Natural Product Synthesis

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The Chemistry of the Polycyclic Polyprenylated Acylphloroglucinols

*Jean-Alexandre Richard, Rebecca H. Pouwer, and David Y.-K. Chen**

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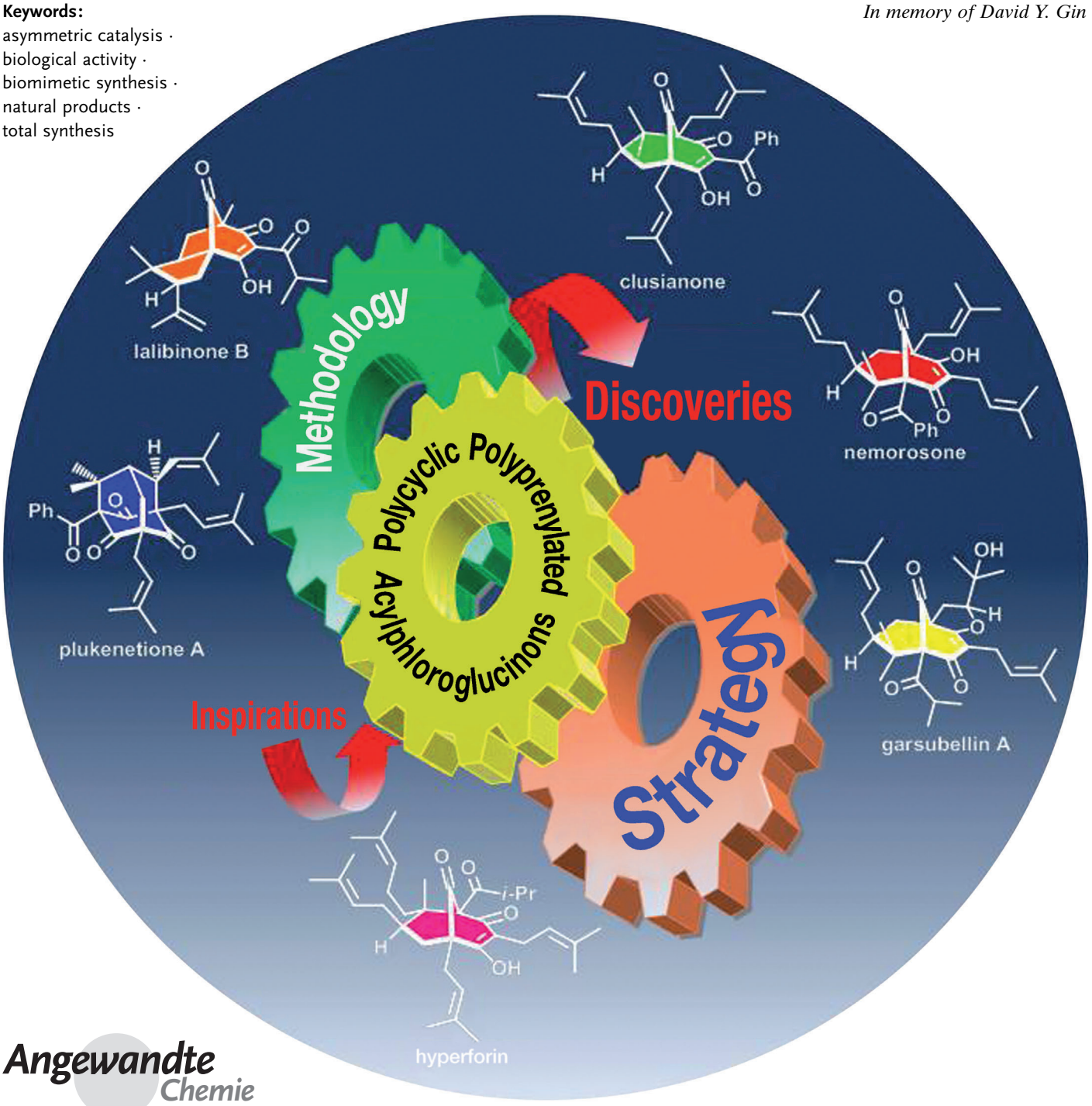
asymmetric catalysis · biological activity · biomimetic synthesis · natural products · total synthesis

In memory of David Y. Gin



With their fascinating biological profiles and stunningly complex molecular architectures, the polycyclic polyprenylated acylphloroglucinols (PPAPs) have long provided a fertile playing field for synthetic organic chemists. In particular, the recent advent of innovative synthetic methods and strategies together with C–C bond-forming reactions and asymmetric catalysis have revitalized this field tremendously. Consequently, PPAP targets which once seemed beyond reach have now been synthesized. This Review aims to highlight the recent achievements in the total synthesis of PPAPs, as well as notable methods developed for the construction of the bicyclo[3.3.1] core of these chemically and biologically intriguing molecules.

From the Contents

1. Introduction

The polycyclic polyprenylated acylphloroglucinols (PPAPs) constitute a family of natural products whose antiseptic, antidepressant, and antibiotic properties have been known for centuries. Interest in these early therapeutic uses has been revitalized in recent years as a result of the isolation of the active ingredients from the extract mixtures traditionally used as folk medicines.[1] Apart from their exciting range of biological activities, a further point of interest for this class of molecules lies in their intriguing chemical structure, which features a bicyclo[3.3.1]nonane-2,4,9-trione or bicyclo[3.2.1]octane-2,4,8-trione core that is densely decorated with prenyl, geranyl, or more highly substituted side chains. The PPAPs have, so far, been classified into three types (A, B, or C), depending on their isomeric forms. All PPAPs contain an acyl group (COR^3) and a quaternary center adjacent to a bridgehead carbon atom ($C(R^2)_2$). The classification of a PPAP as type A, B, or C depends on the relative position of these two groups: type A PPAPs bear the acyl group at the bridgehead position adjacent to the quaternary center; type C PPAPs bear the acyl group at the opposite bridgehead position relative to the quaternary center; and type B PPAPs bear alkyl groups (R^1, R^4) at the bridgehead carbon atoms while the acyl group is located at the α position to the β-hydroxy enone (Figure 1).[2]

When the structural similarities between the PPAPs are considered, the broad spectrum of biological activities exhibited by these compounds is particularly striking (Figure 2). Indeed, activities as varied as anticancer, anti-HIV, antidepressant, antibacterial, antimalarial, antioxidant, antiulcer, anti-inflammatory, and anti-neurodegenerative[3] have been reported to date. It is beyond the scope of this Review to discuss the biological profile of PPAPs in depth. Furthermore, the structural assignment of the PPAPs has been extensively reviewed by Ciochina and Grossman, and will not be discussed here.[1a]

From a synthetic perspective, it is not surprising that the promising biological profiles of the PPAPs combined with their challenging structures have stimulated a great deal of interest from the synthetic community. A number of strategies developed for the construction of the bicyclo-[3.3.1]nonane system have been reported and reviewed by Peters,[4] and more recently by Butkus.[5] Although the work discussed therein largely focused on relatively unfunctionalized structures outside of the context of the PPAPs, it did provide some interesting insights concerning the foreseeable synthetic challenges. Ciochina and Grossman[1a] as well as Singh et al.[1d] have independently also provided overviews on the early synthetic approaches towards the PPAPs. However, considerable advances remained unaddressed, particularly those that culminated in the recent total syntheses of several type A and type B PPAPs in both racemic and optically active forms. The purpose of this Review is to provide an overview of the total syntheses of PPAPs together with the ingenious synthetic approaches that have been developed in recent years, highlighting the newest synthetic methods and current limitations. We hope this Review will be a source of inspiration for instilling new ideas, and will encourage chemists to seek further advances in the PPAP field. As a consequence of the large volume of primary literature on the synthesis of PPAPs, we have not been able to include everything, and we apologize to those scientists whose work has been omitted or inadvertently overlooked.[1e]

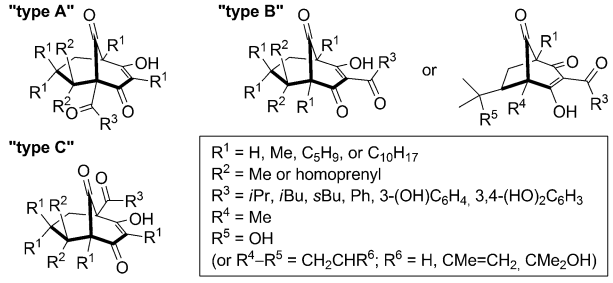


Figure 1. Type A, B, and C PPAPs.

[*] Dr. J.-A. Richard, Dr. R. H. Pouwer
Chemical Synthesis Laboratory@Biopolis
Institute of Chemical and Engineering Sciences (ICES)
Agency for Science, Technology and Research (A*STAR)
11 Biopolis Way, The Helios Block, no. 03-08
Singapore 138667 (Singapore)
Prof. Dr. D. Y.-K. Chen
Department of Chemistry, Seoul National University
Gwanak-1 Gwanak-ro, Gwanak-gu, Seoul 151-742 (South Korea)
E-mail: davidchen@snu.ac.kr

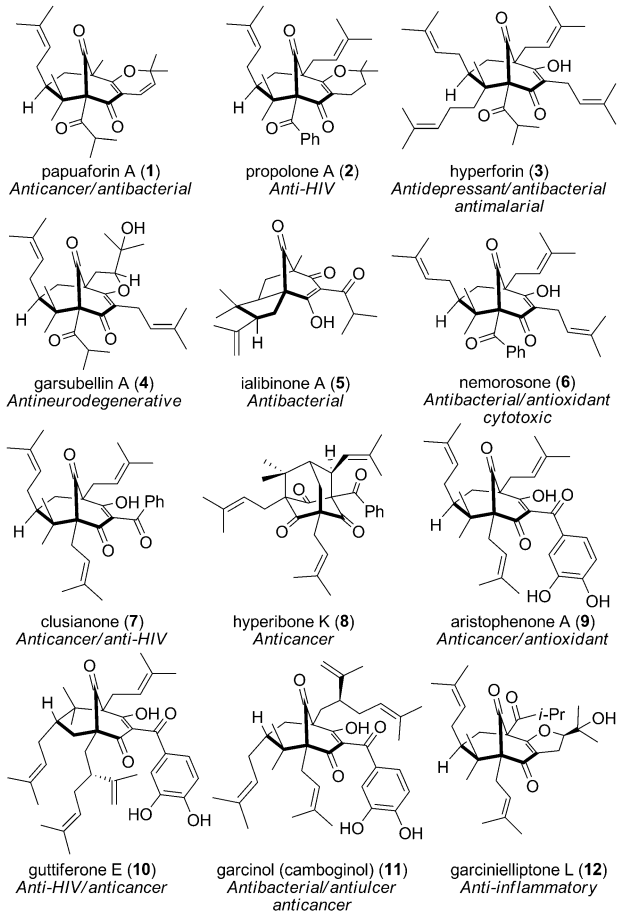


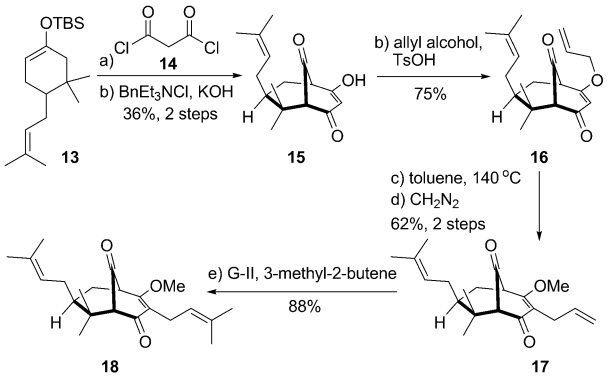
Figure 2. Molecular structures of selected PPAPs along with their reported biological activities.

2. Total Syntheses of PPAPs

2.1. The Effenberger Cyclization Approach

2.1.1. Stoltz's Preliminary Work

In 2002, Spessard and Stoltz reported one of the landmark studies in the synthesis towards the PPAPs, therein demonstrating for the first time the application of the Effenberger annulation[6] for the construction of the bicyclic skeleton of



Scheme 1. Synthesis of the PPAP core by an Effenberger cyclization strategy, according to Stoltz and Spessard (2002).[7]

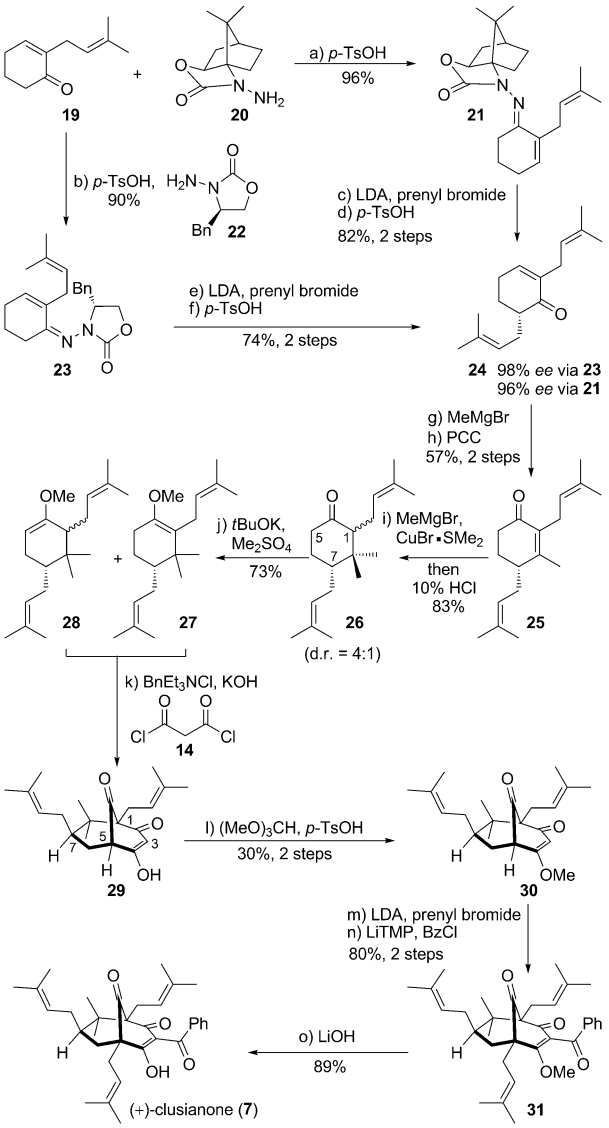
the PPAPs (Scheme 1).[7] In this study, modification of Effenberger's original protocol enabled the construction of the bicyclo[3.3.1] system **15** from TBS enol ether **13** in 36% yield (from the ketone precursor of TBS enol ether **13**), through the combined action of malonyl dichloride and KOH under phase-transfer conditions. Despite the modest yield, this one-step protocol was particularly attractive in view of its expediency, since the ketone precursor of silyl enol ether **13** could be readily recovered and recycled. Furthermore, this ring-annulation process was found to be completely stereoselective, with the prenyl substituent in bicycle **15** exhibiting an *anti* orientation relative to the newly formed 1,3-diketone moiety. With bicyclic intermediate **15** in hand, the additional prenyl group was installed by taking advantage of a Claisen rearrangement of allyl enol ether **16**.[8] The obtained rearrangement product underwent further methylation with CH_2N_2 (62% overall yield from **16**) and olefin cross-metathesis with 3-methyl-2-butene (second-generation Grubbs catalyst; 88% yield)[9] to afford the doubly prenylated bicycle **18**, which contains the key structural elements found in a diverse array of PPAPs. Although the work described therein simply served as a model study for the PPAPs, the importance of this seminal report cannot be overstated, as it served as a foundation for many future synthetic efforts towards the PPAPs.

