CHEMICAL REVIEWS

REVIEW

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# Semipinacol Rearrangement in Natural Product Synthesis

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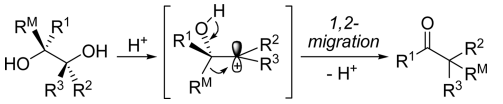
## 1. INTRODUCTION

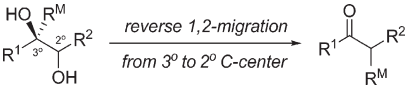
The pinacol rearrangement[1] is a well-known reaction. It refers to the acid-catalyzed transformation of 1,2-diols to ketones or aldehydes by 1,2-migration of a C−C or C−H bond toward the vicinal carbocation (Scheme 1). Although its use is limited because of disadvantages such as poor regio- and diastereoselectivity and unpredictable side reactions, the analogous semipinacol rearrangement reactions[1c,2] have remained an active area of research for synthetic chemists over the past decades, focused on expanding the utility and application of this fascinating series of reactions.

The term "semipinacol" was first coined by Tiffeneau in 1923 to describe a special type of pinacol rearrangement in which the tertiary−secondary 1,2-diol undergoes an unusual 1,2-migration toward the secondary center, rather than the tertiary one (Scheme 2).[3] Now that several variations on this rearrangement have emerged, the concept has been extended to describe *all such rearrangements that are either related to, or reminiscent of, the pinacol rearrangement*.[2] A universal description shown in Scheme 3 may be more helpful for organic chemists to recognize and appreciate the semipinacol rearrangement. Mechanistically, *all such processes share a common reactive species in which an electrophilic carbon center, including but not limited to carbocations, is vicinal to an oxygen-containing carbon and can drive the 1,2-migration of a C−C or C−H bond to terminate the process, generating a carbonyl group*.[4] This is arguably the most attractive feature of the semipinacol rearrangement, as a variety of methods can be used to generate these electrophilic carbon centers. Simply by taking advantage of this versatility, organic chemists have created many ingenious versions of the rearrangement.

**Scheme 1. Classical Pinacol Rearrangement**




**Scheme 2. Original Definition of Semipinacol Rearrangement**




A classification scheme of the semipinacol rearrangement has been established based on the type of electrophilic carbon center. Reactions are categorized into the following four types.

Type I refers to the rearrangement of 2-heterosubstituted alcohols and their derivatives (Scheme 4). In this reaction, good leaving groups such as OMs, OTs, Cl, Br, I, $N_2$, SR, and SeR are usually attached to the electrophilic carbon center. The 1,2-migration is facilitated by the loss of the leaving group under either acidic or basic conditions.

Type II refers to rearrangements of allylic alcohols and their derivatives (Scheme 5). The electrophilic carbon center is a carbocation that can be generated by the addition of an

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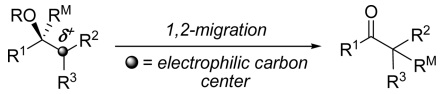
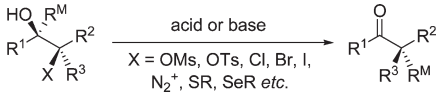
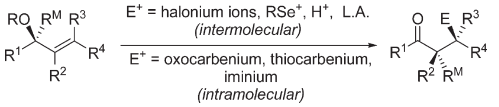
**Scheme 3. General Description of the Semipinacol Rearrangement**



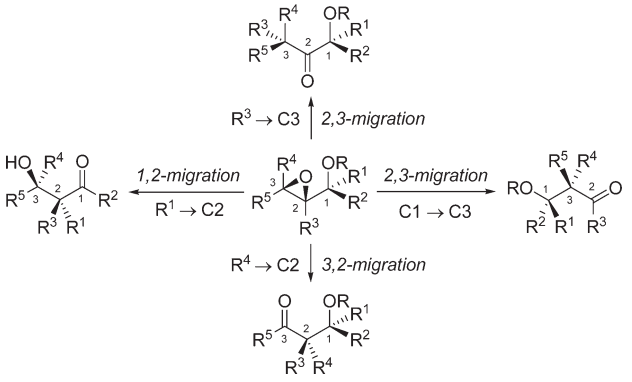

**Scheme 4. Type I Rearrangement**




**Scheme 5. Type II Rearrangement**




**Scheme 6. Type III Rearrangement**




electrophile to a C=C bond. Generally, electrophiles such as halogeniums, selenium cations, and Brønsted and Lewis acids initiate intermolecular rearrangements. In contrast, oxocarbeniums, thiocarbeniums, and iminiums mainly undergo intramolecular ones. The latter case is now widely known as the Prins-pinacol rearrangement after a series of elegant studies carried out in Overman's group.[5]

Type III refers to rearrangements of epoxides.[6] Investigations in this field have focused largely on the rearrangement of 2,3-epoxy alcohols and their derivatives (Scheme 6).[7] In this case, the electrophilic carbon center corresponds to either carbon of the oxirane, and the migration is driven by acid-promoted epoxide ring-opening. Depending on the structural features of the substrate and on reaction conditions, the rearrangement can proceed via 1,2-, 2,3-, or 3,2-migration (based on the numbering in 2,3-epoxy alcohols).

Type IV refers to rearrangements of tertiary α-hydroxy ketones and imines (Scheme 7). This reaction is also known as the "acyloin rearrangement" or "α-ketol rearrangement".[8] Because an enolization/protonation is impossible for tertiary α-hydroxy ketones and imines, the 1,2-migration of the C−C bond toward the electrophilic carbon center of the carbonyl or imine group is believed to account for this rearrangement.

Compared to the classical pinacol rearrangement, the semipinacol rearrangement has several remarkable advantages. (1) The reaction is not restricted to 1,2-diols. A much broader scope of substrates can be used to generate more diverse products such as aldehyde aldol adducts and *β*-halo and *β*-amino ketones. (2) The rearrangement is compatible with a variety of reaction conditions: it can proceed under acidic, basic, or even neutral conditions depending on the substrates. (3) Regioselectivity, which can be a problem in the pinacol rearrangement, is not an issue in semipinacol rearrangement because several approaches can be used to create the vicinal electrophilic center in a site-specific way. (4) The migratory aptitude of substituents, in addition to following the usual trends observed in pinacol rearrangements, is also often controlled by the stereoelectronic effect, such that the migratory group must be antiperiplanar to the leaving group. Thus, stereospecific rearrangements with inversion of stereochemistry at the migration terminus are observed in most cases. This feature has frequently been exploited to assemble continuous stereocenters containing a quarternary carbon[9] with high diastereoselectivity. (5) The semipinacol rearrangement can be a key part of tandem reactions, such as when it is combined with the reaction forming the electrophilic carbon center, or when the carbonyl group formed in the rearrangement is subsequently functionalized.[10]

This review is intended to highlight applications of the semipinacol rearrangement in natural product synthesis and provide an updated overview of its tremendous power and versatility. The scope is largely confined to total syntheses with only a few model studies and emerging methodologies discussed where appropriate. Examples were collected up to the end of 2010 and organized along the classification scheme described above. In addition, two sections discuss biomimetic syntheses involving semipinacol rearrangement and recent applications of the pinacol rearrangement. Although in some examples that we cite the authors did not use the term "semipinacol" to label their rearrangements, we believe it is suitable to cover these works in the review from either a reaction type or mechanistic point of view. Only representative examples of the syntheses of analogue series are discussed; more cases can be found in the references. Although we have tried to make this review as comprehensive as possible, an exhaustive survey of this area is impractical. Therefore, we would like to apologize in advance to the researchers whose work this review may have missed.

## 2. REARRANGEMENT OF 2-HETEROSUBSTITUTED ALCOHOLS

### 2.1. Sulfonates as Leaving Group

The semipinacol rearrangement of 1,2-hydroxy sulfonates and their analogues has been found to be reproducibly efficient in both acyclic and cyclic systems. Both Lewis acids and bases can promote the 1,2-migration with loss of a good leaving group such as OMs or OTs.

Tsuchihashi and co-workers developed an efficient organoaluminum-promoted semipinacol rearrangement of lactate-derived 1,2-hydroxy mesylate.[11] The reaction proceeded through a proposed Al-chelated intermediate **8** to give enantiomerically pure α-chiral ketones with full inversion at the C−OMs stereocenter. This methodology was successfully used for the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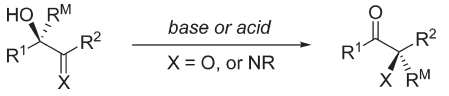
convergent total synthesis of protomycinolide IV (Scheme 8).[12] The chiral mesyloxy ketone **1** was first reduced by DIBALH. Then the resulting aluminum alkoxide underwent an $AlEt_3$-promoted, stereospecific 1,2-alkenyl migration and concomitant reduction to provide **2** in 85% yield. No *E*/*Z* isomerization of the alkenyl geometry occurred during migration. A similar procedure was used to prepare ketone **6** from tertiary 1,2-hydroxy mesylate **5**. In subsequent steps, **2** and **6** were converted to the key coupling precursors **4** and **7**, which were ultimately transformed to protomycinolide IV.

In Rawal and co-workers' total synthesis of ent-elisapterosin B, mesylated ketal **10** was used for the rearrangement (Scheme 9).[13] Upon treatment with excess $CaCO_3$ as an acid scavenger, **10** underwent a stereospecific 1,2-aryl migration via bridging phenonium ion **11** to generate ester **12** containing the required stereochemistry of the anti configuration in 72% yield. Subsequent transformations involving an endo-intramolecular Diels–Alder reaction of quinone **13** and a biomimetic oxidative cyclization of *epi*-ent-elisabethin A yielded the desired product.

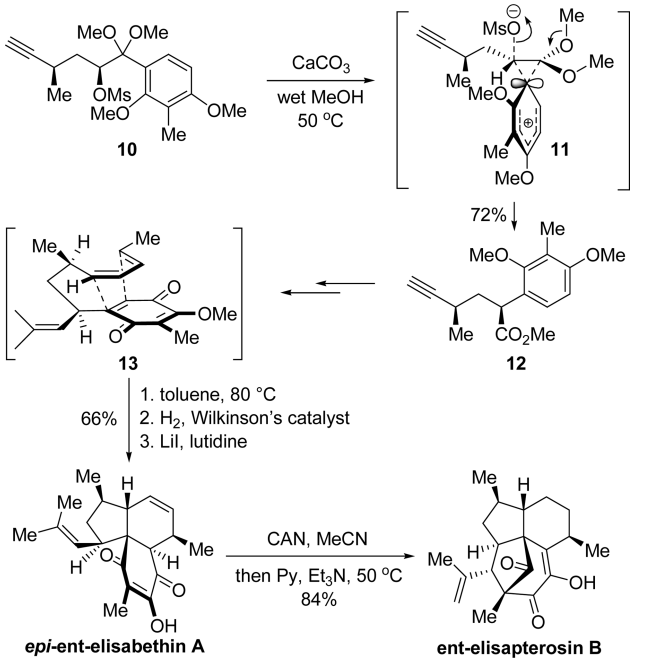
Isoedunol and $\beta$-araneosene, metabolites of the terrestrial mold *Sordaria araneosa*, have a common "dolabellane" framework found in many biologically active natural products. In Kingsbury and Corey's syntheses of these molecules,[14] an elegant strategy based on sequential ring expansion was used to assemble the trans-fused 5,11-membered ring system (Scheme 10). Tsuchihashi's protocol was used to transform cyclopropyl carbinol **14** to cyclobutanone **16** in 90% yield, creating an angular methyl-bearing quaternary carbon center. The bifunctional role of $AlMe_3$ in inducing a concerted rearrangement via the chelated intermediate **15** is believed to account for the excellent stereochemical control. This explanation is supported by the observation that using PPTS as catalyst in the reaction led to partial racemization. During the study of the second ring expansion, Corey and co-workers observed that whereas the cis-diol **18** could be transformed into the fused 5,11-bicyclic ketone **19** via the desired 1,2-migration of the C1–C4 bond, the rearrangement of trans-diol **17** gave only the bridged 5,12-bicyclopentanone **20** via 1,2-migration of the C3–C4 bond. On the basis of X-ray crystallographic analysis of both **17** and **18**, the authors proposed that the conformational rigidity imposed by the 12-membered ring orients different C–C bonds antiperiplanar to the secondary C–O bond in **MsO-17** (trans) and **MsO-18** (cis). Thus, the stereospecific 1,2-migration gave **20** and **19**, respectively.

Nemoto and Fukumoto developed a series of useful approaches for the syntheses of chiral cyclobutanones (Scheme 11).[15] One of the methods is based on a semipinacol rearrangement of the 1,2-hydroxy mesylate mixture **21**, which features an oxathiane as a chiral auxiliary.[16] Upon acid treatment, each isomer underwent stereospecific cyclopropyl ring expansion. Then, isomerization of the resulting 1:1 cyclobutanone mixture with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) led to the desired **22** as the major

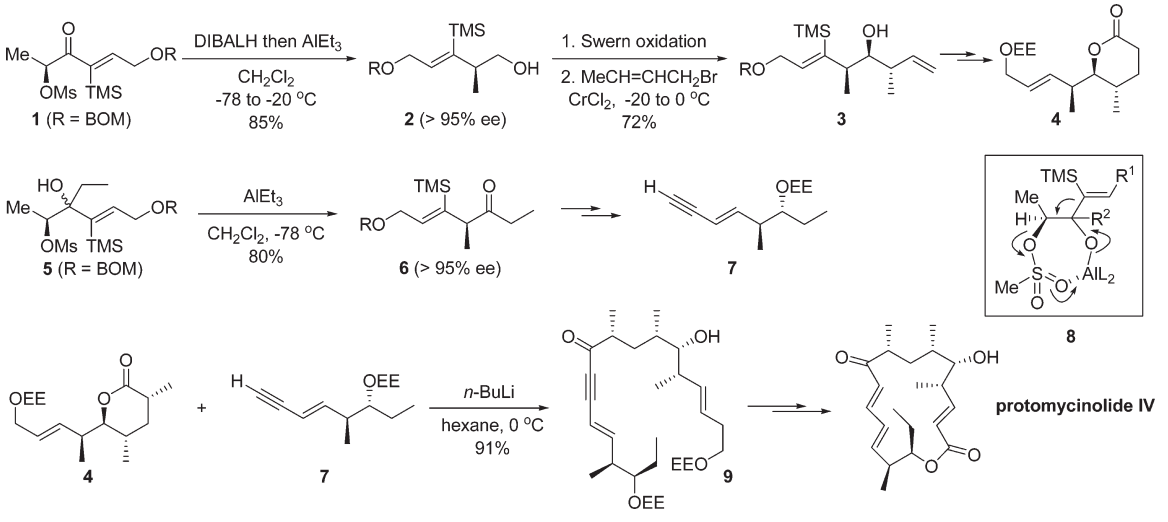
**Scheme 7. Type IV Rearrangement**




**Scheme 9. Rawal's Total Synthesis of Ent-elisapterosin B**




**Scheme 8. Tsuchihashi's Total Synthesis of Protomycinolide IV**





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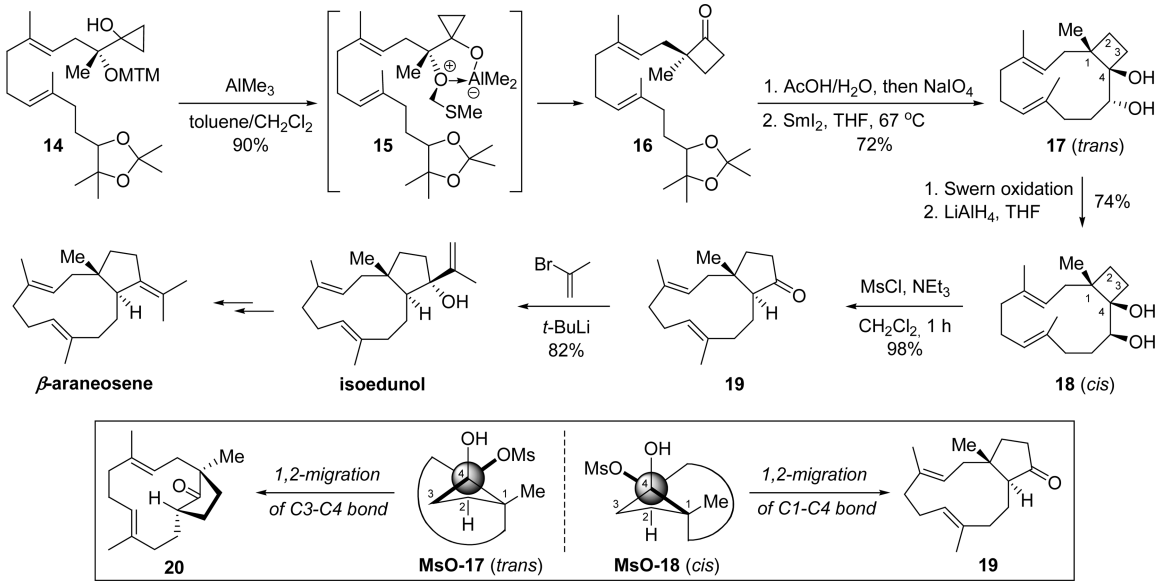
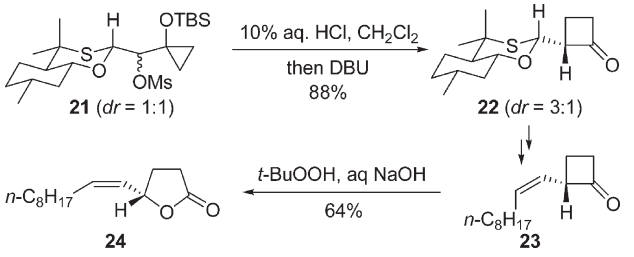
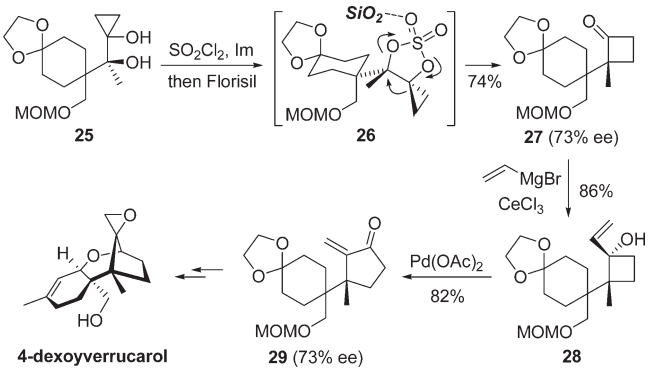
**Scheme 10. Corey's Total Syntheses of Isoedunol and β-Araneosene**




**Scheme 11. Nemoto and Fukumoto's Total Synthesis of Pheromone**



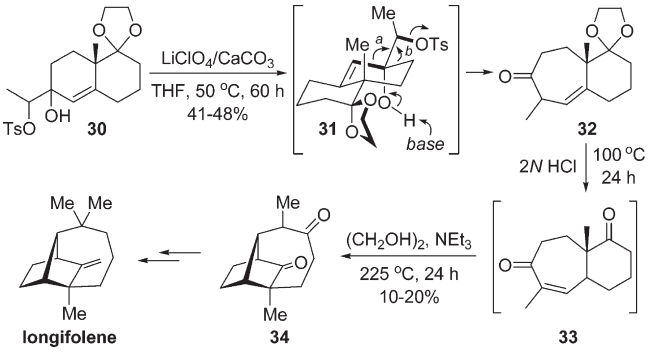

**Scheme 12. Nemoto and Fukumoto's Total Synthesis of 4-Deoxyverrucarol**




separable diastereomer. Compound **22** has been used as a building block in the syntheses of several pheromones of Japanese beetles, such as **24**.

In the asymmetric synthesis of 4-deoxyverrucarol, Nemoto, Ihara, and co-workers used a more convenient one-pot process to form the chiral cyclobutanone intermediate **27** (Scheme 12).[17] On treatment with $SO_2Cl_2$ in the presence of imidazole, cyclopropyl diol **25** was first transformed to cyclic sulfate **26**, which then underwent a Florisil-promoted ring expansion with loss of $SO_3$ to generate **27** directly in 74% yield. After the transformation to vinylcyclobutanol **28**, a second ring expansion was induced by $Pd(OAc)_2$ to give cyclopentanone **29** in 82% yield. This intermediate was ultimately transformed into the target.

**Scheme 13. Corey's Total Synthesis of Longifolene**




In the total synthesis of longifolene, Corey et al. used a semipinacol rearrangement of the secondary mono-*p*-toluenesulfonate **30** to achieve the solvolytic ring expansion (Scheme 13).[18] Under neutral conditions, the unconjugated cycloheptenone **32** was generated predominantly via pathway a, which involves a more favorable 1,2-migration of the vinyl group, rather than via the alkyl migration in pathway b. Then the conjugated diketone **33**, prepared from acid-catalyzed hydrolysis of **32**, underwent intramolecular Michael cyclization to give the key bridged tricyclic diketone **34**, which was ultimately transformed into longifolene.

In the synthesis of (±)-confertin, Heathcock et al. observed interesting solvolytic behavior in the semipinacol rearrangement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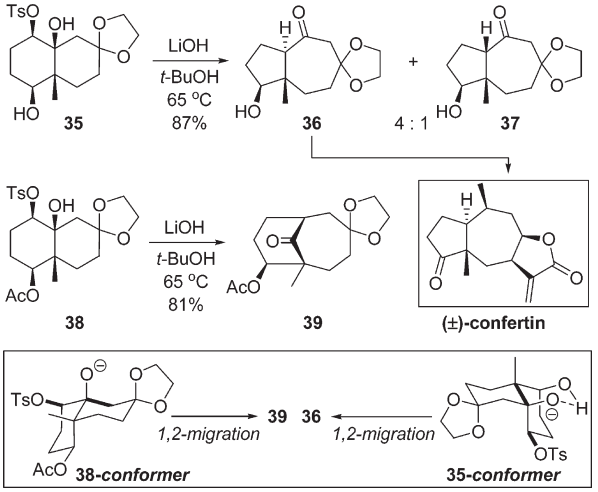
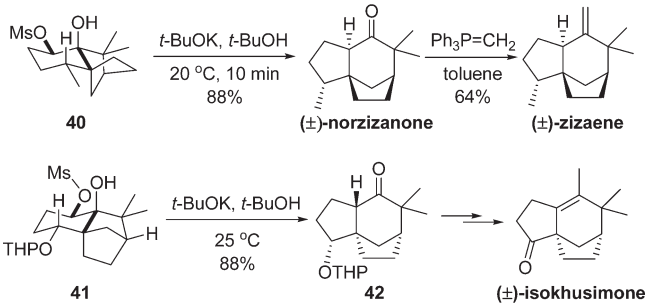
**Scheme 14. Heathcock's Total Synthesis of (±)-Confertin**




**Scheme 15. Mukherjee's Total Syntheses of (±)-Zizaene and (+)-Isokhusimone**



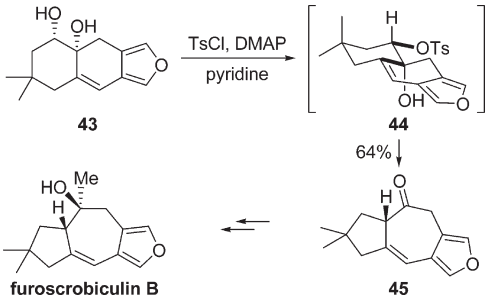

of tosylacetate **35** and tosylalcohol **38** (Scheme 14).[19] Under the same basic conditions of LiOH in *t*-BuOH, **35** was converted into the primary rearrangement product **36** along with its isomer **37** as a result of base-catalyzed equilibration, whereas **38** was transformed to keto acetate **39** with a bridged ring system. The conformational argument offered to explain these different reaction pathways was as follows. After deprotonation of the proximate hydroxyl, **38** is presumed to adopt the conformation **38-conformer**. For tosylalcohol **35**, however, conformation **35-conformer** appears to be more favorable because of the potential benefit from hydrogen bonding with another hydroxyl group. Subsequent 1,2-migration of the different vicinal C−C bonds that are antiperiplanar to the tosylate group generates **36** and **39**, respectively.

Mukherjee and co-workers used a similar strategy in their total syntheses of (±)-zizaene and (±)-isokhusimone (Scheme 15).[20] Treatment of monomesylates **40** and **41** with *t*-BuOK caused a facile rearrangement at room temperature to give (±)-norzizanone and another key intermediate **42**, both in 88% yield.

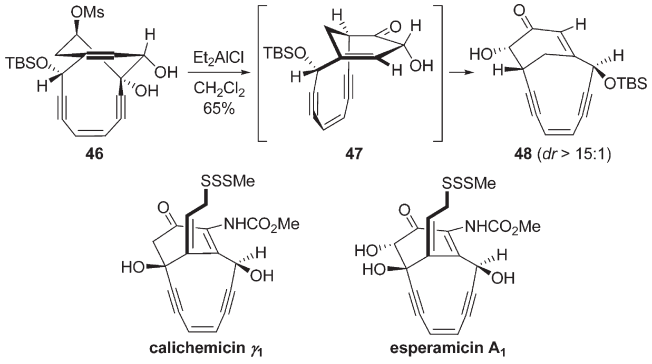
The same rearrangement in a similar ring system was also used by Kanematsu and co-workers in the synthesis of furoscrobiculin B (Scheme 16).[21] Tosylation of the secondary hydroxyl group of cis-diol **43** formed the monotosylate **44** in situ, and this was directly transformed into the intermediate azulenofuran **45** in 64% yield.

The rearrangement is not limited to fused-ring systems: it works equally efficiently in the construction of complex bridged-

**Scheme 16. Kanematsu's Total Synthesis of Furoscrobiculin B**




**Scheme 17. Schreiber's Synthesis of a Bicyclic Core Related to Esperamicin and Calichemicn Aglycones**




ring systems. For example, $Et_2AlCl$-promoted rearrangement of 1,2-hydroxy mesylate **46** was used in Schreiber's synthesis of the bicyclic core **48**, which is related to esperamicin and calichemicin aglycones (Scheme 17).[22] Although the stereochemistry of **48** is consistent with 1,2-migration of the allylic hydrogen in concert with the shift of the acetylene, the acyloin isomer **47** was shown to be the intermediate initially formed. Thus, enolization of **47** produces an enediolate that is expected to be protonated on the diastereoface opposite the enediyne bridge, yielding **48**.

Paquette and co-workers used Tsuchihashi's organoaluminum-promoted semipinacol rearrangement of the 1,2-hydroxy mesylates **49** and **51** as a key step in their total synthesis of (+)-taxusin and its analogues (Scheme 18).[23] The antiperiplanar alignment of the α-oriented OMs leaving group and the vicinal bond in the bridge allowed the desired 1,2-migration to occur stereospecifically, generating the target cores in moderate to excellent yields.

In one of Wang and co-workers' continuing studies of the chemical conversion of C19-diterpenoid alkaloids to taxoids, **53** was converted into **56** in 50% overall yield via an efficient one-pot, four-step approach (Scheme 19).[24] The key steps included a semipinacol rearrangement of mesylate **55** to facilitate a novel ring reconstruction from a bridged ring system to the 4,6-fused ring moiety in **56**.

