indicates that boatlike transition state **C** is of significantly higher energy than transition state **A** or **B**.

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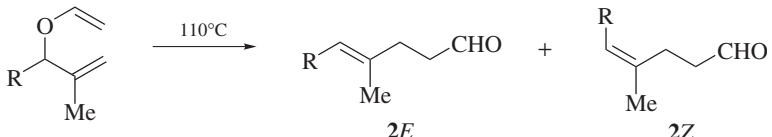
REACTIONS

1.1. Claisen Rearrangement

A very interesting stereochemical outcome is noted for the Claisen rearrangement of substituted allyl vinyl ethers. For example, the allyl vinyl ethers **1** underwent Claisen rearrangement to afford the unsaturated aldehydes **2** in quantitative yields and with high levels of stereoselectivity, which depend largely on the steric bulkiness of the R group[1] (Scheme 1.1a). To explain the stereochemical outcome of the rearrangement, Perrin and Faulkner proposed a six-membered chairlike transition state[1] (Scheme 1.1b). Transition state **A**, leading to formation of the major product, is favored over **B**, in which the bulky alkyl group (R) occupies an axial position, resulting in energetically unfavorable 1,3-diaxial interactions.

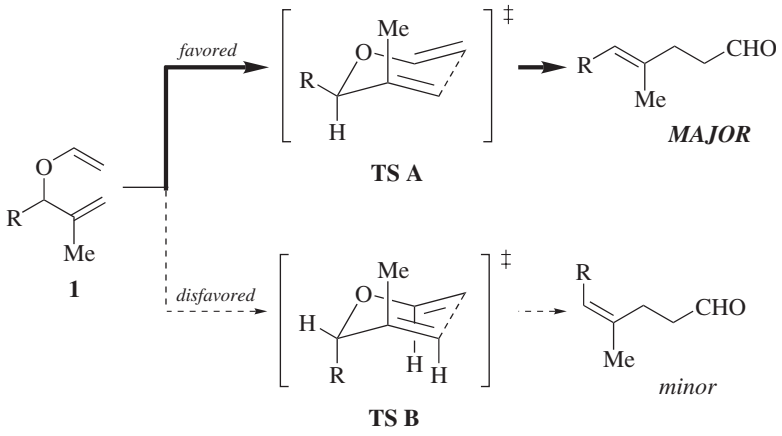
The methyl substituent in 2-methyltetrahydropyran prefers to be in an equatorial position[2] (Scheme 1.1c). The formation of **2***E* (R = Et) as a major isomer in the rearrangement can be understood qualitatively when 2-methyltetrahydropyran is employed as a model system to estimate the energy difference between transition states **A** and **B**.[3] As the Claisen rearrangement is a concerted reaction, the chirality in the starting material is translated directly to the product without loss of optical purity. For example, upon heating the allyl vinyl ethers **3***R* and **3***S* both gave the γ,δ-unsaturated aldehyde **4**[4] (Scheme 1.1d). The degree of chirality transfer was calculated to be 98% after correcting the optical purities of the starting materials. The high level of chirality transfer in the foregoing reactions supports the notion that the reaction goes through a six-membered transition



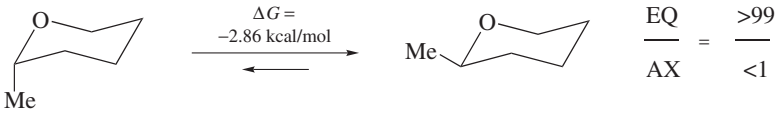
1 **2***E* **2***Z*

R	*E*/*Z*	Yield, %
Et	90 : 10	100
i-Pr	93 : 7	100

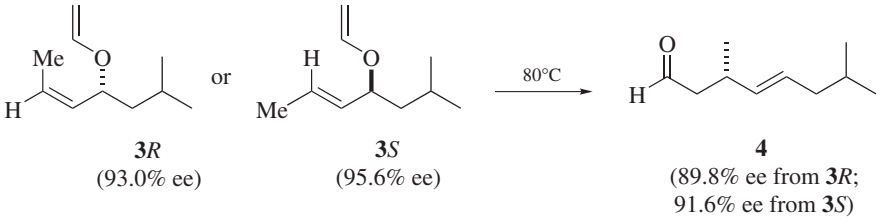
Scheme 1.1a



Scheme 1.1b



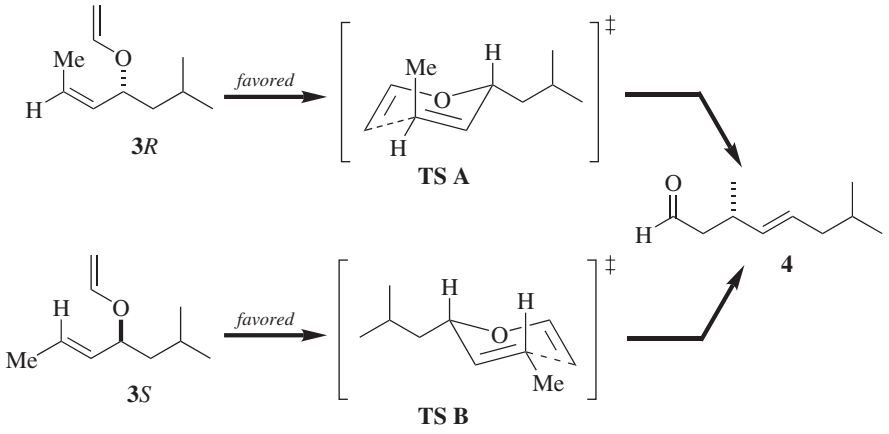
Scheme 1.1c



Scheme 1.1d

state[4] (Scheme 1.1e). The isobutyl group in transition states **A** and **B** occupies an equatorial position in the six-membered chairlike conformation.

The Claisen rearrangement was used in the asymmetric total synthesis of (+)-9(11)-dehydroestrone methyl ether (**5**), a versatile intermediate in the synthesis of estrogens[5] (Scheme 1.1f). The key feature of the synthesis is the successful development of the asymmetric tandem Claisen-ene sequence. Thus, a solution of the cyclic enol ether **6** in toluene was heated in a sealed tube at 180°C for 60 hours to afford the product **9** in 76% isolated yield after deprotection of the silyl enol ether. The Claisen rearrangement of the allyl vinyl ether **6** occurred stereoselectively to give an intermediate (**7**), in which the 8,14-configuration was 90% *syn*. The stereoselectivity in the Claisen rearrangement can be explained



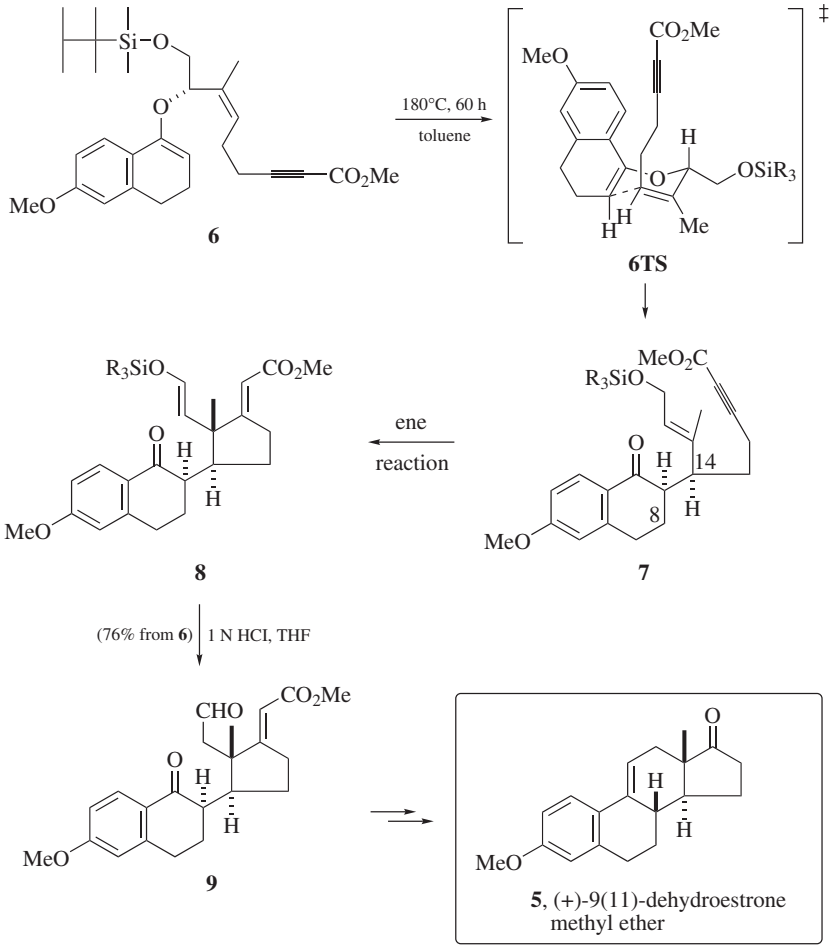
Scheme 1.1e

by the chairlike transition state **6TS**, which has minimal 1,3-diaxial interactions. Therefore, the *S-Z* chirality of the enol ether **6** is transmitted completely to the 14*S* chirality in the Claisen product **7**, along with a high 8,14-*syn* selectivity.

Another application of the Claisen rearrangement is given in Boeckman et al.'s synthesis of (+)-saudin (**10**), a natural product that has been shown to possess in vivo non-insulin-dependent hypoglycemic activity[6] (Scheme 1.1g). The allyl vinyl ether **13** was synthesized by *O*-alkylation of the thermodynamic enolate of **11** with the allylic triflate **12**. The Claisen rearrangement of **13** occurred at -65°C with excess $TiCl_4$ in the presence of Me_3Al as a proton scavenger to afford **14** as the major product. The facial selectivity was rationalized by invoking a six-membered chairlike transition state **13TS**, in which titanium(IV) metal coordinates with oxygens of both the vinyl ether and the ester.

In the total synthesis of the tetrodotoxin **15**, Isobe et al. used the Claisen rearrangement to obtain the highly functionalized intermediate **18**[7] (Scheme 1.1h). The alcohol **16** was treated with 2-methoxypropene and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in tetrahydrofuran (THF) to afford the allyl vinyl ether **17**. Heating **17** in 1,2-dichlorobenzene in the presence of base affected a smooth Claisen rearrangement to provide the ketone **18** in high yield. The Claisen rearrangement was used to prepare an α-allyl carbonyl compound in the total synthesis of garsubellin A (**19**), a polyprenylated phloroglucin natural product with highly potent neurotrophic activity[8] (Scheme 1.1i). *O*-Allylation of the 1,3-diketone **20** with allyl iodide in the presence of 4-Å molecular sieves gave the enol ether **21**. The Claisen rearrangement of **21** with the use of sodium acetate went smoothly to afford the key intermediate (**22**) in excellent yield.

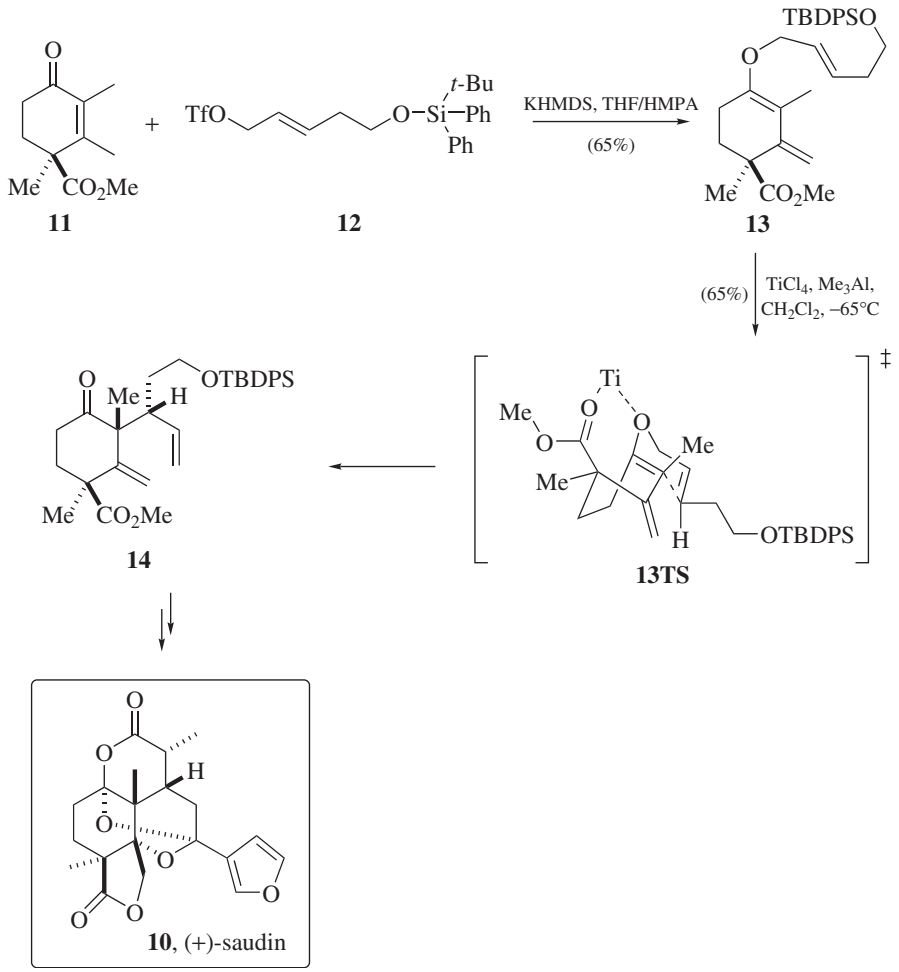
Metal-catalyzed isomerization of unsymmetrical diallyl ethers is a unique route to synthesize allyl vinyl ethers for the Claisen rearrangement. In 1977, Reuter and Salomon reported that heating the diallyl ether **23** in the presence of a catalytic amount of tris(triphenylphosphine)ruthenium(II) dichloride resulted in the



Scheme 1.1f

formation of the γ,δ-unsaturated aldehyde **25**[9] (Scheme 1.1j). The Claisen rearrangement presumably occurred through the intermediate **24**, which was produced via a highly regioselective isomerization of the monosubstituted alkene.

