Natural Product Synthesis Enabled by Domino Processes Incorporating a 1,2-Rearrangement Step

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ABSTRACT: The art of natural product total synthesis is closely associated with two major determinants: the development/application of novel chemical reactions and the innovation in strategic use of classic organic reactions. While purposely seeking/applying a new synthetic methodology allowing nonconventional bond disconnections could shorten the synthetic route, the development of domino processes composed of a series of well-established reactions could also lead to a concise, practical, and aesthetically appealing synthesis. As an important class of textbook reactions, the 1,2-anionotropic rearrangements discovered at the dawn of modern organic chemistry have important bearings not only on chemical synthesis but also on the conceptual breakthroughs in the field. In its basic form, the 1,2-shift affords nothing but a constitutional isomer of the starting material and is therefore not a complexity-generating transformation. However, such a simple 1,2-shift could in fact change the molecular topology if the precursor is cleverly designed. More dramatically, it can metamorphosize the structure of the substrate when it is combined with other transformations in a domino sequence. In this Outlook, we highlight recent examples of natural product synthesis featuring a key domino process incorporating a 1,2-anionotropic rearrangement. Specifically, domino reactions integrating Wagner−Meerwein, pinacol, α-ketol, α-aminoketone, α-iminol, or benzilic acid rearrangements will be discussed.

1. INTRODUCTION

The domino reaction, as defined by Tietze, is a combination of two or more bond-forming reactions under identical conditions wherein the subsequent reactions result as a consequence of the functionality formed in the previous step.[1] It is generally classified according to the reaction mechanism, i.e., cationic, anionic, radical, pericyclic, carbenoid, enzymatic, and transition-metal-catalyzed transformations. In practice, a crossover mechanism is very often involved in a domino sequence, especially in the case of the pericyclic reaction which is most frequently used as a terminating, rather than an initiating, step.[2] This is illustrated in Gleason's elegant synthesis of (−)-virosaine A (**1**) featuring a domino intramolecular ring-opening of epoxide by oxime followed by a [3 + 2] cycloaddition of the resulting nitrone (Scheme 1a).[3] By combining two well-established reactions, i.e., N-alkylation and dipolar cycloaddition, the authors are able to convert a simple oxime **2** to a topologically complex cagelike compound **3** in 92% yield. Many reviews dealing with the application of domino processes in natural product synthesis have been published over the years.[4−9]

Rearrangement reactions involving the migration of an atom or a group from one center to another allow, in many cases, the construction of otherwise difficultly accessible molecular frameworks. The bond reorganization is naturally capable of altering and even metamorphosizing the structure of the original substrate, especially if it is combined with other bond-

forming processes. Overman's aza-Cope/Mannich sequence is an outstanding example of such domino processes that has been successfully applied to the total synthesis of a number of structurally diverse alkaloids.[10] Depicted in Scheme 1b is Overman's total synthesis of (−)-actinophyllic acid (**4**).[11] Simply heating a solution of ammonium salt **5** with paraformaldehyde in MeCN/H$_2$O afforded the natural product **4** in 93% yield via a domino iminium formation/aza-Cope/ Mannich reaction/intramolecular acetalization sequence. Note that four chemical bonds are generated in this operationally simple process; the yield per chemical bond formation is therefore remarkable. Domino reactions involving [*m,n*]-sigmatropic rearrangements have also been reviewed.[12−15]

The 1,2-alkyl/aryl shift is involved in the biosynthesis of a number of important families of natural products. A classic example is shown in Scheme 2. Enzyme-catalyzed cationic polycyclization of the linear 2,3-oxidosqualene afforded the tetracyclic protosterol cation which, upon a series of stereoselective 1,2-H and 1,2-methyl migrations (Wagner−
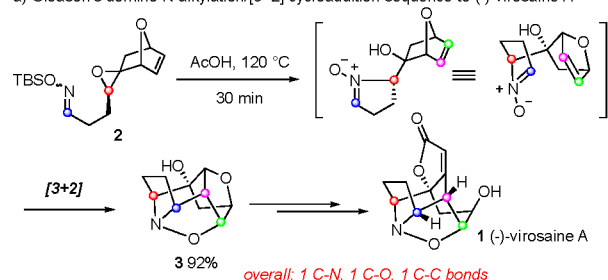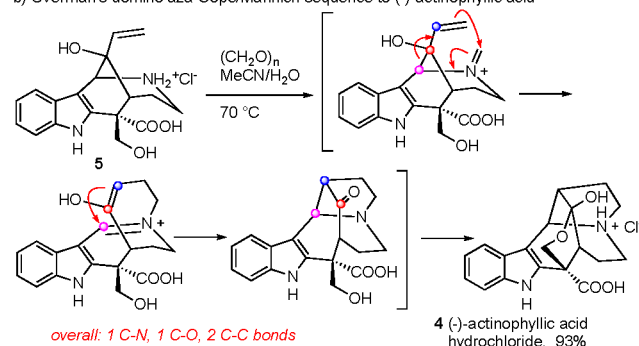
Scheme 1. Domino Reactions in Natural Product Synthesis

a) Gleason's domino N-alkylation/[3+2] cycloaddition sequence to (-)-virosaine A

AcOH, 120 °C
30 min

[3+2]

3 92%

overall: 1 C-N, 1 C-O, 1 C-C bonds

1 (-)-virosaine A

b) Overman's domino aza-Cope/Mannich sequence to (-)-actinophyllic acid

(CH₂O)ₙ
MeCN/H₂O
70 °C

overall: 1 C-N, 1 C-O, 2 C-C bonds

4 (-)-actinophyllic acid
hydrochloride, 93%

Scheme 2. 1,2-Shift in Biosynthesis of Lanosterol

2,3-oxidosqualene

protosterol cation

Wagner-Meerwein rearrangement

two times 1,2-H shift
two times 1,2-Me shift
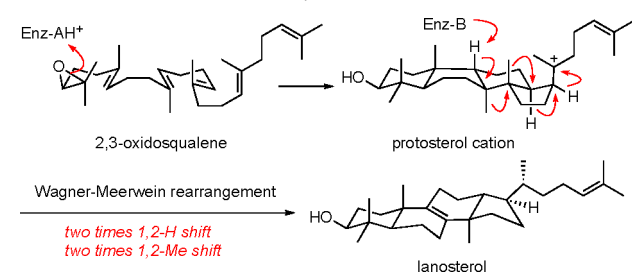
lanosterol

Meerwein rearrangements) followed by deprotonation, was converted to lanosterol, a precursor of all animal and fungal steroids.[16] Total synthesis featuring this type of reaction as a key step has been highlighted in a comprehensive review by Tu and Wang.[17] The alkyne π-activation/cyclization followed by pinacol rearrangement of the resulting carbocation has been summarized in an authoritative account by Kirsch.[18] However, a review dedicated to the development and application of domino processes incorporating a 1,2-rearrangement reaction in natural product synthesis is, to the best of our knowledge, still missing.[19] The purpose of this Outlook aims therefore at filling this gap. The Outlook is not intended to be comprehensive as only selected recent examples will be discussed to illustrate the power of this approach.
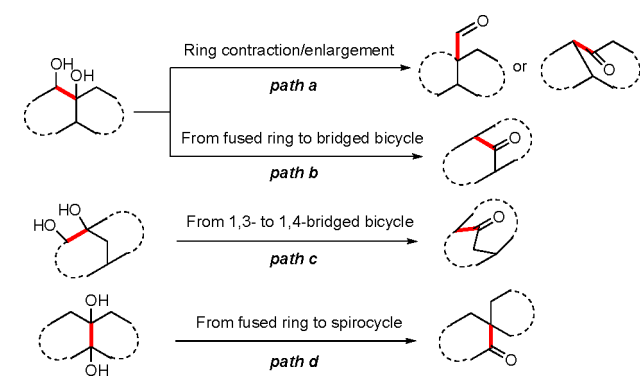
2. 1,2-SHIFT IN DOMINO PROCESSES

