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Studies towards the Total Synthesis of Iboga Alkaloids

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Studies towards the Total Synthesis of Iboga Alkaloids

By

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DISSERTATION

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Abstract

The Iboga alkaloid family of natural products has drawn a lot of attention due to their potential effectiveness for treating substance use disorder. However, their adverse effects including ataxia, nausea, cardiotoxicity, and hallucinations limit their therapeutic potential. Generating non-hallucinogenic analogs of this promising scaffold with increased safety profiles would significantly help combat drug addiction and contribute positively to the current opioid epidemic in America. Current syntheses of ibogaine, which is a member of the family, involve long linear sequences with hash conditions. We are developing a short, modular, and robust synthesis of ibogaine that allows for the rapid generation of structurally diverse analogs. Routes involving key intra- and intermolecular Diels-Alder reactions have both been explored to build the unique isoquinuclidine scaffold of iboga family alkaloids.

Acknowledgments

Time flies, it's hard to believe I have reached to the end of my PhD program. Looking back the past few years, it's more like a dream coming true and there are so many unforgettable moments and many people come to my mind.

I want to thank my advisor, Prof. Olson. I still remember the first time we met in his office when he just started his independent research career in the summer of 2015. His broad knowledge in organic chemistry and psychedelics research was so impressive that I totally believe his research will eventually change the world. It turned out joining his lab is one of the best choices I have made in my life. He is indeed a role model to me, always the first one to come to work and the last one to go home, I could find him working in his office even on weekends, he is also available whenever I need advice. During the time working under his mentorship with countless insightful discussions, I have learned so much, not only about synthetic chemistry, but also the whole process of critical thinking, analyzing and troubleshooting, which has prepared me for my future career. I am very lucky to have the opportunity to work with him.

Thank Jeffrey Walton and Debbie Decker for offering the NMR TA position and department safety TA position. In addition to help me survive graduate school financially, they also teach me a lot regarding NMR instrument and working place safety, which is significantly important for me as a synthetic chemist. I hope they could enjoy their retired life to the fullest.

I also want to thank all my great lab mates. Graduate school is stressful, and life is full of uncertainties, but one thing I'm certain is I wouldn't survive without their support, especially the generous help from Calvin Ly, Lee Dunlap, RJ Tombari and David Favela. As an international student who speaks broken English and knows almost nothing about the culture, they open their arms, spend time hanging out with me, explain anything that I don't understand patiently, making me feel at home all the time. They are more like family to me even I come from a different continent.

There are a lot of thanks to my parents as well. Although my father passed away nine years ago, I still think of him very often. I remembered him telling me to think hard and work hard, telling me to be a better person, which I won't forget for the rest of my life. My mother cares about me so much that during my entire time in graduate school, whenever I talk to her on the phone, she always asks me to go to bed

early for more rest, always tells me she is OK so I won't worry about her. I couldn't thank my parents enough for their selfless love, only hope I could spend more time with my mother in the future.

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Chapter 1. Introduction of Iboga Alkaloids

Chapter 1.1 Nature of origin, biosynthesis

Ibogaine was first isolated in 1901,[1] and its structure was deduced by Bartlett, Dickel, and Taylor in 1958.[2] In 1960, its absolute stereochemistry was unambiguously assigned by X-ray crystallography.[3] The defining features of the iboga architecture include an indole, a 7-membered tetrahydroazepine, and a bicyclic isoquinuclidine (**Figure 1.1**). Since ibogaine's initial discovery, hundreds of alkaloids bearing structural and/or biosynthetic similarities to ibogaine have been identified. The chemical structures of some of the more common iboga alkaloids are highlighted in Figure 1 with the Le Men and Taylor numbering convention indicated.[4] While this review will primarily focus on monomeric iboga alkaloids, dimeric structures containing at least one iboga component are also common and include the notable chemotherapeutics vincristine and vinblastine (**Figure 1.1**). For information on the chemistry and/or biology of this class of bisindole alkaloids, we point the reader to a recent review.[5]

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1. Dybowski J, Landrin E. Concerning Iboga, its excitement-producing properties, its composition, and the new alkaloid it contains, ibogaine. CR Acad. Sci. 1901; 133:748.
2. Bartlett MF, Dickel DF, Taylor WI. The alkaloids of Tabernanthe iboga. Part IV. 1 The structures of ibogamine, ibogaine, tabernanthine and voacangine. J. Am. Chem. Soc., 1958, 80, 126–136.
3. Arai, G., Coppola, J., and Jeffrey, G. The Structure of Ibogaine. Acta Crystallogr., 1960, 13, 553–564.
4. Men, J. L.; Taylor, W. I. Experientia, 1965, 21, 508–510.
5. Martino, E.; Casamassima, G.; Castiglione, S.; Cellupica, E.; Pantalone, S.; Papagni, F.; Rui, M.; Siciliano, A. M.; Collina, S. Bioorganic & Medicinal Chemistry Letters, 2018, 28, 2816–2826.

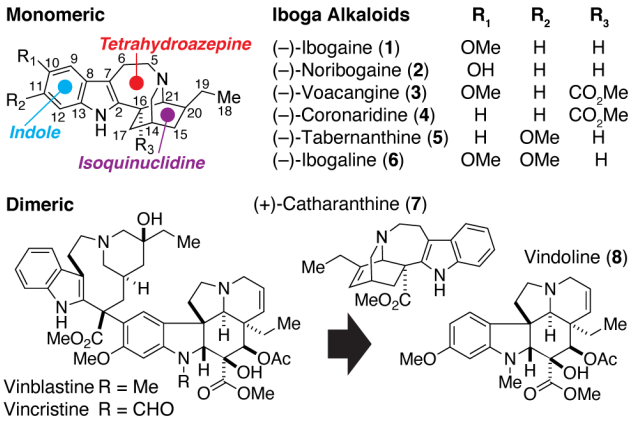


Figure 1.1. Structures of iboga alkaloids and related compounds.

The unique structures of iboga alkaloids have captured the imagination of chemists for decades, while their unusual effects on the brain have challenged conventional ideas about treating substance use disorder. Though substantial progress has been made concerning the chemistry and neuropharmacology of these alkaloids, many unresolved problems and unanswered questions remain. Ibogaine—the prototypical iboga alkaloid with the most neurobiological data—still lacks a truly robust, scalable, enantioselective total synthesis. Moreover, its biological mechanism of action is completely opaque, pushing the limits of what traditional neuropharmacology is capable of explaining. Here, we summarize the history of iboga alkaloid isolation, biosynthesis, total synthesis, analog development, and neuropharmacology with particular emphasis placed on advances made in the past decade.

Chapter 1.1.2. Isolation

Monoterpenoid indole alkaloids (MIA) of the iboga-type are found in a variety of plant species around the world, though historically, isolation of iboga alkaloids has generally been restricted to regions of West Africa.[6] There are hundreds of iboga alkaloids, but the compounds shown in **Figure 1.1** represent some of the most commonly reported in natural product isolation and total synthesis literature. Of these alkaloids, ibogaine has attracted significant attention due to its therapeutic potential (vide infra). However,

6. Pope, H. G. Tabernanthe Iboga: an African Narcotic Plant of Social Importance. Economic Botany, 1969, 23, 174–184.

the isolation of ibogaine from natural sources has been plagued by ethical and environmental challenges,[7] as it only accounts for approximately 0.3% of the root bark weight in *Tabernanthe iboga* (**Table 1.1**). In contrast, significantly larger amounts of voacangine can be extracted from the root bark of *Voacanga africana* (~1.7% of the root bark). As a result, ibogaine is often produced via semi-synthesis starting from voacangine.[10] Conversion of voacangine to ibogaine generally requires a two-step protocol involving saponification of the C16 methyl ester followed by acidification and heating to induce decarboxylation.[7,8] In addition to ibogaine, Table 1 details several other common iboga alkaloids found in the *Tabernanthe* and *Voacanga* genera. Interestingly, catharanthine belongs to the opposite optical series compared to other reported iboga alkaloids and is exclusively found in the *Catharanthus roseus* plant species. The isolated compounds in Table 1 have sparked interest in more recent efforts to determine the alkaloid profiles of plants in the broader Apocynaceae family.

7. Krengel, F.; Mijangos, M. V.; Reyes-Lezama, M.; Reyes-Chilpa, R. Extraction and Conversion Studies of the Antiaddictive Alkaloids Coronaridine, Ibogamine, Voacangine, and Ibogaine from Two Mexican Tabernaemontana Species (Apocynaceae). Chemistry Biodivers., 2019, 16, e1900175.
8. M. Janot, R. Goutarel, US Pat. 2813873A, 1957.

Plant Species	Ibogaine	Ibogamine	Voacangine	Coronaridine	Catharanthine
T. iboga[9,10,11,12]	0.27-0.32	0.097-0.40	0.043-0.28	NR	NR
V. africana[13]	0.25	TR	1.67	TR	NR
T. arborea[13,12]	0.27	0.036	0.96	0.073	NR
C. roseus[14]	NR	NR	NR	NR	0.003-0.099
T. amygdalifolia[12]	0.047	0.76-0.96	0.19-0.22	1.092-1.38	NR

Table 1.1. Approximate yields of iboga alkaloids isolated from the whole root bark of various sources. Percentages indicate the weight of the alkaloid free base relative to the weight of the plant source. TR = trace (< 0.01%). NR = Not Reported.

9. Bouso, J. C.; Fornís, I.; Vilamala, M. V.; Loenen, B. D.; Sainz-Cort, A.; Jiménez-Garrido, D. F.; Santos, R. G. D.; Hallak, J. E. C.; Alcázar-Córcoles, M. Á.; Jenks, C. W. An Analytical Study of Iboga Alkaloids Contained in Tabernanthe Iboga-Derived Products Offered by Ibogaine Treatment Providers. Arch. Clin. Psychiatry, 2020, 47, 51–54.

10. Jenks, CW.; Extraction studies of Tabernanthe iboga and Voacanga africana. Nat Prod Lett., 2002, 16, 71–76.

11. Dickel, D.; Holden, C.; Maxfield, R.; Paszek, L.; Taylor, W. The Alkaloids of Tabernanthe iboga. Part III.1 Isolation Studies. *J. Am. Chem. Soc.,* **1958**, *80*, 123–125.

12. Krengel, F.; Chevalier, Q.; Dickinson, J.; Herrera-Santoyo, J.; Reyes-Chilpa, R. Metabolite Profiling of Anti-Addictive Alkaloids from Four Mexican Tabernaemontana Species and the Entheogenic African Shrub Tabernanthe iboga (Apocynaceae). Chem. Biodiversity., 2019, 16, e1800506.

13. Krengel, F.; Dickinson, J.; Reyes-Chilpa, R. Quantitative Evaluation of a Mexican and a Ghanaian Tabernaemontana Species as Alternatives to Voacanga africana for the Production of Antiaddictive Ibogan Type Alkaloids. Chem. Biodiversity, 2020, 17, e2000002.

14. Ferreres, F.; Pereira, D. M.; Valentão, P.; Oliveira, J. M.; Faria, J.; Gaspar, L.; Sottomayor, M.; Andrade, P. B. Simple and Reproducible HPLC–DAD–ESI-MS/MS Analysis of Alkaloids in Catharanthus Roseus Roots. J. Pharm. Biomed. Anal., 2010, 51, 65–69.

Chapter 1.1.3 Newly isolated iboga alkaloids (2010–2019)

Prior to 2010, iboga alkaloids were primarily isolated from plant species found in western parts of Africa.[6] However, recent reports have noted the discovery of these alkaloids in plants from other regions of the world including Mexico, China, and Malaysia (**Figure 1.2**). Belonging to the Apocynaceae family, the *Ervatamia* genus (also called *Tabernaemontana*) has been found to produce a wide array of interesting iboga-type alkaloids with unique oxidation patterns and complex polycyclic frameworks. In 2014, Ye and co-workers isolated seven new iboga alkaloids from the *Ervatamia officinalis* plant species along with ten previously known compounds including ibogaine, voacangine, and ibogaline.[15] Primarily found in the Guangdong and Hainan Provinces of China, *Ervatamia officinali*s is rich in MIAs.[16] Isolated ervaoffines A and B (**9** and **10**) were characterized using X-ray diffraction and electronic circular dichroism (ECD), and they represent the first iboga-type pseudoindoxyl alkaloids with a C2 spiro carbon configuration opposite that of known members of this class, such as iboluteine (**177**).

15. Tang, B. Q.; Wang, W. J.; Huang, X. J.; Li, G. Q.; Wang, L.; Jiang, R. W.; Yang, T. T.; Shi, L.; Zhang, X. Q.; Ye, W. C. Iboga-Type Alkaloids from Ervatamia officinalis. J. Nat. Prod., 2014, 77, 1839–1846.
16. Pelletier, S. W. Alkaloids: Chemical and Biological Perspectives; John Wiley & Sons: New York, 1988; Vol. 6, Chapter 2, pp 7680

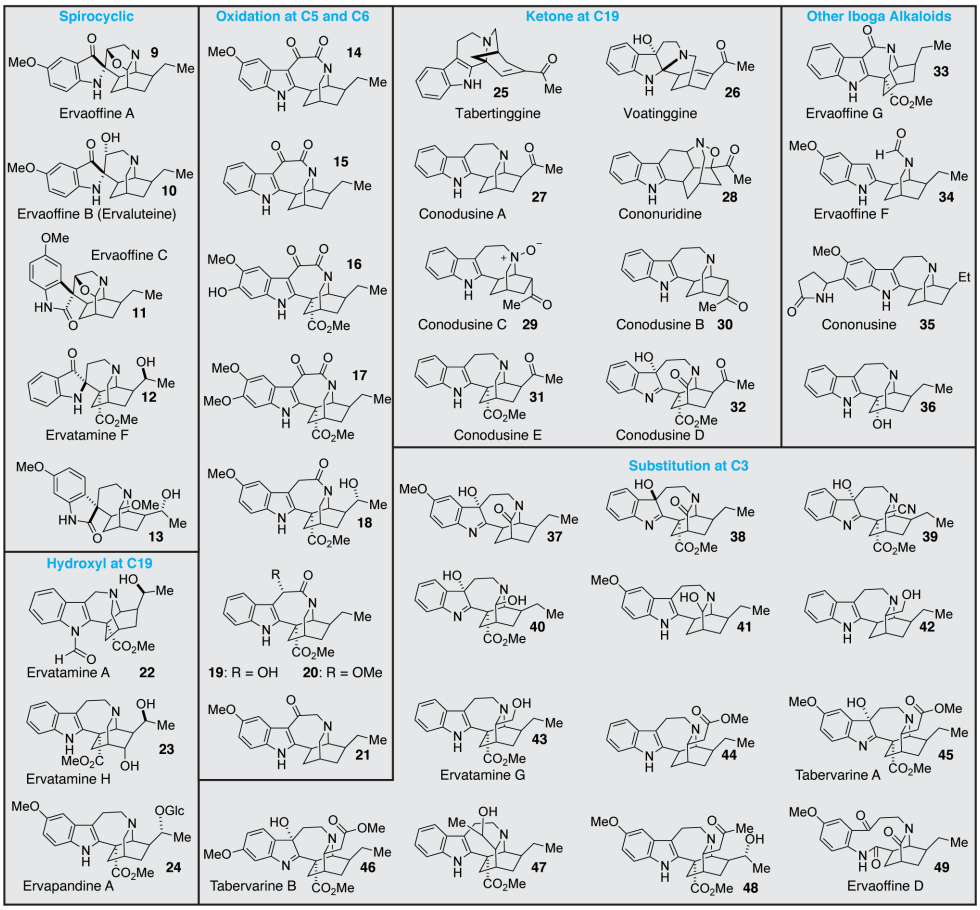
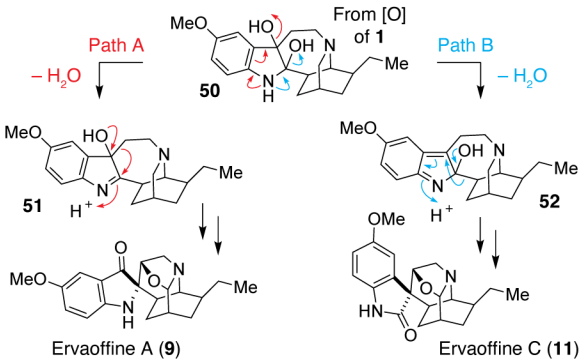


Figure 1.2. Newly isolated iboga alkaloid during the period 2010–2020

In addition to ervaoffines A–D (**9**, **10**, **11**, **49**), **14** and **37** were also isolated from *Ervatamia officinalis* (**Figure 1.2**).[17] These newly isolated alkaloids are likely derived from ibogaine (**1**), which is a major constituent of *Ervatamia* plants. Indole oxidation would lead to intermediate **50**, which could lose an equivalent of water through either Path A or Path B (**Scheme 1.1**). Subsequent pinacol rearrangements would ultimately lead to **9** and **11**, respectively. In 2017, Ye and co-workers isolated several additional ervaoffine alklaoids (**33**, **34**) from *E. officinalis*.[18] The proposed biosynthesis of **33** and **34** involves the generation of a C5–C6 olefin in either ibogaine or coronaridine. Oxidative cleavage of the C5–C6 olefin to

17. Madinaveitia, A.; De La Fuente, G.; Gonzalez, A. Helv. Chim. Acta, 1998, 81, 1645–1653.
18. Liu, Z. W.; Tang, B. Q.; Zhang, Q. H.; Wang, W. J.; Huang, X. J.; Zhang, J.; Shi, L.; Zhang, X. Q.; Ye, W. C. Ervaoffines E–G, three iboga-type alkaloids featuring ring C cleavage and rearrangement from Ervatamia officinalis. RSC Adv., 2017, 7, 21883–21889.

the corresponding dialdehyde would produce an intermediate that could be transformed to **33** and **34** through oxidation followed by amidation or decarboxylation.



Scheme 1.1. Proposed mechanism for the oxidative rearrangement of ibogaine to form ervaoffine A and C

The *Ervatamia* genus consists of approximately 120 species, which are primarily distributed in the subtropical and tropical regions of Australia and Asia. Phytochemical studies of this genus have led to the discovery of MIAs and bisindole alkaloids of various skeletal types.[19,20] In 2015, Gao and co-workers isolated **22**, **23**, **12**, and **43** from *Ervatamia hainanensis* (**Figure 1.2**).[21] Absolute configurations were determined by various methods including X-ray diffraction and ECD spectroscopy. Interestingly, compounds **12**, **22**, and **23** contain an alcohol at C19, suggesting that 19-hydroxycoronaridine is likely a common precursor. Conodusine E (**31**) was also isolated and its biosynthesis likely involves oxidation of 19-hydroxycoronaridine. The newly isolated alkaloid **31** was shown to possess mild anti-inflammatory properties. In 2016, several additional alkaloids from *E. hainanensis* were isolated by Ye and co-workers

19. Kazumasa, Z.; Tomoko, H.; Takahiro, H.; Yusuke, H.; Koichiro, K.; Abdul, R.; Idha, K.; Noor, C. Z.; Motoo, S.; Hiroshi, M. J. Nat. Prod., 2009, 72, 1686−1690.
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21. Zhang, D. B.; Yu, D. G.; Sun, M.; Zhu, X. X.; Yao, X. J.; Zhou, S. Y.; Chen, J. J.; Gao, K. Ervatamines A-I, Anti-inflammatory Monoterpenoid Indole Alkaloids with Diverse Skeletons from Ervatamia hainanensis. J. Nat. Prod., 2015, 78, 1253–1261.

(**Figure 1.2**).[22] Similar to ervatamine G, **38**, **39**, **40** and **47** are all substituted at the C3 position of the isoquinuclidine, with **39** representing the first example of a cyano-substituted oxindole alkaloid.

In 2016, Kam and co-workers mined the Malaysian plant *Tabernaemontana corymbosa* for iboga-type alkaloids.[23] Using NMR, mass spectrometry, and X-ray diffraction analysis, they isolated and characterized the conodusine alkaloids (**27**, **29, 30**, **31**, **32**) (**Figure 1.2**). Since then, other groups have reported the isolation of additional iboga alkaloids (**21**, **28**, **25**, **26**, **10**, **35**) from *T. corymbose*.[24,25,26] The biosynthetic origin of the unusual pyrrolidinone-containing compound **35** is still largely unknown.[26] Alkaloids **25** and **26** possess unprecedented skeletons, possibly derived from a cleavamine precursor (**Scheme 1.2**).[24] The proposed biosynthetic pathway to produce **25** and **26** likely starts from the oxidation of conodusine A (**27**) to **53**. Next, fragmentation of the isoquinuclidine would produce **54**. Hydrolysis of the iminium followed by enamine attack of the resulting aldehyde would produce **56**. Nitrogen attack at the iminium and dehydration would yield **26** (Path A), while tautomerization followed by S_N2' reaction and dehydration (Path B) would yield **25**. Though tabertinggine was only just recently discovered as an optically active natural product, the skeletal framework has been known since 1966 when Büchi inadvertently produced a related compound through an undesired rearrangement.[27] Ultimately, he was able to use this intermediate to complete the first ever total synthesis of ibogaine (vide infra).

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22. Liu, Z. W.; Huang, X. J.; Xiao, H. L.; Liu, G.; Zhang, J.; Shi, L.; Jiang, R. W.; Zhang, X. Q.; Ye, W. C. New iboga-type alkaloids from Ervatamia hainanensis. RSC Adv., 2016, 6, 30277–30284.
23. Nge, C. E.; Chong, K. Nge, C. E.; Chong, K. W.; Thomas, N. F.; Lim, S. H.; Low, Y. Y.; Kam, T. S. Ibogan, Aspidosperman, Vincamine, and Bisindole Alkaloids from a Malayan Tabernaemontana corymbosa: Iboga Alkaloids with C-20α Substitution. J. Nat. Prod., 2016, 79, 1388–1399.
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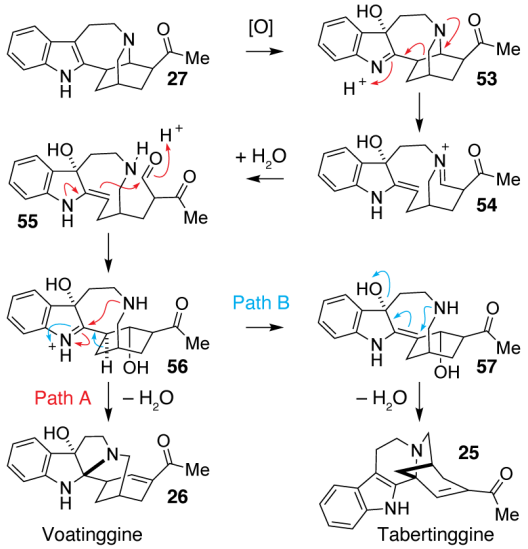
25. Nge, C. E.; Sim, K. S.; Lim, S. H.; Thomas, N. F.; Low, Y. Y.; Kam, T. S. A Hexacyclic Iboga Derived Monoterpenoid Indole with a Contracted Tetrahydroazepine C-Ring and Incorporation of an Isoxazolidine Moiety, a Seco-Corynanthean, an Aspidosperma-Aspidosperma Bisindole with Anticancer Properties, and the Absolute Configuration of the Pyridopyrimidine Indole Alkaloid, Vernavosine. J. Nat. Prod., 2016, 79, 2709–2717.
26. Lim, K. H.; Raja, V. J.; Bradshaw, T. D.; Lim, S. H.; Low, Y. Y.; Kam, T. S. Ibogan, Tacaman and cytotoxic bisindole alkaloids from tabernaemontana. Cononusine, an iboga alkaloid with unusual incorporation of a pyrrolidone moiety. J. Nat. Prod., 2015, 78, 1129–1138.
27. Büchi, G.; Coffen, D. L.; Kocsis, K.; Sonnet, P. E.; Ziegler, F. E. The Total Synthesis of Iboga Alkaloids. J. Am. Chem. Soc., 1966, 88, 3099–3109.



Scheme 1.2. Proposed mechanism for the formation of tabertinggine and voatinggine

The plant species *Tabernaemontana divaricata* is yet another member of the Apocynaceae family that is rich in iboga alkaloids. Commonly found in the Yunnan and Guangxi Provinces of China, phytochemical investigations of *T. divaricata* have led to the isolation and characterization of **13**, **36**, **42**, **44**, **45**, **46**, and **48** (Figure 2 and Table S1).[28,29,30] Most of these newly isolated alkaloids possess substitution at the C3 position of the isoquinuclidine. The biosynthesis of these compounds is likely to proceed through oxidation of simpler iboga alkaloids at C3 followed by C–C bond formation.

Initially believed to be found only in plants native to western Africa, iboga alkaloids are being discovered in a wide variety of Apocynaceae family members found around the world. These new sources may help to ensure that sufficient quantities of iboga alkaloids can be produced for future biological testing. In addition, the isolation of new iboga alkaloids provides important insight into novel biosynthetic pathways.

Chapter 1.1.4 Biosynthesis of iboga alkaloids

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28. Deng, Y.; Bao, M. F.; Shi, B. B.; Wu, J.; Cai, X. H. Three New Indole Alkaloids from Tabernaemontana divaricata. Nat. Prod. Bioprospect., 2018, 8, 183–188.
29. Yuwen, H.; Yuan, Y.; Hao, X.; He, H.; Zhang, Y. Two New Monoterpenoid Indole Alkaloids from Tabernaemontana divaricata. Nat. Prod. Res., 2019, 33, 2139–2144.
30. Li, X. M.; Jiang, X. J.; Wei, G. Z.; Ren, L. H.; Wang, L. X.; Cheng, X. L.; Wang, F. New Iboga-Type Indole Alkaloids from Tabernaemontana divaricata. Nat. Prod. Bioprospect., 2019, 425–429.

Unlike in prokaryotes, the genes encoding metabolic pathways in plants are not typically clustered, making the full elucidation of alkaloid biosynthesis quite challenging. Typically, each individual plant-derived enzyme must be identified, cloned, and isolated to firmly establish a role in the synthesis of a particular alkaloid. Though several enzymes in the production of iboga alkaloids still remain elusive, our knowledge of iboga alkaloid biosynthesis has improved drastically over the past 15 years due in large part to the pioneering work of Sarah O'Connor, Vincenzo De Luca, and others.

Like all MIAs, the iboga alkaloids are derived from tryptamine (**59**), which is produced from the enzymatic decarboxylation of tryptophan (**58**) by tryptophan decarboxylase (TDC) (**Scheme 1.3**).[31,32,33] The remainder of the iboga carbon skeleton can trace its origins to secologanin (**62**), an iridoid synthesized from isopentenyl pyrophosphate (**60**) and dimethylallyl pyrophosphate (**61**) via the non-mevalonate pathway

[31]. Leete, E. Biogenesis of Rauwolfia alkaloids. II. Incorporation of tryptophan into serpentine and reserpine. Tetrahedron, 1961, 14, 35–41.

[32]. Battersby, A. R.; Burnett, A. R.; Parsons, P. G. Partial synthesis and isolation of vincoside and isovincoside: Biosynthesis of the three major classes of indole alkaloids from the beta carboline system., Chem. Comm., 1968, 1282–1284.

[33]. De Luca, V.; Marineau, C.; Brisson, N. Molecular cloning and analysis of a cDNA encoding a plant tryptophan decarboxylase. Proc. Natl. Acad. Sci., 1989, 86, 2582–2586.

(**Scheme 1.3**).[34] Ten enzymes are required to produce **62**,[35,36,37,38,39,40,41] which subsequently reacts with **59** to form strictosidine (**63**). This critical Pictet-Spengler reaction is catalyzed by strictosidine synthase (STR),[42,43] producing **63** as a single enantiomer (Scheme 3). Strictosidine (**63**) is a key intermediate en route to a number of indole alkaloids including those of the ajmalan, corynanthe, aspidosperma, quinoline, and iboga families.[34]

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[34]. O'Connor, S. E.; Maresh, J. J. Chemistry and biology of monoterpene indole alkaloid biosynthesis. Nat. Prod. Rep. 2006, 23, 532–472.

[35]. Miettinen, K.; Dong, L.; Navrot, N. et al. The seco-iridoid pathway from Catharanthus roseus. Nat Comm., 2014, 5, 3606.

[36]. Oudin, A.; Courtois, M.; Rideau, M. et al. The iridoid pathway in Catharanthus roseus alkaloid biosynthesis. Phytochem Rev., 2007, 6, 259–276.

[37]. Rai, A.; Smita, S.; Singh, A.K.; Shanker, K.; Naegegowda, D. A. Heteromeric and Homomeric Geranyl Diphosphate Synthases from Catharanthus roseus and Their Role in Monoterpene Indole Alkaloid Biosynthesis. Mol. Plant., 2013, 6, 1531–1549.

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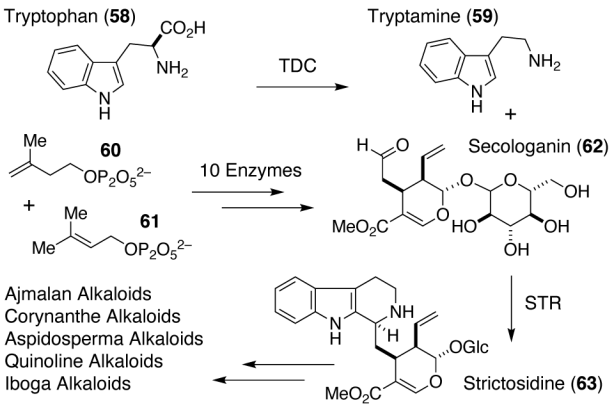
[40]. Murata, J; Roepke, J; Gordon, H; De Luca, V. The Leaf Epidermome of Catharanthus Roseus Reveals its Biochemical Specialization. Plant Cell, 2008, 20, 524–542.

[41]. Irmler, S.; Schröder, G.; St-Pierre, B.; Crouch, N. P.; Hotze, M.; Schmidt, J.; Strack, D.; Matern, U.; Schröder, J. Indole Alkaloid Biosynthesis in Catharanthus Roseus: New Enzyme Activities and Identification of Cytochrome P450 CYP72A1 as Secologanin Synthase. The Plant Journal, 2008, 24, 797–804.

