# A Formal [3 + 3] Cycloaddition Approach to Natural-Product Synthesis

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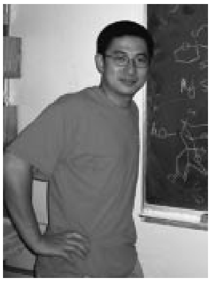
**Keywords:** Cyclization / Cycloaddition / Electrocyclic reactions / Heterocycles / Total synthesis

A formal [3 + 3] cycloaddition strategy for constructing complex heterocycles is reviewed here. This formal cycloaddition involves condensation of α,β-unsaturated iminium salts with 1,3-dicarbonyl equivalents. These reactions consist of a Knoevenagel-type condensation followed by a reversible 6π-electron electrocyclic ring-closure. They constitute a stepwise formal [3 + 3] cycloaddition protocol with the net result being the formation of two σ-bonds in addition to a new stereocenter adjacent to the heteroatom. This review describes in some detail, but not comprehensively, some precedents, problems, solutions, and stereochemical mechanistic issues, and focuses on applications of this formal cycloaddition strategy in natural product synthesis.

## 1. Introduction

Seven years ago, we came across a known annulation reaction. This annulation reaction was first reported by Link[1] in 1944 with 4-hydroxycoumarins, and after three decades of a more-or-less obscured existence, it was studied meticulously by Moreno-Mañas in the 1980s.[2] Mechanistically, this reaction proceeds through the sequence shown in Scheme 1. It commences with a *C*-1,2-addition of 6-alkyl- or 6-aryl-4-hydroxy-2-pyrones **1** to the iminium salt generated in situ from α,β-unsaturated aldehydes **2** and a



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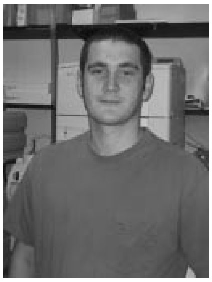

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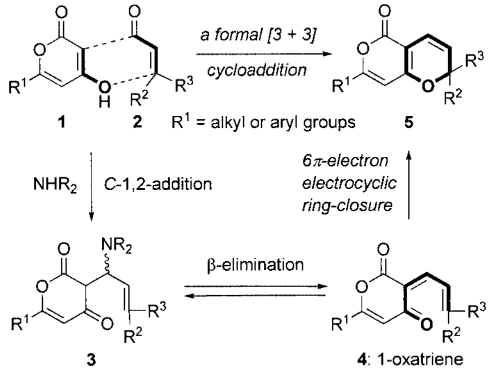


Scheme 1

secondary amine. A subsequent β-elimination gives 1-oxatriene intermediates **4**, which culminates in a Knoevenagel-type condensation, and the sequence concludes with a 6π-electron electrocyclic ring-closure of **4** to give the 2*H*-pyrans **5**.[3]

The overall result is the formation of two σ-bonds and a new stereocenter adjacent to the heterocyclic oxygen atom, thereby constituting a tandem anionic/pericyclic ring-closure sequence. It can be considered formally an equivalent of a [3 + 3] cycloaddition in which the three carbon atoms of aldehyde **2** have been added to the two carbon atoms and one oxygen atom of pyrone **1**.[4,5] We adapted the term [3 + 3] cycloaddition from Seebach's work describing a Stork-type carbo-[3 + 3] annulation reaction between nitroalkenes and enamines.[5]

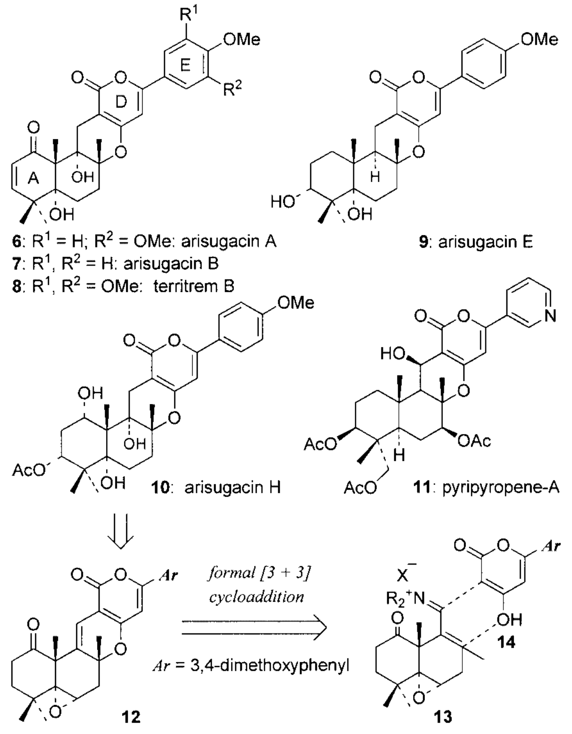
What led us to this annulation reaction was our strong interest in arisugacin A (**6**), a natural product isolated from *Penicillium* sp. Fo-4259 by Õmura (Scheme 2).[6] It is a potent and selective inhibitor of acetylcholinesterase (AChE) with an $IC_{50}$ of 1 nM,[6] and is therefore significant in the treatment of dementia diseases such as Alzheimer's disease (AD).[7,8] The entire arisugacin family [i.e., arisugacin B (**7**), E (**9**), and H (**10**)] features a unique meroterpenoidal structure, a hybrid of a polyketide and a terpenoid, that resembles other medicinally important natural products such as the territrems (**8**),[9] and pyripyropenes (**11**: pyripyropene A),[10] which is a potent inhibitor of acyl-CoA cholesterol acyltransferase (ACAT) (Scheme 2).

It became clear to us that to achieve a practical total synthesis of arisugacin A (**6**) or other family members, as well as their analogs, this formal [3 + 3] cycloaddition method could be invaluable.[11] Specifically, the reaction of α,β-unsaturated iminium salts **13** with 6-aryl-4-hydroxy-2-pyrones **14** should provide a facile access to the advanced pentacyclic intermediate **12** (Scheme 2).

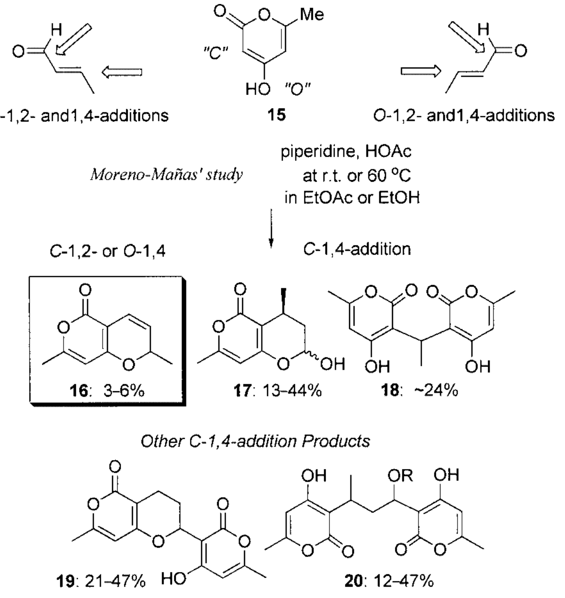
After this brief account of our beginning, we intend, in this microreview, to highlight efforts that were essential in rendering this formal [3 + 3] cycloaddition synthetically useful, and focus primarily on total syntheses of interesting natural products. Because the scope of this microreview is not exhaustive, we sincerely apologize in advance for omitting other significant contributions and elegant variations of this strategy. Finally, we have separated these reactions into two classes: oxa-[3 + 3] formal cycloadditions are those leading to pyrans and aza-[3 + 3] formal cycloadditions are those leading to dihydropyridines.

## 2. Synthetic Problems and Solutions

Despite the obvious synthetic potential of this formal oxa-[3 + 3] cycloaddition, applications have been limited because of the competing reaction pathways due to 1,2- versus 1,4-addition as well as *C*-addition versus *O*-addition (Scheme 3). In Moreno-Mañas' detailed studies,[2] the reac-



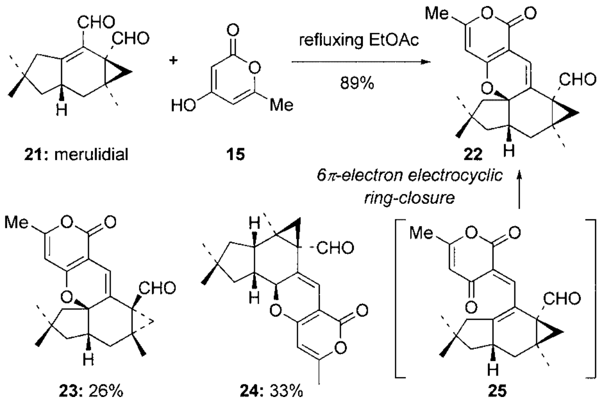
Scheme 2



Scheme 3

tion of 4-hydroxy-6-methyl-2-pyrone (**15**) with crotonaldehyde led to a variety of products such as **16**−**20**, resulting from various competing reaction pathways. The product of our main interest, **16**, was obtained in very low yields, and not at all when cinnamaldehyde was used.[2]

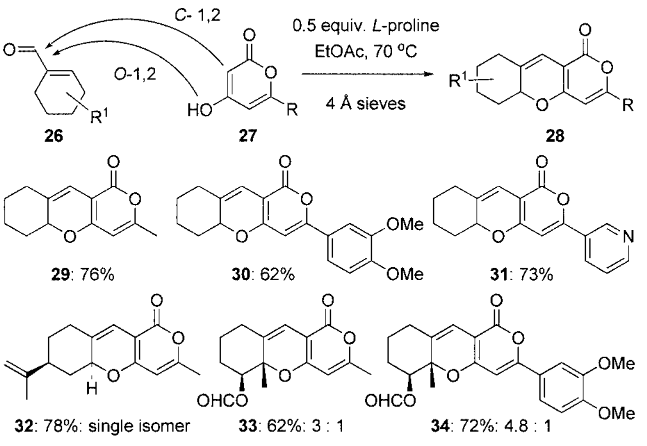
Prior to our own efforts, Jonassohn[12] published an interesting account that describes the reaction of merulidial (**21**), isolated from the fungus *Merulius tremellosus*, with pyrone **15** (triacetic acid; Scheme 4). This reaction does not employ an amine and proceeds simply in refluxing EtOAc to give **22** as a single diastereomer in 89% yield, although reactions that led to other related examples such as **23** and **24** were not as efficient. Jonassohn's study was unique because it suggested that cyclic enals do not necessarily suffer from the crippling competitive pathways mentioned above.



Scheme 4

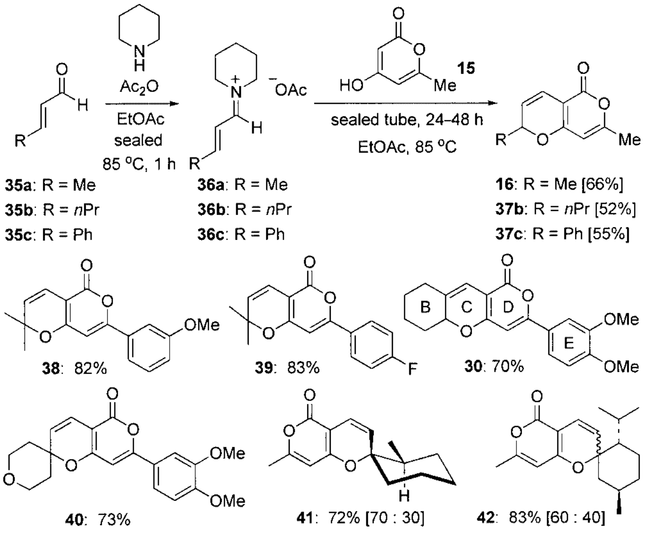
More importantly, because **22** was also isolated from the same fungus, and because the formation of pyrone **15** was also observed during the fermentation,[12] Jonassohn's study implied that the reaction of **21** with **15** could proceed through 1-oxatriene intermediate **25**, and that the formal oxa-[3 + 3] cycloaddition pathway is likely a biomimetic or bioinspired process.

Subsequently, Hua reported an elegant study[13] that preceded our communication.[11,14] In their study, shown in Scheme 5, cyclic enals were employed in view of their interest in arisugacin A (**6**). Again, certain cyclic enals, such as **26**, which possess diminished conjugation, led to improved regiochemical control, providing primarily the formal cycloadducts such as **28** by the *C*-1,2 pathway. Most notably, in addition to excellent yields obtained for products **29**−**34** in the presence of 0.5 equiv. of L-proline, a good level of diastereoselectivity was observed for products **32**−**34**. The preparation of **34** suggested strongly that a total synthesis of arisugacin A by this formal oxa-[3 + 3] cycloaddition strategy should be achievable.



