Synthesis and Optimization of Synthetic Intermediates to Access C21-Oxygenated Aspidosperma Alkaloids

by

Nadide Hazal Avcı

B.S., Chemistry
Boğaziçi University, 2017

Submitted to the Department of Chemistry
In Partial Fulfillment of the Requirement for the Degree of

MASTER OF SCIENCE
IN CHEMISTRY

at the

Massachusetts Institute of Technology

February 2020

Signature redacted

Signature of Author..

Department of Chemistry
January 15, 2020

Signature redacted

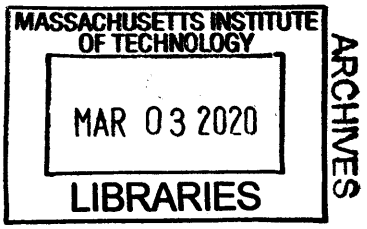
Certified by...

Professor Mohammad Movassaghi
Professor of Chemistry
Thesis Supervisor

Signature redacted

Accepted by.....

Professor Robert W. Field
Haslam and Dewey Professor of Chemistry
Chair, Department Committee on Graduate Students



to my family

Acknowledgements

I would like to thank my advisor, Professor Mohammad Movassaghi, for giving me the opportunity to conduct the research presented in this thesis. I appreciate you providing me with hands-on guidance when needed, fervent chemistry discussion, the flexibility to pursue original ideas, as well as continuously challenging me to tackle complex problems. I would like to thank Professor Steve Buchwald for serving as my thesis chair and providing thoughtful guidance whenever necessary, and Professor Jeremiah A. Johnson for serving on my committee.

Many excellent scientists have paved the way to success in the Movassaghi group, and I am grateful to each of my colleagues who has positively impacted my time here. I would like to thank Dr. Jonathan W. Medley and Dr. Kolby Lynn White for their whose work in the area of aspidosperma alkaloids enabled me to further investigate this natural product family. I want to especially thank those group members who have immeasurably enriched my life at MIT both inside and outside the lab. First to Dr. Alyssa Antropow, who helped mentor me when I first joined to group; to Dr. Matthew M. Pompeo, for his friendship as well as for his skill and attention to detail; to Dr. Vece, for his egregious level of cheerfulness; to Kyan D'Angelo for his leadership and beneficial chemistry discussions; to Tony Scott, for his friendship, constant support and for always demonstrating what a motivated chemist look like; to Katherine L. Walker for being the leading light of the Movassaghi group. I would be remiss if I did not thank Dr. Olga Mukhina, Dr. Brandon Nelson, Dr. Mario Leypold, Chase Olsson, and Kristen Flynn.

I have had the privilege of sharing my experience at MIT with my loving and incredibly supportive husband Ahmet Yeşilçimen. He was there for me each night, good and bad, never ceased to support my goals even when I wavered. It was with his support that I persisted and I believe he deserves as much as credit for my successes as I do.

Finally, I would like to thank my family for all the support and encouragement they have provided throughout the years. To my sister for always believing in me and always having fun with me; to my dad, for always being 'there' for me; and to my mom for all the advice and recipes and for always making sure to stock my favorite foods when I come home to visit. If I did not have you as my family, I would not be who I am today and I would not be preparing to complete my thesis. It is the least I can do to dedicate my thesis to you and the rest of our family.

Synthesis and Optimization of Synthetic Intermediates to Access C21-Oxygenated Aspidosperma Alkaloids

by

Nadide Hazal Avcı

Submitted to the Department of Chemistry
On January 14, 2020 in Partial Fulfillment of the
Requirements for the Degree of Master of Science in
Organic Chemistry

ABSTRACT

I. Synthesis and Optimization of Synthetic Intermediates to Access C21-Oxygenated Aspidosperma Alkaloids

Synthesis and optimization of C21-oxygenated pentacyclic aspidosperma core is described. A highly effective enzymatic resolution of a non-β-branched primary alcohol (*E=22*) allowed rapid preparation of both enantiomeric forms of a C21-oxygenated precursor for synthesis of aspidosperma alkaloids.

Thesis Supervisor: Mohammad Movassaghi
Title: Professor of Chemistry

Table of Contents

Abbrevation

Å	angstrom
app	apparent
aq	aqueous
atm	atmosphere
Bu	butyl
°C	degree Celcius
CAM	ceric ammonium molbydate
cm^{-}	wavenumber
d	days
d	doublet
d	deuterium
δ	parts per million
DART	direct analysis in real time
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
ee	enantiomeric excess
EI	electronspray ionization
FT	fourier transform
g	gram
gCOSY	gradient-selected correlation spectroscopy
h	hour
HMBC	heteronuclear multiple bond correlation
HPLC	high performance liquid chromatograpy
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum correlation
Hz	Hertz
IR	infrared
J	coupling constant
m	medium
m	multiplet
M	molar
M	molecular mass
μ	micro
Me	methyl
min	minute
mol	mole
m/z	mass to charge
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
q	quartet
R*f*	retention factor
s	singlet
s	strong

str	stretch
t	*tert*
t	triplet
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet
Vis	visible
w	weak

INTRODUCTION

The aspidosperma alkaloids, a family containing over 250 structurally diverse members, have been a subject of significant interest over several decades due to their structural complexity and diverse biological activity.[1,2] With isolation yields as low as <0.0018% of these compounds from natural sources,[1,2] the exploration of the biological activity of these compounds is limited. The development of a unified strategy is crucial to accessing these alkaloids and for comprehensive chemical and biological studies. Our group has made significant contributions to the development of a unified strategy, which has enabled the synthesis of 14 aspidosperma alkaloids and many related derivatives to date (Figure 1.1.).[3]

