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# Biogenetically inspired synthesis and skeletal diversification of indole alkaloids

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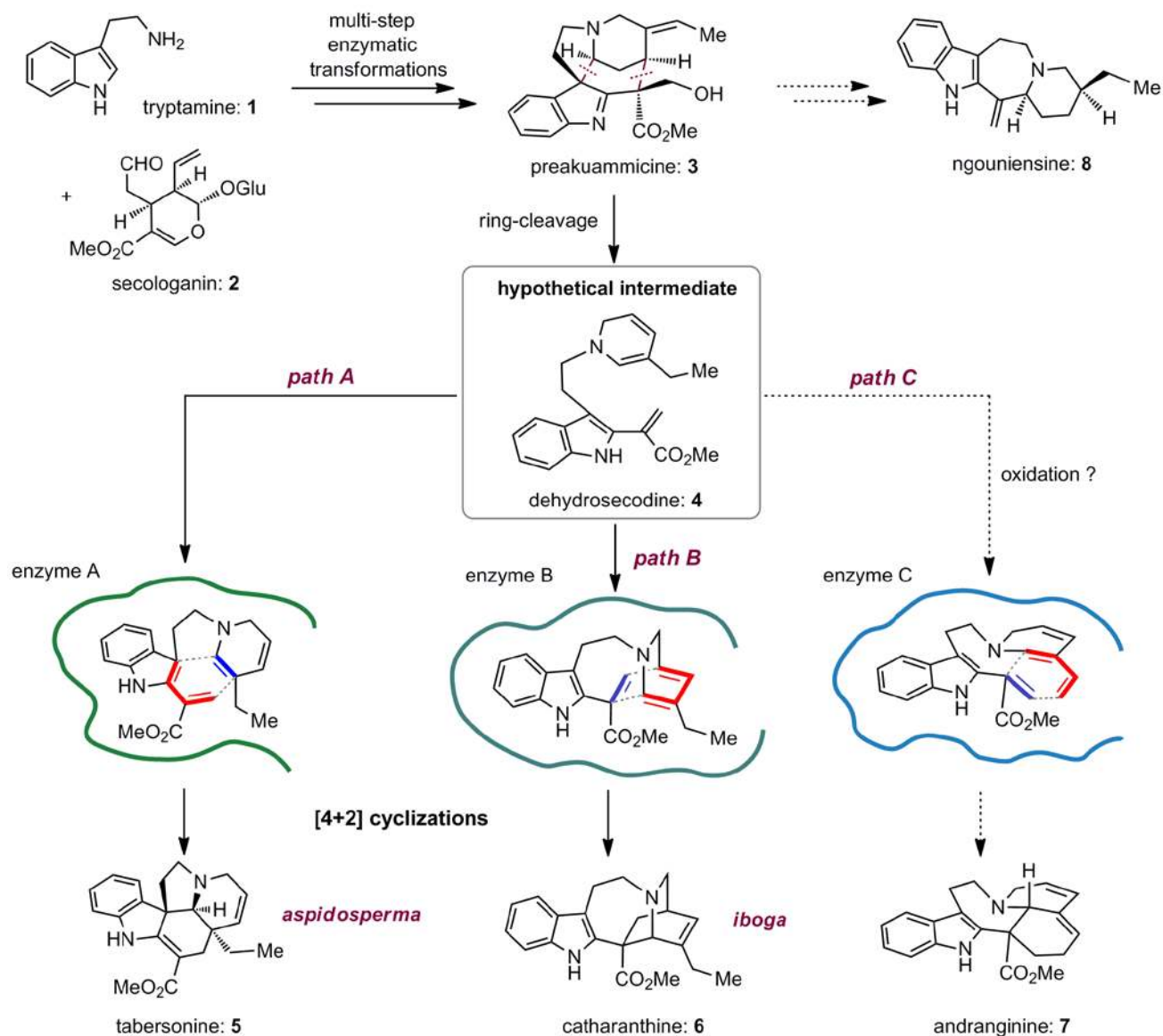
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**Abstract:** To access architecturally complex natural products, chemists usually devise a customized synthetic strategy for constructing a single target skeleton. In contrast, biosynthetic assembly lines often employ divergent intramolecular cyclizations of a polyunsaturated common intermediate to produce diverse arrays of scaffolds. With the aim of integrating such biogenetic strategies, here we show the development of an artificial divergent assembly line generating unprecedented numbers of scaffold variations of terpenoid indole alkaloids. This approach allows not only practical access to multipotent intermediates but also systematic diversification of skeletal, stereochemical, and functional group properties without structural simplification of naturally occurring alkaloids. Three distinct modes of [4+2] cyclizations and two types of redox-mediated annulations provided divergent access to five skeletally distinct scaffolds involving *iboga*-, *aspidosperma*-, *andranginine*-, and *ngouniensine*-type skeletons and a non-natural variant within 6–9 steps from tryptamine. The efficiency of our approach was demonstrated by successful total syntheses of (±)-vincadifformine, (±)-andranginine, and (–)-catharanthine.

Natural products often bear a variety of functional groups on a rigid, architecturally complex, and sp<sup>3</sup>-rich skeleton, which allows specific molecular recognition through multi-point interactions to modulate the functions of target biomacromolecules. Chemical synthesis of natural products and their analogs could provide optimum screening collections for the development of drug candidates

with higher hit rates and a lower probability of side effects.<sup>1-3</sup> While some innovative synthetic approaches have been recently reported to gain efficient access to such molecules as specific modulators of challenging biological targets,<sup>4-11</sup> a potentially general strategy for the development of divergent synthetic process to produce assortments of skeletally diverse and densely functionalized scaffolds remains unsettled and needs to be formulated.