*Jean-Alexandre Richard was born in 1982 in Tours, France. He obtained his PhD in 2008 under the supervision of Professor Pierre-Yves Renard and Dr. Anthony Romieu, working on the development of luminescent probes for molecular imaging. Since 2009 he has been a research fellow in the group of Dr. David Y.-K. Chen at the Chemical Synthesis Laboratory (CSL) @ Biopolis, under the Agency for Science, Technology, and Research (A*Star), Singapore. His research focuses on the total synthesis of natural products.*

*Rebecca Pouwer was born in 1982 in Brisbane, Australia. After completing her PhD at the University of Queensland under the guidance of Dr. Craig M. Williams, she undertook postdoctoral studies at Imperial College London under the guidance of Dr. D. Christopher Braddock. In 2010, she commenced further postdoctoral studies with Dr. David Y.-K. Chen at the Chemical Synthesis Laboratory (CSL) @ Biopolis under the Agency for Science, Technology, and Research (A*Star), Singapore, where she focuses on the total synthesis of complex natural products.*

2.1.2. Coltart's Total Synthesis of (+)-Clusianone (2010)

Inspired by the approaches developed by Marazano and Simpkins (see Sections 2.1.3–2.1.6), Coltart and co-workers reported an asymmetric synthesis of (+)-clusianone (**7**)[10] by a route that is potentially applicable to a diverse collection of natural and designed PPAPs (Scheme 2).[11] In this context, an asymmetric α alkylation of chiral cyclic *N*-aminocarbamate-derived hydrazones (**21** and **23**) was employed to provide entry to the enantiomerically enriched, substituted cyclohexenone **24**.[12] Deprotonation of hydrazones **21** and **23** with LDA followed by alkylation with prenyl bromide afforded, upon hydrolytic removal of the cyclic *N*-aminocarbamate chiral auxiliary, cyclohexenone **24** with 96% *ee* (82% yield) and 98% *ee* (74% yield), respectively. MeMgBr-mediated 1,2-addition to cyclohexenone **24**, followed by an oxidative carbonyl transposition with PCC[13] yielded a cyclohexenone derivative (**25**) that was amenable to the introduction of a variety of substituents at the β position of the PPAPs. Specifically, the addition of methyl cuprate was required for the synthesis of (+)-clusianone (**7**) and yielded cyclohexanone derivative **26** as a 4:1 epimeric mixture at C1 after hydrolytic desilylation of the intermediate TMS silyl enol ether. Construction of the bicyclic framework of clusianone (**7**) called for an Effenberger annulation, whereby cyclohexanone **26** was converted into its methyl enol ether derivatives (as a mixture of regioisomers **27** and **28**) in readiness for this process. Methyl enol ethers **27** and **28** underwent sequential alkylations in the presence of malonyl dichloride under phase-transfer conditions to afford bicycle **29**. The enolizable β-diketone of **29** was further methylated to give bicyclic diketone **30** in 30% yield over the two steps. Bicyclic diketone **30** differs from (+)-clusianone (**7**) merely by the absence of the prenyl and benzoyl substituents. As such, these remaining functionalities were sequentially introduced through the action of LDA/prenyl bromide and LiTMP/BzCl, respectively, which furnished the targeted material in 71% yield from **30** after demethylation (LiOH).

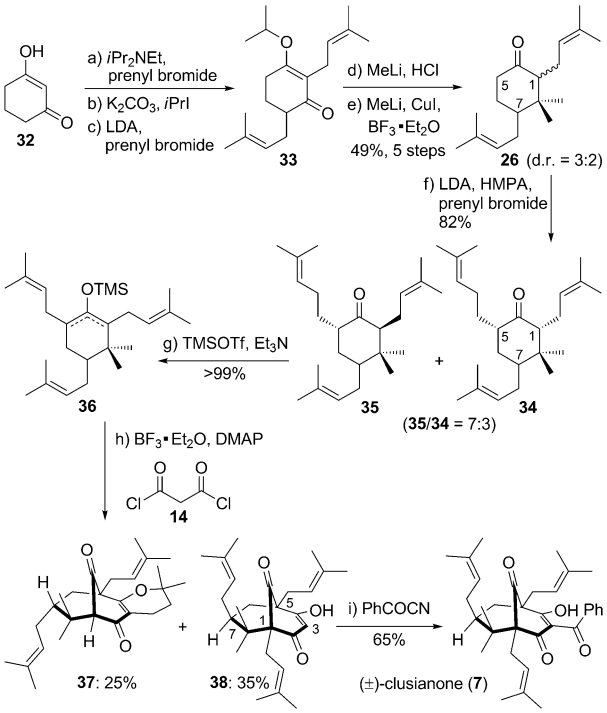


Scheme 2. Total synthesis of (+)-clusianone (**7**) according to Coltart and co-workers (2010).[11]

2.1.3. Marazano's Total Synthesis of (±)-Clusianone (2007)

In the synthesis of (±)-clusianone (**7**) reported by Marazano, Delpech, and co-workers, the bicyclo[3.3.1] core structure was rapidly assembled with concomitant introduction of the C1/C5 quaternary centers (Scheme 3).[14] Their synthesis commenced with the sequential alkylation of 1,3-cyclohexadione (**32**) to afford the doubly prenylated cyclohexenone derivative **33**. Installation of the C8-*gem*-dimethyl substituents took place smoothly through the action of MeLi with acidic workup, followed by methyl cuprate addition to furnish substituted cyclohexanone **26** in 49% overall yield from **32** (epimeric at C7, ca. 3:2). Introduction of the C5-prenyl group of clusianone (**7**) was accomplished through formation of the kinetic lithium enolate of cyclohexanone **26** followed by its reaction with prenyl bromide, thereby affording diastereomeric cyclohexanones **34** and **35** in 82% combined yield (d.r. = ca. 7:3). Treatment of cyclohexanones **34** and **35** with TMSOTf/Et_3N afforded a regioisomeric mixture of TMS silyl enol ethers **36**, thus setting the stage for the construction of the bicyclic system through an Effenberger annulation. The optimized conditions were found after considerable experimentation to entail the treat-

*David Yu-Kai Chen was born in 1976 in Taipei, Taiwan. After completing his PhD at the University of Cambridge in 2001 with Prof. Ian Paterson, he pursued postdoctoral work with Prof. K. C. Nicolaou at The Scripps Research Institute. In 2005, after a short stay at Merck (USA), he was appointed as a Principal Investigator of the CSL @ Biopolis, under the Agency for Science, Technology, and Research (A*Star), Singapore. In 2011, he was appointed Professor of Organic chemistry at the Seoul National University (South Korea). His research focuses on new synthetic strategies for the total synthesis of natural products as well as chemical biology.*

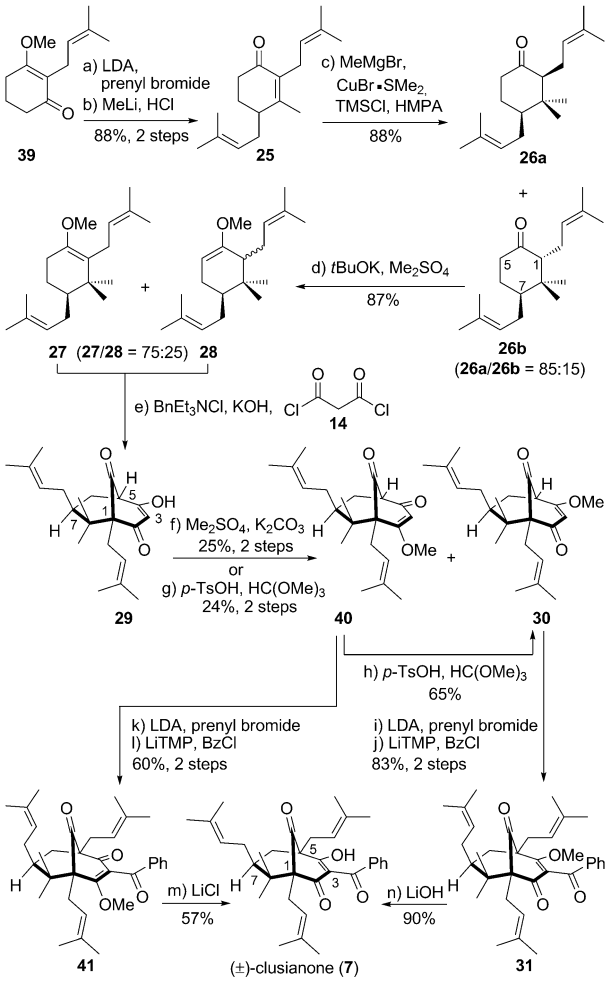


Scheme 3. Total synthesis of (±)-clusianone (**7**), according to Marazano and co-workers (2007).[14]

ment of TMS silyl enol ethers **36** with malonyl dichloride in the presence of $BF_3{\cdot}OEt_2$, whereby the bicycle **38** was obtained in 35% yield, accompanied by tricyclic diketone **37** (25% yield) and recovered cyclohexanones **34** and **35** (22% yield). Despite the modest yield, the simultaneous construction of the two quaternary centers at C1 and C5 was noteworthy. Finally, the synthesis of (±)-clusianone (**7**) was completed through C-acylation with benzoyl cyanide. The complete synthetic sequence required only nine chemical transformations from cyclohexenone **32** and delivered the product in 9% overall yield.

2.1.4. *Simpkins' Total Synthesis of (+)-Clusianone (2006)*

In parallel with the studies disclosed by Marazano and co-workers, the Simpkins research group published a series of reports that documented the preparation of racemic and optically pure clusianone (**7**), in which an Effenberger annulation was at the center of their synthetic strategy for the construction of the bicyclo[3.3.1] core structure (Scheme 4).[15] Prenylation of cyclohexadione derivative **39** in the presence of LDA and prenyl bromide, followed by MeLi-mediated 1,2-addition and acidic workup, afforded the doubly prenylated cyclohexenone **25** in 88% yield over the two steps. 1,4-Addition of the methyl group to cyclohexenone **25** was achieved with a carefully optimized reagent mixture (MeMgBr, TMSCl, HMPA, and $CuBr{\cdot}SMe_2$), which led to an inconsequential mixture of diastereoisomers **26a** and **26b** (ca. 85:15) in 88% yield. Cyclohexanones **26a** and **26b** were converted into methyl enol ethers **27** and **28** in preparation for the proposed Effenberger cyclization,. Treatment of com-

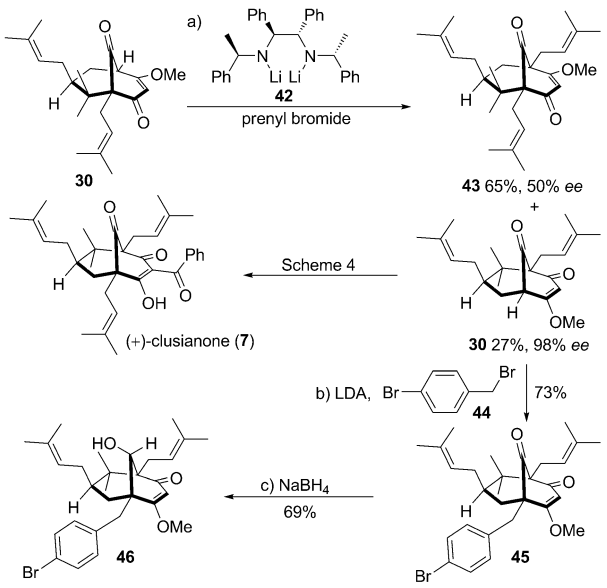


Scheme 4. Total synthesis of (±)-clusianone (**7**), according to Simpkins and co-workers (2006).[15]

pounds **27** and **28** with malonyl dichloride under phase-transfer conditions (KOH, $BnEt_3NCl$) led to the anticipated bicyclic system **29** being obtained as a single isomer (ca. 30% crude material). Similarly, the kinetic TBS silyl enol ether derived from cyclohexanone **26a** also proved to be reactive under the modified Effenberger annulation conditions, and led to bicycle **29**, with results similar to those obtained from methyl enol ethers **27** and **28**. Despite considerable experimentation, Simpkins and co-workers were unable to identify reaction conditions superior to those described earlier.[7] Methylation of enolizable 1,3-diketone **29** was achieved under basic conditions (Me_2SO_4, K_2CO_3) to give a mixture of methyl ethers **30** and **40** in 25% combined yield (ca. 1:1); **40** could be converted into **30** under acidic conditions ($HC(OMe)_3$, TsOH). Alternatively, methyl ether **30** could be obtained exclusively from **29** under acidic conditions ($HC(OMe)_3$, TsOH) in 24% yield. Sequential prenylation and benzoylation at the C5- and C3-positions of bicycles **30** and **40** took place smoothly to afford methyl ethers **31** and **41** in 83% and 60% yield over the two steps, respectively. Final demethylation in the presence of LiOH or LiCl conditions at elevated temperature ultimately funneled both **31** and **41** to

(±)-clusianone (**7**), which exists as a mixture of enol tautomers, thereby completing the total synthesis.

The developed synthetic sequence was amenable to an asymmetric setting, in which a late-stage intermediate in the racemic synthesis was subjected to kinetic resolution to access optically active material (Scheme 5).[16] In this context,

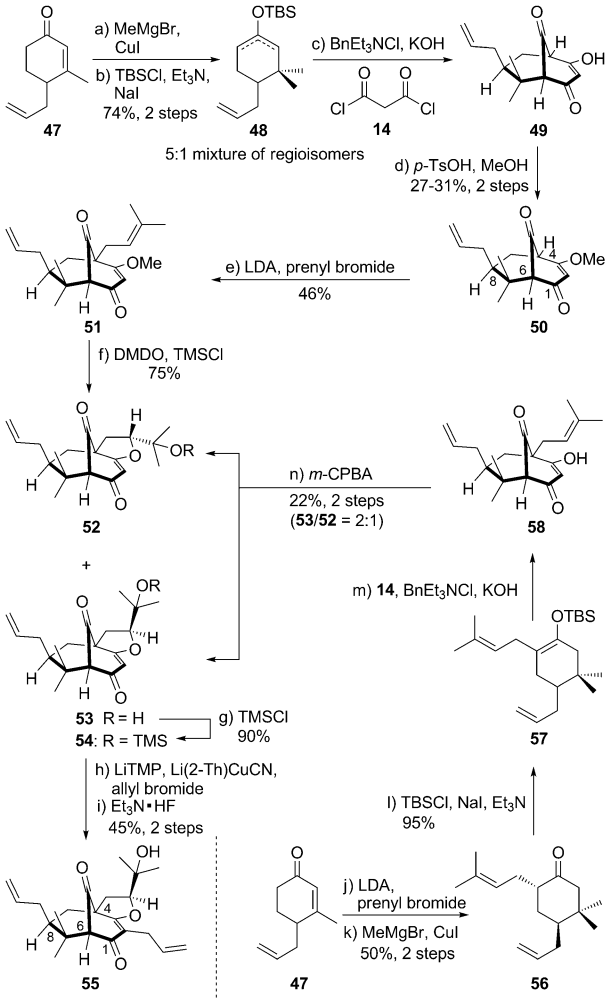


Scheme 5. Kinetic resolution of (±)-**30** for the total synthesis of (+)-cluisianone (**7**), according to Simpkins and co-workers (2007).[16]

instead of the LDA-mediated deprotonation of bicyclic diketone **30** and subsequent prenylation, chiral bis(lithium-amide) **42** was employed to afford prenylated product **43** in 65% yield with 50% *ee*, together with recovered diketone **30** in 24–27% yield and high enantiomeric purity (> 98% *ee*).[17] Optically enriched diketone **30** was subjected to bridgehead benzylation with *p*-bromobenzyl bromide followed by subsequent reduction with $NaBH_4$ to afford a crystalline derivative (**46**), thus allowing confirmation of its absolute configuration. In an analogous fashion, (+)-clusianone (**7**) was conveniently prepared from enantiomerically enriched diketone **30** in accordance with the synthetic sequence developed for the racemic synthesis.

2.1.5. *Simpkins' Formal Synthesis of (±)-Garsubellin (2007)*

In the formal synthesis of garsubellin A (**4**) by Simpkins and co-workers,[18] experience garnered from their related PPAP campaigns proved particularly valuable (Scheme 6).[15b] Their synthesis commenced with the preparation of the Effenberger annulation precursor **48** from cyclohexenone **47** through 1,4-addition of methyl cuprate followed by formation of the TBS silyl enol ether in 74% yield over the two steps. Effenberger annulation in the presence of malonyl dichloride under phase-transfer conditions (KOH, $BnEt_3NCl$) proceeded smoothly to give bicycle **49**, which was methylated under acidic methanolysis conditions to afford methyl ether



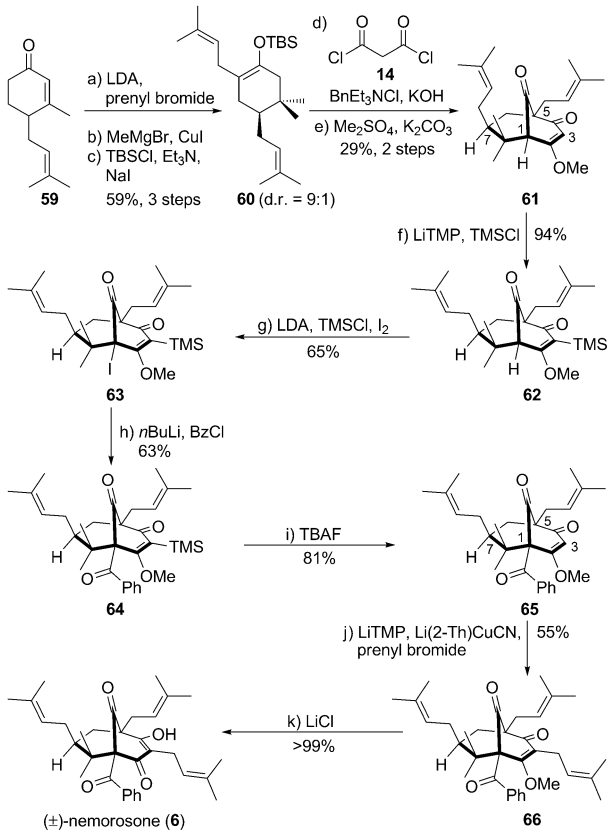
Scheme 6. Formal synthesis of (±)-garsubellin A (**4**), according to Simpkins and co-workers (2007).[15b]

50 as a single regioisomer in 27–31% yield (from **49**). Prenylation of bicycle **50** with LDA/prenyl bromide took place uneventfully in modest yield (46%), uncomplicated by the presence of alternative sites of alkylation (C2 and C6). The introduction of the THF motif necessitated thoughtful consideration, particularly concerning the presence of two potentially competing olefins and the stereochemical outcome of the oxygenation process. Electrophilic oxidation of bicycle **51** with DMDO was selective for the more-electron-rich prenyl olefin in the presence of the terminal olefin of the allyl side chain. Unfortunately, the oxidation was not diastereoselective, and treatment of the diastereomeric epoxide intermediates with TMSCl led to a mixture of tricyclic tetrahydrofurans **52** and **53** (ca. 1:1) in 75% combined yield. Tertiary alcohols **52** and **53** were silylated, and the required stereoisomer **54** was separated, allylated with a cuprate reagent, and desilylated with Et_3·NHF to afford **55** in 45% yield over the two steps. Thus, an advanced intermediate (**55**) in the total synthesis of garsubellin A (**4**) reported by the Danishefsky research group (see Section 2.2.7) was reached, thereby constituting a formal synthesis.