2.1. General Consideration. 1,2-Migration can be divided into three subtypes on the basis of the nature of the migrating group: (a) anionotropic (nucleophilic) rearrangement in which the migrating group moves with its electron pair; (b) cationotropic (electrophilic) rearrangement in which the migrating group shifts without its electron pair; and (c) free radical rearrangement in which the migrating group migrates with one single electron.[20]

At first glance, the 1,2-rearrangement does not seem to be a complexity-generating process as it just provides an isomer of

the starting material. However, such a simple 1,2-shift could in fact change the molecular topology if the migrating group is tethered to the migration terminus. This notion is illustrated in Scheme 3 using pinacol rearrangement of a bicyclic compound as a prototypical reaction.

Scheme 3. Changing the Molecular Topology by 1,2-Alkyl Shift: Cases of Pinacol Rearrangement

Ring contraction/enlargement
path a
or

From fused ring to bridged bicycle
path b

From 1,3- to 1,4-bridged bicycle
path c

From fused ring to spirocycle
path d

In the case where only one hydroxyl group is attached to the ring-fused carbon, the 1,2-alkyl migration could lead either to the ring contraction/ring enlargement product (Scheme 3, path a) or to the bridged bicyclic compounds (Scheme 3, path b) depending on the nature of the substituents and the stereochemistry of the substrates. Conversion of the 1,3-bridged bicycle to the 1,4-bridged system by a 1,2-rearrangement is also a unique strategy that has been successfully developed to access the structural motifs that are otherwise difficultly accessible (Scheme 3, path c). In another scenario wherein both hydroxyl groups are attached to the fused C−C bond, the 1,2-rearrangement would convert the fused bicyclic compounds to the spirocycles (Scheme 3, path d).

In terms of strategic design, an additional attribute associated with the 1,2-rearrangement is that different precursors can be devised for the same targeted skeleton. In Scheme 4 are summarized three different routes on the way to

Scheme 4. Substrate Design: The Same Skeleton Can Be Obtained from Different Substrates

6 ingenol

a)
AlMe₃, DCM, 76%
7 → **8**

b)
AlMe₃, DCM, 82%
9 → **10**

c)
BF₃·OEt₂, DCM, 80%
11 → **12**
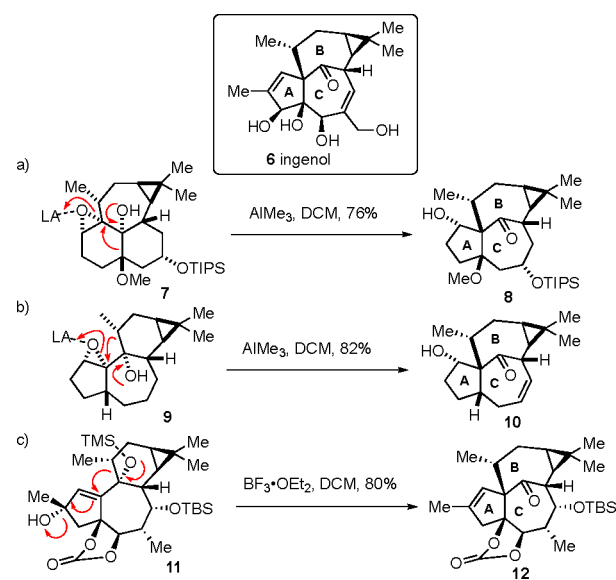
the total synthesis of ingenol featuring a pinacol rearrangement. Treatment of the tricyclic hydroxy epoxide **7** with AlMe₃ afforded compound **8** via a semipinacol rearrangement. In this transformation, a 6/6 fused ring system was converted to a 5/7 fused bicyclic framework (Scheme 4a).[21] Under similar conditions, a 5/7/6 tricyclic compound **9** was rearranged to **10** with the concurrent generation of a 1,3-bridged ring system (Scheme 4b).[22] Finally, vinylogous pinacol rearrangement of **11** provided the highly functionalized tricycle **12** in excellent yield (Scheme 4c).[23]

Obviously, when 1,2-rearrangement processes are used in tandem with other powerful reactions, metamorphosis of the structure of the starting material is to be expected. Integrating such domino processes in a total synthesis endeavor will therefore not only shorten the synthetic sequence but also render the starting material easily accessible. From the perspective of reaction design, it is important to note that such a rearrangement reaction can serve as an initiator, a relay, or a terminating step of a domino process.

2.2. Wagner–Meerwein Rearrangement. The Wagner–Meerwein (WM) rearrangement is a prototypical example of 1,2-anionotropic rearrangement.[24−26] While the requisite carbocation intermediate can be generated from the heterolytic cleavage of the C–X bond under acidic conditions, any transformations generating a formal carbenium ion intermediate can in fact trigger a 1,2-alkyl(aryl)migration producing a thermodynamically more stable carbocation that can be further functionalized. For example, the Au-catalyzed domino cyclizations of enyne[18,27] and alkynediol/1,2-alkyl shift[28] have been developed into powerful methodologies for the synthesis of complex polycyclic ring systems. Of note, the extensive and meticulous mechanistic study on the 1,2-shift of bicyclic monoterpenes by Meerwein allowed him to propose the presence of a carbocation intermediate which is one of the major conceptual breakthroughs in modern organic chemistry.

2.2.1. Total Synthesis of Talatisamine. Talatisamine (**13**), isolated from *Aconitum* species,[29] exhibits interesting antiarrhythmic activities as a K⁺ channel blocker.[30] Structurally, it contains three fused rings, two 1,3-bridged and one 1,4-bridged bicyclic systems. This hexacyclic 6/7/5/6/6/5 ring framework is found in other highly oxygenated C₁₈- and C₁₉-diterpenoid alkaloids.

The first total synthesis of talatisamine (**13**) was accomplished by the group of Wiesner in 1974 with a longest linear sequence of 43 steps.[31] Very recently, Inoue and co-workers reported an alternative strategy featuring a late-stage skeletal rearrangement (Scheme 5).[32] Heating a DMSO solution of compound **14**, prepared from cyclohexenone in 25 steps, in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded rearranged product **15** in 83% yield. The antiperiplanar alignment between the C₉–OTf and C₈–C₁₀ bonds facilitated the regio- and stereoselective migration of C₁₀ from C₈ to C₉. The resulting tertiary allylic cation in **16** was subsequently oxidized by DMSO to afford enone **15** via dimethylsulfonium intermediate **17**. This domino 1,2-WM rearrangement/allylic oxidation sequence allowed the authors not only to build a bridged bicyclic ring system but also to introduce the C16-oxygen functionality found in the natural product. After functional group manipulations, compound **15** was elaborated to **18** which was in turn converted to **19** via the formation of the C7–C17 bond by way of a Hg(OAc)₂ induced oxidative aza-Prins cyclization. Saponification of the acetate afforded talatisamine (**13**).

