ENANTIOSELECTIVE SYNTHESIS OF BIS-HETEROARYL MOLECULES

AND

STUDIES OF CASCADE C-H BOND INSERTION REACTIONS

A Dissertation Presented to

the Faculty of the Department of Chemistry

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree

Doctor of Philosophy

By

Jiun-Le Shih

May 2016

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ABSTRACT

This dissertation presents two major projects. The first is the BINOL-catalyzed 1,4-addition of heteroaryl trifluoroborate salts and its application to the synthesis of the natural product, discoipyrrole D. The second is cascade reactions and their use in the synthesis of azasilacyclopentenes and the natural product, brazilide A.

The synthesis of bis-heteroaryl stereocenters with high enantioselectivities via a BINOL-catalyzed conjugate addition of trifluoroborates to heteroaryl-appended enones and enals will be discussed herein. A proposed mechanism of how trifluoroborate salts interacting with the BINOL catalyst was based on control experiments. Importantly, bench, air, and moisture stable trifluoroborate salts are not only very easy to handle, but also completely shut down an unproductive protodeboronation side reaction. The power of the mild organocatalytic reaction was demonstrated in the synthesis of the bioactive natural product, discoipyrrole D.

The second half describes use of carbene cascade reactions to construct complex molecules like bridged polycycles, propellanes, and heteropolycycles. The propellane core of brazilide A was synthesized by a Rh(II)-catalyzed carbene/alkyne cascade reaction followed by a rearrangement. The final stage of the synthesis still requires installation of a benzopyran motif and oxidation. Moreover, a transition metal-free nitrene initiated cascade reaction was discovered to obtain azasilacyclopentenes. The mechanism of the reaction was informed by detailed control experiments and the characterization of reaction intermediates. The nitrene initiated cascade reaction has opened several valuable directions for future exploration.

TABLE OF CONTENTS

ABBREVIATIONS AND ACRONYMS

Ac	acetyl, acetate
aq	aqueous
BINOL	1,1′-Bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	*n*-butyl
BHT	Butylated hydroxytoluene
Bs	benzenesulfonyl
°C	Degree Celsius
Cap	caprolactamate
Cod	cyclooctadiene
CI	chemical ionization
Cp*	pentamethylcyclopentadienyl
d	doublet
DCE	1,2-dichloroethane
DCM	dichloromethane
DMSO	dimethyl sulfoxide
DMAP	4-dimethylaminopyridine
DBU	1,8-Diazabicycloundec-7-ene
DMP	Dess–Martin periodinane
DIBAL	Diisobutylaluminium hydride

DMDO	Dimethyldioxirane
DMA	dimethylaniline
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
ee	Enantiomeric excess
Et	ethyl
esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid
ESI	electrospray ionization
equiv	equivalent
er	enantiomeric ratio
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron withdrawing group
h	hour
H_2O	water
HRMS	high resolution mass spectroscopy
HPLC	high performance liquid chromatography
Hz	hertz
IC_{50}	50% inhibitory concentration
i-Bu	isobutyl

i-Pr	isopropyl
IR	infrared (spectroscopy)
J	coupling constant
m	multiplet or mili
m/z	mass to charge ratio
Me	methyl
MeCN	acetonitrile
MeOH	methanol
min	minute
mol	mole(s)
MS	molecular sieves
*m*CPBA	*meta*-chloroperoxybenzoic acid
Ms	methanesulfonyl (mesyl)
MOM	methoxymethyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
nOe	Nuclear Overhauser Effect
NCS	*N*-chlorosuccinimide
o	ortho
Pr	propyl
Py	pyridine
Ph	phenyl

PhMe	toluene
ppm	parts per million
q	quartet
R_F	retention factor
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TBDPS	*tert*-butyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	transition metal
TMS	trimethylsilyl
TPA	triphenylacetate
Ts	*p*-toluenesulfonyl
UV	ultraviolet

1. ORGANOCATALYZED ASYMMETRIC CONJUGATE ADDITION OF HETEROARYL TRIFLUOROBORATES

1.1 Background

1.1.1 The Importance of Bis-heteroaryl/aryl Compounds

Bis-heteroaryl and heteroaryl/aryl stereocenters are prevalent motif in a number of bioactive compounds, including natural products and pharmaceutical agents as shown in Figure 1-1.[1] Synthetic strategies using transition metal catalyzed stereospecific, enantioselective, and diastereoselective C-C bond forming reactions have been reported for installing these stereocenters, as well as asymmetric hydrogenation of 1,1–diarylolefins. However, since most of the described methods rely heavily on transition metal catalysis, limited functional group tolerance is observed, especially for nitrogen-containing and electron-rich heteroarenes. Importantly, these problematic structural motifs are highly desirable building blocks from the perspective of medicinal chemistry. On the other hand, many Lewis acid-catalyzed enantioselective approaches are limited by Friedel-Crafts type reactions, which dictate the overall reaction scope with respect to the available starting materials and overall regiochemistry of the product leading to substitution at the most electron-rich position of the substrate. The following chapter describes the successes of widely applicable BINOL catalyzed enantioselecive conjugate addition of heteroaryl trifluoroborates to hetereoaryl appended enones and enals providing a variety of bis-heteroaryl stereocenters.

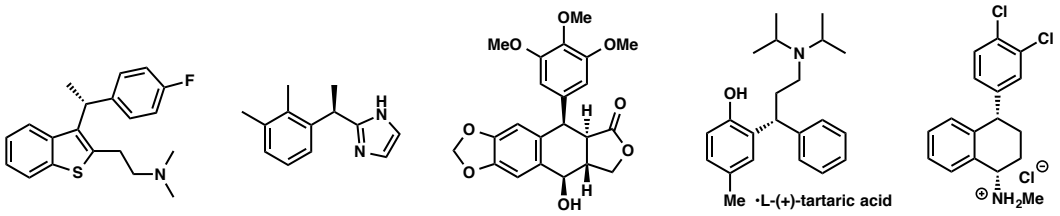


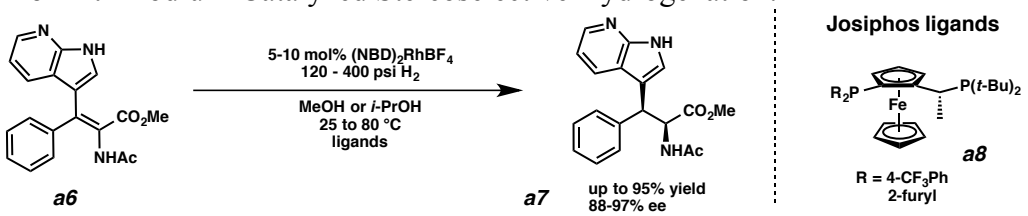
Figure 1-1. Biologically Active Compounds with Bis-heteroaryl and Heteroaryl/Aryl Stereocenters.

1.1.2 Synthetic Methods Leading to Bis-heteroaryl/Aryl Compounds

This section highlights modern approaches in transition metal-catalyzed hydrogenation, cross-coupling, and conjugate addition reactions in order to synthesize bis-heteroaryl/aryl compounds.

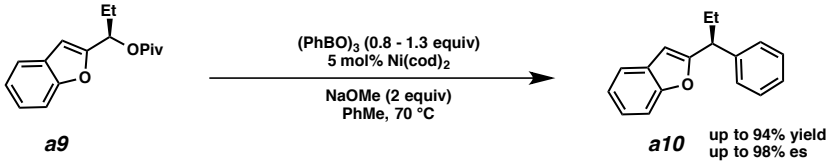
One of the biggest challenges that the asymmetric hydrogenation reactions face is the ability to discriminate between sterically similar aryl groups. Several methodologies that are able to address this issue heavily rely on one of two common approaches, either directing group participation[2a] or a careful ligand control.[2b-d] The department of process chemistry in Merck & Co. reported a rhodium catalyzed diastereo- and enantioselective hydrogenation on the β,β-diaryl amino acid **a6**, which provides a wide scope of β,β-diaryl alanine **a7**.[2e] Over 150 chiral ligands were screened for the reaction and two of the Josiphos family ligands were found to provide the best stereoselectivity and good reaction yield. Furthermore, all four isomers of the *β,β*-diaryl amino acid are easily accessible by hydrogenation of either *E* or *Z* olefin isomers and a combination of the enantiopure ligand, thus demonstrating the robustness of this methodology.

Scheme 1-1. Rhodium-Catalyzed Stereoselective Hydrogenation.



Stereospecific transition metal-catalyzed cross-coupling reactions were developed a targeting new approach towards chiral bis-hetereoaryl/aryl molecules.[3] Starting from the readily available enantioenriched aryl alcohol derivatives **a9**, Watson and coworkers successfully developed a stereospecific nickel-catalyzed coupling reaction with arylboroxines providing a number of chiral bis-aryl compounds **a10** in excellent yield.[4] However, under optimized reaction conditions heteroarene-containing substrates, which are generally considered more challenging substrates, provided only moderate selectivity.

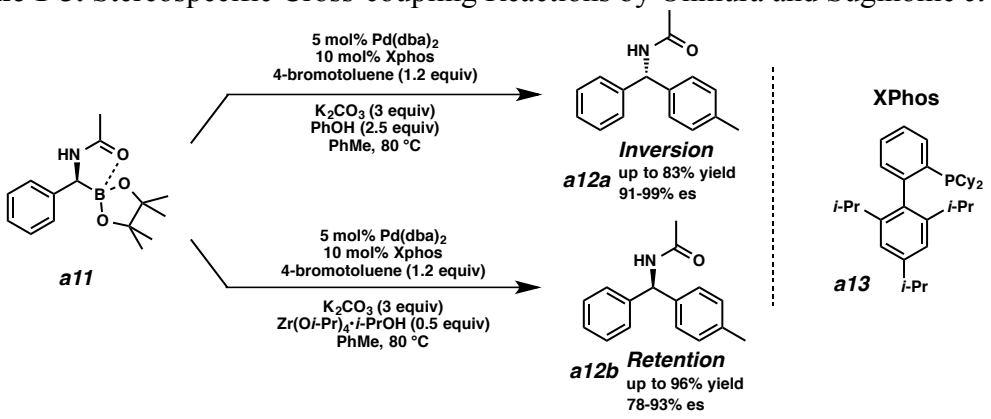
Scheme 1-2. Stereospecific Cross-coupling Reaction Developed by Watson *et al.*



Ohmura, Suginome and coworkers were investigating the chemical reactivity of α-(acetylamino)benzylboronic esters **a11** in Suzuki-Miyaura coupling reactions.[5] In 2011, they reported improved conditions for the overall stereo inversion of the chiral center of substrate **a11**. Remarkably, they were able to develop reaction conditions that allowed for almost complete retention of the stereochemical information of the substrate as well by simply introducing Lewis acidic additives to the reaction mixture. Although a diverse

range of α-(acetylamino)benzylboronic ester compounds **a11** can be readily obtained via the established synthetic methods, the scope of the cross-coupling reaction is fairly small with respect to the aryl substituent of the boronic esters, and no examples of heteroaryl substituted boronates were reported.

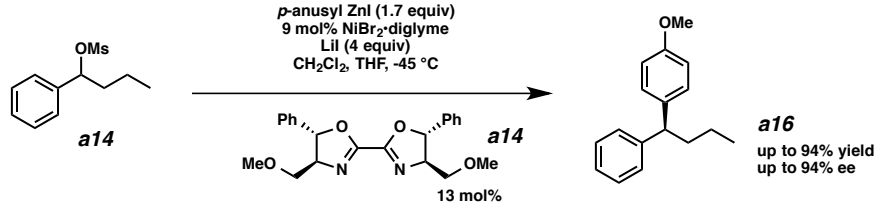
Scheme 1-3. Stereospecific Cross-coupling Reactions by Ohmura and Suginome *et al.*



In 2013, Fu and coworkers described a nickel-catalyzed enantioselective Negishi cross-coupling reaction between benzylic mesylates **a14** and (hetero)aryl zinc reagents affording chiral 1,1-diarylalkanes **a16**.[6] During the mechanistic studies the authors were able to conclude that an iodide ion from the lithium iodide additive replaced the mesylate group, thus forming a benzylic iodide *in situ*. The subsequent oxidative addition of the benzylic electrophile to a low oxidation state nickel species afforded a benzyl-nickel intermediate. Chiral bisoxazoline ligand **a15** was found to be a very effective chiral ligand for this transformation and allowed the Fu group to obtain the desired bisaryl products in both good yield and high enantioselectivity. Remarkably, several substrates

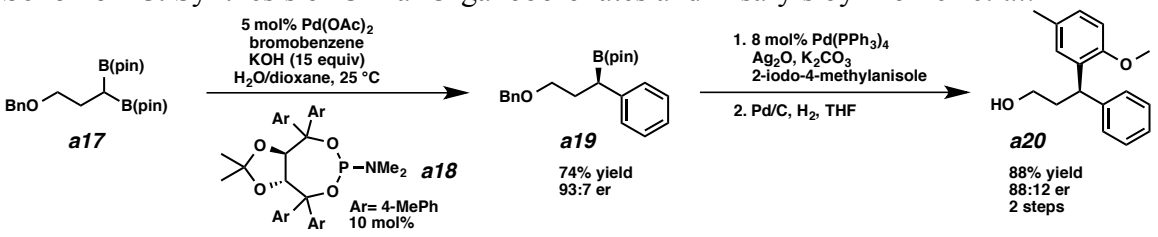
containing heteroarenes, such as furan, thiophene, and a protected indole, were shown to be competent coupling partners.

Scheme 1-4. Fu's Enantioselective Negishi Cross-coupling Reaction.



In 2014 Morken and coworkers reported an efficient Suzuki cross-coupling reaction that affords chiral organoboronates from achiral geminal bis(pinacolboronates) **a17**.[7] The resulting chiral organoboronates can be further cross-coupled with a number of aryl iodides, with only minor racemization taking place, affording enantioenriched bisaryl compounds **a20** in excellent yield.

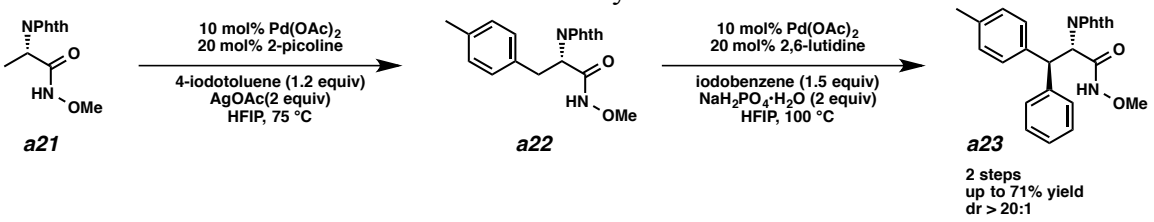
Scheme 1-5. Synthesis of Chiral Organoboronates and Bisaryls by Morken *et al.*



Functionalization of unactivated C-H bonds has received a lot of attention due to its potential to decrease the number of synthetic transformations required in order to obtain a target compound, therefore substantially reducing the amount of chemical waste generated along the way, and ultimately having an overall net-positive environmental and

economic impact on the art of synthesis.[8] Yu and coworkers reported a diastereoselective β-C-H bond arylation of alanine derivatives.[9] The authors identified the *N*-methoxyamide as a suitable substrate that allowed for sequential arylation at the β position of the modified alanine **a21**. By performing the arylation reaction sequentially with two different aryl iodides they were able to install the second stereogenic center in the alanine derivative affording a variety of the β,β-diaryl alanine analogues **a23**.

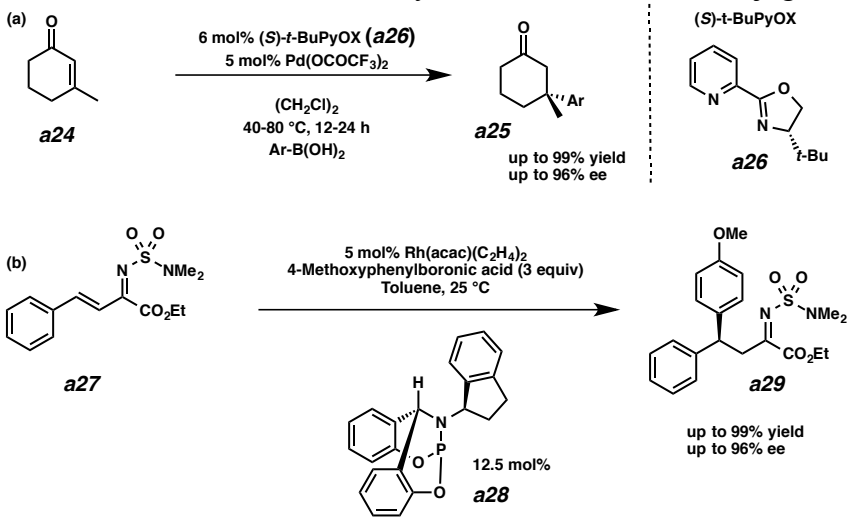
Scheme 1-6. C-H Activations on Alanine **a22** by Yu *et al.*



Over the past decade, the development of novel transition metal-catalyzed asymmetric conjugate addition reactions has received a lot of attention from the synthetic community. Transition metal catalysts such as palladium,[10] rhodium,[11] nickel,[12] and copper[13] have all been successfully applied to creating β-chiral centers starting from α,β-unsaturated carbonyl compounds. For example, Stoltz *et al.* were able to selectively install a tertiary stereocenter in cyclic ketones (Scheme 1-7a).[10a,b] In 2015, Kim and coworkers presented a rhodium-catalyzed enantioselective conjugate addition reaction of arylboronic acids to α,β-unsaturated imino esters **a27** (Scheme 1-7b).[11b] The unique chiral bicyclic bridgehead phosphoramidite ligand **a28** was reported to help successfully control the stereochemical environment in the transition state. A series of chiral

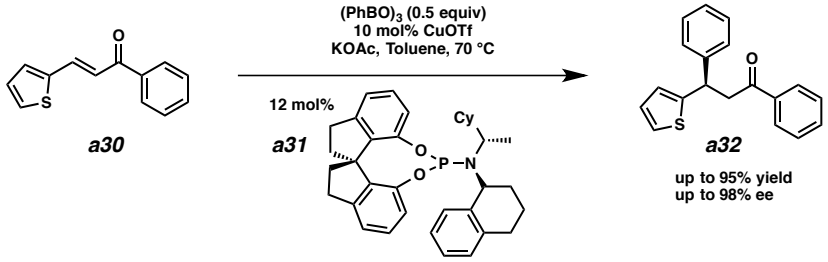
diarylimino esters **a29** have been obtained; however, thiophene was the only heterocycle that has been shown to participate in the reaction.

Scheme 1-7. Palladium- and Rhodium-catalyzed Enantioselective Conjugate Additions.



Although stoichiometric organocuprates were utilized in 1,4-addition reactions for several decades, introduction of catalytic amounts of copper to the nucleophile addition reactions is still relatively rare. In 2016, Hirao, Zhou, and coworkers reported a copper-catalyzed asymmetric 1,4-addition of organoboroxines to enones.[13e] Unfortunately, the electrophile scope is limited to only chalcones, and more importantly heteroaryl boroxines do not perform well in this catalytic reaction.

Scheme 1-8. Copper-catalyzed Asymmetric Chalcone 1,4-Addition by Hirao and Zhou *et al.*



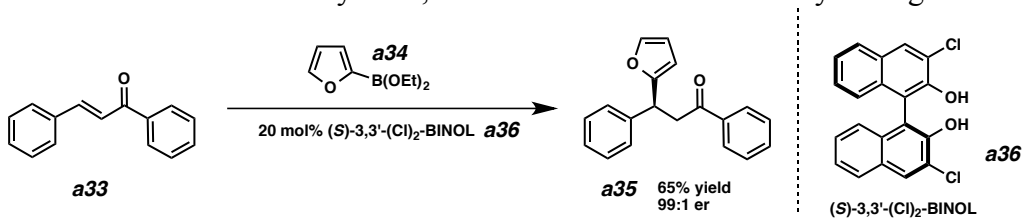
1.1.3 Organocatalyzed Asymmetric Conjugate Addition

Friedel-Crafts type reactions are the most commonly utilized approaches to introduce heteroaryl groups towards the C-C bond construction.[14-18] Importantly, the regiochemical outcome of the Friedel-Crafts reactions for heteroarenes (and broadly in electron-rich aromatic compounds) can be rationalized and predicted based on the electron density distribution in the molecule or appropriate coefficient corresponding to the HOMO of the substrate. However, heteroarene functionalization in the positions that are electronically deactivated is very difficult to achieve using existing electrophilic approaches. Combinations of different Lewis acids and chiral ligands,[15] thioureas,[16] phase transfer catalysts,[17] or iminium catalysis[18] are widely used to promote asymmetric conjugate addition reactions.

Versatile boron-based reagents have been used in reductions,[19] aldol reactions,[20] conjugations,[21] and many other transformations.[22] A variety of heteroaryl/aryl boron-based-reagents are commercially available. A pioneering report by Schaus, Chong, and coworkers using BINOL-based organocatalysts with boronic esters successfully accomplished asymmetric 1,2-addition,[23] and conjugate additions.[24] However, a very

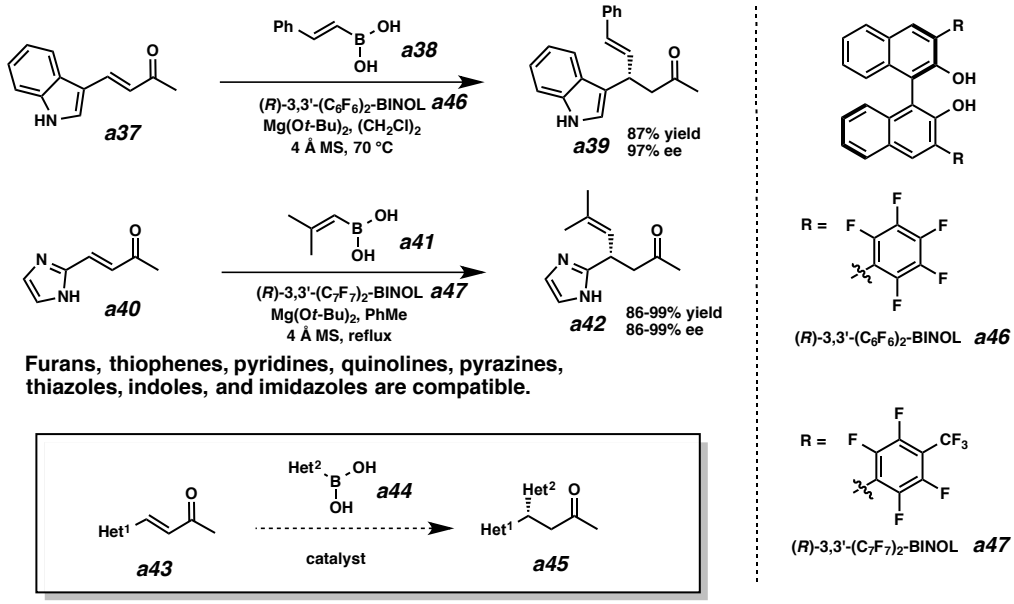
important substrate class, namely heteroaryl-containing compounds, was markedly underrepresented among the scope of nucleophiles employed in their reactions. In 2011, Chong and coworkers reported enantioselective BINOL-catalyzed 1,4-addition of arylboronic esters to chalcones (**a33**).[25] The substrate scope was somewhat limited to arylboronates with only a single example of a heterocycle-derived boron reagent, namely 2-furan boronic ester **a34**. It is well-known that some heteroaryl boronic acids and boronates are very prone to decomposition, therefore it is not unlikely that the forcing reaction conditions resulted in a narrow substrate scope.

Scheme 1-9. The BINOL-catalyzed 1,4-Addition to the Chalcones by Chong *et al.*



We became interested in this organocatalytic transformation and sought to expand the reaction scope and applicability. As a starting point, we modified the 3,3'-positions of the BINOL catalyst with pentafluorophenyl groups and 4-heptafluorotollyl substituents. Our new and improved ligands were found to successfully catalyze conjugate addition of vinyl boronic acids to heteroaryl-appended enones and afford the product with excellent enantioselectivity.[26] We next turned our attention towards the development of the synthetic methodology that allows construction of a bis-heteroaryl chiral center at the β-position of carbonyl-containing substrates through the 1,4-addition of a heteroaryl boron reagent to heteroaryl-appended enones.[27]

Scheme 1-10. BINOL Catalyzed 1,4-Addition to Heteroaryl-appended Enones by May *et al.*



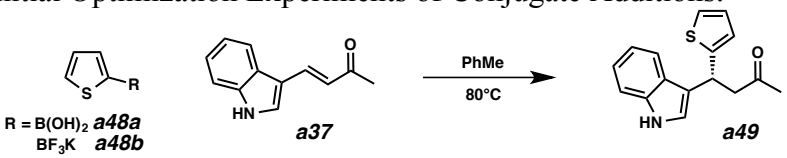
1.2 Reaction Optimization

1.2.1 Reactions Using Boronic Acids and Trifluoroborate Salts

Based on the outstanding reactivity exhibited by our modified BINOL ligands, and 3,3'-$(C_7F_7)_2$-BINOL (**a47**) in particular, we began preliminary screening of the reaction conditions. In the early stages of the optimization we observed a profound influence of the reaction temperature on both reaction yield and enantiopurity of the reaction product. As expected, within a reasonable temperature range the reaction yield is improved at elevated temperature; however, higher reaction temperatures led to a lower enantiomeric excess of the reaction product. We had to compromise on the temperature since the yield of the reaction product and its enantiopurity had an opposite dependence on temperature. Thus, additional experiments allowed us to conclude that reaction

temperatures at or below 80 °C can provide the best enantioselectivity values for the most of substrates and afford satisfactory yields of the reaction product. In addition, we observed that the reactivity trend of heteroaryl boronic acids closely follows that of the Friedel-Crafts reactivity profile of the corresponding parent heterocycles, namely, the more electron rich the position of the heterocycle substituted with the boron is the faster the rate of overall transformation. We discovered that 2-thiophene boronic acid (**a48a**) is the most reactive substrate in our transformation. However the yield of reaction product **a49** varied greatly (from 37% to 86%), presumably due to different levels of an impurity in the commercial starting material.

Table 1-1. Initial Optimization Experiments of Conjugate Additions.



entry	R	Catalyst	Desiccant	Additive	time(h)	Yield	er
1.	$B(OH)_2$	(*R*)-3,3'-$(C_7F_7)_2$-BINOL	4Å MS	Mg(O*t*-Bu)$_2$	12	37-86%	99:1
2.	BF_3K	(*R*)-3,3'-$(C_7F_7)_2$-BINOL	4Å MS	Mg(O*t*-Bu)$_2$	6	99%	99.6:0.4
3.	BF_3K	NA	4Å MS	Mg(O*t*-Bu)$_2$	48	22%	NA
4.	BF_3K	(*R*)-BINOL	4Å MS	Mg(O*t*-Bu)$_2$	48	18%	53.8:46.2
5.	BF_3K	(*R*)-3,3'-$(C_7F_7)_2$-BINOL	4Å MS	NA	6	99%	99.7:0.3
6.	BF_3K	(*R*)-3,3'-$(C_7F_7)_2$-BINOL	NA	NA	12	30%	NA

In addition, careful monitoring of the reaction progress revealed the presence of significant amounts of the protodeboronation product – thiophene. This result implied that most of the boronic acid starting material had decomposed by this side reaction, and

that we needed to either suppress this unproductive pathway or find a starting material that would be stable under the reaction conditions. We turned our attention towards trifluoroborate salts as a suitable alternative, especially since these substrates are already widely used in Suzuki-Miyaura cross-coupling reactions as a more stable reagent alternative to boronic acids and boronates.[28] Gratifyingly, repeating the reaction using potassium 2-thiophene trifluoroborate salt (**a48b**) and butanone **a37** as starting materials quickly generated the corresponding conjugate addition product in quantitative yield and excellent enantioselectivity (entry 2, Table 1-1). Furthermore, additional optimization studies revealed that: 3,3'-$(C_7F_7)_2$-BINOL (**a47**) is indeed the most effective catalyst for this reaction. We can completely eliminate the usage of magnesium di-*tert*-butoxide, and 4 Å MS are essential for the reaction to proceed to completion.

1.2.2 Control Experiment Studies

Although we discovered that using the trifluoroborate salt improved the reaction greatly, the mechanism of its interaction with the BINOL catalyst was not particularly clear. There were several concerns that had to be addressed. First, the boron atom in a boronic acid is sp^2 hybridized and coordinatively unsaturated. Therefore, the empty p orbital of the boron atom is available for bond formation with a BINOL oxygen atom. However, the boron atom in the trifluoroborate salt is coordinatively saturated and sp^3 hybridized, thus lacking the empty coordination site necessary for the coordination with a BINOL oxygen atom. Second, it is well known that when used for the Suzuki reaction the trifluoroborate is slowly hydrolyzed in the presence of base and/or water to generate the

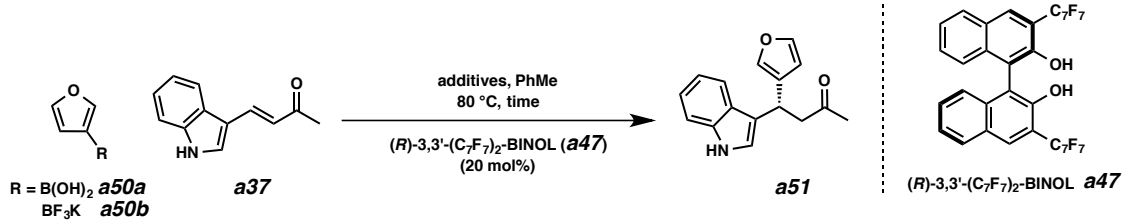
corresponding boronic acid *in situ*, and thus the trifluoroborate serves as a reservoir of the reactive boronic acid that is steadily supplied during the cross-coupling reaction.[29] Since we applied extreme care to ensure anhydrous reaction conditions, the aforementioned hydrolysis reaction is highly improbable. MacMillan and coworkers reported the use of heteroaryl trifluoroborates as nucleophiles without hydrolysis; however, these reactions work well only with highly reactive electrophiles.[30] Third, trifluoroborate salts are poorly soluble in nonpolar solvents such as toluene, so the question arises: Why does the reaction take place in toluene in the first place? Fourth, if the reaction mechanism involves fluoride dissociation from the trifluoroborate salt, then the resulting difluoroborane is likely Lewis acidic enough to cause a racemic background reaction.

Initial attempts to study the model reaction with a thiophene derivative employing NMR spectroscopy failed to provide any insight into the reaction mechanism. Simply mixing and heating stoichiometric amounts of the trifluoroborate and BINOL in deuterated toluene did not result in the formation of any observable signal due to a poor solubility of the starting materials and possibly products In order to investigate the mechanism, we turned our attention to control experiments using the less reactive 3-furanyl trifluoroborate salts **a50b** with a variety of additives.

The trifluoroborate **a50b** performed well in the reaction and consistently provided a good yield of the product (Table 1-2, entry 2). As mentioned previously, no product was formed under in the absence of molecular sieves (entry 3). Silyl chlorides are known to abstract the fluoride from a trifluoroborate,[31] and addition of 1 equivalent of TBSCl to the reaction mixture as an additive promoted the reaction and provided reasonable stereoselectivity (entry 4). In the absence of the BINOL catalyst almost no reaction

product was formed (entry 5). From these experiments, we concluded that the initial step in the overall reaction is dissociation of one of the fluorides from the trifluoroborate, forming difluoroborane. The resulting neutral borane has an empty coordination site on the boron atom, which in turn allows for a strong interaction with the BINOL catalyst to take place and promote the reaction. However, introduction of excess TBSCl provides a moderate yield of product, albeit in completely racemic form (entry 6). The same outcome was observed in the absence of the catalyst (**a47**), therefore supporting the notion that the Lewis acidic nature of the difluoroborane plays an important role in the "uncatalyzed" racemic background reaction (entry 7). Moreover, addition of LiBr (1 equivalent) to the reaction was found to provide similar results as in the case of addition of 1 equivalent of TBSCl (entry 8). We hypothesized that salt metathesis between LiBr and potassium trifluoroborate takes place generating KBr and lithium trifluoroborate salts *in situ*. This newly-formed lithium trifluoroborate is not stable and further decomposes to LiF and difluoroborane, which can undergo a reaction with the BINOL catalyst and promote the asymmetric reaction. KHF_2 provides extra fluoride in the reaction mixture, thus effectively preventing fluoride dissociation from the trifluoroboronate, ultimately resulting in complete loss of reactivity (entry 9). A negative control experiment performed in the presence of 18-crown-6 to completely prevent fluoride dissociation from trifluoroborate predictably shut down the reaction (entry 10).

Table 1-2. Control Experiments for Mechanistic Studies.



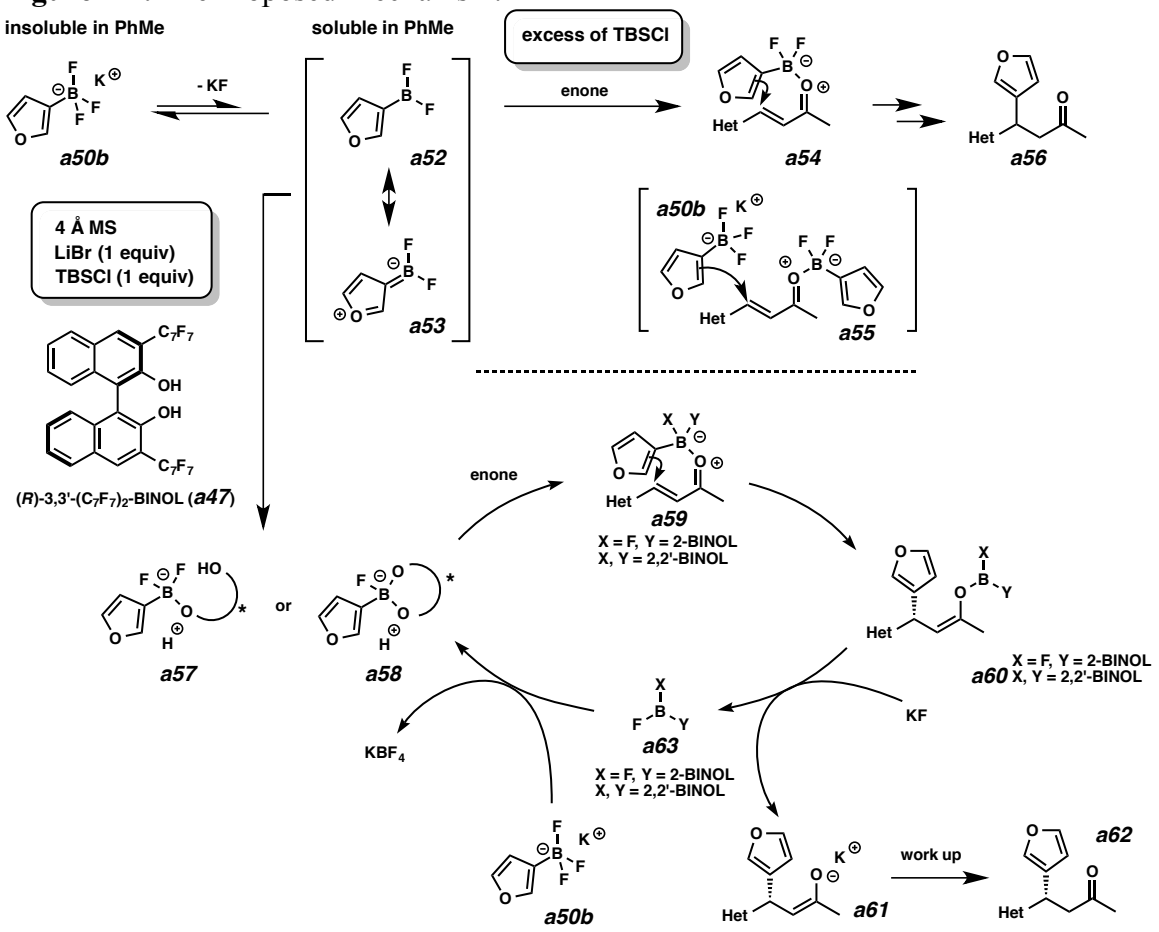
entry	R	additives	time (h)	yield	er
1.	$B(OH)_2$	4 Å MS, $Mg(Ot\text{-}Bu)_2$ (0.1 equiv)	52	50%	98:2
2.	BF_3K	4 Å MS	50	80%	98:2
3.	BF_3K	none	48	0%	ND
4.	BF_3K	TBSCl (1 equiv)	9	53%	91:9
5.	BF_3K	TBSCl (1 equiv), w/o Cat.	48	<5%	ND
6.	BF_3K	TBSCl (9 equiv), 25 °C	23	48%	46:54
7.	BF_3K	TBSCl (9 equiv), w/o Cat., 25 °C	20	48%	46:54
8.	BF_3K	LiBr (1 equiv)	26	55%	90:10
9.	BF_3K	4 Å MS, KHF_2 (9 equiv)	40	<5%	ND
10.	BF_3K	4 Å MS, 18-C-6 (6 equiv)	49	0%	ND

1.2.3 Proposed Mechanism

Based on the control experiments, the following mechanistic picture was proposed for the BINOL-catalyzed conjugate addition of trifluoroborate salts to α,β-unsaturated carbonyl compounds (see Figure 1-2). First of all, in the case of the electron-rich heteroaryl trifluoroborate salts, although a neutral difluoroboron intermediate can conceivably be formed by fluoride ion dissociation from the trifluoroborate through the participation of resonance stabilization, such dissociation does not have a major impact on the overall reaction. Most trifluoroborate salts are not particularly soluble in nonpolar solvents like toluene. Importantly, the addition of a fluoride accepter promotes the formation of a difluoroboron intermediate from the trifluoroborate to a much greater

degree. When the active difluoroborane (**a52**) is generated, it dissolves in the reaction solvent and only then the catalysis starts. However, if an excess of fluoride accepter (excess of TBSCl) is used, a large amount of Lewis acidic diflurororoborane would be present that causes racemic background reactions to take place via either intra- (**a54**) or intermolecular (**a50b** to **55**) mechanisms. Gratifyingly, using mild but very effective reaction conditions (4 Å MS, 1 equiv of TBSCl, or 1 equiv of LiBr) modifies the rate of formation of trifluoroboron intermediate and allows for better control of the reaction. Next, the BINOL catalyst binds to difluoroborane **a52** resulting in either a monodentate (**a57**) or a bidentate (**a58**) complex. Subsequently, the BINOL-boronates have to produce an open coordination site via either dissociation of one fluoride or one hydroxyl group from the boron ate complex in order accommodate the oxygen atom of the enone carbonyl group. Ultimately, after the formation of the coordination complex between the boron reagent and carbonyl compound, it adopts a chair-like transition state during which conjugate addition of the heteroarene to the enone is taking place in a highly enantiocontrolled fashion providing enol borate **a60**. We speculated that KF can break up the enol borate intermediate **a60** forming borate **a63** and potassium enolate **a61**, which after the aqueous work up forms the enantioenriched bisheteroaryl ketone **a62**. Alternatively, the borate **a63** can potentially act as either fluoride scavenger or to facilitate the BINOL/arene transfer with a new trifluoroborate salt **a50b** and reform the BINOL-boronate complex (**a57** or **a58**) in the catalytic cycle.

Figure 1-2. The Proposed Mechanism.



1.3 Reaction Scope

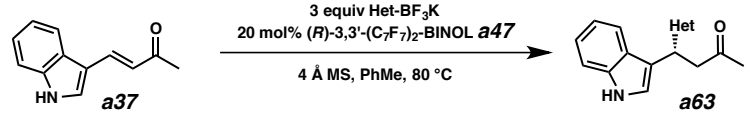
1.3.1 Scope of Trifluoroborate Salts

A broad range of nitrogen-, oxygen-, and sulfur-containing heteroaryl trifluoroborates served as nucleophiles and even halide-substituted thiophenes afforded the product in good yield (entry 2 and 3). As expected, depending on the substitution position on the heteroarene slight differences in substrate reactivity were observed. For example, the less electron-rich 3-thiopehene trifluoroborate (**a68**) required a considerably longer reaction time compared to 2-thiophene trifluoroborate (entry 5). Electron-

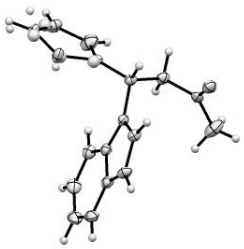
withdrawing groups on the arene (**a67** and **a70**) resulted in somewhat diminished reactivity and therefore required higher reaction temperatures compared to their electron-rich analogs. Importantly, the corresponding regiochemical reactivity of the substrates is controlled by the boron-substituent's position and not the innate electronic bias of the substrate. A dramatic difference in reactivity between boronic acid and trifluoroborate salt forms of the nucleophile is illustrated in the case of pyrrole-based reagents (entry 8 and 9). Even the sterically hindered isoxazole pronucleophile **a73** afforded the product in very good yield. Not only indole nucleophiles (**a74** and **a75**) but also other benzo-fused heteroarenes (**a76** and **a77**) afforded products in excellent yield. One of the advantages of this methodology is the ease of product purification: a simple filtration of the reaction mixture removes both the unreacted salts as well as the molecular sieves. Silica gel chromatography can easily separate the products and recycle the BINOL catalyst **a47**.

The X-ray crystal structures of the thiophene **a49** and the furan **a84** were obtained using the anomalous dispersion effect, allowing determination of the absolute stereochemistry at the chiral center of the product. From this work we were able to assign and predict the absolute stereochemistry produced in the product based on the chirality of the BINOL catalyst.

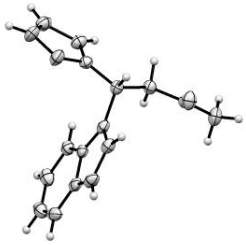
Table 1-3. Heteroaryl Nucleophiles.



entry	Het-BF_3K	product		
1	R = Me	*a64*	*a79*	5 h, 97%, 99:1 er
2	Br	*a65*	*a80*	5 h, 97%, 97:3 er
3	Cl	*a66*	*a81*	6.5 h, 93%, 99:1 er
4	C(O)Me	*a67*	*a82*	120 h, 69%, 97:3 er (PhCl, 110 °C)
5		*a68*	*a83*	53 h, 99%, 99:1 er
6	R= H	*a69*	*a84*	9 h, 96%, 99:1 er
7	CHO	*a70*	*a85*	48 h, 67%, 99:1 er (PhCl, 110 °C)
8	X = BF_3K	*a71*	*a86*	5 h, 74%, 99:1 er
9	$B(OH)_2$	*a72*		5 h, 19%
10		*a73*	*a87*	48 h, 89%, 99:1er
11		*a74*	*a88*	51 h, 78%, 99:1 er
12		*a75*	*a89*	48 h, 97%, 97:3 er
13	X= O	*a76*	*a90*	84 h, 94%, 96:4 er
14	S	*a77*	*a91*	48 h, 87%, 96:4 er
15		*a78*	*a92*	24 h, 80.5% yield, 98:2 er



Crystal structure of **a49**



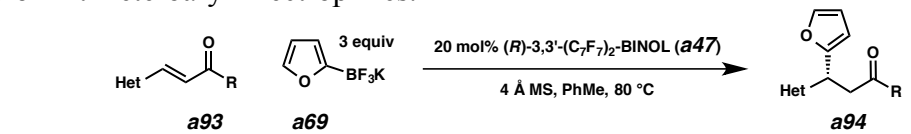
Crystal structure of **a84**

Figure 1-3. The X-ray Crystal Structures of the Thiophene **a49** and the Furan **a84**.

1.3.2 Scope of Electrophiles

Several heterocyclic-appended enones further illustrate the broad substrate scope (Table 1-4). Both electron-rich and electron-deficient heteroarenes generated products in good yields. Thiazole enone **a98** did not afford a product with high enantioselectivity, presumably due to the propensity of the thiazole ring to facilitate the epimerization of the product.[26b] α,β-Unsaturated carbonyl compounds other than ketones were also examined. Unfortunately, substrates containing either ester or amide functionality failed to form products. Nonetheless, this synthetic challenge can be easily overcome by using 2-acyl imidazole **a101**, which represents a latent carboxylate or amide functionality.[15c] Enal **a102** provided the product in a good yield, but due to the intrinsic instability of the product towards silica gel chromatography, the aldehyde was reduced to the corresponding alcohol for ease of purification. Based on our results and the especially good performance of the enal substrate, we grew increasingly confident that this methodology could be employed as a key step towards constructing the bis-heteroaryl chiral center in the synthesis of discoipyrrole D. The discussion of the synthesis of discoipyrrole D will be described in detail in chapter two.

Table 1-4. Heteroaryl Electrophiles.



entry	electrophile	product		entry	electrophile	product	
1	*a95*	*a103*	14 h, 80%, 99:1 er	5	*a99*	*a107*	18 h, 94%, 99:1 er
2	*a96*	*a104*	23 h, 85%, 99:1 er	6	*a100*	*a108*	47 h, 93%, 99:1 er
3	*a97*	*a105*	47 h, 93%, 97:3 er	7	*a101*	*a109*	48 h, 94%, 99:1 er
4	*a98*	*a106*	30 h, 94%, 89:11 er	8	*a102*	*a110*	2 steps, reduced w/$NaBH_4$ 7 h, 84%, 98:2 er

1.4 Conclusions

An efficient method to construct bis-heteroaryl stereocenters with high enantioselectivity via a BINOL-catalyzed conjugate addition of trifluoroborates to heteroaryl-appended enones and enals is discovered. Control experiments suggest that the rate-limiting step involves dissociation of the fluoride ion from trifluoroborate salts, thus generating a difluoroboron intermediate as a key factor for the catalytic cycle. The further development of a modified method to synthesize bis-aryl compounds was then developed

by a colleague, Dr. Thien S. Nguyen. This organocatalytic transformation is performed under relatively mild reaction conditions and does not require expensive reagents or late-transition metal catalysts. Importantly, bench, air, and moisture stable trifluoroborate salts are not only easy to handle, but also completely shut down the unproductive protodeboration side reaction.

1.5 Experimental

1.5.1 Materials and Methods

All reactions were carried out in flame- or oven-dried glassware. THF, toluene and CH_2Cl_2 were purged with argon and dried over activated alumina columns. Flash chromatography was performed on 60 Å silica gel (EMD Chemicals Inc). Preparative plate chromatography was performed on EMD silica gel plates, 60 Å, with UV-254 indicator. Chemical names were generated using CambridgeSoft ChemBioDraw Ultra 12.0. Analysis by HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Chiralpak or Chiralcel (250 mm x 4.6 mm) column (see below for column details). Analytical thin-layer chromatography was performed on EMD silica gel/TLC plates with fluorescent detector 254 nm. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer using the residual solvent peak as an internal standard ($CDCl_3$: 7.24 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR). Hexafluorobenzene (δ = -164.9 ppm) was employed as an external standard in ^{19}F NMR spectra. NMR yields were determined by addition of 0.5 equivalent of methyl (4-nitrophenyl) carboxylate as an internal standard to the crude

reaction mixture. HRMS analyses were performed under contract by UT Austin's mass spectrometric facility via ESI methods on a US10252005 instrument.

HPLC columns for separation of enantiomers:

Chiralpak AY-3: Amylose tris-(5-chloro-2-methylphenylcarbamate) coated on 3 μm silica gel.

Chiralpak AD-H: Amylose tris-(3,5-dimethylphenylcarbamate) coated on 5 μm silica gel.

Chiralpak ID: Amylose tris-(3-chlorophenylcarbamate) immobilized on 5 μm silica gel.

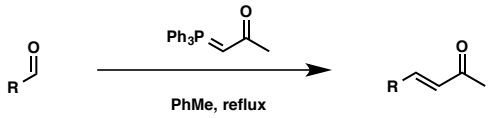
Chiralcel OJ-H: Cellulose tris-(4-methylbenzoate) coated on 5 μm silica gel.

Chiralcel OD-H: Cellulose tris-(3,5-dimethylphenylcarbamate) coated on 5 μm silica gel.

Chiralpak AS-H: Amylose tris-[(S)-α-methylbenzylcarbamate) coated on 5 μm silica gel.

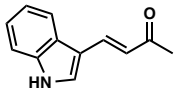
1.5.2 Synthesis of Compounds

General procedure A: the Synthesis of Heteroaryl-appended Enone.



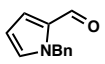
To a flask equipped with a stir bar and a condenser was added carboxaldehyde (2 mmol), 1-(triphenylphosphoranylidene)-2-propanone (1.2 equiv, 764 mg), and toluene (4 mL, 0.5 M). The reaction mixture was refluxed until TLC analysis showed no starting material. After completion, the reaction mixture was concentrated via rotary evaporation. The crude mixture was purified via flash column chromatography with an appropriate eluent on silica gel.

(*E*)-4-(1H-indol-3-yl)but-3-en-2-one (a37)



Enone **a37** was prepared via Wittig reaction following the procedure described in literature. The product was obtained as a brown solid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.51 (bs, 1H), 7.87 (d, *J* = 7.4 Hz, 1H), 7.72 (d, *J* = 16.0 Hz, 1H), 7.48 (d, *J* = 2.8 Hz, 1H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.24–7.18 (m, 2H), 6.74 (d, *J* = 16.0 Hz, 1H), 2.32 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 199.4, 138.0, 137.6, 130.0, 125.6, 123.8, 123.4, 122.0, 120.8, 113.8, 112.3, 27.7. **IR (neat)**: 3139, 2932, 2887, 1659, 1555, 1497, 1446, 1364, 1270, 1247, 1225, 1132, 973, 768 cm^{-1}. NMR data are consistent with the literature report. MP: 140-141 °C.

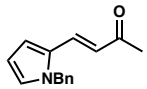
1-benzyl-1*H*-pyrrole-2-carbaldehyde (a95-0)



To a suspension of dry NaH (240 mg, 10 mmol, 2 equiv) in DMF (10 mL) with stirring was added with pyrrole-2-carboxyaldehyde (475.5 mg, 5 mmol, 1 equiv) under Argon at 0 ºC. After 20 minutes, benzyl bromide (1.2 mL, 10 mmol, 2 equiv) was added to the reaction mixture. The reaction was slowly warmed up to room temperature and stirred for 3 hours. TLC analysis (25% ethyl acetate in hexanes) showed no starting material. The reaction mixture was diluted with dichloromethane and washed four times with water, once with brine. The organic solution was dried over $MgSO_4$, filtered and concentrated. The crude reaction mixture was then dry-loaded onto silica gel and purified via flash column chromatography on silica gel with 10% ethyl acetate in hexanes. Pure 1-benzyl-

1*H*-pyrrole-2-carbaldehyde **a95-0** was recovered as dark red oil. (885.7 mg, 4.78 mmol, 95.6% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.31–7.23 (m, 3H), 7.13 (d, *J* = 7.5 Hz, 2H), 6.96 (d, *J* = 3.4 Hz, 2H), 6.26 (t, *J* = 3.4 Hz, 1H), 5.55 (s, 2H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 179.4, 137.5, 131.5, 131.3, 128.6, 127.7, 127.2, 124.8, 110.1, 51.9. **HRMS** (CI) *m/z* (M+): calculated for $C_{12}H_{11}NO$: 185.0841; found 185.037. **R_F**: 0.55 in 25% ethyl acetate in hexanes

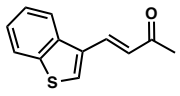
(*E*)-4-(1-benzyl-1*H*-pyrrol-2-yl)but-3-en-2-one (a95)



To a flask equipped with a stir bar and a condenser was added carboxaldehyde **a95-0** (556 mg, 3 mmol, 1 equiv), 1-(triphenylphosphoranylidene)-2-propanone (1.34 g, 3.75 mmol, 1.25 equiv), and toluene (5 mL). The reaction mixture was refluxed for 20 hours. After completion, the reaction mixture was concentrated via rotary evaporation. The crude mixture was purified via column chromatography on silica gel with a 20% ethyl acetate in hexanes as an eluent. The product was obtained as a brown solid. (585.3 mg, 2.60 mmol, 86.6% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 15.5, 1H), 7.31–7.24 (m, 3H), 7.03 (d, *J* = 6.9 Hz, 2H), 6.87 (t, *J* = 2.3 Hz, 1H), 6.76 (dd, *J* = 3.4 Hz, 1.7 Hz, 1H), 6.44 (d, *J* = 16.0 Hz, 1H), 6.26–6.25 (m, 1H), 5.21 (s, 2H), 2.19 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 197.7, 137.2, 130.6, 129.0, 128.9, 127.9, 127.2, 126.3, 122.2, 112.5, 110.1, 50.8, 27.8. **IR (neat):** 1631, 1610, 1469, 1453, 1359, 1327, 1279, 1260, 1246, 1204, 1192, 1071, 1002, 972, 813, 730, 715 cm^{-1}. **HRMS** (CI) *m/z* (M+):

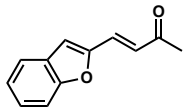
calculated for $C_{15}H_{15}NO$: 225.1154; found 225.1150. **R_F**: 0.27 in 25% ethyl acetate/hexanes. **MP**: 64-66 °C.

(*E*)-4-(benzo[*b*]thiophen-3-yl)but-3-en-2-one (a96)



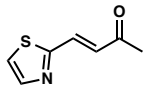
To a flask equipped with a stir bar and a condenser was added thianaphthene-3-carboxaldehyde (161 mg, 1 mmol, 1 equiv), 1-(triphenylphosphoranylidene)-2-propanone (400 mg, 1.25 mmol, 1.25 equiv), and toluene (5 mL). The reaction mixture was refluxed for 20 hours. After completion, the reaction mixture was concentrated via rotary evaporation. The crude mixture was purified via column chromatography on silica gel with 10% ethyl acetate in hexanes as an eluent. The product was obtained as a yellow solid. (200 mg, 0.98 mmol, 98% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 16.0 Hz, 1H), 7.78 (s, 1H), 7.45 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 16.0 Hz, 1H), 2.40 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 198.2, 140.5, 137.1, 134.8, 131.5, 128.4, 127.4, 125.1, 125.0, 123.0, 121.9, 27.7. **IR (neat):** 3085, 1659, 1636, 1617, 1501, 1426, 1358, 1254, 967, 876, 807, 753, 720 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{12}H_{10}OS$: 202.0531; found 202.0527. **R_F**: 0.21 in 10 % ethyl acetate in hexanes. **MP**: 54-55 °C.

(*E*)-4-(benzofuran-2-yl)but-3-en-2-one (a97)



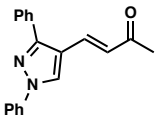
To a flask equipped with a stir bar and a condenser was added benzofuran-2-carbaldehyde (484.8 mg, 3.3 mmol, 1 equiv), 1-(triphenylphosphoranylidene)-2-propanone (1.36 g, 4.2 mmol, 1.25 equiv), and toluene (6 mL). The reaction mixture was refluxed for 20 hours. After completion, the reaction mixture was concentrated via rotary evaporation. The crude mixture was purified via column chromatography on silica gel with 10% ethyl acetate in hexanes as an eluent. The product was obtained as a white solid. (577 mg, 3.1 mmol, 94% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 9.2 Hz, 1H), 7.36 (d, *J* = 15.5 Hz, 1H), 7.34 (dd, *J* = 14.3 Hz, 1.2 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 6.95 (s, 1H), 6.84 (d, *J* = 16.0 Hz, 1H), 2.35 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 197.5, 155.5, 152.3, 129.4, 128.3, 126.6, 126.6, 123.3, 121.7, 112.0, 111.4, 28.2. **IR (neat):** 1654, 1623, 1358, 1255, 1246, 1199, 1123, 1003, 978, 950, 884, 841, 820, 751, 743, 736 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{12}H_{10}O_2$: 186.0681; found 186.0680. **R_F**: 0.45 35% ethyl acetate in hexanes. **MP**: 101-102 °C.

(*E*)-4-(thiazol-2-yl)but-3-en-2-one (a98)



Enone **a98** was prepared via Wittig reaction following the procedure described in literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 3.2 Hz, 1H), 7.61 (d, *J* =16.4 Hz, 1H), 7.44 (d, *J* = 3.2 Hz, 1H), 6.91 (d, *J* = 16.49 Hz, 1H), 2.38 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 197.7, 164.0, 144.9, 134.5, 130.8, 121.7, 27.9. **IR (neat):** 1663, 1256, 1224, 969, 752 cm^{-1}. NMR data are consistent with the literature report.

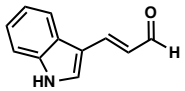
(*E*)-4-(1,3-diphenyl-1H-pyrazol-4-yl)but-3-en-2-one (a100)



To a flask equipped with a stir bar and a condenser was added 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde (498 mg, 2 mmol, 1 equiv), 1-(triphenylphosphoranylidene)-2-propanone (837.7 g, 2.6 mmol, 1.3 equiv), and toluene (6 mL). The reaction mixture was refluxed for 20 hours. After completion, the reaction mixture was concentrated via rotary evaporation. The crude mixture was purified via column chromatography on silica gel with a gradient of 20 to 25% ethyl acetate in hexanes as eluents. The product was obtained as a white solid. (540 mg, 1.87 mmol, 94% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.76 (dd, *J* = 7.5, 1.2 Hz, 2H), 7.66 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.55 (d, *J* = 16.0 Hz, 1H), 7.50–7.42 (m, 5H), 7.33 (t, *J* = 7.5 Hz, 1H), 6.56 (d, *J* = 16.0 Hz, 1H), 2.3 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 198.1, 153.6, 139.3, 134.0, 132.1, 129.5, 128.8, 128.7, 128.6, 127.3, 126.8, 126.3, 119.3, 117.6, 27.2. **IR (neat):** 1644, 1616, 1598,

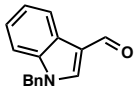
1506, 1537, 1259, 1235, 967, 967, 820, 771, 754, 708, 700, 685, 675 cm^{-1}. **HRMS** (CI) *m/z* (M+H): calculated for $C_{19}H_{17}N_2O$: 289.1341; found 289.1339. $\mathbf{R_F}$: 0.45 in 40% ethyl acetate/hexanes. **MP**: 129-130 °C.

(*E*)-3-(1*H*-indol-3-yl)acrylaldehyde (a102)



Enal **a102** was prepared following the procedure described in literature.[32] The product was obtained as a brown solid. **^{1}H NMR** (500 MHz, CD_3OD): δ 9.53 (d, *J* = 8.1 Hz, 1 H), 8.71 (d, *J* = 15.7 Hz, 1 H), 7.89 (d, *J* = 7.1 Hz, 1 H), 7.83 (s, 1 H), 7.49 (d, *J* = 7.2 Hz, 1 H), 7.30–7.23 (m, 2 H), 6.75 (dd, *J* = 15.7 Hz, 8.1 Hz, 1 H); **^{13}C NMR** (125 MHz, CD_3OD) δ 196.8, 150.9, 139.6, 133.9, 126.7, 124.4, 124.1, 122.9, 121.2, 114.6, 113.5. NMR data are consistent with the literature report.

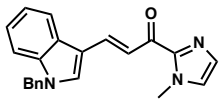
1-benzyl-1*H*-indole-3-carbaldehyde (a101-0)



To a suspension of dry NaH (240 mg, 10 mmol, 2 equiv) in DMF (10 mL) with stirring was added with indole-3-carboxaldehyde (727.9 mg, 5 mmol, 1 equiv) under Argon at 0 ºC. After 20 minutes, to the reaction mixture was added with benzyl bromide (1.2 mL, 10 mmol, 2 equiv). The reaction was slowly warmed up to room temperature and stirred for 3 hours. TLC analysis (50% ethyl acetate in hexanes) showed no starting material. The reaction mixture was diluted with dichloromethane and washed four times with water,

once with brine. The organic solution was dried over $MgSO_4$, filtered and concentrated. The crude reaction mixture was then dry-loaded onto silica gel and purified via flash column chromatography on silica gel with a gradient of 25 to 30% ethyl acetate in hexanes as eluents. The product was obtained as a pale pink solid. (1.14 g, 4.85 mmol, 92% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.98 (s, 1H), 8.34–8.29 (m, 1H), 7.69 (s, 1H), 7.35–7.28 (m, 6H), 7.18–7.16 (m, 2H), 5.34 (s, 2H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 184.6, 138.5, 137.4, 135.3, 129.1, 128.4, 127.2, 125.5, 124.1, 123.0, 122.1, 118.4, 110.3, 50.9. **HRMS** (CI) *m/z* (M+): calculated for $C_{16}H_{13}NO$: 235.0997; found 235.0998. **R_F**: 0.55 in 50% ethyl acetate/hexanes.

(*E*)-3-(1-benzyl-1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)prop-2-en-1-one (a101)



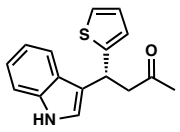
To a flask equipped with a stir bar and a condenser was added 1-benzyl-1*H*-indole-3-carbaldehyde (469 mg, 2 mmol, 1 equiv), 1-(1-methyl-1*H*-imidazole-2-yl)-2-(triphenylphosphoranylidene)-ethanone (962 mg, 2.5 mmol, 1.25 equiv), and toluene (4 mL). The reaction mixture was refluxed for 20 hours. After completion, the reaction mixture was concentrated via rotary evaporation. The crude mixture was purified via column chromatography on silica gel with a gradient of 0 to 5% ethyl acetate in dichloromethane as eluents. The product was obtained as a yellow solid. (375.5 mg, 1.1 mmol, 55% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.16–8.12 (m, 2H), 8.06 (d, J = 16.0 Hz, 1H), 7.62 (s, 1H), 7.38–7.27 (m, 7H), 7.20–7.19 (m, 2H), 7.08 (s, 1H), 5.36 (s, 2H), 4.14 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 180.9, 144.4, 137.5, 136.7, 136.0, 133.1,

128.9, 128.8, 128.0, 127.0, 127.0, 126.7, 123.1, 121.6, 121.0, 118.0, 113.6, 110.4, 50.5, 36.3. **IR (neat):** 1644, 1580, 1570, 1533, 1466, 1453, 1402, 1386, 1365, 1275, 1207, 1178, 1150, 1026, 1014, 976, 968, 844, 784, 769, 761, 731, 702, 696, 683, 659 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{22}H_{19}N_3O$: 341.1528; found 341.1530. $\mathbf{R_F}$: 0.15 in 3% ethyl acetate in dichloromethane. **MP**: 154-156 °C.

General procedure B: the BINOL-catalyzed conjugate addition of potassium heteroaryltrifluoroborate to α,β-unsaturated carboxylate ketone or aldehyde

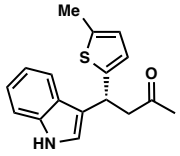
To a 7 mL vial equipped with a stir bar was added powdered 4 Å molecular sieves (250 mg) and the vial was flamed-dried under high vacuum. The vial was cooled to room temperature and back-filled with Argon. The heterocycle-appended enone (0.2 mmol, 1.0 equiv), (*R*)-3,3'-$(C_7F_7)_2$-BINOL (28.7 mg, 0.04 mmol, 0.2 equiv), potassium trifluoroborate salt (0.6 mmol, 3 equiv) were then added. Freshly dried toluene (4 mL) was added. The vial was well sealed by Teflon tape, and the reaction was heated to 80 ºC. The reaction was monitored by TLC analysis. After the reaction is complete, the solution was filtered through a short celite pad and concentrated. The crude reaction mixture was then dry-loaded onto silica gel and purified via flash column chromatography on silica gel with appropriate eluents.

(*R*)-4-(1*H*-indol-3-yl)-4-(thiophen-2-yl)butan-2-one (a49)



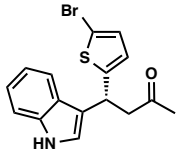
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography on silica gel with a gradient of 0 to 2% ethyl acetate in dichloromethane as eluents. The product was obtained as a white solid. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-70:30, 0.6 ml/ min, UV-254 detector). Trial 1: 51.7 mg, 0.192 mmol, 96% yield (7 h); Trial 2: 53.3 mg, 0.198 mmol, 99% yield; 99.5:0.5 er (7 h); Trial 3: 52.9 mg, 0.197 mmol, 98% yield; 99.1:0.9 er (7 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08 (bs, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.17 (td, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.11-7.06 (m, 2H), 7.00 (d, *J* = 2.3 Hz, 1H), 6.89-6.88 (m, 2H), 5.13 (t, *J* = 7.5 Hz, 1H), 3.32-3.24 (m, 2H), 2.09 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 207.0, 148.4, 136.4, 126.5, 126.0, 124.1, 123.4, 122.2, 121,6, 119.5, 119.3, 118.5, 111.3, 50.9, 33.5, 30.5. **IR (neat):** 3295, 1697, 1435, 1356, 1338, 1260, 1248, 1167, 1102, 1078, 1010, 818, 763, 744, 709 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{16}H_{15}NOS$: 269.0874; found 269.0872. **R_F**: 0.87 in 15% ethyl acetate/dichloromethane. **MP**: 99-100 °C. The solved crystal structure of **a49** has been deposited in The Cambridge Crystallographic Data Centre. CCDC: 1049583.

(*R*)-4-(1*H*-indol-3-yl)-4-(5-methylthiophen-2-yl)butan-2-one (a79)



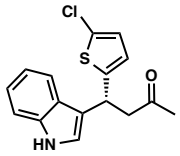
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with 20% ethyl acetate in hexanes as an eluent on silica gel. The product was obtained as a light yellow solid. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-70:30, 0.6 ml/ min, UV-254 detector). Trial 1: 56.1 mg, 0.198 mmol, 99% yield (5.5 h); Trial 2: 53.8 mg, 0.190 mmol, 95% yield; 99.5:0.5 er (5 h); Trial 3: 55.5 mg, 0,196 mmol, 98% yield; 99.7:0.3 er (5 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (bs, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 2.3 Hz, 1H), 6.64 (d, *J* = 3.4 Hz, 1H), 6.50 (d, *J* = 3.4 Hz, 1H), 5.02 (t, *J* = 6.9 Hz, 1H), 3.26-3.18 (m, 2H), 2.36 (s, 3H), 2.09 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 207.2, 145.9, 137.8, 136.4, 126.1, 124.4, 123.8, 122.2, 121.5, 119.5, 119.4, 118.6, 111.2, 50.8, 33.7, 30.5, 15.3. **IR (neat):** 3407, 2929, 1704, 1481, 1456, 1417, 1357, 1338, 1261, 1225, 1148, 1096, 1010, 989, 907, 798, 763, 737, 713 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{17}H_{17}NOS$: 283.1031; found 283.1032. **R_F**: 0.75 in 15% ethyl acetate/dichloromethane. **MP**: 99-100 °C.

(*R*)-4-(5-bromothiophen-2-yl)-4-(1*H*-indol-3-yl)butan-2-one (a80)



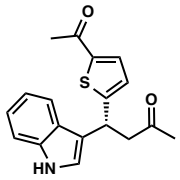
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with a gradient of 15 to 20% ethyl acetate in hexanes as eluents on silica gel. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-70:30, 0.6 ml/ min, UV-254 detector). Trial 1: 65.5 mg, 0.188 mmol, 94% yield (5.5 h); Trial 2: 69.5 mg, 0.199 mmol, 99% yield; 98:8 er (5 h); Trial 3: 66.9 mg, 0.192 mmol, 96% yield; 96:4 er (5 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 (bs, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.08, (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 6.80 (d, *J* = 4.0 Hz, 1H), 6.62 (d, *J* = 4.0 Hz, 1H), 5.02 (t, *J* = 6.9, 1H), 3.25 (dd, *J* = 16.6 Hz, 6.9 Hz, 1H), 3.21 (dd, *J* = 16.6 Hz, 8.0 Hz, 1H), 2.10 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 206.5, 150.3, 136.5, 129.3, 125.9, 124.5, 122.4, 121.5, 119.7, 119.3, 117.8, 111.3, 109.9, 50.4, 33.7, 30.6. **IR (neat):** 3404, 1703, 1458, 1417, 1364, 1334, 1259, 1165, 1108, 1010, 961, 833, 796, 783, 743 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{16}H_{14}BrNOS$: 346.9979; found 346.9986. **R_F**: 0.8 in 15% ethyl acetate/dichloromethane. The product was obtained as a light pinkish solid. **MP**: 140-141 °C.

(*R*)-4-(5-chlorothiophen-2-yl)-4-(1*H*-indol-3-yl)butan-2-one (a81)



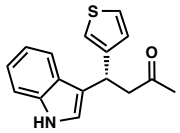
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with a gradient of a gradient of 0 to 3% ethyl acetate in dichloromethane as eluents on silica gel. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-70:30, 0.6 ml/ min, UV-254 detector). Trial 1: 57.7 mg, 0.190 mmol, 95% yield (6.5 h); Trial 2: 55.9 mg, 0.184 mmol, 92% yield; 99.4:0.6 er (6.5 h); Trial 3: 56.0 mg, 0.184 mmol, 92% yield; 99.4:0.6 er (6.5 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 (bs, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 6.66 (d, *J* = 4.0 Hz, 1H), 6.63 (d, *J* = 4.6 Hz, 1H), 5.00 (t, *J* = 6.9 Hz, 1H), 3.25 (dd, *J* = 16.6 Hz, 6.9 Hz, 1H), 3.21 (dd, *J* = 16.6 Hz, 8.0 Hz, 1H), 2.1 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 206.6, 147.4, 136.4, 127.6, 125.9, 125.5, 123.4, 122.4, 121.5, 119.6, 119.2, 117.6, 111.3, 50.3, 33.6, 30.5. **IR (neat):** 3403, 1707, 1458, 1364, 1335, 1165, 1108, 1008, 983, 796, 783, 743 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{16}H_{14}ClNOS$: 303.0485; found 303.0491. **R_F**: 0.75 in 15% ethyl acetate/dichloromethane. The product was obtained as a white solid. **MP**: 108-109 °C.

(*R*)-4-(5-acetylthiophen-2-yl)-4-(1*H*-indol-3-yl)butan-2-one (a82)



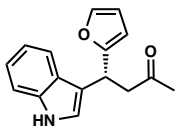
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with a gradient of 0 to 3% ethyl acetate in dichloromethane as eluents on silica gel. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-70:30, 0.6 ml/ min, UV-254 detector). Trial 1: 48.5 mg, 0.156 mmol, 78% yield (in PhCl, 110 °C, 120 h); Trial 2: 44.8 mg, 0.144 mmol, 72% yield; 99.2:0.8 er (in PhCl, 110 °C, 120 h); Trial 3: 40.5 mg, 0.130 mmol, 65% yield; 94.3:5.7 er (in PhCl, 110 °C, 120 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.21 (bs, 1H), 7.47-7.46 (m, 2H), 7.33 (d, J = 8.6 Hz, 1H), 7.17 (td, J = 8.0 Hz, 1.2 Hz, 1H), 7.07-7.04 (m, 2H), 6.91 (d, J = 2.9 Hz, 1H), 5.12 (t, J = 7.5 Hz, 1H), 3.28 (app. AB d, 2H), 2.45 (s, 3H), 2.11 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 206.1, 190.6, 158.6, 142.3, 136.5, 132.7, 132.7, 125.8, 122.5, 121.6, 119.8, 119.1, 117.6, 111.4, 50.4, 33.9, 30.5, 26.4. **IR (neat):** 3319, 1707, 1645, 1451, 1430, 1399, 1359, 1338, 1287, 1277, 1258, 1165, 1141, 1111, 1031, 1007, 931, 817, 781, 768, 754, 682, 656 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{18}H_{17}NO_2S$: 311.0980; found 311.0987. **R_F**: 0.52 in 15% ethyl acetate/dichloromethane. The product was obtained as a light brown solid. **MP**: 149-150 °C.

(*R*)-4-(1*H*-indol-3-yl)-4-(thiophen-3-yl)butan-2-one (a83)



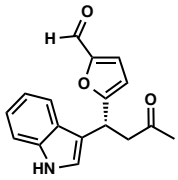
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with a gradient of 0 to 3% ethyl acetate in dichloromethane as eluents on silica gel. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-70:30, 0.6ml/ min, UV-254 detector). Trial 1: 53.0 mg, 0.197 mmol, 98 % yield (50 h); Trial 2: 53.3 mg, 0.198 mmol, 99 % yield; 99.8:0.2 er (50 h); Trial 3: 53.4 mg, 0.198 mmol, 99 % yield; 99.7:0.3 er (50 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08 (bs, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.21-7.15 (m, 2H), 7.06 (td, *J* = 6.9 Hz, 1.2 Hz, 1H), 7.02-7.01 (m, 1H), 6.96 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 4.92 (t, *J* = 7.5 Hz, 1H), 3.24 (dd, *J* = 16.0 Hz, 7.5 Hz, 1H), 3.18 (dd, *J* = 16.0 Hz, 7.5 Hz, 1H), 2.07 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 207.7, 144.8, 136.5, 127.6, 126.2, 125.5, 122.1, 121.5, 120.4, 119.3, 118.5, 111.2, 50.0, 33.7, 30.5. **IR (neat):** 3389, 3350, 1712, 1456, 1429, 1349, 1248, 1225, 1197, 1167, 1099, 1079, 1006, 843, 818, 786, 762, 741, 733, 720, 704, 696, 686 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{16}H_{15}NOS$: 269.0874; found 269.0872. **R_F**: 0.75 in 15% ethyl acetate/dichloromethane. The product was obtained as a white solid. **MP**: 98-99 °C.

(*R*)-4-(furan-2-yl)-4-(1*H*-indol-3-yl)butan-2-one (a84)



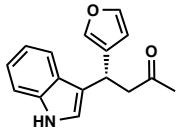
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with a gradient of 15 to 20% ethyl acetate in hexanes as eluents on silica gel. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-70:30, 0.6 ml/ min, UV-254 detector). Trial 1: 47.0 mg, 0.186 mmol, 93% yield (8 h); Trial 2: 50.0 mg, 0.198 mmol, 99% yield; 99.1:0.9 er (8 h); Trial 3: 48.1 mg, 0.190 mmol, 95% yield; 99.1:0.9 er (8 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 (bs, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.33-7.30 (m, 2H), 7.17 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.08 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.02 (d, *J* = 2.9 Hz, 1H), 6.26-6.25 (m, 1H), 6.02 (d, *J* = 3.4 Hz, 1H), 4.90 (t, *J* = 7.5 Hz, 1H), 3.30 (dd, *J* = 16.0 Hz, 7.5 Hz, 1H), 3.15 (dd, *J* = 16.6 Hz, 7.5 Hz, 1H), 2.09 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 207.1, 156.6, 141.16, 136.4, 126.0, 122.1, 122.0, 119.5, 119.2, 116.1, 111.3, 110.2, 105.5, 47.9, 32.0, 30.3. **IR (neat):** 1713, 1504, 1426, 1357, 1229, 1158, 1073, 1007, 919, 761, 730 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{16}H_{15}NO_2$: 253.1103; found 253.1098. **R_F**: 0.72 in 15% ethyl acetate/dichloromethane. The product was obtained as a white solid. **MP**: 88-89 °C. The solved crystal structure of **a84** has been deposited in The Cambridge Crystallographic Data Centre. CCDC: 1049584.

(*R*)-5-(1-(1*H*-indol-3-yl)-3-oxobutyl)furan-2-carbaldehyde (a85)



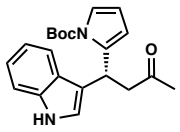
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with a gradient of 0 to 5% ethyl acetate in dichloromethane as eluents on silica gel. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-70:30, 0.6 ml/ min, UV-254 detector). Trial 1: 42.2 mg, 0.150 mmol, 75% yield (PhCl, 110 °C, 48 h); Trial 2: 39.9 mg, 0.142 mmol, 71% yield; 99:1 er (PhCl, 110 °C, 48 h); Trial 3: 38.9 mg, 0.138 mmol, 69 % yield; 99.1:0.9 er (PhCl, 110 °C, 48 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.28 (bs, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.18 (td, *J* = 6.9 Hz, 1.2 Hz, 1H), 7.12-7.06 (m, 3H), 6.24 (d, *J* = 3.4 Hz, 1H), 4.98 (t, *J* = 6.9 Hz, 1H), 3.39 (dd, *J* = 17.2 Hz, 7.5 Hz 1H), 3.19 (dd, *J* = 17.2 Hz, 7.5 Hz, 1H), 2.09 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 206.1, 177.1, 164.1, 151.7, 136.3, 125.7, 122.4, 122.4, 122.3, 119.7, 118.8, 114.3, 111.5, 109.5, 47.1, 32.1, 30.2. **IR (neat):** 3338, 1709, 1660, 1579, 1508, 1457, 1423, 1394, 1354, 1339, 1244, 1161, 1101, 1021, 964, 804, 784, 765, 741 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{17}H_{15}NO_3$: 281.1052; found 281.1057. The product was obtained as a brown oil. **R_F**: 0.42 in 15% ethyl acetate/dichloromethane.

(*R*)-4-(furan-3-yl)-4-(1*H*-indol-3-yl)butan-2-one (a51)



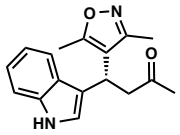
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with a gradient of 15 to 20% ethyl acetate in hexanes as eluents on silica gel. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-70:30, 0.6 ml/ min, UV-254 detector). Trial 1: 46.6 mg, 0.184 mmol, 92% yield (50 h); Trial 2: 40.6 mg, 0.160 mmol, 80% yield; 95.4:4.6 er (50 h); Trial 3: 43.6 mg, 0.172 mmol, 86% yield; 94.7:5.3 er (50 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (bs, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.31 (t, J = 1.7 Hz, 1H), 7.23 (d, J = 1.7 Hz, 1H), 7.17 (td, J = 6.9 Hz, 1.2 Hz, 1H), 7.07 (td, J = 6.9 Hz, 1.2 Hz, 1H), 6.97 (d, J = 2.3 Hz, 1H), 6.27-6.26 (m, 1H), 4.73 (t, J = 6.9 Hz, 1H), 3.17 (dd, J = 16.0 Hz, 6.9 Hz, 1H), 3.09 (dd, J = 16.0 Hz, 8.0 Hz, 1H), 2.08 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 207.5, 142.9, 139.1, 136.5, 128.1, 126.1, 122.1, 121.5, 119.4, 119.4, 118.1, 111.2, 110.3. 49.7, 30.5, 29.1. **IR (neat):** 3407, 1704, 1456, 1417, 1354, 1338, 1265, 1158, 1096, 1067, 1020, 872, 789, 770, 741 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{16}H_{15}NO_2$: 253.1103; found 253.1097. The product was obtained as a yellow oil. **R_F**: 0.72 in 15% ethyl acetate/dichloromethane.

***tert*-butyl (*R*)-2-(1-(1*H*-indol-3-yl)-3-oxobutyl)-1*H*-pyrrole-1-carboxylate (a86)**



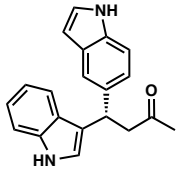
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with a gradient of 10 to 20% ethyl acetate in hexanes as eluents on silica gel. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-70:30, 0.6 ml/ min, UV-254 detector). Trial 1: 51.5 mg, 0.146 mmol, 73% yield (5.5 h); Trial 2: 53.6 mg, 0.152 mmol, 76% yield; 99.1:0.9 er (5.5 h); Trial 3: 51.6 mg, 0.146 mmol, 73% yield; 99.5:0.5 er (5 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (bs, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0Hz, 1H), 7.20-7.19 (m, 1H), 7.14 (td, *J* = 6.9 Hz, 1.2 Hz, 1H), 7.05 (td, *J* = 6.9 Hz, 1.2 Hz, 1H), 6.88 (d, *J* = 2.3 Hz, 1H), 6.03 (t, *J* = 3.4 Hz, 1H), 5.93-5.92 (m, 1H), 5.55 (t, *J* = 8.0 Hz, 1H), 3.18 (dd, *J* = 16.0 Hz, 6.9 Hz, 1H), 3.10 (dd, *J* = 16.0 Hz, 8.0 Hz, 1H), 2.12 (s, 3H), 1.48 (s, 9H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 208.0, 149.4, 137.4,136.4, 126.3, 122.3, 121.9, 121.6, 119.3, 119.2, 117.7, 111.7, 111.1, 109.7, 83.5, 49.7, 31.5, 29.6, 27.9. **IR (neat):** 3334, 2921, 1727, 1703, 1618, 1549, 1487, 1456, 1410, 1369, 1324, 1284, 1256, 1232, 1156, 1115, 1062, 1034, 1011, 909, 883, 843, 824, 814, 800, 773, 742, 723 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{21}H_{24}N_2O_3$: 352.1787; found 352.1791. **R_F**: 0.58 in 15% ethyl acetate/dichloromethane. The product was obtained as a light yellow solid. **MP**: 138-140 °C.

(*R*)-4-(3,5-dimethylisoxazol-4-yl)-4-(1*H*-indol-3-yl)butan-2-one (a87)



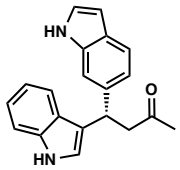
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with a gradient of 0 to 3% ethyl acetate in dichloromethane as eluents on silica gel. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-50:50, 0.6 ml/ min, UV-254 detector). Trial 1: 50.3 mg, 0.178 mmol, 89% yield (48 h); Trial 2: 52.0 mg, 0.184 mmol, 92% yield; 99.7:0.3 er (48 h); Trial 3: 49.2 mg, 0.174 mmol, 87% yield; 99.6:0.4 er (48 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.13 (bs, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.17 (td, *J* = 6.87 Hz, 1.2 Hz, 1H), 7.05-7.02 (m, 1H), 6.93-6.92 (m, 1H), 4.69-4.66 (m, 1H), 3.23 (dd, *J* = 16.6 Hz, 5.7 Hz, 1H), 3.10 (dd, *J* = 16.6 Hz, 9.2 Hz, 1H), 2.36 (s, 3H), 2.14 (s, 3H), 2.12 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 206.5, 165.2, 159.3, 136.7, 126.1, 122.4, 120.9, 119.5, 118.8, 116.2, 114.9, 111.3, 47.3, 30.4, 26.5, 11.5, 10.8. **IR (neat):** 3429, 1712, 1630, 1457, 1419, 1403, 1364, 1336, 1265, 1254, 1184, 1161, 1125, 1105, 1028, 1012, 897, 826, 786, 767, 738, 707, 680 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{17}H_{18}N_2O_2$: 282.1368; found 282.1371. $\mathbf{R_F}$: 0.54 in 15% ethyl acetate/dichloromethane. The product was obtained as a light brown solid. **MP**: 146-148 °C.

(*S*)-4-(1*H*-indol-3-yl)-4-(1*H*-indol-5-yl)butan-2-one (a88)



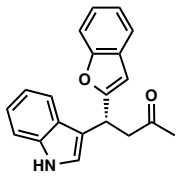
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with a gradient of 0 to 3% ethyl acetate in dichloromethane as eluents on silica gel. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-50:50, 0.6 ml/ min, UV-254 detector). Trial 1: 48.4 mg, 0.160 mmol, 80% yield (48 h); Trial 2: 46.0 mg, 0.152 mmol, 76% yield; 99:1 er (48 h); Trial 3: 48.4 mg, 0.160 mmol, 80% yield; 99.6:0.4 er (54 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (bs, 1H), 7.95 (bs, 1H), 7.56 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 1H), 7.13-7.10 (m, 3H), 7.00-6.96 (m, 2H), 6.45-6.44 (m, 1H), 4.92 (t, *J* = 7.45 Hz, 1H), 3.27 (dd, *J* = 16.0 Hz, 7.5 Hz, 1H), 3.20 (dd, *J* = 16.0 Hz, 8.0 Hz, 1H), 2.06 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 208.5, 136.5, 135.3, 134.6, 127.8, 126.6, 124.4, 122.2, 122.0, 121.3, 119.6, 119.6, 119.3, 119.2, 111.0, 111.0, 102.4, 51.0, 38.6, 30.3. **IR (neat):** 3405, 1699, 1456, 1415, 1338, 1263, 1092, 1010, 763, 729, 700 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{20}H_{18}N_2O$: 302.1419; found 302.1417. **R_F**: 0.67 in 15% ethyl acetate/dichloromethane. The product was obtained as a light brown solid. **MP**: 139-140 °C.

(*S*)-4-(1*H*-indol-3-yl)-4-(1*H*-indol-6-yl)butan-2-one (a89)



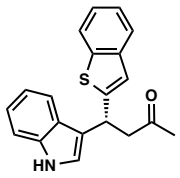
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with a gradient of 0 to 3% ethyl acetate in dichloromethane as eluents on silica gel. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-50:50, 0.6 ml/ min, UV-254 detector). Trial 1: 59.9 mg, 0.198 mmol, 99% yield (48 h); Trial 2: 60.0 mg, 0.198 mmol, 99% yield; 99.8:0.2 er (48 h); Trial 3: 56.8 mg, 0.188 mmol, 94% yield; 99:1 er (48 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (bs, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.24 (s, 1H), 7.12-7.08 (m, 3H), 6.99-6.96 (m, 2H), 6.46-6.45 (m, 1H), 4.92 (t, *J* = 7.5 Hz, 1H), 3.26 (dd, *J* = 16.0 Hz, 7.5 Hz, 1H), 3.20 (dd, *J* = 16.0 Hz, 8.0 Hz, 1H), 2.05 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 208.1, 138.0, 136.6, 136.0, 126.7, 126.4, 124.0, 122.1, 121.3, 120.6, 120.0, 119.7, 119.4, 119.4, 111.0, 110.1, 102.3, 51.0, 38.8, 30.4. **IR (neat):** 3405, 1686, 1455, 1417, 1371, 1338, 1244, 1163, 1095, 1043, 1010, 810, 775, 737 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{20}H_{18}N_2O$: 302.1419; found 302.1419. **R_F**: 0.67 in 15% ethyl acetate in dichloromethane. The product was obtained as a light brown solid. **MP**: 139-140 °C.

(*R*)-4-(benzofuran-2-yl)-4-(1*H*-indol-3-yl)butan-2-one (a90)



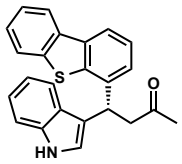
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with 15% ethyl acetate in hexanes as an eluent on silica gel. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-70:30, 0.6 ml/ min, UV-254 detector). Trial 1: 54.0 mg, 0.178 mmol, 89% yield (72 h); Trial 2: 60.0 mg, 0.198 mmol, 99% yield; 94.6:5.4 er (72 h); Trial 3: 57.6 mg, 0.190 mmol, 95% yield; 97.6:2.4 er (72 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07 (bs, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.43-7.34 (m, 3H), 7.21-7.07 (m, 5H), 6.39 (s, 1H), 5.05 (t, *J* = 6.87 Hz, 1H), 3.43 (dd, *J* = 16.6 Hz, 6.9 Hz, 1H), 3.24 (dd, *J* = 16.6 Hz, 7.5 Hz, 1H), 2.12 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 206.6, 159.7, 154.6, 136.4, 128.6, 126.0, 123.4, 122.5, 122.3, 122.2, 120.6, 119.6, 119.3, 115.4, 111.3, 110.9, 102.8, 47.6, 32.4, 30.4. **IR (neat):** 3429, 1708, 1581, 1488, 1454, 1419, 1405, 1363, 1339, 1306, 1276, 1250, 1225, 1161, 1093, 1079, 1058, 1008, 939, 877, 850, 825, 817, 797, 761, 749 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{20}H_{17}NO_2$: 303.1259; found 303.1262. **R_F**: 0.18 in 20% ethyl acetate/hexanes. The product was obtained as a white solid. **MP**: 170-172 °C.

(*R*)-4-(benzo[*b*]thiophen-2-yl)-4-(1*H*-indol-3-yl)butan-2-one (a91)



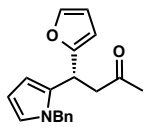
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with a gradient of 0 to 2% ethyl acetate in dichloromethane as eluents on silica gel. HPLC Chiralcel OD-H (hexanes/*i*-PrOH=90:10-70:30, 0.75 ml/ min, UV-254 detector). Trial 1: 57.5 mg, 0.180 mmol, 90% yield (48 h); Trial 2: 53.7 mg, 0.168 mmol, 84% yield; 94:6 er (48 h); Trial 3: 55.6 mg, 0.174 mmol, 87% yield; 97.2:2.8 er (48 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (bs, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.27-7.15 (m, 3H), 7.11-7.10 (m, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 5.18 (t, *J* = 6.9 Hz, 1H), 3.38 (dd, *J* = 16.6 Hz, 7.5 Hz, 1H), 3.33 (dd, *J* = 16.6 Hz, 6.9 Hz, 1H), 2.12 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 206.6, 149.3, 139.8, 139.3, 136.5, 126.1, 124.1, 123.7, 123.1, 122.4, 122.1, 121.7, 120.7, 119.7, 119.4, 117.9, 111.3, 50.3, 34.1, 30.6. **IR (neat):** 3285, 1695, 1455, 1434, 1355, 1338, 1263, 1250, 1224, 1186, 1157, 1129, 1108, 1009, 826, 783, 767, 755, 741, 727, 672 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{20}H_{17}NOS$: 319.1031; found 319.1034. **R_F**: 0.7 in 15% ethyl acetate/dichloromethane. The product was obtained as a white solid. **MP**: 204-205 °C.