## 2.2. Halides as Leaving Group

Halohydrins can undergo semipinacol rearrangement either under basic conditions or in the presence of various silver salts.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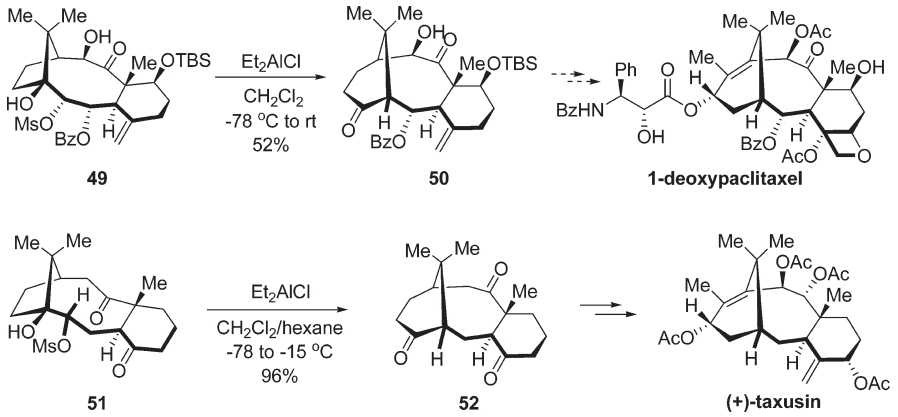
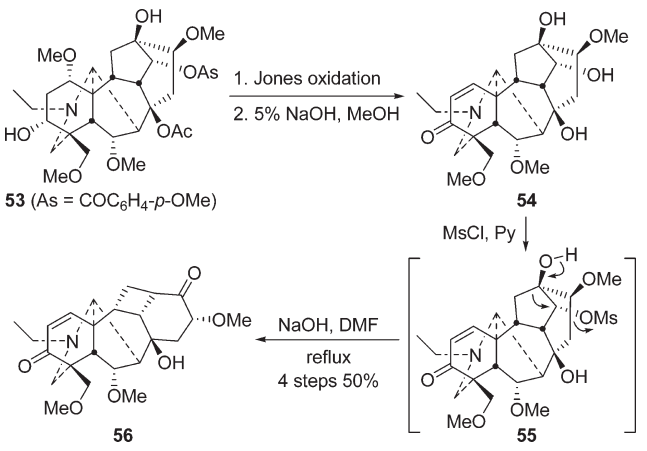
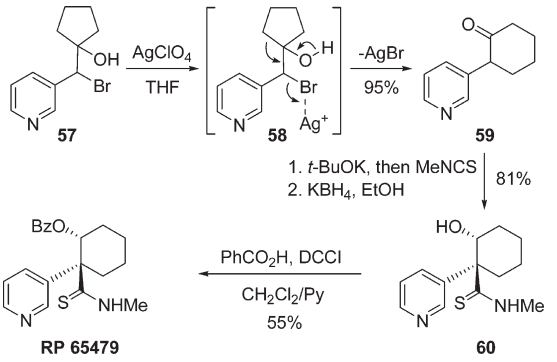
**Scheme 18. Paquette's Total Synthesis of (+)-Taxusin and Synthesis of an Advanced Precursor of 1-Deoxypaclitaxel**




**Scheme 19. Wang's Synthetic Studies of the Chemical Conversion of C19-Diterpenoid Alkaloids to Taxoids**




**Scheme 20. Hart's Total Synthesis of RP 65479**




The 1,2-migration of a C−C bond with the loss of halogen results in the formation of a carbonyl group along with skeletal rearrangement. In addition, a similar pathway involving a halohydrin anion intermediate has been suggested as the mechanism of "*quasi*-Favorskii" rearrangement,[25] in which the cyclopropanone cannot form because the substrate lacks an α-hydrogen or because there is steric hindrance.

In Hart et al.'s synthesis of the potent potassium channel opener RP 65479 (Scheme 20),[26] ketone **59** was prepared in 95% yield by a $AgClO_4$-mediated semipinacol rearrangement of bromohydrin **57**. Trapping of the enolate of **59** with methyl isothiocyanate, followed by reduction and esterification, produced RP 65479 in 55% yield.

Using the rearrangement of bromohydrin to transform bicycle-[2.2.2]-octane to bicycle-[3.2.1]-octane, Fleming and co-workers efficiently synthesized the gelsemine core (Scheme 21).[27] Treatment of epoxy alcohol **61** with $MgBr_2 \cdot OEt_2$ generated the bromohydrin **62**, which then underwent a stereospecific 1,2-migration of the bridged C−C bond, giving ketone **63** in 78% yield. Subsequent intramolecular $S_N2$ substitution formed the pyran ring, giving **64** in 62% overall yield. This compound was then transformed into the gelsemine core.

The female sexual pheromone (±)-sirenin contains a highly substituted cyclopropane moiety fused to a cyclohexene ring, and it has a neopentyl-like quaternary carbon center. In Harding and co-workers' synthesis of this molecule (Scheme 22),[28] $AgNO_3$-mediated semipinacol rearrangement of α-chlorocyclobutanone **65** was used to generate the ring-contracted product **67** diastereoselectively in 53% yield.

The germacrene sesquiterpenes bicyclogermacrene and lepidozene share a structurally related, 10-membered ring skeleton. In McMurry and Bosch's syntheses of these molecules (Scheme 23),[29] a semipinacol rearrangement of the chlorocyclobutanone mixture **68** was used to give a 1.5:1 mixture of cis- and trans-cyclopropyl carboxylic acid isomers **69** in 92% overall yield. Surprisingly, rearrangement of either isomer of **68** returned the original isomeric mixture. After an intramolecular McMurry coupling of the aldehyde derived from **69**, the two natural products were obtained.

Kraus and Shi reported the synthesis of modhephene using a semipinacol rearrangement of bromobicyclo-[3.3.1]-nonenone **70** to construct the key ring skeleton (Scheme 24).[30] After treatment of **70** with methyl phosphonate anion, the nucleophilic addition/ring-contraction sequence occurred smoothly and led to keto ester **72** in 70% yield. After directed hydrogenation using iridium as catalyst and intramolecular nucleophilic addition, vinylogous ester **73** was formed and subsequently converted into modhephene.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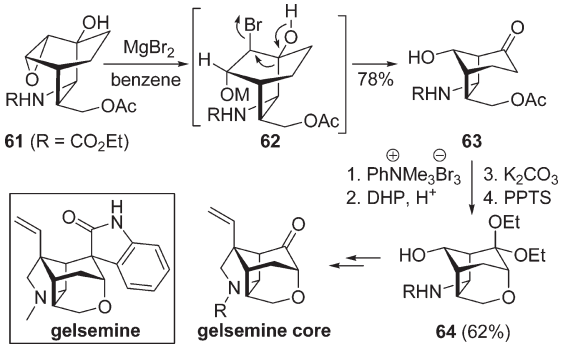
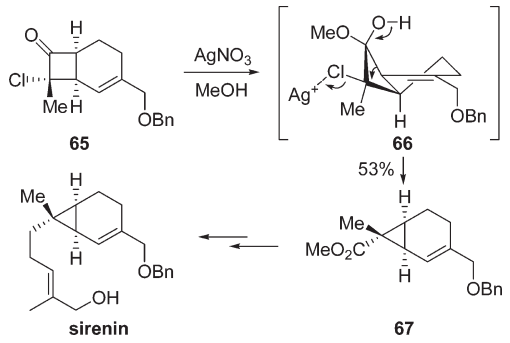
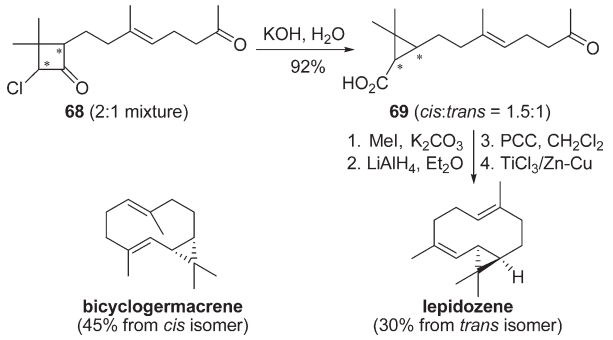
**Scheme 21. Fleming's Approach to Gelsemine**



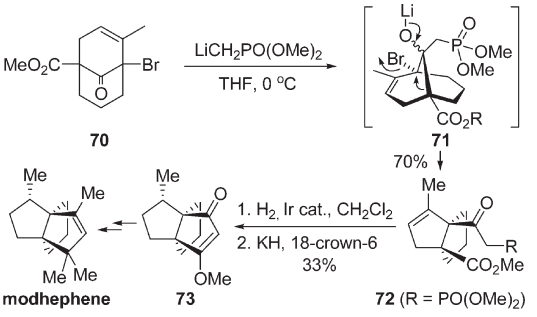

**Scheme 22. Harding's Total Synthesis of (±)-Sirenin**




**Scheme 23. McMurry's Total Syntheses of Bicyclogermacrene and Lepidozene**




**Scheme 24. Kraus' Total Synthesis of Modhephene**




Harmata and co-workers developed a [4 + 3]-cycloaddition/quasi-Favorskii process that has been used to synthesize a range of polycyclic natural products (Scheme 25). For example, in the synthesis of the tricycloclavulone core,[31] addition of isobutenyllithium to the [4 + 3]-cycloadduct **74** at −78 °C generated bromohydrin anion **75**, which then underwent stereospecific ring contraction at −30 °C to give ketone **76** in 90% yield. Subsequent ring-closing metathesis with the first generation of Grubbs catalyst formed the core structure **77** in 50% yield. In the formal synthesis of spatol,[32] reduction and deprotonation of the cycloadduct **78** generated the chlorohydrin anion **79**, which underwent an equally effective ring contraction to give aldehyde **80** directly in 76% yield. A similar strategy was used to synthesize sterpurene.[33]

## 2.3. $N_2$ as Leaving Group

Diazotation of 1,2-amino alcohols by nitrous acid or direct addition of diazoalkane to ketones can lead to efficient ketone homologation.[34] Although the process is widely known as Tiffeneau−Demjanov rearrangement, it occurs by a mechanism similar to that of semipinacol rearrangement. The reaction generally involves a 1,2-diazo hydroxyl zwitterion intermediate, which can undergo 1,2-migration with loss of $N_2$ to give the homologated ketone. Although for unsymmetrical ketones the degree of substitution of either group appears to be of little importance, migration of the less-substituted group is usually preferred in cyclic systems, resulting in various ring-expanded products. As a result of this feature, the reaction has been used reliably in natural product syntheses.

In Greene's total synthesis of (+)-hirsutic acid C (Scheme 26),[35] the rearrangement of cyclobutanone **86** was used to construct the key cyclopentanone **89**. Treatment of **86** with ethyl diazoacetate in the presence of $SbCl_5$ induced a predominantly 1,2-methylene migration (98:2), shown as **87**, to give the keto ester **88**, which was transformed into **89** in 63% overall yield after decarboxylation. Much greater regioselectivity was obtained with $SbCl_5$ than with $BF_3 \cdot OEt_2$ or $BF_4^- \cdot EtO^+$.

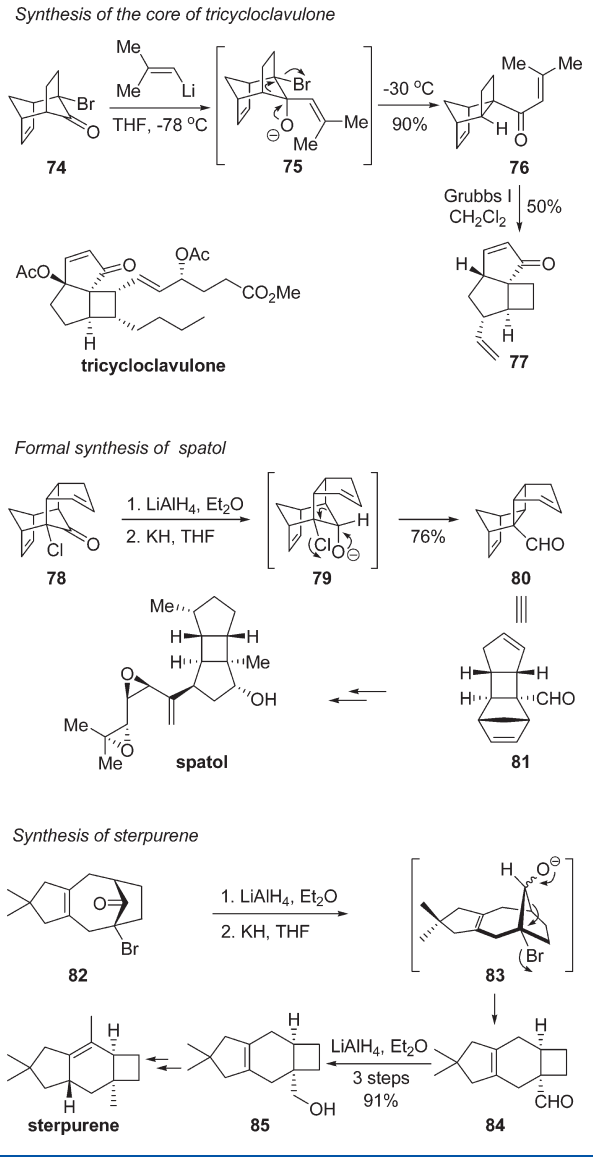
Bakkanes-type sesquiterpenes, which contain a novel spiro-γ-butyrolactone hydrindane, have been the target of a range of synthetic efforts over the past several decades. In Deprés, Greene, and co-workers' synthesis of 9-acetoxyfukinanolide (Scheme 27),[36] exposure of cyclobutanone **90** to ethyl diazoacetate in the presence of $SbCl_5$ furnished the desired ring expansion and gave cyclopentanone **91** in 64% yield with 81:19 regioselectivity. After alcoholysis of the resulting ester group using propargyl alcohol, $Mn(OAc)_3$-mediated radical cyclization was performed to give the spiroketo lactone **93** in 61% yield. Subsequent $SmI_2$-mediated reduction and an interesting retroaldol−aldol equilibration process of **94** (ca. 3.5:1) yielded the target. A similar strategy has been used to synthesize other analogues, such as (−)-bakkenlides III B, C, H, (−)-homogynolide A, and (±)-palmosalide C.[37]

The semipinacol rearrangement to facilitate ring expansion of common and large rings is also useful in natural product syntheses. For example, the rearrangement leading to expansion from 5- to 6-membered rings has been used in Ohta and co-workers' synthesis of (±)-linderol A[38] and Trost et al.'s synthesis of (+)-frondosin A (Scheme 28).[39]

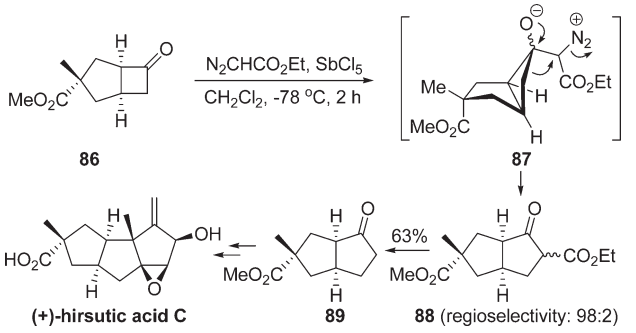
This process was also used to expand from 6- to 7-membered rings in Venkateswaran and co-workers' synthesis of


dx.doi.org/10.1021/cr200055g |Chem. Rev. 2011, 111, 7523–7556

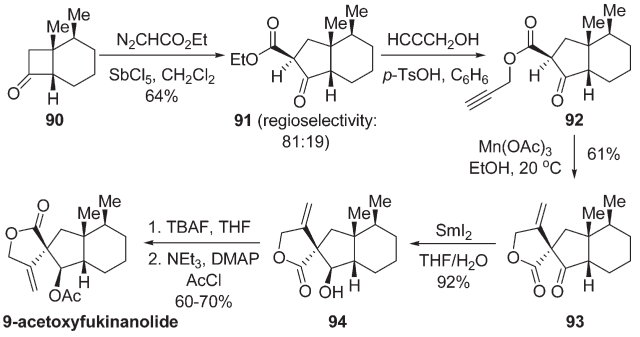
**Scheme 25. Harmata's [4 + 3]-Cycloaddition/Quasi-Favorskii Process in Natural Product Synthesis**



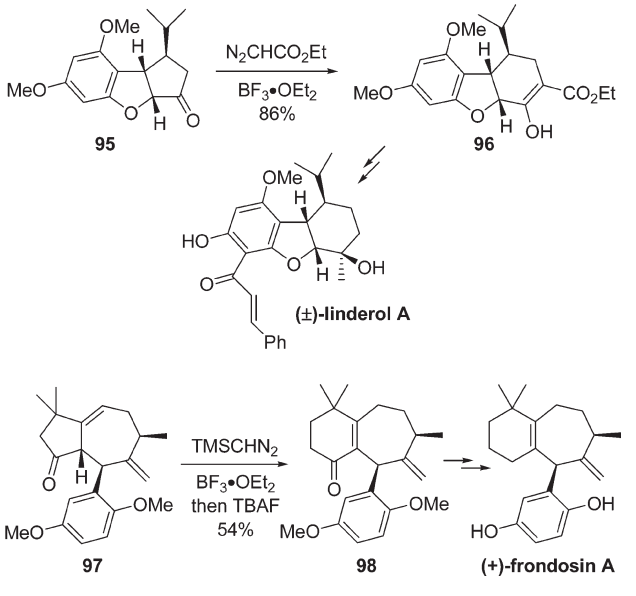

**Scheme 26. Greene's Total Synthesis of (+)-Hirsutic Acid C**




**Scheme 27. Deprés and Greene's Total Synthesis of 9-Acetoxyfukinanolide**




**Scheme 28. Ohta's Synthesis of (±)-Linderol A and Trost's Total Synthesis of (+)-Frondosin A**



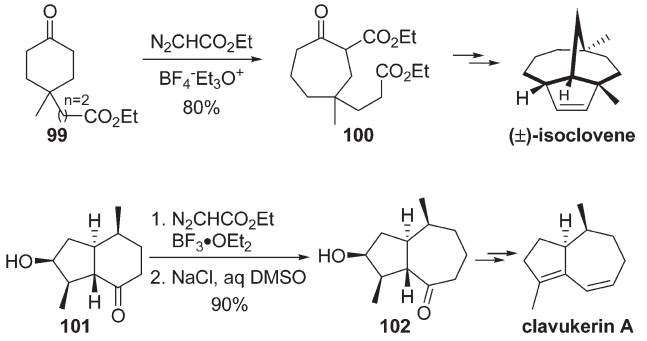

(±)-isoclovenewere[40] and Honda et al.'s synthesis of clavukerin A (Scheme 29).[41] All the rearrangements in Schemes 28 and 29 proceeded via exclusive 1,2-migration of the less substituted methylene group.

Expansion from a 12- to 13-membered ring was used in Nagel et al.'s synthesis of (±)-muscone (Scheme 30).[42] Treatment of 1,2-amino alcohol **103** with sodium nitrite in the presence of $H_2O$ and AcOH transformed it into the 13-membered cycloketone **105** in 50−60% yield.

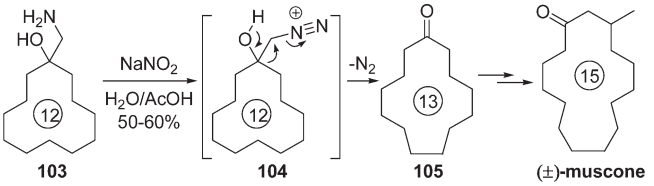
The rearrangement proceeds readily and follows the expected mechanism even in bridged or highly strained polycyclic systems. For instance, in the synthesis of furanosesquiterpene (±)-nakafuran-8 (Scheme 31),[43] Uyehara, Yamamoto, and co-workers employed a sequential ring expansion to establish the key bicycle-[4.2.2]-decane skeleton. The first ring expansion of **107** was performed with $NaNO_2$ and AcOH to give ketone **109** in 61% yield. The second ring expansion was carried out by treating **109** with $TMSCHN_2$ and $BF_3 \cdot OEt_2$ to afford **110** in 67% yield. In both steps, 1,2-migration of the methylene group was the predominant migration, giving 12:1 and 2:1 regioselectivity for **109** and **110**, respectively.


dx.doi.org/10.1021/cr200055g |*Chem. Rev.* 2011, 111, 7523–7556

**Scheme 29. Venkateswaran's Total Synthesis of (±)-Isoclovene and Honda's Total Synthesis of Clavukerin A**




**Scheme 30. Nagel's Total Synthesis of (±)-Muscone**




In Miyashita and Yoshikoshi's synthesis of longipinenes containing a rigid pinane skeleton (Scheme 32),[44] ring expansion of the 1,2-amino alcohol **113** was used to form the homologated ketone **114** in quantitative yield with 90:6 regioselectivity. Those authors provided an insightful mechanistic analysis to explain the highly selective 1,2-migration of the C9−C10 bond. Although migration of the C8−C9 bond is electronically more favorable than that of the less substituted C9−C10 bond, it would lead to a severe steric repulsion between the C2-methyl and C9 positions in the transition state **117**. In contrast, migration of the C9−C10 bond would lead to the sterically more stable transition state **116**. Therefore, steric control appears to dominate over electronic control in the rearrangement.

### 2.4. Thiolates and Selenolates as Leaving Group

Bach and co-workers completed the total synthesis of (±)-fredericamycin using a semipinacol rearrangement of a 1,2-hydroxy thiol compound to construct the spirocyclic skeleton (Scheme 33).[45] Treatment of dithioacetal **118** with bis-((trimethylsilyl)oxy)cyclobutene **119** and $Hg(OCOCF_3)_2$ afforded the cyclobutanone intermediate **120**, which underwent ring expansion via a novel 1,2-acyl migration to yield the key spiro diketone **121** with the CDE ring system in 54% yield.

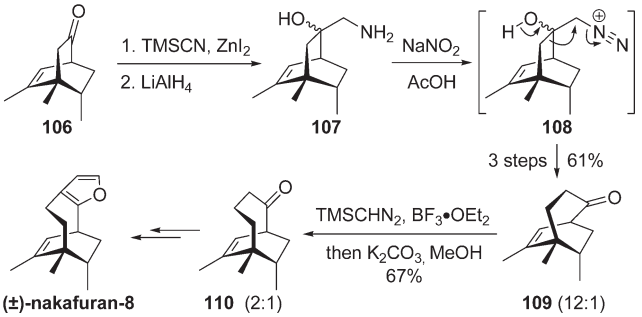
Krief and co-workers developed a concise synthesis of α-cuparenone using semipinacol rearrangement of 1,2-hydroxy seleno compounds to carry out sequential ring expansions (Scheme 34).[46] The first expansion from a 3- to 4-membered ring in 1,2-hydroxy selenocyclopropane **125** was promoted by *p*-TsOH and gave cyclobutanone **126** in 80% yield. The second, $CH_3OSO_2F$-promoted expansion from a 4- to 5-membered ring occurred in the last step to transform **127** directly into α-cuparenone in 82% yield.

## 3. REARRANGEMENT OF ALLYLIC ALCOHOLS

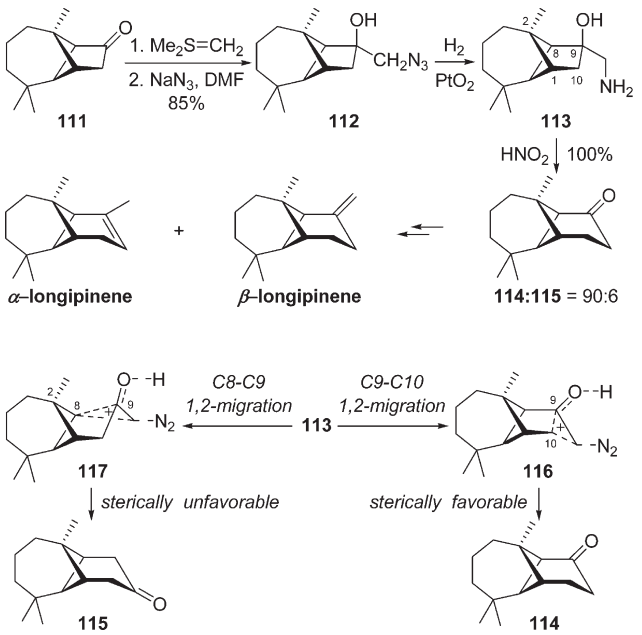
### 3.1. Induced by Halonium Ions

Halonium ions are highly electrophilic species that can induce semipinacol rearrangement of various allylic alcohols and their

**Scheme 31. Uyehara and Yamamoto's Total Synthesis of (±)-Nakafuran-8**




**Scheme 32. Yoshikoshi's Total Synthesis of Longipinenes**

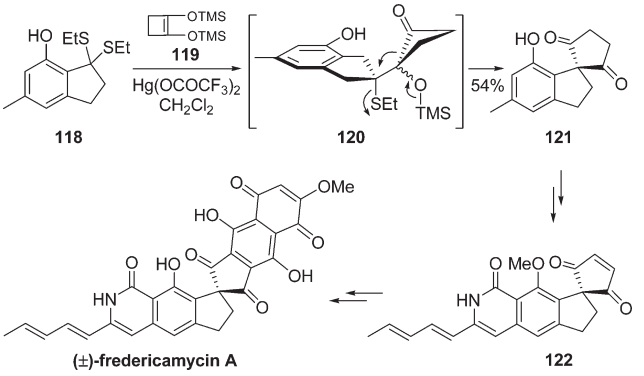



derivatives to give synthetically useful β-halo carbonyl compounds.[47] For example, in Wood and co-workers' elegant total synthesis of (−)-welwitindolinone A isonitrile (Scheme 35),[48] chloronium ion was used to induce such a rearrangement to introduce both a C12 quaternary center and the adjacent neopentyl chlorine diastereoselectively. Treatment of tertiary allylic alcohol **129** with NaOCl and $CeCl_3 \cdot 7H_2O$ triggered the 1,2-methyl migration anti to the chloronium ion and provided chloro ketone **131** in 78% yield as a single diastereomer. Having a sufficiently large protecting group like triisopropylsilyl (TIPS) on the C11 secondary hydroxyl is crucial to overriding the potentially favorable attack of chloronium ion from the least hindered convex face in the rigid structure, as shown in **130**.

