

## Semipinacol Rearrangement in Natural Product Synthesis

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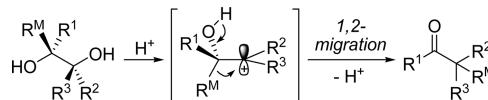
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### 1. INTRODUCTION

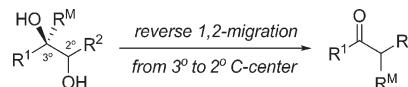
The pinacol rearrangement<sup>1</sup> is a well-known reaction. It refers to the acid-catalyzed transformation of 1,2-diols to ketones or aldehydes by 1,2-migration of a C–C or C–H bond toward the vicinal carbocation (Scheme 1). Although its use is limited because of disadvantages such as poor regio- and diastereoselectivity and unpredictable side reactions, the analogous semipinacol rearrangement reactions<sup>1c,2</sup> 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

### Scheme 1. Classical Pinacol Rearrangement



### Scheme 2. Original Definition of Semipinacol Rearrangement



tertiary–secondary 1,2-diol undergoes an unusual 1,2-migration toward the secondary center, rather than the tertiary one (Scheme 2).<sup>3</sup> 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*.<sup>2</sup> 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*.<sup>4</sup> 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.

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.

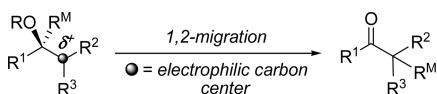
Type I refers to the rearrangement of 2-heterosubstituted alcohols and their derivatives (Scheme 4). In this reaction, good leaving groups such as OMs, OTs, Cl, Br, I, N<sub>2</sub>, SR, and SeR are usually attached to the electrophilic carbon center. The 1,2-migration is facilitated by the loss of the 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

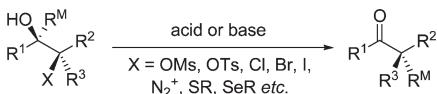
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Published: August 18, 2011

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



**Scheme 4. Type I Rearrangement**



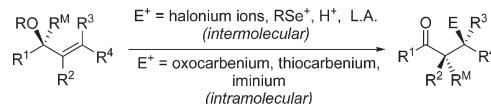
electrophile to a C=C bond. Generally, electrophiles such as halogeniums, selenium cations, and Brønsted and Lewis acids initiate intermolecular rearrangements. In contrast, oxocarbeniums, thiocarbeniums, and iminiums mainly undergo intramolecular ones. The latter case is now widely known as the Prinspinacol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

Type III refers to rearrangements of epoxides.<sup>6</sup> Investigations in this field have focused largely on the rearrangement of 2,3-epoxy alcohols and their derivatives (Scheme 6).<sup>7</sup> 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).

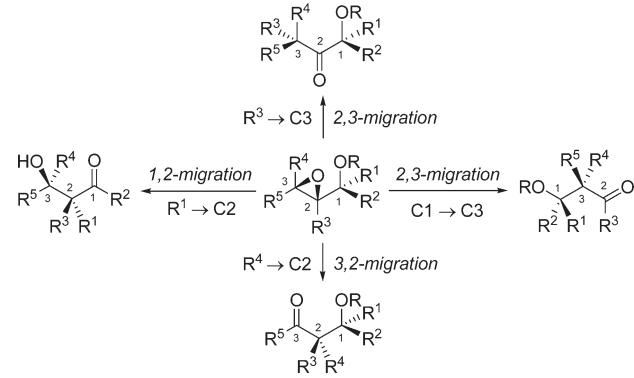
Type IV refers to rearrangements of tertiary  $\alpha$ -hydroxy ketones and imines (Scheme 7). This reaction is also known as the "acyloin rearrangement" or " $\alpha$ -ketol rearrangement".<sup>8</sup> Because an enolization/protonation is impossible for tertiary  $\alpha$ -hydroxy ketones and imines, 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  $\beta$ -halo and  $\beta$ -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 quaternary carbon<sup>9</sup> 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

**Scheme 5. Type II Rearrangement**



**Scheme 6. Type III Rearrangement**



electrophilic carbon center, or when the carbonyl group formed in the rearrangement is subsequently functionalized.<sup>10</sup>

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.

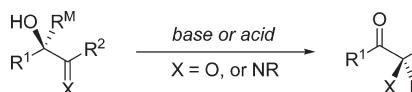
Tsuchihashi and co-workers developed an efficient organoaluminum-promoted semipinacol rearrangement of lactate-derived 1,2-hydroxy mesylate.<sup>11</sup> The reaction proceeded through a proposed Al-chelated intermediate 8 to give enantiomerically pure  $\alpha$ -chiral ketones with full inversion at the C–OMs stereocenter. This methodology was successfully used for the

convergent total synthesis of protomycinolide IV (Scheme 8).<sup>12</sup> The chiral mesyloxy ketone **1** was first reduced by DIBALH. Then the resulting aluminum alkoxide underwent an AlEt<sub>3</sub>-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.

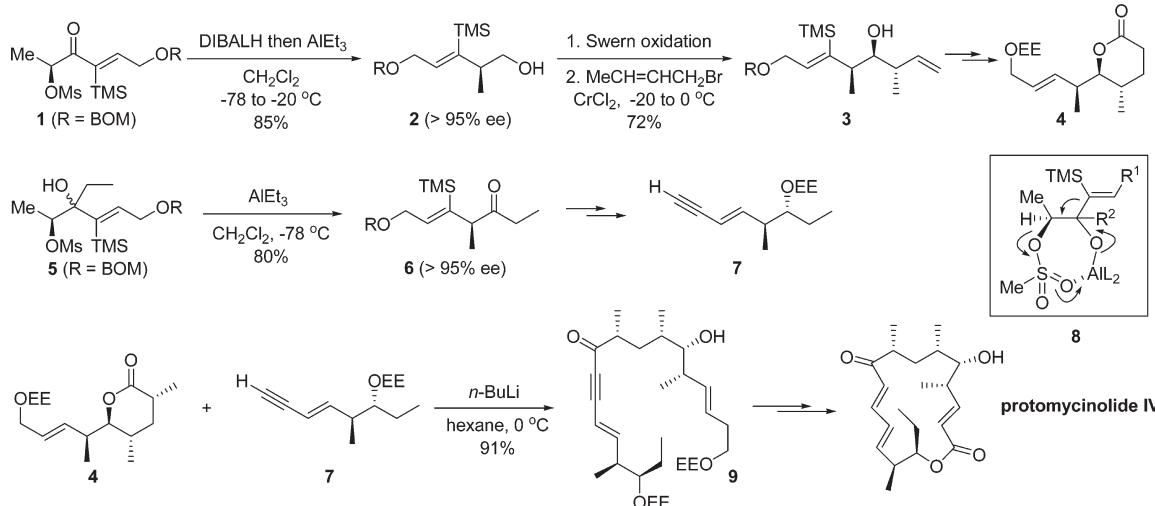
In Rawal and co-workers' total synthesis of ent-elisapterosin B, mesylated ketal **10** was used for the rearrangement (Scheme 9).<sup>13</sup> Upon treatment with excess CaCO<sub>3</sub> as an acid scavenger, **10** underwent a stereospecific 1,2-aryl migration via bridging phenonium ion **11** to generate 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,<sup>14</sup> 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<sub>3</sub> 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-

**Scheme 7. Type IV Rearrangement**



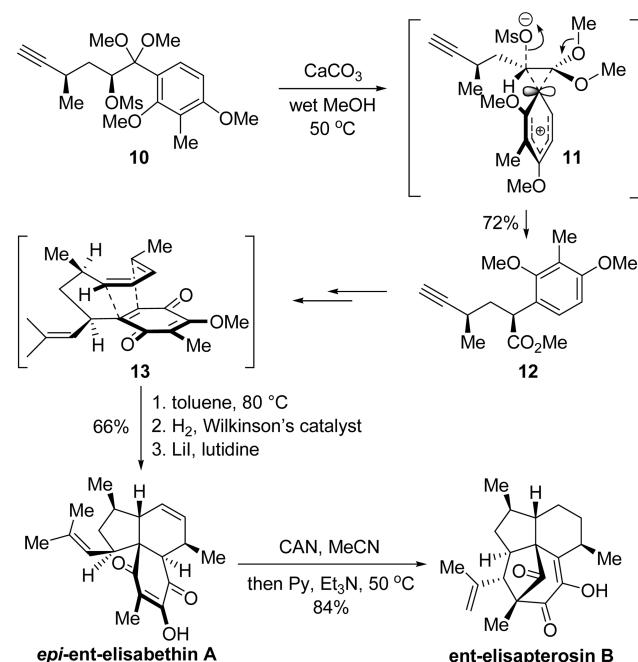
**Scheme 8. Tsuchihashi's Total Synthesis of Protomycinolide IV**

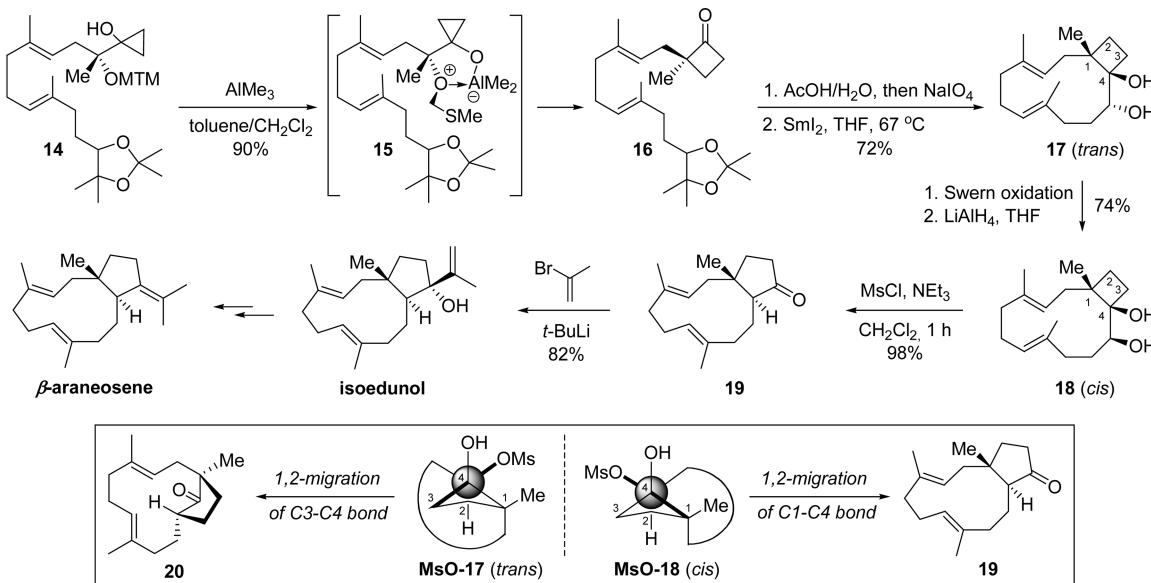


migration of the C1–C4 bond, the rearrangement of trans-diol **17** gave only the bridged 5,12-bicyclopentanone **20** via 1,2-migration of the C3–C4 bond. On the basis of X-ray crystallographic analysis of both **17** and **18**, the authors proposed that the conformational rigidity imposed by the 12-membered 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.

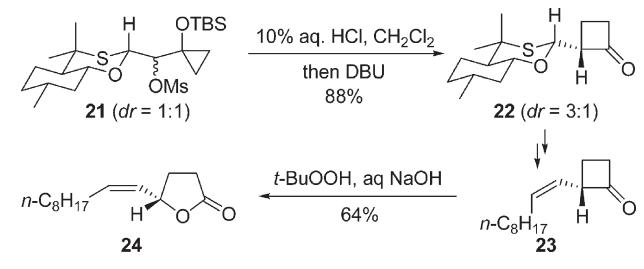
Nemoto and Fukumoto developed a series of useful approaches for the syntheses of chiral cyclobutanones (Scheme 11).<sup>15</sup> One of the methods is based on a semipinacol rearrangement of the 1,2-hydroxy mesylate mixture **21**, which features an oxathiane as a chiral auxiliary.<sup>16</sup> Upon 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 9. Rawal's Total Synthesis of Ent-elisapterosin B**

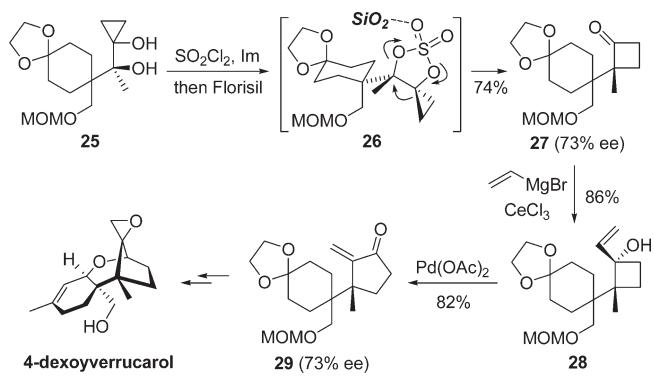


Scheme 10. Corey's Total Syntheses of Isoedunol and  $\beta$ -Araneosene

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



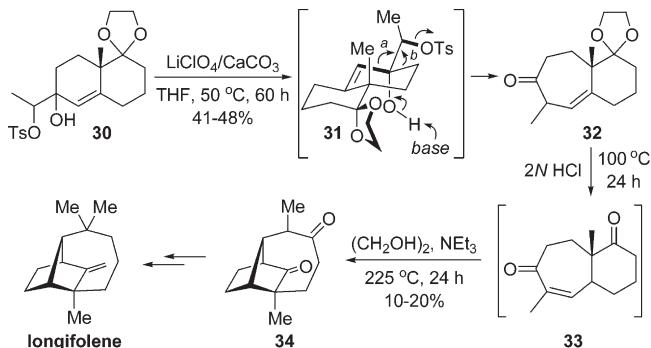
Scheme 12. Nemoto and Fukumoto's Total Synthesis of 4-Deoxyverrucarol



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

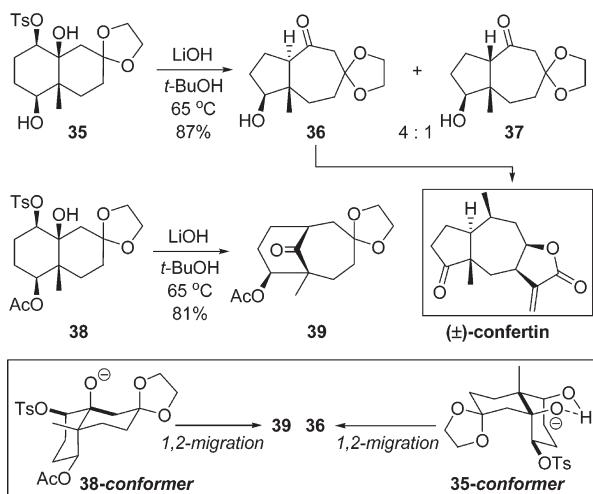
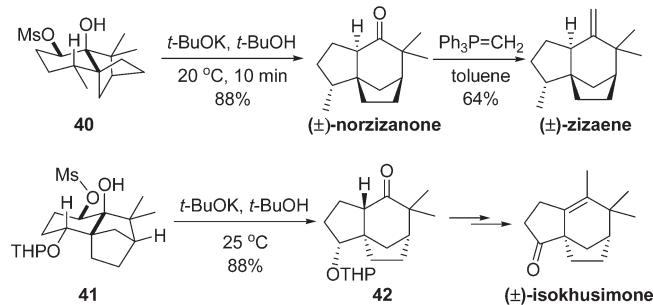
Scheme 13. Corey's Total Synthesis of Longifolene



form the chiral cyclobutanone intermediate 27 (Scheme 12).<sup>17</sup> On treatment with SO<sub>2</sub>Cl<sub>2</sub> 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<sub>3</sub> to generate 27 directly in 74% yield. After the transformation to vinylcyclobutanol 28, a second ring expansion was induced by Pd(OAc)<sub>2</sub> to give cyclopentanone 29 in 82% yield. This intermediate was ultimately transformed into the target.