Scheme 5. Inoue's Total Synthesis of Talatisamine
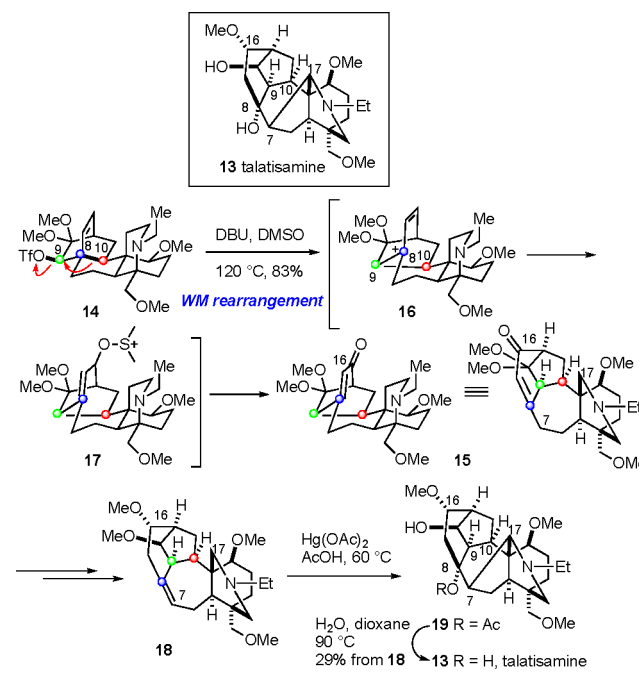
The domino 1,2-WM rearrangement/allylic oxidation has previously been developed by Xu, Wang, and co-workers in their model studies toward the synthesis of **13**.[33]

2.2.2. Total Synthesis of Arcutinidine, Arcutinine, and Arcutine. Arcutinidine (**20a**), arcutinine (**20b**), and arcutine (**20c**), isolated from *Aconitum arcuatum*, belong to C₂₀-diterpenoid alkaloids.[34,35] Biogenetically, it was proposed that they are derived from hetidine type alkaloids via WM rearrangement (Scheme 6).[36,37]

Scheme 6. Li's Total Synthesis of Arcutinidine, Arcutinine, and Arcutine
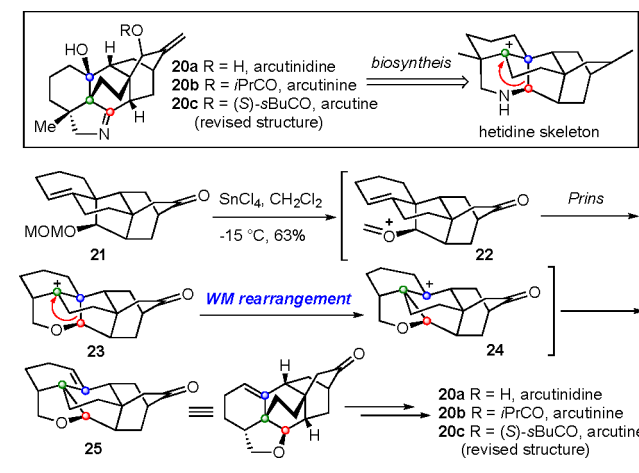
On the basis of this hypothesis, Li and co-workers developed a concise synthesis of these natural products featuring a domino Prins cyclization/WM rearrangement[38] as a key step (Scheme 6).[39] The enantioenriched pentacyclic compound **21** was prepared from (S)-3-bromocyclohex-2-en-1-ol in 7 steps involving an intramolecular Diels–Alder cycloaddition for the construction of the bicyclo[2.2.2]octan-2-one system. Stirring a DCM solution of **21** in the presence of tin tetrachloride at

−15 °C provided **25** in 63% yield. Under these conditions, the fragmentation of the MOM group afforded chemoselectively the oxocarbenium **22** instead of the alternative methyl-(methylene)oxonium. The intramolecular Prins reaction afforded carbocation **23** which underwent WM 1,2-shift to furnish **24**. Regioselective proton elimination of the latter afforded **25**, the precursor of the three targeted natural products **20a**−**20c**. Of note is that the MOM ether in **21** served both as a protecting group of the alcohol in the initial stage of the synthesis and as a precursor of the highly reactive oxocarbenium intermediate. The absolute configuration of the side chain in arcutine (**20c**) has been revised to (S)-2-methylbutanoyl instead of the (R)-enantiomer initially assigned for **20c**.

Qin and co-workers accomplished total syntheses of arcutinidine (**20a**) and arcutinine (**20b**) in the same year using a completely different strategy.[40]

2.2.3. Total Synthesis of (+)-Condyfoline and (−)-Tubifoline. (+)-Condyfoline (**26**), a structural isomer of (−)-tubifoline (**27**) (Scheme 7a), remained a synthetic challenge for many years. Indeed, (+)-condyfoline (**26**) was isolated only as a minor product in a number of syntheses aimed at both **26** and **27**.[41,42]

Our group has recently reported an enantioselective synthesis of these two natural products featuring a TiCl₃-

Scheme 7. Our Group's Total Synthesis of (+)-Condyfoline, (−)-Tubifoline, and (+)-1,2-Dehydroaspidospermidine

a) (+)-Condyfoline and (-)-tubifoline

26 (+)-condyfoline   **27** (-)-tubifoline

b) Total synthesis of (+)-condyfoline

TiCl₃ in 2 M HCl / Imidazole

28   **29**   6π-electron-5-atom electrocyclization

WM rearrangement

30   **31**   **26** (+)-condyfoline

c) Rearrangement of (+)-condyfoline to (-)-tubifoline

Neat, -18 °C / 20 days, 93%

26 (+)-condyfoline

27 (-)-tubifoline

d) Total synthesis of (+)-1,2-dehydroaspidospermidine

SOCl₂, DBU, CH₂Cl₂, 23 °C / then aqueous TiCl₃, NH₄OAc / MeCN, 23 °C, 78%

33   **32** (+)-1,2-dehydroaspidospermidine

mediated reductive cyclization of 2-nitrophenyl substituted alkenes.[43] The key step leading to (+)-condyfoline is depicted in Scheme 7b.[44] Stirring an acetone solution of enantioenriched **28** in the presence of an excess of aqueous TiCl₃ and imidazole at room temperature afforded the natural product (+)-**26** in 86% isolated yield. A sequence of reduction of nitroarene **28** to its nitroso derivative **29** followed by a diastereoselective 6π-electron−5-atom electrocyclization, Wagner−Meerwein 1,2-alkyl migration of the resulting nitrone **30**, and reduction of thusly generated indolenine-N-oxide **31** was proposed to account for the reaction outcome. The presence of imidazole is important in order to suppress the over-reduction of nitrosoarene **29** to aniline. The absolute configuration of the migrating center and its neighboring stereocenter was preserved in the migration process indicating that the 1,2-alkyl shift of nitrone **30** to **31** might proceed through a concerted 1,5-sigmatropic rearrangement. This assumption, supported by DFT calculations, is of decisive importance to the success of our synthesis. Indeed, should the retro-Mannich/Mannich cyclization sequence be operative, the nitrone intermediate **30** would be transformed to tubifoline as a major product in accord with the literature precedents.[41] Finally, a facile and clean conversion of (+)-condyfoline (**26**) to (−)-tubifoline (**27**) via a retro-Mannich/1,3-prototropy/Mannich sequence at low temperature (Scheme 7c) was observed, substantiating further the concertedness in the conversion of **30** to **31**.[45] The equilibrium is believed to be driven by the release of the steric interaction between the ethyl group and the indolenine moiety found in (+)-condyfoline (**26**).