With a view to improve their original route that led to the formal synthesis of garsubellin A (**4**), the C4-prenyl group was introduced prior to the Effenberger annulation. In this case, prenylation of enone **47** (LDA, prenyl bromide) followed by the addition of methyl cuprate to the intermediate enone afforded substituted cyclohexanone **56** in 50% yield over the two steps. Effenberger annulation of the TBS enol ether derivative **57** furnished bicyclic diketone **58** in approximately 29% yield, together with recovered cyclohexanone **56** (58% yield). Epoxidation and subsequent formation of a THF ring in the unprotected enol **58** directly provided tricyclic tertiary alcohols **52** and **53**, with a diastereoselectivity that slightly favored the desired isomer (**53**/**52** ca. 2:1) in 22% overall yield (from **57**).

2.1.6. *Simpkins' Total Synthesis of (±)-Nemorosone (2010)*

During the course of their studies towards a general approach to access the PPAPs through bridgehead alkylation, Simpkins et al. uncovered an unexpected reactivity profile in the total synthesis of nemorosone (**6**; Scheme 7).[19] In this case, the doubly prenylated bicycle **61** was readily prepared from cyclohexenone **59** through α prenylation, methyl cuprate mediated 1,4-addition, thermodynamic TBS silyl enol ether formation, Effenberger annulation, and methylation. Unfortunately, although clean C3-prenylation of **61** could take place in the presence of the mixed higher cuprate, the subsequent metalation occurred preferentially at the newly installed C3-prenyl substituent rather than at the C1 bridgehead. This unexpected result was circumvented by C3-silylation with LiTMP and TMSCl, thus enabling the subsequent C1-lithiation to take place in the presence of either LDA or LiTMP. However, in-line with Danishefsky's observations (see Section 2.2.6), C1-lithiated **62** failed to undergo alkylation with a variety of carbon electrophiles, and iodination only took place in the presence of TMSCl, which was found to be crucial for this process. Halogen–metal exchange of iodide **63** with *n*BuLi followed by reaction with benzoyl chloride afforded bicyclic triketone **64** in 41% overall yield. The TMS moiety was subsequently removed by treatment with TBAF (81% yield). Finally, C3-prenylation in the presence of a mixed higher cuprate reagent, followed by nucleophilic demethylation with LiCl completed the total synthesis of nemorosone (**6**) in 55% overall yield from **65**.

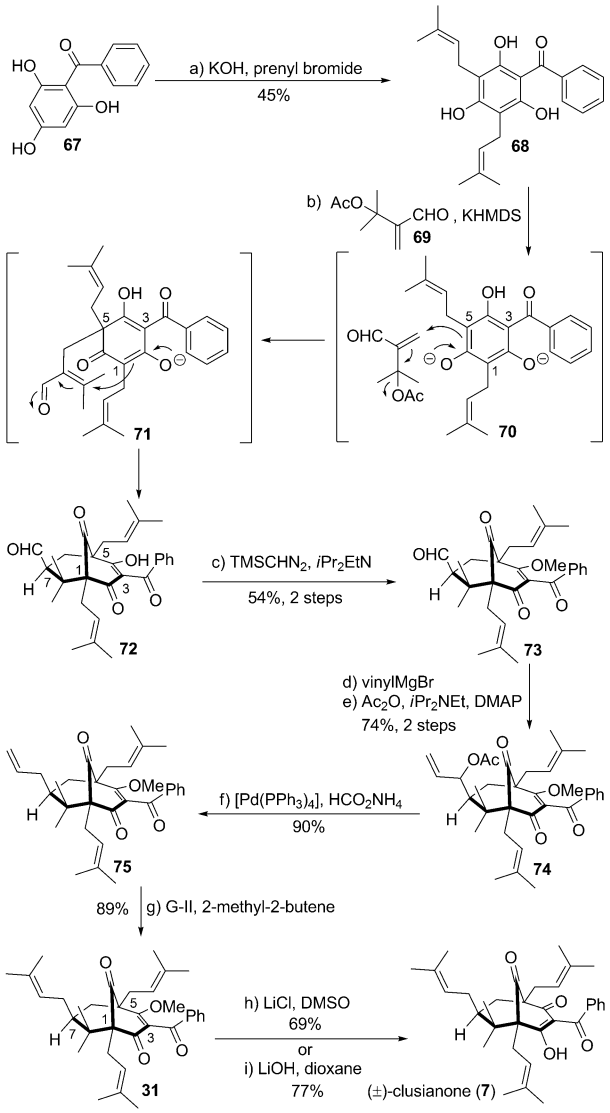


Scheme 7. Total synthesis of (±)-nemorosone (**6**), according to Simpkins et al. (2010).[19a]

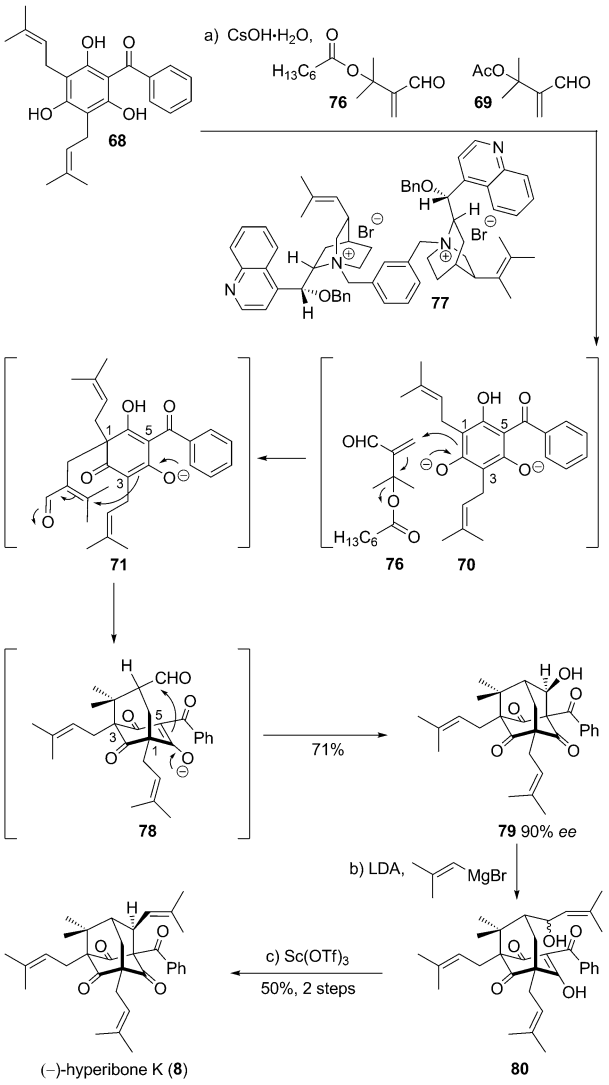
2.2. The Dearomatization Strategy

2.2.1. *Porco's Total Synthesis of (±)-Clusianone (2007)*

Inspired by biosynthetic considerations,[2] Qi and Porco devised an ingenious and highly instructive approach to the PPAPs that ultimately enabled an expedient total synthesis of (±)-clusianone (**7**; Scheme 8).[20] In this approach, an alkylative dearomatization/annulation strategy was developed to access the bicyclic core structure of the PPAPs. Commencing from acylphloroglucinol **67**, double C-prenylation afforded clusiaphenone B (**68**) in 45% yield.[21] A variety of α-acetoxyacrylates, α-acetoxyacrylonitrile, and α-acetoxyvinylsulfones were examined in the alkylative dearomatization/annulation reaction with clusiaphenone B (**68**). Depending on the reaction conditions and the electronic and steric environment of the Michael acceptor, the proposed key reaction afforded monoalkylated dearomatization products in good yields and with high levels of stereoselectivity. Specifically, for the synthesis of (±)-clusianone (**7**), the reaction between α-acetoxyenal **69** and clusiaphenone B (**68**) led to the annulation product **72**, which was readily methylated with $TMSCHN_2$ to facilitate the isolation of the subsequent bicyclic intermediate **73**, in 54% overall yield (from **68**). Conversion of the aldehyde moiety in **73** into the remaining prenyl group in (±)-clusianone (**7**) was executed through a four-step sequence. In this context, addition of a vinyl Grignard reagent to aldehyde **73**, followed by acetylation of the intermediate allylic alcohol afforded allylic acetate **74** in 74% overall yield. Palladium-mediated deacetoxylation[22] and subsequent olefin cross-metathesis with 2-methyl-2-butene in the presence of the second-generation Grubbs catalyst smoothly delivered the C7-prenyl substituent of (±)-clusianone (**7**; 80% yield over the two steps). Finally, treatment of methyl ether **31** with either LiOH or LiCl at elevated temperature resulted in nucleophilic demethylation and furnished (±)-clusianone (**7**) in 77% and 69% yields, respectively, as a mixture of enol tautomers (ca. 4:3).



Scheme 8. Total synthesis of (±)-clusianone (**7**), according to Qi and Porco (2007).[20]



Scheme 9. Total synthesis of (−)-hyperibone K (**8**), according to Porco and co-workers (2010).[23a]

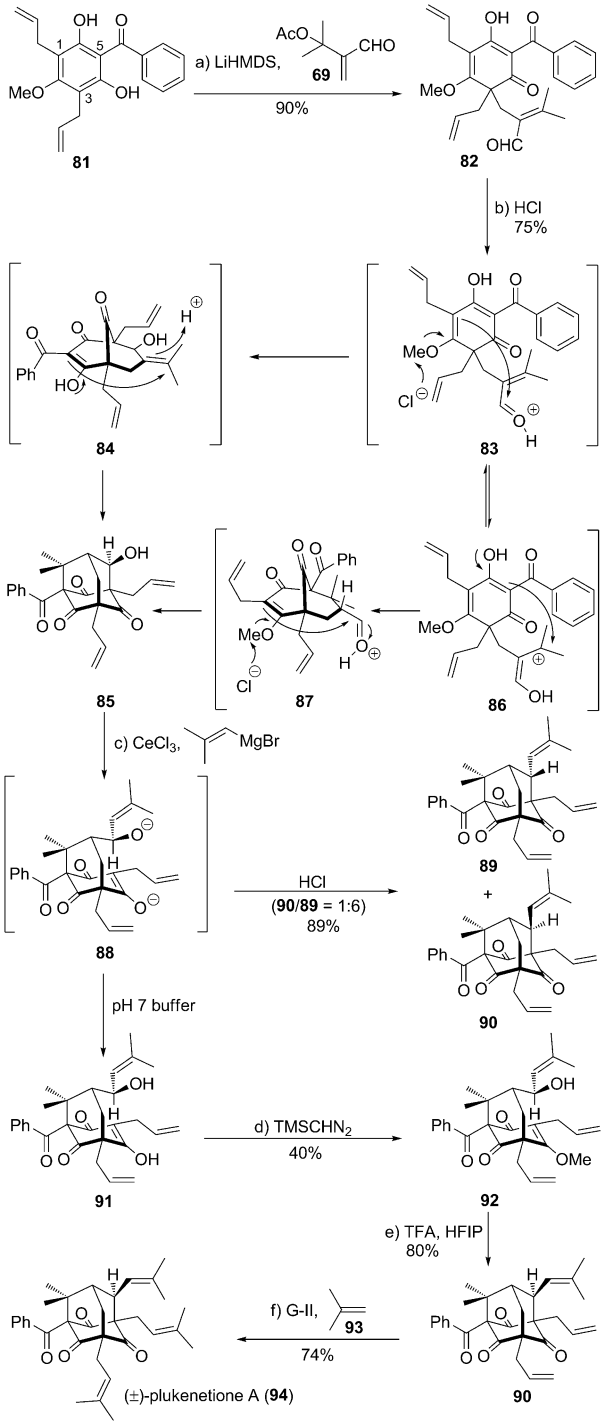
2.2.2. *Porco's Total Synthesis of (−)-Hyperibone K (2010)*

Based on the strategy developed for the synthesis of (±)-clusianone (**7**), Porco and co-workers implemented an asymmetric alkylative dearomatization/annulation reaction in the enantioselective synthesis of the adamantane-containing type B PPAP hyperibone K (**8**; Scheme 9).[23] Commencing from clusiaphenone B (**68**), its enantioselective dearomatization/alkylation with enal **69** (or **76**) was investigated under phase-transfer catalysis conditions in the presence of a cinchona alkaloid as the chirality inducer.[24] After extensive experimentation, dimeric cinchona alkaloid[25] **77** proved to be the most effective catalyst, which, in combination with heptanoate aldehyde **76**, furnished adamantane **79** in 71% yield and 90% *ee*. The global structure and absolute configuration of hydroxyadamantane **79** was secured through X-ray analysis of its *p*-bromobenzoate derivative, while NMR and computational studies were employed to rationalize the mode of action of the phase-transfer (ion pair) catalyst. Further elaboration of the hydroxyadamantane core structure **79** called for a retro-aldol/addition sequence,[26] which took place smoothly upon treatment of hydroxytetraone **79** with LDA followed by 2-methyl-2-propenylmagnesium bromide and afforded an epimeric mixture of allylic alcohols **80**. Intramolecular cyclization of allylic alcohols **80** and regeneration of the adamantane core structure was effected through the action of $Sc(OTf)_3$,[27] a process that proceeded with a high level of diastereoselectivity (>20:1), and furnished (−)-hyperibone K (**8**) in 50% yield (from adamantane **79**). The successful completion of the total synthesis also served to confirm the absolute stereochemistry of the naturally occurring substance.

2.2.3. *Porco's Total Synthesis of (±)-Plukenetione A (2010)*

As an extension of their synthetic studies towards the PPAPs through the alkylative dearomatization/annulation of

clusiaphenone B (**68**), Porco and co-workers later demonstrated a site-selective alkylation that permitted entry to the type A adamantane PPAP plukenetione A (**94**), a regioisomer of hyperibone K (**8**) in terms of the C3-benzoyl and C5-prenyl groups (Scheme 10).[28] In this context, protected clusiaphenone B methyl ether **81** was employed with the intention that the alkylative dearomatization would take place at the C3- and C5-positions rather than at the C1- and C3-positions, as

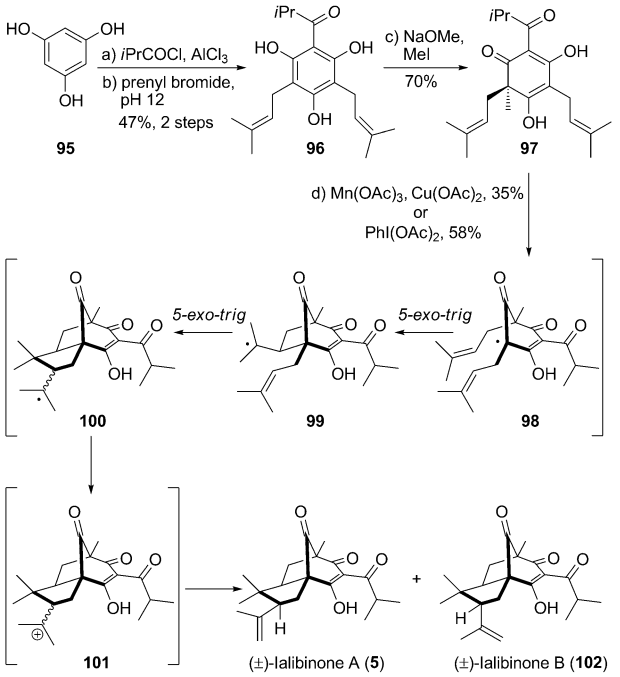


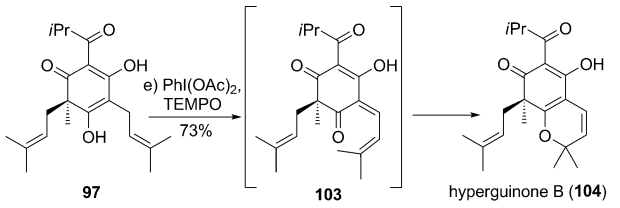
Scheme 10. Total synthesis of (±)-plukenetione A (**94**), according to Porco and co-workers (2010).[28a]

previously observed in the synthesis of (±)-clusianone (**7**) and (+)-hyperibone K (**8**). Thus, treatment of **81** with LiHMDS in the presence of α-acetoxyenal **69** afforded, instead of the expected annulation product, the monoalkylated dearomatized product **82** in 90% yield. The absence of the expected doubly alkylated bicyclo[3.3.1] product was presumably due to a facile and reversible retro-Michael process under basic conditions. A series of studies with enal **82** ultimately revealed that further intramolecular alkylation events took place on exposure to concentrated HCl, and eventually led to the production of adamantane alcohol **85** in 75% yield as a single diastereoisomer. Two mechanistic proposals, differing merely in the order of events in which the C1- and C5-alkylations took place, were put forward to rationalize the formation of adamantane **85**. With adamantane **85**, which represents the core structure of plukenetione A (**94**), secured, a reinvestigation of the previously described retro-aldol/alkenyl-addition sequence (**79**→**8**, Scheme 9) was deemed necessary. In this case, $CeCl_3$-promoted addition of 2-methyl-2-propenylmagnesium bromide[29] followed by acidic workup afforded a diastereomeric mixture of adamantanes **89** and **90** in 89% combined yield, unfortunately in favor of the undesired isomer (**89**/**90** ca. 6:1). A solution to address this late-stage setback was ultimately secured through the isolation of the alkenyl addition product **91** followed by methylation ($TMSCHN_2$, 40% overall yield), and treatment of the resulting allylic alcohol **92** with TFA/HFIP[30] to furnish adamantane **90** as a single diastereoisomer in 80% yield. Final conversion of the allyl side chains into the prenyl groups proceeded uneventfully under the influence of the second-generation Grubbs catalyst and isobutylene, thereby completing a highly efficient and stereoselective total synthesis of plukenetione A (**94**).