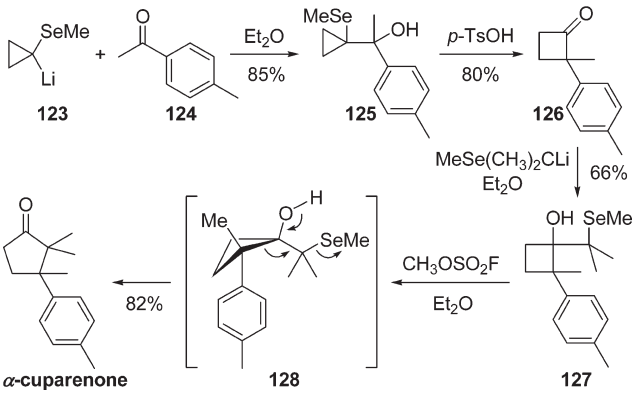
Galanthamine-type *Amaryllidaceae* alkaloids have a common tricyclic benzofuran core with a sterically congested quaternary carbon center located at the bridgehead. Tu and co-workers developed a general approach to these molecules based on a sequential, *N*-bromosuccinimide (NBS)-induced semipinacol rearrangement/desilylation/cyclization process (Scheme 36).[49] When the allylic alcohol mixture **132** (R′ = OTBS, diastereomeric ratio


dx.doi.org/10.1021/cr200055g |*Chem. Rev.* 2011, 111, 7523–7556

**Scheme 33. Bach's Total Synthesis of (±)-Fredericamycin A**




**Scheme 34. Krief's Total Synthesis of α-Cuparenone**

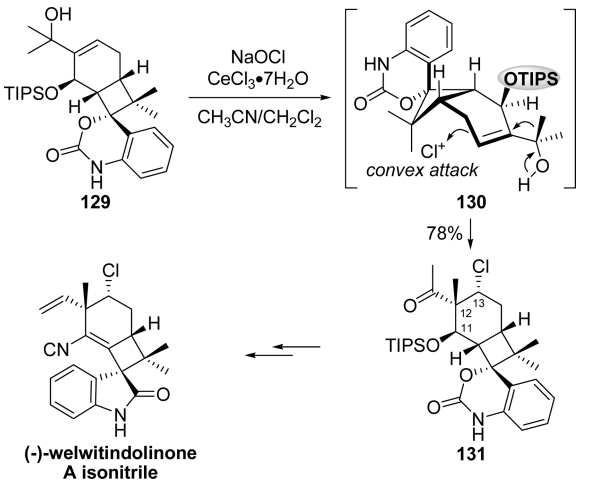



(dr) = 3:2) was treated with NBS in $CH_2Cl_2$, 1,2-aryl migration readily occurred and generated the key β-bromo aldehyde **134** in 95% yield. Because only one diastereomer of **134** was obtained, the reaction exhibited a diastereoselective amplification effect. Applying the DBU-mediated desilyation/cyclization protocol to **134** yielded the benzofuran core **135**, which was eventually converted into (±)-lycoramine and (±)-galanthamine.

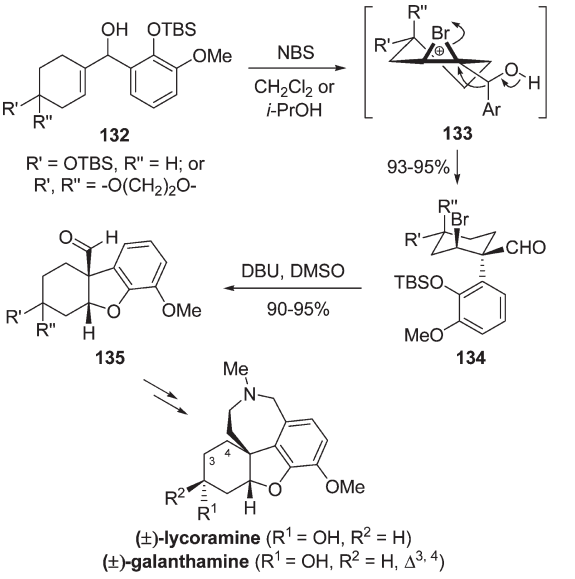
Using the rearrangement as a key step, Tu and co-workers also completed the syntheses of crinine-type *Amaryllidaceae* alkaloids (Scheme 37),[50] which have an aryl-substituted quaternary carbon center structurally related to that of galanthamine-type alkaloids. Treatment of allylic alcohol **136** with NBS in $CH_3CN$ transformed it into β-bromo aldehyde **137** in 95% yield with high diastereoselectivity. Subsequent cyanation and elimination of bromide generated **139**, which underwent an intramolecular Michael addition to yield the common core **140**. From this pivotal intermediate, divergent syntheses of (±)-tazettine, (±)-hemeanthidine, (±)-pretazettine, and (±)-crinamine have been achieved.

Tu and co-workers also developed an NBS-induced semipinacol/Wagner−Meerwein rearrangement sequence to construct the 6,7,7-membered ring skeleton of colchicine (Scheme 38).[51] Treatment of allylic alcohol **141** with NBS in $CH_3CN$ gave the first expansion from a 5- to 6-membered ring, yielding the spiro β-bromo ketone **142** in 65% yield. Next, $AgBF_4$-promoted Wagner−Meerwein rearrangement of **142** led to the second expansion from a 6- to 7-membered ring, forming the unsaturated

**Scheme 35. Wood's Total Synthesis of (−)-Welwitindolinone A Isonitrile**




**Scheme 36. Tu's Total Syntheses of (±)-Lycoramine and (±)-Galanthamine**




ketone **143**. This is the key intermediate in Nakamura's synthesis of colchicine.

In Dake et al.'s studies toward the synthesis of halichlorine (Scheme 39),[52] an NBS-induced semipinacol rearrangement of the enesulfonamide-derived allylic alcohol **144** was used to construct aza-spirocyclic core **146** in 87% yield. The ring expansion proceeded via the exclusive 1,2-migration of the more substituted alkyl group, with retention of stereochemistry at the migrating center. Because the core of **146** is shared by halichlorine, pinnaic acid, and tauropinnaic acid, this approach may be useful for synthesizing these natural products.

### 3.2. Induced by Selenium Ion

Selenium ion has similar electrophilicity as halonium ions, and it can induce the semipinacol rearrangement of allylic alcohols.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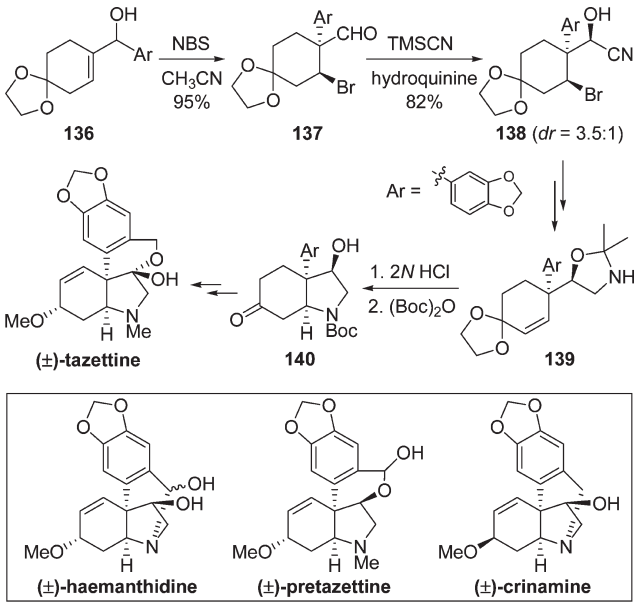
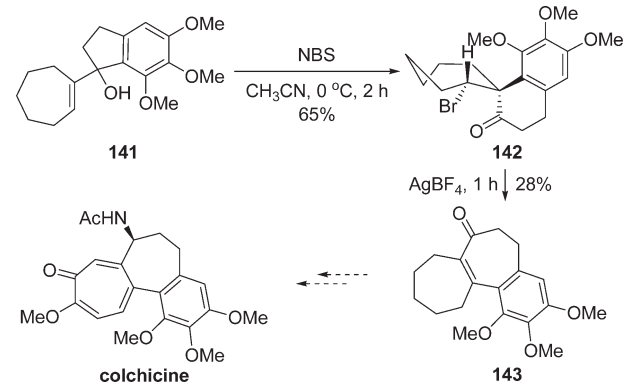
**Scheme 37. Tu's Total Syntheses of (±)-Tazettine, (±)-Haemanthidine, (±)-Pretazettine, and (±)-Crinamine**




**Scheme 38. Tu's Synthetic Studies toward Colchicine**

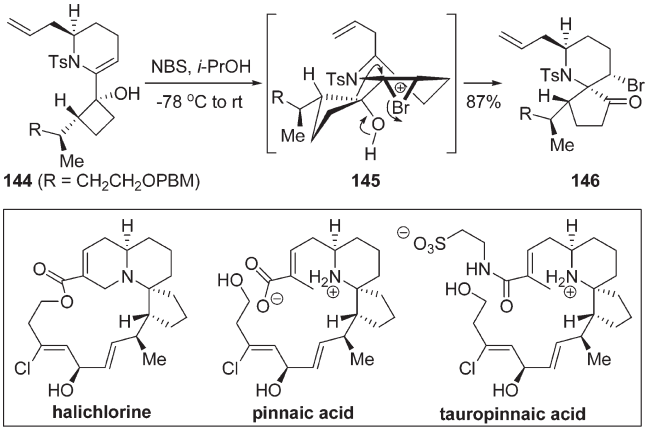



Trost and co-workers reported a selenium-initiated substitutive spiro annulation approach in their total synthesis of plumericin and allamandin (Scheme 40).[53] Electrophilic addition of PhSeBr from the less-hindered convex face of vinylcyclopropanol **147** initiated a highly diastereoselective ring expansion, affording the spirotricyclic cyclobutanone **149** in 88% yield. The subsequent Baeyer–Villiger reaction eliminated the PhSe group and generated lactone **150** in good yield. As a key intermediate, **150** was subsequently transformed into plumericin and then into allamandin.

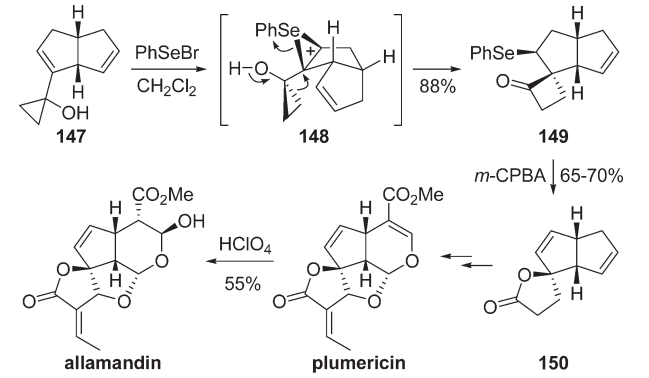
### 3.3. Induced by Brønsted Acids

Paquette and co-workers developed a series of Brønsted acid-induced semipinacol rearrangements of vinyl ether-derived tertiary allylic alcohols.[54] Using this reaction as a key step, several terpenoids containing an oxa-spirocyclic ring have been synthesized. For example, in the syntheses of (+)-dactyloxene B and C (Scheme 41),[55] **151** was first transformed under acidic conditions into the oxonium intermediate **152**, which underwent the

**Scheme 39. Dake's Synthetic Studies toward Halichlorine**




**Scheme 40. Trost's Total Syntheses of Plumericin and Allamandin**




slightly predominant 1,2-migration of the more substituted alkyl group to give two diastereofacial isomers **153** and **154** in 44% and 18% yield, respectively. The method has also been used to synthesize (−)-grindelic acid and theaspirones.

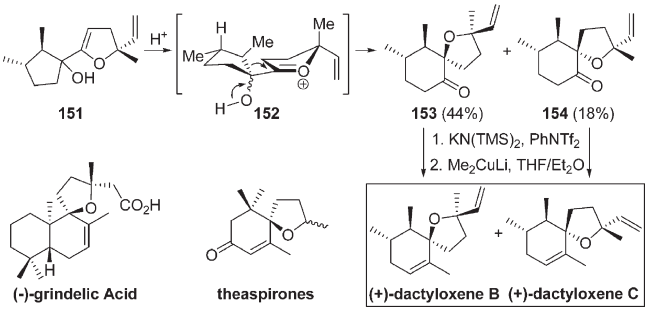
Royer and co-workers' synthesis of (−)-cephalotaxine used a semipinacol rearrangement of the α,β-unsaturated γ-lactam-derived homoallylic alcohol **155** to provide enantiomerically pure 1-aza-spiro ketone **157** (Scheme 42).[56] Treating **155** with HCl transformed it into the proposed α-hydroxy iminium ion **156**, which then underwent ring expansion to give **157** in 86% yield with notable diastereoselective amplification, with the diasteremeric excess (de) value increasing from 4% to 80%.

Piras and co-workers investigated the Brønsted acid-induced semipinacol rearrangement of a range of isopropenyl cyclobutanols **160** (Scheme 43).[57] Treatment of **160** with pyridinium *p*-toluenesulfonate (PPTS) in benzene caused selective 1,2-migration of the more-substituted alkyl group, giving the ring-expansion product **161** in good to excellent yield. The resulting cyclopentanones, which possess two adjacent quaternary carbon centers, have been used as crucial intermediates in the syntheses of cuparene-type sesquiterpenes.

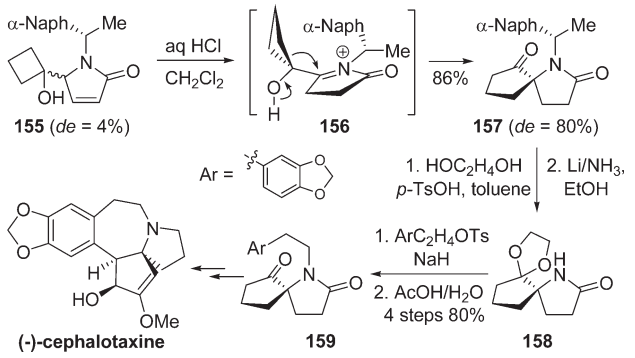
Using the $TpMo(CO)_2$(5-oxo-$\eta^3$-pyridinyl) complex as an enantiomeric scaffold, Liebeskind and co-workers completed a novel asymmetric synthesis of (−)-adaline (Scheme 44).[58] One of the key steps involved an HCl-induced semipinacol


dx.doi.org/10.1021/cr200055g |*Chem. Rev.* 2011, 111, 7523–7556

**Scheme 41. Paquette's Total Syntheses of (+)-Dactyloxene B and C**




**Scheme 42. Royer's Total Synthesis of (−)-Cephalotaxine**



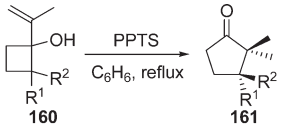

rearrangement of molybdenum $\pi$-complex **168**, which has an allylic alcohol moiety. Treating **168** with HCl caused a stereospecific 1,2-allyl migration, leading to the formation of the chiral α-quaternary pyridine **169** in 78% yield. Subsequent Wacker oxidation, Michael-like 1,5-addition, and removal of TpMo(CO)$_2$ with NOPF$_6$ furnished the key bicyclic enone **172** in 74% overall yield.

### 3.4. Induced by Lewis Acids

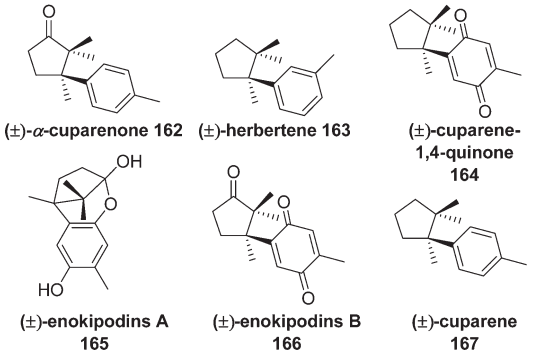
Lewis acids such as $BF_3 \cdot OEt_2$,[59] $Hg(OCOCF_3)_2$,[60] and Pd(II) catalysts have been used to induce the semipinacol rearrangement of allylic alcohols by activating the C=C bond. For example, Nemoto, Fukumoto, and co-workers developed a useful Pd(II)-promoted ring expansion of various chiral vinylcyclobutanols to generate cyclopentanones containing a chiral quaternary carbon center.[61] By combining this process with a strategy for preparing chiral cyclobutanones that they also developed, this group has synthesized several terpenes. For example, in the synthesis of (−)-aplysin (Scheme 45),[62] vinylcyclobutanol **174**, prepared from **173** by the addition of Grignard agent and protection, underwent Pd(OAc)$_2$-promoted ring expansion to give the key intermediate **175** in 89% yield.

Nemoto, Ihara, and co-workers described a tandem Pd(II)-promoted ring-expansion/intramolecular-insertion process to synthesize (+)-equilenin (Scheme 46).[63] The reaction was initiated by coordination of the isopropenyl group in **176** to the Pd(II) complex. This was followed by cyclobutane ring expansion, olefin insertion, and elimination of palladium to give **179** with the desired steroidal framework in 60% yield, predominantly as the trans-diastereoisomer. Solvents proved to be a

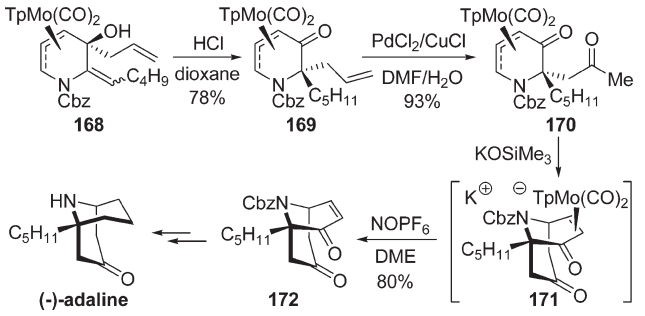
**Scheme 43. Piras' Total Syntheses of (±)-α-Cuparenone and Its Analogues**




| entry | $R^1$ | $R^2$ | yield | natural product |
|---|---|---|---|---|
| 1 | Me | -$C_6H_4$-4-Me- | 76% | **162** |
| 2 | Me | -$C_6H_4$-3-Me- | 70% | **163** |
| 3 | Me | -$C_6H_2$-2-OMe-4-Me-5-OMe | 91-94% | **164, 165, 166** |
| 4 | Me | -$C_6H_2$-2-OMe-4-Me | 91-94% | **167** |




**Scheme 44. Liebeskind's Total Synthesis of (−)-Adaline**




key factor in stereochemical control, because carrying out the reaction in a nonpolar solvent such as toluene gave predominantly the cis-product **180**. The authors suggested that the selectivity depends on the conformation of the isopropenyl group during the reaction. According to this reasoning, in the presence of nonpolar solvent, the ring expansion probably proceeded via the intermediate **177-TSB**, in which the palladium was proposed to be associated with both the olefin and the hydroxyl group. In contrast, the reaction in hexamethylphosphoric triamide (HMPA) probably occurred via **177-TSA**, in which the palladium was associated only with the olefin because it had already coordinated with HMPA, giving the trans-diastereomer **179** as the product.

Toste and co-workers completed the synthesis of (±)-ventricosene using sequential ring expansions catalyzed by Au(I) and Pd(II) (Scheme 47).[64] The enyne **181** was first treated with $Ph_3PAuCl$ and $AgBF_4$ to induce cycloisomerization and generate the cyclopropylmethyl cation **182**, which then underwent ring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expansion to provide the fused cyclobutanone **183** as a single diastereoisomer in 87% yield. Similar to Nemoto's procedure, the second Pd(II)-catalyzed semipinacol ring expansion of the allylic methyl ether **184** was carried out to give **185**, which contains the complete tricyclic skeleton of (±)-ventricosene, in 70% yield.

Liebeskind and co-workers discovered that alkynyl cyclobutanol can also efficiently undergo Pd(II)-catalyzed semipinacol rearrangement. In their synthesis of benzoabikoviromycin (Scheme 48),[65] treatment of **186** with $Pd(OCOCF_3)_2$ in $CH_2Cl_2$ facilitated a stereospecific ring expansion via selective 1,2-migration of the ketal group to give the vinylpalladium intermediate **187**, which was then protonated to give the monoketal **188** in 75% yield with the desired geometry containing an exo-cyclic double bond. The selectivity of the migration was attributed to the formation of the more stable benzylic cationic intermediate.

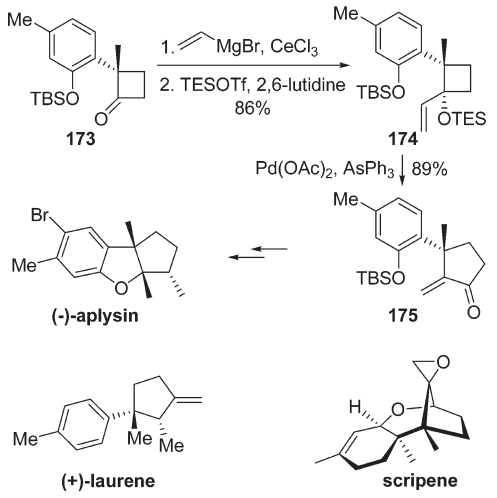
### 3.5. Prins-Pinacol Rearrangement

The Prins-pinacol rearrangement involves a final Prins reaction followed in tandem by a pinacol-like (or semipinacol) rearrangement. It proceeds via electrophilic addition of various carbeniums to the C═C bond of allylic alcohols, resulting in the formation of a cationic center, which then induces successive 1,2-migrations to generate carbonyl groups sequentially. Overman's group has developed an outstanding array of chemistries for performing various types of reactions, and they has demonstrated their power by rapidly constructing complex cyclic natural products. Because his group has already published three reviews on this topic,[5] only advances since 2003 will be discussed in this section.

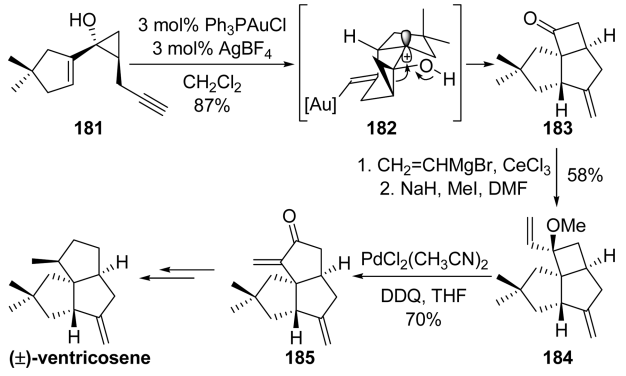
Recently, Cha and co-workers used an intermolecular Prins-pinacol rearrangement as a key step in the total syntheses of cyathin $A_3$ and cyathin $B_2$ (Scheme 49).[66] Cyclopropanol silyl ether **190**, prepared from dienoate **189** via Kulinkovich cyclopropanation and silylation, reacted with acetal **191** in the presence of $TiCl_4$ to afford spiro cyclobutanone **194** as the major product in 78% yield. As expected, the two new C−C bonds in **192** and **193** formed from the opposite side of the angular methyl group. The authors proposed that the preferential cis-1,2-migration during ring expansion might be due in part to the minimization of torsional strain, because trans-addition would go through a transition state in which the newly introduced side chain and the C−C═O bond were fully eclipsed. As a key quaternary carbon scaffold, **194** was then transformed into the core structure **197** with the requisite trans-6/7-ring junction.

Min, Cho, and co-workers developed a Prins-pinacol rearrangement of alkene diols **198** using a range of aldehydes and ketones (Scheme 50).[67] The reaction began with the

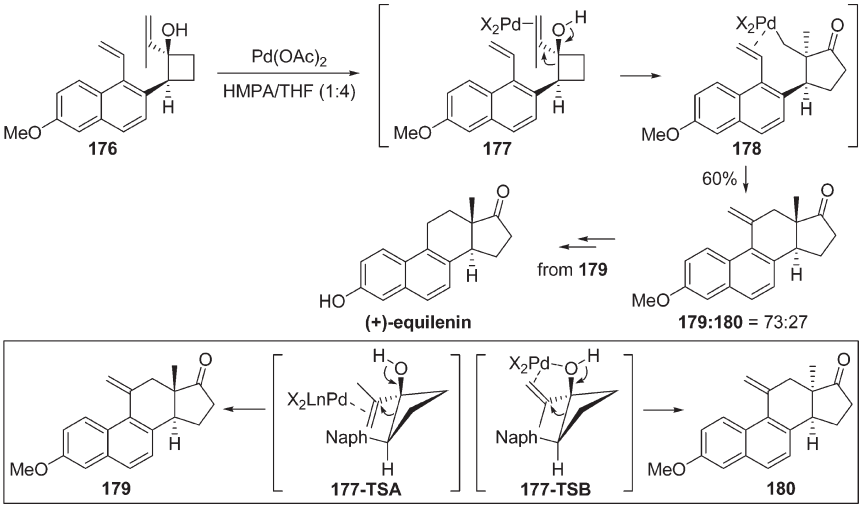
**Scheme 45. Nemoto and Fukumoto's Total Synthesis of (−)-Aplysin**




**Scheme 47. Toste's Total Synthesis of (±)-Ventricosene**




**Scheme 46. Nemoto and Ihara's Asymmetric Total Synthesis of (+)-Equilenin**





dx.doi.org/10.1021/cr200055g |Chem. Rev. 2011, 111, 7523–7556

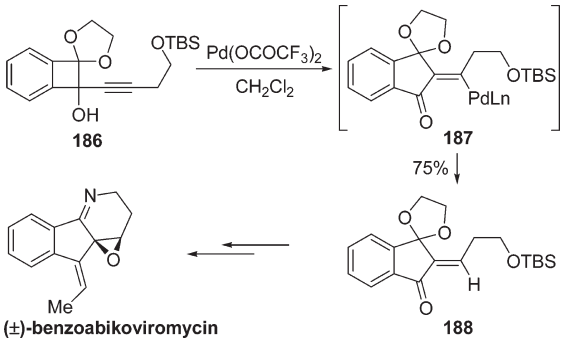
TMSOTf-catalyzed condensation of the primary hydroxyl group of **198** with an aldehyde to generate the oxocarbenium intermediate **199**, which underwent Prins cyclization followed by stereospecific ring contraction of the carbocation **201** to give ketone **202** in 80−90% yield. These spirooxacyclic compounds are attractive targets because they occur in the skeletons of several natural products, such as bakkenolide A, wiphaphysalin F, and epansolide A.

On the basis of a TfOH-promoted Prins-pinacol rearrangement, Elliott and co-workers developed an interesting desymmetrization of cyclohexa-1,4-diene-derived aldehydes (Scheme 51).[68] Treating **203** with TfOH in $CH_2Cl_2$ produced a tricyclic aldehyde **207** with the same stereochemistry as the core of 7-deacetoxyalcyonin acetate, albeit with a meager yield of 32%. Notably, the bisbridged carbocation **205** formed by Prins cyclization underwent successive 1,2-migrations of C−C and C−H bonds to give the unsaturated aldehyde **207** after the C=C bond shift.

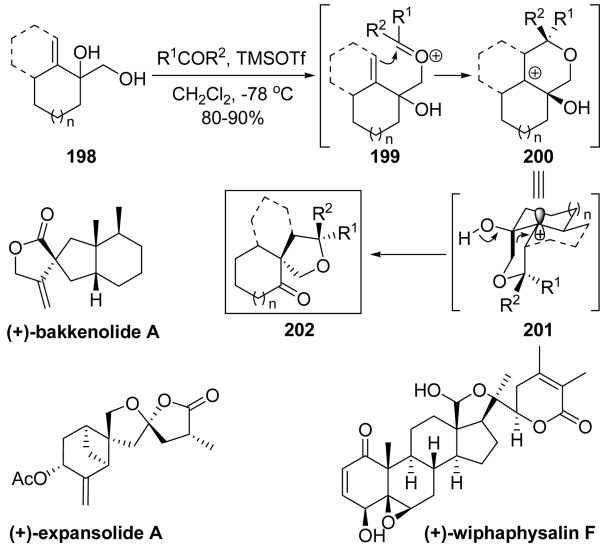
As part of efforts to synthesize isoindolone alkaloid aspergillin PZ, Overman and Velthuisen developed an efficient Prins-pinacol rearrangement to generate either stereoisomer of the 12-oxatricyclo-[6.3.1.0]-dodecane ring system.[69] The key to this stereoselectivity lies in tuning the substrate structure to control the stereochemistry of the transition state between the chair and boat conformations during the Prins cyclization. As shown in Scheme 52, treatment of **208** with $SnCl_4$ in $CH_2Cl_2$ generated oxacarbenium **209** featuring a chair conformation in which the two 6-membered rings adopt a cofacial orientation. The subsequent Prins cyclization gave carbocation **210**, which underwent 1,2-migrations of C−C and C−H bonds to provide **212** and **213** in a 1.6:1 mixture. Compound **213** has the same stereochemistry as 1,5-epoxysalvial-4(14)-ene, which shares the core of salvialane-type sesquiterpenes. Conversely, when a 1,3-dithiane was incorporated adjacent to the acetal in **214**, a boat topography **215** became favorable, leading to the carbocation intermediate **216**. This is because the chair conformation would have caused steric hindrance between the cofacial 6-membered rings. This semipinacol rearrangement afforded **218** in 81% yield with the same trans-stereochemistry as aspergillin PZ.