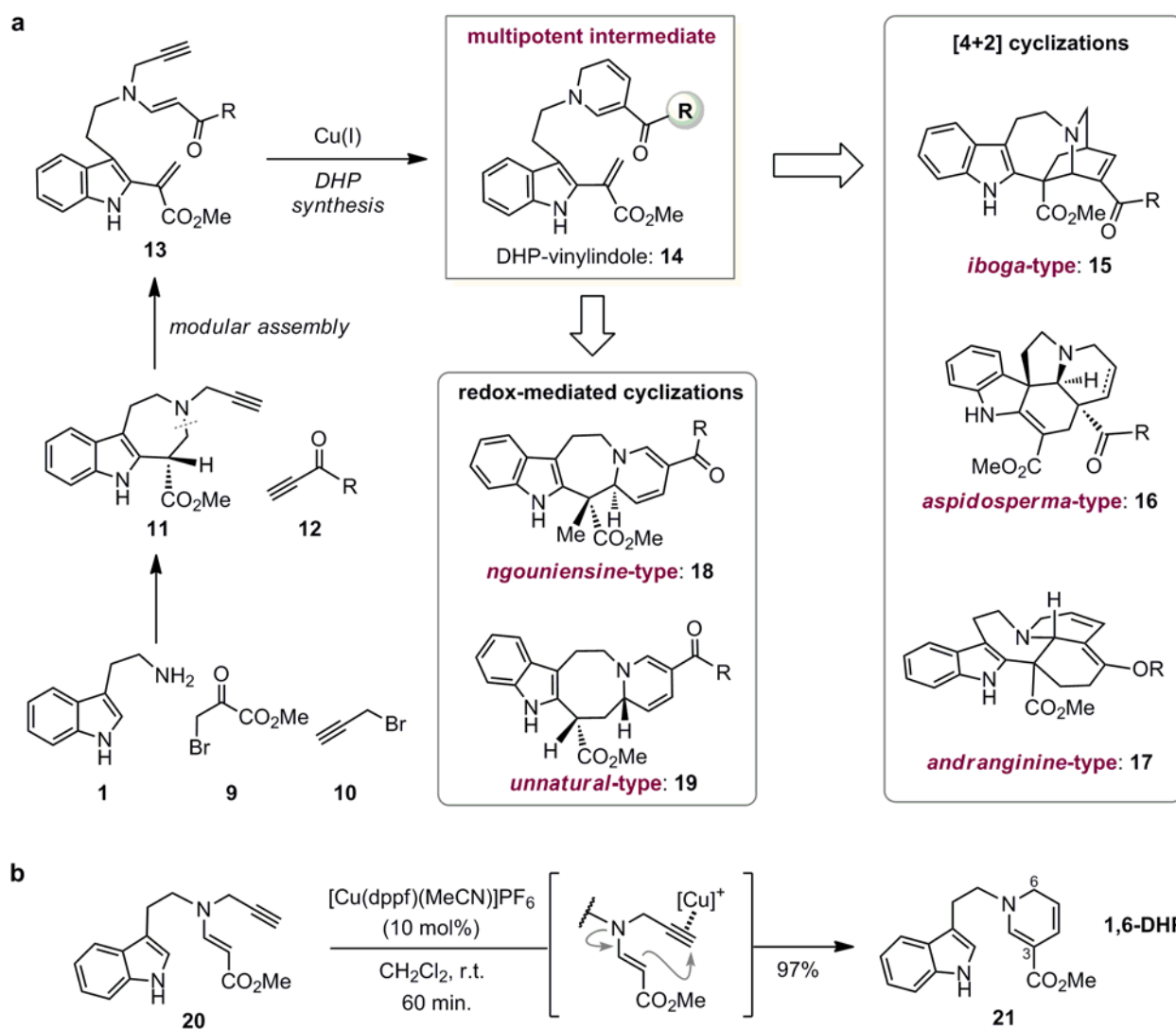
In working toward the total synthesis of a natural product composed of complex cyclic arrays, chemists usually develop a customized synthetic approach for the individual targeted scaffold. In contrast, biosynthetic machinery often exploits a common intermediate, conducting divergent transformations to furnish assortments of architecturally distinct skeletons. For instance, a biogenetic hypothesis for monoterpene indole alkaloids is outlined in Fig. 1.<sup>12</sup> Multistep enzymatic transformations commence with the assembly of tryptamine (**1**) and secologanin (**2**) to produce preakuammicine (**3**). Cleavage of two C-C bonds in the central core of **3** generates the hypothetical key intermediate dehydrosecodine (**4**), composed of a pair of diene units, a dihydropyridine (DHP), and a vinylindole. The intermediate (**4**) may undergo divergent Diels-Alder-type reactions in either of two ways, with the DHP group serving as a dienophile or diene to form the *aspidosperma*-type alkaloid tabersonine (**5**) (path A) or the *iboga*-type catharanthine (**6**) (path B).<sup>13</sup> In addition, a distinct biosynthetic [4+2] cyclization is postulated for andranginine (**7**) (path C), involving an intermediate bearing a cross-conjugated triene with a higher oxidation level than **4**.<sup>14</sup> The architectural complexity as well as the skeletal variation of the cognate alkaloids could be pre-encoded into the polyunsaturated structure of the achiral intermediate (**4**), settled at a branching point of the biogenesis.<sup>15</sup>



**Figure 1 | Proposed biogenesis of indole alkaloids (5–7) and structure of ngouniensine (8).** A hypothetical common intermediate, dehydrosecodine (4) could be biosynthesized through multistep enzymatic transformations starting from union of tryptamine (1) and secologanin (2). A pair of diene units in 4, a dihydropyridine (DHP) and a vinylindole, are thought to be installed through cleavage of two C-C bonds in the central core of an intermediate (3). Divergent [4+2] cyclizations of 4 would form the *aspidosperma*-type alkaloid tabersonine (5, path A) or the *iboga*-type catharanthine (6, path B). A distinct biosynthetic [4+2] cyclization is postulated for andranginine (7, path C), involving an intermediate bearing a cross-conjugated triene.

In the biosynthetic assembly line, the protection of the labile intermediates in an enzyme catalytic site provides kinetic stabilization and regulation of multimodal reactivity, allowing cascade synthesis

with control of chemo-, regio-, stereo-, and even enantioselectivity. In principle, each evolved enzyme possesses a tailored fit that contributes to the catalysis of a particular mode of a skeleton-constructing transformation;<sup>16</sup> hence, the participation of a series of similar but functionally distinct biomacromolecular catalysts is required for skeletal diversification. Meanwhile, chemical emulation of divergent biogenic processes without the assistance of biomolecular catalysts<sup>17</sup> pose challenges, including (I) stabilization of the labile intermediates during handling in laboratory, (II) concise and flexible assembly of building blocks, and (III) systematic implementation of various intramolecular cyclization reactions through site-selective activation of polyunsaturated substrates while suppressing competitive reactions. In this study, we aimed to formulate a chemical strategy not only to build a bioinspired assembly line but also to achieve systematic diversification of the skeletal and stereochemical properties of multicyclic scaffolds without structural simplification of the natural products involved. Herein, we report the successful development of a divergent synthetic process, which generates unprecedented levels of skeletal variation of monoterpene indole alkaloids.