(*R*)-4-(dibenzo[*b*,*d*]thiophen-4-yl)-4-(1*H*-indol-3-yl)butan-2-one (a92)



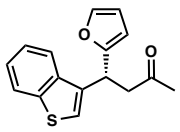
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with a gradient of 0 to 1.5% ethyl acetate in dichloromethane as eluents on silica gel. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-70:30, 0.6 ml/ min, UV-254 detector). Trial 1: 54.6 mg, 0.148 mmol, 74% yield (24 h); Trial 2: 59.7 mg, 0.162 mmol, 81% yield; 98.4:1.6 er (24 h); Trial 3: 60.6 mg, 0.164 mmol, 82% yield; 98.4:1.6 er (24 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.13-8.09 (m, 1H), 8.07 (bs, 1H), 8.00 (dd, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.83-7.80 (m, 1H), 7.44-7.34 (m, 5H), 7.30 (d, *J* = 8.0, 1H), 7.13-7.10 (m, 2H), 6.96 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 5.15 (t, 8.0 Hz, 1H), 3.37 (app. AB d, 2H), 2.14 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 207.4, 139.4, 138.4, 138.2, 136.5, 136.1, 135.8, 126.7, 126.6, 125.2, 124.9, 124.3, 122.7, 122.3, 122.2, 121.6, 119.9, 119.4, 119.3, 116.6, 111.2, 48.4, 37.9, 30.0. **IR (neat):** 3342, 1696, 1458, 1445, 1416, 1403, 1355, 1338, 1290, 1237, 1224, 1101, 1010, 773, 749, 739, 730, 704, 660 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{24}H_{19}NOS$: 369.1187; found 369.1190. **R_F**: 0.81 in 15% ethyl acetate/dichloromethane. The product was obtained as a white solid. **MP**: 181-182 °C.

(*R*)-4-(1-benzyl-1*H*-pyrrol-2-yl)-4-(furan-2-yl)butan-2-one (a103)



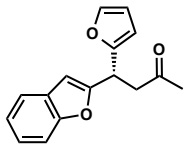
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with a gradient of 5 to 10% diethyl ether in pentanes as eluents on silica gel. HPLC Chiralcel AS-H (hexanes/*i*-PrOH=90:10-80:20, 0.75 ml/ min, UV-254 detector). Trial 1: 46.9 mg, 0.160 mmol, 80% yield (20 h); Trial 2: 49.9 mg, 0.170 mmol, 85% yield; 99.5:0.5 er (14 h); Trial 3: 43.4 mg, 0.148 mmol, 74% yield; 99.3:0.7 er (14 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31-7.23 (m, 4H), 7.00 (d, *J* = 7.5 Hz, 2H), 6.61 (t, *J* = 2.3 Hz, 1H), 6.20-6.19 (m, 1H), 6.15 (t, *J* = 3.4 Hz, 1H), 6.07-6.06 (m, 1H), 5.80 (d, *J* = 3.4 Hz, 1H), 5.07 (dd, *J* = 18.3Hz, 16.0 Hz, 2H). 4.55 (t, *J* = 6.9 Hz, 1H), 3.06 (dd, *J* = 16.7 Hz, 6.9 Hz, 1H), 2.98 (dd, *J* =16.7 Hz, 7.5 Hz, 1H), 2.02 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 206.1, 155.5, 141.4, 138.0, 132.0, 128.6, 127.3, 126.7, 121.7, 110.1, 107.3, 106.3, 105.7, 50.3, 47.8, 31.7, 30.1. **IR (neat):** 2922, 1713, 1586, 1496, 1480, 1453, 1416, 1356, 1292, 1230, 1158, 1072, 1028, 1006, 965, 924, 883, 808 701 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{19}H_{19}NO_2$: 293.1416; found 293.1411. **R_F**: 0.12 in 10% diethyl ether in pentanes. The product was obtained as a yellow solid. **MP**: 90-91 °C.

(*R*)-4-(benzo[*b*]thiophen-3-yl)-4-(furan-2-yl)butan-2-one (a104)



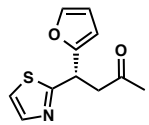
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with 15% ethyl acetate in hexanes as an eluent on silica gel. HPLC Chiralcel AS-H (hexanes/*i*-PrOH=90:10-70:30, 0.75 ml/ min, UV-254 detector). Trial 1: 45.9 mg, 0.170 mmol, 85% yield (21 h); Trial 2: 45.4 mg, 0.168 mmol, 84% yield; 99.2:0.8 er (23 h); Trial 3: 47.0 mg, 0.174 mmol, 87% yield; 99.2:0.8 er (23 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 6.9 Hz, 1.7 Hz, 1H), 7.76 (dd, *J* = 6.9 Hz, 1.7 Hz, 1H), 7.37-7.31 (m, 3H), 7.18 (s, 1H), 6.26 (dd, *J* = 3.4 Hz, 2.3 Hz, 1H), 6.04 (d, *J* = 3.4 Hz, 1H), 5.05 (t, *J* = 7.2 Hz, 1H), 3.34 (dd, *J* = 17.2 Hz, 8.6 Hz, 1H), 3.11 (dd, *J* = 16.2 Hz, 6.3 Hz, 1H), 2.12 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 206.0, 155.1, 141.5, 140.5, 137.7, 136.0, 124.4, 124.1, 122.9, 122.7, 121.8, 110.3, 106.1, 47.3, 34.0, 30.3. **IR (neat):** 1713, 1504, 1426, 1357, 1157, 1007, 761, 729 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{16}H_{14}O_2S$: 270.0715; found 270.0716. **R_F**: 0.55 in 20% ethyl acetate/hexanes. The product was obtained as a yellow oil.

(*S*)-4-(benzofuran-2-yl)-4-(furan-2-yl)butan-2-one (a105)



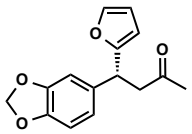
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with 20% diethyl ether in pentane as an eluent on silica gel. HPLC Chiralcel AS-H (hexanes/*i*-PrOH=90:10-70:30, 0.75 ml/ min, UV-254 detector). Trial 1: 46.8 mg, 0.184 mmol, 92% yield (50 h); Trial 2: 47.3 mg, 0.186 mmol, 93% yield; 96.5:3.5 er (47 h); Trial 3: 48.3 mg, 0.190 mmol, 95% yield; 96.2:3.8 er (47 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 1.2 Hz, 1H), 7.22 (td, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.17 (td, *J* = 7.5 Hz, 1.2 Hz, 1H), 6.44 (s, 1H), 6.30 (dd, *J* = 3.4 Hz, 2.3 Hz, 1H), 6.14 (d, *J* = 3.4 Hz, 1H), 4.9 (t, *J* = 7.5 Hz, 1H), 3.28 (dd, *J* = 17.2 Hz, 6.9 Hz, 1H), 3.24 (dd, *J* = 17.2 Hz, 7.5 Hz, 1H), 2.17 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) d 205.3, 157.0, 154.6, 153.2, 141.8, 128.4, 123.7, 122.7, 120.7, 111.0, 110.4, 106.5, 103.2, 45.5, 34.3, 30.2. **IR (neat):** 1707, 1583, 1504, 1454, 1417, 1365, 1299, 1255, 1224, 1189, 1159, 1147, 1135, 1103, 1060, 1031, 1107,, 946, 936, 884, 864, 850, 809, 773, 736 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{16}H_{14}O_3$: 254.0943; found 254.0942. **R_F**: 0.51 in 30% diethyl ether/pentane. The product was obtained as a yellow oil.

(*S*)-4-(furan-2-yl)-4-(thiazol-2-yl)butan-2-one (a106)



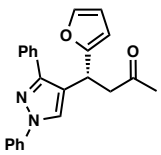
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with a gradient of 0 to 3% ethyl acetate in dichloromethane as eluents on silica gel. HPLC Chiralcel OD-H (hexanes/*i*-PrOH=90:10-70:30, 0.75 ml/ min, UV-254 detector). Trial 1: 39.8 mg, 0.180 mmol, 90% yield (30 h); Trial 2: 42.5 mg, 0.192 mmol, 96% yield; 89.3:10.7 er (30 h); Trial 3: 42.0 mg, 0.190 mmol, 95% yield; 88.8:11.2 er (30 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 2.9 Hz, 1H), 7.33 (d, *J* = 1.2 Hz, 1H), 7.20 (d, *J* = 3.4 Hz, 1H), 6.30 (dd, *J* = 3.4 Hz, 1.7 Hz, 1H), 6.15 (d, *J* = 3.3 Hz, 1H), 5.03 (t, *J* = 6.9 Hz, 1H), 3.53 (dd, *J* = 17.8 Hz, 7.5 Hz, 1H), 3.19 (dd, *J* = 17.8 Hz, 6.3 Hz, 1H), 2.19 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 205.4, 170.3, 153.8, 142.1, 142.1, 119.2, 110.4, 106.8, 46.5, 37.9, 30.2. **IR (neat):** 2921, 2852, 1715, 1500, 1361, 1161, 1146, 1072, 1108, 989, 922, 884, 809, 774, 730 cm^{-1}. **HRMS** (CI) *m/z* (M+H): calculated for $C_{11}H_{12}NO_2S$: 222.0452; found 222.0451. **R_F**: 0.54 in 15% ethyl acetate/dichloromethane. The product was obtained as a yellow oil.

(*R*)-4-(benzo[*d*][1,3]dioxol-5-yl)-4-(furan-2-yl)butan-2-one (a107)



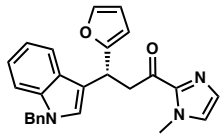
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with 10% ethyl acetate in hexanes as an eluent on silica gel. HPLC Chiralcel AS-H (hexanes/*i*-PrOH=90:10-80:20, 0.75 ml/ min, UV-254 detector). Trial 1: 49.6 mg, 0.192 mmol, 96% yield (23 h); Trial 2: 44.9 mg, 0.174 mmol, 87% yield; 99.1:0.9 er (18 h); Trial 3: 51.1 mg, 0.198 mmol, 99% yield; 99.2:0.8 er (17 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 1.2 Hz, 1H), 6.72-6.68 (m, 3H), 6.25 (dd, *J* = 2.9 Hz, 1.7Hz, 1H), 5.98 (d, *J* = 2.9 Hz, 1H), 5.90-5.89 (m, 2H), 4.50 (t, *J* = 7.5 Hz, 1H), 3.16 (dd, *J* = 16.6 Hz, 7.5 Hz, 1H), 2.95 (dd, *J* = 16.6 Hz, 7.5 Hz, 1H), 2.08 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 206.2, 156.5, 147.7, 146.4, 141.5, 135.5, 120.8, 110.1, 108.2, 108.1, 105.5, 100.9, 48.4, 39.8, 30.5. **IR (neat):** 2921, 1713, 1503, 1485, 1441, 1359, 1239, 1100, 1076, 1158, 1036, 1008, 930, 883, 864, 809, 778, 732 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{15}H_{14}O_4$: 258.0892; found 258.0891. **R_F**: 0.27 in 25% ethyl acetate/hexanes. The product was obtained as a colorless oil.

I-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-4-(furan-2-yl)butan-2-one (a108)



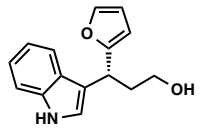
See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with 20% ethyl acetate in hexanes as an eluent on silica gel. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-70:30, 0.6 ml/ min, UV-254 detector). Trial 1: 69.9 mg, 0.196 mmol, 98% yield (50 h); Trial 2: 58.5 mg, 0.164 mmol, 82% yield; 99.5:0.5 er (47 h); Trial 3: 70.6 mg, 0.198 mmol, 99% yield; 99.5:0.5 er (47 h). **^{1}H NMR** (500 MHz, $CDCl_3$) d 7.83 (s, 1H), 7.72-7.69 (m, 2H), 7.65-7.63 (m, 2H), 7.45-7.24 (m, 7H), 6.27-6.26 (m, 1H), 6.01-6.00 (m, 1H), 4.79 (t, *J* = 7.5 Hz, 1H), 3.20 (dd, *J* = 16.6 Hz, 8.0 Hz, 1H). 2.92 (dd, *J* = 16.6 Hz, 6.9 Hz, 1H), 2.05 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) d 205.9, 156.0, 151.3, 141.5, 139.9, 133.1, 129.3, 128.5, 128.3, 128.0, 126.3, 126.3, 121.6, 118.8, 110.3, 105.9, 48.8, 30.6, 30.0. **IR (neat):** 1702, 1597, 1552, 1505, 1450, 1411, 1356, 1335, 1272, 1162, 1069, 1008, 959, 918, 908, 827, 750, 707, 699, 691, 678, 669 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{23}H_{20}N_2O_2$: 356.1525; found 356.1523. **R_F**: 0.33 in 25% ethyl acetate/hexane. The product was obtained as a white solid. **MP**: 94-96 °C.

(*R*)-3-(1-benzyl-1*H*-indol-3-yl)-3-(furan-2-yl)-1-(1-methyl-1*H*-imidazol-2-yl)propan-1-one (a109)



See the general procedure for 1,4-conjugate addition above. The crude reaction mixture was purified via flash column chromatography with a gradient of 0 to 3% ethyl acetate in dichloromethane as eluents on silica gel. HPLC Chiralcel AD-H (hexanes/*i*-PrOH=90:10-50:50, 0.6 ml/ min, UV-254 detector). Trial 1: 74.5 mg, 0.182 mmol, 91% yield (48 h); Trial 2: 78.6 mg, 0.192 mmol, 96% yield; 98.5:1.5 er (48 h); Trial 3: 78.7 mg, 0.192 mmol, 96% yield; 99.8:0.2 er (48 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.30-7.05 (m, 11H), 6.95 (s, 1H), 6.25-6.24 (m, 1H), 6.12-6.11 (m, 1H), 5.27-5.10 (m, 3H), 4.03 (dd, *J* = 16.6 Hz, 8.0 Hz, 1H), 3.86 (dd, *J* = 16.6 Hz, 7.5 Hz, 1H), 3.90 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 190.5, 157.1, 143.0, 141.1, 137.5, 136.5, 129.0, 128.6, 127.4, 127.1, 126.8, 126.6, 126.2, 121.7, 119.5, 119.1, 115.7, 110.0, 109.6, 105.3, 49.9, 43.5, 36.0, 31.8. **IR (neat):** 1732, 1671, 1504, 1495, 1465, 1404, 1356, 1333, 1290, 1266, 1242, 1153, 1076, 1043, 1011, 978, 938, 914, 883, 765, 734, 696 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{26}H_{23}N_3O_2$: 409.1790; found 409.1790. $\mathbf{R_F}$: 0.36 in 5% ethyl acetate/dichloromethane. The product was obtained as a yellow solid. **MP**: 117-118 °C.

(*R*)-3-(furan-2-yl)-3-(1H-indol-3-yl)propan-1-ol (a110)



To a 7 ml vial equipped with a stir bar was added powdered 4 Å molecular sieves (250 mg) and the vial was flamed-dried under high vacuum. The vial was cooled to room temperature and back-filled with Argon. The indole-appended enal (34.4 mg, 0.2 mmol, 1.0 equiv), (*R*)-$(C_7F_7)_2$-BINOL (28.7 mg, 0.04 mmol, 0.2 equiv), potassium furan-2-trifluoroborate salt (0.6 mmol, 3 equiv) were then added. Freshly dried toluene (4 mL) was added. The vial was well sealed by Teflon tape, and the reaction was heated to 80 ºC. The reaction was monitored by TLC analysis. After the reaction is complete, the solution was filtered through a short celite pad and concentrated. The crude reaction mixture was transferred to a flamed-dried flask via anhydrous THF (4 mL) and was cooled down to 0 ºC. $NaBH_4$ (47 mg, 1.2 mmol, 6 equiv) was added. The reaction was slowly warm up to 25 ºC. After 13 hours, water (2 mL) was added. The reaction mixture was extracted with ethyl acetate (3 mL x 3), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give crude product. The crude reaction mixture was purified via flash column chromatography with a gradient of 0 to 3% ethyl acetate in dichloromethane as eluents on silica gel. HPLC Chiralcel AS-H (hexanes/*i*-PrOH = 80:20-50:50, 0.75ml/ min, UV-254 detector). Trial 1: 43.4 mg, 0.180 mmol, 90% yield; Trial 2: 39.6 mg, 0.164 mmol, 82% yield; 98.2:1.8 er; Trial 3: 41.0 mg, 0.170 mmol, 85% yield; 98.2:1.8 er. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (bs, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.33-7.31 (m, 2H), 7.19-7.16 (m, 1H), 7.11-7.04 (m, 2H), 6.28-6.21 (m, 1H), 6.09-6.08 (m, 1H), 4.48 (t, *J* = 7.5 Hz, 1H), 3.69-3.62 (m, 2H), 2.42-2.26 (m,

2H), 1.52 (bs, 1H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) d 157.6, 141.1, 136.4, 126.4, 122.0, 121.8, 119.4, 119.3, 116.6, 111.2, 110.0, 105.3, 61.0, 36.8, 33.0. **IR (neat):** 3409, 1504, 1456, 1419, 1338, 1224, 1144, 1095, 1006, 924, 883, 804, 780, 732 cm^{-1}. **HRMS** (CI) *m/z* (M-H): calculated for $C_{15}H_{15}NO_2$: 240.1025; found 240.1024. **R_F1**: 0.72 in 5% ethyl acetate in dichloromethane (the 1,4-conjugate addition product). **R_F2**: 0.36 in 5% ethyl acetate in dichloromethane (the reduction product). The product was obtained as a orange oil.

1.6 References

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2. STUDIES TOWARD THE SYNTHESIS OF DISCOIPYRROLE D

2.1 Natural Products Discoipyrrole A-D

The structures of discoipyrroles A-D (**b1-4**) were revealed by John B. MacMillan and coworkers in 2013 (Figure 2-1).[1] Bioactivity studies showed that the discoipyrrole family exhibits discoidin domain receptor 2 (DDR2)-dependent inhibition. The unique 3-H-benzo[*d*]pyrrolo[1,3]oxazine-3,5-dione skeleton was found in discoipyrrole A, B and D; discoipyrrole D, however, has an additional 3-indolyl-propylene glycol motif.

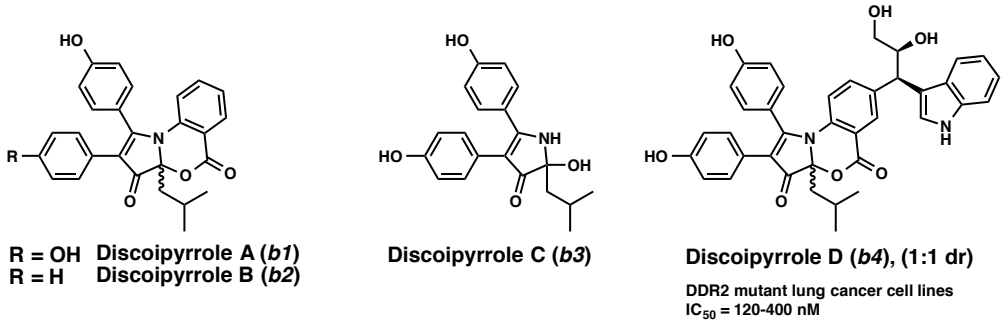


Figure 2-1. Structures of Natural Products Discoipyrrole A-D.

A number of control experiments done by the MacMillan group concluded that the core structure is formed by the growth media of *B. hunanensis*, and it can also be synthesized by Bronsted acid catalyzed three component coupling reaction (Figure 2-2). In addition, a mechanism for the biosynthesis of discoipyrrole A (**b1**) was proposed (Scheme 2-1). Hydroxysattabacin (**b7**) is initially oxidized to a diketone **b8**, which tautomerizes to a more stable enol **b9**. The structure of the enol form was confirmed by isolation from *B. hunanensis*. In the next step, an aldol reaction takes place between enal

b9 and 4-hydroxybenzaldehyde (**b5**), followed by oxidation to produce triketone **b10**. Finally, a series of condensation reactions between anthranilic acid (**b6**) and triketone **b10** generates the iminium ion **b13**, which cyclizes with the participation of the neighboring carboxylic acid group to afford discoipyrrole A (**b1**). However, a possible Mannich-type pathway was also proposed in which an imine is formed from 4-hydroxybenaldehyde (**b5**) and anthranilic acid (**b6**), followed by the addition of enol **b9**.

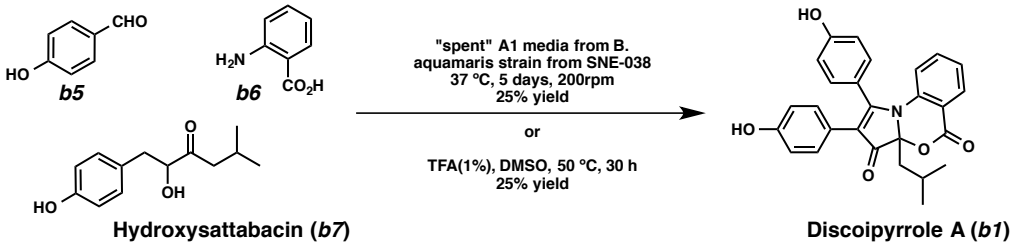
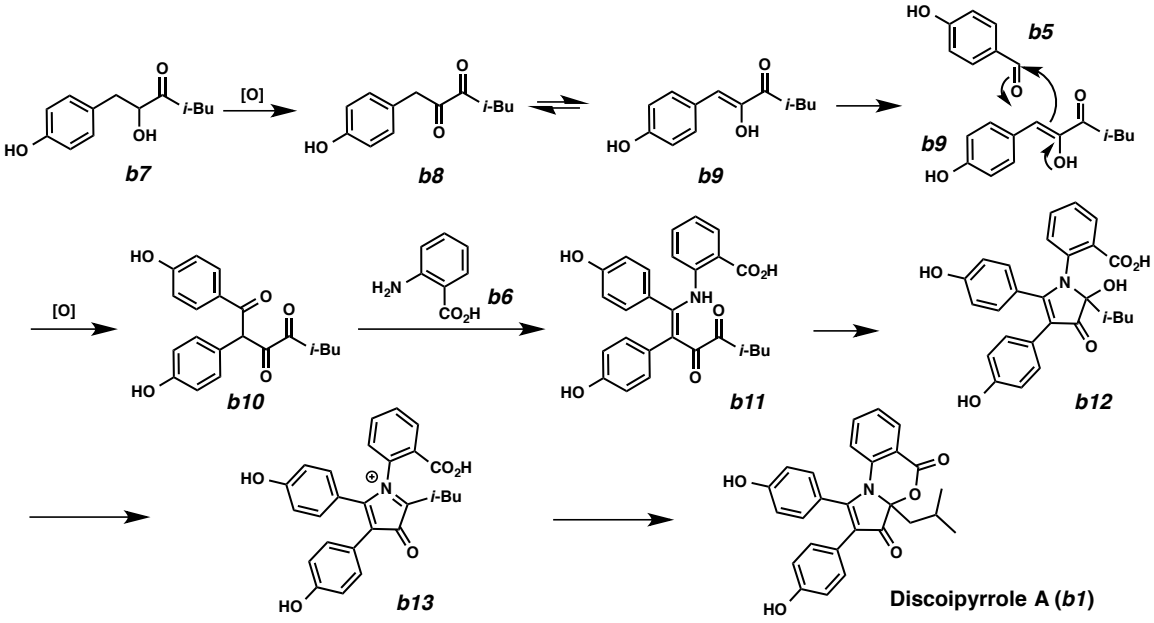


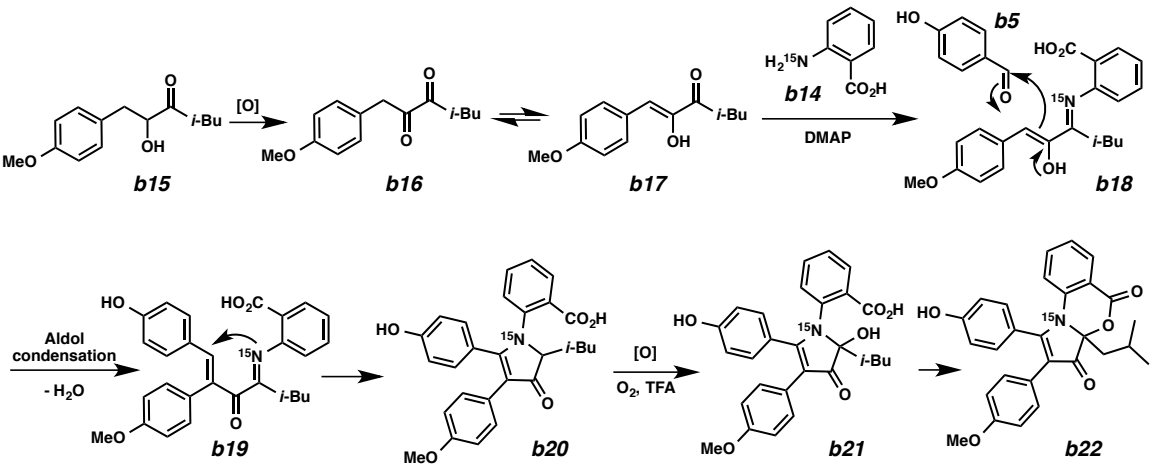
Figure 2-2. Biosynthesis and Organic Synthesis of Discoipyrrole A (**b1**).

Scheme 2-1. The Mechanism Proposed by MacMillan *et al.* for Biosynthesis of **b1** in 2013.



In 2016, MacMillan and coworkers carefully studied the mechanism of this three component coupling reaction using ^{15}N labeled anthranilic acid **b14** as a starting material for the reaction.[2] By continuously monitoring ^{1}H-^{15}N NMR, they directly observed NMR signals of the intermediates in the reaction and revised the mechanism to that proposed in Scheme 2-2. After enol **b17** is generated from the oxidation of methyl hydroxysattabacin **b15**, anthranilic acid (**b14**) condenses with the enol **b17** to produce imine enol **b18**. Next, an aldol condensation with imine enol **b18** and 4-hydroxybenaldehyde (**b5**) leads to the enoneimine **b19**, which quickly cyclized to produce vinylogous amide **b20**. Finally, the second oxidation produces hemiaminal **b21**, which leads to formation of the acid condensation product — methyl discoipyrrole A **b22**.

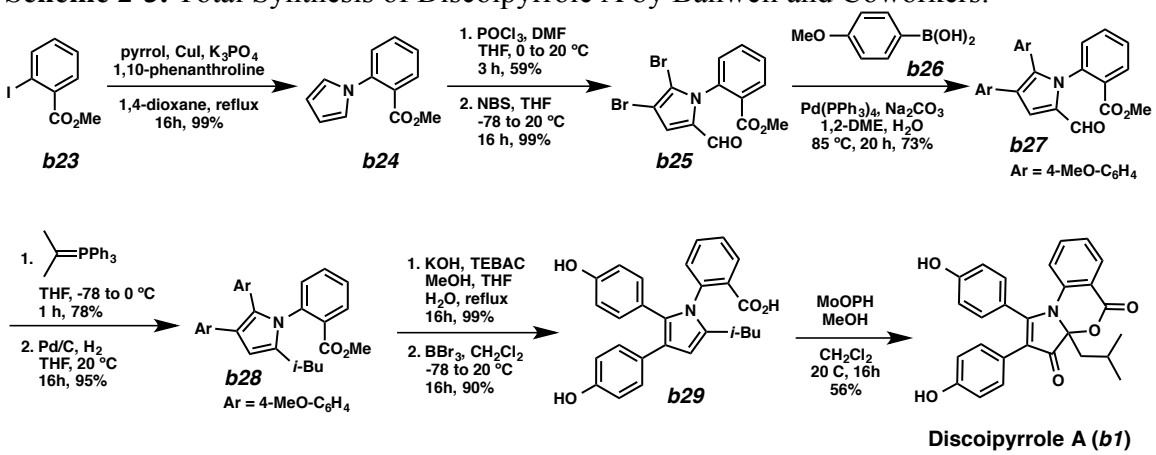
Scheme 2-2. The Revised Mechanism for Formation of **b22**.



Banwell and coworkers reported a synthetic strategy for the discoipyrroles in 2016 that differed from the biosynthesis (Scheme 2-3).[3] Instead of using a three component coupling reaction, they adopted an Ullmann-Goldberg reaction, Suzuki-Miyaura cross coupling, Vilsmeier-Haak formylation, Wittig reaction, and hydrogenation

sequence to synthesize substituted pyrrole **b28**. In the final steps of the synthesis, they removed all of the protecting groups and then used oxoperoxymolybdenum(pyridine) (hexamethylphosphoric triamide) (MoOPH) as an effective oxidant to cyclize discoipyrrole A (**b1**).

Scheme 2-3. Total Synthesis of Discoipyrrole A by Banwell and Coworkers.



2.2 Synthetic Plan for Discoipyrrole D

2.2.1 Retrosynthesis

Discoipyrrole D (**b4**) contains an indolyl propylene glycol motif attached to the hetrocyclic discoipyrrole core. This unique motif is also present in a few other natural products — cytoblastin (**b30**)[4] and mucronatins A (**b31**) and B (**b32**).[5] The efficient methodology mentioned in chapter one was proposed to be a good solution to synthesize these natural products.[6]

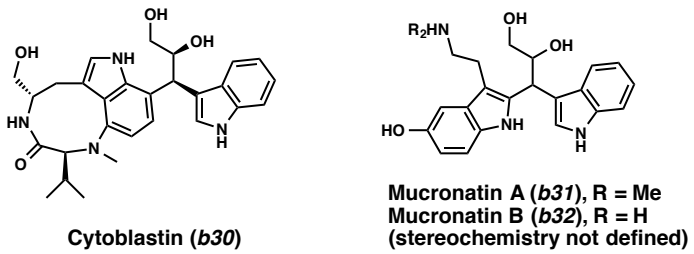
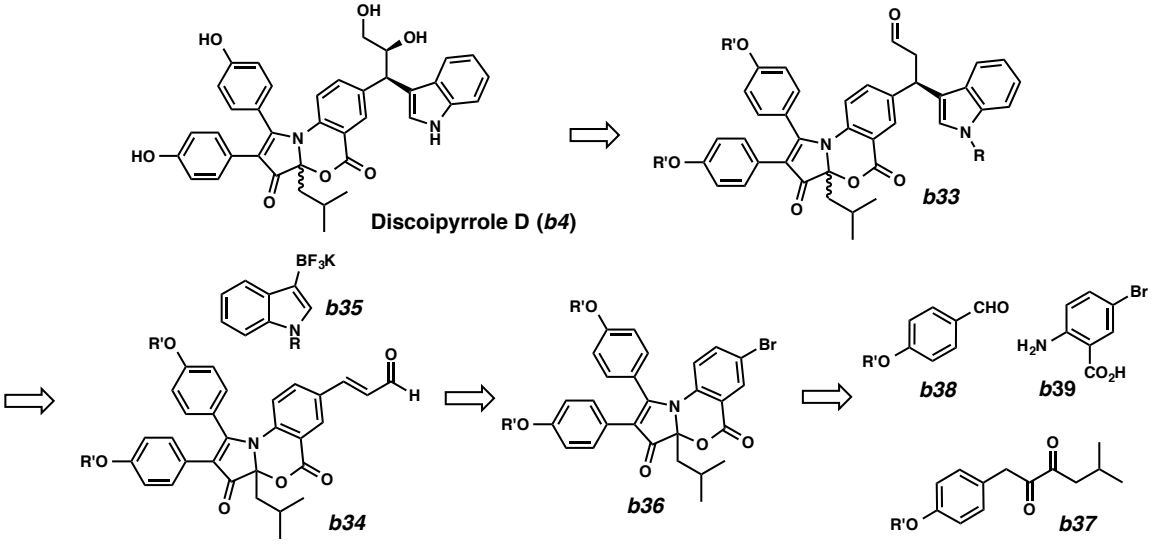


Figure 2-3. Structures of Cytoblastin (**b30**) and Mucronatin A (**b31**) and B (**b32**).

In the retrosynthetic analysis, 3-indole trifluoroborate salts (**b35**) could add in a 1,4-addition to the discoipyrrole enal **b34** to construct the bis-heteroaryl chiral center (see **b33**). In order to finish the synthesis of the 3-indolyl propylene glycol motif, this adduct, aldehyde **b33**, has to be converted to the diol enantioselectively. A synthetic strategy was devised to obtain 22-bromo-discoipyrrole A **b36**, to which an unsaturated aldehyde can be easily introduced via Heck reaction. To shorten the overall synthetic steps, the three-component coupling reaction reported by MacMillan and coworkers was adopted.

Scheme 2-4. Retrosynthesis of Discoipyrrole D (**b4**).

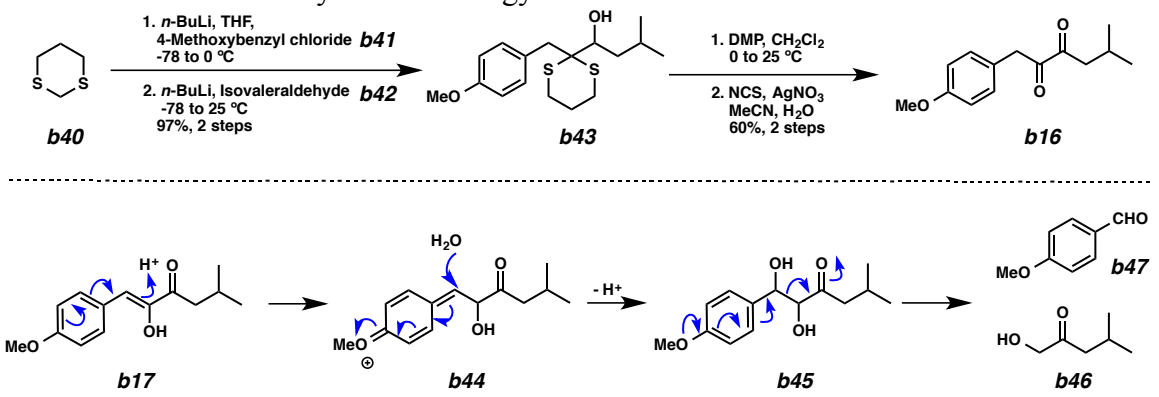


2.2.2 Synthesis of Indolyl Discoipyrrole Aldehyde

Hydroxysattabacin (**b7**) was used in the original three-component coupling reaction. It can be either extracted from bacteria or synthesized in several steps.[7] In addition, it is known that hydroxysattabacin can be oxidized to a diketone prior to reacting with an amino group. As a result, directly using diketone **b16** to the coupling reaction could possibly simplify the reaction.

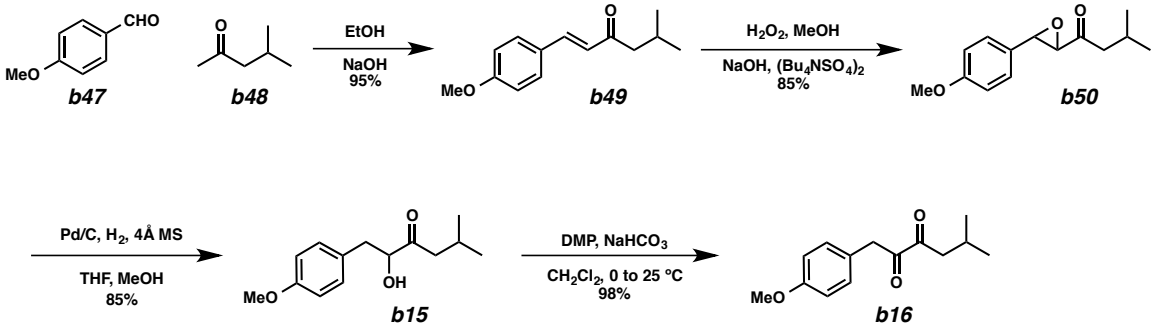
1,3-Dithiane (**b40**) is a useful synthetic reagent in ketone synthesis.[8] It is considered to be a carbonyl synthon but is used as a nucleophile, thus representing an umpolung strategy. The dithiane alcohol **b43** is prepared in high yield after a sequence of nucleophilic substitution/addition in a one pot reaction. Next, the hydroxyl group was oxidized under very mild conditions to provide a ketone, and then the dithiane group was removed by oxidative hydrolysis producing diketone **b16** in moderate yield. However, the diketone **b16** is unstable during silica gel chromatography, during which it can undergo acid catalyzed hydrolysis (Scheme 2-5). This problematic decomposition pathway limits the scale of its synthesis.[1]

Scheme 2-5. The First Synthetic Strategy for Diketone **b16**.



A second synthetic strategy for diketone **b16** was also realized. The enone **b49** is obtained on a multi-gram scale via an aldol condensation between methyl isobutyl ketone (**b48**) and *p*-anisaldehyde (**b47**). Epoxidation [9] of the enone **b49** followed by hydrogenolysis produced hydroxyl ketone **b15**. Finally, the hydroxyl ketone **b15** was oxidized to the diketone **b16** in excellent yield. In this pathway, the diketone **b16** is extracted from the crude reaction mixture with hexanes without column chromatography, which prevents the decomposition from taking place. With this scale up synthesis of the diketone **b16**, our attention turned to the three-component coupling reaction.

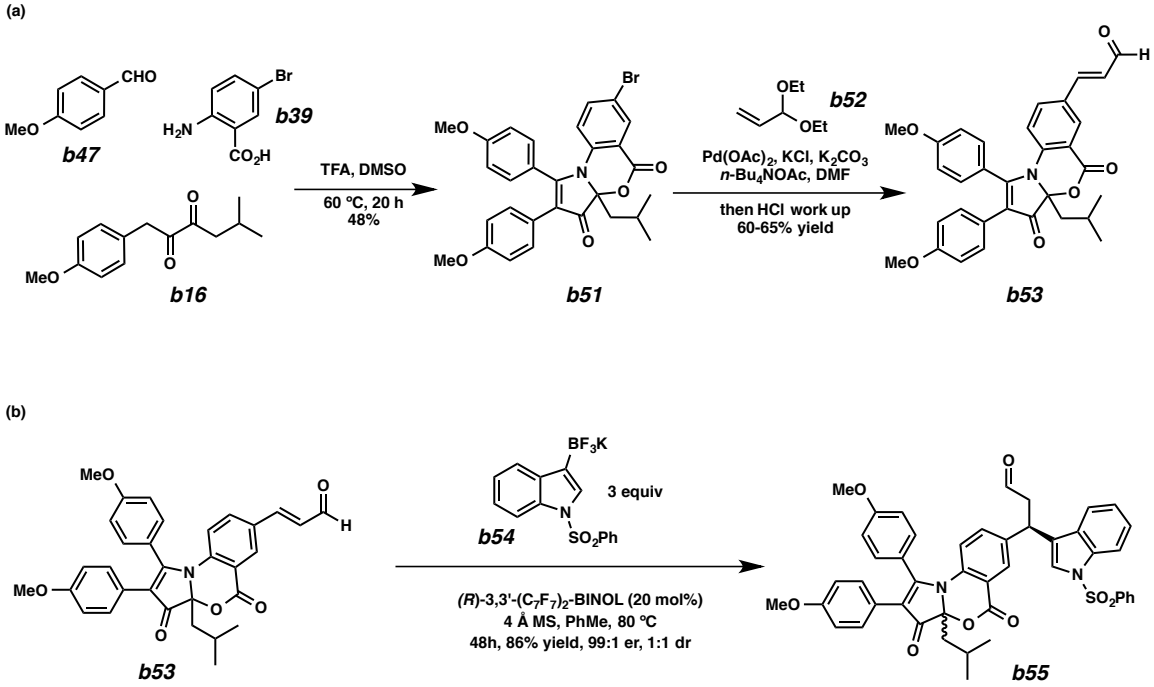
Scheme 2-6. The Second Synthetic Strategy for Diketone **b16**.



A modified three-component coupling reaction provided dimethyl-22-Br-discoipyrrole A **b51** on large scale (Scheme 2-7a). In addition, an unsaturated aldehyde motif was installed successfully via Heck coupling reaction between **b51** and acrolein diethyl acetal **b52** followed by an acidic hydrolysis.[10] Although this discoipyrrole core is highly prone to decomposition, the benzenesulfonyl 3-indole trifluoroborate salt **b54** successfully adds in a conjugate fashion to the discoipyrrole enal **b53** when catalyzed by

(*R*)-3,3'-$(C_7F_7)_2$-BINOL, affording indolyl discoipyrrole aldehyde **b55** in high yield and excellent enantioselectivity.[6]

Scheme 2-7. The Forward Synthesis of Indolyl Discoipyrrole Aldehyde **b55**.



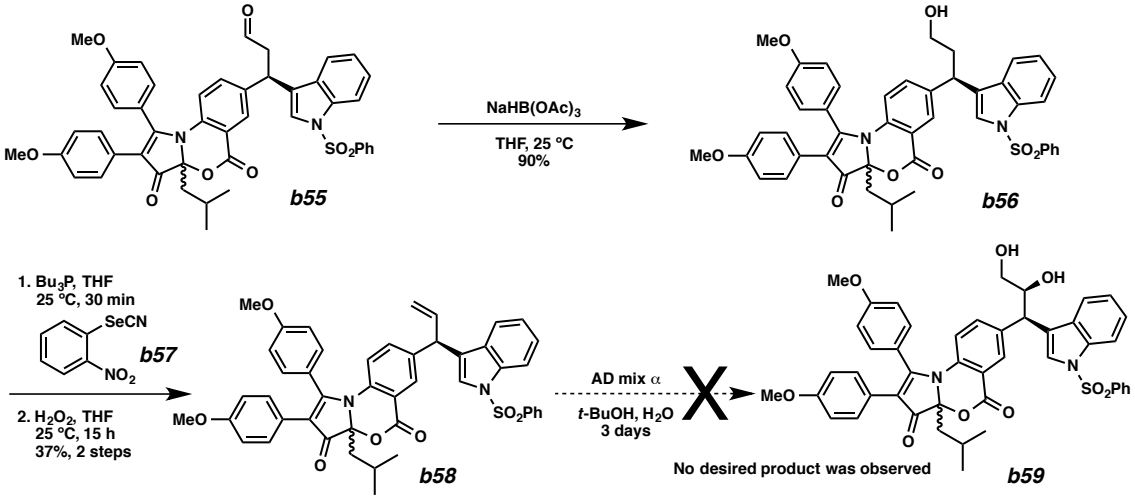
2.2.3 Synthesis of the Indolyl Propylene Glycol

To finish the synthesis of discoipyrrole D, the aldehyde **b55** has to be converted to a diol motif and all protecting groups have to be removed. The first synthetic plan was to convert the aldehyde group of **b55** to a vinyl group, which can be oxidized to a diol enantioselectively. Sharpless asymmetric dihydroxylation of olefins, which is a well-developed method and has been applied to many syntheses,[11] will be employed.

The aldehyde was reduced under mild reaction conditions using sodium triacetoxyborohydride ($NaHB(OAc)_3$), resulting in alcohol **b56**. Sodium borohydride

($NaBH_4$) was also tested as a reductant, but the discoipyrrole core did not tolerate this reagent and underwent decomposition. Next, the vinyl group of **b58** was obtained from the alcohol **b56** using a Grieco elimination.[12] However, Sharpless asymmetric dihydroxylation failed to work with the olefin **b58**, and the desired diol product was not observed. After performing an extensive screening of a large number of different reaction conditions, the discoipyrrole core structure was concluded to be very sensitive towards Lewis acids, amine bases, and hard nucleophiles. So a mild chemoselective and enantioselective oxidation was needed for diol synthesis.

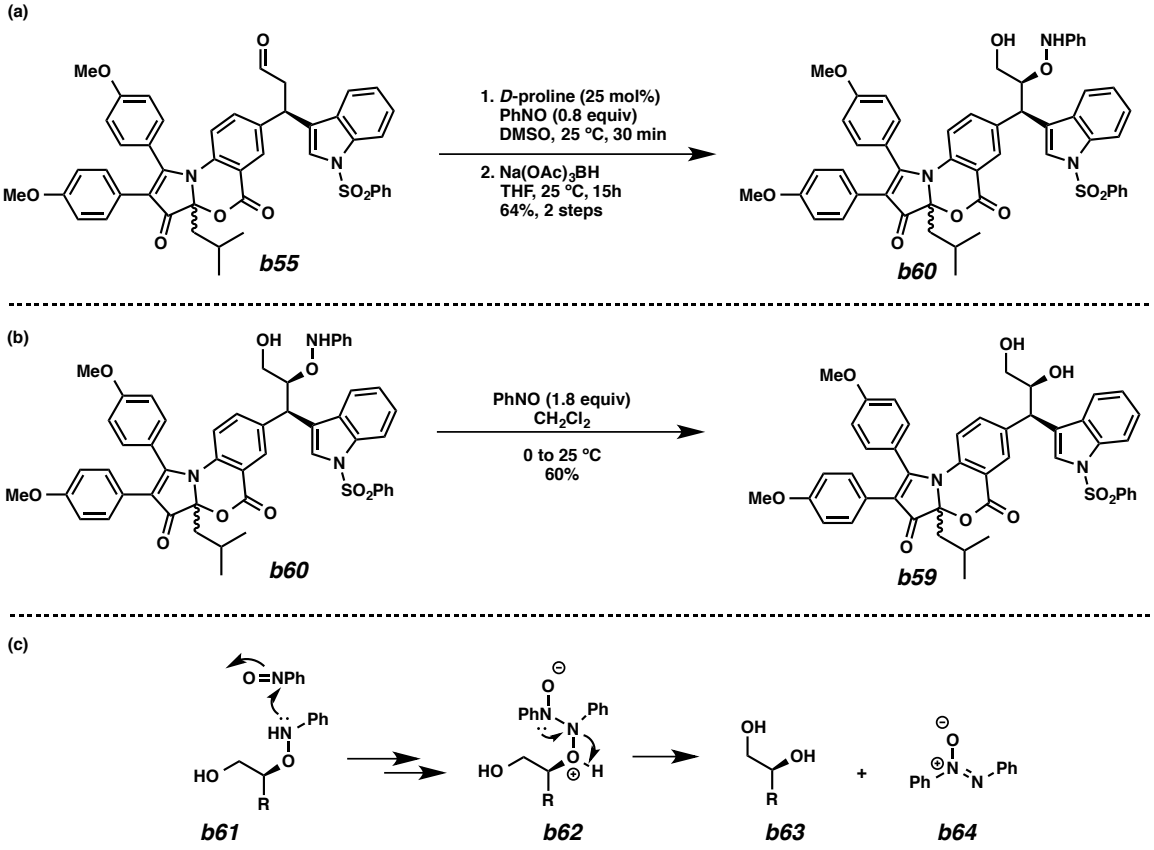
Scheme 2-8. The First Forward Synthesis of the Diol Motif.



A proline controlled α-aminoxylation[13] reaction with aldehyde **b55** kept the discoipyrrole core intact and 2-aminoxy alcohol **b60** was provided in good yield after reduction (Scheme 2-9a). Attempted N-O bond cleavage using zinc or iron under acidic conditions led to complete decomposition of the starting material. Fortunately, addition of nitrosobenzene to 2-aminoxy alcohol **b60** easily cleaved the N-O bond without

destroying the discoipyrrole core and successfully generated diol **b59** (Scheme 2-9b). Nitrosobenzene is believed to act as an electrophile by attacking the nitrogen atom of the substrate (Scheme 2-9c). After proton exchange, trans-azoxybenzene **b64** was eliminated and the diol motif **b63** was generated.[13c]

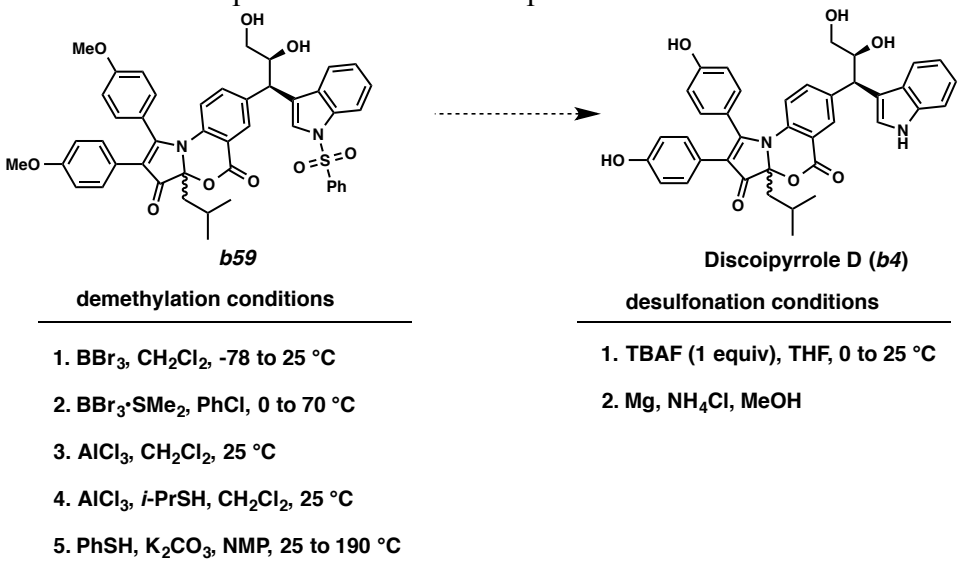
Scheme 2-9. The Second Forward Synthesis of the Diol Motif.



Global deprotection was supposed to be the final stage of the synthesis. Unfortunately, after numerous attempts, neither the methyl groups nor benzenesulfonyl group could be removed (scheme 2-10).[14] In order to complete the synthesis, either the protecting groups have to be modified at earlier steps or the synthetic plan for

discoipyrrole D needs to be redesigned. Nonetheless, we have proven our synthetic strategy viable and very straightforward by synthesizing protected discoipyrrole D **b4** in a highly convergent manner.[6]

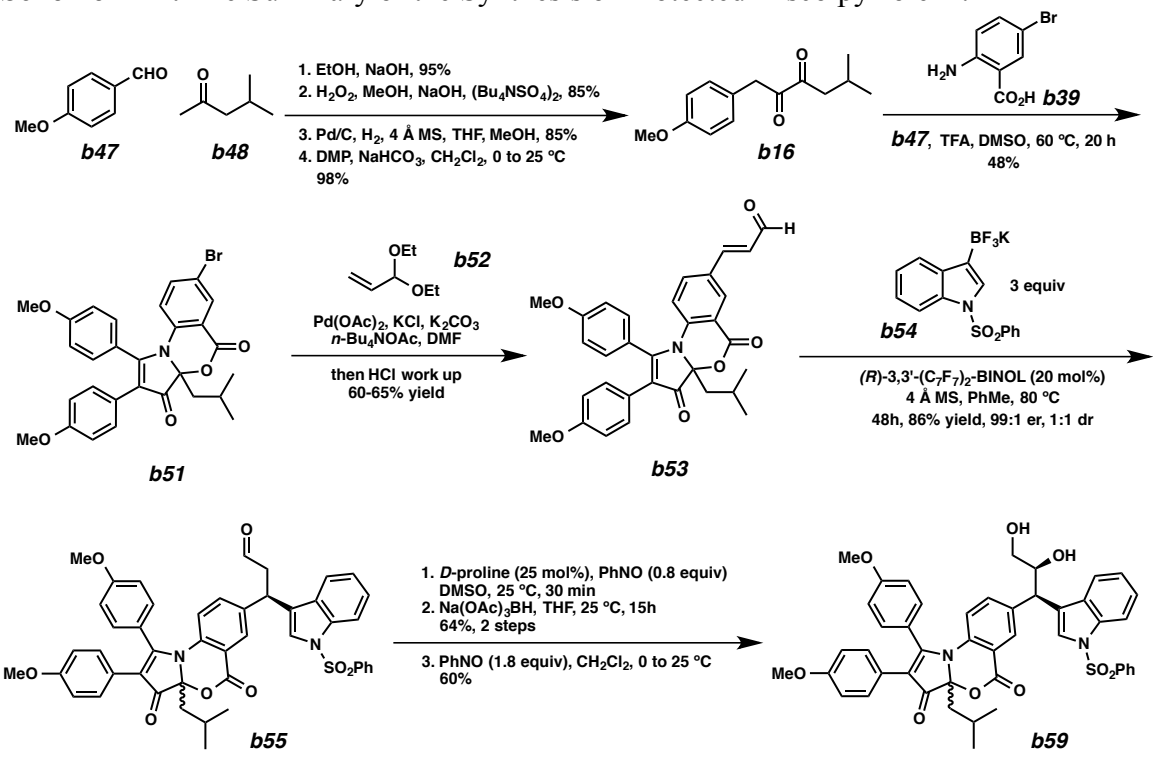
Scheme 2-10. The Attempted Conditions for Deprotection.



2.3 Conclusions and Future Approach

The key intermediate in the three component coupling reaction, diketone **b16**, can be prepared on large scale for discoipyrrole core synthesis. The methodology mentioned in chapter one was successfully applied to synthesize the bisheterocyclic stereocenter in aldehyde **b55**, linking a discoipyrrole core and a 3-indole group. In addition, the diol **b59** was synthesized by a proline-controlled oxidation, followed by a series of reductions.

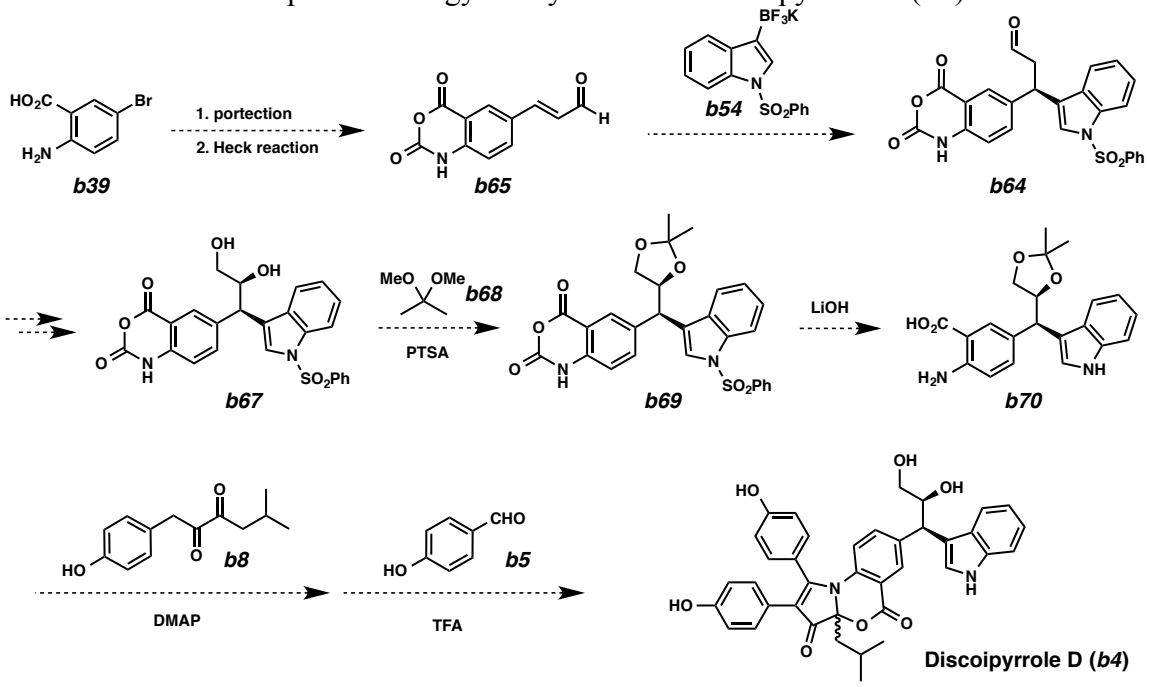
Scheme 2-11. The Summary of the Synthesis of Protected Discoipyrrole D.



At the end of the synthesis, a lot of difficulties with removal of protecting groups were encountered. Unfortunately, the employment of acetyl, benzoyl or silyl protecting groups on the starting materials instead of the methyl ethers leads to synthetic incompatibility and cross-reactivity later on in the synthesis; therefore these groups are not compatible with the strategy as well. Moreover, an additional problem is that the discoipyrrole core is very sensitive towards a number of Lewis acids and general basic conditions. In order to keep this fragile core intact, it would be a good idea to synthesize it in the final step. So a third synthetic plan is proposed and shown in Scheme 2-12. In this synthetic route, the 3-indolyl propylene glycol will be built up on the amino benzoic acid first. The diol motif in **b69** has to be protected as an acetal prior to the three component coupling reaction in order to avoid side reactions. In 2016 MacMillan and

coworkers reported that trifluoroacetic acid is mild enough reagent to be used in the second step of the coupling reaction, and it could also promote hydrolysis of the acetal group (**b4**) in the same reaction to finish the discoipyrrole D (**b4**).

Scheme 2-12. The Proposed Strategy for Synthesis of Discoipyrrole D (**b4**).



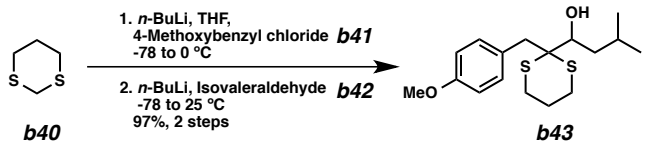
2.4 Experimental

2.4.1 Materials and Methods

All reactions were carried out in flame- or oven-dried glassware. Dichloromethane, diethyl ether, tetrahydrofuran, and toluene were purged with argon and dried over activated alumina columns. Flash chromatography was performed on 60 Å silica gel (EMD Chemicals Inc). Preparative plate chromatography was performed on EMD silica gel plates, 60 Å, with UV-254 indicator. Chemical names were generated

using CambridgeSoft ChemBioDraw Ultra 12.0. Analysis by HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Chiralpak or Chiralcel (250 mm x 4.6 mm) column (see below for column details). Analytical thin-layer chromatography was performed on EMD silica gel/TLC plates with fluorescent detector 254 nm. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer using the residual solvent peak as an internal standard ($CDCl_3$: 7.24 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR). Hexafluorobenzene (δ = -164.9 ppm) was employed as an external standard in ^{19}F NMR spectra. HRMS analyses were performed under contract by UT Austin's mass spectrometric facility via ESI methods on a US10252005 instrument. **HPLC columns for separation of enantiomers**: Chiralpak ID: Amylose tris-(3-chlorophenylcarbamate) immobilized on 5 μm silica gel. **Materials**: Commercially available compounds were purchased from Sigma-Aldrich Chemical Co., Oakwood Chemical, Acros Organics, Alfa Aesar, Matrix Scientific or TCI America and were used without further purification.

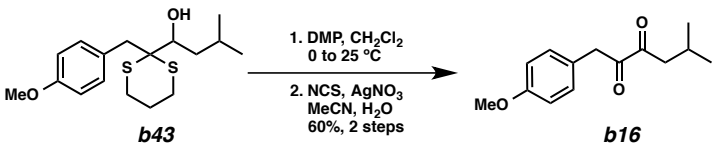
2.4.2 Synthesis of Compounds



1-(2-(4-methoxybenzyl)-1,3-dithian-2-yl)-3-methylbutan-1-ol (b43)

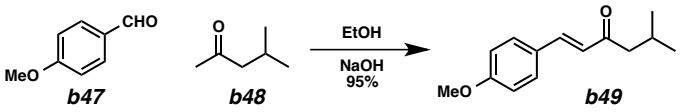
To a flame-dried 100 mL round-bottom flask was added 1,3-dithiane **b40** (721 mg, 6 mmol, 1 equiv) and THF (40 mL). The reaction was cooled to -78 °C. After the solution

was stirred for 10 min, *n*-BuLi (2.5 M, 2.9 mL, 7.2 mmol, 1.2 equiv) was added into the reaction. The solution was slowly warmed to 0 °C for 20 min. The reaction was cooled back to -78 °C, and 4-methyoxybenzyl chloride **b41** (1.2 mL, 8.4 mmol, 1.4 equiv) was added. The reaction was slowly warmed to 0 °C for 1 h. Next, the reaction was cooled down to -78 °C, and *n*-BuLi (2.5 M, 3.6 mL, 9 mmol, 1.5 equiv) was added. The reaction was slowly warmed to 0 °C for 20 min. The reaction was cooled back to -78 °C, and isovaleraldehyde **b42** (1.3 mL, 12 mmol, 2 equiv) was added. The reaction was slowly warmed to 25 °C for 2 h. The reaction was quenched with adding saturated NH_4Cl solution (40 mL). The mixtures were extracted with ethyl acetate (40 mL x3). The organics was washed with brine, dried over $MgSO_4$, filtered through a celte pad, and concentrated. The crude product was purified by column chromatography on silica gel with a gradient of 15 to 20 % ethyl acetate in hexane as eluents. The product was obtained as a white solid. (1.9 g, 97% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.12 (d, *J* = 9.6 Hz, 1H), 3.77 (s, 3H), 3.11 (d, *J* = 14.6 Hz, 1H), 2.93 (ddt, *J* = 14.7, 11.3, 3.6 Hz, 2H), 2.81 (d, *J* = 14.6 Hz, 1H), 2.52 (dt, *J* = 14.3, 4.3 Hz, 2H), 2.00–1.76 (m, 3H), 1.76 (s, 1H), 1.52 (ddd, *J* = 13.5, 10.1, 3.6 Hz, 1H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.38, 132.10, 127.75, 112.81, 69.62, 59.83, 54.97, 39.05, 38.97, 25.87, 25.78, 25.04, 23.97, 23.70, 21.58. **IR(neat)** 3435, 2942, 1583, 1496, 1366, 1275, 1248, 1173, 1066, 1280, 831, 812, 768 cm^{-1}. **HRMS** (ESI) *m/z* (M+Na): calculated for $C_{17}H_{26}O_2S_2$: 429.1266; found 339.1258. **R_F**: 0.36 in 35% ethyl acetate/hexane. **MP**: 60-62 °C



b43 b16

To a flame-dried 100 mL round-bottom flask was added alcohol **b43** (1.9 g, 5.82 mmol, 1 equiv), CH_2Cl_2 (22 mL), and the mixture was cooled to 0 °C. Dess-Matin periodinane (1.7g, 3.9 mmol, 1.3 equiv) was added to the reaction in one portion. After the TLC analysis showed no starting material, the reaction was filtered through a celite pad and concentrated. To the crude reaction mixture was then added MeCN (93 mL) and water (33 mL). *N*-chlorosuccinimide (2 g, 15 mmol, 5 equiv) and $AgNO_3$ (2.56 g, 15 mmol, 5 equiv) were then added. The reaction was stirred for 15 min. To the solution was added 10% $Na_2S_2O_{3(aq)}$ (40 mL), saturated $NaHCO_{3(aq)}$ (40 mL), brine (40 mL). The solution was extracted with ethyl acetate (100 mL x 3). The organics was washed with brine, dried over $MgSO_4$, filtered through a celite pad, and concentrated. The crude product was purified by column chromatography on silica gel with a gradient of 5 to 10 % ethyl acetate in hexane as eluents. $\mathbf{R_F}$: 0.27 in 10% ethyl acetate/hexane.

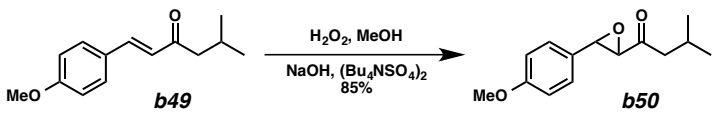


b47 b48 b49

(*E*)-1-(4-methoxyphenyl)-5-methylhex-1-en-3-one (b49)

To a solution of *p*-anisaldehyde (6 mL, 50 mmol, 1 equiv) and isobutyl methyl ketone (7.6 mL, 60 mmol, 1.2 equiv) in ethanol (50 mL) was add water (10 mL) and 2.5N $NaOH_{(aq)}$ (20 mL) at 0 ºC. The reaction was warmed up to room temperature and stirred for 24 hours. The reaction mixture was cooled down to 0 ºC, and 2.5 N $HCl_{(aq)}$ was added

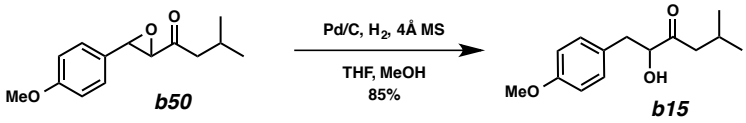
slowly to the mixture until pH = 7. The crude reaction was concentrated via rotary evaporation. The crude product was recovered by filtration. The collect product was washed with cold ethanol and water to give pure (*E*)-1-(4-methoxyphenyl)-5-methylhex-1-en-3-one as light yellow solid. (10.5 g, 47.5 mmol, 95% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47–7.43 (m, 3H), 6.86 (m, 2H), 6.57 (d, *J* = 16.0 Hz, 1H), 3.77 (s, 3H), 2.45 (d, *J* = 6.9 Hz, 2H), 2.21–2.13 (m, 1H), 0.92 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 200.2, 161.4, 142.1, 129.8, 127.0, 124.2, 114.2, 55.2, 49.6, 25.2, 22.6. **IR (neat):** 2955, 1682, 1592, 1509, 1463, 1442, 1420, 1364, 1320, 1300, 1255, 1172, 1144, 1108, 1060, 1026, 988, 965, 893, 845, 832, 809, 771, 687 cm^{-1}. **HRMS** (CI) *m/z* (M+H): calculated for $C_{14}H_{19}O_2$: 219.1385; found 219.1381. **MP**: 40-41 °C.



1-(3-(4-methoxyphenyl)oxiran-2-yl)-3-methylbutan-1-one (b50)

To a stirred solution of (*E*)-1-(4-methoxyphenyl)-5-methylhex-1-en-3-one (5.46 g, 25 mmol, 1 equiv) in methanol (100 mL) was added tetrabutylammonium peroxydisulfate (16.7 g, 25 mmol, 1 equiv), H_2O_2 (2.5 mL, 25 mmol, 30% in H_2O) and NaOH (1 g, 25 mmol, 1 equiv) at 25 °C. The reaction mixture was stirred for 12 hours. To the reaction was added saturated NH_4Cl solution (100 mL) and the mixture was extracted with diethyl ether (100 mL x 6). The combined ethereal layers were washed with brine, dried over anhydrous $MgSO_4$, filtered through a celite pad, and concentrated via rotary evaporation to give pure 1-(3-(4-methoxyphenyl)oxiran-2-yl)-3-methylbutan-1-one as white solid. (4.98 g, 21.3 mmol, 85% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 9.2 Hz, 2H),

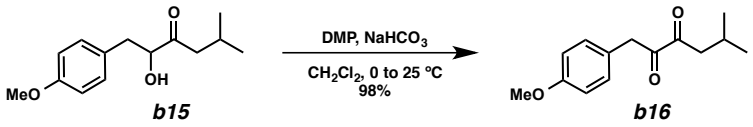
6.86 (d, *J* = 8.7 Hz, 2H), 3.88 (d, *J* = 1.8 Hz, 1H), 3.78 (s, 3H), 3.47 (d, *J* = 1.8 Hz, 1H), 2.41 (dd, *J* = 16.0, 6.4 Hz, 1H), 2.29–2.14 (m, 2H), 0.94–0.92 (m, 6H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 205.9, 160.1, 127.0, 127.0, 114.1, 63.2, 57.8, 55.3, 46.5, 24.1, 22.6, 22.5. **IR (neat):** 2958, 1701, 1610, 1584, 1513, 1469, 1440, 1366, 1307, 1293, 1248, 1200, 1114, 1087, 1061, 1029, 898, 880, 849, 834, 818, 797, 749, 723 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{14}H_{18}O_3$: 234.1256; found 234.1252. **MP**: 95-97 °C.



2-hydroxy-1-(4-methoxyphenyl)-5-methylhexan-3-one (b15)

To a 250 mL flask equipped with a stir bar was added powdered 4 Å molecular sieves (5 g) and the flask was flamed-dried under high vacuum. The flask was cooled to room temperature and back filled with argon. 1-(3-(4-methoxyphenyl)oxiran-2-yl)-3-methylbutan-1-one (4.7 g, 20 mmol, 1 equiv), THF (80 mL), methanol (40 mL), and 10% palladium/carbon catalyst (1 g, 0.05 equiv) were added carefully. The mixture was saturated by hydrogen gas and stirred under hydrogen atmosphere for 3 hours. The mixture was filtered through a celite pad, and the filter was wash with ethyl acetate (250 mL). The crude reaction mixture was concentrated and purified via flash column chromatography on silica gel with a gradient of 10 to 15% ethyl acetate in hexanes as eluents. The product was obtained as a yellow oil. (4.5 g, 19 mmol, 95% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.15–7.11 (m, 2H), 6.83–6.81 (m, 2H), 4.34–4.29 (m, 1H), 3.77 (s, 3H), 3.39 (d, *J* = 5.5 Hz, 1H), 3.06 (dd, *J* = 14.2 Hz, 4.1 Hz, 1H), 2.76 (dd, *J* = 14.2, 7.3

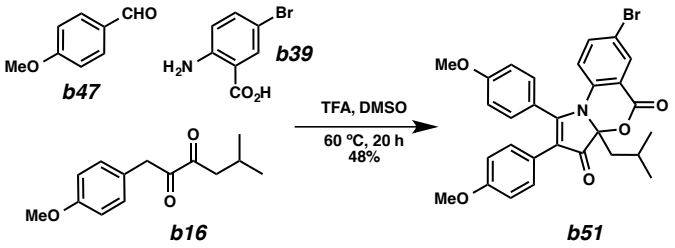
Hz, 1H), 2.35 (d, J = 6.9 Hz, 2H), 2.21–2.11 (m, 1H), 0.90 (d, J = 6.4 Hz, 6H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 211.3, 158.5, 130.3, 128.5, 113.9, 55.2, 47.4, 39.1, 24.6, 22.6, 22.6. **IR (neat):** 3467, 2956, 2871, 2836, 1708, 1611, 1584, 1511, 1465, 1441, 1398, 1366, 1299, 1245, 1177, 1112, 1033, 949, 826, 758 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{14}H_{20}O_3$: 236.1412; found 236.1411. **R_F**: 0.3 in 15% ethyl acetate/hexanes.



1-(4-methoxyphenyl)-5-methylhexane-2,3-dione (b16)

To a 100 mL flame-dried flask was add 2-hydroxy-1-(4-methoxyphenyl)-5-methylhexan-3-one **b15** (2.88 g, 12.2 mmol, 1 equiv), dichloromethane (50 mL), and sodium bicarbonate (1.23 g, 14.6 mmol, 1.2 equiv). The reaction was cooled down to 0 ºC and stirred for 5 minutes. Dess-Martin periodinane (6.2 g, 14.6 mmol, 1.2 equiv) was added into the solution. The reaction was warmed up to room temperature and stirred for 4 hours. The reaction mixture was filtered through a celite pad and concentrated. The crude mixture was dissolved in hexanes (100 mL) and the solution was filtered through a celite pad. The filter was washed with hexanes (50 mL) three times. The organic solution was concentrated and the pure diketone product was obtained as a yellow oil. (2.8 g, 12.0 mmol, 98% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.10 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.0 Hz, 2H), 3.95 (s, 2H), 3.77 (s, 3H), 2.55 (d, J = 6.9 Hz, 2H), 2.07–1.99 (m, 1H), 0.84 (d, J = 6.3 Hz, 6H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 199.7, 196.5, 158.7, 130.7, 124.0, 114.1, 55.0, 44.8, 41.7, 24.0, 22.3. **IR (neat):** 2958, 2872, 1705, 1598, 1577, 1511, 1465,

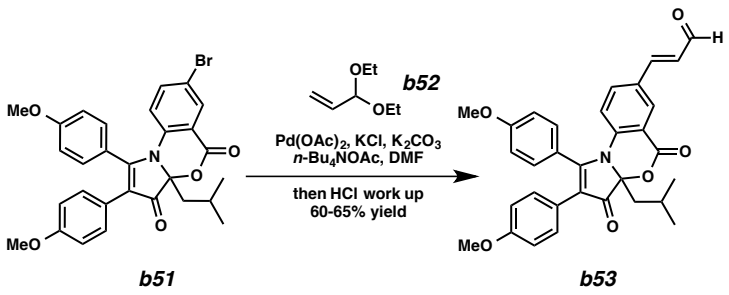
1426, 1368, 1301, 1248, 1216, 1159, 1108, 1030, 945, 831, 766, 680 cm^{-1}. **HRMS** (CI) *m/z* (M+): calculated for $C_{14}H_{18}O_3$: 234.1256; found 234.1251. $\mathbf{R_F}$: 0.42 in 10% ethyl acetate/hexanes. *Note:* Diketone **b16** is not stable through column chromatography on silica gel.



7-bromo-3a-isobutyl-1,2-bis(4-methoxyphenyl)-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-3,5(3a*H*)-dione (b51)

To a 25 mL flame-dried flask was added 2-amino-5-bromobenzoic acid (**b39**, 432 mg, 2 mmol, 2 equiv), *p*-anisaldehyde (**b47**, 0.25mL, 2 mmol, 2 equiv), 1-(4-methoxyphenyl)-5-methylhexane-2,3-dione (**b16**, 234.3 mg, 1 mmol, 1 equiv), and DMSO (3 mL) at 25 °C. The reaction was stirred for 5 min, and trifluoroacetic acid (0.6 mL, 7.8 mmol, 7.8 equiv) was added into the reaction. The reaction was heated to 60 ºC. After 22 hours, the reaction was cooled down and diluted with dichloromethane (10 mL), and water (10 mL). The reaction mixture was extracted with dichloromethane (10 mL x 3). The organics was dried over anhydrous $MgSO_4$, filtered though a celite pad, and concentrated. The crude reaction mixture was then dry-loaded onto silica gel and purified via flash column chromatography on silica gel with a gradient of 10 to 20% ethyl acetate in hexanes as eluents. The product was obtained as a yellow solid. (263 mg, 0.48 mmol, 48% yield) Note: a gradient of 1 to 2% ethyl acetate in toluene or 1% ethyl acetate in

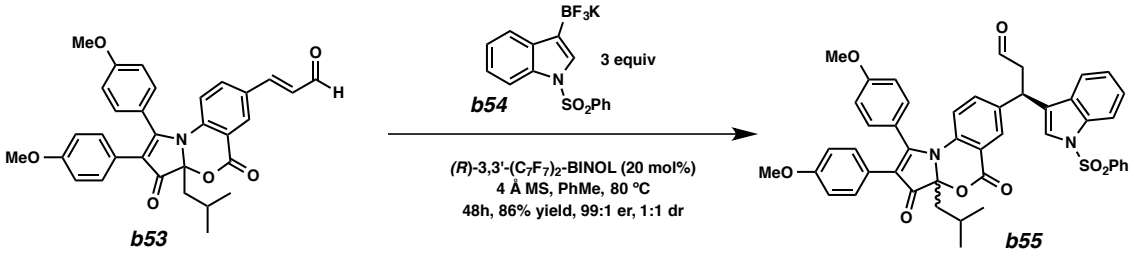
dichloromethane were used as eluents in some cases to obtain clean product. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 2.3 Hz, 1H), 7.38 (dd, *J* = 8.6 Hz, 2.3 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.9 (d, *J* = 9.2 Hz, 2H), 6.7 (d, *J* = 9.2 Hz, 2H), 6.16 (d, *J* = 8.6 Hz, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 2.32 (dd, *J* = 14.3 Hz, 5.7 Hz, 1H), 1.93 (dd, *J* = 14.3 Hz, 6.9 Hz, 1H), 1.76-1.70 (m, 1H), 0.92 (d, *J* = 6.3 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 193.8, 167.9, 161.3, 160.6, 158.5, 137.4, 136.3, 133.4, 130.1, 130.0, 123.3, 121.2, 120.9, 119.5, 117.6, 115.5, 114.7, 113.6, 91.1, 55.4, 55.1, 41.7, 24.0, 23.8, 22.9. **IR (neat):** 1733, 1701, 1607, 1596, 1577, 1518, 1476, 1366, 1292, 1250, 1220, 1173, 1066, 1022, 842, 824, 804, 767 cm^{-1}. **HRMS** (CI) *m/z* (M+H): calculated for $C_{29}H_{27}{}^{81}BrNO_5$: 550.1052; found 550.1046. (CI) *m/z* (M+H): calculated for $C_{29}H_{27}{}^{79}BrNO_5$: 548.1073; found 548.1060. (CI) *m/z* (M+): calculated for $C_{29}H_{26}{}^{81}BrNO_5$: 549.0974; found 549.1003. (CI) *m/z* (M+): calculated for $C_{29}H_{26}{}^{79}BrNO_5$: 547.0994; found 547.0994. **R_F**: 0.21 in 20% ethyl acetate/hexanes; 0.33 in 3% ethyl acetate/toluene. **MP**: 165-166 °C.



(*E*)-3-(3a-isobutyl-1,2-bis(4-methoxyphenyl)-3,5-dioxo-3,3a-dihydro-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazin-7-yl)acrylaldehyde (b53)

To a 20 mL flame-dried vial was added **(±)-b51** (274.2 mg, 0.5 mmol, 1 equiv), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv), KCl (37.3 mg, 0.5 mmol, 1 equiv), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol, 0.2 equiv), $(n\text{-Bu})_4NOAc$ (151 mg, 0.5 mmol, 1 equiv) and degased DMF (4 mL) at room temperature. To the reaction was then added acrolein diethyl acetal (0.4 mL, 2.62 mmol, 5.2 equiv) and the reaction was heated to 80 ºC. After 16 hours, the reaction was cooled down to room temperature and 2.5N $HCl_{(aq)}$ (4 mL) was added. The reaction was stirred for 30 minutes and then extracted with ethyl acetate (10 mL x3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, and filtered through a celite pad. The crude reaction mixture was then dry-loaded onto silica gel and purified via flash column chromatography on silica gel with a gradient of 15 to 25% ethyl acetate in hexanes as eluents. The product was obtained as a yellow solid. (170.5 mg, 0.33 mmol, 65% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.66 (d, *J* = 7.5 Hz, 1H), 8.21 (d, *J* = 2.3 Hz, 1H), 7.48 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.38 (d, *J* = 16.0 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 2H), 7.07–7.04 (m, 2H), 6.96–6.94 (m, 2H), 6.74–6.70 (m, 2H), 6.63 (dd, *J* = 16.0 Hz, 7.5 Hz, 1H), 6.32 (d, *J* = 8.6 Hz, 1H), 3.85 (s, 3H), 3.72 (s, 3H), 3.32 (dd, *J* = 14.3 Hz, 5.7 Hz, 1H), 1.95 (dd, *J* = 13.8 Hz, 6.9 Hz, 1H), 1.79–1.70 (m, 1H), 0.92 (d, *J* = 6.3 Hz, 3H),

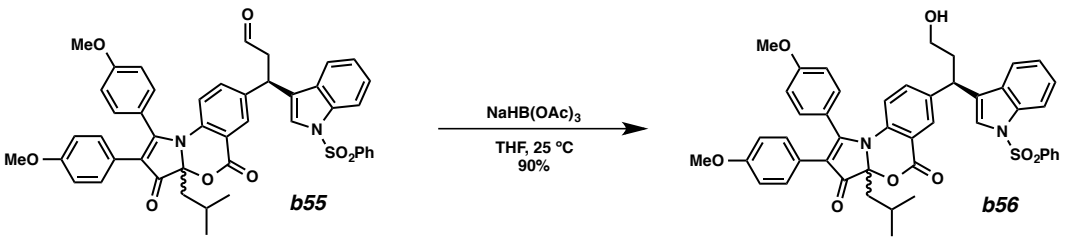
0.81 (d, J = 6.3 Hz, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 193.7, 193.0, 167.2, 161.3, 161.1, 158.6, 149.7, 139.0, 133.2, 131.4, 130.1, 130.0, 130.0, 129.0, 121.8, 121.0, 120.8, 118.1, 116.2, 114.8, 113.7, 90.1, 55.4, 55.1, 42.2, 23.9, 23.9, 22.9. **IR (neat):** 1738, 1675, 1606, 1582, 1519, 1495, 1464, 1433, 1384, 1291, 1248, 1172, 1117, 1087, 1066, 1025, 971, 833, 807, 789, 770 cm^{-1}. **HRMS** (CI) *m/z* (M+H): calculated for $C_{32}H_{30}NO_6$: 524.2073; found 524.21. (CI) *m/z* (M+): calculated for $C_{32}H_{29}NO_6$: 523.1995; found 523.1992. **R_F**: 0.33 40% ethyl acetate/hexane. **MP**: 110-112 °C.



(3*R*)-3-(3a-isobutyl-1,2-bis(4-methoxyphenyl)-3,5-dioxo-3,3a-dihydro-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazin-7-yl)-3-(1-(phenylsulfonyl)-1*H*-indol-3-yl)propanal (b55)

To a 7 mL vial equipped with a stir bar was added powdered 4 Å molecular sieves (250 mg) and the vial was flamed-dried under high vacuum. The vial was cooled to room temperature and back-filled with Argon. The enal **(±)-b53** (52.3 mg, 0.1 mmol, 1.0 equiv), (*R*)-3,3'-$(C_7F_7)_2$-BINOL (14.4 mg, 0.02 mmol, 0.2 equiv), potassium 1-(phenylsulfonyl)-3-indoletrifluoroborate (**b54**, 109 mg, 0.3 mmol, 3 equiv) were then added. Freshly dried toluene (2 mL) was added. The vial was well sealed by Teflon tape, and the reaction was heated to 80 ºC. After 48 hours, the solution was filtered through a short celite pad and concentrated. The crude reaction mixture was then dry-loaded onto silica gel and purified

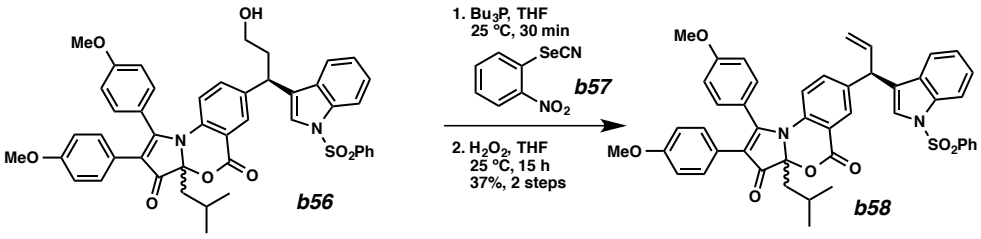
via flash column chromatography on silica gel with 35% ethyl acetate as an eluent. The product was obtained as an orange solid. (68 mg, 0.087 mmol, 87% yield, 99:1 er, 1:1 dr). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.72 (s, 2H), 7.96–7.90 (m, 4H), 7.83–7.82 (m, 2H), 7.53–7.49 (m, 2H), 7.45–7.42 (m, 6H), 7.29–7.25 (m, 2H), 7.19–7.02 (m, 14H), 6.90–6.85 (m, 4H), 6.70 (d, *J* = 8.0 Hz, 4H), 6.22–6.20 (m, 2H), 4.75–4.71 (m, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 3.70 (s, 6H), 3.25–3.09 (m, 4H), 2.31–2.24 (m, 2H), 1.94–1.85 (m, 2H), 1.74–1.67 (m, 2H), 0.90–0.88 (m, 6H), 0.77-0.76 (m, 6H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 199.4, 199.4, 194.2, 168.5, 161.8, 161.7, 161.3, 158.5, 138.7, 138.6, 137.8, 136.4, 135.7, 135.6, 134.4, 134.3, 134.1, 130.3, 130.3, 130.1, 130.1, 129.6, 129.6, 129.6, 129.5, 129.4, 126.8, 125.4, 124.1, 124.0, 123.5, 123.5, 123.5, 122.2, 122.2, 121.6, 121.2, 121.1, 119.9, 119.8, 118.2, 118.1, 115.3, 115.3, 114.7, 114.0, 113.9, 113.7, 91.2, 55.5, 55.5, 55.2, 49.0, 49.0, 42.1, 42.0, 35.7, 35.6, 24.2, 24.0, 24.0, 23.1, 23.1. **IR (neat):** 3367, 1725, 1694, 1610, 1582, 1496, 1446, 1367, 1291, 1248, 1173, 1132, 1086, 1068, 1027, 963, 879, 831, 805, 789, 746, 725, 685 cm^{-1}. **HRMS** (ESI) *m/z* (M+H): calculated for $C_{46}H_{41}N_2O_8S$: 781.2578; found 781.2564. **R_F**: 0.21 in 40% ethyl acetate/hexanes. HPLC Chiralpak ID (hexane/*i*-PrOH = 60:40, 0.5 mL/min, UV-254 detector). >99:1 er, 1:1 dr. *Note:* 1. NMR data contain two diastereomers. 2. Potassium 1-(phenylsulfonyl)-3-indoletrifluoroborate **b54** is commercially available in Sigma-Aldrich.



7-((*R*)-3-hydroxy-1-(1-(phenylsulfonyl)-1*H*-indol-3-yl)propyl)-3a-isobutyl-1,2-bis(4-methoxyphenyl)-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-3,5(3a*H*)-dione (b56)

To a 5 mL flame-dried flask was added aldehyde **b55** (23.2 mg, 0.03 mmol, 1 equiv) and THF (1 mL) at 25 ºC. $NaHB(OAc)_3$ (7 mg, 0.033 mmol, 1.1 equiv) was added. The reaction was monitored by TLC analysis. Additional $NaHB(OAc)_3$ (7 mg, 0.033 mmol, 1.1 equiv) was added after 1 hour. After the reaction is finished, the reaction was dry-load onto silica gel, and the reaction mixture was purified by flash column chromatography on silica gel with a gradient of 40 to 45% ethyl acetate in hexanes as eluents. The product was obtained as a yellow solid. (21.5 mg, 90% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98–7.91 (m, 4H), 7.87–7.82 (m, 4H), 7.57–7.38 (m, 8H), 7.30–7.23 (m, 6H), 7.22–7.17 (m, 2H), 7.16–7.00 (m, 12H), 6.92–6.82 (m, 4H), 6.75–6.67 (m, 4H), 6.25–6.16 (m, 2H), 4.36–4.28 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.72 (s, 6H), 3.67–3.59 (m, 2H), 3.59–3.51 (m, 2H), 2.44–2.23 (m, 4H), 2.24–2.10 (m, 2H), 1.96–1.83 (m, 2H), 1.77–1.64 (m, 2H), 1.51 (s, 2H), 0.95–0.85 (m, 6H), 0.79–0.71 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.07, 168.48, 168.45, 161.83, 161.79, 161.09, 158.37, 139.72, 139.65, 137.85, 135.93, 135.51, 135.45, 134.24, 134.16, 133.91, 130.14, 130.07, 129.99, 129.71, 129.63, 129.37, 126.63, 125.20, 125.09, 125.00, 123.17, 122.99, 122.03, 121.96, 121.49, 121.20, 121.10, 119.92, 119.81, 117.93, 117.77, 115.10, 115.05, 114.51, 113.79, 113.59, 91.12, 60.03, 55.36, 55.13, 41.99, 41.86, 37.59, 23.94, 23.84, 22.97. **IR(neat)** 3511, 3094, 1716, 1613,

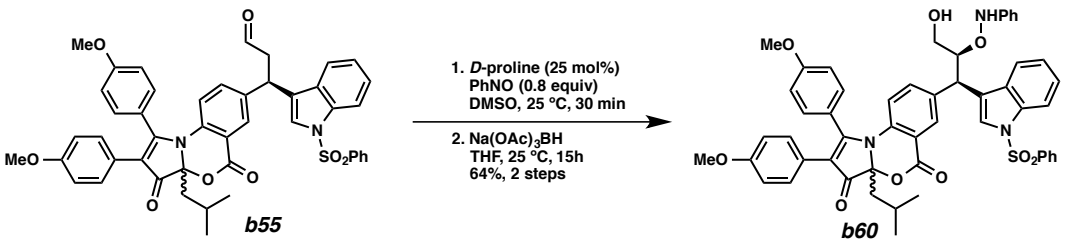
1584, 1520, 1351, 1291, 1172, 1026, 766, 721, 685 cm^{-1}. **HRMS** (ESI) *m/z* (M+Na): calculated for $C_{46}H_{42}N_2O_8S$: 805.2554; found 805.2558. $\mathbf{R_F}$: 0.2 in 50% ethyl acetate/hexanes. **MP:** 129-131 °C.