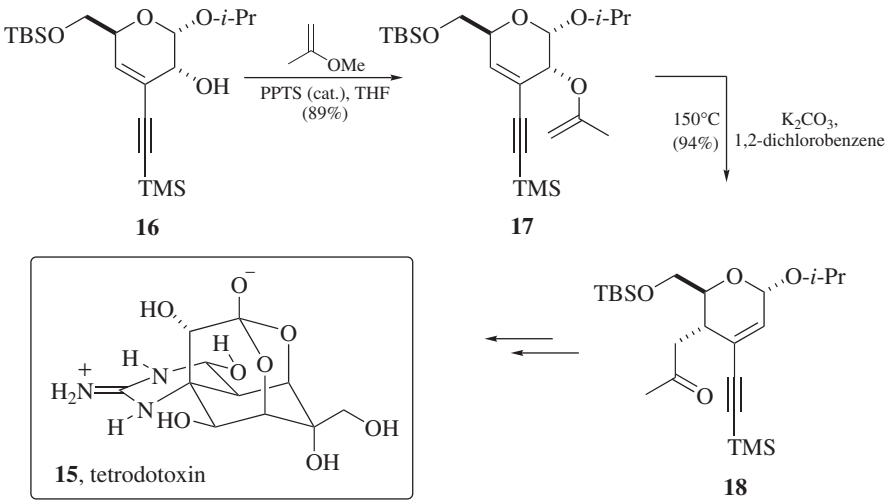
In accessing chiral allyl vinyl ethers for Claisen rearrangement reactions, Nelson et al. employed the iridium-mediated isomerization strategy. Thus, the requisite enantioenriched diallyl ether substrate **28** was synthesized via a highly enantioselective diethylzinc–aldehyde addition protocol[10] (Scheme 1.1k). The enantioselective addition of Et_2Zn to cinnamaldehyde catalyzed by (−)-3-*exo*-morpholinoisoborneol (MIB; **26**)[11] provided an intermediate zinc alkoxide (**27**). Treatment of **27** with acetic acid followed by *O*-allylation in the presence of palladium acetate delivered the **28** in 73% yield and 93% ee. Isomerization of **28** with a catalytic amount of the iridium complex afforded the allyl vinyl ether



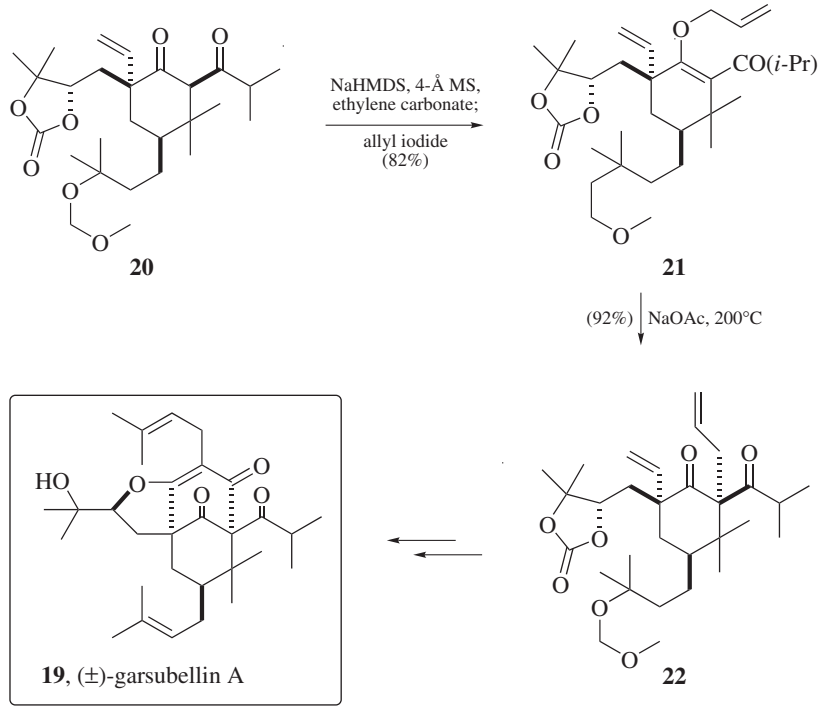
Scheme 1.1g

29, which then underwent Claisen rearrangement to produce the γ,δ-unsaturated aldehyde **30** (*syn*/*anti* = 95 : 5) without loss of optical purity.

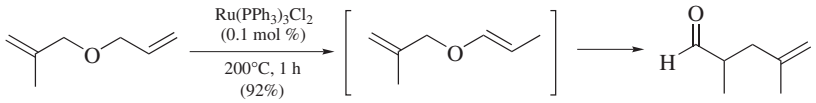
Nelson and Wang completed an enantioselective synthesis of (+)-calopin dimethyl ether (**31**), highlighting the potential utility of the olefin isomerization–Claisen rearrangement strategy in asymmetric synthesis[12] (Scheme 1.1l). Reaction of 2,3-dimethoxy-4-methylbenzaldehyde (**32**) with Meyers's lithio enaminophosphonate reagent gave the enal **33**, which was then subjected to the (−)-MIB (**26**)-catalyzed addition of Et_2Zn, acetic acid treatment, and palladium-catalyzed *O*-allylation to afford the diallyl ether **34** in high enantioselectivity. Isomerization–Claisen rearrangement of **34** and the in situ reduction of the intermediate aldehyde generated the 2,3-*syn*-disubstituted 4-heptenol (**35**) (90% ee, *syn*/*anti* = 94 : 6).



Scheme 1.1h

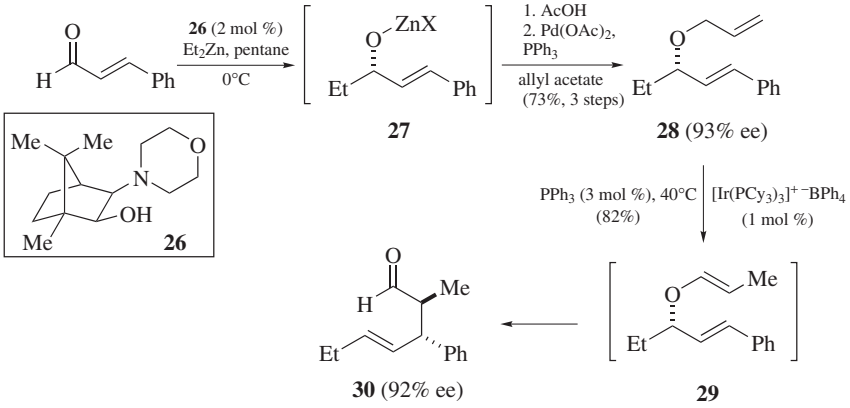


Scheme 1.1i



23 **24** **25**

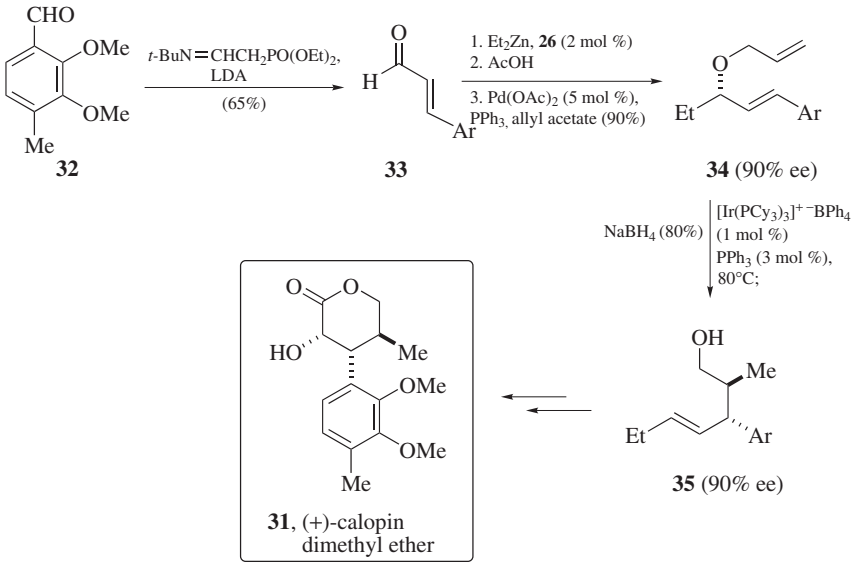
Scheme 1.1j



27 **28** (93% ee) **29** **30** (92% ee)

26

Scheme 1.1k



32 **33** **34** (90% ee) **35** (90% ee)

31, (+)-calopin dimethyl ether

Scheme 1.1l

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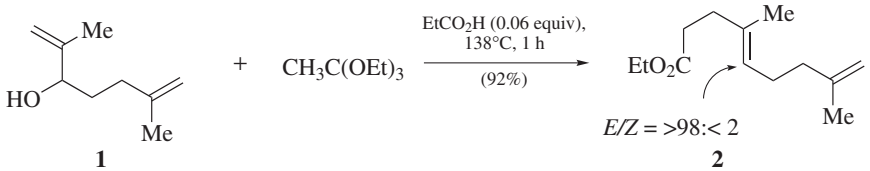
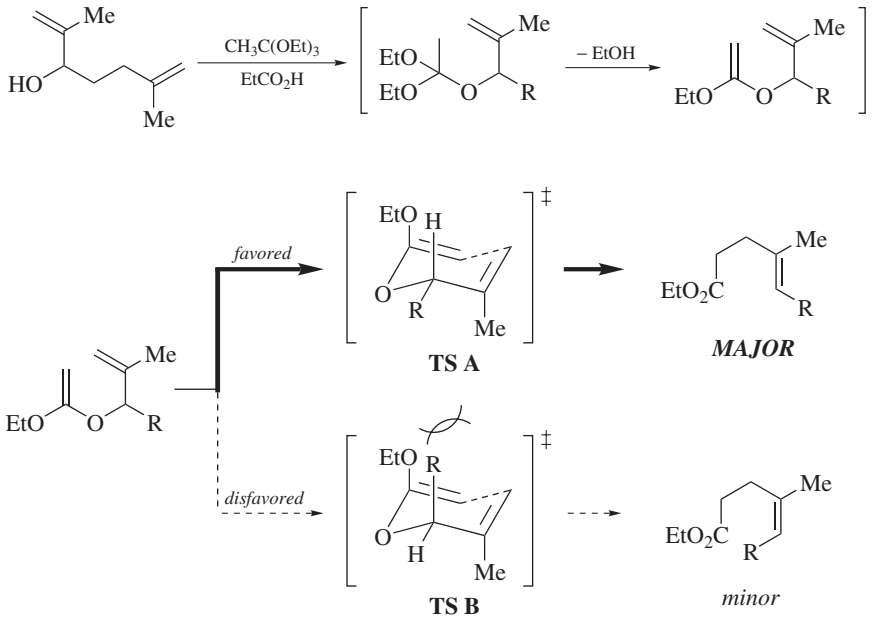
1.2. Johnson–Claisen Rearrangement

In 1970, Johnson and others reported a highly stereoselective synthesis of *trans*-trisubstituted olefinic bonds via the Claisen rearrangement. The alcohol **1**, on heating with 7 equivalents of ethyl orthoacetate and a catalytic amount of propionic acid at 138°C for 1 hour while distilling ethanol, was converted to the diene ester **2** in 92% yield and with more than 98% (*E*)-isomer[1] (Scheme 1.2a). Heating a mixture of allylic alcohol and ethyl orthoacetate in the presence of a small amount of propionic acid gives a mixed orthoacetate that loses ethanol to form the ketene acetal, which then undergoes a [3,3]-sigmatropic rearrangement[1] (Scheme 1.2b). The outstanding stereoselectivity observed in the Johnson–Claisen rearrangement can be explained by a six-membered transition state where the nonbonded interaction between the ethoxy and R groups is a determining factor[2] (Scheme 1.2b).

