Published in final edited form as:

Nat Rev Chem. 2022 March ; 6(3): 170–181. doi:10.1038/s41570-021-00345-7.

Natural product anticipation through synthesis

Belinda E. Hetzler[1], **Dirk Trauner**[1,✉], **Andrew L. Lawrence**[2,✉]

[1]Department of Chemistry, New York University, New York, NY, USA.

[2]EaStCHEM School of Chemistry, University of Edinburgh, Edinburgh, UK.

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 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 have occurred independently. Finally, we highlight cases where a potential natural product structure has been suggested as a result of synthetic endeavours but not yet confirmed by isolation, inviting further collaborations between synthetic and natural product chemists.

The total synthesis of natural products has always been a major goal in 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 as a result of total synthesis[1,2]. Consequently, the emphasis in the field has shifted more towards reaction development and the definition of efficient synthetic strategies. In some cases, the desire to achieve a particular transformation en route to a natural product has led to the invention of new reactions or reagents that did not exist previously[3]. If a total synthesis is suitably efficient, it might also be used to deliver a prized natural product on a scale that can other wise only be procured at great expense or by ignoring environmental concerns[4]. Many other motivations

✉ dirktrauner@nyu.edu; a.lawrence@ed.ac.uk.

The authors contributed equally to all aspects of the article.

Competing interests

The authors declare no competing interests.

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 were undoubtedly many cases where a compound was prepared in the laboratory and considered 'synthetic' that was subsequently identified as a natural product. For instance, using his eponymous method, Gabriel made aminoacetone (**1**) in 1893 (REFS[7,8]). It was not until 1959 that the molecule was detected in nature, when Elliott identified it as a metabolite of *Staphylococcus aureus*[9] (FIG. 1). Similarly, the amino acid proline (**2**) was first synthesized and characterized by Willstätter, in racemic form, during his studies on coca alkaloids in 1900 (REF.[10]). Shortly afterwards, and before Willstätter could publish his work, Fischer identified proline as a hydrolysis product of albumin and it was, thus, added to the canon of proteinogenic amino acids[11,12] (FIG. 1). A more recent, and considerably more complex, case is that of 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 (REFS[13,14]) (FIG. 1). 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** (REFS[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 colleagues found enantiomerically pure (−)-**4** and (−)-**5** in *Erythroxylon monogynum* and named the hydrocarbons (−)-atisirene and (−)-isoatisirene, respectively[20] (FIG. 1). 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, thus, how much of a surprise their subsequent isolation was.

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 3D structure[21–23]. While fascinating, this aspect of anticipation is beyond the scope of this Review.

Unexpected products

In 2010, Lee and colleagues 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**)[25] (FIG. 2a). To mimic this process 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[26] (FIG. 2c). Therefore, Lee and colleagues rationalized that guajadial (**11**) and its diastereomer **12** 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 with **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 colleagues already suspected that **12** and **13** might represent as-yet-undiscovered natural products. Indeed, while they were preparing the manuscript describing their synthesis, isomer **12** was isolated from *P. guajava* by Zhang and colleagues and named psidial A (REF.[27]). In 2017, isomer **13** was also isolated from the leaves of *P. guajava* by the Yin group and named psiguajadial L (REF.[28]) (FIG. 2a).

In 2019, the Xie group reported the synthesis of the dimeric caryophyllene meroterpenoid psiguajdianone (**21**), which they had isolated from *P. guajava*[29] (FIG. 2b). Following similar biomimetic logic to Lee and colleagues, a Knoevenagel condensation of phloroglucinol derivative **15** with *para*-formaldehyde (**14**) led to the transient formation of a rapidly interconverting mixture of tautomeric *ortho*-quinone methides **16a** and **16b** (REF.[24]) (FIG. 2b). *Hetero*-Diels–Alder reactions between these tautomers (**16a** and **16b**) and caryophyllene (**7**), in either 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 *P. guajava* and named them psiguajanones A–D (FIG. 2b).

(±)-Incarviditone (**24**) is a racemic natural product isolated in 2009 from *Incarvillea delavayi* by Zhang and colleagues[30] (FIG. 3a). 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 colleagues investigated the feasibility of a proposed domino *oxa*-Michael/Michael dimerization of (±)-rengyolone (**22**)[31] (FIG. 3a). 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**, originating from the coupling of two 'unlike' enantiomers of (±)-rengyolone (**22**), was isolated in 23% yield. 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**)[34–36] (FIG. 3b). The isomeric nature of these compounds led Trauner and Beaudry to suggest that irradiation with sunlight stimulates (*E,E,E,Z*)-configured spectinabilin (**29**) to undergo conversion 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 SNF-4435D (**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 SNF-4435D (**33** and **34**) and a truncated spectinabilin analogue **35**, which was named 'orinocin' (FIG. 3b). It was 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 liquid chromatography and gas chromatography–mass spectrometry 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 et al. reported a biomimetic vinylcyclobutane rearrangement of sceptrin (**37**) to give ageliferin (**38**)[40] (FIG. 3c). 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**)[41] (FIG. 3c). 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 colleagues 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, the ratio of nagelamide E to ageliferin was similar when isolated from the natural source (1:24) and when prepared synthetically (1:20) (FIG. 3c).

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 colleagues embarked upon

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 (REF.[45]). A biosynthetic pathway, supported by discrete Fourier transform calculations, 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 tautomerization to give *ortho*-quinone methide **46**, which undergoes a final *oxa*-6π electrocyclization to yield exiguamine B (**47**) (FIG. 4).

‘Missing’ natural products

The xanthanolides are a large family of sesquiterpenoids that usually contain a γ-butyrolactone fused to a seven-membered ring. They include pungiolides A (**49**), B (**50**) and E (**51**), which evidently stem from Diels–Alder dimerization of 8-epi-xanthatin (**48**), followed by isomerizations and oxidations[46–50] (FIG. 5a). Tang and colleagues disclosed the total synthesis of various monomeric xanthanolides, including 8-epi-xanthatin (**48**) and its epimer xanthatin (**52**), which features a *trans*-fused butyrolactone[51,52]. 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**. This outcome was rationalized by assuming that 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[53–57] (FIG. 5c). 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** (REFS[58,59]) (FIG. 5e). Using similar conditions, they also dimerized methoxy-anthraquinone **59**, which led to the then unknown 2,2′-epi-cytoskyrin

A (**62**) (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[60]. 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 sacogl ossan mollusc *Placobranchus ocellatus*[61,62]. 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 bicyclo[4.2.0]octadienes, (±)-**67** (ocellapyrone A) and (±)-**68** (REF.[63]). The latter was subjected to singlet oxygen, which gave the endoperoxide ocellapyrone B (**69**). Ruthenium-catalysed isomerization then yielded bisepoxide **70**, the 14-methyl homologue 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, Li, Guo and Nay reported the isolation of 14-methylelysiapyrone from *P. ocellatus*[64] (FIG. 6a).

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[65–69]. The natural products share a common carbon skeleton but feature different heterocyclic ring systems (**72**–**75**)[70] (FIG. 6b). Garg, Garcia-Garibay and colleagues 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[71]. Accordingly, they set out to synthesize this type using a photodecarbonylation strategy. Thus, ketone **76** was subjected to irradiation in the solid state, the product of which, following 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 re-examination of an extract from *Psychotria colorata*, **80** could be identified as a genuine natural product and was named psychotriadine. Incidentally, meso-chimonanthine **75** itself is an anticipated natural product, as it was isolated from *Calycanthus floridus* in 1967, just a few days after its synthesis from *N*-methyl tryptamine[72].

