# Natural product anticipation through synthesis

# Natural Product Anticipation Through Synthesis

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Abstract | Natural product synthesis remains one of the most vibrant and intellectually rewarding areas of chemistry, although the justifications for pursuing it have evolved over time. In the early years, the emphasis lay on structure elucidation and confirmation through synthesis, as exemplified by the celebrated studies on cocaine, morphine, strychnine and chlorophyll. This was followed by a phase where the sheer demonstration that highly complex molecules could be recreated in the laboratory in a rational manner was enough to justify the economic expense and intellectual agonies of a synthesis. Since then, syntheses of natural products have served as platforms for the demonstration of elegant strategies, for inventing new methodology "on the fly", or to demonstrate the usefulness and scope of methods established with simpler molecules. We now add another aspect that we find fascinating, viz. "Natural Product Anticipation". In this review, we survey cases where the synthesis of a compound in the laboratory has preceded its isolation from Nature. The focus of our review lies on examples where this anticipation of a natural product has triggered a successful search or where synthesis and isolation occurred independently. Finally, we highlight cases where such a possibility has been suggested but not yet confirmed, inviting further collaborations between synthetic and natural product chemists.

The total synthesis of natural products has always been a major factor in the development of organic chemistry. The reasons for pursuing it have evolved as the field has progressed. In its early history, total synthesis mostly served to confirm the constitution and configuration of readily available natural products. With the advent of X-ray crystallography, NMR spectroscopy, and mass spectrometry, this aspect has become less important, although numerous recent cases exist where the structure of a natural product was settled through total synthesis.[1,2] As a consequence, the emphasis has shifted more toward reaction development and the definition of efficient synthetic strategies. In some cases, the desire to achieve a particular transformation has led to the invention of new reactions or reagents that did not exist before.[3] If a total synthesis is sufficiently efficient, it can also be used to deliver a prized natural product on scale that can otherwise only be procured at great expense or by ignoring environmental concerns.[4] Many other motivations for total synthesis exist, ranging from its value as a training ground for medicinal chemists to the satisfaction that comes with solving the sheer intellectual challenge that it represents.[5,6] In this account, we wish to highlight yet another reason to pursue it: *Natural Product Anticipation*.

In the early days of organic synthesis, there must have been many cases where a compound was prepared in the laboratory and considered "synthetic" that was subsequently identified as a natural product. For instance, Gabriel made aminoacetone (**1**) in 1893 using his eponymous method.[7,8] The molecule was not detected in Nature until 1959, when Elliott identified it as a metabolite of *Staphylococcus aureus* (FIG. 1).[9] The amino acid proline (**2**) was first synthesized and characterized

by Willstätter, in racemic form, during his studies on *Coca* alkaloids in 1900.[10] Shortly afterwards, and before Willstätter could publish his work, it was identified by Fischer as a hydrolysis product of albumin and added to the canon of proteinogenic amino acids (FIG. 1).[11,12] A more recent and considerably more complex case is $13^2$, $17^3$-cyclopheophorbide enol (**3**), a porphyrin synthesized in the Eschenmoser laboratory as early as 1971 and isolated as a natural product from the sponge *Darwinella oxeata* in 1986 (FIG. 1).[13,14] It was also found in 1999 as a "molecular fossil" in various marine sediments.[15] In 1963, Bell and Ireland published synthetic studies towards the diterpene alkaloid (+)-atisine.[16] They arrived at the racemic hydrocarbon (±)-**4**, which contained the full carbon skeleton of their target. The exocyclic double bond of (±)-**4** could also be isomerized to give the endocyclic alkene (±)-**5**.[16,17] Around the same time, Zalkow and Girota reported the first part of their synthetic efforts towards (+)-atisine (**6**), where they prepared intermediate (+)-**4** in optically pure form.[18,19] Two years later, Dev and co-workers found enantiomerically pure (–)-**4** and (–)-**5** in *Erythroxylon monogynum* and named the hydrocarbons (–)-atisirene and (–)-isoatisirene, respectively (FIG. 1).[20] Since complex terpenoids are generally biosynthesized from reduced precursors, one wonders whether Bell, Ireland and Zalkow suspected that their synthetic intermediates could be genuine natural products and how much of a surprise their subsequent isolation was.

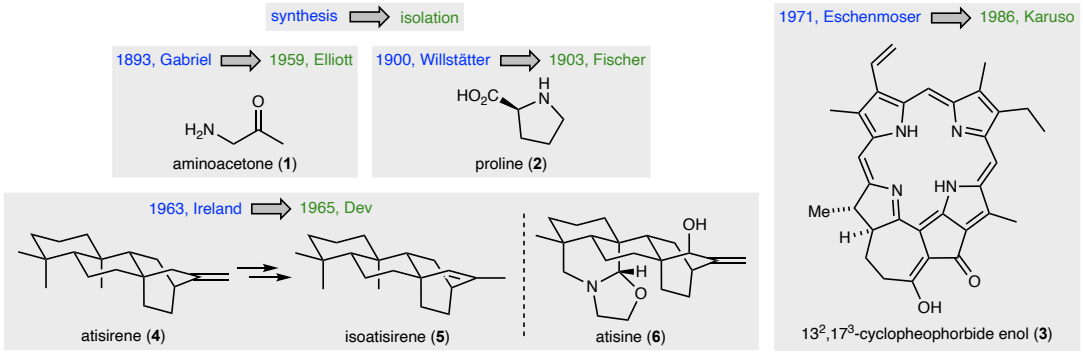


Fig. 1 | **Notable examples of "Unwitting" Natural Product Anticipation.** For these early examples there is no evidence to suggest the synthetic chemists envisaged that these structures would be later identified as natural products. The year and corresponding author are highlighted in blue for the reported synthesis, and in green for the subsequent isolation.

Numerous other examples of such "unwitting" discoveries exist. In this account, however, we will focus on what we consider the most satisfying type of natural product anticipation: wherein synthetic compounds were first made in the laboratory, suspected to occur in Nature, and subsequently confirmed as genuine natural products. Such predictions are usually based on biosynthetic considerations, the existence of analogous compounds, or on the reactivity of a natural product that was previously unrecognized. Hence, they often originate from biomimetic (or "bioinspired") syntheses, which attempt to emulate certain patterns found in Nature. These anticipated natural products are typically observed in the same natural source as the originally investigated natural product. In addition to confirmed cases, we will list compounds that have been anticipated but, for various reasons, not yet isolated. Our hope is that several of these compounds will be revealed as true natural products in the not-too-distant future. We do not cover natural product anticipation here that is based on genome mining and molecular network analysis. These powerful computational methods can predict not only the existence of natural products and their constitution but in some cases even their configuration and three dimensional structure.[21–23] While fascinating, this aspect of anticipation is beyond the scope of this review.