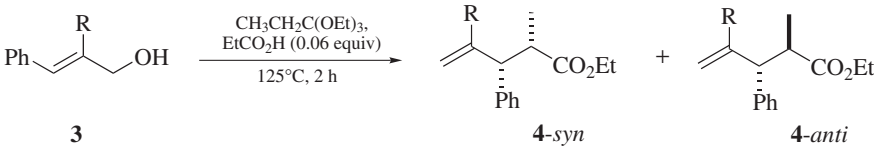
Other indirect evidence for the existence of a six-membered transition state in the Johnson–Claisen rearrangement is found in Daub et al.'s experiments[3] (Scheme 1.2c). When cinnamyl alcohol was heated with triethylorthopropionate in the presence of an acid catalyst, the products were obtained



Scheme 1.2a



Scheme 1.2b



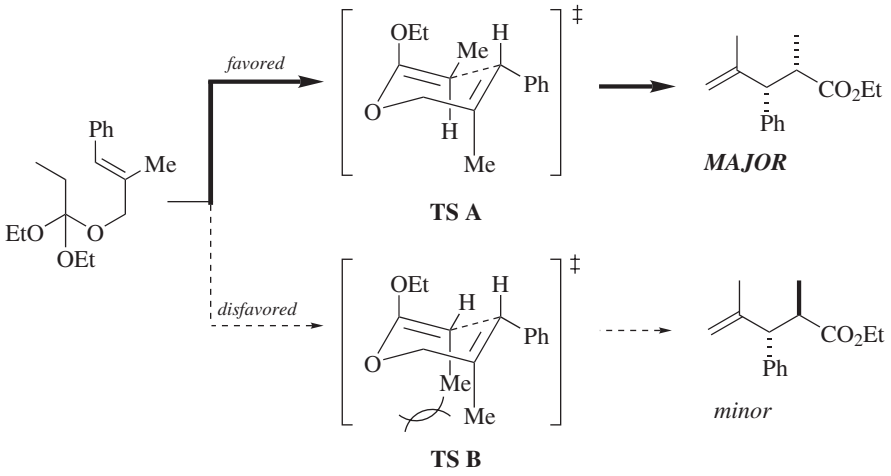
3 **4**-*syn* **4**-*anti*

R	*syn*/*anti*	Yield, %
H	60:40	72
CH_3	85:15	65

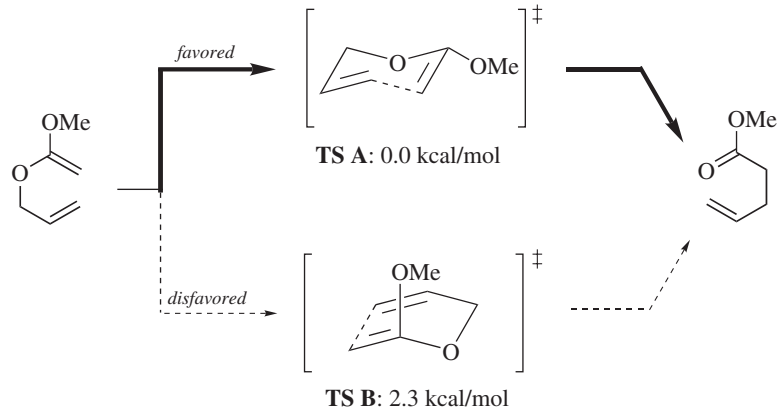
Scheme 1.2c

in 60 : 40 selectivity, slightly favoring the *syn*-isomer. The *syn*-selectivity improved to 85 : 15 for the rearrangement reaction of the ketene acetal of (*E*)-2-methyl-3-phenyl-2-propen-1-ol (Scheme 1.2c).

The increased *syn*/*anti* selectivity observed in the Johnson–Claisen rearrangement of the ketene acetal from the trisubstituted alkene is an indication that the reaction goes through a six-membered chairlike transition state[4] (Scheme 1.2d). Transition state **B** is disfavored compared to state **A**, due to the developing 1,3-diaxial interactions between the two methyl groups in the transition state.



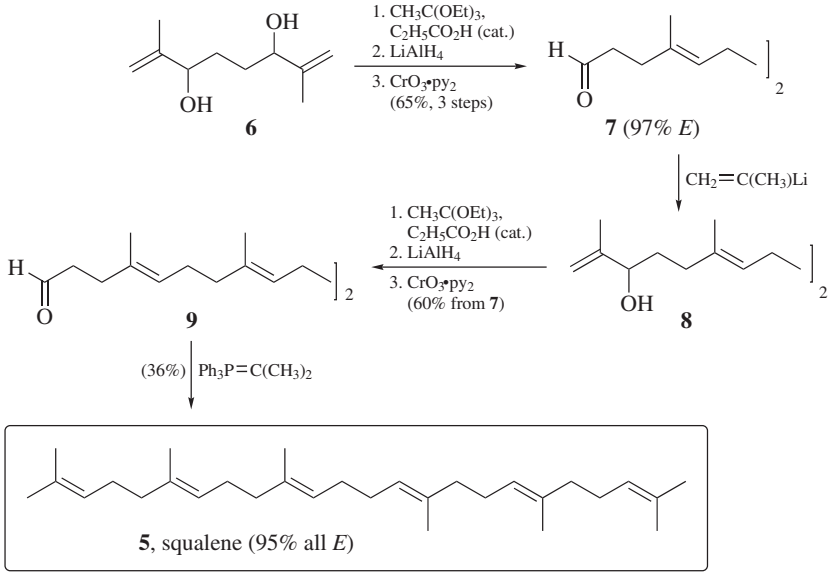
Scheme 1.2d



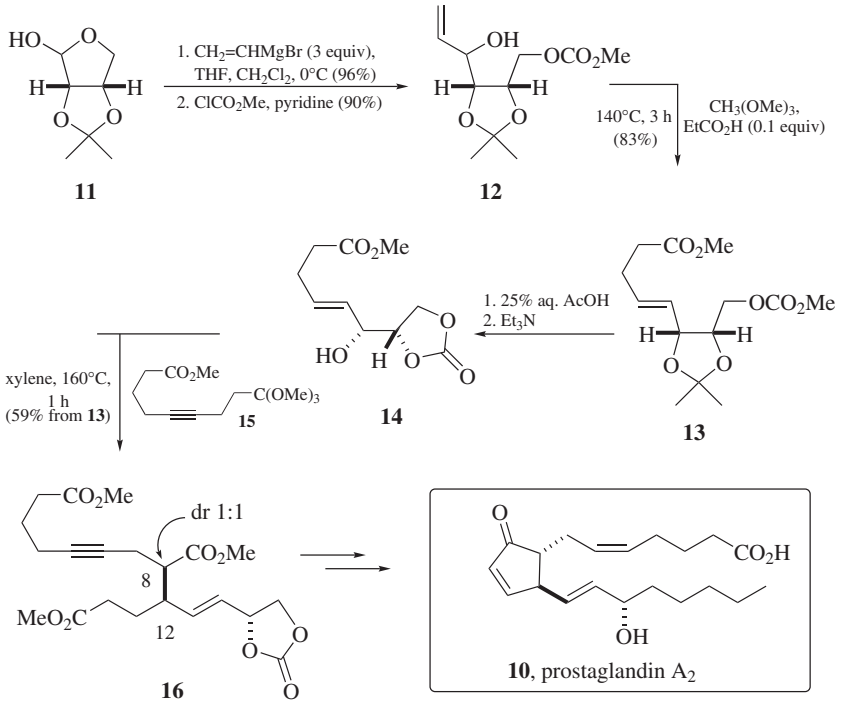
Scheme 1.2e

The preference for a chairlike transition state in the Johnson–Claisen rearrangement is supported by further Houk et al.'s computational studies (Scheme 1.2e).[5] For the rearrangement of the parent methyl ketene acetal, chairlike transition state **A** is favored over boatlike transition state **B** by 2.3 kcal/mol.

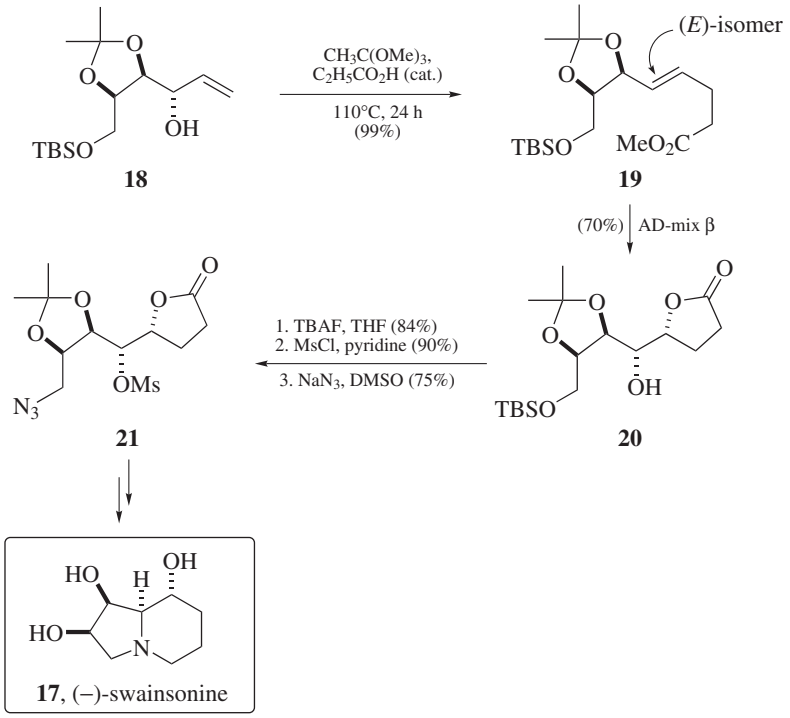
Johnson et al. used their newly developed orthoester Claisen reaction to achieve a highly stereoselective total synthesis of all-*trans* squalene (**5**)[1] (Scheme 1.2f). The diene diol **6** underwent Johnson–Claisen rearrangement when it was heated with ethyl orthoacetate in the presence of propionic acid for 3 h at 138°C. The diene dialdehyde **7**, obtained by treatment of the resulting ester with lithium aluminum hydride followed by oxidation with Collins reagent, reacted with 2-propenyllithium to give the tetraene diol **8**. The tetraene dialdehyde **9**, which



Scheme 1.2f



Scheme 1.2g

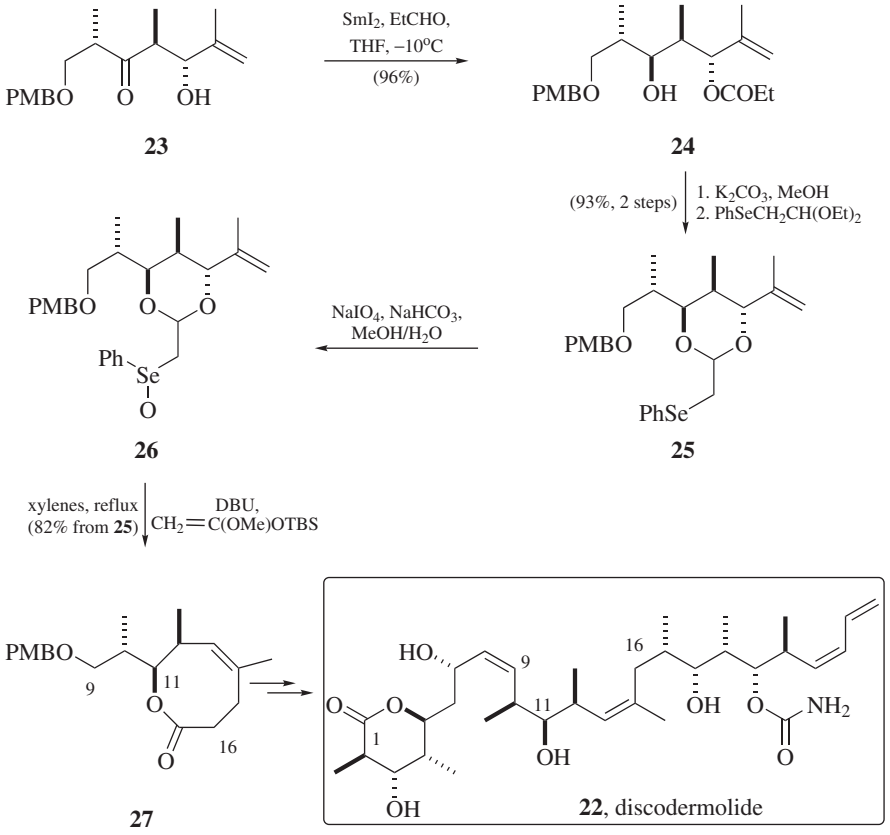


Scheme 1.2h

was accessed by the same reaction sequence as that for the conversion of **6** to **7**, afforded squalene upon treatment with isopropylidenetriphenylphosphorane in 36% yield.

In the total synthesis of prostaglandin A_2 (PGA_2; **10**), Stork and Raucher used two Johnson–Claisen rearrangements to obtain the key intermediates[6] (Scheme 1.2g). The first Johnson–Claisen rearrangement was carried out by heating the allylic alcohol **12**, derived from 2,3-isopropylidene-L-erythrose (**11**), with trimethyl orthoacetate to afford the unsaturated ester **13** with an (*E*)-geometry. Hydrolysis of the acetonide followed by treatment with triethylamine afforded the allylic alcohol **14**. The second Johnson–Claisen rearrangement of the allylic alcohol **14** with the orthoester **15** produced **16** in good yield. The chirality at the C_{12} center in **16** was secured by virtue of chirality transfer of a carbon–oxygen bond in **14** through a six-membered chairlike transition state in the rearrangement. The formation of a 1 : 1 mixture at the C_8 center is due to the nonstereoselective generation of the ketene acetal precursor of the rearrangement.