3a-isobutyl-1,2-bis(4-methoxyphenyl)-7-((*R*)-1-(1-(phenylsulfonyl)-1*H*-indol-3-yl)allyl)-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-3,5(3a*H*)-dione (b58)

To a 5 mL flame-dried flask was added alcohol **b56** (33 mg, 0.04 mmol, 1 equiv) and THF (1.2 mL) at 25 ºC. The toxic 2-nitrophenyl selenocyanate **b57** (36 mg, 0.158 mmol, 3.8 equiv) was carefully added in the reaction. Bu_3P (46 µL, 0.18 mmol, 4.3 equiv) was added and the reaction was stirred for 30 min. After TLC analysis showed no starting material, EtOH (0.1 mL) was added into the reaction, and the reaction was concentrated. To the reaction mixture was added THF (2 mL) and the reaction was cooled to 0 ºC. $H_2O_{2(aq)}$ (30 %, 0.1 mL) was added into the reaction. After TLC analysis showed no starting material, the reaction mixture was dry-loaded onto silica gel and purified by flash column chromatography on silica gel with a gradient of 15 to 20% ethyl acetate in hexanes as eluents. The product was obtained as a yellow solid. (11.5 mg, 35% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99–7.89 (m, 4H), 7.88–7.75 (m, 4H), 7.58–7.48 (m, 2H), 7.49–7.39 (m, 4H), 7.33–7.01 (m, 16H), 6.96–6.84 (m, 4H), 6.75–6.68 (m, 4H), 6.28–6.10 (m, 4H), 5.27–5.22 (m, 2H), 5.03–4.94 (m, 2H), 4.83–4.77 (m, 2H), 3.83 (s, 3H),

3.81 (s, 3H), 3.72 (s, 6H), 2.37–2.26 (m, 2H), 2.00–1.89 (m, 2H), 1.81–1.66 (m, 2H), 0.94–0.90 (m, 6H), 0.82–0.77 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.06, 168.41, 161.77, 161.12, 158.39, 138.17, 137.85, 137.66, 137.56, 136.11, 135.57, 135.55, 134.58, 134.56, 134.41, 133.93, 133.92, 130.30, 130.18, 130.01, 129.74, 129.37, 126.66, 125.02, 124.99, 124.33, 124.11, 124.07, 123.19, 123.15, 122.01, 121.51, 121.22, 121.15, 120.12, 120.02, 118.04, 117.92, 117.67, 117.61, 115.10, 115.07, 114.54, 113.82, 113.61, 91.13, 55.36, 45.68, 41.96, 29.69, 23.97, 23.96, 23.86, 23.05, 23.01. **IR(neat)** 3092, 2958, 1716, 1613, 1525, 1444, 1367, 1350, 1250, 1172, 1071, 1024, 1002, 823, 779, 723, 685 cm^{-1}. **HRMS** (ESI) *m/z* (M+Na): calculated for $C_{46}H_{40}N_2O_7S$: 787.2448; found 787.2452. **R_F**: 0.21 in 30% ethyl acetate/hexanes. **MP:** 106-108 °C.

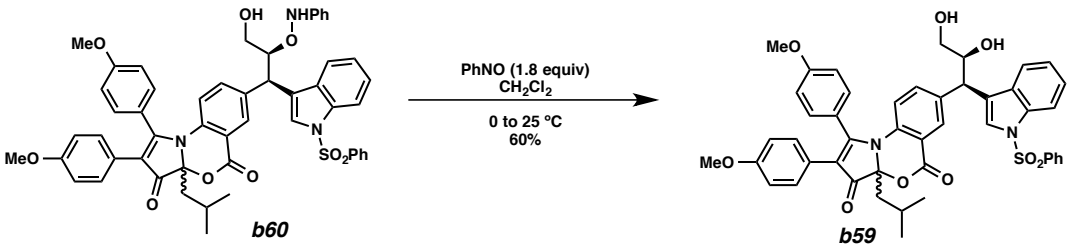


7-((1*R*,2*S*)-3-hydroxy-2-((phenylamino)oxy)-1-(1-(phenylsulfonyl)-1*H*-indol-3-yl)propyl)-3a-isobutyl-1,2-bis(4-methoxyphenyl)-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-3,5(3a*H*)-dione (b60)

To a flame-dried vial was added **b55** (40 mg, 0.05 mmol, 1.2 equiv), nitrosobenzene (4.5 mg, 0.042 mmol, 1 equiv), and anhydrous DMSO (0.15 mL). The reaction was stirred for 5 minutes, and then *D*-proline (1.2 mg, 0.01 mmol, 0.25 equiv) was added to the reaction. The reaction was stirred for 30 minutes, and the color of the solution changed from green to dark orange. The reaction mixture was diluted with ethyl acetate (2 mL), and water (1

mL) was added. The crude mixture was extracted with ethyl acetate (1 mL x5). The organic solution was dried over anhydrous $MgSO_4$, filtered through a short celite pad, and concentrated. The crude compounds were dissolved in THF (2 mL) and cooled down to 0 ºC. After the reaction was stirred for 5 minutes, $Na(OAc)_3BH$ (37 mg, 0.17 mmol, 4.2 equiv) was added, and the reaction was stirred for 15 hours. The crude reaction mixture was dry-loaded onto silica gel and purified via flash column chromatography on silica gel with a gradient of 25 to 35% ethyl acetate as eluents. The product was obtained as an orange solid. (24.4 mg, 0.027 mmol, 64% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 1.7 Hz, 1H), 8.08 (d, *J* = 2.3 Hz, 1H), 7.96–7.93 (m, 2H), 7.85–7.82 (m, 2H), 7.61 (s, 1H), 7.59 (s, 1H), 7.53–7.27 (m, 10H), 7.18–7.03 (m, 6H), 6.95–6.91 (m, 2H), 6.86–6.84 (m, 2H), 6.81–6.79 (m, 2H), 6.72–6.69 (m, 8H), 6.24–6.21 (m, 2H), 4.62–4.58 (m, 2H), 4.54–4.52 (m, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.71 (s, 6H), 2.42 (bs, 2H), 2.32–2.26 (m, 2H), 1.96–1.87 (m, 2H), 1.76–1.70 (m, 2H), 1.63 (bs, 2H), 0.91–0.86 (m, 6H), 0.78–0.76 (m, 6H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 194.1, 171.2, 168.5, 168.4, 161.7, 161.1, 158.4, 147.8, 147.8, 137.8, 136.5, 136.4, 136.2, 136.2, 135.5, 135.1, 135.0, 134.0, 131.0, 130.7, 130.2, 130.0, 129.7, 129.4, 129.1, 129.0, 126.7, 125.2, 125.1, 123.9, 123.8, 123.4, 123.2, 122.8, 122.2, 121.7, 121.5, 121.5, 121.2, 121.1, 119.7, 119.6, 117.7, 117.5, 115.2, 115.1, 115.0, 115.0, 114.6, 113.8, 113.6, 91.1, 84.9, 84.7, 63.2, 63.1, 60.4, 55.3, 55.1, 53.4, 42.0, 41.9, 29.7, 29.7, 29.5, 29.3, 29.2, 24.1, 23.9, 23.9, 23.0, 22.9, 21.0, 14.2, 14.1. **IR (neat):** 2925, 1732, 1698, 1610, 1582, 1519, 1495, 1446, 1367, 1292, 1249, 1173, 1132, 1090, 1068, 1025, 972, 832, 789, 766, 746, 725, 685 cm^{-1}. **HRMS** (ESI) *m/z* (M+H): calculated for $C_{52}H_{48}N_3O_9S$: 890.3106; found 890.3086. **R_F1**: 0.55 in 50% ethyl

acetate in hexanes (proline-controlled oxidation product). $\mathbf{R_F2}$: 0.24 in 50% ethyl acetate in hexanes (reduction product). *Note:* NMR data contain two diastereomers.



7-((1*R*,2*S*)-2,3-dihydroxy-1-(1-(phenylsulfonyl)-1*H*-indol-3-yl)propyl)-3a-isobutyl-1,2-bis(4-methoxyphenyl)-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-3,5(3a*H*)-dione (b59)

To a solution of **b60** (25 mg, 0.028 mmol, 1 equiv) in dichloromethane (1 mL) was added nitrosobenzene (5.6 mg, 0.052 mmol, 1.8 equiv) at 0 ºC. The reaction was slowly warmed up to room temperature and stirred for 15 hours. The crude reaction mixture was dry-loaded onto silica gel and purified via flash column chromatography on silica gel with a gradient of 50 to 60% ethyl acetate in hexanes as eluents. The product was obtained as a yellow solid. (13.5 mg, 0.169 mmol, 60% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.0 Hz, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.95–7.92 (m, 2H), 7.85–7.83 (m, 4H), 7.67 (s, 2H), 7.51–5.48 (m, 2H), 7.43–7.40 (m, 4H), 7.29–7.25 (m, 6H), 7.15–7.02 (m, 10H), 6.89–6.85 (m, 4H), 6.71–6.69 (m, 4H), 6.22 (t, *J* = 8.2 Hz, 2H), 4.38–4.37 (m, 2H), 4.24 (d, J = 6.9 Hz, 1H), 4.21 (d, J = 6.9 Hz, 1H) 3.83 (s, 3H), 3.81 (s, 3H), 3.71 (s, 6H), 3.63–3.62 (m, 2H), 3.40–3.43 (m, 2H), 2.72 (bs, 1H), 2.62 (bs, 1H), 2.29–2.24 (m, 4H), 1.95–1.89 (m, 2H), 1.73–1.68 (m, 2H), 0.89–0.88 (m, 6H), 0.77–0.75 (m, 6H). **^{13}C NMR** (150.91 MHz, $CDCl_3$) δ 194.3, 194.2, 168.8, 168.7, 161.9, 161.2, 158.4, 137.8, 136.4,

136.3, 136.1, 135.6, 135.5, 135.1, 135.0, 133.9, 130.9, 130.7, 130.2, 130.1, 130.0, 129.4, 129.4, 126.7, 126.7, 125.1, 125.1, 123.9, 123.8, 123.3, 122.8, 122.5, 121.6, 121.6, 121.5, 121.1, 121.1, 119.6, 119.6, 117.7, 117.5, 115.2, 115.1, 114.6, 114.5, 113.8, 113.8, 113.6, 91.2, 73.2, 73.0, 64.9, 64.8, 55.4, 55.1, 44.1, 44.1, 42.0, 42.0, 29.7, 29.3, 23.9, 23.9, 23.8, 23.0, 22.9. **IR (neat):** 3363, 2923, 1732, 1698, 1610, 1581, 1519, 1496, 1446, 1367, 1291, 1248, 1173, 1132, 1119, 1090, 1067, 1024, 971, 830, 805, 789, 766, 746, 725, 685 cm^{-1}. **HRMS** (ESI) *m/z* (M+H): calculated for $C_{46}H_{43}N_2O_9S$: 799.2684; found 799.2671. $\mathbf{R_F}$: 0.15 in 60% ethyl acetate/hexanes. *Note:* 1. NMR data contain two diastereomers. 2. $^3J_{HH}$ between C-32/C-33 of **b59** was measured 6.9 Hz in $CDCl_3$ at each diastereomers that is corresponded to $^3J_{HH}$ between C-32/C-33 of discoipyrrol D ($^3J_{HH}$ between C-32/C-33 = 7.8 Hz in methanol-d4).

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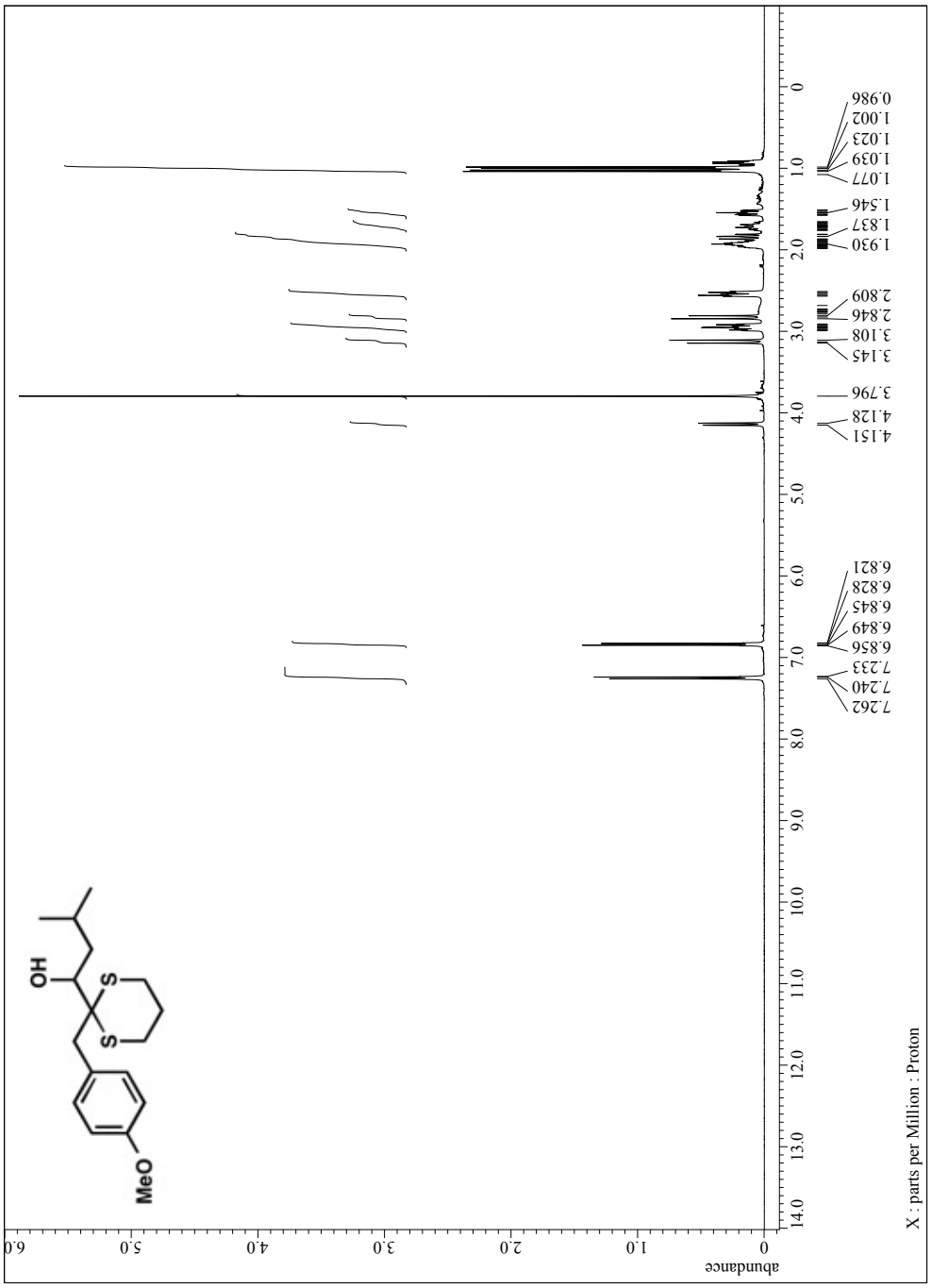
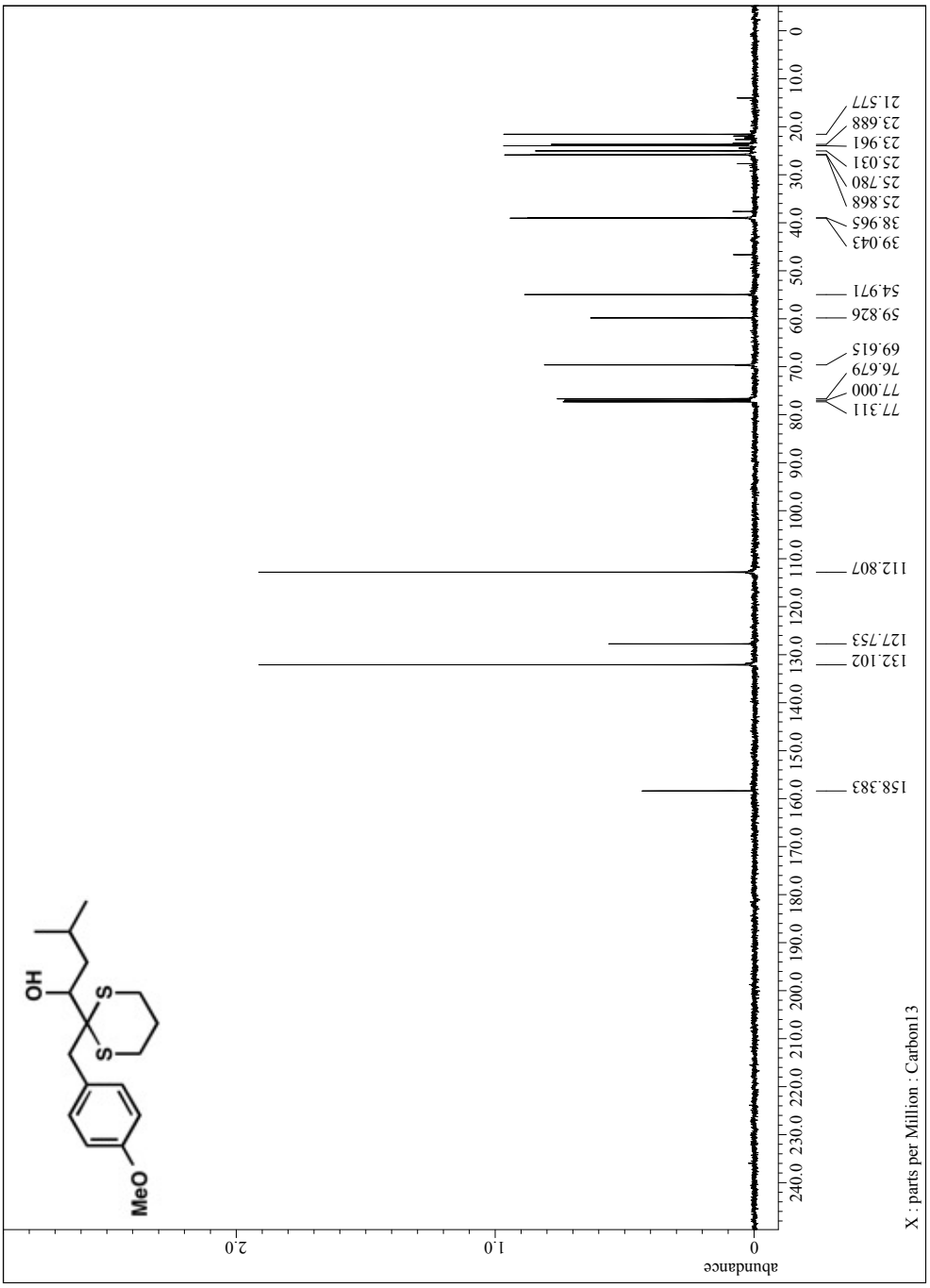
APPENDIX-CHAPTER TWO

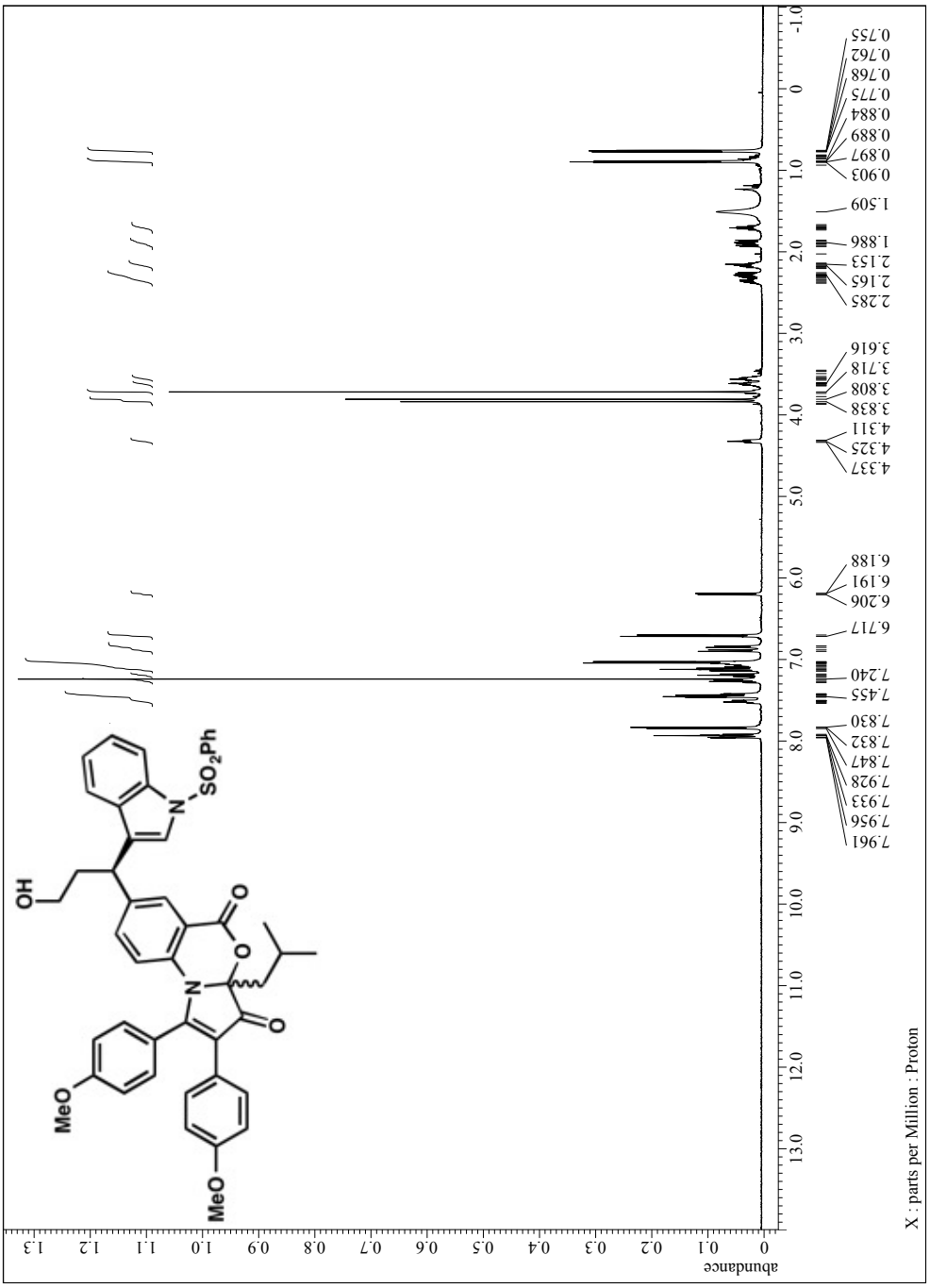
Spectra Relevant to Chapter Two: Studies toward the Synthesis of Discoipyrrole D



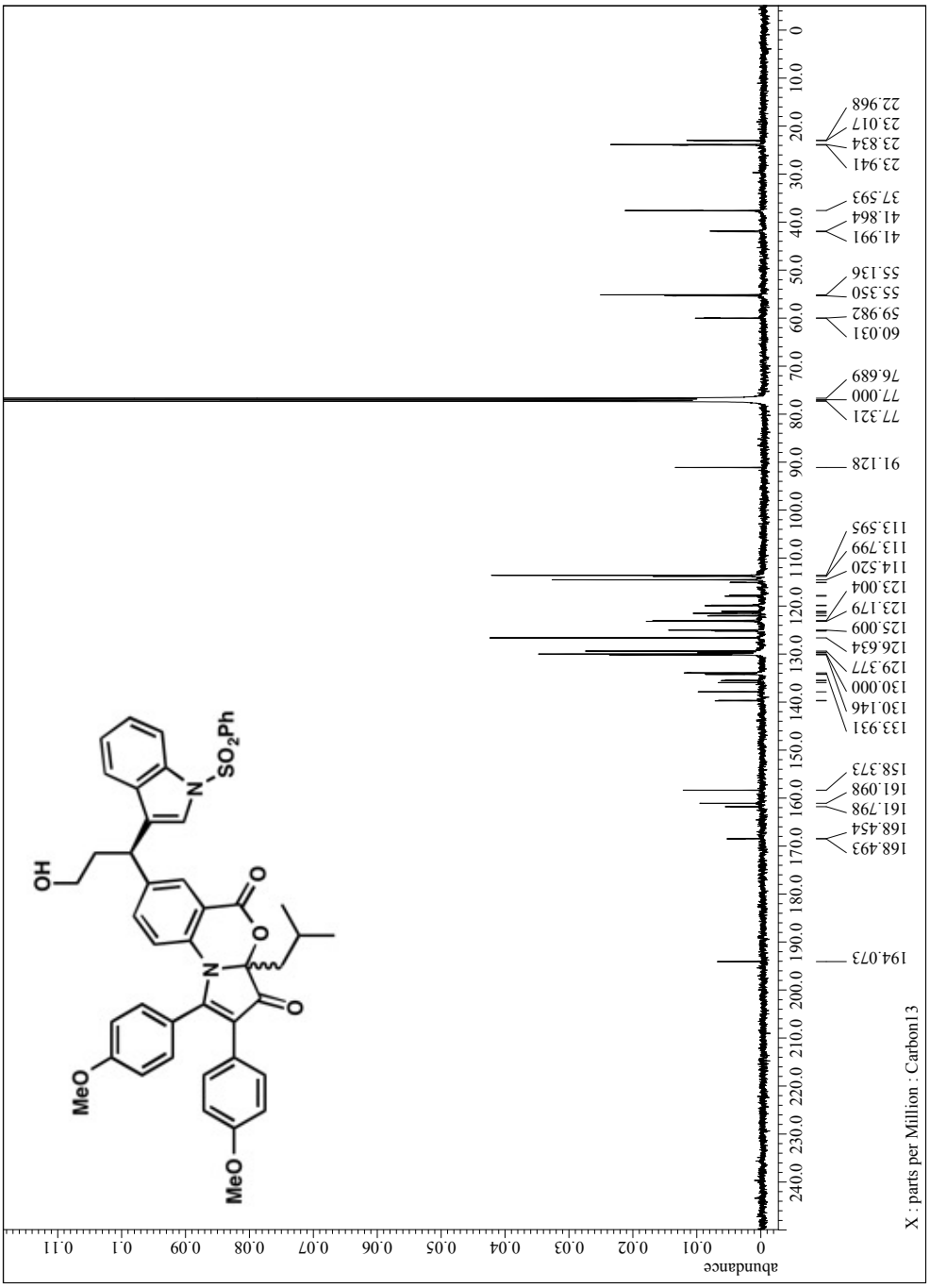
^{1}H NMR for compound **b43**



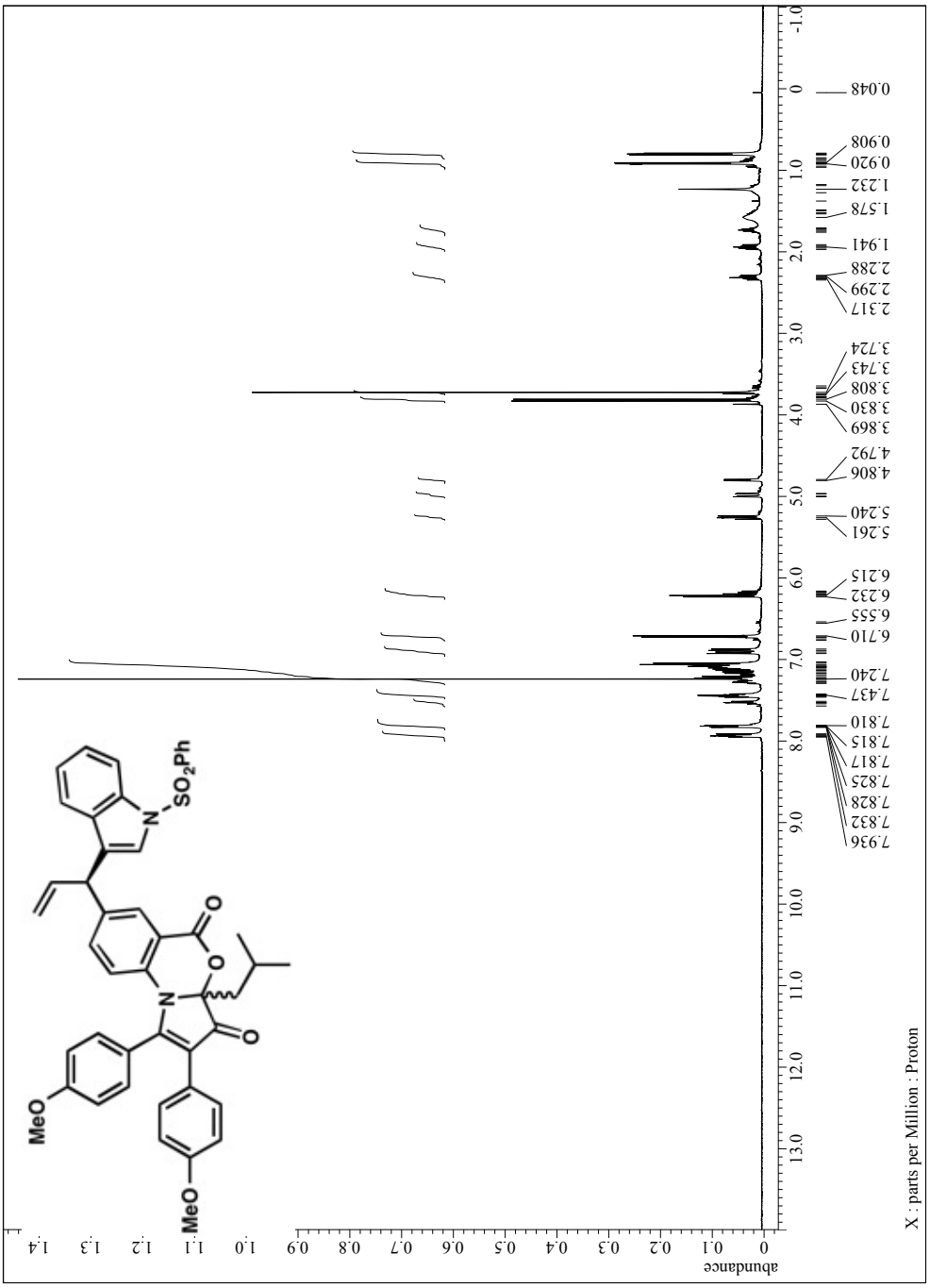
^{13}C NMR for compound **b43**



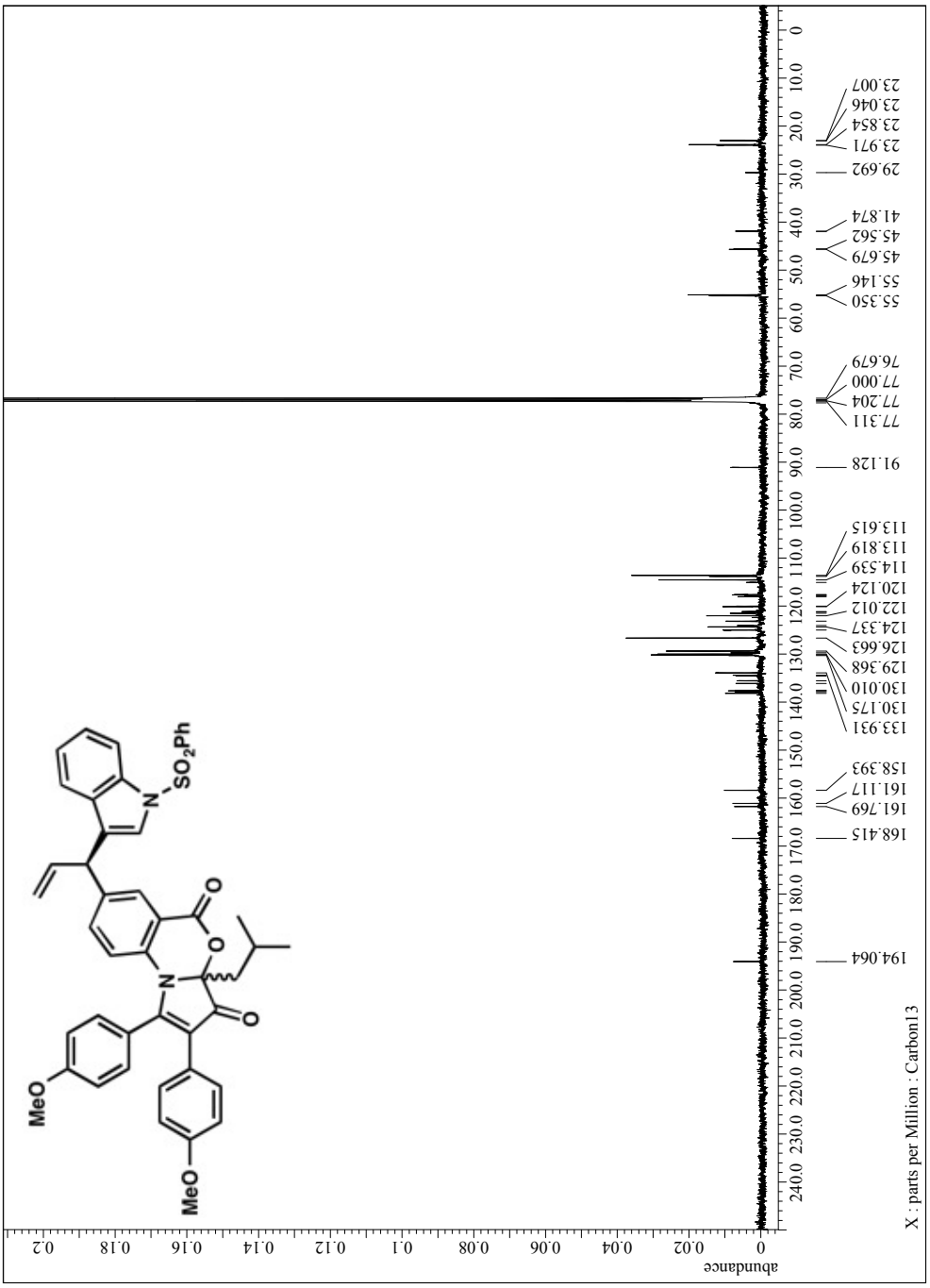
^{1}H NMR for compound **b56**



^{13}C NMR for compound **b56**



^{1}H NMR for compound **b58**



^{13}C NMR for compound **b58**

3. STUDIES TOWARD THE SYNTHESIS OF BRAZILIDE A

3.1 Background

3.1.1 Natural Product Brazilide A

Brazilin (**c1**), haematoxylin (**c2**), haematoxylane (**c3**), brazilein (**c4**), and brazilide A (**c5**) were isolated from Sappan Lignum, the heartwood of *Caesalpinia sappan* L., which is used in traditional Chinese medicine as a hemostatic, emmenagogue and anti-inflammatory agent (Figure 3-1).[1] Several studies report the bioactivities of brazilin (**c1**), brazilein (**c2**) and their analogs;[2] however, there have been no reports describing the bioactivity of brazilide A (**c5**) to date.

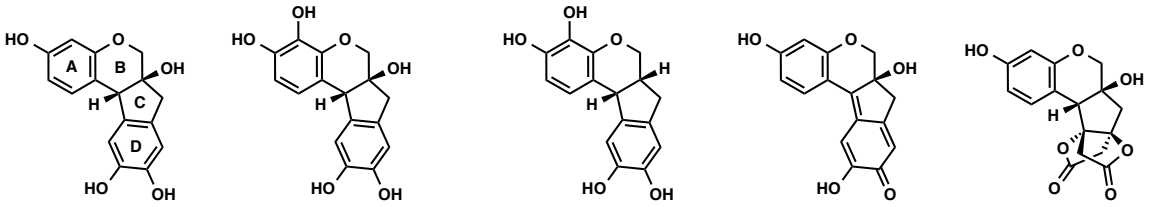


Figure 3-1. Natural Products Isolated from *Caesalpinia Sappan.*

All of the natural products in the brazilin family contain similar core structures based on dihydrobenzopyran and indan. Studies have shown that brazilein (**c4**) is formed from the oxidation of brazilin (**c1**).[3] In 2002 it was postulated that brazilide A (**c5**) is a product of further oxidation of brazilein (**c4**) that takes place either in nature or during the isolation process.[1] Unlike other members of the braziline family, brazilide A (**c5**) does not include an aromatic ring D but contains a special propellane structure. The tricyclic

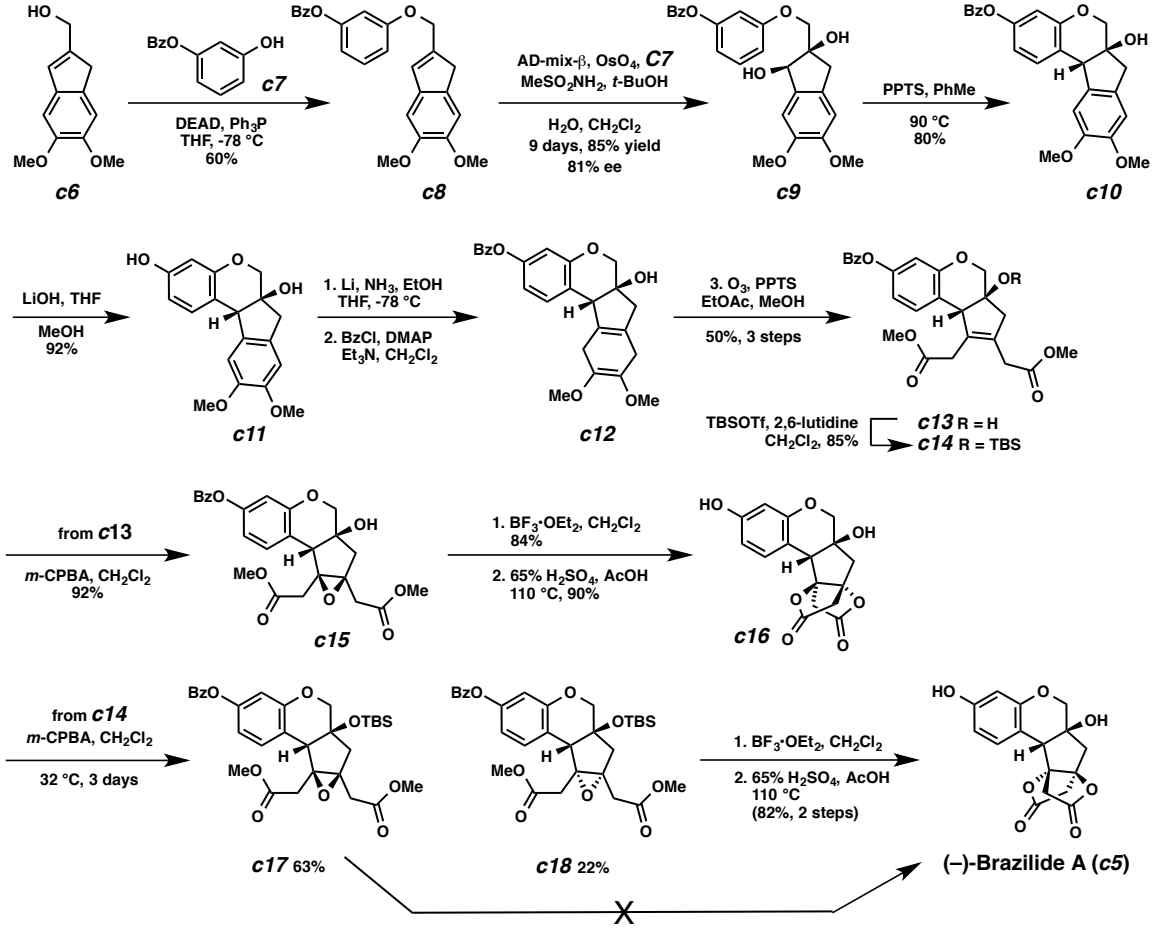
propellane structure is formed by the fusion of a bis-lactone moiety with the C ring in the brazilin family and is the most synthetically challenging aspect of the structure. There are several reports on the total syntheses of brazilin (**c1**) and brazilein (**c4**),[4] but only one total synthesis of brazilide A (**c5**) reported in 2013,[5] a further testament to its structural complexity.

3.1.2 Total Synthesis of Brazilide A

In 2013, Zhang, Yang and coworkers reported the first total synthesis of (+)-brazilide A (Scheme 3-1).[5] Their synthetic strategy was inspired by the natural process of oxidation of brazilin (**c1**). Indene alcohol **c6** was prepared based on their previously described synthesis in 4 synthetic steps.[4b] Next, benzoyl-protected resorcinol **c7** was installed via Mitsunobu reaction, providing ether **c8**. Modified Sharpless asymmetric dihydroxylation was used to construct the key tertiary alcohol in good yield and enantioselectivity. Finally, the core brazilin structure **c10** was finished after linking the dihydrobenzopyran ring via a Friedel-Crafts reaction at the benzylic position. The bis-lactone ring of brazilide A was approached using stepwise manipulations: benzoyl-deprotection, Birch reduction, benzoyl-protection, ozonolysis, and silyl group protection afforded diester **c14**. Directed epoxidation of the olefin **c13** provided a single diastereomer of the epoxide **c15**. However, epoxide **c15** cyclizes to provide the wrong diastereomer **c16**. Therefore an alternative approach was adopted in order to remove the directing group effect and to sterically block that face by protecting the hydroxyl group of **c14** as a TBS ether. Unfortunately, this epoxidation afforded the diastereomeric epoxide

c18 only as a minor product, which lowers the overall yield of the route. Finally, Lewis acid triggered cyclization, followed by acidic deprotection of the silyl ether resulted in brazilide A (**c5**) in 16 synthetic steps and 1.6% overall yield.

Scheme 3-1. The Total Synthesis of Brazilide A by Zhang and Yang *et al.*



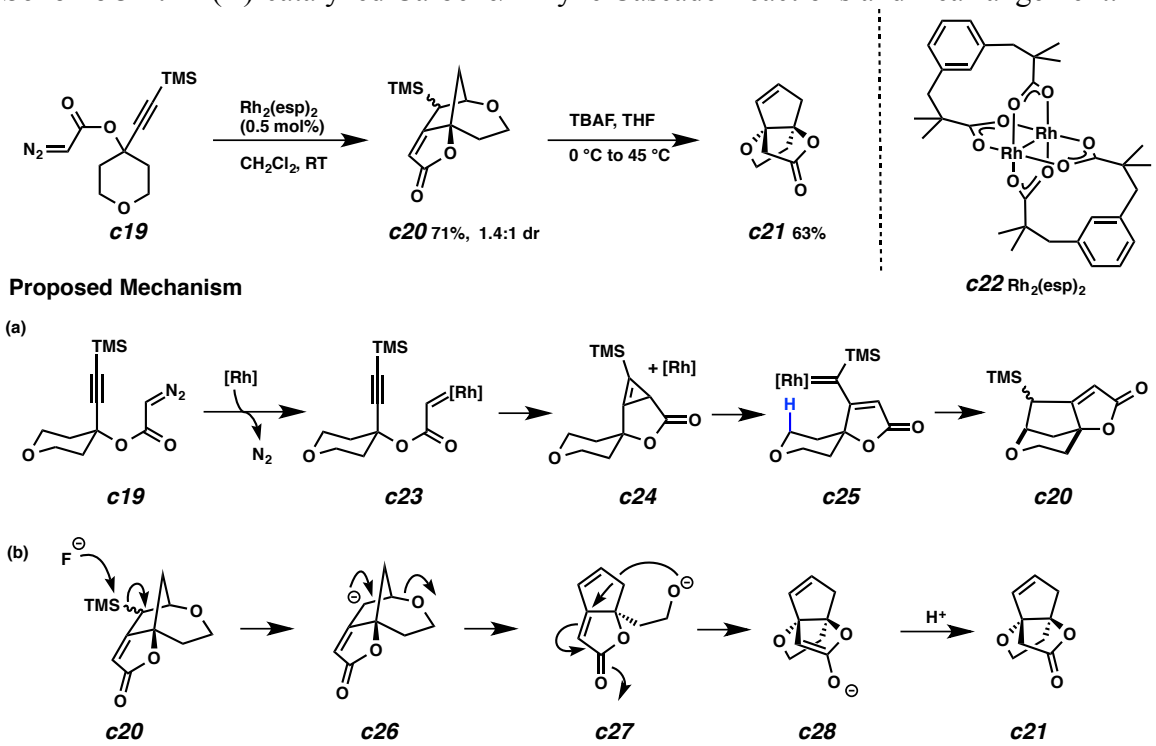
3.2 Synthetic Plan for Brazilide A

3.2.1 Introduction of Rh(II)-catalyzed Carbene/Alkyne Cascade Reactions

After examination of the synthesis described by Zhang and Yang of brazilide A, it became apparent that the major pitfall in their route was the late-stage stereoselective formation of the bis-lactone motif. Instead of building up the core structure of brazilin, followed by oxidation in the end, our synthetic strategy has been to build the propellane core first and then to introduce a resorcinol moiety to finish the benzopyran motif.

An efficient synthesis of the core of brazilide A (**c5**) was proposed based on our previously developed methodology. In 2012, our group discovered a novel Rh(II)-catalyzed carbene/alkyne cascade reaction (Scheme 3-2).[6] Treatment of the alkynyl diazoester **c19** with $Rh_2(esp)_2$ causes diazo decomposition and rhodium carbene formation (**c23**), which is presumably followed by cyclization to form cyclopropene **c24** as a short-lived intermediate.[7] Further, cyclopropene/carbene rearrangement[8] affords a secondary Rh carbene intermediate **c25**, which inserts into a transannular C-H bond resulting in a bridged polycycle **c20**. It was also found that treatment of this bridged polycycle **c20** with tetrabutylammonium fluoride (TBAF) at 45 °C results in the removal of the trimethylsilyl group and formation of the primary alkoxide **c27** via elimination. Finally, the alkoxide group undergoes a conjugate addition to the unsaturated lactone in **c27**, followed by protonation of the resulting enolate to afford propellane **c21** in a good yield. The bis-lactone **c21** corresponds to the core skeleton in brazilide A, and we decided to take advantage of this transformation as a key step in the synthesis of this natural product.

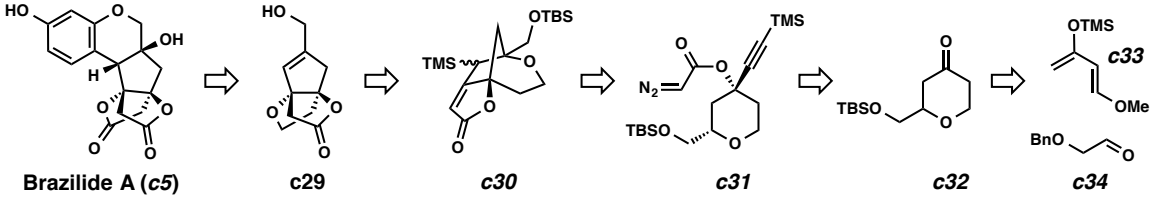
Scheme 3-2. Rh(II)-catalyzed Carbene/Alkyne Cascade Reactions and Rearrangement.



3.2.2 The First Strategy

To accommodate the late stage benzopyran synthesis, the allyl alcohol motif on the propellane **c29** was designed for introducing a resorcinol motif by Mitsunobu reaction or allylic substitution (Scheme 3-3). In order to have this allyl alcohol group on propellane **c29**, a side chain (CH_2OTBS) can be preinstalled on the alkynyl diazoester **c31** prior to its reaction with the Rh(II) catalyst. This diazoester **c31** can be synthesized from the corresponding tetrahydropyran-4-one **c32**, which can be prepared via a hetero-Diels-Alder reaction of Danishefsky's diene (**c33**) with benzyloxyacetaldehyde (**c34**).[9]

Scheme 3-3. The First Retrosynthetic Plan for Brazilide A.

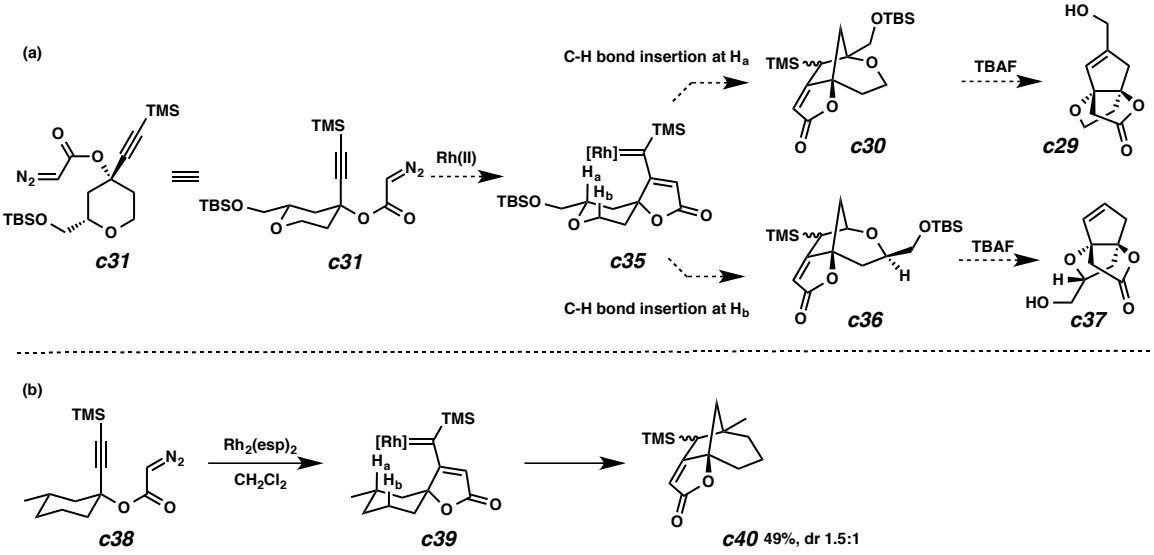


There are some common trends in site selectivity for C-H bond insertions with of Rh-carbenes.[10] (1) Usually five-membered ring formation is preferred in intramolecular cyclization. (2) Electronically, the trend of C-H bond reactivity is 3° > 2° > 1°. However, sterically the trend of C-H bond reactivity is 1° > 2° > 3°. Electronic factors often dominate intramolecular reactions. (3) Electron-donating groups that increase the electron density of the C-H bond will increase the rate of C-H bond insertion. Conversely, electron-withdrawing groups will decrease the rate of C-H bond insertion.

Keeping this information in mind, we considered the C-H bond insertion step (**c35**) in the cascade reaction for brazilide A (Scheme 3-4a). There are two different hydrogen atoms in the intermediate **c35** that can react with the Rh carbene, H_a and H_b. An insertion reaction taking place at H_a will provide the desired propellane structure after rearrangement. Alternatively, an insertion reaction taking place at H_b will result in the wrong propellane isomer. Both of H_a and H_b are located in the alpha position relative to the oxygen atom and, therefore, are activated by a favorable electron density increase due to the lone electron pair on oxygen donating to the antibonding orbitals of the C-H bonds. However, Adams showed this was a weak effect for endocyclic oxygens.[11] Following this line of thought, insertion into H_a and H_b would be equally probable. However, H_a is on a tertiary carbon and H_b is on a secondary carbon. We expected the methine H_a to be

slightly more activated compared to the methylene H_b. Therefore the C-H bond insertion step would prefer to react at H_a, providing the desired product **c30**. Employment of the 3-methylcyclohexyl-based substrate **c38** as a model system confirmed that the majority of C-H bond insertion is taking place at the methine position (Scheme 3-4b).[6] This result supported the feasibility of our strategy.

Scheme 3-4. Consideration of the C-H Bond Insertion Step and Model System.



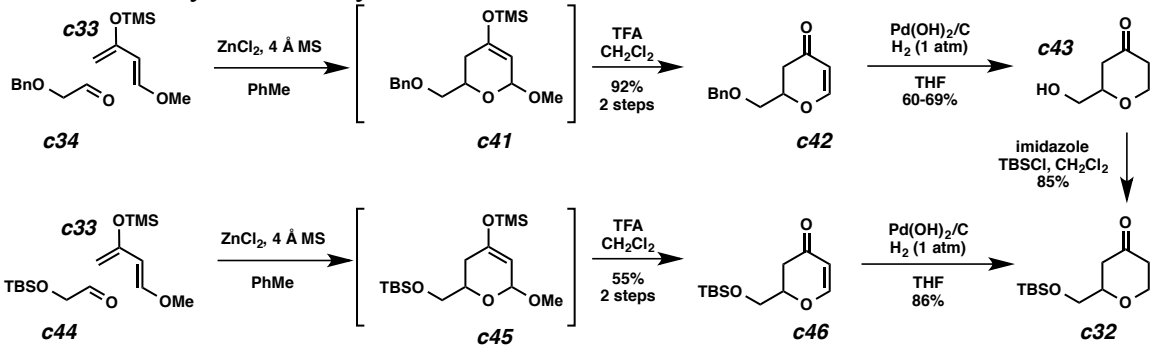
3.2.3 Synthesis of the Propellane Intermediate c29

The forward synthesis of brazilide A begins with a hetero-Diels-Alder reaction between Danishefsky's diene (**c33**) and benzyloxyacetaldehyde (**c34**) (Scheme 3-5). With the well-established procedure,[9d] benzyl protected enone **c42** was prepared in good yield. Since benzylic hydrogens are highly reactive toward C-H bond insertion reactions, the protecting group was switched to a TBS group. Palladium catalyzed hydrogenation and hydrogenolysis on **c42** gave problematic overreduction. Fortunately, Pearlman's catalyst

(palladium hydroxide on carbon) provided clean hydroxyl pyran-4-one **c43** in moderate yields. Hydroxyl pyran-4-one **c43** was subsequently protected with TBS-Cl leading to the desired ketone **c32** in three steps.

Alternatively, TBS protected aldehyde **c44** could undergo a hetero-Diels-Alder reaction that resulted in fewer synthetic steps. Due to the increased steric influence of the TBS protecting group, the overall reaction yield was lower compared to the initial pathway. Hydrogenation of the intermediate enone **c46** using Pearlman's catalyst afforded the desired ketone **c32** in 86% yield.

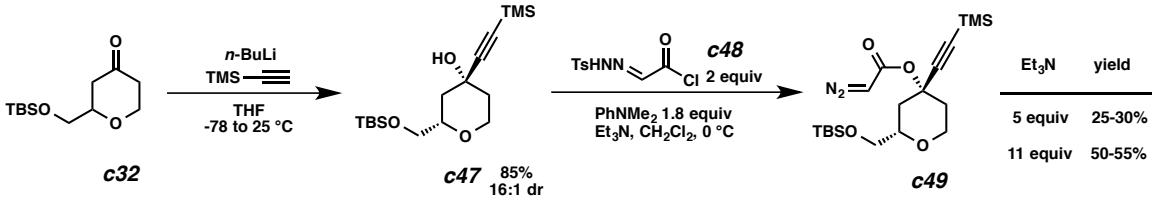
Scheme 3-5. Synthesis of Pyranone **c32**.



Trimethylsilylacetylide addition to **c32** generated propargyl alcohol **c47** with high diastereoselectivity (Scheme 3-6). In addition, the diazo-transfer reagent (**c48**) was prepared following a known procedure.[12] However, initial attempts to prepare diazoester **c49** employing the sterically hindered propargyl alcohol and fewer equivalents of the triethylamine base resulted in very low yields. After extensive optimization and fine-tuning of key reaction parameters, increasing the amount of triethylamine to 11

equivalents improved the reaction yield to 55%, which allowed the preparation of large quantities of diazoester **c49**.

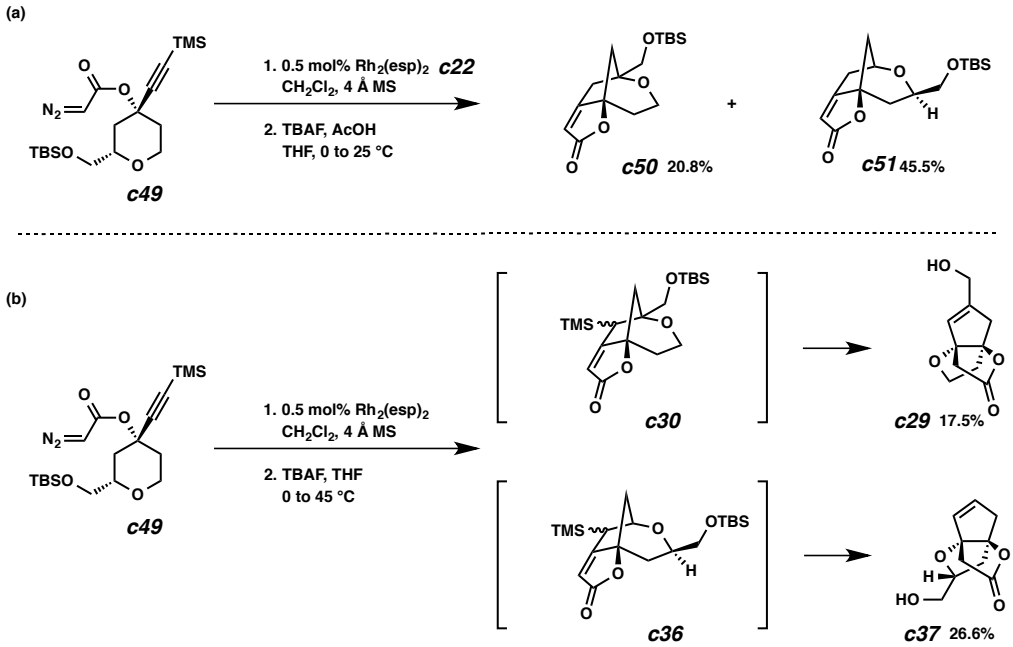
Scheme 3-6. Synthesis of Diazoester **c49**.



Treatment of diazoester **c49** with $Rh_2(esp)_2$ (**c22**) provided a mixture of four isomers, which hampered efficient purification of the reaction products and structural identification. Desilylation of the crude reaction mixture with buffered TBAF afforded two major products **c50** and **c51** (Scheme 3-7a). Unfortunately, the desired 2-oxabicyclo[3.2.1]octane **c50** was only a minor component of the mixture, which implies that the C-H bond insertion reaction predominantly took place at the methylene H_b instead of the desired H_a position.

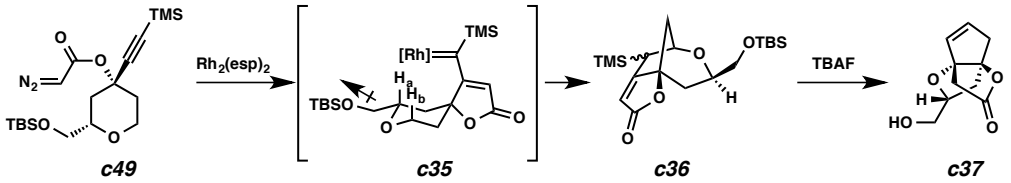
In addition, the rearrangement was tested directly after the cascade reaction without any purification. The results again showed that the desired propellane **c29** is the minor product (Scheme 3-7b), and that the major product **c37** comes from the C-H bond insertion at the methylene position (H_b), consistent with the earlier observation.

Scheme 3-7. Cascade Reactions of Diazoester **c49**.



These results indicate that the C-H bond insertion step occurs at the methylene hydrogen over the methine hydrogen due to methylene hydrogen being more electron-rich and less sterically hindered compared to methine hydrogen. For the conformation of the carbene **c49** shown in Scheme 3-8, even though the endocyclic oxygen activates both of the methine and methylene hydrogens, the OTBS group of the side tether acts as an inductive electron-withdrawing group and reduces the electron density on the methine hydrogen. This effect makes the methine (H_a) in **c35** less electron-rich than the methylene hydrogen (H_b), so that the C-H bond insertion occurs at the methylene hydrogen in preference to the methine hydrogen, resulting in the observed reactivity.[10]

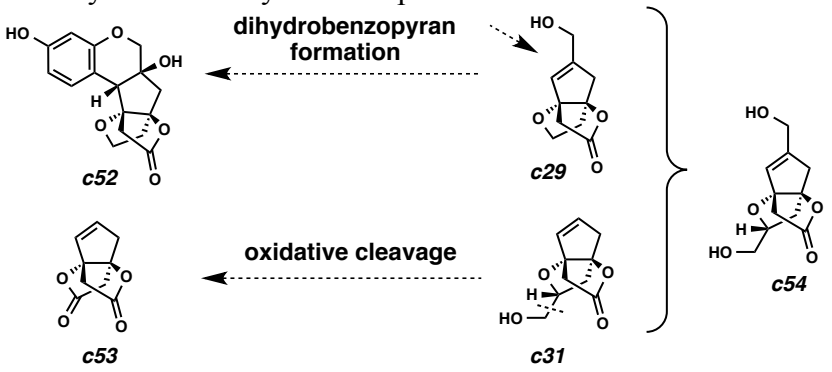
Scheme 3-8. Undesired Cascade Reaction Due to Electronic Effect.



3.2.4 The Second Strategy

In order to address this unexpected problem, a second synthetic strategy was envisioned (Scheme 3-9). The allyl alcohol was retained in order to incorporate the resorcinol. On the other hand, the alcohol in the major product **c31** could be useful to synthesize a lactone motif via an oxidative C-C bond cleavage.[13] As a result, diol **c54** is expected to not only give a lactone through oxidative C-C bond cleavage but also allows for the benzopyran motif to be introduced in order to complete brazilide A (**c5**) synthesis.

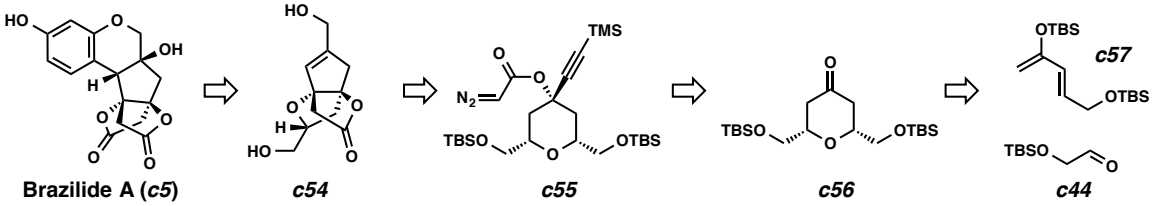
Scheme 3-9. The Synthetic Analysis of Propellane Diol **c54**.



A second retrosynthetic plan is shown in Scheme 3-10. Symmetric alkynyl diazoester **c55** was designed for the cascade reaction in order to obtain the diol **c54**. The C_s symmetric alkynyl diazoester **c55** could be easily obtained from pyranone **c56**, which

in turn can be obtained through a hetero-Diels-Alder reaction of diene **c57** and aldehyde **c44**.

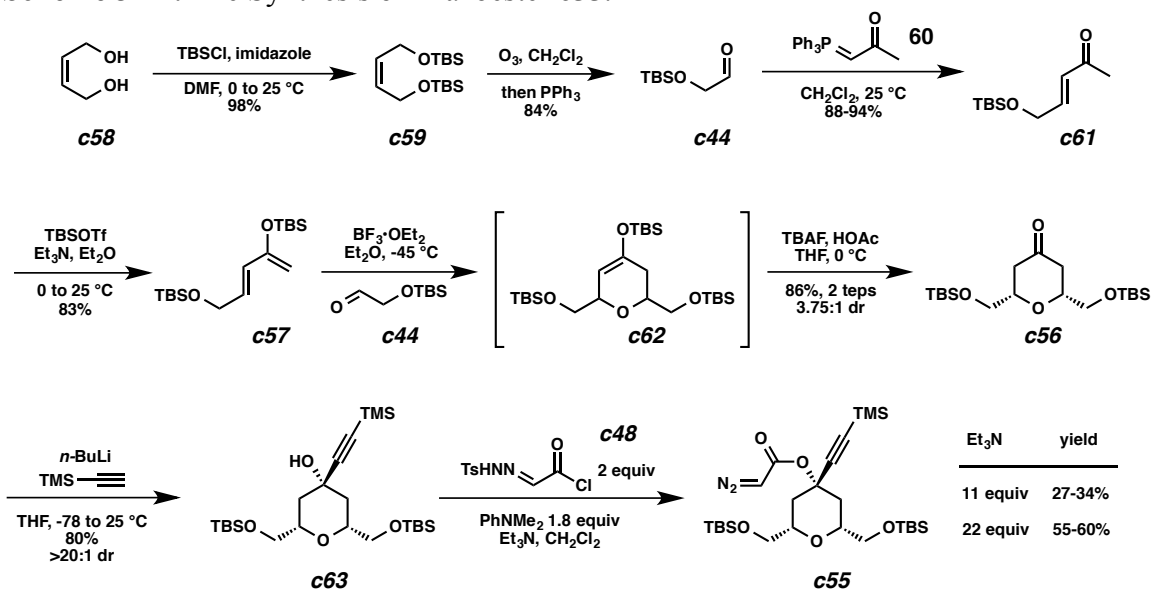
Scheme 3-10. The Second Retrosynthesis of Brazilide A.



3.2.5 Synthesis of the Second Propellane c54

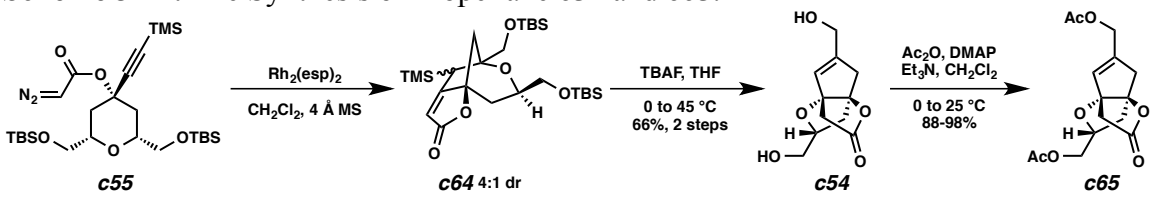
Aldehyde **c44** was used as a starting material in the first synthetic route and is commercially available. However, this pricy chemical can be synthesized in two steps on a relatively large scale from the TBS protection on cis-2-butene-1,4-diol (**c58**) followed by ozonolysis (Scheme 3-11). This (tert-butyldimethylsilyloxy)acetaldehyde (**c44**) serves not only as a starting material for diene **c57** by a Wittig reaction and soft silyl-enolization sequence, but also as a component of hetero-Diels-Alder reaction to afford the desired symmetric pyranone **c56**.[9e] Several Lewis acids were tested, and boron trifluoride diethyl etherate was found to be the best reagent for this cyclization. In addition, in this hetero-Diels-Alder reaction, aldehyde **c44** had to be employed as a limiting reagent to avoid an aldol reaction between intermediate **c62** and the aldehyde **c44**. The propargyl alcohol **c63** was synthesized by alkynyl addition to the carbonyl group of the pyranone in 80% yield. The yield of the diazoester formation reaction was improved to 60% by increasing the amount of added trimethylamine base to 22 equivalents.

Scheme 3-11. The Synthesis of Diazoester **c55**.



Treatment of symmetric diazoester **c55** with $Rh_2(esp)_2$ afforded two diastereomers **c64** in a 4:1 ratio as observed by NMR spectroscopy of the crude reaction mixture. That reaction mixture was reacted with TBAF in order to effect structural rearrangement and afford the desired propellane **c54** as a single diastereomer in 66% yield (Scheme 3-12). Propellane diol **c54** contains two different alcohol groups: an allylic alcohol and a primary alcohol. It was rather difficult to chemically differentiate the two alcohol groups in compound **c54**, so acetylation of the propellane **c54** hydroxyl groups was employed so they would not interfere with the subsequent transition metal-catalyzed cross-coupling reactions.

Scheme 3-12. The Synthesis of Propellane **c54** and **c65**.



c55 *c64* 4:1 dr *c54* *c65*

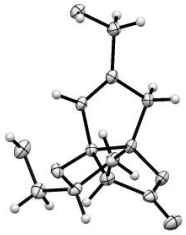
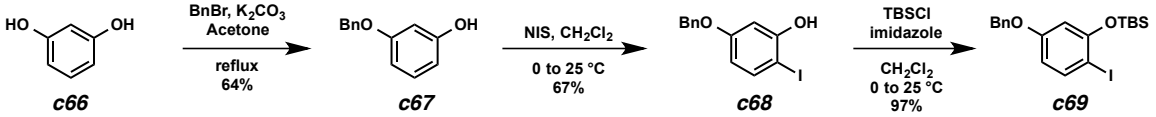


Figure 3-2. X-ray Crystal Structure of Propellane Diol **c54**.

Having protected propellane diol **c65** in hand, we approached the construction of a benzopyran moiety. Protected resorcinols (**c67** and **c69**) were identified as potential starting materials (Scheme 3-13). After mono-protection of resorcinol with a benzyl group, an iodo substituent was regioselectively introduced on to **c67** by *N*-iodosuccinimide (NIS) treatment.[14] Finally, a TBS protection of the remaining hydroxyl group resulted in a fully protected advanced resorcinol iodide **c69**.

Scheme 3-13. The Synthesis of Protected Iodoresorcinol **c69**.

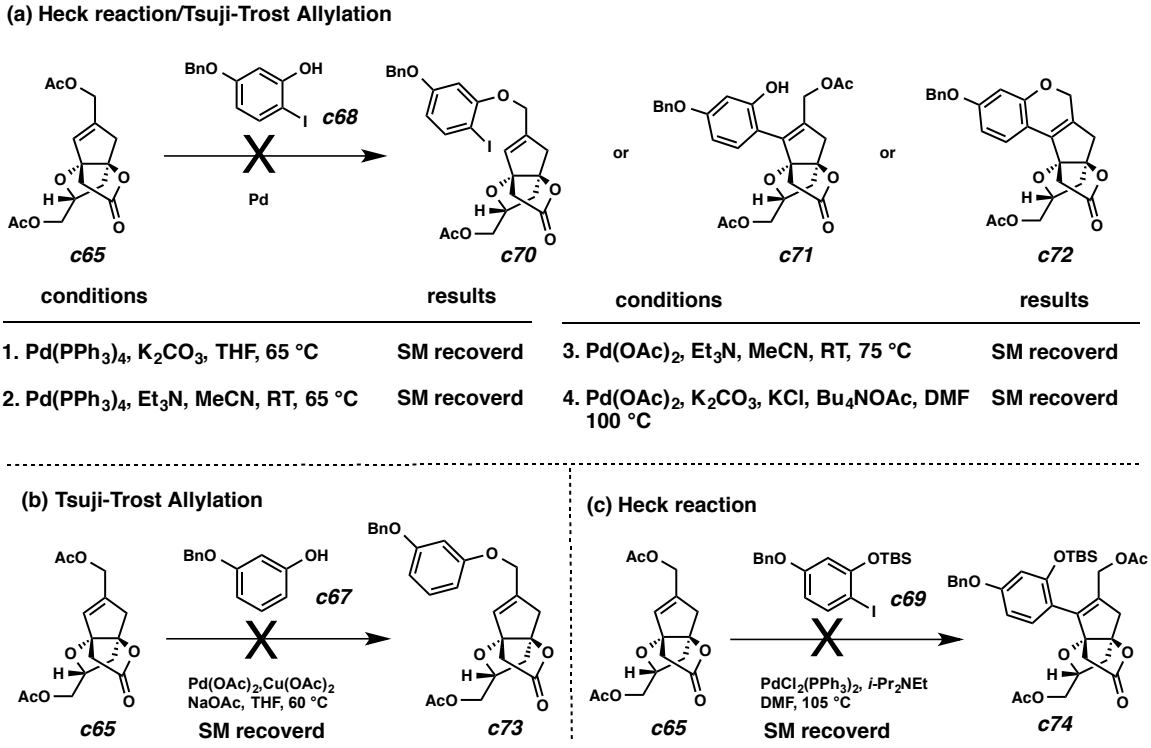


c66 *c67* *c68* *c69*

Next, the synthetic plan combines a Heck reaction and a Tsuji-Trost allylation in order to build up the benzopyran motif (Scheme 3-14a). However, employment of iodo

resorcinol **c68** as a coupling component in this tandem reaction was not successful. Unfortunately, we did not observe any tandem coupling product (**c72**),[15] Heck reaction product (**c71**),[16] or allylation product (**c70**).[17] An attempted reaction of a simplified coupling component — protected resorcinol **c67** — with propellane **c65** led only to the recovery of the starting material. Similarly, subjecting the fully protected iodo resorcinol **c69** and propellane **c65** to a Heck reaction yet again led to the recovery of the starting material (Scheme 3-14c).

Scheme 3-14. Cross Coupling with Resorcinols and Propellane **c65**.



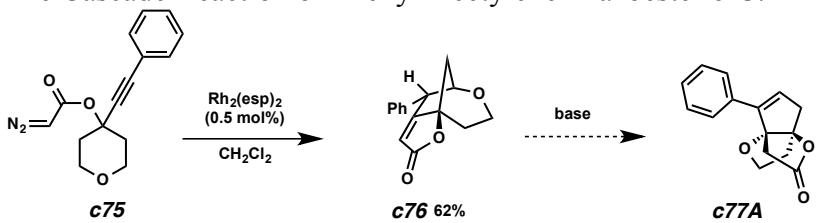
In the Tsuji-Trost allylation reaction, the palladium catalyst pre-coordinates to the olefin and is followed by either nucleophilic attack on one of the allylic positions or ligand exchange and reductive elimination from the palladium center to afford the

product. Based on this mechanistic rationale, we considered it to be highly likely that palladium is not able to approach to the olefin because of the sterically hindered environment, especially since up to 85% of the starting material is recovered. Additionally, the protodehalogenation of the protected iodo-resorcinol **c68** and **c69** in the Heck reaction corroborated the lack of reactivity for the propellane and suggested that the transition metal is unable to approach the olefin due to steric hindrance.

3.2.6 The Third Strategy

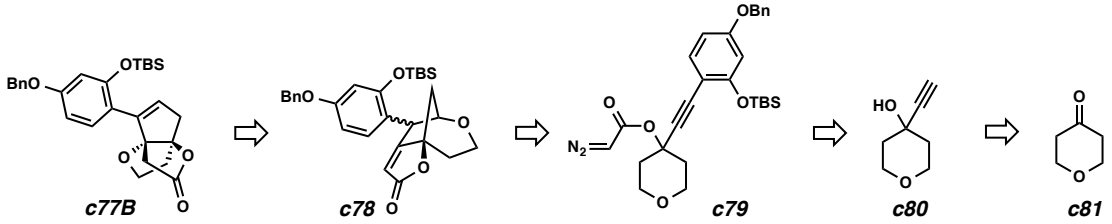
Although core propellane structure **c54** has been successfully synthesized, a problem with the formation of the benzopyran appeared at the next stage in the synthesis. Previously reported studies have shown that the phenyl acetylene diazoester **c75** can be easily converted into corresponding phenyl substituted bridged polycycle **c76** (Figure 3-2).[6] This polycycle **c76** is expected to rearrange into a propellane structure **c77A** under mildly basic conditions. More importantly, the phenyl group will be located at the sterically hindered vinyl position of the propellane after rearrangement. Replacement of the phenyl group with resorcinol would be a viable approach to brazilide A (**c5**).

Figure 3-2. The Cascade Reaction of Phenyl Acetylene Diazoester **c75**.



In order to test this hypothesis, a synthetic pathway was quickly designed for a simple model substrate. Aryl propellane **c77B** results from rearrangement of bridged polycycle **c78**, which is expected to be generated from the di-substituted phenyl acetylene diazoester **c79** through the Rh(II) catalyzed cascade reaction (Scheme 3-15). A Sonogashira cross-coupling reaction[18] can link the aryl group with the terminal alkyne **c80**, which can be conveniently prepared from pyranone **c81** and ethynyl magnesium bromide.

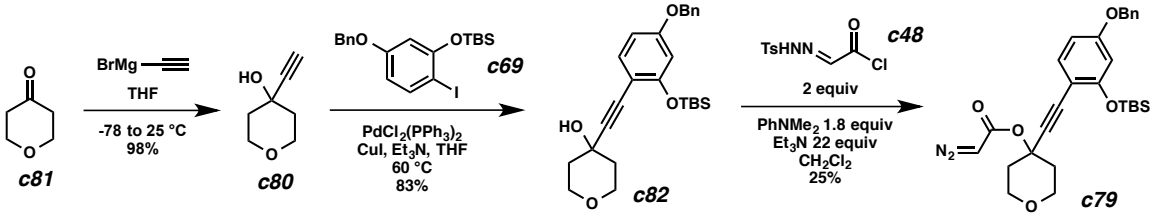
Scheme 3-15. Retrosynthesis of Aryl Propellane **c77B**.



3.2.7 Synthesis of the Third Propellane c77B

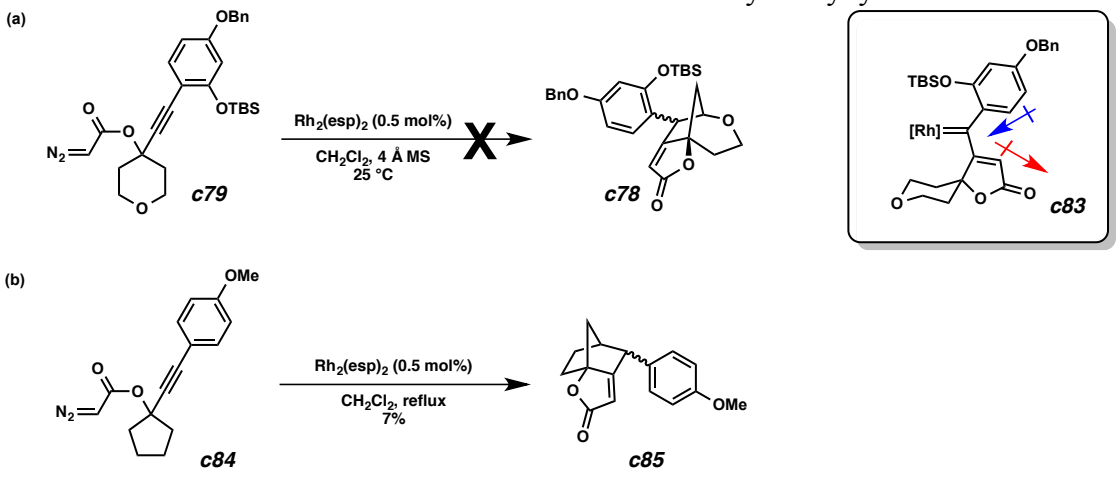
Propargyl alcohol **c80** was directly prepared from pyranone **c81** and subsequently underwent a cross-coupling reaction with protected iodoresorcinol **c69** to give aryl propargyl alcohol **c82**. In the next step, diazoester formation with the previously described conditions afforded the product in low yield, presumably due to the instability of the silyl ether protecting group under the basic conditions.

Scheme 3-16. The Synthesis of Diazoester **79**.



Diazoester **c79** was subjected to the Rh(II)-catalyzed cascade reaction conditions (Scheme 3-17a). NMR analysis of the crude reaction mixture showed that the major component of the reaction mixture was the diazoester. This result was similar to a previously described observation, that the 4-methoxyphenyl acetylene diazoester **c84** provides only 7% yield of the desired product under very forcing conditions (Scheme 3-17b).

Scheme 3-17. The Cascade Reaction of Electron Rich Aryl Alkynyl Diazoester **c79**.



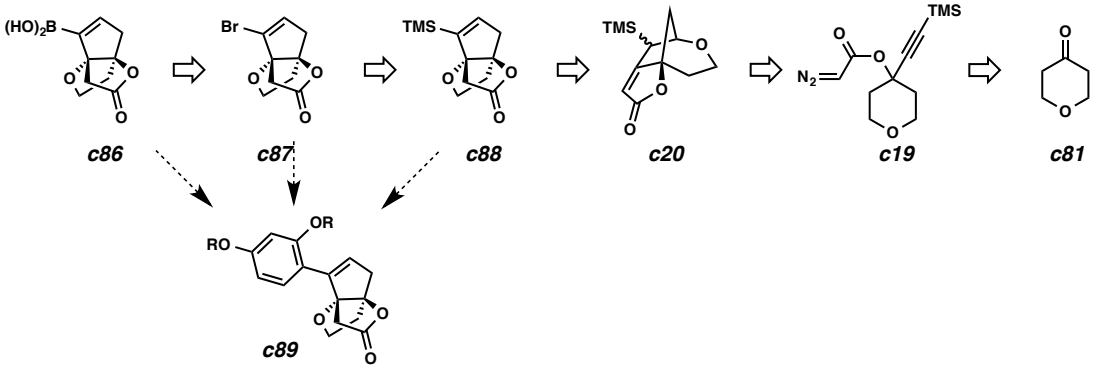
We hypothesize that when the Rh(II) catalyst reacts with these electron rich aryl acetylene substrates, the new-formed butenolide rhodium carbene is stabilized by the neighboring electron-rich aryl group so that the electrophilicity of the carbene is

decreased. As a result, this less electrophilic carbene failed to insert into the C-H bond (see **c83**). Since there is only 0.5 mol% of $Rh_2(esp)_2$ in the reaction, all the catalyst is sequestered in the donor-acceptor carbene **c83** in a non-reactive resting state. Most of the starting material would not have an opportunity to react with the catalyst. This inefficiency of the C-H bond insertion as a terminating step shuts down the reaction and thwarts this strategy.

3.2.8 The Fourth Strategy

Because an electron-rich aromatic group on the alkyne shuts down the cascade reaction, our attention was turned back towards introduction of the aryl group to the propellane via a cross-coupling reaction. The synthesis of the bridged polycycle **c20** has been previously described in only 3 steps from commercially available starting materials.

Scheme 3-18. Retrosynthetic Analysis of Aryl Propellane **c89**.



Polycycle **c20** is expected to undergo rearrangement to propellane **c88** under mildly basic conditions, leaving TMS group intact. This vinyl TMS group can be

employed as a nucleophilic coupling partner in a Hiyama-Denmark coupling reaction.[19] Alternatively, bromodesilylation of propellane **c88** can afford vinyl bromide **c87**, which can be subsequently used in a cross-coupling with an aryl nucleophile catalyzed by transition metals.[20] Vinyl bromide **c87** can be potentially converted into a vinyl boronic acid **c86**, which is a useful coupling partner for Suzuki-Miyaura cross-coupling reactions.[21]

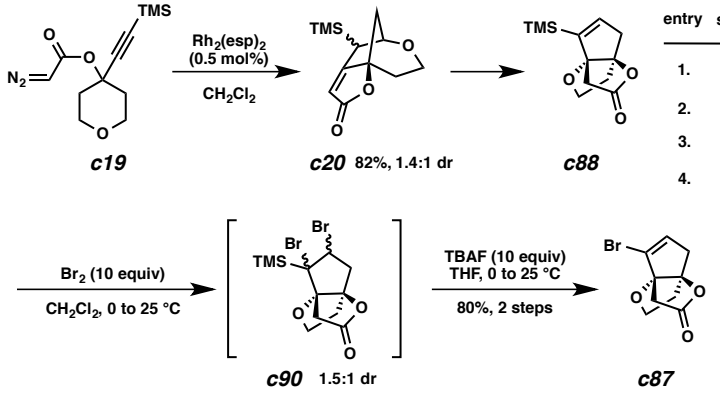
3.2.9 Synthesis of the Vinyl Silane Propellane c88

The preparation of diazoester **c19** starting from tetrahydro-4H-pyran-4-one (**c81**) had been developed previously.[6] Next, the cascade reaction was successfully scaled up with **c19** to 5 mmol, which in turn allowed the preparation of enough of the bridged polycycle **c20** to initiate extensive optimization of the reaction conditions (Scheme 3-19). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was found to facilitate the rearrangement of polycycle **c20** into propellane **c88**. Even though substoichiometric or catalytic amounts of DBU promoted the reaction, stoichiometric amounts were used to improve the yield of propellane **c88**.

Halogenative desilylation was studied next using a variety of reaction conditions and reagents. Several common halogenative desilylation procedures were examined; for example (1) iodine,[22] (2) *N*-iodosuccinimide (NIS) with silver nitrate,[23] (3) NIS with 2,6-lutidine in hexafluoroisopropanol,[24] (4) *N*-bromosuccinimide (NBS),[25] and (4) pyridinium tribromide with triethylamine.[26] However, none of the reagents and conditions employed proved effective and only starting material was recovered. Gratifyingly, we observed the

formation of dibromide propellane **c90** after subjecting the olefin starting material to 1.3 equivalents of elemental bromine.[27] Subsequent extensive reaction optimization revealed that the reaction reaches completion when the amount of bromine was increased to 10 equivalents. Without isolating the dibromo propellane **c90**, the crude reaction mixture was treated with an excess of tetrabutylammonium fluoride (TBAF), providing vinyl bromide **c87** in good yield.

Scheme 3-19. Synthesis of Vinyl TMS Propellane **c88** and Bromo Propellane **c87**.

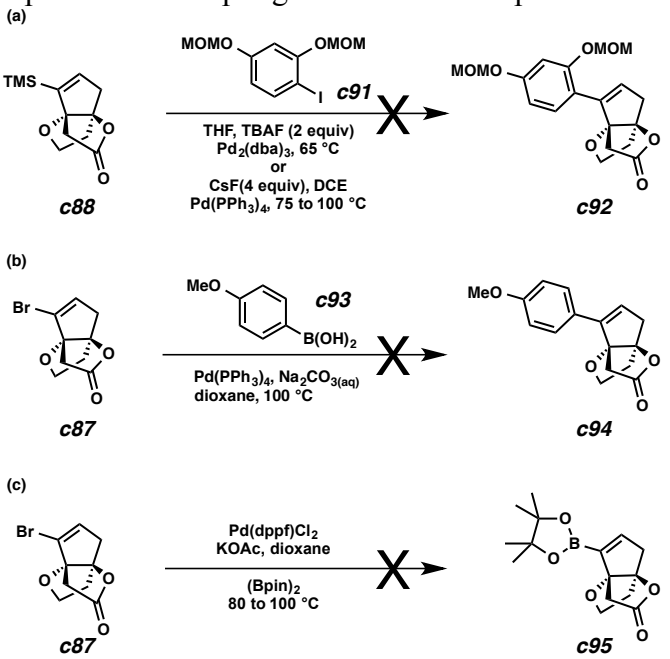


entry	solvent	DBU	temperature	yield
1.	THF	1.1 equiv	0 to 25 °C	25%
2.	CH_2Cl_2	0.5 equiv	0 to 25 °C	36%
3.	CH_2Cl_2	1.1 equiv	0 °C	72%
4.	CH_2Cl_2	1.2 equiv	0 to 25 °C	56%

Numerous attempts of Hiyama-Denmark coupling reaction using the vinyl TMS propellane **c88** and MOM protected resorcinol iodide **c91** proved unsuccessful (Scheme 3-20a).[19] Disappointingly, a preliminary trial using typical Suzuki cross-coupling conditions with 4-methoxyphenyl boronic acid (**c93**) and vinyl bromide **c87** was not successful (Scheme 3-20b).[28] In addition, even conversion of the vinyl bromide **c87** into vinyl boronate **c95** proved to be fruitless (Scheme 3-20c).[21] Presumably, the steric bulk around the bromide substituent prevented the oxidative addition of the palladium catalyst from taking place and therefore left the starting material unchanged. However, there are

still a great number of other conditions for cross-coupling, many of which are useful for sterically hindered substrates.[29] We still believe that cross-coupling conditions can be identified to install an aryl group on the propellane.

Scheme 3-20. Attempted Cross Coupling Reactions on Propellanes.



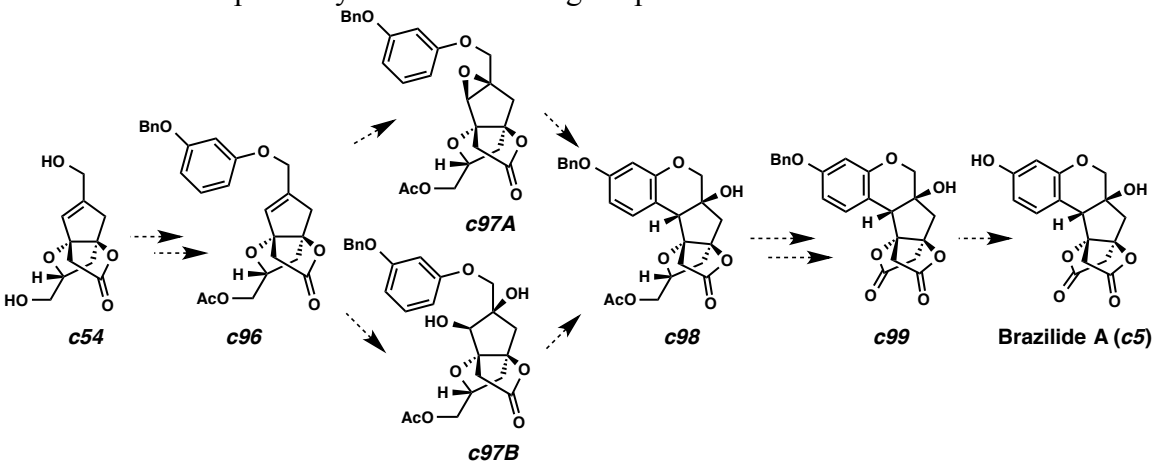
3.3 Conclusion and Proposed Future Studies

Two advanced synthetic intermediates for brazilide A have been synthesized, **c54** and **c87**. In the first strategy, an unproductive side reaction took place during the C-H bond insertion at the key cascade reaction. By redesigning the synthetic plan, this issue was addressed by employing a more symmetric substrate in the cascade reaction, which allowed for the successful construction of propellane diol **c54**. Unfortunately, due to the steric bulk surrounding the propellane core, traditional transition metal catalyzed cross-

coupling reactions like the Heck reaction and the Tsuji-Trost allylation failed to install a resorcinol motif onto the propellane core.

