Enantioselective synthesis of 1,6-dihydropyridines with application to natural product synthesis; Racemic total synthesis of the fungal metabolite collybolide

by

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Abstract

Azaheterocycles, a common feature of many bioactive natural products, are still challenging motifs to construct in an asymmetric fashion. Dihydropyridines are advantageous intermediates in the synthesis of such heterocycles, but previous methods to synthesize such compounds usually required specialized starting materials. Dihydropyridines can be converted to the corresponding tetrahydropyridines and piperidines through functionalization reactions, or they can be rearomatized to form the corresponding pyridine. We investigated the use of boronic acid nucleophiles with rhodium catalysis to create 1,6-dihydropyridines for use as strategic intermediates in natural product synthesis. We have reported the formation of 1,6-dihydropyridines, which contain fully substituted stereogenic centers, using aryl and alkenyl boronic acids. Our dearomatization methodology has demonstrated a range of functional group tolerance that includes alkenes, free alcohols, ethers, amides, esters, halides, and other heterocycles. Next, we applied our methodology to the synthesis of the indoloquinolizine structural scaffold, a motif found in many polycyclic indole alkaloids.

Digressing from azaheterocycle methodologies, we developed a 10-step racemic total synthesis of collybolide, as well as an asymmetric formal synthesis of collybolide, to facilitate the potential creation of unnatural derivatives. Although collybolide has been touted as a potent non-nitrogenous κ-opioid, independent analysis of our synthetic racemate indicates that the compound has no appreciable κOR activity.

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Ac	Acetyl
acac	Acetylacetonate
BINAP	([1,1'-binaphthalene]-2,2'-diyl)bis(diphenylphosphane)
Bn	Benzyl
B(neop)	Boronic acid neopentylglycol ester
Bpin	Boronic acid pinacol ester
Bz	Benzoyl
Cbz	Benzyl chloroformyl
COD	Cyclooctodiene
coe	Cyclooctene
Cy	Cyclohexyl
DABCO	(1,4-diazabicyclo[2.2.2]octane)
DCE	1,2-dichloroethane
DCM	Dichloromethane
DHP	Dihydropyridine
DME	1,2-dimethoxyethane
DMF	Dimethylformamide
EDTA	Ethylenediaminetetraacetic acid
Equiv	Equivalents
Et	Ethyl
GPCR	G-protein coupled receptor
^{i}Bu	Isobutyl
^{i}Pr	Isopropyl
κOR	Kappa opioid receptor
LDA	Lithium diisopropylamide

LDE	Lithium diethylamide
Me	Methyl
NBS	N-bromosuccinimide
NHC	N-heterocyclic carbene
Ph	Phenyl
PhMe	Toluene
Pr	Propyl
Py	Pyridine
TBA	Tetrabutylamonium
TBS	Tert-butyldimethylsilyl
^{t}Bu	Tert-butyl
TIPS	Triisopropylsilyl
THF	Tetrahydrofuran
THP	Tetrahydropyridine
TMS	Trimethylsilyl
TsOH	*p*-Toluenesulfonic acid

Chapter 1: Synthesis of 1,6-dihydropyridines *via* enantioselective addition of boronic acids to pyridinium salts

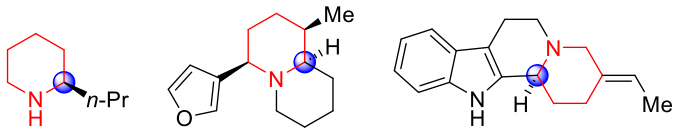
Parts of this chapter are reproduced from Robinson, D. J.; Spurlin, S. P.; Gorden, J. D.; and Karimov, R. R. *ACS Catal.* **2020,** 10, 51−55.

1.1. Azaheterocycles and the importance of dihydropyridines

1.1.1. Prevalence and stereochemical features of six-membered azaheterocycles in bioactive molecules.

Six-membered azaheterocycles are the most prevalent structural motif found in pharmaceutical compounds, and the marketing of these compounds continues to be a significant source of revenue for the pharmaceutical industry.[1,2] Additionally, six-membered azaheterocycles also have agrochemical applications, and the motif is prevalent in alkaloid natural products (Figure 1.1), ranging from simple piperidine alkaloids like coniine (**1.1**) to more complex polycyclic alkaloids like nuphar indolizidine (**1.2**) and deplancheine (**1.3**).[3]

Figure 1.1. Examples of alkaloids containing six-membered azaheterocycles with a stereogenic center alpha to the endocyclic nitrogen.

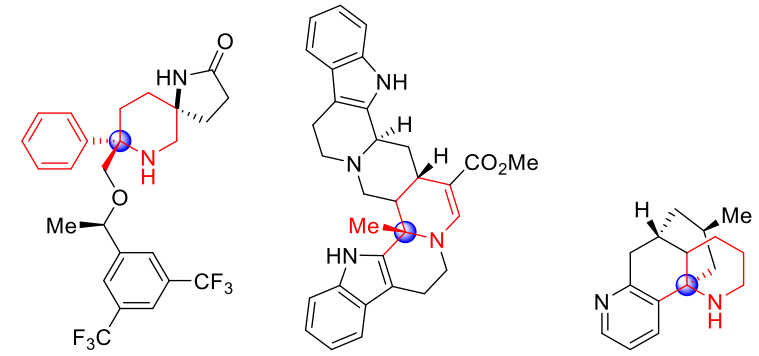


Coniine (1.1) | Nuphar indolizidine (1.2) | Deplancheine (1.3)

Non-aromatic six-membered azaheterocycles in bioactive molecules often contain stereogenic centers around the ring. It is not uncommon for bioactive azaheterocycles to incorporate an additional element of structural complexity compared to those represented in Figure 1.1, a fully substituted stereogenic center alpha to the endocyclic nitrogen. Examples of such

molecules include rolapitant (**1.4**), an NK1 receptor antagonist that has recently been approved for treating delayed phase of chemotherapy-induced nausea and vomiting, and alkaloids roxburghine D (**1.5**) and lycodine (**1.6**) (Figure 1.2). Despite the wide abundance of these azaheterocycles in natural products and synthetic bioactive compounds, methods for their synthesis, especially the ones that contain fully substituted stereocenters, are limited as the synthesis of quaternary centers in general remains one of the great challenges in organic chemistry.[4-8]

Figure 1.2. Examples of bioactive six-membered azaheterocycles with a fully substituted stereocenter.



Rolapitant (1.4)
NK1 receptor antagonist

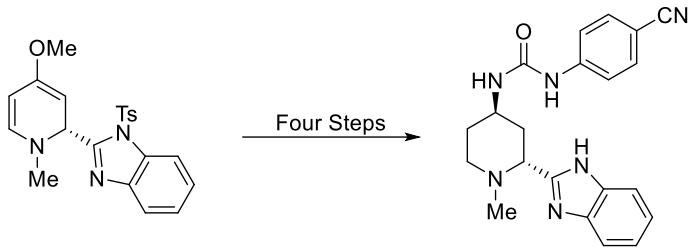
Roxburghine D (1.5)

Lycodine (1.6)

1.1.2. Synthetic utility of dihydropyridines for the synthesis of six-membered nitrogen heterocycles.

Dihydropyridines (DHPs) have been strategically employed in the synthesis of azaheterocycles due to the innate versatility of their unsaturation. In addition to selective functionalizations facilitating the construction of substituted tetrahydropyridines and piperidines, DHPs can be oxidized to afford the corresponding aromatic compound.[9-11] The Comins group alone has synthesized upwards of forty alkaloids utilizing DHP intermediates,[12-20] and the production scale synthesis of glasdegib (**1.7**), an FDA approved treatment for acute geriatric myeloid leukemia, utilizes DHP **1.8** as a key intermediate (Figure 1.3).[21]

Figure 1.3. Application of a 4-methoxypyridine derived 1,6-DHP in the synthesis of glasdegib.



1.8 Glasdegib (1.7)

1.1.3. Catalytic dearomatization approach for the synthesis of DHPs.

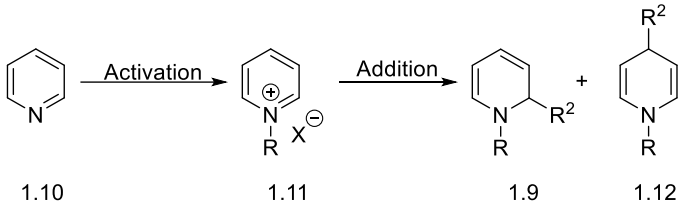
Although there are numerous methods of constructing DHPs via cyclization and cycloaddition reactions,[22-30] a more direct strategy is through the dearomatization of pyridines. Catalytic dearomatization of pyridines is an attractive approach toward the synthesis of DHPs because of the following: (1) pyridines are widely available commercially and through chemical synthesis; (2) by controlling the regioselectivity of the dearomatization, a variety of DHPs could be accessed (Scheme 1.1).[12,31-42] Previous efforts on the catalytic enantioselective dearomatization of pyridines have focused on the hydrogenation of the heteroarene double bonds[43-53] and addition of nucleophiles to activated pyridines[54–64] and related heteroarenes.[65-67] Despite the surge of research interest in asymmetric heteroarene hydrogenation, complete reduction of highly substituted pyridines is still challenging, and the hydrogenation method cannot establish a fully substituted stereogenic center as one of the substituents introduced is hydrogen. Catalytic nucleophilic additions to activated pyridines on the other hand have mainly focused on the dearomatization reactions of unsubstituted or symmetrically substituted N-acyl and N-alkylpyridiniums. Examples of these reactions include addition of arylboronic acids,[54,65] alkynes,[55,56] aryl and alkyl zinc reagents,[57–59] indoles,[60,66] and other nucleophiles[61-64] to pyridinium and quinolinium salts. Despite these advances in heteroarene dearomatization, there was no

general method reported for the dearomative formation of the fully substituted stereocenters starting from either N-alkyl or N-acylpyridinium salts with practical yield and enantioselectivity.

1.2. Dearomatization methods for the synthesis of 1,6-DHPs

Dearomatization of pyridines (**1.10**) requires activation, in the form of pyridinium salts (**1.11**) (Scheme 1.1), to lower the energy of their lowest unoccupied molecular orbital and increase their electrophilicity.[68] With respect to the synthesis of 1,6-DHPs, there are two main activation strategies, N-alkyl and N-acyl activation.[69,70]

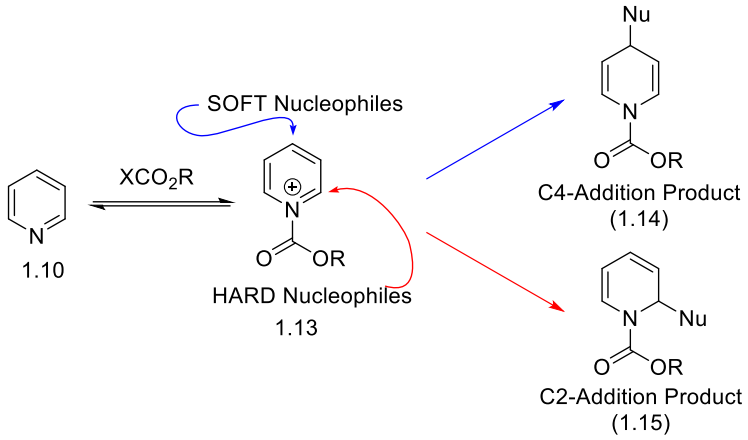
Scheme 1.1. General strategy for the synthesis of DHPs via dearomatization.



1.2.1. N-acyl activation

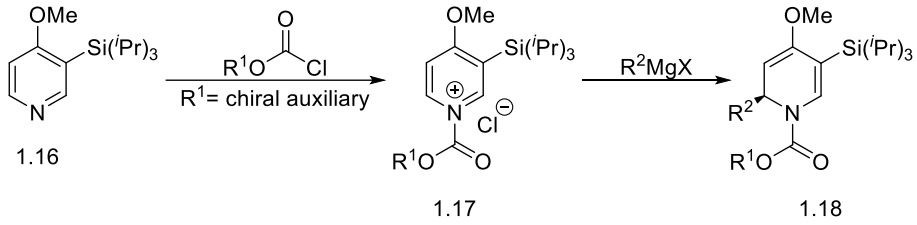
N-acyl pyridiniums have been employed to achieve α-functionalization with organometallic reagents to generate 1,6-DHPs, work pioneered by Yamaguchi, but these N-acyl salts suffer from instability at ambient temperature due to an equilibrium with the parent pyridine.[71] Yamaguchi observed different levels of regioselectivity, regarding the formation of 1,6-DHPs (**1.15**) vs 1,4-DHPs (**1.14**), dependent upon the type of organometallic nucleophile utilized in the dearomatization. The general regioselectivity trends for nucleophilic addition to N-acyl pyridiniums are outlined in Scheme 1.2.

Scheme 1.2. Regioselectivity for nucleophilic addition to N-acyl pyridiniums.



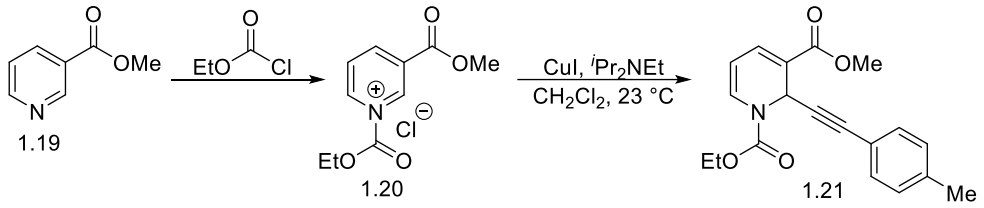
Grignard reagents have seen extensive use in nucleophilic dearomatizations by the Comins group, with chiral auxiliaries being employed to influence addition selectivity. For example, in the dearomatization of pyridinium **1.17** (Scheme 1.3), the use of a chiral chloroformate activator and a triisopropyl silane directing group effectively dictated the regio- and enantioselectivity of the Grignard addition, affording DHP **1.18.**

Scheme 1.3. Dearomatization with substrate-controlled selectivity.



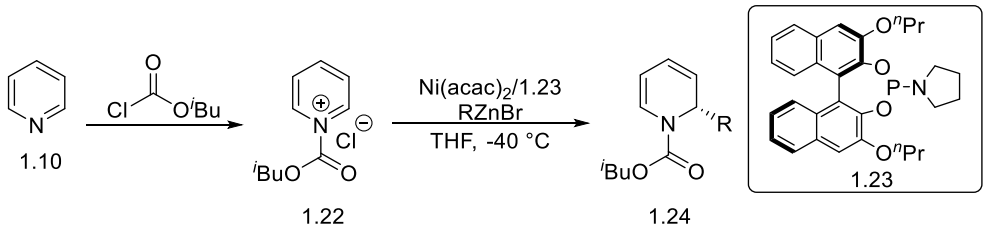
Constructing 1,6-DHPs from N-acyl pyridiniums utilizing organometallic catalysis presents an alternative to substrate-controlled strategies. One such approach, which avoids the use of superfluous directing groups, was reported by Sathiaiah and coworkers using alkyne nucleophiles (Scheme 1.4).[72-74] The copper-catalyzed addition of alkynes to nicotinate salt **1.20** preferentially afforded the corresponding 1,6-DHP (**1.21**).

Scheme 1.4. Sathaiah's copper-catalyzed addition of alkynes.



The Doyle group has applied nickel catalysis to affect nucleophilic dearomatization of N-acyl pyridiniums using arylzinc reagents (Scheme 1.5), yet their methodology suffers from decreased selectivity and lower yields when non-symmetric pyridiniums are used.[75,76]

Scheme 1.5. Doyle's nickel-catalyzed addition of arylzinc reagents.

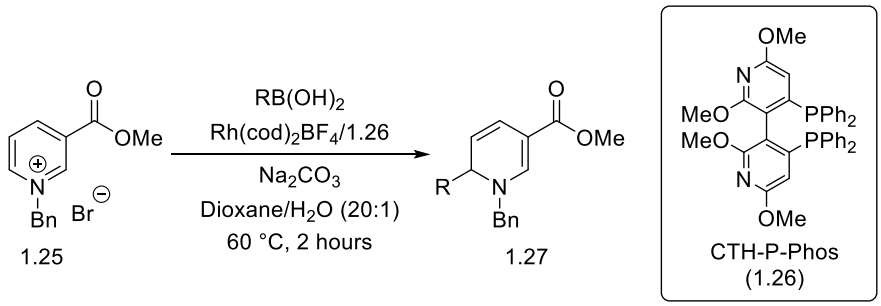


1.2.2. N-alkyl activation

N-alkyl pyridinium salts, in contrast to N-acyl pyridiniums, are typically bench stable at ambient temperature, yet the corresponding N-alkyl DHPs suffer from reduced stability in comparison to N-acyl DHPs. As a result, N-alkyl activation is more conducive to reactions with electron poor azaheterocycles such as nicotinates. Despite the reduced stability innate to N-alkyl DHPs, they have proven useful in total synthesis applications.[9-11,77,78]

The Merck process group developed a rhodium catalyzed method to dearomatize N-alkyl pyridinium salts utilizing boronic acid nucleophiles (Scheme 1.6).[54] This approach offers a relatively high level of versatility since there is a vast selection of boronic acids commercially available, and boronic acid nucleophiles are less basic than comparable organometallic reagents, thus providing a greater level of functional group tolerance.

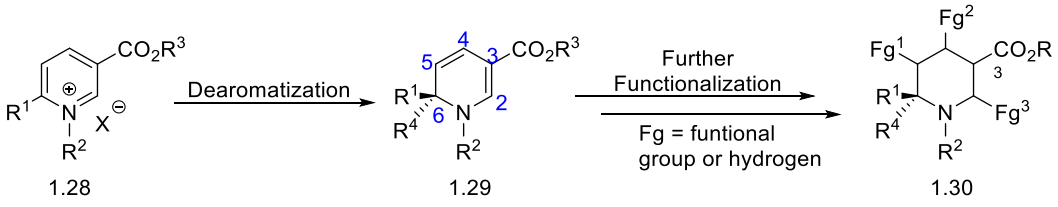
Scheme 1.6. Merck's rhodium-catalyzed addition of boronic acids.



1.2.3. Rhodium-catalyzed dearomatization of N-alkyl nicotinate salts for the synthesis of dihydropyridines with a fully substituted stereocenter

We have reported the rhodium-catalyzed dearomatization of N-alkyl nicotinic acid esters (**1.28**) for the synthesis of dihydropyridines that contain a fully substituted stereocenter at the C-6 position (Scheme 1.7). We have chosen nicotinic acid ester-derived pyridinium salts, as the regioselective dearomatization of these salts lead to dihydropyridines (**1.29**) that contain two double bonds with distinct reactivities (Scheme 1.7). One of these double bonds, C4=C5, typically reacts as a C=C double bond while the C2=C3 bond is part of the vinylogous carbamate, and thus resembles the reactivity of that functional group.[79] Together these reactivities would provide a versatile reactivity profile for the dearomatization products (**1.29**) to synthesize functionalized nonaromatic azaheterocycles where at least one of the stereocenters is fully substituted.

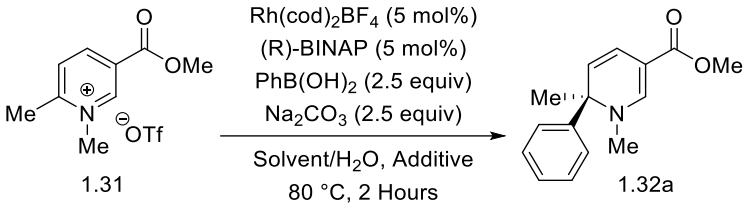
Scheme 1.7. Dearomatization approach to the synthesis of highly substituted piperidines.



1.3. Optimization of reaction conditions

We initiated our studies using N-methylpyridinium triflate **1.31** as a substrate, which is readily available from the reaction of methyl 6-methylnicotinate and methyl triflate (Table 1.1). Initial reactions were conducted at 80 °C in a 2:1 THF/water mixture as the solvent, phenyl boronic acid as the nucleophile, and $Rh(cod)_2BF_4$/(R)-BINAP as the catalyst. We were delighted to find out that under these conditions dihydropyridine (**1.32a**) was formed in excellent enantioselectivity and regioselectivity albeit in low yield (Table 1.1, entry 1). To improve the yield, we evaluated several solvents and found that ethereal solvents gave a higher yield than that of toluene and 1,6-dichloroethane (Table 1.1, entries 1−5). To further improve the yield of the reaction, we investigated KPF_6 as an additive with the idea that a more soluble anion PF_6 may improve solubility of the pyridinium salts in organic solvents. In fact, the addition of two equivalents of KPF_6 improved the yield in all solvents tested while the highest yield was obtained in 1,4-dioxane (Table 1.1, entries 6−8). Lastly, we evaluated the impact of amount of water on the yield of the reaction (Table 1.1, entries 9−11). Increasing the amount of water from 0.5 to 1 mL yielded only a trace amount dearomatization product, while decreasing the amount of water to 0.25 or 0.1 mL significantly improved the yield. As the enantiomeric excess slightly decreased for the 0.1 mL water case, we decided to go with the 0.25 mL water as the optimal reaction conditions. It is worth noting that the reaction did not work without the addition of $Rh(cod)_2BF_4$ or (R)-BINAP (Table 1.1, entries 12 and 13) and gave only trace amounts of the product without addition of the water (Table 1.1, entry 14).

Table 1.1. Optimization of reaction conditions.



Entry	Solvent	Water	Additive	Yield (%)[a]	ee (%)[b]
1	THF	0.50 mL	none	27	96
2	Dioxane	0.50 mL	none	39	ND
3	DME	0.50 mL	none	27	ND
4	DCE	0.50 mL	none	24	ND
5	PhMe	0.50 mL	none	25	ND
6	Dioxane	0.50 mL	KPF_6	52	ND
7	THF	0.50 mL	KPF_6	45	ND
8	DME	0.50 mL	KPF_6	47	ND
9	Dioxane	1.00 mL	none	<5	ND
10	**Dioxane**	**0.25 mL**	**none**	**84**	**94**
11	**Dioxane**	**0.10 mL**	**none**	**86**	**92**
12[c]	Dioxane	0.25 mL	none	0	ND
13[d]	Dioxane	0.25 mL	none	0	ND
14	Dioxane	none	none	<5	ND

[a]Yield of 1.32a was reported and based on the analysis of ^{1}H NMR spectra of the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard. [b]Enantiomeric excess (ee) was determined by chiral HPLC. [c]No $Rh(cod)_2BF_4$ was added. [d]No (R)-BINAP was added.

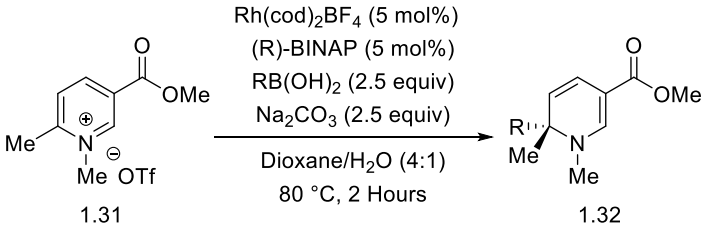
1.4. Reaction scope

1.4.1. Scope of boronic acids

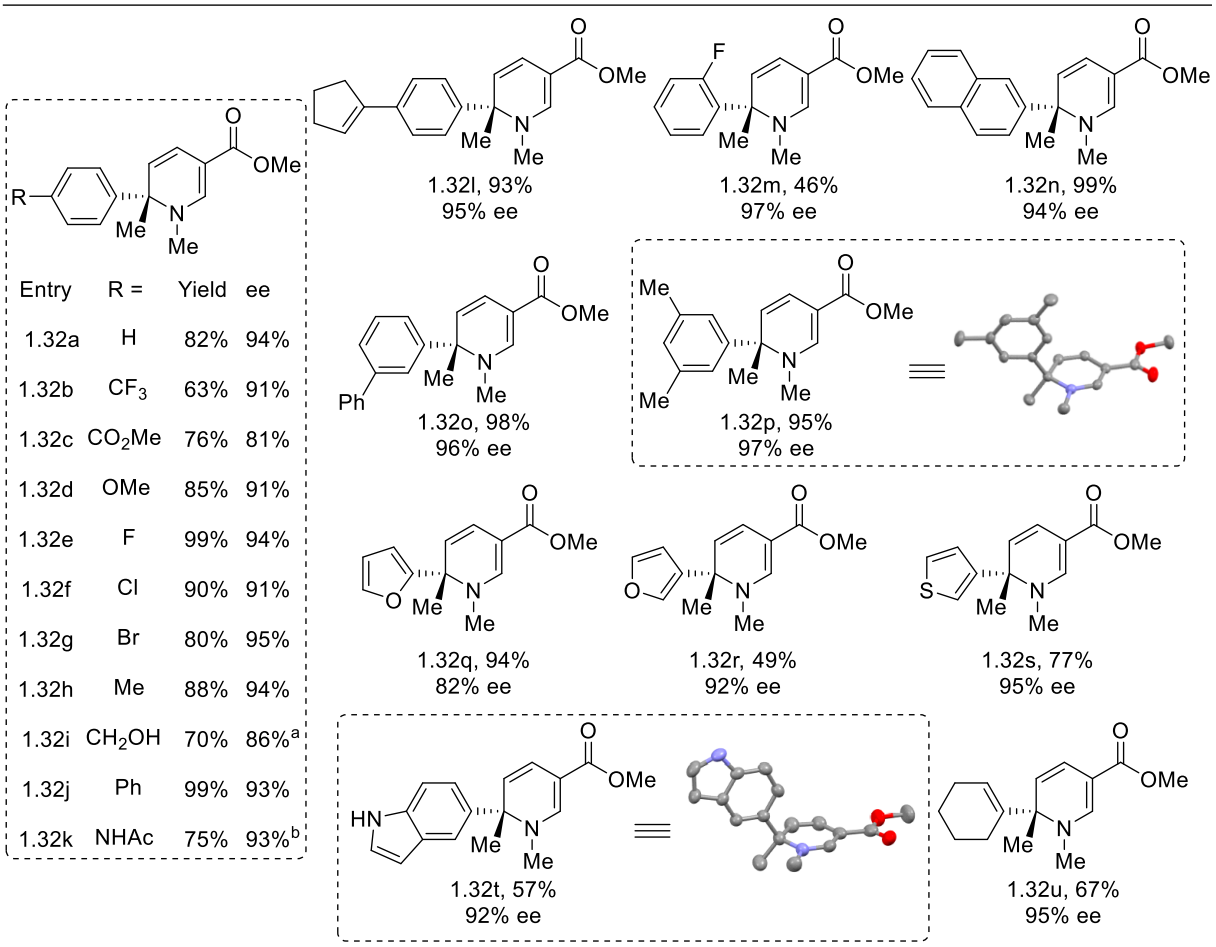
With the optimal reaction conditions in hand, we investigated the scope of the boronic acids in this reaction. Boronic acids containing ester, amide, ether, olefin, alcohol, halide functional groups reacted to give the corresponding dearomatization products (**1.32**) in good to excellent yield and excellent enantioselectivities (Table 1.2). Regioselectivity of the addition was also high where no C-4 addition product was observed, while the ratio of the C-6 versus C-2 addition products was greater than 15:1 favoring the C-6 addition product. Both electron-donating and electron-withdrawing groups are well tolerated, although boronic acids containing electron-withdrawing

groups gave dihydropyridines in slightly diminished yields and enantioselectivities (Table 1.2, **1.32b** and **1.32c**). Substituents at the ortho and meta positions of aryl boronic acids also tolerated delivering the expected products without erosion of enantioselectivity (Table 1.2, **1.32b−l,** and **1.32n−p**). The yield of the reaction was lower for the ortho-substituted boronic acid (Table 1.2, **1.32m**), while the enantioselectivity remained high. Heterocycles are important building blocks in medicinal chemistry. Considering this, we have evaluated several heteroarene boronic acids under the optimal reaction conditions. Furan-, thiophene-, and indole-containing boronic acids reacted to give the corresponding dearomatized products in good to excellent yield and excellent enantioselectivities (Table 1.2, **1.32q−t**) with only slight erosion of enantioselectivity when furan-2-boronic acid was used (Table 1.2, **1.32q**). Finally, an alkenyl boronic acid also reacted to give the corresponding dihydropyridine derivative in excellent enantioselectivity (Table 1.2, **1.32u**). Absolute stereochemistry of the two products (**1.32p** and **1.32t**) was determined to be (R) using X-ray crystallography.

Table 1.2: Scope of rhodium-catalyzed synthesis of dihydropyridines containing a fully substituted stereocenter.



Entry	R =	Yield	ee
1.32a	H	82%	94%
1.32b	CF_3	63%	91%
1.32c	CO_2Me	76%	81%
1.32d	OMe	85%	91%
1.32e	F	99%	94%
1.32f	Cl	90%	91%
1.32g	Br	80%	95%
1.32h	Me	88%	94%
1.32i	CH_2OH	70%	86%[a]
1.32j	Ph	99%	93%
1.32k	NHAc	75%	93%[b]

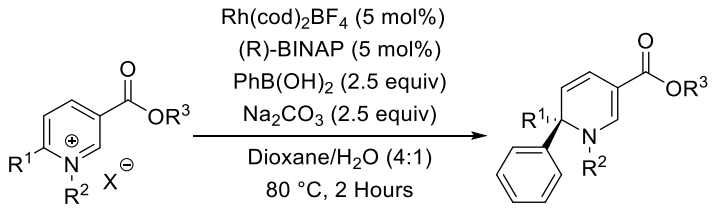


1.4.2. Substitutions to the nicotinate salt

After establishing the scope of the boronic acids, we turned our attention to investigate the influence of pyridinium substituents and counter-anions on the yield and stereoselectivity of this reaction by systematically varying the ester, C-6, and N-alkyl substituents and counter-anions (Table 1.3). In our optimization studies, we have observed that pyridinium salts that are more

soluble in organic solvents give the dearomatization product in higher yield compared with the less soluble pyridinium salts (Table 1.3, entries 6−8). This trend was further evidenced by the fact that more hydrophobic pyridiniums, which contain larger alkyl substituents or more hydrophobic counter-anions consistently gave higher yields than those that are less hydrophobic (Table 1.3, entry 1 vs entry 2 and entry 2 vs entries 3 and 4). Altering the C-6 substituent (Table 1.3, entry 8 vs Table 1.2, **1.32a**) or ester group (Table 1.3, entry 3 vs Table 1.2, **1.32a**) did not significantly influence the enantioselectivity of the reactions. However, substituents that are sterically bulkier than the methyl group at the N-alkyl site resulted in diminished enantiomeric excess (Table 1.3, entries 6 and 7).

Table 1.3: Evaluation of substituent and counter anion effects on the yield and enantioselectivity of the dearomatization.



1.S4-1.S10 1.S13-1.S16

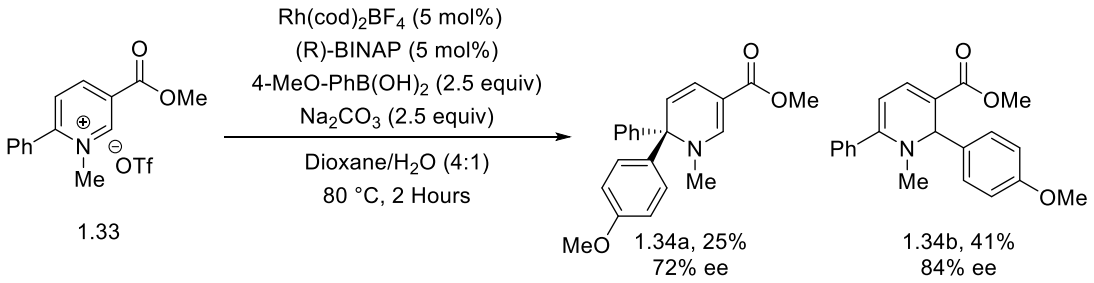
Entry	R^1	R^2	R^3	X	Yield (%)[a]	ee (%)[b]
1	Me	Me	Me	I	6	96
2	Me	Me	^{i}Bu	I	75	95
3	Me	Me	^{t}Bu	OTf	80	93
4	Me	Me	^{i}Bu	PF_6	99	91
5	Me	Me	^{i}Bu	BF_4	75	93
6	Me	Et	Me	Br	31	84
7	Me	Bn	Me	Br	56	66
8	Et	Me	Me	OTf	67	97

[a] Isolated yield is reported. [b] Enantiomeric excess (ee) was determined by chiral HPLC.

In general, dearomative nucleophilic addition to pyridinium salts takes place at C-2, C-4, and C-6 positions. In all reactions described in Table 1.2 and Table 1.3, formation of a small amount (<5%) of constitutional isomer of the major product where the addition occurred at the C-2 position instead of the C-6 position was observed. No C-4 addition product was detected in any

of these reactions. Presumably, this is because C-2 or C-6 are closer to the electron-withdrawing nitrogen atom; thus, these two positions are more activated. To further probe the steric influence of the C-6 substituent on the regioselectivity of the reaction, we synthesized pyridinium salt **1.33** which contains a sterically bulky phenyl group at the C-6 position (Scheme 1.8). When this pyridinium salt was subjected to the standard reaction conditions, C-2 addition product **1.34b** was observed as the major product. Enantioselectivity of the reaction was still good, giving the highly sterically hindered C-6 addition product **1.34a** in 72% *ee* and constitutional isomer **1.34b** in 84% *ee*.

Scheme 1.8: Dearomatization of a pyridinium salt with sterically hindered C-6 substituent.

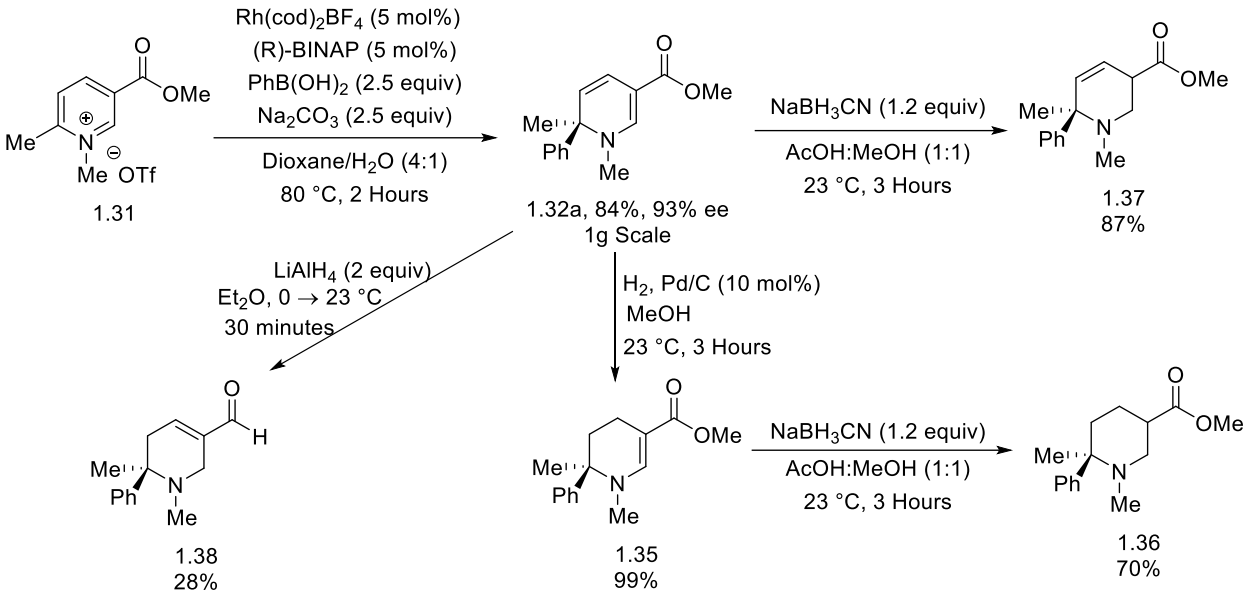


1.5. Functionalization of the 1,6-dihydropyridine product 1.32a

To demonstrate that the two double bonds of the dihydropyridines **1.32a** can be selectively functionalized, we carried out several reductive derivatization reactions (Scheme 1.9). To do this, we first carried out the initial dearomatization reaction on gram scale. At this scale, yield and enantioselectivity remained essentially the same compared to the standard 0.2 mmol scale reaction, which demonstrates the scalability of this dearomatization reaction. Hydrogenation of the dihydropyridine **1.32a** resulted in the vinylogous carbamate **1.35** in excellent yield and purity. This carbamate can be further reduced to piperidine **1.36** using sodium cyanoborohydride. Treatment of **1.32a** with cyanoborohydride selectively reduces the C2=C3 double bond delivering **1.37** as a 1:1 mixture of diastereomers in 87% overall yield. Interestingly, when $LiAlH_4$ was used as a

reductant, instead of complete reduction of the C2=C3 double bond and ester group to primary alcohol, aldehyde **1.38** was obtained in 28% yield as the major product.

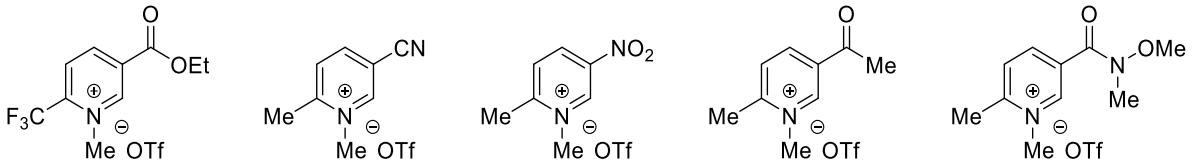
Scheme 1.9: Gram-scale synthesis and derivatization of dihydropyridine 1.32a.



1.6. Method shortcomings

Although the method developed by us shows a broad scope, dearomatization of certain pyridinium salts proved to be challenging. particularly, highly electrophilic pyridinium salts such as **1.39**−**1.42** did not produce the corresponding dearomatization products (Figure 1.4). The main side product observed in these reactions was the product of addition of hydroxide to the pyridinium salts under basic reaction conditions. The amide **1.43** gave some product, although the yield was again low. We are currently working toward overcoming these limitations to further expand the substrate scope for this important reaction.

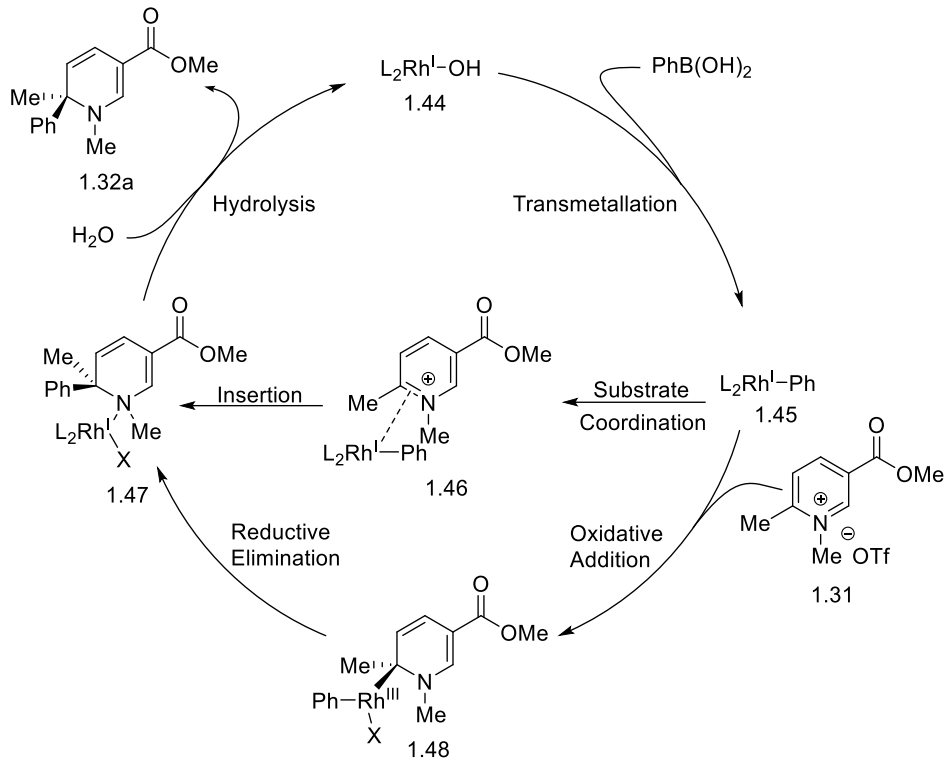
Figure 1.4. Pyridinium salts that did not yield corresponding dearomatization products.



1.7. Mechanism proposal

Mechanistically, two possible catalytic cycles could be envisioned for this transformation (Scheme 1.10). The first one involves a reactivity that resembles the rhodium-catalyzed conjugate addition reactions of boronic acids with Michael acceptors. The key steps in this mechanism involve (1) transmetalation of ligated Rh(I) **1.44** to give aryl rhodium species **1.45**; (2) coordination of the pyridinium salt; (3) insertion of the C=N bond into the Rh−Ar bond; and (4) hydrolysis of the product **1.32a** from **1.47** to regenerate the catalyst **1.44**. An alternative mechanism has a resemblance to the rhodium-catalyzed allylic substitution reactions and involves (1) transmetalation of ligated Rh(I) **1.44** to give aryl rhodium species **1.45**; (2) oxidative addition of Rh(I)-Ar species **1.45** to pyridinium salts to form **1.49**; (3) reductive elimination; and (4) hydrolysis of the product **1.32a** from **1.47** to regenerate the catalyst **1.44**. Experimental and computational studies to understand detailed mechanism of this reaction are currently ongoing in our laboratory.

Scheme 1.10: Possible catalytic cycles for Rh-catalyzed dearomatization of N-alkyl nicotinate salts.



1.8. Conclusions

In conclusion, we report a practical method for the dearomatization of pyridinium salts using boronic acid nucleophiles and readily available Rh/BINAP catalyst system to access dihydropyridines that contain a fully substituted stereogenic center. The dearomatization reaction proceeded with high yield and enantioselectivity and demonstrated excellent functional group tolerance. We have also demonstrated that this dearomatization reaction can be carried out in gram scale, and the dearomatization products can be selectively functionalized to deliver tetrahydropyridine and piperidine derivatives.

1.9. Experimental section

1.9.1. Materials and methods

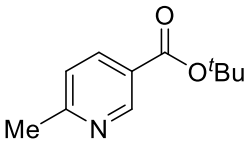
Reactions were performed in flame-dried sealed tubes or modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper under a positive pressure of nitrogen or inside nitrogen filled glovebox using 1 dram or 4 dram vials unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe. The appropriate starting materials and reagents were dried via azeotropic removal of water with toluene. Molecular sieves were activated at 350 °C then flame-dried under vacuum immediately prior to use. Organic solutions were concentrated by rotary evaporation below 40 °C. Flash column chromatography was performed employing 230–400 mesh silica gel. Thin-layer chromatography was performed using glass plates pre-coated to a depth of 0.25 mm with 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm) and visualized under UV light (254 and 360 nm), or stained with Ceric Ammonium Molybdate in concentrated H_2SO_4.

Dichloromethane, tetrahydrofuran, diethyl ether, dimethylformamide, dimethoxyethane and toluene were purified by passage through two packed columns of neutral alumina under an argon atmosphere.[47] Methanol was dried by storing over 3A molecular sieves for at least 36 hours. Amines were distilled from CaH_2 at 760 torr. All other chemicals were obtained from commercial vendors and were used without further purification unless otherwise noted.

Automated flash chromatography was performed with a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns. Infrared (IR) spectra were obtained using a *Thermo Scientific™ Nicolet™ iS50* FTIRspectrophotometer. Data are presented as the frequency of absorption (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were acquired on commercial instruments (400 and 600 MHz) at Auburn University NMR facility. Carbon-13

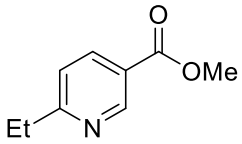
nuclear magnetic resonance (^{13}C NMR) spectra were acquired at 100 and 151MHz. Fluorine-19 nuclear magnetic resonance (19F NMR) spectra were acquired at 235 MHz. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual peaks in the NMR solvent (d-chloroform: δ 7.26 for ^{1}H NMR, δ 77.16 for ^{13}C NMR; d4-methanol: δ 3.31 for ^{1}H NMR, δ 49.00 for ^{13}C NMR). Data are presented as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), coupling constant in Hertz (Hz), integration.

1.9.2. Synthesis of pyridine starting materials



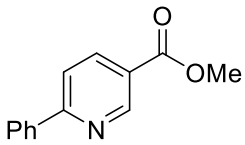
***tert*-Butyl 6-methylpyridine-3-carboxylate (1.S1)**

To a stirred solution of 6-methylpyridine carboxylic acid (6.86 g, 50.0 mmol, 1.0 equiv) in CH_2Cl_2 (85 mL) under nitrogen atmosphere was added (in this order) *t*-BuOH (7.12 mL, 75.0 mmol, 1.5 equiv), DMAP (2.45 g, 20.0 mmol, 0.40 equiv), and DCC (20.6 g, 100 mmol, 2.0 equiv). The solution was stirred for 20 hours at 23 °C and filtered through celite. The solids and celite were further washed with CH_2Cl_2 (100 mL) and the solvent was evaporated under reduced pressure. The residue was purified via flash column chromatography to yield **1.S1** as a colorless oil. **Yield** 7.50 g (78%); **TLC** R_f 0.19 (hexanes:EtOAc 9:1). The ^{1}H and ^{13}C spectral data match those of the reported molecule.[48] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.04 (dd, *J* = 7.8, 2.1 Hz, 1H), 7.12 (dd, *J* = 7.9, 3.7 Hz, 1H), 2.52 (d, *J* = 4.1 Hz, 3H), 1.51 (d, *J* = 4.5 Hz, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.6, 162.5, 150.4, 137.2, 124.9, 122.7, 81.7, 28.1, 24.7.



methyl 6-phenylpyridine-3-carboxylate (1.S2)

In a N_2 filled glove box, dppf (91.5 mg, 0.165 mmol, 0.11 equiv) and $Pd(OAc)_2$ (34 mg, 0.15 mmol, 0.10 equiv) were dissolved in 4 mL of dioxane in a 4-dram vial and allowed to stir for 10 min to prepare the solution of the catalyst. This solution was then added to a flame dried Schlenk tube (25 mL) that contained a stir bar and methyl-6-bromonicotinate (324 mg, 1.50 mmol, 1.0 equiv) and stirred until homogenous solution was obtained. 1M solution of Et_2Zn in PhMe (1.80 mL, 1.80 mmol, 1.20 equiv) was added dropwise. The Schlenk tube was sealed and transferred to a Schlenk line where it was then heated at 80 °C with stirring for 16 hours. The reaction mixture was cooled to ambient temperature, diluted to 25 mL with Et_2O, filtered through a plug of silica gel and then celite, and concentrated *in vacuo*. The brown crude mixture was purified via automated flash chromatography to afford **1.S2**. **Yield:** 210 mg (85%) The ^1H and ^{13}C spectral data match those of the reported molecule.[49] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.13 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 3.87 (s, 3H), 2.83 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.9, 165.7, 150.2, 137.3, 123.2, 121.5, 52.03, 31.33, 13.4; **HRMS** (ESI) *m/z* calc'd for $C_9H_{12}NO_2$ $[M+H]^+$: 166.0863, found 166.0869.



methyl 6-phenylpyridine-3-carboxylate (1.S3)

To a flame dried Schlenk tube (25 mL) charged with stir bar and methyl-6-bromonicotinate (432 mg, 2.00 mmol, 1.0 equiv), $PhB(OH)_2$ (366 mg, 3.00 mmol, 1.5 equiv) was added under N_2. The reaction vessel was transferred to a N_2 filled glove box where $Pd(PPh_3)_4$ (116 mg, 0.100 mmol, 0.05 equiv) was added followed by PhMe (10 mL). The tube was sealed and transferred to a Schlenk line where degassed 2M aqueous Na_2CO_3 (2 mL, 4 mmol, 2 equiv) was added under N_2. The reaction vessel was sealed and heated at 80° C for 16

hours. The reaction mixture was cooled to ambient temperature, diluted to 25 mL with EtOAc, filtered through silica and then celite, and concentrated *in vacuo*. The orange crude mixture was purified via automated flash chromatography to give **1.S3**. **Yield:** 373 mg (87%). The ^{1}H and ^{13}C spectral data match those of the reported molecule.[50] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.28 (d, *J* = 1.3 Hz, 1H), 8.35 (dd, *J* = 8.3, 2.1 Hz, 1H), 8.06 (d, *J* = 6.7 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.53 – 7.44 (m, 3H), 3.98 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.7, 160.7, 150.8, 138.0, 137.9, 130.0, 128.9, 127.3, 124.1, 119.8, 52.4; **HRMS** (ESI) *m/z* calc'd for $C_{13}H_{12}NO_2$ $[M+H]^+$: 214.0863, found 214.0864.

