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ARTICLE

An Invocation for Computational Evaluation of Isomerization Transforms: Cationic Skeletal Reorganizations as a Case Study

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This review article describes how cationic rearrangement reactions can be used in natural product total synthesis as a case study for the many productive ways by which isomerization reactions are enabling for synthesis. This review argues that isomerization reactions in particular are well suited for computational evaluation, as relatively simple calculations can provide significant insight.

1. Introduction

As the structural diversity of natural product skeletons continues to increase, the various molecules uncovered each pose their own unique challenges to chemical synthesis. One of the classic ways to tame these daunting chemical features is to effect isomerization reactions that metamorphosize unique carbocyclic skeletons back to familiar topologies.[1] In doing so, powerful methodologies and strategies can then be applied to further reduce structural complexity. As a case study in isomerization reactions, this review article analyses several select recent examples of carbocationic skeletal reorganizations that have enabled the synthesis of complex natural products. We selected carbocationic rearrangement as a case study because of our group's recent efforts in this area.[2]

In many cases, the carbocationic rearrangements highlighted in this review article were the subject of detailed computational evaluation after their experimental viability had been demonstrated. While this retrospective analysis leads to greater levels of fundamental understanding of these chemical reactions, performing calculations prospectively de-risks proposed synthetic pathways and enables rapid access to desired structures.[2c] The viability of studying these proposed transformations using quantum chemical calculations derives from well-established assessment of various types of reactions by these methods.[3] For this reason, we argue for conducting calculations prospectively to allow for heightened understanding of the energetic landscapes before embarking on experimental campaigns.

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Originally spurred by stunning biosyntheses whereby intricate architectural reorganizations occur, chemists employ these cationic structural reorganizations strategically in the synthesis of complex natural products. This review will focus on novel cationic approaches to molecules with an emphasis on the last decade and will specifically hone in on topics which have previously not been reviewed in-depth. Some powerful carbocationic rearrangements such as the use of polyolefin cyclisations[4] and semipinacol rearrangements[5] will not be the focus here since these reactions are already well-documented in previous reviews. Instead, several strategic modes of rearrangements, rather than distinct reactions, will be covered in our review: cyclisation reactions initiated by cationic intermediates, ring expansion of medium sized ring systems enabled by cationic intermediates, ring expansion of strained ring systems enabled by cationic intermediates, ring contraction enabled by cationic intermediates and metal mediated carbocationic reactions. Through these modes of reactivity, we wish to highlight the insightful approaches numerous researchers have taken to strategically and structurally reorganize intermediates in the synthesis of natural products.

2. Cyclisation Reactions Initiated by Cationic Intermediates

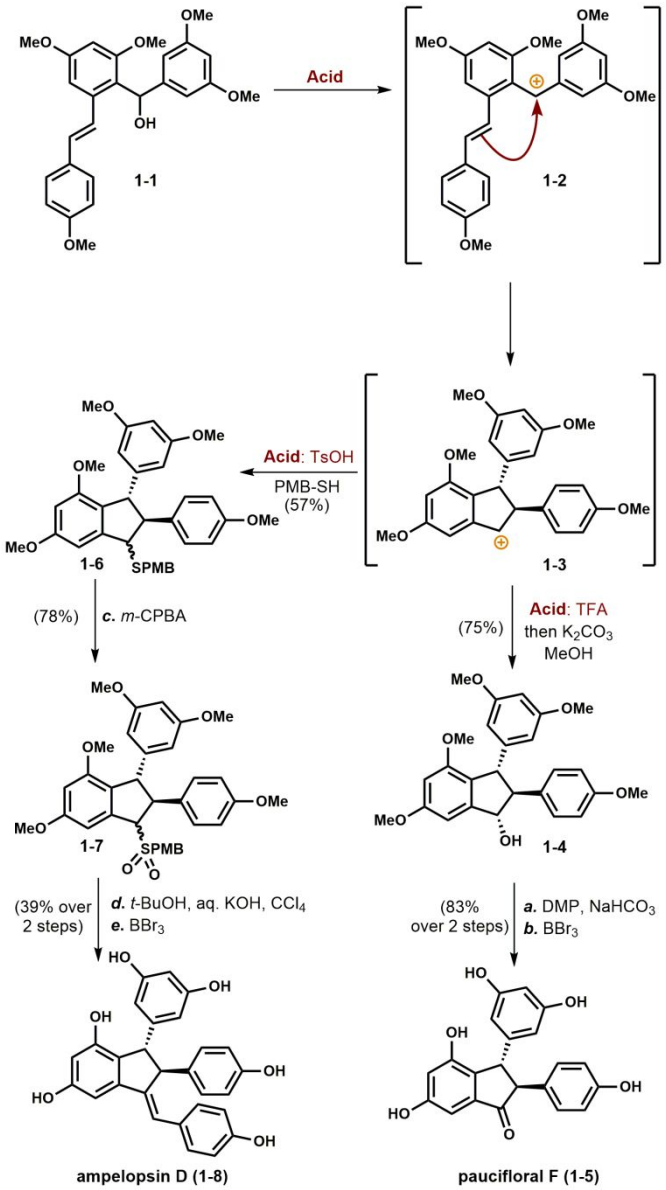
One of the most powerful means to increase molecular complexity using carbocations involves ring formation from acyclic precursors. The most notable example of such a transformation is the polyolefin cyclisation, and several reviews have appeared on application of this strategy.[4] The energetics associated with this polyolefin cyclisation pathway have been computed by Jorgensen,[6] and have been well-recognized to be thermodynamically favourable since early studies into the biosynthesis of steroids.[3b]

2.1. Snyder's Synthesis of (±)-Paucifloral F and (±)-Ampelopsin D (2007, 2009)

The dimeric polyphenol containing natural products based on a resveratrol monomer, such as paucifloral F (**1-5**) and ampelopsin D (**1-8**), have been isolated from grapevines and various *Dipterocarpaceae* species all over the world.[7] This class of natural products has displayed a plethora of biological activities ranging from anti-inflammatory to anti-cancer. [8]

Many synthetic approaches to the resveratrol dimers have derived from the proposed biogenesis of this class of molecules, which involves either a carbocationic or radical dimerization.[9] This biomimetic strategy has resulted in highly engineered monomer fragments or unselective coupling reactions. To circumvent this potential obstacle, Snyder and co-workers approached the synthesis of the resveratrol dimers **1-5** and **1-8** through the strategic use of a divergent cationic intermediate (Scheme 1).[10]

The key carbocationic cyclisation reaction was initiated by treatment of benzylic alcohol **1-1** with acid, either trifluoroacetic acid (TFA) or *p*-toluenesulfonic acid (TsOH), forming a stabilized benzylic carbocation **1-2** which was engaged by the pendant olefin to produce a carbocationic intermediate **1-3**. Notably, the carbocation could diverge via different pathways when the protic acid was modified (Scheme 1). When **1-3** was formed in the presence of TFA, it was trapped with a trifluoroacetate ion to form an intermediate benzylic trifluoroacetate, which was cleaved on basic workup to give alcohol **1-4** in 75% yield. **1-4** was converted to paucifloral F (**1-5**) after an oxidation and deprotection sequence with 83% yield of **1-5** over two steps. Alternatively, when Snyder and co-workers employed TsOH as the acid source in the presence of *para*-methoxybenzyl thiol, **1-6** was obtained in 57% yield. Oxidation of the sulfide to the sulfone (**1-7**) was accomplished with *m*-CPBA in 78% yield. Sulfone **1-7** could be transformed to ampelopsin D (**1-8**) after a Ramberg–Bäcklund rearrangement and subsequent methyl ether deprotection in 39% over the two-step sequence.



Scheme 1. Snyder's Synthesis of (±)-Paucifloral F and (±)-Ampelopsin D

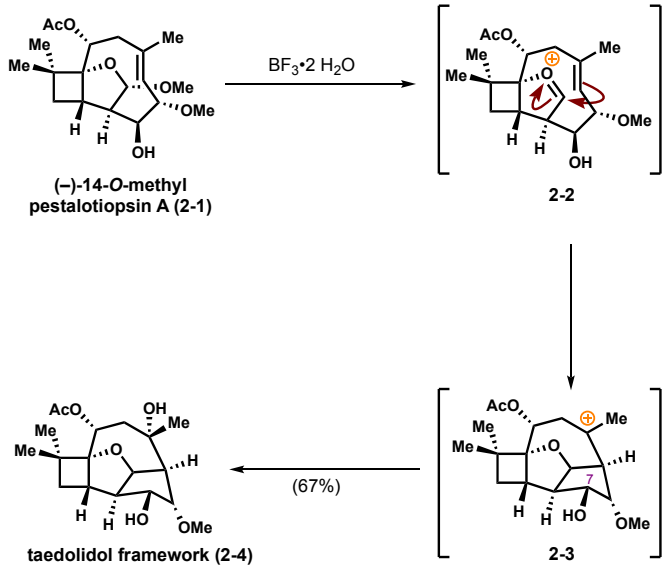
2.2. Procter's Synthesis of (−)-14-*O*-methyl Pestalotiopsin A and Taedolidol Skeleton (2008)

Pestalotiopsin A is a caryophyllene derived sesquiterpene containing an oxatricyclic framework, and is believed to be a biosynthetic precursor to the stereochemically rich caged taedolidol terpenoids.[11] Pestalotiopsin A was first isolated by Clardy and co-workers in 1996 from an endophytic fungus associated with the bark and leaves of the Pacific yew, *Taxus brevifolia*.[11] Intense interest in secondary metabolites formed by the Pacific yew plant has led to the discovery of many biologically active compounds, including the FDA approved therapeutic Taxol.[12] Pestalotiopsin A was shown to have both immunosuppressive activity and cytotoxicity with an IC_{50} of 3 μg/mL.[11]

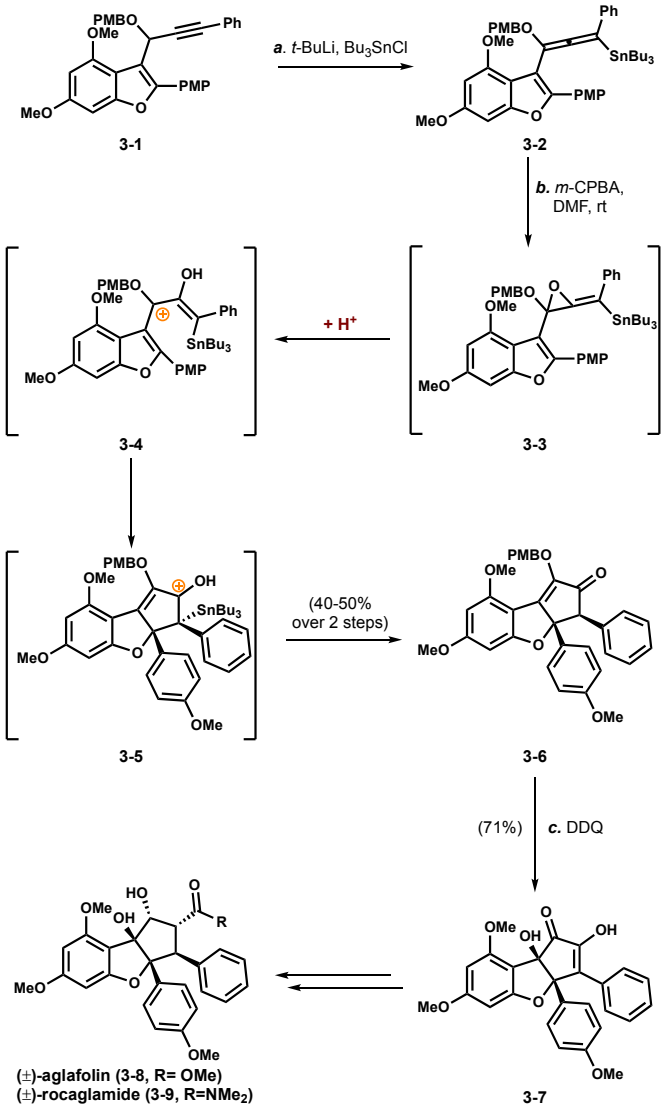
Over the past two-decades, many synthetic studies have been conducted on pestalotiopsin A and related molecules.[13] In 2008, Procter and co-workers completed the synthesis of (–)-14-*O*-methyl pestalotiopsin A (**2-1**).[14] The oxabicyclic framework of the natural product was constructed by a SmI_2-mediated 4-*exo*-trig cyclisation, and the [6.2.1] bridged tricycle was formed through a Nozaki-Hiyama-Kishi cyclisation.

