OL Organic Letters

pubs.acs.org/OrgLett Letter

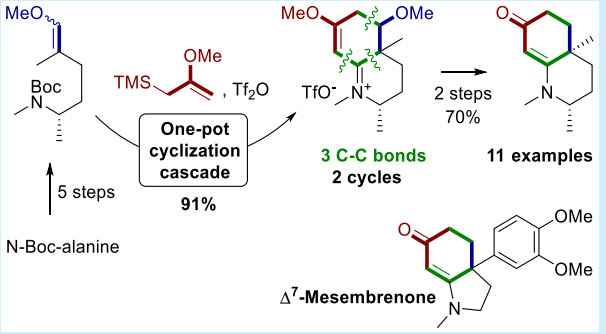
Functionalized Polyhydroquinolines from Amino Acids Using a Key One-Pot Cyclization Cascade and Application to the Synthesis of (±)-Δ^7-Mesembrenone

Shawn Gallagher-Duval, Vincent Lapointe, and Guillaume Bélanger*

Cite This: *Org. Lett.* 2021, 23, 8606–8611 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Substituted polyhydroquinolines are ubiquitous skeletal cores found in drugs and bioactive natural products. As a new route to access this motif, we successfully developed a one-pot cyclization cascade with high chemocontrol and diastereoselectivity. The sequence generates two cycles, three carbon−carbon bonds, and an all-carbon quaternary center in a highly convergent process. Functionalized polyhydroquinolines and congeners can be accessed from commercially available amino acids. This versatile and robust strategy was applied to the synthesis of (±)-Δ^7-mesembrenone.



Polyhydroquinolines are present in numerous natural products and active pharmaceutical intermediates.[1−3] Selected examples shown in Figure 1 exemplify their wide

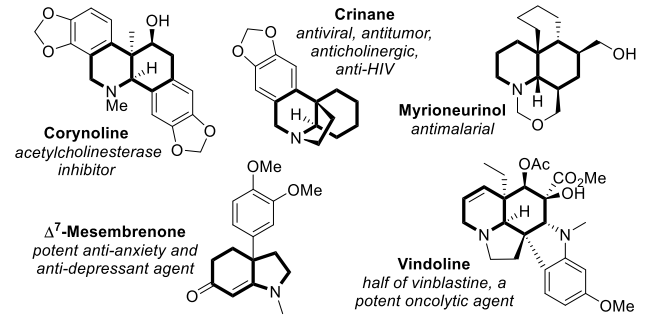
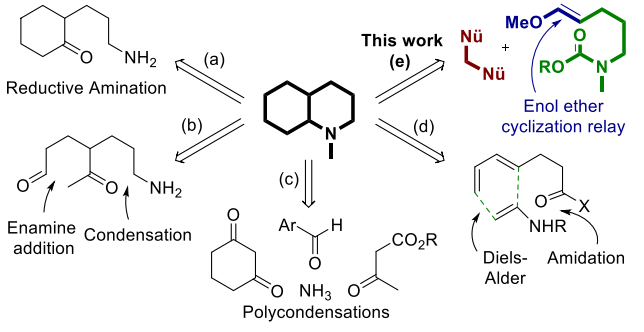


Figure 1. Selected bioactive polyhydroquinoline-based alkaloids.

spectrum of biological activities, ranging from acetylcholinesterase inhibition, often associated with potential treatment of Alzheimer's disease, to anticancer and antiviral properties.[4] Saturated polycyclic frameworks are particularly appealing for medicinal chemistry programs,[5] and aza-bicyclic cores of natural products or natural product-inspired derivatives occupy a unique place among privileged structures.[6]

Over the years, several approaches were developed to access polyhydroquinolines (Scheme 1). Classical routes consist of reductive amination (a)[7] and condensation chemistry through enamine intermediates generated (b)[8] intra- or (c)[9] intermolecularly. The latter is particularly interesting because this multicomponent variant is highly convergent, although the

Scheme 1. Classical Approaches to Polyhydroquinolines



substrate scope is limited. Another approach (d) uses a Diels−Alder cycloaddition followed by lactam formation.[10] In all of these methods, the amine partner is used as a nucleophile in condensation or amidation reactions. Therefore, C−N bond formation is always involved.

