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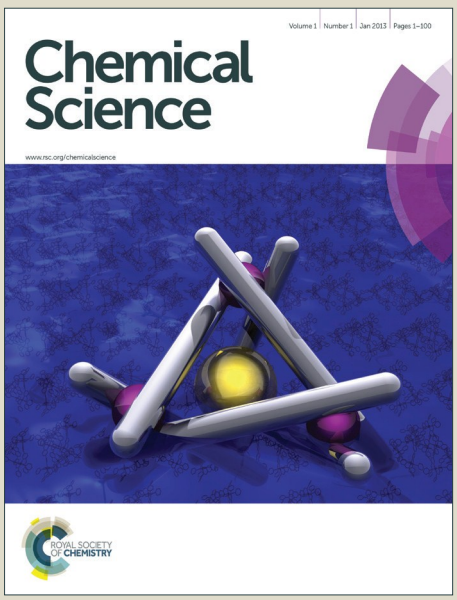

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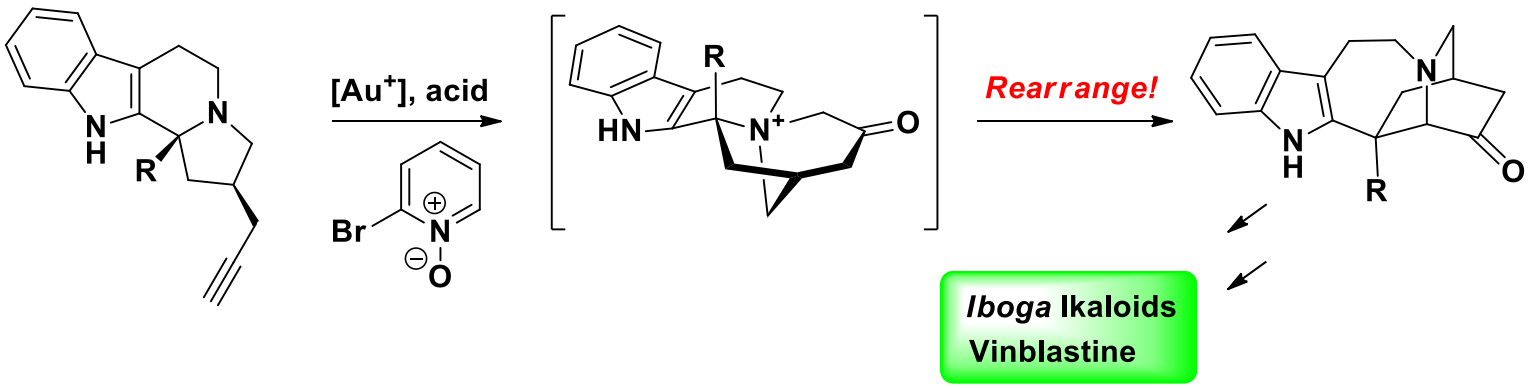
An efficient and unified strategy for the enantioselective syntheses of various *iboga* alkaloids and vinblastine has been developed. A gold-catalyzed oxidation of terminal alkyne followed by cyclization was optimized for the preparation of quaternary ammoniums, which underwent Stevens rearrangement to afford the desired framework. Our 10-step synthesis of vinblastine lead to the observation of an activity cliff using new vinblastine analogs.



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EDGE ARTICLE

Enantioselective Synthesis of *Iboga* Alkaloids and Vinblastine via Rearrangements of Quaternary Ammoniums†

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An efficient and novel strategy for the enantioselective syntheses of various *iboga* alkaloids has been developed. The salient features include a gold-catalyzed oxidation of terminal alkyne followed by cyclization, a Stevens rearrangement and a tandem sequence that combines the gold-catalyzed oxidation, cyclization and [1,2]-shift. The catharanthine analogs provided by our approach were further converted to the *vinca* alkaloid vinblastine and its analogs, which confirmed the remarkable sensitivity of the cytotoxicity to the C20' substituent of vinblastine.

Introduction

Total synthesis of complex natural product small molecules invites the examination of various methodologies in a complicated system, which at times reveals current limitations and inspires new advances.[1] Importantly, total synthesis could also provide valuable analogs to explore the structure-activity relationships of targeted chemotypes.[2] We have been interested in using rearrangement reactions that lead to dramatic change in molecular skeletons to develop novel and efficient synthetic routes towards various biologically active natural products.[3] Herein, we describe a concise and collective synthesis[4] of *iboga* alkaloids and vinblastine that further substantiates these concepts.

The *iboga* alkaloid family of natural products comprises over 60 members of monoterpene indoles that share a common pentacyclic skeleton of ibogamine (Fig. 1).[5] Among the various neurological activities of ibogamine (**1**) and ibogaine (**2**), the most exciting ones are their capability to attenuate the addiction to a number of drugs, while the molecular mechanism of action remains largely elusive.[6] Ibogaine, as the most abundant alkaloid in the root bark of the shrub *Tabernanhe iboga*, has even been studied in the clinical setting.[6] Interestingly, both enantiomers of ibogamine are not only active in reducing the self-administration of cocaine and morphine in rats but also devoid of tremorigenic activity—a side effect exhibited by ibogaine, which hence deserve further investigation.[7] Catharanthine (**3**) and its derivative dihydrocatharanthine (**4**) have recently been identified among the most potent TRPM8 antagonists and modulate the cold-induced pain signals as well as mammalian thermoregulation.[8] More importantly, the conversion of catharanthine to the potent anti-cancer drug vinblastine (**5**) via a one-pot procedure has boosted the value of this iboga alkaloid, and its derivatives have led to vinblastine analogs revealing insightful structure-activity relationships.[9]

