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DEVELOPMENT OF DEAROMATIVE FUNCTIONALIZATIONS IN ORGANIC CHEMISTRY

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Chapter 1: Dearomatization Introduction

1.1 Classic Dearomatization

Aromatic compounds are some of the most abundant and inexpensive raw materials available to chemists. These molecules play a significant role in modern society as their functionalized products are used to access a wide range of valuable intermediates for fuels, paints, polymers, pharmaceuticals, and agrochemicals. Unsurprisingly, the reactivity of these molecules has been well documented and is unique compared with the reactivity of other organic compounds. This is due to their high electronic stabilization, which renders them inert to many traditional chemical transformations but provides them with a unique avenue of reactivity.[1] Reactions that could introduce functionality while also removing the aromatic nature of these compounds, dearomative functionalizations, proved to be challenging. Therefore, reliable methods that can carry out this type of transformation are highly sought after. Several strategies for the dearomatization of organic compounds have been developed over the years. However, many of the commonly used dearomative strategies do not incorporate functionality through the dearomatization process and the compounds need to be subjected to many further manipulations to install the desired level of functionalization (**Figure 1.1**).[1-5] One of the most used dearomative transformation is the hydrogenation, which generally proceeds in a similar fashion to olefin hydrogenation however under more forcing conditions.[6-7] Despite the lack of functionality introduced, it

is still a highly synthetically useful reaction and has been used to access numerous bioactive compounds, such as the antiviral drug oseltamivir (Tamiflu) (**1.1**).[8-10] Another strategy is the venerable Birch reduction.[11] This reaction involves the initial single-electron reduction of the arene, followed by the addition of another electron, resulting in the formation of 1,4- dienes. Oxidative dearomatization is also commonly used to dearomatize arenes.[12] It involves the addition of a nucleophile into an activated phenol, providing γ-substituted dienone products. This approach has been used in many syntheses, including the synthesis of morphine (**1.2**).[13-15] Other approaches such as microbial oxidation employs an enzyme designed to dihydroxylate arenes in order to access dihydrodiols.[16] It has also been used in a variety of total syntheses including approaches toward (–)-doxycycline (**1.3**).[17] Another strategy, the *meta*-photocycloaddition initially developed by Wender and coworkers,[18] involves the ultra-violet light-mediated cycloaddition of an arene and an olefin to provide the bicyclic system shown in **Figure 1.1**. This strategy was applied in the synthesis of bioactive compounds in the total synthesis of (+)-nominine.[19,20] The last example of a dearomative functionalization reaction is transition-metal-mediated dearomatization. Several metals such as Os, Ru, Re, Cr and Mn have been shown to form complexes which can adopt either an η^2 - or η^6 - coordination mode that greatly reduces the aromatic character of arene and allows them to react with electrophiles or nucleophiles, depending on the transition-metal used. [21-24] Subsequent oxidative decomplexation is required to isolate the desired dearomatized products. While this strategy can provide

access to highly complex products, the toxicity and cost of forming these stoichiometric arene complexes have limited their synthetic use.

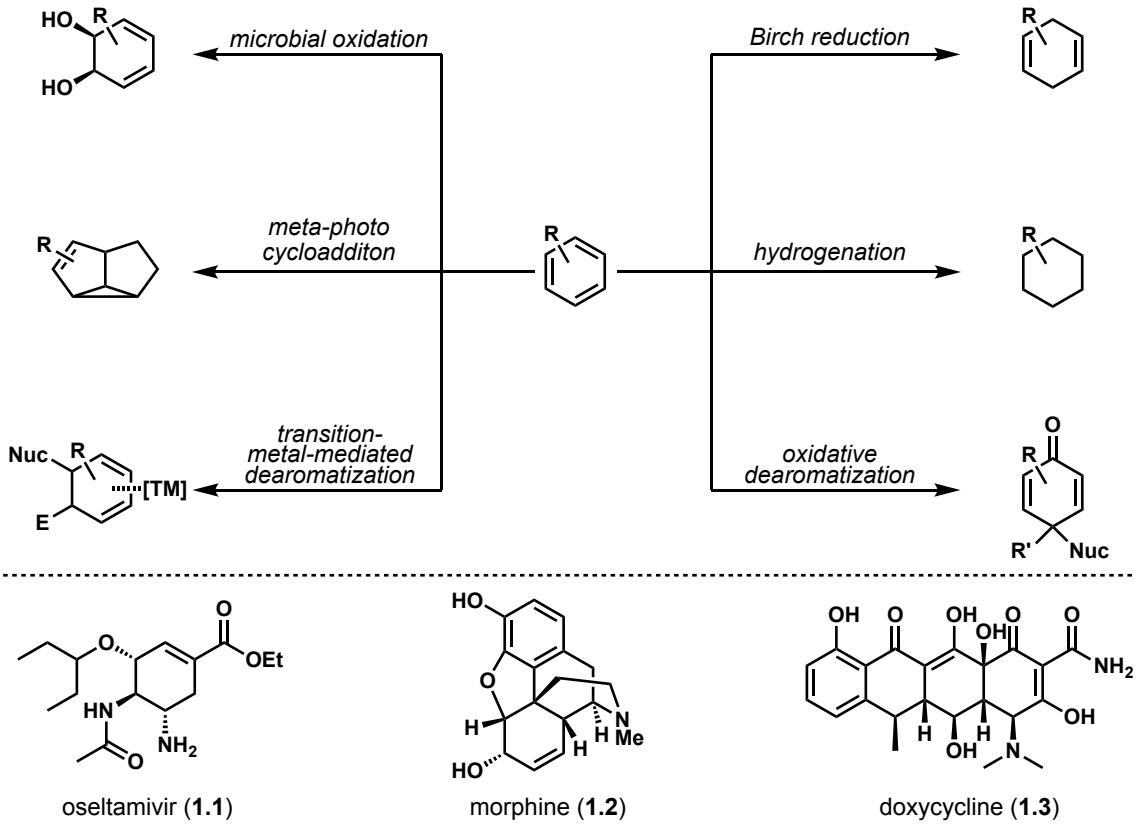

Figure 1.1. Current strategies for arene dearomatization and natural products they can provide access to.

1.2 Arenophile-Mediated Dearomatization

In 1984, Sheridan and coworkers published a unique strategy involving visible-light-promoted dearomative [4+2] cycloaddition between naphthalene (**1.4**) and N-methyl-1,2,4-triazoline-3,5-dione (MTAD) (**1.5**),[25] delivering the naphthalene-MTAD para-cycloadduct **1.6** (**Figure 1.2**). They were able to isolate this product in a 40% yield, however, it had a half-life of just 12 hours at room temperature. A few years later, a similar transformation was reported from the same group on benzene (**1.7**),[26] however, this cycloadduct, **1.8**, was much less stable than **1.6,** and they were only able to observe its formation using low-temperature NMR. The half-life of this benzene-MTAD cycloadduct (**1.8**) was calculated to be 1 hour at 0 °C. Although MTAD is known to participate in thermal [4+2] reactions,[27] these reports established its highly efficient and selective photocycloaddition on simple arenes such as benzene and naphthalene. To further understand this reactivity, Sheridan performed several mechanistic studies in order to elucidate some of the details of this transformation.[28,29] Sheridan's results from quantum yield data, suggested that the photoaddition of MTAD and naphthalene proceeds via both singlet and triplet MTAD states and that it is most likely a concerted process. He showed that electron transfer from naphthalene to singlet excited MTAD (^{1}MTAD*) is an exergonic process, while electron transfer from benzene to ^{1}MTAD* is an endergonic process. This suggests that the cycloaddition between a polynuclear arene and MTAD

could be proceeding through a different mechanism than the cycloaddition between a mononuclear arene and MTAD. Years later, Breton and co-workers have reported on the reversibility of the cycloaddition between MTAD and a variety of naphthalene derivatives.[30] Based on these reports[28-30], these cycloadditions are thought to proceed likely through the formation and collapse of one of the two exciplex's shown in **Figure 1.2**. In the case of a photo-induced electron transfer exciplex (which can be estimated by Rehm-Weller model),[32] the arenophile (MTAD) is first excited by visible light. This excited species can then form an exciplex with an arene, and if the HOMO of the arene is higher in energy than the arenophile's SOMO, then an electron transfer can occur. Our group performed a computational frontier molecular orbital analysis of several small organic molecules using benzene (1a) (HOMO = −9.9 eV) and naphthalene (2a) (HOMO = −8.4 eV) as benchmarks (**Figure 1.2b**). Thus, a number of different 1,2,4-triazoline-3,5-diones, A1 (HOMO = −11.2 eV, LUMO = −9.7 eV), A2 (HOMO = −10.8 eV, LUMO = −9.7 eV), A4 (HOMO = −10.8 eV, LUMO = −9.3 eV) and A5 (HOMO = −10.4 eV, LUMO = −8.9 eV), and certain symmetric cyclic (Z)-diazo-containing compounds connected to electrondeficient groups, such as A3 (HOMO = −10.9 eV, LUMO = −9.5 eV) and A6 (HOMO = −9.9 eV, LUMO = −8.8 eV), were found to meet the electronic criteria to react with benzene. Although A1, A2 and A4 all showed the desired reactivity, our group decided to continue our investigations with 4-methyl-1,2,4-triazoline-3,5-dione (**1.5**) because of the ease of its preparation and its stability.

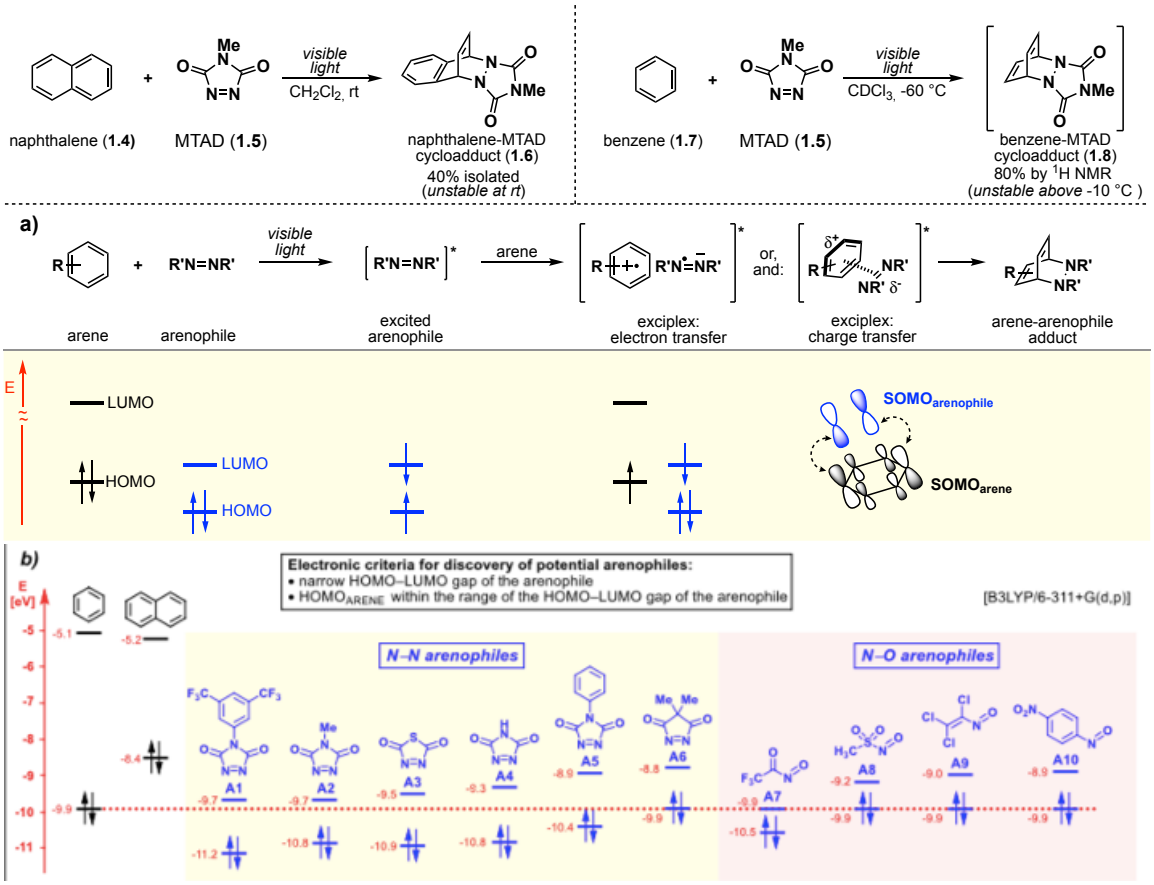

Figure 1.2. a) Initial discovery of MTAD as an arenophile, mechanistic hypotheses and b) relative energies.

Another possibility is the formation of a charge transfer complex, since this has also been shown to be a viable pathway to form the cycloadducts, due to the correlation of decreasing E_{CT}(MTAD) (energies of the charge-transfer absorption bands between MTAD and various substituted benzenes) with decreasing E_{pa} (peak potentials determined by cyclic voltammetry).[28,32] The synthetic potential that these arene-MTAD cycloadducts possess, brought our laboratory, over the past years, to explore their reactivity. We have noted several aspects regarding these cycloadditions in our research that highlight the synthetic

utility of these intermediates: 1) Simple commercial-grade visible light diodes are strong enough to quantitatively yield the cycloadducts in few hours on small scale. Additionally, the reactions can be monitored colorimetrically as the characteristic bright pink color of MTAD disappears once the cycloaddition is complete. 2) Various solvents can be used to perform these cycloadditions, including dichloromethane, ethyl acetate, propionitrile, and acetone. 3) While Sheridan initially reported the decomposition of the benzene-MTAD cycloadduct at –10 °C, we found that it is only stable at temperatures below –50 °C. Slow cycloreversion back to MTAD (**1.5**) and benzene (**1.7**) was observed between –50 °C and – 30 °C, and rapid cycloreversion was observed above –20 °C.

With these principles in mind, we have developed two main types of reactivity: 1) olefin functionalization, in which we intercept the newly formed double bond and functionalize it employing known olefin chemistry and 2) allylic substitution, in which we can harness the bis-allylic bridgehead amide bond as a leaving group in an allylic substitution reaction. These reaction manifolds have proven highly synthetically useful, and we have been able to access a variety of unique compounds that have allowed for the facile synthesis of multiple medicinally relevant compounds.

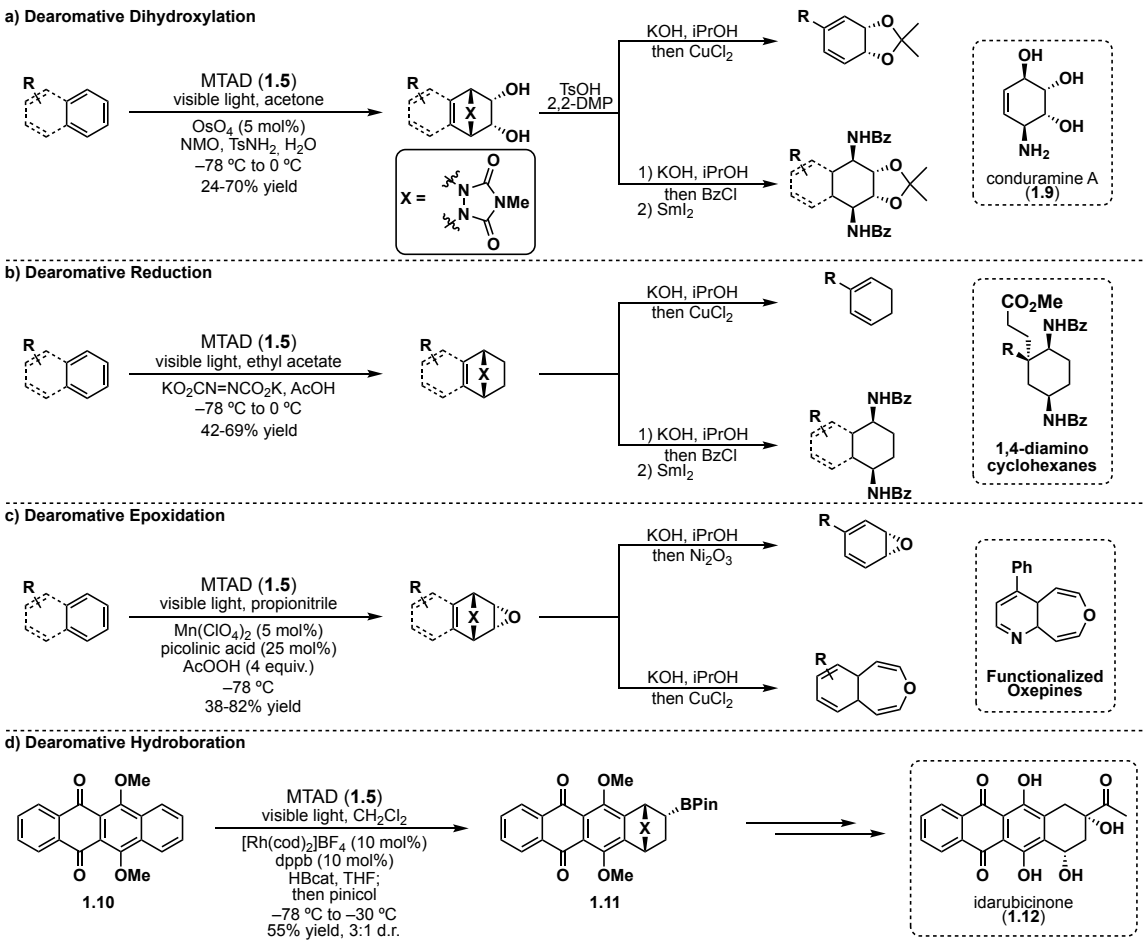

Figure 1.3. Olefin functionalization of the arene-MTAD cycloadducts. a) Dearomative Dihydroxylation. b) Dearomative Reduction. c) Dearomative Epoxidation. d) Dearomative Hydroboration.

The first strategy developed by our laboratory was a dearomative dihydroxylation. We found that treating these cycloadducts with Upjohn dihydroxylation conditions with $TsNH_2$ as additive, provided the desired diols (**Figure 1.3a**).[33] This reaction was performed on several monosubstituted benzenes as well as substituted naphthalenes. After protection as acetonide, the corresponding dihydrodiols could be obtained by cleaving the urazole

ring to the cyclic hydrazine using KOH, followed by $CuCl_2$ oxidation of the cyclic hydrazine which could undergo cycloreversion to release N_2 and deliver the product. Diaminodiols could also be obtained by first benzoylation of the cyclic hydrazine intermediate, followed by treatment with SmI_2 to cleave the N–N bond (**Figure 1.3a**). This method has been used to access multiple bioactive compounds, such as the glycosidase inhibitor conduramine A (**1.9**). Another strategy made use of diimide reduction conditions on these cycloadducts in order to access dearomative reduction products (**Figure 1.3b**).[34] We have been able to derivatize these dienes to obtain substituted 1,3-cyclohexadienes as well as 1,4-diamino cyclohexanes. Dearomative epoxidation reactions have also been shown to proceed smoothly (**Figure 1.3c**).[35] When performing cycloreversion on these epoxides we found that the monoarenes were in equilibrium between the oxepine and the corresponding arene oxide species, favoring the arene oxide. On the other hand, when cycloreverting substituted naphthalene epoxides, we found that they selectively formed the benzoxepine species. Finally, the latest olefin functionalization strategy reported was the dearomative hydroboration.[36] While this strategy is highly limited in its scope, only providing the desired products on polynuclear arenes, its synthetic utility is promising. We have been able to employ this strategy towards the total synthesis of idarubicinone (**1.12**), the aglycone of the FDA-approved anthracycline idarubicin.

Aside from olefin functionalization advances of these cycloadducts, our group has also made considerable progresses in the allylic substitution of these intermediates. Our

initial findings in this area consisted of a dearomative trans-1,2-carboamination reaction, employing Grignard reagents and a nickel catalyst.[37,38] This transformation has been applied also to synthesize a variety of other products with different nucleophiles and constitutional isomeric selectivity.

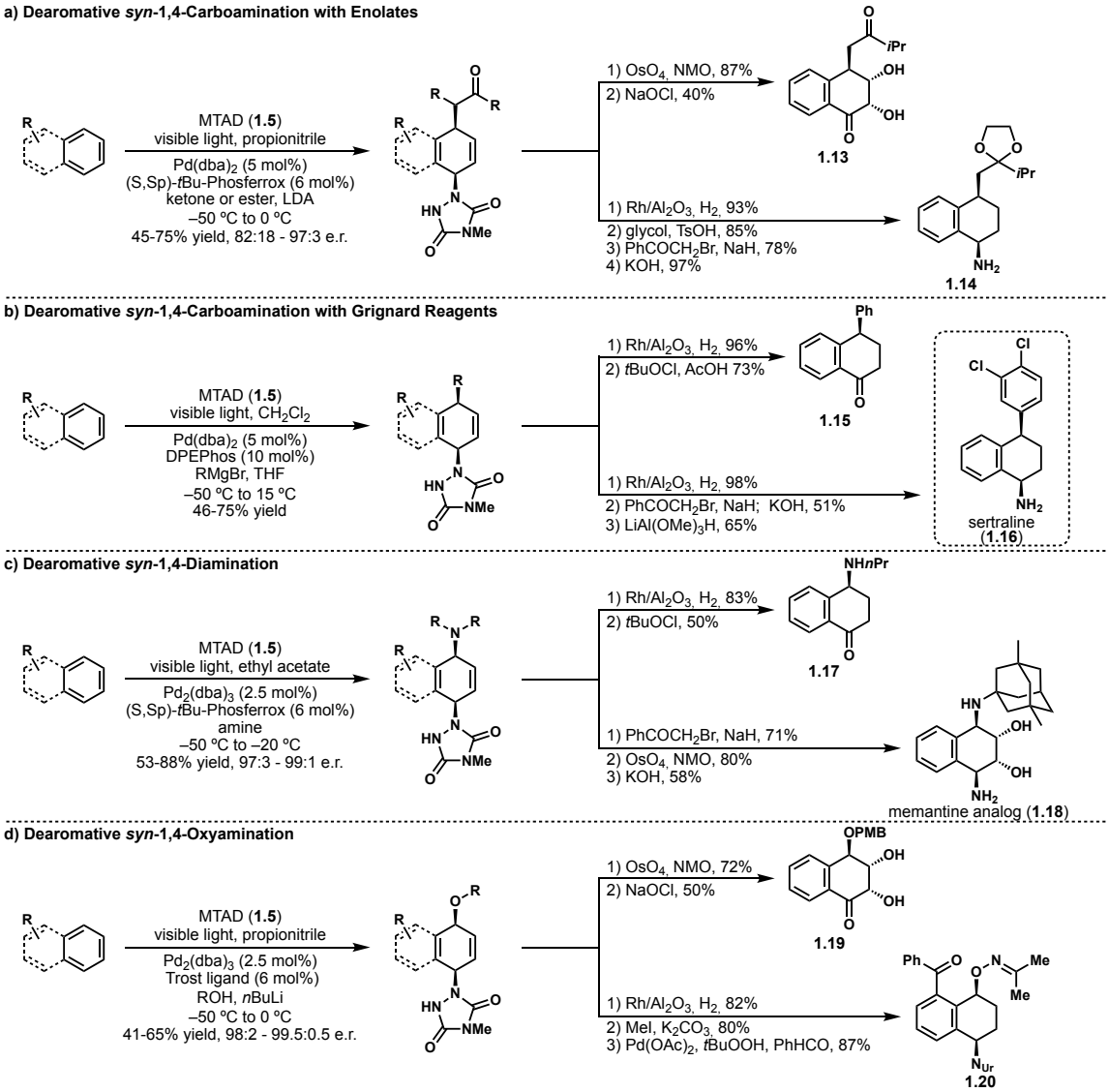

Figure 1.4. Allylic substitution of the arene-MTAD cycloadducts. a) Dearomative *syn*-1,4-Carboamination

with Enolates. b) Dearomative *syn*-1,4-Carboamination with Grignard Reagents. c) Dearomative *syn*-1,4-Diamination. d) Dearomative *syn*-1,4-Oxyamination.

After the dearomative *trans*-1,2-carboamination conditions were developed, we found out that we could employ enolates, using palladium in place of nickel.[39] This enantioselective dearomative *syn*-1,4-carboamination with enolates was able to provide a variety of chiral 1,4-cyclohexadienes that could be further elaborated to various substituted cyclohexanes and tetrahydronaphthalenes. Upjohn dihydroxylation of these products followed by oxidative cleavage of the urazole ring was able to provide dihydroxyketone **1.13** (**Figure 1.4a**). Furthermore, Rh/Al_2O_3 catalyzed reduction, acetyl protection, and urazole alkylation with $PhCOCH_2Br$ set up a base-mediated urazole cleavage that provided free amine **1.14**. Similar conditions employing Grignard reagents provided similarly substituted products,[40] synthetizing ketone **1.15** through a reduction and oxidation sequence. Additionally, a similar steps used to access **1.14** could be employed to achieve sertraline (**1.16**), a commonly used selective serotonin reuptake inhibitor (SSRI). An enantioselective dearomative *syn*-1,4-diamination was also developed using a palladium catalyst and amine nucleophiles.[41] We were able to show that these products could be used to synthesize amino ketones such as **1.17** as well as diaminodiols such as the memantine analog **1.18**. Lastly, lithiated oximes and benzyl alcohols were used as nucleophiles for this palladium-catalyzed allylic substitution reaction.[42] Using similar functionalization strategies as before we have been able to show that we can access the *para*- methoxybenzyl

protected ketone triol **1.19**. Furthermore, we were able to show that we could harness the oxime we had installed as a directing group to perform a directed C-H acylation reaction, providing diaryl ketone **1.20**. These dearomative strategies offer rapid access to more complex, and synthetically useful intermediates from readily available sources of hydrocarbons. In this dissertation, I will describe our recent efforts to expand this chemistry. Chapter 2 will focus on the description of the development of a novel dearomative functionalization reaction. Chapter 3 will describe the use of the dearomative *trans*-1,2-carboamination reaction towards the incomplete synthesis of the *Amaryllidaceae* isocarbostyril alkaloids belonging to the homolycorine family.

