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Synthesis of most polyene natural product motifs using just 12 building blocks and one coupling reaction

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The inherent modularity of polypeptides, oligonucleotides and oligosaccharides has been harnessed to achieve generalized synthesis platforms. Importantly, like these other targets, most small-molecule natural products are biosynthesized via iterative coupling of bifunctional building blocks. This suggests that many small molecules also possess inherent modularity commensurate with systematic building block-based construction. Supporting this hypothesis, here we report that the polyene motifs found in >75% of all known polyene natural products can be synthesized using just 12 building blocks and one coupling reaction. Using the same general retrosynthetic algorithm and reaction conditions, this platform enabled both the synthesis of a wide range of polyene frameworks that covered all of this natural-product chemical space and the first total syntheses of the polyene natural products asnipyrone B, physarigin A and neurosporaxanthin β-D-glucopyranoside. Collectively, these results suggest the potential for a more generalized approach to making small molecules in the laboratory.

Most of the molecules found in living systems are prepared naturally via the iterative assembly of a limited number of bifunctional building blocks (Fig. 1a)[1]. For example, proteins are usually derived from just 20 amino acids, and DNA and RNA are each made from only four nucleotides[1]. Capitalizing on this inherent modularity, generalized strategies based on building blocks have been developed for efficient, flexible and fully automated access to these molecules in the laboratory[2–4], and the resulting impacts on science, medicine and technology have been transformational. In a similar vein, a recent analysis revealed that 75% of all mammalian oligosaccharides comprise just 36 monosaccharide units[5], and an increasingly general platform for automated oligosaccharide synthesis is broadening access to this class of biomolecules as well[6]. In stark contrast, traditionally the laboratory synthesis of small-molecule natural products has involved the customized development of a unique pathway and collection of building blocks to access each target. As a result, despite many important advances in accessing individual structures, small-molecule synthesis remains a relatively inefficient and inflexible process practised almost exclusively by specialists.

Importantly, like their peptide, oligonucleotide and oligosaccharide counterparts, most small-molecule natural products are biosynthesized via iterative building block assembly (Fig. 1b)[1]. For example, polyketides are constructed from malonyl coenzyme A (CoA) and methylmalonyl CoA, polyterpenes from isopentenyl and dimethylallyl pyrophosphate, fatty acids from malonyl CoA, non-ribosomal peptides from amino acids and polyphenylpropanoids from phenylpyruvic acid. This suggests that a systematic approach based on building blocks should make many small molecules similarly attainable.

With this goal in mind, we aim to identify substructural motifs that are prevalent in natural products and transform them into minimized collections of bifunctional building blocks compatible with iterative assembly[7–10]. Polyene natural products provide an excellent opportunity for exploring this concept, as they are well represented across all major biosynthetic classes (Fig. 1c)[11]. These molecules also perform a wide range of important functions, including serving as pharmaceutical agents[12], pigments for light harvesting[13], fluorescent probes[14], quenchers of reactive oxygen species[15] and transducers of solar energy into mechanical energy[16]. Synthesis of these natural products is made challenging by their sensitivities to light, oxygen and many common reagents, including protic and Lewis acids, as well as by difficulties in controlling the stereochemistry of each double bond. Common methods for the synthesis of polyenes include olefin-generating reactions[11], such as the Wittig, Horner–Wadsworth–Emmons and Julia olefinations, but these stereoselective processes often suffer from a lack of stereocontrol. Reactions based on transition metals[17,18] with organozinc, organostannane, organosilicon and organoboron intermediates have the important advantage of stereospecificity; that is, the stereochemistry in the building blocks can be translated faithfully into the products, but the required building blocks and/or intermediates often suffer from instability and/or toxicity.

The preparation of polyenes via cross-coupling of non-toxic organoboron intermediates has been impeded specifically by the instability of polyenyl boronic acids[19], yet some progress has been made, including several recent examples that involve iterative cross-coupling with stable *N*-methyliminodiacetic acid (MIDA) boronates[20–23]. In this type of synthesis, bifunctional haloboronic acid building blocks with all of the required functional groups preinstalled in the correct oxidation states and with the desired stereochemical relationships are linked together sequentially using only the stereospecific Suzuki–Miyaura cross-coupling reaction in an iterative manner. The MIDA ligand prevents random oligomerization via reversible attenuation of the reactivity of the borane terminus[21,22], analogous to the way a 9-fluorenyl-methoxycarbonyl (FMOC) group enables the precise assembly of amino acids. MIDA boronates are also convenient to prepare, analyse, purify and store, and more than 170 are now commercially available[24]. Collectively, these features have enabled the simple, efficient and flexible synthesis of a wide range of small-molecule natural products[21,23,25–30], pharmaceutical agents[31–34], ligands[35,36] and materials[37] via iterative cross-coupling.