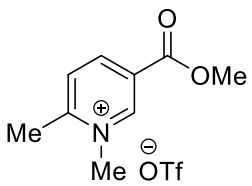
1.9.3. Synthesis of N-alkyl pyridinium salts

1) General procedure for pyridinium salts using MeOTf (GP)

In a Schlenk flask, specified nicotinic ester (1.0 equiv) was dissolved in CH_2Cl_2 (10 mL/g) and cooled in an ice water bath. MeOTf (1.1 equiv) was added slowly via syringe and the reaction mixture was stirred overnight allowing it to warm to ambient temperature. Approximately 1/3 of the CH_2Cl_2 was removed under reduced pressure to obtain light yellow oil. Pyridinium salt was isolated from this oil according to the general isolation protocol described below.

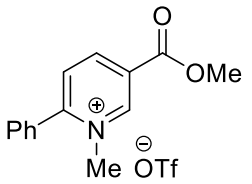
2) General procedure for isolation of pyridinium salts (GIP)

Crude pyridinium salt solution was slowly added to a beaker containing rapidly stirring Et_2O (50 mL/g). Stirring was continued for an additional 30 min at which point, pyridinium salt precipitated out. This precipitate was filtered off and washed with Et_2O (3 x 10 mL/g) to give pyridinium salt as white to off white solid unless otherwise noted.



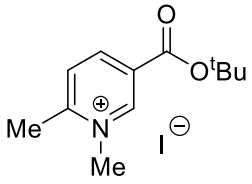
5-(methoxycarbonyl)-1,2-dimethylpypiridin-1-ium triflate (1.31)

Prepared from methyl 6-methylpyridine carboxylate (3.02 g, 20.0 mmol, 1.0 equiv) according to GP and isolated according to GIP to give **1.31** as a white solid. **Yield:** 5.80 g (87%); **FTIR** 3014.96, 2969.35, 1732.49, 1637.39; **^{1}H NMR** (600 MHz, CD_3OD) δ 7.83 (s, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 8.2 Hz, 1H), 2.75 (s, 3H), 2.41 (s, 3H), 1.29 (s, 3H); **^{13}C NMR** (151 MHz, CD_3OD) δ 163.5, 161.5, 148.8, 145.7, 130.8, 129.5, 121.7 (q, *J* = 318.6 Hz), 53.9, 46.9; **^{19}F NMR** (235 MHz, CD_3OD) δ -80.02; **HRMS** (ESI) *m/z* calc'd for $C_{10}H_{14}NO_2$ $[M]^+$ 166.0863, found 166.0870.



5-(methoxycarbonyl)-1-methyl-2-phenylpyridin-1-ium triflate (1.33)

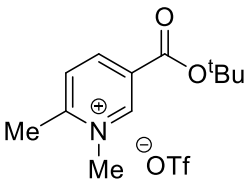
Prepared from **1.S3** (350 mg, 1.64 mmol, 1.0 equiv) according to GP and isolated according to GIP to give **1.33** as a white solid. **Yield:** 539 mg (87%). **FTIR:** 2994, 2944, 2842, 1715, 1592**; ^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.92 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.68 – 7.60 (m, 5H), 4.36 (s, 3H), 4.04 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.7, 159.2, 148.7, 144.8, 132.2, 130.7, 129.9, 129.7, 129.3, 128.9, 53.9, 48.5; **^{19}F NMR** (235 MHz, $CDCl_3$) δ -78.44. **HRMS** (ESI) *m/z* calc'd for $C_{14}H_{14}NO_2$ $[M]^+$: 228.1019, found 228.1018.



5-(*tert*-butoxycarbonyl)-1,2-dimethylpypiridin-1-ium iodide (1.S4)

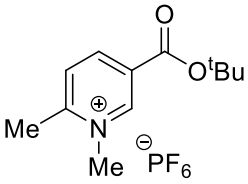
To a vial charged with a stir bar and **1.S1** (1.00 g, 1.0 equiv, 5.18 mmol), was added MeI (0.484 mL, 7.77 mmol, 1.5 equiv). The vial was fitted with a Teflon lined cap and stirred at 23 °C for 16 hours. The reaction was worked up following GIP to afford **1.S4** as a white powder. **Yield** 905 mg (52%); **FTIR** 3035.68, 2989.08, 2973.70, 1718.41, 1641.31; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.73 (d, *J* = 8.1 Hz, 1H), 8.08 (d, *J* = 8.2 Hz,

1H), 7.26 (s, 1H), 4.62 (s, 3H), 3.11 (s, 3H), 1.64 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 160.0, 159.6, 147.1, 144.8, 130.4, 130.2, 85.5, 48.7, 28.2, 23.0; **HRMS** (ESI) *m/z* calc'd for $C_{12}H_{18}NO_2^+$ $[M]^+$ 208.1332, found 208.1329.



5-(*tert*-butoxycarbonyl)-1,2-dimethylpypiridin-1-ium triflate (1.S5)

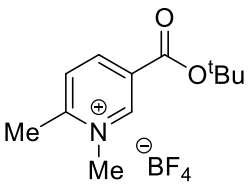
To a stirred solution of **1.S4** (200 mg, 0.596 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) in a 50 mL round-bottomed flask was added solution of NaOTf (102 mg, 0.596 mmol, 1.0 equiv) in H_2O (10 mL). The biphasic solution was stirred vigorously for 1 hour at 23 °C. The CH_2Cl_2 layer was separated and dried over $MgSO_4$. Solids were filtered off and CH_2Cl_2 layer was concentrated to afford **1.S5** as a dark purple solid. **Yield** 171 mg (80%); **FTIR** 2982.45, 2251.38, 1724.75, 1640.84; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.72 (d, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 4.48 (s, 3H), 2.99 (s, 3H), 1.62 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 160.1, 159.5, 147.1, 144.6, 130.0, 129.9, 123.6, 121.5, 120.5 (q, *J* = 320.6 Hz), 119.4, 117.3, 85.1, 47.6, 28.0, 21.7; **^{19}F NMR** (235 MHz, $CDCl_3$) δ -78.53; **HRMS** (ESI) *m/z* calc'd for $C_{12}H_{18}NO_2^+$ $[M]^+$ 208.1332, found 208.1337.



5-(*tert*-butoxycarbonyl)-1,2-dimethylpypiridin-1-ium hexafluoro-phosphate (1.S6)

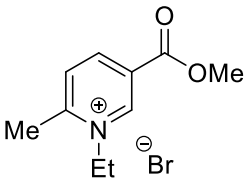
To a stirred solution of **1.S4** (200 mg, 0.596 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL). in a 50 mL round-bottomed flask was added a solution of KPF_6 (109 mg, 0.596 mmol, 1.0 equiv) in H_2O (10 mL). The biphasic solution was stirred vigorously for 1 hour at 23 °C. The CH_2Cl_2 layer was separated and dried over $MgSO_4$. Solids were filtered off and CH_2Cl_2 layer was concentrated to afford **1.S6** as an off green solid. **Yield** 188 mg (90%); **FTIR** 3100.51, 2976.93, 1718.41, 1641.31; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.70 (d, *J* = 8.2 Hz, 1H), 7.92 (d,

J = 8.2 Hz, 1H), 4.33 (s, 3H), 2.89 (s, 3H), 1.61 (s, 9H); **^{13}C NMR** (151 MHz, CD_3OD) δ 162.0, 161.0, 148.6, 145.6, 131.0, 130.6, 85.5, 46.8, 28.1, 20.7; **^{19}F NMR** (235 MHz, $CDCl_3$) δ -73.37 (d, J = 711.9 Hz); **^{31}P NMR** (101 MHz, $CDCl_3$) δ -144.38 (hept, J = 711.5 Hz); **HRMS** (ESI) *m/z* calc'd for $C_{12}H_{18}NO_2^+$ $[M]^+$ 208.1332, found 208.1330.



5-(*tert*-butoxycarbonyl)-1,2-dimethylpypiridin-1-ium tetrafluoro-borate (1.S7)

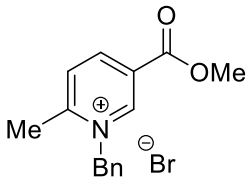
To a stirred solution of **1.S4** (200 mg, 0.596 mmol, 1.0 equiv) and CH_2Cl_2 (10 mL) in a 50 mL round-bottomed flask was added a solution of KBF_4 (75.1 mg, 0.596 mmol, 1.0 equiv) in H_2O (10 mL). The biphasic solution was stirred vigorously for 1 hour at 23 °C. The CH_2Cl_2 layer was separated and dried over $MgSO_4$. Solids were filtered off and CH_2Cl_2 layer was concentrated to afford **1.S7** as a light green solid. **Yield** 87.9 mg (50%); **FTIR** 3041.48, 3105.54, 2982.77, 1719.96, 1642.98, 1565.21; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.72 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 8.2 Hz, 1H), 4.51 (s, 3H), 3.02 (s, 3H), 1.63 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 160.1, 159.6, 147.1, 144.6, 130.0, 129.8, 85.2, 47.3, 28.0, 21.4; **^{19}F NMR** (235 MHz, $CDCl_3$) δ -153.00; **HRMS** (ESI) *m/z* calc'd for $C_{12}H_{18}NO_2^+$ $[M]^+$ 208.1332, found 208.1344.



5-(methoxycarbonyl)-1-ethyl-2-methylpypiridin-1-ium bromide (1.S8)

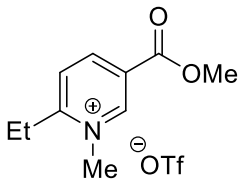
To a 4-dram vial charged with stir bar and methyl 6-methyl-nicotinate (756 mg, 5.00 mmol, 1.0 equiv) was added ethyl bromide (0.45 mL, 6.0 mmol, 1.2 equiv). The vial was fitted with a Teflon-lined cap and heated at 80 °C for 12 hours. The reaction was worked up following GIP to afford **1.S8** as a light brown solid. **Yield** 360.3 mg (28%); **FTIR** 3438.4, 301.92, 3003.28, 1729.83; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.58 (s, 1H), 8.80 (d, J = 7.8 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 5.06 (q, J = 6.9 Hz, 2H), 4.04 (s, 3H), 3.15 (s, 3H), 1.69 (t,

J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 161.8, 159.2, 146.1, 144.6, 131.3, 128.5, 55.0, 53.7, 21.5, 15.6; **HRMS** (ESI) *m/z* calc'd $C_9H_{12}NO_2$ $[M]^+$ 180.1019, found 180.1024.



5-(methoxycarbonyl)-1-benzyl-2-methylpypiridin-1-ium bromide (1.S9)

Compound **1.S9** was synthesized according to a reported procedure and the ^{1}H and ^{13}C spectral data match those of the reported molecule.[51] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.80 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.37 – 7.29 (m, 2H), 6.28 (s, 2H), 3.99 (s, 3H), 3.12 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 161.8, 160.5, 146.7, 144.9, 131.1, 130.9, 129.9, 129.9, 128.5, 128.3, 63.0, 53.9, 22.5.



2-ethyl-5-(methoxycarbonyl)-1-methylpyridin-1-ium triflate (1.S10)

To a 25 mL Schlenk tube charged with stir bar and solution of methyl 6-ethylpyridine-3-carboxylate (200 mg, 1.21 mmol, 1.00 equiv) in CH_2Cl_2 (3.1 mL), MeOTf (238 mg, 1.45 mmol, 1.20 equiv) was added dropwise under N_2 at 4 °C, and the reaction was gradually warmed to ambient temperature after addition of methyl triflate. After 12 hours, the reaction mixture was added dropwise to 400 mL of stirring 1:1 Et_2O/Hex. After an hour of additional stirring, the precipitate was collected and washed with 5 mL of cold ether to afford **1.S10**. **Yield:** 380 mg (95%). **FTIR:** **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.83 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 4.43 (s, 3H), 4.03 (s, 3H), 3.22 (q, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 163.9, 161.9, 147.9, 144.8, 128.0, 127.2, 123.6, 121.5, 119.4, 117.3, 77.3, 77.1, 76.9, 53.7, 53.5, 46.6, 26.6, 10.9; **^{19}F NMR** (235 MHz, $CDCl_3$) δ -78.61 (s); **HRMS** (ESI) *m/z* calc'd for $C_{10}H_{14}NO_2$ $[M]^+$: 180.1019, found 180.1024.

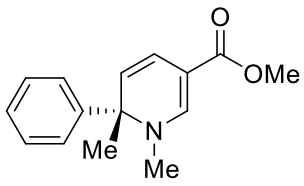
1.9.4. Synthesis of dihydropyridines *via* dearomatization

1) Preparation of the Rh catalyst stock solution:

In a nitrogen filled glove box $Rh(cod)_2BF_4$ (64 mg, 0.16 mmol, 1.0 equiv) and (R)-BINAP (99 mg, 0.16 mmol, 1.0 equiv) was weighed into a 4-dram vial and dissolved in dioxane (16 mL). This solution was used in the dearomatization reactions below. To prepare the racemic dearomatization products racemic BINAP was used to prepare the catalyst.

2) General procedure for dearomatization of N-alkyl pyridinium salts:

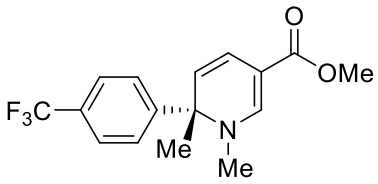
The specified pyridinium salt (0.20 mmol, 1.0 equiv), aryl boronic acid (0.50 mmol, 2.5 equiv), and Na_2CO_3 (53 mg, 0.50 mmol, 2.5 equiv), were measured into a 1-dram scintillation vial on the benchtop. The vial was then transferred into the glovebox where 1.0 mL of the solution of the catalyst was added into the vial. The vial was sealed with a Teflon lined septa cap and brought outside the glovebox. Degassed water (250 µL) was added to the reaction mixture via syringe and the reaction mixture was heated at 80 °C for 2 hours. The vial was then removed from the heating block and diluted with 2 mL of EtOAc. The reaction mixture was dried with 1.0 g of $MgSO_4$ and filtered through basic Al_2O_3. Al_2O_3 was washed with additional EtOAc (2 x 4 mL), and the combined filtrate was concentrated to give brown residue. The residue was purified by flash column chromatography on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (24-gram silica gel column) using a hexanes:EtOAc gradient (0 to 100% EtOAc) to give **1.32-1.34** as a light-yellow oil unless otherwise noted.



methyl (6S)-1,6-dimethyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (1.32a)

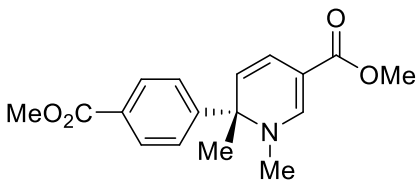
Dihydropyridine **1.32a** was synthesized from pyridinium **1.31** and phenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium

salts. **Yield:** 40 mg **(**82%); The **enantiomeric excess** was determined by HPLC analysis to be 94%ee (254 nm, 25℃); t_{minor} = 14.7 min, t_{major} = 16.3 min [(Chiralpak ID) hexane/i-PrOH, 90:10, 1.0 mL/min]; **TLC** R_f 0.56 (Hex:EtOAc 1:1); **FTIR:** 3055, 3025, 2976, 2947, 1677, 1634, 1588; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** -0.3728 (c 0.046 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.32 (s, 1H), 7.29 – 7.25 (m, 1H), 6.31 (d, *J* = 9.8 Hz, 1H), 4.77 (d, *J* = 9.9 Hz, 1H), 3.70 (s, 3H), 2.72 (s, 3H), 1.75 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.1, 147.7, 145.6, 128.5, 127.6, 126.5, 120.0, 118.0, 94.6, 63.2, 50.8, 38.4, 24.8; **HRMS** (ESI) *m/z* calc'd for $C_{15}H_{18}NO_2$ $[M+H]^+$ 244.1332, found 244.1347.



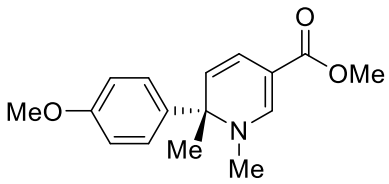
methyl (6*S*)-1,6-dimethyl-6-[4-(trifluoromethyl)phenyl]-1,6-dihydro-pyridine-3-carboxylate (1.32b)

Dihydropyridine **1.32b** was synthesized from pyridinium **1.31** and 4-(trifluoromethyl)phenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 39 mg **(**63%); The **enantiomeric excess** was determined by HPLC analysis to be 91%ee (254 nm, 25℃); t_{minor} = 13.1 min, t_{major} = 13.8 min [(Chiralpak IG) hexane/*i*-PrOH, 90:10, 1.0 mL/min]; **TLC** R_f 0.57 (Hex:EtOAc 1:1); **FTIR:** 2978, 2948, 1681, 1637, 1569; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** 0.2700 (c 0.020 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.34 (s, 1H), 6.32 (d, *J* = 9.9 Hz, 1H), 4.75 (d, *J* = 10.0 Hz, 1H), 3.70 (s, 3H), 2.73 (s, 3H), 1.78 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.9, 149.4, 147.6, 129.68 (q, *J* = 32.5 Hz), 126.8, 125.6 (q, *J* = 3.6 Hz), 124.0 (q, *J* = 272.2 Hz), 119.4, 118.7, 95.2, 63.2, 50.9, 38.4, 24.9; **^{19}F NMR** (235 MHz, $CDCl_3$) δ -62.55; **HRMS:** (ESI) *m/z* **c**alc'd for $C_{19}H_{17}F_3NO$ $[M+H]^+$ 312.1206, found 312.1196.



methyl (6*S*)-6-(4-methoxycarbonylphenyl) -1,6-dihydropyridine-3-carboxylate (1.32c)

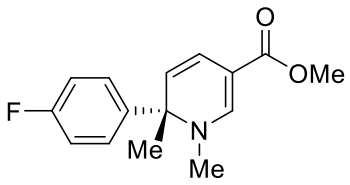
Dihydropyridine **1.32c** was synthesized from pyridinium **1.31** and 4-methoxycarbonylphenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 46 mg **(**76%); The **enantiomeric excess** was determined by HPLC analysis to be 81%ee (254 nm, 25℃); t_{minor} = 26.8 min, t_{major} = 23.4 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.44 (Hex:EtOAc 1:1); **FTIR:** 2949, 1720, 1678, 1636, 1567; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** 0.2288 (c 0.090 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.33 (s, 1H), 6.30 (d, *J* = 9.9 Hz, 1H), 4.74 (d, *J* = 10.0 Hz, 1H), 3.90 (s, 3H), 3.69 (s, 3H), 2.71 (s, 3H), 1.77 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.0, 166.8, 150.4, 147.7, 129.9, 129.3, 126.5, 119.5, 118.6, 95.0, 63.4, 52.4, 50.9, 38.5, 25.0; **HRMS:** (ESI) *m/z* **c**alc'd for $C_{17}H_{20}NO_4$ $[M+H]^+$ 302.1387, found 302.1381.



methyl (6*S*)-6-(4-methoxyphenyl)-1,6-dimethyl-1,6-dihydro-pyridine-3-carboxylate (1.32d)

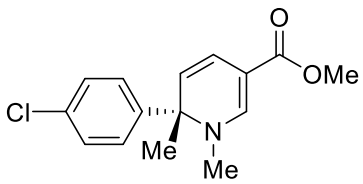
Dihydropyridine **1.32d** was synthesized from pyridinium **1.31** and 4-methoxyphenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 52 mg **(**95%); The **enantiomeric excess** was determined by HPLC analysis to be 91%ee (254 nm, 25℃); t_{minor} = 13.3 min, t_{major} = 14.3min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.50 (Hex:EtOAc 1:1); **FTIR:** 3050, 2946, 2836, 1676, 1635, 1568; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** -1.2092 (c 0.086 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 2H), 7.30 (s, 1H), 6.91 – 6.83 (m, 2H), 6.30 (d, *J* = 10.0 Hz, 1H), 4.75 (d, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 2.70 (s, 3H), 1.71 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.2, 158.8, 147.6, 138.0,

127.9, 120.1, 117.9, 113.6, 94.5, 62.69, 55.4, 50.8, 38.3, 24.9; **HRMS:** (ESI) *m/z* calc'd for $C_{16}H_{20}NO_3$ $[M+H]^+$ 274.1438, found 274.1437.



methyl (6*S*)-6-(4-methoxyphenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (1.32e)

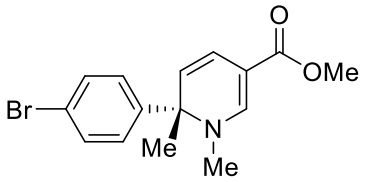
Dihydropyridine **1.32e** was synthesized from pyridinium **1.31** and 4-fluorophenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 52 mg **(**99%); The **enantiomeric excess** was determined by HPLC analysis to be 94%ee (254 nm, 25℃); t_{minor} = 9.8 min, t_{major} = 10.5 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.37 (Hex:EtOAc 4:1); **FTIR:** 3052, 2977, 2947, 1677, 1636, 1569; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** -0.6176 (c 0.057 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.31 (s, 1H), 7.04 (t, *J* = 8.5 Hz, 2H), 6.31 (d, *J* = 9.7 Hz, 1H), 4.75 (d, *J* = 9.9 Hz, 1H), 3.70 (s, 3H), 2.71 (s, 3H), 1.73 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.1, 162.8, 161.2, 147.5, 141.6 (d, *J* = 3.1 Hz), 128.4 (d, *J* = 8.1 Hz). 119.8, 118.2, 115.3, 115.2, 94.7, 62.7, 50.8, 38.3, 25.0. **^{19}F NMR** (235 MHz, $CDCl_3$) δ -114.95; **HRMS:** (ESI) *m/z* **c**alc'd for $C_{18}H_{17}FNO$ $[M+H]^+$ 262.1238, found 262.1237.



methyl (6*S*)-6-(4-chlorophenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (1.32f)

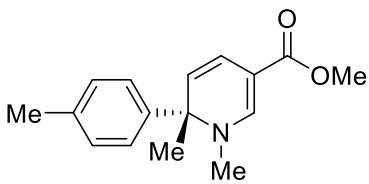
Dihydropyridine **1.32f** was synthesized from pyridinium **1.31** and 4-chlorophenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 50 mg (90%); The **enantiomeric excess** was determined by HPLC analysis to be 91%ee (254 nm, 25℃); t_{minor} = 18.3 min, t_{major} = 18.9 min [(Chiralpak IG) hexane/*i*-PrOH, 90:10, 1.0 mL/min]; **TLC** R_f 0.77 (Hex:EtOAc 1:1); **FTIR:** 3051, 2975, 2946, 1677, 1636,

1567; $[\alpha]_D^{20}$**:** -0.4905 (c 0.057 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 – 7.39 (7.40 (d, *J* = 6.8 Hz, 2H), 7.33 (s, 1H), 7.31 (d, *J* = 6.6 Hz, 2H), 6.30 (d, *J* = 10.0 Hz, 1H), 4.73 (d, *J* = 10.0 Hz, 1H), 3.69 (s, 3H), 2.71 (s, 3H), 1.72 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.0, 147.6, 144.2, 133.5, 128.7, 128.0, 119.6, 118.4, 94.9, 62.9, 50.9, 38.4, 24.9; **HRMS:** (ESI) *m/z* calc'd for $C_{15}H_{17}ClNO_2$ $[M+H]^+$ 278.0942, found 278.0951.



methyl (6*S*)-6-(4-bromophenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (1.32g)

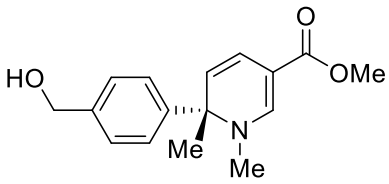
Dihydropyridine **1.32g** was synthesized from pyridinium **1.31** and 4-bromophenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 51.4 mg (80%); The **enantiomeric excess** was determined by HPLC analysis to be 95%ee (254 nm, 25℃); t_{minor} = 17.7 min, t_{major} = 16.2 min [(Chiralpak IE) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.48 (hexanes:EtOAc, 3:2); $[\alpha]_D^{20}$ -3.16 (*c* 0.095 $CHCl_3$); **FTIR** 1949.06, 1736.57, 1678.07, 1636.69; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.30 (s, 1H), 6.30 (d, *J* = 9.9 Hz, 1H), 4.73 (d, *J* = 9.9 Hz, 1H), 3.69 (s, 3H), 2.71 (s, 3H), 1.72 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.0, 147.6, 144.8, 131.7, 128.4, 121.8, 119.7, 118.6, 95.1, 63.1, 50.9, 38.4, 24.9; **HRMS** (ESI) *m/z* calc'd for $C_{15}H_{17}NO_2$ $[M+H]^+$ 322.0437, found 322.0455.



methyl (6*S*)-6-(4-methylphenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (1.32h)

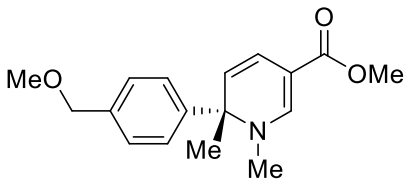
Dihydropyridine **1.32h** was synthesized from pyridinium **1.31** and 4-methylphenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 45.2 mg (88%); The **enantiomeric excess** was determined by HPLC

analysis to be 94%ee (254 nm, 25℃); t_{minor} = 9.1 min, t_{major} = 9.8 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.55 (hexanes:EtOAc, 3:2); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -8.06 (*c* 0.783 $CHCl_3$); **FTIR** 3050, 2974, 2945, 2922, 1677, 1639, 1567; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.8 Hz, 2H), 7.32 (s, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 6.29 (d, *J* = 9.8 Hz, 1H), 4.75 (d, *J* = 9.9 Hz, 1H), 3.70 (s, 3H), 2.71 (s, 3H), 2.34 (s, 3H), 1.72 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 167.2, 147.7, 142.8, 137.3, 129.2, 126.5, 120.1, 117.9, 94.5, 63.0, 50.8, 38.4, 24.9, 21.1; **HRMS** (ESI) *m*/*z* calc'd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1489, found 258.1502.



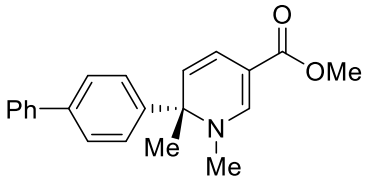
methyl (6*S*)-6-(4-hydroxymethylphenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (1.32i)

Dihydropyridine **1.32i** was synthesized from pyridinium **1.31** and 4-hydroxymethylphenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 38.2 mg (70%); **enantiomeric excess:** We were not able to achieve acceptable separation for this compound on chiral HPLC. For ee see derivative **S11; TLC** R_f 0.1 (hexanes:EtOAc, 3:2); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -4.24 (*c* 0.726 $CHCl_3$); **FTIR** 3414, 3051, 2973, 2946, 2872, 1664; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.31 (s, 1H), 6.27 (d, *J* = 9.8 Hz, 1H), 4.72 (t, *J* = 12.2 Hz, 1H), 4.68 (s, 2H), 3.68 (s, 3H), 2.70 (s, 3H), 1.73 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.2, 147.7, 145.7, 138.0, 129.2, 124.4, 120.2, 117.7, 94.4, 63.2, 50.8, 38.5, 24.9, 21.6; **HRMS** (ESI) *m/z* calc'd for $C_{16}H_{20}NO_3$ $[M+H]^+$ 274.1438, found 274.1438.



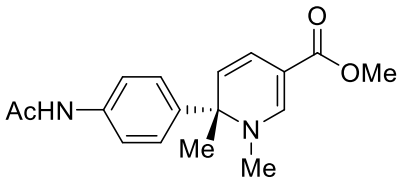
methyl (6*S*)-6-(4-methoxymethylphenyl)-1,6-dimethyl-1,6-dihydro-pyridine-3-carboxylate (1.S11)

To determine the enantiomeric excess of dihydropyridine **1.32i**, it was converted to the methyl ether **1.S11** through the following procedure: To a stirred solution of **1.32i** (12.1 mg, 0.0440 mmol, 1.0 equiv) in dry DMF (1.0 mL) in a Schlenk flask at 0 °C was added sodium hydride (60% dispersion in mineral oil) (2.25 mg, 0.0530 mmol, 1.2 equiv) in one addition. The solution was stirred for 30 minutes. Methyl Iodide (4.65 µl, 0.066 mmol, 1.5 equiv) was added via syringe. The solution was warmed to 23 °C and stirred for 3 hours. The reaction was quenched with NH_4Cl (1.0 ml) and then diluted with H_2O (5.0 ml) and extracted three times with diethyl ether (3 x 5.0 ml). The combined ether layers were dried over sodium sulfate. Solids were filtered off and the filtrate was evaporated to give a residue. This residue was purified via flash column chromatography to afford **1.S11** as a colorless oil. **Yield** 8.6 mg (68%); The **enantiomeric excess** was determined by HPLC analysis to be 86% ee (254 nm, 25℃); t_{minor} = 15.5 min, t_{major} = 16.8 min [(Chiralpak ID) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.45 (hexanes:EtOAc, 3:2); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -0.011 (*c* 0.055 $CHCl_3$); **FTIR** 3055.94, 2976.93, 2849.30, 2818.91, 1677.98, 1635.91; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.5 Hz, 2H), 7.35 – 7.30 (m, 3H), 6.31 (d, *J* = 9.7 Hz, 1H), 4.76 (d, *J* = 9.8 Hz, 1H), 4.45 (s, 2H), 3.70 (s, 3H), 3.41 (s, 3H), 2.71 (s, 3H), 1.74 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.1, 147.6, 145.1, 137.6, 127.9, 126.6, 120.0, 118.1, 94.8, 74.3, 63.1, 58.4, 50.7, 38.3, 24.8; **HRMS** (ESI) *m/z* calc'd for $C_{17}H_{22}NO_3$ $[M+H]^+$ 288.1594, found 288.1610.



methyl (6*S*)-6-(4-biphenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (1.32j)

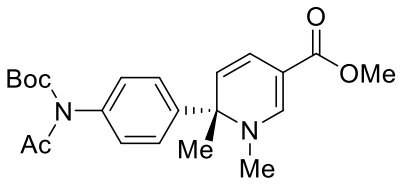
Dihydropyridine **1.32j** was synthesized from pyridinium **1.31** and 4-biphenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 43.4 mg (99%); The **enantiomeric excess** was determined by HPLC analysis to be 93% ee (254 nm, 25℃); t_{minor} = 14.7 min, t_{major} = 15.7 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.26 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -6.64 (*c* 1.456, $CHCl_3$); **FTIR** 3041, 3025, 2991, 2966, 2941, 1682; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.0 Hz, 3H), 7.55 (d, *J* = 7.1 Hz, 2H), 7.45 (t, *J* = 6.9 Hz, 2H), 7.37 (s, 2H), 6.35 (d, *J* = 9.8 Hz, 1H), 5.29 (s, 1H), 4.82 (d, *J* = 9.9 Hz, 1H), 3.72 (s, 3H), 2.77 (s, 3H), 1.79 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.1, 147.7, 144.6, 140.5, 140.4, 128.9, 127.6, 127.2, 127.2, 127.0, 120.0, 118.2, 94.7, 63.1, 50.8, 38.5, 25.0; **HRMS** (ESI) *m*/*z* calc'd for $C_{19}H_{23}NO_2$ $[M+H]^+$ 320.1645, found 320.1626.



methyl (6*S*)-6-(4-acetamidophenyl)-1,6-dimethyl-1,6-dihydro-pyridine-3-carboxylate (1.32k)

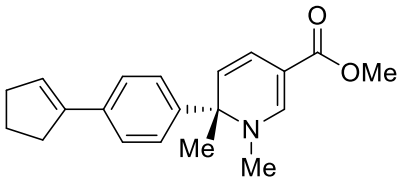
Dihydropyridine **1.32k** was synthesized from pyridinium **1.31** and 4-acetamidophenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield**: 45 mg (75%); **enantiomeric excess:** We were not able to achieve acceptable separation for this compound on chiral HPLC. For ee see derivative **1.S12; TLC** R_f 0.12 (Hex:EtOAc 1:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** -0.9158 (c 0.227 $CHCl_3$); **FTIR:** 3052, 2976, 2947, 1668, 1633, 1600, 1568, 1530; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.23 (d, *J* = 9.9 Hz, 1H), 4.69 (d, *J* = 9.9 Hz, 1H), 3.66 (s, 3H), 2.63 (s, 3H), 2.12 (d, *J* = 15.0 Hz, 3H), 1.67 (s, 3H).; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 169.3, 167.4, 147.9, 141.0,

137.8, 127.1, 120.1, 119.7, 117.8, 94.2, 62.9, 50.9, 38.4, 25.0, 24.5.**; HRMS:** (ESI) *m/z* calc'd $C_{17}H_{20}N_2O_3Na$ $[M+Na]^+$ 323.1366, found 323.1382.



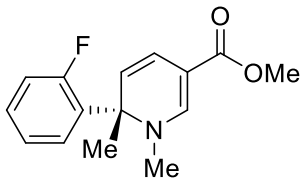
methyl (6S)-6-[*p*-(N-acetyl-N-tert-butoxycarbonylamino)phenyl]-1-methyl-6-methyl-1,6-dihydropyridine-3-carboxylate (1.S12)

To a 500 µL Schlenk tube charged with stir bar, dihydropyridine **1.32k** (20.0 mg, 0.066, 1 equiv), and DMAP (4.00 mg, 0.033 mmol, 0.50 equiv), DMF (75 µL) was added. Boc_2O (22 mg, 0.098 mmol, 1.5 equiv) was then added and the reaction mixture was stirred for 1.5 hours at ambient temperature. The reaction was quenched into H_2O (5 mL), extracted with EtOAc. EtOAc layer was dried over $MgSO_4$. Solids were removed through filtration over a pad of silica then celite, and concentrated. Crude mixture was purified via automated flash chromatography to yield **1.S12.** Y**ield:** 25 mg **(**96%). The **enantiomeric excess** was determined by HPLC analysis to be 93% ee (254 nm, 25℃); t_{minor} = 22.8 min, t_{major} = 25.3 min [(Chiralpak ID) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.57 (Hex:EtOAc 1:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** -0.4642 (c 0.063 $CHCl_3$); **FTIR:** 3053, 2977, 2947, 1736, 1682, 1637, 1570; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.25 (d, *J* = 9.9 Hz, 1H), 4.72 (d, *J* = 9.9 Hz, 1H), 3.64 (s, 3H), 2.65 (s, 3H), 2.53 (s, 3H), 1.69 (s, 3H), 1.31 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.1, 167.1, 152.7, 147.5, 145.0, 138.1, 128.2, 127.4, 119.8, 118.2, 94.8, 83.5, 63.0, 50.8, 38.3, 27.8, 26.7, 24.8.; **HRMS:** (ESI) *m/z* **c**alc'd for $C_{20}H_{30}N_2O_5Na$ $[M+Na]^+$ 401.2071, found 401.2060.



methyl (6*S*)-6-[4-(cyclopent-1-en-1-yl)phenyl]-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (1.32l)

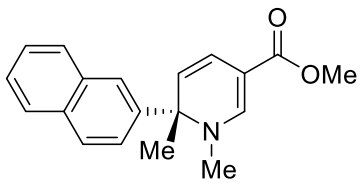
Dihydropyridine **1.32l** was synthesized from pyridinium **1.31** and (4-cyclopent-1-en-1-yl)phenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 58 mg (93%); The **enantiomeric excess** was determined by HPLC analysis to be 95% ee (254 nm, 25℃); t_{minor} = 13.2 min, t_{major} = 14.6 min [(Chiralpak IA) hexane/*i*-PrOH, 95:5, 1.0 mL/min]; **TLC** R_f 0.79 (Hex:EtOAc 1:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:**-0.780 (c 0.003 $CHCl_3$); **FTIR:** 3050, 2949, 2845, 1735, 1679, 1636, 1572; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 (q, *J* = 8.5 Hz, 3H), 7.32 (s, 1H), 7.26 (s, 1H), 6.31 (d, *J* = 9.9 Hz, 1H), 6.21 (s, 1H), 4.76 (d, *J* = 9.9 Hz, 1H), 3.70 (s, 3H), 2.80 – 2.67 (m, 5H), 2.59 – 2.46 (m, 2H), 2.07 – 1.92 (m, 2H), 1.74 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.2, 147.7, 144.0, 141.8, 136.0, 126.9, 126.5, 125.6, 119.94, 118.0, 94.6, 63.1, 50.8, 38.4, 33.4, 33.2, 24.8, 23.4**; HRMS:** (ESI) *m/z* calc'd for $C_{20}H_{24}NO_2$ $[M+H]^+$ 310.1802, found 310.1807.



methyl (6*S*)-6-(2-fluorophenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (1.32m)

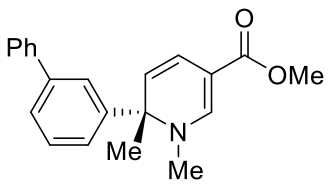
Dihydropyridine **1.32m** was synthesized from pyridinium **1.31** and 2-fluorophenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 24 mg **(**46%); The **enantiomeric excess** was determined by HPLC analysis to be 94% ee (254 nm, 25℃); t_{minor} = 20.8 min, t_{major} = 21.9 min [(Chiralpak ID) hexane/*i*-PrOH, 90:10, 1.0 mL/min]; **TLC** R_f 0.71 (Hex:EtOAc 1:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** 0.6886 (c 0.070 $CHCl_3$); **FTIR:** 3057, 2978, 2946, 1678, 1636, 1567; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 3H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.09 (dd, *J* = 11.7, 8.2 Hz, 1H), 6.35 (d, *J* = 9.8 Hz, 1H), 4.93 (d, *J* = 9.8 Hz, 1H), 3.72 (s, 3H), 2.88 (s, 3H), 1.85 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.1, 161.5, 159.8, 147.6,

131.0 (d, *J* = 10.7 Hz), 129.8 (d, *J* = 8.7 Hz), 127.8 (d, *J* = 3.4 Hz), 124.1 (d, *J* = 3.6 Hz), 119.1, 117.9, 117.1, 116.9, 95.5, 62.1, 50.8, 38.7, 26.3 (d, *J* = 3.3 Hz); **HRMS:** (ESI) *m/z* **c**alc'd for $C_{15}H_{17}NO_2F$ $[M+H]^+$: 262.1239 found: 262.1240.



methyl (6*S*)-6-(2-napthalen-2-yl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (1.32n)

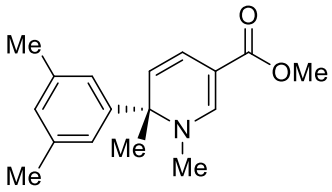
Dihydropyridine **1.32n** was synthesized from pyridinium **1.31** and 2-napthalen-2-ylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 58.0 (99%); The **enantiomeric excess** was determined by HPLC analysis to be 94% ee (254 nm, 25℃); t_{minor} = 14.6 min, t_{major} = 12.0 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.26 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -1.14 (*c* 2.686 $CHCl_3$); **FTIR** 3053, 2974, 2945, 1675, 1634; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 14.6, 7.9 Hz, 3H), 7.78 – 7.73 (m, *J* = 10.9 Hz, 2H), 7.54 – 7.47 (m, 2H), 7.39 (s, 1H), 6.36 (d, *J* = 9.8 Hz, 1H), 4.81 (d, *J* = 9.9 Hz, 1H), 3.73 (s, 3H), 2.72 (s, 3H), 1.87 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.2, 147.8, 142.7, 132.8, 132.6, 128.7, 128.4, 127.6, 126.5, 126.4, 125.7, 123.9, 119.8, 118.4, 94.7, 63.5, 50.8, 38.4, 24.9; **HRMS** (ESI) *m/z* Calc'd for $C_{19}H_{20}NO_2$ $[M+H]^+$ 294.1489, found 294.1485.



methyl (6*S*)-6-([1,1'-biphenyl]-3-yl)-1,6-dimethyl-1,6-dihydro-pyridine-3-carboxylate (1.32o)

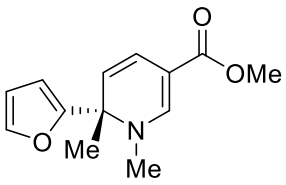
Dihydropyridine **1.32o** was synthesized from pyridinium **1.31** and 1,1'-biphenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 61.5 mg (98%); The **enantiomeric excess** was determined by HPLC analysis to be 96% ee (254 nm, 25℃); t_{minor} = 13.9 min, t_{major} = 10.5 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.29 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -5.32 (*c* 1.003 $CHCl_3$);

FTIR 3054, 3029, 2974, 2945, 2246, 1677, 1635; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.59 (d, *J* = 7.1 Hz, 2H), 7.52 (d, *J* = 6.4 Hz, 1H), 7.49 – 7.43 (m, 4H), 7.40 – 7.35 (m, 2H), 6.35 (d, *J* = 9.8 Hz, 1H), 4.83 (d, *J* = 9.8 Hz, 1H), 3.72 (s, 3H), 2.77 (s, 3H), 1.81 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.2, 147.7, 146.3, 141.5, 141.0, 129.0, 128.9, 127.6, 127.3, 126.5, 125.5, 120.0, 118.2, 94.7, 63.4, 53.6, 50.8, 38.5, 24.9; **HRMS** (ESI) *m*/*z* calc'd for $C_{21}H_{22}O_2$ $[M+H]^+$ 320.1645, found 320.1642.



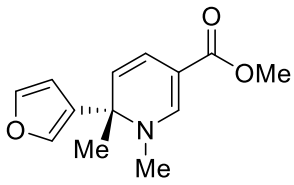
methyl (6*S*)-6-(3,5-dimethylphenyl)-1,6-dimethyl-1,6-dihydro-pyridine-3-carboxylate (1.32p)

Dihydropyridine **1.32p** was synthesized from pyridinium **1.31** and 3,5-dimethylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 51.5 mg (95%); The **enantiomeric excess** was determined by HPLC analysis to be 97% ee (254 nm, 25℃); t_{minor} = 7.2 min, t_{major} = 8.6 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.35 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -6.65 (*c* 0.526 $CHCl_3$); **FTIR** 3050, 2980, 2940, 2910, 2850; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.06 (s, 2H), 6.91 (s, 1H), 6.28 (d, *J* = 9.8 Hz, 1H), 4.74 (d, *J* = 9.9 Hz, 1H), 3.71 (s, 3H), 2.72 (s, 3H), 2.32 (s, 6H), 1.71 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.3 147.8, 145.8, 138.1, 129.2, 124.4, 120.2, 117.8, 94.4, 63.2, 50.8, 38.5, 25.0, 21.6; **HRMS** (ESI) *m*/*z* calc'd for $C_{17}H_{22}NO_2$ $[M+H]^+$ 272.1645, found 272.1653. Single crystals suitable for **X-Ray** analysis were obtained by slow evaporation of diethylether from a solution of **1.32p** in a mixture of diethylether and hexanes. CCDC registry number 1921656.



methyl (6*S*)-6-(furan-2-yl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (1.32q)

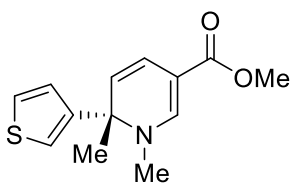
Dihydropyridine **1.32q** was synthesized from pyridinium **1.31** and furan-2-ylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 44 mg (94%); The **enantiomeric excess** was determined by HPLC analysis to be 82% ee (254 nm, 25℃); t_{minor} = 23.0 min, t_{major} = 23.9 min [(Chiralpak IG) hexane/*i*-PrOH, 90:10, 1.0 mL/min]; **TLC** R_f 0.74 (Hex:EtOAc 1:1); **FTIR:** 2980, 2947, 1677, 1637, 1568; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** -1.8176 (c 0.057 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.30 (s, 1H), 6.48 (d, *J* = 9.6 Hz, 1H), 6.37 (d, *J* = 1.1 Hz, 1H), 6.28 (d, *J* = 1.1 Hz, 1H), 4.85 (d, *J* = 9.8 Hz, 1H), 3.71 (s, 3H), 2.84 (s, 3H), 1.68 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.0, 156.9, 147.2, 142.9, 120.5, 116.2, 110.3, 107.6, 95.4, 59.2, 50.8, 38.5, 24.3; **HRMS:** (ESI) *m/z* calc'd for $C_{13}H_{16}NO_3$ $[M+H]^+$ 234.1125, found 234.1141.



methyl (6*S*)-6-(furan-3-yl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (1.32r)

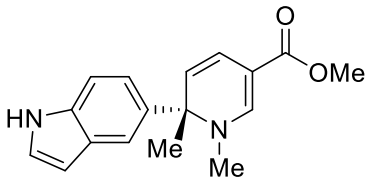
Dihydropyridine **1.32r** was synthesized from pyridinium **1.31** and furan-3-ylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 23 mg **(**49%); The **enantiomeric excess** was determined by HPLC analysis to be 92% ee (254 nm, 25℃); t_{minor} = 10.2 min, t_{major} = 11.1 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.71 (Hex:EtOAc 1:1); **FTIR:** 3051, 2976, 2947, 1676, 1636, 1568; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** -0.9525 (c 0.026 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.33 (s, 1H), 7.31 – 7.28 (m, 2H), 6.50 (s, 1H), 6.37 (d, *J* = 9.8 Hz, 1H), 4.81 (d, *J* = 9.9 Hz, 1H), 3.72 (s, 3H), 2.85 (s, 3H), 1.66 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.2, 147.6, 143.9, 138.6, 131.0, 119.4, 118.5, 110.1,

95.2, 57.9, 50.9, 38.2, 25.5; **HRMS:** (ESI) *m/z* calc'd for $C_{13}H_{16}NO_3$ $[M+H]^+$ 234.1125, found 234.1131.



methyl (6*S*)-6-(thiophen-3-yl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (1.32s)

Dihydropyridine **1.32s** was synthesized from pyridinium **1.31** and thiophen-3-ylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 38.3 mg (77%); The **enantiomeric excess** was determined by HPLC analysis to be 95% ee (254 nm, 25℃); t_{minor} = 11.1 min, t_{major} = 12.6 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.29 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -11.21 (*c* 0.616 $CHCl_3$); **FTIR** 3100, 3049, 2975, 2945, 1673, 1634; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.27 (s, *J* = 1.5 Hz, 1H), 7.17 (s, 1H), 6.38 (d, *J* = 9.8 Hz, 1H), 4.86 (d, *J* = 9.9 Hz, 1H), 3.75 (s, 3H), 2.83 (s, *J* = 14.4 Hz, 3H), 1.79 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.1, 147.5, 147.3, 127.6, 126.4, 120.8, 119.1, 118.7, 95.0, 60.7, 50.8, 38.3, 25.8; **HRMS** (ESI) *m/z* calc'd for $C_{13}H_{16}NO_2S$ $[M+H]^+$ 250.0896, found 250.0896.