1.3 References

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Chapter 2: Development of Novel Dearomative Arenophile-Based Cyclopropanation

2.1 Introduction

Medium-sized rings occupy a unique chemical space and can be valuable in a variety of different fields, such as medicinal and materials chemistry.[1] Specifically, benzo-fused medium-sized ring structures that contain several substituents are of great importance, as shown by various bioactive benzo-fused cycloheptatriene-containing compounds. This type of motif is present in several natural products and biologically active compounds such as colchicine (**2.1**), a drug used to treat gout as well as familial Mediterranean fever[2] and the benzosuberones bearing coumarin moieties **2.2**, which showed promising growth inhibition effects on alveolar adenocarcinoma, cervical cancer and breast adenocarcinoma cell lines.[3] Moreover, this scaffold is also present in theaflavin (**2.3**) and derivatives thereof, which are antioxidant benzotropones possessing numerous biological activities (antipathogenic and anticancer activity) and can also be used to treat heart disease, hypertension, and diabetes;[4-5] and in the estrogen receptor (ER) modulators **2.4** (**Figure 2.1A**).[6] The first synthesis of a benzocycloheptatriene compound was reported in 1955 by Hargreaves and Downie who found that toluene pyrolysis led to the formation of 3,4-benzocycloheptatriene.[7] Later, in 1958, Wittig and coworkers reported another synthesis of 3,4-benzocycloheptatriene, which proceeded through the reaction of

phthalaldehyde (**2.5**) with bis-ylide **2.6**.[8] In 1970, Rh^{II}-catalyzed cyclopropanation was employed by Swenton and Madigan to access these types of compounds. Cyclopropanation of 1,4-dihydronaphthalene (**2.7**), followed by benzylic bromination with NBS and ring expansion through reductive debromination with Zn was able to provide the desired 3,4-benzocycloheptatriene.[9] Later, in 1974, Swenton and coworkers further demonstrated how 3,4-benzocycloheptatriene derivatives can be accessed from benzosuberone derivatives (**2.8**) through bromination, base-mediated elimination, tosyl hydrazone formation and treatment with base.[10]

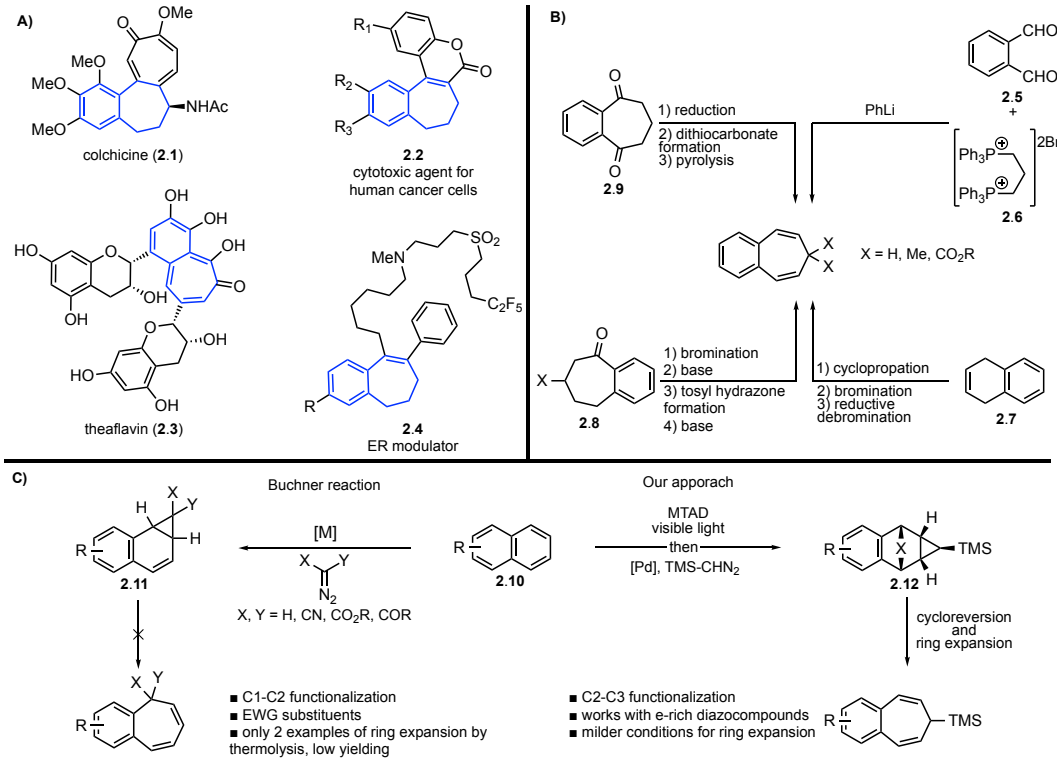


Figure 2.1. A) Examples of biologically active compounds containing the benzocycloheptatriene moiety. B) Previous methods for preparation of 3,4-benzocycloheptatrienes. C) Polynuclear arenes direct cyclopropanation, Buchner reaction and this work.

Finally, in 1986, another approach from Descotes and coworkers showed how 3,4-benzocycloheptatriene could be synthetized through reduction of diketone **2.9**, transformation of the resulting diol to dithiocarbonates followed by thermolysis of this intermediate, providing the desired product in low yield (**Figure 2.1B**).[11]

Another way to form benzocycloheptatrienes could be through dearomatization. Aromatic compounds are important and abundant feedstock chemicals from petrochemical refining. Dearomative transformations of these simple scaffolds have allowed to turn them into more valuable products.[12-14] Several strategies have been developed to convert simple arenes into versatile intermediates, one of these is the Buchner ring expansion. This reaction was first discovered in 1885,[15] and proceeded through the addition of ethyl diazoacetate to benzene. Mononuclear arenes have received particular attention in this field, forming norcaradienes which are in equilibrium with their cycloheptatriene form.[16] Several inherent challenges concerning the regio- and stereoselectivity, as well as the tautomeric composition have been addressed over the years by many groups.[17-19] On the other hand, the same transformation on polynuclear arenes (**2.10**), which occurs exclusively on the C1-C2 bond, stops at the benzonorcaradiene form due to geometrical constraints and loss of aromaticity during the valence bond tautomerization (**2.11**).[20] Only two examples are known in which thermal decomposition of benzonorcaradienes gives 3,4-benzocycloheptatriene as a product, however both occurred in low yield.[21-22] To address this gap, we hypothesized to use a different dearomative approach:

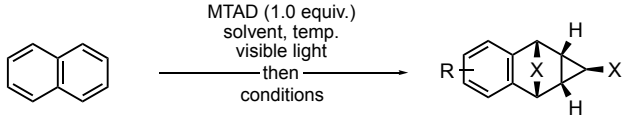
dearomatization of naphthalene derivatives (**2.10**) using MTAD, followed by palladium-catalyzed cyclopropanation with TMS-diazomethane provided cyclopropanated products **2.12** on the former C2-C3 bond of naphthalene. Subsequently, cycloreversion followed by ring expansion of the cyclopropane product gave 3,4-benzocycloheptatriene products in high yields with broad functional groups tolerance (**Figure 2.1C**).

2.2 Development of Dearomative Cyclopropanation of Polycyclic arenes

Our initial investigation into the synthesis of benzocycloheptatrienes began with the cyclopropanation of the cycloadduct formed from MTAD and naphthalene (**2.13**).[23] We explored a variety of well-established strategies for cyclopropanation including the Simmons-Smith reaction (entry 1), rhodium-catalyzed cyclopropanation (entries 2 and 3), as well as iron-, gold- and copper-catalyzed cyclopropanation (entries 4-7) . Unfortunately, neither of these reactions led to the formation of the desired products (**2.14a** and **2.14b**). However, we found that palladium-catalyzed cyclopropanation employing diazomethane, generated in situ from Diazald, gave a promising 16% yield of the desired product **2.14a** (entry 8). Wanting to use a less dangerous and easier to handle diazo compound, we found that a solution of TMS-CHN_2 in hexanes was also able to access the cyclopropanated product **2.14c** (entry 9). After an intense screening of temperature (entry 10), palladium sources and solvents (entries 11-22), we ultimately identified $Pd_2(dba)_3 \cdot CHCl_3$ as best catalyst source and that running the reaction at −50 °C in EtOAc was able to provide higher

yields of the desired product **2.14c** (79%, entry 23). Noteworthy, we found that 3 equivalents of TMS-CHN_2 were necessary to achieve synthetically useful yields (entry 24).

Table 2.1 Discovery and optimization of dearomative arenophile-based cyclopropanation.[a]



2.13
2 equiv.

2.14a (X = H)
2.14b (X = CO_2Et)
2.14c (X = TMS)

Entry	TM [mol%]	Reagent [equiv.]	Solvent	Temp. [°C]	Yield [%]
1	-	$EtZn_2$ (5)	CH_2Cl_2	-78 to 25	0
2	$Rh_2(OAc)_4$ (5)	N_2CHCO_2Et (3)	CH_2Cl_2	-78 to 25	0
3	$[Rh_2(cap)_4]$ (5)	N_2CHCO_2Et (3)	CH_2Cl_2	-78 to 25	0
4	Fe(TPP) (10)	N_2CHCO_2Et (3)	CH_2Cl_2	-78 to 25	0
5	$(Ph_3P)AuCl$ (5)	N_2CHCO_2Et (3)	CH_2Cl_2	-78 to 25	0
6	[(IPr)AuCl] (5)	N_2CHCO_2Et (3)	CH_2Cl_2	-78 to 25	0
7	CuOTf (2)	N_2CHCO_2Et (3)	CH_2Cl_2	-78 to 25	0
8	$Pd(OAc)_2$ (5)	CH_2N_2 (3)	CH_2Cl_2	-78 to 25	16
9	$Pd(OAc)_2$ (5)	$TMSCHN_2$ (3)	CH_2Cl_2	-78 to 25	5
10	$Pd(OAc)_2$ (5)	$TMSCHN_2$ (3)	CH_2Cl_2	-50 to 25	28
11	$Pd(TFA)_2$ (5)	$TMSCHN_2$ (3)	CH_2Cl_2	-50 to 25	45
12	$Pd(Piv)_2$ (5)	$TMSCHN_2$ (3)	CH_2Cl_2	-50 to 25	51
13	$PdCl_2$ (5)	$TMSCHN_2$ (3)	CH_2Cl_2	-50 to 25	52
14	$PdCl_2$ (5)	$TMSCHN_2$ (3)	EtCN	-50 to 25	0
15	$PdCl_2$ (5)	$TMSCHN_2$ (3)	acetone	-50 to 25	51
16	$PdCl_2$ (5)	$TMSCHN_2$ (3)	EtOAc	-50 to 25	58
17	$Pd(OAc)_2$ (5)	$TMSCHN_2$ (3)	EtOAc	-50 to 25	50
18	$Pd(Piv)_2$ (5)	$TMSCHN_2$ (3)	EtOAc	-50 to 25	57
19	$Pd(TFA)_2$ (5)	$TMSCHN_2$ (3)	EtOAc	-50 to 25	60

20	$[Pd(allyl)Cl]_2$ (5)	$TMSCHN_2$ (3)	EtOAc	-50 to 25	35
21	$PdCl_2(PPh_3)_2$ (5)	$TMSCHN_2$ (3)	EtOAc	-50 to 25	0
22	Pd_2dba_3 (5)	$TMSCHN_2$ (3)	EtOAc	-50 to 25	64
23	$Pd_2dba_3{\cdot}CHCl_3$ (5)	$TMSCHN_2$ (3)	EtOAc	-50 to 25	79
24	$Pd_2dba_3{\cdot}CHCl_3$ (5)	$TMSCHN_2$ (1.5)	EtOAc	-50 to 25	35

[a] Standard reaction conditions: MTAD (1.0 mmol, 1.0 equiv.), naphthalene (2.0 mmol, 2.0 equiv.), solvent (0.2 M), visible light, temperature, 12 h; then addition of a solution of catalyst, diazo reagent, temperature, 18 h. dba = dibenzylideneacetone

Having identified optimal conditions for the cyclopropanation, we started exploring the compatibility of this chemistry with different functionalities. Several 1-, 2- and 1,4-substituted naphthalene derivatives were tested which provided moderate to good yields of the desired products (**Figure 2.2**). We found that a variety of functionalities were tolerated, such as chlorine, fluorine and trifluoromethyl (**2.15 – 2.18**), nitrile (**2.19** and **2.20**) and nitro group (**2.21**). Ketones and aldehydes worked but were quite unstable upon purification, so we opted to first protect them as dimethoxyacetals (**2.22 – 2.25**), which proved to be more stable. Moreover, trimethylsilyl (**2.26**), phenyl (**2.27**) and ester group worked as well (**2.28 – 2.33**). To further broaden the scope of the cyclopropanation, we tested polycyclic heteroarenes such as quinolines and their derivatives. Although plain quinoline didn't react at all, these conditions translated well for 2-substituted quinoline derivatives possessing phenyl (**2.34**), tert-butyl (**2.35**), ester (**2.36**), alkoxy (**2.37**), chlorine (**2.38**) and trifluoromethyl (**2.39**) group next to the nitrogen. Also, benzo[*h*]quinoline (**2.40**) proved a viable substrate for this transformation. Noteworthy, in all cases the

palladium-catalyzed cyclopropanation delivered the products as a single diastereoisomer (see crystallographic data of compound **2.14c**). Subsequently, we started exploring the retrocycloaddition step, to reveal the desired benzocycloheptatrienes. The cycloreversion proceeded smoothly applying the same conditions used for the dearomative epoxidation developed by our group.[24] Exposure of polycyclic compound **2.14c** to KOH in *i*-PrOH at 40 °C, followed by copper-catalyzed oxidation under oxygen atmosphere, gave the desired product **2.41** in 75% yield. In this sequence, urazole undergoes partial hydrolysis/decarboxylation and the resulting cyclic semicarbazide intermediate is subjected to further oxidation,[25] resulting in extrusion of dinitrogen and ring expansion. Most of the functionalities that were tolerated in the previous step were found to still work well (**2.42 – 2.54**, **Figure 2.3**), with the only exception of the ester groups which were hydrolyzed during treatment with KOH and couldn't get oxidized in the following step, probably due to complexation of the carboxyl or phenoxyl group to the copper. The ketones and aldehydes, protected as acetals, were deprotected during the acid workup to reveal the desired products (**2.49 – 2.52**). Notably, during the Cu-catalyzed cycloreversion step, a complete protodesilylation and olefin isomerization occurred in the case of **2.55** and **2.56**, furnishing products as 9H-cyclohepta[b]pyridine derivatives.

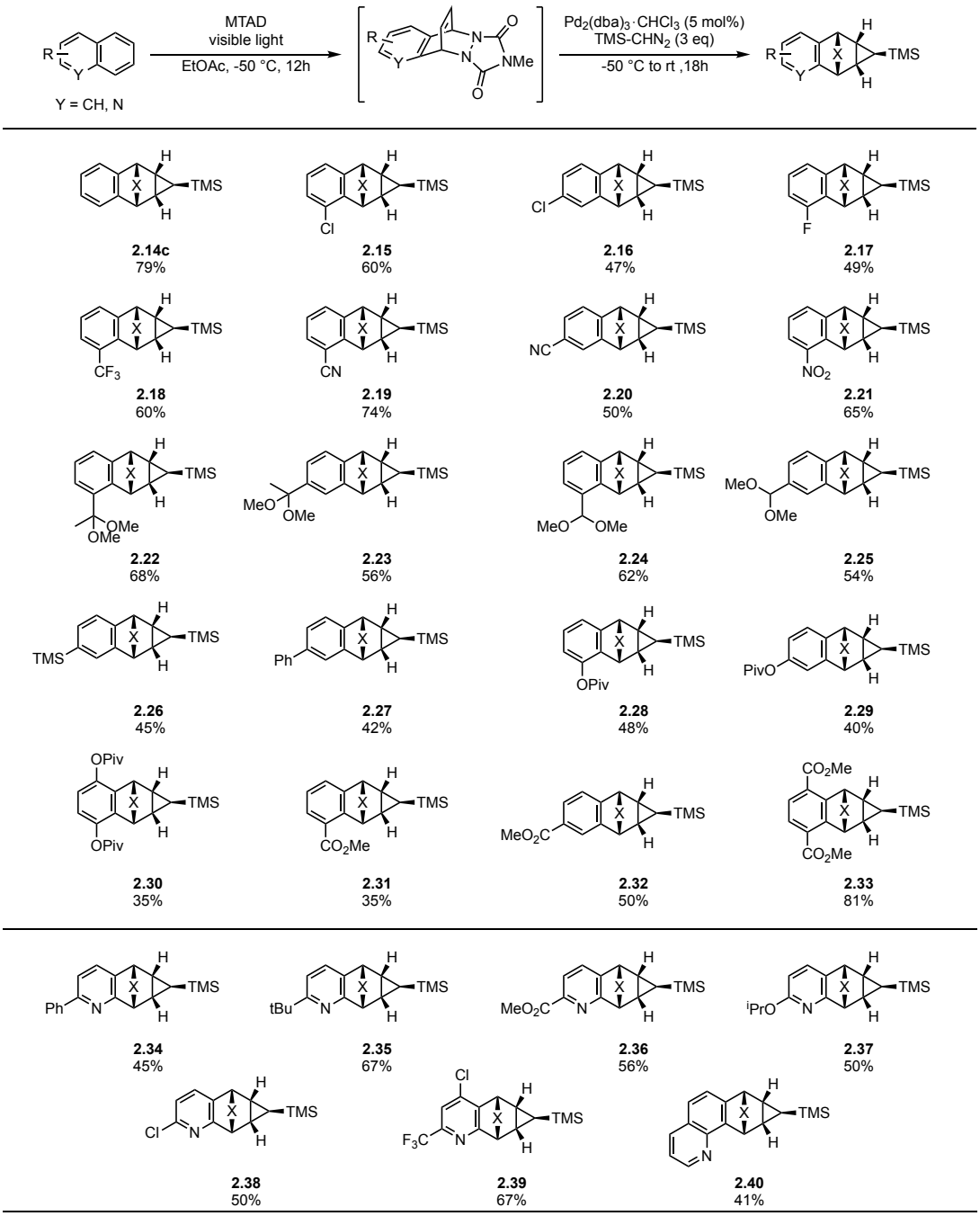


Figure 2.2. Scope of the cyclopropanation step on naphthalenes and quinolines.

On the other hand, the use of Ni_2O_3 was required to secure products **2.57 – 2.60**, as inseparable mixtures of silylated and protodesilylated products were observed under Cu-catalyzed oxidation. Importantly, no nitrogen oxidation at the heterocyclic nucleus was observed under these conditions. Noteworthy, when compound **2.39** was treated with the aforementioned conditions, the product resulting from S_NAr with the solvent was partially observed. This observation made us change the solvent from *i*-PrOH to a less sterically hindered EtOH, which resulted in higher conversion of the starting material to the product **2.59**.

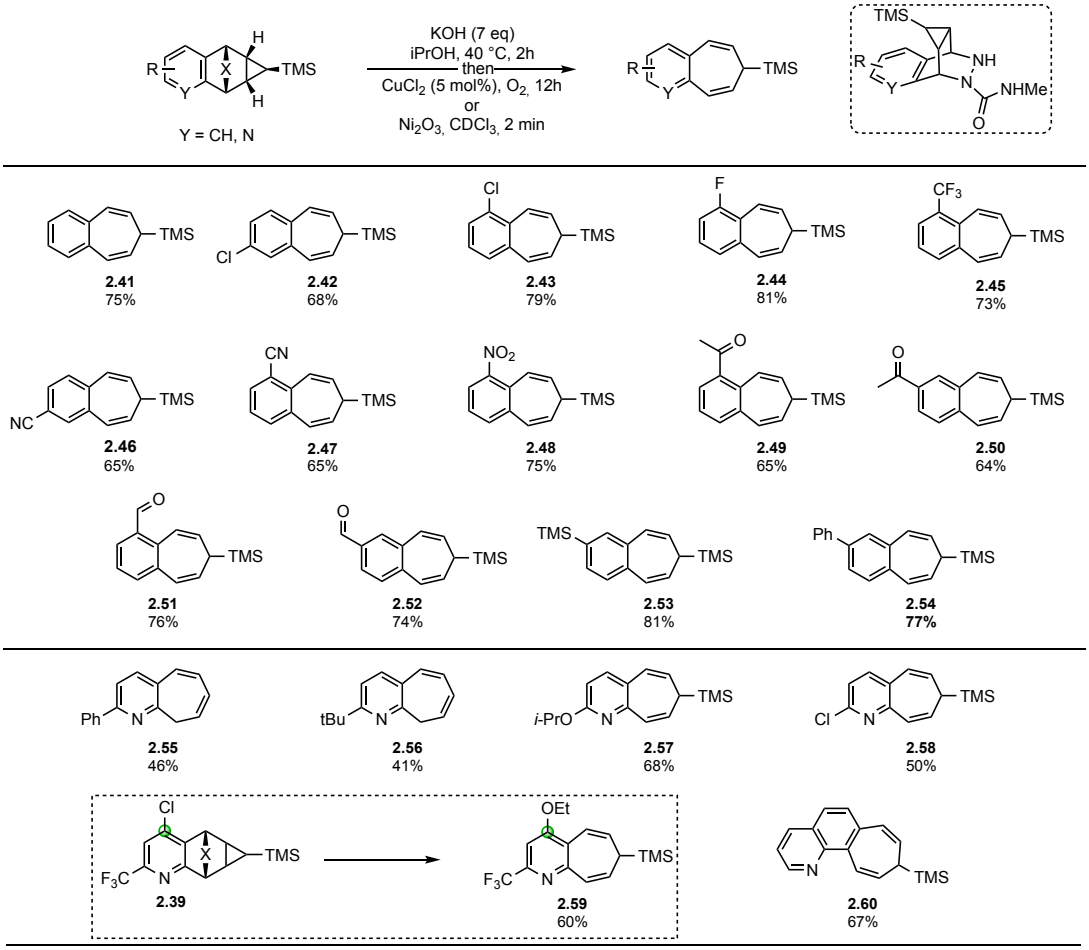


Figure 2.3. Scope of the retrocycloaddition step on naphthalenes and quinolines.

Silyl-substituted benzocycloheptatrienes of this type are not known, giving the opportunity to explore their reactivity, ultimately giving access to diverse and structurally elaborated small molecules (**Figure 2.4**). Thus, treatment with nitrile oxide gave diastereomeric [3+2] dipolar cycloaddition products **2.61a** and **2.61b**.[26] Also, a diastereoselective Upjohn dihydroxylation[27] provided diol **2.62** as a single diastereoisomer, which could undergo desilylation upon treatment with KH (**2.63**).[28] The

relative stereochemistry of compound **2.62** was assessed through formation of diester **2.64** and X-ray crystallography of this product. Exposure of compound **2.41** to $BF_3 \cdot Et_2O$ resulted in olefin isomerization (**2.65**), while standard hydrogenation gave complete reduction of the diene motif (**2.66**). The direct TMS-group removal proved possible with compound **2.41**,[29] albeit concurrent olefin isomerization to 1,2-benzotropilidene **2.67** was observed under required conditions. Furthermore, this diene substrate can undergo oxidation with CrO_3/pyridine, providing 2,3-benzotropone (**2.68**) and 4,5-benzotropone (**2.69**). These same conditions applied on compound **2.41** provided 2,3-benzotropone derivative **2.70**. Finally, in order to obtain unsubstituted 3,4-benzotropilidene (**2.71**), the desilylation was executed concurrently with the cycloreversion step on intermediate **2.14c**, constituting the first direct and practical CH_2 insertion strategy into the 2,3-position of the polycyclic arenes.

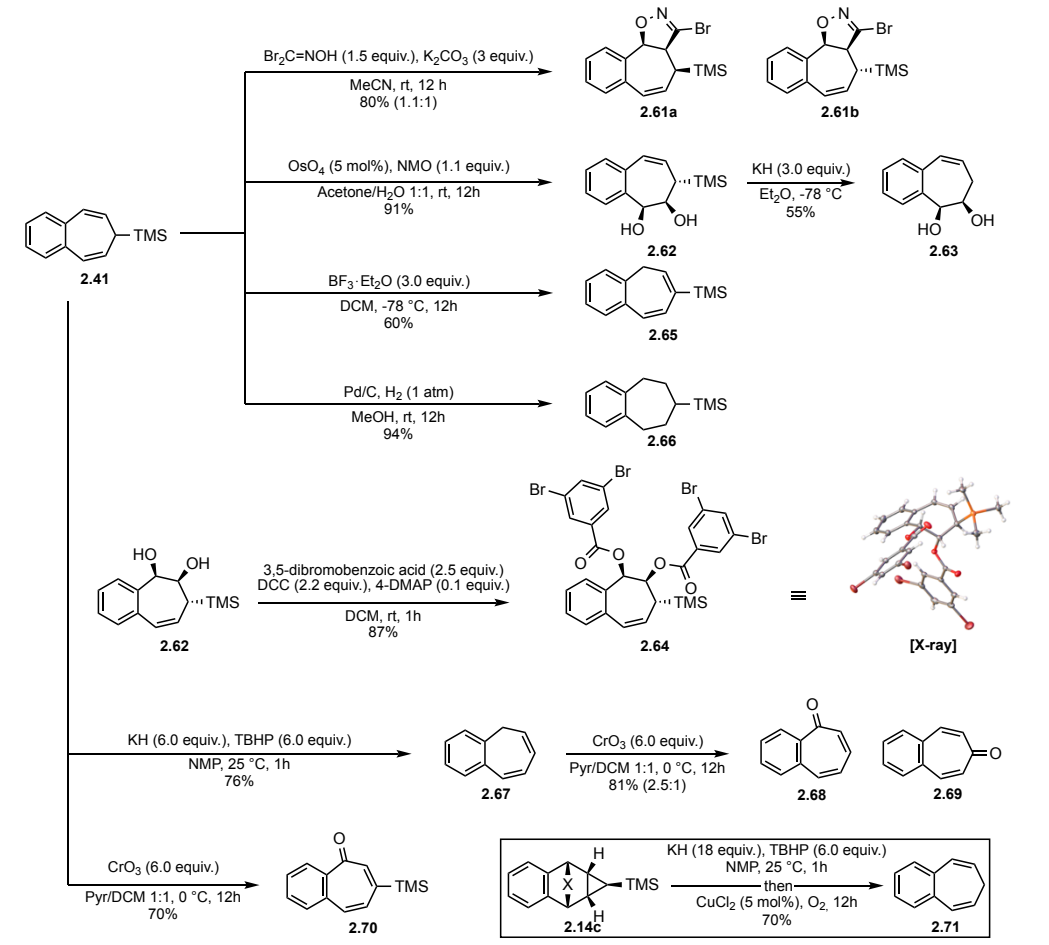


Figure 2.4. Diversification of product **2.41** and two-step methylene 2,3-insertion into naphthalene.

2.3 Conclusions

In summary, we were able to develop a dearomative ring-expansion of simple and nonactivated polycyclic arenes and heteroarenes through an arenophile-based cycloaddition and palladium-catalyzed cyclopropanation strategy. This approach resulted in cyclopropanation, followed by ring-expansion on the 2,3-site of arenes, providing a Buchner-like reaction to occur, giving access to (aza)benzocycloheptatrienes which can be functionalized in several ways, including oxidation to benzotropone intermediates and other elaborated benzocycloheptanes. Due to the common occurrence of these structural motifs in biologically active compounds, as well as lack of rapid synthetic approach for their preparation, this methodology is expected to find application in medicinal and natural products chemistry.