Scheme 5

Building on these studies, we continued our own efforts and developed a more general solution to render acyclic enals useful in this formal cycloaddition reaction. To solve the competing reaction pathway problem or to improve the pathway leading to the desired 2*H*-pyran, an extensive experimental modification was required. Eventually, we utilized preformed α,β-unsaturated iminium salts instead of generating them in situ.[14,15]

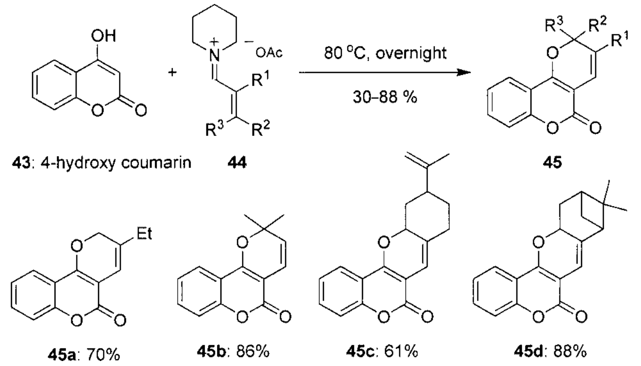


Scheme 6

As shown in Scheme 6, the enals **35a**−**c** were incubated in the presence of 1 equiv. of piperidine and 1 equiv. of $Ac_2O$ (added at −10 °C) in EtOAc at 85 °C in a sealed flask under $N_2$ for between 45 min and 1 h. The solution containing the iminium salt **36a**−**c** was then transferred without cooling to a solution of pyrone **15** in EtOAc. After stirring at 85 °C in a sealed flask for an additional 24−48 h, the desired 2*H*-pyrans **16**, **37b**, and **37c** were isolated in good yields.[14,15]

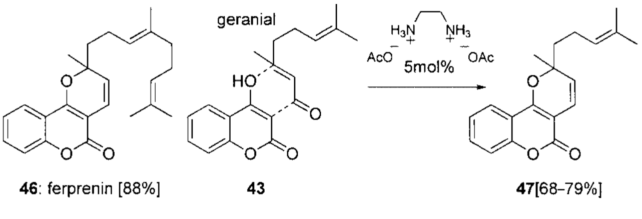
The use of α,β-unsaturated iminium salts is a general and efficient solution for the regioselectivity problem, leading exclusively to 2*H*-pyranyl products by the *C*-1,2-addition pathway. The reaction of pyrone **15** led to the pyran product **16** in an improved yield, and also gave previously unknown products **37b** and **37c** (Scheme 6). Our protocol allowed the preparation of analogs such as **30**, **38**, and **39**, with **30** being isolated in yields similar to Hua's. In addition, we were able to construct oxa-spirocycles, such as **40**−**42**, with **41** (the major isomer is shown) and **42** possessing moderate diastereoselectivities.[16]

The control of regioselectivity by using preformed α,β-unsaturated iminium salts in this formal cycloaddition reaction was recently validated in an account by Cravotto (Scheme 7).[17] Reaction of 4-hydroxycoumarin (**43**) with a series of α,β-unsaturated iminium salts, pre-generated from their respective enals under conditions similar to those we have reported, led to pyranocoumarins such as **45a–d** in good yields, and, notably, with a β-unsubstituted enal also being suitable (see **45a**). No stereochemical information was provided for **45c** and **45d** but they appeared to be single isomers.



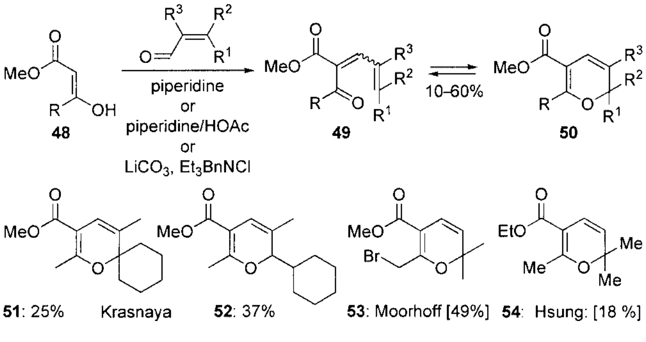
Scheme 7

In contrast, Appendino, Cravotto, and Palmisano,[18] previously reported a related study because of their interests in the pyranocoumarin family of natural products such as ferprenin **46** (Scheme 8). When treating 4-hydroxycoumarin (**43**) with a variety of enals, they found that, with exceptions such as products **46** and **47**, all other reactions afforded an array of products similar to those described by Moreno-Mañas[2] through related competing reaction pathways.



Scheme 8

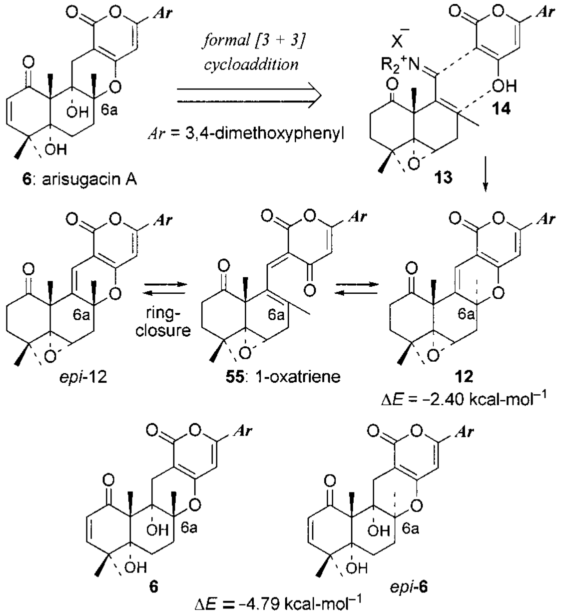
What remains as the major challenge in this formal oxa-[3 + 3] cycloaddition is to employ acyclic β-oxo nucleophiles such as **48** (Scheme 9). As shown by both Krasnaya[19] and Moorhoff,[20] reaction of **48** with enals generally affords an equilibrating mixture of 1-oxatrienes **49** and the desired 2*H*-pyrans **50**. While the equilibrium is substrate-dependent, there are only a few cases (**51–53**) in which the desired 2*H*-pyrans dominate the equilibrium.[19,20] Our own attempts also failed, as shown with pyran **54**, which was obtained in only 18% yield after prolonged heating.[21]



Scheme 9

## 3. Arisugacin A and Pyripyropene A

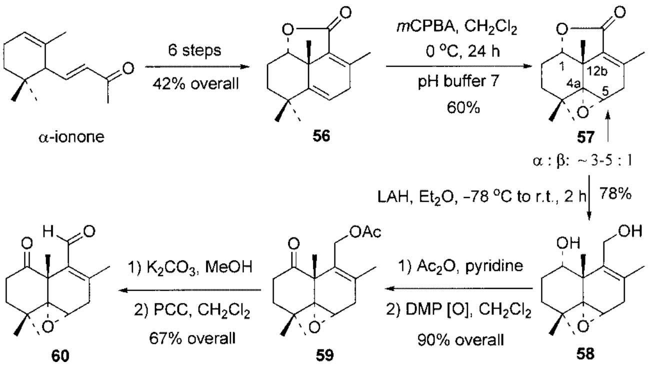
Although the proposed route for the synthesis of arisugacin A (Scheme 10) should be feasible, based on our development of the key formal [3 + 3] cycloaddition step (**13** + **14** → **12**),[14,15] there are two major uncertainties that could have rendered this effort futile. First, sterically congested α,β-unsaturated iminium salts such as **13** can impede the formal [3 + 3] cycloaddition, although Jonassohn's[12] work provides some assurance. Secondly, and more significantly, despite reports by Jonassohn[12] and Hua,[13] as well as our own results,[16] the ability to control the stereochemistry of the angular methyl group at C-6a through this key formal [3 + 3] cycloaddition reaction was quite speculative.



Scheme 10

However, because the 6π-electron electrocyclic ring-closure of the respective 1-oxatriene **55** was found to be reversible,[15,22] a favorable diastereoselectivity could be achieved leading to the thermodynamically more stable isomer **12**, in which the C-6a methyl group is in the β-position (Scheme 10). The pentacycle **12** is more favored than *epi*-**12** by about 2.40 kcal·mol$^{-1}$ using PM3 calculations (Spartan™). In addition, calculations showed that arisugacin A (**6**) with a C-6a β-methyl group is more stable than the *epi*-**6** isomer (C-6a methyl group is α) by about 4.79 kcal·mol$^{-1}$.

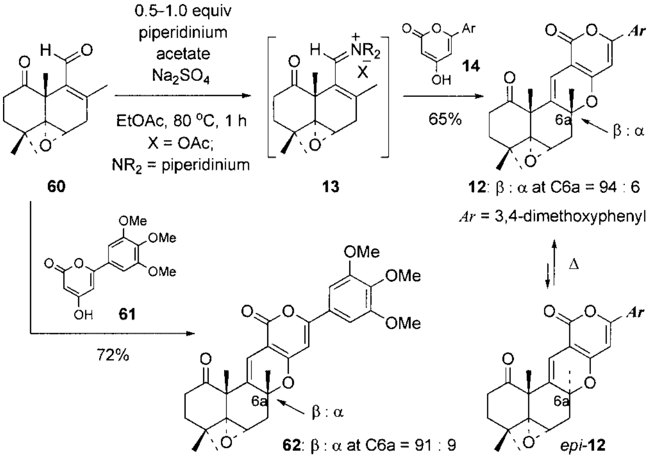
Encouraged by these calculations, the racemic lactone **56** was prepared readily in six steps from α-ionone in 42%



Scheme 11

overall yield using known methods (Scheme 11).[23,24] Epoxidation of **56** with buffered *m*CPBA led to α-epoxy-lactone **57** in 60% yield. The corresponding β-epoxy isomer was also isolated in 10−20% yield but was readily separated from α-epoxy isomer **57**. LAH reduction of α-epoxy-lactone **57** led to epoxy-diol **58** in 78% yield, with the epoxide group remaining intact when the reaction was carried out at low temperature. Standard functional-group manipulations gave aldehyde **60** in four steps with an overall yield of 60%.

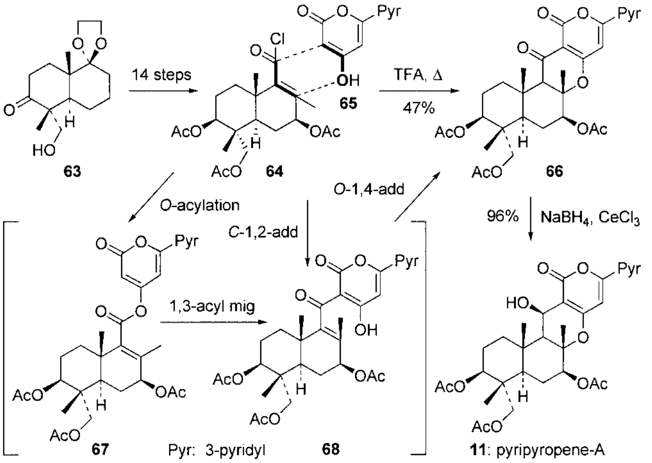
The iminium salt intermediate **13** was generated from **60** upon reaction with 0.5−1.0 equiv. of piperidinium acetate in the presence of $Na_2SO_4$ at 80 °C for 1 h, and subsequent reaction with pyrone **14** at 80 °C for 20 h led to pentacycle **12** in 65% yield with a diastereomeric ratio of 94:6 (Scheme 12).[25] The angular methyl group at C-6a was established as β for the major isomer of **12** and α for the minor isomer *epi*-**12** by NOE experiments. Under the same conditions using pyrone **61**,[26] pentacycle **62**, an analog of territrem B (**8**), was obtained in 72% yield with a diastereomeric ratio of 91:9 in favor of the same major isomer.



Scheme 12

The high diastereoselectivity obtained in these reactions is likely a result of the reversible 6π-electron electrocyclic ring-closure.[15,22] We were able to isolate the pure minor isomer *epi*-**12** and equilibrate it quantitatively to the desired major isomer **12** under thermal conditions,[15] thereby strongly suggesting the reversibility of the ring-closure of 1-oxatriene **55** (see Scheme 10). It is noteworthy that Õmura and Sunazuka[27] independently published an identical route to the same pentacycle **12**.

Our formal oxa-[3 + 3] cycloaddition approach is related to another variation involving α,β-unsaturated acyl chlorides that was elegantly displayed in Smith and Õmura's total synthesis of pyripyropene A (**11**).[10b] As shown in Scheme 13, acyl chloride **64**, derived from **63** in 14 steps, reacts with pyrone **65** in TFA at 80 °C to give the key pentacycle **66**, a penultimate intermediate, in 47% yield. Mechanistically, this probably occurs in a sequence of *O*-acylation, 1,3-acyl migration (or possibly a direct *C*-acylation), and *O*-1,4-addition via **67** and **68**.



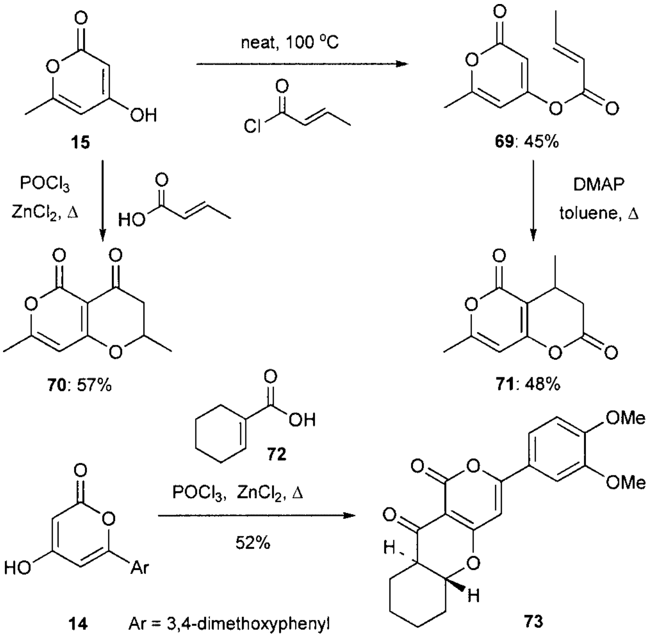
Scheme 13

We have also examined this acyl chloride oxa-[3 + 3] formal cycloaddition using simple model systems because we had hoped this would be a viable route to arisugacin A.[28] However, we found that the 1,3-acyl migration was not prominent as suggested by the isolation of ester **69** while finding no desired product (see **70** in Scheme 14). Subsequently, under basic conditions, only lactone **71**, which has the wrong regiochemistry needed for arisugacin synthesis, was formed.