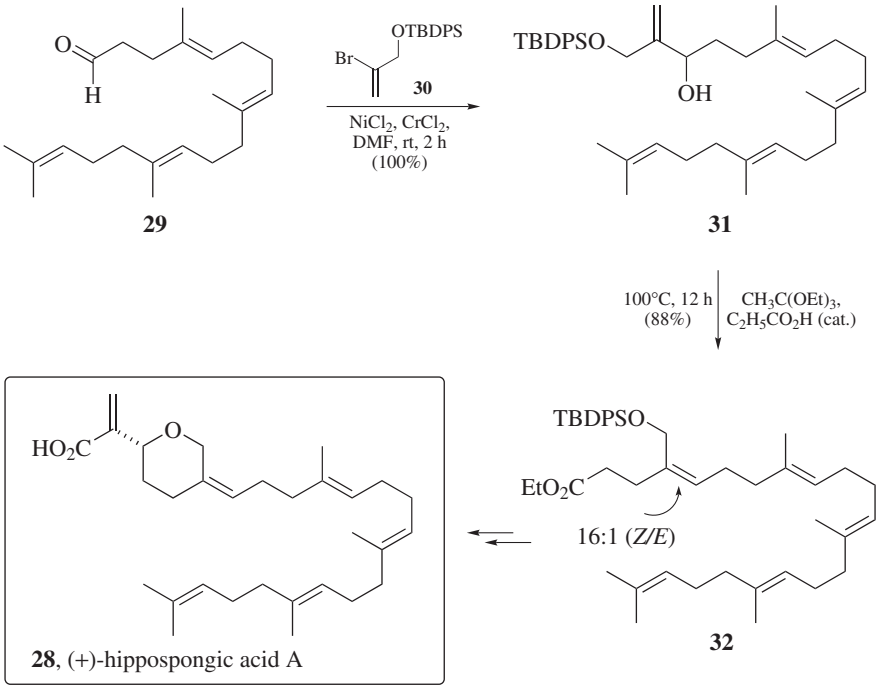
Pearson and Hembre synthesized a key intermediate (**19**) using the Johnson–Claisen rearrangement protocol in the total synthesis of the indolizidine



Scheme 1.2i

alkaloid (−)-swainsonine (**17**), a potent anticancer drug as an inhibitor of many mannosidases[7] (Scheme 1.2h). When the allylic alcohol **18** was heated in toluene with trimethyl orthoacetate in the presence of a catalytic amount of propionic acid with the constant removal of methanol, the γ,δ-unsaturated ester desired (**19**) was obtained in nearly quantitative yield with the (*E*)-alkene geometry. Oxidative lactonization via Sharpless dihydroxylation[8] of the alkene **19** provided the lactone desired (**20**) in 70% yield along with the other diastereomer in 9% isolated yield. Deprotection of the silyl ether, mesylation, and selective substitution of the less hindered primary mesylate of the diol produced the monoazide **21**. Further synthetic manipulations to the azide **21** provided 4.5 g of target molecule **17**, successfully demonstrating a practical synthesis of (−)-swainsonine.

In the total synthesis of a polyketide natural product, (+)-discodermolide (**22**), Paterson and co-workers synthesized the C_9-C_{16} fragment **27** using a Johnson-Claisen rearrangement[9] (Scheme 1.2i). Evans–Tishchenko reduction[10] of



Scheme 1.2j

the β-hydroxy ketone **23** gave the *anti*-1,3-diol monoester **24** (see Chapter 4). Methanolysis followed by transacetalization afforded the selenide **25**. Oxidation of **25** with $NaIO_4$ resulted in the formation of the selenoxide **26**, which underwent β-elimination upon treatment with DBU. The ketene acetal thus generated underwent a highly stereoselective Johnson–Claisen rearrangement, via a six-membered chairlike transition state, to provide the eight-membered lactone **27** in excellent yield.

The natural product (+)-hippospongic acid A (**28**) shows a variety of biological activities, such as inhibition of gastrulation in starfish embryos and induction of apotosis in the human gastric cancer cell line. In the synthesis of **28**, Trost et al. prepared a key intermediate via a Johnson–Claisen rearrangement reaction[11] (Scheme 1.2j). The Nozaki–Hiyama–Kishi reaction[12] of the aldehyde **29** with the vinyl bromide **30** gave the allylic alcohol **31** in quantitative yield under mild reaction conditions. When the alcohol **31** was subjected to a Johnson–Claisen rearrangement at 100 °C, the product desired (**32**) was obtained in excellent yield with high stereoselectivity around the newly formed double bond. The stereochemical outcome of the rearrangement reaction is rationalized by a six-membered transition state.

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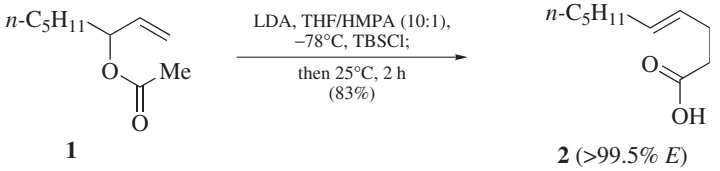
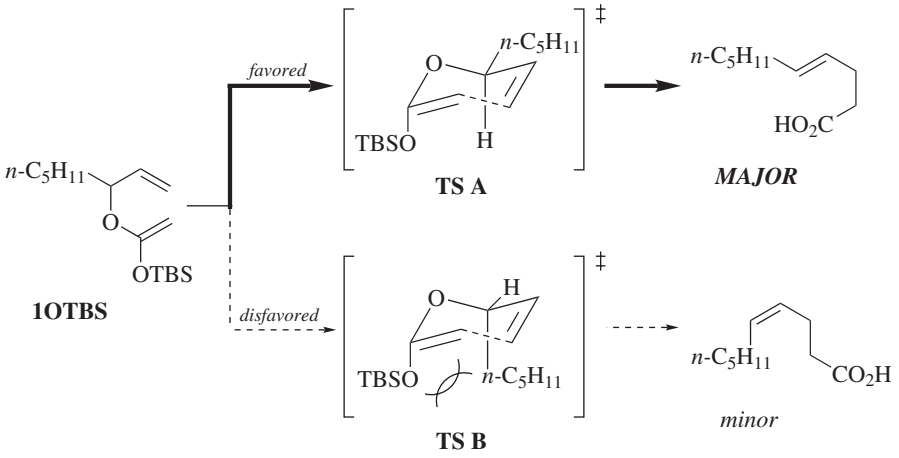
1.3. Ireland–Claisen Rearrangement

In 1976, Ireland et al. reported that [3,3]-sigmatropic rearrangement of allylic esters as enolate anions or corresponding silylketene acetals produces the γ,δ- unsaturated acids in good yields and with excellent levels of diastereoselectivity. For example, rearrangement of the ester **1** afforded (*E*)-4-decenoic acid (**2**) with greater than 99% stereoselectivity and in high yield[1] (Scheme 1.3a). The *tert*-butyldimethylsilylketeneacetal **1OTBS**, generated by successive treatment of **1** with lithium diisopropylamide (LDA) and *tert*-butyldimethylsilyl chloride at -78°C, undergoes rearrangement via a six-membered chairlike transition state[2] (Scheme 1.3b). An examination of nonbonded interactions readily indicates which of the two possible transition states will be favored. The equatorial disposition of the R group puts transition state **A** at lower energy, which results in predominant formation of the *E*-isomer.

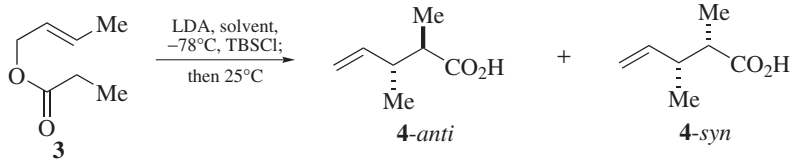


1 **2** (>99.5% *E*)

Scheme 1.3a

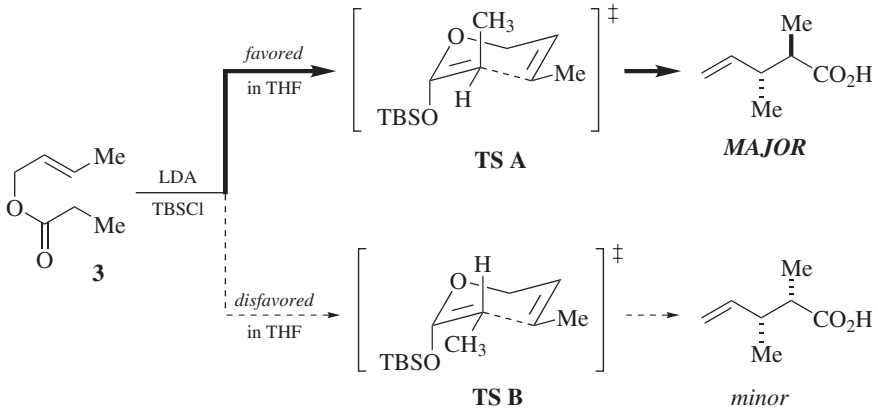


Scheme 1.3b

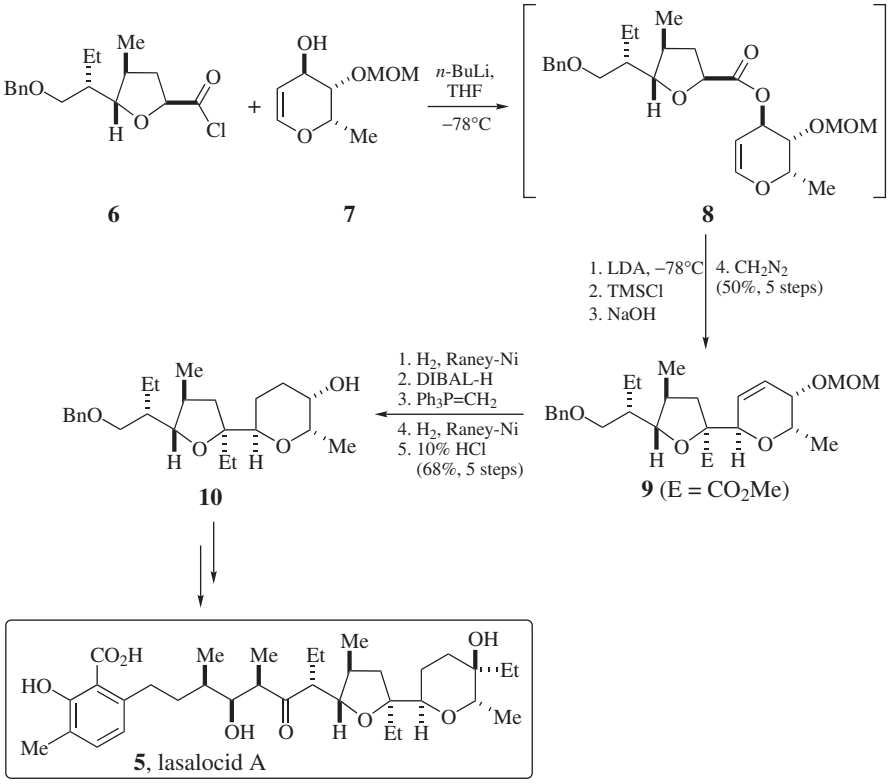


Solvent	*anti*/*syn*	Yield, %
THF	87:13	79
THF/HMPA (77:23)	19:81	73

Scheme 1.3c



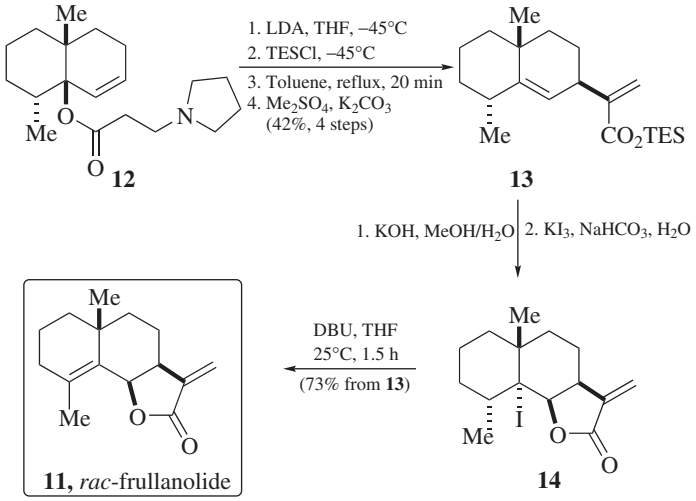
Scheme 1.3d



Scheme 1.3e

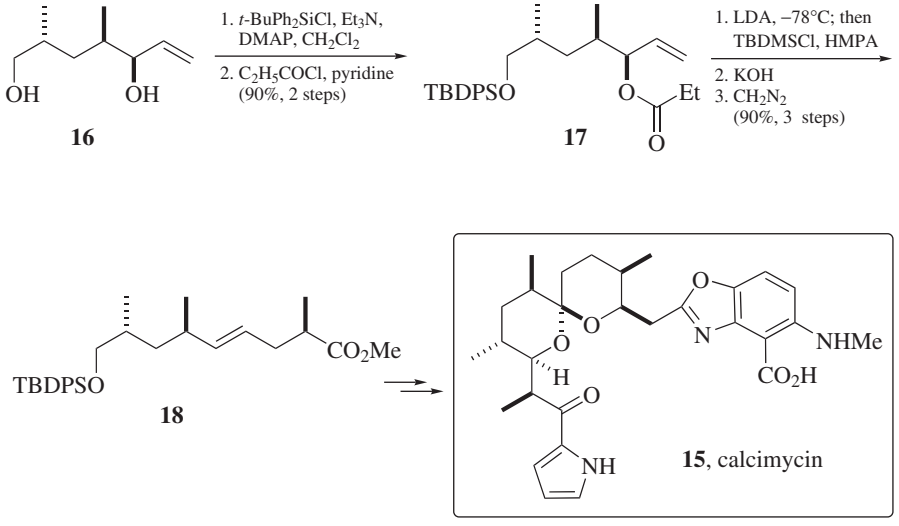
As the Ireland–Claisen rearrangement proceeds through a six-membered chair-like transition state, the stereochemistry about the newly formed carbon–carbon single bond can be predicted from the geometries of the double bonds in the starting 1,5-dienes.[1] For example, the stereochemical outcome of the rearrangement of (*E*)-crotyl propanoate (**3**) depends on the solvents used. The *anti*-isomer is obtained as a major isomer in THF, whereas the *syn*-isomer is the major product when the reaction was carried out with hexamethylphosphoramide (HMPA) as a cosolvent (Scheme 1.3c). Again, these results can be explained via a six-membered transition state (Scheme 1.3d). In THF, the (*E*)-enol ether is formed preferentially and subsequently undergoes a [3,3]-sigmatropic rearrangement via transition state **A**. When HMPA is used as a cosolvent along with THF, the (Z)-enol ether becomes a major isomer, resulting in the formation of **4**-*syn*.[1]