**Figure 2 | Outline of a biogenetically inspired synthetic process to furnish alkaloidal scaffolds. a,**

Synthetic strategy for a divergent process featuring reactivity modulation of an achiral poly-unsaturated intermediate (**14**) through manipulation of the carbonyl group conjugated with the dihydropyridine (DHP) unit. Modular assembly of tryptamine (**1**) and building blocks (**9**, **10** and **12**) followed by cyclization of ene-yne (**13**) would allow rapid and flexible access to the common intermediate (**14**). Three distinct modes of bioinspired [4+2] cyclizations could produce assortments of naturally occurring scaffolds (**15–17**). Distinct modes of annulations were devised through redox-activations of the DHP unit to furnish either the tetracyclic framework (**18**) of ngouniense or the unnatural skeleton (**19**). **b**, Rapid formation of 1,6-DHP ring using Cu(I) catalysis. The optimum conditions for the 6-endo cyclization of ene-yne were explored using the model substrate (**20**). dppf, 1,1'-bis(diphenylphosphino)ferrocene.

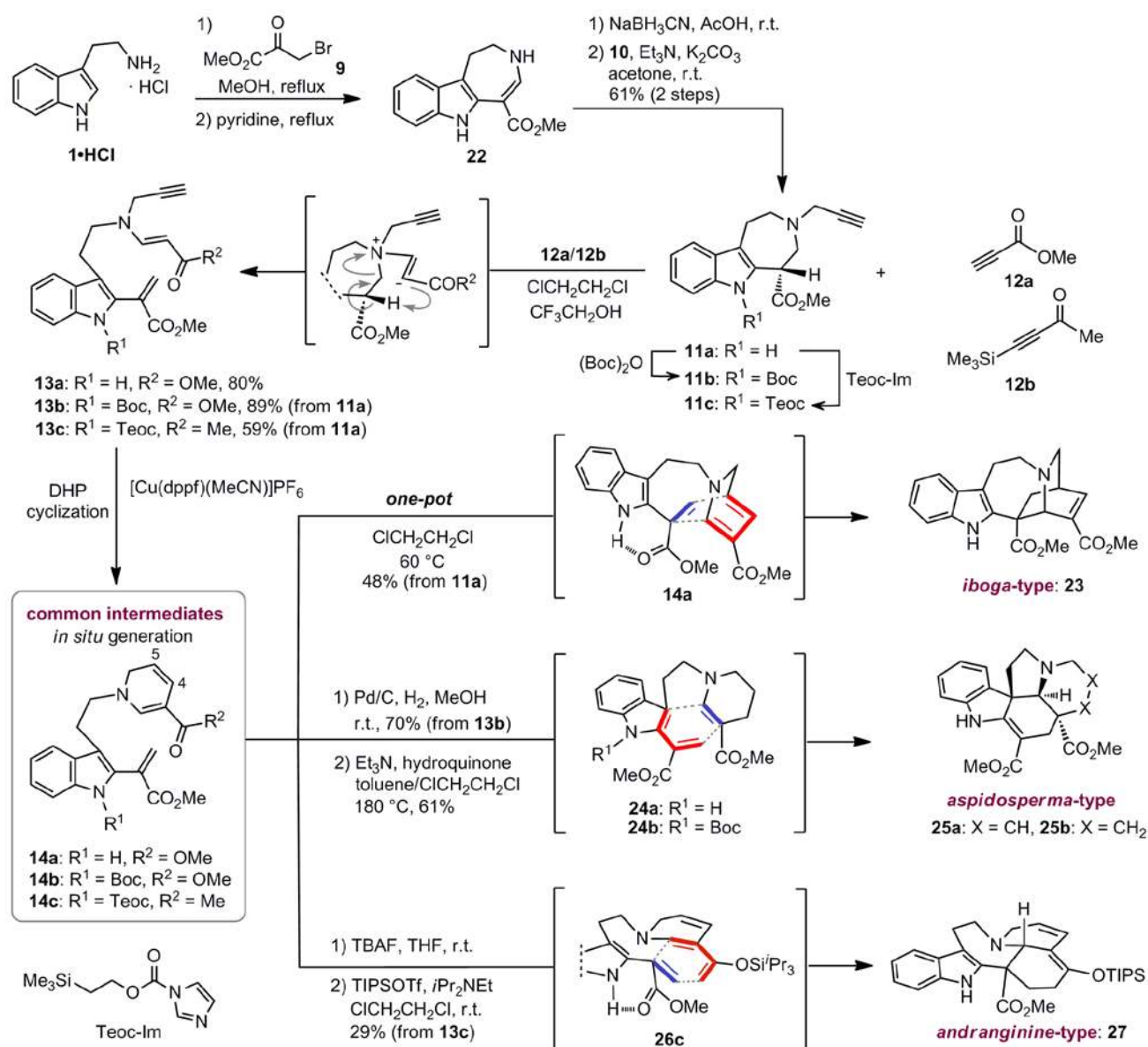
## Results and discussion

**Design of the divergent synthetic process.** To explore a biogenetically inspired synthetic approach, we first considered the dehydrosecodeine (**4**). Unfortunately, the hypothetical intermediate (**4**) has not been isolated or synthesized, presumably because the DHP unit of **4**, containing an ethyl substituent, may be labile to oxidation and oligomerization. In this study, we designed the artificial pluripotent intermediate (**14**) with intention of stabilizing the polyunsaturated system and thus installed an electron-withdrawing carbonyl group in place of the ethyl substituent (Fig. 2a). In addition, the attachment of various substituents to the carbonyl group could modify the reactivity of the DHP unit for systematic implementation of intramolecular cyclizations with control of regio- and stereoselectivity. We devised three types of bioinspired [4+2] cyclizations of **14**, leading to **15–17**, by manipulating the DHP unit conjugated with the carbonyl group. Moreover, redox activations of the DHP unit of **14** were explored to achieve distinct modes of annulations to furnish either the tetracyclic framework (**18**) of ngouniensine (**8**)<sup>18</sup> or the unnatural skeleton (**19**). We also conceived a late-stage chiral induction by attaching an auxiliary to the carbonyl group to accomplish enantioselective synthesis.

