Biogenetically inspired synthesis and skeletal diversification of indole alkaloids

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Oguri, H. *et al.*
Nature Chem. **2014**, *6*, 57.

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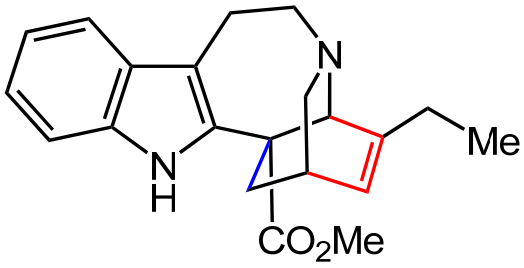
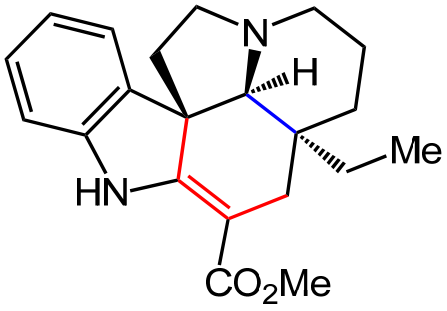
Introduction



Catharanthine
长春质碱

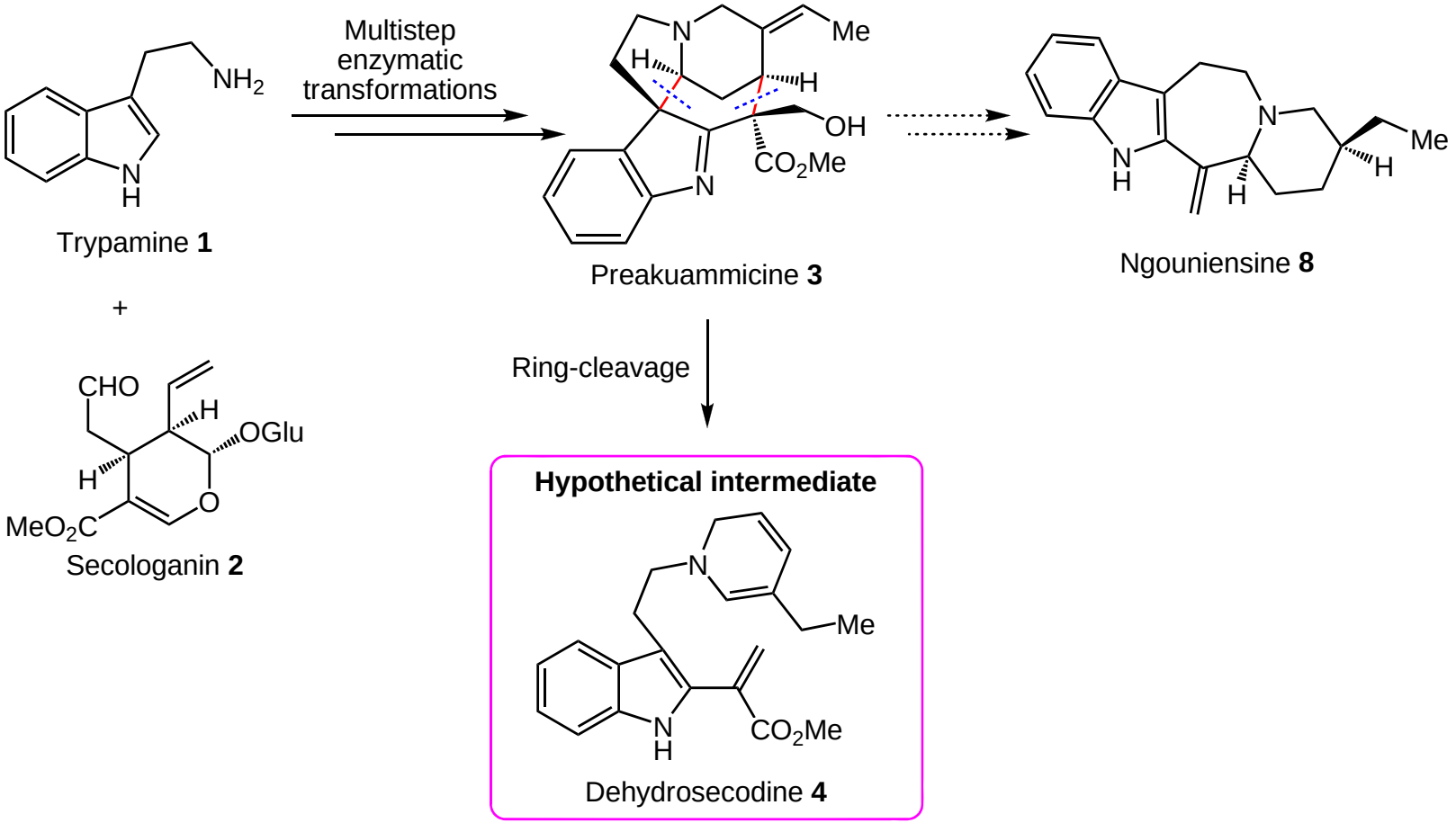
Catharanthus roseus
长春花



Vincadifformine
右旋异形蔓长春花胺

Kopsia officinalis Tsiang et P.T.
柯蒲木

