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Natural Product Synthesis: the Endless Quest for an Unreachable Perfection

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TOTAL SYNTHESIS, NATURAL PRODUCTS, BIOSYNTHESIS, STEREOSELECTIVITY

ABSTRACT: Total synthesis is a field in constant progress. Its practitioners aim at developing ideal synthetic strategies to build complex molecules. By such, they are both a driving force and a showcase of the progress of organic synthesis. In this perspective, we discuss recent notable total syntheses. The syntheses selected herein are classified depending on the key strategic considerations for each approach.

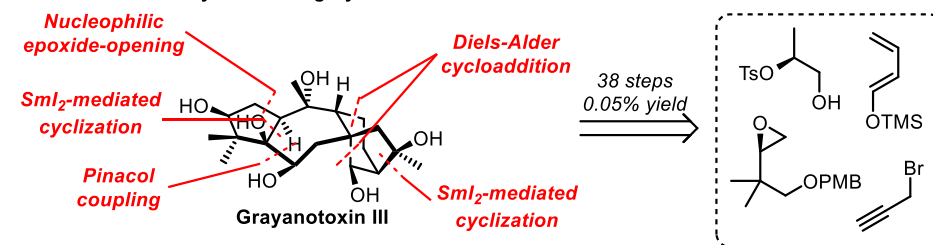
INTRODUCTION

Natural product synthesis, the art of building complex molecular architectures using the science of organic chemistry, is often seen as one of the most challenging yet fruitful fields of chemical science. Despite recurrent criticism regarding its supposed decline, it is “*as exciting as ever and here to stay*”, as stated by Baran.¹ Not only is it the testing ground for new methods and strategies in organic synthesis,² but it also serves the fields of phytochemistry through structure elucidation³ and medicinal chemistry as the first move in many drug discovery campaigns.⁴ Moreover, total synthesis could be considered as the showcase of progress made in the field of organic synthesis. For example, 1994 the group of Shirahama achieved the first enantioselective synthesis of grayanotoxin III in 38 steps and 0.05% overall yield, a real feat at the time (Scheme 1).⁵ 28 years later, the group of Luo reported the synthesis of the same molecule in only half the amount of steps and an overall yield 4 times higher (19 steps and 0.2% overall yield).^{6,7}

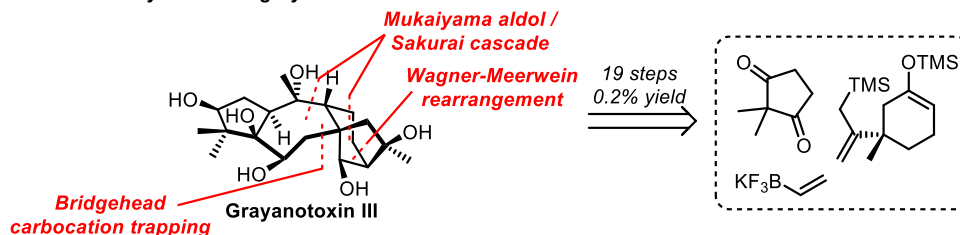
The last few years have seen many successes in total synthesis, confirming Baran's statement. The quest for an ideal synthesis has driven organic chemistry practitioners to-

wards designing efficient and elegant strategies.⁸ The concept of ideality has been defined as the percentage of “productive steps” in the synthetic route, although the same authors clearly indicate that it should not be the sole indicator to judge the quality of a total synthesis.⁹ Indeed, step count, atom and redox economy, scale or yield are other key indicators of the efficiency and practicability of a synthesis. Moreover, one could argue that the indicators which should be taken into account to judge the quality of a synthesis might also depend on the synthesis' purpose. In the synthesis of a potential drug candidate, scalability is more important than in a synthesis for structure elucidation purpose. In this perspective article, we will try to highlight recent efficient total syntheses. This collection is very personal and will by no means be exhaustive. The selected syntheses will be classified in three categories depending on the key consideration: i) divergent syntheses, in which the most important strategic consideration is to identify the right late intermediate; ii) hemisyntheses, in which the key is to remodel the skeleton of an abundant natural product; iii) concise syntheses, in which one or two strategic disconnection allow to greatly simplify the retrosynthesis.

1994: Shirahama's synthesis of grayanotoxin III



2022: Luo's synthesis of grayanotoxin III



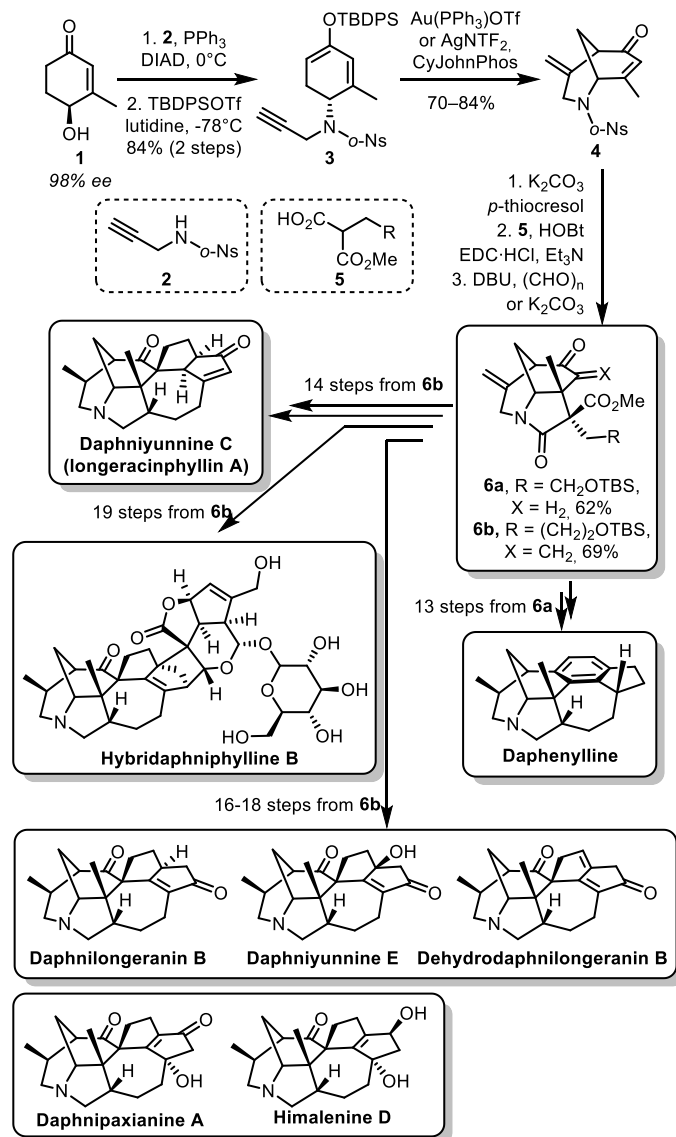
Scheme 1. Evolution of grayanotoxin III synthesis

IDENTIFYING THE RIGHT COMMON INTERMEDIATE: COLLECTIVE TOTAL SYNTHESIS

The huge diversity of complex natural products which can be considered as interesting targets for total synthesis can look overwhelming. A creative solution to this challenge has been found by using a same strategy to reach various natural products.¹⁰ Sometimes termed “divergent synthesis”, “collective synthesis” as defined by MacMillan¹¹ or “structure-pattern-based synthesis” as phrased by Gaich,¹² this approach relies on the identification of a key common intermediate which already bears part of the complexity of a natural product, from which diversity could be accessed in the late stages of the synthesis. These approaches have led to various successes in recent years.