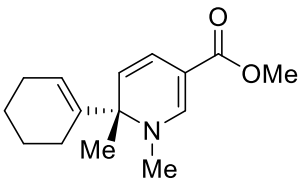


methyl (6*S*)-6-(1*H*-indol-5-yl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (1.32t)

Dihydropyridine **1.32t** was synthesized from pyridinium **1.31** and 1*H*-indol-5-ylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 32.1 (57%); The **enantiomeric excess** was determined by HPLC analysis to be 92% ee (254 nm, 25℃); t_{minor} = 20.7 min, t_{major} = 10.0 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.32 (hexanes:EtOAc, 3:2); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -0.71 (*c* 20.953 $CHCl_3$); **FTIR** 3390, 3310, 2940, 2480; **^{1}H NMR** (600 MHz, $_{CD3OD}$) δ 7.62 (s, 1H), 7.42 (s, 1H), 7.38 (d, *J* = 7.6

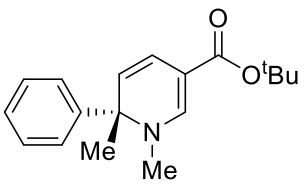
Hz, 1H), 7.33 (s, 1H), 7.24 (s, 1H), 6.45 (s, 1H), 6.22 (d, *J* = 9.2 Hz, 1H), 4.82 (d, *J* = 9.1 Hz, 1H), 3.68 (s, 3H), 2.73 (s, 3H), 1.81 (s, 3H); **^{13}C NMR** (151 MHz, CD_3OD) δ 168.2, 148.3, 136.3, 135.5, 127.7, 125.0, 120.8, 120.8, 117.4, 116.5, 111.0, 101.5, 93.3, 63.5, 49.9, 37.4, 24.2; **HRMS** (ESI) *m*/*z* calc'd for $C_{17}H_{19}N_2O_2$ $[M+H]^+$ 283.1441, found 283.1442.

Single crystals suitable for **X-Ray** analysis were obtained by slow evaporation of diethylether from a solution of **8t** in a mixture of diethylether and hexanes. CCDC registry number 1920061.



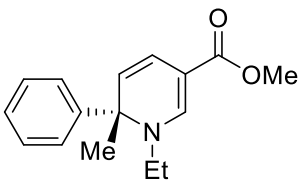
methyl (6*S*)-6-(cyclohex-1-ene-1-yl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (1.32u)

Dihydropyridine **1.32u** was synthesized from pyridinium **1.31** and cyclohex-1-ene-1ylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 33.1 (67%); The **enantiomeric excess** was determined by HPLC analysis to be 95% ee (254 nm, 25℃); t_{minor} = 16.3 min, t_{major} = 17.3 min [(Chiralpak IE) hexane/*i*-PrOH, 90:10, 1.0 mL/min]; **TLC** R*f* 0.33 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -0.005 (*c* 0.310 $CHCl_3$); **FTIR** 2925.19, 2855.26, 1681.86, 1634.24; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26 (s, 1H) 6.28 (d, *J* = 9.8 Hz, 1H), 5.61 (s, 1H), 4.54 (d, *J* = 9.8 Hz, 1H), 3.66 (s, 3H), 2.78 (s, 3H), 2.24 (d, *J* = 16.8 Hz, 1H), 2.07 (s, 2H), 1.89 (d, *J* = 16.8 Hz, 1H), 1.67 – 1.56 (m, 2H), 1.55 (d, *J* = 5.4 Hz, 2H), 1.42 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.1, 148.5, 140.2, 122.5, 120.0, 118.9, 94.3, 64.4, 50.6, 37.5, 25.3, 25.2, 24.2, 23.0, 22.2; **HRMS** (ESI) *m/z* calc'd for $C_{15}H_{22}NO_2$ $[M+H]^+$ 248.1645, found 248.1651.



***tert*-butyl (6*S*)-6-(phenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (1.S13)**

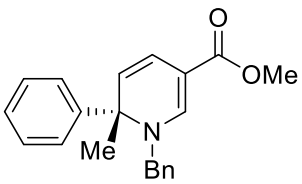
Dihydropyridine **1.S13** was synthesized from pyridinium salts **1.S4**, **1.S5**, **1.S6**, **1.S7** and phenyl boronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. Yields and enantiomeric excess for each case was as follows: from **1.S4** (67.0 mg, 75% yield, 95% ee), from **1.S5** (71.4 mg, 80% yield, 93% ee), from **1.S6** (70.6 mg, 99% yield, 91% ee), and from **1.S7** (59.0 mg, 75% yield, 90% ee). The **enantiomeric excess** was determined by HPLC analysis (254 nm, 25℃); t_{minor} = 5.2 min, t_{major} = 5.6 min [(Chiralpak ID) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.63 (hexanes:EtOAc, 4:1), $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -2.11 (*c* 0.060 $CHCl_3$); **FTIR** 2973.91, 2929.11, 1729.93, 1673.98; **^{1}H NMR** (600 MHz, CDCl3) δ 7.51 (d, J = 7.6 Hz, 2H), 7.40 (t, J = 7.7 Hz, 2H), 7.32 – 7.28 (m, 1H), 6.30 (d, J = 9.8 Hz, 1H), 4.78 (d, J = 9.9 Hz, 1H), 2.73 (s, 3H), 1.77 (s, 3H), 1.52 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.5, 147.1, 145.9, 128.5, 127.5, 126.7, 119.8, 118.4, 96.3, 78.6, 63.2, 38.4, 28.7, 24.8; **HRMS** (ESI) calc'd for $C_{18}H_{23}NO_2Na$ $[M+Na]^+$ 308.1621, found 308.1625.



methyl (6*S*)-1-ethyl-6-methyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (1.S14)

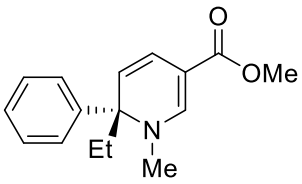
Dihydropyridine **1.S14** was synthesized from pyridinium **1.S8** and phenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield**: 16 mg (31%); The **enantiomeric excess** was determined by HPLC analysis to be 84% ee (254 nm, 25℃); t_{minor} = 9.1 min, t_{major} = 8.2 min [(Chiralpak ID) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.28 (Hex:EtOAc 4:1);); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: -0.675 (*c* 0.027 $CHCl_3$) **FTIR:** 2977, 2945, 1678, 1636, 1566; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.13 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 3.87 (s, 3H), 2.83 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (151

MHz, $CDCl_3$) δ 167.2, 146.4, 145.4, 128.4, 127.6, 126.8, 120.3, 117.8, 94.9, 63.8, 50.8, 44.4, 26.1, 16.3. **HRMS:** (ESI) *m/z* calc'd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1489, found 258.1503.



methyl (6*S*)-1-benzyl-6-methyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (1.S15)

Dihydropyridine **1.S15** was synthesized from pyridinium **1.S9** and phenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 36 mg (56%); The **enantiomeric excess** was determined by HPLC analysis to be 66% ee (254 nm, 25℃); t_{minor} = 8.8 min, t_{major} = 8.1 min [(Chiralpak ID) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **R**f: 0.30 (Hex:EtOAc 4:1)**; FTIR:** 3059, 2979, 2946, 1679, 1637, 1566; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.9 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 3H), 7.33 (t, *J* = 7.6 Hz, 3H), 7.30 – 7.26 (m, 1H), 7.13 (d, *J* = 7.6 Hz, 2H), 6.41 (d, *J* = 10.0 Hz, 1H), 4.91 (d, *J* = 10.0 Hz, 1H), 4.12 (s, 2H), 3.71 (s, 3H), 1.73 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.1, 146.3, 146.0, 137.6, 128.8, 128.5, 127.8, 127.7, 127.5, 127.0, 121.0, 118.1, 96.0, 63.9, 53.7, 50.9, 26.3; **HRMS:** (ESI) *m/z* **c**alc'd for $C_{21}H_{22}NO_2$ $[M+H]^+$ 320.1645, found 320.1647.

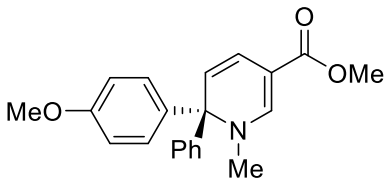


methyl (6*S*)-6-ethyl-1-methyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (1.S16)

Dihydropyridine **1.S16** was synthesized from pyridinium **1.S10** and phenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 34 mg **(**67%); The **enantiomeric excess** was determined by HPLC analysis to be 97% ee (254 nm, 25℃); t_{minor} = 8.4 min, t_{major} = 8.8 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.26 (Hex:EtOAc 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** -0.3225 (c 0.053 $CHCl_3$); **FTIR:** 3054, 2968, 2943, 1677, 1635, 1568; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.1 Hz, 2H), 7.44 (s, 1H),

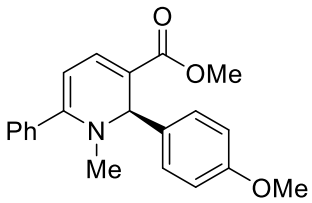
7.39 (t, *J* = 7.7 Hz, 2H), 7.29 (dd, *J* = 8.5, 6.1 Hz, 1H), 6.43 (d, *J* = 10.0 Hz, 1H), 4.61 (d, *J* = 10.1 Hz, 1H), 3.73 (s, 3H), 2.70 (s, 3H), 2.33 (dq, *J* = 14.4, 7.2 Hz, 1H), 1.74 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.16 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.2, 148.9, 146.0, 128.5, 127.6, 126.7, 119.7, 118.3, 94.2, 67.2, 50.7, 38.0, 29.1, 8.4; **HRMS:** (ESI) *m/z* **c**alc'd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1489, found 258.1492.

Compounds **1.34a** and **1.34b** were synthesized by reacting pyridinium salt **1.33** with 4-methoxyphenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts.



methyl (6*S*)-6-phenyl-6-(4-methoxyphenyl)-1-methyl-1,6-dihydro-pyridine-3-carboxylate (1.34a)

Yield 16.8 mg (25 %); The **enantiomeric excess** was determined by HPLC analysis to be 72% ee (254 nm, 25℃); t_{minor} = 14.2 min, t_{major} = 11.9 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.23 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -12.667 (c 0.060 $CHCl_3$); **FTIR** 2946.96, 2835.69, 1679.37, 1607.34; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.34 – 7.27 (m, 5H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.40 (d, *J* = 9.8 Hz, 1H), 5.08 (d, *J* = 9.8 Hz, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 2.71 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.2, 158.8, 147.0, 143.1, 135.1, 130.0, 128.5, 127.9, 127.3, 119.8, 118.0, 113.6, 95.5, 70.6, 55.5, 50.9, 40.7; **HRMS** (ESI) calc'd for $C_{21}H_{22}NO_3$ $[M+H]^+$ 336.1594, found 336.1599.

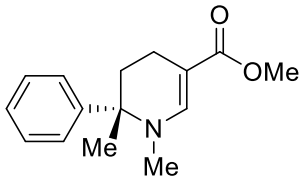


methyl (6*S*)-6-phenyl-1-(4-methoxyphenyl)-1-methyl-1,2-dihydro-pyridine-3-carboxylate (1.34b)

Yield 27.5 mg **(**41 %); The **enantiomeric excess** was determined by HPLC analysis to be 84% ee (254 nm, 25℃); t_{minor} = 10.6 min, t_{major} = 8.8 min [(Chiralpak IG)

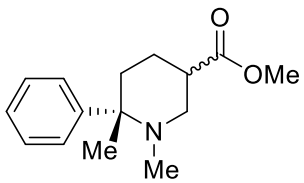
hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.41 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ 16.000 (c 0.060 $CHCl_3$); **FTIR** 2946.88, 1732.67, 1684.96, 1607.07,; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.37 – 7.32 (m, *J* = 3.7 Hz, 3H), 7.30 – 7.24 (m, 3H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.46 (s, 1H), 5.01 (d, *J* = 6.4 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 2.93 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.2, 159.3, 153.2, 136.8, 135.1, 134.5, 129.2, 128.5, 128.2, 127.9, 113.8, 109.9, 97.8, 62.5, 55.3, 51.4, 40.8; **HRMS** (ESI) calc'd for $C_{21}H_{22}NO_3$ $[M+H]^+$ 336.1594, found 336.1616.

1.9.5. Functionalization of DHP 1.32a



methyl (6S)-1,6-dimethyl-6-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (1.35)

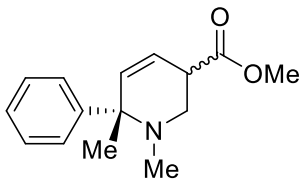
To a septa-capped vial charged with **1.32a** (24.5 mg, 0.100 mmol, 1.0 equiv) and 10% Pd/C (10.6 mg, 0.01 mmol, 0.1 equiv) was added MeOH (1 mL). A balloon filled with hydrogen was inserted through the septum via a needle. The reaction was stirred for 3 hours at 23 °C and filtered through celite. The celite was rinsed with a further 5 mL of MeOH and the filtrate concentrated to afford **1.35** as a colorless oil. **Yield** 24.4 mg (99%); **TLC** R_f 0.4 (CH_2Cl_2); **FTIR** 2943.78, 2849.73, 1676.47, 1606.26; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -2.400 (c 0.075 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.27 – 7.20 (m, *J* = 21.0, 7.9 Hz, 3H), 3.67 (s, 3H), 2.81 (s, 3H), 2.30 – 2.23 (m, 1H), 2.00 – 1.92 (m, 2H), 1.85 – 1.76 (m, 1H), 1.61 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 169.1, 148.0, 144.3, 128.7, 127.1, 125.6, 94.7, 59.9, 50.8, 38.6, 38.2, 23.8, 18.3; **HRMS** (ESI) *m/z* calc'd for $C_{15}H_{20}NO_2$ $[M+H]^+$ 246.1489, found 246.1494.



methyl (6S)-1,6-dimethyl-6-phenylpiperidine-3-carboxylate (1.36)

To a Teflon lined septa-capped vial charged with **1.35** (24.4 mg, 0.100 mmol, 1.0 equiv) was added 0.5 mL of glacial acetic acid. A solution of

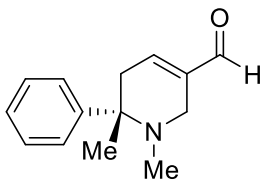
$NaBH_3CN$ (7.54 mg, 0.12 mmol, 1.2 equiv) in MeOH (1.0 mL) was then added to the stirring solution of **1.35**. The mixture was stirred for three hours, diluted with diethyl ether and acidified with 3 mL of 1M HCl. The ether layer was removed and washed 3 times with 2 mL of 1M HCl. The combined aqueous layer was neutralized with saturated $NaHCO_3$, extracted with EtOAc (3 x 5 mL). The combined organic layers were concentrated to afford a colorless oil residue. The residue was purified by flash chromatography to afford **1.36** as an inseparable 1.3:1 mixture of C3 diastereomers. Isomers were characterized as a pair of diastereomers, NMR shifts are reported using HSQC to determine which peaks belong to the major and minor products. Indeterminable peaks are reported as the mixture. Yield 16.1 mg (65%) **TLC** R_f 0.55 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ 9.778 (c 0.030 $CHCl_3$); **FTIR:** 2947.78, 2844.76, 2798.44, 1732.10, 1600.06; **^{1}H NMR** (600 MHz, $CDCl_3$) (for major diastereomer) δ 7.59 – 7.53 (m, 2H), 3.01 – 2.97 (m, *J* = 11.4 Hz, 1H), 1.96 (s, 3H), 1.37 (s, 3H); (for minor diastereomer) 7.51 (d, *J* = 7.2 Hz, 2H), 3.12 – 3.08 (m, *J* = 12.6 Hz, 1H), 2.15 (s, 3H), 1.31 (s, 3H); (for the mixture of diastereomers) 7.35 – 7.28 (m, 2H), 7.21 (dd, *J* = 15.6, 7.0 Hz, 1H), 3.70 (s, 3H) 2.83 – 2.62 (m, 2H), 2.03 – 1.88 (m, 2H), 1.79 – 1.49 (m, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ (for major diastereomer) 126.21, 51.51, 39.28, 11.21; (for minor diastereomer) 126.33, 51.43, 38.53, 22.75; (for the mixture of diastereomers) 175.15, 174.99, 149.48, 149.02, 128.22, 126.44, 59.39, 59.24, 51.57, 42.67, 24.17, 41.99; **HRMS** (ESI) *m/z* calc'd for $C_{15}H_{22}NO_2$ $[M+H]^+$: 248.1645, found 248.1651.



methyl (6S)-1,6-dimethyl-6-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (1.37)

To a 4 mL Schlenk tube charged with stir bar and solution of **1.32a** (46.0 mg, 0.20 mmol, 1.00 equiv) in AcOH (500 µL), $NaBH_3CN$ (15 mg, 0.24 mmol, 1.2 equiv) in MeOH (1 mL) was added under N_2. The reaction was stirred for four hours, diluted to 4 mL with

EtOAc, quenched with 10% HCl (250 µL), and neutralized with $NaHCO_3$. The organics were filtered through basic alumina and then celite, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was purified via automated flash chromatography to yield a 1:1 mixture of diastereomers. **Yield:** 42 mg (85%) **^{1}H NMR** (600 MHz, $CDCl_3$) δ (for 1:1 mixture of diastereomers) 7.50 – 7.42 (m, 5H), 7.32 (ddd, *J* = 10.8, 9.5, 5.4 Hz, 5H), 5.86 (dd, *J* = 9.9, 4.1 Hz, 1H), 5.82 (dd, *J* = 9.9, 1.8 Hz, 1H), 5.65 (dd, *J* = 9.9, 1.7 Hz, 1H), 5.59 (dd, *J* = 10.0, 2.6 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.54 – 3.49 (m, 1H), 3.25 (d, *J* = 4.1 Hz, 1H), 3.01 – 2.85 (m, 4H), 2.09 (s, 6H), 1.47 (s, 3H), 1.45 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) (for 1:1 mixture of diastereomers) δ 173.3, 138.0, 137.4, 128.3, 128.0, 127.9, 127.7, 127.2, 126.9, 126.4, 120.1, 119.9, 60.4, 57.4, 52.2, 51.8, 49.9, 48.7, 48.7, 42.1, 41.3, 38.3, 38.3, 16.3; **HRMS** (ESI) *m/z* calc'd for $C_{15}H_{20}NO_2$ $[M+H]^+$ 246.1489, found 246.1500.



(6S)-1,6-dimethyl-6-phenyl-1,2,5,6-tetrahydropyridine-3-carbaldehyde (1.38)

To a stirred solution of $LiAlH_4$ (37.9 mg, 1.00 mmol, 10.0 equiv) in dry Et_2O (1.0 mL), in a 1-dram vial fitted with a Teflon lined septa cap, was added a solution of **1.32a** in dry Et_2O at 23 °C. After 30 minutes of vigorous stirring, the reaction was diluted with 2 mL of Et_2O and cooled to 0 °C. To this solution was sequentially added H_2O (40 µl), 15% NaOH (aq.) (40 µl), and further H_2O (120 µl). The reaction was warmed to 23 °C, stirred for 15 minutes, dried over $MgSO_4$, filtered, and concentrated. The pale-yellow oil was purified by flash column chromatography to afford **1.38** as a clear oil. **Yield** 6.2 mg (28%); **TLC** R_f 0.19 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ 17.333 (*c* 0.03, $CHCl_3$); **FTIR** 2975.22, 2929.10, 2850.7, 2787.1, 2116.61, 1678.05; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.31 – 7.22 (m, 2H), 6.95 (s, 1H), 3.47 (d, *J* = 17.9 Hz, 1H), 3.28 (d, *J* = 17.8 Hz, 1H), 2.88 (dd, *J* =

19.6, 2.3 Hz, 1H), 2.44 (d, *J* = 19.6 Hz, 1H), 2.06 (s, 3H), 1.34 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 192.7, 148.2, 146.0, 138.9, 128.5, 127.1, 126.5, 58.3, 47.9, 38.4, 18.0, 1.2; **HRMS** (ESI) *m/z* calc'd for $C_{14}H_{18}NO$ $[M+H]^+$ 215.1383, found 216.1379.

1.10. References

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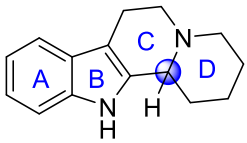
Chapter 2: Formal synthesis of deplancheine *via* dearomatization of nicotinate salts

2.1. Indoloquinolizine alkaloids

2.1.1. Biological activities of indoloquinolizine alkaloids.

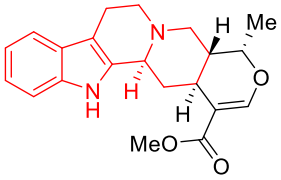
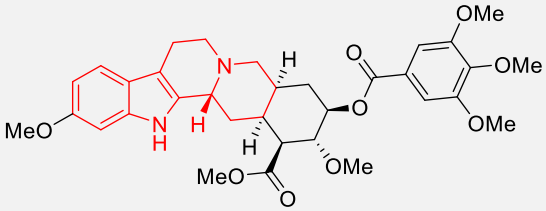
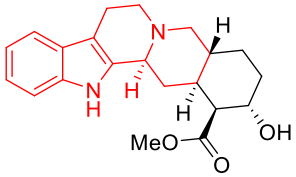
Figure 2.1. The indoloquinolizine scaffold with ring designation.

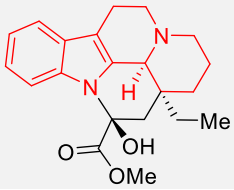
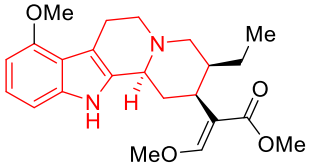
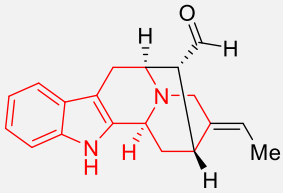
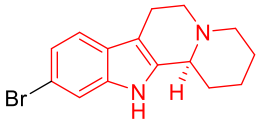


2.1

The indoloquinolizine motif, an indole-fused quinoline scaffold (Figure 2.1), is present in alkaloids isolated from both terrestrial and marine sources.[1] This family of alkaloids has exhibited diverse biological activities, as demonstrated by **2.2-2.8** in Table 2.1, including the FDA approved antihypertensive reserpine (**2.8**).[2-8] Because of the pharmacological potential associated with this class of alkaloids, constructing the tetracyclic scaffold and dictating stereochemistry at the C-D ring junction has been of interest to the synthetic community.

Table 2.1. Examples of indoloquinolizine alkaloids with reported bioactivities.

Alkaloid	Structure	Natural Occurrence	Biological Activity
Ajmalicine (**2.2**)		*Rauvolfia serpentina, Catharanthus roseus, Mitragyna speciosa*	Antihypertensive
Reserpine (**2.3**)		*Rauvolfia serpentina*	Antihypertensive
Corynanthine (**2.4**)		*Rauvolfia* and *Corynanthe*	α_1 and α_2 Adrenergic Receptor Antagonist

Alkaloid	Structure	Natural Occurrence	Biological Activity
Vincamine (**2.5**)		*Vinca minor*	Spasmolytic
Mitragynine (**2.6**)		*Mitragyna speciosa*	μ-opioid Receptor Agonist
Vellosimine (**2.7**)		*Vellosimia*	Antipyretic
Arborescidine A (**2.8**)		*Pseudodistoma arborescens*	Antiproliferative

2.1.2. Common reactions for constructing the indoloquinolizine core.

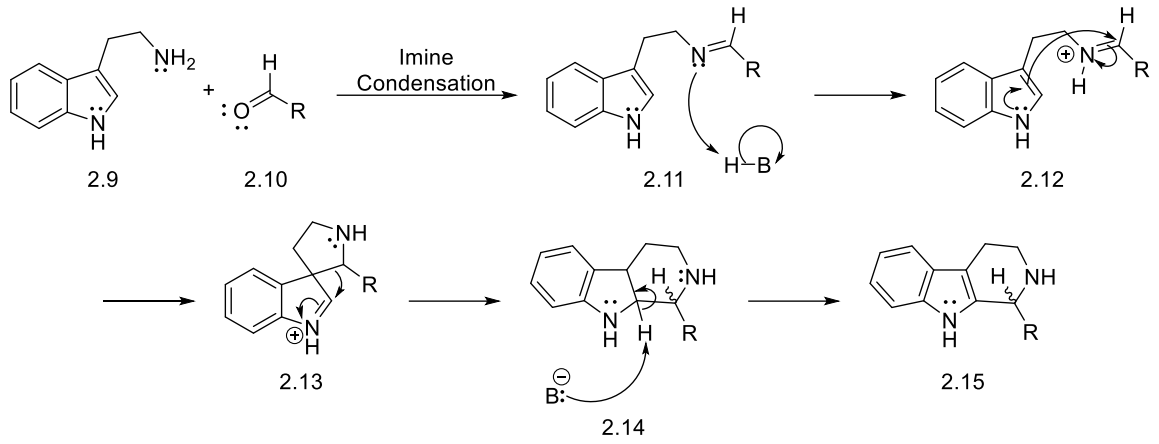
Despite the functional diversity present in the indoloquinolizine family, two reactions, the Pictet-Spengler reaction and the Bischler-Napieralski reaction, have predominantly been employed to form the C-ring of the indoloquinolizine motif. Below, we discuss these two reactions in more detail.

1) The Pictet-Spengler reaction

The Pictet-Spengler reaction, although published originally in 1911, still demonstrates efficacy in modern synthesis of complex indoloquinolizine alkaloids.[9] As overviewed in Scheme 2.1, condensation of a tryptamine (**2.9**) and an aldehyde (**2.10**) provides imine **2.11**, and protonation affords iminium **2.12**, which is electrophilic enough to promote dearomatization of the indole system to form spirocycle **2.13**. The subsequent Plancher rearrangement of spirocycle **2.13** affords hexahydrocarboline intermediate **2.14**, and the conjugate base from iminium formation

removes the original indole C-2 proton, which rearomatizes the indole system, to provide a tetrahydro-β-carboline (**2.15**).

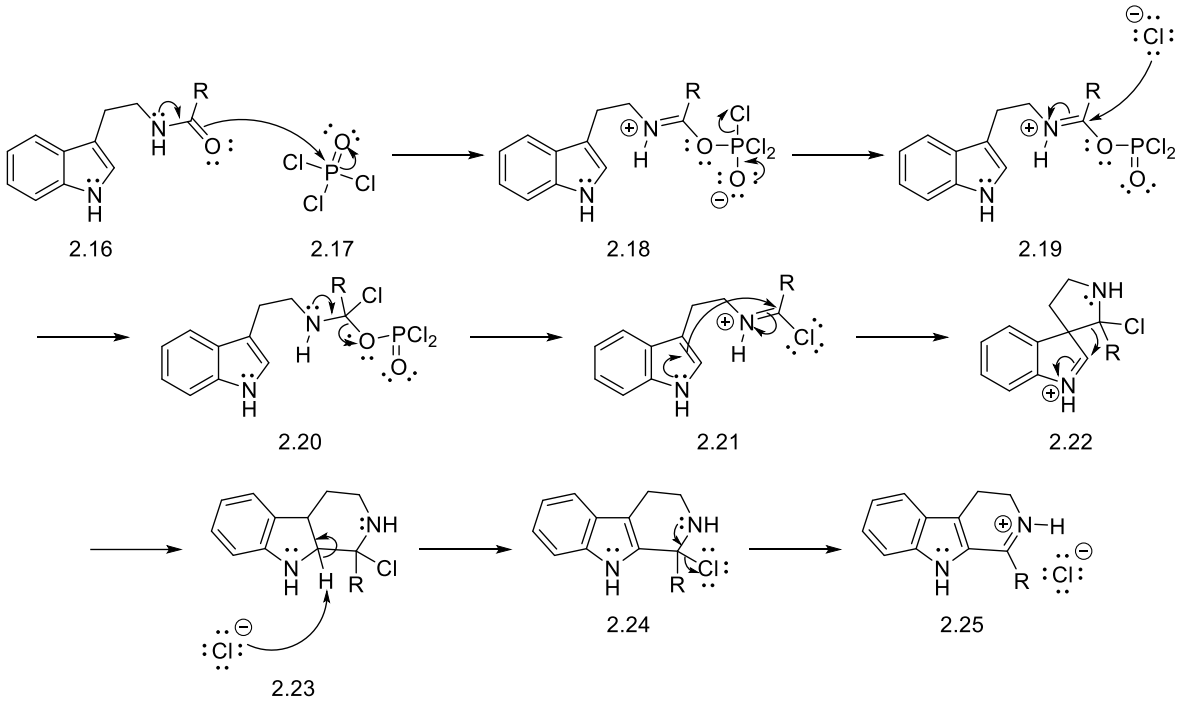
Scheme 2.1. The general mechanism of the Pictet-Spengler reaction.



2) The Bischler-Napieralski reaction

The Bischler-Napieralski reaction, predating the works of Pictet and Spengler by eighteen years, utilizes β-indolethylamides (**2.16**) and $POCl_3$ (**2.17**) to generate iminium **2.21** (Scheme 2.2), which reacts in a similar manner to the Pictet-Spengler iminium intermediate **2.12**.[10] The electrophilicity of iminium **2.21** promotes dearomatization/spirocyclization to form **2.22**, and C-2 functionalization is achieved via Plancher rearrangement to afford hexahydrocarboline **2.23**. Removal of the original indole C-2 proton restores aromaticity, and rearomatized intermediate **2.24** undergoes elimination of the chloride substituent to provide a dihydro-β-carboline iminium (**2.25**).

Scheme 2.2. The general mechanism of the Bischler-Napieralski reaction.



2.1.3. Common strategies for constructing the indoloquinolizine core

Strategies to synthesize indoloquinolizine alkaloids can largely be categorized by the order in which the ring systems are generated, the two most common being formation of the piperidine ring last (ABC+D) and coupling of the indole moiety to a tethered piperidine derivative (ABD+C).

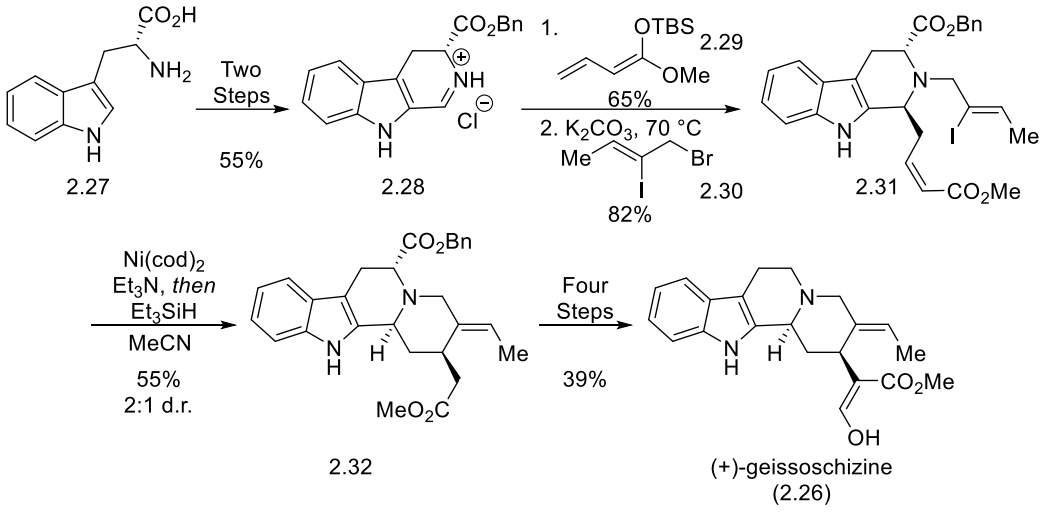
2.1.3.1. Recent ABC+D strategies for constructing the indoloquinolizine core.

A. Jarret's synthesis of (+)-geissoschizine

In 2018, Jarret and coworkers devised a synthesis of (+)-geissochizine (**2.26**, Scheme 2.3) that generated iminium salt **2.28** from tryptamine **2.27** via a Pictet-Spengler reaction followed by esterification.[11] The use of formaldehyde in the Pictet-Spengler reaction precluded the unselective formation of the C-D ring juncture stereocenter, but the resulting iminium facilitated the use of a Mannich reaction with enol ether **2.29**. This allowed for greater control in dictating the

stereochemistry of the C-D ring juncture, as the addition would predominantly occur from the less hindered face, and N-alkylation with **2.30** furnished intermediate **2.31**. The D-ring of the indoloquinolizine scaffold was formed by subjecting **2.31** to reductive cyclization mediated by $Ni(cod)_2$ to afford indoloquinolizine **2.32**, albeit with only a 2:1 ratio of diastereomers. From indoloquinolizine intermediate **2.32**, the authors accessed (+)-geissochizine in four additional steps that removed the benzyl ester and formylated the methyl ester substituent.

Scheme 2.3. Overview of the ABC+D strategy used in Jarret's 2018 synthesis of (+)-geissoschizine.

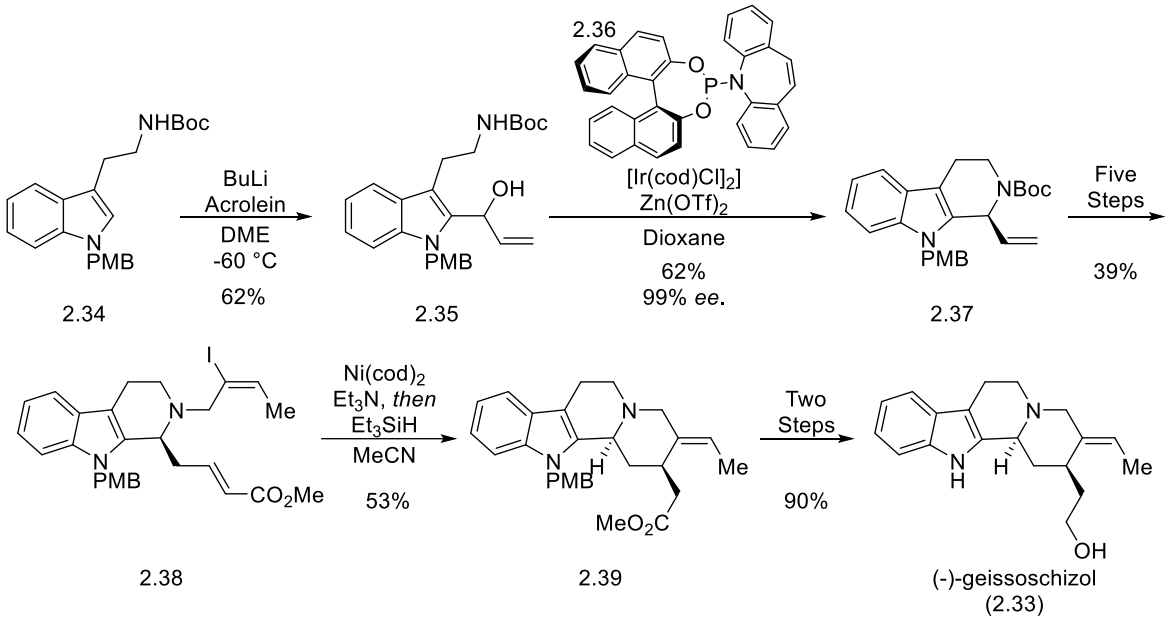


B. Zheng's synthesis of (-)-geissoschizol

In 2017, Zheng and coworkers developed a synthesis of (-)-geissoschizol (**2.33**, Scheme 2.4) that strategically employed iridium catalyzed allylic amidation as an alternative to using the Pictet-Spengler reaction.[12] Allylic alcohol **2.35**, derived from protected tryptamine **2.34** and acrolein, was subjected to iridium catalyzed ring closure with ligand (S)-Carreira (**2.36**) and promoter $Zn(OTf)_2$. This catalytic approach afforded tetrahydrocarboline **2.37** with an enantiomeric excess of 99%. From tetrahydrocarboline **2.37**, a sequence of five reactions provided intermediate **2.38** which was suitably functionalized for reductive cyclization, mediated by

$Ni(cod)_2$, to forge the final ring and deliver indoloquinolizine **2.39**. From indoloquinolizine **2.39**, geissoschizol was accessed in two additional steps by deprotecting the indole nitrogen and reduced the ester to an alcohol.

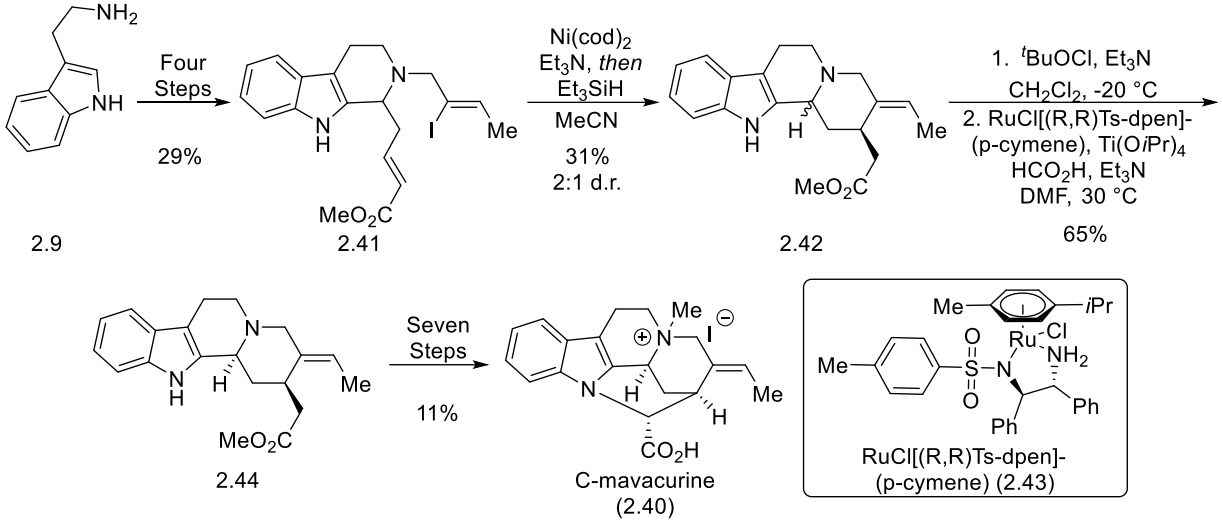
Scheme 2.4. Overview of the ABC+D strategy used in Zheng's 2017 synthesis of (-)-geissoschizol.



C. Sato's synthesis of C-mavacurine

A 2019 synthesis of C-mavacurine (**2.40**, Scheme 2.5), by Sato and coworkers, employed the same strategy used in Jarret's synthesis of geissochizine (**2.26**) to form their indoloquinolizine scaffold.[13] Intermediate **2.41**, created in four steps from tryptamine (**2.9**), was subjected to $Ni(cod)_2$ mediated reductive cyclization to forge indoloquinolizine **2.42** with a 2:1 ratio of diastereomers, comparable to Jarret's synthesis. However, unlike in the synthesis of geissochizine, an iminium intermediate was generated using the undesired *trans*-diastereomer of **2.42**, and transfer hydrogenation with a Noyori catalyst (**2.43**), in the presence of formic acid and triethylamine, effected efficient epimerization to the desire *cis*-diastereomer (**2.44**). From **2.44,** C-mavacurine was accessed in seven additional steps.

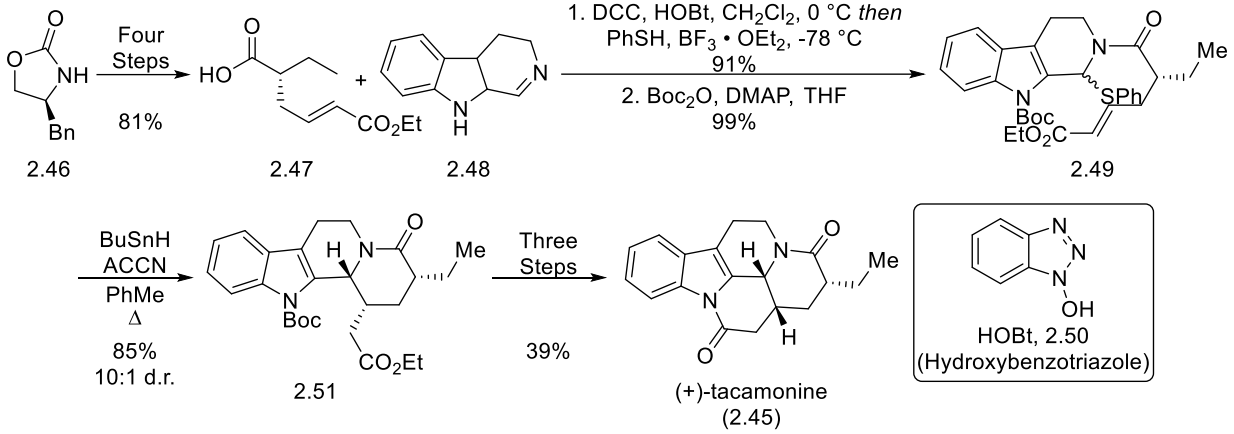
Scheme 2.5. Overview of the ABC+D strategy used in Sato's 2019 synthesis of C-mavacurine.



D. Smith's synthesis of (+)-tacamonine

The 2019 synthesis of (+)-tacamonine (**2.45**, Scheme 2.6), by Smith and coworkers, demonstrated an alternative radical ring closure method to form the indoloquinolizine D-ring.[14] Cyclization precursor α-phenylsulfanyl amide **2.49** was obtained by amide coupling of Pictet-Spengler product **2.48** and acid **2.47**, generated in four steps from **2.46**, followed by treatment with PhSH in the presence boron trifluoride etherate and subsequent Boc-protection of the indole. Phenylsulfanyl amide **2.49** underwent radical cyclization upon exposure to Bn_3SnH and ACCN in refluxing toluene to afford indoloquinolizine **2.51**. From **2.51**, (+)-tacamonine was obtained in three additional steps that effected removal of the Boc protecting group, ester reduction, and oxidative cyclization.

Scheme 2.6. Overview of the ABC+D strategy used in Smith's 2019 synthesis of (+)-tacamonine.

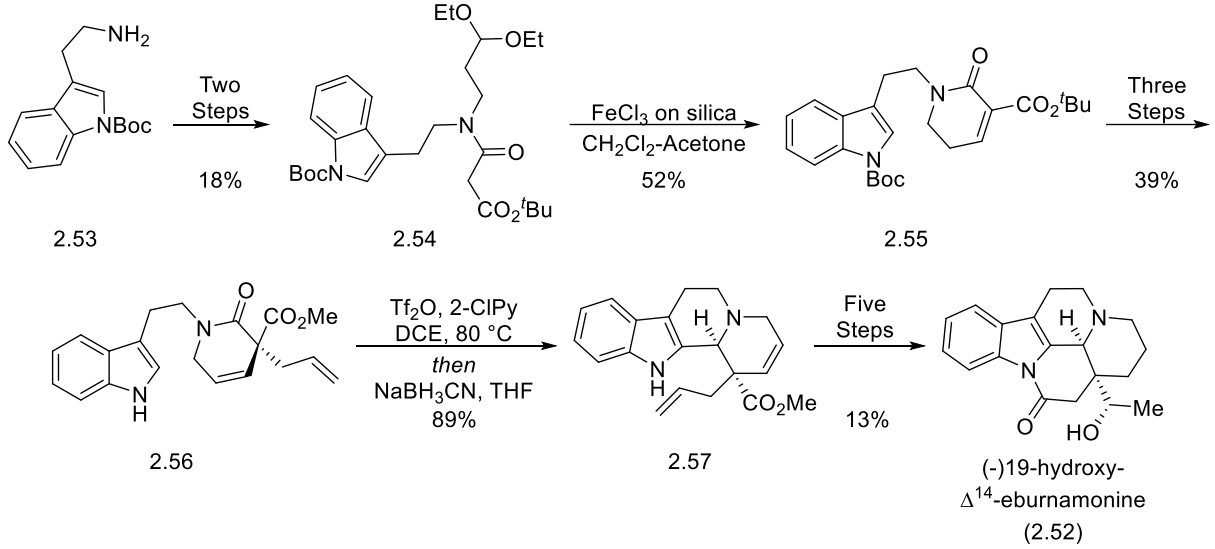


2.1.3.2. Recent applications of ABD+C synthetic strategies

A. Trost's synthesis of (-)19-hydroxy-Δ^{14}-eburnamonine

In 2017, Trost devised a synthesis of (-)19-hydroxy-Δ^{14}-eburnamonine (**2.52**, Scheme 2.7) that strategically used a modification of the Bischler–Napieralski reaction to complete the indoloquinolizine scaffold.[15] Amide **2.54**, created from Boc-protected tryptamine **2.53** in two steps, was exposed to $FeCl_3$, adsorbed onto silica, to provide α,β-unsaturated lactam **2.55** via ketal cleavage and subsequent cyclization. From α,β-unsaturated lactam **2.55**, lactam **2.56** was obtained after a sequence of allylic alkylation, deprotection, and transesterification. Lactam **2.56** was subjected to Movassaghi's modified Bischler–Napieralski conditions to afford indoloquinolizine **2.57**. From indoloquinolizine **2.57**, (-)19-hydroxy-Δ^{14}-eburnamonine was accessed in an additional five steps.

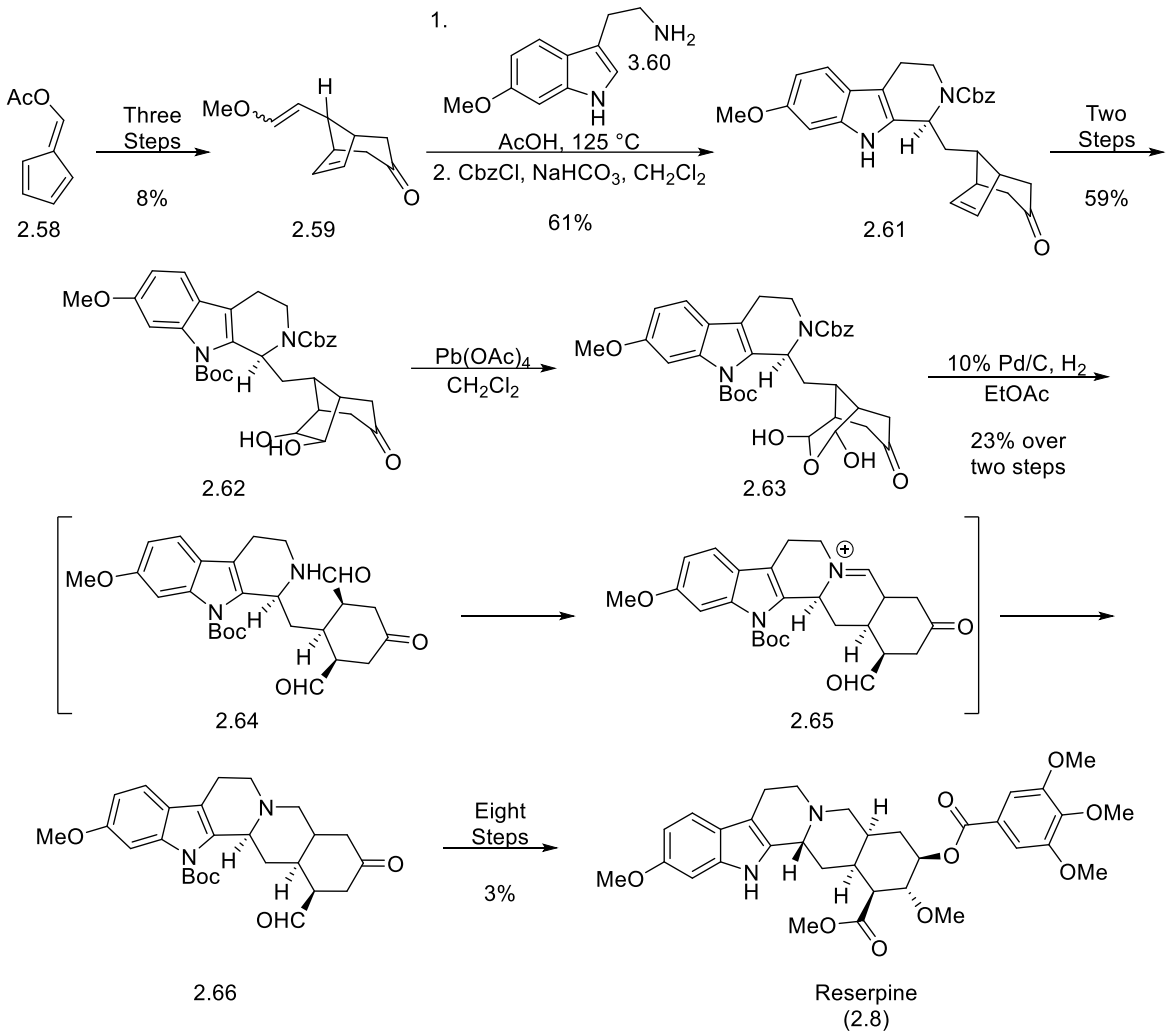
Scheme 2.7. Overview of the ABD+C strategy used in Trost's 2019 synthesis of (-)19-hydroxy-Δ^{14}-eburnamonine.