2.4 References

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2.5 Experimental section

General experimental:

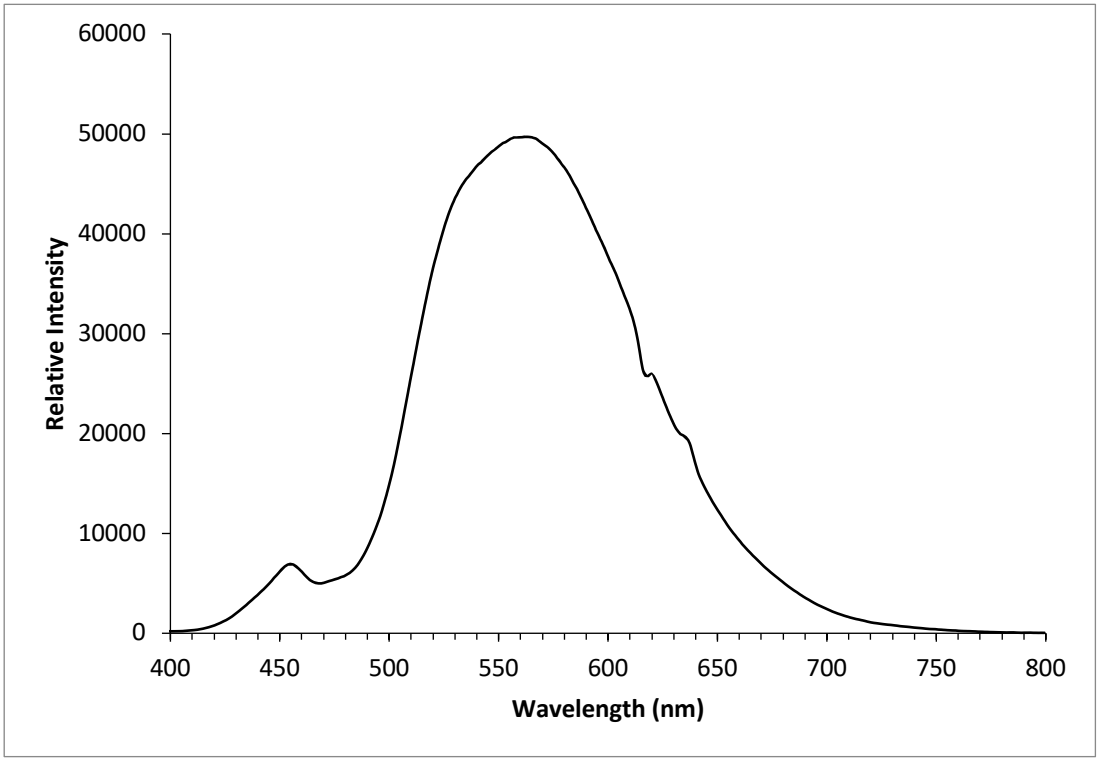
Unless otherwise noted, all reactions were carried out under an ambient atmosphere. All chemicals were purchased from commercial suppliers and used as received. *N*-methyl-1,2,4-triazoline-3,5-dione (MTAD) was prepared based on the literature procedures[1] and was resublimed before use. Dry dichloromethane (CH_2Cl_2), and tetrahydrofuran (THF) were obtained by passing commercially available anhydrous, oxygen-free HPLC-grade solvents through activated alumina columns. Analytical thin-layer chromatography was performed on Merck silica gel 60 F254 aluminum plates. Visualization was accomplished with UV light and/or potassium permanganate ($KMnO_4$). Retention factor (R_f) values reported were measured using a 5 × 2 cm TLC plate in a developing chamber containing the solvent system described. Flash column chromatography was performed using Silicycle SiliaFlash® P60 (SiO_2, 40-63 μm particle size, 230-400 mesh). ^1H and ^{13}C NMR spectra were recorded on Bruker 500 (500 MHz, ^1H; 126 MHz, ^{13}C) or Varian Unity Inova 500 (500 MHz, ^1H) spectrometers. Spectra are referenced to residual chloroform (δ = 7.26 ppm, ^1H; 77.16 ppm, ^{13}C), residual methanol (δ = 3.31 ppm, ^1H; 49.00 ppm, ^{13}C), residual benzene (δ = 7.16 ppm, ^1H; 128.06 ppm, ^{13}C), residual H_2O (δ = 4.76 ppm, ^1H) or residual dimethyl sulfoxide (δ = 2.50 ppm, ^1H; 39.5 ppm, ^{13}C). Chemical shifts are reported in parts per million (ppm). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants *J* are reported in Hertz (Hz). Mass spectrometry (MS) was performed by the University of Illinois Mass Spectrometry Laboratory. Electrospray ionization (ESI+) spectra were performed using a time-of-flight (TOF) mass analyzer. Data are reported in the form of m/z (intensity relative to the base peak = 100). For several compounds, Waters Q-TOF Ultima ESI and Agilent 6230 ESI TOF LC/MS spectrometers were used to obtain the high-resolution mass spectra. Infrared spectra were measured neat on a Perkin-Elmer spectrum BX FT-IR spectrometer. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 0–33% T); m (medium, 34–66% T), w (weak, 67–100% T), and br (broad). Visible-light spectrum of LED was recorded using an Avantes Sensline Avaspec-ULS TEC Spectrometer. Melting points of solids, compounds that solidified after chromatography, were measured on a Buchi B-540 melting point apparatus and are uncorrected. Optical rotations were recorded on a Jasco P-2000 polarimeter at 589 nm, and are reported in units of 10^{-1} (deg cm^2 g^{-1}). HPLC was performed on a Shimadzu Prominence HPLC system with SPD-M20A UV/VIS Photodiode array detector (220 nm).

LC-MS was performed on a Shimadzu Nexera XR UHPLC system with SPD-M30A UV/VIS Photodiode array detector and LC-MS 2020 mass spectrometer. The x-ray diffraction experiments were conducted using Bruker D8 Venture/Photon 100 diffractometer or Bruker APEX-II CCD diffractometer. Using Olex2,[6] the structure was solved with ShelXT[7] structure solution program using Intrinsic Phasing solution method, and the XL[8] refinement package using Least Squares minimization.

LED light source:

Generic cool white light LED corn bulbs were used for the photochemical experiments. These can be obtained from several manufacturers over amazon.com and proved to give consistent results as well as identical visible spectra. Detailed info:

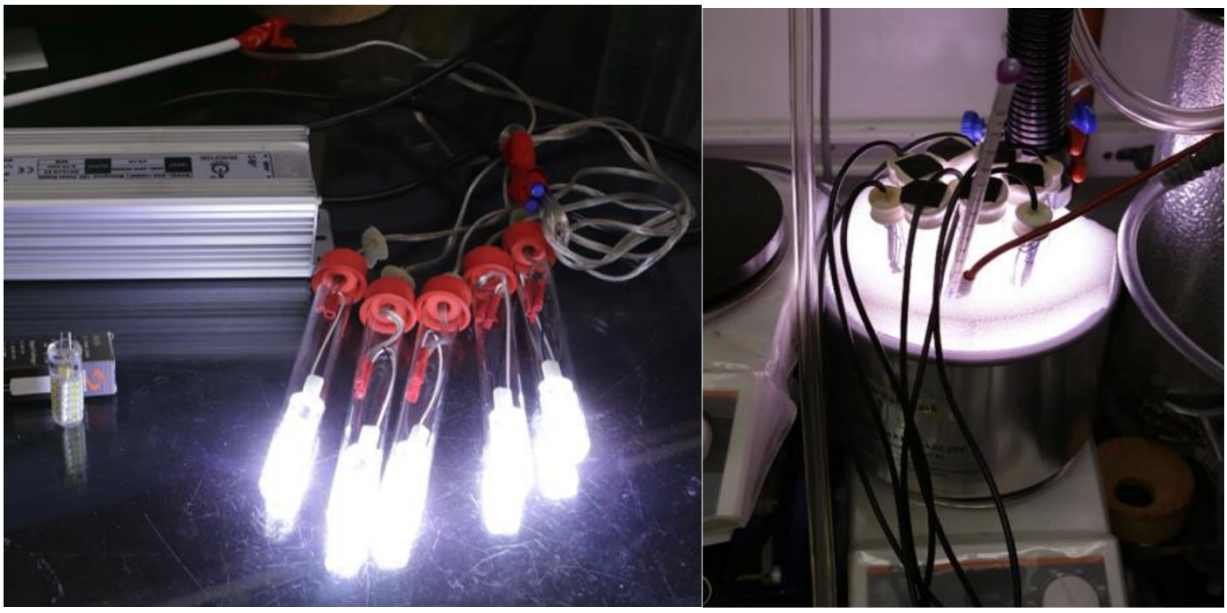
Socket: G4
LED Chip: 48 LEDs SMD 2835
Consume wattage: 4W
Input voltage: AC / DC 12V
Beam degree: 360 degrees
Color temperature: 6500K (Cool White)
Initial Lumens (lm): 290



Spectra S1. Spectrum of a LED bulb used.

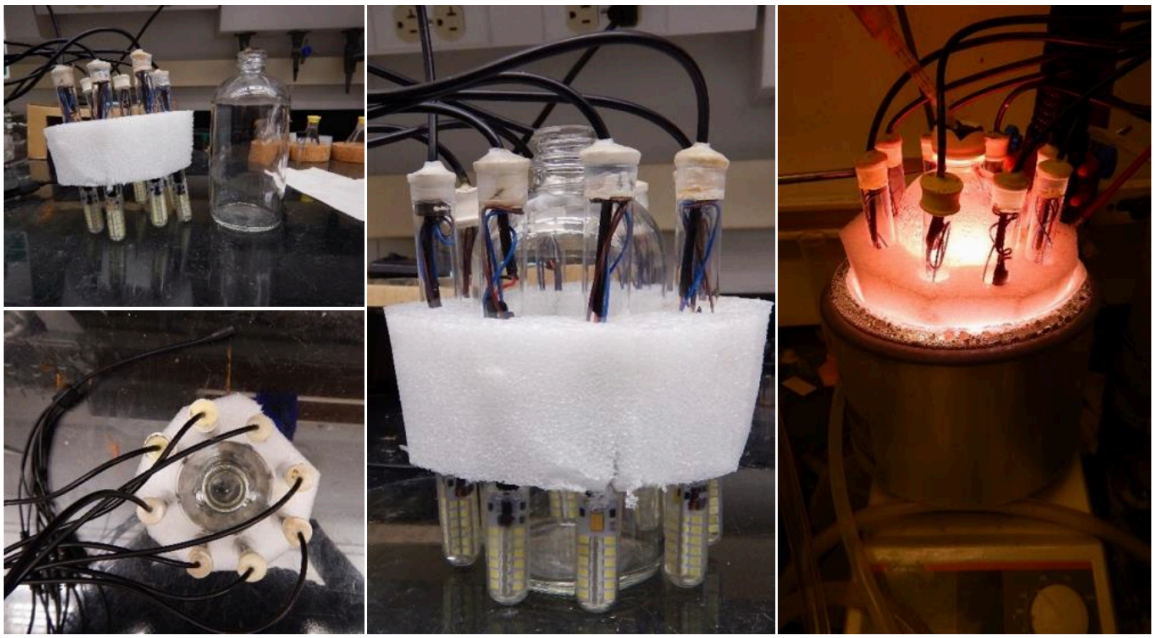
Set-up for small scale reactions (< 2.0 mmol scale)

Six 4 W LED corn bulbs (12V, cool white light 6500K) were wired to a suitable 12V power supply, then sealed into test tubes and capped with septa (Picture S1). Lights and reaction tubes were arranged in a merry-go-round fashion for maximal exposure of each reaction vessel to light source and submerged in a −78 °C bath. Generally, up to four 1.0 mmol scale reactions can be run in the same bath using five 4 W lamps positioned around them.



Picture S1. Assembly of LED bulbs from small-scale photochemical reactions.

Set-up for large scale reactions (2 - 10 mmol scale)

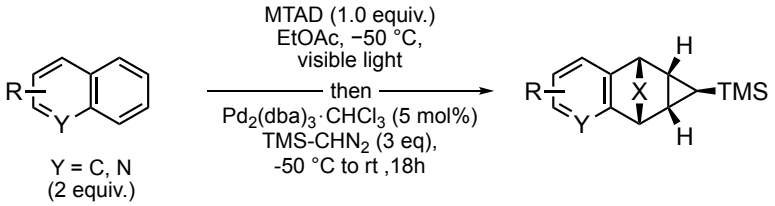


Picture S2. Photochemical set-up for large scale reactions.

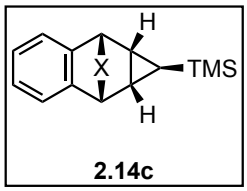
Set-up for large scale reactions (2 - 10 mmol scale)

Picture S3. Photochemical set-up for large scale reactions.

General procedure for dearomative cyclopropanation with polycyclic arenes



A solution of *N*-methyl-1,2,4-triazoline-3,5-dione (MTAD, 113.4 mg, 1.0 mmol, 1.0 equiv.) and arene (2.0 mmol, 2.0 equiv.) in dry and degassed ethyl acetate (5.0 mL) was irradiated with LED lights at −50 °C under a nitrogen atmosphere. Upon decolorization, which generally proceeds within 8 – 12 hours with the described setup, a suspension of $Pd_2(dba)_3{\cdot}CHCl_3$ (51.76 mg, 0.05 mmol, 0.05 equiv.) in dry and degassed ethyl acetate (2 mL, sonicated for 1 minute), was added dropwise to the solution, followed by dropwise addition of (trimethylsilyl)diazomethane (2.0 M solution in hexanes, 1.5 mL, 3.0 mmol, 3.0 equiv.). After addition, the cold bath was allowed to slowly warm up from −50 °C to room temperature, over 18 hours. The reaction was quenched by adding acetic acid (350 μL, 6 equiv.) and left to stir for 15 minutes. The solution was filtered through celite and concentrated under reduced pressure. The residue was purified by flash chromatography to give the desired compound.



Synthesis of compound 2.14c: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1 to 4:1) as a yellow solid (259 mg, 79%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$)

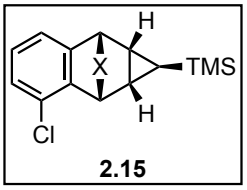
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 5.4, 3.2 Hz, 2H), 7.20 (dd, *J* = 5.4, 3.2 Hz, 2H), 5.54 (dd, *J* = 3.2, 2.0 Hz, 2H), 2.83 (s, 3H), 1.63 (ddd, *J* = 5.2, 3.3, 2.0 Hz, 2H), -0.09 (s, 9H), -1.16 (t, *J* = 5.2 Hz, 1H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.34, 131.09, 129.23, 124.02, 57.89, 25.22, 12.61, -2.26.

HRMS: (ESI-TOF, m/z) calcd. for $C_{17}H_{21}N_3O_2Si$ $[M + H]^+$, 328.1481; found: 328.1476.

IR: (ATR, neat, cm^{-1}) = 2954 (w), 1771 (m), 1704 (s), 1446 (m), 1388 (m), 1246 (m), 1227 (w), 1202 (w), 1170 (w), 1047 (w), 964 (m), 923 (w), 837 (s), 755 (m), 701 (w), 666 (w), 555 (m), 505 (w).

m.p. = 166 – 169 °C



2.15

Synthesis of compound 2.15: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (217 mg, 60%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

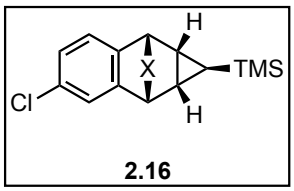
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.26 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.09 – 7.05 (m, 1H), 5.98 (d, *J* = 4.8 Hz, 1H), 5.49 (d, *J* = 4.8 Hz, 1H), 2.81 (s, 3H), 1.63 (dt, *J* = 7.6, 5.0 Hz, 1H), 1.59 (dt, *J* = 7.6, 4.9 Hz, 1H), -0.11 (s, 9H), -1.20 (t, *J* = 5.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.18, 157.05, 132.82, 130.08, 129.79, 129.61, 129.14, 122.48, 57.49, 54.49, 25.27, 11.99, 11.95, 8.56, -2.35.

HRMS: (ESI-TOF, m/z) calcd. for $C_{17}H_{20}ClN_3O_2Si$ $[M + H]^+$, 362.1092; found: 362.1080.

IR: (ATR, neat, cm^{-1}) = 2229 (w), 1771 (m), 1705 (s), 1457 (m), 1449 (m), 1395 (m), 1246 (w), 1200 (w), 1174 (w), 1035 (w), 965 (m), 869 (m), 840 (s), 764 (m), 712 (w), 675 (w), 585 (m), 489 (w).

m.p. = 184 – 185 °C



2.16

Synthesis of compound 2.16: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (181 mg, 50%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

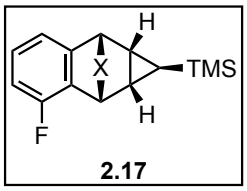
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.20 (d, *J* = 2.0 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 5.50 (dt, *J* = 10.4, 2.5 Hz, 2H), 2.84 (s, 3H), 1.62 (td, *J* = 7.2, 6.1, 3.2 Hz, 3H), -0.08 (s, 9H), -1.15 (t, *J* = 5.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.37, 157.32, 135.09, 132.64, 129.52, 129.46, 125.52, 124.55, 57.52, 57.39, 25.39, 12.61, 12.42, 8.89, -2.20.

HRMS: (ESI-TOF, m/z) calcd. for $C_{17}H_{20}ClN_3O_2Si$ $[M + H]^+$, 362.1092; found: 362.1085.

IR: (ATR, neat, cm^{-1}) = 2958 (w), 1765 (m), 1705 (s), 1451 (m), 1394 (m), 1245 (m), 1200 (w), 1174 (w), 999 (w), 967 (m), 869 (m), 837 (s), 815 (w), 765 (m), 748 (w), 637 (w), 530 (m), 506 (w).

m.p. = 190 – 192 °C



2.17

Synthesis of compound 2.17: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 10:1 to 9:1) as a yellow solid (169 mg, 49%).

R_f = 0.30 (SiO_2, hexanes:ethyl acetate = 9:1, UV, $KMnO_4$)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (ddd, *J* = 8.4, 7.4, 5.2 Hz, 1H), 7.12 – 7.05 (m, 1H), 6.98 (d, *J* = 7.4 Hz, 1H), 5.90 (d, *J* = 4.6 Hz, 1H), 5.53 (dd, *J* = 4.6, 1.7 Hz, 1H), 2.84 (s, 3H), 1.63 (ddt, *J* = 12.0, 7.7, 3.9 Hz, 2H), -0.09 (s, 9H), -1.14 (t, *J* = 5.1 Hz, 1H).

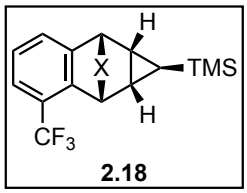
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.24, 157.18, 156.66 (d, *J* = 250.7 Hz), 133.47 (d, *J* = 4.6 Hz), 130.66 (d, *J* = 7.5 Hz), 119.81 (d, *J* = 3.6 Hz), 117.96 (d, *J* = 18.3 Hz), 116.35 (d, *J* = 20.7 Hz), 57.26, 51.66, 25.34, 12.32, 8.74, -2.25.

^{19}F NMR (471 MHz, $CDCl_3$) δ -122.86.

HRMS: (ESI-TOF, m/z) calcd. for $C_{17}H_{20}FN_3O_2Si$ $[M + H]^+$, 346.1387; found: 346.1380.

IR: (ATR, neat, cm^{-1}) = 2959 (w), 1772 (m), 1705 (s), 1476 (m), 1448 (m), 1392 (m), 1247 (m), 1204 (w), 1154 (w), 994 (w), 962 (m), 834 (s), 815 (w), 758 (m), 746 (w), 738 (w), 731 (m), 472 (w).

m.p. = 144 – 147 °C



2.18

Synthesis of compound 2.18: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (237 mg, 60%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 5.97 (d, *J* = 4.7 Hz, 1H), 5.58 (d, *J* = 4.4 Hz, 1H), 2.85 (s, 3H), 1.67 (tt, *J* = 8.0, 3.9 Hz, 2H), -0.11 (s, 9H), -1.33 (t, *J* = 5.1 Hz, 1H).

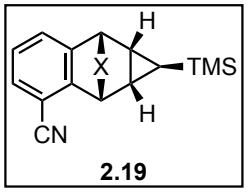
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.13, 156.39, 132.75, 129.62, 129.25, 127.89, 125.95 (q, *J* = 4.7 Hz), 125.9 (q, *J* = 27 Hz), 123.37 (q, *J* = 274 Hz), 57.15, 54.32, 25.43, 12.04, 9.01, -2.41.

^{19}F NMR (471 MHz, $CDCl_3$) δ -60.10.

HRMS: (ESI-TOF, m/z) calcd. for $C_{18}H_{20}F_3N_3O_2Si$ $[M + H]^+$, 396.1355; found: 396.1342.

IR: (ATR, neat, cm^{-1}) = 2961 (w), 1766 (m), 1716 (s), 1457 (m), 1397 (m), 1320 (m), 1249 (m), 1211 (w), 1176 (w), 1163 (m), 1124 (s), 968 (m), 871 (w), 841 (m), 758 (m), 743 (w), 731 (m), 555 (w).

m.p. = 213 – 215 °C



2.19

Synthesis of compound 2.19: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (261 mg, 74%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 9:1, UV, $KMnO_4$).

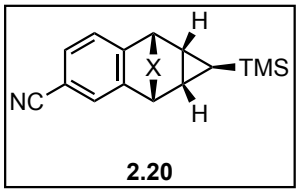
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.56 – 7.39 (m, 2H), 5.91 (d, *J* = 4.8 Hz, 1H), 5.57 (d, *J* = 4.8 Hz, 1H), 2.83 (s, 3H), 1.71 (dt, *J* = 7.4, 5.0 Hz, 1H), 1.66 (dt, *J* = 7.5, 4.9 Hz, 1H), -0.09 (s, 10H), -1.28 (t, *J* = 5.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.34, 157.05, 134.23, 132.62, 132.32, 129.90, 128.55, 115.80, 108.62, 57.40, 55.72, 25.42, 12.06, 11.88, 8.85, -2.26.

HRMS: (ESI-TOF, m/z) calcd. for $C_{18}H_{20}N_4O_2Si$ $[M + H]^+$, 353.1434; found: 353.1430.

IR: (ATR, neat, cm^{-1}) = 2228 (w), 1771 (m), 1705 (s), 1447 (m), 1396 (m), 1247 (m), 1228 (w), 1201 (w), 1174 (w), 1046 (w), 963 (m), 926 (w), 837 (s), 767 (m), 710 (w), 656 (w), 522 (m), 477 (w).

m.p. = 229 – 232 °C



2.20

Synthesis of compound 2.20: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (176 mg, 50%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 9:1, UV, $KMnO_4$).

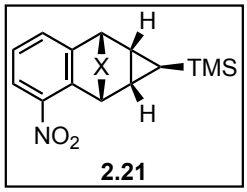
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.49 (d, *J* = 1.4 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 5.57 (q, *J* = 2.9 Hz, 2H), 2.83 (s, 3H), 1.67 (dt, *J* = 5.3, 2.5 Hz, 2H), -0.08 (s, 9H), -1.23 (t, *J* = 5.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.18, 135.55, 133.60, 132.21, 127.57, 125.06, 117.98, 113.46, 57.37, 57.18, 25.42, 12.24, 12.07, 9.05, -2.26.

HRMS: (ESI-TOF, m/z) calcd. for $C_{18}H_{20}N_4O_2Si$ $[M + H]^+$, 353.1434; found: 353.1432.

IR: (ATR, neat, cm^{-1}) = 2229 (w), 1770 (m), 1705 (s), 1448 (m), 1394 (m), 1245 (m), 1199 (w), 1177 (w), 1001 (w), 972 (w), 962 (m), 869 (s), 830 (s), 767 (m), 710 (w), 656 (w), 542 (m), 489 (w).

m.p. = 182 – 184 °C



2.21

Synthesis of compound 2.21: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (242 mg, 65%).

R_f = 0.30 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

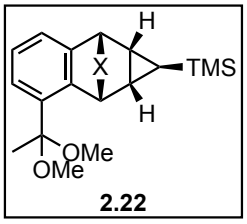
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.57 – 7.46 (m, 2H), 6.61 (d, *J* = 5.2 Hz, 1H), 5.60 (d, *J* = 4.7 Hz, 1H), 2.82 (s, 3H), 1.75 (dt, *J* = 7.6, 5.2 Hz, 1H), 1.68 (dt, *J* = 7.5, 4.9 Hz, 1H), -0.09 (d, *J* = 1.2 Hz, 9H), -1.19 (t, *J* = 5.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.19, 156.65, 144.19, 133.54, 129.84, 126.49, 124.87, 57.20, 53.48, 25.38, 11.71, 11.49, 9.11, -2.33.

HRMS: (ESI-TOF, m/z) calcd. for $C_{17}H_{20}N_4O_4Si$ $[M + H]^+$, 373.1332; found: 373.1323.

IR: (ATR, neat, cm^{-1}) = 2958 (w), 1770 (m), 1704 (s), 1555 (m), 1455 (m), 1401 (m), 1370 (m), 1201 (w), 1180 (w), 1001 (w), 966 (m), 869 (m), 840 (s), 820 (w), 766 (m), 747 (w), 640 (w), 531 (m), 505 (w).

m.p. = 218 – 220 °C



2.22

Synthesis of compound 2.22: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (283 mg, 68%).

R_f = 0.30 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

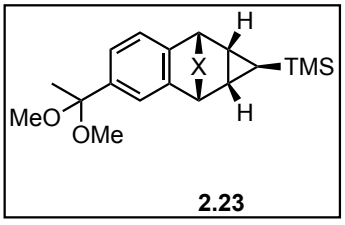
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 7.3 Hz, 1H), 6.45 (d, *J* = 4.3 Hz, 1H), 5.51 (d, *J* = 4.0 Hz, 1H), 3.25 (s, 3H), 3.10 (s, 3H), 2.88 (s, 3H), 1.60 (s, 4H), -0.14 (s, 9H), -1.27 (t, *J* = 5.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.35, 155.88, 138.56, 132.14, 129.26, 128.65, 128.35, 124.07, 101.58, 57.37, 54.13, 49.30, 48.85, 25.92, 25.35, 12.83, 12.56, 9.01, -2.33.

HRMS: (ESI-TOF, m/z) calcd. for $C_{21}H_{29}N_3O_4Si$ $[M + Na]^+$, 438.1849; found: 438.1835.

IR: (ATR, neat, cm^{-1}) = 2950 (w), 1766 (m), 1704 (s), 1451 (m), 1393 (m), 1275 (w), 1249 (m), 1201 (w), 1148 (m), 1037 (w), 958 (m), 872 (m), 868 (m) 837 (s), 766 (m), 763 (m), 570 (w).

m.p. = 70 – 71 °C



2.23

Synthesis of compound 2.23: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (233 mg, 56%).

R_f = 0.30 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

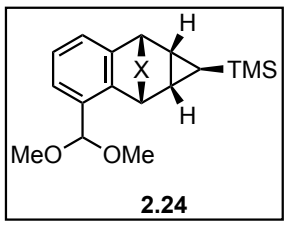
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.33 (d, *J* = 1.7 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 5.51 (dd, *J* = 4.0, 1.3 Hz, 2H), 3.12 (d, *J* = 3.6 Hz, 6H), 2.80 (s, 3H), 1.65 – 1.55 (m, 2H), 1.48 (s, 3H), -0.13 (s, 8H), -1.24 (t, *J* = 5.2 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 157.21, 157.13, 144.12, 130.95, 130.51, 127.11, 123.81, 122.17, 101.48, 58.13, 57.62, 49.07, 49.05, 26.06, 25.21, 12.73, 12.64, 8.53, -2.22.

HRMS: (ESI-TOF, m/z) calcd. for $C_{21}H_{29}N_3O_4Si$ [M + Na]$^+$, 438.1849; found: 438.1821.

IR: (ATR, neat, cm^{-1}) = 2952 (w), 1768 (m), 1704 (s), 1449 (m), 1392 (m), 1264 (w), 1198 (m), 1168 (m), 1143 (w), 1037 (w), 958 (m), 873 (m), 867 (m) 835 (s), 761 (m), 733 (m), 561 (w).

m.p. = 67 – 70 °C



2.24

Synthesis of compound 2.24: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (283 mg, 62%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

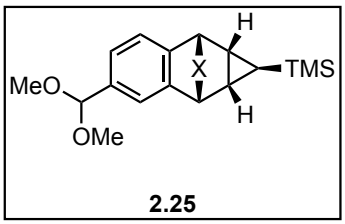
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.9 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 6.06 (d, *J* = 4.5 Hz, 1H), 5.61 (s, 1H), 5.50 (d, *J* = 4.2 Hz, 1H), 3.45 (s, 3H), 3.02 (s, 3H), 2.80 (s, 3H), 1.61 (q, *J* = 4.5 Hz, 2H), -0.12 (s, 9H), -1.24 (t, *J* = 5.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.47, 157.35, 133.17, 131.34, 129.73, 128.50, 127.61, 124.32, 100.16, 57.87, 54.85, 53.92, 49.91, 25.25, 12.28, 12.08, 8.93, -2.35.