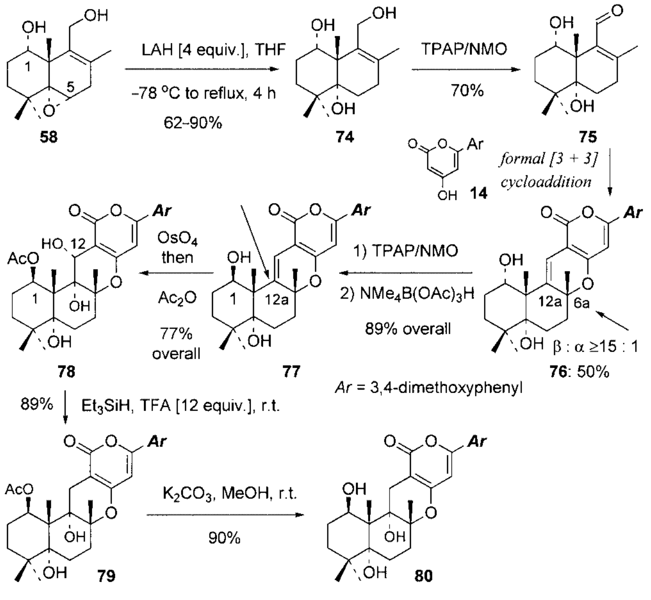
Ultimately, we found that α,β-unsaturated acids could react directly with pyrone **15** in the presence of $ZnCl_2$ in neat $POCl_3$ at 80−90 °C to give lactone **70** in 57% yield.[28] The acyl chloride intermediate was presumably generated in situ. To demonstrate the utility in arisugacin synthesis, tetracycle **73** was prepared in 52% yield from acid **72** and pyrone **14**. However, we abandoned this route because most of these conditions are too harsh and most likely will not be useful beyond simple model substrates, and because we had succeeded in the oxa-[3 + 3] formal cycloaddition using α,β-unsaturated iminium salts.

To complete our total synthesis efforts, we encountered numerous agonizing problems,[29] and there were also unexpected but interesting rearrangements observed by us[30a] as well as by Jung.[30b] These have been summarized elsewhere.[31] The final route is shown in Scheme 15.

Triol **74** was attained by LAH reduction of epoxy diol **58**; subsequent tetrapropylammonium perruthenate (TPAP)



Scheme 14

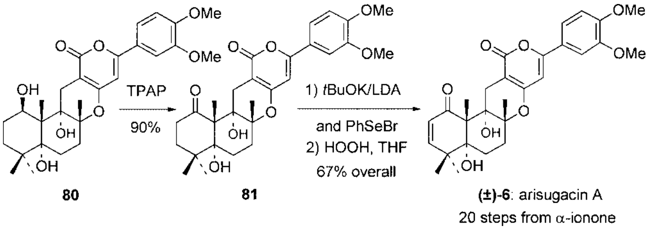


Scheme 15

oxidation without protecting either the C-1 or C-4a hydroxy groups gave enal **75** in 70% yield. Reaction of enal **75** with pyrone **14** under our standard oxa-[3 + 3] conditions led to pentacycle **76** essentially as a single diastereomer in 50% yield. Subsequent oxidation of **78** using Ley's TPAP/NMO and a directed reduction using $Me_4NB(OAc)_3H$ in AcOH gave exclusively diol **77** in 89% yield with C-1 β-OH (Scheme 15).[32]

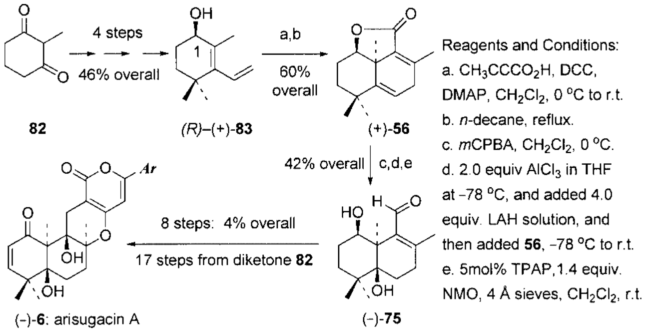
However, a major challenge involved installation of the C-12a angular hydroxy group in the C-ring (see arrow in **77**).[29] To solve this problem, dihydroxylation[33] of **77** was performed using $OsO_4$ in pyridine to afford the desired tetraol intermediate **78** in 77% yield as a single diastereomer after acylating the accessible secondary C-1 hydroxy group. Removal of the C-12 OH group in **78** by reaction with $Et_3SiH$ and 12 equiv. of TFA gave **79** in 89% yield;[33] deacylation of **79** gave the desired triol **80** in 90% yield.

Ley's TPAP oxidation of triol **80** gave pentacycle **81** in 90% yield (Scheme 16). Schlosser's base, prepared by deprotonating diisopropylamine with *n*BuLi in the presence of KO*t*Bu, was effective in the selenation of **81** using PhSeBr. Subsequent oxidative elimination of the selenide intermediate by reaction with $H_2O_2$ led to (±)-arisugacin A (**6**) in 67% yield for the last two steps.[34] We note that Õmura and Sunazuka have also published their total synthesis efforts employing virtually identical chemistry,[35] further supporting the usefulness of this formal oxa-[3 + 3] cycloaddition strategy for natural-product synthesis.



Scheme 16

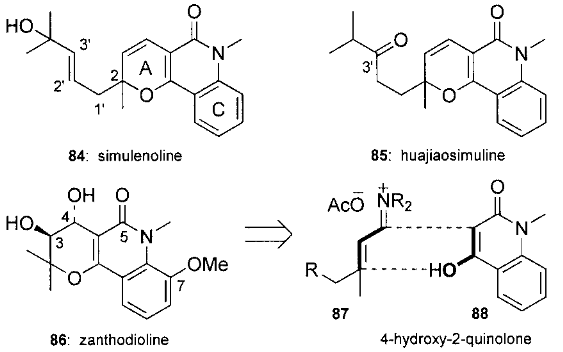
To achieve a total synthesis of (−)-arisugacin A (**6**), (*R*)-**83** was obtained readily from 2-methyl-1,3-cyclohexanedione (**82**) in four steps with an overall yield of 46%, featuring a vinylogous ester formation, a Stork−Danheiser double α-methylation,[24,36,37] a vinyl Grignard addition followed by acidic workup,[36] and an asymmetric Corey-Bakshi-Shibata (CBS) reduction (Scheme 17).[38,39] Subsequent chemistry, leading to (−)-arisugacin A [(−)-**6**] via (−)-**75**,[40] was identical to the racemic synthesis, and the total number of steps was reduced to 17.[41] A total synthesis of (+)-arisugacin A was recently completed by Õmura and Sunazuka.[35a]



Scheme 17

## 4. Pyranoquinoline Alkaloids

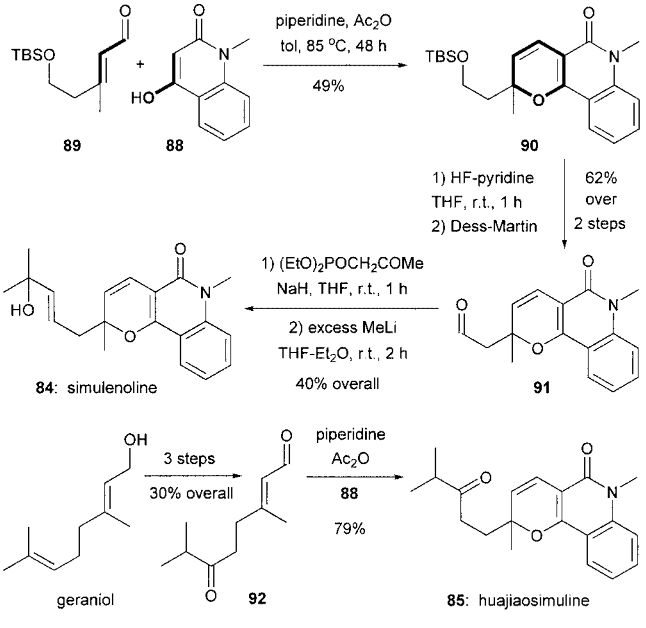
The pyranoquinoline alkaloids simulenoline (**84**)[42,43] and huajiaosimuline (**85**)[44] were first isolated from root barks of *Zanthoxylum simulans*, a shrub found in China (Scheme 18). A third pyranoquinoline alkaloid, zanthodioline (**86**), isolated from the same species was recently disclosed in the literature.[42] These novel monoterpenoid pyranoquinolines are potent inhibitors of platelet aggregation,[42] although only huajiaosimuline is toxic towards several cultured human-cell lines, especially the estrogen receptor-positive breast cancer cells, ZR-75-1.[44]



Scheme 18

Structurally, these alkaloids offer a unique opportunity to showcase the oxa-[3 + 3] formal cycloaddition using α,β-unsaturated iminium salts **87** and 4-hydroxy-2-quinolone **88**; these endeavors would help in assigning the relative stereochemistry of zanthodioline (**86**), which had only been tentatively reported.[42]

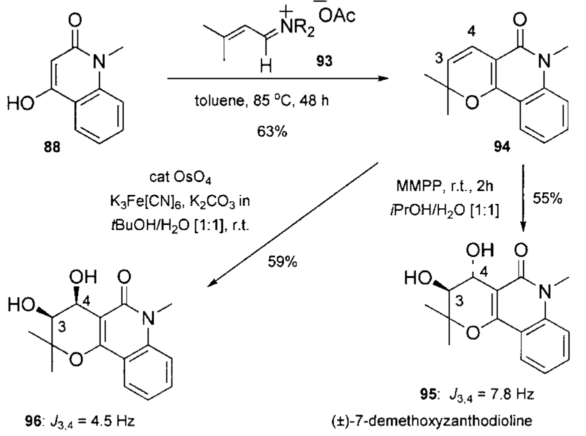
The reaction of α,β-unsaturated aldehyde **89**, prepared from homopropargyl alcohol in three steps, with 4-hydroxy-2-quinolone **88** under standard conditions provided the desired tricyclic pyran **90** in 49% yield (Scheme 19). Removal of the TBS group with HF/pyridine in THF, and Dess–Martin oxidation of the intermediate alcohol gave aldehyde **91** in 62% overall yield. A modified Wittig olefination using $(EtO)_2POCH_2COMe$ and NaH yielded an enone with a *trans*/*cis* ratio of 95:5; subsequent addition of excess MeLi to this enone provided simulenoline (**84**) in 40% overall yield.[45]



Scheme 19

A facile total synthesis of huajiaosimuline (**85**) was also achieved, as shown in Scheme 19.[45] The formal oxa-[3 + 3] cycloaddition reaction of **88** with oxo enal **92**, prepared from geraniol in three steps,[46] afforded huajiaosimuline (**85**) in 79% yield; the oxo group survived the reaction conditions.

The total synthesis of (±)-7-demethoxyzanthodioline (**95**, see Scheme 20) was accomplished by the formal cycloaddition of **88** with α,β-unsaturated iminium salt **93**. This reaction led to the tricyclic compound **94** in 63% yield under the standard conditions. Compound **94** is itself a natural product, *N*-methylflindersane, which was isolated from the same root bark.[43,47] Flindersane (–NH without the *N*-Me group) itself was synthesized in 1975 by de Groot[48] using the same formal oxa-[3 + 3] cycloaddition strategy, albeit with different reaction conditions. Based on our work associated with arisugacin A,[33] dihydroxylation of the endocyclic C-3–C-4 olefin in the pyranyl ring of **94** with magnesium monoperoxyphthalate (MMPP) in *i*PrOH/$H_2O$ (1:1) at room temperature led to the formation of (±)-7-demethoxyzanthodioline (**95**) in 55% yield with a *trans*/*cis* ratio of 9:1.[45]

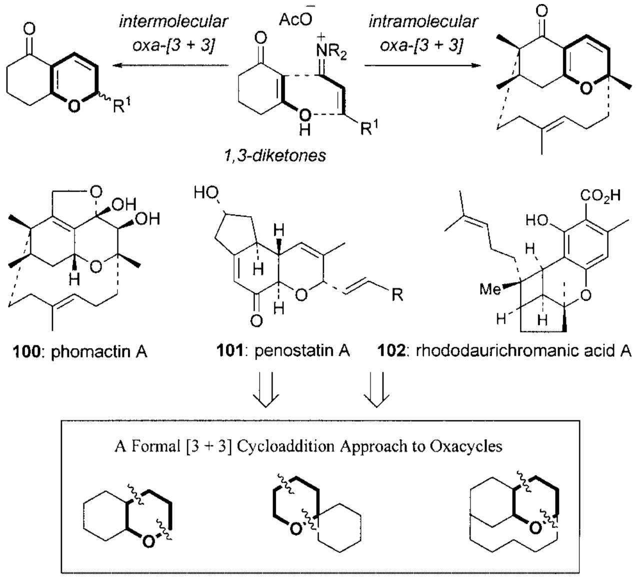


Scheme 20

The $J_{3\text{-H},4\text{-H}}$ vicinal coupling constant in the *trans* isomer is 7.8 Hz, while it is 4.5 Hz for the *cis* isomer **96**. The *cis* isomer **96** was directly prepared in 59% yield from **94** in the presence of a catalytic amount of $OsO_4$ and $K_3Fe(CN)_6$ in *t*BuOH/$H_2O$ (1:1) at room temperature.[45] We unambiguously confirmed the tentatively assigned *trans* relative configuration at C-3 and C-4 of zanthodioline (**86**) by comparing its coupling constant with the reported value (7.8 Hz).[42] More significantly, these exercises further support the bio-inspired aspect of this formal oxa-[3 + 3] cycloaddition reaction.[45]

## 5. Chromanoids and Chromenoids

The formal oxa-[3 + 3] cycloaddition reaction is a useful tandem anionic/pericyclic process or tandem Knoevenagel condensation/pericyclic ring-closure sequence, and Tietze has already elegantly summarized the significance of tandem strategies in natural-product synthesis.[49] We envisioned that by using 1,3-diketones (Scheme 21), this formal cycloaddition strategy could provide a unique approach to 1-oxadecalins and oxa-spirocycles that are well represented in biologically relevant natural products such as phomactin A (**100**),[50,51] penostatin A (**101**),[52] and rhododaurichromanic acid A (**102**).[53]