However, propellane diol **c54** is still considered to be a valuable intermediate in our synthesis of brazilide A. In a future plan, a regioselective Mitsunobu reaction followed by protection can afford resorcinol propellane ether **c96** (Scheme 3-21). Next, an epoxidation of the olefin would generate propellane epoxide **c97A**, or a dihydroxylation of the alkene could give propellane diol **c97B**. From epoxide **c97A** or diol **c97B**, the hydroxyl benzopyran motif can be built up via a Friedel-Crafts reaction. At the final stage of the synthesis, the lactone has to be formed by a C-C bond oxidative cleavage, and deprotection will provide brazilide A (**c5**).

Scheme 3-21. Proposed Synthesis Plan using Propellane Diol **c54**.

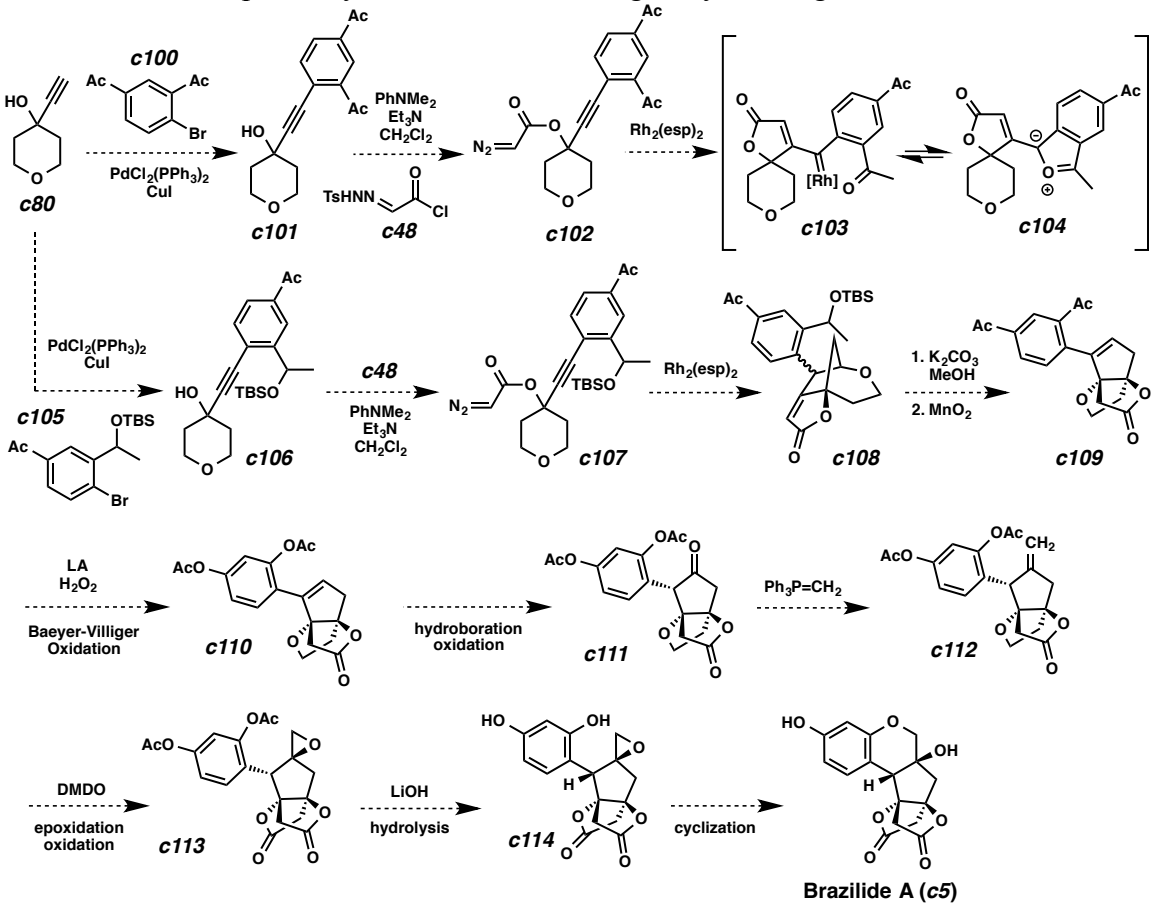


On the other hand, the formation of the C-C bond linking the resorcinol motif and the propellane was also given the attention. Treatment of resorcinol alkynyl diazoester **c79** with a Rh(II) catalyst presumably generated a weakly electrophilic butenolide rhodium carbene **c83** as a non-reactive resting intermediate, which did not perform a C-H

bond insertion in the terminating step. As a result, the reaction failed to produce the desired bridge polycycle **c79**.

To address this issue, electron deficient 2,4-diacetylaryl alkynyl diazoester **c102** would be expected to generate a stronger electrophilic rhodium carbene **c103** that should be able to perform C-H bond insertion (Scheme 3-22). However, the ortho-acetyl group could potentially form an ylide with the carbene (see **c104**),[30] which might shut down the reaction. In order to avoid this ylide formation, ortho-silyl ether substrate **c107** can be employed in the cascade reaction to generate bridged polycycle **c108**. After base-promoted rearrangement of **c108** followed by mild oxidation (MnO_2), 2,4-diacetylaryl propellane **c109** could be synthesized. Treatment of Baeyer-Villiger oxidation to **c109** can give 2,4-diacetatearyl propellane **c110**, which can be transferred to ketone **c111** by hydroboration and oxidation. Next, a chemoselective Wittig reaction to the ketone **c111** can provide terminal olefin **c112** without affecting other ester groups. Treating **c112** with dimethyldioxirane (DMDO)[31] can not only generate an epoxide motif in **c133**, but also oxidize the cyclic ether to lactone. Hydrolysis of **c113** will produce resorcinol propellane **c114**, which can finish brazilide A (**c5**) by a base promoted exo-epoxide cyclization in the same reaction.

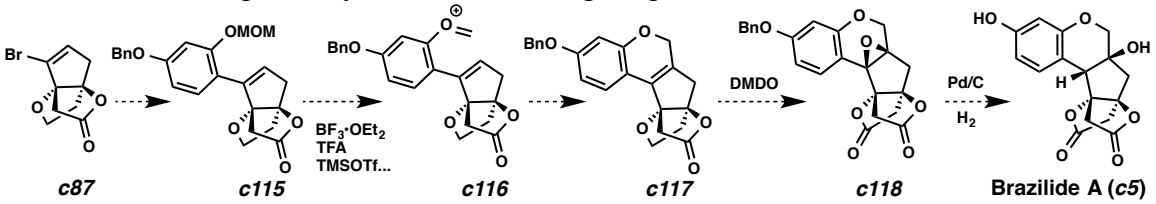
Scheme 3-22. Proposed Synthesis Plan Involving Baeyer-Villiger Oxidation.



To our delight, vinyl bromide **c87** can be easily prepared in a simple manner for future tests of cross-coupling reactions. In this future plan, the modified Suzuki or Negishi cross-coupling reactions,[32] which are typically used for sterically hindered substrates, are expected to provide an aryl propellane **c115** (Scheme 3-23). The ortho MOM ether serves a dual role, both as a protecting group and as a source of a methylene carbon for cyclization to form benzopyran **c117**. This transformation — a Prins reaction — will be triggered using Lewis or Bronsted acids.[33] Additionally, dimethyldioxirane (DMDO)[31] can both oxidize the tetrahydrofuran motif to a lactone and the olefin to an epoxide. A precise number of equivalents of DMDO will need to be used

in order to avoid possible overoxidation of the benzopyran. To finish the synthesis of brazilide A (**c5**), palladium catalyzed hydrogenolysis will be adopted to reduce the epoxide regioselectively and remove the benzyl group. The resulting synthetic route is shorter than the first plan, and we are likely to focus on this shorter pathway in the near future.

Scheme 3-23. Proposed Synthesis Plan Using Propellane Bromide **c87**.



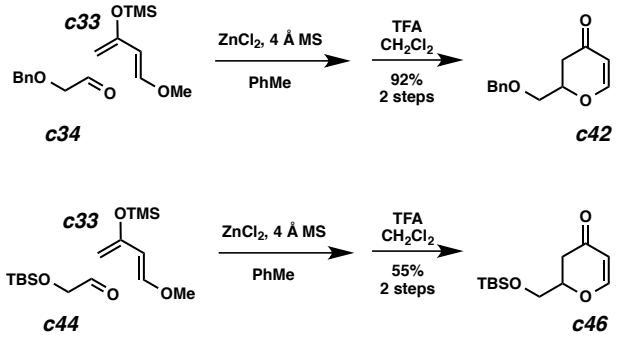
3.4 Experimental

3.4.1 Materials and Methods

General Considerations

All reactions were carried out in flame- or oven-dried glassware. Dichloromethane, diethyl ether, tetrahydrofuran, and toluene were purged with argon and dried over activated alumina columns. Flash chromatography was performed on 60 Å silica gel (EMD Chemicals Inc). Analytical thin-layer chromatography was performed on EMD silica gel/TLC plates with fluorescent indicator 254 nm. Chemical names were generated using Cambridgesoft ChemBioDraw Ultra 12.0. The ^{1}H, ^{13}C NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer using the residual solvent peak as an internal reference ($CDCl_3$: 7.24 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR. Methanol-d_4: 4.78 ppm for ^{1}H NMR and 49.2 ppm for ^{13}C NMR.). IR spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. HRMS analyses were performed under contract by the mass spectrometric facility at UT Austin via positive mode ESI or CI methods on a US10252005 instrument. Commercially available compounds were purchased from Sigma-Aldrich Chemical Co., Oakwood Chemical, Acros Organics, Alfa Aesar, Matrix Scientific or TCI America and were used without further purification.

3.4.2 Synthesis of Compounds



2-((benzyloxy)methyl)-2,3-dihydro-4*H*-pyran-4-one (c42)

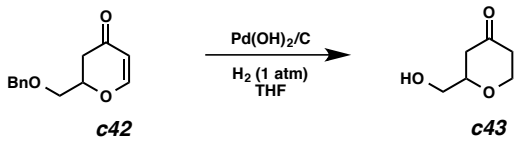
To a 25 mL round-bottom flask equipped with a stir bar was added powdered 4 Å molecular sieves (1.5 g) and the flask was flame-dried under high vacuum. The flask was cooled to room temperature and back-filled with Argon. $ZnCl_2$ (540 mg, 0.43 equiv) and PhMe (16.5 mL) were added to the flask, which was cooled to 0 °C. To the solution was added aldehyde **c34** (1.3 mL, 9.2 mmol) and diene **c33** (2.55 mL, 13.1 mmol, 1.5 equiv). The reaction mixture was slowly warmed up to 25 °C. After 48 h, the reaction was filtered through a short celite pad and concentrated under reduced pressure. To the crude reaction mixture was added CH_2Cl_2 (6 mL), and the solution was cooled to 0 °C, followed by the addition of trifluoroacetic acid (6 mL). The reaction was slowly warmed up to 25 °C and stirred for 2 h. Then saturated $NaHCO_{3(aq)}$ (50 mL) was added to the mixture, and the mixture was extracted with ethyl acetate (30 mL x 3). The organic solution was dried over $MgSO_4$, filtered through a celite pad, and concentrated. The crude product was purified by column chromatography on silica gel with a gradient of 15 to 20% ethyl acetate in hexane as eluents. The product was obtained as a yellow oil. (1.86 g, 92% yield). The NMR data are consistent with the literature.[9d] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41–7.24 (m, 5H), 5.39 (d, J = 5.9 Hz, 1H), 4.65–4.50 (m, 3H), 3.79–3.57 (m,

2H), 2.71 (dd, *J* = 16.9, 14.2 Hz, 1H), 2.37 (dd, *J* = 16.9, 3.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.9, 162.9, 137.3, 128.4, 127.9, 127.6, 10670, 78.2, 73.4, 70.5, 38.2. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{13}H_{14}O_3$: 241.0835; found 241.0837.

2-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,3-dihydro-4*H*-pyran-4-one (c46)

To a 25 mL round-bottom flask equipped with a stir bar was added powdered 4 Å molecular sieves (400 mg) and the flask was flame-dried under high vacuum. The flask was cooled to room temperature and back-filled with Argon. $ZnCl_2$ (110 mg, 0.40 equiv) and PhMe (4 mL) were added to the flask, which was cooled to 0 °C. To the solution was added aldehyde **c44** (0.4 mL, 2 mmol) and diene **c33** (0.7 mL, 2.44 mmol, 1.22 equiv). The reaction mixture was slowly warmed up to 25 °C. After 48 h, the reaction was filtered through a short celite pad and concentrated under reduced pressure. To the crude reaction mixture was added CH_2Cl_2 (8 mL), and the solution was cooled to 0 °C, followed by the addition of trifluoroacetic acid (50 μL). The reaction was slowly warmed up to 25 °C and stirred for 2 h. Then saturated $NaHCO_{3(aq)}$ (20 mL) was added and the mixture was extracted with ethyl acetate (15 mL x 3). The organic solution was dried over $MgSO_4$, filtered through a celite pad, and concentrated. The crude product was purified by column chromatography on silica gel with a gradient of 15 to 20% ethyl acetate in hexane as eluents. The product was obtained as a yellow oil. (266.6 mg, 55% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 6.0 Hz, 1H), 5.33 (d, *J* = 5.3 Hz, 1H), 4.39 (dq, *J* = 14.0, 4.0 Hz, 1H), 3.83 (dd, *J* = 11.2, 3.8 Hz, 1H), 3.75 (dd, *J* = 11.3, 4.5 Hz, 1H), 2.66 (dd, *J* = 17.0, 13.9 Hz, 1H), 2.39–2.27 (m, 1H), 0.83 (s, 9H), 0.02 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.3, 162.9, 106.8, 79.5, 64.1, 38.0, 25.7, 18.2, -5.5, -

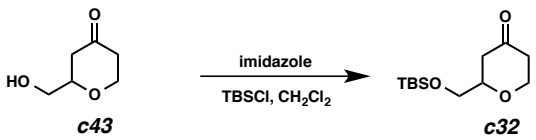
5.5. **IR(neat)** 2928, 2856, 1676, 1595, 1222, 1134, 1100, 1045, 1024, 905, 834, 777 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{12}H_{22}O_{3Si}$: 265.1230; found 265.1238. $\mathbf{R_F}$: 0.3 in 35% ethyl acetate/hexane.



c42 *c43*

2-(hydroxymethyl)tetrahydro-4*H*-pyran-4-one (c43)

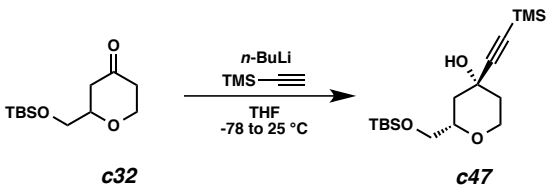
To a flame-dried round-bottom flask was added THF (25 mL), enone **c42** (533 mg, 2.44 mmol), and $Pd(OH)_2/C$ (100 mg) at 25 °C. The mixture was saturated by hydrogen gas and stirred under hydrogen atmosphere (1 atm) for 9.5 h. The reaction mixture was filtered through a celite pad and concentrated. The crude product was purified by column chromatography on silica gel with 80% ethyl acetate in hexane as an eluent. The product was obtained as a colorless oil. (241.7 mg, 76% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.39–4.24 (m, 1H), 3.81–3.65 (m, 3H), 3.64–3.51 (m, 1H), 2.67–2.53 (m, 1H), 2.53–2.41 (m, 1H), 2.38–2.26 (m, 2H), 2.01 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 206.4, 78.1, 66.6, 65.3, 43.8, 42.0. **IR(neat)** 3425, 2868, 1712, 1160, 1090, 1057, 1031, 997, 955, 768, 726, 696 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_6H_{10}O_3$: 153.0522; found 153.0519. $\mathbf{R_F}$: 0.6 in 10% $MeOH/CH_2Cl_2$.



c43 *c32*

2-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydro-4*H*-pyran-4-one (C32)

To a flame-dried round-bottom flask was added ketone **c43** (424 mg, 3.2 mmol), imidazole (765 mg, 11.2 mmol, 3.5 equiv), and CH_2Cl_2 (6.5 mL). The reaction was stirred for 10 min at 0 °C before adding TBS-Cl (1.2 g, 8 mmol, 2.5 equiv). The reaction was slowly warmed up to 25 °C and stirred for 1.5 h. To the reaction mixture was added saturated $NaHCO_{3(aq)}$ (10 mL) and the mixtures were extracted with CH_2Cl_2 (10 mL x 3). The organic solution was washed by saturated $NaCl_{(aq)}$ once and dried over $MgSO_4$. The crude solution was filtered through a celite pad and concentrated. The crude product was purified by column chromatography on silica gel with a gradient of 10 to 35 % ethyl acetate in hexane as eluents. The product was obtained as a white solid. (673.4 mg, 86% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.35–4.22 (m, 1H), 3.77–3.56 (m, 4H), 2.68–2.48 (m, 1H), 2.49–2.24 (m, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.2, 78.3, 66.5, 65.9, 44.5, 42.1, 25.9, 18.4. **IR (neat)** 2928, 2856, 1710, 1470, 1462, 1413, 1359, 1328, 1255, 1160, 1126, 1098, 928, 857, 833, 812, 771 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{12}H_{24}O_3Si$: 267.1387; found 267.1391. **R_F**: 0.77 in 10% MeOH/CH_2Cl_2. **MP:** 33-35 °C.

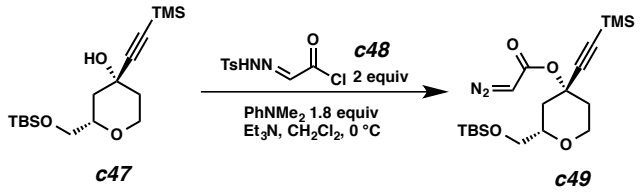


c32 *c47*

(2*S*,4*R*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((trimethylsilyl)ethynyl)tetrahydro-2*H*-pyran-4-ol (c47)

To a flame-dried 50 mL round-bottom flask was add *n*-BuLi (2.5 M, 4.5 mL, 11.3 mmol, 1.8 equiv) and THF (5 mL). The mixture was cooled to -78 °C and stirred for 5 min. To the mixture was added TMS acetylene (1.6 mL, 11.3 mmol, 1.8 equiv), and the mixture was stirred for 20 min. The ketone **c32** (1.5 g, 6 mmol) was transferred into the reaction using THF (6 mL). The reaction was stirred for 5 h and then warmed up to 25 °C. After TLC analysis showed no starting material, saturated $NH_4Cl_{(aq)}$ (20 mL) was added and the mixture was extracted with diethyl ether (15 mL x3). The organic solution was washed with saturated $NaCl_{(aq)}$ once and dried over $MgSO_4$. The crude solution was filtered through a celite pad and concentrated. The crude product was purified by column chromatography on silica gel with a gradient of 0 to 3% ethyl acetate in CH_2Cl_2 as eluents first. The overlapping mixtures were collected and purified by column chromatography on silica gel with a gradient of 10 to 20% diethyl ether in pentane as eluents. The product was obtained as a white solid. (1.65 g, 80% yield, 16:1 dr, 5% yield of the minor diasteromer). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.97 (ddd, *J* = 11.9, 4.7, 1.8 Hz, 1H), 3.73–3.50 (m, 4H), 2.39 (s, 1H), 2.01–1.91 (m, 1H), 1.87–1.78 (m, 1H), 1.79–1.66 (m, 1H), 1.51–1.38 (m, 1H), 0.86 (s, 9H), 0.14 (s, 9H), 0.04 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 107.2, 90.1, 75.8, 67.1, 65.7, 65.0, 41.9, 39.6, 25.6, 18.1, -0.5. **IR(neat)** 3383, 2956, 2928, 2854, 2164, 1473, 1359, 1322, 1148, 1113, 1070, 1037, 946, 922, 863,

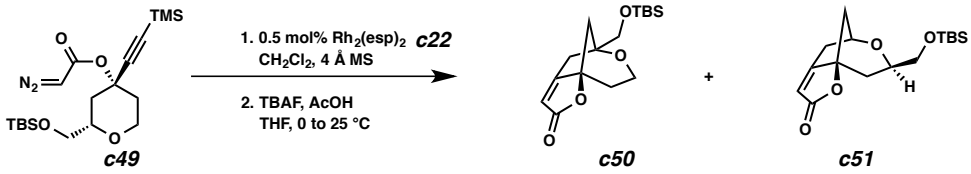
833, 774 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{17}H_{34}O_3Si_2$: 365.1939; found 365.1953. $\mathbf{R_F}$: 0.21 in 50% ethyl acetate/CH_2Cl_2. **MP:** 49-51 °C.



(2*S*,4*R*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((trimethylsilyl)ethynyl)tetrahydro-2*H*-pyran-4-yl 2-diazoacetate (c49)

A flame-dried round-bottom flask was charged with the alcohol **c47** (1.58 g, 4.6 mmol) under an argon atmosphere. Glyoxylic acid chloride *p*-toluenesulfonylhydrazone **c48** (2.4 g, 9.2 mmol, 2 equiv) was added. To the mixture was added CH_2Cl_2 (27 mL) at 0 °C, followed by the addition of *N*,*N*-dimethyl aniline (1.1 mL, 1.8 equiv). The reaction was stirred for 45 min before adding triethylamine (7.1 mL, 50 mmol, 11 equiv). The mixture was stirred an additional 2 h and concentrated. To the crude mixture was added 20% ethyl acetate in hexanes (60 mL). The organic solution was washed with concentrated citric acid (15 mL x 2) and brine, dried over $MgSO_4$, filtered through a celite pad, and concentrated. The crude product was purified by column chromatography on silica gel with CH_2Cl_2 first. The overlapping mixtures of the Ts-hydrazone and diazoester were collected and purified with a gradient of 5 to 10% diethyl ether in pentane as eluents. The product was obtained as a yellow oil. (942 mg, 50% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.68 (s, 1H), 3.97 (ddd, *J* = 12.0, 4.7, 1.7 Hz, 1H), 3.76–3.51 (m, 4H), 2.31 (ddt, *J* = 18.8, 10.6, 2.3 Hz, 2H), 1.81 (td, *J* = 12.5, 4.7 Hz, 1H), 1.64–1.51 (m, 1H), 0.87 (s, 9H), 0.16 (s, 9H), 0.04 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ~165 (missing), 103.2, 93.2,

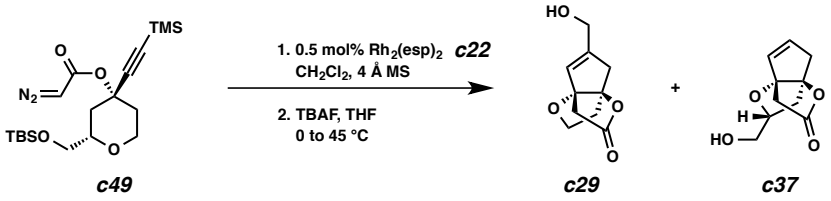
75.5, 74.7, 66.1, 64.7, 46.7, 40.0, 37.7, 25.9, 18.4, -0.2. **IR(neat)** 3189, 2956, 2927, 2856, 2109, 1784, 1705, 1362, 1161, 1101, 1069, 937, 913, 834, 776, 758 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{19}H_{34}N_2O_4Si_2$: 433.1949; found 433.1963. $\mathbf{R_F}$: 0.5 in 30% diethyl ether/pentane.



To a 250 mL round-bottom flask equipped with a stir bar was added powdered 4 Å molecular sieves (1 g) and the flask was flame-dried under high vacuum. The flask was cooled to room temperature and back-filled with Argon, followed by the addition of $Rh_2(esp)_2$ (2.4 mg, 0.003 mmol, 0.006 equiv), and CH_2Cl_2 (50 mL). The diazoester **c49** (200 mg, 0.49 mmol) was slowly added into the flask using CH_2Cl_2 (50 mL) over 20 min with vigorous stirring. After the addition finished, the reaction was stirred for an additional 5 min and TLC analysis showed no starting material. The reaction was filtered through a celite pad and concentrated. To the reaction mixture was added THF (5 mL), and the solution was cooled to 0 °C. To the solution was added acetic acid (60 μL) and TBAF (1 M, 1.1 mL, 2.2 equiv). The reaction was allowed to warm up to 25 °C, and it was stirred for 30 min, then saturated $NaHCO_{3(aq)}$ (10 mL) was added. The mixture was extracted with diethyl ether (10 mL x3), and the combined organics was washed with brine, dried over $MgSO_4$, filtered through a celite pad, and concentrated. The crude mixture was purified by column chromatography on silica gel with a gradient of 10 to 20% ethyl acetate in hexane as eluents.

(5*S*,8a*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5,7,8-tetrahydro-2*H*-5,8a-methanofuro[2,3-*d*]oxepin-2-one (c50) Bridged tricycle **c50** was isolate as a yellowish oil. (31.4 mg, 20.8% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.75 (s, 1H), 4.04 (dd, *J* = 12.1, 7.0 Hz, 1H), 3.84 (td, *J* = 12.2, 4.4 Hz, 1H), 3.60 (q, *J* = 10.3 Hz, 3H), 2.83 (d, *J* = 19.8 Hz, 1H), 2.68 (d, *J* = 19.7 Hz, 1H), 2.44 (td, *J* = 12.4, 7.3 Hz, 1H), 1.81 (s, 2H), 1.55 (dd, *J* = 12.6, 4.8 Hz, 1H), 0.84 (s, 9H), 0.03 (d, *J* = 2.9 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.9, 173.8, 112.9, 91.4, 86.7, 65.5, 61.4, 43.8, 36.3, 30.2, 25.8, 18.2, -5.5. **IR(neat)** 2952, 2928, 2856, 1778, 1749, 1361, 1301, 1230, 1118, 1096, 938, 897, 884, 875, 833 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{16}H_{26}O_4Si_2$: 333.1493; found 333.1500. **R_F**: 0.42 in 35% ethyl acetate/hexane.

(5*S*,7*R*,8a*S*)-7-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5,7,8-tetrahydro-2*H*-5,8a-methanofuro[2,3-*d*]oxepin-2-one (c51) Bridged tricycle **c51** was isolated as a white solid. (68.6 mg, 45.5% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.76 (s, 1H), 4.74 (t, *J* = 4.3 Hz, 1H), 3.94–3.79 (m, 1H), 3.64 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.56 (dd, *J* = 10.6, 5.0 Hz, 1H), 2.91 (dt, *J* = 19.7, 2.6 Hz, 1H), 2.73 (dd, *J* = 19.6, 5.3 Hz, 1H), 2.17 (t, *J* = 11.8 Hz, 1H), 2.05 (dd, *J* = 10.8, 2.8 Hz, 1H), 1.70–1.54 (m, 2H), 0.85 (s, 9H), 0.02 (d, *J* = 2.2 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.8, 173.7, 113.0, 90.9, 76.9, 71.2, 65.7, 42.4, 38.8, 29.7, 25.8, 18.3, -5.4, -5.4. **IR(neat)** 3097, 2956, 2923, 2882, 2854, 1770, 1745, 1245, 1202, 1184, 1162, 1119, 1098, 1086, 1074, 1029, 1017, 978, 939, 899, 879, 830, 794, 781, 750 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{16}H_{26}O_4Si_2$: 333.1493; found 333.1501. **R_F**: 0.27 in 35% ethyl acetate/hexane. **MP:** 70-73 °C.



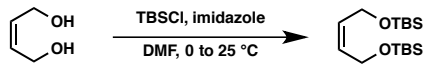
c49 *c29* *c37*

To a 250 mL round-bottom flask equipped with a stir bar was added powdered 4 Å molecular sieves (1 g) and the flask was flame-dried under high vacuum. The flask was cooled to room temperature and back-filled with Argon, followed by the addition of $Rh_2(esp)_2$ (2.8 mg, 0.0036 mmol, 0.005 equiv), and CH_2Cl_2 (100 mL). The diazoester **c49** (300 mg, 0.73 mmol) was slowly added into the flask using CH_2Cl_2 (46 mL) over 20 min with vigorous stirring. After the addition finished, the reaction was stirred for an additional 5 min and TLC analysis showed no starting material. The reaction was filtered through a celite pad and concentrated. To the reaction mixture was added THF (7.5 mL), and the solution was cooled to 0 °C. To the solution was added TBAF (1 M, 2.2 mL, 3 equiv). The reaction was allowed to warm up to 45 °C, and it was stirred for 30 min. The reaction was cooled to 25 °C, then saturated $NaHCO_{3(aq)}$ (10 mL) was added. The mixture was extracted with diethyl ether (10 mL x3), and the combined organics was washed with brine, dried over $MgSO_4$, filtered through a celite pad, and concentrated. The crude mixture was purified by column chromatography on silica gel with 70% ethyl acetate in hexane or 3% MeOH in CH_2Cl_2 as eluents.

(3a*S*,6a*R*)-5-(hydroxymethyl)-2,3-dihydro-4*H*-3a,6a-(epoxyethano)cyclopenta[*b*]furan-8-one (c29) Allyl alcohol **c29** was obtained as a white waxy solid. (25.1 mg, 17.5% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.70 (t, J = 2.1

Hz, 1H), 4.16 (s, 2H), 3.94 (dt, *J* = 9.2, 6.5 Hz, 1H), 3.85 (dt, *J* = 9.3, 6.5 Hz, 1H), 2.92–2.70 (m, 4H), 2.36 (dt, *J* = 13.2, 6.6 Hz, 1H), 2.15 (dt, *J* = 13.0, 6.4 Hz, 1H), 1.78 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.8, 146.8, 124.3, 98.8, 97.8, 67.1, 61.2, 43.7, 40.4, 40.0. **IR (neat)** 3427, 2986, 2918, 2848, 1767, 1440, 1295, 1246, 1184, 1116, 1087, 1070, 995, 866, 825, 746, 670 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{10}H_{12}O_4$: 219.0628; found 219.0628. **R_F**: 0.36 in ethyl acetate.

(2*R*,3a*S*,6a*R*)-2-(hydroxymethyl)-2,3-dihydro-4*H*-3a,6a-(epoxyethano)cyclopenta[*b*]furan-8-one (c37) Alcohol **c37** was obtained as a white waxy solid. (37.3 mg, 26.6% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.93–5.80 (m, 1H), 5.83–5.71 (m, 1H), 4.29–4.19 (m, 1H), 3.82 (dd, *J* = 12.2, 2.9 Hz, 1H), 3.54 (dd, *J* = 12.1, 4.4 Hz, 1H), 2.96–2.67 (m, 4H), 2.45 (dd, *J* = 13.8, 5.0 Hz, 1H), 1.99 (dd, *J* = 13.9, 10.7 Hz, 1H), 1.85 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.7, 132.1, 131.7, 100.1, 99.1, 79.8, 62.8, 43.4, 40.2, 39.6. **IR (neat)** 3425, 2986, 2918, 2851, 1765, 1443, 1293, 1250, 1184, 1113, 1088, 1070, 995, 865, 824, 747, 672 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{10}H_{12}O_4$: 219.0628; found 219.0628. **R_F**: 0.33 in ethyl acetate.

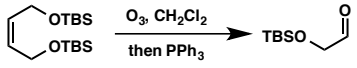


c58 ***c59***

(*Z*)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodec-6-ene(c59)

To a flame-dried flask equipped with a stir bar was added imidazole (9.1g, 133.8 mmol, 2.2 equiv), *cis*-2-butene-1,4-diol **c58** (5 mL, 60.8 mmol), and DMF (80 mL). The solution was then cooled to 0 °C. After the mixture was stirred for 10 min, TBSCl (18.4 g, 133.8

mmol, 2.2 equiv) was added to the flask. The reaction was stirred for 16 h at 25 °C. To the reaction mixture was added water (300 mL), and the mixture were extracted with diethyl ether (120 mL x3). The combined organics was washed with brine, dried over $MgSO_4$, filtered through a celite pad, and concentrated. The crude product was purified by column chromatography on silica gel with 3 % ethyl acetate in hexane as an eluent. The product was obtained as a colorless oil. (18.9 g, 99% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.53 (t, *J* = 3.6 Hz, 2H), 4.21 (d, *J* = 3.9 Hz, 4H), 0.88 (s, 18H), 0.05 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 130.1, 59.6, 25.9, 18.3, -5.2. **IR (neat)** 2954, 2928, 2885, 2856, 1471, 1462, 1361, 1252, 1074, 1005, 938, 832, 772 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{16}H_{36}O_4Si_2$: 339.2146; found 339.2160. **R_F**: 0.3 in 3% ethyl acetate/hexanes.

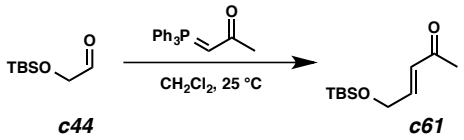


c59 *c44*

2-((*tert*-butyldimethylsilyl)oxy)acetaldehyde (c44)

To a flame-dried three-neck round-bottom flask equipped with a stir bar was added silyl ether **c59** (7.5 g, 19.0 mmol) and CH_2Cl_2 (150 mL) under nitrogen atmosphere. The flask was cooled to -78 °C and the mixture was stirred for 10 min. The left neck was connected to a tubing, which is inserted into a 10% $KI_{(aq)}$ solution (500 mL). Into the middle neck was put a Teflon stopper. The right neck was connected to the ozone generator. A stream of ozone was bubbled through the solution via a glass tube until the solution turned to blue. The ozone generator was turned off and a stream of oxygen was bubbled through the solution via a glass tube until the solution turned to colorless. The reaction was put

under a nitrogen atmosphere, and PPh_3 (7.3 g, 22.2 mmol, 1.17 equiv) was added to the reaction at -78 °C. The reaction was allowed to warm up to 25 °C for 3 h. The crude reaction mixture was concentrated. The vacuum distillation (0.250 mmHg, 130 °C) of the crude mixture provided aldehyde **c44** as a colorless oil. (5.86 g, 88% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 4.16 (d, J = 0.7 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.1, 69.5, 25.7, 18.3, -5.5. **R_F**: 0.45 in 5% ethyl acetate/hexanes.

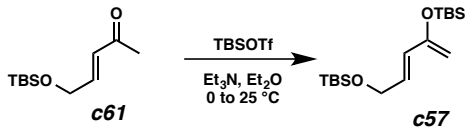


c44 *c61*

(*E*)-5-((*tert*-butyldimethylsilyl)oxy)pent-3-en-2-one (c61)

To a flame-dried flask equipped with a stir bar was added aldehyde **c44** (3 g, 17.3 mmol), 1-(triphenylphosphoranylidene)-2-propanone (6.9 g, 21.7 mmol, 1.25 equiv), and CH_2Cl_2 (30 mL). The reaction mixture was stirred at 25 °C until TLC analysis showed no starting material. After completion, the reaction mixture was concentrated via rotary evaporation. The crude mixture was purified via flash column chromatography with 5% ethyl acetate in hexanes as an eluent on silica gel. The product was obtained as a colorless oil. (3.4 g, 90% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.78 (dt, J = 15.7, 3.6 Hz, 1H), 6.29 (dt, J = 15.7, 2.2 Hz, 1H), 4.32 (dd, J = 3.6, 2.2 Hz, 2H), 2.22 (s, 3H), 0.87 (s, 9H), 0.04 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.3, 146.2, 128.7, 62.1, 27.2, 25.8, 18.3. **IR(neat)** 2955, 2929, 2885, 2856, 1699, 1678, 1634, 1472, 1445, 1360, 1252, 1134, 1078, 1005,

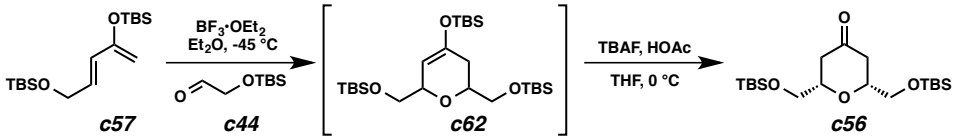
937, 913, 833, 810, 775 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{11}H_{22}O_2Si$: 237.1281; found 237.1288. $\mathbf{R_F}$: 0.3 in 10% ethyl acetate/hexanes.



c61 *c57*

(*E*)-2,2,3,3,10,10,11,11-octamethyl-5-methylene-4,9-dioxa-3,10-disiladodec-6-ene (c57)

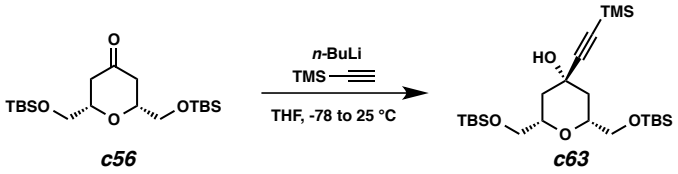
To a flame-dried flask equipped with a stir bar was added enone **c61** (2.23 g, 10.1 mmol) and triethylamine (7.2 mL, 50 mmol, 5 equiv) at 0 °C. To the mixture was slowly added TBSOTf (3.1 mL, 13 mmol, 1.3 equiv), and the reaction was stirred for 1 h. To the mixture was then added diethyl ether (7.5 mL), and the mixture was warmed to 25 °C. After TLC analysis showed no starting material, to the reaction mixture was added saturated $NaHCO_{3(aq)}$(20 mL). The mixtures were extracted by hexanes (20 mL x3). The organic layer was washed with saturated $NH_4Cl_{(aq)}$ (10 mL), saturated $NaHCO_{3(aq)}$ (10 mL), and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered through neutral Al_2O_3 pad, and concentrated to give clean diene **c57** as a colorless oil without further purification. (2.87 g, 84%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.08–5.99 (m, 2H), 4.29–4.21 (m, 4H), 0.95 (s, 9H), 0.90 (s, 9H), 0.16 (s, 6H), 0.06 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.8, 129.9, 127.2, 95.1, 63.0, 25.9, 25.8, 18.4, 18.3, -4.7, -5.2. **IR (neat)** 2955, 2929, 2885, 2857, 1682, 1472, 1463, 1361, 1253, 1073, 1022, 938, 963, 832, 811 cm^{-1}. $\mathbf{R_F}$: 0.75 in 5% diethyl ether/pentane.



(2*R*,6*S*)-2,6-bis(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydro-4*H*-pyran-4-one (c56)

To a 125 mL round-bottom flask equipped with a stir bar was added powdered 4 Å molecular sieves (1.8 g), and the flask was flame-dried under high vacuum. The flask was cooled to room temperature and back-filled with Argon. To the flask was added aldehyde **c44** (1.4 mL, 7.17 mmol, 1 equiv), diethyl ether (70 mL), and BF_3•OEt_2 (0.9 mL, 7.2 mmol, 1 equiv) at -45 °C. After the solution was stirred for 10 min, diene **c57** (2.88 g, 8.75 mmol, 1.22 equiv) was added to the solution. After TLC analysis showed no starting material, triethylamine (2 mL) was added to the reaction. To the mixture was added water (20 mL), and it was extracted by ether (150 mL x3). The organic solution was washed by brine, dried over $MgSO_4$, filtered through an Al_2O_3 pad, and concentrated. To the crude reaction mixture was added THF (30 mL) and the solution was cooled to 0 °C. To the reaction was added acetic acid (0.8 mL) and TBAF (1M, 9.3 mL, 9.3 mmol, 1.3 equiv). After TLC analysis showed no starting material, to the mixture was added water (20 mL), and mixtures were extracted by ether (50 mL x3). The organic solution was washed by brine, dried over $MgSO_4$, filtered through a celite pad, and concentrated. The crude mixture was purified via flash column chromatography on silica gel with 10% diethyl ether in hexanes as an eluent. The product was obtained as a colorless oil. (2.4 g, 86 %

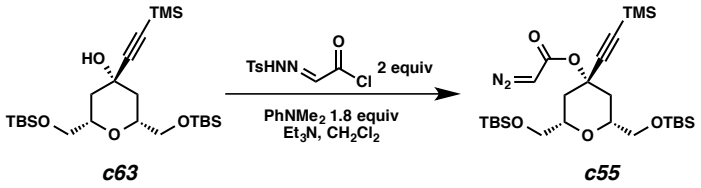
yield in total, 3.75:1 dr; 67.9% yield of the cis isomer **c56**). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.74–3.59 (m, 6H), 2.38–2.28 (m, 4H), 0.84 (s, 18H), 0.02 (s, 6H), 0.01 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 207.7, 77.4, 65.7, 44.1, 25.8, 18.3, -5.4, -5.4. **IR (neat)** 2954, 2928, 2856, 1722, 1472, 1463, 1361, 1310, 1285, 1148, 1114, 1022, 939, 895, 832, 813 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{19}H_{40}O_4Si_2$: 411.2357; found 411.2369. **R_F**: 0.21 in 5% diethyl ether/hexane.



(2*R*,4*s*,6*S*)-2,6-bis(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((trimethylsilyl)ethynyl)tetrahydro-2*H*-pyran-4-ol (c63)

To a flame-dried 25 mL round-bottom flask was add *n*-BuLi (2.5 M, 3.2 mL, 8 mmol, 2 equiv) and THF (5 mL). The mixture was cooled to -78 °C and stirred for 5 min. To the mixture was added TMS acetylene (1.2 mL, 8 mmol, 2 equiv) and it was stirred for 20 min. The ketone **c56** (1.56 g, 4 mmol) was transferred into the reaction using THF (5 mL). The reaction was stirred for 5 h and then warmed up to 25 °C. After TLC analysis showed no starting material, saturated $NH_4Cl_{(aq)}$ (20 mL) was added to the reaction and the mixture was extracted with diethyl ether (15 mL x3). The organic layer was washed with saturated $NaCl_{(aq)}$ (20 mL) once and dried over $MgSO_4$. The crude solution was filtered through a celite pad and concentrated. The crude product was purified by column chromatography on silica gel with a gradient of 0 to 3% ethyl acetate in CH_2Cl_2 as eluents. The product was obtained as a white solid. (1.78 g, 80% yield, >20:1 dr). **^{1}H**

NMR (500 MHz, $CDCl_3$) δ 3.69 (dd, *J* = 10.3, 5.1 Hz, 2H), 3.64–3.56 (m, 2H), 3.54 (dd, *J* = 10.3, 5.7 Hz, 2H), 2.24 (s, 1H), 1.99 (dd, *J* = 11.9, 2.1 Hz, 2H), 1.38 (t, *J* = 11.8 Hz, 2H), 0.86 (s, 18H), 0.14 (s, 9H), 0.03 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 107.8, 90.4, 75.7, 67.7, 65.9, 42.2, 25.9, 18.3, -0.1, -5.2, -5.2. **IR (neat)** 3418, 2954, 2927, 2856, 2166, 1297, 1249, 1111, 937, 888, 831, 777 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{24}H_{50}O_4Si_3$: 509.2909; found 509.2925. **R_F**: 0.36 in 2% ethyl acetate/CH_2Cl_2. **MP:** 55-57 °C.

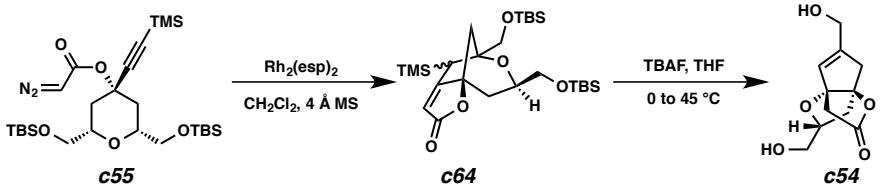


c63 *c55*

(2*R*,4*s*,6*S*)-2,6-bis(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((trimethylsilyl)ethynyl)tetrahydro-2*H*-pyran-4-yl 2-diazoacetate (c55)

A flame-dried round-bottom flask was charged with the alcohol **c63** (977 mg, 2 mmol) under an argon atmosphere. Glyoxylic acid chloride *p*-toluenesulfonylhydrazone **c48** (1.1 g, 4 mmol, 2 equiv) was added. To the mixture was added CH_2Cl_2 (6 mL) at 0 °C, followed by the addition of *N*,*N*-dimethyl aniline (0.5 mL, 2 equiv). The reaction was stirred for 45 min before adding triethylamine (6.1 mL, 44 mmol, 22 equiv). The mixture was stirred an additional 2 h and concentrated. To the crude mixture was added 5% ethyl acetate in hexanes (30 mL), and the organic solution was washed with concentrated citric acid (10 mL x 2) and brine. The organic solution was dried over $MgSO_4$, filtered through a celite pad, and concentrated. The crude product was purified by column chromatography on silica gel with a 4% diethyl ether in pentane as an eluent. The product

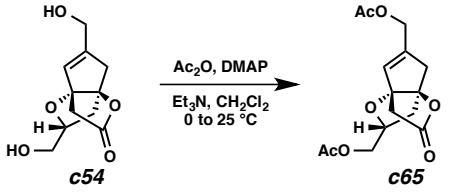
was obtained as a yellow oil. (610 mg, 55% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.67 (s, 1H), 3.74–3.62 (m, 4H), 3.60–3.51 (m, 2H), 2.40 (d, *J* = 12.1 Hz, 2H), 1.51 (t, *J* = 11.6 Hz, 2H), 0.87 (s, 18H), 0.16 (s, 9H), 0.04 (s, 12H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ ~165 (missing), 103.6, 92.9, 75.1, 66.0, 39.8, 25.9, 18.4, -0.1, -5.2, -5.2. **IR (neat)** 2955, 2928, 2856, 2108, 1783, 1706, 1472, 1362, 1250, 1231, 1148, 1112, 1030, 938, 832, 774, 735 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{26}H_{50}N_2O_5Si_3$: 577.2920; found 577.2905. **R_F**: 0.5 in 15% diethyl ether/pentane.



(2*R*,3a*S*,6a*R*)-2,5-bis(hydroxymethyl)-2,3-dihydro-4*H*-3a,6a-(epoxyethano)cyclopenta[*b*]furan-8-one (c54)

To a 250 mL round-bottom flask equipped with a stir bar was added powdered 4 Å molecular sieves and the flask was flamed-dried under high vacuum. The flask was then cooled down to room temperature and back-filled with Argon. $Rh_2(esp)_2$ (3.6 mg, 4.7 μmol, 0.5 mol%) and anhydrous dichloromethane (60 mL) were added. To this vigorously stirred solution was added dropwise via syringe pump a solution of diazoester **c55** (524.1 mg, 0.944 mmol) in anhydrous dichloromethane (35 mL) over 15 minutes at room temperature. After the end of the addition, the reaction was stirred for an additional 5 min and the TLC showed no starting material. The solution was filtered through a short celite pad and concentrated via rotary evaporation. The crude reaction mixture was dissolved in anhydrous tetrahydrofuran (9.5 mL) under Argon, and the reaction was

cooled to 0 ºC. TBAF (1 M in THF, 4.3 mL, 4.3 mmol, 4.5 equiv) was added dropwise. The reaction was warmed to 45 ºC and stirred for 1 hour. TLC analysis (10% methanol in dichloromethane) showed no starting material. To the crude reaction mixture was added silica gel and the solvent was concentrated via rotary evaporation. The dry-loaded reaction mixture was purified via flash column chromatography on silica gel using 5% MeOH in dichloromethane as an eluent. The product **c54** was obtained as a white solid (136.7 mg, 64% yield in two steps). **^{1}H NMR** (500 MHz, Methanol-d_4) δ 5.78–5.55 (m, 1H), 4.09–4.00 (m, 1H), 3.96 (s, 2H), 3.55 (dd, J = 11.8, 3.8 Hz, 1H), 3.44 (dd, J = 11.8, 5.4 Hz, 1H), 2.75 (s, 2H), 2.71 (d, J = 17.8 Hz, 1H), 2.57 (d, J = 17.7 Hz, 1H), 2.34 (dd, J = 13.7, 5.0 Hz, 1H), 1.82 (dd, J = 13.8, 10.5 Hz, 1H). **^{13}C NMR** (126 MHz, Methanol-d_4) δ 178.4, 147.5, 126.7, 101.6, 100.2, 81.6, 64.4, 61.6, 44.1, 41.9, 41.4. **IR (neat)** 3292, 2958, 2867, 2839, 1772, 1448, 1431, 1289, 1262, 1231, 1189, 1171, 1144, 1090, 1073, 1057, 1034, 1019, 984, 972, 939, 919, 877, 857, 695 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{11}H_{14}O_5$: 249.0733; found 249.0734. **R_F**: 0.3 in 10% methanol/CH_2Cl_2. **MP:** 157-160 °C.

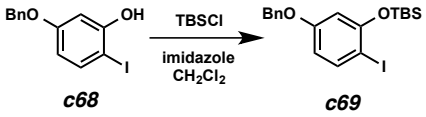


c54 *c65*

((2*R*,3a*S*,6a*R*)-8-oxo-2,3-dihydro-4*H*-3a,6a-(epoxyethano)cyclopenta[*b*]furan-2,5-diyl)bis(methylene) diacetate (c65)

To a flame-dried flask equipped with a stir bar was added diol **c54** (158.4 mg, 0.7 mmol, 1 equiv), 4-(dimethylamino)pyridine (DMAP) (17 mg, 0.14mmol, 0.2 equiv), CH_2Cl_2 (7

mL), and Et_3N (2 mL, 14 mmol, 20 equiv) at 0 ºC. Acetic anhydride (0.33 mL, 3.5 mmol, 5 equiv) was added slowly and the reaction was allowed to warm to 25 ºC. After TLC analysis showed no starting material, saturated $NaHCO_3$ (10 mL) was added to the reaction. The mixtures were extracted with CH_2Cl_2 (10 mL x 3). The organics was washed by brine, dried over $MgSO_4$, and filtered through a celite pad. To the crude reaction mixture was added silica gel and the solvent was concentrated via rotary evaporation. The dry-loaded reaction mixture was purified by column chromatography on silica gel with 40% ethyl acetate in hexanes as an eluent. The product was obtained as a colorless oil. (214 mg, 98% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.89–5.76 (m, 1H), 4.55 (s, 2H), 4.37–4.19 (m, 2H), 4.06–3.91 (m, 1H), 2.99–2.65 (m, 4H), 2.61–2.48 (m, 1H), 2.13–1.97 (m, 6H), 1.88–1.73 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.2, 170.6, 170.3, 140.4, 127.7, 98.8, 98.6, 77.0, 64.8, 61.8, 43.4, 41.1, 40.0, 20.8, 20.7. **IR(neat)** 2940, 1778, 1734, 1438, 1370, 1223, 1188, 1086, 1037, 974, 930, 836, 748 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{15}H_{18}O_7$: 333.0945; found 333.0951. **R_F**: 0.36 in 50 % ethyl acetate/hexanes.

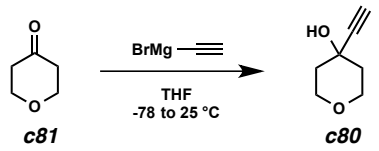


c68 *c69*

(5-(benzyloxy)-2-iodophenoxy)(*tert*-butyl)dimethylsilane (c69)

To a flame-dried flask equipped with a stir bar was added phenol **c68** (326 mg, 1 mmol, 1 equiv), imidazole (68.1 mg, 1 mmol, 1 equiv), and CH_2Cl_2 (5 mL). TBSCl (180 mg, 1.2 mmol, 1.2 equiv) was added at 0 ºC. The reaction was allowed to warm to 25 ºC and stirred for 2 h. Saturate $NaHCO_{3(aq)}$ (5 mL) was added to the reaction, and the mixtures

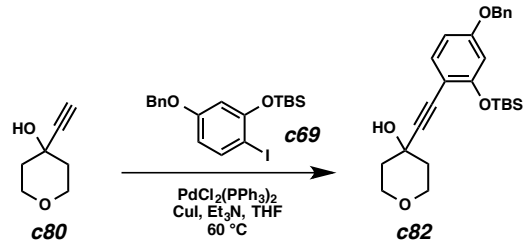
were extracted with CH_2Cl_2 (15 mL x3). The organics was washed with brine, dried over $MgSO_4$, filtered through a celite pad, and concentrated. The crude product was purified by column chromatography on silica gel with hexanes as an eluent. The product was obtained as a colorless oil. (426 mg, 97% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.6 Hz, 1H), 7.44–7.29 (m, 5H), 6.48 (d, *J* = 2.8 Hz, 1H), 6.41 (dd, *J* = 8.6, 2.8 Hz, 1H), 5.02 (s, 2H), 1.06 (s, 9H), 0.25 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.0, 155.8, 139.1, 136.5, 128.6, 128.1, 127.3, 109.6, 106.4, 79.7, 70.2, 25.8, 18.3, -4.1. **IR(neat)** 2928, 2856, 1567, 1462, 1406, 1314, 1296, 1116, 1040, 939, 833, 778 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{19}H_{25}IO_2Si$: 463.0561; found 463.0569. **R_F**: 0.2 in hexanes. Note: Phenol **c68** was prepared following a literature procedure.[14]



4-ethynyltetrahydro-2*H*-pyran-4-ol (c80)

To a flame-dried flask equipped with a stir bar was added ethynylmagnesium bromide (0.5 M in THF, 12 mL, 6 mmol, 1.2 equiv) and the solution was cooled to 0 ºC. The ketone **c81** (0.46 mL, 5 mmol, 1 equiv) was slowly added to the reaction. The reaction was allowed to warm to 25 ºC and stirred for 2 h. Saturate $NH_4Cl_{(aq)}$ (20 mL) was added to the reaction, and the mixtures were extracted with diethyl ether (15 mL x3). The organic solution was washed with brine, dried over $MgSO_4$, filtered through a celite pad, and concentrated. The crude product was purified by column chromatography on silica gel with a gradient of 20 to 25% ethyl acetate in hexanes as eluents. The product was

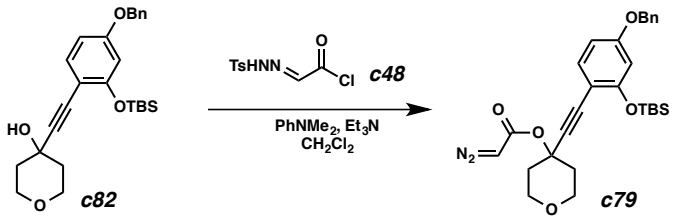
obtained as a white solid. (617 mg, 98% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.86 (dt, *J* = 11.7, 4.3 Hz, 2H), 3.61 (ddd, *J* = 11.7, 9.2, 2.9 Hz, 2H), 3.14 (s, 1H), 2.51 (s, 1H), 1.95–1.83 (m, 2H), 1.82–1.68 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 86.3, 72.9, 65.4, 64.6, 39.6. **IR(neat)** 3383, 3270, 2965, 2939, 2863, 1463, 1447, 1303, 1270, 1193, 1155, 1127, 1089, 1028, 1011, 929, 914, 834, 698, 670 cm^{-1}. **HRMS** (CI) *m/z* $(M-H)^+$: calculated for $C_7H_9O_2$: 125.0603; found 125.0603. **R_F**: 0.15 in 20% ethyl acetate/hexanes. **MP:** 50-51 °C.



4-((4-(benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)phenyl)ethynyl)tetrahydro-2*H*-pyran-4-ol (c82)

To a flame-dried 25 mL flask equipped with a condenser and a stir bar was added aryl iodide **c69** (181.4 mg, 0.41 mmol, 1 equiv), alcohol **c80** (68.2 mg, 0.54 mmol, 1.3 equiv), CuI (3.1 mg, 0.016 mmol, 0.04 equiv), and $PdCl_2(PPh_3)_2$ (11.5 mg, 0.016 mmol, 0.04 equiv) under Argon. Degased THF (2 mL) and Et_3N (3 mL) were added to the reaction and it was heated to 60 ºC for 13 h. After the reaction was cooled to 25 ºC, water (10 mL) was added to the reaction. The mixtures were extracted with diethyl ether (10 mL x3). The organic solution was washed by brine, dried over $MgSO_4$, filtered through a celite pad, and concentrated. The crude product was purified by column chromatography on silica gel with 20% ethyl acetate in hexanes as an eluent. The product was obtained as an

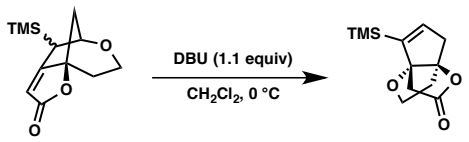
orange oil. (149 mg, 83% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44–7.25 (m, 6H), 6.54 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 5.02 (s, 2H), 3.97–3.84 (m, 2H), 3.78–3.66 (m, 2H), 2.12 (s, 1H), 2.06–1.92 (m, 2H), 1.94–1.78 (m, 2H), 0.99 (s, 9H), 0.19 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.9, 157.5, 136.4, 134.5, 128.6, 128.5, 127.3, 107.8, 107.3, 106.6, 93.3, 82.1, 70.0, 66.1, 65.8, 64.8, 60.4, 40.0, 25.7, 18.2, 15.2, 14.1, -4.3. **IR(neat)** 3388, 2953, 2928, 2857, 2216, 1500, 1454, 1419, 1295, 1253, 1153, 1123, 1107, 1095, 1068, 914, 835, 780, 734 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{26}H_{34}O_4Si$: 461.2119; found 461.2129. **R_F**: 0.36 in 30% ethyl acetate/hexanes.



4-((4-(benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)phenyl)ethynyl)tetrahydro-2*H*-pyran-4-yl 2-diazoacetate (c79)

A flame-dried round-bottom flask was charged with the alcohol **c82** (627 mg, 1.43 mmol) under an argon atmosphere. Glyoxylic acid chloride *p*-toluenesulfonylhydrazone **c48** (745 mg, 2.86 mmol, 2 equiv) was added. To the mixture was added CH_2Cl_2 (4.8 mL) at 0 °C, followed by an addition of *N*,*N*-dimethyl aniline (0.55 mL, 3 equiv). The reaction was stirred for 45 min before adding triethylamine (4.4 mL, 44 mmol, 31.5 equiv). The mixture was stirred an additional 2 h and concentrated. To the crude mixture was added 25% ethyl acetate in hexanes (30 mL). The organic solution was washed with concentrated citric acid (10 mL x 2) and brine. The solution was dried over $MgSO_4$,

filtered through a celite pad, and concentrated. The crude product was purified by column chromatography on silica gel with a gradient of 10 to 25% diethyl ether in pentane as eluents. The product was obtained as a yellow oil. (181 mg, 25% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45–7.25 (m, 6H), 6.52 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.36 (d, *J* = 2.3 Hz, 1H), 5.01 (s, 2H), 4.70 (s, 1H), 3.89–3.69 (m, 4H), 2.34–2.21 (m, 2H), 2.19–2.05 (m, 2H), 0.98 (s, 9H), 0.18 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.0, 157.6, 136.5, 135.0, 128.6, 128.1, 127.4, 107.8, 107.3, 106.6, 89.4, 84.5, 74.2, 70.1, 64.5, 46.6, 37.9, 25.7, 18.2, -4.3. **R_F**: 0.3 in 30% diethyl ether/pentane.

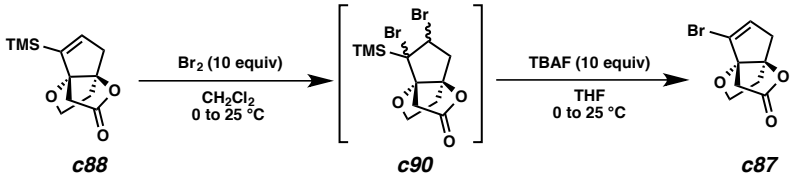


c20 ***c88***

(3a*S*,6a*S*)-6-(trimethylsilyl)-2,3-dihydro-4*H*-3a,6a-(epoxyethano)cyclopenta[*b*]furan-8-one (c88)

To a flame-dried round-bottom flask was charged with the bridged tricycle **c20** (238 mg, 1 mmol, 1 equiv), CH_2Cl_2 (20 mL). DBU (165 μL, 1.1 mmol, 1.1 equiv) was added slowly at 0 °C. The reaction was monitored carefully by TLC analysis until it was showed no starting material. To the crude reaction mixture was added silica gel and the solvent was concentrated via rotary evaporation. The dry-loaded reaction mixture was purified by column chromatography on silica gel with 10% ethyl acetate in hexanes as an eluent. The product was obtained as a white solid. (150 mg, 63% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.96 (t, *J* = 2.3 Hz, 1H), 3.97–3.88 (m, 1H), 3.77–3.67 (m, 1H), 2.90 (d, *J* = 18.9 Hz, 1H), 2.82 (dd, *J* = 7.1, 2.3 Hz, 2H), 2.65 (d, *J* = 18.7 Hz, 1H), 2.42–2.29 (m,

1H), 2.15–2.03 (m, 1H), 0.12 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.3, 145.9, 140.9, 102.7, 100.4, 66.8, 45.7, 41.2, 40.1, -1.2. **IR(neat)** 2959, 2922, 2888, 1770, 1299, 1279, 1246, 1214, 1187, 1165, 1074, 1016, 937, 903, 865, 828, 756, 696 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_{12}H_{18}O_3Si$: 261.0917; found 261.0919. **R_F**: 0.55 in 25% ethyl acetate/hexanes. **MP:** 66-68 °C.



(3a*S*,6a*S*)-6-bromo-2,3-dihydro-4*H*-3a,6a-(epoxyethano)cyclopenta[*b*]furan-8-one (c87)

A flame-dried round-bottom flask was charged with the bridged cycle **c88** (71.5 mg, 0.3 mmol, 1 equiv), CH_2Cl_2 (3 mL). Br_2 (0.15 mL, 3 mmol, 10 equiv) was added slowly at 0 °C. The reaction was slowly warmed to 25 °C and stirred for 14 h. After TLC analysis showed no starting material. CH_2Cl_2 (3 mL) was added to the reaction, followed by an addition of 10 % $Na_2S_2O_{3(aq)}$ (10 mL). The reaction mixture was extracted with diethyl ether (10 mL x3). The organic solution was washed with brine, dried over $MgSO_4$, filtered through a celite pad, and concentrated. To the crude compound was added THF (3 mL) at 0 °C and then slowly added TBAF (1 M, 3 mL, 10 equiv). The reaction was stirred at 0 °C for 3 h and warmed up to 25 °C for 30 min. To the reaction was added water (10 mL), and the mixtures were extracted with diethyl ether (10 mL x3). The organic solution was washed with brine, dried over $MgSO_4$, filtered through a celite pad, and concentrated. To the crude reaction mixture was added silica gel and the solvent was

concentrated via rotary evaporation. The dry-loaded reaction mixture was purified by column chromatography on silica gel with 20 % ethyl acetate in hexanes as an eluent. The product was obtained as a yellowish solid. (59 mg, 80% yield,). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.96 (t, *J* = 2.5 Hz, 1H), 4.08–4.01 (m, 1H), 3.88–3.80 (m, 1H), 2.86 (s, 2H), 2.78 (t, *J* = 2.8 Hz, 2H), 2.45–2.33 (m, 1H), 2.29–2.19 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.1, 132.2, 121.3, 98.2, 96.7, 67.5, 43.8, 40.5, 39.2. **IR(neat)** 2993, 2946, 2881, 1775, 1439, 1306, 1290, 1264, 1238, 1207, 1185, 1160, 1142, 1078, 1015, 968, 940, 900, 859, 823, 808 cm^{-1}. **HRMS** (ESI) *m/z* $(M+Na)^+$: calculated for $C_9H_9BrO_3$: 266.9627; found 266.9634. **R_F**: 0.18 in 2% ethyl acetate/hexanes. **MP:** 108-109 °C.

3.4.3 Crystallographic Data

Crystal data and structure refinement for compound c54

Empirical formula	$C_{11}H_{14}O_5$
Formula weight	226.22
Crystallization solvent	Methanol
Crystal habit	Block
Crystal size	0.5 x 0.4 x 0.3 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker DUO APEX II CCD	
Wavelength	1.54178 Å MoKα	
Data collection temperature	133(2) K	
Unit cell dimensions	a = 5.7375(9) Å	α = 90.00°
	b = 7.9217(12) Å	β = 96.614(5)°
	c = 23.143(3) Å	γ = 90.00°
Volume	1044.87 $Å_3$	
Z	4	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Density	1.438 mg/m^3	
F(000)	480	
Reflections collected	6272	
Absorption coefficient	0.964	

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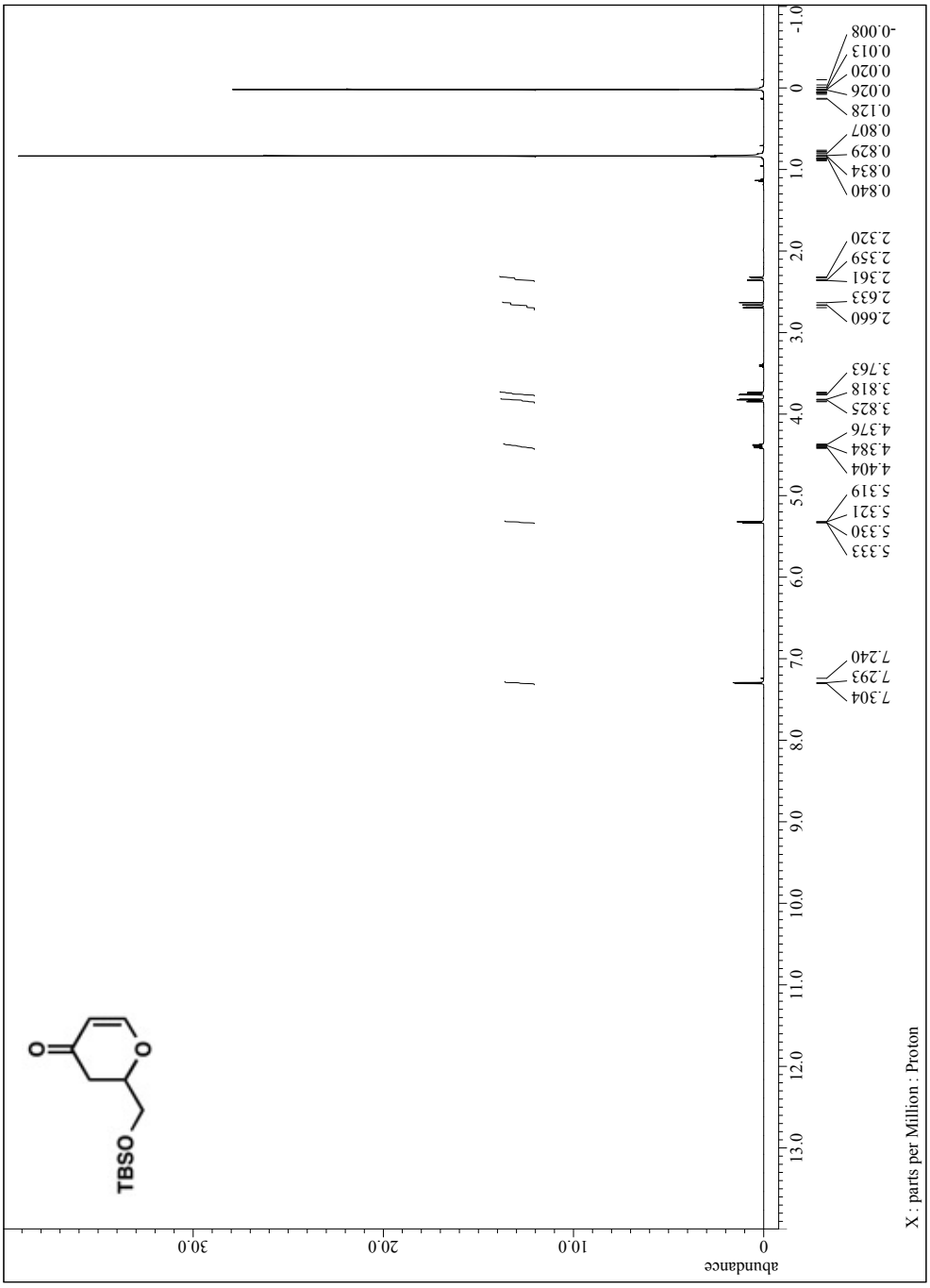
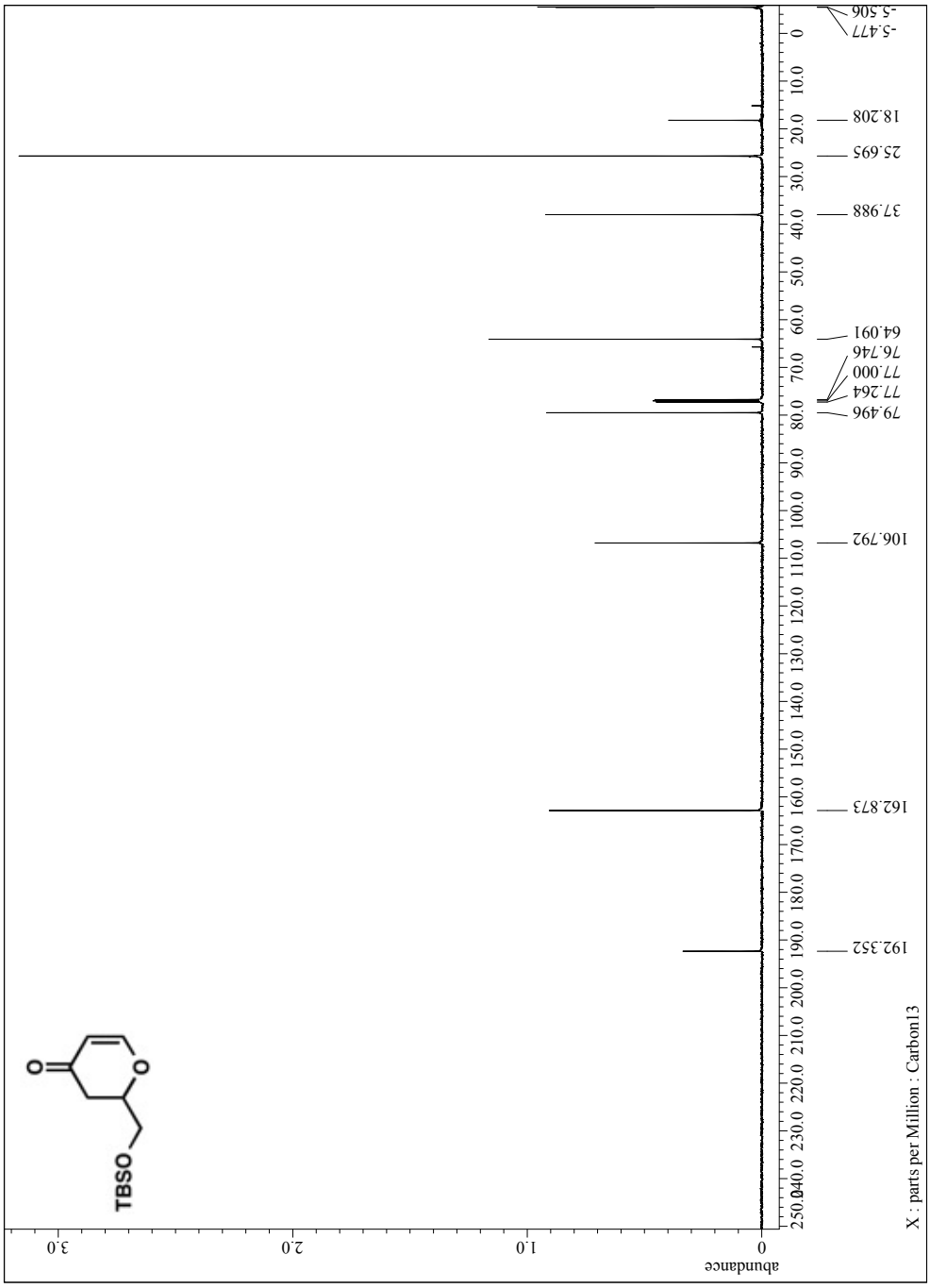
APPENDIX-CHAPTER THREE

Spectra Relevant to Chapter Three: Studies Toward the Synthesis of Brazilide A



^{1}H NMR for compound **c46**



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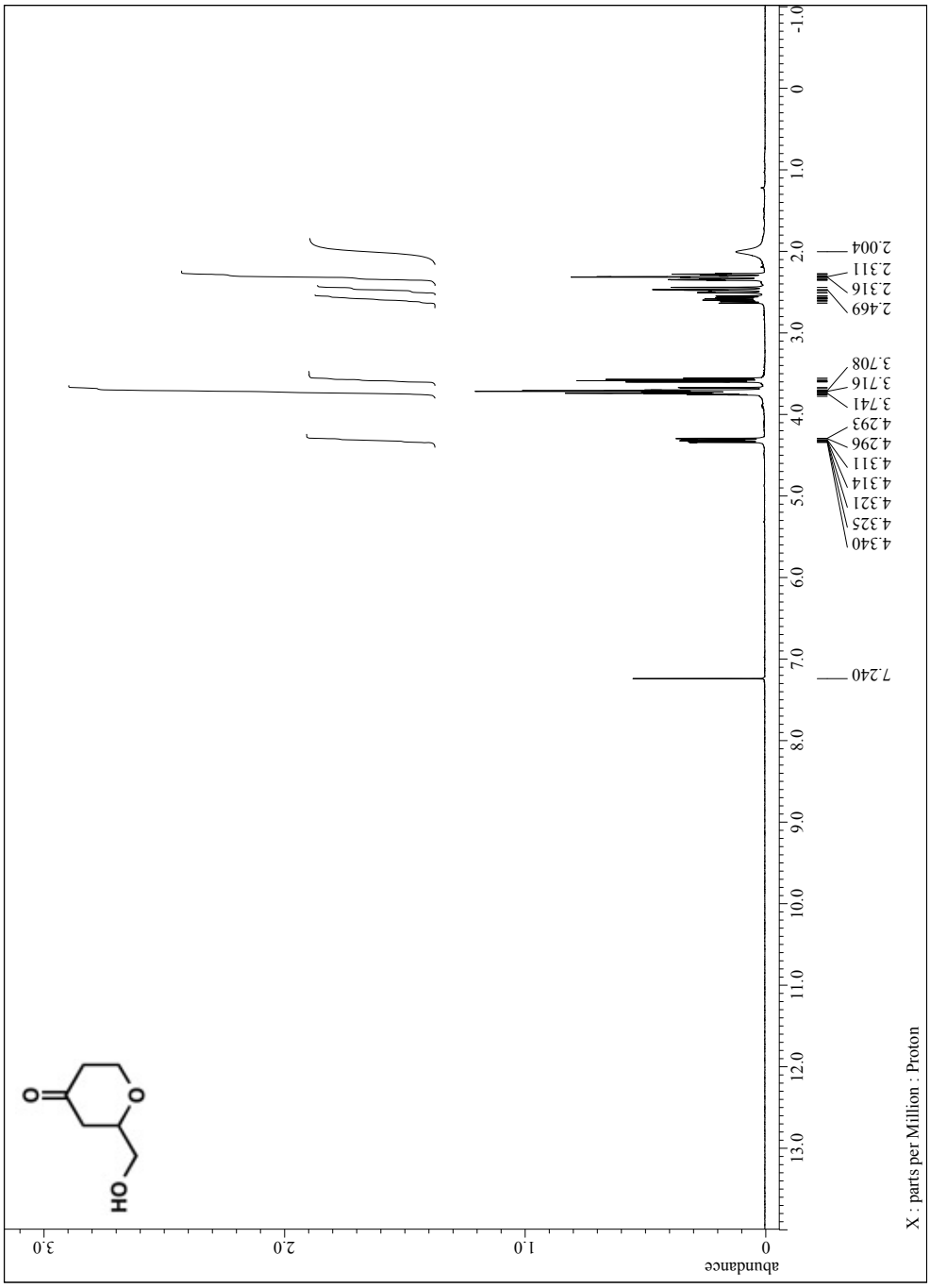

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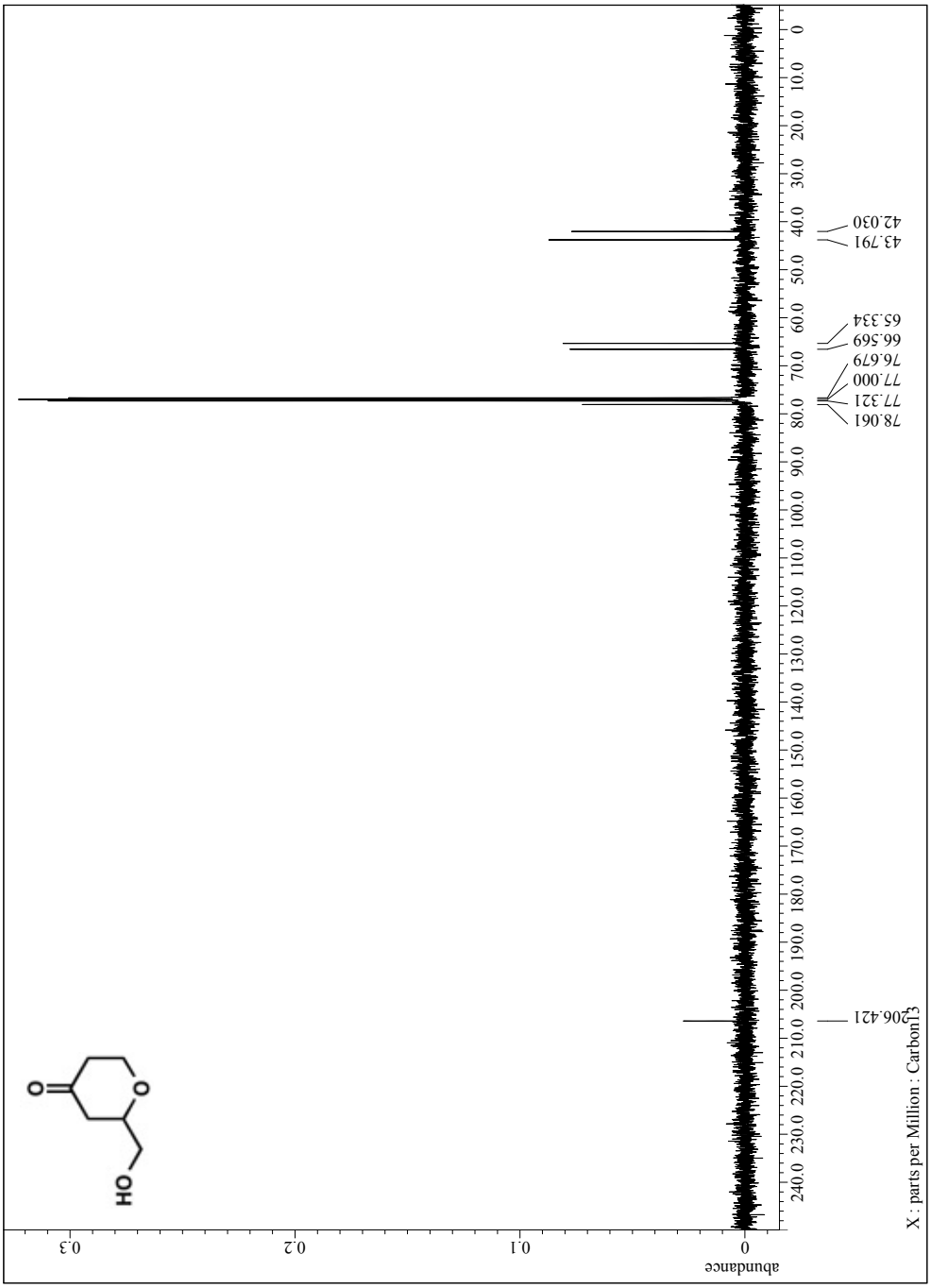
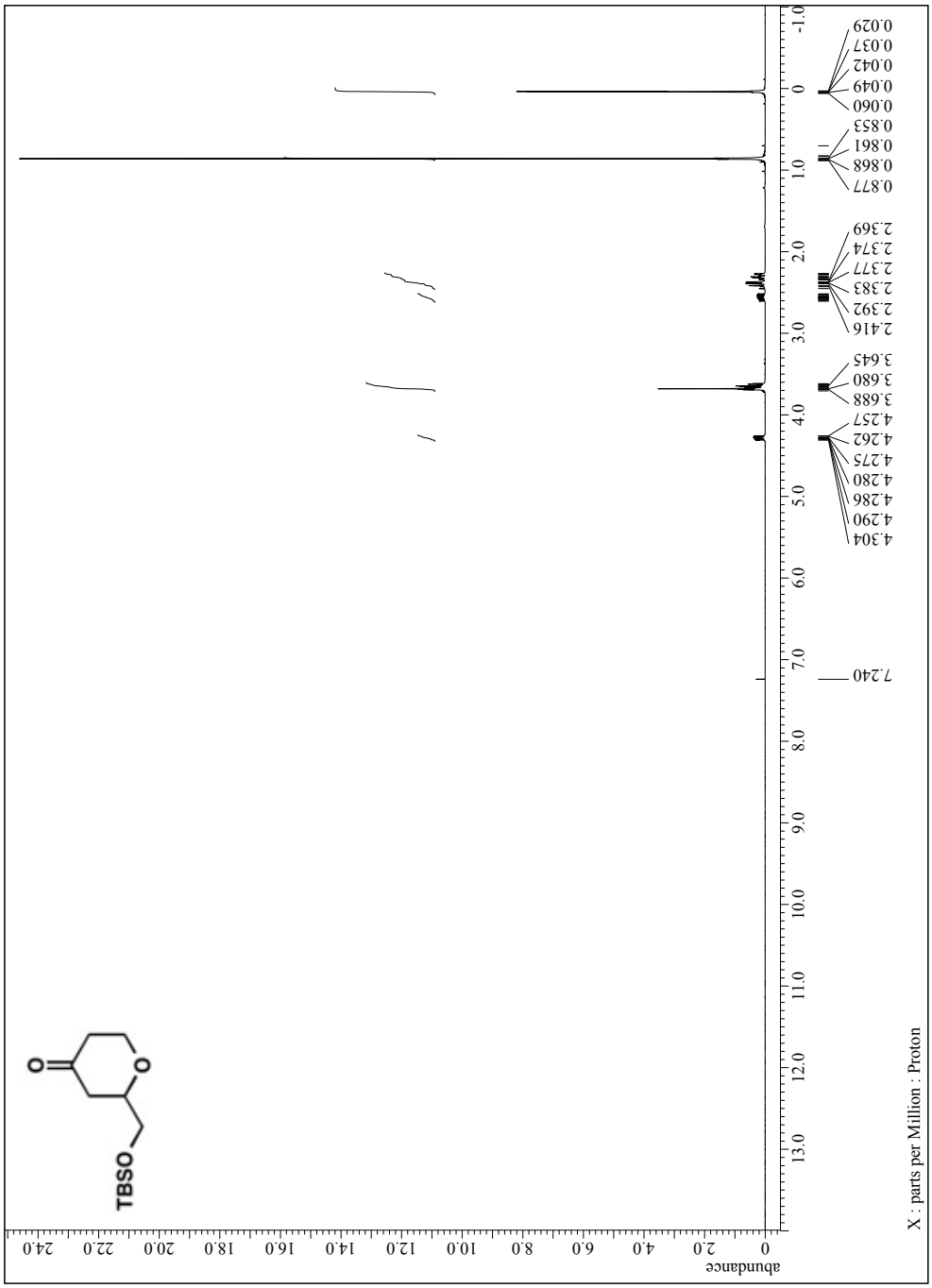


^{13}C NMR for compound **c43**



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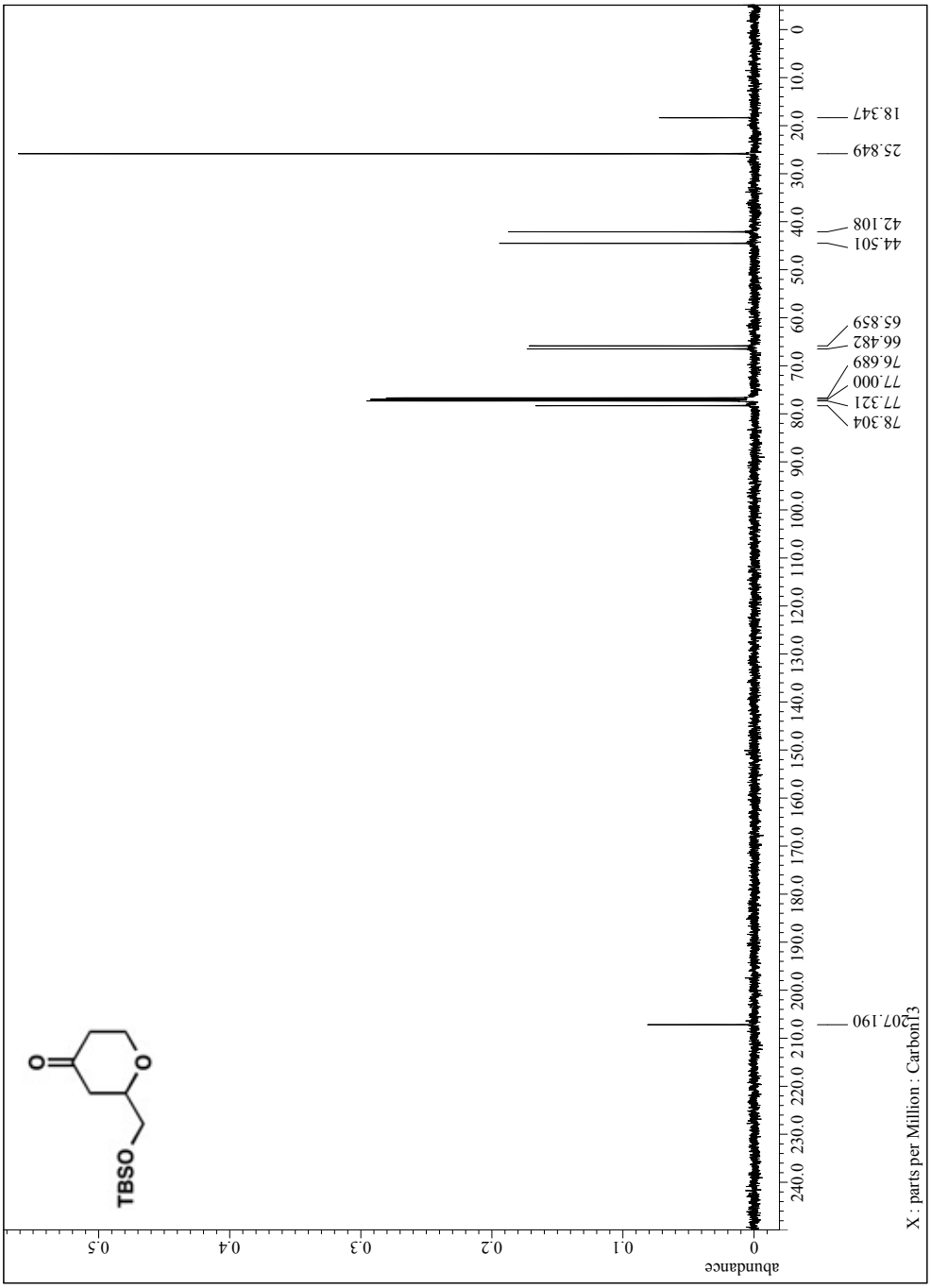