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).<sup>18</sup> 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 ( $\pm$ )-confertin, Heathcock et al. observed interesting solvolytic behavior in the semipinacol rearrangement

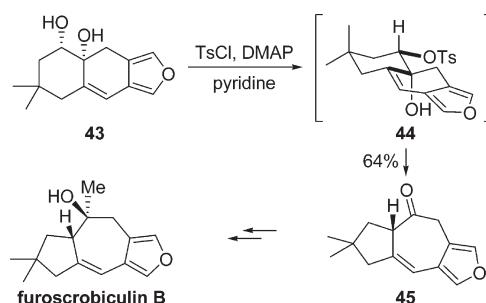
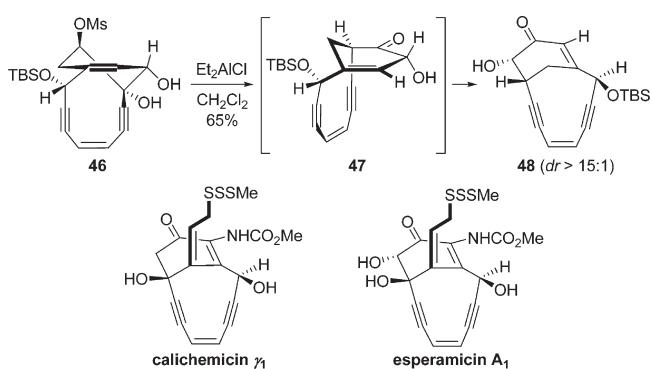
**Scheme 14.** Heathcock's Total Synthesis of ( $\pm$ )-Confertin**Scheme 15.** Mukherjee's Total Syntheses of ( $\pm$ )-Zizaene and (+)-Isokhusimone

of tosylacetate 35 and tosylalcohol 38 (Scheme 14).<sup>19</sup> 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 ( $\pm$ )-zizaene and ( $\pm$ )-isokhusimone (Scheme 15).<sup>20</sup> Treatment of monomesylates 40 and 41 with *t*-BuOK caused a facile rearrangement at room temperature to give ( $\pm$ )-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).<sup>21</sup> 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 Calichemicin Aglycones

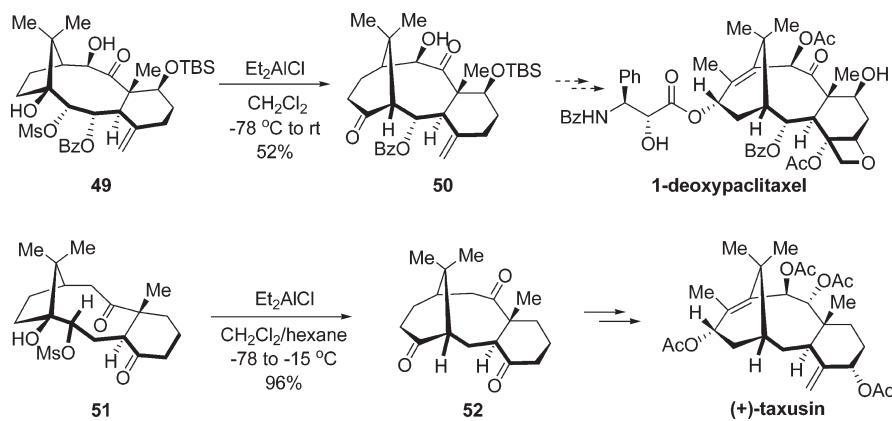
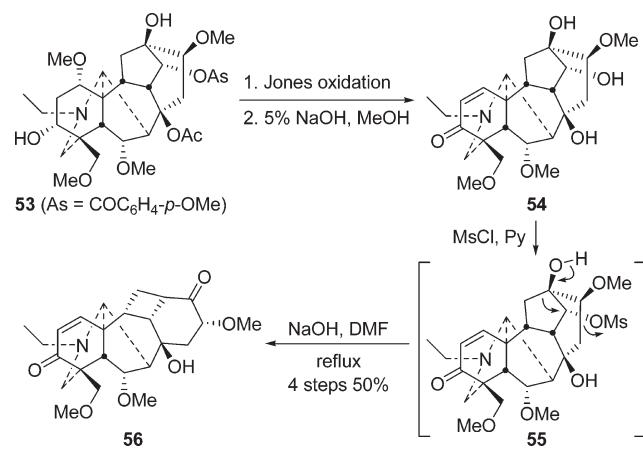
ring systems. For example, Et<sub>2</sub>AlCl-promoted rearrangement of 1,2-hydroxy mesylate 46 was used in Schreiber's synthesis of the bicyclic core 48, which is related to esperamicin and calichemicin aglycones (Scheme 17).<sup>22</sup> Although the stereochemistry of 48 is consistent with 1,2-migration 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).<sup>23</sup> The antiperiplanar alignment of the  $\alpha$ -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).<sup>24</sup> 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

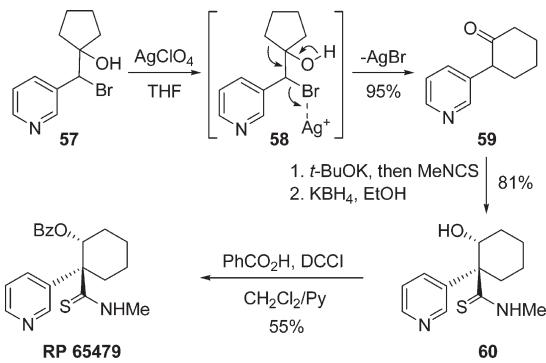
Halohydrins can undergo semipinacol rearrangement either under basic conditions or in the presence of various silver salts.

**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

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 halo-hydrin anion intermediate has been suggested as the mechanism of “quasi-Favorskii” rearrangement,<sup>25</sup> in which the cyclopropanone cannot form because the substrate lacks an  $\alpha$ -hydrogen or because there is steric hindrance.

In Hart et al.’s synthesis of the potent potassium channel opener RP 65479 (Scheme 20),<sup>26</sup> ketone 59 was prepared in 95% yield by a  $\text{AgClO}_4$ -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.

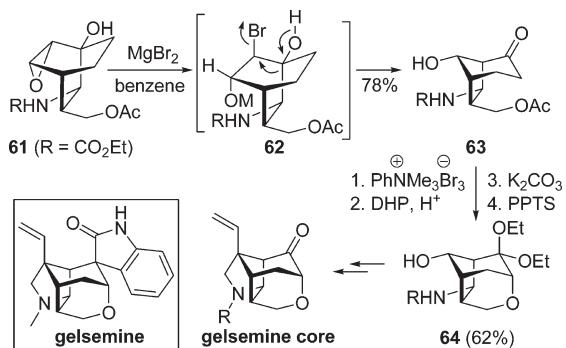
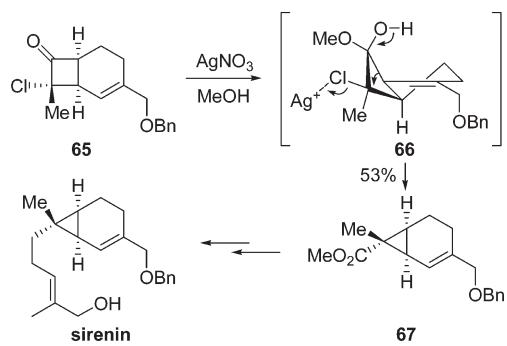
Using the rearrangement of bromohydrin to transform bicyclic-[2.2.2]-octane to bicyclic-[3.2.1]-octane, Fleming and co-workers efficiently synthesized the gelsemine core (Scheme 21).<sup>27</sup> Treatment of epoxy alcohol 61 with  $\text{MgBr}_2 \cdot \text{OEt}_2$  generated the bromohydrin 62, which then underwent a stereospecific 1,2-migration of the bridged C–C bond, giving ketone 63 in 78% yield. Subsequent intramolecular  $\text{S}_{\text{N}}2$  substitution formed the pyran ring, giving 64 in 62% overall yield. This compound was then transformed into the gelsemine core.

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

The female sexual pheromone ( $\pm$ )-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),<sup>28</sup>  $\text{AgNO}_3$ -mediated semipinacol rearrangement of  $\alpha$ -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),<sup>29</sup> 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.

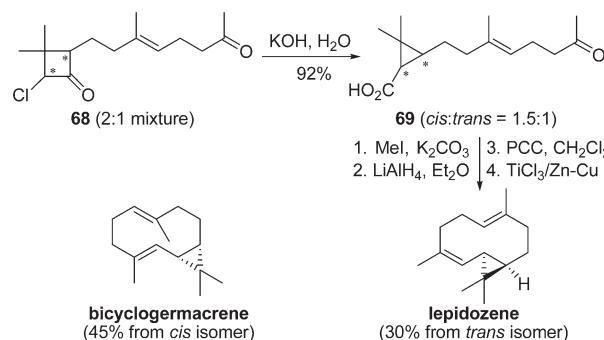
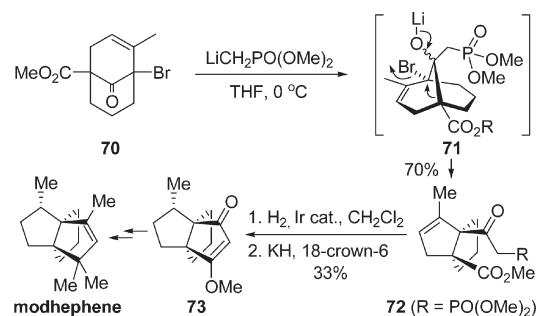
Kraus and Shi reported the synthesis of modhephene using a semipinacol rearrangement of bromobicyclo-[3.3.1]-nonenone 70 to construct the key ring skeleton (Scheme 24).<sup>30</sup> After treatment of 70 with methyl phosphonate anion, the nucleophilic addition/ring-contraction sequence occurred smoothly 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.

**Scheme 21. Fleming's Approach to Gelsemine****Scheme 22. Harding's Total Synthesis of ( $\pm$ )-Sirenin**

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,<sup>31</sup> addition of isobut enyl-lithium to the [4 + 3]-cycloadduct 74 at  $-78^\circ\text{C}$  generated bromohydrin anion 75, which then underwent stereospecific ring contraction at  $-30^\circ\text{C}$  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 spatal,<sup>32</sup> 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.<sup>33</sup>

### 2.3. N<sub>2</sub> as Leaving Group

Diazotization of 1,2-amino alcohols by nitrous acid or direct addition of diazoalkane to ketones can lead to efficient ketone homologation.<sup>34</sup> 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<sub>2</sub> 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.

**Scheme 23. McMurry's Total Syntheses of Bicyclogermacrene and Lepidozene****Scheme 24. Kraus' Total Synthesis of Modhephene**

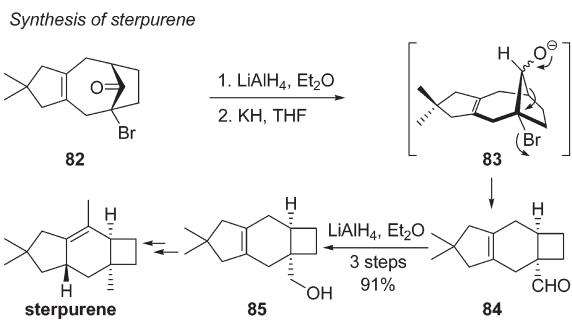
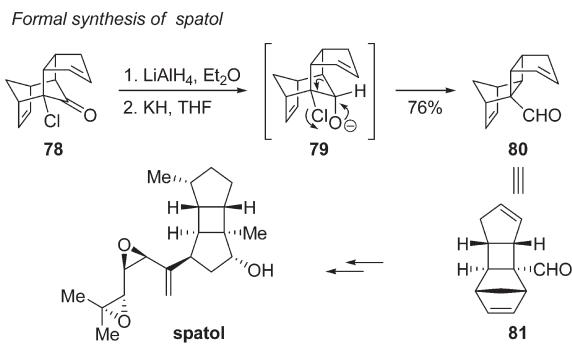
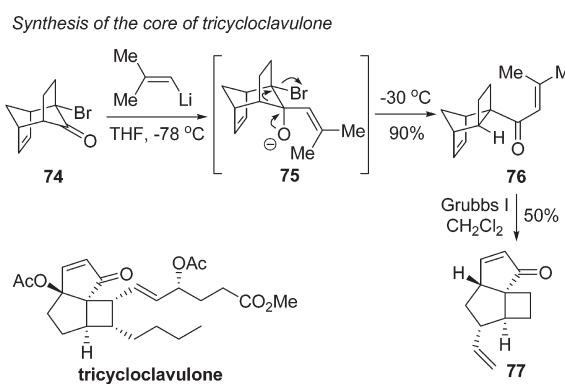
In Greene's total synthesis of (+)-hirsutic acid C (Scheme 26),<sup>35</sup> the rearrangement of cyclobutanone 86 was used to construct the key cyclopentanone 89. Treatment of 86 with ethyl diazoacetate in the presence of SbCl<sub>5</sub> induced a predominantly 1,2-methylene migration (98:2), shown 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<sub>5</sub> than with BF<sub>3</sub>·OEt<sub>2</sub> or BF<sub>4</sub><sup>-</sup>·EtO<sup>+</sup>.

Bakkanes-type sesquiterpenes, which contain a novel spiro- $\gamma$ -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),<sup>36</sup> exposure of cyclobutanone 90 to ethyl diazoacetate in the presence of SbCl<sub>5</sub> 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)<sub>3</sub>-mediated radical cyclization was performed to give the spiroketo lactone 93 in 61% yield. Subsequent SmI<sub>2</sub>-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 (−)-bakkenolides III B, C, H, (−)-homogynolide A, and (±)-palmosalide C.<sup>37</sup>

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<sup>38</sup> and Trost et al.'s synthesis of (+)-frondosin A (Scheme 28).<sup>39</sup>

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

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

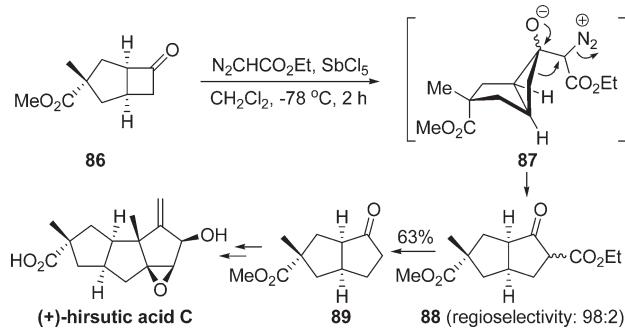


( $\pm$ )-isoclovenewere<sup>40</sup> and Honda et al.'s synthesis of clavukerin A (Scheme 29).<sup>41</sup> All the rearrangements in Schemes 28 and 29 proceeded via exclusive 1,2-migration of the less substituted methylene group.

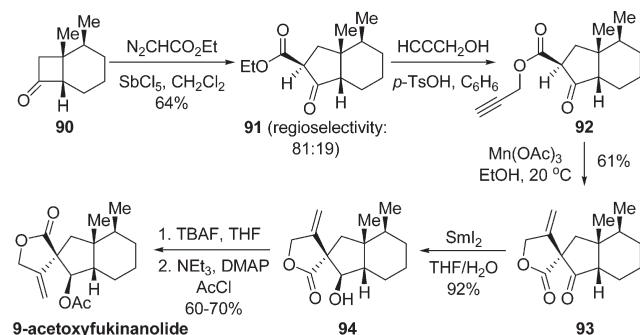
Expansion from a 12- to 13-membered ring was used in Nagel et al.'s synthesis of ( $\pm$ )-muscone (Scheme 30).<sup>42</sup> Treatment of 1,2-amino alcohol 103 with sodium nitrite in the presence of H<sub>2</sub>O and AcOH transformed it into the 13-membered cycloketone 105 in 50–60% yield.