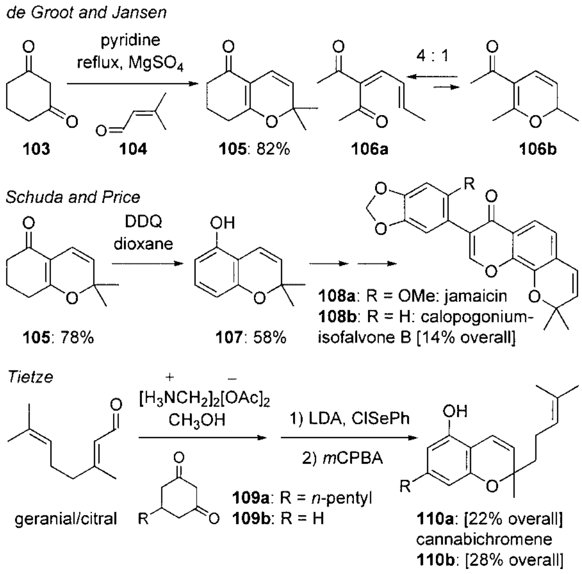


Scheme 21

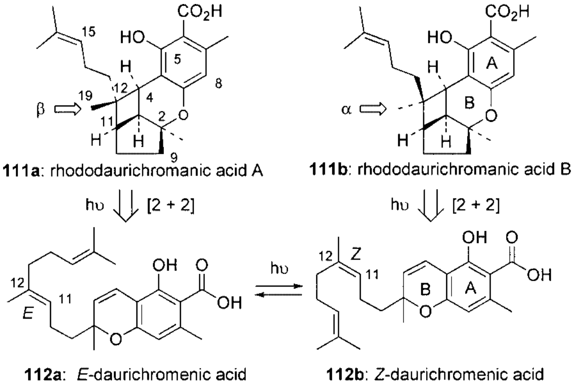
As we pursued this methodology,[15,54] we realized that de Groot,[48] Tietze,[55] and Schuda,[56] had already laid down some strong foundations. As briefly summarized in Scheme 22, de Groot and Jansen, who completed a total synthesis of flindersane from 4-hydroxy-2-quinolone,[48] also reported a series of reactions exemplified by boiling 1,3-cyclohexanedione **103** with enal **104** in pyridine to give 1-oxadecalinone **105** in 82% yield. They also documented the lack of success using acyclic diketones — a 4:1 equilibrating mixture was again found in favor of the 1-oxatriene **106a**.

Schuda and Price[56] subsequently employed 1-oxadecalinone **105** in total syntheses of jamaicin (**108a**) and calopogonium isoflavone B (**108b**), isolated from *Piscidia erythrina*[57] and *Calopogonium mucunoides*,[58] respectively (Scheme 22). The synthesis featured the use of DDQ in aromatizing **105** to the chromene nucleus **107**. Meanwhile, Tietze[55] reported his synthesis of cannabichromene (**110a**), isolated from *Cannabis sativa L.*,[59] featuring the same formal oxa-[3 + 3] cycloaddition reaction of citral and 1,3-diketone **109a**, as well as a stepwise but improved aromatization protocol.

Based on these excellent precedents, we pursued total syntheses of new chromanic acids. Rhododaurichromanic acids A and B (**111a** and **111b**) can be isolated[60] from *rhododendron dauricum*,[61] a plant native to areas of northern China, east Siberia, and Hokkaido, Japan (Scheme 23). A known natural product, daurichromenic acid (**112a**), was also isolated during the same study.[62] While **112a** is a highly potent anti-HIV agent, with an $EC_{50}$ of 5.67 ng/mL and a therapeutic index (TI) of 3710,[62] rhododaurichromanic acid A (**111a**) exhibits only a relatively potent anti-HIV activity, with an $EC_{50}$ of 0.37 μg/mL and a TI of 91.9. Although rhododaurichromanic acid B (**111b**) differs from **111a** only at the C-12 stereocenter, it possesses no activity. The biosynthetic relationship between **111a** and **112a** is reported to be a photochemical [2 + 2] cycloaddition in conjunction with an isomerization of the C-11−C-12 olefin from (*E*) in **112a** to (*Z*) in **112b** that could give **111b** upon cycloaddition.[60]



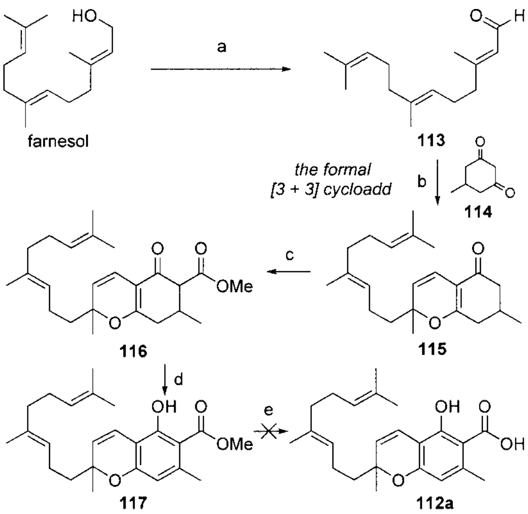
Scheme 22



Scheme 23

As shown in Scheme 24, aldehyde **113**, the precursor for preparing the appropriate α,β-unsaturated iminium salt, was obtained quantitatively by $SO_3$/pyridine oxidation of (*E*,*E*)-farnesol. An α,β-unsaturated iminium salt was generated by heating **113** at 90 °C in the presence of piperidine and $Ac_2O$,[15,54] and the subsequent formal cycloaddition with 5-methyl-1,3-cyclohexanedione (**114**) was accomplished on a multi-gram scale to give the desired adduct **115** as a 1:1 mixture of two diastereomers in 70% yield.

The formation of β-oxto ester **116** as a mixture of isomers was accomplished by addition of the lithium enloate derived from **115** to Mander's reagent (Scheme 24). DDQ oxi-

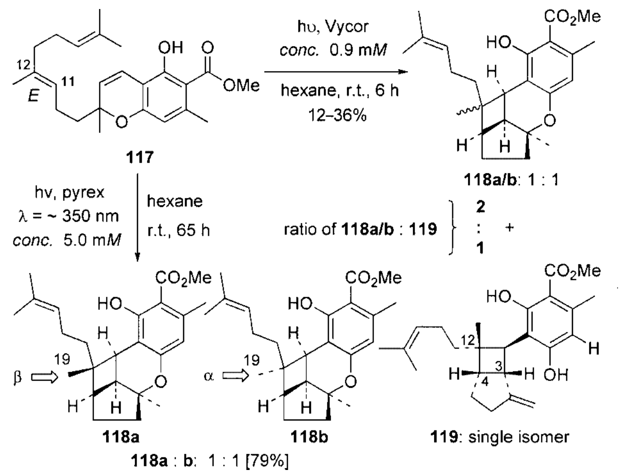


Reagents and Conditions: **a.** DMSO, $CH_2Cl_2$, $SO_3$-pyridine, $Et_3N$; [94%]. **b.** piperidine, $Ac_2O$, 90 °C, EtOAc, 1 h; and then added to **114** in toluene, 90 °C 12–18 h; [70%]. **c.** LDA, THF, –78 °C, and then added to $NCCO_2Me$; [71%]. **d.** DDQ, toluene, reflux; [44%]. **e.** KOH, NaOH, LiOH, $AlCl_3$, or $BBr_3$.

Scheme 24

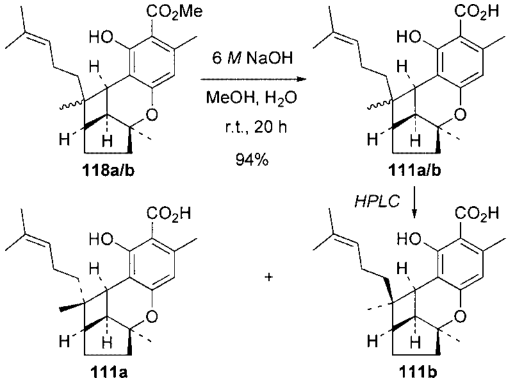
dation of **116** led to the racemic methyl daurichromenic ester **117** in 44% yield. However, numerous attempts to saponify ester **117** failed to give (±)-(*E*)-daurichromenic acid (**112a**). In most cases, decarboxylation occurred instead. To circumvent this problem, we examined the photochemical [2 + 2] cycloaddition of ester **117**.

As shown in Scheme 25, irradiation of **117** in hexane (0.9 mM) using a medium-pressure mercury-lamp with a Vycor filter led to rapid disappearance of the starting material, and afforded the desired cycloadducts **118a** and **118b** in a 1:1 ratio with an overall yield varying between 12 and 36%. Formation of the cycloadduct **118b** is a direct result of photochemical isomerization of the C-11–C-12 olefin in **117** from (*E*) to (*Z*) prior to [2 + 2] cycloaddition. The bicyclo[3.2.0]heptane **119** was also isolated as a single isomer (Scheme 25).[63] Irradiation of **117** in hexane (5.0 mM) using Pyrex as a cut-off filter provided a cleaner outcome, affording cycloadducts **118a** and **118b** in 79% yield as a 1:1 isomeric mixture, although the reaction took longer.



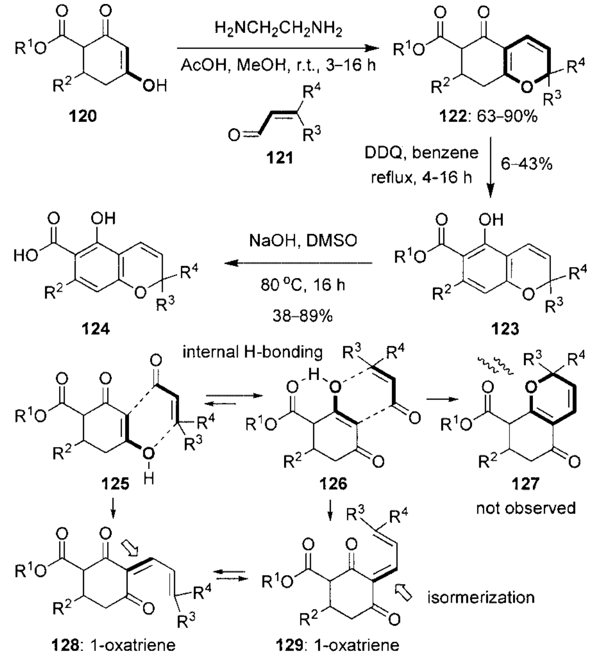
Scheme 25

To complete the total synthesis, cycloadducts **118a** and **118b** were saponified with 6 M aqueous NaOH in THF/MeOH, without any complications, to give rhododaurichromanic acids A and B (**111a** and **111b**) in 94% overall combined yield before separation by HPLC (Scheme 26).[60] Despite the complexity of (±)-rhododaurichromanic acids A and B, their syntheses were accomplished in six steps (excluding HPLC separation) with a 15% overall yield for the mixture of A and B.[63]



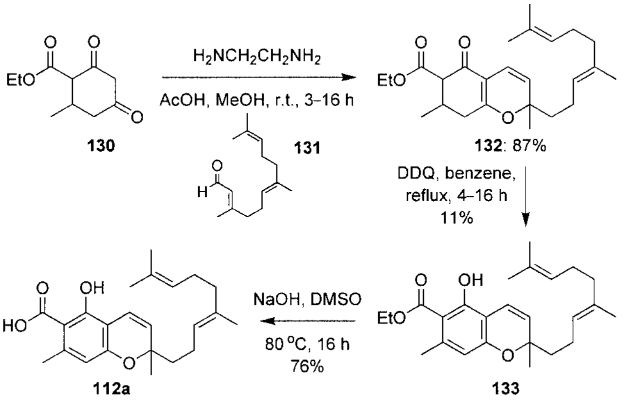
Scheme 26

More recently, Wilson[64] has approached daurichromenic acid and analogs in a similar way. As shown in Scheme 27, he used dioxo esters **120** and Tietze's conditions[55] in the oxa-[3 + 3] formal cycloaddition of a variety of different aldehydes **121** to give cycloadducts **122** in excellent yields. Their DDQ aromatization also suffered in yields, although the saponification, leading to daurichromenic acid analogs **124**, appeared to be effective.



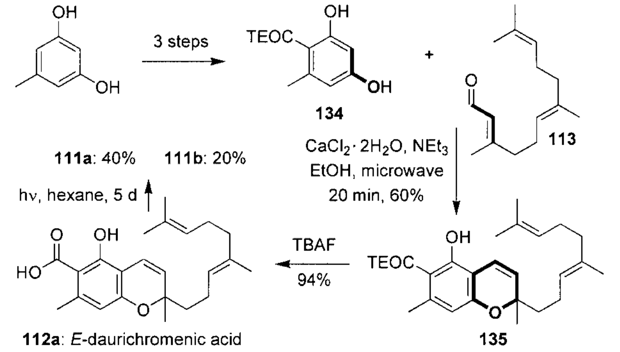
Scheme 27

The most remarkable aspect of Wilson's study[64] is that he only isolated cycloadduct **122**, which can be rationalized regiochemically as shown in **125**, while observing none of the regioisomer **127** derived from **126**. One could invoke that the initial tautomeric forms shown in **125** and **126** (likely favored due to internal hydrogen bonding) could favor the formation of either of the two 1-oxatrienes **127** and **128** after Knoevenagel-type condensation. However, given that 1-oxatrienes **127** and **128** could equilibrate under reaction conditions, the origin of the observed regioselectivity remains unclear. The relative product stability (**122** vs. **127**) with the excessive steric interactions could serve as an explanation. Wilson's work led to an eventual total synthesis of daurichromenic acid **112a** (Scheme 28).[64]



Scheme 28

The most elegant syntheses of rhododaurichromanic acid A (**111a**) and B (**111b**), and of daurichromenic acid (**112a**), were reported by Jin.[65] Jin's synthesis features a unique microwave-assisted formal oxa-[3 + 3] cycloaddition of resorcinol derivatives with enals, and provides a rapid and novel approach to chromenes (Scheme 29). It also bypasses the DDQ aromatization that was problematic in our[63] and Wilson's synthesis.[64] Their regioselectivity of this resorcinol/oxa-[3 + 3] formal cycloaddition was also excellent.