**Unexpected products formed in the laboratory, then found in Nature**

In 2010, Lee and co-workers disclosed a biomimetic total synthesis of guajadial (**11**), the prototypical member of the caryophyllene-derived family of meroterpenoids isolated from *Psidium guajava* (the common guava).[24,25] The biosynthesis of guajadial (**11**) was proposed to involve a *hetero*-Diels–Alder reaction between *ortho*-quinone methide **10** and caryophyllene (**7**) (FIG. 2a).[25] To mimic this in the laboratory, diformylphloroglucinol **9** was slowly added to an aqueous mixture of benzaldehyde (**8**) and caryophyllene (**7**). This gave guajadial (**11**) together with two unexpected diastereomers **12** and **13**. It was known that caryophyllene (**7**) adopts two major conformations in solution, the βα- and ββ-conformers, which differ in the relative disposition of the methylene and alkenyl methyl group (FIG. 2c).[26] Therefore, Lee and co-workers rationalized that guajadial (**11**) and its diastereomer **11** originate from *hetero*-Diels–Alder reactions involving the major conformer βα-**7**, whereas diastereomer **13** results from the minor conformer ββ-**7** (FIG. 2a). The isolated yields of **11** and **12** (from βα-**7**) compared to **13** (from ββ-**7**) are in good agreement with the reported βα/ββ conformation populations of caryophyllene (**7**) (FIG. 2c). Given the biomimetic nature of this reaction, Lee and co-workers suspected that **12** and **13** might represent as-yet-undiscovered natural products. During the preparation of their manuscript, isomer **12** was indeed isolated from *P. guajava* by Zhang and co-workers and named psidial A.[27] In 2017, isomer **13** was also isolated from the leaves of *P. guajava* by the Yin group and named psiguajadial L (FIG. 2a).[28]

In 2019, the Xie group reported the synthesis of the dimeric caryophyllene meroterpenoid psiguajdianone (**21**), which they had isolated from *P. guajava* (FIG. 2b).[29] Following a similar biomimetic logic as Lee and co-workers, a Knoevenagel condensation of phloroglucinol-derivative **15** with *para*-formaldehyde (**14**) lead to the transient formation of a rapidly interconverting mixture of tautomeric *ortho*-quinone methides **16a** and **16b** (FIG. 2b). *Hetero*-Diels–Alder reactions between these tautomers (**16a** and **16b**) and caryophyllene (**7**), either in its ββ- or βα-form, gave four different cycloadducts. Following reduction of the formyl group using $NaBH_3CN$, four isomeric products **17**–**20** were isolated, one of which (**20**) was the proposed precursor towards psiguajdianone (**21**). Treatment of **20** with AgOAc then gave the desired dimer **21**. Guided by their synthetic samples, they successfully isolated all four monomers **17**–**20** from *Psidium guajava* and named them psiguajanones A–D (FIG. 2b).

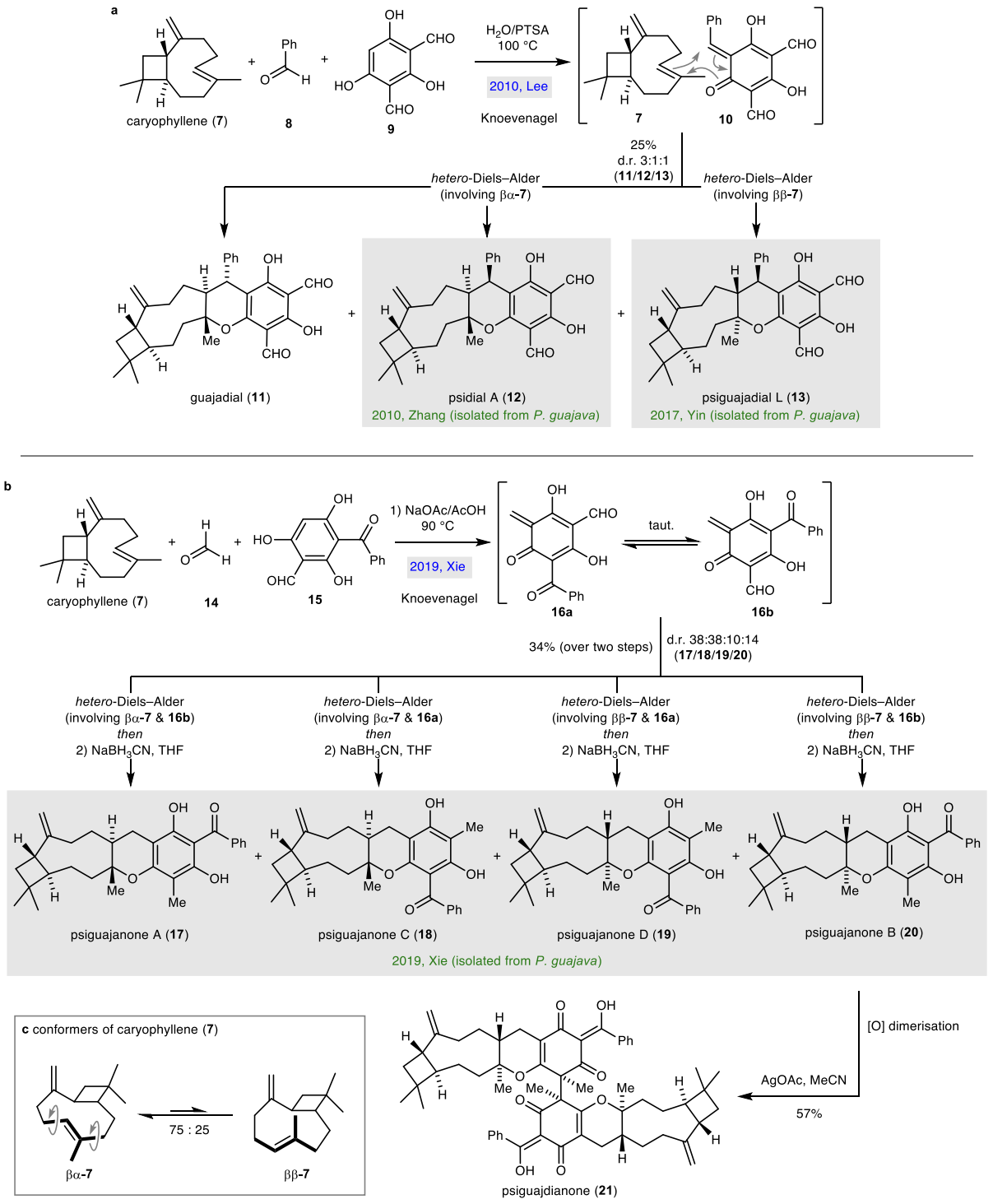


Fig. 2 | **Anticipation of caryophyllene-derived meroterpenoids from *Psidium guajava*. a** | Anticipation of psidial A (**12**) and psiguajadial L (**13**), through a multi-component biomimetic reaction. **b** | Anticipation of the psiguajanones A-D (**17-20**), through a multi-component biomimetic reaction, followed by reduction. **c** | The βα- and ββ-conformers of caryophyllene (**7**).