HRMS: (ESI-TOF, m/z) calcd. for $C_{20}H_{27}N_3O_4Si$ [M + Na]$^+$, 424.1669; found: 424.1655.

IR: (ATR, neat, cm^{-1}) = 2951 (w), 1769 (m), 1704 (s), 1449 (m), 1393 (m), 1247 (w), 1199 (m), 1172 (w), 1144 (m), 1030 (w), 1000 (m), 964 (m), 868 (m) 836 (s), 778 (m), 764 (m), 732 (m).

m.p. = 73 – 74 °C



2.25

Synthesis of compound 2.25: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (217 mg, 54%).

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

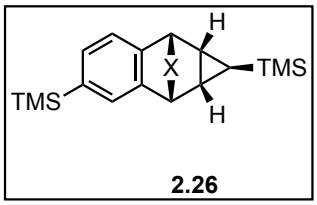
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 1H), 7.28 (d, *J* = 1.6 Hz, 1H), 7.18 (d, *J* = 7.7 Hz, 1H), 5.52 (dt, *J* = 3.8, 1.4 Hz, 2H), 5.36 (s, 1H), 3.31 (s, 3H), 3.29 (s, 3H), 2.81 (s, 3H), 1.63 – 1.57 (m, 2H), -0.12 (s, 8H), -1.20 (t, *J* = 5.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.25, 157.21, 139.35, 131.32, 131.06, 127.53, 123.99, 122.61, 102.73, 57.99, 57.67, 53.09, 53.04, 25.25, 12.64, 12.62, 8.65, -2.23.

HRMS: (ESI-TOF, m/z) calcd. for $C_{20}H_{27}N_3O_4Si$ $[M + Na]^+$, 424.1669; found: 424.1661.

IR: (ATR, neat, cm^{-1}) = 2952 (w), 1768 (m), 1710 (s), 1455 (m), 1388 (m), 1245 (w), 1201 (m), 1174 (w), 1140 (m), 1025 (w), 998 (m), 965 (m), 868 (m) 837 (s), 778 (m), 764 (m), 732 (m).

m.p. = 69 – 71 °C



2.26

Synthesis of compound 2.26: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 10:1) as a yellow solid (180 mg, 45%)

.

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 9:1, UV, $KMnO_4$).

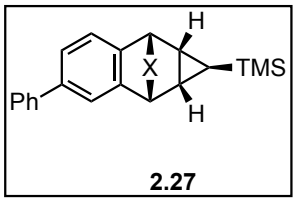
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 1H), 7.26 (d, *J* = 3.6 Hz, 1H), 7.13 (d, *J* = 7.3 Hz, 1H), 5.50 (t, *J* = 4.2 Hz, 2H), 2.82 (s, 3H), 1.59 (q, *J* = 4.7 Hz, 2H), 0.24 (s, 9H), -0.11 (s, 10H), -1.20 (t, *J* = 5.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.02, 142.21, 134.31, 131.60, 130.40, 128.49, 123.13, 76.93, 57.97, 57.69, 25.27, 12.88, 12.69, 8.51, -1.02, -2.21.

HRMS: (ESI-TOF, m/z) calcd. for $C_{20}H_{29}N_3O_2Si_2$ $[M + H]^+$, 400.1877; found: 400.1867.

IR: (ATR, neat, cm^{-1}) = 2950 (w), 1766 (m), 1704 (s), 1449 (m), 1392 (m), 1248 (w), 1206 (m), 1170 (w), 995 (m), 954 (w), 868 (m) 828 (s), 779 (m), 751 (m), 733 (m), 693 (w), 634 (m).

m.p. = 67 – 70 °C



2.27

Synthesis of compound 2.27: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (169 mg, 42%).

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

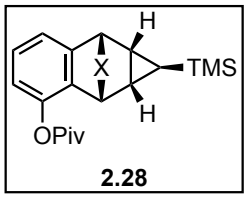
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 9.2, 7.4 Hz, 3H), 7.46 – 7.39 (m, 3H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.28 – 7.23 (m, 1H), 5.58 (dt, *J* = 9.4, 2.6 Hz, 2H), 2.84 (s, 3H), 1.69 – 1.61 (m, 2H), -0.08 (s, 9H), -1.07 (t, *J* = 5.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.36, 157.29, 142.22, 140.05, 131.69, 130.07, 129.01, 127.92, 127.79, 127.22, 124.47, 122.75, 58.11, 57.70, 25.34, 12.86, 12.79, 8.77, -2.19.

HRMS: (ESI-TOF, m/z) calcd. for $C_{23}H_{25}N_3O_2Si$ $[M + H]^+$, 404.1770; found: 404.1781.

IR: (ATR, neat, cm^{-1}) = 2952 (w), 1764 (m), 1698 (s), 1446 (m), 1388 (m), 1253 (w), 1244 (m), 1218 (w), 1171 (m), 993 (w), 967 (m) 955 (m), 834 (s), 761 (s), 751 (m), 735 (w), 568 (m).

m.p. = 190 – 193 °C



2.28

Synthesis of compound 2.28: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (205 mg, 48%).

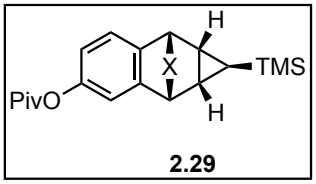
R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (t, *J* = 7.8 Hz, 1H), 7.19 – 7.06 (m, 2H), 5.61 (dd, *J* = 7.3, 4.7 Hz, 2H), 2.92 (s, 3H), 1.72 – 1.63 (m, 2H), 1.50 (s, 7H), 0.00 (s, 9H), -0.89 (t, *J* = 5.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.90, 159.62, 159.42, 147.72, 134.92, 132.05, 125.87, 124.86, 123.54, 59.75, 54.84, 41.56, 29.49, 27.51, 14.75, 14.19, 11.26, -0.21.

HRMS: (ESI-TOF, m/z) calcd. for $C_{22}H_{29}N_3O_4Si$ $[M + H]^+$, 428.1942; found: 428.1953.

m.p. = 140 – 142 °C



2.29

Synthesis of compound 2.29: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (171 mg, 40%).

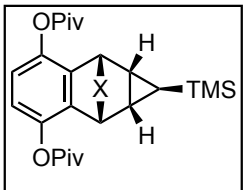
R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.1 Hz, 1H), 7.19 – 7.14 (m, 1H), 7.04 (d, *J* = 2.2 Hz, 1H), 5.71 – 5.45 (m, 2H), 2.93 (s, 3H), 1.70 (t, *J* = 2.7 Hz, 2H), 1.43 (d, *J* = 1.0 Hz, 10H), 0.00 (d, *J* = 1.0 Hz, 9H), -0.99 (t, *J* = 5.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.06, 159.55, 153.74, 134.34, 130.58, 127.36, 124.43, 119.95, 59.99, 59.73, 41.46, 29.40, 27.55, 15.01, 14.68, 10.98, 0.00.

HRMS: (ESI-TOF, m/z) calcd. for $C_{22}H_{29}N_3O_4Si$ $[M + H]^+$, 428.1942; found: 428.1966.

m.p. = 125 – 128 °C



2.30

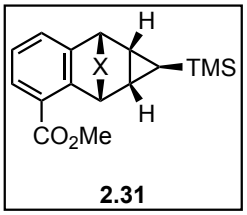
Synthesis of compound 2.30: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (184 mg, 35%).

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (s, 2H), 5.53 (dd, *J* = 3.3, 2.0 Hz, 2H), 2.87 (s, 3H), 1.60 (ddd, *J* = 5.4, 3.3, 2.0 Hz, 3H), 1.44 (s, 21H), -0.03 (s, 9H), -0.74 (t, *J* = 5.2 Hz, 1H).

HRMS: (ESI-TOF, m/z) calcd. for $C_{27}H_{37}N_3O_6Si$ $[M + H]^+$, 528.2513; found: 528.2525.

m.p. = 137 – 138 °C



2.31

Synthesis of compound 2.31: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (135 mg, 35%).

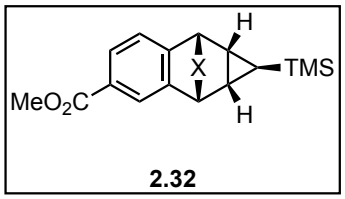
R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 9:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.8 Hz, 1H), 7.48 (dd, *J* = 27.7, 7.5 Hz, 1H), 6.92 (d, *J* = 5.1 Hz, 1H), 5.64 (d, *J* = 4.7 Hz, 2H), 4.05 (s, 3H), 2.92 (s, 3H), 1.89 – 1.60 (m, 2H), 0.00 (s, 9H), -1.13 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.42, 159.53, 159.03, 134.91, 134.60, 133.21, 131.07, 130.66, 127.98, 59.86, 56.36, 54.81, 27.54, 14.28, 14.26, 11.03, -0.00.

HRMS: (ESI-TOF, m/z) calcd. for $C_{19}H_{23}N_3O_4Si$ $[M + H]^+$, 386.1544; found: 386.1558.

m.p. = 97 – 100 °C



2.32

Synthesis of compound 2.32: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (193 mg, 50%).

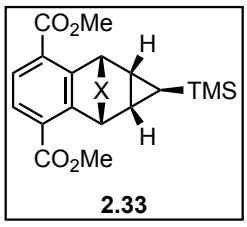
R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 9:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.97 (d, *J* = 1.7 Hz, 1H), 7.38 (d, *J* = 7.7 Hz, 1H), 5.77 – 5.55 (m, 2H), 4.00 (d, *J* = 1.7 Hz, 3H), 2.91 (d, *J* = 1.5 Hz, 3H), 1.76 (ddd, *J* = 5.3, 3.7, 1.7 Hz, 2H), 0.00 (d, *J* = 1.6 Hz, 9H), -1.10 (t, *J* = 5.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.58, 159.52, 159.51, 145.66, 137.78, 133.57, 133.46, 133.13, 132.85, 131.33, 130.76, 127.81, 127.50, 126.51, 60.02, 59.81, 55.82, 54.71, 27.57, 14.80, 14.54, 11.14, 0.04, 0.02, -0.00.

HRMS: (ESI-TOF, m/z) calcd. for $C_{19}H_{23}N_3O_4Si$ $[M + H]^+$, 386.1544; found: 386.1562.

m.p. = 110 – 113 °C



2.33

Synthesis of compound 2.33: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (359 mg, 81%).

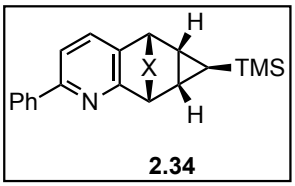
R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 9:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (t, *J* = 2.8 Hz, 2H), 6.90 (t, *J* = 2.8 Hz, 2H), 4.21 – 3.94 (m, 6H), 2.91 (t, *J* = 2.9 Hz, 3H), 1.88 – 1.67 (m, 2H), 0.00 (d, *J* = 2.8 Hz, 7H), -1.12 – -1.20 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.80, 158.94, 136.03, 132.52, 131.34, 55.76, 55.17, 27.60, 13.73, 11.11, 0.02, -0.00.

HRMS: (ESI-TOF, m/z) calcd. for $C_{21}H_{25}N_3O_6Si$ $[M + H]^+$, 444.1632; found: 444.1648.

m.p. = 142 – 143 °C



2.34

Synthesis of compound 2.34: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (182 mg, 45%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

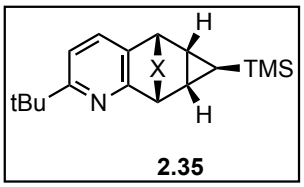
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 – 7.97 (m, 2H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.49 – 7.44 (m, 2H), 7.44 – 7.39 (m, 1H), 5.77 (d, *J* = 4.9 Hz, 1H), 5.63 (d, *J* = 4.8 Hz, 1H), 2.88 (s, 3H), 1.73 (dt, *J* = 7.5, 5.1 Hz, 1H), 1.67 (dt, *J* = 7.6, 5.0 Hz, 1H), -0.09 (s, 8H), -1.10 (t, *J* = 5.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.09, 157.01, 156.53, 151.31, 138.43, 132.58, 129.60, 128.96, 127.18, 124.64, 120.81, 59.74, 56.68, 25.45, 12.89, 12.12, 8.47, -2.21.

HRMS: (ESI-TOF, m/z) calcd. for $C_{22}H_{24}N_4O_2Si$ $[M + H]^+$, 405.1747; found: 405.1727.

IR: (ATR, neat, cm^{-1}) = 2950 (w), 1767 (m), 1695 (s), 1456 (m), 1438 (s), 1391 (m), 1263 (m), 1249 (m), 1164 (m), 990 (w), 961 (m) 878 (m), 835 (s), 820 (m), 759 (s), 691 (s), 576 (m).

m.p. = 155 – 157 °C



2.35

Synthesis of compound 2.35: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (258 mg, 67%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

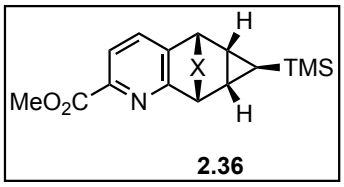
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 5.65 (d, *J* = 4.9 Hz, 1H), 5.56 (d, *J* = 4.7 Hz, 1H), 2.88 (s, 3H), 1.66 (dt, *J* = 7.4, 5.1 Hz, 1H), 1.60 (dt, *J* = 7.5, 4.9 Hz, 1H), 1.32 (s, 9H), -0.11 (s, 9H), -1.28 (t, *J* = 5.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.45, 156.81, 156.34, 150.23, 131.73, 123.24, 119.32, 59.72, 56.60, 37.78, 30.29, 25.41, 12.83, 12.17, 8.06, -2.22.

HRMS: (ESI-TOF, m/z) calcd. for $C_{20}H_{28}N_4O_2Si$ $[M + H]^+$, 385.2060; found: 385.2052.

IR: (ATR, neat, cm^{-1}) = 2957 (w), 1769 (m), 1702 (s), 1443 (m), 1389 (s), 1263 (m), 1248 (m), 1212 (m), 1166 (m), 1026 (w), 995 (m) 963 (m), 867 (w), 832 (s), 760 (m), 746 (m), 624 (m), 543 (m).

m.p. = 149 – 150 °C



2.36

Synthesis of compound 2.36: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (216 mg, 56%).

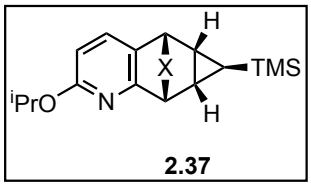
R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 5.96 (d, *J* = 4.9 Hz, 1H), 5.77 (d, *J* = 4.8 Hz, 1H), 4.11 (s, 3H), 2.97 (s, 3H), 1.83 (d, *J* = 19.5 Hz, 1H), 0.06 – -0.08 (m, 9H), -1.14 (t, *J* = 5.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.46, 159.11, 158.59, 153.91, 150.59, 135.15, 132.10, 128.49, 61.59, 58.71, 55.59, 27.76, 14.67, 14.18, 10.90, 0.00.

HRMS: (ESI-TOF, m/z) calcd. for $C_{18}H_{22}N_4O_4Si$ $[M + H]^+$, 387.3040; found: 387.3059.

m.p. = 160 – 162 °C



2.37

Synthesis of compound 2.37: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 10:1) as a yellow solid (193 mg, 50%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 9:1, UV, $KMnO_4$).

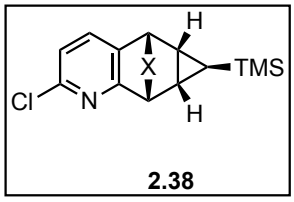
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.2 Hz, 1H), 6.59 (d, *J* = 8.2 Hz, 1H), 5.49 (d, *J* = 4.5 Hz, 2H), 5.25 (dp, *J* = 12.3, 6.2 Hz, 1H), 2.84 (s, 3H), 1.57 (q, *J* = 5.0 Hz, 2H), 1.27 (t, *J* = 6.5 Hz, 6H), -0.12 (s, 9H), -1.20 (t, *J* = 5.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.14, 157.14, 156.73, 148.74, 134.69, 118.34, 111.39, 68.85, 59.36, 56.59, 25.31, 21.99, 21.97, 12.95, 11.68, 8.17, -2.29.

HRMS: (ESI-TOF, m/z) calcd. for $C_{19}H_{26}N_4O_3Si$ $[M + H]^+$, 387.1852; found: 387.1847.

IR: (ATR, neat, cm^{-1}) = 2950 (w), 1770 (m), 1705 (s), 1600 (m), 1452 (s), 1430 (m), 1393 (m), 1299 (m), 1250 (m), 1168 (w), 1105 (m) 972 (m), 955 (w), 868 (m), 834 (s), 808 (m), 765 (m), 726 (m), 569 (m).

m.p. = 150 – 151 °C



2.38

Synthesis of compound 2.38: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 4:1) as a yellow solid (181 mg, 50%).

R_f = 0.2 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

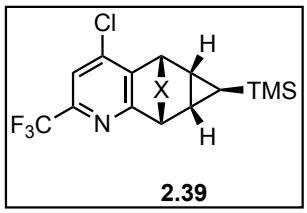
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 5.66 (d, *J* = 4.8 Hz, 1H), 5.60 (d, *J* = 4.7 Hz, 1H), 2.89 (s, 3H), 1.72 – 1.68 (m, 1H), 1.66 (dt, *J* = 7.5, 5.0 Hz, 1H), -0.08 (s, 9H), -1.21 (t, *J* = 5.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.03, 156.48, 152.07, 151.67, 134.60, 125.08, 125.03, 58.98, 56.18, 25.53, 12.45, 11.66, 8.67, -2.25.

HRMS: (ESI-TOF, m/z) calcd. for $C_{16}H_{19}ClN_4O_2Si$ $[M + H]^+$, 363.1044; found: 363.1035.

IR: (ATR, neat, cm^{-1}) = 2953 (w), 1775 (m), 1706 (s), 1567 (w), 1457 (m), 1424 (m), 1399 (m), 1253 (w), 1200 (m), 1170 (w), 1114 (m) 996 (m), 961 (m), 869 (m), 834 (s), 766 (m), 656 (m).

m.p. = 203 – 206 °C



2.39

Synthesis of compound 2.39: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 9:1) as a yellow solid (289 mg, 67%).

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 6.04 (d, *J* = 4.5 Hz, 1H), 5.76 (d, *J* = 4.6 Hz, 1H), 2.91 (s, 3H), 1.74 (tt, *J* = 7.7, 3.8 Hz, 3H), -0.07 (s, 9H), -1.27 (t, *J* = 5.1 Hz, 1H).

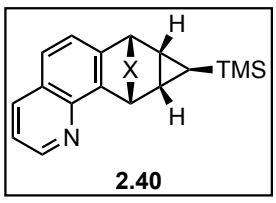
^{13}C NMR (126 MHz, $CDCl_3$) δ 156.47, 156.05, 153.16, 149.54, 149.25, 148.97, 148.68, 141.30, 128.04, 122.34, 122.32, 122.29, 122.27, 121.79, 119.61, 58.78, 53.23, 25.65, 11.79, 11.41, 8.41, -2.34.

^{19}F NMR (471 MHz, $CDCl_3$) δ -68.48.

HRMS: (ESI-TOF, m/z) calcd. for $C_{17}H_{18}ClF_3N_4O_2Si$ $[M + H]^+$, 431.0918; found: 431.0912.

IR: (ATR, neat, cm^{-1}) = 2955 (w), 1770 (m), 1711 (s), 1448 (m), 1390 (m), 1380 (m), 1345 (m), 1307 (w), 1135 (s) 972 (m), 955 (w), 868 (m), 838 (s), 808 (m), 765 (m), 726 (m), 569 (m).

m.p. = 185 – 186 °C



2.40

Synthesis of compound 2.40: Following General Procedure (1.0 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 4:1) as a yellow solid (155 mg, 41%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 7:3, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 6.87

(d, J = 4.8 Hz, 1H), 5.73 (d, J = 4.8 Hz, 1H), 2.76 (s, 3H), 1.78 (dt, J = 7.5, 5.0 Hz, 1H), 1.68 (dt, J = 7.5, 5.0 Hz, 1H), -0.13 (s, 9H), -1.26 (t, J = 5.1 Hz, 1H).

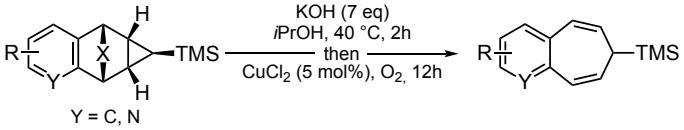
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.70, 157.24, 151.80, 142.63, 136.47, 131.64, 129.10, 128.75, 128.41, 122.71, 121.84, 58.10, 52.77, 25.33, 12.15, 12.07, 8.75, -2.13.

HRMS: (ESI-TOF, m/z) calcd. for $C_{20}H_{22}N_4O_2Si$ $[M + H]^+$, 379.1590; found: 379.1584.

IR: (ATR, neat, cm^{-1}) = 2955 (w), 1769 (m), 1699 (s), 1455 (m), 1441 (m), 1391 (m), 1247 (m), 1211 (w), 1169 (m) 972 (m), 955 (w), 868 (m), 835 (s), 808 (m), 765 (m), 726 (m), 551 (m).

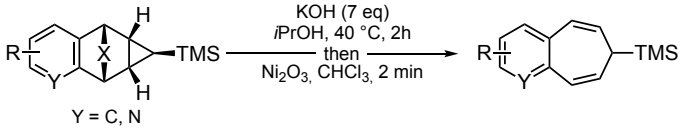
m.p. = 203 – 206 °C

General procedure A for the synthesis of benzocycloheptatrienes

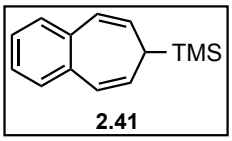


To a vial containing finely ground KOH (156 mg, 5.0 equiv., 90 wt%), and substrate (0.500 mmol, 1.0 equiv.) under nitrogen was added *i*-PrOH (5.0 mL, 0.1 M) and degassed with nitrogen/sonication for 15 min. The reaction was heated to 40 °C with vigorous stirring (700 rpm) and progress was monitored by TLC in 30 min intervals. Upon completion, the reaction was cooled in an ice bath and H_2O (5.0 mL) was added. AcOH is then carefully added dropwise until pH = 5, upon which gas evolution is observed. $CuCl_2$ dihydrate (4.3 mg, 25 μmol, 5.0 mol%). was then added as a solid, followed by sparging with oxygen, and the reaction was stirred for 10-16 h under an atmosphere of oxygen (balloon). Upon completion, the reaction was partitioned between CH_2Cl_2 (10 mL) and saturated brine (10 mL) and the organic layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and isolated by flash chromatography (SiO_2, hexanes:ethyl acetate mixtures).

General procedure B for the synthesis of benzocycloheptatrienes



To a vial containing finely ground KOH (156 mg, 5.0 equiv., 90 wt%), and substrate (0.500 mmol, 1.0 equiv.) under nitrogen was added *i*-PrOH (5.0 mL, 0.1 M) and degassed with nitrogen/sonication for 15 min. The reaction was heated to 40 °C with vigorous stirring (700 rpm) and progress was monitored by TLC in 30 min intervals. Upon completion, the reaction was cooled in an ice bath and H_2O (5.0 mL) was added. AcOH is then carefully added dropwise until pH = 5, upon which gas evolution is observed. The semicarbazide intermediate was then extracted out with ethyl acetate (3 × 5 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated under reduced pressure. This mixture containing the semicarbazide was added to the vial, followed by $CHCl_3$ (5.0 mL, 0.1 M), and sparged with nitrogen for 15 minutes. Next, nickel oxide (Ni_2O_3, 30% active basis, 830 mg, 3.0 equiv.) was added as a solid under a stream of nitrogen (note: vigorous gas evolution was observed). The solution was agitated 2 minutes, filtered through a celite plug, washed thoroughly with CH_2Cl_2, concentrated under vacuum, and isolated by flash chromatography (SiO_2, hexanes:ethyl acetate mixtures).



2.41

Synthesis of compound 2.41: Following General Procedure A (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (81 mg, 75%).

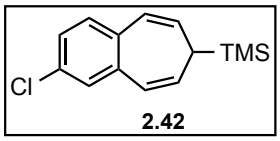
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (dd, *J* = 5.7, 3.3 Hz, 2H), 6.89 (dd, *J* = 5.6, 3.4 Hz, 2H), 6.09 (d, *J* = 11.3 Hz, 2H), 5.46 (dd, *J* = 11.3, 8.3 Hz, 2H), 2.34 (t, *J* = 8.3 Hz, 1H), -0.01 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.92, 132.83, 130.71, 128.70, 126.60, 37.05, -2.88.

HRMS: (ESI-TOF, m/z) calcd. for $C_{14}H_{19}Si$ $[M + H]^+$, 214.1178; found: 214.1177.

IR: (ATR, neat, cm^{-1}) = 2953 (w), 1770 (w), 1449 (w), 1439 (w), 1314 (w), 1247 (m), 1114 (w), 1058 (w) 1038 (w), 1001 (w), 834 (s), 790 (m), 747 (m), 728 (m), 630 (m), 484 (m).



2.42

Synthesis of compound 2.42: Following General Procedure A (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (85 mg, 68%).

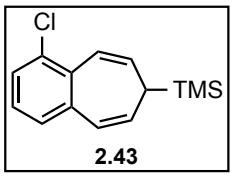
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.87 (d, *J* = 2.3 Hz, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 6.01 (dd, *J* = 19.1, 11.5 Hz, 2H), 5.54 – 5.42 (m, 2H), 2.36 (t, *J* = 8.2 Hz, 1H), -0.00 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.58, 136.41, 134.47, 133.22, 131.97, 131.94, 130.25, 127.65, 127.41, 126.44, 37.29, -2.88.

HRMS: (ESI-TOF, m/z) calcd. for $C_{14}H_{18}ClSi$ $[M + H]^+$, 247.0710; found: 247.0718.

IR: (ATR, neat, cm^{-1}) = 2954 (w), 1586 (w), 1485 (w), 1409 (m), 1247 (s), 1125 (w), 1098 (m), 878 (w), 834 (s), 808 (s), 788 (m), 749 (m), 730 (m), 706 (m), 692 (w), 649 (m), 495 (w).



2.43

Synthesis of compound 2.43: Following General Procedure A (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (99 mg, 79%).

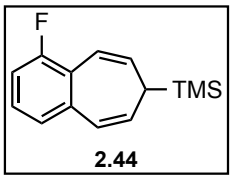
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 11.4 Hz, 1H), 6.19 (d, *J* = 11.2 Hz, 1H), 5.72 (dd, *J* = 11.5, 8.8 Hz, 1H), 5.68 – 5.61 (m, 1H), 2.37 (t, *J* = 8.7 Hz, 1H), -0.03 – -0.07 (m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.87, 135.42, 135.40, 135.37, 134.83, 133.95, 129.26, 127.87, 127.45, 127.26, 124.55, 36.32, -2.57.

HRMS: (ESI-TOF, m/z) calcd. for $C_{14}H_{18}ClSi$ $[M + H]^+$, 247.0710; found: 247.0715.

IR: (ATR, neat, cm^{-1}) = 2954 (w), 1556 (w), 1459 (w), 1432 (m), 1248 (s), 1131 (w), 1030 (w), 899 (w), 834 (s), 808 (s), 794 (m), 763 (m), 730 (m), 716 (m), 691 (w), 654 (m), 520 (w).