The rearrangement proceeds readily and follows the expected mechanism even in bridged or highly strained polycyclic systems. For instance, in the synthesis of furanoesquiterpene ( $\pm$ )-nakafuran-8 (Scheme 31),<sup>43</sup> Uyehara, Yamamoto, and co-workers employed a sequential ring expansion to establish the key bicyclo-[4.2.2]-decane skeleton. The first ring expansion of 107 was performed with NaNO<sub>2</sub> and AcOH to give ketone 109 in 61% yield. The second ring expansion was carried out by treating

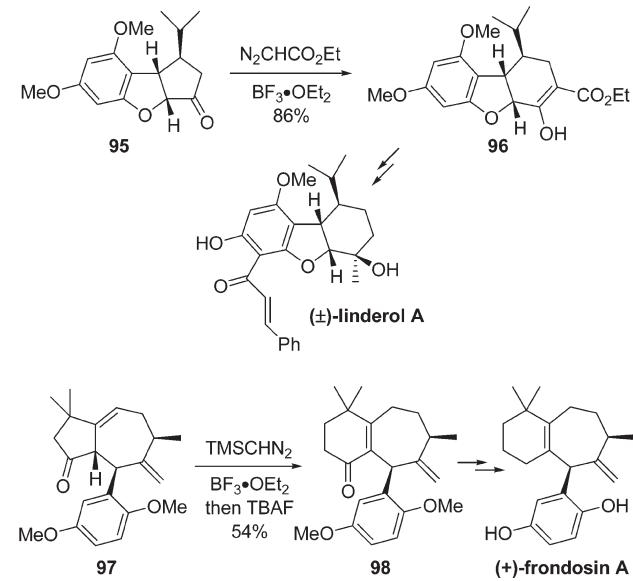
**Scheme 26.** Greene's Total Synthesis of (+)-Hirsutic Acid C



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

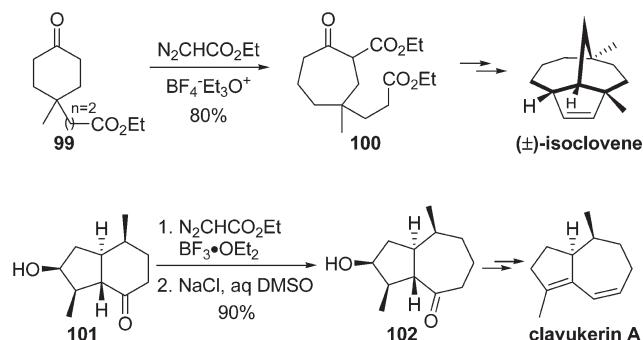


**Scheme 28.** Ohta's Synthesis of ( $\pm$ )-Linderol A and Trost's Total Synthesis of (+)-Frondosin A

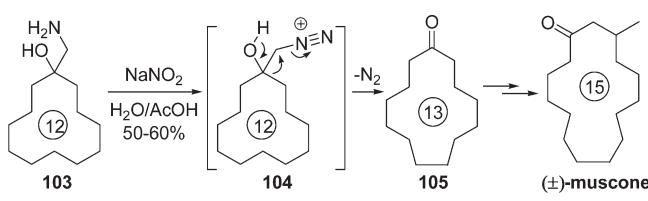


109 with TMSCHN<sub>2</sub> and BF<sub>3</sub>·OEt<sub>2</sub> to afford 110 in 67% yield. In both steps, 1,2-migration of the methylene group was the predominant migration, giving 12:1 and 2:1 regioselectivity for 109 and 110, respectively.

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



**Scheme 30.** Nagel's Total Synthesis of  $(\pm)$ -Muscone



In Miyashita and Yoshikoshi's synthesis of longipinenes containing a rigid pinane skeleton (Scheme 32),<sup>44</sup> 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  $(\pm)$ -fredericamycin using a semipinacol rearrangement of a 1,2-hydroxy thiol compound to construct the spirocyclic skeleton (Scheme 33).<sup>45</sup> 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.

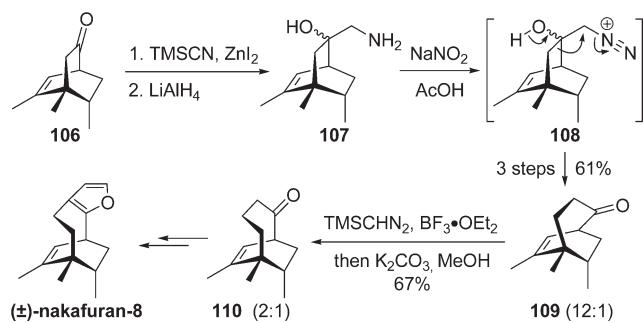
Krief and co-workers developed a concise synthesis of  $\alpha$ -cuparenone using semipinacol rearrangement of 1,2-hydroxy seleno compounds to carry out sequential ring expansions (Scheme 34).<sup>46</sup> The first expansion from a 3- to 4-membered ring in 1,2-hydroxy selenocyclopropane 125 was promoted 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  $\alpha$ -cuparenone in 82% yield.

### 3. REARRANGEMENT OF ALLYLIC ALCOHOLS

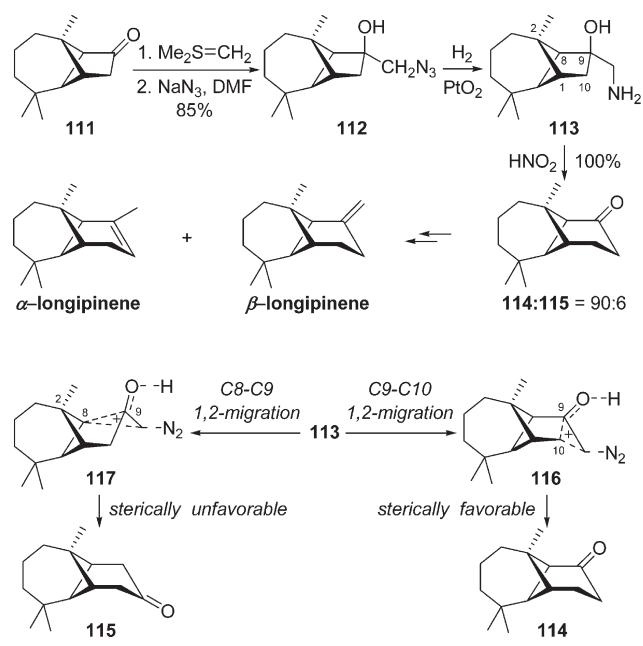
#### 3.1. Induced by Halonium Ions

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  $(\pm)$ -Nakafuran-8

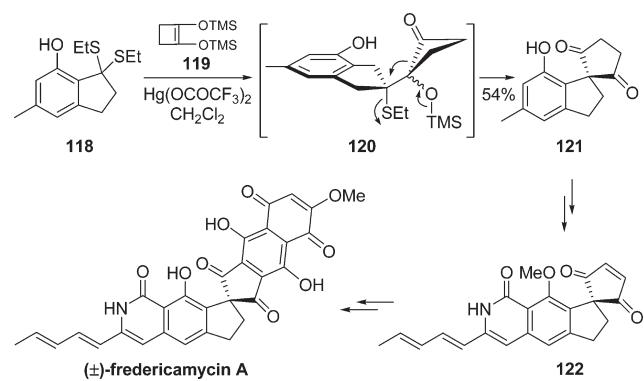
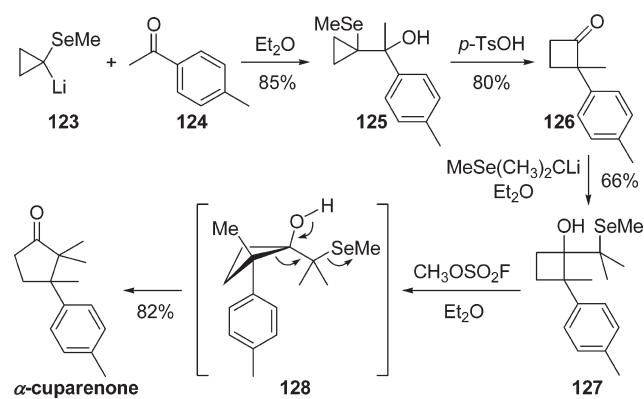


**Scheme 32.** Yoshikoshi's Total Synthesis of Longipinenes



derivatives to give synthetically useful  $\beta$ -halo carbonyl compounds.<sup>47</sup> For example, in Wood and co-workers' elegant total synthesis of  $(-)$ -welwitindolinone A isonitrile (Scheme 35),<sup>48</sup> 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.

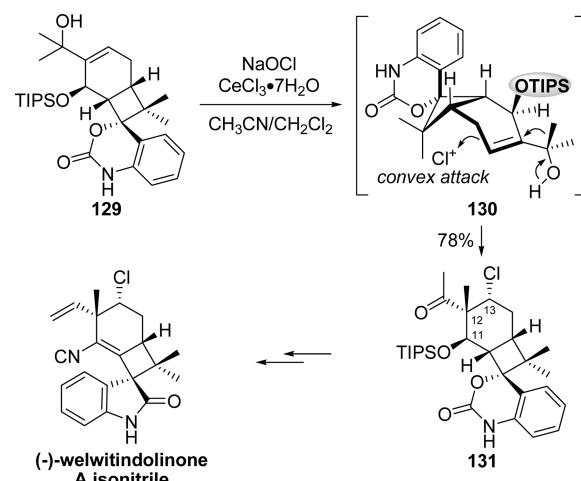
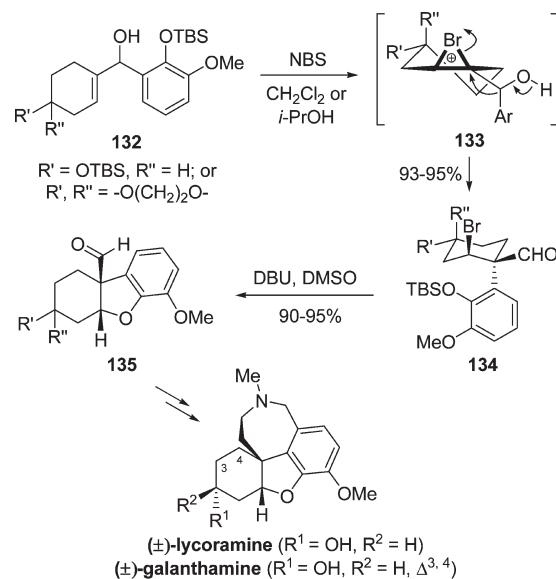
Galanthamine-type *Amaryllidaceae* alkaloids have a common tricyclic benzofuran core with a sterically congested quaternary carbon center located at the bridgehead. Tu and co-workers developed a general approach to these molecules based on a sequential, *N*-bromosuccinimide (NBS)-induced semipinacol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

**Scheme 33.** Bach's Total Synthesis of ( $\pm$ )-Fredericamycin A**Scheme 34.** Krief's Total Synthesis of  $\alpha$ -Cuparenone

(dr) = 3:2) was treated with NBS in CH<sub>2</sub>Cl<sub>2</sub>, 1,2-aryl migration readily occurred and generated the key  $\beta$ -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 desilylation/cyclization protocol to 134 yielded the benzofuran core 135, which was eventually converted into ( $\pm$ )-lycoramine and ( $\pm$ )-galanthamine.

Using the rearrangement as a key step, Tu and co-workers also completed the syntheses of crinine-type *Amaryllidaceae* alkaloids (Scheme 37),<sup>50</sup> 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<sub>3</sub>CN transformed it into  $\beta$ -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 ( $\pm$ )-tazettine, ( $\pm$ )-hemeanthidine, ( $\pm$ )-pretazettine, and ( $\pm$ )-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).<sup>51</sup> Treatment of allylic alcohol 141 with NBS in CH<sub>3</sub>CN gave the first expansion from a 5- to 6-membered ring, yielding the spiro  $\beta$ -bromo ketone 142 in 65% yield. Next, AgBF<sub>4</sub>-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 ( $\pm$ )-Lycoramine and ( $\pm$ )-Galanthamine

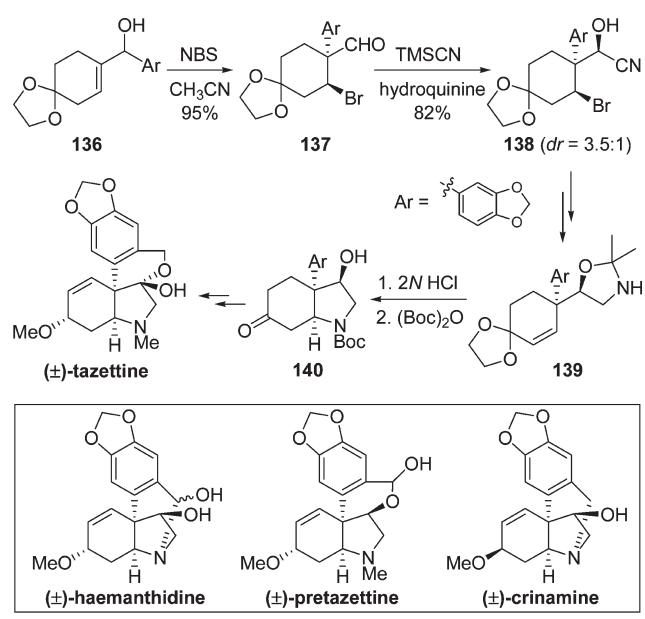
ketone 143. This is the key intermediate in Nakamura's synthesis of colchicine.

In Dake et al.'s studies toward the synthesis of halichlorine (Scheme 39),<sup>52</sup> 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 tauropinnic acid, this approach may be useful for synthesizing these natural products.

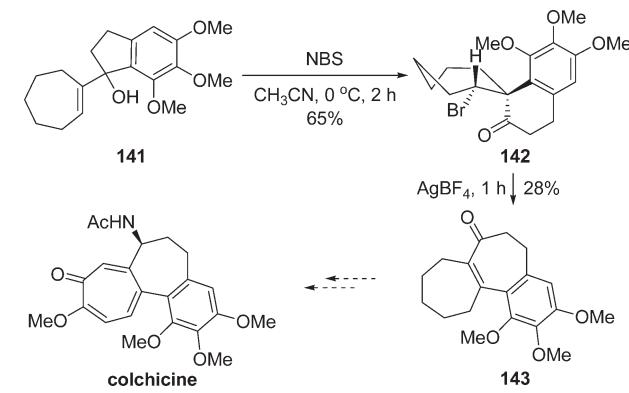
### 3.2. Induced by Selenium Ion

Selenium ion has similar electrophilicity as halonium ions, and it can induce the semipinacol rearrangement of allylic alcohols.

**Scheme 37.** Tu's Total Syntheses of ( $\pm$ )-Tazettine, ( $\pm$ )-Haemanthidine, ( $\pm$ )-Pretazettine, and ( $\pm$ )-Crinamine



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

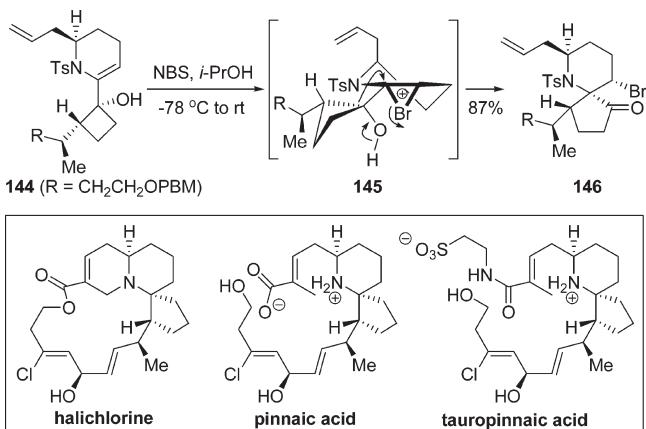


Trost and co-workers reported a selenium-initiated substitutive spiro annulation approach in their total synthesis of plumericin and allamandin (Scheme 40).<sup>53</sup> Electrophilic addition of PhSeBr from the less-hindered convex face of vinylcyclopropanol 147 initiated a highly diastereoselective 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.

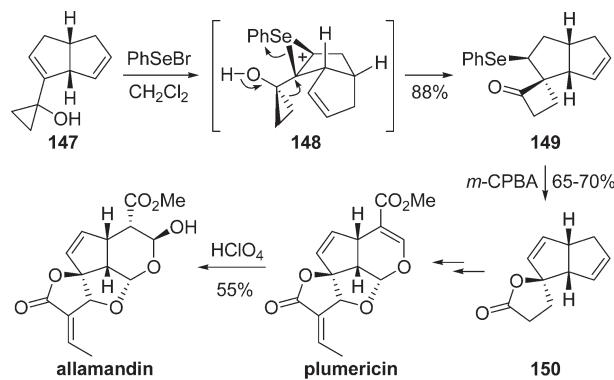
### 3.3. Induced by Brønsted Acids

Paquette and co-workers developed a series of Brønsted acid-induced semipinacol rearrangements of vinyl ether-derived tertiary allylic alcohols.<sup>54</sup> 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),<sup>55</sup> 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



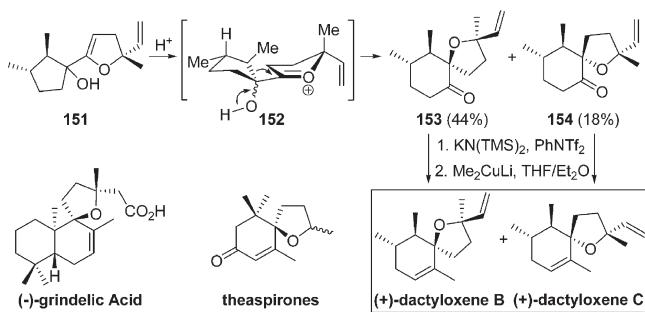
slightly predominant 1,2-migration of the more substituted alkyl group to give two diastereofacial isomers 153 and 154 in 44% and 18% yield, respectively. The method has also been used to synthesize (–)-grindelic acid and theaspirones.