(±)-Incarviditone (**24**) is a racemic natural product isolated in 2009 from *Incarvillea delevayi* by Zhang and co-workers (FIG. 3a).[30] It formulates as a homochiral dimer – a combination of two "like" enantiomers – of the co-isolated natural product (±)-rengyolone (**22**). Intrigued by homochiral-selectivity in a presumably non-enzymatic biogenesis, Lawrence and co-workers investigated the feasibility of a proposed domino *oxa*-Michael/Michael dimerization of (±)-rengyolone (**22**) (FIG. 3a).[31] Treatment of **21** with sub-stoichiometric $K_2CO_3$ in $(CH_2Cl)_2$

successfully gave (±)-incarviditone (**24**) in 19% yield. An even more complex dimer, (±)-**25**, was isolated in 23% yield, which originated from the coupling of two "unlike" enantiomers of (±)-rengyolone (**22**). This heterochiral dimerization follows the same *oxa*-Michael/Michael cascade proposed for (±)-incarviditone (**24**), but the heterochiral dimer (±)-**27** undergoes a subsequent aldol-reaction to give (±)-**25** (FIG. 3a). During the preparation of a manuscript detailing this total synthesis, the Zhang group disclosed the isolation of the heterochiral product (±)-**25**, which they named incarvilleatone, from *Incarvillea younghusbandii*.[32] (±)-**24** and (±)-**25** belong to a growing number of natural products that have been isolated as true racemates.[33]

Spectinabilin (**29**) is an unusual nitroaryl-containing tetraene that was found in *Streptomyces spectabilis* together with the two bicyclo[4.2.0]octadienes SNF-4435C (**33**) and SNF-4435D (**34**) (FIG. 3b).[34–36] The isomeric nature of these compounds led Trauner and coworkers to the suggestion that under irradiation with sunlight (*E*,*E*,*E*,*Z*)-configured spectinabilin (**29**) is converted into the (*E*,*Z*,*Z*,*Z*)-polyene **30**, which then undergoes a thermal 8π-6π electrocyclization cascade.[37] Subsequently, Hertweck investigated the fermentation broth of *S. orinoci*, a related bacterial species that produces spectinabilin (**29**).[38] When the fermentation was carried out in the dark, no SNF-4435C or D (**33** or **34**) was detected. However, when the culture was exposed to daylight and artificial light at room temperature, the bicyclo[4.2.0]octadienes were also formed in *S. orinoci*. Interestingly, irradiation of purified (+)-spectinabilin (**29**) gave SNF-4435C and D (**33** and **34**) and a truncated spectinabilin analog **35**, which was named "orinocin" (FIG. 3b). The authors proposed that under irradiation, the 8π-6π electrocyclization cascade continues with a light-mediated retro-[2+2] cycloaddition, forming orinocin (**35**) *via* the extrusion of mesitylene (**36**). Reinvestigation of the fermentation broth with LC- and GC-MS indeed led to the detection of orinocin (**35**), as well as mesitylene (**36**). This confirmed mesitylene as a polyketide natural product formed through a photochemical "polyene-splicing" reaction.

Marine-derived dimeric pyrrole-imidazole alkaloids, such as ageliferin (**38**) and palau'amine, have attracted significant interest from the synthetic community.[39] In 2004, Baran and co-workers reported a biomimetic vinylcyclobutane rearrangement of sceptrin (**37**) to give ageliferin (**38**) (FIG. 3c).[40] This synthetic evidence gave support to their hypothesis that ageliferin (**38**) was not the result of a [4+2]-cycloaddition but was instead a rearrangement product of sceptrin (**37**), which can be seen as a [2+2]-cycloadduct of hymenidin (**40**) (FIG. 3c).[41] When the biomimetic vinyl cyclobutane rearrangement was conducted on a larger scale, a minor product, *epi*-ageliferin (**39**), was isolated as well. Whilst this synthetic work was ongoing, Kobayashi and co-workers investigated extracts from the Okinawan marine sponge *Agelas* sp. and found a new family of dimeric pyrrole-imidazole alkaloids, the nagelamides.[42] The structure of one of these metabolites, nagelamide E, matched *epi*-ageliferin (**39**). Notably, nagelamide E was isolated in a similar ratio to ageliferin (1:24) as during the total synthesis (1:20) (FIG. 3c).