Building on this momentum, we decided to ask the question, how many bifunctional MIDA boronate building blocks would be

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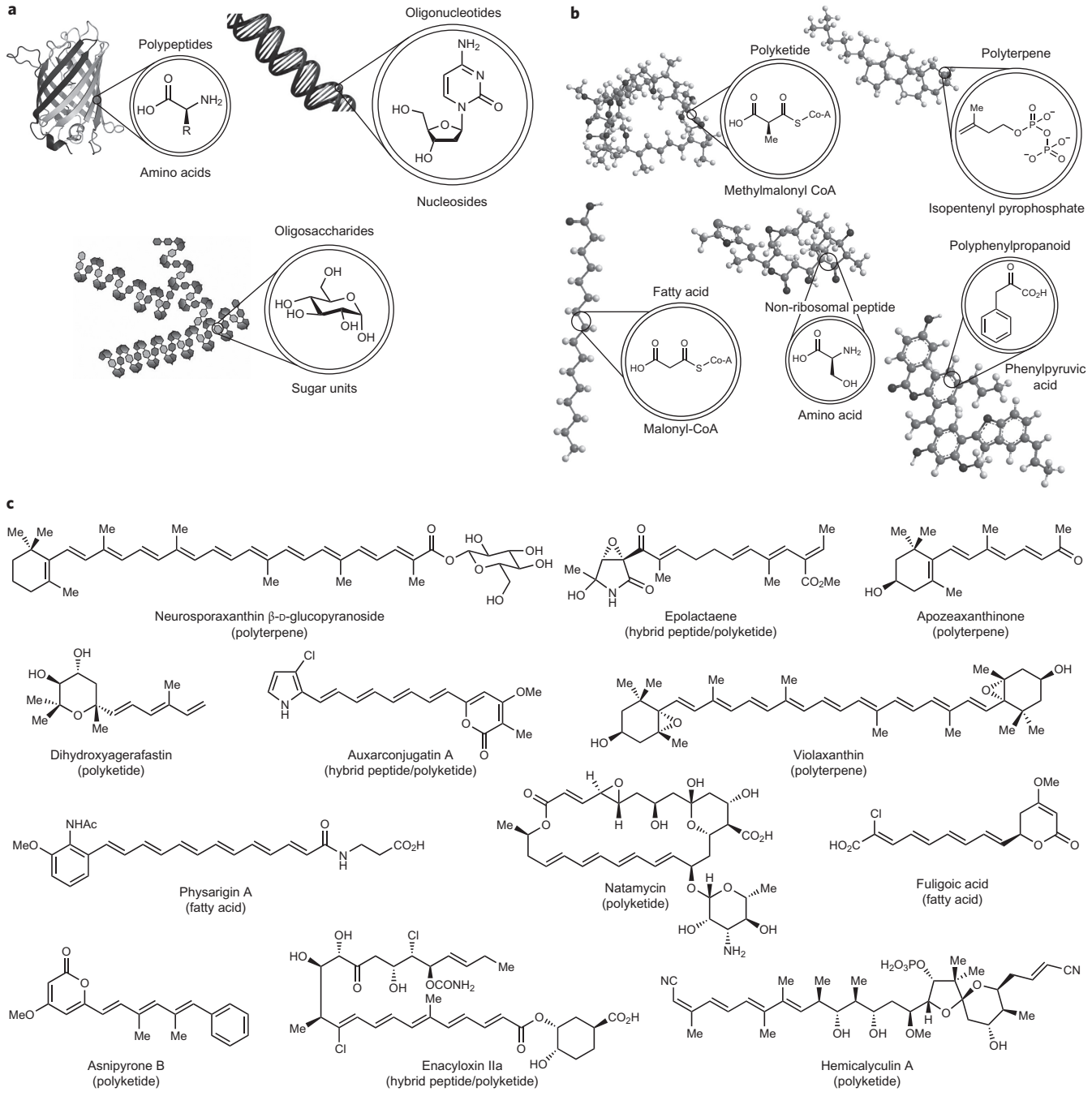


Figure 1 | The iterative assembly of bifunctional building blocks is a versatile strategy for the preparation of small molecules. a, Nature biosynthesizes macromolecules, including polypeptides, oligonucleotides and oligosaccharides, via the iterative coupling of building blocks. **b**, Nature similarly prepares small molecules derived from a range of biosynthetic pathways via the iterative assembly of bifunctional building blocks. **c**, A collection of polyene natural products from a variety of biosynthetic pathways.

required to make most of the polyene motifs found in nature? To find the answer, we devised a general retrosynthetic algorithm for systematically deconstructing these motifs into the minimum total number of building blocks. This analysis generated the intriguing hypothesis that the polyene motifs found in >75% of all polyene natural products can be prepared using just 12 MIDA boronate building blocks and one coupling reaction. As described below, we have tested and confirmed this hypothesis.

Results

The *Dictionary of Natural Products*[38], a comprehensive database of small molecules isolated from natural sources and characterized to date (238,541 as of 15 January 2012) was used to identify all known polyene natural products. Specifically, a substructure search for a polyene, defined as three or more carbon–carbon double bonds in conjugation, none of which are contained in a <12-membered ring, returned 2,839 natural products. Importantly, this set includes small molecules derived from all major biosynthetic classes: polyterpenes, polyketides, fatty acids, hybrid peptide/polyketides and polyphenylpropanoids (Fig. 1c).