A 6-step synthesis of 1,2-dehydroaspidospermidine (**32**) has also been developed based on the same TiCl₃-promoted domino process. The ultimate step converting the tertiary alcohol **33** to **32** is depicted in Scheme 7d. A cascade of dehydration/reduction/cyclization/1,2-shift/reduction was proposed to account for the reaction outcome.[44]
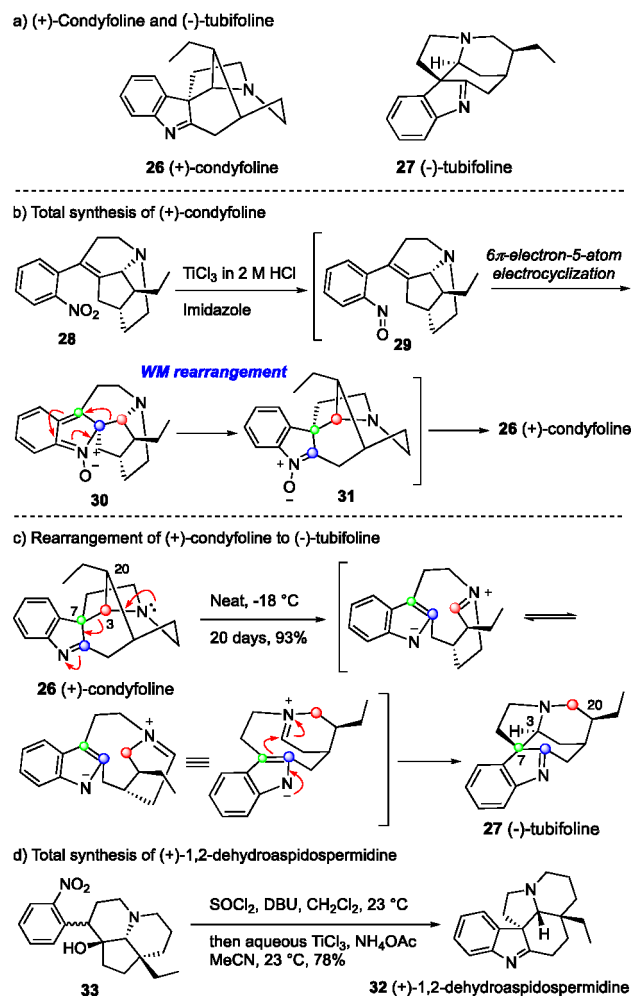
Since the 2,3,3-trisubstituted indolenine moiety constitutes an integral part of many biologically important monoterpene indole alkaloids, the TiCl₃-mediated reductive cyclization of tetrasubstituted alkenes bearing a 2-nitrophenyl substituent is expected to be an interesting alternative to reach this type of azabicyclic skeleton.

2.3. Pinacol Rearrangement. The pinacol rearrangement, discovered by Fittig in 1860, converts the vicinal diols to aldehydes/ketones under acidic conditions.[46−50] Although it was discovered almost 40 years before the Wagner−Meerwein rearrangement, it is considered to be a subclass of the latter reaction.
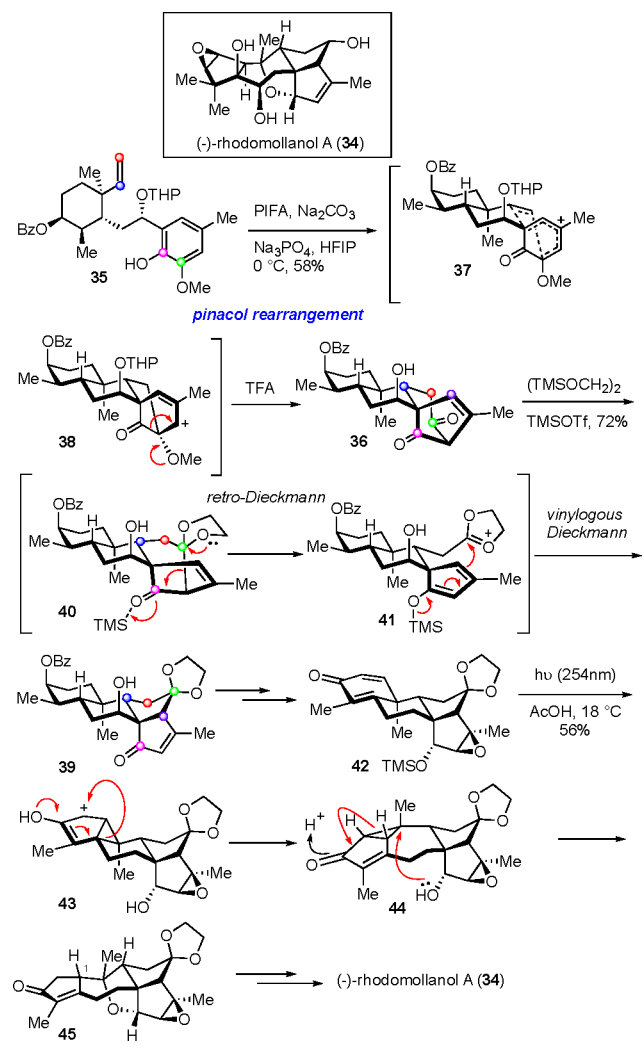
2.3.1. Total Synthesis of (−)-Rhodomollanol A. (−)-Rhodomollanol A (**34**) is a highly oxygenated grayanane type diterpenoid with an unusual [3,5,7,5,5,5] hexacyclic framework. Structurally, it has a central 7-oxabicyclo[4.2.1]nonane core which is in turn fused with three cyclopentanes and has 11 contiguous stereocenters.[51] Compound **34** displays a moderate PTP1B inhibitory activity.