Royer and co-workers' synthesis of (–)-cephalotaxine used a semipinacol rearrangement of the  $\alpha,\beta$ -unsaturated  $\gamma$ -lactam-derived homoallylic alcohol 155 to provide enantiomerically pure 1-aza-spiro ketone 157 (Scheme 42).<sup>56</sup> Treating 155 with HCl transformed it into the proposed  $\alpha$ -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%.

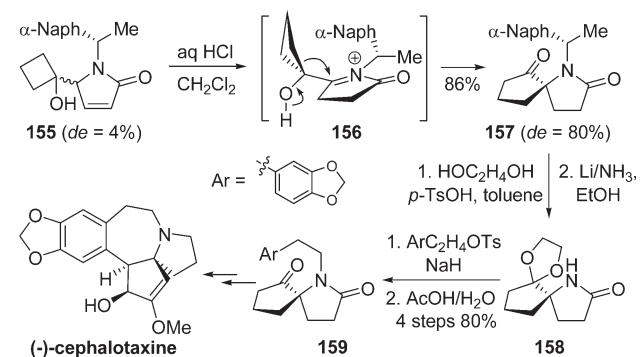
Piras and co-workers investigated the Brønsted acid-induced semipinacol rearrangement of a range of isopropenyl cyclobutanes 160 (Scheme 43).<sup>57</sup> Treatment of 160 with pyridinium *p*-toluenesulfonate (PPTS) in benzene caused selective 1,2-migration of the more-substituted alkyl group, giving 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  $\text{TpMo}(\text{CO})_2(5\text{-oxo-}\eta^3\text{-pyridinyl})$  complex as an enantiomeric scaffold, Liebeskind and co-workers completed a novel asymmetric synthesis of (–)-adaline (Scheme 44).<sup>58</sup> One of the key steps involved an HCl-induced semipinacol

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



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



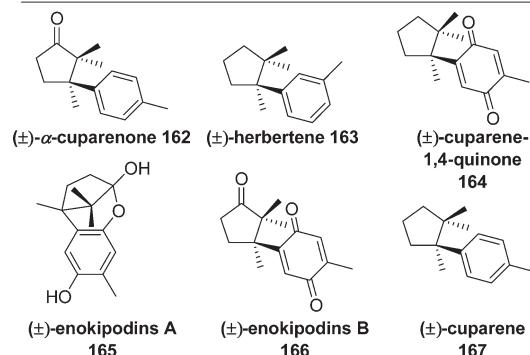
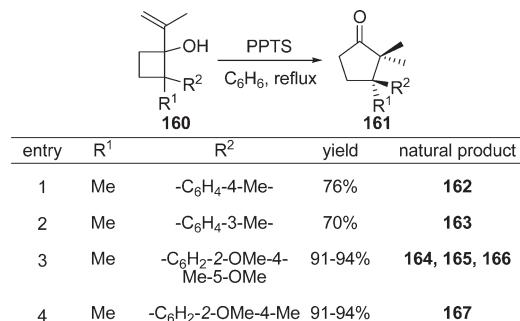
rearrangement of molybdenum  $\pi$ -complex 168, which has an allylic alcohol moiety. Treating 168 with HCl caused a stereospecific 1,2-allyl migration, leading to the formation of the chiral  $\alpha$ -quaternary pyridine 169 in 78% yield. Subsequent Wacker oxidation, Michael-like 1,5-addition, and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

### 3.4. Induced by Lewis Acids

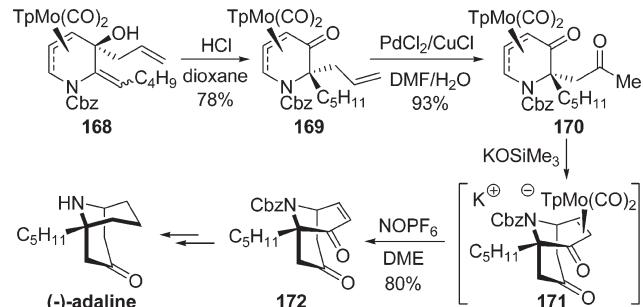
Lewis acids such as  $\text{BF}_3 \cdot \text{OEt}_2$ ,<sup>59</sup>  $\text{Hg}(\text{OCOCF}_3)_2$ ,<sup>60</sup> and Pd(II) catalysts have been used to induce the semipinacol rearrangement of allylic alcohols by activating the  $\text{C}=\text{C}$  bond. For example, Nemoto, Fukumoto, and co-workers developed a useful Pd(II)-promoted ring expansion of various chiral vinylcyclobutans to generate cyclopentanones containing a chiral quaternary carbon center.<sup>61</sup> 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),<sup>62</sup> vinylcyclobutanol 174, prepared from 173 by the addition of Grignard agent and protection, underwent  $\text{Pd}(\text{OAc})_2$ -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).<sup>63</sup> 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 steroid framework in 60% yield, predominantly as the trans-diastereoisomer. Solvents proved to be a

**Scheme 43. Piras' Total Syntheses of ( $\pm$ )- $\alpha$ -Cuparenone and Its Analogues**



**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 ( $\pm$ )-ventricosene using sequential ring expansions catalyzed by Au(I) and Pd(II) (Scheme 47).<sup>64</sup> The enyne 181 was first treated with  $\text{Ph}_3\text{PAuCl}$  and  $\text{AgBF}_4$  to induce cycloisomerization and generate the cyclopropylmethyl cation 182, which then underwent ring

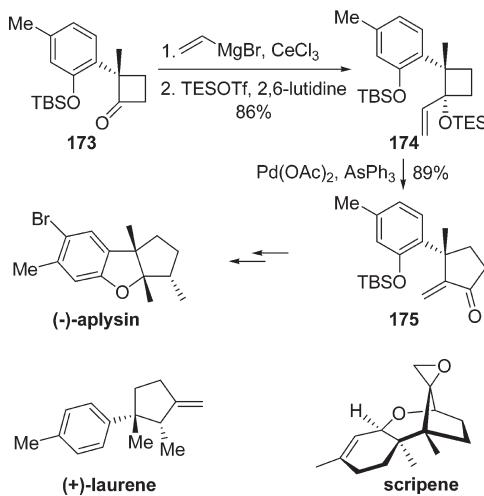
expansion to provide the fused cyclobutanone **183** as a single diastereoisomer in 87% yield. Similar to Nemoto's procedure, the second Pd(II)-catalyzed semipinacol ring expansion of the allylic methyl ether **184** was carried out to give **185**, which contains the complete tricyclic skeleton of ( $\pm$ )-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),<sup>65</sup> treatment of **186** with  $\text{Pd}(\text{OCOCF}_3)_2$  in  $\text{CH}_2\text{Cl}_2$  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 mono-ketal **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.

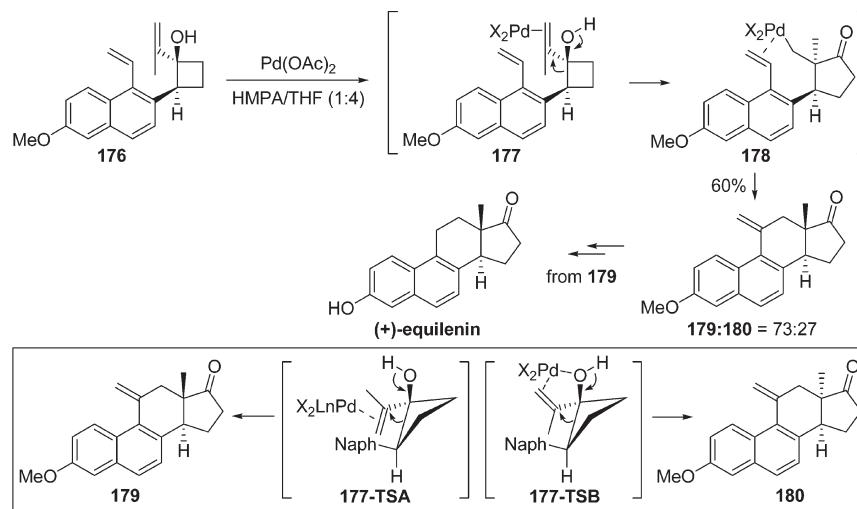
### 3.5. Prins-Pinacol Rearrangement

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  $\text{C}=\text{C}$  bond of allylic alcohols, resulting in the

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



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

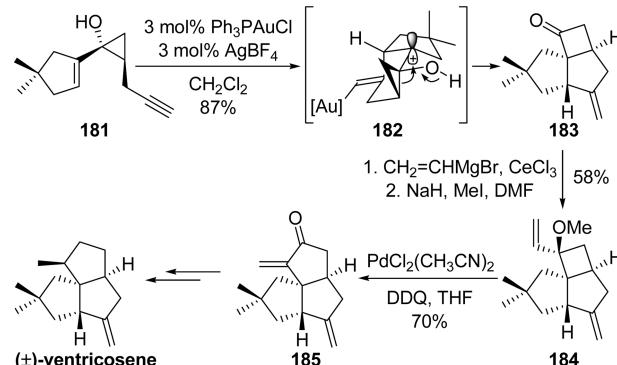


formation of a cationic center, which then induces successive 1,2-migrations to generate carbonyl groups sequentially. Overman's group has developed an outstanding array of chemistries for performing various types of reactions, and they have demonstrated their power by rapidly constructing complex cyclic natural products. Because his group has already published three reviews on this topic,<sup>5</sup> 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<sub>3</sub> and cyathin B<sub>2</sub> (Scheme 49).<sup>66</sup> Cyclopropanol silyl ether **190**, prepared from dienoate **189** via Kulinkovich cyclopropanation and silylation, reacted with acetal **191** in the presence of  $\text{TiCl}_4$  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).<sup>67</sup> The reaction began with the

**Scheme 47.** Toste's Total Synthesis of ( $\pm$ )-Ventricosene

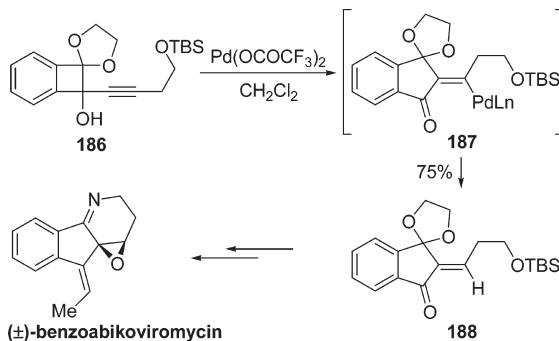


TMSOTf-catalyzed condensation of the primary hydroxyl group of **198** with an aldehyde to generate the oxocarbenium intermediate **199**, which underwent Prins cyclization followed by stereospecific ring contraction of the carbocation **201** to give ketone **202** in 80–90% yield. These spirooxacyclic compounds are attractive targets because they occur in the skeletons of several natural products, such as bakkenolide A, wiphophysalin 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).<sup>68</sup> Treating **203** with TfOH in CH<sub>2</sub>Cl<sub>2</sub> 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.<sup>69</sup> 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<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> generated

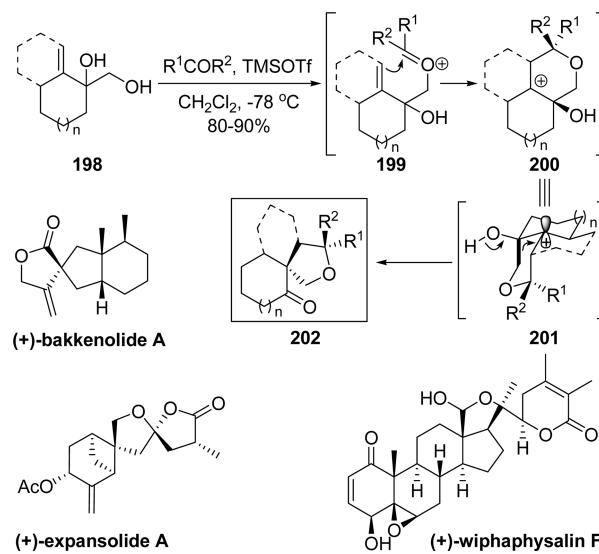
**Scheme 48. Liebeskind's Total Synthesis of ( $\pm$ )-Benzoabikoviromycin**



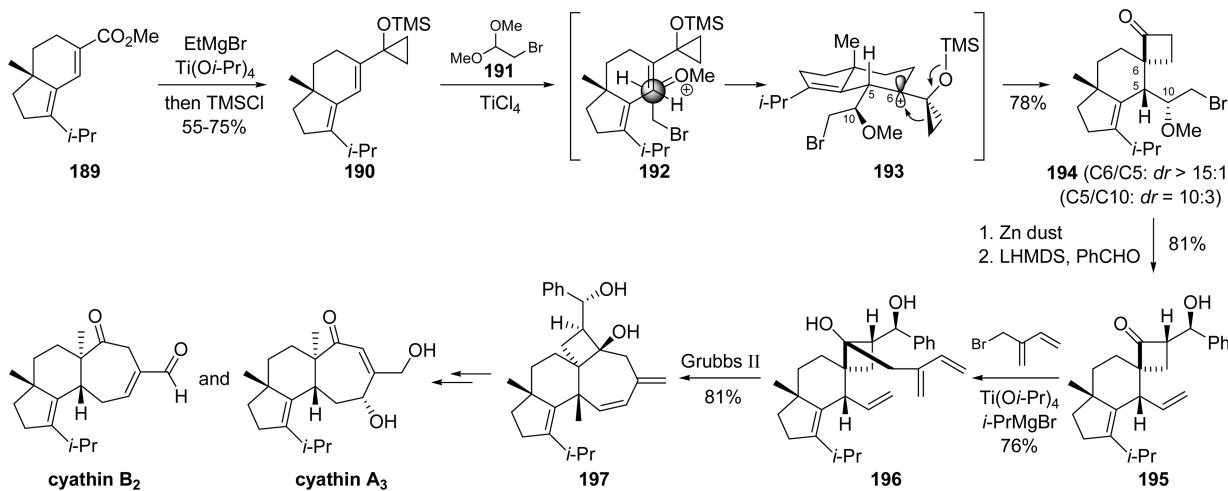
oxacarbenium **209** featuring a chair conformation in which the two 6-membered rings adopt a cofacial orientation. The subsequent Prins cyclization gave carbocation **210**, which underwent 1,2-migrations of C–C and C–H bonds to provide **212** and **213** in a 1.6:1 mixture. Compound **213** has the same stereochemistry as 1,5-epoxysalvin-4(14)-ene, which shares the core of salvia-lane-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 semi-pinacol rearrangement afforded **218** in 81% yield with the same trans-stereochemistry as aspergillin PZ.

The synthetically challenging bicyclic-[*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).<sup>70</sup> In this

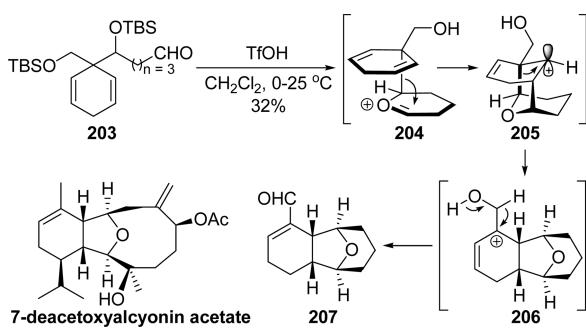
**Scheme 50. Min and Cho's Stereocontrolled Synthesis of Spiro Oxabicycles via Prins-Pinacol Annulation**



**Scheme 49. Cha's Total Syntheses of Cyathin A<sub>3</sub> and Cyathin B<sub>2</sub>**



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



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).<sup>71</sup> 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.