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 molluscs from ultraviolet light in the shallow waters of their natural habitat. (−)-Tridachiahydropyrone (**83**) was isolated in 1996 from *E. crispata*[73] (FIG. 7a). In 2009, Moses and colleagues 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[74]. Interestingly, a side product, termed

'phototridachiahydropyrone' (**84**) was isolated that was presumably formed by a subsequent [1,3]-sigmatropic rearrangement of **83**. Ultraviolet light was found to be necessary to promote the shift of the side chain. In 2015, Gavagnin et al., who originally isolated (−)-tridachiahydropyrone (**83**), reinvestigated the extract of *E. crispata* and successfully isolated (−)-phototridachiahydropyrone (**84**)[75] (FIG. 7a).

The antibiotic polyketide abyssomicin C (**89**) was isolated in 2004 from the marine actinomycete *Verrucosispora* strain AB-18–032 by Süssmuth and colleagues[76] (FIG. 7b). 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[77,78]. Treatment of intermediate **85** with phenyliodine(III) bis(trifluoroacetate) (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 be separated by high-performance liquid chromatography. 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, Fiedler and colleagues isolated *atrop*-abyssomicin C (**86**) as the main component from the culture broth of *Verrucosispora* AB-18–032, along with abyssomicin C (**89**)[79] (FIG. 7b). Upon high-performance liquid chromatography purification with acidic solvents, *atrop*-abyssomicin C (**86**) was depleted and abyssomicin C (**89**) was formed. Interestingly, iso-abyssomicin 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.

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 shown 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.

Acknowledgements

B.E.H. thanks New York University for a MacCracken fellowship. The authors thank B. S. Matsuura for helpful discussions. The authors thank B. S. Matsuura, A. J. E. Novak and K.- P. Rühmann for their critical review of the manuscript.

References

1. Nicolaou KC & Snyder SA Chasing molecules that were never there: misassigned natural products and the role of chemical synthesis in modern structure elucidation. Angew. Chem. Int. Ed 44, 1012–1044 (2005).
2. Brown PD & Lawrence AL The importance of asking “how and why?” in natural product structure elucidation. Nat. Prod. Rep 34, 1193–1202 (2017). [PubMed: 28850146]
3. Sheehan JC & Henery-Logan KR The total synthesis of penicillin V. J. Am. Chem. Soc 79, 1262–1263 (1957).
4. Kuttruff CA, Eastgate MD & Baran PS Natural product synthesis in the age of scalability. Nat. Prod. Rep 31, 419–432 (2014). [PubMed: 24337165]
5. Baran PS Natural product total synthesis: as exciting as ever and here to stay. J. Am. Chem. Soc 140, 4751–4755 (2018). [PubMed: 29635919]
6. Trauner D Finding function and form. Nat. Prod. Rep 31, 411–413 (2014). [PubMed: 24595414]
7. Gabriel S & Pinkus G Zur Kenntniss der Amidoketone. Ber. Dtsch. Chem. Ges 26, 2197–2209 (1893).
8. Gabriel S & Colman J Zur Kenntniss des Amidoacetons. Ber. Dtsch. Chem. Ges 35, 3805–3811 (1902).
9. Elliott WH Amino-acetone: its isolation and role in metabolism. Nature 183, 1051–1052 (1959). [PubMed: 13644279]
10. Willstätter R Synthese der Hygrinsäure. Ber. Dtsch. Chem. Ges 33, 1160–1166 (1900).
11. Fischer E & Abderhalden E Ober die verdauung einiger Eiweißkörper durch Pankreasfermente. Biol. Chem 39, 81–94 (1903).
12. Willstätter R From My Life: The Memoirs of Richard Willstätter (Plunkett Lake, 2016).
13. Falk H, Hoornaert G, Isenring H-P & Eschenmoser A Über Enolderivate der Chlorophyllreihe. Darstellung von 13^2,17^3-Cyclophäophorbid-enolen. Vorläufige Mitteilung. Helv. Chim. Acta 58, 2347–2357 (1975).
14. Karuso P et al. 13^2,17^3-Cyclopheophorbide enol, the first porphyrin isolated from a sponge. Tetrahedron Lett. 27, 2177–2178 (1986).
15. Ocampo R, Sachs JP & Repeta DJ Isolation and structure determination of the unstable 13^2, 17^3-Cyclopheophorbide a enol from recent sediments. Geochim. Cosmochim. Acta 63, 3743–3749 (1999).
16. Bell RA & Ireland RE The construction of the C/D ring system present in the diterpenoid alkaloids atisine and garryfoline. Tetrahedron Lett. 4, 269–273 (1963).
17. Church RF, Ireland RE & Marshall JA The stereospecific total synthesis of d1–8β-carbomethoxy13-oxopodocarpane, a degradation product of phyllocladene. Tetrahedron Lett. 1, 1–4 (1960).
18. Zalkow LH & Girotra NN The synthesis of 5a, 8,8-trimethyl-3, 10a-ethanoperhydrophenanthrene. Terpenes. VII. J. Org. Chem 28, 2037–2039 (1963).
19. Zalkow LH & Girotra NN Studies in the synthesis of atisine. Terpenes. X. J. Org. Chem 29, 1299–1302 (1964).
20. Kapadi AH, Sobti RR & Dev S The diterpenoids of *Erythroxylon monogynum* — V atisirene, isoatisirene and devadarene. Tetrahedron Lett. 6, 2729–2735 (1965).

21. Bonneau N et al. An unprecedented blue chromophore found in nature using a “chemistry first” and molecular networking approach: discovery of dactylocyanines A–H. Chem. Eur. J 23, 14454–14461 (2017). [PubMed: 28815818]
22. Fox Ramos AE et al. CANPA: computer-assisted natural products anticipation. Anal. Chem 91, 11247–11252 (2019). [PubMed: 31369240]
23. Medema MH & Fischbach MA Computational approaches to natural product discovery. Nat. Chem. Biol 11, 639–648 (2015). [PubMed: 26284671]
24. Lawrence AL et al. A short biomimetic synthesis of the meroterpenoids guajadial and psidial A. Org. Lett 12, 1676–1679 (2010). [PubMed: 20235528]
25. Yang X-L, Hsieh K-L & Liu J-K Guajadial: an unusual meroterpenoid from guava leaves psidium guajava. Org. Lett 9, 5135–5138 (2007). [PubMed: 17985919]
26. Collado IG, Hanson JR & Macías-Sánchez AJ Recent advances in the chemistry of caryophyllene. Nat. Prod. Rep 15, 187–204 (1998).
27. Fu H-Z, Luo Y-M, Li C-J, Yang J-Z & Zhang D-M Psidials A–C, three unusual meroterpenoids from the leaves of *Psidium guajava* L. Org. Lett 12, 656–659 (2010). [PubMed: 20078113]
28. Tang G-H et al. Psiguajadials A–K: unusual *Psidium* meroterpenoids as phosphodiesterase-4 inhibitors from the leaves of *Psidium guajava*. Sci. Rep 7, 1047 (2017). [PubMed: 28432317]
29. Ning S, Liu Z, Wang Z, Liao M & Xie Z Biomimetic synthesis of psiguajdianone guided discovery of the meroterpenoids from *Psidium guajava*. Org. Lett 21, 8700–8704 (2019). [PubMed: 31609125]
30. Chen Y-Q, Shen Y-H, Su Y-Q, Kong L-Y & Zhang W-D Incarviditone: a novel cytotoxic benzofuranone dimer from *Incarvillea delavayi* Bureau et Franchet. Chem. Biodivers 6, 779–783 (2009). [PubMed: 19479844]
31. Brown PD, Willis AC, Sherburn MS & Lawrence AL Total synthesis of incarviditone and incarvilleatone. Org. Lett 14, 4537–4539 (2012). [PubMed: 22931401]
32. Gao Y-P et al. Incarvilleatone, a new cyclohexylethanoid dimer from *Incarvillea younghusbandii* and its inhibition against nitric oxide (NO) release. Org. Lett 14, 1954–1957 (2012). [PubMed: 22483266]
33. Novak AJE & Trauner D Reflections on racemic natural products. Trends Chem. 2, 1052–1065 (2020).
34. Kakinuma K, Hanson CA & Rinehart KL Spectinabilin, a new nitro-containing metabolite isolated from *Streptomyces spectabilis*. Tetrahedron 32, 217–222 (1976).
35. Takahashi K, Tsuda E & Kurosawa K SNF4435C and D, novel imimmosuppressants produced by a strain of *Streptomyces spectabilis*. II. Structure elucidation. J. Antibiot 54, 548–553 (2001).
36. Kurosawa K, Takahashi K & Tsuda E SNF4435C and D, novel immunosuppressants produced by a strain of *Streptomyces spectabilis*. I. Taxonomy, fermentation, isolation and biological activities. J. Antibiot 54, 541–547 (2001).
37. Beaudry CM & Trauner D Total synthesis of (−)-SNF4435 C and (+)-SNF4435 D. Org. Lett 7, 4475–4477 (2005). [PubMed: 16178562]
38. Müller M et al. Photochemical origin of the immunosuppressive SNF4435C/D and formation of orinocin through “polyene splicing”. Angew. Chem. Int. Ed 45, 7835–7838 (2006).
39. Lindel T Chemistry and biology of the pyrrole–imidazole alkaloids. Alkaloids Chem. Biol 77, 117–219 (2017). [PubMed: 28212701]
40. Baran PS, O’Malley DP & Zografos AL Sceptrin as a potential biosynthetic precursor to complex pyrrole–imidazole alkaloids: the total synthesis of ageliferin. Angew. Chem. Int. Ed 43, 2674–2677 (2004).
41. Northrop BH, O’Malley DP, Zografos AL, Baran PS & Houk KN Mechanism of the vinylcyclobutane rearrangement of sceptrin to ageliferin and nagelamide E. Angew. Chem. Int. Ed 45, 4126–4130 (2006).
42. Endo T et al. Nagelamides A–H, new dimeric bromopyrrole alkaloids from marine sponge *Agelas* species. J. Nat. Prod 67, 1262–1267 (2004). [PubMed: 15332839]