With an ultimate goal of efficacy and versatility for the preparation of substituted polyhydroquinolines, we wanted to assemble both the carbocycle and the piperidine rings in a single procedure. The latter would bring together a linear carbamate substrate and a dinucleophile partner (e). Our

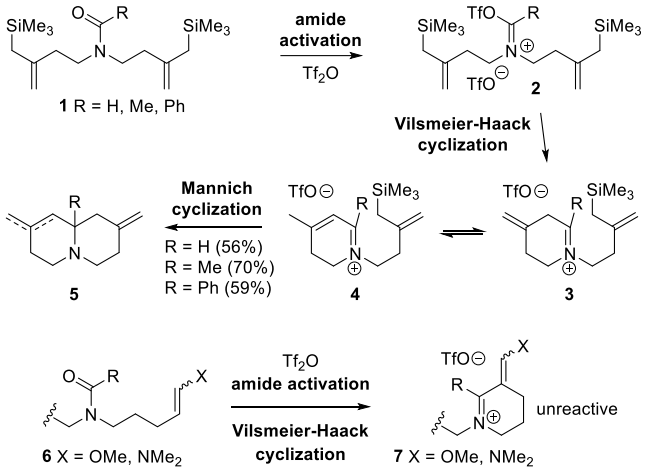
Received: September 29, 2021
Published: October 25, 2021

https://doi.org/10.1021/acs.orglett.1c03323
Org. Lett. 2021, 23, 8606–8611

approach does not imply C−N bond formation, contrary to all previously reported methods, and thus brings a novel synthetic avenue to this framework. Ideally, carbamate substrates would be prepared from commercially available amino acids in short order. As an additional element of originality, we contemplated the idea to use a methyl enol ether as a polyvalent cyclization relay, acting as both a nucleophile and an electrophile partner in the polycyclization reaction.

We previously reported the activation of amides followed by sequential trapping with pendent allylsilane and allylstannane nucleophiles (Scheme 2).[11,12] While studying the scope of this

Scheme 2. Reactivity Issues in Our Previous Work on Double Cyclization with Activated Amides

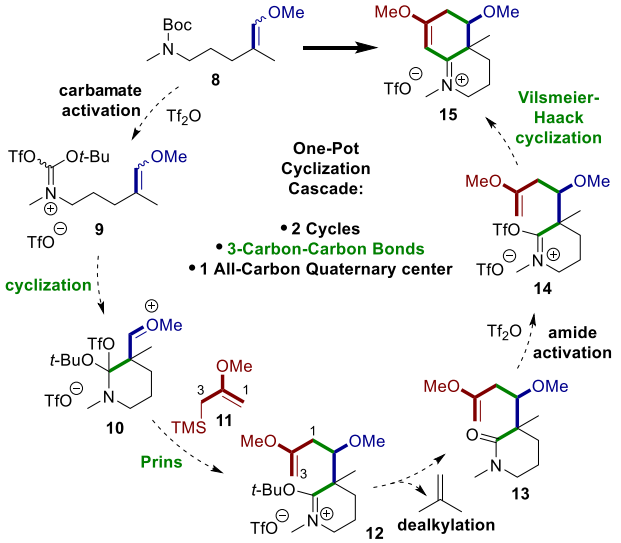


method, we faced reactivity issues; upon amide activation, the resulting highly reactive triflyliminium ion **2** is trapped readily with a first nucleophile, leaving the least reactive iminium ion **3** to engage in the Mannich cyclization. As a result, partial conjugation occurred prior to cyclization (cf. **4**), leading to a mixture of quinolizidines **5** in moderate yields. Although increasing the reactivity of the nucleophiles (enol ether or enamine **6**) might seem appealing at first glance, it resulted in an unreactive conjugated iminium ion **7**. We thus opted to rather increase the electrophilicity of the iminium ion by switching to activation of a functional group of higher oxidation state, namely a carbamate.

Our approach is depicted in Scheme 3. The strategy we envisaged consists of a cyclization cascade that would generate three carbon−carbon bonds, two cycles, and an all-carbon quaternary center in a single operation.[13] Less common than amide or formamide activation, activation of carbamates is a powerful tool that has been used in fascinating methodologies and natural product syntheses.[14,15]

The activation of carbamate **8** would result in a triflyliminium ion **9** bearing a methyl enol ether nucleophile. Activation conditions and the compatibility of enol ethers as non-aromatic carbon π-nucleophiles are inspired from our previous work with amides in Vilsmeier−Haack-type reactions.[11,16] To prevent conjugation of the iminium ion with the enol ether after cyclization [cf. **7**, where X = OMe (Scheme 2)], we decided to use a C-substituted enol ether, although the generated quaternary center may hamper the final cyclization. Upon ring closure, high-energy oxycarbenium ion **10** would need to be trapped rapidly in a Prins reaction with an external nucleophile **11** (Scheme 3). Hence, the methyl enol ether on