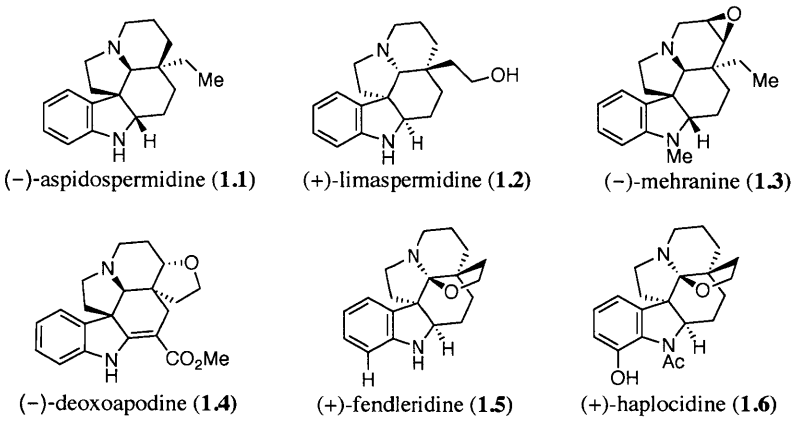


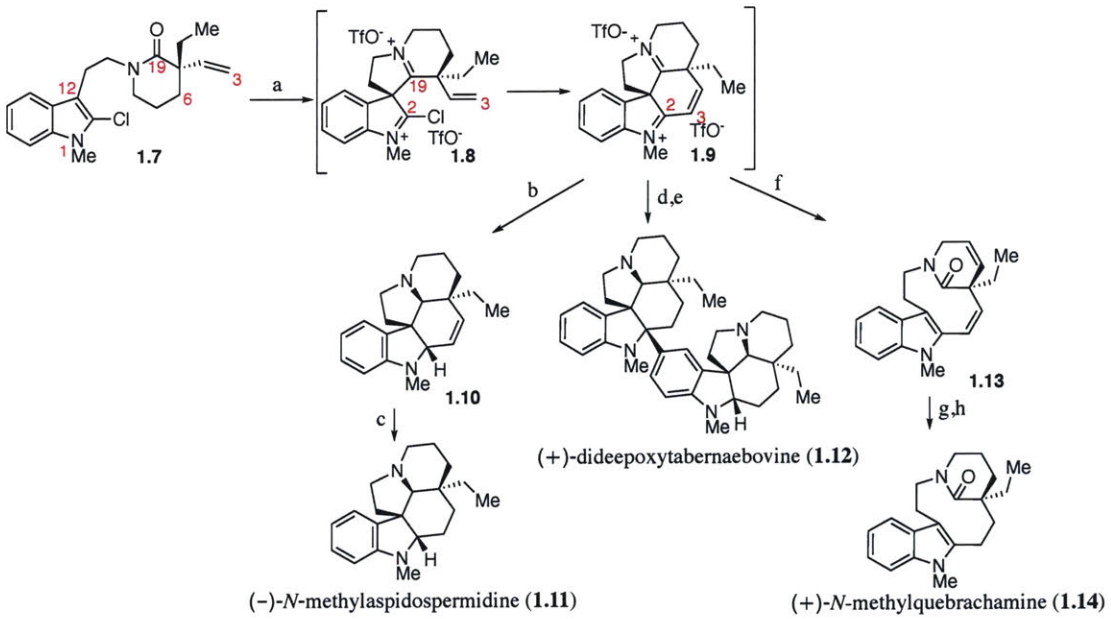
Figure 1.1. Representative aspidosperma alkaloids synthesized by our group.

Within the aspidosperma alkaloid family, there is a subset of compounds that possess oxygenation at C21-position. There are four structural variations of these C21-oxygenated aspidosperma alkaloids: an open form as seen in (+)-limaspermidine (**1.2**),[4,5] a hexacyclic indoline possessing a C19-hemiaminal ether bond as seen in the fendleridine (**1.5**)[6] series, a hexacylic indoline possessing a C21, C6-ether linkage seen in the deoxoapodine (**1.4**)[7] series, and a heptacyclic indoline possessing C21, C4-ether linkage that is present in the obscurvidine[8] series.

We aim to develop a unified strategy to access a common, versatile intermediate that would allow us to access the entire C21-oxygenated subfamily. Given the natural occurrence of the characteristic aspidosperma skeleton with C21-oxygenation in both enantiomeric forms, we sought a synthetic strategy that would allow for stereochemical divergence at late-stage in order to access each C21-oxygenated subfamily from a common precursor.

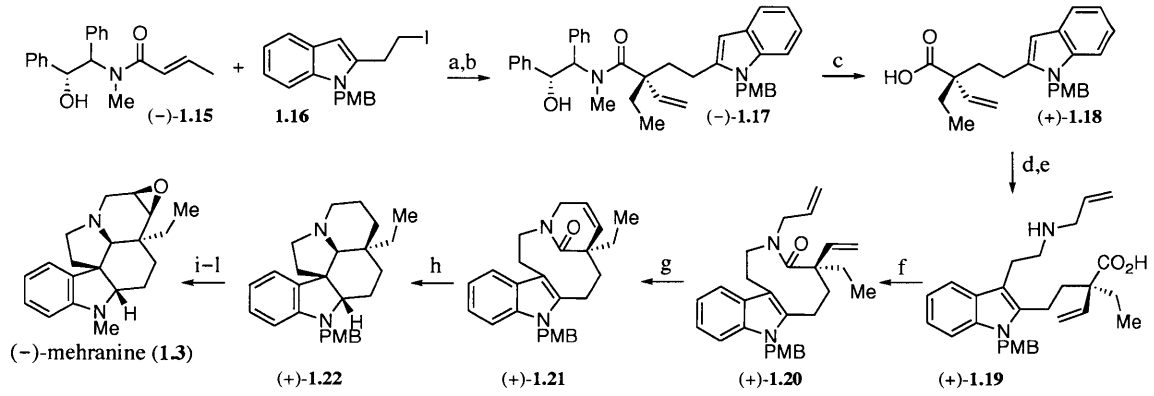
Results and Discussion

Triple Cyclization Cascade Approach. Our group has developed many methodologies which utilize trifluoromethanesulfonic anhydride[9], including the development of an interrupted Bischler-Napieralski reaction.[10] Dr. Jonathan Medley was able to expand the interrupted Bischler-Napieralski spirocyclization reaction to obtain the pentacyclic aspidosperma indoline core. (Scheme 1.1).[11]



Scheme 1.1. Synthesis of (–)-*N*-methylaspidospermidine (**1.11**), (+)-dideepoxytabernaebovine (**1.12**), and (+)-*N*-methylquebrachamine (**1.14**). Conditions: (a) Tf_2O, 3-cyanopyridine, MeCN 85 °C. (b) $NaBH_3CN$, 50%. (c) H_2, Pt/C, THF, 100%. (d) 85 °C; $NaBH(OMe)_3$, 72%. (e) H_2, Pt/C, THF, 84%. (f) $NaO(O)CCF_3$, TFA, H_2O, 70 °C, 57%. (g) H_2, Pt/C, THF. (h) LAH, THF, 82% (2 steps)

Electrophilic amide activation of lactam **1.7** with Tf_2O in the presence of 3-cyanopyridine resulted in the formation of tetracyclic diiminium ion **1.8**. The C2-chlorine and the C5-vinyl group, enable the formation of pentacyclic diiminium ion **1.9** from tetracyclic diiminium ion **1.8** under the electrophilic amide activation conditions. The C2-chlorine atom increases the electrophilic character at C2 in tetracyclic diiminium ion **1.8**, allowing for the pendant C5 vinyl group to act as a nucleophilic partner, thereby forging the C2, C3-bond. With this route to the pentacyclic core of the aspidosperma alkaloids in hand, we sought to expand this method to access the C21-oxygenated aspidosperma alkaloids. After evaluation of different substrates and conditions for double cyclization our group sought a more robust method that improved the diastereoselectivity of the cyclization and allowed for greater flexibility and functionalization.