The sensitive DHP unit in the intermediate (**14**) should be formed just prior to the divergent cyclization reactions. Retrosynthetically, chemoselective activation of the alkynyl group in ene-yne (**13**) would allow 6-*endo* cyclization to afford **14**. With the intention of flexibly incorporating a series of enamincarbonyl moieties into the precursors, we devised a union of a tricyclic precursor (**11**) with an ethynylcarbonyl compound (**12**), accompanied by Hofmann elimination, to generate the ene-yne (**13**) containing a vinylindole unit. The precursor (**11**), a  $\beta$ -amino acid derivative, should be readily available by assembly of tryptamine (**1**) with methyl 3-bromo-2-oxopropanoate (**9**) and propargyl bromide (**10**).

**Development of Cu(I)-catalyzed cyclization to form the DHP ring.** With this strategic planning in mind, we first sought to develop an expedient protocol for the conversion of ene-yne (**13**) to the DHP-vinylindole intermediate (**14**) (Fig. 2b). Whereas approaches to the synthesis of substituted pyridines via oxidation of temporarily formed DHPs have been relatively well explored,<sup>19-21</sup> protocols for obtaining DHP rings via metal-catalyzed 6-*endo* cyclization of *N*-propargyl enamino-carbonyls are limited.<sup>22,23</sup> In our system, rapid construction of the 1,6-DHP ring was required under very mild conditions without causing further intra- and intermolecular reactions of the elaborate  $\pi$ -conjugated systems in **14**. As shown in Fig. 2b, investigation using the model substrate (**20**) allowed us to identify the optimum conditions that employ a cationic Cu(I) catalyst as an efficient alkyne activator. Upon treatment of **20** with a catalytic amount (10 mol%) of [Cu(dppf)(MeCN)]PF<sub>6</sub><sup>24</sup> in dichloromethane, 6-*endo* cyclization proceeded smoothly within 60 min at room temperature to afford the desired 1,6-DHP (**21**) in 97% yield without affecting the non-protected indole or the resulting DHP ring located in the vicinity.





**Figure 3 | Unified synthetic process for divergent access to 23, 25, and 27 through distinct [4+2] cyclization reactions.** Pictet-Spengler reaction of tryptamine (**1**) with **9** and subsequent ring expansion produced **22**. Reduction followed by *N*-propargylation gave **11a**. Assemblies of **11** with ethynylcarbonyl unit (**12**) could generate a zwitterionic intermediate effecting Hofmann elimination to afford ene-yne (**13**). Cu(I)-catalyzed cyclization of **13a** followed by [4+2] cyclization allowed a streamlined synthesis of *iboga*-type scaffold **23**. The *aspidosperma*-type scaffold (**25b**) was synthesized through regioselective hydrogenation of **14b** and a different [4+2] cyclization. A distinct [4+2] cyclization was realized through conversion of **14c** into **26c** to produce *andranginine*-type scaffold (**27**). Boc, *t*-butoxycarbonyl; Teoc, 2-(trimethylsilyl)ethoxycarbonyl; Im, imidazole; dppf, 1,1'-bis(diphenylphosphino)ferrocene; DHP, dihydropyridine; TBAF, tetra-*n*-butylammonium fluoride; TIPSOTf, triisopropylsilyl trifluoromethanesulfonate.

**Synthesis of a precursor for DHP cyclization, ene-yne (13a).** Having developed a sensible approach to formation of the 1,6-DHP ring, we synthesized ene-yne (**13a**), bearing a vinylindole unit, from tryptamine (**1**) in 5 steps (Fig. 3). A Pictet-Spengler reaction of **1** with **9** and subsequent ring expansion gave **22**, based on a reported protocol.<sup>25</sup> Reduction of **22** with sodium cyanoborohydride in acetic acid and subsequent *N*-propargylation produced **11a** in 61% yield (2 steps). Simultaneous installation of the enaminoester group and the *gem*-substituted vinylindole unit was efficiently achieved upon treatment of **11a** with methyl propiolate (**12a**) to furnish **13a**. Presumably, a zwitterionic intermediate would be capable of causing regioselective Hofmann elimination spontaneously. The use of 2,2,2-trifluoroethanol as a co-solvent with 1,2-dichloroethane was critical in gaining single-step access to **13a** in greater than 80% yield. Since the ene-yne (**13a**) was prone to gradual dimerization under concentrated conditions, it was used directly in subsequent conversions without chromatographic purification in most cases.

**Bioinspired divergent [4+2] cyclization reactions.** Next, the formation of DHP-vinylindole intermediate (**14**) and the implementation of a series of [4+2] cyclization reactions were explored (Fig. 3). Upon treatment of a crude mixture containing **13a** with [Cu(dppf)(MeCN)]PF<sub>6</sub> (10 mol%) at 60 °C, a cascade of reactions—DHP formation (**13a**→**14a**) and subsequent Diels-Alder-type reaction—proceeded smoothly in one-pot to produce *iboga*-type (**23**) in 48% yield from **11a**. The streamlined synthesis of the *iboga* skeleton possessing an additional carbonyl functional group was achieved in 6 steps from **1** without protection of the indole group. In contrast, for substrates bearing a *tert*-butoxycarbonyl (Boc) group or a simple methyl substituent at the indole N1 position, the same conversion produced only trace amounts of the corresponding *iboga*-type cycloadducts, whereas Cu(I)-catalyzed DHP formation took place efficiently regardless of the indole substituent (see Supporting Information). It is likely that the contribution of hydrogen bonding between the indole NH and the carbonyl oxygen of the  $\alpha,\beta$ -unsaturated methylester in **14a** not only increased the

electrophilicity of the dienophile but also fixed the conformation appropriately for cyclization to form the *iboga*-skeleton (**23**).