In the context of a total synthesis campaign targeting the *Daphniphyllum* alkaloids, the group of Li identified a tricyclic structure common to most members of the family as a key intermediate. This could be accessed from known hydroxy enone **1** (easily obtained with high enantiomeric excess in six steps from *m*-methylanisole).¹³ The allylic alcohol was substituted by a propargylamide **2** under Mitsunobu conditions followed by formation of an enol ether **3** (Scheme 2). The bridged piperidine ring **4** was formed through a Au- or Ag-catalyzed Conia-ene reaction. Deprotection of the amine, amide coupling and intramolecular Michael addition allowed the formation of the fused γ -lactam ring **6a** or **6b**. An important point is the scalability of this synthesis. In all cases, the tricyclic intermediate was obtained on multigram scale, a crucial asset to successfully complete the syntheses. From **6a**, a 13 steps sequence allowed the formation of daphenylline.¹⁴ The key steps were a 6π -electrocyclization / oxidation for the formation of the aromatic ring and Giese addition for the 7-membered ring. On the other hand, a 14 steps sequence from **6b** led to the formation of daphniyunnine C.¹⁵ In this case, the key steps were an intramolecular conjugate addition for the formation of the 7-membered ring, a Lu (3+2)-cycloaddition and an intramolecular Horner-Wadsworth-

Emmons reaction for the formation of the two fused cyclopentanes. A similar approach was also applied to the synthesis of daphnilongeranin B, daphniyunnine E, dehydrodaphnilongeranin B and hybridaphniphylline B.¹⁶ The strategy was later on adapted for the synthesis of daphnipaxianine A and himalenine D.¹⁷

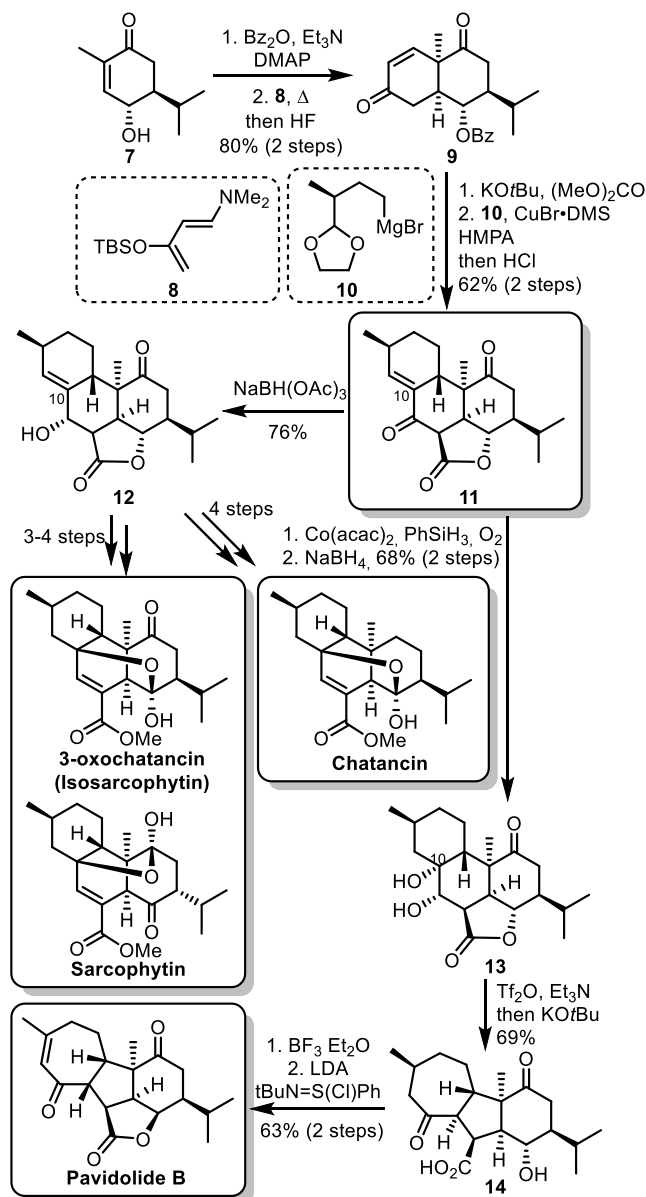


Scheme 2. Li's divergent synthesis of *Daphniphyllum* alkaloids

In this work, the identification of an efficient approach for the formation of the tricyclic core common to most *Daphniphyllum* alkaloids was the key to success and allowed the authors to achieve the synthesis of 8 very complex natural products in an impressively short amount of time.

In 2019, the group of Ding reported the synthesis of various cembranoids from the sarcophytin family.¹⁸ The synthesis started from known hydroxy enone **7**, synthesized in two steps from carvone.¹⁹ The hydroxyl moiety was protected prior to a Diels-Alder cycloaddition with Rawal diene **8** (Scheme 3). The resulting *cis*-decalin **9** reacted with dimethyl carbonate to form the tricyclic core bearing a γ -lactone, which underwent conjugate addition and *in situ* cyclization under acidic conditions to achieve the fused tetracycle **11**. This became the key intermediate for the synthesis of sarcophytin, chatancin, 3-oxochatancin and pavidolide B. A chemoselective reduction of the enone

11 led to allylic alcohol **12**, from which a sequence of exhaustive ketone reduction, Mukaiyama hydration, elimination, transesterification and oxidation led to the formation of chatancin. On the other hand, from **12** a sequence of Mukaiyama hydration, elimination and oxidation led to 3-oxochatancin, which could be further epimerized to form sarcophytin. Moreover, this synthesis allowed to reassigned the structure of isosarcophytin as 3-oxochatancin. From **11**, performing the Mukaiyama hydration prior to ketone reduction allowed to obtain the opposite stereoselectivity at C¹⁰. This configuration allowed a semi-pinacol rearrangement to occur by treatment of **13** with Tf₂O in basic conditions, affording the tetracyclic core **14**. From there, lactonization and oxidation led to the formation of pavidolide B. Remarkably, the lactonization occurred with inversion of configuration at the hydroxyl moiety, probably through the formation of a transient cyclopropyl intermediate.

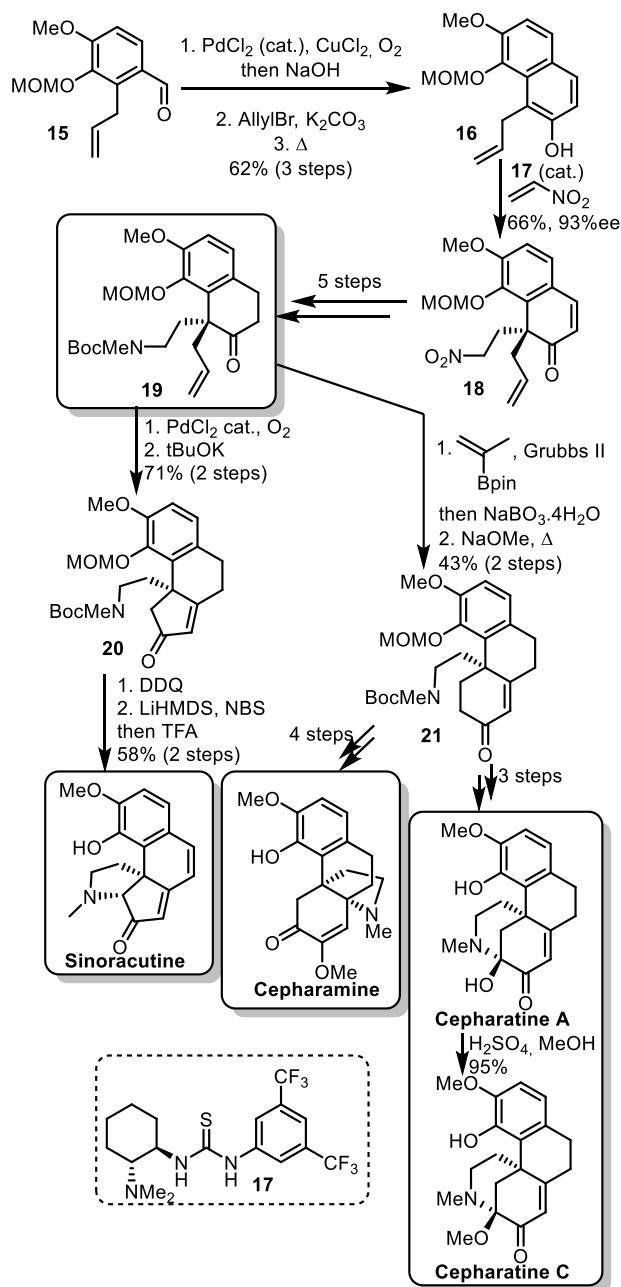


Scheme 3. Ding's synthesis of cembranoids from the sarcophytin family

Overall, Ding's efficient strategy led to the formation of 4 diverse natural products from the sarcophytin family in 10–11 steps (4–5 steps from key intermediate **11**).