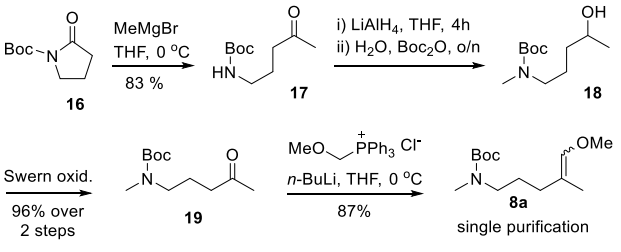
Scheme 3. Envisaged Key One-Pot Cyclization Cascade



substrate **8** would have a dual role because it serves as a nucleophile in the trapping of iminium ion **9** and as an electrophile in the ensuing Prins reaction. External enol ether **11** is designed as a 1,3-dinucleophile. After the Prins addition, desilylation of C3 would generate a new enol ether that could ultimately engage in a third nucleophilic addition. Ejection of the triflate anion would lead to an unstable alkoxyiminium ion **12** that would readily dealkylate to the corresponding amide **13**.[17] The use of an excess of triflic anhydride (Tf_2O) would serve to activate the latter,[18,19] now all set for a final Vilsmeier−Haack-type cyclization with the pendent enol ether. We anticipated the full successive reactions to occur in a cascade process, without further intervention, all the way to an iminium ion **15** sufficiently stabilized by conjugation to allow for its isolation and characterization.

To test such an ambitious reaction cascade, model compound **8a** was prepared in only four steps (Scheme 4).

Scheme 4. Synthesis of Model Compound 8a



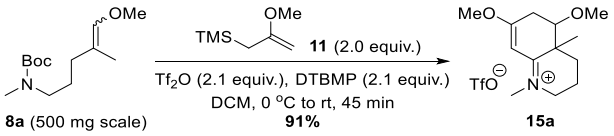
A methyl Grignard addition on commercially available *N*-Boc-pyrrolidine-2-one (**16**) afforded ketone **17**. Both the carbamate and the ketone were reduced with lithium aluminum hydride to the corresponding (*N*-methylamino)alcohol **18** that was Boc-protected in the reaction quenching. After a Swern oxidation, the resulting ketone **19** was olefinated to methyl enol ether **8a**. All transformations are robust; yields are good to excellent, and the whole sequence was performed in 3 days with a single purification.

When substrate **8a** was activated with an excess of triflic anhydride in the presence of a non-nucleophilic base (DTBMP) and dinucleophile **11**, the complete cascade of carbamate activation, cyclization, Prins addition, dealkylation,

https://doi.org/10.1021/acs.orglett.1c03323
Org. Lett. 2021, 23, 8606−8611

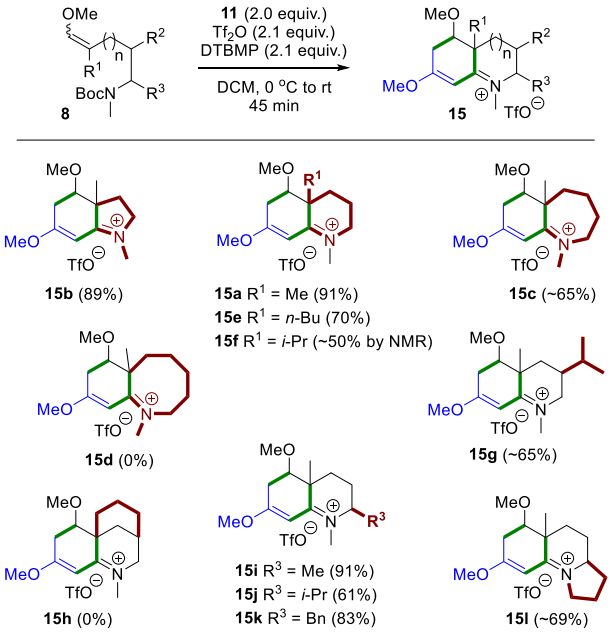
amide activation, and Vilsmeier–Haack cyclization occurred within 45 min at rt (Scheme 5). Bicyclic iminium ion **15a** was isolated in an excellent 91% yield.

Scheme 5. Key Cyclization Cascade with Compound 8a



Encouraged by such a spectacular result, we elaborated the substrates to study the scope of the key one-pot six-transformation cascade (Scheme 6). In particular, we wanted