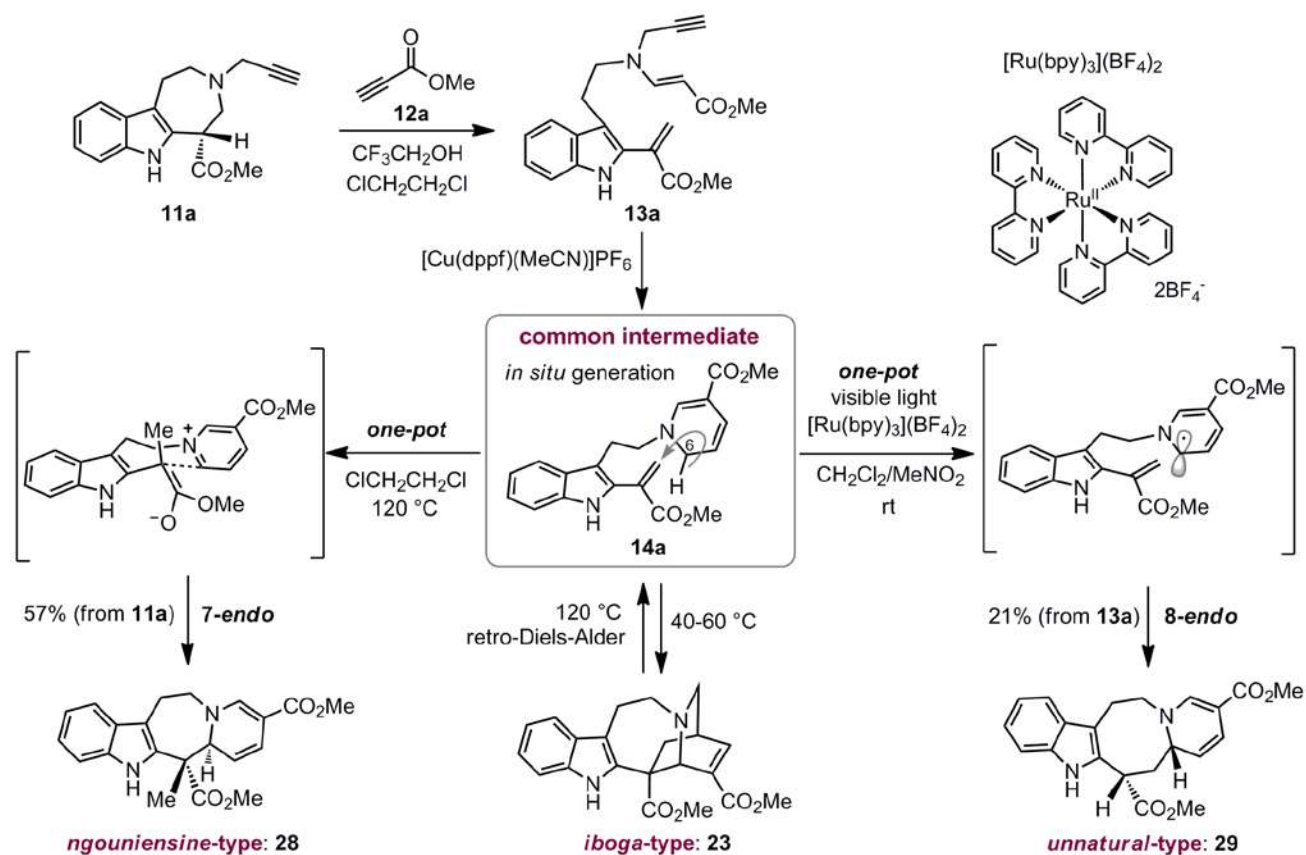
Next, we aimed to achieve a distinct mode of [4+2] cyclization leading to the *aspidosperma*-skeleton (**25**) (Fig. 3). Despite extensive efforts to activate **14a** with various Lewis/Brønsted acids and bases, formation of the *iboga*-skeleton (**23**) and oxidation to pyridinium salts occurred predominantly. The *aspidosperma*-skeleton (**25a**) was obtained, in less than 5% yield, only when **14a** was carefully treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) at low temperature (see Supporting Information). In order to suppress the formation of the *iboga*-skeleton as well as the oxidation of the DHP ring, we were obliged to protect the indole nitrogen and also to reduce the C4-C5 double bond in the DHP ring. Protection of **11a** with a Boc group and subsequent assembly of **11b** with **12a** via Hofmann elimination gave ene-yne (**13b**) in good yields. Cu(I)-catalyzed DHP formation and subsequent site-selective hydrogenation of the resulting **14b** provided isolable tetrahydropyridine (**24b**) in 70% yield (2 steps). Microwave-assisted heating of **24b** at 180 °C with hydroquinone (a polymerization inhibitor) and triethylamine<sup>26</sup> effected thermal decomposition of the Boc group (**24b**→**24a**) followed by [4+2] cyclization, giving rise to the *aspidosperma*-skeleton (**25b**) in 61% yield.

We then turned our attention to achieving a distinct [4+2] annulation via intermediate (**26c**) bearing cross-conjugated triene to yield the *andranginine*-type scaffold (**27**) (Fig. 3). To this end, we examined the installation of a methylketone group into the versatile intermediate (**14c**) to generate the triene (**26c**) through silylenol ether formation. Cu(I)-catalyzed 6-*endo* cyclization of the corresponding ene-yne (**13c**) bearing the methylketone group, however, required gentle heating at 45 °C to form the DHP ring. From a practical point of view, protection of the indole nitrogen should be beneficial in suppressing competitive cyclization leading to the *iboga*-skeleton and other side reactions. In fact, protection with a 2-(trimethylsilyl)ethoxycarbonyl (Teoc) group (**11a**→**11c**)

ensured stabilities of **13c** and **14c** upon conversion of **11c** into **14c**. The tricycle (**11c**) and 4-trimethylsilyl-3-butyne-2-one (**12b**) were efficiently assembled via Hofmann elimination to give the desired ene-yne (**13c**) with the loss of a trimethylsilyl group. The resulting **13c** was subjected to sequential operations—Cu(I)-catalyzed DHP formation at 45 °C, producing **14c**, and removal of the Teoc group with tetrabutylammonium fluoride (TBAF) followed by treatment with triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) at room temperature—to generate the intermediate (**26c**) having a silylenol ether. The desired mode of [4+2] cyclization of **26c** occurred spontaneously to furnish the *andranginine*-type scaffold (**27**) (29% for 3 steps from **13c**). Thus far, we have implemented three distinct bioinspired Diels-Alder-type cyclization reactions of intermediates (**14a**, **24a**, and **26c**) leading to a series of alkaloidal scaffolds, **23**, **25b**, and **27**.