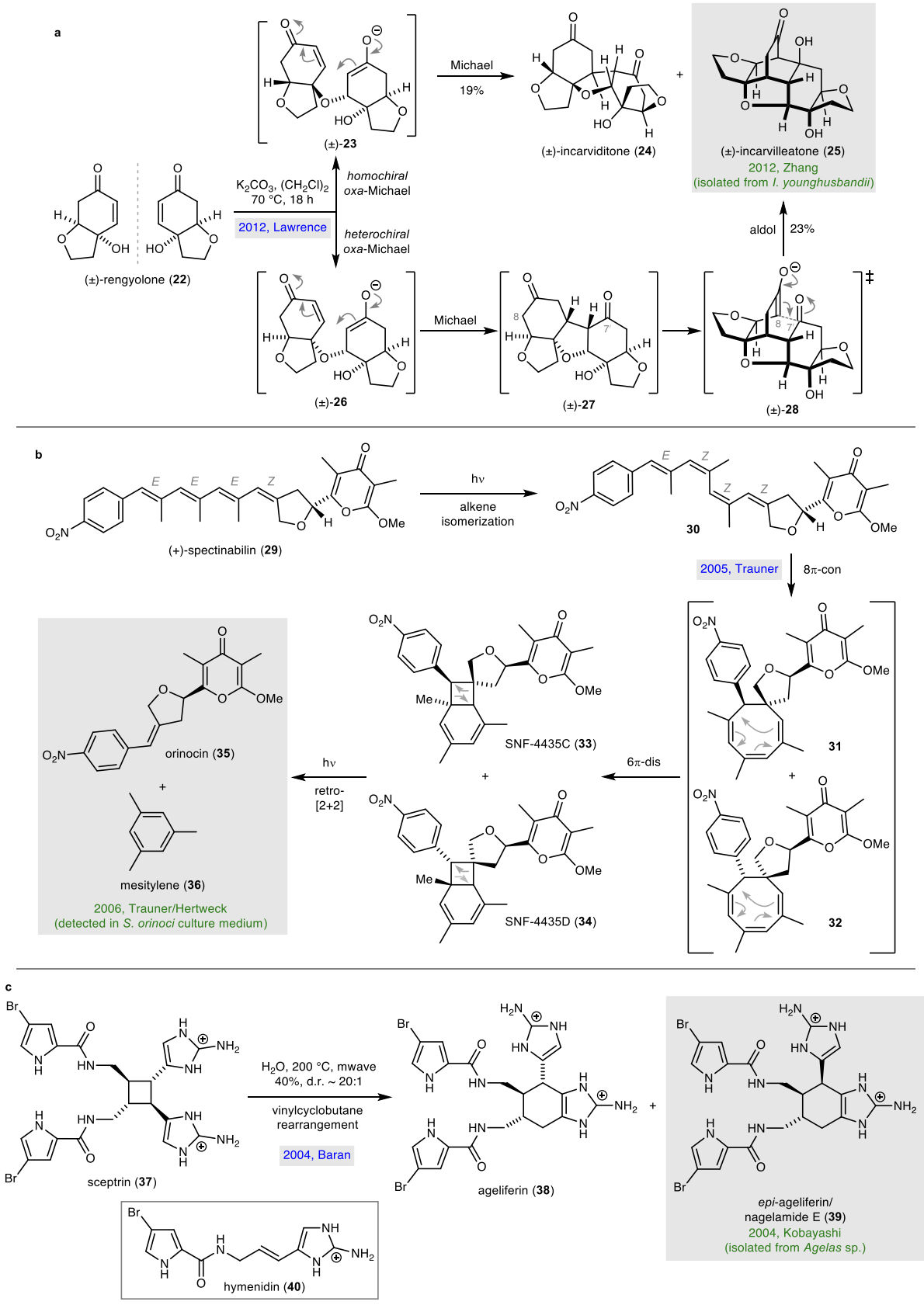


Fig. 3 | **Anticipation of incarvilleatone, mesitylene and nagelamide E. a** | Homochiral dimerization of (±)-rengyolone (**22**) gives the intended target, (±)-incaviditone (**24**), whereas heterochiral dimerization gives the anticipated natural product, (±)-incarvilleatone (**25**). **b** | Photochemical retro-[2+2] cycloaddition of the SNF-4435C and 4435D (**33** & **34**) gives mesitylene (**36**) and orinocin (**35**). **c** | Vinylcyclobutane rearrangement of sceptrin gives the intended target ageliferin (**38**), and the anticipated natural product, nagelamide E (**39**).

The unusual alkaloid exiguamine A (**43**) was isolated as a racemate from the marine sponge *Neopetrosia exigua* and was shown to be a potent indoleamine-2,3-dioxygenase inhibitor.[43] Intrigued by its unusual structure, Trauner and coworkers set out for its total synthesis.[44,45] Their biosynthetic hypothesis stipulated that the simple starting materials tryptophan, glycine and dopamine come together to yield *ortho*-quinone methide intermediate (**42**), which would undergo an *oxa*-6π-electrocyclization to form (±)-exiguamine A (**43**) (FIG. 4). When catechol **41** was exposed to 10 equivalents of silver (II) oxide, under acidic conditions, (±)-exiguamine A (**43**) was formed (FIG. 4). However, when 20-fold excess of silver (II) oxide was used, a new, hydroxylated derivative (**47**) was isolated as a single diastereomer. After communication with the isolation chemist Andersen, **47** was subsequently found in *N. exigua* and named exiguamine B. Supported by DFT calculations, a biosynthetic pathway was proposed that explains the formation of exiguamine A or B from the *bis*-quinone intermediate **44**, a tautomer of **42**. *Oxa*-6π-electrocyclization of **44** places an oxygen at the benzylic position of the *ortho*-quinone **45**, which in the presence of a large excess of oxidant can be irreversibly intercepted through oxidation and tautomerisation to give *ortho*-quinone methide **46**, which undergoes a final *oxa*-6π-electrocyclization to yield exiguamine B (**47**) (FIG. 4).

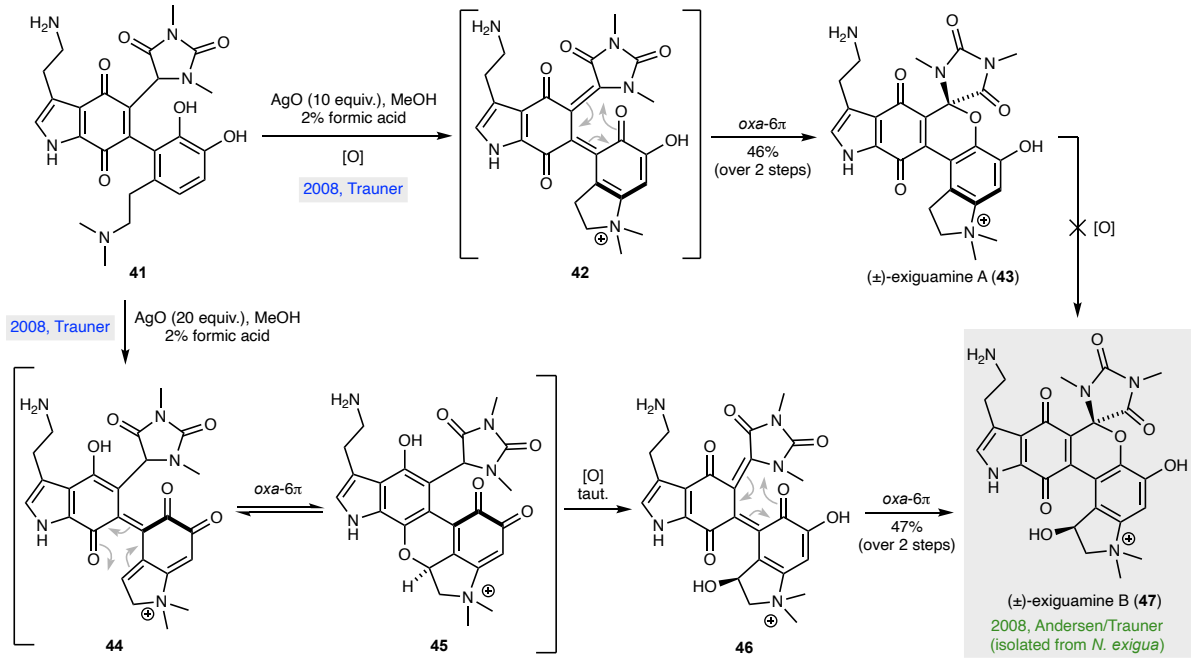


Fig. 4. | **Anticipation of exiguamine B.** Oxidation of catechol **41** with 10 equivalents of AgO gives the intended target exiguamine A (**43**), whereas use of 20 equivalents gives the anticipated natural product exiguamine B (**47**).