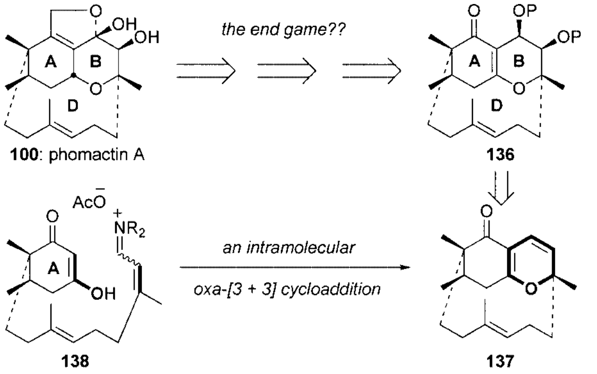


Scheme 29

In addition, Jin's synthesis provides a clever solution for problems encountered during saponification of methyl or ethyl daurichromenic esters. They used resorcinol **134**, which contains the trimethylsilyl ethyl ester functionality (trimethylsilylethoxycarbonyl = TEOC), and revealed the carboxylic acid group effectively at the end by reaction with TBAF. This total synthesis represents a more direct approach to the chromene nucleus from resorcinol **134**, and could have a much broader practical impact on the synthesis of chromenes and chromans.

## 6. Phomactin A

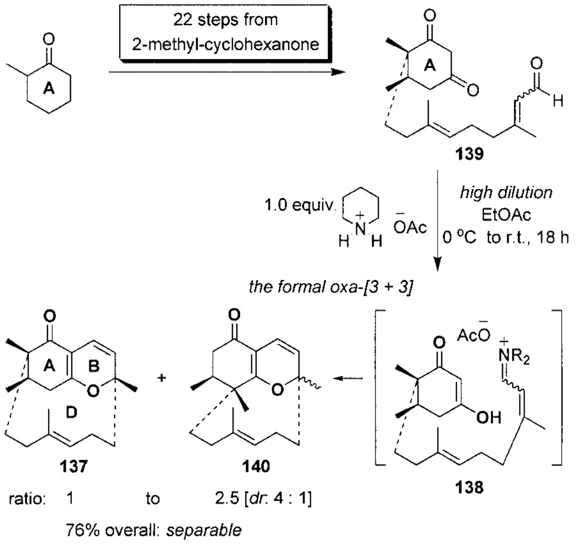
We recognized that this formal oxa-[3 + 3] cycloaddition reaction has never been employed in an intramolecular manner. While the feasibility issues such as the regio- and stereoselectivity of the intramolecular cycloaddition loom large, its success would provide a novel approach towards phomactin A (**100**),[50,51,66] in which the 12-membered D-ring (or the belt) is assembled at the onset instead of being constructed near the end.[51,66] Our approach to the synthesis of phomactin A (**100**) is outlined in Scheme 30.



Scheme 30

Phomactin A (**100**) was first isolated in 1991 by Sugano and co-workers from the culture filtrate of *Phoma* sp. (SANK 11486), a parasitic fungus found growing on the shell of a crab, *Chinoecetes opilio*, harvested off the coast of Fukui prefecture, Japan.[50] The phomactins, as a class, display novel biological activity as platelet-activating factor (PAF) aggregation inhibitors (**100**; $IC_{50}$ = 10 μM). PAF is a phospholipid mediator that is alleged to have a role in asthma and other inflammatory diseases.[50] The first total synthesis of a phomactin (phomactin D) was not achieved until 1996.[50] Despite the efforts of a number of groups to synthesize the phomactin core,[50,66] a total synthesis of phomactin A was not achieved until 2002 when Pattenden [(±)-**100**],[51a] and then Halcomb [(+)-**100**][51b] in 2003, reported their successes.

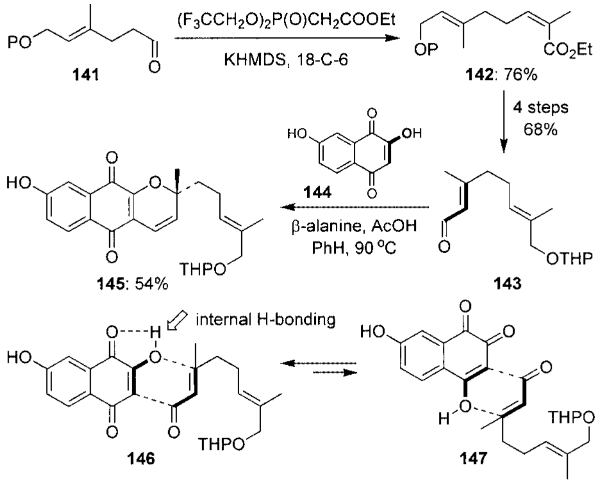
Although we intended to reserve this review for completed natural-product syntheses, and we have not yet achieved that in our phomactin endeavor, we wish to include our preliminary work here to demonstrate the feasibility of an intramolecular oxa-[3 + 3] formal cycloaddition.[67] As summarized in Scheme 31, enal **139** can be attained from 2-methylcyclohexanone in 22 steps. The ensuing intramolecular oxa-[3 + 3] formal cycloaddition of the iminium intermediate **138** led to a mixture of three isomers. The desired isomer **137** was found as a single isomer whereas the undesired regioisomer **140** was found as a 4:1 diastereomeric ratio.[67]



Scheme 31

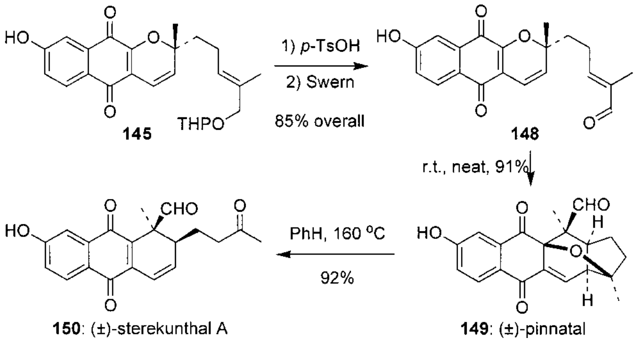
## 7. Pinnatal and Sterekunthal

The best demonstration of the bio-inspired aspect of the formal oxa-[3 + 3] cycloaddition was recently accomplished by Trauner.[68] The formal oxa-[3 + 3] cycloaddition of enal **143**, derived from aldehyde **141**, with hydroxynaphthoquinone **144** under Hua's conditions[13] led to pyranonaphthoquinone **145** in 54% yield as a single regioisomer (Scheme 32). Interestingly, the undesired regioisomer that can arise from **147** was not seen. In comparison with the results reported by Wilson,[64] this observation implies that internal hydrogen bonding leading to a more favored tautomer (i.e., **146**) may have no impact on regioselectivity.



Scheme 32

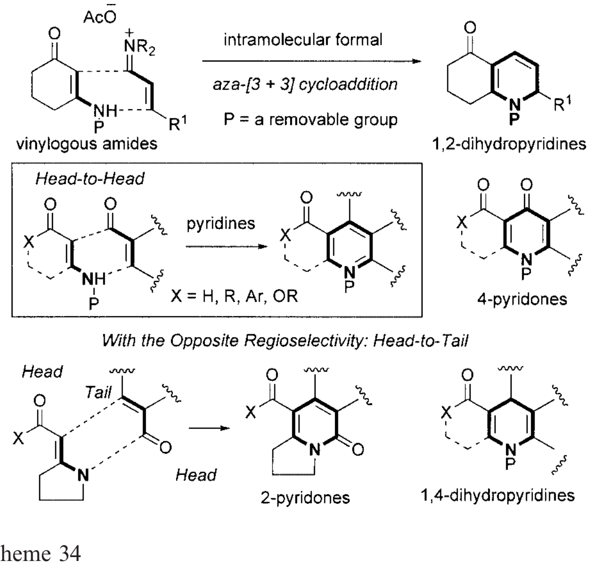
Subsequent deprotection of the THP group in **145**, followed by oxidation, led to the enal **148** (Scheme 33). Trauner[68] then elegantly employed an intramolecular Diels–Alder cycloaddition followed by a retro-hetero-Diels–Alder cycloaddition to form (±)-pinnatal (**149**) and (±)-sterekunthal (**150**),[69] respectively. This endeavor further reinforced the biomimetic aspect of the oxa-[3 + 3] formal cycloaddition. Trauner's work is especially clever from our perspective because we had already reported a related Diels–Alder cycloaddition — in our case it was intermolecular — retro-hetero-Diels–Alder cycloaddition sequence.[15,70] We recognized that these 2*H*-pyrans could serve as excellent dienes but failed to find a useful application.



Scheme 33

## 8. A Formal Aza-[3 + 3] Cycloaddition

We then investigated the formal [3 + 3] cycloaddition of vinylogous amides with α,β-unsaturated iminium salts as a viable method to construct dihydropyridines (Scheme 34). Annulation reactions of vinylogous amides with α,β-unsaturated carbonyl systems already represent a powerful synthetic approach for the synthesis of nitrogen heterocycles and related nitrogen alkaloids.[71,72] Most of these reactions have led to pyridines, and in some cases, 2-pyridones, 4-pyridones, and 1,4-dihydropyridnes have been reported (Scheme 34).[71] All these reactions constitute a formal aza-[3 + 3] cycloaddition in which the six-membered



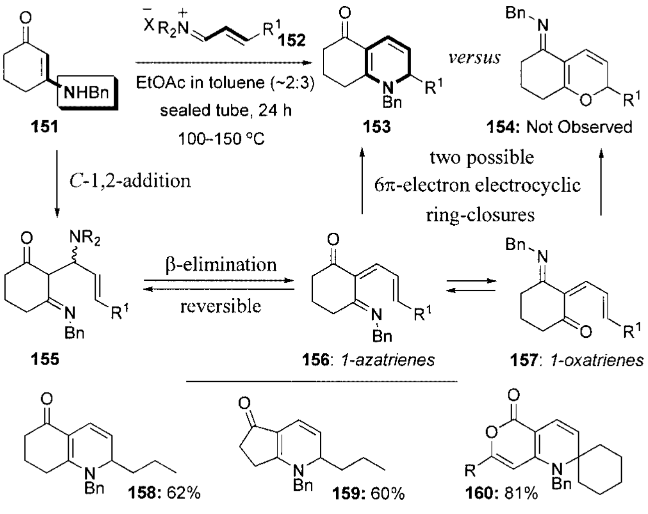
Scheme 34

nitrogen heterocycle is formed from the two carbon atoms and the nitrogen atom of the vinylogous amide, with the other three carbon atoms coming from the α,β-unsaturated carbonyl system.

Two possible regiochemical alignments can be commonly found in these reactions. The formation of pyridines or 4-pyridones mainly results from a head-to-head (both carbonyl groups point in the same direction) regiochemical alignment, and products such as 2-pyridones and 1,4-dihydropyridines are the result of a head-to-tail (carbonyl groups point in opposite directions) alignment. Although a variety of α,β-unsaturated carbonyl systems had been employed in these reactions, α,β-unsaturated iminium salts had not been used,[73,74] and 1,2-dihydropyidines had rarely been found in these reactions.[71]

### 8.1. Concept and Feasibility

The feasibility was readily established, and reactions of vinylogous amide **151** with α,β-unsaturated iminium salts **152** were found to be very efficient, leading exclusively to 1,2-dihydropyridines **153** (Scheme 35).[54,75] Mechanistically, a Knoevenagel condensation should lead to 1-azatriene **156** and 1-oxatriene **157**, and a subsequent 6π-electron electrocyclic ring-closure of **156** and **157** should give formal cycloadducts **153** and **154**, respectively, with **154** being the undesired outcome. However, cycloadduct **154** was not observed, implying that 6π-electron electrocyclic ring-closure of 1-azatriene **156** is favored over that of 1-oxatriene **157**.

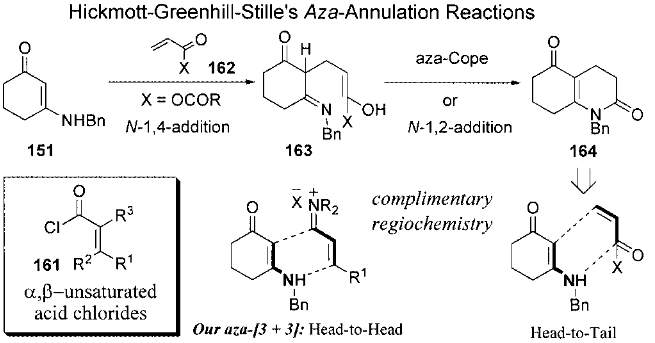


Scheme 35

Although 6π-electron electrocyclic ring-closures of 1-oxatrienes[3] and 1-azatrienes[76] have been studied extensively, such competition is not very well known. Again, while there could be an electronic origin for such selectivity, the product stability is perhaps another dictating factor, with **153** being more stable because it contains a vinylogous amide motif. Our formal aza-[3 + 3] cycloaddition provides a rapid construction of 1,2-dihydropyridines (see **158–160**) from simple and accessible vinylogous amides.