In 2021, Zhu and co-workers described a strategy for the synthesis of hasubanan alkaloids with diverse skeletons.²⁰ The strategy relied on a late formation of the fused or bridged pyrrolidine or piperidine ring from a common intermediate. The synthesis started from known aldehyde **15**, easily accessible in 3 steps from isovanillin.²¹ **15** underwent a one-pot Wacker oxidation / aldol condensation, followed by an *O*-allylation and Claisen rearrangement, affording naphthalene derivative **16** (Scheme 4). The naphthol moiety could undergo an enantioselective dearomative alkylation using nitro ethene and Takemoto's catalyst **17**. The resulting intermediate could undergo a 5-step sequence involving various reductions and protection of the amine group to form the common intermediate **19**. From **19**, a Wacker oxidation and aldol condensation afforded cyclopentenone **20**, from which an oxidation and α -bromination / cyclization led to sinoracutine. On the other hand, a cross metathesis using isopropenylboronic acid pinacol ester followed by Brown oxidation and aldol condensation afforded cyclohexanone **21**. The enone could undergo a conjugate addition of the amino group and redox adjustments to complete the synthesis of cepharamine. On the other hand, a series of oxidations, deprotection then cyclization to afford cepharatine A and C.

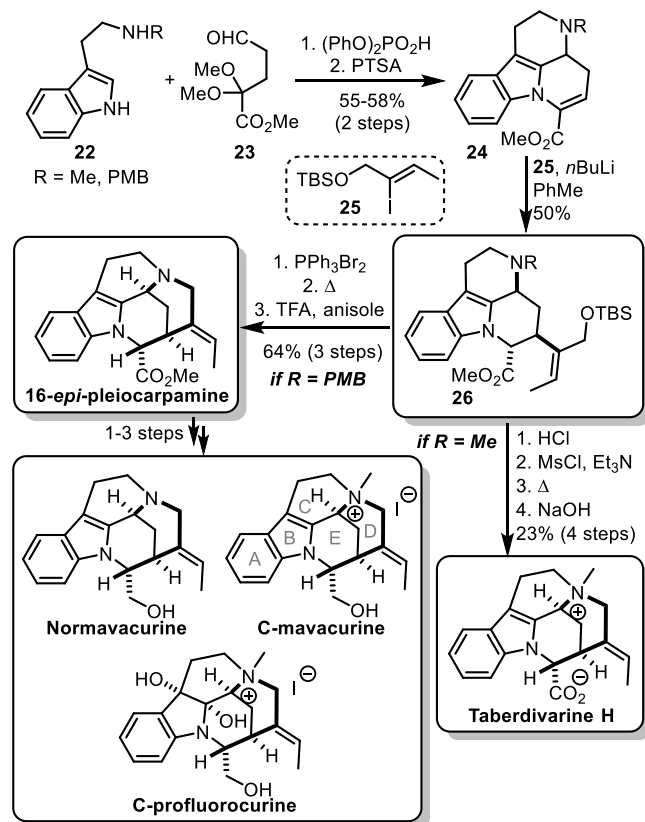
In this synthetic sequence, the authors judiciously chose **19** as a common intermediate for both cyclopentenone **20** and cyclohexanone **21**, from which the synthesis of various hasubanan alkaloids could be achieved efficiently. It should be noted that the syntheses relied on similar sequences of aldol condensation, oxidations, desaturation or deprotection after the point of divergence **19**, which probably contributed to a quick conclusion of this synthesis.



Scheme 4. Zhu's synthesis of hasubanan alkaloids

Following an interest for the mavacuran alkaloid family,²² the group of Vincent recently reported a new approach to access the mavacuran skeleton.²³ Unlike previous approaches, this strategy relies on a late formation of the D ring. For that, the tetracyclic structure bearing rings A, B, C and E was prepared by a Pictet-Spengler reaction between protected tryptamine **22** and aldehyde **23**, easily obtained in 3 steps from 4-bromobutene (Scheme 5). After acidic treatment, the dimethyl acetal was deprotected and directly condensed with the indole, affording tetracyclic intermediate **24**. The α,β -unsaturated ester could undergo a 1,4-addition using an organolithium in toluene, an unconventional reactivity which was serendipitously discovered by the authors. The resulting intermediate **26** was the pivotal intermediate of the synthesis. From there, in the

case of a PMB-protected amine the protected primary alcohol could be converted to a primary bromide, which could be substituted by the tertiary amine prior to cleavage of the PMB group, affording 16-*epi*-pleiocarpamine, which could easily be elaborated into normavacurine, C-mavacurine and C-profluorocurine in a few steps. On the other hand, in the case of a simple methylated amine the primary alcohol could be deprotected, mesylated prior to cyclization and saponification of the ester to lead to taberdivarine H.



Scheme 5. Vincent's synthesis of mavacuran alkaloids

Overall, through the identification of pivotal intermediate **26** and late formation of the D ring, the synthesis of various mavacurane alkaloids could be achieved in a remarkably concise manner.

Later on the same year, the group of Magauer reported a versatile approach for the synthesis of various sesquiterpene alkaloids.²⁴ The flexibility of this synthesis is allowed by the development of a divergent polyene cyclization reaction. The precursor for the polyene cyclization was prepared by assembling farnesyl bromide **27** and indole derivative **28** by lithiation / alkylation, enantioselective dihydroxylation and formation of an epoxide **30**. Deprotection of the benzene sulfonyl group and bromination at C³ position of the indole allowed to form **31**, which upon treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ underwent an uncommon *N*-terminated polyene cyclization affording a mixture of diastereoisomers **32a** and **32b**. The former could be oxidized into polysin, while the latter was converted into greenwayodendrin-3-one, greenwayodendrin-3 α -ol and polyavolensin. On the other hand, **30** could undergo a more classical C-terminated polyene cyclization by treatment with MsOH in HFIP. The resulting diastereoisomers **33a** and **33b** could be further elaborated into polyveoline and greenwaylac-tams A, B and C.

This work is an excellent example showcasing the power of divergent synthesis: a divergent polyene cyclization cascade was developed, allowing to access two different skeletons from common intermediate **30**, further leading to the synthesis of 9 natural products.