Procter and co-workers interconverted (−)-14-*O*-methyl-pestalotiopsin A (**2-1**) to the structurally more complex taedolidol framework (**2-4**) through an acid-mediated reorganization (Scheme 2). Ionization of the acetal present in **2-1** with $BF_3 \bullet 2H_2O$ resulted in an oxocarbenium ion (**2-2**) that initiated an alkene cyclisation to give carbocation **2-3**. The carbocation was intercepted with a molecule of water to form **2-4**, which possesses many of the key features of the taedolidol framework, in 67% yield. The authors observed a shift in reactivity when protic acids were employed instead-cyclisation of the C7 alcohol onto the carbocation.

2.3. Frontier's Synthesis of (±)-Aglafolin and Related Natural Products (2009)



Scheme 2. Procter's Carbocationic Rearrangement of (−)-14-*O*-methyl Pestalotiopsin A to Taedolidol Skeleton



Scheme 3. Frontier's Synthesis of (±)-Aglafolin and Related Natural Products

In 1982, King and co-workers isolated the tetrahydrocyclopenta[*b*]benzofuran natural product rocaglamide (**3-9**) from *Aglaia elliptiflia*.[15] Rocaglamide was shown to have potent antileukemic activity against P388 leukemia in CDF_1 mice.[16] The dense stereochemical arrangement of five contiguous stereocentres that decorate the cyclopentane ring mark a considerable challenge for the synthesis of **3-8** and **3-9**.[17]

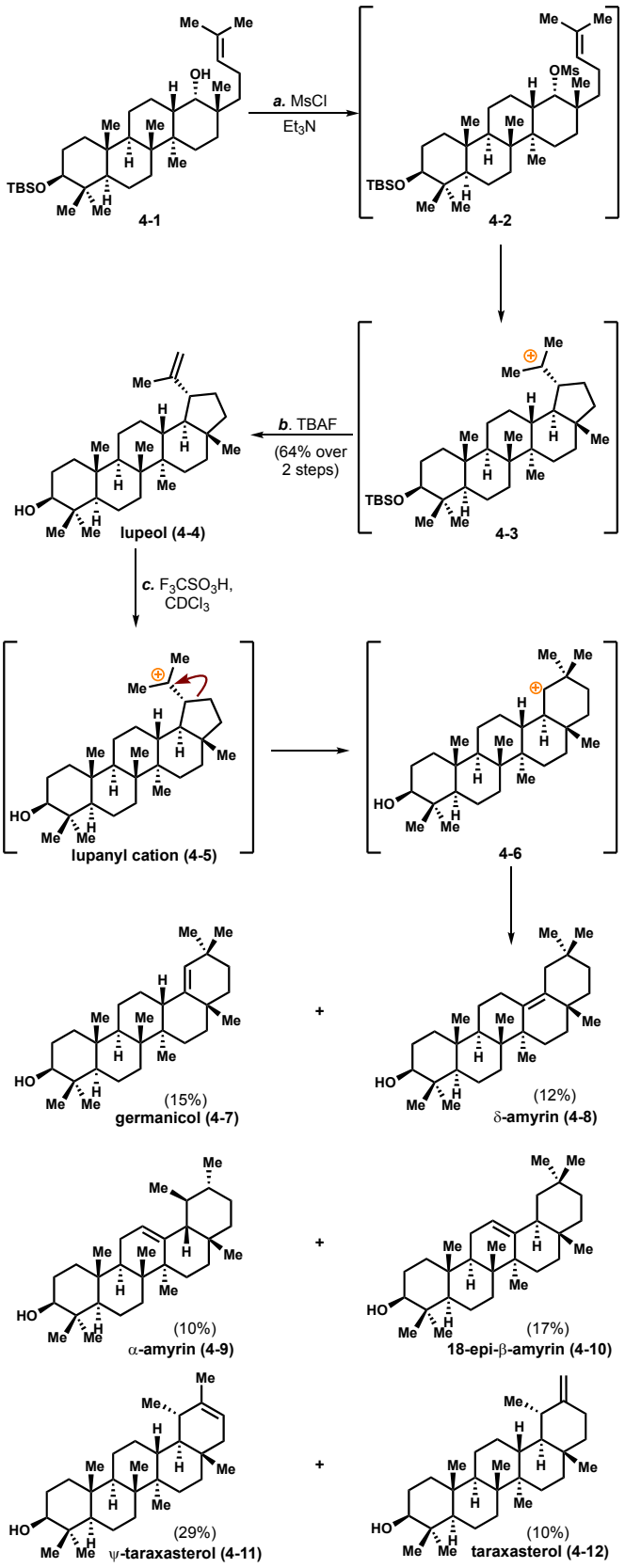
Frontier and co-workers tackled the challenge of forming this polyfunctionalized cyclopentane ring through a peroxy-acid initiated Nazarov cyclisation cascade (Scheme 3).[18] Propargylic deprotonation of **3-1** followed by trapping with Bu_3SnCl furnished allene **3-2**. Selective epoxidation of the most nucleophilic position of allene **3-2** with *m*-CPBA gave rise to **3-3**, which under the reaction conditions formed carbocation **3-4.** An ensuing Nazarov cyclisation furnished the fused tricyclic core (**3-5**). Concomitant loss of the stannyl group resulted in enone **3-6** in 40-50% yield over two steps. Under oxidative conditions intermediate **3-7** was formed in 71% yield, which was further elaborated to (±)-aglafolin (**3-8**) via a four-step sequence. Conversion of the methyl ester to the *N*,*N*-dimethyl amide furnished (±)-rocaglamide (**3-9**).

2.4. Corey's Synthesis of Lupeol (2009)

Carbocationic rearrangements have been demonstrated to be a very powerful strategy in accessing polycyclic structures.[19] Lupeol (**4-4**), a pentacyclic triterpenoid natural product, was first isolated over a half-century ago.[20] In the intervening decades, studies on the biological properties of **4-4** have revealed its many activities, including anti-inflammatory and anti-cancer.[21] Stork and co-workers completed a landmark total synthesis of lupeol in 1971,[22] and in 2009 Corey and Surendra efficiently completed the first enantioselective synthesis of **4-4**.[23]

The enantioselective synthesis of lupeol began with (*S*)-epoxy-geraniol acetate, which was efficiently converted to the tetracyclic core of **4-1** by a dearomative polyolefin cyclisation. Following a cationic isomerization, alkylation and further functional group manipulation, the key intermediate **4-1** was formed (Scheme 4).

Formation of the A-ring occurred spontaneously upon treatment of **4-1** under mesylation conditions, via the intermediacy of mesylate **4-2**. Upon cleavage of the mesylate leaving group, the resulting carbocation was intercepted by the proximal alkene to furnish the presumed lupanyl-type cationic intermediate **4-3**.[24] Silyl ether deprotection with TBAF revealed lupeol (**4-4**). With a route to **4-4** completed, the authors wanted to study the facile skeletal rearrangement of the lupanyl cation (**4-5**) to the germanicyl and oleanyl (β-amyrin) cations, a process computed to be thermodynamically favourable by around 10 kcal/mol due to relief of conformational strain.[25] Under dilute acidic conditions, 20 mM CF_3SO_3H in $CDCl_3$, the lupanyl cation (**4-5**) was formed from **4-4**, which triggered an alkyl migration to furnish secondary carbocation **4-6**. Loss of a proton gave rise to germanicol (**4-7**). Numerous additional natural products, namely δ-amyrin (**4-8**), α-amyrin (**4-9**), 18-epi-β-amyrin (**4-10**), ψ-taraxasterol (**4-11**) and taraxasterol (**4-12**),



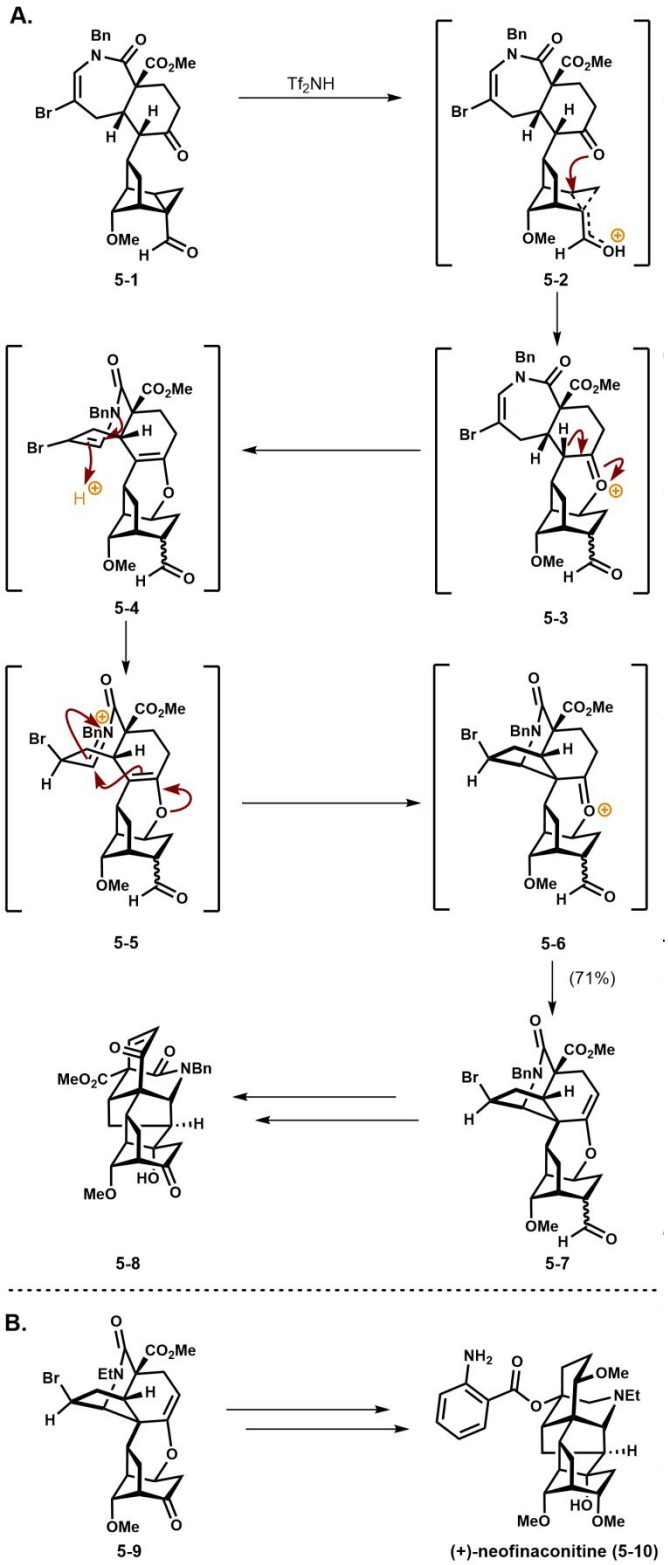
Scheme 4. Corey's Synthesis of Lupeol and Related Pentacyclic Triterpenes