Scheme 6. Scope of the Key One-Pot Cyclization Cascade

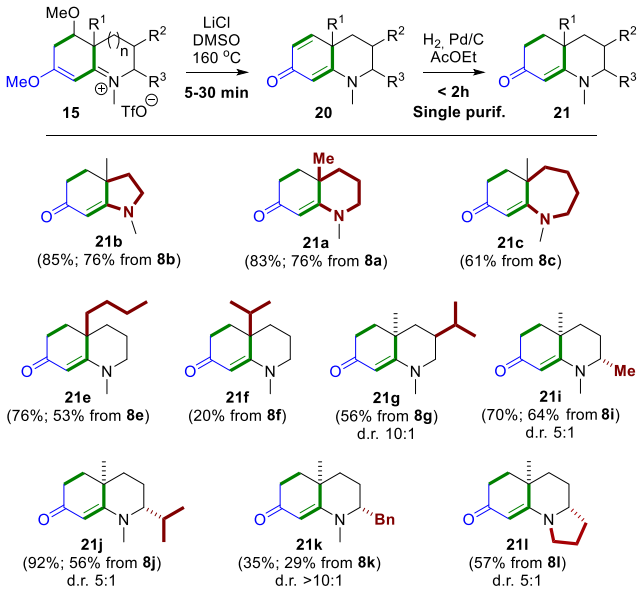


to evaluate the possibility of accessing different ring sizes in fused and bridged systems, substitution at the ring junction, and substitution around the aza-cycle.

Once submitted to the reaction conditions, precursors **8b**, **8a**, and **8c** easily afforded the five-, six-, and seven-membered aza-cycles **15b**, **15a**, and **15c**, respectively, in good to excellent yields.[20] Known to be difficult to achieve, eight-membered ring **15d** could not be obtained, and the activated precursor degraded over time. Different alkyl groups (R^1) on the quaternary center at the ring junction were also accessible. Not surprisingly, the yield decreased with increasing steric hindrance from methyl to *n*-butyl to the bulkier isopropyl group (see **15a**, **15e**, and **15f**, respectively). The latter was well-tolerated when positioned in R^2 (**15g**) or R^3 (**15j**). The bridged system presumably incorporated too much ring constraint, resulting in no conversion (**15h**). Finally, all precursors derived from natural amino acids (cf. **8i–l**) were cleanly converted to their respective R^3-substituted iminium ions **15i–l**, respectively, in good yields.[21] All *β*-methoxy-*α*,*β*-unsaturated iminium products **15** were stable and isolated, and several were even successfully purified by standard flash chromatography (cf. **15a**, **15b**, **15e**, and **15i–k**).

To further increase the synthetic value of the aza-bicyclic products, we investigated methods to transform *β*-methoxy-*α*,*β*-unsaturated iminium products **15** into enaminones. The enaminone functional group is present in several bioactive molecules, in addition to being known as a versatile synthetic lever for further derivatization.[22,23] Although all acidic or basic hydrolysis methods performed on compounds **15** found limited success, Krapcho dealkylation conditions proved to be the most efficient method for forming the enaminone. Hence, iminium ions **15** were heated in DMSO in the presence of lithium chloride for only 5–30 min. Under these conditions, once the enaminone is generated, the methoxy group was eliminated readily, leading to the corresponding enone **20** (Scheme 7). The latter was treated directly under hydrogenation conditions to produce the desired stable enaminone **21**.

Scheme 7. Transformation to Enaminone Products 21



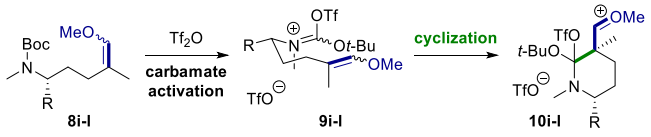
In general, the dealkylation and hydrogenation steps worked well, mostly in >60% yields, with an average yield of 55% over three steps from cyclization precursors **8**. The five- and six-membered rings gave conversions higher than those of seven-membered ring analogues (cf. **21a** and **21b** vs **21c**). Smaller substituents on the quaternary center resulted in higher yields for enaminone formation (cf. **21b**, **21e**, and **21f**), although no trend was observed for substitution on the piperidine ring (see **21g–l**).

For products **21g–l** bearing two stereogenic centers, diastereomeric ratios were good (5:1) to excellent (>10:1).[24,25] A diastereomeric preference could be rationalized using a simple chairlike model for the addition of the enol ether to activated carbamate **9**, placing the substituent in an equatorial orientation (Scheme 8).

To demonstrate the value of this synthetic approach, we then focused on the synthesis of (±)-Δ^7-mesembrenone. This natural product is a major constituent of *Sceletium namaquense* and was recently linked to a potent inhibitory effect on the 5-HT transporter, which could be used to treat a variety of psychological and psychiatric disorders, including anxiety and depression.[26] This alkaloid is also a precursor of mesembrine, which is a well-documented natural product. With more than

https://doi.org/10.1021/acs.orglett.1c03323
Org. Lett. 2021, 23, 8606–8611

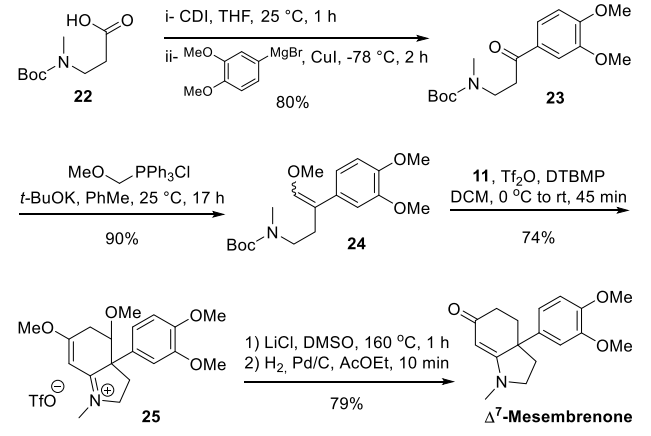
Scheme 8. Diastereomeric Preference in the Cyclization of Activated Carbamates 9i–l



