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Stereocontrolled Synthesis of Bicyclo[4.2.0]octadienes for SNF 4435 C and D Analogs, Bielschowskysin, and (+/-)-Kingianin A

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Keunsoo Kim

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Abstract of the Dissertation

Stereocontrolled Synthesis of Bicyclo[4.2.0]octadienes for SNF 4435 C and D Analogs, Bielschowskysin, and (+/-)-Kingianin A

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Despite a growing interest in biological activities of natural products that contain the bicyclo[4.2.0]octadiene ring system such as SNF 4435 C and SNF 4435 D, an asymmetric version of 8π, 6π electrocyclization has remained unattained. While investigating (2E,4Z,6Z,8E)-tetraene substrates bearing amide- or oxazoline-based chiral auxiliaries, a rationally designed chiral 4,5-*trans*-diphenyl oxazoline auxiliary provided an impressive stereoselectivity (70 de%) in the 8π ring closure. Confirmation of the major isomer from the diastereomeric bicyclooctadienes was determined based on X-ray structure analysis of a SNF analog bearing (*S*)-phenylglycinol moiety. This first example of chiral induction generated by the trans-4,5-diphenyl oxazoline auxiliary in 8π electrocyclization directly affords enantiomeric carboxylic acids **(**R = CO_2H) which are key intermediates for elaboration to stereochemically homogeneous analogs of the SNF multidrug-resistance reversal agents. On the other hand, asymmetric Shi

epoxidation and aspartate-catalyzed asymmetric epoxidation were adopted to convert racemic SNF analogs to their enantiomerically pure forms**.**

While synthesizing the highly substituted cyclobutane core of bielschowskysin, tetraene substrates with 1,2-fused ring were cyclized to leading exclusively to endo products in the 8π, 6π electrocyclization. In addition, the double ring closure was critically influenced by the methyl group adjacent to the aryl group.

Progress toward the total synthesis of (+/-)-kingianin A, which is interested in its unique pentacyclic framework and potential biological activity, has been focused on model-based testing for 8π, 6π electrocyclization and cation radical catalyzed Diels-Alder reaction. This issue is currently under active investigation in our laboratory.

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List of Abbreviations

A	alpha
B	beta
Π	pi bond, or orbital
π*	antibonding orbital
1^{o}	primary
2^{o}	secondary
3^{o}	tertiary
Ac	Acetyl
AcOH	Acetic acid
Ac_2O	Acetic anhydride
aq.	Aqueous
Ar	Aryl
Bd	Broad doublet
Bn	Benzyl
Bs	Broad singlet
CSA	10-Camphorsulfonic acid
D	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DILAL-H	Diisobutylaluminum hydride
DIPEA	Diisopropylethylamine
DMM	Dimethoxymethane
DMF	N,N-Dimethylformamide
ee	Enantiomeric excess
eq.	Equivalent
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate

G	Gram
H	Hour(s)
HMPA	Hexamethylphosphoramid
Hz	Hertz
IC_{50}	Concentration for 50% inhibition
*i*Pr	Isopropyl
IR	Infrared spectroscopy
in vacuo	Under vacuum
J	First order coupling constant (NMR)
LAH	Lithium aluminum hydride
M	Multiplet
MDR	Multi drug resistance
Me	Methyl
Mg	Milligram
MHz	Megahertz
Min	Minute(s)
mL	Milliliter
Mmol	Millimole
Mol	Mole
Mp	Melting point
MS	Mass spectrometry
Ms	Methanesulfonyl
MTPACl	α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride
m/z	Mass-charge ratio
NaHMDS	Sodium 1,1,1,3,3,3-hexamethyldisilazide
NMR	Nuclear magnetic resonance
Ph	Phenyl
Ppm	Parts per million
Py	Pyridine
Q	Quartet
R_f	Retention factor

Rt	Room temperature
S	Singlet
T	Time, or triplet (NMR)
TBAF	Tetra-N-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethane sulfonate
THF	Tetradydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	para-Toluenesulfonyl (tosyl)
UV	Ultraviolet

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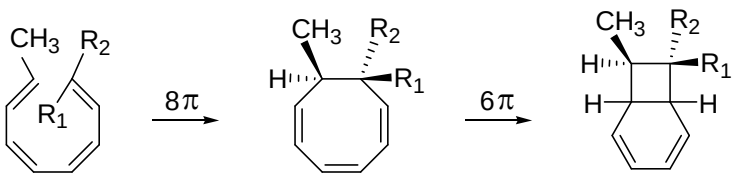
Chapter I

Asymmetric Induction in 8π Electrocyclizations Toward Synthesis of SNF 4435 C & D Analogs

1.1. Introduction

1.1.1. Background

Marvell and Huisgen demonstrated that ring closures of 2,4,6,8-octatetraenes (**1a, 1b)** to cycloocta-1,3,5-trienes (**2a, 2b)**, which are subsequently converted to bicyclo[4.2.0]octadienes (**3a, 3b)**, proceed by the stereospecific eight-electron conrotatory valence isomerization. Since that time, a great attention has been paid to reveal the mechanism and stereochemistry of the 8π, 6π electrocyclization (Scheme 1).[1-5]



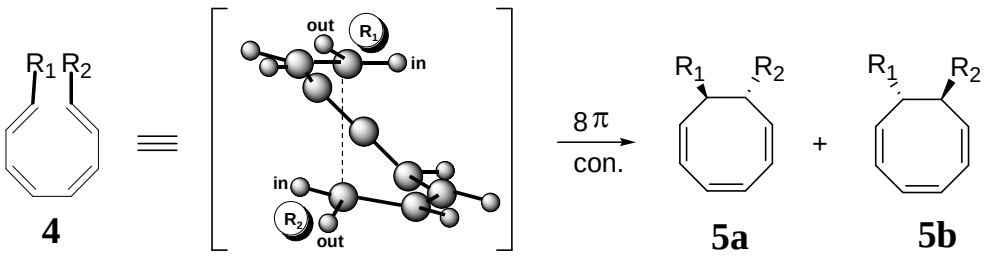
1 **2** **3**

a $R_1 = CH_3$, $R_2 = H$
b $R_1 = H$, $R_2 = CH_3$

Scheme 1. 8π, 6π electrocyclization of 1,3,5,7-octateraenes **1a** and **1b**.

The notable idea of the double ring closure also marked a major contribution to developing the Woodward-Hoffman rules. However, until now there have been no examples of 1,3,5,7-octatetraenes undergoing stereocontrolled double cyclization to produce enantiomerically pure bicyclo[4.2.0]octadienes or at least their enantioenriched forms.

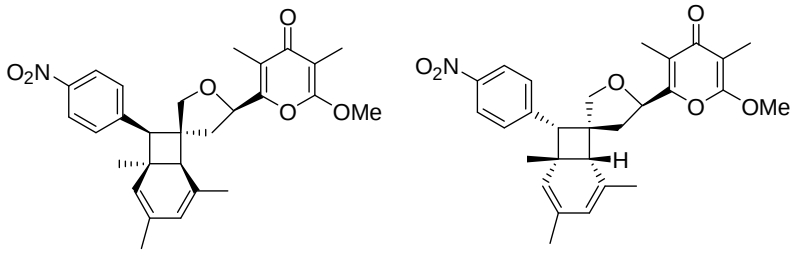
In 1993, Houk and co-workers, for the first time, examined by ab initio and semi-empirical calculations the relative stereochemistry of the 8π conrotatory ring closure of 1,3,5,7-octatetraenes (**4)** to afford diastereomeric cyclooctatrienes **5a** and **5b**.[6]



Scheme 2. Computer-based investigation of stereoselectivity in 8π electrocyclization.

Bicyclooctadienes are desirable because they have been found in a number of natural products. In the early 1980's, Black and co-workers proposed that a biomimetic synthesis of the racemic endiandric acids might be performed via 8π, 6π double electrocyclization.[7-11] The hypothesis was immediately adopted for the total syntheses of endiandric acids A - G by the Nicolaou group.[12-15]

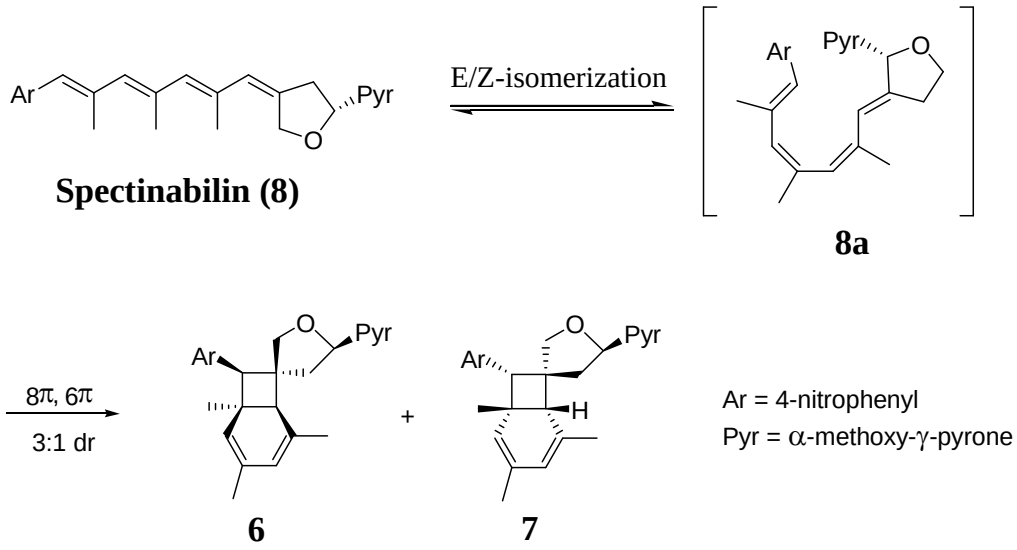
In 2001, SNF 4435 C (**6**) and SNF 4435 D (**7**), congeners of spectinabilin (**8**), were isolated from the culture broth of Streptomyces spectabilis.[16] The highly unsaturated polyketides showed potent immunosuppressive activity in vitro and selective suppression of B-cell proliferation versus T-cell proliferation with IC_{50} values of 0.8 μM for SNF 4435 C and 0.2 μM for SNF 4435 D.[17] In addition, reversal of multidrug resistance (MDR) in tumor cells turned the natural products into high potential candidates for the development of anticancer drugs.[18,19] The relative stereochemistry of the two SNF compounds was established on the basis of nOe experiments. These products are presented in Figure 1 and designated as SNF 4435 C (**6**) and SNF 4435 D (**7**).



SNF 4435 C (**6**) SNF 4435 D (**7**)

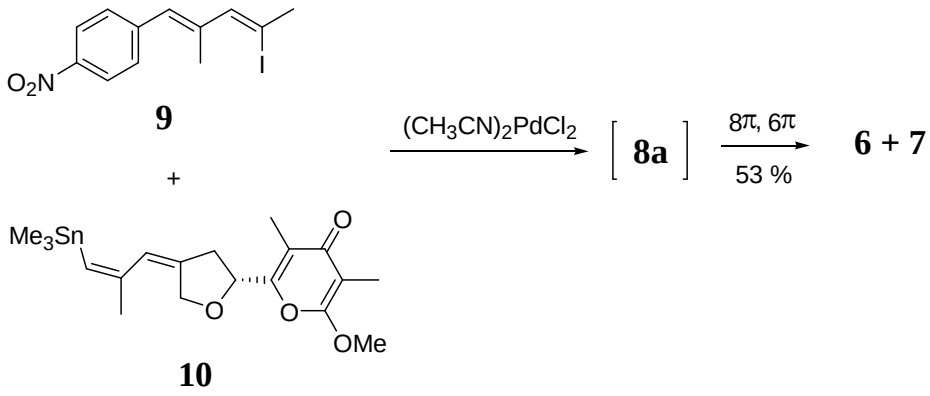
Figure 1. Structure of SNF 4435 C (**6**) and SNF 4435 D (**7**).

Although the same chirality on the γ-pyrone moiety makes them diastereomers**,** the bicyclooctadiene frameworks in **6** and **7** have an enantiomeric relationship. Their unique stereoisomeric relationship attracts considerable attention not only because it can lead to understand different biological activity of the SNF compounds, but also because it may help to elucidate an origin of stereoselectivity observed in 8π, 6π electrocyclization (Scheme 3).



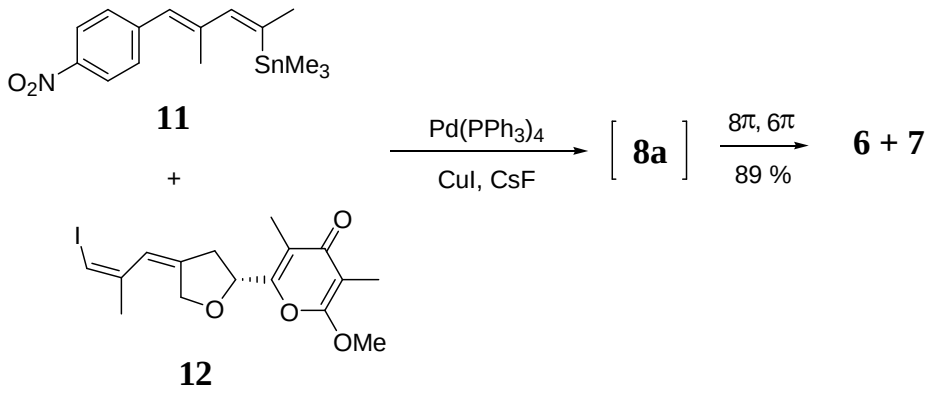
Scheme 3. Biomimetic synthesis of the two SNF compounds (**6** and **7)** from spectinabilin **8**.

The proposed biosynthetic origin of the SNF compounds was synthetically supported by Parker, Trauner, and Baldwin independently. In Parker's synthesis, vinyl iodide **9** underwent cross-coupling with vinyl stannane **10** to provide tetraene **8a**, which then underwent a spontaneous 8π, 6π electrocyclization (Scheme 4).[20]



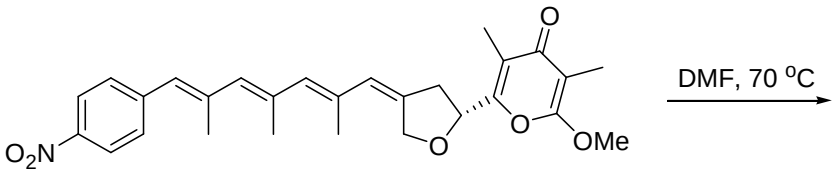
Scheme 4. Parker's total synthesis of SNF 4435 C and D.

The Trauner group performed stannylation of vinyl iodide **9** to generate vinyl stannane **11**, which underwent the key cross-coupling with vinyl iodide **12** in high yield (Scheme 5).[21]

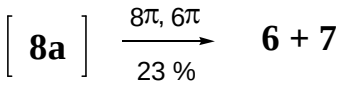


Scheme 5. Trauner's total synthesis of SNF 4435 C and D.

The Baldwin group focused on a total synthesis of spectinabilin (**8**), which subsequently underwent palladium-mediated isomerization followed by the double electrocyclization to yield the SNF compounds (Scheme 6).[22]



Spectinabilin (8)



Scheme 6. Baldwin's total synthesis of SNF 4435 C and D.

Ocellapyrones A (**13**) and B (**14**)[23]**,** elysiapyrones A (**15**) and B (**16**)[24], and shimalactones A (**17**) and B (**18**)[25] were newly isolated with the same backbone of SNF 4435 C and D (Figure 2). Bicyclo[4.2.0]octadienes (**14a**, **15a** and **16a**) may be considered as key precursors to the ocellapyrone B and the elysiapyrones A and B. Ocellapyrones (**13** and **14**) and elysiapyrones (**15** and **16**) were isolated as enantiomerically pure forms. Like SNF 4435 C and D, shimalactones (**17** and **18**) were obtained as a diastereomeric mixture. Total syntheses of these SNF relatives (**13** to **18)** presented in Figure 2 have been accomplished by synthetic strategies similar to those applied for the total synthesis of the the SNF 4435 compounds.[26-28] Total syntheses of the natural products (**13** to **18**) by the Trauner group produced racemic compounds. SNF compounds and shimalactones were prepared by total synthesis without presence of any supporting chiral appendage. For the ocellapyrones and elysiapyrones, a chiral source might contribute to their optical activities. Therefore, asymmetric version of 8π, 6π electrocyclization in the synthesis of those natural products may be necessary to lead to a solution.

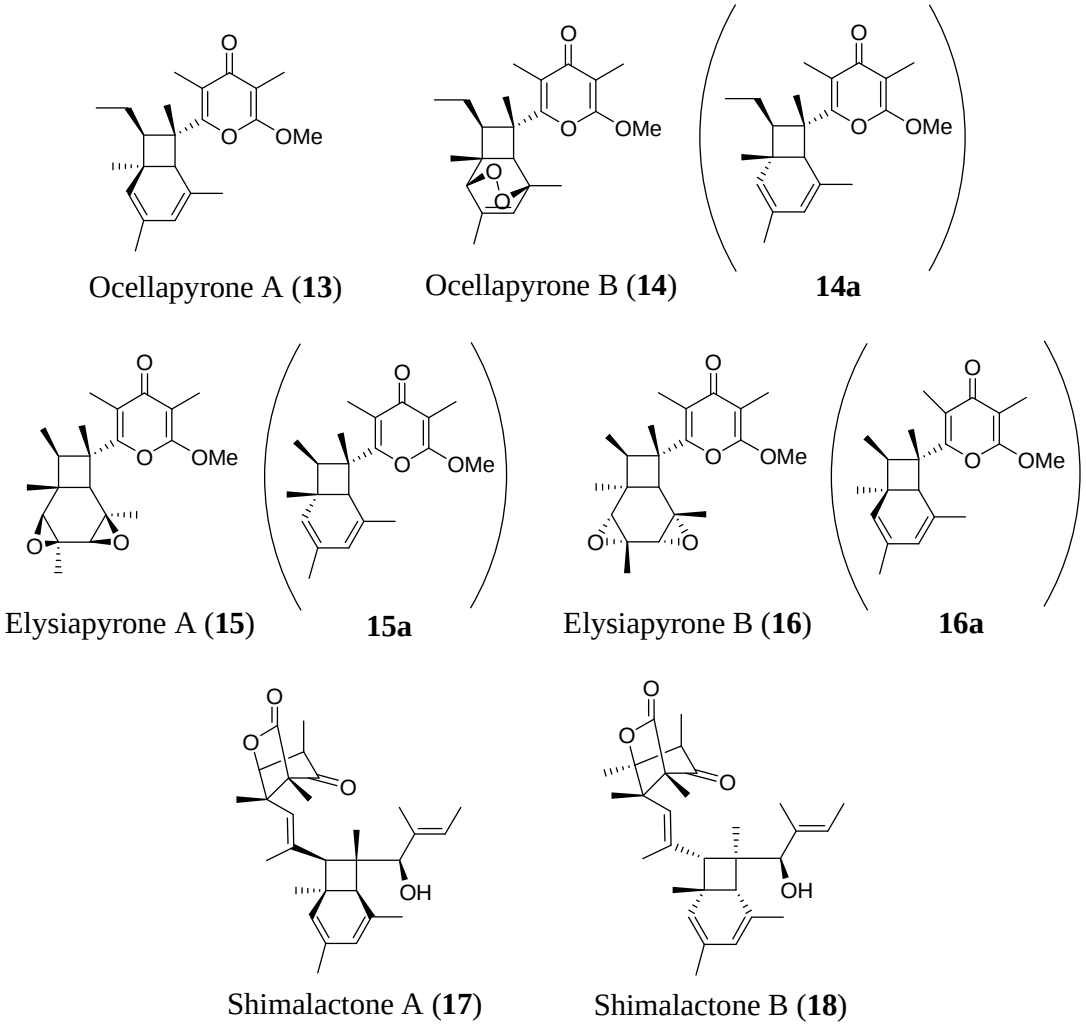
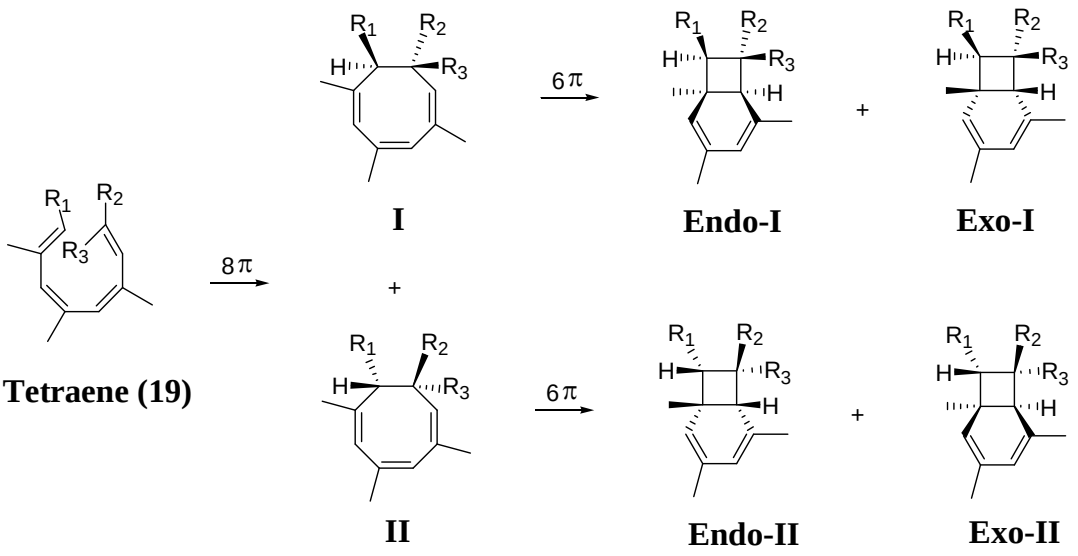


Figure 2. Natural products containing the same backbone of the SNF compounds.

The first synthesis for the SNF compounds was performed by Parker group.[29] They investigated an unexpected high stereoselectivity in the 6π ring closure because only a single racemic bicyclooctadiene was produced from (E,Z,Z,E)-tetraene precursor **19** (Scheme 7).



Scheme 7. Possible 8π, 6π electrocyclization products from achiral tetrane **19**.

According to Parker, 6π electrocyclization could be controlled by the choice of a functionalized substituent which is oriented to endo or exo conformation (Figure 3). Endo conformer was designated in which the nitrophenyl substituent is tucked under the bicylooctadiene ring. Their experimental result showed that if R_E on **20** is introduced at the outward position on the terminal olefin and R_Z on **20** is H, endo products will predominate. As a result, they demonstrated that steric hindrance between the nitrophenyl group and the vicinal methyl substituent disfavors the transition state leading to exo product. On the other hand, a large R_Z group disfavors the endo conformation. Therefore, formation of the two products is totally dependent on the size of the R_E and R_Z group introduced.

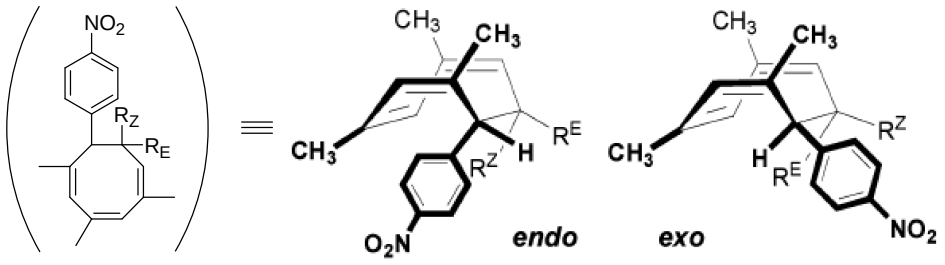
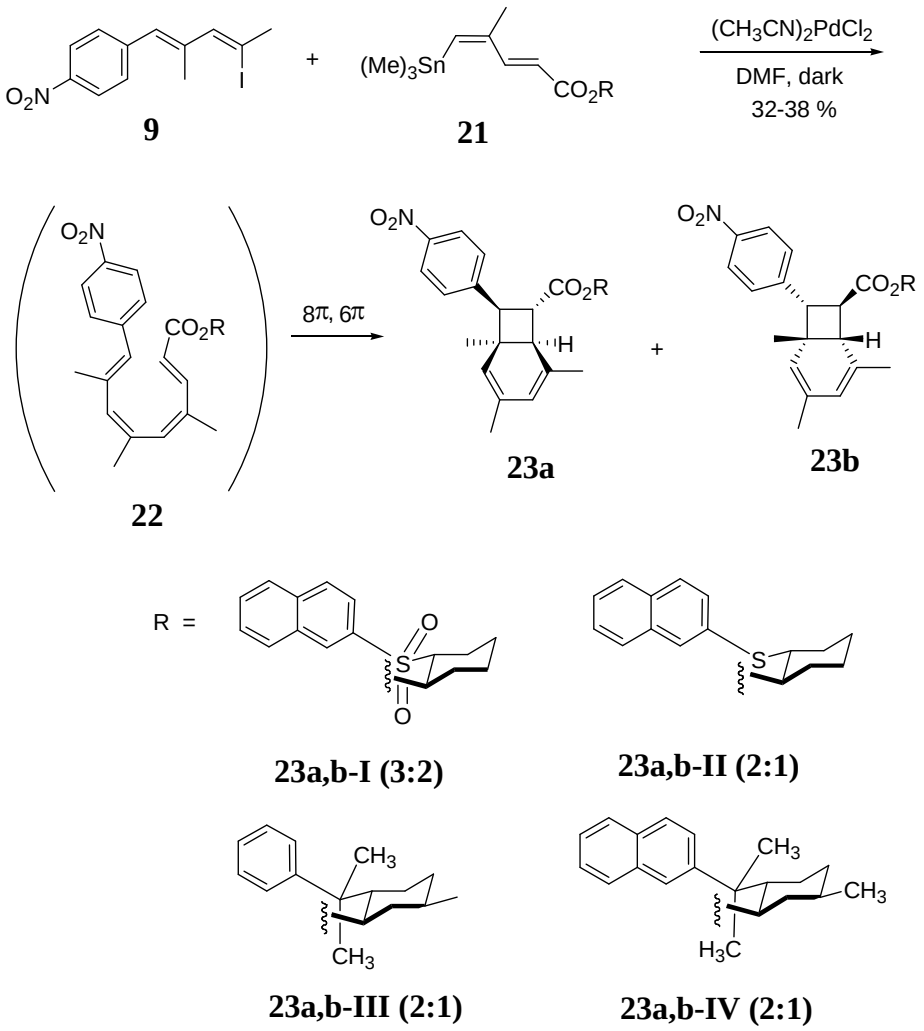


Figure 3. Proposed transition states supported by endo and exo conformation.

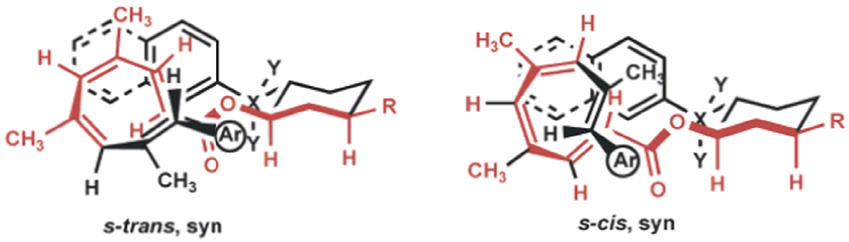
The impressive stereoselectivity controlled during the 6π electrocyclization provides a valuable advantage for the preparation of chiral bicyclooctadienes because product analysis could be simplified to the ratio of two endo diastereomers.

In 2006, chiral induction in the 8π electrocyclization of (2E, 4Z, 6Z, 8E)-octatetraene substrates **22** bearing Corey-Sarakinos sulfone-based chiral auxiliaries was investigated by the Parker group.[30,31] In particular, they postulated that an effect of π stacking between an aromatic moiety in the auxiliaries and the unsaturated ester in the octatetraene substrate might produce stereospecificity in the process of 8π electrocyclization. However, the first 8π electrocyclization induced by chiral auxiliaries did not lead a large selectivity among diastereomers. The diastereomeric ratio (dr) hovered near 2:1 for **23a,b-II** and 3:2 for **23a,b-I** (Scheme 8).



Scheme 8. Chiral induction in the 8π electrocyclization of tetraenic esters **22**.

The relatively low diastereoselectivity is consistent with two nearly isoenergetic helical transition states, *s-trans,syn* **24a** and *s-cis, syn* **24b** (Figure 4).

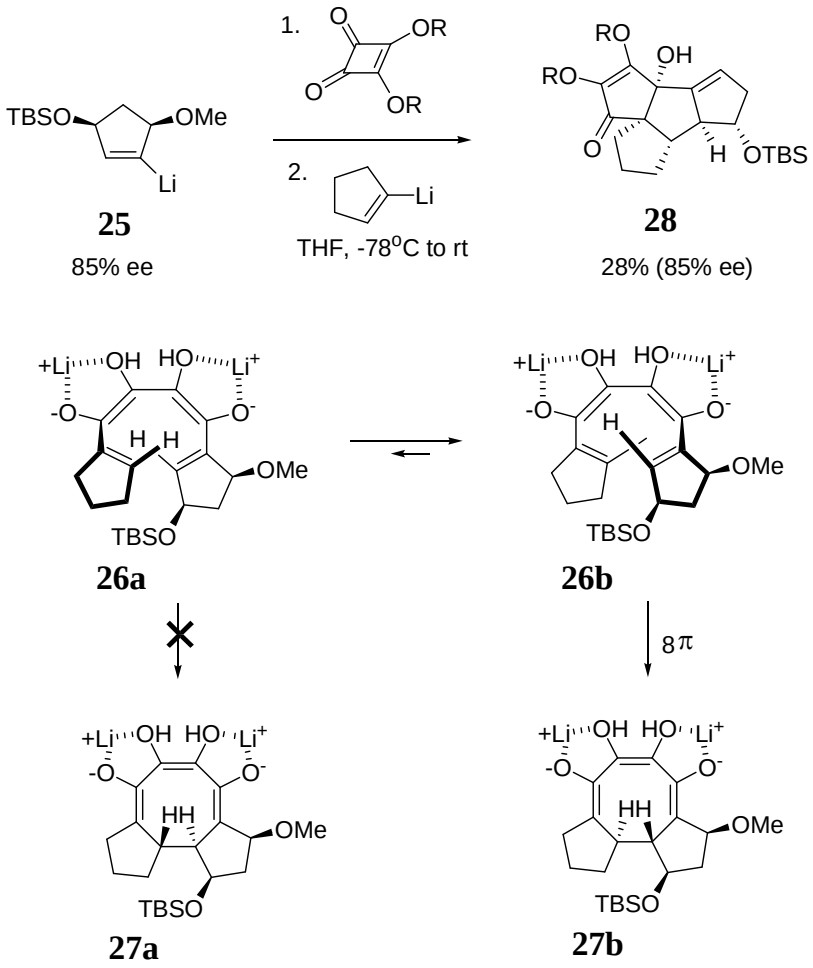


24a **24b**

Figure 4. Two possible helical transition state conformations.

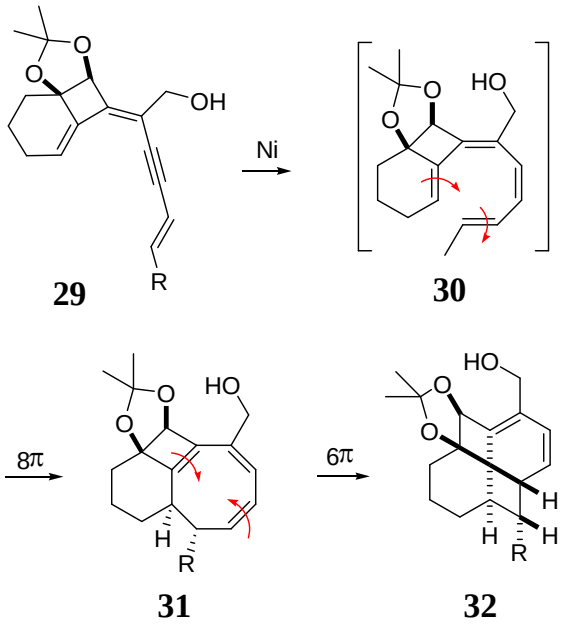
For predominance of one diaseteromeric SNF analog, the energies of the two helical conformations **24a** and **24b** should be significantly different. Then one direction of conrotatory 8π ring closure would be favored.

Despite the considerable attention to 8π, 6π electrocyclic reactions, it is rare to find examples where stereocontrolled 8π, 6π electrocyclization was applied to the synthesis of cyclic compounds including natural products. In 1998, Paquette and co-workers achieved modest levels of chiral induction in a related sequence which was carried out via stereocontrolled 8π electrocyclization and a transannular aldol cascade to **28**.[32,33] High diastereoselectivity was observed in the 8π conrotatory ring closure. The source of chirality is in the precursor **25** (Scheme 9).



Scheme 9. Modest levels of chiral induction in 8π electrocyclization by Paquette.

Recently, in the synthesis of [4.6.4.6]fenestradienes **32**, the Suffert group reported that tetraene **30**, which was generated from trienyne **29** by P-2 Ni ($Ni(OAc)_2.4(H_2O)$) via cis-selective semihydrogenation, underwent 8π electrocyclization to yield a single isomer **31** (Scheme 10).[34,35] The authors proposed that the unusually high stereoselectivity results from torquoselectivity observed in the 8π electrocyclic cascade reaction.



Scheme 10. Torquoselective 8π electrocyclization in the formation of **32**.

The asymmetric 6π electrocyclization has been actively investigated. Notable achievements were reported by the Hsung[36,37], Trauner[38], List[39], and Martin[40,41] groups. However, similar strategies have not been applied to the 8π electrocyclization.

1.1.2. A new approach for the preparation of chiral SNF analogs

In order to develop new types of tetraene substrates, we reexamined tetraenic esters **22** because, to the best of our knowledge, the (E,Z,Z,E)-octatetraene substrates bearing chiral auxiliaries are considered as the most reliable method for the synthesis of chiral SNF analogs. Firstly, in an attempt to preserve the SNF framework, 4-nitrophenyl and 4,6,8-trimethyl moiety are required. The (2E,4Z,6Z,8E)-tetraene carbon skeleton should be maintained for endo selective 6π ring closure. Therefore, our interest automatically focuses on new chiral auxiliaries which can generate chiral induction in 8π electrocyclization. Specifically, new auxiliaries were designed to create a more rigid linker between the tetraene backbone and the auxiliaries compared to the ester linkage shown in **22** (Figure 5).

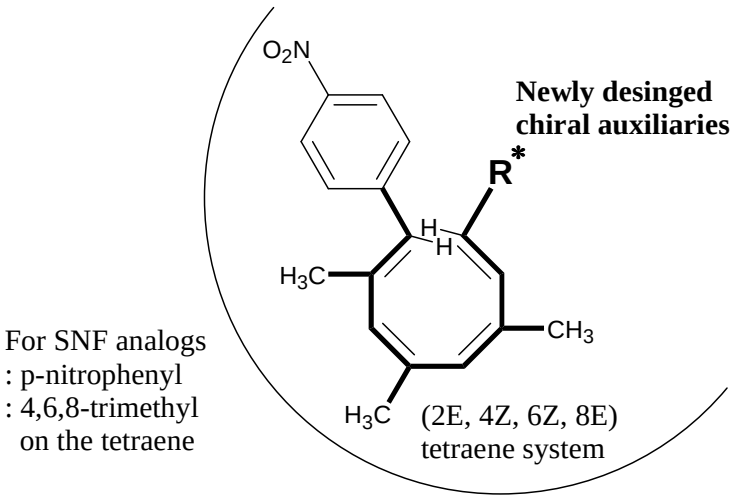


Figure 5. Optimization of tetraene substrates to asymmetric 8π electrocyclization.

Development of new synthetic routes for preparing (2E,4Z,6Z,8E)-tetraene substrates also will be important. Baldwin's coupling method,[42] which significantly accelerates reactivity in Stille coupling, is synthetically more efficient in terms of high yield and short reaction time. Also, if stannylation can be applied to a diene bearing 4-nitrophenyl group, we can vary its coupling partner and test a number of chiral auxiliaries. In addition, we can predict higher yield from the cross-coupling between **11** and iododiene-containing auxiliaries. (See Scheme 5.) Finally, alternative palladium-mediated cross-coupling reactions need to be examined, due to the well-known toxicity of the tin moiety used for Stille coupling.

Development of new chiral auxiliaries is mainly based on two transition states; s-*cis* (A) and s-*trans* helical conformation (B). Among potential auxiliary candidates are chiral phenylglycinol and its derivatives, especially because of the rigid nature of the amide (peptide) bond. In addition, they are desirable if they can be readily transformed to produce corresponding oxazoline auxiliaries via intramolecular cyclization. Presumably, introducing a C-2 symmetric or pseudo C-2 symmetric functional group on an oxazoline would favor one of the four possible transition states over the others.

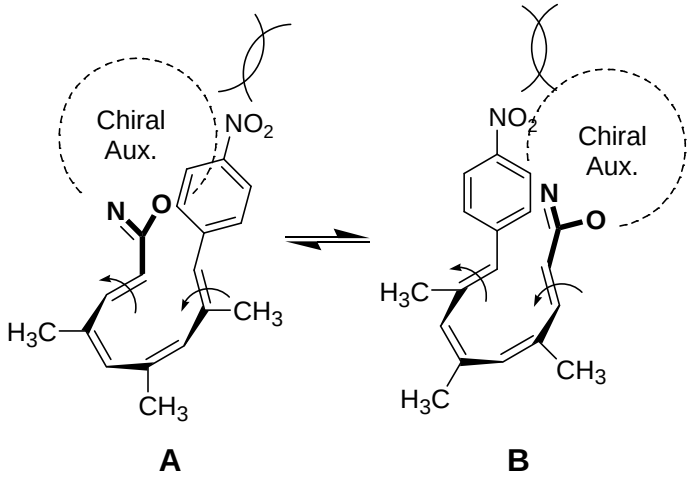


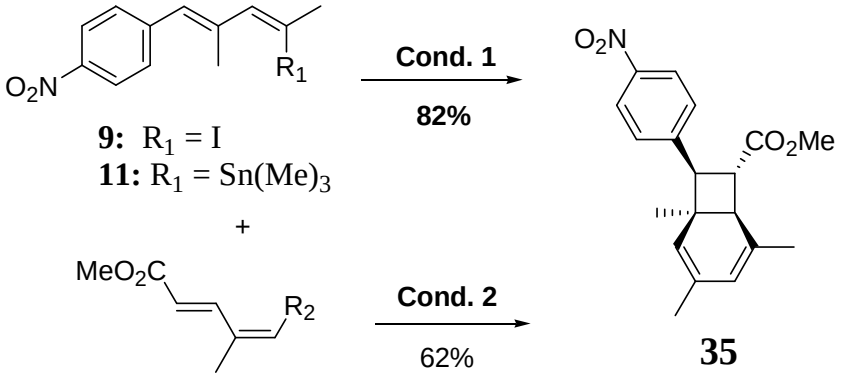
Figure 6. New chiral auxiliaries based on two transition states; s-*cis* (A) and s-*trans* helical conformation (B).

The auxiliaries in bicyclooctadienes need to be readily hydrolyzed to corresponding carboxylic acids, which are key intermediates for the preparation of enantiomerically pure SNF analogs. Determination of absolute stereochemistry of chiral SNF analogs will be important due to the different biological activities shown in SNF 4435 C and D. Besides, it will be a great support to understand the stereochemistry in the process of 8π conrotatory ring closure.

1.2. Result and Discussion

1.2.1. Investigation of cross-coupling methods

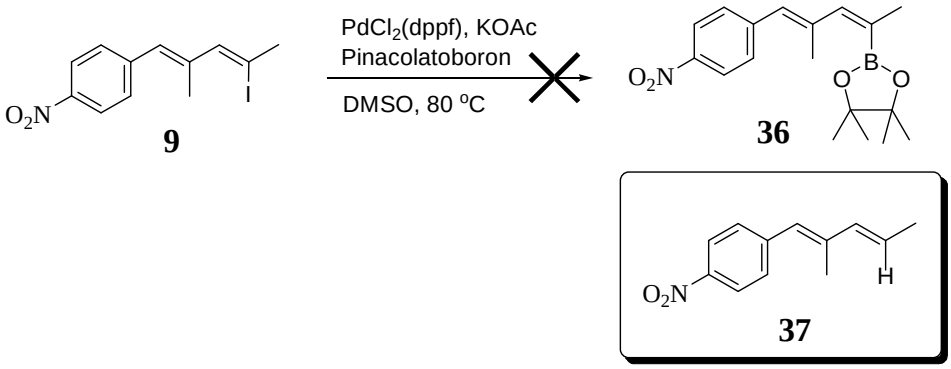
The Stille coupling method (Cond. 1) developed by Baldwin afforded bicyclooctadiene **35** in higher yield and shorter reaction time compared to the previous coupling method (Cond. 2). (See Scheme 11.) Especially, stannylation on iodiene **9** was synthetically very useful because vinyl stannane **11**, which is known,[21] can be prepared by 3 steps from cheap 4-nitrobenzaldehyde.



Reagents and conditions: Cond. 1) **11**, **33,** CsF, CuI(I), $Pd(PPh_3)_4$, DMF, 45°C, 2 h, dark; Cond. 2) **9**, **34**, $Pd(CH_3CN)_2Cl_2$, DMF, rt, 16-20 h, dark

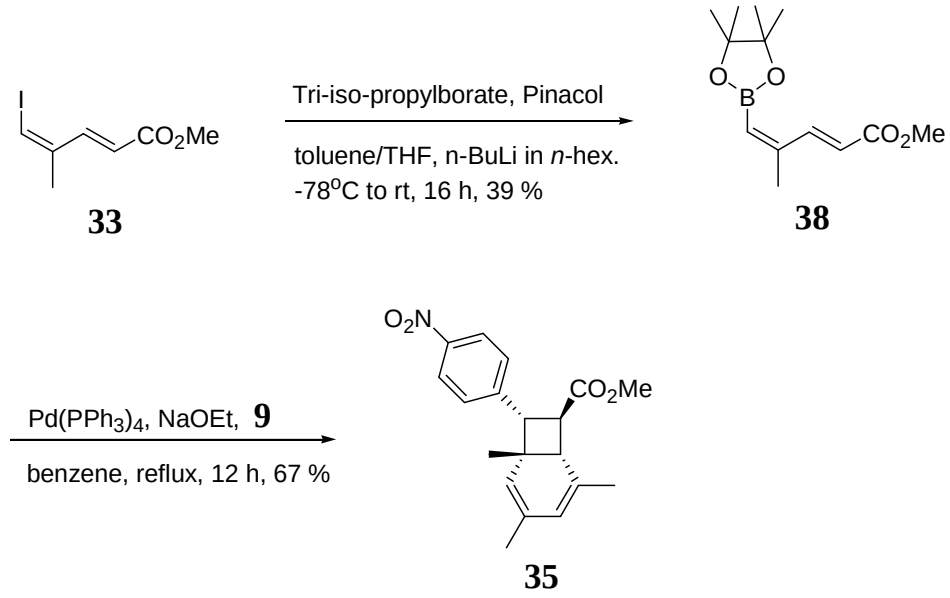
Scheme 11. Preparation of bicyclooctadiene **35** by Baldwin's method.

However, due to instability, toxicity, and relatively low yield of **11**, we turned our focus into Suzuki-Miyaura coupling which might solve the problems generated under Stille coupling condition.[43-47] A solution of iododiene **9** and pinacolatoboron was thoroughly deoxygenated before adding $PdCl_2$(dppf), and then stirred at 80 °C for 3 h (Scheme 12).[48]



Scheme 12. Synthetic attempt to afford (2Z,4E)-boronic ester **36**.

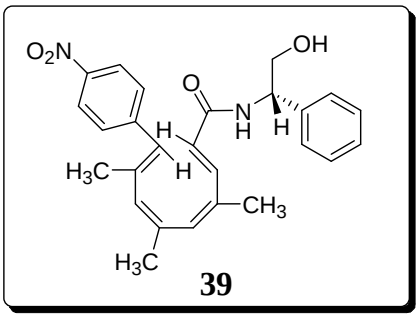
Instead of the desired **36**, the reduced form **37** was afforded as a major product. Addition of dppf as an additive under the same reaction conditions did not improve the boronylation. Presumably, introduction of the boron moiety might be significantly interrupted, due to steric hindrance generated by the methyl group on the terminal carbon. Our assumption was supported by boronylation of the less hindered iododiene **33**. Iododiene **33** was treated with tri-iso-propylborate and *n*-butyllithium, followed by adding pinacol to afford boronic ester **38**.[43] However, the overall yield of this scheme was too low to replace the stannylation route. On the other hand, under general Suzuki-Miyaura coupling conditions,[44] **38** was successfully coupled with **9** to yield bicyclooctadiene **35** with 67 % yield (Scheme 13).



Scheme 13. Preparation of bicyclooctadiene **35** via Suzuki-Miyaura coupling.

1.2.2. Investigation of asymmetric 8π electrocyclization of tetraene substrates bearing newly designed chiral auxiliaries

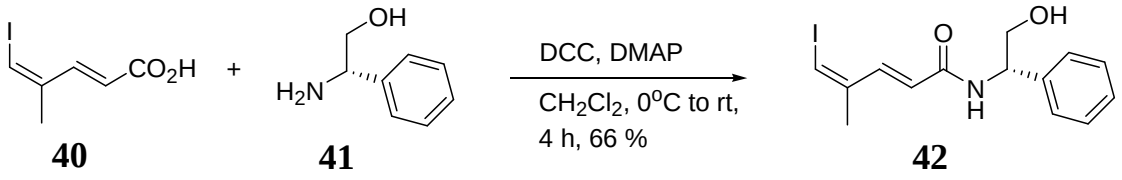
1.2.2.1. Asymmetric induction by (S)-phenylglycinol based auxiliary



39

Figure 7. Structure of a tetraene substrate bearing (*S*)-phenylglycinol **39**.

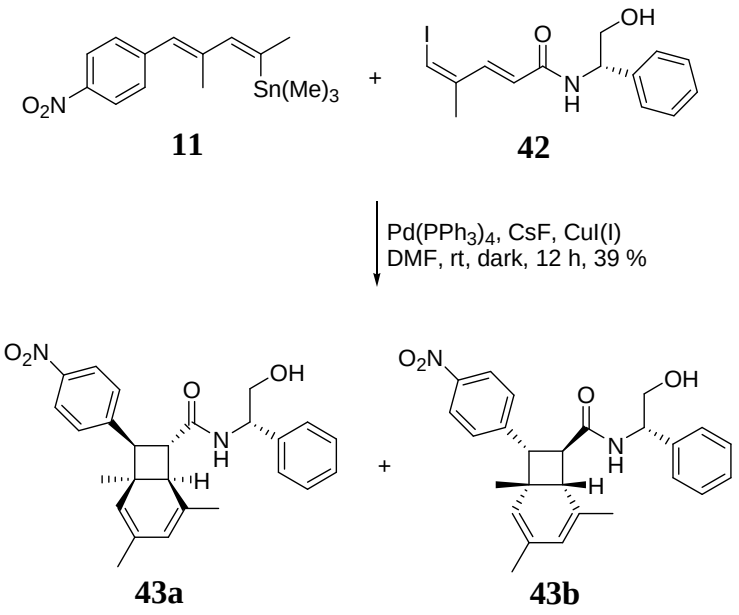
Phenylglycinol is a widely used chiral auxiliary because its origin is based on the amino acid chiral pool.[49] Iododiene-amide **42** was readily prepared by coupling between iododienoic acid **40,** which was prepared by hydrolysis of **31** and coupling with (S)-phenylglycinol **41** in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP).[50] (See Scheme 14.**)**



40 **41** **42**

Scheme 14. Preparation of iododiene-amide **42**.

For Stille coupling, iododiene **9** was subjected to trimethylstannylation with hexamethylditin and $PdCl_2(CN)_2$ in HMPA to produce vinyl stannane **11** in moderate yield.[21] Due to its low stability, after purifying on a short pad of basic alumina, **11** was immediately subjected to the coupling-tandem cyclization. Coupling between **11** and **42** under Baldwin's modified coupling conditions[11] generated tetraene substrate **39** which underwent 8π, 6π electrocyclization to afford a mixture of diastereomeric SNF analogs **43a** and **43b** (Scheme 15).



Scheme 15. Asymmetric 8π electrocyclization of the tetraene **39**.

Low stereoselectivity was observed with a diastereomeric ratio of 1 : 2 (**43a** : **43b)** on the basis of ^{1}H NMR analysis. The expected driving force from both the amide linkage and the steric effect of the phenyl group on the auxiliary was not large. Interestingly, unlike any other diastereomeric SNF analogs, bicyclo[4.2.0]octadienes **43a** and **43b** were easily separated by flash column chromatography. According to Helmchen,[51-55] the order of a pair of diastereomeric amides bearing chiral phenylglycinol on the liquid adsorption chromatography is consistent with the following model: The diastereomers in which both faces of the common plane have apolar substrates (**44-R** and **45-R**) is eluted first, due to the weak affinity of both faces of the amide plane to the silica gel (Figure 7).

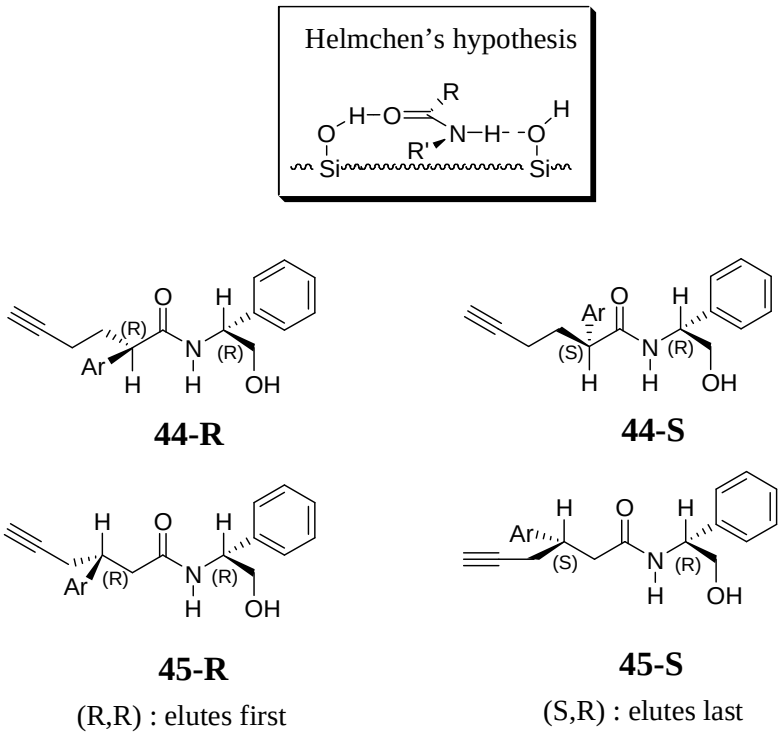


Figure 8. Helmchen's hypothesis and examples of order of chromatographic elution of diastereomeric phenylglycinol amides.

The postulate can further support a relationship between the planar conformation of α- or β-substituted amide diastereomers and their absolute configurational assignment.[56] However, since α-chirality in compounds **43a** and **43b** is continuous with the adjacent stereogenic centers on the cyclobutane ring, the rigid structure of the common plane ($CHCH_2C(=O)NHCH$) is not so clearly adopted in **43a** and **43b**. Therefore, relative stereochemistry of either **43a** or **43b** needed to be determined by crystallographic analysis. Eventually, the slower moving isomer **43a** was recrystallized from $CHCl_3$/n-hexane, and then slow evaporation from a solution in MeOH/Et_2O produced needles that were suitable for X-ray analysis. The relative stereochemistry of **43a** was determined as shown (Figure 8).

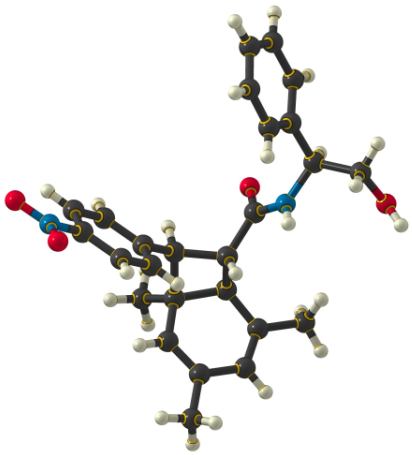
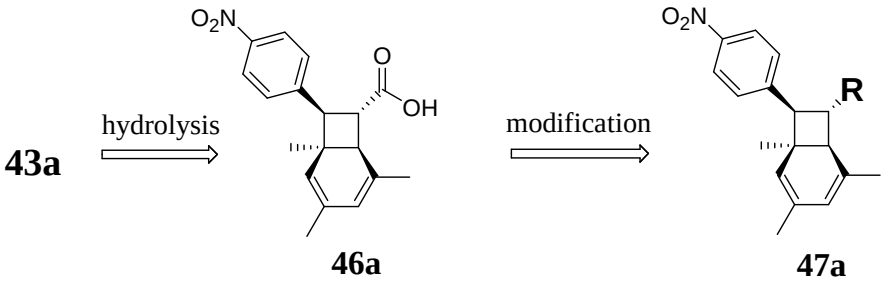


Figure 9. X-ray crystal structure of chiral SNF analog **43a**.

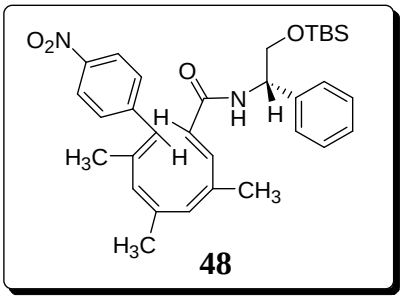
Although the phenylglycinol auxiliary did not boost stereoselectivity in the 8π electrocyclization, it may be a very useful system because of the notable separation ability. If either **43a** or **43b** can be smoothly converted into the corresponding acid, which is considered as a key SNF analog, it could provide a substantial milestone towards the preparation of chiral SNF analogs (Scheme 16).



(For the **43b**; enantiomeric **46b** and **47b**)

Scheme 16. Strategy towards synthesis of chiral SNF analogs from **43a** or **43b**.

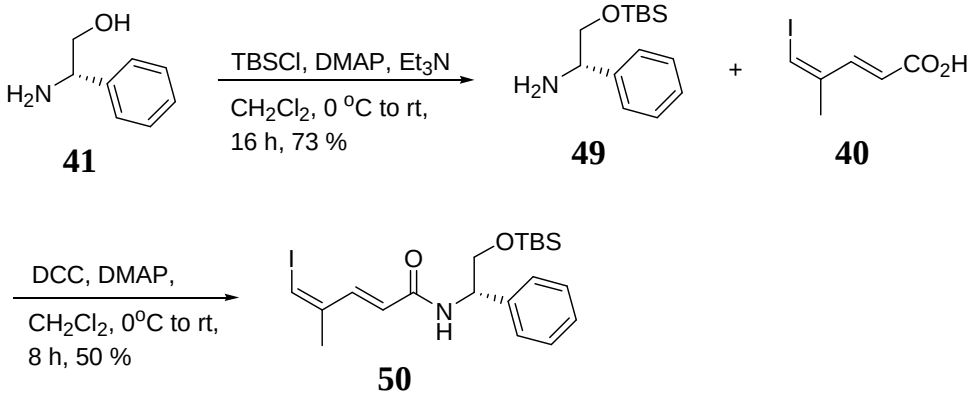
1.2.2.2. Asymmetric induction by TBS protected phenylglycinol based auxiliary



48

Figure 10. Structure of a tetraene substrate bearing TBS protected (*S*)-phenylglycinol **48**.

In order to explore additional chiral auxiliaries, the TBS group was introduced on the phenylglycinol **41**. The silyl-protected amine **49** was readily prepared with TBS-Cl and triethylamine.[57] Under the given conditions, compound **49** was coupled with carboxylic acid **40** to yield iododiene-amide **50** (Scheme 17).

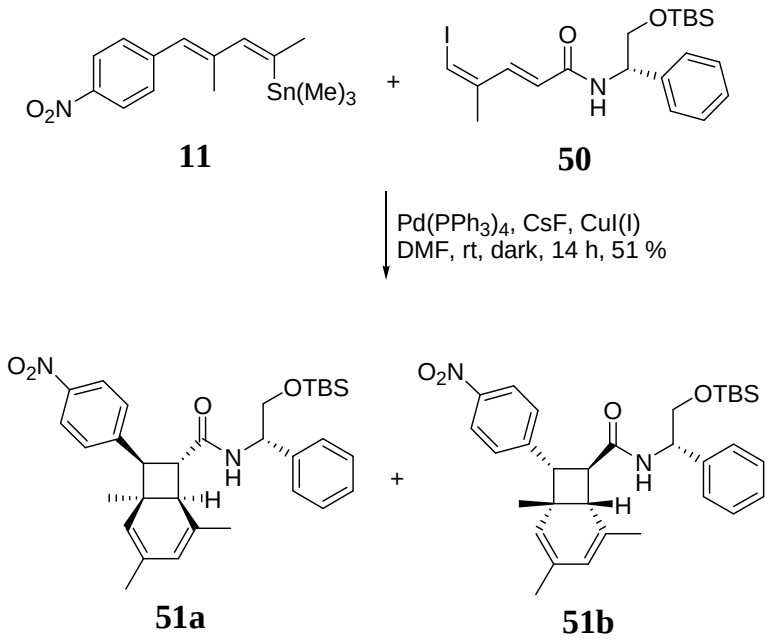


41 **49** **40**

50

Scheme 17. Preparation of iododiene-amide **50**.

Coupling between **11** and **50** provided tetraene **48,** and then the two inseparable diastereomeric SNF analogs **51a** and **51b** were afforded via 8π, 6π electrocyclization with 51 % yield (Scheme 18).



Scheme 18. Asymmetric 8π electrocyclization of the tetraene **48**.

1H NMR analysis indicated that **51a** and **51b** were produced in a ratio of 1:1. Evidently, the s-*cis*, syn and s-*trans*, syn transition state conformations during conrotatory 8π ring closure are nearly isoenergetic. As a result, chiral induction of tetraene substrate **48** was not impressive.

1.2.2.3. Asymmetric induction by phenylglycinol-derived tertiary amide auxiliary

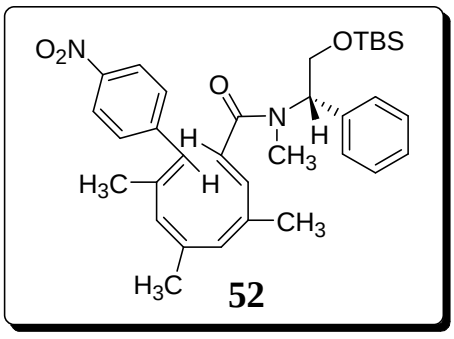
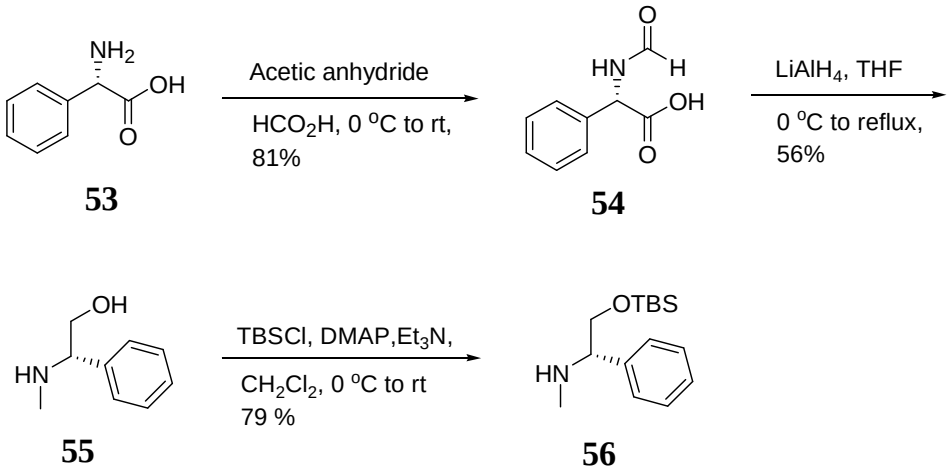


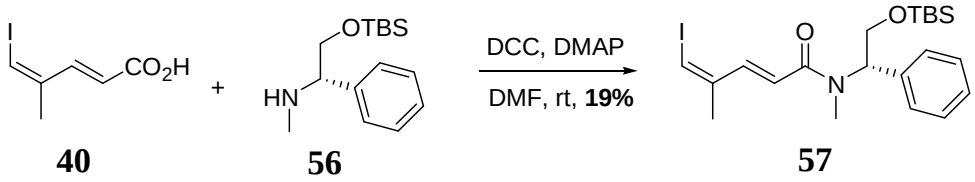
Figure 11. Structure of a tetraene substrate bearing *N*-methyl-O-TBS phenylglycinol **52**.

We thought that an amide linker, with a second substituent on the nitrogen, may disfavor either s-*cis*, syn or s-*trans*, syn transition state. For the preparation of the designed iododiene-amide **57**, (S)-(+)-2-phenylglycine **53** was treated with formic acid and acetic anhydride to provide formamide **54.** Then, reduction afforded (S)-*N*-methyl-2-phenyl-2-aminoethanol **55**.[58] The TBS group was introduced under basic conditions to give the *N*-methyl-O-TBS amine **56** (Scheme 19).



Scheme 19. Preparation of amine **56**.

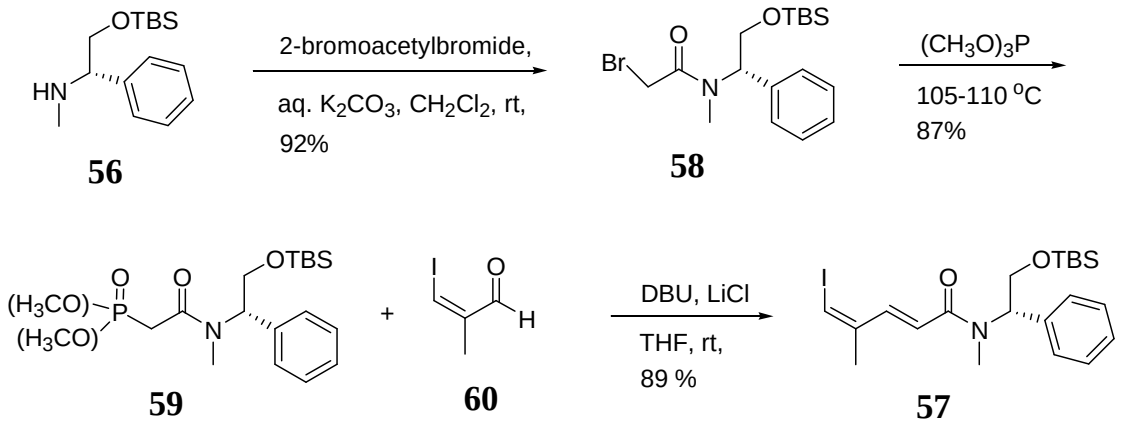
Coupling between **40** and **56** was performed by treatment with DCC and DMAP. However, unlike coupling between **40** and **49** under the same reaction conditions, the reaction gave product **57** in low yield (Scheme 20).



Scheme 20. Direct coupling to generate the iododiene-amide **57**.

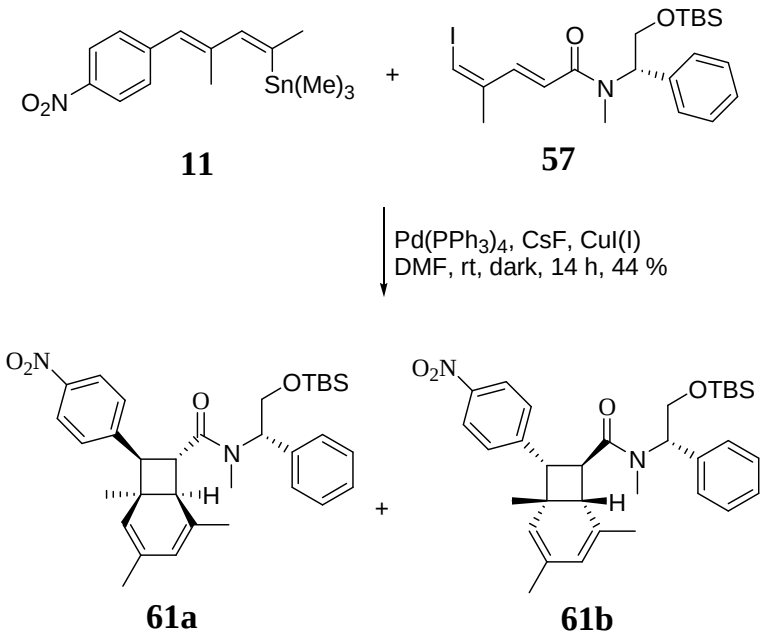
Due to the low yield, the Michaelis-Arbuzov reaction and then Horner–Wadsworth–Emmons (HWE) reaction sequence were adopted as an alternate synthetic route. Chiral bromoacetamide

58 was readily prepared by the treatment of **56** with bromoacetyl bromide in 92 % yield. Treatment with trimethylphosphite afforded chiral phosphonoacetamide **59**. Finally, **57** was successfully prepared from HWE reaction with **59** and iodoaldehyde **60,** which was generated in situ from the corresponding alcohol. Overall yield of **57** from **56** significantly increased to 70 % with 3 steps (Scheme 21).



Scheme 21. Preparation of iododiene-amide **57**.

Hoping to generate bias between the s-*cis*, syn or s-*trans*, syn transition state, we examined the asymmetric 8π electrocyclization of tetraene **52**. Again, there was no preference for either diatereomer. An inseparable 1:1 mixture of two SNF analogs **61a** and **61b** was produced in 44 % yield (Scheme 22).



Scheme 22. Asymmetric 8π electrocyclization of the tetraene **52**.

Due to the continued low stereoselectivity, we concluded that phenylglycinol **41** in itself and its derived auxiliaries **49** and **56** were inefficient to apply chiral induction to tetraene substrates in 8π electrocyclization.

1.2.2.4. Asymmetric induction by C2-symmetrized tertiary amide based auxiliary

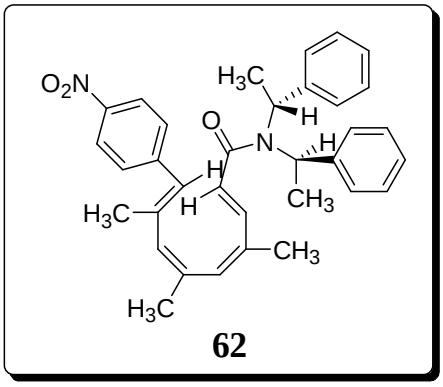
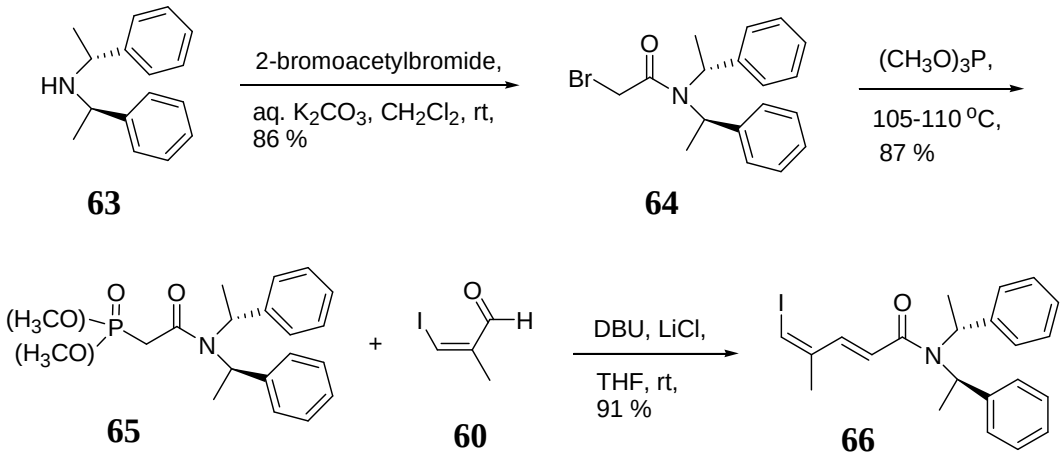


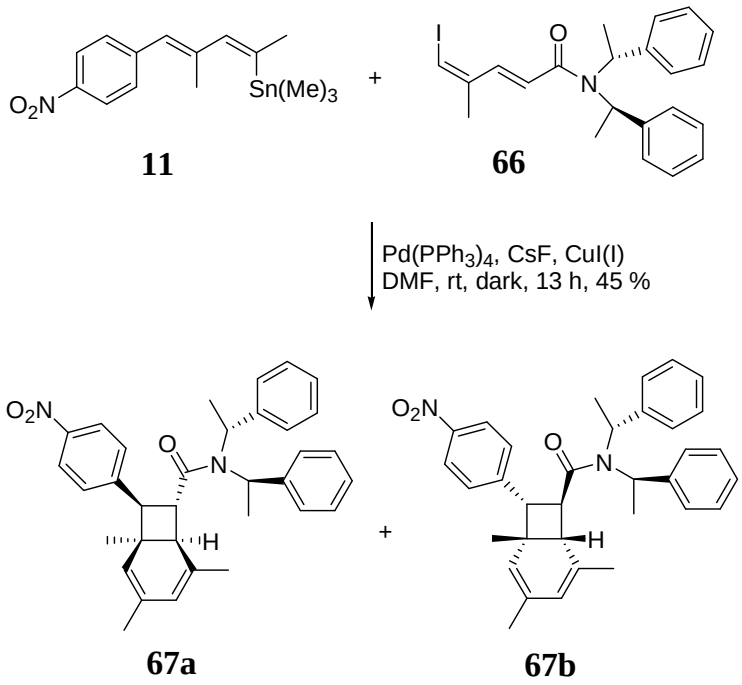
Figure 12. Structure of a tetraene substrate bearing bis-phenylethylamine **62**.

Besides a tertiary amide linkage, if we introduce C2-symmetrized moiety on an auxiliary, chiral induction in 8π electrocyclization of a tetraene substrate bearing the auxiliary might be superior to phenylglycinol-derived auxiliaries. We chose commercially available bis[(S)-1-phenylethyl]amine **63** as a suitable candidate. Iododiene-amide **66** was prepared from the same reaction sequence applied to **57**. Michaelis-Arbuzov reaction of **63** provided amide **64.** Then treatment with trimethylphosphite afforded chiral phosphonoacetamide **65**. HWE reaction between **60** and **65** afforded **66** with 68 % overall yield from **63** (Scheme 23).



Scheme 23. Preparation of iododiene-amide **66**.

Coupling of iododiene **66** with the stannyl diene **11** gave two separable diastereomeric SNF analogs **67a** and **67b** which were afforded in a ratio of 2 : 3 or 3 : 2. The faster moving isomer (27 %) was obtained in slightly greater amounts compared to the slower moving isomer (18 %). (See Scheme 24.)



Scheme 24. Asymmetric 8π electrocyclization of tetraene **62**.

1.2.2.5. Asymmetric induction by oxazolidinone based auxiliary

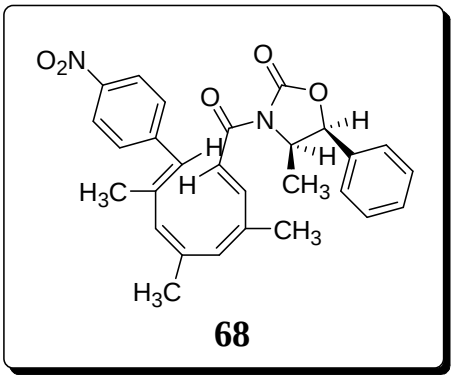
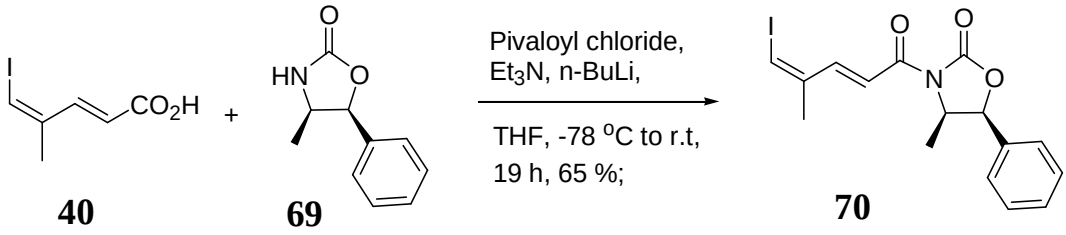


Figure 13. Structure of a tetraene substrate bearing oxazolidinone **68**.

We focused on dipole interactions that might favor one of the four possible transition states over the others. Evans oxazolidinones are commonly used as chiral auxiliairy sources. We anticipated a metal-chelated intermediate that might generate a preference for one of the helical

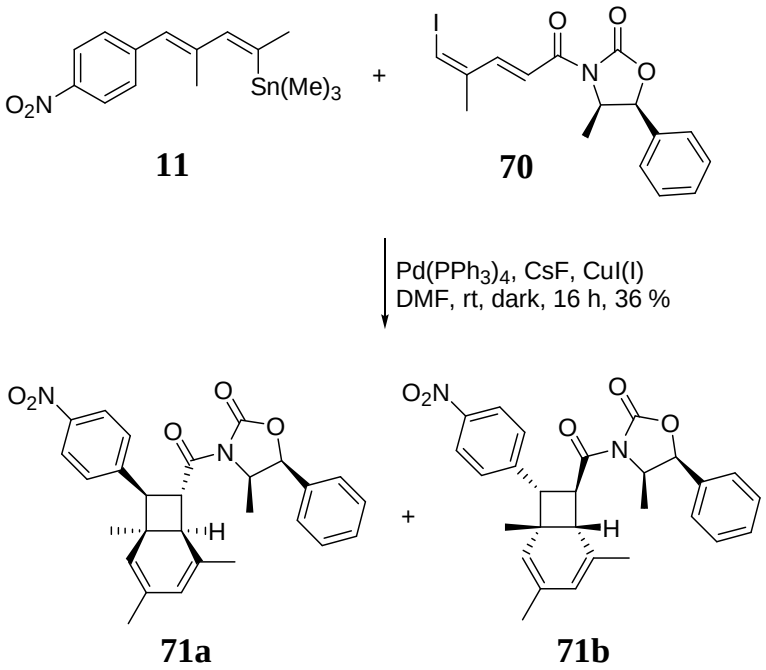
transition states in 8π electrocyclization. Therefore acid **40** was treated with pivaloyl chloride in the presence of triethylamine to generate the corresponding acid chloride in situ. Then, oxazolidinone **69**, which was deprotonated with n-BuLi, was added to produce iododiene-oxazolidinone **70** in 65 % yield (Scheme 25).



40 **69** **70**

Scheme 25. Preparation of the iododiene-oxazolidinone **70**.

With **70** in hand, the coupling/ 8π, 6π electrocyclization was performed under the given reaction conditions. There was no preference for either of the diastereomeric SNF analogs **71a** or **71b,** which were obtained in a ratio of 1 : 1 in 36 % overall yield (Scheme 26).

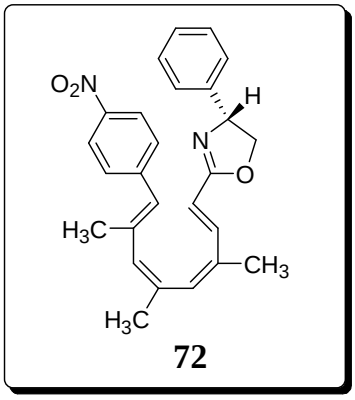


11 **70** **71a** **71b**

Scheme 26. Asymmetric 8π electrocyclization of tetraene **68**.

Again, the ring closure proved to be non-stereoselective. Probably, the expected metal-chelate intermediate did not form. The poor dr indicated that amide linkages might not be effective to generate chiral induction in 8π electrocyclization of tetraene substrates.

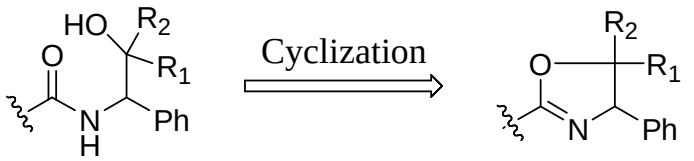
1.2.2.6. Asymmetric induction by non-C2 symmetrized oxazoline chiral auxiliary



72

Figure 14. Structure of a tetraene substrate bearing 4-phenyl-oxazoline **72**.

We returned to our attention to iododiene-amide **42** because we realized that the hydroxyl amide on **42** can be converted into the corresponding oxazoline moiety via an intramolecular cyclization. Furthermore, various kinds of oxazoline auxiliaries can be prepared from phenylglycinol derived amides (Figure 14).[59] One more advantage expected from oxazolines is that they can be transformed easily into the corresponding carboxylic acid derivatives. Generally, cleavage of an amide bond needs harsher reaction conditions.

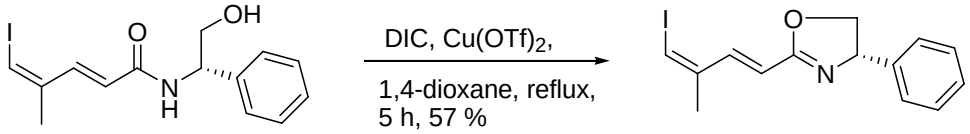


Amide **Oxazoline**

1^o OH group; DIC, $Cu(OTf)_2$
2^o OH group; a) Mesylation
b) Intramolecular S_N2 reaction
3^o OH group; H^+ mediated S_N1 reaction

Figure 15. Preparation of oxazoline auxiliaries from phenylglycinol and its derivatives.

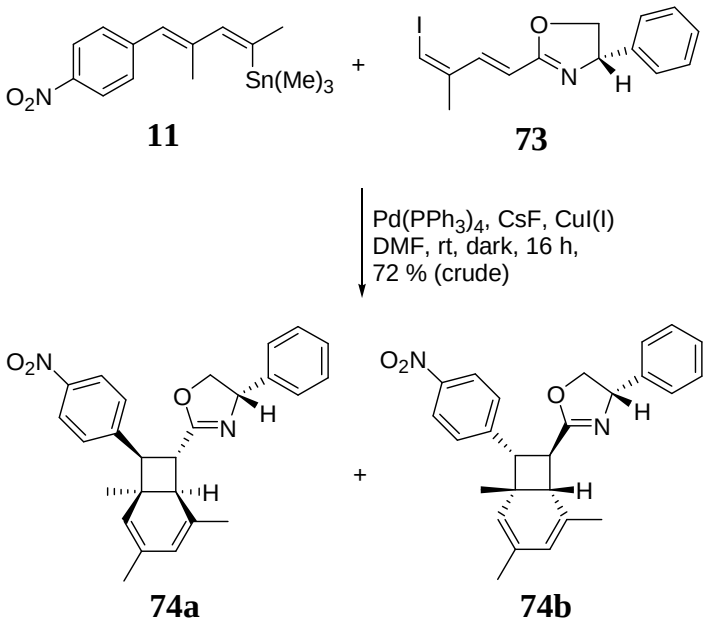
In order to support the idea that C2-symmetry on oxazoline-based auxiliary could reduce the number of possible transition states, we tested tetraene **72** as a control model. First, iododiene-oxazoline **73** was prepared from amide **42** by an intramolecular S_N2 type cyclization, mediated by copper triflate and diisopropylcarbodiimide (DIC), in modest yield (Scheme 27).



42 **73**

Scheme 27. Preparation of iododiene-oxazoline **73**.

As we expected, two inseparable diatereomeric SNF analogs **74a** and **74b** were produced in a ratio of 1 : 1 (Scheme 28).



Scheme 28. Asymmetric 8π electrocyclization of tetraene **72**.

The result stressed that both the oxazoline ring and C2-symmetry on the auxiliary are required for chiral induction in 8π electrocyclization of a tetraene substrate.

1.2.2.7. Asymmetric induction by C2 symmetrized oxazoline based auxiliary

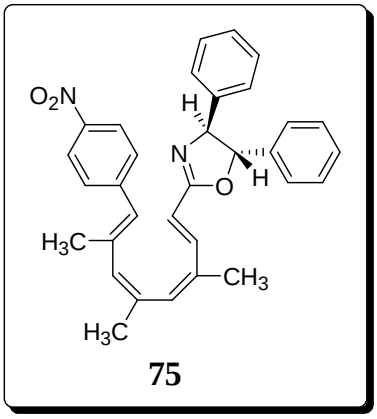
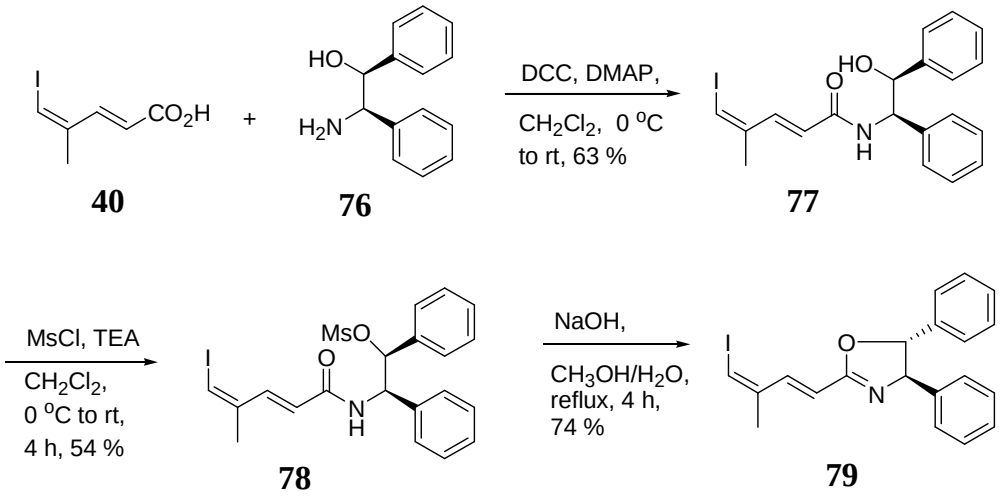


Figure 16. Structure of a tetraene substrate bearing *trans*-4,5-diphenyl oxazoline **75**.

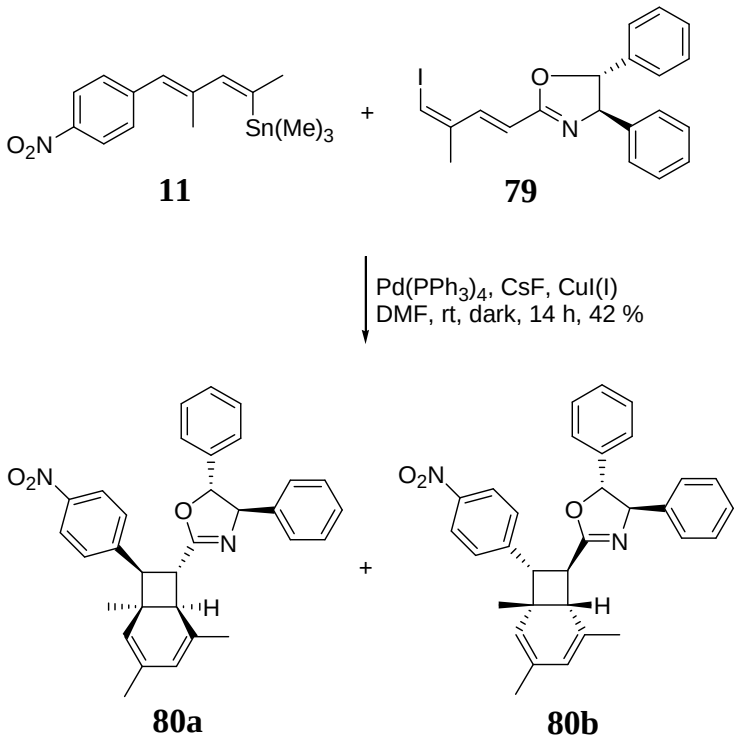
Commercially available (S,R)-1,2-diphenyl aminoalcohol **76** was chosen because it can generate *trans*-4,5-diphenyl moiety on oxazoline ring. Aminoalcohol **76** was coupled with **40** by the treatment with DCC and DMAP to afford iododiene-amide **77**. Mesylation of **77** provided **78,** and cyclization under basic conditions yielded iododiene-oxazoline **79** (Scheme 29)



40 **76** **77** **78** **79**

Scheme 29. Preparation of iododiene-oxazoline **79**.

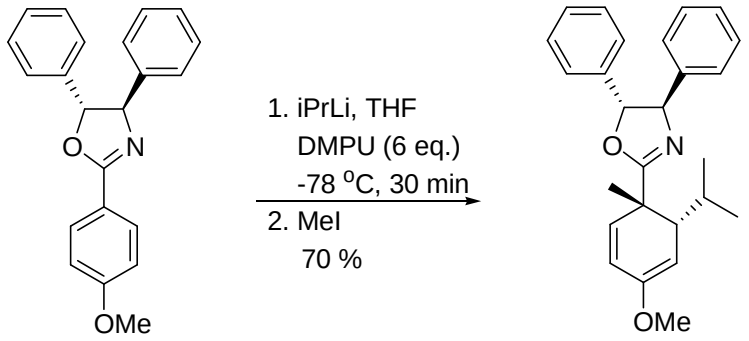
The 8π, 6π electrocyclization of tetraene **75**, which was generated by Stille coupling between **11** and **79,** afforded two inseparable diastereomeric SNF analogs **80a** and **80b** in 42 % yield (Scheme 30).



Scheme 30. Asymmetric 8π electrocyclization of tetraene **75**.

In this case, two diatereomeric bicyclooctadienes **80a** and **80b** were produced in a ratio of 1 : 6 on the basis of ^{1}H NMR analysis. However, it was not easy to calculate the exact stereoselectivity because **80a** and **80b** showed the same chemical shifts for all protons, except for those protons on one of the three CH_3 group in the bicyclooctadiene skeleton. Presumably, due to effective C2-symmetry on the oxazoline, the hydrogens in **80a** and **80b** are exposed to very similar magnetic fields.

The only example using the same oxazoline auxiliary system in asymmetric synthesis was reported by the Clayden group at 2008.[60] They adopted the auxiliary for the stereoselective dearomatizing addition of MeI to the benzene ring of **81**. Treatment with excess 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) stereospecifically introduced both an isopropyl moiety from isopropyl lithium and methyl moiety to yield a single diastereomer **82**. (Scheme 31).

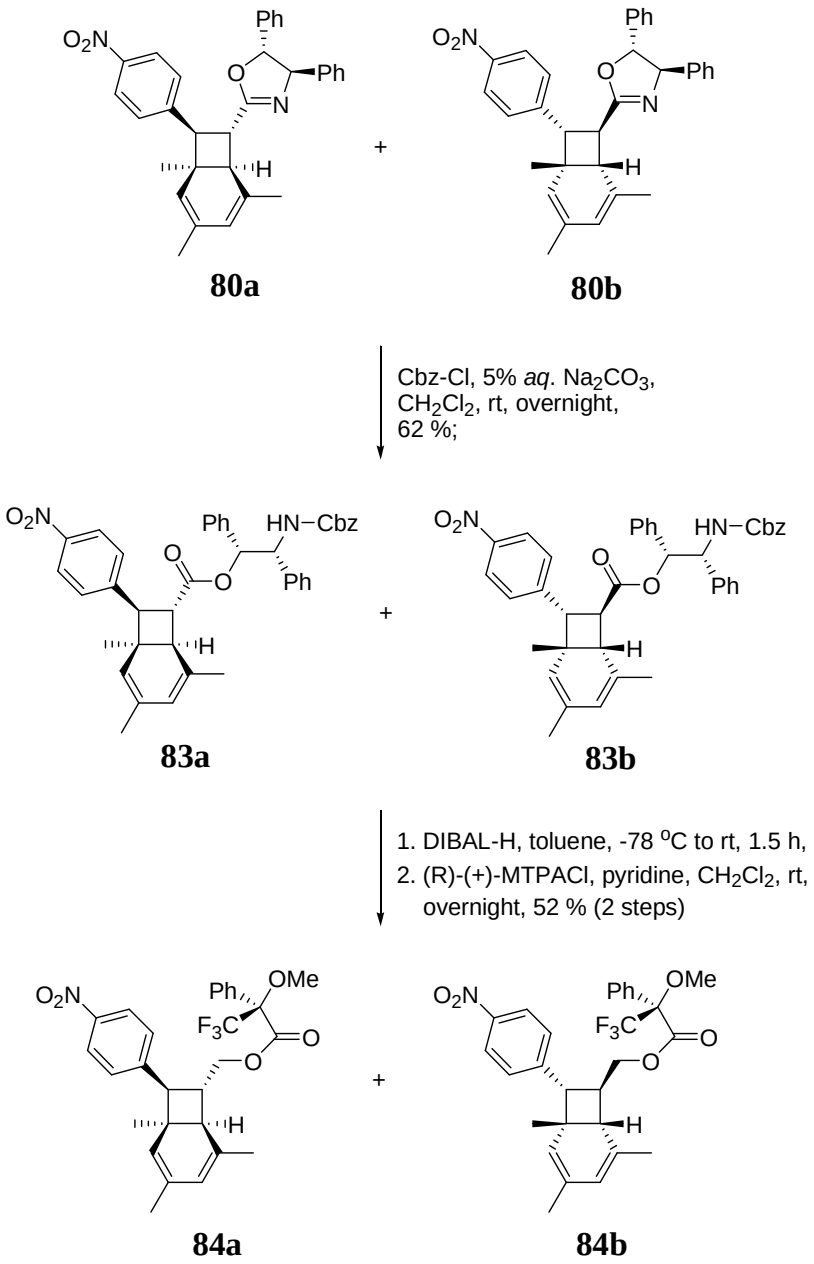


81 **82**

Scheme 31. DMPU-promoted dearomatization by the 4,5-*trans*-diphenyloxazoline auxiliary.

According to Clayden, the configuration of **82** may arise from coordination of isopropyllithium to the basic nitrogen atom of the oxazoline, followed by 1,4-addition to the 2-position of the 4-methoxyphenyl ring from the face anti to the 4-phenyl substituent of the oxazoline ring.

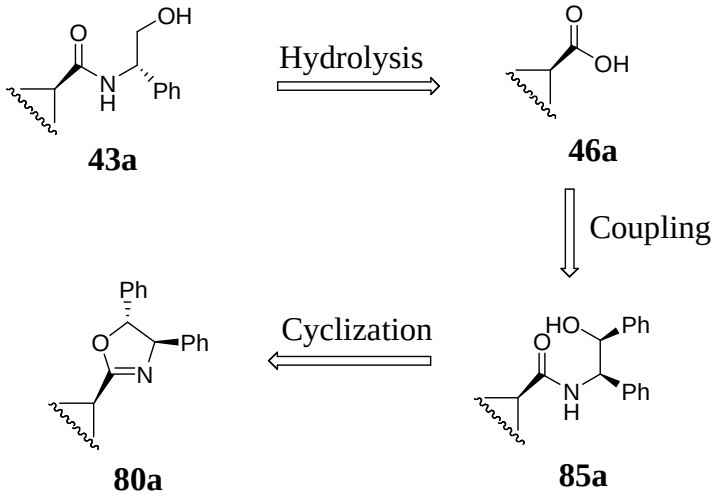
With the asymmetric 8π electrocyclization of tetraene **75**, accurate calculation of the diastereoselectivity in **80a** and **80b** was performed based on Mosher ester analysis. The inseparable mixture of **80a** and **80b** was treated with Cbz-Cl to be converted into the corresponding bicyclooctadienes **83a** and **83b** with 62 % yield.[61] Reduction by DIBAL-H, followed by introducing (R)-MTPA-Cl afforded corresponding (S)-Mosher esters **84a** and **84b** in 52 % for the two steps (Scheme 32).[61] The diastereomeric ratio observed in **84a** and **84b** confirmed that **80a** and **80b** were produced with 1 : 6 ratio. To the best of our knowledge, this is the first example of an asymmetric 8π electrocyclization influenced by a *trans*-4,5-diphenyl oxazoline auxiliary.



Scheme 32. Preparation of (S)-Mosher esters **84a** and **84b**.

Determination of relative stereochemistry of the major isomer from **80a** and **80b** was equally as important as improvement of stereoselectivity in 8π electrocyclization, due to the significantly different biological activities shown in SNF 4435 C and D. In addition, the confirmed relative stereochemistry may support an understanding of helical transition states involved in the 8π ring closure. Our initial strategy focused on enantiomeric SNF analog **43a,** the structure of which was determined using X-ray crystallography. Hydrolysis of **43a** provides the

corresponding carboxylic acid **46a**. Introduction of (S,R)-diphenylglycinol **76** to **46a** would afford **85a**, followed by cyclization to yield enatiomeric bicyclooctadiene **80a** (Scheme 33). 1H NMR spectra of **80a** should be exactly matched with that of one isomer from a mixture of **80a** and **80b.**



Scheme 33. Transformation of known **43a** into **80a**.

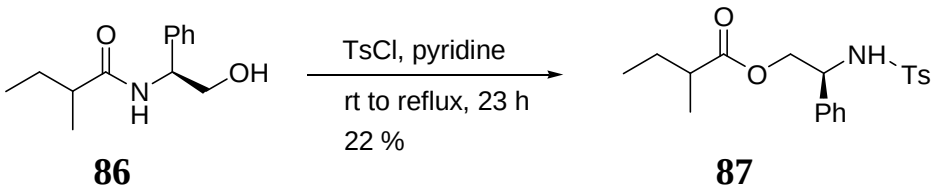
Despite much synthetic efforts, hydrolysis of both amides **43a** and **43b** was not successful.[49,63-65] (See Table 1.)

Table 1. Results of hydrolysis of **43a** and **43b**.

Starting	Reaction conditions	Result
43a	1N *aq*. HCl/EtOH, reflux, 3 h	Neither starting material nor product
	1N *aq*. KOH/EtOH, reflux, 3 h	
	1N *aq*. NaOH/EtOH, reflux, 2.2 h	
43b	1N *aq*. NaOH/EtOH, 80 ^{o}C, 3 h	
	1N *aq*. NaOH/EtOH, 70 ^{o}C, 3 h	Most starting material was recovered

Presumably, compounds **43a** and **43b** might be vulnerable under harsh acidic or basic conditions. Especially, high temperature might more provoke decomposition of the bicyclo[4.2.0]ocatadiene framework. Therefore, relatively mild hydrolysis conditions are needed for compounds **43a** and

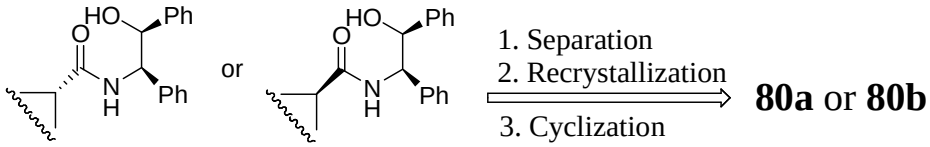
43b. A model compound **86** was treated with *p*-TsCl in pyridine solution to afford ester **87** (Scheme 34).[66] Due to the low yield, however, this method could not apply to **43a** or **43b**.