To determine the minimum number of bifunctional MIDA boronate building blocks that would be required to access the polyene motifs found in most of these natural products and maximize the stability of the corresponding building blocks and intermediates,

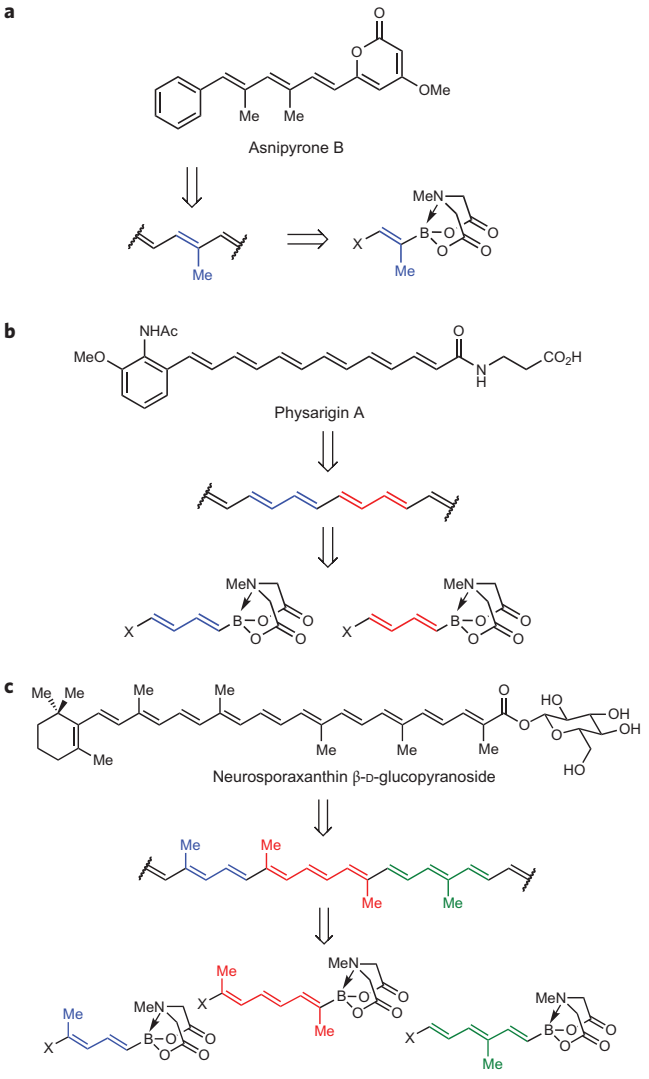


Figure 2 | Three examples of applying the standardized three-step retrosynthetic algorithm to polyene natural products not synthesized previously. a, Asnipyrone B. **b**, Physarigin A. **c**, Neurosporaxanthin β-D-glucopyranoside.

we developed the following systematic three-step retrosynthetic algorithm: (1) the polyene motif is identified as the polyene framework minus the two olefinic termini, (2) using mono-, di- and triene haloalkenyl MIDA boronates, the polyene motif is dissected into the fewest number of building blocks that are as similar in size as possible and (3) disconnections are chosen such that the length of the longest polyenyl borane intermediate in each pathway is minimized.

The following examples demonstrate the application of this general retrosynthetic algorithm to three structurally diverse and not previously synthesized polyene natural products derived from a range of biosynthetic pathways (Fig. 2). Asnipyrone B is a polyketide-derived polyene natural product isolated from *Aspergillus niger*[39] (Fig. 2a). Applying the algorithm, the targeted motif is identified as a simple *trans*-monoene, and a single bifunctional building block would be required. Importantly, this same substructure is also found in more than 1,200 other polyene natural products, including epolactaene, apozeaxanthione and dihydroxyagerafastin (Fig. 1c), which reveals that the same bifunctional building block could contribute to the construction of many other natural products.

Using the same algorithm, the polyene motif of the fatty-acid-derived natural product physarigin A[40] is identified as a tetraene, which is then dissected into two copies of the same dienyl building block (Fig. 2b). This dienyl substructure is also found in more than 350 additional polyene natural products, including auxarconjugatin A, natamycin and fuligoic acid (Fig. 1c), which again reveals the potential for a high degree of overlapping building-block utility.

In a third example, the complex polyene motif found in the polyterpene-derived natural product neurosporaxanthin β-D-glucopyranoside[41] is identified as the corresponding octaene (Fig. 2c). Following the general retrosynthetic guidelines, this motif is dissected into the fewest number of building blocks of similar size, that is, a diene and two trienes. To minimize the length, and therefore maximize the stability of the polyenyl borane intermediates, the algorithm first selects coupling a diene building block followed by two different trienes. As a result, three building blocks are identified as being required for this synthesis. Importantly, at least one of these building blocks is similarly identified as potentially contributory to the synthesis of over 1,100 other polyene natural products, including violaxanthin, enacyloxin IIa and hemicalyculin A (Fig. 1c), which again demonstrates the potential for a high degree of redundant building-block utilization.

Systematic manual application of this same algorithm to all 2,839 polyene natural products and filtering for a maximum overlap in building-block utilization revealed a striking result: theoretically, only 12 bifunctional haloalkenyl MIDA boronate building blocks (**BB1–BB12**, Fig. 3a) are required to access the polyene motifs found in >75% of polyene natural products. Efficient and stereospecific syntheses of all 12 of these building blocks was accomplished readily by taking advantage of many of the enabling features of the MIDA boronate platform, which include compatibility of the MIDA boronate group with many different types of reaction conditions and purification by column chromatography (see Supplementary Information), and already four of these building blocks (**BB1–BB4**) are commercially available.