40 different syntheses of mesembrine[27] and several syntheses of Δ^7-mesembrenone[28] already reported in the literature, this type of alkaloid represents a great benchmark for evaluating the applicability and efficacy of our synthetic methodology.

The synthesis of cyclization precursor **24** was accomplished in just two steps from commercially available Boc-β-sarcosine [**22** (Scheme 9)]. Activation of carbamate **24** in our cyclization

Scheme 9. Total Synthesis of (±)-Δ^7-Mesembrenone



cascade conditions afforded the iminium ion **25** in 74% yield. The ensuing Krapcho demethylation and hydrogenation yielded (±)-Δ^7-mesembrenone in 79% yield over these two steps. This route compares to the shortest and most efficient syntheses of this natural product.[29]

In summary, the methodology we developed is an effective approach for generating high-value polyhydroquinolines, as well as cyclohexapyrrolidine and azepane congeners. The key step precursors are readily prepared from amino acids in only four or five steps. The one-pot cyclization cascade uses a *tert*-butylcarbamate as a sequential double electrophile, an internal methyl enol ether as a cyclization relay, and an external dinucleophile in a highly chemocontrolled reaction sequence. The resulting stable and isolable β-methoxy-α,β-unsaturated iminium products can be transformed into enaminones as attractive synthetic levers. Building up libraries of such products is rapid because polyhydroquinolines could be obtained in no more than 5 days and as few as three purifications with an average overall yield of ∼20% from commercially available amino acids, which sets the stage for applications in medicinal chemistry. This methodology was also used to synthesize (±)-Δ^7-mesembrenone in only five steps from commercially available Boc-β-sarcosine in 42% overall yield.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c03323.

Experimental procedures, characterization data, and copies of the ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Guillaume Bélanger − *Département de chimie, Université de Sherbrooke, Sherbrooke, Québec, Canada J1K 2R1;* orcid.org/0000-0002-7454-8760; Email: Guillaume.Belanger@USherbrooke.ca

Authors

Shawn Gallagher-Duval − *Département de chimie, Université de Sherbrooke, Sherbrooke, Québec, Canada J1K 2R1*

Vincent Lapointe − *Département de chimie, Université de Sherbrooke, Sherbrooke, Québec, Canada J1K 2R1*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c03323

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Dr. Johnathan Boudreault and Mr. Olivier Gagnon (Département de chimie, Université de Sherbrooke) are acknowledged for their early work on a related project. S.G.-D. thanks the Université de Sherbrooke, the Famille Roger Beaudoin, and Hydro-Québec for fellowships. V.L. thanks NSERC, FRQNT, the Université de Sherbrooke, and Hydro-Québec for fellowships. This research was supported by the Natural Science and Engineering Research Council (NSERC) of Canada and the Université de Sherbrooke.

■ DEDICATION

Dedicated to Emeritus Professor Dr. Jean Lessard, colleague and mentor.

■ REFERENCES

(1) Crow, W. D.; Michael, M. The Alkaloids of KopsiaLongiflora Merrill. I. Isolation of the Alkaloids. *Aust. J. Chem.* **1955**, *8*, 129−135.

(2) Deutsch, H. F.; Evenson, M. A.; Drescher, P.; Sparwasser, C.; Madsen, P. O. Isolation and Biological Activity of Aspidospermine and Quebrachamine from an Aspidosperma Tree Source. *J. Pharm. Biomed. Anal.* **1994**, *12*, 1283−1287.

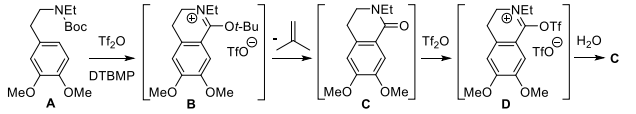
(3) Jin, Z. Amaryllidaceae and Sceletium Alkaloids. *Nat. Prod. Rep.* **2003**, *20*, 606−614.