86 **87**

Scheme 34. Hydrolysis of amide **86**.

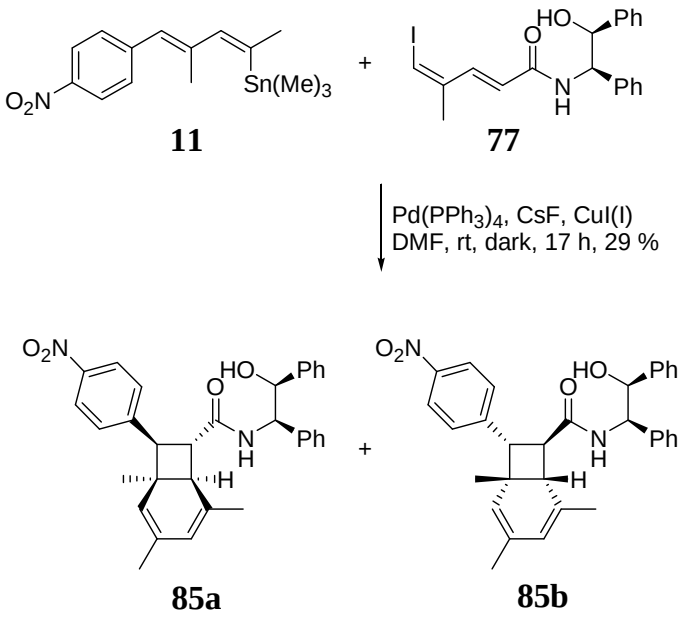
Our focus turned to the separation of **85a** and **85b**. We cautiously predicted that like **43a** and **43b,** the two diastereomers **85a** and **85b** might show similar behavior on silica gel. If we were able to obtain either pure **85a** or **85b**, its relative stereochemistry could be determined by X-ray crystallography. Therefore, structural elucidation of the major isomer from **80a** and **80b** could be used to assign the relative stereochemisty of **85a** or **85b** (Scheme 35).



85a **85b**

Scheme 35. Determination of relative stereochemistry of **80a** or **80b** from **85a** or **85b**.

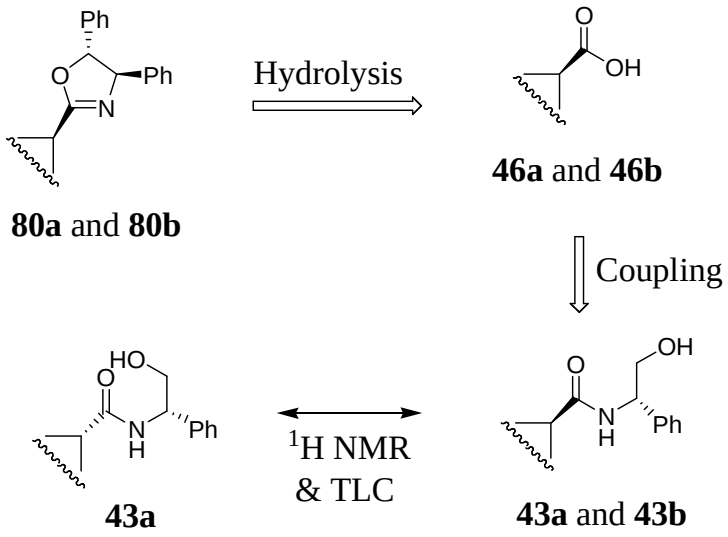
Two diastereomeric SNF analogs **85a** and **85b** were produced in a ratio of 1 : 1 under the given conditions (Scheme 36).



Scheme 36. Preparation of SNF analogs **85a** and **85b**.

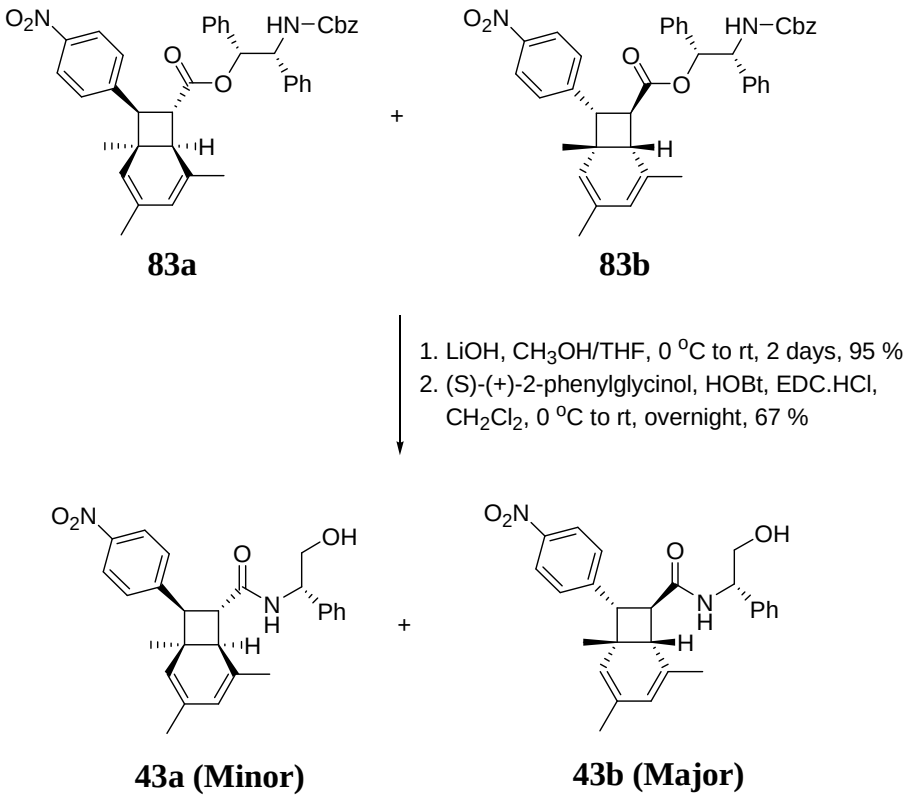
Initially, the same TLC condition, which clearly separated **43a** and **43b,** applied to **85a** and **85b.** However, only single spot was observed under UV. A lot of trials slightly increased the ratio between **85a** and **85b** from 1 : 1 to 1 : 2.

We reexamined the first strategy shown in Scheme 33. We thought that if the dr between **80a** and **80b** is not changed throughout hydrolysis and coupling sequence, the relative stereochemistry of the major isomer from **80a** and **80b** can be indirectly determined by comparing with the known **43a** (Scheme 37). The major isomer from **80a** and **80b** should correspond to **43a** or its diastereomer **43b.**



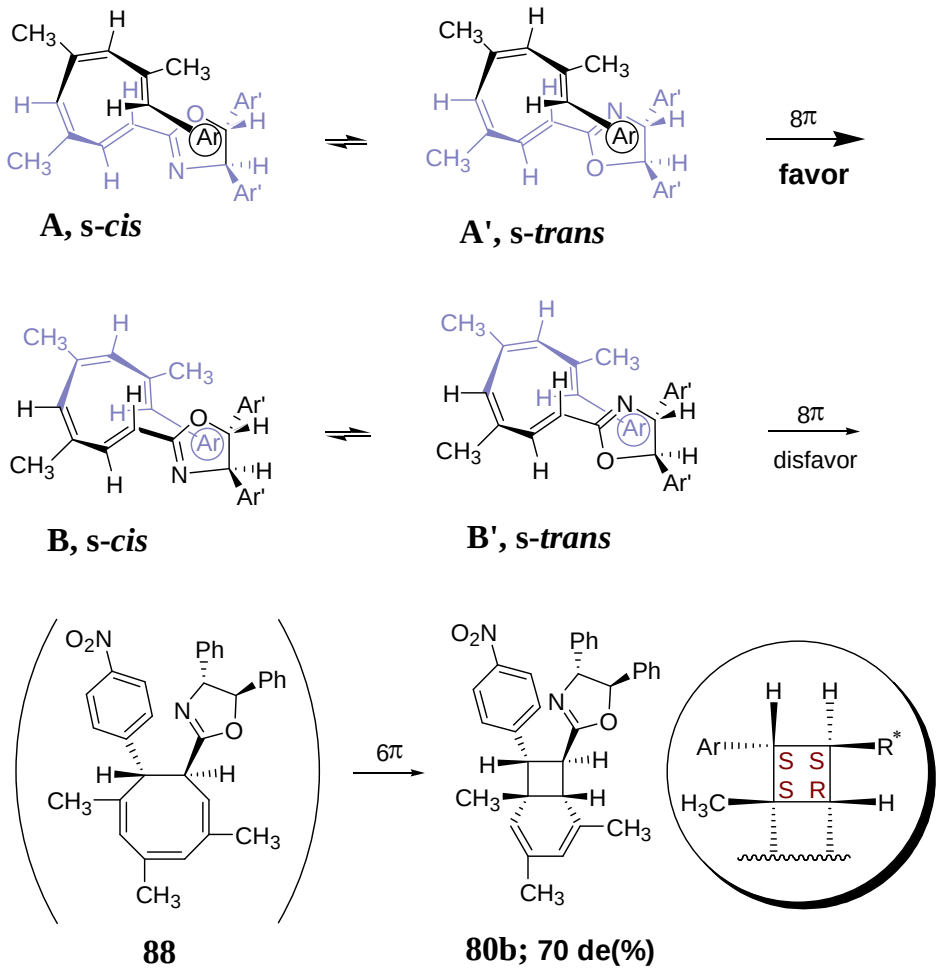
Scheme 37. Reverse transformation of the 1 : 6 mixture **80a** and **80b**.

Diastereomeric **83a** and **83b**, which was directly prepared from the 1 : 6 mixture of **80a** and **80b**, was hydrolyzed with LiOH in a mixture of methanol and THF to afford corresponding carboxylic acids **46a** and **46b**.[67] Then, (S)-(+)-2-phenylglycinol **41** was introduced to racemic **46a** and **46b** by the treatment of N-hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) to yield **43a** and **43b** (Scheme 38).[62] TLC behavior of the major isomer was inconsistent with that of authentic **43a** and consistent with that of authentic **43b**. Therefore, we were able to designate the major isomer from the 1 : 6 mixture as **80b**.



Scheme 38. Determination of the relative stereochemistry of **80b**.

Determination of the relative stereochemistry of **80b** lends support to our original hypothesis**.** Due to the pseudo C2-symmetry, conformations (**A** : **A'** and **B** : **B'**) generated from tetraene **75** are considered as almost equal in energy. It could reduce the number of possible conformations for the transition states from four to two (Scheme 39). In addition, we cautiously predict that helical transition state conformations of **A** and **A'** would be more favorable than those of **B** and **B'** because **A** and **A'** may be interrupted by less steric hindrance between the 4-nitrophenyl and either phenyl on the auxiliary in the state for conrotatory ring closure. Therefore, cyclooctatriene intermediate **88** is preferred and bicyclooctadiene **80b** is produced as the major product.



Scheme 39. Proposed mechanism to lead the major **80b**.

1.2.2.8. Asymmetric induction by sterically more hindered oxazoline based auxiliary

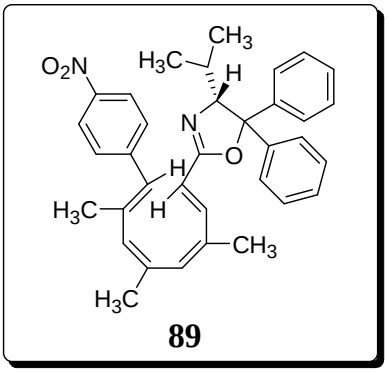
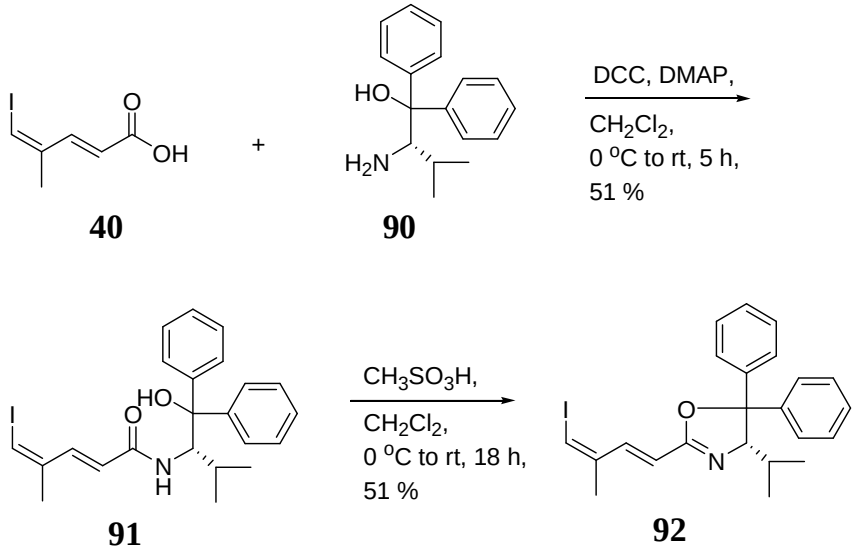


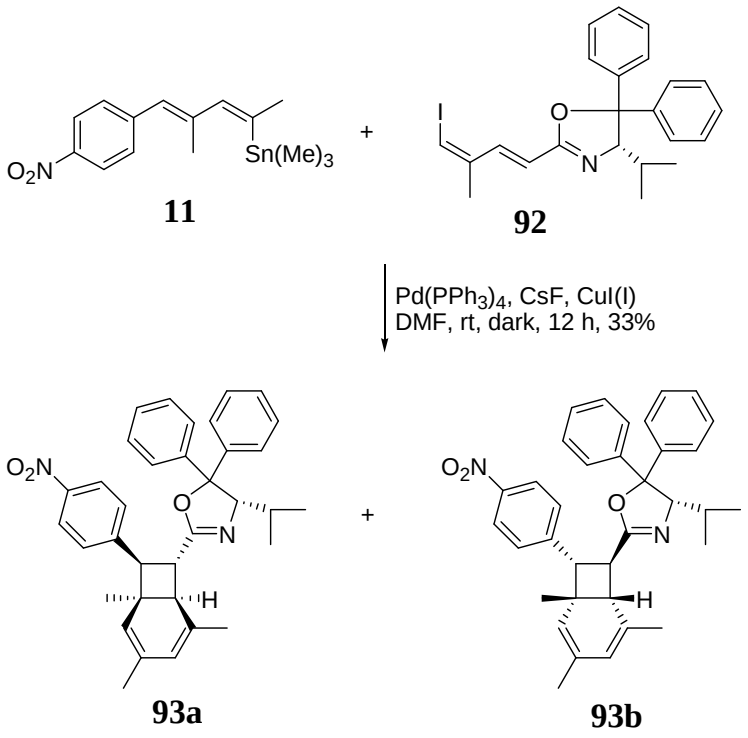
Figure 17. Structure of a tetraene substrate bearing *gem*-diphenyl and isopropyl oxazoline **89**.

With the confidence that 8π (8π, 6π) electrocyclization can be stereochemically controlled, we thought that introducing an additional substituent on the oxazoline auxiliary would more greatly disfavor two of the transition states for closure but not after, substantially, the product ratio. Therefore, we tested the tetraene substrate bearing *gem*-diphenyl and isopropyl groups (**89)**. For the preparation of iododiene-oxazoline **92,** (S)-(-)-2-amino-3-methyl-1,1-diphenylbutan-1-ol **90**, which is inexpensive and commercially available, and **40** were coupled under DCC and DMAP to produce iododiene-amide **91**. Treatment of methanesulfonic acid of **91** directly afforded **92** with a modest yield (Scheme 40).



Scheme 40. Preparation of iododiene-oxazoline **92**.

Vinly stannane **11** and iododiene-oxazoline **92** were coupled via Stille coupling reaction in the dark, and simultaneously cyclized to yield 33 % of an inseparable mixture of diastereomeric SNF analogs **93a** and **93b** in a ratio of 3:1 or 1 : 3 (Scheme 41).



Scheme 41. Asymmetric 8π electrocyclization of tetraene **89**.

Although a larger moiety was introduced on the oxazoline in the tetraene substrate **89**, dr was not impressive. Presumably, the effect of the additional substituents is not simple. The rationally designed tetraene **75** might be an optimized system towards chiral induction of the 8π electrocyclization.

1.2.2.9. Asymmetric induction by trans-dinaphthyl based oxazoline auxiliary

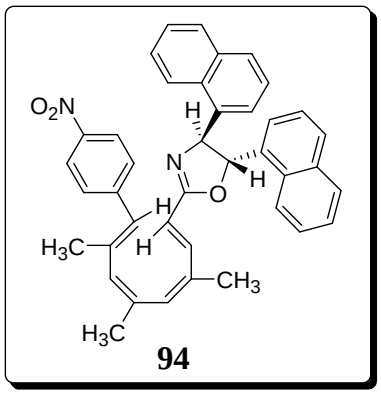
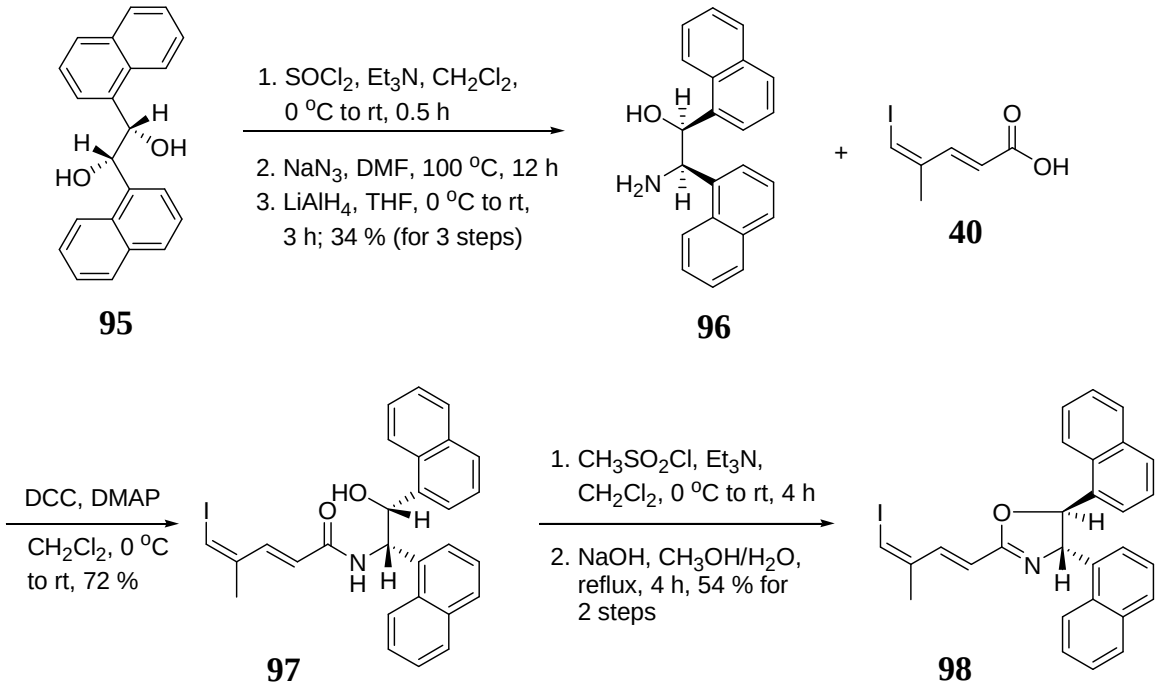


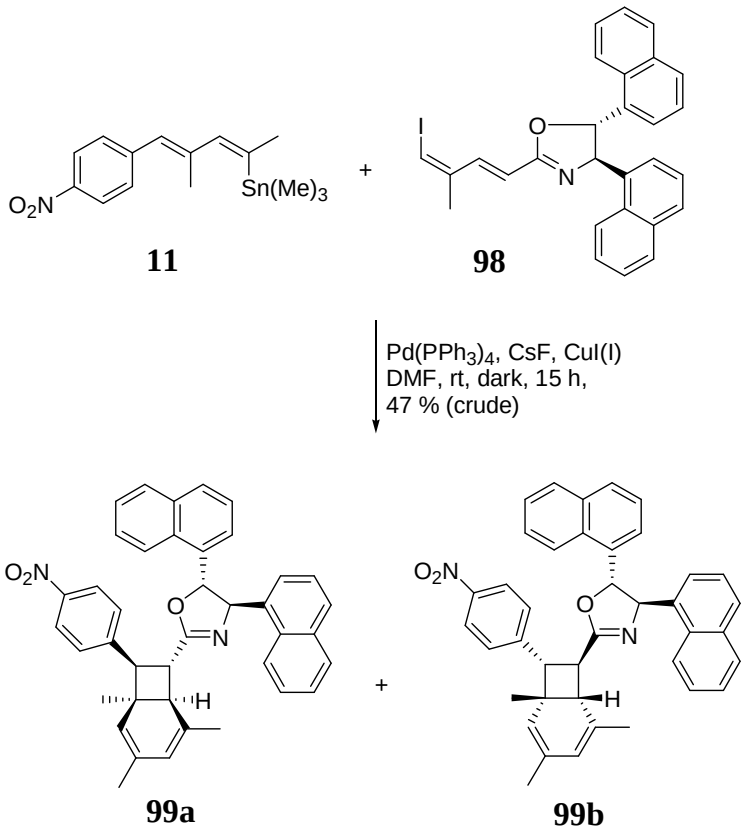
Figure 18. Struture of a tetraene substrate bearing *trans*-4,5-binaphthyl oxazoline **94**.

In order to improve the dr of tetraene **75**, we investigated bigger aryl groups in the oxazoline auxiliary, which should have *trans* geometry. First, we designed a tetraene substrate bearing 4,5-dinaphthyl oxazoline **94** (Figure 17). Commercially available chiral diol **95** was treated with thionyl chloride to form a cyclic sulfite, which was subsequently opened by the azide ion. Treatment of $LiAlH_4$ converted the azide compound into aminoalcohol **96,** followed by recrystallization.[68] Then **96** and **40** were coupled in the presence of DCC and DMAP to afford iododiene-amide **97**. Finally, methanesulfonyl chloride was used to convert alcohol **97** to mesylate, which was cyclized under basic conditions to afford iododiene-oxazolone **98** (Scheme 42).



Scheme 42. Preparation of iododiene-oxazoline **98**.

Under the given reaction conditions, **11** and **98** were coupled, and then double cyclized to provide two diastereomeric SNF analogs **99a** and **99b** (Scheme 43). Unlike **80a** and **80b**, bicyclooctadienes **99a** and **99b** was unable to separate. In addition, we could not find any critical signals in the proton NMR.



Scheme 43. Asymmetric 8π electrocyclization of tetraene **94**.

1.2.2.10. Asymmetric induction by trans-ditolyl based oxazoline auxiliary

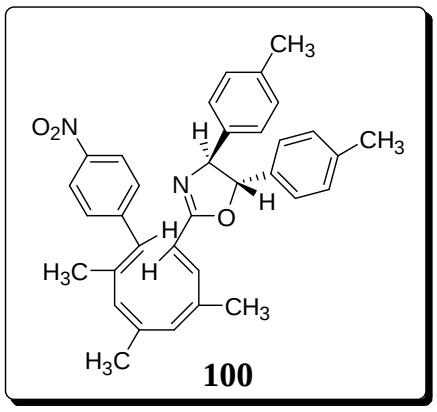
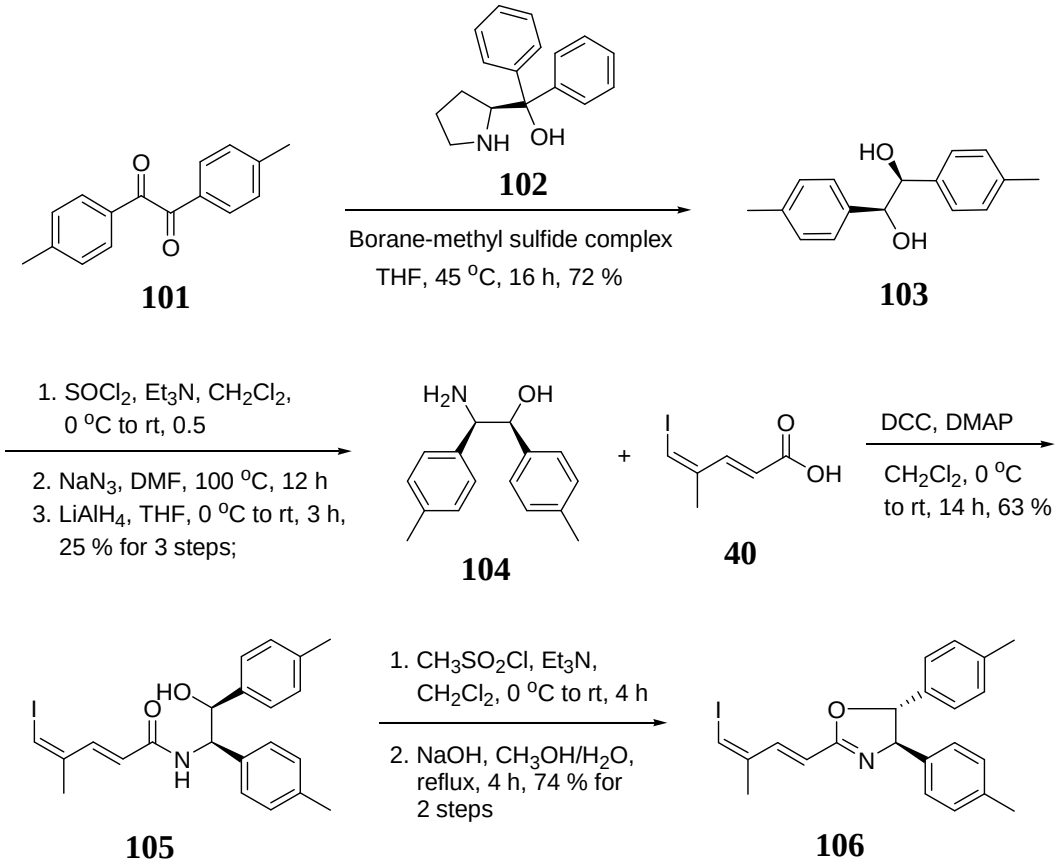


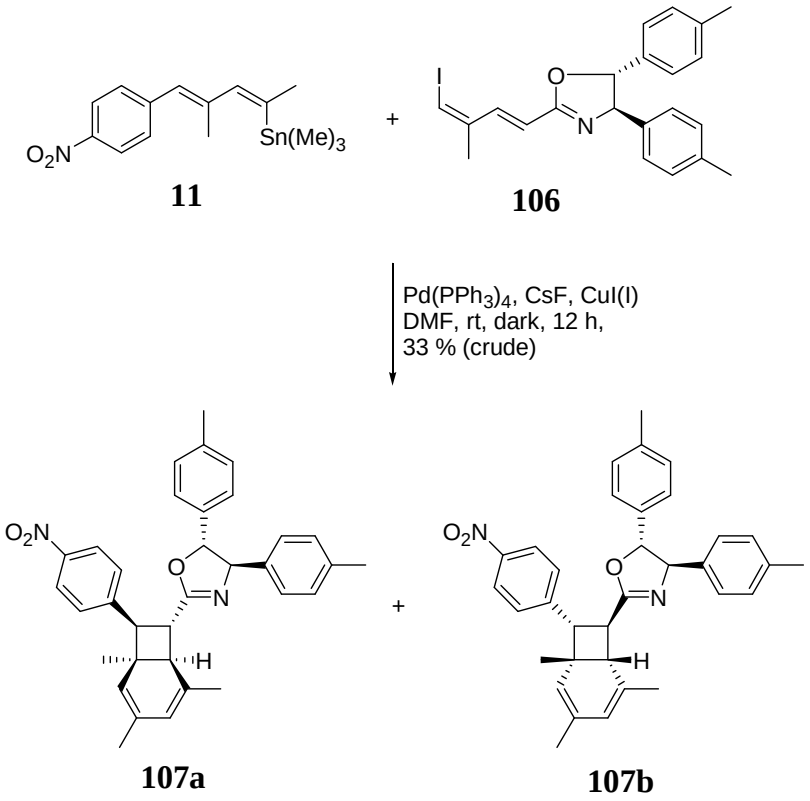
Figure 19. Structure of a tetraene substrate bearing *trans*-4,5-ditolyl oxazoline **100**.

Tetraene substrate **100** was designed to generate a bigger steric effect, which might improve stereoselectivity compared to tetraene **75.** The known C2-symmetric diol **103** was prepared from the 1,2-diketone **101** via stereoreoselective oxazaborolidine-catalyzed **102** reduction with borane-methyl sulfide complex (BMS).[69] Chiral diol **103** was treated with thionyl chloride to form a cyclic sulfite, which was subsequently opened by the azide ion. Treatment with $LiAlH_4$ converted the azide into corresponding aminoalcohol **104,** followed by recrystallization.[67] **104** and **40** were coupled in the presence of DCC and DMAP to afford iododiene-amide **105.** Finally, the hydroxyl group in **105** was converted to corresponding mesylate, which was cyclized under basic conditions to afford iododiene-oxazoline **106** (Scheme 44).



Scheme 44. Preparation of iododiene-oxazoline **106**.

Compounds **11** and **106** were coupled to produce the tetraene **100**, which then cyclized to give two diastereomeric SNF analogs **107a** and **107b** (Scheme 45). However, like **99a** and **99b,** bicyclooctadienes **107a** and **107b** was unable to separate. In addition, we could not find any critical signals in the proton NMR.



Scheme 45. Asymmetric 8π electrocyclization of tetraene **100**.

1.3. Conclusion

Preparation of optically pure SNF analogs was thoroughly examined by chiral induction in 8π electrocyclization of a series of (2E, 4Z, 6Z, 8E)-tetraene substrates bearing amide- and oxazoline-based chiral auxiliaries. The rationally designed chiral *trans*-4,5-diphenyl oxazoline auxiliary on the tetraene substrate **75** showed promising stereoselectivity (dr, 1 : 6) in asymmetric 8π electrocyclization. In addition, the first X-ray crystal structure of the chiral SNF analog **43a** significantly contributed to determining absolute stereochemistry of the major isomer **80b** from the asymmetric reaction. Assignment of absolute stereochemistry to **80b** supported the hypothesis that the oxazoline auxiliary on the tetraene substrate **75** prefers one of the four helical transition states in the process of 8π conrotatory ring closure. To our knowledge, 8π electrocyclization of **75** is the first example of the exploitation of pseudo C-2 symmetry of *trans*-4,5-disubstituted oxazolines for asymmetric induction. This notable stereoselectivity observed in the 8π electrocyclization could directly lead to the development of analogs of the SNF multidrug resistance reversal agent.

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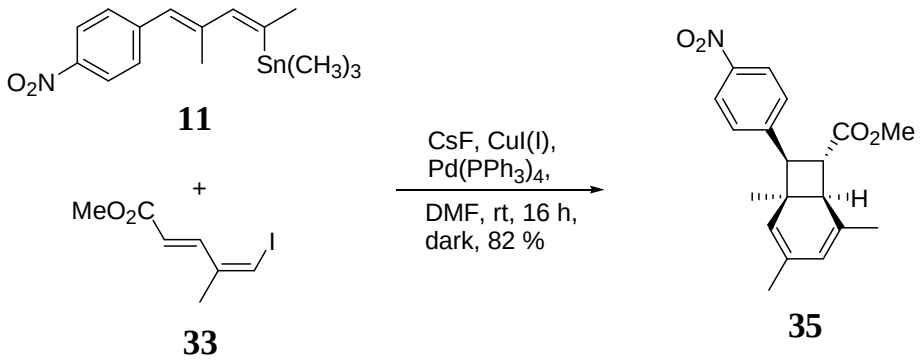
1.5. Experimental section

General experimental methods

All air- and moisture-sensitive reactions were carried out under argon (Ar) atmosphere with freshly distilled solvents and oven-dried or flame-dried glassware. Handling of solvents and solutions for air- and moisture-sensitive reactions was performed by carefully dried glass syringe or cannula under a positive pressure of Ar atmosphere. Unless indicated otherwise, commercially available reagents were used as supplied without further purification. Tetrahedrofuran (THF) and diethyl ether (Et_2O) for reactions were distilled from sodium-benzophenone ketyl and dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Dimethylforamide (DMF), extra dried with molecular sieve, was purchased from ACROS and carefully maintained under a positive pressure. For Stille coupling-8π, 6π electrocyclizations, the reaction mixture was thoroughly degassed with a stream of Ar both before and after adding tetrakis triphenylphosphine palladium. Then it was immediately wrapped with aluminum foil.

Chromatography was carried out with HPLC grade ethyl acetate (EtOAc), *n*-hexane, and methanol. All experiments were monitored by thin layer chromatography (TLC). Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or staining with a 10% solution of phosphomolybdenic acid (PMA) in ethanol and then heating. Flash chromatography was carried out with Fisher brand silica gel (170-400 mesh). For diastereomeric bicyclooctadienes, preparative TLC was performed on Whatman® TLC plates (1000 μm). All ^{1}H NMR spectra for bicyclo[4.2.0]octadiene compounds were recorded with a Varian Inova-600 (600 MHz) instrument. Multiplicities are abbreviated as follows: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet, bs = broad singlet. All ^{13}C NMR spectra were recorded with a Varian Inova-400 (100 MHz) spectrometer. Infrared spectra were collected with a Perkin-Elmer 1600 Series FT-IR instrument. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer at the University of Illinois at Urbana–Champaign. X-ray crystallography was performed on an Oxford Gemini X-Ray Diffractometer.

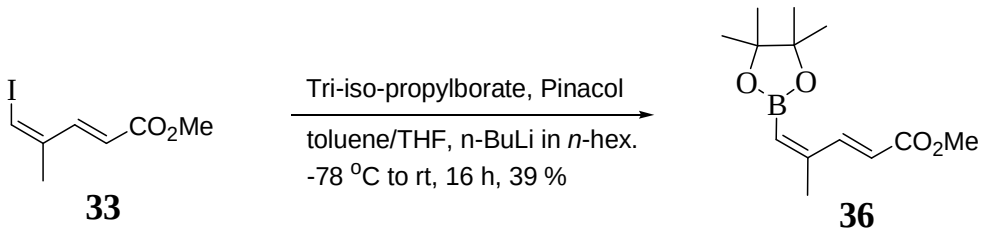
Diastereomeric excesse (% de) for bicyclooctadienes were calculated on the basis of the ^{1}H NMR spectra.



Racemic bicyclooctadiene 35 from Stille coupling. To a solution of vinyl stannane **11** (45 mg, 0.12 mmol) and iododiene **33** (32 mg, 0.12 mmol) in anhydrous DMF (1.7 mL) were added cesium fluoride, CsF (40 mg, 0.24 mmol) and copper iodide, CuI(I) (5 mg, 0.02 mmol) at rt under degassing with a stream of Ar. After adding tetrakis triphenylphosphine palladium, $Pd(PPh_3)_4$ (14 mg, 0.01 mmol), the reaction flask was immediately wrapped with aluminum foil and was continued deoxygenating for further 5 min. The reaction mixture stirred for 16 h, and then diluted with EtOAc (25 mL). The organic layer was washed with saturated NH_4Cl solution (3 x 25 mL). The combined *aq*. layers were extracted with EtOAc (3 x 25 mL), and the combined organic solution was dried over $MgSO_4$, and concentrated under vacuum. The residue was purified on silica gel with $EtOA_C$/ n-hexane (1/9) to give 32 mg (82 %) of **35** as pale yellow oil.

R_f: 0.6 (EtOAc/*n*-Hexane, 1/9). IR: *v* 2931, 1518, 1344, 1111, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 5.45 (s, 1H), 4.41 (s, 1H), 3.73 (d, *J* = 10.4 Hz, 1H), 3.70 (s, 1H), 3.47 (dd, *J* = 10.4 Hz, 9.2 Hz, 1H), 2.73 (d, *J* = 9.2 Hz, 1H), 1.79 (s, 3H), 1.61 (s, 3H), 1.25 (s, 3H).

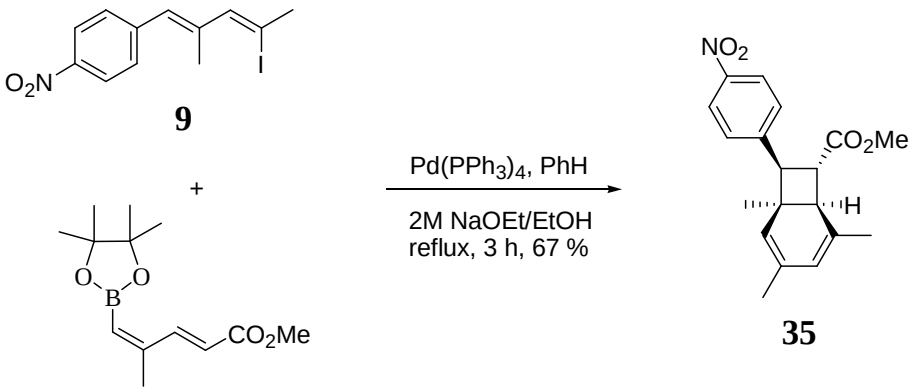
* Spectroscopic properties were in agreement with literature values.[1]



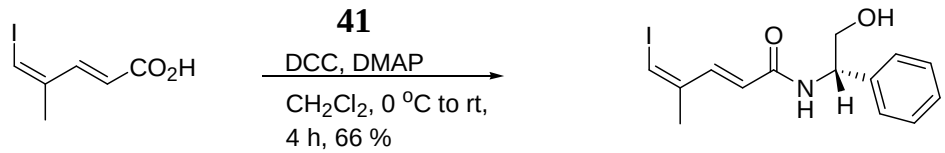
[1] Parker, K. A.; Lim, Y. H. *Org Lett* **2004**, *6*, 161.

Boronic ester 36. To a solution of iododiene **33** (54 mg, 0.21 mmol) and triisopropyl borate (72 μL, 0.31 mmol) in a mixture of toluene (1.7 mL) and THF (0.5 mL) at -78 ^{o}C was added *n*-butyllithium, 1.6 M solution in hexanes (190 μL, 0.30mmol). The reaction mixture was stirred at -78 ^{o}C for 0.5 h and pinacol (55 μL, 0.46 mmol) was added at the same temperature. The mixture was protected from light by aluminum foil and allowed to warm to rt and stirred for 16 h. The reaction mixture was then diluted with Et_2O, and then washed with saturated NH_4Cl, H_2O, and brine. The organic layer was dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel column chromatography (Et_2O:*n*-hexane, 1:9) to provide 21.4 mg (39 %) of **36** as a yellow solid.

R_f: 0.34 (EtOAc/*n*-hexane, 1/5); ^{1}H NMR (600 MHz, CD_3OD): δ 8.23 (d, J = 15.6 Hz, 1H), 5.98 (d, J = 15.6 Hz, 1H), 5.69 (s, 1H), 3.77 (s, 3H), 1.98 (s, 3H), 1.29 (s, 12H).



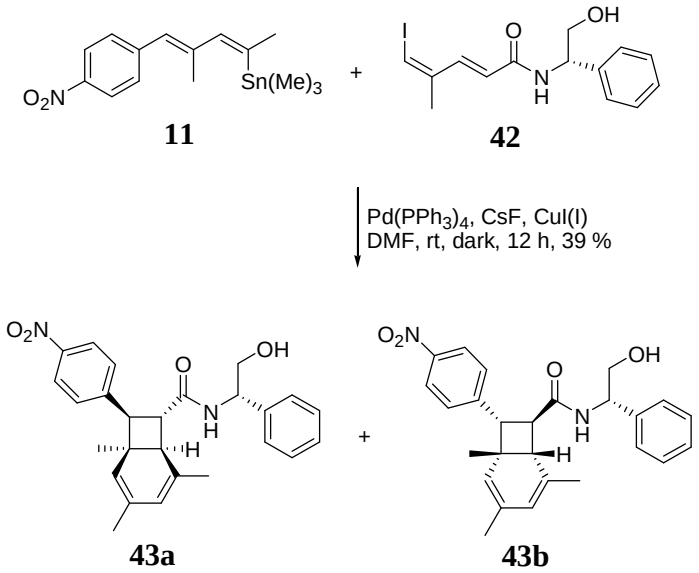
Racemic bicyclooctadiene 35 via Suzuki-Miyaura coupling. To a solution of vinyl iodide **9** (26.1 mg, 0.08 mmol) and boronic ester **36** (21.4 mg, 0.08 mmol) in dried benzene (3.0 mL) was added 2M NaOEt in EtOH (90 μL, 0.18 mmol). And then, $Pd(PPh_3)_4$ (9.1 mg, 0.008 mmol) was added under Ar atmosphere. The reaction flask was immediately wrapped with aluminum foil and refluxed for 3 h. The reaction mixture was diluted with EtOAc (25 mL). The organic layer was washed with saturated NH_4Cl solution (3 x 25 mL). The combined *aq*. layers were extracted with EtOAc (3 x 25 mL), dried over $MgSO_4$, and concentrated under vacuum. Preparative chromatography (EtOAc:*n*-hexane, 1:9) afforded 17. 5 mg (67 %) of **35** as pale yellow oil. *Spectroscopic properties of **35** from Suzuki-Miyaura coupling were in agreement with **35** values from the Stille coupling.



40 **42**

Iododiene-amide 42. To a solution of (*S*)-(+)-2-phenylglycinol **41** (132.1 mg, 0.96 mmol) and dienoic acid **40** (210.4 mg, 0.89 mmol) in dry CH_2Cl_2 (30 mL) was slowly added dicyclohexylcarbodiimide (DCC) (197.2 mg, 0.96 mmol) and 4-(*N*,*N*-dimethylamino) pyridine (DMAP) (13.1 mg, 0.11 mmol) in dry CH_2Cl_2 (12 mL) at 0 °C under Ar atmosphere. The reaction mixture was allowed to warm to rt. After stirring for further 4 h, the reaction mixture was filtered through a Celite® and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:1) to provide 210.3 mg (66 %) of **42** as a white solid.

R_f: 0.30 (EtOAc/*n*-hexane, 1/1); IR: 3390, 1646, 1600, 1417 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.53 (d, J = 15.2 Hz, 1H), 7.22-7.32 (m, 5H), 6.60 (s, 1H), 6.36 (d, J = 15.2 Hz, 1H), 5.06 (t, J = 4.0 Hz, 1H), 3.75 (m, 2H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 166.7, 141.2, 139.9, 128.4, 127.3, 126.9, 125.2, 86.2, 65.0, 56.1, 19.7; HRMS(ESI-MS) Calcd. for $C_{14}H_{17}INO_2$ $[(M + H)]^+$ 358.0226, found 358.0297.

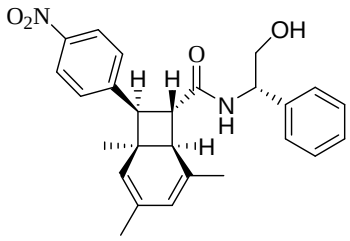


11 **42**

43a **43b**

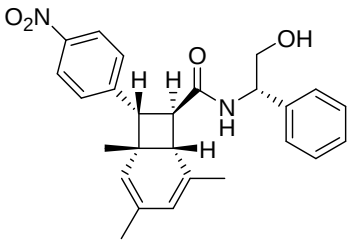
SNF analogs 43a and 43b. To a solution of vinyl stannane **11** (32.4 mg, 0.088 mmol) and iododiene-amide **42** (30.9 mg, 0.087 mmol) in anhydrous DMF (3.6 mL) were added cesium fluoride, CsF (30.0 mg, 0.197 mmol) and copper iodide, CuI(I) (3.8 mg, 0.020 mmol) at rt under deoxygenating with a stream of Ar. After adding $Pd(PPh_3)_4$ (10.2 mg, 0.009 mmol), the reaction flask was immediately wrapped with aluminum foil and was continued deoxygenating for further 5 min. The reaction mixture was stirred for 12 h, and then diluted with EtOAc (25 mL). The organic layer was washed with saturated NH_4Cl solution (3 x 25 mL). The combined *aq*. layers were extracted with EtOAc (3 x 25 mL), and the combined organic solution was dried over $MgSO_4$, and concentrated under vacuum. Preparative chromatography (EtOAc:*n*-hexane, 1:1) afforded 5.1 mg (14 %) of **43a** and 9.5 mg (25 %) of 4**3b** in a ratio of 2 : 3.

43a (slower moving isomer)



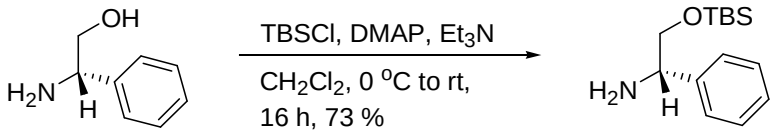
R_f: 0.30 (EtOAc/*n*-hexane, 1/1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.17 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.14-7.30 (m, 5H), 6.04 (d, J = 5.4 Hz, 1H), 5.49 (s, 1H), 5.06 (dd, J = 11.4 Hz, 4.8 Hz, 1H), 4.48 (s, 1H), 3.88 (d, J = 5.4 Hz, 2H), 3.79 (d, J = 10.2 Hz, 1H), 3.31 (dd, J = 9.6 Hz, 9.0 Hz, 1H), 2.80 (d, J = 9.0 Hz, 1H), 1.84 (s, 3H), 1.65 (s, 3H), 1.25 (s, 3H).

43b (faster moving isomer)



R_f: 0.40 (EtOAc/*n*-hexane, 1/1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.19 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.24-7.35 (m, 5H), 6.09 (d, J = 6.0 Hz, 1H), 5.46 (s, 1H), 5.04 (dd, J = 11.4 Hz,

4.8 Hz, 1H), 4.48 (s, 1H), 3.84 (d, *J* = 5.4 Hz, 2H), 3.83 (d, *J* = 10.8 Hz, 1H), 3.30 (dd, *J* = 9.3 Hz, 8.4 Hz, 1H), 2.73 (d, *J* = 9.0 Hz, 1H), 1.71 (s, 3H), 1.64 (s, 3H), 1.24 (s, 3H).

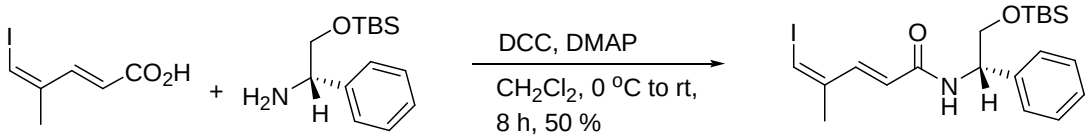


41 **49**

TBS protected amine 49. To a stirring solution of (*S*)-(+)-2-phenylglycinol **41** (98.1 mg, 0.71 mmol) in dry CH_2Cl_2 (2.5 mL) was added triethylamine (180 μL, 1.29 mmol) followed by DMAP (9.0 mg, 0.07 mmol). After 5 min, *tert*-butyldiphenylchlorosilane (TBS-Cl) (214.5 mg, 0.78 mmol) was added in one portion. The reaction mixture was stirred for 16 h at rt, quenched with H_2O (5 mL), and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:3 to 1:2) to provide 129.2 mg (73 %) of **49** as colorless oil.

R_f: 0.66 (EtOAc/*n*-hexane, 1/2); IR: 3388, 1603, 1257, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.47 (m, 5H), 4.14 (dd, *J* = 8.4 Hz, 3.9 Hz,1H), 3.80 (dd, *J* = 9.8 Hz, 3.9 Hz, 1H), 3.59 (dd, *J* = 9.6 Hz, 8.4 Hz, 1H), 1.90 (bs, 2H), 0.97 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.6, 127.6, 127.2, 57.9, 26.2, 18.6, -5.1.

* Spectroscopic properties were in agreement with literature values.[2]



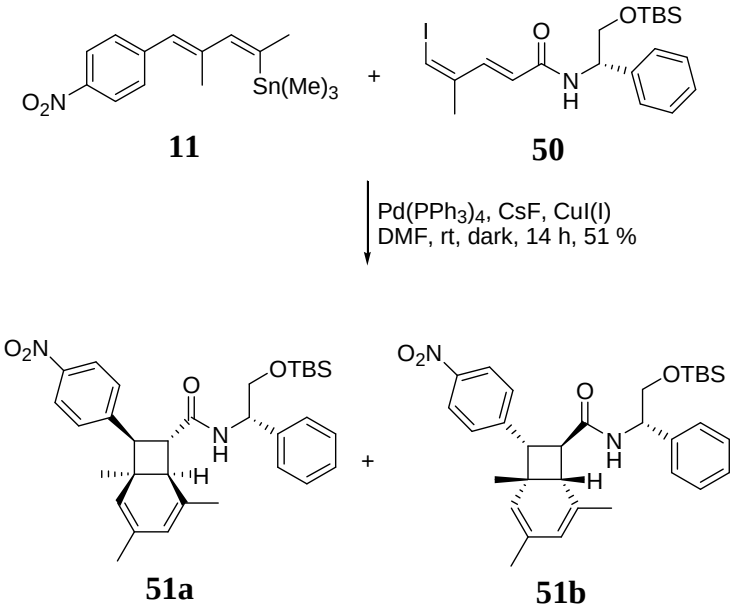
40 **49** **50**

Iododiene-amide 50. To a solution of amine **49** (49.2 mg, 0.20 mmol) and dienoic acid **40** (45.6 mg, 0.19 mmol) in dry CH_2Cl_2 (2.0 mL) was slowly added DCC (47.6 mg, 0.23 mmol) and

[2] Palomo, C; Aizpurua, J. M.; Balentova, Ea; Jimenez, A; Oyarbide, J; Fratila, R. M.; Miranda, J. I. *Org Lett* **2007**, 9, 101.

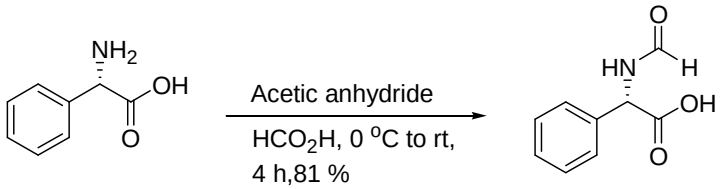
DMAP (5.6 mg, 0.05 mmol) in dry CH_2Cl_2 (1.0 mL) at 0 ^oC under Ar atmosphere. The reaction mixture was allowed to warm to rt. After stirring for further 8 h, the reaction mixture was filtered through a Celite® and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:5) to provide 45.0 mg (50 %) of **50** as viscous oil.

R_f: 0.40 (EtOAc/*n*-hexane, 1/5); IR: 3284, 3060, 1651, 1614, 1539 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 15.6 Hz, 2H), 7.23-7.30 (m, 5H), 6.53 (s, 1H), 6.40 (d, J = 7.6 Hz, 1H), 6.06 (d, J = 15.2 Hz, 1H), 5.10 (tt, J = 4.0 Hz, 4.0 Hz, 1H), 3.93 (dd, J = 10.4 Hz, 4.4 Hz, 1H), 3.84 (dd, J = 10.4 Hz, 4.4 Hz, 1H), 1.98 (s, 3H), 0.83 (s, 9H), -0.08 (d, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 141.6, 140.8, 140.2, 128.6, 127.6, 127.1, 125.3, 87.0, 66.3, 54.9, 26.1, 21.3, 18.5, -5.4; HRMS(ESI-MS) Calcd. for $C_{20}H_{31}INO_2Si$ $[(M + H)]^+$ 472.1091, found 472.1173.



SNF analogs 51a and 51b. To a solution of vinyl stannane **11** (12.4 mg, 0.034 mmol) and iododiene-amide **50** (16.2 mg, 0.034 mmol) in anhydrous DMF (1.2 mL) were added cesium fluoride, CsF (10.5 mg, 0.069 mmol) and copper iodide, CuI(I) (1.3 mg, 0.007 mmol) at rt under degassing with a stream of Ar. After adding tetrakis triphenylphosphine palladium, $Pd(PPh_3)_4$ (4.0 mg, 0.004 mmol), the reaction flask was immediately wrapped with aluminum foil and continued deoxygenating for further 5 min. The reaction mixture stirred for 14 h, and then

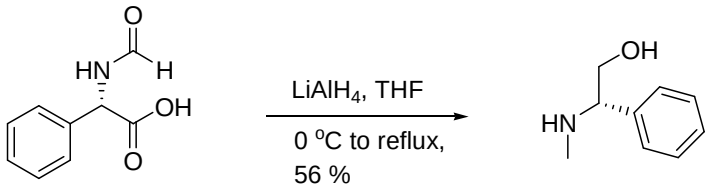
diluted with EtOAc (25 mL). The organic layer was washed with saturated NH_4Cl solution (3 x 25 mL). The combined *aq*. layers were extracted with EtOAc (3 x 25 mL), dried over $MgSO_4$, and concentrated under vacuum. Preparative chromatography (EtOAc:*n*-hexane, 1/5) afforded 9.7 mg (51 %) of an inseparable mixture of diastereomeric **51a** and **51b** in a ratio of 2 : 3 or 3 : 2. R_f: 0.47 (EtOAc/*n*-hexane, 1/5); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18 (d, J = 8.4 Hz, 2H,), 7.36 (d, J = 8.4 Hz, 2H), 7.09-7.29 (m, 5H), 6.15 (d, J = 7.8 Hz, 0.5H), 6.13 (d, J = 10.8 Hz, 0.5H), 5.48 (s, 0.4H), 5.46 (s, 0.6H), 4.97 (m, 1H), 4.47 (s, 0.4H), 4.45 (s, 0.6H), 3.79-3.86 (m, 2H), 3.71 (dd, J = 10.8 Hz, 9.6 Hz, 1H), 3.33 (t, J = 9.0 Hz, 0.4H), 3.29 (t, J = 9.0 Hz, 0.6H), 2.80 (d, J = 8.4 Hz, 0.4H), 2.75 (d, J = 9.0 Hz, 0.6H), 1.83 (s, 1.25H), 1.74 (s, 1.75H), 1.66 (s, 1.25H), 1.64 (s, 1.75H), 1.23 (s, 1.75H), 1.23 (s, 1.25H), 0.75 (s, 3.6H), 0.74 (s, 6.4H), 0.14-0.20 (m, 6H).



53 **54**

Formamide 54. To a stirred solution of *S*-(+)-2-amino-2-phenylacetic acid **53** (5.0 g, 0.17 mmol) in 40 mL of 80% HCO_2H was added dropwise acetic anhydride (21 mL) at 0 °C. After the reaction mixture was stirred at 0 °C for 10 min and at rt for 4 h, the reaction mixture was treated with 15 mL of water. The solvent was removed under reduced pressure and the residue was recrystallized from water to give 5.2 g (81 %) of **54** as needles.

^{1}H NMR (300 MHz, DMSO-d6): δ 8.91 (d, J = 7.2 Hz, 1H), 8.06 (1H, s), 7.31-7.38 (m, 5H), 5.38 (d, J = 7.8 Hz, 1H).* Spectroscopic properties were in agreement with literature values.[3]

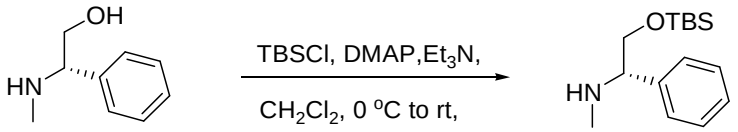


54 **55**

[3] Huszthy, P.; Oue, M.; Bradshaw, J. S.; Zhu, C. Y.; Wang, T. M.; Dalley, N. K.; Curtis, J. C.; Izatt, R. M. *J Org Chem* **1992**, *57*, 5383.

Amine 55. To a stirred suspension of $LiAlH_4$ (890 mg, 23 mmol) in 12 mL of dry and pure THF was added dropwise formamide **54** (490 mg, 3.24mmol) dissolved in 4 mL of THF at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 30 min, at rt for 3 h and at reflux temperature for 9 h. The reaction mixture was cooled to 0 ^oC and 50 mL of 15% aqueous NaOH was slowly added, and then the solid was removed by filtration and washed with THF. The combined filtrate and washing solutions were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified on silica gel with CH_3OH/ CH_2Cl_2 (1/7) to give 274 mg (56 %) of **55** as a white solid.

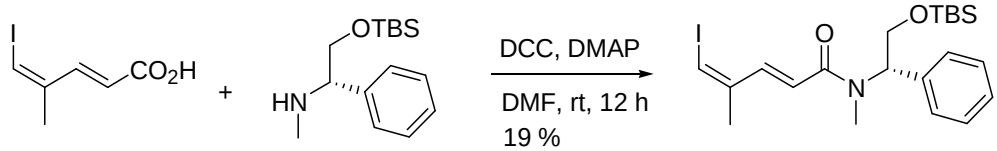
R_f: 0.50 (CH_3OH/ CH_2Cl_2, 1/7). ^1H NMR (300 MHz, DMSO-d6): δ 7.26-7.34 (m, 5H), 3.57-3.74 (m, 3H), 2.36 (3H, s). * Spectroscopic properties were in agreement with literature values.[3]



55 **56**

TBS protected amine 56. To a stirring solution of amine **55** (66 mg, 0.44 mmol) in CH_2Cl_2 (1.5 mL) was added triethylamine (115 μL, 1.14 mmol) followed by DMAP (5.4 mg, 0.04 mmol). After 5 min, *tert*-butyldiphenylchlorosilane (131 mg, 0.87 mmol) was added in one portion. The reaction mixture was stirred at rt at 14 h and then neutralized with 1N HCl. The filtrate was concentrated under reduced pressure. The crude compound was purified on silica gel with EtOAc/*n*-hexane (1/6) to give 87 mg (79 %) of **56** as pale yellow oil.

R_f: 0.27 (EtOAc/*n*-Hexane, 1/6). ^1H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 5H), 3.62 (m, 3H), 2.30 (s, 3H), 0.89 (s, 9H), 0.029 (s, 6H).

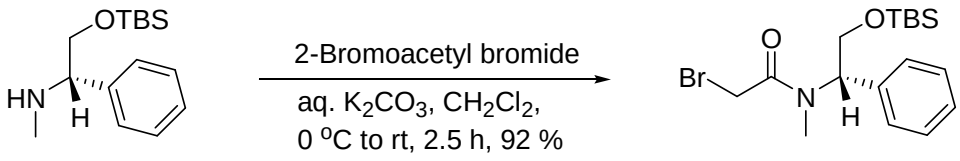


40 **56** **57**

Iododiene-amide 57. To a solution of N-methylamine **56** (87.2 mg, 0.33 mmol) and dienoic acid **40** (83.1 mg, 0.35 mmol) in dry CH_2Cl_2 (30 mL) was slowly added dicyclohexyl-

carbodiimide (DCC) (79.9 mg, 0.39 mmol) and 4-(*N*,*N*-dimethylamino) pyridine (DMAP) (6.0 mg, 0.05 mmol) in dry CH_2Cl_2 (4 mL) at 0 ^oC under Ar atmosphere. The reaction mixture was allowed to warm to rt. After stirring for 12 h, the reaction mixture was filtered through a Celite® and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:1) to provide 30.4 mg (19 %) of **57** as a white solid.

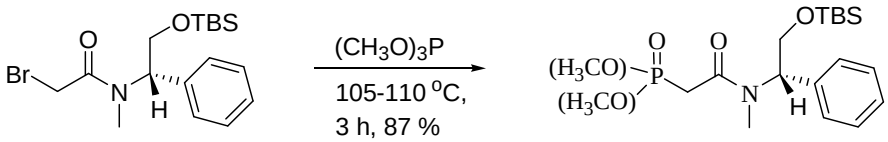
R_f: 0.55 (EtOAc/*n*-hexane, 1/6); IR: 2928, 2856, 1641, 1601, 1118 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.64 (d, J = 15.0 Hz, 0.5H), 7.54 (d, J = 15.0 Hz, 0.5H), 7.21-7.35 (m, 5H), 6.65 (d, J = 15.6 Hz, 0.5H), 6.53 (d, J = 15.6 Hz, 0.5H) 6.49 (s, 1H), 5.90 (s, 0.5H), 5.17 (s, 0.5H), 4.16 (t, J = 5.4 Hz, 0.5H), 4.14 (d, J = 4.8 Hz, 1H), 4.06 (t, J = 9.6 Hz, 0.5H), 2.92 (s, 1.5H), 2.80 (s, 1.5H), 2.02 (s, 1.5H), 1.97 (s, 1.5H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 143.0, 142.0, 141.2, 138.2, 129.0, 128.7, 128.3, 127.6, 127.2, 124.0, 122.8, 86.6, 85.8, 62.1, 57.6, 26.0, 21.4, 18.3, -5.3; HRMS(ESI-MS) Calcd. for $C_{21}H_{33}INO_2Si$ $[(M + H)]^+$ 486.1247, found 486.1320.



56 **58**

Bromoacetamides 58. To a mixture of K_2CO_3 (108.0 mg, 0.79 mmol) and amine **56** (151.0 mg, 0.56 mmol) in a 3:2 mixture of CH_2Cl_2 and H_2O (7.5 mL) at 0 ^oC was added dropwise bromoacetyl bromide (120 μL, 1.38 mmol). The reaction mixture was allowed to warm to rt, stirred for further 4 h, and quenched with H_2O (5 mL). After extracting with CH_2Cl_2 (3 x 10 mL), the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:1) to provide 280.0 mg (92 %) of **58** as colorless viscous oil.

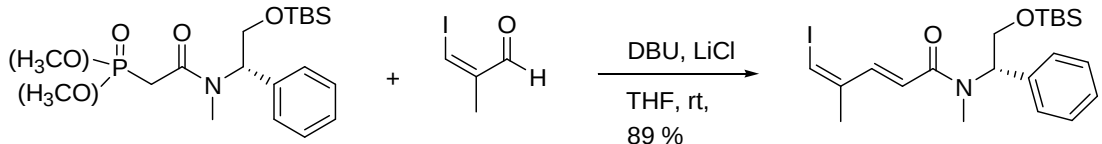
R_f: 0.42 (EtOAc/*n*-hexane, 1/3); ^1H NMR (300 MHz, $CDCl_3$): δ 7.21-7.37 (m, 5H), 5.77 (t, J = 6.0 Hz, 0.5H), 5.16 (dd, J = 9.8 Hz, 4.2 Hz, 0.5H), 4.35 (d, J = 10.5 Hz, 0.5H), 3.90-4.20 (m, 3.5H), 2.92 (s, 1.5H), 2.67 (s, 1.5H), 0.90 (s, 4.5H), 0.88 (s, 4.5H), 0.08 - 0.11 (m, 6H).



58 **59**

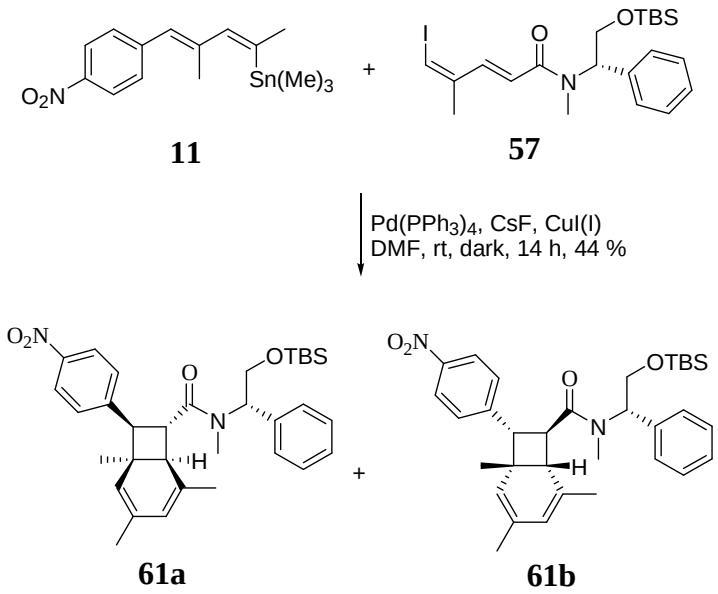
Phosphonoacetamide 59. A mixture of **58** (251.2 mg, 0.65 mmol) and trimethylphosphite (0.7 mL, 5.99 mmol) was heated for 3 h at 105-110 ^{o}C. The reaction mixture was allowed to cool to rt, and then evaporated to remove volatile compounds under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane:CH_3OH, 5:3:2) to provide 233.4 mg (87 %) of **59** as colorless viscous oil.

R_f: 0.53 (EtOAc/*n*-hexane/CH_3OH, 5/3/2); IR: 2850, 1640, 1253, 1033 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.36 (m, 5H), 5.82 (t, J = 6.0 Hz, 0.5H), 5.25 (dd, J = 9.5 Hz, 3.6 Hz, 0.5H), 4.00-4.17 (m, 2H), 3.72-3.83 (m, 8H), 2.94 (s, 1.5H), 2.69 (s, 1.5H), 0.89 (s, 4.5H), 0.88 (s, 4.5H), 0.07-0.09 (m, 6H).



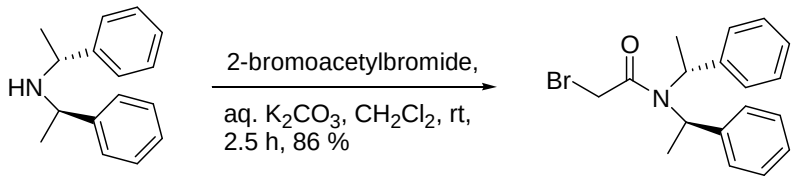
59 **60** **57**

Iododiene-amide 57 via HWE reaction. To a stirred suspension solution of **59** (232.8 mg, 0.56 mmol), 1,8-diazabicyclo- [5.4.0]undec-7-ene (DBU) (260.3 mg, 1.71 mmol), and LiCl (72.1 mg, 1.70 mmol) in dry THF (24 mL) was added a solution of (Z)-3-iodo-2-methyl-propenal **60**, which was prepared in situ from (*Z*)-3-iodo-2-methylprop-2-en-1-ol (104.9 mg, 0.53 mmol), in dry THF (6.0 mL) was added by syringe over 10 min at 0 ^{o}C under Ar atmosphere. The resulting solution was allowed to warm to rt and completed by checking with TLC. The reaction mixture was quenched with saturated NH_4Cl (60 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:5) to provide 227.4 mg (89 %) of **57** as colorless viscous oil. *Spectroscopic properties of **57** from DCC and DMAP coupling were in agreement with **57** values from HWE reaction.



SNF analogs 61a and 61b. To a solution of vinyl stannane **11** (12.9 mg, 0.035 mmol) and iododiene-amide **57** (14.5 mg, 0.030 mmol) in anhydrous DMF (1.2 mL) were added cesium fluoride, CsF (9.7 mg, 0.064 mmol) and copper iodide, CuI(I) (1.2 mg, 0.006 mmol) at rt under deoxygenating with a stream of Ar. After adding $Pd(PPh_3)_4$ (4.7 mg, 0.004 mmol), the reaction flask was immediately wrapped with aluminum foil and continued deoxygenating for further 5 min. The reaction mixture stirred for 14 h, and then diluted with EtOAc (10 mL). The organic layer was washed with saturated NH_4Cl solution (3 x 10 mL). The combined *aq*. layers were extracted with EtOAc (3 x 10 mL), dried over $MgSO_4$, and concentrated under vacuum. Preparative chromatography (EtOAc/*n*-hexane, 1/5) afforded 7.3 mg (44 %) of an inseparable mixture of **61a** and **61b** in a ratio of 1 : 1.

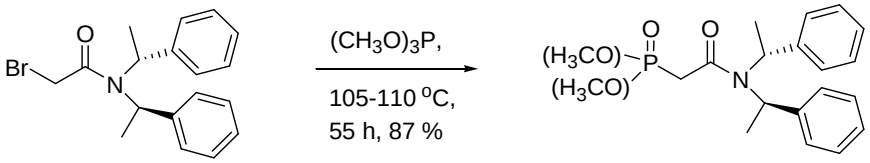
R_f: 0.52 (EtOAc/*n*-hexane, 1/5); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.15 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.21-7.38 (m, 5H), 6.92 (d, J = 7.2 Hz, 1H), 6.73 (d, J = 9.0 Hz, 1H), 5.86 (t, J = 6.0 Hz, 0.5H), 5.53 (s, 0.5H), 5.45 (s, 0.5H), 4.84 (t, J = 6.6 Hz, 0.5H), 4.52 (s, 0.5H), 4.31 (s, 0.5H), 4.06-4.17 (m, 1H), 4.03 (d, J = 6.0 Hz, 1H), 3.98 (d, J = 9.6 Hz, 0.5H), 3.88 (d, J = 6.6 Hz, 0.5H), 3.78 (t, J = 9.6 Hz, 0.5H), 3.73 (t, J = 9.6 Hz, 0.5H), 3.03 (s, 1.5H), 2.96 (d, J = 11.4 Hz, 0.5H), 2.85 (d, J = 8.4 Hz, 0.5H), 2.76 (s, 1.5H), 1.86 (s, 1.5H), 1.66 (s, 1.5H), 1.65 (s, 3H), 1.26 (s, 3H), 0.90 (s, 4.5H), 0.88 (s, 4.5H), -0.06-0.08 (m, 6H).



63 **64**

Bromoacetamide 64. To a mixture of K_2CO_3 (395.4 mg, 2.90 mmol) and (*S*)-(α-methylbenzyl)benzylamine **63** (445.0 mg, 1.98 mmol) in a 3:2 mixture of CH_2Cl_2/ H_2O (25 mL) was added dropwise bromoacetyl bromide (0.30 mL, 3.45 mmol) at 0 ^oC. The reaction mixture was stirred for 2.5 h at rt, and then quenched with H_2O (15 mL). After extracting with CH_2Cl_2 (3 x 30 mL), the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:3) to provide 593.2 mg (87 %) of **64** as pale yellow sticky oil.

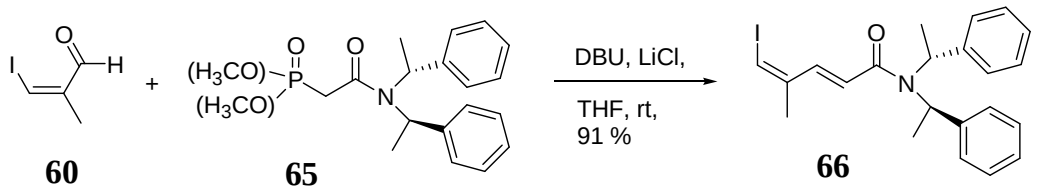
R_f: 0.27 (EtOAc/*n*-hexane, 3/7); IR: 2979, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.98-7.21 (m, 10H), 5.17 (bs, 1H), 5.01 (bs, 1H), 3.94 (dd, *J* = 16.4 Hz, 11.6 Hz, 2H), 1.78 (bs, 3H), 1.71 (bs, 3H).



64 **65**

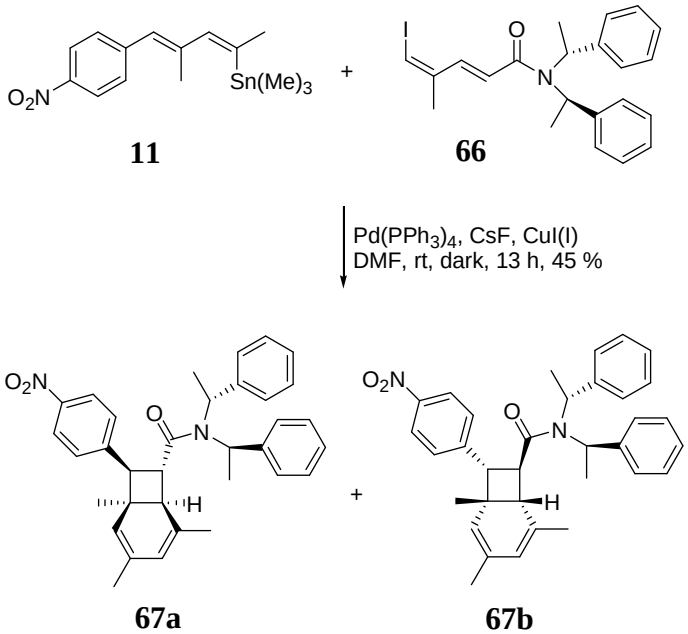
Phosphonoacetamide 65. A mixture of bromoacetamide **64** (314.8 mg, 0.91 mmol) and trimethylphosphite (1.0 mL, 8.48 mmol) was heated for 7 h at 105-110 ^oC. The reaction mixture was allowed to cool to rt, and then evaporated to remove volatile compounds under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane:CH_3OH, 5:4:1) to provide 295.2 mg (86 %) of **65** as white solid.

R_f: 0.53 (EtOAc/*n*-hexane/CH_3OH, 5/4/1); IR: 1654, 1052 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.10-7.21 (m, 10H), 5.40 (bs, 1H), 5.05 (d, *J* = 6.0 Hz, 1H), 3.75 (t, *J* = 10.8 Hz, 6H), 2.80-2.95 (m, 2H), 1.79 (d, *J* = 7.2 Hz, 3H), 1.72 (d, *J* = 6.6 Hz, 3H).



60 **65** **66**

Iododiene-amide 66. A solution of phosphonoacetamide **65** (72.8 mg, 0.19 mmol) in dry THF (8.0 mL) was treated with DBU (90.6 mg, 0.59 mmol) and LiCl (25.2 mg, 0.59 mmol) at rt under Ar atmosphere. After stirring for 5 min, (Z)-3-iodo-2-methyl-propenal **60** in THF (1.5 mL), which was prepared in situ from (*Z*)-3-iodo-2-methylprop-2-en-1-ol (43.2 mg, 0.22 mmol), was added by syringe over 5 min. The reaction mixture stirred for 14 h at rt, quenched by addition of saturated NH_4Cl solution (15 mL), and extracted with EtOAc (3 x 15 mL). The combined extracts were washed with H_2O (15 mL) followed by brine (15 mL), dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:5) to provide 77.1 mg (91 %) of **66** as colorless viscous oil. R_f: 0.53 (EtOAc/*n*-hexane, 1/5); IR: 2977, 1637, 1596 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.20 (d, 1H, J = 15.6 Hz), 7.09-7.39 (m, 10H), 6.66 (s, 1H), 6.20 (bs, 1H), 5.84 (d, J = 15.0 Hz, 1H), 4.82 (bs, 1H), 1.75 (bs, 6H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 141.5, 141.3, 128.6, 125.7, 86.0, 21.1; HRMS(ESI-MS) Calcd. for $C_{22}H_{25}INO$ $[(M + H)]^+$ 446.0903, found 446.0983.



11 **66**

67a **67b**

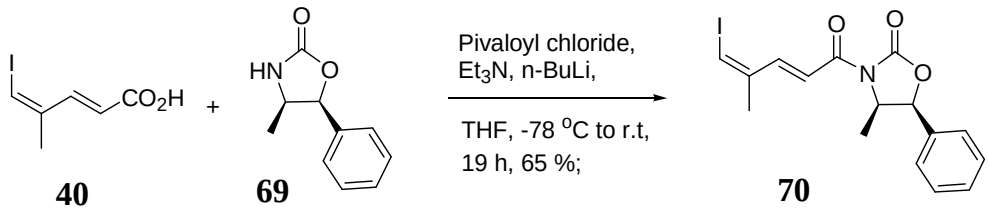
SNF analogs 67a and 67b. To a solution of vinyl stannane **11** (37.5 mg, 0.102 mmol) and iododiene-amide **66** (47.8 mg, 0.107 mmol) in anhydrous DMF (4.0 mL) were added cesium fluoride, CsF (33.1 mg, 0.218 mmol) and copper iodide, CuI(I) (4.2 mg, 0.022 mmol) at rt under deoxygenating with a stream of Ar. After adding $Pd(PPh_3)_4$ (12.3 mg, 0.011 mmol), the reaction flask was immediately wrapped with aluminum foil and continued deoxygenating for further 5 min. The reaction mixture stirred for 13 h, and then diluted with EtOAc (15 mL). The organic layer was washed with saturated NH_4Cl solution (3 x 15 mL). The combined *aq*. layers were extracted with EtOAc (3 x 15 mL), dried over $MgSO_4$, and concentrated under vacuum. Preparative chromatography (EtOAc:*n*-hexane, 1:5) afforded 9.6 mg (18 %) of **67a** or **67b** and 14.5 mg (27 %) of **67a** or **67b** in a ratio of 2 (slower moving isomer) : 3 (faster moving isomer).

The slower moving isomer

R_f: 0.50 (EtOAc/*n*-hexane, 1/5); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 (d, J = 7.8 Hz, 2H), 7.13-7.19 (m, 6H), 7.03 (t, J = 6.6 Hz, 2H), 6.74 (bs, 2H), 6.63 (bs, 2H), 5.56-5.59 (bs, 1H), 5.55 (s, 1H), 4.78 (d, J = 5.4 Hz, 1H), 4.30 (s, 1H), 3.80 (d, J = 9.0 Hz, 2H), 3.60 (dd, J = 8.1 Hz, 7.8 Hz, 1H), 2.88 (d, J = 8.4 Hz, 1H), 1.74 (s, 3H), 1.67 (s, 3H), 1.66 (d, J = 7.2 Hz, 3H), 1.63 (bs, 3H), 1.14 (s, 3H).

The faster moving isomer

R_f: 0.55 (EtOAc/*n*-hexane, 1/5); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.11 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.11-7.20 (m, 6H), 7.01 (bs, 2H), 6.79 (d, J = 7.8 Hz, 2H), 5.46 (s, 1H), 5.27 (s, 1H), 5.21 (bs, 1H), 4.96 (d, J = 6.0 Hz, 1H), 4.45 (s, 1H), 3.79 (d, J = 9.6 Hz, 2H), 3.67 (dd, J = 8.7 Hz, 8.4 Hz, 1H), 2.95 (d, J = 8.4 Hz, 1H), 1.68 (d, J = 6.6 Hz, 3H), 1.64 (s, 3H), 1.63 (s, 3H), 1.50 (d, J = 6.6 Hz, 3H), 1.18 (s, 3H).

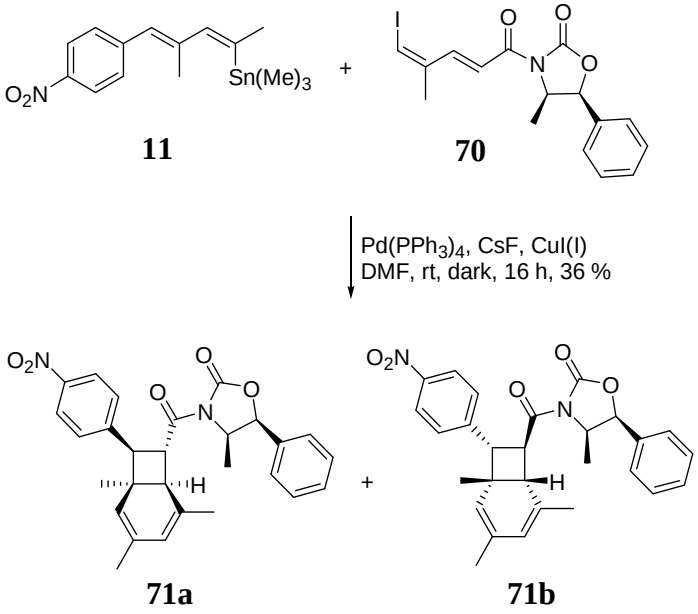


40 **69** **70**

Iododiene-oxazolidinone 70. To a stirred solution of dienoic acid **40** (200.5 mg, 0.84 mmol) and triethylamine (160 μL, 1.15 mmol) in dry THF (12 mL) was added pivaloyl chloride (112.4 mg, 0.93 mmol) at -78^{o}C. The resulting slurry solution was stirred for 15 min at -78 ^{o}C,

continued for further 45 min at 0 ^{o}C, and then the solution was again cooled to -78 ^{o}C. In a separate flask, a stirred solution of (4*R*, 5*S*)-4-methyl-5-phenyl-2-oxazolidinone **69** (158.0 mg, 0.89 mmol) in dry THF (12 mL) was treated with *n*-butyllithium (2.0M in *n*-hexane) (0.6 mL, 0.89 mmol) at -78 ^{o}C, and the resulting metalated solution was added to the dienoate slurry by syringe over 10 min. The resulting viscous slurry was stirred for 20 min at -78 ^{o}C, and then allowed to warm to rt and stirred for 6 h. The reaction mixture was quenched by the addition of H_2O (25 mL) and the organic solvent was removed under vacuum. The residue was taken up in CH_2Cl_2 (3 x 30 mL) and washed successfully with portions of 0.5N HCl (25 mL), saturated *aq*. $NaHCO_3$, (25 mL), and brine (25 mL). And then, the organic solution was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:6) to provide 220.0 mg (65 %) of **70** as white solid.

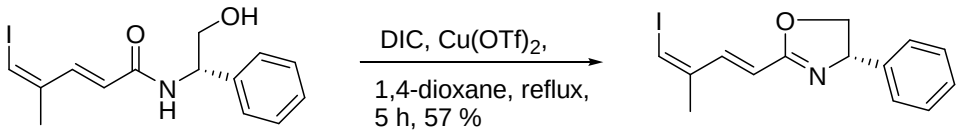
R_f: 0.33 (EtOAc/*n*-hexane, 1/6); IR: 1779, 1678, 1605, 1351 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 15.6 Hz, 1H), 7.49 (d, *J* = 15.2 Hz, 1H), 7.29-7.41 (m, 5H), 6.70 (s, 1H), 5.68 (d, *J* = 7.2 Hz, 1H), 4.83 (m, 1H), 2.06 (s, 3H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 153.3, 146.3, 141.7, 133.5, 129.0, 128.9, 125.9, 121.8, 89.8, 79.3, 55.3, 21.4, 14.8; HRMS(ESI-MS) Calcd. for $C_{16}H_{17}INO_3$ $[(M + H)]^+$ 398.0175, found 398.0260.



SNF analogs 71a and 71b. To a solution of vinyl stannane **11** (34.0 mg, 0.092 mmol) and iododiene-oxazolidinone **70** (41.7 mg, 0.107 mmol) in anhydrous DMF (3.0 mL) were added

cesium fluoride, CsF (27.4 mg, 0.180 mmol) and copper iodide, CuI(I) (5.0 mg, 0.026 mmol) at rt under deoxygenating with a stream of Ar. After adding $Pd(PPh_3)_4$ (13.5 mg, 0.011 mmol), the reaction flask was immediately wrapped with aluminum foil and continued deoxygenating for further 5 min. The reaction mixture stirred for 12-16 h, and then was diluted with EtOAc (25 mL). The organic layer was washed with saturated NH_4Cl solution (3 x 25 mL). The combined *aq*. layers were extracted with EtOAc (3 x 25 mL), dried over $MgSO_4$, and concentrated under vacuum. Preparative chromatography (EtOAc:*n*-hexane, 1:6) afforded 15.7 mg (36 %) of an inseparable mixture of **71a** and **71b** in a ratio of 1 : 1.

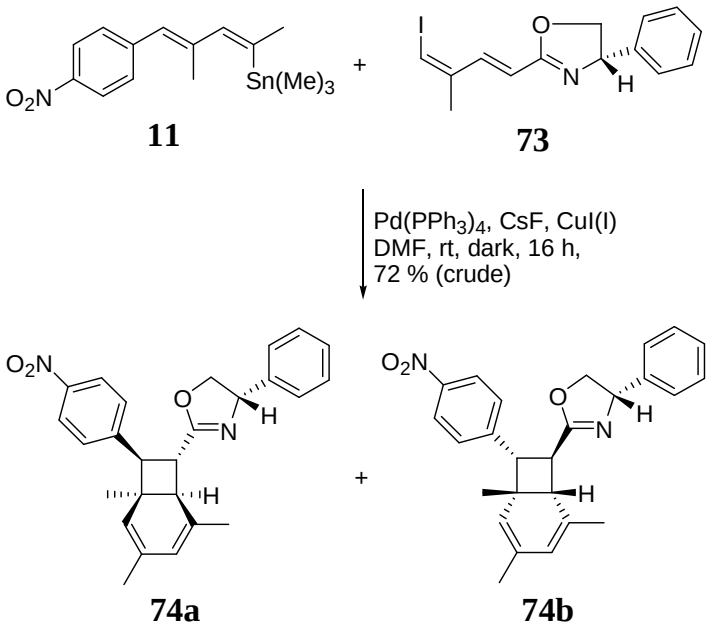
R_f: 0.42 (EtOAc/*n*-hexane, 1/6); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18 (d, J = 9.0 Hz, 1H), 8.17 (d, J = 9.0 Hz, 1H), 7.24-7.46 (m, 7H), 5.62 (d, J = 7.2 Hz, 0.5H), 5.59 (d, J = 7.2 Hz, 0.5H), 5.51 (s, 0.5H), 5.50 (s, 0.5H), 5.13 (t, J = 9.0 Hz, 0.5H), 5.11 (t, J = 9.0 Hz, 0.5H), 4.76 (q, J = 6.6 Hz, 1H), 4.42 (s, 0.5H), 4.41 (s, 0.5H), 3.90 (d, J = 10.2 Hz, 0.5H), 3.84 (d, J = 10.2 Hz, 0.5H), 2.86 (d, J = 8.4 Hz, 0.5H), 2.80 (d, J = 8.4 Hz, 0.5H), 1.73 (s, 1.5H), 1.69 (s, 1.5H), 1.67 (s, 1.5H), 1.67 (s, 1.5H), 1.28 (s, 3H), 0.91 (d, J = 7.2 Hz, 1.5H), 0.82 (d, J = 6.0 Hz, 1.5H).



42 **73**

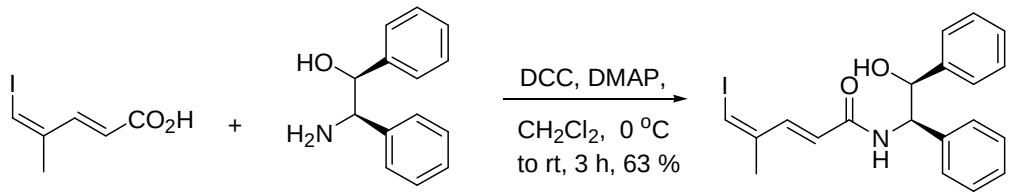
Iododiene-oxazoline 73. To a solution of iododiene-amide **42** (92.0 mg, 0.26 mmol)) and copper(II) trifluoromethanesulfonate, $Cu(OTf)_2$ (9.1 mg, 0.03 mmol) in 1,4-dioxane (4.0 mL) was added *N*,*N'*-diisopropylcarbodiimde (DIC) (40 μL, 0.26 mmol) in one portion. The reaction solution was heated for 5 h at reflux. The resulting white precipitate was removed by filtration and washed with EtOAc (5 mL). The combined filtrate was concentrated in vacuum, and the oily residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:2) to provide 49.2 mg (57 %) of **73** as viscous oil.

R_f: 0.80 (EtOAc/*n*-hexane, 1/1); IR: 3061, 3031, 2916, 1646 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, J = 15.9 Hz, 1H), 7.26-7.40 (m, 5H), 6.67 (s, 1H), 6.58 (d, J = 16.2 Hz, 1H), 5.38 (dd, J = 9.9 Hz, 8.4 Hz, 1H), 4.87 (t, J = 9.0 Hz, 1H), 4.39 (d, J = 14.7 Hz, 1H), 2.06 (s, 3H).



SNF analogs 74a and 74b. To a solution of vinyl stannane **11** (17.8 mg, 0.048 mmol) and iododiene-oxazoline **73** (11.2 mg, 0.033 mmol) in anhydrous DMF (1.0 mL) were added cesium fluoride, CsF (11.1 mg, 0.073 mmol) and copper iodide, CuI(I) (2.1 mg, 0.011 mmol) at rt under deoxygenating with a stream of Ar. After adding $Pd(PPh_3)_4$ (6.0 mg, 0.005mmol), the reaction flask was immediately wrapped with aluminum foil and continued deoxygenating for further 5 min. The reaction mixture stirred for 16 h, and then diluted with EtOAc (25 mL). The organic layer was washed with saturated NH_4Cl solution (3 x 25 mL). The combined *aq*. layers were extracted with EtOAc (3 x 25 mL), dried over $MgSO_4$, and concentrated under vacuum. Flash column chromatography (EtOAc:*n*-hexane, 1:3) afforded 9.8 mg (72 %) of an inseparable mixture of crude **74a** and **74b** including byproduct in a ratio of 1 : 1 : 1.

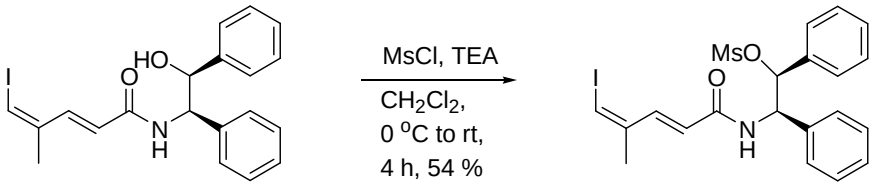
R_f: 0.37 (EtOAc/*n*-hexane, 1/3); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.35 (d, J = 7.8 Hz, 1.33H), 8.19 (d, J = 8.4 Hz, 0.67H), 7.53 (d, J = 7.8 Hz, 0.67H), 7.50 (d, J = 7.8 Hz, 0.67H), 7.28-7.42 (m, 5.66H), 5.61(bs, 1.34H), 5.58 (s, 0.34H), 5.57 (s, 0.33H), 5.47 (s, 0.33H), 5.19 (d, J = 9.6 Hz, 1.34H), 4.87 (dd, J = 6.3 Hz, 4.2 Hz, 0.34H), 4.84 (t, J = 6.6 Hz, 0.34H), 4.79 (t, J = 6.6 Hz, 0.34H), 4.52 (d, J = 10.8 Hz, 0.34H), 4.48 (s, 0.33H), 4.46 (s, 0.34H), 4.41 (s, 0.33H), 4.37 (dd, J = 7.8 Hz, 4.2 Hz, 0.33H), 4.30 (s, 1.33H), 4.15 (dd, J = 10.2 Hz, 9.0 Hz, 0.34H), 4.09 (dd, J = 9.9 Hz, 9.0 Hz, 0.34H), 3.74 (d, J = 10.8 Hz, 0.34H), 3.51 (dd, J = 9.6 Hz, 9.0 Hz, 0.34H), 3.35 (d, J = 8.4 Hz, 0.34H), 3.19 (bs, 0.34H), 2.77 (d, J = 9.6 Hz, 0.34H), 1.82 (s, 1H), 1.79 (s, 2H), 1.68 (s, 1H), 1.67 (s, 1H), 1.63 (s, 1H), 1.42 (s, 1H), 1.38 (s, 1H), 1.27 (s, 1H).



40 **76** **77**

Iododiene-amide 77. To a solution of (1*R*, 2*R*)-2-amino-1,2-diphenylethanol **76** (154.3 mg, 0.72 mmol) and dienoic acid **40** (189.7 mg, 0.79 mmol) in dry CH_2Cl_2 (20 mL) was slowly added DCC (159.0 mg, 0.77 mmol) and DMAP (10.6 mg, 0.09 mmol) in dry CH_2Cl_2 (8.0 mL) at 0 ^oC under Ar atmosphere. The reaction mixture was stirred for 3 h at rt, filtered through a Celite®, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 2:3) to provide 196.8 mg (63 %) of **77** as a white solid.

R_f: 0.57 (EtOAc/*n*-hexane, 1/2); IR: 3364, 1646, 1610, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 15.6 Hz, 1H), 7.22 (m, 6H), 7.02 (m, 4H), 6.56 (s, 1H), 6.40 (d, *J* = 7.2 Hz, 1H), 6.05 (d, *J* = 15.6 Hz, 1H), 5.39 (dd, *J* = 4.2 Hz, 3.6 Hz, 1H), 5.13 (d, *J* = 4.2 Hz, 1H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 142.2, 140.8, 139.9, 137.0, 128.1, 126.7, 124.8, 87.5, 59.9, 21.2.

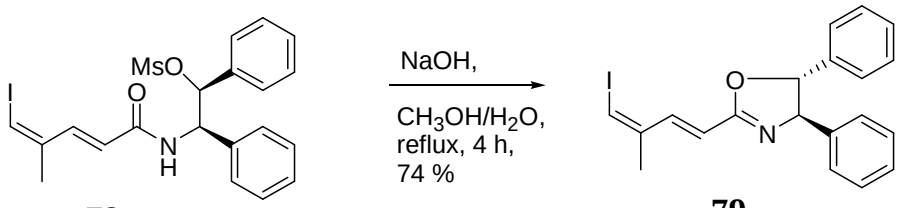


77 **78**

Mesylate 78. To an ice-cooled solution of iododiene-amide **77** (79.0 mg, 0.18 mmol) and triethylamine (90 μL, 0.64 mmol) in dry CH_2Cl_2 (3.2 mL) was added methanesulfonyl chloride (30 μL, 0.39 mmol) via syringe in one portion. The reaction mixture was allowed to warm to rt and stirred for 4 h. Then saturated NH_4Cl solution was poured into the reaction mixture and the organic layer was separated. The water layer was extracted by CH_2Cl_2 (3 x 10 ml) and the combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum The residue

was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:2.5) to provide 50.0 mg (54 %) of **78** as sticky oil.

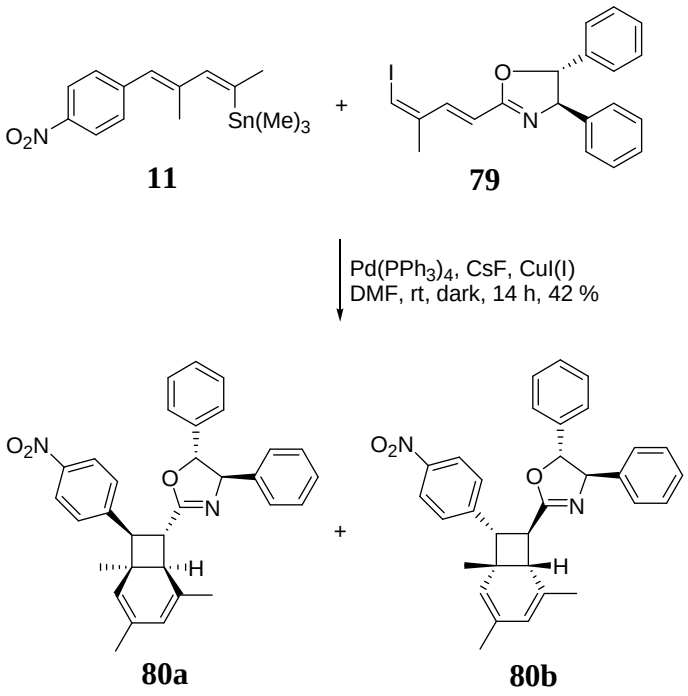
R_f: 0.64 (EtOAc/*n*-hexane, 1:2.5); IR: 3285, 3056, 1715, 1625, 1326, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 15.6 Hz, 1H), 7.17-7.24 (m, 10H), 6.55 (s, 1H), 6.06 (d, J = 7.2 Hz, 1H), 5.98 (d, J = 15.6 Hz, 1H), 5.62 (d, J = 8.0 Hz, 1H), 4.86 (t, J = 7.6 Hz, 1H), 2.42 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 145.9, 137.8, 136.8, 136.0, 128.9, 128.7, 127.3, 117.4, 77.9, 62.8, 42.0, 12.7.