B. Park's synthesis of reserpine

In Park's 2018 synthesis of reserpine (**2.8**, Scheme 2.8), another alternative method of D-ring closure was presented.[16] Enol ether **2.59**, obtained in three steps from **2.58**, acted as a masked aldehyde in a Pictet-Spengler reaction with tryptamine **2.60,** and subsequent Cbz-protection afforded tetrahydrocarboline **2.61**. Diol **2.62** was created from **2.61** in two steps that effected Boc-protection and dihydroxylation. Upon exposure to $Pb(OAc)_4$, diol **2.62** was transformed into bis-hemiacetal **2.63**, and palladium mediated hydrogenation of hemiacetal **2.63** resulted in Cbz-deprotection and aldehyde formation, yielding dialdehyde **2.64**. Dialdehyde **2.64** underwent an intramolecular condensation to afford iminium **2.65**, and in-situ hydrogenation of the iminium provided indoloquinolizine **2.66**. From **2.66**, reserpine was obtained in eight additional steps.

Scheme 2.8. Overview of the ABD+C strategy used in Park's 2018 synthesis of reserpine.

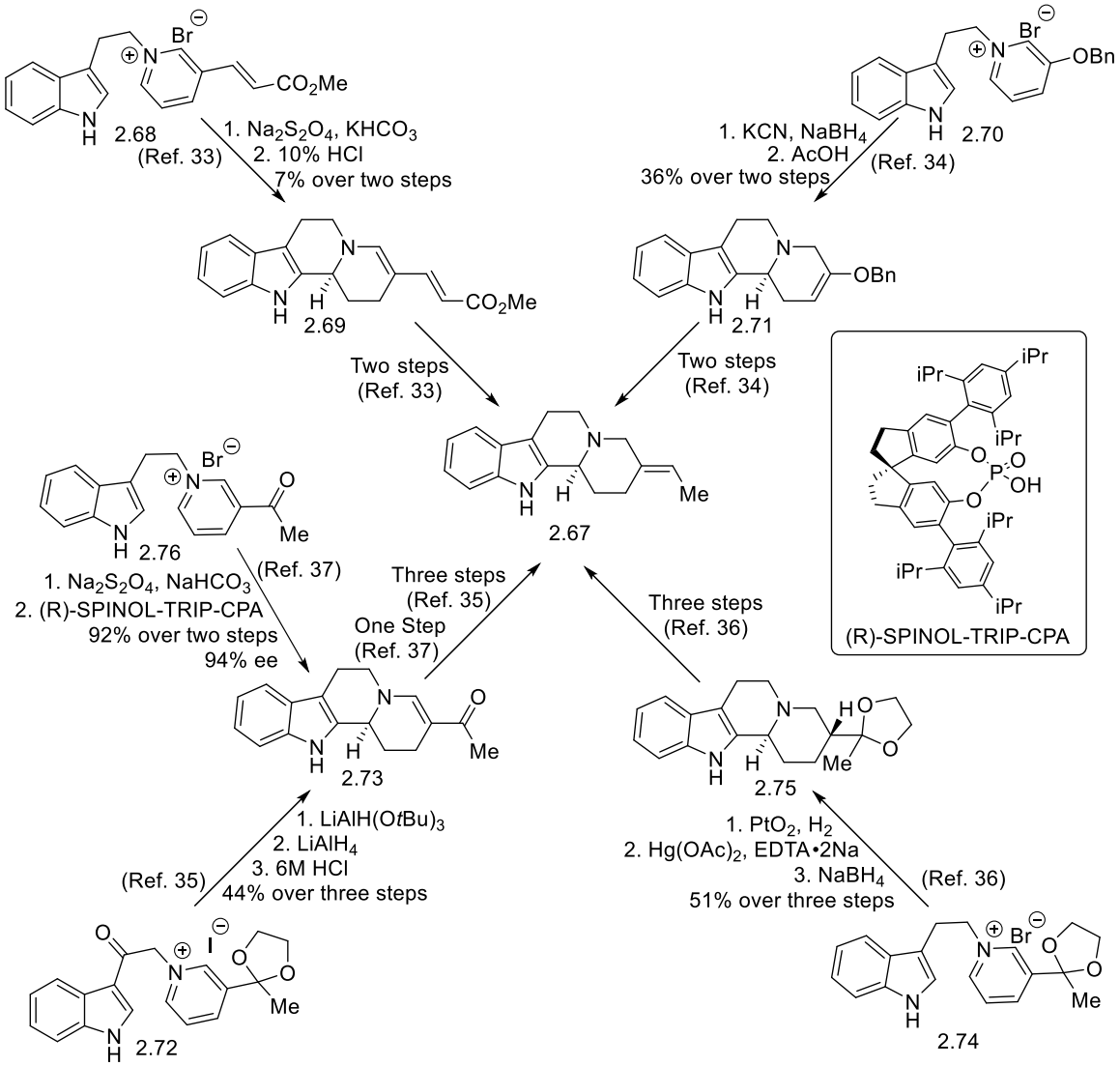


2.2. Formal synthesis of deplancheine *via* dearomatization of nicotinate salts

Indole alkaloids, and by extension those with a tetracyclic indolo[2,3-a]quinolizine scaffold, have garnered the interest of chemists and biologists for decades due to their diverse pharmacological properties and the challenge presented by their structural architectures. [17-19] Despite lacking any appreciable bioactivity, deplancheine (**2.67**) has become a cornerstone for demonstrating synthetic methodologies to forge indoloquinolizine alkaloids because of the relatively incomplex structure compared to the alkaloids discussed previously discussed.[3,19-30]

Our recent work on rhodium-catalyzed dearomatization of pyridinium salts, which facilitated a synthesis of nuphar alkaloid, inspired an investigation into the further application of our pyridinium chemistry to access indoloquinolizine alkaloids.[31-32] Herein, we report a formal synthesis of the natural product deplancheine that utilizes the rhodium-catalyzed dearomatization as the key step. Pyridinium dearomatization has been employed previously in the synthesis of deplancheine, yet the scope was primarily limited to indol-3-ylethylpyridinium salts. These previous approaches are summarized in Scheme 2.9.[33-37]

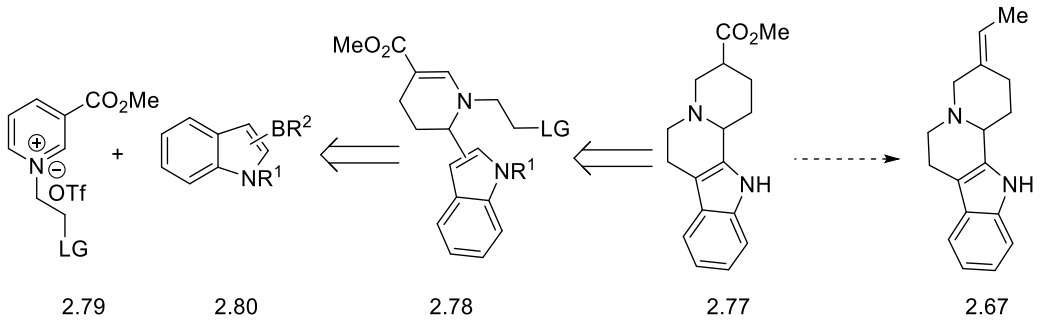
Scheme 2.9. Previous applications of pyridinium salts in the synthesis of deplancheine.



2.2.1. Retrosynthetic analysis

Our retrosynthetic analysis to access deplancheine involved an ABD+C strategy, via intermediate **2.77 (**Scheme 2.10). Conversion of **2.77** to deplancheine has been previously established by Ihara.[14] We anticipated that **2.77** could be secured by intramolecular indole C3-alkylation of tetrahydropyridine **2.78** followed by reduction of the corresponding vinylogous carbamate. Tetrahydropyridine **2.78** would be constructed from an N-alkyl methyl nicotinate salt (**2.79**) and an indole boronic acid derivative (**2.80**) using our rhodium catalyzed dearomatization methodology.

Scheme 2.10. Retrosynthesis of Ihara's deplancheine intermediate 2.77.



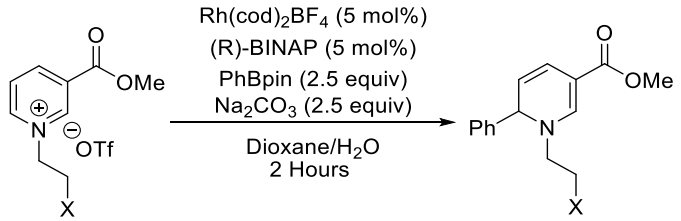
2.2.2. Synthesis of intermediate 2.77

2.2.2.1. Optimization of reaction parameters for the dearomatization of functionalized N-ethyl nicotinate salts

A key to successful execution of the strategy outlined in Scheme 2.10 was identification of an appropriate leaving group in intermediate 2.78, which would enable future construction of the C ring of deplancheine. Towards this goal, we initially screened nicotinate salts **2.81-2.83** (Table 2.2) with phenyl boronic pinacol ester (**2.86**) serving as surrogate for costlier indole boronic acid substrates. Despite our methodology being compatible with unprotected alcohols, attempts to use hydroxyethyl nicotinate salt **2.81** (Table 2.2, entries 1-3) were unfruitful as our standard conditions

with phenyl boronic pinacol ester simply afforded dealkylated methyl nicotinate. Nicotinate salt **2.82**, with a TBS protected tether, successfully underwent dearomatization to deliver the corresponding phenyl substituted dihydropyridine (Table 2.2, entries 4-6). Although the yields with the TBS protected tether were promising, this tether would require additional steps to remove the TBS protecting group and convert the corresponding primary alcohol to a leaving group in order to enable the indole alkylation. Thus, we continued our screening with nicotinate salt **2.83** where the chloride could act directly as a leaving group. Under our standard $Rh(cod)_2BF_4$/BINAP conditions, **2.83** afforded the corresponding phenyl substituted dihydropyridine in lower yields compared to **2.82** (Table 2.2, entries 7-9 vs, entries 4-6).

Table 2.2. Screening of nicotinate salts.



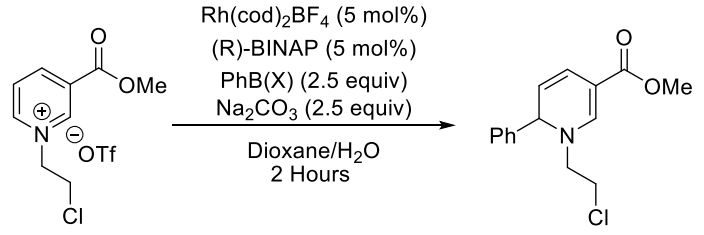
Entry	Tail Substituent	Temperature	Yield (%)[a]
1	OH	40 °C	0
2	OH	60 °C	0
3	OH	80 °C	0
4	OTBS	40 °C	40
5	OTBS	60 °C	40
6	OTBS	80 °C	45
7	Cl	40 °C	10
8	Cl	60 °C	15
9	Cl	80 °C	20

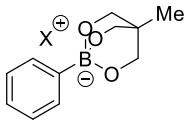
[a]Yields were based on the analysis of ^1H NMR spectra of the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard.

With a suitable nicotinate salt in hand, we investigated the impact of using different boronic acid derivatives other than pinacol esters on dearomatization yields (Table 2.3). Reactions were conducted with boronic acid derivatives **2.87-2.90** serving as nucleophiles, and $Rh(cod)_2BF_4$/(R)-

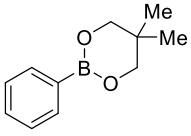
BINAP as the catalyst. We were delighted to find that boronates **2.87a-d** provided dihydropyridine **2.S3** with a significant improvement in yield compared to pinacol esters (Table 2.3, entries 1-4, 6 vs Table 2.2, entries 7-9). Using neopentyl ester **2.88** resulted in improved yields comparable to boronate **2.87** (Table 2.3, entries 7-8 vs entries 1-6), yet catechol ester **2.89** (Table 2.3, entries 9-10) only produced trace amounts of dihydropyridine **2.S3.** Trifluoroborate **2.90** was evaluated (Table 2.3, entries 11-12), and it demonstrated the best performance of the boronic acid derivatives screened, providing dihydropyridine **2.S3** in 55% yield at 80 °C.

Table 2.3. Impact of boronic acid derivatives on dearomatization yields.



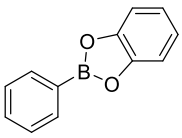


2.87a (X = K)
2.87b (X = Na)
2.87c (X = Cs)
2.87d (X = TBA)

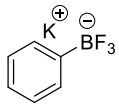


2.88

Entry	$PhB(OH)_2$ Derivative	Temperature	Yield (%)[a]
1	$KPhB(OR)_3$ (2.87a)	40 °C	35
2	$KPhB(OR)_3$ (2.87a)	60 °C	50
3	$KPhB(OR)_3$ (2.87a)	80 °C	30
4	$NaPhB(OR)_3$ (2.87b)	60 °C	50
5	$CsPhB(OR)_3$ (2.87c)	60 °C	25
6	$(TBA)PhB(OR)_3$ (2.87d)	60 °C	30
7	PhB(neop) (2.88)	60 °C	55
8	PhB(neop) (2.88)	80 °C	30
9	PhB(cat) (2.89)	60 °C	<5
10	PhB(cat) (2.89)	80 °C	<5
11	$KPhBF_3$ (2.90)	60 °C	15
12	**$KPhBF_3$** (2.90)	**80** °C	**55**



2.89



2.90

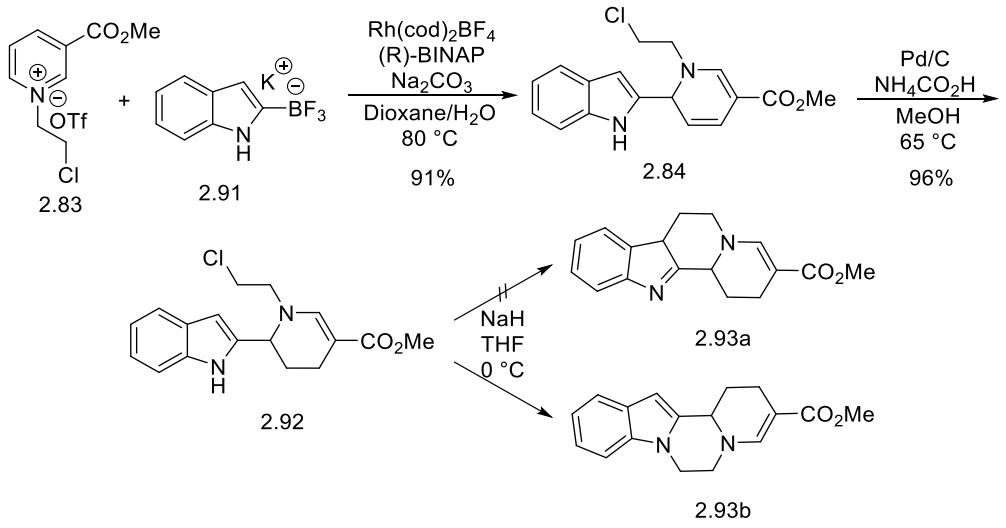
[a]Yield was based on the analysis of ^1H NMR spectra of the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard.

2.2.2.2. First generation synthesis of intermediate 2.77 using 2-indole boron nucleophiles.

Using the optimal reaction conditions, indole trifluoroborate salt **2.91** was reacted with nicotinate salt **2.84** to forge dihydropyridine **2.84** in 91% yield (Scheme 2.11). Reduction of

dihydropyridine **2.84** via catalytic transfer hydrogenation afforded tetrahydropyridine **2.92** in 96% yield with chromatographic purity. We attempted to complete the indolo[2,3-*a*]quinolizine scaffold by treating tetrahydropyridine **2.92** with sodium hydride, but unfortunately the cyclization occurred at the N1 position of the indole yielding **2.93b** rather than at desired C3 position (**2.93a**). This lamentable chemoselectivity compelled a revision of our synthetic strategy; we decided to utilize indole-3-boronic acid derivatives to preclude N-alkylation of the indole.

Scheme 2.11. Unsuccessful cyclization with 2-indole substitution.

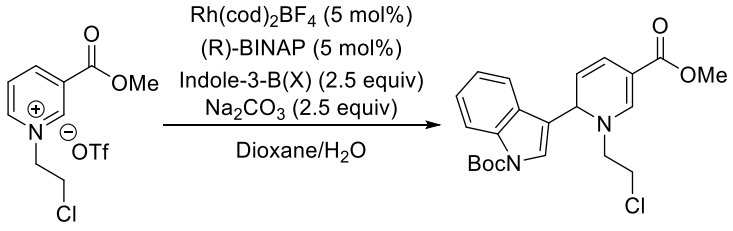


2.2.2.3. Second generation synthesis of intermediate 2.77 using 3-indole boron nucleophiles.

Reaction of the 1-Boc-3-indole trifluoroborate with pyridinium **2.83** provided the DHP **2.85** in 45% yield (Table 2.4, entry 1). Interestingly, 1-Boc-3-indole boron pinacol ester gave comparable yield to that of the trifluoroborate salt (Table 2.4, entry 2). Upon screening the impact of reactions times on reaction yield, we observed a steady drop in yields after the first hour at 80 °C and 60 °C (Table 2.4, entries 2-4 and 5-7). When we decreased the reaction temperature to 45 °C, not only was there no indication of yield degradation after the first hour, but also a significant

improvement in yields (Table 2.4, entries 8-9). Decreasing the reaction temperature further to ambient temperature had no effect on yields (Table 2.4, entries 10-12), and there was no indication of yield degradation at prolonged reaction times (Table 2.4, entry 13). Since yields were comparable at 45 °C and ambient temperature after two hours, we decided to go with ambient temperature as the optimal reaction condition.

Table 2.4. Optimization of dearomatization conditions to produce DHP 2.85.



2.83 2.85

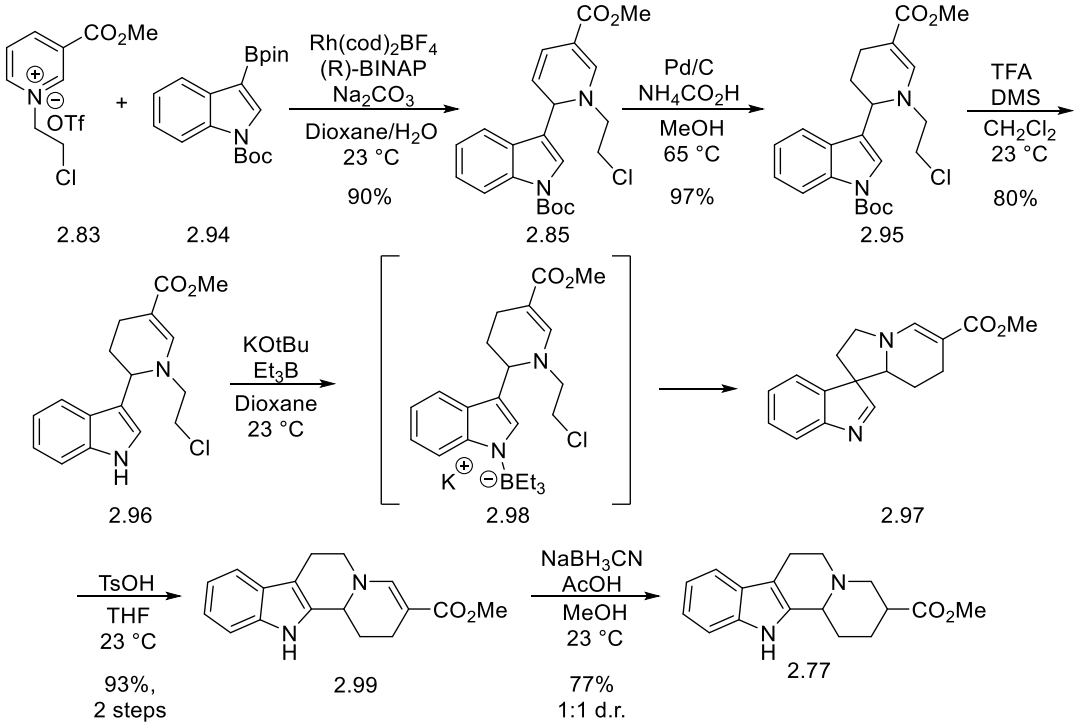
Entry	Boronic Acid Derivative	Time	Temperature	Yield (%)[a]
1	1-Boc-indole-3-BF_3 K	3 hours	80 °C	45
2	1-Boc-indole-3-Bpin	1 hour	80 °C	40
3	1-Boc-indole-3-Bpin	2 hours	80 °C	35
4	1-Boc-indole-3-Bpin	4 hours	80 °C	30
5	1-Boc-indole-3-Bpin	1 hour	60 °C	65
6	1-Boc-indole-3-Bpin	2 hours	60 °C	60
7	1-Boc-indole-3-Bpin	4 hours	60 °C	50
8	1-Boc-indole-3-Bpin	1 hour	45 °C	75
9	1-Boc-indole-3-Bpin	2 hours	45 °C	80
10	1-Boc-indole-3-Bpin	1 hour	23 °C	65
11	**1-Boc-indole-3-Bpin**	**2 hours**	**23 °C**	**80**
12	**1-Boc-indole-3-Bpin**	**4 hours**	**23 °C**	**80**
13	**1-Boc-indole-3-Bpin**	**12 hours**	**23 °C**	**80**

[a]Yields were based on the analysis of ^{1}H NMR spectra of the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard.

DHP 2.85 was advanced to target Ihara's intermediate according to Scheme 2.12. It is worth noting that the reaction yield increased to 90% when it was scaled up to 1.2 mmol from 0.2 mmol scale which was used during the reaction optimization studies. Palladium catalyzed transfer hydrogenation of dihydropyridine **2.85** provided tetrahydropyridine **2.95** in 97% yield. Tetrahydropyridine **2.95** was treated with TFA to cleave the Boc protecting group, affording indole

2.96 in 80% yield. Spirocyclization of **2.96** to indolenine **2.97** proved to be nontrivial since oligomerization and decomposition also occurred upon addition of base, but an efficient spirocyclization to indolenine **2.97** was finally achieved via N-indolyltriethylborate intermediate **2.98**.[38] Without purification, indolenine **2.97** was treated with a catalytic amount of TsOH monohydrate to furnish indoloquinolizine **2.99,** via Ciamician-Plancher rearrangement, in 93% yield over two steps.[39] Reduction of **2.99** with cyanoborohydride afforded indoloquinolizine **2.77** in 77% yield with a 1:1 ratio of diastereomers, thus converging with Ihara's synthesis.

Scheme 2.12. Synthesis of Ihara's deplancheine intermediate.

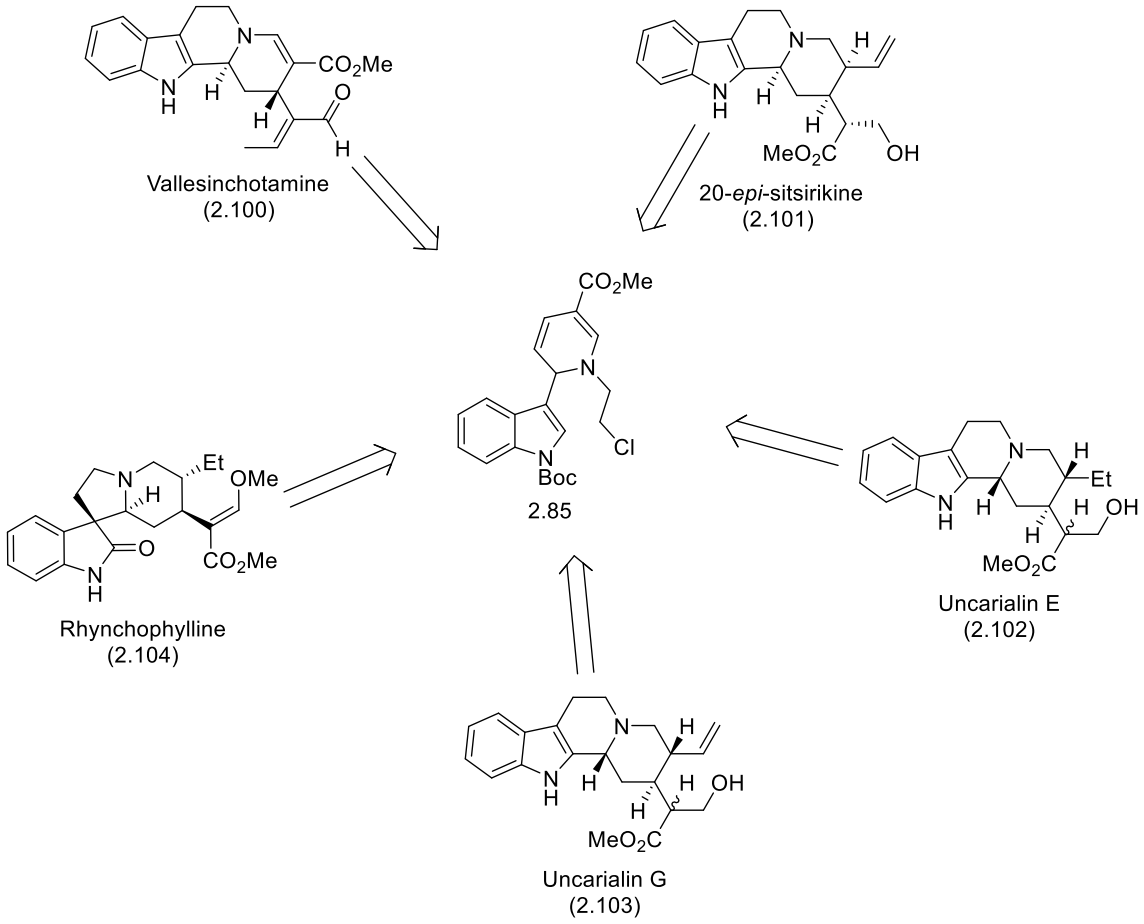


2.3. Future Directions

The optical purity of the chiral compounds described in this chapter has yet to be determined. If the standard Rh/BINAP system fails to deliver synthetic intermediates in sufficient enantiomeric excess, further optimization and ligand screening will be required. Once access to optically pure DHP **2.85** has been confirmed, the applicability of this method could be greatly

expanded by strategically functionalizing the DHP rather than simply reducing it. Figure 2.2 highlights several bioactive natural products that are potentially accessible with adequate C4 functionalization of the DHP, but the appropriate natural product reviews should be consulted for a more comprehensive summary.[40-42] Vallesinchotamine (**2.100**) has demonstrated antiproliferative effects with regard to human melanoma cells, and 20-*epi*-sitsirikine (**2.101**) has displayed significant cytotoxic effects against cancer cell lines HCT-116 (colon cancer), PC-3 (prostate cancer), and HepG2 (liver cancer).[43,44] Uncarialins E and G (**2.102** and **2.103**) were found to be potent agonists of the 5-HT_{1A} receptor, with EC_{50} values from 0.1± 0.1 μM to 2.2 ± 0.1 μM, and rhynchophylline (**2.104**) acts as both a calcium channel blocker and a non-competitive NMDA antagonist, with an IC_{50} value of 43.2 μM.[45-47]

Figure 2.2. Bioactive alkaloids that are potentially accessible through the strategic functionalization of DHP 2.85.



2.4. Conclusions

In summary, we have employed our rhodium-catalyzed dearomatization of pyridiniums to construct dihydropyridines that are suitably functionalized to access indolo[2,3-*a*]quinolizine alkaloids, as demonstrated by the synthesis of known deplancheine intermediate **2.77**. This application of our catalysis serves to introduce a new strategy for synthesizing polycyclic indole alkaloids, and future investigations into the strategic functionalization of DHP **2.85** may provide access to an even broader range of bioactive indole alkaloids.

2.5. Experimental section

2.5.1. Materials and methods

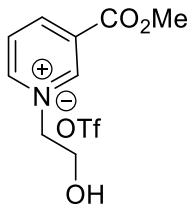
Reactions were performed in flame-dried sealed tubes or modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper under a positive pressure of nitrogen or inside nitrogen filled glovebox unless otherwise noted. Air and moisture sensitive liquids and solutions were transferred via syringe. The appropriate starting materials and reagents were dried via azeotropic removal of water with toluene or heptane. Molecular sieves were activated at 200°C under vacuum. Organic solutions were concentrated by rotary evaporation below 40 °C. Flash column chromatography was performed employing 230–400 mesh silica gel. Dry column vacuum chromatography was performed with 500-800 mesh silica gel. Thin-layer chromatography was performed using glass plates pre-coated to a depth of 0.25 mm with 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm) and visualized with UV light (254 and 360 nm), iodine adsorbed onto silica, or stained with Ceric Ammonium Molybdate in concentrated H_2SO_4.

Dichloromethane, diethyl ether, dioxane, tetrahydrofuran, and toluene were purified by passage through two packed columns of neutral alumina under an argon atmosphere.[46] DMSO was distilled from CaH_2 below 1 torr. Amines were distilled from CaH_2 at 760 torr. All other chemicals were obtained from commercial vendors and were used without further purification unless otherwise noted.

Proton and carbon-13 nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on a Bruker Avance III instrument; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual proton in the NMR solvent (d-chloroform: δ 7.26 for ^{1}H NMR, δ 77.16 for ^{13}C NMR; d4-methanol: δ 3.31 for ^{1}H NMR, δ 49.00 for ^{13}C NMR). Data are presented as follows: chemical shift, multiplicity (s =

singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), coupling constant in Hertz (Hz), integration.

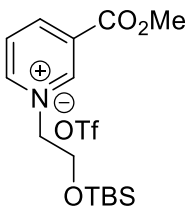
2.5.2. Synthesis of nicotinate salts 2.81-2.83



methyl 1-(2-hydroxyethyl)-1-pyridinium-3-carboxylate trifluoromethanesulfonate (2.81)

To a 25 mL Schlenk tube charged with stir bar and methyl nicotinate (5.47 mmol, 750 mg, 1.0 equiv), 2-bromoethanol (21.9 mmol, 1.55 mL, 4.0 equiv) was added, and the reaction was heated overnight at 100 °C. Once cooled to ambient temperature, the reaction solution was triturated in 100 mL of stirring Et_2O. The precipitate was filtered and azeotropically dried with heptane to afford the crude bromide salt. **Crude yield** 1.95 mmol, 512 mg, 36%

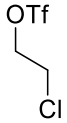
To a 50 mL round bottom flask charged with stir bar and solution of the crude bromide salt (1.19 mmol, 312 mg, 1.0 equiv) in anhydrous EtOH (21.0 mL), a solution of AgOTf (1.19 mmol, 306 mg, 1.0 equiv) in anhydrous EtOH (1.20 mL) was added dropwise at ambient temperature. Upon complete addition of the AgOTf solution, the reaction was stirred for an additional 15 minutes. The reaction solution was then filtered through a short celite plug and concentrated. The crude residue was redissolved in a minimal amount of acetone and carefully floated atop 75.0 mL of Et_2O. After 12 hours at ambient temperature, the solutions had equilibrated. The precipitate was then filtered and azeotropically dried with heptane to afford **2.81** as a white solid. **Yield** 0.698 mmol, 275 mg, 25% **^{1}H NMR** (500 MHz, CD_3CN) δ 9.39 (d, J = 1.8 Hz, 1H), 9.14 (dt, J = 6.3, 1.5 Hz, 1H), 8.93 (dt, J = 8.1, 1.5 Hz, 1H), 8.18 (dd, J = 8.1, 6.1 Hz, 1H), 4.85 (dd, J = 5.8, 4.1 Hz, 2H), 3.99 (s, 3H), 3.75 (t, J = 6.0 Hz, 1H), 3.46 (t, J = 6.0 Hz, 1H).



methyl 1-{2-[(*tert*-butyl)bis(methyl)siloxy]ethyl}-1-pyridinium-3-carboxylate trifluoromethanesulfonate (2.82)

To a 5 mL Schlenk tube charged with stir bar and methyl nicotinate (2.34 mmol, 321 mg, 1.0 equiv), a solution of (2-bromoethoxy)(tert-butyl)bis(methyl)silane (2.93 mmol, 700 mg, 1.25 equiv) in MeCN (3.00 mL) was added, and the reaction was heated overnight at 80 °C. Once cooled to ambient temperature, the reaction solution was triturated in 50.0 mL of stirring Et_2O. The precipitate was filtered and azeotropically dried with heptane to afford the crude bromide salt. **Crude yield** 1.51 mmol, 568 mg, 64%

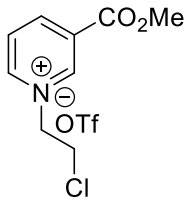
To a 25 mL round bottom flask charged with stir bar and solution of the crude bromide salt (1.51 mmol, 568 mg, 1.0 equiv) in acetone (5.0 mL), a solution of AgOTf (1.51 mmol, 388 mg, 1.0 equiv) in acetone (1.50 mL) was added dropwise at ambient temperature. Upon complete addition of the AgOTf solution, the reaction was stirred for an additional 20 minutes. The reaction solution was then filtered through a short celite plug and concentrated. The crude residue was redissolved in a minimal amount of EtOAc, carefully floated atop 75.0 mL of hexanes, and placed in a -20 °C freezer overnight. The precipitate was then filtered and azeotropically dried with heptane to afford **2.82** as a white solid. **Yield** 1.29 mmol, 574 mg, 55% **^{1}H NMR** (500 MHz, CD_3CN) δ 9.36 (s, 1H), 9.13 – 8.99 (m, 2H), 8.28 (dt, *J* = 9.8, 5.1 Hz, 1H), 4.93 – 4.80 (m, 2H), 4.14 (t, *J* = 4.9 Hz, 2H), 4.04 (d, *J* = 3.5 Hz, 3H), 0.85 (s, 9H).



2-chloroethyl trifluoromethanesulfonate (2.S4)

To a 50 mL Schlenk flask charged with stir bar and solution of 2-chloroethanol (14.9 mmol, 1.00 mL, 1.0 equiv) in DCM (12.0 mL) cooled to 0 °C, 2,6-lutidine (17.9 mmol, 2.07 mL, 1.2 equiv) was slowly added, followed by Tf_2O (16.4 mmol, 2.75 mL, 1.1 equiv). After stirring at 0 °C for 90 minutes, the reaction was diluted to 50.0 mL with Et_2O, washed with cooled 1M HCl (5

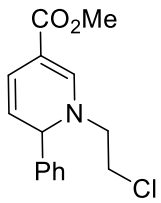
mL X 3), dried over anhydrous Na_2SO_4, filtered, and concentrated to afford **2.S4** as a red oil. **Yield** 12.1 mmol, 2.56 g, 81% **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.70 (t, *J* = 5.7 Hz, 2H), 3.80 (t, *J* = 5.7 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 118.6 (q, *J* = 319.6 Hz), 74.7, 40.2. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -74.47.



methyl 1-(2-chloroethyl)-1-pyridinium-3-carboxylate trifluoromethanesulfonate (2.83)

To a 10 mL Schlenk flask charged with stir bar and methyl nicotinate (9.28 mmol, 1.27 g, 1.0 equiv), a solution of **2.S** (12.1 mmol, 2.56 g, 1.3 equiv) in $CHCl_3$ (9.4 mL) was slowly added. After stirring overnight at ambient temperature, the reaction solution was triturated in 100 mL of stirring Et_2O. The precipitate was filtered and azeotropically dried with heptane to afford **2.83** as a peach-colored powder. **Yield** 8.66 mmol, 3.03 g, 93% **^{1}H NMR** (500 MHz, CD_3CN) δ 9.31 (d, *J* = 1.7 Hz, 1H), 9.01 (dt, *J* = 8.2, 1.5 Hz, 1H), 8.95 (dt, *J* = 6.1, 1.5 Hz, 1H), 8.22 (dd, *J* = 8.2, 6.1 Hz, 1H), 4.98 (t, *J* = 5.6 Hz, 2H), 4.13 (t, *J* = 5.6 Hz, 2H), 4.02 (s, 3H). **^{13}C NMR** (126 MHz, CD_3CN) δ 162.54, 148.85, 147.28, 146.96, 131.80, 129.48, 123.12 (q, *J* = 318.7 Hz), 63.37, 54.22, 43.63. **^{19}F NMR** (471 MHz, CD_3CN) δ -79.30.

2.5.3. General procedure for dearomatization reactions with phenyl boronic acid derivatives

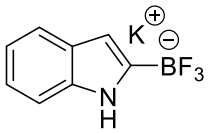


methyl 1-(2-chloroethyl)-6-phenyl-1,6-dihydropyridine-3-carboxylate (2.S3)

To a 1 dram vial charged with **2.83** (0.100 mmol, 35.0 mg, 1.0 equiv), boronic acid derivative (0.250 mmol, 2.5 equiv), and Na_2CO_3 (0.250 mmol, 27.0 mg, 2.5 equiv), a solution of $Rh(cod)_2BF_4$ (0.005 mmol, 2.00 mg, 0.05 equiv) and (R)-BINAP (0.005 mmol, 3.10 mg, 0.05 equiv) in dioxane (1.00 mL) was added in a nitrogen atmosphere glovebox. The vial was sealed with a Teflon lined septum cap and moved to a fume hood. Degassed

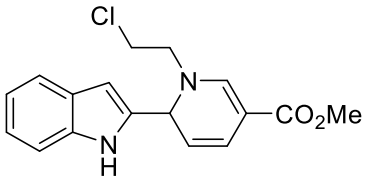
water (50.0 μL) was added through the septum, and the reaction was stirred for 2 hours at the specified temperature. The reaction was then diluted to 4.00 mL of Et_2O, dried over anhydrous $MgSO_4$, filtered through basic alumina, and concentrated. To the crude residue, a stock solution of 1,3,5-trimethoxybenzene (0.033 mmol, 5.60 mg, 0.33 equiv) in $CHCl_3$ (1.00 mL) was added. The solvent was removed *in vacuo,* and the crude residue with internal standard was redissolved in $CDCl_3$ for analysis. The crude reaction yields were determined by ^1H NMR integration with the internal standard. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.38 (m, 1H), 7.36 (d, *J* = 4.4 Hz, 3H), 7.35 – 7.29 (m, 2H), 6.41 (dt, *J* = 10.0, 1.4 Hz, 1H), 5.23 – 5.20 (m, 1H), 5.11 (ddd, *J* = 10.0, 4.3, 0.7 Hz, 1H), 3.71 (s, 3H), 3.52 – 3.39 (m, 3H), 3.27 – 3.21 (m, 1H).

2.5.4. Synthesis of 2-indole intermediates



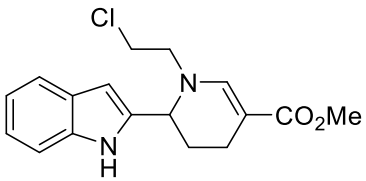
potassium trifluoro(2-indolyl)boranuide (2.91)

To a 10 mL Schlenk flask charged with stir bar and indole-2-boronic acid pinacol ester (1.00 mmol, 243 mg, 1.0 equiv), MeOH (2.00 mL) was added followed by MeCN (2.00 mL) and a solution of KF (4.00 mmol, 232 mg, 4.00 equiv) in H_2O (400 μL). After stirring at ambient temperature for 3 minutes, a solution of tartaric acid (2.05 mmol, 308 mg, 2.05 equiv) in THF (1.50 mL) was added dropwise. After an additional 10 minutes of stirring at ambient temperature, the reaction was diluted with 3.00 mL of MeCN. An additional 1.00 mL of MeCN was added 5 minutes later, and the reaction was filtered through celite. The filtrate was concentrated, and the resulting semi-solid residue was azeotropically dried with heptane to afford **2.91** as a brown solid. **Yield** 0.849 mmol, 198 mg, 85% **^{1}H NMR** (500 MHz, MeOD) δ 7.42 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.86 (t, *J* = 7.3 Hz, 1H). **^{19}F NMR** (471 MHz, MeOD) δ -142.09.



methyl 1-(2-chloroethyl)-6-(2-indolyl)-1,6-dihydronicotinate (2.84)

To a 1 dram vial charged with **2.83** (0.250 mmol, 87.0 mg, 1.0 equiv), **2.91** (0.625 mmol, 146 mg, 2.5 equiv), and Na_2CO_3 (0.625 mmol, 66.0 mg, 2.5 equiv), a solution of $Rh(cod)_2BF_4$ (0.013 mmol, 5.80 mg, 0.05 equiv) and (R)-BINAP (0.013 mmol, 7.80 mg, 0.05 equiv) in dioxane (2.50 mL) was added in a nitrogen atmosphere glovebox. The vial was sealed with a Teflon lined septum cap and moved to a fume hood. Degassed water (250 μL) was added through the septum, and the reaction was stirred at 80 °C for 2 hours. The reaction was then diluted with 6.00 mL of Et_2O, dried over anhydrous Na_2SO_4, filtered through basic alumina, and concentrated. The crude residue was purified by automated flash chromatography on a Teledyne Isco Combiflash® R_f system with a 4.00 g Redi*Sep* Gold™ column, using a gradient of 0% to 100% EtOAc in hexane, to afford **2.84** as a yellow foam. **Yield** 0.230 mmol, 73.0 mg, 91% **TLC** R_f 0.21 (1:1 Et_2O:hexanes, I_2 stain). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.37 (t, *J* = 4.2 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 9.9 Hz, 1H), 6.42 – 6.39 (m, 1H), 5.43 (d, *J* = 4.5 Hz, 1H), 5.18 (dd, *J* = 9.9, 4.5 Hz, 1H), 3.75 (s, 3H), 3.64 (dt, *J* = 14.3, 5.8 Hz, 1H), 3.56 (dt, *J* = 12.5, 6.4 Hz, 1H), 3.44 (dt, *J* = 11.6, 5.9 Hz, 1H), 3.27 (dt, *J* = 13.8, 6.6 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.9, 146.4, 137.4, 137.0, 127.7, 123.0, 122.0, 121.0, 120.3, 112.3, 111.5, 100.8, 97.1, 56.0, 55.2, 51.1, 41.3.

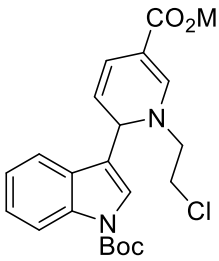


methyl 1-(2-chloroethyl)-6-(2-indolyl)-1,4,5,6-tetrahydronicotinate (2.92)

To a 3.00 mL Schlenk tube charged with stir bar, **2.84** (0.088 mmol, 28.0 mg, 1.0 equiv), Pd/C (10%, 0.009 mmol, 9.4 mg, 0.1 equiv), and NH_4CO_2H (0.884 mmol, 56.0 mg, 10.0 equiv), MeOH (450 μL) was added, and the reaction was stirred at 65 °C, under

elevated nitrogen pressure, for 2.5 hours. Once cooled, the reaction was diluted with EtOAC (6.00 mL), filtered through basic alumina, and concentrated to afford **2.92** as an off-white solid. **Yield** 0.088 mmol, 28 mg, 99%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.59 – 7.57 (m, 1H), 7.55 (dt, *J* = 8.4, 2.0 Hz, 1H), 7.34 (dt, *J* = 8.8, 2.1 Hz, 1H), 7.17 (ddt, *J* = 9.3, 7.3, 1.8 Hz, 1H), 7.10 (ddt, *J* = 9.5, 5.9, 1.8 Hz, 1H), 6.35 (q, *J* = 2.3 Hz, 1H), 4.65 – 4.61 (m, 1H), 3.73 (s, 3H), 3.55 – 3.50 (m, 1H), 3.47 (qd, *J* = 5.6, 3.2 Hz, 3H), 2.55 – 2.46 (m, 1H), 2.21 – 2.04 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 168.9, 145.4, 138.7, 136.2, 128.1, 122.3, 120.5, 120.3, 111.2, 100.8, 96.5, 55.7, 54.0, 51.1, 42.6, 28.3, 17.6.