(4) (a) Kim, D. K. Inhibitory Effect of Corynoline Isolated from the Aerial Parts Ofcorydalis Incisa on the Acetylcholinesterase. *Arch. Pharmacal Res.* **2002**, *25*, 817−819. (b) Nocket, A. J.; Weinreb, S. M. Total Synthesis of the Tetracyclic Antimalarial Alkaloid (±)-Myrioneurinol. *Angew. Chem., Int. Ed.* **2014**, *53*, 14162−14165 and references cited therein. (c) Gorman, M.; Neuss, N.; Biemann, K. Vinca Alkaloids. X[1]. The Structure of Vindoline. *J. Am. Chem. Soc.* **1962**, *84*, 1058−1059. (d) Gao, Y.-R.; Wang, D.-Y.; Wang, Y.-Q. Asymmetric Syntheses of Amaryllidaceae Alkaloids (−)-Crinane and (+)-4a-Dehydroxycrinamabine. *Org. Lett.* **2017**, *19*, 3516−3519 and references cited therein.

(5) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752−6756.

(6) (a) Bharate, S. S.; Mignani, S.; Vishwakarma, R. A. Why Are the Majority of Active Compounds in the CNS Domain Natural Products? A Critical Analysis. *J. Med. Chem.* **2018**, *61*, 10345−10174. (b) Kim, J.; Kim, H.; Park, S. B. Privileged Structures: Efficient