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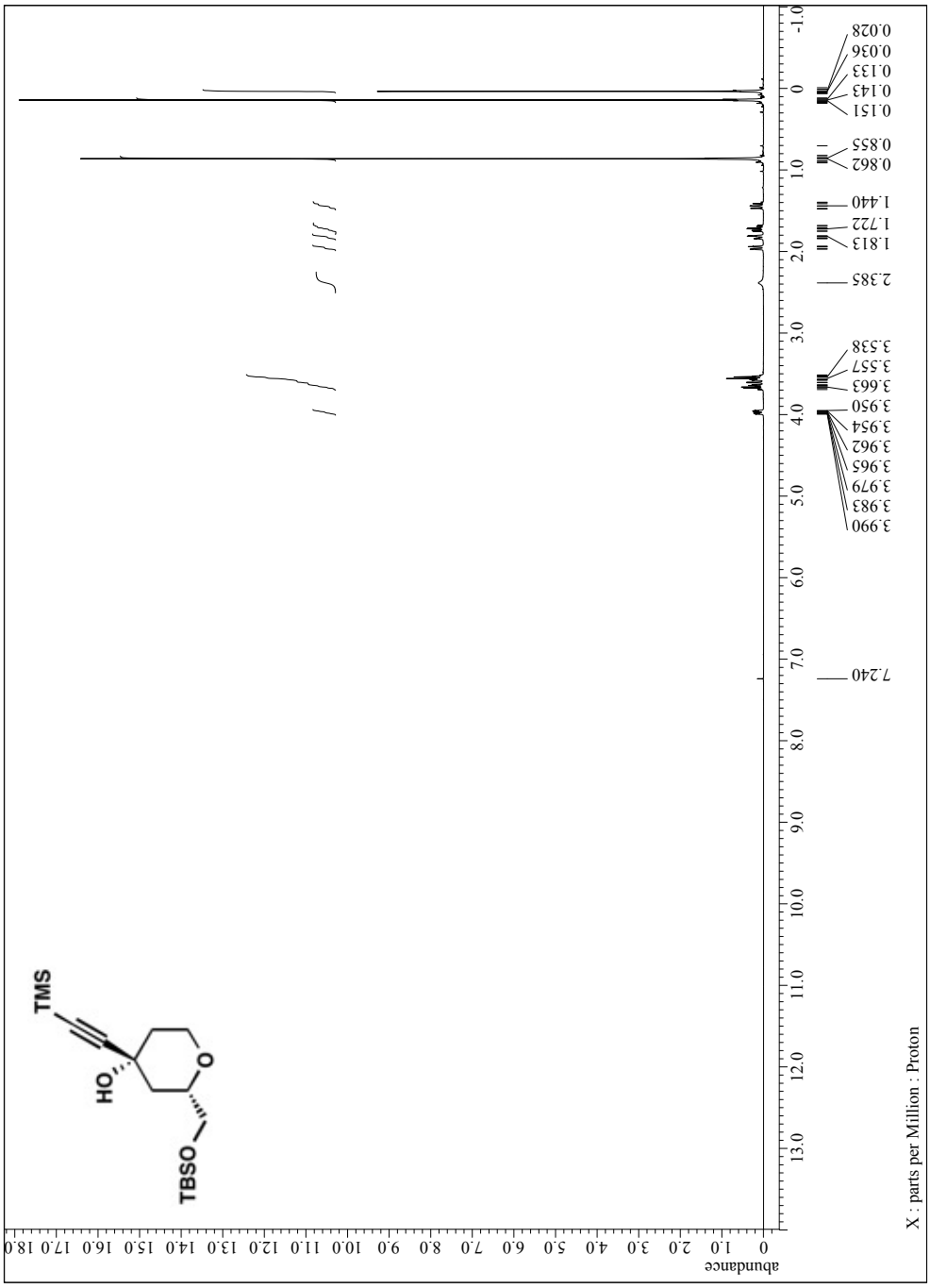

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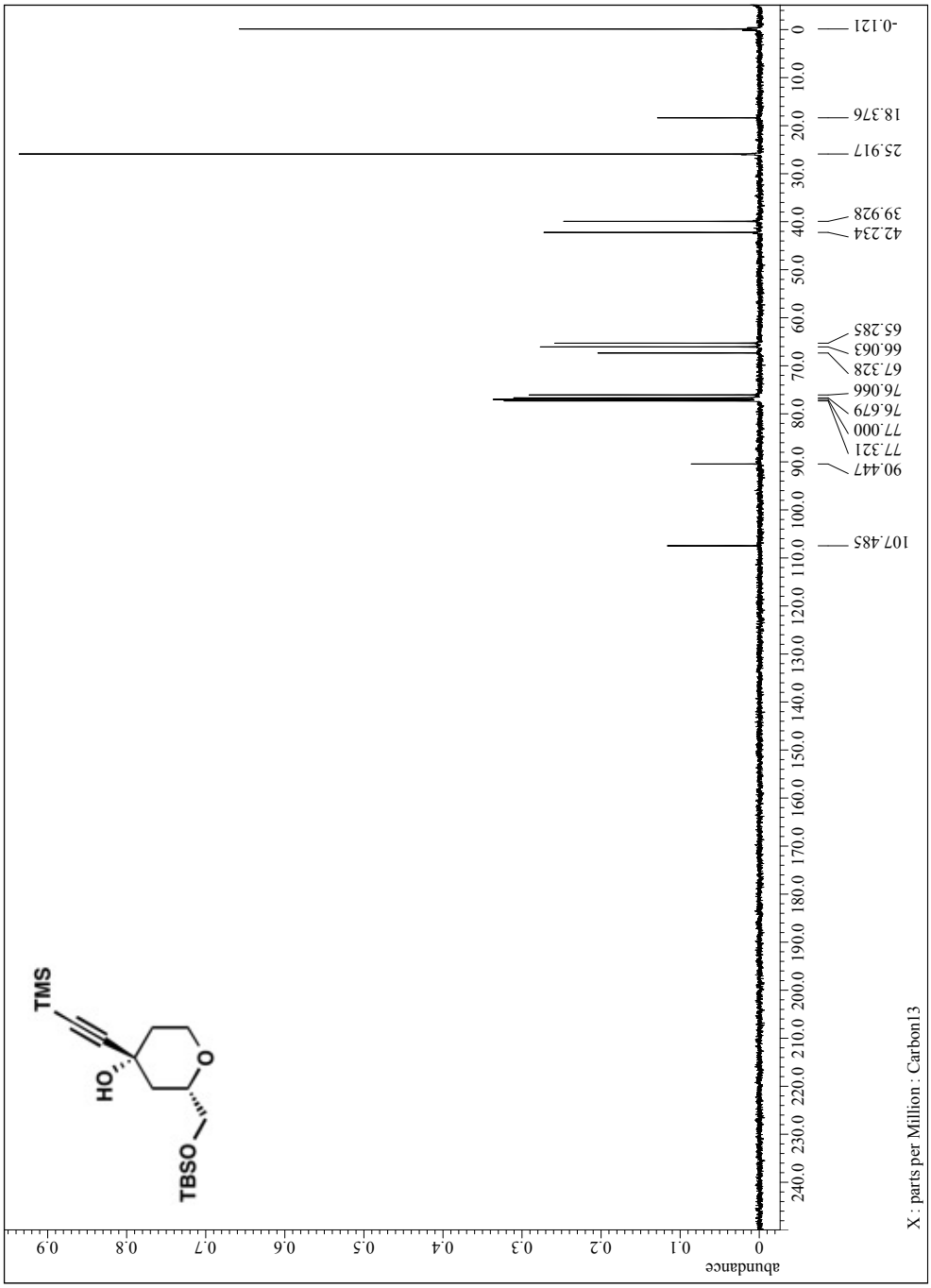

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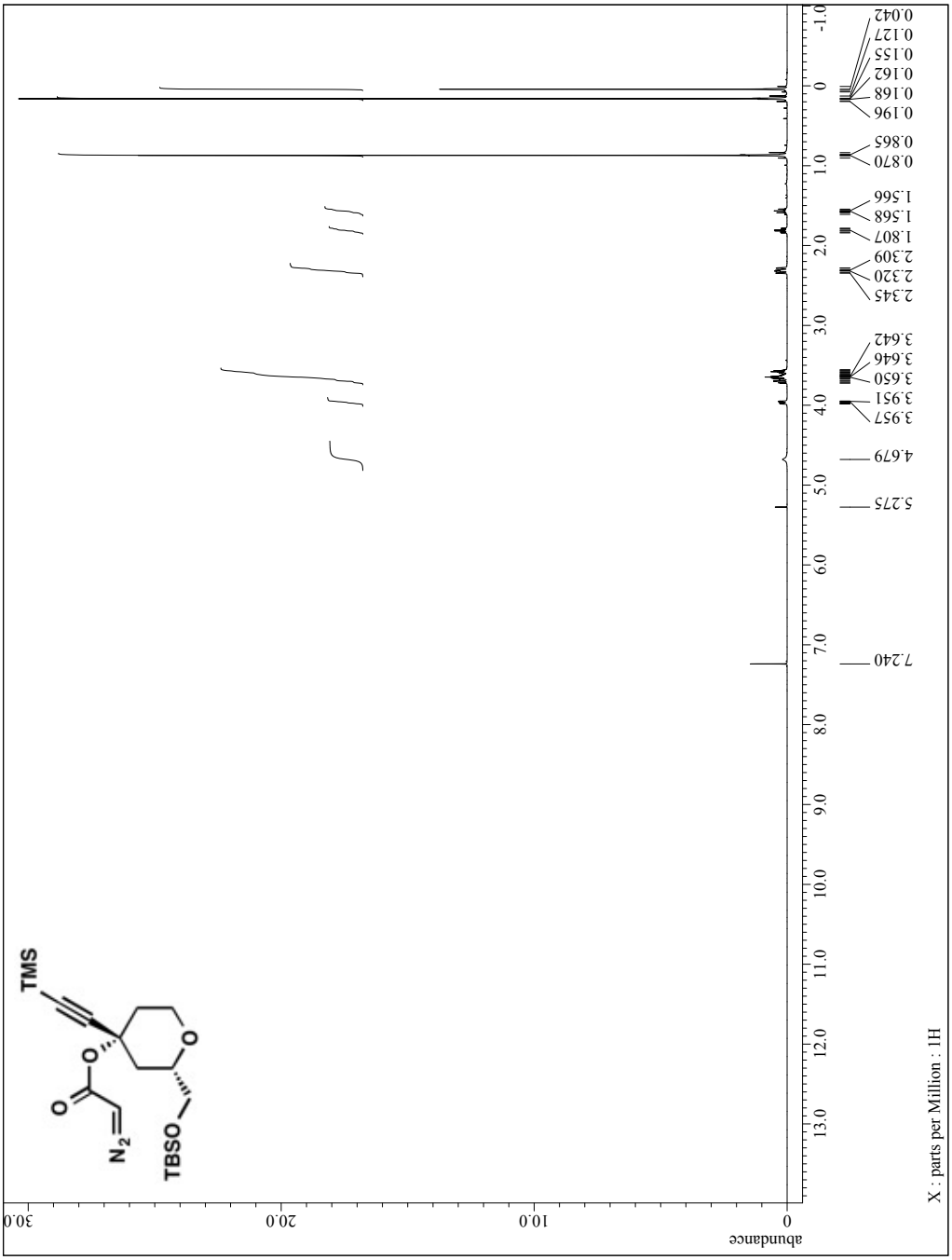

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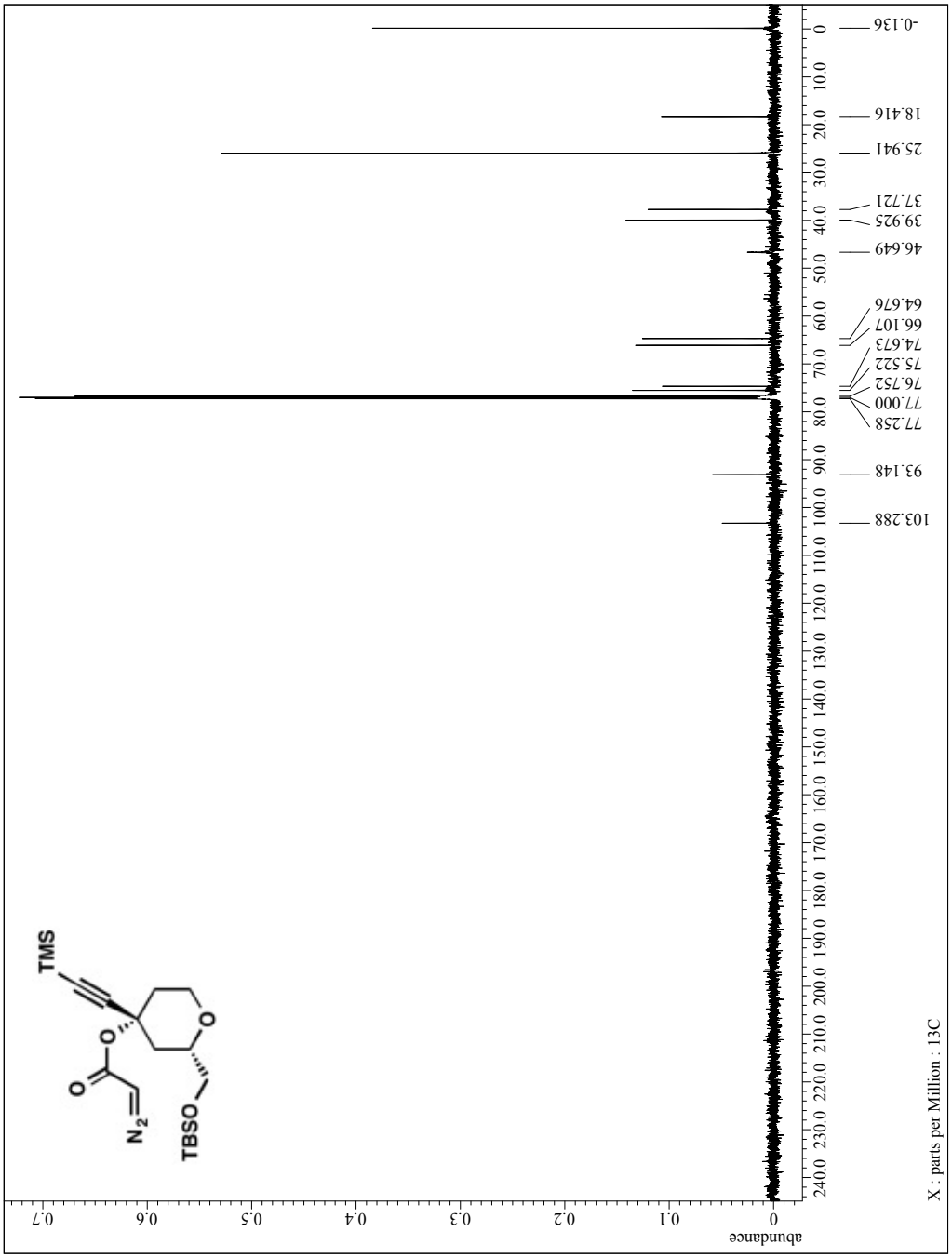

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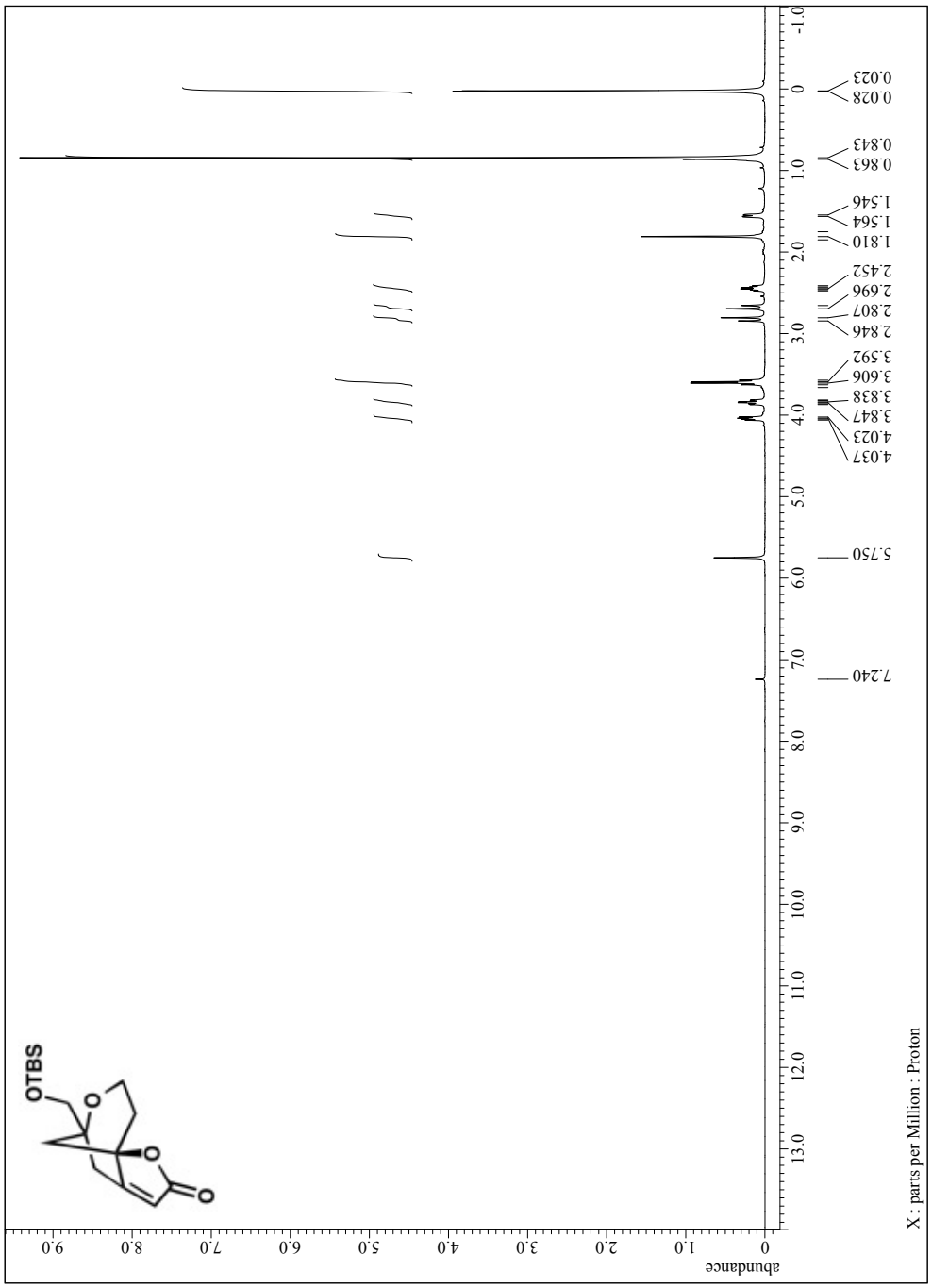

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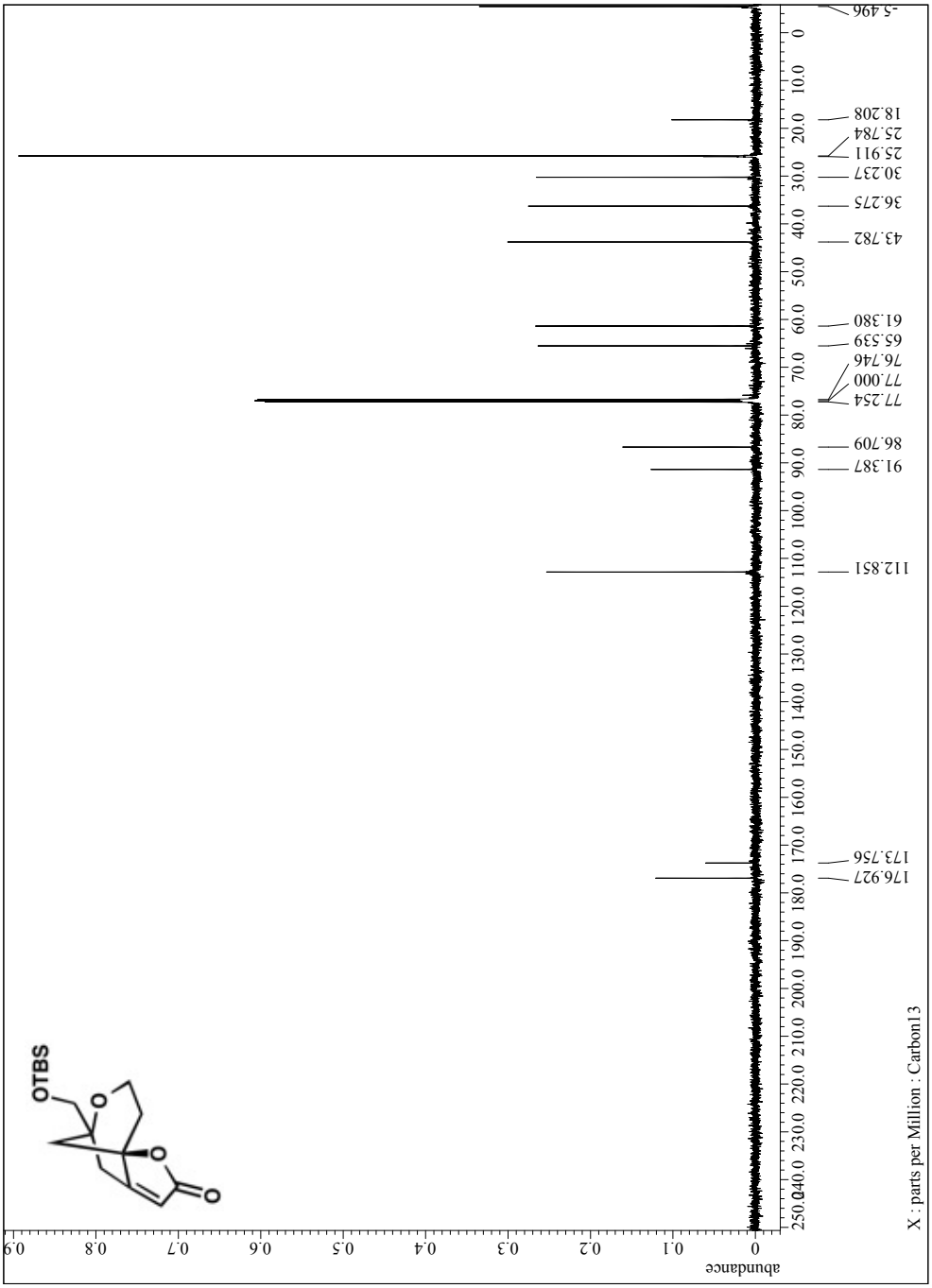
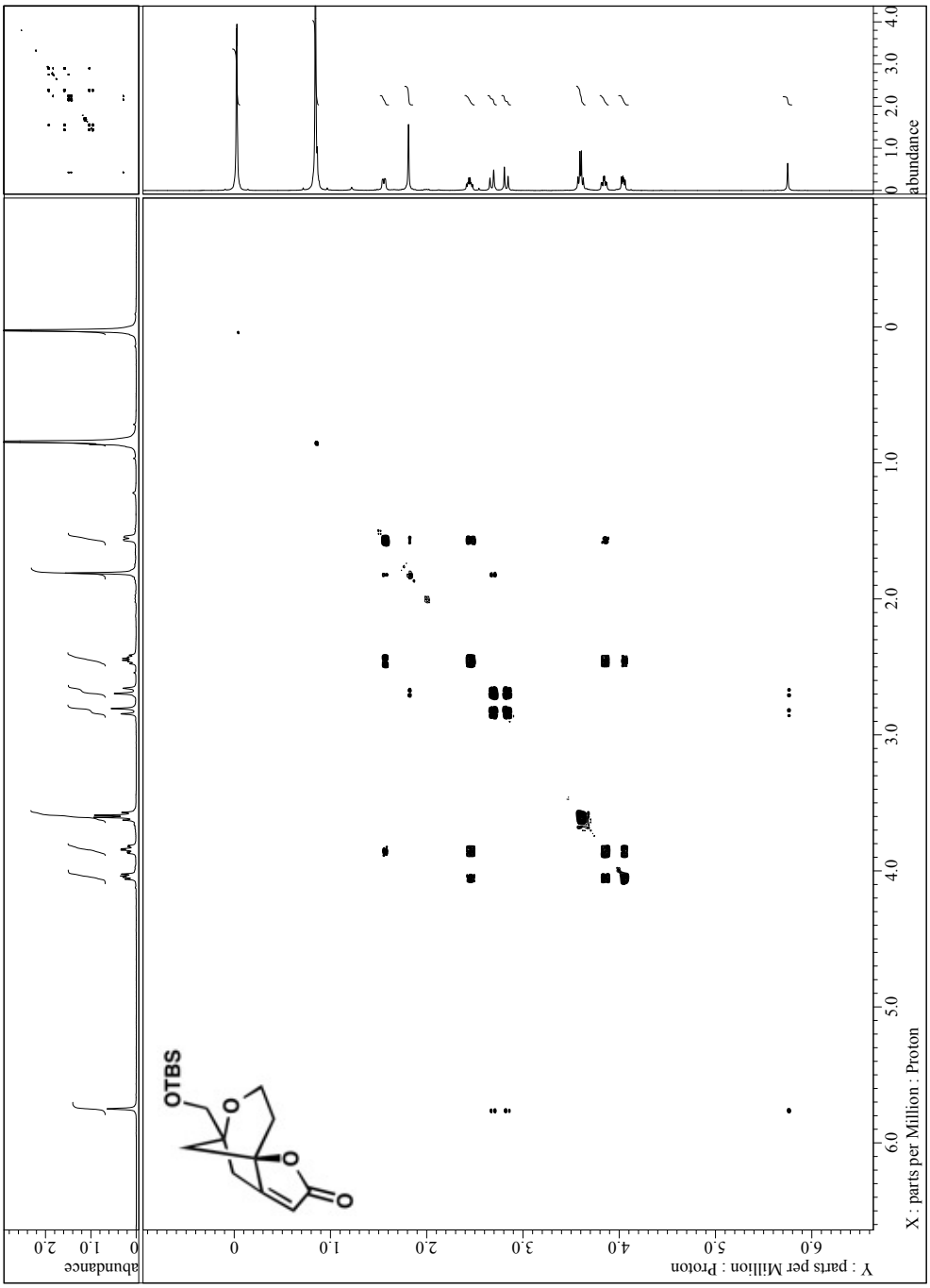


^{13}C NMR for compound **c50**



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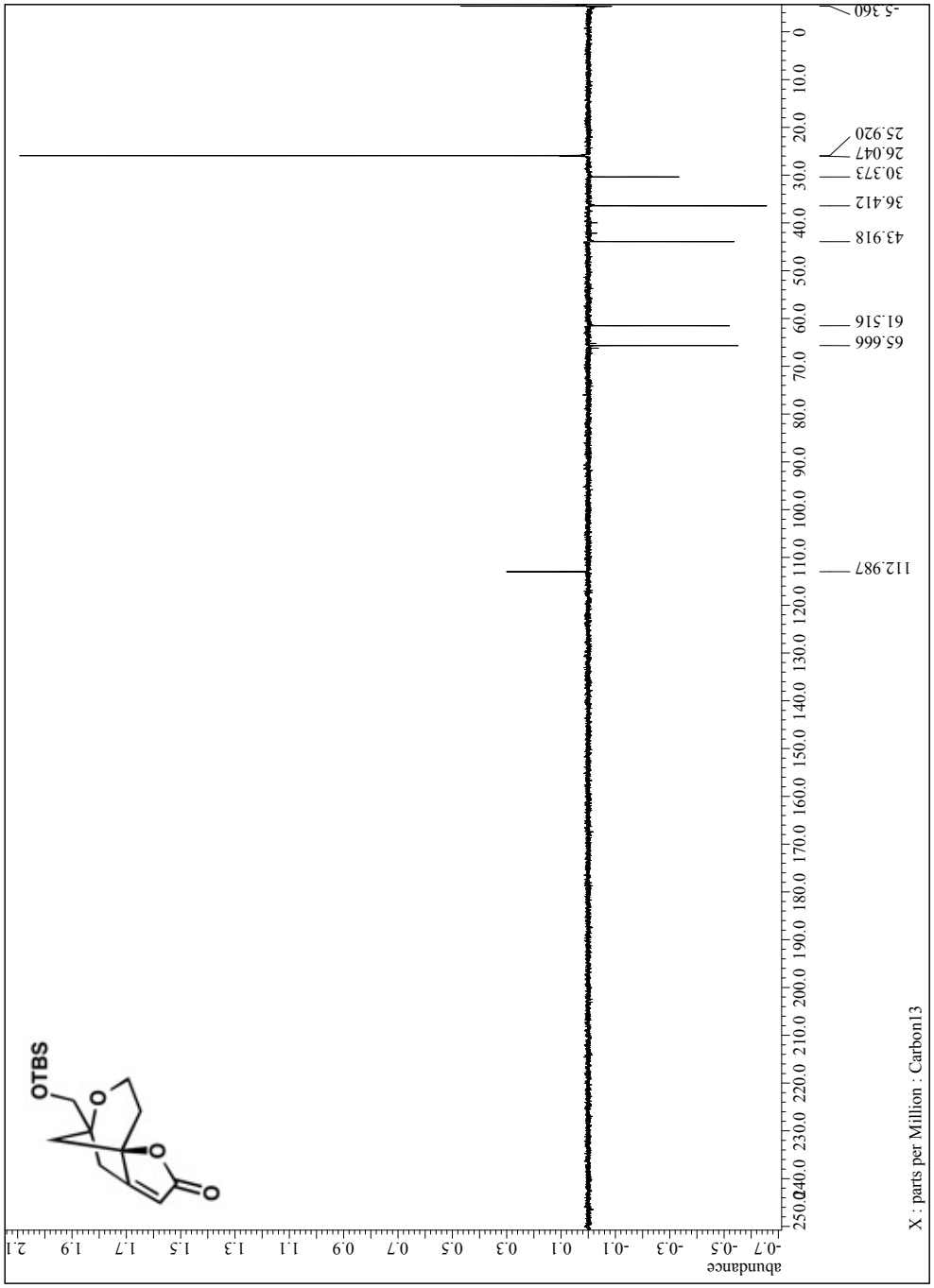

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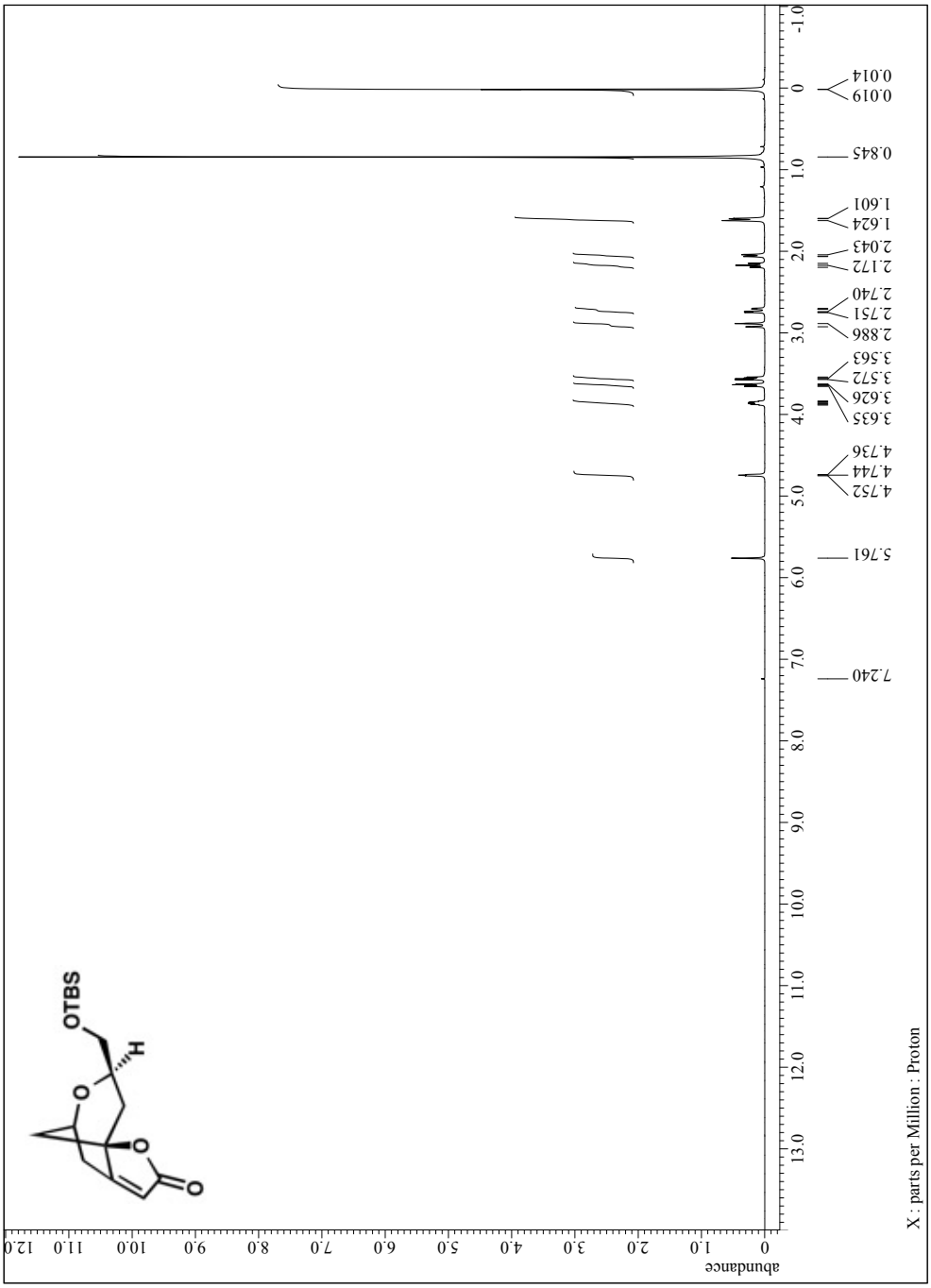

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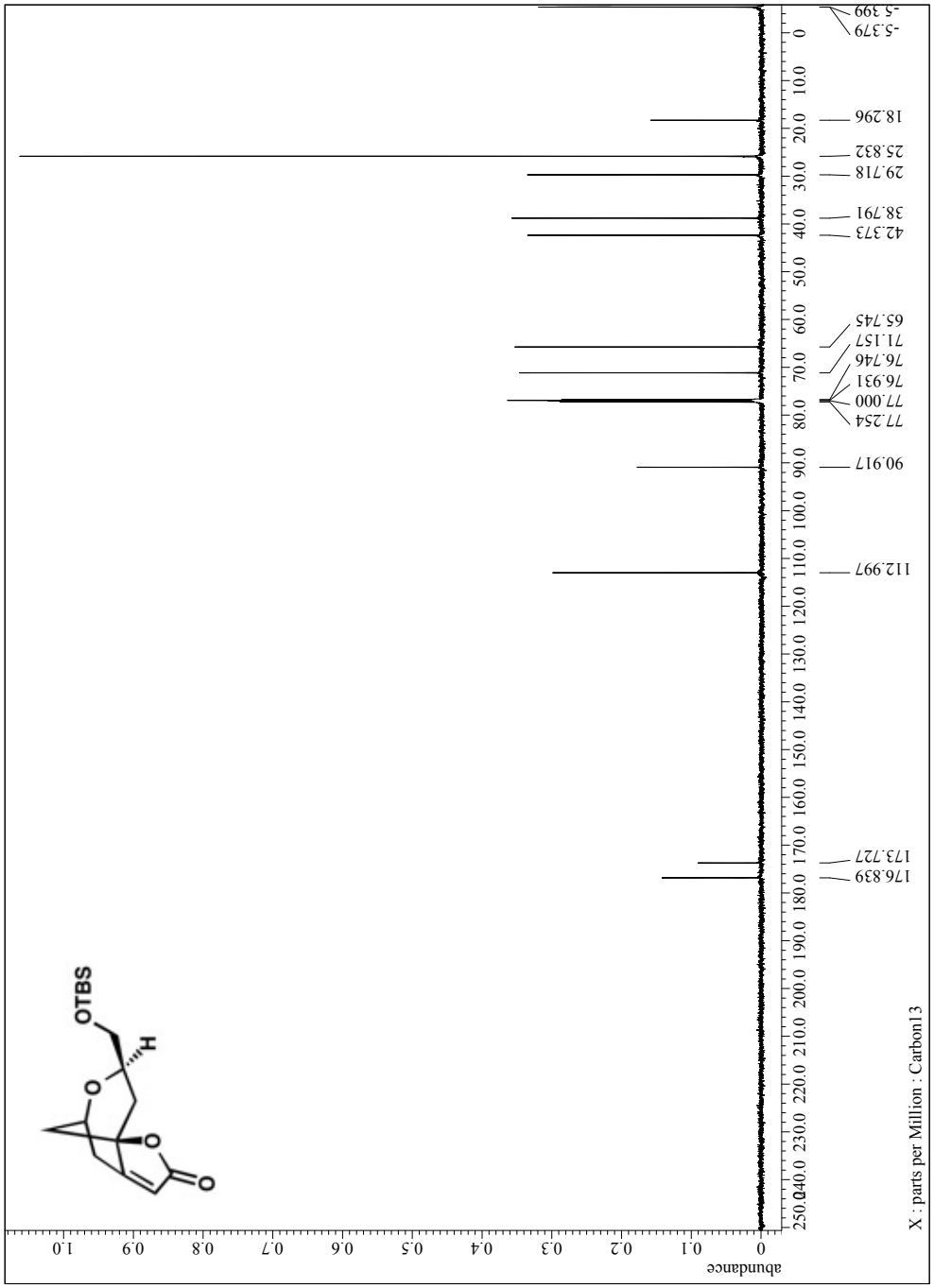

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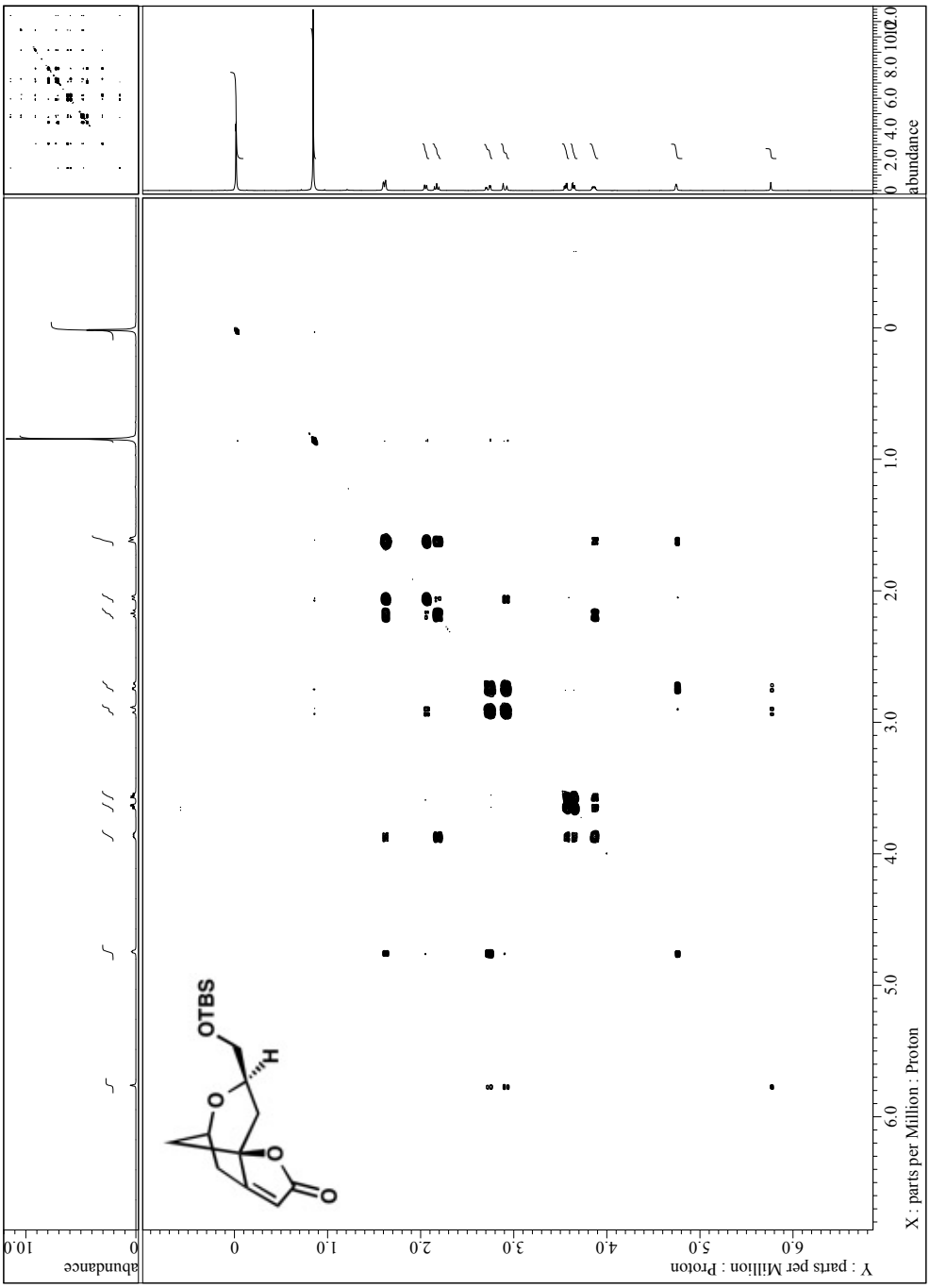

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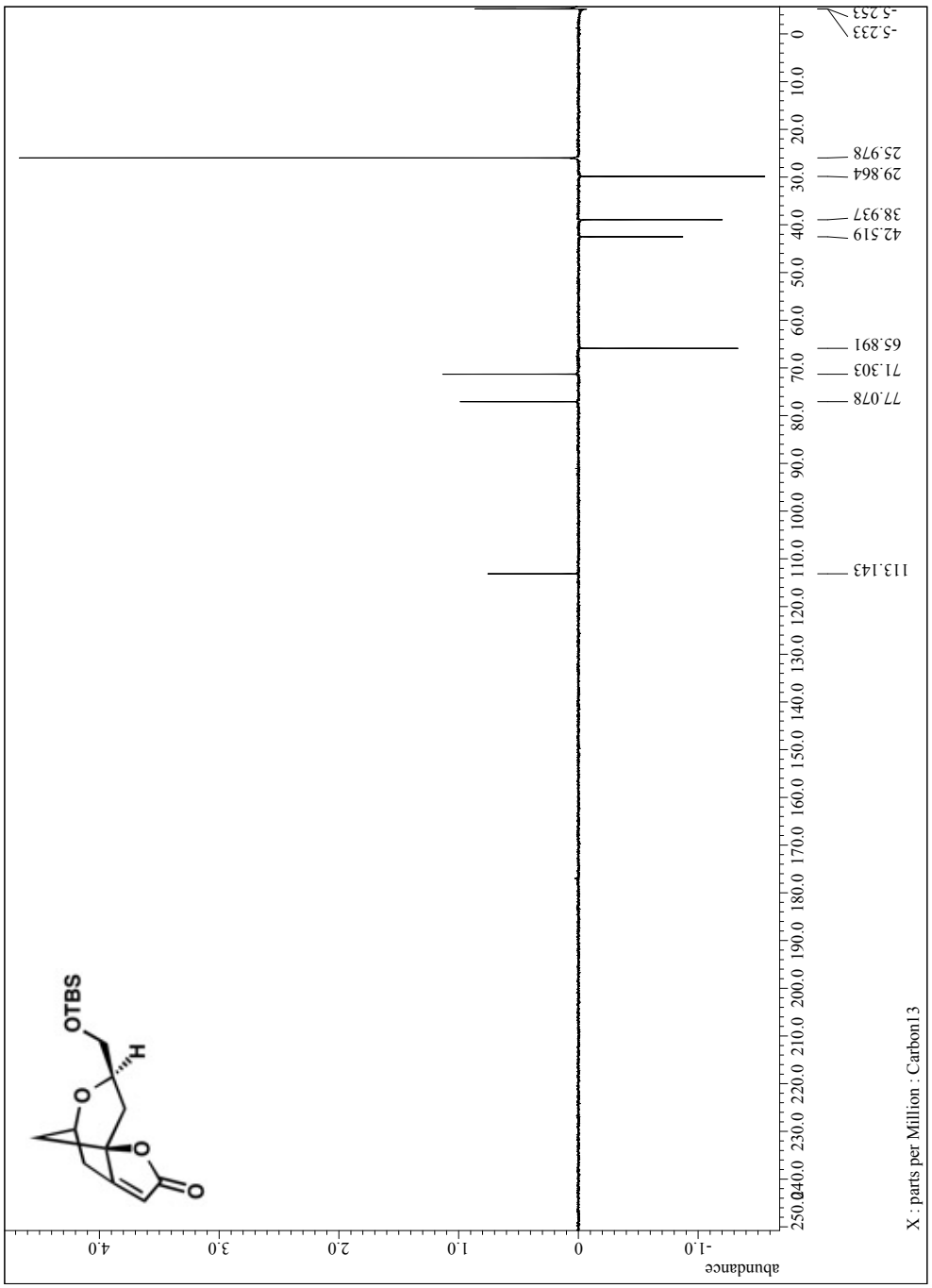

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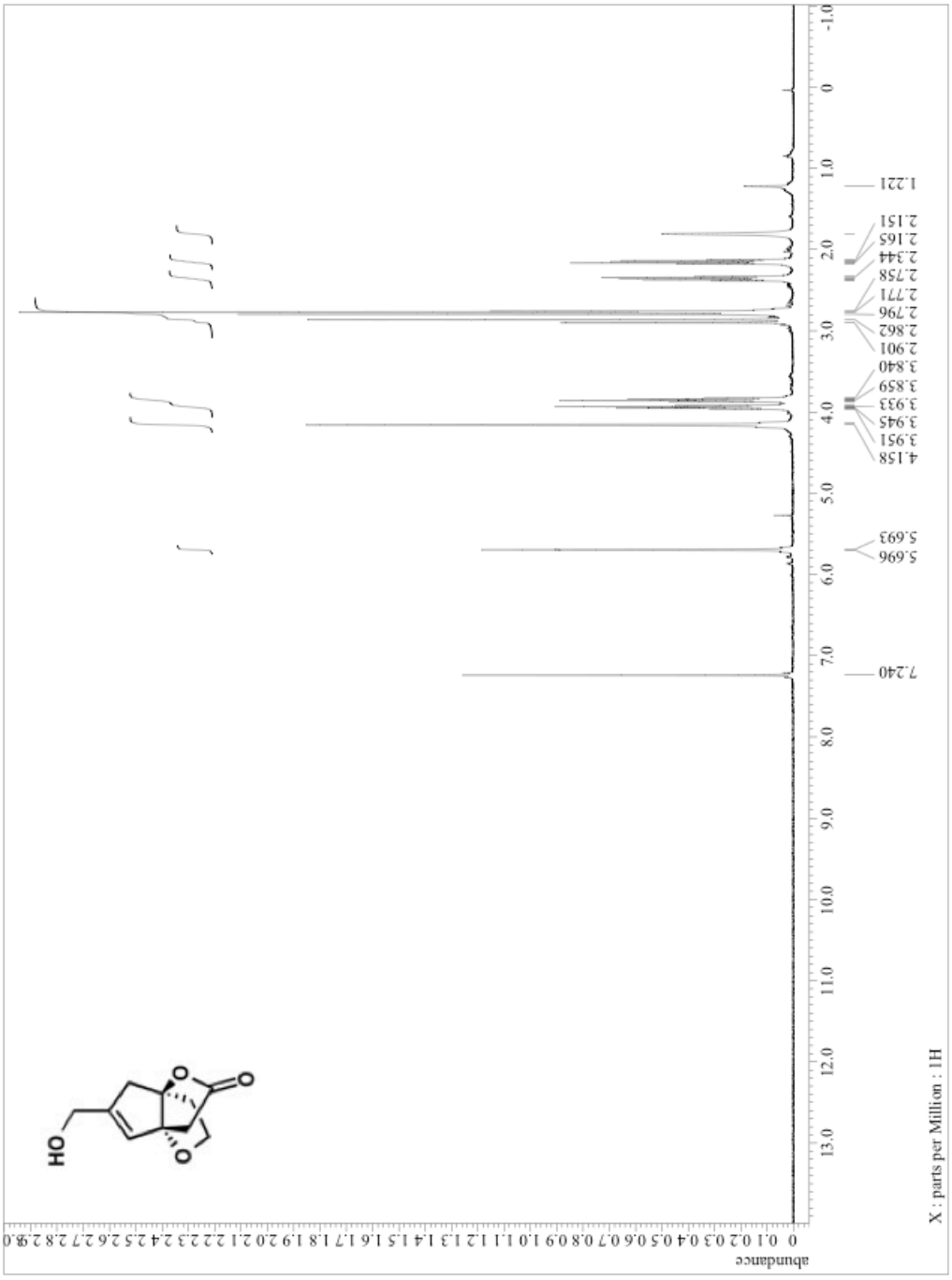

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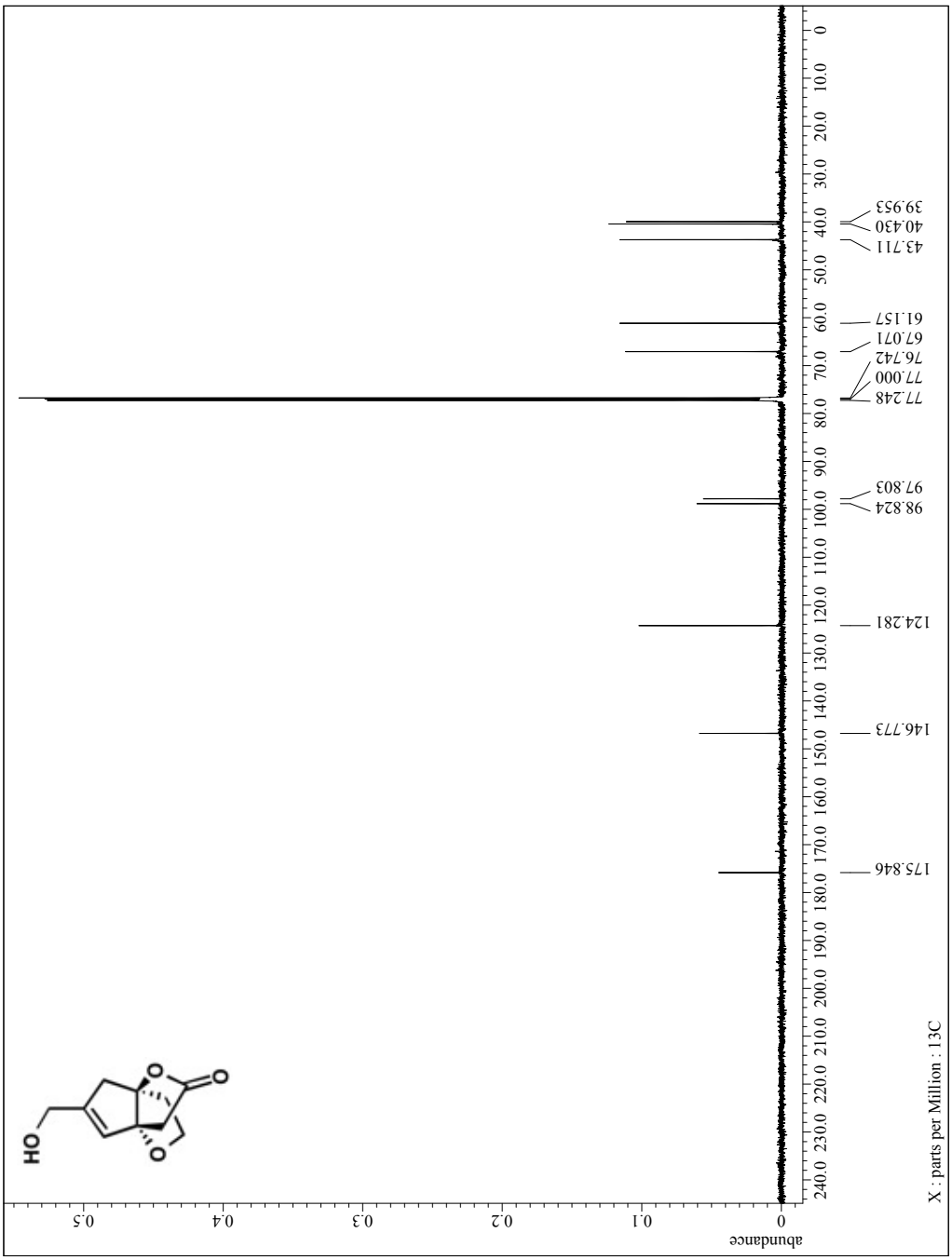

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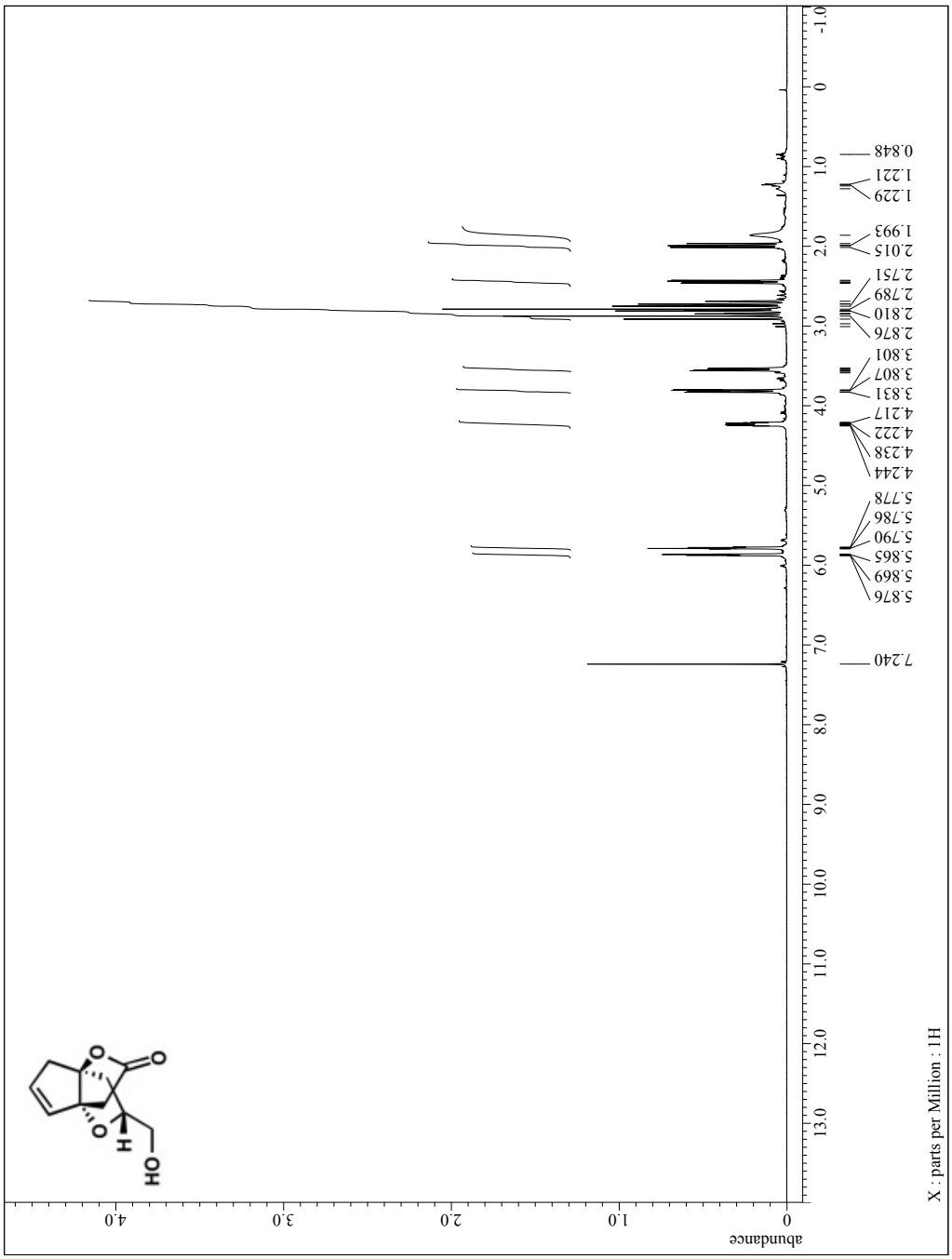

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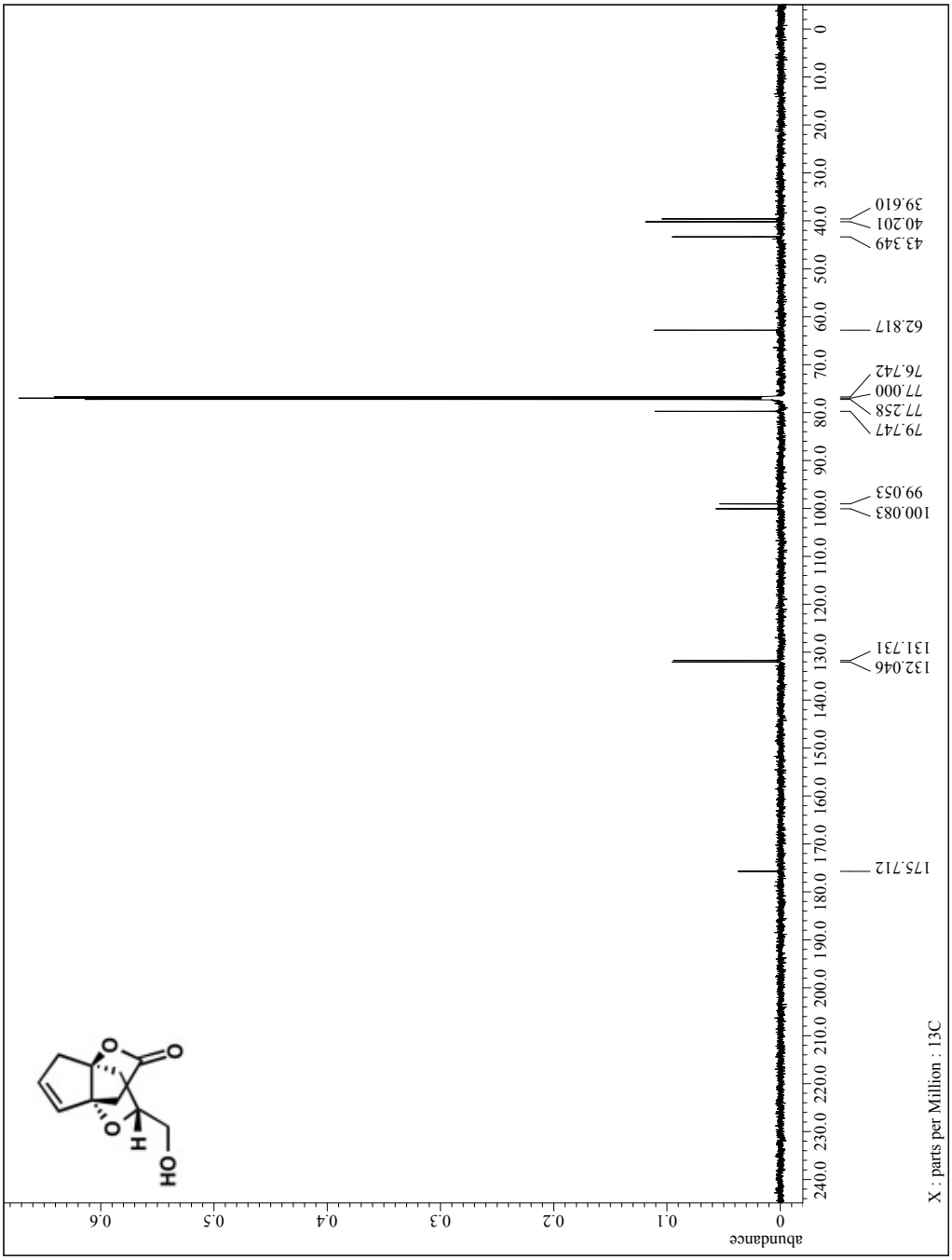

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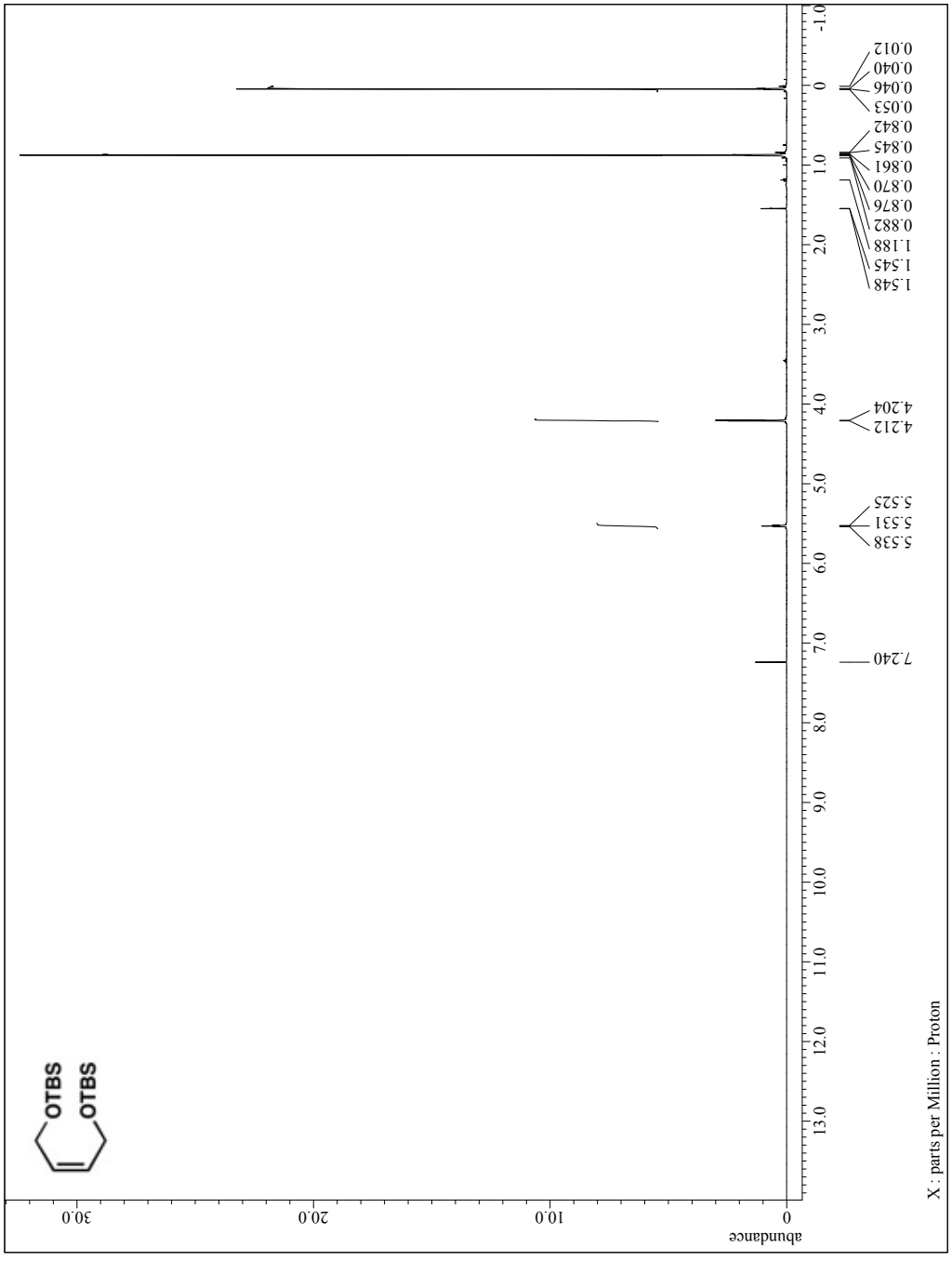

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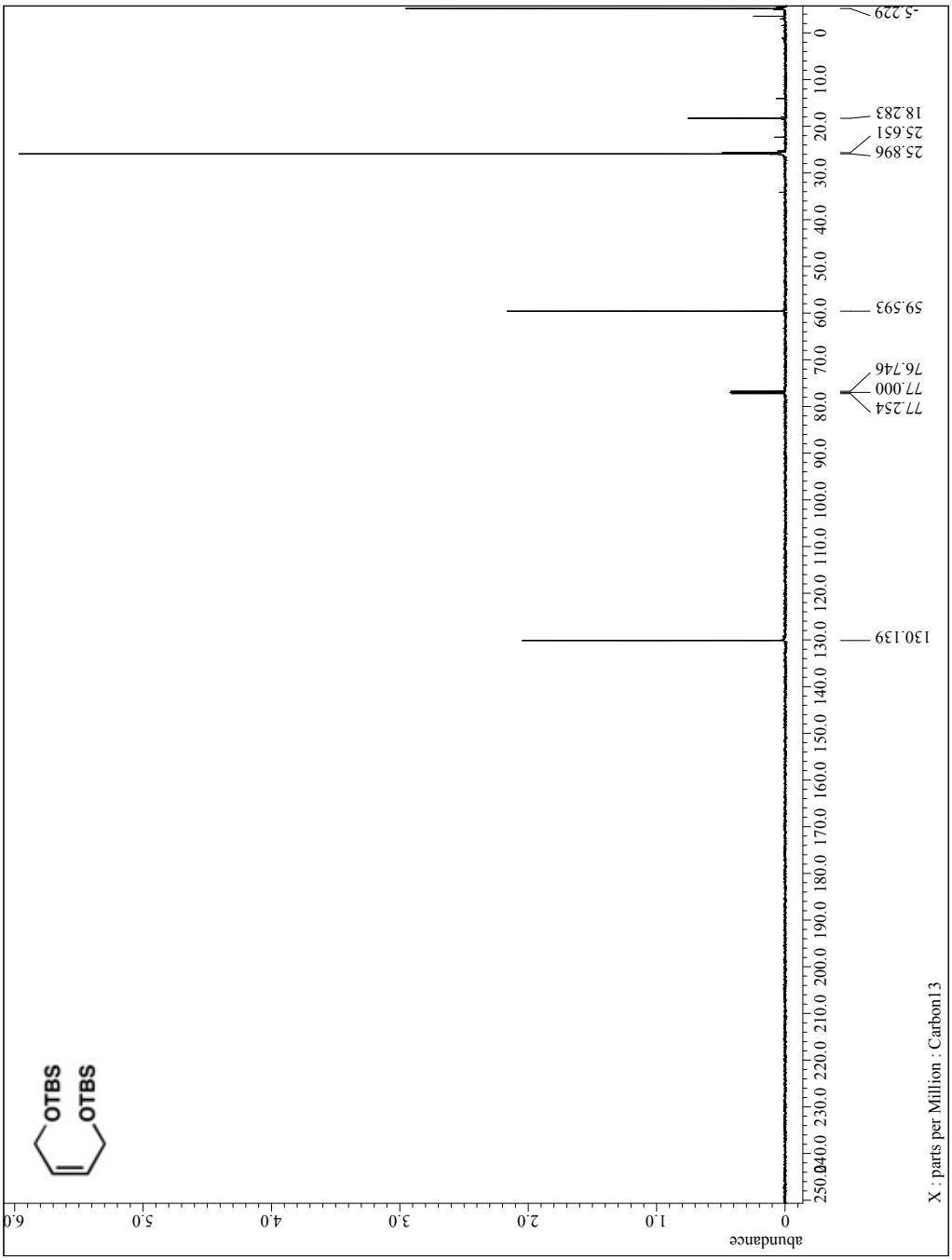

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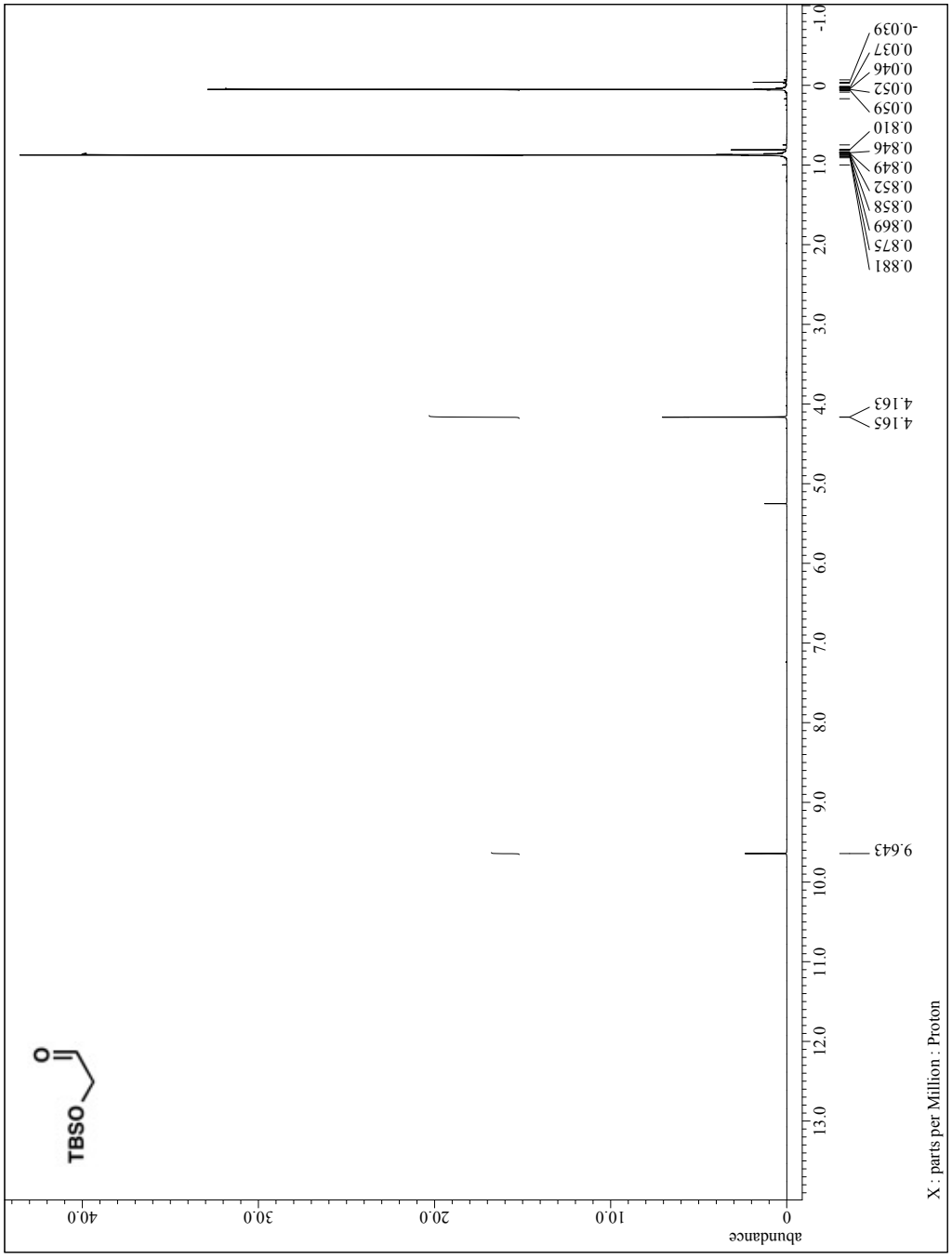

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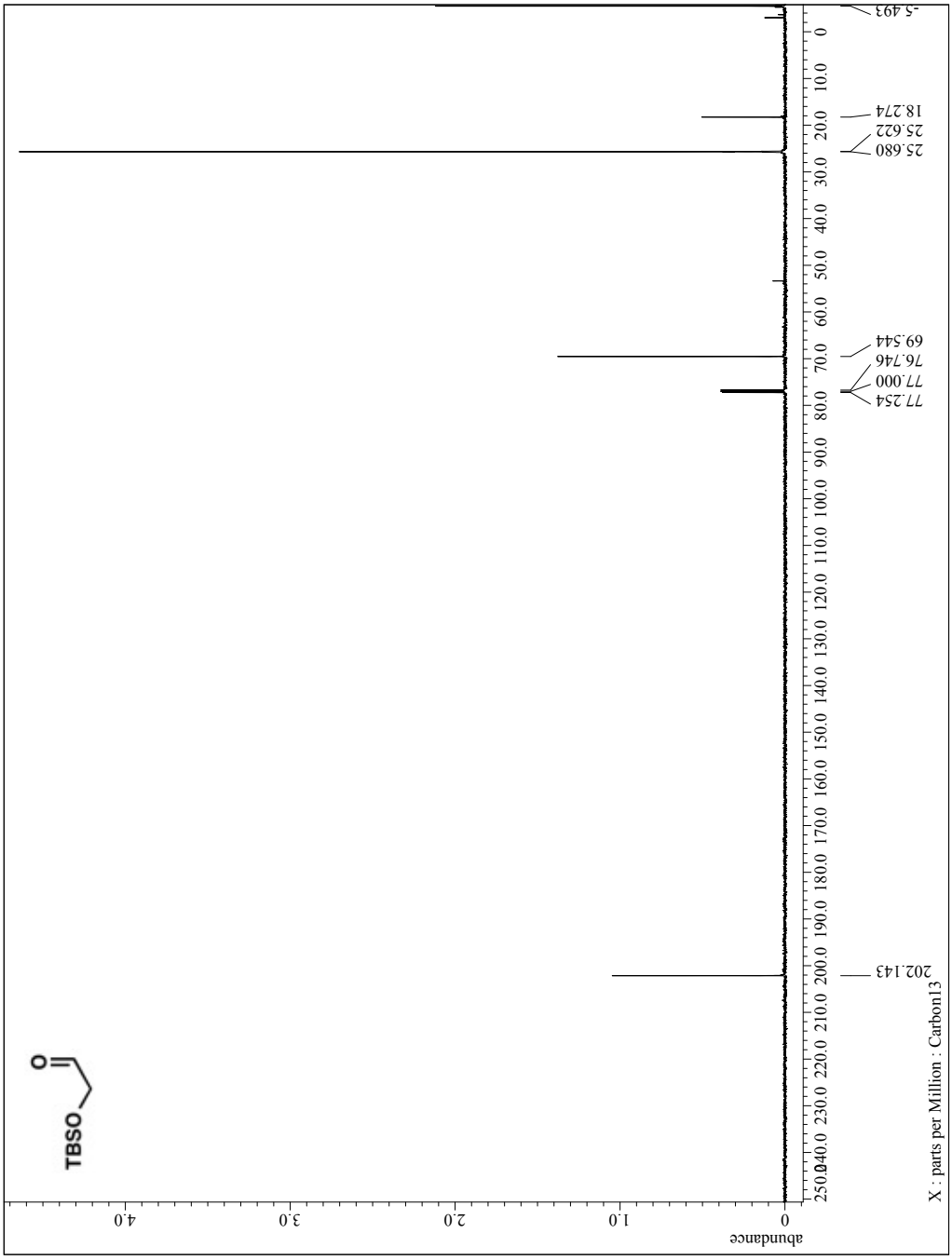

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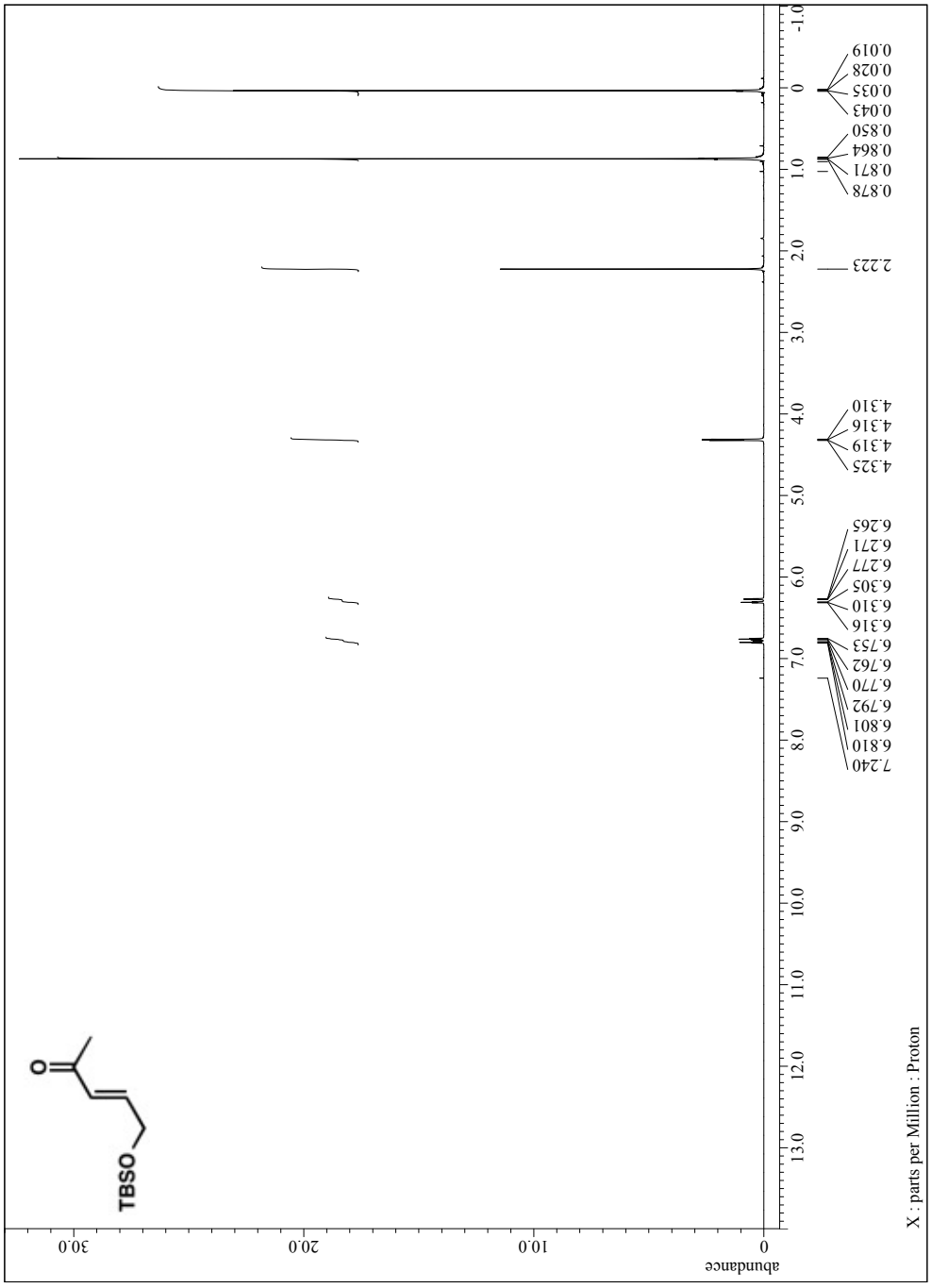

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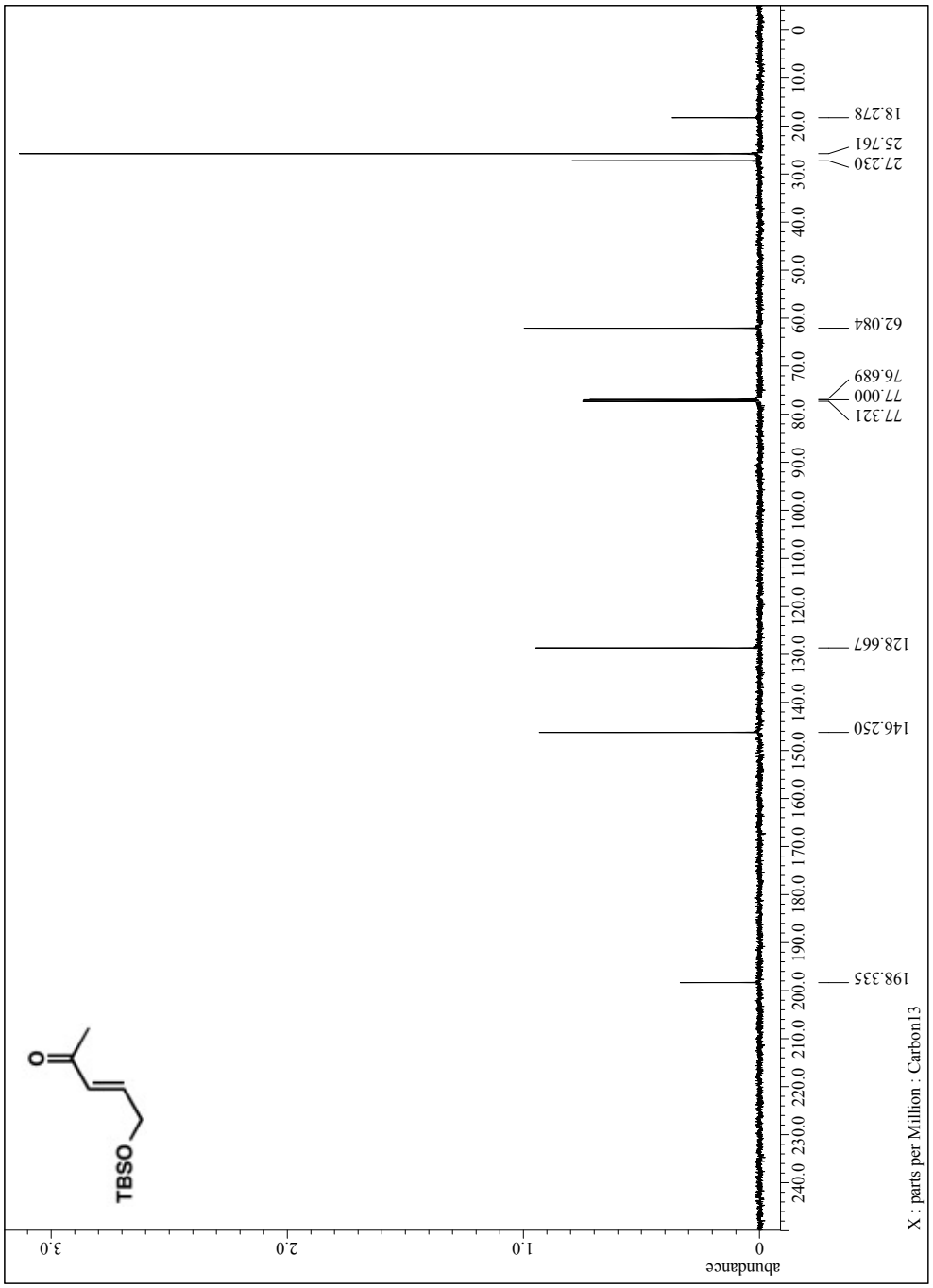

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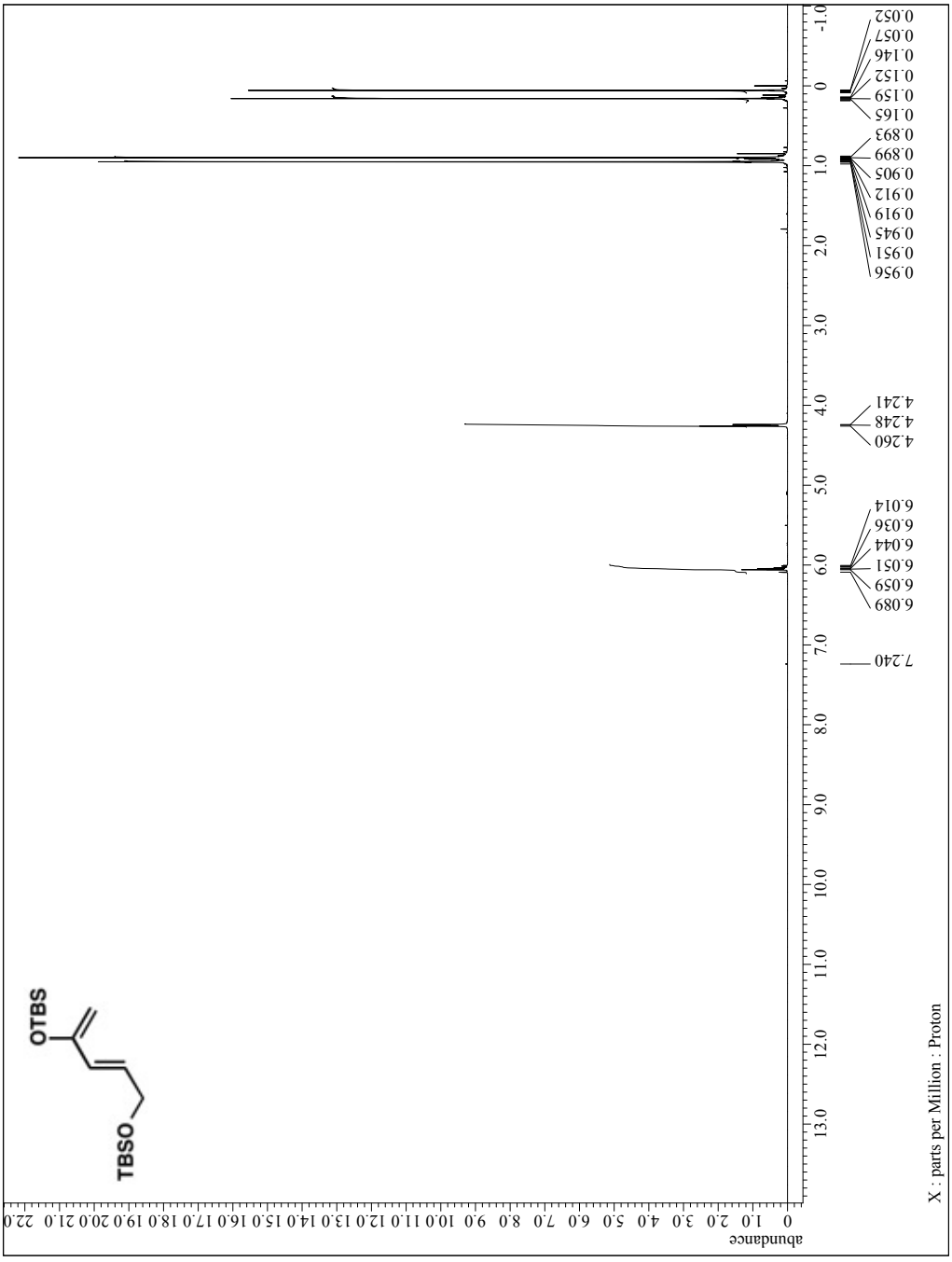

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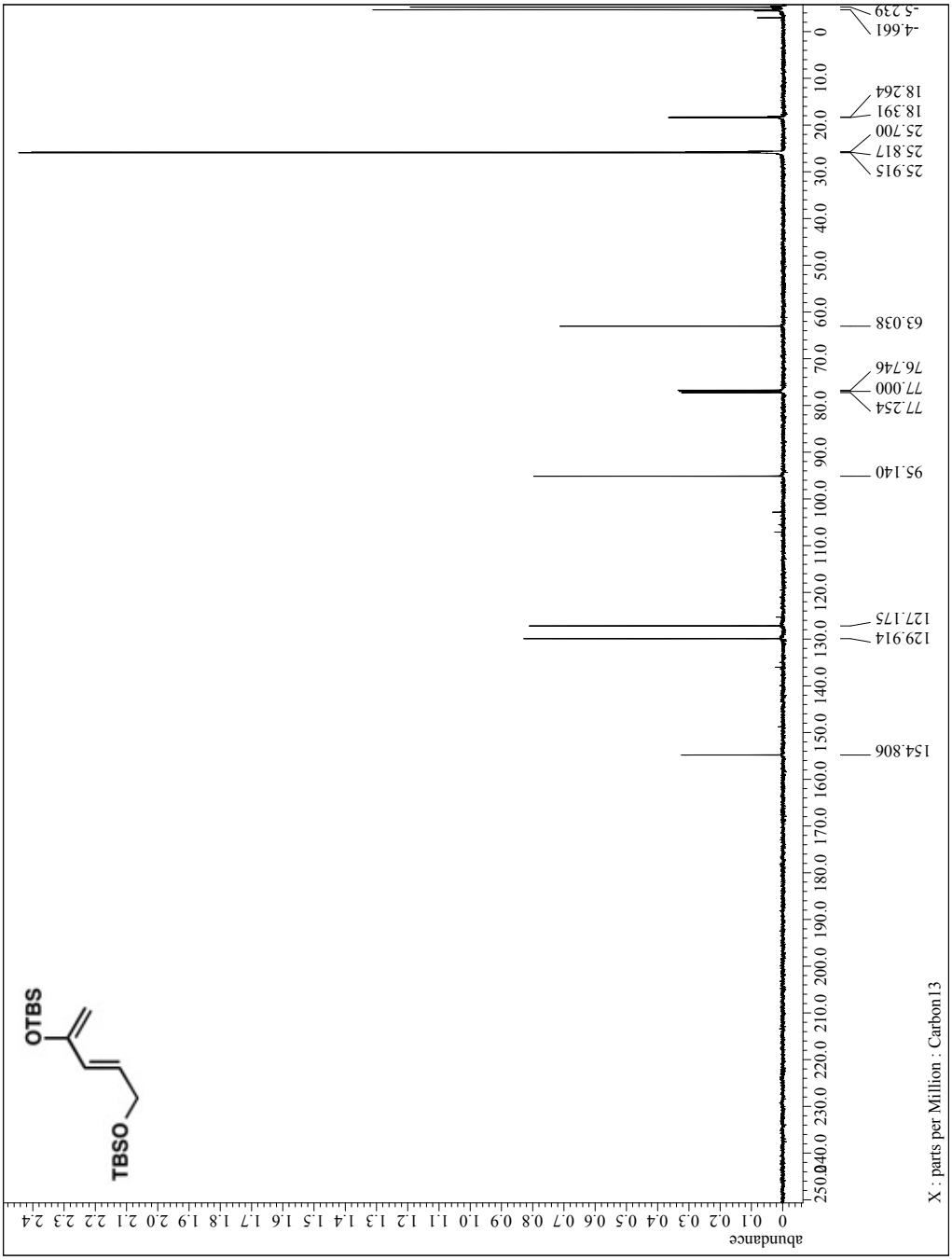