**"Missing" natural products synthesized in the laboratory, then found in Nature**

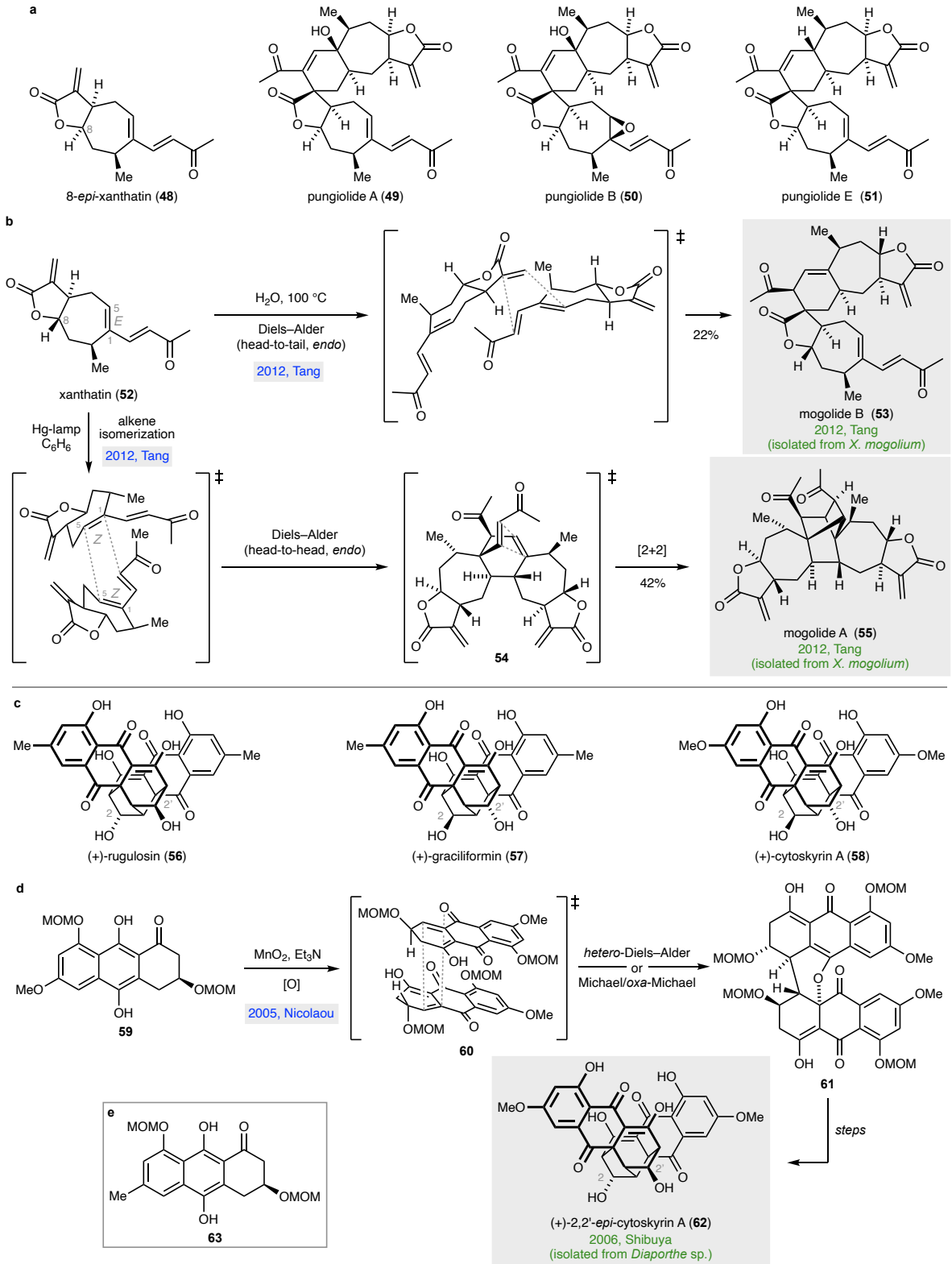


Fig. 5 | **Anticipation of "missing" dimeric natural products. a** | Known dimeric xanthanolides natural products (**49**-**51**) and their biosynthetic monomer 8-*epi*-xanthatin (**48**). **b** | Dimerization of xanthatin (**52**) leads to the anticipated natural products mogolides A and B (**53** & **55**) **c** | Known bisanthraquinone natural products (**56**-**58**). **d** | Oxidative dimerization of monomer **59** leads to the anticipated natural product 2,2'-*epi*-cytoskyrin A (**62**). **e** | Monomer **63**, used by Nicolaou and co-workers to access rugulosin (**56**).

The xanthanolides are a large family of sesquiterpenoids that usually contain a γ-butyrolactone fused to a seven-membered ring. They include pungiolide A (**49**), B (**50**), and E (**51**), which evidently stem from Diels–Alder dimerization of 8-*epi*-xanthatin (**48**) followed by isomerizations and oxidations (FIG. 5a). Tang and coworkers disclosed the total synthesis of various monomeric xanthanolides, including 8-*epi*-xanthatin (**48**) and its epimer xanthatin (**52**), which features a *trans*-fused butyrolactone.[46,47] With **52** in hand, they investigated the formation of dimers analogous to pungiolide E (**51**), assuming that this epimer would undergo analogous dimerizations. Heating xanthatin (**52**) yielded the dimer **53** *via* a thermal "head-to-tail", *endo*-selective Diels–Alder reaction (FIG. 5b). By contrast, under photochemical conditions xanthatin (**52**) dimerized to give the "head-to-head" dimeric xanthanolide **55**. The authors reasoned that irradiation led to isomerization of the C1-C5 double-bond to form a highly reactive *trans*-cycloheptene, which could then undergo a "head-to-head" Diels–Alder homodimerization. The resulting intermediate **54** then underwent an intramolecular [2+2]-cycloaddition to form **55** (FIG. 5b). Since no dimeric xanthanolides based on xanthatin (**52**) were known at the time of the investigations, the authors reinvestigated the natural source, *Xanthium mogolium*, a medicinal plant found in Northeast China. Remarkably, they isolated the predicted natural products **53** and **55**, which they named mogolides A and B, respectively.

The bisanthraquinone natural products rugulosin (**56**), graciliformin (**57**), and cytoskyrin A (**58**) are of fungal and lichen origin and show marked bioactivities (FIG. 5c).[48–53] Rugulosin (**56**) and graciliformin (**57**) differ in their configurations at C2 and C2' and are homodimers of a methyl-substituted anthraquinone. Cytoskyrin A (**58**) is a homodimer of a similar, methoxy-substituted anthraquinone, the configuration of which corresponds to graciliformin (**57**). By analogy to rugulosin, a second methoxy-substituted dimer could exist in Nature. In 2005, the Nicolaou group reported the biomimetic synthesis of (+)-rugulosin (**56**) through an oxidative dimerization of **63** (FIG. 5e).[54][55] Using similar conditions, they also dimerized methoxy-anthraquinone **59**, which led to the then unknown 2,2'-*epi*-cytoskrin A (**61**) (FIG. 5d). A year later, the Shibuya group found (+)-**62** in the fungus *Diaporthe* sp. confirming the suspected existence of the second dimer in nature.[51] Interestingly, graciliformin (**57**) and cytoskyrin A (**58**), which bear the secondary hydroxy groups in an *endo* position, have not yet been synthesized in the laboratory.