2.44

Synthesis of compound 2.44: Following General Procedure A (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (94 mg, 81%).

R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

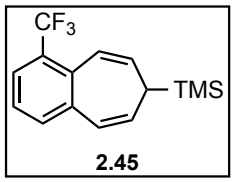
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (td, *J* = 7.9, 5.6 Hz, 1H), 6.73 – 6.68 (m, 1H), 6.37 (d, *J* = 11.5 Hz, 1H), 6.14 (d, *J* = 11.4 Hz, 1H), 5.60 (dd, *J* = 11.6, 8.5 Hz, 1H), 5.54 (dd, *J* = 11.4, 8.5 Hz, 1H), 2.37 (t, *J* = 8.4 Hz, 1H), -0.01 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.17 (d, *J* = 246.6 Hz), 139.92, 134.44, 134.17, 128.03 (d, *J* = 3.4 Hz), 127.66 (d, *J* = 9.7 Hz), 126.22 (d, *J* = 3.1 Hz), 125.71 (d, *J* = 11.9 Hz), 119.32 (d, *J* = 9.4 Hz), 113.13 (d, *J* = 23.6 Hz), 36.87, -2.81.

^{19}F NMR (471 MHz, $CDCl_3$) δ -119.31.

HRMS: (ESI-TOF, m/z) calcd. for $C_{14}H_{18}FSi$ $[M + H]^+$, 232.1084; found: 232.1085.

IR: (ATR, neat, cm^{-1}) = 2970 (w), 2953 (w), 1738 (s), 1446 (m), 1421 (m), 1365 (s), 1228 (s), 1217 (s), 836 (m), 823 (s), 806 (s), 782 (m), 758 (m), 731 (m), 540 (m), 527 (w), 513 (m)



2.45

Synthesis of compound 2.45: Following General Procedure A (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (103 mg, 73%).

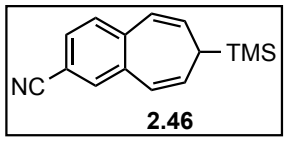
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 5.7, 3.5 Hz, 1H), 7.15 (q, *J* = 3.3, 2.2 Hz, 2H), 6.54 (dq, *J* = 11.3, 2.5 Hz, 1H), 6.26 (d, *J* = 11.0 Hz, 1H), 5.75 (dddd, *J* = 13.1, 10.1, 8.8, 1.2 Hz, 2H), 2.37 (t, *J* = 8.9 Hz, 1H), -0.10 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.72, 136.65, 136.62, 136.17, 134.20, 128.38 (q, *J* = 28.7 Hz), 127.89, 125.98, 124.6 (q, *J* = 274,7 Hz), 124.01 (q, *J* = 6.1 Hz), 123.40 (q, *J* = 2.5 Hz), 36.28, -2.46.
^{19}F NMR (471 MHz, $CDCl_3$) δ -60.62.

HRMS: (ESI-TOF, m/z) calcd. for $C_{15}H_{18}F_3Si$ $[M + H]^+$, 282.1052; found: 282.1047.

IR: (ATR, neat, cm^{-1}) = 2970 (w), 1467 (w), 1449 (w), 1395 (w), 1311 (s), 1249 (m), 1155 (m), 1117 (s), 1081 (m), 908 (w), 836 (s), 824 (s), 803 (m), 781 (m), 766 (m), 733 (m), 651 (w), 602 (w), 514 (m).



2.46

Synthesis of compound 2.46: Following General Procedure A (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (78 mg, 65%).

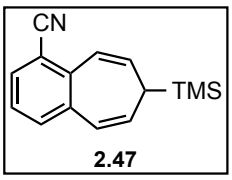
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 6.18 (dd, *J* = 23.0, 11.5 Hz, 2H), 5.73 (ddt, *J* = 11.2, 8.3, 1.2 Hz, 1H), 5.69 – 5.60 (m, 1H), 2.56 (t, *J* = 8.2 Hz, 1H), 0.14 (d, *J* = 1.1 Hz, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.95, 139.15, 138.49, 136.05, 134.68, 131.00, 127.23, 126.72, 124.43, 118.36, 112.47, 37.65, -2.81.

HRMS: (ESI-TOF, m/z) calcd. for $C_{15}H_{18}NSi$ $[M + H]^+$, 240.1209; found: 240.1208.

IR: (ATR, neat, cm^{-1}) = 2952 (w), 2224 (m), 1494 (w), 1246 (m), 1126 (w), 1081 (w), 1060 (w) 1009 (w), 983 (w), 830 (s), 805 (w), 789 (m), 757 (m), 728 (m), 650 (m), 544 (w), 497 (m).



2.47

Synthesis of compound 2.47: Following General Procedure A (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (78 mg, 65%).

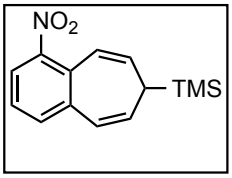
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 6.0, 3.2 Hz, 1H), 7.11 – 7.05 (m, 2H), 6.53 (d, *J* = 11.5 Hz, 1H), 6.10 (d, *J* = 11.4 Hz, 1H), 5.75 (ddd, *J* = 11.6, 8.6, 1.5 Hz, 1H), 5.58 (ddd, *J* = 11.6, 8.4, 1.5 Hz, 1H), 2.43 (t, *J* = 8.5 Hz, 1H), -0.03 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.95, 139.15, 138.49, 136.05, 134.68, 131.00, 127.23, 126.72, 124.43, 118.36, 112.47, 37.65, -2.81.

HRMS: (ESI-TOF, m/z) calcd. for $C_{15}H_{18}NSi$ $[M + H]^+$, 240.1209; found: 240.1207.

IR: (ATR, neat, cm^{-1}) = 2953 (w), 2225 (m), 1460 (w), 1248 (m), 1102 (w), 1080 (w), 1061 (w) 1009 (w), 983 (w), 835 (s), 805 (w), 782 (m), 757 (m), 732 (m), 650 (m), 544 (w), 484 (m).



Synthesis of compound 2.48: Following General Procedure A (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (98 mg, 75%).

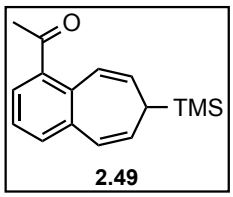
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dt, *J* = 7.5, 3.8 Hz, 1H), 7.18 – 7.11 (m, 2H), 6.25 (d, *J* = 11.3 Hz, 1H), 6.20 (d, *J* = 11.4 Hz, 1H), 5.79 – 5.69 (m, 2H), 2.41 (t, *J* = 8.8 Hz, 1H), -0.03 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.47, 139.98, 137.53, 137.03, 133.95, 131.49, 127.19, 126.69, 121.59, 121.50, 36.72, -2.50.

HRMS: (ESI-TOF, m/z) calcd. for $C_{14}H_{18}NO_2Si$ $[M + H]^+$, 258.0950; found: 258.0944.

IR: (ATR, neat, cm^{-1}) = 2970 (w), 1522 (s), 1446 (m), 1450 (w), 1351 (m), 1248 (m), 1101 (w), 1063 (w), 1008 (w), 835 (s), 818 (m), 788 (m), 736 (m), 610 (w), 540 (w), 485 (w).



2.49

Synthesis of compound 2.49: Following General Procedure A (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (83 mg, 65%).

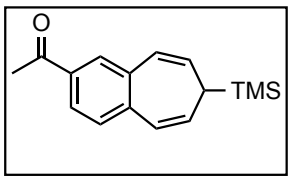
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.05 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.31 (d, *J* = 11.4 Hz, 1H), 6.24 (d, *J* = 11.2 Hz, 1H), 5.70 – 5.61 (m, 2H), 2.53 (s, 3H), 2.34 (t, *J* = 8.7 Hz, 1H), -0.04 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 204.65, 141.02, 138.85, 135.70, 135.51, 134.45, 133.01, 128.31, 126.25, 125.61, 125.33, 36.24, 31.19, -2.43.

HRMS: (ESI-TOF, m/z) calcd. for $C_{16}H_{21}OSi$ $[M + H]^+$, 257.1362; found: 257.1362.

IR: (ATR, neat, cm^{-1}) = 2955 (w), 1738 (m), 1678 (s), 1595 (m), 1355 (m), 1272 (s), 1247 (m), 1225 (m) 1218 (m), 1192 (m), 1125 (m), 1081 (w), 976 (w), 862 (s), 834 (s), 789 (m), 728 (m), 698 (w), 613 (w), 487 (w).



Synthesis of compound 2.50: Following General Procedure A (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (82 mg, 64%).

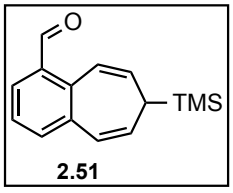
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dt, *J* = 8.0, 1.4 Hz, 1H), 7.46 (d, *J* = 1.9 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.11 (dd, *J* = 11.5, 8.9 Hz, 2H), 5.62 – 5.55 (m, 1H), 5.48 (dd, *J* = 11.6, 8.3 Hz, 1H), 2.54 (d, *J* = 1.0 Hz, 3H), 2.41 (t, *J* = 8.2 Hz, 1H), -0.00 (d, *J* = 1.0 Hz, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.69, 142.79, 138.08, 136.36, 135.14, 133.88, 130.90, 130.69, 128.08, 127.90, 126.81, 37.90, 26.63, -2.92.

HRMS: (ESI-TOF, m/z) calcd. for $C_{16}H_{21}OSi$ $[M + H]^+$, 257.1362; found: 257.1355.

IR: (ATR, neat, cm^{-1}) = 2960 (w), 1740 (m), 1682 (s), 1590 (m), 1350 (m), 1281 (s), 1255 (m), 1250 (m) 1212 (m), 1191 (m), 1122 (m), 1084 (w), 981 (w), 866 (s), 835 (s), 789 (m), 725 (m), 690 (w), 615 (w), 487 (w).



Synthesis of compound 2.51: Following General Procedure A (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (92 mg, 76%).

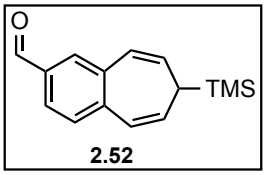
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.34 (s, 1H), 7.58 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.22 – 7.19 (m, 1H), 7.04 (d, *J* = 11.3 Hz, 1H), 6.28 (d, *J* = 11.1 Hz, 1H), 5.83 (ddd, *J* = 11.4, 8.9, 1.2 Hz, 1H), 5.71 (ddd, *J* = 11.2, 8.5, 1.2 Hz, 1H), 2.37 (t, *J* = 8.8 Hz, 1H), -0.07 (s, 10H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 192.65, 139.88, 139.25, 136.97, 136.23, 136.05, 133.66, 129.92, 128.03, 126.59, 123.32, 36.47, -2.38.

HRMS: (ESI-TOF, m/z) calcd. for $C_{15}H_{19}OSi$ $[M + H]^+$, 243.1205; found: 243.1201.

IR: (ATR, neat, cm^{-1}) = 2955 (w), 1738 (m), 1693 (m), 1595 (w), 1365 (s), 1247 (s), 1229 (s), 1217 (s), 1111 (m), 1051 (m), 862 (s), 834 (s), 789 (m), 728 (m), 691 (w), 613 (w), 514 (w).



2.52

Synthesis of compound 2.52: Following General Procedure A (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (90 mg, 74%).

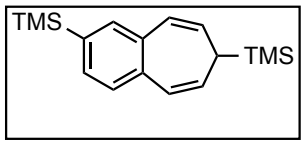
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 9.85 (s, 1H), 7.49 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.35 (d, *J* = 1.8 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.13 (dd, *J* = 11.5, 6.6 Hz, 2H), 5.64 (ddd, *J* = 11.6, 8.3, 1.5 Hz, 1H), 5.52 (ddd, *J* = 11.5, 8.2, 1.5 Hz, 1H), 2.45 (t, *J* = 8.2 Hz, 1H), 0.00 (s, 8H).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 191.99, 191.97, 191.96, 144.61, 139.13, 137.76, 135.14, 134.95, 132.14, 131.71, 128.30, 128.17, 127.97, 38.55, -2.91.

HRMS: (ESI-TOF, m/z) calcd. for $C_{15}H_{19}OSi$ $[M + H]^+$, 243.1205; found: 243.1200.

IR: (ATR, neat, cm^{-1}) = 2950 (w), 1740 (m), 1700 (m), 1593 (w), 1362 (s), 1250 (s), 1230 (s), 1216 (s), 1116 (m), 898 (s), 836 (s), 789 (m), 728 (m), 691 (w), 613 (w), 514 (w).



Synthesis of compound 2.53: Following General Procedure A (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (114 mg, 81%).

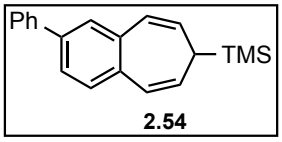
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.01 (s, 1H), 6.86 (d, *J* = 7.4 Hz, 1H), 6.08 (dd, *J* = 15.4, 11.5 Hz, 2H), 5.50 – 5.41 (m, 2H), 2.35 (t, *J* = 8.1 Hz, 1H), 0.23 (s, 8H), -0.00 (s, 8H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.51, 138.27, 136.87, 135.88, 133.01, 132.45, 131.68, 129.93, 129.03, 128.76, 37.21, -1.03, -2.91.

HRMS: (ESI-TOF, m/z) calcd. for $C_{17}H_{27}Si_2$ $[M + H]^+$, 286.1573; found: 286.1581.

IR: (ATR, neat, cm^{-1}) = 2970 (w), 1738 (m), 1419 (w), 1365 (s), 1246 (s), 1229 (m), 1217 (s), 1112 (m), 1100 (w), 894 (w), 833 (s), 789 (m), 728 (m), 691 (w), 613 (w), 514 (w).



2.54

Synthesis of compound 2.54: Following General Procedure A (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (112 mg, 77%).

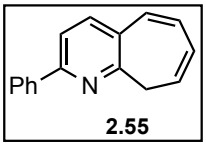
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.56 (m, 2H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.35 – 7.29 (m, 1H), 7.28 – 7.23 (m, 1H), 7.15 (d, *J* = 2.0 Hz, 1H), 6.96 (d, *J* = 7.9 Hz, 1H), 6.14 (dd, *J* = 19.4, 11.5 Hz, 2H), 5.53 – 5.45 (m, 2H), 2.39 (t, *J* = 8.2 Hz, 1H), 0.02 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.67, 139.11, 138.22, 137.01, 133.03, 132.84, 131.31, 129.42, 128.82, 128.69, 128.29, 127.31, 126.83, 125.12, 37.28, -2.85.

HRMS: (ESI-TOF, m/z) calcd. for $C_{20}H_{23}Si$ $[M + H]^+$, 290.1491; found: 290.1497.

IR: (ATR, neat, cm^{-1}) = 2971 (w), 1738 (m), 1482 (m), 1366 (s), 1355 (s), 1229 (m), 1217 (s), 1112 (m), 831 (s), 791 (m), 756 (s), 693 (w), 650 (w), 486 (w).



2.55

Synthesis of compound 2.55: Following General Procedure A (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (50 mg, 46%).

R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

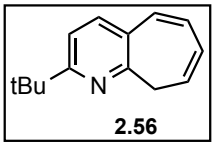
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.99 (m, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.44 – 7.37 (m, 1H), 6.99 (d, *J* = 11.3 Hz, 1H), 6.59 (dd,

J = 11.3, 5.5 Hz, 1H), 6.21 (dd, *J* = 9.8, 5.4 Hz, 1H), 5.90 (dt, *J* = 9.8, 6.9 Hz, 1H), 3.39 (d, *J* = 6.9 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.55, 153.14, 139.42, 136.39, 130.20, 129.72, 129.32, 128.98, 128.90, 128.88, 127.07, 126.62, 126.24, 118.08, 38.05.

HRMS: (ESI-TOF, m/z) calcd. for $C_{16}H_{14}N$ $[M + H]^+$, 220.1126; found: 220.1124.

IR: (ATR, neat, cm^{-1}) = 3016 (w), 2970 (w), 1738 (s), 1579 (w), 1447 (m), 1455 (m), 1366 (s), 1228 (s), 1217 (s), 761 (w), 727 (w), 712 (w), 691 (m), 653 (w).



2.56

Synthesis of compound 2.56: Following General Procedure A (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (41 mg, 41%).

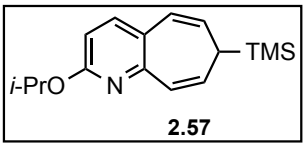
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.1 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 11.3 Hz, 1H), 6.51 (dd, *J* = 11.4, 5.4 Hz, 1H), 6.16 (dd, *J* = 9.8, 5.4 Hz, 1H), 5.86 (dt, *J* = 10.0, 6.9 Hz, 1H), 3.27 (d, *J* = 6.9 Hz, 2H), 1.35 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.69, 152.01, 135.70, 130.54, 128.87, 127.72, 126.65, 125.99, 116.43, 38.14, 37.40, 30.35, 29.86.

HRMS: (ESI-TOF, m/z) calcd. for $C_{14}H_{18}N$ $[M + H]^+$, 200.1439; found: 200.1439.

IR: (ATR, neat, cm^{-1}) = 3016 (w), 2970 (w), 1738 (s), 1586 (w), 1456 (m), 1427 (m), 1365 (s), 1228 (s), 1217 (s), 1205 (s), 1143 (w), 1092 (w), 834 (w), 671 (w).



2.57

Synthesis of compound 2.57: Following General Procedure B (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (93 mg, 68%).

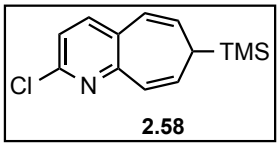
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.3 Hz, 1H), 6.33 (d, *J* = 8.3 Hz, 1H), 6.19 (d, *J* = 11.6 Hz, 1H), 5.96 (d, *J* = 11.2 Hz, 1H), 5.65 (ddd, *J* = 11.3, 8.6, 1.3 Hz, 1H), 5.37 (ddd, *J* = 11.0, 8.3, 1.3 Hz, 1H), 5.29 – 5.20 (m, *J* = 6.2 Hz, 1H), 2.36 (t, *J* = 8.4 Hz, 1H), 1.31 (dd, *J* = 6.2, 3.4 Hz, 7H), -0.02 (s, 10H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.83, 154.11, 140.64, 135.64, 130.69, 130.45, 127.36, 125.75, 108.31, 67.82, 36.67, 22.20, 22.14, -2.91.

HRMS: (ESI-TOF, m/z) calcd. for $C_{16}H_{24}NOSi$ $[M + H]^+$, 274.1627; found: 274.1626.

IR: (ATR, neat, cm^{-1}) = 3015 (w), 1587 (s), 1558 (m), 1458 (s), 1381 (w), 1370 (w), 1263 (s), 1248 (s), 1139 (w), 1101 (s), 988 (m), 862 (s), 833 (s), 806 (m), 751 (m), 732 (m), 693 (w).



2.58

Synthesis of compound 2.58: Following General Procedure B (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (62 mg, 50%).

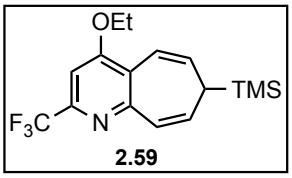
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.23 (d, *J* = 11.8 Hz, 1H), 5.95 (d, *J* = 11.4 Hz, 1H), 5.71 (ddd, *J* = 11.7, 8.5, 1.4 Hz, 1H), 5.51 (ddd, *J* = 11.4, 8.3, 1.4 Hz, 1H), 2.46 (t, *J* = 8.4 Hz, 1H), 0.00 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.16, 147.66, 140.04, 138.39, 135.08, 133.26, 129.58, 124.68, 121.28, 37.99, -3.00.

HRMS: (ESI-TOF, m/z) calcd. for $C_{13}H_{17}ClNSi$ $[M + H]^+$, 250.0819; found: 250.0814.

IR: (ATR, neat, cm^{-1}) = 2968 (w), 1573 (m), 1548 (m), 1438 (s), 1423 (m), 1249 (s), 1178 (w), 1146 (w), 1132 (w), 1109 (m), 1080 (w), 925 (m), 862 (s), 835 (s), 808 (m), 761 (s), 735 (w), 699 (w).



2.59

Synthesis of compound 2.59: Ethanol was used instead of *i*-PrOH. Following General Procedure B (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (98 mg, 60%).

R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

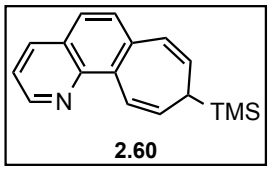
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (s, 1H), 6.43 (d, *J* = 11.5 Hz, 1H), 6.37 (dd, *J* = 11.6, 1.4 Hz, 1H), 5.81 (ddd, *J* = 11.6, 8.5, 1.4 Hz, 1H), 5.67 (ddd, *J* = 11.6, 8.5, 1.4 Hz, 1H), 4.17 (ddt, *J* = 16.4, 14.2, 7.0 Hz, 1H), 4.12 – 4.03 (m, 1H), 2.44 (t, *J* = 8.5 Hz, 1H), 1.47 (t, *J* = 7.1 Hz, 3H), -0.03 (s, 8H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.25, 157.59, 146.93, 146.71, 146.48, 146.25, 139.11, 135.50, 129.93, 125.77, 118.60, 101.18, 101.16, 64.65, 37.40, 14.59, -2.87.

^{19}F NMR (471 MHz, $CDCl_3$) δ -69.20.

HRMS: (ESI-TOF, m/z) calcd. for $C_{16}H_{21}F_3NOSi$ $[M + H]^+$, 328.1345; found: 328.1341.

IR: (ATR, neat, cm^{-1}) = 2966 (w), 1738 (s), 1580 (m), 1420 (s), 1382 (s), 1360 (s), 1341 (s), 1279 (m), 1237 (s), 1172 (s), 1136 (s), 1080 (s), 916 (m), 830 (s), 796 (s), 751 (m), 732 (m), 631 (m).



2.60

Synthesis of compound 2.60: Following General Procedure B (0.5 mmol scale) the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 100:0 to 50:1) as a yellow oil (89 mg, 67%).

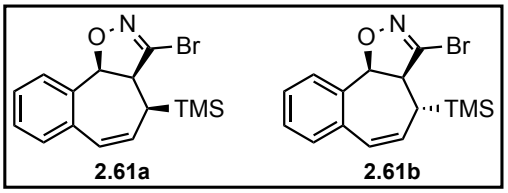
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (dd, *J* = 4.1, 1.9 Hz, 1H), 8.02 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.60 (d, *J* = 11.1 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.33 (dd, *J* = 8.1, 4.2 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 6.40 (d, *J* = 10.8 Hz, 1H), 5.77 (dddd, *J* = 29.1, 10.8, 8.5, 1.2 Hz, 2H), 2.30 (t, *J* = 8.5 Hz, 1H), -0.09 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.39, 146.61, 138.84, 136.08, 135.56, 135.42, 132.54, 129.75, 128.66, 126.64, 125.96, 124.44, 120.84, 35.34, -2.59.

HRMS: (ESI-TOF, m/z) calcd. for $C_{17}H_{20}NSi$ $[M + H]^+$, 266.1365; found: 266.1359.

IR: (ATR, neat, cm^{-1}) = 2952 (w), 1599 (m), 1496 (w), 1453 (w), 1411 (w), 1372 (w), 1247 (s), 1134 (w), 1002 (w), 976 (w), 889 (w), 864 (s), 835 (s), 771 (m), 745 (m), 647 (w).



Synthesis of compounds 2.61a and 2.61b: A 4 mL vial was charged with benzocycloheptatriene **2.41** (22 mg, 0.1 mmol, 1.0 equiv.), hydroxycarbonimidic dibromide (28 mg, 1.5 equiv., 0.15 mmol), potassium carbonate (39 mg, 3.0 equiv., 0.3 mmol), and acetonitrile (1 mL). The reaction mixture was left to stir at room temperature overnight. Upon completion, the reaction was partitioned with H_2O (3 mL) and ethyl acetate (3 mL). The aqueous phase was extracted with ethyl acetate (3 × 3 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The ^1H NMR of the crude reaction mixture revealed 1:1 mixture of diastereisomers **2.61a** and **2.61b**. The resulting crude mixture was dry-loaded onto celite and isolated by flash chromatography (SiO_2, hexanes: ethyl acetate = 1:0 to 5:1) to give the desired compounds as colorless solids (14 + 13 mg, 80% combined yield).

$\mathbf{R_f}$ = 0.3, 0.25 (SiO_2, hexanes:ethyl acetate = 9:1, UV, $KMnO_4$).

^{1}H NMR 2.61a (500 MHz, $CDCl_3$) δ 7.34 (ddt, *J* = 8.7, 6.8, 3.4 Hz, 1H), 7.26 (d, *J* = 3.4 Hz, 1H), 7.22 (q, *J* = 2.8 Hz, 2H), 7.15 (dd, *J* = 7.8, 3.8 Hz, 1H), 6.48 (dt, *J* = 11.2, 2.9 Hz, 1H), 6.21 (tt, *J* = 11.5, 3.0 Hz, 1H), 5.45 (dt, *J* = 10.7, 3.2 Hz, 1H), 4.55 (dt, *J* = 10.9, 2.9 Hz, 1H), 2.25 – 2.19 (m, 1H), -0.26 (t, *J* = 3.0 Hz, 9H).

^{13}C NMR 2.61a (126 MHz, $CDCl_3$) δ 140.93, 139.38, 133.25, 133.13, 131.99, 130.15, 128.68, 128.54, 127.14, 97.05, 60.68, 37.05, -1.39.

^{1}H NMR 2.61b (500 MHz, $CDCl_3$) δ 7.32 (td, *J* = 7.5, 1.4 Hz, 1H), 7.27 (d, *J* = 7.0 Hz, 2H), 7.18 (dd, *J* = 8.2, 6.8 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.50 (d, *J* = 11.3 Hz, 1H), 6.04 (dd, *J* = 11.3, 9.6 Hz, 1H), 5.48 (d, *J* = 10.8 Hz, 1H), 4.00 (dd, *J* = 10.8, 1.8 Hz, 1H), 2.04 (dd, *J* = 9.6, 1.6 Hz, 1H), -0.26 (d, *J* = 0.9 Hz, 9H).

^{13}C NMR 2.61b (126 MHz, $CDCl_3$) δ 144.71, 139.77, 134.26, 132.52, 130.91, 130.88, 130.78, 129.75, 127.09, 87.62, 66.81, 30.33, -1.41.

HRMS 2.61a: (ESI-TOF, m/z) calcd. for $C_{15}H_{19}BrNOSi$ $[M + H]^+$, 336.0419; found: 336.0415.

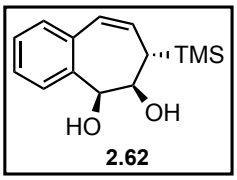
HRMS 2.61b: (ESI-TOF, m/z) calcd. for $C_{15}H_{19}BrNOSi$ $[M + H]^+$, 336.0419; found: 336.0421.

IR 2.61a: (ATR, neat, cm^{-1}) = 2966 (w), 1738 (s), 1448 (m), 1366 (m), 1249 (s), 1230 (m), 1216 (m), 1209 (m), 881 (m), 872 (m), 834 (s), 783 (s), 749 (s), 531 (w).