Chemical "Navigators" toward Unexplored Biologically Relevant Chemical Spaces. *J. Am. Chem. Soc.* **2014**, *136*, 14629−14638.
(7) McLeod, M. C.; Aubé, J. Efficient Access to sp^3-Rich Tricyclic Amine Scaffolds through Diels−Alder Reactions of Azide-Containing Silyloxydienes. *Tetrahedron* **2016**, *72*, 3766−3774.
(8) Lee, A. S.; Liau, B. B.; Shair, M. D. A. Unified Strategy for the Synthesis of 7-Membered-Ring-Containing Lycopodium Alkaloids. *J. Am. Chem. Soc.* **2014**, *136*, 13442−13452.
(9) Saha, M.; Luireingam, T. S.; Merry, T.; Pal, A. K. Catalyst-Free, Knoevenagel−Michael Addition Reaction of Dimedone under Microwave Irradiation: An Efficient One-Pot Synthesis of Polyhydroquinoline Derivatives. *J. Heterocycl. Chem.* **2013**, *50*, 941−944.
(10) Wang, N.; Du, S.; Li, D.; Jiang, X. Divergent Asymmetric Total Synthesis of (+)-Vincadifformine, (−)-Quebrachamine, (+)-Aspidospermidine, (−)-Aspidospermine, (−)-Pyrifolidine, and Related Natural Products. *Org. Lett.* **2017**, *19*, 3167−3170.
(11) (a) Bélanger, G.; O'Brien, G.; Larouche-Gauthier, R. Rapid Assembly of Quinolizidines via Consecutive Nucleophilic Cyclizations onto Activated Amides. *Org. Lett.* **2011**, *13*, 4268−4271. (b) Bélanger, G.; Dupuis, M.; Larouche-Gauthier, R. Asymmetric Total Synthesis of (+)-Virosine A via Sequential Nucleophilic Cyclizations onto an Activated Formamide. *J. Org. Chem.* **2012**, *77*, 3215−3221.
(12) For a selection of lead references on amide activation and addition of carbon nucleophiles, see: (a) Bechara, W. S.; Pelletier, G.; Charette, A. B. Chemoselective synthesis of ketones and ketimines by addition of organometallic reagents to secondary amides. *Nat. Chem.* **2012**, *4*, 228−234. (b) Xiao, K.-J.; Luo, J.-M.; Xia, X.-E.; Wang, Y.; Huang, P.-Q. General One-Pot Reductive gem-Bis-Alkylation of Tertiary Lactams/Amides: Rapid Construction of 1-Azaspirocycles and Formal Total Synthesis of (±)-Cephalotaxine. *Chem. - Eur. J.* **2013**, *19*, 13075−13086. (c) White, K. L.; Mewald, M.; Movassaghi, M. Direct Observation of Intermediates Involved in the Interruption of the Bischler−Napieralski Reaction. *J. Org. Chem.* **2015**, *80*, 7403−7411. (d) Kaiser, D.; Bauer, A.; Lemmerer, M.; Maulide, N. Amide activation: an emerging tool for chemoselective synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7899−7925.
(13) Such multicomponent reactions are often seen as green chemistry approaches. See: (a) Touré, B. B.; Hall, D. G. Natural Product Synthesis Using Multicomponent Reaction Strategies. *Chem. Rev.* **2009**, *109*, 4439−4486. (b) Anastas, P.; Eghbali, N. Green Chemistry: Principles and Practice. *Chem. Soc. Rev.* **2010**, *39*, 301−312.
(14) (a) Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockless, D. C. R.; Holman, J. W.; Read, R. W.; Wu, A. W. Trifluoromethanesulfonic Anhydride−4-(*N*,*N*-Dimethylamino)-Pyridine as a Reagent Combination for Effecting Bischler−Napieraiski Cyclisation under Mild Conditions: Application to Total Syntheses of the Amaryllidaceae Alkaloids *N*-Methylcrinasiadine, Anhydrolycorinone, Hippadine and Oxoassoanine. *J. Chem. Soc., Chem. Commun.* **1995**, 2551−2553. (b) Wang, X.-J.; Tan, J.; Grozinger, K. A Significantly Improved Condition for Cyclization of Phenethylcarbamates to N-Alkylated 3,4-Dihydroisoquinolones. *Tetrahedron Lett.* **1998**, *39*, 6609−6612. (c) Pampín, M. C.; Estévez, J. C.; Estévez, R. J.; Suau, R.; Castedo, L. First Total Syntheses of the 1,2,3,4-Tetrahydronaphtho[2,1-*f*]isoquinolinesAnnoretine and Litebamine. *Tetrahedron* **2003**, *59*, 8057−8065. (d) Lee, S.-H.; Matsushita, H.; Clapham, B.; Janda, K. D. The Direct Conversion of Carbamates to Ureas Using Aluminum Amides. *Tetrahedron* **2004**, *60*, 3439−3443. (e) Adachi, S.; Watanabe, K.; Iwata, Y.; Kameda, S.; Miyaoka, Y.; Onozuka, M.; Mitsui, R.; Saikawa, Y.; Nakata, M. Total Syntheses of Lactonamycin and Lactonamycin Z with Late-Stage A-Ring Formation and Glycosylation. *Angew. Chem., Int. Ed.* **2013**, *52*, 2087−2091. (f) Spyropoulos, C.; Kokotos, C. G. One-Pot Synthesis of Ureas from Boc-Protected Amines. *J. Org. Chem.* **2014**, *79*, 4477−4483. (g) Kim, H.-K.; Lee, A. One-pot synthesis of carbamates and thiocarbamates from Boc-protected amines. *Tetrahedron Lett.* **2016**, *57*, 4890−4892.
(15) To the best of our knowledge, there is a single example of carbamate activation used to generate carbon−carbon bonds in total synthesis, by the group of Magnus, to access Kopsia alkaloids. See: Magnus, P.; Gazzard, L.; Hobson, L.; Payne, A. H.; Rainey, T. J.; Westlund, N.; Lynch, V. Synthesis of the Kopsia Alkaloids (±)-Pauciflorine B, (±)-Lahadinine B, (±)-Kopsidasine, (±)-Kopsidasine-N-Oxide, (±)-Kopsijasminilam and (±)-11-Methoxykopsilongine. *Tetrahedron* **2002**, *58*, 3423−3443.
(16) (a) Boudreault, J.; Lévesque, F.; Bélanger, G. Studies toward Total Synthesis of (±)-Caldaphnidine C via One-Pot Sequential Intramolecular Vilsmeier−Haack and AzomethineYlide 1,3-Dipolar Cycloaddition. *J. Org. Chem.* **2016**, *81*, 9247−9268. (b) Hauduc, C.; Bélanger, G. General Approach toward Aspidospermatan-Type Alkaloids Using One-Pot Vilsmeier−Haack Cyclization and AzomethineYlide Cycloaddition. *J. Org. Chem.* **2017**, *82*, 4703−4712. (c) Boissarie, P.; Bélanger, G. Short Approach toward the Non-racemic A,B,E Tricyclic Core of Calyciphylline B-Type Alkaloids. *Org. Lett.* **2017**, *19*, 3739−3742.
(17) For alkoxyiminium ion dealkylation, see ref 14e.
(18) Amide intermediate **13** is not expected to be isolated because its activation is faster than activation of the initial carbamate **8**. For a report of selective amide activation in the presence of *tert*-butylcarbamates, see: Liu, H.; Yang, Z.; Pan, Z. Synthesis of highly substituted imidazolidine-2,4-dione (hydantoin) through Tf_2O-mediated dual activation of Boc-protected dipeptidyl Compounds. *Org. Lett.* **2014**, *16*, 5902−5905.
(19) In a control experiment, when carbamate **A** was treated with 1 equiv of Tf_2O in the presence of DTBMP, partial activation led to the expected lactam **C**, but the latter reacted faster with Tf_2O than the starting carbamate **A**, leading to partial conversion. Conversion was complete when 2 equiv of Tf_2O was used.