2.2.4. *Simpkins' Total Synthesis of (±)-Ialibinone A and B (2010)*

To illustrate the power of cascade reactions in the synthesis of PPAPs,[31] Simpkins and Weller demonstrated an expedient synthesis of ialibinones A (**5**) and B (**102**) through a Mn^{III}-mediated domino cyclization (Scheme 11).[32] The doubly prenylated acylphloroglucinol **96** was prepared from phloroglucinol (**95**) through a Friedel–Crafts acylation followed by double prenylation. This two-step process proceeded in 47% overall yield. Regioselective introduction of the methyl group with concomitant dearomatization was achieved by using MeI/NaOMe, and furnished the substituted acylphloroglucinol **97**, which exists in its tautomeric forms, in 70% yield. Gratifyingly, **97** was smoothly transformed with $Mn(OAc)_3/Cu(OAc)_2$[33] to ialibinones A (**5**) and B (**102**) in 35% combined yield (**5**/**102** ca. 41:59) by a process that involved sequential 5-*exo*-*trig* cyclizations. Despite the modest yield, rapid construction of the polycyclic framework by a route that mimicked the biosynthetic pathway is noteworthy. Over-oxidation could account for the poor mass recovery during this final process.





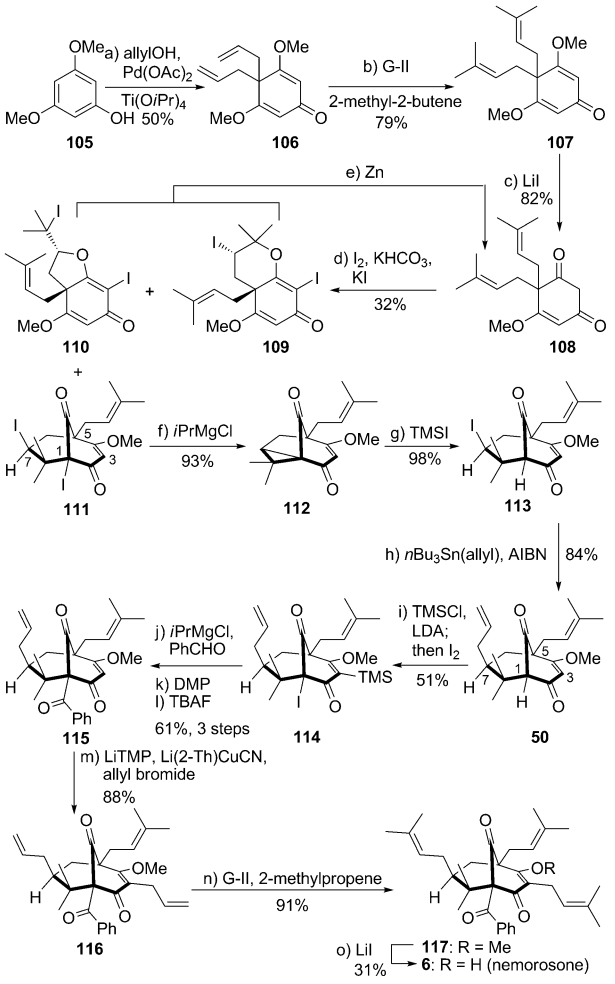
Scheme 11. Total syntheses of (±)-ialibinone A (**5**) and B (**102**), according to Simpkins and Weller (2010) and George et al., (2010), and total synthesis of hyperguinone B, according to George et al. (2010).[32a,34]

2.2.5. George's Total Synthesis of (±)-Ialibinone A and B and Hyperguinone B (2010)

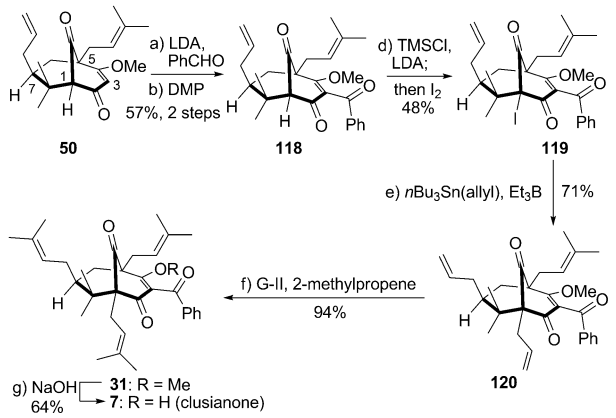
Independently, George et al. also reported an identical domino radical cyclization process, where $PhI(OAc)_2$ was used as the oxidant to afford ialibinones A (**5**) and B (**102**) in a superior yield (58%) as an approximately 1:1 diastereomeric mixture.[34] Interestingly, when TEMPO[35] was introduced to the reaction mixture, (±)-hyperguinone B (**104**)[36] was obtained in 73% yield as an approximately 3:1 mixture of enol tautomers, instead of the previously observed ialibinones A (**5**) and B (**102**). A 6π electrocyclization of the oxidized *o*-quinone methide **103** was put forward to account for this alternative reaction pathway. The selective formation of (±)-hyperguinone B (**104**) is noteworthy considering the presence of two prenyl substituents and three phenolic oxygen atoms (Scheme 11).

2.2.6. Danishefsky's Total Synthesis of (±)-Nemorosone and (±)-Clusianone (2007)

In parallel to early investigations towards clusianone (**7**) by Porco and co-workers, the Danishefsky research group devised a divergent synthetic strategy that ultimately enabled the total synthesis of both nemorosone (**6**) and clusianone (**7**, Schemes 12 and 13, respectively).[37] The common intermediate **50** that served as the branching point towards the two naturally occurring PPAPs was constructed by utilizing the allylative dearomatization and iodinative cyclization methods developed by the research group. In this context, 3,5-dimethoxyphenol (**105**) underwent a π-allylpalladium transformation in the presence of allyl alcohol, $Ti(OiPr)_4$, and $Pd(OAc)_2$ to afford the dearomatized doubly allylated product **106** in 50% yield.[38] Conversion of the two allyl substituents to the prenyl side chains took place smoothly under the influence of the second-generation Grubbs catalyst in the presence of 2-methyl-2-butene. The so-obtained doubly prenylated cyclohexadienone **107** was mono-demethylated with LiI and 2,4,6-collidine to afford cyclohexadione **108** in 65% yield over the two steps. With the stage set for the construction of the bicyclo[3.3.1] system, doubly prenylated dione **108** was subjected to iodinative cyclization to afford the desired bicycle **111** (32% yield), which was accompanied by fused bicyclic by-products **109** and **110** (29% and 24% yield, respectively). Fortunately, the two latter species could be



Scheme 12. Total synthesis of (±)-nemorosone (**6**), according to Danishefsky and co-workers (2007).[37]



Scheme 13. Total synthesis of (±)-clusianone (**7**), according to Danishefsky and co-workers (2007).[37]

conveniently recycled to cyclohexadione **108** under reductive conditions (Zn) in 78% yield (from **109**) and 87% yield (from **110**), respectively. Diiodide **111** was converted into monoiodide **113** through the intermediacy of cyclopropane **112** in a two-step operation that involved *i*PrMgBr and TMSI (91% overall yield). The iodo subsitutent in **113** facilitated the subsequent alkylation through a radical process with allyl tributyltin and AIBN that proceeded diastereoselectively in 84% yield.[39] The functionalization of bicycle **50** was studied in depth, particularly with respect to the alkylation at the C1- and C3-positions. A strategy that first led to the total synthesis of nemorosone (**6**) featured a novel TMSCl-mediated deprotonation of bicycle **50** followed by an oxidative quench with iodine, which afforded iodide **114** in 51% yield. Halogen–metal exchange of iodide **114** with *i*PrMgCl[40] followed by an electrophilic quench of the intermediate organomagnesium species with benzaldehyde and subsequent oxidation (DMP)[41] installed the C1-benzoyl group of nemorosone (**6**), where the so-obtained bicyclic TMS-silane was desilylated with TBAF to afford triketone **115** in 61% yield over the three steps. The introduction of the C3 substituent called for addition of the mixed higher order cuprate and concomittant alkylation with allyl bromide, thereby furnishing doubly allylated bicycle **116** in 88% yield. Conversion of the allyl side chains into the prenyl substituents proceeded smoothly through the action of the second-generation Grubbs catalyst and 2-methylpropene. Final demethylation of methyl ether **117** with LiI and 2,4,6-collidine completed the total synthesis of nemorosone (**6**).

The synthesis of clusianone (**7**) could also be accomplished starting from the bicyclic intermediate **50**. Benzoylation at the C3-position through the action of LDA-benzaldehyde followed by oxidation with DMP yielded **118** in 57% overall yield (Scheme 13). The reluctance of bicyclic intermediate **118** to undergo direct alkylation once again necessitated conversion into its iodide derivative **119** (LDA, TMSCl, I_2), which subsequently underwent radical alkylation (allyl tributyltin, Et_3B) to furnish the C1-allylated compound **120** in 34% yield from **118**. The application of a double olefin cross-metathesis once again proved highly effective to install the two prenyl substituents (94% yield). The so-obtained compound **31** underwent a final demethylation under less drastic conditions than those used for the synthesis of nemorosone (**6**) (aq NaOH, 64% yield) to complete the total synthesis of clusianone (**7**).

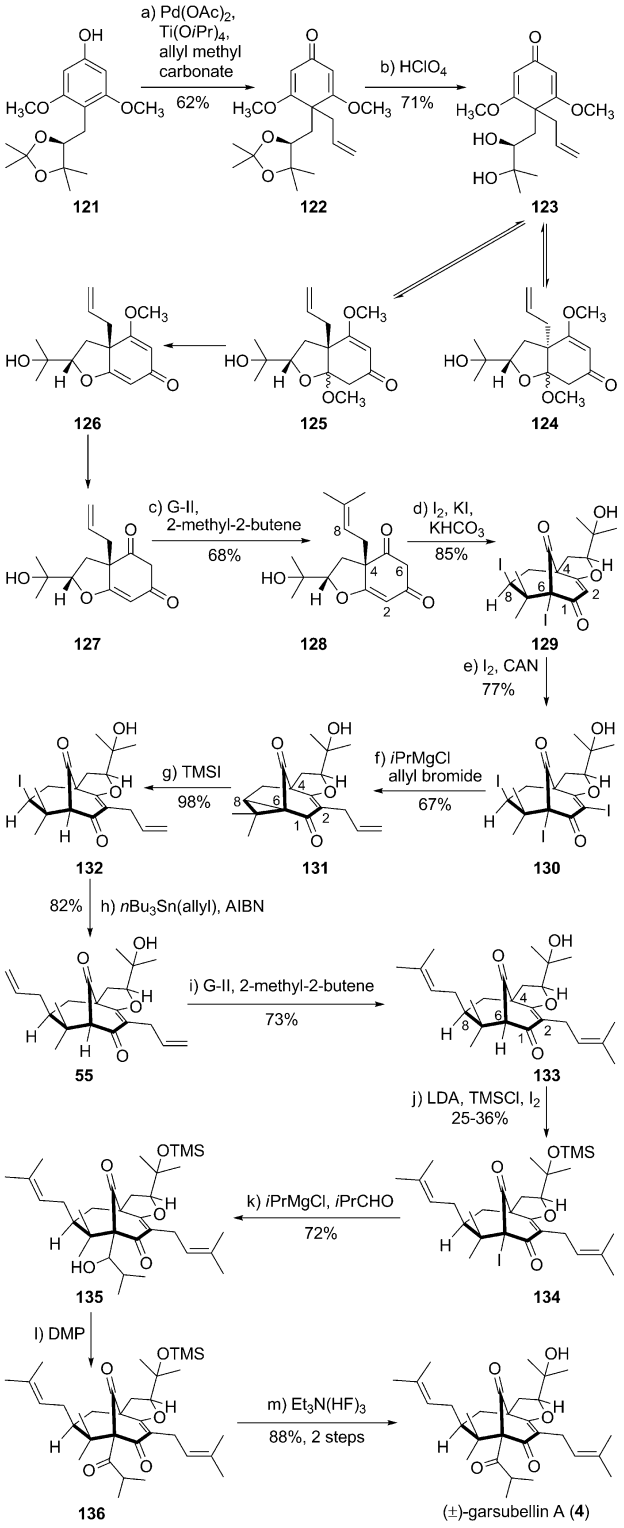
2.2.7. Danishefsky's Total Synthesis of (±)-Garsubellin (2006)

The total synthesis of garsubellin A (**4**) reported by the Danishefsky research group is both elegant and instructive (Scheme 14).[42] In this approach, the readily accessible substituted phloroglucinol **121** underwent π-allylpalladium-mediated dearomatization in the presence of allyl carbonate, $Ti(OiPr)_4$, and $Pd(OAc)_2$ to afford cyclohexadienone **122** in 62% yield. Construction of the THF substructure in garsubellin A (**4**) was effected upon removal of the acetonide moiety in **122** under acidic conditions. A series of equilibrium species (**123**–**125**) ultimately funneled the reaction pathway to the bicyclic dienone **126**, and subsequently to the demethylated diketone **127** in 71% yield. The allyl substituent of **127** was then converted into the prenyl group through olefin cross-metathesis (second-generation Grubbs catalyst, 2-methyl-2-butene). The terminal methyl groups of the prenyl functionality faithfully translated to the *gem*-dimethyl substituent on the bicyclic scaffold of garsubellin A (**4**) through iodinative cyclization of the prenylated diketone **128** (85% yield). Further oxidative iodination of **129** under the influence of I_2 and CAN introduced an additional iodine residue at the C2-position, which facilitated alkylation at this position through halogen–metal exchange, transmetalation, and an electrophilic quench with allyl bromide. This C2-allylation of **130** took place with the concomitant formation of an intermediate cyclopropane **131** (67% yield). Treatment of **131** with TMSI restored the bicyclo[3.3.1] system with the introduction of an iodine residue in readiness for further synthetic elaboration. Indeed, iodide **132** underwent radical allylation with AIBN and allyl tributyltin diastereoselectively in 82% yield. The so-obtained doubly allylated adduct **55** was then readily converted into its prenyl derivative **133** through olefin cross-metathesis. At this juncture, introduction of the isopropyl carbonyl side chain at the C6-position of garsubellin A (**4**) was the remaining hurdle that separated compound **133** from the target molecule. This final objective necessitated the preparation of the iodide intermediate **134** by using LDA, TMSCl, and I_2, followed by subsequent halogen–metal exchange and an electrophilic quench with isobutyraldehyde to afford alcohol **135** (18–26% yield over two steps). Finally, oxidation of **135** with DMP and desilylation with $Et_3N(HF)_3$ furnished the natural product in 88% overall yield from **135**.