resulting from the intermediate carbocation following alkyl migration or directly from germanicol were observed in this study.

2.5. Gin's Synthesis of (+)-Neofinaconitine (2013)

Neofinaconitine (**5-10**),[26] a C19-norditerpenoid alkaloid, and related family members are isolated from the *Aconitum* and

Delphinium plants and have analgesic properties.[27] This potent biological activity has made the aconitum alkaloids attractive targets for total synthesis, although few total syntheses have been completed prior to the work by Gin and co-workers.[28]



Scheme 5. (A) Carbocationic Rearrangement Cascade. (B) Gin's revised strategy in the synthesis of (+)-Neofinaconitine

A cationic structural reorganization was employed by Gin and co-workers to aid in the assembly of the core structure of neofinaconitine (**5-8**) (Scheme 5A).[29] Treatment of intermediate **5-1** with triflimide was postulated to generate a delocalized carbocation intermediate (**5-2**) that was engaged by the proximal ketone resulting in oxocarbenium **5-3.** A subsequent isomerization and deprotonation formed the dihydropyran (**5-4**). An ensuing protonation of the enamine resulted in an activated iminium intermediate (**5-5**) in which the dihydropyran substructure could engage **5-5** in a second cyclisation event to furnish cationic intermediate **5-6**. A resulting proton-transfer gave rise to enol ether **5-7** in 71% yield, which could be advanced to the core structure of neofinaconitine (**5-8**). Although this cationic cascade formed several crucial bonds in the molecule, ultimately the authors comment that the low material throughput necessitated pursuing an alternative synthetic route (Scheme 5B). The completion of the total synthesis involved the analogous intermediate **5-9**.

2.6. Porco's Synthesis of (−)-Clusianone (2014)

The polyprenylated polycyclic acylphloroglucinols (PPAPs), typified by clusianone (**6-4**), are a diverse class of natural products which are isolated from *Hypericum perforatum*.[30] The PPAPs exhibit a wide range of biological activities, including neuroprotective and antiviral activities.[31] Aside from the intriguing biological properties that these secondary metabolites exhibit, the synthetically daunting bicyclo[3.3.1]nonane scaffold has led to many creative synthetic approaches to the PPAP framework,[31] including the landmark total synthesis of garsubellin A by Danishefsky and Siegel[32] and the recent synthesis of hyperforin by Maimone and co-workers.[33]

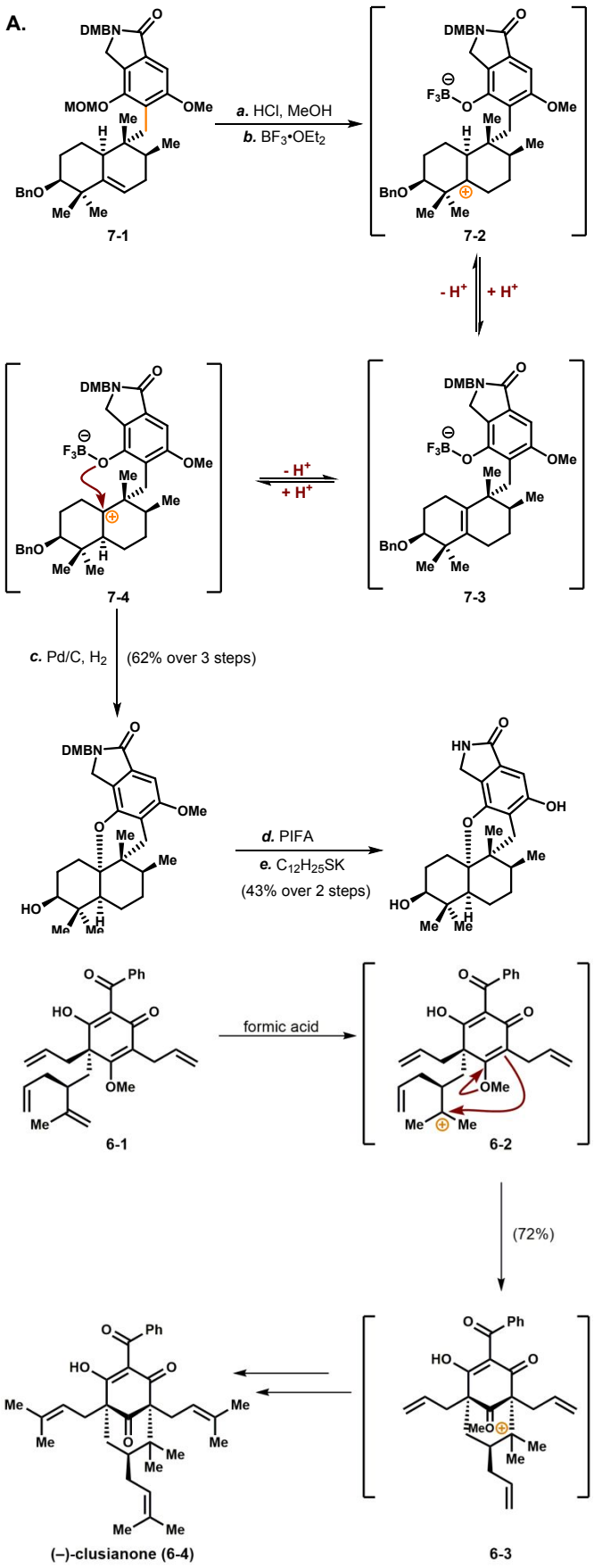
[13] K. Takao, N. Hayakawa, K. Yamada, T. Yamaguchi, O. Morita, S. Kawasaki and K. Tadano, *Angew. Chem., Int. Ed.*, 2008, **47**, 3426–3429.
[14] T. M. Baker, D. J. Edmonds, D. Hamilton, C. J. O'Brien and D.

The Porco group has tackled the total syntheses of many structurally diverse PPAPs,[34] including (−)-clusianone **6-4** in 2014.[35] Many of these works have been completed by employing cationic cyclisations and reorganizations as the key enabling transformation in the synthesis. Their total synthesis of **6-4** was realized through a remarkably selective cyclisation of methyl enol ether onto a tertiary carbocation (**6-2**), formed from the treatment of **6-1** with formic acid (Scheme 6). The cationic cyclisation resulted in the formation of the highly substituted bicyclo[3.3.1]none framework (**6-3**) in 72% yield, which was converted to (−)-clusianone (**6-4**) through an olefin metathesis reaction with isobutene. Porco and co-workers note that >70 acids were examined to mediate this diastereo- and regioselective transformation, and only formic acid led to the desired *C*-cyclisation adduct, which suggested that formic acid played a unique role in the desired selectivity in this transformation. The authors postulated that the formate anion may play a role in the transition state of this transformation, such as sterically disfavouring one face of the molecule.

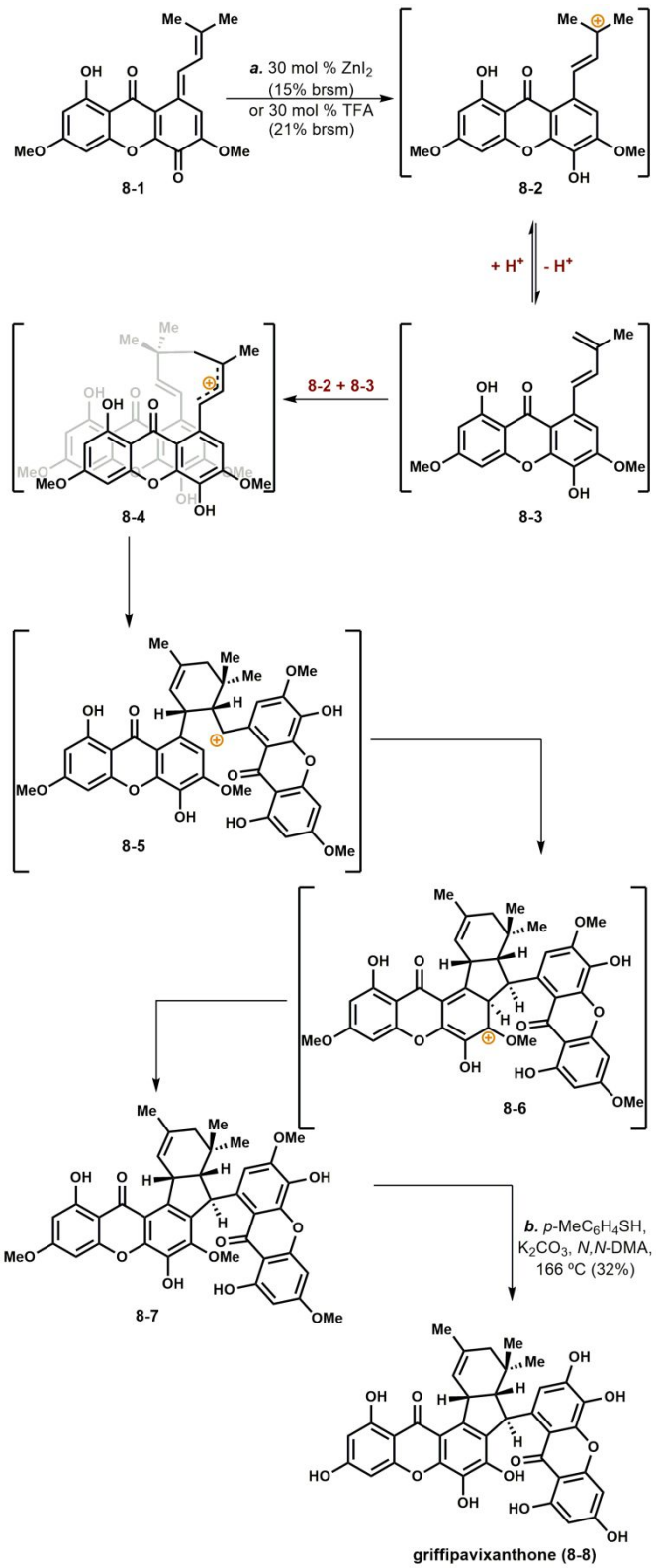
2.7. Magauer's Synthesis of (+)-Stachyflin (2016)