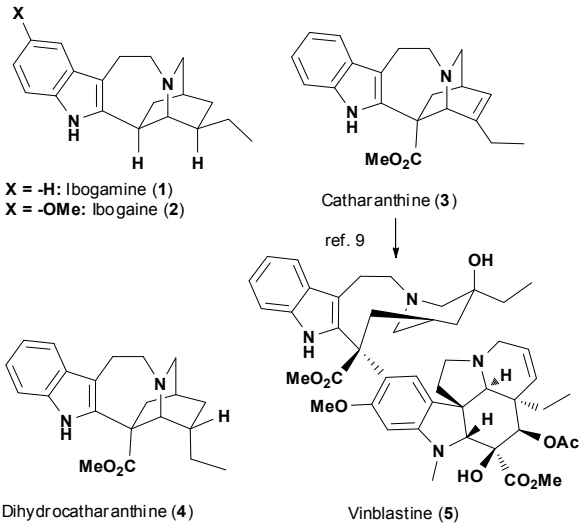

Fig. 1 Representative *iboga* alkaloids and vinblastine.

Despite a variety of synthetic approaches towards different *iboga* alkaloids that have been reported, the enantioselective total syntheses remain relatively sparse.[10-13] Since Trost's group published the elegant synthesis of enantioenriched ibogamine in 1978,[11] the preparation of chiral isoquinuclidine fragments followed by the construction of the C2-C16 bond in

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterisation data for all compounds are provided. CCDC 1433182, CCDC 1433188 and CCDC 1433180. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

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the late stage (catharanthine numbering, throughout) has become the focus of the asymmetric synthesis studies.[12] The only two exceptions are the efficient synthesis of (–)-ibogamine and (–)-catharanthine by White's group and Oguri's group respectively, both employing the asymmetric Diels-Alder reaction.[13] An alternative approach to prepare such a privileged skeleton, especially in an enantioselective manner, would be a valuable addition to current synthetic endeavours and more importantly, enable flexible structural changes of this chemotype.

Results and discussion

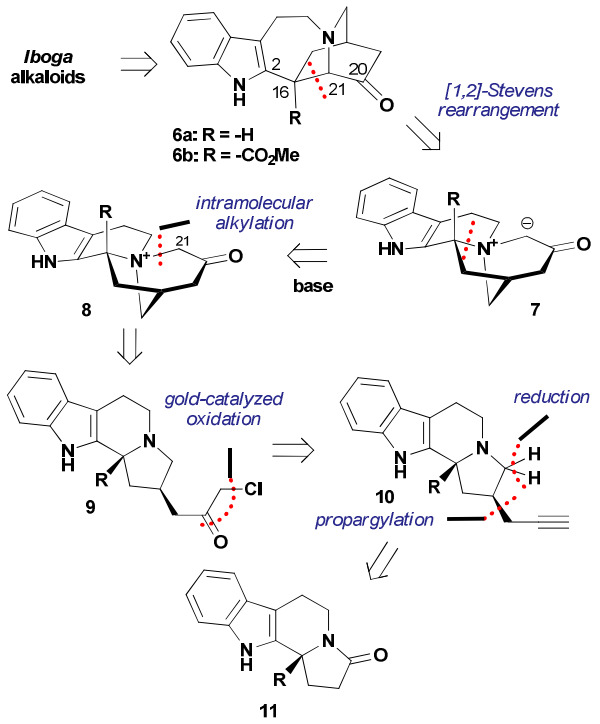
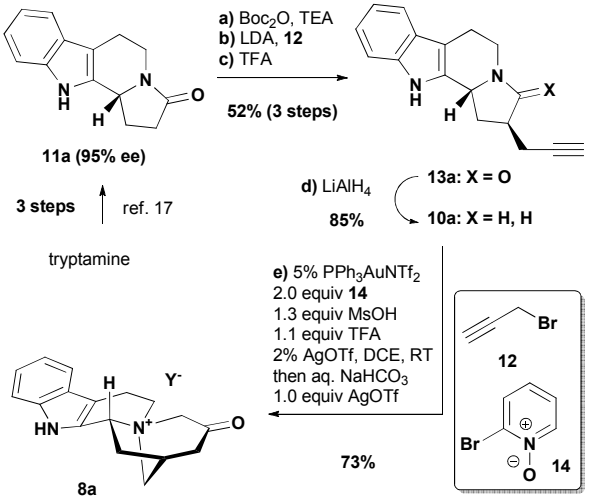


Fig. 2 Retrosynthetic analysis of *iboga* alkaloids based on the [1,2]-Stevens rearrangement reaction.

While seeking a unified strategy to access *iboga* alkaloids with and without the methoxycarbonyl group at C16, we envisioned two late-stage intermediates **6a** and **6b** (Fig. 2). The C20 carbonyl group of **6** could be a versatile handle for derivatization to the bioactive natural products as well as useful small-molecule probes. Inspired by the transannular cyclization accomplished by Kutney and co-workers,[10b] as well as recent advances in the fragmentation of C16-C21 bond,[14] we decided to explore the [1,2]-Stevens rearrangement of ammonium ylide **7** to construct the C16-C21 bond and give structurally compact **6**.[15] Given zwitterion **7** could be generated from quaternary ammonium **8** upon treatment with base due to the enhanced acidity at C21, **6** would therefore be accessible from **8** in one step. This key precursor **8** could be prepared by intramolecular alkylation of tertiary amine **9**, for which we hypothesized the recently developed gold-catalyzed conversion of terminal alkynes to α–chloromethyl ketones could find application.[16] Thus, tertiary amine **10** became the precursor for **9**, which could be traced back to the known amide **11** via propargylation and reduction.[17,18]



Scheme 1 Preparation of quaternary ammonium **8a**. Reagents and conditions: (a) Boc_2O (3.0 equiv), TEA (1.1 equiv), DMAP (0.2 equiv), DCM, RT, 14 h, 89%; (b) LDA (1.2 equiv), propargyl bromide **12** (2.5 equiv), −78 °C to RT, 2 h, THF; (c) TFA (5.0 equiv), DCM, RT, 16 h; 58% over two steps; (d) $LiAlH_4$ (3.0 equiv), THF, 80 °C, 1 h, 85%; (e) PPh_3AuNTf_2 (5 mol%), **14** (2.0 equiv), MsOH (1.3 equiv), TFA (1.1 equiv), AgOTf (2 mol%), DCE, RT, 6 h; then $NaHCO_3$ (sat.), AgOTf (1.0 equiv), RT, 73%.