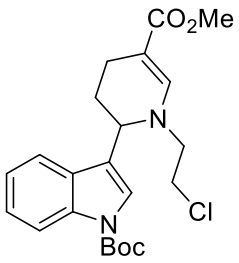
2.5.5. Synthesis of Ihara's deplancheine intermediate (2.77)



***tert*-butyl 3-[1-(2-chloroethyl)-5-methoxycarbonyl-1,2-dihydro-2-pyridyl]-1-indolecarboxylate (2.85)**

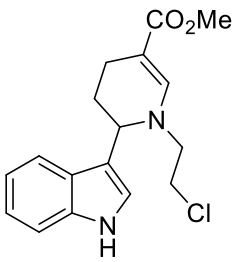
To a 20 mL vial charged with **2.83** (1.20 mmol, 420 mg, 1.0 equiv), indole-3-boronic acid pinacol ester (1.80 mmol, 618 mg, 1.5 equiv), and Na_2CO_3 (1.80 mmol, 191 mg, 1.5 equiv), a solution of $Rh(cod)_2BF_4$ (0.06 mmol, 28 mg, 0.05 equiv) and (R)-BINAP (0.06 mmol, 40 mg, 0.05 equiv) in THF (12.0 mL) was added in a nitrogen atmosphere glovebox. The vial was sealed with a Teflon lined septum cap and moved to a fume hood. Degassed water (1.20 mL) was added through the septum, and the reaction was stirred at ambient temperature overnight. The reaction was then diluted with 25.0 mL of Et_2O, dried over anhydrous Na_2SO_4, filtered through basic alumina, and concentrated. The crude residue was purified by automated flash chromatography on a Teledyne Isco Combiflash® R_f system with a 12.0 g Redi*Sep* Gold™ column, using a gradient of 0% to 100% EtOAc in hexane, to afford **2.85** as a yellow solid. **Yield** 1.07 mmol, 448 mg, 90% **TLC** R_f 0.30 (1:4 EtOAc:Hexanes, I_2 stain). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.5 Hz, 1H), 7.62 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.45 (s, 1H), 7.32 (t, *J* = 1.0 Hz, 1H),

7.24 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.14 (ddd, *J* = 8.1, 7.3, 1.0 Hz, 1H), 6.34 (dt, *J* = 10.0, 1.5 Hz, 1H), 5.53 (dd, *J* = 4.0, 1.6 Hz, 1H), 4.94 (ddd, *J* = 10.0, 3.9, 0.8 Hz, 1H), 3.64 (s, 3H), 3.48 – 3.34 (m, 3H), 3.14 – 3.07 (m, 1H), 1.58 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.8, 149.6, 146.6, 136.1, 128.1, 125.0, 123.2, 123.1, 121.3, 121.0, 120.2, 115.5, 113.6, 96.6, 84.3, 55.3, 54.8, 50.8, 40.9, 28.2, 28.1, 28.1.



tert-butyl 3-[1-(2-chloroethyl)-5-methoxycarbonyl-1,2,3,4-tetrahydro-2-pyridyl]-1-indolecarboxylate (2.95)

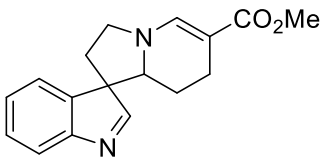
To a 10 mL Schlenk flask charged with stir bar, **2.85** (0.545 mmol, 227 mg, 1.0 equiv), Pd/C (10%, 0.054 mmol, 58.0 mg, 0.1 equiv), and NH_4CO_2H (5.44 mmol, 343 mg, 10.0 equiv), MeOH (2.70 mL) was added, and the reaction was stirred at 65 °C, under elevated nitrogen pressure, for 2.5 hours. Once cooled, the reaction was diluted with EtOAC (15.0 mL), filtered through basic alumina, and concentrated to afford **2.95** as pale-yellow solid. **Yield** 0.528 mmol, 221 mg, 97%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08 – 8.00 (m, 1H), 7.50 (d, *J* = 4.1 Hz, 1H), 7.43 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.31 (d, *J* = 4.4 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.19 – 7.14 (m, 1H), 4.62 (t, *J* = 4.4 Hz, 1H), 3.63 (d, *J* = 4.8 Hz, 3H), 3.52 – 3.43 (m, 2H), 3.40 (t, *J* = 5.7 Hz, 2H), 2.33 (dt, *J* = 14.4, 4.1 Hz, 1H), 2.11 (dq, *J* = 13.3, 4.3 Hz, 1H), 2.02 – 1.86 (m, 2H), 1.59 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.8, 149.6, 145.3, 135.9, 128.1, 124.8, 123.6, 122.8, 120.3, 119.0, 115.7, 96.0, 95.9, 84.2, 55.4, 52.5, 50.8, 42.6, 28.3, 28.2, 27.1, 17.3.



methyl 1-(2-chloroethyl)-6-(1*H*-indol-3-yl)-1,4,5,6-tetrahydropyridine-3-carboxylate (2.96)

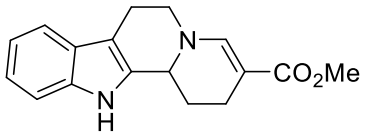
To a 10 mL Schlenk flask charged with stir bar and **2.95** (0.528 mmol, 221 mg, 1.0 equiv), a solution of DMS (5.28 mmol, 390 µL, 10.0 equiv) in DCM

(1.70 mL) was added, followed by the dropwise addition of TFA (22.2 mmol, 1.70 mL, 42.0 equiv). After stirring for 4 hours at ambient temperature, the reaction was quenched into a stirring slurry of $NaHCO_3$ in saturated aqueous $NaHCO_3$. The product was extracted into EtOAc (10 mL X 3), and the combined organic layers were rinsed with brine (10.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to afford **2.96** as a yellow foam. **Yield** 0.424 mmol, 135 mg, 80%. **^{1}H** NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.60 (d, *J* = 1.1 Hz, 1H), 7.57 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.39 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.22 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.99 (d, *J* = 2.5 Hz, 1H), 4.77 (t, *J* = 4.4 Hz, 1H), 3.72 (s, 3H), 3.55 – 3.46 (m, 3H), 3.46 – 3.38 (m, 1H), 2.44 – 2.38 (m, 1H), 2.18 (dq, *J* = 12.5, 4.5 Hz, 1H), 2.11 – 2.03 (m, 1H), 1.98 (ddt, *J* = 12.6, 10.0, 4.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.2, 145.9, 136.7, 125.4, 122.5, 119.9, 118.7, 116.0, 111.7, 95.5, 55.5, 52.8, 50.9, 42.7, 27.8, 17.5.



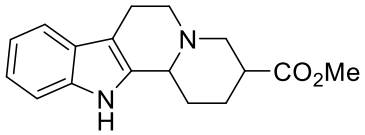
methyl 3',7',8',8a'-tetrahydro-2'*H*-spiro[indole-3,1'-indolizine]-6'-carboxylate (2.97)

To a 1 mL Schlenk tube charged with stir bar and **2.96** (0.094 mmol, 30.0 mg, 1.0 equiv), KO^{t}Bu (0.104 mmol, 12.0 mg, 1.1 equiv) was added in a nitrogen atmosphere glovebox, followed by dioxane (400 µL). The tube was sealed and moved to a fume hood where a solution of Et_3B (1M in hexane, 0.104 mmol, 104 µL, 1.1 equiv) was added. After stirring for 2.5 hours at ambient temperature, the reaction was quenched with saturated aqueous NH_4Cl, diluted with EtOAc (6.00 mL), dried over anhydrous $MgSO_4$, filtered through basic alumina, and concentrated to afford **2.97** as a red-orange foam. **Crude Yield** 0.094 mmol, 27.0 mg, 99%



methyl 7,17-diazatetracyclo[8.7.0.0^{2,7}.0^{11,16}]heptadeca-1(10),5,11,13,15-pentaene-5-carboxylate (2.99)

To a 1 mL Schlenk tube charged with stir bar and unpurified **2.97** (0.094 mmol, 27.0 mg, 1.0 equiv), TsOH•H_2O (0.029 mmol, 5.50 mg, 0.3 equiv) was added, followed by THF (900 µL). After stirring overnight at ambient temperature, the reaction was quenched with saturated aqueous $NaHCO_3$, diluted with EtOAc (6.00 mL), dried over anhydrous Na_2SO_4, filtered through basic alumina, and concentrated to afford **2.99** as a white solid. **Yield** 0.089 mmol, 25.0 mg, 93% **TLC** R_f 0.71 (3:1 EtOAc:hexanes, I_2 stain). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.45 – 7.40 (m, 2H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.13 – 7.09 (m, 1H), 7.08 – 7.03 (m, 1H), 4.42 – 4.38 (m, 1H), 3.63 (s, 3H), 3.57 (ddd, *J* = 12.7, 5.6, 1.4 Hz, 1H), 3.50 (dd, *J* = 11.9, 4.0 Hz, 1H), 2.89 – 2.81 (m, 1H), 2.71 (ddt, *J* = 15.0, 3.5, 1.5 Hz, 1H), 2.53 – 2.47 (m, 1H), 2.37 – 2.30 (m, 2H), 1.73 (tdd, *J* = 14.3, 10.0, 5.5 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 169.1, 146.6, 136.3, 133.0, 127.0, 122.2, 119.9, 118.4, 111.1, 108.6, 94.9, 52.0, 51.0, 50.9, 28.6, 22.1, 20.6.



methyl 7,17-diazatetracyclo[8.7.0.0^{2,7}.0^{11,16}]heptadeca-1(10),11,13,15-tetraene-5-carboxylate (2.77)

To a 5 mL Schlenk tube charged with stir bar and **2.77** (0.188 mmol, 53.0 mg, 1.0 equiv), $NaBH_3CN$ (0.207 mmol, 13.0 mg, 1.1 equiv) was added, followed by AcOH (400 µL) and MeOH (1.20 mL). After stirring at ambient temperature for 3 hours and 15 minutes, the reaction was quenched with 1M HCl and stirred for 15 minutes. The solution was then neutralized with saturated aqueous $NaHCO_3$, and the product was extracted into EtOAc (10.0 mL X 3). The combined organic layers were rinsed with brine (5.00 mL), dried over anhydrous Na_2SO_4, filtered through basic alumina, and concentrated. The crude residue was purified by automated flash chromatography on a Teledyne Isco Combiflash® R_f system with a 4.00 g Redi*Sep* Gold™ column, using a gradient

of 0% to 100% EtOAc in hexane, to afford the diastereomers of **2.77** as white solids. **Yield** 0.144 mmol, 41.0 mg, 77% **TLC** R_f 0.51 (1:1 EtOAc:hexanes, I_2 stain or UV). **^{1}H NMR** (500 MHz, CDCl3) δ 7.70 (s, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.31 (dd, J = 7.8, 1.1 Hz, 1H), 7.14 (td, J = 7.6, 1.3 Hz, 1H), 7.09 (td, J = 7.4, 1.1 Hz, 1H), 3.71 (s, 3H), 3.27 (dddd, J = 17.9, 10.9, 4.3, 2.1 Hz, 2H), 3.13 – 3.08 (m, 1H), 3.04 – 2.95 (m, 1H), 2.82 (tt, J = 11.7, 4.0 Hz, 1H), 2.77 – 2.66 (m, 2H), 2.51 (t, J = 11.4 Hz, 1H), 2.28 – 2.13 (m, 2H), 1.72 – 1.62 (m, 2H).

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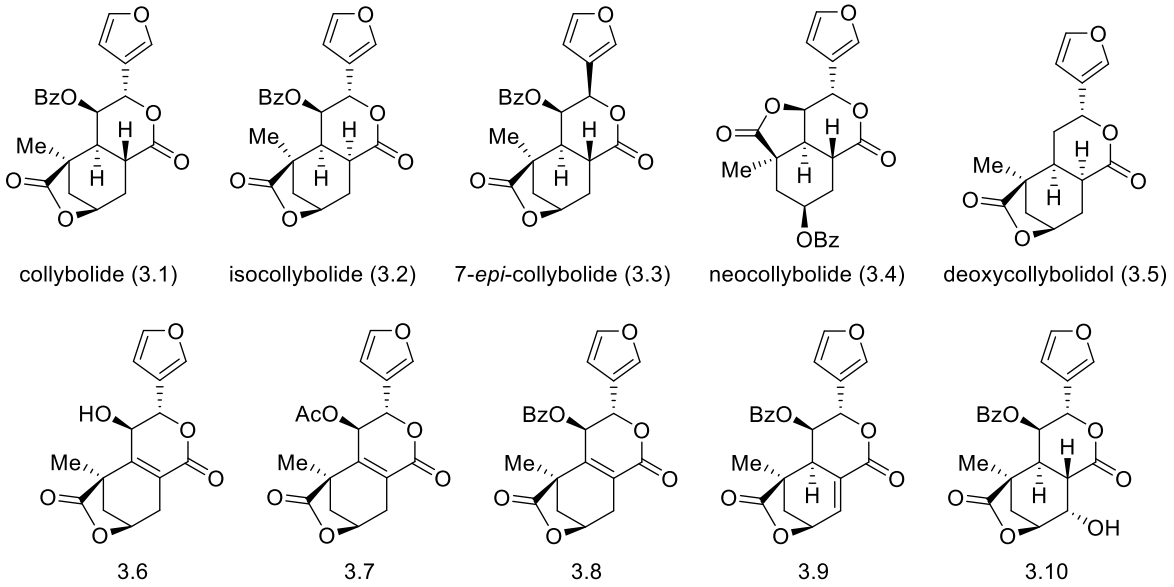
Chapter 3: Total synthesis of *Collybia maculata* metabolite, collybolide

In 1974, two sesquiterpenes, collybolide (**3.1**) and isocollybolide (**3.2**), were isolated from the fruiting bodies of the mushroom *Collybia maculata.*[1] The structures of **3.1** and **3.2** (Figure 3.1) contain a novel tricyclic core bearing both a γ-lactone and a δ-lactone with furyl and benzoate substituents. The related compounds 7-*epi*-collybolide (**3.3**) and neocollybolide (**3.4**) were also obtained, but as artifacts resulting from the extraction and purification techniques employed.[2] In 1986, an extraction from the fruiting bodies of *Collybia peronata* afforded deoxycollybidol (**3.5**), an isocollybolide terpenoid without the furyl substituent.[3] A scrupulous reinvestigation into the secondary metabolites of *Collybia maculata* took place in 2000, utilizing extraction with ethyl acetate at -20 °C rather than acetone or $CHCl_3$/MeOH at ambient temperature, and five new collybolide related terpenoids (**3.6-3.10**) were isolated.[4]

Figure 3.1. Terpenoids isolated from *Collybia* basidiomycetes.



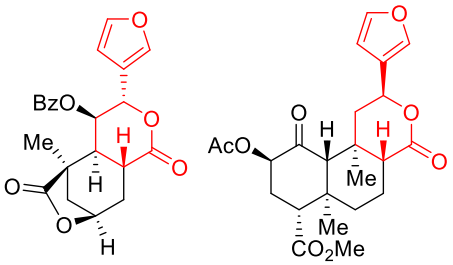
3.1. Biological activity of collybolide

Traditional opioids, such as morphine, hydrocodone, and oxycodone, produce analgesic effects by targeting μ-opioid receptors, but μ-opioids also result in negative side effects such as

euphoria, respiratory depression, and physical dependence.[5,6] However, the μ-receptor is one of three receptors that comprise the opioid receptor family; all three possess the potential for inducing analgesic effect.[7] Due to the increased rate of fatal opioid overdoses, alternatives to traditional μ-opioids, in particular κ-opioids, have been of interest to the medicinal chemistry community.

Salvinorin A (**3.11**) was isolated from *Salvia divinorum,* a mint used in spiritual practices by the Mazatec people of Oaxaca, by Ortega in 1982, and it has since been found to be a potent opioid agonist.[8,9] Binding assays revealed an 18 nM affinity for the κ-opioid receptor, yet greater than 10,000 nM affinity for μ- and δ-opioid receptors.[10] Although highly selective toward the κ-opioid receptor, salvinorin A is non-biased regarding signal transduction pathways; upon binding, signal transduction occurs via both G-protien coupled receptors (GPCR) and β-arrestin-2 pathways.[11-15] Studies have indicated a correlation between the compound's adverse psychotropic effects and the recruitment of β-arrestin-2, so compounds that demonstrate a bias for GPCR signal transduction have been of interest for the development of therapeutic κ-opioids.[16]

Figure 3.2. Structures of collybolide and salvinorin A with the furyl-δ-lactone motif highlighted.



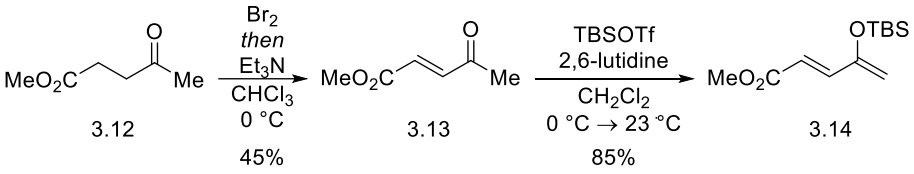
Collybolide (3.1) Salvinorin A (3.11)

After being generally unnoticed for decades, collybolide was evaluated for opioid activity in 2016 because it contains the furyl-δ-lactone motif also present in salvinorin A (Figure 3.2).[17] The studies indicated that collybolide, like salvinorin A, expresses a high selectivity for the κ-opioid receptor, but, unlike salvinorin A, collybolide exhibited biased GPCR signaling and an

absence of psychotropic properties. The inherent potential of such a selective and biased opioid agonist for developing next-generation therapeutics attracted the interest of the medicinal chemistry community and spurred efforts to synthetically produce collybolide.[18-22] These results prompted a need for strategies to access synthetic collybolide to further investigate the pharmacology of biased agonism.

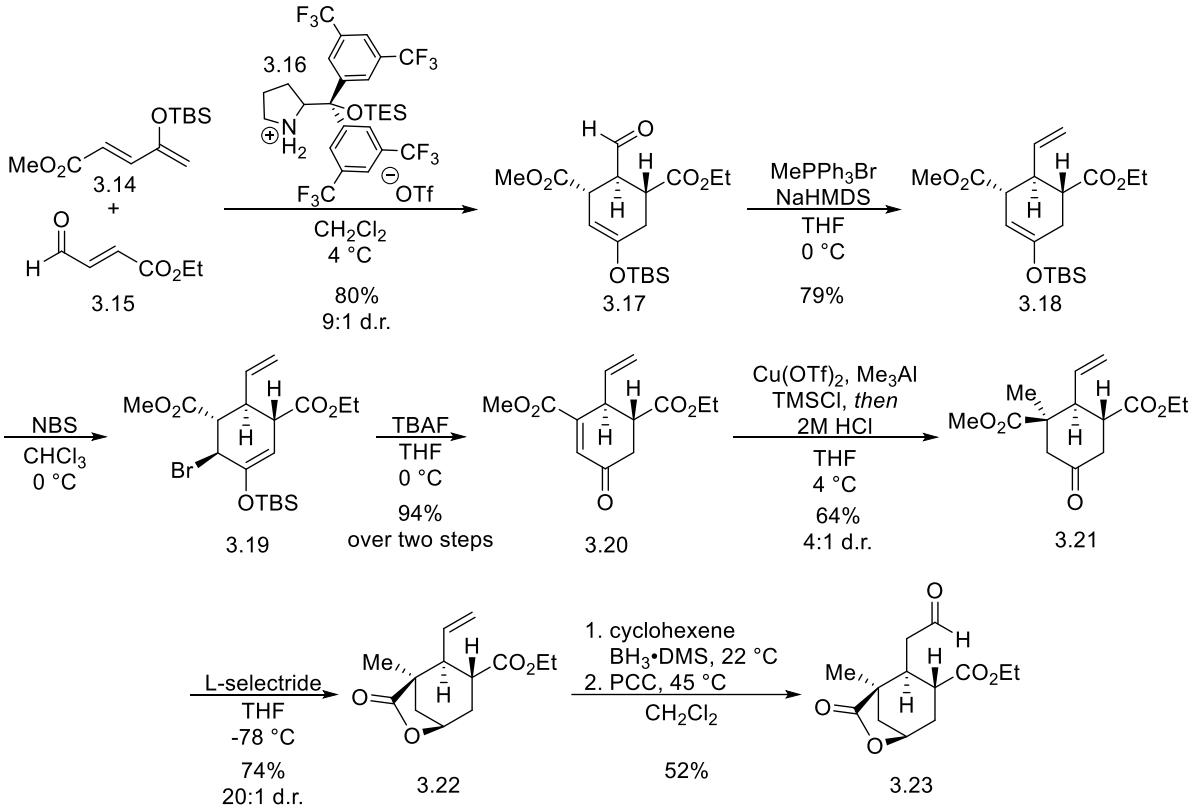
3.2. Previously reported synthesis of collybolide

Scheme 3.1. Synthesis of cycloaddition starting material 3.14.



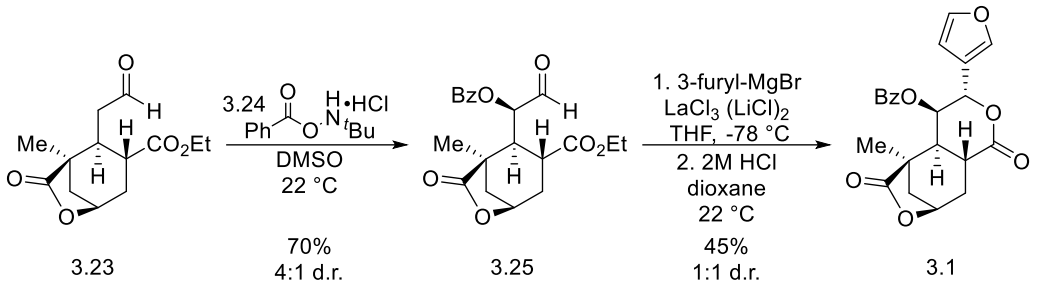
The first, and only, reported synthesis of collybolide was by the Shenvi group in 2022, in the midst of our own synthetic endeavor, and they accessed both enantiomers of collybolide in twelve steps starting from **3.12.**[23] Bromination of **3.12** and subsequent elimination afforded α,β-unsaturated ketone **3.13** in 45% yield (Scheme 3.1), and treatment of **3.13** with TBSOTf provided silyl enol ether **3.14** in 85% yield.

Scheme 3.2. Synthesis of aldehyde 3.23.



Silyl enol ether **3.14** was then used in an asymmetric cycloaddition with aldehyde **3.15**, catalyzed by Hayashi-Jorgensen catalyst **3.16**, to furnish cycloadduct **3.17** in 80% yield over four days (Scheme 3.2). Wittig olefination of **3.17** provided alkene **3.18** in 79% yield, and a sequence of bromination and TBS-deprotection afforded α,β-unsaturated ketone **3.20** in 94% yield, via brominated intermediate **3.19**. Unsaturated ketone **3.20** was subjected to conjugate addition with $AlMe_3$, in the presence of $Cu(OTf)_2$, to forge cyclohexanone **3.21** in 64% yield. Reduction of **3.21** with L-selectride resulted in the formation of lactone **3.22** in 74% yield. A one-pot hydroboration-oxidation of **3.22**, employing dicyclohexylborane and PCC, gave aldehyde **3.23** in 52% yield.

Scheme 3.3. Construction of the furyl-δ-lactone and collybolide.



Continuing with aldehyde 3.23, α-benzoylation was achieved with ammonium reagent 3.24, providing aldehyde 3.25 in 70% yield (Scheme **3.**3). The furyl-δ-lactone was completed in a two-step sequence of furyl addition to aldehyde 3.25, with an organolanthanum reagent, and subsequent transesterification of the resulting alcohol (45% yield over two steps) to furnish optically pure collybolide (3.1) in 2% total yield over twelve steps.

The Shenvi group reported that the biological activity, established by multiple independent biochemical assays and in vivo studies, had been wrongly ascribed, and that neither optical antipode of collybolide exhibits κOR agonism. Although the structure of synthetic collybolide matched the natural product, neither enantiomer of synthetic collybolide was found to agonize the κ-opioid receptor.

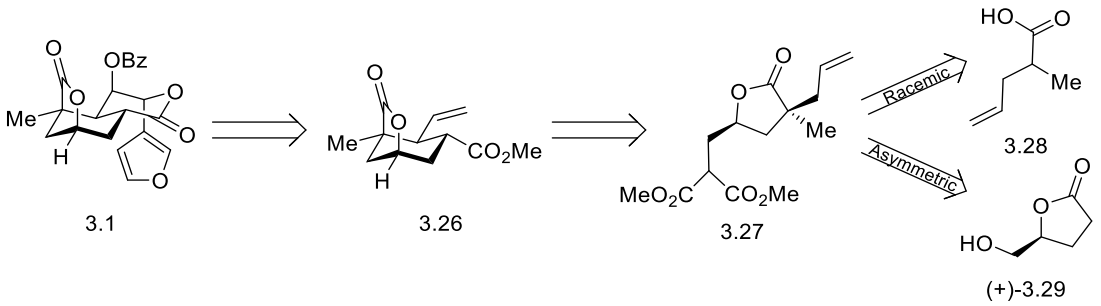
3.3. Our synthetic approach to collybolide

3.3.1. Retrosynthesis of collybolide

Herein, we report a synthesis of racemic collybolide, as well as an asymmetric formal synthesis, to facilitate further investigation into collybolide's biological activity. Our retrosynthetic strategy to obtain **3.1** is outlined in Scheme 3.4. We determined that the furyl-δ-lactone would be the last ring formed with benzoyl and furyl substituents being installed via functionalization of the olefin present in **3.26.** Construction of bicycle **3.26** would rely upon a key allylic substitution with

an allylic acetate derived from malonate **3.27**. We imagined that malonate **3.27** would be accessible from the corresponding iodolactone, and that iodolactone was envisioned to be a convergence point in the synthesis for racemic material starting from 2-methyl-4-pentenoic acid (**3.28**) and optically pure material originating from γ-butyrolactone **(+)-3.29**.

Scheme 3.4. Retrosynthesis of collybolide.

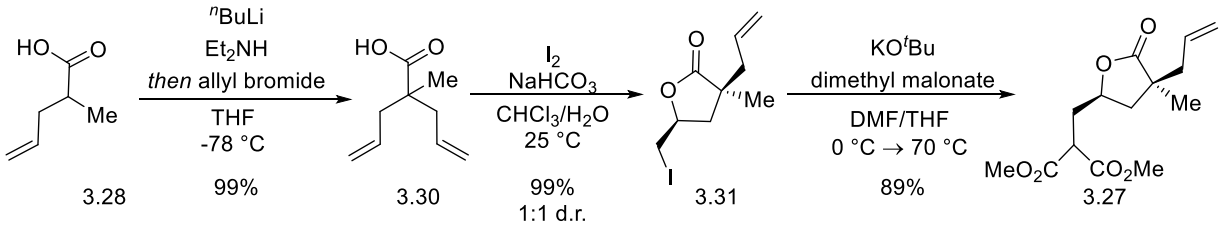


3.3.2. Synthesis of malonate 3.27

The racemic synthesis commenced with the decagram scale allylation of commercially available carboxylic acid **3.28** (Scheme 3.5) utilizing lithium diethylamide (LDE) and subsequent trapping of the dianion with allyl bromide to quantitatively afford carboxylic acid **3.30** with chromatographic purity following workup.[24] Lithium diisopropylamide (LDA) was initially employed in efforts to produce carboxylic acid **3.30**, but LDA's unreliability in generation the necessary dianion combined with an inability to separate unconsumed starting material from product, via chromatography or distillation, forced us to search for more amenable reaction conditions. The Parra group's work on dianion formation led us to investigate the efficacy of LDE in streamlining the assembly **3.30**, and we were rewarded with quantitative yields at the cost of an excess of allyl bromide being required to accommodate for the increased nucleophilicity compared to LDA.[24] Carboxylic acid **3.30** was subjected to kinetic iodolactonization on decagram scale (99% yield with a 1:1 ratio of diastereomers) to provide the desired diastereomer of lactone **3.31** in 45% yield after dry column vacuum chromatography. The undesired diastereomer of iodolactone **3.31**

was recycled via reductive cleavage using metallic zinc, quantitatively reforming carboxylic acid **3.30** in sufficient purity for re-subjection to iodolactonization without further purification.[25] Alkylation of dimethyl malonate with iodolactone **3.31** furnished malonate **3.27** in 89% yield.

Scheme 3.5. Synthesis of malonate 3.27.

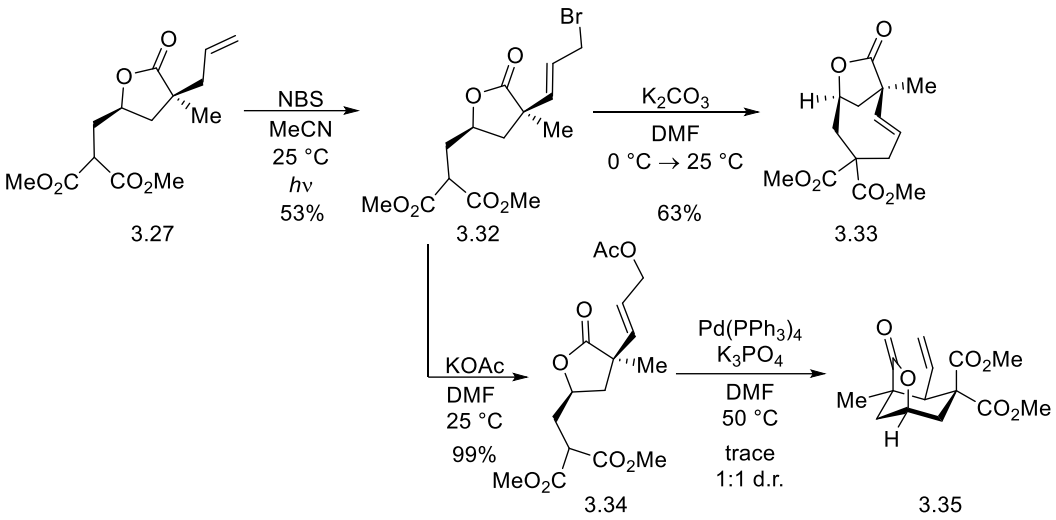


3.3.3. Synthesis of bicycle 3.26

3.3.3.1. Allylic substitution utilizing an allylic bromide.

With an enolizable malonate installed to serve as a pronucleophile for allylic substitution, we needed to functionalize the olefin present in **3.27** to enable later generation of a π-allyl species. Our initial allylic substitution strategy to create the bicyclic core employed bromide **3.32** (Scheme 3.6) which was formed via allylic bromination of malonate **3.27** in 53% yield. However, under basic conditions, bromide **3.32** underwent an E2 elimination to generate bicycle **3.33** in 63% yield.

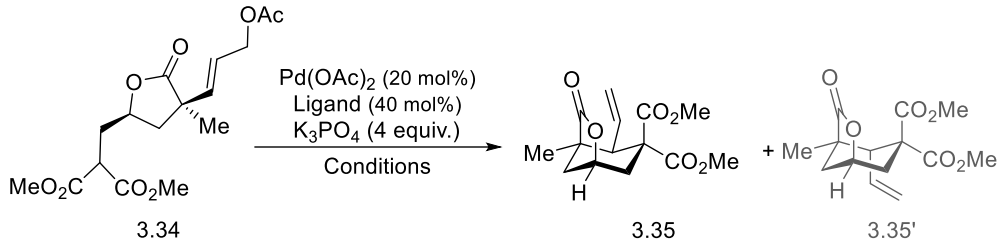
Scheme 3.6. Initial attempts at allylic substitution cyclization.



3.3.3.2. Allylic substitution utilizing an allylic acetate.

Realizing that a less labile leaving group was necessary, bromide **3.32** was converted into acetate **3.34** with KOAc in excellent yield, and initial tests of acetate **3.34** under palladium tetrakis catalyzed allylic substitution conditions revealed trace amounts of bicycle **3.35,** confirming that intramolecular allylic substitution was a viable means of forging collybolide's bicyclic core.[26,27] Appreciating the synthetic potential of acetate **3.35**, we sought a more concise synthesis. Applying the work of Stahl and coworkers, palladium catalyzed aerobic C-H acetoxylation of **3.27** under one atmosphere of oxygen successfully delivered linear allylic acetate **3.34,** but the reaction yields were deleteriously variable.[28,29] Elevating the oxygen pressure to four atmospheres not only attenuated the variability in reaction yields, but also allowed for the acetoxylation to be carried out on gram scale which afforded **3.34** in 81% yield. With a streamlined synthesis of **3.34** established (Scheme 3.7), we set about screening conditions to elicit efficient cyclization. A screening of 28 ligands (see Table 3.1 for reactions that resulted in product formation) indicated a correlation between electron-rich ligands and conversion of **3.34**, whereas ligands with greater steric influence

Table 3.1. Allylic substitution cyclization ligand screening.



3.34 3.35 3.35'

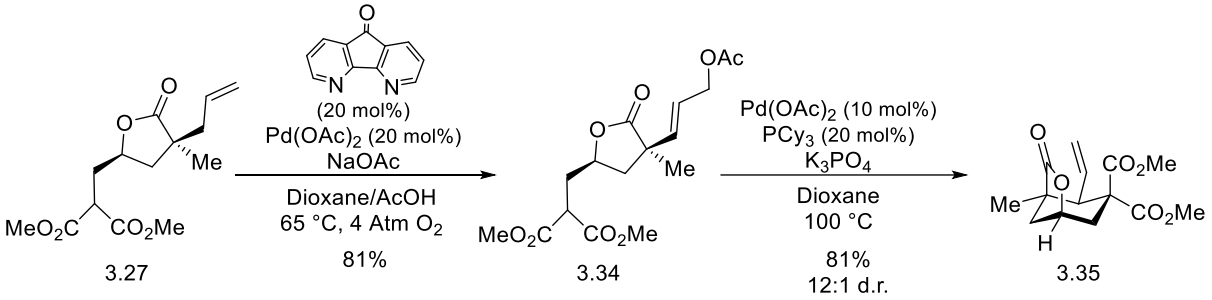
Entry	Ligand	Solvent	Temperature	Time	Yield	d.r.
1	dppf	THF	65 °C	3 Hrs	2%	1:1
2	(S,S) Me-BPE	THF	65 °C	3 Hrs	6%	1:1
3	P*t*Bu$_3$	THF	65 °C	3 Hrs	7%	6:1
4	(S) *i*Pr-PHOX	THF	65 °C	3 Hrs	8%	2:1
5	(R) DM-BINAP	THF	65 °C	3 Hrs	9%	1:1
6	dmpe	THF	65 °C	3 Hrs	10%	1:1
7	(-) NORPHOS	THF	65 °C	3 Hrs	15%	1:1
8	PPh$_2$Me	THF	65 °C	3 Hrs	22%	1:1
9	dppp	THF	65 °C	3 Hrs	25%	1:1
10	PPh$_3$	THF	65 °C	3 Hrs	26%	2:1
11	dppe	THF	65 °C	3 Hrs	30%	1:1
12	P(2-furyl)$_3$	THF	65 °C	3 Hrs	30%	2:1
13	XANTPHOS	THF	65 °C	3 Hrs	65%	1.5:1
14	P(pentafluorophenyl)$_3$	THF	80 °C	12 Hrs	5%	1:1
15	P(OPh)$_3$	THF	80 °C	3 Hrs	27%	6:1
16	XPhos	THF	80 °C	12 Hrs	85%	2:1
17	P(4-fluorophenyl)$_3$	Dioxane	100 °C	6 Hrs	55%	10:1
18	P(*o*-tolyl)$_3$	Dioxane	100 °C	6 Hrs	55%	10:1
19	P(*n*Bu)$_3$	Dioxane	100 °C	6 Hrs	55%	3:1
20	P(*i*pr)$_3$	Dioxane	100 °C	6 Hrs	62%	6:1
21	SPhos	Dioxane	100 °C	6 Hrs	75%	2:1
22	DPEphos	Dioxane	100 °C	6 Hrs	78%	1.2:1
23	P(*p*-tolyl)$_3$	Dioxane	100 °C	6 Hrs	83%	3:1
24	**PCy$_3$**	**Dioxane**	**100 °C**	**6 Hrs**	**96%**	**20:1**

Reactions were conducted on 0.058 mmol scale with 2.50 mL solvent. Crude yields and diastereomeric ratios were determined by ^{1}H NMR integration with pivaldehyde internal standard.

favored the formation of desired diastereomer **3.35**, as demonstrated by *ortho* and *para* substituted tritolyl phosphines (Table 3.1 entry 18 vs entry 23). Hypothesizing that a bulky electron-rich monophosphine might be capable of conducting the cyclization both diastereoselectively and in synthetically useful yields, tricyclohexylphosphine and triadamantylphosphine were screened. Although triadamantylphosphine failed to deliver cyclized product, tricyclohexylphosphine (Table

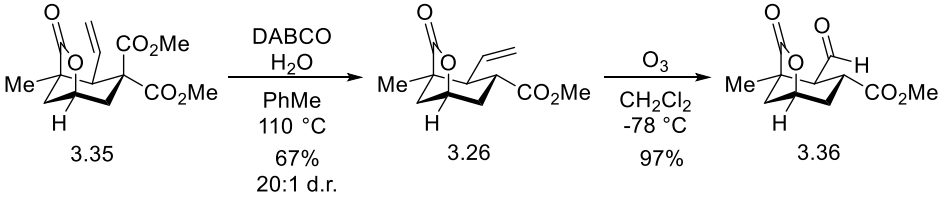
3.1 entry 24) afforded **3.35** not only in the highest yield, but also with the greatest diastereoselectivity of the 30 ligands screened. The allylic substitution was effectively scaled up, with a decreased catalyst loading of 10 mol% palladium, to provide bicycle **3.35** in 81% yield with a 12:1 ratio of diastereomers.

Scheme 3.7. Improved synthesis of bicycle 3.35.



Construction of the δ-lactone using the olefin present in **3.35** proved nontrivial as the substrate resisted functionalization attempts with epoxidation, dihydroxylation, and even robust ozonolysis, leaving the substrate unscathed. Suspecting that steric hindrance from the γ-lactone, methyl substituent, and geminal diester was retarding reactivity, bicycle **3.35** was decarboxymethylated with DABCO (Scheme 3.8), since conventional Krapcho conditions were unsuccessful, to deliver bicycle **3.26** in 67% yield.[30,31] Although anhydrous conditions were used in Miles' methodology, the addition of water proved crucial in minimizing variability in reaction yields, potentially to inhibit decomposition by quenching the resulting enolate. With the olefin less encumbered, bicycle **3.26** succumbed to ozonolysis providing aldehyde **3.36** in 97% yield, which confirmed that **3.26** is amenable to further functionalization.

Scheme 3.8. Synthesis of Intermediate 3.26 and initial functionalization.

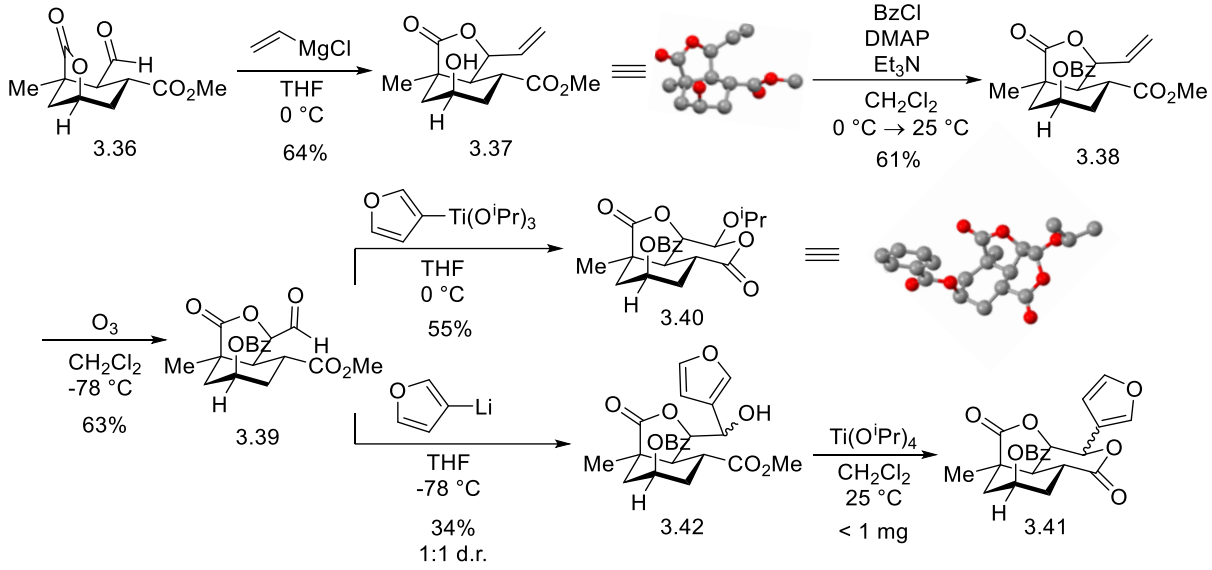


3.3.4. Construction of the furyl-δ-lactone motif

3.3.4.1. Functionalization with vinyl Grignard; An impromptu synthesis of neocollybolides

Continuing with aldehyde **3.36** (Scheme 3.9), vinyl Grignard was employed to reinstall the last carbon unit of the δ-lactone ring. Unfortunately, Grignard addition furnished alcohol **3.37** in 64% yield rather than the expected allylic alcohol, and this rearrangement went unnoticed until later attempts to install the furan moiety. Alcohol **3.37** facilitated an impromptu synthesis of the neocollybolide scaffold with benzoyl protection providing triester **3.38** in 61% yield, and subsequently subjecting **3.38** to ozonolysis afforded aldehyde **3.39** in 63% yield. Inspired by the precedent of organotitanium reagents being employed in the construction of furyl-δ-lactone motifs, aldehyde **3.39** was treated with (3-furyl)Ti(O^iPr)$_3$ which curiously generated isopropoxide addition product **3.40** in 55% yield.[32-35] X-ray crystallography of **3.40** revealed both the isopropoxide addition as well as the transesterification. Uncertain as to whether the rearrangement was another unexpected outcome of being exposed to the organotitanium reagent or if it took place during a prior reaction, the structure of alcohol **3.37** was reevaluated, this time using X-ray crystallography, which revealed the transesterification was a consequence of the Grignard addition.

Scheme 3.9. Synthesis of neocollybolide (3.41).



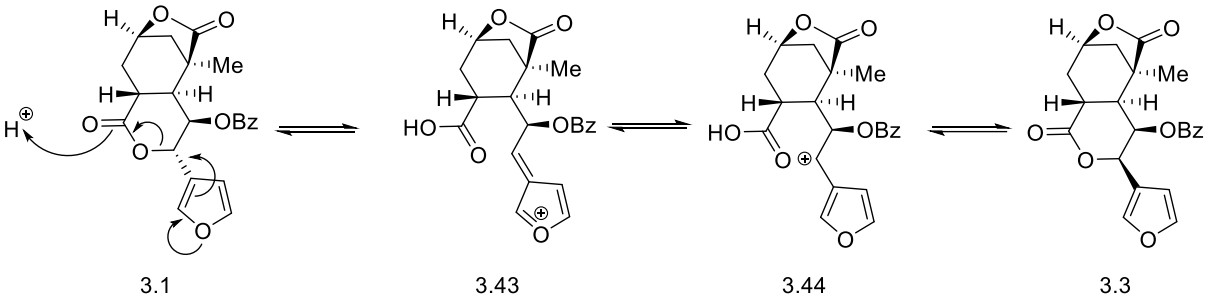
With the knowledge that aldehyde **3.36** was in fact a precursor for neocollybolide (**3.41**), we decided to continue attempts at constructing the furyl-δ-lactone moiety. Treatment of **3.39** with furyllithium afforded alcohol **3.42** as a mixture of diastereomers in 34% yield, and a microscale transesterification of **3.42** using $Ti(O^iPr)_4$ furnished a sub-milligram quantity neocollybolide (**3.41**) as a mixture of diastereomers.

3.3.4.2. Attempts at dibenzoylation of a furan-substituted *trans*-olefin to access collybolide.

The observed proclivity for rearrangement to a neocollybolide core prompted us to reassess our strategy to sidestep promiscuous alkoxides, thus eliminating the possibility of a stepwise installation of the benzoyl moiety. To combat the potential neocollybolide rearrangement, the second-generation strategy we adopted hinged upon dibenzoylation of a furan-substituted *trans*-olefin. Inspired by the acid promoted ring opening responsible for the epimerization of collybolide to epicollyoblide (**3.3**) (Scheme 3.10), we posited that a benzoyl ester alpha to the furan might be susceptible to elimination under acidic conditions, generating oxonium intermediate **3.43**.

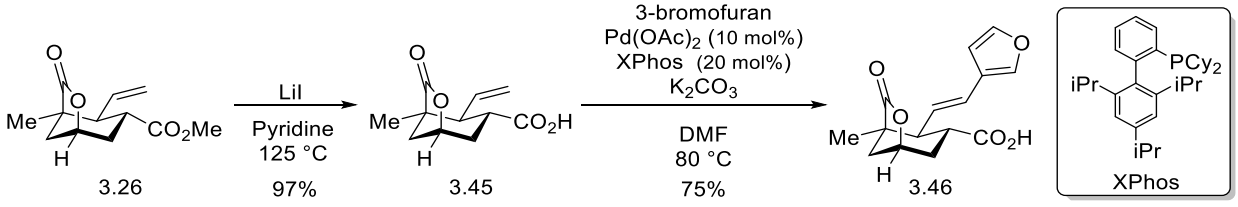
Tautomerization of oxonium **3.43** rearomatizes the furan moiety, affording α-aryl carbanion **3.44**, which would be intercepted intramolecularly to form the furyl-δ-lactone.[1]

Scheme 3.10. Collybolide epimerization via acid-promoted ring opening.



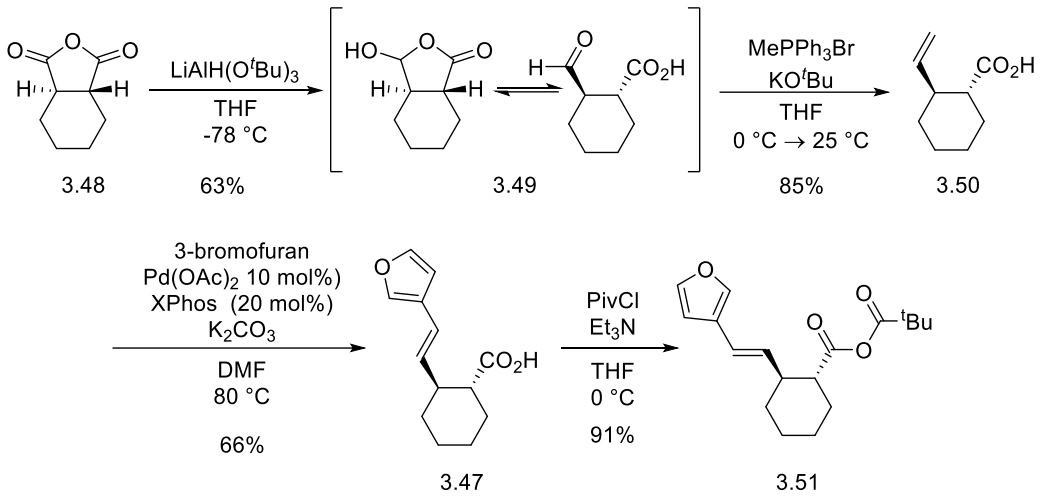
The second-generation attempted synthesis of the furyl-δ-lactone commenced with deprotection of bicycle **3.26** (Scheme 3.11) to furnish carboxylic acid **3.45** in 97% yield, and acid **3.45** was then subjected to carboxylate directed Heck coupling developed by Shenvi's group.[6] The coupling provided acid **3.46** in 75% yield, leaving only benzoylation and cyclization between **3.46** and collybolide.

Scheme 3.11. Synthesis of furan-substituted *trans*-olefin 3.46.



Preliminary reaction screens using acid **3.46** indicated a low likelihood of recovering starting material; due to the tedious purification of iodolactone **3.31** and multiple palladium catalyzed reactions needed to produce acid **3.46**, we developed a model system to continue with reaction screening. Sharing both a furan-substituted *trans*-olefin and carboxylic acid moiety as vicinal substituents of a cyclohexane core, structural similitude permitted the use of model **3.47** as a surrogate for acid **3.46** in exploratory efforts to install the requisite benzoyl moiety.

Scheme 3.12. Synthesis of furan-substituted *trans*-olefin models compounds.



Model **3.47** was created in three steps (Scheme 3.12) starting from commercially available anhydride **3.48**. Gram-scale reduction of anhydride **3.48** with LiAlH(OtBu)$_3$ afforded aldehyde **3.49** in 63% yield, and Wittig olefination of **3.49** provided terminal olefin **3.50** in 85% yield. Application of the previously used Heck conditions to olefin **3.50** successfully furnished model **3.47** (66% yield) in 35% yield over three steps.

Resuming the attempt to achieve dibenzoylation, now with a more expendable substrate in hand, we turned to Woodward-Prevost methodologies. Modifications to the hypervalent iodine mediated Woodward-Prevost methodologies established by the groups of Sudalai and Li demonstrated some success in installing the requisite benzoyl moiety, yet unfortunately the conditions were too harsh for the furan to survive.[37-38] Since our furan substrates demonstrated an incompatibility with hypervalent iodine, we moved on to conditions originally reported by Woodward and Prevost in search of better chemoselectivity. The classic silver conditions were applied to **3.47**, but they too failed to provide the desired dibenzoyl substrate resulting in complex reaction mixtures or recovered starting material when attempted at lower temperatures.[39] The work of Cambie and coworkers established a lower temperature variation of the Woodward-Prevost

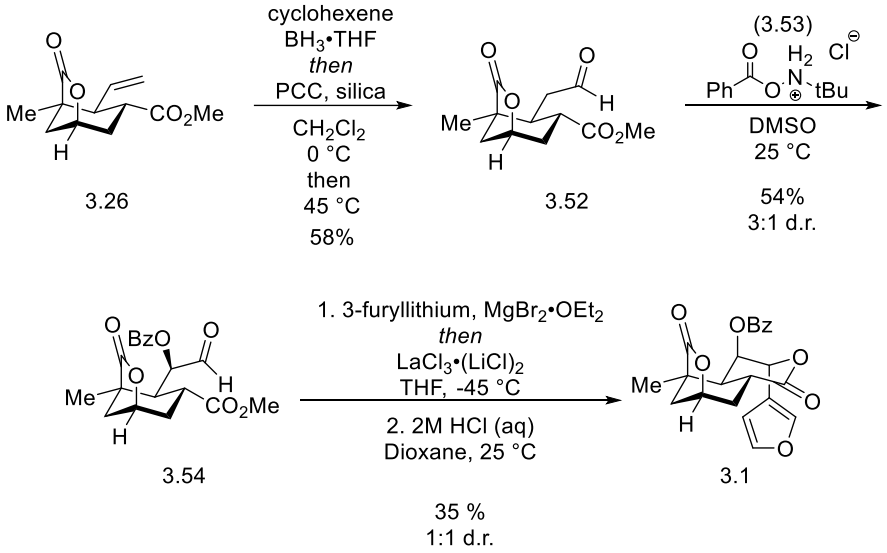
reaction, using odious Thallium (I) carboxylates rather than silver, so we attempted the dibenzoylation with TlOBz.[40,41] Despite milder conditions, olefin functionalization attempts were unfruitful, even with the addition of 18-crown-6 to make the benzoate more nucleophilic by sequestering the thallium counterions. We transformed model compound **3.25** into pivalic mixed anhydride **3.51** (in 91% yield) to minimize potential side reactions involving the carboxylic acid moiety, but subjecting pivalic mixed anhydride **3.51** to dibenzoylation conditions also proved ineffectual.