In the 1980s Clardy and co-workers first reported the isolation of several tetracyclic meroterpenoids, such as aureol (**7-7**), from a marine sponge.[36] Since this seminal report, many additional congeners of this meroterpenoid family have been identified and have shown promising anti-cancer, antiviral, and antibiotic activities.[37] Although there have been numerous elegantly completed total syntheses of various members of this natural product family,[38] including the previous work by Magauer and co-workers on this synthesis of cyclosmenospongine (**7-8**),[39] no unified route existed to these meroterpenoids prior to the recent work by Magauer and co-workers.[40]

They assembled the core structure of (+)-stachyflin (**7-6**) through the convergent fragment coupling of an isoindolinone and a decalin component to form the highlighted bond in **7-1** by a sp^2–sp^3 Negishi cross-coupling (Scheme 7A). Treatment of **7-1** with acidic methanol led to deprotection of the MOM-ether on the isoindolinone subunit. The key cationic reaction was initiated by treatment of the resulting phenol with BF_3•OEt_2, which led to the presumed tertiary carbocation **7-2**. Subsequent loss of a proton could form the tetrasubstituted alkene intermediate **7-3**. Protonation of the resulting alkene (**7-3**) could form another tertiary carbocation (**7-4**), in which the phenol could cyclise to form the desired *cis*-decalin linkage in **7-5** with 62% yield over three steps. An alternative mechanism for the cascade transformation including a direct 1,2-hydride shift following alkene protonation is also possible.[39e] Stachyflin (**7-6**) was furnished following removal of the protecting groups in 43% yield over two steps. An analogous strategy was adapted to allow access to additional congeners of this meroterpenoid family of natural products (Scheme 7B), such as aureol (**7-7**), cyclosmenospongine (**7-8**), mamanuthaquinone, and unnatural derivatives. This modular total synthesis enabled efficient access to six natural products and fifteen synthetic analogues.



Scheme 6. Porco's Synthesis of (−)-Clusianone



Scheme 8. Porco's Synthesis of (±)-Griffipavixanthone

2.8. Porco's Synthesis of (±)-Griffipavixanthone (2017)

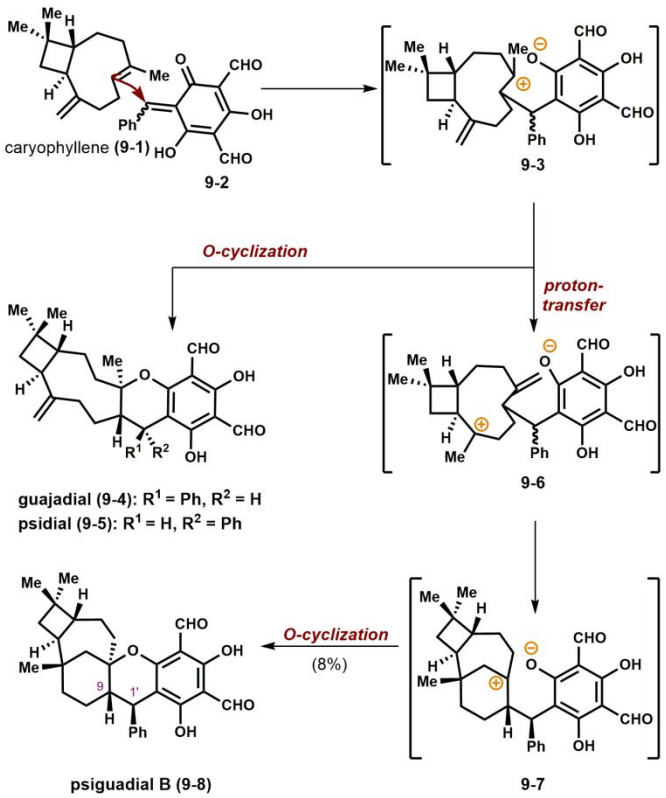
Griffipavixanthone (**8-8**), a dimeric xanthone natural product, possesses a synthetically demanding carbocyclic core, in which the monomeric units are presumed to be derived biosynthetically by an apparent Diels-Alder cycloaddition.[41] Aside from the unique structural features of **8-8**, this natural product exhibits a range of exciting biological activities, including anti-cancer[42] and antioxidant properties.[43] To assemble **8-8**, the Porco group envisioned accessing this dimeric natural product via a cation-initiated stepwise [4+2] cycloaddition and structural reorganization of two monomers.[44]

The paraquinone methide monomer **8-1** was treated with either a Lewis acid (ZnI_2) or a Brønsted acid (TFA) which formed the proposed tertiary carbocation **8-2** following alkene protonation and aromatization (Scheme 8). Combination of cation **8-2** with diene **8-3**, which itself was derived from **8-1**, resulted in a delocalized benzylic carbocation **8-4** that underwent stereoisomerization in order to access the necessary conformation for intramolecular carbon–carbon bond formation, resulting in **8-5**. Arylation of the resulting benzylic carbocation furnished arenium **8-6**, which underwent another aromatization event to give rise to **8-7** in 15% and 21% yield employing ZnI_2 and TFA respectively. DFT computations suggested the benzylic carbocation intermediate (**8-5**) with the two xanthone moieties in a *cis*-relationship was 7.6 kcal/mol more stable than the one with *trans*-configuration.[44] In addition, the calculated transition state barrier for the subsequent irreversible cyclisation was calculated to be 4.5 kcal/mol lower for the *cis*-diastereomer, presumably due to the lower strain energy of the *cis*-fused polycyclic ring system. Demethylation led to griffipavixanthone (**8-8**) in 32% yield. This efficient total synthesis of griffipavixanthone (**8-8**) by Porco and co-workers elegantly fashioned together two simple monomeric units through a biomimetic carbocationic cyclisation cascade, which forms three C–C bonds in a single step.

2.9. Cramer's Synthesis of Psiguadial B (2017)

Psiguadial B (**9-8**), a structurally complex caryophyllene derived meroterpenoid natural product, was first isolated by Ye and co-workers in 2010 from *Psidium guajava*.[45] Preliminary biological evaluation of the natural product revealed potent and selective antitumor activity against HepG2 (IC_{50} = 45.62 nM).[45] The sterically demanding central bicyclo[4.3.1]decane ring of Psiguadial B (**9-8**) is fused to a *trans*-cyclobutane and a complex chromane heterocycle. Reisman and co-workers completed the first synthesis of **9-8** through an abiotic approach, which involved an innovative tandem Wolff rearrangement, asymmetric ketene addition, and subsequent C–H vinylation.[46]

Cramer and co-workers utilized a biomimetic strategy to complete Psiguadial B in a single step (Scheme 9).[47] This transformation employed the abundant terpene precursor caryophyllene (**9-1**), benzaldehyde, and diformylphloroglucinol (**9-2**). One postulated pathway involves caryophyllene engaging **9-2** in a Michael addition to form intermediate **9-3**. At this juncture, **9-3** may diverge to form two different natural product scaffolds, **9-4**/**9-5** and **9-8**. Guajadial (**9-4**), and the benzylic epimer psidial (**9-5**), can form after cyclisation of the phenolate anion onto the tertiary carbocation. Alternatively, proton-transfer and bond rotation may result in intermediate **9-6**, which may be engaged by the exocyclic



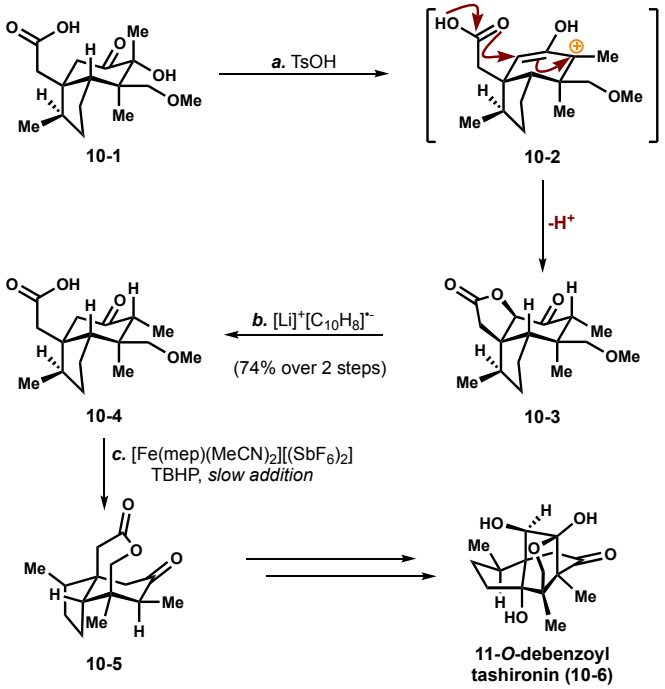
Scheme 9. Cramer's Synthesis of Psiguadial B

olefin to generate a bridgehead carbocation **9-7**. Following C–O bond formation psiguadial B (**9-8**) is formed in 8% yield.

In order to gain further insight into the mechanism of this cascade transformation, the authors attempted to convert **9-4** and **9-5** to **9-8** under the same reaction conditions, although psiguadial B was not observed. Furthermore, investigations on the feasibility of a hetero-Diels Alder reaction resulted in 1',9-*epi*-**9-8.** While both the experimental and computational efforts by the authors to verify a concerted Alder-ene transformation were unsuccessful, DFT calculations showed Michael addition between **9-1** and **9-2** was exergonic.[47] Based on these combined experimental and computational results, the authors postulated the biosynthesis of psiguadial B (**9-8**) involved an initial Michael addition between caryophyllene (**9-1**) and *ortho*-quinone methide (**9-2**), followed by a series of proton transfers and cationic cyclisations. The strategic implementation of a carbocationic cascade inspired by the biosynthesis of this class of natural products resulted in an efficient one-step synthesis of **9-8**.