We commenced our studies with chiral amide **11a**, which was prepared from tryptamine in 3 steps via an organocatalytic Pictet-Spengler reaction reported by Jacobsen's group (Scheme 1).[17] The introduction of the propargyl group was achieved with the protection of the nitrogen atom, and the following deprotection afforded a pair of readily separable diastereomers, whereas the desired **13a** was isolated as the major product in 52% yield over 3 steps. Subsequent reduction of **13a** by $LiAlH_4$ produced tertiary amine **10a** smoothly in 85% yield. We ultimately developed a one-pot procedure that converted **10a** to quaternary ammonium **8a** in good yield (see the Supporting Information for the determination of the counteranion).

The extensive optimization of this gold-catalyzed reaction followed by intramolecular alkylation was carried out using racemic **10a** (Table 1 and Table S1). The basicity of tertiary amine **10a** is detrimental to the cationic gold catalysis and needs to be neutralized with the addition of another equivalent of acid.[16b,19] Using 10 mol% $(Ph_3P)AuNTf_2$ catalyst and 2 equiv MsOH additive, we examined a variety of oxidants to identify 2-bromopyridine *N*-oxide **14** as the optimal one (Table S1). The formation of intermediate **15** was supported by LCMS analysis, which underwent facile cyclization upon the treatment of reaction mixture with the saturated aqueous solution of sodium bicarbonate. The end product **8a** was obtained in 47% yield with the recovery of 39% starting material **10a** (Table 1, entry 1). Inspired by the screening of acid additive to improve the conversion in similar transformations,[20] we discovered complete consumption of

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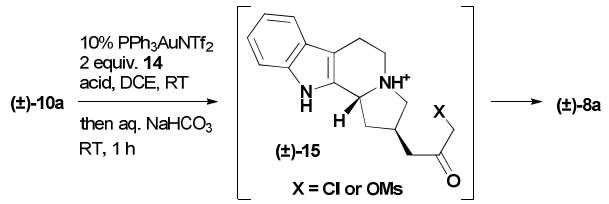
10a was achieved in 20 h at room temperature with 1.3 equiv MsOH and 1.1 equiv TFA as the acid additives to afford **8a** in 63% isolated yield (entry 2). The addition of 3 mol% AgOTf significantly accelerated the reaction,[21] which gave **8a** in 69% yield on an even larger scale (200 mg scale, entry 3). We intentionally lowered the gold catalyst loading to 5 mol% for the gram scale reaction and found the first step went to completion in 8 h at room temperature but **8a** was isolated in only 51% yield after workup (entry 4). The condition for the gram scale reaction was further improved by discovering the addition of 1 equiv AgOTf effectively promoted the cyclization step, which eventually afforded **8a** in 74% isolated yield (entry 5).

Table 1 Gold-Catalyzed Synthesis of **8a**: Selected Optimization[a]

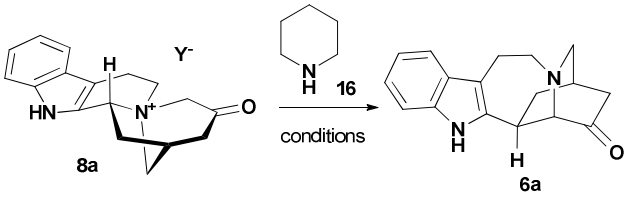


Entry	Acid	Time	Yield[b]
1	2.1 equiv MsOH	24 h	47%[c]
2	1.3 equiv MsOH, 1.1 equiv TFA	20 h	63%
3	1.3 equiv MsOH, 1.1 equiv TFA	6 h	69%[d]
4	1.3 equiv MsOH, 1.1 equiv TFA	8 h	51%[e]
5	1.3 equiv MsOH, 1.1 equiv TFA	8 h	74%[f]

[a] [**10a**] = 0.1 M (0.12 mmol). [b] Isolated yield after flash chromatography. [c] 39% starting material **10a** was recovered. [d] 200 mg scale reaction, 3% AgOTf was added as an additive. [e] 1 g scale reaction, 5% PPh_3AuNTf_2, 2% AgOTf as additive. [f] 3 g scale reaction, 5% PPh_3AuNTf_2, 2% AgOTf as additive, 1 equiv AgOTf was added with $NaHCO_3$ (s, aq.) to facilitate the cyclization.