Proposed biogenesis of indole alkaloids



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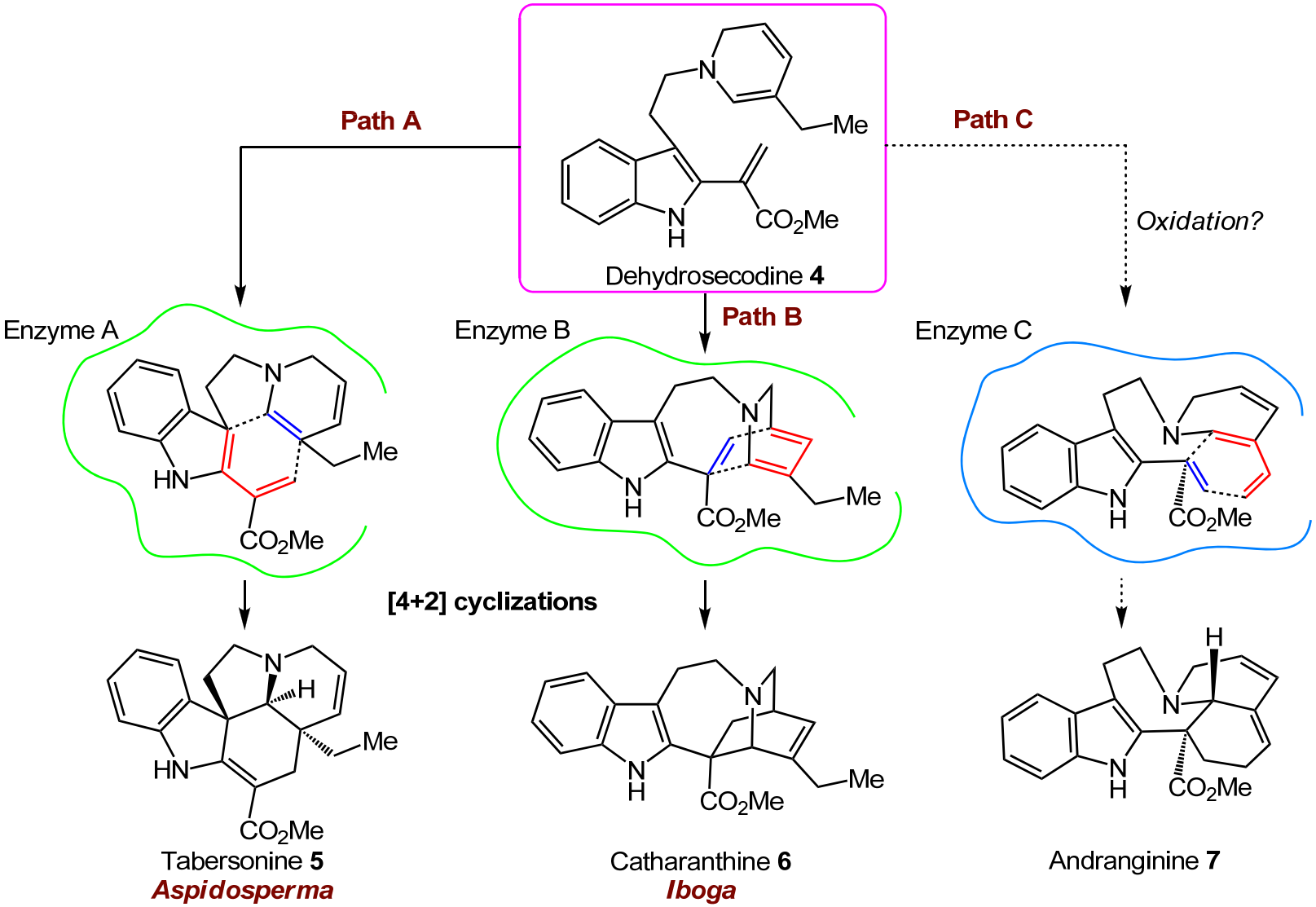
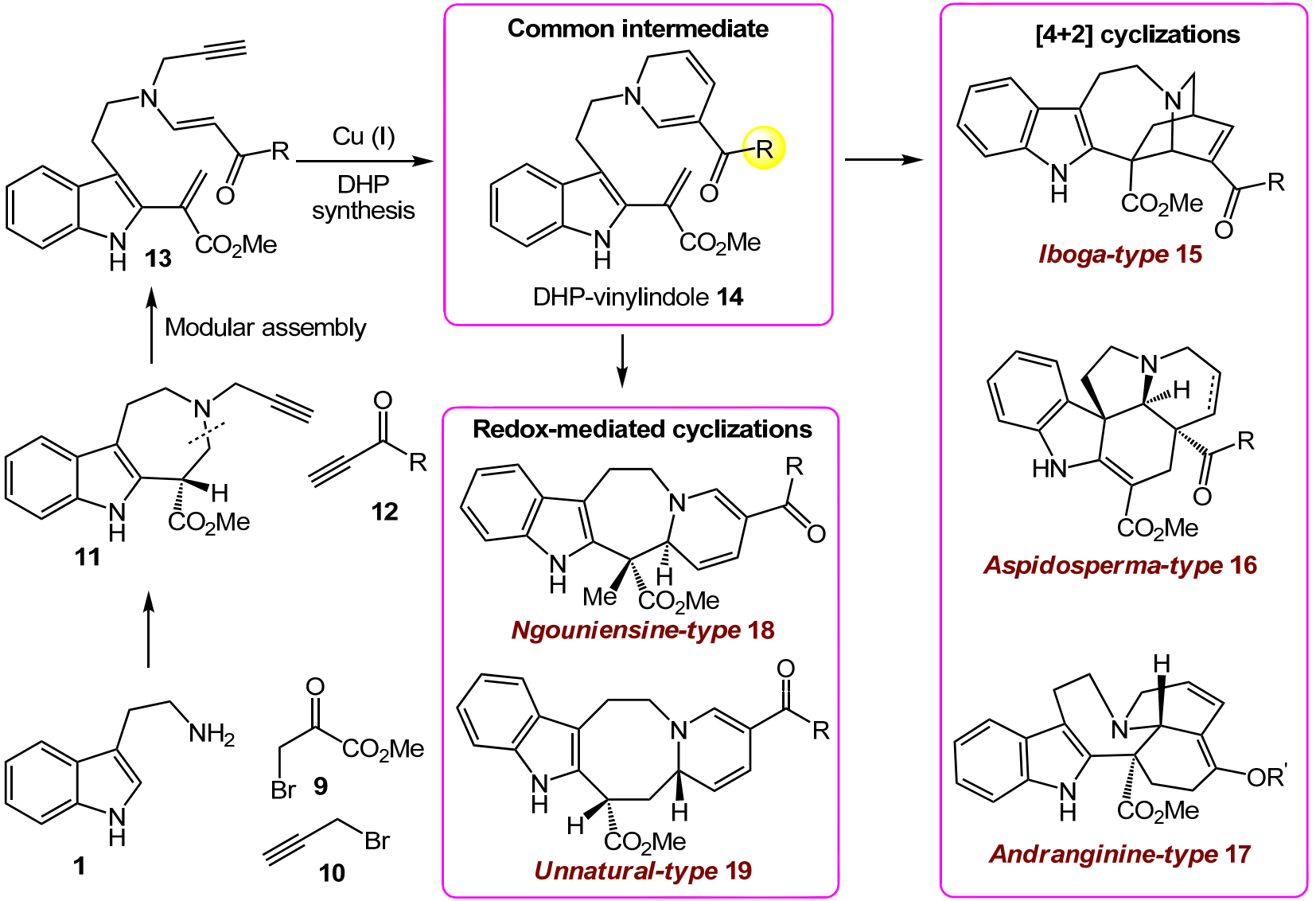
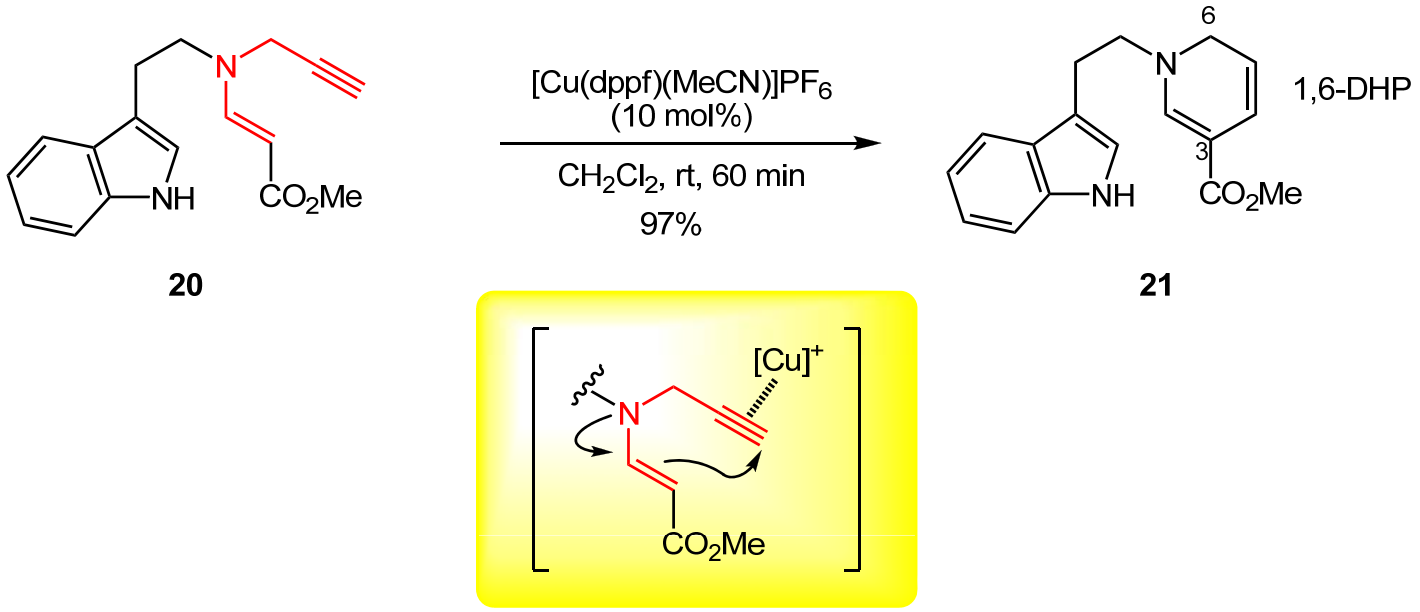
Proposed biogenesis of indole alkaloids