43. Brastianos HC et al. Exiguamine A, an indoleamine2,3-dioxygenase (IDO) inhibitor isolated from the marine sponge *Neopetrosia exigua*. J. Am. Chem. Soc 128, 16046–16047 (2006). [PubMed: 17165752]
44. Sofiyev V, Lumb J, Volgraf M & Trauner D Total synthesis of exiguamines A and B inspired by catecholamine chemistry. Chem. Eur. J 18, 4999–5005 (2012). [PubMed: 22415756]
45. Volgraf M et al. Biomimetic synthesis of the IDO inhibitors exiguamine A and B. Nat. Chem. Biol 4, 535–537 (2008). [PubMed: 18677305]
46. Minato H & Horibe I Structure and stereochemistry of Xanthumin, a stereoisomer of Xanthinin. J. Chem. Soc. Resumed 1965, 7009–7017 (1965).
47. Ahmed AA, Mahmoud AA & El-Gamal AA A xanthanolide diol and a dimeric xanthanolide from *Xanthium* species. Planta Med. 65, 470–472 (1999). [PubMed: 17260271]
48. Nour AMM et al. The antiprotozoal activity of sixteen asteraceae species native to Sudan and bioactivity-guided isolation of xanthanolides from *Xanthium brasilicum*. Planta Med. 75, 1363–1368 (2009). [PubMed: 19431098]
49. Wang L et al. Cytotoxic sesquiterpene lactones from aerial parts of *Xanthium sibiricum*. Planta Med. 79, 661–665 (2013). [PubMed: 23702839]
50. Feng J et al. Enantioselective and collective total syntheses of xanthanolides. Angew. Chem. Int. Ed 56, 16323–16327 (2017).
51. Ren W et al. Enantioselective and collective syntheses of xanthanolides involving a controllable dyotropic rearrangement of *cis*-β-lactones. Angew. Chem. Int. Ed 51, 6984–6988 (2012).
52. Shang H et al. Biomimetic synthesis: discovery of xanthanolide dimers. Angew. Chem. Int. Ed 53, 14494–14498 (2014).
53. Brady SF, Singh MP, Janso JE & Clardy J Cytoskyrins A and B, new BIA active bisanthraquinones isolated from an endophytic fungus. Org. Lett 2, 4047–4049 (2000). [PubMed: 11112640]
54. Jadulco R et al. New metabolites from sponge-derived fungi *Curvularia lunata* and *Cladosporium herbarum*. J. Nat. Prod 65, 730–733 (2002). [PubMed: 12027752]
55. Ejiri H, Sankawa U & Shibata S Graciliformin and its acetates in *Cladonia graciliformis*. Phytochemistry 14, 277–279 (1975).
56. Yamazaki H, Koyama N, Ōmura S & Tomoda H New rugulosins, anti-MRSA antibiotics, produced by *Penicillium radicum* FKI-3765–2. Org. Lett 12, 1572–1575 (2010). [PubMed: 20222683]
57. Ogihara Y, Kobayashi NM & Shibata S Further studies on the bianthraquinones of *Penicillium islandicum* Sopp. Tetrahedron Lett. 9, 1881–1886 (1968).
58. Nicolaou KC, Lim YH, Papageorgiou CD & Piper JL Total synthesis of (+)-rugulosin and (+)-2,2′-epi-cytoskyrin A through cascade reactions. Angew. Chem. Int. Ed 44, 7917–7921 (2005).
59. Nicolaou KC, Lim YH, Piper JL & Papageorgiou CD Total syntheses of 2,2′-epi-cytoskyrin A, rugulosin, and the alleged structure of rugulin. J. Am. Chem. Soc 129, 4001–4013 (2007). [PubMed: 17355133]
60. Agusta A, Ohashi K & Shibuya H Bisanthraquinone metabolites produced by the endophytic fungus *Diaporthe* sp. Chem. Pharm. Bull 54, 579–582 (2006).
61. Manzo E et al. New γ-pyrone propionates from the Indian Ocean sacoglossan *Placobranchus ocellatus*. Tetrahedron Lett. 46, 465–468 (2005).
62. Cueto M, D'Croz L, Maté JL, San-Martín A & Darias J Elysiapyrones from *Elysia Diomedea*. Do such metabolites evidence an enzymatically assisted electrocyclization cascade for the biosynthesis of their bicyclo[4.2.0]octane core? Org. Lett 7, 415–418 (2005). [PubMed: 15673253]
63. Miller AK & Trauner D Mining the tetraene manifold: total synthesis of complex pyrones from *Placobranchus ocellatus*. Angew. Chem. Int. Ed 44, 4602–4606 (2005).
64. Wu Q et al. Complex polypropionates from a South China Sea photosynthetic mollusk: isolation and biomimetic synthesis highlighting novel rearrangements. Angew. Chem. Int. Ed 59, 12105–12112 (2020).
65. Eccles RG Calycanthine. Drug. Circular Chem. Gaz 32, 65 (1888).
66. Steven A & Overman LE Total synthesis of complex cyclotryptamine alkaloids: stereocontrolled construction of quaternary carbon stereocenters. Angew. Chem. Int. Ed 46, 5488–5508 (2007).