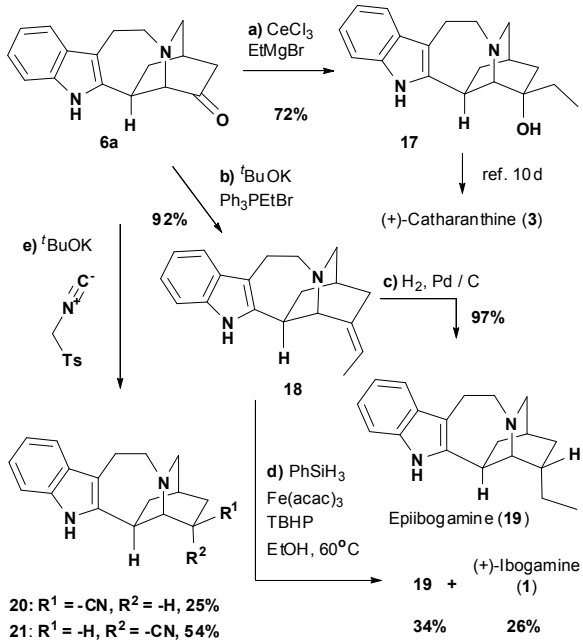
With abundant **8a** in hand, we proceeded to test the Stevens rearrangement. Initial efforts in base, solvent and temperature screening proved unfruitful, leading to either starting material recovery or decomposition (Table S2). Inspired by the development of organocatalytic sigmatropic reactions,[22] we shifted our focus to exploiting a novel Stevens rearrangement through the intermediacy of an enamine.[23] By examining a variety of amines (Table S3), we identified that 5 equiv of piperidine **16** could promote the desired transformation in methanol even if the isolated yield of **6a** was only 11% after heating at 170°C for 8 h in a sealed tube (Table 2, entry 1).[24] We therefore turned to microwave technology and found that it was more effective than conventional thermal conditions (entry 2).[25] Through a series of optimization including the amount of **16** (entry 3), solvent (entry 4), concentration and heating sequence (entry 5), the *iboga* alkaloid framework **6a** was eventually obtained from **8a** in 50~60% isolated yield (over 90% yield based on starting material recovery). Furthermore, when *N*-methylmorpholine was employed in place of piperidine **16** under the optimized reaction conditions, we did not observe the formation of **6a** and starting material **8a** was recovered in 88% yield, thus suggesting the formal Stevens rearrangement was not base mediated. To the best of our knowledge, this transformation represents the first example of Stevens rearrangement through secondary amine catalysis.

Table 2 Rearrangement of **8a** to **6a**: Selected Optimization



Entry	Conditions[a]	Conversion[b]	Yield[c]
1	5 equiv **16**, MeOH, 170 °C, 8 h[d]	46%	13%
2	5 equiv **16**, MeOH, 120 °C (mW), 12 h	N.D.	21%
3	0.4 equiv **16**, MeOH, 120 °C (mW), 8 h	N.D.	32%[e]
4	0.4 equiv **16**, HFIP, 150 °C (mW), 3 h	45%	47%[e,f]
5	0.4 equiv **16**, HFIP, 150 °C (mW), 3 h	58%	56%[e,f,g]

[a] [**8a**] = 0.1 M (0.075 mmol). [b] Conversion was calculated based on the recovery of **8a**. [c] Isolated yield after column chromatography. [d] The reaction was carried out in a sealed tube. [e] The reaction vial was pretreated by *N,O*-bis(trimethylsilyl)acetamide. [f] [**8a**] = 0.5 M (1 mmol). [g] The heating sequence was composed of 12 cycles with each cycle including irradiation to 150 °C for 15 min and 50 °C for 15 min.



Scheme 2 Formal synthesis of catharanthine (**3**) and total synthesis of ibogamine (**1**). Reagents and conditions: (a) $CeCl_3$ (2.5 equiv), EtMgBr (2.0 equiv), THF, 0.5 h, 72%; (b) ^tBuOK (3.0 equiv), Ph_3PEtBr (3.0 equiv), THF, 2 h, 92%; (c) H_2, Pd/C (2.0 equiv), MeOH, 2 h, 97%; (d) $PhSiH_3$ (2.5 equiv), $Fe(acac)_3$ (0.8 equiv), TBHP (1.5 equiv), EtOH, 60 °C, 6 h; **19**, 34%; **1**, 26%; (e) ^tBuOK (2.5 equiv), TosMIC (1.3 equiv), EtOH (1.7 equiv), DME, 12 h; **20**, 25%; **21**, 54%.

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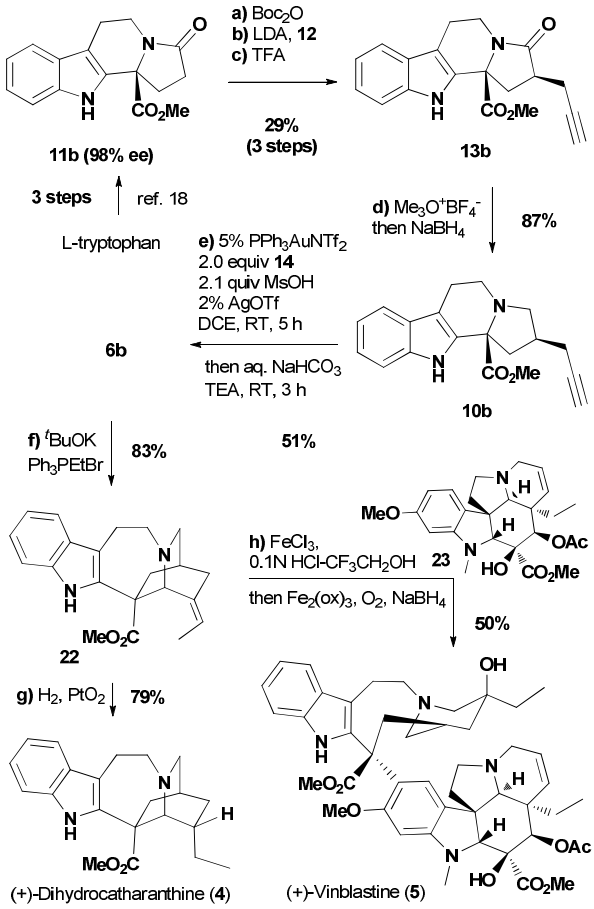