2.10. Maimone's Synthesis of 11-*O*-debenzoyl Tashironin (2019)

The lactone containing terpenes isolated from the *Illicium* plant are a diverse class of sesquiterpenes with over a hundred family members.[48] The *illicium* sesquiterpenoids display potent and selective neurotrophic and neurotoxic biological activities,[49] and thus have attracted numerous synthetic efforts toward the various family members.[50] One member of the *illicium* sesquiterpenoids,



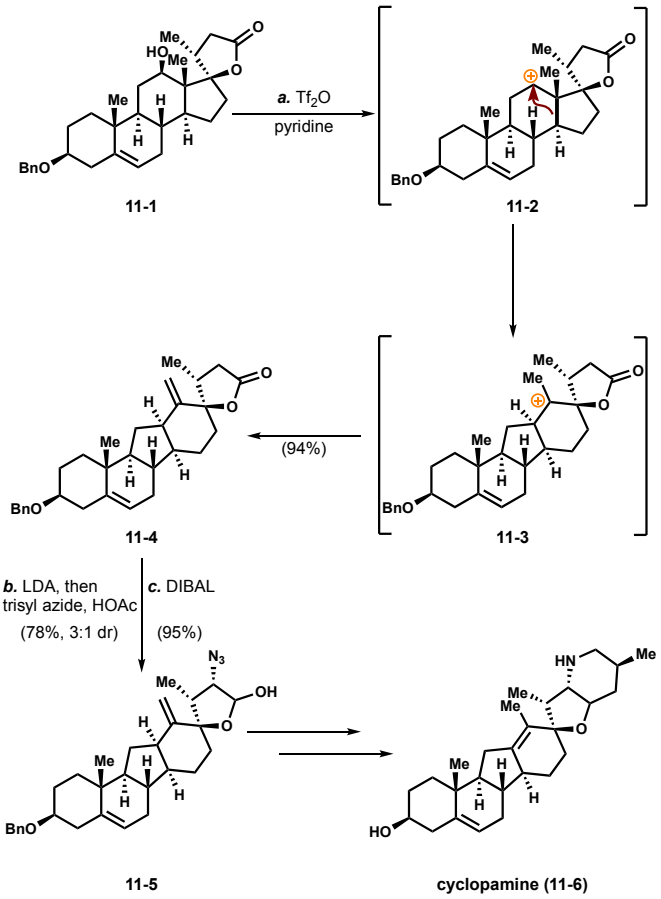
Scheme 10. Maimone's Synthesis of 11-*O*-debenzoyl Tashironin

jiadifenolide, has shown particular exciting biological activity for promoting neurite outgrowth, and thus has been the focus of many elegant synthetic efforts over the past decade.[51]

Recently, Maimone and co-workers employed an innovative approach toward this family of natural products, which relied on the oxidative functionalization of a widely available terpene feedstock, (+)-cedrol.[52] In their total synthesis of 11-*O*-debenzoyl tashironin (**10-6**),[53] the authors were able to oxidatively manipulate (+)-cedrol to form **10-1**, which upon treatment with TsOH formed the presumed oxy-allyl carbocation **10-2** (Scheme 10). The pendent carboxylic acid cyclised on to the formed allylic carbocation to furnish intermediate **10-3** after tautomerization and proton transfer**.** Reductive cleavage of the lactone by lithium naphthalenide afforded acid **10-4** in 74% yield over two steps, which was transformed to lactone **10-5** after C–H oxidation and lactone formation. **10-5** could then be further manipulated to intercept a key intermediate in Shenvi's synthesis of 11-*O*-debenzoyl tashironin (**10-6**).[54]

3. Ring Expansion of Medium Sized Ring Systems Enabled by Cationic Intermediates

The rearrangement of fused ring systems in order to obtain other less accessible fused ring systems does not necessarily increase molecular complexity from a structural standpoint.[55] However, structural rearrangements increase molecular complexity from a synthetic standpoint: more readily accessible synthetic intermediates or chiral pool starting materials[56] can be transformed by powerful synthetic methods. The conversion of one polycycle to



Scheme 11. Giannis' Synthesis of Cyclopamine

another is also a broadly recognized strategy for expanding medicinal chemistry libraries.[57]

3.1. Giannis' Synthesis of Cyclopamine (2009)

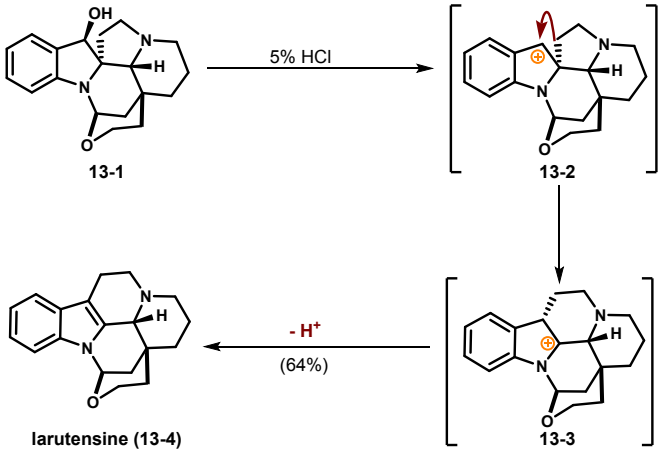
Cyclopamine (**11-6**), a steroidal alkaloid isolated from the corn lily (*Veratrum californicum*), was first identified in 1957 following an investigation of the alarming observation of lambs being born with one eye located in the centre of their foreheads.[58] Since this point, it was identified as the first known inhibitor of the hedgehog signalling pathway, which is important to the development of malignancies in many cancers.[59] The intriguing biological properties that cyclopamine exhibits may be due to a range of unique structural features, such as the highly rearranged steroidal skeleton and the highly substituted furanyl spirocycle.

Giannis and co-workers retrosynthetically traced **11-6** back to 12β-hydroxy steroid as a structural goal, which could be converted to **11-1** and then structurally reorganized by a cationic ring expansion (Scheme 11).[60] The cationic rearrangement was initiated by treatment of alcohol **11-1** with Tf_2O and pyridine furnishing carbocation **11-2**. An ensuing 1,2-alkyl migration resulted in **11-3**, which is more likely to proceed via a concerted process.[2b] The cationic rearrangement gave rise to an isomeric mixture of olefins with a ratio of 7:3 favouring the exocyclic olefin in 94% combined yield. The major product was treated with LDA and then trisyl azide and AcOH to furnish the α-azido lactone in 78% yield and 3:1 dr. An ensuing reduction with DIBAL resulted in lactol **11-5**, which was further transformed to cyclopamine **(11-6)** in 9 steps.

3.2. Baran's Synthesis of (+)-Ingenol (2013)

In 1968, the diterpenoid ingenol (**12-4**) was first isolated from the plant *Euphorbia ingens* and has been shown to possess anti-cancer and anti-HIV properties.[61] Structurally, ingenol contains a unique and synthetically demanding *in/out*-bicyclo[4.4.1]undecane. Previous completed total syntheses of this natural product demonstrated several possible solutions to synthesize this unique skeleton.[62]

In 2013, Baran and co-workers completed the synthesis of (+)-ingenol (**12-4**).[63] Their strategy involved structural interconversion of a tigliane-type scaffold (**12-1**) to the ingenol framework through a biomimetic vinylogous pinacol rearrangement (Scheme 12). Treatment of **12-1** with $BF_3{\bullet}OEt_2$ ionizes the tertiary alcohol, resulting in an allylic carbocation (**12-2**) and thus initiating the vinylogous pinacol rearrangement to form **12-3**. Initial attempts to perform this rearrangement resulted in numerous by-products, including alcohol elimination, and it was found that careful control of the reaction conditions resulted in 80% yield of **12-3**. Furthermore, these experimental results were analysed computationally afterwards to gain additional mechanistic insight. It was hypothesized that the presence of the –TMS protecting group on the alcohol lowers both the ΔG and $\Delta G^{\ddagger}$, making the reaction both thermodynamically and kinetically favourable.[64]



Scheme 13. Zhu's synthesis of (±)-Larutensine

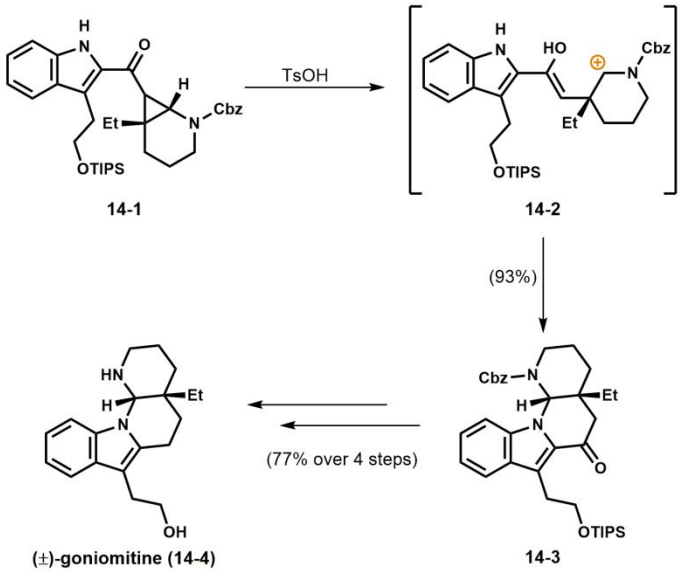
3.3. Zhu's Synthesis of (±)-Larutensine (2019)

Isolated in 1991 from the bark and stem of *Kopsia larutensis*, larutensine (**13-4**) belongs to the eburnane family of monoterpene indole alkaloid natural products.[65] Characterized by the fused polycyclic core, many members of the family have been shown to possess vasodilation and anti-bacterial properties.[66] Due to these intriguing architectural features and noteworthy biological activities, the eburnane alkaloids have been pursued as targets by numerous synthetic chemists and therefore many elegant syntheses have been developed.[67]

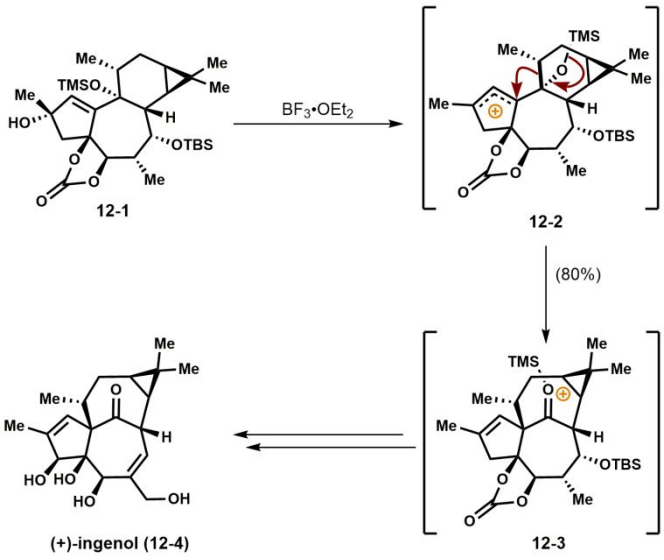
Zhu and co-workers departed from traditional synthetic logic toward *Kopsia* alkaloids and employed a common oxindole intermediate,[68] that could provide access to numerous alkaloid natural products upon skeletal rearrangement. In their synthesis of (±)-larutensine (**13-4**), a structural reorganization of **13-1** was triggered upon treatment with dilute HCl (Scheme 13). Alcohol **13-1** was ionized to form an intermediate benzylic carbocation **13-2**, which stabilized by resonance with indoline nitrogen, followed by 1,2-alkyl shift to furnish tertiary carbocation **13-3**. Aromatization of the indole substructure resulted in larutensine in 64% yield. The authors employed a similar scaffold rearrangement to form several other alkaloid natural products.[68]

4. Ring Expansion of Strained Ring Systems Enabled by Cationic Intermediates

A useful driving force for cationic rearrangements is the release of ring strain. The most common application of this strategy is the opening or expansion of 3- and 4-membered rings, which possess around 28 and 26 kcal/mol of ring strain, respectively.[69] The strategic coupling of cycloaddition reactions to cationic ring opening can lead



Scheme 14. Waser's Synthesis of (±)-Goniomitine



Scheme 12. Baran's Synthesis of (+)-Ingenol

to diverse, and more synthetically challenging ring systems. This is a particularly enabling strategy as cycloaddition reactions provide a reliable means to access these strained ring systems.