Scheme 1.2 Enantioselective total synthesis of (−)-mehranine (**1.3**). Conditions: (a) lithium 2,2,6,6-tetramethylpiperidine, LiCl, THF, 0 °C; THF, −40 to 23 °C, 54%. (b) lithium diisopropylamide, LiCl, THF, −78 to 0 °C; *N,N'*-dimethylpropylene urea, −40 °C; EtI −40 °C, 69%, >30:1 dr. (c) *n*-Bu_4NOH, H_2O, *t*-BuOH, 100 °C, 99%, >99% ee (d) *N*-allyl-*N*-(2,2-dimethoxyethyl)-2,2,2-trifluoroacetamide, TFA, Et_3SiH, CH_2Cl_2, 75%. (e) NaOH, H_2O, MeOH, 100 °C, 99%. (f) PPh_3, I_2, *i*-Pr_2Net, CH_2Cl_2, −5 to 23 °C, 78%. (g) 2nd generation Hoveyda-Grubbs catalyst, $ClCH_2CH_2Cl$, 80 °C, 87%. (h) Tf_2O, *n*-Bu_3SnH, MeCN; $NaHB(OMe)_3$, THF, 89%, >20:1 dr. (i) thiophenol, TFA, 79%. (j) Ac_2O, HCO_2H, 91%. (k) *m*-CPBA, TFA, CH_2Cl_2, 77%. (l) *n*-Bu_3SnH, Tf_2O, CH_2Cl_2, −20 to 23 °C, 86%. *m*-CPBA = *meta*-chloroperbenzoic acid.

Transannular Cyclization Approach. In our synthesis of (−)-mehranine (**1.3**) developed

by Dr. Jonathan W. Medley and Dr. Marius Mewald, early installation of the C5-stereocenter was effected through two sequential alkylations of (+)-(*1R,2R*)-pseudoephenamine-based crotonamide (–)-**1.15** (Scheme 1.2).[12] After hydrolysis, carboxylic acid (+)-**1.18** was afforded in quantitative yield with >99% enantiomeric excess. Friedel-Crafts type reductive C12-alkylation followed by hydrolysis provided amino acid (+)-**1.19**. Macrolactam formation and ring-closing metathesis using Hoveyda-Grubbs II catalyst afforded key intermediate lactam (+)-**1.21**. Electrophilic activation of lactam (+)-**1.21** with trifluoromethanesulfonic acid led to efficient formation of the versatile pentacycle (+)-**1.22** as a single diastereomer. The first total synthesis of (–)-mehranine (**1.3**) was completed through exchange of the para-methoxybenzyl group for a formyl group which enabled a stereoselective epoxidation followed by formamide reduction using trifluoromethanesulfonic acid and tri-*n*-butyltinhydride to afford the desired alkaloid (–)-**1.3**. Our versatile cyclization strategy has served as the foundation for our unified synthesis of aspidosperma alkalodis.[3c-f]

---

(1) (a) Saxton, J.E. Alkaloids of the Aspidospermine Group. In The Alkaloids, Chemistry and Biology; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol 51, pp 1–197. (b) O'Connor, S. E. Alkaloids. In *Comprehensive Natural Products II;* Mander, L., Liu, H.-W., Eds.; Elsevier: Amsterdam, 2010; Vol *1,* pp 977–1007.

(2) For a review of aspidosperma alkadoids synthesis, see: (a) Lopchuk J. M. *Prog. Heterocycl. Chem.* **2011**, *23*, 1. For selected total syntheses of aspidosperma alkaoids, see: (b) Harley-Mason, J.; Kaplan, M. *Chem. Commun.* **1967**, *18*, 915. (c) Kutney, J. P.; Abdurahman, N.; Gletsos, C.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1970**, *92,* 1727. (d) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103,* 6990. (e) Gallagher, T.; Magnus, P.; Huffman, J. *J Am. Chem. Soc.* **1982**, *104,* 1140. (f) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T.; Takeda, E. *Tetrahedron* **1983**, *39*, 3657 (g) Node, M.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc.* **1987**, *109*, 7901. (h) Node M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55,* 517. (i) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V.H. *J. Am. Chem. Soc.* **2002**, *124,* 4628. (j) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475,* 183. (k) Zhao, S.; Andrade, R. B. *J Am. Chem. Soc.* **2013**, *135,* 13334. (l) Wagnieres, O.; Xu, *Z.;* Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 15102.

(3) (a) Medley, J. W.; Movassaghi, M. *Angew. Chem. Int. Ed.* **2012**, *51,* 4572. (b) Medley, J. W.;

Movassaghi, M. *Org. Lett.* **2013**, *15,* 3614. (c) Mewald, M.; Medley, J. W.; Movassaghi, M. *Angew. Chem. Int. Ed.* **2014**, *53,* 11634. (d) White, K. L.; Mewald, M.; Movassaghi, M. *J. Org. Chem.* **2015**, *80,* 7403. (e) White, K. L.; Movassaghi, M. *J. Am. Chem. Soc.* **2016,** *138,* 11383. (f) Kang, T.; White, K. L.; Mann, T. J.; Hoveyda, A. H.; Movassaghi, M. *Angew. Chem. Int. Ed.* **2017,** *56,* 13857.

(4) Medina, J. D.; Digenova, L. *Planta. Med.* **1979**, *37*, 165.

(5) (a) Tan, S. H.; Banwell, M. G.; Willis, A. C.; Reekie, T. A. *Org. Lett.* **2012**, *14,* 5621. (b) Zhang, S.-X.; Shen, X.-L.; Li, Z.-Q.; Zou, L.-W.; Wang, F.-Q.; Zhang, H.-B.; Shao, *Z.*-H. *J. Org. Chem.* **2013**, *78,* 11444. (c) Chen, Z.; Zhou, S.; Jia, Y. *J. Org. Chem.* **2015**, *80,* 12545. (d) Du, J.-Y.; Zeng, C.; Han, X.-J.; Qu, H.; Zhao, X.-H.; An, X.-T.; Fan, C.-A. *J. Am. Chem. Soc.* **2015,** *137,* 4267.

(6) (a) Brown, K. S.; Budzikiewicz, H.; Djerassi, C. *Tetrehedron Lett.* **1963**, *4*, 1731. (b) Walser, A.; Djerassi, C. *Helv. Chim. Acta.* **1965**, *48,* 391. (c) Burnell, R. H.; Medina, J. D.; Ayer, W. A. *Can. J. Chem.* **1966**, *44,* 28. (d) Mitaine, A. C.; Mesbah, K.; Richard, B.; Petermann, C.; Arrazola, S.; Moretti, C.; Zeches-Hanrot, M.; Le Men Olivier, L. *Planta Med.* **1996**, 62, 458.