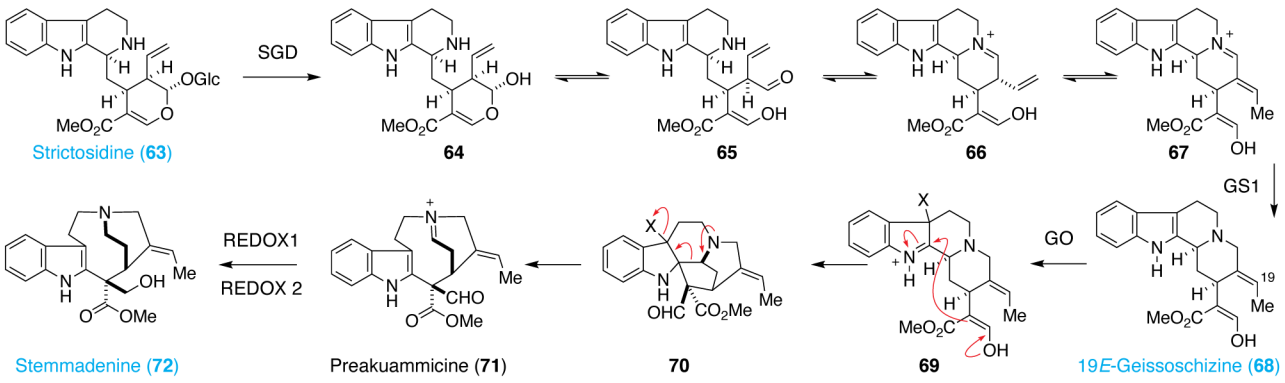
[42]. De Waal A.; Meijer A.H.; Verpoorte R. Strictosidine synthase from Catharanthus roseus: Purification and Characterization of Multiple Forms. Biochem. J., 1995, 306, 571–580.

[43]. McKnight, T.D.; Roessner, C.A.; Devagupta, R.; Scott, A.I.; Nessler, C.L. Nucleotide Sequence of a cDNA Encoding the Vacuolar Protein Strictosidine Synthase from Catharanthus roseus. Nucleic Acids Res., 1990, 18, 4939.



Scheme 1.3. Biosynthesis of strictosidine

Many of the enzymes in *T. iboga* and *C. roseus* share a high degree of sequence homology, and thus, the biosynthetic pathways leading to ibogaine and catharanthine are quite similar until their late-stage divergence from dehydrosecodine (**77**). A number of the compounds en route to the iboga alkaloids are short-lived or produced in such small quantities that characterization via LC-MS has been challenging. As a result, many of the intermediates in the biosynthetic pathway to iboga alkaloids have been proposed based on the structures of their precursors and products. Whenever possible, we indicate which intermediates have actually been isolated.



Scheme 1.4. Biosynthesis of stemmadenine. Compounds that have been isolated are highlighted in blue.

The first step in the biosynthesis of iboga alkaloids from strictosidine (**63**) involves glycosidic bond cleavage catalyzed by strictosidine β-deglucosidase (SGD) to produce the six-membered lactol **64** (Scheme 4).[44,45] Opening of the lactol produces aldehyde **65**, which rapidly condenses with the secondary amine to yield iminium **66**. Isomerization to the more conjugated system produces **67**, which is immediately reduced by geissoschizine synthase 1 (GS1) to produce **68**.[46] Oxidation of the indole by geissoschizine oxidase (GO) yields **69**, which immediately undergoes intramolecular Mannich reaction followed by Grob fragmentation to yield preakuammicine (**71**).[47] As **71** is unstable, the iminium is rapidly reduced by REDOX1. The identification of REDOX1 was made possible due to its sequence homology to GS1, another iminium reductase.[47] Subsequent reduction of the aldehyde by REDOX2 produces the stable intermediate stemmadenine (**72**).[47]

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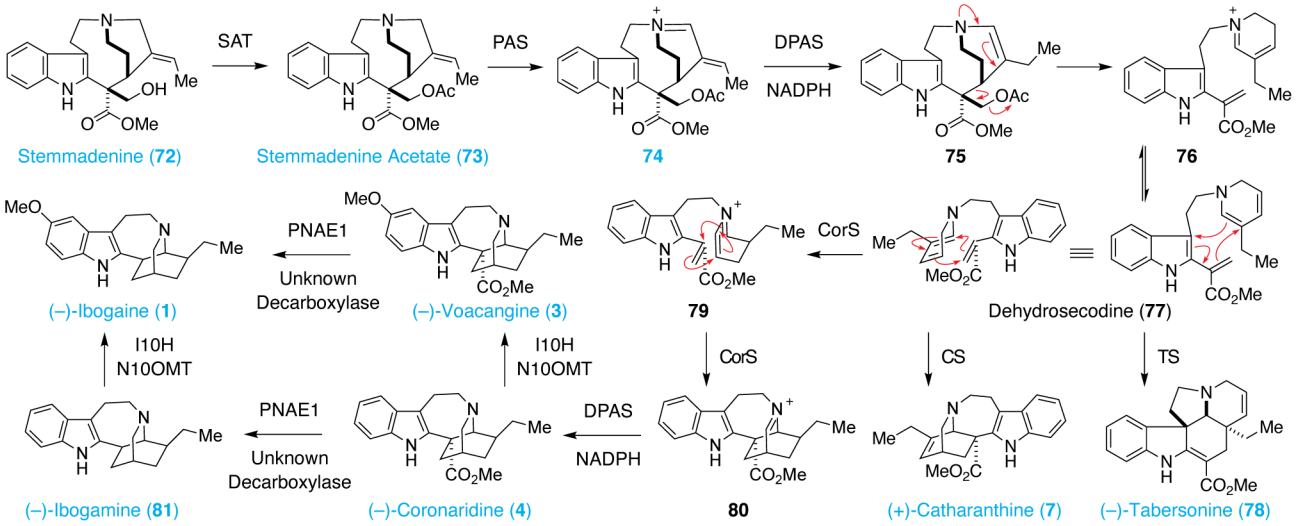
44. Hemscheidt T.; Zenk M. H. Glucosidases involved in indole alkaloid biosynthesis of Catharanthus roseus cell cultures. FEBS Lett. 1980, 110:187–191

45. Geerlings, A.; Martinez-Lozano Ibanez M.; Memelink, J.; van der Heijden R.; Verpoorte, R. Molecular Cloning and Analysis of Strictosidine β-D-Glucosidase, an Enzyme in Terpenoid Indole Alkaloid Biosynthesis in *Catharanthus roseus.* J Biol Chem. 2000, 275, 3051–3056.

46. Qu, Y.; Thamm, A. M. K.; Czerwinski, M.; Masada, S.; Kim, K. H.; Jones, G.; Liang, P.; Luca, V. D. Geissoschizine Synthase Controls Flux in the Formation of Monoterpenoid Indole Alkaloids in a Catharanthus Roseus Mutant. Planta, 2017, 247, 625–634.

47. Qu, Y.; Easson, M. E. A. M.; Simionescu, R.; Hajicek, J.; Thamm, A. M. K.; Salim, V.; Luca, V. D. Solution of the Multistep Pathway for Assembly of Corynanthean, Strychnos, Iboga, and Aspidosperma Monoterpenoid Indole Alkaloids from 19E-Geissoschizine. PNAS, 2018, 115, 3180–3185.



Scheme 1.5. Biosynthesis of iboga and aspidosperma alkaloids. Compounds that have been isolated are highlighted in blue.

The conversion of stemmadenine (**72**) to dehydrosecodine (**77**) is a common pathway en route to both iboga and aspidosperma alkaloids (Scheme 5). First, stemmadenine (**72**) is acetylated by stemmadenine O-acetyltransferase (SAT) to afford stemmadenine acetate (**73**).[47] Oxidation by precondylocarpine acetate synthase (PAS) produces iminium **74**, which is reduced by dihydroprecondylocarpine acetate synthase (DPAS) in the presence of NADPH to yield the key enamine intermediate **75**.[48] Fragmentation produces iminium **76**, which tautomerizes to the critical intermediate dehydrosecodine (**77**).[48] Dehydrosecodine (**77**) represents the point of divergence for the aspidosperma and iboga biosynthetic pathways. However, it has never been isolated, presumably due to the unstable nature of the *N*-alkyl dihydropyridine. When O'Connor and co-workers subjected **73** to PAS and DPAS, they were able to isolate angryline (**82**) as a mixture of enantiomers (Figure 3).[52] Angryline represents a stable precursor to dehydrosecodine (**77**) and is produced from an intramolecular Diels-Alder reaction between the iminium group of **77** and the vinylindole (**Figure 3**).

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48. Caputi, L.; Franke, J.; Farrow, S. C.; Chung, K.; Payne, R. M. E.; Nguyen, T.-D.; Dang, T.-T. T.; Carqueijeiro, I. S. T.; Koudounas, K.; Bernonville, T. D. D.; Ameyaw, B.; Jones, D. M.; Vieira, I. J. C.; Courdavault, V.; O'Connor, S. E. Missing Enzymes in the Biosynthesis of the Anticancer Drug Vinblastine in Madagascar Periwinkle. Science, 2018, 360, 1235–1239.

In the presence of tabersonine synthase (TS), dehydrosecodine (**77**) can undergo a Diels-Alder-like reaction to produce tabersonine (**78**).[49] However, it is currently unclear if natural enzymes like TS are capable of catalyzing truly concerted Diels-Alder reactions.[50] Reorientation of dehydrosecodine (**77**) reveals that it has the potential to undergo a second Diels-Alder-like reaction to form (+)-catharanthine (**7**) (**Scheme 1.5**). This reaction is likely to occur through a stepwise mechanism. When (+)-catharanthine (**7**) was incubated with catharanthine synthase (CS), the product of a retro Mannich reaction was observed, indicating that the forward reaction is likely to proceed through conjugate addition of the vinylogous enamine followed by Mannich reaction.[51,52] Such stepwise formal Diels-Alder reactions are known to be favored with very electron-rich dienes, very electron-deficient dienophiles, or under conditions that stabilize the zwitterionic intermediate.[53] In this case, the reaction must be templated by CS, as only one enantiomer is formed.[48]

One of the most intriguing aspects of iboga alkaloid biosynthesis is the fact that *C. roseus* and *T. iboga* produce natural products of the opposite enantiomeric series (e.g., (+)-catharanthine and (–)-coronaridine, respectively). One might assume that *T. iboga* generates (–)-catharanthine, which in principle could be reduced to yield (–)-coronaridine (**7**). However, (–)-catharanthine has never been isolated, suggesting that this pathway does not exist in nature. Instead, deuterium labeling studies have shown that coronaridine synthase (CorS) catalyzes the isomerization of **77** to **79** followed by a very unusual [4+2] cycloaddition to produce **80** (**Scheme 1.5**).[49,52] While imino Diels-Alder reactions are well known,[54] the

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[49] . Farrow, S. C.; Kamileen, M. O.; Caputi, L.; Bussey, K.; Mundy, J. E. A.; Mcatee, R. C.; Stephenson, C. R. J.; O'Connor, S. E. Biosynthesis of an Anti-Addiction Agent from the Iboga Plant. J. Am. Chem. Soc., 2019, 141, 12979–12983.

[50]. Klas, K.; Tsukamoto, S.; Sherman, D. H.; Williams, R. M. Natural Diels–Alderases: Elusive and Irresistable. J. Org. Chem., 2015, 80, 11672–11685.

[51]. Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. Preparation of 15-oxo-16-methoxycarbonyl-15, 20-dihydrocleavamine and Coupling Reaction with Vindoline. Heterocycles., 1981,15, 245–250.

[52]. Caputi, L.; Franke, J.; Bussey, K.; Farrow, S. C.; Vieira, I. J. C.; Stevenson, C. E. M.; Lawson, D. M.; O'Connor, S. E. Structural Basis of Cycloaddition in Biosynthesis of Iboga and Aspidosperma Alkaloids. Nat. Chem. Biol. 2020, 16, 383–386.

[53]. Linder, M.; Brinck, T. Stepwise Diels-Alder: More Than Just An Oddity? A Computational Mechanistic Study. J. Org. Chem., 2012, 77, 6563–6573.

[54]. Buonora, P.; Olsen, J.-C.; Oh, T. Recent Developments in Imino Diels–Alder Reactions. Tetrahedron, 2001, 57, 6099–6138.

product **80** is formally an anti-Bredt olefin when drawn as the iminium resonance structure. This reactive species is immediately reduced by DPAS to afford (–)-coronaridine (**4**).[49]

When angryline is exposed to TS, CS, or CorS/DPAS it produces tabersonine (**78**), (+)-catharanthine (**7**), and (–)-coronaridine (**4**), respectively.[52] The formation of three distinct chiral natural products from a common achiral intermediate is a hallmark of iboga/aspidosperma biosynthesis (**Figure 1.3**)

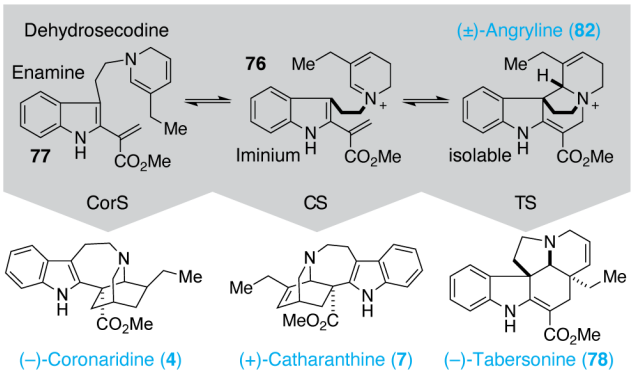

Figure 1.3. Racemic angryline gives rise to three chiral natural products through the intermediacy of achiral dehydrosecodine. Isolable compounds are highlighted in blue.

Conversion of **4** to 10-hydroxycoronaridine is accomplished by the P450 enzyme ibogamine-10-hydroxylase (I10H) (Scheme 5).[55] Methylation by noribogaine-10-*O*-methyltransferase (N10OMT) produces (–)-voacangine (**3**).[55] Polyneudridine aldehyde esterase-like 1 (PNAE1) has been shown to convert both **3** and **4** to their corresponding carboxylic acids.[49,56] However, the pathways converting these acids to ibogaine and ibogamine still have not been fully elucidated. The O'Connor group reported that the hydrolysis product of **3** does spontaneously decarboxylate to produce ibogaine.[49] However, this reaction

[55]. Farrow S.C.; Kamileen, M.O.; Meades, J.; Ameyaw, B.; Xiao, Y.; O'Connor, S.E. Cytochrome P450 and O-Methyltransferase Catalyze the Final Steps in the Biosynthesis of the Anti-addictive Alkaloid Ibogaine from Tabernanthe iboga. J Biol Chem., 2018, 293,13821–13833.

[56]. Dogru, E.; Warzecha, H.; Seibel, F.; Haebel, S.; Lottspeich, F.; Stöckigt, J. The Gene Encoding Polyneuridine Aldehyde Esterase of Monoterpenoid Indole Alkaloid Biosynthesis in Plants Is an Ortholog of Theα/β Hydrolase Super Family. Eur. J. Biochem. 2000, 267, 1397–1406.

is slow, and heating is required to increase its rate. Furthermore, this transformation does not proceed when the hydrolysis product of **4** is heated. Therefore, it is likely that an unidentified decarboxylase(s) is responsible for the final step in the biosynthesis of ibogaine and ibogamine. Furthermore, ibogamine can be converted to ibogaine via I10H-mediated hydroxylation followed by N10OMT-catalyzed *O*-methylation.[55] However, when noribogaine (**2**) is used as a substrate, N10OMT exhibits a low turnover rate suggesting that this transformation might actually be mediated by a currently unidentified *O*-methylase.

Tabersonine is known to be hydroxylated at the C11 position by tabersonine 16-hydrolase (T16H); however, a similar hydroxylase(s) acting on the iboga scaffold to produce tabernanthine (**5**) or ibogaline (**6**) has not been identified. Through sequence homology, five additional P450s related to T16H and I10H were identified in *T. iboga*. These enzymes were cloned, but they did not catalyze the C11-hydroxylation of either coronaridine or ibogamine.[55] Therefore, it is possible that tabernanthine (**5**) and ibogaline (**6**) are produced from an oxidase unrelated to the P450 family.

The enzymes that produce iboga and aspidosperma alkaloids have been shown to be somewhat promiscuous. An interesting study by the O'Connor group involved feeding substituted tryptamines to a *C. roseus* hairy root culture.[57] Using LC-MS, they concluded that the unnatural tryptamine derivatives were incorporated into the scaffolds of the natural products. Feeding studies are only one approach for producing "unnatural" natural products. The O'Connor group has also expressed several prokaryotic halogenases or engineered halogenases, such as RebH, in *C. roseus*, leading to the production of chlorinated tabersonine analogs.[58,59]

Chapter 1.2 Historical synthesis of iboga alkaloids

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[57]. McCoy, E.; O'Connor, S. E. Directed biosynthesis of alkaloid analogs in the medicinal plant Catharanthus roseus. J. Am. Chem. Soc. 2006, 128,14276–14277.

[58]. Runguphan, W.; Qu, X.; O'Connor, S. E. Integrating Carbon-Halogen Bond Formation into Medicinal Plant Metabolism., Nature 2010, 468, 461–464.

[59]. Glenn, W. S.; Nims, E.; O'Connor, S. E. Reengineering a Tryptophan Halogenase to Preferentially Chlorinate a Direct Alkaloid Precursor. J. Am. Chem. Soc., 2011, 133, 19346−19349.

Since Büchi's pioneering synthesis of ibogaine in 1966,[27] there have been numerous synthetic approaches to iboga alkaloids. For a comprehensive analysis of strategies prior to 2011, we refer the reader to an excellent review by Sinha and co-workers.[60] Here, we focus on historical strategies for constructing the isoquinuclidine, tetrahydroazepine, and indole ring systems characteristic of this alkaloid family.

Chapter 1.2.1. Construction of the Isoquinuclidine

The isoquinuclidine ring system represents a structural focal point for the iboga alkaloids.[61] Methods to construct this [2.2.2] bicycle have centered around three fundamental strategies—cycloaddition, transannular cyclization, and radical rearrangement (**Figures 1.4–1.6**). The cycloaddition strategy was first successfully utilized by Büchi and co-workers (**Figure 1.4**).[62,27] Their approach involved the reduction of nicotinamide pyridinium **83** with sodium borohydride to give a regioisomeric mixture of dienes **84** and **85**. When this mixture was subjected to a Diels-Alder reaction with methyl vinyl ketone (MVK), only dihydropyridine **85** underwent cycloaddition, yielding isoquinuclidine **86** in 13% yield as a mixture of epimers over two steps. The authors postulated that the greater electron delocalization of **84** prevents cycloaddition with MVK.

Most syntheses that have adopted this approach have opted to transform the substituent on the dienophile into the exo C20 ethyl group of the iboga alkaloids.[27,63,64] This poses an obvious challenge given the inherent endo selectivity of most Diels-Alder reactions. To overcome this issue, Sames and co-workers took advantage of the acidic protons alpha to the carbonyl (**Figure 1.4**).[64] By treating a 3:1 endo:exo mixture of the Diels-Alder adducts with base, they achieved epimerization to a thermodynamic ratio (2:3)

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60. Jana, G. K.; Paul, S.; Sinha, S. Progress in the Synthesis of Iboga-Alkaloids and Their Congeners. Organic Preparations and Procedures International, 2011, 43, 541–573.
61. Sundberg, R. J.; Smith, S. Q. The Alkaloids, 2002, 59, 281–386.
62. Büchi, G.; Coffen, D. L.; Kocsis, K.; Sonnet, P. E.; Ziegler, F. E. The Total Synthesis of (±)-Ibogamine and of (±)-Epiibogamine. J. Am. Chem. Soc., 1965, 87, 2073–2075.
63. Jana, G. K.; Sinha, S. Total Synthesis of Ibogaine, Epiibogaine and Their Analogues. Tetrahedron, 2012, 68, 7155–7165.
64. Kruegel, A. C.; Rakshit, S.; Li, X.; Sames, D. Constructing Iboga Alkaloids via C–H Bond Functionalization: Examination of the Direct and Catalytic Union of Heteroarenes and Isoquinuclidine Alkenes. J. Org. Chem., 2015, 80, 2062–2071.

of **88** and **89**. After exo enrichment, conversion to the tosylhydrazones **90** and **91** allowed for separation via crystallization. Fukuyama and co-workers sought to avoid endo/exo diastereoselectivity issues altogether by performing the Diels-Alder reaction with a symmetrical dienophile (Figure 4).[65] Treatment of trans-dibromide **92** with DABCO afforded the requisite dihydropyridine **93**, which was then reacted with dimethyl methylenemalonate to give isoquinuclidine **94** in 94% yield over two steps.

In the approaches described above, the Diels-Alder reactions were uncatalyzed, leading to racemic mixtures of isoquinuclidines. Recently, Batey and co-workers reported an enantioselective Diels-Alder reaction of dihydropyridine **87** with acrolein in the presence of a valine-derived organocatalyst (**Figure 1.4**),[66] leading to a formal synthesis of (+)-catharanthine. In 2006, Borschberg and co-workers reported another enantioselective synthesis of an iboga alkaloid, although their approach involved an intramolecular nitrone-olefin [3+2] cycloaddition (**Figure 1.4**).[67,68] Key intermediate **96** was synthesized from L-glutamic acid and (2S)-but-3-en-2-ol. A crucial chirality transfer in the Ireland-Claisen rearrangement of a silyl ketene acetal afforded intermediate **96** in high diastereoselectivity. The subsequent 1,3-dipolar cycloaddition produced **97** in 67% yield.

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65. Reding, M. T.; Fukuyama, T. Stereocontrolled Total Synthesis of (±)-Catharanthine via Radical-Mediated Indole Formation. Org. Lett., 1999, 1, 973–976.
66. Kim, S. J.; Batey, R. A. Enantioselective Isoquinuclidine Synthesis via Sequential Diels–Alder/Visible-Light Photoredox C–C Bond Cleavage: A Formal Synthesis of the Indole Alkaloid Catharanthine. Organic Chemistry Frontiers, 2018, 5, 2934–2939.
67. Höck, S.; Borschberg, H.J. Enantioselective Synthesis of Key Intermediates in a Novel Approach towards the Iboga-Alkaloid Family. Helvetica Chimica Acta, 2003, 86, 1397–1409.
68. Höck, S.; Borschberg, H.J. Enantioselective Synthesis of (−)-(19R)-Ibogamin-19-ol. Helvetica Chimica Acta, 2006, 89, 542–557.

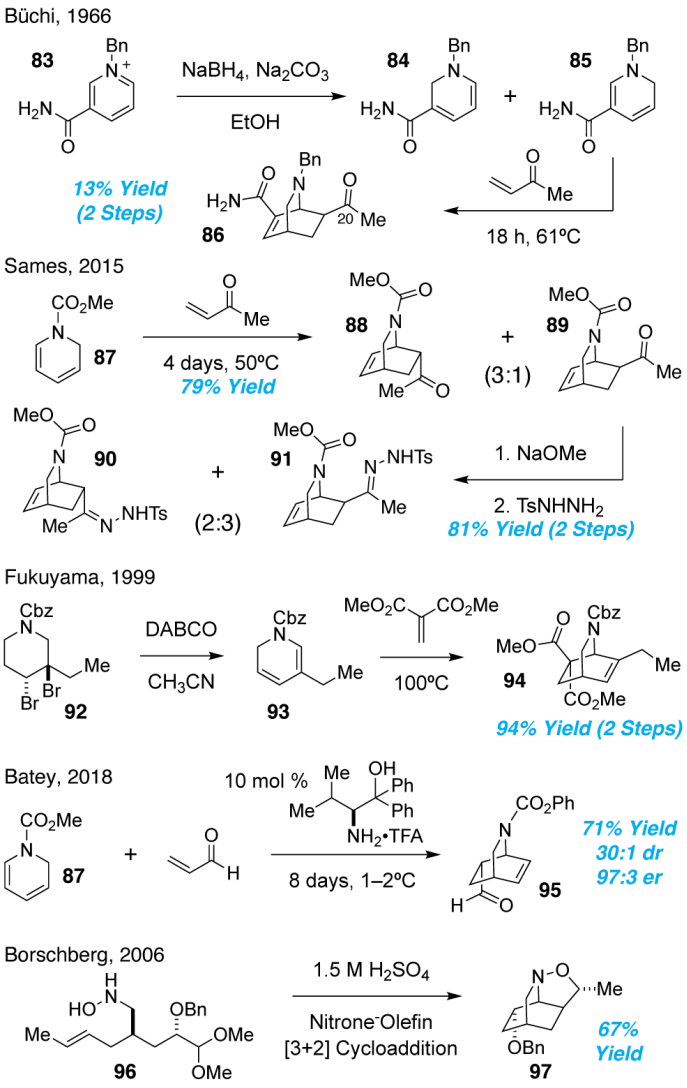

Figure 1.4. Cycloaddition approaches to the isoquinuclidine of iboga alkaloids

Another common approach to accessing the isoquinuclidine framework of iboga alkaloids involves the transannular cyclization of an amine derivative. Huffman and co-workers were the first to employ this strategy in 1965.[69,70] Ring opening of cyclic epoxy ester **98** followed by transannular amidation produced the isoquinuclidine in a single step. Subsequent tosylation of the C16 alcohol afforded intermediate **100** in 57% yield over two steps (**Figure 1.5**). However, when this strategy was applied to the synthesis of

[69]. Huffman, J. W.; Rao, C. B. S.; Kamiya, T. The Synthesis of Desethylibogamine. J. Am. Chem. Soc., 1965, 87, 2288–2288.

[70]. Huffman, J. W.; Rao, C. B. S.; Kamiya, T. The Synthesis of Desethylibogamine. J. Am. Chem. Soc., 1967, 32, 697–700.

ibogamine, the yields were greatly reduced owing to the complex mixture of diastereomeric products obtained during the synthesis of epoxide **99**.[71]

Variants of the transannular cyclization strategy have involved the preassembly of the indole and/or tetrahydroazepine rings prior to formation of the isoquinuclidine (**Figure 1.5**). The approach taken by Grieco and co-workers mirrored that of Huffman and produced **103** in excellent yield.[72] A hallmark of both of the Huffman and Grieco syntheses is the incorporation of an enolizable proton at what will become the bridgehead position, enabling both diastereomers to be converted to the desired isoquinuclidine.

A related approach pioneered by Sallay established what would become the tetrahydroazepine of ibogamine prior to transannular alkylation forming **105**.[73] White and co-workers improved upon the racemic Sallay synthesis by constructing **104** using an asymmetric Diels-Alder reaction as the key step (**Figure 1.5**). Base-mediated cyclization afforded **105** in high yield, which was converted to (–)-ibogamine.[74]

In addition to classic acylation and alkylation reactions, several other transannular cyclizations have been utilized to access the isoquinuclidine core of iboga alkaloids. For example, Nagata and co-workers favored the use of a transannular aziridination reaction,[75,76,77] while Trost and co-workers relied on Pd-catalyzed allylic alkylation.[78,79] Trost's 1978 synthesis of (+)-ibogamine was a landmark paper for the field (**Figure 1.5**). Use of a chiral auxiliary enabled an asymmetric Diels-Alder reaction (60% ee), and the product was subjected to reductive amination to produce **106**. Treatment of **106** with Pd^0 led to **107**, which

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71. Huffman, J. W.; Shanmugasundaram, G.; Sawdaye, R.; Raveendranath, P. C.; Desai, R. C. A Formal Synthesis of (±)-Ibogamine. J. Org. Chem., 1985, 50, 1460–1464.
72. Henry, K. J.; Grieco, P. A.; Dubay, W. J. A Novel Approach to Iboga Alkaloids: Total Synthesis of (±)-Ibogamine and (±)-Epi-Ibogamine. Tetrahedron Letters, 1996, 37, 8289–8292.
73. Sallay, S. I. Total Synthesis of DL-Ibogamine. J. Am. Chem. Soc.,1967, 89, 6762–6763.
74. White, J. D.; Choi, Y. Catalyzed Asymmetric Diels−Alder Reaction of Benzoquinone. Total Synthesis of (−)-Ibogamine. Org. Lett., 2000, 2, 2373–2376.
75. Nagata, W.; Hirai, S.; Okumura, T.; Kawata, K. A Stereochemical Controlled Total Synthesis of DL-Ibogamine and DL-Epiibogamine. J. Am. Chem. Soc., 1968, 90, 1650–1651.
76. Hirai, S.; Kawata, K.; Nagata, W. Total Synthesis of (±)-Coronaridine and an Improved Synthesis of (±)–Ibogamine. Chem. Commun., 1968, 719, 1016–1017.
77. Nagata, W.; Hirai, S.; Kawata, K.; Aoki, T. One-Step Synthesis of Bridged Aziridines. J. Am. Chem. Soc., 1967, 89, 5045–5046.
78. Trost, B. M.; Godleski, S. A.; Genet, J. P. A Total Synthesis of Racemic and Optically Active Ibogamine. Utilization and Mechanism of a New Silver Ion Assisted Palladium Catalyzed Cyclization. J. Am. Chem. Soc.,1978, 100, 3930–3931.
79. Trost, B. M.; Genet, J. P. Palladium Catalyzed Cyclizations to Alkaloid Skeletons. Facile Synthesis of Desethylibogamine. J. Am. Chem. Soc.,1976, 98, 8516–8517.

was converted to the natural product through a metal-catalyzed olefin arylation. Trost's synthesis was the first to use transition metal catalysis to access an iboga alkaloid, and it set precedent for many similar strategies to follow.

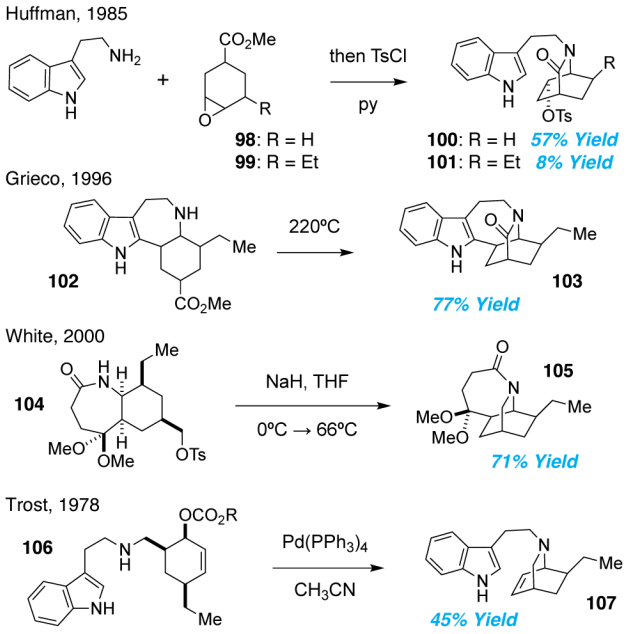

Figure 1.5. Transannular cyclization approaches to the isoquinuclidine of iboga alkaloids

Generally, methods to form the isoquinuclidine of iboga alkaloids have started from either an acyclic, cyclic, or fused cyclic precursor. In 2005, Hodgson developed an alternative strategy starting from an existing bridged bicycle (**Figure 1.6**).[80] An enantioselective desymmetrization of meso tropenone **108** gave radical precursor **109** in 46% yield over four steps. Reduction of the ketone with $NaBH_4$ gave the corresponding bromohydrin, which was then transformed into **113** via homoallylic radical rearrangement. This one-pot procedure led to an efficient formal synthesis of (+)-ibogamine.