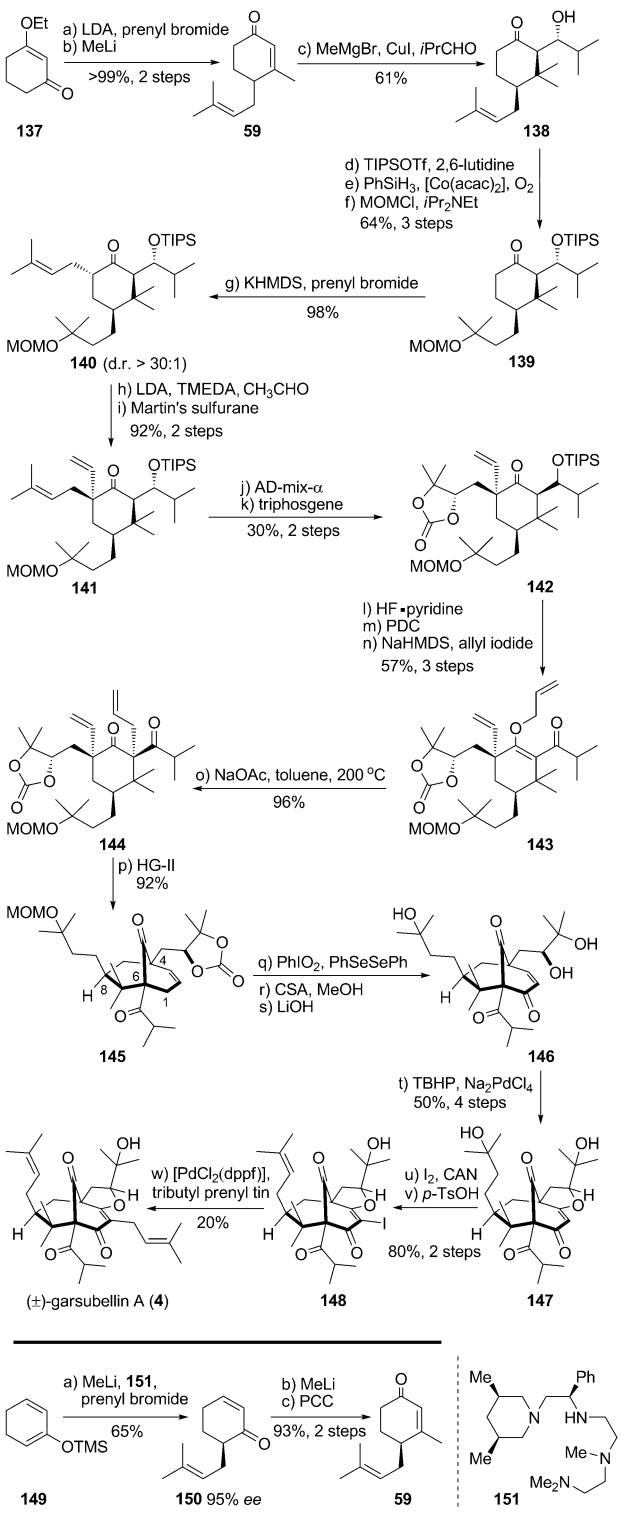
2.3. Shibasaki's Total Syntheses

2.3.1. Total Synthesis of (±)-Garsubellin A (2005)

In 2005, after a series of preliminary studies[43] that revealed valuable insight concerning the feasibility and stereochemical control in the construction of the bicyclo-[3.3.1] core structure and the THF motif, Shibasaki and co-workers reported the first total synthesis of (±)-garsubellin A (**4**; Scheme 15).[44] Their successful synthetic route com-



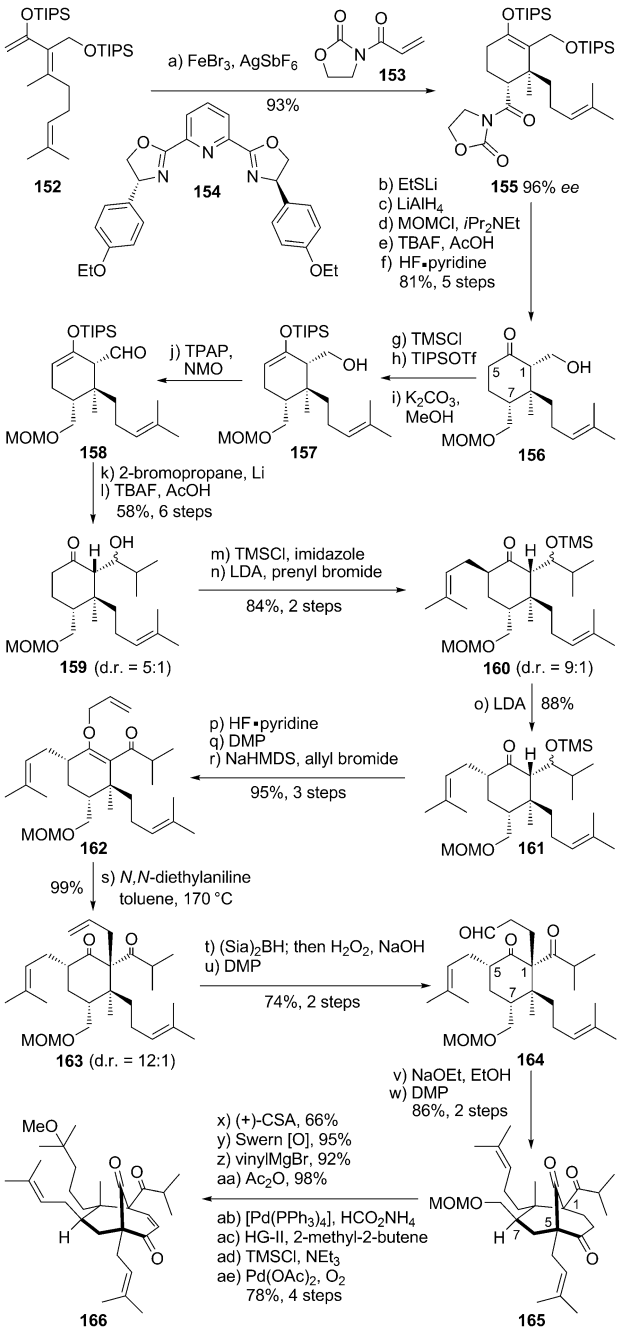
Scheme 14. Total synthesis of (±)-garsubellin A (**4**), according to Siegel and Danishefsky (2006).[42]



Scheme 15. The total synthesis of (±)-garsubellin A (**4**) and the approach towards an asymmetric version, according to Shibasaki and co-workers (2005).[44]

menced from cyclohexadione derivative **137**, which underwent α-prenylation and MeLi-mediated 1,2-addition to afford cyclohexenone **59** in quantitative yield over the two steps. 1,4-Addition to enone **59** through the action of methyl cuprate, followed by in situ interception of the intermediate magnesium enolate with isobutyraldehyde gave the *anti*-aldol product **138** in 61% yield. A series of functional group interconversions were carried out in preparation for the second prenylation event, namely, silylation of alcohol **138** and alkene hydration with $PhSiH_3$, $[Co(acac)_2]$, and O_2

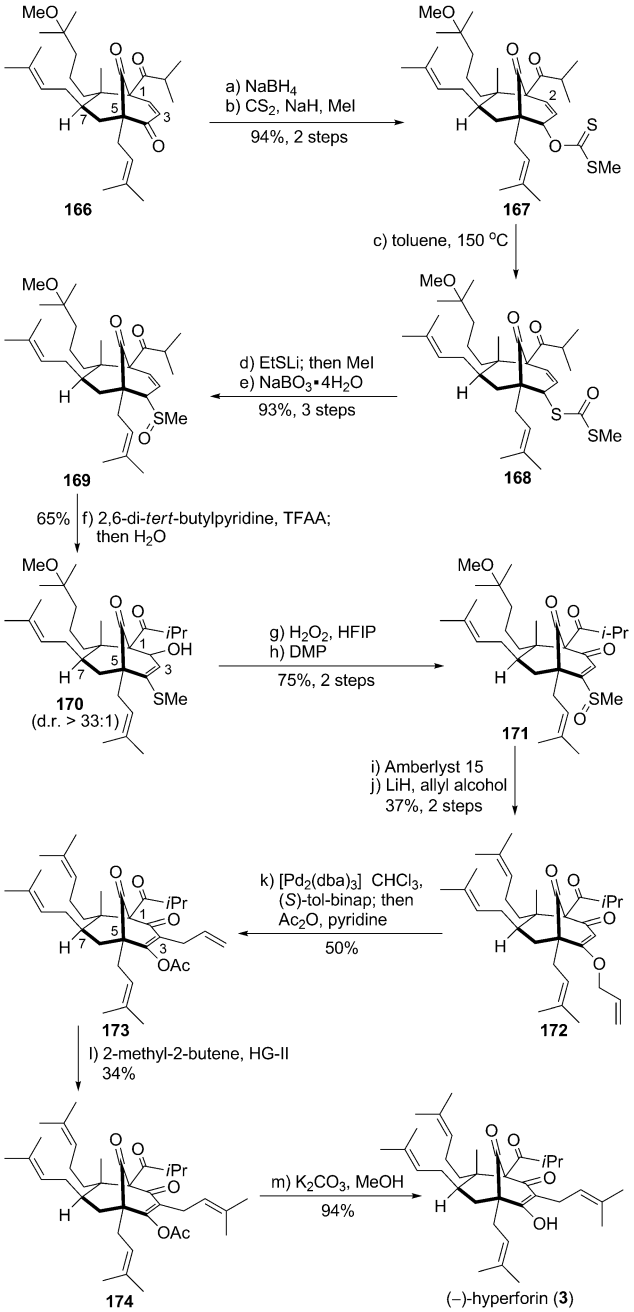
followed by MOM protection of the resulting tertiary alcohol (64% yield, three steps). Prenylation of ketone **139** took place with high levels of diastereoselectivity (>30:1) and efficiency (98% yield) to afford ketone **140**. The less sterically hindered α position of ketone **140** participated in a second aldol reaction with acetaldehyde under the influence of LDA-TMEDA to afford, upon dehydration of the secondary alcohol intermediate with Martin's sulfurane,[45] α-vinyl ketone **141** in 92% overall yield. The two olefins in **141** were differentiated through Sharpless dihydroxylation[46] (d.r. = 1:1) followed by formation of a cyclic carbonate with triphosgene (30% yield over two steps), where the former process also served to oxidize the prenyl olefin for the formation of the THF ring later in the synthesis. The method originally developed by the Shibasaki research group for the construction of the bicyclo[3.3.1] core involved an intramolecular aldol reaction,[43c] but this was found to be unsuitable for the real system, thereby necessitating the development of an alternative strategy. In this context, conversion of TIPS ether **142** into allyl enol ether **143** proceeded uneventfully (HF·pyridine, PDC, NaHMDS-allyl iodide; 57% over the three steps), with **143** undergoing a thermally induced Claisen rearrangement to furnish diene **144** in 96% yield.[8] With the stage set for the construction of the bicyclo[3.3.1] system through ring-closing olefin metathesis,[47] diene **144** was smoothly converted into bridged bicycle **145** in 92% yield in the presence of the Hoveyda–Grubbs catalyst.[48] Formation of the THF ring within garsubellin A (**4**) was achieved through an intramolecular Wacker-type oxidative cyclization,[49] where the precursor **146** was prepared from alkene **145** through allylic oxidation with $(PhSe)_2$ and $PhIO_2$, liberation of the MOM-protected tertiary alcohol, and hydrolysis of the cyclic carbonate. Indeed, oxidative cyclization of dihydroxyenone **146** proceeded smoothly under palladium catalysis (50% yield over the four steps), which was followed by iodination and acid-promoted dehydration to restore the prenyl group (80% yield over the two steps). Finally, attachment of the remaining prenyl group by Stille coupling completed the total synthesis of garsubellin A (**4**). The Shibasaki research group further demonstrated that enantiomerically enriched cyclohexenone **59** could be prepared using the asymmetric alkylation method developed by Koga and co-workers, thus paving the way for an asymmetric synthesis of garsubellin A (**4**).[50]



Scheme 16. Synthesis of intermediate **166** in the total synthesis of (−)-hyperforin (**3**), according to Shibasaki and co-workers (2010).[52]

2.3.2. *Total Synthesis of (−)-Hyperforin (2010)*

Of all the synthetic advances made in the PPAP field, the asymmetric total synthesis of hyperforin (**3**),[51] reported by the Shibasaki research group in 2010, nearly 30 years after its initial isolation, stands as the most recognizable achievement (Schemes 16 and 17).[52] This study elegantly highlighted the state-of-the-art methods in asymmetric catalysis, and illustrated ingenious solutions to address the challenging carbon framework and functionalities displayed by this historical target. Their synthesis began with an asymmetric Diels–Alder reaction between TIPS enol ether **152** (diene) and the oxazolidinone acrylamide derivative **153** (dienophile), promoted by cationic iron–pybox complex **154**, to afford substituted cyclohexane **155** in excellent yield and isomeric purity (96% *ee*, d.r. > 33:1).[53] This reaction, pioneered by the Shibasaki research group, which simultaneously installed the two neighboring quaternary and tertiary centers with high structural and stereochemical fidelity, also proved to be highly effective on a 20 g scale (average 89% *ee*). A series of functional and protecting group manipulations on substituted cyclohexane **155** afforded β-hydroxy ketone **156** as a mixture of diastereoisomers epimeric at C1 (ca. 1:1). Both C1 epimers of ketone **156** underwent the subsequent transformation with comparable efficiency. The synthesis and following discus-



Scheme 17. Total synthesis of (−)-hyperforin (**3**), according to Shibasaki and co-workers (2010).[52]

sions are thus limited to diastereoisomer **156**. The reluctance of hydroxy ketone **156** to undergo direct oxidation (to afford the corresponding keto aldehyde) and subsequent introduction of the isopropyl group necessitated the protection of the ketone moiety in **156** as its TIPS enol ether. The so-obtained alcohol **157** was then oxidized with TPAP and NMO[54] and treated with isopropyllithium to afford β-hydroxy ketone **159** (d.r. = ca. 5:1) upon desilylation. Despite the lengthy synthetic sequence that merely introduced an additional isopropyl group, this six-step transformation of **156** to **159** proceeded with remarkable efficiency and in 58% overall yield. Prenylation of the TMS ether derived from **159** (94% yield) proceeded smoothly and diastereoselectively under the influence of LDA, HMPA, and prenyl bromide to furnish **160** in 89% yield as an enriched 9:1 mixture of C10 epimers.

The collective experience from the earlier PPAP syntheses by the Shibasaki research group led to the use of an intramolecular aldol reaction to forge the bicyclo[3.3.1] core of hyperforin (**3**). The intramolecular aldol precursor **164**, which contained the C1 quaternary center, was prepared by a Claisen rearrangement;[8] model studies suggested the stereochemical outcome of this process depends heavily on the stereochemistry of the C5-prenyl group.[43] As such, epimerization of α-prenyl ketone **160** with LDA and an aqueous NH_4Cl quench was carried out (d.r. > 33:1), and the resulting substituted cyclohexanone **161** was converted into allyl enol ether **162** through desilylation (HF·Py), oxidation (DMP, 96% yield over the two steps), and O-allylation with NaHMDS and allyl bromide (> 99% yield). Allyl enol ether **162** underwent the anticipated Claisen rearrangement with remarkable efficiency (> 99% yield) and high diastereoselectivity (d.r. = ca. 12:1), with the inclusion of *N*,*N*-diethylaniline as an acid scavenger being crucial. Chemoselective hydroboration of the terminal olefin of **163** with $(Sia)_2BH$ and H_2O_2 (81% yield) followed by oxidation with DMP to aldehyde **164** (91% yield) set the stage for the intramolecular aldol reaction, which proceeded uneventfully in the presence of NaOEt. The resulting aldol product was then oxidized to generate ketone **165** (DMP) in 86% overall yield. Triketone **165** was further elaborated with additional functionalities found in hyperforin (**3**), as well as with reactive handles that enabled further synthetic manipulations. As such, intermediate **166**, which contained the two prenyl substituents (installed through π-allylpalladium chemistry[20,22] followed by olefin cross-metathesis) and the enone motif (by a palladium enolate oxidation)[55] was readily prepared.

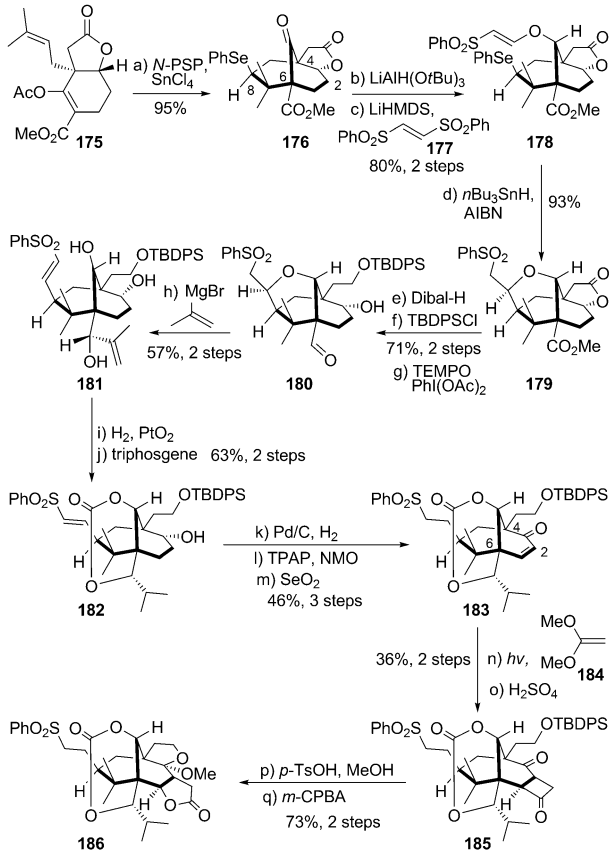
The seemingly simple operation to convert the enone moiety in **166** into the corresponding enolizable 1,3-diketone, in fact, proved to be the most challenging task in the synthesis of hyperforin (**3**) by Shibasaki and co-workers (Scheme 17). A variety of inter- and intramolecular strategies met with little success. Ultimately, a solution was realized through the application of a vinylogous Pummerer rearrangement.[56] Enone **166** was converted into xanthate **167** with the view to functionalize C2 through a [3,3] sigmatropic rearrangement, but dithioate **168** was unexpectedly produced through a [1,3] sigmatropic rearrangement.[57] Its hydrolysis followed by methylation with MeI and oxidation provided allylic sulfoxide **169**, which was set for the key transformation. Under their optimized conditions and using the bulky base 2,6-di-*tert*-butylpyridine, a vinylogous Pummerer rearrangement of allylic sulfoxide **169** took place preferentially to the normal Pummerer rearrangement (4:1) and smoothly provided allylic alcohol **170** in 65% yield. Subsequent sequential oxidations with H_2O_2 and then DMP (75% overall yield) gave enone sulfoxide **171**. Introduction of the remaining C3-prenyl substituent of the hyperforin (**3**) scaffold took advantage of a Claisen rearrangement of allyl enol ether **172**, which was prepared from **171** through an addition/elimination process. A palladium-promoted Claisen rearrangement of **172** presumably proceeded through the intermediacy of a π-allylpal-

ladium species, with the resulting enolizable 1,3-diketone temporarily masked as its enol acetate **173** (Ac_2O, py; 50% yield). The allyl side chain of **173** was converted into the corresponding prenyl group through olefin cross-metathesis, and the 1,3-diketone was unveiled upon deacetylation with K_2CO_3 in MeOH to realize the first total synthesis of (−)-hyperforin (**3**), the antipode of the naturally occurring substance, as confirmed by optical rotation measurements.