67. Schmidt MA & Movassaghi M New strategies for the synthesis of hexahydropyrroloindole alkaloids inspired by biosynthetic hypotheses. Synlett 2008, 313–324 (2008).
68. Trost BM & Osipov M Recent advances on the total syntheses of the communesin alkaloids and perophoramidine. Chem. Weinh. Bergstr. Ger 21, 16318–16343 (2015).
69. Xu J-B & Cheng K-J Studies on the alkaloids of the calycanthaceae and their syntheses. Molecules 20, 6715–6738 (2015). [PubMed: 25884552]
70. May JA & Stoltz B The structural and synthetic implications of the biosynthesis of the calycanthaceous alkaloids, the communesins, and nomofungin. Tetrahedron 62, 5262–5271 (2006).
71. Dotson JJ, Bachman JL, Garcia-Garibay MA & Garg NK Discovery and total synthesis of a bis(cyclotryptamine) alkaloid bearing the elusive piperidinoindoline scaffold. J. Am. Chem. Soc 142, 11685–11690 (2020). [PubMed: 32520547]
72. Hall ES, McCapra F & Scott AI Biogenetic-type synthesis of the calycanthaceous alkaloids. Tetrahedron 23, 4131–4141 (1967). [PubMed: 6065628]
73. Gavagnin M, Mollo E, Cimino G & Ortea J A new γ-dihydropyrone-propionate from the Caribbean sacoglossan *Tridachia crispata*. Tetrahedron Lett. 37, 4259–4262 (1996).
74. Sharma P, Lygo B, Lewis W & Moses JE Biomimetic synthesis and structural reassignment of the tridachiahydropyrones. J. Am. Chem. Soc 131, 5966–5972 (2009). [PubMed: 19341238]
75. Gavagnin M, Mollo E & Cimino G Is phototridachiahydropyrone a true natural product? Rev. Bras. Farmacogn 25, 588–591 (2015).
76. Bister B et al. Abyssomicin C — A polycyclic antibiotic from a marine *Verrucosispora* strain as an inhibitor of the *p*-aminobenzoic acid/tetrahydrofolate biosynthesis pathway. Angew. Chem. Int. Ed 43, 2574–2576 (2004).
77. Nicolaou KC & Harrison ST Total synthesis of abyssomicin C, atrop-abyssomicin C, and abyssomicin D: implications for natural origins of atrop-abyssomicin C. J. Am. Chem. Soc 129, 429–440 (2007). [PubMed: 17212423]
78. Nicolaou KC & Harrison ST Total synthesis of abyssomicin C and atrop-abyssomicin C. Angew. Chem. Int. Ed 45, 3256–3260 (2006).
79. Keller S et al. Abyssomicins G and H and atrop-abyssomicin C from the marine *Verrucosispora* strain AB-18–032. J. Antibiot 60, 391–394 (2007).
80. Ellerbrock P, Armanino N, Ilg MK, Webster R & Trauner D An eight-step synthesis of epicolactone reveals its biosynthetic origin. Nat. Chem 7, 879–882 (2015). [PubMed: 26492007]
81. Yan Z et al. Fused multicyclic polyketides with a two-spiro-carbon skeleton from mangrove-derived endophytic fungus *Epicoccum nigrum* SCNU-F0002. RSC Adv. 10, 28560–28566 (2020). [PubMed: 35520073]
82. Greshock TJ & Williams RM Improved biomimetic total synthesis of d,l-stephacidin A. Org. Lett 9, 4255–4258 (2007). [PubMed: 17854197]
83. Qin W-F et al. Total synthesis of (−)-depyranoversicolamide B. Chem. Commun 51, 16143–16146 (2015).
84. Xu X, Zhang X, Nong X, Wang J & Qi S Brevianamides and mycophenolic acid derivatives from the deep-sea-derived fungus *Penicillium brevicompactum* DFFSCS025. Mar. Drugs 15, 43 (2017). [PubMed: 28218640]
85. Crombie L & Ponsford R Synthesis of (±)-deoxybruceol. Chem. Commun. Lond 1968, 368a (1968).
86. Crombie L & Ponsford R Pyridine-catalysed condensation of citral with phloroglucinols, a novel reaction leading to tetracyclic bis-ethers and chromenes. Two-step synthesis of (±)-deoxybruceol. J. Chem. Soc. C Org 1971, 788–795 (1971).
87. Ghisalberti EL et al. Structural studies in the bruceol system. J. Chem. Soc. Perkin Trans 2, 583–589 (1981).
88. Day AJ, Sumby CJ & George JH Biomimetic synthetic studies on the bruceol family of meroterpenoid natural products. J. Org. Chem 85, 2103–2117 (2020). [PubMed: 31849214]

89. Harada N et al. Total synthesis, absolute configuration, and later isolation of (−)-prehalenaquinone, a putative biosynthetic precursor to the marine natural products: halenaquinone and xestoquinone. J. Org. Chem 59, 6606–6613 (1994).

90. Matsuura BS, Kölle P, Trauner D, de Vivie-Riedle R & Meier R Unravelling photochemical relationships among natural products from *Aplysia dactylomela*. ACS Cent. Sci 3, 39–46 (2017). [PubMed: 28149951]

91. Kotammagari TK, Gonnade RG & Bhattacharya AK Biomimetic total synthesis of angiopterlactone B and other potential natural products. Org. Lett 19, 3564–3567 (2017). [PubMed: 28613899]

92. Nicolaou KC, Sanchini S, Wu TR & Sarlah D Total synthesis and structural revision of biyouyanagin B. Chem. Eur. J 16, 7678–7682 (2010). [PubMed: 20572192]

93. Löbermann F, Mayer P & Trauner D Biomimetic synthesis of (−)-pycnanthuquinone C through the Diels–Alder reaction of a vinyl quinone. Angew. Chem. Int. Ed 49, 6199–6202 (2010).

94. Ma D, Liu Y & Wang Z Biomimetic total synthesis of (±)-homodimericin A. Angew. Chem. Int. Ed 56, 7886–7889 (2017).

95. Stichnoth D et al. Photochemical formation of intricarene. Nat. Commun 5, 5597 (2014). [PubMed: 25470600]

96. Brown PD & Lawrence AL Total synthesis of millingtonine. Angew. Chem. Int. Ed 128, 8421–8425 (2016).

97. Brown PD, Willis AC, Sherburn MS & Lawrence AL Total synthesis and structural revision of the alkaloid incargranine B. Angew. Chem 125, 13515–13517 (2013).

98. Purgett TJ, Dyer MW, Bickel B, McNeely J & Porco JA Gold(I)-mediated cycloisomerization/cycloaddition enables bioinspired syntheses of neonectrolides B–E and analogues. J. Am. Chem. Soc 141, 15135–15144 (2019). [PubMed: 31469554]

99. Novak AJE, Grigglestone CE & Trauner D A biomimetic synthesis elucidates the origin of preuisolactone A. J. Am. Chem. Soc 141, 15515–15518 (2019). [PubMed: 31518120]

100. Li H, Korotkov A, Chapman CW, Eastman A & Wu J Enantioselective formal syntheses of 11 nuphar alkaloids and discovery of potent apoptotic monomeric analogues. Angew. Chem. Int. Ed 55, 3509–3513 (2016).

101. Breunig M, Yuan P & Gaich T An unexpected transannular [4+2] cycloaddition during the total synthesis of (+)-norcembrene 5. Angew. Chem. Int. Ed 59, 5521–5525 (2020).