Scheme 3 Syntheses of dihydrocatharanthine (**4**) and vinblastine (**5**). Reagents and conditions: (a) Boc_2O (3.0 equiv), TEA (1.1 equiv), DMAP (0.2 equiv), DCM, RT, 14 h, 87%; (b) LDA (1.2 equiv), **12** (2.5 equiv), THF, 12 h; (c) TFA (5.0 equiv), DCM, 16h, 33% over two steps; (d) Trimethyloxonium tetrafluoroborate (2.5 equiv), 2,6-di-*tert*-butylpyridine (3.5 equiv), DCM, 12 h; then $NaBH_4$ (0.5 equiv), MeOH, 0.5 h, 87%; (e) PPh_3AuNTf_2 (5 mol%), **14** (2.0 equiv), MsOH (2.1 equiv), AgOTf (2 mol%), DCE, RT, 5 h; then $NaHCO_3$ (sat.), TEA (3.0 equiv), RT, 3 h, 51%; (f) ^{t}BuOK (3.0 equiv), Ph_3PEtBr (3.0 equiv), THF, 2 h, 83%; (g) H_2, PtO_2 (0.3 equiv), MeOH, 15 h, 79%; (h) vindoline **23** (1.2 equiv), HCl-CF_3CH_2OH, $FeCl_3$ (5.0 equiv), 2 h; $Fe_2(ox)_3$ (30 equiv), O_2; then $NaBH_4$ (20 equiv), 0 ^{o}C, 0.5 h, 50%.

The stage was set for the late-stage functional group manipulations of **6a** (Scheme 2). First, the addition of an organocerium reagent prepared from ethylmagnesium bromide to the ketone afforded **17** as a single diastereomer, effectively completing the formal synthesis of (+)-catharanthine (**3**).[10d,12c] The Wittig reaction was then employed to convert **6a** to olefin **18**, whereas the *Z* configuration of the trisubstituted olefin was assigned by the NOESY experiment (see Supporting Information for details). Hydrogenation of alkene **18** using activated Pd/C as the catalyst afforded epiibogamine **19** in 97% yield.[26] The high stereoselectivity could be attributed to the preferential addition of H_2 from the less hindered side of the molecule. Therefore we turned to the radical-based hydrogenation of electron-neutral alkenes initiated by hydrogen atom transfer.[27] While manganese and cobalt-based catalyst precursors also produced **19** as the predominant product (Table S4), we were delighted to find $Fe(acac)_3$, the precatalyst reported by Baran and co-workers for reductive alkene coupling,[28] afforded separable **19** and (+)-ibogamine **1** in 34% and 26% yield, respectively. The key intermediate **6a** could be expediently decorated to other interesting derivatives with *iboga* alkaloid skeleton. For instance, reductive cyanation of ketone **6a** with tosylmethylisocyanide produced a pair of separable diastereomers **20** and **21** in 25% and 54% yield, respectively.[29] The structures of racemic **19** and **20** were determined unambiguously by X-ray crystallography,[30] while the analytic data of **1** and **17** corresponded well with those in the literature.[12a,12c]

Encouraged by the completion of (+)-ibogamine (**1**), we moved towards the synthetic study of the *iboga* alkaloids with the methoxycarbonyl group at C16 (Scheme 3). Amide **13b** was prepared from known compound **11b** with excellent enantiopurity[18] following the same procedures depicted in Scheme 1, while the undesired diastereomeric amide could also be converted to **13b** readily (see Supporting Information for details). Selective reduction of amide carbonyl group in **13b** subsequently afforded tertiary amine **10b**.[31] We fortunately isolated a trace amount of the rearranged product **6b** after the work-up of the gold-catalyzed oxidation reaction of **10b**, indicating the [1,2]-shift was quite facile in the presence of the C16 methoxycarbonyl group. Therefore, the gold-catalyzed oxidation was followed by addition of the saturated aqueous solution of sodium bicarbonate and excess triethylamine to promote the cyclization and rearrangement. Gratifyingly, this one-pot procedure afforded ketone **6b** in 51% yield from **10b** under mild reaction conditions. The Wittig reaction of **6b** gave rise to **22**—a catharanthine isomer with an exocyclic versus endocyclic double bond. Hydrogenation of **22** afforded dihydrocatharanthine (**4**) in 79% yield. Interestingly, **22** differs with a known compound derived from catharanthine in the olefin geometry.[32] Eventually, employing the conditions reported by Boger and coworkers,[32a] we successfully made vinblastine (**5**) in 50% yield by coupling **22** with commercially available vindoline **23**.

It is noteworthy that chiral compound **6b**, which was prepared from L-tryptophan in 8 steps, would be a valuable synthetic intermediate towards vinblastine analogs. To illustrate this point, compounds **24** and **25**, vinblastine analogs differing only in the C20' substituent, were readily prepared by employing the Wittig reaction of **6b** followed by the biomimetic coupling (Fig. 3). We also prepared fluoroalkene **27** using reagent **26**,[33] whereas the *E* configuration of the olefin was assigned by the NOESY experiment (see Supporting Information for details). Interestingly, coupling of **27** with vindoline (**23**) afforded aldehyde **28** in 68% yield (see Fig. S1 for a proposed mechanism). The cytotoxicity of **24** and **25** were measured in HCT116 cell line using vinblastine (**5**) as a positive control. Our data indicated **24** was over 100-fold less active than vinblastine, and **25** was even less active than **24**. Based on a 40-step total synthesis, Fukuyama's group has reported inactive vinblastine analogs with C20' acetylene functionalities that differ significantly in size and shape with