3. Miscellaneous Synthetic Strategies towards the Bicyclo[3.3.1]nonane Skeleton of the PPAPs

3.1. Nicolaou's Selenium-Mediated Cyclization

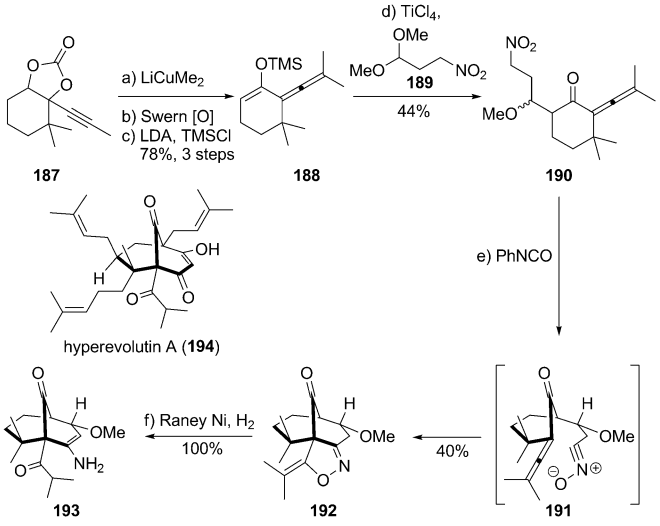
Nicolaou et al. had already demonstrated a synthetic approach to access the highly functionalized [3.3.1] core structure of garsubellin A as early as 1999 (Scheme 18).[58] In this approach, treatment of enol acetate **175** with *N*-(phenylseleno)phthalimide) (*N*-PSP) and $SnCl_4$ cleanly afforded bicycle **176** in 95% yield. This remarkable process, which simutaneously generated two neighboring quaternary centers through a *6-endo* cyclization also conveniently installed a selenyl residue in readiness for further synthetic transformations. Reduction of the ketone functionality within bicycle **176** by using $LiAlH(OtBu)_3$ followed by treatment of the resulting secondary alcohol with **177** afforded alkenyl sulfone intermediate **178**, which was poised for functionalization of its C8-position through an intramolecular radical cyclization. Indeed, the anticipated carbon–carbon bond formation took place smoothly on treatment of selenide **178** with nBu_3SnH and AIBN at elevated temperature to give tetracyclic sulfone **179** in 93% yield. Next, adjustments of the oxidation state and protecting groups permitted the introduction of an isopropenyl moiety through Grignard addition to the intermediate aldehyde **180**, which also induced a retro-hetero-Michael reaction of the β-alkoxy sulfone functionality to furnish bicyclic alkenyl sulfone **181**. Further synthetic transformations from bicyclic sulfone **181** installed a cyclic carbonate and an enone moiety, introduced through a SeO_2-mediated oxidation, to yield **183**. A novel strategy involving a photochemical [2+2] cycloaddition of enone **183** with 1,1-dimethoxyethylene followed by an acidic quench was then employed for the C1/C2 functionalization, which furnished cyclobutanone **185** in 36% overall yield. To conclude this study, exposure of **185** to acidic methanolysis conditions followed by Baeyer–Villiger oxidation delivered tetracyclic lactone **186** in 73% overall yield, an intermediate that constituted a highly advanced core structure of garsubellin A (**4**).



Scheme 18. Synthesis of the core of garsubellin A (**4**) by a selenium-mediated cyclization, according to Nicolaou et al. (1999).[58a]

3.2. Young's Intramolecular Allene–Nitrile Oxide Cycloaddition

In their efforts towards the total synthesis of hyperevolutin A (**194**),[59] Young and Zeng demonstrated a novel entry to the bicyclo[3.3.1] core structure of the PPAPs by exploiting an allene–nitrile oxide cycloaddition reaction as the key step (Scheme 19).[60] Treatment of carbonate **187** with Gilman's reagent[61] followed by Swern oxidation[62] furnished the corresponding ketone, which was converted into its TMS enol ether derivative (**188**) through the combined action of LDA and TMSCl (78% overall yield from **187**). A Mukaiyama aldol reaction of **188** with dimethyl acetal **189**

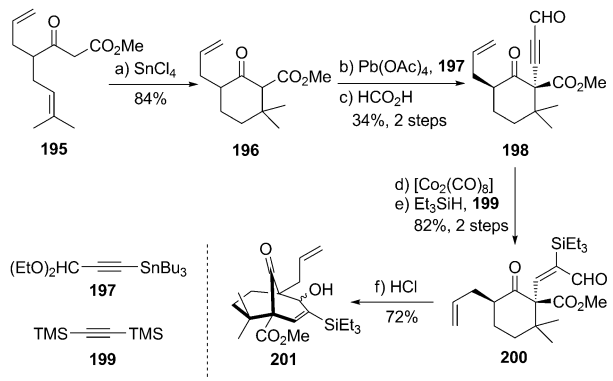


Scheme 19. Synthesis of the PPAP core by an intramolecular allene-nitrile oxide cycloaddition, according to Young and Zeng (2002).[60a]

delivered nitroallene **190** in 44% yield (ca. 1:1 mixture of diastereomers).[63] Exposure of **190** to phenyl isocyanate generated the 1,3-dipole **191** as a transient species that participated in the proposed intramolecular [3+2] cycloaddition with the proximal allene moiety to afford isoxazoline **192** in 40% yield.[64] Finally, reductive cleavage of isoxazoline **192** with Raney nickel and H_2 provided the bicyclo[3.3.1] system **193** and concomitantly unveiled the bridgehead isopropyl ketone.

3.3. Grossman's Alkynylation/Aldol Strategy

In the synthetic studies towards the PPAPs reported by Ciochina and Grossman, the construction of the bicyclo[3.3.1] system was realized through a strategy that is synthetically equivalent to attaching *cis*-β-chloroacrolein to the C2- and C6-positions of cyclohexanone (Scheme 20).[65] Thus, cyclohexanone **196** was prepared from β-keto ester **195** through

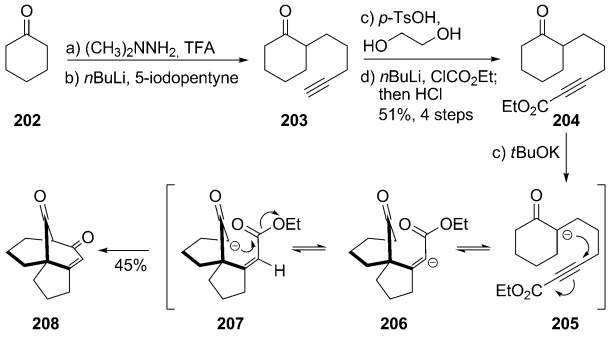


Scheme 20. Synthesis of the PPAP core by an alkynylation/aldol strategy, according to Ciochina and Grossman (2003).[65]

a 6-*endo* cyclization in the presence of the Lewis acid $SnCl_4$ (84% yield).[66] Carbon–carbon bond formation at the C2-position of β-keto ester **196** was achieved with a $Pb(OAc)_4$-mediated alkynylation reaction with alkynyl stannane **197**.[67] Removal of acetal from the coupling product with HCO_2H then afforded alkynyl aldehyde **198** in 34% yield over the two steps. In preparation for the ring-closing event to forge the bicyclo[3.3.1] system, selective partial reduction of the alkynyl moiety of **198** was required, which necessitated extra precautions because of the presence of the unprotected terminal olefin. Eventually, a *syn*-hydrosilylation through the $[Co_2(CO)_6]$ complex of alkyne **198** was achieved in 82% yield (from **198**) with complete regio- and stereoselectivity.[68] An intramolecular aldol reaction of alkenyl enal **200** proceeded smoothly to afford **201** as a diastereomeric mixture of alcohols, thus completing the targeted [3.3.1] core structure of the PPAPs together with the two bridgehead quaternary centers.

3.4. Miesch's Intramolecular Conjugate Addition/Dieckmann Cyclization Cascade

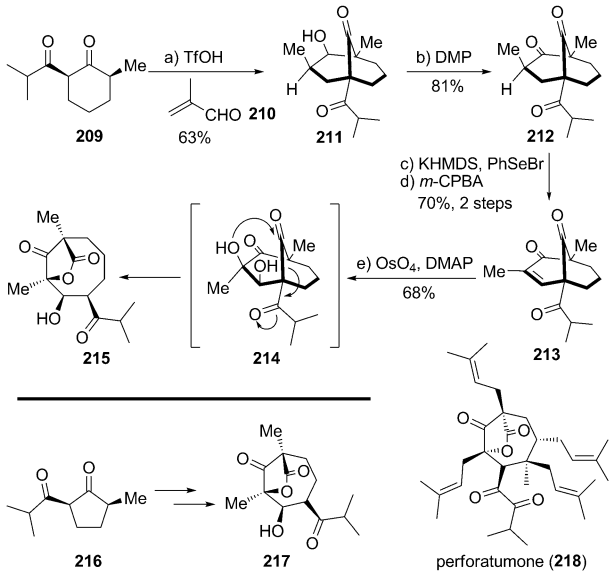
During the course of a study on the reactivity profile of acetylenic ω-ketoesters under basic conditions, Klein and Miesch uncovered that, depending on the base employed and the length of the pendent alkynyl side chain, a variety of polycyclic structures could be obtained through a cascade sequence (Scheme 21).[69] Treatment of cyclohexanone **204** with *t*BuOK led to the formation of tricyclic keto enone **208** (45% yield), which harbored the PPAP core framework. Mechanistically, this multistep cascade reaction was presumably initiated through the intramolecular 1,4-addition of the carbanion in **205** onto its pendent alkynyl ester side chain. The resulting anionic spirocyclic enoate **206** then underwent internal proton transfer to form *Z* alkene **207**, whose anionic charge allowed its participation in a Dieckmann process in the final ring-closing event.



Scheme 21. Synthesis of the PPAP core by an intramolecular conjugate addition to the acetylenic ester followed by a Dieckmann cyclization cascade, according to Klein and Miesch (2003).[69]

3.5. Nicolaou's Michael Addition/Aldol/Oxidation Approach towards Perforatumone A

Nicolaou et al. successfully designed and executed an interesting strategy to access a variety of naturally occurring or designed bridged polycyclic systems, for example, those represented by hyperforin (**3**) and perforatumone (**218**, Scheme 22).[70] Their developed synthetic sequence originated from simple cyclic ketones that underwent a series of carbon–carbon bond-forming and -breaking reactions to afford the targeted polycyclic skeleton in a highly stereoselective manner. For example, diketone **209** underwent a TfOH-promoted sequential Michael addition and intramolecular aldol reaction with methacrolein to afford bicyclic hydroxy diketone **211** (63% yield), which possesses the bicyclo[3.3.1] motif present in a diverse array of PPAPs. Oxidation of alcohol **211** with DMP (81% yield) followed by a site-selective introduction of unsaturation (KHMDS, PhSeBr; *m*-CPBA), set the stage for the second key reaction. Indeed, OsO_4-mediated dihydroxylation of enone **213** in the presence of DMAP triggered a facile bond-rearrangement sequence, as depicted in structure **214**, and ultimately led to the bicyclic lactone **215** in 68% yield. However, bicyclic lactone **215**



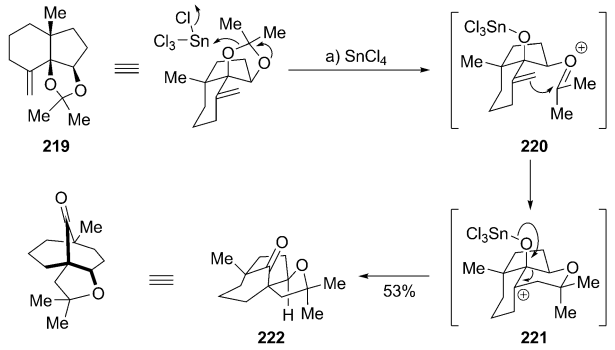
Scheme 22. Synthesis of the core of perforatumone A (**218**) by a Michael addition/aldol/oxidation strategy according to Nicolaou et al. (2005).[70a]

contains one additional carbon atom compared to the perforatumone core structure. Thus, the developed synthetic sequence was applied to cyclopentanone derivative **216**, which proceeded uneventfully to afford the bicyclic diketolactone **217**.

3.6. Barriault's Cationic Cyclization Cascade

During their studies towards the synthesis of highly functionalized bicyclo[*m.n.*1] alkanones, Arns and Barriault ingeniously devised and successfully implemented a Lewis acid mediated triple domino reaction that involved a Diels–Alder/Prins/pinacol cascade.[71] This process enabled the preparation of a variety of bridged polycyclic structures closely resembling the core structures of a number of natural products (Scheme 23).[72]

In particular, treatment of the 5,6-bicyclic alkenylketal **219** with $SnCl_4$ smoothly delivered bridged tricyclic ketone

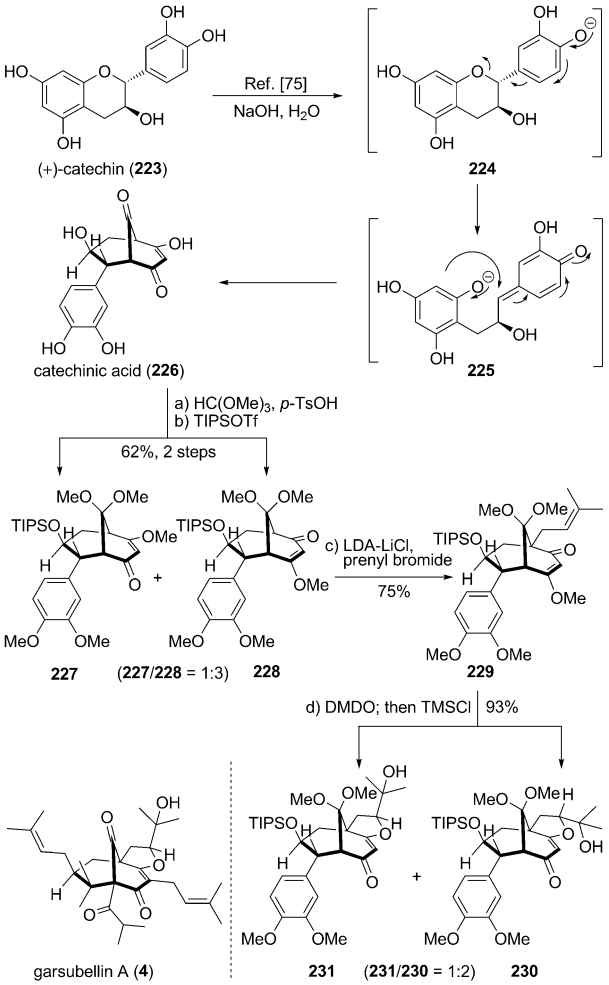


Scheme 23. Synthesis of the PPAP core by a cationic cyclization cascade according to Barriault and co-workers (2005).[72]

222 in 53% yield. The research group proposed a pathway that involved the generation of oxonium species **220**, followed by an intramolecular Prins cyclization and finally a pinacol rearrangement of the cationic intermediate to afford the targeted [3.3.1]nonane system.[73] This highly ingenious approach, which simultaneously furnished three rings and two bridgehead quaternary centers in **222** from a synthetically readily accessible 5,6-bicycle **219**, is particularly noteworthy.