Trauner and Miller pursued the biomimetic synthesis of pyrone natural products isolated from the sacoglossan mollusk *Placobranchus ocellatus*.[56,57] To this end, (*E*,*Z*,*Z*,*E*)-tetraene **66** was prepared using a Stille–Liebeskind coupling of alkenyl stannane **64** with alkenyl iodide **65** (FIG. 6a). The resulting tetraene underwent an *in situ* 8π–6π electrocyclization cascade to give a 1:9 mixture of racemic bicylo[4.2.0]octadienes, (±)-**67** (ocellapyrone A) and (±)-**68**.[58] The latter was subjected to singlet oxygen, which gave the endoperoxide ocellapyrone B (**69**). Ruthenium-catalyzed isomerization then yielded bisepoxide **70**, the 14-methyl homolog of the known bis-epoxide elysiapyrone A (**71**), which had been isolated from the "sap-sucking" sacoglossan sea slug *Elysia diomedea*. The ease with which endoperoxides can be converted into bis-epoxides, even in the absence of a transition metal catalyst, suggested that **70** may also occur in Nature. Indeed, in 2020 Guo, Liu and Nay reported the isolation of 14-methylelysiapyrone from *P. ocellatus* (FIG. 6a).[59]

The bis(cyclotryptamine) alkaloids have been of interest since the isolation of the first congener in 1888 and numerous total syntheses, biosynthetic studies, and isolations have been reported.[60–64] The natural products share a common carbon skeleton but feature different heterocyclic ring systems (**72**-**75**) (FIG. 6b).[65] Garg, Garcia-Garibay and co-workers were intrigued by the fact that no family members with a piperidinoindoline structure had been isolated although this is conceivable based on a postulated common biosynthetic precursor.[66] Accordingly, they set out to synthesize this type

using a photodecarbonylation strategy. Thus, ketone **76** was subjected to irradiation in the solid state, which after deprotection afforded the bispyrrolidinone **77** (FIG. 6c). *N*-methylation followed by azidation then yielded $C_2$-symmetric precursor **78**. Reduction of the aryl azides to the corresponding anilines with concomitant transamidation, cyclocondensation and reduction of one of the two amidines gave the unsymmetrical piperidinoindoline **79**. This intermediate could be oxidized to $C_2$-symmetric piperidinoindoline **80**, which, like its precursor, was suspected to be a natural product. Indeed, upon reexamination of an extract from *Psychotria colorata*, **80** could be identified as a genuine natural product and was named psychotriadine. Incidentally, meso-chimonantine **75** itself is an anticipated natural product, as it was isolated from *C. floridus* in 1967, just a few days after its synthesis from *N*-methyl tryptamine. [67]

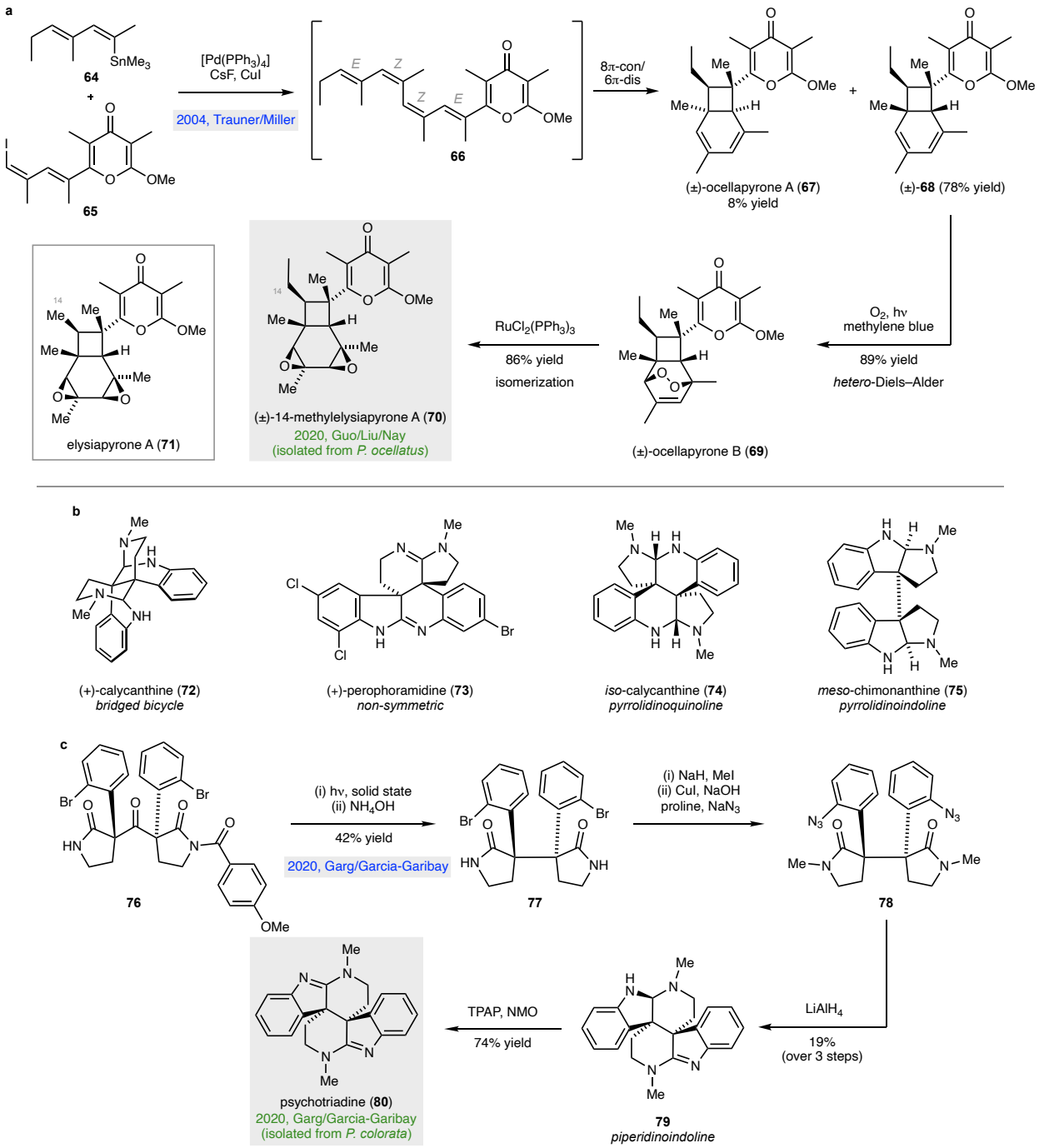


Fig. 6 | **Anticipation of 14-methylelysiapyrone A and psychotriadine. a** | Biomimetic total synthesis of the anticipated natural product, 14-methylelysiapyrone A (**70**). **b** | Known bis(cyclotryptamine) alkaloids with different isomeric scaffolds. **c** | Total synthesis of a newly anticipated piperidinoindoline-type bis(cyclotryptamine) alkaloid, psychotriadine (**80**).