IR 2.61b: (ATR, neat, cm^{-1}) = 2968 (w), 1743 (s), 1449 (m), 1366 (m), 1253 (s), 1229 (m), 1217 (m), 1209 (m), 880 (m), 870 (m), 834 (s), 783 (s), 749 (s), 531 (w).

m.p. 2.61a = 182 – 184 °C

m.p. 2.61b = 179 – 182 °C



2.62

Synthesis of compound 2.62: To a stirred solution of benzocycloheptatriene **2.41** (200 mg, 0.98 mmol, 1.0 equiv.) and NMO (115 mg, 0.98 mmol, 1.0 equiv.), in acetone:H_2O (10 mL, 4:1) at 25 °C was added OsO_4 (240 μL, 0.2 M in MeCN, 0.05 mmol, 5.0 mol%) and the resulting mixture was stirred overnight until complete conversion as judged by TLC. The reagents were quenched with a 10% aqueous solution of $Na_2S_2O_3$ (5 mL), and the resulting solution was stirred for 30 min. The aqueous phase was extracted with DCM (3 × 5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture was dry-loaded onto celite and isolated by flash chromatography (SiO_2, hexanes: ethyl acetate = 7:3) to give the desired compounds as a brown oil (211 mg, 91%).

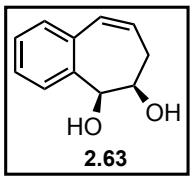
R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 7:3, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.27 (dd, *J* = 12.0, 2.1 Hz, 1H), 5.68 (dd, *J* = 12.0, 5.7 Hz, 1H), 4.67 (s, 1H), 4.03 (d, *J* = 6.8 Hz, 1H), 3.24 – 2.87 (m, 1H), 2.53 (s, 1H), 2.00 – 1.80 (m, 1H), -0.07 (s, 10H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.40, 134.48, 130.72, 130.54, 128.68, 127.83, 126.94, 79.01, 76.57, 39.18, -2.21.

HRMS: (ESI-TOF, m/z) calcd. For $C_{14}H_{20}O_2NaSi$ $[M + Na]^+$, 271.1130; found: 271.1124.

IR: (ATR, neat, cm^{-1}) = 3266 (m), 1360 (m), 1247 (s), 1090 (m), 1063 (m), 1048 (m), 988 (m), 888 (m), 875 (m), 833 (s), 785 (m), 747 (m), 696 (m), 527 (w) 485 (m).



2.63

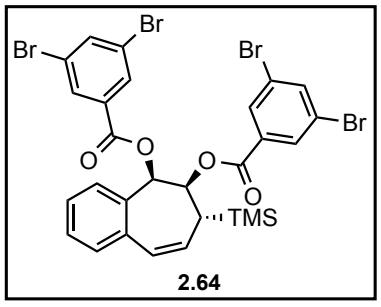
Synthesis of compound 2.63: To a stirred solution of diol **2.62** (54 mg, 0.22 mmol, 1 equiv.) dissolved in dry THF (2.2 mL), at -78 °C was added KH (80 mg, 0.65 mmol, 3 equiv., 35% in mineral oil). After 2 h of stirring the reaction was quenched with a 1.0 M solution of HCl (5 mL),), extracted with DCM (3 x 5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture was dry-loaded onto celite and isolated by flash chromatography (SiO_2, hexanes: ethyl acetate = 7:3 to 1:1) to give the desired compounds as a colorless liquid (21 mg, 55%).

$\mathbf{R_f}$ = 0.25 (SiO_2, hexanes:ethyl acetate = 1:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, CD_3OH) δ 7.42 (dd, *J* = 7.2, 1.7 Hz, 1H), 7.19 (d, *J* = 1.7 Hz, 0H), 7.16 (dd, *J* = 7.2, 1.8 Hz, 1H), 6.41 (dt, *J* = 11.9, 1.9 Hz, 1H), 5.80 (dt, *J* = 11.9, 5.0 Hz, 1H), 4.77 (d, *J* = 1.7 Hz, 1H), 4.16 (ddd, *J* = 8.5, 6.8, 1.8 Hz, 1H), 2.55 (ddd, *J* = 8.9, 4.6, 2.1 Hz, 2H).

^{13}C NMR (126 MHz, CD_3OH) δ 139.71, 136.37, 131.96, 130.69, 130.24, 128.58, 127.88, 79.02, 74.64, 35.32.

HRMS: (ESI-TOF, m/z) calcd. for $C_{11}H_{13}O_2$ $[M + H]^+$, 177.0916; found: 177.0918.
IR: (ATR, neat, cm^{-1}) = 2970 (w), 2415 (w), 1738 (s), 1450 (m), 1366 (s), 1229 (s), 1217 (s), 1206 (s), 1036 (m), 976 (m), 954 (m), 921 (w), 782 (m), 761 (m), 701 (m), 630 (m), 507 (m).



2.64

Synthesis of compound 2.64: To a stirred solution of diol **2.62** (40 mg, 0.16 mmol, 1 equiv.) dissolved in dry DCM (1.6 mL), were added sequentially 3,5-dibromobenzoic acid (110 mg, 0.40 mmol, 2.5 equiv.), 4-DMAP (2.0 mg, 0.016 mmol, 0.1 equiv) and DCC (73 mg, 0.35 mmol, 2.2 equiv.). After 1 h of stirring the reaction was diluted with hexanes (5 mL), washed with water (2 x 2 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was dry-loaded onto celite

and isolated by flash chromatography (SiO_2, hexanes: ethyl acetate = 10:1 to 9:1) to give the desired compounds as a white solid (108 mg, 87%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 9:1, UV, $KMnO_4$).

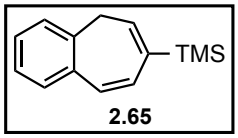
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 1.8 Hz, 2H), 7.87 (d, *J* = 1.9 Hz, 1H), 7.80 (d, *J* = 1.8 Hz, 1H), 7.76 (s, 2H), 7.39 – 7.33 (m, 2H), 7.32 – 7.24 (m, 3H), 6.55 (dd, *J* = 12.4, 2.3 Hz, 1H), 6.36 (s, 1H), 5.91 (dd, *J* = 12.3, 4.8 Hz, 1H), 5.69 (d, *J* = 6.4 Hz, 1H), 2.56 – 2.51 (m, 1H), 0.16 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.32, 163.26, 138.75, 138.54, 133.28, 132.32, 131.74, 131.52, 130.88, 129.10, 128.70, 127.22, 127.10, 123.29, 123.14, -2.14.

HRMS: (ESI-TOF, m/z) calcd. for $C_{28}H_{25}Br_4O_4Si$ $[M + H]^+$, 773.1011; found: 773.1009.

IR: (ATR, neat, cm^{-1}) = 1717 (s), 1557 (m), 1272 (m), 1250 (s), 1139 (m), 1127 (m), 1003 (m), 970 (m), 914 (m), 876 (m), 841 (m), 780 (m), 741 (m), 696 (m), 654 (m).

m.p. = 150 – 151 °C



2.65

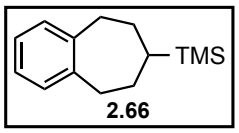
Synthesis of compound 2.65: To a stirred solution of benzocycloheptatriene **2.41** (50 mg, 0.23 mmol, 1.0 equiv.) dissolved in dry DCM (2.3 mL, 0.1 M) at -78 °C, was added $BF_3{\cdot}Et_2O$ (0.086 mL, 0.70 mmol, 3 equiv.) dropwise. After 2 h of stirring at -78 °C the reaction was quenched with water (5 mL), extracted with DCM (3 x 5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture was dry-loaded onto celite and isolated by flash chromatography (SiO_2, hexanes: ethyl acetate = 50:1) to give the desired compounds as a colorless liquid (30 mg, 60%).

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (ddd, *J* = 13.2, 7.5, 1.4 Hz, 2H), 7.22 (td, *J* = 7.5, 1.3 Hz, 1H), 7.18 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.07 (d, *J* = 11.3 Hz, 1H), 6.63 (d, *J* = 11.3 Hz, 1H), 5.97 (t, *J* = 6.6 Hz, 1H), 3.03 (d, *J* = 6.6 Hz, 2H), 0.09 (s, 8H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 138.26, 136.68, 136.30, 133.88, 131.77, 131.72, 128.50, 128.07, 127.38, 125.51, 36.49, -1.36.

HRMS: (ESI-TOF, m/z) calcd. For $C_{14}H_{18}Si$ $[M + H]^+$, 214.1178; found: 214.1181.

IR: (ATR, neat, cm^{-1}) = 2970 (w), 1738 (s), 1435 (w), 1365 (s), 1228 (s), 1216 (s), 1206 (s), 1092 (w), 894 (w), 835 (w), 788 (w), 746 (w), 696 (m), 654 (m).



2.66

Synthesis of compound 2.66: Benzocycloheptatriene **2.41** (22 mg, 0.1 mmol) was charged into a 4 mL vial and methanol (1.0 mL, 0.1 M) was added. The solution was sparged with nitrogen under sonication for 15 minutes, followed by the addition of Pd/C (8 mg, 5 mol%). And sparged for an additional 10 minutes. The reaction mixture was sparged with hydrogen (1 atm) for 3 minutes and left to stir overnight. The reaction was filtered through celite and concentrated under reduced pressure to yield the desired compound as a colorless oil (21 mg, 94%).

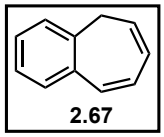
R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (s, 4H), 2.95 – 2.79 (m, 5H), 1.98 (dddd, *J* = 13.7, 6.8, 2.9, 1.5 Hz, 2H), 1.28 – 1.16 (m, 3H), 0.99 (tt, *J* = 12.7, 2.8 Hz, 1H), -0.05 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.74, 128.97, 126.00, 38.87, 32.84, 28.70, -3.20.

HRMS: (ESI-TOF, m/z) calcd. For $C_{14}H_{22}Si$ $[M + H]^+$, 218.1491; found: 218.1493.

IR: (ATR, neat, cm^{-1}) = 3016 (w), 2970 (w), 2910 (w), 1738 (s), 1448 (m), 1365 (s), 1246 (s), 1228 (m), 1217 (s), 1206 (s), 940 (w), 859 (m), 832 (m), 747 (m), 696 (m), 527 (w).


2.67

Synthesis of compound 2.67: To a solution of KH (650 mg, 5.68 mmol, 6 equiv., 35% in mineral oil) in dry NMP (4.0 mL) was added TBHP (1.032 mL, 5.68 mmol, 6 equiv., 5.0 – 6.0 M in decane) at 0 °C dropwise (caution! Gas evolution). After stirring for 15 minutes at room temperature, a solution of benzocycloheptatriene **2.41** (200 mg, 0.95 mmol, 1.0 equiv.) in dry NMP (4.0 mL) was added dropwise. After 1 h of stirring at room temperature, the reaction was quenched with a 10% aqueous solution of $Na_2S_2O_3$ (10 mL) followed by water (10 mL), extracted with DCM (3 x 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture was isolated by flash chromatography (SiO_2, pentane: diethyl ether = 50:1) to give the desired compounds as a colorless liquid (102 mg, 76%). (caution! The product is slightly volatile).

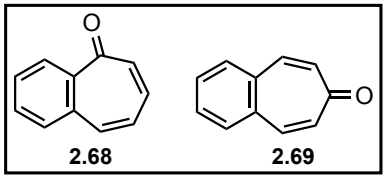
R_f = 0.3 (SiO_2, pentane: diethyl ether = 50:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 2H), 7.27 – 7.20 (m, 1H), 7.20 – 7.16 (m, 1H), 7.10 (d, *J* = 11.5 Hz, 1H), 6.49 (ddd, *J* = 11.5, 5.4, 1.3 Hz, 1H), 6.13 – 6.06 (m, 1H), 5.81 (dtd, *J* = 10.1, 6.9, 1.3 Hz, 1H), 3.06 (d, *J* = 6.8 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.57, 136.25, 133.63, 128.91, 128.76, 128.04, 127.65, 127.32, 126.04, 125.70, 34.69.

HRMS: (ESI-TOF, m/z) calcd. for $C_{11}H_{11}$ $[M + H]^+$, 143.1105; found: 143.1101.

IR: (ATR, neat, cm^{-1}) = 3016 (m), 2970 (w), 1738 (s), 1486 (w), 1450 (w), 1433 (w), 1366 (s), 1228 (s), 1217 (s), 1206 (s), 824 (w), 790 (m), 768 (m), 744 (w), 689 (s), 597 (w).



Synthesis of compounds 2.68 and 2.69: To a stirring solution of CrO_3 (220 mg, 2.2 mmol, 6 equiv.) in pyridine:DCM (3.4 ml, 1:1) at 0 °C was added compound **2.67** (52 mg, 0.37 mmol. 1 equiv.) dissolved in DCM (0.7 mL) and the resulting mixture was allowed to warm to room temperature and stirred overnight until complete conversion as judged by TLC. The reagents were quenched with a 10% aqueous solution of $Na_2S_2O_3$ (5 mL), and the resulting solution was stirred for 30 min. The aqueous phase was extracted with DCM (3 × 5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture was dry-loaded onto celite and isolated by flash chromatography (SiO_2, hexanes: ethyl acetate = 10:1) to give the desired compounds as brown oil (33 mg + 13 mg, 81%).

R_f = 0.3, 0.1 (SiO_2, hexanes: ethyl acetate = 10:1, UV, $KMnO_4$).

^{1}H NMR 2.68 (500 MHz, $CDCl_3$) δ 8.54 – 8.46 (m, 1H), 7.75 – 7.62 (m, 4H), 7.32 (d, *J* = 11.6 Hz, 1H), 7.06 (ddd, *J* = 12.2, 7.8, 1.1 Hz, 1H), 6.95 (dt, *J* = 12.1, 1.1 Hz, 1H), 6.70 (ddd, *J* = 11.6, 7.8, 1.2 Hz, 1H).

^{13}C NMR 2.68 (126 MHz, $CDCl_3$) δ 188.54, 139.64, 139.08, 136.43, 136.06, 135.61, 134.00, 132.47, 131.01, 130.63, 126.82.

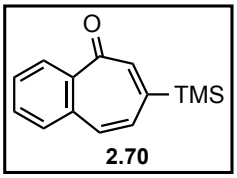
^{1}H NMR 2.69 (500 MHz, $CDCl_3$) δ 7.69 (dt, *J* = 7.4, 3.7 Hz, 2H), 7.60 (dd, *J* = 5.8, 3.4 Hz, 2H), 7.47 (d, *J* = 12.2 Hz, 2H), 6.88 – 6.77 (m, 2H).

^{13}C NMR 2.69 (126 MHz, $CDCl_3$) δ 188.52, 141.61, 136.15, 135.13, 134.15, 130.62.

HRMS 2.68: (ESI-TOF, m/z) calcd. for $C_{11}H_9O$ $[M + H]^+$, 157.0653; found: 157.0650.

HRMS 2.69: (ESI-TOF, m/z) calcd. for $C_{11}H_9O$ $[M + H]^+$, 157.0653; found: 157.0649.

IR 2.68: (ATR, neat, cm^{-1}) = 2970 (w), 1738 (s), 1676 (w), 1639 (w), 1585 (m), 1574 (m), 1467 (w), 1447 (w), 1366 (s), 1308 (w), 1229 (s), 1217 (m), 1207 (s), 1171 (w), 800 (w), 770 (m), 712 (w).
IR 2.69: (ATR, neat, cm^{-1}) = 2968 (w), 1740 (s), 1677 (w), 1637 (w), 1586 (m), 1564 (m), 1470 (w), 1435 (w), 1355 (s), 1312 (w), 1232 (s), 1215 (m), 1204 (s), 1173 (w), 822 (w), 772 (m), 732 (w).



2.70

Synthesis of compound 2.70: To a stirring solution of CrO_3 (319 mg, 3.19 mmol, 6 equiv.) in pyridine: DCM (4 ml, 1:1) at 0 °C was added benzocycloheptatriene **2.41** (114 mg, 0.532 mmol. 1 equiv.) dissolved in DCM (0.8 mL) and the resulting mixture was allowed to warm to room temperature and stirred overnight until complete conversion as judged by TLC. The reagents were quenched with a 10% aqueous solution of $Na_2S_2O_3$ (5 mL), and the resulting solution was stirred for 30 min. The aqueous phase was extracted with DCM (3 × 5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture was dry-loaded onto celite and isolated by flash chromatography (SiO_2, hexanes: ethyl acetate = 20:1) to give the desired compounds as a brown oil (85 mg, 70%).

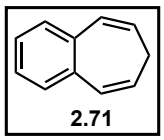
$\mathbf{R_f}$ = 0.3 (SiO_2, hexanes: ethyl acetate = 20:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.32 – 7.20 (m, 3H), 6.87 (d, *J* = 11.4 Hz, 1H), 6.74 (s, 1H), 6.41 (d, *J* = 11.5 Hz, 1H), -0.10 (s, 10H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.69, 150.33, 141.62, 139.07, 137.67, 135.99, 133.24, 132.33, 130.66, 130.28, 129.91, -1.62.

HRMS: (ESI-TOF, m/z) calcd. for $C_{14}H_{17}OSi$ $[M + H]^+$, 229.1049; found: 229.1046.

IR: (ATR, neat, cm^{-1}) = 2954 (w), 1738 (s), 1625 (m), 1584 (s), 1427 (w), 1366 (m), 1338 (m), 1304 (m), 1249 (s), 1229 (m), 1217 (s), 1206 (s), 989 (s), 840 (s), 822 (s), 778 (m), 729 (w).



2.71

Synthesis of compound 2.71: To a solution of KH (367 mg, 8.25 mmol, 18 equiv., 90%) in dry NMP (2.5 mL) was added TBHP (0.5 mL, 2.75 mmol, 6 equiv., 5.0 – 6.0 M in decane) at 0 °C dropwise (caution! Gas evolution). After stirring for 15 minutes at room temperature, a solution of cyclopropane **2.14c** (150 mg, 0.458 mmol, 1.0 equiv.) in dry NMP (2.0 mL) was added dropwise. Upon completion, the reaction was cooled in an ice bath and water (4.5 mL) was added. AcOH is then carefully added dropwise until pH = 5, upon which gas evolution is observed. $CuCl_2$ dihydrate (4.0 mg, 25 μmol, 0.05 mol%). was then added as a solid, followed by sparging with oxygen, and the reaction was stirred for 10-16 h under an atmosphere of oxygen (balloon). Upon completion, the reaction was partitioned between CH_2Cl_2 (10 mL) and saturated brine (10 mL), and the organic layer was extracted with CH_2Cl_2 (3 × 10 mL). The resulting crude mixture was isolated by flash chromatography (SiO_2, pentane: diethyl ether = 50:1) to give the desired compounds as a colorless liquid (46 mg, 70%). (caution! The product is slightly volatile).

R_f = 0.3 (SiO_2, pentane: diethyl ether = 50:1, UV, $KMnO_4$).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dt, *J* = 7.3, 3.7 Hz, 1H), 7.26 – 7.21 (m, 3H), 6.60 (d, *J* = 10.3 Hz, 1H), 5.85 (dt, *J* = 10.2, 6.5 Hz, 1H), 2.49 (t, *J* = 6.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.24, 130.61, 130.39, 128.55, 126.17, 26.40.

HRMS: (ESI-TOF, m/z) calcd. for $C_{11}H_{11}$ $[M + H]^+$, 143.1105; found: 143.1102.

IR: (ATR, neat, cm^{-1}) = 3014 (m), 2966 (w), 1738 (s), 1480 (w), 1448 (w), 1435 (w), 1360 (m), 1230 (s), 1216 (s), 1203 (s), 830 (w), 812 (w), 792 (m), 769 (m), 740 (w), 694 (s), 600 (w).

Crystallographic data

X-ray diffraction experiments were carried out on single crystals mounted on Cryo-loops using Paratone-N or Krytox oils. The data was collected on Bruker D8 Venture / Photon II or on a Bruker APEX II diffractometers in George L. Clark X-ray Facility at UIUC. Multi-scan absorption correction was applied. The space group was determined in XPREP (Bruker AXS). The solutions were obtained using Intrinsic Phasing method, as implemented in SHELXT, and refined using full-matrix least squares against F^2 , as implemented in SHELXL, using OLEX2 as the graphical user interface.

Crystallographic data for compound 2.14c

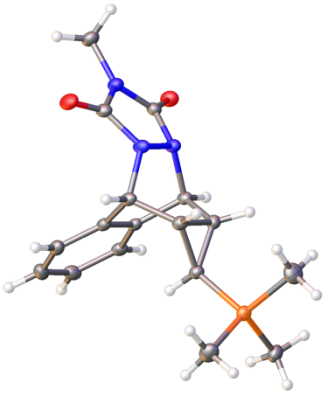


Table 2.14c Crystal data and structure refinement.

CCDC	2129869
Empirical formula	$C_{17}H_{21}N_3O_2Si$
Formula weight	327.46
Temperature/K	99.99
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	26.2536(4)
b/Å	11.6384(2)
c/Å	29.4236(4)
α/°	90
β/°	107.01
γ/°	90
Volume/Å^3	8596.9(2)
Z	20
ρ_{calc}g/cm^3	1.265
μ/mm^{-1}	0.149
F(000)	3480.0
Crystal size/mm^3	0.631 × 0.48 × 0.372
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.284 to 56.596
Index ranges	-34 ≤ h ≤ 35, -15 ≤ k ≤ 15, -39 ≤ l ≤ 37
Reflections collected	278930
Independent reflections	21341 [R_{int} = 0.0513, R_{sigma} = 0.0202]
Data/restraints/parameters	21341/18/1056
Goodness-of-fit on F^2	1.024
Final R indexes [I>=2σ (I)]	R_1 = 0.0343, wR_2 = 0.0876
Final R indexes [all data]	R_1 = 0.0422, wR_2 = 0.0940
Largest diff. peak/hole / e Å^{-3}	0.35/-0.27

Crystallographic data for compound 2.64

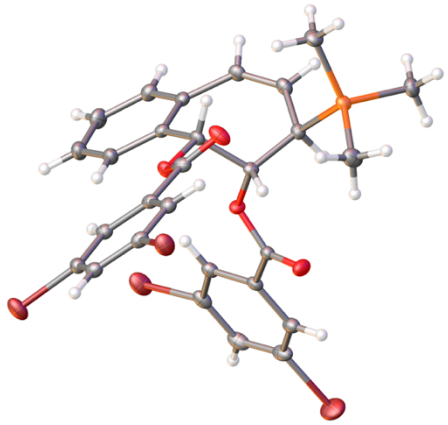


Table 2.64 Crystal data and structure refinement.

CCDC	2129868
Empirical formula	$C_{28}H_{24}Br_4O_4Si$
Formula weight	772.20
Temperature/K	100.00
Crystal system	monoclinic
Space group	C2/c
a/Å	38.408(2)
b/Å	9.4430(4)
c/Å	16.6160(8)
α/°	90
β/°	108.776(2)
γ/°	90
Volume/Å^3	5705.7(5)
Z	8
ρ_{calc}g/cm^3	1.798
μ/mm^{-1}	5.717
F(000)	3024.0
Crystal size/mm^3	0.306 × 0.264 × 0.172
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.456 to 56.592
Index ranges	-51 ≤ h ≤ 47, -12 ≤ k ≤ 12, -22 ≤ l ≤ 22
Reflections collected	87936
Independent reflections	7099 [R_{int} = 0.0340, R_{sigma} = 0.0150]
Data/restraints/parameters	7099/0/338
Goodness-of-fit on F^2	1.027
Final R indexes [I>=2σ (I)]	R_1 = 0.0187, wR_2 = 0.0447
Final R indexes [all data]	R_1 = 0.0212, wR_2 = 0.0456
Largest diff. peak/hole / e Å^{-3}	0.59/-0.43

Chapter 3: Attempts of Synthesis of Amaryllidaceae Homolycorine Alkaloids

3.1 Introduction

The earliest records of cancer in mankind history are traced back to ancient Egypt (around 1600BC).[1] Furthermore, it turns out to have been common during the classical Greek epoch (510BC to 323BC) due to the "Father of medicine" Hippocrates who described the tumor ramifications as "karkinos". Plants have played, for centuries if not millennia, a major role as source of medicines to cure several illnesses, no less so in cancer therapy.[2] In particular, over 3000 plant taxa have shown effects against cancer among many cultures around the globe. The anticancer potential of the *Amaryllidaceae* family herbs has been known for centuries and even Hippocrates noted that prescribing *Narcissus* oils helped for the treatment of tumors.[3] Therefore, this family acquired major interest for its biological activities. The alkaloid lycorine **3.1** was the first to be described, as well as the first to be tested for and to exhibit antiproliferative effects,[4] but these observations from the 1920s were mainly unnoticed until in 1960s narciclasine **3.2** was extracted from the bulbs of various flowers from the *Narcissus* genus and described as a potent antiproliferative agent.[5] The phenanthridones such as narciclasine **3.2** are among the most potent natural compounds screened against the NCI (National Cancer Institute) panel of 60 human cancer cell lines.[6] The main characteristic of narciclasine **3.2** is its ability to

induce apoptosis (or programmed cell death) selectively in cancer cells, leaving normal cells largely intact. Although the lycorine alkaloids of the *Amaryllidaceae* have not shown nanomolar level of activities seen with some of the phenanthridone alkaloids, they have nonetheless provided a rich source of compounds (>150) in cytotoxicity evaluations.[5] Several other alkaloids occur in the *Amaryllidaceae* family, arising from different oxidative coupling reactions from their common biogenetic precursor: norbelladine **3.3**.[7] The homolycorine alkaloids, together with others, are classified as one of the minor alkaloid groups of the family. Due to the importance of the aforementioned main alkaloids in cancer treatment, there has been significant interest in the homolycorine alkaloids as a new source of potential biologically active compounds. The members of this subfamily are distinguished in having a contiguous ring system comprising of aryl, pyran, hexyl and pyrrolidine ring moieties (**Figure 3.1)**.

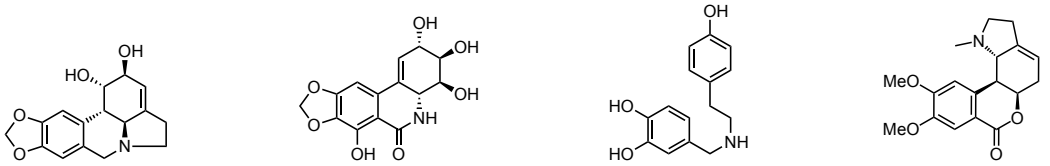


Figure 3.1. The Amaryllidaceae alkaloids (+)-lycorine (**3.1**), (+)-narciclasine (**3.2**), norbelladine (**3.3**) and (+)-homolycorine (**3.4**).