4.1. Waser's Synthesis of (±)-Goniomitine (2010)

In 1987, the indole alkaloid goniomitine (**14-4**) was isolated from the bark of *Gonioma Malagasy* and its structure was assigned by correlation to the related *Aspidosperm*a alkaloids.[70] Biosynthetically it is also proposed to arise from the *Aspidosperma* natural products via a cationic structural fragmentation and reorganization.[70] **14-4** has served as a testing ground for many innovative synthetic methodologies.[71]

Waser and co-workers approached the total synthesis of (±)-goniomitine (**14-4**) through application of their stepwise homo-Nazarov cyclisation of an aminocyclopropane (Scheme 14).[72] The aminocyclopropane precursor **14-1** was assembled through an enamine cyclopropanation and addition of a C2 lithiated indole into a Weinreb amide. Treatment of the ketone linkage in **14-1** with TsOH triggered the opening of the cyclopropane ring, which resulted in the presumed intermediate **14-2**. The ensuing cationic structure (**14-2**), which is stabilized by the neighbouring carbamate nitrogen, was then engaged by the indole nitrogen to form the tetracyclic core in **14-3** in 93% yield. (±)-Goniomitine (**14-4**) could be accessed following an efficient four-step deprotection/reduction sequence. Additionally, the authors applied an analogous synthetic strategy toward the formal synthesis of aspidospermidine.

4.2. Fukuyama's Synthesis of (+)-Lyconadin A (2011)

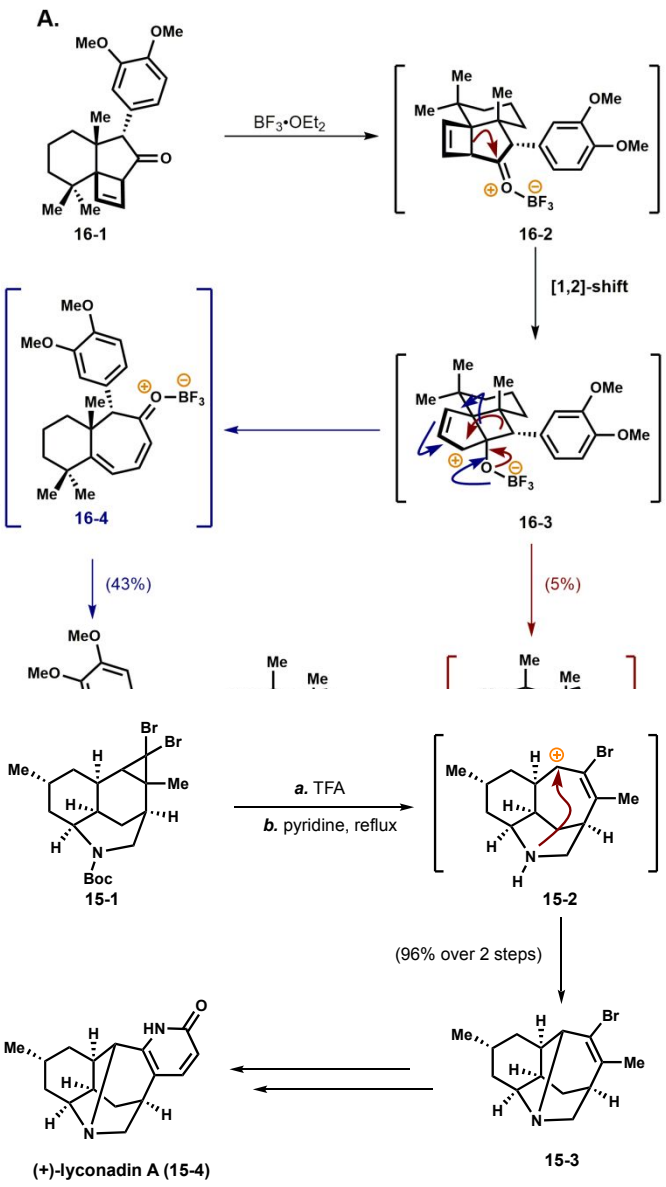
The alkaloids isolated from the *Lycopodium* plant represent a diverse group of structurally complex natural products possessing a range of biological activities.[73] Lyconadin A, a stereochemically rich and sterically congested pentacyclic congener of the *Lycopodium* natural products, has been the target of many synthetic efforts.[74] In 2011, Fukuyama and co-workers completed their total synthesis of (+)-lyconadin A (**15-4**) by generating the challenging bicyclo[5.4.0]undecane from a structural rearrangement of a strained dibromocyclopropane.[75]

The synthesis of **15-4** by Fukuyama and co-workers features a cationic reorganization of dibromocyclopropane **15-1**, in which the *cis*-decalin framework was generated by a structurally simplifying Diels-Alder transformation. Upon treatment of **15-1** with TFA the *N*-Boc protecting group was removed. A subsequent Woodward-Hoffmann-DePuy reaction was ensued upon subjection of **15-1** to refluxing pyridine conditions to generate an intermediate allylic carbocation **15-2** (Scheme 15), which may occur through an electrocyclic ring opening with concomitant loss of bromide.[76] The pendent amine could cyclise onto the intermediate carbocation to furnish the requisite bicyclo[5.4.0]undecane framework (**15-3**) present in (+)-lyconadin A (**15-4**) in 96% yield over two steps. The formed vinyl bromide could be quickly converted to the 2-pyridone substructure in **15-4** through an innovative sequence involving a vinyl-nitroso intermediate.

4.3. Stoltz's Synthesis of (+)-Liphagal (2011)

Liphagal (**16-9**), a meroterpenoid natural product with a unique tetracyclic architecture, was isolated from the sea sponge *Aka coralliphaga* in 2006.[77] Aside from the intriguing structural features of **16-9**, it was shown to be a potent and selective inhibitor of phosphatidylinositol 3-kinase (PI3K), a promising target for cancer treatment.[78] Stoltz and co-workers completed the first enantioselective synthesis of (+)-liphagal (**16-9**) through a late-stage installation of the furan substructure and a strategic cyclobutene ring expansion.[79]

While Stoltz and co-workers were exploring this key ring expansion of cyclobutene **16-1** in their synthesis of (+)-liphagal, an intriguing structural rearrangement was encountered (Scheme 16A). Upon treatment of **16-1** with BF_3•OEt_2 coordination of the Lewis-basic ketone (**16-2**) triggered a 1,2-alkyl shift to form an intermediate allylic carbocation (**16-3**). A Grob-type fragmentation of **16-3** furnished the seven-member ring intermediate **16-4**, and after



Scheme 15. Fukuyama's Synthesis of (+)-Lyconadin A

workup the dienone **16-5** in 43% yield. As a competing pathway, another 1,2-alkyl shift was also observed to form the bicyclo[2.2.1]heptanone scaffold (**16-6**) and **16-7** in 5% yield after workup. In order to avoid this undesired carbocationic reorganization, they modified the starting material to bromide **16-8**, which could be accessed directly from **16-1** (Scheme 16B). A high yielding ring expansion from the 5-4 ring system to the seven-membered ring was accomplished using microwave heating at 250 °C, which could then be parlayed to (+)-liphagal (**16-9**) in an effective sequence.

4.4. Baran's Synthesis of Steviol and Isosteviol (2013)

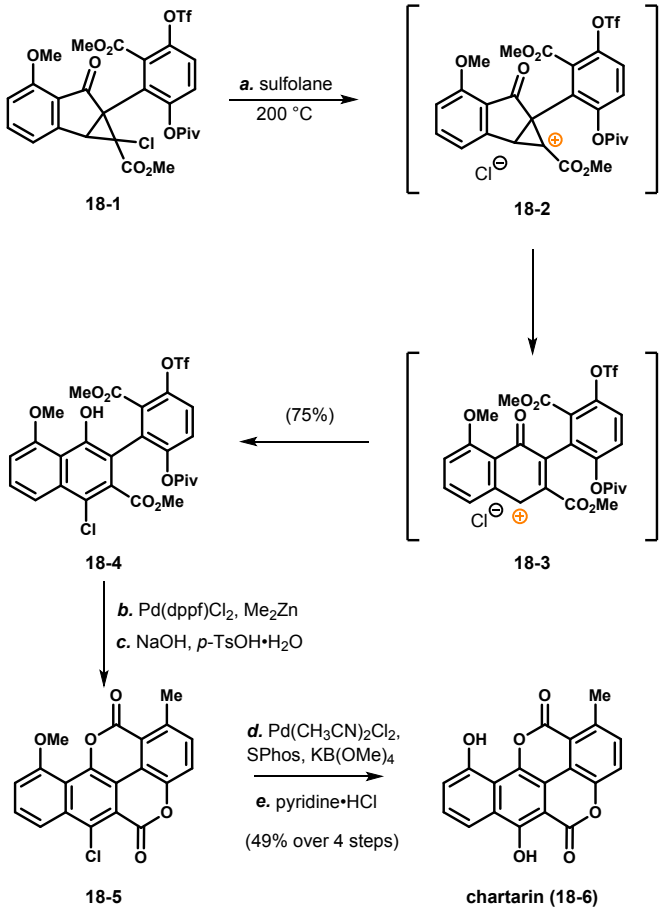
The *ent*-kaurane diterpenoids are a class of natural products that are highly varied both in terms of skeletal arrangement and oxidation state.[80] Due to this variance in oxidation state many biosynthetic skeletal rearrangements have been proposed in the interconversion of various *ent*-kaurene natural products, including the rearrangement of steviol (**17-5**) to isosteviol (**17-4**). Many groups have independently synthesized **17-4** and **17-5**,[81] although the direct conversion by skeletal reorganization was unknown prior to the work by Baran and co-workers.[82]

In order to access the requisite precursor for the interconversion of the bicyclo[3.2.1]nonanes, Baran and co-workers leveraged several overbred intermediates[83] for the generation of the necessary functional handles present in **17-4** (Scheme 17A). Treatment of diol **17-1** with HBr resulted in a secondary carbocation (**17-2**). Subsequent alkyl shift led to the rearranged bicyclo[3.2.1]nonane **17-3**. Oxidation of the primary alcohol to the carboxylic acid with CrO_3 furnished (±)-isosteviol (**17-4**) in 70% yield over 2 steps. Utilizing steviol (**17-5**) as a reactant under analogous acidic conditions demonstrated the first direct conversion of (±)-steviol (**17-5**) to (±)-isosteviol (**17-4**), which was obtained in 90% yield (Scheme 17B).