The synthetically challenging bicycle-[*m.n.*1]-alkanone cores with a quaternary carbon center adjacent to a bridged ketone are embedded in various complex natural products, such as garsubellin A, penostatin F, and ingenol. Barriault and co-workers efficiently constructed these molecules by designing an elaborate Prins-pinacol rearrangement of ketals **219** (Scheme 53).[70] In this

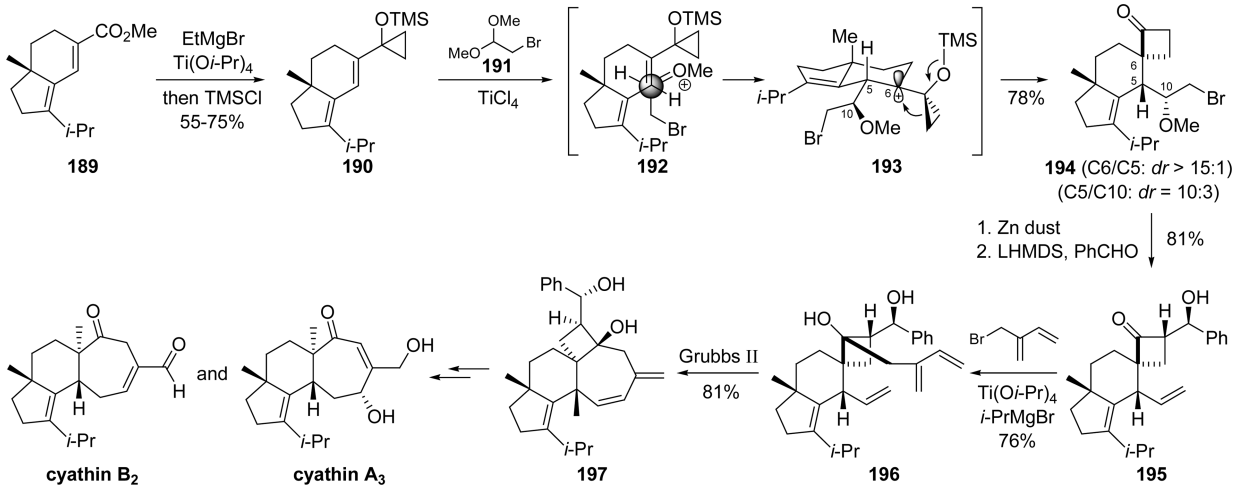
**Scheme 48. Liebeskind's Total Synthesis of (±)-Benzoabikoviromycin**




**Scheme 50. Min and Cho's Stereocontrolled Synthesis of Spiro Oxabicycles via Prins-Pinacol Annulation**



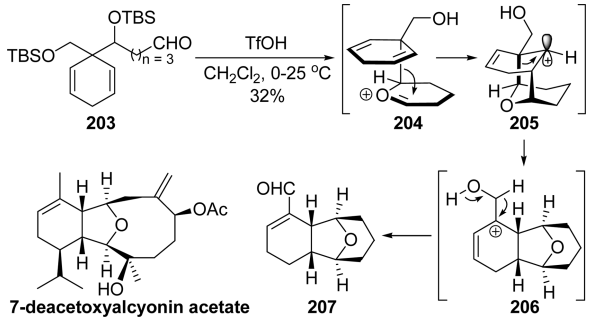

**Scheme 49. Cha's Total Syntheses of Cyathin $A_3$ and Cyathin $B_2$**



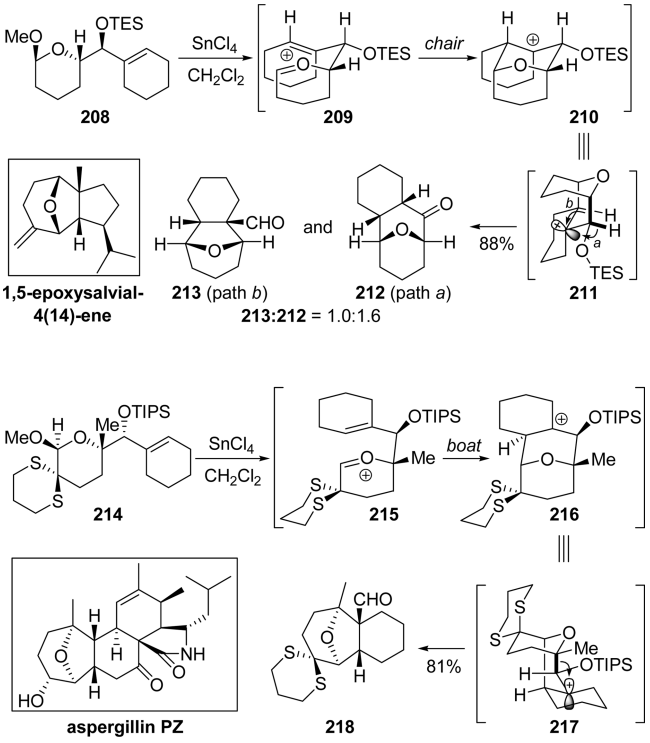


dx.doi.org/10.1021/cr200055g |*Chem. Rev.* 2011, 111, 7523–7556

**Scheme 51. Elliott's Prins-Pinacol Desymmetrization of Cyclohexa-1,4-dienes**




**Scheme 52. Overman's Stereocontrolled Construction of Either Stereoisomer of 12-Oxatricyclo-[6.3.1.0]-dodecanes**




process, the key oxacarbenium **220** was generated by Lewis acid-promoted ketal ring-opening. After transformation of **219** to carbocation **221** via Prins cyclization, the antiperiplanar 1,2-migration of the C1−C2 bond to the C10 cationic center afforded the desired bicyclic ketone **222**. This process was combined with a Diels−Alder reaction to generate the greater molecular complexity in a single step. The Diels−Alder reaction of diene **223** and Gassman-type dienophiles generated the endo-cycloadducts **224** in situ, which underwent Prins-pinacol rearrangement to give ketone **225** in medium to excellent yields.

Epibatidine, isolated from the skin of the Ecuadorian poison frog *Epipedobates tricolor*, has a substituted 7-azabicyclo-[2.2.1]-heptane skeleton and acts as a powerful analgesic. Armstrong and co-workers developed a concise approach to this molecule based on an aza-Prins-pinacol rearrangement (Scheme 54).[71] In the reaction, *N*-acyliminium ion **227** initiated the process by giving the exo-aldehyde **229** in 32% yield as a single stereoisomer. As the key intermediate, **229** was then converted into (±)-epibatidine and (±)-epiboxidine by further transformations.

## 4. REARRANGEMENT OF EPOXIDES

Acid-promoted semipinacol rearrangement of epoxides via 1,2-migration induced by an oxirane ring-opening has shown wide utilities in natural product syntheses. In this section, we will focus on the versatile applications of the rearrangement of 2,3-epoxy alcohols and their derivatives. In addition, we will discuss some applications of the rearrangement of other epoxide derivatives, such as 2,3-epoxy ketones and simple epoxides.

### 4.1. 2,3-Epoxy Alcohols and the Derivatives

Since Cheer and Johnson's seminal work in 1968,[72] the semipinacol rearrangement of 2,3-epoxy alcohols and their derivatives has been extensively investigated in both cyclic and acyclic systems.[7] The following advantages make this process extremely useful in natural product syntheses. First, a variety of Lewis acids can affect the rearrangement when used in either a stoichiometric or a catalytic amount. Second, since the migrating group generally attacks anti to the epoxide, the process can be executed with excellent stereochemical control, and the stereochemistry at the migrating carbon can be rigorously retained in most cases. Third, the reaction can generate various aldol-type products diastereoselectively, and even enantioselectively if enantiopure 2,3-epoxy alcohols are used as substrates, which are readily prepared via Sharpless asymmetric epoxidation (SAE). Most of these products, which contain a stereogenic quaternary carbon center at the migration terminus, are difficult or impossible to obtain by the classical aldol reaction. Fourth, the resulting carbonyl group can serve as a reactive site to support tandem reactions. Examples discussed in this section are organized according to the type III migration illustrated in Scheme 6.

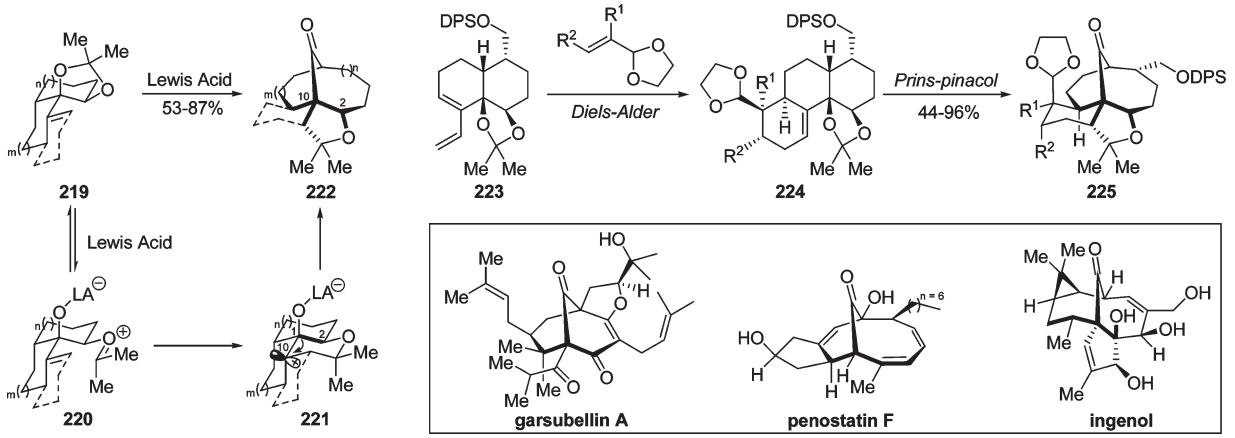
**4.1.1. 1,2-Migration.** Of the three types of semipinacol rearrangements in 2,3-epoxy alcohols, the one occurring via 1,2-migration finds the most diverse uses in natural product syntheses. This reaction can occur at different stages of the synthesis and provides various acyclic or cyclic key intermediates.

Danishefsky and co-workers completed the total synthesis of (−)-peribysin E using a semipinacol ring contraction of triethylsilyl (TES)-protected 2,3-epoxy alcohol **233** to construct the B-ring. With $TiCl_4$ as the Lewis acid, the expected aldehyde **235** was obtained in 50% yield with the requisite stereochemistry at the C7 quaternary carbon center (Scheme 55).[73] Interestingly, reaction of a non-TES-protected diol with a range of Lewis acids led only to the recovery of the starting material and the decomposed products. The authors attributed this to the incompatibility between the hydroxyl group and the Lewis acid. HCl-mediated cyclization of **235** afforded the C-ring and provided (−)-peribysin E. The naturally occurring (+)-peribysin E has also been obtained by the same route using (*R*)-carvone as the starting material.

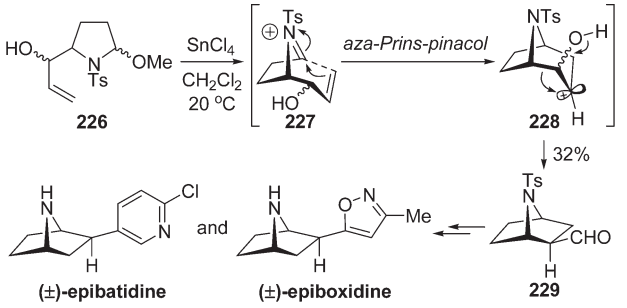
Ingenol, a prototypical diterpene of ingenanes, has been the subject of numerous studies because of its novel structure featuring a highly strained "inside−outside" trans-intrabridgehead stereochemistry in the BC ring system. Tanino, Kuwajima, and co-workers synthesized this natural product using an elegant strategy based on the semipinacol rearrangement of 2,3-epoxy alcohol (Scheme 56).[74] Treatment of **237** with $AlMe_3$ led to a


dx.doi.org/10.1021/cr200055g |*Chem. Rev.* 2011, 111, 7523–7556

**Scheme 53. Barriault's Synthesis of Highly Functionalized Bicycle-[*m.n.*1]-alkanones via the Prins-Pinacol Reaction**




**Scheme 54. Armstrong's Total Syntheses of (±)-Epibatidine and (±)-Epiboxidine**




facile, stereospecific 1,2-migration to give β-hydroxy ketone **239** in 76% overall yield. Compound **239** has the complete ABCD ring system of ingenol as well as the requisite stereochemistry at the C10 quaternary center.

Cha and co-workers used a similar strategy, but with a quite different ring system, in their synthesis of ingenol (Scheme 57).[75] In this case as well, the semipinacol rearrangement of 2,3-epoxy alcohol **241** at the late stage allowed rapid, efficient assembly of the carbocyclic core **243** in 82% yield. The stereochemistry of C4 in **241** was suggested to be crucial to ensure the desired 1,2-migration of the C9−C11 bond. According to the molecular model of **241**, the C10−O bond is antiperiplanar to the C9−C11 bond, which satisfies the stereoelectronic requirements perfectly, whereas the C8−C9 bond is nearly orthogonal, as shown in **242**.

In the synthesis of (+)-maaliol (Scheme 58), Wijnberg, de Groot, and co-workers used a semipinacol rearrangement of cis-2,3-epoxy silyl ether **244** to transform a 5,7-membered ring system to a 6,6-membered one.[76] Treatment of **244** with $TiCl_4$ in $CH_2C1_2$ at −78 °C generated β-hydroxy ketone **245** in 94% yield. Ketone **245** has a trans-fused 6,6-membered ring skeleton and the desired angular hydroxymethyl group at the C7 quaternary center.

Over the past decade, Tu and co-workers have developed a set of semipinacol rearrangements of 2,3-epoxy alcohols.[77] For example, a tandem semipinacol/Schmidt reaction of 1-siloxy 2,3-epoxy azides has been established[77h] for the rapid construction of aza-quaternary alkaloids such as stemonamine (Scheme 59).[78] Treating **246** with $TiCl_4$ in $CH_2Cl_2$ at −78 to 0 °C transformed it into bicyclic lactam **249** as a single isomer in 68% yield. Successive, stereospecific 1,2-migrations, as shown in the chelate transition states **247** and **248**, ensured formation of the desired ring skeleton. Subsequent pyridinium chlorochromate (PCC) oxidation, ozonolysis, and aldol reaction generated the tricyclic lactam **250**, which was then converted into (±)-stemonamine.

Tu's group used a similar strategy to synthesize (±)-cephalotaxine (Scheme 60).[79] Dropwise addition of 1-siloxy 2,3-epoxy azide **251** to $TiCl_4$ gave the rearranged product β-hydroxy ketone **252** in 80% yield. While **252** failed to undergo subsequent *N*-insertion, the Schmidt reaction of the corresponding diketone proceeded smoothly and produced the key lactam **253** in 66% overall yield.

Dake and co-workers completed a formal synthesis of fasicularin using a semipinacol rearrangement of enamide-derived 2,3-epoxy silyl ether **254** to build the critical aza-spirocyclic skeleton (Scheme 61).[80] Treatment of **254** with $TiCl_4$ led to the desired ring-expanded product **255** in 96% yield with clean stereochemical control of the quaternary carbon center formed at the B,C-ring junction. Subsequent transformations, including mesylation, elimination, and enolation, yielded vinyl triflate **257**, which underwent Suzuki coupling with **258** and then an intramolecular $S_N2$ reaction to furnish fasicularin.

Suzuki and co-workers have shown that the acyclic 2,3-epoxy silyl ether containing a Co-complexed alkynyl group can also undergo a semipinacol rearrangement to introduce the quaternary carbon center stereoselectively.[81] As shown in their syntheses of furaquinocin-type antibiotics (Scheme 62),[82] treatment of **260** with $TiCl_4$ and $Et_3SiH$ led to a facile 1,2-migration of the Co-complexed alkynyl group, followed by in situ reduction of the formed aldehyde, giving the 1,3-diol **261** in 89% yield after oxidation. The Co-complexed substrate clearly showed much higher migratory ability in this reaction than did the normal alkynyl group. The Sonogashira reaction with aryl iodide **263** was performed on the *tert*-butyldimethylsilyl (TBS)-protected diol **262** to afford furaquinocins A, B, D, and H.

Tsuchihashi, Suzuki, and co-workers have applied a semipinacol rearrangement/reduction sequence to acyclic 2,3-epoxy alcohols bearing a trimethylsilyl (TMS)-vinyl group at C1 (Scheme 63).[83] Two effects of the TMS group were noted. First, the TMS-vinyl group showed a rate-enhancement effect relative to a simple vinyl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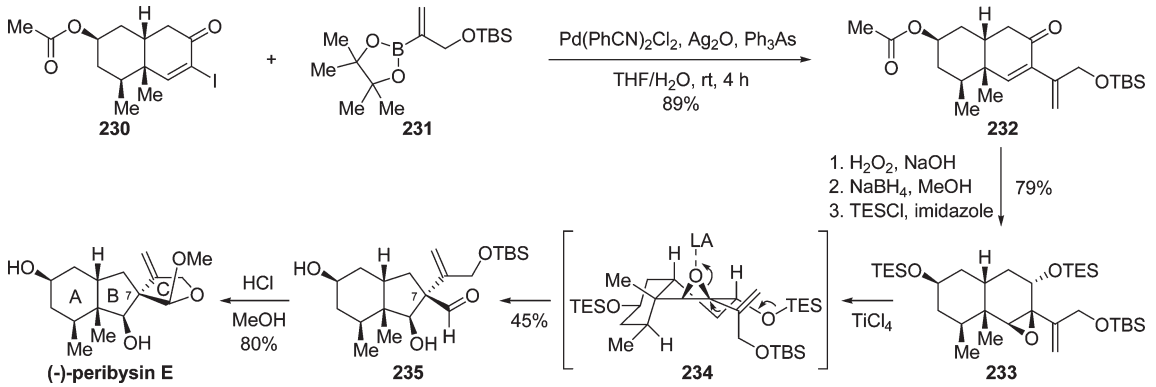
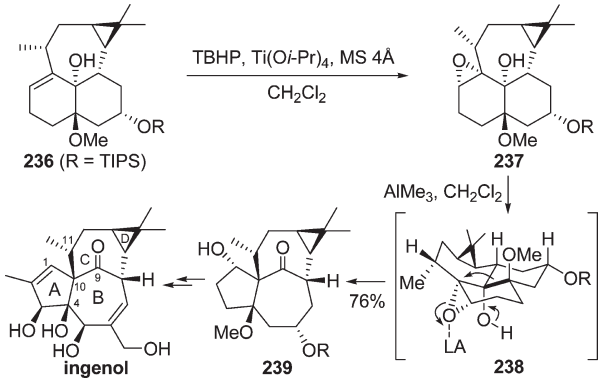
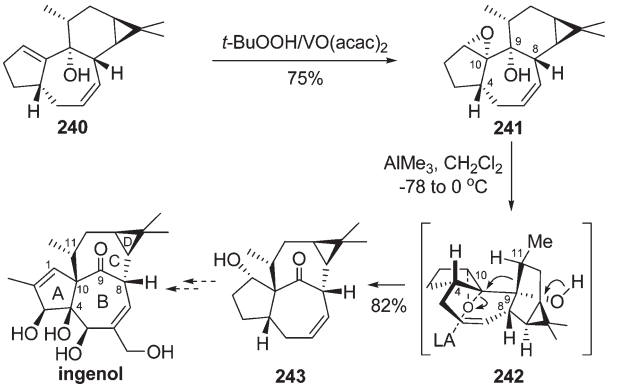
**Scheme 55. Danishefsky's Total Synthesis of (−)-Peribysin E**




**Scheme 56. Tanino and Kuwajima's Total Synthesis of Ingenol**

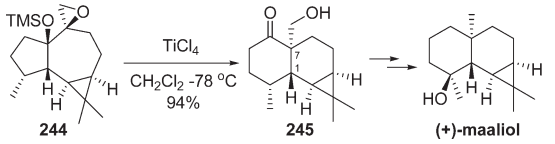



**Scheme 57. Cha's Rapid Access to the "In and Out"-Tetracyclic Core of Ingenol**

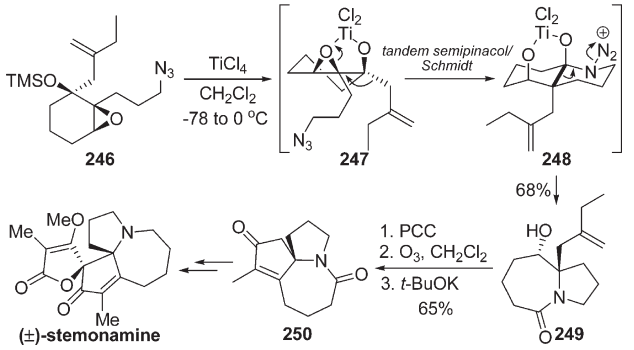



group because of its higher migratory ability. Second, the TMS group exerted a strong 1,2-stereodirecting effect, such that reduction of the resulting aldol (**269** to **270**) gave 1,3-anti-diol as a single isomer. In contrast, the simple vinyl substituted system in **266** showed a 1,3-effect, leading to 1,3-syn-diol **267** as the predominant product. On the basis of this methodology,

**Scheme 58. Wijnberg and de Groot's Total Synthesis of (+)-Maaliol**




**Scheme 59. Tu's Total Synthesis of (±)-Stemonamine**




avenaciolide and isoavenaciolide were synthesized from the 2,3-epoxy alcohol analogues **265** and **268**, respectively.[84]

Jung and co-workers developed a useful "nonaldol aldol" process based on the semipinacol rearrangement of acyclic 2,3-epoxy silyl ethers.[85] The rearrangement features an unusual 1,2-migration of a C−H bond and provides the pivotal aldehyde aldol products with excellent diastereoselectivity in good yields. Jung's research group prepared the C1−C11 subunit of tedanolides by performing successive rounds of this process, as shown in the transformations from **271** to **272** and from **273** to **274** (Scheme 64).[86]

Using such a process at an early stage, Jung and co-workers recently completed the total synthesis of auripyrone A (Scheme 65).[87] The 2,3-epoxy silyl ether **275** was transformed into the aldehyde **276** in 86% yield with 20:1 diastereoselectivity. This aldehyde contains the requisite syn, anti-stereochemistry from C10 to C12, which is crucial for the construction of other stereocenters around the spiroketal core.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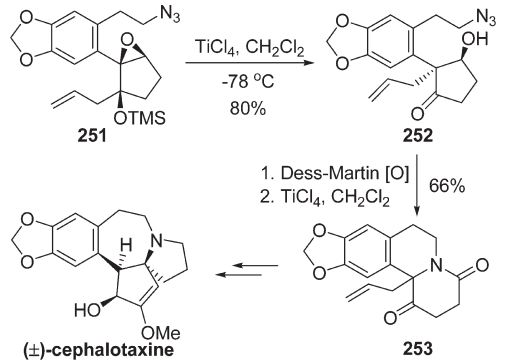
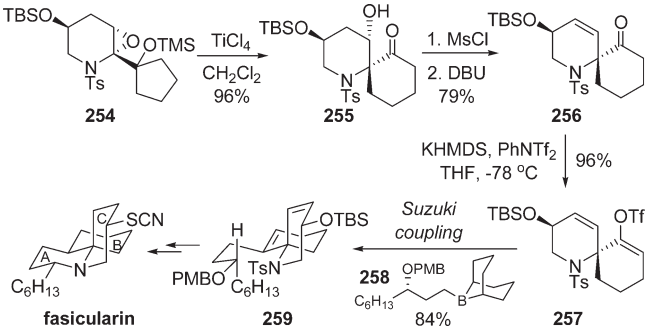
**Scheme 60. Tu's Formal Total Synthesis of (±)-Cephalotaxine**




**Scheme 61. Dake's Formal Total Synthesis of Fasicularin**

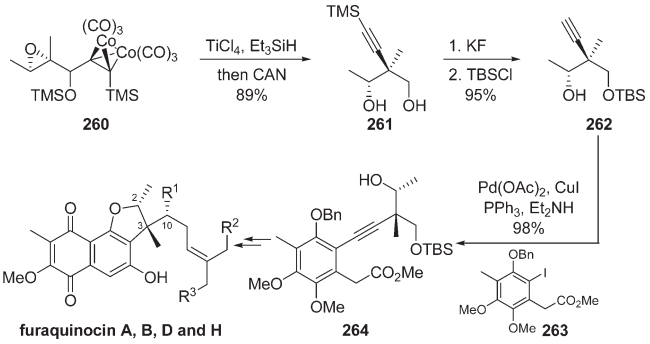



Using Jung's nonaldol aldol process as one of the key steps, Sammakia and co-workers achieved the total synthesis of the oxopolyene macrolide RK-397 (Scheme 66).[88] Rearrangement of **278** gave the aldehyde **279** in 95% yield with 24:1 diastereoselectivity, which possesses the desired C30 and C31 stereocenters in the target.

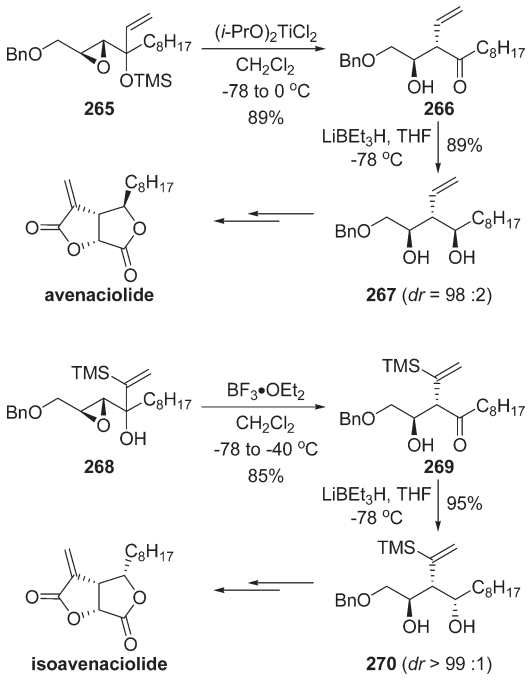
Tu and co-workers discovered that, similar to 2,3-epoxy alcohols, 2,3-aziridino alcohols can also undergo Lewis acid-catalyzed semipinacol rearrangement, giving various α-quaternary, β-amino carbonyl compounds in good yields and with high diastereoselectivity.[89] The group used this reaction as a key step to develop a general approach to the cis-3a-aryloctahydroindole alkaloids (Scheme 67).[90] Treatment of 2,3-aziridino alcohol **282** with $ZnBr_2$ in $CH_2Cl_2$ caused aziridine ring-opening and 1,2-aryl migration to give amino aldehyde **283** as a single stereoisomer in >95% yield. Subsequent aldehyde homologation and cyclization yielded the core structure **284**, which was further transformed to (±)-crinane and (±)-mesembrine.