(7) (a) Azoug, M.; Loukaci, A.; Richard, B.; Nuzillard, J.-M.; Moreti, C.; Zeches-Hanrot, M.; Le Men-Olivier, L. *Phytochemistry* **1995**, *39,* 1223. (b) Bui, A.-M.; Das, B. C.; Potier, P. *Phytochemistry* **1980**, *19,* 1473. (c) "Indole Alkaloids." Grundon, M. F. in *The Alkaloids;* The Chemical Society, Burlington House: London, 1977; Vol. 7, p 223. (d) Iglesias, R.; Diatta, L. *Rev. Cenic. Cienc. Fis.* **1975,** *6*,141.

(8) (a) Kahrl, J.; Gebreyes. T; Djerassi, C. *Tetrahedron Lett.* **1971**, 2527. (b) Harper, J. K.; Dunkel, R.; Wood, S. G.; Owen, N. L.; Li, D.; Cates, R. G.; Grant, D. M. *J. Chem. Soc.-Perkin Transactions 2* **1996**, 91.

(9) (a) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 14254. (b) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem . Soc.* **2007**,*129*, 10096. (c) Movassaghi, M; Hill, M. D. *Org. Lett.* **2008**, *10, 3485.* (d) Medley, J. W.; Movassaghi, M. *J. Org. Chem.* **2009**, *74,* 1341. (e) Medley, J.W.; Movassaghi, M. *J. Org. Chem.* **2009**, *74,* 1341. (f) Ahmad, O.K.; Medley, J.W.; Coste, A.; Movassaghi , M. *Org. Synth.* **2012,** *89*, 549–561.

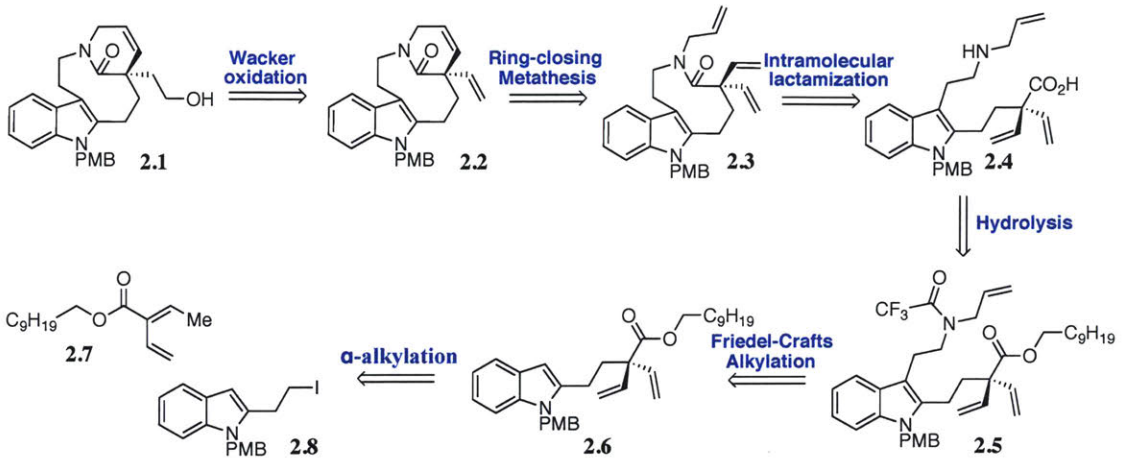
(10) Medley, J. W.; Movassaghi, M. *Org. Lett.* **2013**, *15, 3614.*

(11) Medley, J. W.; Movassaghi, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4572.

(12) Morales, M. R.; Mellem, K. T.; Myers, A. G. *Angew. Chem. Int. Ed.* **2012**, *51,* 4568.

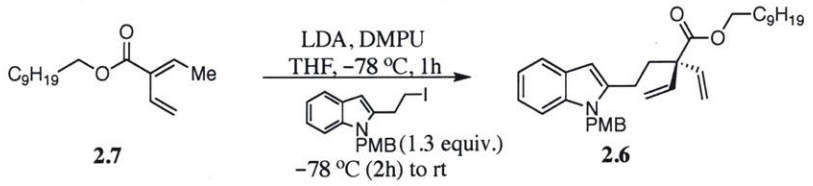
RESULTS AND DISCUSSION

Given the natural occurrence of the characteristic aspidosperma skeleton with C21-oxygenation in both enantiomeric forms, we decided to use enzymatic kinetic resolution as a synthetic strategy that would allow for an advanced-stage stereochemical divergence. Dr. Kolby L. White recognized the alcohol **2.1** as a suitable precursor for enantiomerically enriched lactam **2.9** in order to access aspidosperma core.[1]



Scheme 2.1. Retrosynthetic Analysis of Alcohol **2.1**

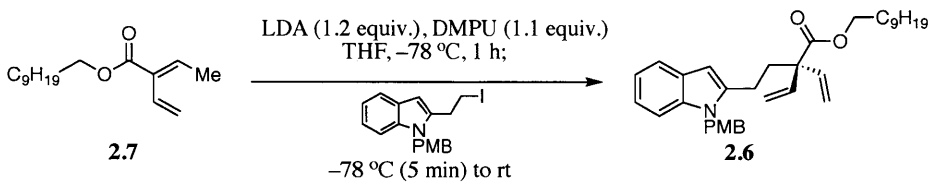
I mainly focused on the synthesis of enantiomerically enriched lactam **2.9** and the optimization of the synthetic route to this attractive precursor.



Entry	LDA	DMPU	Yield
1	1.2 equiv.	10.0 equiv.	20%
2	1.2 equiv.	1.1 equiv.	10%
3	***1.6 equiv.***	***10.0 equiv.***	***25%***
4	1.8 equiv.	10.0 equiv.	0%

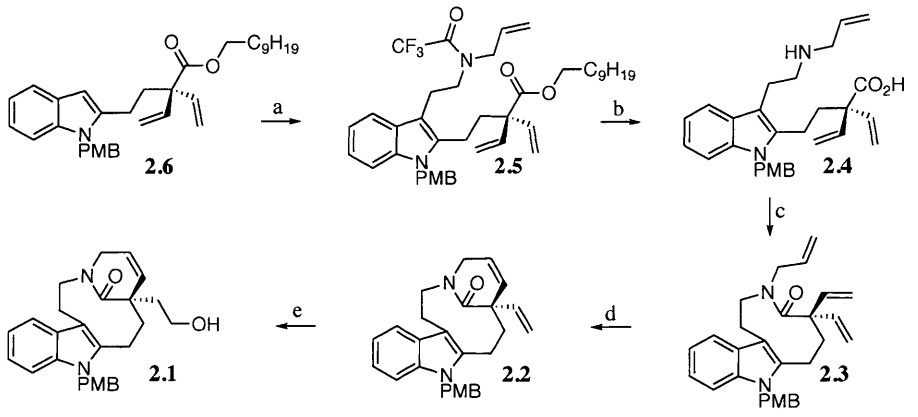
Table 2.1. Selected Optimization Data of α-Alkylation