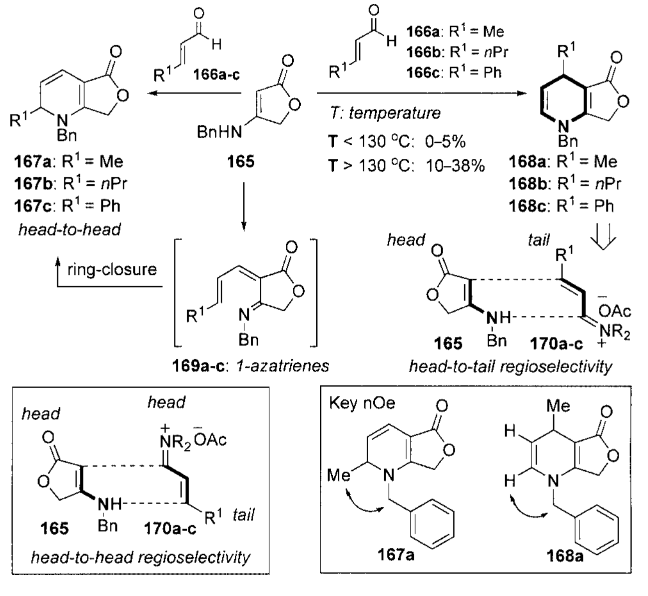
### 8.2. Regiochemical Issues

The regiochemistry (head-to-head) of this formal aza-[3 + 3] cycloaddition is the opposite to Hickmott, Greenhill, and Stille's aza annulation using acyl chlorides (**161**) or anhydrides (**151** + **162** → **164** in Scheme 36).[77–79] These two formal aza-[3 + 3] cycloadditions should therefore complement one another.



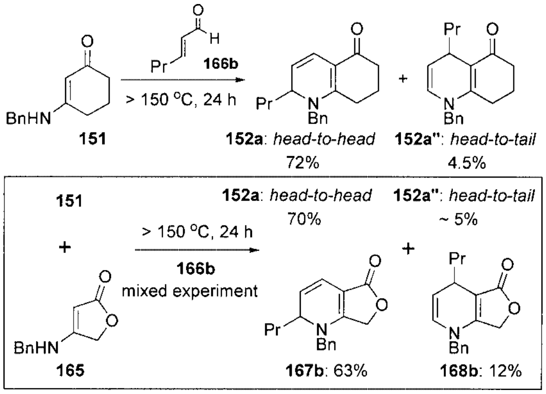
Scheme 36

It was not until recently when we examined the formal aza-[3 + 3] cycloaddition reaction of tetronamide **165** as a latent acyclic vinylogous amide that we found substantial amounts of the head-to-tail regioisomers **168a–c** in addition to desired cycloadducts **167a–c** (head-to-head; Scheme 37).[80] A closer examination revealed that this is a temperature-dependent phenomenon: when the reaction temperature was less than 130 °C, hardly any (< 5%) of the regioisomers **168a–c** was observed from their respective reactions, whereas when the temperature was raised above 130 °C as much as 10–38% of **168a–c** could be detected.



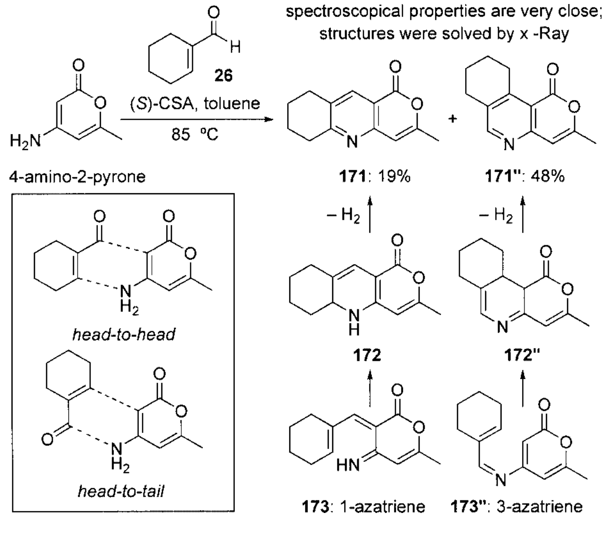
Scheme 37

We repeated the reaction of vinylogous amide **151** with **166b** at temperatures above 150 °C (Scheme 38).[80] Only if we were careful could we detect the head-to-tail regioisomer **152a′′** in the $^1$H NMR spectrum of the crude reaction mixture and isolate it in 4.5% yield. This result reaffirms that the reaction temperature is a critical factor, and explains why. When this reaction was first carried out at a temperature between 100 and 150 °C, we observed no significant amounts of any other regioisomers.[54] We are not certain at this point why the reaction temperature affects the two reaction pathways. Furthermore, when a mixed experiment was carried out using both **151** and **165**, we found that at temperatures greater than 150 °C the head-to-tail regioisomer **168b**, derived from treating **165** with **166b**, was consistently isolated in higher yields than **152a''**, derivrd from vinylogous amide **151**. This suggests that tetronamides such as **165** are more prone to annulate with α,β-unsaturated iminium salts in a head-to-tail manner.



Scheme 38

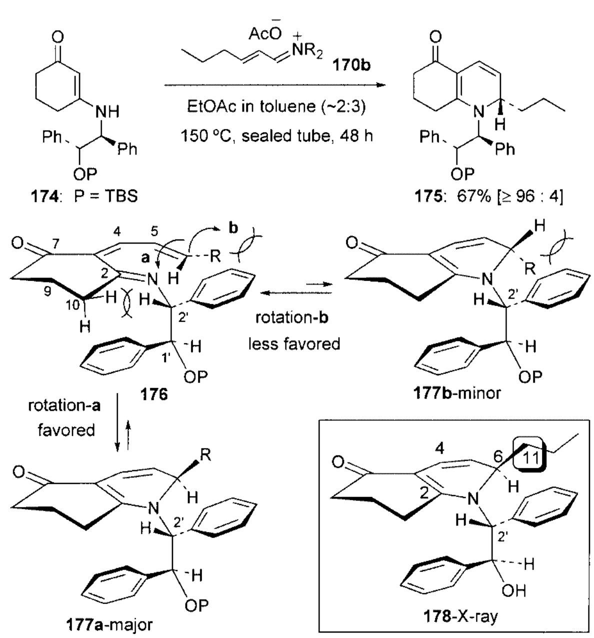
Hua[81] has also documented that the head-to-tail regioisomer **172''** is the major product when unprotected 4-amino-2-pyrone reacts with enal **26** in the presence of CSA (Scheme 39). The formation of head-to-tail regioisomer **172''** was rationalized by ring-closure of 3-azatriene **173''**, which is different from the mechanism proposed by Hickmott.[77,78] We believe this assessment is probably correct, given that we did not observe any head-to-tail regioisomers when we used protected 4-amino-2-pyrones or secondary vinylogous amides.[54] Intriguingly, the final products that Hua isolated were pyridines **171** and **171''**,[81] which again are products that we found predominately in our studies using tetronamides.[80]



Scheme 39

### 8.3. A Stereoselective Aza-[3 + 3] Formal Cycloaddition

We were able to achieve a stereoselective formal aza-[3 + 3] cycloaddition using chiral vinylogous amides such as **174**, leading to 1,2-dihydropyridines **175** in a highly diastereoselective manner (Scheme 40).[82] Given the vast number of nitrogen alkaloids that are known to possess this stereogenic center adjacent to the nitrogen atom, this stereoselective reaction represents an attractive entry to natural products with the 1-azadecalinic structural motif.[71,72,83] Most significantly, this stereoselective manifold would represent the first example of a stereoselective $6\pi$-electron electrocyclic ring-closure of 1-azatrienes,[76,84] which are key intermediates in these reactions.[22]



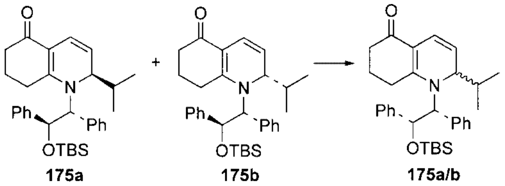
Scheme 40

The high diastereoselectivity was proposed to be a result of a key rotational preference in 1-azatrienes **176** (Scheme 40). Rotational preferences that lead to stereoselective construction of sp$^2$- and sp$^3$-hybridized stereocenters have excellent precedents in various pericyclic processes, and such stereoselectivity has been appropriately termed as torquoselectivity.[85,86] Rotation of the vinyl strand in **176** in direction *a* and direction *b* would lead to diastereomers **177a** or **177b**, respectively.

Based on the X-ray crystal structure of the desilylated dihydropyridine **178**, we proposed that 1-azatriene **176** assumes a similar conformational preference as the final product. This assumption equips **176** with a conformation where the C-2′ phenyl group is almost $\pi$-stacked with the C-5–C-6 alkene, and there can be two possible rotations for the C-5–C-6 vinyl strand in **176** during the ring-closure. Rotation *a* should be favored leading to the isomer **177a**, which is the observed major diastereomer, while rotation *b* is less favored as it leads to severe steric interaction between the R and the C-2′ phenyl group.[22,82]

While the rotational preference provides one explanation for the observed diastereoselectivity in the ring-closure of 1-azatrienes, the reversibility of ring-closure likely plays a significant role as well because there is ample precedent regarding the reversibility of the ring-closure of 1-heterotrienes.[3,76,85] The major isomer of **177a** is the thermodynamically more stable one with the least amount of steric congestion between the R and C-2′ phenyl group.

To establish such reversibility, a sample of **175** enriched in the minor isomer (28:72 major/minor) was heated in [D$_8$]toluene for 66 h (Scheme 41).[22] Although the final isomeric ratio of **175a/175b** eventually matched that observed from the reaction, the rate of equilibration from the minor isomer to the major isomer appeared to be slow, especially at temperatures below 150 °C. This suggests that the reversibility of ring-closure ultimately provides the diastereomeric ratio based on the thermodynamic stability of the two diastereomers; a rotational preference during the ring-closure of 1-azatrienes likely plays a role initially in setting up a ratio reflecting the thermodynamic ratio.



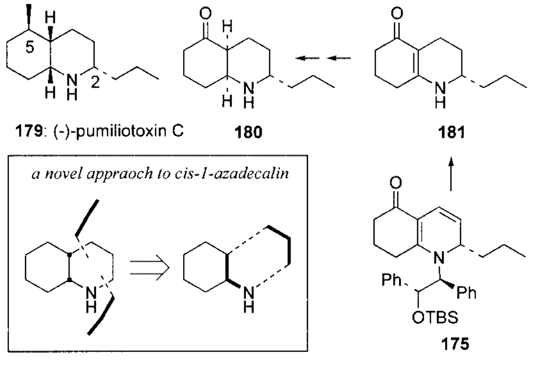
**175a** : **b**: 28 : 72

| | temp | time | a : b |
|---|---|---|---|
| | 80 °C | 20 h | 30 : 70 |
| | 110 | 28 | 44 : 56 |
| | 110 | 43 | 51 : 49 |
| | 110 | 49 | 61 : 39 |
| The observed ratio was ≥ 96 : 4 | 150 | 66 | ≥ 96 : 4 |

Scheme 41

### 8.4. Synthesis of epi-Pumiliotoxin C

Having achieved a mechanistic understanding of this formal aza-[3 + 3] cycloaddition, we pursued a proof-of-concept synthetic application to illustrate the utility of dihydropyridines such as **175** in constructing *cis*-1-azadecalins such as **180** related to the dendrobatid alkaloid pumiliotoxin C (**179**; Scheme 42).[78e,87–89] This exercise illustrates the feasibility of this formal aza-[3 + 3] cycloaddition in alkaloid synthesis.[22]

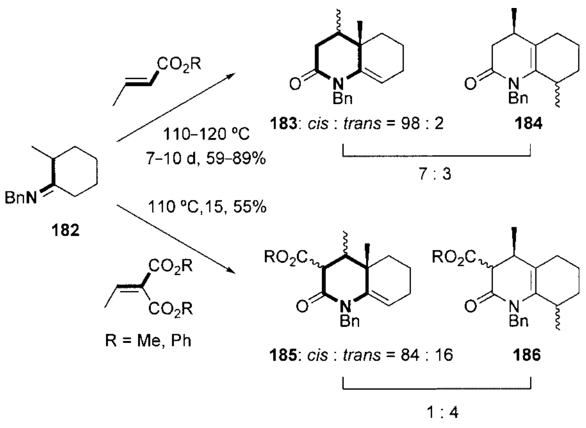


Scheme 42

## 9. Recent Examples and Variations

In this section we intend to highlight some recent examples in constructing piperidines by formal aza-[3 + 3] cycloaddition, and because of our recent highlight on the chemistry involving the formation of pyridines,[73,74,90] we will describe here only those examples leading to piperidines or dihydropyridines. We will not comment on the elegant work done by Stille in the 1990s,[78] although some of their endeavors will be echoed with examples shown here.

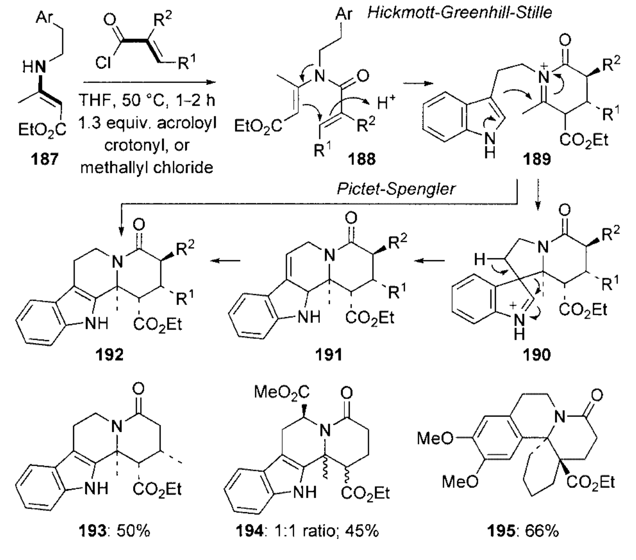
Jabin[91] has recently reported a study illustrating stereoselective Hickmott–Greenhill–Stille-type aza annulation. Jabin's work is similar to that reported by Stille,[78] except that acrylic esters and imines (**182**) were used (Scheme 43) instead of chlorides (or anhydrides) and vinylogous amides. Stereoselectivities were quite high, although isomeric enamides were found (**183** versus **184**, and **185** versus **186**) with variable ratios.