The group of Ding recently reported the first total synthesis of (−)-rhodomollanol A (**34**) characterized by a series of well-orchestrated domino reactions and skeletal rearrangements (Scheme 8).[52] Treatment of vinylphenol **35** with PIFA under optimized conditions (Na₂CO₃, Na₃PO₄, HFIP, 0 °C) provided **36** as a single diastereomer in over 58% yield on the gram scale. The reaction went through a sequence of oxidative-dearomatization-induced (ODI)-[5 + 2] cycloaddi-

Scheme 8. Ding's Total Synthesis of (−)-Rhodomollanol A

C2, and C3). The characteristic structural feature of this class of monoterpene indole alkaloids is the presence of a C7−C16 bond that creates a rigid and cage-like framework. The fascinating molecular architecture in conjunction with their interesting biological activities has attracted the attention of synthetic chemists for many years.[6,54,55]

A unified strategy toward the synthesis of the three natural products has been developed by the group of Zu.[56,57] The spiroindoline **49** was converted to tetracycle **50** under mild acidic conditions in 76% yield (Scheme 9). The sequence of

Scheme 9. Zu's Divergent Total Synthesis of Calophyline A, Deformylcorymine, and Strictamine

tion[53] of carbenium ion intermediate **37** followed by a pinacol type 1,2-acyl migration of the resulting carbocation **38**. Regioselective acetalization of the 1,3-dicarbonyl compound **36** [(TMSOCH₂)₂, TMSOTf] afforded a rearranged product **39** via a *retro*-Dieckmann/vinylogous Dieckmann cascade, reshaping therefore the bicyclo[3.2.1] system to a [5,5]-fused bicyclic framework. After functional group manipulation, divinyl ketone **42** was obtained and subjected to UV irradiation. Photo-Nazarov cyclization presumably generated allylic carbocation **43**, triggering the ring expansion of the central cyclohexane ring to furnish **44** via 1,4-alkyl migration. Under acidic conditions (AcOH as solvent), the trimethylsilyl ether was cleaved, and intramolecular ring-opening of the cyclopropane by the tethered hydroxyl group furnished **45** in 56% yield. The latter was subsequently converted to (−)-rhodomollanol A (**34**) in 12 steps. Overall, the authors cleverly exploited a series of skeletal rearrangements to construct the much sought after scaffold of (−)-rhodomollanol A.

2.3.2. Divergent Total Synthesis of Calophyline A, Deformylcorymine, and Strictamine. Calophyline A (**46**), deformylcorymine (**47**), and strictamine (**48**) are members of the akuammiline family of natural products.[6] They all possess a rigid and cagelike structure differing in the ring connectivity between N4 and the central cyclohexane ring carbons (C14,

aza-pinacol rearrangement followed by β-hydroxy elimination and intramolecular aza-Michael addition accounted for the reaction outcome.[58] It is interesting to note that formation of the N3−C14 bond prevailed over the alternative N3−C2 bond under these reaction conditions. Conventional functional group manipulation transformed **50** to **51** which was further converted to calophyline (**46**).

A formal 1,3-migration of N4 from C14 to C2 was realized under single-electron transfer (SET) reductive conditions. Thus, reduction of **51** with SmI₂ afforded ketyl **52** which was further reduced to carbanion **53** via a second SET process. β-Elimination of the latter cleaved the N4−C14 bond to afford intermediate **54** which, upon cyclization via the formation of the N4−C2 bond and protonation of enolate, furnished **55**. Reductive *N*-methylation followed by diastereoselective reduction of ketone function transformed **55** to the

deformylcorymine (**47**). On the other hand, when a large excess of SmI$_2$ was used, compound **55** can be further reduced to carbanion via a double SET process to **56** which, upon β-elimination, would provide enolate **57**. Tautomerization of the latter followed by hemiaminal formation converted **57** to **58**, an immediate precursor of strictamine (**48**).[59−61]

2.3.3. Total Synthesis of Brevianamide A. (+)-Brevianamides A (**59**) and B (**60**), the first examples of [2.2.2]-diazaoctane alkaloids, were isolated by Birch in 1969.[62] Brevianamide A (**59**), the major isolated diastereomer (d.r. ≥ 9:1), displays potent antifeedant activity against the larvae of the insect pests *Spodoptera frugiperda* (fall armyworm) and *Heliothis virescens* (tobacco budworm). It was proposed that the bicyclo[2.2.2]diazaoctane cores of these natural products could be biosynthesized via an intramolecular hetero-Diels−Alder cycloaddition.[63] However, the control of relative stereochemistry in laboratory synthesis following this biosynthetic hypothesis turned out to be challenging.

Lawrence and co-workers proposed a revised biosynthetic hypothesis implicating (+)-dehydrodeoxybrevianamide E (**61**) as a biosynthetic precursor of **59** (Scheme 10).[64] To validate

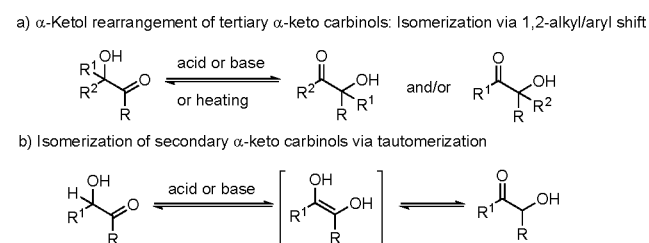**Scheme 10. Lawrence's Total Synthesis of (+)-Brevianamides A and B**
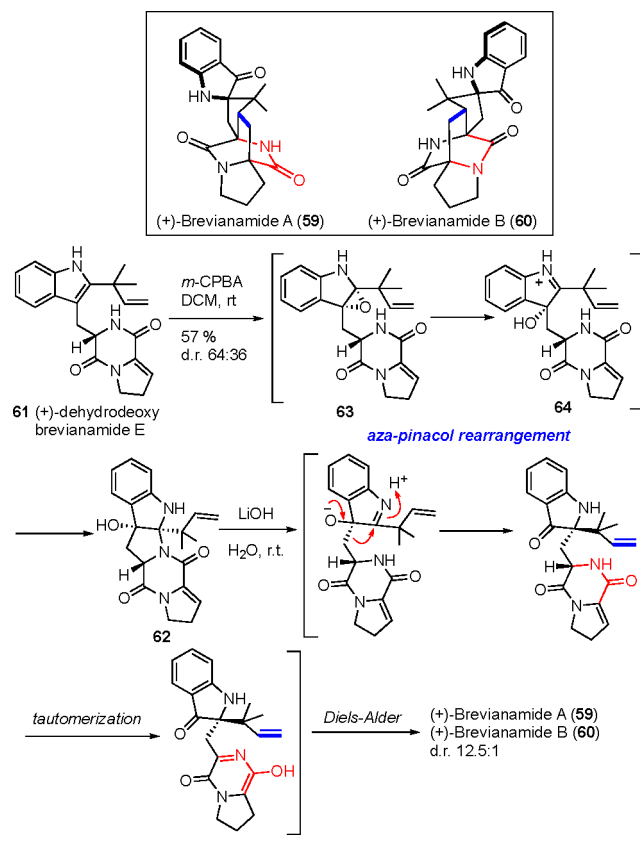
this assumption, they first developed an efficient 5-step synthesis of **61** starting from (*S*)-tryptophan methyl ester. Oxidation of **61** with *m*CPBA furnished compound **62** together with its diastereomer (structure not shown, d.r. 1.8:1). Mechanistically, chemo- and stereoselective epoxidation of the indole nucleus at the expense of the enamine unit followed by ring-opening of the resulting epoxide **63** would afford iminium **64** which underwent 5-*exo*-trig-cyclization to afford the pentacyclic aminal **62**. Treatment of **62** with lithium

hydroxide in water at room temperature triggered a domino sequence involving a retro-5-*exo*-trig-cyclization/1,2-alkyl shift/tautomerization/intramolecular Diels−Alder reaction to provide (+)-brevianamide A (**59**) and (+)-brevianamide B (**60**) (d.r. 12.5:1) in 63% overall yield. Taking into consideration that (+)-brevianamides A and B were isolated from natural sources in a similar ratio, the authors suggested that the Diels−Alder reaction, in this particular case, might occur spontaneously in nature without the assistance of Diels−Alderase.