The biosynthesis of homolycorine-type alkaloids is strictly related to the lycorine-type ones. It was demonstrated that the first intermediate towards the formation of both

lycorine (**3.1**) and homolycorine (**3.4**) is norpluviine (**3.6**), arising from an ortho-para phenol oxidative coupling, starting from 4'-methylnorbelladine (**3.5**) as a precursor. Norpluviine (**3.6**) can then be converted to lycorine (**3.1**) through a sequence which comprises epoxidation, followed by ring opening and allylic rearrangement. Another route is benzylic oxidation at C6 of norpluviine (**3.6**), followed by ring opening, rotation and ring formation. Finally, N, O-methylation and subsequent oxidation produce homolycorine (**3.4**) (**Figure 3.2**).[8-10]

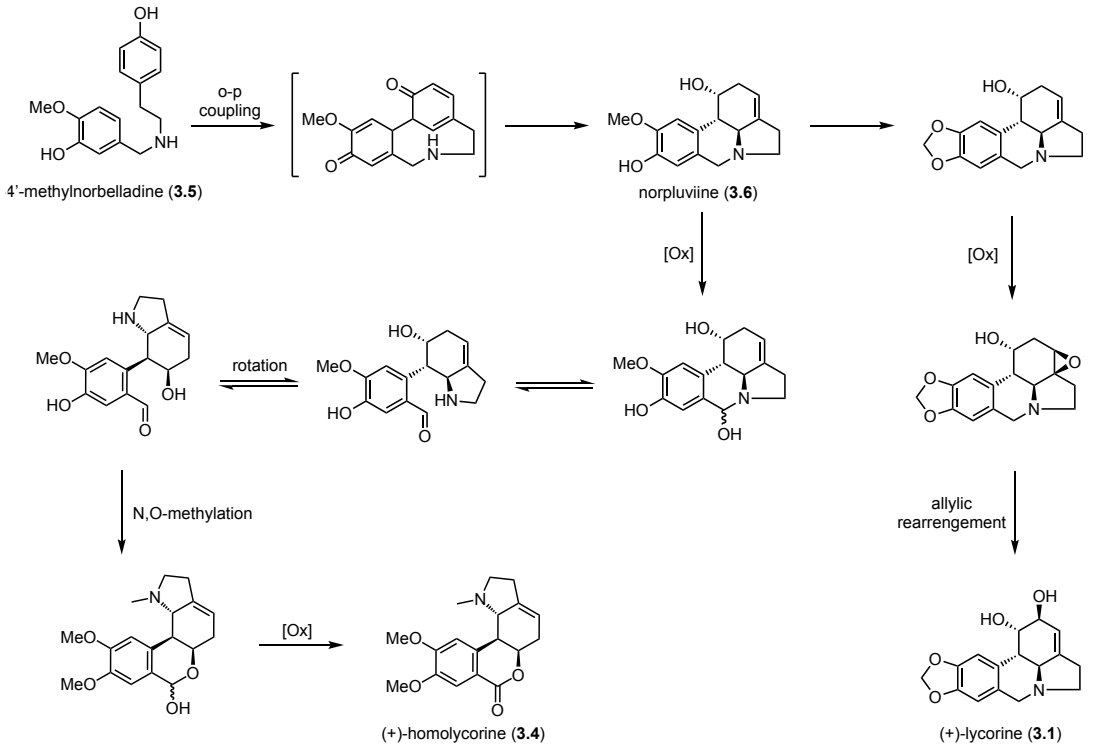


Figure 3.2. Biosynthesis of lycorine (**3.1**) and homolycorine (**3.4**) from norpluviine intermediate (**3.6**).

Despite the increasing interest towards this class of alkaloids, not many syntheses were developed, with clivonine (**3.7**) as the only member being synthetized in both a racemic and enantioselective fashion.[11-15] The Irie group was the first one to accomplish its racemic total synthesis in 1973, through cycloaddition of fumaric acid (**3.8**) and 3,4-methylenedioxyphenyl allyl carbinol (**3.9**) in boiling acetic anhydride as key step to build the core, achieving the desired product in 16 steps.[11] After almost 50 years from the first synthesis, Spivey and coworkers reported a new approach towards racemic clivonine (**3.7**), starting from enone **3.10**, employing a retro-Cope elimination protocol to give **3.11**, followed by the Bischler-Napieralski reaction to afford ring B closure product. Noteworthy, from this lycorine-type product they showed a biomimetic ring-switch which corroborated experimentally the biogenetic hypothesis by Barton 50 years prior.[12]

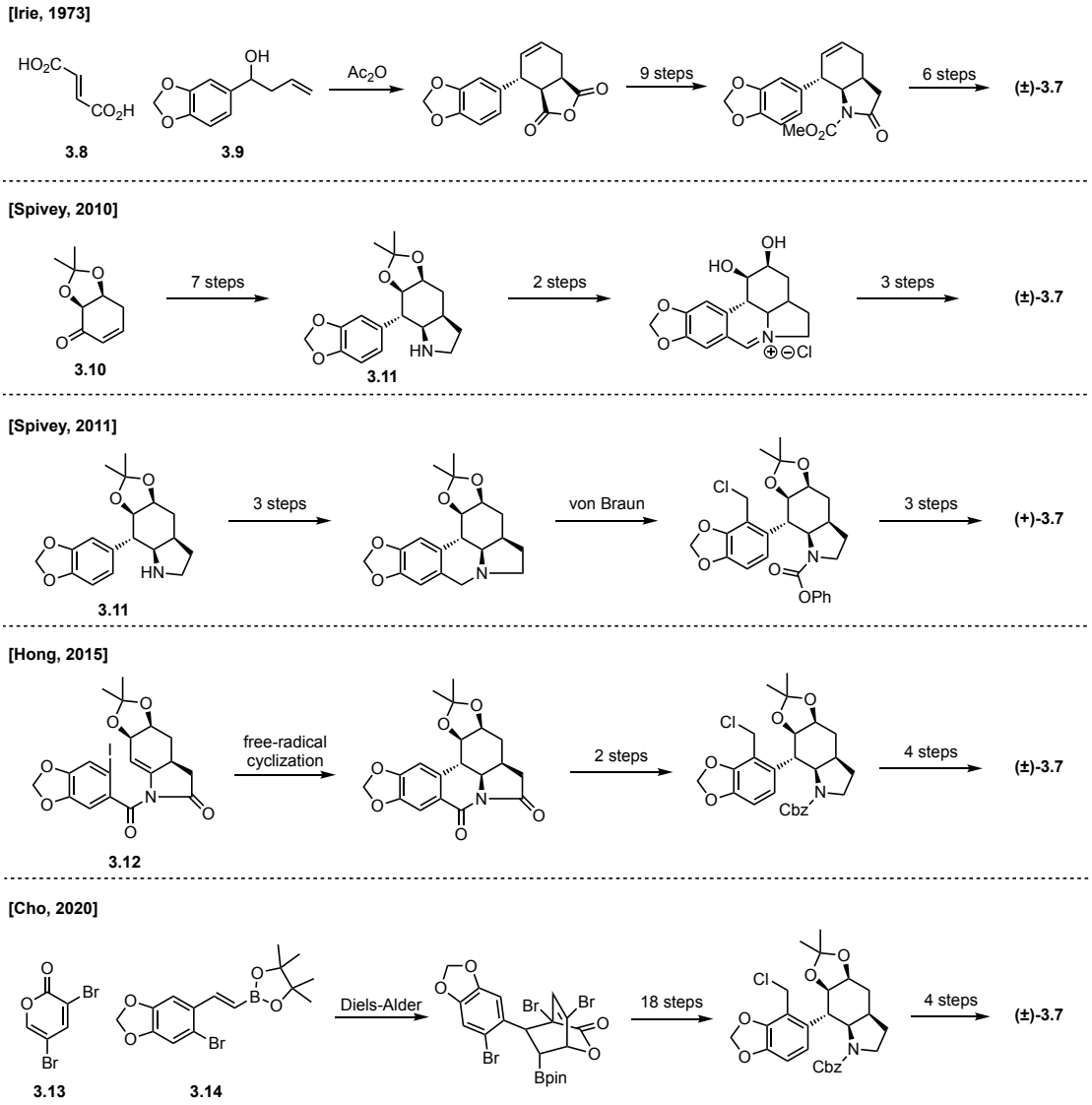


Figure 3.3. Reported syntheses of clivonine (**3.7**).

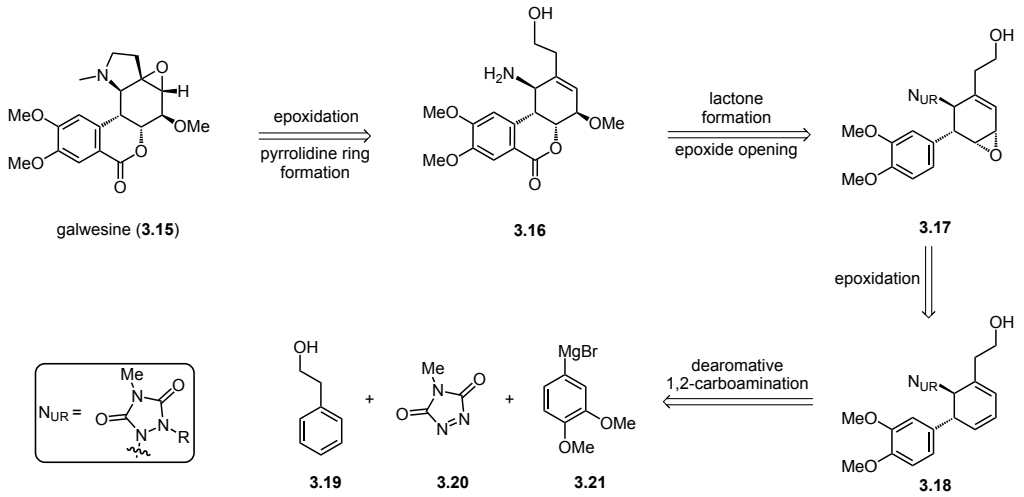
The following year the same group achieved the first asymmetric synthesis of (+)-clivonine (**3.7**) starting from enantiomerically pure enone **3.10** and applying a von Braun-type cleavage of the benzylic C-N bond by means of phenylchloroformate.[13,16] In 2015,

Hong and coworkers built the lycorine-type intermediate through an intramolecular 6-endo-trig free-radical cyclization of enamide **3.12**. The resulting product was then submitted to von Braun cleavage, similarly to the previous approach by Spivey et al.[14] Finally, in 2020 Cho and coworkers reported the racemic total synthesis of clivonine (**3.7**) using a novel approach via Diels-Alder reaction of 3,5-dibromo-2-pyrone **3.13** and piperonylvinyl boronate **3.14**. From the cycloaddition product they intercepted the same intermediate from the Hong group's synthesis (**Figure 3.3**).[15]

3.2 Retrosynthetic Analysis

The member of the homolycorine group we chose to attempt the synthesis was galwesine **3.15**, since not much is known about its biological properties (probably due to the few species of plants where this compound can be found)[17] and to date no total synthesis of this compound has been reported. As shown previously, the most established procedure to accomplish the synthesis of clivonine, has been through a biomimetic ring-switch or von Braun-type cleavage from a lycorine-type intermediate. Keeping in mind these procedures as alternatives, we sought a faster route to access the pyrrolidine and lactone rings. Our first disconnections consist of epoxide and pyrrolidine ring formation tracking back to amino alcohol **3.16**. Our next disconnections rely on lactone ring construction after an allylic epoxide opening of intermediate **3.17**. This compound could be derived from a regioselective epoxidation of diene **3.18**. Finally, diene **3.18** can be

assembled through dearomative trans-1,2-carboamination from phenethyl alcohol **3.19**, MTAD **3.20** and Grignard reagent **3.21 (Scheme 3.1)**.



Scheme 3.1. Retrosynthetic analysis of galwesine **3.15**.

3.3 Galwesine

With this strategy in mind we started exploring the dearomative 1,2-carboamination to achieve compound **3.18**. This strategy has been developed by our group, employing MTAD **3.20** and several Grignard reagents to access 1,2-carboaminated dienes. After the generation of benzene-MTAD cycloadduct, nickel can coordinate both olefins, generating complex I. Subsequent oxidative addition would form complex II which can transmetallate and perform reductive elimination to complex IV, which finally by decomplexation regenerates nickel catalyst and deliver the 1,2 carboaminated product. Noteworthy, this transformation can be performed asymmetrically employing chiral

ligands and the reductive elimination is the enantioinduction step, since complex III has a plane of symmetry and is amenable for desymmetrization (**Figure 3.4**).

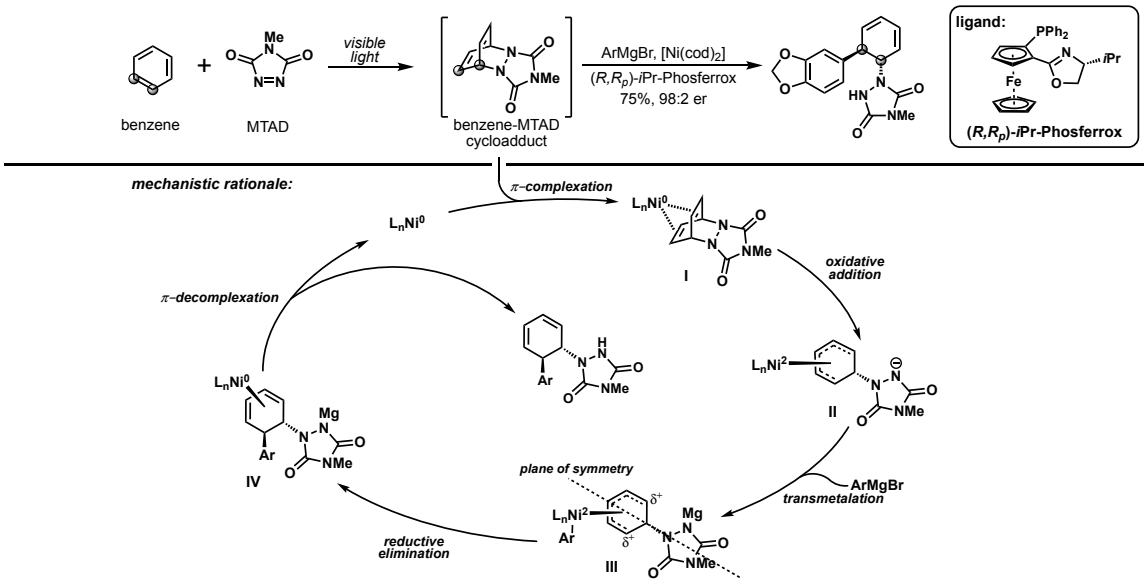
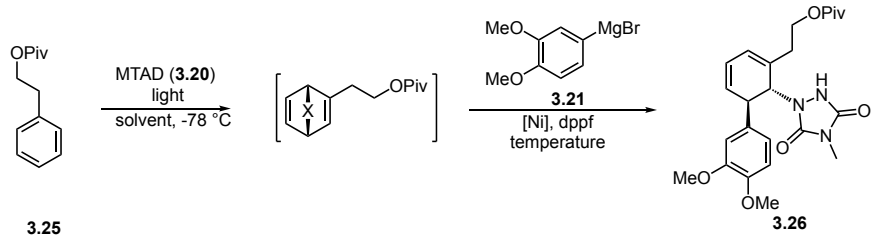


Figure 3.4. Dearomative *trans*-1,2-carboamination reaction and our proposed mechanistic rationale.

In the original study,[18] Grignard reagent **3.21** was never employed, but similar ones were used, even though only on unsubstituted benzene. First attempts with pivalate protected phenethyl alcohol **3.25** gave only traces of the desired compound. After screening some reaction conditions (**Table 3.1**), we found out how Grignard reagent's molarity and the temperature of addition, are of absolute importance to the reaction yield (entry 6). In this specific case, a slightly more diluted Grignard reagent gives synthetically useful results. This first step could be easily performed up to 10g scale of MTAD **3.20**.

Table 3.1. Optimization of 1,2-carboamination reaction with Grignard reagent **3.21**.[a]



3.25 **3.26**

Entry	Conditions	Yield [%]
1	DCM, [Ni(acac)$_2$] (1.5 mol%), dppf (2 mol%), **3.21** (3.0 equiv.), -78 to 25 °C	0
2	DCM, [Ni(acac)$_2$] (5.0 mol%), dppf (10 mol%), **3.21** (3.0 equiv.), -78 to 25 °C	5
3	DCM, [Ni(cod)$_2$] (5.0 mol%), dppf (10 mol%), **3.21** (3.0 equiv.), -78 to 25 °C	7
4	DCM, [Ni(cod)$_2$] (5.0 mol%), dppf (10 mol%), **3.21** (3.0 equiv.), -50 to 25 °C	15
5	DCM, [Ni(cod)$_2$] (10.0 mol%), dppf (20 mol%), **3.21** (3.0 equiv.), -50 to 25 °C	28
6[a],[b]	DCM, [Ni(cod)$_2$] (10.0 mol%), dppf (20 mol%), **3.21** (2.0 equiv.), -50 to 25 °C	50
7	DCM, [Ni(cod)$_2$] (10.0 mol%), dppf (20 mol%), **3.21** (1.0 equiv.), -50 to 25 °C	25

[a] Standard reaction conditions: MTAD (**3.20**, 1.0 mmol, 1.0 equiv.), pivalate protected phenethyl alcohol (**3.25**, 10.0 mmol, 10.0 equiv.), solvent (0.2 M), visible light, temperature, 12 h; then Grignard reagent (**3.21**, 2.5 mmol, 2.5 equiv.), solution of catalyst [Ni precursor (x mol %), dppf (y mol %), DCM], temperature, 3 h. [b] Decagram scale reaction conditions: MTAD (**3.20**, 88.5 mmol, 1.0 equiv.), pivalate protected phenethyl alcohol (**3.25**, 885.0 mmol, 10.0 equiv.), solvent (0.2 M), visible light, temperature, 12 h; then Grignard reagent (**3.21**, 221.5 mmol, 2.5 equiv.), solution of catalyst [Ni precursor (x mol %), dppf (y mol %), DCM], temperature, 3 h.

After this first step optimization, we investigated the choice of a protecting group for the urazole moiety, since in our group we previously observed that it can act as a directing group for epoxidation reactions, giving the undesired diastereoselectivity.

Moreover, the optimal protecting group should also be later used to cleave the urazole ring down to an amine. Several protecting groups were investigated: methyl (**3.27**), tert-butyloxycarbonyl (Boc) (**3.28**), benzyl (**3.29**), acetophenone (**3.30**), acetonitrile (**3.31**) and benzoyl group (**3.32**). Despite the use of reductive and/or basic conditions, none of these strategies gave the desired product **3.33** or similar products. When benzoyl group was employed, we hypothesized that single electron reduction by SmI_2 could be a viable option for the direct cleavage of the N-N bond.[19]

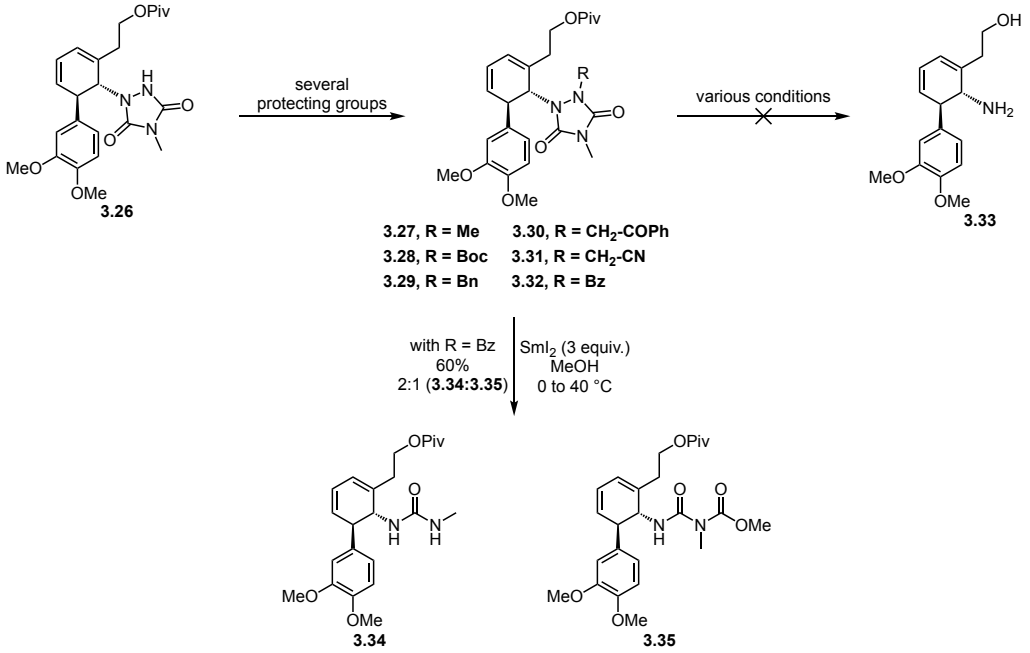


Figure 3.5. Protecting group and urazole cleavage conditions investigation.

Treatment of compound **3.32** with SmI_2 in MeOH actually led to N-N bond cleavage giving urea **3.34** and mixed urea-carbamate **3.35** in 60% total yield (**Figure 3.5**).

After these results, we were convinced that benzoyl was the protecting group we were looking for. Knowing this, we decided to postpone the cleavage of the urazole moiety, to use its steric and electronic properties for the regio- and diastereoselective epoxidation which we envisioned. We hypothesized that the inductively withdrawing urazole moiety would deactivate the vicinal olefin, enabling selective epoxidation of the distal olefin of the diene, while its steric hindrance would guide the facial selectivity on the opposite side, as also shown in previous examples from our group.[20] Unfortunately, employing mCPBA as epoxidating agent selectively reacted with the more substituted olefin in high yield. On the other hand, using freshly distilled DMDO gave selective epoxidation of less substituted olefin, although low yielding. After further optimization, we were pleased to observe that generating DMDO in situ, in presence of catalytic amount of EDTA, proved to be higher yielding, delivering product **3.36** in 85% yield, presumably on the opposite face of urazole moiety due to results from previously reported transformations on similar substrates by our group.[20] Compound **3.36** was subsequently submitted to CSA-mediated allylic epoxide opening in methanol, delivering product **3.37** in 71% yield, which was readily TBS-protected. Noteworthy, using TBSCl as silylating agent gave no conversion to the product, probably due to the high steric hindrance of the alcohol, making necessary to use a more activated reagent as TBSOTf to provide compound **3.38** in 70% yield. At this point of the synthesis, we decided to postpone lactone ring formation and apply the previously tested conditions for urazole cleavage by treatment of SmI_2 in methanol which gave urea **3.39** in

an unoptimized 35% yield. The remaining steps for the synthesis of galwesine (**3.15**) would be pyrrolidine ring formation by activation of primary alcohol and nucleophilic substitution from urea (**3.40**), followed by $LiAl(OMe)_3H$ reduction to provide desired product **3.41**.[21] Subsequently, bromination of aryl ring, followed by carbonylative coupling[22-24] and TBAF deprotection would generate lactone product **3.42** which can lastly be submitted to epoxidation, providing natural product galwesine (**3.15**) (**Figure 3.6**).

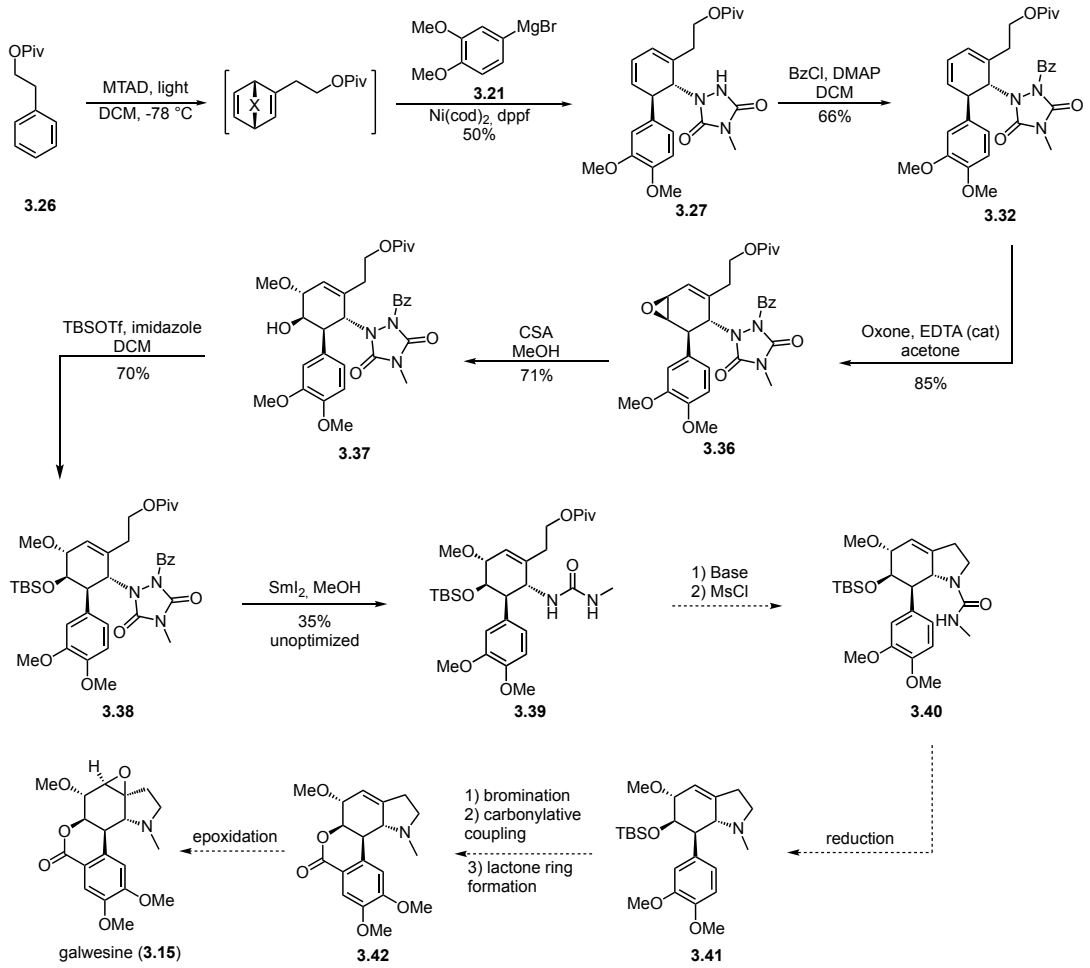


Figure 3.6. Current progess towards the total synthesis of galwesine (**3.15**) and future directions.

3.4 Conclusions

In conclusion, although we were not able to finish the total synthesis of homolycorine-type alkaloid galwesine **3.15**, we still made some steps forward to a possible new approach towards the construction of the homolycorine core. This was achieved through optimization of the dearomative 1,2-carboamination conditions which gave good yields up to 10 gram scale of MTAD. We were able to selectively epoxidize the disubstituted olefin in presence of the trisubstituted one, by in-situ generation of DMDO. Lastly, we were able to show a different approach for the protection and subsequent cleavage of the urazole moiety, although the yields are not fully optimized, yet.

3.5 References

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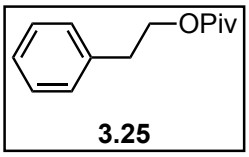
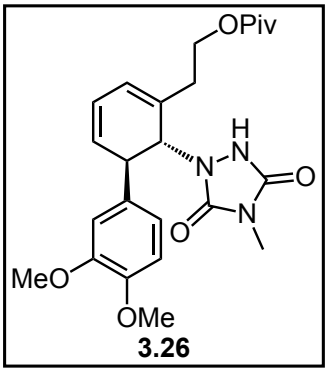
3.6 Experimental section



3.25

Synthesis of compound 3.25: To a solution of phenethyl alcohol (12.0 mL, 100.0 mmol, 1.0 equiv.) in DCM (200.0 mL) were added DMAP (1.22 g, 10.0 mmol, 0.1 equiv.) and Et_3N (13.9 mL, 100.0 mmol, 1.0 equiv.). The solution was cooled to 0 °C, then PivCl (13.5 mL, 110.0 mmol, 1.1 equiv.) was added dropwise. The solution was let to warm up to room temperature then left stirring overnight. The reaction was carefully quenched with water (50 mL) then a saturated solution of $NaHCO_3$ (50 mL), extracted with DCM (3 x 100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture was dry-loaded onto celite and isolated by flash chromatography (SiO_2, hexanes:diethyl ether = 1:0 to 95:5) to give the desired compounds as a colorless liquid (19 g, 92%).
Spectral data consistent with that reported in the literature.