3.7. Simpkins' Chiral Pool Approach from (+)-Catechin

In a conceptually contrasting approach to their strategies based on Effenberger annulation, Simpkins and co-workers used a base-mediated rearrangement of (+)-catechin (**223**) to provide a novel entry to the bicyclo[3.3.1] system of the PPAPs (Scheme 24).[74] First discovered by Sears et al. nearly 40 years ago,[75] the conversion of (+)-catechin (**223**) into catechinic acid (**226**) under the influence of aqueous NaOH, presumably through the intermediacy of **224** and **225**, was a remarkable transformation that remained underexplored by the synthetic community. With the bicyclo[3.3.1] scaffold

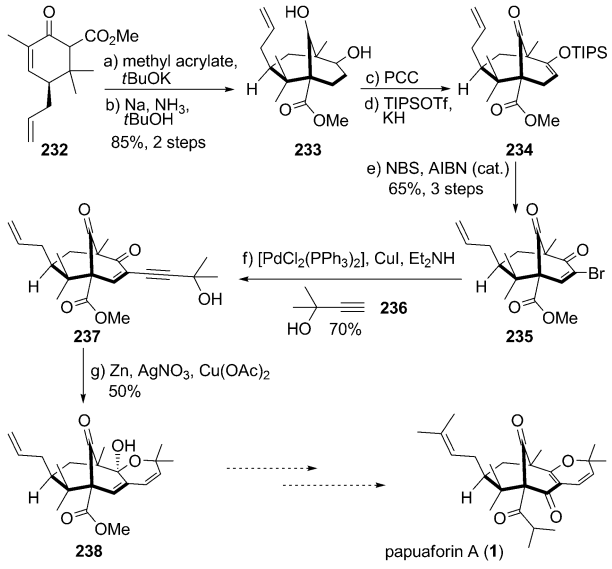


Scheme 24. Synthesis of the PPAP core by a base-mediated rearrangement from (+)-catechin (**223**), according to Simpkins and co-workers (2007).[74]

conveniently secured, methylation of catechinic acid (**226**) under acidic conditions ($HC(OMe)_3$, TsOH) occurred with concomitant formation of a dimethylketal. A subsequent silylation with TIPSOTf afforded a separable mixture of methyl ethers **227** and **228** in 62% overall yield (**227**/**228** ca. 1:3). Bridgehead alkylation of methyl ether **228** was not straightforward, and a practical solution was ultimately established through deprotonation with LDA-LiCl followed by an external quench with prenyl bromide to furnish the alkylation product **229** in 75% yield. In view of their synthetic investigations towards garsubellin (**4**), the THF moiety was installed through treatment of **229** with DMDO, followed by subjecting the crude epoxide to TMSCl to afford a mixture of **230** and **231** (ca. 2:1) in 93% combined yield.

3.8. Kraus' Michael Addition/Birch Reduction/Cyclization Approach towards Papuaforin A

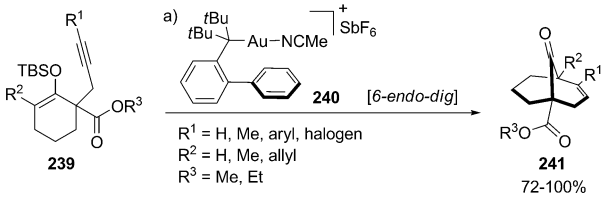
Papuaforin A (**1**) is a 2*H*-pyran-containing PPAP which exhibits moderate cytotoxic activity towards the KB cell line and modest antibacterial activity against *Micrococus luteus*, *Staphylococus epidermidis*, and *Bacillus cereus*.[36] In the study of the total synthesis of papuaforin A (**1**) by Kraus and co-workers, the construction of the bicyclo[3.3.1] system featured a Michael addition of cyclohexenone derivative **232** to methyl acrylate, followed by a Birch reduction/cyclization[76] to deliver diol **233** in 85% yield over two steps (Scheme 25).[77] In preparation for the formation of the 2*H*-pyran moiety, diol **233** was oxidized to the corresponding diketone, and was subsequently converted into TIPS silyl enol ether **234** under the action of KH and TIPSOTf. For the introduction of the necessary functional group for the construction of the 2*H*-pyran motif, substrate-dependent bromination of TIPS enol ether **234** and its relatives was studied in depth, under both thermal and photolytic conditions. Ultimately, treatment of TIPS enol ether **234** with NBS/AIBN at elevated temperature afforded α-bromoenone **235** in 75% yield. The successful Sonogashira reaction between bromide **235** and propargyl alcohol **236** required the use of diethylamine as the solvent. The so-obtained cross-coupling product **237** underwent partial and stereoselective reduction of its alkyne moiety in the presenec of Zn, $AgNO_3$, and $Cu(OAc)_2$[78] to afford pyran hemiketal **238** (35% yield over two steps), which is a valuable intermediate in the synthesis of papuaforin A (**1**).



Scheme 25. Synthesis of the core of papuaforin A (**1**) by a Michael addition/Birch reduction/cyclization strategy, according to Kraus and Jeon (2008).[77a]

3.9. Barriault's Gold-Catalyzed Cyclization

The recent advent of gold-catalyzed carbon–carbon bond-forming reactions[79] presented an enticing opportunity for the preparation of the polycyclic core structure of the PPAPs, and was first realized by Barriault and co-workers (Scheme 26).[80] After careful examination of the reaction conditions, a combination of catalyst **240** and acetone as the solvent was found to afford the best yields (72–100%) and selectivity for the 6-*endo-dig* cyclization product. This mild and efficient process, which generated the bicyclo[3.3.1] core structure of the PPAPs, demonstrated wide substituent tolerance, particularly in the cyclizations that led to bridged bicycles with two bridgehead quaternary centers.

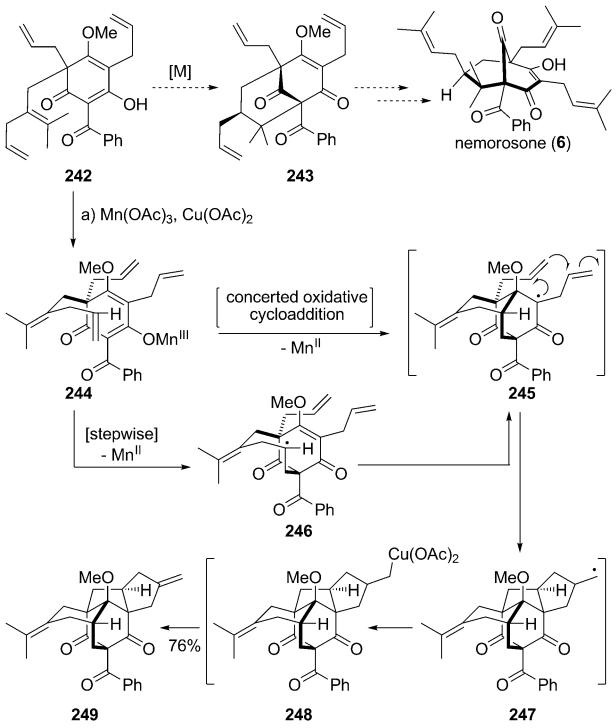


Scheme 26. Synthesis of the PPAP core by a gold-catalyzed *6-endo-dig* cyclization, according to Barriault and co-workers (2009).[80]

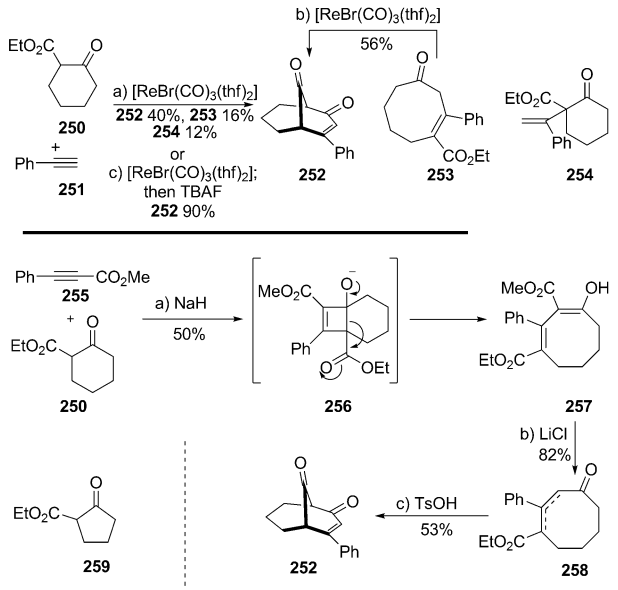
3.10. Porco's Radical Cyclization Cascade

Having successfully demonstrated their alkylative dearomatization/annulation strategy in the total synthesis of (±)-clusianone (**7**) and (+)-hyperibone K (**8**), the Porco research group was interested in developing a related strategy for the synthesis of nemorosone (**6**), an isomer of clusianone (**7**, Scheme 27).[81]

Their initial idea was based on an enolate/enol oxidation approach, where the dearomatized product **242** was expected to generate a radical upon treatment with a suitable metal ion, such as Mn^{III}, Cu^{II}, Fe^{III}, and Ce^{IV}, and then cyclize to afford intermediate **243** as a key synthetic precursor towards nemorosone (**6**). However, it was serendipitously discovered that, instead of the anticipated bicyclo[3.3.1] triketone **243**, a bridged pentacyclic compound **249** was isolated in 76% yield as the sole product. Two mechanistic proposals were put forward to rationalize this unexpected result. In the concerted pathway, an oxidative cycloaddition process could take place after formation of the manganese enolate **244** to generate the



Scheme 27. Synthesis of the PPAP core by a $Mn(OAc)_3/Cu(OAc)_2$-mediated cascade, according to Mitasev and Porco (2009).[81]



Scheme 28. Synthesis of the PPAP core from the reaction of alkynes with cyclic β-ketoesters, according to Kuninobu, Takai et al. (2009) as well as Dixon and co-workers (2011).[83,86]

radical species **245**, which could subsequently undergo sequential 5-*exo* cyclizations at its two pendent allyl side chains to afford the observed product **249**. Alternatively, stepwise radical cyclizations through the intermediacy of radical **246**, which could also converge to the identical radical species **245** and subsequently to the product **249**, cannot be excluded. Although not directly applicable in the context of PPAP synthesis, this method was further explored, and demonstrated broad substrate scope for accessing a variety of complex polycyclic framework.

3.11. Takai's Transannulation Strategy

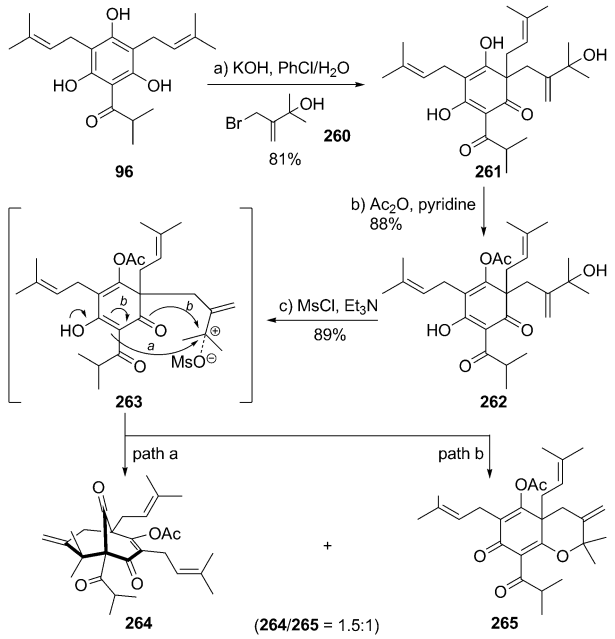
In a conceptually contrasting approach, the construction of the bicyclo[3.3.1] system through transannular cyclization of a macrocyclic precursor[82] to forge the carbonyl bridge was independently demonstrated by the research groups of Kuninobu and Takai as well as Dixon (Scheme 28).[83] Kuninobu, Takai, and co-workers discovered that treatment of a reaction mixture that contained cyclic β-keto ester **250** and terminal alkyne **251** with catalytic amounts of $[ReBr(CO)_3(thf)_2]$ led to bicyclo[3.3.1] keto enone **252** (40% yield) together with cyclooctanone **253** (16% yield) and α,α′-disubstituted β-keto ester **254** (12% yield). The reaction is believed to take place through the initial rhenium-mediated insertion of terminal alkyne **251** into β-keto ester **250**,[84] followed by tautomerization and subsequent transannular cyclization to afford bicycle **252**. Indeed, resubjecting cyclooctanone **253** to the same reaction conditions afforded bicycle **252** in 56% yield. The efficiency of this overall process could be greatly improved by treating the crude reaction mixture with TBAF, which led to the formation of bicycle **252** in 90% overall yield.

3.12. Dixon's Transannulation Strategy

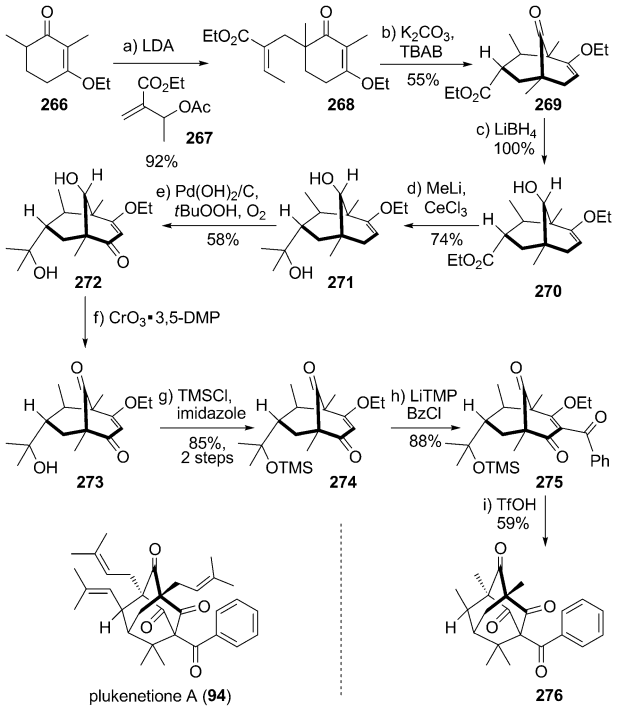
The synthesis of bicycle **252** by Dixon and co-workers originated from an unexpected discovery during their synthetic studies towards daphniyunnine D.[85] Cyclooctenone **258** was prepared through a set of optimized conditions that involved a formal [2+2] cycloaddition reaction between β-keto ester **250** and alkyne **255**, followed by a Grob-type fragmentation of the resulting bicyclic intermediate **256**, and decarboxylation of **257** (LiCl). Careful studies of the reaction conditions revealed that the transannular cyclization of keto ester **258** proceeded smoothly under acidic conditions to deliver the bicyclic keto enone **252** in 53% yield. It is noteworthy that this approach could also be readily applied to cyclopentanone derivative **259**, in stark contrast to the rhenium-mediated reaction reported by Kuninobu and Takai, which failed to take place with substrate **259** (Scheme 28).[86]

3.13. Couladouros' Biomimetic Dearomatization Approach towards Type A PPAPs

With a biomimetic approach towards the type A PPAPs in mind, Couladouros et al. reported an expedient synthesis of the highly functionalized bicyclic intermediate **264** through a strategy that closely resembles the pioneering approach by Porco and co-workers (Scheme 29).[87]



Scheme 29. Synthesis of the PPAP core by a C-alkylation and cation cyclization strategy, according to Couladouros et al. (2009).[87]



Scheme 30. Synthesis of the core of plukenetione (**94**) by a Michael addition/cyclization strategy, according to Takagi et al. (2008).[89]

An alkylative dearomatization/annulation reaction of acylphloroglucinol **96** with tertiary alcohol **260** was carried out under carefully controlled pH conditions to afford, after selective acetylation, the colupulone analogue **262** in 71% overall yield. While their initial attempts to cyclize intermediate **262** through an acid-induced generation of a carbocation proved unfruitful, conversion of tertiary alcohol **262** into the corresponding mesylate led to spontaneous formation of the bicyclo[3.3.1] structure **264** and the O-alkylation product **265** (ratio ca. 1.5:1) in 89% combined yield.