78 **79**

Iododiene-oxazoline 79. Mesylate **78** (50.0 mg, 0.10 mmol) was dissolved in methanol (1.0 mL) and a solution of NaOH (15.1 mg, 0.38 mmol) in H_2O (1.0 mL) was added in one portion. After refluxing for 4 h, the reaction mixture was allowed to cool to rt and the solvent was concentrated under vacuum. After adding H_2O (10 mL), the *aq*. layers were extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:2.5) to provide 30.6 mg (74 %) of **79** as a viscous oil.

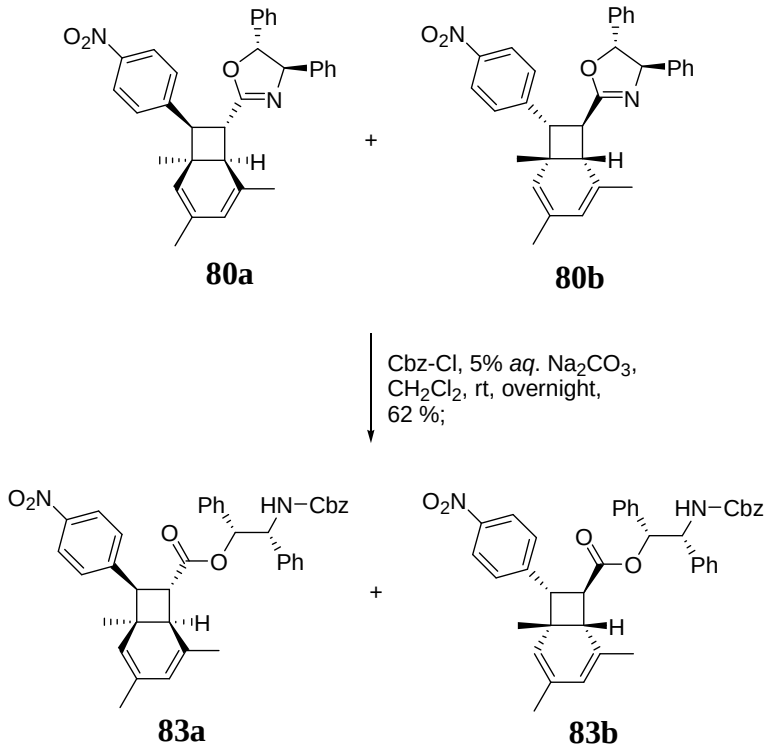
R_f: 0.57 (EtOAc/*n*-hexane, 1/2); IR: 3062, 3032, 2916, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 15.6 Hz, 1H), 7.24-7.41 (m, 10H), 6.57 (s, 1H), 6.50 (d, J = 15.6 Hz, 1H), 5.35 (d, J = 7.6 Hz, 1H), 5.13 (d, J = 7.6 Hz, 1H), 2.06 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 142.0, 141.5, 140.3, 129.0, 128.1, 126.0, 119.3, 89.1, 86.9, 78.7, 21.1; HRMS(ESI-MS) Calcd. for $C_{20}H_{19}INO$ $[(M + H)]^+$ 416.0433, found 416.0504.



SNF analogs 80a and 80b. To a solution of vinyl stannane **11** (29.4 mg, 0.080 mmol) and iododiene-oxazoline **79** (32.2 mg, 0.077 mmol) in anhydrous DMF (2.2 mL) were added cesium fluoride, CsF (27.4 mg, 0.180 mmol) and copper iodide, CuI(I) (5.0 mg, 0.026 mmol) at rt under deoxygenatingwith a stream of Ar. After adding $Pd(PPh_3)_4$ (9.5 mg, 0.008 mmol), the reaction flask was immediately wrapped with aluminum foil and continued deoxygenating for further 5 min. The reaction mixture stirred for 12-16 h, and then diluted with EtOAc (25 mL). The organic layer was washed with saturated NH_4Cl solution (3 x 25 mL). The combined *aq*. layers were extracted with EtOAc (3 x 25 mL), dried over $MgSO_4$, and concentrated under vacuum. Preparative chromatography (EtOAc:*n*-hexane, 1/5) afforded 15.8 mg (42 %) of an inseparable mixture of **80a** and **80b** in a ratio of 1 : 5.

R_f: 0.38 (EtOAc/*n*-hexane, 1/5); IR: 3054, 2916, 1660, 1599, 1520, 1348, 1265 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.21 (d, J = 9.0 Hz, 2H), 7.44 (d, J = 9.0 Hz, 2H), 7.24-7.38 (m, 8H), 7.14 (d, J = 7.2 Hz, 2H), 5.50 (s, 1H), 5.24 (d, J = 6.6 Hz, 1H), 5.07 (d, J = 7.2 Hz, 0.85H), 5.03 (d, J = 7.2 Hz, 0.15H), 4.52 (s, 1H), 4.00 + 3.97 (d, J = 10.2 Hz, 1H), 3.72 (t, J = 9.6 Hz, 1H), 2.96 + 2.94 (d, J = 9.6 Hz, 1H), 1.90 (s, 0.49H), 1.85 (s, 2.51H), 1.65 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 145.6, 133.7, 131.5, 129.2, 128.5, 128.4, 127.1, 126.5, 126.0, 123.9,

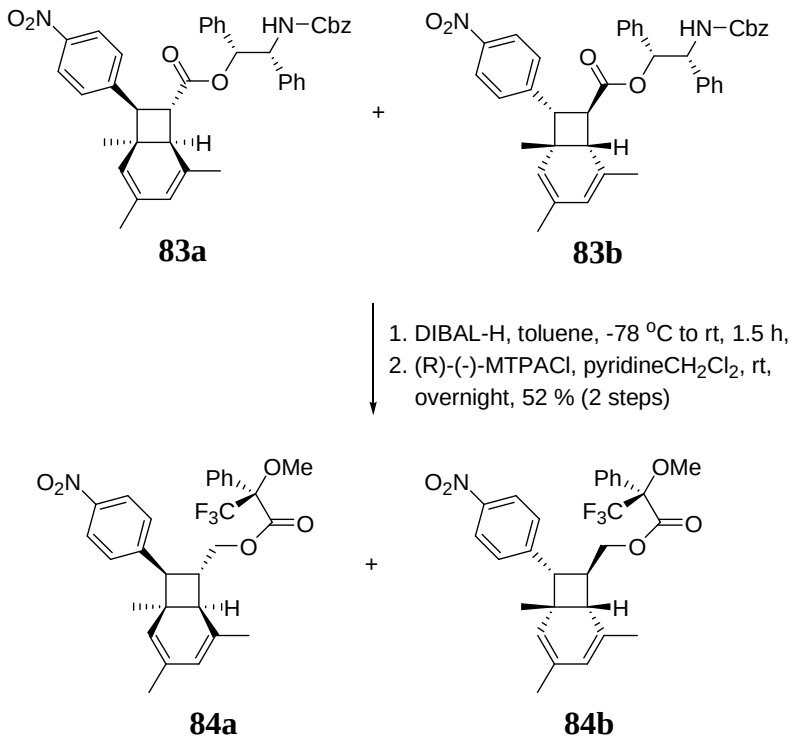
123.8, 123.1, 121.4, 121.3, 90.3, 57.1, 56.6, 47.2, 46.1, 45.2, 44.6, 40.9, 28.6, 22.3, 22.2, 22.1, 22.0; HRMS(ESI-MS) Calcd. for $C_{32}H_{31}N_2O_3$ $[(M + H)]^+$ 491.2256, found 491.2344.



SNF analogs 83a and 83b. To a solution of bicyclooctadienes **80a** and **80b** (15.3 mg, 0.031 mmol) in dry CH_2Cl_2 (0.5 mL), 5% *aq*. Na_2CO_3 (0.5 mL) and benzyl chloroformate (Cbz-Cl) (9.7 mg, 0.057 mmol) was added at rt and then stirred overnight. After addition of H_2O (1.5 mL), the resulting solution was extracted with CH_2Cl_2. Then the combined organic layers were washed first with 5% *aq*. Na_2CO_3, second with H_2O, and then dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by preparative chromatography (EtOAc/*n*-hexane, 1:5) to provide 12.4 mg (62 %) of an inseparable mixture of diastereomeric **83a** and **83b** as sticky oil.

R_f: 0.38 (EtOAc/*n*-hexane, 1/5); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.16 + 8.14 (d, J = 7.8 Hz, 2H), 7.37 (d, J = 4.8 Hz, 2H), 7.29 (d, J = 7.8 Hz, 2H), 7.23-7.35 (m, 5H), 7.20 (dd, J = 3.0 Hz, 2.4 Hz, 2H), 7.16 (t, J = 7.2 Hz, 2H), 7.05 (dd, J = 3.0 Hz, 2.4 Hz, 2H), 6.99 (d, J = 7.8 Hz, 2H), 6.07 (d, J = 6.0 Hz, 0.17H), 6.03 (d, J = 6.6 Hz, 0.83H), 5.44 (s, 1H), 5.36 + 5.27 (bs, 1H), 5.10 (s, 1H), 5.01 (t, J = 9.6 Hz, 1H), 4.98 (d, J = 17.4 Hz, 1H), 4.42 (s, 1H), 3.61 (d, J = 10.2 Hz,

1H), 3.46 (t, *J* = 9.3 Hz, 1H), 2.70 (d, *J* = 8.4 Hz, 0.83H), 2.64 (d, *J* = 9.0 Hz, 0.17H), 1.68 + 1.66 (s, 3H), 1.63 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 155.8, 147.1, 145.6, 138.3, 136.7, 136.4, 134.3, 131.4, 128.5, 128.3, 127.2, 123.8, 123.6, 121.3, 121.1, 94.6, 77.9, 67.2, 56.8, 46.1, 45.5, 45.3, 44.5, 28.7, 22.3, 21.6.

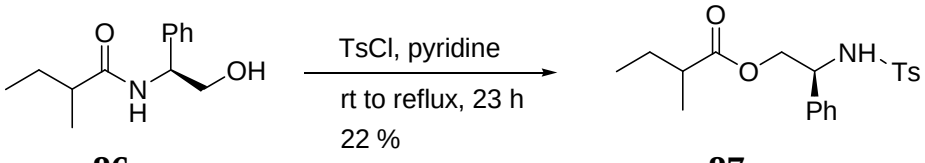


(S)-Mosher esters 84a and 84b. To a stirred solution of bicyclooctadienes **83a** and **83b** (7.8 mg, 0.012 mmol) in dry toluene (0.5 mL) was added diisobutylaluminum hydride (DIBAL-H) (1.0 M in CH_2Cl_2 35 μL, 0.024 mmol) via syringe at -78 °C. The reaction mixture was stirred for 30 min at -78 °C, and then allowed to warm to rt. The reaction solution was again cooled to 0 °C, quenched with EtOAc (0.5 mL), and allowed to warm to rt. After pouring H_2O (2 mL) into the reaction solution, the *aq*. layer was extracted by CH_2Cl_2 (2 x 3 ml) and the combined extracts were washed with saturated NH_4Cl solution and brine. The organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to afford 4.2 mg of crude bicyclo[4.2.0]octadiene substrate bearing methyl alcohol as yellow solid. The crude (4.2 mg, 0.014 mmol) of CH_2Cl_2 (1.4 mL) solution was treated with DMAP (3.6 mg, 0.030 mmol). Then (R)-(-)-α-methoxy-α-trifluoromethylphenylacetyl chloride, (R)-MTPA-Cl, (10 μL, 0.039 mmol)

was added via syringe and the reaction solution was stirred overnight. After removing volatile compounds under vacuum, the residue was purified by preparative chromatography (EtOAc/*n*-hexane, 1:5) to provide 3.2 mg (52 % for the two steps) of an inseparable mixture of diastereomeric **84a** and **84b** in a ratio of 1: 6.

R_f: 0.59 (EtOAc/*n*-hexane, 1/5); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.10 (d, J = 8.4 Hz, 2H), 7.23-7.42 (m, 7H), 5.42 (s, 0.16H), 5.40 (s, 0.84H), 4.48 (dd, J = 7.8 Hz, 6.0 Hz, 0.86H), 4.33 (s, 1H), 4.32 (m, 0.28H), 4.22 (dd, J = 11.4 Hz, 6.4 Hz, 0.86H), 3.44 (s, 2.56H), 3.41 (s, 0.44H), 3.28 (d, J = 10.2 Hz, 1H), 3.01 (m, 1H), 2.26 (d, J = 8.4 Hz, 1H), 1.69 (s, 3H), 1.60 (s, 3H), 1.23 (s, 3H).

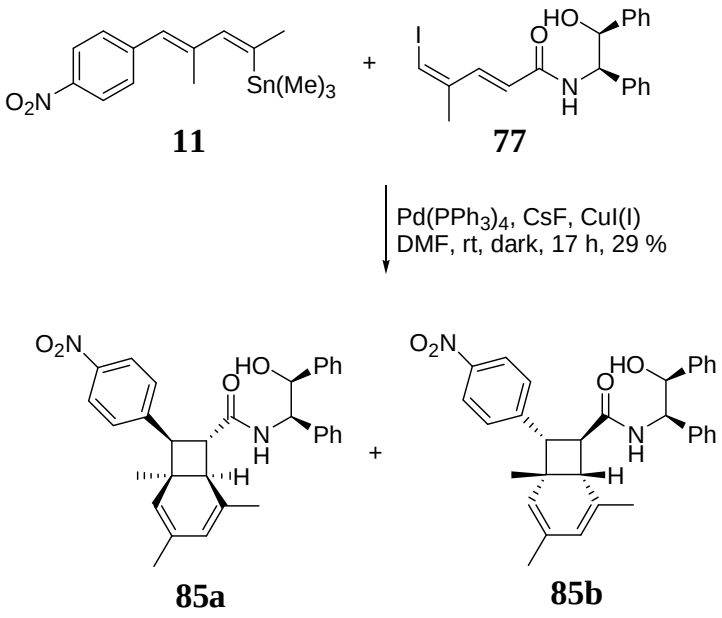
* The inseparable mixture of diastereomeric **84a** and **84b** (6:1 mixture) was prepared from bicyclooctadienes **83a** and **83b** using (S)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride, (R)-MTPA-Cl



86 **87**

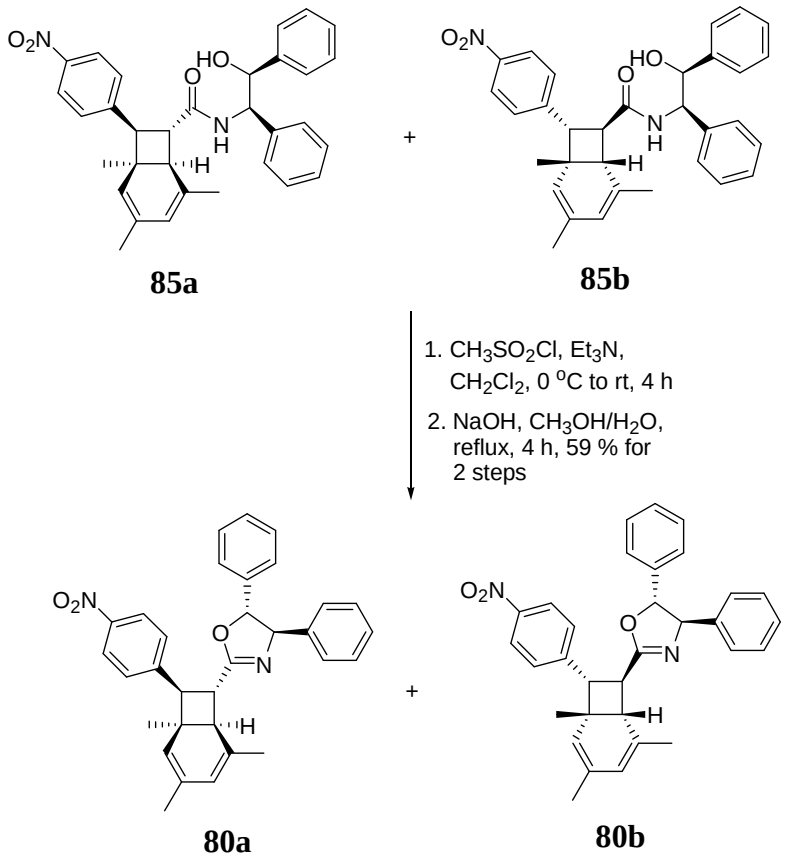
Ester 87. To a solution of amide **86** (20.5 mg, 0.09 mmol) in pyridine (0.3 mL) was added *p*-toluenesulfonyl chloride, TsCl (43 mg, 0.23 mmol) under Ar atmosphere. The reaction mixture was heated under reflux for 23 h. Then, the reaction mixture was allowed to cool to rt. After removing volatile compounds under vacuum, the residue was purified by silica gel column chromatography (EtOAc/*n*-hexane, 1:4) to provide 7.5 mg (22 %) of **87** as pale yellow solid.

R_f: 0.25 (EtOAc/*n*-hexane, 1/4); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71-7.52 (m, 4H), 7.20-7.10 (m, 5H), 5.11 (m, 0.5H), 4.63 (m, 0.5H), 4.23 (m, 2H), 2.36 (s, 3H), 1.71-1.54 (m, 2H), 1.45-1.24 (m, 2H), 1.04 (dd, J = 7.2 Hz, 3.6 Hz, 1.5H), 0.92 (t, J = 6.6 Hz, 1.5H), 0.89 (d, J = 7.2 Hz, 1.5H), 0.81 (t, J = 6.6 Hz, 1.5H).

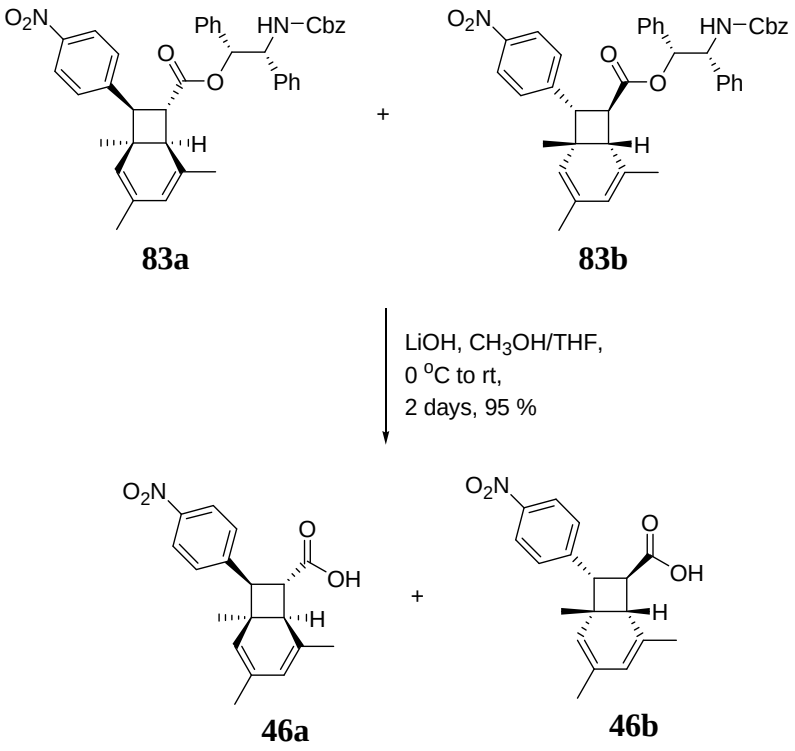


SNF analogs 85a and 85b. To a solution of iododiene-amide **77** (33.4 mg, 0.077 mmol) and vinyl stannane **11** (32.5 mg, 0.088 mmol) in anhydrous DMF (2.0 mL) were added CsF (22.6 mg, 0.151 mmol) and CuI(I) (5.6 mg, 0.029 mmol) at rt under deoxygenating with a stream of Ar. After adding $Pd(PPh_3)_4$ (11.3 mg, 0.001 mmol), the reaction flask was immediately wrapped with aluminum foil and continued deoxygenating for 5 min. The reaction mixture stirred for further 17 h, and then diluted with EtOAc (5 mL). The organic layer was washed with saturated NH_4Cl solution (3 x 5 mL). The combined *aq*. layers were extracted with EtOAc (3 x 5 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by preparative chromatography (EtOAc:*n*-hexane, 1:2) to provide 11.8 mg (29 %) of an inseparable mixture of diastereomeric **85a** and **85b** as a white solid.

R_f: 0.45 (EtOAc/*n*-hexane, 1/2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.19 (d, J = 8.4 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H) 7.29 (d, J = 8.4 Hz, 1H), 7.10-7.24 (m, 6H), 7.01 (d, J = 7.2 Hz, 1H), 6.98 (d, J = 7.2 Hz, 1H), 6.92 (d, J = 7.2 Hz, 1H), 6.88 (d, J = 7.2 Hz, 1H), 6.01 (d, J = 8.4 Hz, 1H), 5.96 (d, J = 8.4 Hz, 1H), 5.48 (s, 0.5H), 5.43 (s, 0.5H), 5.25 (dd, J = 8.4 Hz, 7.8 Hz, 0.5H), 5.21 (dd, J = 8.4 Hz, 7.8 Hz, 0.5H), 3.75 (d, J = 10.2 Hz, 0.5H), 3.74 (d, J = 10.2 Hz, 0.5H), 3.69 (d, J = 10.2 Hz, 0.5H), 3.68 (d, J = 9.6 Hz, 0.5H), 3.30 (dd, J = 9.3 Hz, 8.4 Hz, 0.5H), 3.25 (dd, J = 9.3 Hz, 8.4 Hz, 0.5H), 2.75 (d, J = 8.4 Hz, 0.5H), 2.67 (d, J = 9.0 Hz, 0.5H), 1.78 (s, 1.5H), 1.65 (s, 1.5H), 1.63 (s, 3H), 1.24 (s, 1.5H), 1.22 (s, 1.5H).

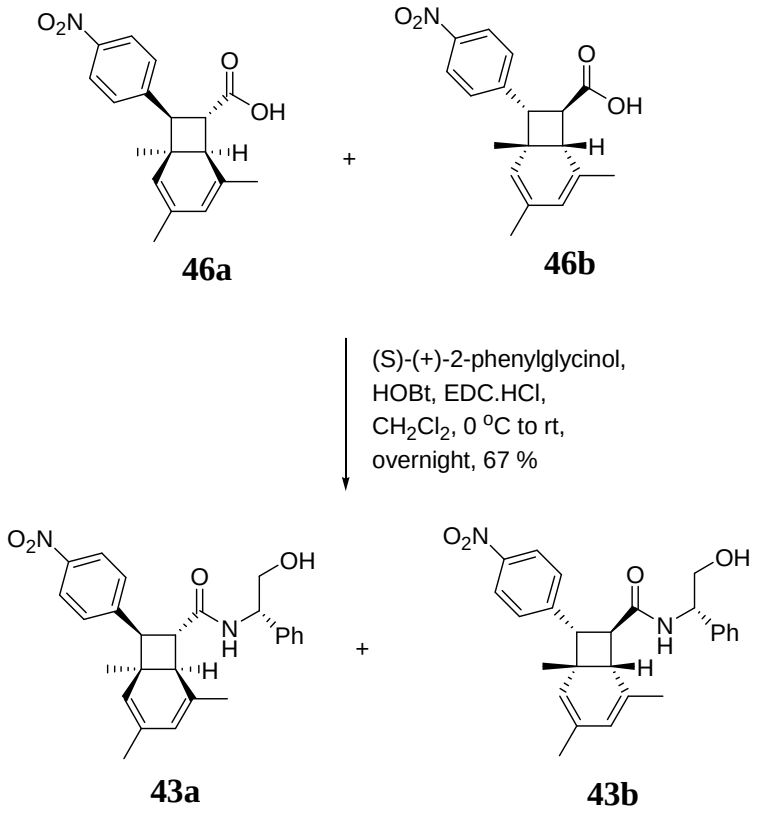


SNF analogs 80a and 80b (1:1 mixture). To an ice-cooled solution of bicyclooctadienes **85a** and **85b** (11.8 mg, 0.023 mmol) and triethylamine (20 μL, 0.143 mmol) in dry CH_2Cl_2 (1.0 mL) was added dropwise methanesulfonyl chloride (5 μL, 0.065 mmol) in dry CH_2Cl_2 (0.5 mL) via syringe. The reaction mixture was allowed to warm to rt and stirred overnight. Then saturated NH_4Cl solution (10 mL) was poured into the reaction mixture and the organic layer was separated. The *aq*. layer was extracted with CH_2Cl_2 (2 x 5 ml) and the combined extracts were dried over $MgSO_4$ and the solvent was removed under vacuum to afford 4.7 mg (43 %) of crude **80a** and **80b** as pale yellow solid. * Spectroscopic properties of authentic **80a** and **80b** (1:1 mixture) were in agreement with **80a** and **80b** (1:6 mixture) values.

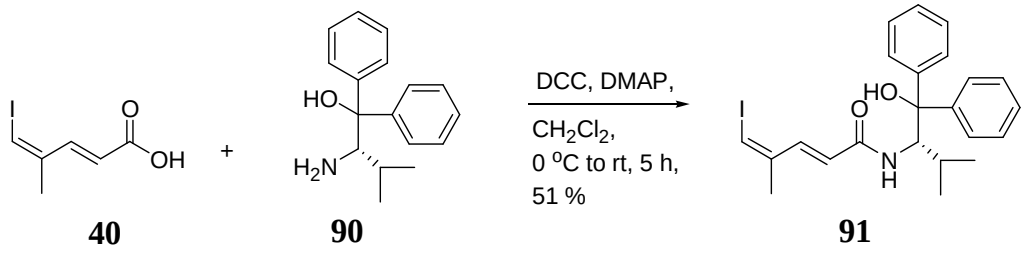


SNF analogs 46a and 46b. To a solution of bicyclooctadienes **83a** and **83b** (12.4 mg, 0.019 mmol) in dry THF (1.0 mL) and CH_3OH (0.5 mL), LiOH (4.1 mg, 0.171 mmol) was added at 0 ^oC. The reaction mixture was stirred 2 days at rt, and washed with H_2O (5 mL). The combined solution was acidified to pH = 2 and then extracted with Et_2O (3 x 5 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by preparative chromatography (EtOAc:*n*-hexane, 1:2) provide 5.6 mg (95 %) of **46a** and **46b** as a white solid.

R_f: 0.51 (EtOAc/*n*-hexane, 1/2); ^1H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 5.47 (s, 1H), 4.42 (s, 1H), 3.74 (d, J = 10.5 Hz, 1H), 3.49 (dd, J = 9.0 Hz, 1H), 2.76 (d, J = 9.0 Hz, 1H), 1.81 (s, 3H), 1.62 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3, 147.1, 145.6, 134.2, 131.4, 128.3, 123.7, 122.8, 122.7, 121.3, 121.2, 56.1, 46.0, 45.8, 44.5, 28.6, 22.2, 21.7.

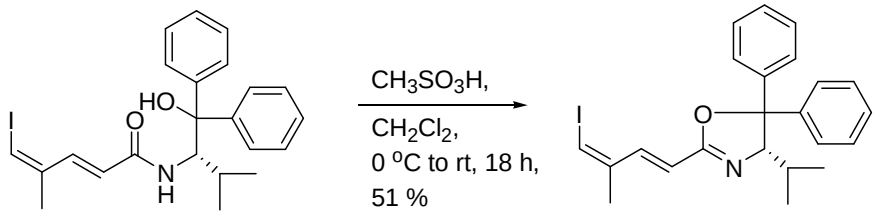


SNF analogs 43a and 43b (1:6 mixture). To a stirred solution of bicyclooctadienes **46a** and **46b** (5.6 mg, 0.018 mmol) in dry CH_2Cl_2 (1.0 mL) were added (S)-(+)-2-phenylglycinol **41** (5.1 mg, 0.037 mmol), 1-hydroxybenzotriazole (HOBt) (3.0 mg, 0.023 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl (EDC· HCl) (6.9 mg, 0.036 mmol). The mixture was stirred for 1 h at 0 °C, allowed to warm to rt, and then followed overnight. The reaction mixture was washed with 5% *aq*. citric acid, saturated *aq*. $NaHCO_3$, and saturated NaCl. Then, the organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to provide crude **43a** and **43b**. *R_f value on TLC of **43b** was in agreement with that of authentic **43b**.



Iododiene-amide 91. To a solution of (*S*)-(-)-α,α-diphenyl-2-pyrrolidine-methanol **90** (114.7 mg, 0.45 mmol) and dienoic acid **40** (104.0 mg, 0.44 mmol) in dry CH_2Cl_2 (10 mL) was slowly added DCC (87 mg, 0.42 mmol) and DMAP (7.0 mg, 0.06 mmol) in dry CH_2Cl_2 (8.0 mL) at 0 ^oC under Ar atmosphere. The reaction mixture was allowed to warm to rt. After stirring for further 5 h, the reaction mixture was filtered on a Celite® and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:3) to provide 106.2 mg (51 %) of **91** as a white solid.

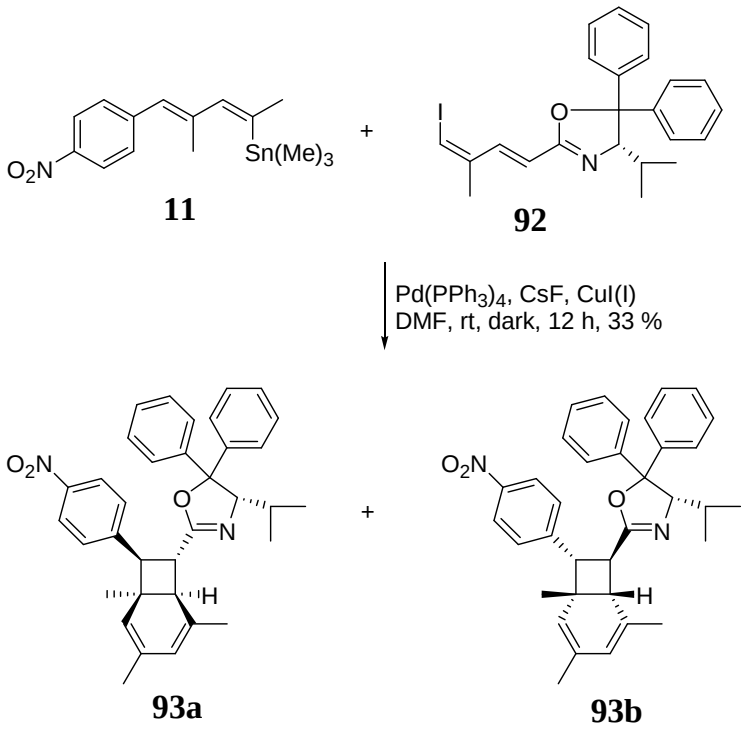
R_f: 0.42 (EtOAc/*n*-hexane, 1/3); IR: 3416, 3291, 1641, 1609, 1127 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.17–7.49 (m, 11H), 6.52 (s, 1H), 6.27 (d, J = 9.0 Hz, 1H), 5.94 (d, J = 15.6 Hz, 1H), 5.08 (dd, J = 9.9 Hz, 2.4 Hz, 1H), 1.92 (d, J = 1.2 Hz, 3H), 0.92 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 146.6, 145.7, 141.3, 140.8, 128.7, 128.6, 127.1, 127.0, 125.6, 119.6, 87.0, 82.4, 58.3, 29.5, 23.2, 21.3, 18.1.



91 **92**

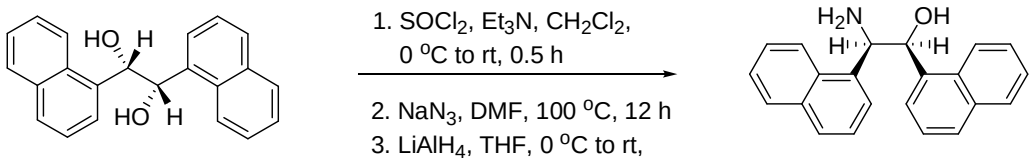
Iododiene-oxazoline 92. Methanesulfonic acid (22 μL, 0.34 mmol) was added dropwise to a solution of iododiene-amide **91** (47 mg, 0.10 mmol) in dry CH_2Cl_2 (4.7 mL) at 0 ^oC under Ar atmosphere. The reaction mixture was allowed to warm to rt and stirred for further 18 h. The resulting solution was diluted with CH_2Cl_2 (20 mL), washed with *aq*. $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL). The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:3) to provide 23.0 mg (51 %) of **92** as a white solid.

R_f: 0.65 (EtOAc/*n*-hexane, 1/3); IR: 3059, 2959, 1651, 970, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, J = 16.2 Hz, 1H), 7.25-7.57 (m, 10H), 6.54 (s, 1H), 6.43 (d, J = 15.9 Hz, 1H), 4.71 (d, J = 4.5 Hz, 1H), 2.04 (d, J = 1.5 Hz, 3H), 1.85 (m, 1H), 1.02 (d, J = 6.9 Hz, 3H), 0.59 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2, 145.3, 141.6, 140.6, 128.6, 128.1, 128.0, 127.6, 127.1, 126.3, 119.6, 93.0, 86.3, 79.7, 30.4, 22.2, 21.1, 17.1; HRMS(ESI-MS) Calcd. for $C_{23}H_{25}INO$ $[(M + H)]^+$ 458.0903, found 458.0977.



SNF analogs 93a and 93b. To a solution of vinyl stannane **11** (20.8 mg, 0.057 mmol) and iododiene-oxazoline **92** (22.9 mg, 0.050 mmol) in anhydrous DMF (1.5 mL) were added cesium fluoride, CsF (18.2 mg, 0.120 mmol) and copper iodide, CuI(I) (2.5 mg, 0.013 mmol) at rt under deoxygenating with a stream of Ar. After adding $Pd(PPh_3)_4$ (6.9 mg, 0.006 mmol), the reaction flask was immediately wrapped with aluminum foil and continued deoxygenating for further 5 min. The reaction mixture stirred for 12-16 h, and then diluted with EtOAc (25 mL). The organic layer was washed with saturated NH_4Cl solution (3 x 25 mL). The combined *aq*. layers were extracted with EtOAc (3 x 25 mL), dried over $MgSO_4$, and concentrated under vacuum. Preparative chromatography (EtOAc:*n*-hexane, 1:5) afforded 8.9 mg (33 %) of an inseparable mixture of diastereomeric **93a** and **93b** in a ratio of 1 : 3 or 3 : 1.

R_f: 0.50 (EtOAc/*n*-hexane, 1/5); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.17 (d, J = 7.8 Hz, 0.5H), 8.15 (d, J = 9.0 Hz, 1.5H), 7.22-7.47 (m, 12H), 5.45 (s, 1H), 4.64 (br, 1H), 4.51 (s, 0.75H), 4.49 (s, 0.25H), 3.90 (br, 0.75H), 3.78 (br, 0.25H), 3.63 (bs, 1H), 2.88 (bs, 0.25H), 2.78 (bs, 0.25H), 1.72 (m, 1H), 1.61 (s, 6H), 1.30 (s, 3H), 0.97 (d, J = 6.6 Hz, 0.75H), 0.96 (d, J = 6.0 Hz, 2.25H), 0.48 (d, J = 6.6 Hz, 0.75H), 0.43 (d, J = 6.6 Hz, 2.25H).



95 **96**

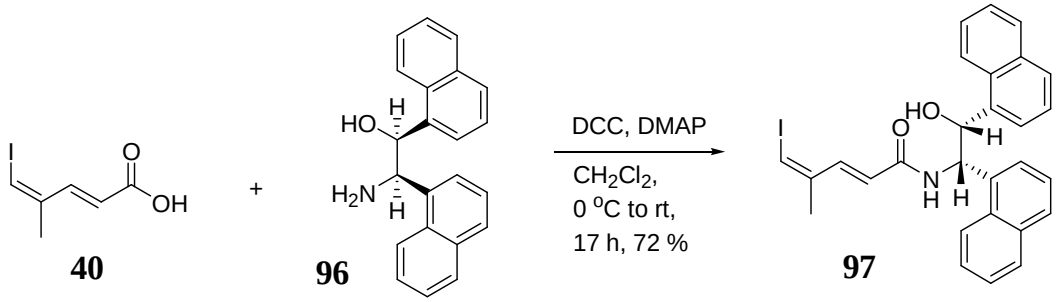
Aminoalcohol 96.[4] To a stirred solution of (S,S)-(-)-1,2-di(1-naphthyl)-1,2-ethane-diol **95** (250 mg, 0.80 mmol) and triethylamine (0.44 mL, 3.18 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C was added $SOCl_2$ (85 μL, 1.19 mmol) dropwise under Ar atmosphere. After the reaction mixture was stirred for 15 min. at 0 °C, the reaction was diluted with cold Et_2O after the starting material was completely consumed by TLC. The resulting solution was washed with cold H_2O and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum to afford 253 mg of the crude cyclic sulfite as sticky pale yellow oil, which was used in the next step without further purification. A mixture of the crude cyclic sulfite (253 mg, 0.70 mmol) and NaN_3 (115 mg, 1.77 mmol) in anhydrous DMF (4.0 mL) was stirred under Ar for 12 h at 100 °C. The reaction mixture was diluted with Et_2O, washed with H_2O and brine, dried over $MgSO_4$, and then concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:4) to provide 170 mg (63 %) of azide compound as white solid.

R_f: 0.41 (EtOAc/n-Hexane, 1/4). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96-7.57 (m, 6H), 7.57 -7.54 (m, 2H), 7.54 -7.36 (m, 6H), 5.92 (d, *J* = 6.8 Hz, 1H), 5.82 (d, *J* = 6.4 Hz, 1H), 2.07 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.9, 134.0, 133.8, 132.0, 131.8, 131.4, 129.5, 129.2, 129.1, 126.7, 126.5, 126.0, 125.8, 125.4, 125.4, 123.1, 123.0, 94.6, 73.4, 67.4, 22.9.

To a stirred suspension of $LiAlH_4$ (20 mg, 0.53 mmol) in dry THF (4.0 mL) at 0 °C was slowly added the azide (170 mg, 0.50 mmol) under Ar atmosphere. The resulting green reaction mixture was allowed to warm to rt over a period of 3 h. And then, the dark gray suspension was diluted with THF and carefully quenched by sequential addition of H_2O (0.4 mL), 15% NaOH (0.4 mL), and again H_2O (1.2 mL). The resulting solution was stirred at rt for a further 30 min, and a white precipitate was removed by filtration. The clear solution was extracted with EtOAc and H_20 and the organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by recrystallization (100% toluene) to afford 85 mg (54 %) of **96** as needle crsystal.

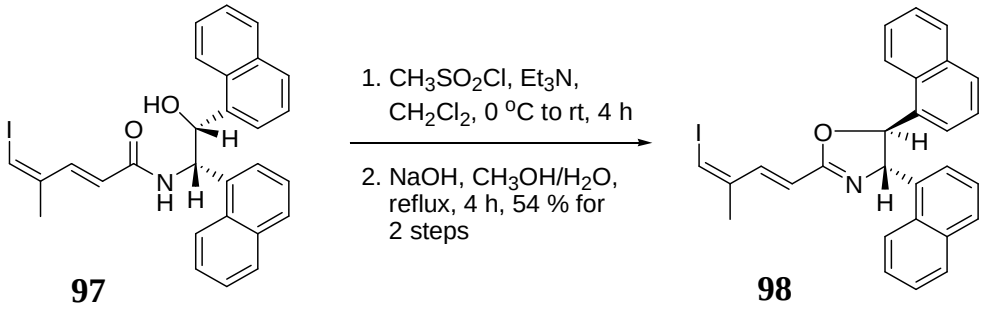
[4] Marks, T. J.; Hong, S. W.; Tian, S.; Metz, M. V. *J Am Chem Soc* **2003**, *125*, 14768.

R_f: 0.30 (EtOAc/n-Hexane, 1/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89-7.54 (m, 6H), 7.51 -7.31 (m, 8H), 5.87 (d, *J* = 5.4 Hz, 1H), 5.34 (d, *J* = 5.1 Hz, 1H), 2.55 (bs, 3H).



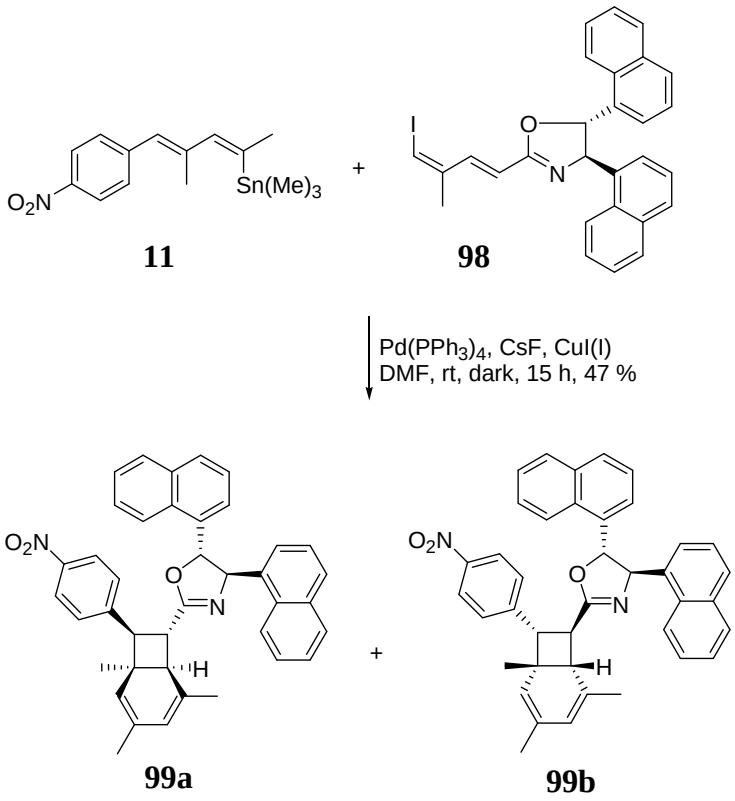
Iododiene-amide 97. To a solution of aminoalcohol **96** (67 mg, 0.21 mmol) and dienoic acid **40** (52 mg, 0.22 mmol) in dry CH_2Cl_2 (10 mL) was slowly added DCC (45 mg, 0.22 mmol) and DMAP (4 mg, 0.03 mmol) in dry CH_2Cl_2 (6.0 mL) at 0 °C under Ar atmosphere. The reaction mixture was allowed to warm to rt. After stirring for further 17 h, the reaction mixture was filtered through a Celite® and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 2:3) to provide 79.7 mg (72 %) of **97** as pale yellow solid.

R_f: 0.72 (EtOAc/n-Hexane, 2/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (m, 1H), 7.74 -6.94 (m, 13H), 6.86 (t, *J* = 7.6 Hz, 1H), 6.86 (d/d, *J* = 5.6 Hz, *J* = 3.6 Hz, 1H), 6.48 (s, 1H), 6.12 (d, *J* = 3.2 Hz, 1H), 6.04 (d, *J* = 15.2 Hz, 1H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 142.2, 140.9, 135.9, 133.6, 133.5, 133.4, 132.0, 129.0, 128.9, 128.5, 128.4, 128.2, 128.2, 126.6, 126.0, 126.0, 125.5, 125.0, 124.2, 122.9, 122.9, 87.6, 72.3, 53.3, 21.2.



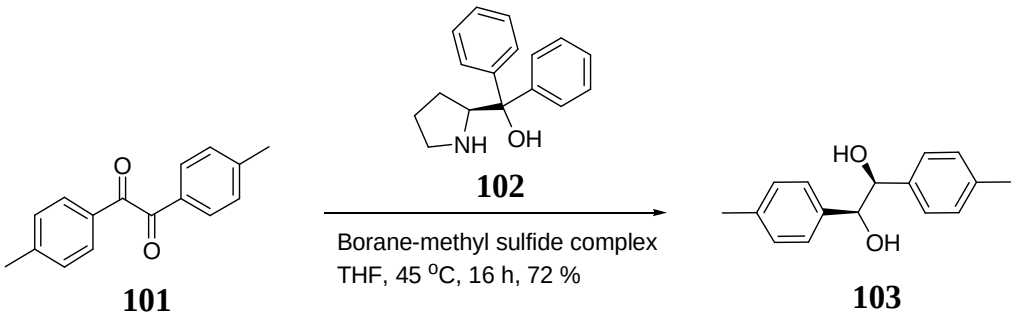
Iododiene-oxazoline 98. To an ice-cooled solution of iododiene-amide **97** (79.7 mg, 0.15 mmol) and triethylamine (75 μL, 0.53 mmol) in dry CH_2Cl_2 (2.6 mL) was added methanesulfonyl chloride (25 μL, 0.32 mmol) via syringe in one portion. The reaction mixture was allowed to warm to rt and stirred for further 3 h. Then saturated NH_4Cl solution was poured into the reaction mixture and the organic layer was separated. The water layer was extracted by CH_2Cl_2 (3 x 10 ml) and the combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:2) to provide 77.1 mg (84 %) of crude mesiylate compound as yellow solid. The mesiylate (77.1 mg, 0.12 mmol) was dissolved in methanol (1.2 mL) and a solution of NaOH (17.9 mg, 0.44 mmol) in H_2O (1.2 mL) was added in one portion. After refluxing for 4 h, the reaction mixture was allowed to cool to rt and the solvent was concentrated under vacuum. After adding H_2O (10 mL), the *aq*. layers were extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:2) to provide 42.9 mg (54 % for 2 steps) of **98** as pale yellow solid.

R_f: 0.57 (EtOAc/n-Hexane, 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.91 (m, 5H), 7.37 -7.62 (m, 11H), 7.24 (t, *J* = 6.8 Hz, 1H), 7.14 (t, *J* = 6.8 Hz, 1H), 6.62 (d, *J* = 16.8 Hz, 1H), 6.59 (s, 1H), 6.23 (d, *J* = 6.4 Hz, 1H), 6.08 (d, *J* = 6.8 Hz, 1H), 2.08 (d, *J* = 0.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 141.5, 137.4, 135.6, 134.2, 133.6, 131.0, 130.3, 129.6, 129.3, 129.0, 128.9, 126.8, 126.4, 126.0, 125.7, 124.7, 123.5. 119.2, 87.2, 86.6, 74.0, 21.2, 21.1; HRMS(ESI-MS) Calcd. for $C_{32}H_{31}N_2O_3$ $[(M + H)]^+$ 515.0711, found 515.0832.



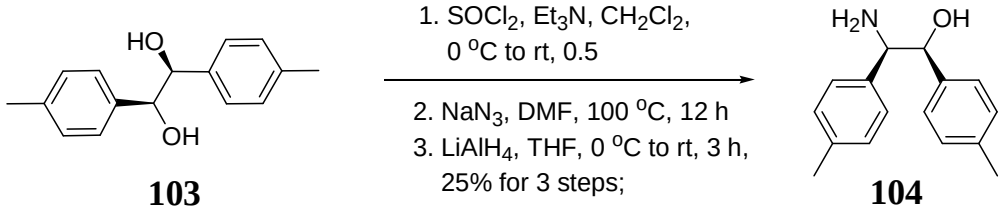
SNF analogs 99a and 99b. To a solution of vinyl stannane **11** (20.8 mg, 0.057 mmol) and iododiene-oxazoline **98** (25.5 mg, 0.048 mmol) in 1:1 mixture of anhydrous DMF and CH_2Cl_2 (1.7 mL) were added cesium fluoride, CsF (17.0 mg, 0.112 mmol) and copper iodide, CuI(I) (2.8 mg, 0.014 mmol) at rt under deoxygenating with a stream of Ar. After adding tetrakis triphenylphosphine palladium, $Pd(PPh_3)_4$ (7.2 mg, 0.006 mmol), the reaction flask was immediately wrapped with aluminum foil and continued deoxygenating for further 5 min. The reaction mixture stirred for 15 h, and then diluted with EtOAc (25 mL). The organic layer was washed with saturated NH_4Cl solution (3 x 25 mL). The combined *aq*. layers were extracted with EtOAc (3 x 25 mL), dried over $MgSO_4$, and concentrated under vacuum. Preparative chromatography (EtOAc:*n*-hexane, 1:5) afforded 17.0 mg of an inseparable crude mixture of diastereomeric **99a** and **99b**.

R_f: 0.56 (EtOAc/*n*-hexane, 1/5) ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.25 (d, *J* = 9.0Hz, 2H), 7.56 (d, *J* = 9.0Hz, 2H), 7.05-7.92 (m, 14H), 6.06 (d, *J* = 18.0 Hz, 2H,), 5.50 (s, 1H), 4.55 (s, 1H), 4.09 (d, *J* = 10.2 Hz, 1H,), 3.89 (t, *J* = 9.0Hz, 1H), 3.04 (d, *J* = 8.4 Hz ,1H), 1.79 (s, 3H), 1.65 (s, 3H), 1.35 (s, 3H).



Diol 103. To a stirred solution of (S)-diphenylprolinol **102** (127 mg, 0.50 mmol) in anhydrous THF (5.0 mL) was added 2M borane-dimethylsulfied solution in toluene (5.0 mL, 10.0 mmol), and the reaction mixture was stirred while temperature was maintained at 45 °C for 16 h to obtain a solution of the catalyst. The resulting mixture was treated dropwise over 10 min with a solution of 1,2-diketone **101** (2.95 g, 12.4 mmol) in THF (6.0 mL) at 45 °C. After the addition, the mixture was stirred fro 5 min and quenched cautiously with MeOH (1.0 mL) and stirred for an additional 30 min. Most of the sovent was evaporated and the residue was directly purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:9), and further purified by recrystallization (100 % MeOH) to provide 2.12 g (72 %) of **103** as needles.

R_f: 0.59 (EtOAc/n-Hexane, 1/29). ^{1}H NMR (300 MHz, $CDCl_3$): 7.05 (s, 8H), 4.68 (s, 2H), 2.30 (s, 6H). * Spectroscopic properties were in agreement with literature values.[5]



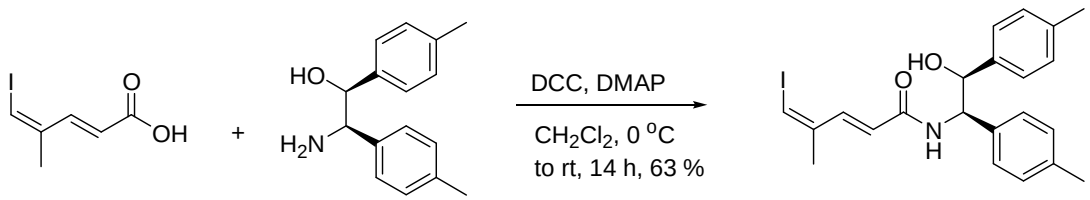
Aminoalcohol 104. To a stirred solution of (S,S)-diol **103** (217 mg, 0.90 mmol) and triethylamine (0.60 mL, 4.34 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C was added $SOCl_2$ (135 μL, 1.89 mmol) dropwise under Ar atmosphere. After the reaction mixture was stirred for 15 min. at 0 °C, the reaction was diluted with cold Et_2O after the starting material was completely consumed by TLC. The resulting solution was washed with cold H_2O and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum to afford 232.5 mg of the crude cyclic

[5] Marks, T. J.; Hong, S. W.; Tian, S.; Metz, M. V. *J Am Chem Soc* **2003**, *125*, 14768.

sulfite as red solid, which was used in the next step without further purification. A mixture of the crude cyclic sulfite (232.5 mg, 0.81 mmol) and NaN_3 (130 mg, 2.00 mmol) in anhydrous DMF (4.6 mL) was stirred under Ar for 13 h at 100 ^oC. The reaction mixture was diluted with Et_2O, washed with H_2O and brine, dried over $MgSO_4$, and then concentrated under vacuum to afford 144 mg of the crude azide as viscous pale yellow, which was used in the next step without further purification. R_f: 0.68 (EtOAc/n-Hexane, 1/4). ^1H NMR (300 MHz, $CDCl_3$): δ 7.26-7.15 (m, 8H), 4.76 (d, *J* = 6.9 Hz, 1H), 4.63 (d, *J* = 6.9 Hz, 1H), 2.37 (s, 6H).

To a stirred suspension of $LiAlH_4$ (22 mg, 0.58 mmol) in dry THF (5.0 mL) at 0 ^oC was slowly added the azide (144 mg, 0.54 mmol) under Ar atmosphere. The resulting green reaction mixture was allowed to warm to rt over a period of 3 h. And then, the dark gray suspension was diluted with THF and carefully quenched by sequential addition of H_2O (0.5 mL), 15% NaOH (0.5 mL), and again H_2O (1.5 mL). The resulting solution was stirred at rt for 30 min, and a white precipitate was removed by filtration. The clear solution was extracted with EtOAc. Then, the organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was directly purified by recrystallization (1 mL of 100% toluene) to afford 69.7 mg (32 % for 3 steps) of **104** as needles.

R_f: 0.29 (EtOAc/n-Hexane, 1/4). ^1H NMR (600 MHz, $CDCl_3$): δ 7.10-7.05 (m, 8H), 4.81 (bs, 2H), 4.73 (d, *J* = 6.0 Hz, 1H), 3.99 (d, *J* = 6.0 Hz, 1H), 3.0 (m, 1H), 2.30 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 138.1, 137.6, 137.4, 129.2, 129.6, 127.5, 127.2, 78.1, 61.8, 21.3.

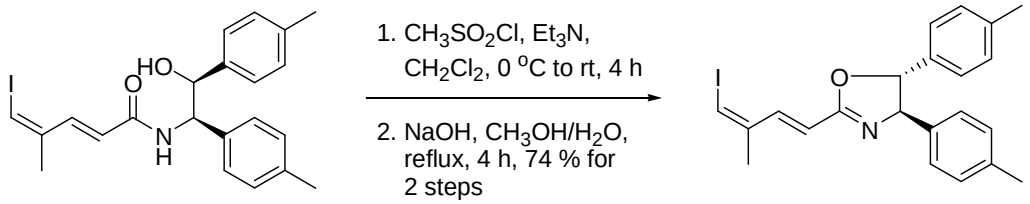


40 **104** **105**

Iododiene-amide 105. To a solution of aminoalcohol **104** (104.1 mg, 0.43 mmol) and dienoic acid **40** (109 mg, 0.43 mmol) in dry CH_2Cl_2 (7.5 mL) was slowly added DCC (100 mg, 0.49 mmol) and DMAP (7.5 mg, 0.06 mmol) in dry CH_2Cl_2 (5.0 mL) at 0 ^oC under Ar atmosphere. The reaction mixture was allowed to warm to rt. After stirring for further 14 h, the reaction mixture was filtered on a Celite® and the filtrate was concentrated under vacuum. The residue

was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:2) to provide 121.1 mg (63 %) of **105** as a pale yellow solid.

R_f: 0.73 (EtOAc/n-Hexane, 2/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 15.2 Hz, 1H), 7.04-6.92 (m, 8H), 6.54 (s, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 6.03 (d, *J* = 15.6 Hz, 1H), 5.30 (m, 1H), 5.04 (d, *J* = 4.0 Hz, 1H), 2.28 (s, 6H), 1.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 140.8, 137.7, 137.7, 136.9, 134.2, 129.1, 128.9, 128.0, 126.8, 124.8, 87.6, 59.8, 21.3, 21.2.

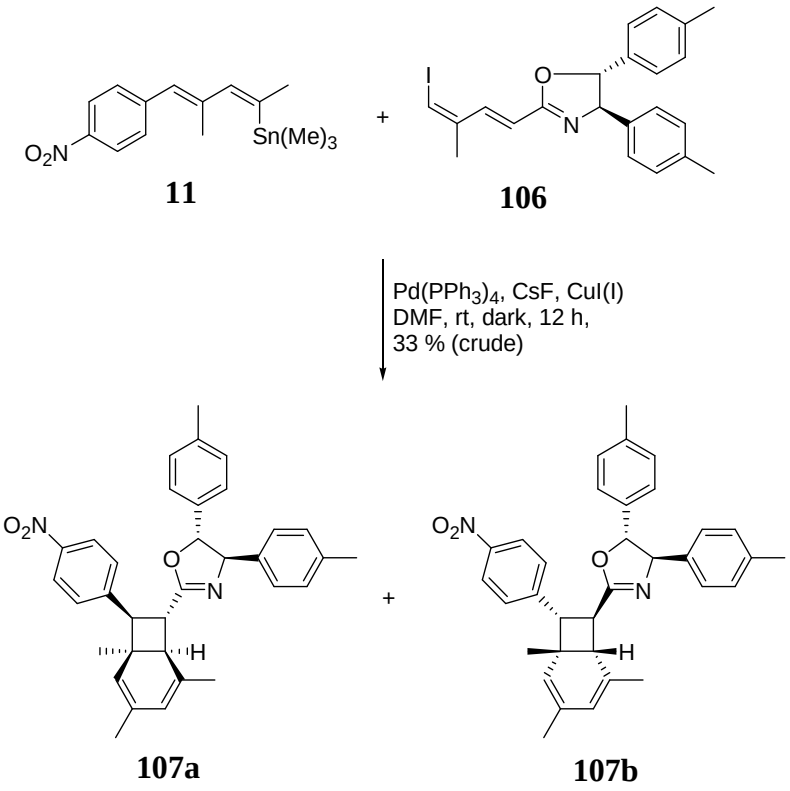


105 **106**

Iododiene-oxazoline 106. To an ice-cooled solution of iododiene-amide **105** (79.7 mg, 0.15 mmol) and triethylamine (75 μL, 0.53 mmol) in dry CH_2Cl_2 (2.6 mL) was added methanesulfonyl chloride (25 μL, 0.32 mmol) via syringe in one portion. The reaction mixture was allowed to warm to rt and stirred for further 3 h. Then saturated NH_4Cl solution was poured into the reaction mixture and the organic layer was separated. The water layer was extracted by CH_2Cl_2 (3 x 10 ml) and the combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:2) to provide 77.1 mg (84 %) of crude mesilate xxx as yellow solid. The mesilate (77.1 mg, 0.12 mmol) was dissolved in methanol (1.2 mL) and a solution of NaOH (17.9 mg, 0.44 mmol) in H_2O (1.2 mL) was added in one portion. After refluxing for 4 h, the reaction mixture was allowed to cool to rt and the solvent was concentrated under vacuum. After adding H_2O (10 mL), the *aq*. layers were extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:2) to provide 42.9 mg (54 % for 2 steps) of **106** as pale yellow solid.

R_f: 0.59 (EtOAc/n-Hexane, 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 16.0 Hz, 1H), 7.16 - 7.30 (m, 8H), 6.59 (s, 1H), 6.52 (d, *J* = 15.6 Hz, 1H), 5.33 (d, *J* = 8.0 Hz, 1H), 5.13 (d, *J* = 7.6 Hz, 1H), 2.42 (s, 3H), 2.39 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 141.5,

138.9, 138.6, 137.6, 137.5, 129.8, 126.7, 126.1, 119.7, 89.1, 86.4, 78.7, 21.5, 21.4, 21.3, 21.2, 21.1; HRMS(ESI-MS) Calcd. for $C_{32}H_{31}N_2O_3$ $[(M + H)]^+$ 444.0736, found 444.0830.



SNF analogs 107a and 107b. To a solution of vinyl stannane **11** (20.8 mg, 0.057 mmol) and iododiene-oxazoline **106** (22.9 mg, 0.050 mmol) in anhydrous DMF (1.5 mL) were added cesium fluoride, CsF (18.2 mg, 0.120 mmol) and copper iodide, CuI(I) (2.5 mg, 0.013 mmol) at rt under deoxygenating with a stream of Ar. After adding $Pd(PPh_3)_4$ (6.9 mg, 0.006 mmol), the reaction flask was immediately wrapped with aluminum foil and continued deoxygenating for further 5 min. The reaction mixture stirred for 12-16 h, and then diluted with EtOAc (25 mL). The organic layer was washed with saturated NH_4Cl solution (3 x 25 mL). The combined *aq*. layers were extracted with EtOAc (3 x 25 mL), dried over $MgSO_4$, and concentrated under vacuum. Preparative chromatography (EtOAc:*n*-hexane, 1:5) afforded 8.9 mg (33 %) of a crude inseparable mixture of diastereomeric **107a** and **107b**.

R_f: 0.60 (EtOAc/*n*-Hexane, 1/5) ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.06-7.45 (m, 8H), 5.58 (s, 1H), 5.78 + 5.74 (d/d, *J* = 21.6 Hz, 4.2 Hz, 2H), 4.50

(s, 1H), 4.45 (d, *J* = 10.2 Hz, 1H), 4.26 (t, *J* = 8.4 Hz, 1H), 3.29 (d, *J* = 9.6 Hz, 1H,), 2.40 + 2.33 (s, 3H), 1.77 (s, 3H), 1.68 (s, 3H), 1.39 (s, 3H).

Chapter II

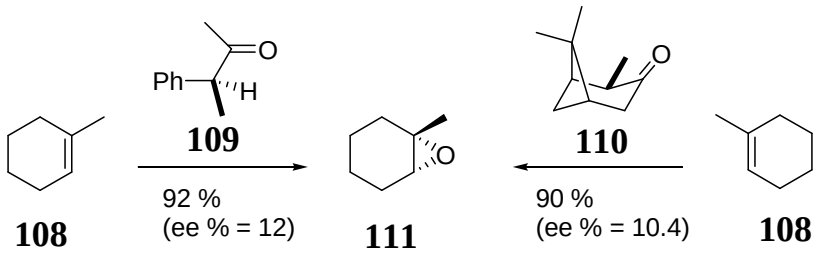
Shi Epoxidations Toward Preparation of Chiral SNF Analogues

2.1. Introduction

2.1.1. Background

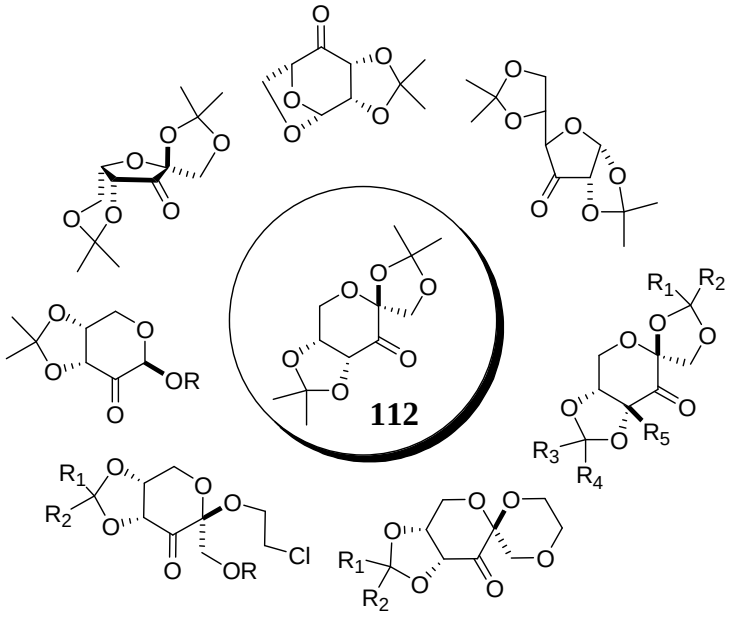
Preparing optically active epoxides from olefins is a very important problem in organic synthesis because the chiral epoxides can be converted into a number of enantiomerically pure molecules such as natural products. Various effective and powerful systems have been disclosed over the years for the preparation of chiral epoxides.[1,2] Specifically, in the early 1980s, Sharpless discovered asymmetric epoxidations of allylic alcohols with chiral titanium catalyst, now known as "the Sharpless asymmetric epoxidation reaction".[3,4] Chiral manganese (III)-complexes that catalyze epoxidations of *cis*-olefins were investigated by the Jacobsen and Katsuki groups independently.[5-7] Recently, using a vanadium catalyst, stereoselective epoxidations of homoallylic alcohols were successfully performed by the Yamamoto group.[8]

On the other hand, organocatalytic asymmetric epoxidations were examined by introducing chiral dioxirane catalysts derived from corresponding ketones to different types of olefins, particularly unfuctionalized trans and trisubstituted forms. In 1984, Curci and co-workers demonstrated that 1-methylcyclohexene **108** can be stereoselectively epoxidized to lead to the corresponding epoxide **111** via dioxirane intermediates derived from chiral ketone-catalysts (**109** or **110**).[9] (See scheme 46.)



Scheme 46. Examples of the first chiral ketone-catalyzed epoxidations.

Among a variety of chiral ketone-based dioxirane catalysts, a D-fructose-derived ketone **112** showed excellent regio- and steteroselectivity and broad functional group tolerance in epoxidation of olefins (Figure 19).[10]



R_1, R_2 = Alkyl, Phenyl, TBS, Acetyl. R_3, R_4 = Alky, Benzyl, R_5 = H, F

Figure 20. Carbohydrate-based and related ketone catalysts.

Shi and co-workers demonstrated that epoxidation induced by the chiral oxirane, which is generated *in situ* from ketone **112**, has unique advantages: (1) the stereogenic centers are close to the reacting center; (2) the presence of fused ring(s) or a quaternary center α to the carbonyl group minimizes the epimerization of the stereogenic centers; and (3) possible competing approaches of an olefin to the reacting dioxirane can be controlled by sterically blocking one face or using a *C*2- or pseudo-*C*2-symmetric element. According to Shi, optimized pH condition is very critical because at low pH, Oxone® is stable, but **112** rapidly decomposes. On the other hand, at high pH, Oxone® loses its function due to decomposition.

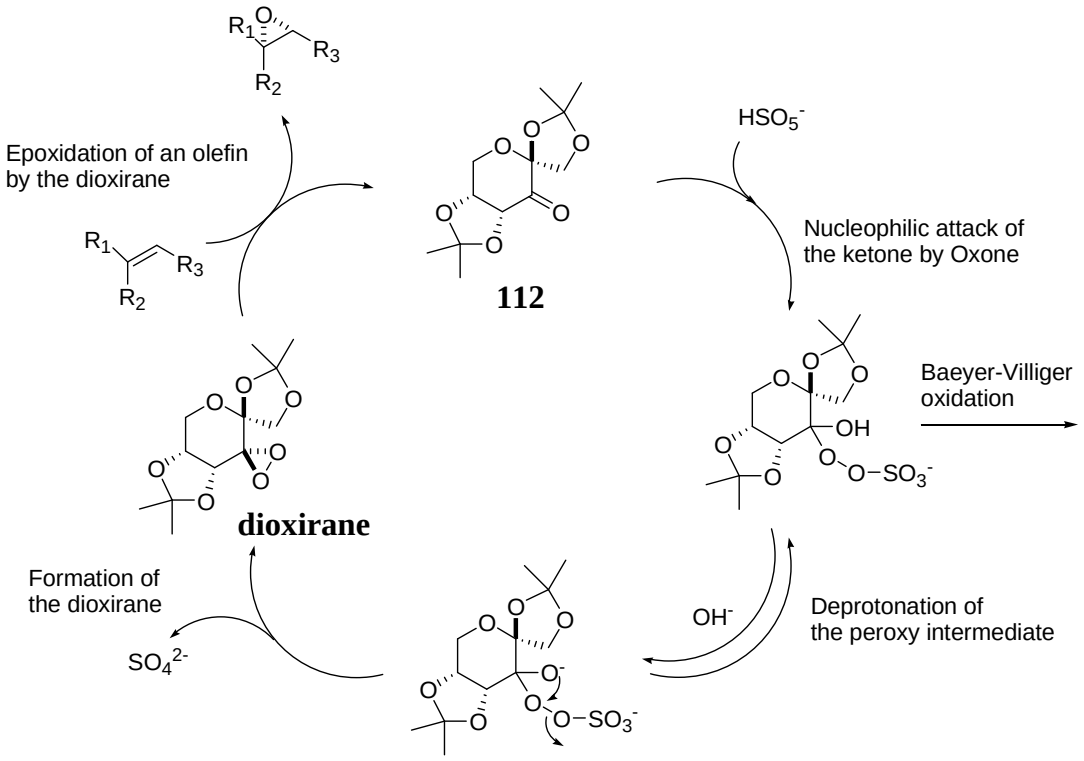


Figure 21. Dioxirane catalyst derived from **112** mediated epoxidation pathways.

As a result, pH 10.5 prepared with K_2CO_3 or KOH provides an optimized reaction condition. Asymmetric epoxidation mediated by the chiral ketone **112**, is known as " the Shi asymmetric epoxidation reaction"(Figure 20).[11]

The high regio- and stereoselectivity observed in the Shi epoxidation can be explained on the basis of transition state analysis. Baumstark and co-workers proposed two extreme transition state geometries; spiro and planar. They demonstrated that a kinetic study of epoxidations of *cis*- and *trans*-hexenes with dimethyldioxirane was consistent with the preference of spiro over planar transition states.[12,13] Computational studies also supported that the stabilizing interaction of an oxygen lone pair with the π^* orbital of an olefin shown in **TS-I** may result in a predominant adduct via the spiro transition state. **TS-II** represents the relatively unfavorable planar transition state (Figure 21).[14,15]

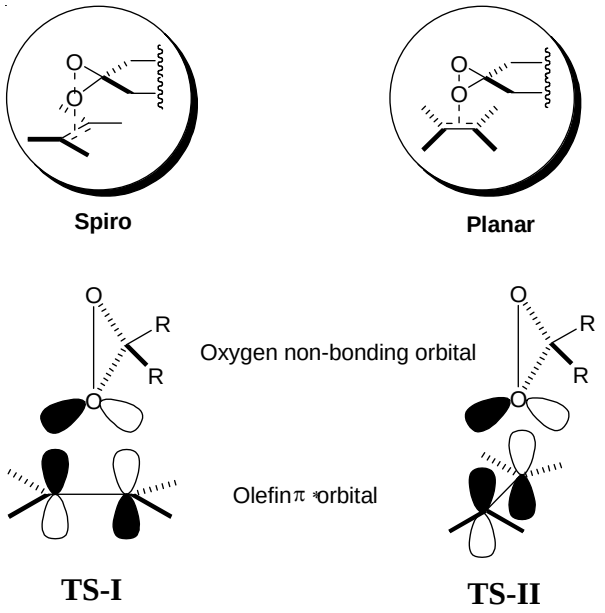


Figure 22. Spiro and planar transition state for the dioxirane expoxidation of olefins.

Therefore, a preferable geometry would be afforded by minimizing steric hindrance between trisubstituted olefins and the dioxirane derived from **112**. The transition state with the spiro geometry is considered more favorable than that with the planar geometry in the Shi system. The lowest energy spiro transition state should be **Spiro TS-I** (Figure 22).[16]

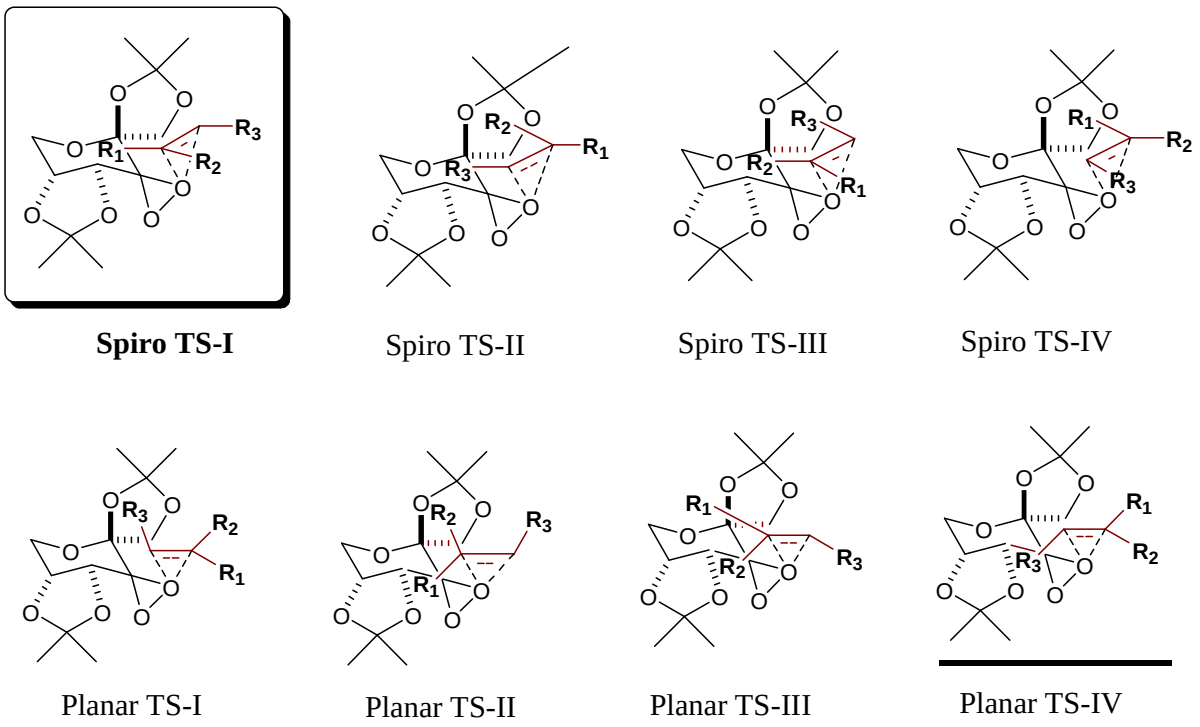
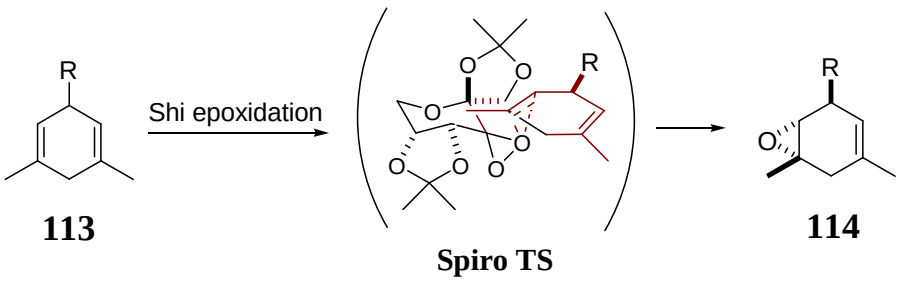


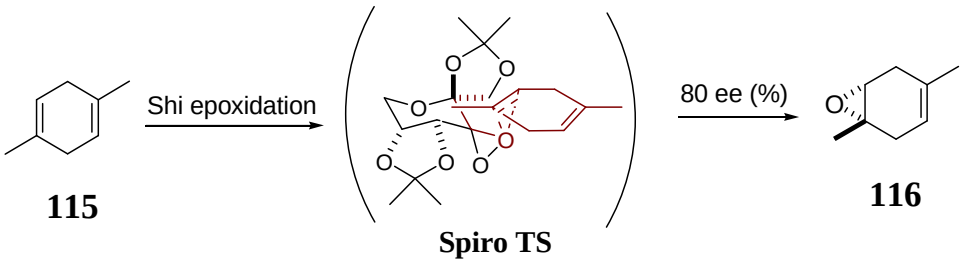
Figure 23. Transition state analysis in the Shi asymmetric epoxidation.

Numerous examples of epoxidations performed by the Shi group showed high regio- and stereoselectivity, probably resulting from a preferred spiro transition state.[17-23] Among them were desymmetrization and kinetic resolution of 1,3-dimethyl-1,4-cyclohexadiene bearing a stereogenic center at the allylic position **113** and 1,4-dimethyl-1,4-cyclohexadiene **115**. Shi epoxidations of **113** successfully produced enantioenriched monoepoxide **114** predominantly via spiro transition state (Scheme 47).[16]



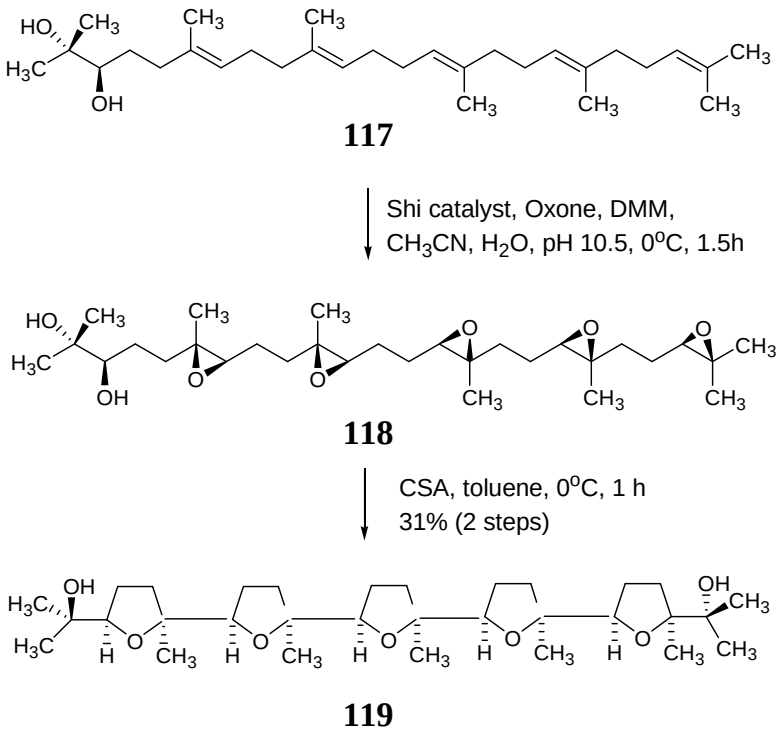
Scheme 47. Shi asymmetric epoxidation of 1,5-dimethyl-1,4-cyclohexadiene **113**.

Regio- and enantioselective epoxidation of **115** mediated by the chiral dioxirane derived from **112** provided enantioenriched monoepoxide **116** (Scheme 48).[16]



Scheme 48. Shi asymmetric epoxidation of 1,4-dimethyl-1,4-cyclohexadiene **115**.

Shi asymmetric epoxidation has been introduced as a key strategy in the total synthesis of natural products and other complex molecules.[24-28] Among them was progress towards the total synthesis of squalenoid glabrescol. For the construction of five chiral tetrahydrofuran rings in (*R*)-2,3-dihydroxy-2,3-dihydrosqualene **117**, Xiong and Corey adopted the Shi method. Epoxidations of each of the trisubstituted double bonds in **117** were achieved with remarkable enantioselection using the Shi chiral dioxirane derived from **112** to lead to the pentaepoxide **118**. Treatment with camphor-10-sulfonic acid (CSA) gave the pentaoxacyclic structure **119** (Scheme 49).[28]



Scheme 49. Shi asymmetric epoxidation of dihydrosqualene **117**.

2.1.2. Preparation of chiral SNF analogs by Shi asymmetric epoxidation

In challenges for preparing enantiomerically pure natural products, Shi asymmetric epoxidations of trisubstituted cis-olefins have provided enough potential to compete with other stereoselective epoxidations. Our particular interest in the Shi epoxidation focuses on preparation of enantiomerically pure monoepoxide **120** which might be elaborated to chiral SNF analog **35**. Shi asymmetric epoxidation via kinetic resolution can be considered as a potentially efficient route to provide chiral SNF analogs (Figure 23).

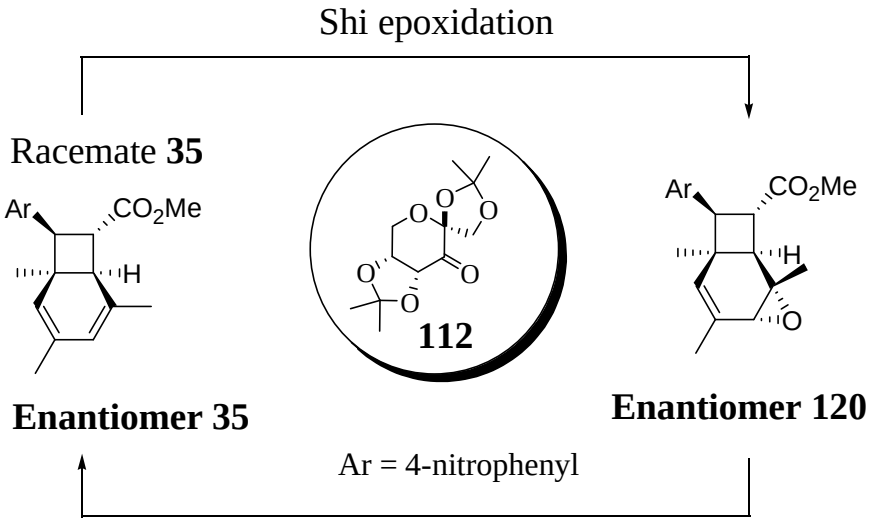


Figure 24. A strategy for obtaining chiral SNF analog **35** via Shi epoxidation.

The Shi epoxidation provided excellent regio- and stereoselectivity for the 1,5-dimethyl- or 1,3-dimethyl-1,4-cyclohexadiene substrates. (See Schemes 44 and 45.) The bicyclooctadiene **35** is considered as a suitable substrate because methyl ester **35** can be readily converted into corresponding carboxylic acid **46,** which is a key intermediate for the construction of chiral analogs of the SNF multidrug resistance reversal agents. (See Scheme 13 in Chapter I.)

In principle, eight regio- and stereoisomeric monoepoxide isomers **120** and **121** can be produced from racemic bicyclooctadiene **35** (Figure 24).

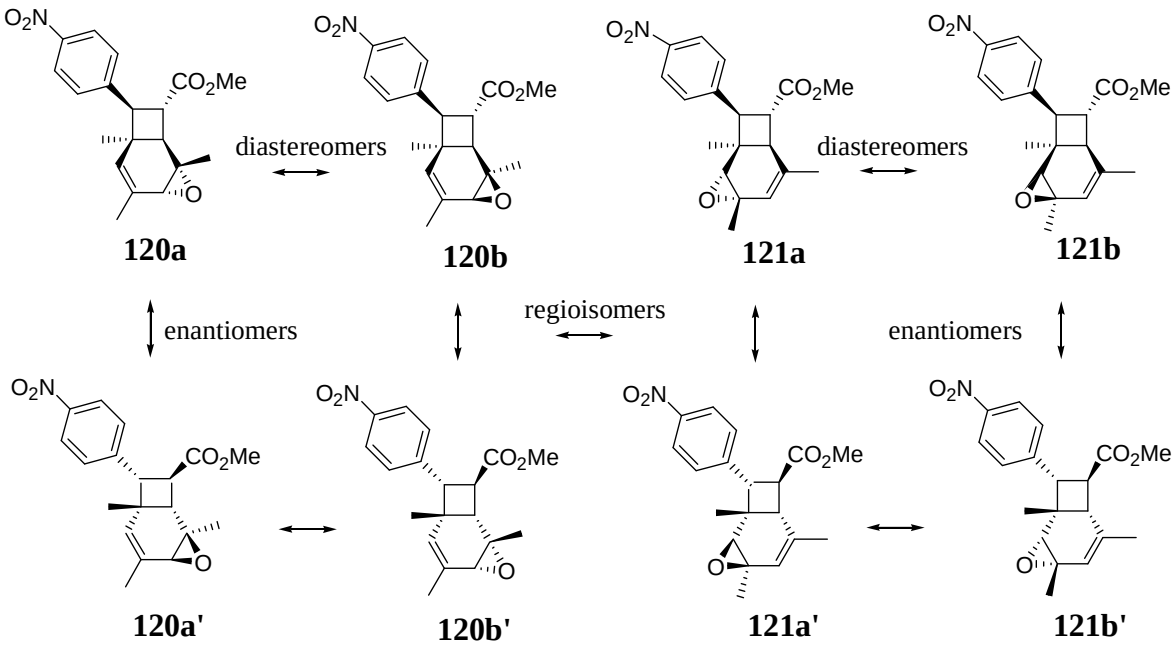


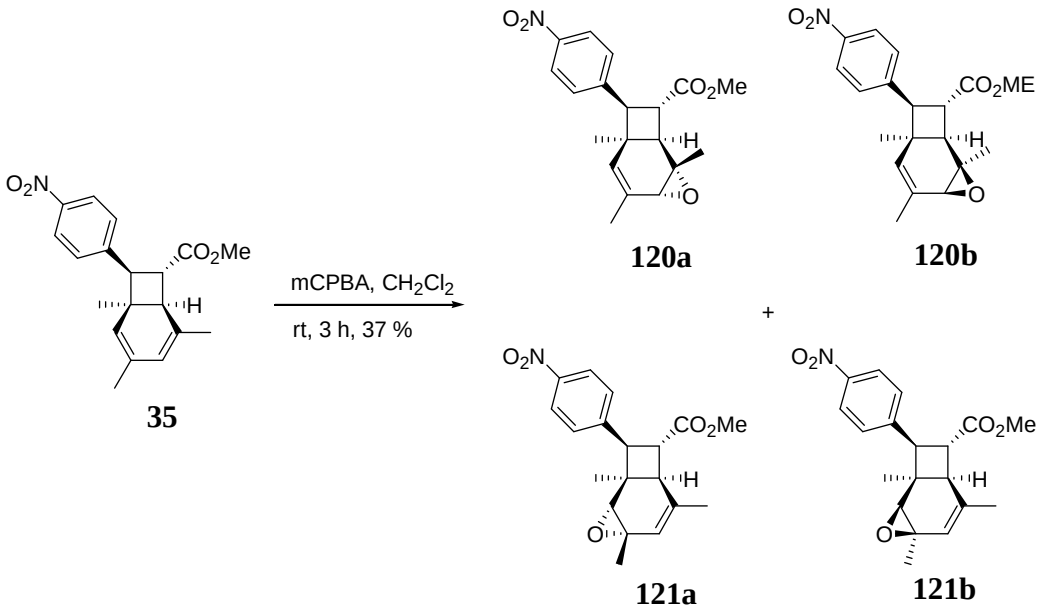
Figure 25. Structural relationship between monoepoxides **120** and **121**.

Due to the steric effect of the methyl group on the ring junction of **35**, high regio- and stereoselectivity is anticipated that will lead predominantly to monoepoxides **120**. The 4-nitrophenyl group is considered closer to the olefin, which is adjacent to the methyl group on the ring junction. Therefore, the dioxirane to the olefin might be unfavorable.

2.2. Result and Discussion

2.2.1. Shi asymmetric epoxidations of the bicyclo[4.2.0]octadiene 35.

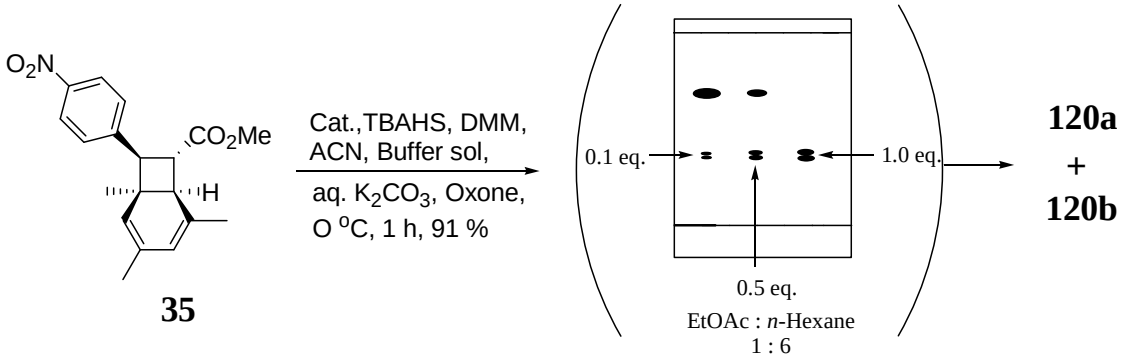
Bicyclooctadiene **35** was readily prepared from Stille coupling and tandem 8π, 6π electrocyclization. (See Scheme 11 in Chapter I.)[29] For comparison of affinity and catalytic ability of the dioxirane catalyst derived from ketone **112**, epoxidation of **35** was performed with 0.5 eq. of meta-chloroperoxybenzoic acid (mCPBA) (Scheme 50). As expected, four diastereomeric monoepoxides **120a/b** and **121a/b** were observed on the basis of ^{1}H NMR analysis. The ratio was 35 : 5 : 5 : 55 (**120a** : **120b** : **121a** : **121b**).



Scheme 50. mCPBA-derived epoxidation of bicyclooctadiene **35**.

Shi asymmetric epoxidation of **35** was carried out in the presence of 0.5 eq. of Oxone® and 50 mol% of the ketone **112** under monitoring by TLC.[30] After adding 0.1 eq. of Oxone®, two spots immediately appeared with similar intensity by analysis with UV and with 10 % PMA solution in EtOH. The ratio of the two spots was preserved until 0.5 eq. of Oxone® was

consumed. Eventually, **35** was completely oxidized by addition of 1.0 eq. of Oxone® to yield two separable diastereomeric monoexpoxides **120a** and **120b** (Scheme 51).



Scheme 51. Shi expoxidation of **35** and in-process monitoring by TLC.

Monoepoxides **120a** and **120b** were produced in almost equal amounts. Their geometries were determined on the basis of nOe experiments (Figure 25).

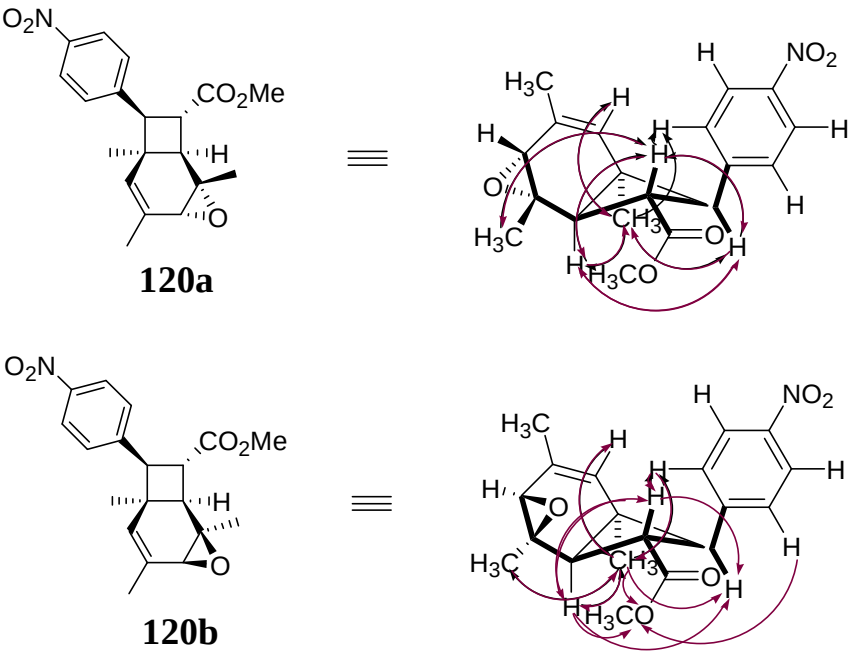
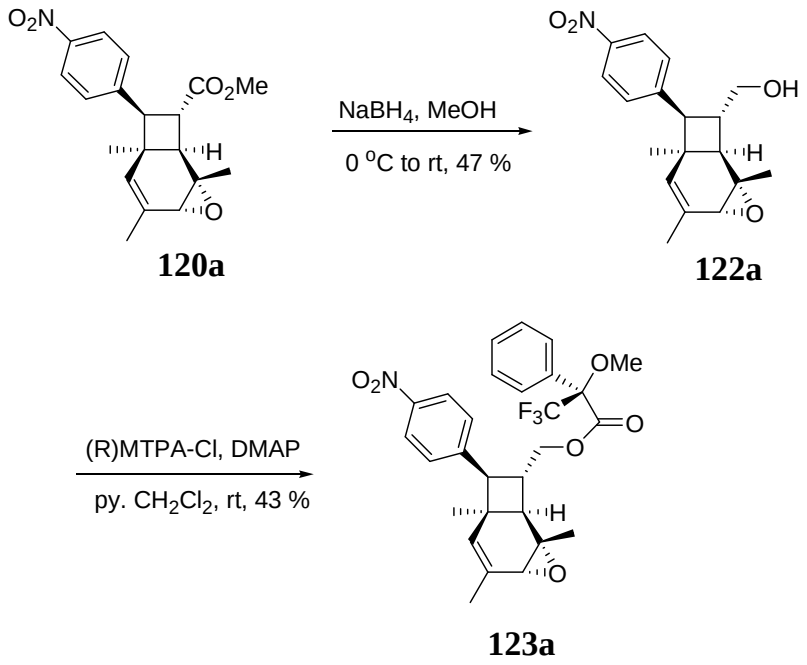


Figure 26. Structure determination of **120a** and **120b** by NOE experiment.

Despite high regioselectivity and yield, the stereochemical communication between bicyclooctadiene **35** and the dioxirane catalyst derived from the ketone **112** was not efficient. Mosher ester analysis approach was adopted in order to determine stereochemistry of **120a** and **120b**.[31] **120a** was treated with $NaBH_4$ in MeOH for selective reduction of the methyl ester moiety in the presence of epoxide moiety.[32] Initially, 7.0 eq. of $NaBH_4$ was used to convert ester **120a** into corresponding hydroxyl compound **122a**. To complete the reduction of **120a**, an additional 7.0 eq. of $NaBH_4$ was again added, but the conversion ratio was not improved. **122a** was directly treated with R-(-)-Mosher's reagent to produce corresponding (S)-Mosher ester **123a** (Scheme 52). Interestingly **123a** exhibited a single set of peaks in the proton NMR spectra.



Scheme 52. Mosher ester analysis of **120a**.

The two geminal protons of the methylene attached to the ester linkage showed the same peak pattern as that of bicyclooctadiene **84b**. According to Kobayashi,[33] the absolute configuration of primary alcohols possessing a branched methyl group can be assigned on a basis of the chemical shift differences of the geminal protons. Presumably, the relative stereochemistry of (S)-Mosher ester **123a** may be the opposite of (R)-Mosher ester **84a**, whose absolute stereochemistry was already determined on the basis of X-ray crystallography of the SNF analog **43a.** It may be

consistent with (S)-Mosher ester **84b.** However, Kobayashi and co-workers also mentioned that this method could not be applied for C2-branched primary alcohols with a conjugated group or a consecutive chiral center at C3.[34] Therefore, it is not quiet obvious that the absolute configuration of monoepoxide **(S)-123b** is the same of that of bicyclooctadiene **(S)-84b** (Figure 26).