**4.1.2. 3,2-Migration.** In some cases, 3,2-migration instead of 1,2-migration occurs during the rearrangement. This process has efficient applications in natural product syntheses, although only a few examples have been reported. For example, in Kimura et al.'s asymmetric synthesis of (*S*)-noremopamil (Scheme 68),[91] treatment of chiral 2,3-epoxy silyl ether **285** with **288** [MAD, methyl aluminum bis(4-methyl-2,6-di-*tert*-butylphenoxide)] facilitated the expected 3,2-migration of the isopropyl group to afford aldehyde **286** in 99% yield with diastereoselective generation of the quaternary carbon center.

**Scheme 62. Suzuki's Total Syntheses of Furaquinocins A, B, D, and H**



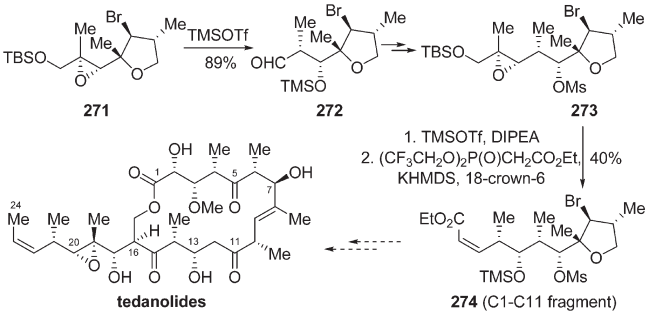

**Scheme 63. Tsuchihashi and Suzuki's Total Syntheses of Avenaciolide and Isoavenaciolide**



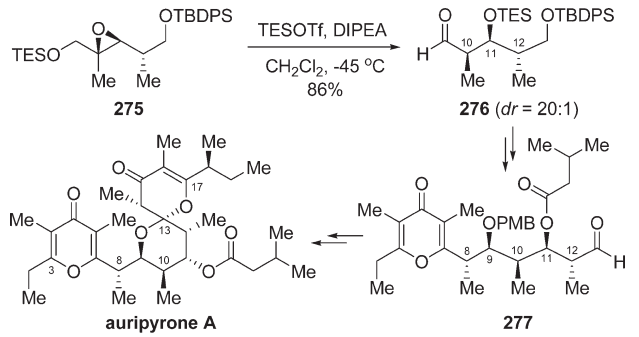

Kita and co-workers' model study of the total synthesis of fredericamycin A revealed an interesting migration selectivity of trans- and cis-benzofused epoxyacylate **289** and **292** during semipinacol rearrangement (Scheme 69).[92] Under the same conditions, whereas the trans-isomer **289** was converted to the desired spirocyclic product **291** via a 3,2-migration of a C−C bond, the cis-isomer **292** underwent a 1,2-migration of the C−H bond adjacent to the benzoyl group, giving enone **294** as a single product. The authors explained this by suggesting that both isomers **289** and **292** underwent regioselective epoxide opening to give the more stable benzylic carbocations **290** and **293**, respectively. In **290**, the C−C bond in the 6-membered ring is oriented antiperiplanar to the empty vicinyl *p* orbital, leading to 3,2-migration to give the desired spirocyclic **291**. Because such a situation does not exist in **293**, the alternative 1,2-migration of the C−H bond adjacent to the benzoyl group took place, giving


dx.doi.org/10.1021/cr200055g |*Chem. Rev.* 2011, 111, 7523–7556

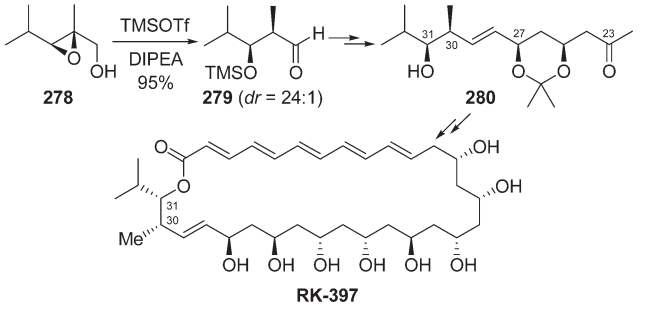
**Scheme 64. Jung's Synthesis of the C1−C11 Subunit of Tedanolides**



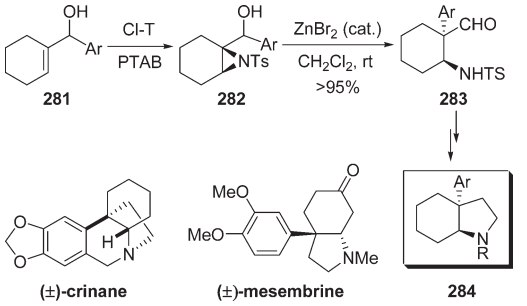

**Scheme 65. Jung's Total Synthesis of Auripyrone A**




**Scheme 66. Sammakia's Total Synthesis of RK-397**




**Scheme 67. Tu's Total Syntheses of (±)-Crinane and (±)-Mesembrine**




the enone **294** as the product. Moreover, the benzoyl group was found to be essential to migration selectivity, since reactions of other trans-substrates (−OSiMe$_2$*t*-Bu and −OMe) led only to enone **294**. The authors proposed that the electron-donating effect of −OSiMe$_2$*t*-Bu or −OMe accelerates the hydride shift rather than the skeletal rearrangement. On the basis of the results of these model studies, rearrangement of the epoxy camphanoate **295** was used to construct the optically pure spiro CDEF-ring core **297**, which was subsequently transformed into fredericamycin A.

Nemoto, Fukumoto, and co-workers applied a tandem, asymmetric epoxidation/ring-expansion process to cyclopropylidene ethonals **298** to prepare cyclobutanones **300** containing a chiral quaternary carbon (Scheme 70).[93] Oxidation of the resulting cyclobutanones provided various chiral lactones **301**, which have been used as key intermediates in the syntheses of (+)-ipomeamarone,[94] (+)-α-bisabolol,[95] and (−)-mesembrine.[96]

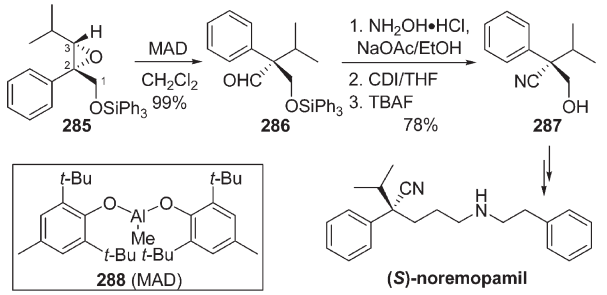
In the synthesis of (−)-mesembrine (Scheme 71), under classical SAE conditions, allylic alcohol **302** containing an *ortho*-TMS group on the phenyl ring was directly converted into cyclobutanone **303** with 92% ee in 65% yield. Interestingly, when **306** was used as the substrate, the reaction gave **307** in a higher yield of 82% but with a lower stereoselectivity of 63% enantiomeric excess (ee). The authors provided the following explanation to account for this remarkable substituent effect. In the reaction of **306**, the preferred transition states are **epoxy-306-TSA** and **epoxy-306-TSB**, in which the formed benzylic carbocation can be stabilized by overlap with the phenyl group. Thus, despite the high reactivity of **306**, epimerization is feasible. In contrast, in the case of the TMS group, because of the expected steric hindrance between TMS and the hydroxyl methyl and cyclopropyl groups, the preferred transition states are predicted to be **epoxy-302-TSA** and **epoxy-302-TSB**. In both, the phenyl group is apparently no longer coplanar with the potential carbocation center. Thus, the lack of such stabilization should reduce reactivity, preventing the epimerization from taking place.

**4.1.3. 2,3-Migration.** In the 1980s, Yamamoto and co-workers described a series of elegant studies on semipinacol rearrangements of 2,3-epoxy silyl ethers.[97] The most representative of these rearrangements is the reaction promoted by a hindered Al-based Lewis acid such as methylaluminum bis(4-bromo-2,6-di-*tert*-butyl phenoxide) (MABR) (Scheme 72). Generally, substrates possess two substituents or a cation-stabilizing group at the C3 position. Selective ring-opening at C3 tends to lead to a site-specific 2,3-migration, producing various enantiopure 2-quaternary aldehyde aldols. The bulky ligand on the catalyst is believed to be crucial for the rearrangement. First, repulsion between the ligand and the siloxy methyl moiety is expected to facilitate the desired alkyl migration. Second, the bulk of the ligand would probably also inhibit the siloxymethyl moiety from interacting with the resulting cation as either a base or a nucleophile. This reaction has been widely used in natural product syntheses, especially during the early stage while preparing the key chiral building blocks on a large scale. For example, both enantiomers of the 2-quaternary aldehyde **310** have been produced by a MABR-promoted semipinacol rearrangement of chiral **308**, prepared from geraniol via SAE. Using **310** as the key precursor, Shishido, Li, and co-workers have synthesized a range of natural products, including (−)-anastrephin,[98] furanoterpene,[99] (+)-kuhistaferone,[100] and (*R*)-bakuchiol.[101]

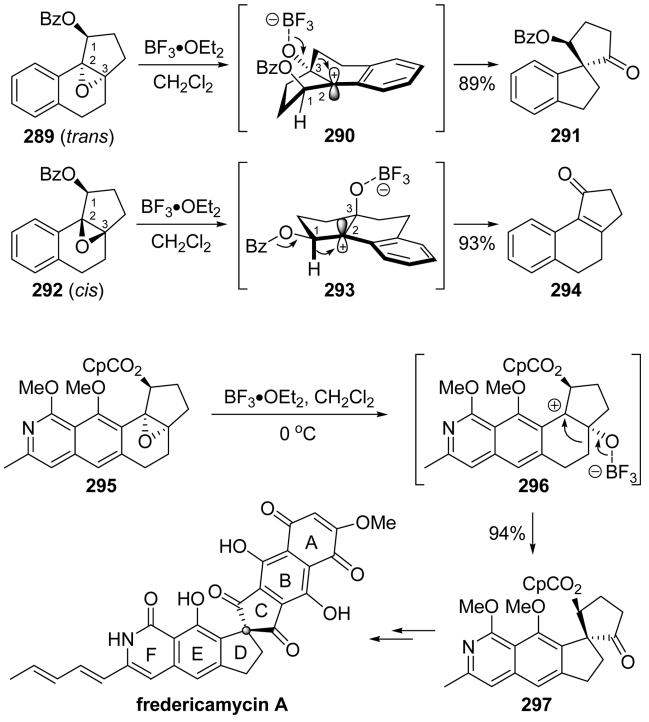
Dake and co-workers reported the synthesis of the epimeric 1,22-dihydroxynitianes using Yamamoto's protocol to establish the key quaternary carbon center at the ring junction (Scheme 73).[102]


dx.doi.org/10.1021/cr200055g |*Chem. Rev.* 2011, 111, 7523–7556

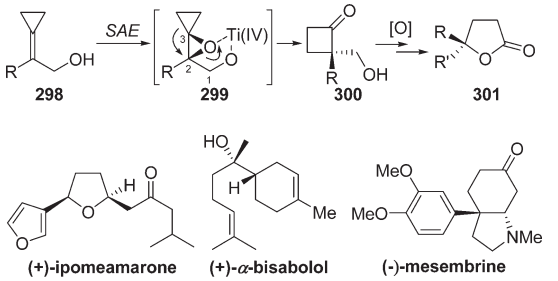
**Scheme 68. Kimura's Total Synthesis of (*S*)-Noremopamil**



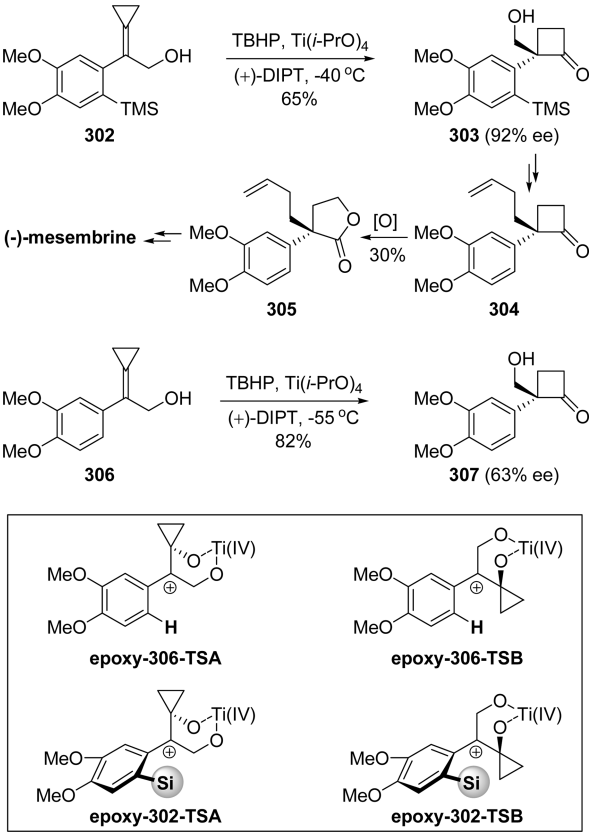

**Scheme 69. Kita's Total Synthesis of Fredericamycin A**




**Scheme 70. Nemoto and Fukumoto's Tandem Asymmetric Epoxidation/Ring-Expansion Process**




**Scheme 71. Nemoto and Fukumoto's Total Synthesis of (−)-Mesembrine**




Treatment of **311** with MABR in $CH_2Cl_2$ generated the aldehyde **312** in 95% yield with 94% ee. Subsequent Pauson–Khand and Norrish I photo reactions then afforded vinylstannane **314** with stereoselective creation of two additional stereocenters controlled by the existing quaternary center in **312**. Stille coupling of **314** with **315** gave the advanced intermediate **316**, which was ultimately converted into the target as a structural hybrid of nitiol.

In Chen and co-workers' recently described total syntheses of nakiterpiosin and nakiterpiosinone (Scheme 74),[103] Yamamoto's protocol was used to convert the 2,3-epoxy silyl ether **317** to chiral aldehyde **318** in 85% yield. From **318**, one of the key components **319** featuring the right side of the target was obtained with the desired introduction of three other stereocenters controlled by the C20 stereocenter in **318**.

Kita and co-workers used a semipinacol rearrangement of 3-aryl-2,3-epoxy acylate **320** in the synthesis of (+)-sporochnol A containing a chiral benzylic quaternary carbon center (Scheme 75).[104]

Treatment of **320** with $Al(OC_6F_5)_3$ led to a regioselective C3-cleavage of the oxirane ring, and the subsequent 2,3-migration of the methyl group provided cyclopentanone **321** in 96% yield. The excellent regioselectivity of the C–O bond cleavage was attributed to the double effect of the electron-withdrawing nature of the acyloxy alkyl group and the stabilizing ability of the electron-rich aryl group. As a key step, the reaction has been used in the syntheses of (−)-aphanorphine, (−)-α-herbertenol, and (−)-herbertenediol.[105]

## 4.2. Simple Epoxides and 2,3-Epoxy Ketones

Srikrishna et al. investigated the semipinacol rearrangement of tetrasubstituted cyclic epoxides. These compounds, which contain one electron-withdrawing substitution, can undergo reliable,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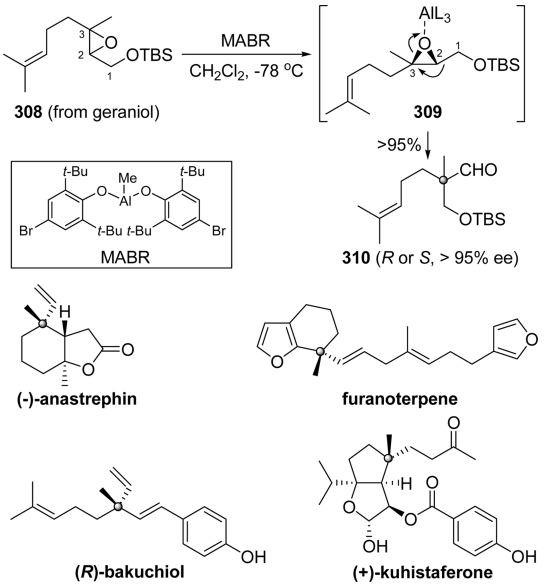
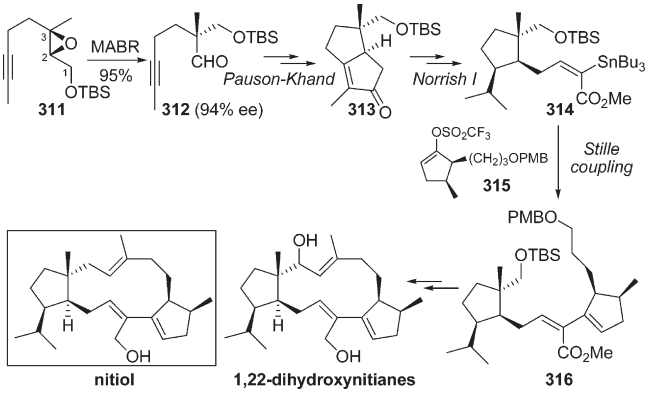
**Scheme 72. Yamamoto's Semipinacol Rearrangements of 2,3-Epoxy Silyl Ethers Promoted by MABR**



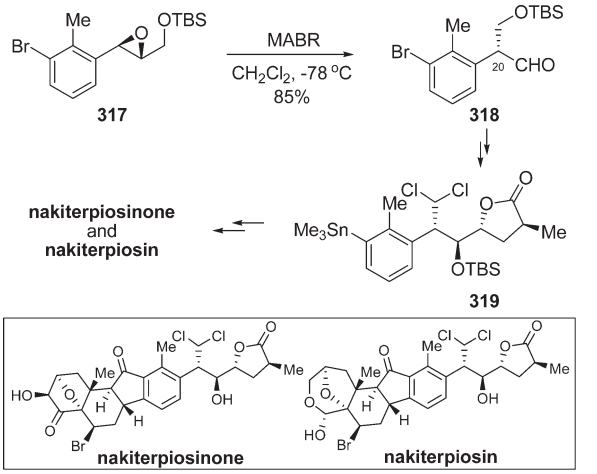

**Scheme 73. Dake's Total Synthesis of 1,22-Dihydroxynitianes**



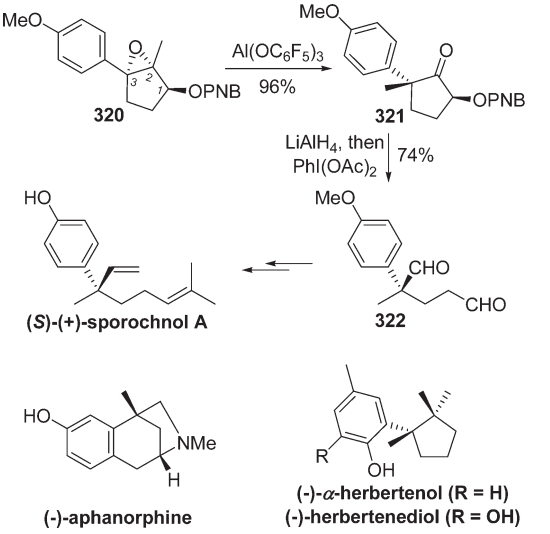

regioselective epoxide opening, which affords the ring-contracted products in good yields. As shown in the syntheses of microbiotol-type sesquiterpenes (Scheme 76), such a rearrangement occurred in **323**, as a result of which an $\alpha,\beta$-unsaturated ester bonded to the oxirane; this compound was used to form the cyclopentyl ketone **324** in 90% yield.[106] Further elaboration of **324** led to the formation of diazo ketone **325**, which underwent intramolecular cyclopropanation and Wittig olefination to give (+)-$\beta$-microbiotene in 56% yield. This method was also used to synthesize other terpenes featuring a cyclopentane ring with multiple quaternary carbon centers.[107]

Under acidic conditions, tetrasubstituted 2,3-epoxy cyclohexenone **326** underwent a similar ring contraction via regioselective epoxide opening to afford the 1,3-diketone **327** in 74% yield (Scheme 77). Using **327** as a key intermediate, Srikrishna and Ramasastry completed the syntheses of several phytoalexins, including the spirocyclic (+)-solavetivone and its [2 + 2]-cycloadduct (+)-solanascone.[108]

**Scheme 74. Chen's Total Syntheses of Nakiterpiosin and Nakiterpiosinone**



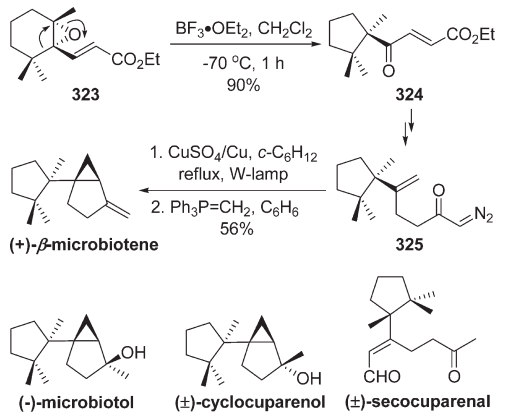

**Scheme 75. Kita's Total Syntheses of (*S*)-(+)-Sporochnol A, (−)-Aphanorphine, (−)-α-Herbertenol, and (−)-Herbertenediol**



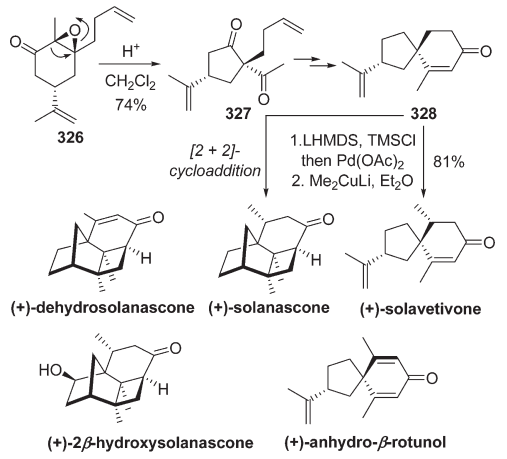

Cazes and co-workers used a semipinacol rearrangement of trisubstituted 2,3-epoxy cyclohexenones **329** to form the 1,3-keto aldehydes **330** in medium to good yields (Scheme 78). Keto aldehyde **330** was subsequently transformed to pseudoiridolactones **331**, which are embedded in several terpene natural products, such as guyanin, xestolide, and methylated iridoid glycoside.[109]

Lyngbyatoxin A is one of the causative agents of a severe contact dermatitis commonly known as "swimmers' itch". Tanner and co-workers prepared its core structure **334** using a semipinacol rearrangement of the chiral vinyl epoxide **332** (Scheme 79).[110] Regioselective ring-opening at the benzylic position and 1,2-migration of the vinyl group created the crucial quaternary carbon center and gave the aldehyde **333** in 52% yield.

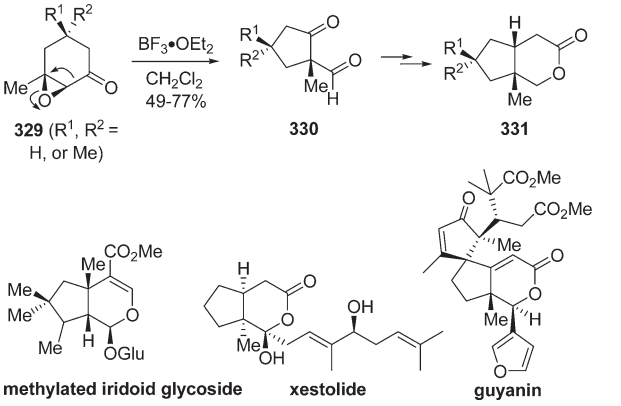
**Scheme 76. Srikrishna's Total Syntheses of (−)-Microbiotol and (+)-β-Microbiotene**



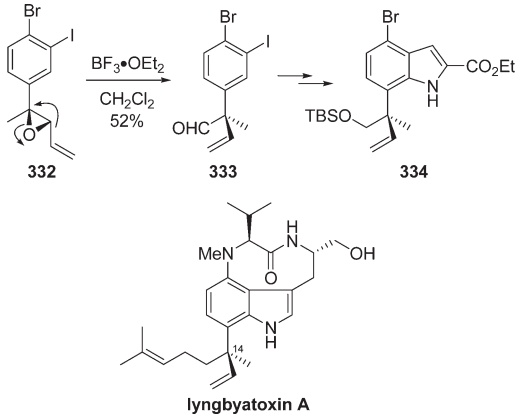

**Scheme 77. Srikrishna's Total Syntheses of (+)-Solavetivone and (+)-Solanascon**




**Scheme 78. Cazes' Synthesis of Pseudoiridolactones**




**Scheme 79. Tanner's Enantioselective Formation of Lyngbyatoxin A Core**




## 5. REARRANGEMENT OF α-HYDROXY KETONES AND IMINES

It is well-known that tertiary α-hydroxy aldehydes, ketones, and imines can undergo "acyloin rearrangement" or "α-ketol rearrangement" to form isomeric products. Because an enolization/protonation process is impossible for these compounds, a semipinacol rearrangement pathway involving 1,2-migration of a C−C bond was invoked to explain this isomerization. Because of its intrinsic reversibility, the process usually occurs when the expected product is thermodynamically more stable than its precursor. Because Paquette and Hofferberth published a comprehensive review of this topic in 2003,[8] this section will discuss only those applications in natural product syntheses published after that year.

1,4-Epoxy cyclononane exists as a core skeleton in bioactive terpenoids such as dihydroparthenolide diol, eremantholide A, and eleutherobin. Oltra and co-workers developed a concise synthesis of one such structure (**338**) based on a tandem transannular cyclization and ring-contraction process (Scheme 80).[111] As shown in **337**, the whole process was initiated by a Lewis acid-promoted epoxide ring-opening of **336** and terminated by the rearrangement of the α-tertiary hydroxy ketone moiety. The process rapidly achieved molecular rigidity and complexity in a stereoselective manner, giving **338** in an overall yield of 72%.

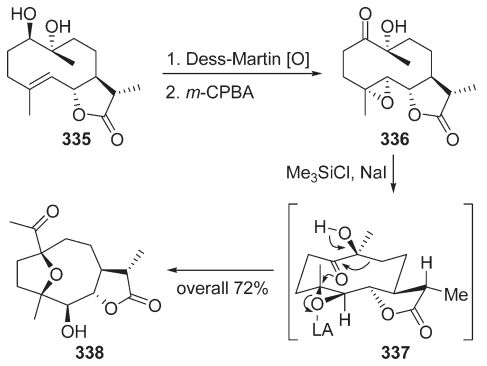
The complex rocaglate silverstrol isolated from the plant *Aglaia foveolata* has been the target of an impressive array of synthetic efforts. In Porco and co-workers' state-of-the-art approach to this molecule (Scheme 81), the α-tertiary hydroxy ketone **342** was prepared from an asymmetric [3 + 2]-photocycloaddition of **339** and **340**, and then a base-mediated rearrangement was carried out to give the rocaglamide core **343** in 89% yield.[112] Formation of the enolate of β-keto ester **343** under basic conditions was proposed to drive the ketol equilibrium shift toward the rocaglamide core.

Liu and McWhorter described the synthesis of 8-desbromohinckdentine A using an $HCO_2H$-promoted rearrangement of the α-tertiary hydroxy imine **344** (Scheme 82).[113] The stereospecific 1,2-migration of the allyl group established the key C12 quaternary carbon center, giving indolone **345** in 96% yield. After transformation of **345** to the hinckdentine A core **346**, the final bromination reaction then provided the target in 92% yield.