The α-alkylation product **2.6** of ester **2.7** with indole iodide was one of the key intermediates of our synthesis due to its divinylic structure which is required for the preparation of alcohol **2.1**, a suitable precursor for the enantiomerically enriched lactam. This alkylation provided rapid access to divinyl ester **2.6** from readily available starting materials, which can be prepared in seven steps total from crotonyl chloride and 2-iodoaniline.[1] We wanted to improve access to divinyl ester **2.6** by probing the parameters of this sensitive α-alkylation. We found that *N,N'*-dimethylpropylene urea can be used to increase the yield depending on the amount of lithium diisoproylamide (Table 2.1. Entry 1–4). Based on Entry 4, we showed that there is a fine balance for the amount of lithium diisoproylamide that was used, since we observed only the elimination product of indole iodide. We found that the excess lithium diisoproylamide can be detrimental since it can promote the elimination of our electrophile. In addition, the introduction of excess *N,N'*-dimethylpropylene urea can be used to adjust the effectiveness of lithium diisoproylamide as a base. After examining variety of conditions related with lithium diisoproylamide and *N,N'*-dimethylpropylene urea, we turned our attention to the effect of reaction temperature for the desired α-alkylation. Though we originally thought that keeping the reaction at –78 °C would prevent the undesired Claisen condensation of the ester **2.7** and promote α-alkylation rather than elimination of indole iodide, warming the reaction mixture to 25 °C after the addition of electrophile at –78 °C delivered the divinyl ester **2.6** in 46% yield on multigram scale in a reproducible manner.



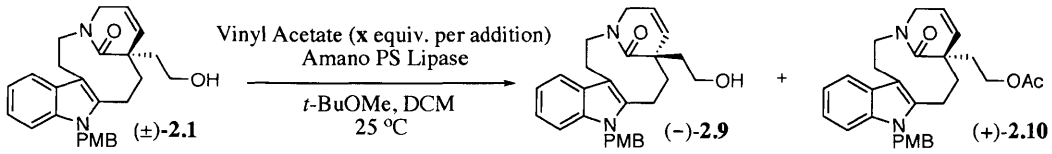
Scheme 2.2. Preparation of Divinyl Ester **2.6**

With access to divinyl ester **2.6**, I next focused to the the synthesis of C21-hydroxlated lactam (±)-**2.1** (Scheme 2.3.).[1]



Scheme 2.3. Synthesis of C21-hydroxylated lactam (±)-**2.1** Conditions: (a) *N*-allyl-*N*-(2,2-dimethoxyethyl)-2,2,2-trifluoroacetamide, TFA, Et_3SiH, CH_2Cl_2, 89%. (b) NaOH, MeOH, 100 °C, 98%. (c) PPh_3, I_2, *i*-Pr_2-NEt, CH_2Cl_2, −5 to 23 °C, 78%. (d) 2nd generation Hoveyda-Grubbs catalyst, $ClCH_2CH_2Cl$, 80 °C, 79%. (e) $Pd(OAc)_2$, *p*-benzoquinone, MeCN, H_2O, $HClO_4$; $NaBH_4$, 79%.

Trifluoroacetic acid-mediated Friedel-Crafts type reductive alkylation of indole **2.6** gave trifluoroacetyltryptamine **2.5** in 89% yield. The tandem hydrolysis of trifluoroacetamide and the decanol ester provided the amino acid **2.4** in 98% yield. The following intramolecular lactamization step required optimization to avoid low yield. I have demonstrated that vigorous stirring with slow, inverse addition of solution of amino acid **2.4** and Hünig's base in dichloromethane to a solution of triphenylphospine and iodine in dichloromethane under infinite dilution conditions delivered the lactam **2.3** in 78% yield. Treatment of triene **2.3** with Hoveyda-Grubbs II[2,3] catalyst afforded lactam **2.2** in 79% yield. The C21-oxygenation was introduced through Wacker-Tsuji oxidation of lactam **2.2** and in situ reduction of the resulting C21-aldehyde to give alcohol (±)-**2.1** in 79% yield. The C5-quaternary center of alkene is likely responsible for the anti-Markovnikov hydration of the alpha-olefin.

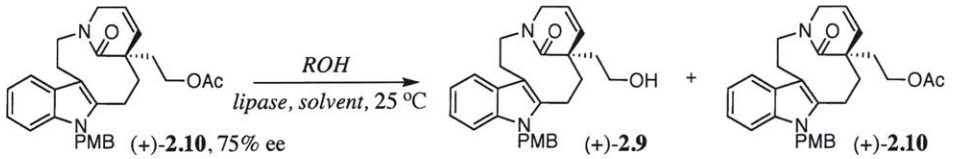


Entry	x (equiv.)	Vinyl Acetate (total equiv.)	Time	Conversion	ee of (−)-**2.9**	ee of (+)-**2.10**
1	1.5	4.5	10 h	50%	64%	75%
2	5.0	50	10 h	64%	95%	70%
3	***10***	***50***	***5 h***	***64%***	***98%***	***52%***

Table 2.2. Enzymatic resolution of alcohol (±)-**2.1**

I next focused on the resolution of alcohol (±)-**2.1** in order to access the lactam **2.9** in both enantiomeric forms. Whereas the kinetic resolution of primary alcohols with β-branching and a good collection of secondary alcohols were well studied, the resolution of non-β-branched primary alcohols was not well established.[4,5] Dr. Kolby L. White showed on the substrate (±)-**2.1** the lipase from *Burkholderia cepacia* (Amano PS lipase) was selective for (–) enantiomer of alcohol (±)-**2.1** (E =22)[6] with *tert*-butyl methyl ether as solvent afforded desired enantiomer of alcohol (–)-**2.9** with synthetically useful level of enantiomeric enrichment (92% ee at 55% conversion). However, we were not able to obtain high enantiomeric enrichment by using 4.5 equivalents of acyl donor with portion wise addition over 10 hours, which might be due to the low conversion of the substrate (Table 2.2., Entry 1). I was able to access the desired level of enantiomeric enrichment by increasing the amount of the acyl donor (Table 2.2., Entry 2). We also demonstrated that 10 hours was not ultimately necessary for the desired transformation. Optimal conditions afforded alcohol (–)-**2.9** in 36% Yield, (5h) with an excellent level of enantiomeric excess (>98%) along with

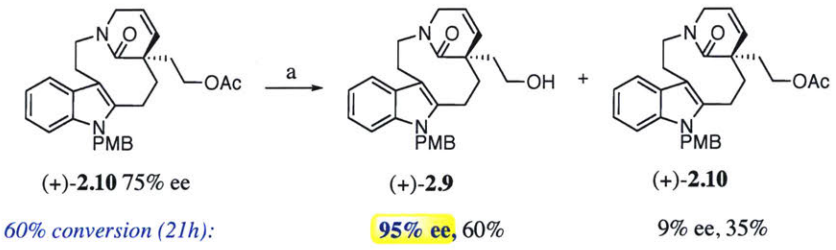
isolation of (+)-acetate **2.10** in 60% Yield, 52% ee on >250 mg scale (Table 2.2., Entry 3).