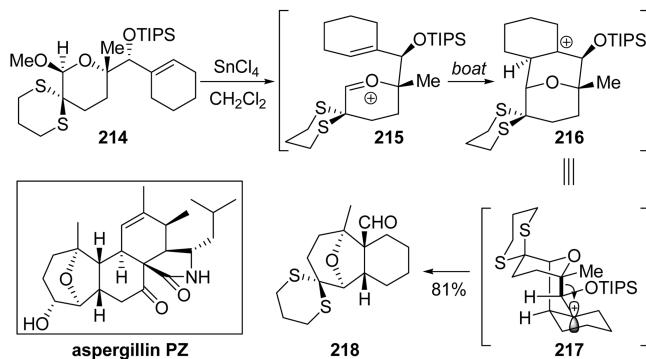
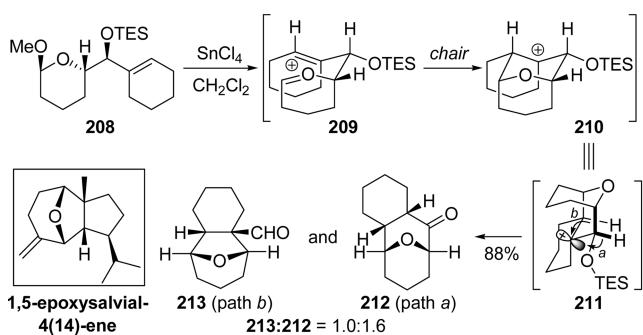
#### 4. REARRANGEMENT OF EPOXIDES

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,<sup>72</sup> the semipinacol rearrangement of 2,3-epoxy alcohols and their derivatives has been extensively investigated in both cyclic and acyclic systems.<sup>7</sup> 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

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

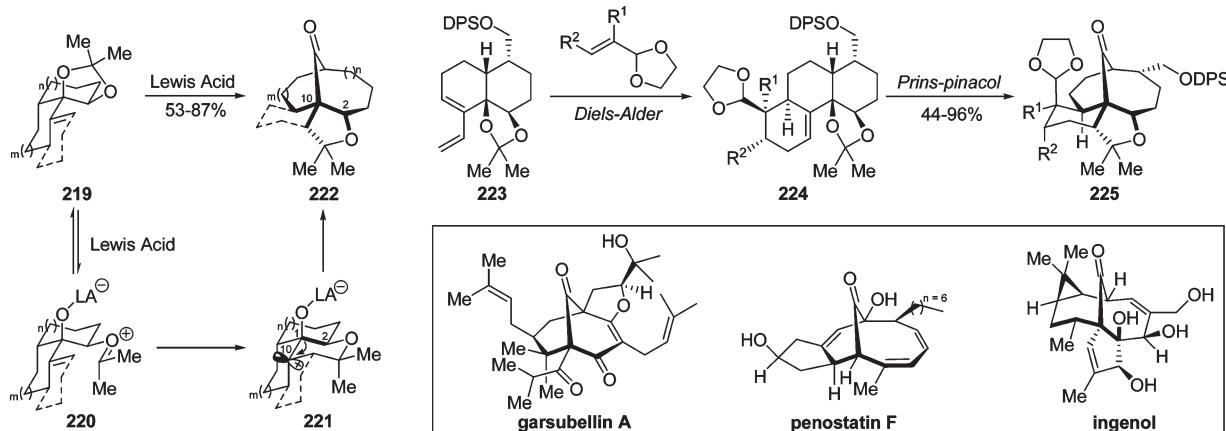
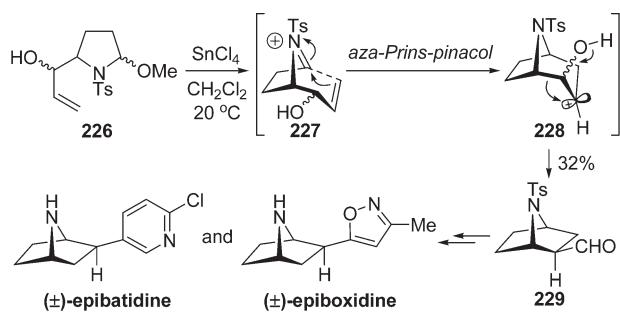


carbon center at the migration terminus, are difficult or impossible to obtain by the classical aldol reaction. Fourth, the resulting carbonyl group can serve as a reactive site to support tandem reactions. Examples discussed in this section are organized according to the type III migration illustrated 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<sub>4</sub> 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).<sup>73</sup> 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 **237** (Scheme 56).<sup>74</sup> Treatment of **237** with AlMe<sub>3</sub> led to a

**Scheme 53.** Barriault's Synthesis of Highly Functionalized Bicyclo-[*m.n.1*]-alkanones via the Prins-Pinacol Reaction**Scheme 54.** Armstrong's Total Syntheses of ( $\pm$ )-Epibatidine and ( $\pm$ )-Epiboxidine

facile, stereospecific 1,2-migration to give  $\beta$ -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).<sup>75</sup> 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.<sup>76</sup> Treatment of 244 with TiCl<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> at –78 °C generated  $\beta$ -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.<sup>77</sup> For example, a tandem semipinacol/Schmidt reaction of 1-siloxy 2,3-epoxy azides has been established<sup>77h</sup> for the rapid construction of aza-quaternary alkaloids such as stemonamine

(Scheme 59).<sup>78</sup> Treating 246 with TiCl<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> 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 ( $\pm$ )-stemonamine.

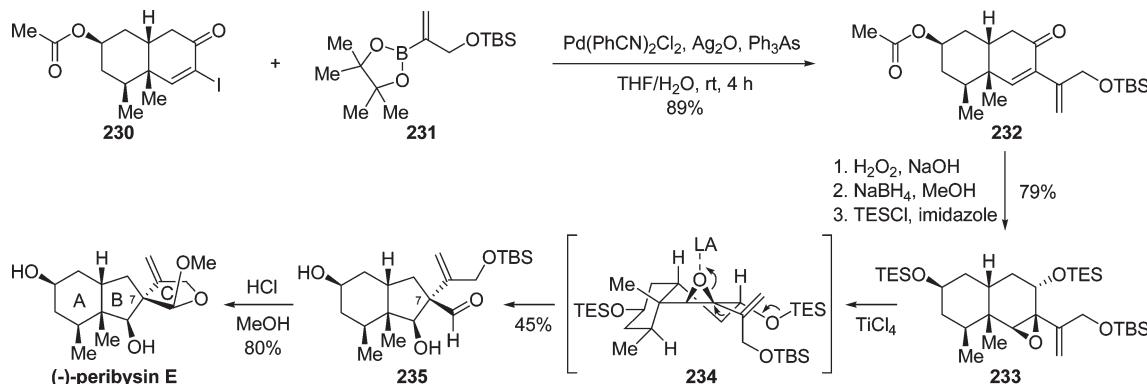
Tu's group used a similar strategy to synthesize ( $\pm$ )-cephalotaxine (Scheme 60).<sup>79</sup> Dropwise addition of 1-siloxyl 2,3-epoxy azide 251 to TiCl<sub>4</sub> gave the rearranged product  $\beta$ -hydroxy ketone 252 in 80% yield. While 252 failed to undergo subsequent N-insertion, the Schmidt 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).<sup>80</sup> Treatment of 254 with TiCl<sub>4</sub> 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<sub>N</sub>2 reaction to furnish fasicularin.

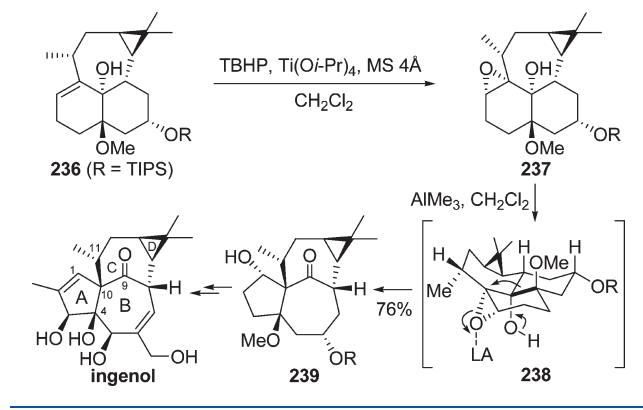
Suzuki and co-workers have shown that the acyclic 2,3-epoxy silyl ether containing a Co-complexed alkynyl group can also undergo a semipinacol rearrangement to introduce the quaternary carbon center stereoselectively.<sup>81</sup> As shown in their syntheses of furaquinocin-type antibiotics (Scheme 62),<sup>82</sup> treatment of 260 with TiCl<sub>4</sub> and Et<sub>3</sub>SiH 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).<sup>83</sup> Two effects of the TMS group were noted. First, the TMS-vinyl group showed a rate-enhancement effect relative to a simple vinyl

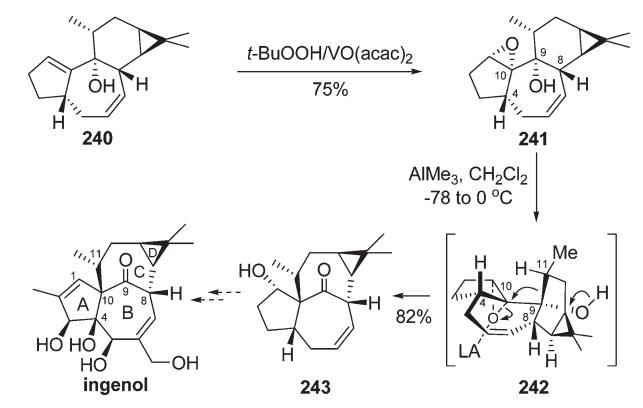
Scheme 55. Danishefsky's Total Synthesis of (-)-Peribysin E



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

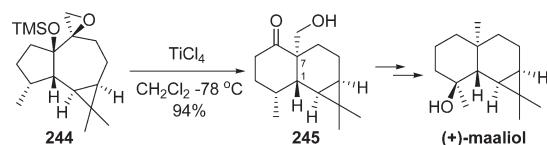
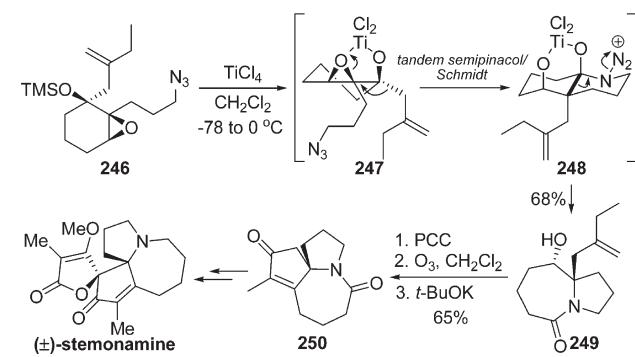


Scheme 57. Cha's Rapid Access to the "In and Out"-Tetracyclic Core of Ingenol



group because of its higher migratory ability. Second, the TMS group exerted a strong 1,2-stereodirecting effect, such that reduction of the resulting aldon (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

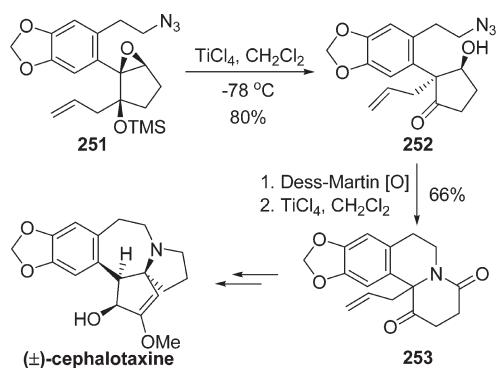
Scheme 59. Tu's Total Synthesis of ( $\pm$ )-Stemonamine

avenaciolide and isoavenaciolide were synthesized from the 2,3-epoxy alcohol analogues 265 and 268, respectively.<sup>84</sup>

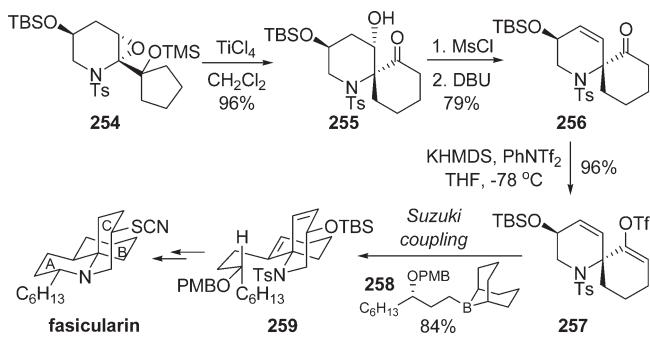
Jung and co-workers developed a useful "nonaldol aldol" process based on the semipinacol rearrangement of acyclic 2,3-epoxy silyl ethers.<sup>85</sup> The rearrangement features an unusual 1,2-migration of a C–H bond and provides the pivotal aldehyde aldol products with excellent diastereoselectivity 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).<sup>86</sup>

Using such a process at an early stage, Jung and co-workers recently completed the total synthesis of auripyrone A (Scheme 65).<sup>87</sup> 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.

**Scheme 60.** Tu's Formal Total Synthesis of ( $\pm$ )-Cephalotaxine



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

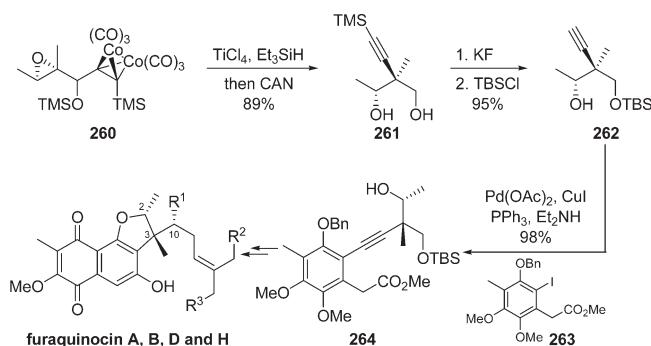


Using Jung's nonaldol aldol process as one of the key steps, Sammakia and co-workers achieved the total synthesis of the oxopolyene macrolide RK-397 (Scheme 66).<sup>88</sup> Rearrangement of 278 gave the aldehyde 279 in 95% yield with 24:1 diastereoselectivity, which possesses the desired C30 and C31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

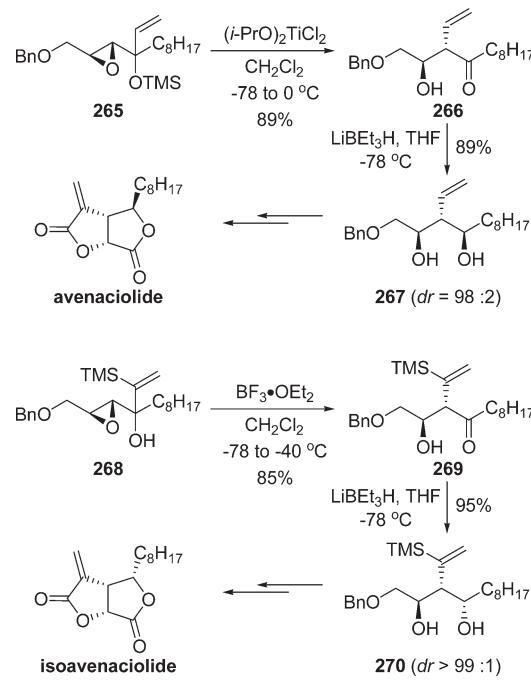
Tu and co-workers discovered that, similar to 2,3-epoxy alcohols, 2,3-aziridino alcohols can also undergo Lewis acid-catalyzed semipinacol rearrangement, giving various  $\alpha$ -quaternary,  $\beta$ -amino carbonyl compounds in good yields and with high diastereoselectivity.<sup>89</sup> The group used this reaction as a key step to develop a general approach to the cis-3a-aryloctahydroindole alkaloids (Scheme 67).<sup>90</sup> Treatment of 2,3-aziridino alcohol 282 with ZnBr<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> 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 ( $\pm$ )-crinane and ( $\pm$ )-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),<sup>91</sup> 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

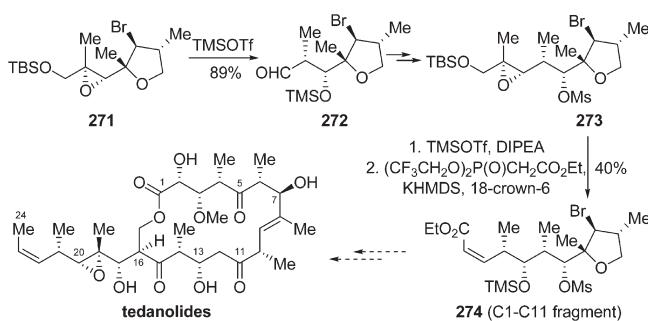


**Scheme 63.** Tsuchihashi and Suzuki's Total Syntheses of Avenaciolide and Isoavenaciolide

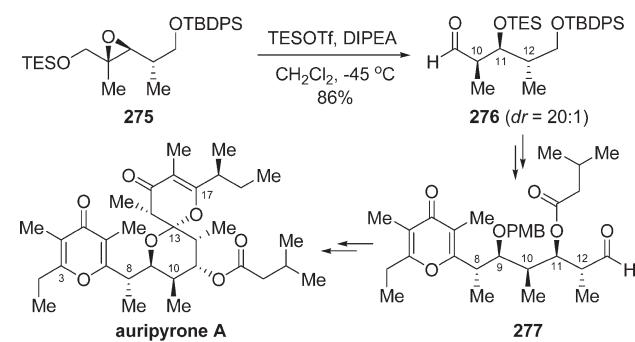


Kita and co-workers' model study of the total synthesis of fredericamycin A revealed an interesting migration selectivity of trans- and cis-benzofused epoxyacylate 289 and 292 during semipinacol rearrangement (Scheme 69).<sup>92</sup> Under the same conditions, whereas the trans-isomer 289 was converted 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 vicinal *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

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



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

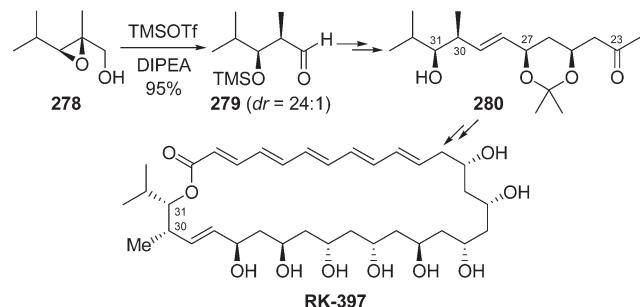


the enone 294 as the product. Moreover, the benzoyl group was found to be essential to migration selectivity, since reactions of other trans-substrates ( $-OSiMe_2t\text{-}Bu$  and  $-OMe$ ) led only to enone 294. The authors proposed that the electron-donating effect of  $-OSiMe_2t\text{-}Bu$  or  $-OMe$  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.