Claisen rearrangements of silylketene acetals have been used in numerous organic syntheses of natural products.[3] Ireland used his newly developed ester enolate Claisen rearrangement in the total synthesis of lasalocid A (X537A) (**5**), a polyether ionophore antibiotic natural product with a broad range of biological potency (Scheme 1.3e).[4] The ester **8**, which was prepared by the reaction

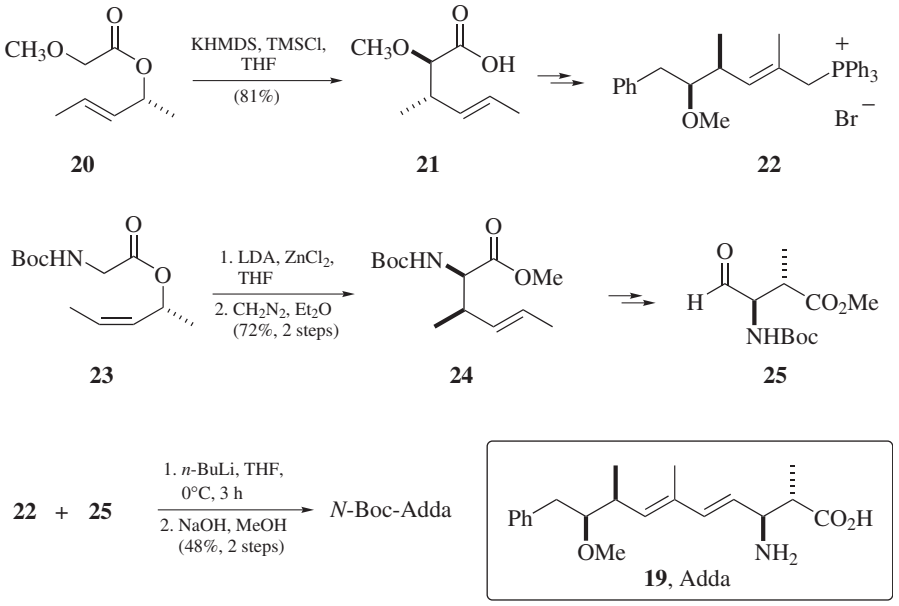


Scheme 1.3f

of the acyl chloride **6** from α-D-glucosaccharinic acid lactone and the glycal **7** from 6-deoxy-L-glucose, underwent Ireland–Claisen rearrangement to provide the tetrahydrofuran **9** in 50% yield after hydrolysis and esterification. The tetrahydrofuran **10** was eventually utilized as a key intermediate in Ireland's total synthesis of lasalocid A.[5]



Scheme 1.3g



Scheme 1.3h

Still and Schneider employed Ireland–Claisen rearrangement in the total synthesis of (±)-frullanolide (**11**)[6] (Scheme 1.3f). The key step of the synthesis is efficient Ireland–Claisen rearrangement of the β-pyrrolidinopropionate ester **12**. The triethylsilylketene acetal rearranged in toluene at reflux and the pyrrolidine moiety was eliminated after stirring with a mixture of dimethyl sulfate and potassium carbonate in methanol to afford the α-substituted acrylic ester (**13**). Saponification followed by iodolactonization gave the iodolactone **14**, which upon treatment with DBU led to (±)-frullanolide.

In total synthesis of the structurally unique natural product calcimycin (**15**), Grieco and others used Ireland–Claisen rearrangement of the ester **17** to synthesize the key intermediate (**18**)[7] (Scheme 1.3g). Monosilylation of the diol **16** followed by treatment with propionyl chloride in pyridine gave rise to the ester **17** in 90% yield. Treatment of **17** with LDA in THF at -78°C, subsequent addition of *tert*-butyldimethylsilyl chloride in HMPA, and brief heating of the resulting silylketene acetal provided the corresponding silyl ester. Subsequent hydrolysis of the silyl ester and esterification with diazomethane gave **18** in 90% yield from **17**.

The C_{20} amino acid (2*S*,3*S*,8*S*,9*S*,4*E*,6*E*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid (Adda; **19**) is a molecule of interest to biologists and organic chemists as a component of the hepatotoxic cyclic peptides called *microcystins*. Kim and Toogood used Ireland–Claisen rearrangement in their successful synthesis of Adda[8] (Scheme 1.3h). The ester **20** underwent highly diastereoselective Ireland–Claisen rearrangement to provide the acid **21**. Conversion of this acid to the phosphonium bromide **22** was achieved in nine

steps. Another Ireland–Claisen rearrangement of **23** in the presence of $ZnCl_2$[9] efficiently afforded the ester **24**. Wittig reaction of the two fragments **22** and **25**, followed by saponification, provided *N*-Boc-protected Adda.

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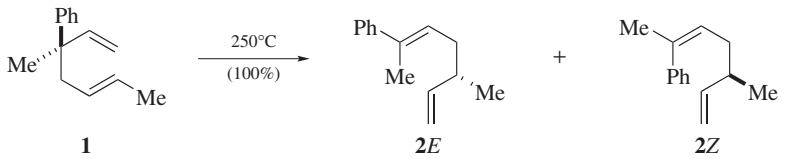
1.4. Cope Rearrangement

Because of the concerted nature of the mechanism of Cope rearrangement, chirality at C_3 in the starting material leads to enantiospecific formation of the new chiral center in the product. For example, Cope rearrangement of (3*R*,5*E*)-3-methyl-3-phenyl-1,5-heptadiene (**1**) at 250°C resulted in an 87 : 13 mixture of *trans*- and *cis*-3-methyl-6-phenyl-1,5-heptadiene in quantitative yield[1] (Scheme 1.4a). The optical purity of the starting material is 95% ee, and those of the products are 91% ee for **2***E* and 89% ee for **2***Z*. Thus, the optical integrity of the starting material is preserved during thermal rearrangement, suggesting that the rearrangement is concerted.

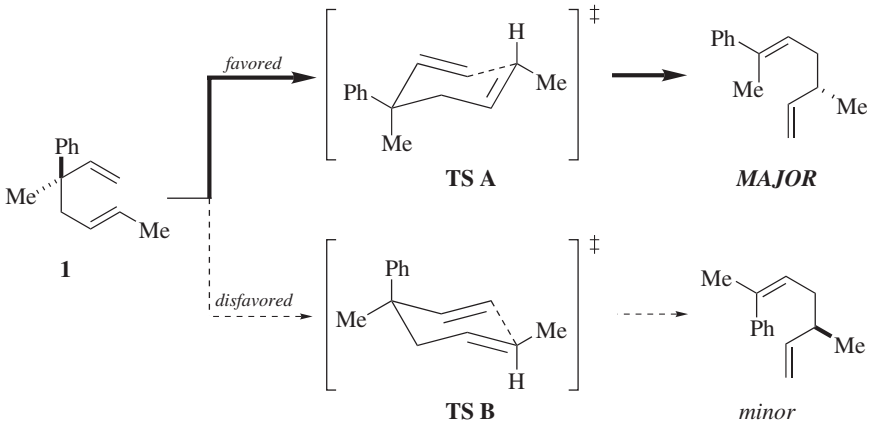
The stereochemical outcome of the above reaction is explained in terms of a six-membered chairlike transition state[1] (Scheme 1.4b). The 87 : 13 preference for



1 **2***E* **2***Z*

2*E*/**2***Z* = 87:13

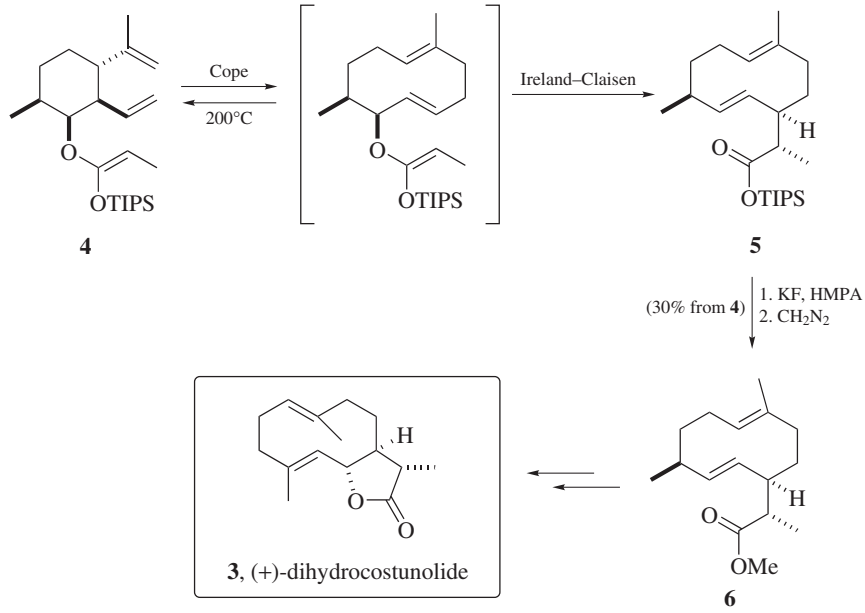
Scheme 1.4a



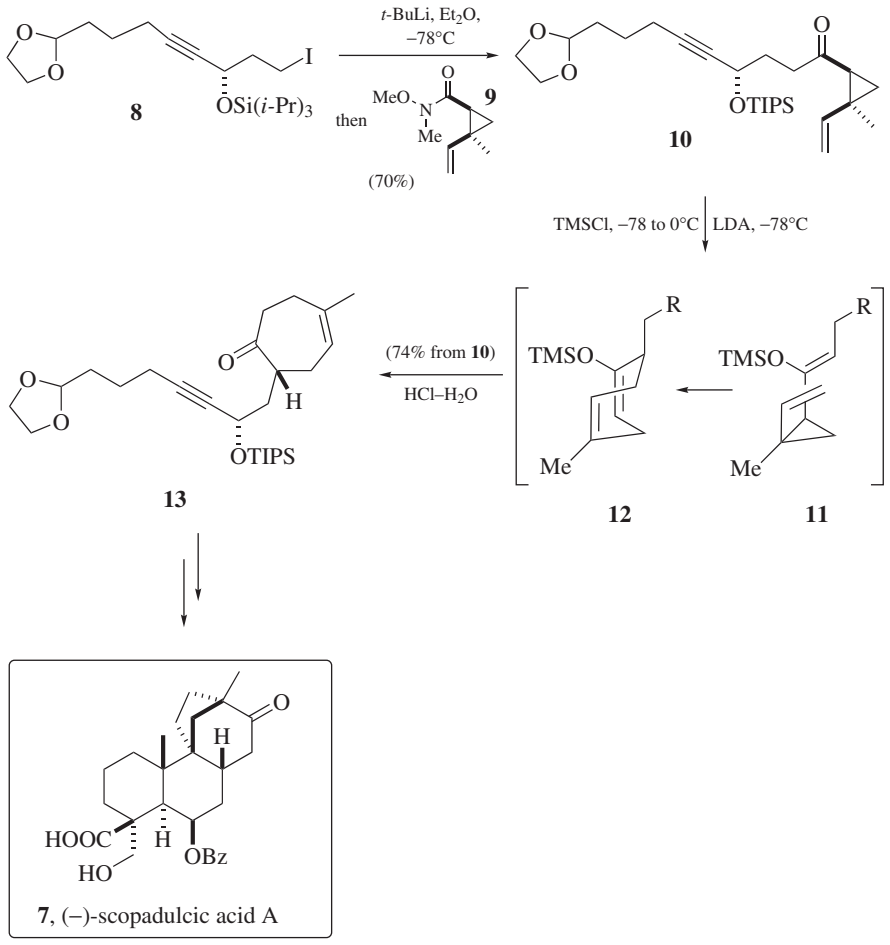
Scheme 1.4b

2*E* corresponds to a free-energy difference of about 2 kcal/mol between transition states **A** and **B**. Based on the A-values of the monosubstituted cyclohexanes, it was understood that transition state **A** in which the phenyl subsitituent group occupies an equatorial position would be favored over **B**.