Entry	Lipase	Solvent	Conversion	ROH (equiv)	ee of (+)-**2.9**	ee of (+)-**2.10**	Additives (equiv)
1	Amano PS Lipase	*t*-BuOMe	N/A	H_2O (10)	-	-	
2	Amano PS Lipase	toluene	N/A	H_2O (10)	-	-	
3	CCL	*t*-BuOMe	56%	H_2O (10)	82%	13%	
4	CCL	*t*-BuOMe	50%	H_2O (10)	90%	9%	Et_3N (1)
5	CCL	*t*-BuOMe	57%	H_2O (10)	85%	12%	
6	CCL	*t*-BuOMe	49%	H_2O (10)	89%	11%	Et_3N (2)
7	CCL	*t*-BuOMe	52%	H_2O (100)	84%	15%	Et_3N (1)
8	***CCL***	***t-BuOMe***	***59%***	***H_2O (10)***	***92%***	***9%***	***2,6-Lutidine (2)***

Table 2.3. Enzymatic hydrolysis of acetate (+)-**2.10**

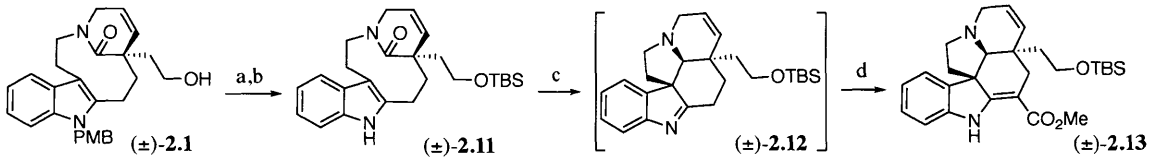
Next we sought to optimize the hydrolytic resolution to increase the enantiopurity of recovered acetate (+)-**2.10**. Amano PS lipase mediated hydrolysis of acetate resulted in no conversion to the desired alcohol. With further experimentation we discovered that the use of CCL to give alcohol (+)-**2.9** (92% ee, 59%, Entry 8) with excellent potential for the synthesis of the characteristic (*S*)-C5-aspidosperma skeleton containing C21-oxygenation.



Scheme 2.4. Preparation of alcohol (+)-**2.9**. Reagents and conditions: (a) CCL, H_2O (15 equiv.), 2,6-Lutidine (1 equiv.), *t*-BuOMe, 21h, 23 °C.

With these promising conditions available for resolution of alcohol (±)-**2.1**, we turned our

attention to further optimization of the hydrolytic resolution. A slight decrease in the amount of 2,6-Lutidine as additive with CCL afforded the alcohol (+)-**2.9** in 60% Yield (21h) with a very good level of enantiomeric excess (95%) along with the isolation of acetate (+)-**2.10**.



Scheme 2.5. Synthesis of vinylogous carbamate (±)-**2.13** conditions: (a) TBSCl, DMAP, imidazole, *N*,*N*-Dimethylformamide. (b) Na (s), NH_3 (*l*), THF, –78 °C, 85% (2 Steps). (c) DIBAL-H, THF, 0 °C. (d) *n*-butyllithium, $NCCO_2CH_3$, –78 °C, THF, 57%. (2 Steps).

Given our access to both enantiomers of the alcohols, we next focused to the synthesis of pentacylic core of aspidosperma alkaloids. Alcohol (±)-**2.1** was converted into the corresponding *tert*-butyldimethylsilyl ether which then subjected to Birch reduction using using sodium metal in liquid ammonia to afford lactam (±)-**2.11** in 85% yield over two steps. Next, we required optimal conditions for transannular cyclization to secure pentacyclic aspidosperma core. While we previously conducted transannular cyclization of N1-protected lactam through an electrophilic amide activation strategy to access the corresponding C19-iminium ion for further derivatization, we envisioned a partial reduction would be most effective for conversion of imine (±)-**2.12** to pentacylic vinylogous carbamate (±)-**2.13**. Inspired by our recent method developed by Dr. Alyssa Antropow, exposure of lactam (±)-**2.11** to diisobutylaluminum hydride enabled direct formation of pentacyclic imine (±)-**2.12**.[7,8] The resulting pentacyclic imine was deprotonated by treatment with *n*-butyllithium and the corresponding metalloenamine was captured with methyl cyanoformate to provide the necessary pentacyclic vinylogous carbamate (±)-**2.13** in 57% yield over two steps.

Conclusion

In summary, we have developed and optimized an unified strategy to access pentacyclic aspidosperma core, that would allow us to access the entire C21-oxygenated subfamily. The critical C21-oxygenated lactam, prepared in both enentiomerically enriched forms using a highly effective enzymatic resolution of a challenging non-β-branched primary alcohol, can serve as a branching point to access various aspidosperma alkaloids.

---

(1) White, K. L.; Movassaghi, M. *J. Am. Chem. Soc.* **2016**, *138,* 11383.
(2) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000,** *122,* 8168.
(3) Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009,** *131*, 943.
(4) (a) ''Resolution of Enantiomers via Biocatalysis'' Sih, C. J.; Wu, S. H. *Topics Stereochem.* **1989**, *19*, 63. (b) ''General Aspects and Optimization of Enantioselective Biocatalysis in Organic Solvents: The Use of Lipases'' Chen, C. S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695. (c) ''Esterolytic and Lipolytic Enzymes in Organic Synthesis'' Boland, W.; Frössl, C.; Lorenz, M. *Synthesis* **1991**, *1991*, 1049.
(5) (a) ''Preparative Production of Optically Active Esters and Alcohols Using Esterase-Catalyzed Stereospecific Transesterification in Organic Media.'' Cambou, B.; Klibanov, A. M. *J. Am. Chem. Soc.* **1984**, *106*, 2687. (b) ''An Enzyme-catalyzed Synthesis of Natural a-Tocopherol'' Mizuguchi, E.; Takemoto, M.; Achiwa, L. *Tetrahedron: Asymmetry* **1993,** *4*, 1961. (c) ''Kinetic Resolution of Primary Alcohols Having Remote Stereogenic Centers: Lipase Mediated Kinetic Resolution of (±)-3-chloro-3-arylpropanols'' Isleyen, A.; Tanyeli, C.; Dogan, O. *Tetrahedron: Asymmetry* **2006**, *17*, 1561.
(6) *E* value is calculated based on Ref (2).
(7) Antropow, A. H.; Garcia, N. R.; White, K. L.; Movassaghi, M. *Org. Lett.* **2018**, *20*, 3647–3650.
(8) Antropow, A. H.; 2018, ''Synthesis and Anticancer Evaluation of Agelastatin Alkaloid Derivatives and Enantioselective Total Synthesis of Aspidosperma Alkaloids'' Doctor of Philosophy in organic chemistry, Massachusetts Institute of Technology, Cambridge.