R_f = 0.6 (SiO_2, hexanes:diethyl ether = 95:5, UV, $KMnO_4$).



3.26

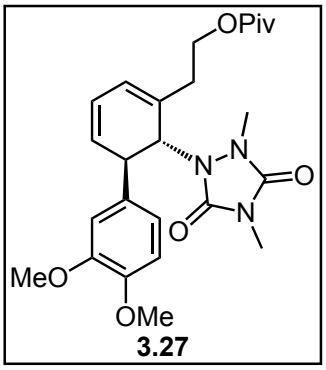
Synthesis of compound 3.26: In an oven-dried test tube, MTAD (**3.20**, 10.0 g, 88.5 mmol, 1.0 equiv.) was dissolved in anhydrous DCM (440 mL) under nitrogen atmosphere and cooled to –78 °C. Compound **3.25** (150.0 g, 885.0 mmol, 10.0 equiv.) was slowly added and the solution was stirred for five minutes. The pink solution was irradiated with LED lights at –78 °C until complete loss of color. Upon decolorization, the LED lights were turned off and a pre-cooled (–78 °C) solution of $[Ni(cod)_2]$ (2.43 g, 8.85 mmol, 10 mol%) and dppf (9.92 g, 17.7 mmol, 20 mol%) in DCM (20 mL) was added, followed by dropwise addition of 3,4-dimethoxyphenylmagnesium bromide (**3.21**, 111 mL, 2.0 M in THF, 221.5 mmol, 2.5 equiv.) at the rate to keep the internal temperature below –65 °C. After addition, the cold bath temperature was warmed to –45 °C and allowed to slowly warm to 0 °C over 3 h. Reaction vessel was removed from the cold bath, stirred at room temperature for 15 min, and then aq. HCl (200 mL, 1 M) was added. The organic phase was separated and the aqueous phase was extracted with DCM (2 × 300 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography

(SiO_2, hexanes:EtOAc = 3:1 → 1:1) to give the desired compound as a orange solid (18 g, 50%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 1:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 6.13 (d, *J* = 9.8 Hz, 2H), 6.00 – 5.84 (m, 1H), 4.88 (d, *J* = 4.6 Hz, 1H), 4.28 – 4.10 (m, 1H), 4.04 (dt, *J* = 12.0, 6.3 Hz, 1H), 3.86 (d, *J* = 5.8 Hz, 7H), 3.07 (s, 3H), 2.40 (t, *J* = 6.5 Hz, 2H), 1.14 (s, 7H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 155.4, 152.4, 149.9, 147.0, 141.3, 133.9, 130.2, 124.4, 121.3, 119.1, 112.5, 109.8, 68.2, 63.3, 56.9, 38.7, 33.8, 32.6, 27.7, 26.9.



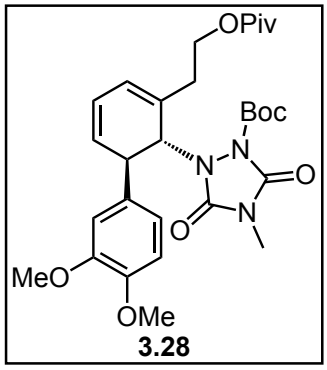
3.27

Synthesis of compound 3.27: To a solution of **3.26** (2.0 g, 4.0 mmol, 1.0 equiv.) in DCM (40 mL) was added K_2CO_3 (6.0 g, 40.0 mmol, 10.0 equiv.) and Me_2SO_4 (10 mL, 40.0 mmol, 10.0 equiv.) then stirred at 35 °C for 8 h. The mixture was cooled to 0 °C and 5% aq. NH_4OH (50 mL) was added, the phases were separated, and the aqueous phase was extracted with DCM (2 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes:EtOAc = 5:1 → 3:1) to give the desired compound as a colorless solid (1.42g, 75%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 3:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.69 (s, 3H), 6.18 – 5.94 (m, 2H), 5.87 – 5.70 (m, 1H), 4.98 (d, *J* = 7.4 Hz, 1H), 4.09 (td, *J* = 6.6, 2.0 Hz, 2H), 3.78 (d, *J* = 1.4 Hz, 7H), 3.69 – 3.56 (m, 1H), 3.09 (s, 3H), 2.94 (s, 3H), 2.40 (q, *J* = 7.3 Hz, 2H), 1.07 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.7, 154.3, 150.2, 149.5, 145.6, 142.5, 134.2, 131.2, 124.7, 120.2, 119.3, 113.7, 108.7, 66.5, 62.1, 55.8, 41.3, 37.7, 34.2, 32.6, 27.7, 26.9.



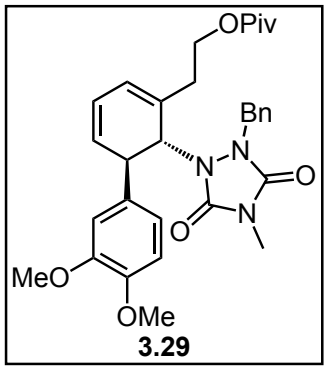
3.28

Synthesis of compound 3.28: To a solution of **3.26** (1.0 g, 2.0 mmol, 1.0 equiv.) in DCM (20 mL) was added DMAP (50.0 mg, 0.2 mmol, 0.1 equiv.) and Boc_2O (920 uL, 4.0 mmol, 2.0 equiv). The mixture was stirred for 3 h then water (20 mL) was added, the phases were separated, and the aqueous phase was extracted with DCM (2 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes:EtOAc = 5:1 → 3:1) to give the desired compound as a colorless solid (780 mg, 70%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 3:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 – 6.58 (m, 3H), 6.00 (ddd, *J* = 9.4, 5.6, 2.0 Hz, 1H), 5.91 (dt, *J* = 5.7, 1.5 Hz, 1H), 5.75 – 5.65 (m, 1H), 5.12 – 5.00 (m, 1H), 3.82 (d, *J* = 6.1 Hz, 6H), 3.73 (ddd, *J* = 8.9, 4.2, 2.0 Hz, 1H), 2.94 (s, 3H), 2.53 (td, *J* = 6.7, 2.8 Hz, 2H), 1.51 (s, 9H), 1.12 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 156.2, 153.4, 151.4, 149.8, 146.7, 140.5, 134.2, 131.2, 124.7, 120.2, 119.3, 113.7, 108.7, 84.3, 66.5, 62.1, 55.8, 41.3, 37.7, 34.2, 32.6, 28.8, 26.9.



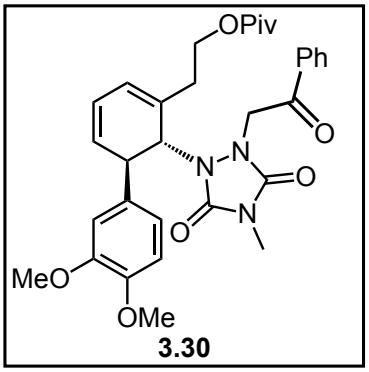
3.29

Synthesis of compound 3.29: To a solution of **3.26** (1.0 g, 2.0 mmol, 1.0 equiv.) in DCM (20 mL) was added BnCl (460 uL, 4.0 mmol, 2.0 equiv). The mixture was stirred for 12 h then water (20 mL) was added, the phases were separated, and the aqueous phase was extracted with DCM (2 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes:EtOAc = 5:1 → 3:1) to give the desired compound as a colorless solid (790 mg, 72%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 3:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.67 (m, 2H), 7.41 (t, *J* = 7.8 Hz, 3H), 6.72 – 6.58 (m, 3H), 6.08 (ddd, *J* = 9.6, 5.7, 1.7 Hz, 1H), 5.92 – 5.84 (m, 1H), 5.80 (dd, *J* = 9.5, 4.8 Hz, 1H), 5.05 – 4.85 (m, 4H), 3.87 (td, *J* = 6.3, 4.8 Hz, 2H), 3.64 – 3.57 (m, 1H), 3.08 (s, 3H), 2.10 (t, *J* = 6.5 Hz, 2H), 0.97 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 155.6, 153.2, 148.9, 145.7, 139.5, 135.2, 132.6, 128.5, 126.8, 125.2, 120.2, 118.3, 112.7, 108.7, 84.3, 66.5, 62.1, 55.8, 52.4, 41.3, 37.7, 34.2, 32.6, 26.9.



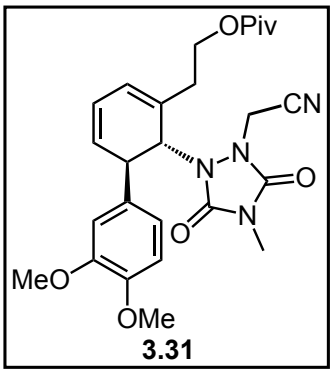
3.30

Synthesis of compound 3.30: To a solution of **3.26** (1.0 g, 2.0 mmol, 1.0 equiv.) in DCM (20 mL) was added DMAP (50.0 mg, 0.2 mmol, 0.1 equiv.) and 2-bromoacetophenone (800 mg, 4.0 mmol, 2.0 equiv). The mixture was stirred for 12 h then water (20 mL) was added, the phases were separated, and the aqueous phase was extracted with DCM (2 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes:EtOAc = 5:1 → 3:1) to give the desired compound as a colorless solid (920 mg, 80%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 3:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.3 Hz, 2H), 7.48 (dt, *J* = 15.0, 7.2 Hz, 4H), 6.72 (s, 4H), 5.72 (d, *J* = 18.9 Hz, 3H), 5.16 (d, *J* = 18.1 Hz, 1H), 4.83 (d, *J* = 2.9 Hz, 1H), 4.55 (d, *J* = 10.7 Hz, 1H), 4.17 (dd, *J* = 8.1, 5.3 Hz, 2H), 3.78 (d, *J* = 3.9 Hz, 8H), 2.58 (s, 3H), 1.12 (s, 10H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 195.2, 175.4, 156.6, 152.6, 149.7, 144.7, 139.5, 135.2, 133.2, 132.6, 128.5, 125.2, 120.2, 118.2, 112.3, 107.7, 85.3, 65.7, 60.9, 55.8, 52.4, 42.3, 38.2, 35.1, 33.1, 26.7.



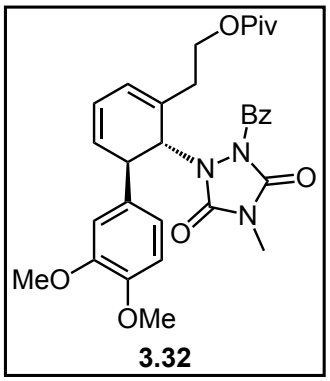
3.31

Synthesis of compound 3.31: To a solution of **3.26** (1.0 g, 2.0 mmol, 1.0 equiv.) in DCM (20 mL) was added $KHCO_3$ (1.1 g, 10.0 mmol, 5.0 equiv.) and iodoacetonitrile (730 uL, 10.0 mmol, 5.0 equiv) in a pressure tube and heated at 85 °C. The mixture was stirred for 24 h then water (20 mL) was added, the phases were separated, and the aqueous phase was extracted with DCM (2 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes:EtOAc = 5:1 → 3:1) to give the desired compound as a yellow solid (795 mg, 80%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 3:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.69 (s, 3H), 6.18 – 5.94 (m, 2H), 5.87 – 5.70 (m, 1H), 4.98 (d, *J* = 7.4 Hz, 1H), 4.12 (td, *J* = 6.6, 2.0 Hz, 2H), 4.05 (s, 2H), 3.78 (d, *J* = 1.4 Hz, 7H), 3.69 – 3.56 (m, 1H), 3.09 (s, 3H), 2.94 (s, 3H), 2.40 (q, *J* = 7.3 Hz, 2H), 1.07 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 153.6, 151.1, 149.2, 144.9, 141.7, 134.6, 131.7, 124.8, 120.1, 119.6, 114.6, 112.7, 108.7, 66.5, 62.1, 55.6, 42.3, 40.2, 37.7, 35.2, 31.6, 27.6, 26.6.



3.32

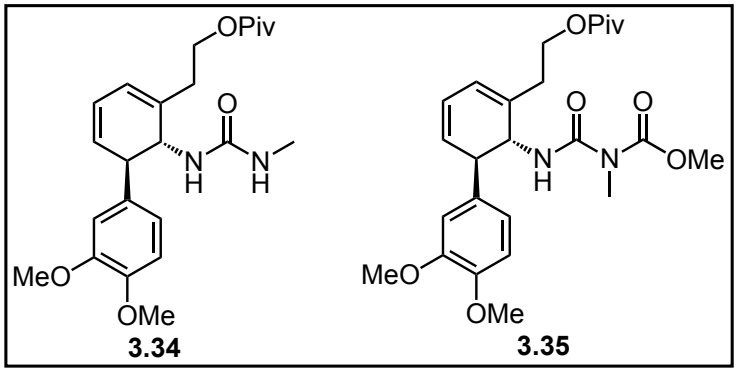
Synthesis of compound 3.32: To a solution of **3.26** (1.0 g, 2.0 mmol, 1.0 equiv.) in DCM (20 mL) was added DMAP (50.0 mg, 0.2 mmol, 0.1 equiv.) and BzCl (470 uL, 4.0 mmol, 2.0 equiv). The mixture was stirred for 12 h then water (20 mL) was added, the phases were separated, and the aqueous phase was extracted with DCM (2 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes:EtOAc = 5:1 → 3:1) to give the desired compound as a colorless solid (920 mg, 80%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 3:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 14.4 Hz, 3H), 7.45 (d, *J* = 7.8 Hz, 2H), 6.87 – 6.69 (m, 3H), 5.96 (dd, *J* = 15.0, 7.1 Hz, 2H), 5.79 (dd, *J* = 9.4, 4.6 Hz, 1H), 5.05 (d, *J* =

7.8 Hz, 1H), 4.39 – 4.16 (m, 2H), 4.07 – 3.92 (m, 1H), 3.89 (t, *J* = 4.6 Hz, 3H), 3.79 (t, *J* = 4.5 Hz, 3H), 3.10 (t, *J* = 4.6 Hz, 3H), 2.66 (d, *J* = 7.3 Hz, 2H), 1.16 (dd, *J* = 7.0, 3.1 Hz, 10H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 172.2, 154.2, 152.1, 149.2, 142.2, 134.6, 134.2, 132.1, 131.7, 128.8, 124.8, 120.1, 119.6, 114.6, 113.2, 109.7, 65.9, 61.9, 55.6, 41.3, 38.7, 34.2, 31.6, 27.6, 26.6.



3.34 **3.35**

Synthesis of compounds 3.34 and 3.35: To a solution of **3.32** (1.0 g, 2.0 mmol, 1.0 equiv.) in dry and degassed MeOH (20 mL) was added a solution of SmI_2 in THF (60 mL, 6.0 mmol, 3.0 equiv) at 0 °C for 15 minutes. The mixture was then heated to 40 °C for 12 h then Rochelle's salt (20 mL) was added, the phases were separated, and the aqueous phase was extracted with DCM (2 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:MeOH = 40:1 → 20:1) to give the desired compounds as a colorless liquid (330 + 189 mg, 40% + 20%).

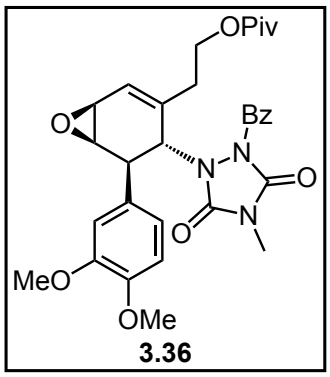
R_f = 0.25, 0.30 (SiO_2, DCM:MeOH = 20:1, UV, $KMnO_4$).

^{1}H NMR 3.34 (500 MHz, $CDCl_3$) δ 6.88 (d, *J* = 2.0 Hz, 1H), 6.84 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.79 – 6.75 (m, 2H), 6.21 (dd, *J* = 9.5, 5.4 Hz, 1H), 5.94 (d, *J* = 5.4 Hz, 1H), 5.85 (dd, *J* = 9.5, 5.4 Hz, 1H), 4.44 (dd, *J* = 8.3, 2.8 Hz, 1H), 4.08 – 3.91 (m, 2H), 3.86 (s, 4H), 3.84 (s, 4H), 3.73 – 3.64 (m, 1H), 3.24 (s, 3H), 3.06 (s, 1H), 2.34 (t, *J* = 6.8 Hz, 2H), 1.13 (s, 8H).

^{13}C NMR 3.34 (126 MHz, $CDCl_3$) 178.99, 178.58, 157.17, 155.74, 154.37, 153.67, 149.24, 149.04, 148.48, 132.47, 131.80, 128.58, 127.49, 126.26, 124.21, 123.56, 122.80, 120.01, 111.43, 62.46, 59.74, 56.04, 54.43, 46.40, 45.12, 38.92, 34.65, 30.49, 29.85, 27.30, 25.43.

^{1}H NMR 3.35 (500 MHz, $CDCl_3$) δ 8.78 (d, *J* = 8.3 Hz, 1H), 6.91 – 6.81 (m, 2H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.24 (dd, *J* = 9.5, 5.4 Hz, 1H), 5.95 (d, *J* = 5.4 Hz, 1H), 5.85 (dd, *J* = 9.5, 5.5 Hz, 1H), 4.44 (dt, *J* = 8.6, 1.8 Hz, 1H), 4.02 – 3.94 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.79 (d, *J* = 1.0 Hz, 3H), 3.71 – 3.66 (m, 1H), 3.24 (d, *J* = 1.0 Hz, 3H), 2.34 (qt, *J* = 14.7, 6.7 Hz, 2H), 1.12 (d, *J* = 1.1 Hz, 9H).

^{13}C NMR 3.35 (126 MHz, $CDCl_3$) δ 178.45, 156.86, 154.32, 149.00, 148.07, 132.78, 131.69, 127.00, 124.35, 123.07, 120.01, 111.43, 111.26, 62.20, 56.00, 54.11, 53.71, 46.26, 38.77, 34.42, 30.91, 29.84, 27.24.



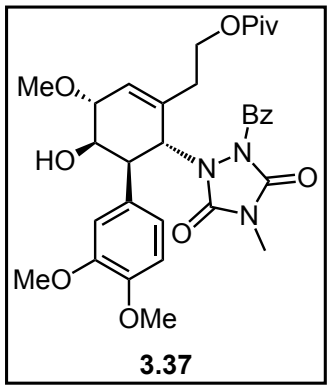
3.36

Synthesis of compound 3.36: To a stirred solution of diene **3.32** (1.0 g, 1.8 mmol, 1.0 equiv.) and EDTA (11.2 mg, 18.0 μmol, 1.0 mol%) in a mixture of acetone, DCM, and sat. aq. $NaHCO_3$ (20 mL 1:10:20) was dropwise added Oxone® (1.8 g, 3.6 mmol. 2.0 equiv.) in water (8 mL) at 0 °C. The reaction was stirred at 0 °C for 30 minutes then was allowed to warm to 25 °C and stir for 8 hours. Then another aliquot of Oxone® 1.8 g, 3.6 mmol. 2.0 equiv.) in water (8 mL) at 0 °C and the reaction was stirred at 0 °C for 30 minutes then was allowed to warm to 25 °C and stir for 8 hours. the phases were separated, and the aqueous phase was extracted with DCM (2 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes:EtOAc = 4:1 → 2:1) to give the desired compound as a colorless solid (920 mg, 80%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 2:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (t, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 7.7 Hz, 2H), 6.81 – 6.66 (m, 2H), 5.89 (t, *J* = 3.6 Hz, 1H), 4.50 (d, *J* = 10.9 Hz, 1H), 4.34 (t, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 3.55 (s, 3H), 3.44 (d, *J* = 4.2 Hz, 1H), 3.38 (d, *J* = 4.3 Hz, 1H), 3.00 (s, 3H), 2.97 – 2.89 (m, 1H), 2.69 (dt, *J* = 24.0, 8.7 Hz, 1H), 1.17 (s, 10H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.53, 170.14, 163.87, 151.75, 149.21, 148.04, 140.90, 133.36, 131.94, 130.36, 129.52, 127.24, 126.76, 119.60, 118.31, 110.43, 109.29, 61.25, 60.84, 59.38, 56.47, 55.03, 54.89, 52.41, 49.41, 46.81, 40.29, 37.76, 30.11, 28.68, 26.25, 24.47, 20.04, 13.18.



3.37

Synthesis of compound 3.37: To a stirred solution of epoxide **3.36** (1.0 g, 1.64 mmol, 1.0 equiv.) in MeOH/$CHCl_3$ 1:1 (7 + 7 mL) was added CSA (76 mg, 0.33 mmol, 0.2 equiv) and stirred at 25 °C for 5 h. Sat. aq. $NaHCO_3$ was added, the phases were separated, and the aqueous phase was extracted with DCM (2 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes:EtOAc = 3:1 → 2:1) to give the desired compound as a colorless liquid (709 mg, 71%).

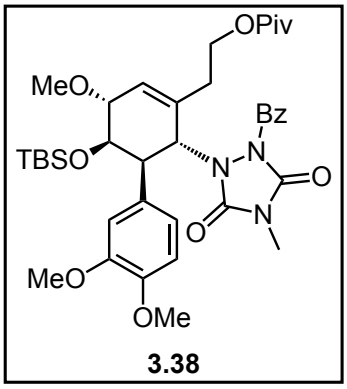
R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 1:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, DMSO-*d*$_6$, **20 °C**) δ 7.41 (t, *J* = 7.6 Hz, 1.25H), 7.29 (t, *J* = 7.6 Hz, 2.5H), 7.12 (d, *J* = 7.7 Hz, 1.75H), 6.81 – 6.66 (m, 2.5H), 5.58 – 5.48 (m, 0.5H), 4.45 – 4.38 (m, 0.75H), 4.30 – 4.19 (m, 2.5H), 3.78 (s, 3H), 3.52 (s, 3H), 3.41 – 3.33 (m, 1.25H), 3.23 – 3.13 (m, 1H), 3.00 (s, 3H), 2.97 – 2.89 (m, 0.75H), 2.69 (dt, *J* = 24.0, 8.7 Hz, 1H), 1.17 (s, 10H).

^{13}C NMR (126 MHz, DMSO-*d*$_6$, **20 °C**) δ 177.23, 170.02, 163.66, 150.68, 149.12, 147.04, 139.88, 132.33, 131.77, 130.32, 128.72, 127.19, 125.91, 119.58, 118.21, 111.24, 109.19, 84.72, 67.35, 60.64, 58.92, 57.07, 55.23, 53.41, 49.31, 47.21, 40.39, 37.66, 30.21, 27.88, 26.45, 24.37, 21.02.

^{1}H NMR (500 MHz, DMSO-*d*$_6$, **100 °C**) δ 7.27 (s, 1H), 7.12 (s, 2H), 6.93 (s, 2H), 6.56 (s, 2H), 5.55 (s, 1H), 4.40 (s, 1H), 4.12 (s, 2H), 3.68 (s, 3H), 3.55 (s, 3H), 3.24 (s, 1H), 3.19 (s, 1H), 3.00 (s, 3H), 2.90 (s, 1H), 2.69 (s, 1H), 1.17 (s, 10H).

^{13}C NMR (126 MHz, DMSO-*d*$_6$, **100 °C**) δ 178.53, 162.14, 159.27, 151.75, 147.04, 140.90, 132.84, 130.66, 128.92, 127.24, 119.20, 117.31, 110.21, 108.59, 61.75, 60.24, 56.97, 54.03, 53.89, 52.14, 48.49, 46.21, 41.29, 37.66, 30.51, 27.68, 26.25, 24.47, 20.04.



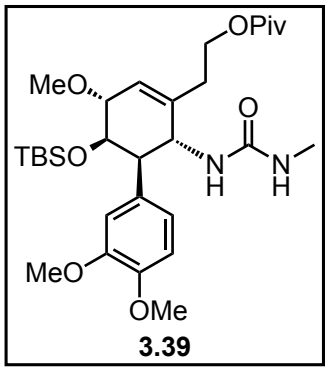
3.38

Synthesis of compound 3.38: To a stirred solution of epoxide **3.37** (500.0 mg, 0.82 mmol, 1.0 equiv.) in $CHCl_3$ (8 mL) were added imidazole (225.0 mg, 3.3 mmol, 4 equiv.) TBSOTf (300 uL, 1.64 mmol, 2.0 equiv) and stirred at 50 °C for 5 h. Sat. aq. $NaHCO_3$ was added, the phases were separated, and the aqueous phase was extracted with DCM (2 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes:EtOAc = 5:1 → 4:1) to give the desired compound as a colorless liquid (415 mg, 70%).

R_f = 0.25 (SiO_2, hexanes:ethyl acetate = 4:1, UV, $KMnO_4$).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.43 (t, J = 7.4 Hz, 1.25H), 7.33 (t, J = 7.5 Hz, 2H), 7.11 (d, J = 7.7 Hz, 1.5H), 6.80 – 6.71 (m, 2.5H), 5.58 – 5.49 (m, 1H), 4.57 – 4.42 (m, 0.75H), 4.28 – 4.18 (m, 2.5H), 3.75 (s, 3H), 3.57 (s, 3H), 3.45 – 3.32 (m, 1.25H), 3.28 – 3.15 (m, 1H), 2.98 (s, 3H), 2.91 – 2.79 (m, 1H), 2.59 (dt, J = 24.0, 8.7 Hz, 1H), 1.12 (s, 10H), 1.01 (s, 10H), 0.20 (s, 7H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 177.43, 169.12, 164.66, 150.48, 149.62, 146.04, 138.68, 133.43, 132.17, 130.18, 128.43, 126.63, 124.61, 119.85, 118.12, 111.74, 108.19, 84.72, 67.35, 60.64, 58.92, 57.07, 55.23, 53.41, 49.31, 47.21, 40.39, 37.66, 30.21, 27.88, 25.95, 24.37, 21.02, 0.02.



3.39

Synthesis of compounds 3.39: To a solution of **3.38** (100.0 mg, 0.4 mmol, 1.0 equiv.) in dry and degassed MeOH (4 mL) was added a solution of SmI_2 in THF (12 mL, 1.2 mmol, 3.0 equiv) at 0 °C for 15 minutes. The mixture was then heated to 40 °C for 12 h then Rochelle's salt (5 mL) was added, the phases were separated, and the aqueous phase was extracted with DCM (2 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:MeOH = 40:1 → 20:1) to give the desired compounds as a colorless liquid (65 mg, 35%).

R_f = 0.25 (SiO_2, DCM:MeOH = 20:1, UV, $KMnO_4$).

^{1}H NMR 3.34 (500 MHz, $CDCl_3$) δ 6.98 (d, *J* = 2.0 Hz, 1H), 6.83 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.79 – 6.72 (m, 2H), 6.18 (dd, *J* = 9.5, 5.4 Hz, 1H), 5.94 (d, *J* = 5.4 Hz, 1H), 4.58 (dd, *J* = 9.5, 5.4 Hz, 1H), 4.44 (dd, *J* = 8.3, 2.8 Hz, 1H), 4.08 – 3.91 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.73 – 3.64 (m, 1H), 3.14 (s, 3H), 3.06 (s, 1H), 2.34 (t, *J* = 6.8 Hz, 2H), 1.13 (s, 8H), 1.01 (s, 10H), 0.20 (s, 7H).

^{13}C NMR 3.34 (126 MHz, $CDCl_3$) 179.11, 178.46, 157.49, 155.46, 154.29, 152.57, 149.15, 148.82, 132.27, 131.69, 128.45, 127.84, 126.69, 124.12, 123.66, 122.07, 121.10, 111.34, 63.64, 60.51, 56.24, 54.73, 47.33, 45.02, 39.92, 36.63, 30.69, 29.75, 27.30, 25.93, 0.02.