When we first attempted to construct complex polyene motifs via iteratively coupling these building blocks together, we encountered an important limitation[21]. Specifically, although the polyenyl MIDA boronate intermediates were stable, many of the deprotected polyenyl boronic acid intermediates were not[25,26], which resulted in poor or no yields of the desired final products. Alternatively, we found that the corresponding polyenyl boronic esters, which can also be formed readily via transligation of MIDA boronates with pinacol, are much more stable. The challenge with using pinacol esters as intermediates, however, is that they generally require aqueous basic conditions for subsequent cross-coupling[42], and such conditions are incompatible with the aqueous base-labile MIDA boronate protecting group on the bifunctional building blocks. As an opportunity to overcome this potential impasse, it was determined that when dimethylsulfoxide (DMSO) is employed as solvent, vinyl pinacol boronic esters can be cross-coupled under anhydrous conditions[26,43]. We thus envisioned a modified iterative cross-coupling cycle that involved the initial coupling of a pinacol boronic ester to a bifunctional halo MIDA boronate building block under anhydrous DMSO conditions followed by deprotection of the resulting MIDA boronate to generate a new pinacol boronic ester suitable for the next round of coupling (Fig. 3b).

With the goal to develop a maximally general platform, we further sought to identify common reaction conditions for coupling polyenyl pinacol esters with haloalkenyl MIDA boronate building blocks and to transform the resulting polyenyl MIDA boronates into the corresponding pinacol boronic esters. For the latter, we found that a wide range of polyenyl MIDA boronates of varying lengths and with varying substitution patterns can all be converted into the corresponding pinacol esters using the same conditions: pinacol and $NaHCO_3$ in MeOH at 45 °C for three hours. Moreover, we found that polyenyl pinacol esters of varying length, stereochemistry and methyl-substitution patterns can all

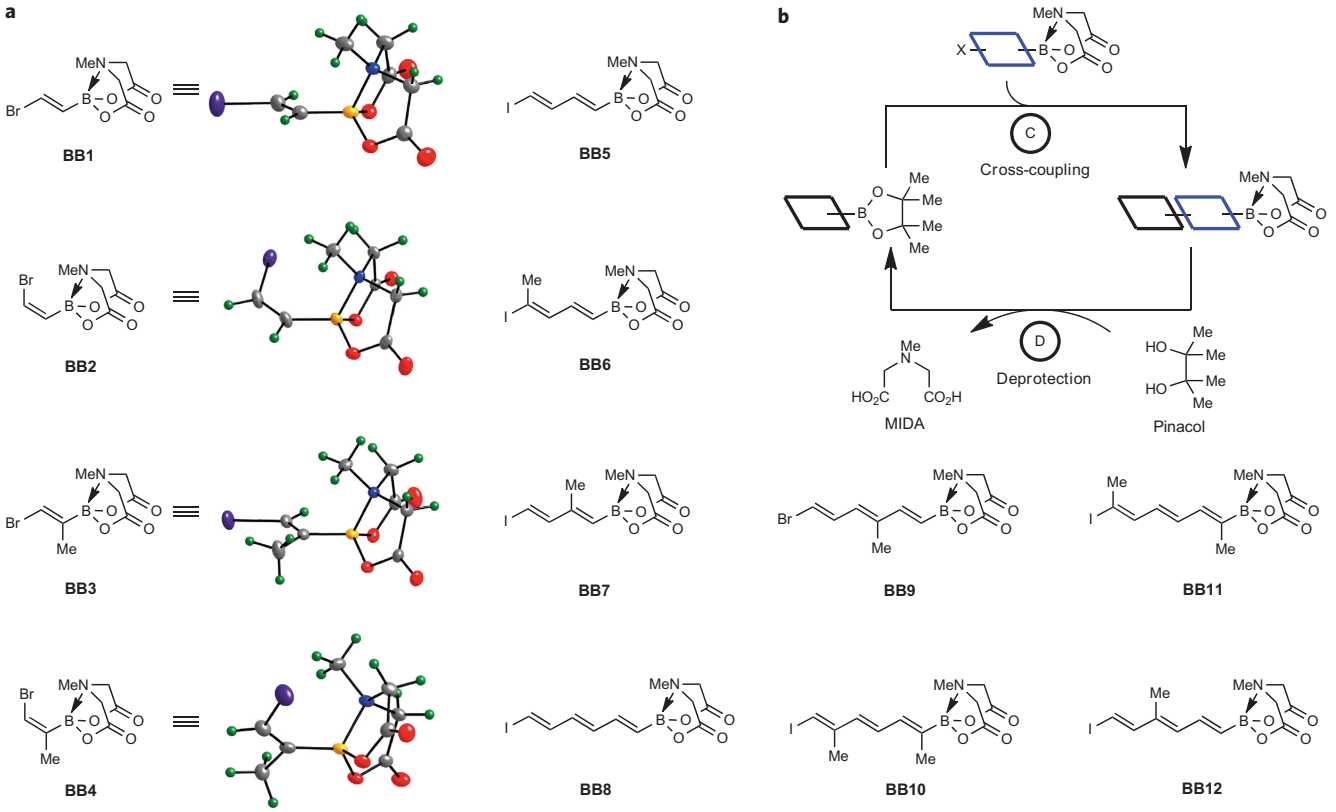


Figure 3 | A general platform for making polyene motifs via iterative cross-coupling. a, A collection of 12 bifunctional MIDA boronate building blocks **BB1–BB12** can be used to synthesize the polyene motifs found in >75% of all polyene natural products. **b**, An iterative cross-coupling strategy that involves the coupling (C in circle) of a pinacol boronic ester to a bifunctional halo MIDA boronate building block followed by deprotection (D in circle) of the resulting MIDA boronate to generate a new pinacol boronic ester suitable for the next round of coupling. Trapezoids represent building blocks.

be coupled to mono-, di- and trienyl bromide and iodide bifunctional MIDA boronate building blocks using the same set of cross-coupling conditions: XPhos (dicyclohexyl(2′,4′,6′-triisopropyl-2-biphenylyl)phosphine) palladacycle precatalyst[44], Cs_2CO_3 and DMSO. Further, it was determined that final couplings between a polyenyl MIDA boronate intermediate and capping vinyl-halide building block can be best achieved using a common set of aqueous basic conditions (XPhos palladacycle precatalyst, NaOH and THF·H_2O) to promote the *in situ* release of an unstable, but also highly reactive, polyenyl boronic acid directly from the corresponding stable polyenyl MIDA boronate[45].