102. Nicolaou KC, Chen Q, Li R, Anami Y & Tsuchikama K Total synthesis of the monomeric unit of lomaiviticin A. J. Am. Chem. Soc 142, 20201–20207 (2020). [PubMed: 33186022]

103. Zheng K, Shen D, Zhang B & Hong R Landscape of lankacidin biomimetic synthesis: structural revisions and biogenetic implications. J. Org. Chem 85, 13818–13836 (2020). [PubMed: 32985194]

104. Su S, Seiple IB, Young IS & Baran PS Total syntheses of (±)-massadine and massadine chloride. J. Am. Chem. Soc 130, 16490–16491 (2008). [PubMed: 19049446]

105. Strych S et al. Biomimetic total synthesis of santalin Y. Angew. Chem. Int. Ed 54, 5079–5083 (2015).

106. Gao Y et al. Isolation and biomimetic synthesis of (±)-guajadial B, a novel meroterpenoid from *Psidium guajava*. Org. Lett 14, 5936–5939 (2012). [PubMed: 23163238]

107. Yang B et al. Asymmetric total synthesis and biosynthetic implications of perovskones, hydrangenone, and hydrangenone B. J. Am. Chem. Soc 143, 6370–6375 (2021). [PubMed: 33886312]

108. Long X, Wu H, Ding Y, Qu C & Deng J Biosynthetically inspired divergent syntheses of merocytochalasans. Chem 7, 212–223 (2021).

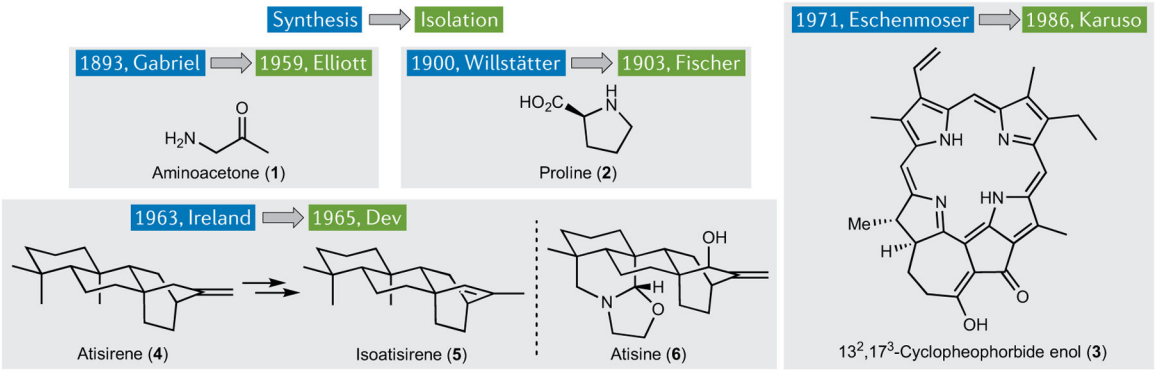

Fig. 1 |. Notable examples of 'unwitting' natural product anticipation[7–20].

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.

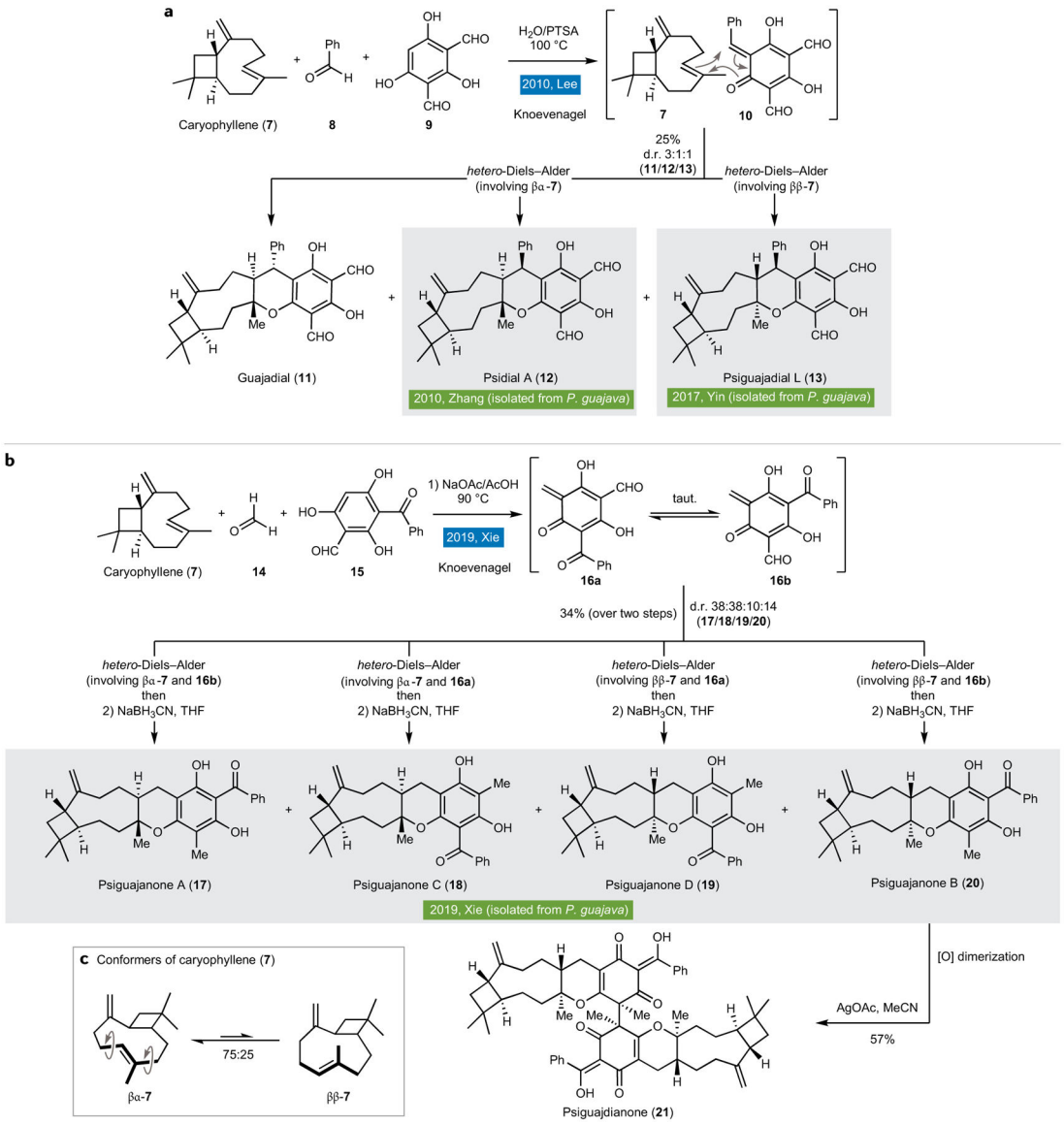

Fig. 2 |. Anticipation of caryophyllene-derived meroterpenoids from *Psidium guajava*.

a | Anticipation of psidial A (**12**) and psiguajadial L (**13**) through a multicomponent biomimetic reaction[24,25,27,28]. **b** | Anticipation of the psiguajanones A–D (**17**–**20**) through a multicomponent biomimetic reaction, followed by reduction[29]. **c** | The βα and ββ conformers of caryophyllene (**7**)[26]. *P. guajava*, *Psidium guajava*.