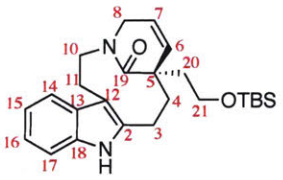
Experimental Section

General Procedures. All reactions were performed in oven-dried or flame-dried round bottom flasks, modified Schlenk (Kjeldahl shape) flasks or glass pressure vessels. The flasks were fitted with rubber septa or Teflon-wrapped glass stoppers, and reactions were conducted under a positive pressure of argon. Cannulae or gas-tight syringes with stainless steel needles were used to transfer air- or moisture-sensitive liquids. Flash column chromatography was performed as described by Still et al.[1] using granular silica gel (60-Å pore size, 40–63 μm, 4–6% H_2O content, Zeochem). Analytical thin layer chromatography (TLC) was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm) or basic alumina impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to short wave ultraviolet light (254 nm) and irreversibly stained by treatment with an aqueous solution of ceric ammonium molybdate (CAM) followed by heating (~1 min) on a hot plate (~250 °C) . Organic solutions were concentrated at 29–30 °C on rotary evaporators capable of achieving a minimum pressure of ~2 Torr.

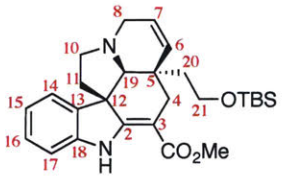
Materials. Commercial reagents and solvents were used as received with the following exceptions: dichloromethane, dichloromethane, and *N,N*-dimethylformamide were purchased from J.T. Baker (Cycletainer ™) and were purified by a method of Grubbs et al. under positive argon pressure.[2] All other solvents and chemicals were purchased from Sigma-Aldrich.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian INOVA-500 spectrometer. Chemical shifts are recorded in parts per million on the δ scale and are referenced from the residual protium in the NMR solvent ($CHCl_3$: δ 7.26).[3] Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant(s) in Hertz, integration, assignment]. Carbon^{13} nuclear magnetic resonance spectra were recorded with a Varian INOVA-500 spectrometer and are recorded in parts per million on the scale and are referenced from the carbon resonances of the solvent ($CDCl_3$: δ 77.16).[3] Data are reported as follows: chemical shift (assignment). Infrared data were obtained with a Perkin-Elmer 2000 FTIR and are reported as follows: [frequency of absorption (cm^-), intensity of absorption (s = strong, m = medium, w = weak, br = broad), assignment]. We thank Dr. Li Li at the Massachusetts Institute of Technology Department of Chemistry instrumentation facility for obtaining mass spectroscopic data. High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics APEXIV 4.7 Tesla FT-ICR-MS using a direct analysis in real time (DART) ionization source.

Positional Numbering System. In assigning the ^{1}H and ^{13}C data of all intermediates en route to our synthetic derivatives, we have employed a uniform numbering system.

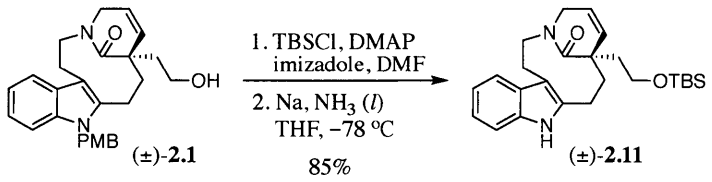


(±)-**2.11**



(±)-**2.13**

1. Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
2. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. *Organometallics* **1996**, *15*, 1518.
3. Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldber, K. I. *Organometallics* **2010**, *29*, 2176.



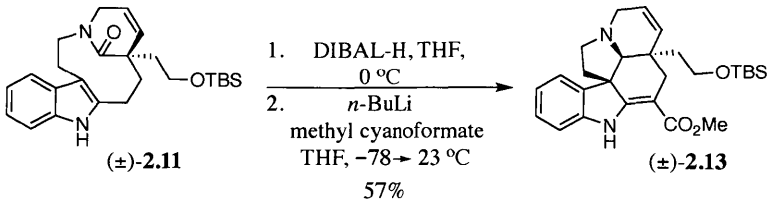
Lactam (±)-2.11:

4-(Dimethylamino)pyridine (9.0 mg, 74 μmol, 0.20 equiv) was added to a mixture of (±)-**2.1** (159 mg, 369 μmol, 1 equiv) , *tert*-butyldimethylsilyl chloride (83.5 mg, 554 μmol, 1.50 equiv) and imidazole (37.7 mg, 554 μmol, 1.50 equiv) in *N,N*-dimethylformamide (2.8 mL) at 23 °C. After 3h, saturated aqueous sodium bicarbonate solution (8 mL) was added to the reaction mixture. The layers were separated, and the aqueous layer was further extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were further extracted with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 20% ethyl acetate in hexates) to afford *N*-para-methoxybenzyl lactam as a white foam.

A solution of the *N*-para-methoxybenzyl lactam prepared above in THF (30 mL) was added to liquid ammonia (~ 60 mL) at –78 °C. After 15 min, sodium (83 mg, 3.72 mmol, 10 equiv) mmol, was added to the mixture as solid in two portions, and the mixture was stirred at –78 °C. After 3h, solid ammonium chloride (1 g) was added to the blue suspension. After 5 min, the ammonia was evaporated by slowly warming the colorless suspensiton to 23 °C. After evaporation of the solvent, water (10 mL) and dichloromethane (10 mL) were added to the residue and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL), were dried over anhydrous sodium sultafe, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column choromatography on silica gel (eluent: 20% ethyl acetate in hexanes) to afford lactam (±)-**2.11**, (133 mg, 85%) as a white solid. Structural assignments were made using additional information from gCOSY, gHSQC, and gHMBC experiments.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.72 (s, 1H, N**H**), 7.46 (d, J = 7.1 Hz, 1H, C_{14}**H**), 7.19 (d, J = 7.3 Hz, 1H, C_{17}**H**), 7.06 (dtd, J = 13.1, 7.2, 3.7 Hz, 2H, C_{15}**H**, C_{16}**H**), 5.88 – 5.79 (m, 1H, C_7**H**), 5.57 (dt, J = 10.0, 2.1 Hz, 1H, C_6**H**), 4.45 (ddd, J = 13.6, 11.5, 2.4 Hz, 1H, C_{10}**H$_a$**), 4.17 (d, J = 18.0 Hz, 1H, C_8**H$_a$**), 3.93 – 3.84 (m, 1H, C_8**H$_b$**), 3.53 (hd, J = 10.1, 9.2, 6.1 Hz, 2H, C_{21}**H**), 3.00 (dt, J = 14.8, 3.1 Hz, 1H, C_{11}**H$_a$**), 2.84 (ddd, J = 14.8, 11.5, 3.1 Hz, 1H, C_{11}**H$_b$**), 2.74 – 2.65 (m, 2H, C_3**H$_a$**, C_{10}**H$_b$**), 2.63 – 2.56 (m, 1H, C_3**H$_b$**), 2.27 (ddd, J = 13.0, 8.3, 6.5 Hz, 1H, C_{20}**H$_a$**), 2.17 (dd, J = 13.4, 10.4 Hz, 1H, C_4**H$_a$**), 1.94 – 1.87 (m, 1H, C_4**H$_b$**), 1.47 (ddd, J = 13.3, 7.8, 5.5 Hz, 1H, C_{20}**H$_b$**), 0.84 (s, 9H, $SiC(CH_3)_3$), -0.02 (s, 6H, $Si(CH_3)_2$).