With these building blocks and the general reaction conditions in hand, we sought to test the hypothesis that, collectively, they can enable the preparation of most of the polyenes found in nature. To enable such an experiment, we identified a collection of polyene motifs that represent the corresponding chemical space occupied by >75% of all polyene natural products (**A**–**O**, Fig. 4). This collection includes both *trans*- and *cis*-olefins, various methyl-substitution patterns and a wide range of chain lengths (from three to ten double bonds), and thus represents a substantial challenge for the development of a common synthesis platform.

Utilizing only the aforementioned general retrosynthetic algorithm, the same 12 MIDA boronate building blocks and common deprotection and cross-coupling conditions, we attempted to synthesize all of the targeted polyene motifs **1**–**15**, with MIDA boronate **16** and vinyl iodide **17** serving as representative natural-product-like capping groups. Without any *ad hoc* optimization of the platform, all of the targeted polyene motifs were prepared successfully (Table 1).

These syntheses ranged from a single round of iterative cross-coupling to generate triene **1** to four iterations to generate the highly complex decaene **15**. The yields for the deprotection steps were generally outstanding, even with very long and complex polyene intermediates. Importantly, although the yields for the cross-couplings tended to decrease somewhat as the length of the polyene intermediates grew larger, the predictability of this trend enabled us to begin each sequence with the appropriate amounts of the required building blocks and thereby produce milligram quantities of the targeted final products in every case. Successful syntheses of these targets demonstrates a general approach to the polyene motifs found in >75% of all the polyene natural products isolated to date.

Encouraged by the broad applicability of this platform, we further targeted its application to complete the first total syntheses of a series of polyene natural products that represent a range of biosynthetic pathways, namely the polyketide asnipyrone B (natural product 1 (**NP1**)), the fatty-acid physarigin A (**NP2**) and the polyterpene neurosporaxanthin β-D-glucopyranoside (**NP3**) (Fig. 5), using the same retrosynthetic algorithm, collection of bifunctional building blocks and common reaction conditions. Therefore, applying this approach to each of these total syntheses only required the preparation of the corresponding capping elements. Thus, relative to the traditional design of an individualized synthesis route to each natural product, preparation of all the corresponding customized building blocks and *ad hoc* optimization of all the reaction conditions required to couple those building blocks together, this systematized approach has major advantages. Moreover, as described below, more than 75% of the capping elements represented in the complete collection of polyene natural products fall into just 20 general structural categories for which common synthetic routes exist or can be readily envisioned.