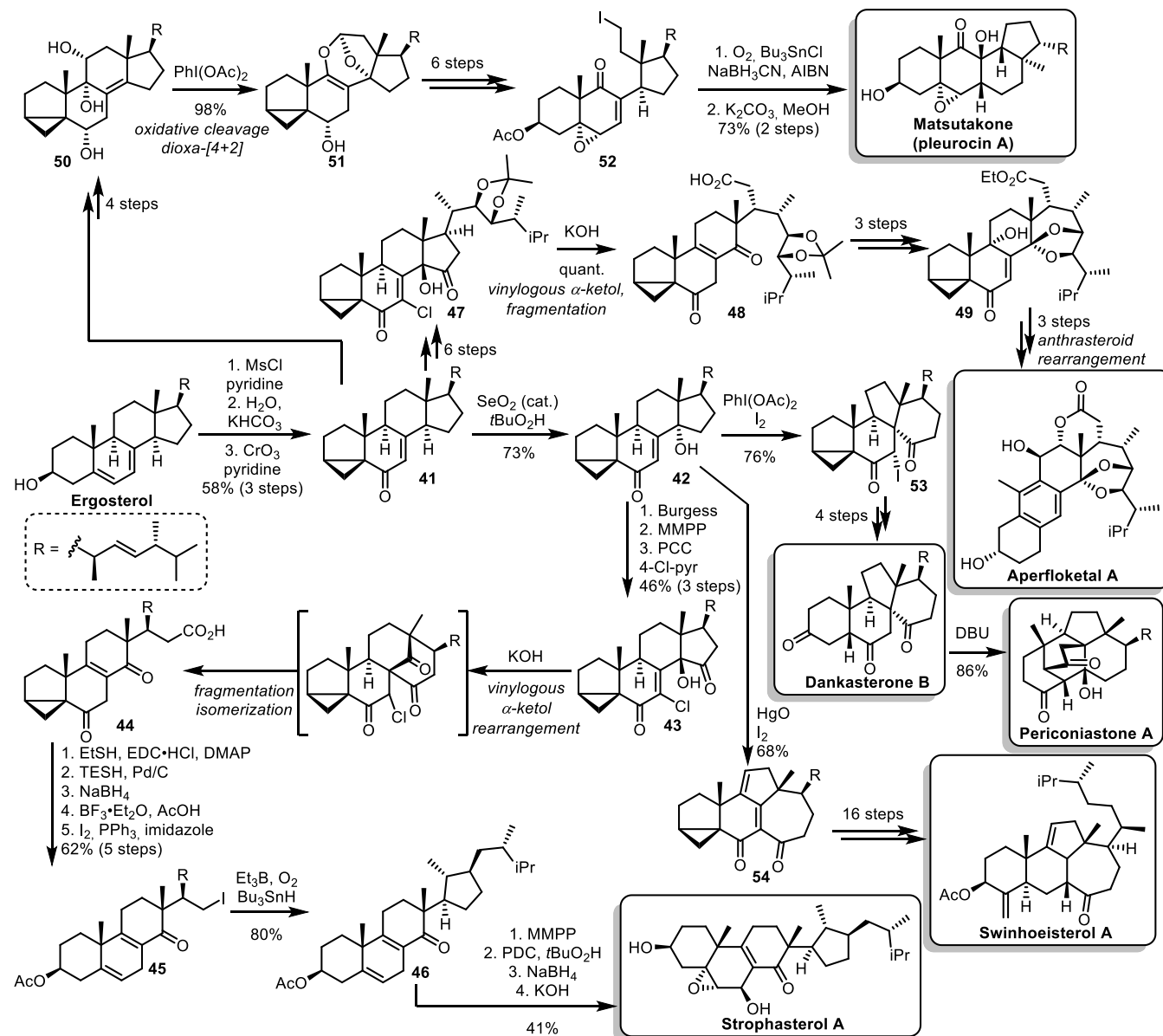
The example described above showcase the power of collective synthesis. The key point in this kind of approach is to identify a suitable late intermediate which will bear part of the target's complexity while allowing to access a diversity of natural products or analogs, as well as an efficient approach to reach this late intermediate.

IDENTIFYING THE RIGHT STARTING MATERIAL: HEMISYNTHESIS AND SKELETAL EDITING

Hemisynthesis or semisynthesis is the specific case in which a molecule is synthesized using a natural product as starting material.²⁶ The flagship example of this approach is docetaxel and paclitaxel hemisynthesis from 10-deacetylbaaccatin III.²⁷ Beyond classical functionalization of nat-

ural products, the emergence of C–C bond activation, rearrangements and other selective C–C cleavages has led to innovative strategies of skeletal editing. Through those, the synthesis of complex structures from abundant natural products with a completely different skeleton has been possible. The advantage of these approaches is the possibility to use a starting material already possessing part of the atoms and complexity of the target molecule.

In recent years, the group of Heretsch engaged in a semisynthesis campaign targeting various triterpenoid structures starting from ergosterol. The authors use the reversible conversion of ergosterol into *i*-steroids²⁸ as a way to mask the eastern part of ergosterol while introducing an enone which will serve as chemical handle to further oxidize and edit the western part (Scheme 8).



Scheme 8. Heretsch's syntheses of triterpenes by skeletal rearrangements from ergosterol

In 2016, Heretsch described the synthesis of strophasterol A starting from ergosterol.²⁹ After conversion into *i*-steroid **41**, an allylic oxidation led to **42**. A series of

selective oxidations afforded α -ketol **43** which, upon treatment in basic conditions, underwent a vinylogous α -ketol

rearrangement, followed by a fragmentation and isomerization. From the resulting intermediate **44**, the carboxylic acid moiety was reduced and iodinated, while the eastern part was regenerated by reduction of the ketone and treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and acetic acid. Iodide **45** underwent a reductive radical cyclization to form cyclopentane ring **46**, and further redox adjustments concluded the synthesis of strophasterol A. Later on, the same group applied a similar strategy to the synthesis of aperfloketal A.³⁰ A series of selective oxidations from *i*-steroid **41** afforded **47**, from which a similar vinylogous α -ketol rearrangement / fragmentation / isomerization cascade gave **48**. A sequence of esterification, oxidation and deprotection allowed the formation of ketal **49**, which further underwent a 3-step sequence involving an anthrasteroid rearrangement as the key step, leading to aperfloketal A.

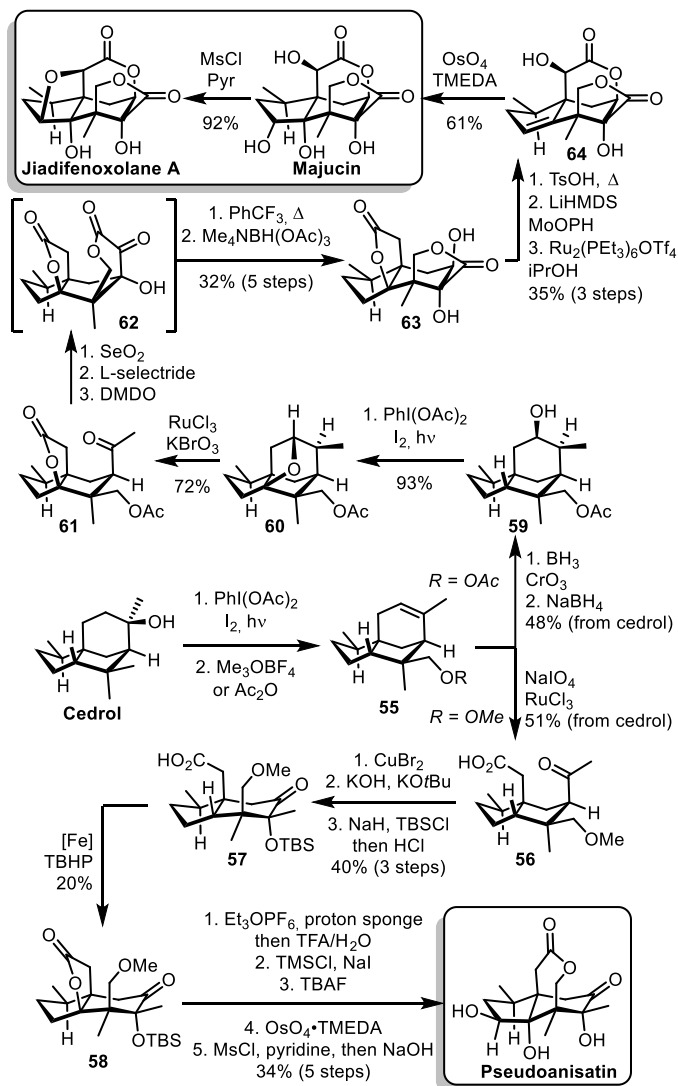
In 2019, Heretsch and co-workers used *i*-steroid **41** as an intermediate for the synthesis of matsutakone (pleurocin A).³¹ A series of redox adjustments led to the formation of *vic*-diol **50**, which could undergo an oxidative cleavage, followed by a formal dioxo-[4+2] cycloaddition to afford ketal **51**. Further adjustment of the functional groups, including formation of an iodide in place of the ketal and regeneration of the skeleton's eastern part led to intermediate **52** bearing a primary iodide and an enone. These would prefigure the key radical cyclization, completing the synthesis of matsutakone.