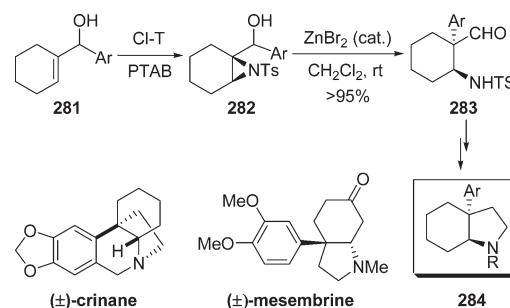
Nemoto, Fukumoto, and co-workers applied a tandem, asymmetric epoxidation/ring-expansion process to cyclopropylidene ethonals 298 to prepare cyclobutanones 300 containing a chiral quaternary carbon (Scheme 70).<sup>93</sup> Oxidation of the resulting cyclobutanones provided various chiral lactones 301,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

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% enantioselective 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

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



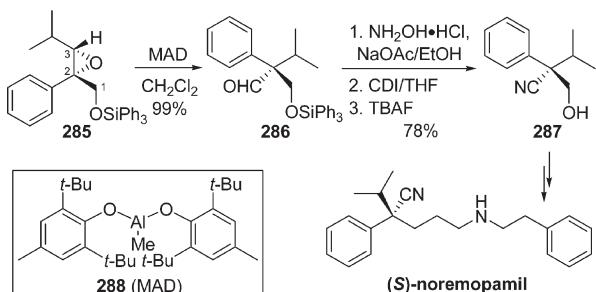
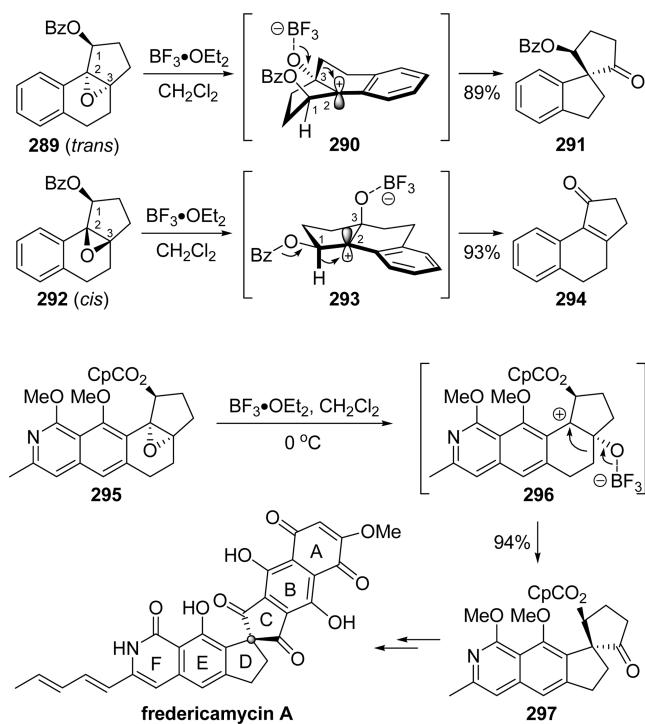
**Scheme 67.** Tu's Total Syntheses of (±)-Crinane and (±)-Mesembrine



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.<sup>97</sup> 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 (−)-anastrephrin,<sup>98</sup> furanoterpenes,<sup>99</sup> (+)-kuhistaferone,<sup>100</sup> and (*R*)-bakuchiol.<sup>101</sup>

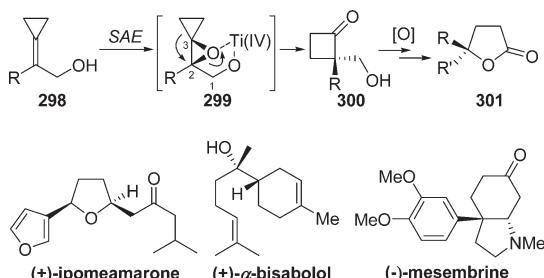
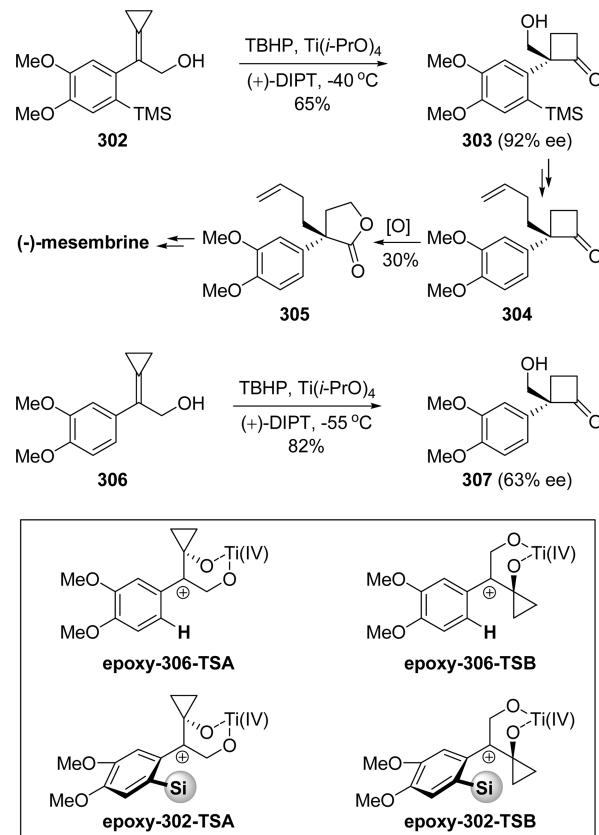
Dake and co-workers reported the synthesis of the epimeric 1,22-dihydroxynitianes using Yamamoto's protocol to establish the key quaternary carbon center at the ring junction (Scheme 73).<sup>102</sup>

**Scheme 68.** Kimura's Total Synthesis of (*S*)-Noremopamil**Scheme 69.** Kita's Total Synthesis of Fredericamycin A

Treatment of 311 with MABR in  $\text{CH}_2\text{Cl}_2$  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 nitiotol.

In Chen and co-workers' recently described total syntheses of nakiterpiosin and nakiterpiosinone (Scheme 74),<sup>103</sup> 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).<sup>104</sup>

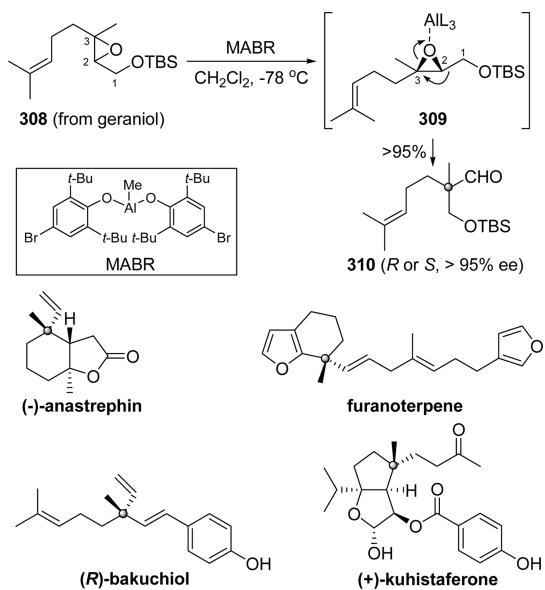
**Scheme 70.** Nemoto and Fukumoto's Tandem Asymmetric Epoxidation/Ring-Expansion Process**Scheme 71.** Nemoto and Fukumoto's Total Synthesis of (-)-Mesembrine

Treatment of 320 with  $\text{Al}(\text{OC}_6\text{F}_5)_3$  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, (–)- $\alpha$ -herbertenol, and (–)-herbertenediol.<sup>105</sup>

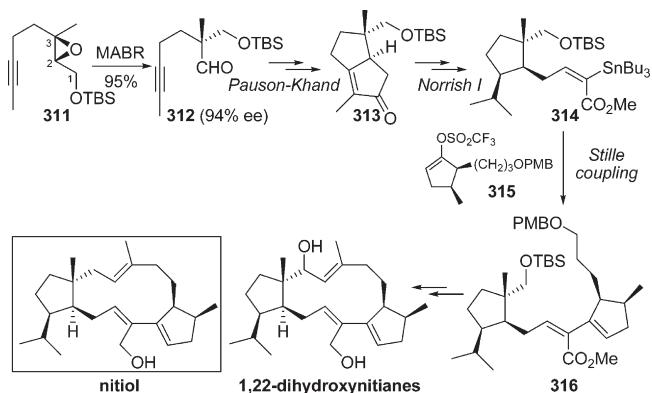
#### 4.2. Simple Epoxides and 2,3-Epoxy Ketones

Srikrishna et al. investigated the semipinacol rearrangement of tetrasubstituted cyclic epoxides. These compounds, which contain one electron-withdrawing substitution, can undergo reliable,

**Scheme 72.** Yamamoto's Semipinacol Rearrangements of 2,3-Epoxy Silyl Ethers Promoted by MABR



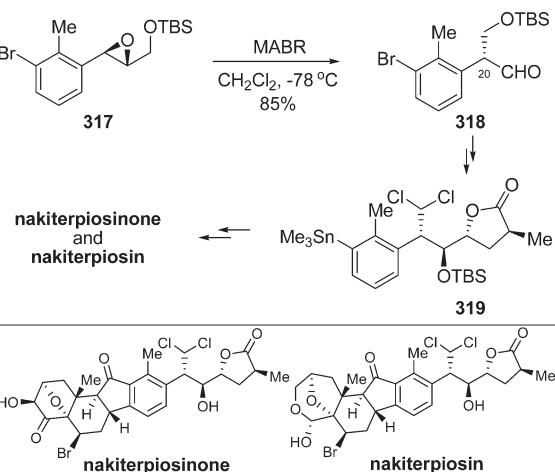
**Scheme 73.** Dake's Total Synthesis of 1,22-Dihydroxynitianes



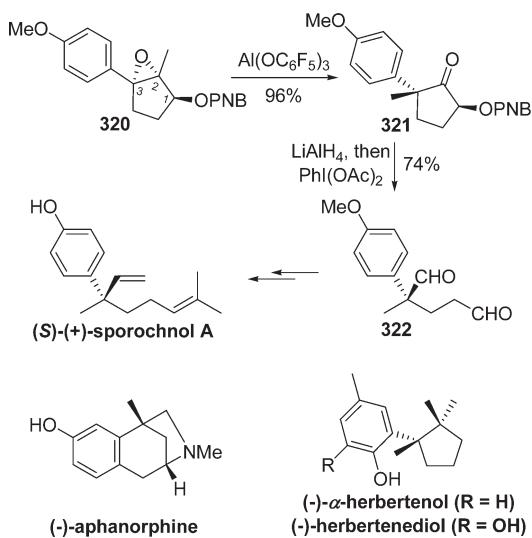
regioselective epoxide opening, which affords the ring-contracted products in good yields. As shown in the syntheses of microbiotol-type sesquiterpenes (Scheme 76), such a rearrangement occurred in 323, as a result of which an  $\alpha,\beta$ -unsaturated ester bonded to the oxirane; this compound was used to form the cyclopentyl ketone 324 in 90% yield.<sup>106</sup> 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.<sup>107</sup>

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.<sup>108</sup>

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



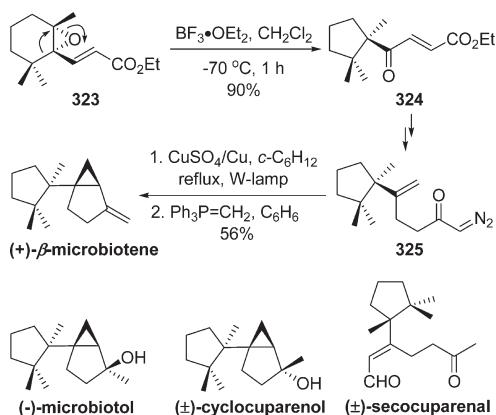
**Scheme 75.** Kita's Total Syntheses of  $(S)$ - $(+)$ -Sporochnol A,  $(-)$ -Aphanorphine,  $(-)$ - $\alpha$ -Herbertenol, and  $(-)$ -Herbertenediol



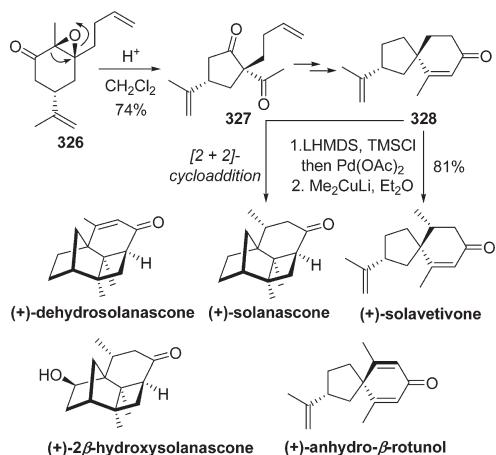
Cazes and co-workers used a semipinacol rearrangement of trisubstituted 2,3-epoxy cyclohexenones 329 to form the 1,3-keto aldehydes 330 in medium to good yields (Scheme 78). Keto aldehyde 330 was subsequently transformed to pseudoiridolactones 331, which are embedded in several terpene natural products,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

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).<sup>110</sup> 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 (+)- $\beta$ -Microbiotene



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

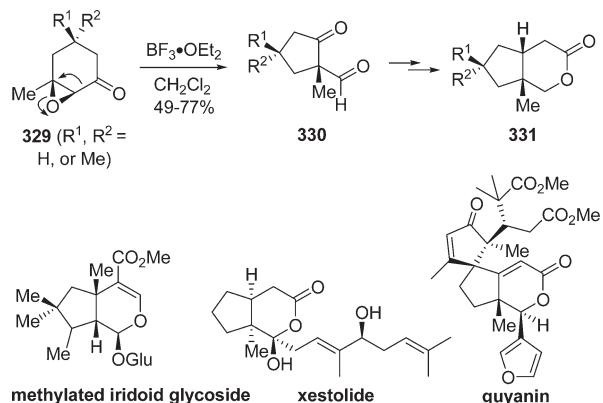


## 5. REARRANGEMENT OF $\alpha$ -HYDROXY KETONES AND IMINES

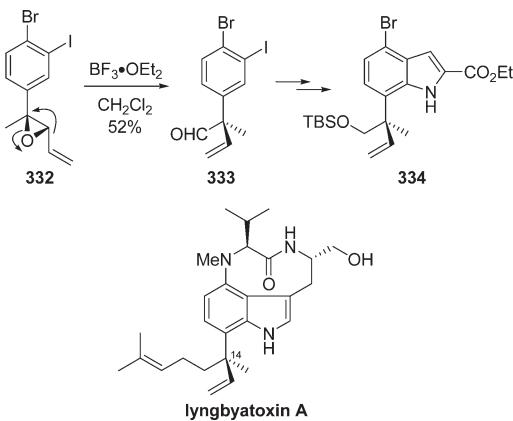
It is well-known that tertiary  $\alpha$ -hydroxy aldehydes, ketones, and imines can undergo “acyloin rearrangement” or “ $\alpha$ -ketol rearrangement” to form isomeric products. Because an enolization/protonation process is impossible for these compounds, a semipinacol rearrangement pathway involving 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,<sup>8</sup> 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, eremanolide 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).<sup>111</sup> As shown in 337, the whole process was initiated by a Lewis acid-promoted epoxide ring-opening of 336 and terminated by

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



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



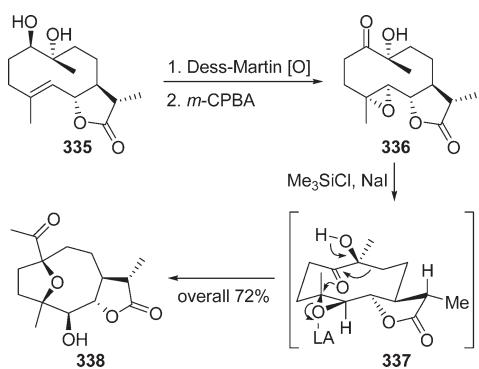
the rearrangement of the  $\alpha$ -tertiary hydroxy ketone moiety. The process rapidly achieved molecular rigidity and complexity in a stereoselective manner, giving 338 in an overall yield of 72%.