^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C):	δ 171.9 (**C**$_{19}$), 135.8 (**C**$_{13}$), 135.6 (**C**$_2$), 131.3 (**C**$_6$), 128.4 (**C**$_{18}$), 121.4 (**C**$_{15}$), 120.5 (**C**$_7$), 119.1 (**C**$_{16}$), 117.8 (**C**$_{14}$), 110.5 (**C**$_{17}$), 109.7 (**C**$_{12}$), 60.3 (**C**$_{21}$), 49.1 (**C**$_8$), 46.1 (**C**$_{10}$), 45.7 (**C**$_4$), 44.3 (**C**$_5$), 41.0 (**C**$_{20}$), 26.0 (SiC(**C**H$_3$)$_3$), 21.8 (**C**$_3$), 21.7 (**C**$_{11}$), 18.3 (Si**C**(CH$_3$)$_3$), −5.2 (Si**C**$_a$H$_3$), −5.3 (Si**C**$_b$H$_3$).
FTIR (thin film) cm^{-1}:	3296 (s), 2926 (m), 1632 (s), 1465 (m), 1250 (m).
HRMS (ESI) (*m/z*):	calc'd for $C_{25}H_{37}N_2O_2Si$ $[M+H]^+$: 425.2624, found: 425.2622.
TLC (30% ethyl acetate in hexanes), R*f*:	0.35 (UV, CAM)



(±)-**2.11** (±)-**2.13**

Vinylogous Carbamate (±)-2.13:

Diisobutylaluminum hydride (1.0 M in hexanes, 0.63 mL, 631 μmol, 4.0 equiv) was added slowly via syringe to a solution of indole (±)-**2.11** (67.4 mg, 158 μmol, 1 equiv) in THF (3.2 mL) at 0 °C. After 3h, an aqueous solution of Rochelle's salt (10 mL) was added and the solution was stirred vigorously, and the resulting solution was allowed to warm to 23 °C. After 1h, a saturated aqueous solution of sodium chloride (15 mL) and ethyl acetate (15 mL) were added and the layers were separated. The aqueous layer was extracted further with ethyl acetate (3 × 20 mL) and the combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on basic alumina (eluent: 10% ethyl acetate in hexanes) to afford pentacylic imine (±)-**2.12** as a clear thin film.

A solution of *n*-butyllithium (2.23 M, 0.116 mL, 260 μmol, 2.00 equiv) was added via syringe to a solution of pentacyclic imine prepared above in THF (3.3 mL) at −78 °C. After 30 min, methyl cyanoformate (40.8 μL, 521 μmol, 4.00 equiv) was added via syringe. After 30 min, the cold bath was removed and solution was allowed to warm to 23 °C. After 30 min, saturated aqueous sodium bicarbonate solution (10 mL) was added to the reaction mixture. The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 7% ethyl acetate in hexanes) to afford pentacylic vinylogous carbamate (±)-**2.13** (42.0 mg, 57%) as a colorless thin film. Structural assignments were made using additional information from gCOSY, gHSQC and gHMBC experiments.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.99 (s, 1H, N**H**), 7.22 (d, J = 7.3 Hz, 1H, C_{14}**H**), 7.14 (t, J = 7.6 Hz, 1H, C_{16}**H**), 6.87 (t, J = 7.4 Hz, 1H, C_{15}**H**), 6.82 (d, J = 7.7 Hz, 1H, C_{17}**H**), 5.85 – 5.74 (m, 2H, C_6**H**, C_7**H**), 3.77 (s, 3H, OC(O)C**H**$_3$), 3.47 (ddt, J = 26.0, 9.8, 4.8 Hz, 3H, C_{21}**H**$_2$, C_8**H**$_a$), 3.18 (d, J = 15.8 Hz, 1H, , C_8**H**$_b$), 3.08 – 2.99 (m, 1H, C_{10}**H**$_b$), 2.72 (d, J = 4.1 Hz, 2H, C_{19}**H**, C_{10}**H**$_a$), 2.49 (s, 2H, C_4**H**$_2$), 2.06 (tt, J = 10.9, 3.9 Hz, 1H, C_{11}**H**$_a$), 1.79 (dd, J = 11.7, 4.6 Hz, 1H, C_{11}**H**$_b$), 1.23 – 1.16 (m, 2H, C_{20}**H**$_2$), 0.78 (s, 9H, SiC(C**H**$_3$)$_3$), -0.12 (d, J = 7.7 Hz, 6H, Si(C**H**$_3$)$_2$).

^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C):	δ 169.0 ($O\mathbf{C}(O)CH_3$), 167.0 ($\mathbf{C}_2$), 143.3 ($\mathbf{C}_{18}$), 138.0 ($\mathbf{C}_{13}$), 133.8 ($\mathbf{C}_6$), 127.9 ($\mathbf{C}_{16}$), 125.0 ($\mathbf{C}_7$), 121.6 ($\mathbf{C}_{14}$), 120.8 ($\mathbf{C}_{15}$), 109.5 ($\mathbf{C}_{17}$), 92.3 ($\mathbf{C}_3$), 69.9 ($\mathbf{C}_{19}$), 59.4 ($\mathbf{C}_{21}$), 55.3 ($\mathbf{C}_{12}$), 51.2, ($OC(O)\mathbf{C}H_3$) 51.1 ($\mathbf{C}_{10}$), 50.7 ($\mathbf{C}_8$), 44.8 ($\mathbf{C}_{11}$), 40.5 ($\mathbf{C}_5$), 37.2 ($\mathbf{C}_{20}$), 29.3 ($\mathbf{C}_4$), 26.1 ($SiC(\mathbf{C}H_3)_3$), 18.5 ($Si\mathbf{C}(CH_3)_3$), −5.4 ($Si(\mathbf{C}H_3)_2$).
FTIR (thin film) cm^{-1}:	3370 (w), 2927 (w), 1675 (s), 1608 (s), 1464 (m), 1253 (m), 1099 (w).
HRMS (ESI) (*m/z*):	calc'd for $C_{27}H_{39}N_2O_3Si$ $[M+H]^+$: 467.2730, found: 467.2722.
TLC (15% ethyl acetate in hexanes), R*f*:	0.32 (UV, CAM)