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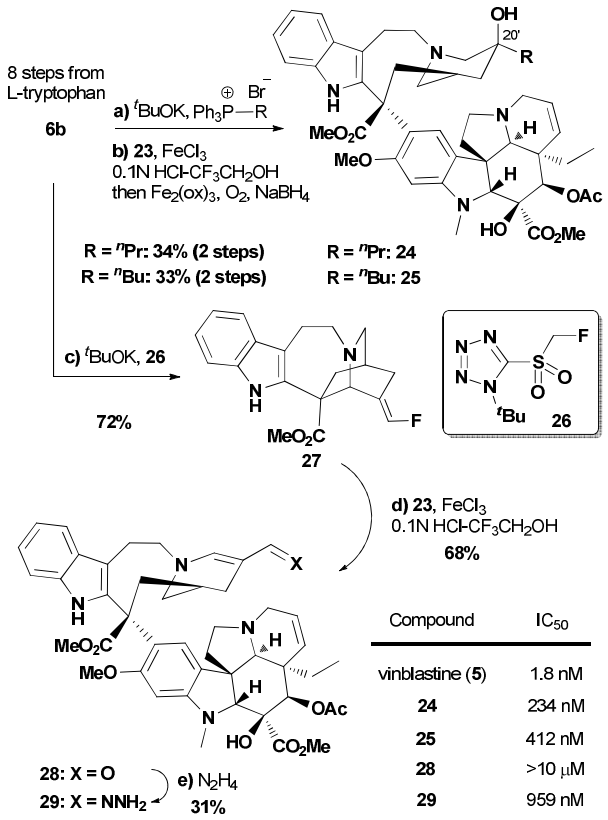
the ethyl group of the natural product.[34] Herein we showed that even a subtle change—with the C20' alkyl substituent length extended for one (**24**) or two more carbons (**25**)—was enough to dramatically decrease the potency. This could be rationalized by the X-ray crystallographic analysis of the vinblastine-tubulin interactions, in which the C20' ethyl substituent of vinblastine is embedded in a hydrophobic binding site.[35] Interestingly, the aldehyde analog of vinblastine, compound **28**, almost lost the ability to inhibit the growth of HCT116 cells. However, compound **29**, obtained by condensation of **28** with hydrazine, showed decent cytotoxicity (IC_{50} = 959 nM). This observation implied the necessity of a hydrogen bond donor around the C20' position,[36] while further investigation is needed to provide more insight into the hydrazone analog.



Compound	IC_{50}
vinblastine (**5**)	1.8 nM
24	234 nM
25	412 nM
28	>10 μM
29	959 nM

Fig. 3 Synthesis of vinblastine analogs and their cell growth inhibitory activity.

Conclusions

In summary, we have accomplished a unique and general route for the enantioselective synthesis of *iboga* alkaloids by developing a Stevens rearrangement through secondary amine catalysis and an oxidation/cyclization/rearrangement tandem sequence. The precise mechanism of the rearrangement remains to be investigated to identify whether a radical or an ionic intermediate is involved. Nonetheless, both reactions have the potential to be applied in the synthesis of a myriad of complex alkaloids. This study nicely exemplifies the total synthesis of complex natural products serves as not only a driving force for advancing the synthetic methodology but also an important source for providing analogs. Furthermore, this practical approach to modify *iboga* alkaloids and vinblastine paves the way for studies into their pronounced pharmacological properties using state-of-the-art chemical biology technologies, which are underway in our group and will be reported in due course.

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Notes and references

1 R. W. Hoffmann, *Angew. Chem., Int. Ed.*, 2013, **52**, 123-130.
2 P. A. Wender and B. L. Miller, *Nature*, 2009, **460**, 197-201.
3 (a) W. Ren, Y. Bian, Z. Zhang, H. Shang, P. Zhang, Y. Chen, Z. Yang, T. Luo and Y. Tang, *Angew. Chem., Int. Ed.*, 2012, **51**, 6984-6988; (b) J. Fu, Y. Gu, H. Yuan, T. Luo, S. Liu, Y. Lan, J. Gong and Z. Yang, *Nat. Commun.*, 2015, **6**, doi: 10.1038/ncomms9617; Rearrangement reactions have been used extensively in the organic synthesis of natural products. For some recent examples, see: (c) C. L. Martin, L. E. Overman and J. M. Rohde, *J. Am. Chem. Soc.*, 2010, **132**, 4894-4906; (d) L. Jørgensen, S. J. McKerrall, C. A. Kuttruff, F. Ungeheuer, J. Felding and P. S. Baran, *Science*, 2013, **341**, 878-882; (e) C. W. Plummer, C. S. Wei, C. E. Yozwiak, A. Soheili, S. O. Smithback and J. L. Leighton, *J. Am. Chem. Soc.*, 2014, **136**, 9878-9881; (f) C. P. Ting and T. J. Maimone, *J. Am. Chem. Soc.*, 2015, **137**, 10516-10519.
4 S. B. Jones, B. Simmons, A. Mastracchio and D. W. C. MacMillan, *Nature* 2011, **475**, 183-188.
5 K. R. Alper, *Alkaloids Chem. Biol.*, 2001, **56**, 1-38.
6 (a) P. Popik, R. T. Layer and P. Skolnick, *Pharmacol. Rev.*, 1995, **47**, 235-253. (b) C. Jenks, *Nat. Prod. Lett.*, 2002, **16**, 71-76.
7 S. D. Glick, M. E. Kuehne, J. Raucci, T. E. Wilson, D. Larson, R. W. Jr. Keller and J. N. Carlson, *Brain Res.*, 1994, **657**, 14-22.
8 Y. Terada, M. Kitajima, F. Taguchi, H. Takayama, S. Horie and T. Watanabe, *J. Nat. Prod.*, 2014, **77**, 1831-1838.
9 (a) H. Ishikawa, D. A. Colby and D. L. Boger, *J. Am. Chem. Soc.*, 2008, **130**, 420-421; (b) For a recent review, see: J. E. Sears and D. L. Boger, *Acc. Chem. Res.*, 2015, **48**, 653-662.
10 For a recent review, see: (a) G. K. Jana, S. Paul and S. Sinha, *Org. Prep. Proced. Int.*, 2011, **43**, 541–573 (b) J. P. Kutney, R. T. Brown and E. Piers, *J. Am. Chem. Soc.*, 1964, **86**, 2287-2288; (c) G. Buchi, D. L. Coffen, K. Kocsis, P. E. Sonnet and F. E. Ziegler, *J. Am. Chem. Soc.*, 1965, **87**, 2073-2075; (d) G. Büchi, P. Kulsa, K. Ogasawara and R. L. Rosati, *J. Am. Chem. Soc.*, 1970, **92**, 999-1005; (e) J. W. Huffman, G. Shanmagusundaram, R. Sawdaye, P. C. Raveendranath and R. C. Desai, *J. Org. Chem.*, 1985, **50**, 1460-1464; (f) M. E. Kuehne and P. J. Reider, *J. Org. Chem.*, 1985, **50**, 1464-1467; (g) W. Nagata, H. Hirai, T.