## A natural product has unexpected reactivity

Marine gastropods produce a large variety of polypropionate-derived natural products. These compounds are suspected to act as a sunscreen to protect the mollusks from UV-light in the shallow waters of their natural habitat. (–)-Tridachiahydropyrone (**83**) was isolated in 1996 from *Elysia crispata* (FIG. 7a).[68] In 2009, Moses and coworkers reported a biomimetic synthesis of racemic tridachiahydropyrone, which involved a photoinduced alkene isomerization of the linear all-*E* polyene chain in **81**, followed by a photochemical conrotatory 6π-electrocyclization.[69] Interestingly, a side-product, termed "phototridachiahydropyrone" (**84**) was isolated that was presumably formed by a subsequent [1,3]-sigmatropic rearrangement of **83**. UV light was found to be necessary to promote the shift of the side chain. In 2015, Gavagnin and coworkers, who originally isolated (–)-tridachiahydropyrone (**83**), reinvestigated the extract of *Elysia crispata* and successfully isolated (−)-phototridachiahydropyrone (**84**) (FIG. 7a).[70]

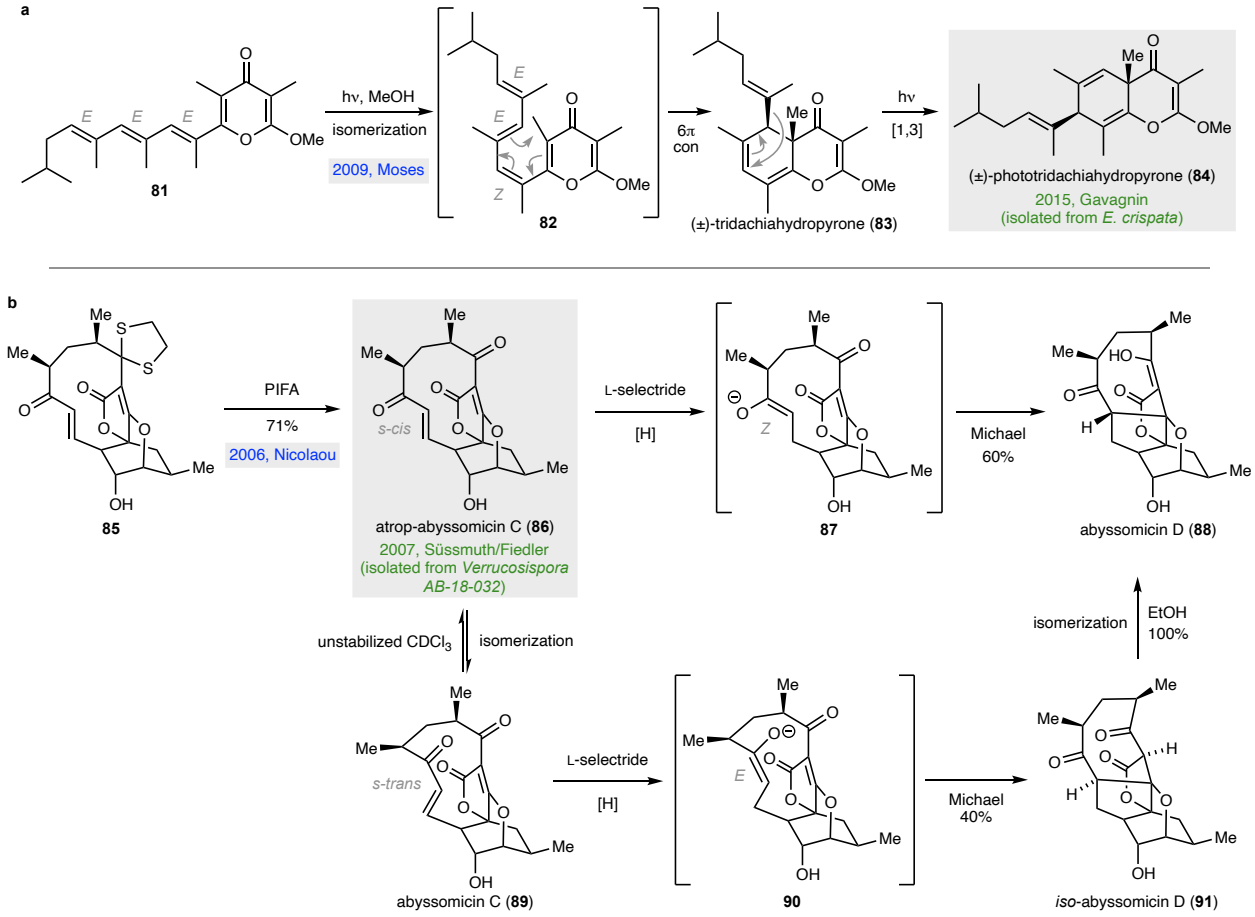


Fig. 7 | **Anticipation of phototridachiahydropyrone and atrop-abyssomicin C. a** | Biomimetic total synthesis of the anticipated natural product, phototridachiahydropyrone (**84**) *via* photochemical [1,3]-sigmatropic rearrangement of tridachiahydropyrone (**83**). **b** | Total synthesis of the anticipated natural product, atrop-abyssomicin C (**86**) and its isomerization into the target natural product, abyssomicin C (**89**). It was also found that reduction of atrop-abyssomicin C (**86**) gives abyssomicin D (**88**), whereas reduction of abyssomicin C (**89**) gives *iso*-abyssomicin D (**91**), which is not a known natural product.

The antibiotic polyketide abyssomicin C (**89**) was isolated in 2004 from the marine actinomycete *Verrocosispora* strain AB 18-032 by Süssmuth and Fielder (FIG. 7b).[71] Structurally, abyssomicin C

(**89**) possesses a strained 11-membered ring that contains a reactive α,β-unsaturated ketone and a core tetronate motif. The Nicolaou group set out to achieve the biomimetic total synthesis of this intriguing natural product.[72,73] Treatment of intermediate **85** with PIFA to effect a dithioketal deprotection did not yield the desired product **89**, but a compound that was identified as an atropisomer **86** (FIG. 7b). Upon exposure to acidic $CDCl_3$, atrop-abyssomicin C (**86**) underwent gradual isomerization to abyssomicin C (**89**), which could by separated by HPLC. During an attempted biomimetic conversion of abyssomicin C (**89**) into abyssomicin D (**88**) *via* conjugate reduction of the enone, followed by intramolecular Michael addition, the authors exclusively isolated a diastereomer named *iso*-abyssomicin D (**91**). The latter slowly isomerized into abyssomicin D (**88**) upon standing in ethanol. By contrast, treatment of atrop-abyssomicin C (**86**) with L-selectride gave abyssomicin D (**88**) directly (FIG. 7b). These results suggest that atrop-abyssomicin C (**86**) could also be a natural product that is enzymatically reduced and converted into abyssomicin D (**88**). Indeed, in 2007 Süssmuth and Fiedler isolated atrop-abyssomicin C (**86**) as the main component from the culture broth of *Verrucosispora* AB-18-032 along with abyssomicin C (**89**) (FIG. 7b).[74] Upon HPLC purification with acidic solvents atrop-abyssomicin C (**86**) was depleted and abyssomicin C (**89**) was formed. Interestingly, *iso*-abyssomycin D (**91**) has yet to be found in Nature.