[80]. Hodgson, D. M.; Galano, J.M. Enantioselective Access to Isoquinuclidines by Tropenone Desymmetrization and Homoallylic Radical Rearrangement: Synthesis of (+)-Ibogamine. Org. Lett., 2005, 7, 2221–2224.

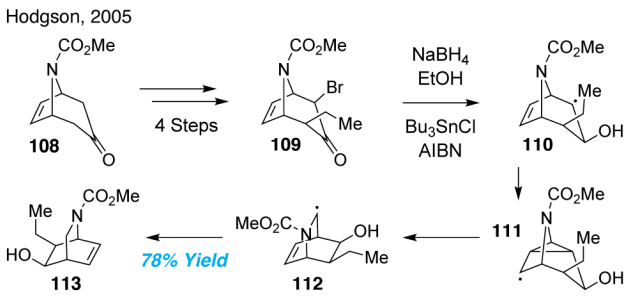

Figure 1.6. Hodgson's radical rearrangement approach to the isoquinuclidine cyclization approaches to the isoquinuclidine of iboga alkaloids

Chapter 1.2.2 Construction of tetrahydroazepine

The 7-membered tetrahydroazepine is a crucial structural element linking the indole and isoquinuclidine rings of the iboga alkaloids. Most syntheses have relied on one of three strategies for its construction—formation of the C2–C16 bond, indole–isoquinuclidine linkage, or ring-expansion. The C2–C16 bond disconnection was first explored by Nagata in 1968[75] and later exploited by Imanishi.[81] The cyclization of **114** was achieved by refluxing in a stoichiometric amount of *p*-TsOH for a short duration. Treatment of the resulting tosylate with *in situ* generated AlH_3 produced ibogamine (**81**) in reasonable yields (**Figure 1.7**). In 1985, Huffman employed an alternative strategy using tosylate **115**. Lewis acid-mediated cyclization of **115** followed by reduction of the lactam gave **81** in 32% yield over two steps (**Figure 1.7**).

The C2–C16 bond disconnection was also key feature of Trost's 1978 synthesis.[78] Using a novel Pd-catalyzed olefin arylation, Trost and co-workers were able to forge the C2–C16 bond from **107** using a mixture of palladium and silver (**Figure 1.7**). Reduction of the resulting organopalladium species afforded (+)-ibogamine in 43% yield. In 2015, Sames applied a slight modification of this C–H activation strategy by using a preformed palladium tetrafluoroborate catalyst instead of a combination of $PdCl_2(CH_3CN)_2$ and $AgBF_4$.[64] This result suggests that silver is not directly involved in cyclization and serves merely to facilitate chloride exchange for a noncoordinating tetrafluoroborate, thus generating a more active catalyst. Though

[81]. Imanishi, T.; Yagi, N.; Hanaoka, M. 1,6-Dihydro-3(2H)-Pyridinones. X. 2-Azabicyclo(2.2.2)Octane Ring Formation via Intramolecular Michael Reaction: Total Synthesis of (±)-Ibogamine and (±)-Epiibogamine. Chemical & Pharmaceutical Bulletin, 1985, 33, 4202–4211.

interesting, the methods developed by Trost and Sames suffered several drawbacks such as low yields and the need for stoichiometric or supra-stoichiometric amounts of palladium (1–2 eq). In 2012, Sinha employed a modified strategy using only catalytic amounts of palladium catalyst (**Figure 1.7**).[63,82] Pre-functionalization of the indole C2 position with an iodide (**116**) enabled a reductive Heck reaction to be performed using only 10 mol% of $Pd(OAc)_2$. This more economical approach towards the tetrahydroazepine ring system enabled the synthesis of ibogaine (**1**) in 66% yield.

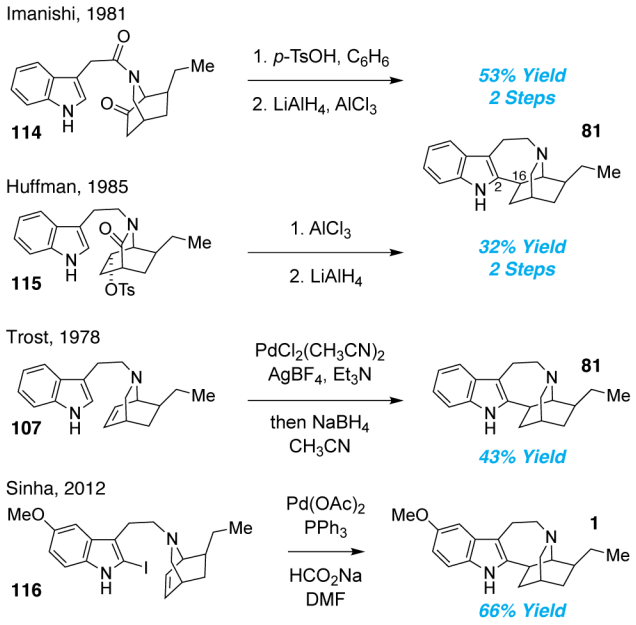

Figure 1.7. Construction of the tetrahydroazepine through C2–C16 bond formation.

Another popular strategy for constructing the tetrahydroazepine involves the introduction of a linker between the nitrogen of the isoquinuclidine and the C3 position of the indole (C7 based on the Le Men and Taylor numbering). Using a method developed by Kutney,[83] Das and co-workers performed a

82. Jana, G. K.; Sinha, S. Reductive Heck Coupling: An Efficient Approach toward the Iboga Alkaloids. Synthesis of Ibogamine, Epiibogamine and Iboga Analogs. Tetrahedron, 2012, 53, 1671–1674.

83. Kutney, J. P.; Fuller, G. B.; Greenhouse, R.; Itoh, I. Selective Debenzylation of Quaternary Salts. The Benzyl Group as an Excellent Protecting Group for Basic Nitrogen Compounds. Synthetic Communications, 1974, 4, 183–187.

debenzylation of a quaternary ammonium salt derived from **117** (**Figure 1.8**).[84] Though they were able to isolate catharanthine, the route was low yielding as formation of the quaternary ammonium salt was challenging. Fukuyama and co-workers took a slightly different approach by deprotecting the isoquinuclidine prior to alkylation.[65] They noticed that hydrogenolysis of **118** also resulted in the reduction of the endocyclic olefin. Instead, a mild and chemoselective deprotection using triethylsilane and palladium acetate afforded catharanthine in a single step. Interestingly, the desired intramolecular S_N2 alkylation occurred readily following carbamate deprotection, presumably due to the highly rigidified nature of the intermediate amine.

Sundberg and co-workers also chose to construct the tetrahydroazepine after the indole and isoquinuclidine rings had already been established (**Figure 1.8**).[85] However, their approach involved the generation of a radical through irradiation of chloroacetamide **119**. Radical cyclization afforded **120** in modest yield.

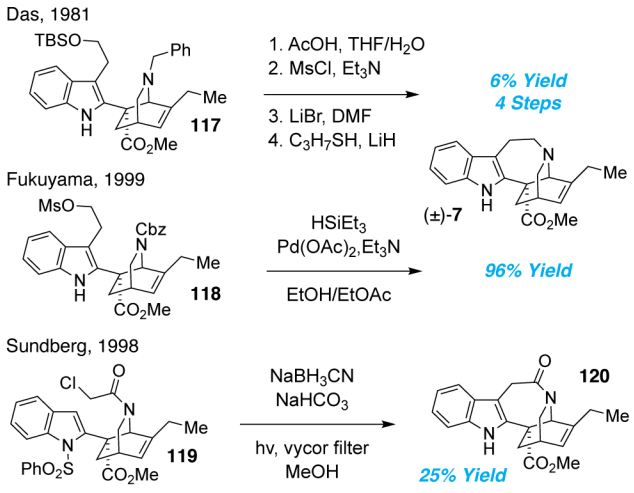

Figure 8. Construction of the tetrahydroazepine through indole–isoquinuclidine linkage.

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84. Marazano, C.; Goff, M.-T. L.; Fourrey, J.L.; Das, B. C. An Unequivocal Synthesis of 1-Benzyl-3-Ethyl-1,6-Dihydropyridine and Its Use for a Biogenetically Modelled Synthesis of (±)-Catharanthine. J. Chem. Soc. Chem. Commun., 1981, 148, 389–391.
85. Sundberg, R. J.; Hong, J.; Smith, S. Q.; Sabat, M.; Tabakovic, I. Synthesis and Oxidative Fragmentation of Catharanthine Analogs. Comparison to the Fragmentation—Coupling of Catharanthine and Vindoline. Tetrahedron, 1998, 54, 6259–6292.

The final strategy used to construct the tetrahydroazepine involves ring expansion, and this was the method by which Büchi first synthesized ibogaine (**Figure 1.9**).[27,62] Treatment of **121** with a mixture of Zn and AcOH resulted in reductive opening of the 6-membered ring. Following protonation at the γ-position, conjugate addition of the amine produced ibogaine in 57% yield. White and co-workers also synthesized the tetrahydroazepine through ring expansion. Beckman rearrangement of **124** yielded **125** in good yield.

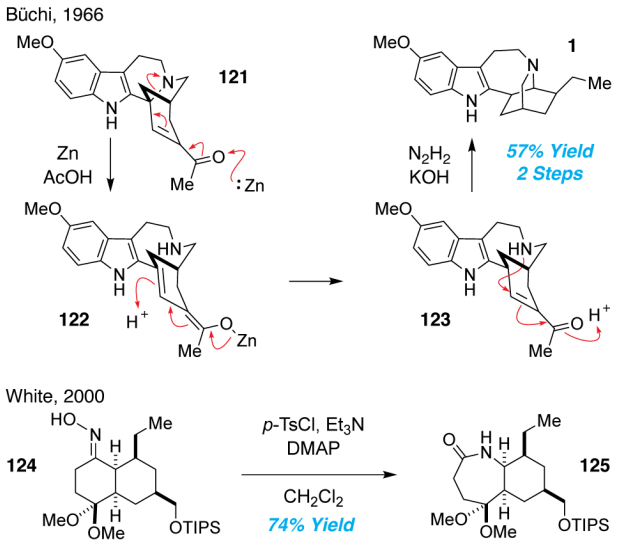

Figure 1.9. Construction of the tetrahydroazepine through ring expansion.

Chapter 1.2.3 Construction of the Indole

The indole ring system of the iboga alkaloids is biosynthetically derived from tryptophan, and most synthetic efforts toward the iboga alkaloids have started from tryptamine derivatives. For example, Büchi's 1966 synthesis of ibogaine involved the coupling of an isoquinuclidine with indole acetic acid.[27] More recently, alternative approaches to generating the indole have been explored (**Figure 1.10**). In 2000, White and co-workers installed the indole at a late-stage through a Fischer indole cyclization of **105** to afford **126** in 66% yield over two steps.[74] Fukuyama and co-workers built the indole through radical cyclization of thioanilide **127**.[65] They noticed that standard tin hydride conditions failed to produce the desired product in acceptable yields. Instead, they found that a phosphorus-based hydrogen atom donor afforded the desired cyclization. Recently, Sinha and co-workers decided to synthesize the indole very early in their synthesis.[63]

Larock annulation of aniline **129** and alkyne **130** provided **131** in modest yield. Very few synthetic strategies towards iboga alkaloids have made the construction of the indole a focal point for the synthesis, perhaps because the 7-membered tetrahydroazepine and bicyclic isoquinuclidine ring systems are viewed as being more challenging to access.

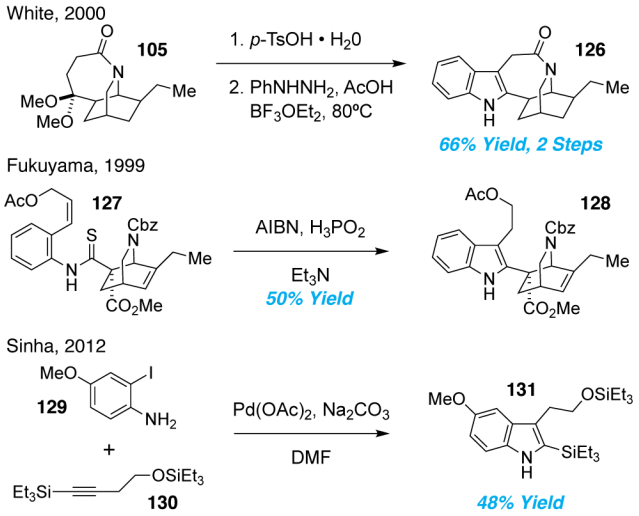

Figure 1.10. Construction of the indole.

Year	Group	Alkaloid(s)	Formation Sequence	Step Count	Overall Yield (%)
1965	Buchi	(±)-Ibogamine (**81**)	Q ® I ® A	14	1.3
1966	Buchi	(±)-Ibogaine (**1**)	Q ® I ® A	15	0.2
1967	Sally	(±)-Ibogamine (**81**)	A ® Q ® I	14	NR
1968	Nagata	(±)-Ibogamine (**81**)	Q ® I ® A	16	0.8
1978	Trost	(+)-Ibogamine (**81**)	I ® Q ® A	NR*	NR*
1981	Hanaoka	(±)-Ibogamine (**81**)	Q ® I ® A	17	3.9
1985	Kuehne	(±)-Ibogamine (**81**)	I/Q ® A	10	2.6
1985	Raucher	(±)-Catharanthine (**7**)	Q ® I ® A	11	9.0

1991	Herdeis	(±)-Ibogamine (**81**)	Q ® I ® A	8	14
1996	Grieco	(±)-Ibogamine (**81**)	I ® Q ® A	9	7.0
1999	Fukuyama	(±)-Catharanthine (**7**)	Q ® I ® A	17	6.0
2000	White	(–)-Ibogamine (**81**)	A ® Q ® I	15	4.6
2001	Kuehne	(–)-Coronaridine (**4**)	I ® Q/A	10	NR
2005	Hodgson	(+)-Ibogamine (**81**)	Q ® I ® A	11	2.0
2006	Borschberg	(–)-19-hydroxyibogamine	Q ® I ® A	20	1.9
2012	Sinha	(±)-Ibogaine (**1**) (±)-Ibogamine (**81**)	Q ® I ® A	9 9	9.4 5.6
2012	Takayama	(–)-Voacangalactone (**169**)	Q ® I ® A	25	3.2
2014	Oguri	(–)-Catharanthine (**7**)	I ® Q/A	10	2.8
2015	Sames	(±)-Ibogamine (**81**)	® I ® A	9	7.3
2016	Luo	(+)-Ibogamine (**81**)	I ® Q/A	12	4.2
2016	She	(±)-Ibogaine (**1**) (±)-Ibogamine (**81**) (±)-Tabertinggine (**25**) (±)-**37** (±)-**51** (±)-Iboluteine (**177**) (±)-Ervaoffines D (**49**)	I ® Q/A	12 12 10 13 13 14 14	4.6 6.0 41 3.2 4.3 3.9 2.9

Table 1.2. Total syntheses of iboga alkaloids. The order in which the indole (I), isoquinuclidine (Q), and tetrahydroazepine (A) rings were formed is indicated. A " / " indicates that two ring systems were formed in the same step. NR = not reported (i.e., not enough information was provided to calculate an overall yield or determine step count). *Trost synthesized (+)-ibogamine from an intermediate in 4 steps

(17% yield). However, the synthesis of this intermediate from simpler precursors was not detailed, and thus, we cannot provide an overall step count and yield for the Trost synthesis.

Chapter 1.3 Biological activity of ibogaine

The anti-addictive properties of ibogaine have been known since the 1960s, though this initial information was based entirely on anecdotal reports from heroin users. Since that time, several open-label and/or retrospective studies have suggested that ibogaine might be useful for treating substance use disorder (SUD) as it appears to reduce drug cravings, decrease symptoms of withdrawal, and prevent relapse.[86,87,88,89,90] Moreover, rodent studies have confirmed the anti-addictive potential of ibogaine by demonstrating the natural product reduces drug self-administration, prevents drug-induced dopamine release in several brain regions, attenuates drug-induced conditioned place preference, and decreases signs of withdrawal.[91,92,93] However, double-blind, placebo-controlled clinical trials firmly establishing the efficacy of ibogaine are still lacking. It is illegal to possess ibogaine in the United States, as it is classified as a schedule I drug. As a result, many people have sought treatment from informal clinics in countries

86. Sheppard, S. G. A preliminary investigation of ibogaine: case reports and recommendations for further study. J. Subst. Abuse Treat., 1994, 11, 379–385.
87. Alper, K. R.; Lotsof, H. S.; Frenken, G. M.; Luciano, D. J.; Bastiaans, J. Treatment of acute opioid withdrawal with ibogaine. Am. J. Addict., 1999, 8, 234–242.
88. Schenberg, E. E.; Comis, M. A. D. C.; Chaves, B. R.; Silveira, D. X. D. Treating Drug Dependence with the Aid of Ibogaine: A Retrospective Study. J. Psychopharmacol., 2014, 28, 993–1000.
89. Mash, D. C.; Duque, L.; Page, B.; Allen-Ferdinand, K. Ibogaine Detoxification Transitions Opioid and Cocaine Abusers Between Dependence and Abstinence: Clinical Observations and Treatment Outcomes. Front. Pharmacol., 2018, 9:529.
90. Mash, D. C.; Kovera, C. A.; Pablo, J.; Tyndale, R. F.; Ervin, F. D.; Williams, I. C.; Singleton, E. G.; Mayor, M. Ibogaine: Complex Pharmacokinetics, Concerns for Safety, and Preliminary Efficacy Measures. Ann N Y Acad. Sci., 2000, 914, 394–401.
91. Cappendijk, S. L.; Dzoljic, M. R. Inhibitory Effects of Ibogaine on Cocaine Self-Administration in Rats. Eur. J. Pharmacol., 1993, 241(2-3), 261–265.
92. Maisonneuve, I. M.; Keller, R. W.; Glick, S. D. Interactions between Ibogaine, a Potential Anti-Addictive Agent, and Morphine: An in Vivo Microdialysis Study. Eur. J. Pharmacol., 1991, 199, 35−42.
93. Parker, L. A.; Siegel, S. Chapter 11 Modulation of the Effects of Rewarding Drugs by Ibogaine. The Alkaloids: Chemistry and Biology, 2001, 211–225.

where ibogaine is not regulated.[94] For information on the history and pharmacology of ibogaine, we point the reader to several excellent reviews on these subjects.[95,96,97,98]

Despite ibogaine's promising therapeutic efficacy, major safety concerns have tempered excitement for its clinical development. First and foremost, ibogaine is known to cause long-lasting hallucinations,[97] and at very high doses it can lead to tremors and Purkinje cell death in rats.[99] However, its cardiotoxicity has been the biggest concern. Ibogaine inhibits hERG potassium channels in the heart,[100,101] with several deaths being linked to its adverse effects on heart function.[102,103] Ibogaine is very nonpolar, as evidenced by the fact that it readily accumulates in adipose tissue,[104] and it is well known that hERG inhibition is a major liability for many non-polar, basic amines.[105] Previously, ibogaine was sold in France as a neurotherapeutic, however its adverse effects led to its removal from the market.[95] Since that time, a major goal for the field has been to identify ibogaine congeners with similar therapeutic efficacies, but improved safety profiles.

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94. Brown, T. K. Ibogaine in the treatment of substance dependence. Current Drug Abuse Reviews, 2013, 6, 3–16.
95. Wasko, M. J.; Witt-Enderby, P. A.; Surratt, C. K. DARK Classics in Chemical Neuroscience: Ibogaine. ACS Chem. Neurosci., 2018, 9, 2475–2483.
96. Maciulaitis, R.; Kontrimaviciute, V.; Bressolle, F. M.; Briedis, V. Ibogaine, an anti-addictive drug: pharmacology and time to go further in development. A narrative review. Hum. Exp. Toxicol., 2008, 27, 181–94.
97. Alper, K. R. Ibogaine: a review. Alkaloids Chem Biol., 2001, 56, 1–38.
98. Popik, P.; Layer, R. T.; Skolnick, P. 100 Years of Ibogaine: Neurochemical and Pharmacological Actions of a Putative Anti-Addictive Drug. Pharmacol. Rev., 1995, 47, 235−253.
99. Ohearn, E.; Molliver, M. Degeneration of Purkinje Cells in Parasagittal Zones of the Cerebellar Vermis after Treatment with Ibogaine or Harmaline. Neuroscience, 1993, 55, 303–310.
100. Koenig, X.; Kovar, M.; Boehm, S.; Sandtner, W.; Hilber, K. Anti-Addiction Drug Ibogaine Inhibits HERG Channels: A Cardiac Arrhythmia Risk. Addict. Biol., 2014, 19, 237−239.
101. Thurner, P.; Stary-Weinzinger, A.; Gafar, H.; Gawali, V. S.; Kudlacek, O.; Zezula, J.; Hilber, K.; Boehm, S.; Sandtner, W.; Koenig, X. Mechanism of HERG Channel Block by the Psychoactive Indole Alkaloid Ibogaine. J. Pharmacol. Exp. Ther., 2014, 348, 346−358.
102. Alper, K. R.; Stajic, M.; Gill, J. R. Fatalities Temporally Associated with the Ingestion of Ibogaine. J. Forensic Sci., 2012, 57, 398−412.
103. Koenig, X.; Hilber, K. The Anti-Addiction Drug Ibogaine and the Heart: A Delicate Relation. Molecules, 2015, 20, 2208− 2228.
104. Hough, L. B.; Pearl, S. M.; Glick, S. D. Tissue Distribution of Ibogaine after Intraperitoneal and Subcutaneous Administration. Life Sci., 1996, 58, 119−122.
105. Jamieson, C.; Moir, E. M.; Rankovic, Z.; Wishart, G. Medicinal chemistry of hERG optimizations: Highlights and hang-ups. J. Med. Chem., 2006, 49, 5029–5046.

Chapter 1.4 Conclusion

A number of advances have been made in the past 10 years regarding iboga chemistry and biology. We now know how the antipodal series of these alkaloids are generated from a common achiral precursor, and biomimetic approaches are enabling the rapid synthesis of several iboga family members. Furthermore, new clues have emerged regarding how iboga alkaloids might produce long-lasting neurotherapeutic effects. However, there are still a number of chemical and biological challenges that need to be addressed if we are to rationally engineer safe and effective medicines for treating neuropsychiatric disorders based on the iboga core structure.

Chapter 2. Intramolecular Diels-Alder Reaction Route towards Ibogaine

Chapter 2.1. Retrosynthesis

While there have been numerous approaches to ibogamine (desmethoxy-ibogaine), catharanthine, and other related iboga alkaloids since their discoveries, there have only been four total syntheses of ibogaine[1,2,3] [4] published to date. With the exception of a patent application,[5] no total syntheses of noribogaine have been reported. Chronologically, the previous syntheses of ibogaine were accomplished in 15, 14, 9 and 12 steps with overall yields of 0.14%, <1%, 3.37%, and 4.81%, respectively. While pioneering at the time, each of these approaches is racemic and suffers from high step count, low yields, and limited modularity. The vast majority of approaches towards iboga alkaloids (including all three ibogaine syntheses) have focused on late-stage formation of the C2–C16 bond as the key step in the synthesis (**Figure 2-1**).

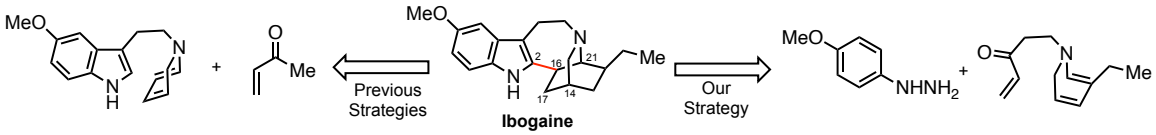

Figure 2-1. Retrosynthetic analysis of the iboga scaffold.

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1. Büchi, G.; Coffen, D. L.; Kocsis, K.; Sonnet, P. E.; Ziegler, F. E. The Total Synthesis of Iboga Alkaloids., *J. Am. Chem. Soc.*, **1966**, *88*, 3099–3109.
2. Jana, G. K.; Sinha, S. Total Synthesis of Ibogaine, Epiibogaine and Their Analogues. *Tetrahedron*, **2012**, *68*, 7155–7165.
3. Zhao, G.; Xie, X.; Sun, H.; Yuan, Z.; Zhong, Z.; Tang, S.; She, X. Bioinspired Collective Syntheses of Iboga-Type Indole Alkaloids. *Org. Lett.*, **2016**, *18*, 2447–2450.
4. Rosenmund, P.; Haase, W. H.; Bauer, J.; Frische, R. Synthesen in der Iboga-Reihe, III. Ibogamin, Ibogain und Epiibogamin. *Chem. Ber*. **1975**, *108*, 1871-1895.
5. Moriarty, R. M.; Mash, D. C. "Stereoselective total synthesis of noribogaine." U.S. Patent No. 9,403,837. 2 Aug. 2016.

Unfortunately, this bond has proven challenging to forge, often resulting in low yields with unpredictable results depending on substitution of the indole. Moreover, this approach demands the pre-functionalization of the indole prior to C2–C16 bond formation. For example, in Sinha's[2] synthesis of ibogaine, he prepared a C-2 iodide substituted indole, an unstable molecule prone to decomposition (**Figure 2-2**). This unstable intermediate was then subjected to a reductive Heck in order to couple C2 and C16 by heating to over 100°C. They only got around 50% yield, about half of the material that underwent 13 steps to prepare was lost. Poor yields in the finishing steps present a huge problem in terms of scalability. Additionally, this lack of late-stage functionalization potential is not ideal for the generation of analogs with different substituted indoles. Therefore, we need a strategy that deviates from the traditional routes used to make these molecules, avoiding the troublesome C2–C16 bond formation altogether. Instead of introducing substituted indole at the early stage of the total synthesis, we want to utilize the powerful Fischer indole synthesis reaction to form the aromatic indole ring, which would not only solve the problem mentioned above, but also allows us to access a large number of analogs from a single late-stage intermediate. Since it is known that the aromatic portion of iboga compounds is critical for determining the plasticity-promoting and hallucinogenic properties of these compounds, such a strategy will greatly facilitate the identification of efficacious congeners.

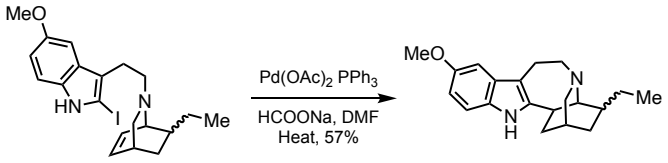

Figure 2-2. C2–C16 connection via harsh reaction condition.

Discovered in 1883 by Emil Fischer[6], the Fischer indole synthesis reaction could form various substituted indole by mixing of substituted phenylhydrazine with aldehyde or ketone under acidic conditions. Its well-studied mechanism could be summarized as the initially formed phenylhydrazone between phenylhydrazine and aldehyde or ketone isomerizes to the respective enamine . After protonation, a cyclic [3,3]-sigmatropic rearrangement occurs to produce an imine. The resulting imine forms a cyclic aminoacetal (or aminal), which under acid catalysis eliminates NH_3, resulting in the energetically favorable aromatic indole[7] (**Figure 2-3**).

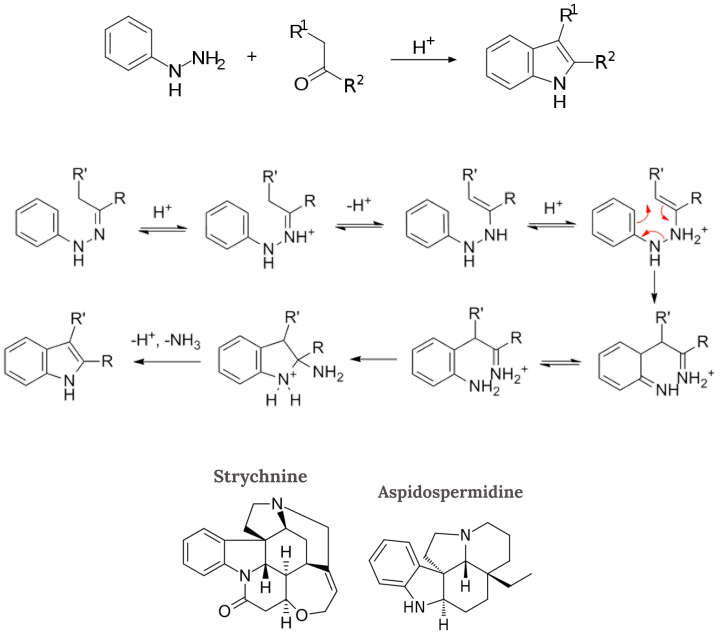

Figure 2-3. Fischer indole synthesis, mechanism and application in total synthesis.

6. Fischer, E.; Jourdan, F. (1883). "Ueber die Hydrazine der Brenztraubensäure". *Berichte der Deutschen Chemischen Gesellschaft*. **16** (2): 2241–2245.

7. Alen, C. F. H.; Wilson, C. V. (1943). "The Use of N15 as a Tracer Element in Chemical Reactions. The Mechanism of the Fischer Indole Synthesis". *J. Am. Chem. Soc.* **1943**, 65, 4, 611–612

After more than one hundred years, although other novel indole formation reactions have been developed[8], the Fischer indole reaction is still considered as the most well-established and practical strategy in terms of relatively milder reaction condition and functional group tolerance. Thus, there are significant numbers of indole alkaloid synthesis in the literature that utilize this method to build indole moieties such as Strychnine and Aspidospermidine (**Figure 2-3**)[9]. In addition, the large library of readily available and cheap substituted phenylhydrazines provides another huge advantage to this method.

With that proposal in mind, the iboga scaffold could be disassembled into two fragments, substituted phenlyhydrazine, which is cheap and commercially available, and to the key intermediate **1**, in which the ketone will provide the functional moiety needed for the transformation (**Figure 2-4**).