**Redox-mediated cyclization reactions leading to 28 and 29.** Further skeletal diversifications were then explored through redox activation of the DHP unit (Fig. 4). To achieve an alternative cyclization of **14a**, we first envisaged two-electron oxidation of the DHP ring to generate a pyridinium species. Indeed, when the reaction mixture for the conversion of **13a** to **14a** was heated to 120 °C, a distinct annulation of **14a** took place predominantly, giving tetracyclic scaffold (**28**) in good yield (57% from **11a**). The tetracyclic array of **28** is identical to the framework of naturally occurring ngouniensine (**8**).<sup>27</sup> The relative configuration of **28** was elucidated based on X-ray analysis of the crystalline equivalents (see Supporting Information). Taking into account for the experimental results on the conversions of deuterium labeled **14a** (see Supplementary Schemes S1-S2), **28** could presumably be formed through a hydride shift generating a zwitterionic intermediate composed of a pyridinium cation and an enolate anion, which would undergo subsequent *7-endo* cyclization.<sup>28</sup> In contrast to the identical conversion of **13a** into **14a** under gentle heating at 60 °C, yielding the *iboga*-skeleton (**23**) as the major product (Fig. 3), **23** was not obtained at all at 120 °C. We thus postulated the involvement of a retro-Diels-Alder reaction. When isolated **23** was heated to 120 °C, as expected, we

observed the consumption of **23** and the formation of **28** as the major product (47%, see Supporting Information). It seems probable that the retro-Diels-Alder reaction of kinetically formed **23** regenerates the DHP-vinylindole intermediate (**14a**) at the elevated temperature. Hydride transfer and subsequent cyclization may occur irreversibly to furnish *ngouniensine*-type scaffold (**28**).

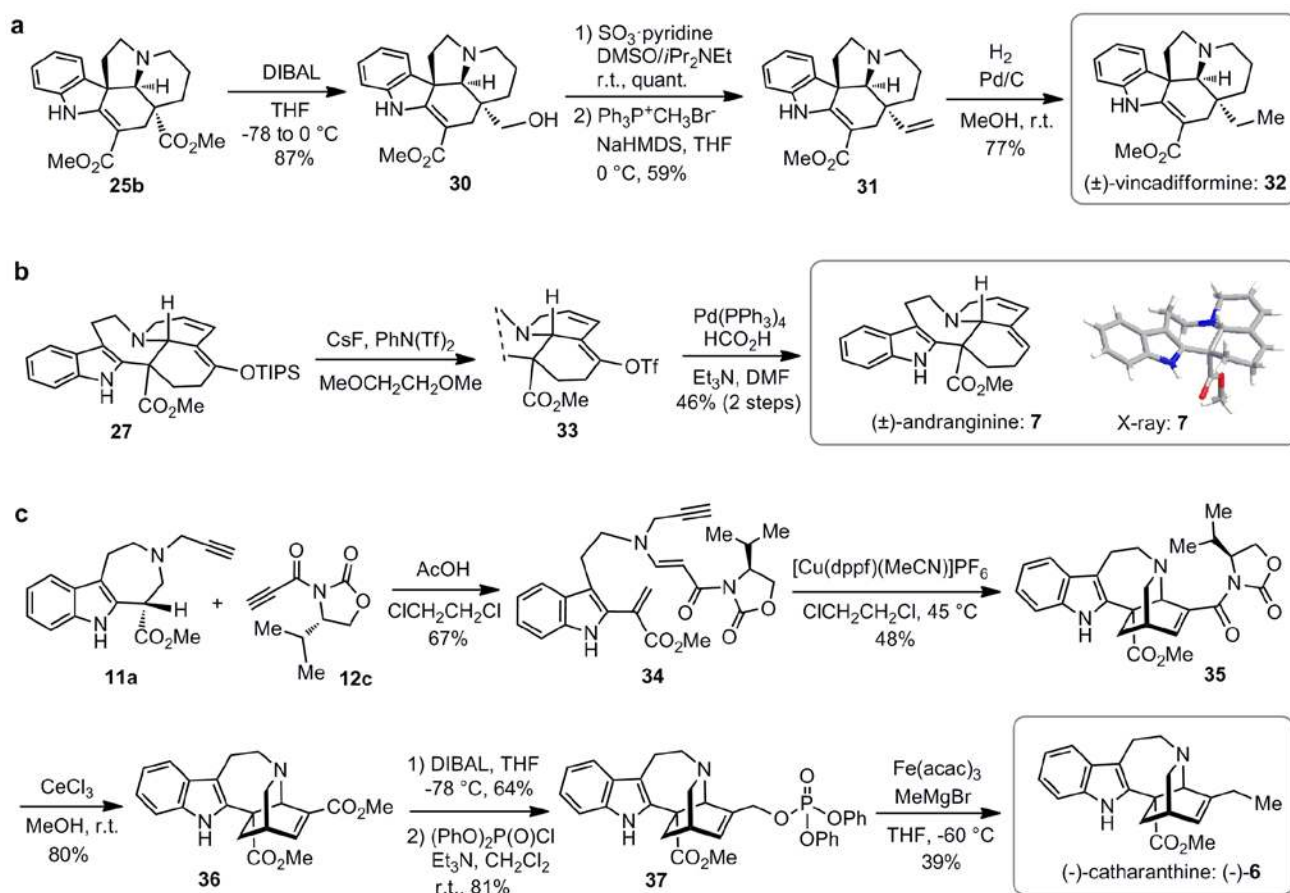


**Figure 4 | Redox-mediated activation of the DHP-vinylindole (**14a**) leading to tetracyclic scaffolds (**28** and **29**), which contain a DHP ring.** The common intermediate (**14a**) generated from **11a** was subjected to either two- or single-electron oxidation process to produce **28** and **29**, respectively. Upon heating at  $120^\circ\text{C}$ , *ngouniensine*-type scaffold (**28**) was obtained as the major product. The involvements of the retro-Diels-Alder reaction (**23**→**14a**), hydride shift followed by 7-*endo*-cyclization of a zwitterionic intermediate were postulated in the formation of **28**. Single-electron oxidation of **14a** provided an *unnatural*-type scaffold (**29**) presumably via 8-*endo*-radical cyclization. bpy, 2,2'-bipyridine; dppf, 1,1'-bis(diphenylphosphino)ferrocene.