## Conclusion and outlook

We hope to have shown that Natural Product Anticipation adds another facet to total synthesis research, further increasing its intellectual intrigue and practical value. Synthetic studies can provide important insights into the formation and reactivity of natural products, whilst delivering valuable synthetic samples to help steer targeted spectroscopic/spectrometric identification and chromatographic separation of new natural products.

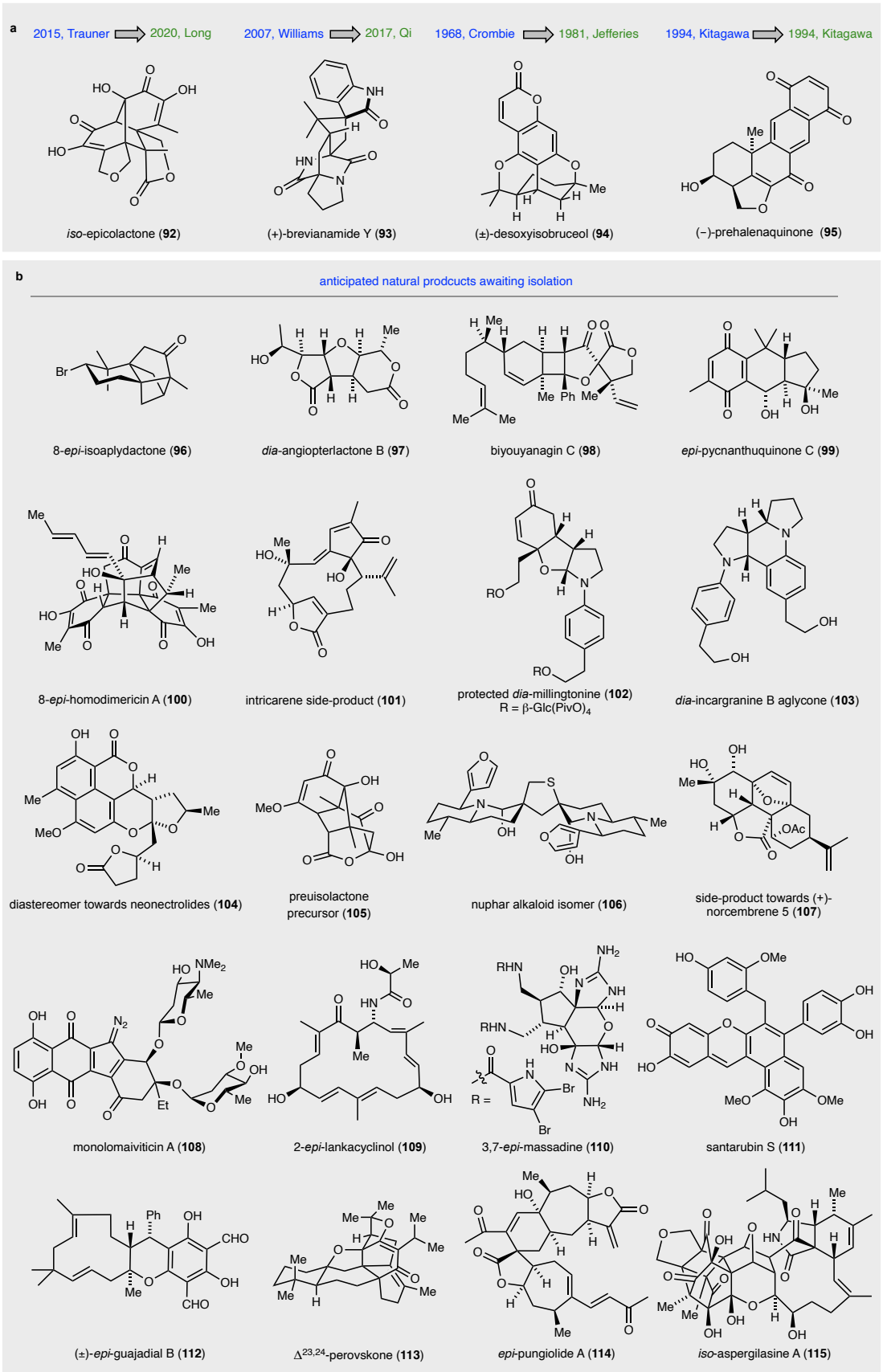


Fig. 8 | **Additional examples for anticipated natural products and suspected natural products awaiting cofirmation. a** | *iso*-epicolactone (**92**)[75,76], (+)-brevianamide Y (**93**),[77–79] (±)-desoxyisobruceol (**94**)[80–83], and (–)-prehalenaquinone

(**95**)[84] are additional examples for molecules that were synthesized in the laboratory prior to their isolation. **b |** Cases of anticipated natural products that await isolation from natural sources: 8-*epi*-isoaplydactone (**96**),[85] *dia*-angiopterlactone B (**97**),[86] biyouyanagin C (**98**),[87] *epi*-pycnanthuquinone C (**99**),[88] 8-*epi*-homodimericin A (**100**),[89] intricarene side-product (**101**),[90] protected *dia*-millingtonine (**102**)[91], *dia*-incargranine B aglycone (**103**)[92], diastereomer towards neonectrolides (**104**)[93], preuisolactone precursor (**105**)[94], nuphar alkaloid isomer (**106**)[95], side-product towards (+)-norcembrene 5 (**107**)[96], monolomaiviticin A (**108**)[97], 2-*epi*-lankacyclinol (**109**)[98], 3,7-*epi*-massadine (**110**)[99], santarubin S (**111**)[100], *epi*-guajadial B (**112**)[101], $\Delta^{23,24}$-perovskone (**113**)[102], *epi*-pungiolide A (**114**)[103], and *iso*-aspergilasine A (**115**)[104].

This review cannot be comprehensive since it relies mostly on our own experience in the field of biomimetic natural product synthesis and is limited by difficulties in finding diffuse information in the vast chemical literature. Anticipated natural products are often not identified as such in writing, perhaps reflecting an innate reluctance of scientists to publish speculations. The true story behind their prediction and isolation is sometimes buried in personal accounts. We are, therefore, indebted to many colleagues and friends for their suggestions and insights, which were invaluable in collating the examples we have presented. There are many more cases of natural product anticipation that could not be covered in detail in this review and a selection thereof is shown in FIG. 8a. A sample of anticipated natural products awaiting confirmation of their natural product credentials is show in FIG. 8b. Hopefully, our account will stimulate further collaborations between synthetic and natural product chemists, and lead to new examples of anticipated natural products to add to this already impressive list.

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