Biogenetically inspired synthesis of indole alkaloids

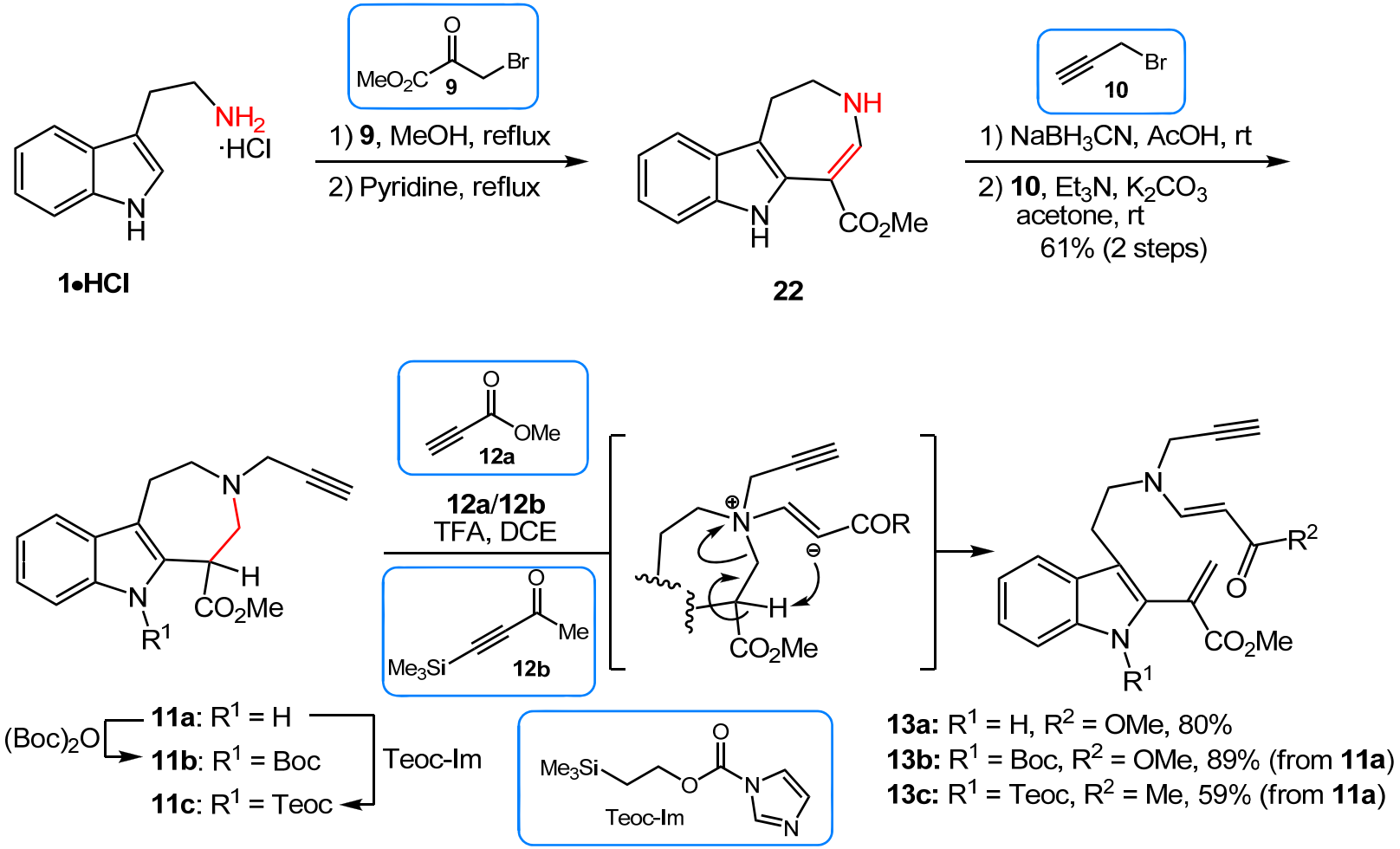


Rapid formation of 1,6-DHP ring using Cu(I) catalysis

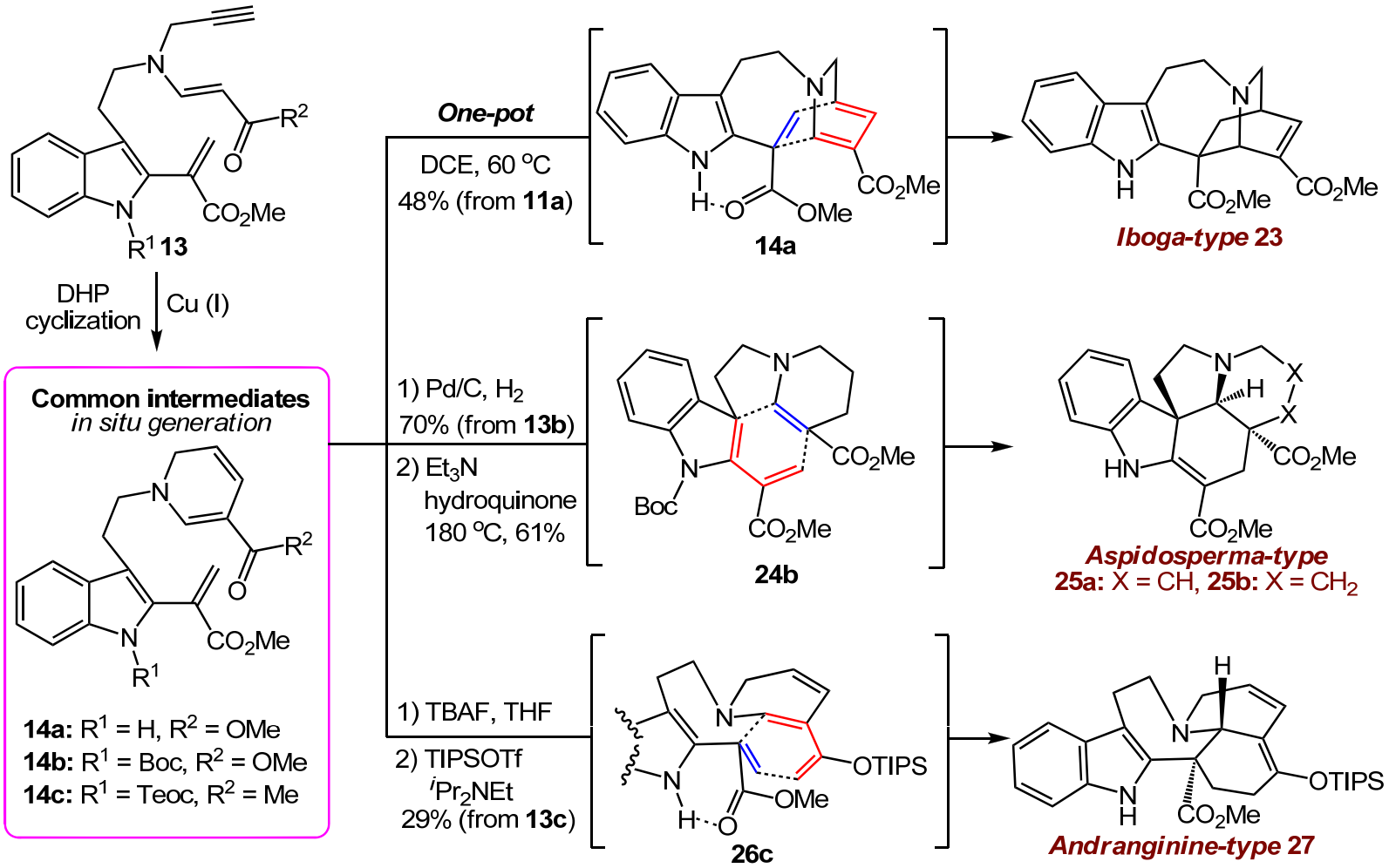


20 **21**

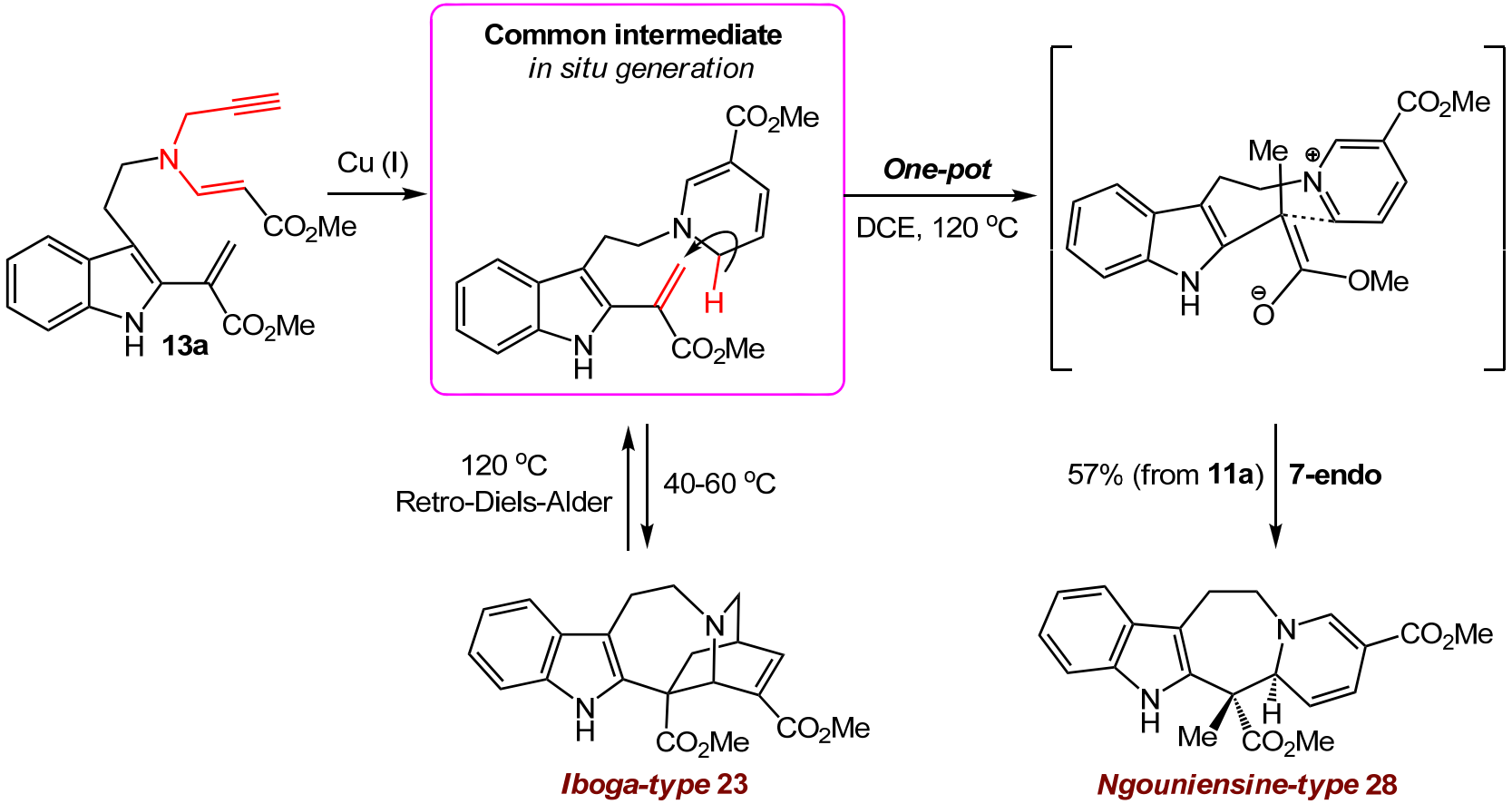
Divergent synthesis of indole alkaloids



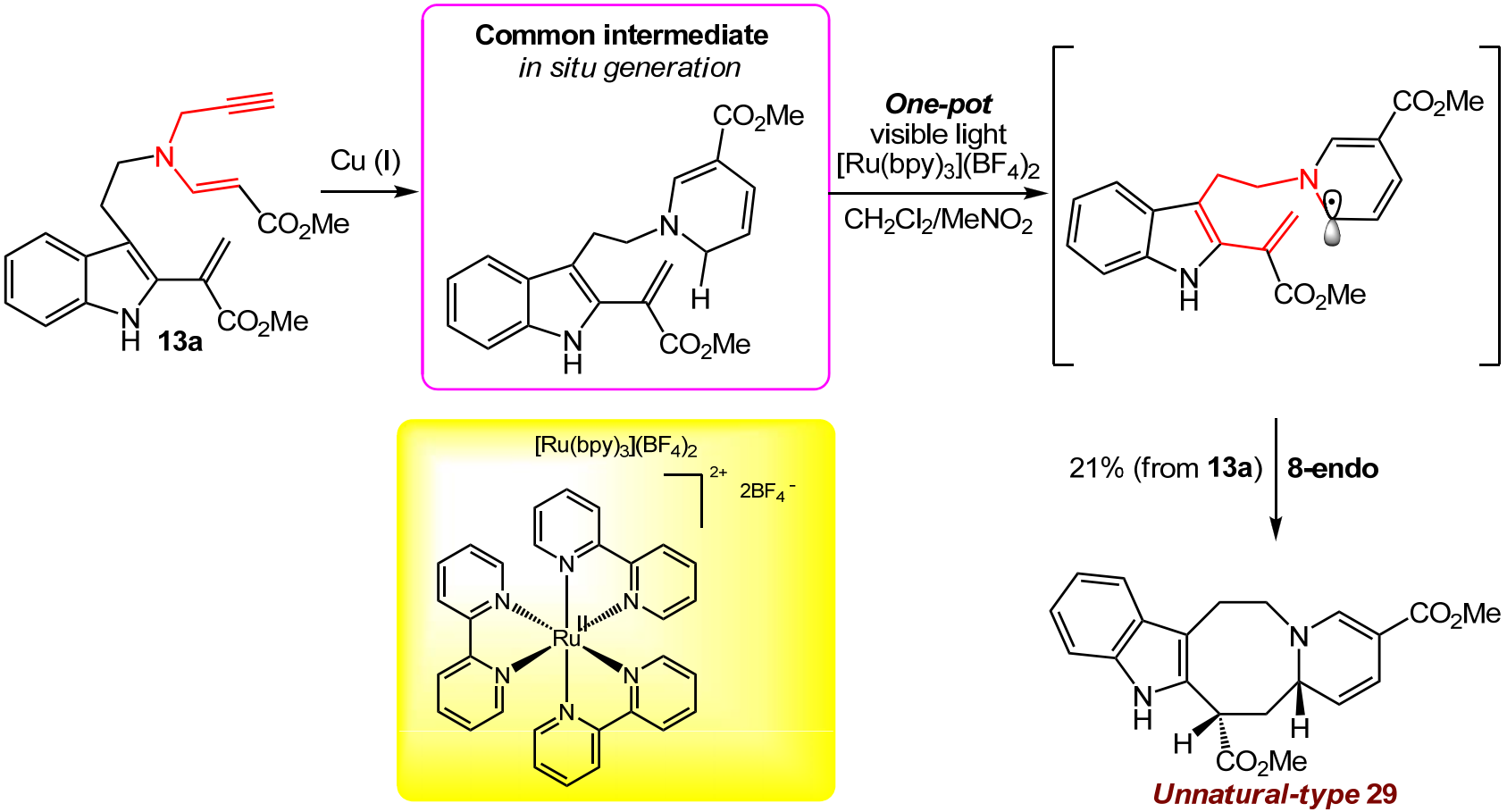
Divergent synthesis of indole alkaloids



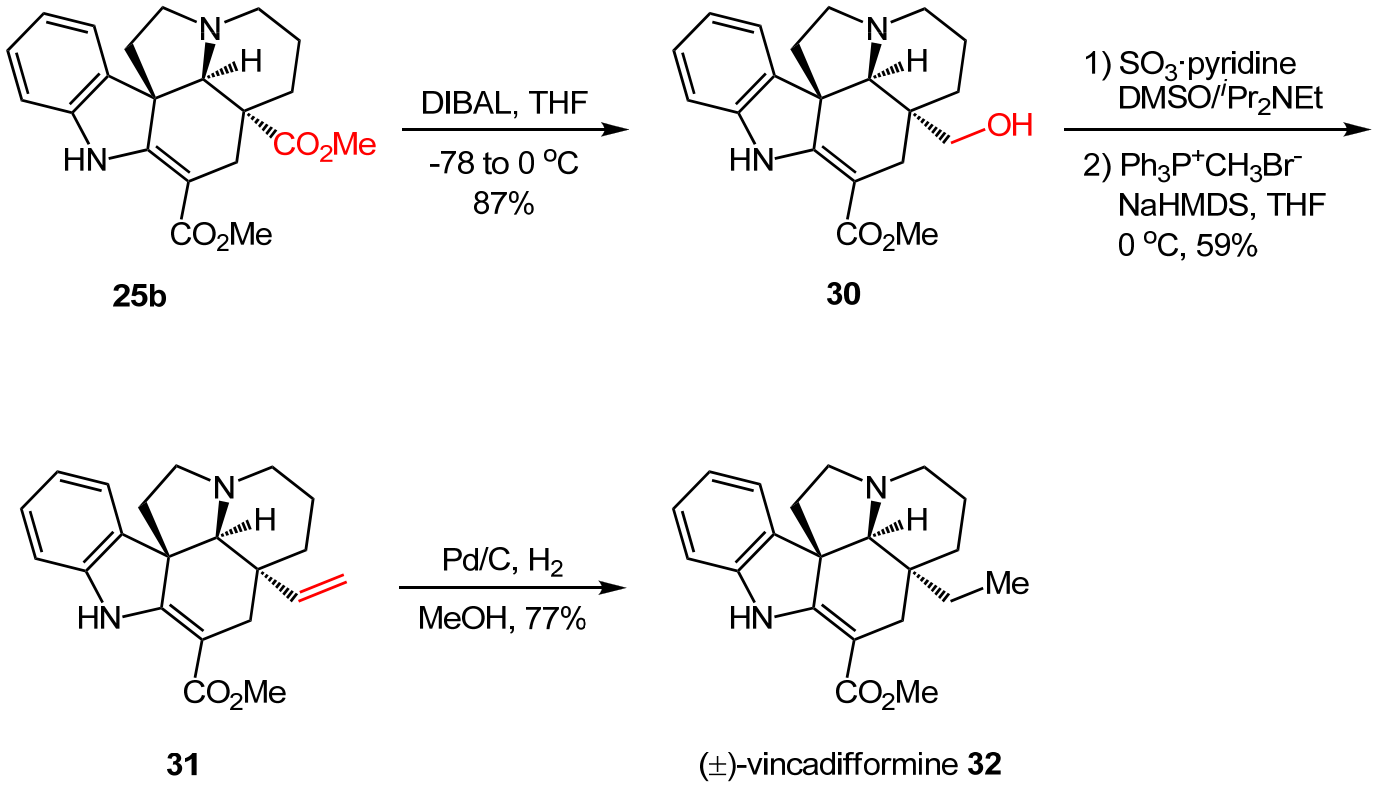
Divergent synthesis of indole alkaloids



Divergent synthesis of indole alkaloids

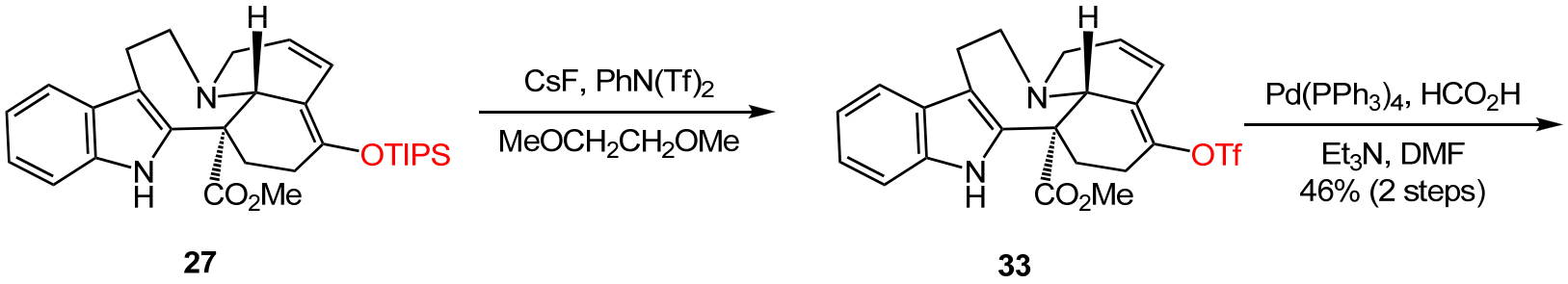


Total synthesis of three natural products

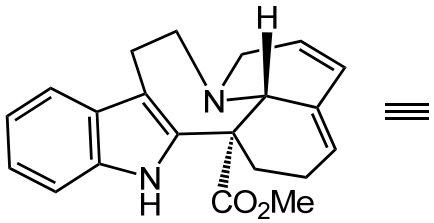


25b **30** **31** (±)-vincadifformine **32**