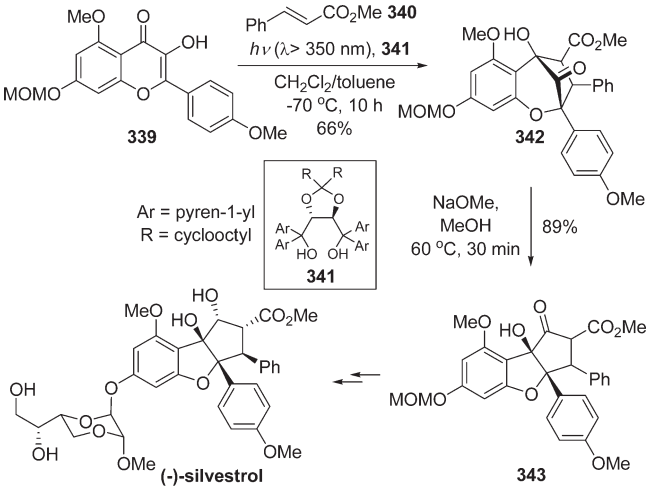
The rearrangement of α-hydroxy imine is also effective for preparing the spirocyclic alkaloids if the migrating group is tethered to the indole moiety at the C2 position. Such cases


dx.doi.org/10.1021/cr200055g |Chem. Rev. 2011, 111, 7523–7556

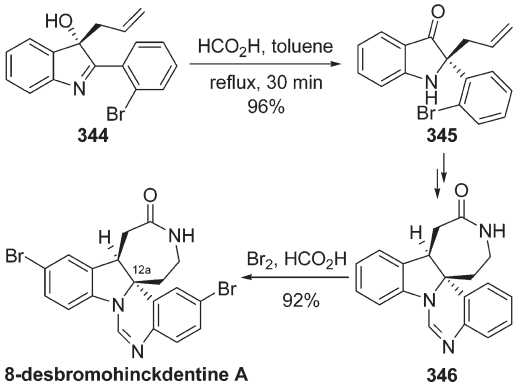
**Scheme 80. Oltra's Tandem Transannular Cyclization and Ring-Contraction Processes Toward Oxygen-Bridged Terpenoids**



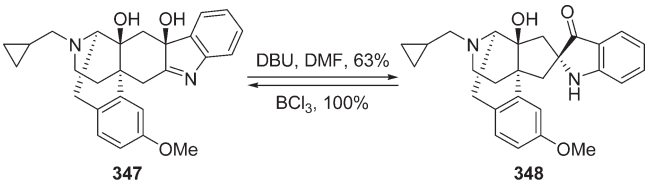

**Scheme 81. Porco's Enantioselective Synthesis of (−)-Silvestrol**




**Scheme 82. McWhorter's Synthesis of 8-Desbromohinckdentine A**




**Scheme 83. Nagase's Synthesis of a Spiroindolinonyl-C-normorphinan Derivative**




can be found in recent studies by Nagase and co-workers on indolomorphinan alkaloids (Scheme 83).[114] Treatment of indoleninomorphinan **347** with DBU gave the spiro indolone **348** in 63% yield. Interestingly, **348** can be converted back into **347** when promoted by $BCl_3$. This process provides a practical interconversion between these two structures and is useful for the design of druglike compound libraries.

## 6. BIOMIMETIC SYNTHESIS INVOLVING SEMIPINACOL REARRANGEMENT

In some natural product biosyntheses, semipinacol rearrangement has been proposed to play a key role in crucial skeleton transformations. Generally, oxidase-catalyzed oxidation is believed to occur first, generating an active intermediate such as a carbocation or epoxide. These species then undergo rearrangement, probably without interacting with any enzyme, either in a spontaneous way or promoted by acid or base. In this section, several examples of biomimetic syntheses involving semipinacol rearrangements are discussed, along with some interesting studies about factors that affect the efficiency and stereoselectivity of the rearrangement in biosyntheses.

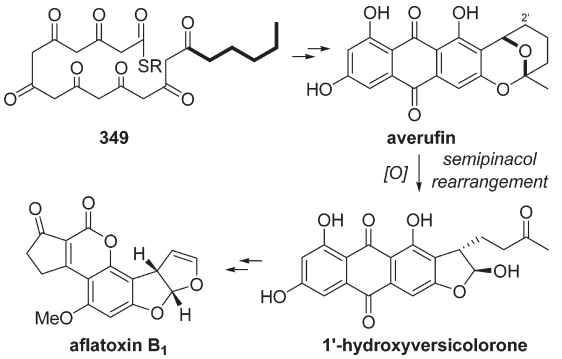
The biogenetic synthesis of aflatoxin $B_1$, which contains an unusual bisfuran moiety, has been proposed to use polyketide **349** as starting material and to proceed via a series of enzyme-catalyzed oxidative rearrangements (Scheme 84). During the process, transformation from averufin to 1′-hydroxyversicolorone has been proposed to proceed via oxidation at C-2′, followed by a semipinacol rearrangement.[115] Townsend and co-workers have carried out a series of investigations, using both biosynthetic and chemical experiments,[116] to gain greater mechanistic understanding of this transformation.

Originally, the *A. nidulans* metabolite nidurufin was proposed to be involved in this rearrangement (Scheme 85). The structure of **350** presents an ideal antiperiplanar orientation of the migrating and leaving groups, which facilitates the rearrangement. However, neither the labeled nidurufin nor its 2′-epimer was detectably incorporated into aflatoxin $B_1$. In addition, a very slow rearrangement of exo-mesylated nidurufin derivative **351** was observed, although the desired rearrangement products **353** and **354** were obtained after 19 h in tetrafluoroethylene (TFE) at 80 °C. This low reactivity was proposed to be the result of the strong electron-withdrawing effect of the O-1′ nucleus and the electron deficiency of the anthraquinone migrating group. On the basis of these results, the authors concluded that nidurufin is not involved in the biosynthesis of aflatoxin because of the significant kinetic barriers in the pathway, although enzyme involvement could reduce these barriers.

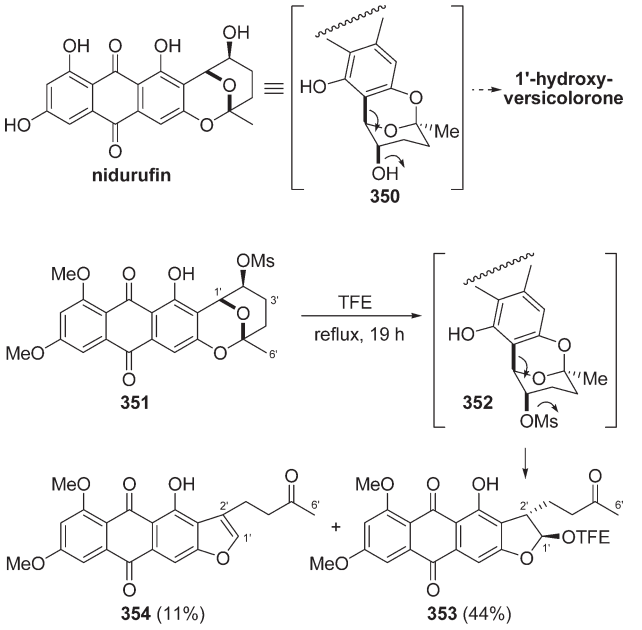
Townsend and co-workers then described an alternative mechanistic profile featuring a closed form of the bicyclic ketal side chain, as shown in **355** (Scheme 86). Support for this possibility was obtained in a labeling experiment in which $^{18}O$-induced isotopic shifts were observed at C-5′ in **358**. In addition, deuterium-labeling experiments carried out in similar systems showed


dx.doi.org/10.1021/cr200055g |*Chem. Rev.* 2011, 111, 7523–7556

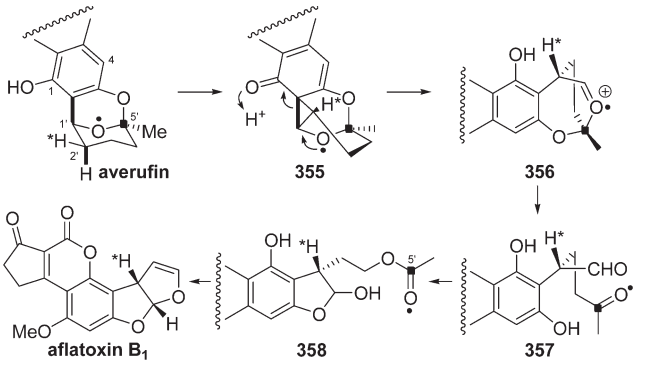
**Scheme 84. Biogenetic Synthesis of Aflatoxin $B_1$**




**Scheme 85. Townsend's Original Proposal of Aflatoxin $B_1$ Biosynthesis Involving Nidurufin**




**Scheme 86. Townsend's Modified Scheme for Biosynthesis of Aflatoxin $B_1$**




that the oxidative step led to the specific loss of the 2′-axial H but not the 2′-equatorial *H. This is consistent with the stereoelectronic argument shown in the oxidation of averufin to **355**.

The related model reaction of exo-iodide **359** was examined to probe the nature of the oxidation of averufin (Scheme 87). Because various radical reactions led only to the simple reduction product **360** (R = H) and trace amounts of oxidation product generated by $O_2$ were observed, oxidation of averufin via radical intermediates was initially excluded. However, in tests of cation-mediated oxidation, treatment of **359** with $AgOCOCF_3$ indeed gave the desired hydroxyl versicolorone **361** biomimetically in 70% yield. In contrast, treatment with AgOAc produced the much more attractive **362**, which appeared to be generated by acetate ion attacking **359** from the opposite face of the anthraquinone. Thus, chemical experiments strongly support the cationic pathway in Scheme 86.

Liphagal, a tetracyclic meroterpenoid, shows excellent inhibitory activity against phosphoinositide-3-kinase α in a primary fluorescent polarization enzyme assay. Andersen and co-workers proposed a biogenetic pathway[117] in which polyene cyclization would be used to transform **363** into the known natural product siphonodictyal B (Scheme 88). A sequence of epoxidation, epoxide ring-opening, and ring expansion with 1,2-migration of the *ortho*-quinone methide via **364** and **365** would lead to the fused benzofuran **366**, which could then be transformed into liphagal by dehydration.

Inspired by Andersen's biogenetic proposal, George et al. completed a biomimetic synthesis of (+)-liphagal (Scheme 89).[118] The key step featured a trifluoroacetic acid (TFA)-promoted semipinacol rearrangement of diol **367** to generate the highly stabilized benzylic carbocation **368**, which underwent selective 1,2-migration of the C9−C10 bond to give cycloheptanone **369**. Subsequent dehydration of **369** then formed the benzofuran core **370** in 74% yield overall. A similar strategy is also found in Manzaneda's biomimetic synthesis of (+)-liphagal,[119] which was published around the same time as George's synthesis.

Asteltoxin, isolated from toxic maize cultures of *Aspergillus stellatus* Curzi, belongs to a group of structurally related trienic α-pyrones. It has a unique and highly functionalized 2,8-dioxabicyclo-[3.3.0]-octane core possessing a quaternary carbon embedded in an array of six stereocenters. On the basis of extensive $^{13}C$ and $^{18}O$ labeling experiments, Vleggaar and co-workers suggested that the biogenetic synthesis of asteltoxin starts with a polyepoxidation of the polyene precursor **371** to generate the epoxy alcohol **373** (Scheme 90). A subsequent semipinacol rearrangement involving a 2,3-migration would then provide the branched aldehyde **374**, which could be further converted into the bistetrahydrofuran core **376**.[120]

Using a procedure paralleling Vleggaar's biosynthetic proposal, Cha and co-workers completed the enantioselective total synthesis of (+)-asteltoxin (Scheme 91).[121] Treatment of the chiral epimeric mixture of 2,3-epoxy silyl ether **377** with $TiCl_4$ facilitated a smooth semipinacol rearrangement, producing the aldehyde **378** as a single isomer in 96% yield. The expected 1,2-migration of the vinyl group diastereoselectively created a C5 quaternary carbon center in (+)-asteltoxin. Subsequent transformations, including dihydroxylation and hydrolysis, converted the aldehyde **378** into the bistetrahydrofuran core **380**, which was ultimately converted into the natural product.

Mytiloxanthin has been proposed to form biogenetically from the 5,6-epoxy carotenoid halocynthiaxanthin (Scheme 92).[122]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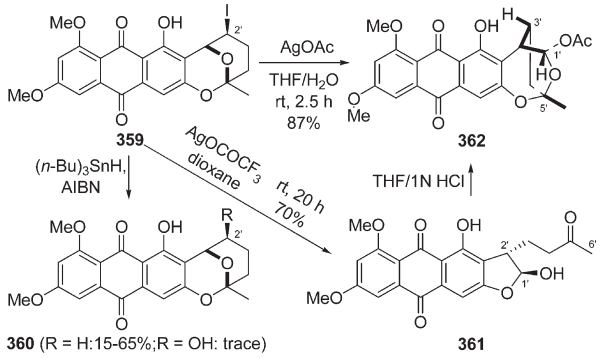
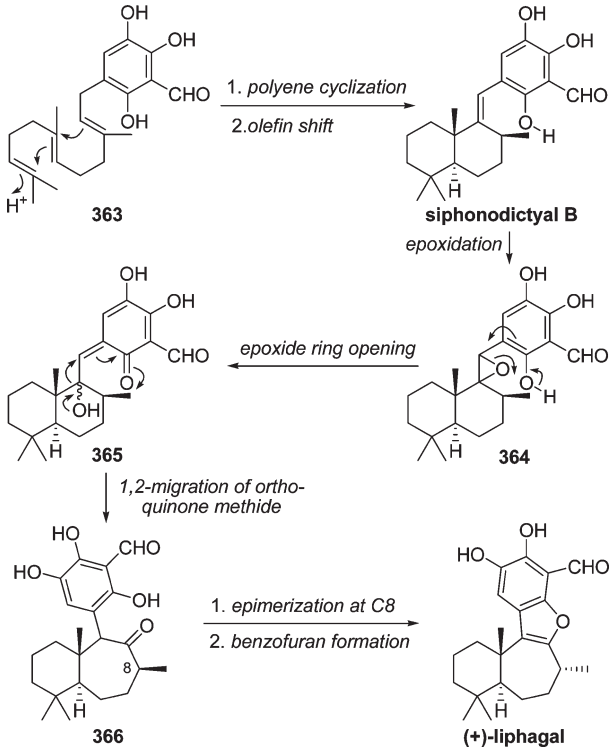
**Scheme 87. Support for Carbocation Involvement in Averufin Oxidation**



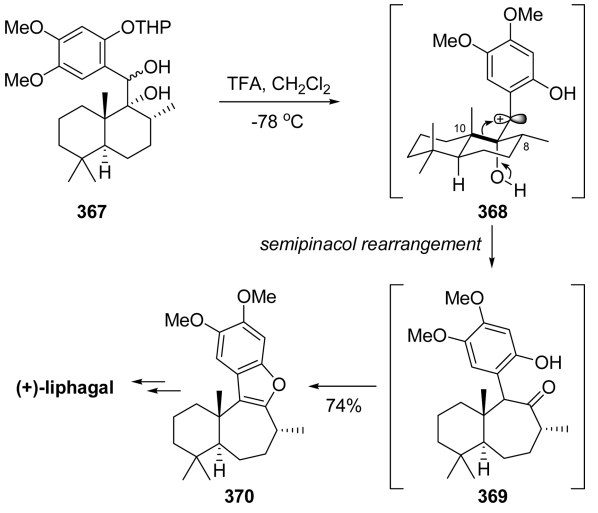

**Scheme 88. Andersen's Proposed Biosynthesis of (+)-Liphagal**



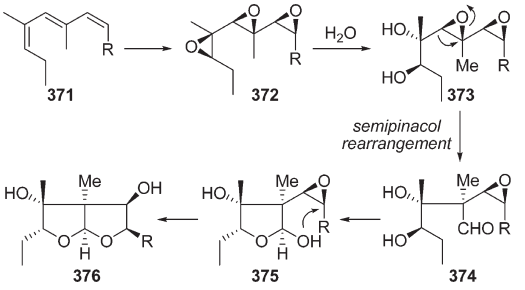

In this proposal, the key transformations include a semipinacol rearrangement of cyclohexanyl epoxide, which could undergo regioselective ring-opening at C5 and subsequent 1,2-migration of the C1−C6 bond to give the ring-contracted cyclopentyl ketone moiety in mytiloxanthin.

On the basis of this proposal, Ito and co-workers achieved the biomimetic synthesis of mytiloxanthin by treating the tetrasubstituted epoxide **381** with $(p\text{-}BrC_6H_5)_3N^+ \cdot SbCl_6^-$. As proposed, this reaction gave the rearranged product **382** in overall 93% yield (Scheme 93).[123] The same strategy has been used to synthesize other analogues such as capsanthin, capsorubin, and capsanthin 3,6-epoxide.[124]

**Scheme 89. George's Biomimetic Synthesis of (+)-Liphagal**




**Scheme 90. Vleggaar's Proposed Biosynthesis of the (+)-Asteltoxin Core**



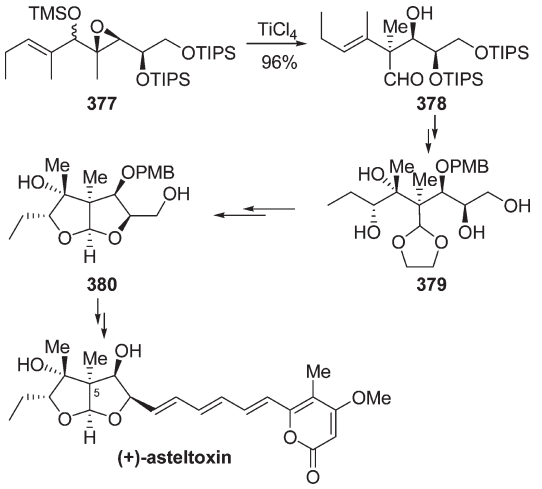

According to the biosynthetic model proposed by Iguchi et al., sesterterpenoid (−)-hyrtiosal is synthesized in nature from a cheilanthane skeleton via a semipinacol rearrangement of epoxide intermediate **383** (Scheme 94).[125] On the basis of this hypothesis, similar biomimetic approaches to this molecule were reported by Basabe et al.[126] and Imamura and co-workers.[127] In their syntheses, treatment of epoxides **384** and **386** with $BF_3 \cdot OEt_2$ led to the same regioselective ring-opening at the trisubstituted position and gave the aldehydes **385** and **387** in high yield after ring contraction.

Brevianamides, an unusual family of fungal metabolites, possess structurally intriguing features due to their unique bicycle-[2.2.2]-diazaoctane core and spiroindoxyl ring system.[128] In the past two decades, Williams and co-workers have carried out an array of biosynthetic studies and accomplished elegant biomimetic syntheses of these natural products and related prenylated indole alkaloids.[129] In their modified biosynthetic hypothesis (Scheme 95),[130] a stereospecific semipinacol rearrangement of **388** was proposed to generate the key indoxyl compound **389**, thereby creating a quaternary carbon center. After oxidation of **389** to **390**, a biological intramolecular Diels−Alder cycloaddition was proposed to lead to the formation of brevianamides A and B, respectively.

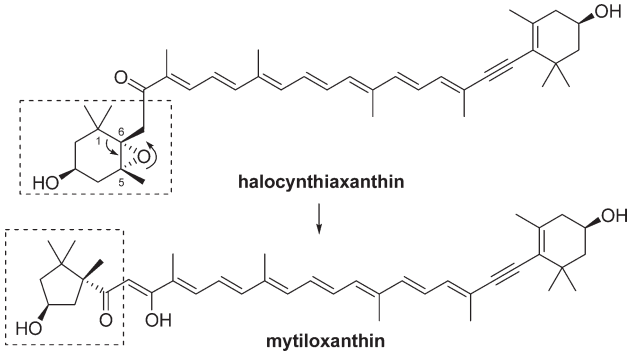
Following a strategy similar to the proposal above, Williams et al. completed the synthesis of brevianamide B (Scheme 96).[131]


dx.doi.org/10.1021/cr200055g |Chem. Rev. 2011, 111, 7523–7556

**Scheme 91. Cha's Total Synthesis of (+)-Asteltoxin**




**Scheme 92. Biosynthetic Relationship between Mytiloxanthin and 5,6-Epoxy Carotenoid Halocynthiaxanthin**

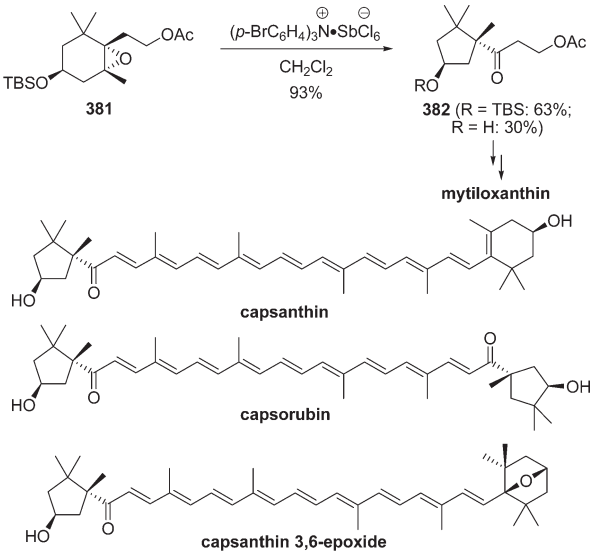



Epoxidation and the acidic hydrolysis of the minor isomer of intramolecular Diels–Alder (IMDA) adduct **392** afforded the hydroxyindolenine precursor **393**. Then a base-induced semipinacol rearrangement established the spiroindoxyl moiety via ring contraction, providing brevianamide B in 65% yield after acidic hydrolysis.

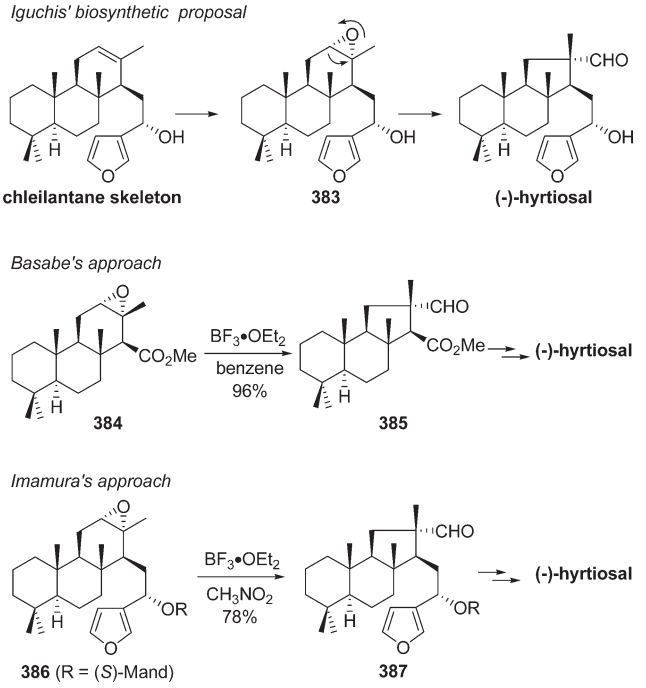
In their synthesis of (+)-paraherquamide B (Scheme 97),[132] Williams and co-workers used an oxidation and semipinacol rearrangement process to construct the spiro oxindole moiety that was different from the process to synthesize the spiroindoxyl ring of brevianamides. Indole oxidation with *t*-BuOCl led to chloroindolenine **394**, which was first transformed to the proposed intermediate **395**, which then underwent a semipinacol rearrangement to produce the spiro oxindole **396** in 76% yield. The antiperiplanar alignment of the Cl leaving group and the migrating group ensured that the desired 1,2-migration occurred with perfect stereospecificity.

Williams and co-workers later developed a more efficient tandem epoxidation/semipinacol rearrangement sequence to form the spiro oxindole moiety. As shown in their synthesis of notoamide B (Scheme 98),[133] treatment of the IMDA adduct stephacidin A with oxaziridine **398** gave the oxidized intermediate **399**, which then underwent ring contraction to give the target directly in 73% yield.