3.3.4.3. α-benzoylation and furyl addition to access collybolide

Since a dibenzoylated substrate remained elusive, we were forced, once again, to reevaluate our synthetic strategy, leaving furan incorporation until after benzoylation. This third-generation strategy to construct the furyl-δ-lactone centered upon terminal oxidation of olefin **3.26** to provide an aldehyde that could facilitate incorporation of both benzoyl and furyl moieties. Oxidation of the terminal olefin to the corresponding aldehyde proved to be a non-trivial endeavor, potentially again due to the olefin being hindered sterically. Hydroborations of **3.26** employing either 9-BBN or BH3•THF were unsuccessful, so we attempted to overcome this by utilizing a vinyl boronate as an aldehyde precursor instead of an alkylborane. The vinyl boronate (**3.S1**) was successfully prepared by a Boron-Wittig with aldehyde **3.36** despite the transitory alkoxide intermediate.[42] However, to our dismay, the vinyl boronate spurned our oxidation efforts.[43] An effective hydroboration of **3.26** was finally achieved with dicyclohexylborane, and aldehyde **3.52**was finally obtained in 58% yield by oxidation of the trialkylborane intermediate with PCC. In an effort to attenuate the steric influences that plagued previous steps, the α-oxygenation methodology developed by Tomkinson and coworkers was applied achieve α-benzoylation of **3.52** with the rational that a [3,3]-sigmatropic rearrangement to install the benzoate would be less inveigled by

the steric environment as compared to an intermolecular approach.[44,45] Using ammonium reagent **3.53**, aldehyde **3.52** was successfully benzoylated (Scheme 3.13) to afford aldehyde **3.54** in 54% yield. With the benzoyl moiety installed, the final challenge was installing the furan and cyclization to form the furyl-δ-lactone. Furyllithium was initially investigated due to its utility with the neocollybolide scaffold, but the furyllithium addition to densely functionalized **3.54** failed to deliver neither collybolide nor an alcohol substrate that could be transesterified. We then attempted to install the furan in a catalytic fashion using boron derived furan sources, with aldehyde **3.52** being used in exploratory reactions, yet rhodium, nickel, and zinc catalyzed furyl additions were fruitless. Rh/NHC catalyst systems resulted in too complex of a reaction mixture, likely due to the aqueous basic conditions required, and the aldehyde was unconsumed by base-free Ni/NHC or base-free Zn/amino-alcohol catalyst systems.[46-51]

Scheme 3.13. Successful construction of the furyl-δ-lactone and collybolide.



Upon noting that similar furan-related problems were encountered in Shenvi's synthesis, which employed an eerily similar endgame substrate (**3.25**), the addition of the furan was finally accomplished by employing a furyllanthanum reagent, and subsequent acid catalyzed transesterification (35% yield over two steps) finally provided collybolide **(3.1**) in 2% overall yield

in ten steps.[23,52] ^{1}H NMR (Figure 3.3) and ^{13}C NMR spectra both match with the isolated natural product (Table 3.2 and Table 3.3 respectively).

Figure 3.3. ^{1}H NMR spectrum of synthetic collybolide with the ^{1}H NMR spectrum[1] of the isolated natural product superimposed.

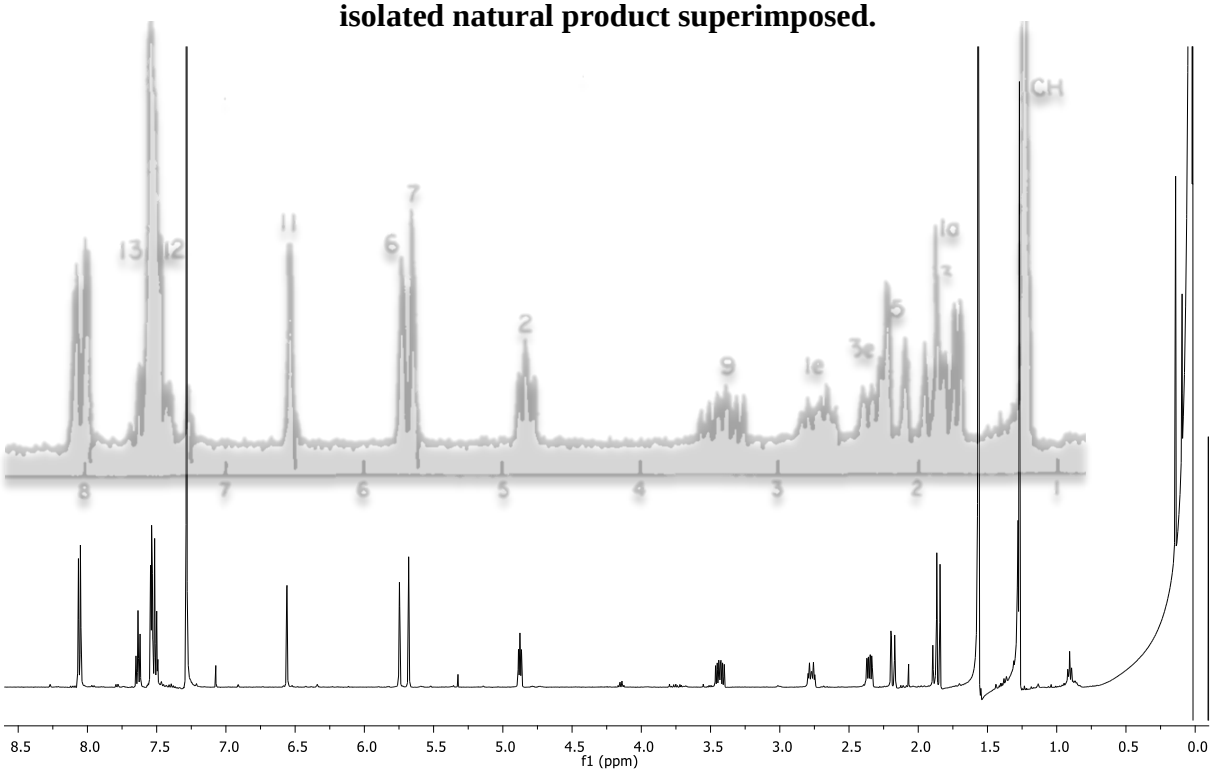
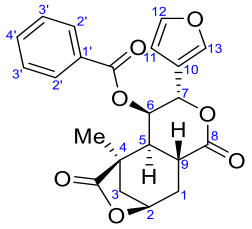


Table 3.2. ^{1}H NMR comparison of synthetic collybolide and isolated natural product.

	Isolated Collybolide (100 MHz, $CDCl_3$)[1]	Synthetic Collybolide (500 MHz, $CDCl_3$)	Δppm
Me	1.20	1.24	0.04
3e	2.27	2.33	0.06
3a	1.79	1.84	0.05
2	4.79	4.85	0.06
1e	2.69	2.71	0.02
1a	1.80	1.84	0.04
9	3.38	3.41	0.03
5	2.14	2.16	0.02
6	5.71	5.72	0.01
7	5.63	5.66	0.03
11	6.51	6.54	0.03
12 13	7.3-7.5	7.46-7.53	0.03
2'	-	8.02-8.05	-
3'	-	7.46-7.53	-
4'	-	7.61	-

Table 3.3. ^{13}C NMR comparison of synthetic collybolide and isolated natural product.



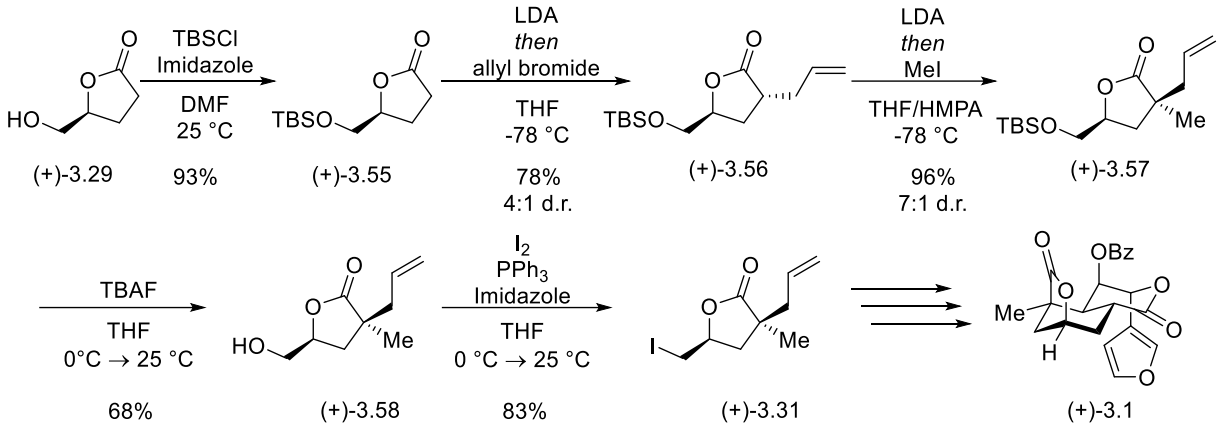
	Isolated Collybolide (100 MHz, $CDCl_3$)[1]	Synthetic Collybolide (126 MHz, $CDCl_3$)	Δppm
1	29.6	29.7	0.1
2	68.2	68.3	0.1
3	44.6	44.8	0.2
4	42.6	42.7	0.1
5	34.3	34.4	0.1
6	73.8	73.9	0.1
7	79.7	79.8	0.1
8	170.1	170.3	0.2
9	42.2	42.3	0.1
10	123.5	123.7	0.2
11	107.6	107.7	0.1
12	139.8	139.8	0.0
13	144.5	144.6	0.1
14	17.4	17.5	0.1
15	176.4	176.6	0.2
***C*OC$_6$H$_5$**	165.5	165.9	0.4
1'	128.5	128.6	0.1
2'	133.7	133.8	0.1
3'	128.5 130.0	128.7 130.2	0.2 0.2

3.3.5. Formal synthesis of enantiopure collybolide

To access enantiopure collybolide, we developed an asymmetric synthesis of iodolactone **3.8** (Scheme 3.14) which began with the TBS protection of commercially available (+)-hydroxymethyl-γ-butyrolactone **(+)-(3.29)** to afford silyl ether **(+)-3.55** in 93% yield. The requisite allyl moiety was installed by treating **(+)-3.55** with LDA and quenching the enolate with allyl bromide to give **(+)-3.56** in 78% yield. Since the TBS protecting group also serves as a directing group, the stereochemistry of the quaternary center was established when the enolate of **(+)-3.56** was quenched with methyl iodide furnishing **(+)-3.57** in 96% yield.[53,54] The silyl ether was cleaved

with TBAF to provide alcohol **(+)-3.58** in 68% yield, and an Appel reaction with **(+)-3.58** gave iodolactone **(+)-3.31,** an optically pure substitute for **3.31** in our reaction sequence, in 83% yield.

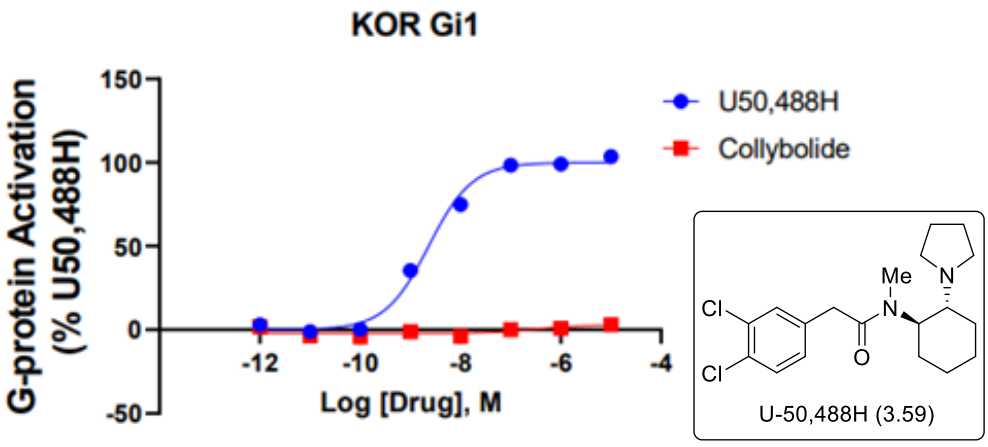
Scheme 3.14 Formal synthesis of optically pure collybolide.



3.3.6. Conclusions

In summary, the first racemic total synthesis of collybolide was achieved in 10 steps starting from 2-methyl-4-pentenoic acid as well as a formal synthesis to access enantiopure collybolide in 13 steps from hydroxymethyl-γ-butyrolactone. Accessing racemic collybolide allowed for an independent analysis of the compound's G-protein signaling, and the synthetic racemate did not demonstrate κOR agonism in the assay, as seen in Figure 3.4, when compared to the κOR control U50,488H (**3.59**).[55] The racemate's lack of G-protein activation reinforces Shenvi's assertion that neither enantiomer acts as a κOR ligand and that the natural product's reported activity is likely due to an unknown contaminant.

Figure 3.4. Synthetic collybolide racemate G-protein signaling compared to κ -opioid agonist standard U-50,488.



3.4. Experimental section

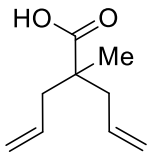
3.4.1. Materials and methods

Reactions were performed in flame-dried sealed tubes or modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper under a positive pressure of nitrogen or inside nitrogen filled glovebox unless otherwise noted. Air and moisture sensitive liquids and solutions were transferred via syringe. The appropriate starting materials and reagents were dried via azeotropic removal of water with toluene or heptane. Molecular sieves were activated at 200°C under vacuum. Organic solutions were concentrated by rotary evaporation below 40 °C. Flash column chromatography was performed employing 230–400 mesh silica gel. Dry column vacuum chromatography was performed with 500-800 mesh silica gel. Thin-layer chromatography was performed using glass plates pre-coated to a depth of 0.25 mm with 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm) and visualized with UV light (254 and 360 nm), iodine adsorbed onto silica, or stained with Ceric Ammonium Molybdate in concentrated H_2SO_4.

Dichloromethane, diethyl ether, DMF, dioxane, tetrahydrofuran, and toluene were purified by passage through two packed columns of neutral alumina under an argon atmosphere.[46] DMSO was distilled from CaH_2 below 1 torr. Amines were distilled from CaH_2 at 760 torr. Prior to use, 3-bromofuran was passed through a plug of basic alumina approximately a centimeter in length. All other chemicals were obtained from commercial vendors and were used without further purification unless otherwise noted.

Proton and carbon-13 nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on a Bruker Avance III instrument; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual proton in the NMR solvent (d-chloroform: δ 7.26 for ^{1}H NMR, δ 77.16 for ^{13}C NMR; d4-methanol: δ 3.31 for ^{1}H NMR, δ 49.00 for ^{13}C NMR). Data are presented as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), coupling constant in Hertz (Hz), integration.

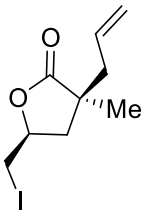
3.4.2. Synthesis of intermediate 3.27



2-methyl-2-(prop-2-en-1-yl)pent-4-enoic acid (3.30)

To a 500 mL Schlenk flask charged with stir bar and solution of Et_2NH (210 mmol, 21.7 mL, 3.0 equiv) in THF (60.0 mL) cooled to -78 °C, *n*-BuLi (2.50M in hexane, 210 mmol, 89.0 mL, 3.0 equiv) was slowly added. The reaction was stirred at -78 °C for 10 minutes before warming to 0 °C. After 30 minutes at 0 °C, the LDE solution was cooled back to -78 °C, and a solution of 2-methyl-4-pentenoic acid (70.0 mmol, 8.42 mL, 1.0 equiv) in THF (13.0 mL) was cannula transferred at -78 °C. Once the transfer was complete, the reaction was stirred at -78 °C for 10 minutes after which the cooling bath was removed, and the reaction was allowed to warm to ambient temperature. After stirring for an hour at ambient temperature, the

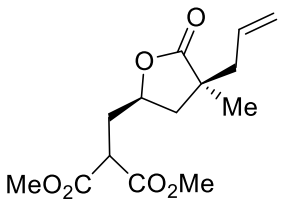
reaction was cooled back down to -78 °C. Allyl bromide (350 mmol, 42.3 mL, 5.0 equiv) was slowly added, and the reaction was allowed to gradually warm to ambient temperature overnight. The reaction was then quenched with 1M HCl and subsequently acidified to a pH of 2 or lower, the organic layer was separated, and the aqueous was extracted with Et_2O (200 mL X 2). The combined organic layers were washed with brine (50.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to afford **3.30** as a pale-yellow oil. **Yield** 70.0 mmol, 10.8 g, 99% **TLC** R_f 0.58 (1:4 EtOAc/Hexanes, I_2) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.17 (m, 2H), 6.58 – 6.52 (m, 4H), 3.78 (dddt, *J* = 66.6, 13.8, 7.6, 1.2 Hz, 4H), 2.61 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 183.7, 133.6, 118.6, 46.0, 42.7, 21.2. **HRMS** (ESI) *m/z* Calcd for $C_9H_{15}O_2$ $[M+H]^+$: 155.1067, found 155.1067.



(3*S*,5*S*)-5-(iodomethyl)-3-methyl-3-(prop-2-en-1-yl)oxolan-2-one (3.31)

To a 250 mL round bottom flask charged with stir bar and solution of **3.30** (18.1 mmol, 2.79 g, 1.0 equiv) in $CHCl_3$ (52.0 mL), iodine (36.2 mmol, 9.18 g, 2.0 equiv) was added followed by saturated aqueous $NaHCO_3$ (52.0 mL). The reaction was stirred at ambient temperature shielded from light until TLC indicated full consumption of starting material. Upon full consumption of the starting material, the reaction was quenched with saturated $Na_2S_2O_{3(aq)}$. Once the solution was devoid of color, the organic layer was separated, and the aqueous was extracted with DCM (30.0 mL X 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude mixture of diastereomers was purified via dry column vacuum chromatography (0% to 20% EtOAc in hexanes) to afford **3.31** as a yellow oil. **Yield** 8.20 mmol, 2.19 g, 45% **TLC** R_f 0.65 (1:1 EtOAc/Hexanes, I_2) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.71 (dddd, *J* = 16.8, 10.3, 8.5, 6.4 Hz, 1H), 5.19 – 5.10 (m, 2H), 4.46 (dddd, *J* = 9.7, 7.4, 6.2, 4.7 Hz, 1H), 3.40 (dd, *J* = 10.3, 4.7 Hz, 1H), 3.23 (dd, *J* = 10.3, 7.5 Hz, 1H), 2.44 – 2.38

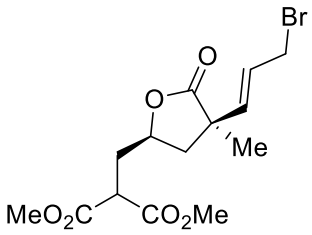
(m, 1H), 2.28 (dd, *J* = 13.9, 8.4 Hz, 1H), 2.15 (dd, *J* = 13.0, 6.2 Hz, 1H), 1.91 (dd, *J* = 13.0, 9.6 Hz, 1H), 1.26 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 180.2, 132.8, 119.8, 75.6, 44.8, 41.9, 40.5, 23.3, 7.0. **HRMS** (ESI) *m/z* Calcd for $C_9H_{14}O_2I$ $[M+H]^+$: 281.0033, found 281.0032.



dimethyl {[(2*R*,4*S*)-4-methyl-5-oxo-4-(prop-2-en-1-yl)oxolan-2-yl]methyl}propanedioate (3.27)

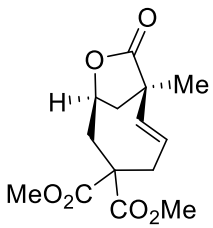
To a 50 mL Schlenk flask charged with stir bar and solution of KO*t*Bu (15.7 mmol, 1.76 g, 2.0 equiv) in DMF (24.0 mL) cooled to 0 °C, dimethyl malonate (15.7 mmol, 1.80 mL, 2.0 equiv) was slowly added. The reaction was stirred at 0 °C for 15 minutes followed by warming to ambient temperature. After 20 minutes at ambient temperature, a solution of **3.31** (7.84 mmol, 2.09 g, 1.0 equiv) in THF (18.0 mL) was cannula transferred to the enolate solution. Once the transfer was complete, the reaction was warmed to 70 °C and stirred for an additional 90 minutes after which it was quenched with saturated $NH_4Cl_{(aq)}$. The organic layer was separated, and the aqueous was extracted with Et_2O (60.0 mL + 40.0 mL X 2). The combined organic layers were washed with DI H_2O (30.0 mL X 3), rinsed with brine (20.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using silica gel chromatography (0% to 35% EtOAc in hexanes) to afford **3.27** as a colorless oil. **Yield** 6.96 mmol, 1.98 g, 89% **TLC** R_f 0.51 (1:1 EtOAc/Hexanes, CAM stain) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.69 (dddd, *J* = 16.7, 10.2, 8.4, 6.3 Hz, 1H), 5.18 – 5.09 (m, 2H), 4.46 (tdd, *J* = 9.6, 6.1, 3.2 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.71 – 3.64 (m, 1H), 2.42 – 2.35 (m, 1H), 2.35 – 2.23 (m, 2H), 2.10 (ddd, *J* = 14.5, 9.6, 4.9 Hz, 1H), 2.02 (dd, *J* = 12.8, 6.1 Hz, 1H), 1.88 (dd, *J* = 12.9, 9.9 Hz, 1H), 1.24 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 179.6, 168.6, 168.6, 132.6, 118.9, 74.1, 52.2, 52.2, 47.8, 43.4, 41.4, 39.0, 34.3, 22.2. **HRMS** (ESI) *m/z* Calcd for $C_{14}H_{21}O_6$ $[M+H]^+$: 285.1333, found 285.1332.

3.4.3. Synthesis of intermediate 3.26



dimethyl ({(3*R*,5*R*)-3-[(*E*)-3-bromo-1-propenyl]-3-methyl-2-oxo-4,5-dihydro-5-furyl}methyl)malonate (3.32)

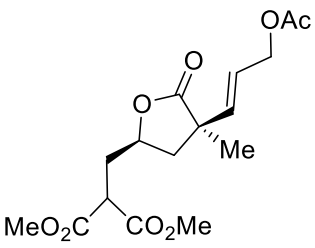
To a two-dram vial charged with stir bar and **3.27** (0.246 mmol, 70.0 mg, 1.0 equiv), NBS (0.246 mmol, 44.0 mg, 1.0 equiv) was added followed by degassed MeCN (4.0 mL). The vial was sealed, and the reaction was irradiated by a 34.0 W blue LED Kessil Lamp while stirring (distance from lamp was 5.0 cm). After four hours, the irradiation was halted. The reaction was quenched with saturated $Na_2S_2O_{3(aq)}$ and diluted to 8.0 mL with EtOAc. The organic layer was separated, and the aqueous was extracted with EtOAc (10.0 mL X 3). The combined organic layers were washed with DI H_2O (5.0 mL), rinsed with brine (5.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using silica gel chromatography (0% to 20% EtOAc in hexanes) to afford **3.32** as a pale-orange oil. **Yield** 0.129 mmol, 47.0 mg, 53% **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.94 (d, *J* = 16.0 Hz, 1H), 5.80 (dt, *J* = 15.3, 7.6 Hz, 1H), 4.53 (tdd, *J* = 9.4, 6.0, 3.0 Hz, 1H), 3.99 – 3.92 (m, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 3.69 (dd, *J* = 10.0, 4.8 Hz, 1H), 2.38 – 2.31 (m, 1H), 2.28 (dd, *J* = 12.9, 5.9 Hz, 1H), 2.14 (ddd, *J* = 14.5, 9.9, 4.9 Hz, 1H), 2.05 – 2.00 (m, 1H), 1.35 (d, *J* = 2.5 Hz, 3H).



dimethyl (1*R*,2*E*,7*S*)-1-methyl-9-oxo-8-oxabicyclo[5.2.1]dec-2-ene-5,5-dicarboxylate (3.33)

To a 50 mL Schlenk flask charged with stir bar and suspension of K_2CO_3 (1.19 mmol, 165 mg, 1.1 equiv) in DMF (21.0 mL) cooled to 0 °C, a solution of **3.32** (1.09 mmol, 395 mg, 1.0 equiv) in DMF (4.0 mL) was slowly added. The reaction was stirred at 0 °C for 15 minutes followed by warming to ambient temperature. The reaction was stirred at ambient temperature overnight after which it was quenched with saturated $NH_4Cl_{(aq)}$ and diluted

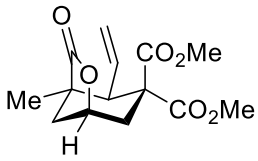
with DI H_2O (20.0 mL). The aqueous solution was extracted with EtOAc (75.0 mL X 3), and the combined organic layers were washed with DI H_2O (10.0 mL X 2), rinsed with brine (10.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using silica gel chromatography (0% to 50%EtOAc in hexanes) to afford **3.33** as a white solid. **Yield** 0.686 mmol, 194 mg, 63% **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.62 (d, *J* = 15.7 Hz, 1H), 5.44 – 5.35 (m, 1H), 4.46 – 4.38 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 2.90 – 2.81 (m, 1H), 2.71 (ddd, *J* = 14.3, 6.8, 1.4 Hz, 1H), 2.33 (dd, *J* = 13.6, 9.1 Hz, 1H), 2.28 – 2.23 (m, 1H), 2.20 – 2.10 (m, 2H), 1.31 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 179.2, 170.9, 170.8, 138.2, 124.3, 74.6, 57.1, 53.0, 45.1, 40.2, 38.9, 36.7, 26.4.



dimethyl ({(3*R*,5*R*)-3-[(*E*)-3-acetoxy-1-propenyl]-3-methyl-2-oxo-4,5-dihydro-5-furyl}methyl)malonate (3.34)

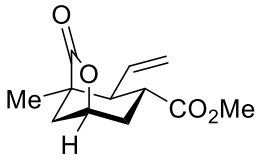
To a 10 mL Erlenmeyer flask charged with stir bar and **3.27** (2.08 mmol, 590 mg, 1.0 equiv), $Pd(OAc)_2$ trimer (0.415 mmol, 93.2 mg, 0.2 equiv) was added followed by 4,5-diazafluoren-9-one (0.519 mmol, 94.6 mg, 0.3 equiv), NaOAc (0.415 mmol, 34.0 mg, 0.2 equiv), AcOH (33.2 mmol, 1.90 mL, 16.0 equiv), and dioxane (4.00 mL). The solution was purged with O_2 for 10 minutes, the flask was outfitted with a polypropylene cap punctured with an 18G needle, and the reaction was placed in a Parr pressure reactor. The pressure reactor was purged with O_2, pressurized to 60 psi, and heated at 65 °C. After 2 days, the reaction was removed from the pressure vessel and concentrated. The residue was redissolved in DCM (15.0 mL), filtered through a celite plug, and concentrated. The crude was purified using silica gel chromatography (0% to 50% EtOAc in hexanes) to afford **3.34** as a slightly yellow oil. **Yield:** 1.12 mmol, 576 mg, 81% **TLC** R_f 0.36 (1:1 EtOAc/Hexanes, I_2 or CAM stain) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.91 (dt, *J* = 15.8, 1.4 Hz, 1H), 5.70 – 5.64 (m, 1H), 4.55 – 4.48 (m, 2H),

3.74 (s, 3H), 3.72 (s, 3H), 3.65 (dd, *J* = 9.6, 5.0 Hz, 1H), 2.31 (ddd, *J* = 14.4, 9.6, 3.3 Hz, 1H), 2.24 (dd, *J* = 12.8, 6.1 Hz, 1H), 2.14 (dd, *J* = 9.7, 5.0 Hz, 1H), 2.03 (s, 3H), 1.33 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 178.4, 170.77, 169.2, 169.2, 135.89, 124.9, 74.8, 64.4, 52.9, 52.9, 48.3, 46.0, 41.3, 34.9, 23.4, 21.0. **HRMS** (ESI) *m/z* Calcd for $C_{16}H_{23}O_8$ $[M+H]^+$: 343.1387, found 343.1387.



dimethyl (5*S*)-2-ethenyl-1-methyl-7-oxo-6-oxabicyclo[3.2.1]octane-3,3-dicarboxylate (3.35)

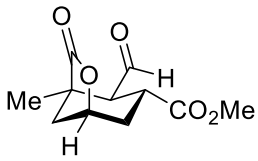
To eleven 20 mL vials each charged with stir bar and **3.11** (0.449 mmol, 154 mg, 1.0 equiv), $Pd(OAc)_2$ (0.0449 mmol, 10.1 mg, 0.1 equiv) was added in a nitrogen atmosphere glovebox followed by triclyclohexylphosphine (0.0989 mmol, 22.8 mg, 0.2 equiv), K_3PO_4 (1.79 mmol, 382 mg, 4.0 equiv), and degassed dioxane (15.0 mL). The vials were sealed with PTFE lined caps and moved to a fume hood where they were stirred at 100 °C. After 5 hours, the reactions were cooled then pooled, diluted with Et_2O (150 mL), filtered through a plug of celite, and concentrated. The crude residue was purified using silica gel chromatography (0% to 35% EtOAc in hexanes) to afford **3.12** as a yellow solid. **Yield** 2.21 mmol, 779 mg, 56% **TLC** R_f 0.42 (1:1 EtOAc/Hexanes, I_2 or CAM stain) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.10 (dt, J = 17.0, 10.2 Hz, 1H), 4.97 (dd, J = 10.1, 1.9 Hz, 1H), 4.86 (dd, J = 17.0, 1.8 Hz, 1H), 4.64 (ddd, J = 6.0, 4.5, 1.4 Hz, 1H), 3.57 (s, 3H), 3.56 (s, 3H), 2.89 (ddd, J = 14.8, 4.6, 1.9 Hz, 1H), 2.68 (d, J = 10.3 Hz, 1H), 2.27 – 2.16 (m, 2H), 1.86 (d, J = 11.8 Hz, 1H), 1.01 (s, 3H). **^{13}C NMR** (126 MHz, CDCl3) δ 177.7, 171.9, 170.0, 134.8, 119.0, 74.0, 58.9, 55.6, 53.1, 52.6, 45.0, 43.0, 36.1, 19.8. **HRMS** (ESI) *m/z* Calcd for $C_{14}H_{19}O_6$ $[M+H]^+$: 283.1176 , found 283.1175.



methyl (3*R*,5*R*)-2-ethenyl-1-methyl-7-oxo-6-oxabicyclo[3.2.1]octane-3-carboxylate (3.26)

To a 25 mL Schlenk tube charged with stir bar and **3.35** (1.20 mmol, 339 mg, 1.0 equiv), DABCO (4.80 mmol, 539 mg, 4.0 equiv) was added followed by PhMe (12.0 mL) and DI H_2O (24.0 mmol, 433 µL, 20.0 equiv). The tube was sealed and heated at 110 °C for 18 hours. Once cooled, the reaction was diluted with 10.0 mL of EtOAc and quenched with 1M HCl. The organic layer was separated, and the aqueous was extracted with EtOAc (50.0 mL + 30.0 mL X 2). The combined organics were washed with 1M HCl (10.0 mL X 2) then brine (10.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using silica gel chromatography (0% to 35% EtOAc in hexanes) to afford **3.26** as a white solid with a 20:1 ratio of diastereomers. **Yield** 0.803 mmol, 180 mg, 67% **TLC** R_f 0.62 (1:1 EtOAc/Hexanes, I_2 or CAM stain) **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.51 (dt, *J* = 16.9, 9.9 Hz, 1H), 5.07 – 4.98 (m, 2H), 4.73 (t, *J* = 5.4 Hz, 1H), 3.58 (d, *J* = 1.1 Hz, 3H), 2.58 (td, *J* = 11.5, 6.5 Hz, 1H), 2.42 (dd, *J* = 11.4, 9.6 Hz, 1H), 2.25 (dddd, *J* = 11.2, 7.0, 4.6, 2.3 Hz, 2H), 1.86 (d, *J* = 11.8 Hz, 1H), 1.72 (dd, *J* = 13.8, 11.6 Hz, 1H), 1.08 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 178.1, 173.9, 135.0, 118.8, 74.4, 51.8, 50.7, 43.6, 43.6, 43.6, 31.6, 19.3. **HRMS** (ESI) *m/z* Calcd for $C_{12}H_{17}O_4$ $[M+H]^+$: 255.1121, found 255.1122.

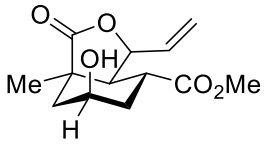
3.4.4. Functionalization with vinyl Grignard



methyl (3*R*,5*R*)-2-formyl-1-methyl-7-oxo-6-oxabicyclo[3.2.1]octane-3-carboxylate (3.36)

To a 50 mL three-neck flask charged with stir bar and solution of **3.26** (1.75 mmol, 392 mg, 1.0 equiv) in DCM (7.00 mL) cooled to -78 °C, O_3 was passed through the reaction solution until a royal blue coloration developed. At this point, the O_3 flow was stopped, and N_2

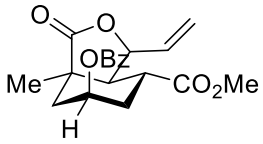
was passed through the solution until the coloration dissipated. The reaction was then quenched at -78 °C with DMS (35.0 mmol, 2.57 mL, 20.0 equiv), and the solution was stirred at -78 °C for an additional 10 minutes after which the bath was removed allowing the reaction to gradually warm to ambient temperature as it stirred overnight. The reaction was diluted with DCM (13.0 mL), washed with DI H_2O (5.00 mL X 3), rinsed with brine (5.00 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to afford **3.36** as a white solid. **Yield** 1.70 mmol, 385 mg, 97% **TLC** R_f 0.34 (1:1 EtOAc/Hexanes, CAM stain) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.67 (d, *J* = 3.1 Hz, 1H), 4.84 (dd, *J* = 6.0, 4.7 Hz, 1H), 3.67 (s, 3H), 3.17 (td, *J* = 11.7, 6.9 Hz, 1H), 2.72 (dd, *J* = 11.6, 3.1 Hz, 1H), 2.50 (dddd, *J* = 13.6, 6.6, 4.6, 1.8 Hz, 1H), 2.28 (ddd, *J* = 12.0, 6.2, 1.8 Hz, 1H), 1.94 (d, *J* = 12.0 Hz, 1H), 1.77 (ddd, *J* = 14.1, 11.7, 1.0 Hz, 1H), 1.38 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 199.3, 176.9, 173.1, 74.3, 55.7, 52.6, 43.8, 43.4, 36.8, 30.5, 18.9. **HRMS** (ESI) *m/z* Calcd for $C_{11}H_{15}O_5$ $[M+H]^+$: 227.0914, found 227.0915.



methyl (4*R*,6*R*)-3-ethenyl-6-hydroxy-7a-methyl-1-oxooctahydro-2-benzofuran-4-carboxylate (3.37)

To a 25 mL Schlenk flask charged with stir bar and solution of **3.36** (1.63 mmol, 396 mg, 1.0 equiv) in THF (16.0 mL) cooled to 0 °C, a solution of vinyl magnesium chloride (2.00M in THF, 1.63 mmol, 816 µL, 1.0 equiv) was slowly added. The reaction was stirred for an hour at 0 °C, and subsequently it was quenched at 0 °C with saturated $NH_4Cl_{(aq)}$. The organic layer was separated, and the aqueous was extracted with EtOAc (30.0 mL + 20.0 mL X 2). The combined organic layers were washed with DI H_2O (20.0 mL), rinsed with brine (20.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using silica gel chromatography (0% to 50% EtOAc in hexanes) to afford **3.37** as a white solid. **Yield** 1.04 mmol, 264 mg, 64% **TLC** R_f 0.42 (1:1 EtOAc/Hexanes, I_2 or CAM stain) **^{1}H NMR** (500 MHz, $CDCl_3$)

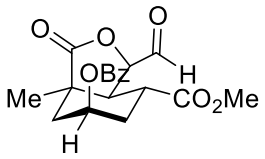
δ 5.77 (ddd, *J* = 17.2, 10.8, 5.5 Hz, 1H), 5.50 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.29 (dt, *J* = 10.8, 1.4 Hz, 1H), 5.16 – 5.11 (m, 1H), 4.19 (dq, *J* = 4.8, 2.6 Hz, 1H), 3.65 (s, 3H), 2.96 (ddd, *J* = 13.0, 11.2, 4.0 Hz, 1H), 2.76 (dd, *J* = 11.2, 4.9 Hz, 1H), 2.38 (dt, *J* = 15.1, 2.7 Hz, 1H), 2.10 (dtd, *J* = 13.4, 4.1, 2.3 Hz, 1H), 1.66 (s, 1H), 1.57 (dd, *J* = 15.0, 2.8 Hz, 1H), 1.41 (td, *J* = 13.2, 1.9 Hz, 1H), 1.35 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 180.8, 176.4, 131.0, 119.0, 79.6, 63.9, 52.0, 46.3, 41.3, 38.9, 34.1, 33.6, 24.8. **HRMS** (ESI) *m/z* Calcd for $C_{13}H_{19}O_5$ $[M+H]^+$: 255.1227, found 255.1227.



methyl (4*R*,6*R*)-6-(benzoyloxy)-3-ethenyl-7a-methyl-1-oxooctahydro-2-benzofuran-4-carboxylate (3.38)

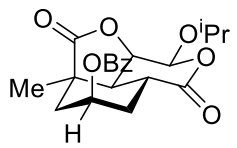
To a 10 mL Schlenk flask charged with stir bar and solution of **3.37** (0.653 mmol, 166 mg, 1.0 equiv) in DCM (6.5 mL) cooled to 0 °C, Et_3N (6.53 mmol, 910 µL, 10.0 equiv) was added followed by DMAP (0.131 mmol, 16.0 mg, 0.2 equiv) and BzCl (1.96 mmol, 228 µL, 3.0 equiv). After stirring for 15 minutes at 0 °C, the reaction was allowed to warm to ambient temperature at which it was stirred until TLC indicated consumption of the starting material. The reaction was quenched with saturated aqueous $NaHCO_3$ and diluted to 10 mL with DCM. The organic layer was separated, and the aqueous was extracted with DCM (20.0 mL X 3). The combined organic layers were washed with DI H_2O (5.0 mL), rinsed with brine (5.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using silica gel chromatography (0% to 20% EtOAc in hexanes) to afford **3.38** as a white solid. **Yield** 0.396 mmol, 142 mg, 61% **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 – 7.98 (m, 2H), 7.59 – 7.54 (m, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 5.77 (ddd, *J* = 16.7, 10.8, 5.3 Hz, 1H), 5.50 (dt, *J* = 17.3, 1.5 Hz, 1H), 5.35 (q, *J* = 3.0 Hz, 1H), 5.32 – 5.27 (m, 1H), 5.16 (t, *J* = 5.2 Hz, 1H), 3.65 (s, 3H), 2.85 (dd, *J* = 11.3, 4.9 Hz, 1H), 2.77 (ddd, *J* = 13.0, 11.2, 3.8 Hz, 1H), 2.71 (dt, *J* = 15.1, 2.6 Hz, 1H), 2.36 (dq, *J* = 13.9, 3.8 Hz, 1H), 1.65 (dd, *J* = 15.2, 3.3 Hz, 1H), 1.61 (dd, *J* = 13.5, 2.0 Hz, 1H), 1.42 (s, 3H). **^{13}C NMR**

(126 MHz, $CDCl_3$) δ 179.0, 175.6, 164.7, 133.2, 131.1, 129.9, 128.7, 119.1, 79.2, 67.3, 52.2, 46.3, 41.8, 35.8, 35.4, 31.8, 25.3.



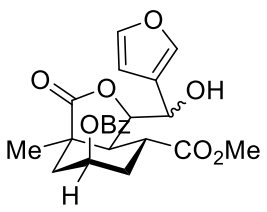
methyl 6-(benzoyloxy)-3-formyl-7a-methyl-1-oxooctahydro-2-benzofuran-4-carboxylate (3.39)

To a one-dram vial charged with stir bar and solution of **3.38** (0.650 mmol, 233 mg, 1.0 equiv) in DCM (2.5 mL) cooled to -78 °C, O_3 was passed through the reaction solution until a royal blue coloration developed. At this point, the O_3 flow was stopped, and N_2 was passed through the solution until the coloration dissipated. The reaction was then quenched at -78 °C with DMS (13.0 mmol, 955 μL, 20.0 equiv), and the solution was stirred at -78 °C for an additional 10 minutes after which the bath was removed, allowing the reaction to gradually warm to ambient temperature as it stirred overnight. The reaction was diluted with DCM (15.0 mL), washed with DI H_2O (5.00 mL X 2), rinsed with brine (5.00 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using silica gel chromatography (0% to 50% EtOAc in hexanes) to afford **3.39** as a white solid. **Yield** 0.141 mmol, 148 mg, 63% **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.71 (d, *J* = 1.3 Hz, 1H), 7.97 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.56 – 7.52 (m, 1H), 7.46 – 7.42 (m, 2H), 5.32 (dq, *J* = 5.3, 3.0 Hz, 1H), 5.00 (dd, *J* = 5.3, 1.4 Hz, 1H), 3.63 (s, 3H), 3.11 (dd, *J* = 11.0, 5.3 Hz, 1H), 2.80 (ddd, *J* = 13.0, 11.0, 4.0 Hz, 1H), 2.66 (dt, *J* = 15.2, 2.6 Hz, 1H), 2.34 (dtd, *J* = 14.1, 4.1, 2.1 Hz, 1H), 1.66 (dd, *J* = 15.2, 3.3 Hz, 1H), 1.60 (ddd, *J* = 14.1, 13.0, 2.1 Hz, 1H), 1.36 (s, 3H).



8-isopropoxy-2a-methyl-2,6-dioxo-2a,3,4,5,5a,8,8a,8b-octahydro-1,7-dioxa-4-acenaphthylenyl benzoate (3.40)

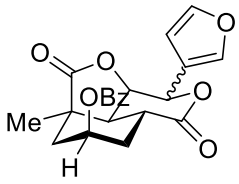
To a 1 mL Schlenk tube charged with stir bar and solution of (3-furyl)Ti(O^iPr)$_3$ (0.50M in PhMe, 0.055 mmol, 111 µL, 2.0 equiv) cooled to 0 °C, a solution of **3.39** in THF (240 µL) was slowly added. After stirring for an hour at 0 °C, the reaction was quenched at 0 °C with saturated aqueous $Na_2S_2O_3$. Once warmed to ambient temperature, saturated aqueous sodium tartrate (500 µL) was added, and the reaction was stirred for another five minutes; the reaction was then diluted with 10 mL of EtOAc. The organic layer was separated, and the aqueous was extracted with EtOAc (10.0 mL X 2). The combined organic layers were washed with DI H_2O (5.0 mL), rinsed with brine (5.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using silica gel chromatography (0% to 20% EtOAc in hexanes) to afford **3.40** as a white solid. **Yield** 0.154 mmol, 6.00 mg, 55% **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 – 7.94 (m, 2H), 7.56 (td, *J* = 7.3, 1.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 5.46 (h, *J* = 2.6 Hz, 1H), 5.37 (d, *J* = 4.4 Hz, 1H), 4.76 (t, *J* = 4.9 Hz, 1H), 4.11 (hept, *J* = 6.2 Hz, 1H), 2.68 (dt, *J* = 15.7, 2.2 Hz, 1H), 2.53 (tt, *J* = 12.7, 3.0 Hz, 2H), 2.22 (dd, *J* = 12.8, 5.5 Hz, 1H), 1.73 – 1.67 (m, 2H), 1.35 (s, 3H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.26 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.5, 171.1, 165.6, 133.4, 129.9, 129.9, 128.7, 102.0, 78.9, 73.6, 67.3, 44.4, 41.8, 34.9, 33.6, 27.4, 24.5, 23.3, 21.6.



methyl (4*R*)-6-benzoyloxy-3-[(3-furyl)hydroxymethyl]-7a-methyl-1-oxooctahydro-4-isobenzofuroate (3.42)

To a 10 mL Schlenk tube charged with stir bar and solution of 3-bromofuran (0.033 mmol, 3.00 µL, 1.2 equiv) in THF (500 µL) cooled to -78 °C, n-BuLi (2.85M in hexane, 0.033 mmol, 11.6 µL, 1.2 equiv) was added, and the reaction was stirred at -78

°C for 30 minutes. The solution of furyllithium was cannula transferred, at -78 °C, to a solution of **3.39** (0.028 mmol, 10.0 mg, 1.0 equiv) in THF (300 μL) cooled to -78 °C, and the reaction was maintained at -78 °C until TLC indicated consumption of starting material. After 45 minutes, the reaction was quenched at -78 °C with saturated aqueous NH_4Cl and allowed to warm to ambient temperature. The organic layer was then separated, and the aqueous was extracted with EtOAc (6.00 mL X 3). The combined organic layers were washed with brine (3.00 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using preparative TLC (50% EtOAc in hexanes) to afford diastereomers of **3.42** in a 1:1 ratio as white residue. **Yield** 0.009 mmol, 4.00 mg, 34% **^{1}H NMR$_A$** (600 MHz, $CDCl_3$) δ 8.05 – 8.00 (m, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.39 (d, *J* = 2.1 Hz, 1H), 6.45 (t, *J* = 2.3 Hz, 1H), 5.34 (s, 1H), 5.06 (dd, *J* = 22.9, 5.3 Hz, 2H), 3.60 (s, 3H), 3.22 – 3.14 (m, 1H), 2.93 (dd, *J* = 11.2, 4.9 Hz, 1H), 2.71 (d, *J* = 15.1 Hz, 1H), 2.60 (s, 1H), 2.40 (d, *J* = 14.3 Hz, 1H), 1.69 (dd, *J* = 15.1, 3.4 Hz, 1H), 1.59 (dd, *J* = 22.7, 9.4 Hz, 2H), 1.46 (s, 3H). **^{1}H NMR$_B$** (600 MHz, CDCl3) δ 8.04 – 8.00 (m, 2H), 7.58 – 7.54 (m, 1H), 7.49 – 7.45 (m, 3H), 7.39 (s, 1H), 6.52 – 6.49 (m, 1H), 4.94 (d, *J* = 3.4 Hz, 1H), 4.81 (dd, *J* = 5.0, 3.3 Hz, 1H), 3.64 (s, 3H), 3.38 – 3.31 (m, 1H), 2.88 (dd, *J* = 11.0, 5.0 Hz, 1H), 2.70 (d, *J* = 15.6 Hz, 1H), 2.43 (d, *J* = 14.6 Hz, 1H), 1.69 (dd, *J* = 15.2, 3.6 Hz, 1H), 1.59 (td, *J* = 13.8, 2.1 Hz, 2H), 1.43 (s, 3H).