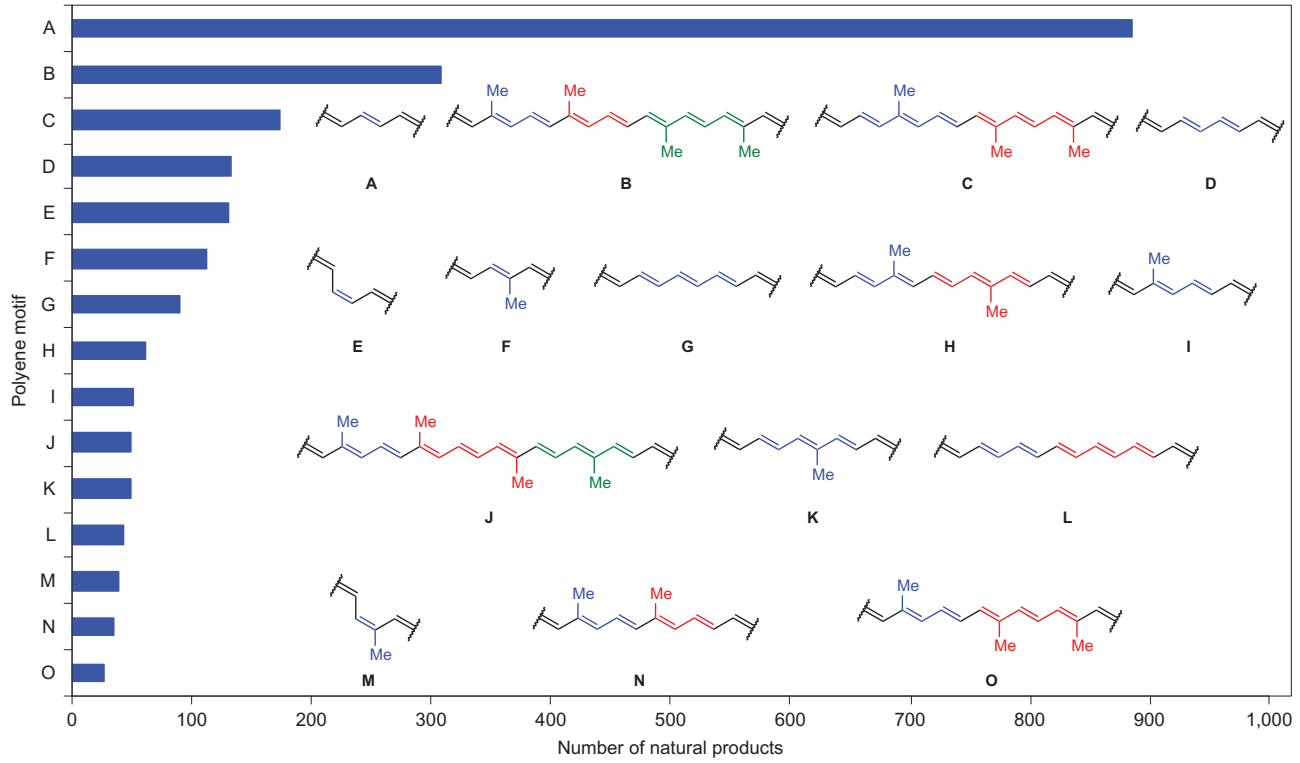


Figure 4 | A collection of polyene motifs collectively found in >75% of all polyene natural products.

After facile preparation of the required capping elements (Supplementary Information)[46,47], preparation of asnipyrone B (**NP1**) commenced with a standardized deprotection of MIDA boronate **18** and coupling with commercially available halo MIDA boronate **BB3** to provide diene **19** (Fig. 5a). This sterically encumbered 1,3-methyl-substituted motif was prepared readily without modification of the general reaction conditions. Application of the general *in situ* deprotection/coupling conditions with capping building block **20** completed a very efficient and fully stereocontrolled first total synthesis of this natural product.

Physarigin A (**NP2**) similarly only required preparation of the capping building blocks **21** and **22**. The latter is a variant of a known building block[48], and preparation of the former was facilitated greatly by using another commercially available MIDA boronate (Supplementary Information) (Fig. 5b)[49]. In the event, deprotection of **21** and cross-coupling to **BB5** using our standardized conditions provided the triene **23** in good yield. Another round of deprotection and coupling with the same bifunctional building block established the structure of the targeted pentaene intermediate **24**. A final cross-coupling with halide **22** completed the first total synthesis of physarigin A.

Finally, we questioned whether this platform could enable the total synthesis of the complex polyene natural product neurosporaxanthin β-D-glucopyranoside (**NP3**) (Fig. 5c). Again, the corresponding capping elements were accessed readily (Supplementary Information), and the synthesis commenced via deprotection of MIDA boronate **25** and subsequent cross-coupling of the resulting pinacol boronic ester with diene **BB6** to provide tetraene **26**. A second, third and fourth iteration of couplings with building blocks **BB11**, **BB9** and **27**, respectively, without any *ad hoc* optimization of our previously established standard conditions, followed by removal of the protecting groups, readily provided the first synthetic access to this highly complex polyene natural product.

All of these results collectively support the conclusion that most polyene natural product motifs can now be prepared using just 12 building blocks and one coupling reaction.