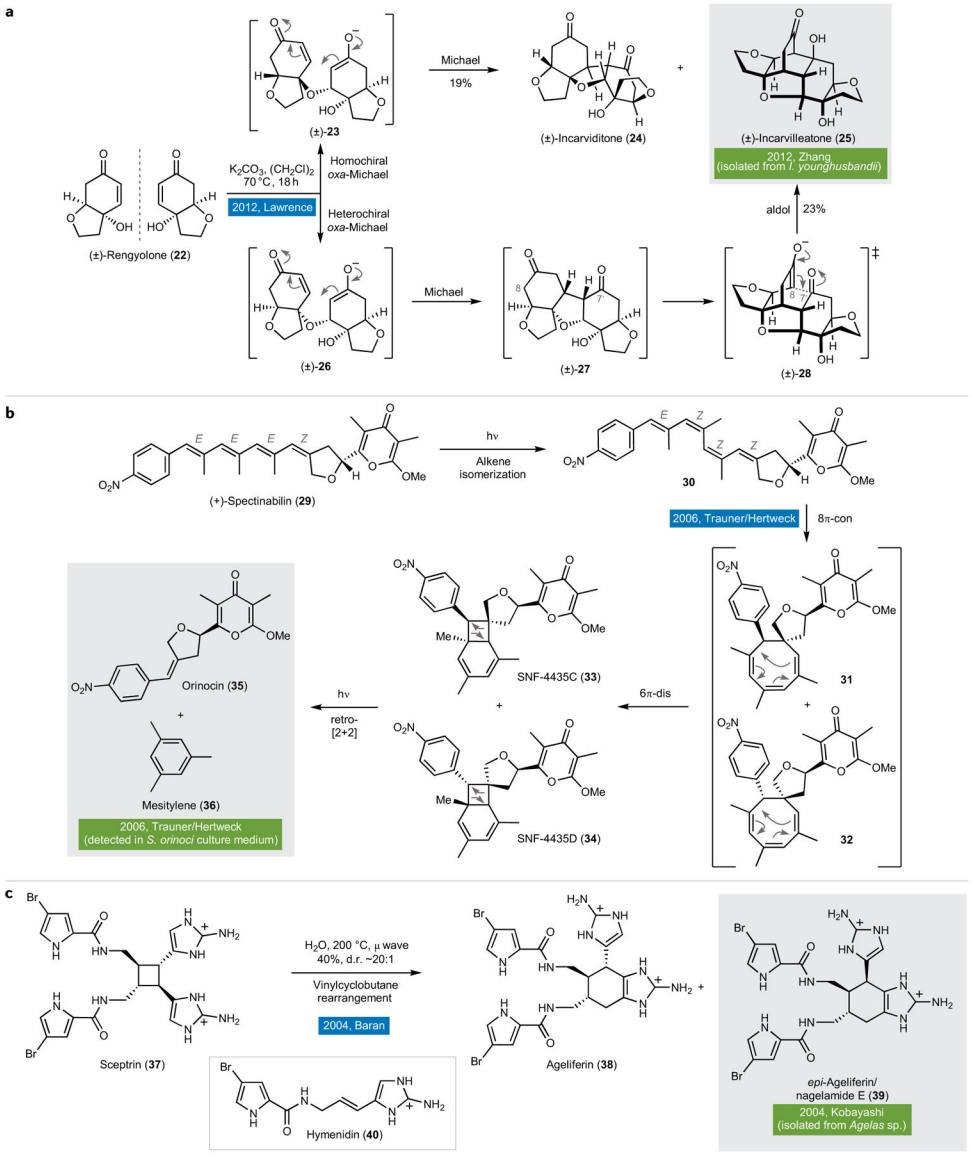

Fig. 3 |. Anticipation of incarvilleatone, mesitylene and nagelamide E.

a | Homochiral dimerization of (±)-rengyolone (**22**) gives the intended target, (±)-incariditone (**24**), whereas heterochiral dimerization gives the anticipated natural product, (±)-incarvilleatone (**25**)[30–32]. **b** | Photochemical retro-[2+2] cycloaddition of the SNF-4435C and SNF-4435D (**33** and **34**) gives mesitylene (**36**) and orinocin (**35**)[34–38]. **c** | Vinylcyclobutane rearrangement of sceptrin gives the intended target ageliferin (**38**) and the anticipated natural product nagelamide E (**39**)[40–42]. *I. younghusbandii*, *Incarvillea younghusbandii*; *S. orinoci*, *Streptomyces orinoci*.

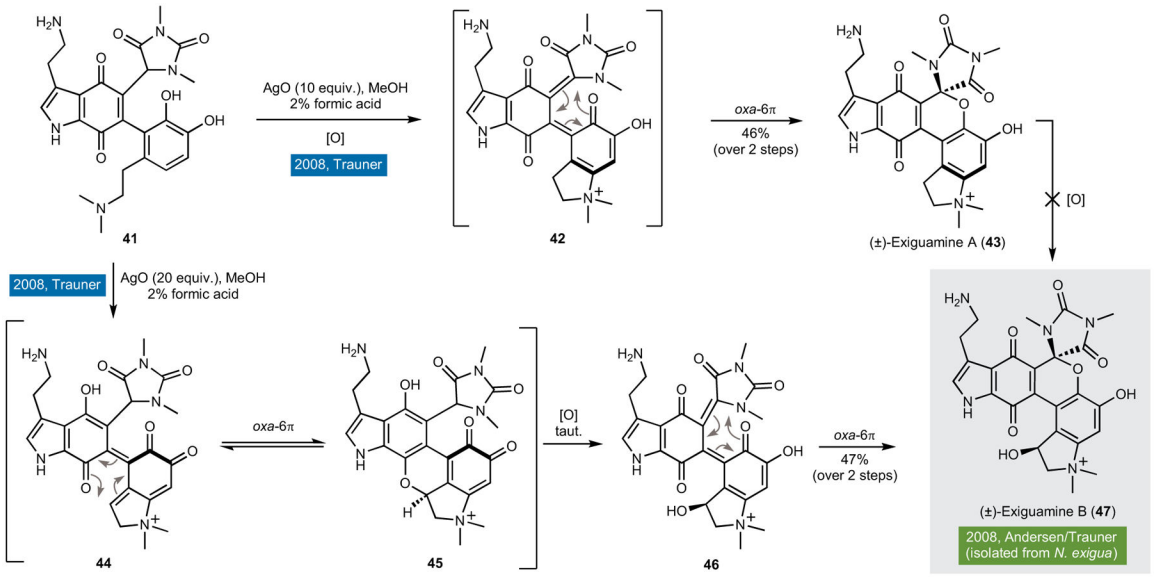

Fig. 4 |. Anticipation of exiguamine B.

Oxidation of catechol **41** with 10 equivalents of AgO gives the intended target exiguamine A (**43**), whereas the use of 20 equivalents gives the anticipated natural product exiguamine B (**47**)[43–45]. *N. exigua*, *Neopetrosia exigua*.