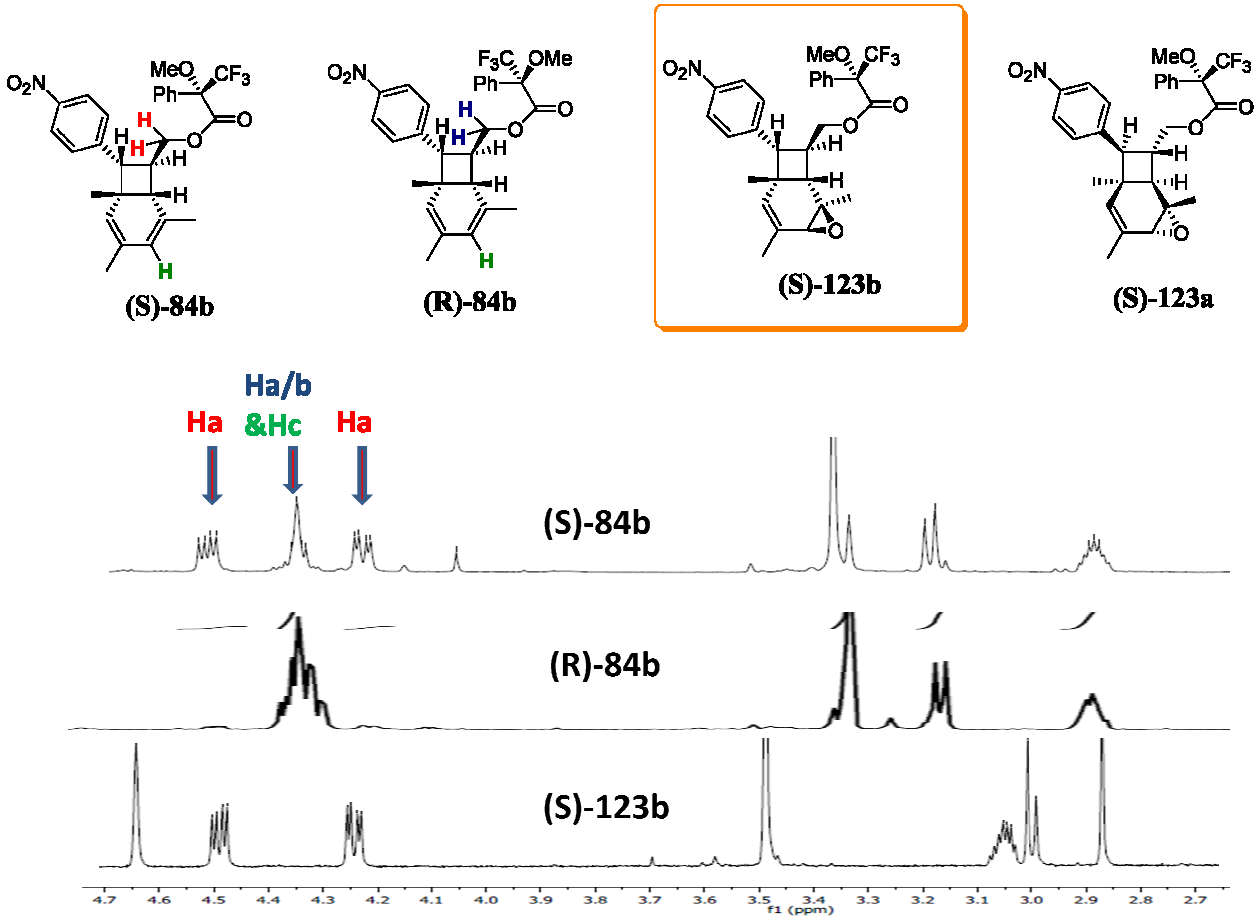
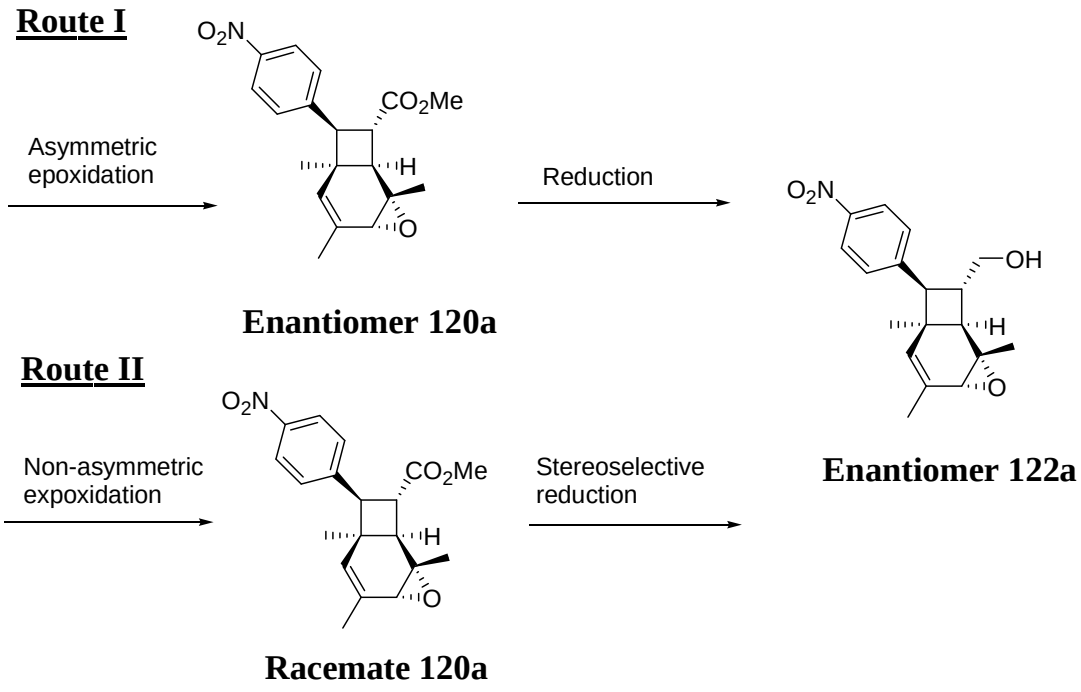


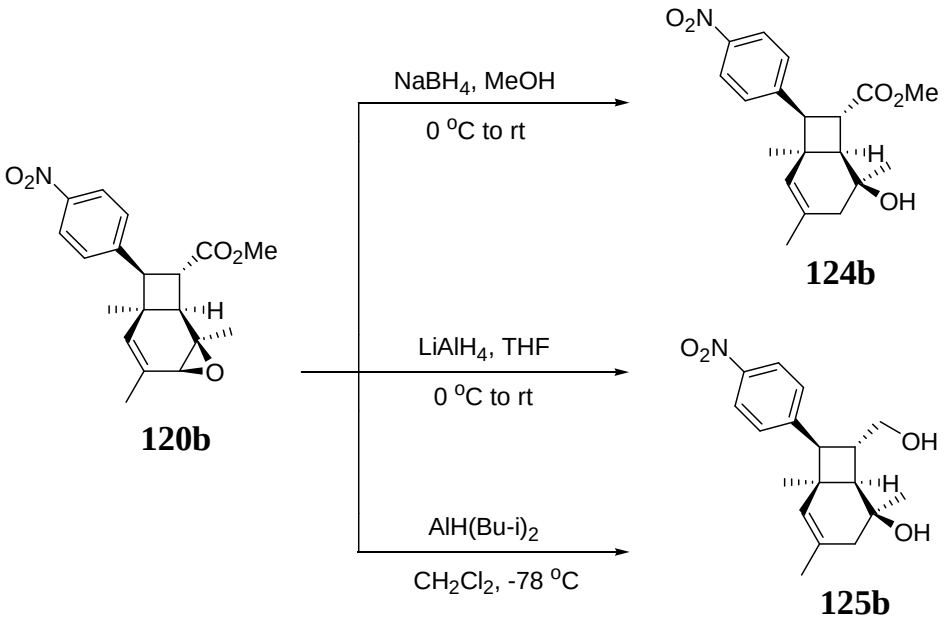
Figure 27. Comparison between Mosher esters **84a**, **84b,** and **123b**.

Two pathways can be considered to generate enantiomeric monoepoxide **120a**. (See below Scheme 53).



Scheme 53. Possible pathways for generating the enantiomer **122a**.

According to Route I, although Shi epoxidation of **35** yielded the two diastereomers **120a** and **120b**, monoepoxide **120a** was produced as a single enantiomer. Reduction led directly to the corresponding hydroxyl compound **122a**. Further study focused on reduction of the other diastereomer, compound **120b**. Interestingly, the methyl ester group in **120b** was not reduced despite treatment with an extremely large excess of $NaBH_4$. Instead, a small amount of **124b** resulting from epoxide ring opening of **120b** was produced. Introducing stronger reducing agents such as $LiAlH_4$[35,36] and DIBAL-H [37] only afforded over-reduced diol **125b** (Scheme 54).



Scheme 54. Synthetic attempt towards selective reduction of methyl ester in **120b**.

2.2.2. Shi epoxidation of endo bicyclooctadiene 128 and exo 129

Particular interest in endo bicyclooctadiene **128** was based on its unique structure, because the methyl group on the cyclobutane ring can generate steric hindrance against approach of the dioxirane catalyst to the top face (Figure 27).

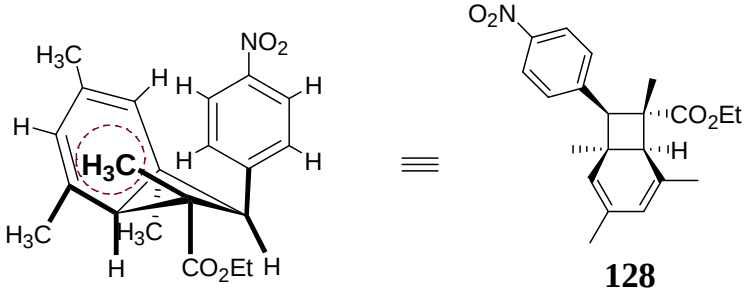
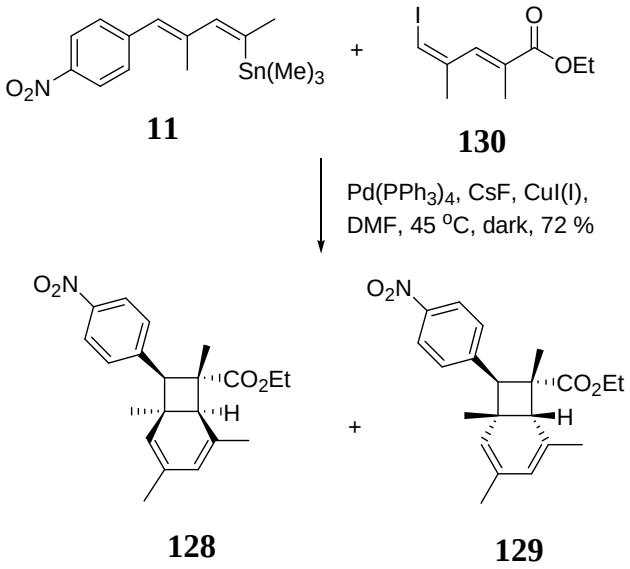


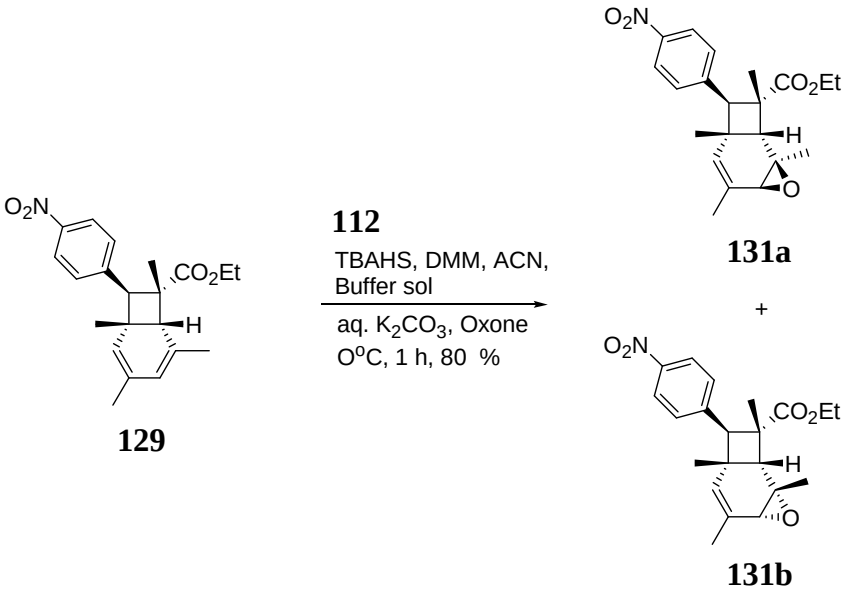
Figure 28. Steric effect anticipated by the methyl group in endo **128**.

The endo racemic bicyclooctadiene **128** along with exo **129** was prepared from Stille coupling between **11** and **130**, and then tandem 8π, 6π electrocyclization (Scheme 55).[38]



Scheme 55. Preparation of endo **128** and exo **129**.

Firstly due to structural similarity between diastereomeric bicyclooctadienes **128** and **129**, we examined Shi epoxidation with exo **129**. Under the given conditions, Shi asymmetric expoxidation of **129** afforded two diastereomeric monoepoxides **131a** and **131b** with 80 % yield in a ratio of 1 : 1 (Scheme 56).



Scheme 56. Shi epoxidation of exo bicyclooctadiene **129**.

No significantly different phenomenon was observed compared to the epoxidation of **35**. Presumably, the methyl group in exo **129** which is not oriented toward the cyclohexadiene ring might not contribute to generating steric effect during the Shi epoxidation (Figure 28).

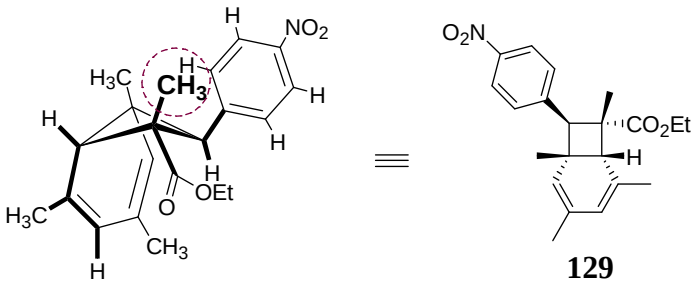
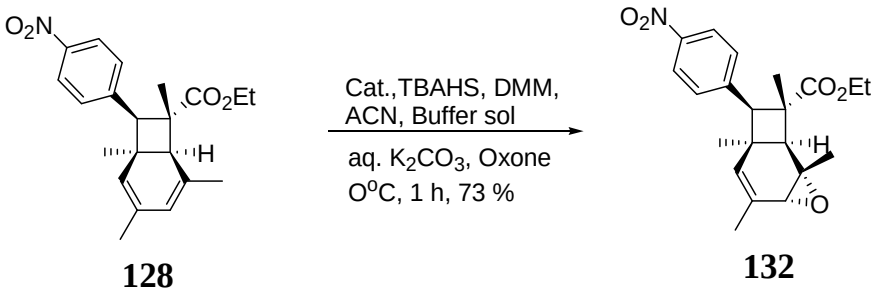


Figure 29. Structural geometry of exo **129**.

Shi epoxidation of endo **128** was performed under the given reaction conditions (Scheme 57). A single monoepoxide **132** was produced on the basis of TLC and ^{1}H NMR analysis. Interestingly **132** showed exactly the same chemical shifts and splitting patterns for all protons as either monoepoxide **131a** or **131b,** which were afforded from exo **129**. The experiment was repeated with the same result.



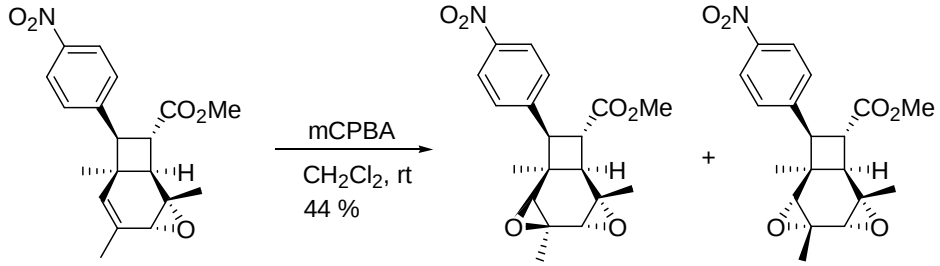
Scheme 57. Shi epoxidation of endo bicycloctadiene **128**.

In order to investigate the unusual phenomenon observed in the epoxidation of endo **128**, Shi epoxidation of a mixture of **128** and **129** was performed with 0.45 eq of Oxone® under a common set of reaction conditions. The crude ^{1}H NMR spectrum indicated that two monoepoxides were produced in a ratio of 1.00 : 1.81 (the faster moving isomer : the slower moving isomer). Chemical shifts and splitting patterns of the two monoepoxides were consistent with that of **131a** and **131b**. On the other hand, bicyclooctadienes **128** and **129** were recovered in a ratio of 1.00 : 1.35 (endo **128** : exo **129)**. As starting materials, the ratio between **128** and **129**

was 1.00 : 1.79 (endo **128** : exo **129)**. Interestingly, after performing preparative TLC, the ratio between the two monoepoxides was 1.00 : 0.32 (the faster moving isomer : the slower moving isomer). According to the ^{1}H NMR analysis, the ratio did not change after a 2-day standing.

2.2.3. Bisepoxidation of monoepoxides 120a and 120b

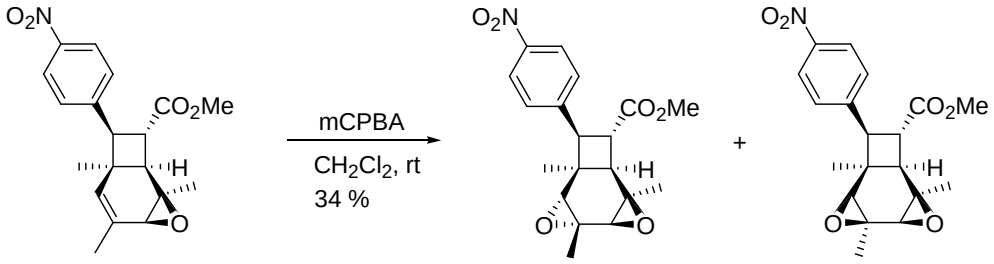
No bisepoxides were observed in the Shi epoxidations of bicyclooctadiene substrates tested. However, epoxidation of monoepoxide **120a** with mCPBA successfully afforded diastereomeric bisepoxides **133a** and **133b** in the presence of mCPBA (Scheme 58).[41]



120a **133a** **133b**

Scheme 58. Epoxidation of monoepoxide **120a**.

Under the given reaction conditions, monoepoxide **120b** also produced two diastereomeric bisepoxides **134a** and **134b** (Scheme 59).



120b **134a** **134b**

Scheme 59. Epoxidation of monoepoxide **120b**.

2.3. Conclusion

Shi epoxidation of racemic bicyclooctadiene substrates was examined to prepare corresponding enantiomeric monoepoxides which could be precursors of chiral SNF analogs. High regioselectivity and yield were observed, but any notable stereoselectivity was not obtained throughout Shi asymmetric epoxidation induced by the chiral dioxirane catalyst derived from ketone **112**. Experimental results from the Mosher ester analysis of **120a** and the Shi epoxidation of endo **128** and exo **129** may be supported by future experiments. Epoxidation of monoepoxides **121a** and **121b** envisioned high potential for preparing chiral 1,3-diepoxide moieties which could be applied to the total synthesis of elysiapyrones A and B.

2.4. Reference

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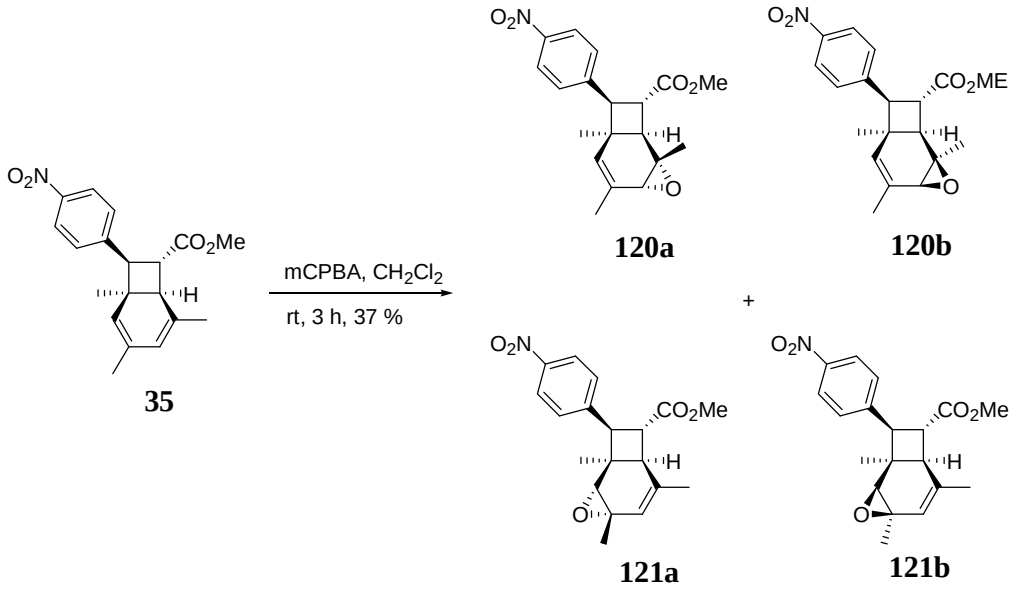
2.5. Experimental section



Monoepoxides 120a/b and 121a/b. To a solution of bicyclooctadiene **35** (20 mg, 0.06 mmol) in CH_2Cl_2 (0.4 mL) was added mCPBA (6.0 mg, 0.03 mmol) at rt. After stirring for 3 h at rt, EtOAc was poured into the reaction mixture, and washed with saturated $NaHCO_3$, $Na_2S_2O_3$, saturated NH_4Cl, and brine. The organic layers were concentrated under vacuum. The residue was purified by preparative chromatography to give 7.6 mg (37 %) of separable mixture of two monoepoxides **121b** and **120a** (6.4 mg) in a ratio of 3 : 2 and inseparable mixture of the other monoepoxides **121a** and **120b** (1.2 mg) in a ratio of 1 : 1. Also, 10.2 mg (51 %) of **35** was recovered.

121b

R_f: 0.60 (EtOAc/n-hexane, 1/6). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.15 (d, *J* = 9.0 Hz, 2H), 7.16 (d, *J* = 9.0 Hz, 2H), 4.78 (s, 1H), 3.70 (s, 3H), 3.43 (d, *J* = 10.2 Hz, 1H), 3.16 (dd, *J* = 9.9 Hz, 9.6 Hz, 1H), 2.91 (s, 1H), 2.77 (d, *J* = 9.6 Hz, 1H), 1.82 (s, 3H), 1.39 (s, 3H), 1.31 (s, 3H).

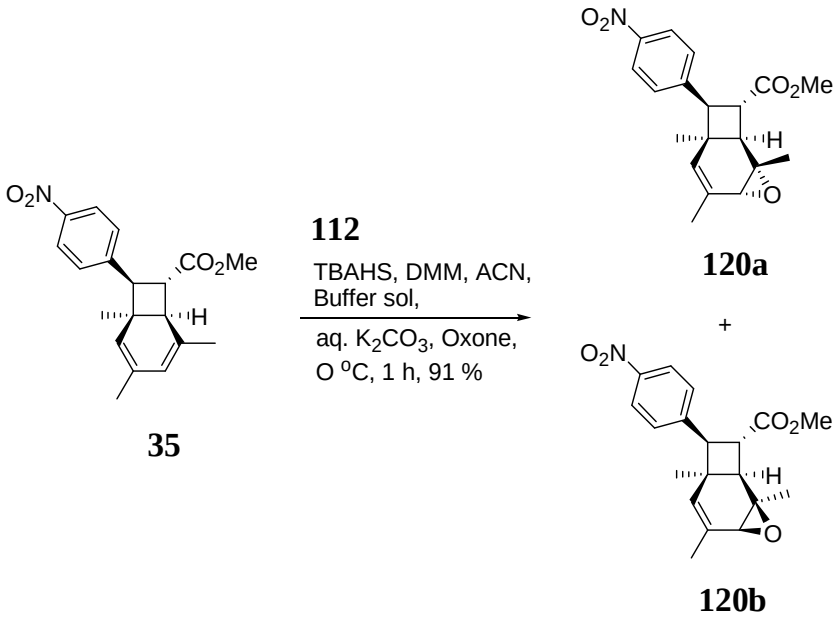
121a and 120b

R_f: 0.55 (EtOAc/n-hexane, 1/6). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.15 + 8.16 (d, *J* = 8.4 Hz, 2H), 7.22 + 7.30 (d, *J* = 8.4 Hz, 2H), 4.70 + 4.73 (s, 1H), 3.69 + 3.70 (s, 3H), 3.54 (dd, *J* = 9.3 Hz, 8.4 Hz, 0.5H), 3.47 (d, *J* = 10.2 Hz, 0.5H), 3.43 (d, *J* = 10.2 Hz, 0.5H), 3.15 (dd, *J* = 9.9 Hz, 9.6 Hz,

0.5H), 2.91 (s, 0.5H), 2.90 (s, 0.5H), 2.79 (d, *J* = 9.0 Hz, 1H), 2.71 (d, *J* = 8.4 Hz, 1H), 2.69 (d, *J* = 9.0 Hz, 1H),1.82 (s, 3H), 1.50 (s, 1.5H), 1.40 (s, 1.5H), 1.32 (s, 3H).

120a

R_f: 0.50 (EtOAc/n-hexane, 1/6). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18 (d, *J* = 9.0 Hz, 2H), 7.26 (d, *J* = 9.0 Hz, 2H), 4.67 (s, 1H), 3.71 (s, 3H), 3.48 (d, *J* = 10.5 Hz, 1H), 3.14 (t, *J* = 9.9 Hz, 1H), 2.91 (s, 1H), 2.80 (d, *J* = 9.6 Hz, 1H), 1.82 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H).



Monoepoxides 120a and 120b. To a solution of bicyclooctadiene **35** (25 mg, 0.076 mmol), catalyst **112** (10 mg, 0.039 mmol), and TBAHS (2 mg, 0.006 mmol) in DMM (1.5 mL), ACN (0.8 mL), and buffer solution (0.05 M $Na_2B_4O_7.10H_2O$ in 4 x 10^{-4} M Na_2-EDTA, 1.5 mL) were added a solution of Oxone® (51 mg, 0.083 mmol) in aq. Na_2EDTA (4 x10^{-4} M, 1.5 mL) and a solution of K_2CO_3 (116 mg, 0.853 mmol) in water (1.5 mL) separately at the same time at 0 °C over 40 min. The reaction mixture was quenched with H_2O, extracted with *n*-pentane, washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by preparative chromatography to give 24 mg (91%) of separable mixture of **120a** and **120b** in a ratio of 1 : 1 as pale yellow oil.

120a

R_f: 0.50 (EtOAc/n-hexane, 1/6). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18 (d, *J* = 9.0 Hz, 2H),

7.26 (d, *J* = 9.0 Hz, 2H), 4.67 (s, 1H), 3.71 (s, 3H), 3.48 (d, *J* = 10.5 Hz, 1H), 3.14 (t, *J* = 9.9 Hz, 1H), 2.91 (s, 1H), 2.80 (d, *J* = 9.6 Hz, 1H), 1.82 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 174.4, 145.9, 132.3, 128.8, 128.7, 123.6, 57.4, 55.0, 52.2, 50.7, 44.2, 43.3, 39.8, 31.1, 29.4, 23.8, 22.1.

120b

R_f: 0.55 (EtOAc/n-hexane, 1/6). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 9.0 Hz, 2H), 4.71 (s, 1H), 3.70 (s, 3H), 3.55 (t, *J* = 10.2 Hz, 1H), 3.44 (d, *J* = 10.2 Hz, 1H), 2.91 (s, 1H), 2.69 (d, *J* = 8.4 Hz, 1H), 1.81 (s, 3H), 1.51 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 173.5, 147.1, 145.1, 132.1, 128.5, 127.7, 123.8, 62.6, 58.4, 52.3, 51.2, 44.5, 42.9, 41.7, 29.7, 22.8, 19.8.

Difference NOE for **120a**

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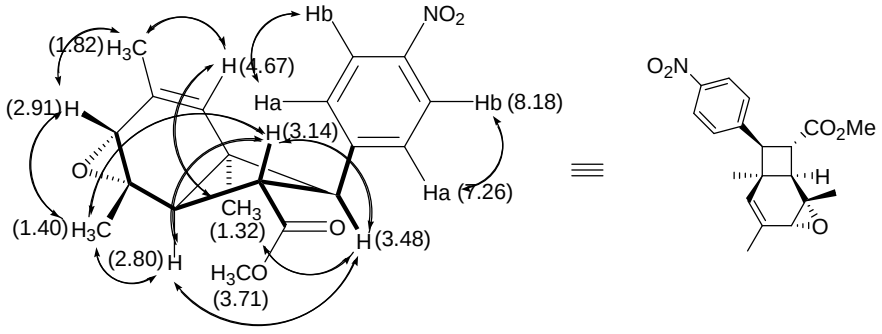


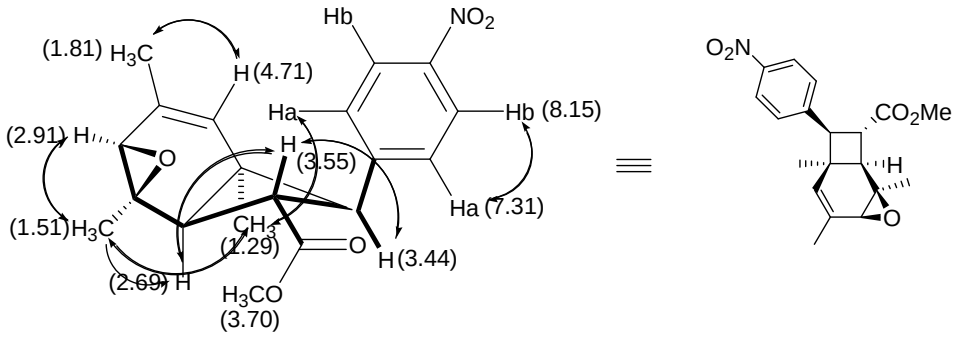
<Difference NOE chart of **120a** >

Irradiated (saturate) peak	Enhanced peaks
3.18 ppm	7.26 ppm, 3.48 ppm, 2.80 ppm, 1.40 ppm
4.67 ppm	7.26 ppm, 2.80 ppm, 1.32 ppm
2.91 ppm	1.82 ppm, 1.40 ppm
3.48 ppm	7.26 ppm, 3.18 ppm, 1.32 ppm
1.32 ppm	7.26 ppm, 3.48 ppm, 2.80 ppm
1.82 ppm	4.67 ppm
2.80 ppm	3.48 ppm, 3.18 ppm, 1.40 ppm, 1.32 ppm
1.32 ppm	7.26 ppm, 4.67 ppm, 3.48 ppm, 2.80 ppm

1.40 ppm	3.18 ppm, 2.91 ppm, 2.80 ppm
8.18 ppm	7.26 ppm

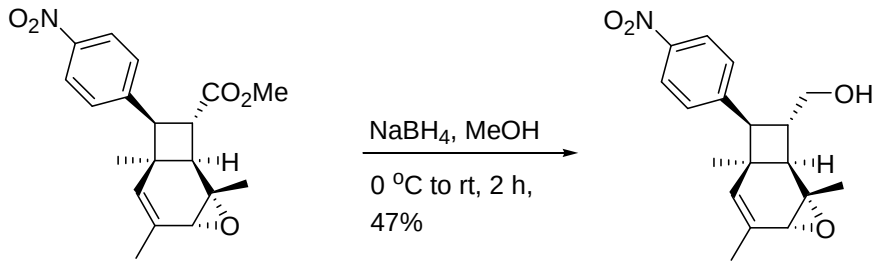
Difference NOE for **120b**

<Selected NOE signals of **120b** >



<Difference NOE chart of **120b** >

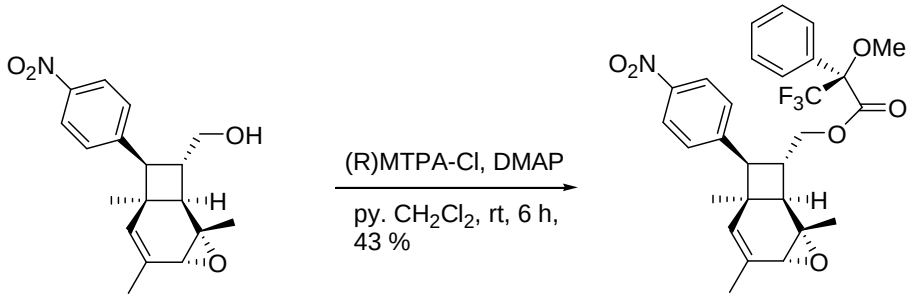
Irradiated (saturate) peak	Enhanced peaks
3.55 ppm	7.31 ppm, 3.44 ppm, 2.69 ppm
4.71 ppm	7.31 ppm, 1.81 ppm, 1.29 ppm
2.91 ppm	7.31 ppm, 1.81 ppm, 1.51 ppm,
3.44 ppm	7.31 ppm, 3.55 ppm, 2.69 ppm, 1.29 ppm
1.29 ppm	7.31 ppm, 4.71 ppm, 3.70 ppm, 3.44 ppm, 2.69 ppm, 1.51 ppm
1.81 ppm	4.71 ppm, 2.91 ppm
2.69 ppm	3.44 ppm, 3.70 ppm, 3.55 ppm, 1.51 ppm, 1.29 ppm
1.51 ppm	2.91 ppm, 2.69 ppm, 1.29 ppm
2.91 ppm	7.31 ppm, 1.81 ppm, 1.51 ppm,
8.15 ppm	7.31 ppm



120a **122a**

Monoepoxide 122a. To a stirred solution of **120a** (4.2 mg, 0.012 mmol) in MeOH (0.4 mL) was added $NaBH_4$ (2.7 mg, 0.071 mmol) in three portions at 0 °C. Then, the reaction mixture was allowed to warm to rt and stirred for 30 min. After monitoring the reaction by TLC, $NaBH_4$ (2.5 mg, 0.066 mmol) was again added in three portions at rt. The reaction mixture was concentrated under vacuum. The residue was purified by preparative chromatography to give 1.8 mg (47 %) of **122a** as pale yellow oil.

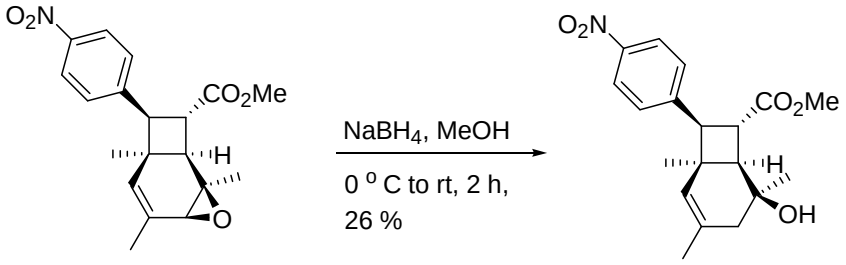
R_f: 0.21 (EtOAc/hexane, 1/3). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 4.70 (s, 1H), 3.76 (m, 1H), 3.69 (m, 1H), 3.08 (d, *J* = 9.6 Hz, 1H), 2.89 (m, 1H), 2.29 (d, *J* = 8.4 Hz, 1H), 1.81 (s, 3H), 1.45 (s, 3H), 1.26 (s, 3H).



122a **123a**

(S)-Mosher ester 123a. To a solution of monoepoxide **122a** (1.8 mg, 0.006 mmol) in CH_2Cl_2 (0.5 mL) was added DMAP (3.2 mg, 0.026 mmol) and pyridine 2.5μL, 0.030 mmol) at rt. After (R)-MTPA-Cl (4 μL, 0.021 mmol)) was added in a one portion, the reaction mixture was stirred for 6 h at rt. The reaction mixture was filtered on a Celite® and then, the reaction mixture was concentrated under vacuum. The residue was purified by preparative chromatography to give 1.3 mg (43 %) of **123a** as pale yellow oil.

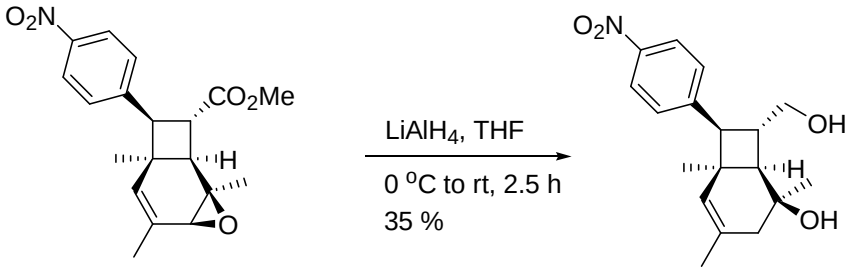
R_f: 0.59 (EtOAc/n-hexane, 1/3). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.34-7.40 (m, 3H), 7.18 (d, *J* = 9.0 Hz, 2H), 4.66 (s, 1H), 4.50 (dd, *J* = 8.4 Hz, 4.8 Hz, 1H), 4.25 (dd, *J* = 7.8 Hz, 4.2 Hz, 1H), 3.48 (s, 3H), 3.05 (m, 1H), 2.99 (d, *J* = 4.2 Hz, 1H), 2.85 (s, 3H), 2.17 (d, *J* = 7.8 Hz, 1H), 1.81 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H).



120b **124b**

Alcohol 124b from $NaBH_4$. To a stirred solution of monoepoxide **120b** (3.2 mg, 0.01 mmol) in MeOH (0.5 mL) was added $NaBH_4$ (2.0 mg, 0.053 mmol) in three portions at 0 ^{o}C. Then, the reaction mixture was allowed to warm to rt and stirred for 30 min. After monitoring the reaction by TLC, $NaBH_4$ (6.0 mg, 0.159 mmol) was again added in three portions at rt during 1.5 h. The reaction mixture was concentrated under vacuum. The residue was purified by preparative chromatography to give 1.1 mg (26 %) of **124b** as pale yellow oil.

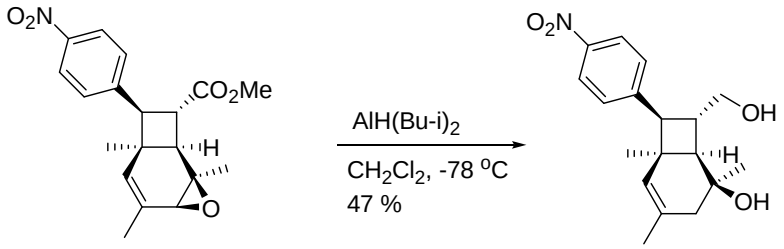
R_f: 0.19 (EtOAc/hexane, 1/3). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.15 (d, *J* = 9.0 Hz, 2H), 7.23 (d, *J* = 9.0 Hz, 2H), 4.75 (s, 1H), 3.68 (s, 3H), 3.59 (d, *J* = 10.2 Hz, 1H), 2.82 (t, *J* = 10.2 Hz, 1H), 2.52 (t, *J* = 10.2 Hz, 1H), 2.30 (d, *J* = 18.0 Hz, 1H), 2.05 (d, *J* = 18.0 Hz, 1H), 1.64 (s, 3H), 1.41 (s, 3H), 1.26 (s, 3H).



120b **125b**

Diol 125b from $LiAlH_4$. To a solution of monoepoxide **120b** (2.2 mg, 0.007 mmol) in dry THF (0.6 mL) was added $LiALH_4$ (0.94 mg, 0.02 mmol) at 0 ^oC. The reaction mixture was stirred for 2.5 h at rt, and quenched with EtOAc followed by 50% aqueous potassium sodium tartrate. The resulting solution was allowed to warm to rt and washed with CH_2Cl_2. The organic layers were concentrated under vacuum. The residue was purified by preparative chromatography to give 0.6 mg (35 %) of **125b** as pale yellow oil.

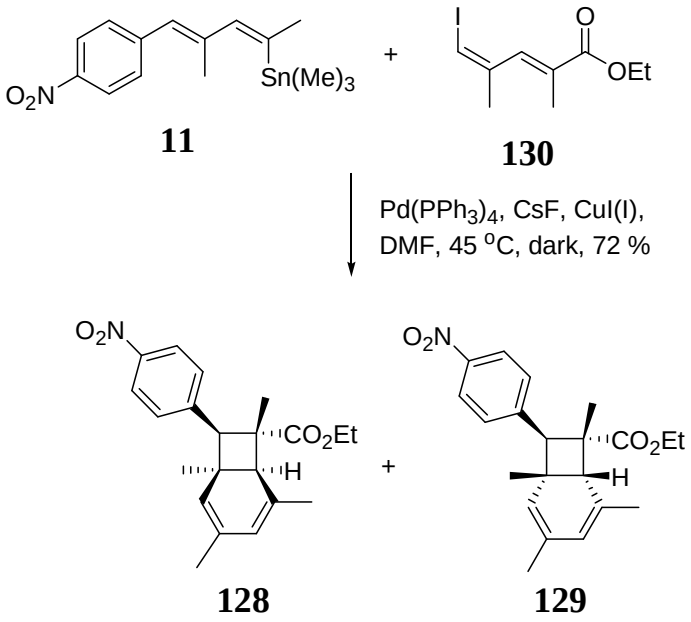
R_f: 0.10 (EtOAc/n-hexane, 1/3). ^1H NMR (600 MHz, $CDCl_3$): δ 8.15 (d, *J* = 9.0 Hz, 2H), 7.23 (d, *J* = 9.0 Hz, 2H), 4.75 (s, 1H), 3.68 (s, 3H), 3.59 (d, *J* = 10.2 Hz, 1H), 2.82 (dd, *J* = 9.9 Hz, 9.6 Hz, 1H), 2.52 (d, *J* = 10.2 Hz, 1H), 2.30 (d, *J* = 18.0 Hz, 1H), 2.05 (d, *J* = 18.0 Hz, 1H), 1.64 (s, 3H), 1.41 (s, 3H), 1.26 (s, 3H).



120b **125b**

Diol 125b from DIBAL-H. To a solution of monoepoxide **120b** (1.8 mg, 0.006 mmol) in dry CH_2Cl_2 (0.6 mL) was added DIBAL-H (1.0M of n-hexane, 40 μL) at -78 ^oC. The reaction mixture was stirred for 1.5 h at -78 ^oC, and quenched with EtOAc followed by 50% aqueous potassium sodium tartrate. The resulting solution was allowed to warm to rt and washed with CH_2Cl_2. The organic layers were concentrated under vacuum. The residue was purified by preparative chromatography to give 0.8 mg (47 %) of **125b** as pale yellow oil.

R_f: 0.10 (EtOAc/n-hexane, 1/3). ^1H NMR (600 MHz, $CDCl_3$): δ 8.15 (d, *J* = 9.0 Hz, 2H), 7.23 (d, *J* = 9.0 Hz, 2H), 4.75 (s, 1H), 3.68 (s, 3H), 3.59 (d, *J* = 10.2 Hz, 1H), 2.82 (dd, *J* = 9.9 Hz, 9.6 Hz, 1H), 2.52 (d, *J* = 10.2 Hz, 1H), 2.30 (d, *J* = 18.0 Hz, 1H), 2.05 (d, *J* = 18.0 Hz, 1H), 1.64 (s, 3H), 1.41 (s, 3H), 1.26 (s, 3H).



Endo 128 and Exo 129. To a solution of iododiene **130** (62 mg, 0.22 mmol) and vinyl stannane **11** (84mg, 0.23 mmol) in anhydrous DMF (4.0 mL) were added CsF (67 mg, 0.42 mmol), CuI (8 mg, 0.04 mmol) at rt under degassing with a stream of Ar. After adding $Pd(Ph_3P)_4$ (27 mg, 0.02 mmol), the reaction flask was immediately wrapped with aluminum foil and continued degassing for further 5 min. The reaction mixture was stirred for 3 h at 45 ^oC, allowed to cool to rt, and then diluted with EtOAc (30 mL). The organic layer was washed with saturated NH_4Cl solution (3 x 20 mL). The combined *aq*. layers were extracted with EtOAc (3 x 30 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by chromatography on silica gel (EtOAc/*n*-hexane, 1:8) to provide 57 mg (72 %) of separable mixture of **128** and **129** in a ratio of 3 : 5 as pale yellow oil.

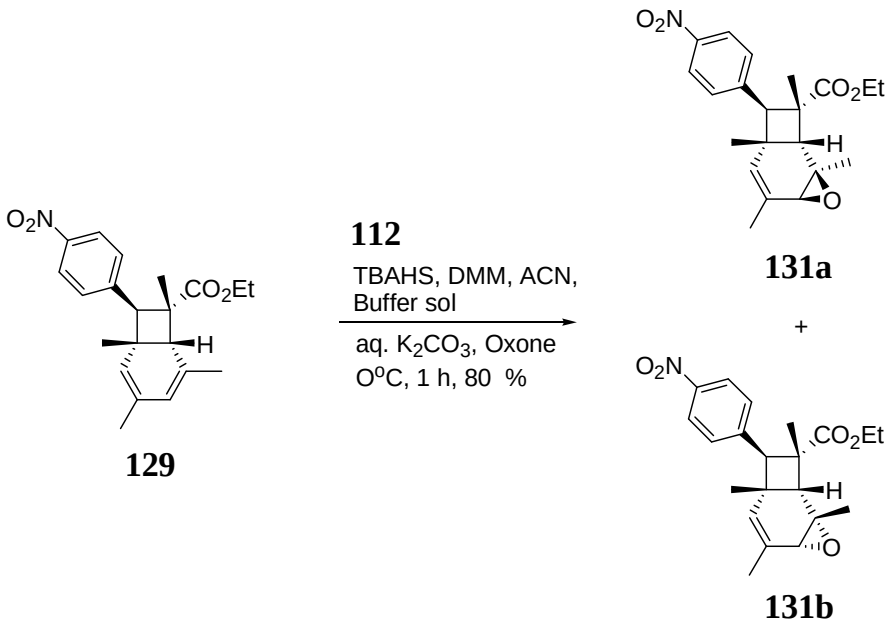
Endo 128

R_f: 0.5 (Et_2O/ *n*-pentane, 1/8). ^1H NMR (600 MHz, $CDCl_3$): δ 8.14 (d, *J* = 9.0 Hz, 2H), 7. 53 (d, *J* = 9.0 Hz, 2H), 5.63 (s, 1H), 5.17 (s, 1H), 4.15 (q, *J* = 6.6 Hz, 2H), 4.01 (s, 1H), 3.92 (m, 1H), 2.97 (s, 1H), 1.75 (s, 3H), 1.73 (s, 3H), 1.37 (t, *J* = 6.6 Hz, 3H), 1.28 (s, 3H), 1.26 (s, 3H).

Exo 129

R_f: 0.45 (Et_2O/ *n*-pentane, 1/8). ^1H NMR (600 MHz, $CDCl_3$): δ 8.15 (d, *J* = 9.0 Hz, 2H), 7. 42 (d, *J* = 9.0 Hz, 2H), 5.50 (s, 1H), 5.15 (s, 1H), 4.54 (s, 1H), 4.13 (q, *J* = 7.3 Hz, 2H), 2.69 (s, 1H), 1.75 (s, 3H), 1.70 (s, 3H), 1.37 (s, 3H), 1.28 (t, *J* = 7.3 Hz, 3H), 1.10 (s, 3H).

* ^{1}H spectrum of **128** and **129** were in agreement with reference.[6]



Monoepoxides 131a and 131b. To a solution of exo **129** (3.0 mg, 0.008 mmol), catalyst **112** (1.1 mg, 0.004 mmol), and TBAHS (0.3 mg, 0.001 mmol) in DMM (170 μL), ACN (100 μL), and buffer solution (0.05 M $Na_2B_4O_7.10H_2O$ in 4 x 10^{-4} M Na_2-EDTA, 170 μL) were added a solution of Oxone® (2.6 mg, 0.008 mmol) in aq. Na_2EDTA (4 x10^{-4} M, 170 μL) and a solution of K_2CO_3 (12.4 mg, 0.091 mmol) in water (170 μL) separately at the same time at 0 °C over 30 min. The reaction mixture was quenched with H_2O, extracted with *n*-pentane, washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by preparative chromatography to give 2.5 mg (80 %) of separable mixture of **131a** and **131b** in a ratio of 1 : 1 as pale yellow oil.

The slower moving isomer

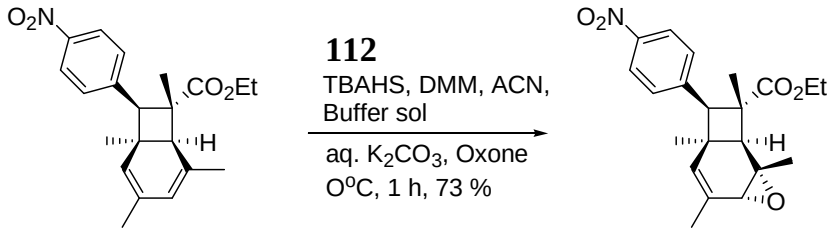
R_f: 0.41 (EtOAc/n-hexane, 1/6). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.20 (d, *J* = 9.0 Hz, 2H), 7.48 (d, *J* = 9.0 Hz, 2H), 5.38 (s, 1H), 4.15 (m, 2H), 3.83 (s, 1H), 3.00 (s, 1H), 2.77 (s, 1H), 1.88 (s, 3H), 1.60 (s, 3H), 1.30 (t, 3H, *J* = 7.8 Hz), 1.25 (s, 3H), 1.16 (s, 3H).

The faster moving isomer

R_f: 0.46 (EtOAc/n-hexane, 1/6). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.16 (d, *J* = 9.0 Hz, 2H), 7.42 (d, *J* = 12.0 Hz, 2H), 5.54 (s, 1H), 4.20 (q, *J* = 14.1 Hz, 6.6 Hz, 2H,), 3.69 (s, 1H), 3.04 (s, 1H), 2.91

[6] Parker, K. A.; Lim, Y. H. *Org Lett* **2004**, *6*, 161.

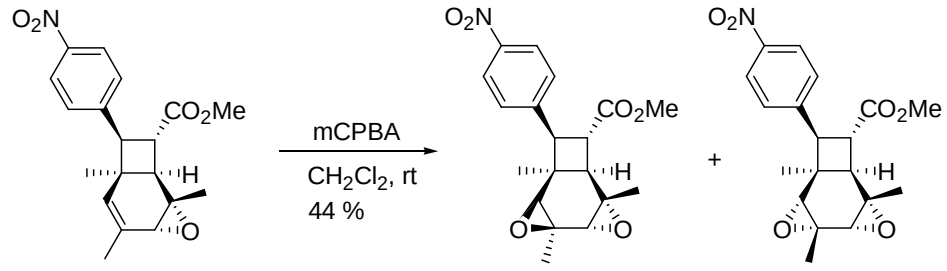
(t, *J* = 18.0 Hz, 1H), 1.95 (d, *J* = 1.2 Hz, 3H), 1.48 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.25 (s, 3H).



128 **132**

Monoepoxide 132. To a solution of endo **128** (3.2 mg, 0.009 mmol), catalyst **112** (1.2 mg, 0.005 mmol), and TBAHS (0.35 mg, 0.001 mmol) in DMM (0.5 mL), ACN (0.2 mL), and buffer solution (0.05 M $Na_2B_4O_7.10H_2O$ in 4 x 10^{-4} M Na_2-EDTA, 0.25 mL) were added a solution of Oxone® (180 μL, 0.009 mmol) in aq. Na_2EDTA (4 x10^{-4} M, 0.25 mL) and a solution of K_2CO_3 (13.2 mg, 0.097 mmol) in water (0.25 mL) separately at the same time at 0 °C over 40 min. The reaction mixture was quenched with H_2O, extracted with *n*-pentane, washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by preparative chromatography to give 2.4 mg (73 %) of **132** as pale yellow oil.

R_f: 0.46 (EtOAc/hexane, 1/6), ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.16 (d, *J* = 9.0 Hz, 2H), 7.42 (d, *J* = 12.0 Hz, 2H), 5.54 (s, 1H), 4.20 (q, *J* = 14.1 Hz, 6.6 Hz, 2H), 3.69 (s, 1H), 3.04 (s, 1H), 2.91 (s, 1H), 1.95 (d, *J* = 1.2 Hz, 3H), 1.48 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.25 (s, 3H).



120a **133a** **133b**

Bisepoxides 133a and 133b. To a stirred solution of monoepoxide **120a** (5.4 mg, 0.016 mmol) in CH_2Cl_2 (0.4 mL), mCPBA (70% assay, 3.8 mg, 0.016 mmol) in CH_2Cl_2 (0.25 mL) was

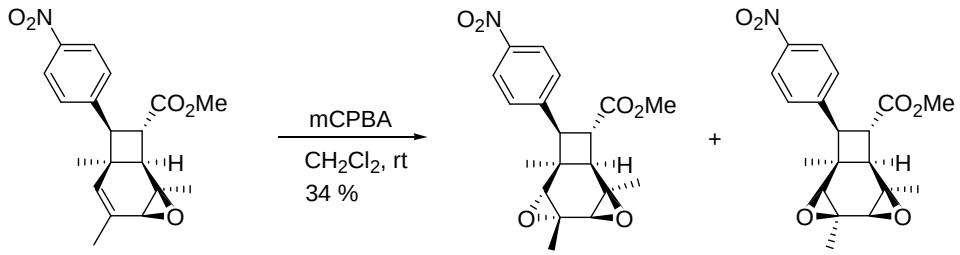
added at rt. After the reaction was completed by monitoring TLC, the reaction mixture was quenched with EtOAc, satd. $NaHCO_3$, and $Na_2S_2O_3$. The organic solution was extracted with satd. $NaHCO_3$, satd. NH_4Cl, and brine. The organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by preparative chromatography to give 2.5 mg (44 %) of separable mixture of **133a** and **133b** as pale yellow oil.

The faster moving isomer

R_f: 0.26 (EtOAc/hexane, 1/3). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 9.0 Hz, 2H), 3.72 (s, 3H), 3.57 (q, *J* = 8.4 Hz, 1H,), 3.56 (s, 1H), 3.11 (s, 1H), 2.73 (d, *J* = 7.8 Hz, 1H), 2.50 (s, 1H), 1.43 (s, 3H), 1.29 (s, 3H).

The slower moving isomer

R_f: 0.11 (EtOAc/hexane, 1/6), ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 9.0 Hz, 2H), 3.74 (s, 3H), 3.66 (d, *J* = 10.8 Hz, 1H), 3.05 (t, *J* = 9.9 Hz, 1H), 3.03 (s, 1H), 2.61 (d, *J* =10.2 Hz, 1H), 2.09 (s, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H).



120b **134a** **134b**

Bisepoxides 134a and 134b. To a stirred solution of monoepoxide **120b** (3.0 mg, 0.009 mmol) in CH_2Cl_2 (0.2 mL), mCPBA (70% assay, 8.4 mg, 0.036 mmol) in CH_2Cl_2 (0.15 mL)was added at rt. After the reaction was completed by monitoring TLC, the reaction mixture was quenched with EtOAc, satd. $NaHCO_3$, and $Na_2S_2O_3$. The organic solution was extracted with satd. $NaHCO_3$, satd. NH_4Cl, and brine. The organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by preparative chromatography to give 1.1 mg (34 %) of **134a** and **134b** as pale yellow oil.

The faster moving isomer

R_f: 0.26 (EtOAc/hexane, 1/3). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.4 Hz, 2H,), 7.48 (d, *J* = 9.0 Hz, 2H), 3.73 (s, 3H), 3.58 (d, *J* = 3.6 Hz, 1H), 3.57 (q, *J* = 8.4 Hz, 3.6 Hz, 1H), 3.17 (s,1H), 2.44 (d, *J* = 7.2 Hz, 1H), 2.03 (s, 1H), 1.41 (s, 3H), (s, 3H), 1.35 (s, 3H).

Chapter III

Aspartate-Catalyzed Asymmetric Epoxidation Towards Preparation of Chiral SNF Analogs

3.1. Introduction

3.1.1. Background

Method development for the preparation of enantiomerically pure epoxides is one of the most important fields of asymmetric catalysis.[1] Current methodology for the catalytic asymmetric epoxidation of olefins heavily depends on the use of chiral metal complexes[2] or on the use of organocatalysts such as chiral ketones.[3] Alternative methods to prepare enantiomerically pure epoxides are the addition of chiral sulfur ylides to aldehydes,[4] or the peptide-catalyzed asymmetric epoxidation of enones (Julia-Colonna epoxidation).[5]

Since 2000, the Miller group has investigated highly enantioselective organocatalysts which result from the combination of short oligopeptides with catalytically active functional groups.[6,7] A notable result was the development of acyl-transfer reactions that employ nucleophilic catalysis by N-methyl histidines.[8] More recently, Miller and co-workers further expanded the role of peptide catalysts towards preparation of enantiomerically pure epoxides. The method is based on the generation of a percarboxylic acid from a carboxylic acid (Figure 29).[9]

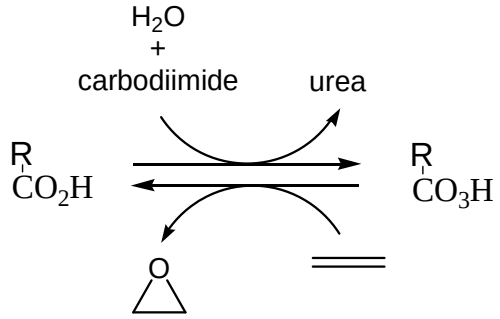
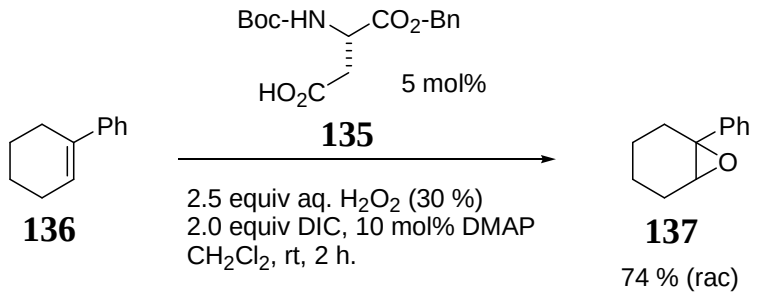


Figure 30. Epoxidation catalysis by an acid and peracid pair.

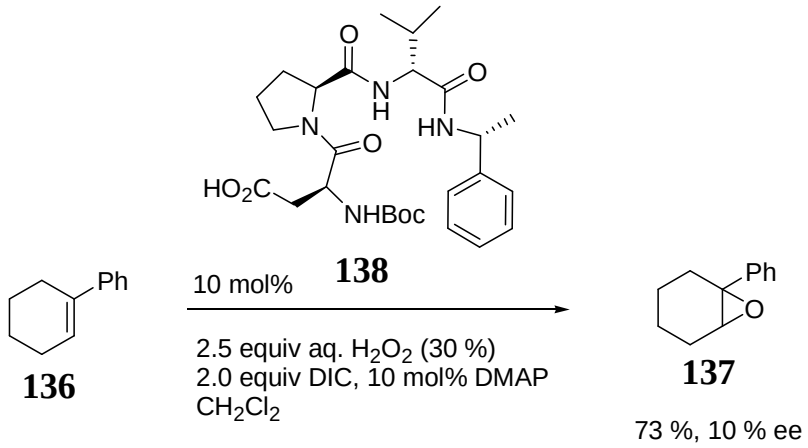
In the early stage of their study, Miller and co-workers employed *N*-Boc-protected-aspartate benzyl ester **135** to establish optimal conditions for epoxidation catalysis based on multiple carboxylic acid–peracid interconversions.[10] A combination of aqueous hydrogen peroxide, diisopropylcarbodiimide (DIC), and dimethylaminopyridine (DMAP) afforded almost 15 turnovers. The resulting epoxide **137** from 1-phenylcyclohexene **136** under the given conditions

was racemic, indicating that the per-aspartate derived from **135** in itself did not affect any significant asymmetric induction (Scheme 60). However, a control experiment established that the epoxidation actually proceeded through the acid/peracid pair as intended.



Scheme 60. Epoxidation of **136** with per-aspartate derived from **135**.

Based on the previous result that hydrogen bonding between substrates and catalysts improved selectivity, Miller and co-workers introduced tripeptide catalyst **138** which was known to adopt β-turn-type structures that support enantioselectivity for other processes.[8] However, while olefin **136** was a substrate for catalytic epoxidation with **138**, the corresponding epoxide **137** was formed with 10 %ee (Scheme 61).

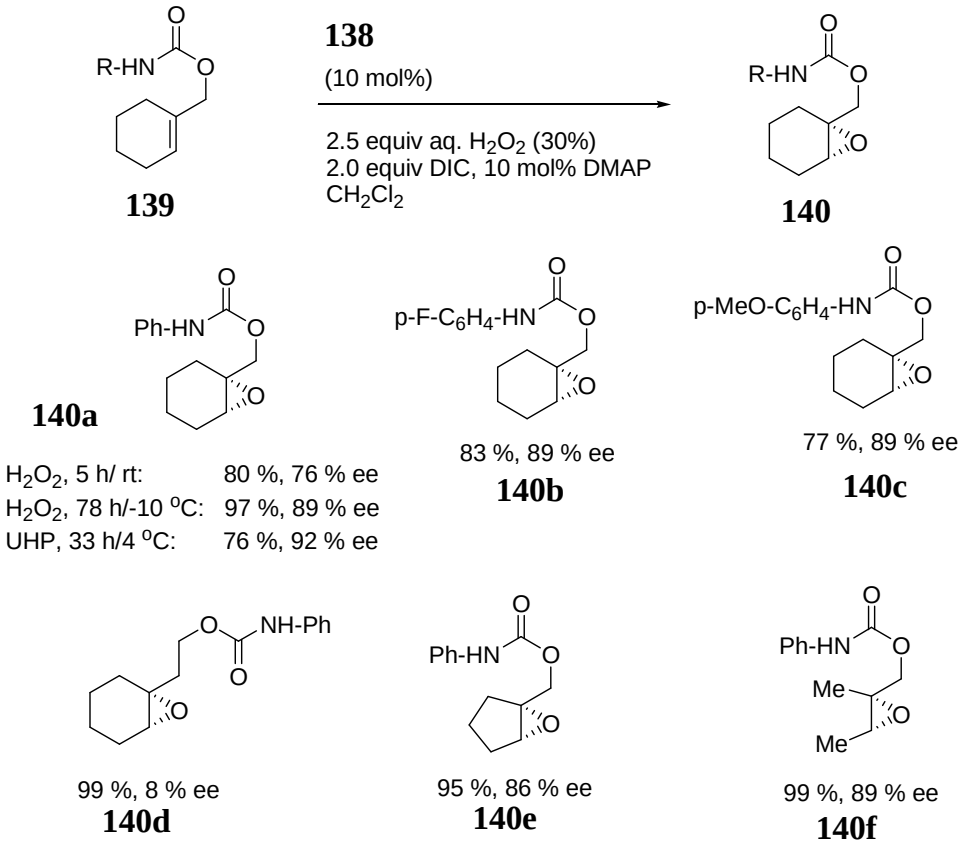


Scheme 61. Epoxidation of **136** with the tripeptide catalyst **138**.

Presumably, a relatively weak hydrogen bond between per-aspartate derived from **138** and olefin **136** in the transition state results in poor stereoselectivity.

3.1.2. Investigation of carbamate substrates to the epoxidation

Various kinds of carbamate moieties, which can improve hydrogen bond ability of catalyst **138**, were introduced in olefin substrates. Good epoxide yields and remarkable enantioselectivities were achieved with this type of substrate. (See Scheme 62.) Interestingly, for substrates **139,** lower reaction temperatures generally led to increased enantioselectivity and additional improvements resulted from the use of hydrogen peroxide/urea clathrathe (UHP) instead of aqueous H_2O_2 (epoxide **140a**).

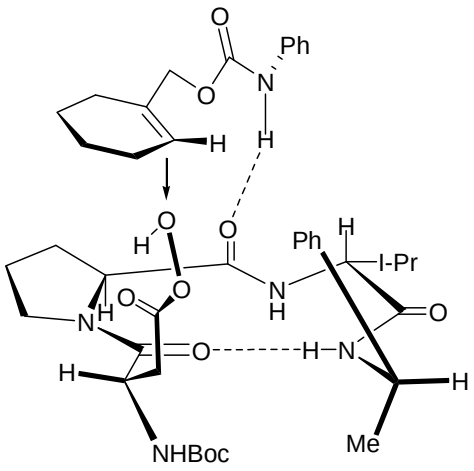


Scheme 62. Asymmetric epoxidation of olefins in the presence of catalyst **138**.

It also revealed that the pendant phenyl carbamate rendered the epoxidation of a cyclopentene and a butene derivative enantioselective (epoxides **140e** and **140f**). Para-fluoro- or para-methoxy-substituted phenyl rings did not lead to a significant change in the efficiency of the

reaction (epoxides **140b** and **140c**). In contrast, elongation of the tether by only one methylene group was deleterious for stereoselectivity. For the epoxide **140d**, only 8 %ee was observed.

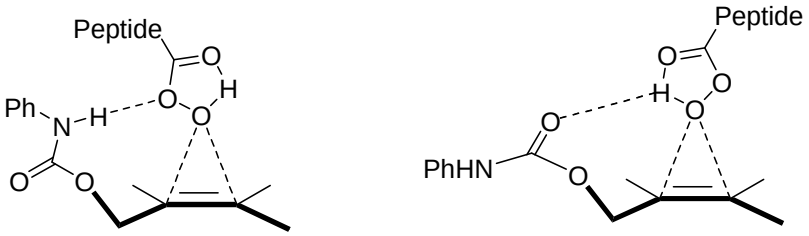
The need for a tethered carbamate and the high sensitivity of the enantioselectivity to the distance between the hydrogen-bonding moiety and the double bond to be epoxidized points to hydrogen bonding as the crucial feature of catalyst–substrate interaction. A number of arrangements can be expected in which the carbamate tether of the substrate may act as a hydrogen-bond donor or acceptor with the amide functional group of the tripeptide **138**. Currently, there are no data available that might indicate a clear preference for possible arrangements. However, a hypothetical hydrogen-bonded transition states proposed by Miller and co-workers shows that the carbamate group of the substrate can be a hydrogen bond donor and the proline carboxamide group of per-aspartate is the acceptor (Figure 30).



Transition state A

Figure 31. Hypothetical transition state A: The peptide-catalyzed epoxidation of carbamate-tethered olefin.

According to Miller, alternative arrangements may be expected in which intermolecular hydrogen bonding involves the peracid moiety. Transition state B and C are consistent with the "Henbest effect" that is the cis selectivity in the hydroxy-directed epoxidation of cyclic allylic alcohols with peracids (Figure 31).[11]



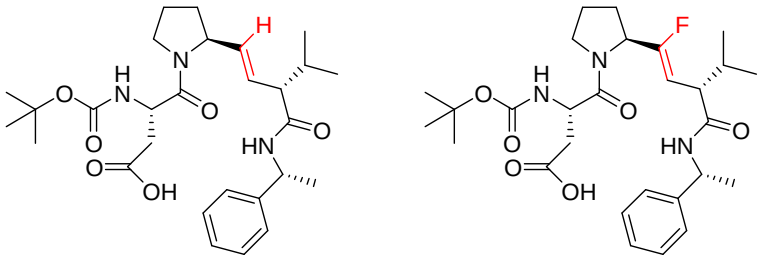
Transition state B **Transition state C**

Figure 32. Hypothetical transition state B and C: Intermolecular hydrogen bonding involved by the peracid moiety.

Although the experimental evaluation of the modes of asymmetric induction is revealed yet, the limiting cases in transition states stress that the tether is necessary to generate stereoselectivity in the epoxidation of substrates in terms of hydrogen bonding.

3.1.3. Optimization of a tripeptide-based chiral catalyst

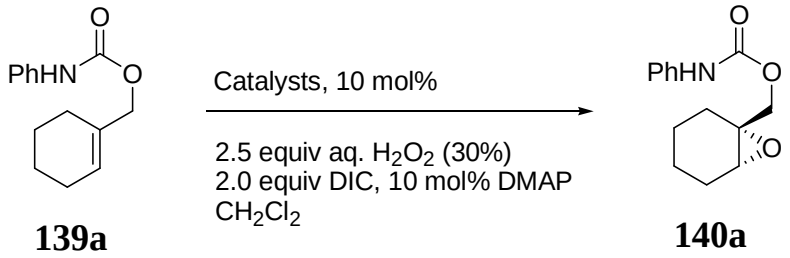
Further investigation of the Asp-catalyzed epoxidations done by the Miller group was focused on the optimization of a peptide-based chiral catalyst. For the functional evaluation of the Pro-d-Val amide, Miller and co-workers prepared alkene **141** and fluoroalkene **142** by replacement of the amide in **138** (Figure 32). Different hydrogen bond donor and acceptor strength between the catalysts and substrate plays a critical role in the formation of chiral epoxide.



141 **142**

Figure 33. Structures of **141** and **142**: Peptidomimetic catalyst analogs of **138**.

Under the given reaction conditions, epoxidation of **139a** was performed in the presence of catalyst analogs, **141** and **142** (Scheme 63).[12]



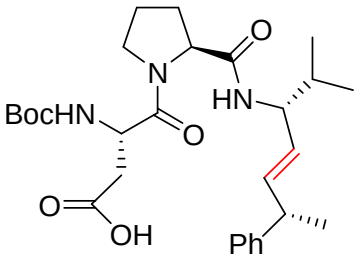
139a **140a**

Catalysts	ee (e.r.)	Conversion
138	81 (9.5 : 1)	63 %
141	16 (1.4 : 1)	98 %
142	52 (3.2 : 1)	98 %

Scheme 63. Experimental evaluation of the proline carboxamide group in **138**.

Relatively low selectivities were observed with **141** and **142**, even though conversion ratio was much higher than the case of **138**. Probably, the significantly different stereoselectivity can be resulted from different strength of hydrogen bonding between the substrate and the catalysts. Therefore, it is reasonable that the amide moiety between proline and valine residue is required to asymmetric epoxidation.

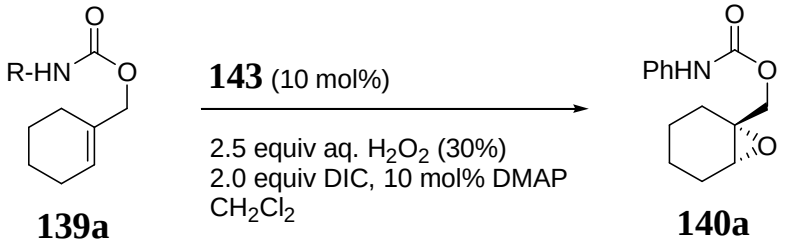
Catalyst **143** was designed and synthesized[12] by olefinic replacement of the C-terminal amide in **138** (Figure 33). In general, intramolecular hydrogen bonding in the Asp-Pro-Val sequence is well known to maintain a β-turn structure.



143

Figure 34. Structure of **143**: Olefinic replacement of the C-terminal amide in **138.**

Under the given reaction conditions, epoxidation of **139a** was performed in the presence of the **143**.[12]



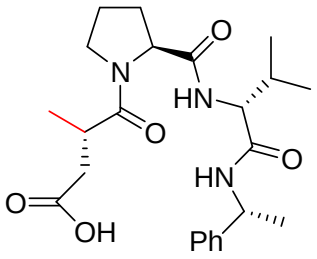
139a **140a**

Catalyst	ee (e.r.)	Conversion
138	81 (9.5 : 1)	63 %
143	16 (1.4 : 1)	98 %

Scheme 64. Experimental evaluation of the C-terminal amide in **138**.

As expected, due to the inevitable removal of the β-turn structure, catalyst **143** led to poor selectivity (Scheme 64). This result strongly suggests an important functional role for the amide residue in the Asp-catalyzed epoxidations.

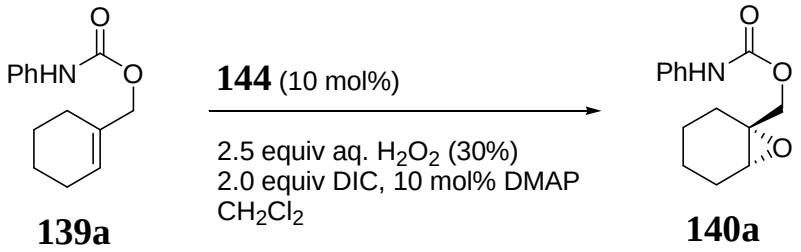
In addition to hydrogen bonding in the structure–function relationships, the NHBoc functionality is considered important enough to be evaluated. Therefore, the NHBoc group was replaced with a methyl group in compound **144** (Figure 34).[12]



144

Figure 35. Structure of **144**: Methyl replacement of the NHBoc group in **138**.

Under a common set of reaction conditions, epoxidation of **139a** with **144** afforded 88 %ee, which is slightly higher compared to **138** (Scheme 65).[12] The NHBoc group might not be required to generate hydrogen bonding interaction with the substrate. Nonetheless, due to the significantly reduced conversion ratio, **144** cannot be compatible with **138**.



139a **140a**

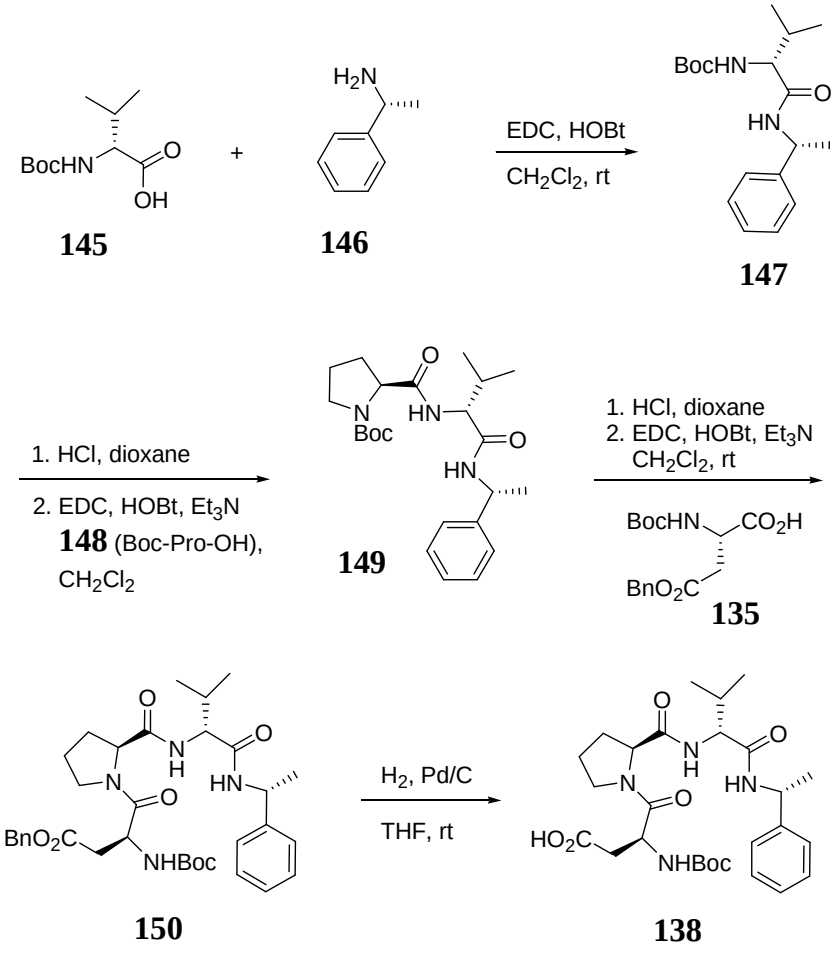
Catalyst	ee (e.r.)	Conversion
138	81 (9.5 : 1)	63 %
144	88 (15.4 : 1)	26 %

Scheme 65. Experimental evaluation of the NHBoc functionality in **138**.

Based on thorough investigation of enantioselective epoxidations of olefin substrates with tri-peptide catalysts done by Miller group, we think that the tripeptide catalyst **138** can afford high regio- and stereoselectivity for the preparation of a monoepoxide substrate that will be a precursor of chiral SNF analog.

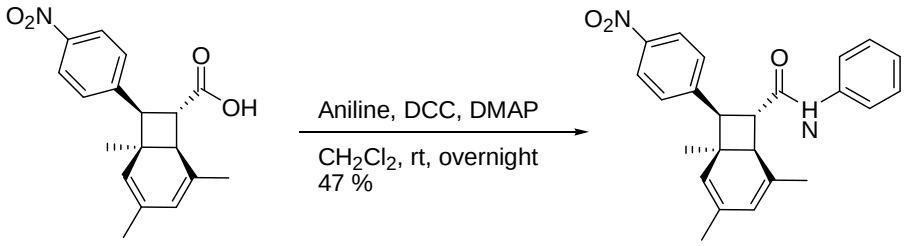
3.2. Result and Discussion

Catalyst **138** was prepared, following Miller's procedure.[10] Boc-D-Val-OH **145** and (*R*)-(+)-α-methylbenzylamine **146** was coupled with the presence of HOBt and EDC to afford **147**. Deprotection of the Boc group in **147** by HCl followed by treatment with HOBt and EDC for coupling Boc-Pro-OH **148** produced Boc-protected dipeptide **149**. The benzyl protected tripeptide **150** was obtained by treatment of **149** with HCl, followed by HOBt and EDC-mediated coupling with the protected aspartate **135**. Finally, deprotection of the benzyl group in tripeptide **150** provided the desired catalyst **138** (Scheme 66).



Scheme 66. Preparation of catalyst **138**.

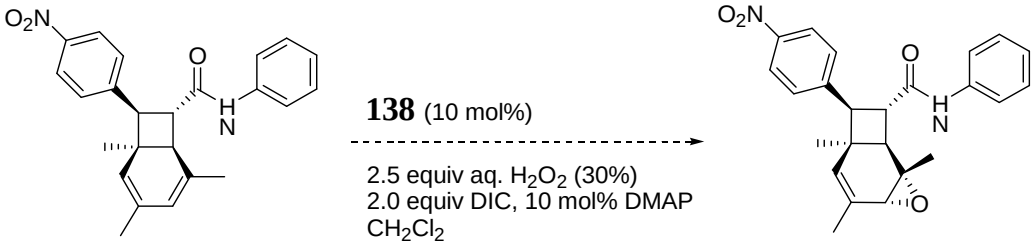
The racemic bicyclo[4.2.0]octadiene **151** was produced by coupling between carboxylic acid **46** and aniline in the presence of DCC and DMAP (Scheme 67).



46 **151**

Scheme 67. Preparation of bicyclooctadiene **151**.

Under a common set of reaction conditions, bicyclooctadiene **151** was treated with catalyst **138** (Scheme 68).



151 **152**

Scheme 68. Synthetic attempt to afford monoepoxide **152** via the Asp-catalyzed epoxidation.

This reaction produced an inseparable mixture, observed in by ^{1}H NMR of the crude product, and it was not clear that monoepoxide **152** was produced. According to Miller, good epoxide yields and enantioselectivities can be only achieved with substrates which have both allylic alcohol moiety and carbamate tether. In addition, the hypothetical transition state A shown in Figure 30 reveals that optimized coordination between bicyclooctadiene **151** and catalyst **138** is very important to produce the corresponding chiral epoxide. Therefore, investigation of a suitable bicyclo[4.2.0]octadiene substrate is necessary to apply the Asp-catalyzed epoxidation.

3.3. Reference

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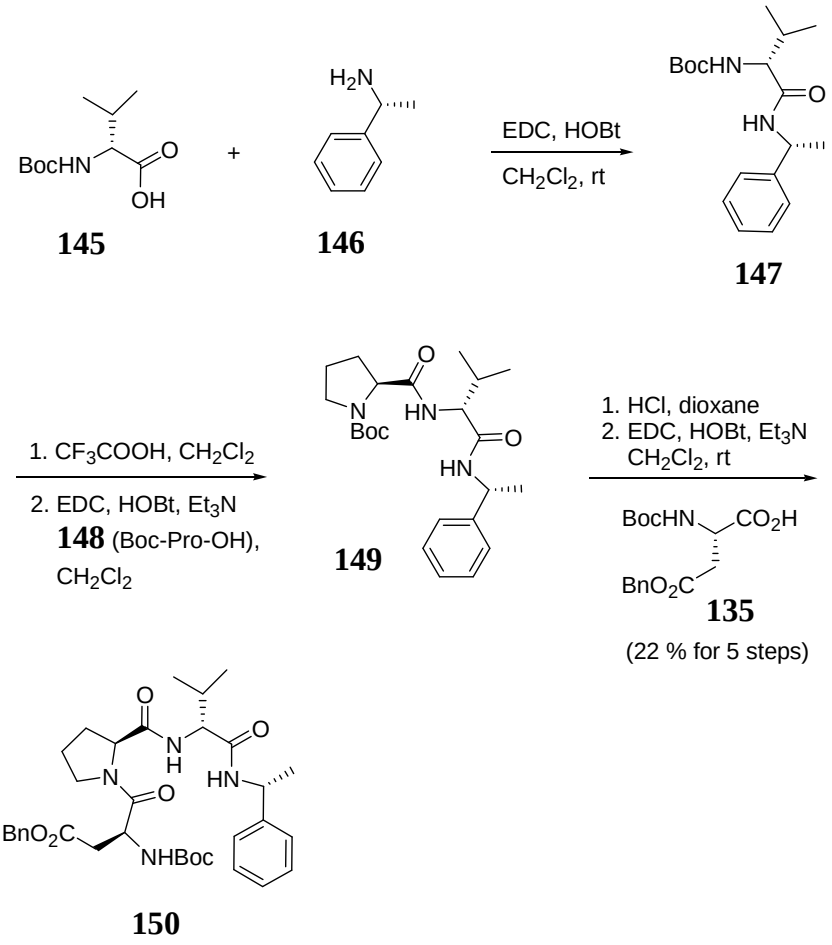
3.4. Experimental section

The tripeptide **138** was prepared according to Miller's procedure.[7]



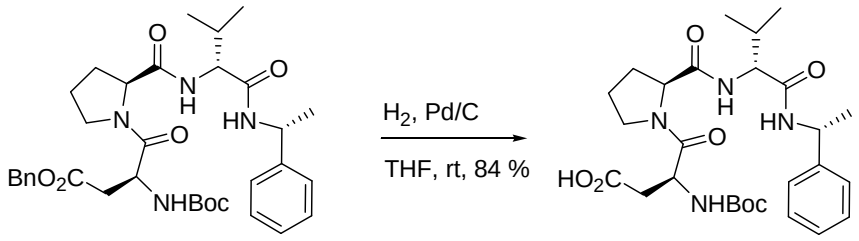
145 **146** **147** **149** **135** (22 % for 5 steps) **150**

Benzyl ester 150. Boc-D-Val-OH **145** (1.08 g, 5.0 mmol), HOBt (841 mg, 5.5 mmol) and EDC (1.05 g, 5.5 mmol) were suspended in dried CH_2Cl_2 (25 mL, 0.2 M) and (*R*)-(+)-α-methylbenzylamine **146** (0.65 mL, 5.5 mmol) was added via syringe in one portion. The resulting clear, colorless solution was stirred at rt overnight. The reaction mixture was then diluted with 300 mL EtOAc, transferred to a separatory funnel and washed with 100 mL of a 0.5 M aqueous solution of citric acid and 100 mL of a saturated aqueous suspension of $NaHCO_3$.

[7] Peris, G.; Jakobsche, C. E.; Miller, S. J. *J Am Chem Soc* **2007**, *129*, 8710.

The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the resulting crude mixture **147** (1.55 g, 4.8 mmol). To a solution of the mixture (1.55 g, 4.8 mmol) in dried CH_2Cl_2, trifluoroacetic acid (8.0 mL) was added and stirred at rt for 1 hr. The excess reagent and solvent was removed under vacuum. The resulting mixture was neutralized by 2N KOH, extracted with CH_2Cl_2 (5 × 50 mL), and dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford sticky oil (670 mg). To the resulting crude mixture were added Boc-Pro-OH **148** (1.13 g, 5.25 mmol), HOBt (841 mg, 5.5 mmol) and EDC (1.05 g, 5.5 mmol). This was suspended in dried CH_2Cl_2 (25 mL, 0.2 M), and allowed to stir at rt for 5 minutes. To the resulting solution, distilled Et3N (0.77 mL, 5.5 mmol) was syringed in, and the resulting solution was allowed to stir at rt overnight. The work up procedure was followed identical to that described above to yield **149.** And, Boc removal was followed identical to that described above. To a solution of the Boc deprotected residue (456 mg) in dried CH_2Cl_2 (15 mL, 0.2 M), Boc-Asp(OBn)-OH **135** (680 mg, 2.2 mmol), HOBt (460 mg, 3.0 mmol) and EDC (520 mg, 2.7 mmol) were added into the reaction flask and allowed to stir at rt for 5 minutes. To the resulting solution, distilled Et_3N (0.4 mL, 2.9 mmol) was syringed in, and the resulting solution was allowed to stir at rt overnight. The work up procedure was identical to that described above. The resulting residue was purified by flash column chromatography (7:3 hexanes:acetone) to yield 675 mg (22 % for 5 steps) of **150** as white solid.

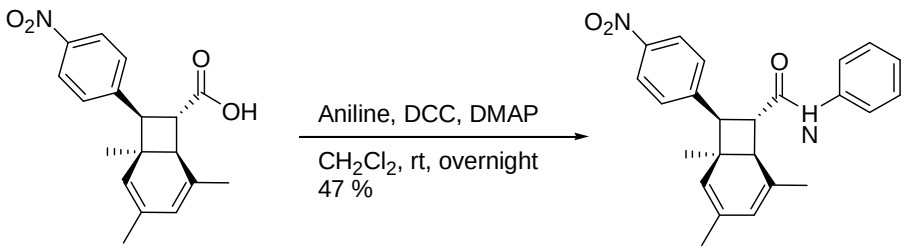
R_f: 0.18 (Acetone/ n-Hexane, 3/7). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.34-7.23 (m, 8H), 7.16 (m, 1H), 6.78 (dd, *J* = 8.0 Hz, 2H), 5.10-5.02 (m, 4H), 4.71 (m, 1H), 4.46-4.44 (m, 1H), 4.15 (t, *J* = 7.3 Hz, 1H), 3.67-3.58 (m, 2H), 2.73 (dd, *J* = 16.1 Hz, 7.3 Hz, 1H), 2.43 (dd, *J* = 16.1 Hz, 5.1 Hz, 1H), 2.28-2.22 (m, 2H), 2.02-1.91 (m, 3H), 1.44 (d, *J* = 6.8 Hz, 3H), 1.39 (s, 9H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.8, 171.1, 171.0, 170.2, 155.1, 143.4, 135.4, 128.8, 128.7, 128.4, 127.4, 126.4, 80.6, 67.1, 61.1, 59.5, 48.8, 47.7, 37.3, 29.4, 28.8, 28.5, 28.4, 25.0, 21.7, 19.4, 17.9.



150 **138**

Acid 138. Benzyl ester **150** (619 mg, 1.0 mmol) was dissolved in THF (5.0 mL, 0.2 M), and the resulting solution was flushed with dry Ar for 5 minutes. Then, Pd on charcoal (10% wt, 130 mg) added in and a H_2 balloon placed on the reaction flask. The resulting suspension was stirred at rt for 18 hours. The suspension was diluted with 120 mL of EtOAc and filtered through celite. The filtrate was concentrated under reduced pressure to afford 482 mg (84 %) of **138** as white solid.

R_f: 0.07 (Acetone/ n-Hexane, 3/7). ^{1}H: (400 MHz, $CDCl_3$) δ 7.30-7.03 (m, 9H), 5.19 (d, *J* = 9.4 Hz, 1H), 5.04 (m, 1H), 4.83 (m, 1H), 4.59 (m, 1H), 4.04 (t, *J* = 8.4 Hz, 1H), 3.73-3.70 (m, 3H), 2.81 (dd, *J* = 15.7 Hz, 8.8 Hz, 1H), 2.62 (dd, *J* = 15.7 Hz, 5.1 Hz, 1H), 2.22-2.10 (m, 1H), 2.08-1.80 (m, 4H), 1.43 (d, *J* = 6.8 Hz, 3H), 1.40 (s, 9H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.3, 171.6, 155.1, 142.9, 128.8, 127.6, 126.4, 80.5, 60.6, 60.0, 47.8, 38.0, 30, 28.5, 28.4, 24.7, 21.8, 19.6, 18.4.



46 **151**

Bicyclooctadiene 151. To a solution of acid **46** (12.3 mg, 0.04 mmol) and aniline (7.5 mg, 0.08 mmol) in dry CH_2Cl_2 (7.5 mL) was slowly added DCC (9.5 mg, 0.05 mmol) and DMAP (1.2 mg, 0.01 mmol) in dry CH_2Cl_2 (1.5 mL) at 0 ^{o}C under Ar atmosphere. The reaction mixture was allowed to warm to rt. After stirring for further 15 h, the reaction mixture was filtered on a Celite® and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:5) to provide 7.2 mg (47 %) of **151** as yellow solid.

R_f: 0.53 (EtOAc/n-Hexane, 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.94 (dd, *J* = 5.2 Hz, 2.8 Hz, 1H), 7.77 (dd, *J* = 5.2 Hz, 2.8 Hz, 1H), 7.49-7.00 (m, 5H), 5.49 (s, 1H), 4.49 (s, 1H), 3.87 (d, *J* = 10.4 Hz, 1H), 3.36 (t, *J* = 9.2 Hz, 1H), 2.83 (d, *J* = 8.4 Hz, 1H), 1.80 (s, 3H), 1.65 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 145.7, 140.8, 134.4, 133.2, 131.2, 129.3, 128.5, 123.9, 119.9, 55.9, 49.5, 46.2, 44.5, 34.6, 22.2.

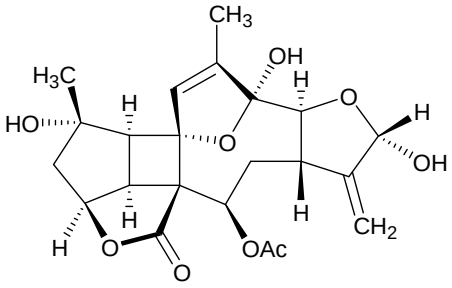
Chapter IV

Stereochemical Control in 8π, 6π Electrocyclizations by a Fused Ring: Studies Toward Total Synthesis of Bielschowskysin

4.1. Introduction

4.1.1. Background

Bielschowskysin is a marine natural product isolated from the Caribbean gorgonian octocoral, Pseudopterogorgia kallos.[1-4] Its skeleton is composed of the highly unprecedented tricyclo[9.3.0.0]tetradecane ring framework. In addition, there are a large number of oxygen-containing functional groups and 11 stereogenic centers on the ring (Figure 35).[5]

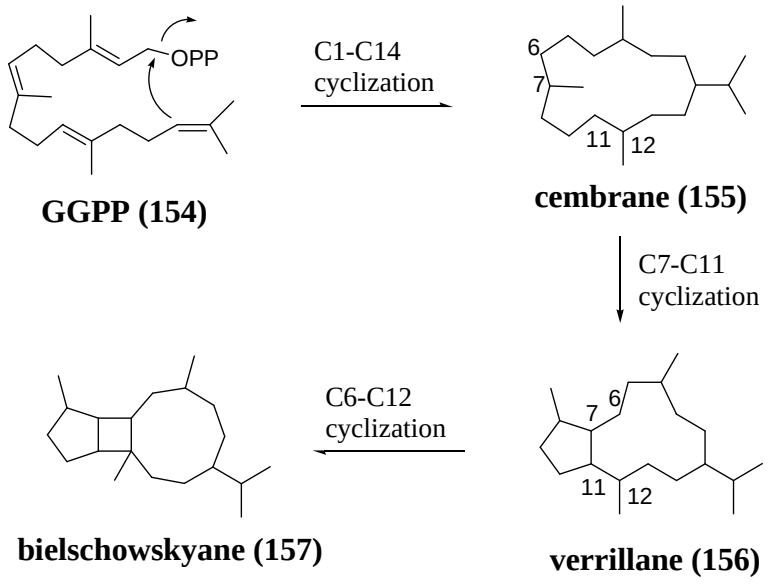


bielschowskysin (153)

Figure 36. Structure of bielschowskysin.

Its biological properties include antimalarial activity against Plasmodium falciparum (IC_{50} = 10 μg mL^{-1}) and potent and selective cytotoxicity against EKVX nonsmall lung cancer cells (GI_{50} < 10 nm) and CAKI-1 renal cancer cells (GI_{50} = 510 nm).[5] Therefore, bielschowskysin is to be ranked one of the most biologically and structurally interesting targets in terms of its complex framework including both challenging stereochemistry and promising biological activity.

According to the biogenesis proposed by Rodriguez,[5] the tricyclo[9.3.0.0]tetradecane ring might be derived from a currently recognized diterpene ring system. Geranylgeranyl pyrophosphate (GGPP) **154** can be converted to the macrocyclic cembrane **155** via C1-C14 cyclization. Double cyclization (C7-C11 in **155** and C6-C12 in **156**) would generate the backbone of bielschowskyane **157** (Scheme 69).

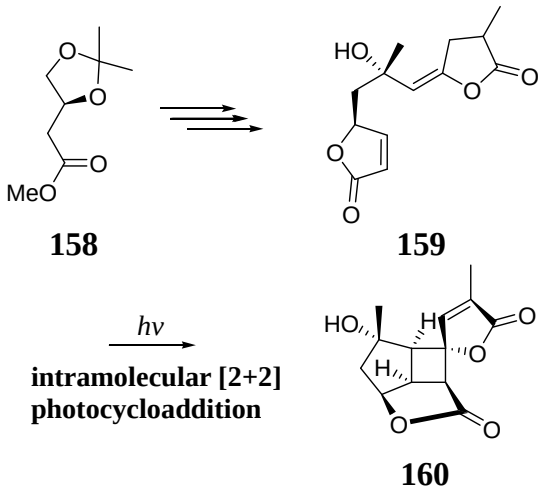


GGPP (154) **cembrane (155)** **bielschowskyane (157)** **verrillane (156)**

Scheme 69. Proposed biogenesis to bielschowskyane skeleton.