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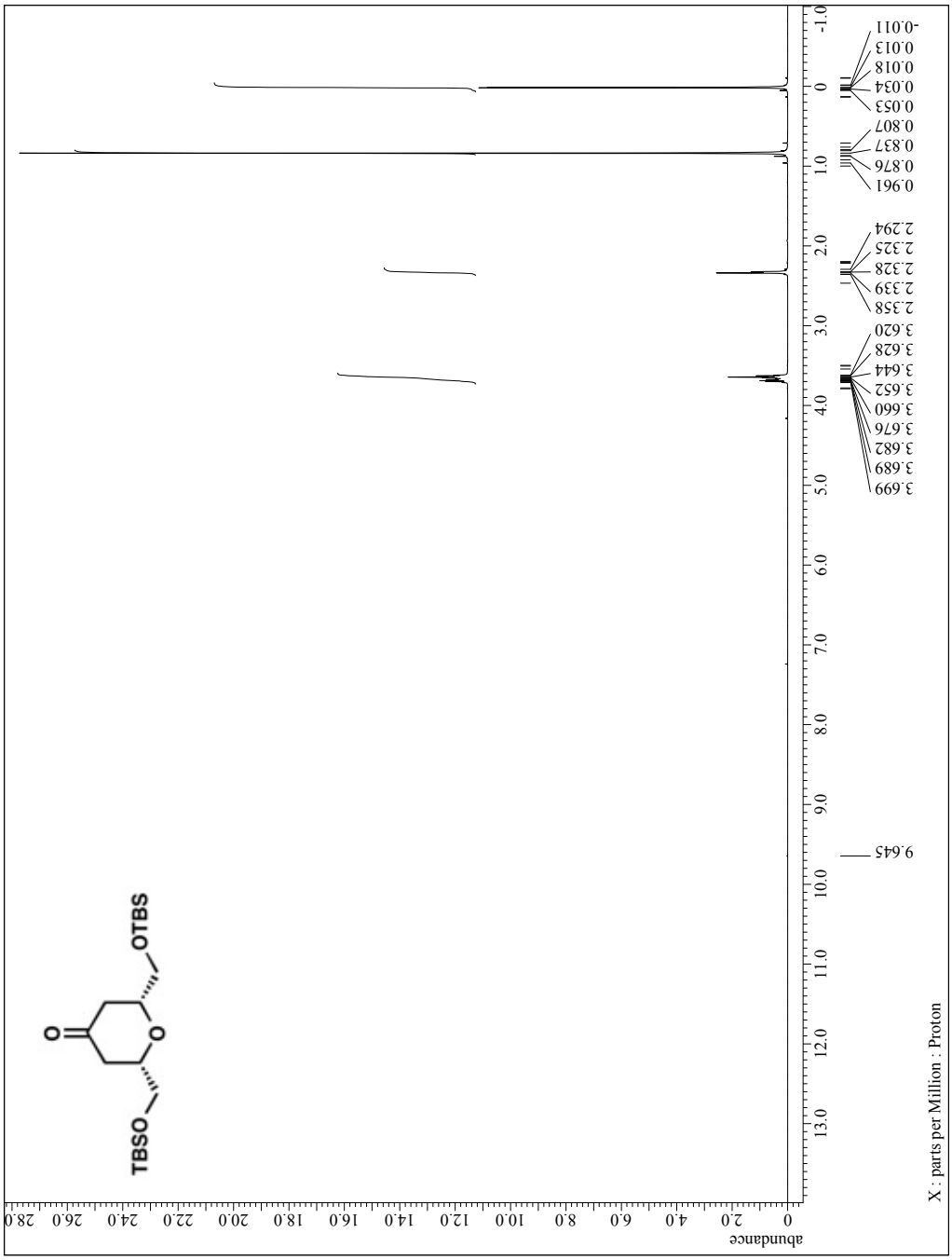

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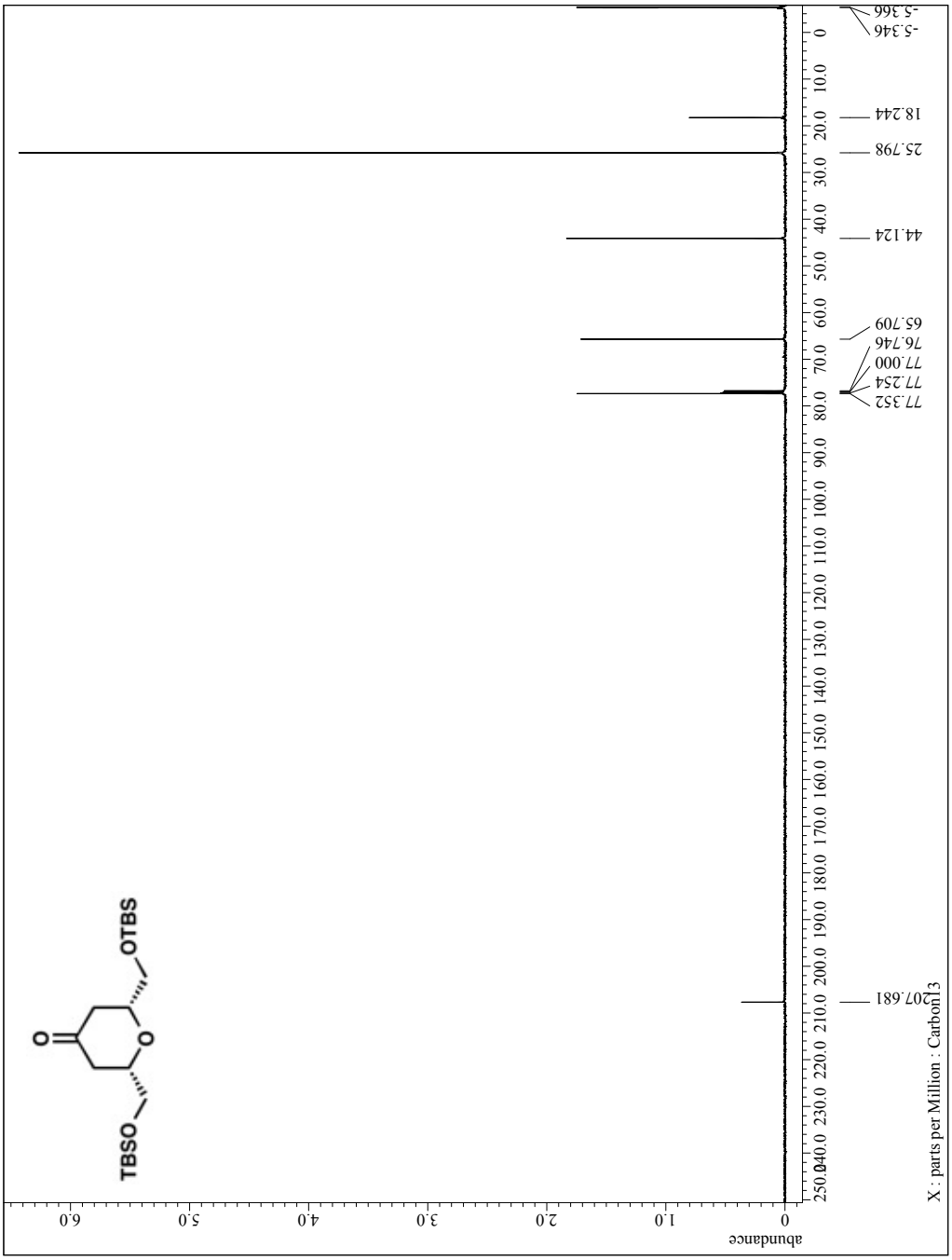

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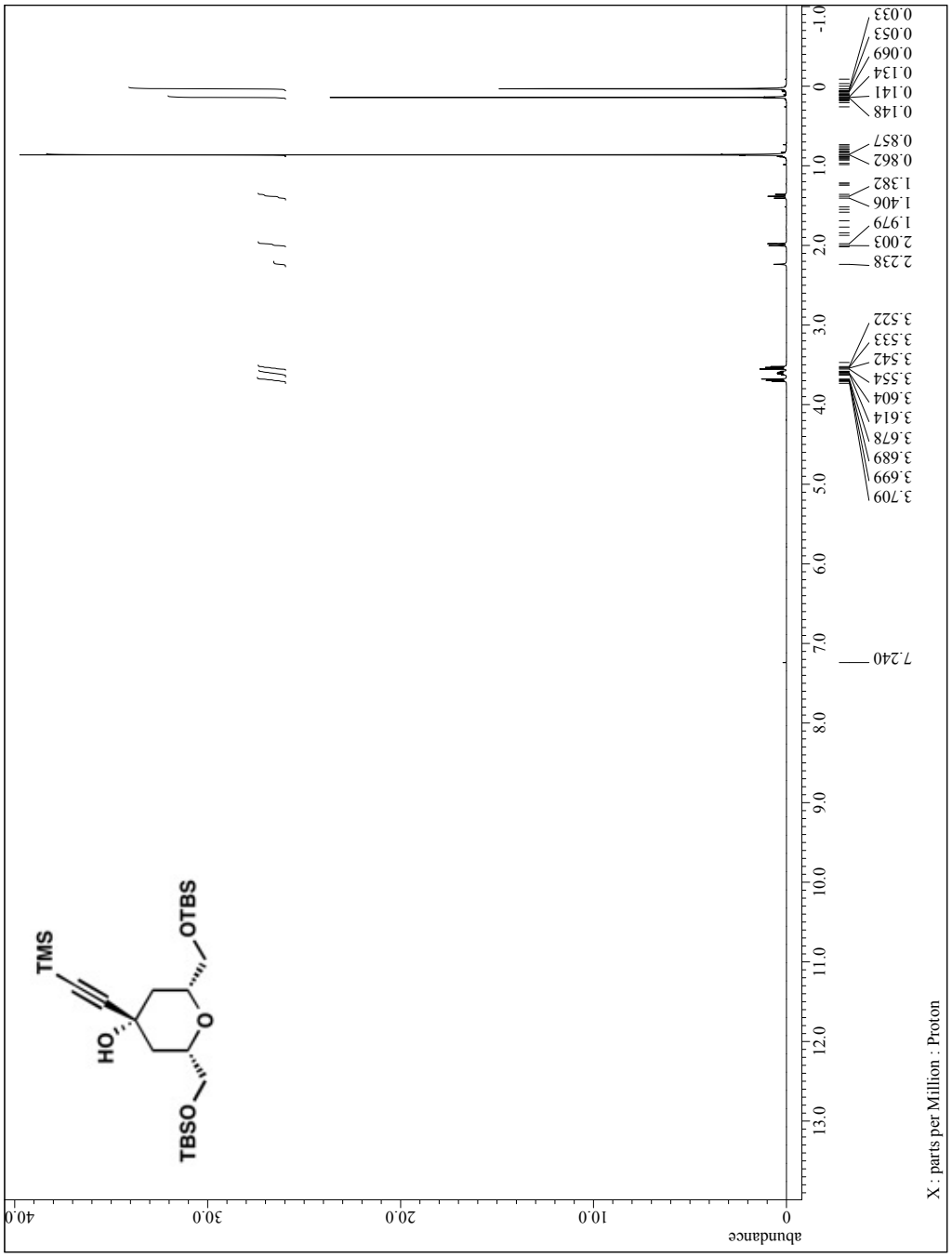

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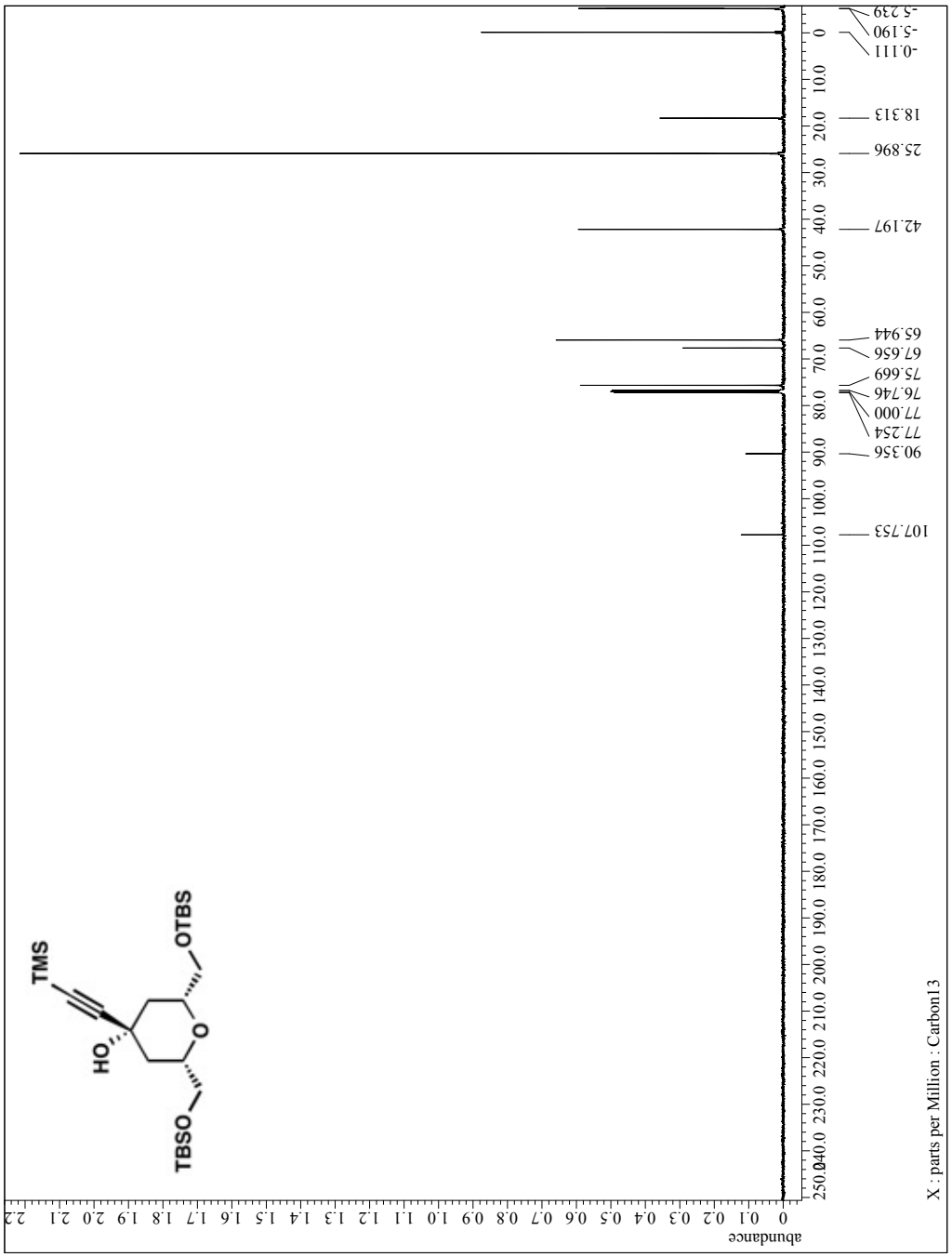

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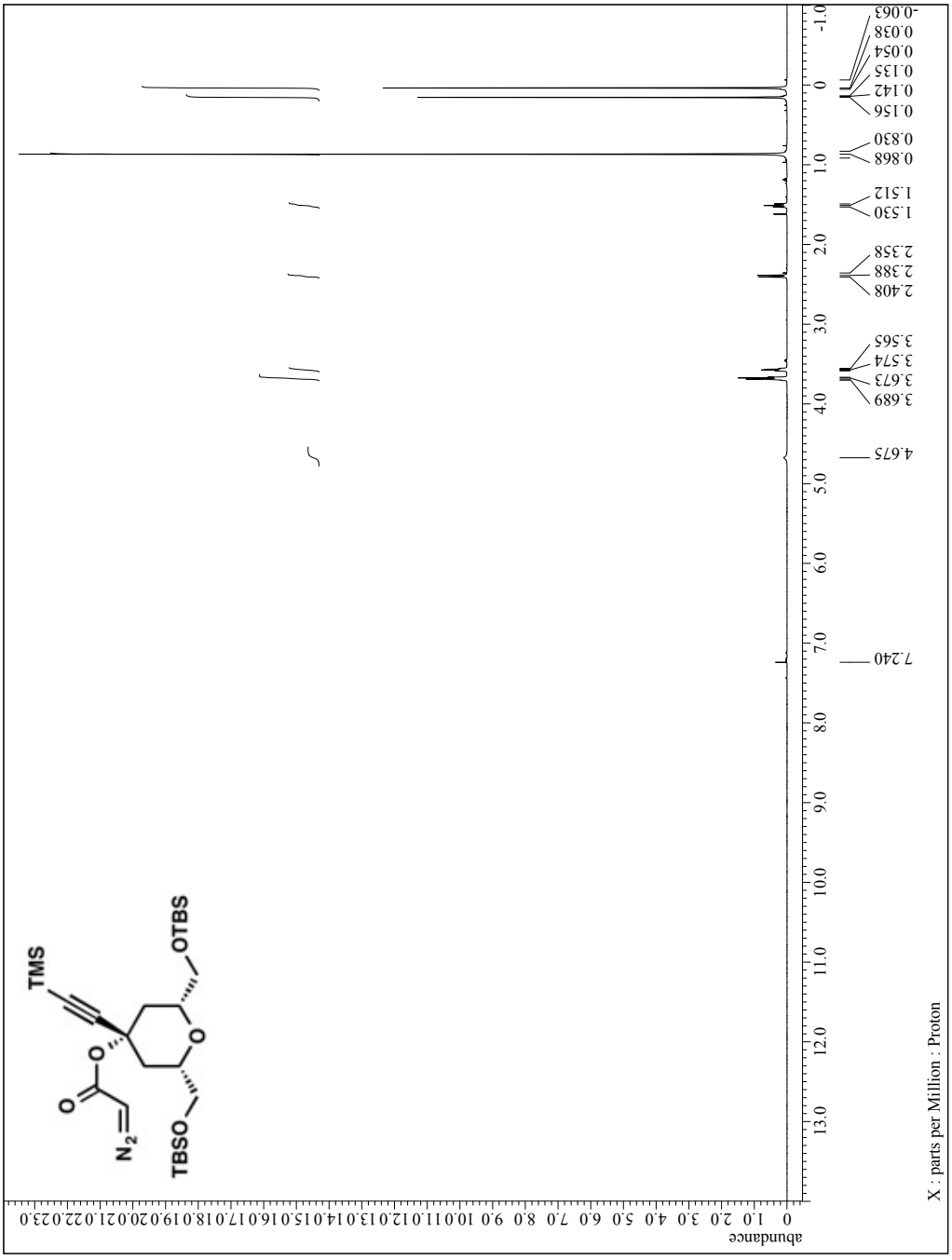

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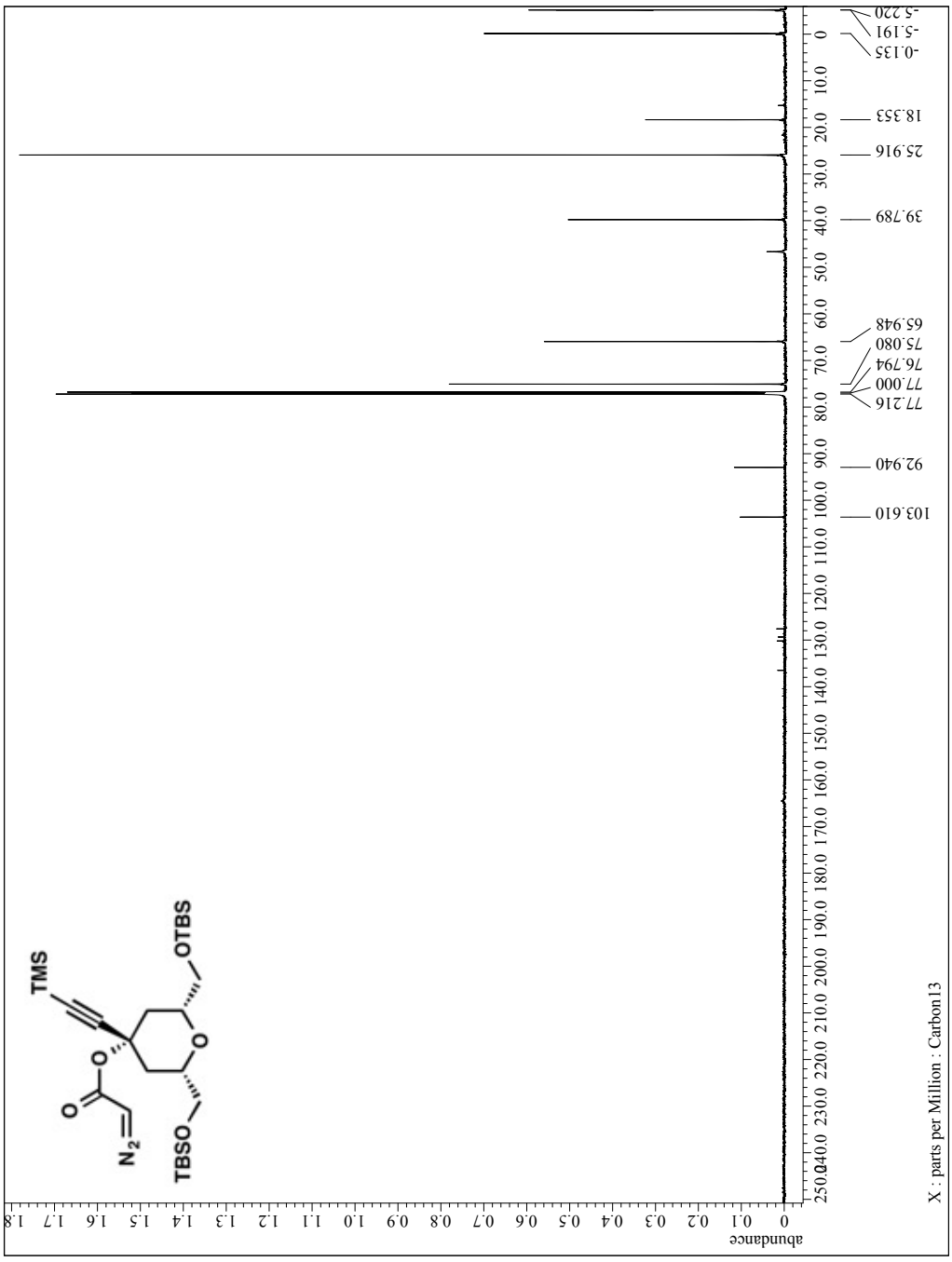

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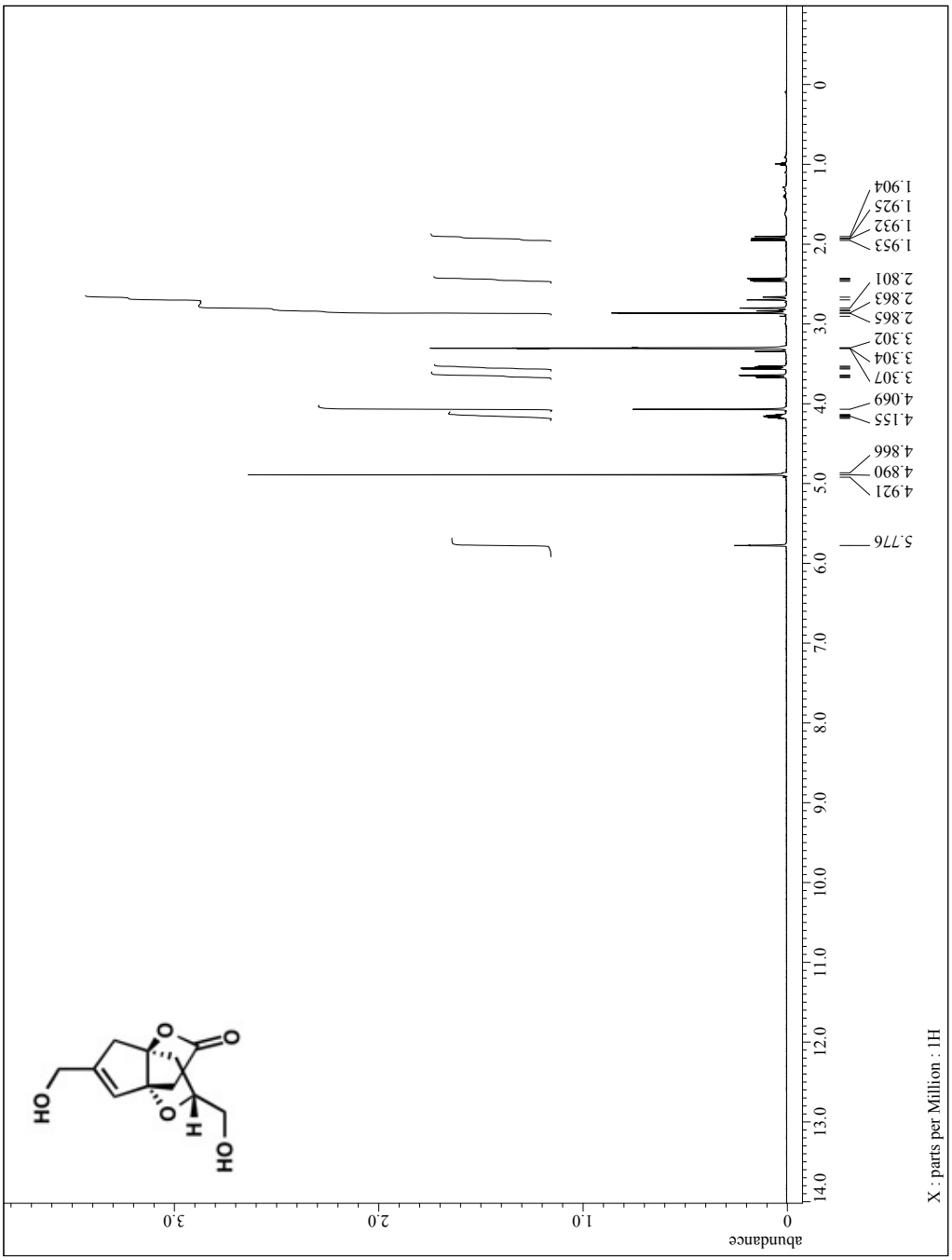

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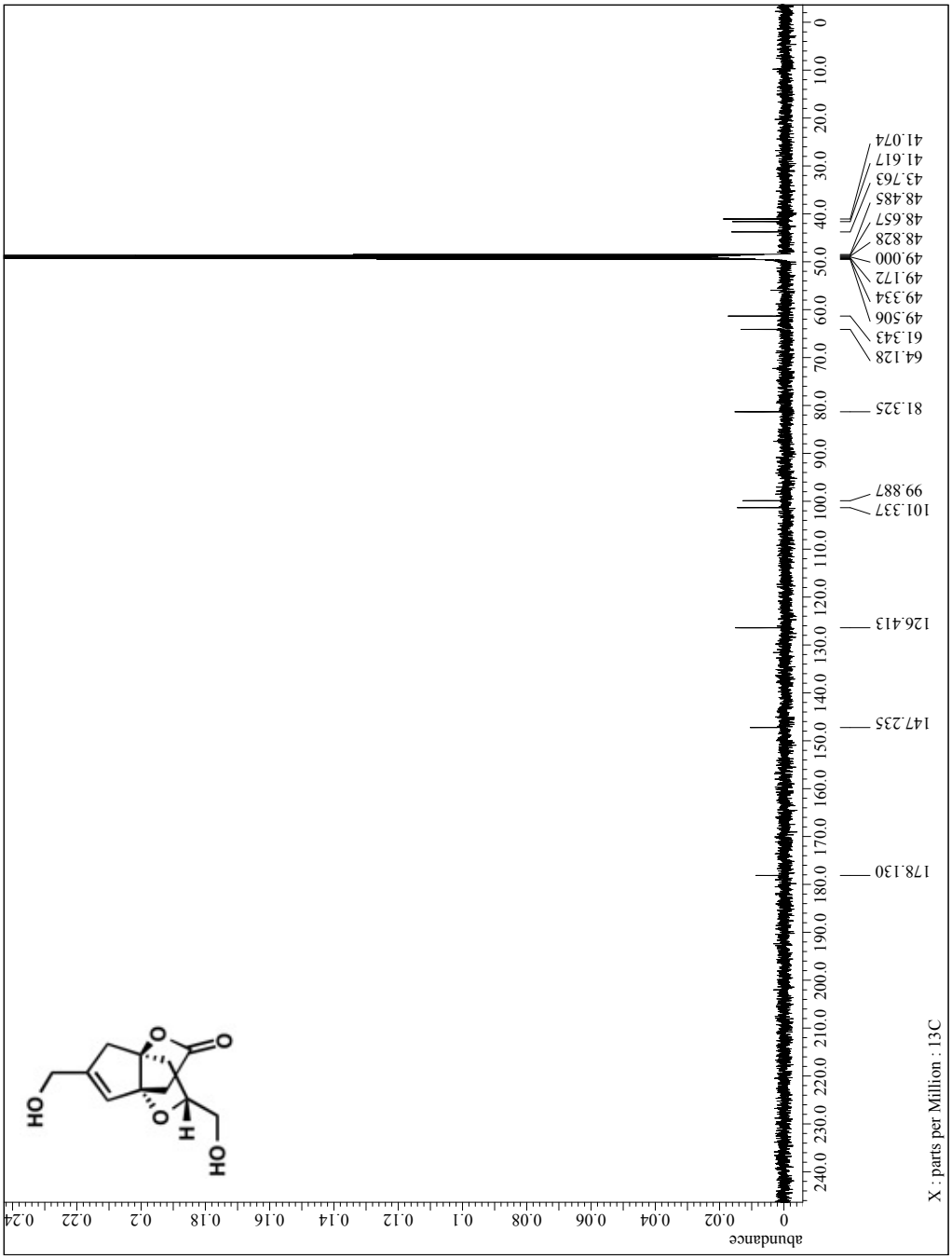

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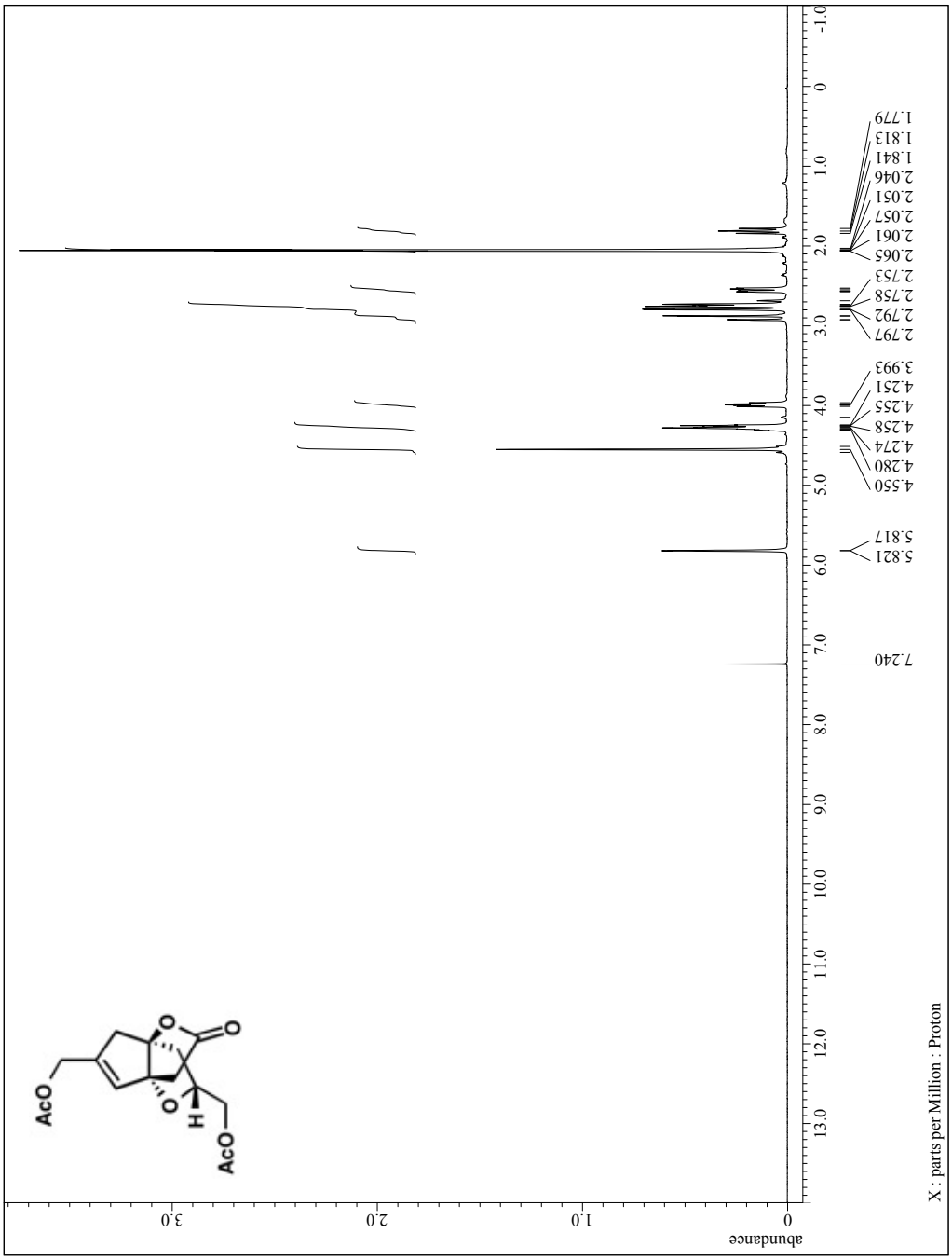
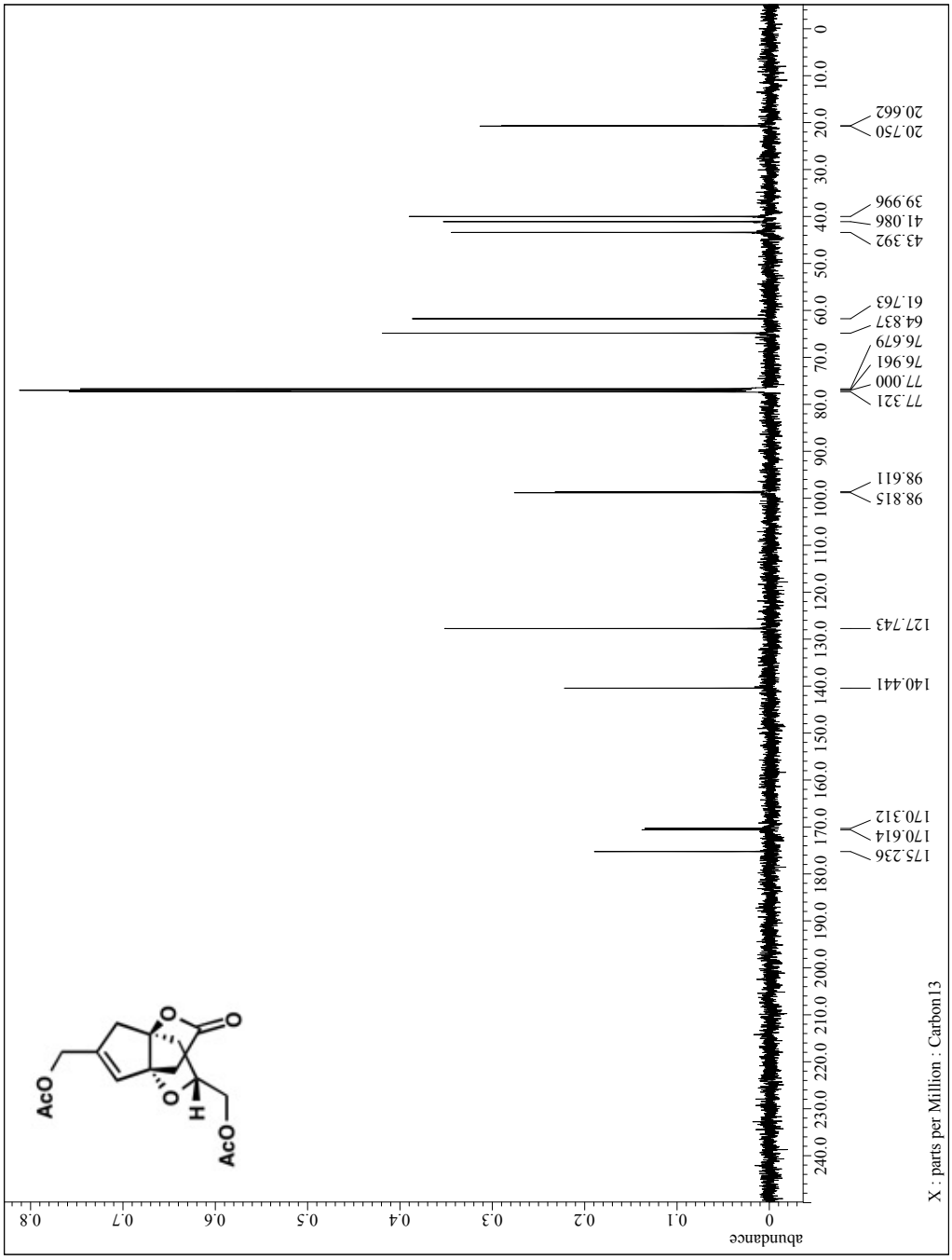
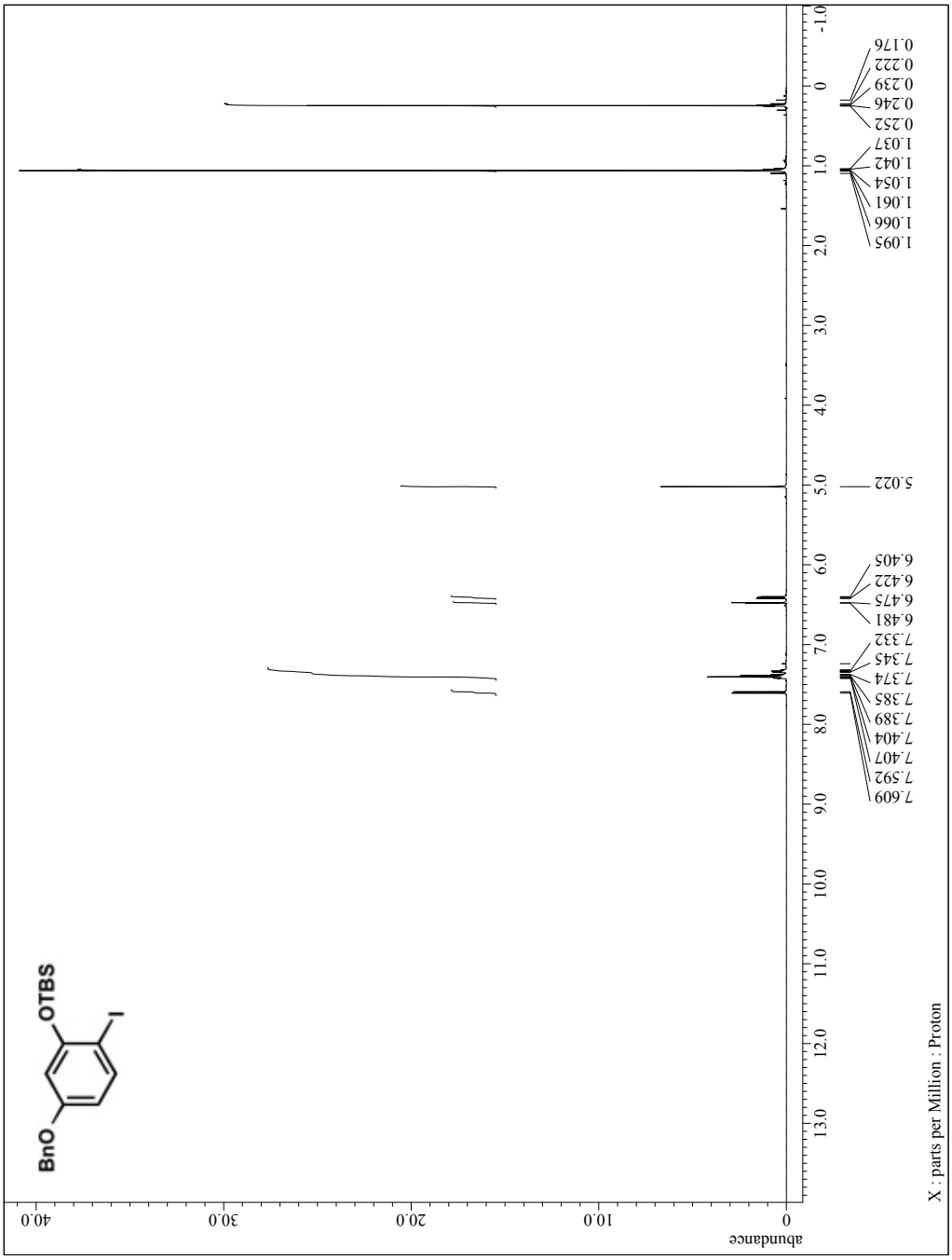


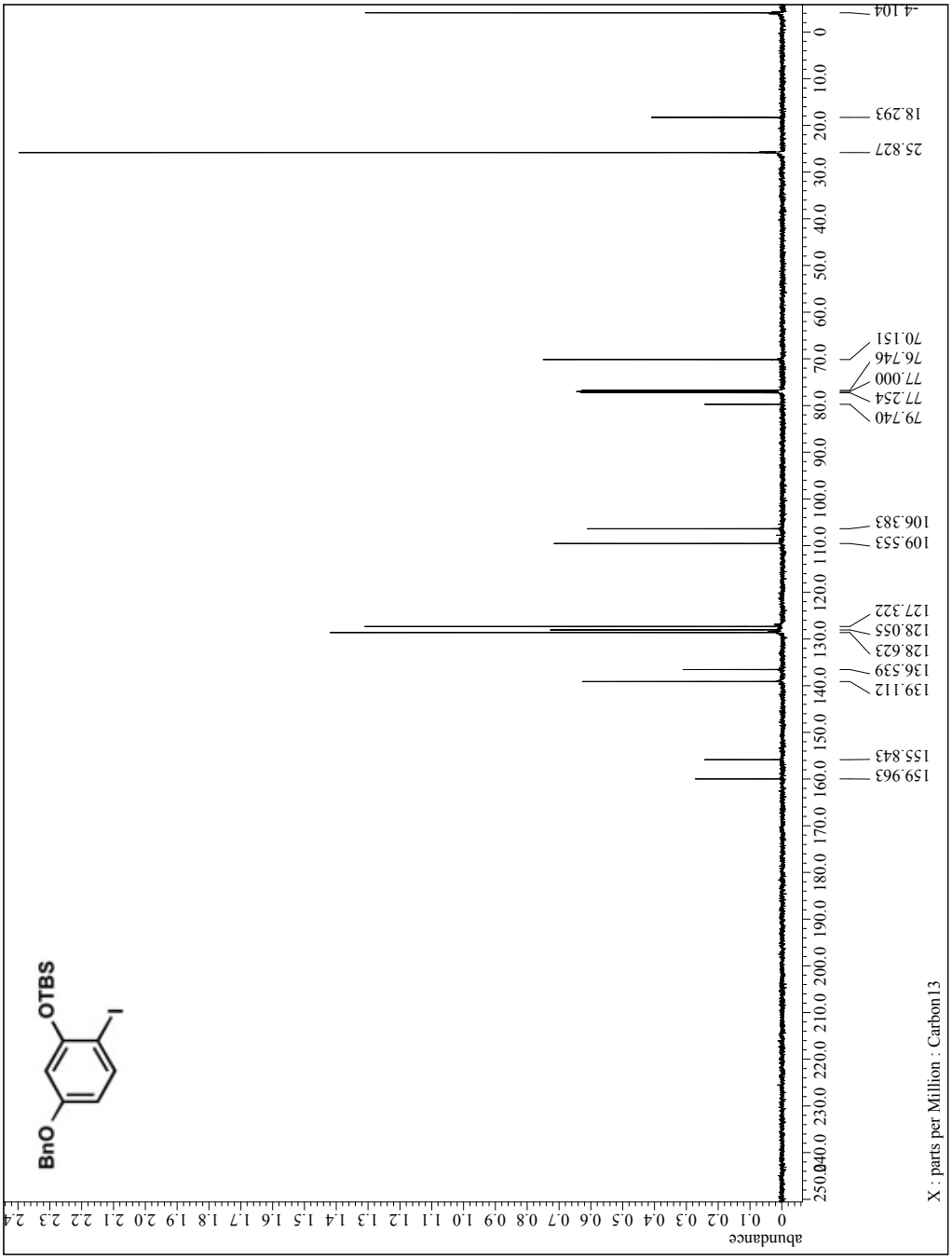
^{1}H NMR for compound **c65**



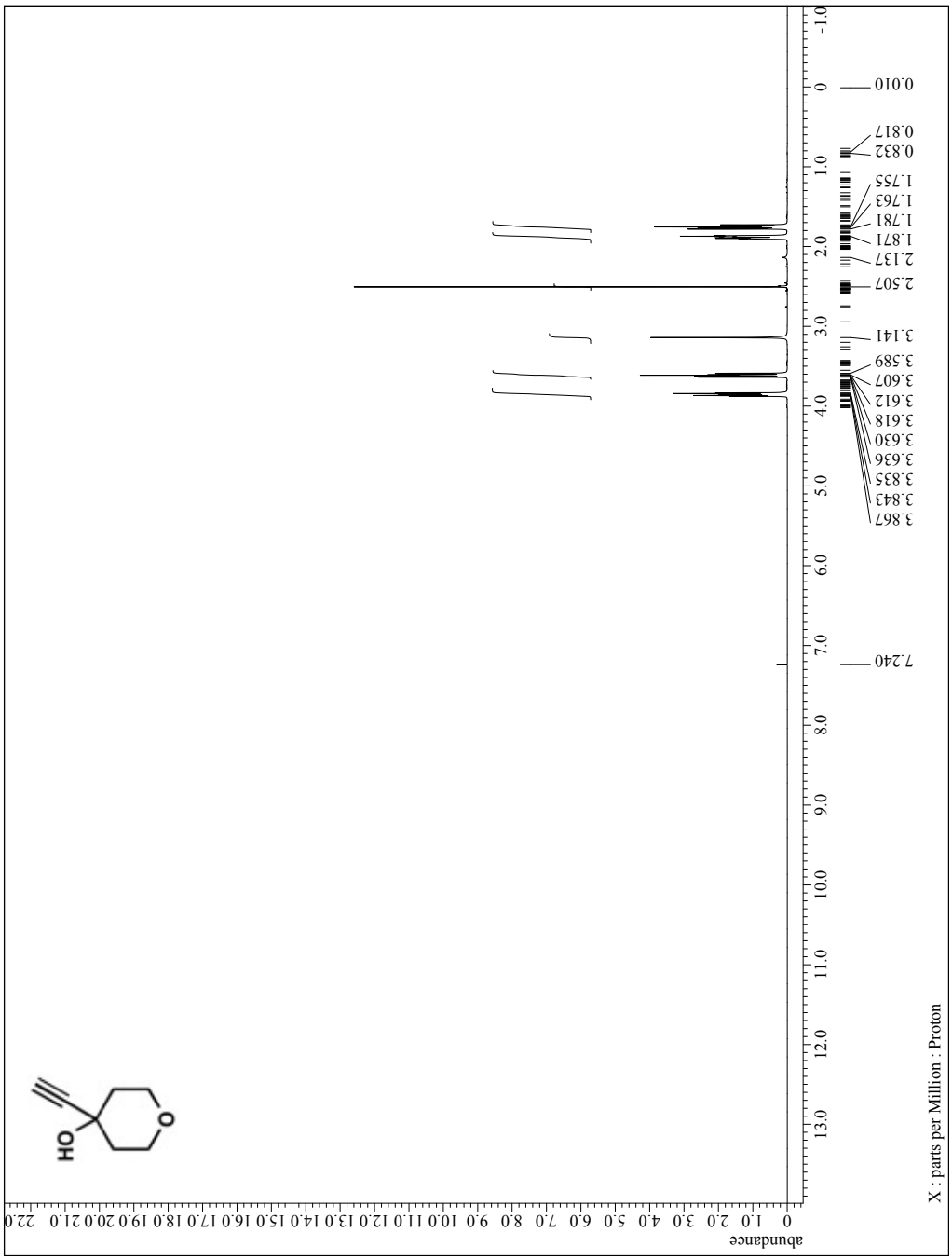
^{13}C NMR for compound **c65**



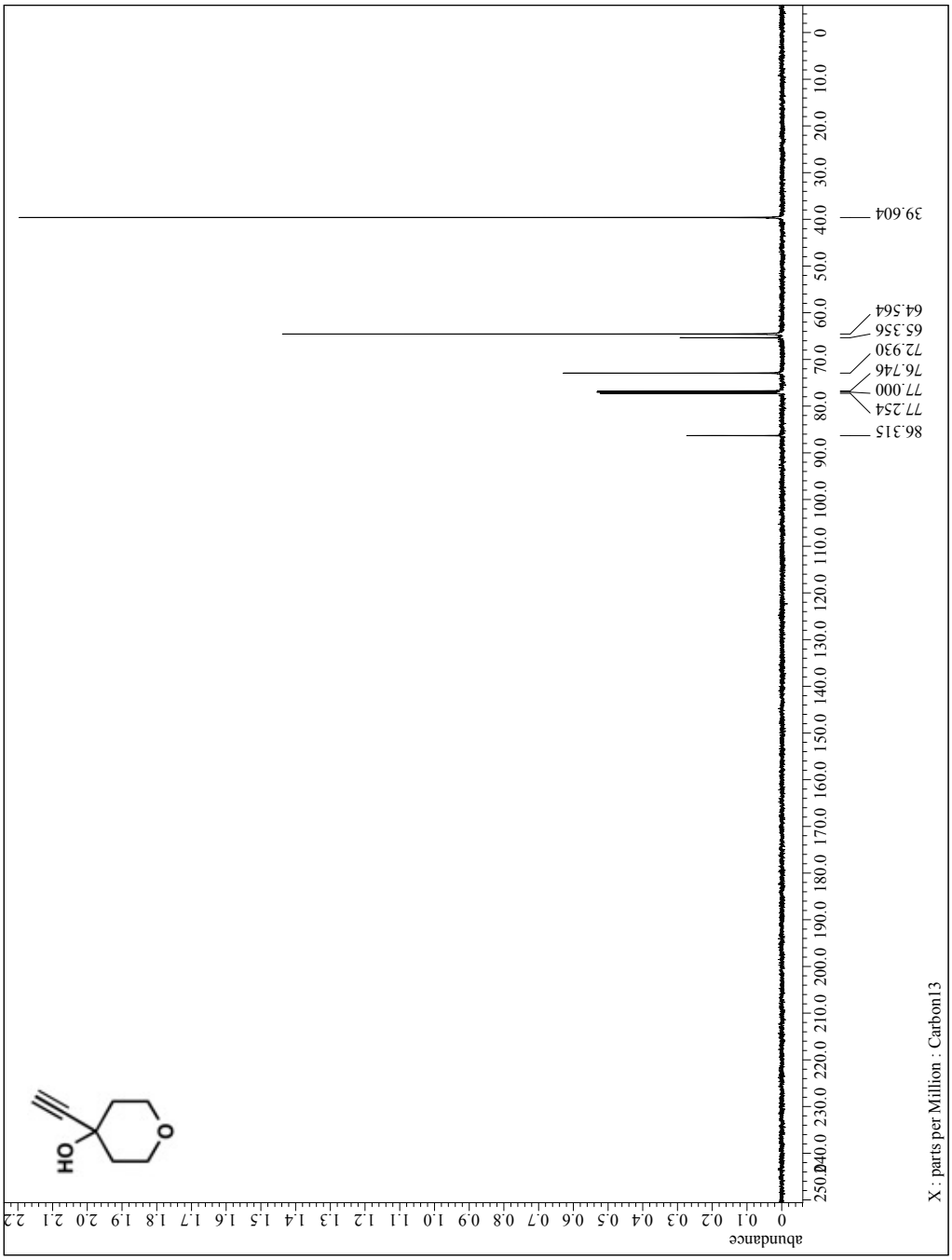
^{1}H NMR for compound **c69**



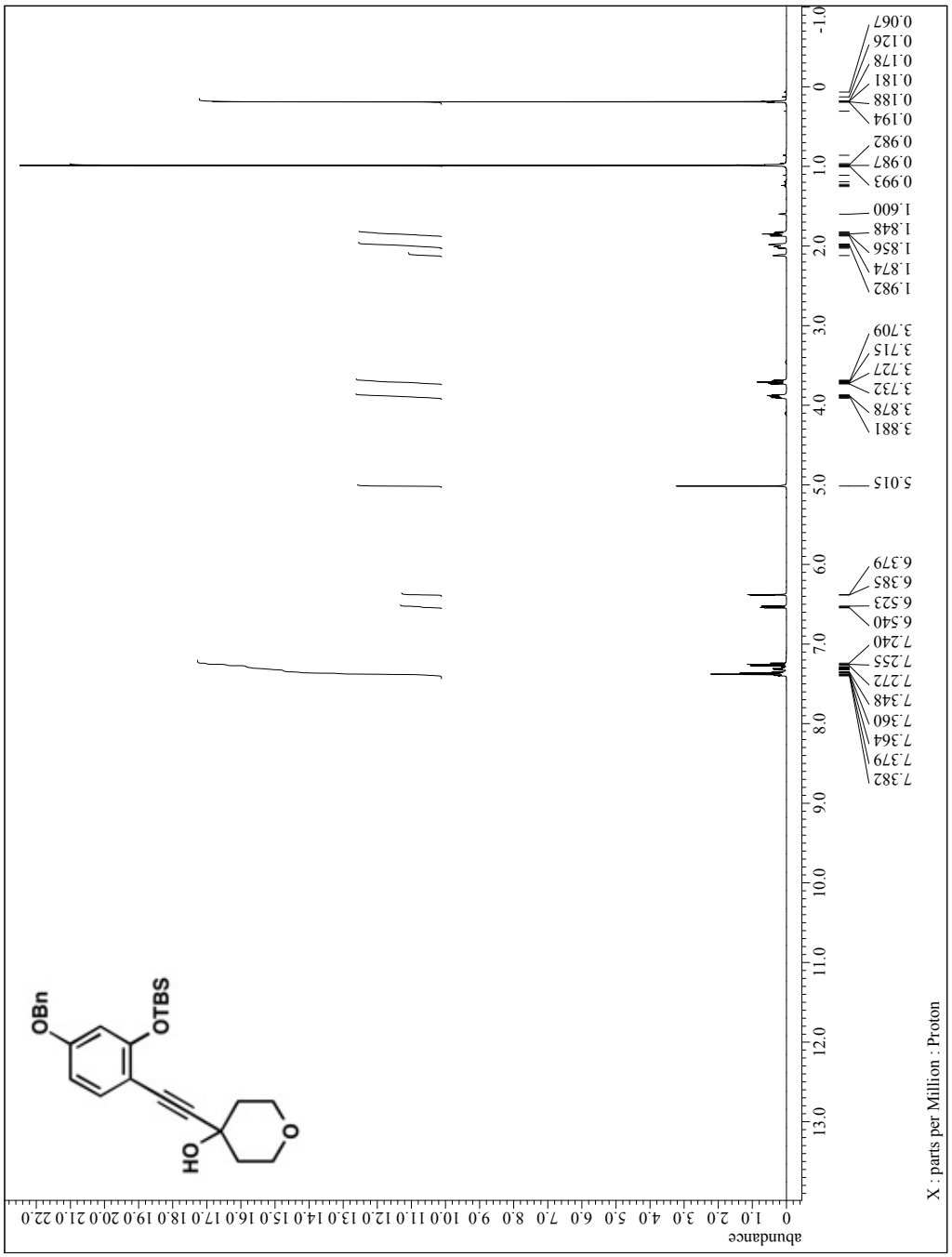
^{13}C NMR for compound **c69**



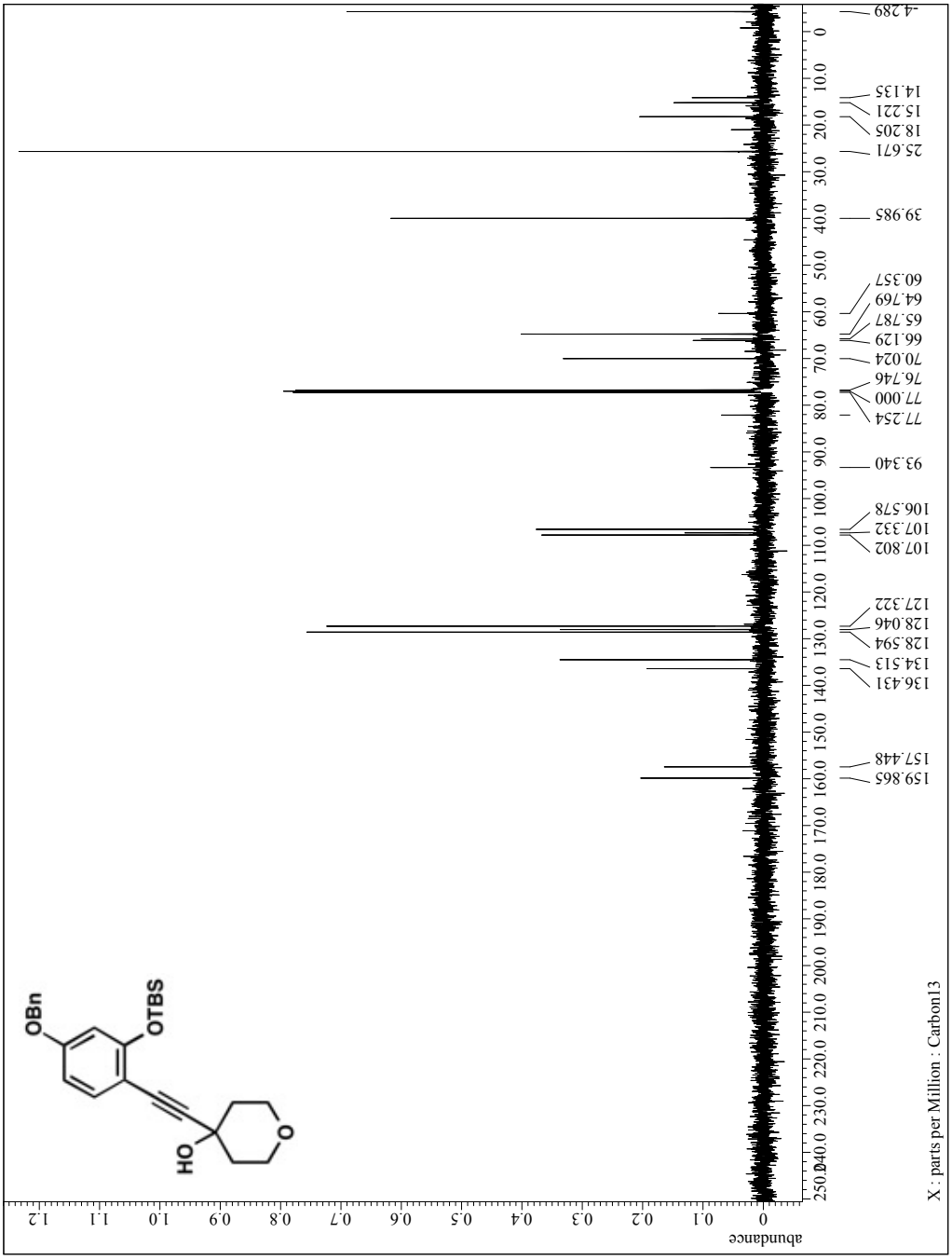
^{1}H NMR for compound **c80**



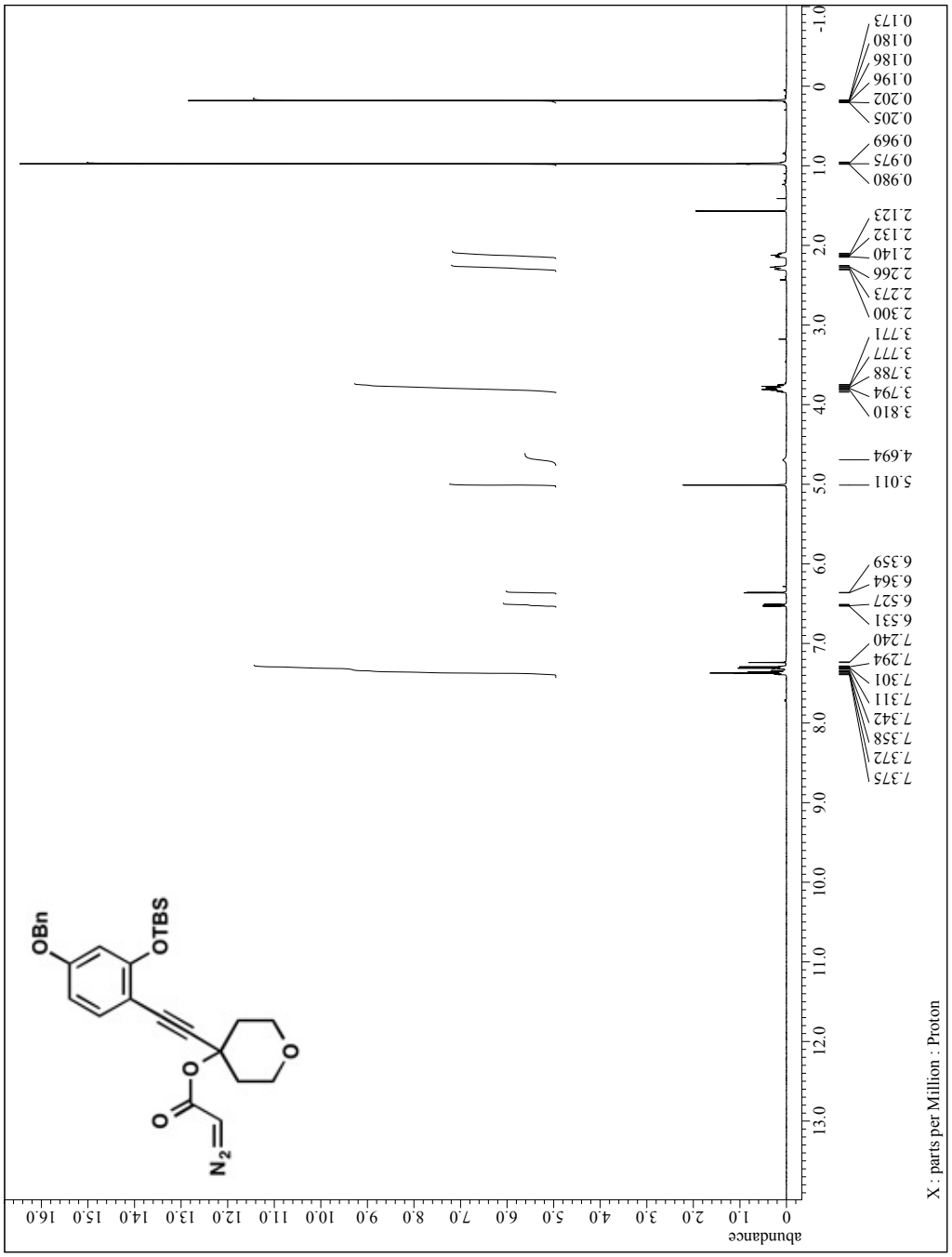
^{13}C NMR for compound **c80**



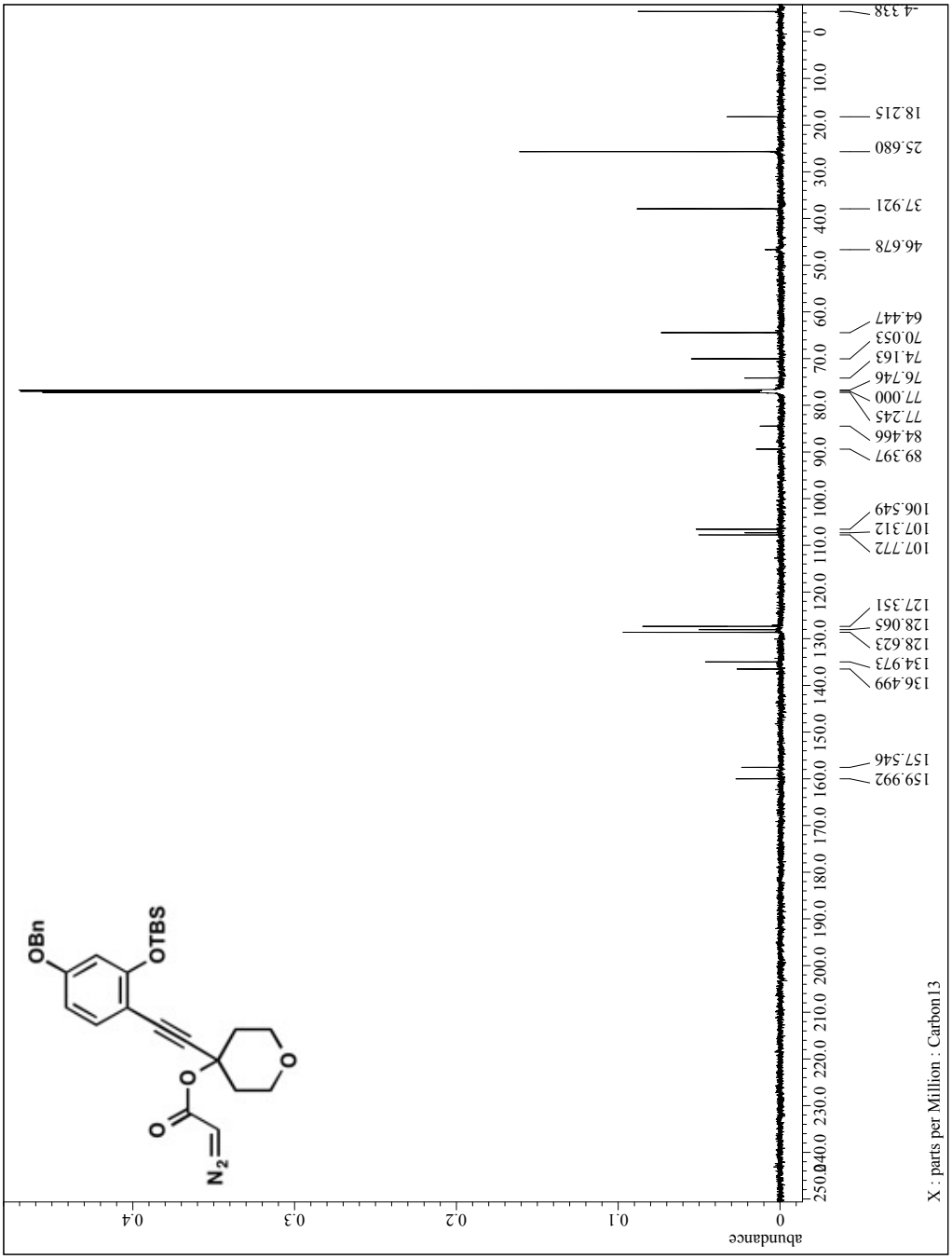
^{1}H NMR for compound **c82**



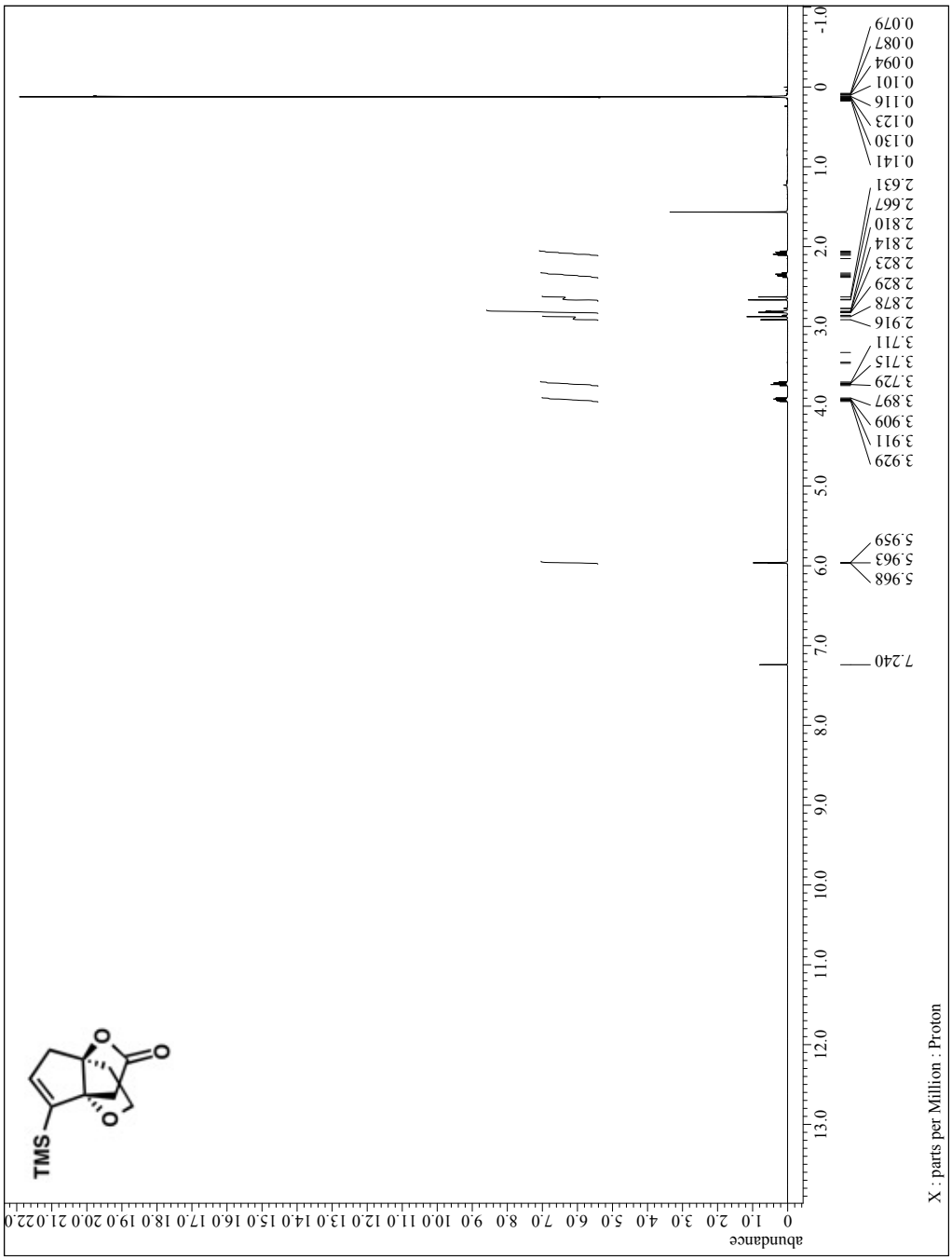
^{13}C NMR for compound **c82**



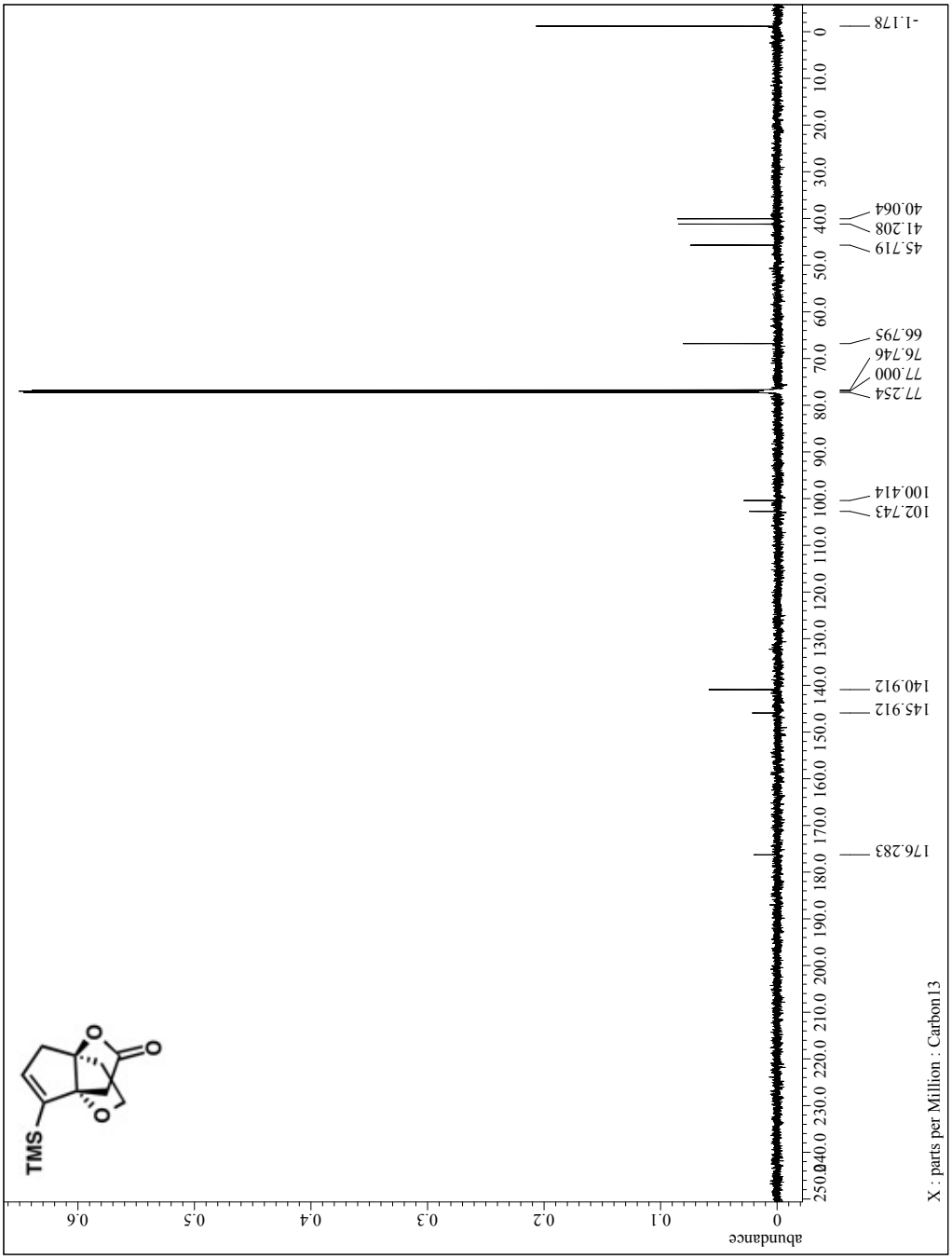
^{1}H NMR for compound **c79**



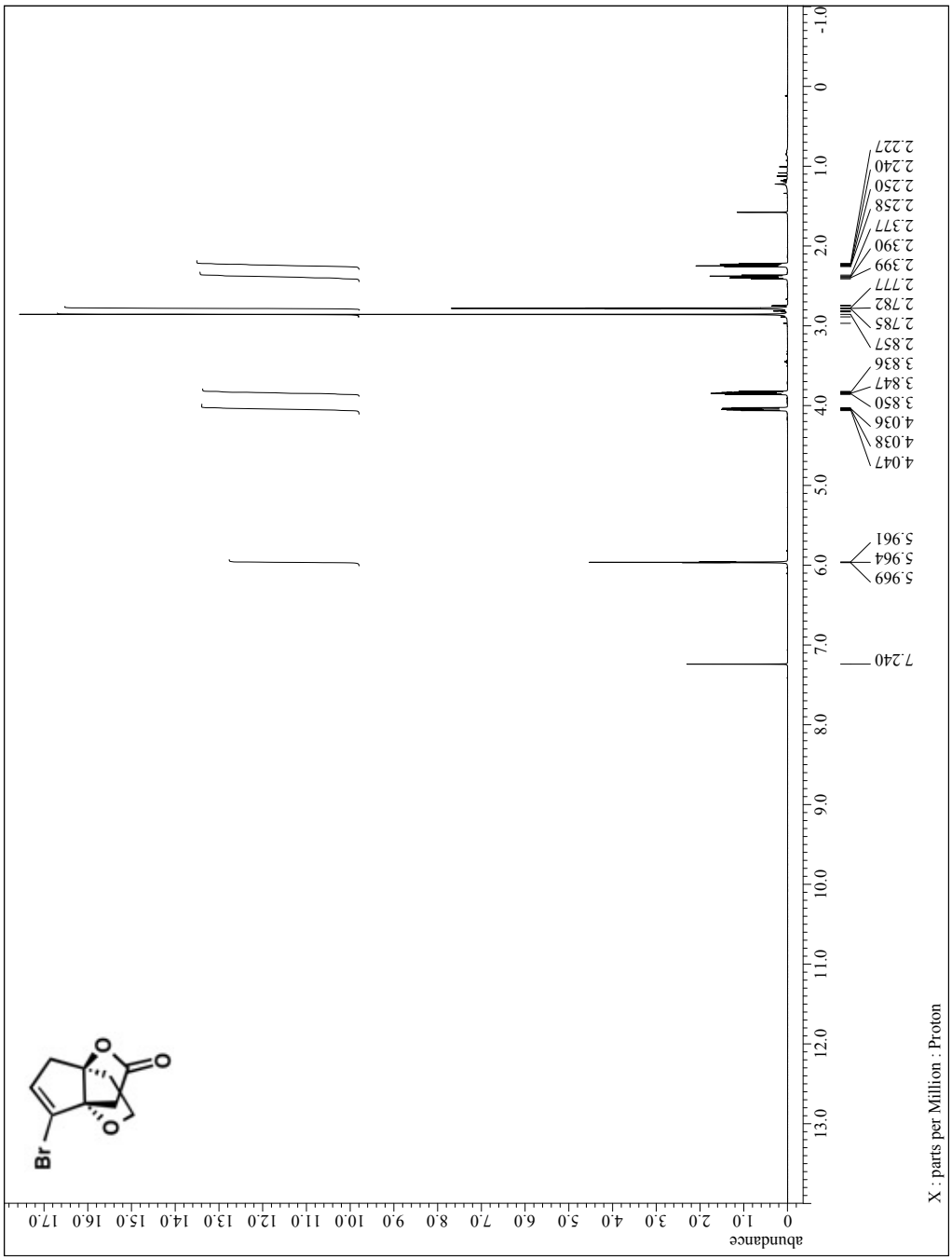
^{13}C NMR for compound **c79**



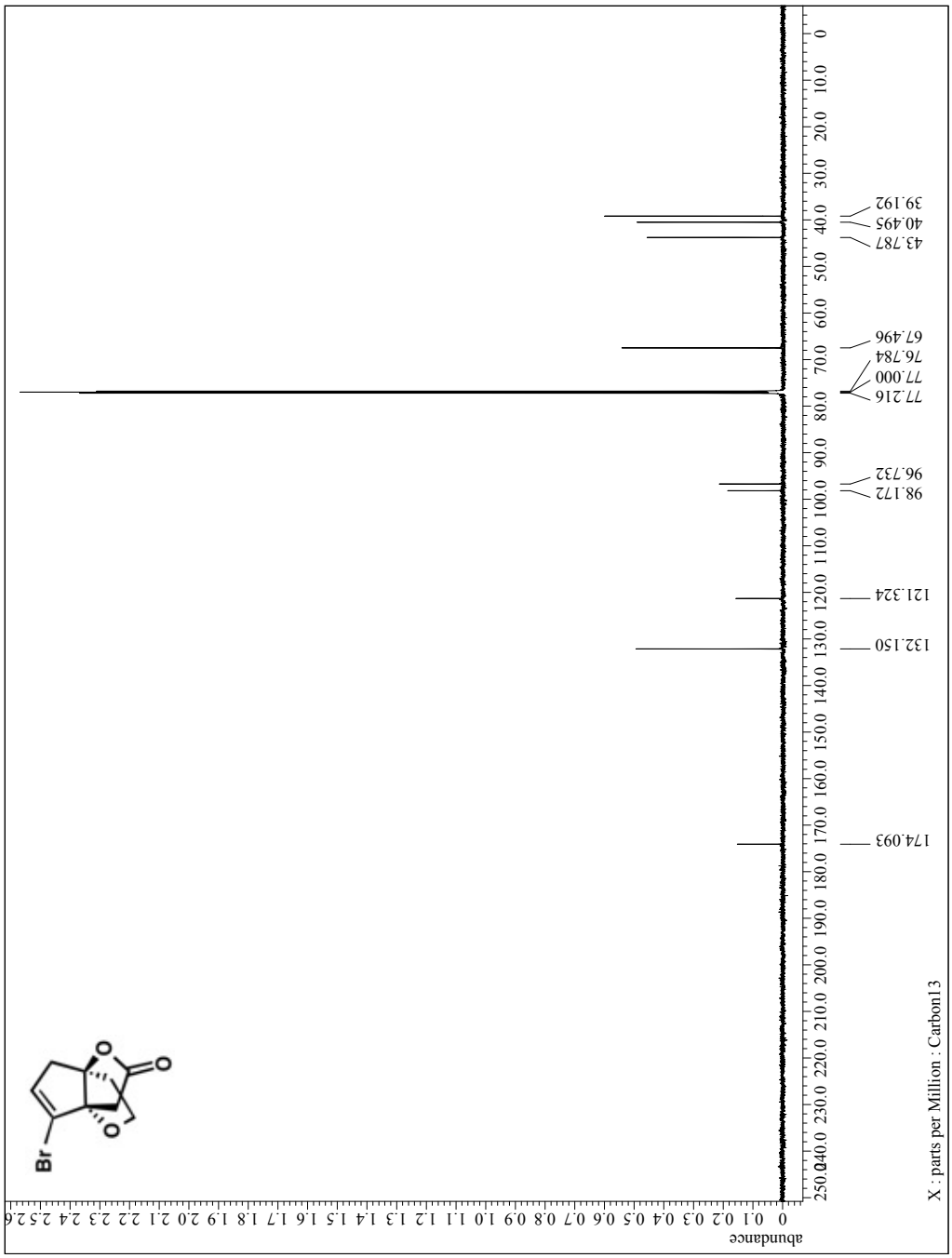
^{1}H NMR for compound **c88**



^{13}C NMR for compound **c88**



^{1}H NMR for compound **c87**



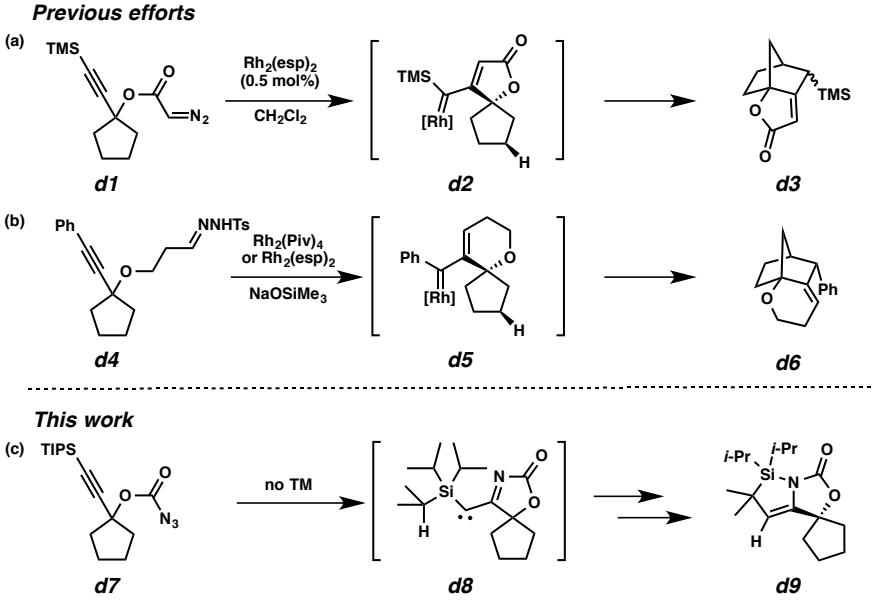
^{13}C NMR for compound **c87**

4. SYNTHESIS OF AZASILACYCLOPENTENES AND SILANOLS VIA HUISGEN CYCLOADDITION-INITIATED CASCADES TERMINATING IN C-H BOND INSERTION/REARRANGEMENT

4.1 Carbene and Nitrene Initiated Cascade Reaction

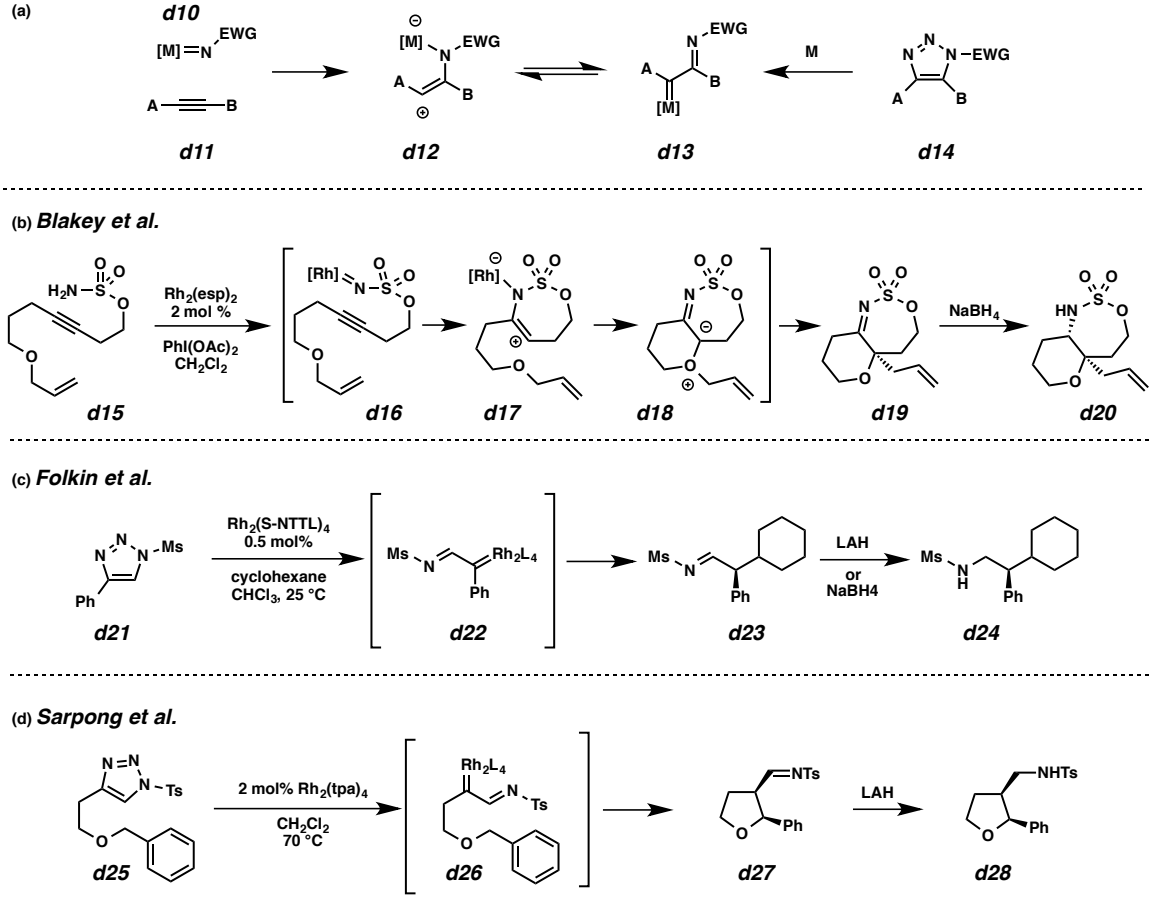
Metallocarbenes have been applied to many organic reactions that include cyclopropanations,[1] Buchner ring expansion,[2] ylide formation,[3] X-H bond insertion (X = N, O, S, Si etc.),[4] and especially C-H bond insertions,[5] which are considered powerful tools for synthetic chemistry.[6] Cascade reactions using highly reactive carbenes allow the more efficient synthesis of complex molecules.[7] Our research group recently reported the formation of bridged polycycles via carbene/alkyne cascade reactions terminated in C-H bond insertion (Scheme 4-1a, b).[8] A variety of polycyclic ring sizes and structural isomers can be obtained by reacting with the C-H bond at different ring positions. We were very interested in expanding on the cascade reaction to also synthesize nitrogen-containing compounds. This desire in turn led to the discovery of the formation of azasilacyclopentene from simple silyl-alkyne carbonazidates (Scheme 4-1c).