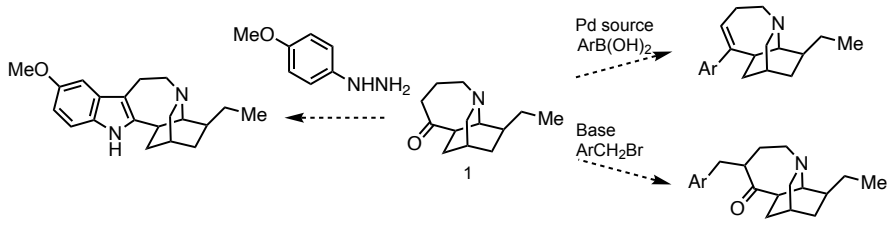

Figure 2-4 Late-stage diversification is enabled by accessing ketione 1.

To our knowledge, there's only one application using a similar strategy for iboga alkaloid synthesis. In 2000, White and co-workers installed the indole at a late-stage through a Fischer indole cyclization to afford ibogamine precursor in 66% yield over two steps and was then eventually converted to ibogamine (**Figure 2-5**)[10]. However, their synthesis suffered from an apparent shortcoming; the protected ketone was

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8 Douglass F. Taber and Pavan K. Tirunahari. Indole synthesis: a review and proposed classification.

Tetrahedron. **2011**, 67, 7195–7210.

9 Heravi, M.; Rohani, S.; Zadsirjan, V.; Zahedi, N. Fischer indole synthesis applied to the total synthesis of natural products. ***RSC Adv.***, **2017**,**7**, 52852-52887

10 White, J. D.; Choi, Y. Catalyzed Asymmetric Diels−Alder Reaction of Benzoquinone. Total Synthesis of (−)-Ibogamine. *Org. Lett.*, **2000**, 2, 2373–2376.

prepared through 14 linear steps in poor total yield. As we are looking for a robust route that has the potential to make iboga analogs in large scale from one intermediate, we need a better strategy to construct the tetrahydroazepine and bicyclic-isoquinuclidine ring system.

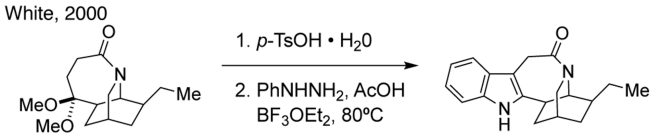


Figure 2-5 The White group application of Fischer indole reaction.

It turns out that the Diels-Alder reaction has proven to be quite effective to construct the C16–C21 and C17–C14 bonds of the tricyclic core; a strategy more akin to the proposed biosynthesis of these alkaloids (**Figure 2-1**).[11] Multiple groups have employed this strategy to construct the target ring system[12][13][14][15][16]. Most syntheses that have adopted this approach have opted to transform the electron-withdrawing substituent on the dienophile into the exo C20 ethyl group of the iboga alkaloids. This poses an obvious challenge given the inherent endo selectivity of most Diels-Alder reactions. To overcome this issue, Sames and co-workers took advantage of the acidic protons alpha to the carbonyl (**Figure 2-6**).[17] By treating a 3:1 endo:exo mixture of the Diels-Alder adducts with base, they achieved epimerization to a

11. Lavaud, C.; Massiot, G. The Iboga Alkaloids. *Prog. Chem. Org. Nat. Prod.*, **2017**, 105, 89–136.
12. Büchi, G.; Coffen, D. L.; Kocsis, K.; Sonnet, P. E.; Ziegler, F. E. The Total Synthesis of Iboga Alkaloids. *J. Am. Chem. Soc.*, **1966**, 88, 3099–3109.
13 Jana, G. K.; Sinha, S. Total Synthesis of Ibogaine, Epiibogaine and Their Analogues. *Tetrahedron*, **2012**, 68, 7155–7165.
14 Kruegel, A. C.; Rakshit, S.; Li, X.; Sames, D. Constructing Iboga Alkaloids via C–H Bond Functionalization: Examination of the Direct and Catalytic Union of Heteroarenes and Isoquinuclidine Alkenes. *J. Org. Chem*., **2015**, 80, 2062–2071.
15 Reding, M. T.; Fukuyama, T. Stereocontrolled Total Synthesis of (±)-Catharanthine via Radical-Mediated Indole Formation. *Org. Lett.*, **1999**, 1, 973–976.
16. Kim, S. J.; Batey, R. A. Enantioselective Isoquinuclidine Synthesis via Sequential Diels–Alder/Visible-Light Photoredox C–C Bond Cleavage: A Formal Synthesis of the Indole Alkaloid Catharanthine. *Org. Chem. Front***, 2018**, 5, 2934–2939
17 Jurcik, V.; Wilhelm, R. Imidazolinium salts as catalysts for the aza-Diels-Alder reaction. *Org. Biomol. Chem.*, **2005**, *3*, 239-244.

thermodynamic ratio (2:3) of endo:exo. After exo enrichment, conversion to the tosylhydrazones allowed for separation via crystallization. Fukuyama and co-workers sought to avoid endo/exo diastereoselectivity issues altogether by performing the Diels-Alder reaction with a symmetrical dienophile (**Figure 2-6**).[15,16] Treatment of trans-dibromide species with DABCO afforded the requisite dihydropyridine, which was then reacted with dimethyl methylenemalonate to give isoquinuclidine in 94% yield over two steps.

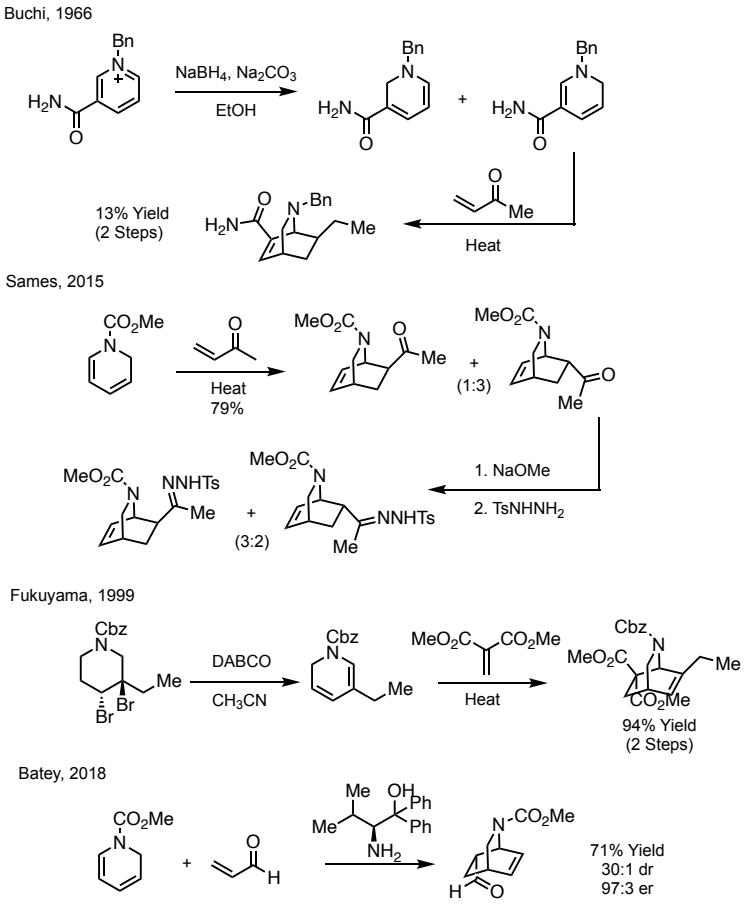


Figure 2-6. Cycloaddition approaches to the isoquinuclidine of iboga alkaloids.

In the approaches described above, the Diels-Alder reactions were uncatalyzed, leading to racemic mixtures of isoquinuclidines. Recently, Batey and co-workers reported an enantioselective Diels-Alder reaction of dihydropyridine with acrolein in the presence of a valine-derived organocatalyst (**Figure 2-6**),[17] leading to a formal synthesis of (+)-catharanthine.

After looking through different strategies, we believe that the most important step is to overcome the endo selectivity problem of the inter-molecular Diels-Alder reaction. An intramolecular Diels-Alder

reaction would solve the issue by providing the tetrahydroazepine and bicyclic isoquinuclidine scaffold without the hassle of dealing with endo-enriched mixtures. (**Figure 2-1**). The enone on the left side will not only provide better orbital overlap for the cycloaddition reaction, but also provide the functional group needed for the Fischer indole synthesis for later aromatic indole installation. Therefore, our synthetic strategy will focus on how to synthesize the enone- 1,2-dihydropyridine intermediate (**Figure 2-1**). In terms of this strategy, one pioneering work was carried out in 1978 by Fowler and coworkers[18], they carried out an intramolecular Diels-Alder reaction between the 1,2-dihydropyridne and terminal alkene in gas phase (**Figure 2-7**). To their surprise, no desired product was found except complex mixtures. We believe there is a need for an electron-withdrawing group next to the alkene to facilitate better orbital overlap. Furthermore, by carrying out the reaction in a favorable solvent and with the help of a Lewis acid, it's likely that the transformation could be achieved.[19]

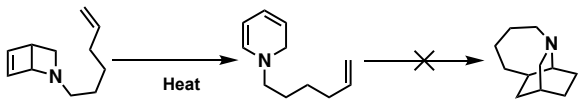


Figure 2-7. Fowler's attempt for intramoleucular Diels-Alder reaction.

Since we can now visualize the desired intermediate needed for the intramolecular Diels Alder, we came up with a complete retrosynthetic analysis (**Figure 2-8**). As deciphered earlier, the aromatic motif could be installed by Fischer indole synthesis; the tetrahydroazepine and bicyclic isoquinuclidine scaffold **2-4** could be prepared from an intramolecular Diels-Alder reaction between the enone and 1,2-dihydropyridine. The preparation of the 1,2-dihydropyridine could be done by reduction of the related

[18] Hasan, I. Fowler, F. W. Thermal rearrangements of 1,2-dihydropyridines. *J. Am. Chem. Soc*. **1978**, 100, 21, 6696–6699.

[19] Fringuelli, F; Girotti, F. Pizzo, L. Vaccaro.A New and Efficient Catalytic System for Diels-Alder Cycloaddition of α,β-Unsaturated Carbonyl Compounds under Solvent-Free Conditions. *Org. Lett.*, **2006**, *8*, 2487-2489.

pyridinium salt, which could be prepared by alkylation reaction between substituted pyridine **2-2** and enone bromide **2-1**.

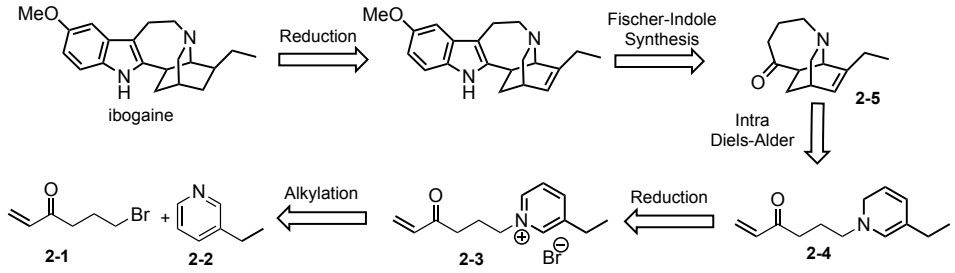


Figure 2-8. Intramolecular Diels-Alder reaction route towards ibogaine

Chapter 2.2. Synthesis

In order to further simplify the synthesis, we began our synthesis with a model substrate, desethylibogaine. There are two reasons for this: desethylibogaine can be obtained from cheap pyridine, plus it is also an analog that we are interested to prepare for biological studies. In theory ibogaine could be prepared easily using the same strategy with ethyl substituted pyridine as the starting material.

First, we attempted to synthesize the enone bromide **2-1** according to the reported reaction in the literature (**Figure 2-9**).[20] While it's known chemistry with a modest yield of 78%, the lack of details prompted us to reinvestigate and optimize the reaction. Our initial trial only afforded 30%, an unacceptable yield on the first step of the route that would dramatically downgrade our total synthesis. Its mechanism is pretty clear, an acryl cation was formed by reaction of the acyl chloride with $AlCl_3$, which being a great electrophile, then reacted with vinylsilanes to form the β-carbocation which eventually hydrolyzed during workup to afford final product enone **2-1**. After carefully carrying out this reaction at low temperature (-40 °C with dry ice/ acetonitrile cooling bath) and adding vinyltrimethylsilane dropwise,

[20] Bajgrowicz, J. A., Hallaoui, El.; Jacquier, R.; Pigiere, C.; Viallefont, P. Organocuprates in a novel synthesis of optically pure amino acids. *Tetrahedron.* **1985**,10, 1833

the yield could be improved to 65%. It is worth noting that the enone bromide product would eventually decompose even stored in freezer (-20°C), which could be because of formation of cyclopropane or an intermolecular addition reaction where one enolate added to another enone.

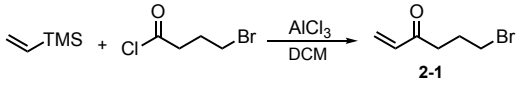


Figure 2-9. Preparation of the enone bromide **2-1**.

With the enone bromide **2-1** in hand, we only need to run the alkylation reaction with pyridine, followed by reduction of the pyridinium, to obtain the intermediate **2-4** needed to effect the intramolecular Diels-Alder reaction. However, after multiple efforts, we only obtained complex mixtures (**Figure 2-10**). Attempts were made to change the order of addition of these reagents, but nothing gave the desired product. Based on LCMS and NMR data, it was determined that the pyridine could not only react with the bromide carbon, forming the desired pyridinium salt, but also could add to the enone, forming an undesired pyridinium as well. It makes sense since the α, β-unsaturated enone itself is a good Michael addition acceptor that could undergo 1,4-addition. With the hope that there should be reactivity difference between the bromide carbon and the enone, we attempted to selectively alkylate the bromide carbon while leaving the enone intact. There were several options to consider: 1) Control the equivalents of pyridine so it could add to one side. 2) Lower the concentration to run the reaction in solvents that favor S_N2 type reaction. 3) Lower the reaction temperature in the hope that the activation energy difference could favor the alkylation. To our disappointment, no matter how many equivalents of pyridine (one or fewer), or in polar aprotic solvent like acetone, or run at low temperature, we only observed complex mixtures. Selective alkylation was extremely challenging in this case probably because of the electrophilic nature of the α, β-unsaturated system[21]. However, since the 1,4- addition product was quite reversible

[21] Oare, D. C.; Heathcock, C. H. Conjugate Addition: "Stereochemistry of the Base-promoted Michael Addition Reaction Top. *Stereochem.* **1989**, 19, 227.

compared to the direct alkylation, we imagined that maybe the enone could be re-generated under basic conditions. Unfortunately, these attempts proved unfruitful even after different bases were tested.

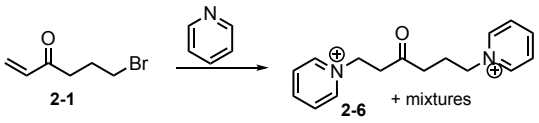


Figure 2-10. Reaction between the enone bromide and pyridine.

To overcome the selectivity issue, the easiest way is to protect the enone **2-1**, therefore it's not electrophilic under the reaction conditions discussed above. Although protection/ deprotection would increase the step count and lower the efficiency of the route, we decided to test it out. The reason behind it was that we would come back to resolve this challenging selectivity issue if the subsequent transformations could be achieved.

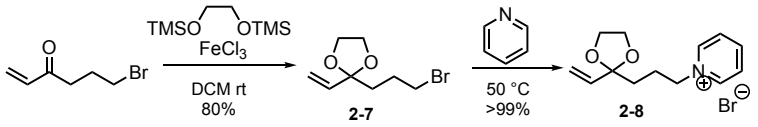


Figure 2-11. Protection of the enone bromide **2-1** fragment.

The most common protecting group for aldehydes and ketones is the ethylene ketal (1,3-dioxolane derivative), which could be easily prepared from the carbonyl compound and ethylene glycol in the presence of either Brønsted acid or lewis acid catalysts. We tested both conditions, one reflux under TsOH/ ethylene glycol condition[22], the other one at room temperature with bis(trimethylsiloxy)ethane/ $FeCl_3$ condition (**Figure 2-11**).[23] We found the latter gave 80% yield while the first only afford 30% with a large amount of unreacted starting material remaining. This poses an enormous issue because the SM

[22] Daignault, R. A.; Eliel, E. L. Preparation of ketals. A reaction mechanism. *Org. Synth*. **1973**, 5, 303.
[23] Tsunoda, T.; Suzuki, M.; Noyori, R. A facile procedure for acetalization under aprotic conditions *Tetrahedron Lett.* **1980**, 21,1357.

and product coelute. The lack of starting material at the end of the Lewis acid catalyzed reaction simplified the purification, a short silica plug could easily purify a 300 mg scale reaction. In addition, the protected product was much more stable than the starting material and wouldn't decompose even after long periods of time, which could be an alternative way to store the unstable enone **2-1**.

Without the hassle of electrophilic enone, the alkylation reaction went smoothly. After treating the ketal with excessive pyridine with mild heating, the alkylation finished in 1 hour with quantitative yield (**Figure 2-11**). Since the pyridinium product **2-8** is not soluble in hexanes, it could be conveniently purified by triturating with hexanes, during which process the excessive pyridine was washed away.

After obtaining the alkylation product **2-8**, it was time to focus on the reduction and intramolecular cycloaddition to achieve the desired tetrahydroazepine/ isoquinuclidine scaffold **2-9**, which should only take two steps. In fact, we envisioned that once the 1,2-dihydropyridine was formed, the cycloaddition probably could happen spontaneously, finishing the two steps synthesis in one pot (**Figure 2-12**).

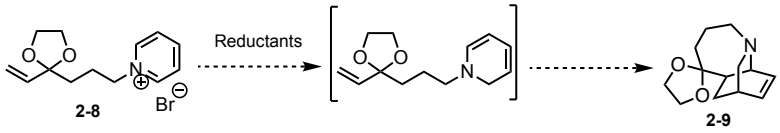


Figure 2-12. Preparation of 1,2-dihydropyridine and following cycloaddition.

Spontaneous Diels-Alder reactions with in-situ generated diene or dienophile could be found in literature with ease.[24] For example, Magnus and colleagues discovered a novel approach for the annulation of indole system by running an intramolecular Diels-Alder reaction with an in-situ generated dienophile (**Figure 2-13**).[22]

[24] Gallagher, T.; Magnus, P. New methods for alkaloid synthesis : Generation of indole-2, 3-diquinomethanes as a route to indole alkaloids. *Tetrahedron.* **1981**, 37, 3889– 3897

Figure 2-13. Example of one-pot cycloaddition with in-situ generated dienophile.

The only concern here is due to the protection, the ketal isn't as good of an electron-withdrawing group as the unprotected ketone thus the following cycloaddition could be challenging since it's lacking orbital overlap between the HOMO and LUMO counterpart. Even if that's the case, there should be plenty of ways to achieve this goal, such as utilizing a Lewis acid to lower the LUMO or simply applying enough heat to allow the molecule to overcome the activation energy barrier. Thus, investigating this strategy could be worth the time and energy.

Due to the electrophilic character, pyridinium salts could be reduced by multiple reducing reagents, such as metals (Na, Li, Zn), a hydride like $NaBH_4$, silanes, and classic precious metals with hydrogen.[25] For our reaction, hydrides are good options considering their mild reaction conditions and low toxicity. By treating the pyridinium salt with $NaBH_4$ in MeOH at low temperature (ice/ water bath), the only product we observed was the over-reduced product tetrahydropyridine **2-10** (**Figure 2-14**). Other hydride sources ($NaCNBH_3$, $NaB(OAc)_3H$, $LiBH_4$, or dimethylphenylsilane) as well as shortening the reaction time to two mins, but unfortunately, the over-reduction product **2-10** was the only product observed.

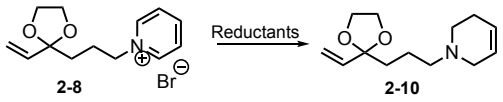


Figure 2-14. Over-reduction of pyridinium salt to afford tetrahydropyridine.

[25] Sowmlah, S.; Esperanca, J.S.S.; Rebelo, L.P.N.; Afonso, C.A.M.. Pyridinium salts: from synthesis to reactivity and applications. *Org. Chem. Front.*, **2018**,5, 453-493

To rationalize this, we believe what happened was after the initial addition of the hydride, the 1,2-dihydropyridine underwent fast solvent-assisted tautomerization to form iminium species **2-11**. **2-11** was then further reduced by the excess hydride. Since the iminium intermediate had a higher reduction potential than the pyridinium counterpart, it was easier to react with the hydride, therefore only 1,4-dihydropyridine by-product could be observed (**Figure 2-15**). A sodium borohydride reduction mechanism study done by Lyle and coworkers in 1965 also supported our proposal.[26]

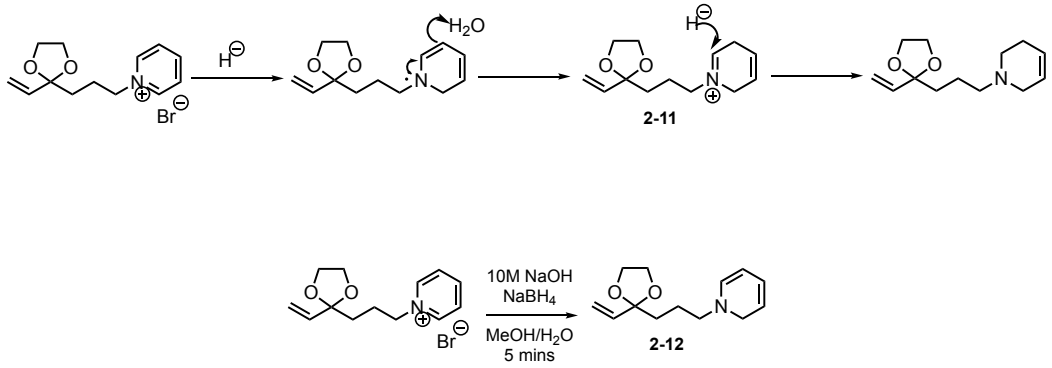


Figure 2-15. Mechanism for the over-reduction reaction.

After figuring out the over-reduction mechanism, to prevent that from happening, we need to prevent the tautomerization process. Considering that pH plays a very important role in enamine-imine tautomerization, at high pH the shortage of a proton source to form the iminium species will force the equilibrium to favor the enamine side. That means that if we run this reaction at high pH solution, then in theory we could capture the 1,2-dihydropyridine intermediate **2-12** and probably the desired intramolecular cycloaddition would occur immediately afterwards.

[26] Anderson, P. S.; Krueger, W. E.; Lyle, R. E. Mechanism of sodium borohydride reduction of pyridinium ions. III. Formation of piperidines. *Tetrahedron Lett*. **1965**, 4011-4017.

With that proposal in mind, we ran the reduction in a 10M NaOH/MeOH solution (**Figure 2-15**). To our delight, after a quick work-up, we finally observed the alkene peaks belonging to the 1,2-dihydropyridine **2-12** in crude NMR (**Figure 2-16**). Although the desired subsequent cycloaddition did not occur at that point, we believed that through careful reaction conditions manipulation, the cycloaddition could be accomplished eventually.

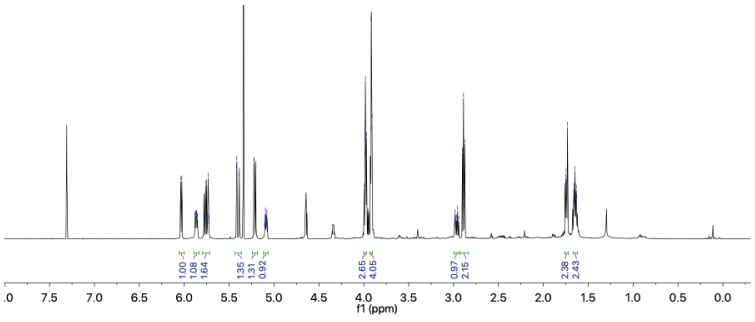


Figure 2-16. Proton NMR spectrum of the 1,2-dihydropyridine.

Before testing the cycloaddition reaction, we tried to purify the 1,2-dihydropyridine intermediate in order to have a better idea of its physical and chemical properties. Despite various purification attempts such as column chromatography or crystallization by forming the pyridinium salt, we couldn't get any pure compound out of the crude mixture. It's apparent that the DHP **2-12** undergoes fast decomposition or other undesired side reactions instead of cycloaddition. While it's not surprising that the 1,2-dihydropyridne could be oxidized by air to restore its thermodynamically more stable aromaticity, it could also form dimers by intermolecular cycloaddition, depending on the substitution pattern of the pyridine ring according to literature.[27]

Next, we eventually decided to investigate the intramolecular Diels-Alder reaction with the crude product due to its highly unstable nature. As mentioned above, this transformation could potentially be

[27] Liberatore, F.; Casini, A.; Carelli, V. Borohydride reduction of pyridinium salts. V. Thermal dimerization of 1,6-dihydro-1-methylpyridine-2-carbonitrile. *J. Org. Chem*. **1975**, 559-563.

completed by either heating enough to overcome the activation energy barrier or by using a Lewis acid catalyst to lower the gap between HOMO/LUMO orbitals. Unfortunately, neither strategy worked in this case, even after testing out elevated temperature and a multitude of Lewis acids such as $AlCl_3$, $ZnCl_2$, MgI_2, TMSOTf, BF_3OEt_2 etc (**Figure 2-17**). Analysis of crude NMRs of these reactions showed that the dihydropyridne peaks disappeared completely, yet the terminal alkene remained which indicates the highly unstable 1,2-DHP isn't a suitable diene substrate for the desired reaction. Further investigation needs to be done to solve this issue.

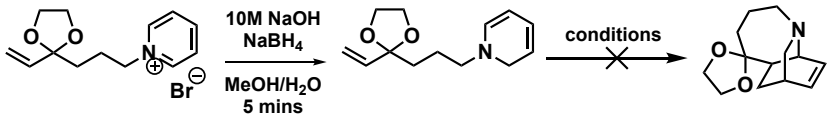
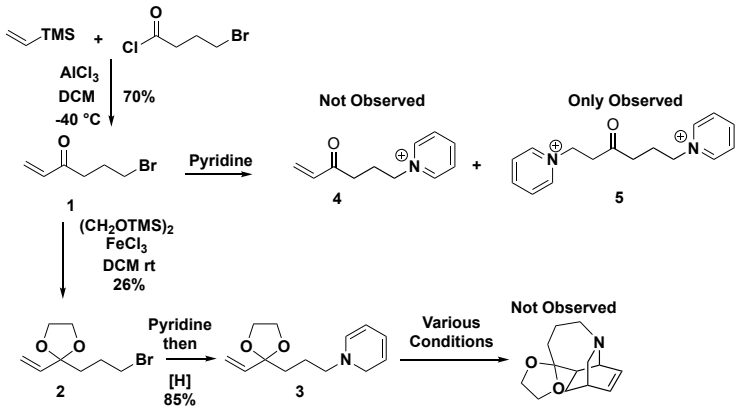


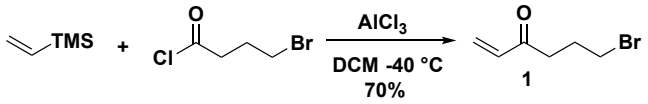
Figure 2-17. Preparation of 1,2-dihydropyridne and attempts for cycloaddition reaction.

Chapter 2.3. CONCLUSION

We have proposed an intramolecular Diels-Alder route to construct the unique tetrahydroazepine and bicyclic isoquinuclidine ring system of the iboga alkaloids. Although significant progress has been made towards the fulfillment of this plan, the key [4+2] cycloaddition reaction hasn't occurred due to the highly unstable nature of the 1,2-DHP motif. Further investigation needs to be done to solve this problem. If this problem is solved, a protecting-free strategy could then be implemented to streamline the synthesis.

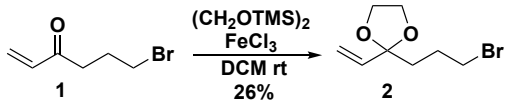
Chapter 2.4. Experimental Procedures and Spectral Data





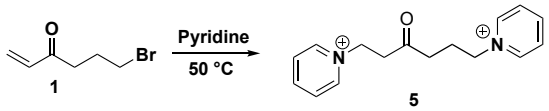
6-bromohex-1-en-3-one (1)

To a 100 ml round-bottomed flask containing 50 ml dry DCM under nitrogen was added $AlCl_3$ (785 mg, 5.9 mmol, 1.1 eq), cooled with acetonitrile/dry ice bath for 20 mins, then 4-bromobutanoyl chloride (0.63 ml, 5.4 mmol, 1eq) was added dropwise. After 20 mins vinyltrimethylsilane (0.63 ml, 5.9 mmol, 1.1 eq) was added dropwise. The reaction was kept under acetonitrile/dry ice bath for 2 hours. Quenched by addition of cold ice water (30 ml), and extracted with DCM (30 ml x 3). The combined organic extracts were washed with brine (20 ml), dried over anhydrous sodium sulfate and concentrated in vacuo. The resulting crude residue was purified by column chromatography (Ethyl acetate/hexane = 1:10) to give compound **1** (660 mg, 70%) as colorless liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.40 (ddd, *J* = 17.7, 10.5, 1.5 Hz, 1H), 6.29 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.90 (dd, *J* = 10.5, 1.0 Hz, 1H), 3.67 – 3.61 (m, 2H), 2.83 (td, *J* = 7.0, 1.5 Hz, 2H), 2.20 – 2.08 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.31, 136.43, 128.54, 37.41, 33.41, 26.52.



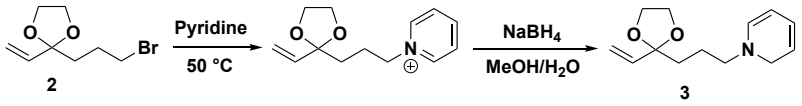
2-(3-bromopropyl)-2-vinyl-1,3-dioxolane (**2)**

To a round-bottomed flask containing 10 ml dry DCM was added vinyl bromide **1** (200 mg, 1.1 mmol, 1.1 eq) at room temperature. Then $(CH_2OTMS)_2$ (470 mg, 2.2 mmol, 2 eq) and $FeCl_3$ (20 mg 0.1 eq) were added separately. The reaction was kept at rt for 1 hours. Quenched by addition of sat. Na_2CO_3 solution (20 ml) and extracted with DCM (10 ml x 3). The combined organic extracts were washed with brine (20 ml), dried over anhydrous sodium sulfate and concentrated in vacuo. The resulting crude residue was purified by column chromatography (Ethyl acetate/hexane = 1:15) to give compound **1** (63 mg, 26%) as colorless liquid. 95 mg starting material **1** was recovered.^{1}H NMR (600 MHz, $CDCl_3$) δ 5.74 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.40 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.21 (dd, *J* = 10.6, 1.7 Hz, 1H), 4.00 – 3.96 (m, 2H), 3.93 – 3.89 (m, 2H), 3.47 (t, *J* = 6.8 Hz, 2H), 2.07 – 1.96 (m, 2H), 1.94 – 1.77 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.43, 115.85, 108.54, 64.62, 36.46, 33.98, 27.00.