Finally, in 2020 the same group reported the synthesis of triterpenes with various skeletons.³² From intermediate **42**, a one-pot radical 1,2-rearrangement / iodination triggered by PhI(OAc)₂ and I₂ afforded intermediate **53**, which could further be elaborated into dankasterone B and periconiastone A. On the other hand, treating the same intermediate with HgO and I₂ allowed a Dowd-Beckwith rearrangement following the 1,2-rearrangement mentioned previously. The resulting structure **54** led to swinhoesterol A after modification of the R chain, selective reductions and regeneration of the eastern part.

Overall, this total synthesis program allowed to use a cheap, abundant although complex starting material, namely ergosterol, for the synthesis of various triterpenoids with diverse skeletons. In particular, the strategies rely on the formation of an *i*-steroid with a key enone moiety which serves as a handle for selective oxidation to further allow skeletal rearrangements.

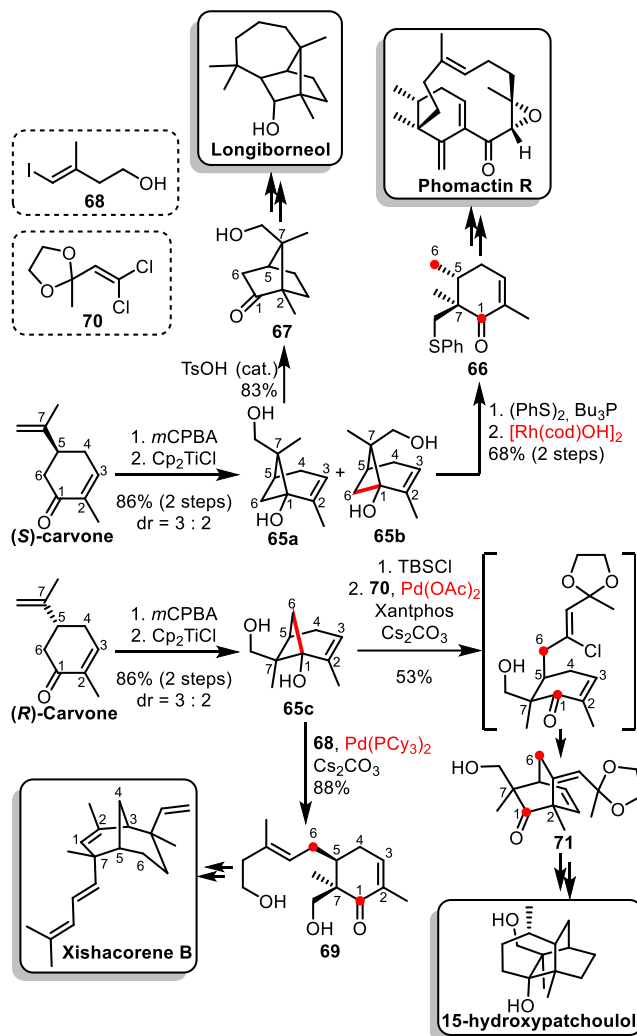
During the last decade, the group of Maimone reported the synthesis of various sesquiterpenoids from cedrol. These syntheses rely mainly on meticulous studies of the possible C–H oxidations of the cedrol core.³³ From cedrol, a Suarez type oxidative cyclization followed by elimination allowed to transfer the oxygen atom of cedrol onto a remote methyl group (Scheme 9). Oxidative cleavage of the newly formed olefin allowed the formation of **56**.³⁴ Oxidation α to the ketone mediated by CuBr₂ followed by α -ketol rearrangement and protection of the tertiary alcohol afforded **57**. The acid moiety of **57** could direct an iron-me-

diated C–H oxidation to form lactone **58**. Finally, a sequence of elimination, deprotection, lactonization, directed dihydroxylation and inversion of the resulting secondary alcohol afforded pseudoanisatin. On the other hand, from **55** a hydroboration led to secondary alcohol **59** after a sequence of oxidation / reduction necessary to obtain the correct relative configuration.³⁵ Again, a Suarez-type oxidative cyclization allowed the formation of the bridged THF structure **60**. Treatment with *in-situ* prepared RuO₄ allowed an impressive C–C bond cleavage. After a series of redox adjustments and lactonization, the intermediate lactone **62** bearing an α -ketol moiety was obtained. The use of DMDO was crucial for this last oxidation to obtain the desired relative configuration. Intermediate **62** was unstable and could undergo an α -ketol rearrangement. After reduction, the tetracyclic structure **63** was obtained. Acid-mediated elimination of the propellalactone, lactonization, α -hydroxylation and inversion of configuration of the newly formed hydroxyl substituent afforded **64**. Finally, directed hydroxylation led to the formation of majucin, which could further undergo a substitution reaction to form the bridged THF structure of jiadifenoxolane A.



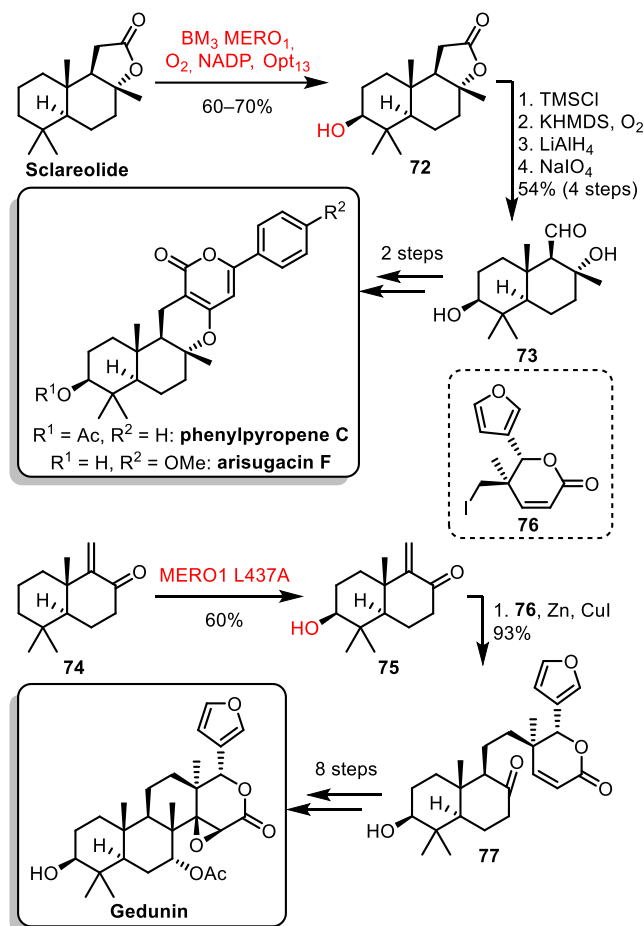
Scheme 9. Maimone's syntheses of sesquiterpenoids from cedrol

An impressive skeletal remodeling, although starting from a more classical terpene building block, carvone, was described by Sarpong and co-workers and applied to various natural products.³⁶ The isopropylene moiety could undergo an epoxidation, followed by Ti^{III}-mediated reductive cyclization.³⁷ The resulting synthetic pinene derivative **65** was isolated as a mixture of two separable diastereoisomers. From the minor diastereoisomer **65b**, the primary alcohol could be converted into a sulfide, prior to a Rh-catalyzed C–C activation to cleave the C¹–C⁶ bond, leading to a rearranged cyclohexene scaffold **66**. This could further be elaborated into various members of the phomactin family.³⁸ On the other hand, the major isomer **65a** could undergo an acid-catalyzed semi-pinacol rearrangement to form camphor-analog **67**, which could also be converted into various members of the longiborneol sesquiterpenoid family.³⁹ Starting from (*R*)-carvone, the same sequence of epoxidation/reductive cyclization led to **65c** as the major isomer. From this pinene derivative, a Pd-catalyzed C¹–C⁷ activation followed by cross-coupling with alkenyl iodide **68** led to the formation of polysubstituted cyclohexanone **69**.⁴⁰ This intermediate later led to the synthesis of xishacorene B via a key transannular Giese cyclization to form the bridged structure. Finally, synthetic pinene derivative **65c** could also be subjected to a Pd-catalyzed C–C activation/cross-coupling/Mizoroki–Heck cyclization with 1,1-dichloro alkene **70**.⁴¹ The resulting bicyclo[2.2.2]octane was a key intermediate in the synthesis of 14- and 15-hydroxy-patchoulol.