Scheme 4-1. Examples of Carbene Cascade Reactions and Current Work.



Highly reactive nitrenes have recently been used in methods for the aziridination of olefins[9] and the C-H amination of alkanes[10] that have been employed in the syntheses of bioactive molecules.[11] In pioneering work from Blakey (Scheme 4-2b),[12] nitrene/alkyne cascades generated a vinyl cation/metalloenamine **d12** that potentially can rearrange to the α-iminometallocarbene **d13** (Scheme 4-2a). Importantly, metallocarbene **d13** is difficult to form from an α-diazoimine but can be directly produced from a transition metal catalyzed triazole ring opening.[13] These two strategies that form vinyl cation **d12** or α-iminocarbene **d13** have been applied toward many syntheses of heterocycles and polycycles.[12,13] The incorporation of C-H bond insertions in these cascade reactions are still rare, with examples such as Folkin's intermolecular C-H bond insertion with alkanes (Scheme 4-2c)[14] and Sarpong's intramolecular C-H bond insertion to synthesize tetrahydrofurans (Scheme 4-2d).[15]

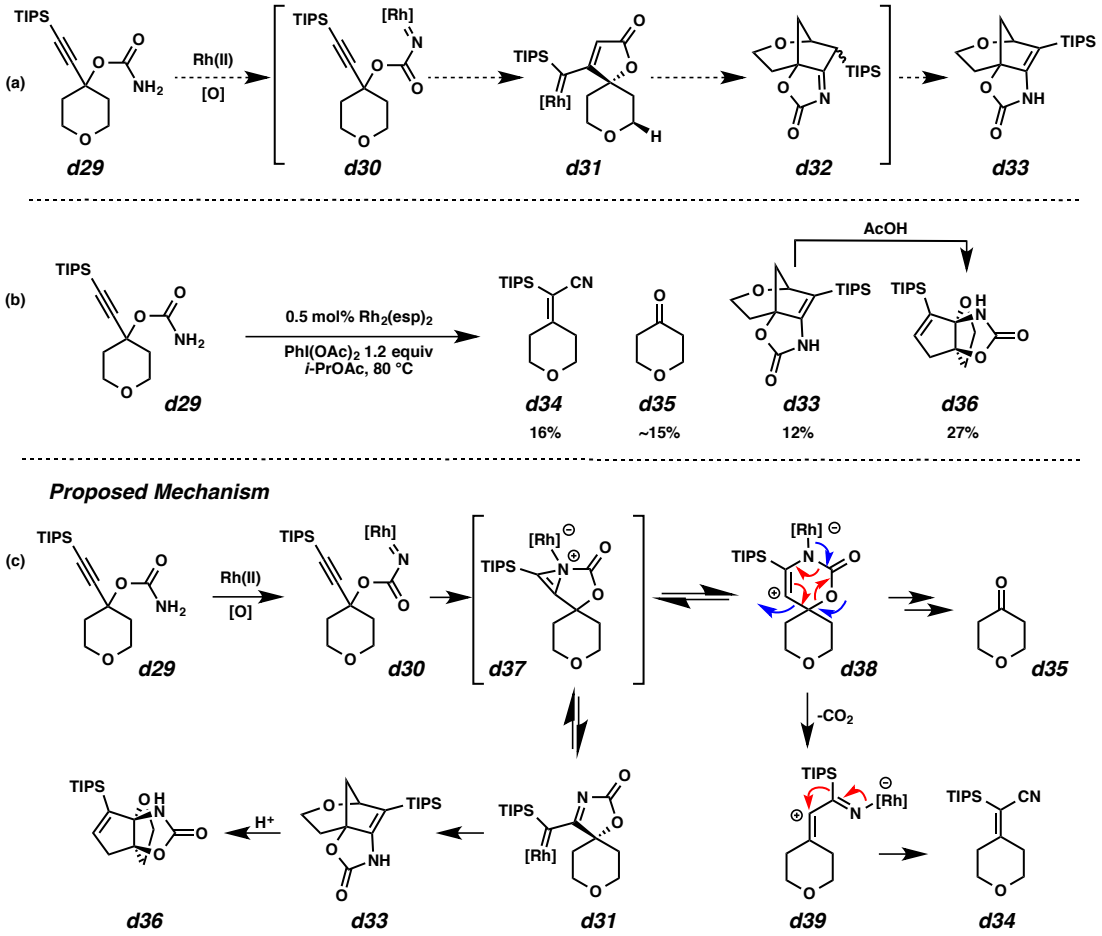
Scheme 4-2. Nitrene/Alkyne Cascades and Triazole/Carbene Cascades.



4.2 Reactions of the Carbamate and the Carbonazidate

In light of these successful carbene/alkyne cascade reactions, we sought to develop a nitrene/alkyne cascade reaction to synthesize nitrogen-containing polycycles (like **d33**, Scheme 4-3a). Initially, treatment of alkynyl carbamate **d29** with $Rh_2(esp)_2$ and $PhI(OAc)_2$ as an oxidant resulted in the formation of multiple products: the predicted bridged polycycle **d33**, the propellane **d36**, the tetrahydropyranone **d35**, and an unexpected silyl vinyl nitrile **d34** (Scheme 4-3b).

Scheme 4-3. The Cascade Reaction of Carbamate **d29**.



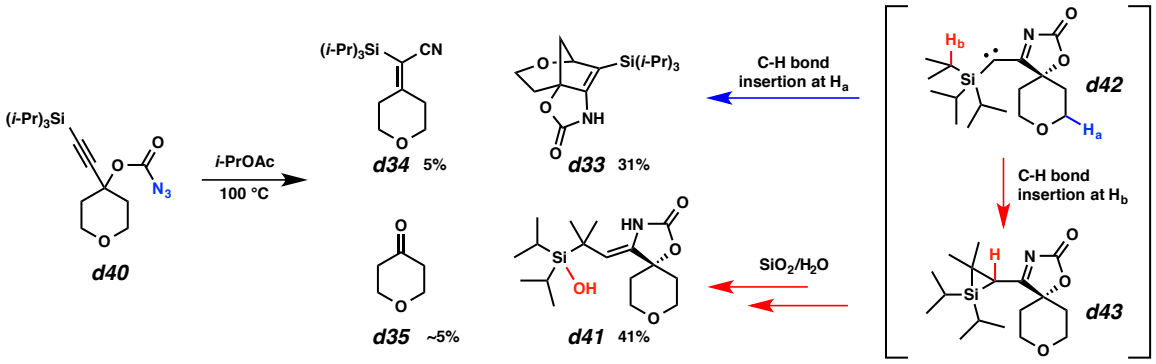
Based on current mechanistic understanding,[11-15] a rhodium nitrene would be initially formed from the carbonate. Reaction with the adjacent alkyne allows the formation of metalloazirine **d37**. The breaking of either of the C-N bonds in the metalloazirine **d37** would result in dramatically different outcomes. First, the breaking of the interior C-N bond would result in ring expansion to form the vinyl cation/metalloenamine **d38**. That intermediate can either experience cleavage of the vinyl/pyran C-C bond followed by hydrolysis to give tetrahydropyranone **d35** (i.e., blue arrows), or it can sigmatropically decarboxylate to produce the vinyl cation/metalloimine

d39 that then undergoes a 1,2-silyl shift[16] to provide the silyl vinyl nitrile **d34** (see red arrows). Another possible pathway is to generate the α-acylimine rhodium carbene **d31** from metalloazirine **d37** via fragmentation of the exterior C-N bond. The resulting carbene may then insert into the ethereal C-H bond of the tetrahydropyran in a transannular fashion to give the bridged tricycle **d33**. A control experiment revealed that acetic acid, produced during the carbamate oxidation, can promote the rearrangement of bridged polycycle **d33** to propellane **d36** in situ.

This exploratory reaction demonstrated that a nitrene/alkyne cascade that results in C-H insertion to generate a C-C bond is possible; however, controlling the selectivity of the reaction pathway was problematic, presumably due to the similar transition state energies of the various available pathways. Consequently, we sought other nitrene precursors to avoid acidic conditions and achieve a selective outcome.

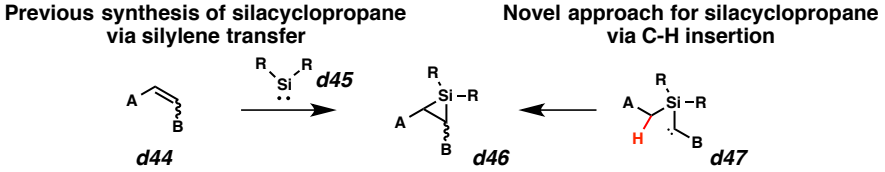
We turned to carbonazidate[17] **d40** for the next study (Scheme 4-4). Reaction optimization allowed an improved yield (31%) of polycycle **d33** at elevated temperature without transition metals. Surprisingly, a new silanol product **d41** was isolated, where presumably the α-imine carbene **d42** can also insert into the methine C-H bond of the silyl isopropyl group to generate silacyclopropane **d43**, which later hydrolyzed to silanol **d41** during chromatography on silica gel. However, a detailed mechanistic study is required to support this hypothesis.

Scheme 4-4. The Cascade Reaction of Carbonazidate **d40**.



In 1964, Goldstein first reported silacyclopropanes,[18] followed by Seyferth[19] and many others.[20] Woerpel and coworkers were pioneers in applying silacyclopropane methods to synthetic organic chemistry,[21] including the synthesis of other silacycles[22] as well as a number of polyketides.[23] The unique but unstable silacyclopropanes have mainly been synthesized via silene cycloaddition to alkenes under thermoactivation, photoactivation, or metal catalyzed conditions (Scheme 4-5). Using C-H bond insertion for C-C bond formation to synthesize silacyclopropanes has rarely been reported.

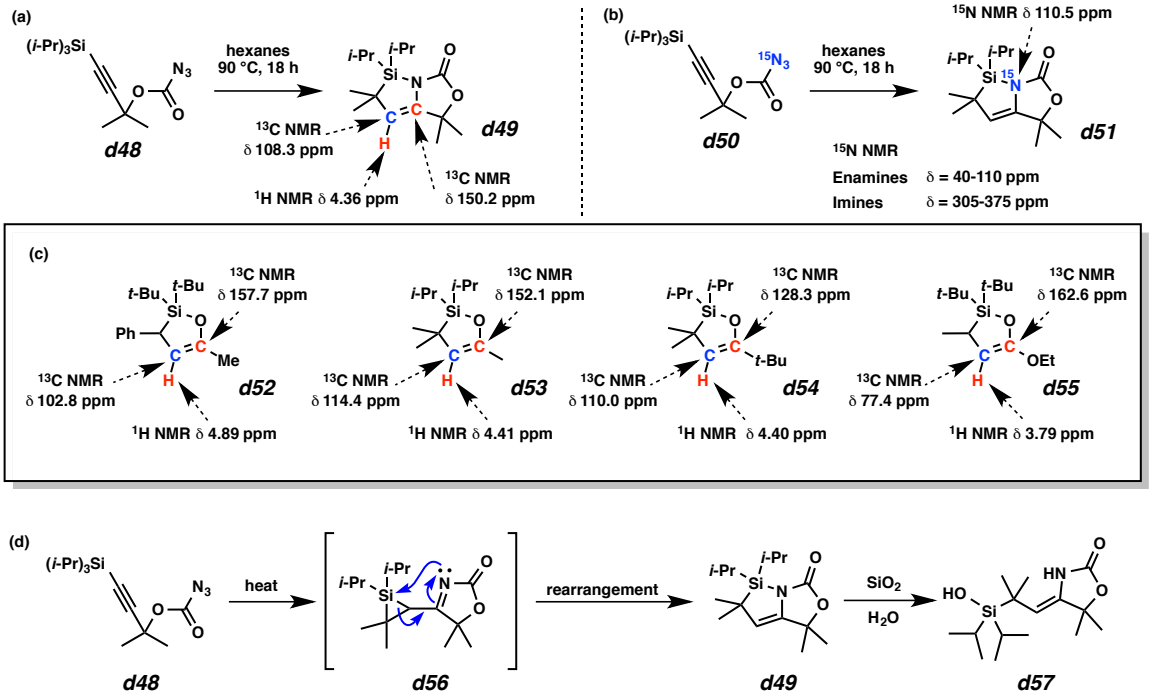
Scheme 4-5. The Formations of Silacyclopropanes.



Acyclic silylacetylene carbonazidate **d48** was next prepared in order to identify the chemical structure before hydrolysis during isolation. After careful ^{1}H and ^{13}C NMR analysis, the structure of the product was determined to be azasilacyclopentene **d49** (Scheme 4-6a). The NMR signals of **d49** (the vinyl proton: 4.36 ppm; enamine carbons:

108.3, 150.2 ppm) matched those of oxasilacyclopentenes (**d52** to **d55**, Scheme 4-6c). In addition, the ^{15}N NMR analysis of ^{15}N enriched azasilacyclopentene **d50** (110.5 ppm, no signals from 305 to 375 ppm)[24] suggested the nitrogen was involved in an enamine motif, which confirmed the assignment from ^{1}H and ^{13}C NMR. Presumably, a rearrangement of the silacyclopropane motif with the imine group generated the azasilacyclopentene motif, which was hydrolyzed to a silanol during silica gel chromatography (Scheme 4-6d).

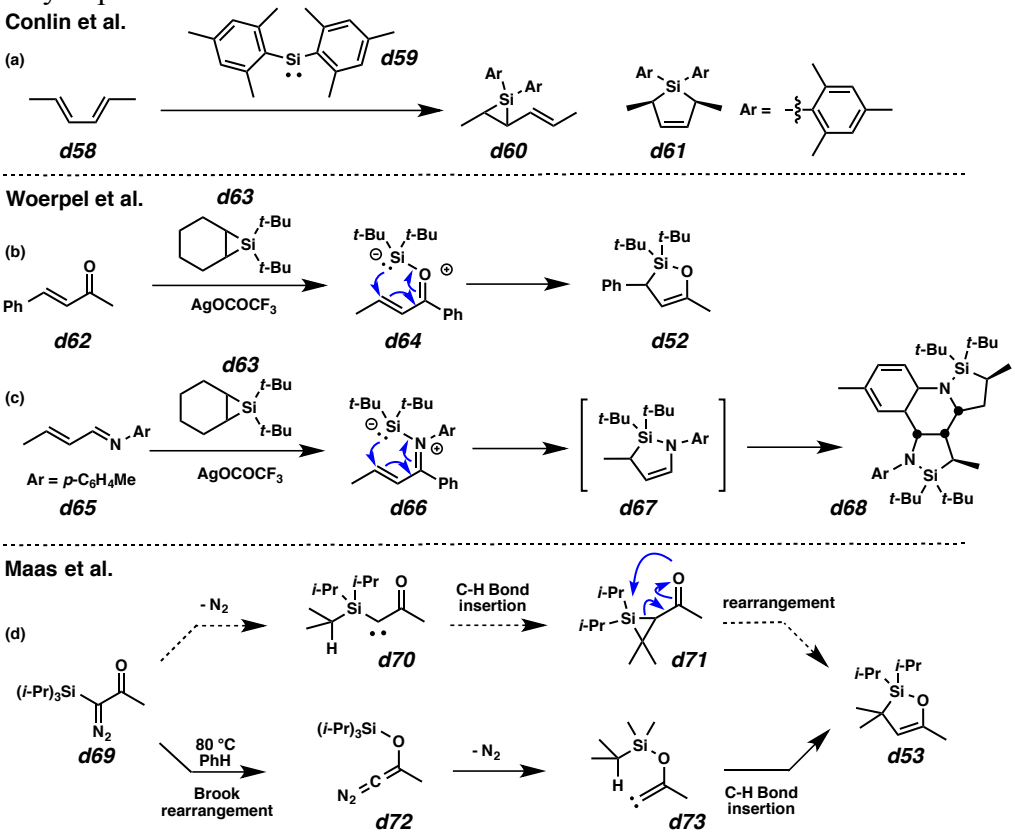
Scheme 4-6. The Identification of the Azasilacyclopentene.



The oxasilacyclopentenes were previously synthesized from silver-catalyzed cyclization of dialkyl silene with enones (Scheme 4-7b)[25] or the thermal rearrangement of α-silyl diazo ketones (Scheme 4-7d).[26] A vinylsilacyclopentene also resulted from [4+1] cycloaddition of a silene with a diene (Scheme 4-7a).[27] The cycloaddition of silene with

an α,β-unsaturated imine was observed to produce an azasilacyclopentene **d67** in situ, which quickly dimerized to the polycycle **d68**.[28] Our cascade reaction is believed to be more simliar to Maas and coworker's studies; they proposed that a Brook rearrangement (incorrectly described as a Wolff rearrangement) took place from **d69** to form diazoethene **d72**, followed by nitrogen extrusion to generate vinylcarbene **d73**, which would then perform a C-H bond insertion to the methine proton giving the oxasilacyclopentenes **d53**. They disagreed with a direct thermolysis pathway where the carbene **d70** performs an α-silyl C-H bond insertion, followed by a rearrangement to give **d53**. They rationalized this thusly: first, the direct thermolysis of a diazoketone to a keto carbene usually happens at higher than 400 °C or via photolysis.[29] Second, no previous reports mention that silicon can activate α-C-H bonds for carbene insertions. Third, the longer bond lengths of C-Si and O-Si can vary the bond angles that allowed the vinyl carbene to approach the methine protone for C-H bond insertion. A detail mechanistic study must be performed for us to differentiate the Brook rearrangement or dediazotization in our cascade reaction.

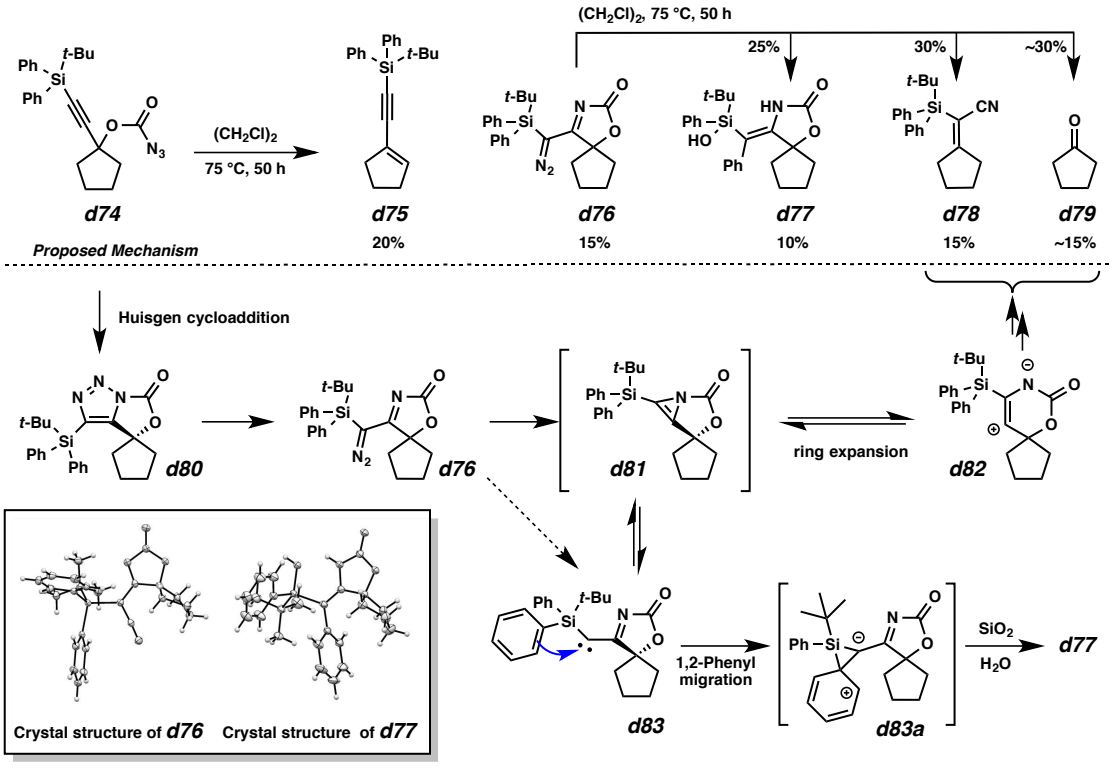
Scheme 4-7. The Formation of Vinylsilacyclopentene, Oxasilacyclopentenes, and Azasilacyclopentene.



Next, a mechanistic investigation was started to understand this non-transition metal-catalyzed regioselective C-H bond activation. *tert*-Butyldiphenyl silylacetylene carbonazidate **d74** was prepared in order to remove any α-silyl C-H bonds so that no silacyclopropane formation could occur (Scheme 4-8). At a lower temperature (75 °C), the reaction proceeded slowly and produced five compounds. The α-diazo oxazolone **d76** was crystallized and analyzed by X-ray diffraction, as well as the silanol **d77**. The identification of α-diazo imine **d76** suggested that the Huisgen cycloaddition[30] generated triazole **d80**, followed by ring opening to the diazo acylimine **d76**. The α-imino carbene **d83** could be directly produced from nitrogen decomposition of diazo **d81**, followed by

1,2-phenyl migration and hydrolysis to give silanol **d77**. Moreover, subjecting the diazo **d76** to the reaction produced not only silanol **d77** but also the silyl vinyl nitrile **d78** and cyclopentanone (**d79**). Presumably, the nitrile **d78** and ketone **d79** are produced from the zwitterion **d82**, which could arise from azirine **d81**. Thus, the nitrogen extrusion should take place from diazo **d76** to form azirine **d81** that could further rearrange to α-imino carbene **d83**[Error! Bookmark not defined.] and zwitterion **d82**.

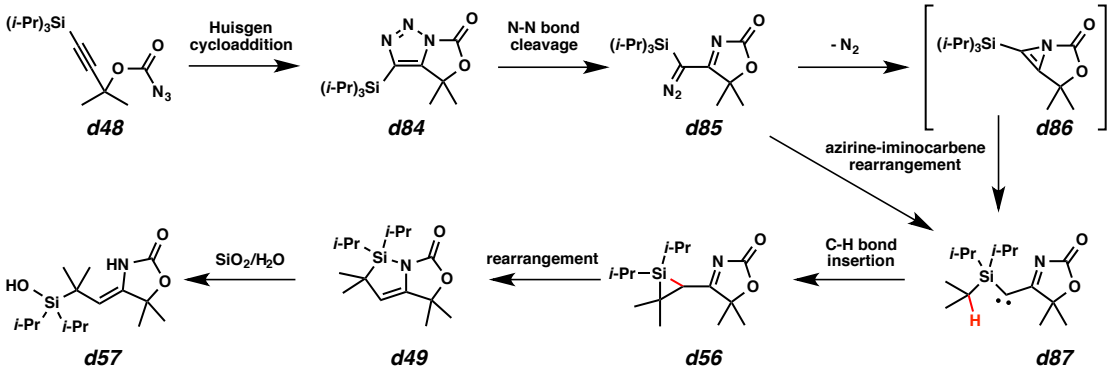
Scheme 4-8. The Cascade Reaction of Carbonazidate **d74**.



Because silanol **d77** was generated form α-diazo imine **d76**, which α-iminocarbene **d83** should be the intermediate in the reaction, the Brook rearrangement pathway is not likely in this cascade reaction. A revised mechanism was proposed

(Scheme 4-9). A Huisgen cycloaddition takes place on carbonazidate **d48** to form a 1,2,3-triazole **d84**, followed by a N-N bond cleavage to form α-diazoimine **d85** that then generates azirine **d86** through nitrogen extrusion. Next the exterior C-N bond cleavage would result in an α-iminocarbene **d87**, which would perform an α-silyl C-H bond insertion to give a silacyclopropane intermediate **d56**. Finally, the rearrangement on the intermediate **d56** produces the azasilacyclopentene **d49**. The silanol **d57** would be generated from hydrolysis of **d49**.

Scheme 4-9. The Revised Mechanism of Cascade Reaction.



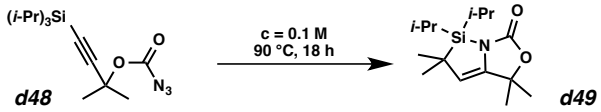
4.3 Reaction Optimization and Reaction Scope

4.3.1 Reaction Optimization

The acyclic silylacetylene carbonazidate d**48** was selected to optimize for azasilacyclopentene formation (Table 4-1). A lower yield of azasilacyclopentene resulted from using a halogenated solvent $(CH_2Cl)_2$ and toluene (entries 2, 3). Using hexanes as the solvent produced a cleaner reaction and a slightly higher yield (entry 4). However,

less productive results were observed when adding $Rh_2(esp)_2$ or Cp*RuCl(cod), which was used as a catalyst for azide-alkyne cycloadditions by Folkin. Elevating the temperature to 100 °C or using cyclohexane as a solvent did not improve the yield.

Table 4-1. Optimization of the Cascade Reaction.



d48 *d49*

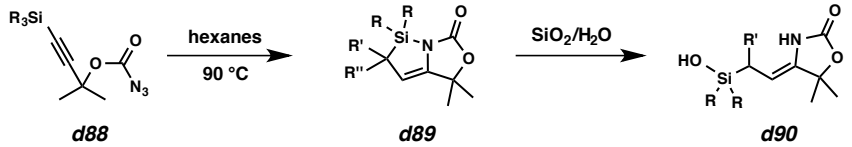
entry	solvent	temperature	NMR yield	entry	solvent	temperature	NMR yield
1	*i*-PrOAc	90 °C	48%	5	hexanes[b]	90 °C	43%
2	$(CH_2Cl)_2$	90 °C	25%	6	hexanes[c]	90 °C	19%
3	toluene	90 °C	31%	7	hexanes	100 °C	43%
4	hexanes	90 °C	53%(50%)[a]	8	cyclohexane	90 °C	31%

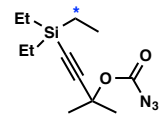
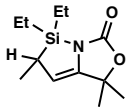
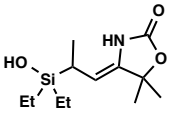
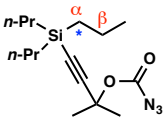
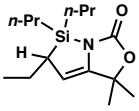
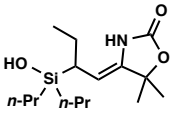
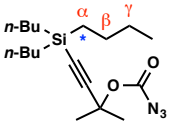
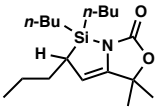
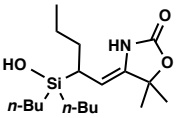
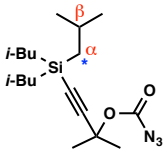
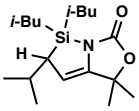
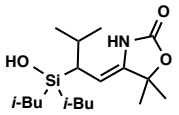
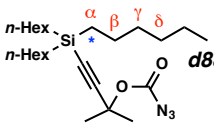
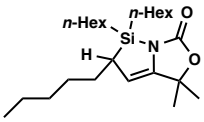
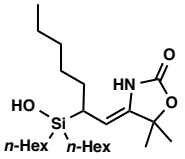
[a]isolated yield of silanol (average of 2 runs); [b]1 mol%$Rh_2(esp)_2$; [c]2 mol% Cp*RuCl(cod)

4.3.2 The Variation of the Alkyl Group on Silicon

We were curious to know if C-H bond insertion would take place at different positions on the silyl carbon chain. If so, a variety of silacycles could be obtained. However, all of the alkyl groups only generated the corresponding azasilacyclopentenes (Table 4-2), indicating that the carbene only inserts into the α-silyl C-H bond. The "β-silicon effect" that stabilizes β-carbocations[31] did not activate the β-C-H bonds. Neither γ- nor δ-C-H bonds reacted either. High regioselectivity was shown even in the isobutyl substrate **d88d**, where the electron-rich β-methine proton was untouched. Although azasilacyclopentenes can be observed in the crude NMR and GC/MS, they do not survive silica gel chromatography. Thus, NMR yields are reported for the azasilacyclopentenes and isolated yields are reported for the corresponded silanols.

Table 4-2. The Variation of the Alkyl Group on Silicon.



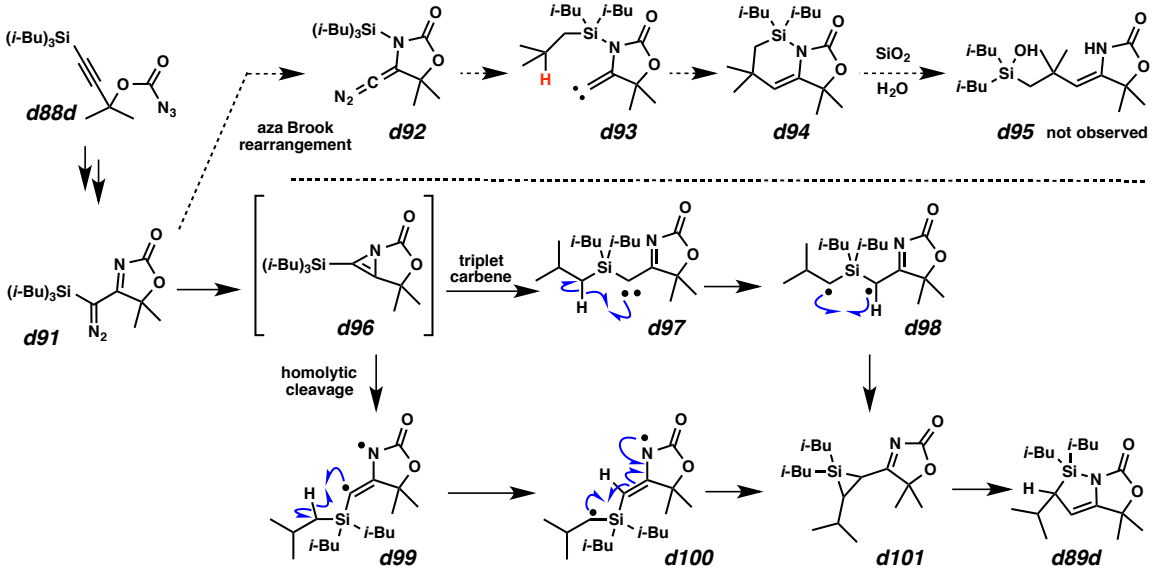
entry	carbonazidate	product		
1	 *d88a*	 *d89a* 38%[a]	 *d90a* 38%[b]	
2	 *d88b*	 *d89b* 42%[a]	 *d90b* 42%[b]	
3	 *d88c*	 *d89c* 56%[a]	 *d90c* 43%[b]	
4	 *d88d*	 *d89d* 55%[a]	 *d90d* 43%[b]	
5	 *d88e*	 *d89e* 56%[a]	 *d90e* 44%[b]	

[a]NMR yield; [b]isolated yield of silanol (average of 2 runs)

Based on results of the substrate **d88d**, the non-metal stabilized carbene **d97** may be a triplet carbene and possess radical character (Scheme 4-10). The reaction would then proceed via hydrogen atom abstraction from the methylene attached to the silicon to generate an α-silyl radical (see **d98**). α-Silyl radicals are stabilized by backbonding from silicon.[32] Then the silacyclopropane **d101** could be formed from diradical combination. From another perspective, homolytic cleavage of the azirine C-N bond would produce the diradical **d99**.[33] The vinyl radical motif of **d99** could abstract the proton from the α-silyl

C-H bond to generate the stable α-silyl radical **d100**, and then provide silacyclopropane **d101** after radical bond formation. Alternatively, an aza-Brook rearrangement/vinyl carbene C-H bond insertion pathway could be considered. However, the C-H bond insertion would likely take place at the electron-rich methine proton to generate azasilacyclohexene **d94**. In fact, its hydrolysis product, the silanol **d95,** was not observed. Thus, the reaction likely does not go through an aza-Brook rearrangement/vinyl carbene C-H bond insertion mechanism.

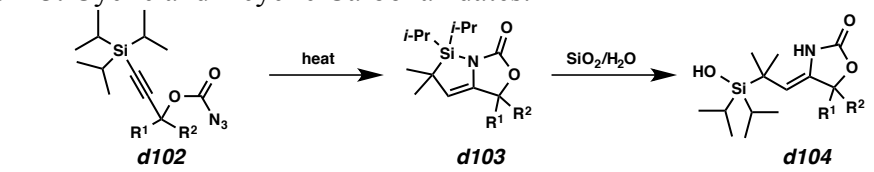
Scheme 4-10. Proposed Carbene Formations.

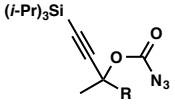
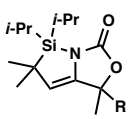
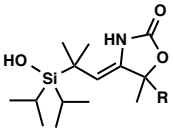
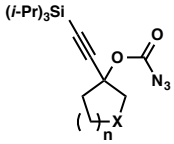
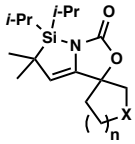
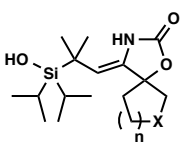
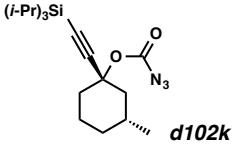
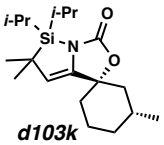
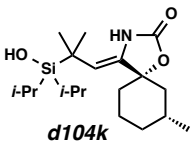
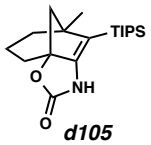
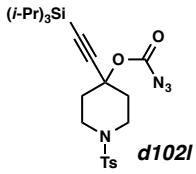
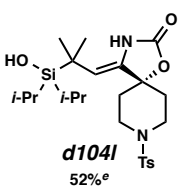
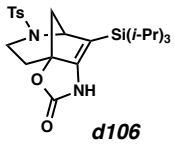
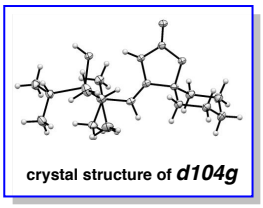


4.3.3 The Variation of Cyclic and Acyclic Carbonazidates

Next, a series of acyclic, cyclic, and heterocyclic carbonazidates were examined (Table 4-3). Varying the alkyl groups at R^1 and R^2 does not significantly affect the formation of azasilacyclopentene. Although an allyl group could potentially undergo cyclopropanation with the intermediate silyl carbene, that does not happen (entry 5). Cyclic substrates provided spiro-oxazolone azasilacyclopentenes (entry 6-10). No bridged polycycles were observed, even for pyrrolidine **d102i** and tetrahydrothiophene **d102j**, where the heteroatoms (N and S) are generally considered to activate α-C-H bonds for carbene insertion. Six-membered rings provided a different result, presumably due to greater conformational flexibility (entries 11 and 12). For the 3-methyl cyclohexane **d102k**, the reaction produced a 1:1 ratio of azasilacyclopentene **d103k** and bridged tricycle **d105**. For the tosyl piperidine **d102l**, the major isolated product was the silanol **d104l**, but some bridged bicycle **d106** was observed.

Table 4-3. Cyclic and Acyclic Carbonazidates.



entry	carbonazidate			product(s)				
			R					
1[a]		d102a	Et		d103a	57%[d]		d104a	51%[e]
2[a]		d102b	*n*-Pr		d103b	55%[d]		d104b	53%[e]
3[a]		d102c	*n*-Bu		d103c	60%[d]		d104c	59%[e]
4[a]		d102d	*i*-Bu		d103d	49%[d]		d104d	43%[e]
5[a]		d102e	allyl		d103e	52%[d]		d104e	50%[e]
			X n					
6[a]		d102f	CH_2 1		d103f	52%[d]		d104f	48%[e]
7[a]		d102g	CH_2 2		d103g	51%[d]		d104g	49%[e]
8[a]		d102h	CH_2 3		d103h	56%[d]		d104h	46%[e]
9[c]		d102i	NTs 1		d103i	50%[d]		d104i	48%[e]
10[c]		d102j	S 1		d103j	45%[d]		d104j	42%[e]
11[b]	 d102k			 d103k 36%[d]			 d104k 35%[e]	 d105 34%[e]	
12[c]	 d102l			 d104l 52%[e]			 d106 21%[e]	 crystal structure of d104g	

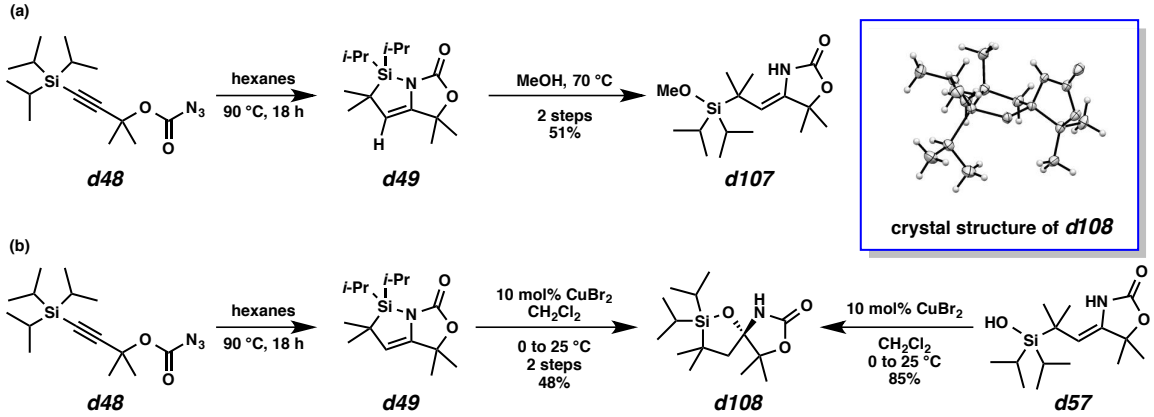
[a] hexanes, 90 °C; [b]hexanes, 100 °C; [c] isopropyl acetate, 100 °C; [d]NMR yield; [e]isolated yield (average of two runs)

4.4 Post Modification

This azasilacyclopentene could be potentially synthetically useful, and we have preliminarily tested a few of its properties. A methyl silyl ether **d107** is obtained in good yield by ring opening of the azasilacyclopentene **d49** in methanol at 70 °C. Treatment of azasilacyclopentene **d49** with $CuBr_2$ generated the spiro hemiaminal **d108**. X-ray

diffraction of a single crystal confirmed the structure. Subjecting the silanol **d57** to $CuBr_2$ also produced **d108**, which suggested that the azasilacyclopentene **d49** is hydrolyzed in situ in the copper catalyzed condition.

Scheme 4-11. Post-Modified Reactions.



4.5 Conclusions and Future Work

In conclusion, we have discovered a novel approach for the synthesis of azasilacyclopentenes via a Huisgen cycloaddition-initiated cascade reaction terminating in C-H bond insertion. A number of azasilacyclopentenes have been synthesized. Control experiments suggest a possible triplet carbene mechanism for the cascades. Preliminary modification of the azasilacyclopentene also showed interesting reactivities. Ongoing efforts will seek selective synthesis of bridged polycycles and vinyl nitriles from the same precursors.

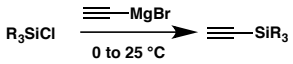
4.6 Experimental

4.6.1 Materials and Methods

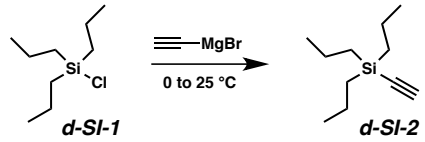
All reactions were carried out in flame or oven-dried glassware. Hexanes, THF, toluene, dichloroethane, and CH_2Cl_2 were purged with argon and dried over activated alumina columns. Isopropyl acetate was dried over Na_2SO_4 before usage. Flash chromatography was performed on 60 Å silica gel (Sorbent Technologies). Analytical thin-layer chromatography was performed on EMD silica gel/TLC plates with fluorescent indicator 254 nm. The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer using the residual solvent peak as an internal reference ($CDCl_3$: 7.24 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR). For ^{13}C NMR, multiplicities were distinguished. NMR yields were determined by addition of 0.5 equivalents of methyl (4-nitrophenyl) carboxylate as an internal standard to the crude reaction mixture. IR spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. GCMS analyses were performed on a Shimadzu GCMS-QP2010S chromatographer equipped with a Shimadzu column (SHRXI-5MS, 0.25 mm x 0.25 u x 30 M). HRMS analyses were performed under contract by UT Austin's mass spectrometric facility via positive mode ESI or CI methods on a US10252005 instrument. Commercially available compounds were purchased from Aldrich Chemical Co., Acros Organics, Alfa Aesar or TCI America and were used without further purification.

4.6.2 Synthesis of Compounds

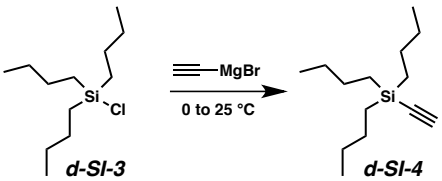
General Procedure A



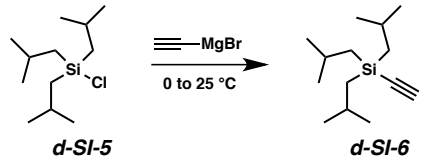
A flame-dried round-bottom flask was charged ethynylmagnesium bromide (1.2 equiv, 0.5M) under an argon atmosphere. The reaction was cooled to 0 °C in an ice bath. The chlorosilane (1.0 equiv) was then added dropwise into the reaction, and the reaction mixture was allowed to warm up to 25 °C and stirred for 12 hours. Afterwards, the reaction was quenched with H_2O and saturated $NH_4Cl_{(aq)}$, and the mixture was extracted with hexanes (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered through a short plug of silica gel and concentrated under reduced pressure to yield the product. No further purification was necessary.



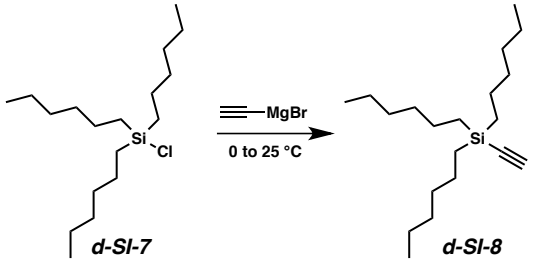
ethynyltri-*n*-propylsilane (d-SI-2) was synthesized from tri-*n*-propylsilyl chloride (2 mL, 1.764 g, 9.15 mmol) using General Procedure A. The product was obtained as a colorless oil. (1.5221 g, 91% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.35 (s, 1H), 1.49–1.33 (m, 6H), 0.96 (t, J = 7.3 Hz, 12H), 0.65–0.55 (m, 6H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 94.0, 88.3, 18.2, 17.4, 15.8. **IR(neat)** 3294, 2955, 2926, 2869, 2033, 1455, 1408, 1333, 1066, 1005, 710, 669 cm^{-1}. **HRMS** (CI) *m/z*: 182.1485 [$(M)^+$; calculated for $C_{11}H_{22}Si$: 182.1491]. **R_F**: 0.79 in 5% EtOAc/Hex.



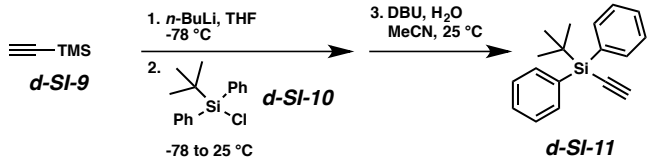
tri-*n*-butyl(ethynyl)silane (d-SI-4) was synthesized from tri-*n*-butylsilyl chloride (2 mL, 1.766 g, 7.52 mmol) using General Procedure A. The product was obtained as a colorless oil. (1.6663 g, 99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.35 (s, 1H), 1.41–1.26 (m, 12H), 0.94-0.80 (m, 9H), 0.67–0.54 (m, 6H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 94.0, 88.3, 26.4, 26.0, 13.8, 12.8. **IR(neat)** 3294, 2956, 2921, 2872, 2857, 2033, 1464, 1408, 1377, 1192, 1081, 1028, 1000, 963, 885, 787, 758, 711, 669 cm^{-1}. **HRMS** (CI) *m/z*: 224.1957 [$(M)^+$; calculated for $C_{14}H_{28}Si$: 224.1960]. **R_F**: 0.79 in 5% EtOAc/Hex.



ethynyltriisobutylsilane (d-SI-6) was synthesized from triisobutylsilyl chloride (0.8 mL, 0.7096 g, 3 mmol) using General Procedure A. The product was obtained as a colorless oil. (0.651 g, 90% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.39 (s, 1H), 1.92–1.79 (m, 3H), 0.96 (d, J = 6.8 Hz, 18H), 0.63 (d, J = 6.9 Hz, 6H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 94.6, 89.5, 26.2, 25.0, 24.7. **IR(neat)** 3284, 2952, 2896, 2867, 2033, 1464, 1400, 1381, 1364, 1328, 1217, 1163, 1093, 1039, 950, 830, 762, 669 cm^{-1}. **HRMS** (CI) *m/z*: 223.1882 [$(M-H)^+$; calculated for $C_{14}H_{27}Si$: 223.1882]. **R_F**: 0.8 in 5% EtOAc/Hex.



ethynyltri-*n*-hexylsilane (d-SI-8) was synthesized from tri-*n*-hexylsilyl chloride (2 mL, 1.7420 g, 5,3 mmol) using General Procedure A. The product was obtained as a colorless oil. (1.6460 g, 99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.34 (s, 1H), 1.40–1.18 (m, 24H), 0.92-0.81 (m, 9H), 0.67–0.53 (m, 6H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 94.0, 88.4, 33.1, 31.5, 23.7, 22.6, 14.1, 13.0. **IR(neat)** 3294, 2956, 2920, 2872, 2854, 2033, 1466, 1408, 1377, 1340, 1182, 1101, 995, 961, 889, 846, 764, 710, 669 cm^{-1}. **HRMS** (CI) *m/z*: 308.2888 [$(M)^+$; calculated for $C_{20}H_{40}Si$: 308.2899]. **R_F**: 0.8 in 5% EtOAc/Hex.

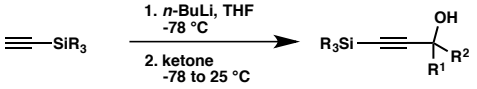


***tert*-butyl(ethynyl)diphenylsilane (d-SI-11)**

A flame-dried round-bottom flask was charged with *n*-BuLi (2.5 M, 1.3 equiv, 39 mmol, 15.6 mL) under an argon atmosphere. Anhydrous THF (0.5 M, 50 ml) was added, and the mixture was cooled to -78 °C in a dry ice/acetone bath. Trimethylsilylacetylene (1.3 equiv, 39 mmol, 5.6 mL) was then added dropwise. After the reaction was stirring for 15 minutes at -78 °C, *tert*-butyl(chloro)diphenylsilane (7.8 mL, 30 mmol) was added dropwisely. The reaction mixture was allowed to warm up to 25 °C and stirred for 2 hours. After completion, saturated NH_4Cl solution was added. The mixture was extracted

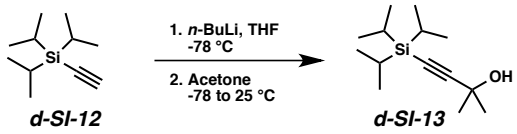
with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was subjected to the next step without further purification. The crude product was dissolved in MeCN (0.5 M, 60 mL) and water (10.0 M, 3 mL). Diazobicycloundecene (DBU, 1.0 equiv, 4.5 mL, 30 mmol) was added into the reaction. The progress of the reaction was monitored by TLC. After completion, the reaction solvent was concentrated to yield crude product, and purification was done by column chromatography on silica gel using a gradient of 0 to 1 % EtOAc in hexanes as eluents. The product was obtained as a white solid. (4.4788 g, 56.5% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83–7.78 (m, 4H), 7.45–7.33 (m, 6H), 2.71 (s, 1H), 1.11 (s, 9H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 135.5, 132.6, 129.6, 127.8, 97.2, 85.4, 26.9, 18.4. **IR(neat)** 3266, 3065, 2959, 2946, 2857, 2035, 1485, 1468, 1426, 1390, 1372, 1361, 1259, 1105, 1007, 820, 742, 691, 660 cm^{-1}. **HRMS** (CI) *m/z*: 264.1333 [$(M)^+$; calculated for $C_{18}H_{20}Si$: 264.1334]. **R_F**: 0.5 in 2% EtOAc/Hex. **MP**: 66-68 °C.

General Procedure B

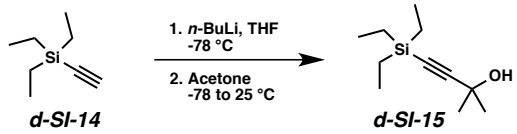


A flame-dried round-bottom flask was charged with *n*-BuLi (2.5 M, 1.2 equiv, 4.8 mmol) under Argon atmosphere. Anhydrous THF (0.5 M, 8 mL) was added, and the reaction was cooled to -78 °C in a dry ice/acetone bath. The silyl acetylene (1.3 equiv, 5.2 mmol) was then added dropwisely. The reaction was allowed to stir for 20 minutes at -78 °C. Then, ketone (1 equiv, 4 mmol) was added dropwise. The reaction mixture was allowed

to warm to 25 °C and stirred for 2 hours. After completion, saturated NH_4Cl solution was added to quench the reaction. The mixture was extracted with Et_2O three times, and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered through a celite pad, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel.

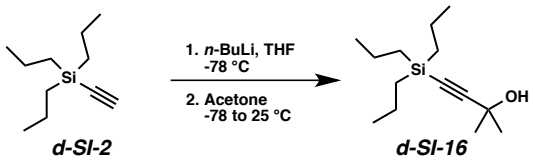


2-methyl-4-(triisopropylsilyl)but-3-yn-2-ol (d-SI-13) was synthesized from triisopropylsilylacetylene and acetone using General Procedure B. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil. (0.777 g, 88% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.92 (s, 1H), 1.51 (s, 6H), 1.08–0.99 (m, 21H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 112.7, 82.1, 65.5, 31.6, 18.6, 11.1. **IR(neat)** 3343, 2942, 2892, 2865, 2167, 2032, 1463, 1364, 1220, 1164, 996, 968, 912, 881, 786, 674, 658 cm^{-1}. **HRMS** (CI) *m/z*: 240.1906 [$(M)^+$; calculated for $C_{14}H_{28}OSi$: 240.1909]. **R_F**: 0.27 in 10% EtOAc/Hex.

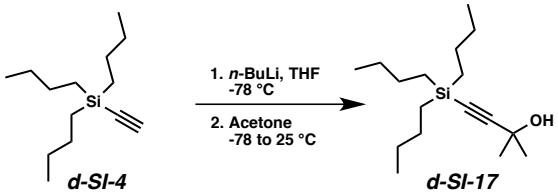


2-methyl-4-(triethylsilyl)but-3-yn-2-ol (d-SI-15) was synthesized from triethylsilylacetylene and acetone using General Procedure B. The crude product was purified by column chromatography on silica gel using 10% Et_2O in pentane as an eluent.

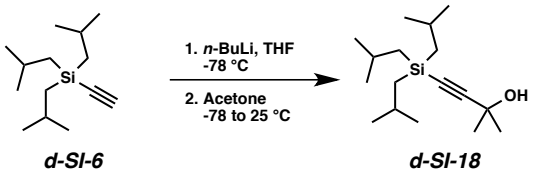
The product was obtained as a colorless oil. (0.7801 g, 98% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.92 (s, 1H), 1.50 (s, 6H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.56 (q, *J* = 8.0 Hz, 6H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 111.9, 83.2, 65.5, 31.5, 7.4, 4.3. **IR(neat)** 3340, 2955, 2912, 2875, 2168, 1457, 1362, 1220, 1164, 1005, 912, 789, 722, 701 cm^{-1}. **HRMS** (CI) *m/z*: 198.1441 [$(M)^+$; calculated for $C_{11}H_{22}OSi$: 198.1440]. **R_F**: 0.15 in 10% Et_2O/pentane.



2-methyl-4-(tripropylsilyl)but-3-yn-2-ol (d-SI-16) was synthesized from tri-*n*-propylsilylacetylene and acetone using General Procedure B. The crude product was purified by column chromatography on silica gel using a gradient of 2 to 5% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (0.9908 g, 98% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.89 (s, 1H), 1.49 (s, 6H), 1.43–1.31 (m, 6H), 0.95 (t, *J* = 7.2 Hz, 9H), 0.61–0.51 (m, 6H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 111.8, 84.1, 65.5, 31.4, 18.2, 17.4, 16.0. **IR(neat)** 3344, 2954, 2926, 2868, 2168, 1455, 1408, 1374, 1362, 1333, 1217, 1164, 1065, 1031, 1004, 912, 786, 814, 739, 699 cm^{-1}. **HRMS** (CI) *m/z*: 240.1905 [$(M)^+$; calculated for $C_{14}H_{28}OSi$: 240.1909]. **R_F**: 0.36 in 10% EtOAc/Hex.

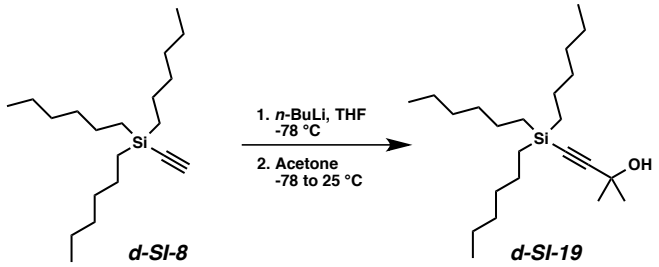


2-methyl-4-(tributylsilyl)but-3-yn-2-ol (d-SI-17) was synthesized from tri-*n*-butylsilylacetylene and acetone using General Procedure B. The crude product was purified by column chromatography on silica gel using a gradient of 2 to 5% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (1.0730 g, 95% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.88 (s, 1H), 1.49 (s, 6H), 1.40–1.19 (m, 12H), 0.94–0.77 (m, 9H), 0.66–0.47 (m, 6H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 111.7, 84.1, 76.9, 65.5, 31.4, 26.4, 26.1, 13.8, 12.9. **IR(neat)** 3295, 2951, 2895, 2867, 2168, 2033, 1463, 1400, 1380, 1163, 1093, 912, 793, 670 cm^{-1}. **HRMS** (CI) *m/z*: 282.2374 [$(M)^+$; calculated for $C_{17}H_{34}OSi$: 282.2379]. **R_F**: 0.42 in 10% EtOAc/Hex.

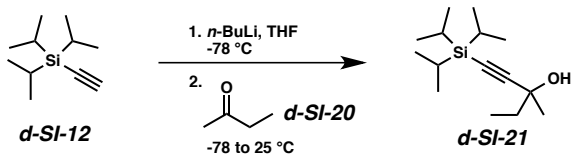


2-methyl-4-(triisobutylsilyl)but-3-yn-2-ol (d-SI-18) was synthesized from triisobutylsilylacetylene and acetone using General Procedure B. The crude product was purified by column chromatography on silica gel using a gradient of 2 to 5% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (1.0730 g, 95% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.90–1.72 (m, 3H), 1.48 (s, 6H), 0.95 (d, J = 6.5 Hz, 18H), 0.59 (d, J = 6.9 Hz, 6H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 112.0, 9.5, 65.4, 31.2, 26.2, 25.0, 24.9. **IR(neat)** 3347, 2951, 2895, 2867, 2168, 1463, 1400, 1379, 1364, 1217, 1163,

1092, 912, 829, 793, 768 cm^{-1}. **HRMS** (CI) *m/z*: 282.2374 [$(M)^+$; calculated for $C_{17}H_{34}OSi$: 282.2379]. $\mathbf{R_F}$: 0.42 in 10% EtOAc/Hex.

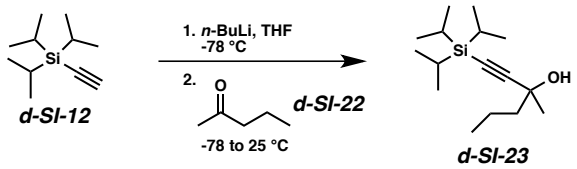


2-methyl-4-(trihexylsilyl)but-3-yn-2-ol (d-SI-19) was synthesized from tri-*n*-hexylsilylacetylene and acetone using General Procedure B. The crude product was purified by column chromatography on silica gel using a gradient of 2 to 5% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (1.3544 g, 92% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.49 (s, 6H), 1.37–1.17 (m, 24H), 0.95–0.80 (m, 9H), 0.64–0.48 (m, 6H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 111.7, 84.2, 65.4, 33.1, 31.5, 31.4, 23.8, 22.6, 14.2, 13.2. **IR(neat)** 3345, 2956, 2920, 2872, 2854, 2167 1457, 1408, 1362, 1219, 1165 968, 913, 846, 791, 700 cm^{-1}. **HRMS** (CI) *m/z*: 367.3386 [$(M+H)^+$; calculated for $C_{23}H_{47}OSi$: 367.3396]. $\mathbf{R_F}$: 0.45 in 10% EtOAc/Hex.

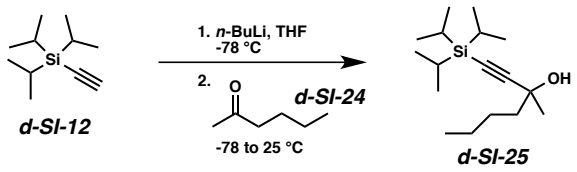


3-methyl-1-(triisopropylsilyl)pent-1-yn-3-ol (d-SI-21) was synthesized from triisopropylsilylacetylene and 2-butanone using General Procedure B. The crude product was purified by column chromatography on silica gel using a gradient of 2 to 5% EtOAc

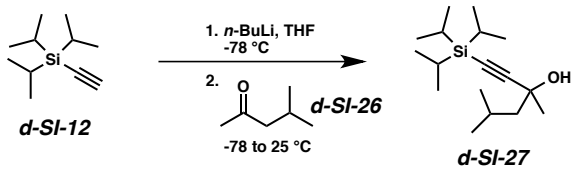
in hexanes as eluents. The product was obtained as a colorless oil. (0.813 g, 89% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.89 (s, 1H), 1.77–1.56 (m, 2H), 1.46 (s, 3H), 1.08–0.96 (m, 24H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 111.4, 83.4, 69.1, 36.6, 29.5, 18.6, 11.1, 9.1. **IR(neat)** 3360, 2941, 2891, 2865, 2165, 1462, 1382, 1366, 1323, 1288, 1157, 1126, 1073, 1053, 1034, 1012, 995, 930, 909, 881, 793, 766, 674, 658 cm^{-1}. **HRMS** (CI) *m/z*: 254.2065 [$(M)^+$; calculated for $C_{15}H_{30}OSi$: 254.2066]. **R_F**: 0.42 in 10% EtOAc/Hex.



3-methyl-1-(triisopropylsilyl)hex-1-yn-3-ol (d-SI-23) was synthesized from triisopropylsilylacetylene and 2-pentanone using General Procedure B. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil. (0.902 g, 84% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.89 (s, 1H), 1.70–1.48 (m, 4H), 1.46 (s, 3H), 1.13–0.97 (m, 21H), 0.94 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 111.7, 83.2, 68.6, 46.0, 30.0, 18.6, 18.1, 14.3, 11.1. **IR(neat)** 3373, 2958, 2941, 2892, 2865, 2165, 1463, 1366, 1382, 1284, 1253, 1159, 1131, 1073, 1051, 1017, 995, 934, 904, 882, 794, 674, 659 cm^{-1}. **HRMS** (CI) m/z: 268.2229 [$(M)^+$; calculated for $C_{16}H_{32}OSi$: 268.2222]. **R_F**: 0.4 in 10% EtOAc/Hex.

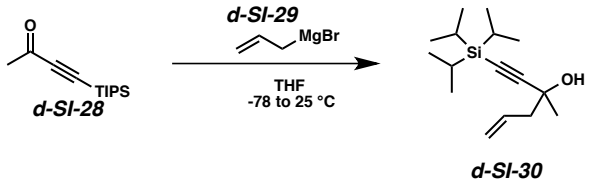


3-methyl-1-(triisopropylsilyl)hept-1-yn-3-ol (d-SI-25) was synthesized from triisopropylsilylacetylene and 2-hexanone using General Procedure B. The crude product was purified by column chromatography on silica gel using a gradient of 2 to 5% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (904 mg, 80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.88 (s, 1H), 1.67–1.45 (m, 4H), 1.46 (s, 3H), 1.41–1.26 (m, 2H), 1.11-0.97 (m, 21H), 0.90 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 111.8, 83.3, 68.6, 43.4, 29.9, 27.0, 22.8, 18.6, 14.1, 11.1. **IR(neat)** 3374, 2941, 2864, 2164, 1463, 1129, 1087, 949, 909, 675, 659 cm^{-1}. **HRMS** (CI) *m/z*: 282.2386 [$(M)^+$; calculated for $C_{17}H_{34}OSi$: 282.2379]. **R_F**: 0.3 in 5% EtOAc/Hex.



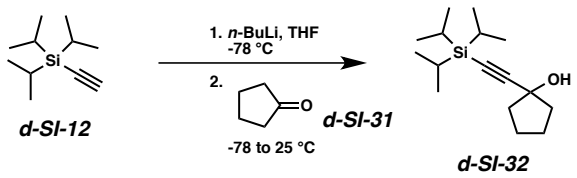
3,5-dimethyl-1-(triisopropylsilyl)hex-1-yn-3-ol (d-SI-27) was synthesized from triisopropylsilylacetylene and methyl isobutyl ketone using General Procedure B. The crude product was purified by column chromatography on silica gel using a gradient of 2 to 5% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (1.1075 g, 98% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.04–1.88 (m, 1H), 1.85 (s, 1H), 1.57 (d, J = 6.2 Hz, 2H), 1.48 (s, 3H), 1.09–0.95 (m, 27H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 112.0, 94.7, 8.6, 68.5, 51.7, 31.3, 25.3, 24.3, 24.1, 18.5, 11.1. **IR(neat)** 3440, 2943, 2865,

2164, 2032, 1463, 1383, 1073, 1045, 1017, 944, 919, 881, 673, 660 cm^{-1}. **HRMS** (CI) m/z: 282.2381 [$(M)^+$; calculated for $C_{17}H_{34}OSi$: 282.2379]. $\mathbf{R_F}$: 0.42 in 10% EtOAc/Hex.

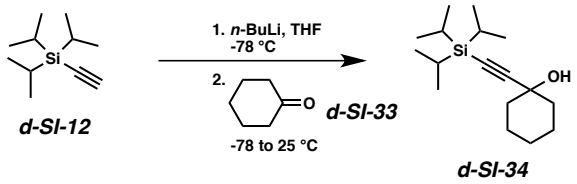


3-methyl-1-(triisopropylsilyl)hex-5-en-1-yn-3-ol (d-SI-30)

To a flame-dried round-bottom flask was added ynone **d-SI-28** (1.12 g, 5 mmol, 1 equiv) and THF (6 mL). The reaction was cooled to -78 °C. After stirring for 10 min at -78 °C, allylmagnesium bromide (1 M in Et_2O, 6 mL, 6 mmol, 1.2 equiv) was added to the reaction. The reaction was allowed to warm to 25 °C. After completion, saturated NH_4Cl solution was added to quench the reaction. The mixture was extracted with Et_2O three times, and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered through a celite pad, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with a gradient of 1 to 2% ethyl acetate in hexanes as eluents. The product was obtained as colorless oil. (1 g, 75% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.02–5.91 (m, 1H), 5.24–5.11 (m, 2H), 2.47 (dd, *J* = 13.4, 6.5 Hz, 1H), 2.36 (dd, *J* = 13.5, 8.1 Hz, 1H), 1.48 (s, 3H), 1.10–0.98 (m, 21H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 133.4, 119.5, 111.1, 83.7, 67.3, 48.3, 29.5, 18.6, 11.1. **IR(neat)** 3373, 2942, 2892, 2865, 2166, 1642, 1463, 1382, 1367, 1260, 1110, 1073, 995, 942, 916, 882, 799, 675 cm^{-1}. **HRMS** (ESI) *m/z*: 289.1962 [$(M+Na)^+$; calculated for $C_{16}H_{30}OSi$: 289.1958]. $\mathbf{R_F}$: 0.21 in 5% EtOAc/Hex.

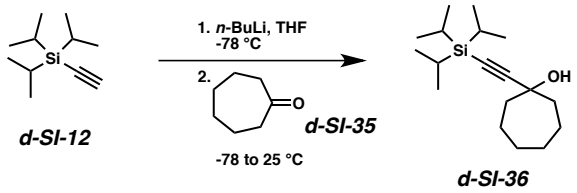


1-((triisopropylsilyl)ethynyl)cyclopentan-1-ol (d-SI-32) was synthesized from triisopropylsilylacetylene and cyclopentanone using General Procedure B. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil. (0.9167 g, 86% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.06–1.62 (m, 8H), 1.09–0.98 (m, 21H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 111.9, 83.1, 74.9, 42.7, 23.5, 18.6, 11.1. **IR(neat)** 3334, 2942, 2891, 2864, 2161, 1462, 1382, 1366, 1314, 1208, 1073, 994, 944, 918, 672 cm^{-1}. **HRMS** (CI) *m/z*: 266.2066 [$(M)^+$; calculated for $C_{16}H_{30}OSi$: 266.2066]. **R_F**: 0.18 in 5% EtOAc/Hex.

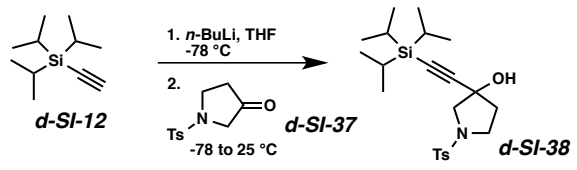


1-((triisopropylsilyl)ethynyl)cyclohexan-1-ol (d-SI-34) was synthesized from triisopropylsilylacetylene and cyclohexanone using General Procedure B. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil. (0.9875 g, 88% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.18 (s, 1H), 1.96–1.83 (m, 2H), 1.72–1.62 (m, 2H), 1.60–1.45 (m, 6H), 1.11–0.92 (m, 21H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 111.5, 84.5, 69.2, 40.1, 25.2, 23.5, 18.6, 11.1. **IR(neat)** 3339, 2934, 2891, 2863, 2163, 1446, 1462, 1382,

1366, 1281, 1257, 1132, 1032, 995, 918, 881, 760, 658 cm^{-1}. **HRMS** (CI) *m/z*: 280.2217 $[(M)^+$; calculated for $C_{17}H_{32}OSi$: 280.2222]. $\mathbf{R_F}$: 0.2 in 5% EtOAc/Hex.

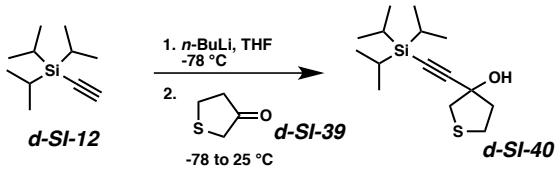


1-((triisopropylsilyl)ethynyl)cycloheptan-1-ol (d-SI-36) was synthesized from triisopropylsilylacetylene and cycloheptanone using General Procedure B. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil. (1.1546 g, 98% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.06–1.89 (m, 2H), 1.86–1.72 (m, 2H), 1.72–1.46 (m, 8H), 1.12–0.87 (m, 21H).**^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 112.5, 83.8, 72.3, 43.2, 27.7, 22.3, 18.6, 11.1. **IR(neat)** 2939, 2863, 2163, 2031, 1461, 1383, 1366, 1242, 1200, 1058, 1018, 995, 920, 882, 795, 750, 723, 673 cm^{-1}. **HRMS** (CI) *m/z*: 294.2369 $[(M)^+$; calculated for $C_{18}H_{34}OSi$: 294.2379]. $\mathbf{R_F}$: 0.36 in 10% EtOAc/Hex.

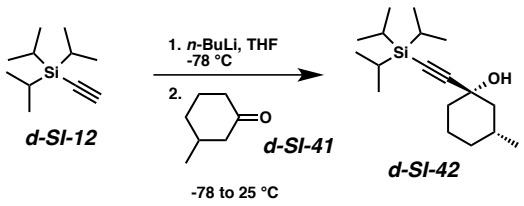


1-tosyl-3-((triisopropylsilyl)ethynyl)pyrrolidin-3-ol (d-SI-38) synthesized from triisopropylsilylacetylene and 1-tosylpyrrolidin-3-one using General Procedure B. The crude product was purified by column chromatography on silica gel using a gradient of 15 to 20% EtOAc in hexanes as eluents. The product was obtained as a white solid.

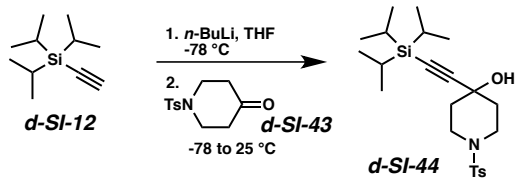
(1.2800 g, 76% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.58–3.42 (m, 3H), 3.41–3.31 (m, 1H), 2.40 (s, 3H), 2.16–2.03 (m, 2H), 1.86 (s, 1H), 1.07–0.90 (m, 21H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 143.5, 133.9, 129.6, 127.5, 106.2, 86.7, 72.0, 61.1, 46.5, 40.9, 21.5, 18.5, 10.9. **IR(neat)** 3455, 2942, 2891, 2864, 2167, 1597, 1462, 1383, 1323, 1304, 1290, 1242, 1153, 1110, 1037, 1017, 997, 925, 881, 804, 756, 699 cm^{-1}. **HRMS** (ESI) *m/z*: 444.2004 [$(M+Na)^+$; calculated for $C_{22}H_{35}NO_3SSiNa$: 444.1999]. **R_F**: 0.3 in 20% EtOAc/Hex. **MP**: 86-87 °C.



3-((triisopropylsilyl)ethynyl)tetrahydrothiophen-3-ol (d-SI-40) was synthesized from triisopropylsilylacetylene and dihydrothiophen-3(2*H*)-one using General Procedure B. The crude product was purified by column chromatography on silica gel using a gradient of 2 to 5% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (0.455 g, 40% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.18 (d, *J* = 11.5 Hz, 1H), 3.06–2.86 (m, 3H), 2.40–2.29 (m, 1H), 2.27 (s, 1H), 2.21–2.09 (m, 1H), 1.15–0.88 (m, 21H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 107.4, 85.6, 75.6, 44.8, 44.5, 28.7, 18.5, 11.0. **IR(neat)** 3382, 2941, 2890, 2864, 2163, 1462, 1428, 1382, 1366, 1270, 1233, 1209, 1061, 1029, 950, 918, 881, 831, 781, 751, 671 cm^{-1}. **HRMS** (CI) *m/z*: 284.1629 [$(M)^+$; calculated for $C_{15}H_{28}OSSi$: 284.1630]. **R_F**: 0.36 in 10% EtOAc/Hex.

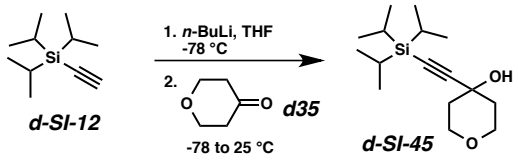


(1*S*,3*R*)-3-methyl-1-((triisopropylsilyl)ethynyl)cyclohexan-1-ol (d-SI-42) was synthesized from triisopropylsilylacetylene and 3-methylcyclohexanone using General Procedure B. The crude product was purified by column chromatography on silica gel using a gradient of 1 to 2% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (0.685 g, 56% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.12 (s, 1H), 1.98–1.87 (m, 2H), 1.79–1.50 (m, 4H), 1.42–1.29 (m, 1H), 1.20–0.95 (m, 22H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.84–0.69 (m, 1H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 111.3, 84.9, 69.9, 48.7, 39.9, 34.0, 30.6, 23.7, 22.1, 18.6, 11.1. **IR(neat)** 3349, 2927, 2892, 2864, 2159, 1460, 1366, 1327, 1073, 1051, 1001, 953, 942, 918, 882, 854, 813, 762, 675 cm^{-1}. **HRMS** (CI) *m/z*: 294.2371 [$(M)^+$; calculated for $C_{18}H_{34}OSi$: 294.2379]. **R_F**: 0.2 in 5% EtOAc/Hex.

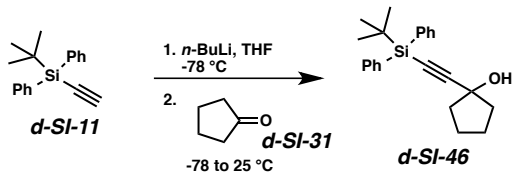


1-tosyl-4-((triisopropylsilyl)ethynyl)piperidin-4-ol (d-SI-44) synthesized from triisopropylsilylacetylene and 1-tosylpiperdin-4-one using General Procedure B. The crude product was purified by column chromatography on silica gel using a gradient of 15 to 20% EtOAc in hexanes as eluents. The product was obtained as a white solid. (1.436 g, 72% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 3.63–3.40 (m, 2H), 2.83–2.64 (m, 2H), 2.42 (s, 3H), 2.08–1.80 (m, 5H),

0.99–0.84 (m, 21H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 143.5, 132.7, 129.6, 127.6, 108.6, 86.9, 66.6, 43.7, 38.6, 21.5, 18.5, 10.9. **IR(neat)** 3493, 2940, 2864, 2170, 1743, 1597, 1494, 1379, 1351, 1319, 1190, 1169, 1158, 1141, 1047, 1002, 955, 801, 766, 730, 706 cm^{-1}. **HRMS** (ESI) *m/z*: 458.2158 [$(M+Na)^+$; calculated for $C_{23}H_{37}NO_3SSiNa$: 458.2156]. **R_F**: 0.24 in 20% EtOAc/Hex. **MP**: 153-154 °C.

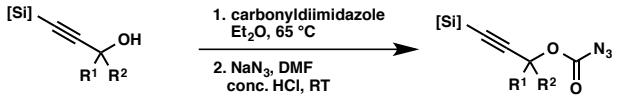


4-((triisopropylsilyl)ethynyl)tetrahydro-2*H*-pyran-4-ol (d-SI-45) was synthesized from triisopropylsilylacetylene and tetrahydro-*4H*-pyran-4-one using General Procedure B. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil. (1.0396 g, 92% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.99–3.82 (m, 2H), 3.73–3.55 (m, 2H), 2.28 (s, 1H), 1.98–1.84 (m, 2H), 1.84–1.74 (m, 2H), 1.13–0.88 (m, 21H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 109.9, 85.9, 66.4, 65.2, 40.2, 18.6, 11.1. **IR(neat)** 3416, 2942, 2891, 2864, 2162, 1463, 1425, 1384, 1366, 1335, 1300, 1275, 1233, 1160, 1134, 1011, 987, 958, 882, 842, 768, 674 cm^{-1}. **HRMS** (CI) *m/z*: 282.2021 [$(M)^+$; calculated for $C_{16}H_{30}O_2Si$: 282.2015]. **R_F**: 0.3 in 20% EtOAc/Hex.



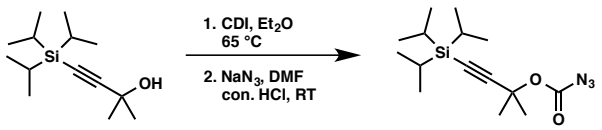
1-((*tert*-butyldiphenylsilyl)ethynyl)cyclopentan-1-ol (d-SI-46) was synthesized from *tert*-butyl(ethynyl)diphenylsilane and cyclopentanone using General Procedure B. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil. (0.976 g, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81–7.72 (m, 4H), 7.44–7.29 (m, 6H), 2.18–1.95 (m, 4H), 1.95–1.69 (m, 4H), 1.06 (s, 9H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 135.5, 133.2, 129.5, 127.7, 114.0, 82.4, 75.0, 42.6, 27.0, 23.5, 18.5. **IR(neat)** 3343, 3070, 2957, 2929, 2856, 2162, 1471, 1428, 1389, 1361, 1258, 1208, 1106, 997, 941, 914, 883, 819, 740 cm^{-1}. **HRMS** (CI) *m/z*: 348.1905 [$(M)^+$; calculated for $C_{23}H_{28}OSi$: 348.1909]. **R_F**: 0.3 in 10% EtOAc/Hex.

General Procedure C



A flame-dried heavy wall pressure vessel was charged with the propargyl alcohol (1.0 equiv, 3 mmol), carbonyldiimidazole (CDI, 2.0 equiv, 6 mmol, 973 mg), and anhydrous Et_2O (0.5M, 6 mL) under an argon atmosphere. The reaction vessel was sealed and heated to reflux in an oil bath (65 °C). The progress of the reaction was monitored by TLC. (the reaction vessel should only be opened when cooled to room temperature!) After reaction is done, the reaction vessel was cooled to room temperature, and the

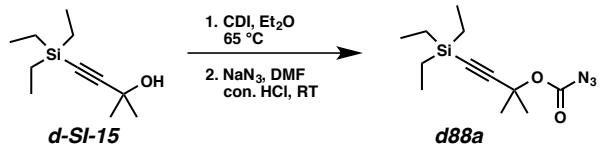
solvent was evaporated under a stream of nitrogen gas. The residue was then dissolved in DMF (0.5M, 6 mL), and NaN_3 (5.0 equiv, 15 mmol, 975 mg) was added in one portion. The reaction mixture was acidified with concentrated HCl until pH ~ 6 (monitored by pH papers). The progress of the reaction was monitored by TLC. After the reaction was finished, deionized water was added and the mixture was extracted with Et_2O three times. The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel. No decomposition of the carbonazidates was observed at room temperature after more than a month, but it is recommended to store the carbonazidates at -20 °C for long-term storage.



d-SI-13 *d48*

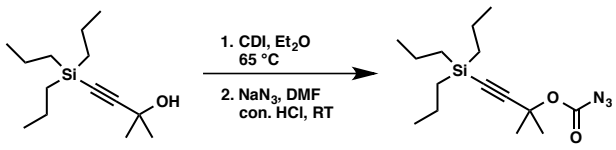
2-methyl-4-(triisopropylsilyl)but-3-yn-2-yl carbonazidate (d48) was synthesized from alcohol **d-SI-13** using General Procedure C. The crude product was purified by column chromatography on silica gel using a gradient of 0.5 to 1% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (0.680 g, 73% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.70 (s, 6H), 1.09–0.94 (m, 21H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 154.8, 106.5, 86.6, 76.3, 28.9, 18.5, 11.0. **IR(neat)** 2942, 2866, 2174, 2129, 1735, 1463, 1383, 1366, 1231, 1193, 1120, 1072, 996, 947, 919, 878, 796, 775, 676 cm^{-1}. **HRMS** (ESI) *m/z*: 332.1764 [$(M+Na)^+$; calculated for $C_{15}H_{27}N_3O_2SiNa$: 332.1765]. **R_F1** = 0.24 in 10% EtOAc/Hex. **R_F2** = 0.42 in 5% EtOAc/Hex. **2-methyl-4-(triisopropylsilyl)but-3-yn-2-yl**

carbonazidate (d50) was prepared from alcohol **d-SI-13** and $Na^{15}N_3$ using General Procedure C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.70 (s, 6H), 1.09–0.94 (m, 21H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 154.8, 106.5, 86.6, 76.3, 28.9, 18.5, 11.0. ^{15}N NMR (40.6 MHz, $CDCl_3$) δ 234.7, 110.9.



d-SI-15 *d88a*

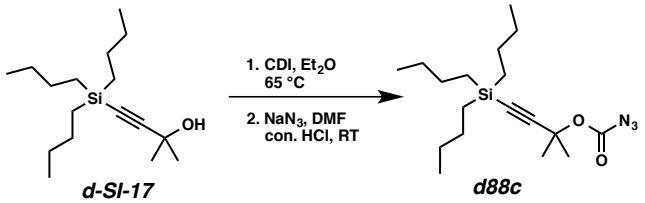
2-methyl-4-(triethylsilyl)but-3-yn-2-yl carbonazidate (d88a) was synthesized from alcohol **d-SI-15** using General Procedure C. The crude product was purified by column chromatography on silica gel using a gradient of 0.5 to 1% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (0.625 g, 78% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.69 (s, 6H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.57 (q, *J* = 8.0 Hz, 6H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 154.9, 105.8, 87.6, 76.3, 28.8, 7.36, 4.2. **IR(neat)** 2956, 2913, 2876, 2174, 2129, 1735, 1458, 1415, 1383, 1366, 1229, 1192, 1119, 1015, 947, 875, 775, 724 cm^{-1}. **HRMS** (CI) *m/z*: 268.1476 [$(M+H)^+$; calculated for $C_{12}H_{22}N_3O_2Si$: 268.1481]. **R_F1** = 0.24 in 10% EtOAc/Hex. **R_F2** = 0.5 in 5% EtOAc/Hex.



d-SI-16 *d88b*

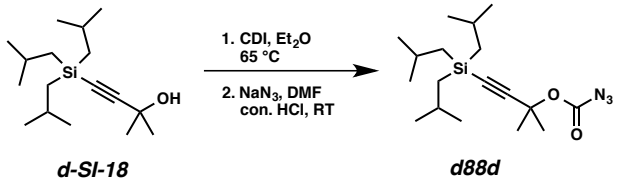
2-methyl-4-(tripropylsilyl)but-3-yn-2-yl carbonazidate (d88b) was synthesized from alcohol **d-SI-16** using General Procedure C. The crude product was purified by column chromatography on silica gel using 0.5% EtOAc in hexanes as an eluent. The product

was obtained as a colorless oil. (0.750 g, 80% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.68 (s, 6H), 1.44–1.29 (m, 6H), 0.95 (t, *J* = 7.4 Hz, 9H), 0.62–0.53 (m, 6H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 154.9, 105.7, 88.4, 76.4, 28.8, 18.1, 17.4, 15.8. **IR(neat)** 2955, 2926, 2869, 2174, 2129, 1760, 1736, 1462, 1365, 1231, 1193, 1119, 1065, 1005, 947, 875, 801, 749 cm^{-1}. **HRMS** (CI) *m/z*: 310.1947 [$(M+H)^+$; calculated for $C_{15}H_{28}N_3O_2Si$: 310.1951]. **R_F1** = 0.24 in 10% EtOAc/Hex. **R_F2** = 0.54 in 2% EtOAc/Hex.



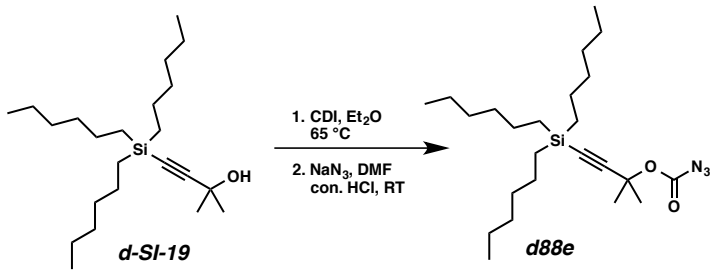
d-SI-17 *d88c*

2-methyl-4-(tributylsilyl)but-3-yn-2-yl carbonazidate (d88c) was synthesized from alcohol **d-SI-17** using General Procedure C. The crude product was purified by column chromatography on silica gel using 0.5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil. (0.824 g, 78% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.69 (s, 6H), 1.38–1.22 (m, 12H), 0.93–0.80 (m, 9H), 0.65–0.50 (m, 6H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 154.9, 105.6, 88.5, 76.4, 28.8, 26.3, 26.0, 13.8, 12.7. **IR(neat)** 2956, 2922, 2872, 2174, 2129, 1736, 1465, 1408, 1378, 1365, 1232, 1192, 1120, 1081, 1028, 999, 947, 876, 799, 749 cm^{-1}. **HRMS** (CI) *m/z*: 352.2422 [$(M+H)^+$; calculated for $C_{18}H_{34}N_3O_2Si$: 352.2420]. **R_F1** = 0.24 in 10% EtOAc/Hex. **R_F2** = 0.6 in 5% EtOAc/Hex.



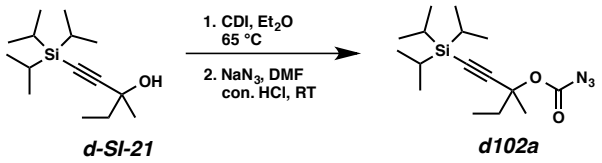
d-SI-18 *d88d*

2-methyl-4-(triisobutylsilyl)but-3-yn-2-yl carbonazidate (d88d) was synthesized from alcohol **d-SI-18** using General Procedure C. The crude product was purified by column chromatography on silica gel using 0.5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil. (0.990 g, 94% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.89–1.74 (m, 3H), 1.67 (s, 6H), 1.00–0.90 (m, 18H), 0.60 (d, J = 7.0 Hz, 6H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 154.9, 105.9, 89.8, 76.4, 28.5, 26.2, 25.0, 24.7. **IR(neat)** 2952, 2895, 2867, 2174, 2130, 2070, 1737, 1531, 1464, 1233, 1193, 1163, 1120, 1093, 1039, 974, 947, 875, 829, 800, 749 cm^{-1}. **HRMS** (ESI) *m/z*: 374.2240 [$(M+Na)^+$; calculated for $C_{18}H_{33}N_3O_2SiNa$: 374.2234]. **R_F1** = 0.24 in 10% EtOAc/Hex. **R_F2** = 0.6 in 5% EtOAc/Hex.



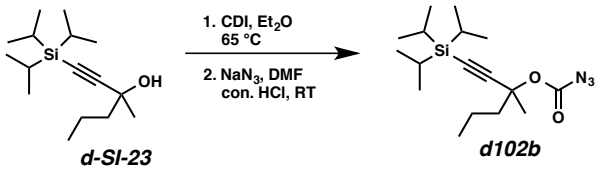
2-methyl-4-(trihexylsilyl)but-3-yn-2-yl carbonazidate (d88e) was synthesized from alcohol **d-SI-19** using General Procedure C. The crude product was purified by column chromatography on silica gel using a gradient of 0 to 2% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (1.0995 g, 84% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.68 (s, 6H), 1.38–1.15 (m, 24H), 0.92–0.81 (m, 9H), 0.63–0.51 (m, 6H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 154.9, 105.6, 88.5, 76.3, 33.0, 31.5, 28.8, 23.8, 22.6, 14.1, 13.0. **IR(neat)** 2956, 2921, 285, 2175, 2129, 1737, 1466, 1381, 1365, 1232, 1192, 1121,

975, 875, 799, 749, 721 cm^{-1}. **HRMS** (CI) *m/z*: 436.3347 $[(M+H)^+$; calculated for $C_{24}H_{46}N_3O_2Si$: 436.3359]. $\mathbf{R_F1}$ = 0.3 in 10% EtOAc/Hex. $\mathbf{R_F2}$ = 0.45 in 2% EtOAc/Hex.



d-SI-21 *d102a*

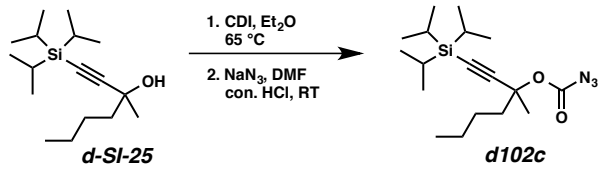
3-methyl-1-(triisopropylsilyl)pent-1-yn-3-yl carbonazidate (d102a) was synthesized from alcohol **d-SI-21** using General Procedure C. The crude product was purified by column chromatography on silica gel using a gradient of 0.5 to 1% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (0.789 g, 81% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.06–1.93 (m, 1H), 1.89–1.77 (m, 1H), 1.69 (s, 3H), 1.09–0.98 (m, 24H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 154.7, 105.3, 87.8, 80.2, 34.5, 26.0, 18.5, 11.0, 8.7. **IR(neat)** 2942, 2865, 2180, 2129, 1741, 1463, 1382, 1299, 1227, 1185, 1152, 1120, 1056, 1032, 997, 951, 881, 786, 748, 676 cm^{-1}. **HRMS** (ESI) *m/z*: 346.1920 $[(M+Na)^+$; calculated for $C_{16}H_{29}N_3O_2SiNa$: 346.1921]. $\mathbf{R_F1}$ = 0.24 in 5% EtOAc/Hex. $\mathbf{R_F2}$ = 0.63 in 5% EtOAc/Hex.



d-SI-23 *d102b*

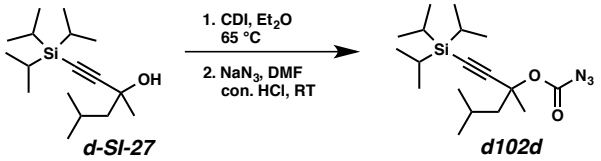
3-methyl-1-(triisopropylsilyl)hex-1-yn-3-yl carbonazidate (d102b) was synthesized from alcohol **d-SI-23** using General Procedure C. The crude product was purified by column chromatography on silica gel using a gradient of 0.5 to 2% EtOAc in hexanes as

eluents. The product was obtained as a colorless oil. (0.737 g, 73% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.94 (ddd, *J* = 13.4, 10.8, 5.6 Hz, 1H), 1.78 (ddd, *J* = 13.6, 10.6, 5.9 Hz, 1H), 1.70 (s, 3H), 1.59–1.43 (m, 2H), 1.14–0.98 (m, 21H), 0.93 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 154.7, 105.6, 87.6, 79.7, 43.4, 26.5, 18.5, 17.6, 14.0, 11.0. **IR(neat)** 2942, 2866, 2182, 2131, 1736, 1463, 1375, 1225, 1181, 1151, 1111, 1078, 1048, 1018, 996, 967, 916, 881, 800, 773, 749, 676 cm^{-1}. **HRMS** (ESI) *m/z*: 360.2075 [$(M+Na)^+$; calculated for $C_{17}H_{31}N_3O_2SiNa$: 360.2078]. **R_F1** = 0.3 in 10% EtOAc/Hex. **R_F2** = 0.45 in 5% EtOAc/Hex.