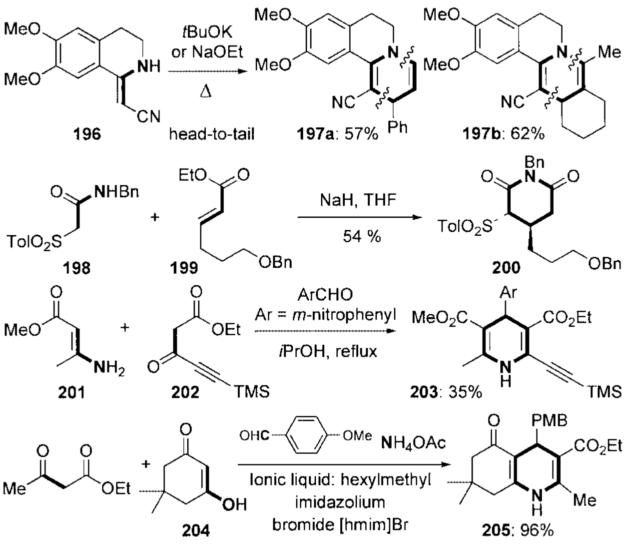
Scheme 43

Abelman[92] has reported an interesting account on tandem Hickmott–Greenhill–Stille aza annulation/Pictet–Spengler cyclization. As shown in Scheme 44, vinylogous urethane **187** reacts with acyl chlorides — anhydrides were used too — to give the *N*-acyl-iminium intermediate **189**, which was trapped by the indole ring in a Pictet–Spengler manner, although the authors proposed that the spirocyclic iminium intermediate **190** undergoes a rearrangement. This work expeditiously builds up the level of complexity in various indoloquinolizidines and isoquinolines, and the level of diastereomeric control is also very high in some cases (cf. **193** and **195**).

A diverse array of formal aza-[3 + 3] cycloadditions are shown in Scheme 45.[93–96] Many of these cases present a head-to-tail regioselectivity, as shown with the reaction of amide **196** with an α,β-unsaturated aldehyde or ketone to give 1,4-dihydropiperidines **197a**[93] and **197b** (see retrosynthetic lines for aldehyde and ketone used). In the case of the reaction of **201**[95] or **204**,[96] in an ionic liquid, this is a formal [3 + 2 + 1] multi-component cycloaddition.



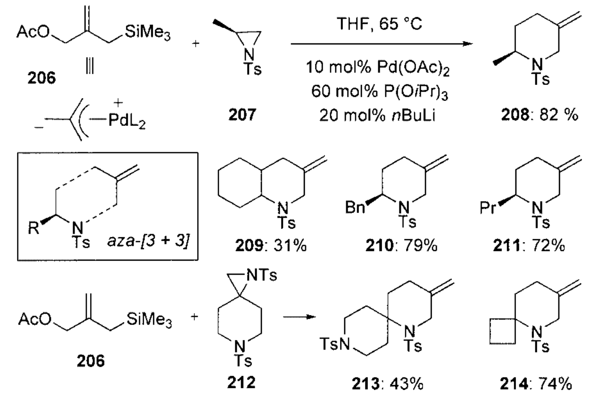
Scheme 44



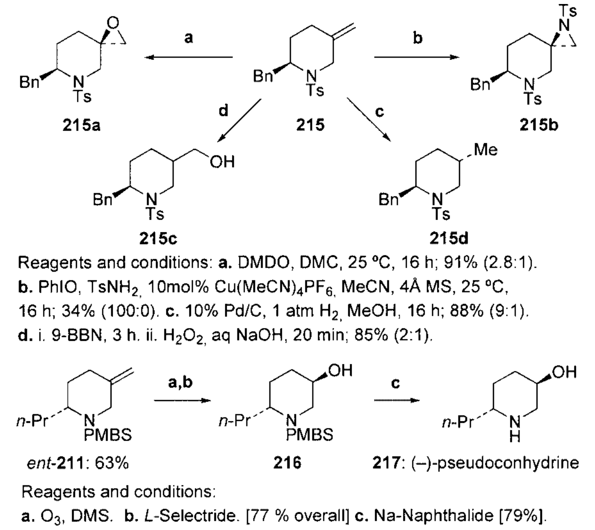
Scheme 45

Harrity[97] has reported a series of reactions describing a clever usage of (trimethylenemethane)palladium complexes in a formal aza-[3 + 3] cycloaddition. Reaction of allyl acetate **206** with aziridine **207** in the presence of 10 mol % of $Pd(OAc)_2$ and 20 mol % of *n*BuLi led to piperidine **208** in 82% yield (Scheme 46). These reactions are stereospecific, with no erosion of stereochemical integrity in the original azridine, and can give aza-spirocycles **213** and **214**. Harrity has applied this methodology by showcasing it in various functionalizations involving an exocyclic olefin (see **215**) and in a total synthesis of (−)-pseudoconhydrine (Scheme 47).

More recently, Dechoux[98] has employed a stereoselective Hickmott−Greenhill−Stille aza annulation en route to the synthesis of (−)-lupinine (**221**) in an impressive overall yield of 19% from (*R*)-phenylglycinol (Scheme 48). Paulvannan and Stille[78d] in 1993 had reported their racemic synthesis using the same aza annulation strategy.



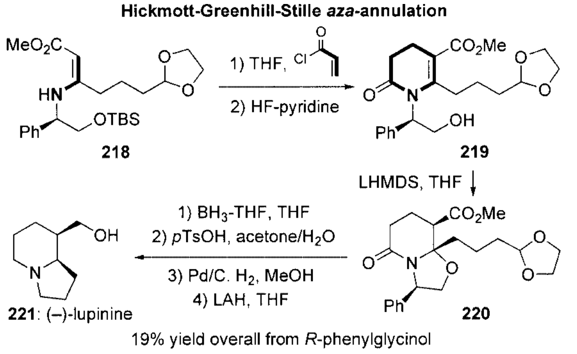
Scheme 46



Reagents and conditions: **a.** DMDO, DMC, 25 °C, 16 h; 91% (2.8:1). **b.** PhIO, $TsNH_2$, 10mol% $Cu(MeCN)_4PF_6$, MeCN, 4Å MS, 25 °C, 16 h; 34% (100:0). **c.** 10% Pd/C, 1 atm $H_2$, MeOH, 16 h; 88% (9:1). **d.** i. 9-BBN, 3 h. ii. $H_2O_2$, aq NaOH, 20 min; 85% (2:1).

Reagents and conditions: **a.** $O_3$, DMS. **b.** *L*-Selectride. [77 % overall] **c.** Na-Naphthalide [79%].

Scheme 47



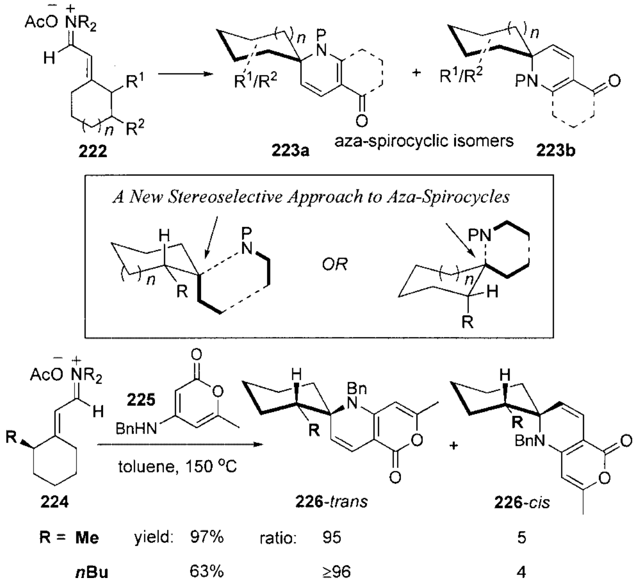
19% yield overall from *R*-phenylglycinol

Scheme 48

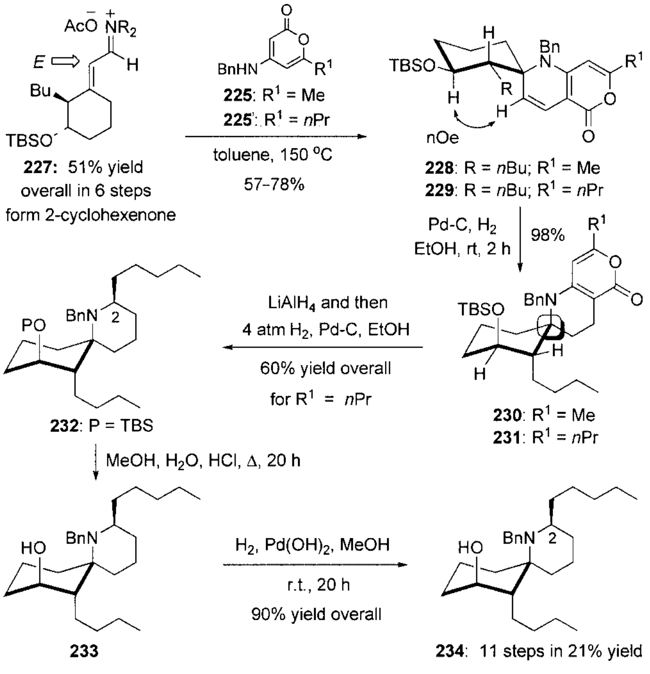
## 10. Perhydrohistrionicotoxin

During our studies, we found that we were able to achieve high diastereoselectivities when using chiral cycloalkylidene α,β-unsaturated iminium salts **222** (Scheme 49), leading to formation of aza-spirocycles **223**.[99] The selectivity is quite high, as shown with the synthesis of **226** (R = Me or *n*Bu).

This allowed us to develop a powerful strategy for stereoselective construction of aza-spirocyclic natural products,[100] and we have applied it to a total synthesis of 2-*epi*-(±)-perhydrohistrionicotoxin (Scheme 50).



Scheme 49



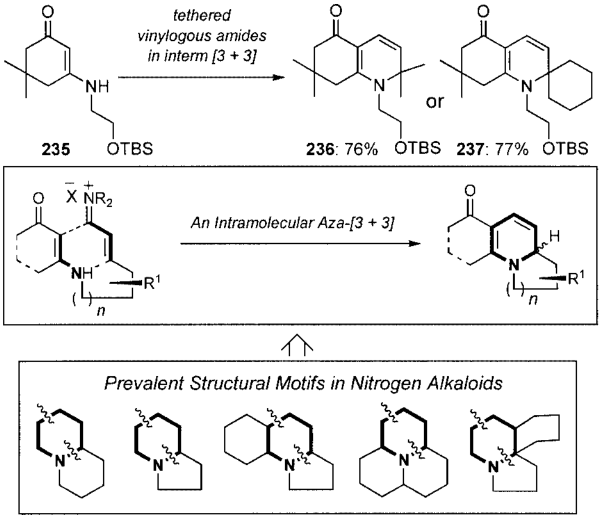
Scheme 50

The cyclohexylidene α,β-unsaturated iminium salt **227** was obtained from 2-cyclohexenone in 51% overall yield for the six steps[101,102] with an (*E*)/(*Z*) ratio of 2:1 (Scheme 50). The (*E*) isomer of **227** reacts with **225** and **225′** to give aza-spirocycles **228** and **229**, respectively, in 57−78% yield as single diastereomers. Hydrogenation of **228** and **229** led to **230** and **231**, quantitatively, thereby furnishing three contiguous stereocenters of perhydrohistrionicotoxin.[100,103−106] In comparison to known approaches to this natural product,[100,104−106] this represents a novel approach to aza-spiroundecane ring systems with a high level of diastereomeric control at the aza-spiro center.

Transformation of the 2-pyrone moiety in **231** into the desired simple *n*-amyl side chain was accomplished by an unprecedented decarboxylation protocol when aza-spirocycle **231** was treated with LAH. After a simple quenching with ethanol, followed by filtration through Celite, the crude mixture was subjected to 4 atm of $H_2$ in the presence of Pd/C (Scheme 50). The product **232** was isolated in a repeatable manner with a consistent yield in the range of 40−60%. Compound **232** was then acidically desilylated and debenzylated with Pearlman's catalyst to give 2-*epi*-(±)-perhydrohistrionicotoxin **234**[106] in 90% overall yield for the last two steps. This completes an 11-step total synthesis in an impressive 21% overall yield from 2-cyclohexenone.