1,1'-(3-oxohexane-1,6-diyl)bis(pyridin-1-ium) (**5)**

Pyridine (22 ul, 0.27 mmol) and of bromide **1**(44 mg, 0.25 mmol) were mixed in a 1 ml glass vial and heated to 50 degrees for 3 hours. The reaction mixture was washed with Ethyl ether and the insoluble glue was characterized to be double addition adduct. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.13 (ddd, *J* = 10.5, 6.6, 1.4 Hz, 4H), 8.63 (tdd, *J* = 7.7, 6.3, 1.4 Hz, 2H), 8.18 (dt, *J* = 7.6, 3.8 Hz, 4H), 4.80 (t, *J* = 6.5 Hz, 2H), 4.62 (t, *J* = 7.2 Hz, 2H), 3.38 – 3.33 (m, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.16 – 2.10 (m, 2H).



1-(3-(2-vinyl-1,3-dioxolan-2-yl)propyl)pyridin-1-ium (Ammonium salt from 2 reacting with pyridine)

60 mg of ketal protected enone **2** (0.27 mmol) was added to a 1ml glass vial. 0.03 ml (1 eq) dry pyridine was added and the mixture was heated to 50 degrees for 1hour. After cooling down to rt, the mixture was washed with ethyl ether, all the solution was removed with pipette and the insoluble product was dried under vacuum. 85 mg of yellow glue was obtained (105%). ^{1}H NMR (600 MHz, CD_3OD) δ 9.10 (d, *J* = 6.0 Hz, 2H), 8.71 – 8.62 (m, 1H), 8.19 (t, *J* = 7.0 Hz, 2H), 5.78 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.42 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.25 (dd, *J* = 10.6, 1.7 Hz, 1H), 4.77 (t, *J* = 7.5 Hz, 2H), 4.06 – 3.94 (m, 2H), 3.94 – 3.83 (m, 2H), 2.20 (p, *J* = 7.5 Hz, 2H), 1.85 – 1.80 (m, 2H).

1-(3-(2-vinyl-1,3-dioxolan-2-yl)propyl)-1,2-dihydropyridine (3)

To a round-bottomed flask containing 0.4 ml MeOH was add the ammonium salt prepared above (40 mg, 0.13 mmol, 1 eq). To another vial containing 0.2 ml 15M NaOH, $NaBH_4$ (2.5 mg 0.5 eq) was added. The methanol solution was transferred to NaOH solution and reacted for 1minute. Then the reaction solution was poured into a separatory funnel containing 1M NaOH (15 ml) and extracted with DCM (20 ml x2). The combined organic extracts were washed with brine (20 ml), dried over anhydrous sodium sulfate and concentrated in vacuo to give dihydropyridine **3** 24 mg (85%). The crude product was used immediately before it fully decomposed. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.03 (dd, *J* = 7.2, 1.0 Hz, 1H), 5.90 – 5.85 (m, 1H), 5.78 – 5.71 (m, 1H), 5.40 (dd, *J* = 17.2, 1.8 Hz, 1H), 5.21 (dd, *J* = 10.6, 1.8 Hz, 1H), 5.09 (dtt, *J* = 9.3, 4.0, 1.2 Hz, 1H), 4.02 – 3.97 (m, 3H), 3.91 (dd, *J* = 4.0, 1.3 Hz, 4H), 3.05 – 2.93 (m, 1H), 2.89 (t, *J* = 7.3 Hz, 2H), 1.80 – 1.69 (m, 2H), 1.69 – 1.58 (m, 2H)

Chapter 3. Intermolecular Diels-Alder Reactions Routes

Chapter 3.1. Retrosynthesis

Chapter 3.1.1. Ring-closing Metathesis Route.

While working on the intramolecular Diels-Alder route, we also explored other possibilities to construct the characteristic tetrahydroazepine and isoquinuclidine scaffold that most iboga alkaloids have in common. The biggest challenge was the preparation of the tetrahydroazepine, since seven-membered rings are known to be highly strained in the transition state, and also have high entropy of activation[1]. In order to achieve this goal, we need to brainstorm to effectively adapt strategies that would lead to the formation of this key ring.

A revolutionary method that came to mind while looking for different routes was Ring-Closing Metathesis (RCM). Since its development in 1980, significant progress has been made regarding the design catalysts, mechanism studies and applications, making it one of the most powerful reactions to construct complex ring systems[2] . Therefore, we hypothesize that the challenging tetrahydroazepine could be prepared by RCM by reaction between two terminal alkenes, followed by subsequent saturation of the alkene product; The terminal alkene could be obtained by either alkylating the free amine with allyl bromide or palladium-catalyzed allylic alkylation of allyl carbamates[3]. The isoquinuclidine motif could be made from

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[1] Casadei, M. A.; Galli, C.; Mandolini, L. Ring-closure reaction. 22. Kinetics of cyclization of diethyl malonates in the range of 4-21-membered rings. Role of ring strain. *J. Am. Chem. Soc.* **1984,** *106*, 1051-1056

[2] Deiters, A.; Martin, S. F. (2004). "Synthesis of Oxygen- and Nitrogen-Containing Heterocycles by Ring-Closing Metathesis". *Chem. Rev.* **104** (5): 2199-2238.

[3] Minami, I.; Ohashi, Y.; Shimizu, I.; Tsuji, J. Palladium-catalyzed reaction of allyl carbamates; allylation of carbonucleophiles, and protection-deprotection of amines. *Tetrahedron Lett*. **1985**, 2449-2452.

an intermolecular Diels-Alder reaction between an enone and a 1,2-dihydropyridine stabilized by the Cbz electron-withdrawing group (**Figure 3-1**).

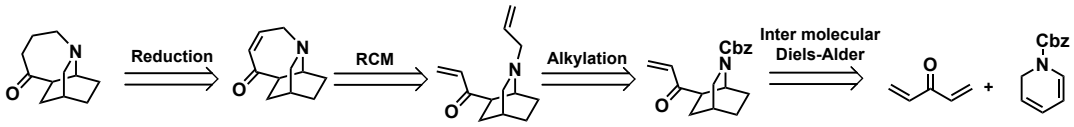


Figure 3-1. Retrosynthetic analysis for ring-closing metathesis route.

Chapter 3.1.2 Cyclopropane Opening Route.

Alternatively, the tetrahydroazepine could be obtained from an enone with cyclopropane that could provide the two carbons needed upon acid-catalyzed ring opening. Such molecule could be easily prepared in large scale by an aldol condensation between cyclopropyl methyl ketone and formaldehyde. The 1,2-dihydropyridine could be prepared by the method mentioned above (**Figure 3-2**).

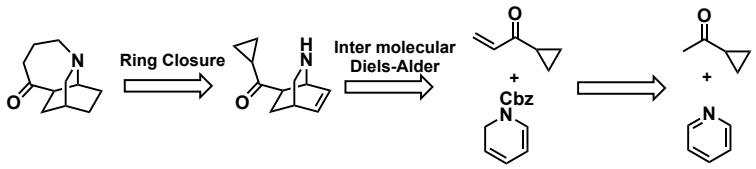


Figure 3-2. Retrosynthetic analysis for the cyclopropane opening route.

Chapter 3.2. Synthesis

Chapter 3.2.1 Attempts for RCM Route

First, we prepared the vinyl enone by treating acrolein with vinyl Grignard reagent in THF. Then, the resulting allylic alcohol product was oxidized with an excess of MnO_2 to achieve a 50% yield after 2 steps. An issue that arose was the volatility of the product, as this made it extremely difficult to handle and often led to contamination of equipment, therefore an alternative way to achieve our desired goal was explored (**Figure 3-3**).

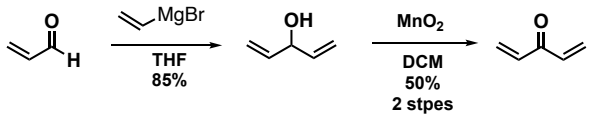


Figure 3-3. Preparation of enone for RCM route.

The solution could be to "mask" the enone as a Weinreb amide, which could be converted to the desired enone by reaction with vinyl Grignard reagent later. The synthesis was quite straightforward, by mixing acryloyl chloride and Weinreb amine under basic conditions, the Weinreb product could be collected in 92% yield. The 1,2- dihydropyridine was prepared by treating pyridine and benzyl chloroformate in ethanol with $NaBH_4$ as the reducing source in quantitative yield.

After obtaining the dienophile (enone) and diene (1,2- Cbz-protected dihydropyridine), we immediately started investigating the intermolecular-Diels Alder reaction to construct the isoquinuclidine scaffold. What we found out was that the reaction could not happen at relatively low temperature (<100 ^{o}C), which makes sense since the Weinreb enone isn't a good dienophile due to the lack of electron-withdrawing group to lower the energy gap between HOMO/LUMO. In order to effect this transformation, we had two options, either try to use Lewis acid additives or heat the mixture at elevated temperatures. To our delight, when reaction mixture is heated to 180 ^{o}C, the desired cycloaddition product could be collected as an exo/endo mixture with roughly 1:2 ratio after purification in modest yields (**Figure 3-4**).

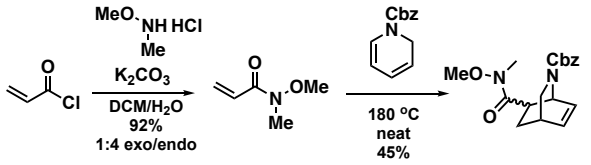


Figure 3-4. Preparation of isoquinuclidine for RCM route.

With the targeted isoquinuclidine in hand, what needed to be done prior to the ring-closing metathesis reaction is install the two terminal alkenes. Thus, we saturated the internal isoquinuclidine olefin with concomitant removal of the Cbz protecting group via hydrogenation, which afforded the free amine in 69% yield. Alkylating the free amine with allyl bromide using NaH as the base worked, but gave less than 30% yield. Although the alkylation yield isn't ideal, there's only one step to form the RCM reaction precursor, and if it does work, we could revisit and optimize the alkylation conditons later. Therefore, we prepared the two terminal alkene RCM precursor by treating the Weinreb amide with vinyl Grignard reagent in THF, leading to desired enone in 45% yield (**Figure 3-5**).

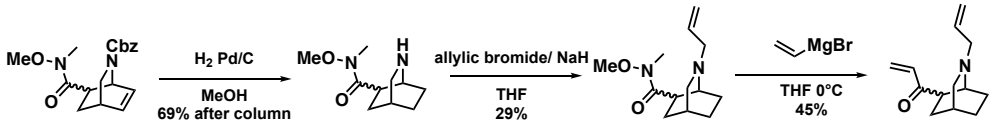


Figure 3-5. Preparation of precursor for the RCM route.

As the synthesis of the RCM precursor was completed, we became eager to determine if this key RCM reaction would happen to provide the critical tetrahydroazepine ring. The procedure we used was treating the RCM precursor with 1% Grubbs 2$_{nd}$ catalyst under different conditions. However, it turned out that when heating the mixture in DCM, no reaction happened, only led to recover of the starting material; When refluxing in Toluene, the precursor fell apart to produce complex mixtures without any desired product detected (**Figure 3-6**).

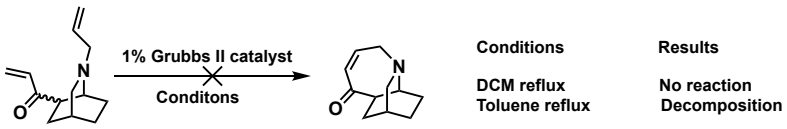


Figure 3-6. RCM reaction attempts.

The rationale for the unsuccessful results could be the basicity of the amine of the precursor, it's known that in precious metal catalyzed reactions, the lone pair of electrons of amines could coordinate to the metals therefore poison the catalysts, resulting in reaction failures. There are several strategies that have been developed to encounter the basic amine issue. One is to use superstoichiometric amounts of precious metal, meaning that although one equivalent of catalyst got sacrificed, there's still active catalyst around that could finish up the reaction. An alternative option is to protonate the amine molecule so it wouldn't coordinate the metal center; The third but not the least is to use amides as masked amines for catalytic reactions, then amines could be obtained by reduction of related amides[4]. Considering the expensive Ru-based catalyst and the vulnerability of the enone under acidic conditions, the non-coordinating amide seems more reasonable. Therefore, we prepared the amide precursor with reaction of between the previously reported free amine and acryloyl chloride. The key RCM reaction is still being actively investigated by our group and more details will be revealed in the near future (**Figure 3-7**).

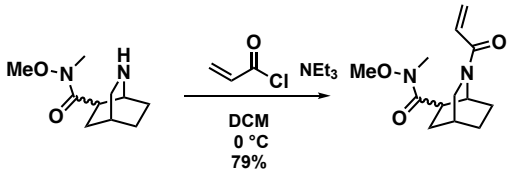


Figure 3-7. Preparation of amide RCM precursor.

[4] Woodward, C. P.; Spiccia, N. D.; Jackson, W. R.; Robinson, A. J. A simple amine protection strategy for olefinmetathesis reactions. *Chem. Commun*., **2011**,47, 779-781.

Chapter 3.2.2 Attempts for Cyclopropane Opening Route.

As discussed above, the two-carbons needed for the tetrayhydroazepine could come from a cyclopropane motif. We prepared the cyclopropane enone through a aldol condensation reaction between crylopropyl methyl ketone and formaldehyde. After screening different conditions, paraformaldehyde turned out to be the best methylene source, the desired enone was isolated in 75% yield after heating cyclopropyl methyl ketone and paraformaldehye in the presence of diisopropylethylamine TFA salt. When mixing the resulting cyclopropane enone with Cbz stabilized 1,2-dihydropyrinde, the intermolecular Diels-Alder reaction occurred at 50 °C due to the ketone's property of being a better dienophile, giving a mixture of 1:2 exo/endo isoquinuclidine product. Since the exo epimer is what is needed for the ring-closure reaction, we could shift the balance towards more exo epimer by taking advantage of the acidity of the proton next to the carbonyl group. Upon treating with base NaOMe, a new 1:1 mixture of the exo/endo was obtained. The following transformation involved removing the Cbz protecting group and saturating the alkene in one pot via hydrogenation, which afforded the cyclopropane free amine in quantitative yield (**Figure 3-8**).

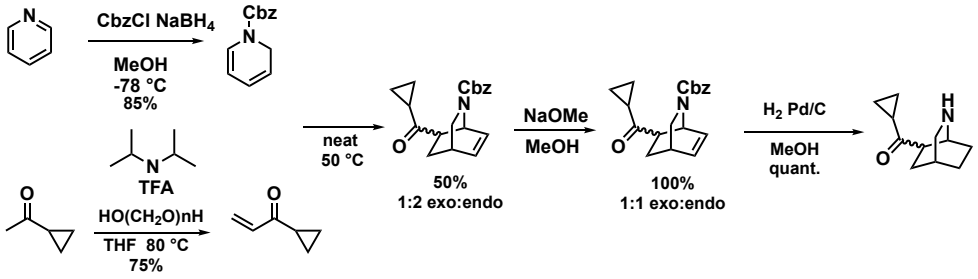


Figure 3-8. Preparation of cyclopropane-opening strategy precursor.

For the necessary the ring-closure, there are two options, either nitrogen attacking the cyclopropane carbon facilitated by Lewis acid that could activate the carbonyl group, or opening the cyclopropane first with some sort of nucleophile/ leaving group, then nitrogen attacking to finish the ring-closure. In theory, the first one would be more straightforward, yet the challenge here is the discriminating

selectivity between activating the carbonyl or coordinating the nitrogen. Therefore, we decided to test out the latter hypothesis first in order to prove the concept of the route. After treating the cyclopropane free amine with hydrogen bromide, a bromide salt formed in quantitative yield, leaving a bromide as a good leaving group. Various bases are currently tested to close the seven-membered ring (**Figure 3-9**).

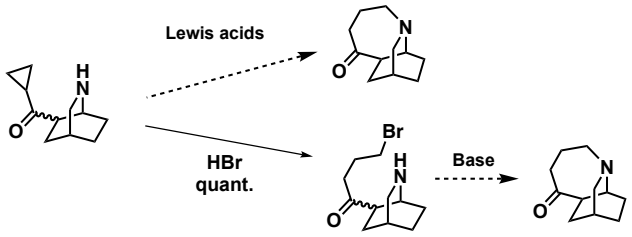


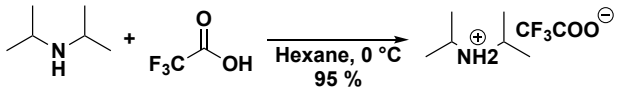
Figure 3-9. Options for ring-closure.

Chapter 3.3. Conclusion

Both ring-closing metathesis route and cyclopropane opening route have been carried out primarily to construct the tetrahydroazepine scaffold, which is one key feature shown in many iboga alkaloid natural products and more experiments are being conducted to finish them.

Chapter 3.4. Experimental Procedures and Spectral Data

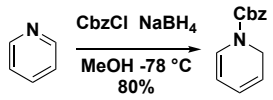
Intermolecular Diels-Alder route for synthesis of desethyl ibogaine



Diisopropylammonium 2,2,2-trifluoroacetate

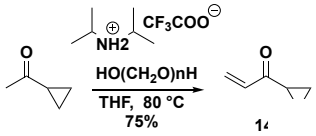
To a stirred mixture of diisopropylamine (100 mmol, 10.1 g) in hexane (100 mL) at 0 °C was added trifluoroacetic acid dropwise (100 mmol, 11.2 g). The reaction mixture was stirred at 0 °C for an additional 25 mins. The solid was filtered and washed with hexane (20 mL), dried under vacuum to afford pure

compound (20.23 g, 95%) as white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 – 8.82 (bs, 2H), 3.37 (hept, *J* = 6.4 Hz, 2H), 1.32 (d, *J* = 6.6 Hz, 12H).^{13}C NMR (101 MHz, $CDCl_3$) δ 161.54 (q, *J* = 35.2 Hz), 116.52 (q, *J* = 292.7 Hz), 46.91, 18.76.



Cbz-Dihydropyridine

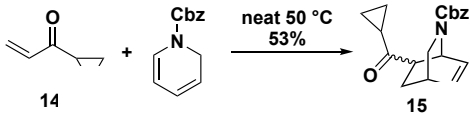
A solution of sodium borohydride (3.8 g, 100 mmol), pyridine (8 ml, 100 mmol) in anhydrous methanol (100 mL) under nitrogen was cooled to -78 degrees with a dry ice/acetone bath. Benzyl chloroformate (14 ml, 100 mmol) was added slowly. After addition, the reaction mixture was stirred at -78 degrees for 3 hours then the reaction mixture was poured into a flask with 100 ml of ice water. The mixture was extracted with hexane (3 x 150 mL). The hexane layers were separated and combined, washed with brine (100 mL), and then dried over sodium sulfate. The hexane solution was filtered and concentrated in vacuo. The crude residue was purified by column chromatography (Ethyl acetate/hexane = 1:5) to give desired product (17.2 g, 80%) as colorless liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 5H), 6.83 (d, *J* = 7.9 Hz, 0.5H), 6.74 (d, *J* = 7.9 Hz, 0.6H), 5.91 – 5.81 (m, 1H), 5.59 – 5.52 (m, 0.6H), 5.47 (dd, *J* = 9.4, 4.6 Hz, 0.5H), 5.23 (d, *J* = 1.9 Hz, 2H), 5.20 (d, *J* = 4.7 Hz, 0.3H), 5.18 – 5.08 (m, 0.7H), 4.42 (dd, *J* = 4.1, 2.1 Hz, 2H).



1-cyclopropylprop-2-en-1-one

Diisopropylammonium 2,2,2-trifluoroacetate (21.5 g, 100 mmol), paraformaldehy (7.5 g, 250 mmol) and cyclopropyl methyl ketone (9.4 ml, 100 mmol) were added to a sealed tube containing 100 ml THF. The

tube was sealed and heated to 80 degrees for 15 hours and then cooled down to rt. The reaction solution was poured into a separatory funnel containing about 300 ml water. Extracted with Ethyl ether, the combined organic extracts were washed with brine (20 ml), dried over anhydrous sodium sulfate and concentrated in vacuo (70 Torr at rt) to afford desired enone **14** (7.2 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (dd, *J* = 17.6, 10.5 Hz, 1H), 6.32 (d, *J* = 17.7 Hz, 1H), 5.86 (d, *J* = 10.5 Hz, 1H), 2.30 – 2.17 (m, 1H), 1.17 – 1.10 (m, 2H), 0.98 (dq, *J* = 7.5, 3.7 Hz, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 201.27, 136.53, 128.01, 18.34, 11.52.



14 15

Cycloaddition adduct

To a sealed tube was added 1-cyclopropylprop-2-en-1-one (3.8 g, 40 mmol) and freshly prepared Cbz-Dihydropyridine (8.6 g, 40 mmol). The tube was sealed and heated to 50 degrees for 12 hours. The crude product was purified by column chromatography (Ethyl acetate/hexane = 1:3) to give mixture 15 (6.1 g, 55%) as colorless liquid. The mixture was partially separated by using 3% EtOAc/DCM as eluent.

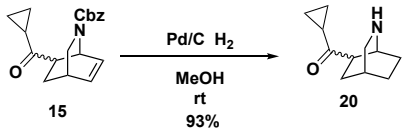
Product exo (complicated due to rotamer)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.30 (m, 5H), 6.56 (ddd, *J* = 7.8, 6.2, 1.5 Hz, 1H), 6.52 – 6.44 (m, 1H), 5.24 (dt, *J* = 6.2, 1.6 Hz, 0.7H), 5.09 (d, *J* = 7.2 Hz, 0.5H), 5.07 (s, 2H), 3.34 (ddd, *J* = 17.6, 10.1, 2.2 Hz, 1H), 3.00 (ddt, *J* = 12.7, 10.0, 2.8 Hz, 1H), 2.91 (ddd, *J* = 10.7, 4.2, 2.1 Hz, 1H), 2.82 (dd, *J* = 4.5, 2.1 Hz, 1H), 2.79 – 2.73 (m, 1H), 2.22 (dt, *J* = 12.8, 2.2 Hz, 1H), 2.11 – 2.06 (m, 1H), 2.01 – 1.94 (m, 1H), 1.47 – 1.35 (m, 1H), 1.09 – 0.79 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.33, 208.73, 155.23, 154.74, 137.03, 136.76, 135.50, 132.26, 131.86, 30.30, 30.12, 23.61, 23.49, 20.04, 19.74, 12.50, 11.36. LRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{21}NO_3$ 312, found 312.

Product endo (complicated due to rotamer)

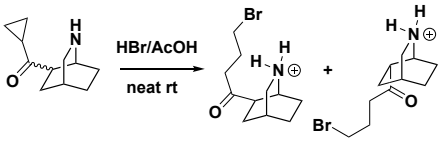
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 5H), 6.41 (ddd, *J* = 8.0, 6.6, 1.3 Hz, 1H), 6.30 (td, *J* = 6.2, 3.1 Hz, 1H), 5.35 – 5.28 (m, 0.6H), 5.19 (s, 0.7H), 5.16 (s, 1.6H), 3.47 – 3.20 (m, 2H), 3.05 (tt, *J* = 10.2, 2.5 Hz, 1H), 2.85 (d, *J* = 5.2 Hz, 1H), 2.08 (tt, *J* = 7.6, 4.7 Hz, 0.7H), 2.04 – 1.95 (m, 0.7H), 1.91 (dd, *J* = 8.4, 3.6 Hz, 1H), 1.75 (ddd, *J* = 12.5, 9.4, 2.5 Hz, 0.7H), 1.21 – 0.77 (m, 4H).^{13}C NMR (100 MHz, $CDCl_3$) δ 208.49, 155.26, 136.82, 134.91, 134.70, 130.41, 130.13, 128.48, 127.97, 127.90, 127.82, 66.92, 52.65, 52.29, 47.20, 46.99, 30.78, 30.54, 25.20, 24.26, 19.44, 19.26, 11.51, 11.21, 10.88, 10.64. LRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{21}NO_3$ 312, found 312.



15 20

2-azabicyclo[2.2.2]octan-6-yl)(cyclopropyl)methanone

To a solution of Cbz-protected starting material (550 mg, 1.7 mmol) in methanol (17 ml) was added 10% Pd/C (55 mg). The solution was sealed and bubbled by hydrogen for 1 minutes then kept reacting for 39 minutes. The solution was filtered and washed with methanol to remove Pd/C. The methanol solution was concentrated in vacuo to provide free amine (292 mg, 93%) LRMS (ESI) m/z $[M+H]^+$ calcd for $C_{11}H_{17}NO$ 179, found 180.



20 21a 21b

6-(4-bromobutanoyl)-2-azabicyclo[2.2.2]octan-2-ium

To a round-bottomed flask containing free amine 20 (393 mg, 2.2 mmol) was added 1.9 ml 33% HBr/AcOH solution. The reaction was stirred at rt for 2 hours and then HBr/AcOH was removed by rot vaping. The crude residue was purified by column chromatography(EtOH/$CHCl_3$= 1:3) to give partially separation.

Product exo ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (bs, 2H), 3.94 (bs, 1H), 3.57 (ddt, *J* = 9.9, 7.2, 2.2 Hz, 1H), 3.47 (t, *J* = 6.3 Hz, 2H), 3.34 (t, *J* = 11.4 Hz, 2H), 2.74 (td, *J* = 6.9, 3.2 Hz, 2H), 2.26 – 1.92 (m, 6H), 1.84 – 1.65 (m, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 206.77, 45.72, 45.25, 44.10, 39.17, 33.05, 26.12, 25.35, 22.86, 22.50, 18.93. LRMS (ESI) m/z $[M+H]^+$ calcd for $C_{11}H_{19}BrNO$ 260, found 260/262.

Product endo ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (bs, 1H), 7.79 (bzs, 1H), 4.04 (s, 1H), 3.53 (t, *J* = 6.3 Hz, 2H), 3.47 – 3.33 (m, 2H), 2.94 – 2.68 (m, 3H), 2.61 – 2.47 (m, 1H), 2.24 (td, *J* = 6.6, 3.8 Hz, 2H), 2.20 – 2.11 (m, 2H), 2.04 – 1.87 (m, 2H), 1.85 – 1.58 (m, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 210.09, 45.02, 45.01, 44.51, 39.24, 33.54, 26.42, 25.98, 22.96, 21.99, 21.95. LRMS (ESI) m/z $[M+H]^+$ calcd for $C_{11}H_{19}BrNO$ 260, foun

Chapter 4. Extrusive Alkylation Methodology

Chapter 4.1. Introduction of C-N Bond Formation Reactions

The N-alkylation of amines presents itself as one of the most widely applied transformations in synthetic chemistry[1]. Alkylated amines are responsible for the biological activity of many naturally occurring alkaloids and are a common motif in many pharmaceutical compounds[2,3]. Traditional methods for achieving N-alkylation generally proceed via S_N2 pathway or reductive amination[4,5,6] (**Figure 4-1**). S_N2 methods of N-alkylation involving an alkyl halide often leads to overalkylation of the amine and a mixture of products. Industrially, most alkylations are conducted using alcohols and employ various expensive catalysts while

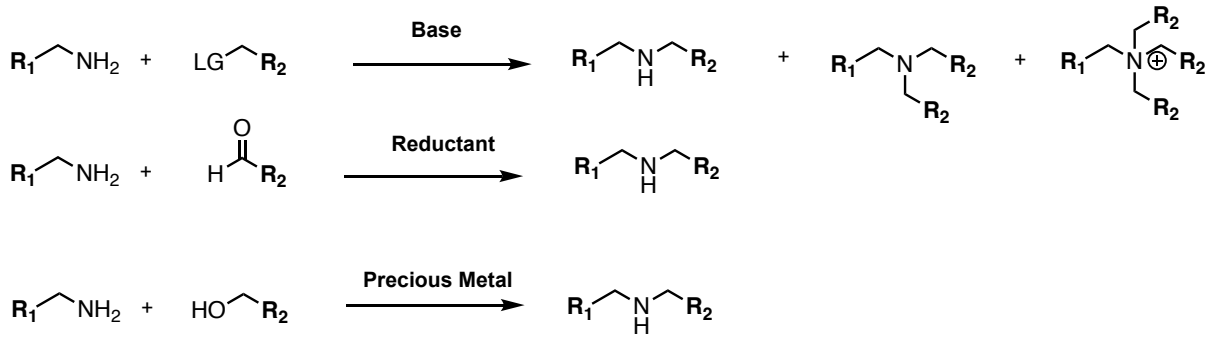


Figure 4-1. Different Nitrogen-Carbon bond methods

[1] Lawrence, S. A. Amines: Synthesis, Properties and Applications; Cambridge University Press: Cambridge, U.K., **2004**.

[2] Kabara, J. J.; Conley, A. J.; Truant, J. P. Relationship of Chemical Structure and Antimicrobial Activity of Alkyl Amides and Amines. *Antimicrobial Agents and Chemotherapy*, **1972**, 2, 492–498.

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[6] Afanasyev, O. I.; Kuchuk, E.; Usanov, D. L.; Chusov, D. Reductive Amination in the Synthesis of Pharmaceuticals. *Chem. Rev*. **2019**, 119, 11857–11911.

demonstrating poor selectivity[7,8,9,10,11,12,13,14]. The reductive amination was developed as a reliable method to circumvent overalkylation, but still encompasses several synthetic limitations. Common reductants for this application can give poor chemoselectivity and generate hazardous byproducts (cyanide and boron species) that are toxic to living cells[6,15]. In addition, reductive aminations generally proceed poorly when using unsaturated or sterically congested carbonyls[16].