Next, we envisioned single-electron oxidation of the 1,6-DHP ring in **14a** to generate a carbon-centered radical species. Since photo-redox synthetic processes often employ

1-benzyl-1,4-dihydronicotinamide (BNAH) with a 1,4-DHP system as a versatile reductant,<sup>29-31</sup> **14a** was treated with a photo-redox catalyst, [Ru(bpy)<sub>3</sub>](BF<sub>4</sub>)<sub>2</sub>, at 0 °C under irradiation with fluorescent light (12 W). The tetracyclic scaffold (**29**), not found in naturally occurring alkaloids, was obtained, albeit in low yield (21%), which may have been consistent with our intention to conduct a redox-mediated 8-*endo* cyclization. Oxidative activations of **14a** in either a two-electron or a single-electron process produced the tetracyclic scaffolds (**28** and **29**) bearing DHP ring in their fused scaffolds, which could provide a versatile platform for further diversification. In this way, we illustrated the systematic generation of skeletally diverse scaffolds (**23**, **25**, and **27–29**) relevant to naturally occurring indole alkaloids within 6–9 steps from tryptamine (**1**).

**Total synthesis of three natural products.** To highlight the applicability and efficiency of the divergent synthetic process, we sought to achieve total syntheses of (±)-vincadifformine (**32**), (±)-andranginine (**7**), and (–)-catharanthine (**6**) (Fig. 5). Since the *aspidosperma*-type scaffold (**25b**) bears the requisite functional array of (±)-vincadifformine (**32**) (Fig. 5a), we carried out a total synthesis to confirm its structure (see Supporting Information for precedent total syntheses of **32**).<sup>5, 32-35</sup> The more sterically hindered methyl ester in **25b** was reduced site-selectively by simple treatment with diisobutylaluminium hydride (DIBAL) to furnish primary alcohol **30** in 87% yield. Oxidation of **30** and subsequent Wittig elongation produced **31**, which contains a vinyl group. Site-selective hydrogenation of **31** gave rise to (±)-vincadifformine (**32**) in 77% yield.



**Figure 5 | Total synthesis of three natural products. a**, Site-selective reduction of methylester (**25b**) followed by oxidation of resulting primary alcohol and Wittig elongation gave **31**. Site-selective hydrogenation of **31** afforded (±)-vincadifformine (**32**). **b**, Direct conversion of silylenol ether (**27**) to vinyl triflate (**33**) and subsequent palladium-catalyzed reduction furnished (±)-andranginine (**7**). **c**, Hofmann elimination triggered by addition of **11a** to **12c** gave **34**. After Cu(I)-catalyzed formation of DHP ring, the critical [4+2] cyclization reaction proceeded with complete diastereocontrol in one-pot to produce **35**. Removal of the chiral auxiliary, site-selective reduction of **36**, and conversion into an allylic phosphate (**37**) followed by Fe-catalyzed cross-coupling with MeMgBr accomplished asymmetric total synthesis of (-)-catharanthine (**6**). DIBAL, diisobutylaluminium hydride; NaHMDS, sodium hexamethyldisilazide; Tf, trifluoromethanesulfonyl; dppf, 1,1'-bis(diphenylphosphino)ferrocene; acac, acetylacetonate.

Next, the conversion of pentacycle (**27**) to (±)-andranginine (**7**) was accomplished by trimming an additional functional group in two steps (Fig. 5b). Direct conversion of **27** bearing a silylenol ether to vinyl triflate (**33**)<sup>36</sup> and subsequent palladium-catalyzed reduction furnished **7** in good yield. X-ray analysis of crystalline **7** confirmed its relative configuration, which was identical to the proposed

structure of andranginine.<sup>37</sup> This is the first example of *de novo* total synthesis of the almost disregarded natural product, (±)-andranginine (**7**), in 11 steps,<sup>38</sup> which lends experimental support to an alternate mode of biosynthetic Diels-Alder-type cyclization diverging from the hypothetical intermediate (**4**).

We then performed enantioselective total synthesis of catharanthine (**6**) (Fig. 5c). To illustrate late-stage asymmetric induction through attachment of a chiral auxiliary to the DHP ring, ene-yne (**34**) with an oxazolidinone group was synthesized by exploiting the modular nature of the assembly line. Hofmann elimination triggered by addition of **11a** to **12c** proceeded efficiently under modified conditions to produce **34** in 67% yield with the loss of a stereogenic center in racemic tricycle (**11a**). Upon treatment of **34** with the Cu(I) catalyst (15 mol%) at 45 °C, a cascade transformation afforded the desired *iboga*-scaffold (**35**) in 48% yield with complete diastereocontrol of the critical [4+2] cyclization reaction. Removal of the chiral auxiliary by CeCl<sub>3</sub>-catalyzed methanolysis gave the corresponding methyl ester (**36**) in 80% yield. Site-selective reduction of **36** with DIBAL produced an allylic alcohol, which was then transformed to an allylic phosphate (**37**) in good yield. An iron-catalyzed cross-coupling reaction with methyl Grignard reagent<sup>39</sup> proceeded regioselectively accomplishing asymmetric total synthesis of (–)-catharanthine (**6**). The absolute configuration was assigned based on optical rotation (see Supporting Information). While there has been pioneering synthetic studies,<sup>26,40-49</sup> the 10-step sequence described herein is the shortest enantiocontrolled total synthesis of (–)-catharanthine (**6**), to the best of our knowledge.<sup>50</sup> Consequently, we have successfully demonstrated that the appropriately functionalized scaffolds generated via three distinct modes of the bioinspired [4+2] cyclizations are readily applicable for achieving total syntheses of (±)-vincadifformine (**32**), (±)-andranginine (**7**), and (–)-catharanthine (**6**).