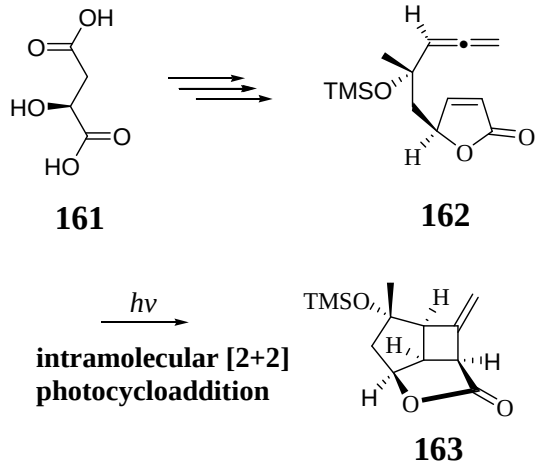
4.1.2. Synthetic approaches toward total synthesis of bielschowskysin

Total synthesis of the highly intriguing natural product has focused on the construction of the tricyclo[9.3.0.0]tetradecane ring framework. The first synthetic approach was performed by the Sulikowski group. Instead of following the proposed biogenesis described above, an intramolecular [2+2] photocycloaddition was adopted as a key strategy to afford the highly substituted cyclobutane in the tricyclo[9.3.0.0]tetradecane framework. The chiral ester **158**, which was prepared from L-malic acid, served as a starting point for the synthesis.[6] The stereoselective intramolecular [2+2] photocycloaddition of the 5-alkylidene-2(5H)-furanone **159** resulted in a single diastereomer **160**. This concise and stereocontrolled assembly of the tetracyclic core was reported as a first effort towards total synthesis of the marine diterpene compound (Scheme 70).[7]



Scheme 70. Synthesis of enantiomeric tetracyclic core **160**.

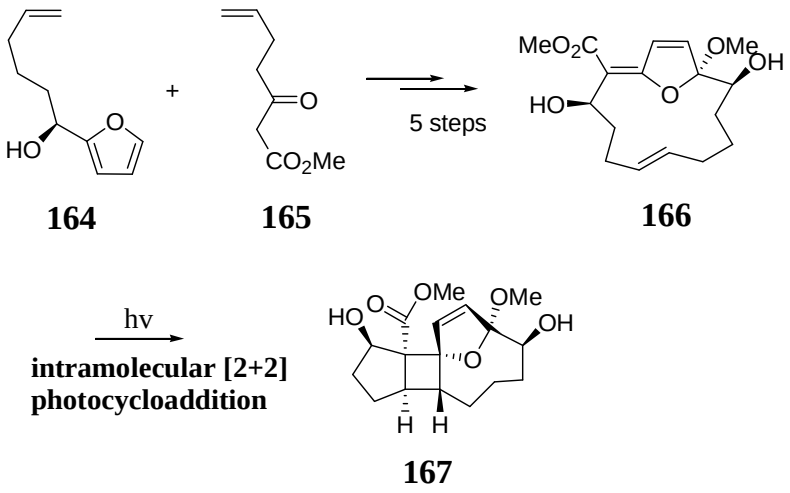
A similar synthetic strategy was independently adopted by the Lear group. They prepared allene-butenolide **162** as a key substrate from L-malic acid **161**. The silylated **162** cleanly underwent a [2+2] cycloaddition to afford a single diastereomeric photoadduct, tricyclo[3.3.0]oxoheptane **163** (Scheme 71).[8]



Scheme 71. Synthesis of tricyclo[3.3.0]oxoheptane **163**.

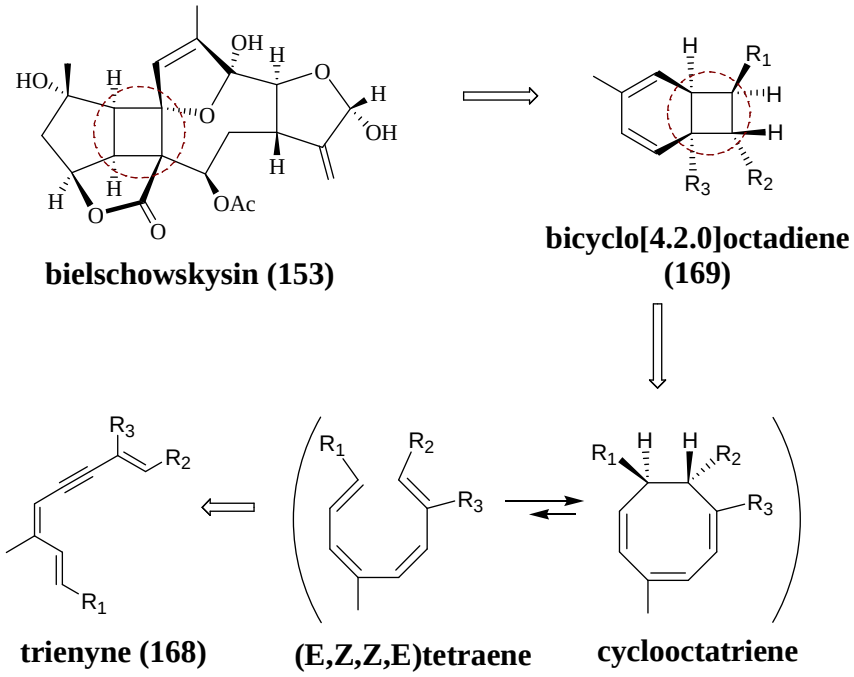
Recently, Nicolaou and co-workers reported the synthesis of a highly functionalized tricyclo[9.3.0.0]tetradecane core **167**. Macrocyclic precursor **166** was prepared with two simple building blocks **164** and **165** via a five-step enantioselective sequence.[9] Finally, the novel

carbocyclic [9.3.0.0] core in bielschowskysin was constructed by an intramolecular [2+2] photocycloaddition (Scheme 72). This expedient synthesis of **167** can be notable for cascade sequences and efficiency.



Scheme 72. Synthesis of the tricyclo[9.3.0.0]tetradecane core **167**.

Unlike the three approaches described above in Schemes 70, 71, and 72, the Parker strategy focused on the semihydrogenation of trienyne precursor **168** and 8π, 6π electrocyclization to afford a highly functionalized cyclobutane core in bielschowskysin. According to Parker, bicyclo[4.2.0]octadiene **169** can be prepared by 8π, 6π double ring closure of (E,Z,Z,E)-tetraene precursor (Scheme 73).[10,11] Stereocontrolled 8π, 6π electrocyclization of **168** might directly control relative stereochemistry of the six substituents on the cyclobutane ring in bielschowskysin.



bielschowskysin (153)

bicyclo[4.2.0]octadiene (169)

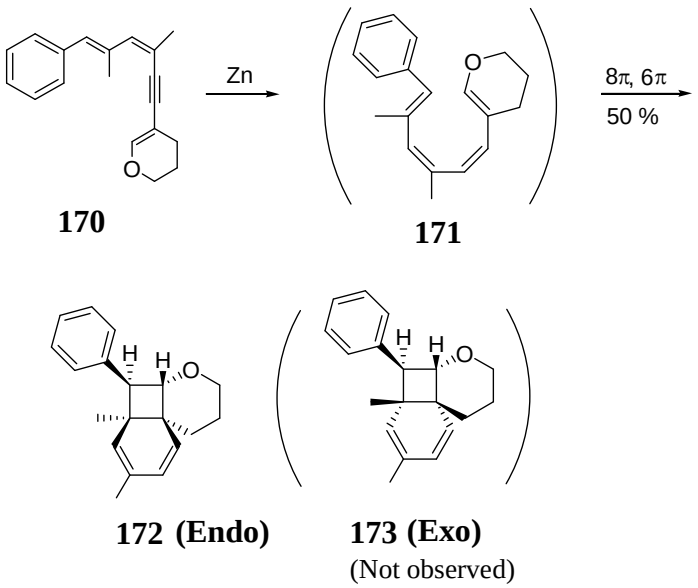
trienyne (168)

(E,Z,Z,E)tetraene

cyclooctatriene

Scheme 73. Retrosynthetic analysis proposed by Parker.

Parker and Zhao designed and synthesized 1,2-annulated trienyne **170** which is a precursor to the corresponding (E,Z,Z,E)-tetraene bearing the 1,2-dihydropyran ring.[12] For the cis-selective semihydrogenation of **170**, zinc activated with copper (II) acetate and silver nitrate was provided as a reducing reagent.[13] Under the given conditions, **170** was converted to the corresponding tetraene **171** followed by the double ring closure to bicyclooctadiene **172**. The 8π, 6π electrocyclization of the tetraene intermediate was stereochemically controlled to provide only endo isomer **172** in which the 1,2-annulated tetrahydropyran was exo and the aryl substituent was endo to the bicyclo[4.2.0]octadiene ring (Scheme 74).[14] The exo isomer **173** was not observed based on proton NMR data.[12] This exclusively endo-selective 8π, 6π ring closure of trienyne **170** provides correctly matched stereochemistry on the cyclobutane ring for bielschowskysin.



170 **171**

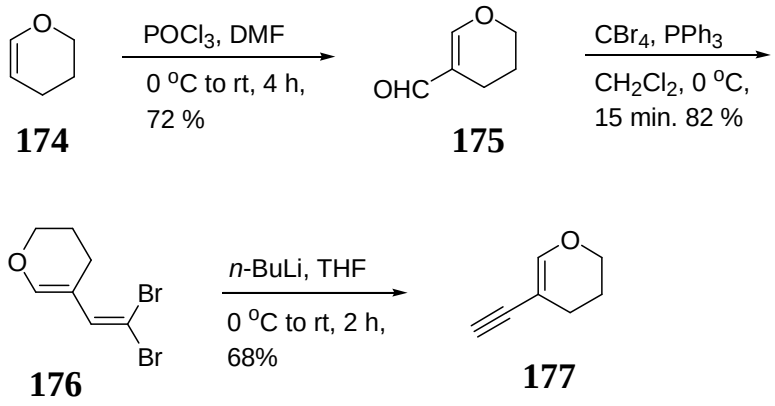
172 (Endo) **173 (Exo)**
(Not observed)

Scheme 74. Endo selective 8π, 6π electrocyclization of trienyne **170**.

In spite of the high stereoselectivity, however, removal of the methyl group on the ring junction of bicyclooctadiene **172** would demand a lot of synthetic effort because bielschowskysin possesses hydrogen at the same position. In addition, the modest yield from the cis-selective semihydrogenation and 8π, 6π electrocyclization sequence needs to be improved.

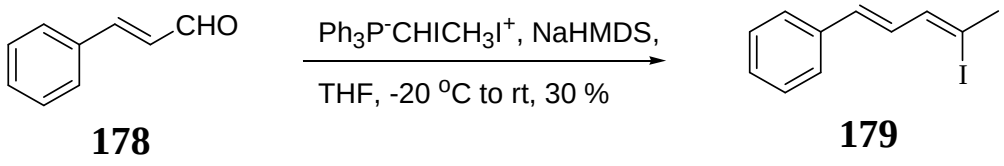
4.2. Result and Discussion

The known 1,2-annulated enyne **177** was prepared following Zhao's synthesis.[12] First, 3,4-(*2H*)-dihydropyran **174** was converted to aldehyde **175** via the Vilsmeier reaction. Then, under Corey-Fuchs reaction conditions, **175** was treated with tetrabromomethane (CBr_4) and triphenylphosphine (PPh_3) to form the dibromoalkene **176,** which was then converted into alkyne **177** (Scheme 75).[15]



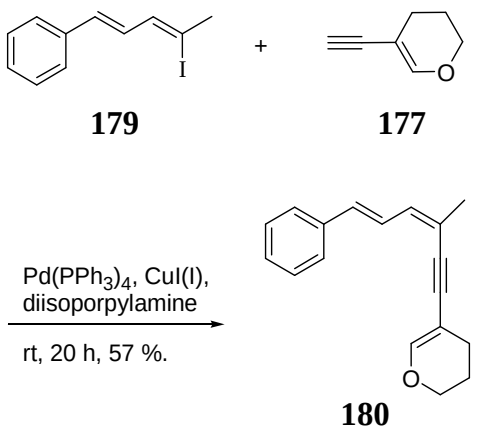
Scheme 75. Preparation of enyne **177**.

Iododiene **179** was afforded from cinnamaldehyde **178** via the Stork-Zhao reaction (Scheme 76).[16] Despite the modest yield, this procedure was a good one for our purpose because no (E,E)-iododiene was observed based on in the proton NMR spectrum of **179**.



Scheme 76. Preparation of iododiene **179**.

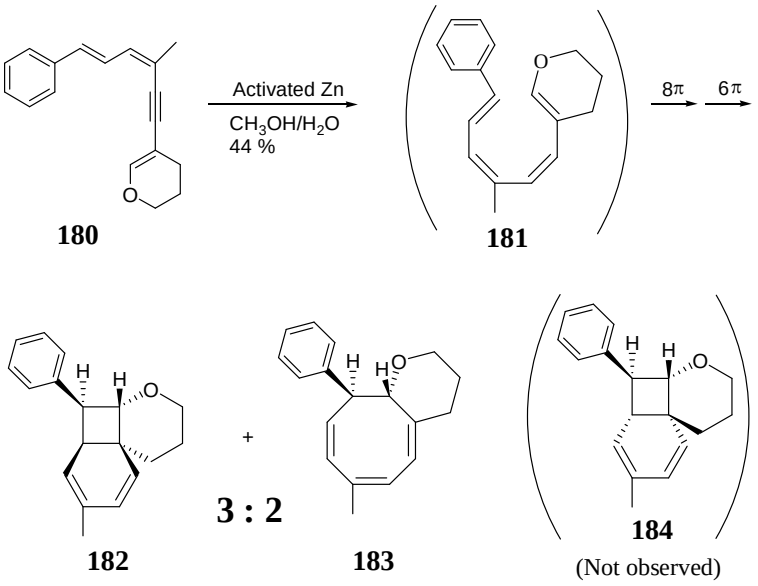
Enyne **177** reacted smoothly with iododiene **179** to yield the desired 1,2-annulated trienyne **180** via Sonogashira coupling conditions (Scheme 77).[17]



179 **177** **180**

Scheme 77. Preparation of 1,2-annulated trienyne **180**.

Next, trienyne **180** was stereoselectively reduced by activated zinc to yield (E,Z,Z,E)-tetraene intermediate **181**. The 8π, 6π double ring closure of **181** generated the corresponding bicyclooctadiene under thermal conditions (Scheme 78).[13] Endo bicyclooctadiene **182** was produced along with cyclooctatriene **183** in a 2 : 3 ratio. The exo isomer **184** was not observed in the proton NMR spectra.



180 **181** **3 : 2** **182** **183** **184** (Not observed)

Scheme 78. 8π, 6π electrocyclization of (E,Z,Z,E)-tetraene **181**.

The isolation of **183** was not expected. Cyclooctatrienes have not been detected in the synthesis of SNF compounds or in the other natural products that contain the same framework. Recently, Moses and co-workers reported the 8π, 6π electrocyclization of (E,Z,Z,E)-tetraene **185** to the two diastereomeric mixture of **187** and **188**, a putative precursors of pre-kingianin A (Figure 36).[19] Interestingly, the (E,Z,Z,E)-tetraene **185** did not isolated after the Stille cross-coupling reaction between alkenyl bromide and alkenyl stannane.

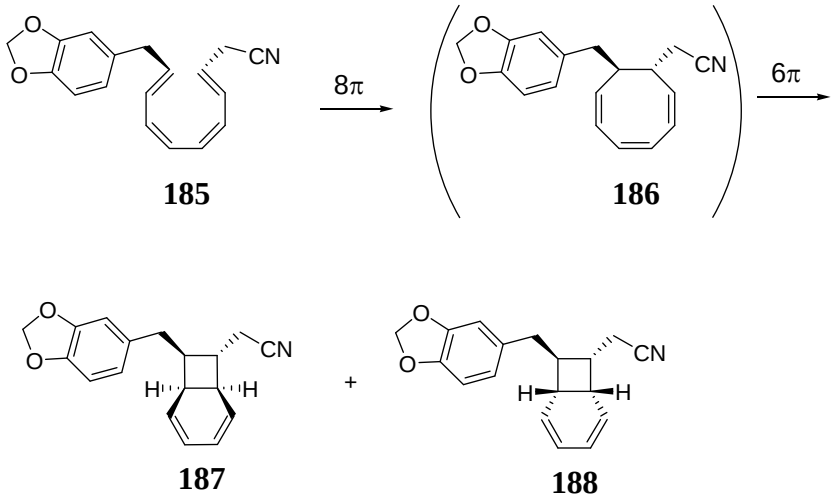


Figure 37. Synthesis of bicyclooctadienes **187** and **188.**

Despite having no methyl groups on the (E,Z,Z,E)-tetraene **185**, the corresponding cyclooctatriene **186** was not detected after 8π, 6π electrocyclization. Therefore we can not attribute its isolation to the absence of methyl groups.

4.3. Conclusion

In the progress of studies toward total synthesis of bielschowskysin, we demonstrated that the tetraene substrate with 1,2-annulated fused ring **181** produced exclusively endo bicyclo[4.2.0]octadiene **182** in 8π, 6π electrocyclization along with cyclooctatriene **183**. Further study suggests that the methyl group on the tetraene **181** promotes the 8π, 6π double ring closure. Nonetheless, the stereochemically controlled 8π, 6π electrocyclization of the 1,2-annulated tetrapyran substrate **181** shows potential for the preparation of the highly substituted cyclobutane ring in bielschowskysin. This could lead to the construction of the tricyclo[9.3.0.0]tetradecane ring framework and eventually total synthesis of bielschowskysin.

4.4. Reference

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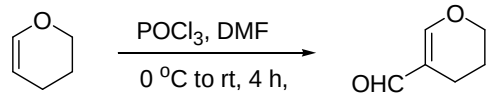
4.5. Experimental Section

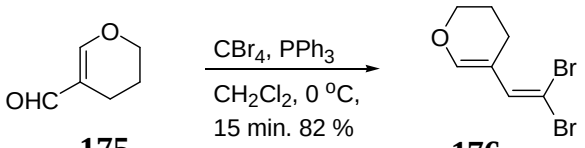
The procedure of Hong Zhao[8] was followed to prepare enyne **177.**



174 **175**

Aldehyde 175. $POCl_3$ (4.2 mL, 45 mmol) was dissolved in dry DMF (85 mL) at 0 °C under Ar. The reaction mixture was agitated for 0.5 h and added dropwise via cannula to a precooled solution of 3, 4-dihydro-2H-pyran **174** (3.0 mL, 33 mmol) in dry DMF (30 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt, then stirred for further 4 h. After quenching with cautious addition of saturated aqueous $NaHCO_3$ under ice-bath, the resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc:*n*-hexane, 1:5) to provide 2.98 g (72 %) of **175** as colorless liquid.

R_f: 0.21 (EtOAc/*n*-hexane, 1/5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1H), 7.27 (s, 1H), 4.15 (t, J = 5.2 Hz, 2H), 2.22 (t, J = 6.4 Hz, 2H), 1.85 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 165.3, 119.7, 68.7, 20.8, 16.8.



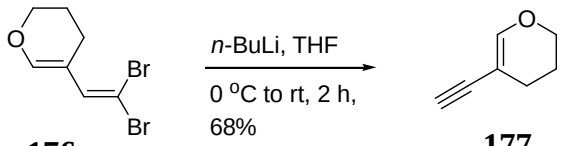
175 **176**

Dibromoolefin 176. To a solution of recrystallized triphenylphosphine, PPh_3 (4.6 g, 17 mmol) in dry CH_2Cl_2 (20 mL) carbon tetrabromide, CBr_4 (2.9 g, 8.7 mmol) was added in one portion to at 0 °C under Ar. The reaction mixture was stirred for 5min, and then a solution of aldehyde **175** (390 mg, 3.5 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise over 3 min. at 0 °C under Ar. After stirring for further 10 min. at 0°C, the dark reddish solution was concentrated

[8] Thesis from Hong Zhao: Part 4. Studies Towards Total Synthesis of Bielschowskysin.

under vacuum. The residue was purified by silica gel chromatography (EtOAc:*n*-hexane, 1:5) to provide 763 mg (82 %) of **176** as colorless oil.

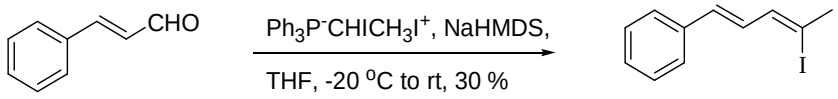
R_f: 0.85 (EtOAc/*n*-hexane, 1/3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.75 (s, 1H), 6.68 (s, 1H), 3.99 (t, J = 6.8 Hz, 2H), 2.51 (t, J = 8.4 Hz, 2H), 2.51 (m, 2H).



176 **177**

Enyne 177. To a solution of dibromoolefine **176** (210 mg, 0.79 mmol) in dry THF (3.7 mL), n-BuLi (0.63 mL of a 2.5 M solution in *n*-hexane, 1.56 mmol) was added dropwise at -78 °C under Ar. After stirring at -78 °C for 1 h, the resulting mixture was allowed to rt, stirred for further 1 h. After quenching with cautious addition of H_2O (4 mL), the resulting solution was extracted with Et_2O (3 x 5 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was distilled by Kugelrohr distillation to provide 58 mg (68 %) of **177** as colorless liquid.

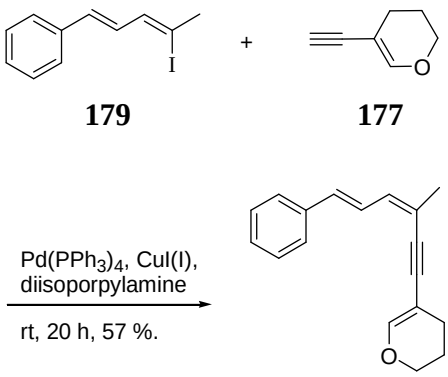
R_f: 0.26 (EtOAc/*n*-hexane, 1/6); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86 (s, 1H), 3.98 (dd, J = 5.3 Hz, 4.8 Hz, 2H), 2.80 (s, 1H), 2.16 (dt, J = 6.3 Hz, 1.5 Hz, 2H), 1.87 (m, 2H).



178 **179**

Iododiene 179. To a stirred solution of the salt (4.52 g, 8.3 mmol) in THF (80 mL) was added sodium hexamethyldisilazane, NaHMDS (5.0 mL of a 2.0 M solution in THF, 100 mmol) at -20 °C under Ar. The resulting red solution was stirred for 5 min. and then a solution of cinnamal **178** (0.95 g, 7.2 mmol) in THF (10 mL) was added dropwise over 15 min. by syringe under Ar. After 30 min, the dark brown solution was allowed to warm to rt , quenched by saturated aqueous NH_4Cl. The resulting solution was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc:*n*-hexane, 1:10) to provide 857 mg (30 %) of **179** as pale yellow solid.

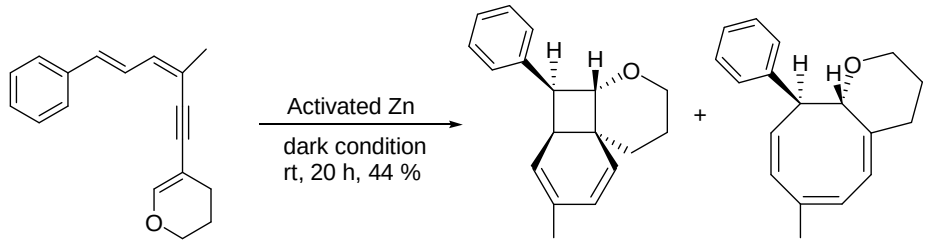
R_f: 0.68 (EtOAc/*n*-hexane, 1/30); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 8.0 Hz, 2H), 7.23-7.33 (m, 3H), 6.81 (dd, J = 12.6 Hz, 9.6 Hz, 1H), 6.67 (d, J = 15.6 Hz, 1H), 6.22 (d, J = 9.6 Hz, 1H), 2.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.2, 134.6, 131.3, 128.9, 128.8, 128.2, 126.8, 102.7, 34.3.



179 **177** **180**

Trienyne 180. To a solution of enyne **177** (42 mg, 0.39 mmol) and iododiene **179** (105 mg, 0.39 mmol) in diisopropylamine (2.0 mL) were added $Pd(PPh_3)_4$ (48 mg, 0.04 mmol) and Cu(I) (6.7 mg, 0.04 mmol) at rt under Ar. After stirring for 24 h, the resulting mixtured was poured into saturated NH_4Cl and extracted 3 times with Et_2O. The combined organic layers were washed with H_2O, brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc:*n*-hexane, 1:30) to provide 56 mg (57 %) of **180** as pale yellow sticky oil.

R_f: 0.47 (EtOAc/*n*-hexane, 1/30); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 7.5 Hz, 2H), 7.22 (d, J = 7.2 Hz, 1H), 7.22 (dd, J = 13.5 Hz, 11.4 Hz, 1H), 6.91 (s, 1H), 6.55 (d, J = 15.6 Hz, 1H), 6.31 (d, J = 10.8 Hz, 1H), 4.03 (d, J = 5.1 Hz, 2H), 3.79 (d, J = 10.2 Hz, 1H), 2.27 (d, J = 6.3 Hz, 2H), 1.98 (s, 3H), 1.93 (m, 2H).



180 **182** **183**

Bicyclooctadiene 182 and cyclooctatriene 183. To a stirred suspension of Zn dust (1.02 g) in H_2O (6 mL) was added $Cu(OAc)_2$ (112 mg) at rt under Ar. After 15 min, $AgNO_3$ (115 mg) was introduced and the mixture was stirred for 30 min, filtered, and washed sequentially with H_2O (11 mL), CH_3OH (11 mL), Acetone (11 mL), and Et_2O (13 mL). The activated Zn was suspended in 50 % aq. CH_3OH (2 mL) and a solution of trienyne **180** (24 mg, 0.1 mmol) in 1 : 1 CH_3OH/H_2O (4 mL) was introduced under Ar. The reaction mixture was stirred overnight at 20 h in the dark condition. The Zn was then filtered through Celite, washed with Et_2O and H_2O. The aqueous layer was 3 times extracted with EtOAc. The combined organic layers were washed with H_2O, brine, and dried over $MgSO_4$. The residue was purified by preparative chromatography (EtOAc:*n*-hexane, 1:25) to provide 11.1 mg (44 %) of an inseparable mixture of **182** and **183** in a ratio of 3 : 2 as pale yellow sticky oil.

R_f: 0.43 (EtOAc/*n*-hexane, 1/25); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (t, J = 7.8 Hz, 2H), 7.26 (d, J = 9.6 Hz, 1H), 7.20 (dd, J = 6.3 Hz, 6.0 Hz, 2H), 5.84 (d, J = 12.6 Hz, 0.37H), 5.82 (d, J = 18.6 Hz, 0.37H), 5.77 (d, J = 9.6 Hz, 1H), 5.69 (dd, J = 9.6 Hz, 7.2 Hz, 0.37H), 5.65 (d, J = 9.6 Hz, 0.64H), 4.69 (d, J = 9.0 Hz, 0.64H), 4.46 (t, J = 9.9 Hz, 1H), 3.97 (dd, J = 9.6 Hz, 7.8 Hz, 0.37H), 3.88 (dd, J = 7.8 Hz, 4.2 Hz, 0.63H), 3.78 (d, J = 6.6 Hz, 2H), 3.70 (m, 0.37H), 3.54 (td, J = 11.4 Hz, 3.0 Hz, 0.37H), 2.98 (d, J = 10.2 Hz, 0.64H), 2.48 (m, 0.37H), 2.38 (m, 0.63H), 2.04 (dt, J = 13.2 Hz, 3.0 Hz, 0.74H), 1.92 (s, 1.11H), 1.71-1.83 (m, 2H), 1.63 (s, 1.89H), 1.59 (dt, J = 13.2 Hz, 3.0 Hz, 1.28H).

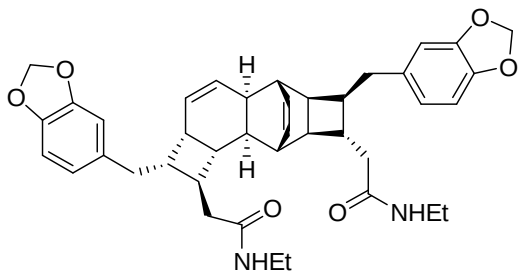
Chapter V

Progress Towards the Total Synthesis of (+/-)- Kingianin A

5.1. Introduction

5.1.1. Background

Recently, **(+/-)**-kingianin A (**189**), a biologically active and structurally interesting compound, was isolated from the trunk bark of *Endiandra kingiana* in the dense rainforest of Kuala Lipis in Malaysia (Figure 37).[1] Although the carbon backbone of the natural product shares minimal structural similarity with the endiandric acids, kingianin A is considered to be produced via a biosynthetically similar pathway.[2]



(+/-)-kingianin A (189)

Figure 38. (+/-)-Kingianin A: A new pentacyclic ring framework.

During the writing of this document, thirteen analogs of kingianin A were reported by Litaudon and co-workers. Kingianins A - N contain the same pentacyclic skeleton and they represent the first members of a new chemical series. According to mass spectrometry and NMR spectroscopy, kingianins A - F are stereoisomers. Other analogs, G - L show structural similarity to one another.[3] Interestingly, kingianins A - N were produced as racemic mixtures. Presumably, like endiandric acids, which were also formed as racemates, kingianins are produced by nonenzymatic electrocyclizations from achiral polyketide precursors. The pentacyclic framework within the kingianins possesses the same regio- and stereochemistry. In addition, the same piece,

which could be derived from safrole, is attached to the cyclobutane ring of kingianins despite the diversity of the other piece (Figure 38).

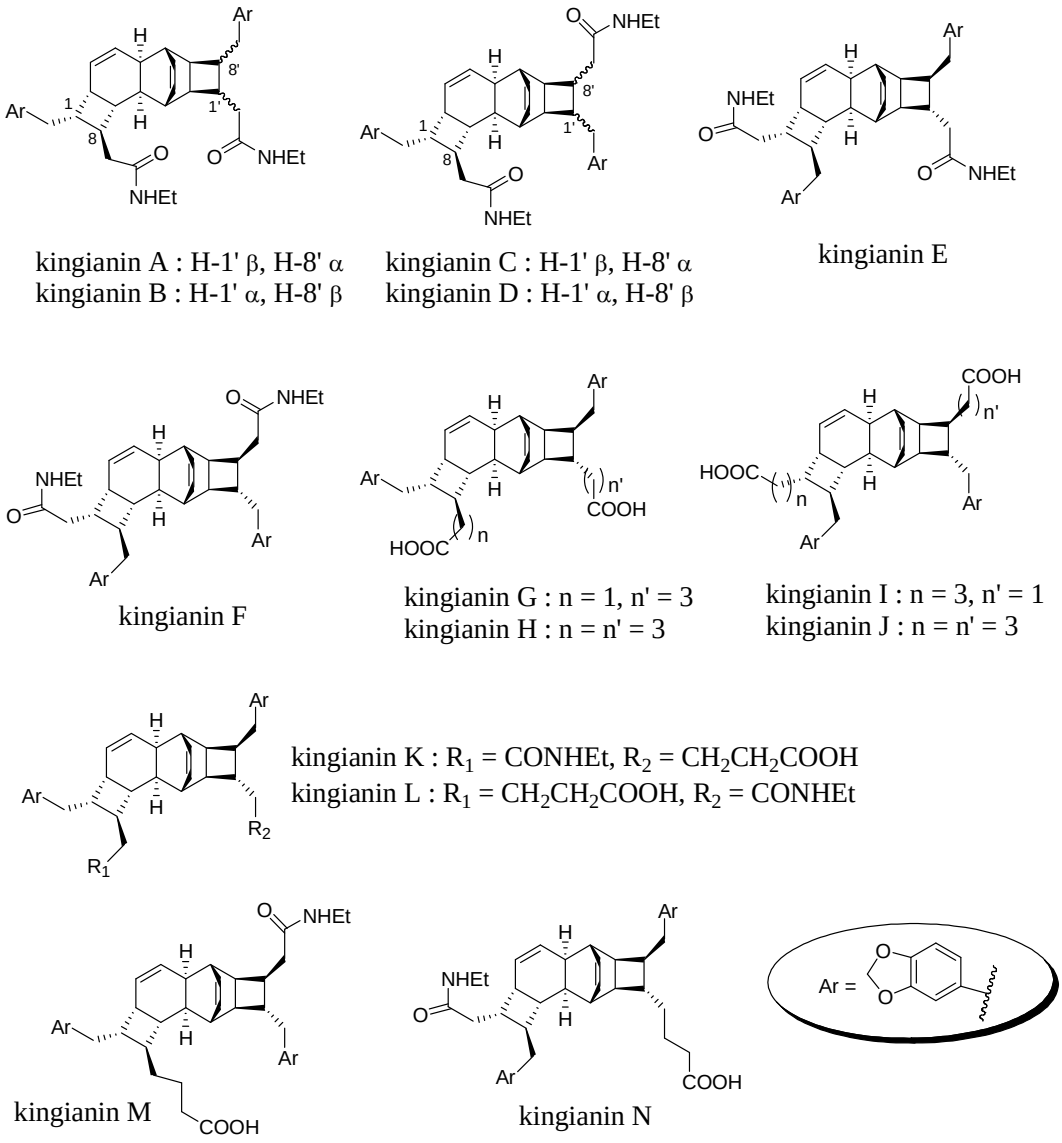
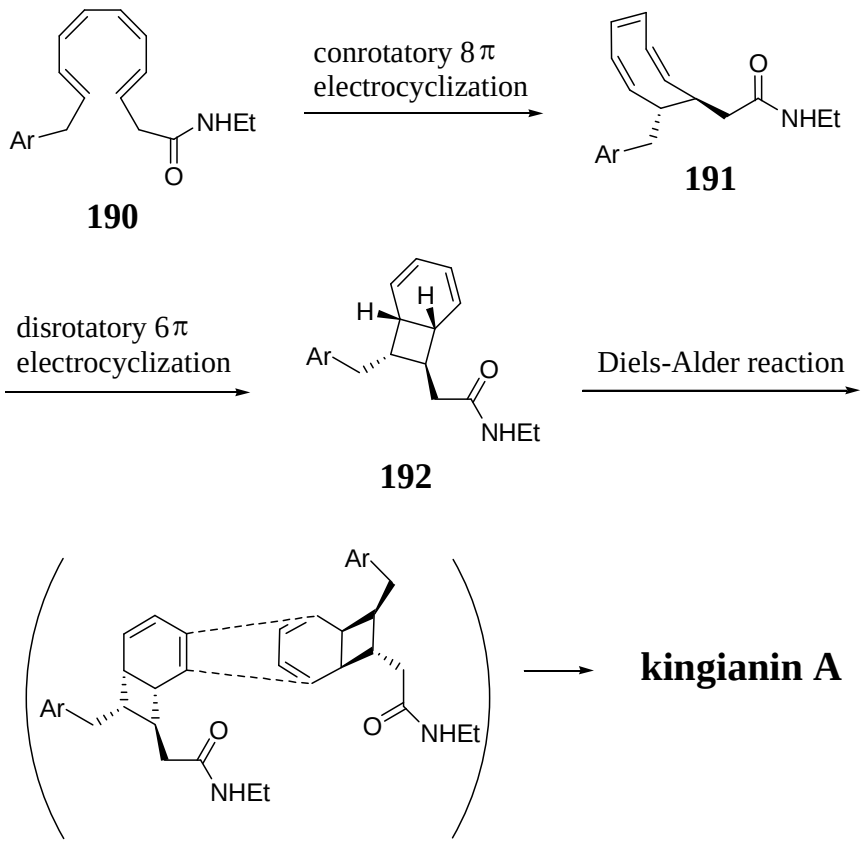


Figure 39. Structure of all kingianins A - N.

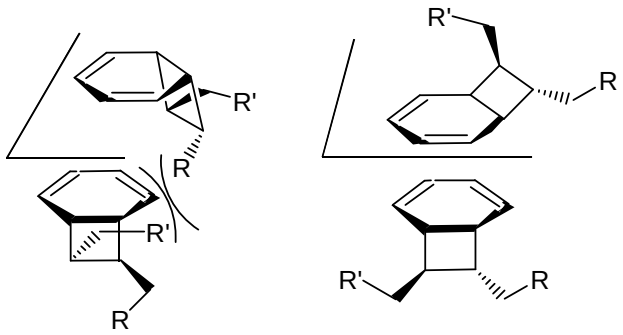
In a binding test to the anti-apoptotic protein Bcl-xL, the kingianins showed promising and potent biological activities suggesting that the natural products could potentially be developed as new anti-cancer drug leads.[4] Interestingly, (-)-enantiomeric kingianins G - L, which were separated by chiral HPLC, showed the most potent binding affinity for the Bcl-xL with Ki values in the low μM range.[3]

According to Litaudon,[1] kingianin A would be formed by a Diels-Alder reaction between two molecules of pre-kingianin A **192**. Probably, (E,Z,Z,E)-tetraene **190** will undergo a 8π, 6π electrocyclization to produce **192** through cyclooctatriene **191** (Scheme 79).



Scheme 79. Litaudon's proposed biomimetic synthesis of kingianin A.

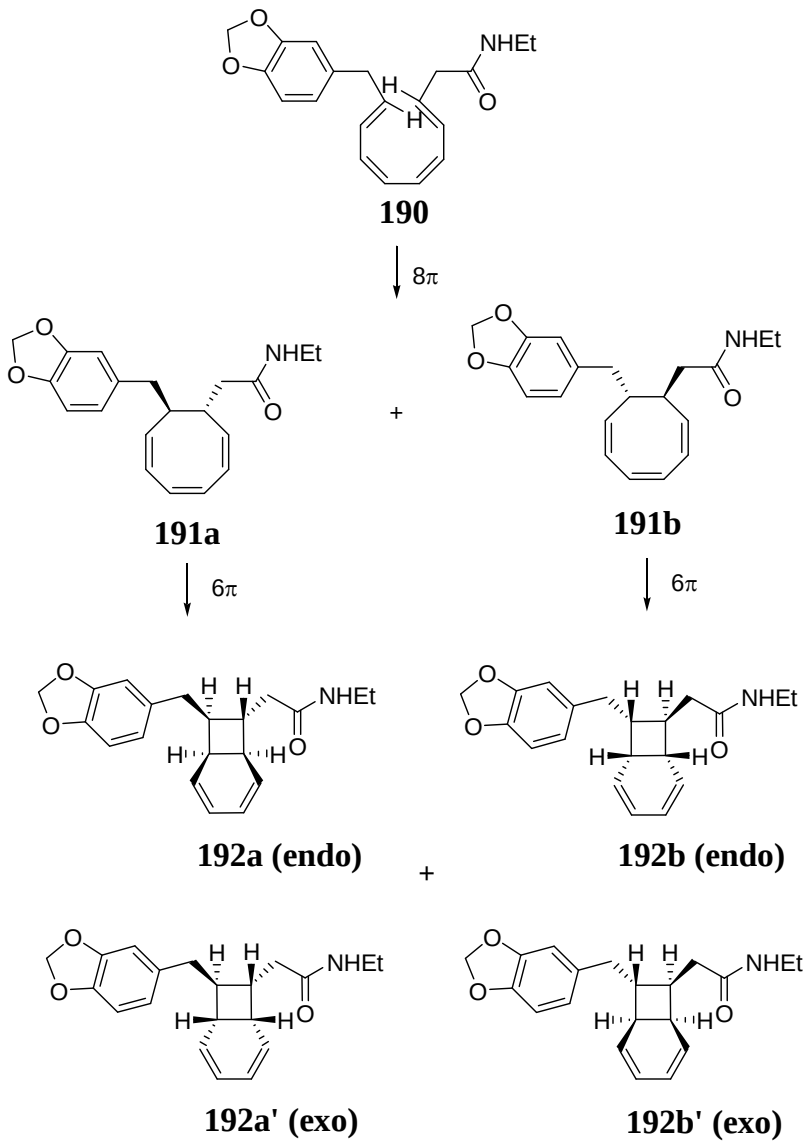
Due to steric hindrance generated between substituents located on the cyclobutane of pre-kingianin A, all cis-configuration at the ring junction may be unfavorable during the Diels-Alder reaction. Therefore, the last step of kingianin A biogenesis may proceed with anti-configuration of the cyclobutane rings. As a result, the regio- and stereochemically same carbon skeletons of the pentacyclic core shown in the kingianin A can be explained by effect of steric hindrance (Figure 39).



Cis-configuration Anti-configuration

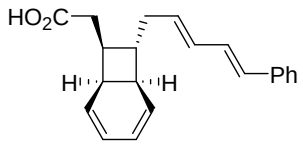
Figure 40. Origin of regio- and stereoselectivity in the formation of kingianin A.

The multiplicity of kingianins may be explained on the basis of a mechanism involved in 8π, 6π double ring closure. Due to non-stereocontrolled 8π electrocyclization, two enantiomers of cyclooctatriene **191a** and **191b** will be formed. In addition, unlike SNF 4435 C and D, which are afforded by endo selective 6π electrocyclization, both endo **192a** and **192b** and exo bicyclooctadienes **192a'** and **192b'** are generated (Scheme 78).[5] Consequently, racemic kingianins A - F will be produced from four stereoisomeric pre-kingianins **192a/b** and **192a'/b'** via intermolecular Diels-Alder reaction.



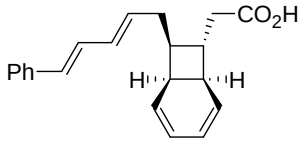
Scheme 80. Possible four stereoisomeric pre-kingianins for kingianins A - F.

Litaudon's hypothesis[1] is in accord with the biogenesis of endiandric acids proposed by Black.[6-8] Interestingly, Nicolaou's biomimetic syntheses of endiandric acids are also focused on 8π, 6π electrocyclization and Diels-Alder reaction.[9-12] Endiandric acids D - G are structurally similar to pre-kingianins **192a/b** and **192a'/b'** (Figure 40). Endiandric acids D (**193)** and E (**194)** are stereoisomers of one another. Likewise, endiandric acids E (**195)** and F (**196)** are stereoisomers.



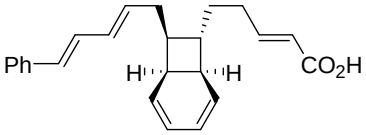
Endiandric acid D

193



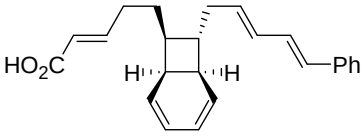
Endiandric acid E

194



Endiandric acid F

195

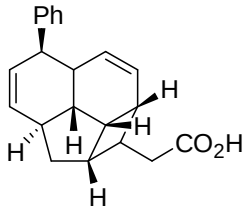


Endiandric acid G

196

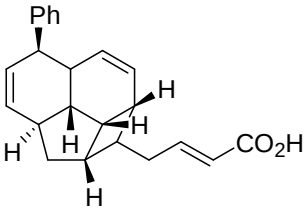
Figure 41. Endiandric acids D - G**:** Structural congeners of pre-kingianins.

Endiandric acids A (**197)** B (**198)** and C (**199)** were synthesized from their corresponding bicyclo[4.2.0]octadiene precursors, endiandric acids E, F, and G via intramolecular Diels-Alder reactions (Figure 41).



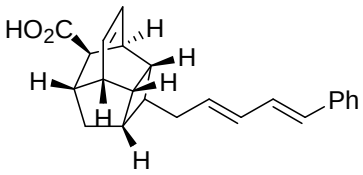
Endiandric acid A

197



Endiandric acid B

198



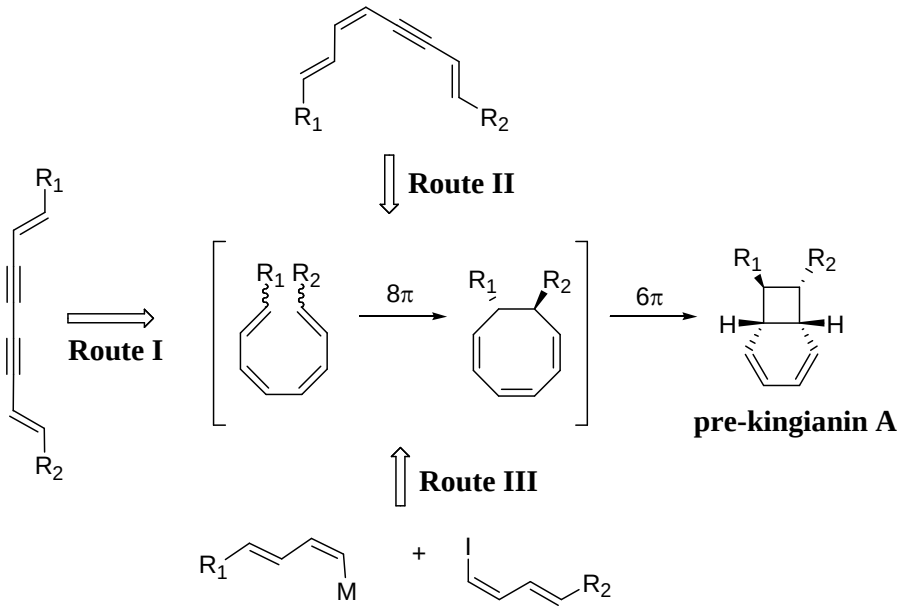
Endiandric acid C

199

Figure 42. Endiandric acids A, B, and C: The Diels-Alder products.

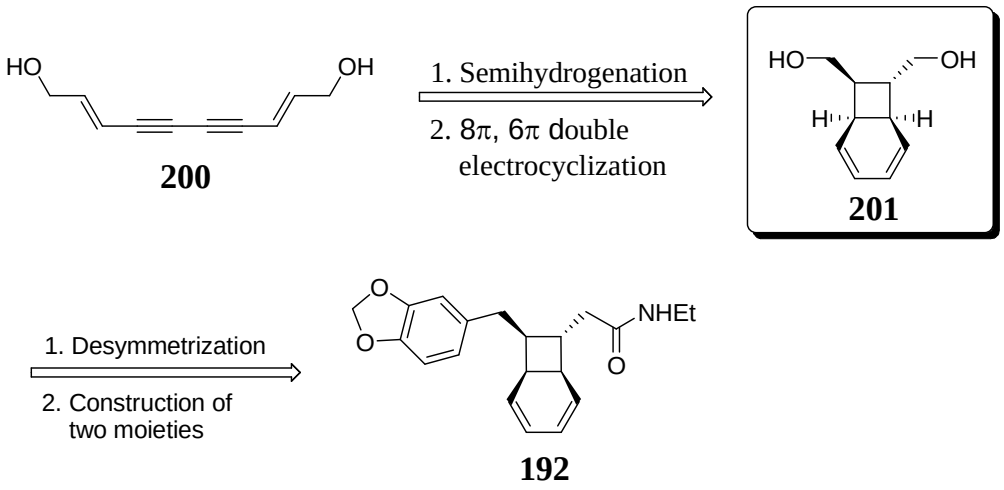
5.1.2. Synthetic strategy to prepare pre-kingianin A

In general, pre-kingianin A can be synthesized via three synthetic routes; semihydrogenation of enynes and 8π, 6π electrocyclization sequence (**Route I** or **II**) and palladium mediated cross-coupling reaction between two (Z,E)-dienes (**Route III**). (See Scheme 81.)



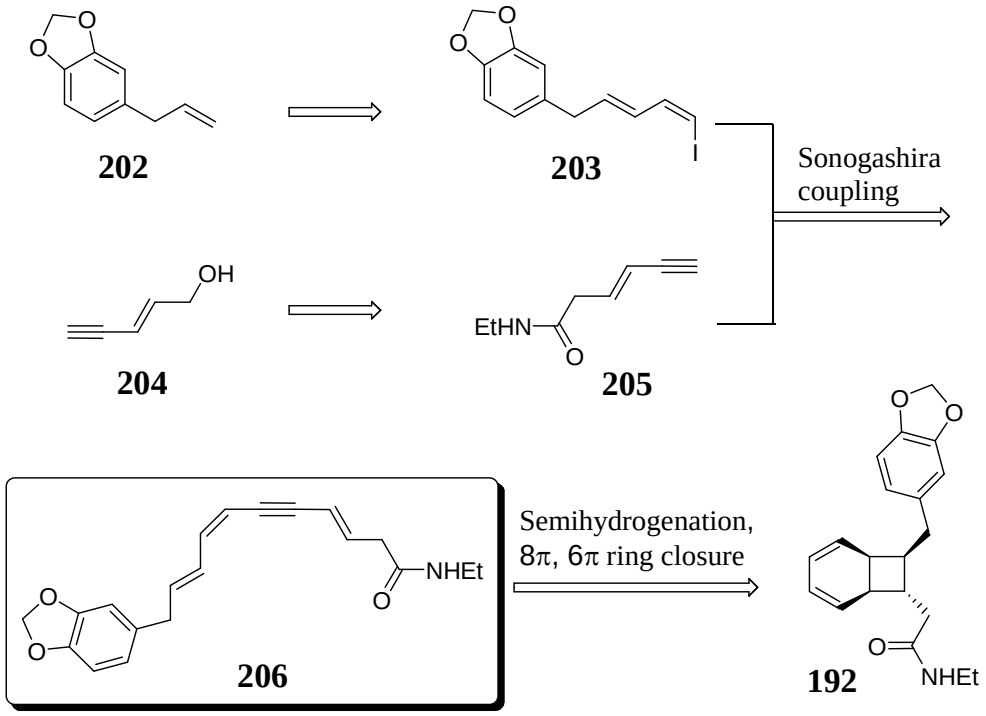
Scheme 81. Possible synthetic routes for the preparation of pre-kingianin A.

The synthetic route I: The known bicyclo[4.2.0]octadiene **201** has been prepared from via cis-selective semihydrogenation of dienyne **200** and then 8π, 6π electrocyclization sequence.[9] Therefore, this method developed by Nicolaou might be the most straightforward way to prepare pre-kingianin A **192** (Scheme 82). However, the procedure would require much effort to introduce two different moieties on the cyclobutane ring of **201**.



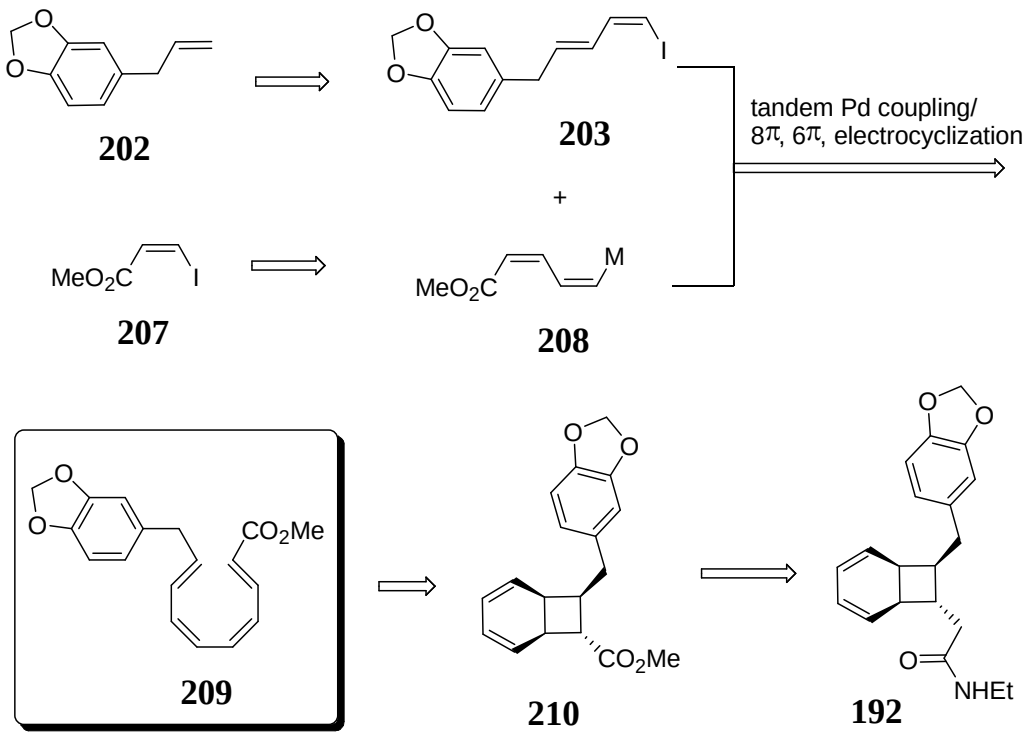
Scheme 82. Bicyclooctadiene **201**: A key intermediate to generate **192**.

Cis-selective semihydrogenation and then 8π, 6π electrocyclization of an enyne precursor in final stage is a suitable synthetic strategy. (See the Route II.) Trienyne **206** can be readily afforded by Sonogashira coupling between iododiene **203** and enyne **205**. The two building blocks can be prepared from commercially available sources, safrole **202** and pent-2-en-4-yn-1-ol **204**. Presumably, semihydrogenation of the monoacetylene in **206** would more efficiently generate a corresponding (E,Z,Z,E)-tetraene substrate compared to the diacetylene moiety in **200** (Scheme 83).



Scheme 83. Trienyne **206**: A key intermediate to generate **192**.

Palladium-mediated cross-coupling reaction is a well known method to prepare bicyclo[4.2.0]octadiene compounds. (See the Route III.) (Z,E)-metallated diene **208** can be prepared from commercial Z-iodo-acrylate **207.** Coupling between **203** and **208** will afford a (E,Z,Z,E)-tetraene **209** which will provide corresponding bicyclooctadiene **210** via 8π, 6π electrocyclization. Finally, the methyl ester in **210** can be converted into desired homologated ethyl amide moiety to yield pre-kingianin A **192** (Scheme 84).



Scheme 84. Tetraene **209**: A key intermediate to generate **192**.

During the writing of this document, Moses and co-workers reported the first synthesis of the pre-kingianin A.[13] Interestingly they adopted a synthetic approach similar to that described in Scheme 84.

Our synthetic route to pre-kingianin A **192** will be reasonable if we adopt one of the three pathways. Specifically, if we have bicyclooctadiene **210** in hand, it will be valuable enough because modification of the methyl ester in **210** can lead to all pre-kingianins A - N (Figure 42).

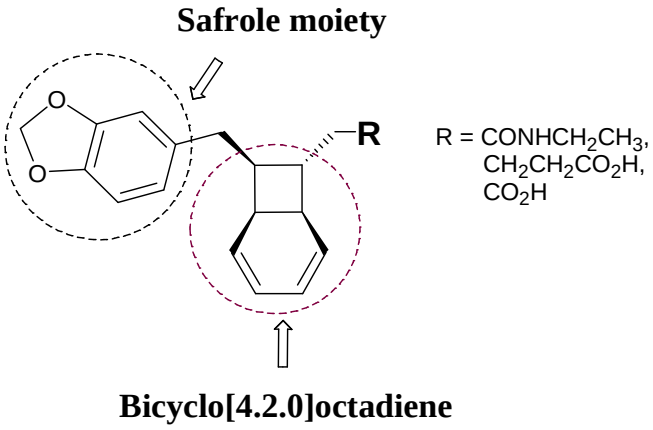
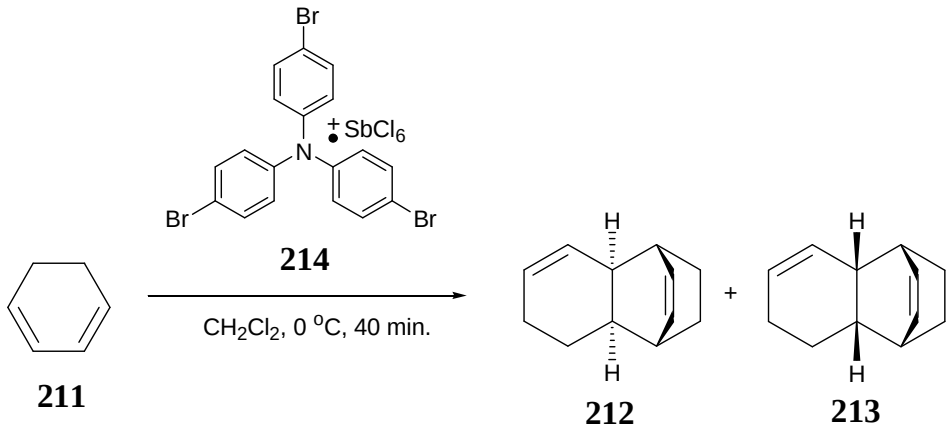


Figure 43. Structurally required framework for all pre-kingianins.

5.1.3. Cation radical catalyzed Diels-Alder reaction

Litaudon proposed that kingianin A is a Diels-Alder product between two pre-kingianin A.[1] Nonetheless, there are no Diels-Alder reactions available to produce pentacyclic carbon skeleton of kingianin A. Recently, Moses group tried Diels-Alder reaction of pre-kingianin A to afford kingianin A. However, they did not obtain any desirable products under traditional Diels-Alder reaction conditions. Among a number of Diels-Alder reactions is cation radical catalyzed Diels-Alder reaction. Bauld and co-workers showed that with radical cation catalysis, he could effect the dimerization of 1,3-cyclohexadiene **211**.[14] A mixture of tricyclics **212** and **213** was successfully affforded in the presence of tris(*p*-bromophenyl)aminium hexachloroantimonate **214** (Scheme 85).[15]



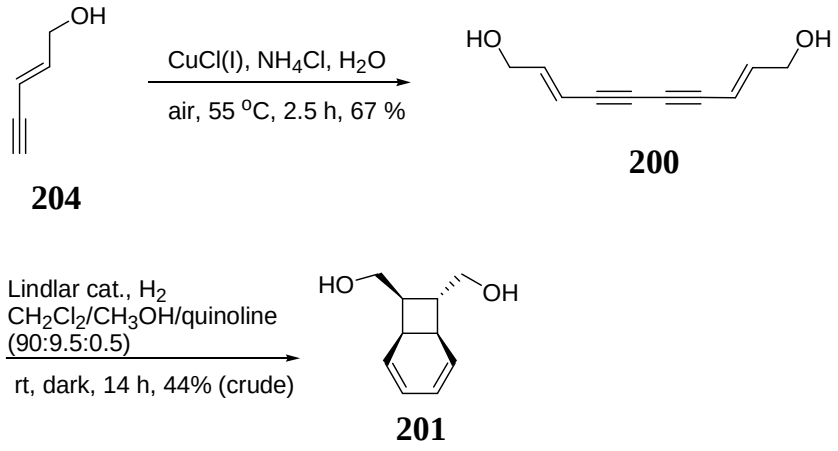
Scheme 85. Cation radical catalyzed Diels-Alder reaction *of* 1,3-cyclohexadiene.

Pre-kingianin A **192** contains the 1,3-cyclohexadiene functionality. Therefore, we strongly believe that if we have **192** in hand, total synthesis of kingianin A can be successfully performed via cation radical catalyzed Diels-Alder reaction. Furthermore, this same strategy could be applicable to prepare for the other kingianins, namely B - N.

5.2. Result and Discussion

5.2.1. Synthetic approach towards preparation of pre-kingianin A

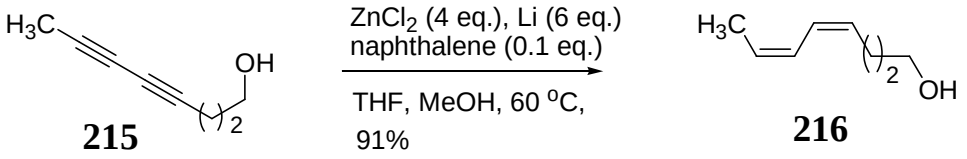
Due to analytic and synthetic simplicity, dihydroxymethyl-bicyclo[4.2.0]octadiene **201** was adopted for the investigation of semihydrogenation and 8π, 6π electrocyclization reaction. The dienyne **200** was prepared by copper-mediated homocoupling of commercially available enyne **204**. Recrystallization of **200** afforded needles. Under the given conditions, dienyne **200** was treated with Lindlar catalyst to transform into corresponding (2E,4Z,6Z,8E)-tetraene intermediate which was spontaneously followed by 8π, 6π electrocyclization to yield **201** (Scheme 86).[9]



Scheme 86. Preparation of dihydroxymethyl-bicyclo[4.2.0]octadiene **201**.

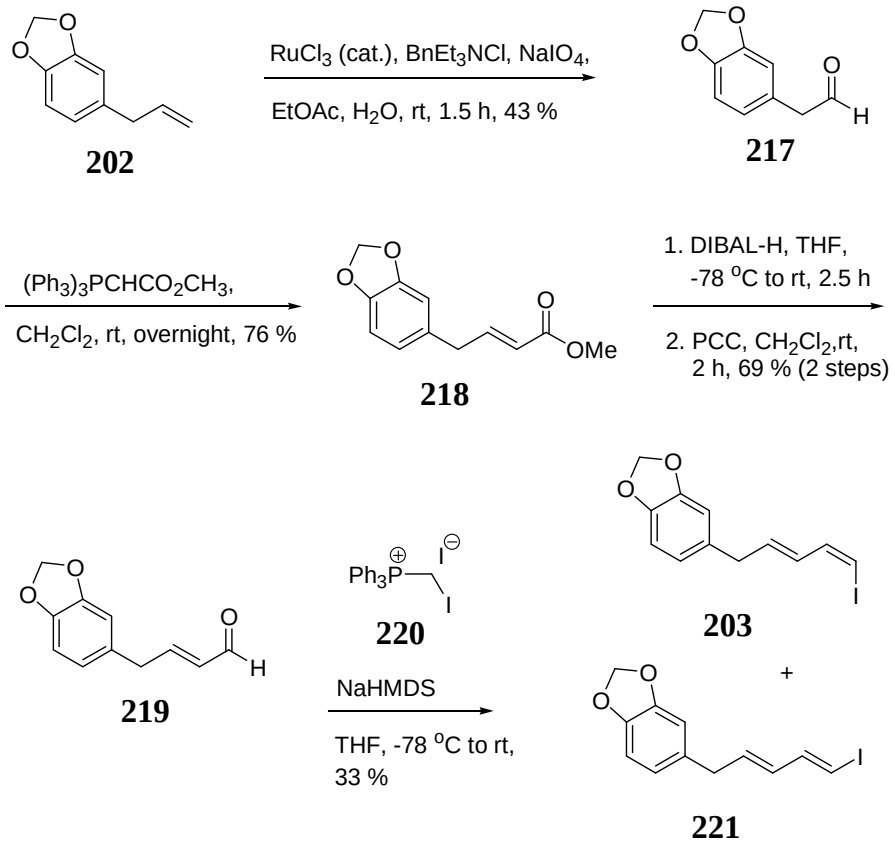
Despite much experimentation, however, semihydrogenation of dienyne **200** did not cleanly yield bicyclooctadiene **201**. Presumably, a mixture of over- and under-reduced products with mixed stereochemistry are produced. The Lindlar catalyst used in the total syntheses of endiandric acids may have a specific capability for cis-selective semihydrogenation of **200**.[9] Otherwise, Nicolaou and co-workers might not have been concerned about inseparable

byproducts because they could easily eliminate undesirable compounds after iodoetherification of **201**.[9] Previously reported claims supported our assumption. Sharma et al stressed that cis-selective hydrogenation of dienynes was not well performed with commercial Lindlar catalyst.[16] Very recently, the De Voss group also mentioned that semihydrogenation of dienyne **215** did not cleanly yield the corresponding (Z,Z)-diene **216** with Lindlar catalyst. De Voss demonstrated that semihydrogenation of **215** was successfully performed under the modified Rieke zinc reduction condition without a mixture of over- and under-reduced products (Scheme 87).[17] In addition, high stereoselectivity and yield were observed throughout a variety of dienyne and monoenyne substrates tested.



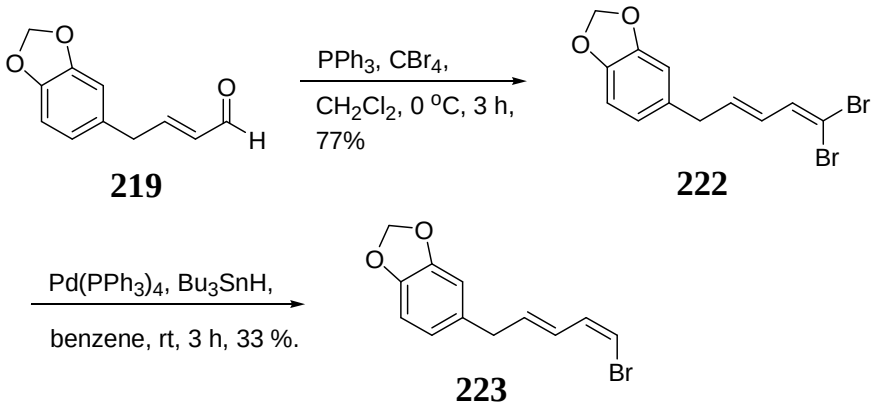
Scheme 87. Rieke zinc reduction to generate pure (Z,Z)-diene **216**.

Our focus, therefore, turned into semihydrogenation of trienyne substrates. (See Scheme 81.) First, we tried to prepare (Z,E)-iododiene **203** from commercially available and cheap **202**. Olefin **202** was cleaved by $NaIO_4$ in the presence of $RuCl_3$ to afford aldehyde **217**.[18] Wittig homologation of **217** with (carboethoxymethylene)-triphenylphosphorane produced ester **218**. Reduction to afford a corresponding alcohol by DIBAL-H and then, oxidation by PCC successfully generated aldehyde **219.** Stork-Zhao olefination of **219** with phosphonium salt **221** gave an inseparable mixture of (Z,E)- **203** and (E,E)-isomer **221** in a ratio of 2 : 1 (Scheme 88).[19]



Scheme 88. Synthetic attempt to prepare (1Z,3E)-iododiene **203**.

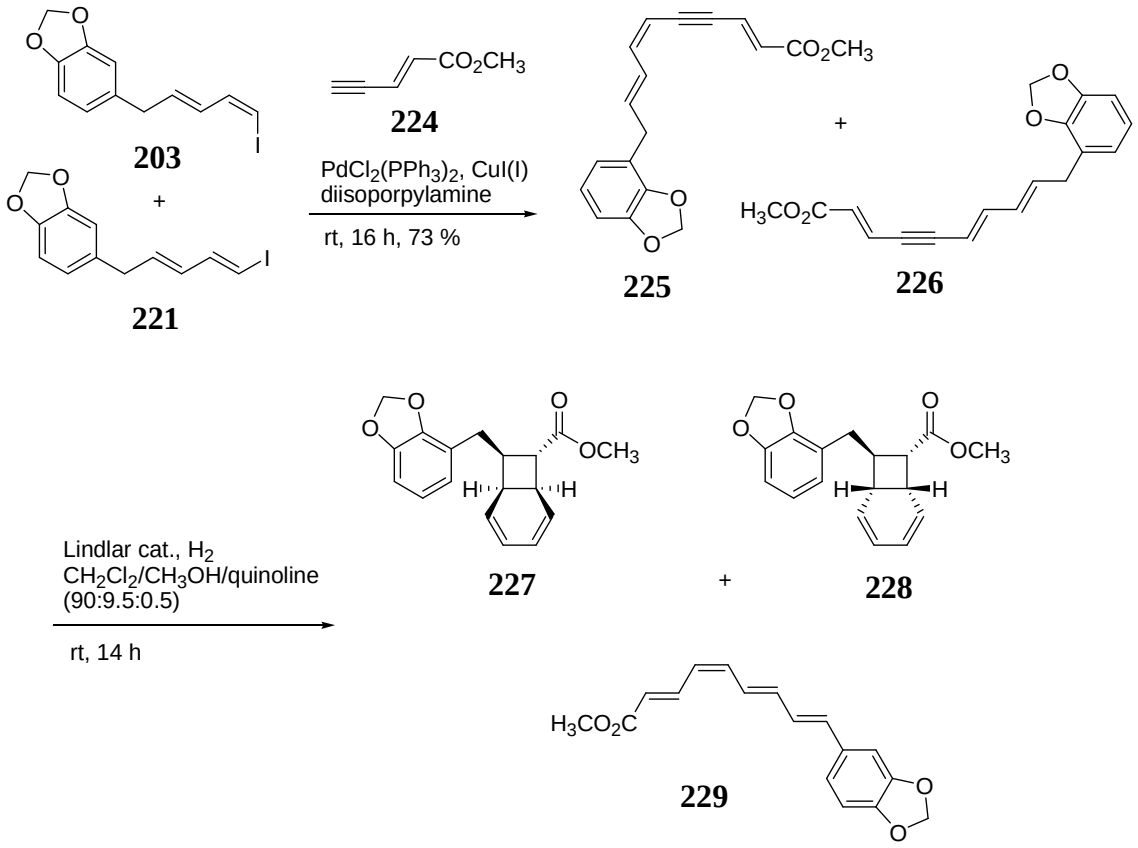
Due to the poor stereoselectivity observed in the Stork-Zhao olefination of **219**, we adopted an alternate method to provide a highly (Z)-selective bromodiene **223**. Aldehyde **219** was converted into dibromide **222** under Corey-Fuchs reaction conditions, and then stereoselectively debrominated by tribuyltin hydride in the presence of palladium to afford exclusively (Z,E)-isomer **223** (Scheme 89).[19]



219 **222** **223**

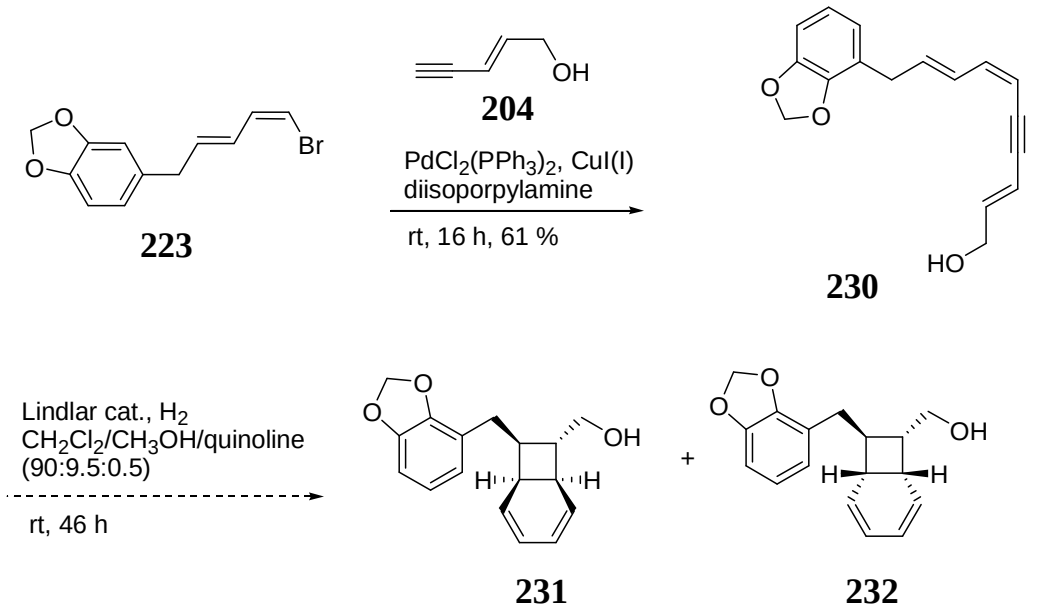
Scheme 89. Preparation of (1Z, 3E)-bromodiene **223**.

Although the desirable iododiene **203** was mixed with corresponding (E,E)-isomer **221,** we thought that the inseparable (E/Z) isomers might be a useful material because the undesired trienyne isomer **226**, which is generated from **221,** will be inactive in the process of 8π, 6π electrocyclization. A mixture of **203** and **221** were coupled with enyne **224** under a common set of Sonogashira coupling conditions. As expected, diastereomeric (Z,E)-trienynes **225** and **226** were produced in a ratio of 2 : 1. Unfortunately, trienynes **225** and **226** were inseparable. Then, mixture of **225** and **226** was reduced by Lindlar catalyst under dark conditions. According to ^{1}H NMR analysis, it was not clear that bicyclo[4.2.0]octadienes **227** and **228** were formed because purification for obtaining a mixture of inseparable **227** and **228** was very challenging. On the other hand, hydrogenation of **226** yielded (E,Z,E,E)-tetraene **229** (Scheme 90).



Scheme 90. Synthetic attempt to synthesize bicyclooctadienes **227** and **228.**

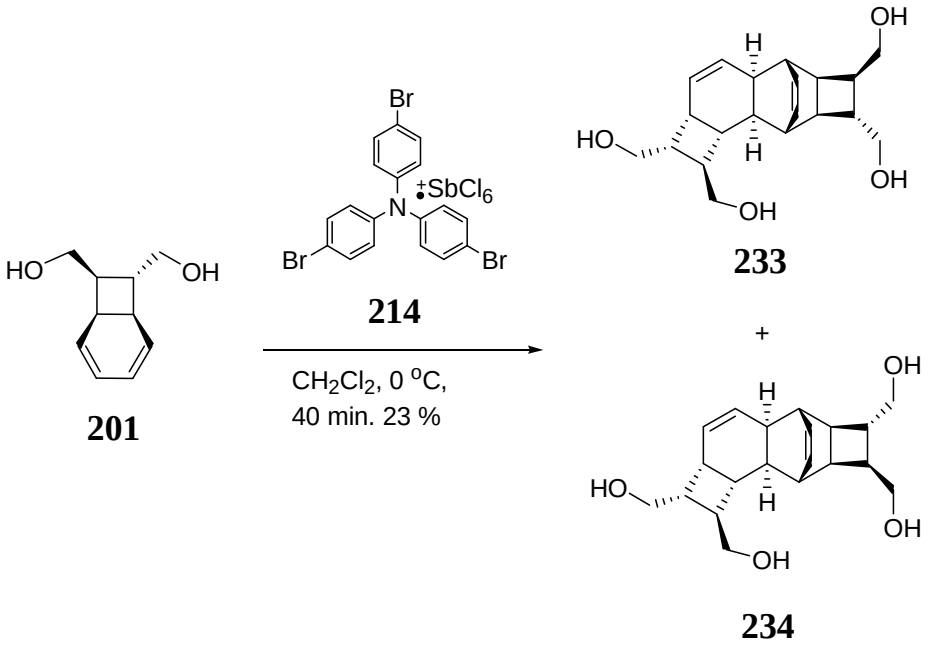
With the preliminary result in hand, we returned to examine the semihydrogenation and 8π, 6π electrocyclization reaction with pure (Z,E)-bromodiene **223**. Under the given Sonagashira coupling conditions, **223** coupled with enyne **204** to afford trienyne **230** in 61 % yield. However, we could not obtain any pure bicyclo[4.2.0]octadienes **231** and **232** in the presence of Lindlar catalyst under the dark conditions (Scheme 91). The result gave us a lot more confidence that alternate semihydrogenation methods such as Rieke zinc method need to be applied to trienyne **230**.



Scheme 91. Synthetic attempt to generate bicyclo[4.2.0]octadienes **231**and **232**.

5.2.2. Cation radical catalyzed Diels-Alder reaction

In spite of relatively low purity, bicyclooctadiene **201** was considered as a potentially informative Diels-Alder substrate because the product mixture will consist of a maximum of two diastereomeric dimers. In addition, we supposed that over- and underreduced forms will be inactive during the cation radical catalyzed Diels-Alder reaction. Bicyclooctadiene **201** was dimerized to provide two diastereomeric pentacyclic tetraols, **233** and **234**, via cation radical catalyzed Diels-Alder reaction mediated by the catalyst **214** (Scheme 92).



Scheme 92. Synthetic attempt to prepare diastereomeric pentacyclic tetraols **233** and **234** via cation radical catalyzed Diels-Alder reaction

Analytical data for inseparable tetraols **233** and **234** on the basis of ^{1}H NMR, ^{13}C NMR, ESI-MS, and IR clearly indicated that two double bonds, which are not conjugated each other and four hydroxymethyl groups exist. In addition, ESI- MS analysis revealed that a m/z 337.2 can be obtained by adding Na^{+} and losing one hydroxyl group from either **233** or **234**. However, we could not confirm diastereomeric ratio between the two expected pentacyclic tetraols because critical protons could not be distinguished by ^{1}H-NMR analysis.

5.3. Conclusion

We have studied the total synthesis of kingianin A. Synthetic efforts toward pre-kingianin A **192** have been based on the construction of bicyclo[4.2.0]octadiene core. Cation radical catalyzed Diels-Alder reaction between two identical bicyclooctadienes **201** afforded diastereomeric pentacyclic tetraols **233** and **234** that possess the same framework of kingianin A. To our knowledge, the cation radical catalyzed Diels-Alder reaction of **201** is considered as a first example for the construction of compounds that contain pentacyclic carbon skeleton. Further investigation will be focused on determining the stereochemistry of the pentacyclic tetraols **233** and **234**. An asymmetric version of 8π, 6π electrocyclization of tetraene substrates will also be investigated to provide enantiomerically pure pre-kingianin A.

5.4. Reference

(1) Litaudon, M.; Leverrier, A.; Dau, M. E. T. H.; Retailleau, P.; Awang, K.; Gueritte, F. *Org Lett* **2010**, *12*, 3638.

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(11) Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J Am Chem Soc* **1982**, *104*, 5558.

(12) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J Am Chem Soc* **1982**, *104*, 5560.

(13) Sharma, P.; Ritson, D. J.; Burnley, J.; Moses, J. E. *Chem Commun* **2011**, *47*, 10605.

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(15) Recently the same experiment was reproduced by our group member, Hee Nam Lim.

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(17) De Voss, J. J.; Matovic, N. J.; Hayes, P. Y.; Penman, K.; Lehmann, R. P. *J Org Chem* **2011**, *76*, 4467.

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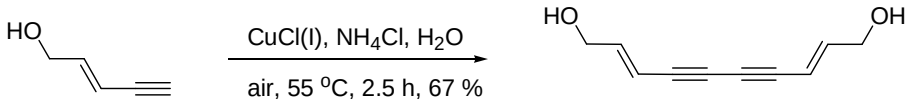
5.5. Experimental section

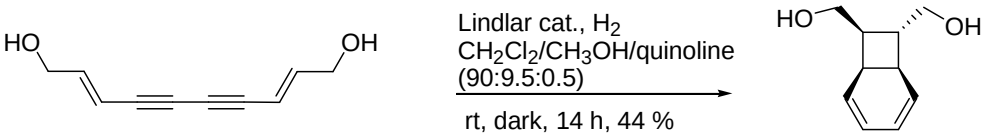


204 **200**

Dienyne 200. To a stirred solution of NH_4Cl (8.2 g, 153 mmol) and CuCl (7.47 g, 76.2 mmol) in H_2O (30 mL) was added pent-2-en-4-yn-1-ol **204** (distilled by Kugelrohr, 1.05 g, 12.8 mmol) over 10 min. at 55 ^oC. Then, air was bubbled through the red solution for 2.5 h. Repeated ethereal extraction afforded 631.7 mg (67 %) of **200** as dark yellow solid. * **200** was further purified by recrystallization (100% boiling H_2O) to provide white needles.

R_f: 0.30 (EtOAc/*n*-hexane, 1/1); ^1H NMR (600 MHz, $CDCl_3$): δ 6.42 (dt, J = 15.6 Hz, 5.0 Hz, 2H), 5.86 (dt, J = 15.6 Hz, 2H), 4.27 (d, J = 2.1 Hz, 1H), 4.25 (d, J = 1.5 Hz, 1H), 1.54 (bs, 2H).

* Spectroscopic properties were in agreement with literature values.[9]

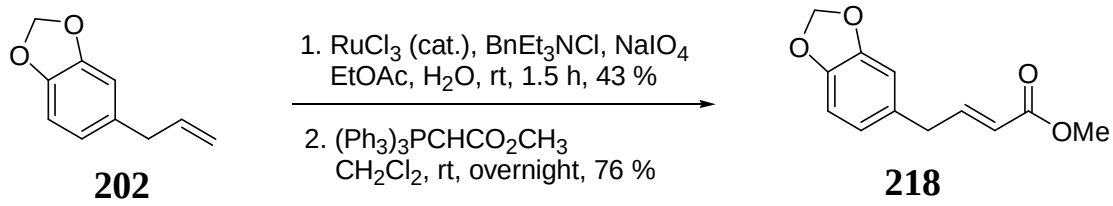


200 **201**

Bicyclooctadiene 201.[10] To a solution of dienyne **200** (137 mg, 0.84 mmol) in CH_2Cl_2/CH_3OH/quinoline (90:9.5:0.5) was added Lindlar catalyst (38 mg) in one portion at rt under Ar. H_2 was bubbled for 5 min into the reaction mixture. Then it was stirred 14 h under H_2. The reaction mixture was filtered through a Celite® and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane:CH_3OH, 7.5:7.5:0.5) to provide 61 mg (44 %) of **201** and an inseparable mixture of under- and over-reduced products as colorless viscous oil.

[9] Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E.; Uenishi, J. *J Am Chem Soc* **1982**, *104*, 5555.
[10] Although compound **196** is known, we could not obtain the spectroscopic properties.

R_f: 0.37 (EtOAc:*n*-hexane:CH_3OH, 7.5/7.5/0.5); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.85 (m, 2H), 5.65 (m, 2H), 3.75 (m, 2H), 3.64 (m, 4H), 3.43 (td, J = 9.9 Hz, 4.2 Hz, 2H), 2.44 (bs, 4H), 2.26 (m, 4H), 2.00-2.17 (m, 6H), 1.39-1.61 (m, 6H).



202 **218**

Ester 218. To a solution of safrole **202** (6.0 g, 37 mmol), $RuCl_3$(III) hydrate (42 mg, 0.20 mmol), and benzyltriethyl- ammonium chloride, (BTEACl, 0.42 g, 1.85 mmol) in EtOAc (70 mL), $NaIO_4$ (39.1 g, 185 mmol) in H_2O (410 mL) was added slowly for 1 h at rt. After stirring for further 1 h, EtOAc (200 mL) was poured into the resulting solution. The organic layer was separated, washed with H_2O, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc:*n*-hexane, 1:20) to provide 2.66 g (44 %) of **217** as colorless oil. * 2.60 g of safrole was recovered from the column chromatography.

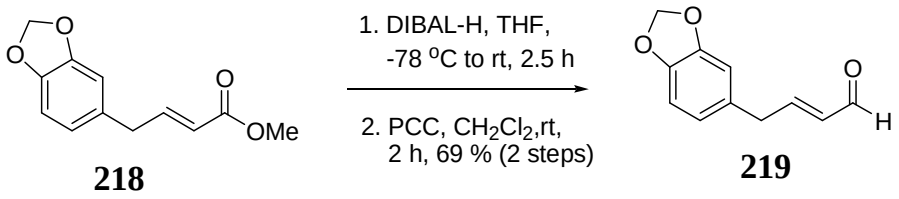
R_f: 0.13 (EtOAc/*n*-hexane, 1/20); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (t, J = 2.2 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.62-6.69 (m, 2H), 5.96 (s, 2H), 3.60 (dd, J = 2.4 Hz, 2H).

To a stirred solution of aldehyde **217** (2.52 g, 15 mmol) in dry CH_2Cl_2 (60 ml) was added (carboethoxymethylene)triphenylphosphorane (7.54 g, 22 mmol) in one portion at rt. The resulting solution was stirred overnight, concentrated under vacuum, redissolved in 10 : 1 petroleum ether/Et_2O solution (v:v). After filtering the precipitated salt, the filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc:*n*-hexane, 1:5) to provide 2.01 g (61 %) of **218** as colorless oil.

R_f: 0.47 (EtOAc/*n*-hexane, 1/5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (dt, J = 15.5 Hz, 6.8 Hz, 1H), 6.77-6.62 (3H, m), 5.94 (2H, s), 5.80 (dt, J = 15.5 Hz, 1.6 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H),3.44 (brd, J = 6.7 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H).

* Spectroscopic properties were in agreement with literature values.[11]

[11] Sharma, P.; Ritson, D. J.; Burnley, J.; Moses, J. E. *Chem Commun* **2011**, *47*, 10605.

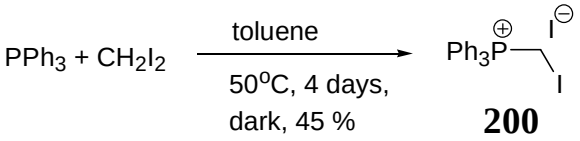


218 **219**

Aldehyde 219. To a stirred solution of ester **218** (1.25 g, 5.68 mmol) in dry THF (30 ml) at -78 °C, DIBAL-H (15 mL of a 1.0 M solution in toluene, 15.0 mmol) was added dropwise over 20 min. The resulting solution was stirred for 1 h at -78 °C, and then for 1 h at -10 °C, before quenching by the cautious addition of 1 M HCl (15 ml). The resulting solution was stirred at rt for 10 minutes until 2 clear phases were formed, then extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to provide 1.09 g (100 %) of crude product as colorless oil, which was used without further purification for the next step. To a suspension of PCC (1.52 g, 7.1 mmol) in dry CH_2Cl_2 (25 mL) was added a solution of (1.09 g, 5.68 mmol) in dry CH_2Cl_2 (15 mL) in one portion at rt. After 2 h, Et_2O (60 mL) was added, then the resulting solution was filtered through Celite, washed thoroughly with fresh Et_2O, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc:*n*-hexane, 1:5) to provide 750 mg (69 % for the 2 steps) of **219** as pale yellow oil.

R_f: 0.21 (EtOAc/*n*-hexane, 1/4); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.50 (d, J = 7.6 Hz, 1H), 6.80 (dt, J = 13.2 Hz, 6.6 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.59-6.63 (m, 2H), 6.06 (ddt, J = 13.2 Hz, 6.4 Hz, 1.2 Hz, 1H), 5.92 (s, 2H), 3.53 (dd, J = 4.0 Hz, 1.4 Hz, 2H).

* Spectroscopic properties were in agreement with literature values.[12]



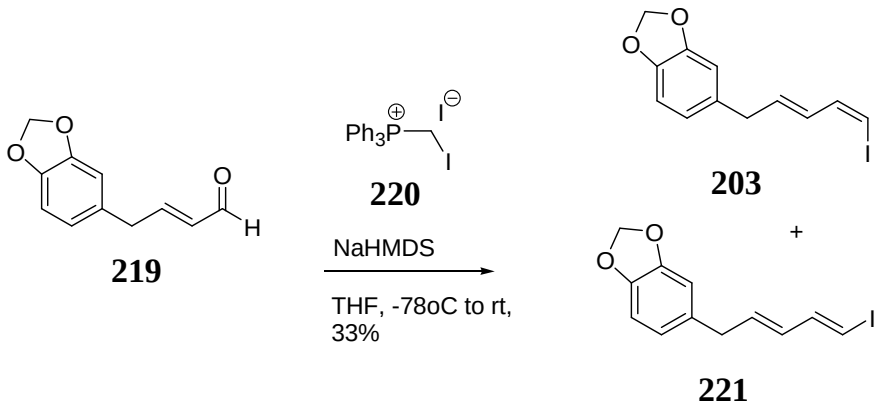
200

Phosphonium salt 200[13] A solution of triphenylphosphine, PPh_3 (50 g, 0.19 mol) and diiodomethane, CH_2I_2 (20 mL, 0.25 mmol) in anhydrous toluene (250 mL) was heated to 50 °C

[12] Sharma, P.; Ritson, D. J.; Burnley, J.; Moses, J. E. *Chem Commun* **2011**, *47*, 10605.

[13] Ian Paterson,. *S. B. Jennifer Kan and Lisa J. Gibson. Org. Lett.*, **2010**, 12, 3724.

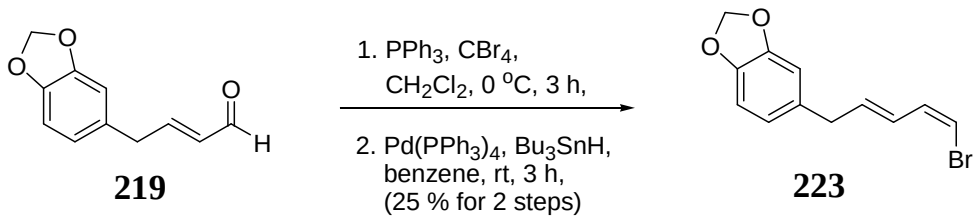
and stirred for 4 days in the absence of light. The resulting solution was allowed to cool to rt, filtered, and washed with anhydrous toluene and Et_2O to provide 23.6 g (45 %) of as white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75-7.94 (m, 15H), 5.08 (d, J = 9.0 Hz, 2H).



219 **220** **203** **221**

(Z/E)-Iododienes 203 and 221. To a stirred suspension of (iodomethyl) triphenylphosphonium iodide **220** (0.36 g, 6.6 mmol) NaHMDS (350 μL of a 2.0 M solution in THF, 7.0 mmol) was added dropwise at rt. After 5 min. the red solution was cooled to -78 ^{o}C. Then a solution of aldehyde **219** (65.1 mg, 0.34 mmol) in dry THF (2.0 mL) was added at such a rate as to keep the internal temperature below -70 ^{o}C. The mixture was stirred at -78 ^{o}C for 15 min, allowed to warm to rt and then stirred for further 2 h. Saturated aqueous NH_4Cl (5 mL) was added, extracted with Et_2O (3 × 10 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc:*n*-hexane, 1:20) to provide 35.2 mg (33 %) of an inseparable mixture of **203** and **221** in a ratio of 2 : 1 (Z : E) as viscous pale yellow oil.

R_f: 0.65 (EtOAc/*n*-hexane, 1/1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.01 (dd, J = 12.3 Hz, 10.2 Hz, 0.33H), 6.68-6.75 (m, 3H), 6.64 (d, J = 5.4 Hz, 0.67H), 6.60 (d, J = 8.4 Hz, 0.33H), 6.29 (dd, J = 13.2 Hz, 10.2 Hz, 0.67H), 6.23 (d, J = 14.4 Hz, 0.33H), 6.17 (d, J = 7.2 Hz, 0.67H), 6.06 (dt, J = 7.2 Hz, 0.67H), 5.92 (s, 2H), 5.84 (d, J = 7.2 Hz, 0.33H), 3.28 (d, J = 6.6 Hz, 2H).



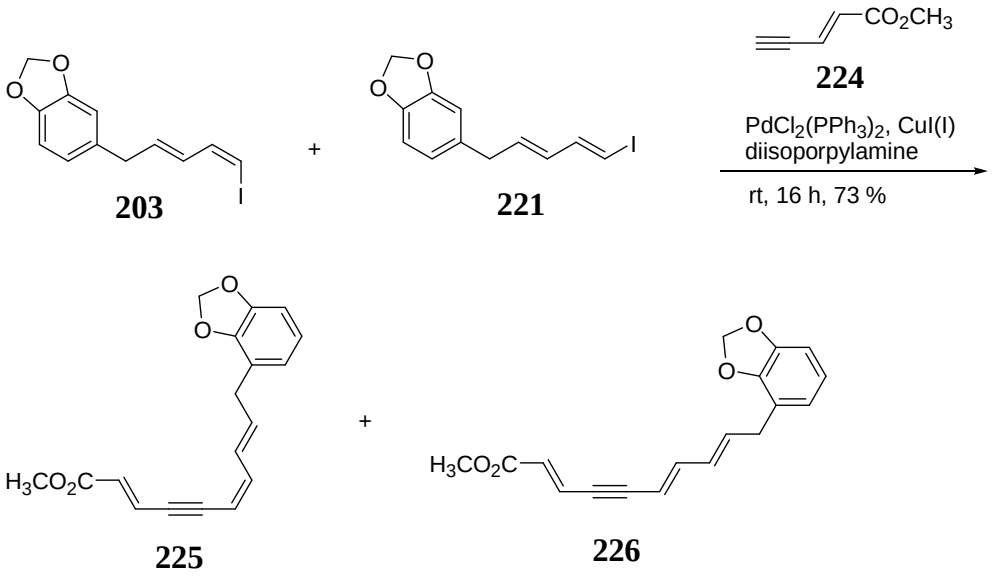
219 **223**

(Z,E)-bromodiene 223. To a stirred solution of CBr_4 (0.72 g, 2.16 mmol) in dry CH_2Cl_2 (10 mL), PPh_3 (1.13 g, 4.33 mmol) was added portionwise over 1 min. at 0 ^oC. After 5 min, a solution of aldehyde **219** (374 mg, 1.97mmol) in dry CH_2Cl_2 (10 mL) was added dropwise over 5min. The resulting solution was stirred at 0 ^oC for 3 h, then washed with H_2O (10 mL), and saturated aqueous $Na_2S_2O_3$ (10 mL), and then dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc:*n*-hexane, 1:15) to provide 522 mg (77 %) of dibromide **222** as viscous dark yellow oil.

To a stirred solution of **222** (522 mg, 1.52 mmol) and $Pd(PPh_3)_4$ (112 mg, 0.1 mmol) in dry benzene (11.0 mL) was added dropwise Bu_3SnH (520 mg, 1.78 mmol) over 3 min. at rt. After 3 h, H_2O (15 mL) was added. The resulting solution was extracted with *n*-hexane, washed with saturated aqueous $Na_2S_2O_3$, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc:*n*-hexane, 1:20) to provide 133.5 mg (33 %) of **223** as colorless oil.

R_f: 0.40 (EtOAc/*n*-hexane, 1/10); ^1H NMR (300 MHz, $CDCl_3$): δ 6.75 (d, J = 8.1 Hz, 1H), 6.62-6.68 (m, 2H), 6.60 (dd, J = 10.2 Hz, 7.2 Hz, 1H), 6.45 (m, 1H), 6.09 (brd, J = 7.2 Hz, 1H), 6.02 (dt, J = 15.0 Hz, 7.1 Hz, 1H), 5.93 (s, 2H), 3.38 (brd, J = 6.9 Hz, 2H).