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Chapter 4.2. Reaction Discovery and Optimization

While we were working on the synthesis of ibogaine analogs, during the cleavage of a Cbz-protecting group, we observed a fair amount of benzyl-protected amine byproduct. The mechanism behind could result from iodide attacking the benzyl carbon displacing the oxygen and forming a trimethylsilyl carbamate and benzyl iodide.During basic workup, the trimethylsilyl carbamate is hydrolyzed then alkylated with the benzyl iodide to afford the benzyl amine (**Figure 4-2**). The rational is consistent with Mark and co-workers study. [17]

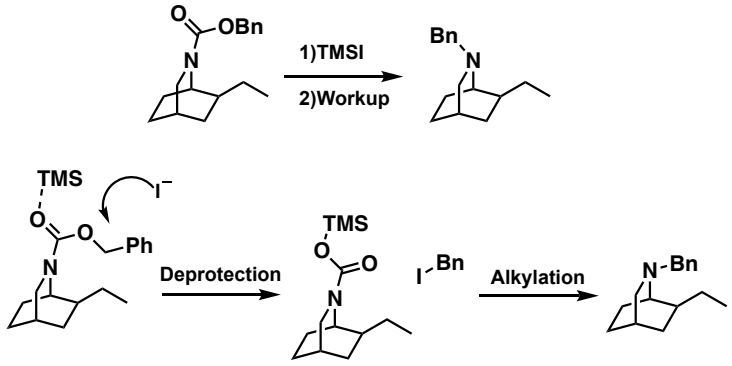


Figure 4-2. Byproduct of TMSI-mediated carbamate cleavage.

This result inspired us to believe that it should not only apply to the reaction above, but a broader range of carbamates that eventually could be a novel way to construct nitrogen-carbon bond through this one-pot, procedure. To make it more practical, we needed to optimize the reaction condition first.

We prepared a model carbamate substrate by reaction between phenethyl alcohol and piperidine with the existence of carbonyldiimidazole (CDI) and believe it could serve as a model reaction that could go through the same process to afford phenethyl piperidine product (**Figure 4-3**).

[17] Jung, M. E.; Lyster, M. A. Conversion of alkyl carbamates into amines via treatment with trimethylsilyl iodide. *Chem. Commun*, **1978**, 315-316.

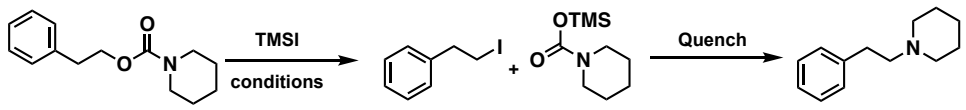


Figure 4-3. Model reaction of extrusive alkylation.

The optimization started with screening solvents for the carbamate cleavage step. It turned out that it could happen in multiple solvents, such as THF, pyridine, DCM, etc., but gave better conversion in acetonitrile. The cleavage in acetonitrile afforded 46% phenethyl iodide when using two equivalents of TMSI at room temperature for three hours (**Table 4-1, entry 4**).

In order to improve the efficiency by shortening the reaction time, we tested additives such as NaI, hoping it could facilitate the iodide attacking, yet the conversion was not better than non-additive conditions, that led us to think trimethylsilyl coordination was also critical for the process and two equivalents of TMSI was already more than enough. Therefore we turned our attention to elevated temperatures. To our delight, upon heating under reflux, the cleavage went to completion within three hours (**Table 4-1, entry 13**). Under microwave assisted conditions the reaction reached completion within 15 mins and increasing the concentration enabled conversion of >99%. **Table 4-1, entry 20**).

Solvent	TMSI Eq.	Concentration [M]	Time	Temp [°C]	Additive	Conversion[a]
THF	2	0.1	3 hr	r.t.	-	18%
Pyridine	2	0.1	3 hr	r.t.	-	33%
DCM	2	0.1	3 hr	r.t.	-	34%
Acetonitrile	2	0.1	3 hr	r.t.	-	46%

Toluene	2	0.1	3 hr	r.t.	-	27%
DMF	2	0.1	3 hr	r.t.	-	28%
$EtNO_2$	2	0.1	3 hr	r.t.	-	26%
Neat	2	-	3 hr	r.t.	-	33%
Acetonitrile	2	0.1	18 hr	r.t.	-	50%
Acetonitrile	5	0.1	3 hr	r.t.	-	55%
Acetonitrile	2	0.1	3 hr	70	-	96%
Acetonitrile	2	1	3 hr	r.t.	-	48%
Acetonitrile	2	0.1	3 hr	82	-	>99%
Acetonitrile	2	0.1	3 hr	r.t.	NaI	40%
Acetonitrile	2	0.1	30 min	82	MW, sealed tube	84%
Acetonitrile	2	0.1	45 min	82	MW, sealed tube	97%
Acetonitrile	2	0.1	60 min	82	MW, sealed tube	>99%
Acetonitrile	2	0.1	30 min	103	MW, sealed tube	97%
Acetonitrile	2	0.1	5 min	123	MW, sealed tube	89%
Acetonitrile	**2**	**0.22 M**	**15 min**	**125**	**MW, sealed tube**	**>99%**

Table 4-1. Optimization of model reaction cleavage step. [a]Conversion determined by ^1H NMR using CH_2Br_2 as an internal standard.

After developing a set of optimal conditions for carbamate deprotection, various quenches were evaluated for amine alkylation. We sought to exploit the relative Si-F and Si-O bond strengths to break down the TMS-carbamate generated in the first step of the reaction. Fluoride additives such as TBAF and

KF led to minimal amounts of product (**Table 4-2, entry 3,4**) while the addition of water alone produced an acidic reaction medium hindering any alkylation (**Table 4-2, entry 1**). Addition of K_2CO_3 led to minimal decarboxylation of the TMS carbamate likely due its low solubility in acetonitrile (**Table 4-2, entry 8**). However, when combined with three equivalents of water, the yield of alkylated amine was dramatically improved (**Table 4-2, entry 9,10**). Surprisingly, no increase in yield was observed when combining the anhydrous fluoride sources with water or other co-solvent mixtures. These results indicate that the inclusion of K_2CO_3 and water played a significant role in creating a sufficient reaction medium for amine alkylation (**Table 4-2**).

Quench[a]	Product Yield[b]
Water	2%
NEt_4BF_4 (s)	1%
KF(s)	21%
TBAF 1M in THF	6%
LiOH	0
LiF	4%
CsF mono hydrate	33%
$2K_2CO_3$	5%
K_2CO_3+KF+H_20	43%
$3K_2CO_3 + 3H_2O$	**76%**

Table 4-2. Optimization of model reaction quench/alkylation step. [a]Reaction were carried out by adding additives to the cleavage mixture and stirred for 12 hours. [b]Conversion determined by ^1H NMR using CH_2Br_2 as an internal standard.

Chapter 4.3. Substrate Scope

Having discovered a set of optimal reaction conditions, we were confident that this protocol should be applicable for a wide range of carbamates. In order to systematically study the flexibility of this reaction, first we synthesized a series of carbamates by coupling different alcohols with piperidine using carbonyldiimidazole (CDI) and subjected them to the optimized reaction condition.

It turned out that in addition to the phenethyl alcohol, many other types alcohols also worked well with this protocol, including alky alcohols such as pentanol, terminal alkene like 5-hexenen-1-ol and allyl alcohol, protected alkyl alcohol. Heterocycles like 1 or 3 substituted indole, furan, hetero atom like chloride and fluoride gave satisfying yields as well (**Figure 4-4**). It is worth noting that the low yields observed are in large part to the challenging nature of purifying free amines. Due to the polarity of these free amines, in some cases it is difficult to separate the alkylated amines from the unalkylated amines via chromatography leading to diminished yields.

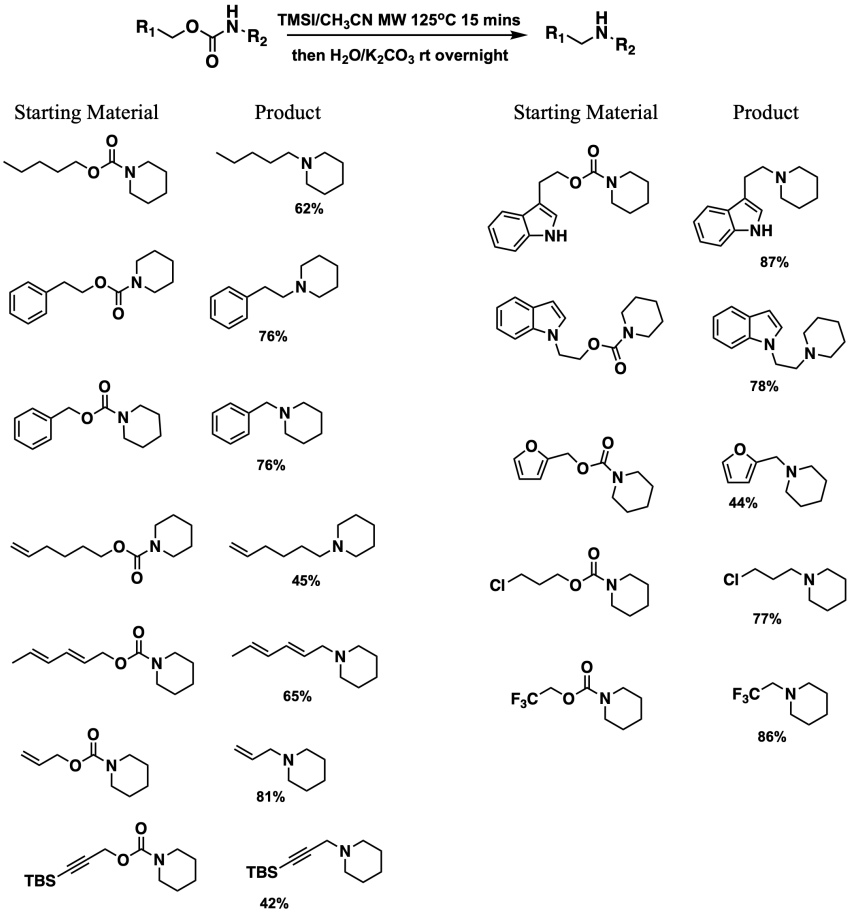


Figure 4-4. Substrate scope involving various alcohols. [a]Reaction were carried out under the optimized condition and isolated yields were calculated after purification.

After exploring the alcohol parts, we moved to test the efficiency when different amines were involved. Again, we prepared a series of carbamtes by coupling different alcohols and free amines and treated them with TMSI under the same condition. As shown in **Figure 4-5**, different types of amines like dimethyl amine, dimethylhydroxylamine, substituted anilines and even protected amino acids could afford amine products with decent yields. The reaction also tolerates others functional groups such as esters and amides also gave good yields.

Since the mechanism involves the extrusion of CO_2, we are interested if it could be used to synthesize cyclic amines. Thus, we prepared several five, six and even seven-membered cyclic carbamates and reacted them with TMSI individually. Aziridines, azetidines and pyrrolidines could be prepared in this way providing a new method for nitrogen-containing ring formation (**Figure 4-5**).

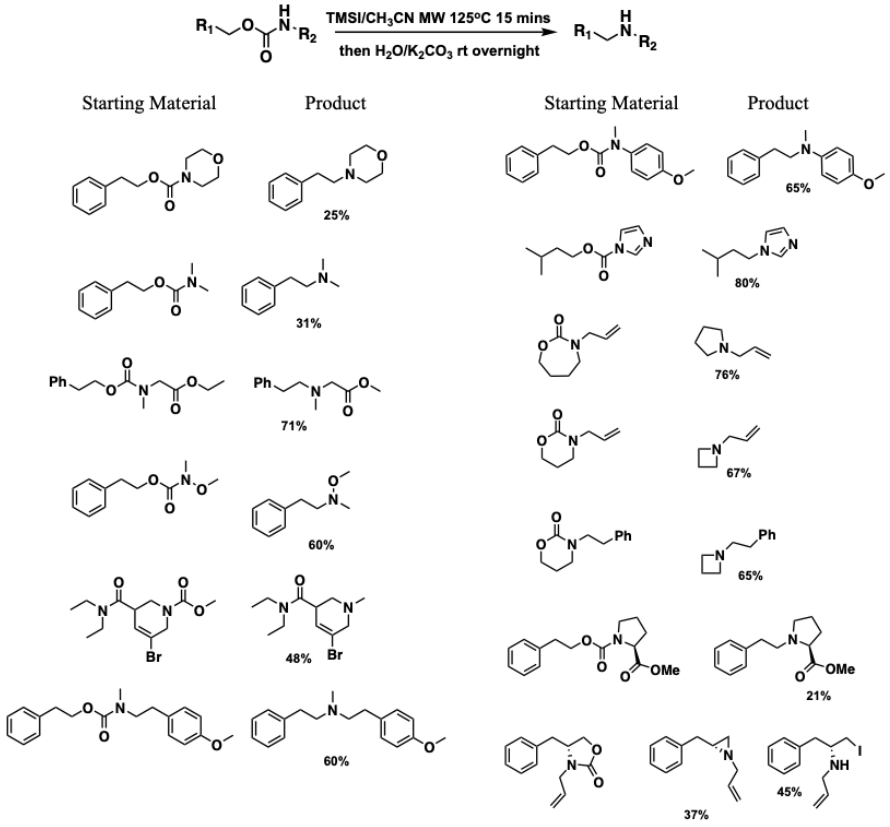


Figure 4-5. Substrate scope involving various alcohols. [a]Reaction were carried out under the optimized condition and isolated yields were calculated after purification.

During the exploration, we did see several carbamates that didn't give amine products as well. For example, the alkylation didn't happen with secondary alcohols, probably due to the steric hinderance. Pyridine substrates only formed a pyridinium byproduct since pyridine itself is nucleophilic and an intra-molecular reaction is much faster than an inter-molecular alkylation. Other substrates that didn't undergo the desired reaction pathway are still under investigation, which could probably reveal more details about this transformation (Figure 4-6).

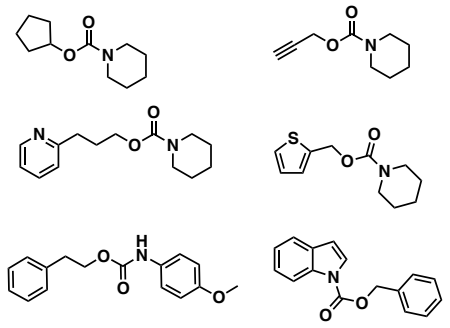


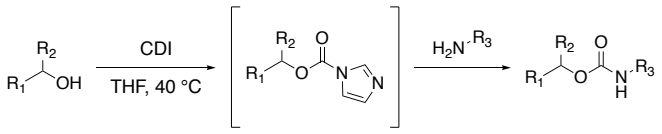
Figure 4-6. Substrate that did not form amine products.

Chapter 4.4 Conclusion

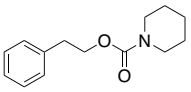
From a byproduct we have developed an efficient and selective process for the construction of carbon-nitrogen bonds through a one-pot sequence involving carbamate cleavage and nucleophilic substitution. This methodology has broad application for a variety of substrates with good functional group tolerance and moderate yields.

Chapter 4.5. Experimental Procedures and Spectral Data

General procedure for the preparation of carbamates substrates



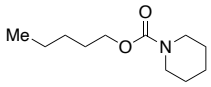
To a solution of substituted alcohol (4.0 mmol, 1.0 equiv) in anhydrous THF (40 mL) was added carbonyldiimidazole (0.972 g, 6.0 mmol, 1.5 equiv) over 1 min. The resulting mixture was capped loosely with a Teflon septum and heated to 40 °C for 4 hours or until alcohol fully consumed via TLC. After cooling to ambient temperature, free amine (12.0 mmol, 3.0 equiv) was added to the solution dropwise. The resulting mixture was capped loosely again and heated to 40 °C for an additional 3 hours. After cooling to ambient temperature, the solution was poured into a separatory funnel containing saturated NH_4Cl solution (100 mL) and extracted with DCM (2 x 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the carbamate compounds.



phenethyl piperidine-1-carboxylate 1a

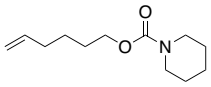
Synthesized from 2-phenylethan-1-ol (0.489 g, 1.0 equiv) and piperidine (1.02 g, 3.0 equiv) following the general procedure for carbamate synthesis. The residue was purified by chromatography on silica gel with hexanes/EtOAc (4:1) to afford **1a** (0.886 g, 95%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.23 (d, *J* = 2.1 Hz, 3H), 4.28 (t, *J* = 2.1 Hz, 2H), 3.38 (s, 4H), 2.94 (t, *J* = 2.1 Hz, 2H), 1.62 – 1.42 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.50, 138.45, 129.10, 128.51, 126.49, 65.80, 44.86, 35.78, 24.52.

HRMS (ES$^+$): *m/z* [M + Na]$^+$ Calcd for $C_{14}H_{19}NO_2Na^+$ 256.1314; Found 256.1316



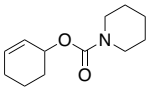
pentyl piperidine-1-carboxylate 1b

Synthesized from 1-pentanol (0.353 g, 1.0 equiv) and piperidine (1.02 g, 3.0 equiv) following the general procedure for carbamate synthesis. The residue was purified by chromatography on silica gel with hexanes/EtOAc (10:1) to afford **1b** (0.776 g, 97%) as a clear oil. ^{1}H NMR (600 MHz, cdcl$_3$) δ 4.04 (t, *J* = 6.7 Hz, 2H), 3.39 (t, *J* = 5.5 Hz, 4H), 1.64 – 1.59 (m, 2H), 1.59 – 1.55 (m, 3H), 1.54 – 1.47 (m, 5H), 1.37 – 1.28 (m, 4H), 0.90 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 154.68, 101.02, 89.75, 53.72, 52.89, 45.10, 26.16, 24.48, 24.42, 16.64, -4.63. HRMS (ES$^+$): *m/z* [M + Na]$^+$ Calcd for $C_{11}H_{21}NO_2Na^+$ 222.1470; Found 222.1470



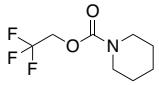
hex-5-en-1-yl piperidine-1-carboxylate 1c

Synthesized from hex-5-en-1-ol (0.401 g, 1.0 equiv) and piperidine (1.02 g, 3.0 equiv) following the general procedure for carbamate synthesis. The residue was purified by chromatography on silica gel with hexanes/EtOAc (4:1) to afford **1c** (0.930 g, 99%) as a clear colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.80 (ddt, *J* = 16.9, 9.9, 6.6 Hz, 1H), 5.05 – 4.92 (m, 2H), 4.10 – 4.03 (m, 2H), 3.44 – 3.36 (m, 4H), 2.08 (q, *J* = 7.3 Hz, 2H), 1.70 – 1.41 (m, 12H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 155.81, 138.68, 114.82, 65.24, 44.87, 33.50, 28.66, 25.83, 25.43, 24.56. HRMS (ES$^+$): *m/z* [M + H]$^+$ Calcd for $C_{12}H_{22}NO_2^+$ 234.1470; Found 234.1473



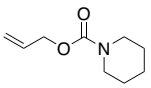
cyclohex-2-en-1-yl piperidine-1-carboxylate 1d

Synthesized from 2-cyclohexen-1-ol (0.393 g, 1.0 equiv) and piperidine (1.02 g, 3.0 equiv) following the general procedure for carbamate synthesis. The residue was purified by chromatography on silica gel with hexanes/EtOAc (3:1) to afford **1d** (0.786 g, 94%) as a pale yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ 5.91 (dtd, *J* = 10.2, 3.7, 1.3 Hz, 1H), 5.78 – 5.71 (m, 1H), 5.20 – 5.14 (m, 1H), 3.41 (dd, *J* = 5.4, 5.4 Hz, 4H), 2.14 – 1.92 (m, 2H), 1.92 – 1.82 (m, 1H), 1.79 – 1.68 (m, 2H), 1.63 – 1.44 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.47, 131.97, 126.92, 77.36, 68.65, 44.87, 28.91, 25.82, 25.10, 24.57, 19.18. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{12}H_{20}NO_2^+$ 210.1494; Found 210.1492



2,2,2-trifluoroethyl piperidine-1-carboxylate 1e

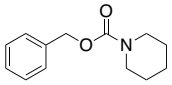
Synthesized from 2,2,2-trifluoroethan-1-ol (0.400 g, 1.0 equiv) and piperidine (1.02 g, 3.0 equiv) following the general procedure for carbamate synthesis. The residue was purified by chromatography on silica gel hexanes/EtOAc (3:1) to afford **1e** (0.726 g, 86%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (q, *J* = 8.6 Hz, 2H), 3.48 – 3.40 (m, 4H), 1.65 – 1.49 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.49, 123.43 (q, $^{1}J_{CF}$ = 277.4 Hz), 61.42 (q, $^{2}J_{CF}$ = 36.2 Hz), 45.30 (d, $^{3}J_{CF}$ = 13.7 Hz), 25.69 (d, $^{4}J_{CF}$ = 25.8 Hz), 24.32. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_8H_{13}F_3NO_2^+$ 212.0898; Found 212.0899



allyl piperidine-1-carboxylate 1f

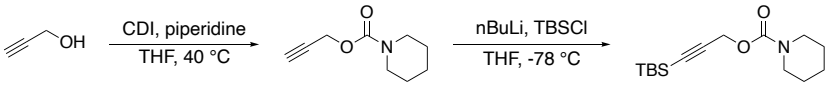
Following a literature procedure[1], to a solution of potassium carbonate (0.276 g, 2.0 mmol, 1 equiv) in THF (20 mL, 0.1 M) was added piperidine (0.341 g, 4.0 mmol, 2.0 equiv) and allyl chloroformate (0.241 g, 2.0 mmol, 1.0 equiv). After stirring for 1 h, water (10 mL) was added and the solution was stirred for 1 h. Water (50 mL) was then added and the mixture. Was extracted with DCM (3 x 30 mL). The combined organic

extracts were washed with saturated brine (2 x 30 mL) and dried over anhydrous $MgSO_4$. The mixture was filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with hexanes/EtOAc (4:1) to afford **1f** (0.676 g, 99%) as a clear colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (ddt, *J* = 17.5, 10.6, 5.5 Hz, 1H), 5.28 (d, *J* = 1.7 Hz, 1H), 5.18 (d, *J* = 1.5 Hz, 1H), 4.57 (d, *J* = 1.6 Hz, 2H), 3.45 – 3.39 (m, 4H), 1.63 – 1.47 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.31, 133.46, 117.15, 65.90, 44.92, 25.80, 24.50. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_9H_{16}NO_2^+$ 170.1181; Found 170.1180



Benzyl piperidine-1-carboxylate 1g

Following a literature procedure[1], to a solution of potassium carbonate (0.276 g, 2.0 mmol, 1 equiv) in THF (20 mL, 0.1 M) was added piperidine (0.341 g, 4.0 mmol, 2.0 equiv) and benzyl chloroformate (0.341 g, 2.0 mmol, 1.0 equiv). After stirring for 1 h, water (10 mL) was added and the solution was stirred for 1 h. Water (50 mL) was then added and the mixture. Was extracted with DCM (3 x 30 mL). The combined organic extracts were washed with saturated brine (2 x 30 mL) and dried over anhydrous $MgSO_4$. The mixture was filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with hexanes/EtOAc (6:1) to afford **1g** (0.390 g, 89%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 4H), 7.34 – 7.28 (m, 1H), 5.13 (s, 2H), 3.47 – 3.42 (m, 4H), 1.62 – 1.49 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.45, 137.15, 128.56, 127.99, 127.91, 66.99, 44.98, 24.49. HRMS (ES^+): *m/z* $[M + Na]^+$ Calcd for $C_{13}H_{17}NO_2Na^+$ 242.1157; Found 242.1157

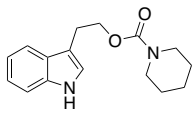


3-(*tert*-butyldimethylsilyl)prop-2-yn-1-yl piperidine-1-carboxylate 1h

To a solution of propargyl alcohol (0.23 mL, 4 mmol, 1.0 equiv) in anhydrous THF (40 mL, 0.1 M) was added carbonyldiimidazole (0.972 g, 6.0 mmol, 1.5 equiv) over 1 min. The resulting mixture was capped loosely with a plastic septum and heated to 40 °C for 4 hours. After cooling to ambient temperature, piperidine (1.2 mL, 12.0 mmol, 3.0 equiv) was added to the solution dropwise. The solution was capped loosely again and heated to 40 °C for an additional 3 h. After cooling to ambient temperature, the solution was poured into a separatory funnel containing saturated aqueous NH_4Cl (100 mL) and extracted with DCM (2 x 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with hexanes/EtOAc (5:1) to afford the alkynyl carbamate (0.461 g, 70%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (d, *J* = 2.4 Hz, 2H), 3.48 – 3.38 (m, 4H), 2.44 (t, *J* = 2.4 Hz, 1H), 1.62 – 1.48 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.58, 78.91, 74.36, 52.88, 45.07, 24.41.

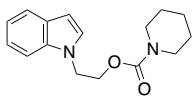
To a solution of carbamate (0.340 g, 2.0 mmol, 1.0 equiv) in anhydrous THF (20 mL, 0.1M) at -78 °C under N_2 atmosphere was added 2.5M n-BuLi (1.2 mL, 3.0 mmol, 1.5 equiv) dropwise. The resulting mixture was stirred at the same temperature for 30 mins before a solution of TBSCl (0.450 g, 3.0 mmol, 1.5 equiv) in THF (5 mL) was added. The mixture was stirred overnight and warmed slowly to rt. The solution was poured into a separatory funnel containing saturated aqueous saturated sodium bicarbonate (100 mL) and extracted with DCM (2 x 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with hexanes/EtOAc (6:1) to afford **1h** (0.561 g, 99%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (s, 2H), 3.46 – 3.40 (m, 4H), 1.59 (m, 2H), 1.54 – 1.52 (m, 4H), 0.94 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.67, 101.01, 89.74, 53.72, 45.09, 26.15, 24.47, 16.63, -4.64. HRMS (ES^+): *m/z* $[M+H]^+$ Calcd for $C_{15}H_{28}NO_2Si^+$ 304.1709; Found 304.1712



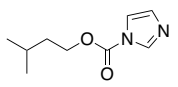
2-(1*H*-indol-3-yl)ethyl piperidine-1-carboxylate 1i

Synthesized from 2-(1*H*-indol-3-yl)ethan-1-ol (0.645 g, 1.0 equiv) and piperidine (1.02 g, 3.0 equiv) following the general procedure for carbamate synthesis. The residue was purified by chromatography on silica gel with hexanes/EtOAc (1:1) to afford **1i** (0.859 g, 79%) as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.19 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.04 (s, 1H), 4.36 (t, *J* = 7.1 Hz, 2H), 3.41 (s, 4H), 3.11 (t, *J* = 7.2 Hz, 2H), 1.59 – 1.54 (m, 2H), 1.51 (s, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.74, 136.29, 127.74, 122.15, 122.05, 119.48, 119.02, 112.65, 111.20, 77.36, 65.47, 44.91, 25.81, 25.37, 24.54. HRMS (ES$^+$): *m/z* [M+Na]$^+$ Calcd for $C_{16}H_{20}N_2O_2Na^+$ 295.1423; Found 295.1429



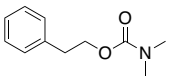
2-(1*H*-indol-1-yl)ethyl piperidine-1-carboxylate 1j

Synthesized from 2-(1*H*-indol-1-yl)ethan-1-ol (0.645 g, 1.0 equiv) and piperidine (1.02 g, 3.0 equiv) following the general procedure for carbamate synthesis. The residue was purified by chromatography on silica gel with hexanes/EtOAc (4:1) to afford **1j** (0.948 g, 87%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 1.0 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.21 (dd, *J* = 7.0, 1.2 Hz, 1H), 7.14 – 7.08 (m, 2H), 6.52 (dd, *J* = 3.2, 0.9 Hz, 1H), 4.39 (s, 4H), 3.32 (d, *J* = 57.4 Hz, 4H), 1.61 – 1.32 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.98, 136.37, 128.72, 128.03, 121.74, 121.09, 119.59, 109.41, 101.79, 63.97, 45.60, 44.95, 25.68, 24.40. HRMS (ES$^+$): *m/z* [M + Na]$^+$ Calcd for $C_{16}H_{20}N_2O_2Na^+$ 295.1423; Found 295.1428



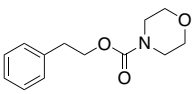
isopentyl 1*H*-imidazole-1-carboxylate 1k

To a solution of 3-methylbutanol (0.353 g, 4.0 mmol, 1.0 equiv) in anhydrous THF (40 mL, 0.1 M) was added carbonyldiimidazole (0.972 g, 6.0 mmol, 1.5 equiv) over 1 min. The resulting mixture was capped loosely with a plastic septum and heated to 40 °C for 4 h. After cooling to ambient temperature, the solution was poured into a separatory funnel containing saturated aqueous Na_2CO_3 solution and extracted with DCM (2 x 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with hexanes/EtOAc (4:1) to afford **1k** (0.510 g, 70%) as a clear colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.41 – 7.40 (m, 1H), 7.07 – 7.04 (m, 1H), 4.44 (t, *J* = 6.7 Hz, 2H), 1.81 – 1.72 (m, 1H), 1.72 – 1.65 (m, 2H), 0.97 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 148.88, 137.20, 130.73, 117.21, 67.20, 37.21, 25.15, 22.51. HRMS (ES$^+$): *m/z* [M + Na]$^+$ Calcd for $C_9H_{14}N_2O_2Na^+$ 205.0953; Found 205.0955



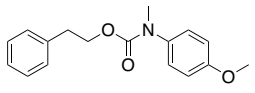
Phenethyl dimethylcarbamate 1l

Synthesized from 2-phenylethan-1-ol (0.489 g, 1.0 equiv) and dimethylamine (0.541 g, 3.0 equiv) following the general procedure for carbamate synthesis. The residue was purified by chromatography on silica gel with hexanes/EtOAc (17:3) to afford **1l** (0.640 g, 83%) as a clear colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.25 – 7.19 (m, 3H), 4.28 (t, *J* = 1.6 Hz, 2H), 2.94 (t, *J* = 6.9 Hz, 2H), 2.88 (d, *J* = 17.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.70, 138.43, 129.10, 128.53, 126.52, 77.36, 65.99, 36.49, 35.93, 35.79. HRMS (ES$^+$): *m/z* [M + H]$^+$ Calcd for $C_{11}H_{16}NO_2^+$ 194.1181; Found 194.1188



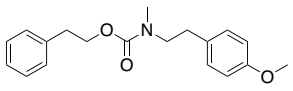
Phenethyl morpholine-4-carboxylate 1m

Synthesized from 2-phenylethan-1-ol (0.489 g, 1.0 equiv) and morpholine (1.05 g, 1.5 equiv) following the general procedure for carbamate synthesis. The residue was purified by chromatography on silica gel with hexanes/EtOAc to afford **1m** (0.817 g, 87%) as a clear yellow oil. ^{1}H NMR (600 MHz, cdcl3) δ 7.33 – 7.28 (m, 2H), 7.25 – 7.20 (m, 3H), 4.31 (t, *J* = 1.4 Hz, 2H), 3.62 (s, 4H), 3.43 (s, 4H), 2.95 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.43, 138.15, 129.04, 128.58, 126.62, 66.70, 66.11, 44.13, 35.66. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{13}H_{18}NO_3^+$ 236.1286; Found 236.1285



phenethyl (4-methoxyphenyl)(methyl)carbamate 1n

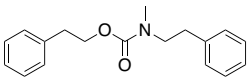
Synthesized from 2-phenylethan-1-ol (0.489 g, 1.0 equiv) and 4-methoxy-*N*-methylaniline (1.65 g, 3.0 equiv) following the general procedure for carbamate synthesis. The residue was purified by chromatography on silica gel with hexanes/EtOAc (19:1) to afford **1n** (0.912 g, 80%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.20 (m, 3H), 7.17 – 6.96 (m, 4H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.30 (t, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.23 (s, 3H), 2.88 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.96, 138.26, 129.18, 128.45, 126.48, 114.17, 66.33, 55.58, 35.55. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{17}H_{20}NO_3^+$ 286.14434; Found 286.1444



phenethyl (4-methoxyphenethyl)(methyl)carbamate 1o

Synthesized from 2-phenylethan-1-ol (0.489 g, 1.0 equiv) and 2-(4-methoxylphenyl)-*N*-methylethan-1-amine (1.98 g, 3.0 equiv) following the general procedure for carbamate synthesis. The residue was purified by chromatography on silica gel with hexanes/EtOAc (4:1) to afford **1o** (1.06 g, 85%) as a clear colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (rotamers observed) δ 7.34 – 7.27 (m, 2H), 7.25 – 7.19 (m, 3H), 7.12 (d, *J* = 8.2 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 2H), 4.33 – 4.22 (m, 2H), 3.78 (s, 3H), 3.48 –

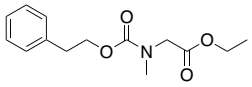
3.30 (m, 2H), 2.98 – 2.88 (m, 2H), 2.84 (s, 2H), 2.77 (s, 2H), 2.65 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) (rotamers observed) δ 158.27, 156.37, 138.43, 131.15, 129.86, 129.05, 128.56, 126.53, 114.02, 65.83, 55.38, 51.28, 50.82, 35.78, 35.67, 35.04, 34.63, 33.71, 33.29. HRMS (ES^+): *m/z* $[M + Na]^+$ Calcd for $C_{19}H_{23}NO_3Na^+$ 336.157569; Found 336.1579



phenethyl methyl(phenethyl)carbamate 1p

Synthesized from 2-phenylethan-1-ol (0.489 g, 1.0 equiv) and *N*-methyl-2-phenylethan-1-amine (1.62 g, 3.0 equiv) following the general procedure for carbamate synthesis. The residue was purified by chromatography on silica gel with hexanes/EtOAc (4:1) to afford **1p** (0.826 g, 73%) as a pale yellow oil.