Scheme 10. Sarpong's skeletal editing from carvone

Directed evolution offers new exciting perspectives for the formation of complex structures.⁴² In 2020, the group of Renata reported the selective C³ hydroxylation of sesquiterpene lactone sclareolide using a P₄₅₀^{BM3} variant.⁴³ From this cheap and abundant starting material, added value hydroxylated product **72** could be obtained efficiently on gram-scale. Protection of the secondary alcohol, hydroxylation α to the lactone, reduction and oxidative cleavage allowed the formation of **73** bearing an aldehyde and secondary alcohol as chemical handles for the construction of meroterpenoids phenylpyropene C and arisugacin F. Although very powerful, the use of this P₄₅₀^{BM3} variant was limited to few substrates. The same authors had to develop a new variant to perform efficiently the selective oxidation of **74**, easily obtained in three steps from sclareolide.⁴⁴ The resulting intermediate **75** could be coupled with iodide **76** through a zincation/conjugate addition. The resulting advanced intermediate **77** was then converted to gedunin in an 8-step sequence.



Scheme 11. Renata's selective hydroxylation of sclareolide derivatives

These selected examples highlight the importance of finding the right starting material in synthesis. Starting from cheap, abundant although complex structures such as sclareolide or ergosterol, the synthesis of various complex natural products could be achieved very efficiently.

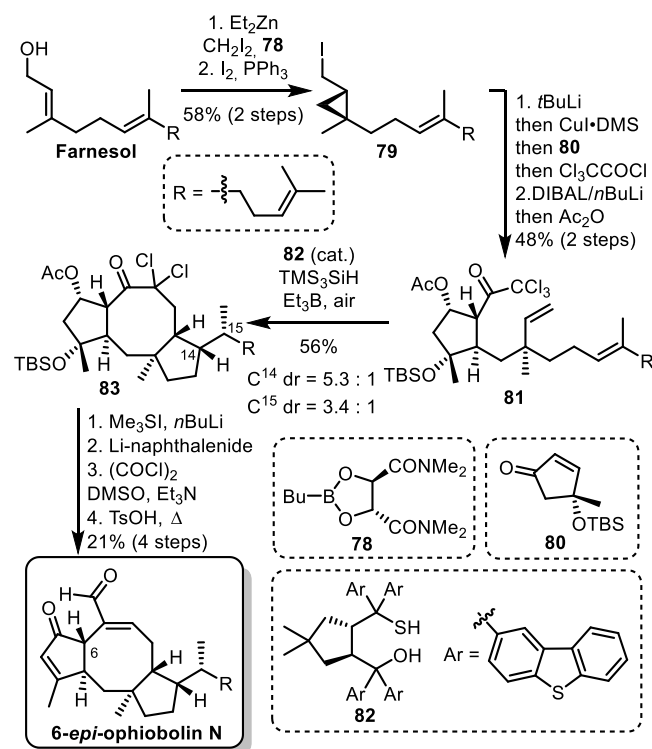
IDENTIFYING THE RIGHT KEY STEP(S) FOR CONCISE SYNTHESSES

The design of a synthetic strategy uses retrosynthetic analysis, the rules of which were established decades ago by Corey. The idea is to identify key disconnections to make the synthesis as concise and efficient as possible.⁴⁵ In recent years, the rise of AI and computer assistance allowed to simplify the reflexion necessary to set up a strategy, and opened new avenues for organic synthesis.⁴⁶ Nevertheless, various recent examples can be cited to show that old-fashion blackboard design of a retrosynthesis can still lead to success.

In 2016 the group of Maimone reported an efficient synthesis of 6-*epi*-ophiobolin N.⁴⁷ The ophiobolins are a family of complex sesterterpenoids displaying a 5-8-5 fused ring system with many stereogenic centers. Maimone's hypothesis was that the tetracyclic core could be constructed by a radical cyclization. This approach would have two main advantages: (i) the substrate for this key cyclization could

be easily accessed from common terpenic precursors such as farnesol and linalool and (ii) after the key cyclization all the stereogenic centers would be set and most functional groups would be at hand's reach.

The synthesis began by an enantioselective Charetté cyclopropanation of farnesol followed by iodination to form **79** (Scheme 12). This was assembled with precursor **80** (easily prepared in 3 steps from linalool) by a one-pot lithiation/transmetalation/conjugate addition/trapping with trichloroacetyl chloride. After reduction of the ketone and protection, a precursor for the key radical cyclization **81** was obtained. The key cyclization was achieved using a chiral thiol catalyst **82** developed for this purpose, Et₃B and air as the radical initiator and TMS₃SiH as the hydrogen radical source. The tricyclic structure **83** was obtained as a mixture of diastereoisomers at C¹⁴ and C¹⁵, which could be separated in the later stages of the synthesis. From **83**, a sequence of Corey-Chaykovsky epoxidation, reductive opening of the epoxide, Swern oxidation and elimination of the tertiary alcohol concluded the synthesis of 6-*epi*-ophiobolin N in 10 steps (longest linear sequence). A few years later, the same authors applied a similar strategy to the synthesis of 6-*epi*-ophiobolin A.⁴⁸

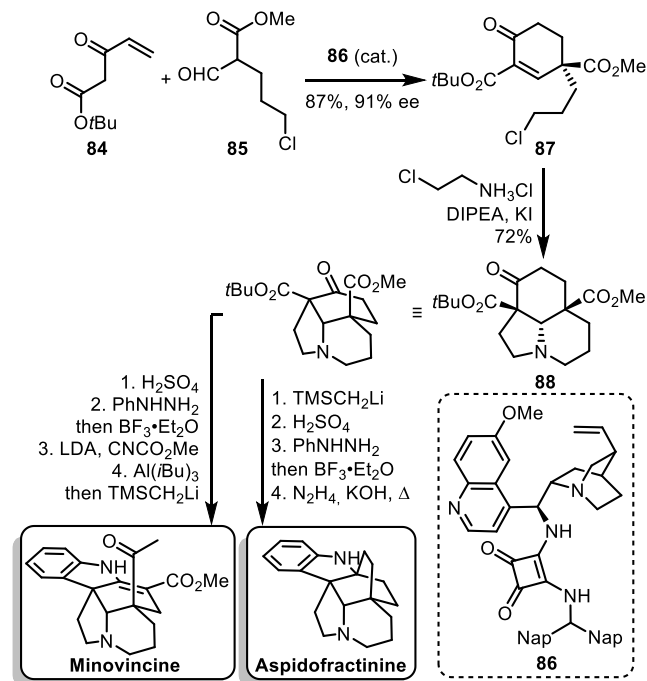


Scheme 12. Maimone's synthesis of 6-*epi*-ophiobolin N

Overall, this work by Maimone led to a very efficient synthesis of the C⁶-epimer of natural ophiobolin N in only 10 steps. This was possible thanks to the identification and development of a key radical cyclization to form the tricyclic structure, but also to a smart experimental design in which many concession steps are performed in the same pot as constructive steps.