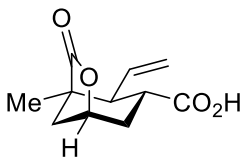
8-(3-furyl)-2a-methyl-2,6-dioxo-2a,3,4,5,5a,8,8a,8b-octahydro-1,7-dioxa-4-acenaphthylenyl benzoate (3.41)

To a 1 mL Schlenk tube charged with stir bar, a few activated 4A molecular sieves, and solution of **3.42** (0.004 mmol, 1.60 mg, 1.0 equiv) in DCM (200 μL), $Ti(O^iPr)_4$ (0.005 mmol, 1.3 μL, 1.2 equiv) was added at ambient temperature. After stirring overnight at ambient temperature, the reaction was diluted to 1.00 mL with DCM and quenched with saturated aqueous

sodium tartrate. The organic layer was then separated, and the aqueous was extracted with DCM (5.00 mL X 3). The combined organic layers were washed with brine (3.00 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using preparative TLC (25% Et_2O in PhMe) to afford **3.41. Yield <1 mg ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.59 – 7.55 (m, 1H), 7.47 – 7.41 (m, 3H), 7.05 – 7.04 (m, 1H), 6.45 (d, *J* = 2.0 Hz, 1H), 6.18 (d, *J* = 9.1 Hz, 1H), 5.52 (q, *J* = 3.1 Hz, 1H), 5.35 (dd, *J* = 9.2, 4.9 Hz, 1H), 3.60 (td, *J* = 12.7, 2.9 Hz, 1H), 2.71 (dt, *J* = 15.5, 2.3 Hz, 1H), 2.66 – 2.61 (m, 1H), 2.40 (dd, *J* = 13.1, 4.9 Hz, 1H), 1.73 (dt, *J* = 14.0, 2.4 Hz, 2H), 1.38 (s, 3H).

The diastereomer **3.42'** (0.004 mmol, 1.5 mg) was transesterified using the same procedure to provide **3.41'**. **Yield <1 mg ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.74 – 7.70 (m, 2H), 7.64 (s, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.44 – 7.37 (m, 3H), 6.49 (s, 1H), 6.04 (d, *J* = 8.5 Hz, 1H), 5.43 (s, 1H), 5.34 (dd, *J* = 8.5, 5.2 Hz, 1H), 3.48 (q, *J* = 7.0 Hz, 1H), 3.01 – 2.91 (m, 1H), 2.70 (d, *J* = 15.6 Hz, 1H), 2.46 – 2.37 (m, 2H), 1.70 – 1.64 (m, 2H), 1.38 (s, 3H).

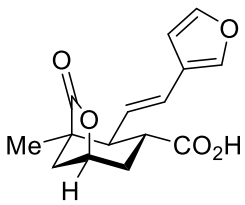
3.4.5. Synthesis of furan-substituted *trans*-olefin 3.46



(3*R*,5*R*)-2-ethenyl-1-methyl-7-oxo-6-oxabicyclo[3.2.1]octane-3-carboxylic acid (3.45)

To a 25 mL Schlenk tube charged with stir bar and **3.26** (0.303 mmol, 68.0 mg, 1.0 equiv), LiI (1.52 mmol, 203 mg, 5.0 equiv) was added followed by anhydrous pyridine (3.00 mL). The tube was sealed and heated at 125 °C for 2 days after which it was quenched with 1M HCl at ambient temperature, acidified to pH 2 or below, and diluted with EtOAc (10.0 mL). The organic layer was separated, and the aqueous was extracted with EtOAc (15.0 mL + 10.0 mL X 2). The combined organic layers were washed with 1M HCl (10 mL x2), rinsed with DI H_2O (10.0 mL) then brine (10.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to afford

3.45 as a white solid. **Yield** 0.290 mmol, 62.0 mg, 97% **TLC** R_f 0.40 (1:1 EtOAc/Hexanes +1% AcOH, I_2 or CAM stain) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.52 (dt, *J* = 16.8, 9.9 Hz, 1H), 5.10 – 5.02 (m, 2H), 4.74 (t, *J* = 5.4 Hz, 1H), 2.59 (td, *J* = 11.5, 6.4 Hz, 1H), 2.41 (t, *J* = 10.5 Hz, 1H), 2.36 – 2.29 (m, 1H), 2.25 (ddd, *J* = 12.0, 6.3, 1.9 Hz, 1H), 1.84 (d, *J* = 11.8 Hz, 1H), 1.72 (t, *J* = 12.7 Hz, 1H), 1.09 (s, 3H). **^{13}C NMR** (126 MHz, MeOD) δ 179.3, 175.4, 135.2, 117.8, 75.2, 50.2, 43.9, 43.5, 43.1, 31.4, 18.3. **HRMS** (ESI) *m/z* Calcd for $C_{11}H_{15}O_4$ $[M+H]^+$: 211.0965, found 211.0964.

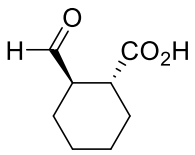


methyl (3*S*)-2-[(*E*)-2-(3-furyl)ethenyl]-1-methyl-7-oxo-6-oxabicyclo[3.2.1]octane-3-carboxylate (3.46)

To a 10 mL Schlenk tube charged with stir bar and **3.45** (0.295 mmol, 62.0 mg, 1.0 equiv), $Pd(OAc)_2$ (0.0295 mmol, 6.60 mg, 0.1 equiv) was added in a nitrogen atmosphere glovebox followed by XPhos (0.0589 mmol, 28.0 mg, 0.2 equiv) and K_2CO_3 (1.18 mmol, 163 mg, 4.0 equiv) The tube was sealed and moved to a fume hood where degassed DMF (3.00 mL) was added. After stirring for 5 minutes at ambient temperature, 3-bromofuran (0.723 mmol, 65.0 µL, 2.5 equiv) was added. The reaction was heated at 80 °C until TLC indicated consumption of starting material after which it was subsequently quenched at ambient temperature with 1M HCl, acidified to pH 2 or below, and diluted with EtOAc (15.0 mL). The organic layer was separated, and the aqueous was extracted with EtOAc (10.0 mL X 3). The combined organic layers were washed with 1M HCl (10.0 mL) followed by 1:1 1M HCl/brine (10.0 mL X 4), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using acidified silica gel chromatography (0% to 35% EtOAc in hexanes +1% AcOH) to afford **3.46** as a white solid. **Yield** 0.221 mmol, 61.0 mg, 75% **TLC** R_f 0.42 (1:1 EtOAc/Hexanes +1% AcOH, I_2 or CAM stain) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 (dq, *J* = 3.3, 1.3 Hz, 2H), 6.52 (t, *J* = 2.0 Hz, 1H), 6.30 (d, *J*

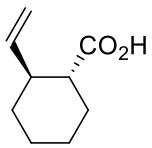
= 15.7 Hz, 1H), 5.66 (dd, *J* = 15.6, 9.7 Hz, 1H), 4.84 – 4.80 (m, 1H), 2.72 (td, *J* = 11.5, 6.4 Hz, 1H), 2.58 (dd, *J* = 11.4, 9.6 Hz, 1H), 2.41 (dddd, *J* = 13.3, 6.4, 4.5, 1.9 Hz, 1H), 2.34 (ddd, *J* = 11.9, 6.2, 1.9 Hz, 1H), 1.92 (d, *J* = 11.8 Hz, 1H), 1.79 (ddd, *J* = 13.7, 11.6, 0.9 Hz, 1H), 1.16 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 178.3, 177.3, 143.7, 140.7, 125.6, 124.1, 123.6, 107.8, 74.4, 49.8, 44.2, 43.8, 43.5, 32.0, 19.7. **HRMS** (ESI) *m/z* Calcd for $C_{15}H_{17}O_5$ $[M+H]^+$: 177.1071, found 277.1071.

3.4.6. Synthesis of furan-substituted *trans*-olefin model compounds



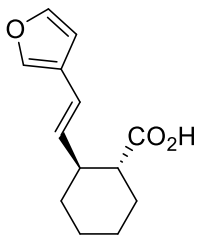
(1*R*,2*R*)-2-formylcyclohexane-1-carboxylic acid (3.49)

To a 100 mL Schlenk flask charged with stir bar and solution of $LiAlH(O^tBu)_3$ (1.0M in THF, 8.50 mmol, 8.5 mL, 1.3 equiv) in THF (48 mL) cooled to -78 °C, a solution of *trans*-1,2-cyclohexanedicarboxylic anhydride (6.49 mmol, 1.00 g, 1.0 equiv) in THF (28 mL) was cannula transferred under positive nitrogen pressure, and the reaction was maintained at -78 °C until TLC indicated consumption of starting material. After seven hours, the reaction was quenched at -78 °C with 3M HCl and allowed to warm to ambient temperature overnight. The product was extracted into EtOAc (75 mL X 3), and the combined organic layers were washed with brine (30.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using acidified silica gel chromatography (0% to 10% EtOAc in hexanes +1% AcOH) to afford **3.49** as a white solid. **Yield** 4.12 mmol, 643 mg, 63% **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 2.69 – 2.61 (m, 1H), 2.57 (td, *J* = 10.7, 3.9 Hz, 1H), 2.17 – 2.02 (m, 2H), 1.86 – 1.74 (m, 2H), 1.49 – 1.13 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.8, 181.2, 51.0, 42.5, 28.6, 25.2, 25.1, 25.0.



(1*R*,2*S*)-2-ethenylcyclohexane-1-carboxylic acid (3.50)

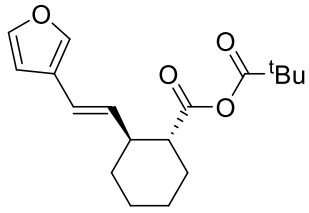
To a 50 mL Schlenk flask charged with stir bar and suspension of $MePh_3PBr$ (8.84 mmol, 3.16 g, 3.0 equiv) in THF (13.8 mL) cooled to 0 °C, a solution of KO^{t}Bu (8.84 mmol, 991 mg, 3.0 equiv) in THF (8.84 mL) was added dropwise. After an additional 40 minutes at 0 °C, a solution of **3.49** (2.95 mmol, 460 mg, 1.0 equiv) in THF (14 mL) was cannula transferred over 20 minutes at 0 °C. After stirring for another 15 minutes at 0 °C, the reaction was allowed to warm and stir at ambient temperature until TLC indicated consumption of starting material. The reaction was then quenched with 1M HCl and acidified to a pH of 2 or lower. The product was extracted into Et_2O (50 mL X 3), and the combined organic layers were washed with DI H_2O (10 mL), rinsed with brine (10.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using acidified silica gel chromatography (0% to 10% EtOAc in hexanes +1% AcOH) to afford **3.50** as a white solid. **Yield** 2.66 mmol, 386 mg, 85% **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.70 (ddd, *J* = 17.9, 10.4, 7.6 Hz, 1H), 5.08 – 5.00 (m, 1H), 4.99 – 4.93 (m, 1H), 2.29 – 2.12 (m, 2H), 1.98 (ddd, *J* = 13.0, 3.4, 1.6 Hz, 1H), 1.77 (tdd, *J* = 15.2, 4.5, 2.2 Hz, 3H), 1.50 (tdd, *J* = 12.9, 11.6, 3.5 Hz, 1H), 1.38 – 1.09 (m, 4H). **^{13}C NMR** (126 MHz, CDCl3) δ 182.1, 141.2, 114.7, 49.3, 43.7, 31.7, 29.5, 25.4, 25.2.



(1*R*,2*S*)-2-[(*E*)-2-(furan-3-yl)ethenyl]cyclohexane-1-carboxylic acid (3.47)

To a 10 mL Schlenk tube charged with stir bar and **3.50** (0.649 mmol, 100 mg, 1.0 equiv), $Pd(OAc)_2$ (0.065 mmol, 14.6 mg, 0.1 equiv) was added in a nitrogen atmosphere glovebox followed by XPhos (0.123 mmol, 61.8 mg, 0.2 equiv), and K_2CO_3 (2.59 mmol, 359 mg, 4.0 equiv). The tube was sealed and moved to a fume hood where degassed DMF (6.5 mL) was added. After stirring for 5 minutes at ambient temperature, 3-bromofuran (1.59 mmol, 143 µL, 2.5 equiv) was added. The reaction was heated at 80 °C until

TLC indicated consumption of starting material. It was subsequently quenched at ambient temperature with 1M HCl and acidified to pH 2 or below. The product was extracted into EtOAc (15.0 mL X 3), and the combined organic layers were washed with 1M HCl (5.0 mL) followed by 1:1 1M HCl/brine (10.0 mL X 4), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was redissolved with Et_2O (10.0 mL), and the product was extracted into saturated aqueous $NaHCO_3$ (5.0 mL X 4). The combined aqueous fractions were neutralized with 2M HCl, and the product was then extracted into EtOAc (15.0 mL X 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to afford **3.47** as an orange solid. **Yield** 0.431mmol, 95.0 mg, 66% **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.06 (s, 1H), 7.33 – 7.28 (m, 2H), 6.47 – 6.44 (m, 1H), 6.25 (d, *J* = 15.8 Hz, 1H), 5.78 (dd, *J* = 15.8, 8.0 Hz, 1H), 2.34 (tdd, *J* = 11.5, 7.9, 3.7 Hz, 1H), 2.24 – 2.17 (m, 1H), 2.00 – 1.95 (m, 1H), 1.84 – 1.72 (m, 4H), 1.50 (qd, *J* = 12.8, 3.6 Hz, 1H), 1.34 (dtd, *J* = 15.6, 12.9, 3.4 Hz, 2H).

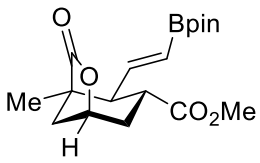


2,2-dimethylpropanoic (1*R*,2*S*)-2-[(*E*)-2-(furan-3-yl)ethenyl]cyclohexanecarboxylic anhydride (3.51)

To a 5 mL Schlenk tube charged with stir bar and solution of **3.47** (0.681 mmol, 150 mg, 1.0 equiv) in THF (1.5 mL) cooled to 0 °C, Et_3N (0.749 mmol, 105 µL, 1.1 equiv) was added dropwise, and the reaction was stirred at 0 °C for 15 minutes. PivCl (0.749 mmol, 92 µL, 1.1 equiv) was then added, and the reaction was maintained at 0 °C for an additional 10 minutes before the cooling bath was removed. After two hours of stirring at ambient temperature, the reaction was diluted to 5 mL with Et_2O, filtered through a *short* silica plug, and concentrated to afford **3.51** as a red oil. **Yield** 0.618 mmol, 188 mg, 91% **^{1}H NMR (500** MHz, $CDCl_3$) δ 7.32 (dt, *J* = 11.3, 1.7 Hz, 2H), 6.46 (d, *J* = 1.9 Hz, 1H), 6.28 (d, *J* = 15.8 Hz, 1H),

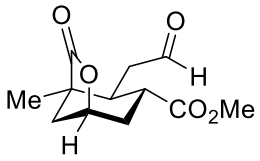
5.81 (dd, *J* = 15.8, 8.1 Hz, 1H), 2.41 – 2.33 (m, 1H), 2.33 – 2.26 (m, 1H), 2.09 – 2.00 (m, 2H), 1.88 – 1.71 (m, 5H), 1.61 – 1.52 (m, 1H), 1.18 (s, 9H).

3.4.7. α-benzoylation and furyl addition



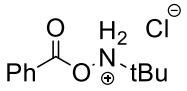
methyl 2-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl]-1-methyl-7-oxo-6-oxabicyclo[3.2.1]octane-3-carboxylate (3.S1)

To a 1 mL Schlenk tube charged with stir bar and solution of LDA (2.24M in hexane, 0.146 mmol, 65.0 µL, 1.1 equiv) in THF (300 µL) cooled to 0 °C, a solution of $CH_2(Bpin)_2$ (0.146 mmol, 39.0 mg, 1.1 equiv) in THF (200 µL) was added. After stirring for 30 minutes at 0 °C, the reaction was cooled to -78 °C, and a solution of **3.36** (0.133 mmol, 30.0 mg, 1.0 equiv) in THF (300 µL) was added dropwise over several minutes. After being kept at -78 °C for an additional 3 hours, the reaction was quenched at -78 °C with saturated aqueous NH_4Cl and allowed to warm to ambient temperature. The organic layer was then separated, and the aqueous was extracted with EtOAc (5.00 mL X 3). The combined organic layers were washed with brine (3.00 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using silica gel chromatography (0% to 35% EtOAc in hexanes) to afford **3.S1** as a white solid. **Yield** 0.071 mmol, 25.0 mg, 54% **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.30 (dd, *J* = 17.7, 9.4 Hz, 1H), 5.44 (d, *J* = 17.7 Hz, 1H), 4.79 – 4.72 (m, 1H), 3.69 (s, 1H), 3.60 (s, 3H), 2.68 (td, *J* = 11.6, 6.3 Hz, 1H), 2.58 – 2.52 (m, 1H), 2.30 – 2.26 (m, 1H), 1.90 (d, *J* = 11.6 Hz, 1H), 1.77 – 1.70 (m, 1H), 1.23 (s, 12H), 1.12 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 199.4, 176.9, 172.9, 101.8, 74.3, 55.2, 52.4, 43.6, 43.3, 36.6, 30.2, 18.6.



methyl (3*R*,5*R*)-1-methyl-7-oxo-2-(2-oxoethyl)-6-oxabicyclo[3.2.1]octane-3-carboxylate (3.52)

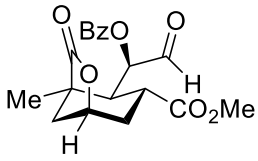
To a 5 mL Schlenk tube charged with stir bar and BH_3•THF (1.00 M, 0.758 mmol, 758 µL, 1.7 equiv) cooled to 0 °C, cyclohexene (1.47 mmol, 149 µL, 3.3 equiv) was added. The solution was stirred at 0 °C for 1.5 hours after which a white precipitate had formed. The solvent was removed *in-vacuo,* the dicyclohexylborane was resuspended in DCM (2.00 mL), and the suspension was stirred at 0 °C for 25 minutes. A solution of **3.26** (0.446 mmol, 100 mg, 1.0 equiv) in DCM (1.00 mL) was cannula transferred at 0 °C over a period of 5 minutes to the cooled borane suspension. Once the transfer was complete, the ice bath was removed, and the reaction was allowed to warm to ambient temperature. When TLC indicated consumption of the olefin after approximately 9 hours, the trialkylborane solution was cannula transferred to a 25 mL Schlenk tube charged with stir bar and a suspension of PCC (4.46 mmol, 961 mg, 10.0 equiv) adsorbed onto silica (901 mg) in DCM (6.60 mL) cooled to 0 °C. The ice bath was removed, and the reaction was heated at 45 °C with vigorous stirring for 2 hours. The reaction was cooled to ambient temperature, diluted to 25.0 mL with Et_2O, filtered through celite, and concentrated. The crude residue was purified using silica gel chromatography (0% to 35% EtOAc in hexanes) to afford **3.52** as a white solid. **Yield** 0.260 mmol, 62.0 mg, 58% **TLC** R_f 0.35 (1:1 EtOAc/Hexanes, CAM stain) **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.70 (s, 1H), 4.76 (t, *J* = 5.2 Hz, 1H), 3.64 (s, 3H), 2.83 (dd, *J* = 18.6, 6.6 Hz, 1H), 2.73 – 2.67 (m, 1H), 2.51 (td, *J* = 11.6, 6.6 Hz, 1H), 2.36 – 2.30 (m, 1H), 2.27 – 2.21 (m, 2H), 1.94 (d, *J* = 11.9 Hz, 1H), 1.79 – 1.73 (m, 1H), 1.10 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 199.5, 178.1, 173.8, 74.4, 52.4, 44.9, 44.0, 43.9, 43.8, 38.0, 32.3, 19.3. **HRMS** (ESI) *m/z* Calcd for $C_{12}H_{17}O_5$ $[M+H]^+$: 241.1071, found 241.1071.



(benzoyloxy)(*tert*-butyl)ammonium chloride (3.53)

Freebase (tert-butylamino) benzoate was synthesized according to a reported procedure and the ^{1}H and ^{13}C spectral data match those of the reported molecule.[47] **Yield** 1.38 mmol, 266 mg, 67% **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (dd, J = 8.4, 1.4 Hz, 2H), 7.20 – 7.15 (m, 1H), 7.08 – 7.03 (m, 2H), 0.84 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.5, 133.1, 129.1, 128.4, 128.4, 55.9, 26.5.

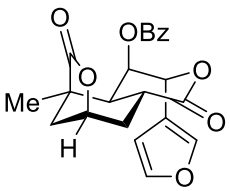
The HCl salt was prepared by dissolving (*tert*-butylamino)benzoate (1.38 mmol, 266 mg, 1.0 equiv) in Et_2O (2.10 mL) and slowly adding a solution of hydrochloric acid (2.0M in Et_2O, 5.82 mmol, 2.90 mL, 4.23 equiv) at ambient temperature. The reaction was stirred for 20 minutes at ambient temperature after which it was diluted to 10.0 mL with hexanes. The white solid was vacuum filtered, rinsed with hexane, and azeotropically dried with heptane under high vacuum to afford **3.53** as a white powder. **Yield** 1.23 mmol, 282 mg, 89%.



methyl (3*R*)-2-(benzoyloxyformylmethyl)-1-methyl-7-oxo-6-oxabicyclo[3.2.1]octane-3-carboxylate (3.54)

To a 3 mL Schlenk tube charged with stir bar and **3.30** (0.208 mmol,50.0 mg, 1.0 equiv), **3.53** (0.283 mmol, 65.0 mg, 1.4 equiv) was added followed by freshly distilled DMSO (2.20 mL). The reaction was stirred at ambient temperature overnight after which it was transferred to a 50 mL round bottom flask charged with stir bar where it was diluted with EtOAc (10.0 mL) and quenched with 2M HCl (10.0 mL). After vigorous stirring until the layers cleared, the organic layer was separated, and the aqueous was extracted with EtOAc (20.0 mL X 3). The combined organic layers were washed with 1M HCl (10.0 mL X 5), rinsed with brine (10.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using silica gel chromatography (0% to 50% EtOAc in hexanes) to afford **3.54** as a white solid with a

19:1 ratio of diastereomers. **Yield** 0.114 mmol, 41.0 mg, 54% **TLC** R_f 0.21 (1:1 EtOAc/Hexanes, CAM stain) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.28 – 8.24 (m, 2H), 7.64 – 7.59 (m, 1H), 7.50 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 2H), 4.78 (ddd, *J* = 5.8, 4.6, 1.1 Hz, 1H), 3.73 (s, 3H), 3.02 – 2.98 (m, 2H), 2.51 – 2.43 (m, 1H), 2.33 (ddd, *J* = 12.0, 6.2, 2.0 Hz, 1H), 2.05 (d, *J* = 11.9 Hz, 1H), 1.84 – 1.78 (m, 1H), 1.26 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 198.5, 177.4, 174.0, 166.8, 134.0, 130.8, 128.7, 128.6, 78.5, 73.9, 46.7, 45.5, 43.4, 40.4, 32.5, 21.6. **HRMS** (ESI) *m/z* Calcd for $C_{19}H_{21}O_7$ $[M+H]^+$: 361.1282, found 361.1278.



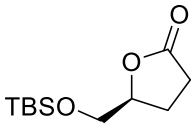
(7*R*)-4-(3-Furyl)-1-methyl-6,11-dioxo-5,10-dioxatricyclo[7.2.1.0^{2,7}]dodec-3-yl benzoate, collybolide (3.1)

To a 5 mL Schlenk tube charged with stir bar solution of *n*-BuLi (2.11M in hexane, 0.588 mmol, 279 μL, 10.6 equiv) in THF (1.00 mL) cooled to -78 °C, 3-bromofuran (0.556 mmol, 50.0 μL, 10.0 equiv) was added. The solution was stirred at -78 °C for 40 minutes after which freshly prepared $MgBr_2$•OEt_2 (1.21 M, 0.556 mmol, 460 μL, 10.0 equiv) was added dropwise. After 30 minutes of stirring at -78 °C, the reaction was warmed to -45 °C and stirred for an additional 20 minutes. A solution of $LaCl_3$•$(LiCl)_2$ (0.600M in THF, 0.558 mmol, 930 μL, 10.6 equiv) was added dropwise, and the reaction was kept at -45 °C for 30 minutes before the resulting organolanthanum solution was titrated with I_2.

To a 3 mL Schlenk tube charged with stir bar and an aliquot of the prepared organolanthanum solution (0.143 M, 0.0611 mmol, 107 μL, 1.1 equiv) cooled to -45 °C, a solution of **3.54** (0.0139 mmol, 5.00 mg, 1.0 equiv) in THF (100 μL) cooled to -45 °C was cannula transferred. The reaction was maintained at -45 °C until TLC indicated consumption of starting material, and subsequently it was quenched at -45 °C with saturated $NH_4Cl_{(aq)}$. Once warmed to ambient temperature, the reaction was diluted to 3 mL with EtOAc, the organic layer was

separated, and the aqueous was extracted with EtOAc (5.00 mL X 3). The combined organic layers were washed with DI H_2O (5.00 mL) and brine (3.00 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. To a 1-dram vial charged with stir bar and the crude residue, a 1:4 solution of aqueous 2M HCl in dioxane was added, and the reaction was stirred at ambient temperature overnight. The reaction was diluted with DI H_2O (800 µL) and extracted with EtOAc (5.00 mL X 3). The combined organic layers were washed with DI H_2O (3.00 mL) and brine (3.00 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude residue was purified using preparative TLC (50% EtOAc in hexanes) to afford **3.1** as a white solid. **Yield** 0.00505 mmol, 2.00 mg, 35% **TLC** R_f 0.55 (1:1 EtOAc/Hexanes, CAM stain) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 – 8.02 (m, 2H), 7.61 (tt, *J* = 7.1, 1.3 Hz, 1H), 7.53 – 7.46 (m, 4H), 6.54 (dd, *J* = 1.9, 1.0 Hz, 1H), 5.72 (t, *J* = 1.6 Hz, 1H), 5.66 (t, *J* = 1.4 Hz, 1H), 4.85 (dd, *J* = 6.0, 4.6 Hz, 1H), 3.41 (ddd, *J* = 13.6, 11.5, 6.1 Hz, 1H), 2.78 – 2.71 (m, 1H), 2.33 (ddd, *J* = 11.9, 6.1, 1.8 Hz, 1H), 2.16 (dd, *J* = 13.7, 1.9 Hz, 1H), 1.87 – 1.81 (m, 2H), 1.24 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.6, 170.3, 165.9, 144.6, 139.8, 133.8, 130.2, 128.7, 128.6, 123.7, 107.7, 79.8, 73.9, 68.3, 44.8, 42.7, 42.3, 34.4, 29.7, 17.5. **HRMS** (ESI) *m/z* Calcd for $C_{22}H_{21}O_7$ $[M+H]^+$: 397.1282, found 397.1281.

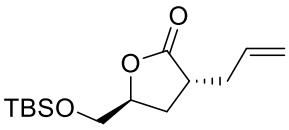
3.4.8. Formal asymmetric synthesis



(*S*)-5-{[(*tert*-Butyl)bis(methyl)siloxy]methyl}-4,5-dihydro-2(3*H*)-furanone ((+)-3.55)

To a 25 mL Schlenk flask charged with stir bar and (5*S*)-5-(hydroxymethyl)oxolan-2-one (17.2 mmol, 1.62 mL, 1.0 equiv) in DMF (16.0 mL), imidazole (25.8 mmol, 1.76 g, 1.5 equiv) was added followed by TBSCl (18.9 mmol, 2.86 g, 1.1 equiv). After stirring at ambient temperature for 4.5 hours, the reaction was diluted with DI H_2O (100 mL) and extracted with EtOAc (75.0 mL + 50.0 mL X 2). The combined organic layers were washed with DI H_2O (25.0 mL) and brine

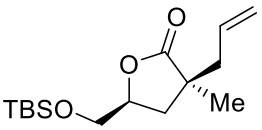
(25.0 mL), dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified using silica gel chromatography (0% to 10% EtOAc in hexanes) to afford **(+)-3.55** as a clear colorless oil. **Yield** 16.0 mmol, 3.69 g, 93% **TLC** R_f 0.48 (1:4 EtOAc/Hexanes, I_2) $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ 0.132 (*c* 0.0333, $CHCl_3$) **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.55 (ddt, *J* = 8.1, 5.0, 3.2 Hz, 1H), 3.82 (dd, *J* = 11.3, 3.2 Hz, 1H), 3.65 (dd, *J* = 11.3, 3.2 Hz, 1H), 2.56 (ddd, *J* = 17.6, 10.2, 7.2 Hz, 1H), 2.42 (ddd, *J* = 17.8, 10.3, 6.2 Hz, 1H), 2.23 (dddd, *J* = 12.8, 10.3, 8.1, 7.2 Hz, 1H), 2.13 (dddd, *J* = 12.8, 10.2, 6.2, 5.0 Hz, 1H), 0.85 (t, *J* = 1.9 Hz, 9H), 0.04 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.5, 80.1, 64.9, 28.6, 25.8, 23.5, 18.2, -5.5, -5.6. **HRMS** (ESI) *m/z* Calcd for $C_{11}H_{23}O_3Si$ $[M+H]^+$: 231.1411, found 231.1410.



(3*R*,5*S*)-3-Allyl-5-{[(*tert*-butyl)bis(methyl)siloxy]methyl}-4,5-dihydro-2(3*H*)-furanone ((+)-3.56)

To a 100 mL Schlenk flask charged with stir bar and solution of *i*Pr_2NH (16.8 mmol, 2.37 mL, 1.1 equiv) in THF (18.0 mL) cooled to -78 °C, *n*-BuLi (2.43 M, 16.8 mmol, 6.92 mL, 1.1 equiv) was slowly added. The LDA solution was stirred at -78 °C for an hour after which a solution of **(+)-3.55** (16.0 mmol, 3.69 g, 1.0 equiv) in THF (29.0 mL) was cannula transferred at -78 °C over a period of an hour. The reaction was stirred at -78 °C for an additional 30 minutes before allyl bromide (32.0 mmol, 2.77 mL, 2.0 equiv) was slowly added. The reaction was kept at -78 °C until TLC indicated consumption of starting material, and subsequently it was quenched at -78 °C with saturated $NH_4Cl_{(aq)}$. The organic layer was separated, and the aqueous was extracted with EtOAc (75.0 mL + 50.0 mL X 2). The combined organic layers were washed with DI H_2O (25.0 mL) and brine (25.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using silica gel chromatography (0% to 10% EtOAc in hexanes) to afford **(+)-3.56** as a clear colorless oil. **Yield** 12.5 mmol, 3.37 g, 78% **TLC** R_f 0.66 (1:4 EtOAc/Hexanes, I_2) $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$

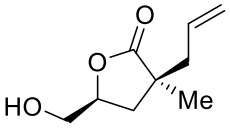
0.144 (*c* 0.0333, $CHCl_3$) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.15 – 5.07 (m, 2H), 4.51 (dq, *J* = 9.0, 3.1 Hz, 1H), 3.84 (dd, *J* = 11.3, 3.1 Hz, 1H), 3.65 (dd, *J* = 11.3, 2.9 Hz, 1H), 2.83 (qd, *J* = 9.2, 4.4 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.34 – 2.19 (m, 2H), 2.02 (dt, *J* = 12.9, 8.8 Hz, 1H), 0.88 (d, *J* = 4.2 Hz, 9H), 0.06 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 179.2, 134.8, 117.7, 78.2, 65.2, 39.3, 35.4, 29.5, 18.4, -5.4, -5.5. **HRMS** (ESI) *m/z* Calcd for $C_{14}H_{27}O_3Si$ $[M+H]^+$: 271.1724, found 271.1723.



(3*S*,5*S*)-3-Allyl-5-{[(*tert*-butyl)bis(methyl)siloxy]methyl}-3-methyl-4,5-dihydro-2(3*H*)-furanone ((+)-3.57)

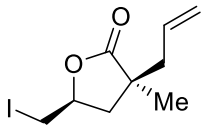
To a 100 mL Schlenk flask charged with stir bar and solution of *i*Pr_2NH (14.9 mmol, 2.10 mL, 1.2 equiv) in THF (16.0 mL) cooled to -78 °C, *n*-BuLi (2.43 M, 13.6 mmol, 5.61 mL, 1.2 equiv) was slowly added. The LDA solution was stirred at -78 °C for an hour after which a solution of **(+)-3.56** (12.4 mmol, 3.35 g, 1.0 equiv) in THF (25.0 mL) and HMPA (2.40 mL) was cannula transferred at -78 °C over a period of 15 minutes. The reaction was stirred at -78 °C for an additional 30 minutes before methyl iodide (24.8 mmol, 1.54 ml, 2.0 equiv) was slowly added. The reaction was kept at -78 °C until TLC indicated consumption of starting material, and subsequently it was quenched at -78 °C with saturated $NH_4Cl_{(aq)}$. The organic layer was separated, and the aqueous was extracted with EtOAc (80.0 mL + 60.0 mL X 2). The combined organic layers were washed with DI H_2O (30.0 mL) and brine (30.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using silica gel chromatography (0% to 10% EtOAc in hexanes) to afford **(+)-3.57** as a colorless solid. **Yield** 11.9 mmol, 3.38 g, 96% **TLC** R_f 0.65 (1:4 EtOAc/Hexanes, I_2) $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ 0.447 (*c* 0.0300, $CHCl_3$) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.73 (dddd, *J* = 17.0, 11.1, 8.3, 6.4 Hz, 1H), 5.19 – 5.09 (m, 2H), 4.48 (ddt, *J* = 10.2, 6.6, 3.9 Hz, 1H), 3.83 (dd, *J* = 11.4, 3.7 Hz, 1H), 3.68 (dd, *J* = 11.4, 4.2 Hz, 1H), 2.43 – 2.36 (m,

1H), 2.29 (dd, *J* = 13.9, 8.3 Hz, 1H), 2.18 (dd, *J* = 12.8, 9.6 Hz, 1H), 1.83 (dd, *J* = 12.7, 6.5 Hz, 1H), 1.26 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 181.0, 133.2, 119.2, 64.0, 43.7, 41.9, 34.8, 25.9, 23.3, 18.3, -5.3, -5.4. **HRMS** (ESI) *m/z* Calcd for $C_{15}H_{29}O_3Si$ $[M+H]^+$: 285.1881, found 285.1880.



(3*S*,5*S*)-5-(hydroxymethyl)-3-methyl-3-(prop-2-en-1-yl)oxolan-2-one ((+)-3.58)

To a 50 mL Schlenk flask charged with stir bar and solution of **(+)-3.57** (1.76 mmol, 500 mg, 1.0 equiv) in THF (14.0 mL) cooled to 0 °C, solution of TBAF in THF (1.00 M, 3.52 mmol, 3.52 mL, 2.0 equiv) was slowly added. The ice bath was allowed to melt, and the reaction gradually warmed to ambient temperature while stirring overnight. The reaction was diluted with Et_2O (100 mL) and washed with saturated $NH_4Cl_{(aq)}$ (20.0 mL X 2). The organic layer was rinsed with brine (15.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using silica gel chromatography (0% to 35% Et_2O in pentane) to afford **(+)-3.58** as a white solid. **Yield** 1.19 mmol, 203 mg, 68% **TLC** R_f 0.19 (1:1 EtOAc/Hexanes, I_2 or CAM stain) $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ 0.638 (*c* 0.0367, $CHCl_3$) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.65 (dddd, *J* = 15.1, 11.3, 8.4, 6.5 Hz, 1H), 5.11 – 5.02 (m, 2H), 4.51 (dtd, *J* = 9.6, 5.9, 2.8 Hz, 1H), 3.83 – 3.74 (m, 1H), 3.63 (s, 1H), 3.55 (dd, *J* = 12.5, 5.3 Hz, 1H), 2.33 – 2.19 (m, 2H), 2.02 (dd, *J* = 12.9, 9.9 Hz, 1H), 1.82 (dd, *J* = 12.8, 6.6 Hz, 1H), 1.19 (d, *J* = 4.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 181.4, 132.8, 119.2, 77.8, 63.6, 43.7, 41.6, 34.6, 22.8. **HRMS** (ESI) *m/z* Calcd for $C_9H_{15}O_3$ $[M+H]^+$: 171.1016, found 171.1016.



(3*S*,5*S*)-5-(iodomethyl)-3-methyl-3-(prop-2-en-1-yl)oxolan-2-one ((+)-3.31)

To a 10 mL Schlenk flask charged with stir bar and solution of (+)**-3.58** (0.29 mmol, 50.0 mg, 1.0 equiv) in THF (3.00 mL) cooled to 0 °C, PPh_3 (0.380 mmol, 100 mg, 1.3 equiv) was added followed by imidazole (0.590 mmol, 40.0 mg, 2.0 equiv) and I_2 (0.350 mmol, 90.0 mg, 1.2 equiv). The resulting orange solution was stirred at 0 °C for 30 minutes after which the ice bath was removed, and the reaction was allowed to warm to ambient temperature. The reaction was stirred at ambient temperature until TLC indicated consumption of the starting material. Once the starting material was consumed, the reaction was quenched with saturated $Na_2S_2O_{3(aq)}$. The organic layer was separated, and the aqueous was extracted with Et_2O (15.0 mL + 10.0 mL X 2). The combined organic layers were washed with saturated $Na_2S_2O_{3(aq)}$ (5.00 mL) then brine (5.00 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified using silica gel chromatography (0% to 10% EtOAc in hexanes) to afford **(+)-3.31** as a clear colorless oil. **Yield** 0.240 mmol, 65.0 mg, 83% **TLC** R_f 0.66 (1:1 EtOAc/Hexanes, I_2 or CAM stain) $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ 0.206 (*c* 0.0350, $CHCl_3$) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.71 (dddd, *J* = 16.8, 10.3, 8.5, 6.4 Hz, 1H), 5.19 – 5.10 (m, 2H), 4.46 (dddd, *J* = 9.7, 7.4, 6.2, 4.7 Hz, 1H), 3.40 (dd, *J* = 10.3, 4.7 Hz, 1H), 3.23 (dd, *J* = 10.3, 7.5 Hz, 1H), 2.44 – 2.38 (m, 1H), 2.28 (dd, *J* = 13.9, 8.4 Hz, 1H), 2.15 (dd, *J* = 13.0, 6.2 Hz, 1H), 1.91 (dd, *J* = 13.0, 9.6 Hz, 1H), 1.26 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 180.2, 132.8, 119.8, 75.6, 44.8, 41.9, 40.5, 23.3, 7.0. **HRMS** (ESI) *m/z* Calcd for $C_9H_{14}O_2I$ $[M+H]^+$: 281.0033, found 281.0033.

3.5. References

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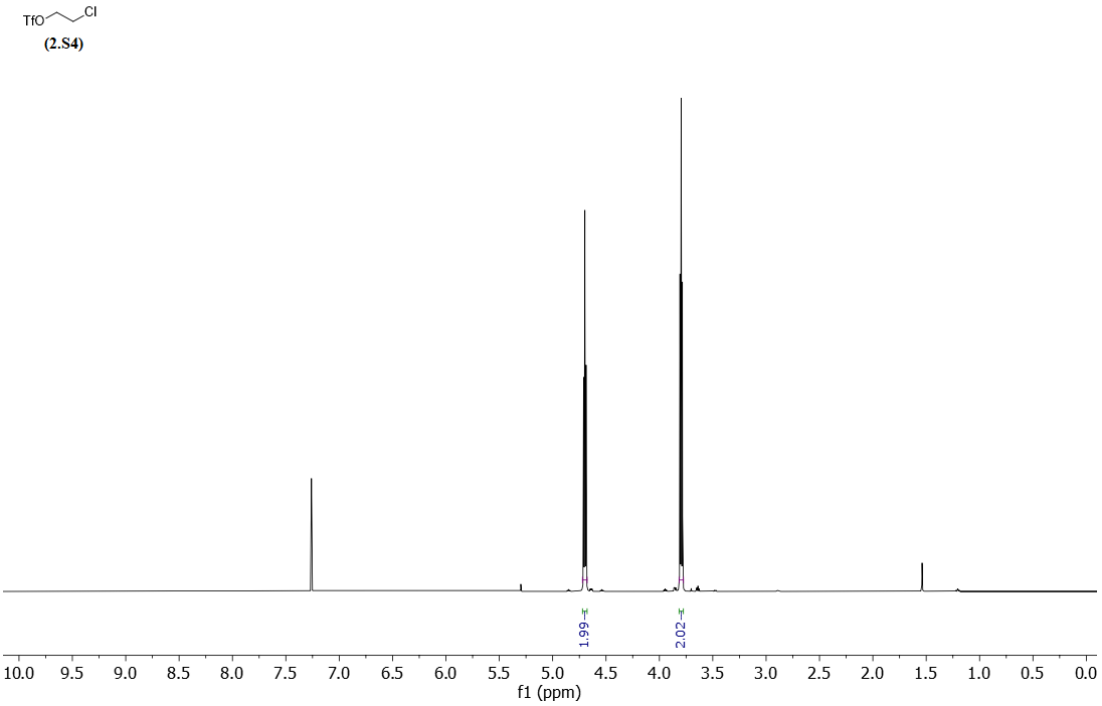
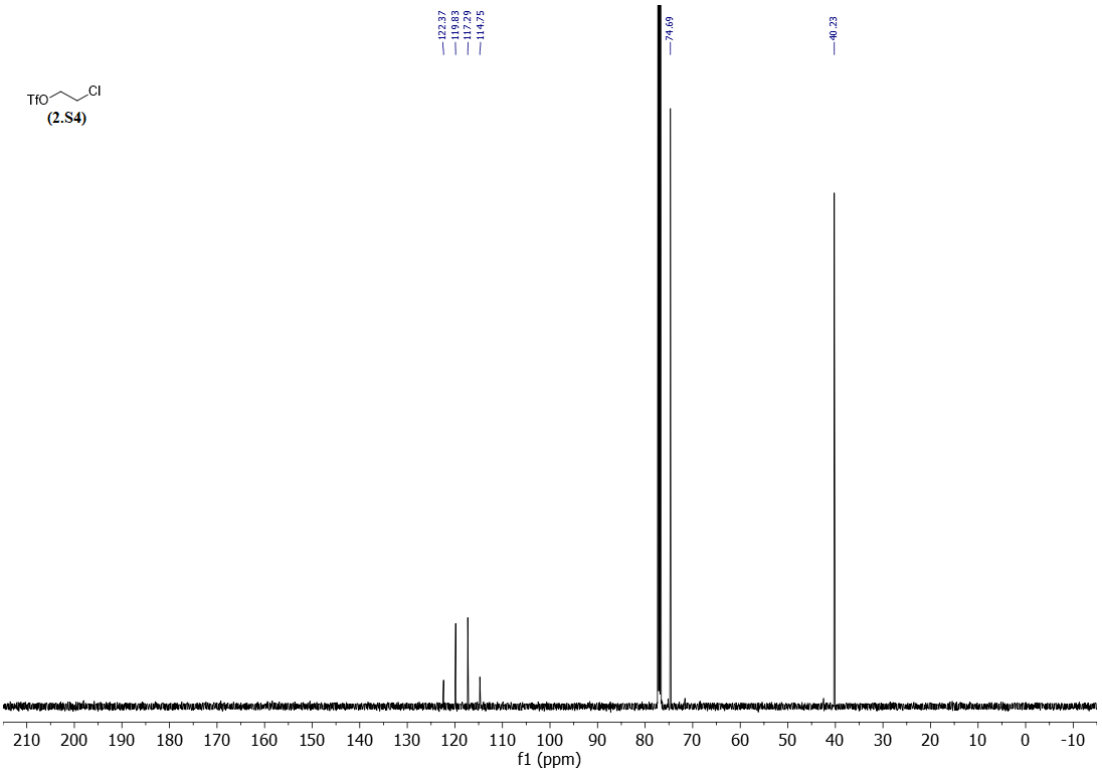
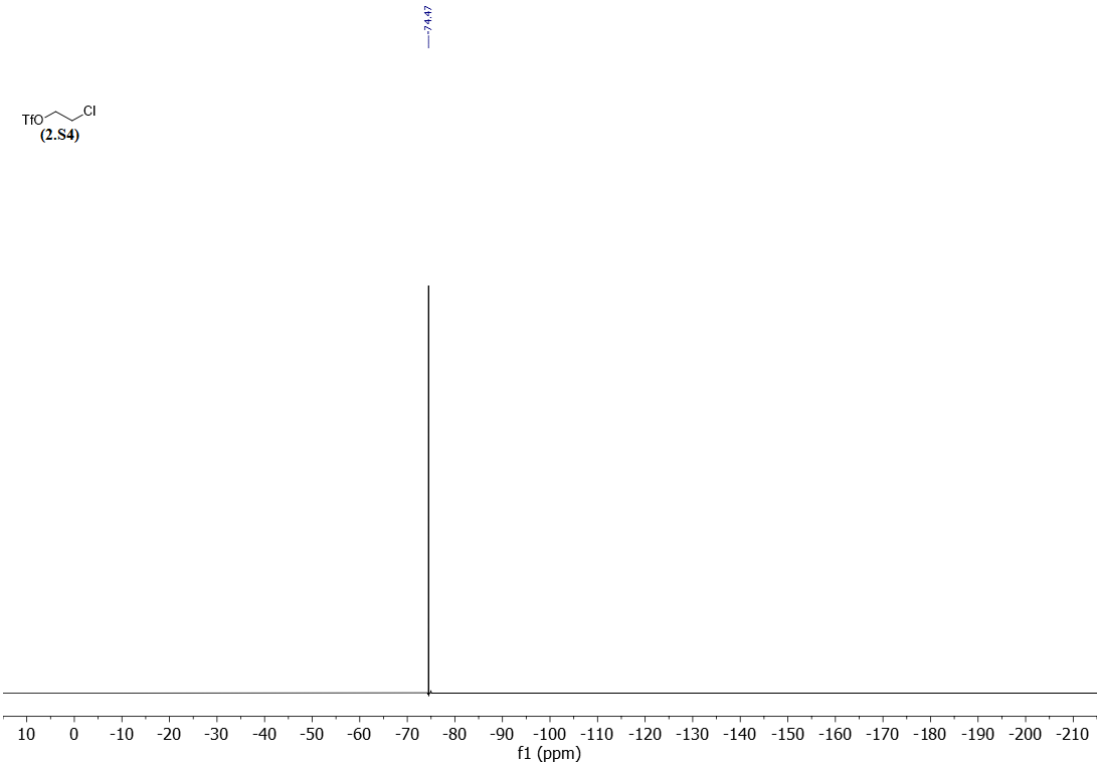
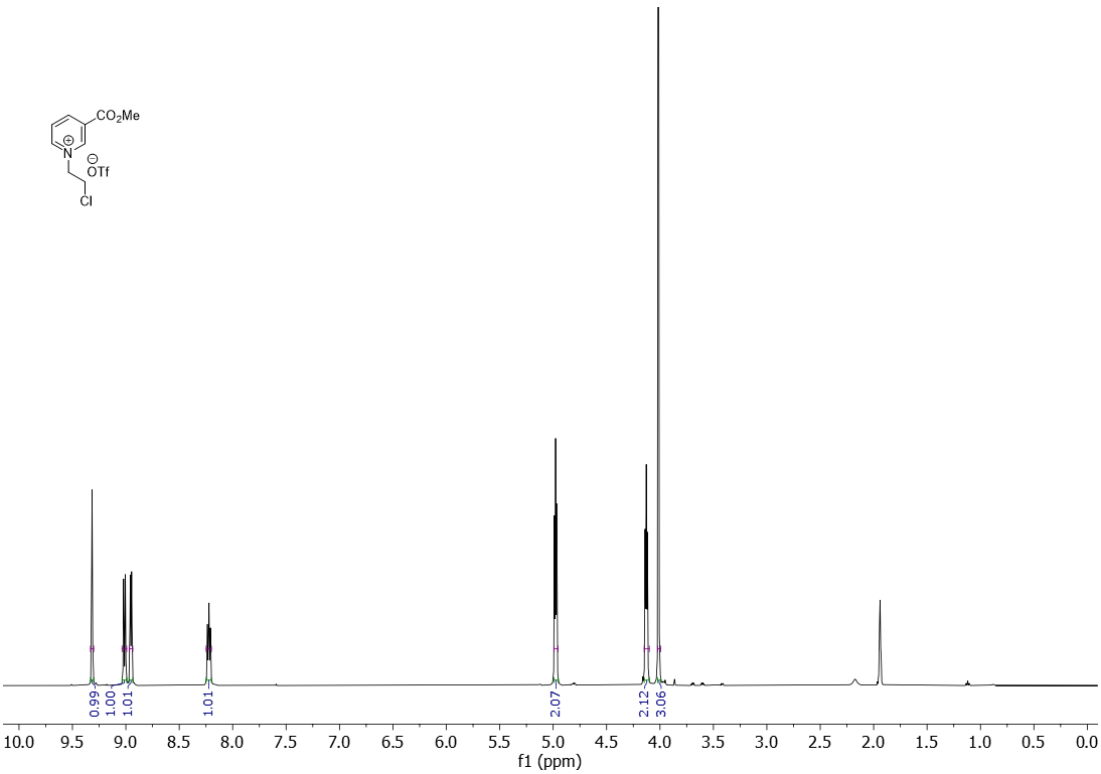
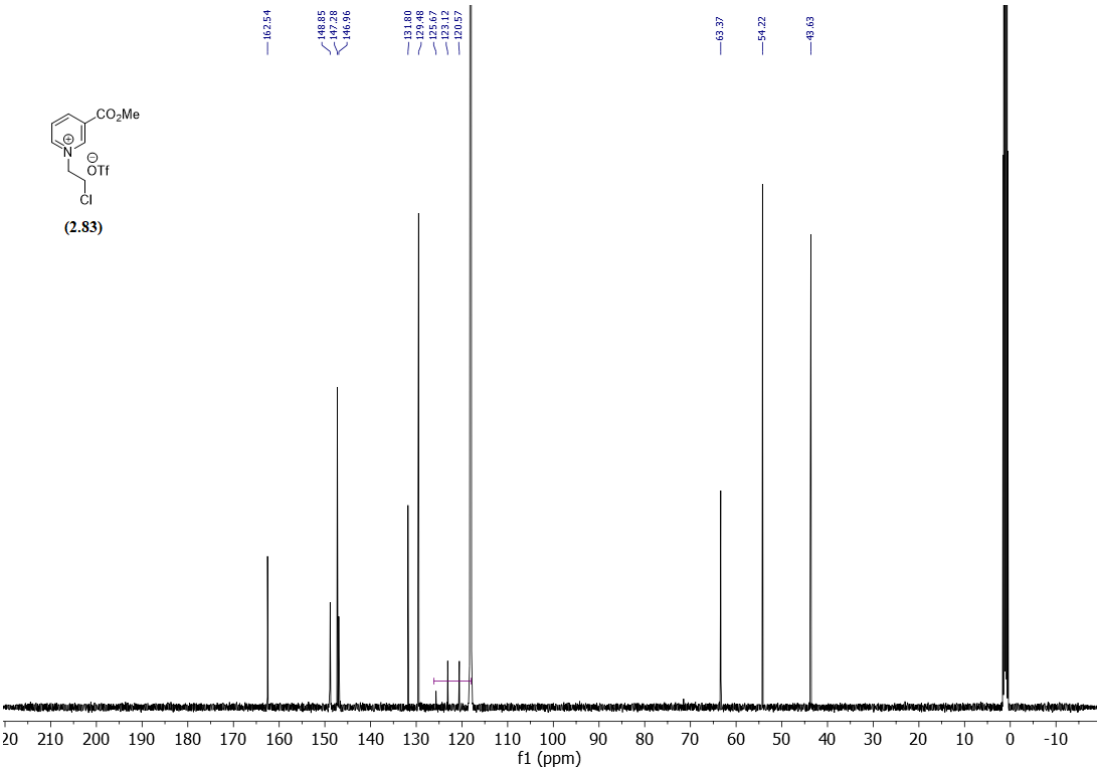
Appendix A: NMR Spectra for Chapter 2 (deplancheine intermediates)