Total synthesis of three natural products

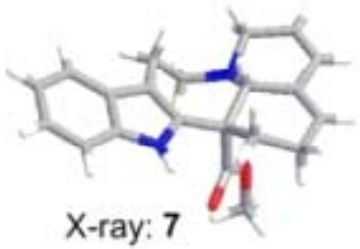


27 **33**



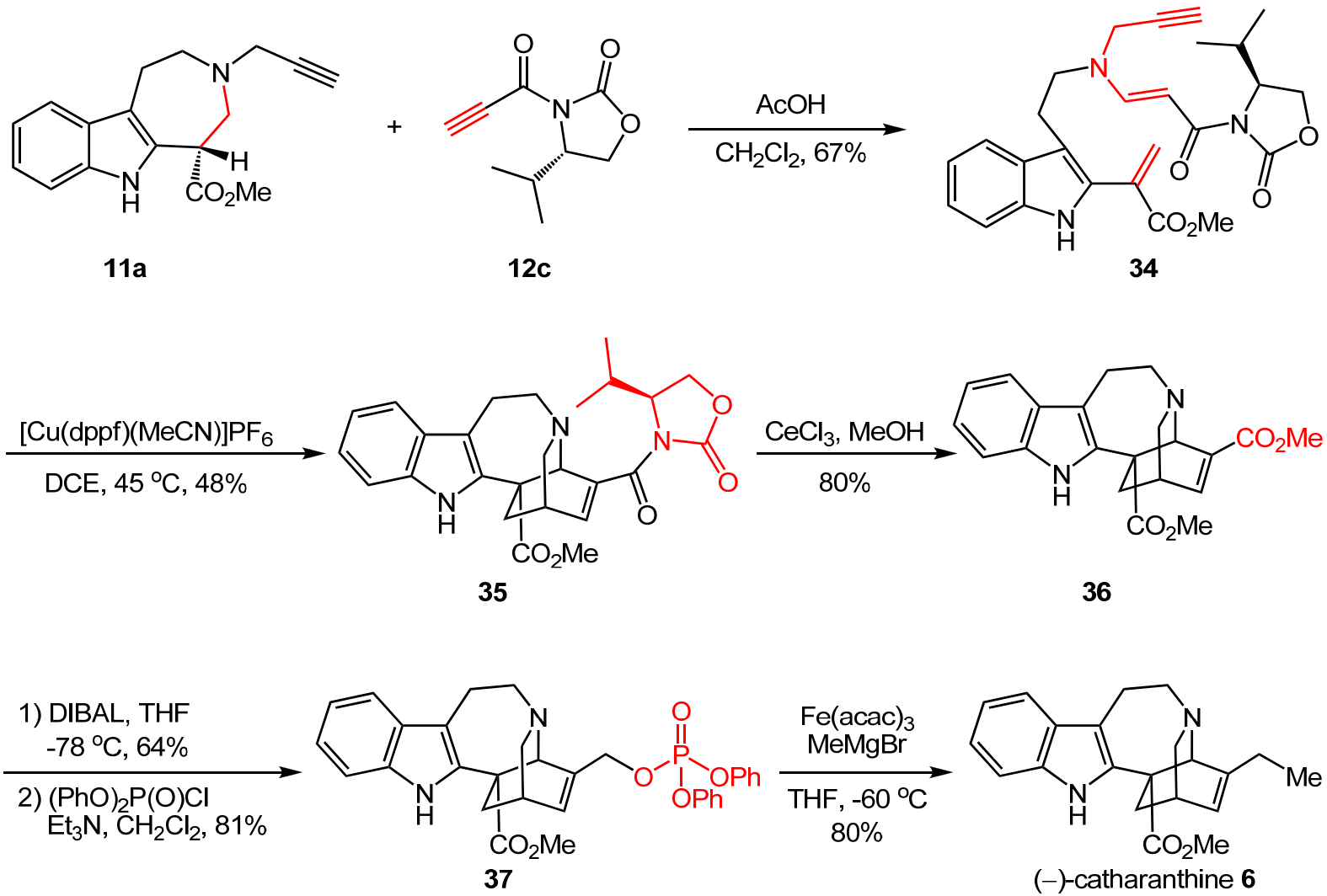
(±)-andranginine **7**

≡



X-ray: **7**

Total synthesis of three natural products



11a + **12c** → **34**

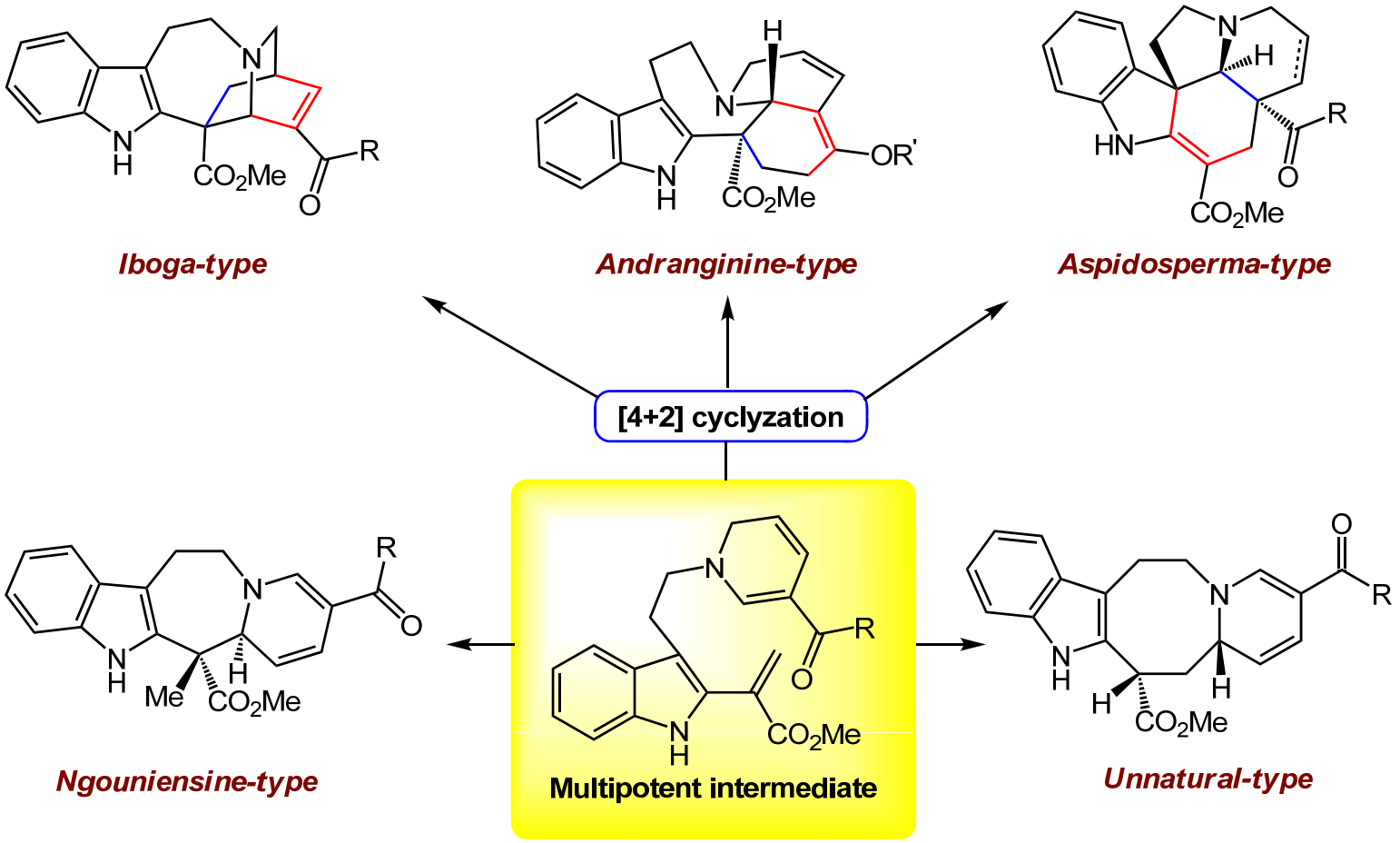
35

36

37

(–)-catharanthine **6**

Summary


Iboga-type
Andranginine-type
Aspidosperma-type
[4+2] cyclyzation
Ngouniensine-type
Multipotent intermediate
Unnatural-type

Natural products often bear a variety of functional groups on a rigid, architecturally complex and sp^3-rich skeleton, a configuration that allows specific molecular recognition