2.4. α-Ketol Rearrangement. The α-ketol rearrangement, also called acyloin rearrangement, transforms the α-hydroxy aldehydes/ketones to their constitutional isomers via a 1,2-alkyl(aryl) migration (Scheme 11a).[65−71] The reaction takes

Scheme 11. α-Ketol Rearrangement vs Tautomerization

a) α-Ketol rearrangement of tertiary α-keto carbinols: Isomerization via 1,2-alkyl/aryl shift

b) Isomerization of secondary α-keto carbinols via tautomerization

place reversibly under acidic, basic, or thermal conditions leading to the thermodynamically more stable isomer. It has been exploited in total synthesis and structural modification of natural products and is involved in the biosynthesis of several classes of natural products. It is important to note that secondary α-keto carbinols can undergo the isomerization via an enediol intermediate (Scheme 11b). It involves formally a H-migration process. However, α-ketol rearrangement refers conventionally to the reaction of tertiary alcohols.

2.4.1. Total Synthesis of Delitschiapyrone A. Delitschiapyrone A (**65**) was isolated in 2014 from a leaf-associated fungus *Delitschia* sp. FL 1581 collected in Florida.[72] Structurally, it is an α-pyrone-naphalenone conjugate with an unprecedented 6/6/5/7/6 pentacyclic ring system. It was proposed that delitschiapyrone A (**65**) was biosynthetically derived from two putative precursors, naphthoquinone **66** and α-pyrone **67** involving a key α-ketol rearrangement step (Scheme 12).

On the basis of this biosynthetic hypothesis, the group of Enomoto accomplished a concise enantioselective total synthesis of (+)-**65** (Scheme 12).[73] Naphthoquinone **66** and α-pyrone **67** were efficiently synthesized in 6 and 4 steps, respectively, from commercially available 4-bromo-3,5-dimethoxybenzoic acid. Heating a heterogeneous mixture of **66** and **67** in water at 35 °C for 2.5 days afforded **65** and cycloadduct **68** in isolated yields of 75% and 22%, respectively. The Diels−Alder cycloaddition between **66** and enantioenriched **67** followed by α-ketol rearrangement of the resulting cycloadduct **68** accounted for the formation of **69**. In situ intramolecular hemiacetalization of the latter afforded delitschiapyrone A (**65**) as a single isolable diastereomer. The last step of this domino process might be kinetically competent pulling therefore the reaction toward the formation of the natural product. In addition to the remarkable synthetic efficiency of the synthetic route, one may note that the presence of a single chiral center in **67** controlled the relative stereochemistry of the five contiguous stereocenters of the natural product **65**. A DFT

**Scheme 12. Enomoto's Total Synthesis of Delitschiapyrone A**
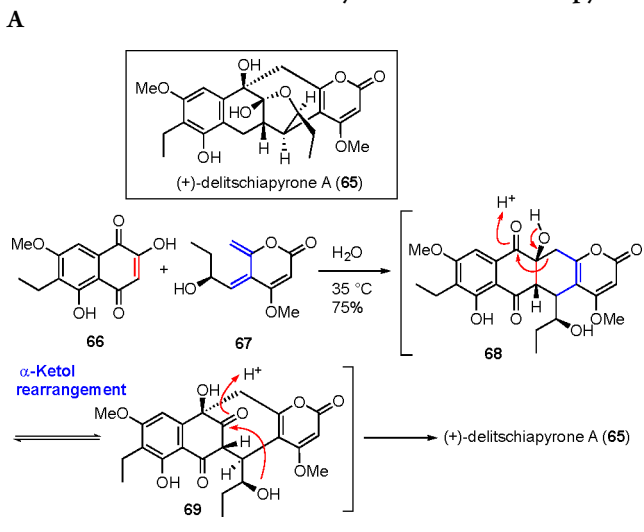
calculation has been performed to rationalize the observed high regio- and diastereo-selectivity of the [4 + 2] cycloaddition.

2.4.2. Total Synthesis of (+)-Strophasterol. (+)-Strophasterol A (**70**), a 14,15-secosterol, was isolated from the mushroom *Stropharia rugosoannulata*. It is a moderator of endoplasmic reticulum stress with promising biological activities against Alzheimer's disease.[74]

An interesting rearrangement sequence has been uncovered by Heretsch and co-workers during the course of their total synthesis of this natural product (Scheme 13).[75] In their

Scheme 13. Heretsch's Total Synthesis of (+)-Strophasterol
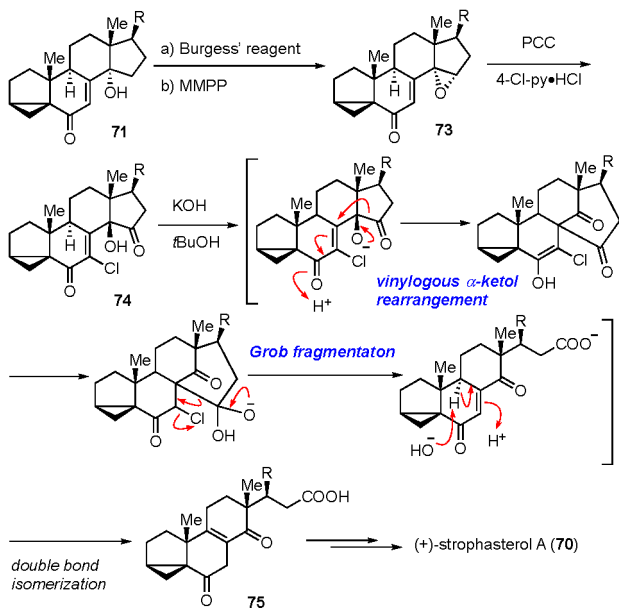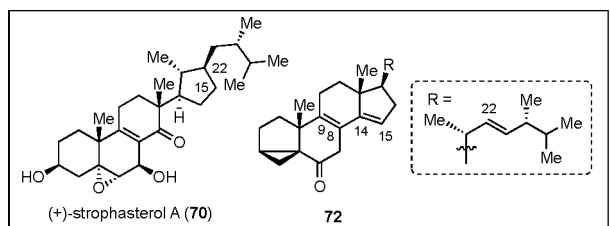
synthesis, cleavage of the C14−C15 bond of the suitably functionalized sterol followed by 5-*exo*-trig radical cyclization to forge the C15−C22 bond was planned to reach (+)-strophasterol A (**70**). Initial trials on the dehydration of **71**, prepared in three steps from (−)-ergosterol, afforded diene **72** with concurrent isomerization of the Δ7,8 double bond to the desired 8,9 position. However, all attempts to chemoselectively oxidize the Δ14,15 double bond of the conjugated diene met with failure. Alternatively, treatment of alcohol **71** with Burgess' reagent generated the conjugated dienone which upon chemo- and regioselective epoxidation with magnesium bis(monoperoxyphthalate) (MMPP) furnished **73** in 67% overall yield. Unexpectedly, oxidation of **73** with PCC in the presence of 4-chloro-pyridinium·HCl not only generated the hydroxyketone function but also introduced a chlorine atom on the adjacent enone functionality to furnish **74** in 68% yield. Taking advantage of the structural feature of **74**, a base-promoted domino process was subsequently developed. Thus, treatment of a *t*BuOH solution of **74** with KOH (5.0 equiv) afforded **75** via a vinylogous α-ketol rearrangement, Grob fragmentation, and double bond isomerization cascade. The overall process is redox-neutral and proceeds in quantitative yield. Compound **75** was then converted to (+)-strophasterol A (**75**) as planned via the formation of the C15−C22 bond by way of a radical cyclization reaction.