(20) For the preparation of substrates **8b−l**, see the Supporting Information.
(21) During the synthesis of substrates **8i−l** from enantiopure amino acids, their corresponding *N*-Boc-amino aldehyde intermediates were prone to rapid partial or complete racemization (see the Supporting Information). For a previous report, see: Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. Synthesis of highly epimerizableN-protectedS-amino aldehydesof high enantiomeric excess. *Tetrahedron Lett.* **2000**, *41*, 1359−1362.
(22) For reviews of enaminones, see: (a) Chattopadhyay, A. K.; Hanessian, S. Cyclic enaminones. Part II: Applications as Versatile Intermediates in Alkaloid Synthesis. *Chem. Commun.* **2015**, *51*, 16450−16467. (b) Negri, G.; Kascheres, C.; Kascheres, A. J. Recent Development in Preparation, Reactivity, and Biological Activity of Enaminoketones and Enaminothiones and Their Utilization to Prepare Heterocyclic Compounds. *J. Heterocycl. Chem.* **2004**, *41*, 461−491.
(23) (a) Kim, Y. W.; Niphakis, M. J.; Georg, G. I. Copper-Assisted Palladium(II)-Catalyzed Direct Arylation of Cyclic Enaminones with Arylboronic Acids. *J. Org. Chem.* **2012**, *77*, 9496−9503. (b) Wan, J.-P.; Hu, D.; Liu, Y.; Li, L.; Wen, C. Copper-Catalyzed Intramolecular Oxidative Amination of Enaminone C−H Bond for the Synthesis of Imidazo[1,2-*a*]pyridines. *Tetrahedron Lett.* **2016**, *57*, 2880−2883.
(24) The relative configuration was determined by NOESY for compounds **21g**, **21i**, and **21k** and by analogy for **21j** and **21l**. Spectra ccan be found in the Supporting Information.
(25) Diastereomeric ratios were determined by analysis of ^1H NMR spectra of the crude material.
(26) For the activity of Δ^7-mesembrenone and congeners, see: Harvey, A. L.; Young, L. C.; Viljoen, A. M.; Gericke, N. P. Pharmacological Actions of the South African Medicinal and Functional Food Plant *Sceletiumtortuosum* and its Principal Alkaloids. *J. Ethnopharmacol.* **2011**, *137*, 1124−1129.
(27) Zhao, Y.; Zhou, Y.; Du, F.; Liang, L.; Zhang, H. Review of Total Synthesis of Mesembrine. *Chin. J. Org. Chem.* **2010**, *30*, 47−59.

https://doi.org/10.1021/acs.orglett.1c03323
Org. Lett. 2021, 23, 8606−8611

(28) All reported syntheses of racemic (refs 28a−e) on enantioenriched (refs 28f and 28g) n^7-mesembrenone count at least five steps, with overall yields ranging from 21% to 42%: (a) Zhao, Y.; Zhou, Y.; Liang, L.; Yang, X.; Du, F.; Li, L.; Zhang, H. Palladium-Catalyzed Sequential Arylation and Allylic Alkylation of Highly Functionalized Ketones: A Concise Synthesis of Mesembrine. *Org. Lett.* **2009**, *11*, 555−558. (b) Zhao, Y. Total synthesis of (±)-Mesembrine. *Chin. J. Org. Chem.* **2009**, *29*, 1829−1831. (c) Michael, J. P.; Howard, A. S.; Katz, R. B.; Zwane, M. I. Formal Syntheses of (±)-Mesembrine and (±)-Dihydromaritidine. *Tetrahedron Lett.* **1992**, *33*, 6023−6024. (d) Howard, A. S.; Katz, R. B.; Michael, J. P. Thiolactams in alkaloid synthesis: a particularly short synthesis of dl-(Δ^7-mesembrenone. *Tetrahedron Lett.* **1983**, *24*, 829−830. (e) Gan, P.; Smith, M. W; Braffman, N. R.; Snyder, S. A. Pyrone Diels−Alder Routes to Indolines and Hydroindolines: Syntheses of Gracilamine, Mesembrine, and Δ^7-Mesembrenone. *Angew. Chem., Int. Ed.* **2016**, *55*, 3625−3630. (f) Spittler, M.; Lutsenko, K.; Czekelius, J. Total Synthesis of (+)-Mesembrine Applying Asymmetric Gold Catalysis. *J. Org. Chem.* **2016**, *81*, 6100−6105. (g) Nunokawa, S.; Minamisawa, M.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. Asymmetric Michael Addition Reaction of α-Aryl-Substituted Lactams Catalyzed by Chiral Quaternary Ammonium Salts Derived from Cinchona Alkaloids: A New Short Synthesis of (+)-Mesembrine. *Synlett* **2015**, *26*, 2301−2305.

(29) Data match those reported in the literature (ref 28e).

https://doi.org/10.1021/acs.orglett.1c03323
Org. Lett. 2021, 23, 8606−8611