The complex rotaglate silverstrol isolated from the plant *Aglia 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  $\alpha$ -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 rotaglamide core 343 in 89% yield.<sup>112</sup> Formation of the enolate of  $\beta$ -keto ester 343 under basic conditions was proposed to drive the ketol equilibrium shift toward the rotaglamide core.

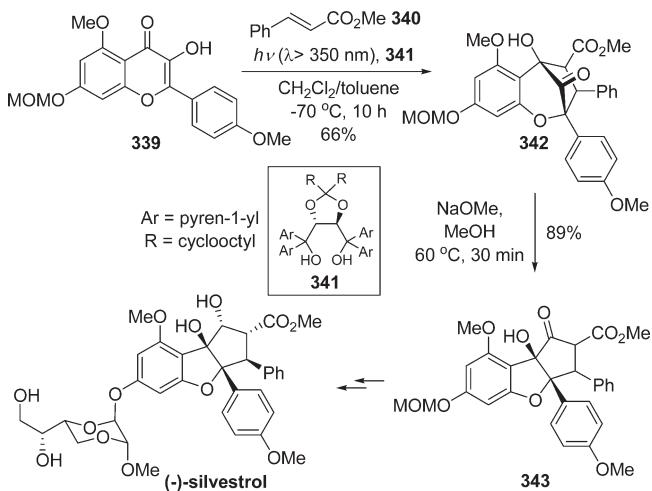
Liu and McWhorter described the synthesis of 8-desbromo-hinckdentine A using an  $\text{HCO}_2\text{H}$ -promoted rearrangement of the  $\alpha$ -tertiary hydroxy imine 344 (Scheme 82).<sup>113</sup> The stereospecific 1,2-migration of the allyl group established the key C12 quaternary carbon center, 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  $\alpha$ -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

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



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

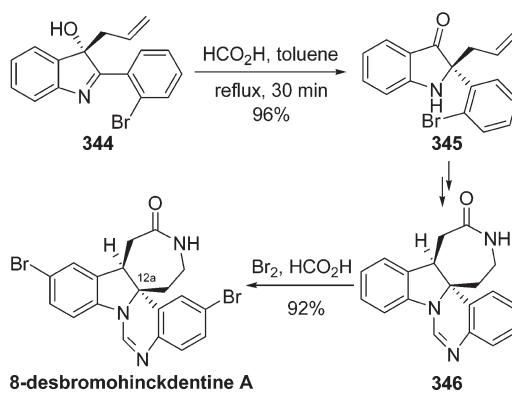


can be found in recent studies by Nagase and co-workers on indolomorphinan alkaloids (Scheme 83).<sup>114</sup> Treatment of indoleninomorphinan 347 with DBU gave the spiro indolone 348 in 63% yield. Interestingly, 348 can be converted back into 347 when promoted by  $\text{BCl}_3$ . This process provides a practical interconversion between these two structures and is useful for the design of druglike compound libraries.

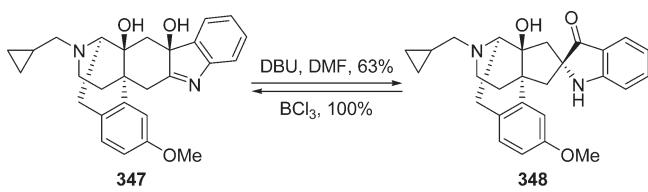
## 6. BIOMIMETIC SYNTHESIS INVOLVING SEMIPINACOL REARRANGEMENT

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.

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



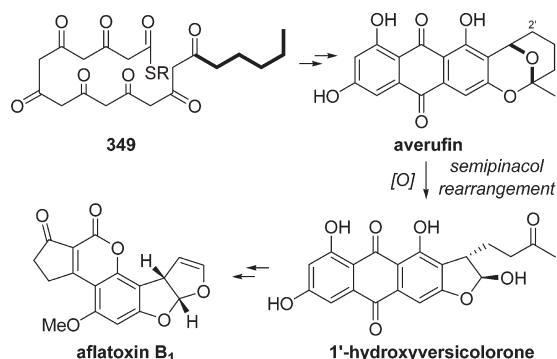
**Scheme 83.** Nagase's Synthesis of a Spiroindolinonyl-C-normorphinan Derivative



The biogenetic synthesis of aflatoxin B<sub>1</sub>, 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.<sup>115</sup> Townsend and co-workers have carried out a series of investigations, using both biosynthetic and chemical experiments,<sup>116</sup> 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<sub>1</sub>. 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 <sup>18</sup>O-induced isotopic shifts were observed at C-5' in 358. In addition, deuterium-labeling experiments carried out in similar systems showed

**Scheme 84. Biogenetic Synthesis of Aflatoxin B<sub>1</sub>**

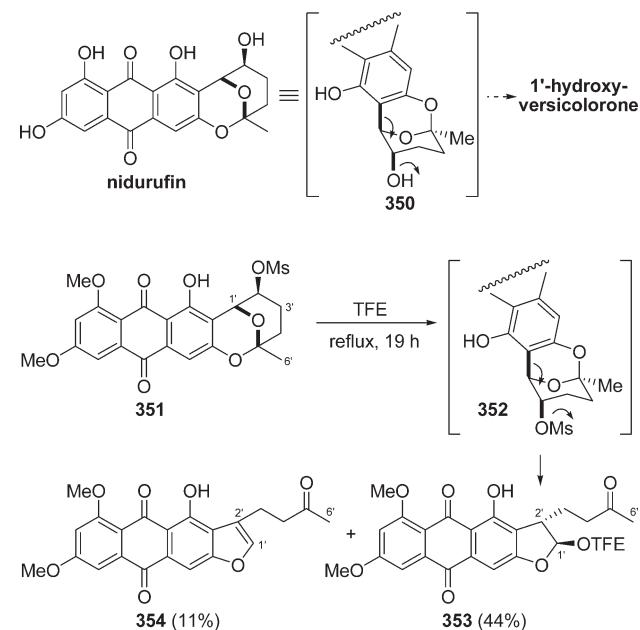
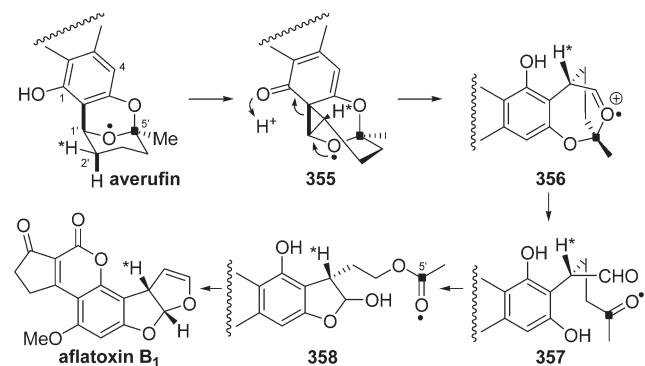
that the oxidative step led to the specific loss of the 2'-axial H but not the 2'-equatorial \*H. This is consistent with the stereoelectronic argument shown in the oxidation of averufin to 355.

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  $\alpha$  in a primary fluorescent polarization enzyme assay. Andersen and co-workers proposed a biogenetic pathway<sup>117</sup> in which polyene cyclization would be used to transform 363 into the known natural product siphonodictyol 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).<sup>118</sup> 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 Manzanares' biomimetic synthesis of (+)-liphagal,<sup>119</sup> 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  $\alpha$ -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

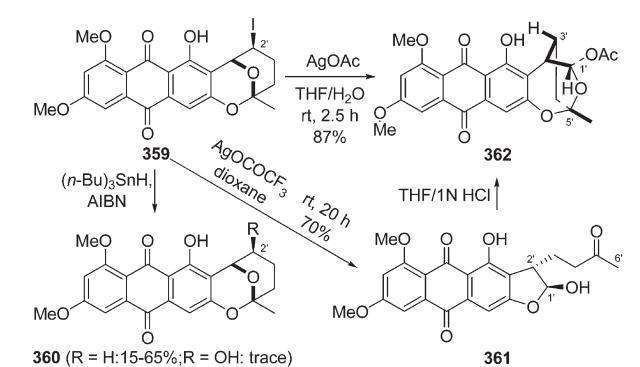
**Scheme 85. Townsend's Original Proposal of Aflatoxin B<sub>1</sub> Biosynthesis Involving Nidurufin****Scheme 86. Townsend's Modified Scheme for Biosynthesis of Aflatoxin B<sub>1</sub>**

semipinacol rearrangement involving a 2,3-migration would then provide the branched aldehyde 374, which could be further converted into the bistetrahydrofuran core 376.<sup>120</sup>

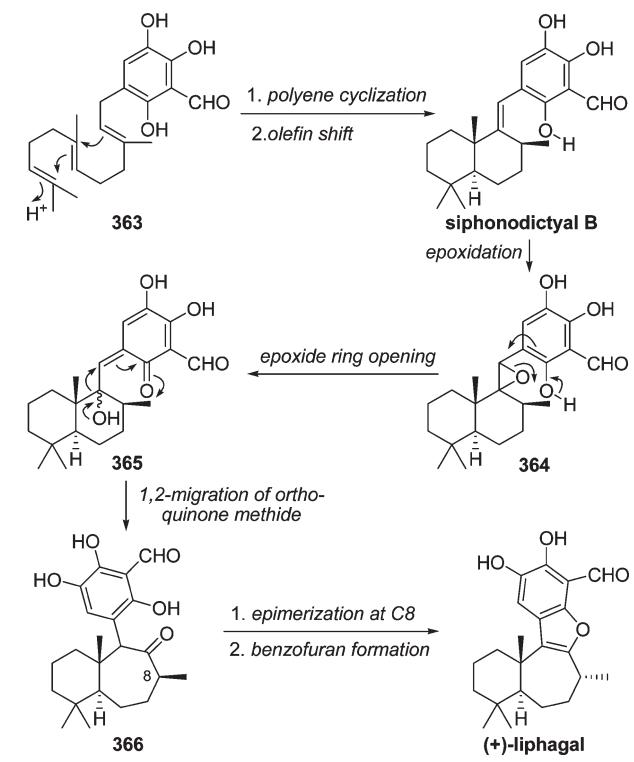
Using a procedure paralleling Vleggaar's biosynthetic proposal, Cha and co-workers completed the enantioselective total synthesis of (+)-asteltoxin (Scheme 91).<sup>121</sup> Treatment of the chiral epimeric mixture of 2,3-epoxy silyl ether 377 with  $TiCl_4$  facilitated a smooth semipinacol rearrangement, 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).<sup>122</sup>

**Scheme 87. Support for Carbocation Involvement in Averufin Oxidation**



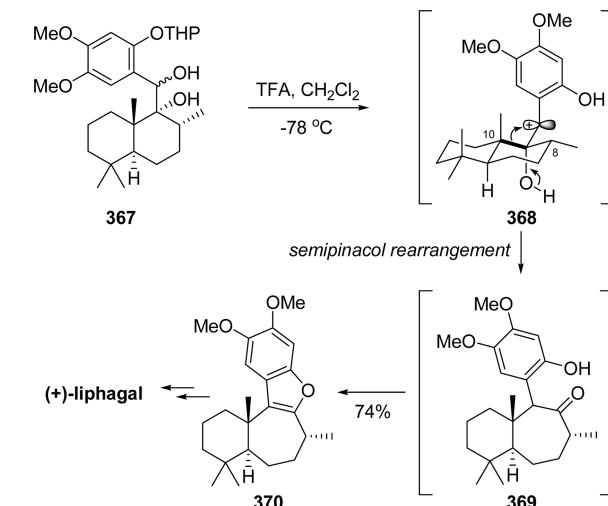
**Scheme 88. Andersen's Proposed Biosynthesis of (+)-Liphagal**



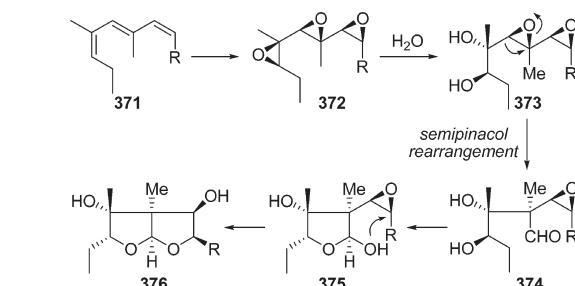
In this proposal, the key transformations include a semipinacol rearrangement of cyclohexenyl epoxide, which could undergo regioselective ring-opening at C5 and subsequent 1,2-migration of the C1–C6 bond to give the ring-contracted cyclopentyl ketone moiety in mytiloxanthin.

On the basis of this proposal, Ito and co-workers achieved the biomimetic synthesis of mytiloxanthin by treating the tetrasubstituted epoxide 381 with  $(p\text{-BrC}_6\text{H}_5)_3\text{N}^+\cdot\text{SbCl}_6^-$ . As proposed, this reaction gave the rearranged product 382 in overall 93% yield (Scheme 93).<sup>123</sup> The same strategy has been used to synthesize other analogues such as capsanthin, capsorubin, and capsanthin 3,6-epoxide.<sup>124</sup>

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



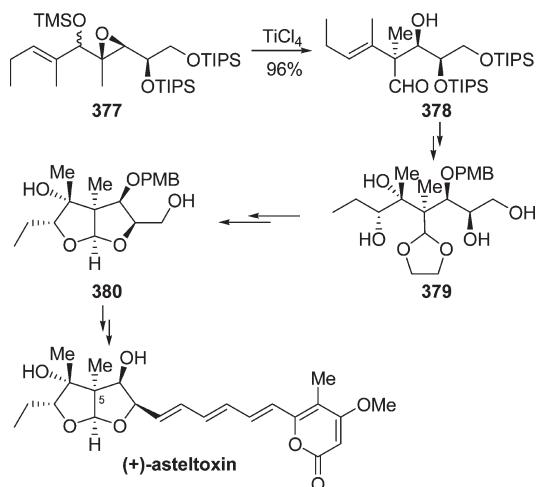
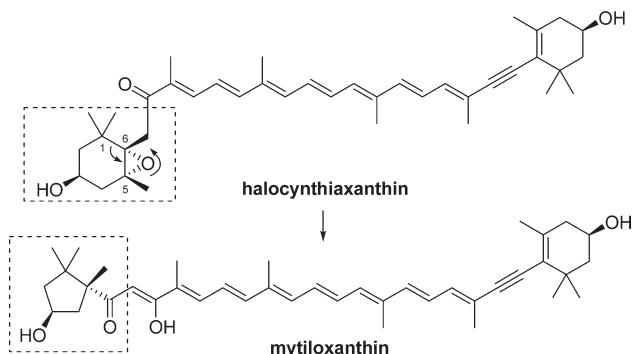
**Scheme 90. Vleggaar's Proposed Biosynthesis of the (+)-Asteltoxin Core**



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).<sup>125</sup> On the basis of this hypothesis, similar biomimetic approaches to this molecule were reported by Basabe et al.<sup>126</sup> and Imamura and co-workers.<sup>127</sup> In their syntheses, treatment of epoxides 384 and 386 with  $\text{BF}_3\cdot\text{OEt}_2$  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 bicyclic-[2.2.2]-diazaoctane core and spiroindoxyl ring system.<sup>128</sup> 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.<sup>129</sup> In their modified biosynthetic hypothesis (Scheme 95),<sup>130</sup> 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.