## 11. Gephyrotoxin

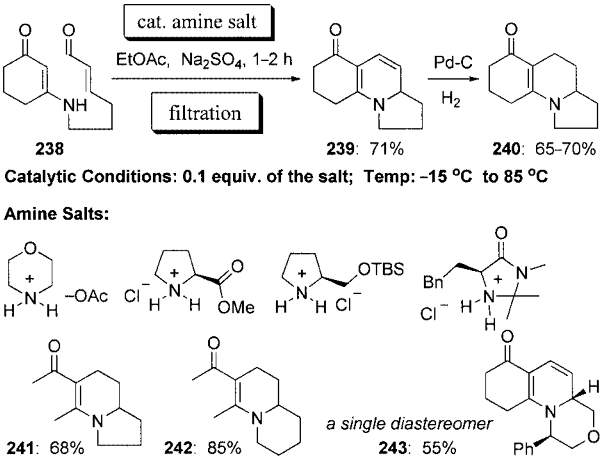
Another advance in this formal aza-[3 + 3] cycloaddition was to develop an intramolecular variant as we recognized that we could tether virtually any substituents onto the nitrogen atom of vinylogous amides such as **235** in an intermolecular formal aza-[3 + 3] cycloaddition (**235** → **236** or **237** in Scheme 51). This should constitute a new strategy for constructing an array of nitrogen heterocyclic structural motifs.[107]



Scheme 51

After extensive screening, the desired cycloadduct **239** was isolated in 71% yield after heating **238** in the presence of 0.5−1.0 equiv. of piperidinium acetate salt at 90−110 °C for 1−2 h (Scheme 52).[107] Under these conditions, the reaction proceeded more quickly and the purification required a simple filtration. Compound **239** proved to be less stable than anticipated, and thus it was hydrogenated to the tricyclic heterocycle **240** in 70% yield.

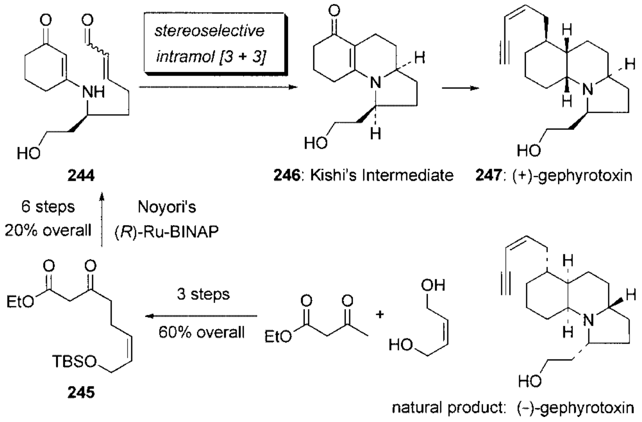
This two-step sequence could be further optimized by reducing the amount of piperidinium salt to 0.1 equiv. and lowering the reaction temperature to 80 °C (Scheme 52). Submitting the crude reaction mixture directly to standard hydrogenation conditions avoided the need to isolate the sensitive heterocycle **239**. This one-pot protocol provided **240** in 65% overall yield from **238**; a range of other amine salts could also be used.



Scheme 52

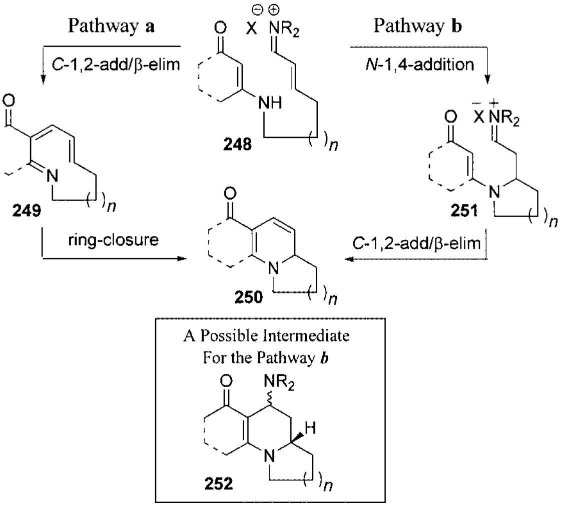
This new reaction protocol proved to be general for the synthesis of **241**–**243**. Successful preparations of **241** and **242** allowed us to design syntheses of natural products from the indolizidine and quinolizidine families.[108] In addition, a high diastereoselectivity could also be achieved in this reaction, as shown with **243**.[107]

Access to the tricyclic heterocycle **240** provides an efficient entry to the tricyclic frame of gephyrotoxin.[109] As shown in Scheme 53, among the three known total syntheses of (±)-gephyrotoxin,[110] Kishi's synthesis involves the intermediate **246**.[110c] The only enantioselective synthesis of (+)-gephyrotoxin reported by Kishi utilizes the optically active **246**, which was prepared in 18 steps.[111] This synthesis represents the sole report indicating that the natural product could be (−)-gephyrotoxin (Scheme 53).[111] We have completed the formal total synthesis of (+)-gephyrotoxin by constructing Kishi's intermediate **246** using a diastereoselective intramolecular aza-[3 + 3] formal cycloaddition of the chiral vinylogous amide **244**.[107]



Scheme 53

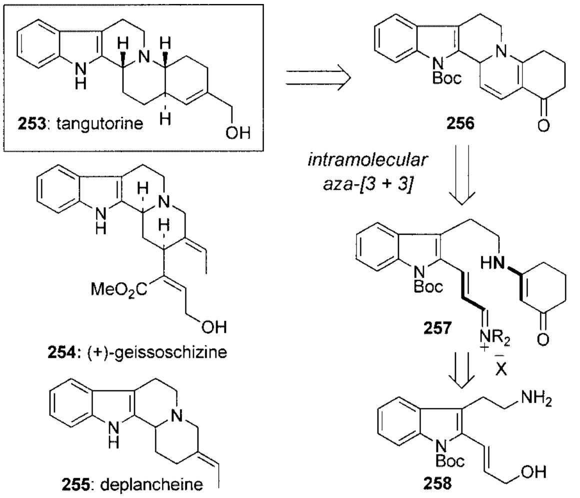
For the intramolecular reaction, the mechanism could also proceed by two possibilities: pathway *a* and pathway *b* (Scheme 54). However, intuition would support pathway *b* since it does not require the initial counterintuitive formation of macrocycle **249** implied in pathway *a*. If this assertion is valid, then the intermediate **252** in pathway *b* should be detectable or isolable, thereby providing support for an *N*-1,4/*C*-1,2 addition pathway. Our results support pathway *b*.[22]



Scheme 54

## 12. Tangutorine

An application of the intramolecular aza-[3 + 3] formal cycloaddition is our total synthesis of tangutorine.[112] (±)-Tangutorine (**253** in Scheme 55) was first isolated from the leaves of *Nitraria tangutorum* by Che and co-workers.[113] It possesses a novel benz[*f*]indolo[2,3-*a*]quinolizidine skeleton and, to date, is the only known β-carboline natural product of this type,[114] although it is related to well-known monot-

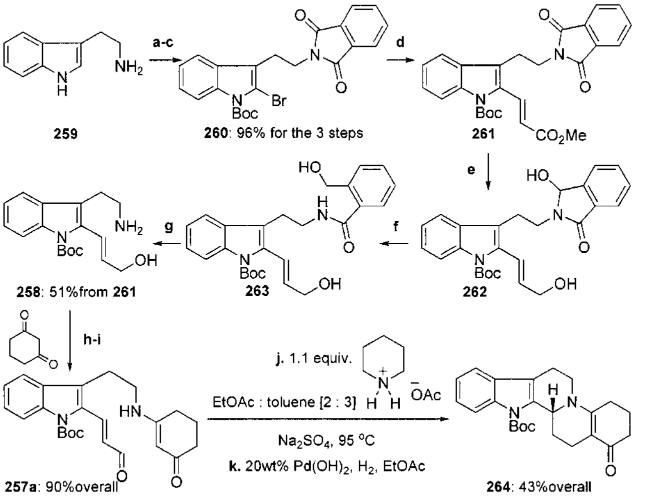


Scheme 55

erpenoid indole alkaloids such as (+)-geissoschizine (**254**)[115,116] and (+)-deplancheine (**255**).[117–119]

Natural products containing the indoloquinolizidine substructure are prevalent among monoterpenoid indole alkaloids that are derived biosynthetically from tryptophan. Synthesis of these monoterpenoid indole alkaloids has often featured the classic Pictet–Spengler cyclization.[120] This strategy was also evident in Jokela's sole total synthesis of tangutorine (**253**).[121] We envisioned that tangutorine should be attainable from pentacycle **256**, and to construct pentacycle **256** we could use an intramolecular aza-[3 + 3] cycloaddition with α,β-unsaturated iminium salt **257**. The α,β-unsaturated aldehyde precursor to **257a** could be obtained from condensation of amino alcohol **258** with 1,3-cyclohexanedione.

To prepare amino alcohol **258**, tryptamine (**259**) was first protected as a phthalimide, and bromination at the C-2 position using pyridinium hydrogen perbromide followed by Boc protection of the indole nitrogen atom gave bromide **260**[122] in 96% yield over the three steps (Scheme 56). Heck coupling of bromide **260** with methyl acrylate in the presence of [Pd(PPh$_3$)$_4$] afforded ester **261** in 82% yield,[123] and reduction of **261** with Dibal-H led to allyl alcohol **262** in which the phthalimido group was also partially reduced. NaBH$_4$ reduction[124] followed by hydrolysis with HOAc was employed to afford the desired amino alcohol **258** in 51% overall yield from **261** with no purifications.

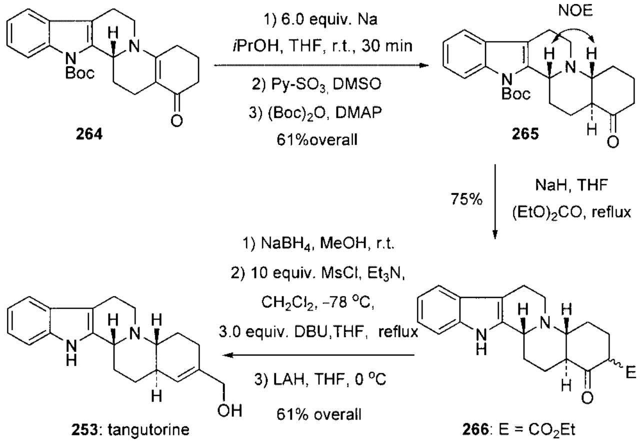


Reagents and conditions. **a.** phthalic anhydride, Et$_3$N, tol, Δ. **b.** pyr-HBr-Br$_2$, CHCl$_3$, THF, –10 °C. **c.** Boc$_2$O, DMAP. **d.** 2.5 mol% Pd$_2$dba$_2$, 5.0 mol% $Pt$Bu$_3$, 1.1 equiv. Cy$_2$NMe, Et$_3$N, toluene, 95 °C, 5.0 equiv. methyl acrylate. **e.** Dibal-H, CH$_2$Cl$_2$, –78 °C, 1 h. **f.** 3.0 equiv. NaBH$_4$, $i$PrNH$_2$ and H$_2$O [6 : 1], r.t.. **g.** AcOH, 85 °C, $i$PrNH$_2$ and H$_2$O [6 : 1]. **h.** 1,3-cylohexanedione, toluene, reflux. **i.** MnO$_2$, CH$_2$Cl$_2$, r.t.

Scheme 56

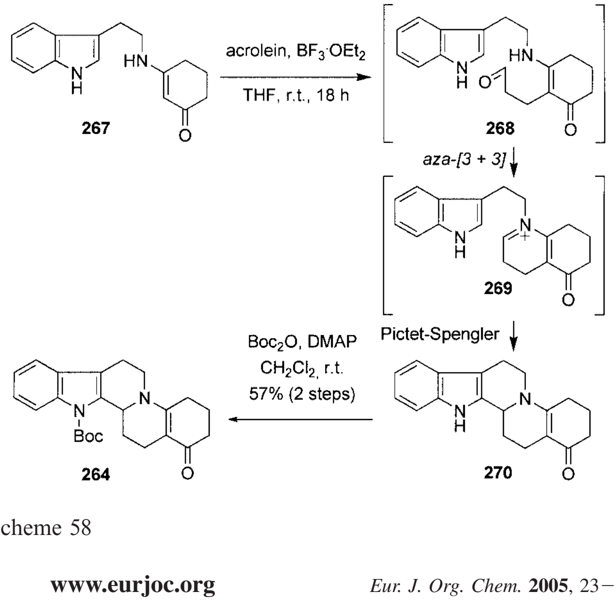
Subsequent condensation of amino alcohol **258** with 1,3-cyclohexanedione, followed by MnO$_2$ oxidation, led to enal **257a**. Under standard intramolecular formal aza-[3 + 3] cycloaddition conditions,[107] the desired pentacycle **264** was isolated in 43% yield overall after hydrogenating the endocyclic olefin. Thus, a viable synthetic approach to tangutorine (**253**), (+)-geissoschizine (**254**), or other tryptophan-derived monoterpenoid indole alkaloids was established.

As shown in Scheme 57, pentacycle **264** can be reduced using the dissolving metal protocol reported by Palmieri for the reduction of vinylogous amides.[125] The extent of the reduction, however, was not easily controlled, as reduction of the carbonyl group and removal of the Boc group were also observed. Thus, re-oxidation with pyridine/SO$_3$ and DMSO, as well as re-protection of the indole nitrogen atom with Boc anhydride, were carried out to give oxo pentacycle **265** as a single diastereomer in 61% yield over three operations. Refluxing pentacycle **265** in THF in the presence of NaH and diethyl carbonate was the most suitable regioselective route to β-oxo ester **266** as a mixture of two diastereomers. Subsequent NaBH$_4$ reduction, elimination, and LAH reduction furnished (±)-tangutorine (**253**) in 61% overall yield.[112,113]



Scheme 57

More recently, Luo and Zhai[126] have put everything beautifully together in a formal synthesis of (±)-tangutorine by preparing intermediate **264** by a clever tandem intermolecular aza-[3 + 3] formal cycloaddition/Pictet–Spengler cyclization strategy (Scheme 58). It is noteworthy that their key aza-[3 + 3] formal cycloaddition employs acrolein, which was unsuccessful in our own previous attempts, and that it likely proceeds through a head-to-tail



Scheme 58

regioselectivity based on related work reported by Winterfeldt.[127,128]

## Conclusions

We have summarized here the development of a formal [3 + 3] cycloaddition and its applications. Given the recent success in natural-product synthesis employing this strategy, we hope this review will provoke interest from the synthetic community to explore this approach for the construction of heterocycles.

## Acknowledgments

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