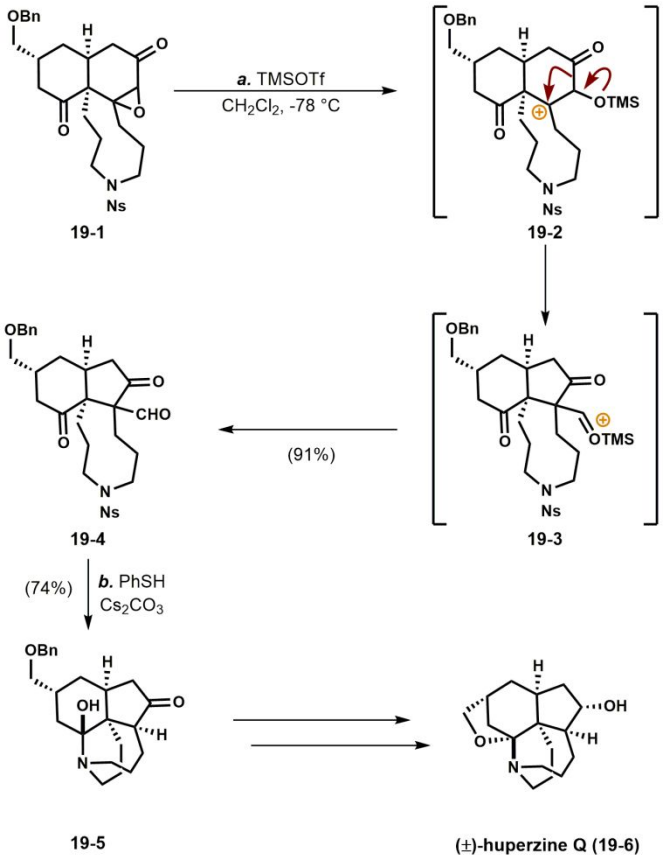
4.5. Magauer's Synthesis of Chartarin (2016)

Chartreusin, a benzonaphthopyranone natural product isolated in 1953 from *Streptomyces chartreusis*, possesses anti-cancer and antibiotic activities.[84] Chartarin (**18-6**), the aglycon of chartreusin, is the main component responsible for DNA intercalation in this class of secondary metabolites. Several synthetic efforts have been directed towards the total synthesis of chartreusin and its aglycon.[85]

Magauer and co-workers were able to rapidly assemble the core structure of chartarin (**18-6**) via an efficient sequence, which allowed gram-scale access to **18-4** (Scheme 18).[86] Utilizing their laboratory's methodology for thermally induced 2π-electrocyclisation, the strained 6-5-3 ring system in **18-1** was converted to a 6-6 ring system (**18-3**)[87] through the intermediacy of carbocation **18-2**.[88] It is proposed that the chloride ion can intercept **18-3**, resulting in the formation of the requisite poly-substituted naphthalene framework (**18-4**) after tautomerization in 75% yield. The dilactone intermediate



Scheme 18. Magauer's Synthesis of Chartarin



Scheme 19. Fukuyama's Synthesis of (±)-Huperzine Q

(**18-5**) was accessed in two steps from **18-4**, which was further manipulated to chartarin (**18-6**) in 49% yield over the four-step sequence.

5. Ring Contraction Enabled by Cationic Intermediates

Readily obtained 6-membered rings can be coaxed into their more strained 5-membered ring systems through the formation of more stabilized carbocations. The ability of a group to stabilize a reactive carbocation can be evaluated computationally to determine if such stabilization overcomes the inherent loss of stability due to formation of a more strained ring.

5.1. Fukuyama's Synthesis of (±)-Huperzine Q (2017)

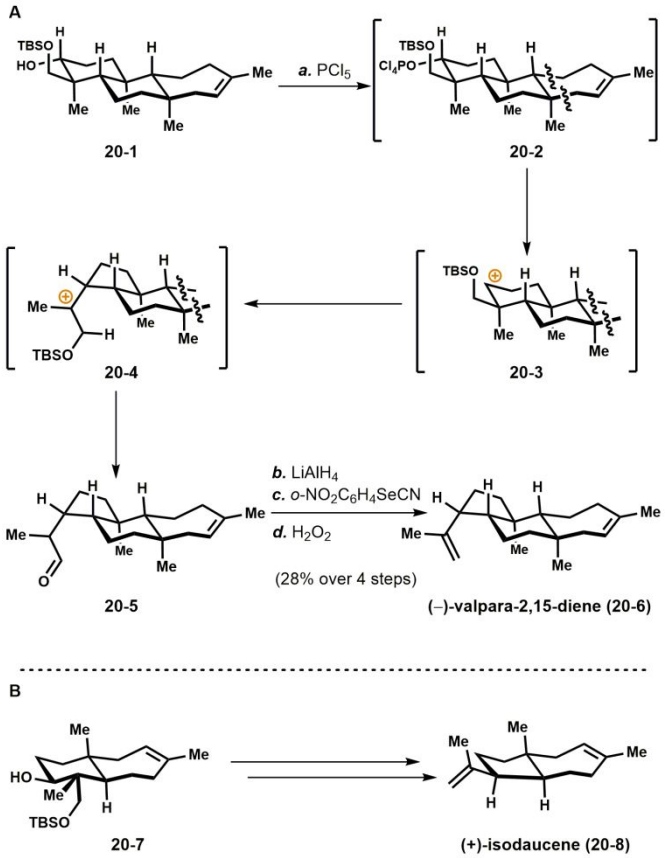
The isolation of huperzine Q (**19-6**), a fawcettimine-type *Lycopodium* alkaloid, by Zhu and co-workers from *Huperzia serrata* in 2002 was guided by the plant's storied history in traditional Chinese herbal medicine.[89] Huperzine Q is characterized by a *cis*-hydrindane core and the *N*,*O*-acetal substructure. This demanding synthetic target has attracted the interest of many synthetic chemists, which has led to the completion of several total syntheses.[90]

Fukuyama and co-workers leveraged a carbocation-mediated ring contraction to construct the *cis*-hydrindane core of (±)-huperzine Q (**19-6**) via interconversion from the more readily accessible *cis*-decalin ring system.[91] The requisite epoxide precursor could be rapidly accessed through a B-alkyl Suzuki, Diels-Alder, and oxidation sequence. Upon treatment of epoxide **19-1** with trimethylsilyl trifluoromethanesulfonate, the proposed epoxide opening resulted in tertiary carbocation **19-2**, which underwent acyl shift and ring contraction to form the intermediate oxocarbenium **19-3** (Scheme 19). Desilylation resulted in the β-keto aldehyde (**19-4**) in 91% yield, which could be transformed into the *cis*-hydrindane core in **19-5** via hemiaminal formation in 74% yield. **19-5** could be further manipulated to access (±)-huperzine Q (**19-6**) in two steps.

5.2. Barrero's Synthesis of (−)-Valpara-2,15-diene and (+)-Isodaucene (2019)

The valparanes are a class of diterpene natural products isolated from the *Cistaceae* plants and generally contain a conserved 5,6,7-tricyclic scaffold. Some of the related congeners have exhibited antiviral and antitumor activities.[92] Barrero and co-workers' synthesis in 2019 was the first approach to this particular family member.[93]

The structurally simplified 6,6,7-ring system (**20-1**) was quickly assembled via a titanium-mediated radical polyolefin cyclisation,



Scheme 20. Barrero's Synthesis of (−)-Valpara-2,15-diene and (+)-Isodaucene

which could serve as a more accessible precursor to the challenging architecture found in the valparanes (Scheme 20A).[94] Conversion of the cyclohexanol ring to the requisite five-membered ring was realized through activation of the unprotected alcohol with PCl_5, generating intermediate **20-2**, which underwent C–O cleavage and formed presumed carbocation **20-3**. A ring contraction initiated by an alkyl shift formed the five-membered ring and a tertiary carbocation (**20-4**). Proton transfer and desilylation upon aqueous work up yielded aldehyde **20-5**. This structure could be converted to the isoprenyl substructure in **20-6** with 28% overall yield over four steps. Barrero and co-workers employed an analogous carbocation-mediated structural reorganization strategy to access the sesquiterpenoid (+)-isodaucene (**20-8**) from **20-7** (Scheme 20B). The authors' approach allowed for the rapid generation of an easily accessible scaffold that could be efficiently rearranged to the desired skeleton present in **20-6** and **20-8**.

5.3. Ang Li's Synthesis of (+)-Arcutinidine, (−)-Arcutinine and (+)-Arcutine (2019)

Arcutinine (**21-7**) and arcutine (**21-8**), which are C_{20}-diterpenoid alkaloids, were first isolated by Bessonova and co-workers from *Aconitum arcuatum*, as well as the saponification product arcutinidine (**21-6**).[95] Biosynthetically, it was postulated that the arcutine skeleton was derived from the hetidine skeleton via a 1,2-alkyl shift, which was supported by the computational investigations conducted by Sarpong and co-workers.[96] The first total synthesis of (−)-arcutinine (**21-7**) was completed by Qin and co-workers in 2019, which entailed an oxidative dearomatization/IMDA cascade.[97]

Li and co-workers leveraged the 1,2-alkyl migration to realize the hetidine skeleton to arcutine skeleton conversion (Scheme 21).[98] Two consecutive Diels-Alder cycloadditions were utilized to construct intermediate **21-1**, which was treated with $SnCl_4$ to lead to the formation of oxocarbenium **21-2**. An ensuing intramolecular cyclization of the nearby cyclohexene resulted in tertiary carbocation intermediate **21-3**, which underwent a Wagner-Meerwein rearrangement to furnish carbocation **21-4**. Loss of proton gave rise to trisubstituted alkene **21-5** in 63% yield, which could be further elaborated to (+)-arcutinidine (**21-6**), (−)-arcutinine (**21-7**) and (+)-arcutine (**21-8**). From a retrosynthetic point of view, this Prins/Wagner-Meerwein cascade transformed the two doubly fused bicyclo[2.2.2]octane moieties in **21-5** to **21-1**, which could be easily accessed from readily available building blocks.