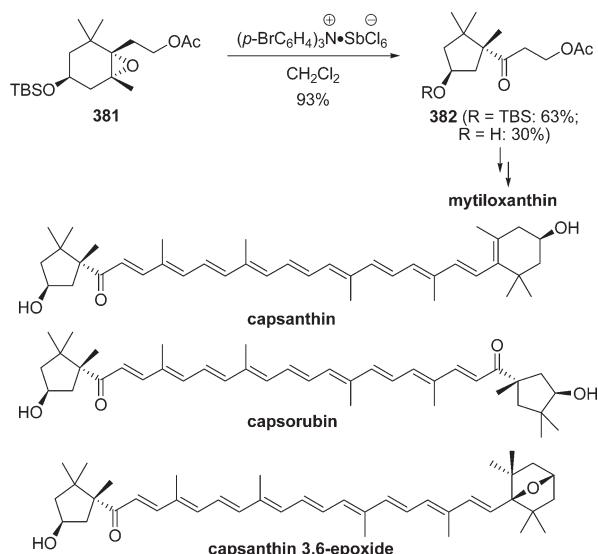
Following a strategy similar to the proposal above, Williams et al. completed the synthesis of brevianamide B (Scheme 96).<sup>131</sup>

**Scheme 91.** Cha's Total Synthesis of (+)-Asteltoxin**Scheme 92.** Biosynthetic Relationship between Mytiloxanthin and 5,6-Epoxy Carotenoid Halocynthiaxanthin

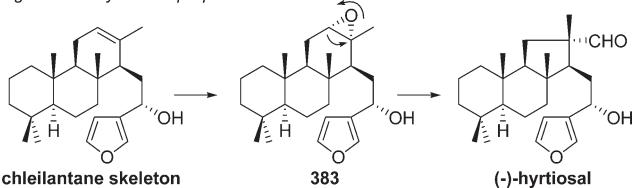
Epoxidation and the acidic hydrolysis of the minor isomer of intramolecular Diels–Alder (IMDA) adduct **392** afforded the hydroxyindolenine precursor **393**. Then a base-induced semipinacol rearrangement established the spiro oxindole moiety via ring contraction, providing brevianamide B in 65% yield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

In their synthesis of (+)-paraherquamide B (Scheme 97),<sup>132</sup> 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 spirooxindole 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.

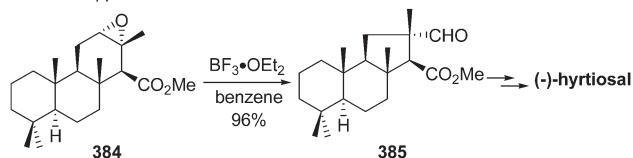
Williams and co-workers later developed a more efficient tandem epoxidation/semipinacol rearrangement sequence to form the spiro oxindole moiety. As shown in their synthesis of notoamide B (Scheme 98),<sup>133</sup> treatment of the IMDA adduct stephacidin A with oxaziridine **398** gave the oxidized 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

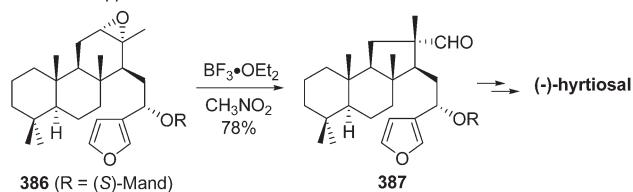
*Iguchi's biosynthetic proposal*



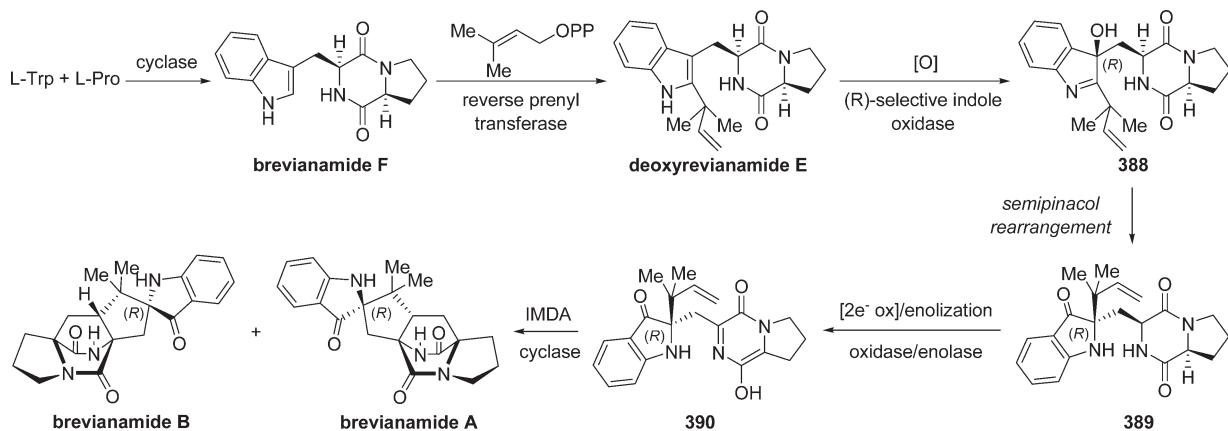
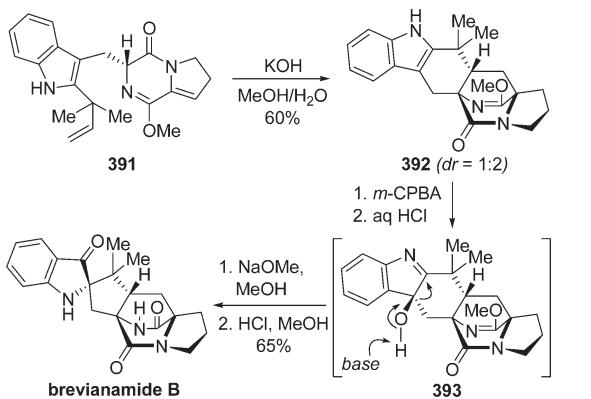
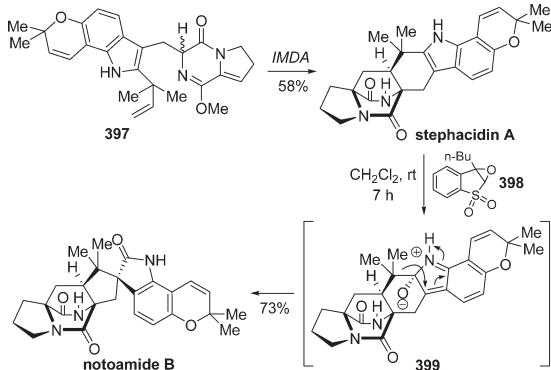
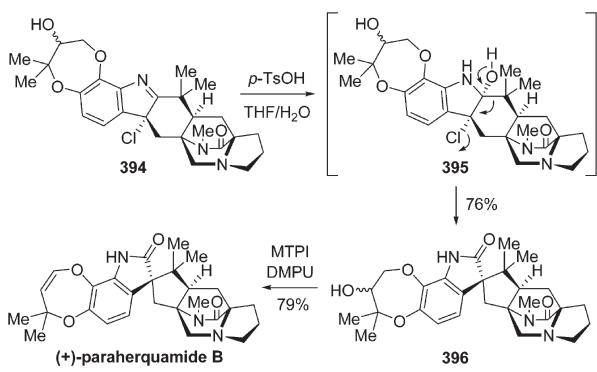
*Basabe's approach*



*Imamura's approach*

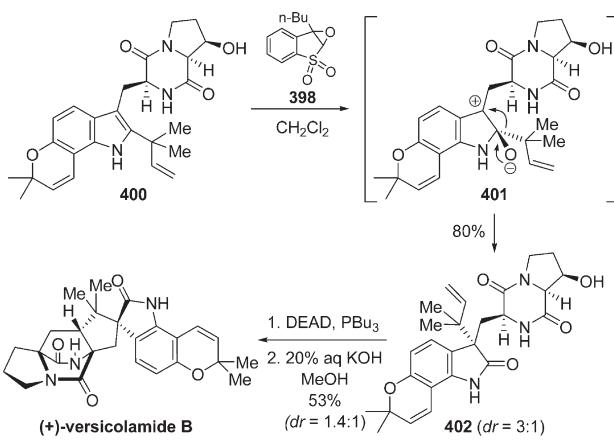


Recently, Williams and co-workers completed the biomimetic syntheses of (+)-versicolamide B (Scheme 99).<sup>134</sup> One of the key steps featured a tandem epoxidation/semipinacol rearrangement of indole **400** to generate oxindole **402** in 80% yield with 3:1 diastereoselectivity. In contrast to 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.

**Scheme 95.** Williams' Proposed Biosynthesis of Brevianamides**Scheme 96.** Williams' Biomimetic Synthesis of Brevianamide B**Scheme 98.** Williams' Biomimetic Synthesis of Notoamide B**Scheme 97.** Williams' Biomimetic Synthesis of (+)-Paraherquamide B

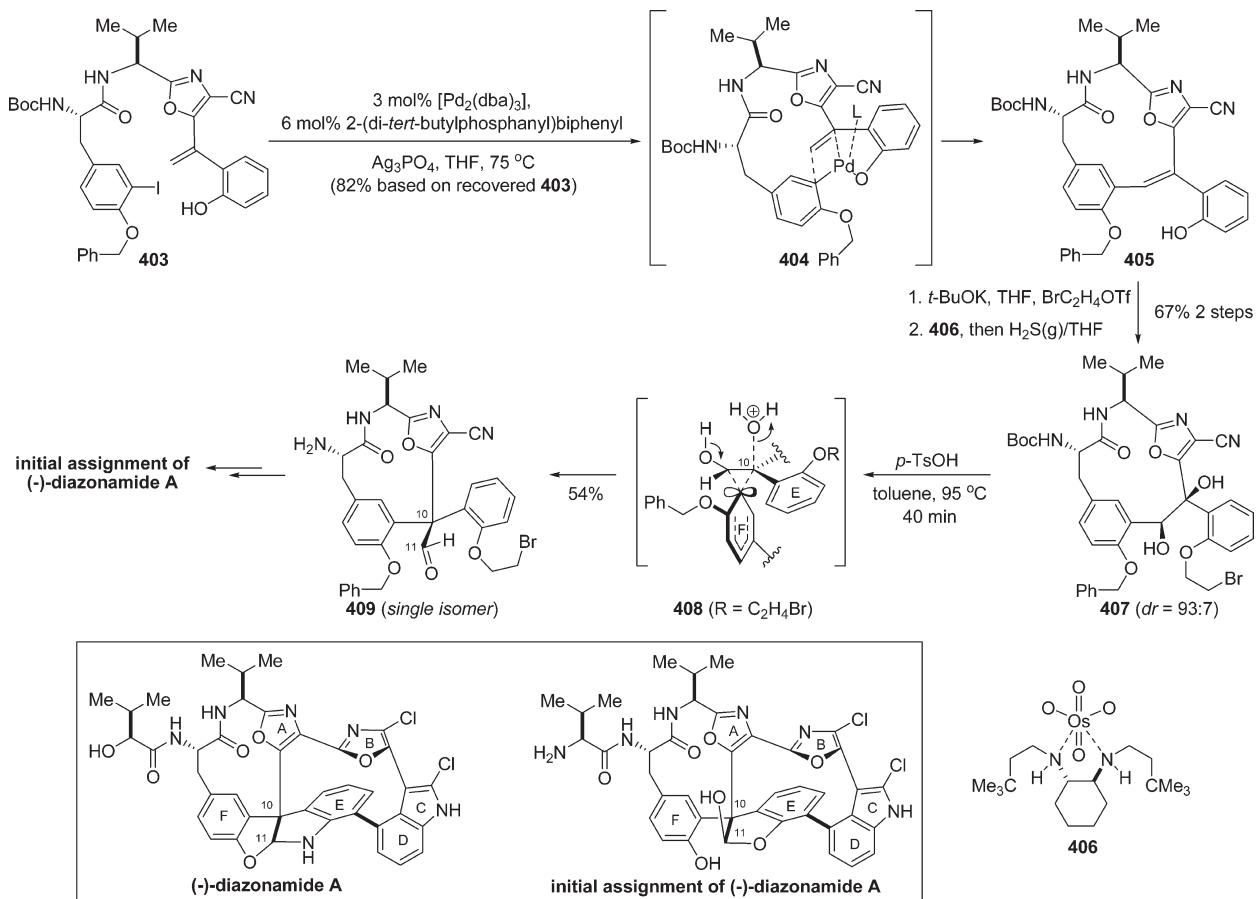
## 7. RECENT APPLICATIONS OF PINACOL REARRANGEMENT

Diazonamide A, as a marine invertebrate secondary metabolite, shows excellent activity at inhibiting the growth of human colorectal carcinoma in vitro.<sup>135</sup> In 2001, Harran and co-workers completed the first total synthesis of the originally proposed

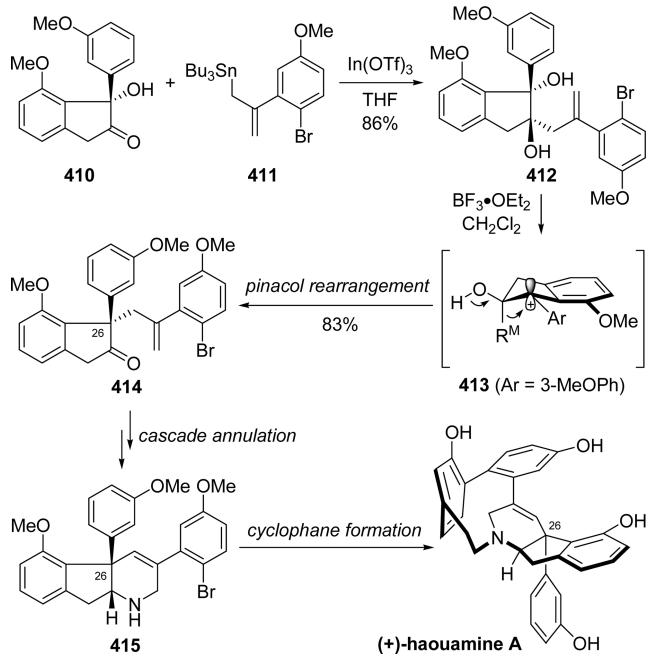
**Scheme 99.** Williams' Biomimetic Synthesis of (+)-Versicolamide B

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).<sup>136</sup> In their synthesis, a Pd(0)-catalyzed Heck endo-cyclization was used to transform 403 into the macrocyclic triarylethylene

Scheme 100. Harran's Synthesis of the Initially Proposed Structure of (-)-Diazonamide A

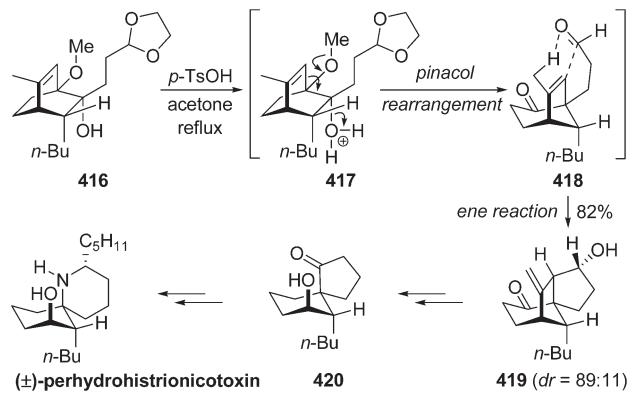


Scheme 101. Baran's Synthesis of (+)-Haouamine A



intermediate 405 in 82% yield. Etherification of phenol and dihydroxylation with OsO<sub>4</sub> complex 406 led to the diol 407 in

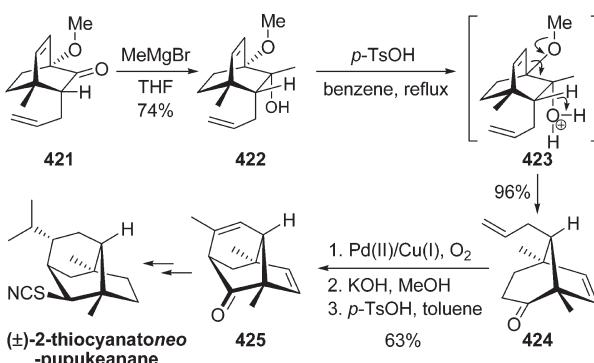
Scheme 102. Kim's Formal Synthesis of (±)-Perhydrohistrionicotoxin



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

**Scheme 103.** Uyehara's Synthesis of ( $\pm$ )-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).<sup>137</sup> Stereoselective allylation of  $\alpha$ -hydroxy ketone **410** with organotin reagent **411** in the presence of  $In(O Tf)_3$  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 ( $\pm$ )-perhydrohistrionicotoxin (Scheme 102), Kim et al. used a tandem pinacol rearrangement/ene reaction to transform a bicyclo-[2.2.2]-octene to a tricyclo-[5.3.1.01,5]-undecane system.<sup>138</sup> 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 bicyclo-[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 ( $\pm$ )-2-thiocyanato-*neo*-pupukeanane (Scheme 103).<sup>139</sup> 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<sup>140</sup> and new tandem reactions, semipinacol rearrangement will continue to play an active role in natural product syntheses.

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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.

## ACKNOWLEDGMENT

This work was supported by the NSFC (Nos. 20732002, 20621091, 20672048, and 20921120404), the "973" program of 2010CB833200, and the "111" program of the MOE.

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- (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  $\alpha$ -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.
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