Raucher et al. used a tandem Cope–Claisen rearrangement during total synthesis of the germacrane sesquiterpene (+)-dihydrocostunolide (**3**)[2] (Scheme 1.4c).



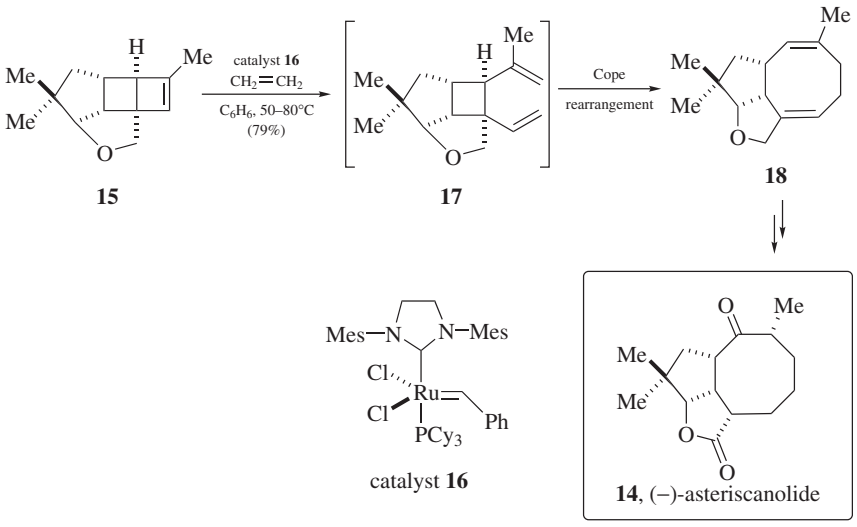
Scheme 1.4c



Scheme 1.4d

A solution of the silylketene acetal **4** in dodecane was subjected to thermolysis at 200°C for 140 minutes. The Cope–Claisen rearrangement product **5** was then treated with KF in HMPA followed by esterification to afford the methyl ester **6**.

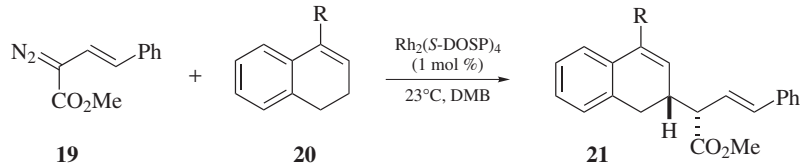
Fox et al. used the Cope rearrangement in total synthesis of the structurally unique tetracyclic diterpene acid (−)-scopadulcic acid A (**7**), which exhibits a broad range of pharmacological activities[3] (Scheme 1.4d). Lithiation of the optically active iodide **8** with *t*-BuLi followed by condensation of the resulting organolithium species with the amide **9** afforded the cyclopropyl ketone **10**. Compound **10** was then treated sequentially with LDA and TMSCl to provide a silyl enol ether intermediate (**11**), which underwent Cope rearrangement to furnish the silyloxy cycloheptadiene **12**. Hydrolysis of **12** then resulted in the cycloheptenone **13** as a single stereoisomer in 74% overall yield.



Scheme 1.4e

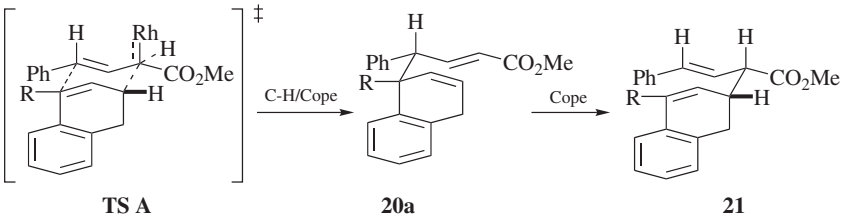
The Cope rearrangement was used in the total synthesis of (−)-asteriscanolide (**14**), a novel sesquiterpene natural product[4] (Scheme 1.4e). Ring-opening metathesis of the cyclobutene **15** with ethylene in the presence of the ruthenium catalyst **16**[5] proceeded smoothly to provide the cyclooctadiene **18** via Cope rearrangement of the intermediate dialkenyl cyclobutane (**17**).

When the vinyldiazoacetate **19**, which can be prepared from benzaldehyde in a one-pot process,[6] was treated in 2,2-dimethylbutane (DMB) with dirhodium tetrakis[(*S*)-*N*-(dodecylbenzenesulfonyl)prolinate] [Rh_2(*S*-DOSP)$_4$] in the presence of 4-methyl or 4-trimethylsilyloxy-1,2-dihydronaphthalene (**20**), the product **21** was obtained with exceptionally high levels of enantio- and diastereo selectivity[7] (Scheme 1.4f).



R	ee, %	de, %	Yield, %
Me	99	>98	92
OTMS	98	>98	55

Scheme 1.4f



TS A **20a** **21**

Scheme 1.4g

The highly enantioselective reaction is explained in terms of a double Cope rearrangement event[7] (Scheme 1.4g). The substrate **20** is approaching from the front side, due to the chiral environment posed by the D_2-symmetric rhodium catalyst.[8] The Cope rearrangement then presumably occurs to form **20a** through chairlike transition state **A**. Another Cope rearrangement of the 1,5-diene **20a** affords the product **21** in a highly stereoselective manner.

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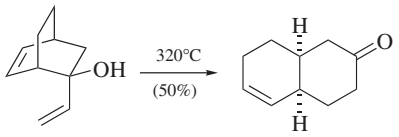
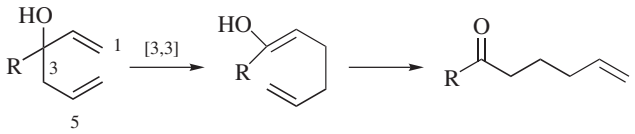
1.5. Anionic Oxy-Cope Rearrangement

In 1964, Berson and Jones reported that heating **1** in the gas phase at 320°C gave *cis*-2-octalone (**2**) in 50% yield[1] (Scheme 1.5a).

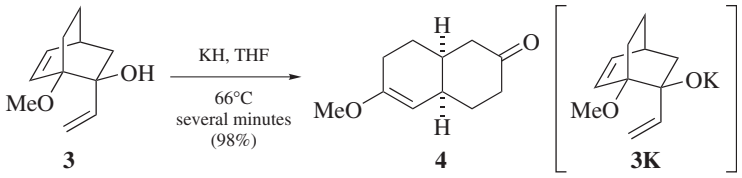


1 **2**

Scheme 1.5a

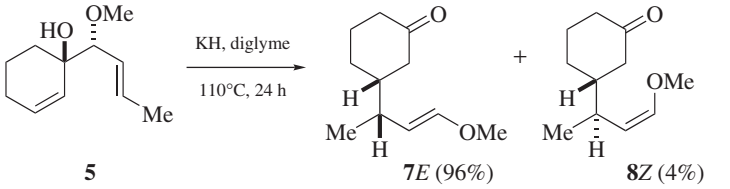


Scheme 1.5b

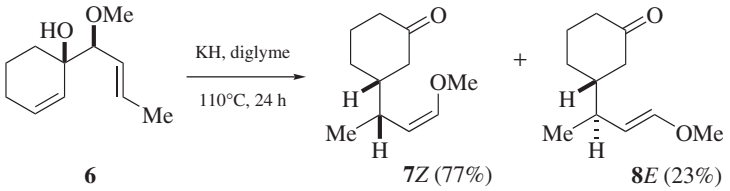


3 **4** **3K**

Scheme 1.5c



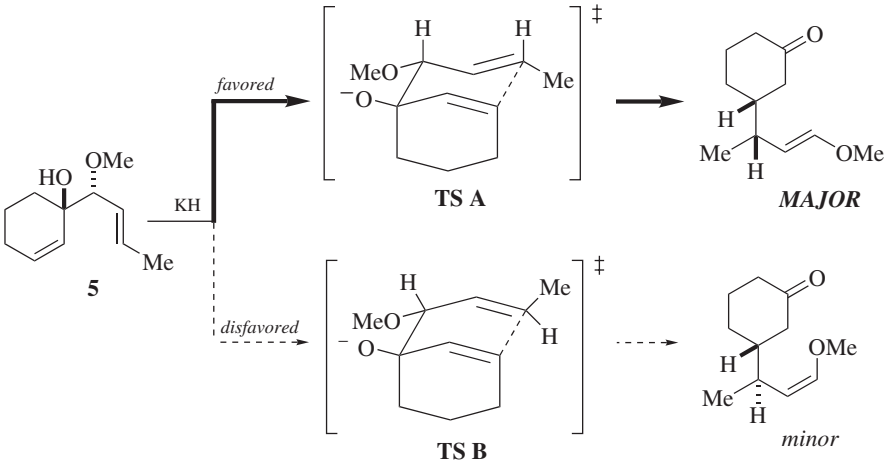
5 **7***E* (96%) **8***Z* (4%)



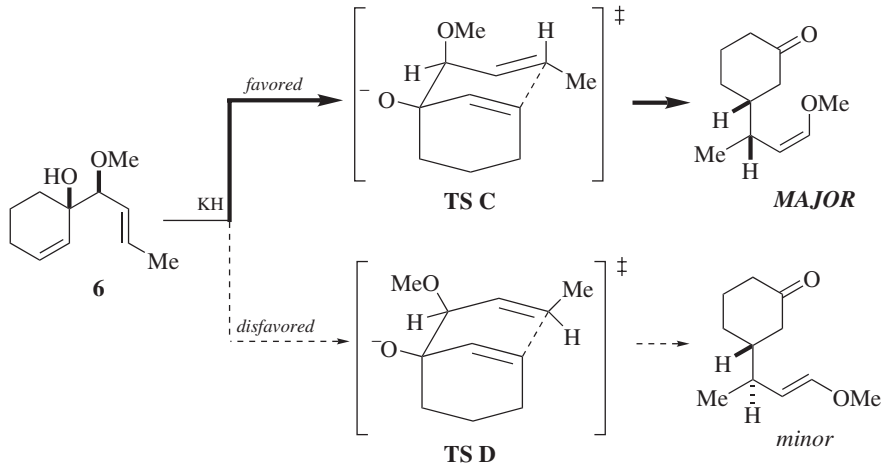
6 **7***Z* (77%) **8***E* (23%)

Scheme 1.5d

Berson proposed the term *oxy-Cope rearrangement* for the reaction, as the reaction is a [3,3]-sigmatropic Cope rearrangement of 3-hydroxy-1,5-hexadiene[1] (Scheme 1.5b). The oxy-Cope rearrangement would be a synthetically useful route to access δ,ε-unsaturated carbonyl compounds from the corresponding secondary or tertiary alcohols if the reaction conditions were mild. In 1975, Evans and Golob discovered that the Cope rearrangement of 3-hydroxy-1,5-hexadienes proceeds extremely fast in the presence of potassium hydride. For example, heating the potassium alkoxide **3K** at 66°C for several minutes in anhydrous THF completed the Cope rearrangement to afford the methoxy ketone in superb yield[2] (Scheme 1.5c). From kinetic experiments it was determined that at 25°C rearrangement of **3K** occurred 10^{12} times faster than **3** in the presence of 1.1 equivalents of 18-crown-6.