In summary, we have developed a unified synthetic process generating unprecedented levels of scaffold variations of natural products without structural simplification. The multipotent DHP-vinylindole intermediates (**14a–c**) were flexibly synthesized through unions of tricycles



(**11a–c**) and ethynylcarbonyl units (**12a–c**) followed by Cu(I)-catalyzed formation of the DHP ring. By harnessing the versatile reactivity of **14**, multiple modes of annulation were systematically implemented. The divergent process allowed a concise and programmable access to four naturally occurring scaffolds (**23**, **25b**, **27**, and **28**) and a non-natural skeletal variant (**29**), each within 6–9 steps from tryptamine (**1**). This synthetic campaign illustrates the concept of reactivity modulation of an achiral poly-unsaturated intermediate in conjunction with modular assembly of building blocks and regio/stereo-controlled cyclizations, which form a foundation for the development of a divergent synthetic process generating a series of natural products and their structural variants having different skeletal, stereochemical and functional group properties. The synthetic strategies and tactics demonstrated herein could be applicable to design artificial assembly lines to furnish collections of natural product-inspired small molecules by emulating biogenesis of other families of secondary metabolites.

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## Figure legends

**Figure 1 | Proposed biogenesis of indole alkaloids (5–7) and structure of ngouniensine (8).** A hypothetical common intermediate, dehydrosecodine (**4**) could be biosynthesized through multistep enzymatic transformations starting from union of tryptamine (**1**) and secologanin (**2**). A pair of diene units in **4**, a dihydropyridine (DHP) and a vinylindole, are thought to be installed through cleavage of two C-C bonds in the central core of an intermediate (**3**). Divergent [4+2] cyclizations of **4** would form the *aspidosperma*-type alkaloid tabersonine (**5**, path A) or the *iboga*-type catharanthine (**6**, path B). A distinct biosynthetic [4+2] cyclization is postulated for andranginine (**7**, path C), involving an intermediate bearing a cross-conjugated triene.

**Figure 2 | Outline of a biogenetically inspired synthetic process to furnish alkaloidal scaffolds. a,**

Synthetic strategy for a divergent process featuring reactivity modulation of an achiral poly-unsaturated intermediate (**14**) through manipulation of the carbonyl group conjugated with the dihydropyridine (DHP) unit. Modular assembly of tryptamine (**1**) and building blocks (**9**, **10** and **12**) followed by cyclization of ene-yne (**13**) would allow rapid and flexible access to the common intermediate (**14**). Three distinct modes of bioinspired [4+2] cyclizations could produce assortments of naturally occurring scaffolds (**15–17**). Distinct modes of annulations were devised through redox-activations of the DHP unit to furnish either the tetracyclic framework (**18**) of ngouniensine or the unnatural skeleton (**19**). **b**, Rapid formation of 1,6-DHP ring using Cu(I) catalysis. The optimum conditions for the 6-*endo* cyclization of ene-yne were explored using the model substrate (**20**). dppf, 1,1'-bis(diphenylphosphino)ferrocene.

**Figure 3 | Unified synthetic process for divergent access to 23, 25, and 27 through distinct [4+2] cyclization reactions.** Pictet-Spengler reaction of tryptamine (**1**) with **9** and subsequent ring expansion produced **22**. Reduction followed by *N*-propargylation gave **11a**. Assemblies of **11** with ethynylcarbonyl unit (**12**) could generate a zwitterionic intermediate effecting Hofmann elimination to afford ene-yne (**13**). Cu(I)-catalyzed cyclization of **13a** followed by [4+2] cyclization allowed a streamlined synthesis of *iboga*-type scaffold **23**. The *aspidosperma*-type scaffold (**25b**) was synthesized through regioselective hydrogenation of **14b** and a different [4+2] cyclization. A distinct [4+2] cyclization was realized through conversion of **14c** into **26c** to produce *andranginine*-type scaffold (**27**). Boc, *t*-butoxycarbonyl; Teoc, 2-(trimethylsilyl)ethoxycarbonyl; Im, imidazole; dppf, 1,1'-bis(diphenylphosphino)ferrocene; DHP, dihydropyridine; TBAF, tetra-*n*-butylammonium fluoride; TIPSOTf, triisopropylsilyl trifluoromethanesulfonate.

**Figure 4 | Redox-mediated activation of the DHP-vinylindole (14a) leading to tetracyclic scaffolds (28 and 29), which contain a DHP ring.** The common intermediate (**14a**) generated from **11a** was subjected to either two- or single-electron oxidation process to produce **28** and **29**, respectively. Upon heating at 120 °C, *ngouniensine*-type scaffold (**28**) was obtained as the major product. The involvements of the retro-Diels-Alder reaction (**23**→**14a**), hydride shift followed by 7-*endo*-cyclization of a zwitterionic intermediate were postulated in the formation of **28**. Single-electron oxidation of **14a** provided an *unnatural*-type scaffold (**29**) presumably via 8-*endo*-radical cyclization. bpy, 2,2'-bipyridine; dppf, 1,1'-bis(diphenylphosphino)ferrocene.

**Figure 5 | Total synthesis of three natural products. a**, Site-selective reduction of methylester (**25b**) followed by oxidation of resulting primary alcohol and Wittig elongation gave **31**. Site-selective hydrogenation of **31** afforded (±)-vincadifformine (**32**). **b**, Direct conversion of silylenol ether (**27**) to vinyl triflate (**33**) and subsequent palladium-catalyzed reduction furnished (±)-andranginine (**7**). **c**, Hofmann elimination triggered by addition of **11a** to **12c** gave **34**. After Cu(I)-catalyzed formation of DHP ring, the critical [4+2] cyclization reaction proceeded with

complete diastereocontrol in one-pot to produce **35**. Removal of the chiral auxiliary, site-selective reduction of **36**, and conversion into an allylic phosphate (**37**) followed by Fe-catalyzed cross-coupling with MeMgBr accomplished asymmetric total synthesis of (–)-catharanthine (**6**). DIBAL, diisobutylaluminium hydride; NaHMDS, sodium hexamethyldisilazide; Tf, trifluoromethanesulfonyl; dppf, 1,1'-bis(diphenylphosphino)ferrocene; acac, acetylacetonate.

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### **Contributions**

H.M. carried out the experimental work. H.M. and H. Oguri conceived the projects, analyzed the experimental results and wrote the manuscript. H. Oikawa discussed the results and provided oversight.

### **Additional information**

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permission information is available online at <http://www.nature.com/reprints>. Correspondence and requests for materials should be addressed to H. Oguri.

### **Competing financial interests**

The authors declare no competing financial interests.