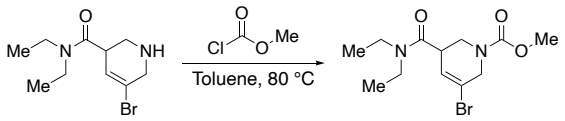
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 4H), 7.25 – 7.18 (m, 5H), 7.12 – 7.05 (m, 1H), 4.34 – 4.21 (m, 2H), 3.53 – 3.34 (m, 2H), 2.99 – 2.66 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.35, 139.15, 138.41, 129.05, 128.94, 128.60, 128.56, 126.53, 126.44, 65.84, 51.13, 50.66, 35.65, 35.02, 34.63, 34.23. HRMS (ES^+): *m/z* $[M + Na]^+$ Calcd for $C_{18}H_{21}NO_2Na^+$ 306.146969; Found 306.1461



ethyl *N*-methyl-*N*-(phenethoxycarbonyl)glycinate 1q

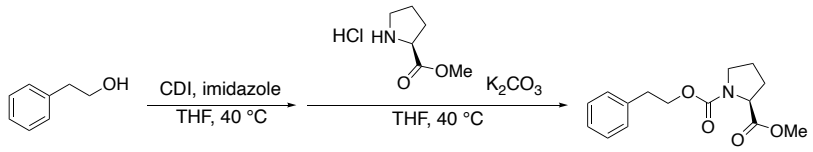
Synthesized from 2-phenylethan-1-ol (0.489 g, 1.0 equiv) and ethyl methylglycinate (1.41 g, 3.0 equiv) following the general procedure for carbamate synthesis. The residue was purified by chromatography on silica gel with hexanes/EtOAc (2:1**)** to afford **1q** (0.489 g, 85%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) (rotamers observed) δ 7.33 – 7.26 (m, 2H), 7.25 – 7.17 (m, 3H), 4.30 (dt, *J* = 9.7, 6.9 Hz, 2H), 4.17 (dq, *J* = 19.7, 7.1 Hz, 2H), 4.01 (s, 1H), 3.90 (s, 1H), 2.98 – 2.96 (m, 2H), 2.95 – 2.89 (m, 3H), 1.26 (dt, *J* = 9.1, 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) (rotamers observed) δ 169.75, 169.61, 156.89, 156.23, 138.22,

129.12, 129.02, 128.56, 128.55, 126.57, 126.54, 66.49, 66.34, 61.26, 50.78, 50.61, 36.02, 35.65, 35.59, 35.33, 14.32. HRMS (ES$^+$): *m/z* [M + Na]$^+$ Calcd for $C_{14}H_{20}NO_4^+$ 266.1392; Found 266.1391



methyl 5-bromo-3-(diethylcarbamoyl)-3,6-dihydropyridine-1(2*H*)-carboxylate 1r

To a solution of 5-bromo-*N*,*N*-diethyl-1,2,3,6-tetrahydropyridine-3-carboxamide (0.550 g, 2.0 mmol, 1.0 equiv) in toluene (5 mL, 0.4 M) was added methyl chloroformate (0.77 mL, 10.0 mmol, 5.0 equiv). The resulting mixture was heated to 60 °C overnight. After cooling to ambient temperature, the solution was poured into a separatory funnel containing saturated aqueous Na_2CO_3 solution (100 mL) and extracted with DCM (2 x 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with hexanes/EtOAc (1:1) to afford **1r** (0.240 g, 38%) as a white solid. 1H NMR (400 MHz, CDCl3) δ 6.13 – 6.00 (m, 1H), 4.42 (dd, *J* = 48.3, 18.1 Hz, 1H), 4.28 – 3.99 (m, 1H), 3.96 – 3.80 (m, 1H), 3.72 (s, 3H), 3.59 – 3.14 (m, 6H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.30, 155.61, 127.15, 126.46, 119.33, 53.11, 49.82, 42.83, 42.22, 40.56, 14.95, 13.12. HRMS (ES$^+$): *m/z* [M + Na]$^+$ Calcd for $C_{12}H_{19}BrN_2O_3Na^+$ 342.047669; Found 342.0476

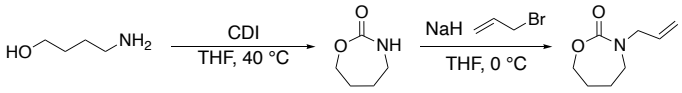


2-methyl 1-phenethyl (*S*)-pyrrolidine-1,2-dicarboxylate 1s

To a solution of phenethyl alcohol (0.732 g, 6.0 mmol, 1.0 equiv) in anhydrous THF (40 mL, 0.1 M) was added carbonyldiimidazole (1.46 g, 9.0 mmol, 1.5 equiv) over 1 min. The resulting mixture was capped loosely with a plastic septum and heated to 40 °C for 4 h. After cooling to ambient temperature, *S*-proline

methyl ester hydrochloride (4.46 g, 27.0 mmol, 3.0 equiv) and potassium carbonate (2.48 g, 18.0 mmol, 3.0 equiv) was added to the solution in portions. The solution was capped loosely again and heated to 40 °C for an additional 3 h. After cooling to ambient temperature, the solution was poured into a separatory funnel containing saturated aqueous NH_4Cl (100 mL) and extracted with DCM (2 x 50 mL). The organic extracts were combined, washed with brine (50 mL) dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with hexanes/EtOAc (1:1) to afford **1s** (1.41 g, 84%) as a white solid.

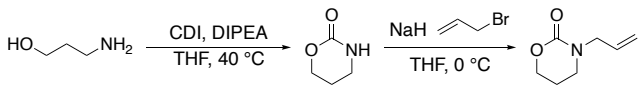
^1H NMR (400 MHz, $CDCl_3$) (rotamers observed) δ 7.33 – 7.26 (m, 2H), 7.25 – 7.17 (m, 3H), 4.40 – 4.18 (m, 3H), 3.74 (s, 1H), 3.63 (s, 2H), 3.62 – 3.56 (m, 1H), 3.56 – 3.45 (m, 1H), 3.43 – 3.34 (m, 1H), 2.95 (td, *J* = 7.0, 2.2 Hz, 1H), 2.89 (t, *J* = 6.9 Hz, 1H), 2.28 – 2.12 (m, 1H), 2.04 – 1.81 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) (rotamers observed) δ 173.34, 155.05, 154.56, 138.28, 138.19, 129.14, 129.02, 128.53, 126.53, 126.50, 66.04, 65.94, 59.18, 58.86, 52.35, 52.23, 46.90, 46.43, 35.73, 35.61, 31.06, 30.04, 24.45, 23.58. HRMS (ES^+): *m/z* $[M + Na]^+$ Calcd for $C_{15}H_{20}NO_4^+$ 278.1392; Found 278.1393



3-allyl-1,3-oxazepan-2-one 1t

Procedure adapted from previous reference.[2] To a solution of 4-amino-1-butanol (0.445 mL, 5.0 mmol, 1.0 equiv) and in anhydrous THF (20 mL, 0.13M) was added carbonyldiimidazole (0.891 g, 5.5 mmol, 1.1 equiv) over 1 min. The resulting mixture was capped loosely with a plastic septum and heated to 40 °C for 4 h. After cooling to 0 °C, NaH (60% dispersion in mineral oil) (0.600 g, 15.0 mmol, 3.0 equiv). The mixture was stirred at the same temperature for 30 mins before allyl bromide (1.3 mL, 15.0 mmol, 3.0 equiv) was added dropwise. The mixture was stirred overnight and warmed slowly to rt. The solution was poured into a separatory funnel containing saturated aqueous Na_2CO_3 solution (100 mL) then extracted with DCM (2 x 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on

silica gel with DCM/MeOH (20:1) to afford **1t** (0.163 g, 21%) as a clear yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 16.5, 10.2, 6.1 Hz, 1H), 5.25 – 5.20 (m, 1H), 5.19 (s, 1H), 4.13 – 4.07 (m, 2H), 3.90 (d, *J* = 1.5 Hz, 2H), 3.25 – 3.19 (m, 2H), 1.85 (ddd, *J* = 7.9, 6.5, 4.8 Hz, 2H), 1.68 (dtd, *J* = 10.6, 5.9, 3.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.57, 133.28, 118.10, 70.48, 53.38, 48.35, 29.10, 26.55. HRMS (ES^+): *m/z* $[M + Na]^+$ Calcd for $C_{15}H_{19}NO_4Na^+$ 178.08440; Found 178.0849

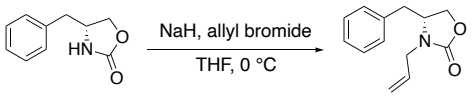


3-allyl-1,3-oxazinan-2-one 1u

Procedures adapted from reference.[2] To a solution of 3-amino-1-propanol (0.380 mL, 5.0 mmol, 1.0 equiv) and DIPEA (1.0 mL, 6.0 mmol, 1.1 equiv) in anhydrous THF (40 mL, 0.13M) was added carbonyldiimidazole (0.972 g, 6.0 mmol, 1.1 equiv) over 1 min. The resulting mixture was capped loosely with a plastic septum and heated to 40 °C for 4 h. After cooling to ambient temperature, the solution was poured into a separatory funnel containing saturated aqueous Na_2CO_3 solution (100 mL) and extracted with DCM (2 x 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with DCM/MeOH (20:1) to afford the N-H carbamate (0.220 g, 43%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (s, 1H), 4.29 – 4.22 (m, 2H), 3.32 (td, *J* = 6.2, 2.4 Hz, 2H), 1.97 – 1.89 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.83, 66.84, 39.75, 21.17.

To an ice-water bath cooled solution of the N-H carbamate (0.195 g, 1.9 mmol, 1.0 equiv) in anhydrous THF (20 mL, 0.095M) under nitrogen was added hexanes pre-washed 60% sodium hydride (0.116 g, 2.9 mmol, 1.5 equiv) over 1 min. The resulting mixture was stirred at the same temperature for 30 mins before allyl bromide (0.25 mL, 2.9 mmol, 1.5 equiv) was added. The mixture was stirred overnight and warmed slowly to rt. The solution was poured into a separatory funnel containing saturated aqueous Na_2CO_3 solution (100 mL) then extracted with DCM (2 x 50 mL). The organic extracts were combined,

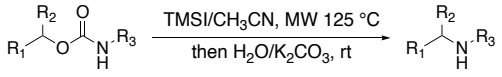
washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with DCM/MeOH (20:1) to afford **1u** (0.165 g, 61%) as a clear yellow oil. ^{1}H NMR (600 MHz, cdcl$_3$) δ 5.84 – 5.76 (m, 1H), 5.23 – 5.16 (m, 2H), 4.29 – 4.23 (m, 2H), 3.97 – 3.93 (m, 2H), 3.26 (td, *J* = 6.2, 1.4 Hz, 2H), 2.03 (tt, *J* = 6.3, 4.8 Hz, 2H). ^{13}C NMR (150 MHz, cdcl$_3$) δ 153.62, 132.57, 117.88, 66.60, 51.82, 44.50, 29.81, 22.36. HRMS (ES$^+$): *m/z* [M + Na]$^+$ Calcd for $C_7H_{11}NO_2Na^+$ 164.06877; Found 164.0698



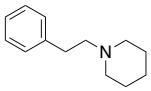
(*R*)-3-allyl-4-benzyloxazolidin-2-one 1v

Procedure adapted from reference.[3] To flask containing anhydrous THF (14.0 mL, 0.2 M) was added (*S*)-4-benzyloxazolidin-2-one (0.500 g, 2.82 mmol, 1.0 equiv). The reaction flask was cooled to 0 °C before NaH (60% dispersion in mineral oil) (0.147 g, 3.67 mmol, 1.3 equiv) was added under nitrogen atmosphere. The mixture was stirred for 10 minutes at 0 °C and then allyl bromide (0.370 mL, 4.23 mmol, 1.5 equiv) was added dropwise into the suspension. After addition of allyl bromide, the mixture was allowed to warm to room temperature and stirring continued for 12 h. The reaction mixture was quenched with distilled water (10.0 mL) and extracted with DCM (3 x 10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with hexanes/EtOAc (3:1) to afford **1v** (0.170 g, 27%) ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35 – 7.28 (m, 2H), 7.27 – 7.24 (m, 1H), 7.16 – 7.12 (m, 2H), 5.80 (dddd, *J* = 17.1, 10.2, 7.8, 4.7 Hz, 1H), 5.30 – 5.21 (m, 2H), 4.28 – 4.20 (m, 1H), 4.20 – 4.15 (m, 1H), 4.05 – 3.97 (m, 2H), 3.63 (ddt, *J* = 15.6, 7.8, 1.1 Hz, 1H), 3.14 (dd, *J* = 13.4, 4.1 Hz, 1H), 2.65 (dd, *J* = 13.7, 4.8 Hz, 1H). ^{13}C NMR (100 MHz, cdcl$_3$) δ 159.65, 136.02, 129.13, 129.11, 129.07, 127.32, 69.66, 53.87, 41.47. HRMS (ES$^+$): *m/z* [M + Na]$^+$ Calcd for $C_7H_{11}NO_2Na^+$ 246.1470; Found 246.1466

General procedure for the extrusive alkylation reactions

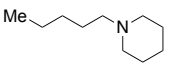


A microwave reaction vial containing carbamate (0.4 mmol, 1.0 equiv) and anhydrous CH_3CN (1.8 mL C=0.22M) was capped. TMSI (0.1 mL, 0.8 mmol, 2 equiv) was added dropwise through syringe. The capped solution was heated under microwave condition (medium, 125 °C) for 15 mins. After cooling to ambient temperature, H_2O (0.021 mL, 1.2 mmol, 3 equiv) was added via syringe, then K_2CO_3 (166 mg, 1.2 mmol, 3 equiv) was added one portion. The mixture was stirred at room temperature for 12 hours. The solution was poured into a separatory funnel containing 100 mL saturated Na_2CO_3 solution then DCM (2 x 50 mL) was used for the extraction. The organic extracts were combined, washed with brine (1 x 50 mL), dried over Na_2SO_4 and concentrate under reduced pressure. The residue was purified by chromatography on silica gel to afford the amine compounds.



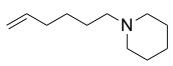
1-phenethylpiperidine 5a

Synthesized from **1a** (93.3 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (9:1) plus 1% NH_4OH to afford **5a** (57.0 mg, 76%) as a clear colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.24 – 7.18 (m, 3H), 2.98 – 2.89 (m, 2H), 2.77 – 2.56 (m, 6H), 1.75 (p, *J* = 5.6 Hz, 4H), 1.58 – 1.46 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.60, 128.86, 128.67, 126.45, 60.84, 54.38, 32.83, 25.22, 23.96. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{13}H_{20}N^+$ 190.1595; Found 190.1593



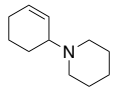
1-pentylpiperidine 5b

Synthesized from **1b** (79.7 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (95:5) plus 0.5% NH_4OH to afford **5b** (38.5 mg, 62%) as a clear colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 4H), 2.40 – 2.34 (m, 2H), 1.65 (p, *J* = 5.7 Hz, 4H), 1.60 – 1.48 (m, 2H), 1.45 (p, *J* = 6.1 Hz, 2H), 1.39 – 1.19 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.45, 54.53, 29.93, 26.16, 25.52, 24.23, 22.69, 14.14. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{10}H_{22}N^+$ 156.1752; Found 156.1753



1-(hex-5-en-1-yl)piperidine 5c

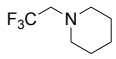
Synthesized from **1c** (84.5 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (9:1) plus 1% NH_4OH to afford **5c** (30.1 mg, 45%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.02 – 4.85 (m, 2H), 2.48 (s, 4H), 2.43 – 2.34 (m, 2H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.71 – 1.60 (m, 4H), 1.60 – 1.50 (m, 2H), 1.49 – 1.40 (m, 2H), 1.35 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.59, 114.70, 59.04, 54.37, 33.58, 26.87, 25.72, 25.30, 24.01. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{11}H_{22}N^+$ 168.1752; Found 168.1755



1-(cyclohex-2-en-1-yl)piperidine 5d

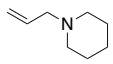
Synthesized from **1d** (83.7 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (19:1) plus 2% NH_4OH to afford **5d** (33.1 mg, 50%) as a clear yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (dtd, *J* = 10.2, 3.7, 1.3 Hz, 1H), 5.78 – 5.71 (m, 1H), 5.17 (dtq, *J* = 5.2, 3.6, 1.8 Hz, 1H), 3.44 – 3.37 (m, 4H), 2.13 – 1.92 (m, 2H), 1.92 – 1.83 (m, 1H), 1.78 – 1.67 (m, 2H), 1.67 – 1.45 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.47, 131.97,

126.92, 68.65, 44.87, 28.91, 25.82, 25.10, 24.57, 19.18. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{11}H_{20}N^+$ 166.1595; Found 166.1599



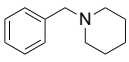
1-(2,2,2-trifluoroethyl)piperidine 5e

Synthesized from **1e** (84.5 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (95:5) plus 2% NH_4OH to afford **5e** (33.1 mg, 50%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.19 – 3.11 (m, 4H), 2.73 (s, 2H), 1.66 (p, *J* = 5.5 Hz, 4H), 1.58 – 1.50 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.82, 34.43, 25.42, 23.75. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_7H_{13}F_3N^+$ 168.1000; Found 168.1001



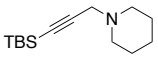
***N*-methyl-*N*-phenethyl-2-phenylethan-1-amine 5f**

Synthesized from **1f** (67.7 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (9:1) plus 1% NH_4OH to afford **5f** (40.6 mg, 81%) as a clear yellow oil. ^1H NMR (400 MHz, CDCl3) δ 5.87 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.19 – 5.07 (m, 2H), 2.94 (dt, *J* = 6.6, 1.3 Hz, 2H), 2.36 (s, 4H), 1.58 (p, *J* = 5.6 Hz, 4H), 1.47 – 1.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.80, 135.78, 117.56, 117.54, 62.80, 54.61, 26.11, 24.49. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_8H_{16}N^+$ 126.1282; Found 126.1280



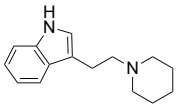
1-benzylpiperidine 5g

Synthesized from **1g** (87.7 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (95:5) plus 2% NH_4OH to afford **5g** (56.8 mg, 81%) as a clear yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 4H), 7.26 – 7.21 (m, 1H), 3.48 (s, 2H), 2.38 (s, 4H), 1.58 (p, *J* = 5.6 Hz, 4H), 1.47 – 1.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.80, 129.36, 128.22, 126.94, 64.05, 54.64, 26.14, 24.55. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{12}H_{18}N^+$ 176.1439; Found 176.1434



1-(3-(*tert*-butyldimethylsilyl)prop-2-yn-1-yl)piperidine 5h

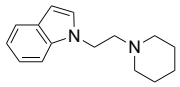
Synthesized from **1h** (112.6 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (95:5) plus 2% NH_4OH to afford **5h** (39.9 mg, 42%) as a clear yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.31 (s, 2H), 2.50 (s, 4H), 1.61 (p, *J* = 5.6 Hz, 5H), 1.47 – 1.38 (m, 2H), 0.94 (s, 9H), 0.10 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.12, 87.90, 53.21, 48.82, 26.27, 26.11, 24.10, 16.64, -4.32. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{14}H_{28}NSi^+$ 238.1991; Found 238.1991



3-(2-(piperidin-1-yl)ethyl)-1*H*-indole 5i

Synthesized from **1i** (108.9 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (95:5) plus 2% NH_4OH to afford **5i** (79.5 mg, 87%) as a clear yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.19 (d, *J* = 7.0 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.04 – 7.03 (m, 1H), 3.05 – 2.97 (m, 2H), 2.75 – 2.68 (m, 2H), 2.57 (s, 4H), 1.68 (p, *J* = 5.7 Hz, 4H), 1.54 – 1.44 (m, 2H). ^{13}C NMR (100

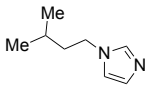
MHz, $CDCl_3$) δ 136.34, 127.46, 121.85, 121.79, 119.13, 118.80, 113.86, 111.30, 59.92, 54.49, 25.65, 24.25, 22.56. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{15}H_{22}N_2^+$ 229.1704; Found 229.1701



1-(2-(piperidin-1-yl)ethyl)-1*H*-indole 5j

Synthesized from **1j** (108.9 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (95:5) plus 2% NH_4OH to afford **5j** (71.2 mg, 78%) as a clear orange oil.

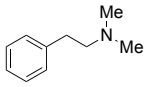
^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.15 (d, *J* = 3.1 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.49 (dd, *J* = 3.2, 0.9 Hz, 1H), 4.30 – 4.23 (m, 2H), 2.76 – 2.69 (m, 2H), 2.52 – 2.43 (m, 4H), 1.61 (p, *J* = 5.6 Hz, 4H), 1.50 – 1.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.10, 128.67, 128.19, 121.51, 121.08, 119.38, 109.39, 101.27, 58.79, 55.06, 44.41, 26.14, 24.39. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{15}H_{21}N_2^+$ 229.1704; Found 229.1701



1-isopentyl-1*H*-imidazole 5k

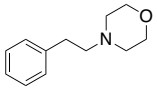
Synthesized from **1k** (72.9 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (93:7) to afford **5k** (34.5 mg, 62%) as a clear yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.05 (s, 1H), 6.90 (s, 1H), 3.94 (dd, *J* = 8.1, 6.7 Hz, 2H), 1.71 – 1.64 (m, 2H), 1.56 (hept, *J* = 6.6 Hz, 1H), 0.94 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (101

MHz, $CDCl_3$) δ 137.14, 129.49, 118.87, 45.40, 40.05, 25.55, 22.39. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_8H_{15}N_2^+$ 139.1235; Found 139.1233



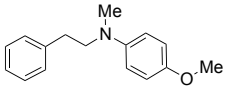
***N,N*-dimethyl-2-phenylethan-1-amine 5l**

Synthesized from **1l** (77.3 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (93:7) to afford **5l** (19.1 mg, 32%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 2H), 7.26 – 7.20 (m, 3H), 3.10 – 3.02 (m, 2H), 3.01 – 2.94 (m, 2H), 2.64 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.49, 128.97, 128.79, 127.07, 60.28, 44.13, 32.30. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{10}H_{16}N^+$ 150.1282; Found 150.1280



4-phenethylmorpholine 5m

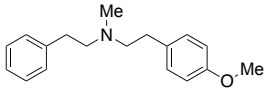
Synthesized from **1m** (94.1 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (93:7) to afford **5m** (19.0 mg, 25%) as a clear yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.23 – 7.18 (m, 3H), 3.78 – 3.72 (m, 4H), 2.85 – 2.78 (m, 2H), 2.64 – 2.57 (m, 2H), 2.57 – 2.49 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.27, 128.82, 128.54, 126.23, 67.12, 61.01, 53.85, 33.46. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{12}H_{18}NO^+$ 192.1388; Found 192.1382



4-methoxy-*N*-methyl-*N*-phenethylaniline 5n

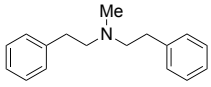
Synthesized from **1n** (114.1 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with hexanes/EtOAc (7:3) to afford **5n** (63.7 mg, 65%) as an off white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 2H), 7.26 – 7.18 (m, 3H), 6.90 – 6.84 (m, 2H), 6.77 – 6.72 (m, 2H), 3.78 (s, 3H), 3.54 – 3.46 (m, 2H), 2.87 (s, 3H), 2.87 – 2.78 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.62, 143.89, 140.03, 128.79, 128.51, 126.13, 114.89, 114.43, 55.87, 55.83, 39.08, 32.75. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{16}H_{12}NO^+$ 242.1545; Found 242.1550



***N*-(4-methoxyphenethyl)-*N*-methyl-2-phenylethan-1-amine 5o**

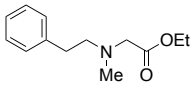
Synthesized from **1o** (125.1 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with hexanes/EtOAc (7:3) to afford **5o** (64.6 mg, 60%) as a clear yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 7H), 7.21 (td, *J* = 6.2, 1.7 Hz, 3H), 7.14 – 7.10 (m, 2H), 6.86 – 6.81 (m, 2H), 3.79 (s, 3H), 2.91 – 2.72 (m, 8H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.23, 139.74, 131.71, 129.75, 128.83, 128.65, 126.39, 114.08, 59.47, 59.26, 55.40, 41.98, 33.32, 32.45. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{18}H_{24}NO^+$ 270.1858; Found 270.1853



***N*-methyl-*N*-phenethyl-2-phenylethan-1-amine 5p**

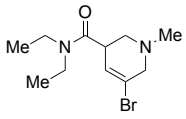
Synthesized from **1p** (113.3 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (19:1) to afford **5p** (62.0 mg, 65%) as a clear yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 4H), 7.26 – 7.18 (m, 8H),

2.91 (dt, *J* = 9.4, 3.6 Hz, 4H), 2.84 (dt, *J* = 10.7, 3.9 Hz, 4H), 2.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.36, 128.84, 128.72, 126.53, 59.09, 41.84, 33.09. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{17}H_{22}N^+$ 240.1752; Found 240.1759



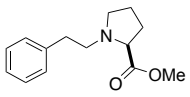
ethyl *N*-methyl-*N*-phenethylglycinate 5q

Synthesized from **1q** (106.1 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (19:1) to afford **5q** (62.8 mg, 71%) as a clear yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.23 – 7.16 (m, 3H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.31 (s, 2H), 2.86 – 2.71 (m, 4H), 2.45 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.04, 140.17, 128.81, 128.53, 126.20, 60.63, 59.09, 58.71, 42.54, 34.25, 14.42. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{13}H_{20}NO_2^+$ 222.1494; Found 222.1499



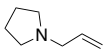
5-bromo-*N*,*N*-diethyl-1-methyl-1,2,3,6-tetrahydropyridine-3-carboxamide 5r

Synthesized from **1r** (127.6 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (19:1) to afford **5r** (52.8 mg, 48%) as a clear orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (s, 1H), 3.67 – 3.60 (m, 1H), 3.40 – 3.30 (m, 5H), 3.33 – 3.28 (m, 2H), 3.11 – 3.03 (m, 1H), 2.87 (dd, *J* = 11.6, 5.3 Hz, 1H), 2.63 (dd, *J* = 11.5, 9.7 Hz, 1H), 2.38 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.34, 125.64, 120.69, 60.79, 53.57, 44.86, 42.15, 41.51, 40.50, 14.99, 13.15. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{11}H_{20}BrN_2O^+$ 275.0759; Found 275.0759



methyl phenethyl-*L*-prolinate 5s

Synthesized from **1s** (110.9 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (93:7) plus 2% NH_4OH to afford **5s** (26.3 mg, 28%) as a clear yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 2H), 7.23 – 7.14 (m, 3H), 3.72 (s, 3H), 3.31 – 3.20 (m, 2H), 2.99 – 2.88 (m, 1H), 2.86 – 2.78 (m, 2H), 2.71 – 2.62 (m, 1H), 2.45 (q, *J* = 8.3 Hz, 1H), 2.21 – 2.07 (m, 1H), 2.02 – 1.89 (m, 2H), 1.91 – 1.77 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.82, 140.24, 128.75, 128.47, 126.18, 66.09, 56.91, 53.69, 51.98, 35.44, 29.55, 23.37. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{14}H_{20}NO_2^+$ 234.1494; Found 234.1493



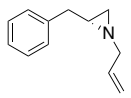
1-allylpyrrolidine 5t

Synthesized from **1t** (62.1 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (92.5:7.5) to afford **5t** (34.7 mg, 78%) as a clear yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.17 (ddt, *J* = 17.1, 1.6, 1.6 Hz, 1H), 5.07 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 3.09 (dt, *J* = 6.6, 1.3 Hz, 2H), 2.54 – 2.46 (m, 4H), 1.84 – 1.70 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.98, 117.03, 59.27, 54.02, 23.53. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_7H_{14}N^+$ 112.1126; Found 112.1141

1-allylazetidine 5u

Synthesized from **1u** (56.5 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (93:7) to afford **5u** (26.0 mg,

67%) as a clear yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.37 (dt, *J* = 10.3, 1.6 Hz, 1H), 5.23 (dt, *J* = 17.2, 1.8 Hz, 1H), 4.06 (dt, *J* = 5.3, 1.7 Hz, 2H), 3.56 – 3.45 (m, 4H), 2.11 (p, *J* = 5.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.46, 129.45, 119.46, 54.33, 46.39, 38.41. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_6H_{12}N^+$ 98.0969; Found 98.0992



(*R*)-1-allyl-2-benzylaziridine 5v

Synthesized from **1v** (86.9 mg, 1.0 equiv) following the general procedure for extrusive alkylation synthesis. The residue was purified by chromatography on silica gel with DCM/MeOH (93:7) to afford **5v** (26.3 mg, 38%) as a clear yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.23 – 7.12 (m, 3H), 5.86 (dddd, *J* = 17.6, 10.1, 7.8, 5.2 Hz, 1H), 5.25 – 5.07 (m, 2H), 3.40 – 3.28 (m, 1H), 3.09 (dd, *J* = 13.8, 7.8 Hz, 1H), 3.02 – 2.89 (m, 1H), 2.85 – 2.68 (m, 2H), 2.59 – 2.49 (m, 1H), 2.34 – 2.25 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.36, 135.52, 129.55, 129.43, 128.41, 128.36, 126.14, 125.99, 117.61, 60.04, 57.27, 53.08. HRMS (ES^+): *m/z* $[M + H]^+$ Calcd for $C_{12}H_{15}N^+$ 174.1282; Found 174.1284

Supplemental References

[1] Aitken, S. J.; Grogan, G.; Chow, C. S. Y.; Turner, N. J.; Flitsch, S. L. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 3365–3370.