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Okumura and K. Kawata, *J. Am. Chem. Soc.*, 1968, **90**, 1650-1651; (h) S. Hiari, K. Kawata and W. Nagata, *Chem. Commun.*, 1968, 1016-1017; (i) T. Imanishi, N. Yagi, H. Shin and M. Hanaoka, *Tetrahedron Lett.*, 1981, **22**, 4001-4004; (j) T. Imanishi and N. Yagi, M. Hanaoka, *Chem. Pharm. Bull.*, 1985, **33**, 4202-4211; (k) G. R. Krow, D. A. Shaw, B. Lynch, W. Lester, S. W. Szczepanski, K. Raghavachari and A. E. Derome, *J. Org. Chem.*, 1988, **53**, 2258-2262; (l) C. Herdeis and C. Hartke-Karger, *Liebigs Ann. Chem.*, 1991, 99-104; (m) P. Rosenmund, W. H. Haase, J. Bauer and R. Frische, *Chem. Ber.*, 1975, **108**, 1871-1895; (n) S. I. Sallay, *J. Am. Chem. Soc.*, 1967, **89**, 6762-6763; (o) M. Ikezaki, T. Wakamastu and Y. Ban, *J. Chem. Soc. D*, 1969, 88-89; (p) K. J. Henrey, P. A. Grieco, Jr. and W. J. DuBay, *Tetrahedron Lett.*, 1996, **37**, 8289-8292; (q) W. G. Bornmann and M. E. Kuhene, *J. Org. Chem.*, 1992, **57**, 1752-1760; (r) A. C. Kruegel, S. Rakshit, X. Li and D. Sames, *J. Org. Chem.*, 2015, **80**, 2062-2071.

11 B. M. Trost, S. A. Godleski and J. P. Genêt, *J. Am. Chem. Soc.*, 1978, **100**, 3930-3931.

12 (a) D. M. Hodgson and J.-M. Galano, *Org. Lett.*, 2005, **7**, 2221-2224; (b) S. Höck and H.-J. Borschberg, *Helv. Chim. Acta.*, 2006, **89**, 542-557; (c) L. Moisan, P. Thuéry, M. Nicolas, E. Doris and B. Rousseau, *Angew. Chem., Int. Ed.*, 2006, **45**, 5334-5336; (d) M. Harada, K. N. Asaba, M. Iwai, N. Kogure, M. Kitajima and H. Takayama, *Org. Lett.*, 2012, **14**, 5800-5803; (e) K. Ishihara, H. Yamada and M. Akakura, *Chem. Commun.*, 2014, **50**, 6357-6360; (f) M. Hatano, Y. Goto, A. Izumiseki, M. Akakura and K. Ishihara, *J. Am. Chem. Soc.*, 2015, **137**, 13472-13475.

13 (a) J. D. White and Y. Choi, *Org. Lett.*, 2000, **2**, 2373-2376; (b) H. Mizoguchi, H. Oikawa and H. Oguri, *Nat. Chem.*, 2014, **6**, 57-64.

14 J. W. Beatty and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2014, **136**, 10270-10273 and references cited therein.

15 (a) T. S. Stevens, E. M. Creighton, A. B. Gordon and M. MacNicol, *J. Chem. Soc.*, 1928, 3193-3197; (b) I. E. Markó in *Comprehensive Organic Synthesis*, *Vol.* 3 (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, 1991, pp. 913-974; (c) M. G. Charest, C. D. Lerner, J. D. Brubaker, D. R. Siegel and A. G. Myers, *Science*, 2005, **308**, 395-398; (d) J. A. Vanecko, H. Wan and F. G. West, *Tetrahedron*, 2006, **62**, 1043-1062; (e) P. Tuzina and P. Somfai, *Org. Lett.*, 2009, **11**, 919-921; (f) T. M. Bott, J. A. Vanecko and F. G. West, *J. Org. Chem.*, 2009, **74**, 2832-2836; (g) M. Valpuesta, M. Ariza, A. Díaz and R. Suau, *Eur. J. Org. Chem.*, 2010, 4393-4401; (h) L. Palombi, *Catal. Commun*., 2011, **12**, 485-488; (i) J. Clayden, M. Donnard, J. Lefranc. and D. J. Tetlow, *Chem. Commun.*, 2011, **47**, 4624-4639; (j) S. Harada, M. Kono, T. Nozaki, Y. Menjo, T. Nemoto and Y. Hamada, *J. Org. Chem*., 2015, **80**, 10317-10333.