**Scheme 93. Ito's Syntheses of Carotenoids and Related Polyenes**




**Scheme 94. Biomimetic Synthesis of Hyrtiosal**




Recently, Williams and co-workers completed the biomimetic syntheses of (+)-versicolamide B (Scheme 99).[134] One of the key steps featured a tandem epoxidation/semipinacol rearrangement of indole **400** to generate oxindole **402** in 80% yield with 3:1 diastereoselectivity. In contrast to the previous syntheses of these types of alkaloids, this step was performed before the IMDA reaction of **402** to yield (+)-versicolamide B. This work provided the first experimental support for the biogenetic hypothesis in Scheme 95, which describes how oxidation, semipinacol rearrangement, and IMDA reaction may occur along a single pathway.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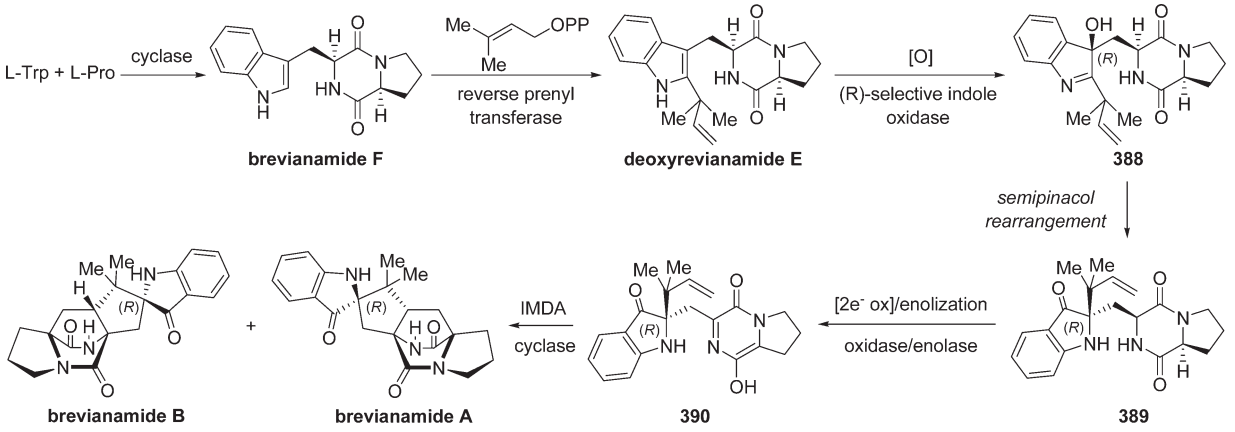
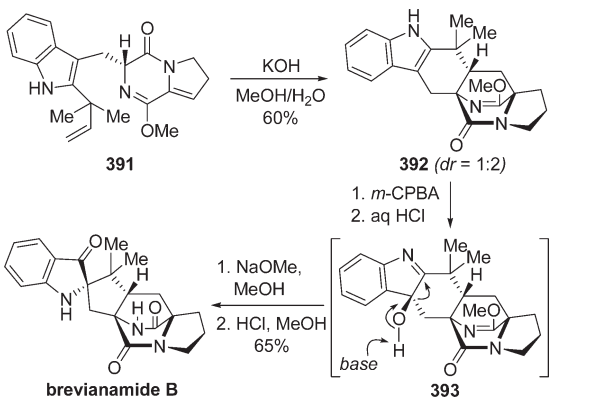
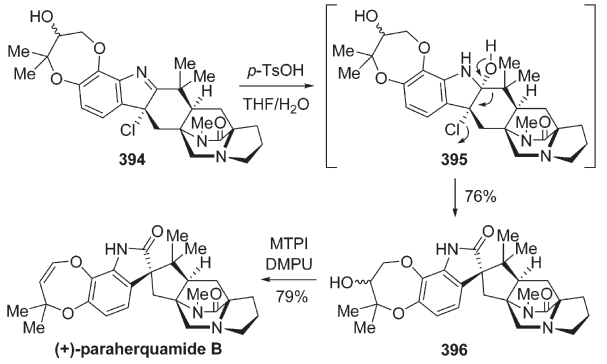
**Scheme 95. Williams' Proposed Biosynthesis of Brevianamides**



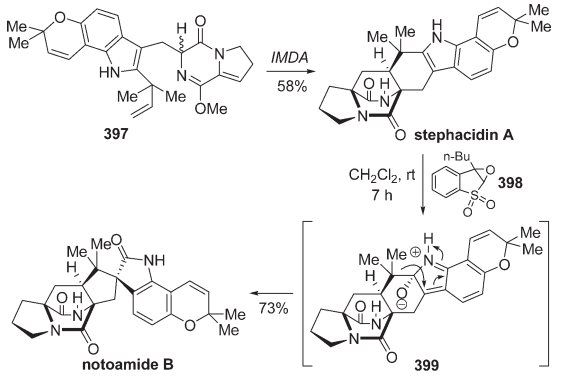

**Scheme 96. Williams' Biomimetic Synthesis of Brevianamide B**



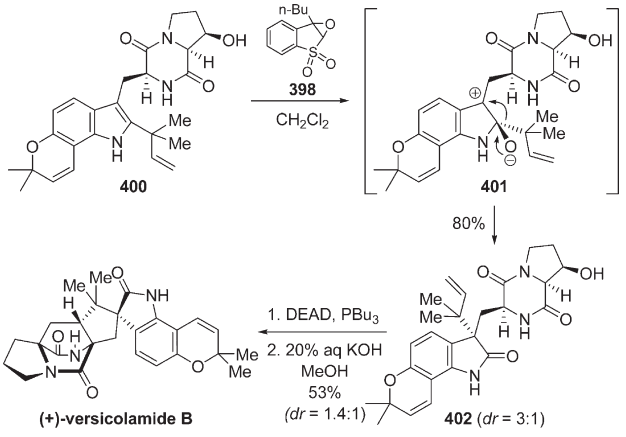

**Scheme 97. Williams' Biomimetic Synthesis of (+)-Paraherquamide B**




**Scheme 98. Williams' Biomimetic Synthesis of Notoamide B**




**Scheme 99. Williams' Biomimetic Synthesis of (+)-Versicolamide B**




## 7. RECENT APPLICATIONS OF PINACOL REARRANGEMENT

Diazonamide A, as a marine invertebrate secondary metabolite, shows excellent activity at inhibiting the growth of human colorectal carcinoma in vitro.[135] In 2001, Harran and co-workers completed the first total synthesis of the originally proposed structure of (−)-diazonamide A, which contains the striking feature of an axial chiral aromatic/heteroaromatic ring network linked at the C10 quaternary carbon center (Scheme 100).[136] In their synthesis, a Pd(0)-catalyzed Heck endo-cyclization was used to transform **403** into the macrocyclic triarylethylene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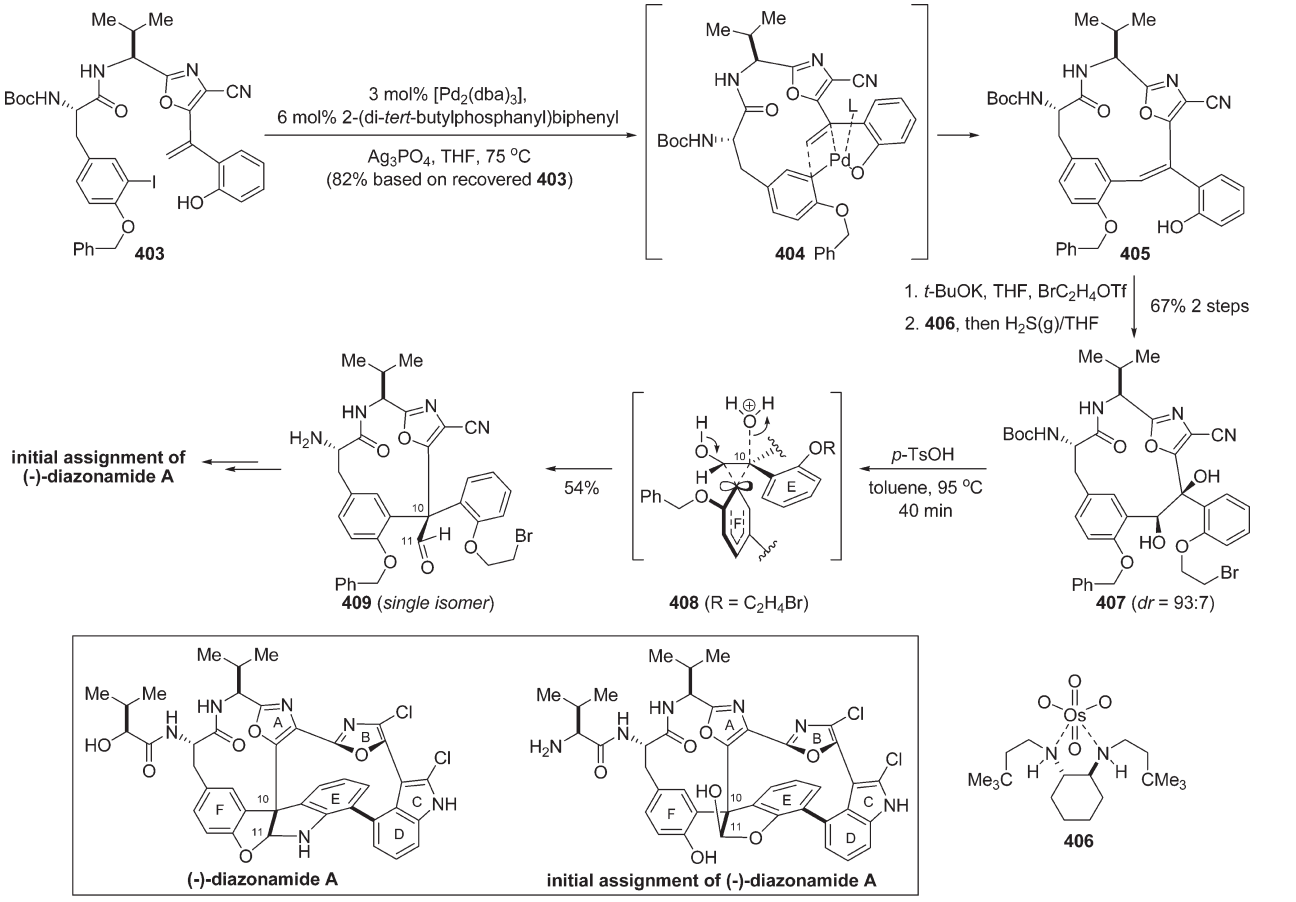
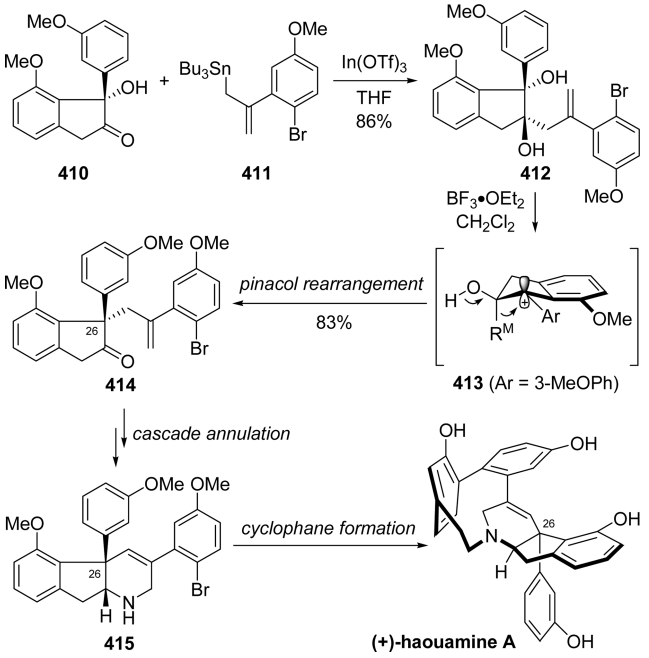
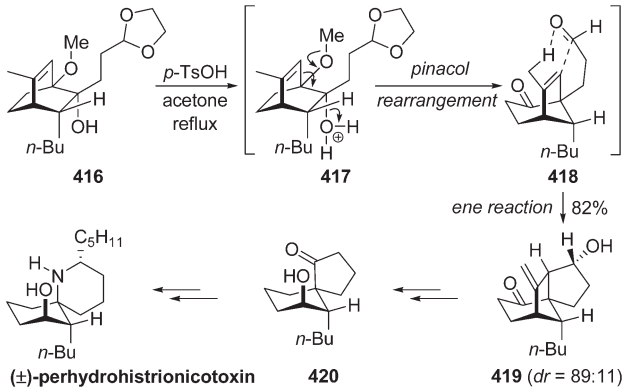
**Scheme 100. Harran's Synthesis of the Initially Proposed Structure of (−)-Diazonamide A**




**Scheme 101. Baran's Synthesis of (+)-Haouamine A**




**Scheme 102. Kim's Formal Synthesis of (±)-Perhydrohistrionicotoxin**




intermediate **405** in 82% yield. Etherification of phenol and dihydroxylationwith $OsO_4$ complex **406** led to the diol **407** in 67% yield with 93:7 diastereofacial selectivity. Then a well-defined pinacol rearrangement of diol **407** was performed with anhydrous *p*-TsOH in toluene to give the ring-contracted triarylacetaldehyde **409** in 54% yield as a single C10 diastereomer. The well-controlled inversion of stereochemistry at C10 from **407** to **409** can be attributed to formation of the bridging phenonium ion **408**.

Haouamine A is a structurally novel alkaloid that shows exquisitely selective anticancer activity against human colon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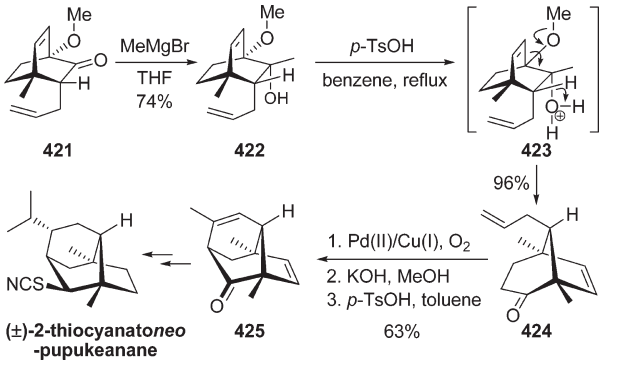
**Scheme 103. Uyehara's Synthesis of (±)-2-Thiocyanato-*neo*-pupukeanane**




carcinoma cells. One of its unique structural features is an indeno tetrahydropyridine ring system with a congested quaternary carbon center at C26. To synthesize this challenging architecture, Baran and co-workers utilized a pinacol rearrangement of diol **412** in their total synthesis of (+)-haouamine A (Scheme 101).[137] Stereoselective allylation of α-hydroxy ketone **410** with organotin reagent **411** in the presence of $In(OTf)_3$ provided the diol **412** in 86% yield. Subsequent treatment with $BF_3 \cdot OEt_2$ initiated a smooth 1,2-migration of the allyl moiety via the carbocation **413**, generating the desired ketone **414** in 83% yield with no loss of stereochemical information. The subsequent cascade of annulation reactions and cyclophane formation led to (+)-haouamine A.

In the formal synthesis of (±)-perhydrohistrionicotoxin (Scheme 102), Kim et al. used a tandem pinacol rearrangement/ene reaction to transform a bicyclo-[2.2.2]-octene to a tricycle-[5.3.1.01,5]-undecane system.[138] When alcohol **416**, derived from a Diels–Alder adduct, was treated with *p*-TsOH, a stereospecific 1,2-shift of the bridged C–C bond occurred readily to give the bicycle-[3.2.1]-octane **418**. Then **418** underwent an ene reaction to afford **419** in 82% overall yield with 89:11 diastereoselectivity. Further transformations to spirocyclic compound **420** completed the formal synthesis of the target.

Uyehara et al. used a similar pinacol rearrangement in their synthesis of (±)-2-thiocyanato-*neo*-pupukeanane (Scheme 103).[139] Tertiary alcohol **422**, prepared from addition of methylmagnesium bromide to ketone **421**, underwent a *p*-TsOH-promoted rearrangement to give ketone **424** in 96% yield as a single isomer. Subsequent Wacker oxidation and an aldol reaction led to the formation of core **425**, which was ultimately transformed into the target.

## 8. SUMMARY AND OUTLOOK

We have reviewed the applications of semipinacol rearrangement in natural product syntheses. These applications showcase the reaction's broad applicability to various structural systems, especially the ring system. In addition, the rearrangement functions in some appealing tandem reactions thus allow the highly efficient construction of complex molecules. In particular, as illustrated in most of the targets, semipinacol rearrangement is exceptionally good for constructing synthetically challenging quaternary carbon centers, which are usually impossible or extremely difficult to create by other methods. We hope the strategies highlighted in this review provide organic chemists with inspiration for their natural product syntheses. We also believe that through the methodological breakthroughs in the development of efficient asymmetric reactions[140] and new tandem reactions, semipinacol rearrangement will continue to play an active role in natural product syntheses.

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## BIOGRAPHIES

Zhen-Lei Song was born in Jiangsu Province, China, in 1978. He obtained his Ph.D. in Organic Chemistry from Lanzhou University with Professor Yong-Qiang Tu in 2005. From 2005 to 2008, he was a postdoctoral associate in Professor Richard Hsung's group at the University of Wisconsin at Madison. Currently, he is Associate Professor at West China School of Pharmacy, Sichuan University. His research interests involve total syntheses of natural products, organosilane chemistry, and medicinal chemistry.

Chun-An Fan was born in Jiangsu Province, China, in 1976. He studied chemistry at Lanzhou University, China, where he received his B.S. in 1999 and completed his Ph.D. with Professor Yong-Qiang Tu in 2004. He then spent one year as a CNRS Postdoctoral Fellow in the laboratory of Professor

Henri B. Kagan at Université de Paris-Sud (XI), France. In November of 2005, he joined the group of Prof. Andreas Gansäuer as an Alexander von Humboldt Research Fellow at Universität Bonn, Germany. In November of 2007, he obtained a full professorship position at Lanzhou University. His current research interests center on synthetic methodology, asymmetric catalysis, and synthesis of structurally interesting and biologically active molecules.

Yong-Qiang Tu was born in Guizhou Province, China, in 1958. He received his B.S. and M.S. from Lanzhou University in 1982 and 1985, respectively. In 1989, he obtained his Ph.D. in organic chemistry from Lanzhou University under the supervision of Prof. Yao-Zu Chen. From 1993 to 1995, he worked as a postdoctoral fellow with Prof. William Kitching at the University of Queensland, Australia. Then he worked as a visiting professor at Bielefeld University, Germany. In 1995, he was appointed a full professor at Lanzhou University and named Director of the State Key Laboratory of Applied Organic Chemistry from 2001 to 2010. In 2009, he was elected an academician of the Chinese Academy of Sciences.

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## REFERENCES

(1) (a) Fittig, R. *Liebigs Ann. Chem.* **1860**, *114*, 54. For reviews, see: (b) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; pp 721−732. (c) Kürti, L., Czakó, B. In *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: Burlington, MA, 2005; pp 350−351. (d) Goess, B. In *Name Reactions for Homologations*; Li, J. J., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, 2009; pp 319−333.

(2) (a) March., J. In *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; p 963. (b) For a review, see: Coveney, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; pp 777−801.

(3) Tiffeneau, M.; Levy, J. *Comptes rendus* **1923**, *176*, 312.

(4) "Wagner−Meerwein rearrangement" refers to *all rearrangement reactions in which the generation of a carbocation is followed by an adjacent 1,2-migration of a C−C or C−H bond to generate a new carbocation center.* Depending on the structure of the substrate, the resulting carbocation can enter many different reaction pathways, which usually include sequential 1,2-migration, elimination to a C=C bond, and nucleophilic attack. Comparing this definition with that of semipinacol rearrangement, we would like to suggest the following. First, from the mechanistic point of view, some semipinacol rearrangements in which a carbocation intermediate may be generated en route to a 1,2-migration, such as rearrangements of allylic alcohols and 2,3-epoxy alcohols, may be considered a type of Wagner−Meerwein rearrangement. However, from the perspective of product type, it is more appropriate to consider such reactions semipinacol rearrangements, because they generate an atypical carbocation (an oxocarbenium intermediate) en route to delivering a carbonyl group. Second, it may not be appropriate to consider some semipinacol rearrangements as Wagner−Meerwein rearrangements when there is no potential carbocation involved, such as in base-promoted rearrangement of 1,2-hydroxy sulfonates, halohydrins, and tertiary α-hydroxy ketones and imines.The fact that the 1,2-migration occurs towards an electrophilic carbon center also differentiates semipinacol rearrangement from other carbonyl-forming 1,2-migrations such as the Schmidt reaction, in which the migration terminus is a nitrogen center rather than a carbon one. In summary, the distinguishing features of semipinacol rearrangement can be described as follows: *1,2-migration of a C−C or C−H bond that is centered on the oxygen-containing carbon and that occurs towards the vicinal electrophilic carbon center, generating a carbonyl group at the end of the process.* These features can be used to determine whether a reaction is a semipinacol rearrangement or not.

(5) For reviews, see: (a) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352. (b) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143.(c) Kürti, L., Czakó, B. In *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: Burlington, MA, 2005; pp 366−367.

(6) For reviews, see: (a) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; pp 733−776. (b) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. (c) Milstein, D.; Buchman, O.; Blum, J. *Tetrahedron Lett.* **1974**, *16*, 2257. (d) Rao., A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323.

(7) For reviews, see: (a) Suzuki, K. *J. Synth. Org. Chem. Jpn.* **1988**, *46*, 49. (b) Snape, T. J. *Chem. Soc. Rev.* **2007**, *36*, 1823. For recent investigations, see:(c) Zhang, L. D.; Guo, H. J.; Pan, Y.; Qi, F. *Chin. J. Chem. Phys.* **2008**, *21*, 547. (d) Wen, S. G.; Liu, W. M.; Liang, Y. M. *J. Org. Chem.* **2008**, *73*, 4342. (e) Jung, M. E.; Allen, D. A. *Org. Lett.* **2008**, *10*, 2039. (f) Widjaja, T.; Fitjer, L.; Meindl, K.; Herbst-Irmer, R. *Tetrahedron* **2008**, *64*, 4304. (g) Xiao, H. Q.; Shu, X. Z.; Ji, K. G.; Qi, C. Z.; Liang, Y. M. *Catal. Commun.* **2009**, *10*, 1824. (h) Haib, A. E.; Benharref, A.; Parrès-Maynadié, S.; Manoury, E.; Daran, J. -C.; Urrutigoïy, M.; Gouygou, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1272. (i) Nowrouzi, F.; Janetzko, J.; Batey, R. A. *Org. Lett.* **2010**, *12*, 5490.

(8) For a review, see: Paquette, L. A.; Hofferberth, J. E. *Org. React.* **2003**, *62*, 477.

(9) For reviews, see: (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (b) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2708. (c) Corey, E. J.; Angel, G.-P. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (d) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (e) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (f) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (g) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (h) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473.(i) *Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (j) Trost, B. M.; Jiang, C. *Synthesis* **2006**, *3*, 369. (k) Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488. (l) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, *36*, 5969. (m) Bella, M.; Gasperi, T. *Synthesis* **2009**, *10*, 1583.

(10) For selective reviews, see: (a) Eilbracht, P.; Baerfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329. (b) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, *5*, 551. (c) Padwa, A. *Pure Appl. Chem.* **2004**, *76*, 1933. (d) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (e) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341. (f) Enders, D.; Grondal, C.; Huettl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (g) Poulin, J.; Grise-Bard, C. M.; Barriault, L. *Chem. Soc. Rev.* **2009**, *38*, 3092.

(h) Alba, A.-N.; Companyo, X.; Viciano, M.; Rios, R. *Curr. Org. Chem.* **2009**, *13*, 1432. (i) Fustero, S.; Sanchez-Rosello, M.; del Pozo, C. *Pure Appl. Chem.* **2010**, *82*, 669. (j) Zhou, J. *Chem. Asian J.* **2010**, *5*, 422. (k) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167.

(11) (a) Suzuki, K.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1982**, *24*, 4997. (b) Suzuki, K.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1984**, *25*, 1817. (c) Suzuki, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *Tetrahedron Lett.* **1984**, *25*, 3715. (d) Suzuki, K.; Ohkuma, T.; Miyazawa, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1986**, *27*, 373.

(12) (a) Suzuki, K.; Tomooka, K.; Matsumoto, T.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1985**, *26*, 3711. (b) Suzuki, K.; Tomooka, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 5221.

(13) Waizumi, N.; Stankovic, A. R.; Rawal, V. H. *J. Am. Chem. Soc.* **2003**, *125*, 13022.

(14) Kingsbury, J. S.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 13813.

(15) For a review, see: Nemoto, H.; Fukumoto, K. *Synlett* **1997**, *8*, 863.

(16) (a) Nemoto, H.; Ishibashi, H.; Mori, M.; Fujita, S.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, *10*, 2835. (b) Nemoto, H.; Ishibashi, H.; Mori, M.; Fujita, S.; Fukumoto, K. *Heterocycles* **1990**, *31*, 1237. (c) Nemoto, H.; Yamada, T.; Ishibashi, H.; Takazawa, J.; Fukumoto, K. *Heterocycles* **1991**, *32*, 863.

(17) (a) Nemoto, H.; Miyata, J.; Hakamata, H.; Nagamochi, M.; Fukumoto, K. *Tetrahedron* **1995**, *51*, 5511. (b) Nemoto, H.; Miyata, J.; Hakamata, H.; Fukumoto, K. *Tetrahedron Lett.* **1995**, *36*, 1055. (c) Nemoto, H.; Miyata, J.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 1933. (d) Miyata, J.; Nemoto, H.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 504.

(18) Corey, E. J.; Ohno, M.; Mitra, R. B.; Vatakencherry, P. A. *J. Am. Chem. Soc.* **1964**, *86*, 478.

(19) Heathcock, C. H.; DelMar, E. G.; Graham, S. L. *J. Am. Chem. Soc.* **1982**, *104*, 1907.

(20) (a) Pal, S. K.; Bhattacharyya, S.; Mukherjee, D. *Tetrahedron Lett.* **1998**, *39*, 8889. (b) Pati, L. C.; Roy, A.; Mukherjee, D. *Tetrahedron Lett.* **2000**, *41*, 10353. (c) Pati, L. C.; Roy, A.; Mukherjee, D. *Tetrahedron* **2002**, *58*, 1773.

(21) (a) Ogino, T.; Kurihara, C.; Baba, Y.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.* **1994**, *17*, 1979. (b) Seki, M.; Sakamoto, T.; Suemune, H.; Kanematsu, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, *11*, 1707.

(22) Schoenen, F. J.; Porco, J. A., Jr.; Schreiber, S. L.; VanDuyne, G. D.; Clardy, J. *Tetrahedron Lett.* **1989**, *30*, 3765.

(23) (a) Paquette, L. A.; Zhao, M. Z. *J. Am. Chem. Soc.* **1998**, *120*, 5203. (b) Guo, X.; Paquette, L. A. *J. Org. Chem.* **2005**, *70*, 315.

(24) (a) Wang, F. P.; Chen, Q. H.; Li, B. G. *Tetrahedron* **2001**, *57*, 4705. (b) Chen, Q. H.; Wang, F. P. *Chem. Pharm. Bull.* **2002**, *50*, 1310. (c) Wang, F. P.; Xu, L. *Tetrahedron* **2005**, *61*, 2149.

(25) For reviews, see: (a) Guijarro, D.; Yus, M. *Curr. Org. Chem.* **2005**, *9*, 1713. (b) Filipski, K. J.; Pfefferkorn, J. A. *Name React. Homologations* **2009**, *Pt. 2*, 438.

(26) Hart, T. W.; Guillochon, D.; Perrier, G.; Sharp, B. W.; Vacher, B. *Tetrahedron Lett.* **1992**, *33*, 5117.

(27) Clarke, C.; Fleming, I.; Fortunak, J. M. D.; Gallagher, P. T.; Honan, M. C.; Mann, A.; Nübling, C. O.; Raithby, P. R.; Wolff, J. J. *Tetrahedron* **1988**, *44*, 3931.

(28) (a) Harding, K. E.; Trotter, J. W. *J. Org. Chem.* **1977**, *42*, 4157. (b) Harding, K. E.; Strickland, J. B.; Pommerville, J. *J. Org. Chem.* **1988**, *53*, 4877.

(29) McMurry, J. E.; Bosch, G. K. *J. Org. Chem.* **1987**, *52*, 4885.

(30) (a) Kraus, G. A.; Shi, J. M. *J. Org. Chem.* **1990**, *55*, 5423. (b) Kraus, G. A.; Shi, J. M. *J. Org. Chem.* **1991**, *56*, 4147.

(31) Harmata, M.; Wacharasindhu, S. *Org. Lett.* **2005**, *7*, 2563.

(32) Harmata, M.; Rashatasakhon, P. *Org. Lett.* **2001**, *3*, 2533.

(33) Harmata, M.; Bohnert, G. J. *Org. Lett.* **2003**, *5*, 59.

(34) (a) Tiffeneau, M.; Weill, P.; Tchoubar, B. *Comptes rendus* **1937**, *205*, 54. For reviews, see:(b) Smith, P. A. S.; Baer, D. R. *Org. React.* **1960**, *11*, 157. (c) Krow, G. R. *Tetrahedron* **1987**, *43*, 3.

(35) Greene, A. E.; Luche, M. J.; Serra, A. A. *J. Org. Chem.* **1985**, *50*, 3957.

(36) Hamelin, O.; Deprés, J. P.; Greene, A. E. *J. Am. Chem. Soc.* **1996**, *118*, 9992.

(37) (a) Hamelin, O.; Wang, Y. Y.; Deprés, J. P.; Greene, A. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 4314. (b) Brocksom, T. J.; Coelho, F.; Deprés, J. P.; Greene, A. E.; Freire de Lima, M. E.; Hamelin, O.; Hartmann, B.; Kanazawa, A. M.; Wang, Y. Y. *J. Am. Chem. Soc.* **2002**, *124*, 15313.

(38) Yamashita, M.; Ohta, N.; Shimizu, T.; Matsumoto, K.; Matsuura, Y.; Kawasaki, I.; Tanaka, T.; Maezaki, N.; Ohta, S. *J. Org. Chem.* **2003**, *68*, 1216.

(39) Trost, B. M.; Hu, Y. M.; Horne, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 11781.

(40) Ahmad, Z.; Goswami, P.; Venkateswaran, R. V. *Tetrahedron* **1989**, *45*, 6833.

(41) Honda, T.; Ishige, H.; Nagase, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, *22*, 3305.