[2] Verbraeken, B.; Hullaert, J.; van Guyse, J.; Hecke, K. V.; Winne, J.; Hoogenboom, R. *J. Am. Chem. Soc.*, **2018**, 140, 50, 17404–17408.

[3] Paul, S.; Guin, J. *Chem. Eur. J.*, **2021**, 27, 4412–4419.

[4] Jana, G. K.; Sinha, S. *Tetrahedron Letters*, **2012**, 53, 1671–1674.

[5] Prosser, A. R.; Liotta, D. C. *Tetrahedron Letters*, **2015**, 56, 3005–3007.

[6] Nge, C. E.; Chong, K. W.; Thomas, N. F.; Lim, S. H.; Low, Y. Y.; Kam, T. S. *J. Nat. Prod.*, **2016**, 79, 5, 1388–1399.

[7] Seong, S.; Lim, H.; Han, S. *Chem*, **2019**, 5, 353–363.

Chapter 5. Total Synthesis of Conodusine A and B

Chapter 5.1. Introduction of conodusine A and B

Conodusine A and B were isolated and fully characterized by Kam and coworkers from the stem-bark extract of a Malayan *Tabernaemontana corymbosa* in 2016[1]. These two natural products possess similar structural features to other iboga family alkaloids such as an indole, tetrahydroazepine and isoquinuclidine ring systems (Figure 5-1). The distinctive difference from other representative iboga alkaloids such as ibogaine, ibogamine and tabernanthine is that instead of having substitutions on the indole ring, conodusine A and B have an oxidized carbon on the side chain. Conodusine A and B are isomeric at C-20, the carbon next to the carbonyl, and hence prone to isomerization.

Since they were discovered relatively recently, not many studies have been done regarding their origin or bioactivity, however considering the structural similarity, it's highly likely they are produced in plants with the same pathway as other iboga alkaloids.

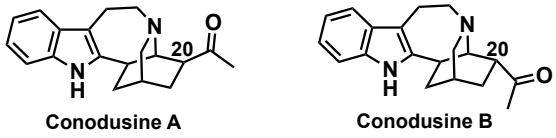


Figure 5-1. The structures of conodusine A and B.

[1] Nge, C. E.; Chong, K. W.; Thomas, N. F.; Lim, S. H.; Low, Y. Y.; Kam, T. T. Ibogan, Aspidosperman, Vincamine, and Bisindole Alkaloids from a Malayan Tabernaemontana corymbosa: Iboga Alkaloids with C-20α Substitution. *J. Nat. Prod.* **2016**, 79, 5, 1388–1399.

Chapter 5.2. Previous chemical syntheses

Long before conodusine A and B were identified as natural products, in 1965, the Büchi group unknowingly synthesized both alkaloids as intermediates while pursing the total synthesis of ibogamine. In their route, conodusine A and B were generated after a novel rearrangement mediated by zinc in 13 steps with 2% total yield (Figure 5-2). [2]

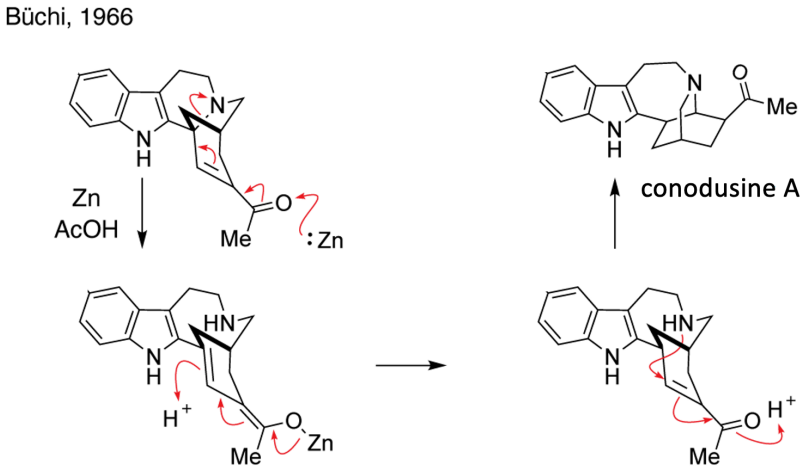


Figure 5-2. The Büchi synthesis of conodusine

Büchi's pioneering efforts inspired a later strategy by She and coworkers in 2016. Their synthesis commenced with the preparation of the indole lactam via a one-pot sequence involving a Pictet-Spengler reaction followed by an intramolecular amidation (**Figure 5-3**). After protection of the indole nitrogen with Boc_2O, an aldol condensation with protected aldehyde produced the alcohol in excellent yield. The secondary alcohol was mesylated and eliminated to afford an α,β-unsaturated lactam that underwent diastereoselective hydrogenation. In a beautiful display of polyfunctional group transformations by the same reagents, treatment with $LiAlH_4$ followed by HCl effectively reduced both the amide and ester while also removing the Boc group and hydrolyzing the ketal. Oxidation of primary alcohol followed by

[2] Büchi, G.; Coffen, D. L.; Kocsis, K.; Sonnet, P. E.; Ziegler, F. E. The Total Synthesis of (±)-Ibogamine and of (±)-Epiibogamine. *J. Am. Chem. Soc.* **1965**, 87, 2073–2075.

intramolecular aldol condensation afforded the same intermediate Büchi had previously made. This reaction is particularly impressive because they achieved 75% yield over two steps. Finally, reduction with zinc in acetic acid finally provided conodusine A and B. Their route was finished in 11 steps with 8.4% total yield[3].

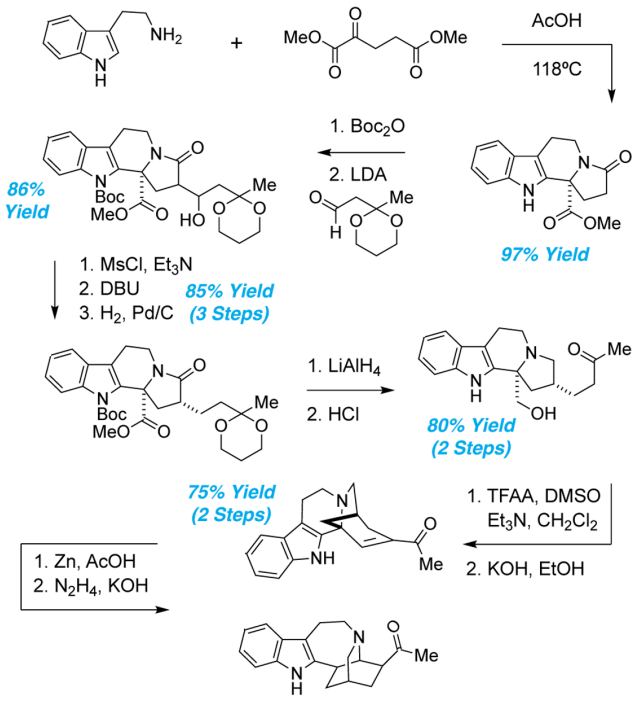


Figure 5-3. The She synthesis of conodusine A and B.

As mentioned earlier, both Büchi and She's unintended synthesis of conodusine A and B occurred while targeting a different natural product. There is only one targeted synthesis since the isolation of these two iboga alkaloids and it was a semi-synthesis done by the Han group in 2019 (Figure 5-4). Their route started from the natural product (+)-catharanthine, which was submitted to hydrogenative isomerization, saponification, followed by the decarboxylation and then treatment of the resulting alkene with borane followed by an oxidative workup with perborate afforded ibogamin-19-ol as a single diastereomer. Further

[3] Zhao, G.; Xie, X.; Sun, H.; Yuan, Z.; Zhong, Z.; Tang, S.; She, X. Bioinspired Collective Syntheses of Iboga-Type Indole Alkaloids. *Org. Lett*. **2016**, 18, 2447–2450.

oxidation of the alcohol using Parikh-Doering oxidation afforded the semi-synthesis of conodusine A and B in 6 steps with 23% yield[4].

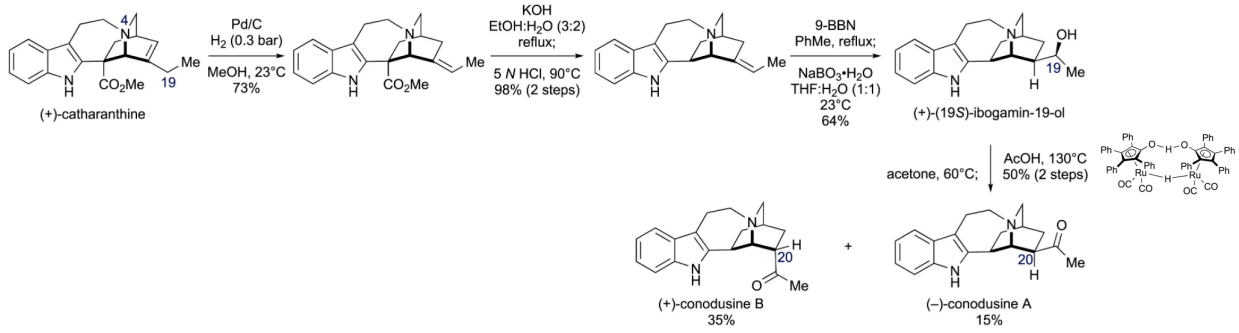


Figure 5-4. The Han semi-synthesis of conodusine A and B from catharanthine.

Chapter 5.3. Retrosynthetic analysis

We decided to implement the novel carbon-nitrogen bond building methodology we developed via the extrusive alkylation reaction by targeting both conodusine A and B. We envisage these two natural products could be prepared from key intermediate **5-1** (Figure 5-5). 5-1 could be transformed into the tetrahydroazepine precusor **5-2** using the reaction that we developed. The tetrahydroazepine ring could be therefore constructed by the C-H activation developed by Trost and co-workders using a mixture of palladium and silver.[5]

For intermediate **5-1**, it would be more straightforward to have a methyl ketone motif on the right side since that would resemble the natural products. However, considering the transformation from **5-1** to **5-2** will require the usage of TMSI reagent, which is well known to generate silyl enol ether with ketones,

[4] Seong, S.; Lim, H.; Han, S. Biosynthetically Inspired Transformation of Iboga to Monomeric Post-Iboga Alkaloids. Chem **2019**, 5, 353–363.

[5] Trost, B. M.; Godleski, S. A.; Genet, J. P. A Total Synthesis of Racemic and Optically Active Ibogamine. Utilization and Mechanism of a New Silver Ion Assisted Palladium Catalyzed Cyclization. *J. Am. Chem. Soc.***1978**, 100, 3930–3931.

the selectivity of the transformation would be compromised. One way to bypass this selectivity issue would be to protect the ketone before the transformation, followed by TMSI reaction. This protecting-deprotecting sequence would increase the step count, lower the atom economy dramatically, and possibly produce lower the overall yield of the total synthesis. While expanding the substrate scope for our TMSI reaction, one substrate that stood out was the ethyl ester carbamate because it was produced in moderate yields. With this in mind, we decided to use a methyl ester that could tolerate the reaction conditions from **5-1** to **5-2.** From previous literature, we know that methyl ester **5-2** could be converted into methyl ketone by reacting with weinreb amine followed by subsequent addition of methyl Grignard reagent. As for the key intermediate **5-1**, it could be prepared from a Diels-Alder reaction between 1,2-dihydropyridine **5-3** and methyl acrylate. The indole-dihydropyridine intermediate **5-3** could be synthesized from commercially available tryptophol and pyridine. The highlight of this route is that the tryptophol motif in the carbamate **5-3** could not only stabilize the air-sensitive dihydropyridine, but could also be integrated into the final product, thus it is considered a protecting-group free strategy.

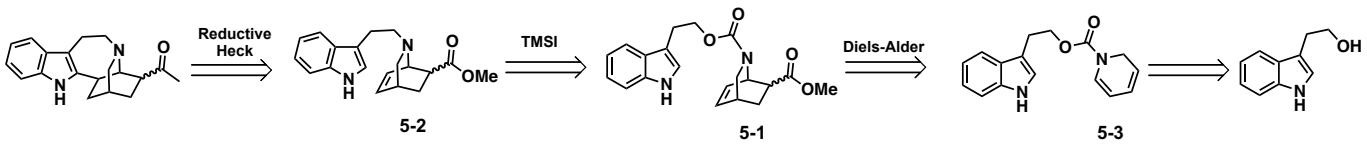


Figure 5-5. Retrosynthesis of conodusine A and B.

Chapter 5.4. Synthesis

We started our attempts to prepare the indole-dihydropyridine **5-3** from tryptophol and pyridine. Initially we imaged it could be made straightforward with carbonyldiimidazole (CDI) providing the carbonyl group followed by reduction with $NaBH_4$, yet those trials proved unsuccessful. The reason behind that is probably the difficulty of replacing the imidazole by pyridine attacking, since both of them are aromatic and nucleophilic. Therefore, we needed to find out alternative ways for the carbamate preparation; that issue was solved by using triphosgene. The desired transformation was achieved by treating tryptophol with triphosgene in the presence of NEt_3 in DCM, then transferred to another flask containing pyridine and

$NaBH_4$ followed by workup, we did observe dihydropyridine by NMR analysis. That inspired us to optimize the procedure. After screening different solvents such as DCM, pyridine, DMF, iPrOH, tBuOH, CF_3OH, acetonitrile and DCE, bases like pyridine and different amines and temperatures from dry ice/ acetone bath to ice/water bath, it turned out that DCE as solvent, NEt_3 as base with ice/ water bath gave the best result. Even better, this procedure could be done within one pot without any compromise. After workup, the crude dihydropyridine 5-3 was mixed with excess methyl acrylate and heated to 80 degrees Celsius for 48h. The indole-isoquinuclidine **5-1** was isolated in 40% yield over 2 steps as a 1:2 exo/endo mixture (Figure 5-6).

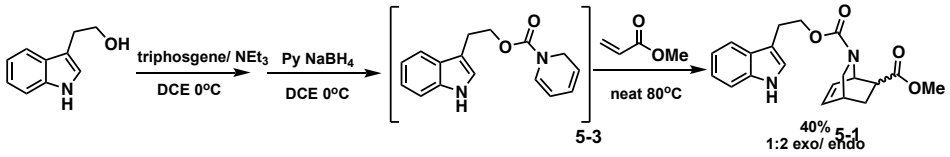


Figure 5-6. Preparation of key intermediate **5-1**.

After collecting the key intermediate **5-1**, we immediately started testing out the extrusive alkylation reaction to construct the carbon-nitrogen bond for the tetrahydroazepine precursor **5-2**. We figured out that although that **5-1** decomposed under microwave conditions, carbamate cleavage could still be effected at room temperature. To our delight, we collected up to 84% of product **5-2** by meticulously optimizing the reaction time and temperature. We found that the ideal condtions for the cleavage were to allow 5-1 to stir with TMSI for four hours at room temperature followed by heating to 60 degrees overnight after the water and potassium carbonate quench. During the process we didn't observe any epimerization of the methyl ester even though base was used (**Figure 5-7**). We concluded this based on NMR analysis.

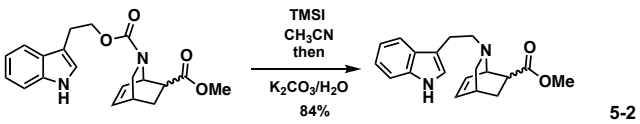


Figure 5-7. Preparation of 5-2 via TMSI-mediated extrusive alkylation.

We tried the ring closures of **5-2** by a novel C-H activation strategy developed by Trost with a 40% isolation yield[5], however, the reaction required stoichiometric amount of palladium and silver and difficult to replicate, resulting in fluctuating yields. We turned our attention to the reductive Heck reaction developed by Sinha[6]. By brominating the C-2 position of the indole with $PhNMe_3Br_3$ as bromine source, C-2 bromide substituted indole could be collected quantitively. After that, the crude bromide indole was treated with 0.1 equiv of tetrakis(triphenylphosphine) palladium and sodium formate in DMSO at elevated temperature to finally afford ring-closure product **5-4** in 45% for 2 steps without epimerization (**Figure 5-7**).

To finalize the total synthesis of these two natural products, the methyl ketone was transformed from the methyl ester **5-2** via a reaction between methyl Grignard reagent and in-situ formed Weinreb amide to produce both conodusine A and B in 65% yield. This completes the total synthesis of conodusine A and B in 3% and 6% overall yield, respectively.

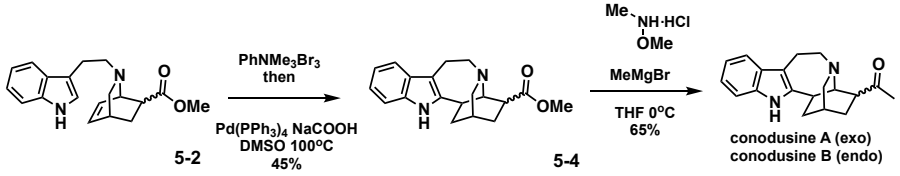


Figure 5-8. Completion of the synthesis of conodusine A and B.

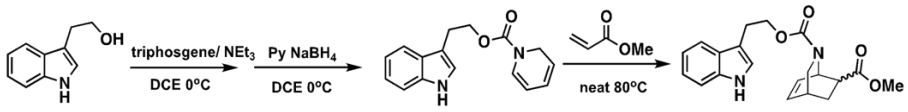
Chapter 5.5. Conclusion

Conodusine A and B, two iboga family alkaloids have been synthesized in 5 steps with 10% total yield (C-H activation route), which is the shortest and highest yield total synthesis so far. The key reactions

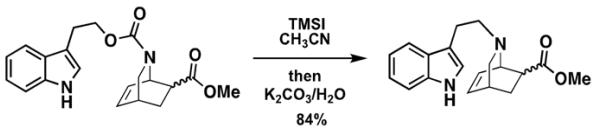
[6] Jana, G. K.; Sinha, S. Reductive Heck Coupling: An Efficient Approach toward the Iboga Alkaloids. Synthesis of Ibogamine, Epiibogamine and Iboga Analogs. *Tetrahedron*, **2012**, 53, 1671–1674.

include an in-situ generated 1,2-dihydropyridine as precursor for the Diels-Alder reaction and TMSI-mediated extrusive alkylation reaction to construct the carbon-nitrogen bond. The latter further demonstrates the robustness of the methodology we developed. Future investigation may focus on combining multiple transformations in one-pot to further simplify the synthesis. Beyond that, more iboga family alkaloids could be prepared from conodusine A and B, such as voatinggine, tabertinggine and conodusine C according to Han group's study[4]. By starting with a different substituted indole, ibogaine should also be able to be synthesized using the same strategy.

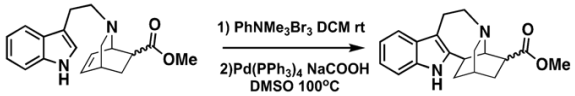
Chapter 5.6. Experimental Procedures and Spectral Data.



To a 0 °C cooled solution of tryptophol (2600 mg, 16 mmol, 1 equiv) in DCE (80 mL) was added NEt_3 (2.2 mL, 16 mmol, 1 equiv). A solution of triphosgene (2007 mg, 67 mmol, 0.4 equiv) in DCE (10 mL) was added dropwise over 2 mins. The solution was stirred at 0 °C for 60 mins, then a suspension of $NaBH_4$(1227 mg, 32 mmol, 2 equiv) in pyridine (2.6 mL, 32 mmol, 2 equiv) was added to the solution over 1 min. The suspension was stirred at 0 °C for 1.5 hour. The suspension was poured into a separatory funnel containing 100 mL cold saturated NH_4Cl solution (Caution! Heat and gas generated during this process). DCM (3 x 50 mL) was used for the extraction. The organic extracts were combined, washed with brine (1 x 50 mL), dried over Na_2SO_4 and concentrate under reduced pressure. The crude dihydropyridine was mixed with methyl acrylate (7.2 mL, 80 mmol, 5 equiv) and heated to 80 °C for 72 hours. The organic extracts were concentrated under reduced pressure and then purified by chromatography on silica gel (EtOAc/Hexane 1:2) to afford the carbamate (2260 mg, 1:2 exo/endo) with 40% yield as colorless liquid.

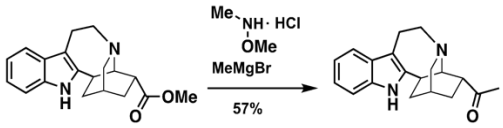


To a solution of the carbamate (800 mg, 2.2 mmol, 1 equiv) in CH_3CN (10 mL) under N_2 was added TMSI (0.64 mL, 4.4 mmol, 2 equiv) dropwise, the solution was stirred at room temperature for 4 hours. H_2O (0.12 mL, 6.6 mmol, 3 euqiv) was added dropsiwe, then K_2CO_3 (912 mg, 6.6 mmol, 3 equiv) was added one portion. The suspention was heated to 60 °C overnight. The suspension was poured into a separatory funnel containing 100 mL saturated Na_2CO_3 solution, DCM (3 x 50 mL) was used for the extraction. The organic extracts were combined, dried over Na_2SO_4, and concentrate under reduced pressure. The residue was purified by chromatography on silica gel (MeOH/DCM 1:15) to afford amine product (533 mg, 82%, exo/endo = 1:2) as light yellow oil.



To a solution of the amine (20 mg, 0.06 mmol, 1 equiv) in DCM (1 mL) was added phenyltrimethylammonium tribromide (27 mg, 1.1 mmol, 1,1 equiv). The solution was stirred at room temperature for 25 mins, then saturated solution of $NaHSO_3$ (5 mL) was added and stirred for 1 min. The solution was poured into a separatory funnel containing 50 mL saturated Na_2CO_3 solution, DCM (3 x 30 mL) was used for the extraction. The organic extracts were combined, dried over Na_2SO_4, and concentrate under reduced pressure. 28 mg of dark oil was collected (>99% yield). The crude product was dissoved in anhydrous DMSO (1 mL) under N_2. $Pd(PPh_3)_4$ (7 mg, 0.006 mmol, 0.1 equiv) and NaCOOH (16 mg, 0.24 mmol, 4 equiv) was added sequentially under N_2. The solution was heated to 100 °C for 90 mins. After cooling to ambient temperature, the solution was poured into a separatory funnel containing 50 mL saturated Na_2CO_3 solution, DCM (3 x 30 mL) was used for the extraction. The organic extracts were combined, dried over Na_2SO_4, and concentrate under reduced pressure. The residue was purified by chromatography on silica gel (MeOH/DCM 1:20) to afford ring-closure product (13 mg, 45% exo/endo =

1:2) as a light yellow oil. Exo product ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.70 (br s, 1H), 7.47 (dd, *J* = 6.3, 2.1 Hz, 1H), 7.26 (dd, *J* = 6.6, 2.4 Hz, 1H), 7.14-7.09 (m, 2H), 3.73 (s, 3H), 3.58 (t, *J* = 2.1 Hz, 1H), 3.39-3.26 (m, 2H), 3.21-3.15 (dd, *J* = 14.5, 4 Hz, 1H), 3.02-3.11 (m, 3H), 2.76-2.71 (ddd, *J* = 10.93, 5.4, 2.2 Hz, 1H), 2.70-2.62 (m, 1H), 2.40-2.33 (dm, *J* = 12 Hz, 1H), 2.08 (m, 1H), 1.98 (m, 1H), 1.79-1.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 175.3, 141.0, 134.7, 129.8, 121.2, 119.3, 118.0, 110.3, 109.6, 56.9, 54.0, 52.0, 49.3, 45.9, 39.8, 34.4, 26.0, 25.9, 20.4 Endo product ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.65 (br s, 1H), 7.41 (d, *J* = 6.9 Hz, 1H), 7.18 (dd, *J* = 7, 1 Hz, 1H), 7.03 (m, 2H), 3.64 (s, 3H), 3.37 (s, 1H), 3.32-3.23 (m, 3H), 3.16-3.07 (m, 3H), 2.95 (dd, *J* = 11.7, 4.8 Hz, 1H), 2.66 (m, 1H), 2.09-2.01 (m, 2H), 1.97-1.84 (m, 2H), 1.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 174.9, 140.7, 134.5, 129.4, 121.4, 119.5, 117.9, 110.4, 109.6, 55.8, 54.4, 52.1, 49.2, 45.5, 35.5, 34.4, 26.0, 25.6, 20.1; Data consistent with Tetrahedron Letters 53 (2012) 1671–1674.



To an ice/H_2O cooled solution of endo methyl ester (10 mg, 0.03 mmol, 1 equiv) with weinreb amine hydrochloride (3.7 mg, 0.036 mmol, 1.2 equiv) in anhydrous THF (1 mL) under N_2 was added methyl magnesium bromide solution (1.3 M in THF, 0.1 mL, 0.13 mmol, 4.5 equiv) dropwise. The cooling bath was removed and the solution was stirred for 4 hours. The solution was poured into a separatory funnel containing 20 mL saturated Na_2CO_3 solution, DCM (3 x 20 mL) was used for the extraction. The organic extracts were combined, dried over Na_2SO_4, and concentrate under reduced pressure. The residue was purified by chromatography on silica gel (MeOH/DCM 1:20) to afford conodusine B (5 mg, 57%) as light yellow oil. ^{1}H NMR (600 MHz, CDCl3): δ 7.89 (s, 1H), 7.46 (d, J = 7.3 Hz, 1H), 7.21 (d, J = 7.3 Hz, 1H), 7.09 (t, J = 6.7 Hz, 1H), 7.07 (t, J = 6.9 Hz, 1H), 3.41–3.35 (m, 2H), 3.34–3.30 (m, 2H), 3.25–3.21 (m, 1H), 3.13 (s, 2H), 2.84 (dd, J = 11.7, 5.1 Hz, 1H), 2.68 (d, J = 14.9 Hz, 1H), 2.20 (s, 3H), 2.15–2.10 (m, 1H), 2.07 (t, J = 12.5 Hz, 1H), 2.00–1.98 (m, 1H), 1.75 (t, J = 12.3 Hz, 1H), 1.61 (dt, J = 13.3, 2.2 Hz, 1H). ^{13}C

NMR (150 MHz, CDCl3): δ 209.8, 141.2, 134.5, 129.5, 121.3, 119.4, 117.9, 110.6, 109.9, 55.6, 54.8, 54.8, 49.7, 35.6, 34.6, 29.3, 26.1, 24.8, 20.3.

Conodusine A was prepared with the same procedure with similar yield (65%) as colorless film. ^{1}H NMR (600 MHz, CDCl3): δ 7.82 (s, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.25 (d, J = 7.7 Hz, 1H), 7.12 (t, J = 7.0 Hz, 1H), 7.09 (t, J = 7.2 Hz, 1H), 3.59 (s, 1H), 3.31 (ddd, J = 16.4, 12.8, 4.2 Hz, 1H), 3.23 (d, J = 14.4 Hz, 1H), 3.12 (dd, J = 13.7, 3.0 Hz, 1H), 3.05 (ddd, J = 11.6, 5.2, 1.7 Hz, 1H), 3.00 (dt, J = 5.3, 2.4 Hz, 1H), 2.98 (app-t, J = 2.7 Hz, 1H), 2.67 (ddd, J = 10.6, 6.5, 3.8 Hz, 1H), 2.63 (app-d, J = 16.3 Hz, 1H), 2.47 (ddd, J = 13.5, 7.0, 3.5 Hz, 1H), 2.19 (s, 3H), 2.10 (t, J = 12.5 Hz, 1H), 2.00–1.97 (m, 1H), 1.72 (ddt, J = 13.2, 4.6, 2.3 Hz, 1H), 1.52 (dt, J = 12.1, 2.0 Hz, 1H). ^{13}C NMR (150 MHz, CDCl3): δ 209.3, 141.5, 134.6, 129.7, 121.3, 119.5, 118.1, 110.5, 109.9, 56.9, 54.5, 54.0, 49.4, 39.9, 34.8, 28.0, 26.3, 24.1, 20.4. Data consistent with *J. Nat. Prod.* **2016**, 79, 1388−1399.