In 2020, the group of Soós reported an expeditious synthesis of minovincine and aspidofractinine.⁴⁹ The synthesis

relied on a quick access to a tricyclic core, followed by late formation of the indole moiety. Enone **84** and malonate derivative **85**, respectively prepared in 2 and 1 step from commercial precursors, were assembled by an enantioselective Robinson annulation using organocatalyst **86** (Scheme 13). The reaction afforded cyclohexenone **87** in good yield and excellent enantioselectivity. Cyclohexenone **87** underwent a cascade of nucleophilic substitutions and conjugate addition in the presence of 2-chloroethylamine, affording the tricyclic core **88**. Remarkably, this intermediate could be prepared on 59 g scale. From there, a sequence of decarboxylation, Fischer indolization, methoxycarbonylation and selective ketone formation led to the formation of minovincine. On the other hand, starting by the methyl ketone formation followed by decarboxylation allowed to achieve an interrupted Fischer indolization to build the bridged structure of aspidofractine. The synthesis was concluded by a Wolff-Kishner reduction of the bridged ketone.

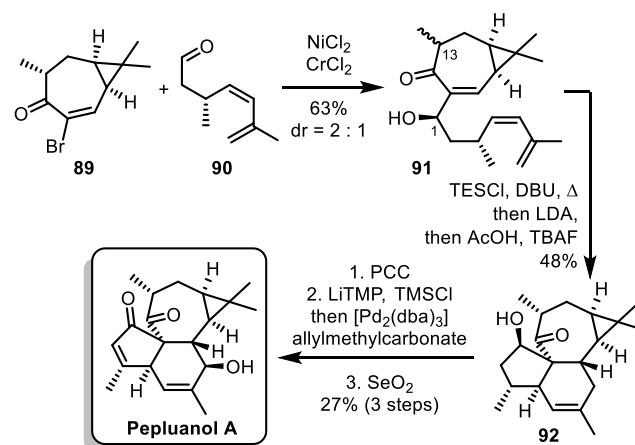


Scheme 13. Soós' synthesis of minovincine and aspidofractinine

In this work, Soós and co-workers achieved a straightforward synthesis of minovincine and aspidofractinine in 8 steps. This was made possible by the quick formation of a tricyclic core using an organocatalytic Robinson annulation and a nucleophilic cascade. The power of this synthesis was showcased by the synthesis of more than 1 g of minovincine.

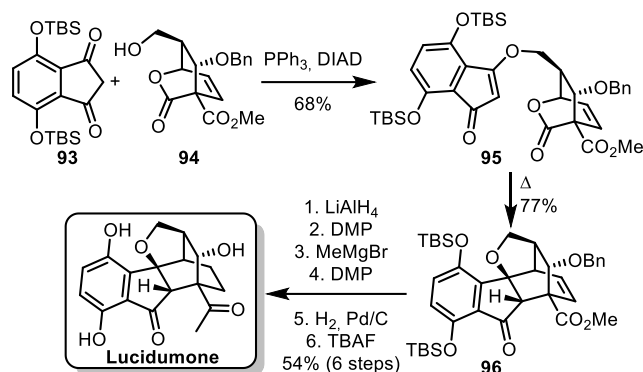
In 2021, the group of Gaich tackled the synthesis of pepluanol A using a key intramolecular Diels-Alder cycloaddition (IMDA).⁵⁰ The synthesis used bicyclic precursor **89**, easily prepared in 5 steps from carene using a procedure previously described by Baran,⁵¹ and aldehyde **90**, prepared in 5 steps from (S)-3-bromo-2-methylpropanol (Scheme 14). These fragments were assembled by a Nozaki-Hiyama-

Kishi reaction, affording a mixture of diastereoisomers at C¹ and C¹³. While the minor diastereoisomer at C¹ could be separated by column chromatography, separating the C¹³-epimers proved to be irrelevant. Indeed, after TES protection of the secondary alcohol, the IMDA reaction proceeded in a diastereoconvergent fashion in the presence of DBU. Nevertheless, the product had the undesired configuration at C¹³ and the authors had to epimerize *in situ* by treatment with LDA. The tetracyclic intermediate **92** was then converted into pepluanol A by a sequence of 3 selective oxidations. Thus, the synthesis of pepluanol A was achieved in 10 steps from commercially available precursors.



Scheme 14. Gaich's synthesis of pepluanol A

In 2022, our group reported the first enantioselective synthesis of lucidumone.⁵² Our strategy relied on a quick assembly of the pentacyclic scaffold using a retro-[4+2]/CO₂ extrusion/IMDA cascade. The precursor for this key step was synthesized from indanedione **93** and bridged bicyclic lactone **94**, respectively synthesized in 4 and 5 steps from commercially available material (Scheme 15). In particular, **94** was made enantioselectively using an inverse electron demand Diels-Alder cycloaddition involving a 2-pyrone.^{53,54} The fragments were assembled under Mitsunobu conditions to form **95**, from which the key retro-[4+2]/CO₂ extrusion/IMDA cascade afforded **96** with the pentacyclic structure of lucidumone. A six-step sequence allowed to convert the methyl ester into a methyl ketone, reduce the endocyclic olefin and cleave the protecting groups to conclude this synthesis in 13 steps (longest linear sequence). Remarkably, 1.6 g of the natural product was synthesized in one batch using this approach.

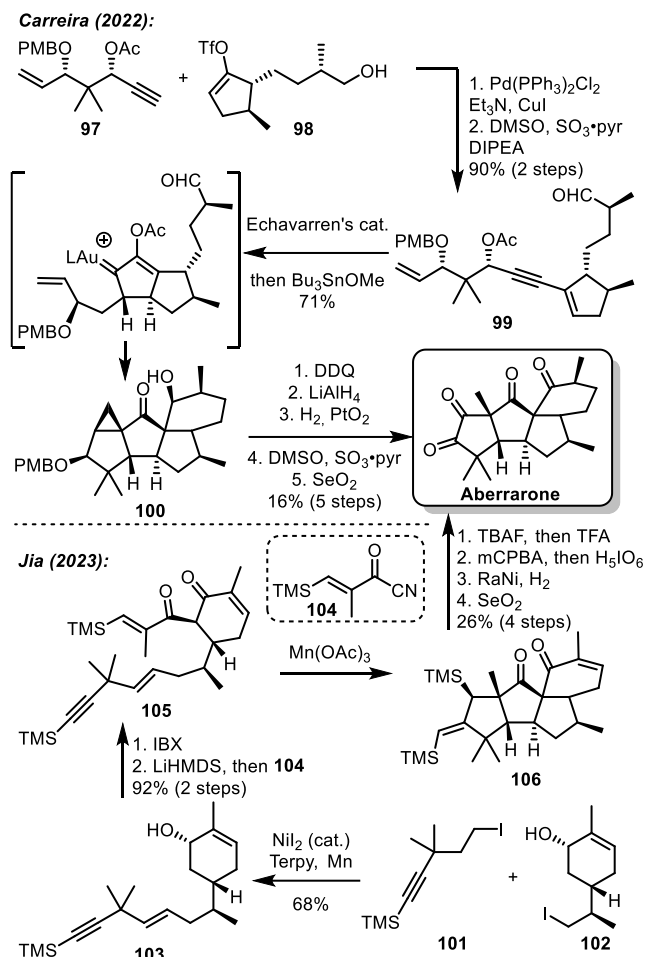


Scheme 15. de la Torre's synthesis of lucidumone

In 2022 the team of Carreira reported an elegant synthesis of aberrarone.⁵⁵ In particular, Carreira's approach features an impressive Au-catalyzed cyclization cascade based on previous studies by Fensterbank and co-workers.⁵⁶ Precursors **97** and **98**, easily obtained in 7 steps from pantolactone and Roche ester respectively, were assembled by a Sonogashira coupling (Scheme 16). After oxidation of the primary alcohol, the precursor **99** was obtained. This could undergo the key Meyer-Schuster/Nazarov cascade, followed by an intramolecular cyclopropanation and aldol reaction to reach the skeleton of aberrarone **100**. From there, redox adjustments allowed to complete the synthesis in 15 steps.