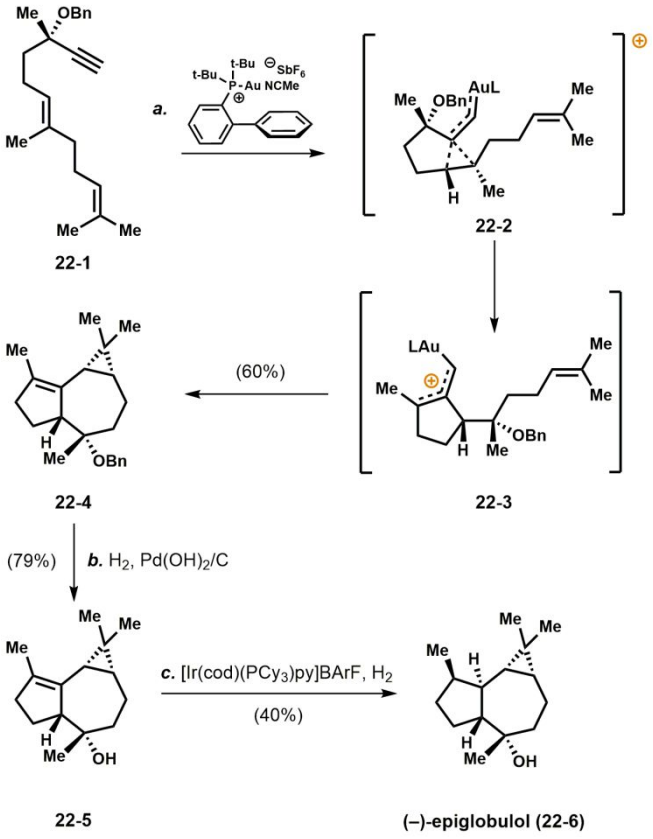
6. Metal Mediated Carbocationic Reactions

Methods that use transition-metal catalysis to stabilise carbocationic intermediates offer new opportunities for controlling cationic rearrangements.

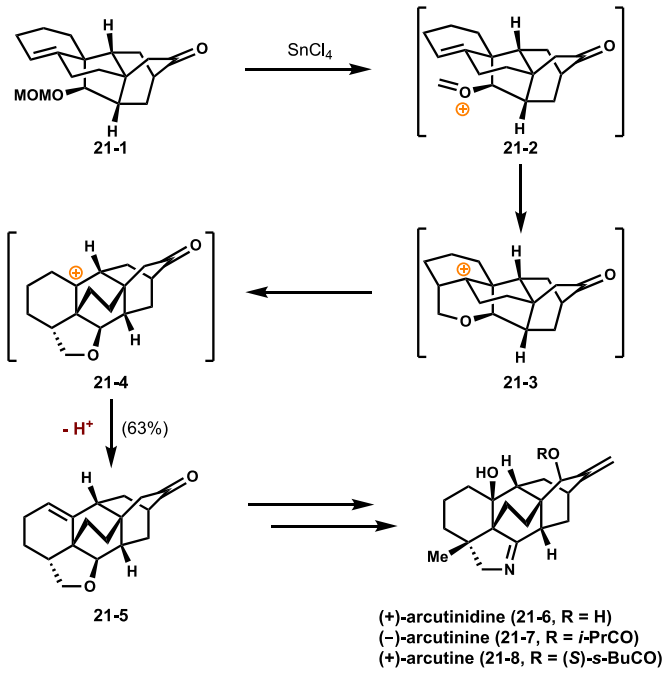
6.1. Echavarren's Synthesis of (−)-Epiglobulol (2014)

Epiglobulol (**22-6**), a sesquiterpenoid that belongs to the aromadendrane family, was isolated from hops and other essential oils.[99] The 5-7-3 ring system present in epiglobulol and related aromadendranes is decorated with six contiguous stereocentres, which has made it a proving ground for interesting retrosynthetic disconnections and new methods development. The first total synthesis of epiglobulol (**22-6**) was reported in 1975 by Gupton and co-workers, employing a photochemical rearrangement to access the 5-7-3 scaffold.[100] Another synthesis by the Sato group includes a Rh(I)-catalyzed hydroacylation/cycloisomerization cascade to construct the 5-7 fused bicycles from a linear precursor.[101]

Echavarren and co-workers applied a gold-catalysed cyclisation cascade to approach epiglobulol (**22-6,** Scheme 22).[102] Treatment of benzyl-protected propargylic alcohol (**22-1**) with [(JohnPhos)Au(MeCN)]SbF_6 initiated a 5-*exo*-dig cyclisation to give rise to carbocation intermediate **22-2**. This is followed by an unusual 1,5-OBn migration leading to the allylic carbocation **22-3**. Intramolecular cyclopropanation formed the 5-7-3 fused tricyclic core in **22-4** in 60% yield, which upon deprotection of the benzyl group furnished **22-5** in 79% yield. Directed hydrogenation of the tetrasubstituted olefin (**22-5**) utilizing Crabtree's catalyst resulted in ( )-epiglobulol (**22-6**) in 40% yield.



Scheme 22. Echavarren's Synthesis of (−)-Epiglobulol



Scheme 21. Ang Li's Synthesis of (+)-Arcutinidine, (−)-Arcutinine and (+)-Arcutine

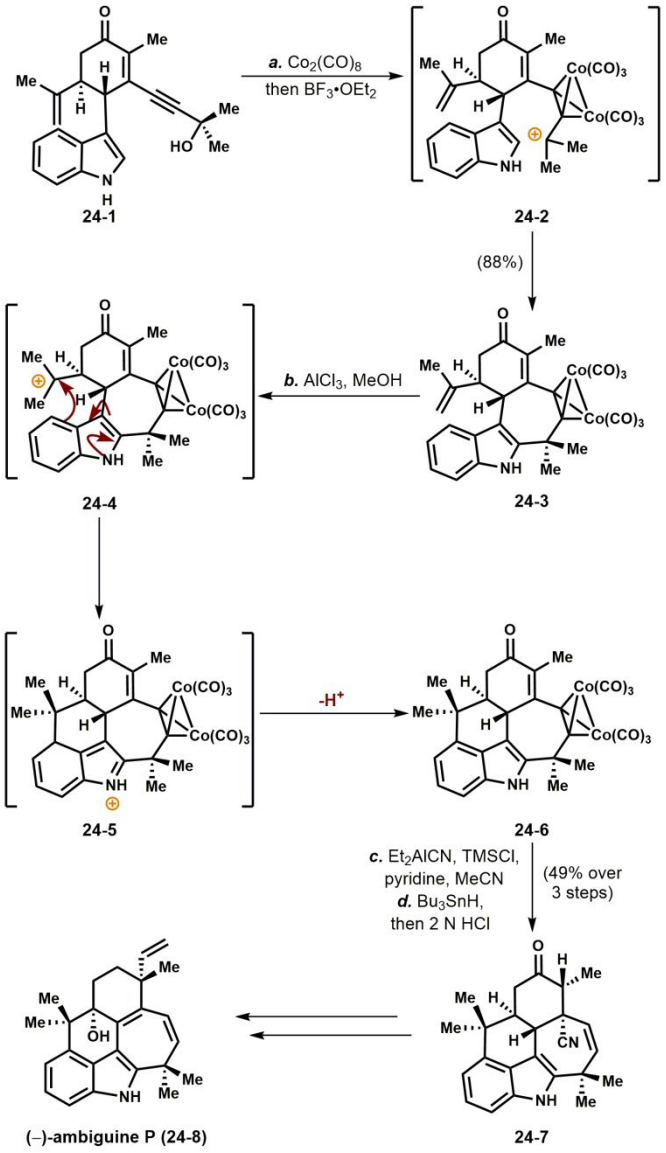
Scheme 23. Carriera's Synthesis of (−)-Merochlorin A

6.2. Carriera's Synthesis of (−)-Merochlorin A (2019)

Merochlorin A (**23-6**), a meroterpenoid isolated from a novel *Streptomyces* sp. strain (CNH-189) from sediment off the California coast, has been shown to have promising antibacterial properties.[103] Moreover, it has a structurally intriguing bicyclo[3.2.1]octane core structure bearing four contiguous stereocentres. Recently, Carriera and co-workers completed the first asymmetric total synthesis of merochlorin A, which allowed for the establishment of the absolute configuration of this molecule (Scheme 23).[104]

Carriera and co-workers approached the synthesis of **23-6** by employing a metal-mediated cationic rearrangement cascade as the key reaction to allow for the generation of most of the structural elements present in **23-6**. Treatment of enantioenriched propargyl acetate **23-1** with [(JohnPhos)Au(MeCN)]SbF_6 initiated a stereoretentive 1,3-acyloxy migration to form allene **23-2**. Subsequent gold(I)-catalysed isomerization of the allene substructure resulted in a stabilized carbocation (**23-3**), which triggered a Nazarov cyclisation to form enol-acetate **23-4**. Finally, an aldol reaction, which also may be catalysed by a gold(I)-complex, results in pentalene **23-5** in 73% yield. **23-5** could be further manipulated to furnish (−)-merochlorin A (**23-6**).

6.3. Sarpong's Synthesis of (−)-Ambiguine P (2019)



Scheme 24. Sarpong's Synthesis of (−)-Ambiguine P

Ambiguines are a family of indole secondary metabolites isolated from the cyanobacteria *Fischerella ambigua*.[105] These natural products feature a fused polycyclic scaffold containing an indole core. Numerous efforts have been devoted to the total synthesis of these molecules, which includes the successful construction of the tetracyclic congeners by the Baran, Rawal, and Maji group.[106] However, the pentacyclic ambiguine P (**24-8**) featuring a seven-membered ring has never succumbed to chemical synthesis until the work of Sarpong and co-workers in 2019.[107]

Sarpong and co-workers forged the seven-membered ring in their synthesis of (−)-ambiguine P (**24-8**) via a key intramolecular Nicholas reaction (Scheme 24). Treatment of the propargyl alcohol intermediate **24-1** with dicobalt octacarbonyl, $Co_2(CO)_8$, and BF_3•Et_2O generates tertiary carbocation **24-2**, which the indole C2 could engage to afford **24-3** in 88% yield**.** Under Lewis acidic conditions, the presumed tertiary carbocation **24-4** was formed and

a Friedel-Crafts alkylation at the indole C4 position was initiated via intermediate **24-5** to furnish the pentacyclic skeleton in **24-6**. Conjugate addition with Nagata's reagent, followed by enolate trapping with TMSCl and reductive removal of the dicobalt complex led to intermediate **24-7** in 49% yield over three steps, which could be further elaborated to access (−)-ambiguine P (**24-8**).

Conclusions

Isomerization reactions offer a unique opportunity to couple powerful synthetic methods with unusual structural motifs. To illustrate this general phenomenon, this review analysed one common isomerization reaction, cationic rearrangements. Cationic rearrangements are enabling in natural product synthesis from cyclisations to ring expansions and contractions.[108]

Isomerization reactions, including cationic rearrangements, are readily investigated using computational techniques to provide meaningful and useful insight into the key transformations under study as described in some of the cases in this report. We argue that calculations should be conducted prospectively during the planning stages of a synthetic effort to assist in the design of routes to natural products. Computational assessment provides a heightened level of understanding that adds to conventional qualitative evaluation.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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