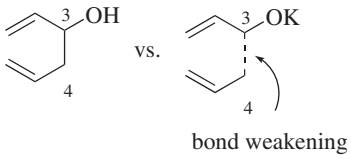
Scheme 1.5e



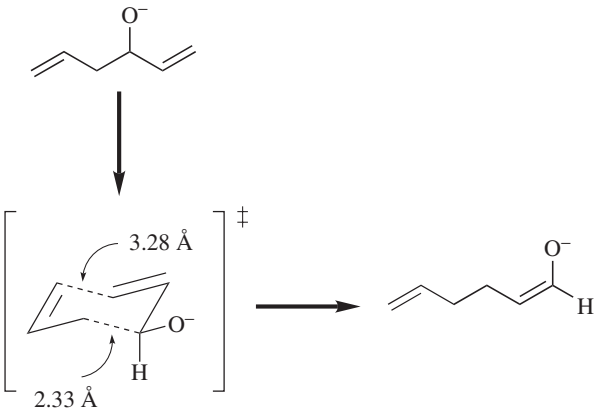
Scheme 1.5f

To gain insights into the possible transition-state geometry of the sigmatropic process, Evans et al. rearranged the diastereomeric dienols **5** and **6**[3] (Scheme 1.5d). When a mixture of **5** and KH was heated in diglyme at 110°C for a day, the rearranged products were obtained in 78% yield and with high diastereoselectivity. Under similar reaction conditions, the dienol **6** also underwent anionic oxy-Cope rearrangement, but with poor diastereoselectivity. The striking difference in the stereoselectivity observed in the rearrangement of **5** and **6** suggests that a six-membered transition state is operating in these reactions. In the rearrangement of **5**, the major product **7***E* is formed via chairlike transition state **A**,

Molecules	Bond Energy, kcal/mol
H—CH_2OH	90.7
H—CH_2OK	79.0



Scheme 1.5g



TS A

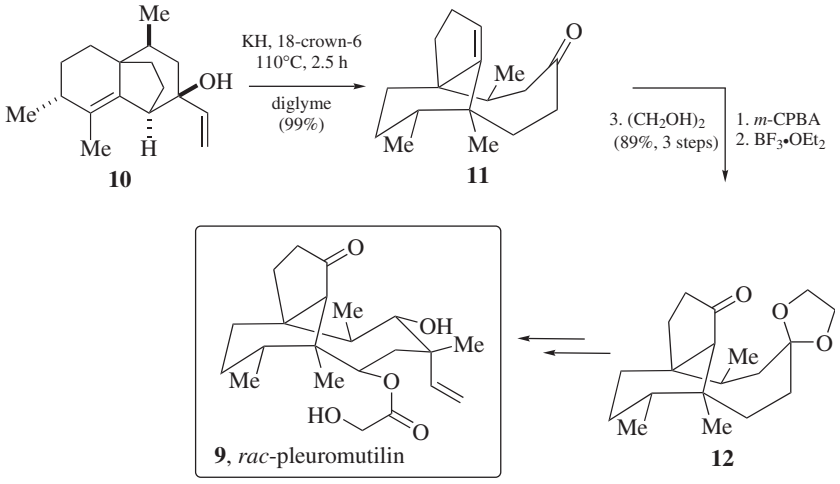
Scheme 1.5h

and the minor product **8***Z* is produced via the boatlike transition state **B** (Scheme 1.5e). The 96 : 4 selectivity indicates that transition state **A** is more stable than **B** by 2.2 kcal/mol.

For the rearrangement of **6**, the major isomer is once again formed through six-membered chairlike transition state **C**[3] (Scheme 1.5f). Because the methoxy substituent in transition state **C** is now in an axial position, the free-energy gap between transition states **C** and **D** becomes narrow, resulting in diminished 3 : 1 diastereoselectivity.

To explain the marked rate enhancement in the anionic oxy-Cope rearrangement, Evans and others conducted theoretical calculations of the carbon–hydrogen bond strengths for methanol and potassium methoxide[4] (Scheme 1.5g). The computations indicate that the carbon–hydrogen bond in KOMe is significantly weaker than that in MeOH. From these studies, it is concluded that weakening of the C_3–C_4 bond is responsible for the rate acceleration in the anionic oxy-Cope rearrangement.

Houk and others performed a computational study with density functional and ab initio calculations to better understand the reaction mechanism of the



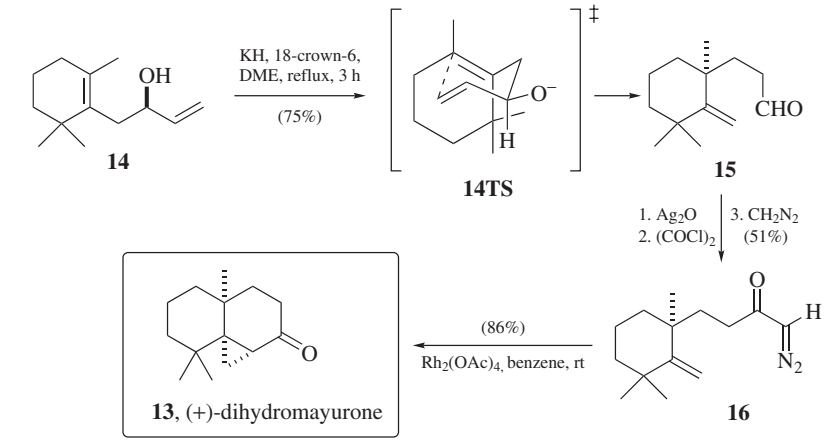
Scheme 1.5i

anionic oxy-Cope rearrangement[5] (Scheme 1.5h). The reaction proceeds via a concerted reaction pathway with an activation energy of 9.9 kcal/mol. Although the six-membered transition-state structure is dissociative, no intermediate is found over the entire course of the rearrangement.

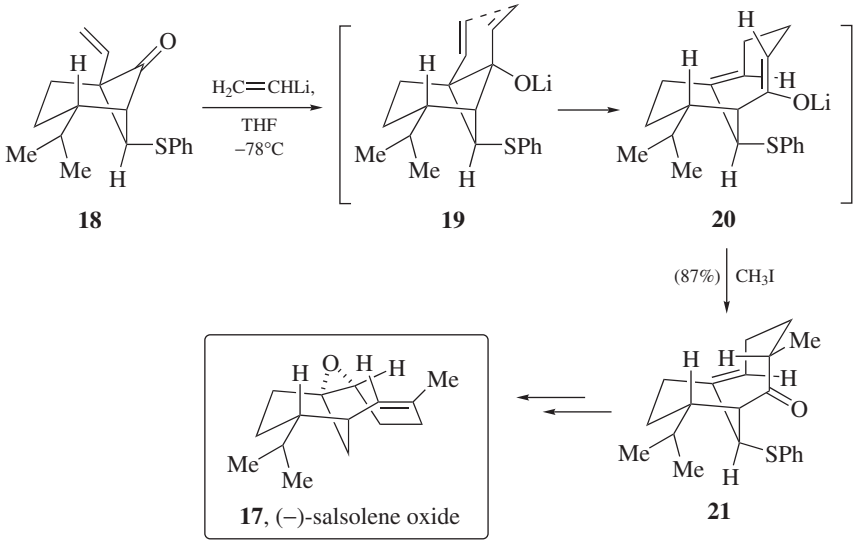
Anionic oxy-Cope rearrangement has been used extensively in the total synthesis of natural products.[6] For example, Boeckman et al. employed a remarkably facile anionic oxy-Cope rearrangement in the total synthesis of (±)-pleuromutilin (**9**), which is utilized as an animal food additive to control dysentery in swine and poultry[7] (Scheme 1.5i). The crucial anionic oxy-Cope rearrangement of the β,β-disubstituted alcohol **10** proceeded cleanly at 110° C on exposure to potassium hydride and 18-crown-6 ether to afford the ketone **11** in 99% yield. Epoxidation of cyclopentene ring and rearrangement of the resulting epoxide followed by selective ketalization gave the ketal **12**.

The anionic oxy-Cope rearrangement was the key step in Lee et al.'s synthesis of (+)-dihydromayurone (**13**)[8] (Scheme 1.5j). When the allylic alcohol **14** was treated with potassium hydride and 18-crown-6 ether to effect the crucial anionic oxy-Cope rearrangement, the aldehyde **15** was obtained in high enantioselectivity. The highly efficient transfer of chirality from the secondary allylic alcohol center to the quaternary carbon center in **15** is indicative of transition state **14TS**, in which the carbon–oxygen bond adopts an equatorial position in the chairlike transition state. The aldehyde **15** was oxidized to the corresponding carboxylic acid, which was in turn converted to the diazo ketone **16** via the corresponding acyl chloride. The target molecule (**13**) was then obtained readily in high yield when the diazo ketone **16** was treated with a catalytic amount of rhodium acetate in benzene.

In the total synthesis of (−)-salsolene oxide (**17**), an architecturally unusual sesquiterpene with an unsaturated bicyclo[5.3.1]undecane core and trisubstituted

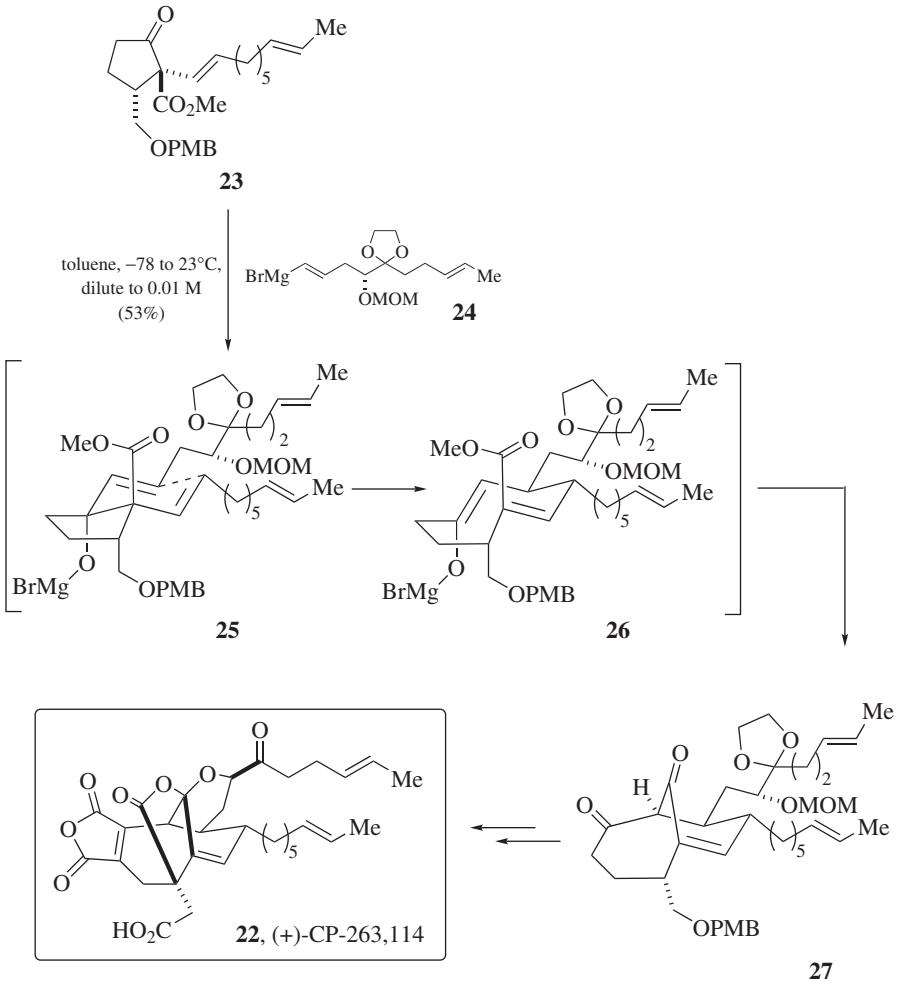


Scheme 1.5j



Scheme 1.5k

oxirane, Paquette and co-workers utilized the anionic oxy-Cope rearrangement to synthesize a key intermediate (**21**)[9] (Scheme 1.5k). The thiophenyl substituent in the bicyclo ketone **18** directed the 1,2-addition of vinyllithium to the *exo*-face of **18**. The ring strain in 1,2-divinylcyclobutanoxide (**19**) was sufficient to promote a facile [3,3]-sigmatropic rearrangement under the reaction conditions. The enolate anion **20** was therefore generated stereoselectively via a six-membered chairlike transition state. Direct methylation of **20** with excess methyl iodide furnished **21**.



Scheme 1.5l

Shair et al. employed anionic oxy-Cope rearrangement in their synthesis of (+)-CP-263,114 (**22**), a fungal metabolite with the ability to inhibit squalene synthase and Ras farnesyltransferase[10] (Scheme 1.5l). The addition of the Grignard reagent **24** into the cyclopentanone (+)-**23** provided a bromomagnesium alkoxide **25**, that underwent anionic oxy-Cope rearrangement to furnish the cyclononadiene **26**. An in situ transannular cyclization of **26** delivered **27**.