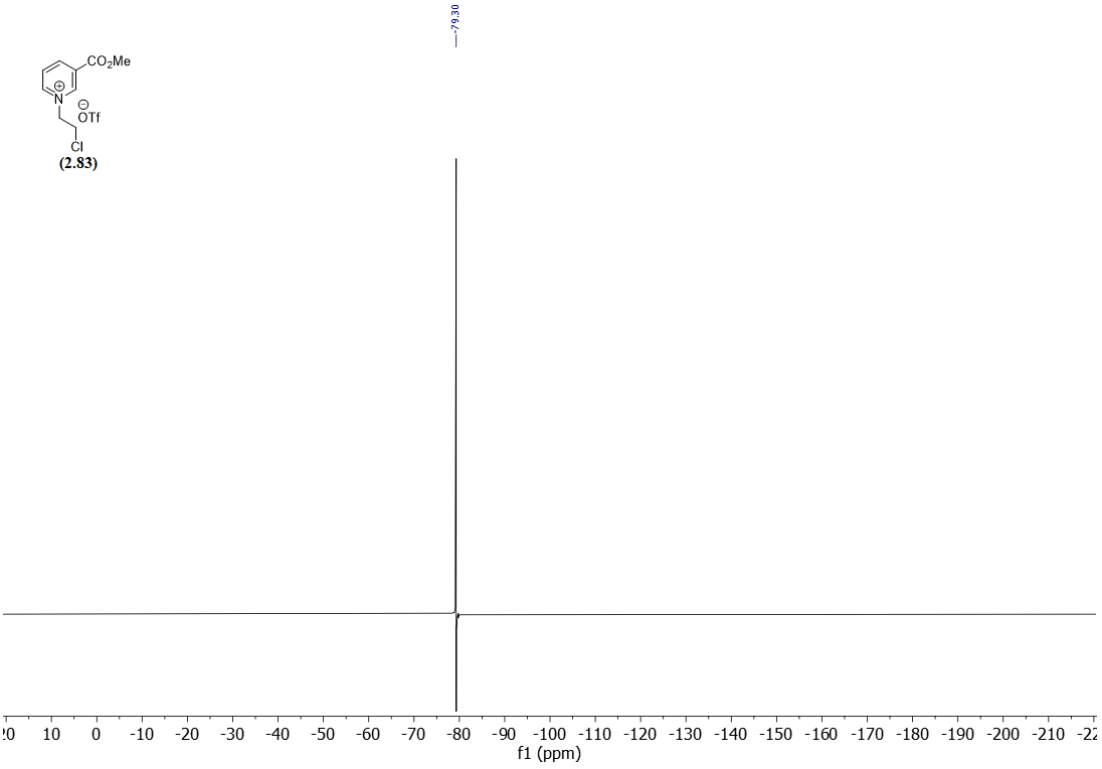


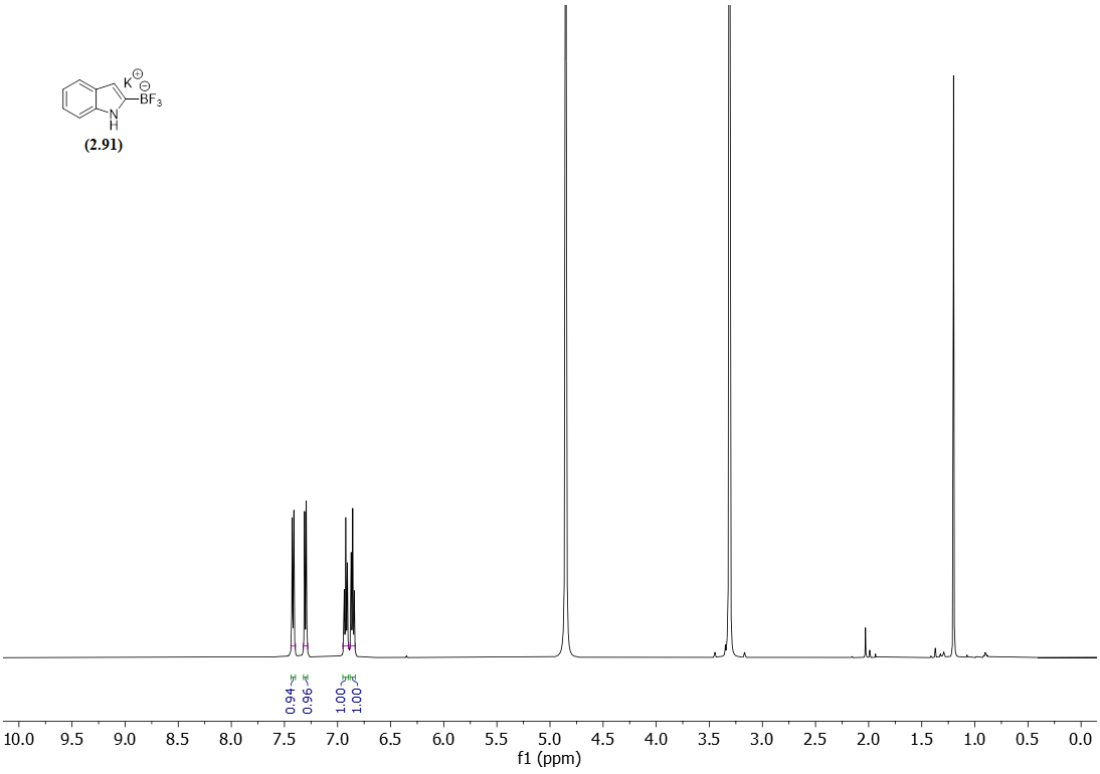


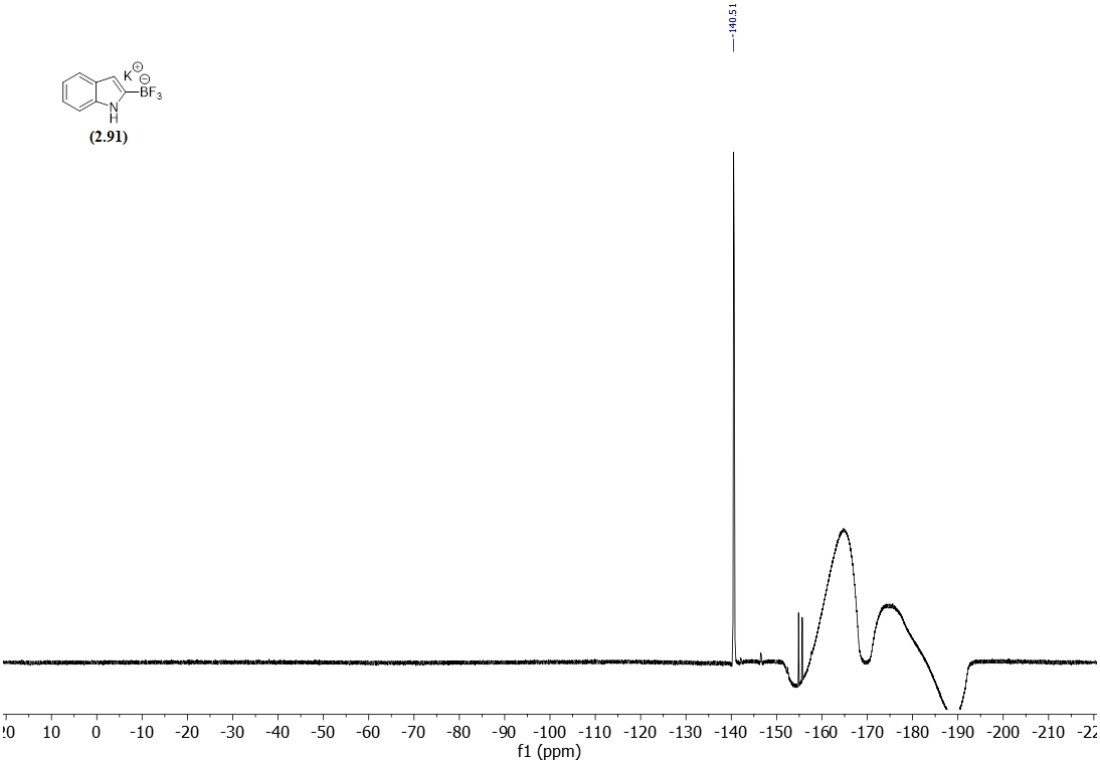

-74.47
TfO
Cl
(2.S4)
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

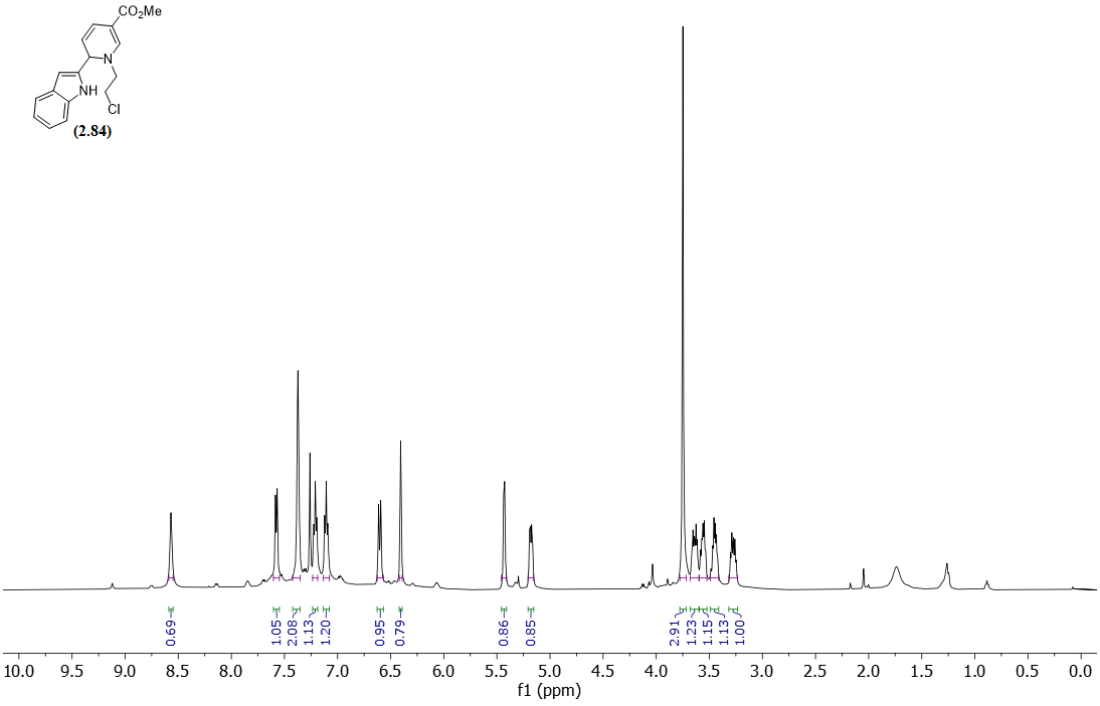

CO2Me
N
OTf
Cl
0.99
1.00
1.01
1.01
2.07
2.12
3.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

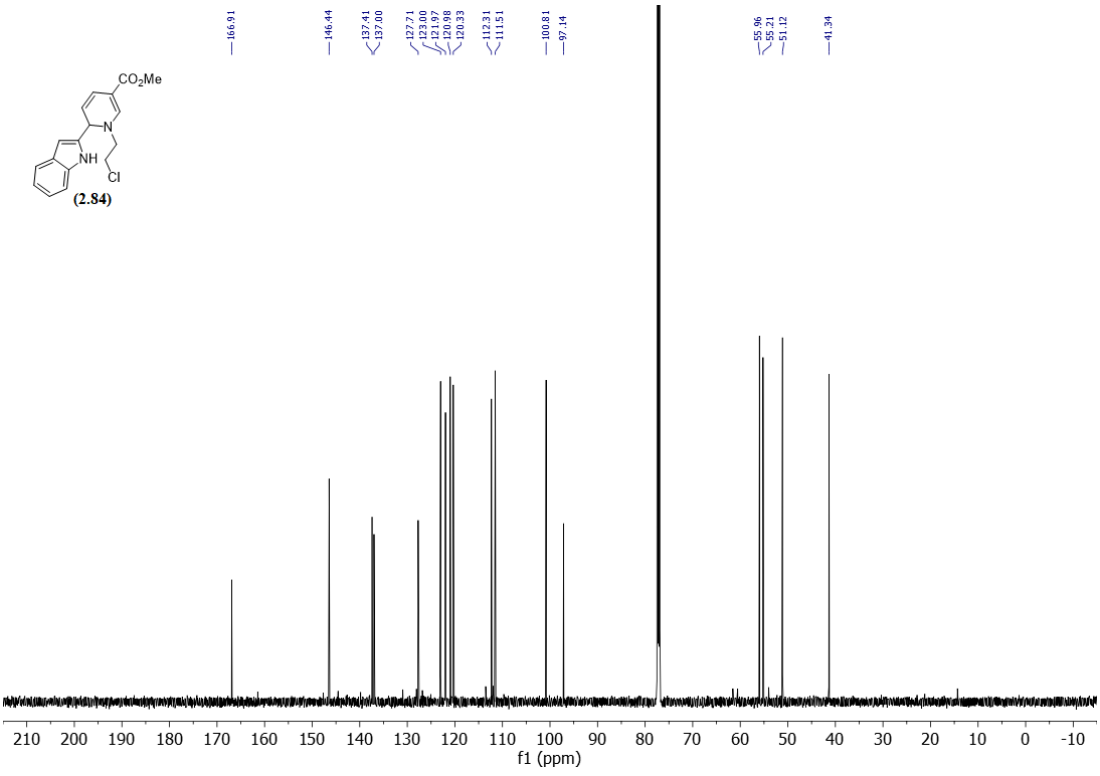

162.54
148.85
147.28
146.96
131.80
130.48
125.67
123.12
120.57
63.37
54.22
43.63
CO2Me
OTf
Cl
(2.83)
f1 (ppm)

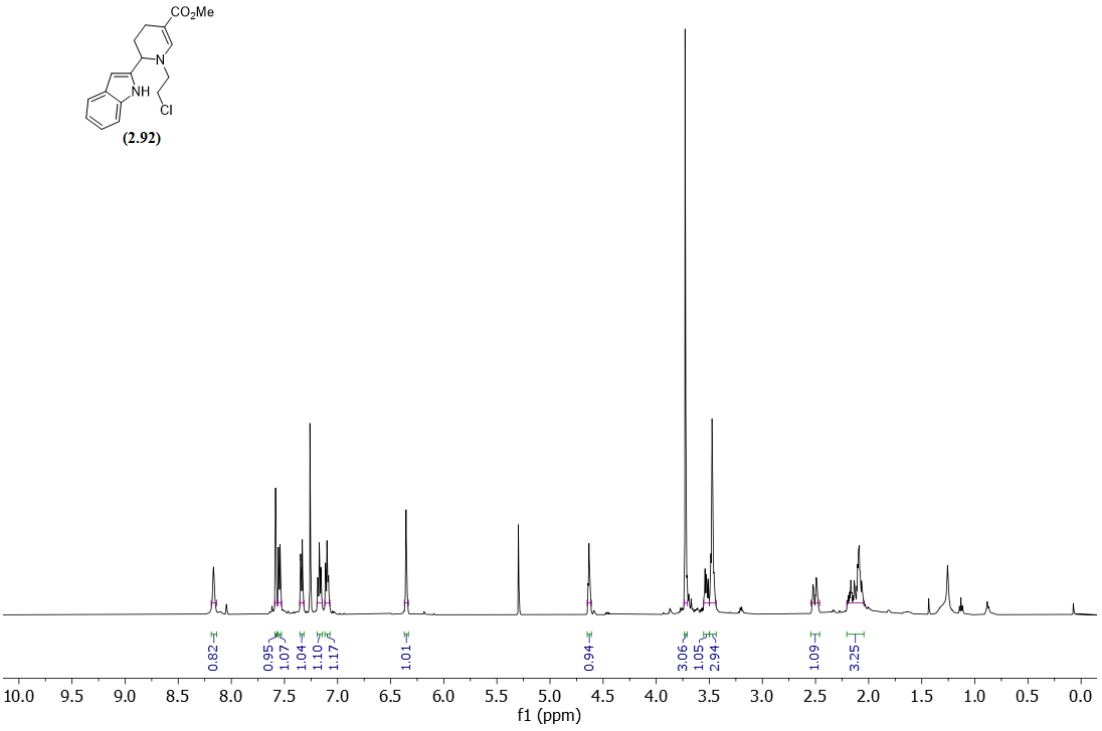

79.30
CO2Me
OTf
Cl
(2.83)
f1 (ppm)

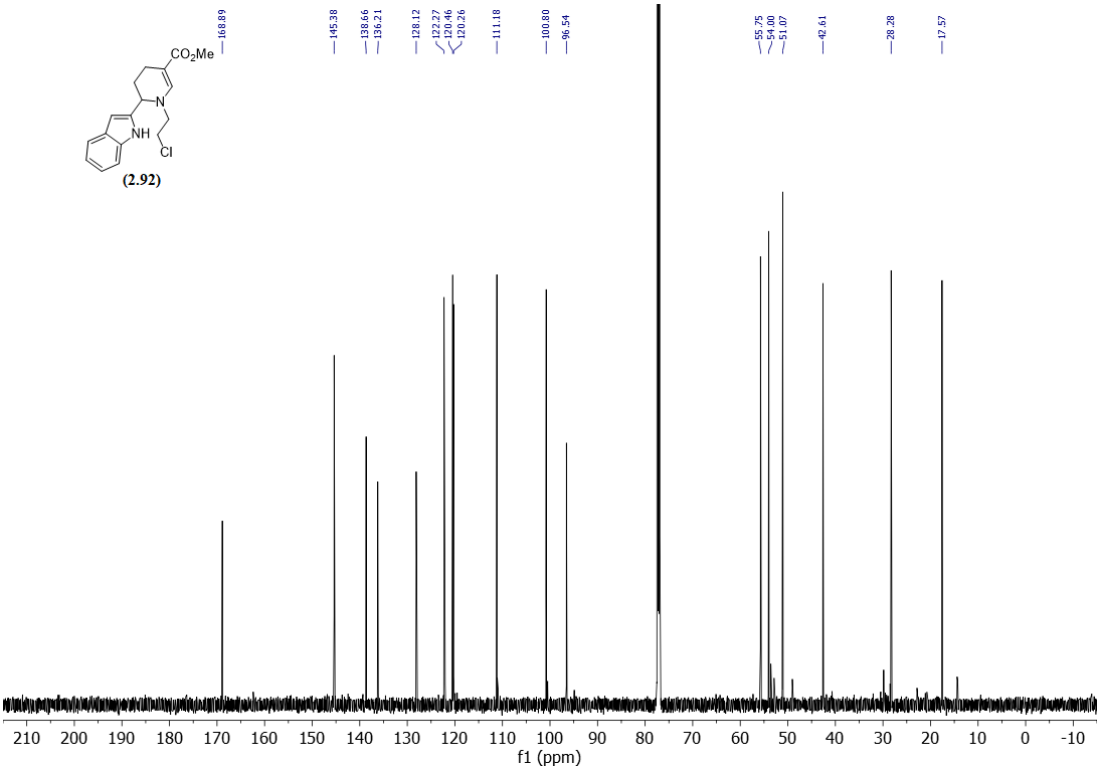

(2.91)
0.94
0.96
1.00
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

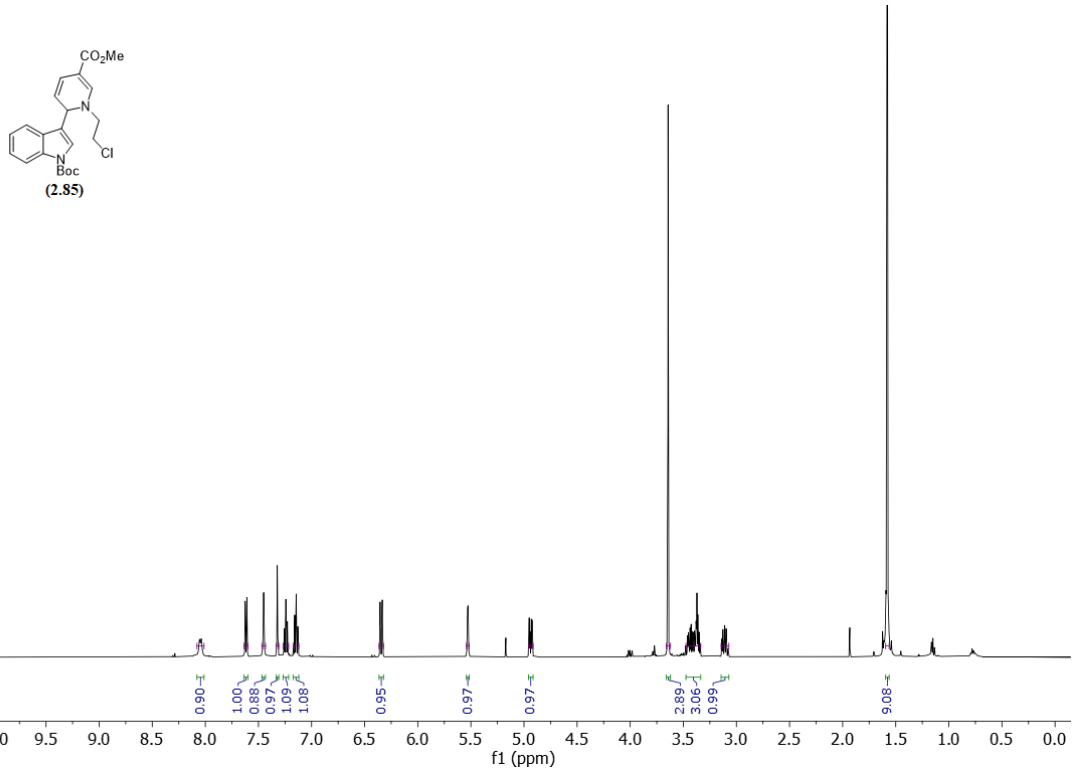

-140.51
(2.91)
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

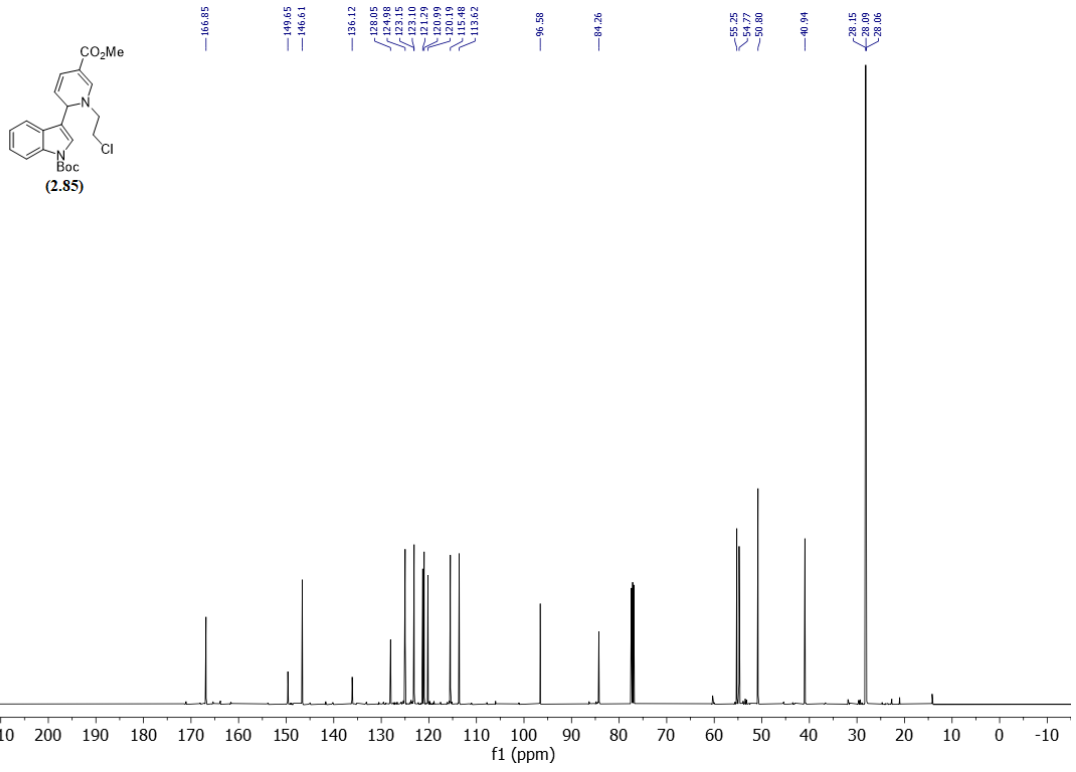

CO2Me
N
NH
Cl
(2.84)
0.69
1.05
2.08
1.13
1.20
0.95
0.79
0.86
0.85
2.91
1.23
1.15
1.13
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

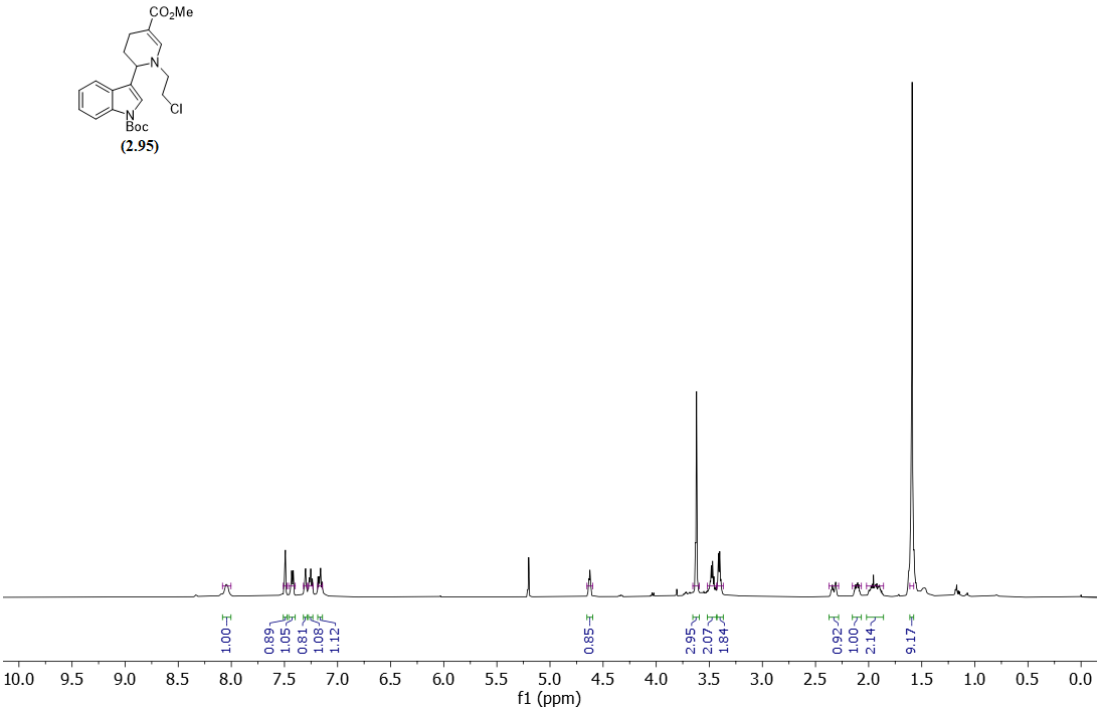

166.91
146.44
137.41
137.00
127.71
123.00
121.97
120.98
120.33
112.31
111.51
100.61
97.14
55.96
55.21
51.12
41.34
CO2Me
N
NH
Cl
(2.84)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

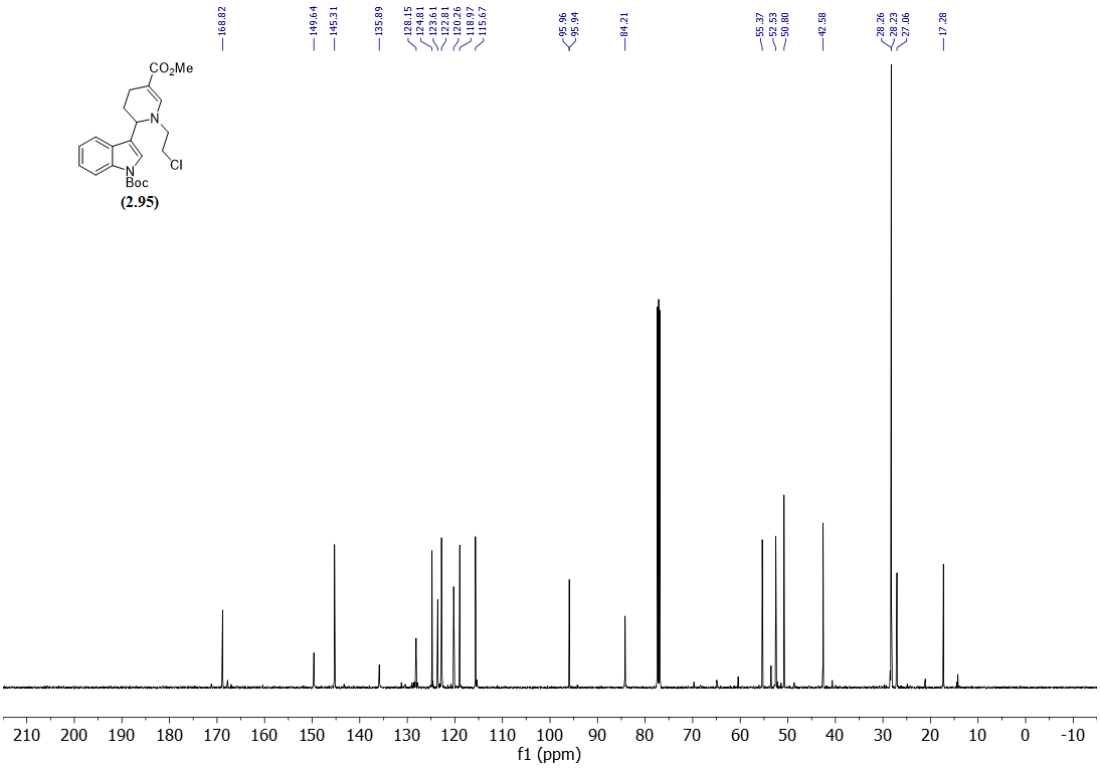

CO2Me
N
NH
Cl
(2.92)
0.82
0.95
1.07
1.04
1.10
1.17
1.01
0.94
3.06
1.05
2.94
1.09
3.25
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

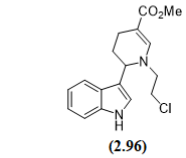

168.89
145.38
138.66
136.21
128.12
122.27
120.46
120.26
111.18
100.80
96.54
55.75
54.00
51.07
42.61
28.28
17.57
CO2Me
N
NH
Cl
(2.92)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CO2Me
N
Cl
N
Boc
(2.85)
0.90
1.00
0.88
0.97
1.09
1.08
0.95
0.97
0.97
2.89
3.06
0.99
9.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


CO2Me
N
Cl
N
Boc
(2.85)
166.85
149.65
146.61
136.12
128.05
124.98
123.15
123.10
121.29
120.99
120.19
115.48
113.62
96.58
84.26
55.25
54.77
50.80
40.94
28.15
28.09
28.06
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

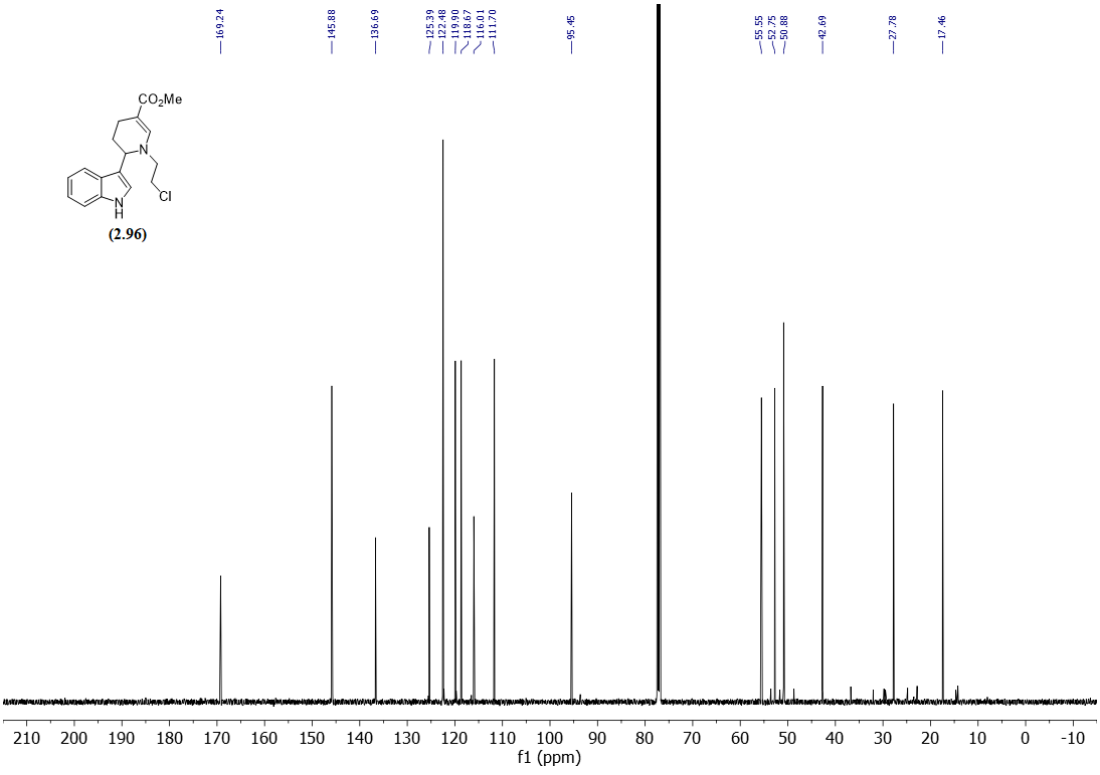

CO2Me
N
Cl
N
Boc
(2.95)
1.00
0.89
1.05
0.81
1.08
1.12
0.85
2.95
2.07
1.84
0.92
1.00
2.14
9.17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


168.82
149.64
145.31
135.89
128.15
124.61
123.61
122.81
120.26
118.97
115.67
95.96
95.94
84.21
55.37
52.53
50.80
42.58
28.26
28.23
27.06
17.28
CO2Me
N
Cl
N
Boc
(2.95)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CO2Me
N
Cl
N
H

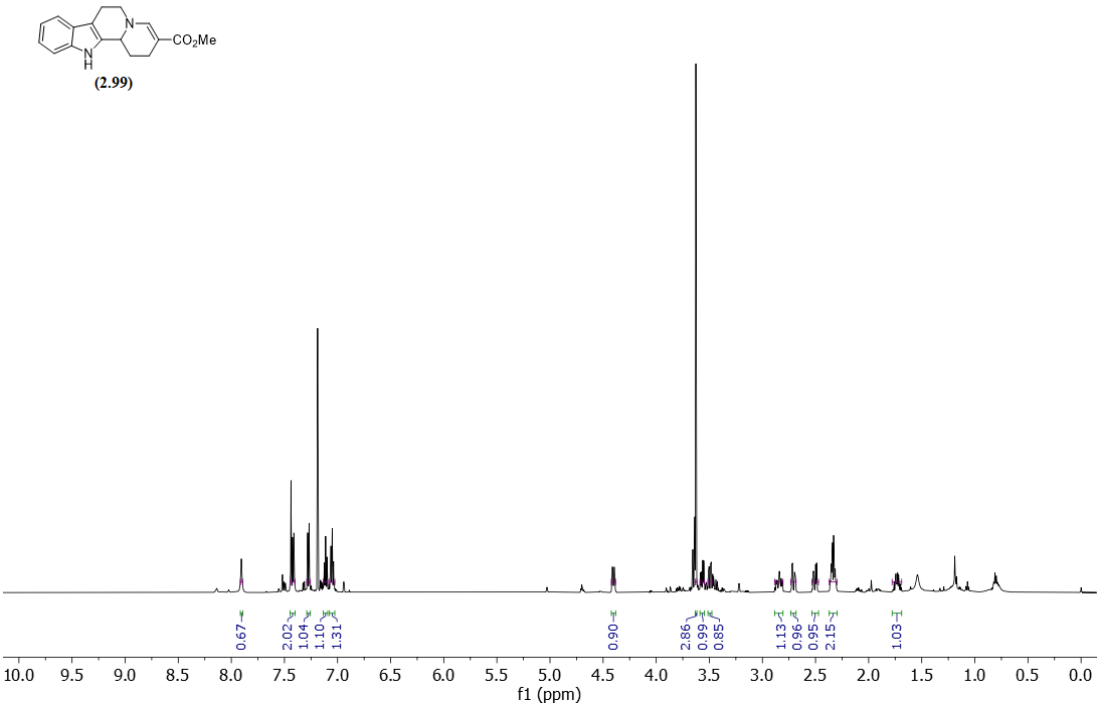
(2.96)

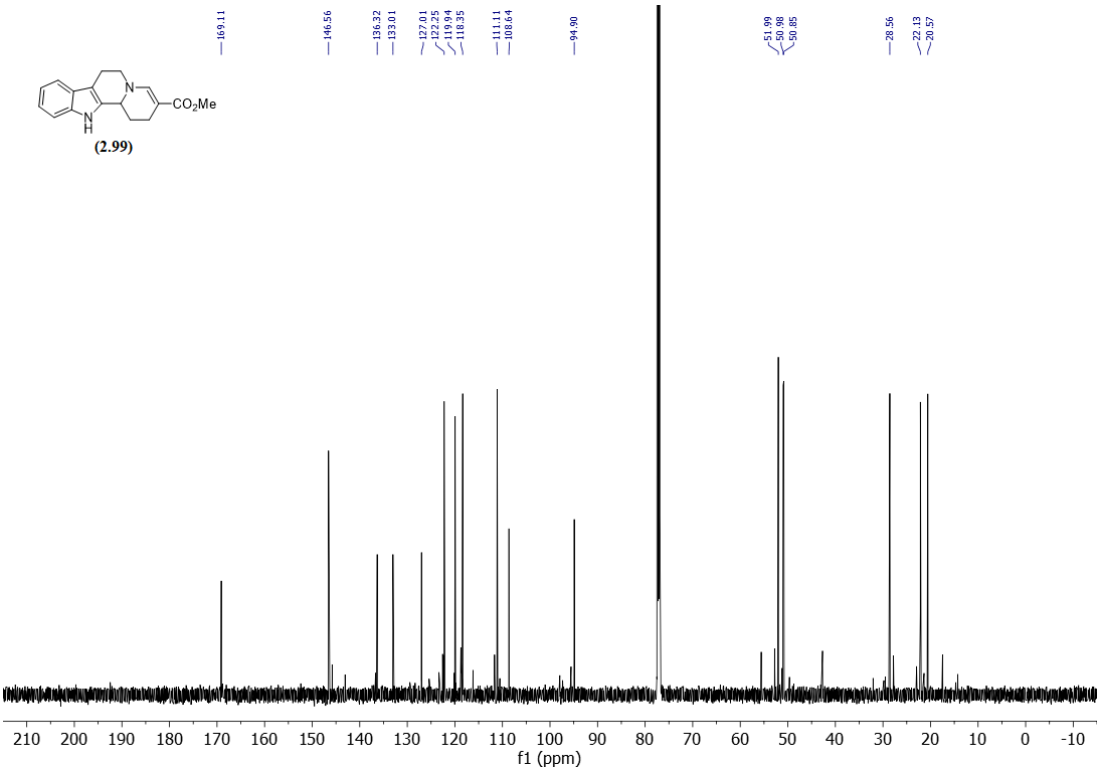
0.88
1.02
1.02
1.06
1.07
1.07
0.98
1.02
3.03
2.33
1.12
1.04
1.06
1.14
1.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

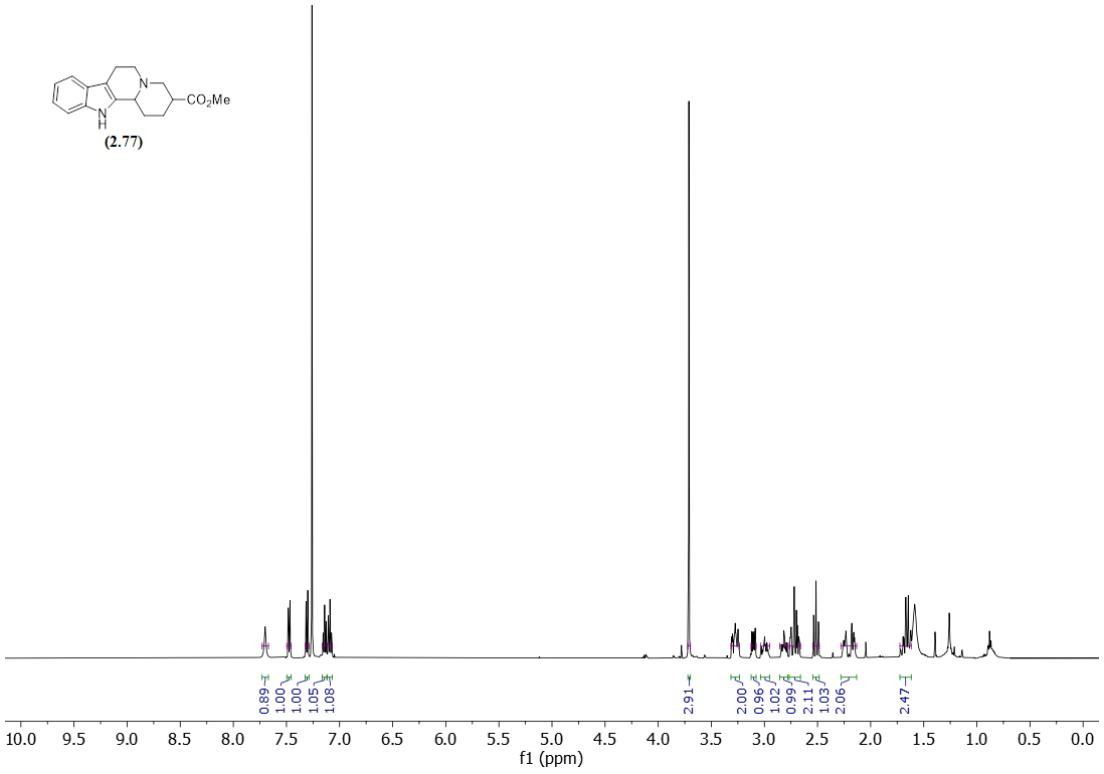

169.24
145.88
136.69
125.39
122.48
119.90
118.67
116.01
111.70
95.45
55.55
52.75
50.88
42.69
27.78
17.46
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

CO2Me
N
Cl
N
H

(2.96)


CO2Me
(2.99)
0.67
2.02
1.04
1.10
1.31
0.90
2.86
0.99
0.85
1.13
0.96
0.95
2.15
1.03
f1 (ppm)


169.11
146.56
136.32
133.01
127.01
122.25
119.44
118.95
111.11
108.64
94.90
51.99
50.98
50.85
28.56
22.13
20.57
CO2Me
(2.99)
f1 (ppm)


CO2Me
(2.77)
0.89
1.00
1.00
1.05
1.08
2.91
2.00
0.96
1.02
0.99
2.11
1.03
2.06
2.47
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)