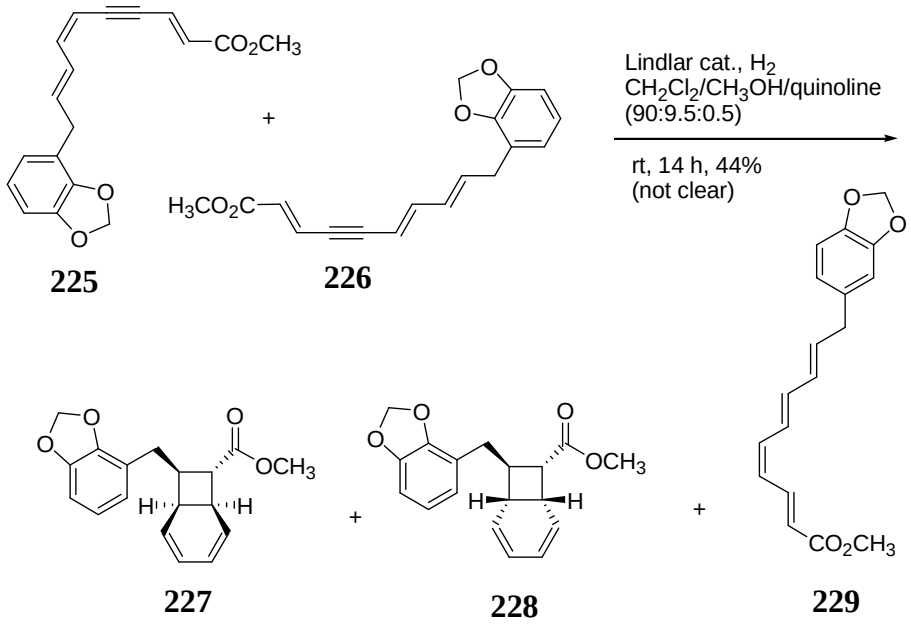
* Spectroscopic properties were in agreement with literature values.[14]



[14] Sharma, P.; Ritson, D. J.; Burnley, J.; Moses, J. E. *Chem Commun* **2011**, *47*, 10605.

Trienyne 225 and 226. To a solution of enyne **224** (7.0 mg, 0.064 mmol) and the mixture of iododienes **203** and **221** (12.2 mg, 0.039 mmol) in diisopropylamine (0.5 mL) were added $Pd(PPh_3)_4$ (5.0 mg, 0.004 mmol) and Cu(I) (trace) at rt under Ar. After stirring for 16 h, the resulting mixture was poured into saturated NH_4Cl and extracted 3 times with EtOAc. The combined organic solution was washed with H_2O, and brine, and dried over $MgSO_4$, and then concentrated under vacuum. The dark brown solid was purified by preparative chromatography (EtOAc:*n*-hexane, 1:1) to provide 8.2 mg (73 %) of an inseparable mixture of **225** and **226** in a ratio of 2 : 1 (Z : E) as a yellow viscous oil.

R_f: 0.47 (EtOAc/*n*-hexane, 1/9); ^{1}H NMR (600 MHz, $CDCl_3$): 6.95 (dd, *J* = 15.6 Hz, 2.7 Hz, 0.67H), 6.89 (dd, *J* = 15.6 Hz, 2.7 Hz, 0.33H),6.75 (d, *J* = 7.8 Hz, 0.67H), 6.74 (d, *J* = 7.8 Hz, 0.33H), 6.58-6.68 (m, 3H), 6.48 (t, *J* = 10.8 Hz, 0.67H), 6.21 (d, *J* = 15.6 Hz, 0.67H), 6.14 (dd, *J* = 12.3 Hz, 10.2 Hz, 0.33H), 6.04 (m, 0.67H), 5.98 (m, 0.33H), 5.93 (s, 2H), 5.68 (dd, *J* = 15.3 Hz, 2.1 Hz, 0.33H),5.53 (dd, *J* = 10.2 Hz, 2.1 Hz, 0.67H), 3.78 (s, 2H), 3. 77 (s, 1H), 3.42 (d, *J* = 6.6 Hz, 1.34H), 3.38 (d, *J* = 7.2 Hz, 0.66H).



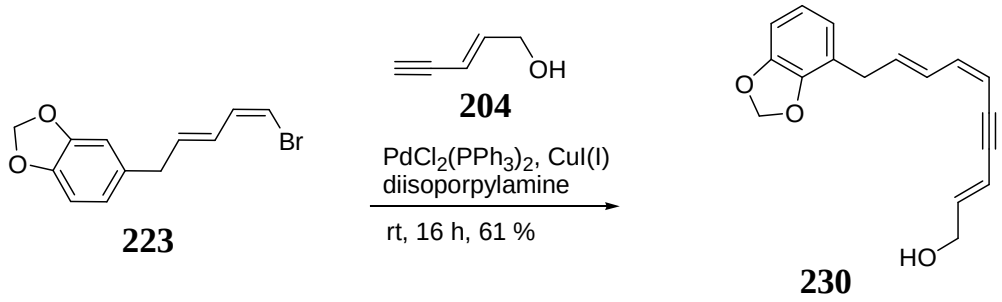
225 **226** **227** **228** **229**

Bicyclooctadienes 227 and 228 To a solution of 2 : 1 mxiture of trienynes **225** and **226** (8.2 mg, 0.023 mmol) in CH_2Cl_2/CH_3OH/quinoline (90:9.5:0.5, 1.2 mL) was added Lindlar catalyst (4.1 mg) in one portion at rt under Ar. The reaction mixtrure was bubbled by H_2 for 5 min, and then stirred 20 h under H_2 condition. The reaction mixture was filtered on a Celite® and the

filtrate was concentrated under vacuum. The residue was purified by preparative chromatography (EtOAc:*n*-hexane, 1 : 3) to provide 3.6 mg (44 %) of an inseparable **227** and **228** and 1.9 mg (23 %) of **229**.

For impure mixture of **227** and **228:** R_f: 0.60 (EtOAc/*n*-hexane, 1/3); ^{1}H NMR (600 MHz, $CDCl_3$): 6.61-6.74 (m, 3H), 6.18-6.01 (m, 2H), 5.99-5.86 (m, 4H) 5.78 (dd, J = 5.4 Hz, 1H), 5.63 (td, *J* = 15.0 Hz, 3.6 Hz, 1H), 3.76 (S, 3H), 3.40 (dd, *J* = 18.6 Hz, 7.2 Hz, 2H), 3.17-2.56 (m, 3H), 2.20 (m, 1H).

For **229**: R_f: 0.70 (EtOAc/*n*-hexane, 1/3); ^{1}H NMR (600 MHz, $CDCl_3$): 7.76 (dd, *J* = 13.2 Hz 1.4 Hz, 1H), 6.61-6.74 (m, 4H), 6.29 (dd, *J* = 11.1 Hz 10.8 Hz, 1H), 6.09 (dd, *J* = 10.8 Hz 10.2 Hz, 1H), 5.99 (dd, *J* = 11.1 Hz 10.8, 1H), 5.85-5.94 (m, 2H), 5.92 (s, 2H), 5.73 (d, *J* = 7.2 Hz, 1H), 3.76 (s, 3H), 3.73 (d, *J* = 11.4 Hz, 2H).

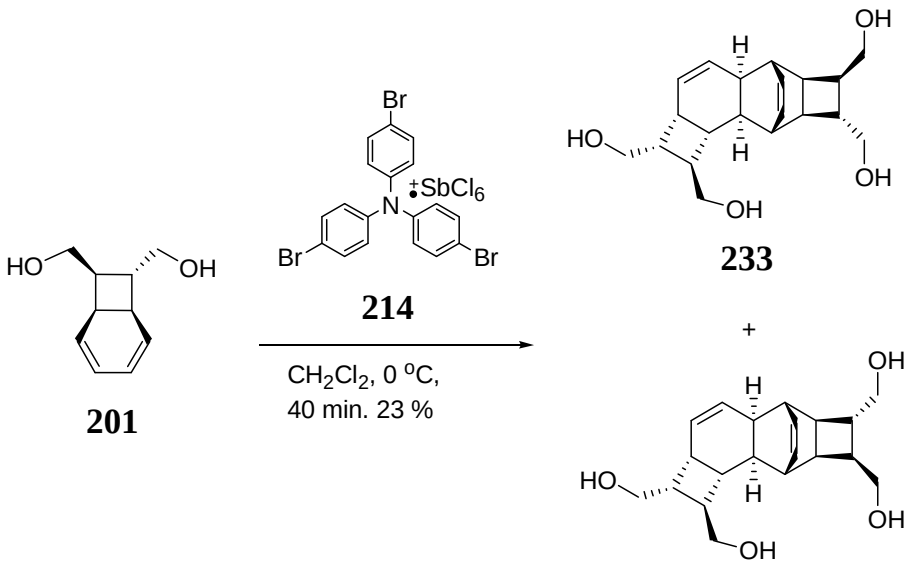


Trienyne 230[15] To a solution of pent-2-en-4-yn-1-ol **204** (7.1 mg, 0.086 mmol), which had been distilled by Kugelrohr, and bromodiene **223** (11.5 mg, 0.043 mmol) in diisopropylamine (100 μL) and ethyl acetate (0.8 mL) were added $PdCl_2(PPh_3)_2$ (1.5 mg, 0.002 mmol) and Cu(I) (trace) at rt under Ar. After stirring for 23 h, the resulting mixture was poured into saturated NH_4Cl and extracted 3 times with EtOAc. The combined organic solution was washed with H_2O, and brine, and then dried over $MgSO_4$, and concentrated under vacuum. The dark brown solid was purified by preparative chromatography (EtOAc:*n*-hexane, 1:1) to provide 7.1 mg (61 %) of **230** as colorless solid.

R_f: 0.57 (EtOAc/*n*-hexane, 1/1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.74 (d, *J* = 7.8 Hz, 1H), 6.68 (s, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.61 (dd, *J* = 13.2 Hz, 11.4 Hz, 1H), 6.37 (t, *J* = 4.8 Hz, 1H), 6.25

[15] A. B. Lemay, K. S. Vulic, W. W. Ogilvie, *J. Org. Chem.*, **2006**, *71*, 3615-3618.

(dt, J = 13.2 Hz, 5.4 Hz, 1H), 5.97 (q, *J* = 7.8 Hz, 1H), 5.95 (d, J = 5.4 Hz, 1H), 5.92 (s, 2H), 5.48 (d, *J* = 10.8 Hz, 1H), 4.25 (d, *J* = 4.2 Hz, 2H), 4.25 (d, *J* = 7.2 Hz, 2H).



Pentacyclic tetraols 233 and 234 To a solution of catalyst **214** (3.6 mg, 0.004 mmol) in CH_2Cl_2 (0.4 mL) was added bicyclooctadiene **201** (11.8 mg, 0.071 mmol) in CH_2Cl_2 (0.2 mL) at 0 ^oC under Ar. When complete by TLC, the reaction mixture was allowed to warm to rt and filtered through a Celite®, and the filtrate was concentrated under vacuum. The residue was purified by preparative chromatography (EtOAc:*n*-hexane:CH_3OH, 100:50:5) to provide 5.5 mg (23 %) of inseparable mixture of **233** and **234** as a colorless viscous oil.

R_f: 0.42 (EtOAc:*n*-hexane:CH_3OH, 100:50:5); ^1H NMR (600 MHz, $CDCl_3$): δ 5.94 (m, 0.64H), 5.86 (m, 2.5H), 5.66 (m, 2H), 3.80 (m, 0.86H), 3.67 (m, 5H), 3.46 (dd, *J* = 7.0 Hz, 4.0 Hz, 2H), 3.57 (m, 1H), 3.46 (m, 4H), 2. 76 (br, 1.3H), 2.62 (m, 0.73H), 2.47 (m, 0.73H), 2.40 (m, 1.7H), 2.27 (bs, 13H), 2.07 (m, 10H), 1.88 (m, 3H), 1.69 (m, 2H), 1.56 (m, 2.5H), 1.40 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ131.5, 131.1, 130.2, 129.2, 49.5, 45.4, 36.3, 35.3, 35.1, 34.4, 33.6, 30.0, 25.6, 24.7, 23.9, 23.9. IR: 3343, 3018, 2921. Mass (ESI positive ion mode): 337.2.

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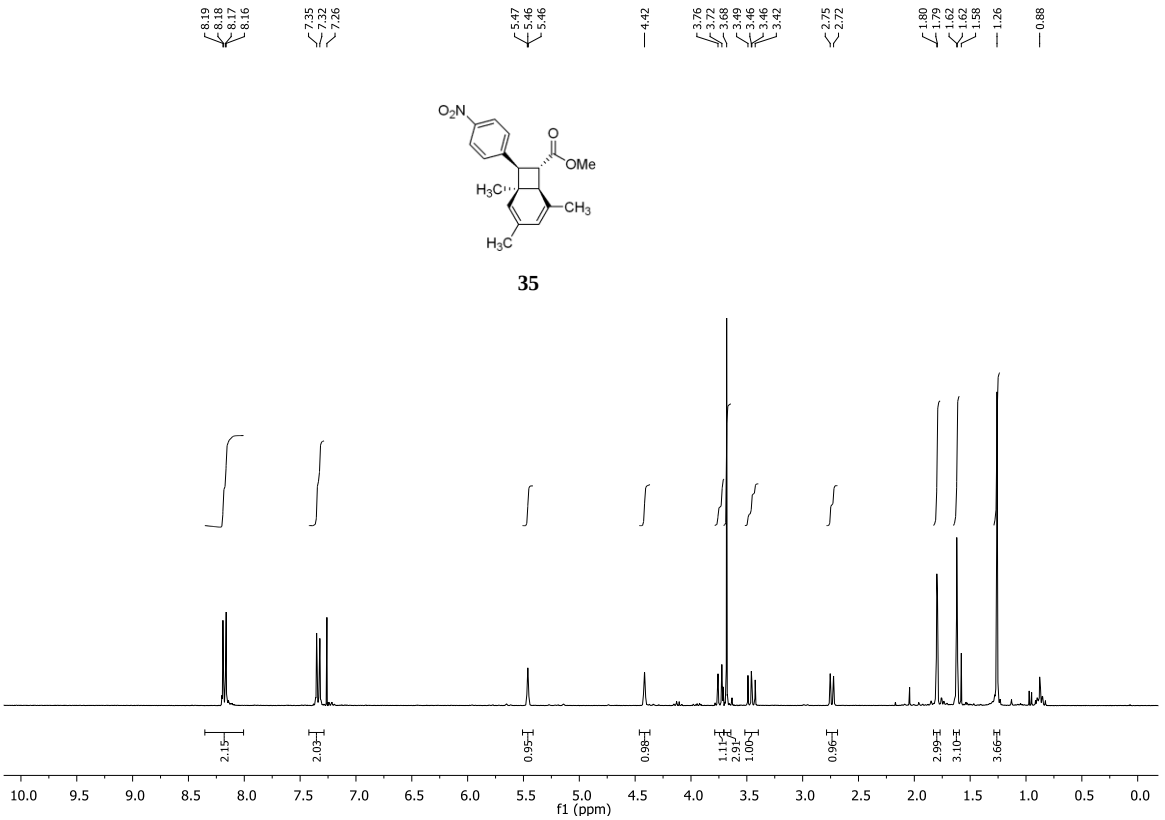
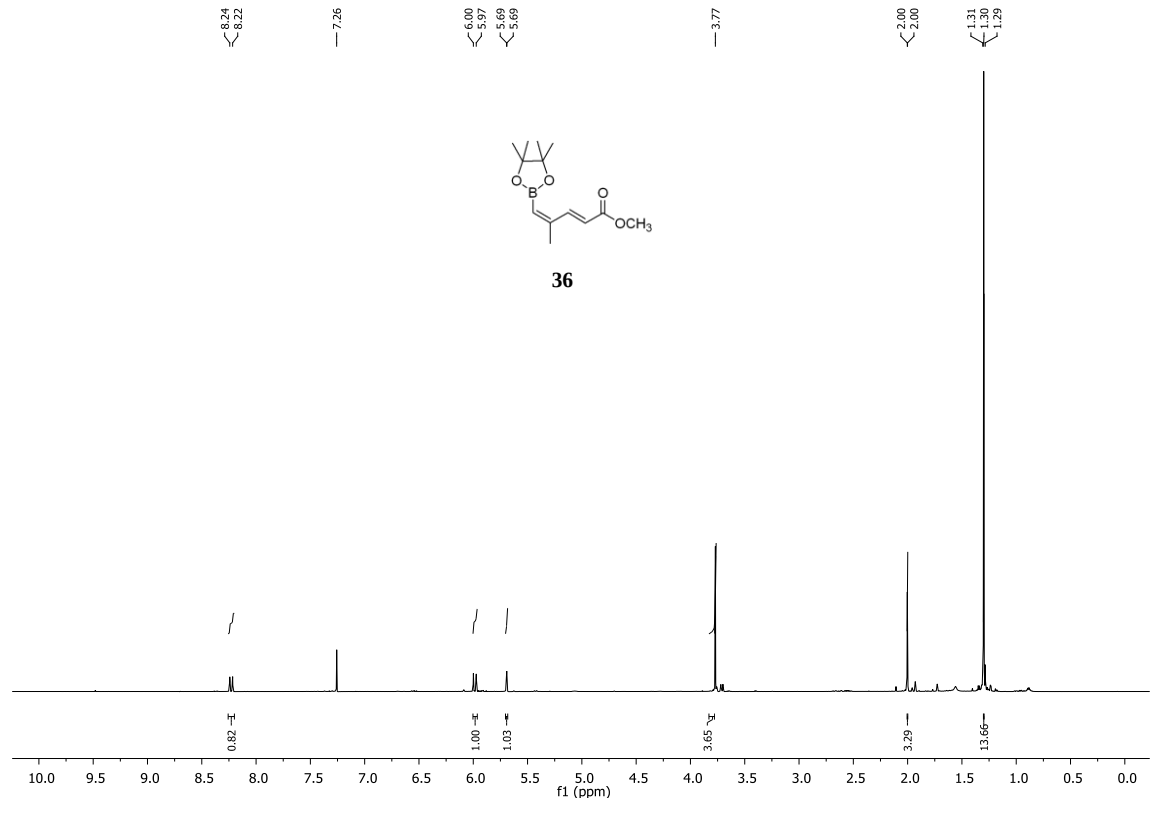
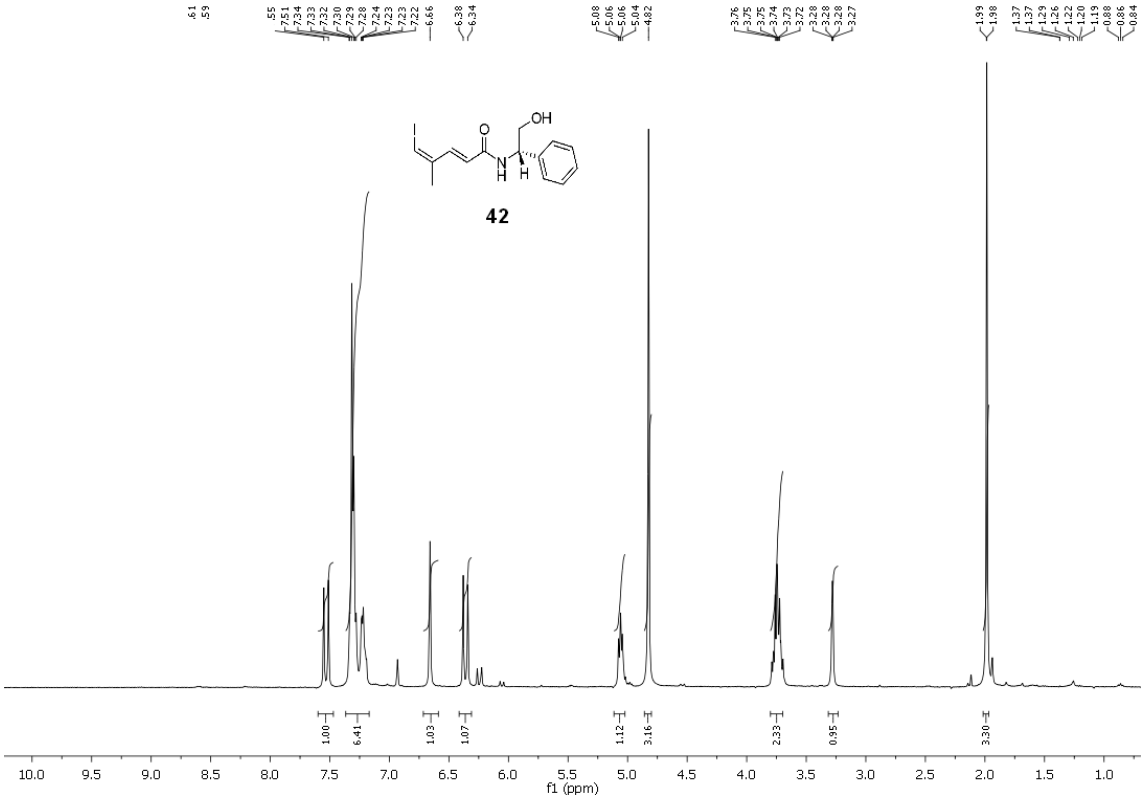
Appendix

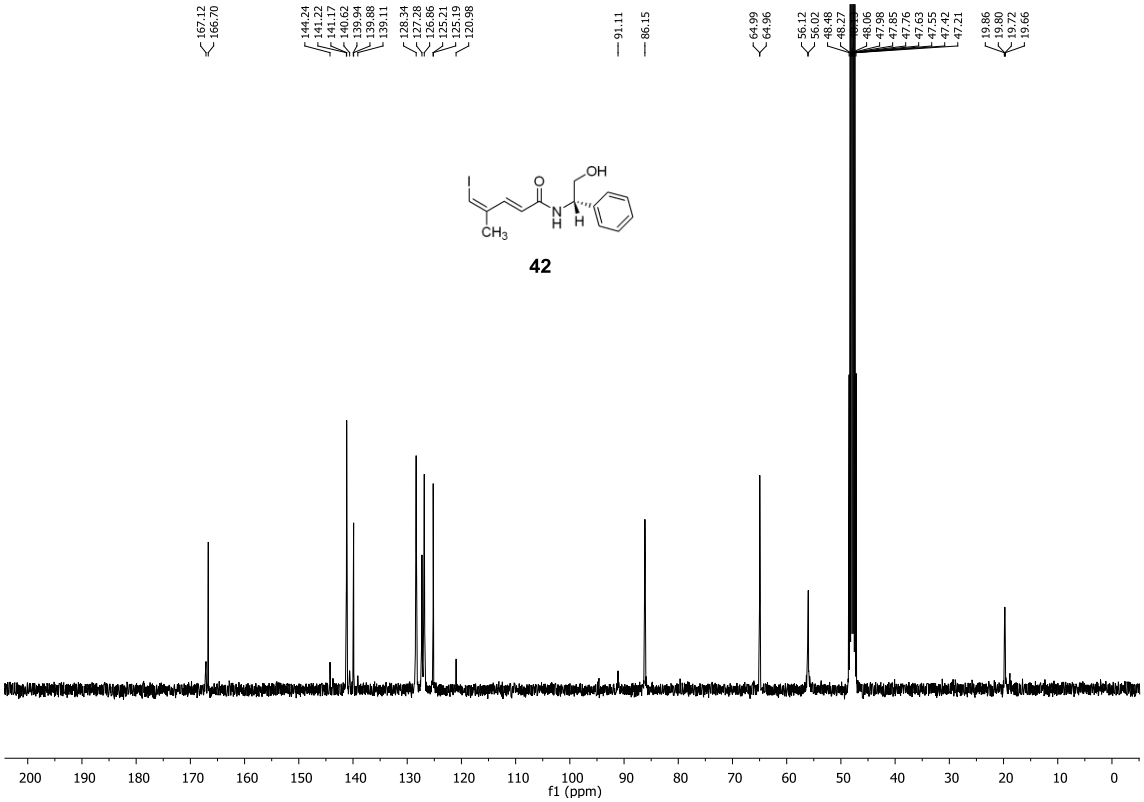

8.19
8.18
8.17
8.16
7.35
7.32
7.26
5.47
5.46
5.46
4.42
3.76
3.72
3.68
3.49
3.46
3.46
3.42
2.75
2.72
1.80
1.79
1.62
1.62
1.58
1.26
0.88
O2N
O
OMe
H3C
CH3
H3C
2.15
2.03
0.95
0.98
1.11
2.91
1.00
0.96
2.99
3.10
3.66
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

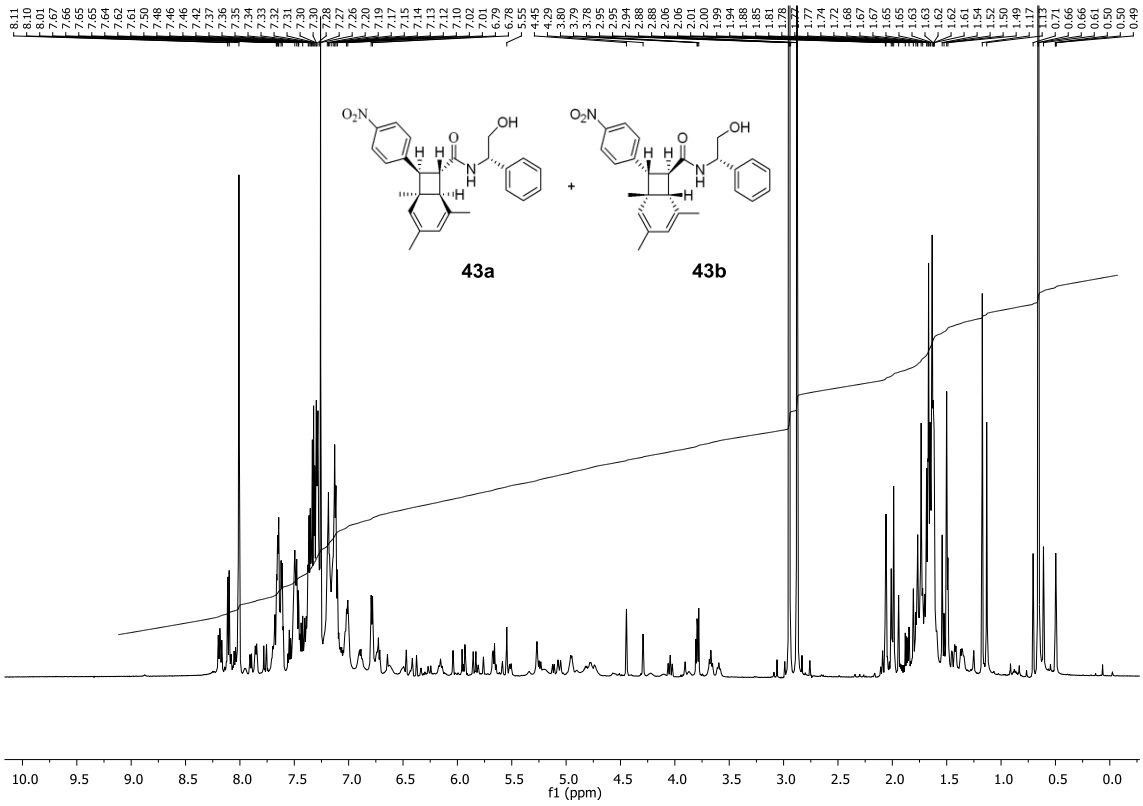
35

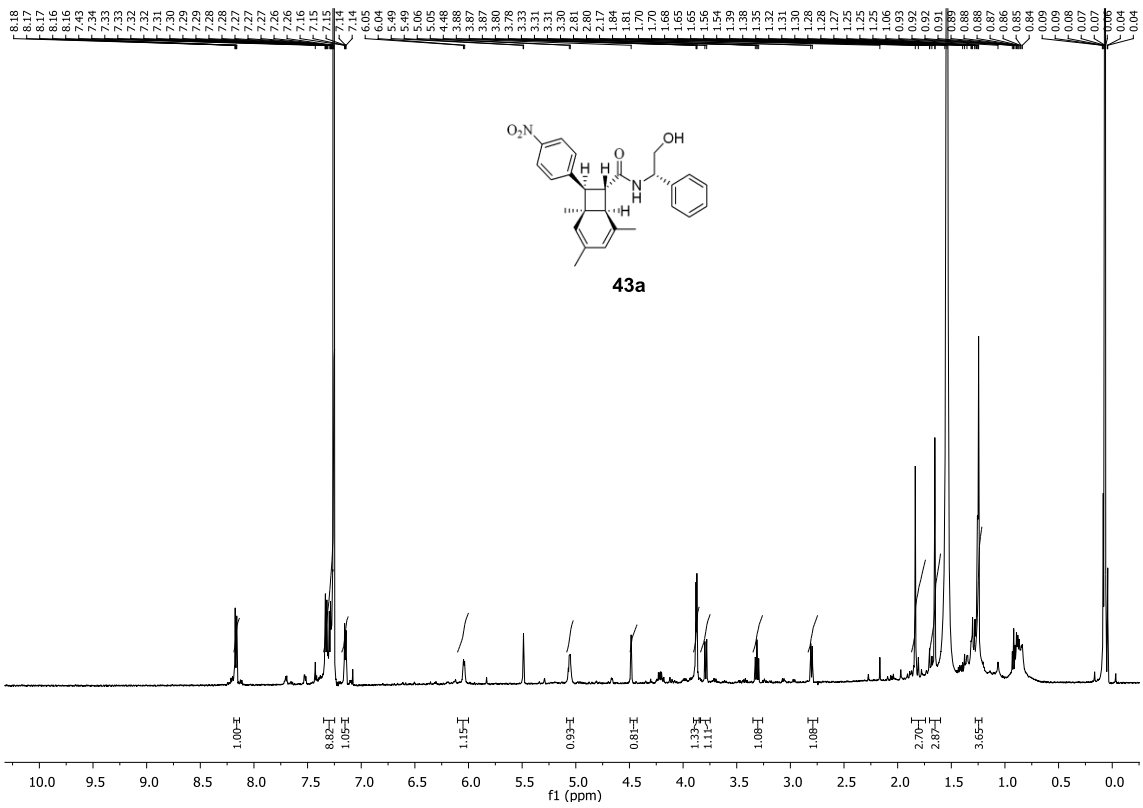

8.24
8.22
7.26
6.00
5.97
5.69
5.69
3.77
2.00
2.00
1.31
1.30
1.29
O
B
O
O
OCH3
0.82
1.00
1.03
3.65
3.29
13.66
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

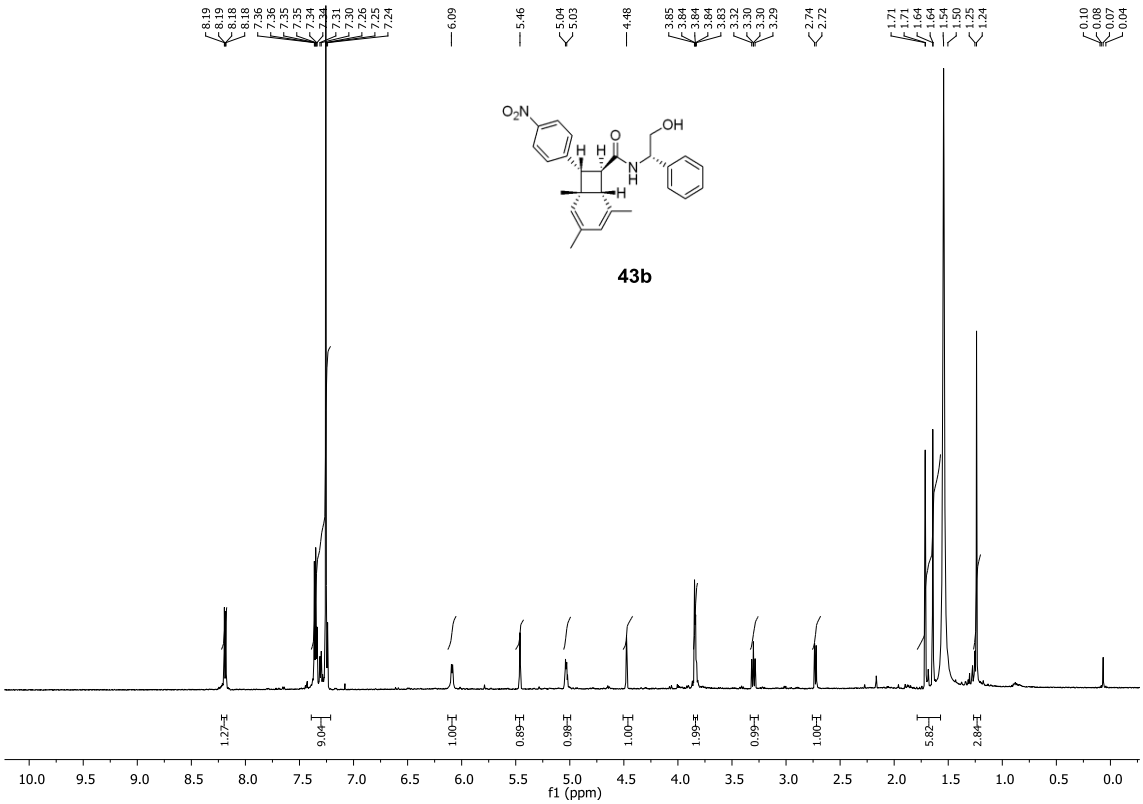
36


OH
O
N
H
I
42
f1 (ppm)

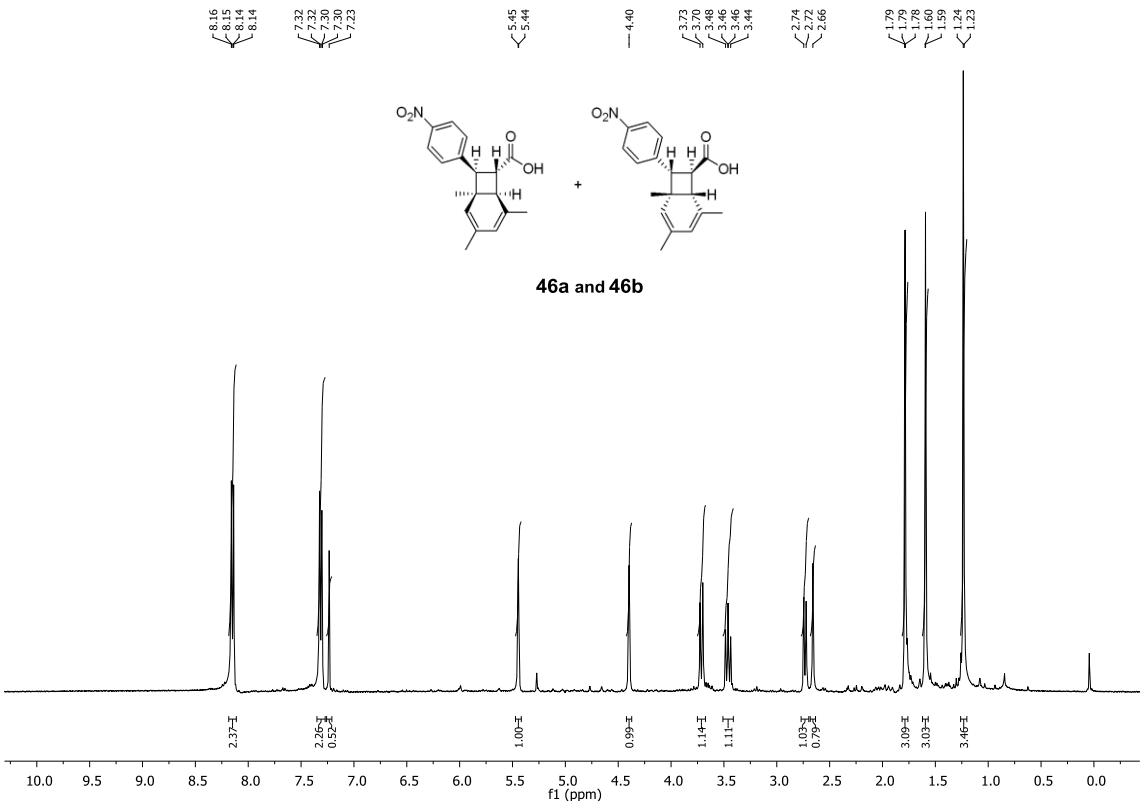

OH
O
N
H
I
CH3
42
f1 (ppm)


43a
43b
f1 (ppm)

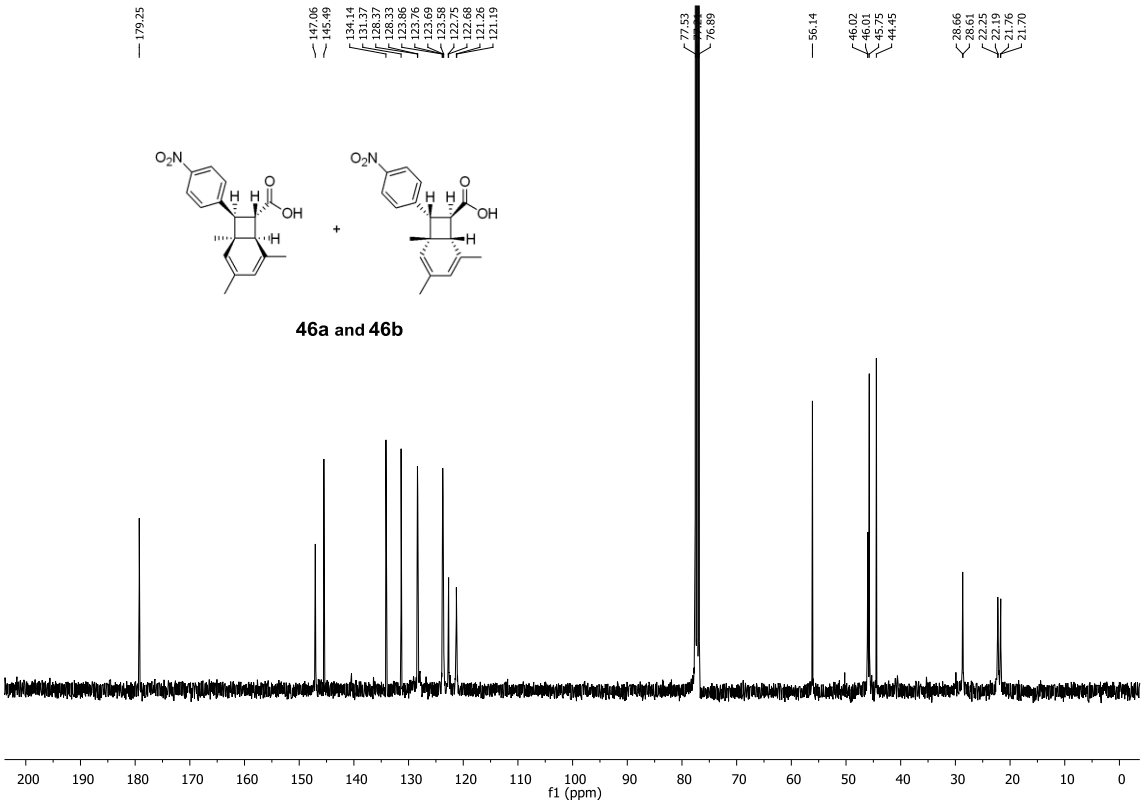

43a
f1 (ppm)



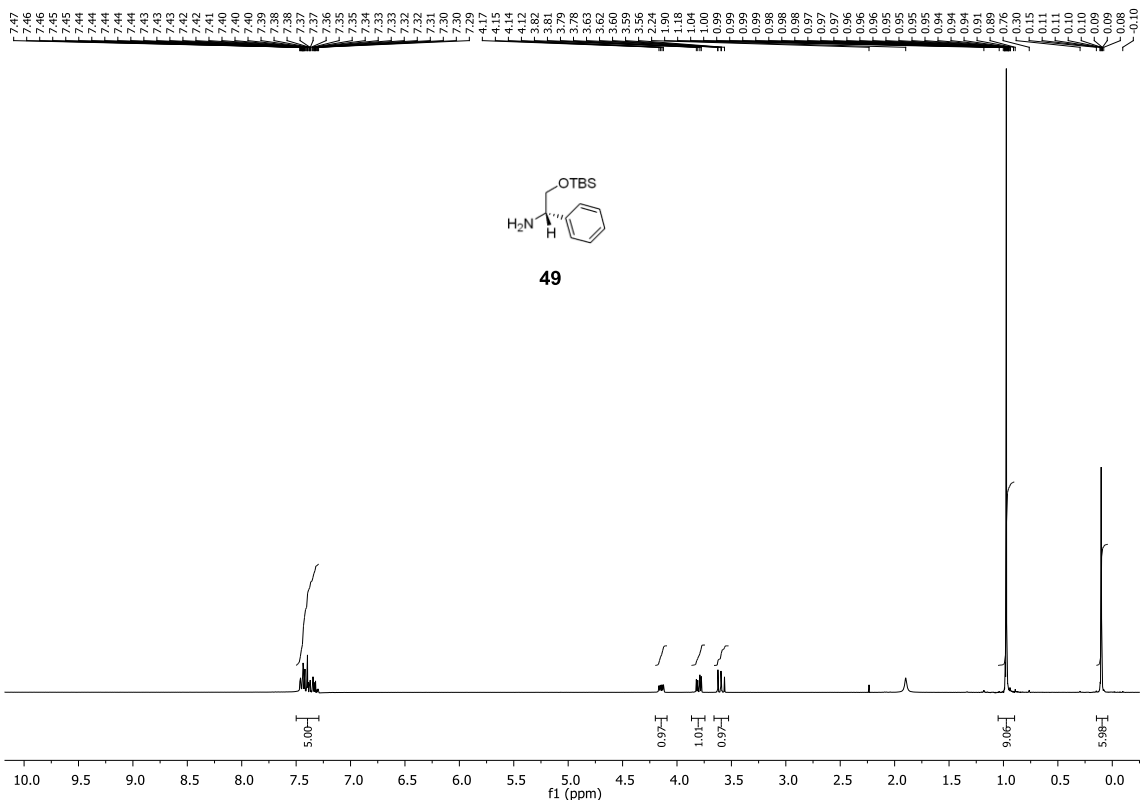
43b



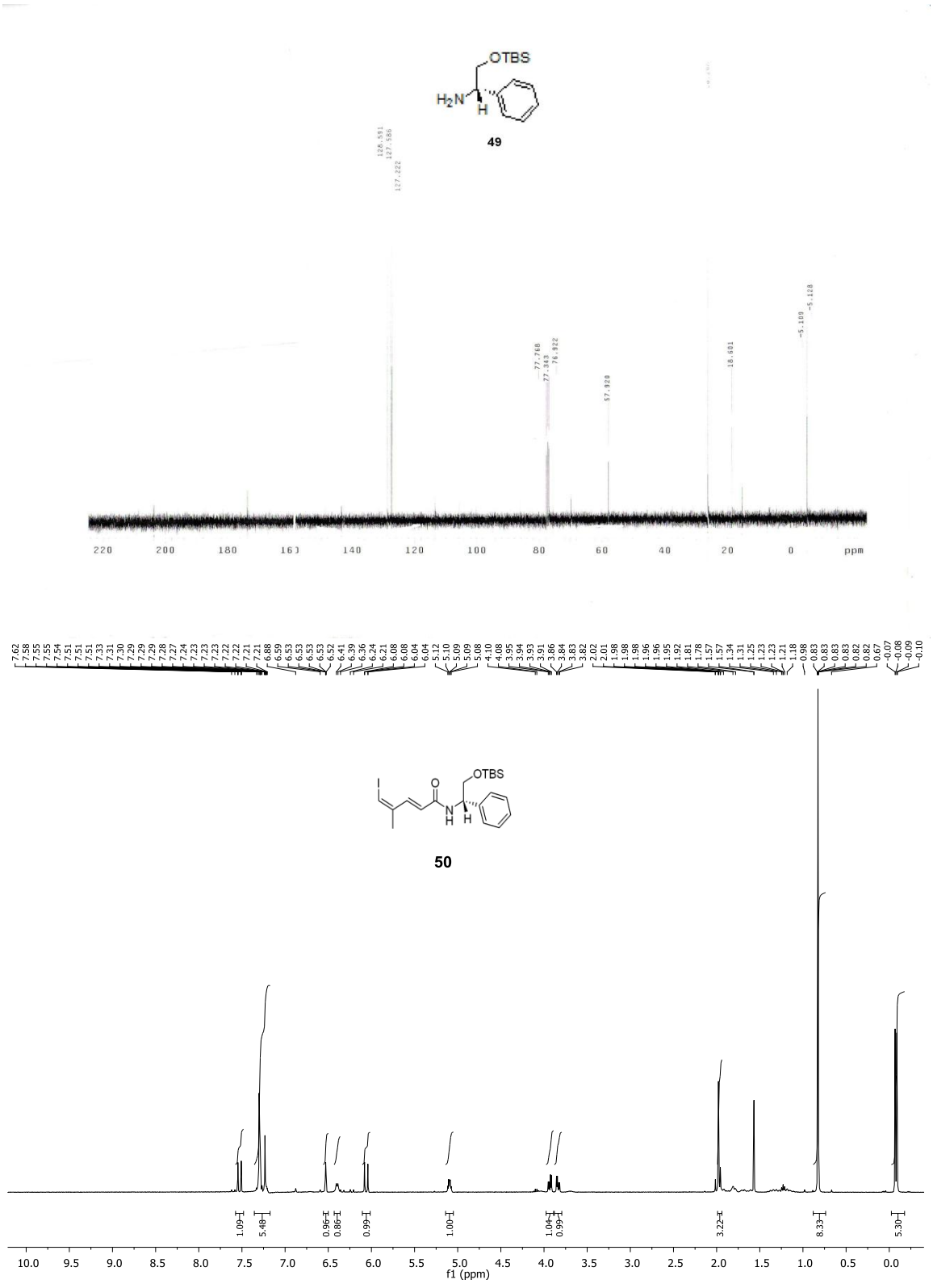
46a and 46b

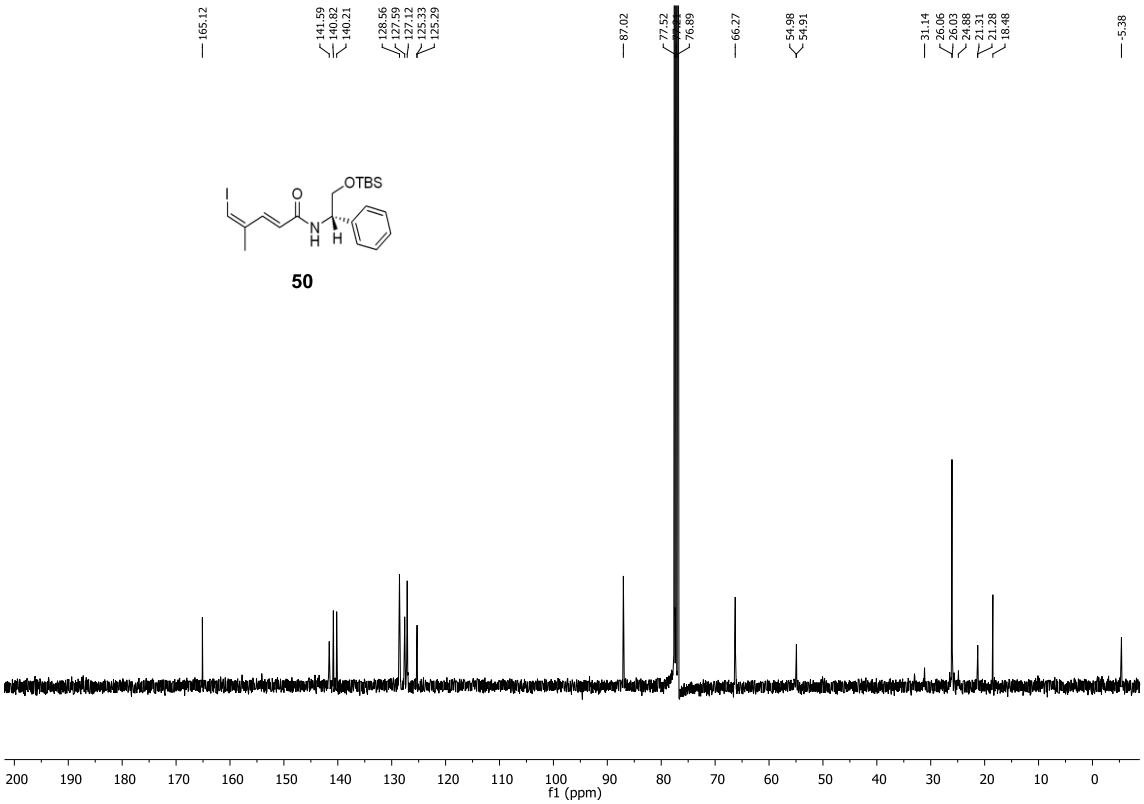


46a and 46b

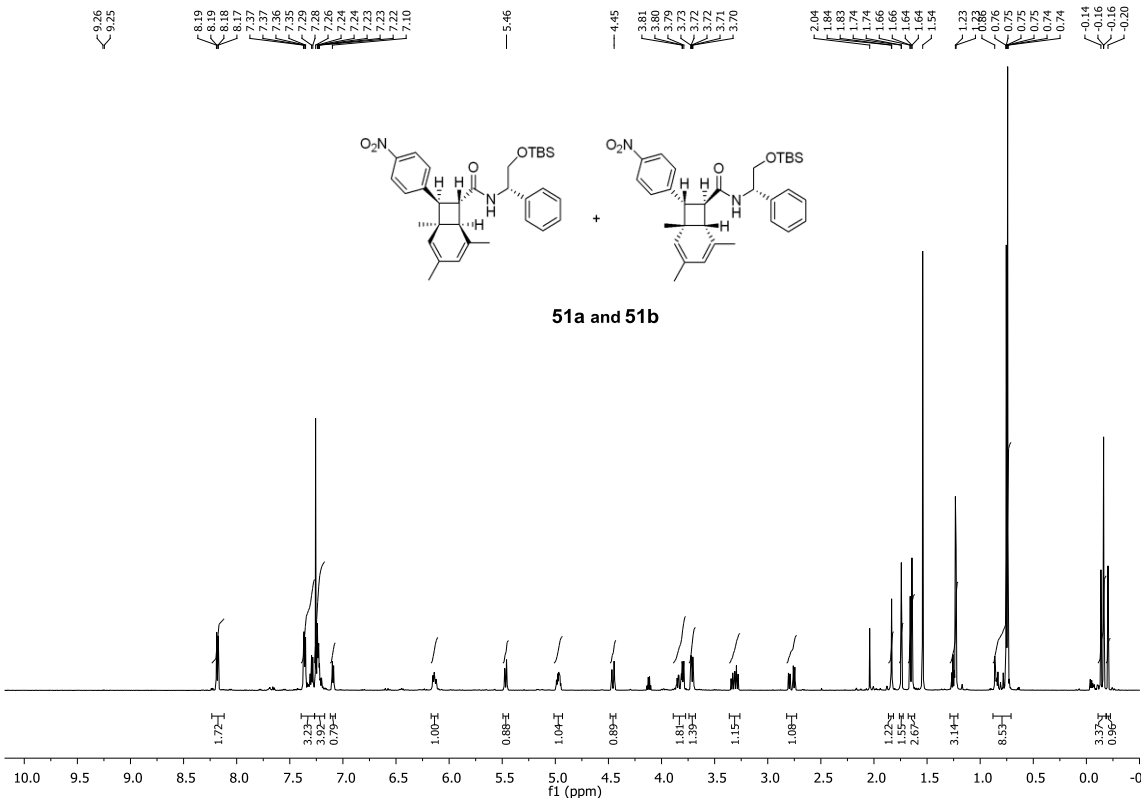


49

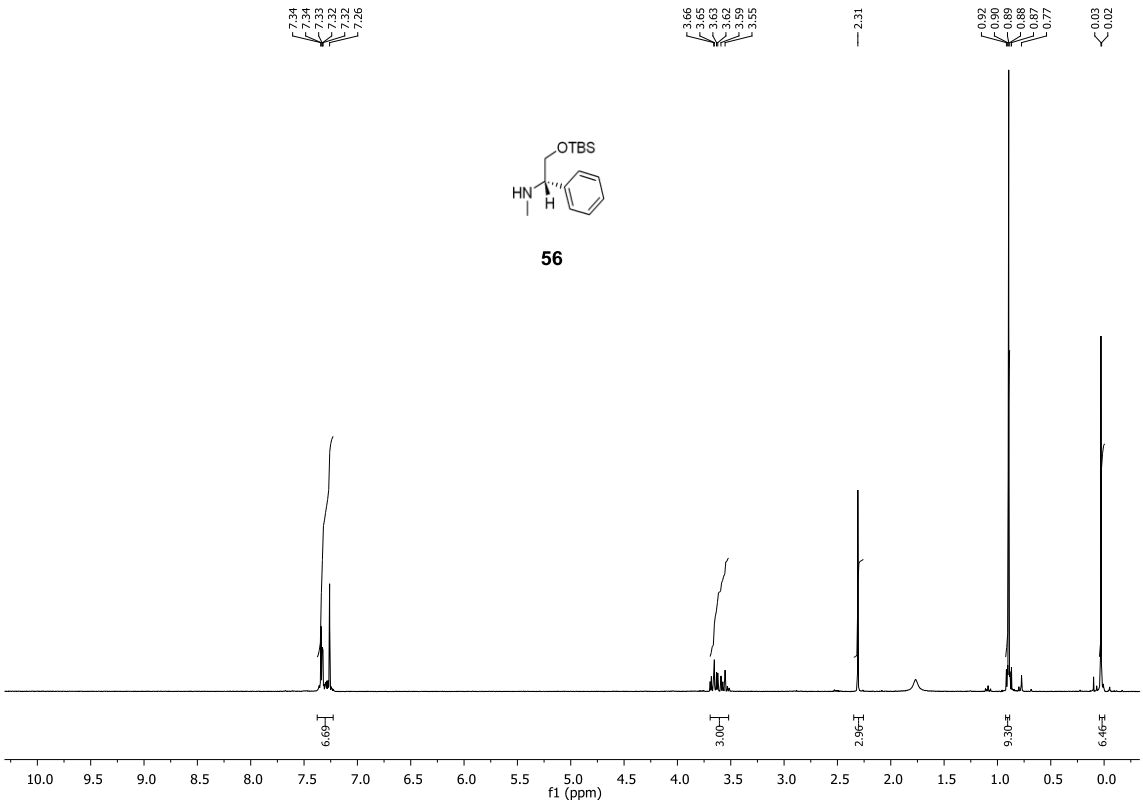

OTBS
H2N
H
49
50
f1 (ppm)



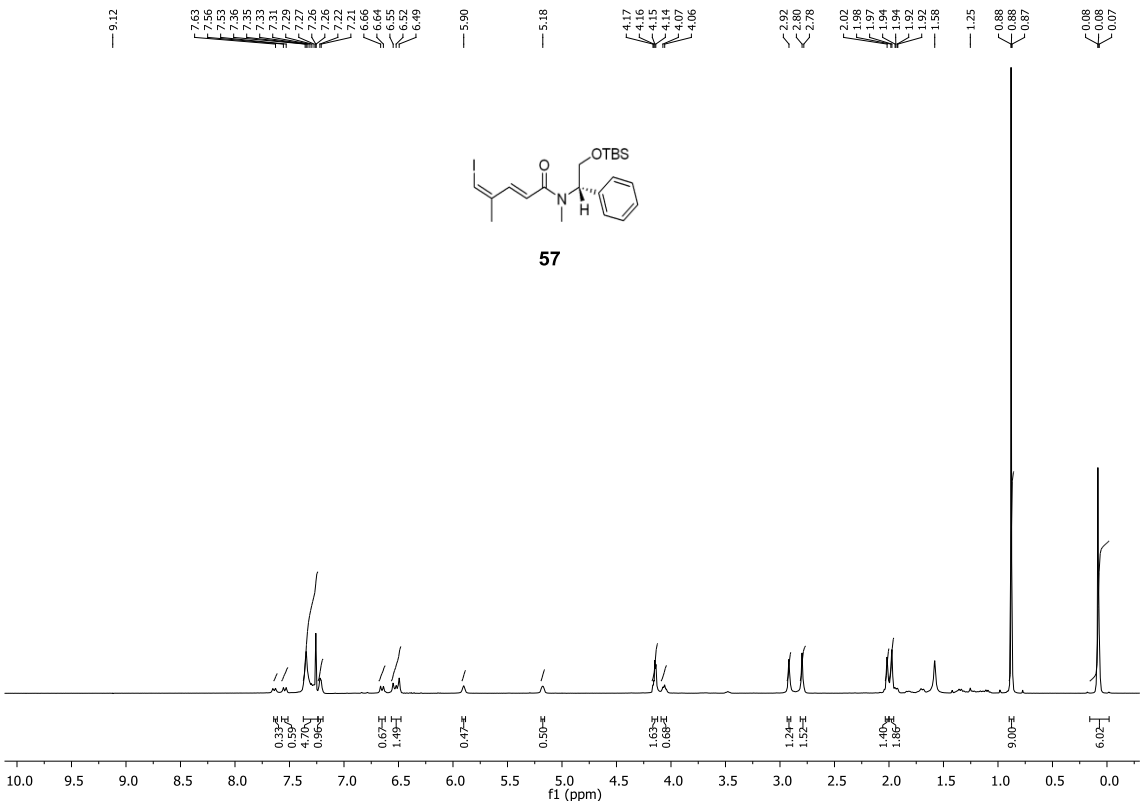
50



51a and 51b


7.34
7.34
7.33
7.32
7.32
7.26
3.66
3.65
3.63
3.62
3.59
3.55
2.31
0.92
0.90
0.89
0.88
0.87
0.77
0.03
0.02
OTBS
HN
H
6.69
3.00
2.96
9.30
6.46
f1 (ppm)

56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7.35
7.33
7.31
7.29
7.27
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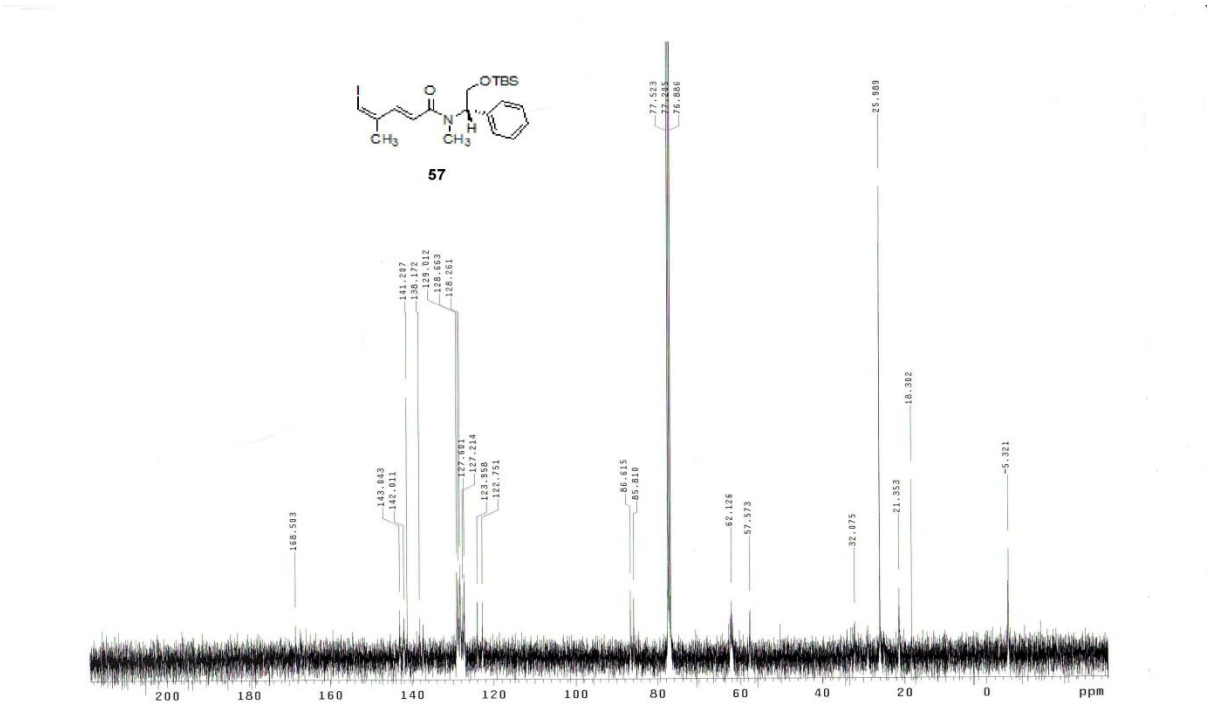
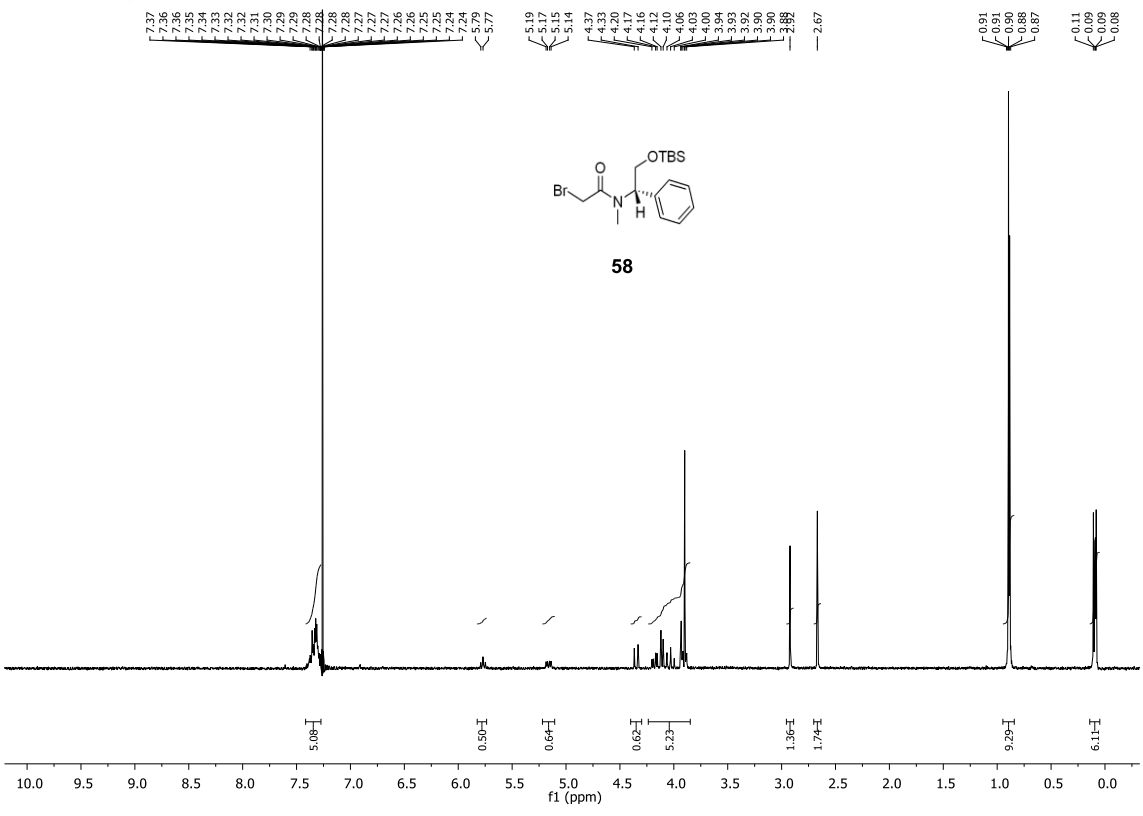
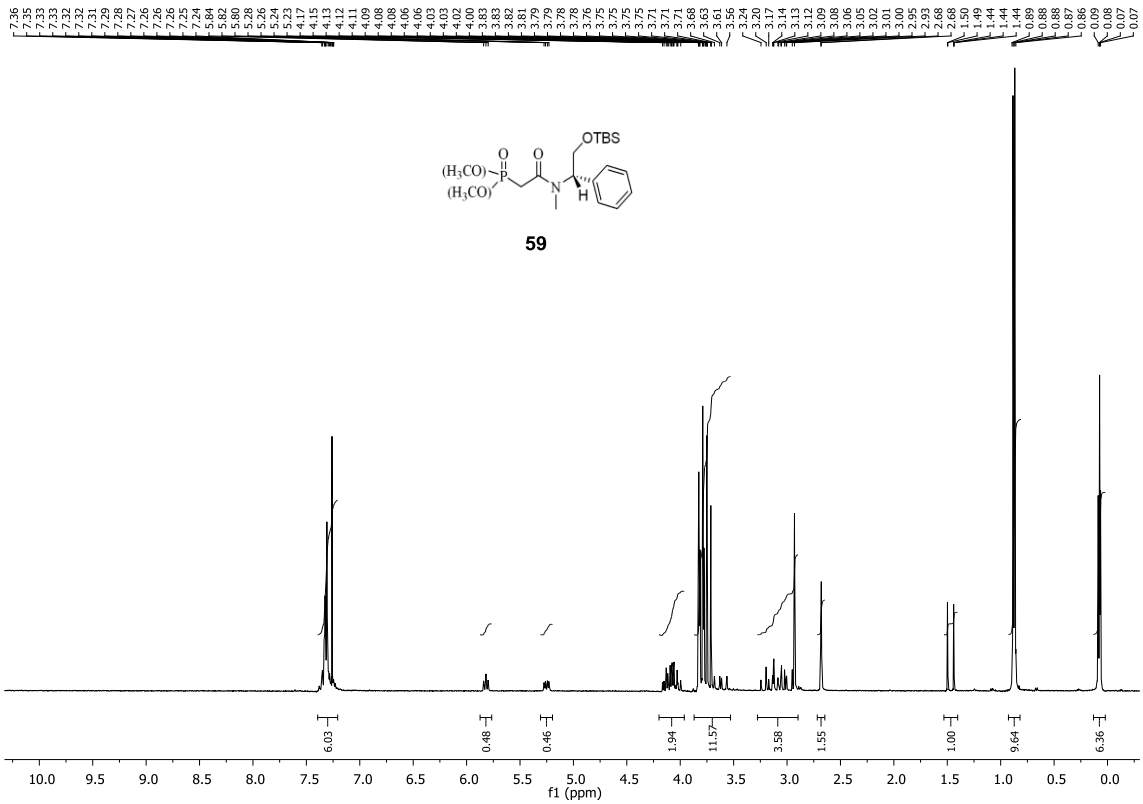
7.26
7.22
7.21
6.66
6.64
6.55
6.52
6.49
5.90
5.18
4.17
4.16
4.15
4.14
4.07
4.06
2.92
2.80
2.78
2.02
1.98
1.97
1.94
1.94
1.92
1.92
1.58
1.25
0.88
0.88
0.87
0.08
0.08
0.07
I
O
N
H
OTBS
0.33
0.59
4.70
0.96
0.67
1.49
0.47
0.50
1.63
0.68
1.24
1.52
1.40
1.86
9.00
6.02
f1 (ppm)

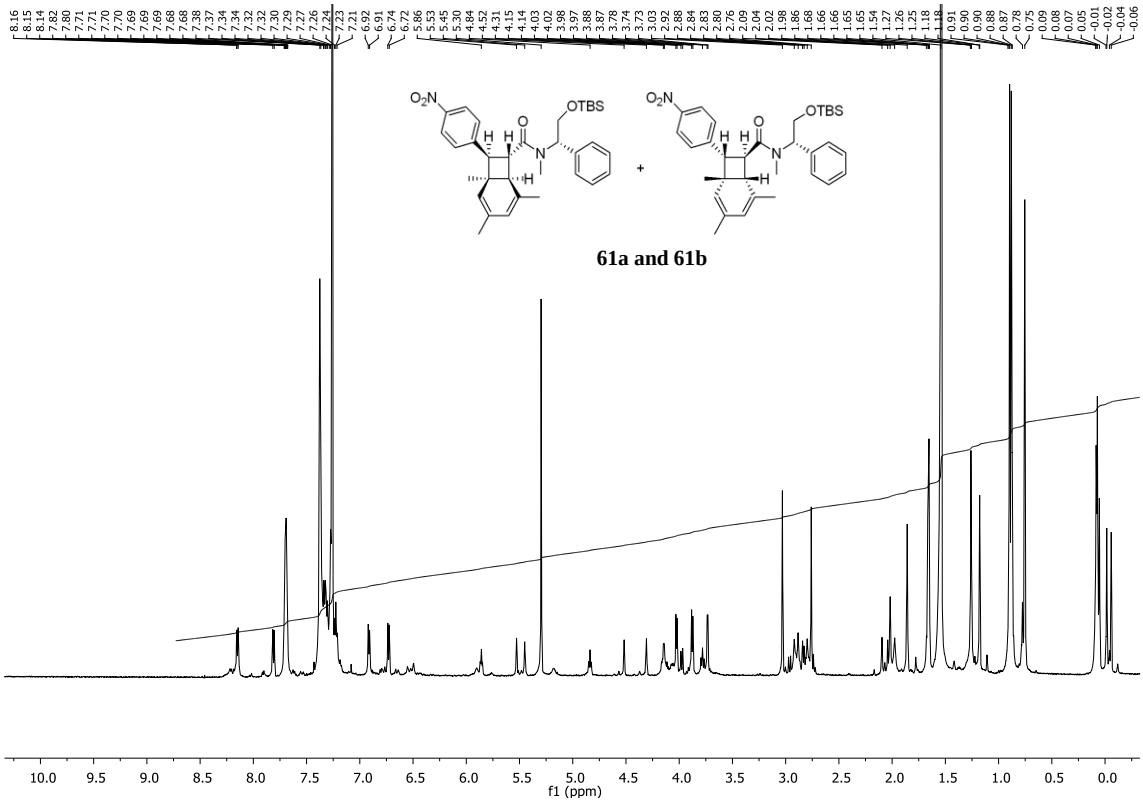
57


OTBS
I
O
N
H
CH3
CH3
57
168.593
143.643
142.611
141.287
130.172
129.012
128.663
128.261
127.681
127.214
123.958
122.751
86.615
85.810
77.523
77.285
76.886
62.126
57.573
32.075
25.989
21.353
18.382
-5.321
200
180
160
140
120
100
80
60
40
20
0
ppm

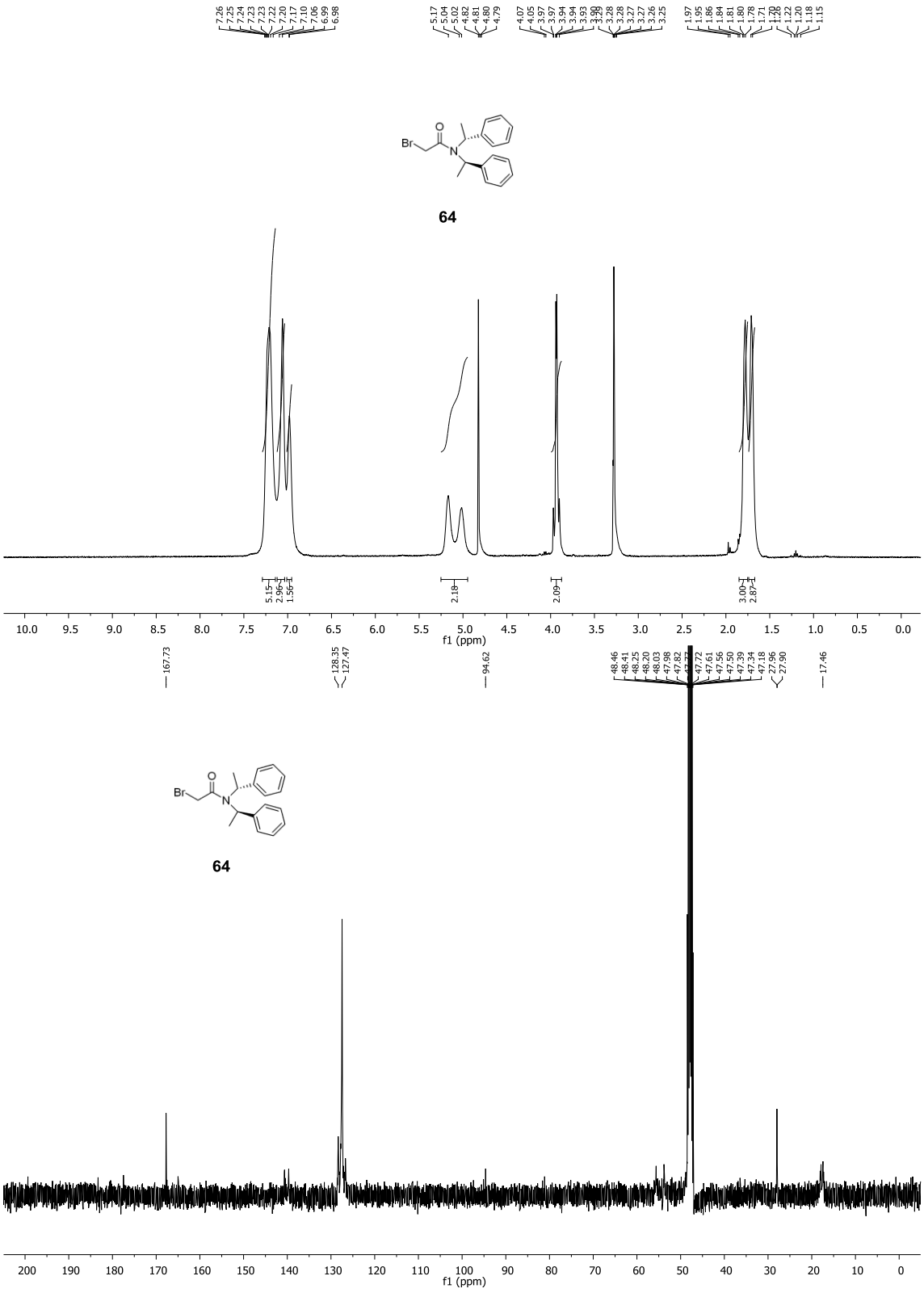

7.37
7.36
7.36
7.35
7.34
7.33
7.32
7.32
7.31
7.30
7.29
7.29
7.28
7.28
7.28
7.27
7.27
7.27
7.26
7.26
7.25
7.25
7.24
7.24
5.79
5.77
5.19
5.17
5.15
5.14
4.37
4.33
4.20
4.17
4.16
4.12
4.10
4.06
4.03
4.00
3.94
3.93
3.92
3.90
3.90
2.67
0.91
0.91
0.90
0.88
0.87
0.11
0.09
0.09
0.08
OTBS
O
Br
N
H
58
5.08
0.50
0.64
0.62
5.23
1.36
1.74
9.29
6.11
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

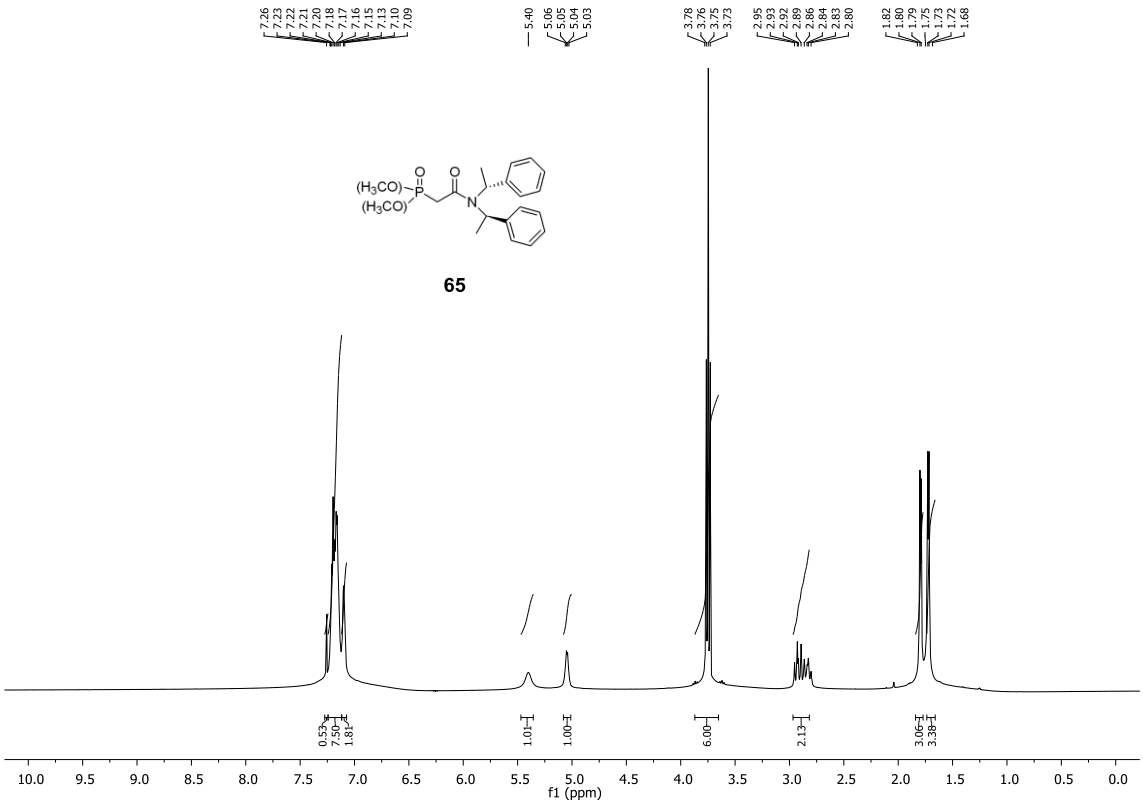


59

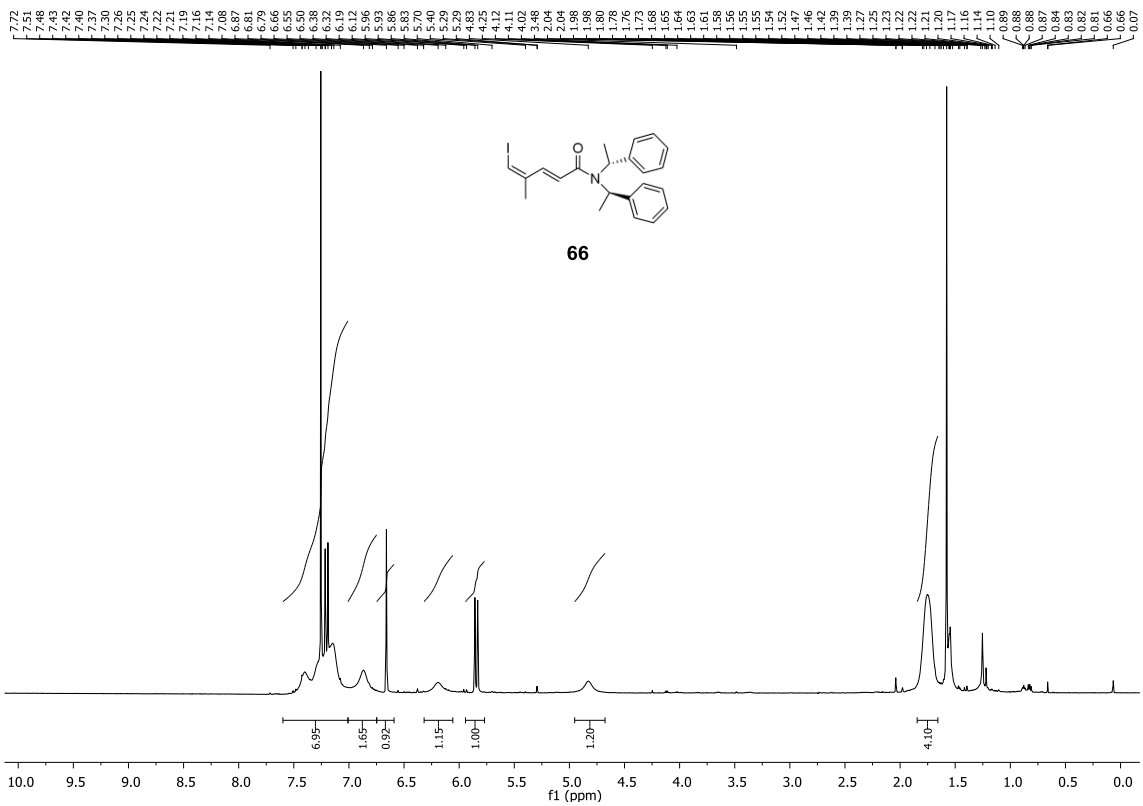


61a and 61b

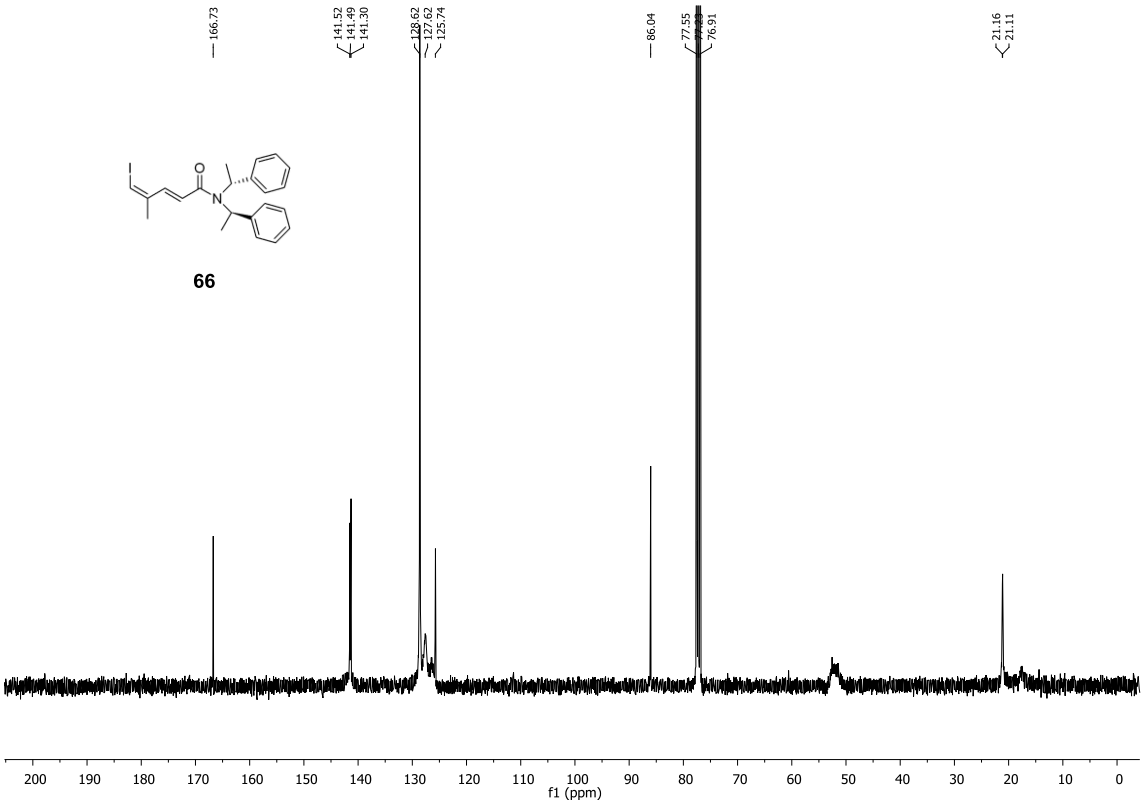

7.26 7.25 7.24 7.23 7.23 7.22 7.20 7.17 7.10 7.06 6.99 6.98
5.17 5.04 5.02 4.82 4.81 4.80 4.79
4.07 4.05 3.97 3.97 3.94 3.94 3.93 3.93 3.29 3.28 3.28 3.27 3.27 3.26 3.25
1.97 1.95 1.86 1.84 1.81 1.80 1.78 1.71 1.70 1.28 1.22 1.20 1.18 1.15
Br
O
N
64
5.15 2.96 1.56 2.18 2.09 3.00 2.87
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
167.73 128.35 127.47 94.62 48.46 48.41 48.25 48.20 48.03 47.98 47.82 47.72 47.61 47.56 47.50 47.39 47.34 47.18 27.96 27.90 17.46
Br
O
N
64
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



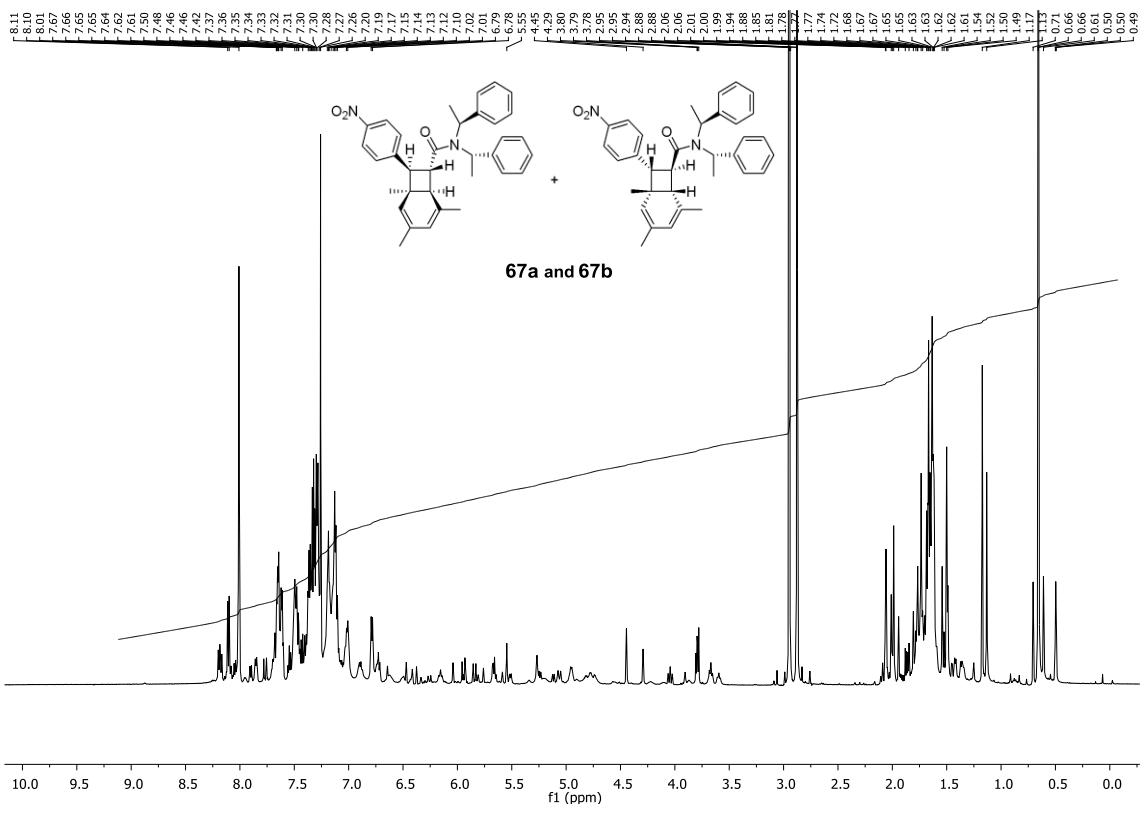
65



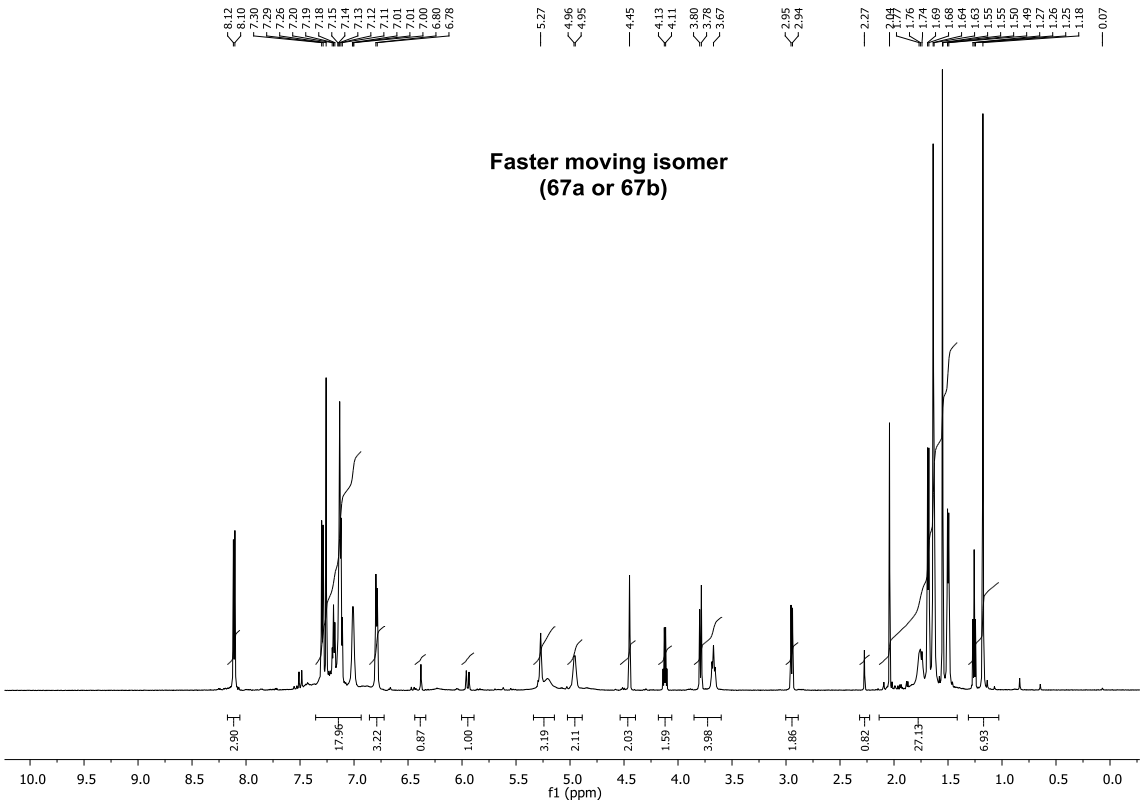
66

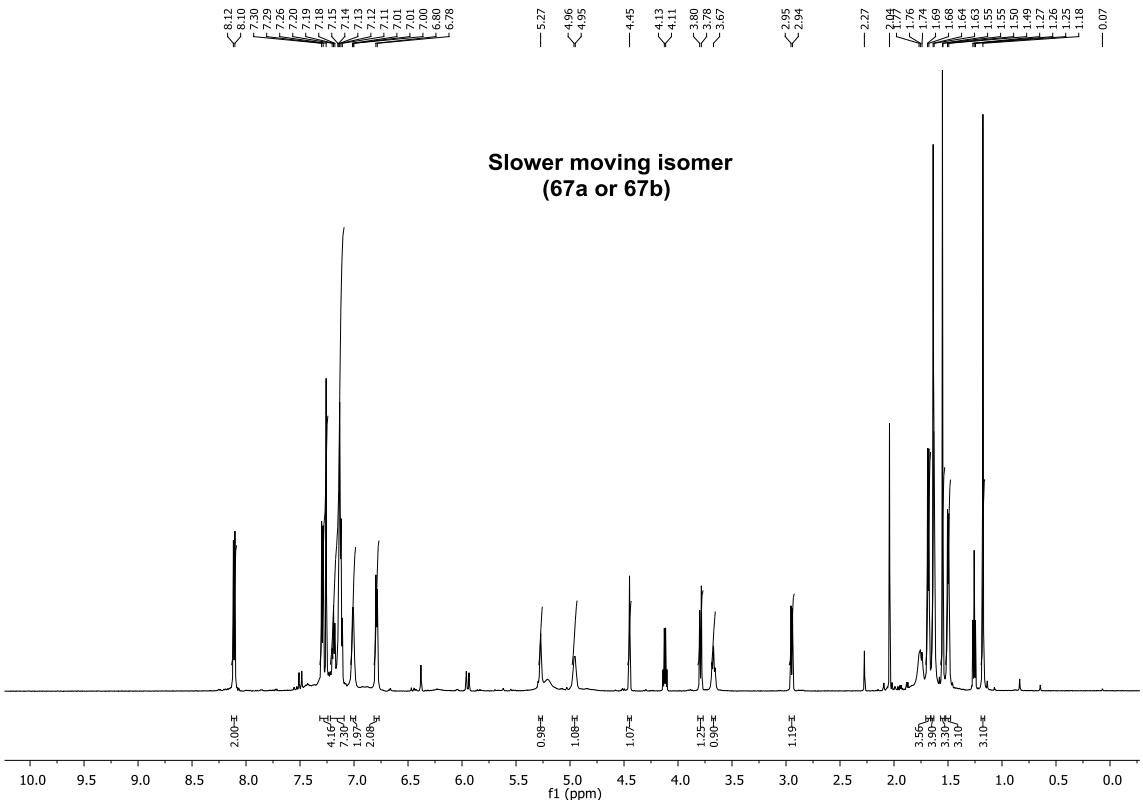


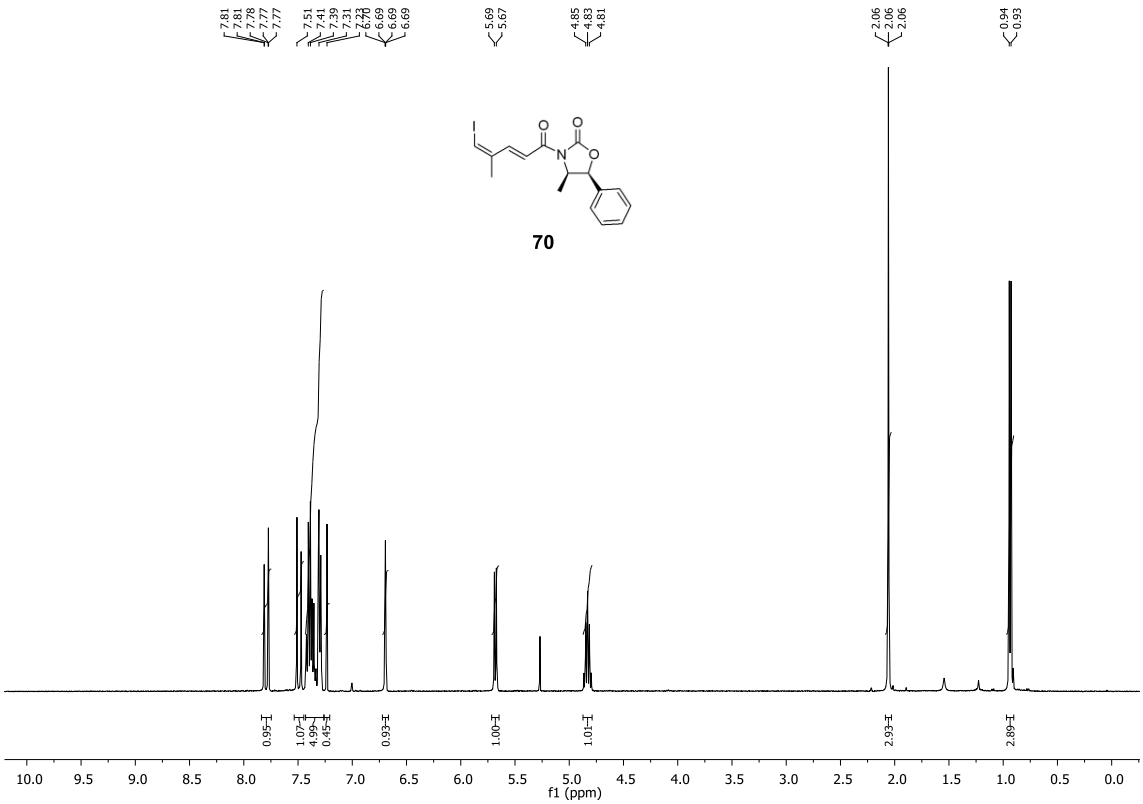
66

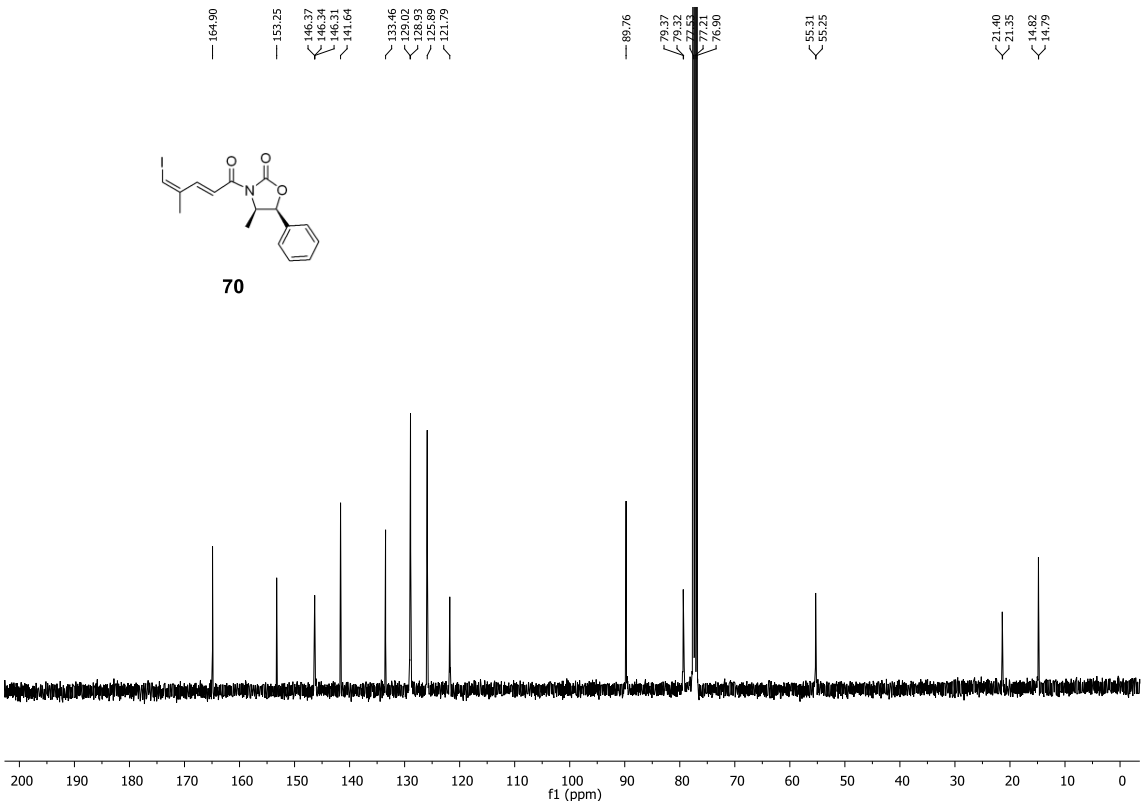


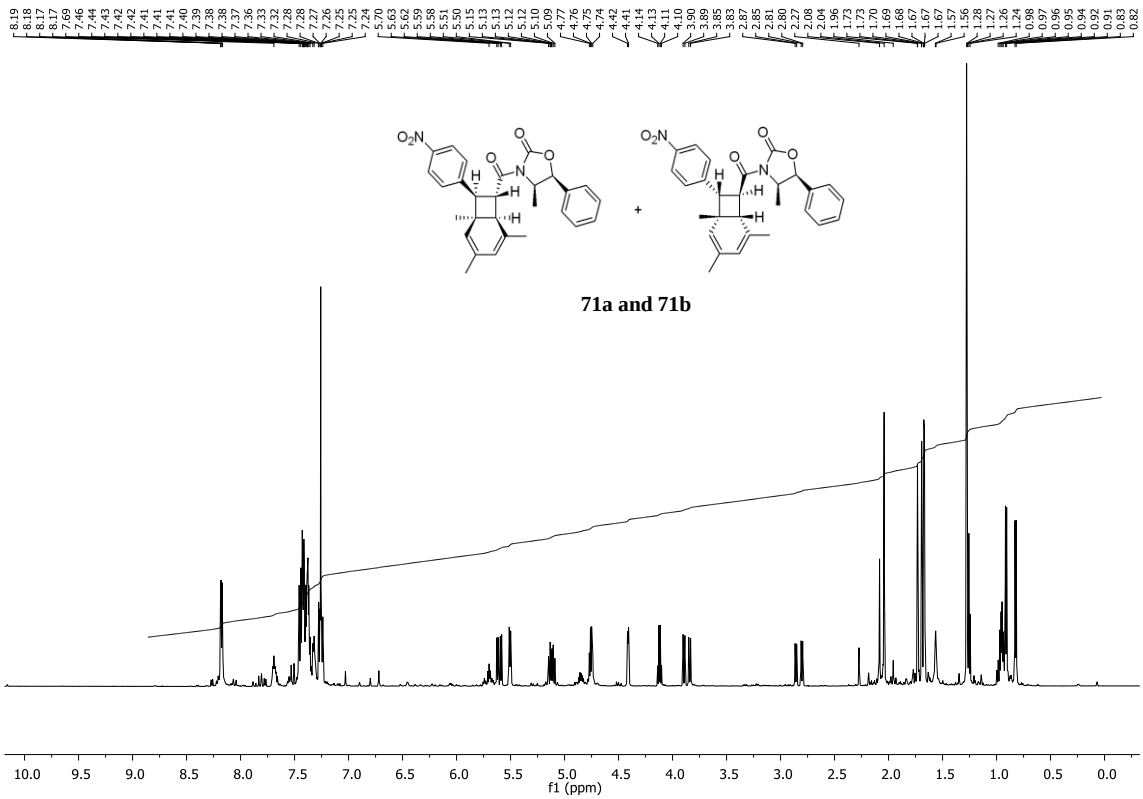
67a and 67b


Faster moving isomer
(67a or 67b)
f1 (ppm)