(42) Nagel, M.; Hansen, H. J.; Fráter, G. *Synlett* **2002**, *2*, 280.

(43) Uyehara, T.; Sugimoto, M.; Suzuki, I.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1989**, *23*, 1841.

(44) Miyashita, M.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1974**, *96*, 1917.

(45) Wendt, J. A.; Gauvreau, P. J.; Bach, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 9921.

(46) Halazy, S.; Zuttenman, F.; Krief, A. *Tetrahedron Lett.* **1982**, *23*, 4385.

(47) For recent advances, see: (a) Martínez, A. G.; Vilar, E. T.; Fraile, A. G.; de la Cerero, S. M.; Maroto, B. L. *Tetrahedron Lett.* **2001**, *42*, 6539. (b) Paquette, L. A.; Owen, D. R.; Bibart, R. T; Seekamp, C. K.; Kahane, A. L.; Lanter, J. C.; Corral, M. A. *J. Org. Chem.* **2001**, *66*, 2828. (c) Ruggles, E. L.; Maleczka, R. E., Jr. *Org. Lett.* **2002**, *4*, 3899. (d) Hamura, T.; Suzuki, T.; Matsumoto, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 6294. (e) Widjaja, T.; Fitjer, L.; Pal, A.; Schmidt, H. G.; Noltemeyer, M.; Diedrich, C.; Grimme, S. *J. Org. Chem.* **2007**, *72*, 9264. (f) Li, J.; Fu, Ch. L; Chen, G. F.; Chai, G. B.; Ma, S. M. *Adv. Synth. Catal.* **2008**, *350*, 1376. (g) Alcaide, B.; Almendros, P.; Luna, A.; Torres, M. R. *Adv. Synth. Catal.* **2010**, *352*, 621.

(48) (a) Reisman, S. E.; Ready, J. M.; Hasuoka, A.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 1448. (b) Reisman, S. E.; Ready, J. M.; Weiss, M. M.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 2087.

(49) (a) Wang, B. M.; Song, Z. L.; Fan, C. A.; Tu, Y. Q.; Chen, W. M. *Synlett* **2003**, *10*, 1497. (b) Fan, C. A.; Tu, Y. Q.; Song, Z. L.; Zhang, E.; Shi, L.; Wang, M.; Wang, B. M.; Zhang, S. Y. *Org. Lett.* **2004**, *6*, 4691. (c) Hu, X. D.; Tu, Y. Q.; Zhang, E.; Gao, S. H.; Wang, S. H.; Wang, A. X.; Fan, C. A.; Wang, M. *Org. Lett.* **2006**, *8*, 1823.

(50) (a) Zhang, F. M.; Tu, Y. Q.; Liu, J. D.; Fan, X. H.; Shi, L.; Hu, X. D.; Wang, S. H.; Zhang, Y. Q. *Tetrahedron* **2006**, *62*, 9446. (b) Liu, J. D.; Wang, S. H.; Zhang, F. M.; Tu, Y. Q.; Zhang, Y. Q. *Synlett* **2009**, *18*, 3040.

(51) Wang, A. X.; Song, Z. L.; Gao, S. H.; Jiang, Y. J.; Yuan, D. Y.; Tu, Y. Q.; Li, N. Z. *Chin. J. Org. Chem.* **2007**, *27*, 1171.

(52) (a) Dake, G. R.; Fenster, M. D. B.; Hurley, P. B.; Patrick, B. O. *J. Org. Chem.* **2004**, *69*, 5668. (b) Hurley, P. B.; Dake, G. R. *J. Org. Chem.* **2008**, *73*, 4131.

(53) (a) Trost, B. M.; Mao, M. K. T.; Balkovec, J. M.; Buhlmayer, P. *J. Am. Chem. Soc.* **1986**, *108*, 4965. (b) Trost, B. M.; Balkovec, J. M.; Mao, M. K. T. *J. Am. Chem. Soc.* **1986**, *108*, 4974.

(54) (a) Paquette, L. A.; Andrews, J. F. P.; Vanucci, C.; Lawhorn, D. E.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3956. (b) Paquette, L. A.; Wang, H. L. *Tetrahedron Lett.* **1995**, *36*, 6005. (c) Paquette, L. A.; Lanter, J. C.; Wang, H. L. *J. Org. Chem.* **1996**, *61*, 1119. (d) Paquette, L. A.; Lanter, J. C.; Johnston, J. N. *J. Org. Chem.* **1997**, *62*, 1702. (e) Paquette, L. A.; Kinney, M. J.; Dullweber, U. *J. Org. Chem.* **1997**, *62*, 1713. (f) Paquette, L. A.; Owen, D. R.; Bibart, R. T.; Seekamp, C. K.; Kahane, A. L.; Lanter, J. C.; Corral, M. A. *J. Org. Chem.*

**2001**, *66*, 2828. (g) Paquette, L. A.; Lanter, J. C.; Owen, D. R.; Fabris, F.; Bibart, R. T.; Alvarez, M. *Heterocycles* **2001**, *54*, 49.

(55) Paquette, L. A.; Lord, M. D.; Negri, J. T. *Tetrahedron Lett.* **1993**, *34*, 5693.

(56) Planas, L.; Perard-Viret, J.; Royer, J. *J. Org. Chem.* **2004**, *69*, 3087.

(57) Bernard, A. M.; Frongia, A.; Secci, F.; Piras, P. P. *Chem. Commun.* **2005**, *30*, 3853.

(58) Coombs, T. C.; Zhang, Y. Q.; Garnier-Amblard, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2009**, *131*, 876.

(59) (a) Barnier, J. P.; Karkour, B.; Salaun, J. *J. Chem. Soc., Chem. Commun.* **1985**, *18*, 1270. (b) Salaun, J.; Karkour, B.; Ollivier, J. *Tetrahedron* **1989**, *45*, 3151. (c) Secci, F.; Frongia, A.; Ollivier, J.; Piras, P. P. *Synthesis* **2007**, *7*, 999.

(60) Kim, S.; Uh, K. H. *Tetrahedron Lett.* **1992**, *33*, 4325.

(61) (a) Nemoto, H.; Nagamochi, M.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1992**, *22*, 1695. (b) Nemoto, H.; Nagamochi, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, *19*, 2329. (c) Nemoto, H.; Shiraki, M.; Fukumoto, K. *Synlett* **1994**, *8*, 599. (d) Nemoto, H.; Miyata, J.; Fukumoto, K. *Tetrahedron* **1996**, *52*, 10363. (e) Nemoto, H.; Yoshida, M.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 6450. (f) Nemoto, H.; Miyata, J.; Yoshida, M.; Raku, N.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 7850. (g) Nemoto, H.; Takahashi, E.; Ihara, M. *Org. Lett.* **1999**, *1*, 517.

(62) Nemoto, H.; Nagamochi, M.; Ishibashi, H.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 74.

(63) Yoshida, M.; Ismail, M. A. H.; Nemoto, H.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, *16*, 2629.

(64) Sethofer, S. G.; Staben, S. T.; Hung, O. Y.; Toste, F. D. *Org. Lett.* **2008**, *10*, 4315.

(65) (a) Liebeskind, L. S.; Mitchell, D.; Foster, B. S. *J. Am. Chem. Soc.* **1987**, *109*, 7908. (b) Mitchell, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 291.

(66) (a) Lysenko, I. L.; Oh, H.-S.; Cha, J. K. *J. Org. Chem.* **2007**, *72*, 7903. (b) Kim, K.; Cha, J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 5334.

(67) Chavre, S. N.; Ullapu, P. R.; Min, S. J.; Lee, J. K.; Pae, A. N.; Kim, Y.; Cho, Y. S. *Org. Lett.* **2009**, *11*, 3834.

(68) Butters, M.; Elliott, M. C.; Hill-Cousins, J. H.; Paine, J. S.; Westwood, A. W. J. *Tetrahedron Lett.* **2008**, *49*, 4446.

(69) Overman, L. E.; Velthuisen, E. J. *Org. Lett.* **2004**, *6*, 3853.

(70) Lavigne, R. M. A.; Riou, M.; Girardin, M.; Morency, L.; Barriault, L. *Org. Lett.* **2005**, *7*, 5921.

(71) (a) Armstrong, A.; Shanahan, S. E. *Org. Lett.* **2005**, *7*, 1335. (b) Armstrong, A.; Bhonoah, Y.; Shanahan, S. E. *J. Org. Chem.* **2007**, *72*, 8019.

(72) Cheer, C. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1968**, *90*, 178.

(73) (a) Angeles, A. R.; Dorn, D. C.; Kou, C. A.; Moore, M. A. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1451. (b) Angeles, A, R.; Waters, S. P.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13765.

(74) Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498.

(75) (a) Epstein, O. L.; Cha, J. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 121. (b) Cha, J. K.; Epstein, O. L. *Tetrahedron* **2006**, *62*, 1329.

(76) Gijsen, H. J. M.; Wijnberg, J. B. P. A.; van Ravenswaay, C.; de Groot, A. *Tetrahedron* **1994**, *50*, 4733.

(77) (a) Tu, Y. Q.; Sun, L. D.; Wang, P. Z. *J. Org. Chem.* **1999**, *64*, 629. (b) Tu, Y. Q.; Fan, C. A.; Ren, S. K.; Chan, A. S. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, *22*, 3791. (c) Fan, C. A.; Wang, B. M.; Tu, Y. Q.; Song, Z. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3877. (d) Fan, C. A.; Hu, X. D.; Tu, Y. Q.; Wang, B. M.; Song, Z. L. *Chem.—Eur. J.* **2003**, *9*, 4301. (e) Li, X.; Wu, B.; Zhao, X. Z.; Jia, Y. X.; Tu, Y. Q.; Li, D. R. *Synlett* **2003**, *5*, 623. (f) Li, D. R.; Xia, W. J.; Tu, Y. Q.; Zhang, F. M.; Shi, L. *Chem. Commun.* **2003**, *6*, 798. (g) Hu, X. D.; Fan, C. A.; Zhang, F. M.; Tu, Y. Q. *Angew. Chem., Int. Ed.* **2004**, *43*, 1702. (h) Gu, P. M.; Zhao, Y. M.; Tu, Y. Q.; Ma, Y. F.; Zhang, F. M. *Org. Lett.* **2006**, *8*, 5271.

(78) Zhao, Y. M.; Gu, P. M.; Tu, Y. Q.; Fan, C. A.; Zhang, Q. W. *Org. Lett.* **2008**, *10*, 1763.

(79) Zhao, Y. M.; Gu, P. M.; Zhang, H. J.; Zhang, Q. W.; Fan, C. A.; Tu, Y. Q.; Zhang, F. M. *J. Org. Chem.* **2009**, *74*, 3211.

(80) (a) Fenster, M. D. B.; Dake, G. R. *Org. Lett.* **2003**, *5*, 4313. (b) Fenster, M. D. B.; Dake, G. R. *Chem.—Eur. J.* **2005**, *11*, 639.

(81) Nagasawa, T.; Taya, K.; Kitamura, M.; Suzuki, K. *J. Am. Chem. Soc.* **1996**, *118*, 8949.

(82) (a) Saito, T.; Morimoto, M.; Akiyama, C.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1995**, *117*, 10757. (b) Saito, T.; Suzuki, T.; Morimoto, M.; Akiyama, C.; Ochiai, T.; Takeuchi, K.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1998**, *120*, 11633.

(83) (a) Suzuki, K.; Miyazawa, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 3515. (b) Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 5891. (c) Shimazaki, M.; Morimoto, M.; Suzuki, K. *Tetrahedron Lett.* **1990**, *31*, 3335.

(84) Suzuki, K.; Miyazawa, M.; Shimazaki, M.; Tsuchihashi, G. *Tetrahedron* **1988**, *44*, 4061.

(85) (a) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208. (b) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379. (c) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12150. (d) Jung, M. E.; Heuvel, A. V. D.; Leach, A. G.; Houk, K. N. *Org. Lett.* **2003**, *5*, 3375. (e) Jung, M. E.; Heuvel, A. V. D. *Org. Lett.* **2003**, *5*, 4705.

(86) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669.

(87) Jung, M. E.; Salehi-Rad, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 8766.

(88) Mitton-Fry, M. J.; Cullen, A. J.; Sammakia, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 1066.

(89) Wang, B. M.; Song, Z. L.; Fan, C. A.; Tu, Y. Q.; Shi, Y. *Org. Lett.* **2002**, *4*, 363.

(90) Song, Z. L.; Wang, B. M.; Tu, Y. Q.; Fan, C. A.; Zhang, S. Y. *Org. Lett.* **2003**, *5*, 2319.

(91) Kimura, T.; Yamamoto, N.; Suzuki, Y.; Kawano, K.; Norimine, Y.; Ito, K.; Nagato, S.; Iimura, Y.; Yonaga, M. *J. Org. Chem.* **2002**, *67*, 6228.

(92) (a) Kita, Y.; Higuchi, K.; Yoshida, Y.; Iio, K.; Kitagaki, S.; Akai, S.; Fujioka, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 683. (b) Kita, Y.; Higuchi, K.; Yoshida, Y.; Iio, K.; Kitagaki, S.; Ueda, K.; Akai, S.; Fujioka, H. *J. Am. Chem. Soc.* **2001**, *123*, 3214.

(93) Nemoto, H; Ishibashi, H.; Nagamochi, M.; Fukumoto, K. *J. Org. Chem.* **1992**, *57*, 1707.

(94) Nemoto, H; Tanabe, T.; Nagamochi, M.; Fukumoto, K. *Heterocycles* **1993**, *35*, 707.

(95) Nemoto, H.; Shiraki, M.; Nagamochi, M.; Fukumoto, K. *Tetrahedron Lett.* **1993**, *34*, 4939.

(96) (a) Nemoto, H; Tanabe, T.; Fukumoto, K. *Tetrahedron Lett.* **1994**, *35*, 6499. (b) Nemoto, H; Tanabe, T.; Fukumoto, K. *J. Org. Chem.* **1995**, *60*, 6785.

(97) (a) Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 3827. (b) Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 6431. (c) Maruoka, K.; Ooi, T.; Nagahara, S.; Yamamoto, H. *Tetrahedron* **1991**, *47*, 6983. (d) Maruoka, K.; Sato, J.; Yamamoto, H. *Tetrahedron* **1992**, *48*, 3749.

(98) Irie, O.; Shishido, K. *Chem. Lett.* **1995**, *1*, 53.

(99) Bando, T.; Shishido, K. *Chem. Commun.* **1996**, *11*, 1357.

(100) Fujita, M.; Shindo, M.; Shishido, K. *Tetrahedron Lett.* **2005**, *46*, 1269.

(101) Du, X. L.; Chen, H. L.; Feng, H. J.; Li, Y. C. *Helv. Chim. Acta* **2008**, *91*, 371.

(102) Wilson, M. S.; Woo, J. C. S.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4237.

(103) (a) Gao, S. H.; Wang, Q. L.; Chen, C. *J. Am. Chem. Soc.* **2009**, *131*, 1410. (b) Gao, S. H.; Wang, Q. L.; Huang, L. J. −S.; Lum, L.; Chen, C. *J. Am. Chem. Soc.* **2010**, *132*, 371.

(104) Kita, Y.; Furukawa, A.; Futamura, J.; Ueda, K.; Sawama, Y.; Hamamoto, H.; Fujioka, H. *J. Org. Chem.* **2001**, *66*, 8779.

(105) Kita, Y.; Futamura, J.; Ohba, Y.; Sawama, Y.; Ganesh, J. K.; Fujioka, H. *J. Org. Chem.* **2003**, *68*, 5917.

(106) Srikrishna, A.; Nagamani, S. A.; Jagadeesh., S. G. *Tetrahedron: Asymmetry* **2005**, *16*, 1569.
(107) (a) Srikrishna, A.; Nagamani, S. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, *23*, 3393. (b) Srikrishna, A.; Shaktikumar, L.; Satyanarayana, G. *ARKIVOC* **2003**, *9*, 69.
(108) (a) Srikrishna, A.; Ramasastry, S. S. V. *Tetrahedron Lett.* **2005**, *46*, 7373. (b) Srikrishna, A.; Ramasastry, S. S. V. *Tetrahedron Lett.* **2006**, *47*, 335.
(109) (a) Guerrab, Z.; Daou, B.; Fkih-Tetouani, S.; Ahmarb, M.; Cazes, B. *Tetrahedron Lett.* **2003**, *44*, 5727. (b) Guerrab, Z.; Daou, B.; Fkih-Tetouani, S.; Ahmarb, M.; Cazes, B. *Tetrahedron* **2007**, *63*, 3367.
(110) (a) Tønder, J. E.; Tanner, D. *Tetrahedron* **2003**, *59*, 6937. (b) Vital, P.; Tanner, D. *Org. Biomol. Chem.* **2006**, *4*, 4292.
(111) Rosales, A.; Estévez, R. E.; Cuerva, J. M.; Oltra, J. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 319.
(112) (a) Gerard, B.; Jones, G., II; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 13620. (b) Gerard, B.; Sangji, S.; O'Leary, D. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 7754. (c) Gerard, B.; Cencic, R.; Pelletier, J.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2007**, *46*, 7831. (d) Roche, S. P.; Cencic, R.; Pelletier, J.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2010**, *49*, 6533.
(113) (a) Liu, Y. H.; McWhorter, W. W., Jr. *J. Org. Chem.* **2003**, *68*, 2618. (b) Liu, Y. H.; McWhorter, W. W., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 4240.
(114) Fujii, H.; Ogawa, R.; Ohata, K.; Nemoto, T.; Nakajima, M.; Hasebe, K.; Mochizuki, H.; Nagase, H. *Bioorg. Med. Chem.* **2009**, *17*, 5983.
(115) (a) Simpson, T. J.; De Jesus, A. E.; Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Chem. Commun.* **1982**, *11*, 631. (b) Townsend, C. A.; Christensen, S. B.; Davis, S. G. *J. Am. Chem. Soc.* **1982**, *104*, 6152. (c) Sankawa, U.; Shimada, H.; Kobayashi, T.; Ebizuka, Y.; Yamamoto, Y.; Noguchi, H.; Seto, H. *Heterocycles* **1982**, *19*, 1053. (d) Townsend, C. A.; Davis, S. G. *J. Chem. Soc., Chem. Commun.* **1983**, *23*, 1420.
(116) (a) Townsend, C. A.; Davis, S. G.; Koreeda, M.; Hulin, B. *J. Org. Chem.* **1985**, *50*, 5428. (b) Townsend, C. A.; Christensen, S. B. *J. Am. Chem. Soc.* **1985**, *107*, 270. (c) Townsend, C. A.; Isomura, Y.; Davis, S. G.; Hodge, J. A. *Tetrahedron* **1989**, *45*, 2263. (d) Minto, R. E.; Townsend, C. A. *Chem. Rev.* **1997**, *97*, 2537.
(117) Marion, F.; Williams, D. E.; Patrick, B. O.; Hollander, I.; Mallon, R.; Kim, S. C.; Roll, D. M.; Feldberg, L.; Van Soest, R.; Andersen, R. J. *Org. Lett.* **2006**, *8*, 321.
(118) George, J. H.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2010**, *12*, 2394.
(119) Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; JoséCano, M.; Haidour, A.; Alvarez-Manzaneda, R. *Org. Lett.* **2010**, *12*, 4450.
(120) (a) Kruger, G. J.; Steyn, P. S.; Vleggaar, R.; Rabie, C. J. *J. Chem. Soc., Chem. Commun.* **1979**, *10*, 441. (b) Steyn, P. S.; Vleggarr, R. *J. Chem. Soc., Chem. Commun.* **1984**, *15*, 977. (c) De Jesus, A. E.; Steyn, P. S.; Vleggarr, R. *J. Chem. Soc., Chem. Commun.* **1985**, *22*, 1633. (d) Vleggaar, R. *Pure Appl. Chem.* **1986**, *58*, 239.
(121) Eom, K. D.; Raman, J. V.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **2003**, *125*, 5415.
(122) (a) Chopra, A. K.; Moss, G. P.; Weedon, B. C. L. *J. Chem. Soc., Chem. Commun.* **1977**, *13*, 467. (b) Chopra, A. K.; Khare, A.; Moss, G. P.; Weedon, B. C. L. *J. Chem. Soc., Perkin Trans. 1* **1988**, *6*, 1383.
(123) (a) Tode, C.; Yamano, Y.; Ito, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, *13*, 1581.
(124) (a) Tode, C.; Yamano, Y.; Ito, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, *24*, 3338. (b) Yamano, Y.; Ito, M. *Chem. Pharm. Bull.* **2001**, *49*, 1662. (c) Yamano, Y.; Ito, M. *Chem. Pharm. Bull.* **2004**, *52*, 780. (d) Yamano, Y.; Ito, M. *Org. Biomol. Chem.* **2007**, *5*, 3207. (e) Yamano, Y.; Ito, M.; Wada, A. *Org. Biomol. Chem.* **2008**, *6*, 3421.
(125) Iguchi, K.; Shimada, Y.; Yamada, Y. *J. Org. Chem.* **1992**, *57*, 522.
(126) Basabe, P.; Diego, A.; Díez, D.; Marcos, I. S.; Mollinedo, F.; Uronesa, J. G. *Synthesis* **2002**, *11*, 1523.
(127) Lunardi, I.; Santiago, G. M. P.; Imamura, P. M. *Tetrahedron Lett.* **2002**, *43*, 3609.
(128) (a) Birch, A. J.; Wright, J. J. *J. Chem. Soc., Chem. Commun.* **1969**, *12*, 644. (b) Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329. (c) Birch, A. J.; Russell, R. A. *Tetrahedron* **1972**, *28*, 2999. (d) Coetzer, J. *Acta Crystallogr.* **1974**, *B30*, 2254. (e) Paterson, R. R. M.; Simmonds, M. J. S.; Kemmelmeier, C.; Blaney, W. M. *Mycol. Res.* **1990**, *94*, 538.
(129) (a) Williams, R. M.; Stocking, E. M.; Sanz-Cevera, J. F. *Top. Curr. Chem.* **2000**, *209*, 97. (b) Williams, R. M. *Chem. Pharm. Bull.* **2002**, *50*, 711. (c) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127. For Williams' syntheses of other prenylated indole alkaloids not discussed in this review, see:(d) Williams, R. M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 808. (e) Williams, R. M.; Sanz-Cervera, J. F.; Sancenón, F.; Marco, J. A.; Halligan, K. *J. Am. Chem. Soc.* **1998**, *120*, 1090. (f) Williams, R. M.; Cao, J.; Tsujishima, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2540. (g) Stocking, E. M.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 1675. (h) Grubbs, A. W.; Artman, G. D., III; Tsukamoto, S.; Williams, R. M. *Angew. Chem., Int. Ed.* **2000**, *46*, 2257. (i) Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 2556. (j) Greshock, T. J.; Grubbs, A. W.; Williams, R. M. *Tetrahedron* **2007**, *63*, 6124. (k) Greshock, T. J.; Williams, R. M. *Org. Lett.* **2007**, *9*, 4255. (l) Miller, K. A.; Welch, T. R.; Greshock, T. J.; Ding, Y. S.; Sherman, D. H.; Williams, R. M. *J. Org. Chem.* **2008**, *73*, 3116. (m) Finefield, J. M.; Williams, R. M. *J. Org. Chem.* **2010**, *75*, 2785.
(130) (a) Baldas, J.; Birch, A. J.; Russell, R. A. *J. Chem. Soc., Perkin Trans.* **1974**, *1*, 50. (b) Williams, R. M.; Kwast, E.; Coffman, H.; Glinka, T. *J. Am. Chem. Soc.* **1989**, *111*, 3064. (c) Sanz-Cervera, J. F.; Glinka, T.; Williams, R. M. *Tetrahedron* **1993**, *49*, 8471. (d) Domingo, L. R.; Sanz-Cervera, J. F.; Williams, R. M.; Picher, M. T.; Marco, J. A. *J. Org. Chem.* **1997**, *62*, 1662.
(131) Williams, R. M.; Sanz-Cervera, J. F.; Sancenón, F.; Marco, J. A.; Halligan, K. M. *Bioorg. Med. Chem.* **1998**, *6*, 1233.
(132) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 557.
(133) Greshock, T. J.; Grubbs, A. W.; Tsukamoto, S.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2262.
(134) Miller, K. A.; Tsukamoto, S.; Williams, R. M. *Nat. Chem.* **2009**, *1*, 63.
(135) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303.
(136) (a) Jeong, S.; Chen, X.; Harran, P. G. *J. Org. Chem.* **1998**, *63*, 8640. (b) Chen, X.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 937. (c) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4765. (d) Li, J.; Chen, X.; Burgett, A. W. G.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 2682. (e) Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4770. For Harran's synthesis of the correct structure of (−)-Diazonamide A, see:(f) Burgett, A. W. G.; Li, Q. Y.; Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4961.
(137) (a) Baran, P. S.; Burns, N. Z. *J. Am. Chem. Soc.* **2006**, *128*, 3908. (b) Burns, N. Z.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 205. (c) Burns, N. Z.; Krylova, I. N.; Hannoush, R. N.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 9172. (d) Burns, N. Z.; Jessing, M.; Baran, P. S. *Tetrahedron* **2009**, *65*, 6600.
(138) Kim, D.; Shim, P. J.; Lee, J.; Park, C. W.; Hong, S. W.; Kim, S. *J. Org. Chem.* **2000**, *65*, 4864.
(139) Uyehara, T.; Onda, K.; Nozaki, N.; Karikomi, M.; Ueno, M.; Sato, T. *Tetrahedron Lett.* **2001**, *42*, 699.
(140) For the fluorinium ion-induced enantioselective semipinacol rearrangement of allylic alcohols, see: (a) Wang, M.; Wang, B. M.; Shi, L.; Tu, Y. Q.; Fan, C. A.; Wang, S. H.; Hu, X. D.; Zhang, S. Y. *Chem. Commun.* **2005**, *44*, 5580. For the palladium- and gold-catalyzed asymmetric rearrangements of allylic and allenylic alcohols, see:(b) Trost, B. M.; Yasukata, T. *J. Am. Chem. Soc.* **2001**, *123*, 7162. (c) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044. (d) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2008**, *130*, 6231. (e) Kleinbeck, F.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 9178. For the organocatalytic asymmetric semipinacol rearrangement of allylic alcolhols, see:(f) Zhang, Q. W.; Fan, C. A.; Zhang, H. J.; Tu, Y. Q.; Zhao, Y. M.; Gu, P. M.; Chen, Z. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8572. (g) Zhang, E.; Fan, C. A.;

Tu, Y. Q.; Zhang, F. M.; Song, Y. L. *J. Am. Chem. Soc.* **2009**, *131*, 14626. For the asymmetric α-ketol rearrangement, see:(h) Brunner, H.; Stöhr, F. *Eur. J. Org. Chem.* **2000**, *15*, 2777. (i) Brunner, H.; Kagan, H. B.; Kreutzer, G. *Tetrahedron: Asymmetry* **2001**, *12*, 497. (j) Brunner, H.; Kagan, H. B.; Kreutzer, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2177. (k) Ooi, T.; Saito, A.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 3220. (l) Ooi, T.; Ohmatsu, K.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 2410. For the asymmetric rearrangement of 2,3-epoxy alcohols, see:(m) Wang, F.; Tu, Y. Q.; Fan, C. A.; Wang, S. H.; Zhang, F. M. *Tetrahedron: Asymmetry* **2002**, *13*, 395. (n) Jeon, S. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9544.