2.5. α-Aminoketone Rearrangement: Total Synthesis of (±)-Terengganensine B. Conversion of α-amino carbonyl compounds to α-iminols via 1,2-alkyl/aryl shift, known as α-aminoketone rearrangement (Scheme 14a), is a thermody-

Scheme 14. α-Aminoketone Rearrangement
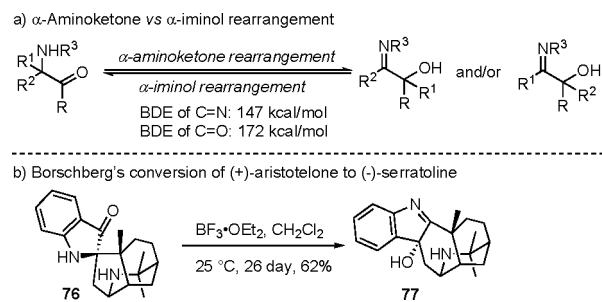
namically unfavorable process because of the stronger C=O relative to C=N bond (BDE of C=O 172 kcal/mol; that of C=N 147 kcal/mol). Indeed the reverse reaction, the α-iminol rearrangement, is a much favored process.[76] However, if the α-aminoketone function is incorporated in a complex ring structure, and if release of the ring strain and other unfavorable steric/electronic interactions are associated with the rearrangement, then the equilibrium can be pulled to α-iminol as is demonstrated by Borschberg and co-workers.[77] Thus, stirring a dichloromethane solution of (+)-aristotelone (**76**) at room temperature in the presence of a large excess of BF$_3$·Et$_2$O triggered a slow α-aminoketone rearrangement to afford (−)-serratoline (**77**) in 62% yield after 26 days (Scheme 14b).

Another way to compensate the thermodynamic penalty of the α-aminoketone rearrangement is to engage the resulting α-iminol to a subsequent kinetically competent transformation leading to a stable product. This rational has been used in our total synthesis of (±)-terengganensine B (**78**, Scheme 15a).[78] Treatment of a methanol solution of the easily accessible polycyclic indolenine **79**[79] with sodium methoxide furnished

Scheme 15. Our Group's Total Synthesis of Terengganensine B

a) Total synthesis of (±)-terengganensine B

b) Total synthesis of (±)-larutensine
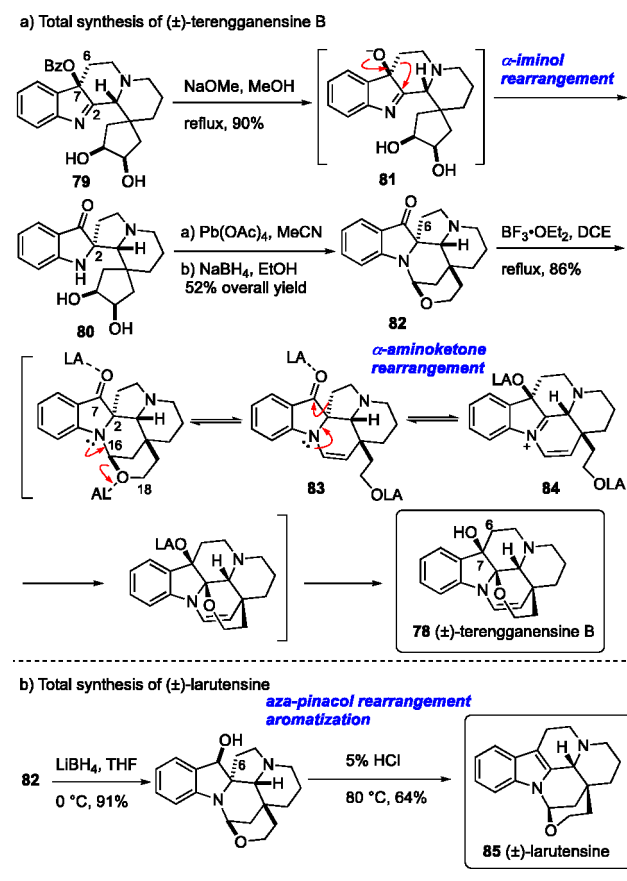
oxindole **80** via an α-iminol rearrangement of intermediate **81**, a reverse pathway of the α-aminoketone rearrangement. Compound **80** was subsequently transformed to the hexacyclic compound **82** involving a key conformation-directed diastereoselective cyclization process. Heating to reflux a dichloroethane solution of **82** in the presence of BF$_3$·Et$_2$O afforded directly the natural product **78** in 86% yield. A sequence of α-aminoketone rearrangement followed by a stepwise 1,3-oxygen shift from C16 to C2 was proposed to account for the reaction outcome.

It is important to note that the α-iminol rearrangement changed the C2 from sp^2 hybridization in **79** to sp^3 hybridization in **80**, essential for the subsequent diastereoselective cyclization, while the α-aminoketone rearrangement moved back the C6 from C2 to C7 with concurrent generation of an electrophilic C2 required for the hemiaminal formation. The hemiacetalization step shifted in turn the rearrangement toward the formation of thermodynamically less stable α-iminol, hence the natural product. This synthesis represents a rare example in which both α-aminoketone and α-iminol rearrangement are exploited to control the stereochemical course and the reaction pathway.

The intermediate **82** has also been converted to (±)-larutensine (**85**) via a sequence of reduction and aza-pinacol/aromatization sequence (Scheme 15b).

2.6. Benzilic Acid Rearrangement: Total Synthesis of Preuisolactone A. The benzilic acid rearrangement (BAR) and benzilic ester rearrangement (BER) convert 1,2-diketones to tertiary α-hydroxy acids and α-hydroxy esters, respectively.[80,81] Mechanistically, the reaction proceeds through

nucleophilic addition of hydroxide or alkoxide to one of the carbonyl groups followed by 1,2-alkyl/aryl shift (Scheme 16a).

Scheme 16. Benzilic Acid (Ester) Rearrangement

a) Benzilic acid (ester) rearrangement

b) Gademann's total synthesis of taiwaniaquinone H
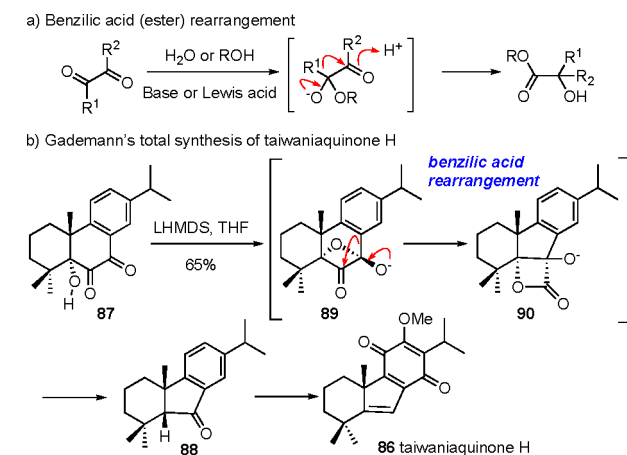
It has been successfully employed in natural product synthesis and in the structure modification of complex natural products, such as FK-506, an important immunosuppressant.[82] Shown in Scheme 16b is Gademann's total synthesis of taiwaniaquinone H (**86**) featuring a key BAR-based ring contraction process. Treatment of a THF solution of tricycle **87** with LHMDS transformed the central cyclohexan-1,2-dione to cyclopentanone **88** via intermediates **89** and **90**.[83] A series of standard transformations converted **88** to the natural product **86**.