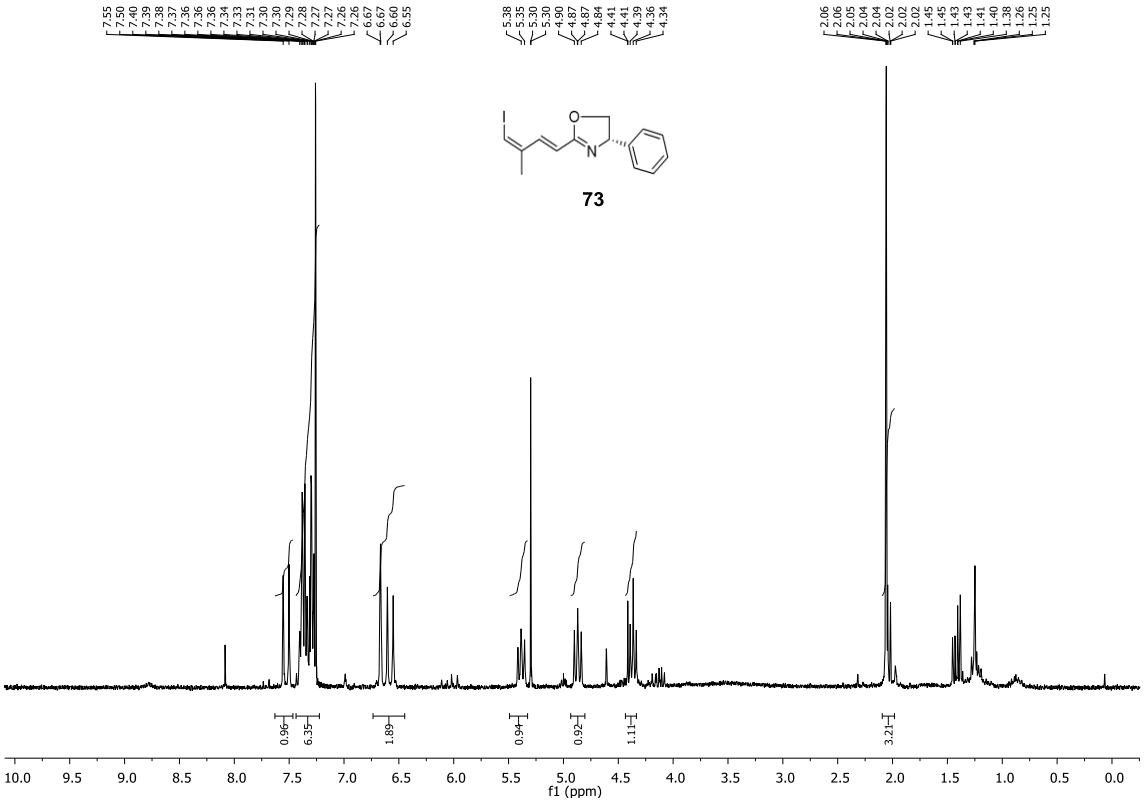

Slower moving isomer
(67a or 67b)
f1 (ppm)


7.81
7.81
7.78
7.77
7.77
7.51
7.41
7.39
7.31
6.69
6.69
6.69
5.69
5.67
4.85
4.83
4.81
2.06
2.06
2.06
0.94
0.93
I
O
O
N
O
70
0.95
1.07
4.99
0.45
0.93
1.00
1.01
2.93
2.89
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

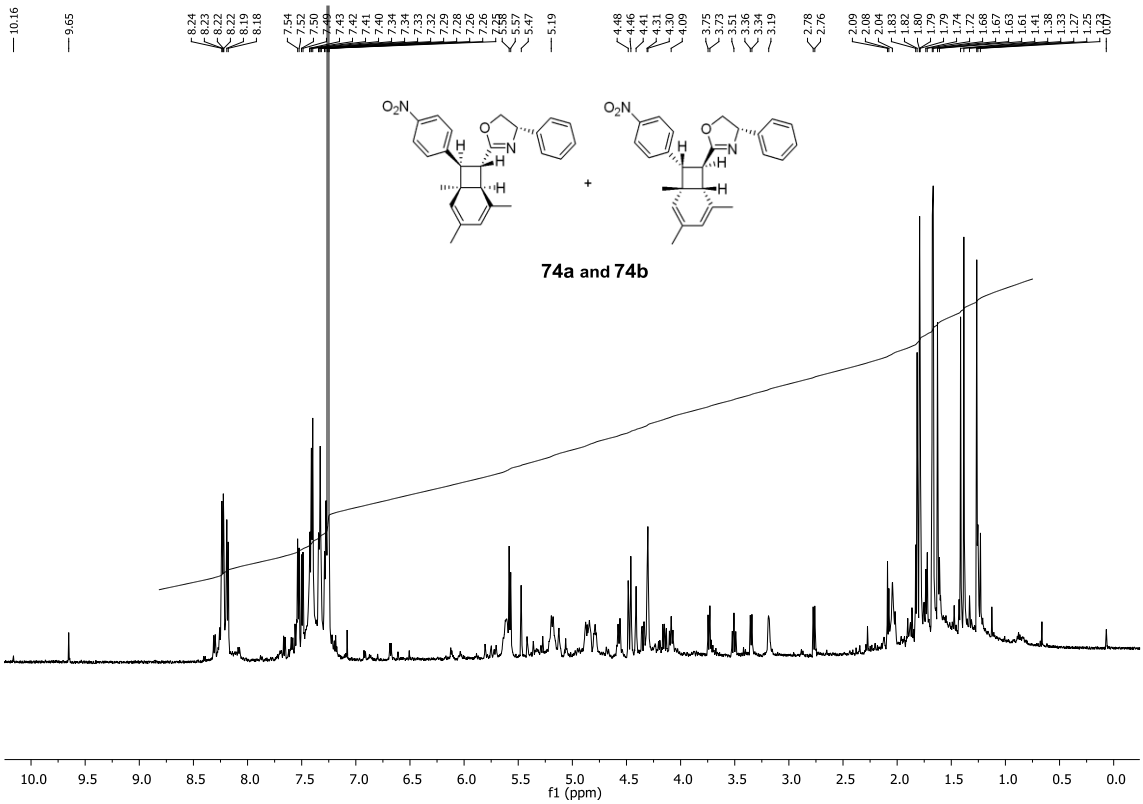

164.90
153.25
146.37
146.34
146.31
141.64
133.46
129.02
128.93
125.89
121.79
89.76
79.37
79.32
77.53
77.21
76.90
55.31
55.25
21.40
21.35
14.82
14.79
I
O
O
N
O
70
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

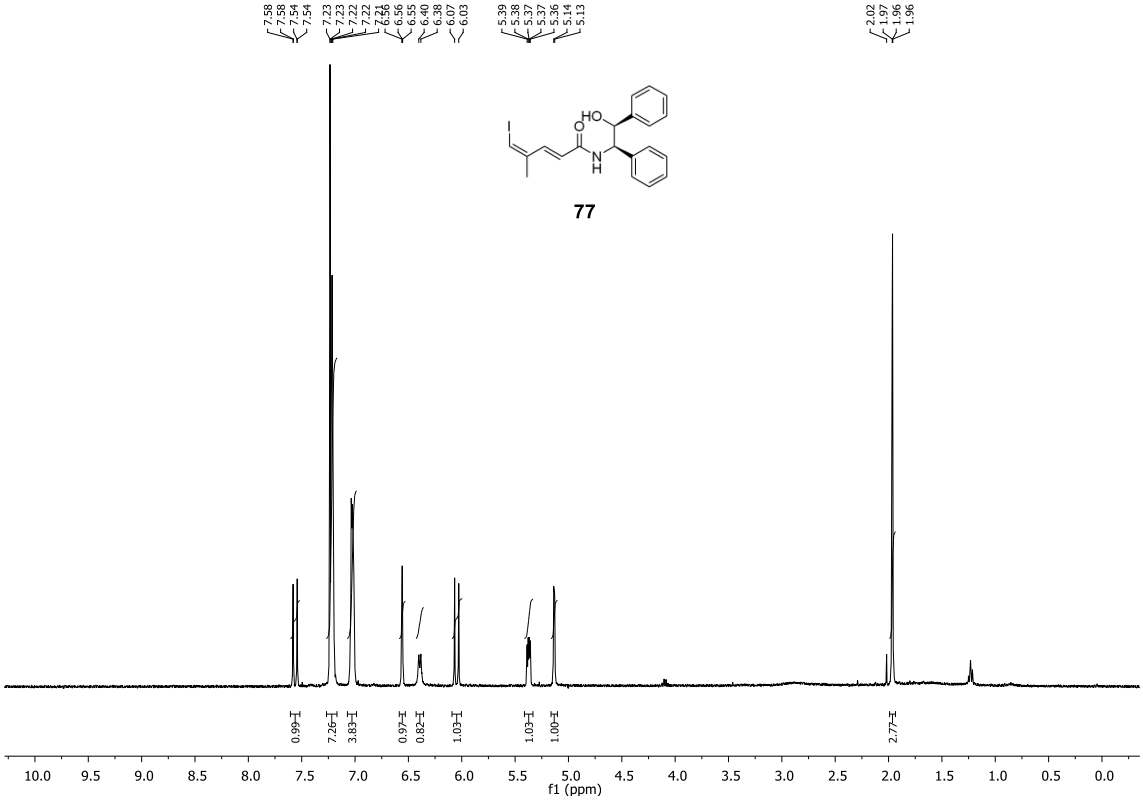


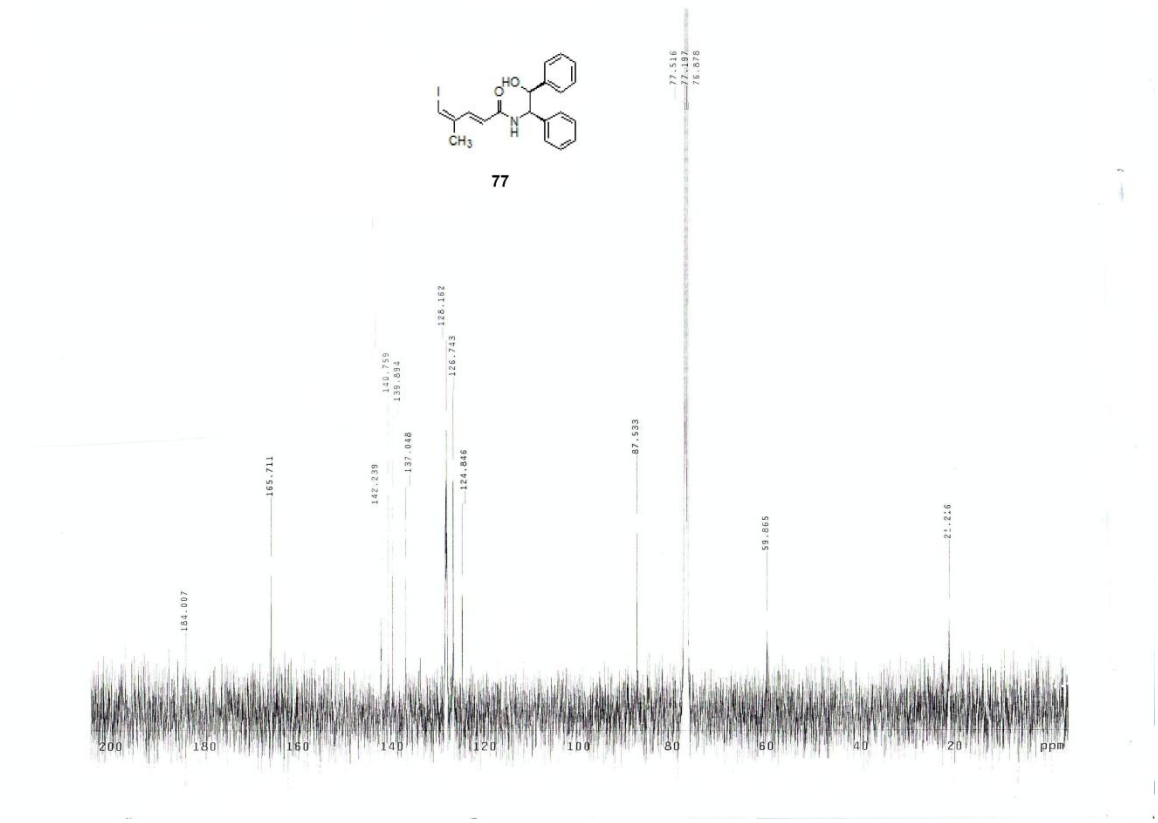
71a and 71b

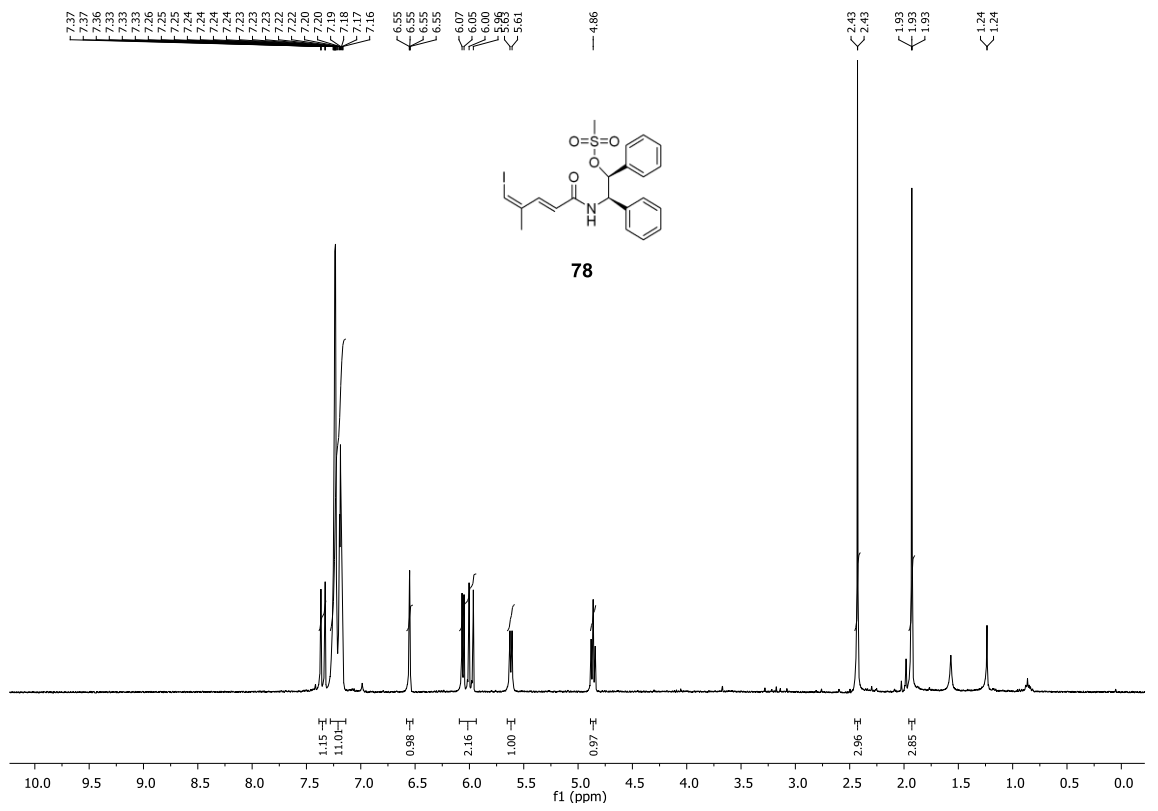


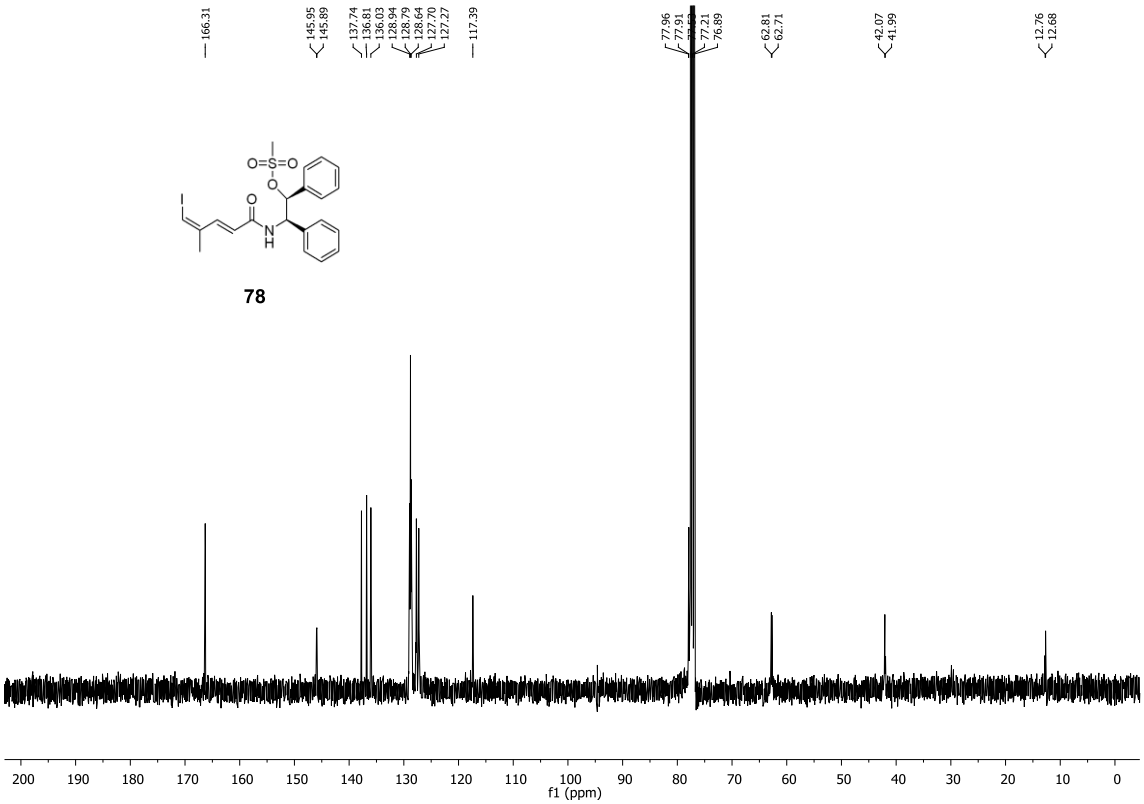
73

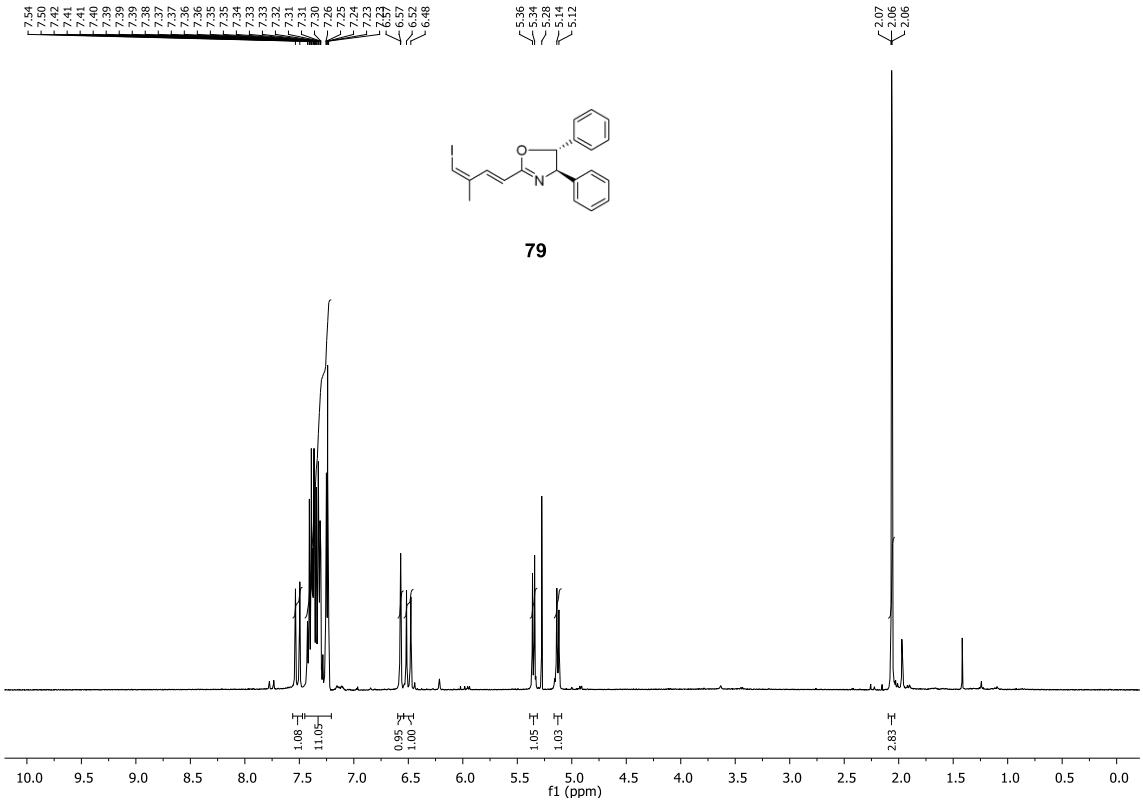

10.16
9.65
8.24
8.23
8.22
8.22
8.19
8.18
7.54
7.52
7.50
7.49
7.43
7.42
7.41
7.40
7.34
7.34
7.33
7.32
7.29
7.28
7.26
7.26
5.58
5.57
5.47
5.19
4.48
4.46
4.41
4.31
4.30
4.09
3.75
3.73
3.51
3.36
3.34
3.19
2.78
2.76
2.09
2.08
2.04
1.83
1.82
1.80
1.79
1.79
1.74
1.72
1.68
1.67
1.63
1.61
1.41
1.38
1.33
1.27
1.25
1.23
0.07
O2N
O2N
74a and 74b
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

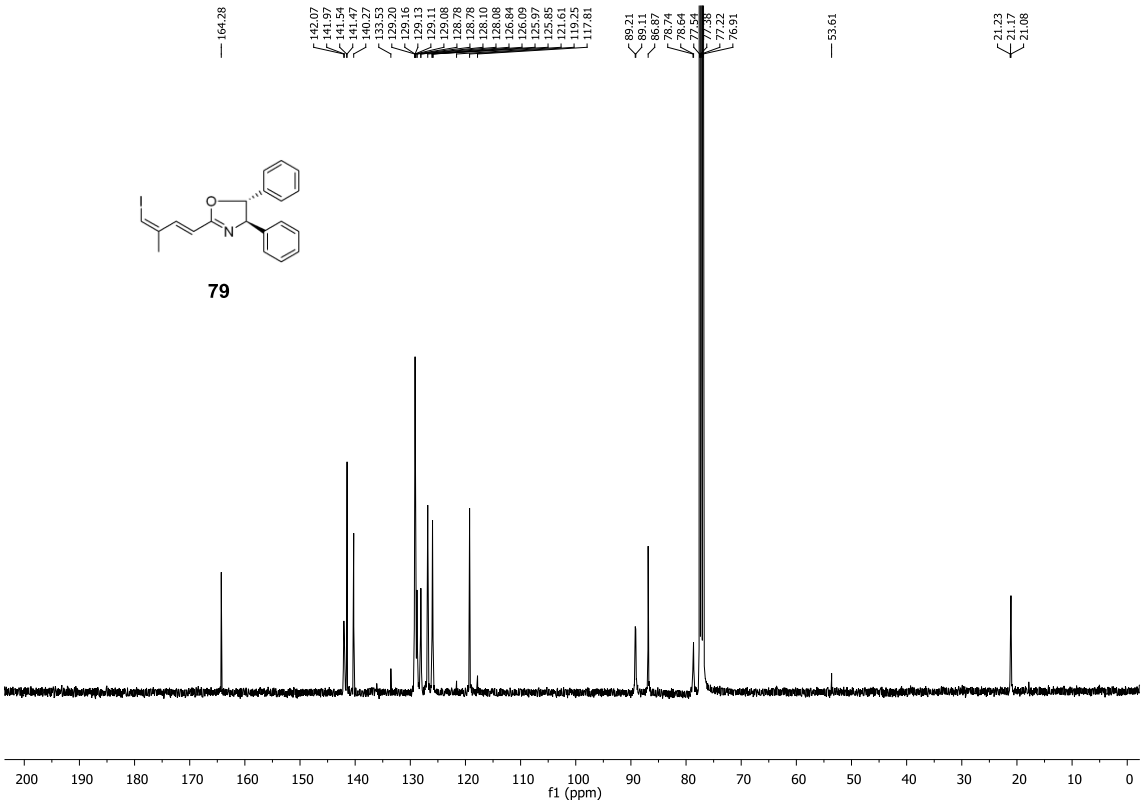

7.58
7.58
7.54
7.54
7.23
7.23
7.22
7.22
6.56
6.55
6.40
6.38
6.07
6.03
5.39
5.38
5.37
5.37
5.36
5.14
5.13
2.02
1.97
1.96
1.96
HO
O
N
H
I
77
0.99
7.26
3.83
0.97
0.82
1.03
1.03
1.00
2.77
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

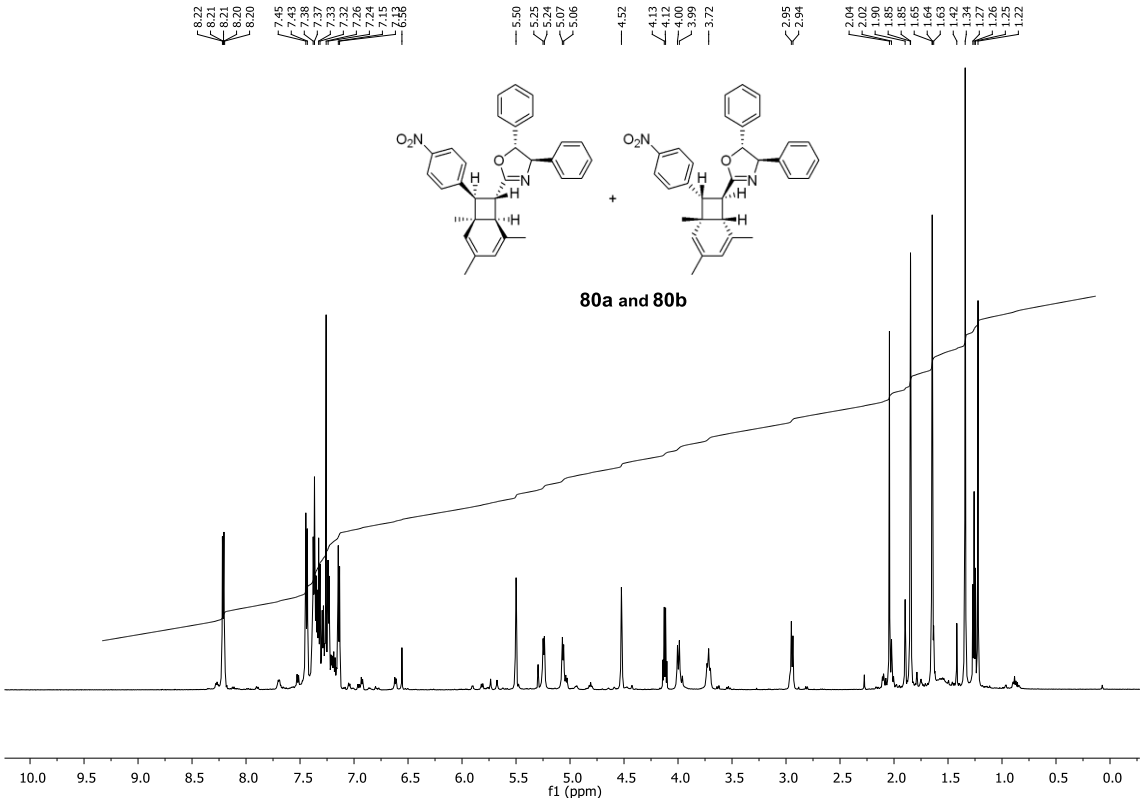

77
184.007
165.711
142.239
140.759
139.893
137.048
126.162
126.743
124.846
87.533
59.865
21.216
77.516
77.202
76.878
200
180
160
140
120
100
80
60
40
20
ppm

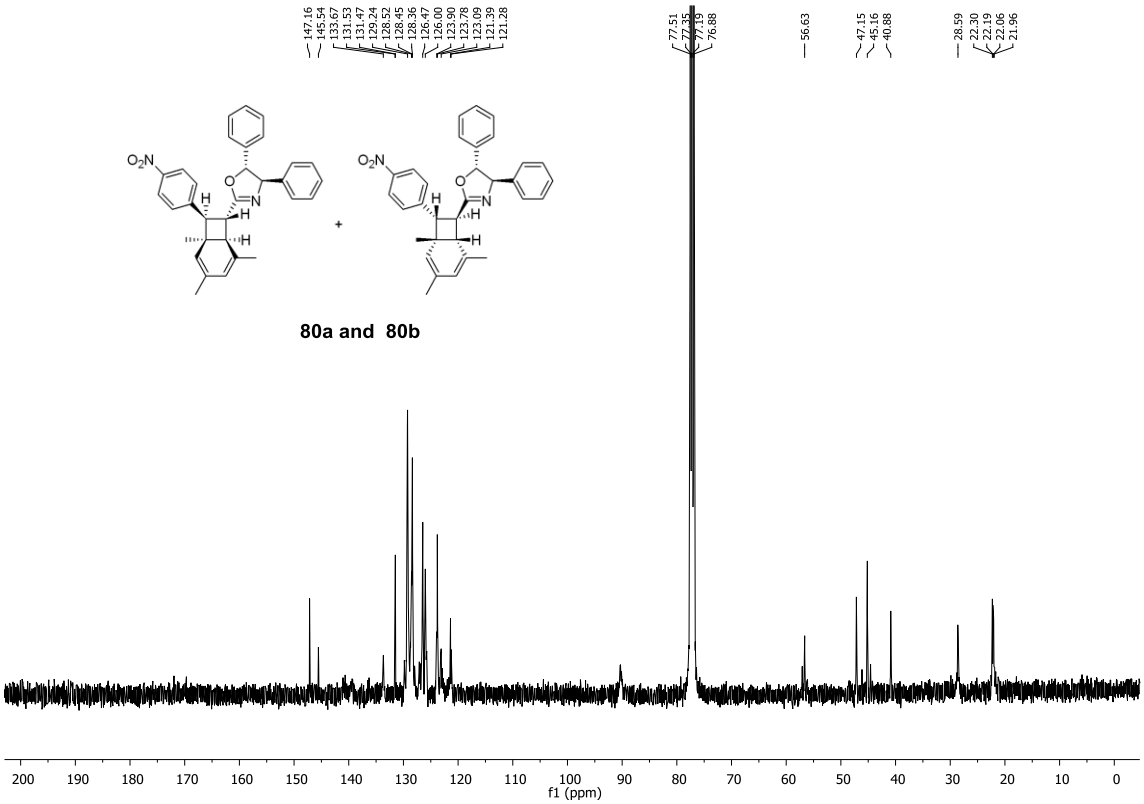

78
7.37
7.37
7.36
7.36
7.33
7.33
7.26
7.25
7.25
7.24
7.24
7.24
7.24
7.23
7.23
7.23
7.22
7.22
7.20
7.20
7.19
7.18
7.17
7.16
6.55
6.55
6.55
6.55
6.07
6.05
6.00
5.96
5.83
5.61
4.86
2.43
2.43
1.93
1.93
1.93
1.24
1.24
1.15
11.01
0.98
2.16
1.00
0.97
2.96
2.85
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

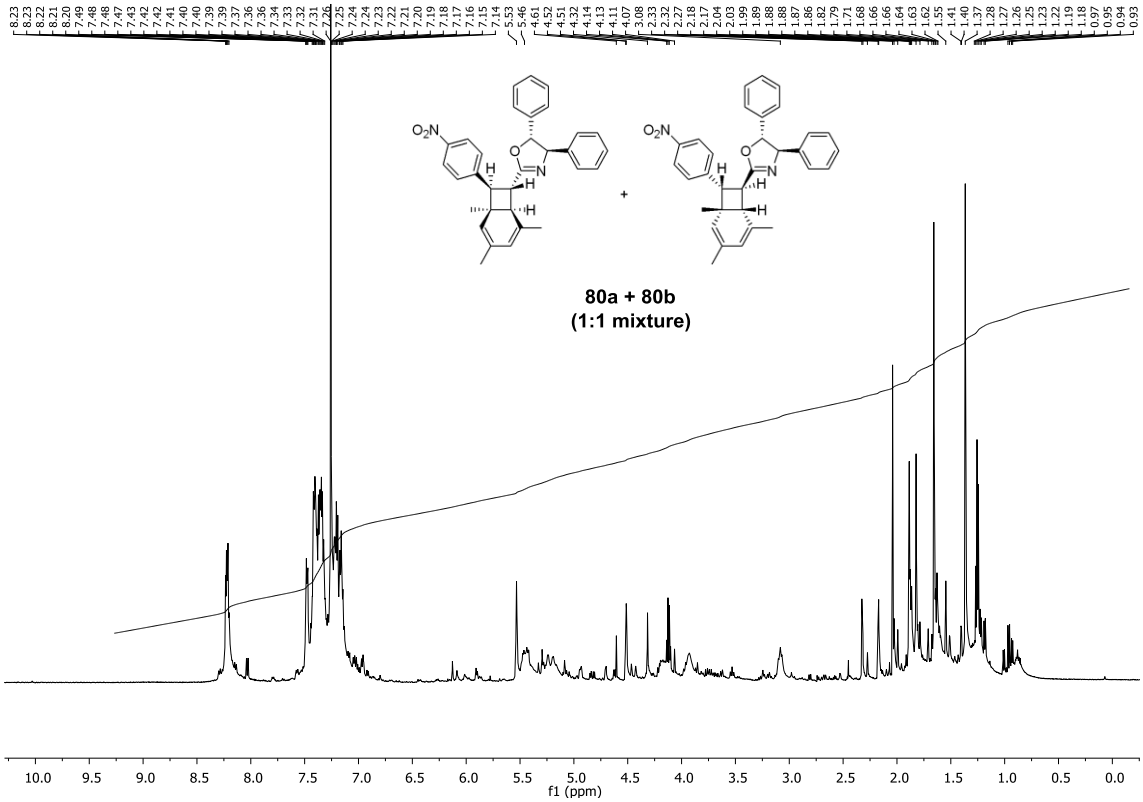

166.31
145.95
145.89
137.74
136.81
136.03
128.94
128.79
128.64
127.70
127.27
117.39
77.96
77.91
77.21
76.89
62.81
62.71
42.07
41.99
12.76
12.68
78
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

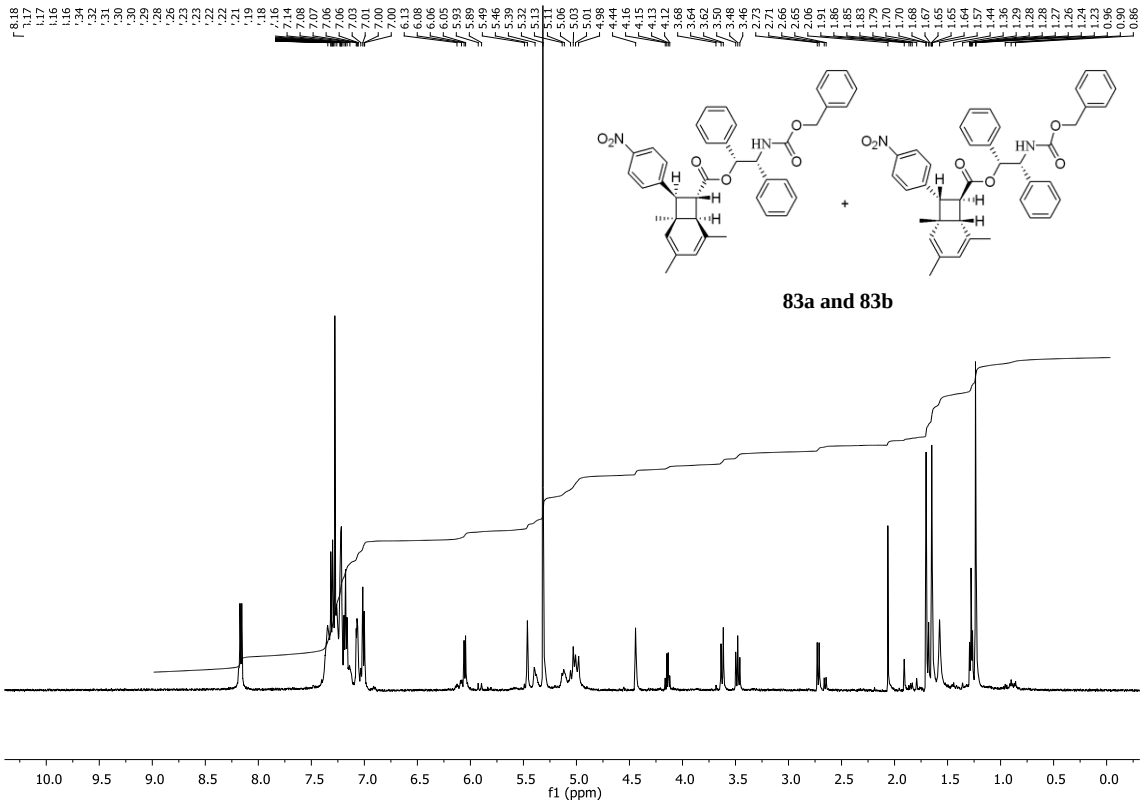

7.54
7.50
7.42
7.41
7.41
7.40
7.39
7.39
7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.31
7.31
7.30
7.26
7.25
7.24
7.23
7.23
6.57
6.52
6.48
5.36
5.34
5.28
5.14
5.12
2.07
2.06
2.06
79
1.08
11.05
0.95
1.00
1.05
1.03
2.83
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


164.28
142.07
141.97
141.54
141.47
140.27
133.53
129.20
129.16
129.13
129.11
129.08
128.78
128.78
128.10
128.08
126.84
126.09
125.97
125.85
121.61
119.25
117.81
89.21
89.11
86.87
78.74
78.64
77.32
77.22
76.91
53.61
21.23
21.17
21.08
79
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

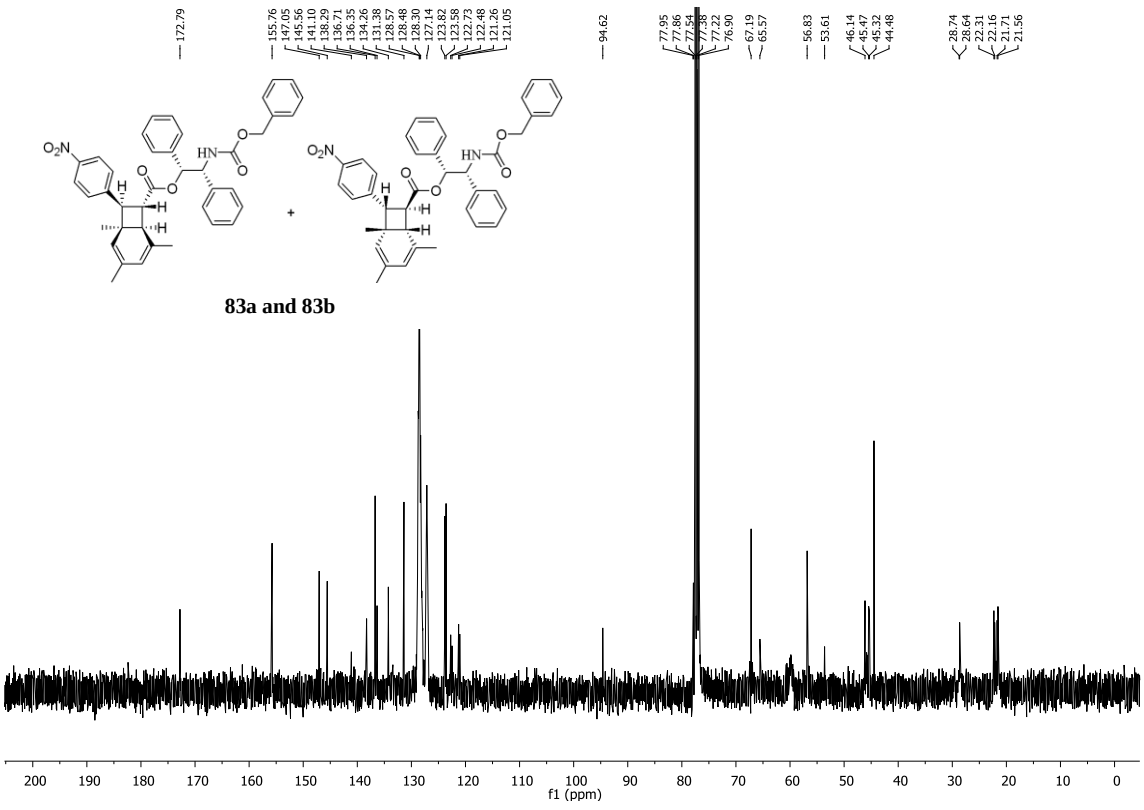

8.22
8.21
8.21
8.20
8.20
7.45
7.43
7.38
7.37
7.33
7.32
7.26
7.24
7.15
7.13
6.56
5.50
5.25
5.24
5.07
5.06
4.52
4.13
4.12
4.00
3.99
3.72
2.95
2.94
2.04
2.02
1.90
1.85
1.85
1.65
1.64
1.63
1.42
1.34
1.27
1.26
1.25
1.22
80a and 80b
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


147.16
145.54
133.67
131.53
131.47
129.24
128.52
128.45
128.36
126.47
126.00
123.90
123.78
123.09
121.39
121.28
77.51
77.35
77.19
76.88
56.63
47.15
45.16
40.88
28.59
22.30
22.19
22.06
21.96
O2N
80a and 80b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

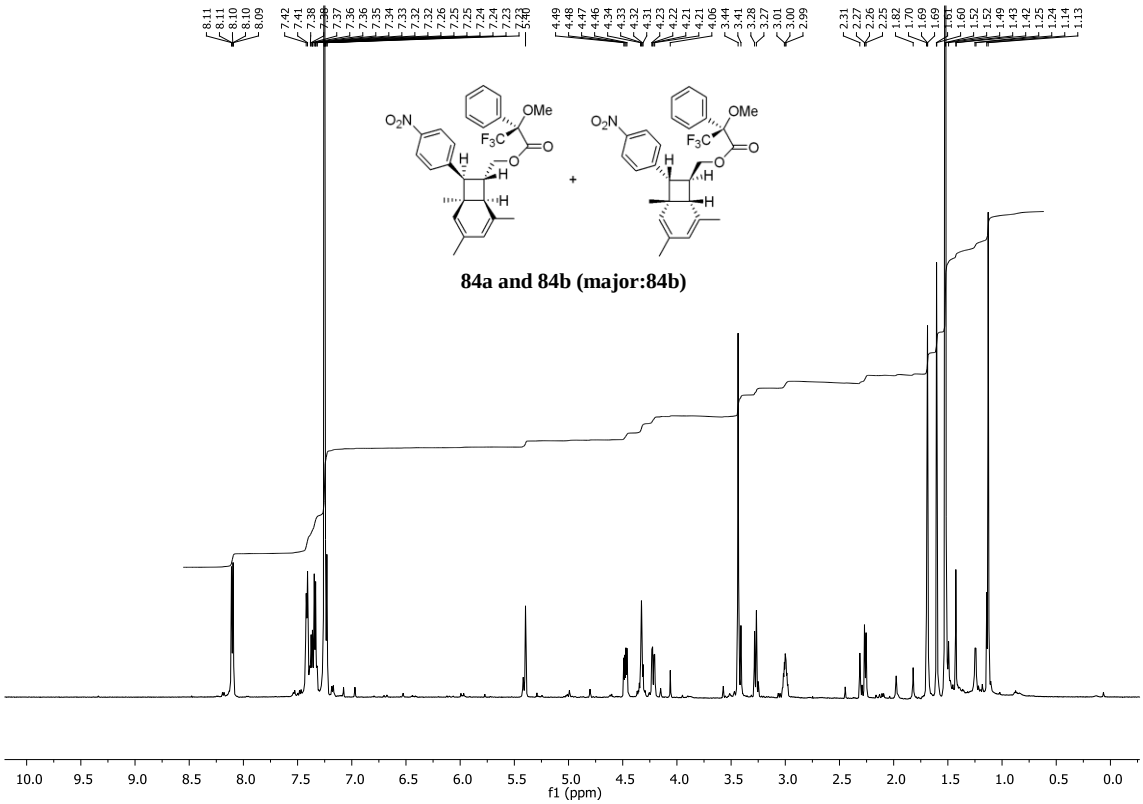

8.23
8.23
8.22
8.21
8.20
7.49
7.48
7.48
7.47
7.43
7.42
7.42
7.41
7.40
7.40
7.39
7.39
7.37
7.36
7.36
7.34
7.33
7.32
7.31
7.26
7.25
7.24
7.24
7.23
7.22
7.21
7.20
7.19
7.18
7.17
7.16
7.15
7.14
5.53
5.46
4.61
4.52
4.51
4.32
4.14
4.13
4.11
4.07
3.08
2.33
2.32
2.27
2.18
2.17
2.04
2.03
1.99
1.89
1.88
1.88
1.87
1.86
1.82
1.79
1.71
1.68
1.66
1.66
1.64
1.63
1.62
1.55
1.41
1.40
1.37
1.28
1.27
1.26
1.25
1.23
1.22
1.19
1.18
0.97
0.95
0.94
0.93
O2N
80a + 80b
(1:1 mixture)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



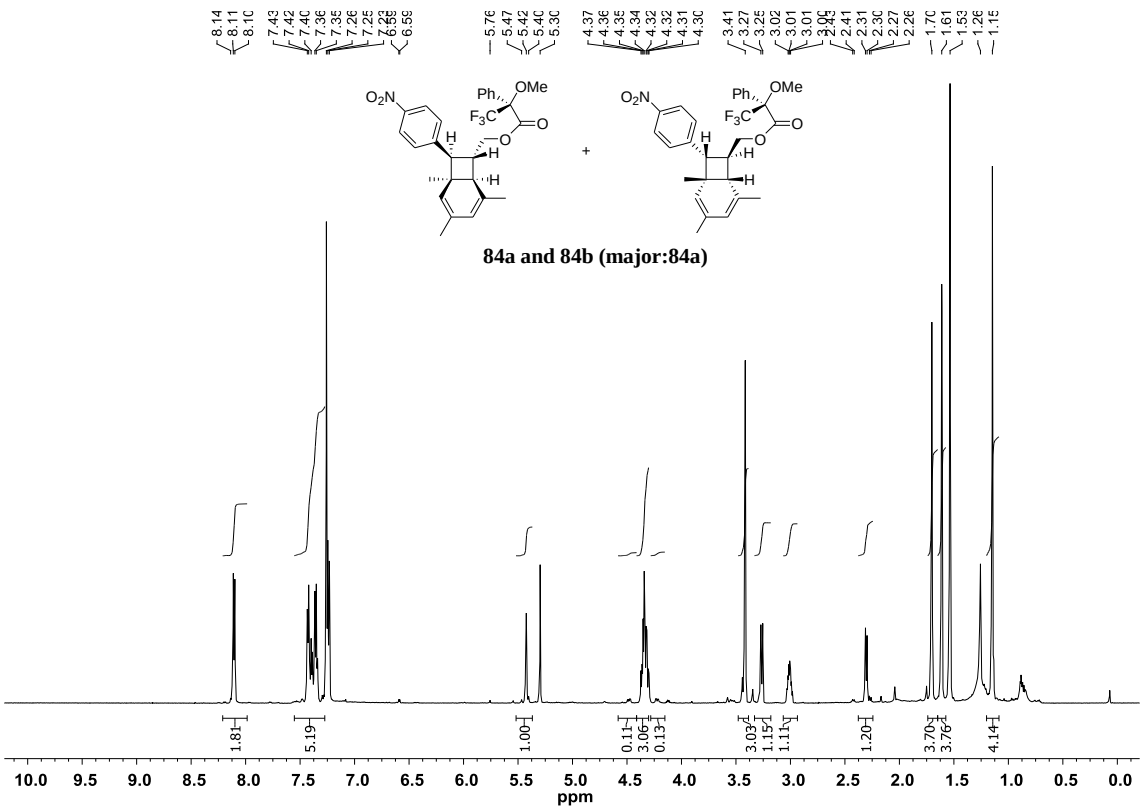
83a and 83b



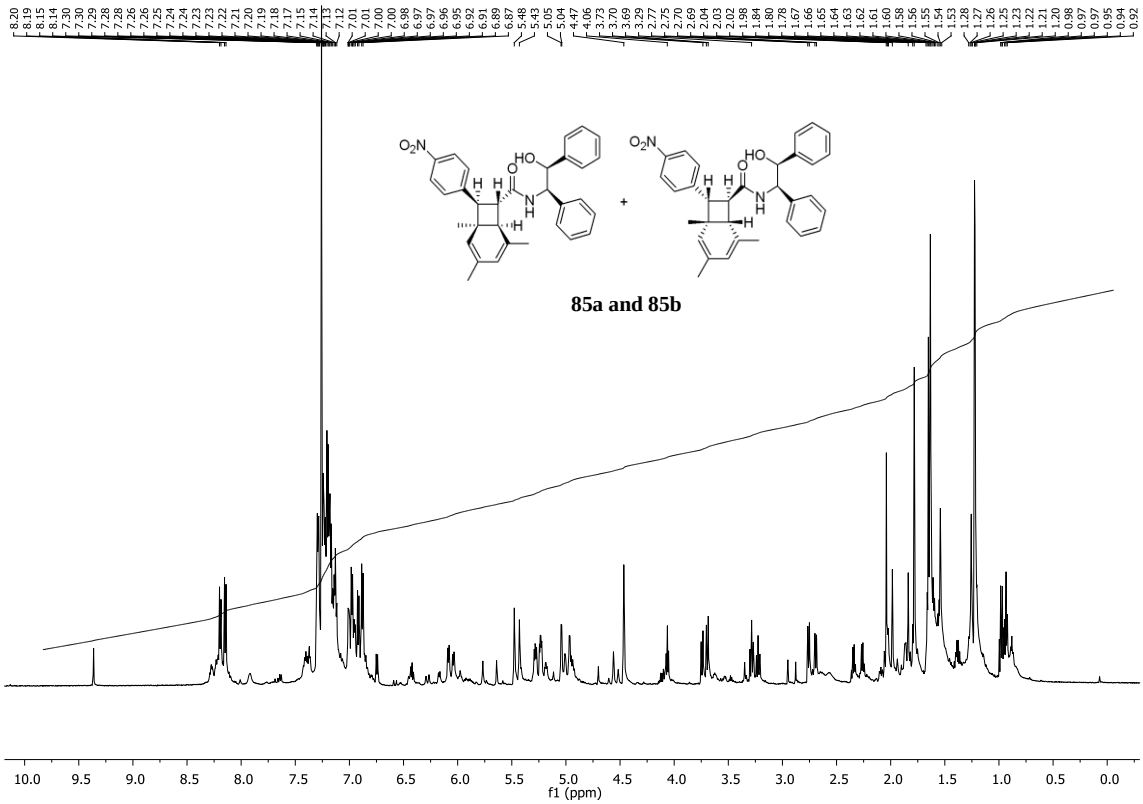
83a and 83b



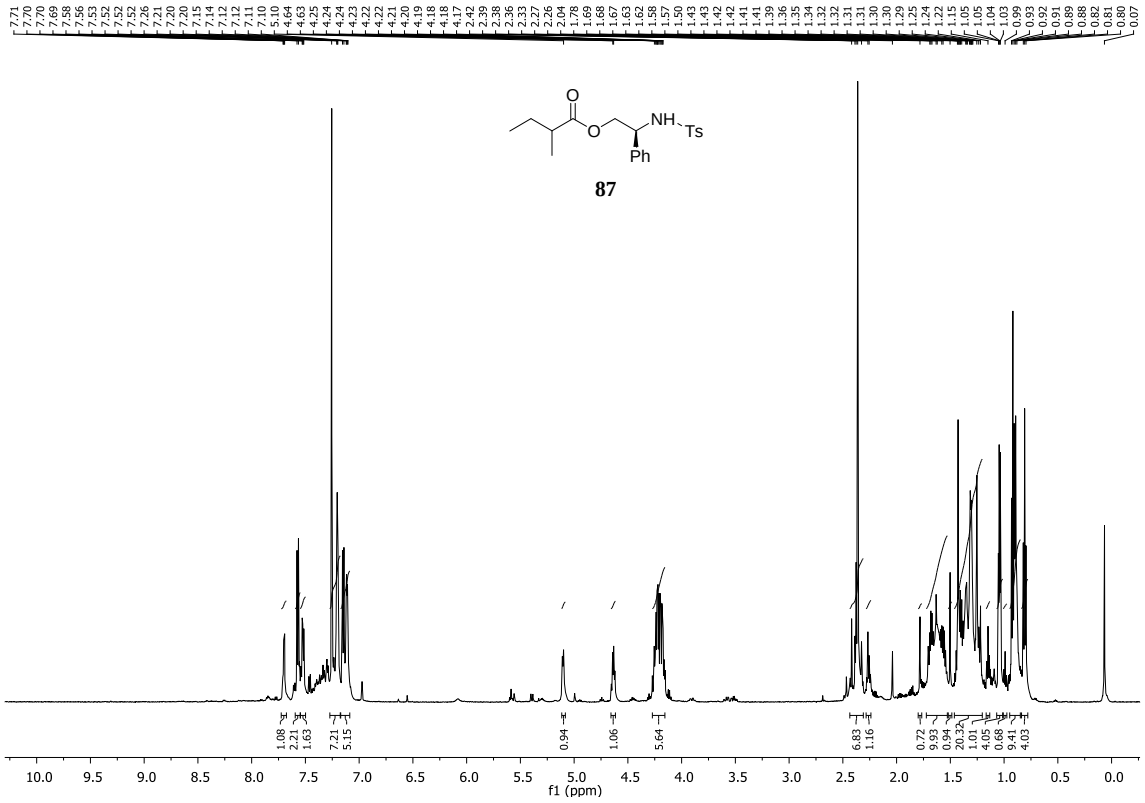
84a and 84b (major:84b)



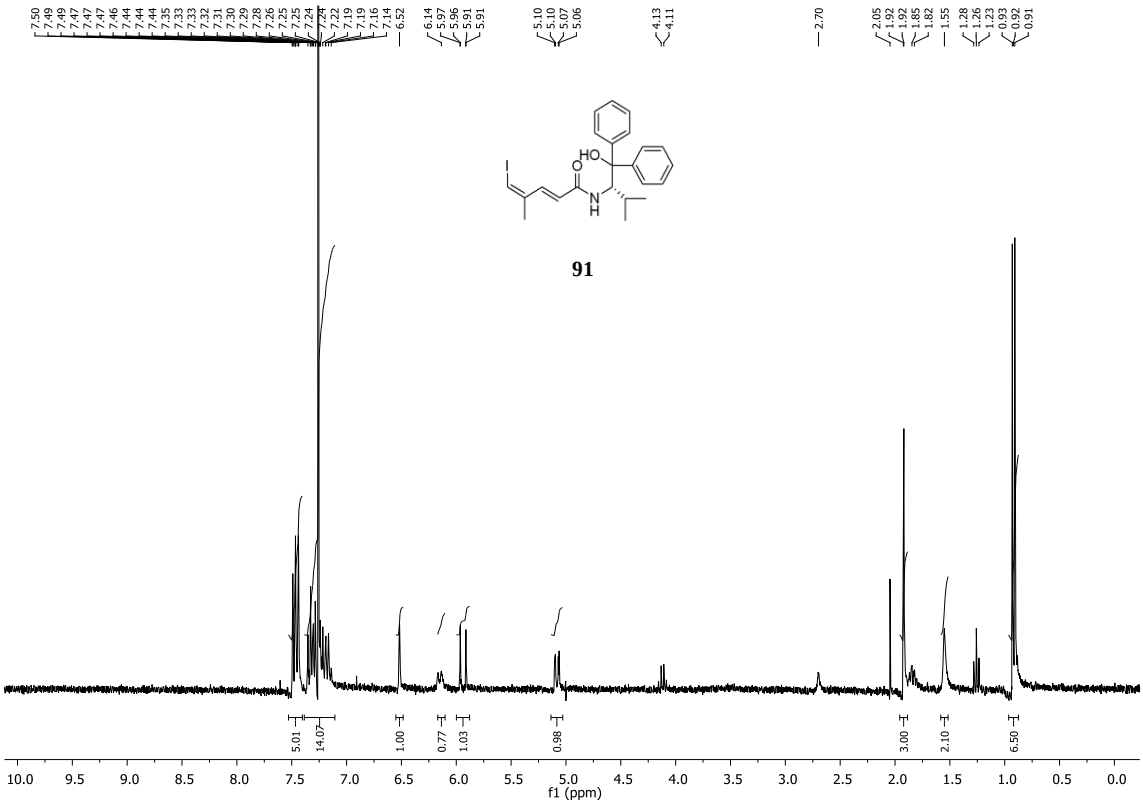
84a and 84b (major:84a)

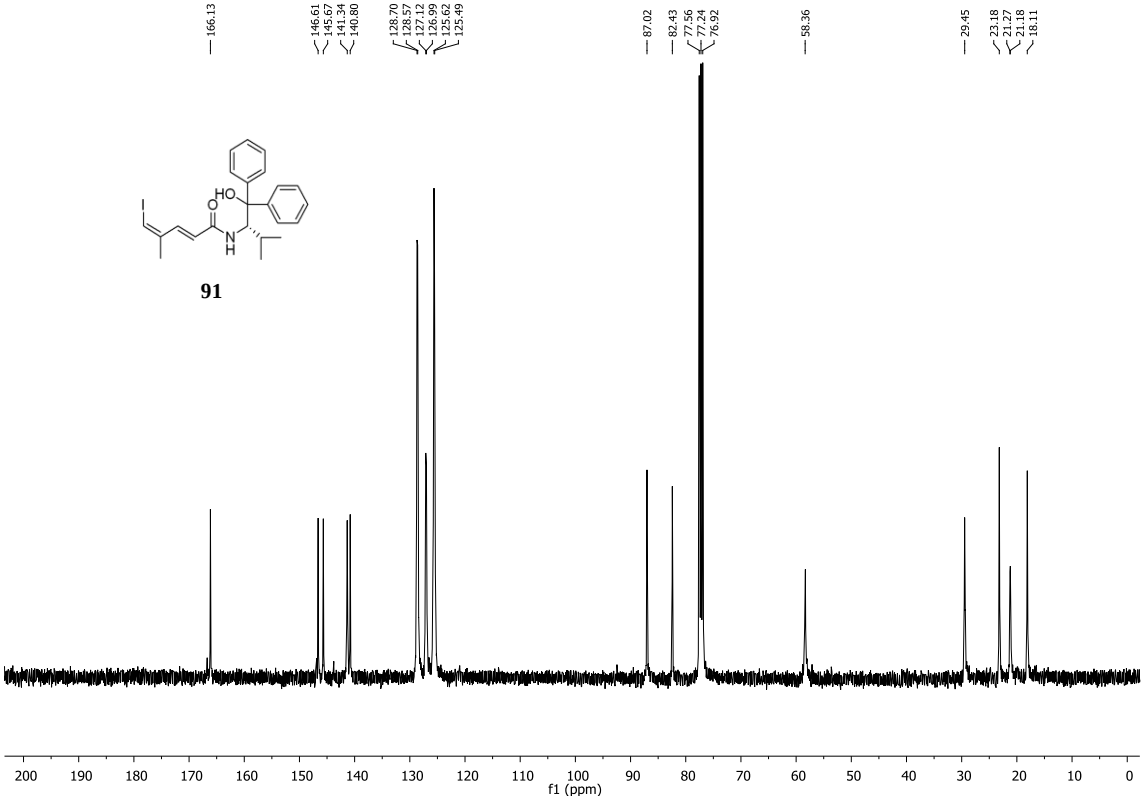


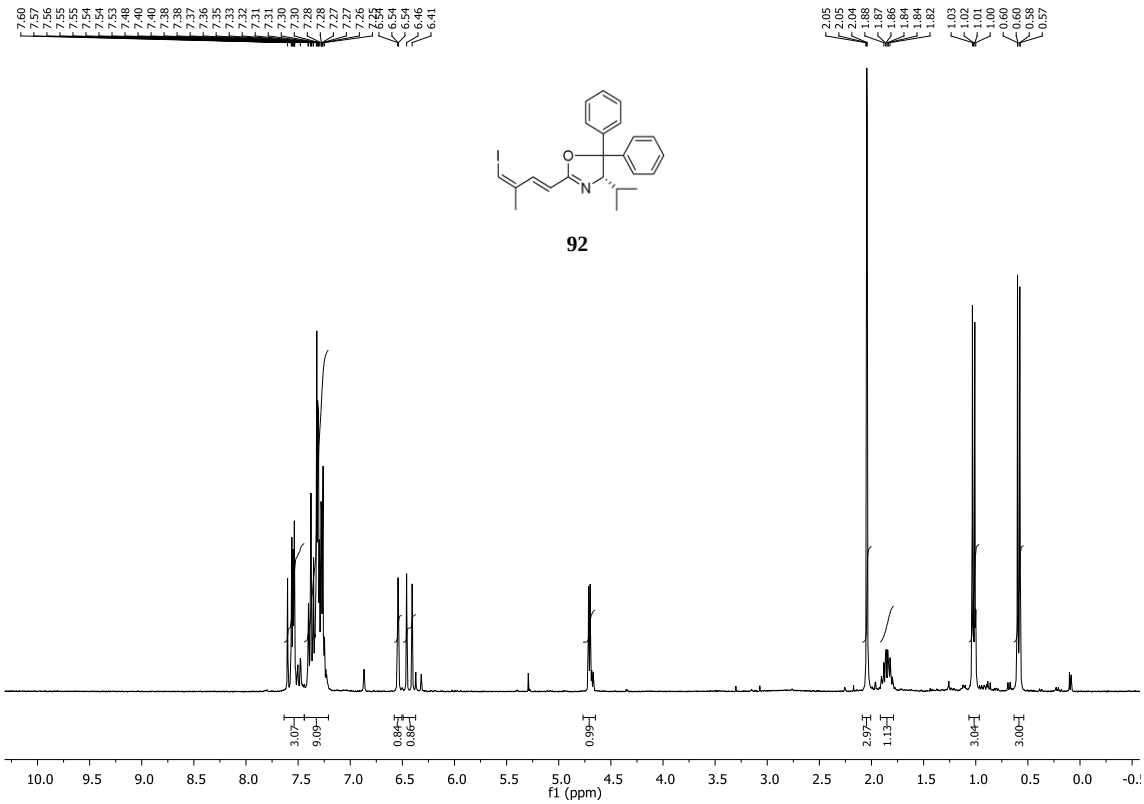
85a and 85b

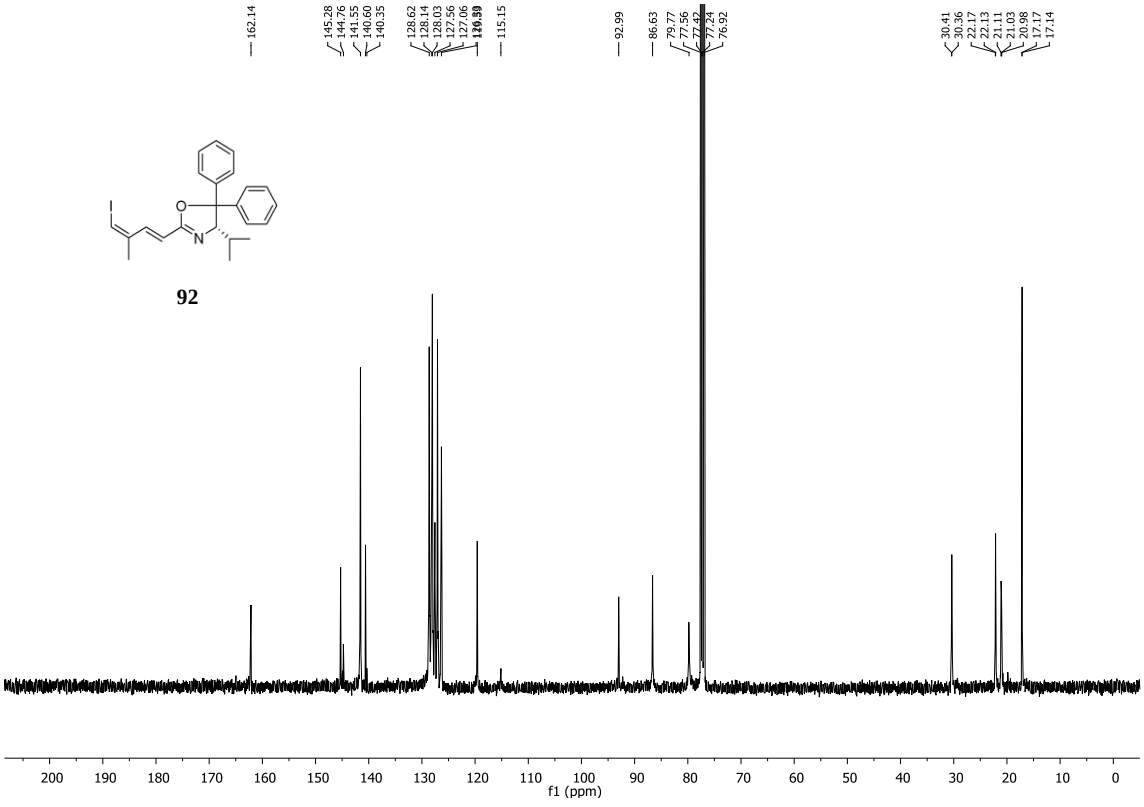


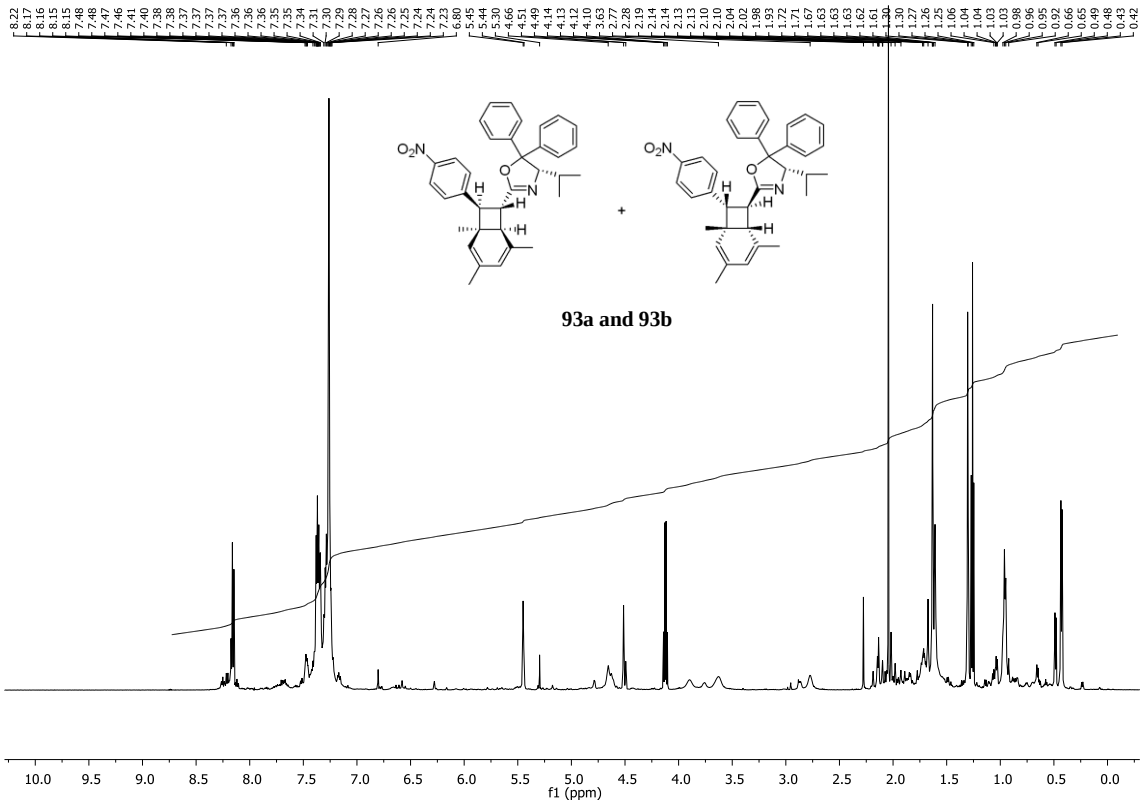
87


7.50 7.49 7.49 7.47 7.47 7.47 7.46 7.44 7.44 7.44 7.35 7.33 7.32 7.31 7.30 7.29 7.28 7.26 7.25 7.25 7.24 7.24 7.22 7.19 7.19 7.16 7.14 6.52
6.14 5.97 5.96 5.91 5.91
5.10 5.10 5.07 5.06
4.13 4.11
2.70
2.05 1.92 1.92 1.85 1.82 1.55 1.28 1.26 1.23 0.93 0.92 0.91
HO
O
N
H
I
91
5.01 14.07 1.00 0.77 1.03 0.98 3.00 2.10 6.50
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

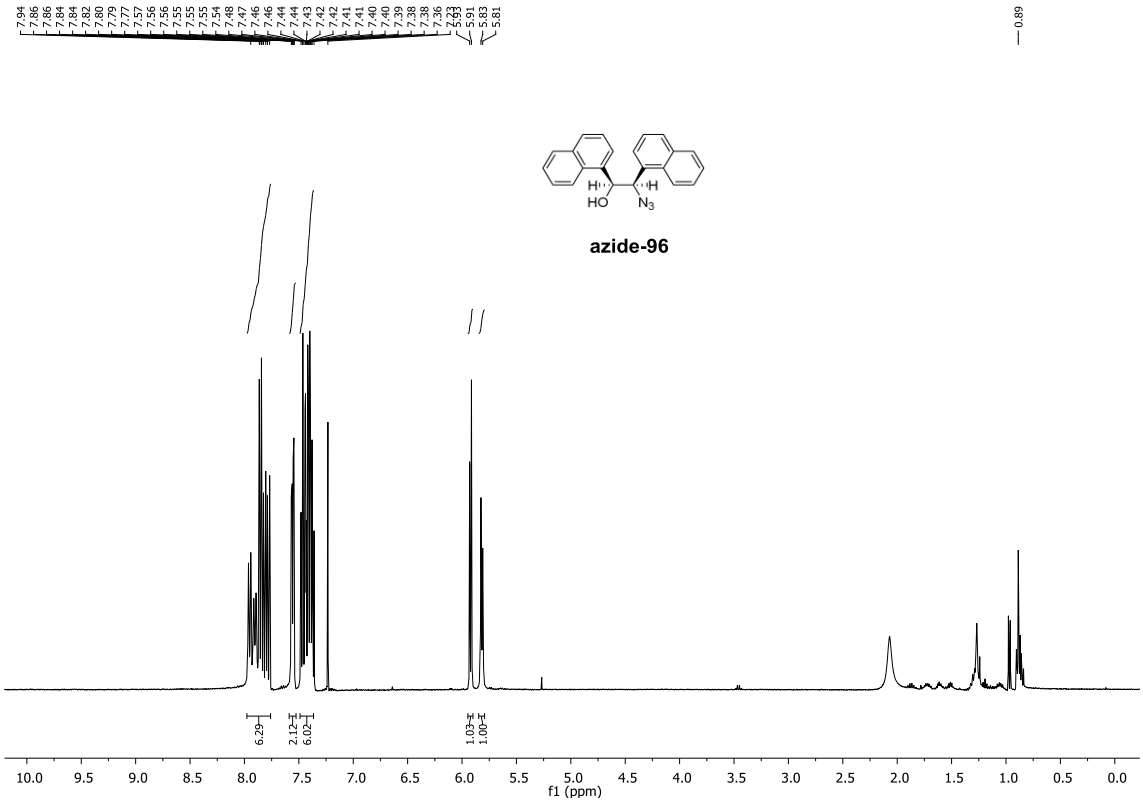

166.13
146.61 145.67 141.34 140.80
128.70 128.57 127.12 126.99 125.62 125.49
87.02
82.43
77.56 77.24 76.92
58.36
29.45
23.18 21.27 21.18 18.11
HO
O
N
H
I
91
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.60 7.57 7.56 7.55 7.54 7.54 7.53 7.48 7.40 7.40 7.38 7.38 7.37 7.36 7.35 7.33 7.32 7.31 7.31 7.30 7.30 7.28 7.28 7.27 7.27 7.26 6.54 6.54 6.54 6.46 6.41
2.05 2.05 2.04 1.88 1.87 1.86 1.84 1.84 1.82 1.03 1.02 1.01 1.00 0.60 0.60 0.58 0.57
I
O
N
92
3.07 9.09 0.84 0.86 0.99 2.97 1.13 3.04 3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

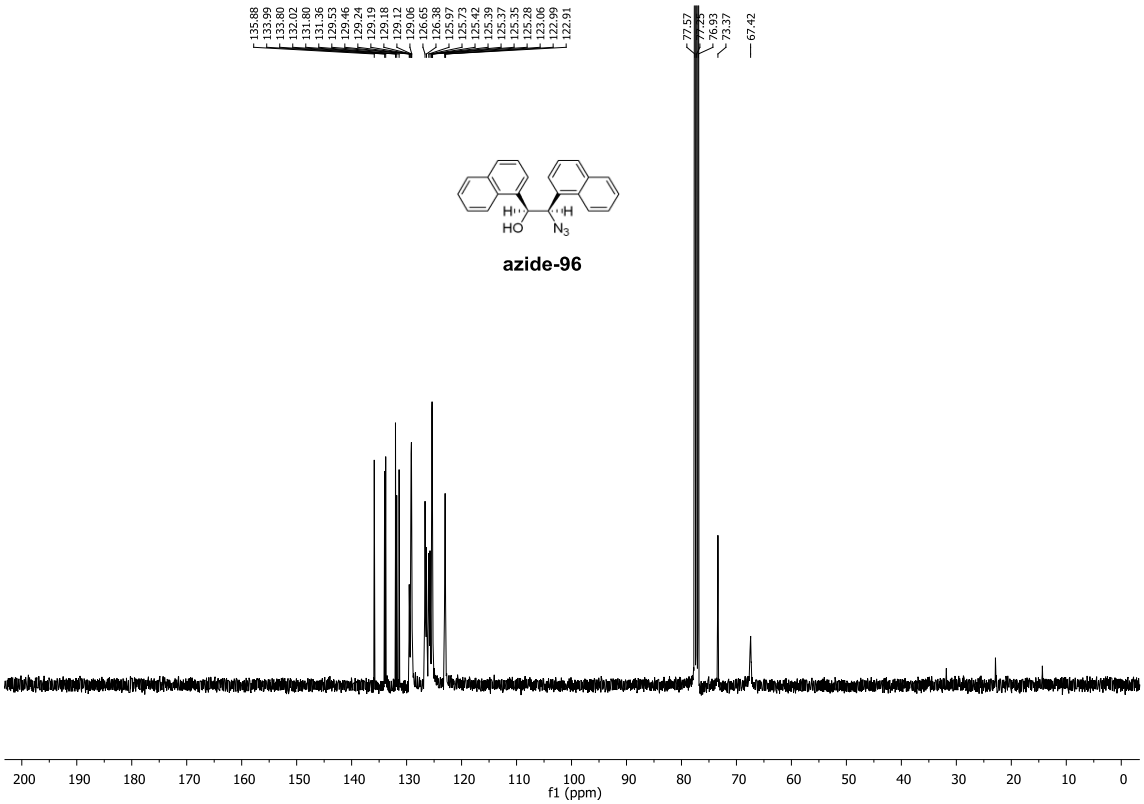

162.14 145.28 144.76 141.55 140.60 140.35 128.62 128.14 128.03 127.56 127.06 115.15 92.99 86.63 79.77 77.56 77.42 77.24 76.92 30.41 30.36 22.17 22.13 21.11 21.03 20.98 17.17 17.14
I
O
N
92
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

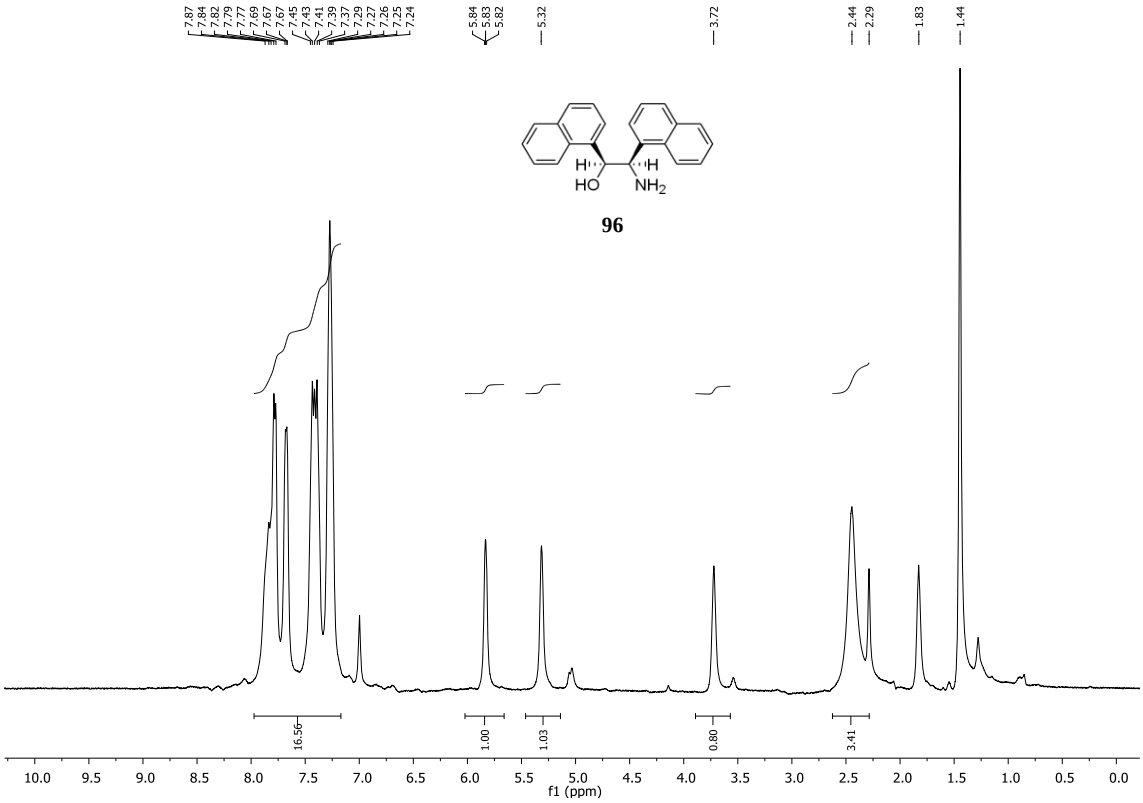


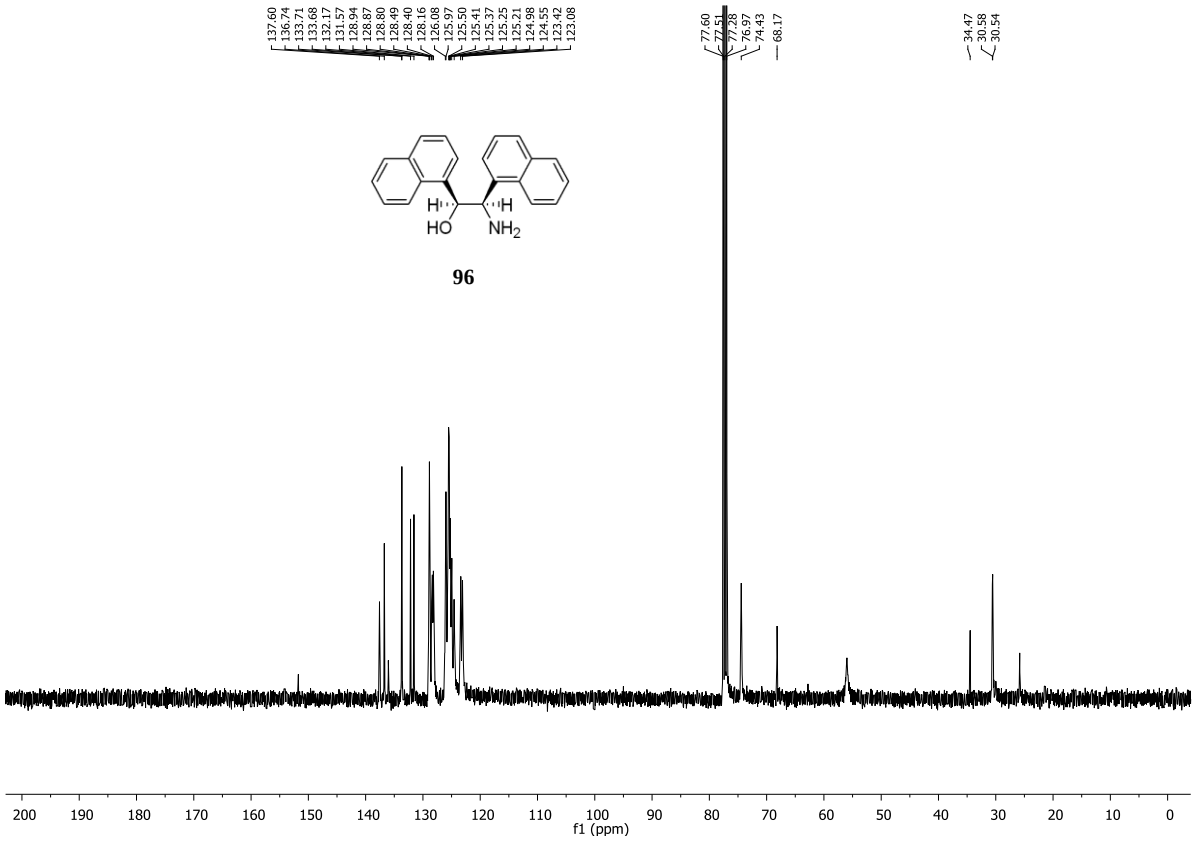
93a and 93b



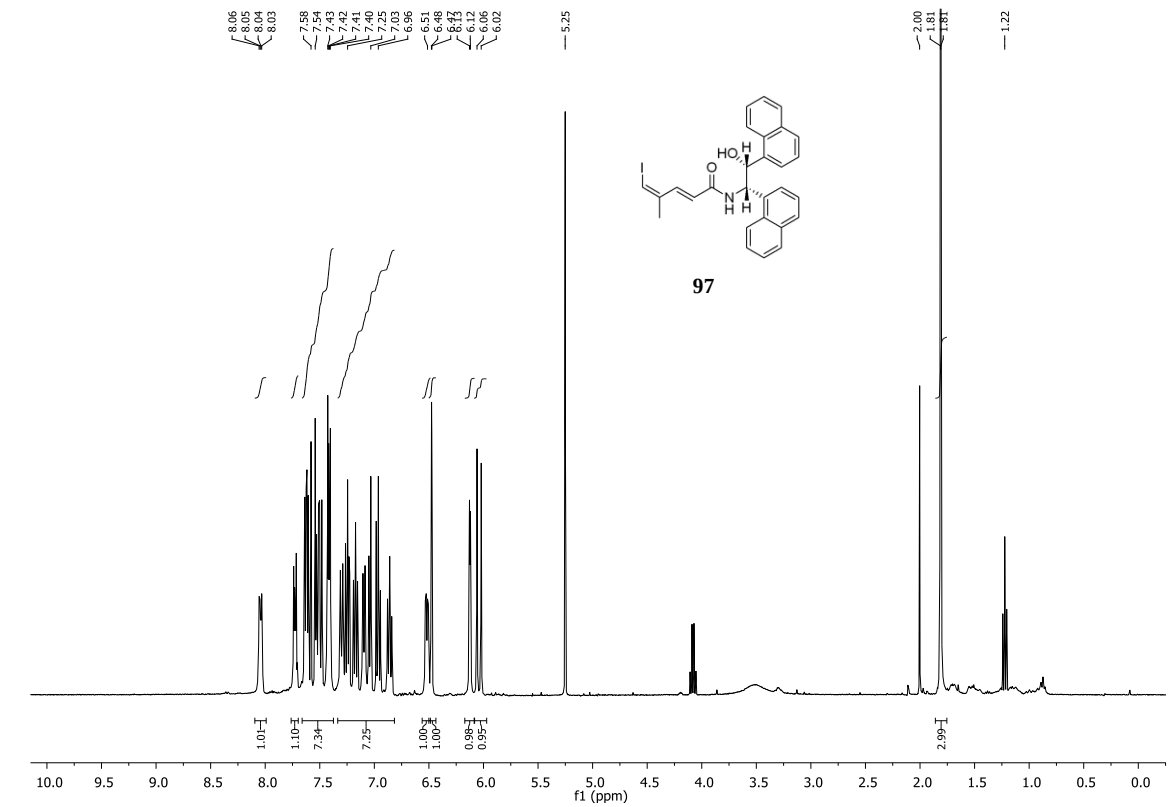
azide-96


135.88
133.99
133.80
132.02
131.80
131.36
129.53
129.46
129.24
129.13
129.18
129.12
129.06
126.65
126.38
125.97
125.73
125.42
125.39
125.37
125.35
125.28
123.06
122.99
122.91
77.57
77.25
76.93
73.37
67.42
azide-96
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

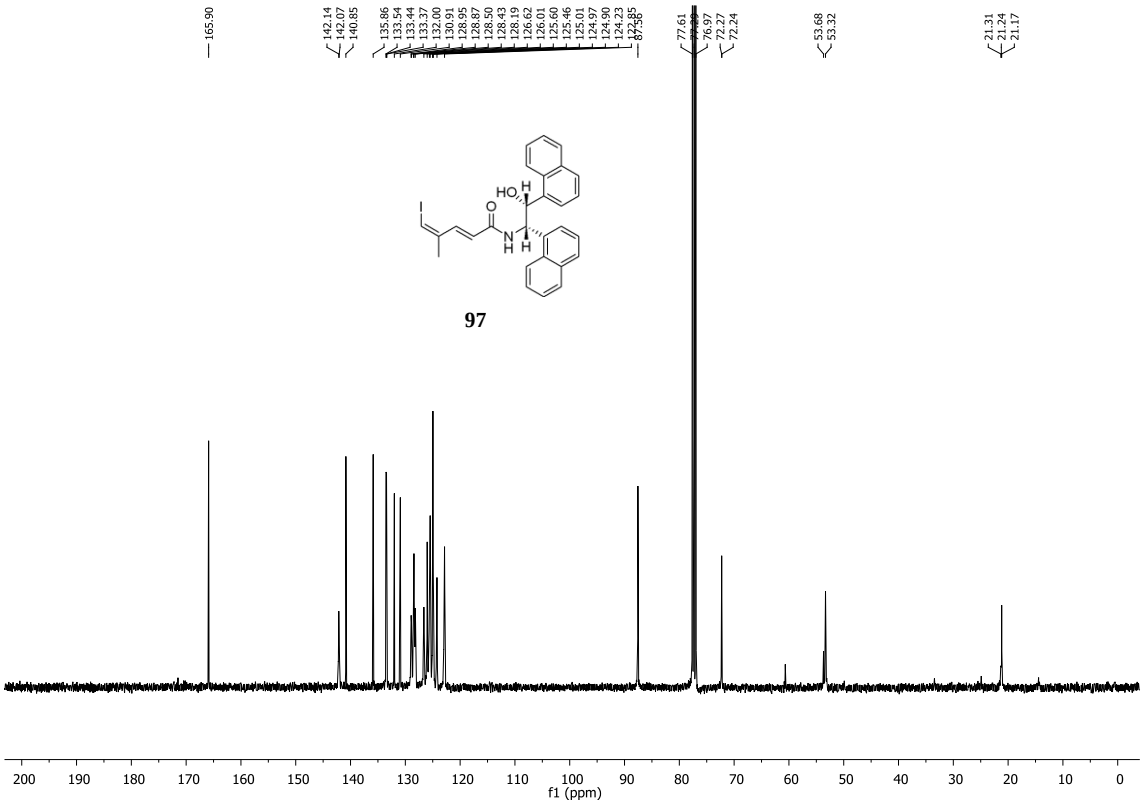

7.87
7.84
7.82
7.79
7.77
7.69
7.67
7.67
7.45
7.43
7.41
7.39
7.37
7.29
7.27
7.26
7.25
7.24
5.84
5.83
5.82
5.32
3.72
2.44
2.29
1.83
1.44
96
16.56
1.00
1.03
0.80
3.41
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