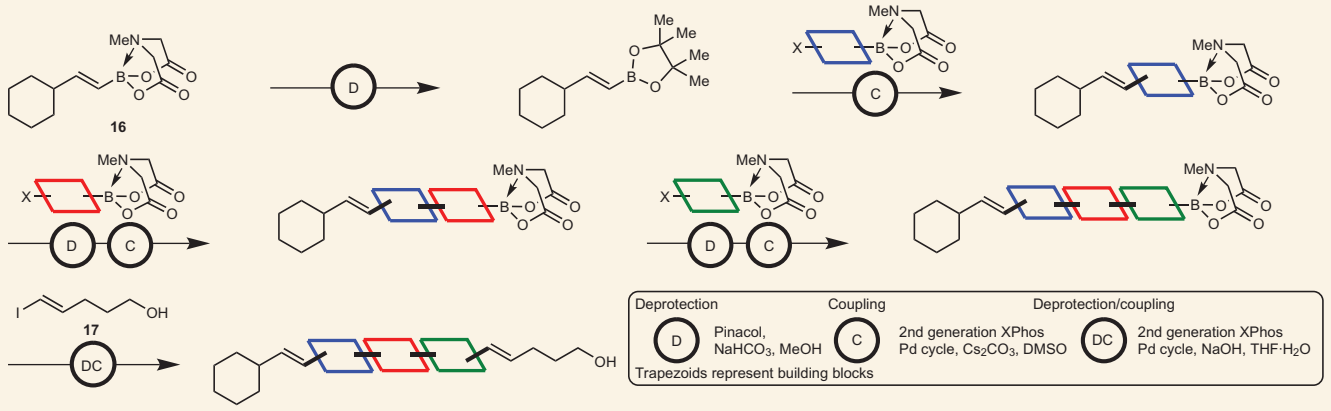
Discussion

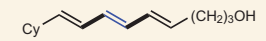
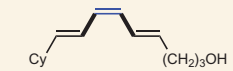
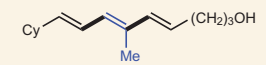
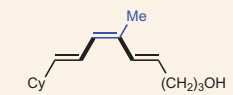
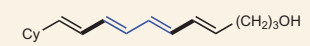
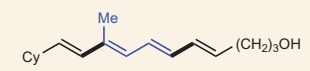
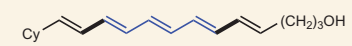
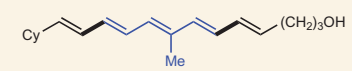
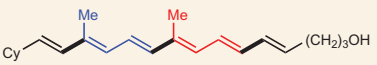
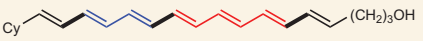
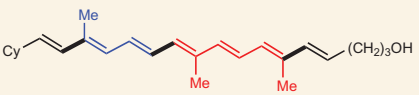
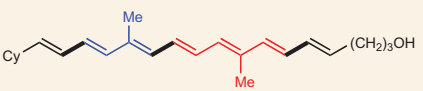
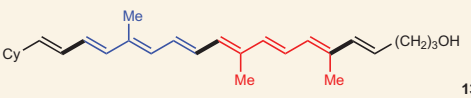
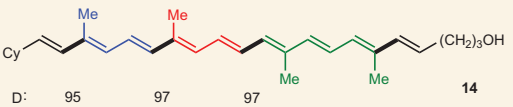
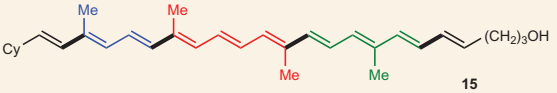
Herein we demonstrate explicitly the synthesis of the polyene motifs found in >75% of all known polyene natural products. These natural products represent much of the diversity found in the complete collection. Further, it is encouraging that accessing >90% of this chemical space would require only 25 building blocks, >95% would require a total of 50 and the motifs found in all polyene natural products could be accessed with only 75 building blocks (Supplementary Information).

Completing the total syntheses via this approach also requires access to the terminal capping elements. Importantly, similar to the high level of structural redundancy found in the polyene motifs, a systematic analysis of the capping elements has also revealed a substantial level of structural overlap (for the complete analysis, see the Supplementary Information). For example, if a unique pair of building blocks was found in each of the 2,839 targets, 5,678 capping elements would be necessary. However, the high level of structural redundancy reduces this number to 1,942 unique building blocks, and just 604 of these building blocks would be needed to access 75% of all the caps found in polyene natural products. Moreover, these 604 building blocks can be subdivided into just 20 common structural classes (for example, α/β-unsaturated esters, allylic alcohols and styrenes), in which most members of each class can probably be accessed using small variations of a common synthetic route. Syntheses of many of these building blocks can be facilitated further by using commercial MIDA boronates that are already available, including **BB1**–**BB4**, just as the capping element **18** in the synthesis of asnipyrone B was prepared in a single step from **BB3**. Finally, alkenyl MIDA boronates can be converted directly into alkenyl halides[27], which allows for the rapid preparation of many halide capping elements from the corresponding readily accessible MIDA boronates.

The 2,839 natural products included in this study represent more than 1% of all the natural products isolated to date. It is stimulating to consider how many building blocks would be

Table 1 | The synthesis of polyene motifs present in >75% of all known polyene natural products.



Polyene motif	MIDA boronates coupled	Polyene product				
A	BB1		1			
	Isolated yields (%)	D: 95	C: 52	DC: 65		
E	BB2		2			
		D: 95	C: 43	DC: 73		
F	BB3		3			
		D: 95	C: 56	DC: 66		
M	BB4		4			
		D: 95	C: 50	DC: 74		
D	BB5		5			
		D: 95	C: 78	DC: 31		
I	BB6		6			
		D: 95	C: 74	DC: 55		
G	BB8		7			
		D: 95	C: 81	DC: 44		
K	BB9		8			
		D: 95	C: 50	DC: 88		
N	BB6, BB6		9			
	Isolated yields (%)	D: 95	97	C: 74	74	DC: 52
L	BB5, BB8		10			
		D: 95	98	C: 78	60	DC: 45
O	BB6, BB10		11			
		D: 95	97	C: 74	48	DC: 29
H	BB7, BB9		12			
		D: 95	91	C: 75	18	DC: 60
C	BB12, BB10		13			
		D: 95	96	C: 32	31	DC: 29
B	BB6, BB6, BB10		14			
		D: 95	97	97	C: 74	74	52	DC: 36
J	BB6, BB11, BB9		15			
		D: 95	97	99	C: 74	51	38	DC: 48