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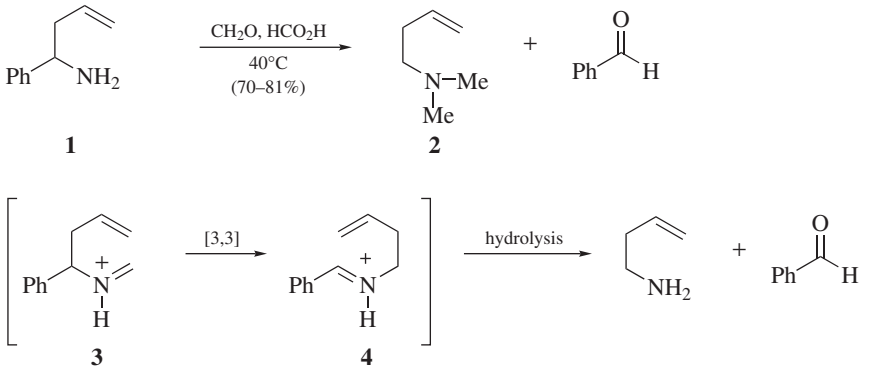
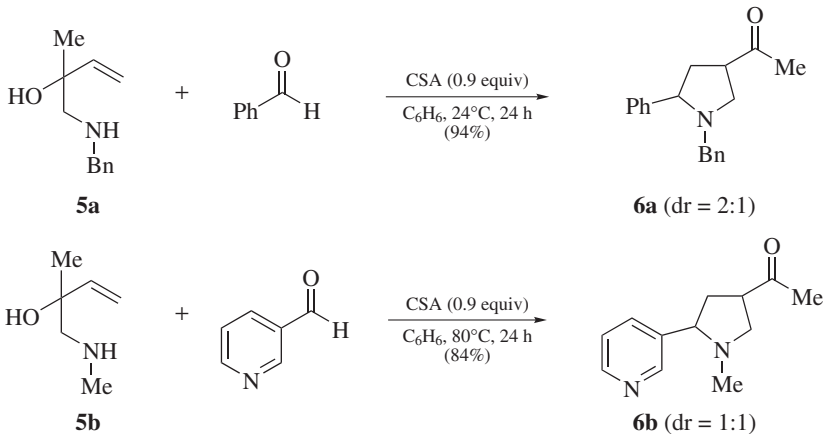
1.6. Aza-Cope–Mannich Reaction

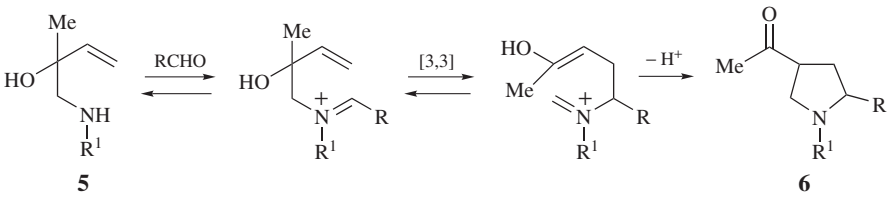
The cationic aza-Cope rearrangement was discovered in 1950 when the α-allylbenzylamine **1** was treated with formaldehyde and formic acid to give two unexpected products, 1-dimethylamino-3-butene (**2**) and benzaldehyde[1] (Scheme 1.6a). It was postulated that the cleavage reaction presumably occurred via a pathway similar to that in the Cope rearrangement. The iminium ion **3** would undergo [3,3]-sigmatropic rearrangement to another iminium ion (**4**), which upon hydrolysis produces homoallylamine and benzaldehyde. The aza-Cope rearrangement is synthetically useful because the rearrangement occurs under mild reaction conditions, and [3,3]-sigmatropic rearrangement typically proceeds with a high level of stereocontrol.



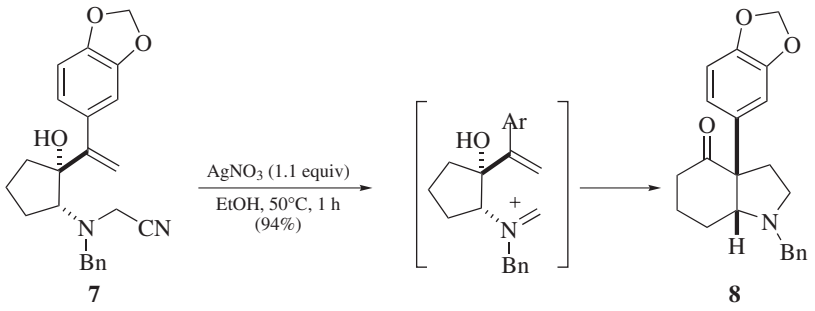
Scheme 1.6a



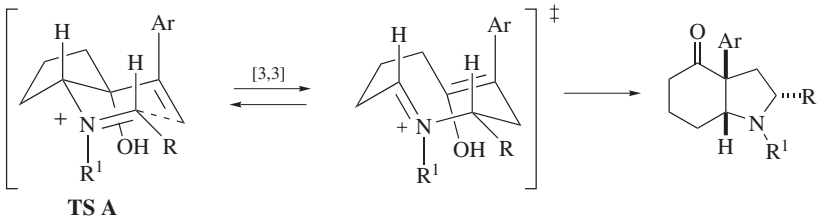
Scheme 1.6b



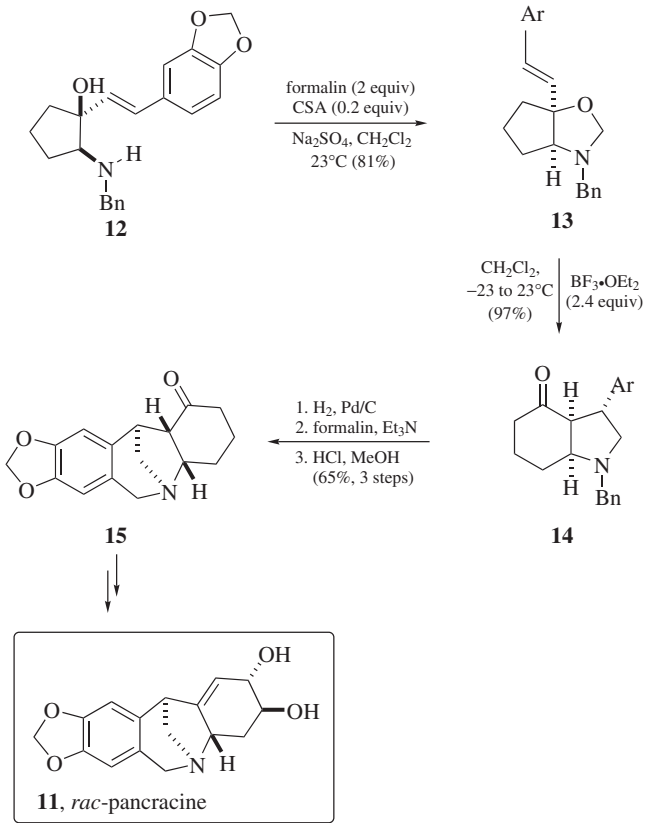
Scheme 1.6c



Scheme 1.6d



Scheme 1.6e



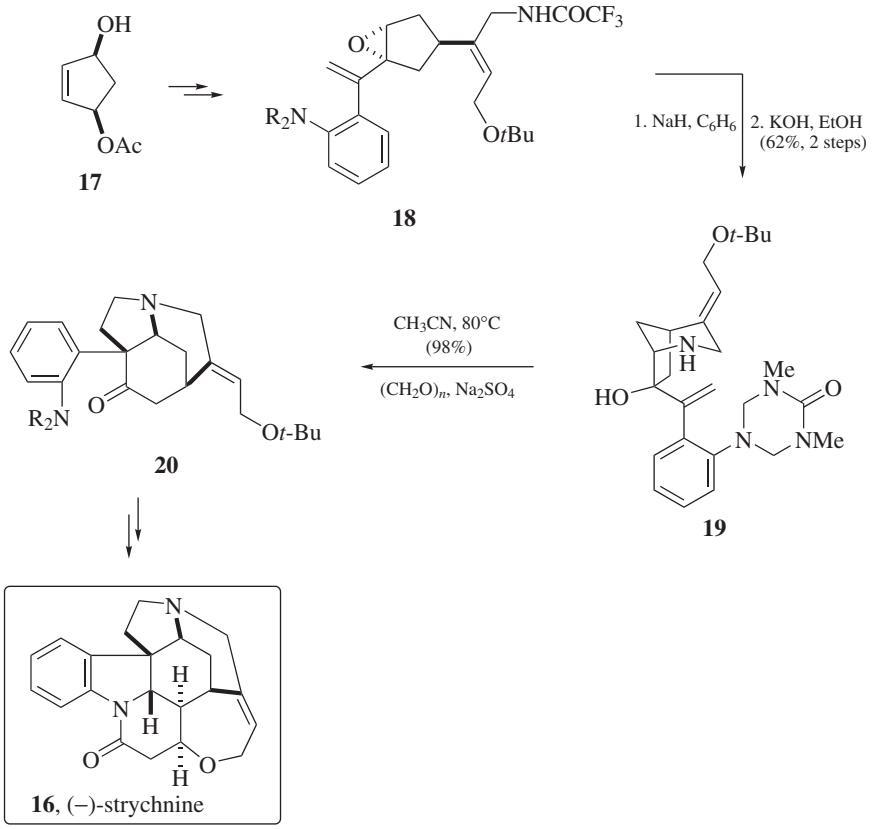
Scheme 1.6f

To control the equilibrium position of the rearrangement, Overman and others introduced a nucleophilic hydroxyl group at the C_2 position to capture the rearranged iminium ion[2] (Scheme 1.6b). Although the levels of diastereoselectivity for the formation of pyrrolidines **6a** and **6b** are low, the tandem cationic aza-Cope–Mannich cyclization provides a variety of substituted 3-acylpyrrolidines in high yields under mild reaction conditions. The first step in the reaction is the

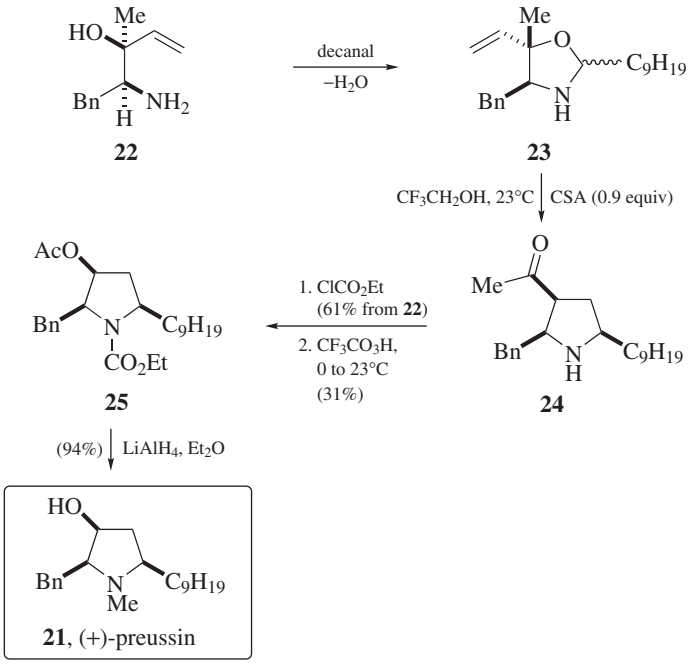
formation of the iminium ion, which undergoes a facile [3,3]-sigmatropic rearrangement to provide an enol iminium intermediate[2] (Scheme 1.6c). Intramolecular attack of the enol on the rearranged iminium ion then produces pyrrolidine.

The chemistry can be extended to the construction of more complex ring systems.[3] When cyclic amino alcohols are subjected to the tandem cationic aza-Cope–Mannich reaction, pyrrolidine-annulated bicyclic products are formed in which the starting ring is now expanded by one number[4] (Scheme 1.6d). For example, when the tandem aza-Cope–Mannich cyclization reactions were performed on the cyclopentanols **7** and **9**, the *cis*-octahydroindoles **8** and **10** were formed, respectively, in high yields as a single diastereomer (Scheme 1.6d). The exclusive formation of a single diastereomer is rationalized in terms of chair-like transition state **A**, in which the *E*-iminium ion isomer rapidly undergoes [3,3]-sigmatropic rearrangement (Scheme 1.6e).

The highly diastereoselective intramolecular aza-Cope–Mannich reaction was used in the total synthesis of (±)-pancracine (**11**), an alkaloid natural product[5]



Scheme 1.6g



Scheme 1.6h

(Scheme 1.6f). Reaction of the *E*-allylic alcohol **12** with formaldehyde in the presence of acid catalyst and sodium sulfate gave the oxazolidine **13**. Exposure of **13** to 2.4 equivalents of $BF_3 \cdot OEt_2$ provided a key intermediate hydroindolone (**14**) in 97% yield as a single diastereomer. Hydrogenolysis of **14** followed by Pictet–Spengler cyclization afforded the methanomorphanthridine ketone **15** in 65% yield.

(−)-Strychnine (**16**), an alkaloid natural product isolated in 1818 from *Strychnos ignatii*, represents one of the most challenging target molecules in organic synthesis. In 1993, Overman used his highly efficient cationic aza-Cope–Mannich cyclization reaction to accomplish the total synthesis of (−)-strychnine[6] (Scheme 1.6g). Treatment of **18**, prepared from (1*R*,4*S*)-(+)-4-hydroxy-2-cyclopentenyl acetate (**17**), with NaH, followed by removal of the trifluoroacetyl group, provided the azabicyclooctane **19**. The crucial aza-Cope–Mannich cyclization was accomplished in essentially quantitative yield in an 800-mg scale reaction to afford the diamine **20**. Further elaboration of the intermediate **20** led to the first asymmetric synthesis of (−)-strychnine (**16**).[7]

Deng and Overman employed the aza-Cope–Mannich reaction in the enantioselective total synthesis of (+)-preussin (**21**), a potent antifungal agent possessing a pyrrolidine skeleton[8] (Scheme 1.6h). Conversion of the amino alcohol **22** to the oxazolidine derivative **23** was readily accomplished by reacting with decanal in hot benzene with removal of water using a Dean–Stark trap. Treatment of

23 with 0.9 equivalent of camphorsulfonic acid (CSA) in CF_3CH_2OH at 23°C yielded the desired all-*cis* pyrrolidine **24** as the major product. Compound **24** was treated directly with ethyl chloroformate followed by Baeyer–Villiger oxidation with trifluoroperoxyacetic acid to afford the product **25**. Finally, reduction of **25** with $LiAlH_4$ in Et_2O provided (+)-preussin (**21**) in 94% yield.

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