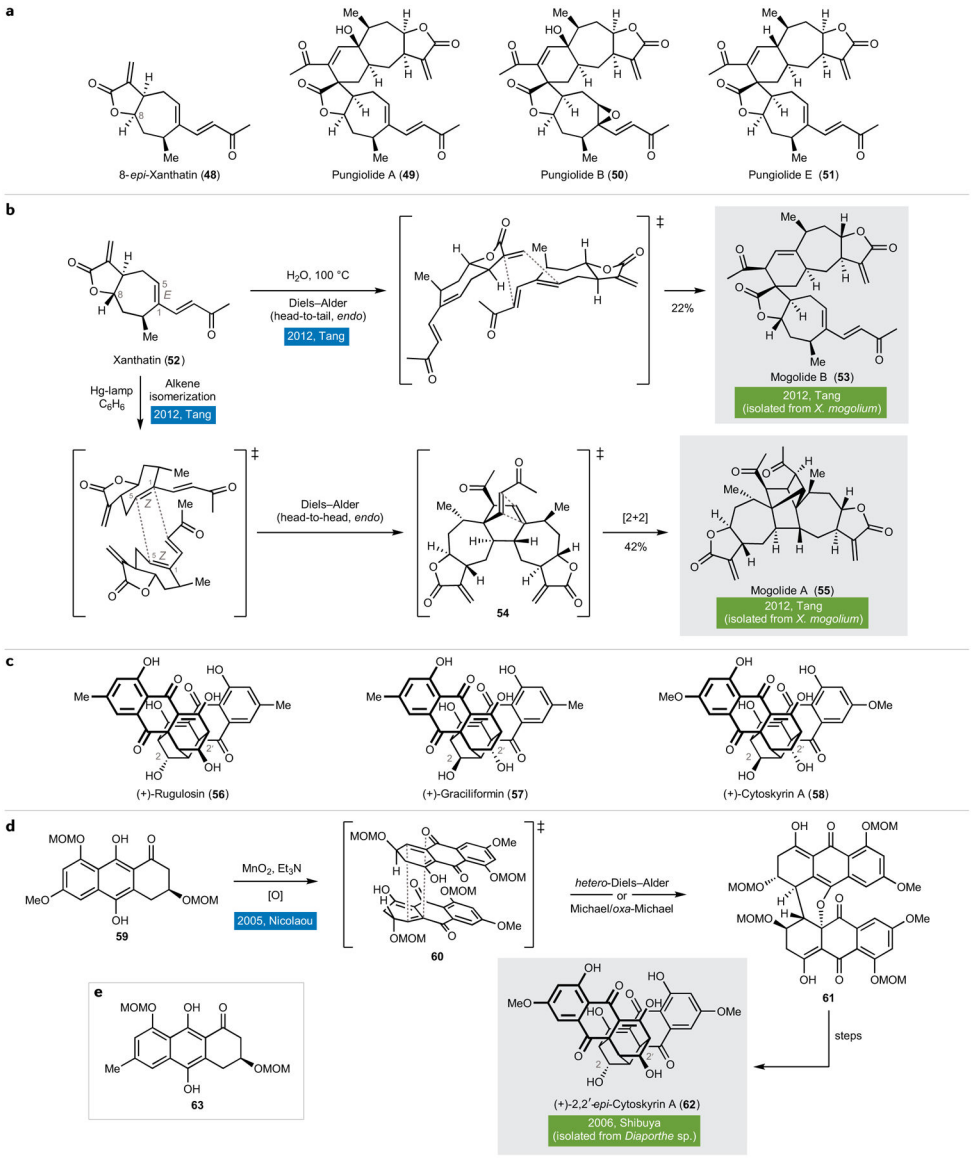

Fig. 5 |. Anticipation of ‘missing’ dimeric natural products.

a | Known dimeric xanthanolides natural products (**49**–**51**) and their biosynthetic monomer 8-epi-xanthatin (**48**)[46–49]. **b** | Dimerization of xanthatin (**52**) leads to the anticipated natural products mogolides A and B (**53** and **55**)[52]. **c** | Known bisanthraquinone natural products (**56**–**58**)[53–57]. **d** | Oxidative dimerization of monomer **59** leads to the anticipated natural product 2,2′-epi-cytoskyrin A (**62**)[58–60]. **e** | Monomer **63**, used by Nicolaou et al. to access rugulosin (**56**)[58,59]. *X. mogolium*, *Xanthium mogolium*.

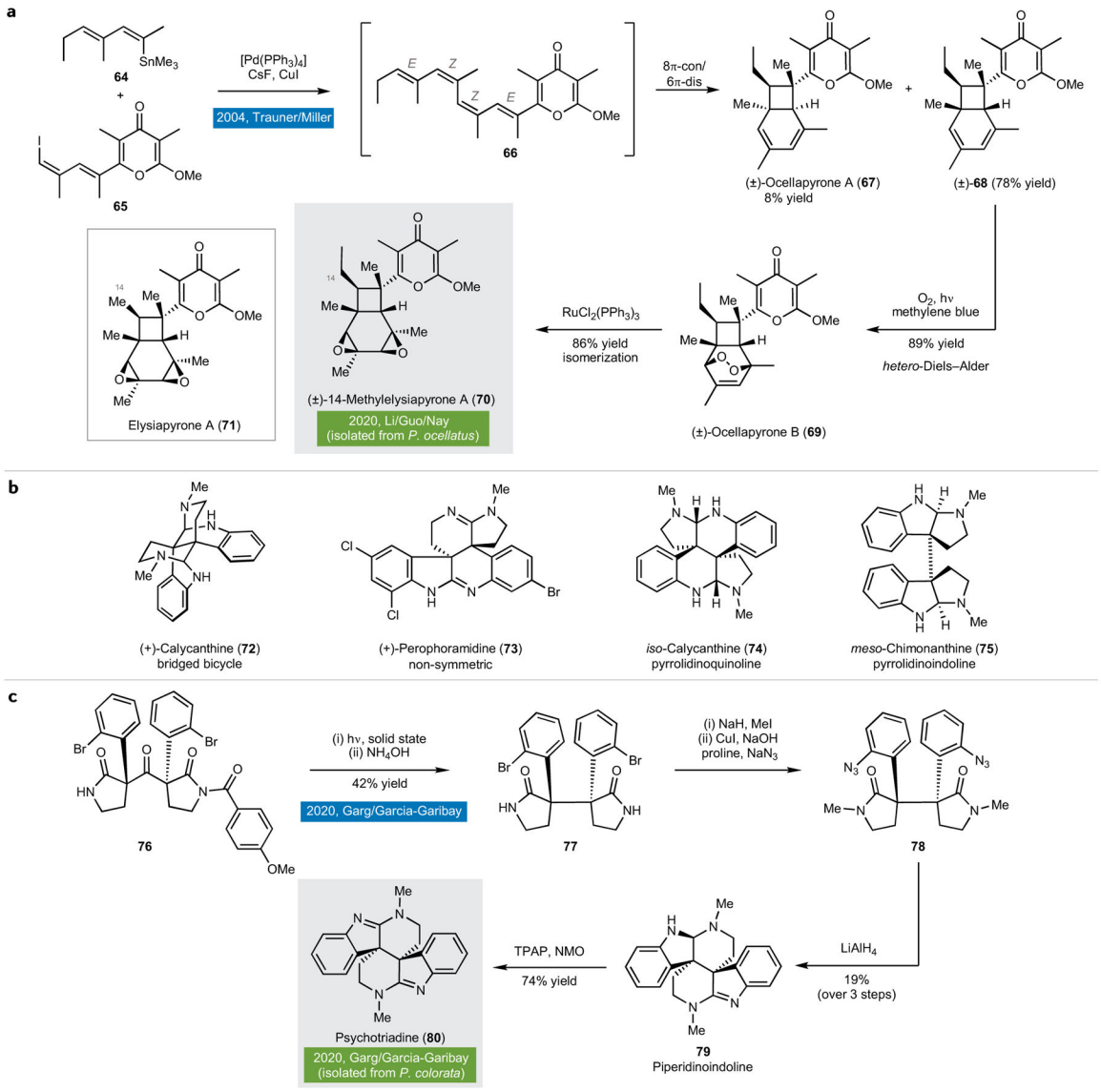

Fig. 6 |. Anticipation of 14-methylelysiapyrone A and psychotriadine.

a | Biomimetic total synthesis of the anticipated natural product, 14-methylelysiapyrone A (**70**)[63,64]. **b** | Known bis(cyclotryptamine) alkaloids with different isomeric scaffolds[65–69]. **c** | Total synthesis of a newly anticipated piperidinoindoline-type bis(cyclotryptamine) alkaloid, psychotriadine (**80**)[71]. *P. colorata*, *Psychotria colorata*; *P. ocellatus*, *Placobranchus ocellatus*.