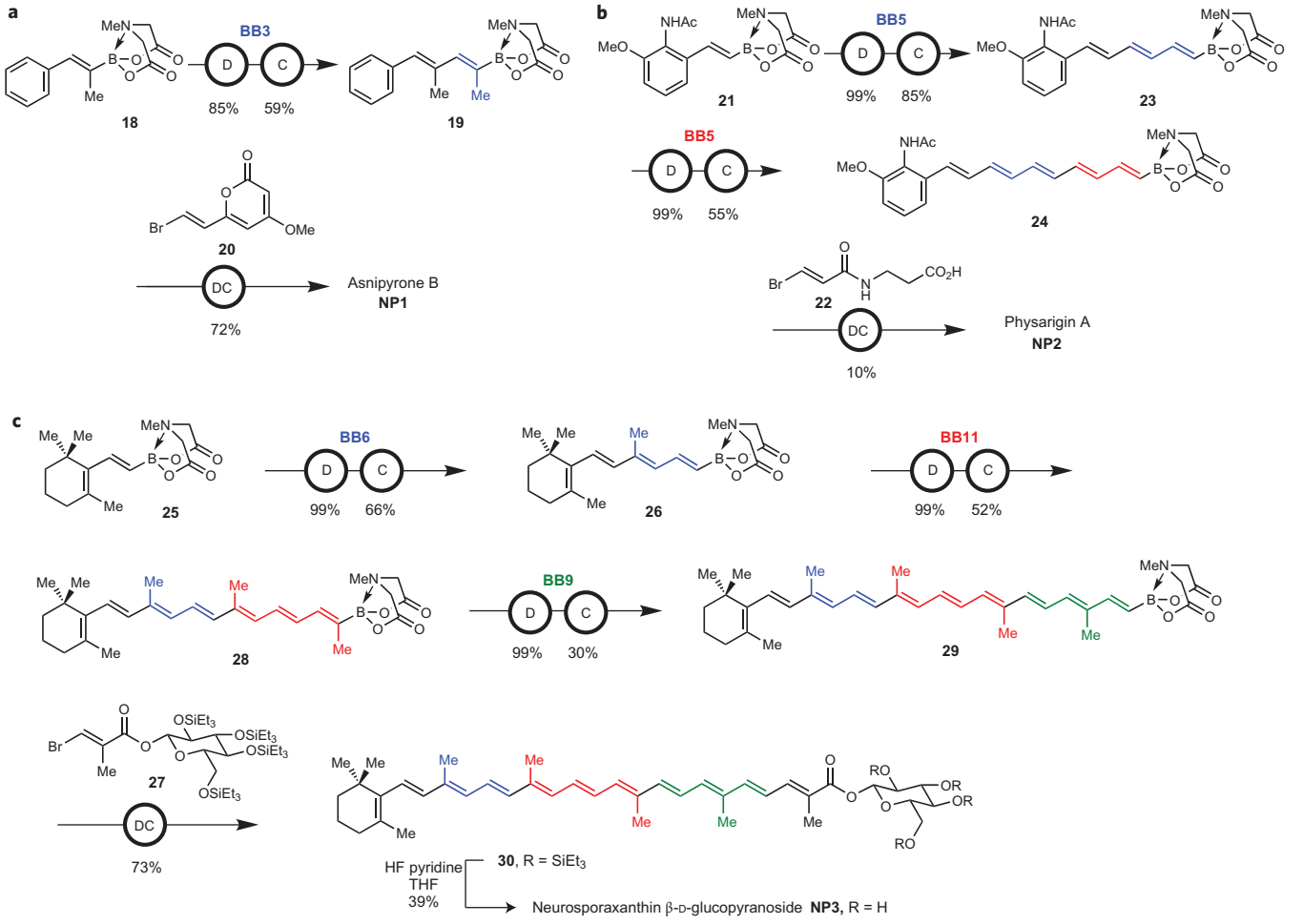


Figure 5 | The total synthesis of three polyene natural products using bifunctional MIDA boronate building blocks and one set of reaction conditions in an iterative fashion. a, The total synthesis of asnipyrone B (**NP1**). **b**, The total synthesis of physarigin A (**NP2**). **c**, The total synthesis of neurosporaxanthin β-D-glucopyranoside (**NP3**). C in circle represents coupling; D in circle represents deprotection; DC in circle represents deprotection/coupling.

required to access most of the remaining 99%. Although the answer to this is not yet known, the strategy demonstrated herein, that is, systematically identifying common motifs and transforming them into bifunctional building blocks compatible with iterative coupling, provides a roadmap for pursuing this problem. For example, we have identified 12 additional common structural motifs that are collectively present in more than 100,000 natural products (Supplementary Information). Half of these motifs have already been transformed into bifunctional halo MIDA boronates that are now commercially available. To achieve the same goal with some of the others will require solutions to frontier methodological problems, which include new chemistry to make and stereospecifically cross-couple Csp^3 boronates. In this vein, it is highly encouraging that there have been many recent advances in methods to prepare and stereoretentively cross-couple Csp^3 boronic acids and/or their derivatives[50].

With at least the conceptual framework for a more-generalized approach to small-molecule synthesis in hand, the prospective impact of fully automating the building-block assembly process is increasingly clear. The achievement of such automation with peptides[2], oligonucleotides[3] and, increasingly, oligosaccharides[4] has had a transformative impact on the respective areas of molecular science. The key to automating iterative synthesis is to find a way to purify the intermediates automatically, and in all of these previous cases, this goal has been achieved via solid-phase synthesis[2–4]. However, unlike their peptide, oligonucleotide and oligosaccharide counterparts, small molecules do not inherently possess a common functional-group handle that can be used for attachment to a solid support. Thus, the generalized automation of small molecule synthesis represents an exceptional problem that will require a distinct solution.

Finally, although we focus herein on a generalized approach to make known polyene natural products, the combinatorial assembly of the building blocks derived from this analysis could provide access to many new polyene natural product-like compounds. Expanding this same concept to include building blocks algorithmically derived from all known natural products could provide practical access to large collections of natural product-like compounds for functional screening.

In summary, the development of a more general and systematic building block-based approach for small-molecule synthesis would substantially expedite and broaden access to the extraordinary functional potential that these molecules possess. The results presented herein demonstrate an actionable roadmap to pursue this objective.

Methods

Full experimental details, procedures and characterization for new compounds are included in the Supplementary Information.

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Author contributions

E.M.W. and M.D.B. conceived the project. E.M.W., J.R. and M.D.B. designed and executed the experiments. E.M.W. and M.D.B. wrote the paper.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to M.D.B.

Competing financial interests

The authors declare no competing financial interests.