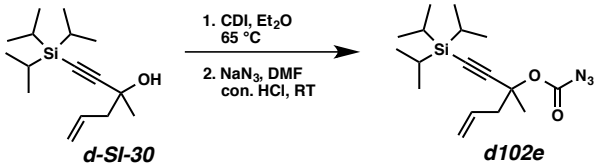
d-SI-25 *d102c*

3-methyl-1-(triisopropylsilyl)hept-1-yn-3-yl carbonazidate (d102c) was synthesized from alcohol **d-SI-25** using General Procedure C. The crude product was purified by column chromatography on silica gel using 0.5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil. (0.739 g, 70% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.96 (ddd, *J* = 13.7, 11.1, 5.3 Hz, 1H), 1.79 (ddd, *J* = 13.6, 11.1, 5.7 Hz, 1H), 1.70 (s, 3H), 1.52–1.39 (m, 2H), 1.39–1.26 (m, 2H), 1.11–0.97 (m, 21H), 0.89 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 154.7, 105.6, 87.7, 79.8, 41.0, 26.4, 26.4, 22.6, 18.5, 14.0, 11.0. **IR(neat)** 2942, 2865, 2182, 2129, 1737, 1463, 1375, 1223, 1129, 1114, 1151, 1082, 1043, 996, 920, 881, 806, 774, 749, 676, 660 cm^{-1}. **HRMS** (ESI) *m/z*: 374.2232 [$(M+Na)^+$; calculated for $C_{18}H_{33}N_3O_2SiNa$: 374.2234]. **R_F1** = 0.2 in 5% EtOAc/Hex. **R_F2** = 0.6 in 5% EtOAc/Hex.



d-SI-27 *d102d*

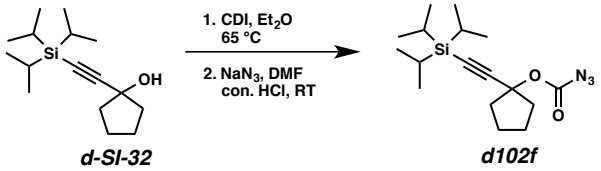
3,5-dimethyl-1-(triisopropylsilyl)hex-1-yn-3-yl carbonazidate (d102d) was synthesized from alcohol **d-SI-27** using General Procedure C. The crude product was purified by column chromatography on silica gel using 0.5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil. (0.526 g, 50% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.05–1.92 (m, 1H), 1.92–1.85 (m, 1H), 1.77–1.65 (m, 4H), 1.13–1.00 (m, 21H), 1.00–0.91 (m, 6H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 154.6, 105.6, 88.0, 79.8, 49.3, 27.3, 25.0, 24.1, 23.6, 18.5, 11.0. **IR(neat)** 2942, 2866, 2182, 2129, 1736, 1463, 1367, 1274, 1225, 1127, 1040, 996, 953, 903, 881, 802, 749, 676, 660 cm^{-1}. **HRMS** (CI) *m/z*: 352.2426 [$(M+H)^+$; calculated for $C_{18}H_{34}N_3O_2Si$: 352.2420]. **R_F1** = 0.2 in 5% EtOAc/Hex. **R_F2** = 0.75 in 5% EtOAc/Hex.



d-SI-30 *d102e*

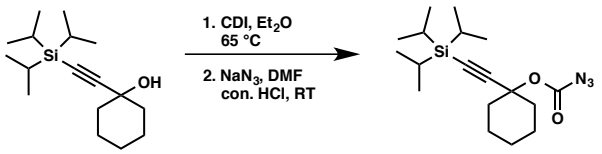
3-methyl-1-(triisopropylsilyl)hex-5-en-1-yn-3-yl carbonazidate (d102e) was synthesized from alcohol **d-SI-30** using General Procedure C. The crude product was purified by column chromatography on silica gel using a gradient of 0 to 0.5% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (0.594 g, 59% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.88–5.80 (m, 1H), 5.19–5.16 (m, 1H), 5.18–5.10 (m, 1H),

2.74 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.62 (dd, *J* = 13.8, 7.5 Hz, 1H), 1.68 (s, 3H), 1.04 (s, 21H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.64, 131.66, 119.61, 105.20, 88.21, 78.44, 45.45, 26.17, 18.51, 11.02. **IR(neat)** 2943, 2865, 2183, 2130, 1737, 1463, 1224, 1143, 1089, 1061, 995, 920, 902, 881, 773, 749 cm^{-1}. **HRMS** (ESI) *m/z*: 358.1924 [$(M+Na)^+$; calculated for $C_{17}H_{29}N_3O_2Si$: 358.1921]. **R_F1** = 0.3 in 10% EtOAc/Hex. **R_F2** = 0.6 in 5% EtOAc/Hex.



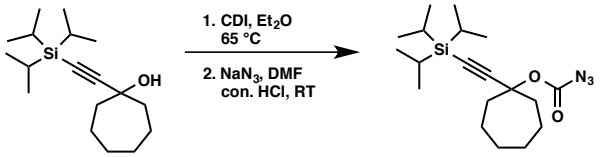
d-SI-32 *d102f*

1-((triisopropylsilyl)ethynyl)cyclopentyl carbonazidate (d102f) was synthesized from alcohol **d-SI-32** using General Procedure C. The crude product was purified by column chromatography on silica gel using 0.5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil. (0.804 g, 80% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.34–2.20 (m, 2H), 2.20–2.08 (m, 2H), 1.81–1.65 (m, 4H), 1.12–0.88 (m, 21H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 155.2, 105.9, 87.3, 84.8, 40.4, 23.2, 18.5, 11.0. **IR(neat)** 2943, 2865, 2173, 2128, 1737, 1463, 1383, 1329, 1228, 1170, 1071, 995, 919, 881, 749, 675 cm^{-1}. **HRMS** (ESI) *m/z*: 358.1921 [$(M+Na)^+$; calculated for $C_{17}H_{29}N_3O_2SiNa$: 358.1921]. **R_F1** = 0.24 in 20% EtOAc/Hex. **R_F2** = 0.6 in 20% EtOAc/Hex.



d-SI-34 *d102g*

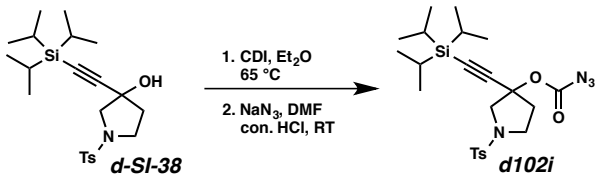
1-((triisopropylsilyl)ethynyl)cyclohexyl carbonazidate (d102g) was synthesized from alcohol **d-SI-34** using General Procedure C. The crude product was purified by column chromatography on silica gel using a gradient of 0.5 to 1% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (0.785 g, 75% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.20 (dt, *J* = 11.5, 4.4 Hz, 2H), 1.79 (dt, *J* = 11.8, 3.8 Hz, 2H), 1.72–1.50 (m, 4H), 1.14–0.90 (m, 21H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 154.5, 105.2, 88.9, 80.2, 37.0, 25.0, 22.9, 18.5, 11.1. **IR(neat)** 2939, 2864, 2183, 2135, 1739, 1463, 1383, 1366, 1296, 1262, 1205, 1170, 1140, 1119, 1071, 941, 918, 881, 852, 839, 676 cm^{-1}. **HRMS** (ESI) *m/z*: 372.2069 [$(M+Na)^+$; calculated for $C_{18}H_{31}N_3O_2SiNa$: 372.2078]. **R_F1** = 0.27 in 10% EtOAc/Hex. **R_F2** = 0.7 in 10% EtOAc/Hex.



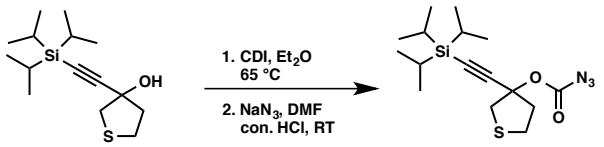
d-SI-36 *d102h*

1-((triisopropylsilyl)ethynyl)cycloheptyl carbonazidate (d102h) was synthesized from alcohol **d-SI-36** using General Procedure C. The crude product was purified by column chromatography on silica gel using a gradient of 0.5 to 1% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (0.816 g, 75% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.28 (ddd, *J* = 14.0, 7.4, 3.1 Hz, 2H), 2.06 (ddd, *J* = 14.3, 8.8, 3.1 Hz, 2H), 1.72–1.50 (m, 8H), 1.14–0.91 (m, 21H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 154.6, 106.2,

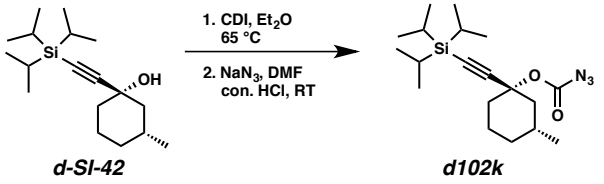
88.3, 83.6, 40.0, 27.9, 22.2, 18.5, 11.1. **IR(neat)** 2940, 2864, 2181, 2130, 2069, 1735, 1527, 1462, 1367, 1286, 1223, 1192, 1176, 1065, 996, 881, 802, 749, 676 cm^{-1}. **HRMS** (ESI) *m/z*: 386.2234 [$(M+Na)^+$; calculated for $C_{19}H_{33}N_3O_2SiNa$: 386.2234]. $\mathbf{R_F1}$ = 0.3 in 10% EtOAc/Hex. $\mathbf{R_F2}$ = 0.67 in 10% EtOAc/Hex.



1-tosyl-3-((triisopropylsilyl)ethynyl)pyrrolidin-3-yl carbonazidate (d102i) was synthesized from alcohol **d-SI-38** using General Procedure C. The crude product was purified by column chromatography on silica gel using a gradient of 5 to 10% EtOAc in hexanes as eluents. The product was obtained as a white solid. (1.1762 g, 80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 4.00 (dd, *J* = 12.8, 1.7 Hz, 1H), 3.64 (d, *J* = 12.7 Hz, 1H), 3.54 (ddd, *J* = 9.6, 8.1, 3.1 Hz, 1H), 3.29 (ddd, *J* = 9.8, 9.7, 6.6 Hz, 1H), 2.50–2.34 (m, 4H), 2.26 (ddd, *J* = 13.7, 10.0, 8.2 Hz, 1H), 1.08–0.87 (m, 21H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 154.7, 143.8, 133.3, 129.7, 127.6, 100.4, 90.9, 80.1, 57.8, 46.1, 38.9, 21.5, 18.4, 10.8. **IR(neat)** 2942, 2891, 2865, 2174, 2129, 1731, 1463, 1384, 1222, 1174, 1086, 1029, 1016, 972, 944, 919, 848, 814, 708, 697, 678 cm^{-1}. **HRMS** (ESI) *m/z*: 513.1967 [$(M+Na)^+$; calculated for $C_{23}H_{34}N_4O_4SSiNa$: 513.1962]. $\mathbf{R_F1}$ = 0.2 in 25% EtOAc/Hex. $\mathbf{R_F2}$ = 0.6 in 25% EtOAc/Hex. **MP**: 72-74 °C.

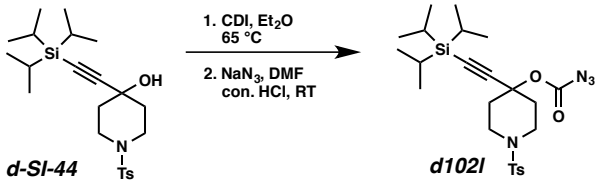


3-((triisopropylsilyl)ethynyl)tetrahydrothiophen-3-yl carbonazidate (d102j) was synthesized from alcohol **d-SI-40** using General Procedure C. The crude product was purified by column chromatography on silica gel using 2% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil. (0.773 g, 73% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.47 (dd, *J* = 12.3, 1.2 Hz, 1H), 3.31 (d, *J* = 12.1 Hz, 1H), 3.05–2.87 (m, 2H), 2.73–2.62 (m, 1H), 2.44–2.24 (m, 1H), 1.12–0.97 (m, 21H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 155.1, 102.1, 89.6, 84.1, 42.9, 41.2, 28.1, 18.5, 11.0. **IR(neat)** 2942, 2891, 2865, 2177, 2132, 1763, 1734, 1463, 1384, 1247, 1228, 1199, 1176, 1072, 1004, 959, 910, 881, 848, 747, 669 cm^{-1}. **HRMS** (CI) *m/z*: 353.1590 [$(M)^+$; calculated for $C_{16}H_{27}N_3O_2SSi$: 353.1593]. **R_F1** = 0.2 in 10% EtOAc/Hex. **R_F2** = 0.48 in 5% EtOAc/Hex.

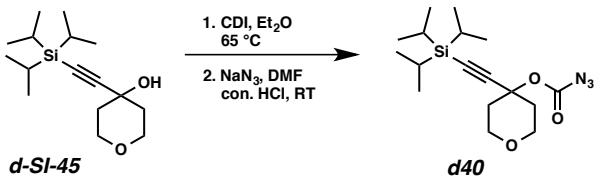


3-methyl-1-((triisopropylsilyl)ethynyl)cyclohexyl carbonazidate (d102k) was synthesized from alcohol **d-SI-42** using General Procedure C. The crude product was purified by column chromatography on silica gel using a gradient of 0.5 to 1% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (1.09 g, 92% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.46–2.29 (m, 1H), 1.88–1.57 (m, 4H), 1.53–1.42 (m, 1H),

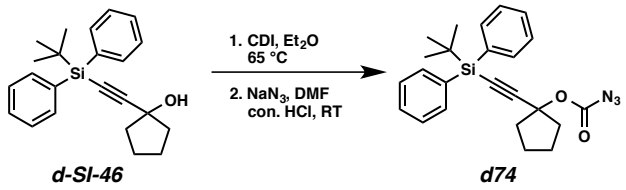
1.27–1.15 (m, 1H), 1.05 (s, 21H), 0.92 (d, J = 6.7 Hz, 3H), 0.89–0.74 (m, 1H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 154.5, 104.9, 89.5, 81.0, 45.1, 36.8, 33.9, 30.2, 23.1, 21.9, 18.6, 11.1. **IR(neat)** 2940, 2865, 2177, 2133, 1738, 1462, 1383, 1298, 1281, 1229, 1209, 1174, 1052, 1016, 974, 914, 881, 748, 675, 660 cm^{-1}. **HRMS** (ESI) *m/z*: 386.2232 [$(M+Na)^+$; calculated for $C_{19}H_{33}N_3O_2SiNa$: 386.2234]. **R_F1** = 0.3 in 10% EtOAc/Hex. **R_F2** = 0.67 in 10% EtOAc/Hex.



1-tosyl-4-((triisopropylsilyl)ethynyl)piperidin-4-yl carbonazidate (d102l) was synthesized from alcohol **d-SI-44** using General Procedure C. The crude product was purified by column chromatography on silica gel using a gradient of 5 to 10% EtOAc in hexanes as eluents. The product was obtained as a white solid. (1.089 g, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 3.57 (ddd, J = 12.4, 4.2, 4.2 Hz, 2H), 2.73 (ddd, J = 11.4, 11.4, 2.8 Hz, 2H), 2.41 (s, 3H), 2.37–2.25 (m, 2H), 2.04 (ddd, J = 12.8, 11.0, 4.0 Hz, 2H), 1.00–0.77 (m, 21H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 154.8, 143.7, 132.4, 129.7, 127.6, 102.5, 91.4, 77.2, 43.3, 35.8, 21.5, 18.4, 10.8. **IR(neat)** 2941, 2864, 2159, 2128, 1736, 1494, 1382, 1302, 1260, 1231, 1211, 1200, 1154, 1109, 1094, 1062, 1032, 960, 800, 767, 746, 729, 709, 679 cm^{-1}. **HRMS** (ESI) *m/z*: 527.2112 [$(M+Na)^+$; calculated for $C_{24}H_{36}N_4O_4SSiNa$: 527.2119]. **R_F1** = 0.2 in 25% EtOAc/Hex. **R_F2** = 0.6 in 25% EtOAc/Hex. **MP**: 107-108 °C.

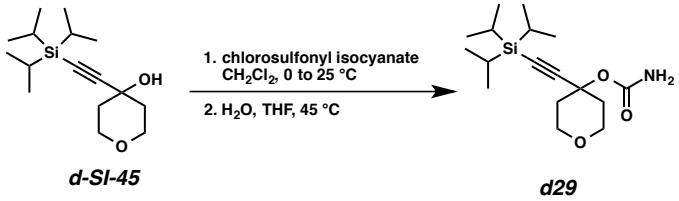


4-((triisopropylsilyl)ethynyl)tetrahydro-2*H*-pyran-4-yl carbonazidate (d40) was synthesized from alcohol **d-SI-45** using General Procedure C. The crude product was purified by column chromatography on silica gel using a gradient of 2 to 5% EtOAc in hexanes as eluents. The product was obtained as a colorless oil. (0.815 g, 77% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.89 (ddd, *J* = 12.1, 4.1, 4.1 Hz, 2H), 3.70 (ddd, *J* = 12.6, 10.2, 2.4 Hz, 2H), 2.25 (ddd, *J* = 13.1, 2.2, 2.2 Hz, 2H), 2.00 (ddd, *J* = 13.8, 10.2, 4.2 Hz, 2H), 1.13–0.98 (m, 21H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 154.7, 103.7, 90.3, 76.9, 64.7, 37.5, 18.5, 11.0. **IR(neat)** 2941, 2864, 2184, 2136, 2070, 1738, 1463, 1385, 1267, 1221, 1153, 1098, 988, 935, 881, 849, 748, 660 cm^{-1}. **HRMS** (CI) *m/z*: 352.2045 [$(M+H)^+$; calculated for $C_{17}H_{30}N_3O_3Si$: 352.2056]. **R_F1** = 0.24 in 20% EtOAc/Hex. **R_F2** = 0.45 in 10% EtOAc/Hex.



1-((*tert*-butyldiphenylsilyl)ethynyl)cyclopentyl carbonazidate (d74) was synthesized from alcohol **d-SI-46** using General Procedure C. The crude product was purified by column chromatography on silica gel using 2% EtOAc in hexanes as an eluent. The product was obtained as a white solid. (0.806 g, 77% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86–7.75 (m, 4H), 7.46–7.33 (m, 6H), 2.46–2.25 (m, 4H), 1.90–1.77 (m, 4H), 1.10 (s,

9H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 155.4, 135.5, 132.8, 129.5, 127.7, 108.1, 86.4, 84.6, 40.4, 26.9, 23.3, 18.6. **IR(neat)** 3069, 2954, 2931, 2856, 2180, 2129, 1737, 1470, 1444, 1427, 1361, 1329, 1239, 1177, 1107, 998, 964, 950, 899, 819, 701 cm^{-1}. **HRMS** (ESI) *m/z*: 440.1763 [$(M+Na)^+$; calculated for $C_{24}H_{27}N_3O_2SiNa$: 440.1765]. **R_F1** = 0.2 in 10% EtOAc/Hex. **R_F2** = 0.2 in 2% EtOAc/Hex. **MP**: 44-45 °C.

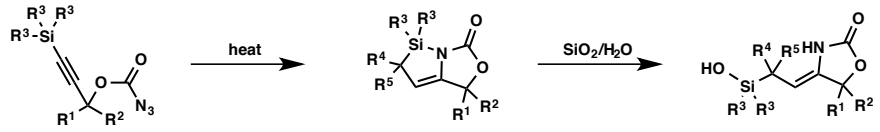


d-SI-45 *d29*

4-((triisopropylsilyl)ethynyl)tetrahydro-2*H*-pyran-4-yl carbamate (d29)

A flame-dried round-bottom flask was charged with chlorosulfonyl isocyanate (1.5 equiv) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.1M) was added, and the mixture was cooled to 0 ˚C in an ice/H_2O bath. The propargyl alcohol **d-SI-45** (0.31 g, 0.26 mmol, 1.0 equiv) dissolved in anhydrous CH_2Cl_2 (0.3M) was then added dropwise. The reaction mixture was allowed to warm to room temperature. After 30 minutes, H_2O (1/10 of the total volume of CH_2Cl_2 added) and THF (1/5 of the total volume) were added. The reaction mixture was refluxed (45 ˚C oil bath) for 30 minutes. Then saturated NaCl solution was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x), and the organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 30% EtOAc in hexanes as an eluent. The product was obtained as a white solid. (0.24 g, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.70 (s, 2H), 3.86 (ddd, *J* = 11.9, 4.1, 4.1 Hz, 2H), 3.71 (ddd, *J* = 12.0, 10.3, 2.5 Hz,

2H), 2.23 (ddd, *J* = 13.4, 4.5, 2.2 Hz, 2H), 1.97 (ddd, *J* = 13.4, 10.3, 4.2 Hz, 2H), 1.16–0.93 (m, 21H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 154.6, 105.8, 88.1, 73.0, 64.7, 38.0, 18.6, 11.1. **IR(neat)** 3429, 3333, 3272, 2941, 2864, 2166, 1723, 1362, 1245, 1204, 1098, 1057, 1025, 972, 906, 845, 819, 780, 718, 680, 663 cm^{-1}. **HRMS** (ESI) *m/z*: 348.1966 [$(M+Na)^+$; calculated for $C_{17}H_{31}NO_3SiNa$: 348.1965]. **R_F**: 0.36 in 30% EtOAc/Hex. **MP**: 82-84 °C.



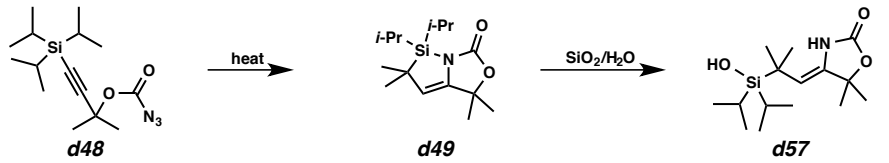
General Procedure D1

A 2 dram vial was charged with a magnetic spin bar, carbonazidate (0.1 mmol), and dry hexanes (0.1M, 1 mL). The reaction vessel was sealed and heated in an oil bath at 90 °C. The progress of the reaction was monitored by TLC. After the reaction was finished (18 h), the reaction vessel was cooled to room temperature and the mixture was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel.

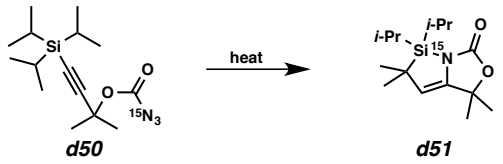
General Procedure D2

A 2 dram vial was charged with a magnetic spin bar, carbonazidate (0.1 mmol), and dry isopropylacetate (0.1M, 1 mL). The reaction vessel was sealed and heated in an oil bath at 100 °C. The progress of the reaction was monitored by TLC. After the reaction was finished (14 h), the reaction vessel was cooled to room temperature and the mixture was

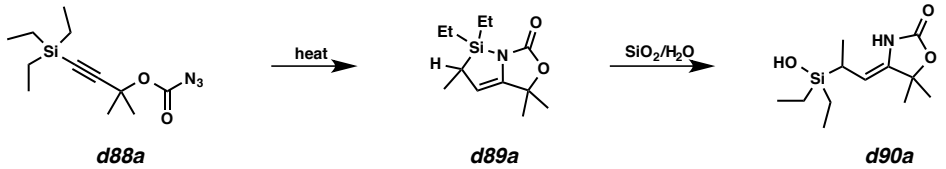
concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel.



(*Z*)-4-(2-(hydroxydiisopropylsilyl)-2-methylpropylidene)-5,5-dimethyloxazolidin-2-one (d57) was synthesized from carbonazidate **d48** using General Procedure D1. The crude product was purified by column chromatography on silica gel using a gradient of 10 to 20% EtOAc in hexanes as eluents. The product was obtained as an amorphous yellowish solid. (trial 1: 15.6 mg, 52% yield; trial 2: 15.0 mg, 50% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 4.52 (s, 1H), 4.22 (s, 1H), 1.44 (s, 6H), 1.13 (s, 6H), 1.10–0.93 (m, 14H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 156.8, 139.4, 107.5, 84.9, 28.1, 25.6, 23.9, 18.4, 18.4, 13.3. **IR(neat)** 3351, 2944, 2866, 1739, 1718, 1690, 1463, 1386, 1207, 1171, 963, 917, 824, 673 cm^{-1}. **HRMS** (ESI) *m/z*: 322.1813 [$(M+Na)^+$; calculated for $C_{15}H_{29}NO_3SiNa$: 322.1809]. **R_F**: 0.2 in 20% EtOAc/Hex. **1,1-diisopropyl-2,2,4,4-tetramethyl-2,4-dihydro-1*H*,6*H*-[1,2]azasilolo[1,5-*c*]oxazol-6-one (d49)** was observed in crude NMR (53% yield).

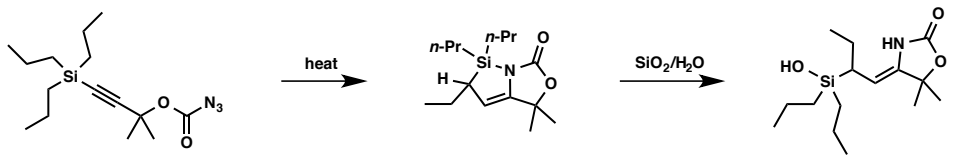


1,1-diisopropyl-2,2,4,4-tetramethyl-2,4-dihydro-1*H*,6*H*-[1,2]azasilolo[1,5-*c*]oxazol-6-one (d51) was synthesized from carbonazidate **d50** using General Procedure D1. The crude reaction mixtures were concentrated. Compound d51 was transferred to a NMR tube with $CDCl_3$. ^{15}N NMR (40.6 MHz, $CDCl_3$) δ 110.5.

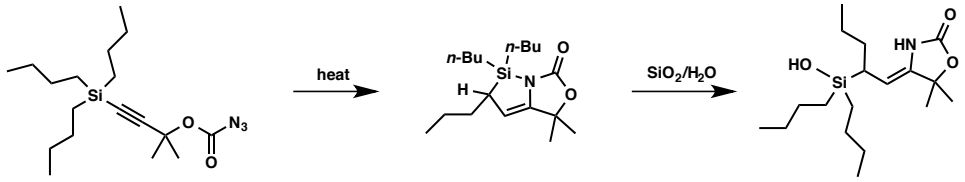


(*Z*)-4-(2-(diethyl(hydroxy)silyl)propylidene)-5,5-dimethyloxazolidin-2-one (d90a) was synthesized from carbonazidate **d88a** using General Procedure D1. The crude product was purified by column chromatography on silica gel using a gradient of 20 to 25% EtOAc in hexanes as eluents. The product was obtained as an amorphous yellowish solid. (trial 1: 10.0 mg, 39% yield; trial 2: 9.8 mg, 38% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.75 (s, 1H), 4.17 (d, *J* = 9.9 Hz, 1H), 3.00 (s, 1H), 1.66 (dq, *J* = 10.2, 7.4 Hz, 1H), 1.47 (s, 6H), 1.06 (d, *J* = 7.4 Hz, 3H), 1.02–0.90 (m, 6H), 0.68–0.49 (m, 4H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 157.9, 138.1, 100.9, 85.0, 28.1, 28.0, 20.6, 15.0, 6.8, 6.5, 4.9, 4.3. **IR(neat)** 3463, 3231, 2953, 2875, 1723, 1698, 1388, 1369, 1325, 1299, 1204, 1186, 1153, 1017, 912, 888, 850, 770, 715, 669 cm^{-1}. **HRMS** (ESI) *m/z*: 280.1342 [$(M+Na)^+$; calculated for $C_{12}H_{23}NO_3SiNa$: 280.1339]. **R_F**: 0.2 in 25% EtOAc/Hex. **1,1-**

diethyl-2,4,4-trimethyl-2,4-dihydro-1*H*,6*H*-[1,2]azasilolo[1,5-*c*]oxazol-6-one (d89a) was observed in crude NMR (38% yield).

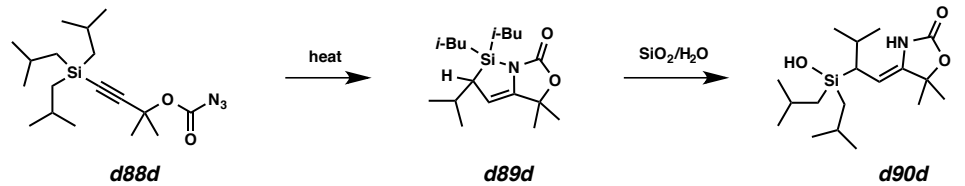


(*Z*)-4-(2-(hydroxydipropylsilyl)butylidene)-5,5-dimethyloxazolidin-2-one (d90b) was synthesized from carbonazidate **d88b** using General Procedure D1. The crude product was purified by column chromatography on silica gel using a gradient of 20 to 25% EtOAc in hexanes as eluents. The product was obtained as a yellow oil. (trial 1: 12.5 mg, 42% yield; trial 2: 13.7 mg, 46% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 4.11 (d, J = 10.5 Hz, 1H), 2.64 (s, 1H), 1.68–1.56 (m, 1H), 1.49 (d, J = 3.4 Hz, 6H), 1.45–1.17 (m, 5H), 1.03–0.90 (m, 6H), 0.88 (t, J = 7.2 Hz, 3H), 0.65–0.50 (m, 4H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 157.6, 139.7, 98.8, 85.0, 29.9, 28.1, 28.0, 22.7, 18.4, 18.4, 16.7, 16.7, 16.5, 16.2, 14.3. **IR(neat)** 3248, 2954, 2927, 2867, 1744, 1699, 1385, 1305, 1178, 1150, 1130, 1008, 894, 838, 752, 675 cm^{-1}. **HRMS** (CI) *m/z*: 298.1835 $[(M-H)^+$; calculated for $C_{15}H_{28}NO_3Si$:298.1838]. **R_F**: 0.15 in 20% EtOAc/Hex. **2-ethyl-4,4-dimethyl-1,1-dipropyl-2,4-dihydro-1*H*,6*H*-[1,2]azasilolo[1,5-*c*]oxazol-6-one (d89b)** was observed in crude NMR (42% yield).



d88c *d89c* *d90c*

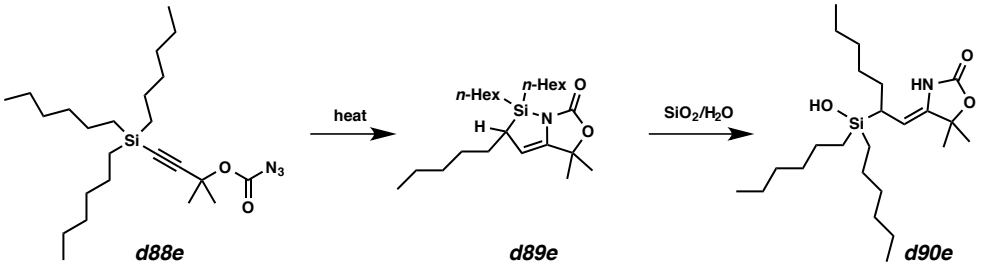
(*Z*)-4-(2-(dibutyl(hydroxy)silyl)pentylidene)-5,5-dimethyloxazolidin-2-one (d90c) was synthesized from carbonazidate **d88c** using General Procedure D1. The crude product was purified by column chromatography on silica gel using a gradient of 15 to 20% EtOAc in hexanes as eluents. The product was obtained as an amorphous yellowish solid. (trial 1: 14.7 mg, 43% yield; trial 2: 14.3 mg, 42% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 4.11 (d, *J* = 10.4 Hz, 1H), 2.65 (s, 1H), 1.56 (td, *J* = 11.1, 2.9 Hz, 1H), 1.48 (s, 6H), 1.43–1.07 (m, 12H), 0.93–0.78 (m, 9H), 0.67–0.48 (m, 4H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 157.6, 139.2, 99.2, 85.0, 31.7, 28.1, 28.0, 27.6, 26.6, 26.6, 25.3, 25.1, 22.6, 13.9, 13.7, 13.7, 13.5, 13.1. **IR(neat)** 3238, 2955, 2923, 2870, 1746, 1699, 1464, 1385, 1307, 1196, 1174, 1132, 1009, 887, 767, 731, 676 cm^{-1}. **HRMS** (ESI) *m/z*: 364.2274 [$(M+Na)^+$; calculated for $C_{18}H_{35}NO_3SiNa$: 364.2278]. **R_F**: 0.2 in 25% EtOAc/Hex. **1,1-dibutyl-4,4-dimethyl-2-propyl-2,4-dihydro-1*H*,6*H*-[1,2]azasilolo[1,5-*c*]oxazol-6-one (d89c)** was observed in crude NMR (56% yield).



d88d *d89d* *d90d*

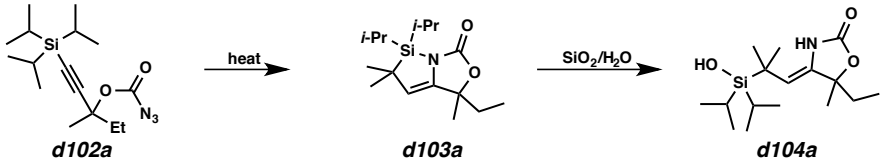
(*Z*)-4-(2-(hydroxydiisobutylsilyl)-3-methylbutylidene)-5,5-dimethyloxazolidin-2-one (d90d) was synthesized from carbonazidate **d88d** using General Procedure D1. The crude

product was purified by column chromatography on silica gel using a gradient of 15 to 20% EtOAc in hexanes as eluents. The product was obtained as an amorphous yellowish solid. (trial 1: 15.0 mg, 44% yield; trial 2: 14.0 mg, 41% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 4.25 (d, *J* = 11.4 Hz, 1H), 2.04–1.91 (m, 1H), 1.91–1.74 (m, 2H), 1.50 (s, 3H), 1.49 (s, 3H), 1.01–0.82 (m, 19H), 0.67–0.49 (m, 4H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 157.7, 140.4, 95.7, 85.0, 36.0, 28.4, 28.0, 28.0, 26.6, 26.5, 26.4, 26.3, 26.2, 25.8, 24.3, 24.2, 23.6, 20.4. **IR(neat)** 3241, 2952, 2866, 1743, 1697, 1464, 1384, 1316, 1218, 1184, 1089, 1009, 822, 797, 757, 744, 674 cm^{-1}. **HRMS** (ESI) *m/z*: 364.2282 [$(M+Na)^+$; calculated for $C_{18}H_{35}NO_3SiNa$: 364.2278]. **R_F**: 0.2 in 25% EtOAc/Hex. **1,1-diisobutyl-2-isopropyl-4,4-dimethyl-2,4-dihydro-1*H*,6*H*-[1,2]azasilolo[1,5-*c*]oxazol-6-one (d89d)** was observed in crude NMR (55% yield).



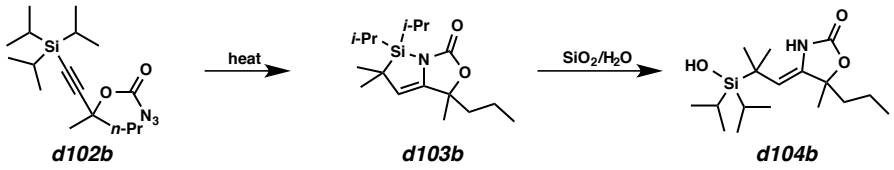
(*Z*)-4-(2-(dihexyl(hydroxy)silyl)heptylidene)-5,5-dimethyloxazolidin-2-one (d90e) was synthesized from carbonazidate **d88e** using General Procedure D1. The crude product was purified by column chromatography on silica gel using a gradient of 10 to 15% EtOAc in hexanes as eluents. The product was obtained as an amorphous yellowish solid. (trial 1: 18.7 mg, 44% yield; trial 2: 19.1 mg, 45% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.58 (s, 1H), 4.11 (d, *J* = 10.6 Hz, 1H), 2.65 (s, 1H), 1.59–1.42 (m, 8H), 1.42–1.05 (m, 23H), 0.94–0.76 (m, 9H), 0.65–0.46 (m, 4H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ

157.6, 139.2, 99.3, 85.0, 33.4, 33.3, 31.6, 31.5, 31.5, 29.4, 29.2, 28.1, 28.0, 27.8, 23.1, 22.8, 22.6, 22.6, 22.6, 14.1, 14.1, 14.1, 13.9, 13.4. **IR(neat)** 3397, 3096, 2957, 2919, 2871, 2852, 1744, 1704, 1461, 1382, 1366, 1328, 1209, 1167, 1031, 1006, 953, 895, 845, 764, 722, 676 cm^{-1}. **HRMS** (ESI) *m/z*: 448.3221 $[(M+Na)^+$; calculated for $C_{24}H_{47}NO_3SiNa$: 448.3217]. $\mathbf{R_F}$: 0.15 in 10% EtOAc/Hex. **1,1-dihexyl-4,4-dimethyl-2-pentyl-2,4-dihydro-1*H*,6*H*-[1,2]azasilolo[1,5-*c*]oxazol-6-one (d89e)** was observed in crude NMR (56% yield).

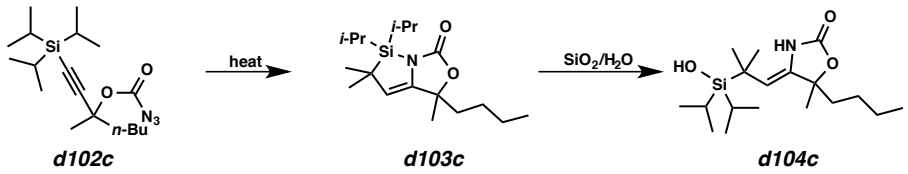


(*Z*)-5-ethyl-4-(2-(hydroxydiisopropylsilyl)-2-methylpropylidene)-5-methyloxazolidin-2-one (d104a) was synthesized from carbonazidate **d102a** using General Procedure D1. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as an amorphous yellowish solid. (trial 1: 16.3 mg, 52% yield; trial 2: 15.9 mg, 51% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.19 (s, 1H), 4.28 (s, 1H), 4.17 (s, 1H), 1.76 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.59 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.41 (s, 3H), 1.14 (d, *J* = 6.2 Hz, 6H), 1.11–0.99 (m, 14H), 0.89 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 157.6, 137.7, 108.1, 87.7, 33.9, 26.7, 26.0, 25.3, 24.0, 18.4, 18.4, 18.4, 18.3, 13.4, 13.4, 7.3. **IR(neat)** 3350, 2969, 2943, 2866, 1736, 1717, 1687, 1462, 1331, 1281, 1248, 1143, 1099, 1033, 1004, 957, 904, 882, 824, 673 cm^{-1}. **HRMS** (ESI) *m/z*: 336.1970 $[(M+Na)^+$; calculated for $C_{16}H_{31}NO_3SiNa$: 336.1965]. $\mathbf{R_F}$: 0.3 in 20% EtOAc/Hex. **4-ethyl-1,1-diisopropyl-**

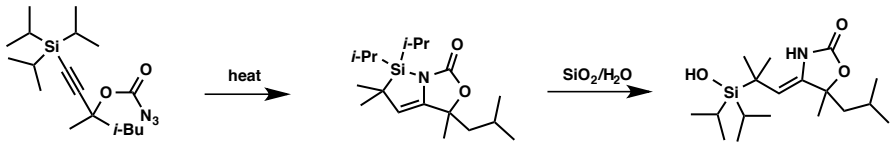
2,2,4-trimethyl-2,4-dihydro-1*H*,6*H*-[1,2]azasilolo[1,5-*c*]oxazol-6-one (d103a) was observed in crude NMR (57% yield).



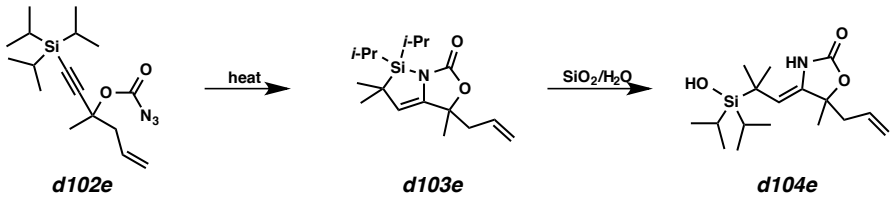
(*Z*)-4-(2-(hydroxydiisopropylsilyl)-2-methylpropylidene)-5-methyl-5-propyloxazolidin-2-one (d104b) was synthesized from carbonazidate **d102b** using General Procedure D1. The crude product was purified by column chromatography on silica gel using a gradient of 10 to 15% EtOAc in hexanes as eluents. The product was obtained as an amorphous yellowish solid. (trial 1: 17.3 mg, 53% yield; trial 2: 17.7 mg, 54% yield;). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.17 (s, 1H), 4.31 (s, 1H), 4.17 (s, 1H), 1.77–1.61 (m, 1H), 1.58–1.46 (m, 1H), 1.40 (s, 3H), 1.39–1.29 (m, 2H), 1.13 (d, *J* = 2.4 Hz, 6H), 1.10–1.01 (m, 14H), 0.88 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 157.5, 138.1, 108.1, 87.4, 43.3, 26.9, 26.0, 25.3, 24.0, 18.4, 18.4, 18.3, 16.3, 14.0, 13.5. **IR(neat)** 3207, 2941, 2863, 1747, 1687, 1463, 1366, 1332, 1291, 1231, 1146, 1078, 1006, 915, 880, 861, 837, 707, 666 cm^{-1}. **HRMS** (ESI) *m/z*: 350.2126 [$(M+Na)^+$; calculated for $C_{17}H_{33}NO_3SiNa$: 350.2122]. **R_F**: 0.27 in 20% EtOAc/Hex. **1,1-diisopropyl-2,2,4-trimethyl-4-propyl-2,4-dihydro-1*H*,6*H*-[1,2]azasilolo[1,5-*c*]oxazol-6-one (d103b)** was observed in crude NMR (55% yield).



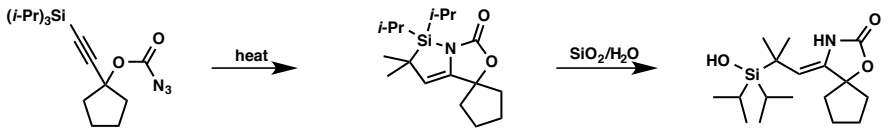
(*Z*)-5-butyl-4-(2-(hydroxydiisopropylsilyl)-2-methylpropylidene)-5-methyloxazolidin-2-one (d104c) was synthesized from carbonazidate **d102c** using General Procedure D1. The crude product was purified by column chromatography on silica gel using a gradient of 10 to 15% EtOAc in hexanes as eluents. The product was obtained as a yellowish oil. (trial 1: 20.2 mg, 59% yield; trial 2: 20.1 mg, 59 % yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.29 (s, 1H), 4.64 (s, 1H), 4.18 (s, 1H), 1.80–1.65 (m, 1H), 1.59–1.48 (m, 1H), 1.40 (s, 3H), 1.36–1.21 (m, 4H), 1.13 (d, *J* = 3.7 Hz, 6H), 1.09–1.03 (m, 14H), 0.85 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 157.7, 138.1, 108.2, 87.7, 40.8, 27.1, 25.9, 25.4, 25.1, 24.0, 22.6, 18.4, 18.4, 18.4, 18.3, 13.9, 13.5, 13.4. **IR(neat)** 3221, 2942, 2865, 1742, 1689, 1464, 1330, 1288, 1144, 1005, 961, 915, 829, 767, 731, 672 cm^{-1}. **HRMS** (ESI) *m/z*: 364.2282 [$(M+Na)^+$; calculated for $C_{18}H_{35}NO_3SiNa$: 364.2278]. **R_F**: 0.3 in 20% EtOAc/Hex. **4-butyl-1,1-diisopropyl-2,2,4-trimethyl-2,4-dihydro-1*H*,6*H*-[1,2]azasilolo[1,5-*c*]oxazol-6-one (d103c)** was observed in crude NMR (60% yield).



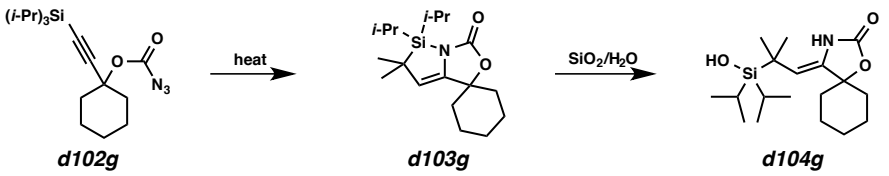
(*Z*)-4-(2-(hydroxydiisopropylsilyl)-2-methylpropylidene)-5-isobutyl-5-methyloxazolidin-2-one (d104d) was synthesized from carbonazidate **d102d** using General Procedure D1. The crude product was purified by column chromatography on silica gel using a gradient of 10 to 15% EtOAc in hexanes as eluents. The product was obtained as a yellowish oil. (trial 1: 14.8 mg, 43% yield; trial 2: 15.4 mg, 45 % yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 4.46 (s, 1H), 4.16 (s, 1H), 1.85–1.72 (m, *J* = 6.5 Hz, 1H), 1.65 (dd, *J* = 14.7, 6.5 Hz, 1H), 1.52 (dd, *J* = 14.8, 5.6 Hz, 1H), 1.40 (s, 3H), 1.14 (d, *J* = 5.6 Hz, 6H), 1.10–0.98 (m, 14H), 0.91 (t, *J* = 6.6 Hz, 6H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 157.5, 138.6, 108.3, 87.8, 49.2, 27.7, 26.1, 25.1, 24.3, 24.3, 24.3, 24.0, 24.0, 18.5, 18.4, 18.4, 18.3, 13.4. **IR(neat)** 3221, 2947, 2866, 1742, 1689, 1464, 1376, 1314, 150, 1007, 915, 880, 829, 792, 767, 731, 672 cm^{-1}. **HRMS** (ESI) *m/z*: 364.2282 [$(M+Na)^+$; calculated for $C_{18}H_{35}NO_3SiNa$: 364.2278]. **R_F**: 0.24 in 20% EtOAc/Hex. **4-isobutyl-1,1-diisopropyl-2,2,4-trimethyl-2,4-dihydro-1*H*,6*H*-[1,2]azasilolo[1,5-*c*]oxazol-6-one (s103d)** was observed in crude NMR (49% yield).



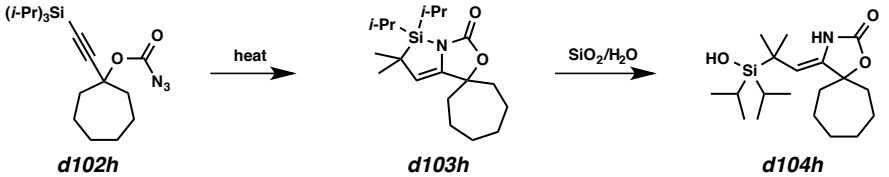
(*Z*)-5-allyl-4-(2-(hydroxydiisopropylsilyl)-2-methylpropylidene)-5-methyloxazolidin-2-one (d102e) was synthesized from carbonazidate **d104e** using General Procedure D1. The crude product was purified by column chromatography on silica gel using a gradient of 10 to 15% EtOAc in hexanes as eluents. The product was obtained as a yellowish oil. (trial 1: 16.3 mg, 50% yield; trial 2: 16.1 mg, 49 % yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.20 (s, 1H), 5.89–5.56 (m, 1H), 5.14–5.12 (m, 1H), 5.11 (d, *J* = 4.4 Hz, 1H), 4.32 (s, 1H), 4.22 (s, 1H), 2.43 (dd, *J* = 14.3, 7.7 Hz, 1H), 2.36 (dd, *J* = 14.2, 6.5 Hz, 1H), 1.42 (s, 3H), 1.13 (s, 6H), 1.10–1.00 (m, 14H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.3, 137.6, 131.1, 119.8, 108.7, 86.3, 45.4, 26.3, 26.0, 25.4, 24.1, 18.4, 18.4, 18.3, 13.4, 13.4. **IR(neat)** 3235, 2944, 2865, 1744, 1690, 1463, 1374, 1329, 1239, 1099, 1046, 1003, 918, 880, 829, 765, 672 cm^{-1}. **HRMS** (ESI) *m/z*: 348.1975 [$(M+Na)^+$; calculated for $C_{17}H_{31}NO_3Si$: 348.1965]. **R_F**: 0.15 in 15% EtOAc/Hex. **4-allyl-1,1-diisopropyl-2,2,4-trimethyl-2,4-dihydro-1*H*,6*H*-[1,2]azasilolo[1,5-*c*]oxazol-6-one (d103e)** was observed in crude NMR (52% yield).



(*Z*)-4-(2-(hydroxydiisopropylsilyl)-2-methylpropylidene)-1-oxa-3-azaspiro[4.4]nonan-2-one (d104f) was synthesized from carbonazidate **d102f** using General Procedure D1. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as an amorphous yellowish solid. (trial 1: 16.6 mg, 51% yield; trial 2: 14.6 mg, 45% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.30 (s, 1H), 4.76 (s, 1H), 4.26 (s, 1H), 2.17–2.03 (m, 2H), 1.92–1.66 (m, 6H), 1.13 (s, 6H), 1.09–1.01 (m, 14H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 157.4, 137.7, 107.9, 95.1, 41.1, 41.1, 25.6, 25.6, 24.2, 24.2, 24.0, 18.4, 18.4, 18.4, 18.4, 13.4, 13.4. **IR(neat)** 3350, 2941, 2864, 1746, 1692, 1464, 1432, 1340, 1311, 1247, 1080, 991, 880, 791, 765, 674 cm^{-1}. **HRMS** (ESI) *m/z*: 348.1970 [$(M+Na)^+$; calculated for $C_{17}H_{31}NO_3SiNa$: 348.1965]. **R_F**: 0.2 in 20% EtOAc/Hex. **1',1'-diisopropyl-2',2'-dimethyl-1',2'-dihydro-6'*H*-spiro[cyclopentane-1,4'-[1,2]azasilolo[1,5-*c*]oxazol]-6'-one (d103f)** was observed in crude NMR (52% yield).

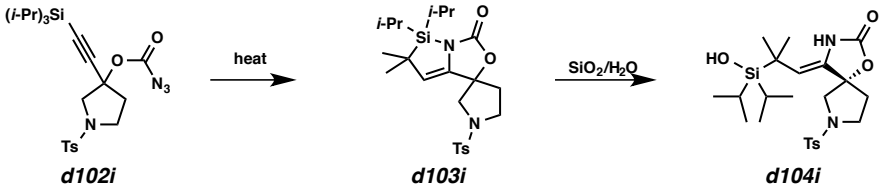


(*Z*)-4-(2-(hydroxydiisopropylsilyl)-2-methylpropylidene)-1-oxa-3-azaspiro[4.5]decan-2-one (d104g) was synthesized from carbonazidate **d102g** using General Procedure D1. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a yellowish solid. (trial 1: 16.9 mg, 50% yield; trial 2: 16.2 mg, 48% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 4.44 (s, 1H), 4.20 (s, 1H), 1.94–1.81 (m, 2H), 1.78–1.54 (m, 6H), 1.53–1.33 (m, 2H), 1.12 (s, 6H), 1.09–0.90 (m, 14H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 157.6, 139.3, 108.3, 86.8, 37.1, 37.1, 25.7, 25.7, 24.7, 23.9, 21.7, 21.7, 18.4, 18.4, 13.4, 13.4. **IR(neat)** 3195, 2931, 2866, 1754, 1690, 1463, 1421, 1306, 1148, 1005, 945, 885, 867, 727, 699, 662 cm^{-1}. **HRMS** (ESI) *m/z*: 362.2127 [$(M+Na)^+$; calculated for $C_{18}H_{33}NO_3SiNa$: 362.2122]. **R_F**: 0.24 in 20% EtOAc/Hex. **MP**: 123-125 °C. **1',1'-diisopropyl-2',2'-dimethyl-1',2'-dihydro-6'*H*-spiro[cyclohexane-1,4'-[1,2]azasilolo[1,5-*c*]oxazol]-6'-one (d103g)** was observed in crude NMR (51% yield).



(*Z*)-4-(2-(hydroxydiisopropylsilyl)-2-methylpropylidene)-1-oxa-3-azaspiro[4.6]undecan-2-one (d104h) was synthesized from carbonazidate **d102h** using General Procedure D1. The crude product was purified by column chromatography on

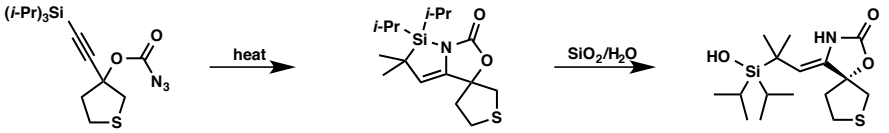
silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as an amorphous white solid. (trial 1: 16.5 mg, 47% yield; trial 2: 16.2 mg, 46% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.20 (s, 1H), 4.61 (s, 1H), 4.25 (s, 1H), 2.05–1.92 (m, 2H), 1.83–1.59 (m, 6H), 1.59–1.45 (m, 4H), 1.12 (s, 6H), 1.09–0.89 (m, 14H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 157.6, 140.9, 108.1, 90.1, 40.8, 28.8, 25.7, 21.9, 18.4, 18.4, 13.5. **IR(neat)** 3282, 2924, 2861, 1740, 1683, 1455, 1444, 1368, 1276, 1143, 1086, 1058, 1003, 952, 869, 849, 821, 786, 663 cm^{-1}. **HRMS** (ESI) *m/z*: 376.2282 $[(M+Na)^+$; calculated for $C_{19}H_{35}NO_3SiNa$: 376.2278]. **R_F**: 0.27 in 20% EtOAc/Hex. **1',1'-diisopropyl-2',2'-dimethyl-1',2'-dihydro-6'*H*-spiro[cycloheptane-1,4'-[1,2]azasilolo[1,5-*c*]oxazol]-6'-one (d103h)** was observed in crude NMR (56% yield).



d102i *d103i* *d104i*

(*Z*)-4-(2-(hydroxydiisopropylsilyl)-2-methylpropylidene)-7-tosyl-1-oxa-3,7-diazaspiro[4.4]nonan-2-one (d104i) was synthesized from carbonazidate **d102i** using General Procedure D2. The crude product was purified by column chromatography on silica gel using 25% EtOAc in hexanes as an eluent. The product was obtained as a white solid. (trial 1: 23.5 mg, 49% yield; trial 2: 23.0 mg, 48% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.31 (s, 1H), 3.74–3.66 (m, 1H), 3.50 (q, *J* = 12.1 Hz, 2H), 3.36 (s, 1H), 3.23 (ddd, *J* = 11.2, 9.6, 6.1 Hz, 1H), 2.42 (s, 3H), 2.16 (dd, *J* = 13.6, 5.9 Hz, 1H), 2.04–1.89 (m, 1H), 1.11 (s, 6H), 1.09–0.86 (m, 14H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 155.6, 144.0, 133.4, 133.3,

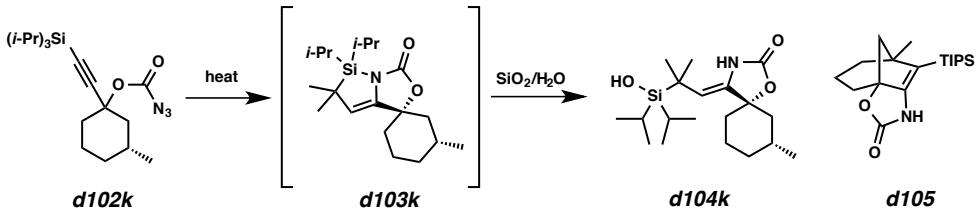
129.9, 127.6, 110.3, 90.4, 59.5, 47.2, 39.8, 25.4, 25.2, 24.2, 21.6, 18.4, 18.4, 18.3, 18.3, 13.2, 13.2. **IR(neat)** 2943, 2865, 1747, 1699, 1597, 1494, 1462, 1360, 1342, 1239, 1167, 1149, 1039, 1017, 993, 949, 910, 815, 732, 764, 706, 660 cm^{-1}. **HRMS** (ESI) *m/z*: 503.2011 [$(M+Na)^+$; calculated for $C_{23}H_{36}N_2O_5SSiNa$: 503.2006]. $\mathbf{R_F}$: 0.24 in 30% EtOAc/Hex. **MP**: 150-152 °C. **1',1'-diisopropyl-2',2'-dimethyl-1-tosyl-1',2'-dihydro-6'*H*-spiro[pyrrolidine-3,4'-[1,2]azasilolo[1,5-*c*]oxazol]-6'-one (d103i)** was observed in crude NMR (50% yield).



d102j *d103j* *d104j*

(*Z*)-4-(2-(hydroxydiisopropylsilyl)-2-methylpropylidene)-1-oxa-7-thia-3-azaspiro[4.4]nonan-2-one (d104j) was synthesized from carbonazidate **d102j** using General Procedure D2. The crude product was purified by column chromatography on silica gel using 25% EtOAc in hexanes as an eluent. The product was obtained as an amorphous white solid. (trial 1: 14.5 mg, 42% yield; trial 2: 14.0 mg, 41% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.36 (s, 1H), 4.48 (s, 1H), 4.45 (s, 1H), 3.16 (d, *J* = 12.1 Hz, 1H), 3.13–3.04 (m, 1H), 3.00 (d, *J* = 12.3 Hz, 1H), 2.98–2.92 (m, 1H), 2.44–2.36 (m, 1H), 2.06–1.95 (m, 1H), 1.14 (s, 6H), 1.10–0.99 (m, 14H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 156.6, 133.7, 109.9, 94.3, 43.2, 42.6, 29.3, 25.5, 25.4, 24.3, 18.4, 18.3, 13.3. **IR(neat)** 3391, 2945, 2864, 1749, 1690, 1623, 1462, 1385, 1371, 1334, 1297, 1278, 1246, 1067, 992, 881, 824, 755, 666 cm^{-1}. **HRMS** (ESI) *m/z*: 366.1534 [$(M+Na)^+$; calculated for $C_{16}H_{29}NO_3SSiNa$: 366.1530]. $\mathbf{R_F}$: 0.21 in 20% EtOAc/Hex. **1',1'-**

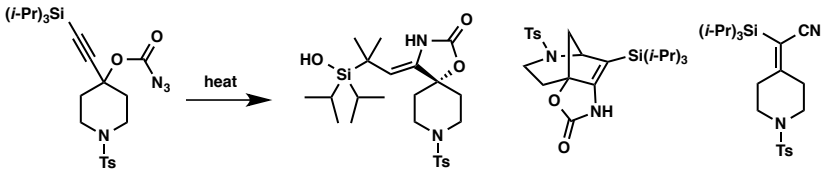
diisopropyl-2',2'-dimethyl-1',2',4,5-tetrahydro-2*H*,6'*H*-spiro[thiophene-3,4'-[1,2]azasilolo[1,5-*c*]oxazol]-6'-one (d103j) was observed in crude NMR (45% yield).



d102k *d103k* *d104k* *d105*

(5*S*,7*R*,*Z*)-4-(2-(hydroxydiisopropylsilyl)-2-methylpropylidene)-7-methyl-1-oxa-3-azaspiro[4.5]decan-2-one (d104k) was synthesized from carbonazidate **d102k** using General Procedure D1. The crude product was purified by column chromatography on silica gel using a gradient of 5 to 10% EtOAc in hexanes as eluents. The product was obtained as an amorphous yellowish solid. (trial 1: 12.4 mg, 35% yield; trial 2: 12.3 mg, 35% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 4.60 (s, 1H), 4.43 (s, 1H), 2.00–1.41 (m, 9H), 1.14 (s, 6H), 1.05 (s, 14H), 0.98 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 157.4, 139.3, 109.8, 86.7, 43.4, 36.2, 32.0, 28.0, 25.8, 25.7, 24.2, 21.4, 19.8, 18.4, 18.4, 18.4, 18.3, 13.5, 13.5. **IR(neat)** 3088, 2926, 2863, 1745, 1678, 1463, 1367, 1323, 1286, 1250, 1206, 1155, 1134, 1058, 972, 935, 921, 826, 791, 668 cm^{-1}. **HRMS** (ESI) *m/z*: 376.2283 [$(M+Na)^+$; calculated for $C_{19}H_{35}NO_3SiNa$: 376.2278]. **R_F**: 0.18 in 15% EtOAc/Hex. **(1*S*,3*R*)-1',1'-diisopropyl-2',2',3-trimethyl-1',2'-dihydro-6'*H*-spiro[cyclohexane-1,4'-[1,2]azasilolo[1,5-*c*]oxazol]-6'-one (d103k)** was observed in crude NMR (36% yield).

(5*S*,8a*S*)-5-methyl-4-(triisopropylsilyl)-5,6,7,8-tetrahydro-5,8a-methanocyclohepta[*d*]oxazol-2(3*H*)-one (d105) was synthesized from carbonazidate **d102k** using General Procedure D1. The crude product was purified by column chromatography on silica gel using a gradient of 5 to 10% EtOAc in hexanes as eluents. The product was obtained as a white solid. (trial 1: 11.3 mg, 34% yield; trial 2: 11.8 mg, 35% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.66 (s, 1H), 2.15–2.01 (m, 1H), 1.86–1.68 (m, 3H), 1.65 (d, *J* = 9.1 Hz, 1H), 1.62–1.52 (m, 1H), 1.43 (d, 1H), 1.32–1.19 (m, 4H), 1.19–0.94 (m, 21H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 158.9, 152.4, 106.1, 92.7, 57.7, 53.7, 32.6, 28.8, 27.8, 20.8, 19.1, 19.1, 19.1, 19.1, 19.1, 17.7, 12.5, 12.5, 12.2. **IR(neat)** 3230, 2938, 2864, 1756, 1629, 1465, 1321, 1277, 1229, 1008, 976, 944, 881, 846, 745, 712, 665 cm^{-1}. **HRMS** (ESI) *m/z*: 358.2177 [$(M+Na)^+$; calculated for $C_{19}H_{33}NO_2SiNa$: 358.2173]. **R_F**: 0.39 in 15% EtOAc/Hex. **MP** 120-122 °C



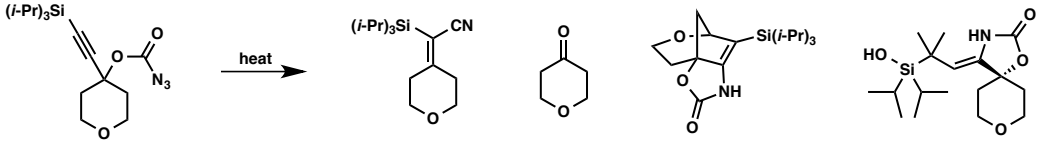
d102l *d104l* *d106* *d106-a*

(*Z*)-4-(2-(hydroxydiisopropylsilyl)-2-methylpropylidene)-8-tosyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one (d104l) was synthesized from carbonazidate **d102l** using General Procedure D2. The crude product was purified by column chromatography on silica gel using a gradient of 10 to 20% EtOAc in hexanes as eluents. The product was obtained as a white solid. (trial 1: 25.7 mg, 52% yield; trial 2: 26.2 mg, 53% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 7.9 Hz,

2H), 4.25 (s, 1H), 3.84–3.67 (m, 3H), 3.35 (t, *J* = 6.1 Hz, 1H), 2.59–2.47 (m, 3H), 2.43 (s, 3H), 1.90–1.82 (m, 2H), 1.11 (s, 6H), 1.06–0.92 (m, 14H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 156.4, 143.9, 136.9, 132.7, 129.9, 127.6, 109.6, 82.9, 45.9, 42.34, 40.6, 36.1, 25.4, 24.0, 21.5, 18.4, 13.3. **IR(neat)** 3335, 2946, 2867, 1745, 1698, 1595, 1464, 1376, 1314, 1259, 1180, 1085, 1003, 944, 932, 913, 894, 877, 765, 742, 721, 675 cm^{-1}. **HRMS** (ESI) *m/z*: 517.2167 [$(M+Na)^+$; calculated for $C_{24}H_{38}N_2O_5SSiNa$: 517.2163]. **R_F**: 0.24 in 30% EtOAc/Hex. **MP**: 201-202 °C.

(5*S*,8a*S*)-6-tosyl-4-(triisopropylsilyl)-5,6,7,8-tetrahydro-5,8a-methanooxazolo[4,5-*d*]azepin-2(3*H*)-one (d106) was synthesized from carbonazidate **d102l** using General Procedure D2. The crude product was purified by column chromatography on silica gel using a gradient of 10 to 20% EtOAc in hexanes as eluents. The product was obtained as a white solid. (trial 1: 9.5 mg, 20% yield; trial 2: 10.0 mg, 21% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.16 (s, 1H), 5.07 (d, *J* = 4.0 Hz, 1H), 3.91 (dd, *J* = 14.7, 6.8 Hz, 1H), 3.47 (ddd, *J* = 14.7, 11.9, 5.4 Hz, 1H), 2.42 (s, 3H), 2.09–2.02 (m, 1H), 1.97–1.86 (m, 1H), 1.65 (d, *J* = 9.7 Hz, 1H), 1.62–1.53 (m, 2H), 1.18–0.93 (m, 21H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 158.1, 156.3, 143.6, 137.5, 129.9, 127.1, 100.5, 91.6, 65.3, 48.2, 40.9, 30.8, 21.6, 18.5, 11.5. **IR(neat)** 3206, 2942, 2863, 1770, 1655, 1597, 1459, 1339, 1297, 1223, 1207, 1165, 1153, 1094, 1009, 959, 926, 902, 767, 729, 706, 661 cm^{-1}. **HRMS** (ESI) *m/z*: 499.2060 [$(M+Na)^+$; calculated for $C_{24}H_{36}N_2O_4SSiNa$: 499.2057]. **R_F**: 0.42 in 30% EtOAc/Hex. **MP**: 199-200 °C.

2-(1-tosylpiperidin-4-ylidene)-2-(triisopropylsilyl)acetonitrile (d106-a) was synthesized from carbonazidate **d102l** using General Procedure D2. The crude product was purified by column chromatography on silica gel using a gradient of 10 to 20% EtOAc in hexanes as an eluent. The product was obtained as a white solid. (trial 1: 4.3 mg, 10% yield; trial 2: 4.8 mg, 11% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 3.15 (t, *J* = 5.9 Hz, 2H), 3.11 (t, *J* = 5.7 Hz, 2H), 2.86 (t, *J* = 5.9 Hz, 2H), 2.51 (t, *J* = 5.9 Hz, 2H), 2.42 (s, 3H), 1.37–1.24 (m, 3H), 1.11–0.90 (m, 18H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 170.4, 144.0, 133.2, 129.8, 127.5, 119.9, 106.3, 46.8, 46.5, 35.9, 34.4, 21.6, 18.5, 12.6. **IR(neat)** 2946, 2863, 2190, 1766, 1656, 1596, 1494, 1357, 1227, 1162, 1101, 1072, 954, 935, 903, 815, 800, 732, 712, 701, 676 cm^{-1}. **HRMS** (ESI) *m/z*: 455.2165 [$(M+Na)^+$; calculated for $C_{23}H_{36}N_2O_2SSiNa$: 455.2159]. **R_F**: 0.6 in 30% EtOAc/Hex. **MP**: 96-98 °C.



d40 *d34* *d35* *d33* *d41*

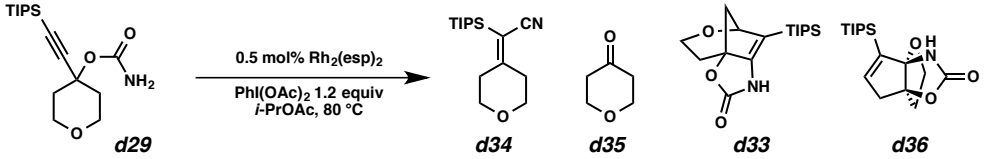
2-(tetrahydro-4*H*-pyran-4-ylidene)-2-(triisopropylsilyl)acetonitrile (d34) was synthesized from carbonazidate **d40** using General Procedure D2. The crude product was purified by column chromatography on silica gel using a gradient of 5 to 20% EtOAc in hexanes as an eluent. The product was obtained as a white solid. (trial 1: 1.4 mg, 5% yield; trial 2: 1.3 mg, 4% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.80 (t, *J* = 5.7 Hz, 2H), 3.74 (t, *J* = 5.7 Hz, 2H), 2.82 (t, *J* = 5.7 Hz, 2H), 2.47 (t, *J* = 5.7 Hz, 2H), 1.41–1.31 (m, 3H), 1.11 (m, 18H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 172.4, 120.5, 104.2, 69.0, 68.5,

38.0, 36.6, 18.7, 13.0. **IR(neat)** 2941, 2889, 2863, 2846, 2195, 1756, 1574, 1459, 1430, 1374, 1318, 1288, 1222, 1264, 1172, 1021, 916, 882, 872, 709, 678 cm^{-1}. **HRMS** (CI) *m/z*: 280.2095 [$(M+H)^+$; calculated for $C_{16}H_{30}NOSi$: 280.2097]. $\mathbf{R_F}$: 0.51 in 20% EtOAc/Hex. **MP** 53-55 °C.

(*Z*)-4-(2-(hydroxydiisopropylsilyl)-2-methylpropylidene)-1,8-dioxa-3-azaspiro[4.5]decan-2-one (d41) was synthesized from carbonazidate **d40** using General Procedure D2. The crude product was purified by column chromatography on silica gel using a gradient of 5 to 20% EtOAc in hexanes as eluents. The product was obtained as a white solid. (trial 1: 15.6 mg, 46% yield; trial 2: 14.0 mg, 41% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.10 (s, 1H), 4.28 (s, 1H), 3.99 (s, 1H), 3.93–3.82 (m, 2H), 3.75 (ddd, *J* = 11.8, 11.9, 2.3 Hz, 2H), 1.91–1.65 (m, 4H), 1.14 (s, 6H), 1.05 (s, 14H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 156.8, 137.8, 109.2, 83.5, 63.8, 37.1, 25.6, 24.0, 18.4, 13.4. **IR(neat)** 3280, 3064, 2951, 2968, 2858, 1748, 1701, 1427, 1385, 1301, 1255, 1244, 1125, 1100, 1021, 1005, 947, 895, 843, 822, 778, 728, 677 cm^{-1}. **HRMS** (ESI) *m/z*: 364.1918 [$(M+Na)^+$; calculated for $C_{17}H_{31}NO_4SiNa$: 364.1915]. $\mathbf{R_F}$: 0.18 in 20% EtOAc/Hex. **MP**: 76-78 °C.

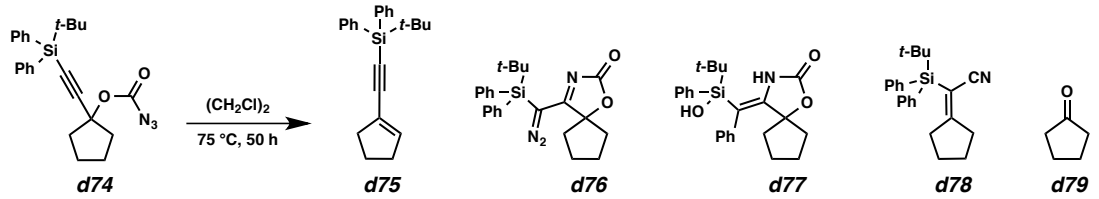
(5*S*,8a*S*)-4-(triisopropylsilyl)-3,5,7,8-tetrahydro-2*H*-5,8a-methanooxepino[4,5-*d*]oxazol-2-one (d33) was synthesized from carbonazidate **d40** using General Procedure D2. The crude product was purified by column chromatography on silica gel using a gradient of 5 to 20% EtOAc in hexanes as eluents. The product was obtained as a white solid. (trial 1: 9.1 mg, 28% yield; trial 2: 10.1 mg, 31% yield). **^{1}H NMR** (500 MHz,

$CDCl_3$) δ 7.06 (s, 1H), 4.98 (d, *J* = 2.9 Hz, 1H), 4.09–4.01 (m, 1H), 3.88 (dd, *J* = 10.9, 6.9 Hz, 1H), 2.34–2.26 (m, 2H), 2.18 (d, *J* = 9.2 Hz, 1H), 1.69–1.63 (m, 1H), 1.19–1.10 (m, 3H), 1.09–1.04 (m, 18H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 158.6, 156.5, 98.2, 91.9, 84.9, 60.6, 52.3, 32.6, 31.1, 18.8, 18.6, 11.8. **IR(neat)** 3204, 2942, 2864, 1752, 1690, 1651, 1337, 1316, 1248, 1219, 162, 1297, 1100, 1069, 1040, 968, 940, 914, 881, 855, 729, 700 cm^{-1}. **HRMS** (ESI) *m/z*: 346.1814 [$(M+Na)^+$; calculated for $C_{17}H_{29}NO_3SiNa$: 346.1809]. **R_F**: 0.39 in 20% EtOAc/Hex. **MP**: 95-97 °C.

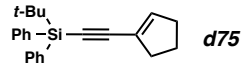


A 2 dram vial was charged with magnetic stir bar, alkynyl carbamate **d29** (65 mg, 0.2 mmol, 1.0 equiv), $PhI(OAc)_2$ (77.3 mg, 0.24 mmol, 1.2 equiv) and $Rh_2(esp)_2$ (0.8 mg, 0.0001 mmol, 0.5 mol%). Isopropyl acetate (2 mL, 0.1M) was added and the vial was sealed. The reaction mixture was heated at 80 ˚C for 21 hours. When cooled to room temperature, solvents were removed via rotary evaporation and the residue was purified by flash column chromatography on silica gel using a gradient of 5 to 20% EtOAc in hexanes as eluents. **2-(tetrahydro-4*H*-pyran-4-ylidene)-2-(triisopropylsilyl)acetonitrile (d34)** was obtained as a white solid. (9 mg, 16% yield). **(5*S*,8a*S*)-4-(triisopropylsilyl)-3,5,7,8-tetrahydro-2*H*-5,8a-methanooxepino[4,5-*d*]oxazol-2-one (d33)** was obtained as a white solid. (8 mg, 12% yield).

(3a*R*,6a*R*)-6-(triisopropylsilyl)-2,3-dihydro-4*H*-3a,6a-(epoxymethanoimino)cyclopenta[*b*]furan-8-one (d36) was obtained as a white solid. (17 mg, 27% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.02 (t, *J* = 2.3 Hz, 1H), 5.54 (s, 1H), 4.10–4.05 (m, 1H), 3.98-3.91 (m, 1H), 2.97–2.80 (m, 2H), 2.52–2.45 (m, 1H), 1.98–1.88 (m, 1H), 1.19–1.01 (m, 21H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 157.8, 144.2, 139.8, 112.1, 97.4, 67.4, 45.1, 38.9, 18.8, 18.7, 18.7, 11.4. **IR(neat)** 3258, 2941, 2864, 1745, 1651, 1574, 1462, 1383, 1335, 1274, 1298, 1066, 1144, 999, 985, 959, 937, 922, 880, 818, 766, 710, 679 cm^{-1}. **HRMS** (ESI) *m/z*: 346.1814 [$(M+Na)^+$; calculated for $C_{17}H_{29}NO_3SiNa$: 346.1809]. **R_F**: 0.3 in 20% EtOAc/Hex. **MP**: 95-97 °C.

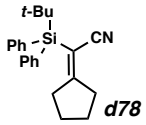


A 2 dram vial was charged with a magnetic spin bar, carbonazidate **d74** (0.3 mmol), and distilled 1,2-dichloroethane (0.1 M, 3 mL). The reaction vessel was sealed and heated in an oil bath at 75 °C. The progress of the reaction was monitored by TLC. After 50 h, the reaction vessel was cooled to room temperature and the mixture was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using a gradient of 2 to 20% EtOAc in hexanes as eluents.



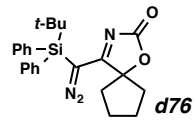
d75

***tert*-butyl(cyclopent-1-en-1-ylethynyl)diphenylsilane (d75)** was obtained as a colorless oil. (19.8 mg, 20% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.85-7.75 (m, 4H), 7.44–7.31 (m, 6H), 6.26–6.20 (m, 1H), 2.62–2.51 (m, 2H), 2.50–2.40 (m, 2H), 2.03–1.88 (m, 2H), 1.08 (s, 9H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 139.9, 135.6, 133.6, 129.4, 127.6, 124.7, 106.7, 90.3, 36.4, 33.4, 27.1, 23.3, 18.6. **IR(neat)** 3069, 2956, 2928, 2891, 2855, 2143, 1470, 1427, 1389, 1360, 1259, 1157, 1107, 1008, 998, 875, 819, 741, 724, 697 cm^{-1}. **HRMS** (CI) *m/z*: 330.1800 [$(M)^+$; calculated for $C_{23}H_{26}Si$: 330.1804]. **R_F**: 0.75 in 10% EtOAc/Hex.



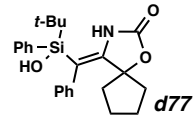
d78

2-(*tert*-butyldiphenylsilyl)-2-cyclopentylideneacetonitrile (d78) was obtained as a white solid. (11.4 mg, 11% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.72–7.66 (m, 4H), 7.45–7.34 (m, 6H), 2.84 (td, *J* = 7.4, 1.7 Hz, 2H), 1.70–1.58 (m, 4H), 1.50–1.39 (m, 2H), 1.12 (s, 9H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 189.7, 135.7, 132.4, 129.7, 128.0, 121.3, 98.4, 38.0, 35.9, 27.1, 26.9, 24.9, 18.7. **IR(neat)** 3048, 2955, 2861, 2194, 1751, 1576, 1450, 1427, 1391, 1362, 1336, 1105, 1011, 997, 941, 821, 742, 700, 686 cm^{-1}. **HRMS** (CI) *m/z*: 346.1995 [$(M+H)^+$; calculated for $C_{23}H_{27}NSi$: 346.1991]. **R_F**: 0.51 in 10% EtOAc/Hex. **MP**: 103-105 °C.



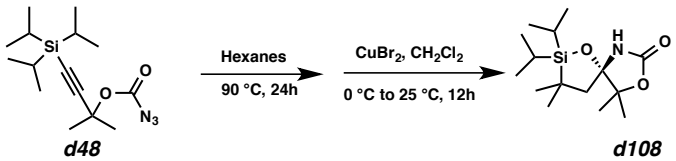
d76

4-((*tert*-butyldiphenylsilyl)(diazo)methyl)-1-oxa-3-azaspiro[4.4]non-3-en-2-one (d76) was obtained as a yellow solid. (18.8 mg, 15% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61–7.55 (m, 4H), 7.49–7.41 (m, 2H), 7.41–7.34 (m, 4H), 2.21–2.06 (m, 4H), 2.06–1.90 (m, 2H), 1.89–1.70 (m, 2H), 1.25 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 195.0, 165.6, 136.5, 135.9, 130.9, 130.4, 128.3, 128.1, 96.6, 37.8, 37.0, 29.0, 27.7, 26.0, 23.4, 19.9. **IR(neat)** 3071, 2955, 2856, 2196, 1579, 1427, 1388, 1359, 1258, 1107, 998, 956, 819, 739, 698 cm^{-1}. **HRMS** (ESI) *m/z*: 440.1767 [$(M+Na)^+$; calculated for $C_{24}H_{27}N_3O_2SiNa$: 440.1765]. **R_F**: 0.21 in 10% EtOAc/Hex. **MP**: 108-109 °C.

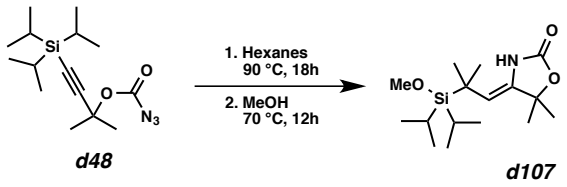


d77

(*Z*)-4-((*tert*-butyl(hydroxy)(phenyl)silyl)(phenyl)methylene)-1-oxa-3-azaspiro[4.4]nonan-2-one (d77) was obtained as a white solid. (12.3 mg, 10% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.46–7.01 (m, 10H), 5.76 (s, 1H), 2.18–1.98 (m, 2H), 1.83–1.72 (m, 1H), 1.72–1.43 (m, 3H), 1.20–1.07 (m, 1H), 0.95 (s, 10H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 157.1, 149.6, 136.8, 134.7, 134.1, 129.5, 127.5, 127.4, 126.5, 107.1, 97.1, 40.7, 38.7, 26.6, 24.2, 20.7. **IR(neat)** 3074, 2949, 2862, 2196, 1980, 1741, 1579, 1428, 1390, 1363, 1262, 1108, 999, 823, 739, 699 cm^{-1}. **HRMS** (ESI) *m/z*: 430.1813 [$(M+Na)^+$; calculated for $C_{24}H_{29}NO_3SiNa$: 430.1809]. **R_F**: 0.15 in 20% EtOAc/Hex. **MP**: 166-168 °C.



(*S*)-2,2-diisopropyl-3,3,9,9-tetramethyl-1,8-dioxa-6-aza-2-silaspiro[4.4]nonan-7-one (d108) A 2 dram vial was charged with a magnetic stir bar, carbonazidate **d48** (0.2 mmol), and dry hexanes (0.1 M, 2 mL). The reaction vessel was sealed and heated in an oil bath at 90 °C. The progress of the reaction was monitored by TLC. After the reaction was finished (24 h), the reaction vessel was cooled to room temperature and the mixture was concentrated under reduced pressure. The crude product was then dissolved in dry dichloromethane (0.1M, 2 mL). The mixture was cooled to 0 °C and stirred for 10 min. $CuBr_2$ (4.5 mg, 0.02 mmol, 0.1 equiv) was added in one portion. The progress of the reaction was monitored by TLC. After 12 h, the reaction mixture was filtered through a short celite pad and concentrated. The crude product was purified by column chromatography on silica gel using a gradient of 10 to 15% EtOAc in hexanes as eluents. Compound **d108** was obtained as a white solid. (trial 1: 29.3 mg, 49% yield; trial 2: 28.7 mg, 48% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.14 (s, 1H), 1.85 (d, J = 14.0 Hz, 1H), 1.71 (d, J = 13.9 Hz, 1H), 1.38 (s, 3H), 1.32 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H), 1.14–0.92 (m, 14H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 158.3, 95.3, 87.9, 48.8, 26.2, 26.2, 24.1, 23.6, 20.6, 17.9, 17.8, 17.6, 17.6, 13.4, 12.4. **IR(neat)** 3255, 2935, 2863, 1746, 1464, 1386, 1370, 1352, 1191, 1105, 1014, 989, 857, 907, 881, 846, 776, 683 cm^{-1}. **HRMS** (ESI) *m/z*: 322.1813 [$(M+Na)^+$; calculated for $C_{15}H_{29}NO_3SiNa$: 322.1809]. **R_F**: 0.15 in 20% EtOAc/Hex. **MP**: 114-116 °C.



(*Z*)-4-(2-(diisopropyl(methoxy)silyl)-2-methylpropylidene)-5,5-dimethyloxazolidin-2-one (d107) A 2 dram vial was charged with a magnetic stir bar, carbonazidate **d48** (0.1 mmol), and dry hexanes (0.1 M, 1 mL). The reaction vessel was sealed and heated in an oil bath at 90 °C. The progress of the reaction was monitored by TLC. After the reaction was finished (18 h), the reaction vessel was cooled to room temperature and the mixture was concentrated under reduced pressure. The crude product was then dissolved in dry methanol (0.1M, 1 mL) in a 2 dram vial. The vial was sealed and the reaction was heated to 70 °C. The progress of the reaction was monitored by TLC. After 12 h, the reaction mixture was cooled and concentrated. The crude product was purified by column chromatography on silica gel using a gradient of 0 to 5% EtOAc in hexanes as eluents. Compound **d107** was obtained as a colorless oil. (16.0 mg, 51% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.37 (s, 1H), 4.15 (s, 1H), 3.59 (s, 3H), 1.41 (s, 6H), 1.23–0.98 (m, 20H). **^{13}C NMR** (150.91 MHz, $CDCl_3$) δ 156.1, 139.6, 107.0, 84.5, 51.8, 28.0, 25.9, 24.5, 18.6, 18.2, 12.8. **IR(neat)** 2945, 2866, 1757, 1688, 1464, 1384, 1297, 1171, 1104, 1067, 1002, 902, 885, 798, 731, 679 cm^{-1}. **HRMS** (ESI) *m/z*: 336.1969 [$(M+Na)^+$; calculated for $C_{16}H_{21}NO_3SiNa$: 336.1965]. $\mathbf{R_F}$: 0.36 in 20% EtOAc/Hex.

4.6.3 Crystallographic Data

Crystal data and structure refinement for compound d76

Empirical formula	$C_{24}H_{27}N_3O_2Si$
Formula weight	417.58 g/mol
Crystallization solvent	Diethyl ether/pentane
Crystal habit	Thick plate
Crystal size	0.35 x 0.30 x 0.08 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker DUO APEX II CCD	
Wavelength	1.54178 Å MoKα	
Data collection temperature	123(2) K	
Unit cell dimensions	a = 13.0101(6) Å	α = 90.00°
	b = 10.7484(5) Å	β = 106.670(1)°
	c = 16.4288(7) Å	γ = 16.4288(7)°
Volume	2200.81(17) $Å_3$	
Z	4	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Density	1.260 mg/m^3	
F(000)	888	
Reflections collected	8098	
Absorption coefficient	1.140	

Crystal data and structure refinement for compound d77

Empirical formula	$C_{24}H_{29}NO_3Si$	
Formula weight	407.57 g/mol	
Crystallization solvent	Ethyl acetate/hexanes	
Crystal habit	Plate	
Crystal size	0.40 x 0.20 x 0.06 mm^3	
Crystal color	Colorless	

Data Collection

Type of diffractometer	Bruker DUO APEX II CCD	
Wavelength	0.71073 Å MoKα	
Data collection temperature	123(2) K	
Unit cell dimensions	a = 8.717(2) Å	α = 108.586(4)°
	b = 9.709(2) Å	β = 101.655(4)°
	c = 14.130(3) Å	γ = 97.748(4)°
Volume	1084.3(4) $Å_3$	
Z	2	
Crystal system	Triclinic	
Space group	P-1	
Density	1.248 mg/m^3	
F(000)	436	
Reflections collected	3371	
Absorption coefficient	0.133	

Crystal data and structure refinement for compound d104g

Empirical formula	$C_{18}H_{33}NO_3Si$
Formula weight	339.54 g/mol
Crystallization solvent	Ethyl acetate/hexanes
Crystal habit	Thin plate
Crystal size	0.4 x 0.3 x 0.08 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker DUO APEX II CCD	
Wavelength	1.54178 Å MoKα	
Data collection temperature	123(2) K	
Unit cell dimensions	a = 9.4673(4) Å	α = 112.855(1)°
	b = 9.5452(3) Å	β = 99.013(1)°
	c = 11.9144(4) Å	γ = 93.323(2)°
Volume	971.51(6) $Å_3$	
Z	2	
Crystal system	Triclinic	
Space group	P-1	
Density	1.161 mg/m^3	
F(000)	372	
Reflections collected	5816	
Absorption coefficient	1.172	

Crystal data and structure refinement for compound d108

Empirical formula	$C_{15}H_{29}NO_3Si$
Formula weight	299.48 g/mol
Crystallization solvent	Diethyl ether/pentane
Crystal habit	Prismatic column
Crystal size	0.45 x 0.2 x 0.10 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker DUO APEX II CCD	
Wavelength	1.54178 Å MoKα	
Data collection temperature	123(2) K	
Unit cell dimensions	a = 9.0924(3) Å	α = 90.00°
	b = 16.5218(6) Å	β = 90.00°
	c = 23.0977(8) Å	γ = 90.00°
Volume	3469.8(2) $Å_3$	
Z	8	
Crystal system	Orthorhombic	
Space group	P 2(1)2(1)2(1)	
Density	1.147 mg/m^3	
F(000)	1312	
Reflections collected	7475	
Absorption coefficient	1.250	

4.7 References

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