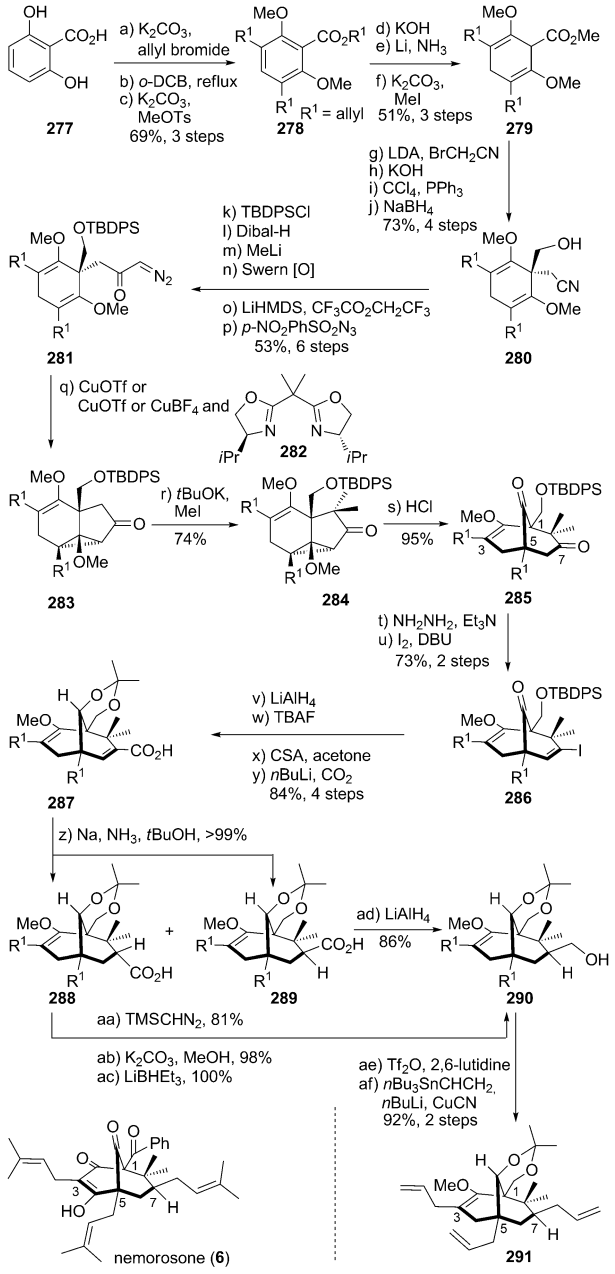
3.14. Takagi's Michael Addition/Cyclization Approach to Plukenetione

In the studies reported by Takagi et al. towards the construction of a highly functionalized adamantane core of plukenetione-type PPAPs,[88] a strategy that featured a sequential Michael addition followed by an acid-catalyzed intramolecular cyclization was successfully demonstrated (Scheme 30).[89] Their synthesis commenced with cyclohexenone derivative **266**, and its treatment with LDA followed by acrylate **267** afforded alkylation product **268** in 92% yield. Under the optimized reaction conditions, the second 1,4-addition took place intramolecularly upon treatment of **268** with K_2CO_3 and TBAB to furnish keto ester **269** in 55% yield. Conversion of the ethyl ester functionality in **269** necessitated temporary conversion of the ketone moiety into the corresponding secondary alcohol by using $LiBH_4$ (100% yield), and the resulting hydroxy ethyl ester **270** was exhaustively methylated with MeLi to give tertiary alcohol **271** (74% yield). Sequential oxidation of the dihydroxy enol ether **271** (first with $Pd(OH)_2/C$, *t*BuOOH, O_2 and then CrO_3·3,5-dimethylpyrazole) delivered keto enone **273** smoothly, and set the stage for the introduction of the benzoyl functionality required in plukenetione A (**94**).

Initial alkylation studies on the unmasked 1,3-diketone of **273**, or through an intramolecular hetero-Michael addition of the tertiary alcohol moiety in **273** and subsequent trapping with benzoyl chloride/cyanide both proved unfruitful, affording only trace amounts of the desired benzoylated product. Ultimately, a solution to this late-stage obstacle called for the temporary protection of the tertiary alcohol in **273**, whereby lithiation of the resulting TMS ether **274** with LiTMP followed by treatment with benzoyl chloride afforded triketone **275** in 88% yield. With the stage set for the assembly of the adamantane core of plukenetione A, the TMS-protected tertiary alcohol underwent ionization under the optimized reaction conditions upon treatment with TfOH, followed by subsequent intramolecular cyclization to afford adamantane **276** in 59% yield. The fully substituted and highly functionalized triketone adamantane **276** differs from plukenetione A (**94**) merely by the absence of the prenyl functionalities.

3.15. Nakada's Intramolecular Cyclopropanation Approach towards Nemorosone

Nakada and co-workers reported a series of studies that showcased a novel approach towards the core structure of the PPAPs. Their approach involved an ingenious intramolecular cyclopropanation reaction followed by regioselective cyclopropane opening promoted by a Lewis acid to furnish the bicyclo[3.3.1] system (Scheme 31).[90] The substrate scope and reaction conditions were examined systematically, and the



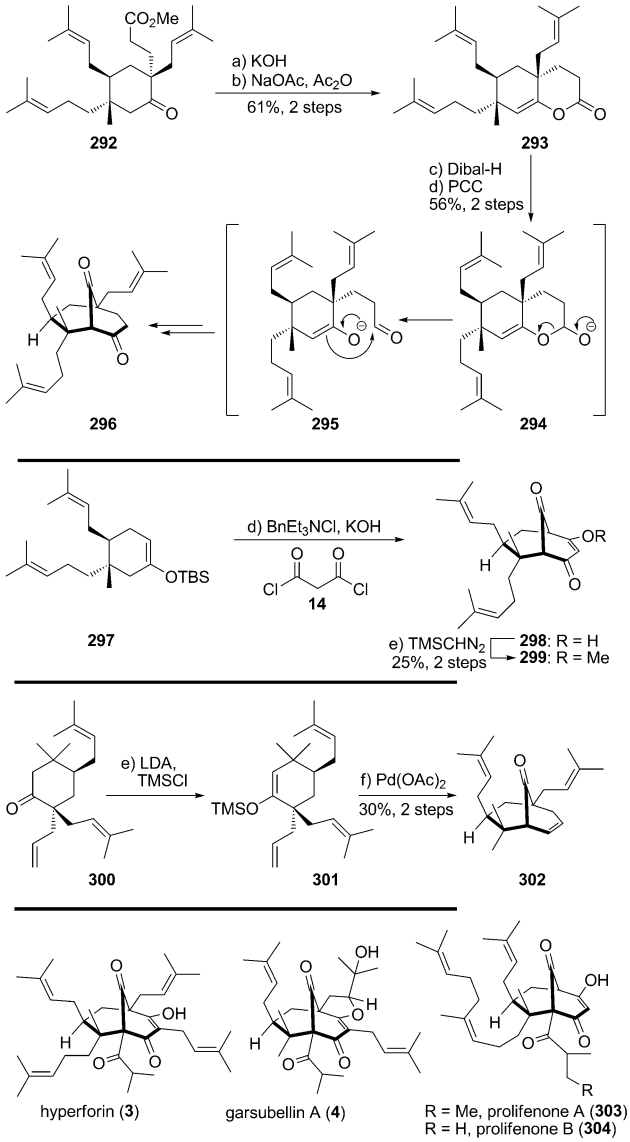
Scheme 31. Synthesis of the PPAP core by an intramolecular cyclopropanation strategy, according to Nakada and co-workers (2010).[90]

developed synthetic strategy also proved amenable to an asymmetric synthesis. In their most advanced study, they synthesized tricyclic acetonide **291**, a highly functionalized core structure with substitutions that resembled the global structure of the naturally occurring nemorosone (**6**). The synthesis of the intramolecular cyclopropanation precursor **281** commenced with the preparation of diallyl dimethoxy methyl ester **278** through O-allylation followed by double aryl Claisen rearrangement and O-methylation (69% overall yield from **277**). Hydrolysis of methyl ester **278** followed by Birch reduction of the resulting acid and another methylation afforded cyclohexadiene derivative **279** (51% yield over three steps), which was alkylated with LDA and $BrCH_2CN$ (81% yield). The methyl ester moiety was reduced to the corresponding primary alcohol through the intermediate acid chloride (90% overall yield). Cyclohexadiene **280** was elaborated to α-diazo ketone **281** in 53% overall yield through a six-step process that ended with a diazo transfer reaction.

The intramolecular cyclopropanation reaction of α-diazo ketone **281** proceeded smoothly in a remarkable 97% yield in the presence of CuOTf, wherein the resulting tricyclic ketone **283** was doubly methylated in 74% yield. Cleavage of the cyclopropane moiety in tricycle **284** upon treatment with HCl afforded bicycle **285** in 95% yield, in readiness for further synthetic operations to decorate its bicyclo[3.3.1] core structure. It is also noteworthy that, after an extensive study of reaction conditions, α-diazo ketone **281** was found to undergo asymmetric intramolecular cyclopropanation in the presence of bis(oxazoline) ligand **282** to afford tricyclic intermediate **283** with 80% *ee*. Introduction of the carbon side chain at C7 was achieved through sequential carbon homologations, first through lithiation of iodide **286** and reaction with carbon dioxide (where acid **288** could be epimerized through its corresponding methyl ester), and then with alcohol **290** through triflation and displacement with vinyllithium.

3.16. Mehta's Approaches towards the Core of the PPAPs

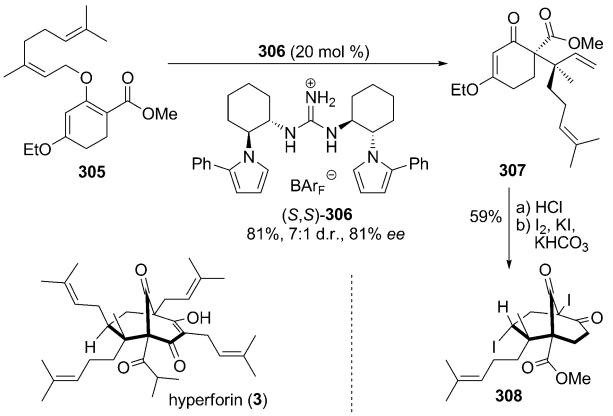
Mehta et al. have made seminal contributions to the synthetic studies towards several members of the PPAP family. Throughout the course of their studies, they have garnered a wealth of information associated with the stereoselective preparation of the substituted cyclohexanone building blocks, and have demonstrated the construction of the bicyclo[3.3.1] core structure of the PPAPs by a variety of strategies (Scheme 32). A key reaction that featured in a number of their synthetic campaigns was the "reconstructive aldol" reaction.[91] As an illustration of this approach, keto ester **292** was transformed to the corresponding fused bicyclic enol ester **293** in 61% overall yield. Reduction of lactone **293** with Dibal-H and subsequent oxidation with PCC afforded bicycle **296** in 56% overall yield. The reaction is believed to proceed through the intermediacy of lactol anion **294**, which would undergo retro-acetalization to afford aldehyde **295** with an internal enolate, followed by an intramolecular aldol reaction. In a separate study, similar to the findings of other research groups, Mehta et al. also demonstrated the feasibility of the Effenberger annulation (**297** to **299**, 25% yield over the two steps) in their synthetic work towards the total synthesis of prolifenones (**303** and **304**) and hyperforin (**3**).[92] Finally, the earlier studies towards an enantiospecific total synthesis of garsubellin A (**4**) by Mehta et al., commencing with α-pinene-derived cyclohexanone intermediate **300**, showcased the utility of transition-metal-mediated carbon–carbon bond formation. In the event, the TMS enol ether **301** underwent a Kende cyclization[93] to afford bicyclo[3.3.1] structure **302** in 30% yield over the two steps.[94]



Scheme 32. Approaches to the synthesis of the PPAP core, according to Mehta et al.[91,92,94]

3.17. Jacobsen's Catalytic Enantioselective Claisen Rearrangement

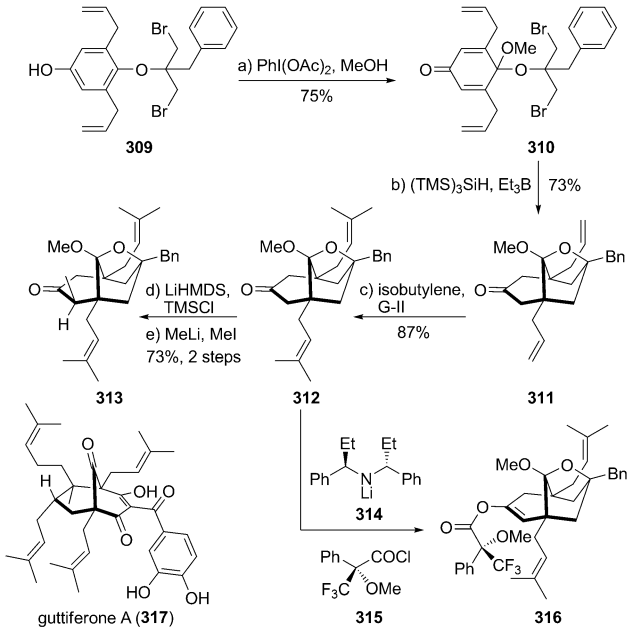
Jacobsen and co-workers reported the synthesis of an optically active bicyclo[3.3.1] system that featured their recently developed catalytic enantioselective Claisen rearrangement of *O*-allyl β-ketoesters (Scheme 33).[95] In their preliminary studies, they demonstrated the Claisen rearrangement of a variety of substituted allyl vinyl ether substrates catalyzed by achiral guanidinium tetraarylborate ion pairs.[96] This approach was later translated to an asymmetric setting, where the treatment of enol ether **305** with catalyst (*S*,*S*)-**306** resulted in the C-allylated product **307** being obtained in 81% yield as an approximate 7:1 mixture of diastereomers, with 81% *ee* for the major isomer. Further elaboration of the Claisen rearrangement product **307** through an iodonium-mediated cyclization furnished the bicyclo[3.3.1] core structure **308** in 59% yield, with the configuration of the contiguous quaternary centers corresponding directly to those of hyperforin (**3**).[97]



Scheme 33. Synthesis of the PPAP core by a catalytic enantioselective Claisen rearrangement strategy, according to Jacobsen and co-workers (2010).[95]

3.18. Njardarson's Double Radical Cyclization/ Desymmetrization Approach towards Guttiferone A

Careful examination of the PPAP constituents revealed that several of its members, particularly those of the guttiferone family, possess a local symmetry that may be exploited synthetically. Based on this concept, the Njardarson research group designed and executed an elegant strategy that featured a late-stage desymmetrization reaction which could potentially provide entry to a large number of natural and designed PPAPs (Scheme 34).[98] As a demonstration,



Scheme 34. Synthesis of the PPAP core by a double radical cyclization/ desymmetrization strategy according to Njardarson and co-workers (2011).[98]

phenol derivative **309** was dearomatized under hypervalent iodine conditions in the presence of MeOH to afford cyclohexadienone **310** (75% yield), which underwent tandem intramolecular radical cyclizations initiated by the two bromine substituents by using $(TMS)_3SiH$ and Et_3B to afford the polycyclic intermediate **311** in 73% yield. The two allyl side chains of **311** were converted into the corresponding prenyl groups by olefin cross-metathesis, and the so-obtained ketone **312** underwent successful desymmetrization through its lithium enolate followed by alkylation with methyl iodide to give α-methyl ketone **313** (73% overall yield). This reaction also served to establish the facial preference of ketone **312** during the alkylation. Finally, the application of chiral amine base **314** enabled an enantioselective enolization of ketone **312** (d.r. = ca. 10:1, determined through the formation of the chiral enol ester **316**), thus showcasing the potential of the developed approach to access enantiomerically enriched material for further synthetic elaborations.

4. Summary and Outlook

The promising biological profile of the PPAPs has triggered a recent surge in investigations of this fascinating family of natural products. Unfortunately, much remains unknown concerning the structure–activity relationship of these molecules, which also translates to a lack of understanding of their mode of biological action and limited clinical success.[99] A primary reason behind this inadequate understanding at the molecular level lies in the synthetic challenge associated with the preparation of both the naturally occurring substances and rationally designed analogues. The early synthetic efforts mainly relied on two strategies: 1) the Effenberger cyclization, or—in a more general sense—the use of substituted cyclohexanones as a precursor for the bicyclo[3.3.1] systems; and 2) the alkylative dearomatization of substituted phenols. The synthesis of PPAPs based on the former strategy tends to suffer from the low-yielding Effenberger cyclizations of highly functionalized precursors, and/or tedious functional group transformations to generate the complex hydrocarbon skeleton from an over simplified bicyclo[3.3.1] system. The latter strategy generally appeared more attractive and promising, presumably because of the fact that it exploits the biomimetic pathway employed by nature to access the PPAPs. Furthermore, the dearomatization strategy could take advantage of the hidden symmetry within the target molecule to drastically shorten the number of synthetic steps. Many impressive and innovative strategies have subsequently been developed, beyond the Effenberger cyclization and alkylative dearomatization, with various levels of success. Furthermore, the importance of the recent advances in asymmetric catalysis, which facilitated entry to optically active PPAPs, cannot be overstated. Undoubtedly, the PPAP field will continue to flourish and reach new heights and maturity, not only in terms of organic synthesis, but also in biology and medicine.

Abbreviations

Ac	acetate
acac	acetylacetonate
AIBN	2,2′-azobis(2-methylpropionitrile)
BAr_F	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAP	2,2′-bis(diphenylphosphanyl)-1,1′-binaphthalene
Bn	benzyl
Bu	butyl
Bz	benzoyl
CAN	ammonium cerium nitrate
CSA	10-camphorsulfonic acid
dba	*trans,trans*-dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
Dibal-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
dppf	1,1′-bis(diphenylphosphanyl)ferrocene
Et	ethyl
G-II	second-generation Grubbs catalyst
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMPA	hexamethylphosphoramide
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LiTMP	lithium tetramethylpiperidide
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MOM	methoxymethyl
Ms	methanesulfonyl
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
NMO	4-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
o-DCB	1,2-dichlorobenzene
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PPAP	polycyclic polyprenylated acylphloroglucinol
Pr	propyl
p-TsOH	*para*-toluenesulfonic acid
pybox	pyridine bisoxazoline
Sia	*sec*-isoamyl
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxide
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl

TPAP tetra-*n*-propylammonium perruthenate
Ts 4-toluenesulfonyl

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