through multipoint interactions to modulate the functions of target biomacromolecules. Chemical synthesis of natural products and their analogues could provide optimum screening collections for the development of drug candidates with higher hit rates and lower probabilities of side effects. Although some innovative synthetic approaches have been recently reported to provide efficient access to such molecules as specific modulators of challenging biological targets, a potentially general strategy for the development of divergent synthetic processes to produce assortments of skeletally diverse and densely functionalized scaffolds remains elusive and needs to be formulated.

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 precursors **14a**-**c** were flexibly synthesized through unions of tricycles (**11a**-**c**) and ethynylcarbonyl units (**12a**-**c**) followed by Cu(I)-catalysed formation of the DHP ring. By harnessing the versatile reactivity of **14**, multiple modes of annulation were systematically implemented. The divergent process allowed concise and programmable access to four naturally occurring scaffolds (**23**, **25b**, **27** and **28**) and a non-natural skeletal variant **29**, each within six to nine steps from tryptamine (**1**).

This synthetic campaign illustrates the concept of reactivity modulation of an achiral polyunsaturated intermediate in conjunction with modular assembly of building blocks and regio/stereo-controlled cyclizations, forming a foundation for the development of a divergent synthetic process generating a series of natural products and their structural variants with different skeletal, stereochemical and functional group properties. The synthetic strategies and tactics demonstrated herein could be applicable to the design of artificial assembly lines to furnish collections of natural product-inspired small molecules by emulating the biogenesis of other families of secondary metabolites.