16 (a) W. He, L. Xie, Y. Xu, J. Xiang and L. Zhang, *Org. Biomol. Chem.*, 2012, **10**, 3168-3171; (b) E. L. Noey, Y. Luo, L. Zhang and K. N. Houk, *J. Am. Chem. Soc.*, 2012, **134**, 1078-1084.

17 I. T. Raheem, P. S. Thiara, E. A. Peterson and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2007, **129**, 13404-13405.

18 (a) P. Magnus, M. Ladlow, C. S. Kim and P. Boniface, *Heterocycles*, 1989, **28**, 951-956; (b) P. Magnus, J. S. Mendoza, A. Stamford, M. Ladlow and P. Willis, *J. Am. Chem. Soc.*, 1992, **114**, 10232-10245.

19 (a) P. de Frémont, N. Marion and S. P. Nolan, *J. Organomet. Chem.*, 2009, **694**, 551-560; (b) R. L. Lalonde, W. E. Brenzovich, D. Benitez, E. Tkatchouk, K. Kelley, W. A. Goddard and F. D. Toste, *Chem. Sci.*, 2010, **1**, 226-233.

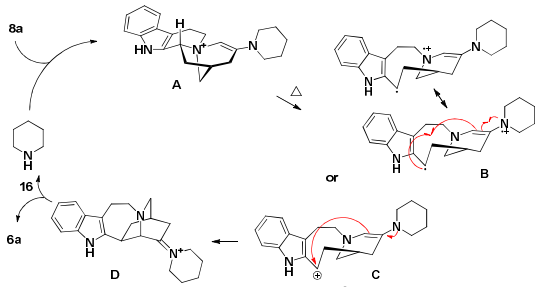
20 (a) L. Ye, L. Cui, G. Zhang and L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 3258-3259; (b) E. P. A. Talbot, M. Richardson, J. M. McKenna and F. D. Toste, *Adv. Synth. Catal.* 2014, **356**, 687-691.

21 J. Han, N. Shimizu, Z. Lu, H. Amii, G. B. Hammond and B. Xu, *Org. Lett.*, 2014, **16**, 3500-3503.

22 (a) G. Valero and A. Moyano, In *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*, (Eds.: P. I. Dalko), Wiley-VCH Verlag GmbH & Co. KGaA, 2013, pp. 1191-1224; (b) A. McNally, B. Evans and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2006, **45**, 2116-2119.

23 (a) H. G. Lindwall and J. S. Maclennan, *J. Am. Chem. Soc.*, 1932, **54**, 4739-4744; (b) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471-5569 and references cited therein; (c) D. W. C. MacMillan, *Nature*, 2008, **455**, 304-308 and references cited therein.

24 A proposed mechanism for **16**-catalyzed formation of **6a**:



When **8a** and **16** were heated at 80 °C in HFIP, the formation of enamine intermediate **A** was supported by LCMS analysis.

25 For a recent review, see: G. B. Dudley, R. Richert and A. E. Stiegman, *Chem. Sci.*, 2015, **6**, 2144-2152.

26 The synthesis of racemic epiibogamine has been reported. See: (a) G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet and F. E. Ziegler, *J. Am. Chem. Soc.*, 1966, **88**, 3099-3109; (b) G. K. Jana and S. Sinha, *Tetrahedron Lett.*, 2012, **53**, 1671-1674.

27 (a) K. Iwasaki, K. K. Wan, A. Oppedisano, S. W. M. Crossley and R. A. Shenvi, *J. Am. Chem. Soc.*, 2014, **136**, 1300-1303; b) S. M. King, X. Ma and S. B. Herzon, *J. Am. Chem. Soc.*, 2014, **136**, 6884-6887.

28 (a) J. C. Lo, Y. Yabe and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 1304-1307; (b) J. C. Lo, J. Gui, Y. Yabe, C.-M. Pan and P. S. Baran, *Nature*, 2014, **516**, 343-348.

29 O. H. Oldenziel, D. Van Leusen and A. M. Van Leusen, *J Org Chem*, 1977, **42**, 3114-3118.

30 CCDC-1433182 (**19**), CCDC-1433188 (**20**) and CCDC-1433180 (**S4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

31 M. Ito, C. W. Clark, M. Mortimore, J. B. Goh and S. F. Martin, *J. Am. Chem. Soc.*, 2001, **123**, 8003-8010.

32 a) H. Ishikawa, D. A. Colby, S. Seto, P. Va, A. Tam, H. Kakei, T. J. Rayl, I. Hwang and D. L. Boger, *J. Am. Chem. Soc.*, 2009, **131**, 4904-4916. b) E. Giovanelli, S. Leroux, L. Moisan, H. Carreyre, P. Thuéry, D.-A. Buisson, A. Meddour, J.-M. Coustard, S. Thibaudeau, B. Rousseau, M. Nicolas, P. Hellier and E. Doris, *Org. Lett.*, 2011, **13**, 4116-4119.

33 L. Zhu, C. Ni, Y. Zhao and J. Hu, *Tetrahedron*, 2010, **66**, 5089-5100.

34 T. Miyazaki, S. Yokoshima, S. Simizu, H. Osada, H. Tokuyama and T. Fukuyama, *Org. Lett.*, 2007, **9**, 4737-4740.

35 (a) B. Gigant, C. Wang, R. B. G. Ravelli, F. Roussi, M. O. Steinmetz, P. A. Curmi, A. Sobel and M. Knossow, *Nature*, 2005, **435**, 519-522; (b) Y. Wang, F. W. Benz, Y. Wu, Q. Wang, Y. Chen, X. Chen, H. Li, Y. Zhang, R. Zhang and J. Yang, *Mol. Pharmacol.* 2016, **89**, 233-242.

36 E. K. Leggans, K. K. Duncan, T. J. Barker, K. D. Schleicher and D. L. Boger, *J. Med. Chem.* 2013, **56**, 628-639.