Preuisolactone A (**91**) was isolated from endophytic fungus *Preussia isomera* in 2019.[84] Its caged structure is characterized by a tricyclo[4.4.0.^{1,6}0^{2,8}]decane framework with two butyrolactones, a vinylogous methyl ether, and a tertiary alcohol. Interestingly, it was isolated as a racemate although it contains seven adjacent stereocenters. In the isolation paper, the authors proposed that preuisolactone A (**91**) could be biosynthetically derived from farnesyl pyrophosphate via a complex cyclization/rearrangement/oxidation sequence.

The fact that compound **91** exists as a racemate prompted Trauner to hypothesize that it is a polyketide derived from oxidative dimerization of catechol **92** and pyrogallol **93**. This hypothesis was validated by a remarkably straightforward total synthesis of **91** accomplished in the same group (Scheme 17).[85] Treatment of an equimolar mixture of catechol **92** and pyrogallol **93** with K$_3$Fe(CN)$_6$ generated two o-quinones **94** and **95**, respectively, which underwent [5 + 2] cycloaddition to furnish the bridged 1,3-diketone **96**. Nucleophilic addition of water to the bridged carbonyl group in **96** provoked the retro-Dieckmann reaction to afford **97** which, upon intramolecular vinylogous aldol addition, was converted to the diosphenol **98**. The latter readily isomerized to its hemiacetal form **99**, presumably via the 1,2-diketone form. Treatment of a mixture of **98/99** with NaOH followed by acidification shifted the equilibrium toward **98**. Adding Koser's reagent to the above mixture triggered a cascade reaction to afford, after aqueous workup, preuisolactone A (**91**) in 57% yield. The reaction went through the I(III)-enolate **100** which rendered effectively the α-carbon of the enol electrophilic, facilitating the lactonization to afford compound **101**. Intramolecular hemiacetalization set the stage for the 1,2-alkyl shift (benzylic acid rearrangement) to furnish preuisolactone A (**91**).

Scheme 17. Trauner's Total Synthesis of Preuisolactone A

**Scheme 18. Proposed Biosynthesis of Aplysiasecosterol A**
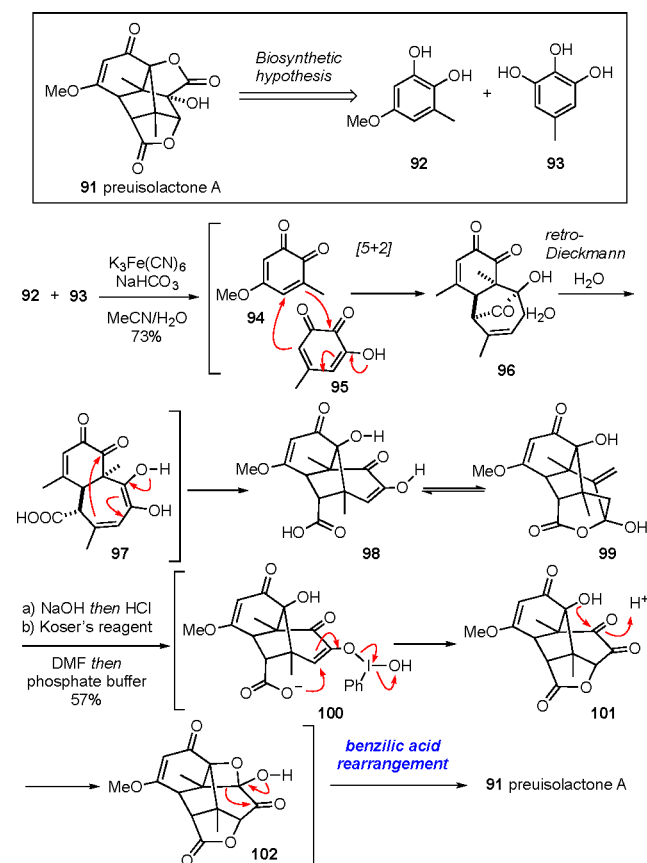
3. SUMMARY AND OUTLOOK

With these selected examples, we hope that we've demonstrated the power of the title domino process in the generation of the molecular complexity and in the development of concise, flexible, and practical synthesis of complex natural products. From the viewpoint of synthesis design, knowledge or a working hypothesis of a natural product's biosynthetic pathway has been a main inspiration for designing cascade reactions involving a 1,2-alkyl shift process. Indeed, the intensive exploration of cationic polycyclization/Wagner−Meerwein rearrangement, a well-established cascade in the biosynthesis of terpenoids (cf. Scheme 3),[86] has led to the discovery of many elegant and practically significant Lewis-acid- and Brønsted-acid-catalyzed laboratory syntheses of terpenoids.[87] In this sense, it is worth noting that the 1,2-rearrangement occurs in nature more often than one might expect. For example, a sequence of α-ketol, vinylogous α-ketol rearrangements followed by acetalization have been proposed as key steps in the biosynthesis of aplysiasecosterol A (**103**), a tricyclic 9,11-secosteroid (Scheme 18).[88] Retrosynthetically, disconnection of the tricyclic core of **103** to bicyclic compound **104** is not an obvious practice but is without doubt appealing and reasonable. Exploiting such a biomimetic approach is therefore expected to offer an elegant and nonconventional synthetic route.

From the viewpoint of reaction design, any chemical reaction leading to a putative carbenium ion or its equivalent could trigger the subsequent 1,2-anionotropic shift. Inversely, a 1,2-anionotropic rearrangement generates also a carbocation or its equivalents that could engender the follow-up trans-formations. Clearly, many options exist for the future
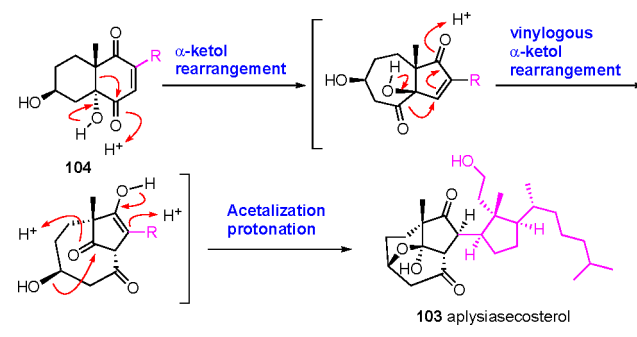
development of the title domino processes, and research in this direction will no doubt contribute to the progress of developing ideal syntheses of complex natural products.[89−91]

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Author Contributions

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Notes

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