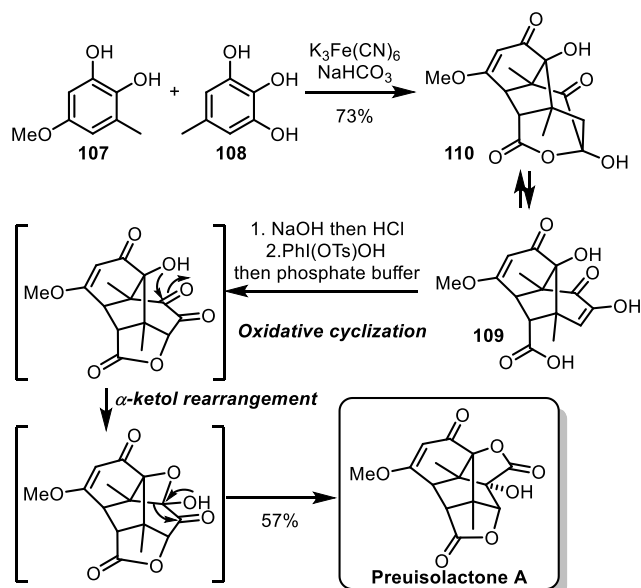
A few months later, the group of Jia reported a different synthesis of the same natural product.⁵⁷ Jia's approach involved intermediates **101** and **102**, synthesized in 2 steps from commercial compounds. The fragments were assembled by a Ni-catalyzed reductive cross coupling to afford **103**. Oxidation of the allylic alcohol and α -acylation allowed the formation of **105**, the precursor for the key cyclization. After treatment with $\text{Mn}(\text{OAc})_3$, **105** underwent a radical cascade leading to the tetracyclic core of aberrarone **106**. Final redox adjustments concluded this synthesis in 12 steps.

While both approach employ an impressive cascade cyclization to form the tetracyclic structure, Jia's approach proved to be slightly shorter. The main advantage of this second approach lies in the quick formation of fragments **101** and **102**.



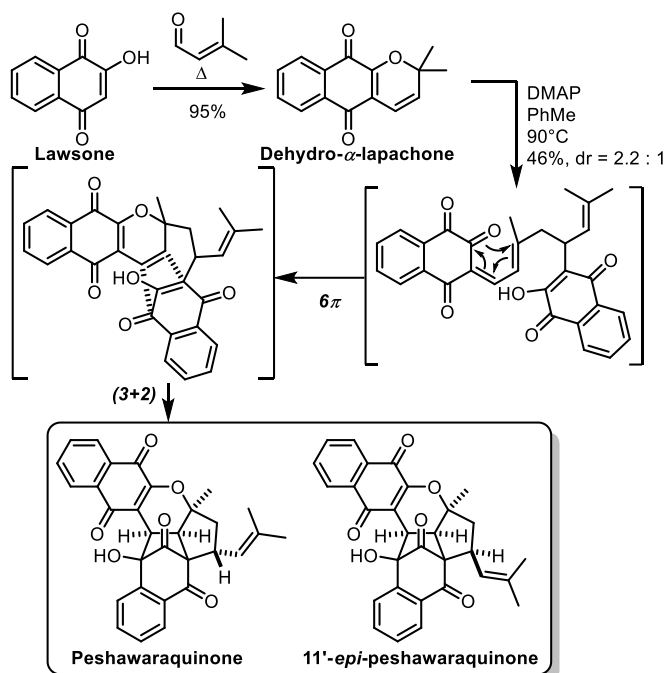
Scheme 16. Carreira and Jia's syntheses of aberrarone

In an effort to find the shortest possible synthesis, biosynthetic considerations are often very valuable.⁵⁸ In this context, Trauner and co-workers recently reported an impressive biomimetic synthesis of preuisolactone A produced by the endophytic fungus *Preussia isomera*.⁵⁹ Trauner's hypothesis was that preuisolactone A was formed in the plant from catechol **107** and pyrogallol **108** by an oxidation/(5+2)-cycloaddition followed by a series of cyclizations, fragmentations and rearrangements. With this in mind, the authors treated precursors **107** and **108** in oxidative conditions and obtained the bridged tricyclic intermediate **109** in equilibrium with its lactol form **110** (Scheme 17). The equilibrium could be displaced towards **109** by treatment in basic conditions followed by acidic work-up. Treatment with Koser's reagent allowed an oxidative cyclization, followed by a cascade lactol formation/ α -ketol rearrangement, affording preuisolactone A in 57%. This very straightforward synthesis (3 steps) could support the author's biosynthetic proposal.



Scheme 17. Trauner's biomimetic synthesis of preisolactone A

With a similar mindset, the groups of George and Lawrence recently studied the biosynthesis of peshawaraquinone, a complex polycyclic meroterpenoid isolated from the tree *Fernandoa adenophylla*.⁶⁰ The hypothesis was that peshawaraquinone was formed by unsymmetrical dimerization starting from dehydro- α -lapachone, a meroterpenoid commonly encountered in these trees. To prove this, the authors first synthesized dehydro- α -lapachone from lawsone by a one-pot Knoevenagel condensation and subsequent oxa- 6π -electrocyclization (Scheme 18). Then, dehydro- α -lapachone was treated with DMAP in toluene. After 6π -electrocyclic ring opening and intermolecular Michael addition, followed by 6π electrocyclization and intramolecular (3+2)-cycloaddition, peshawaraquinone was obtained along with its C¹¹ epimer. Interestingly, when DMAP was replaced by DIPEA, the diastereomeric ratio was reversed. This one-step synthesis of peshawaraquinone from dehydro- α -lapachone could back the author's biosynthetic proposal, while providing a convenient approach in the lab.



Scheme 18. George and Lawrence's synthesis of peshawaraquinone

CONCLUSION

The field of total synthesis still has a rosy future. In this perspective, we have highlighted selected recent achievements in this field. We have tentatively organized them depending on the key strategic question which was tackled in each of these approaches. Some of them dealt with flexibility, through the identification of a key intermediate allowing to access a diversity of targets in the context of collective synthesis. Others blew a wind of change on hemisynthesis, offering unexpected and exciting skeletal remodeling to reach complex targets from already complex but abundant starting materials. Finally, some of them were about simplicity: finding the right disconnection in a classical retrosynthetic design to allow concise approaches towards complex structures. While every synthesis work described above has its own strong point, none of them is perfect. This perpetual search for perfection is what brings the field of organic synthesis forwards, and the reason why it still has good days ahead.

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ABBREVIATIONS

AIBN, azobisisobutyronitrile; cAMP, cyclic adenosine monophosphate; COD, cyclooctadiene; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DIAD, diisopropyl azodicarboxylate; DIPEA, *N,N*-diisopropylethylamine; DMAP, 4-dimethylaminopyridine; DMDO, dimethyldioxirane; DMS, dimethylsulfide; DMSO, dimethylsulfoxide; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HFIP, hexafluoroisopropanol; HMPA, hexamethylphosphoramide; IBX, 2-iodoxybenzoic acid; IMDA, intramolecular Diels-Alder; LDA, lithium diisopropylamide; *m*CPBA, *meta*-chloroperbenzoic acid; MMPP, magnesium monoperoxyphthalate; MOM, methoxymethyl; NIS, *N*-iodosuccinimide; PCC, pyridinium chlorochromate; PDC, pyridinium dichromate; PMB, *para*-methoxybenzyl; PTSA, *para*-toluenesulfonic acid; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; TES, triethylsilyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TMEDA, tetramethylethylenediamine; TMS, trimethylsilyl; TPS, triphenylsilyl.

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