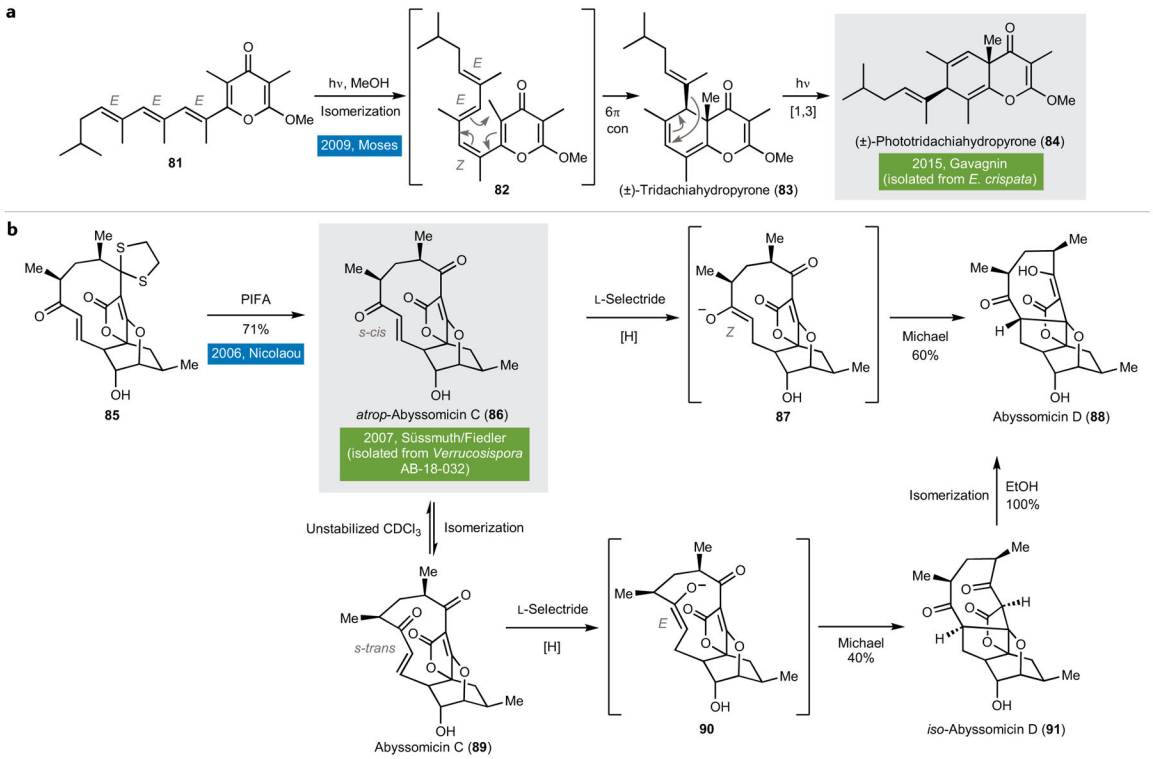

Fig. 7 |. Anticipation of phototridachiahydropyrone and *atrop*-abyssomicin C.

a | Biomimetic total synthesis of the anticipated natural product phototridachiahydropyrone (**84**) via photochemical [1,3]-sigmatropic rearrangement of tridachiahydropyrone (**83**)[74,75]. **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[77–79]. *E. crispata*, *Elysia crispata*; PIFA, phenyliodine(III) bis(trifluoroacetate).

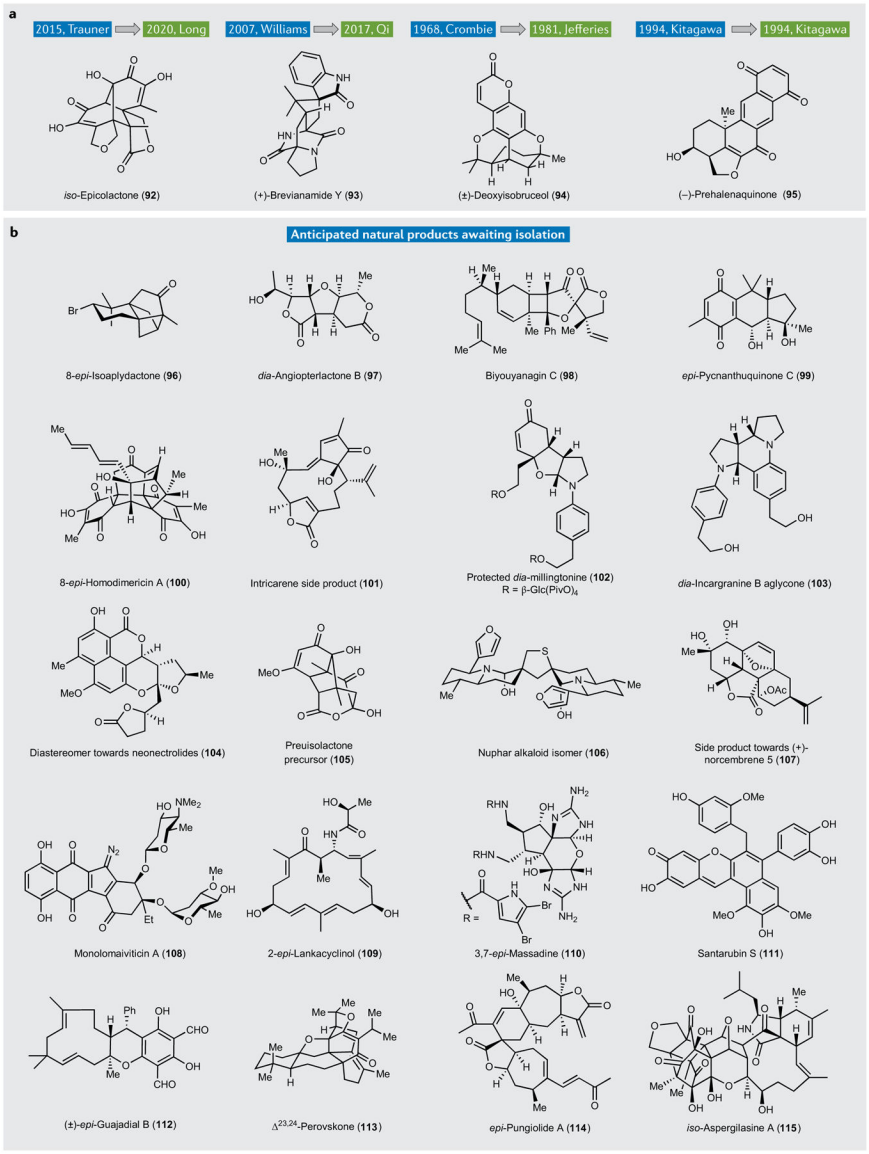

Fig. 8 |. Additional examples for anticipated natural products and suspected natural products awaiting confirmation.

a | iso-Epicolactone (**92**)[80,81], (+)-brevianamide Y (**93**)[82–84], (±)-deoxyisobruceol (**94**)[85–88] and (−)-prehalenaquinone (**95**)[89] 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**)[90], dia-angiopterlactone B (**97**)[91], biyouyanagin C (**98**)[92], epi-pycnanthuquinone C (**99**)[93], 8-epi-homodimericin A (**100**)[94], intricarene side product (**101**)[95], protected dia-millingtonine (**102**)[96], dia-incargranine B aglycone (**103**)[97], diastereomer towards neonectrolides (**104**)[98], preuisolactone precursor (**105**)[99], nuphar alkaloid isomer (**106**)[100], side product towards (+)-norcembrene 5 (**107**)[101], monolomaiviticin A (**108**)[102], 2-epi-lankacyclinol (**109**)[103], 3,7-epi-massadine (**110**)[104], santarubin S (**111**)[105], epi-guajadial B (**112**)[106], $\Delta^{23,24}$-perovskone (**113**)[107], epi-pungiolide A (**114**)[50] and iso-aspergilasine A (**115**)[108].