137.60
136.74
133.71
133.68
132.17
131.57
128.94
128.87
128.80
128.49
128.40
128.16
126.08
125.97
125.50
125.41
125.37
125.25
125.21
124.98
124.55
123.42
123.08
77.60
77.51
77.28
76.97
74.43
68.17
34.47
30.58
30.54
HO
NH2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

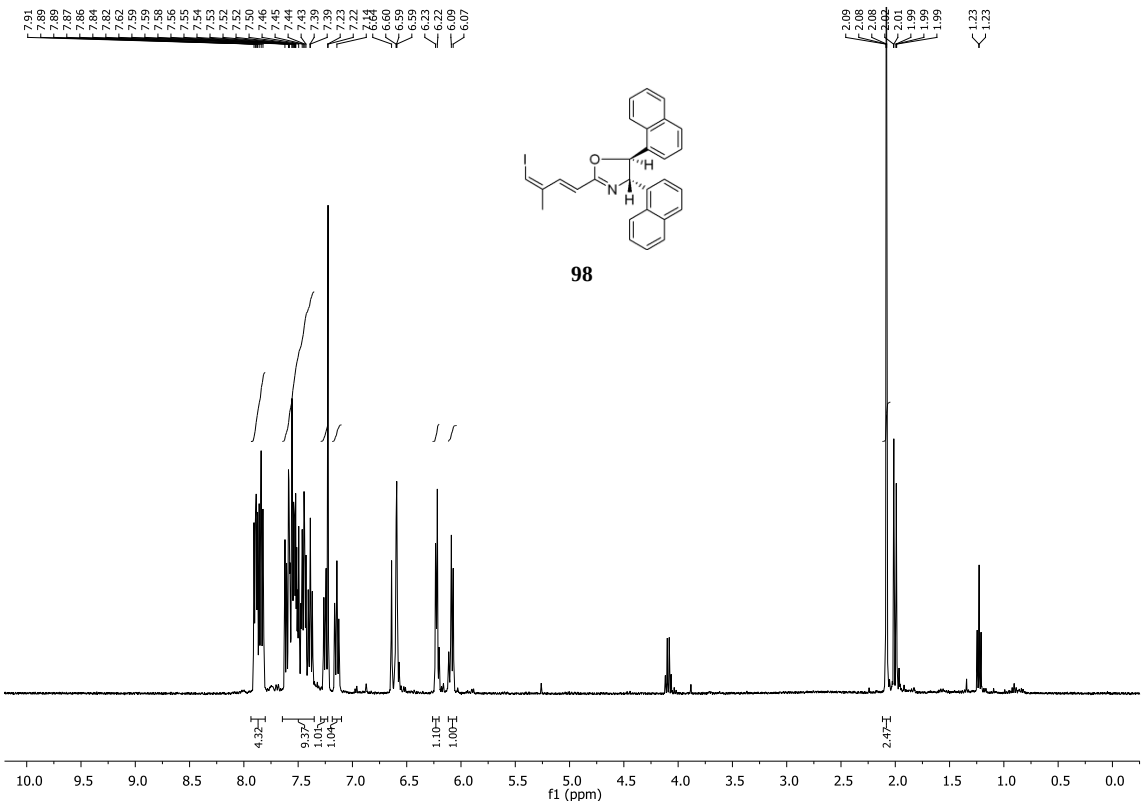
96


8.06
8.05
8.04
8.03
7.58
7.54
7.43
7.42
7.41
7.40
7.25
7.03
6.96
6.51
6.48
6.13
6.12
6.06
6.02
5.25
2.00
1.81
1.01
1.22
HO
O
N
H
1.01
1.10
7.34
7.25
1.00
1.00
0.98
0.95
2.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

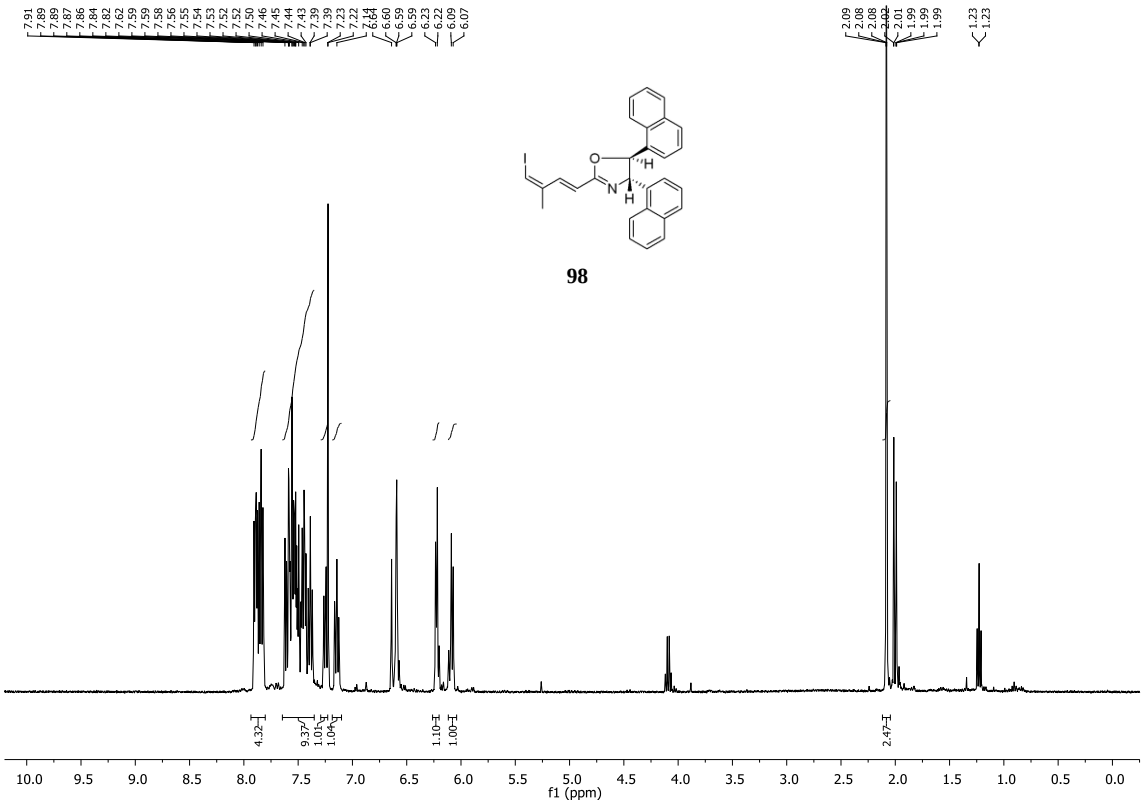
97


165.90
142.14
142.07
140.85
135.86
133.54
133.44
133.37
132.00
130.91
128.95
128.87
128.50
128.43
128.19
126.62
126.01
125.60
125.46
125.01
124.97
124.90
124.23
87.86
77.61
77.27
76.97
72.27
72.24
53.68
53.32
21.31
21.24
21.17
HO
H
O
I
N
H
H
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

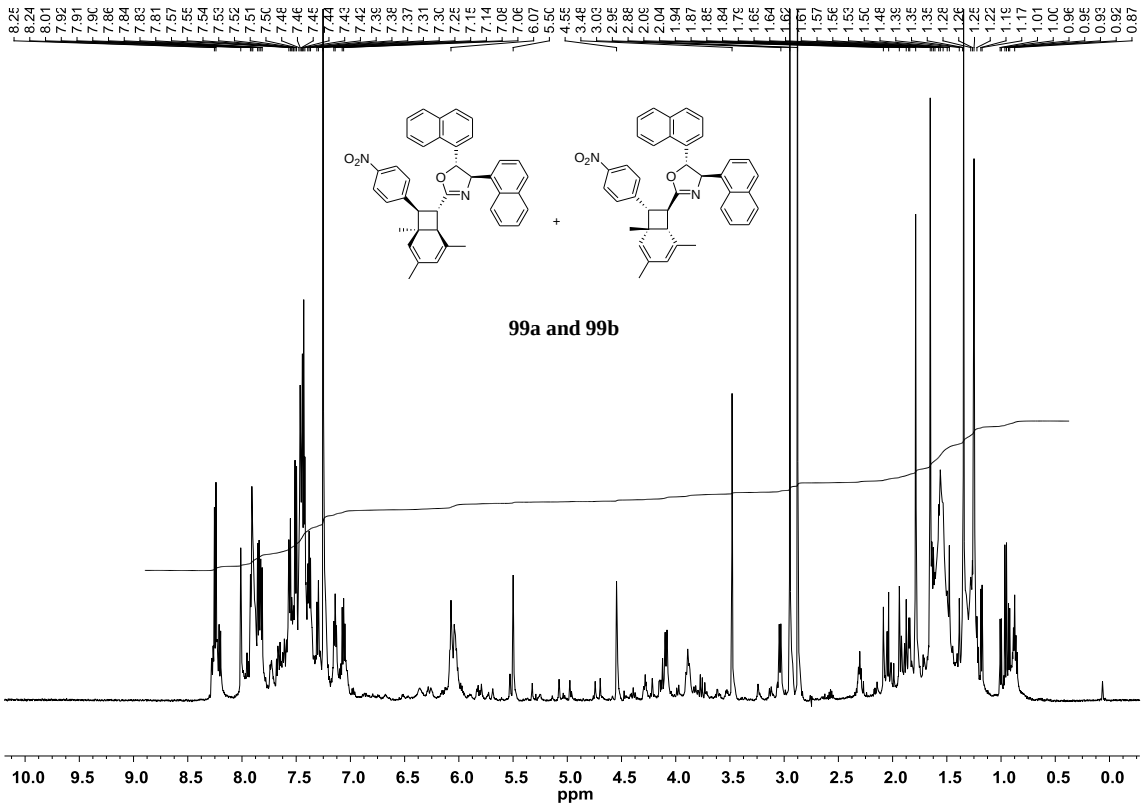
97


7.91
7.89
7.89
7.87
7.86
7.84
7.82
7.62
7.59
7.59
7.58
7.56
7.55
7.54
7.53
7.52
7.52
7.50
7.46
7.45
7.44
7.43
7.39
7.39
7.23
7.22
6.64
6.60
6.59
6.59
6.23
6.22
6.09
6.07
2.09
2.08
2.08
2.03
2.01
1.99
1.99
1.99
1.23
1.23
O
H
N
H
I
4.32
9.37
1.01
1.04
1.10
1.00
2.47
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

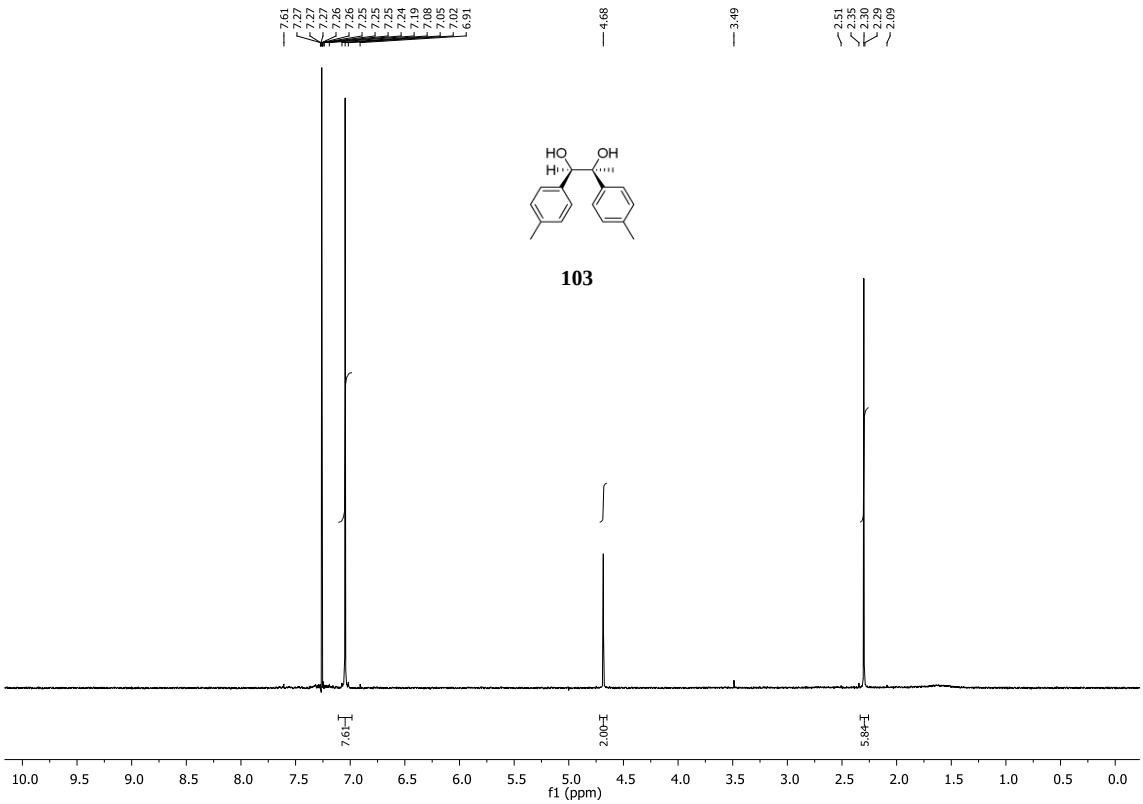
98



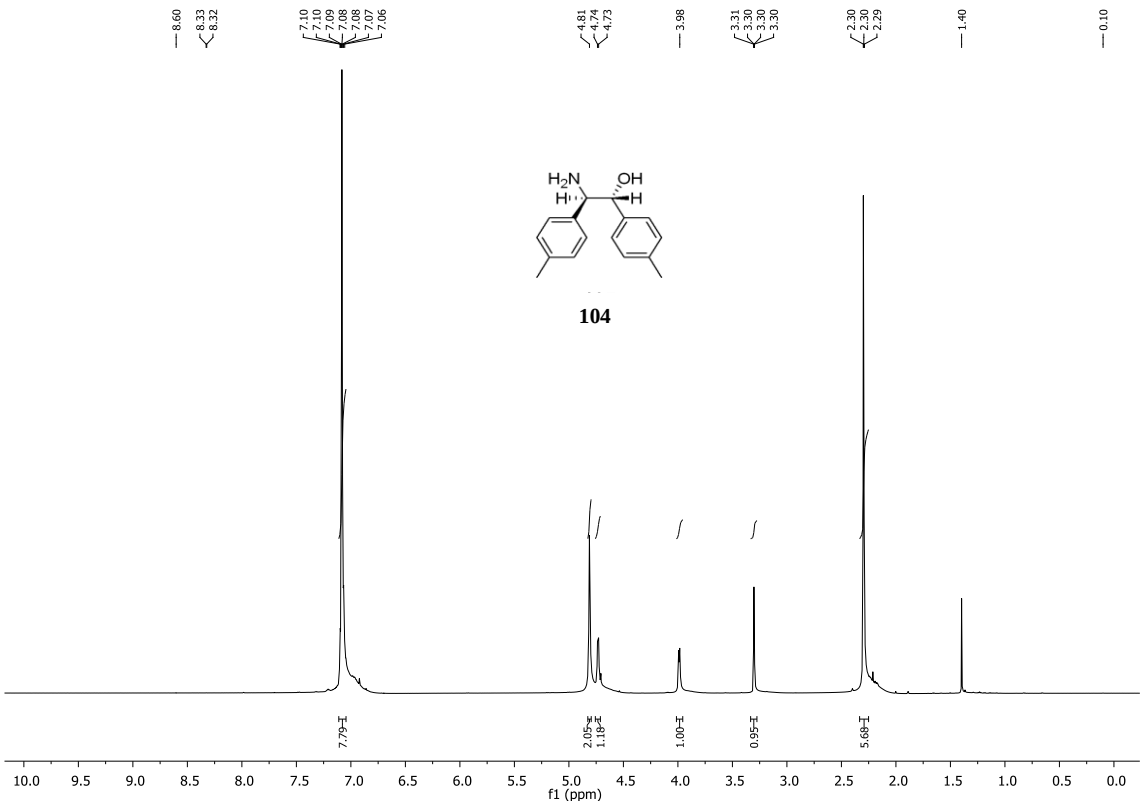
98



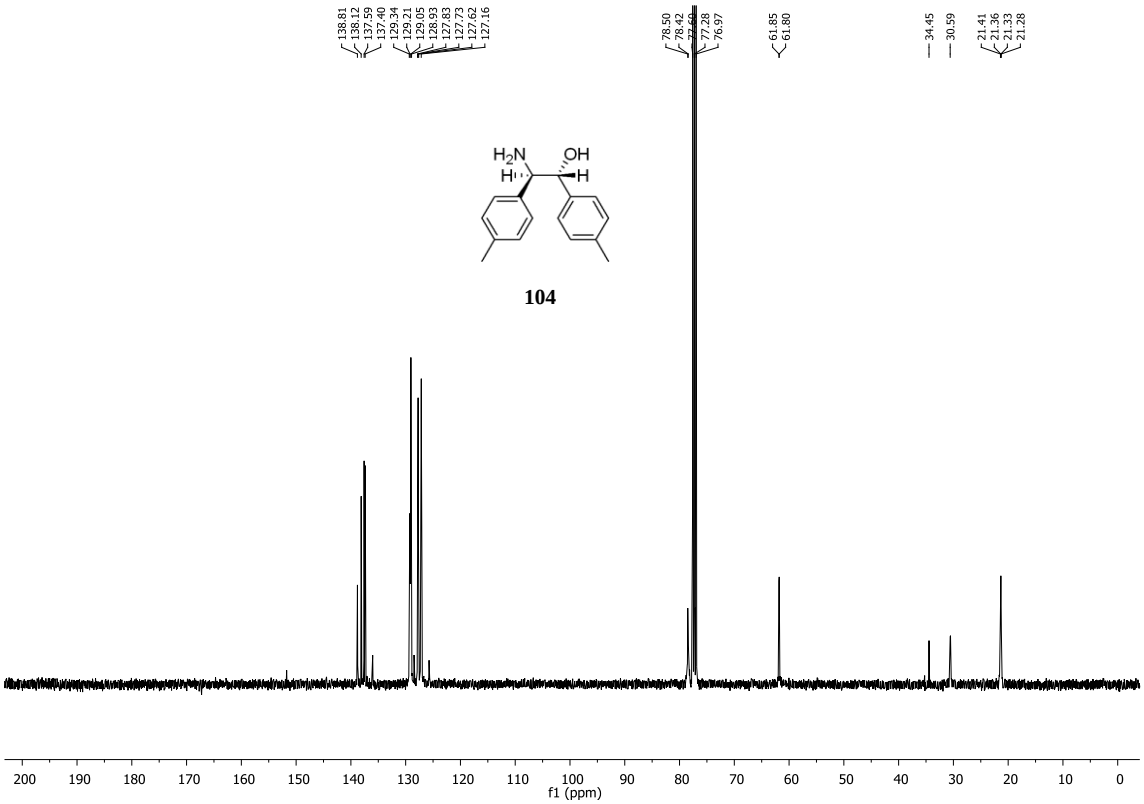
99a and 99b


7.61
7.27
7.27
7.27
7.26
7.26
7.25
7.25
7.25
7.24
7.19
7.08
7.05
7.02
6.91
4.68
3.49
2.51
2.35
2.30
2.29
2.09
HO
OH
H
7.61
2.00
5.84
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

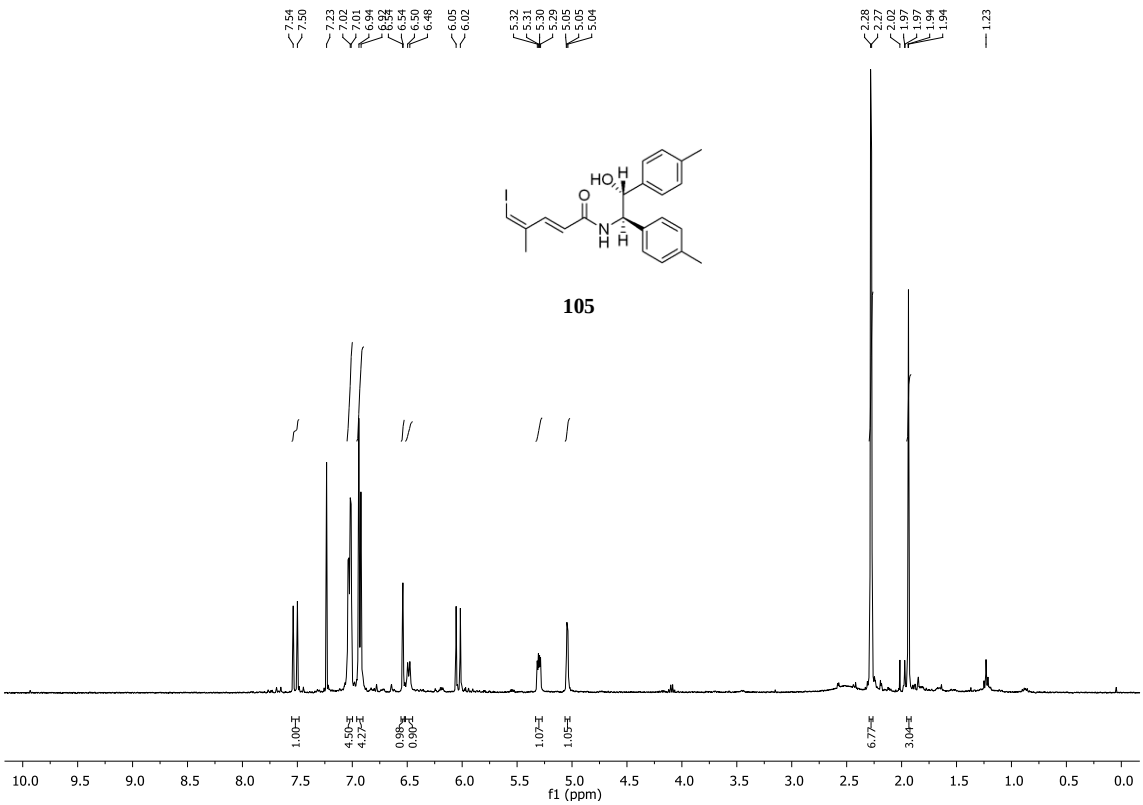
103


8.60
8.33
8.32
7.10
7.10
7.09
7.08
7.08
7.07
7.06
4.81
4.74
4.73
3.98
3.31
3.30
3.30
3.30
2.30
2.30
2.29
1.40
0.10
H2N
H
OH
H
7.79
2.05
1.18
1.00
0.95
5.68
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

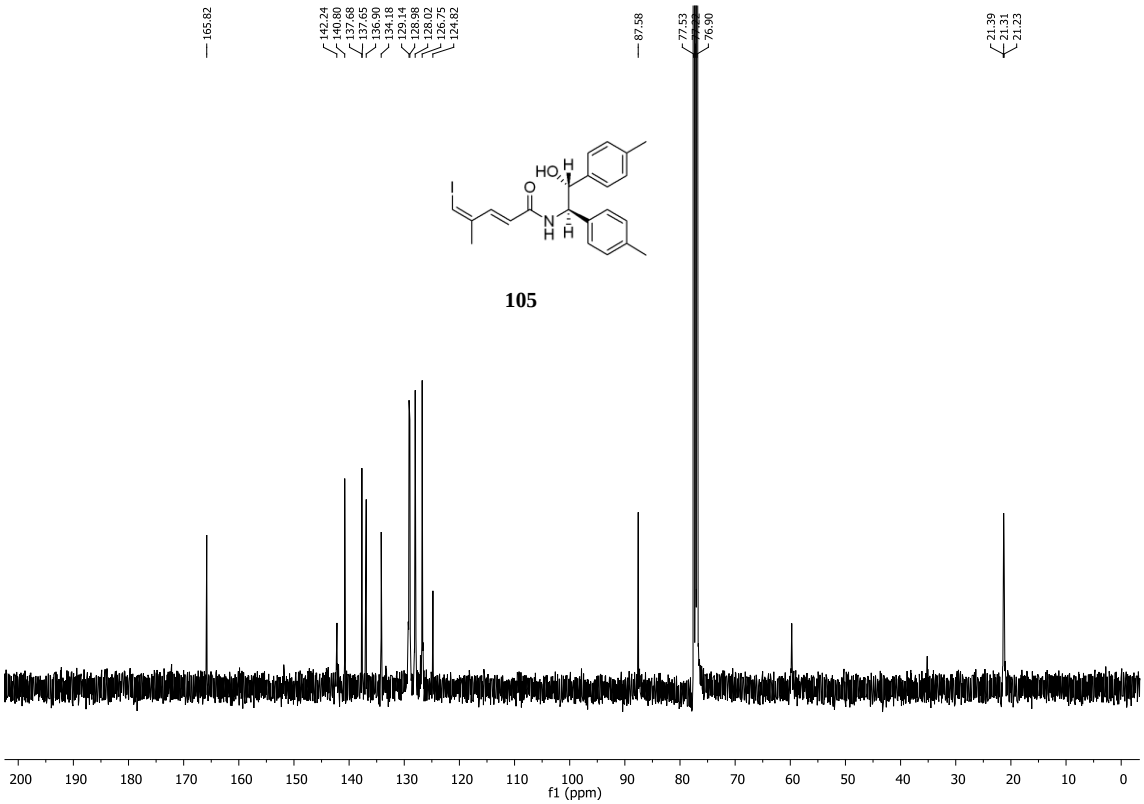
104


138.81
138.12
137.59
137.40
129.34
129.21
129.05
128.93
127.83
127.73
127.62
127.16
78.50
78.42
77.28
76.97
61.85
61.80
34.45
30.59
21.41
21.36
21.33
21.28
H2N
OH
H
H
f1 (ppm)

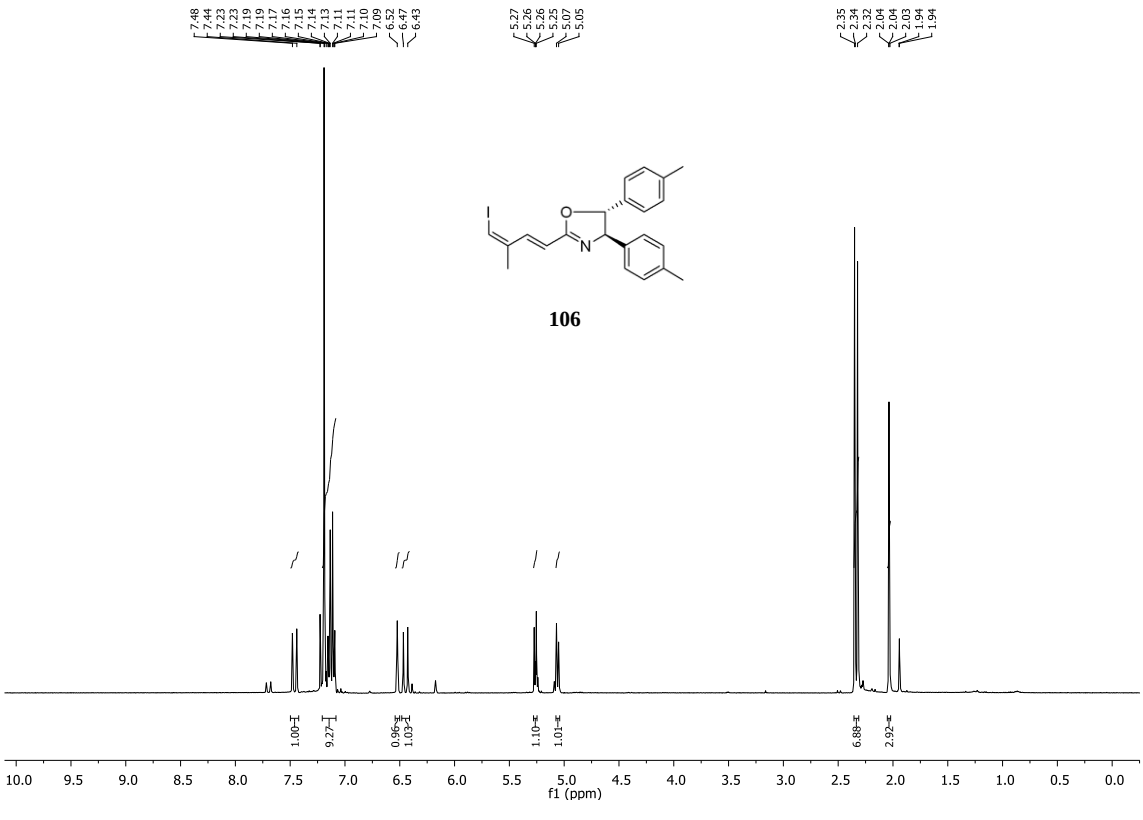
104


7.54
7.50
7.23
7.02
7.01
6.94
6.92
6.54
6.50
6.48
6.05
6.02
5.32
5.31
5.30
5.29
5.05
5.05
5.04
2.28
2.27
2.02
1.97
1.94
1.94
1.23
HO
H
O
I
N
H
1.00
4.50
4.27
0.99
0.90
1.07
1.05
6.77
3.04
f1 (ppm)

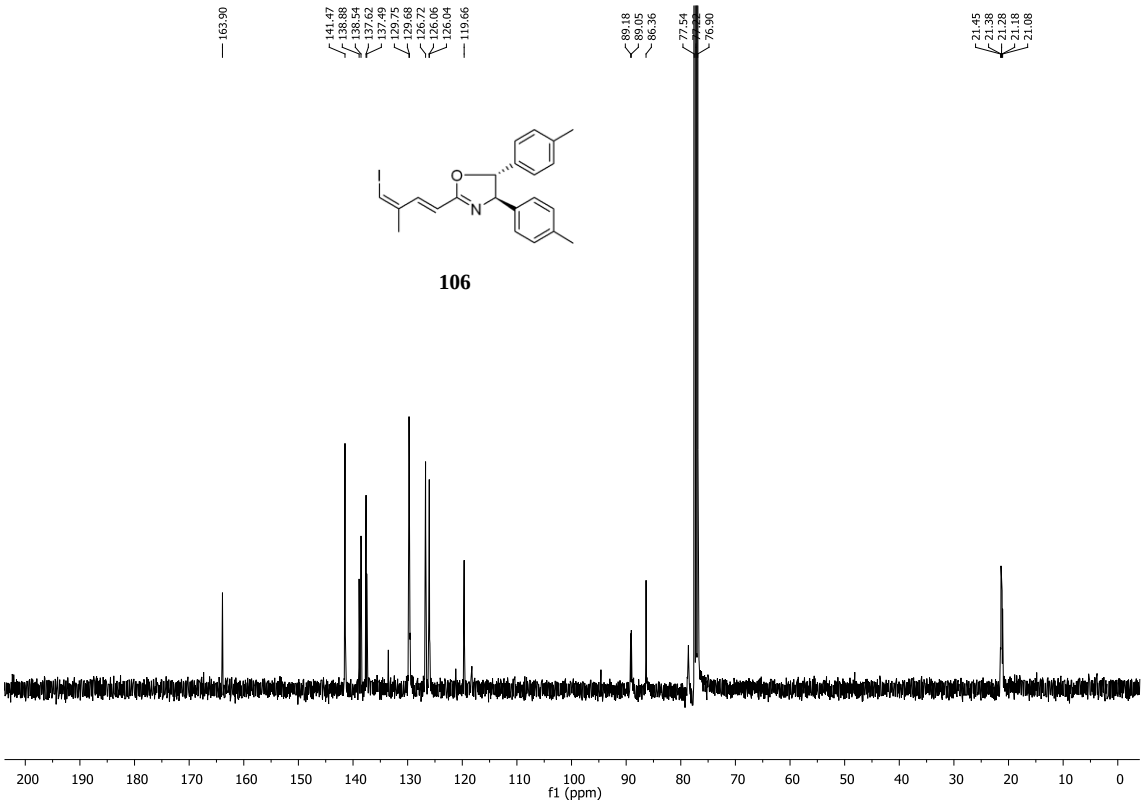
105


165.82
142.24
140.80
137.68
137.65
136.90
134.18
129.14
128.98
128.02
126.75
124.82
87.58
77.53
76.90
21.39
21.31
21.23
HO
H
O
I
N
H
H
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

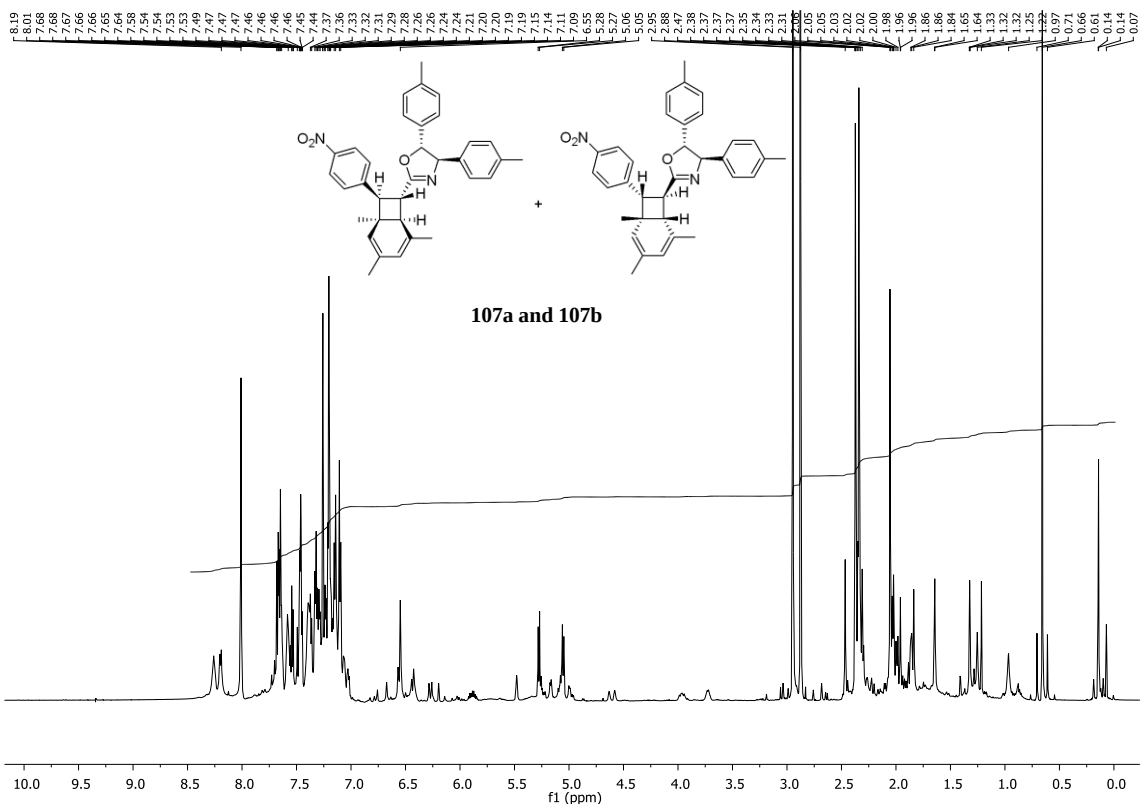
105


7.48
7.44
7.23
7.23
7.19
7.19
7.17
7.16
7.15
7.14
7.13
7.11
7.11
7.10
7.09
6.52
6.47
6.43
5.27
5.26
5.26
5.25
5.07
5.05
2.35
2.34
2.32
2.04
2.04
2.03
1.94
1.94
I
O
N
1.00
9.27
0.96
1.03
1.10
1.01
6.88
2.92
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

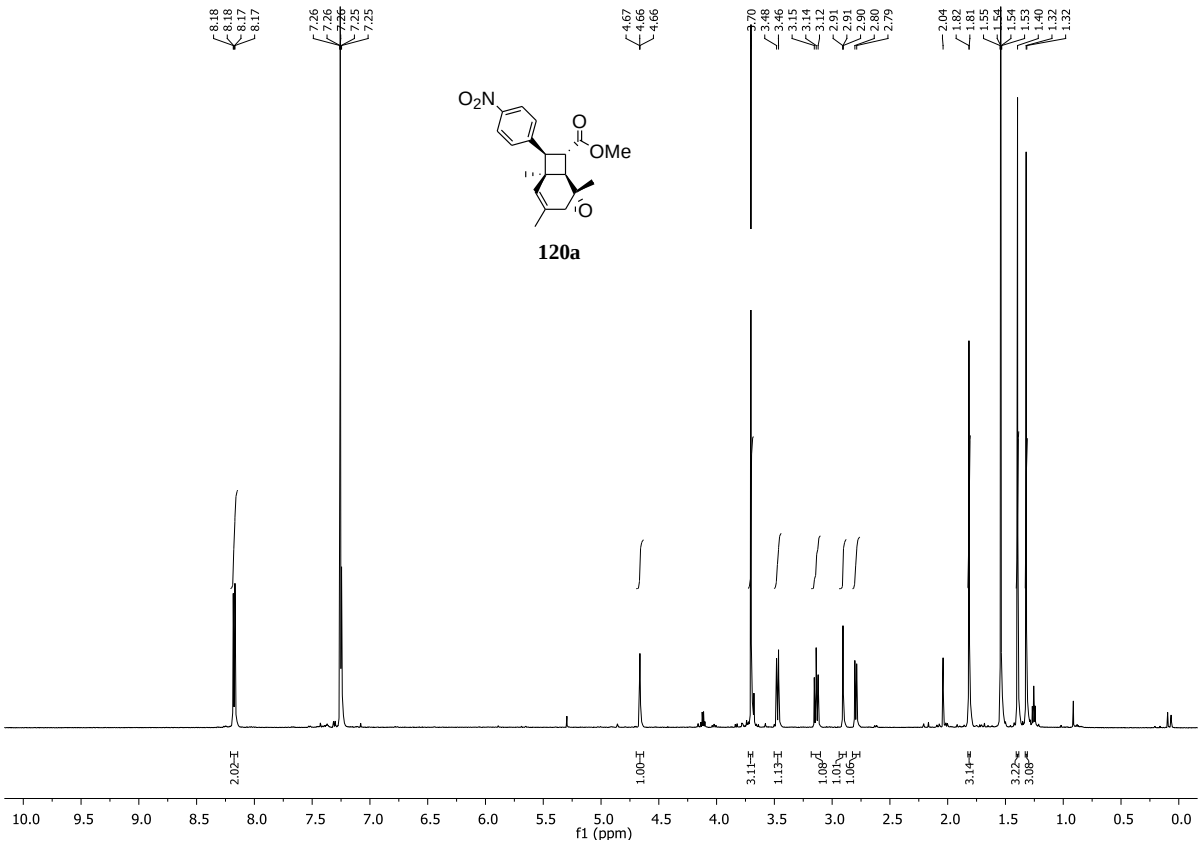
106



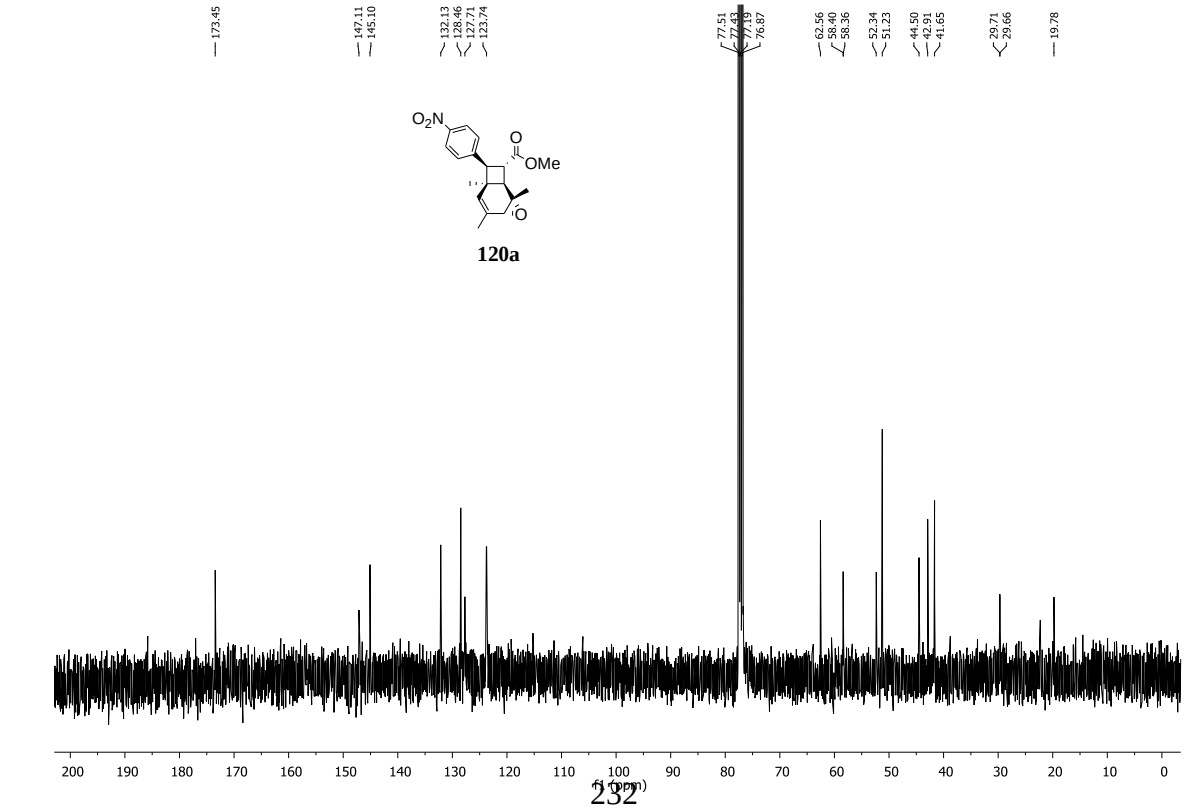
106



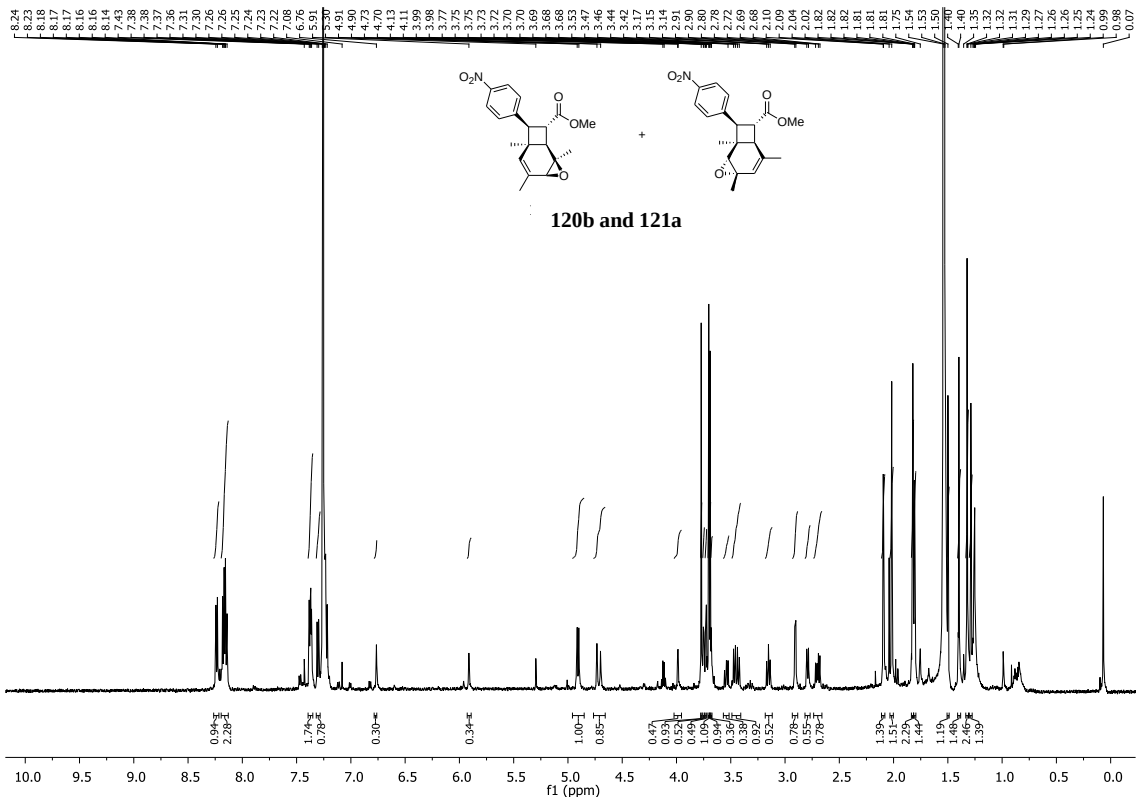
107a and 107b


8.18
8.18
8.17
8.17
7.26
7.26
7.26
7.25
7.25
4.67
4.66
4.66
3.70
3.48
3.46
3.15
3.14
3.12
2.91
2.90
2.80
2.79
2.04
1.82
1.81
1.55
1.54
1.54
1.53
1.40
1.32
1.32
O2N
O
OMe
O
2.02
1.00
3.11
1.13
1.08
1.01
1.06
3.14
3.22
3.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

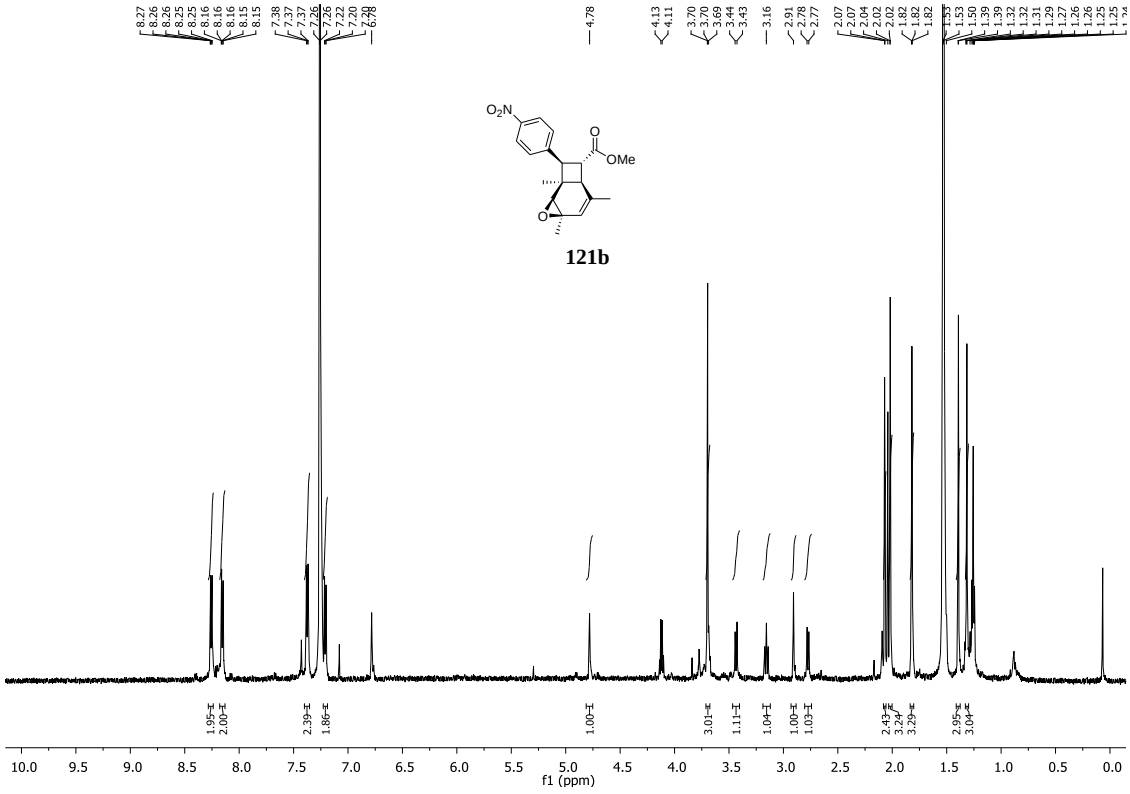
120a


173.45
147.11
145.10
132.13
128.46
127.71
123.74
77.51
77.43
77.19
76.87
62.56
58.40
58.36
52.34
51.23
44.50
42.91
41.65
29.71
29.66
19.78
O2N
O
OMe
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

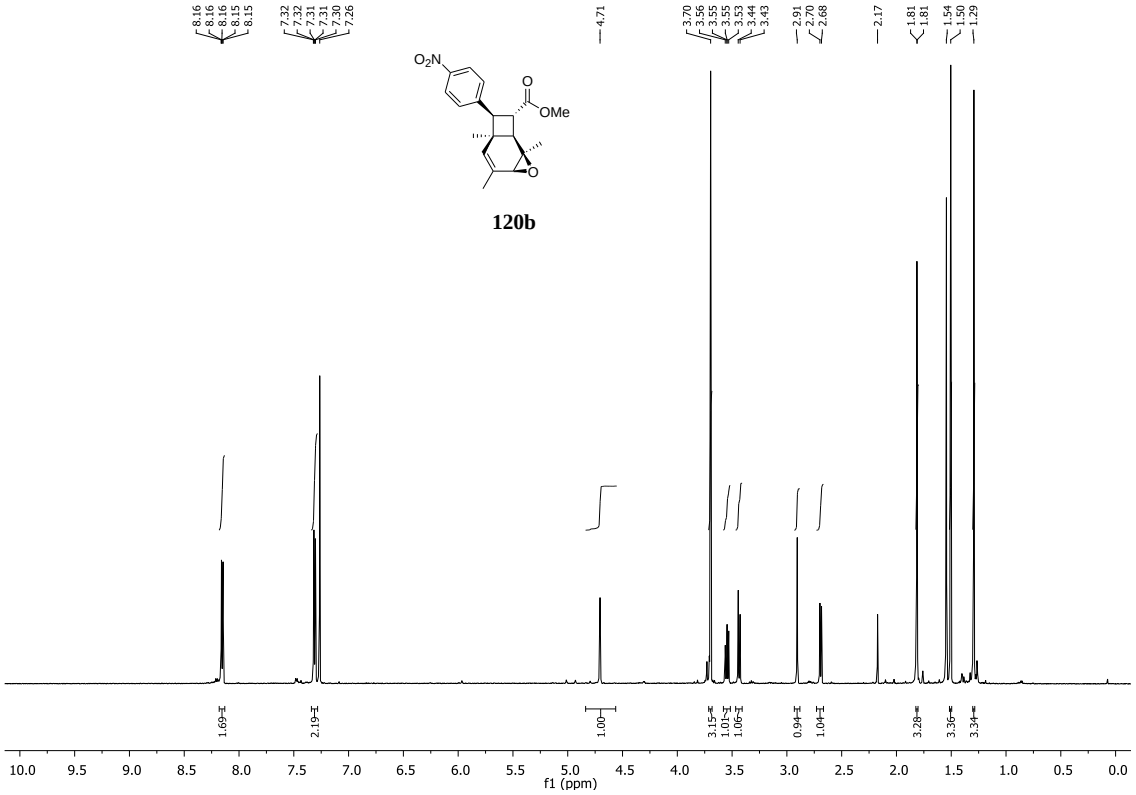
120a



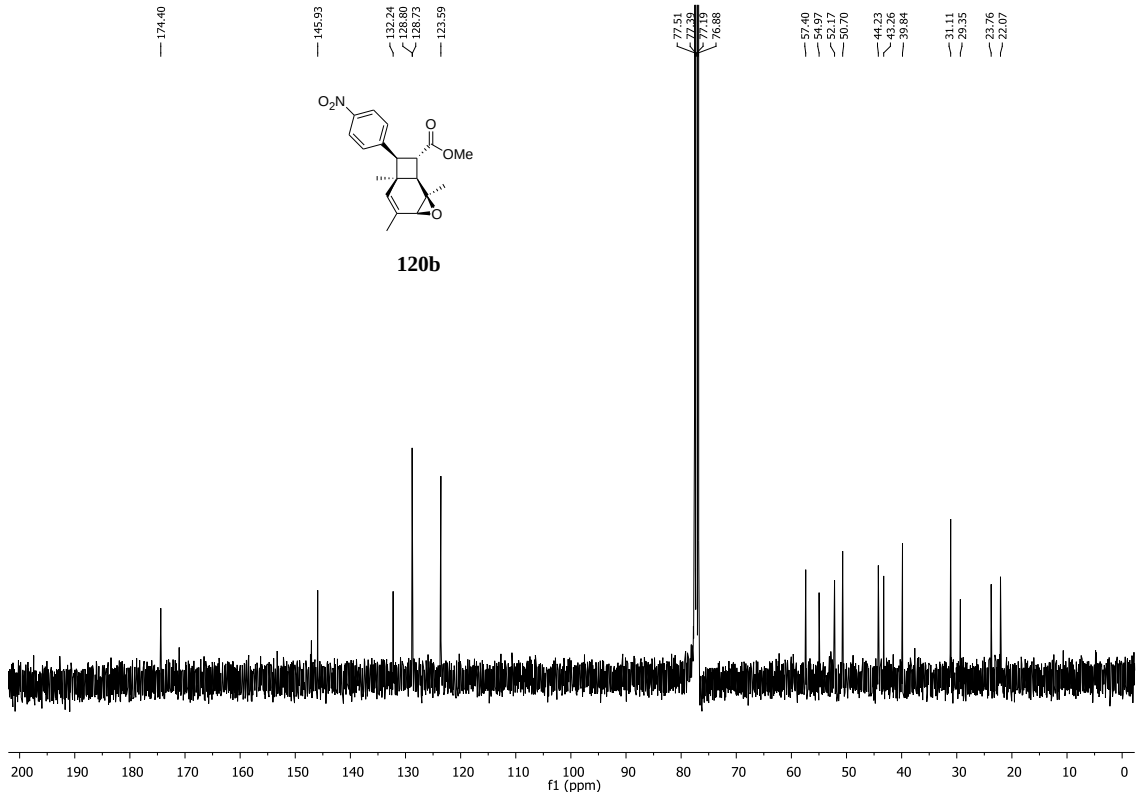
120b and 121a



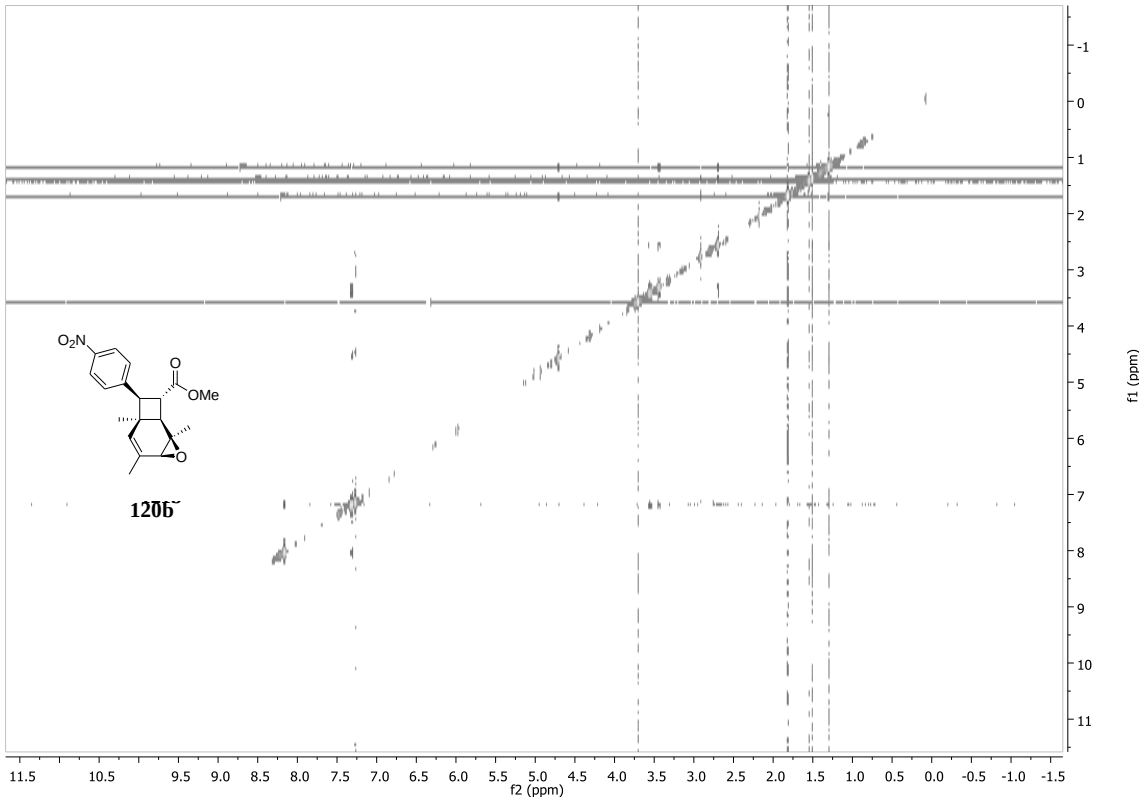
121b


8.16
8.16
8.16
8.15
8.15
7.32
7.32
7.31
7.31
7.30
7.26
4.71
3.70
3.56
3.55
3.55
3.53
3.44
3.43
2.91
2.70
2.68
2.17
1.81
1.81
1.54
1.50
1.29
O2N
O
OMe
O
1.69
2.19
1.00
3.15
1.01
1.06
0.94
1.04
3.28
3.36
3.34
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

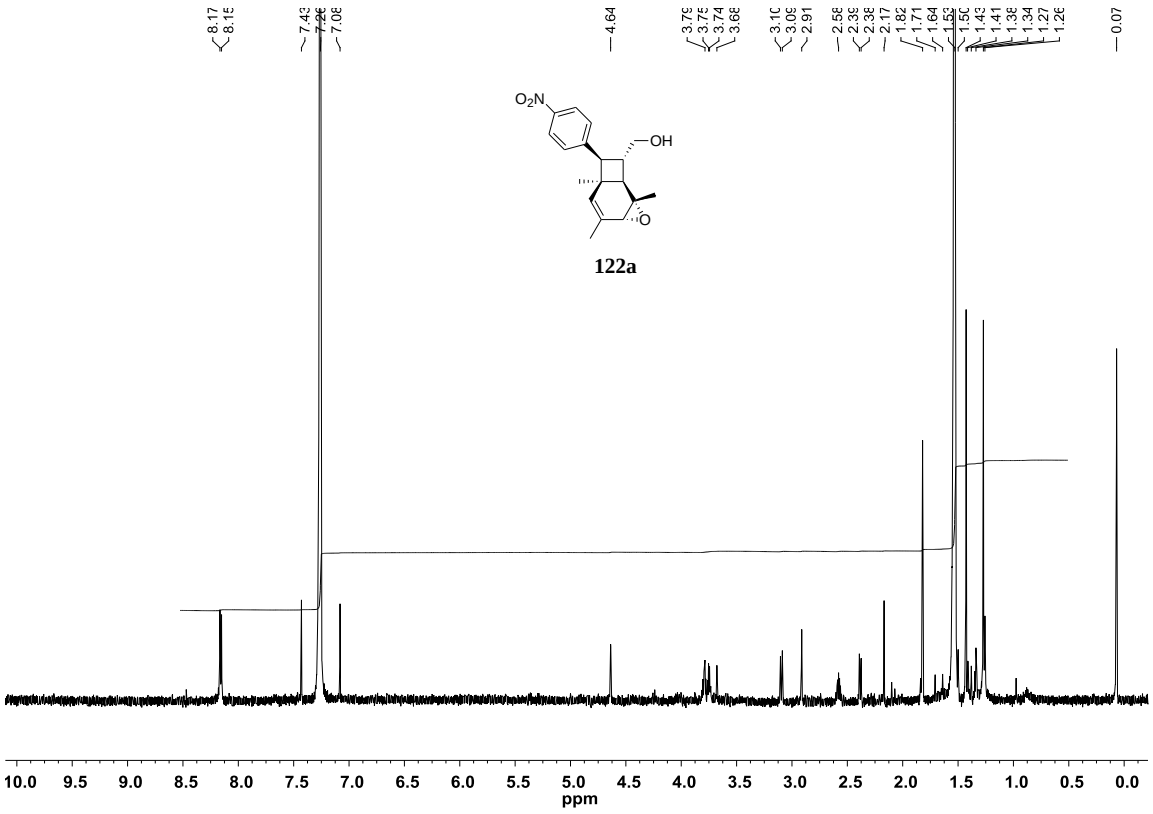
120b


174.40
145.93
132.24
128.80
128.73
123.59
77.51
77.39
77.19
76.88
57.40
54.47
52.17
50.70
44.23
43.26
39.84
31.11
29.35
23.76
22.07
O2N
O
OMe
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

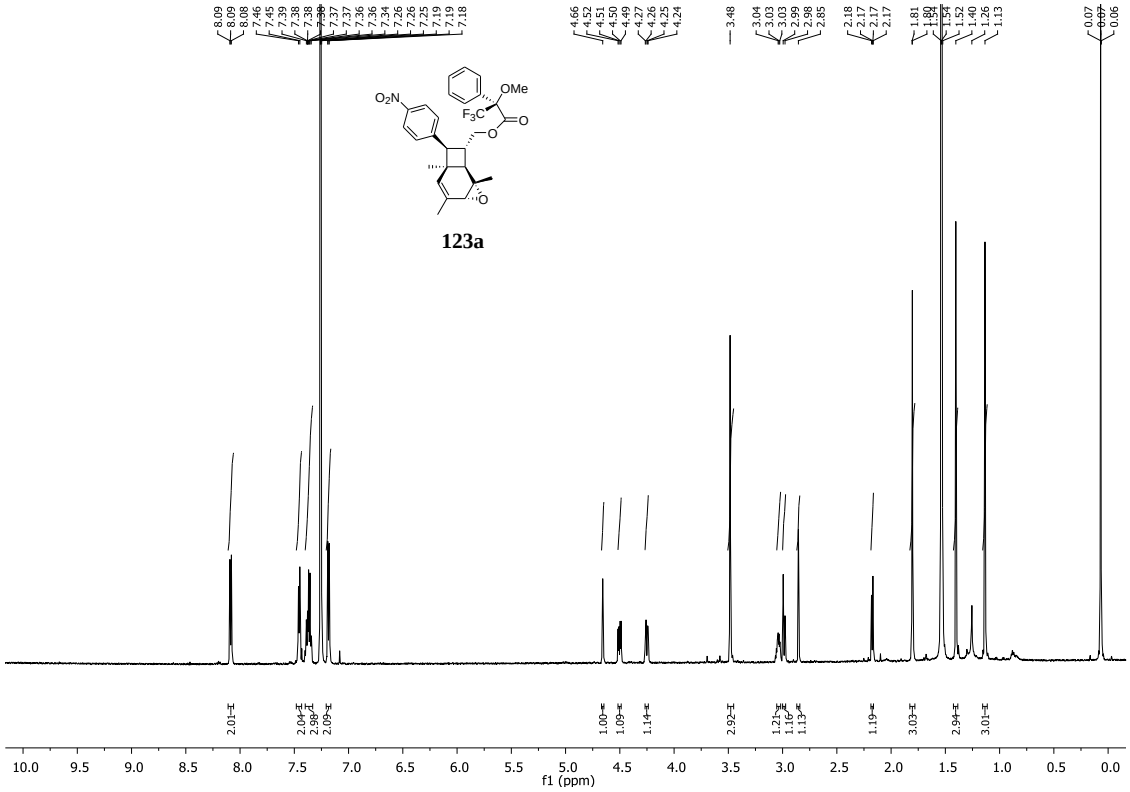
120b



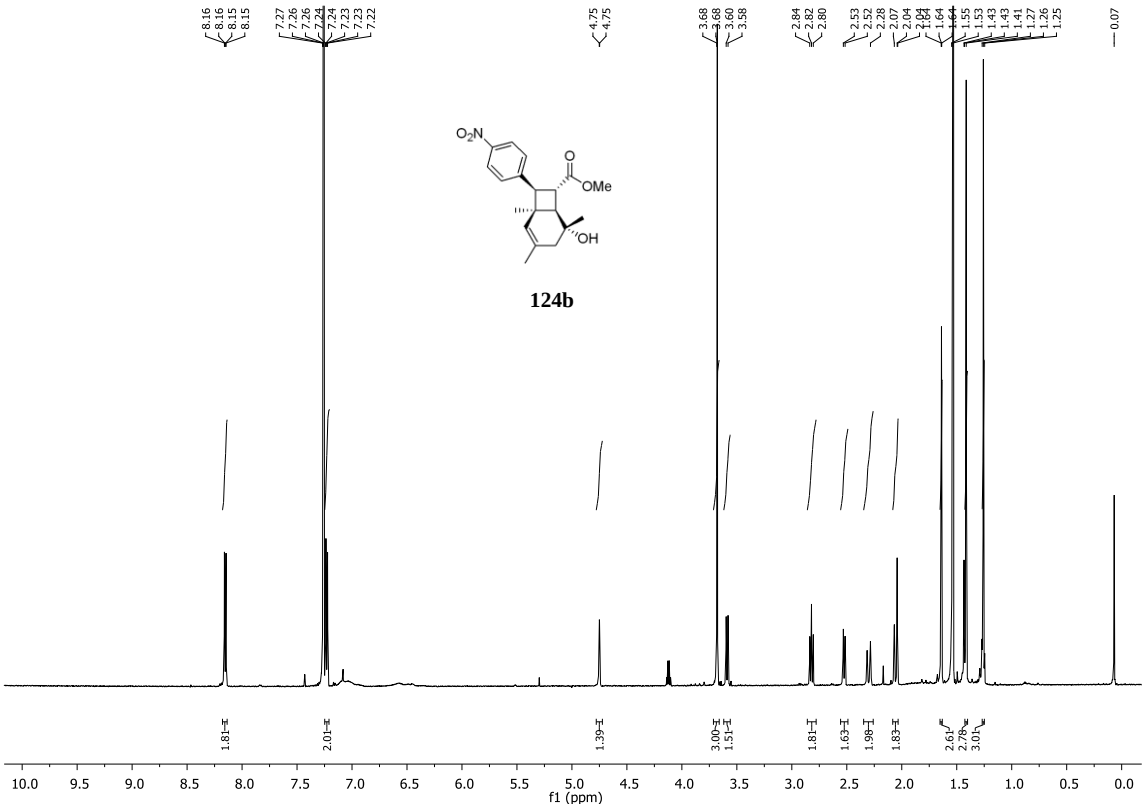
120b



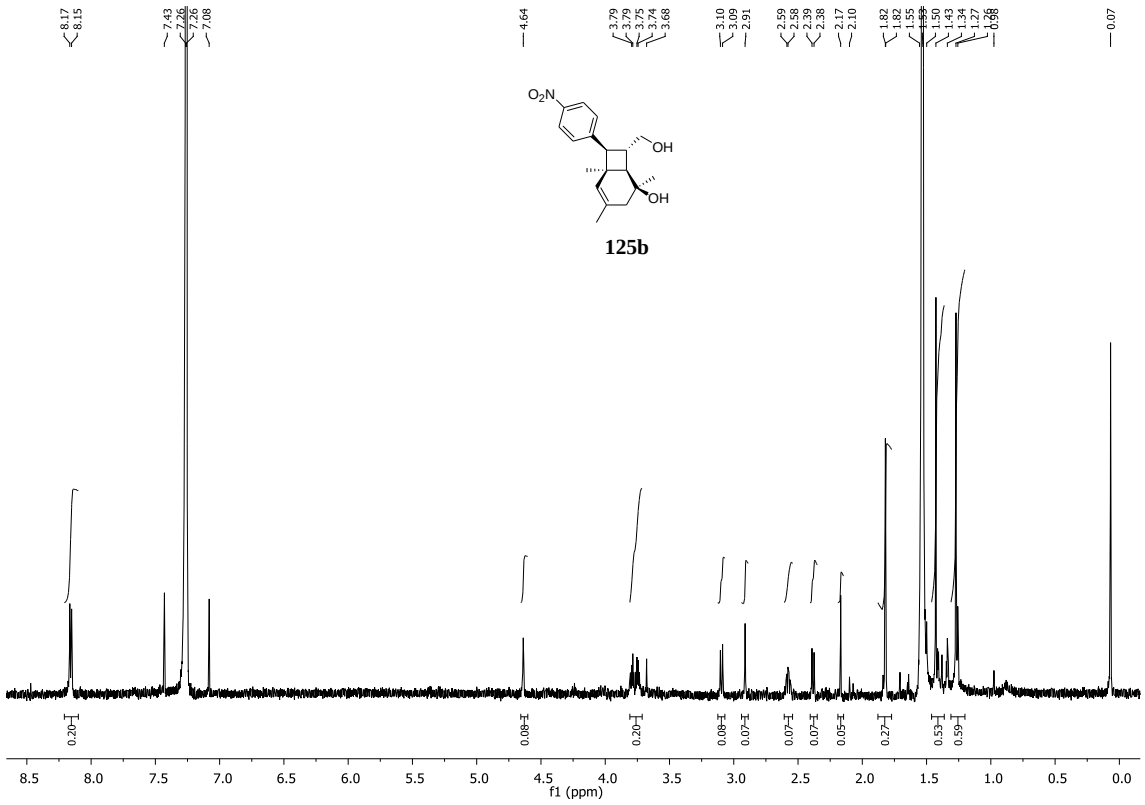
122a


8.09
8.09
8.08
7.46
7.45
7.39
7.38
7.38
7.38
7.37
7.37
7.36
7.36
7.34
7.26
7.26
7.25
7.19
7.19
7.18
4.66
4.52
4.51
4.50
4.49
4.27
4.26
4.25
4.24
3.48
3.04
3.03
3.03
2.99
2.98
2.85
2.18
2.17
2.17
2.17
1.81
1.80
1.54
1.52
1.40
1.26
1.13
0.07
0.07
0.06
O2N
OMe
F3C
O
O
O
2.01
2.04
2.98
2.09
1.00
1.09
1.14
2.92
1.21
1.16
1.13
1.19
3.03
2.94
3.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

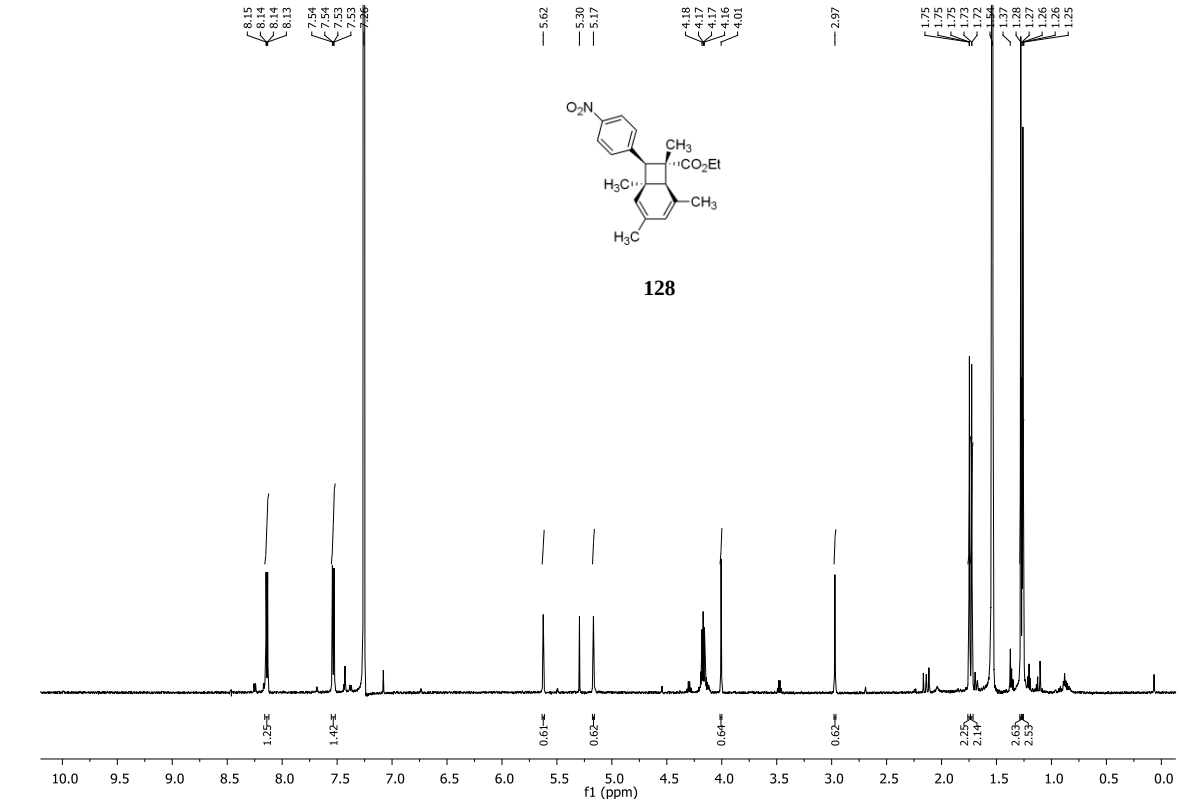
123a


8.16
8.16
8.15
8.15
7.27
7.26
7.26
7.24
7.24
7.23
7.23
7.22
4.75
4.75
3.68
3.68
3.60
3.58
2.84
2.82
2.80
2.53
2.52
2.28
2.07
2.04
1.64
1.55
1.53
1.43
1.43
1.41
1.27
1.26
1.25
0.07
O2N
O
OMe
OH
1.81
2.01
1.39
3.00
1.51
1.81
1.63
1.98
1.83
2.61
2.76
3.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

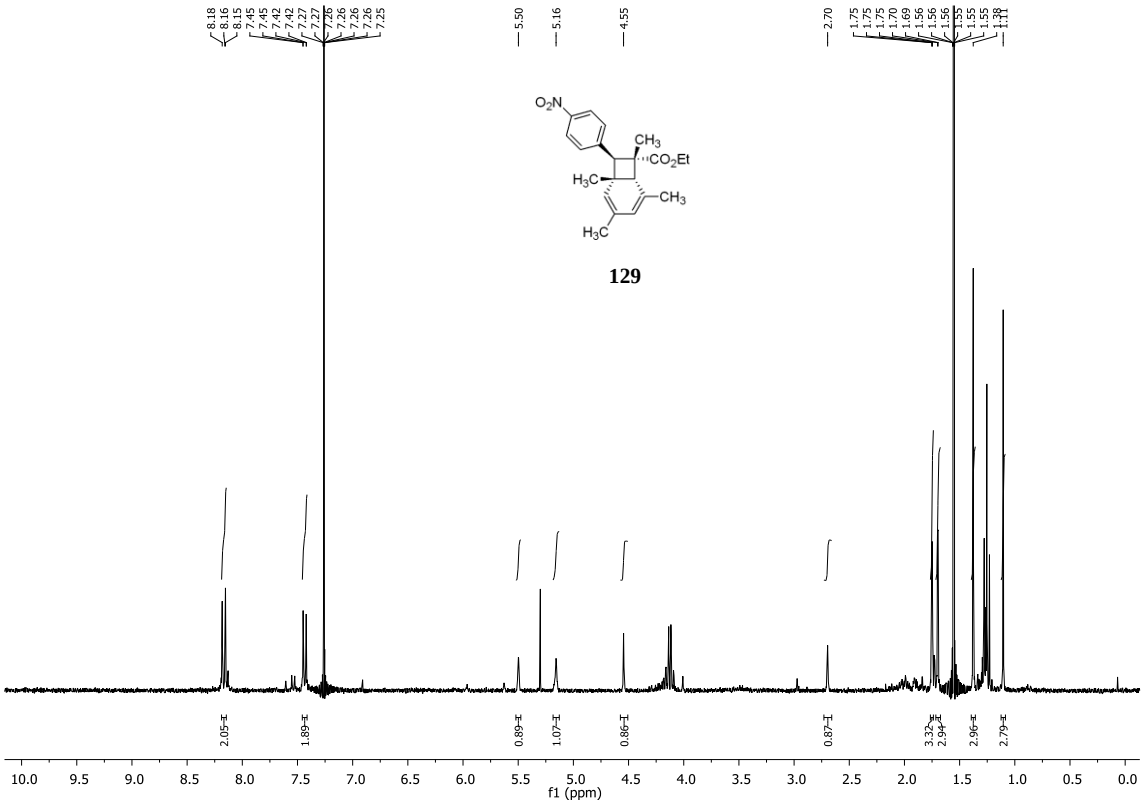
124b


8.17
8.15
7.43
7.26
7.26
7.26
7.08
4.64
3.79
3.79
3.75
3.74
3.68
3.10
3.09
2.91
2.59
2.58
2.39
2.38
2.17
2.10
1.82
1.82
1.55
1.50
1.43
1.34
1.27
0.88
0.07
O2N
OH
OH
0.20
0.08
0.20
0.08
0.07
0.07
0.07
0.05
0.27
0.53
0.59
f1 (ppm)

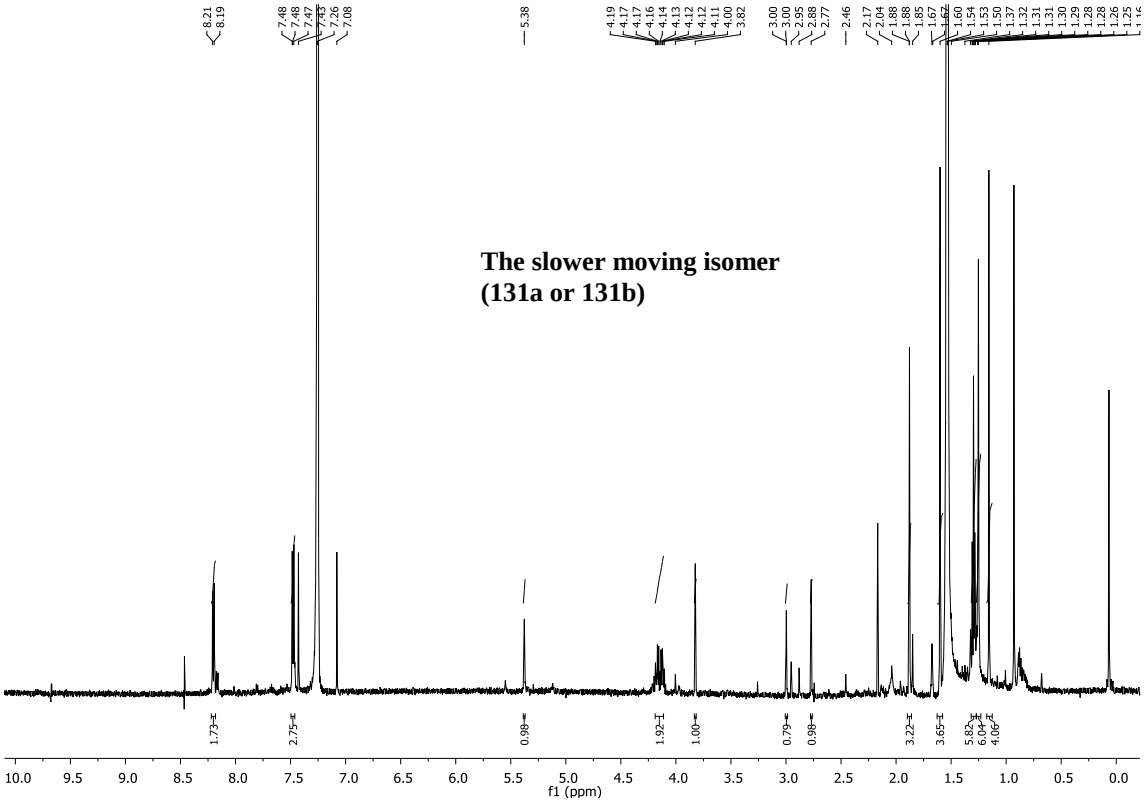
125b


8.15
8.14
8.14
8.13
7.54
7.54
7.53
7.53
5.62
5.30
5.17
4.18
4.17
4.17
4.16
4.01
2.97
1.75
1.75
1.75
1.73
1.72
1.37
1.28
1.27
1.26
1.26
1.25
O2N
CH3
CO2Et
H3C
CH3
H3C
1.25
1.42
0.61
0.62
0.64
0.62
2.25
2.14
2.63
2.53
f1 (ppm)

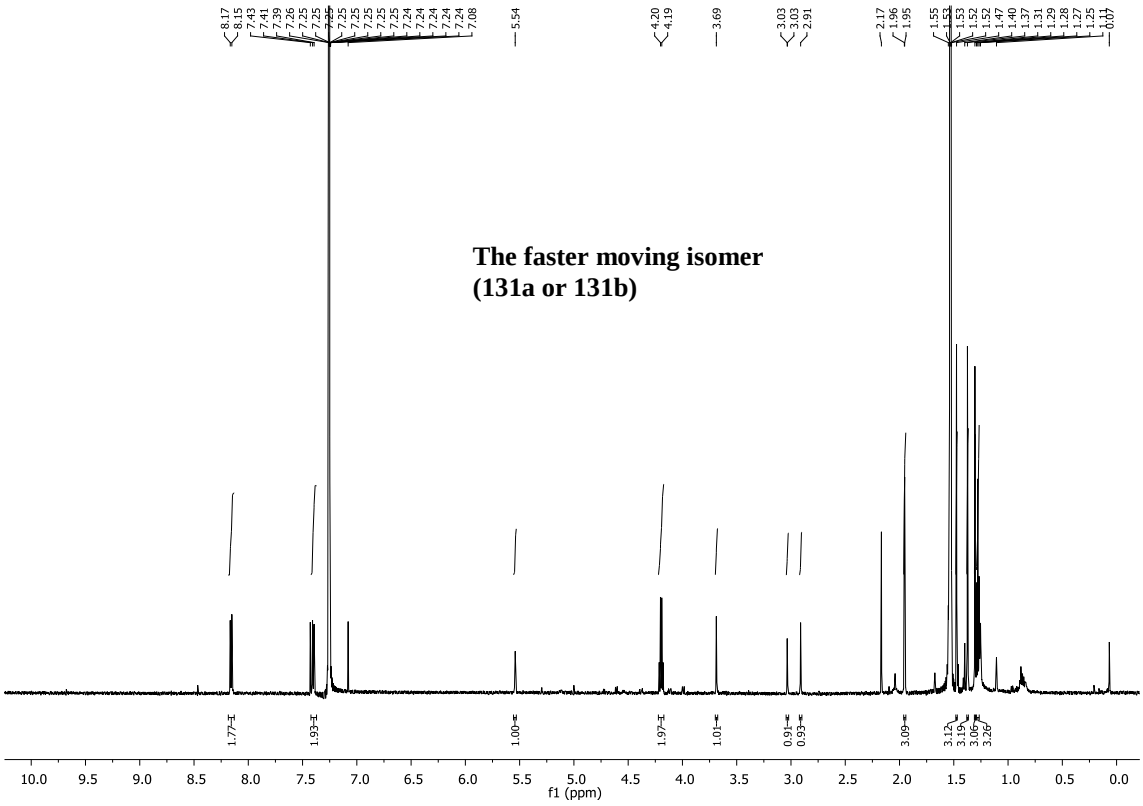
128



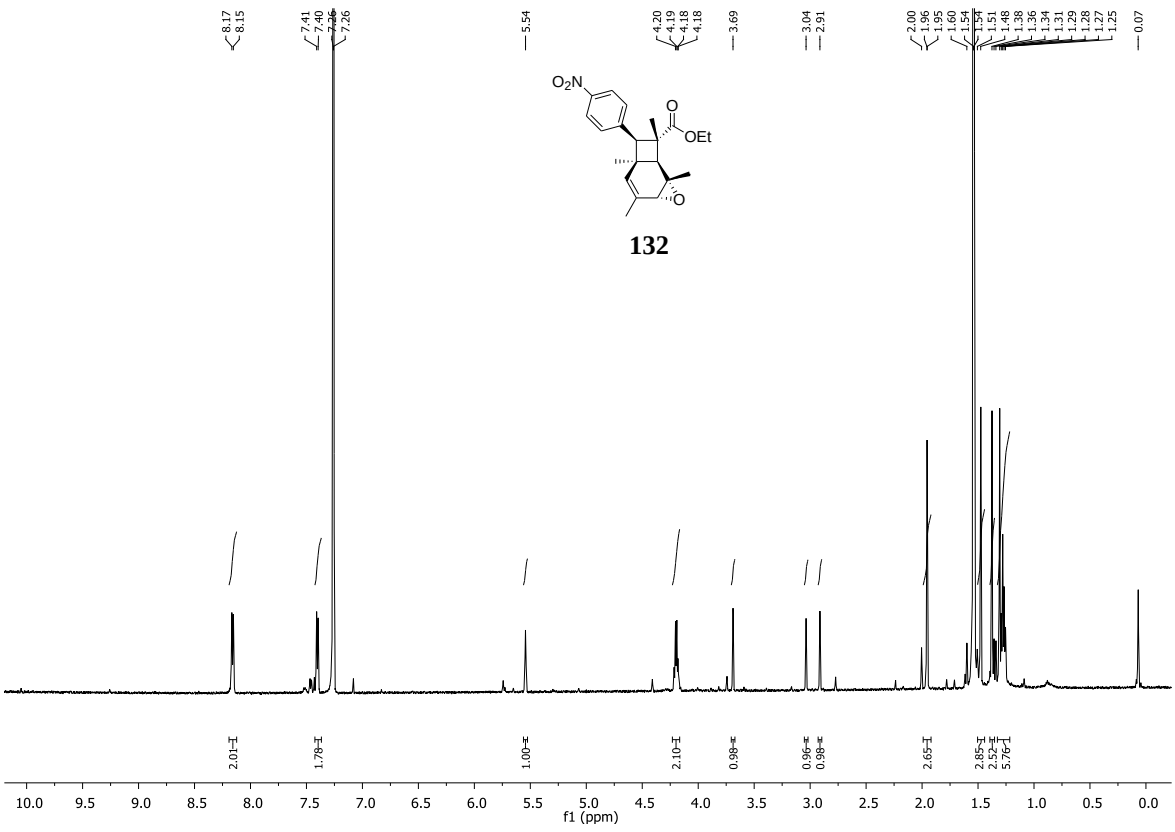
129



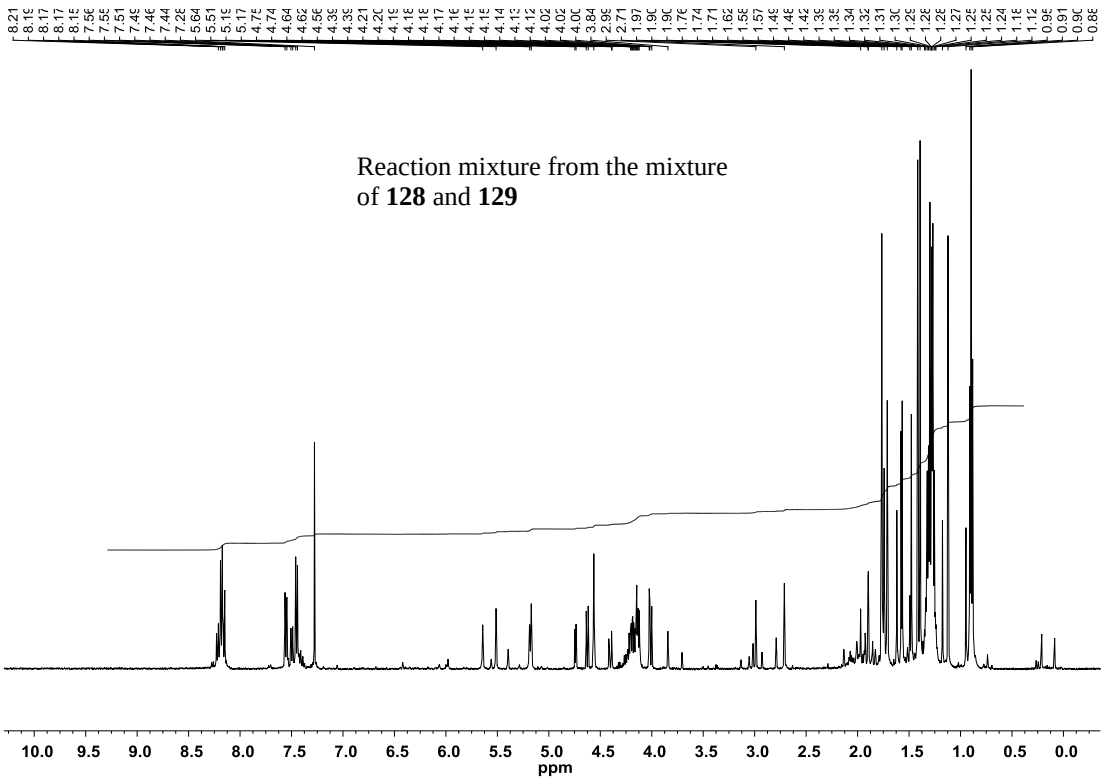
The slower moving isomer (131a or 131b)

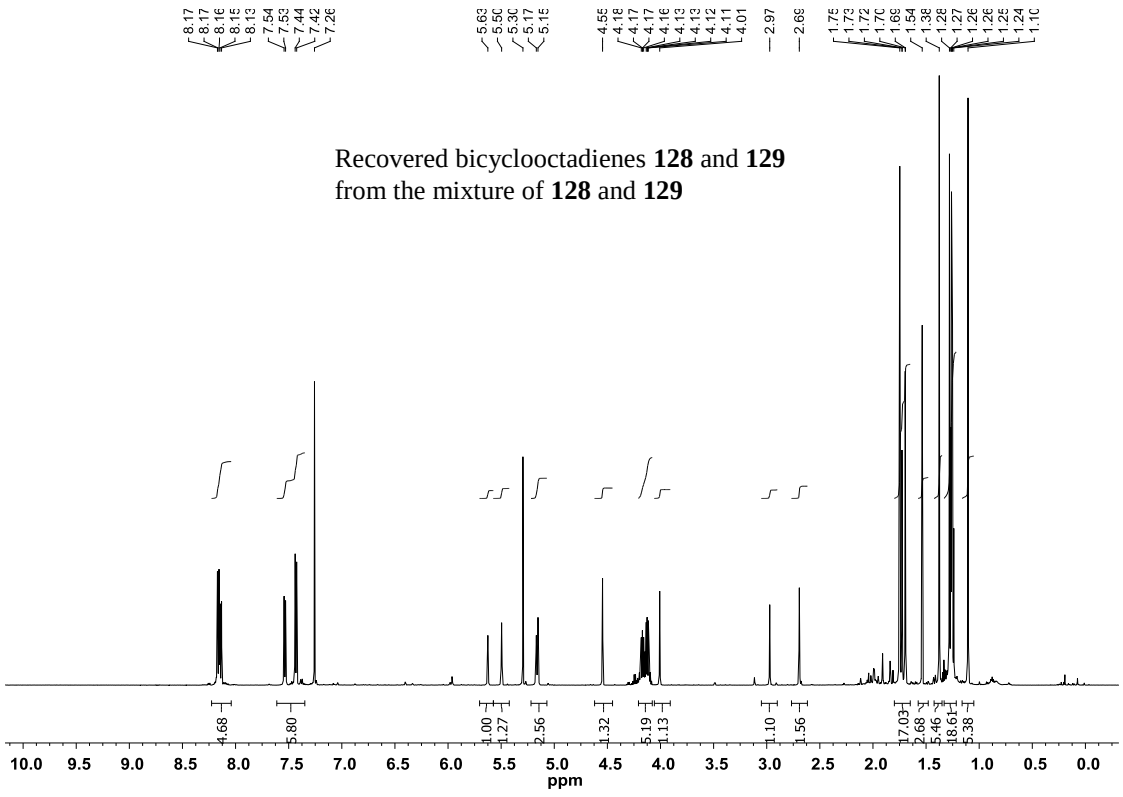


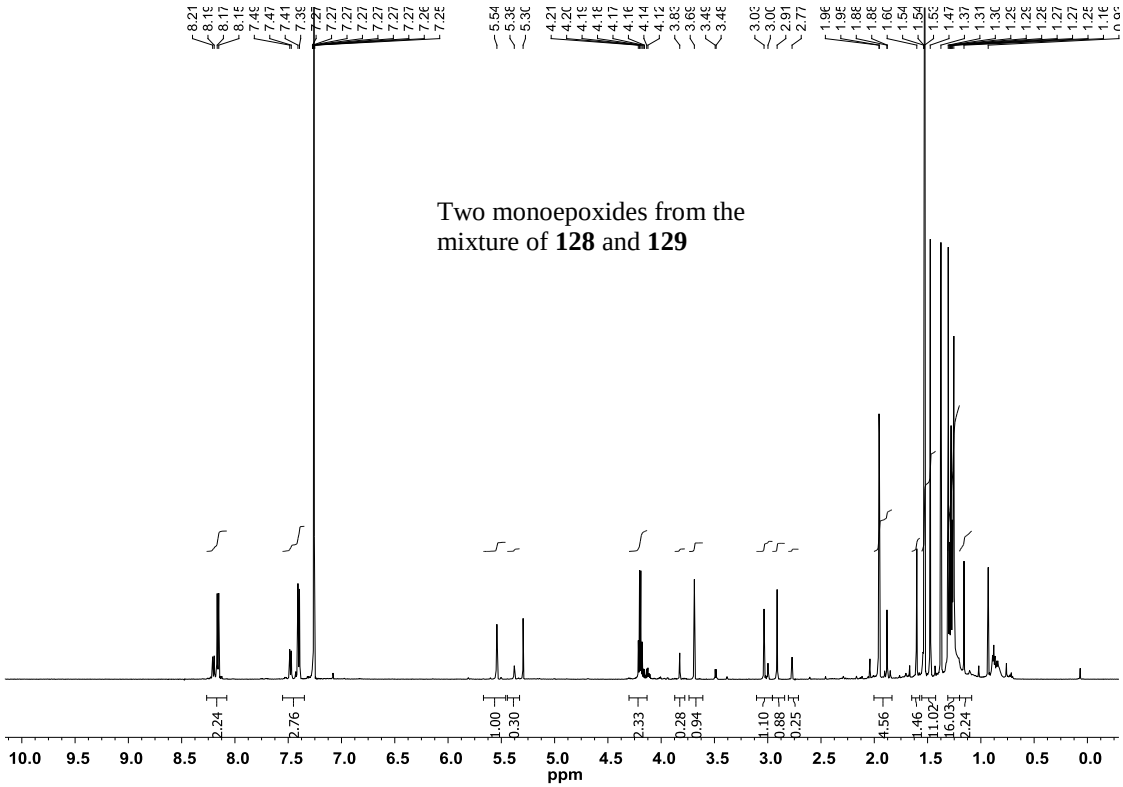
The faster moving isomer
(131a or 131b)

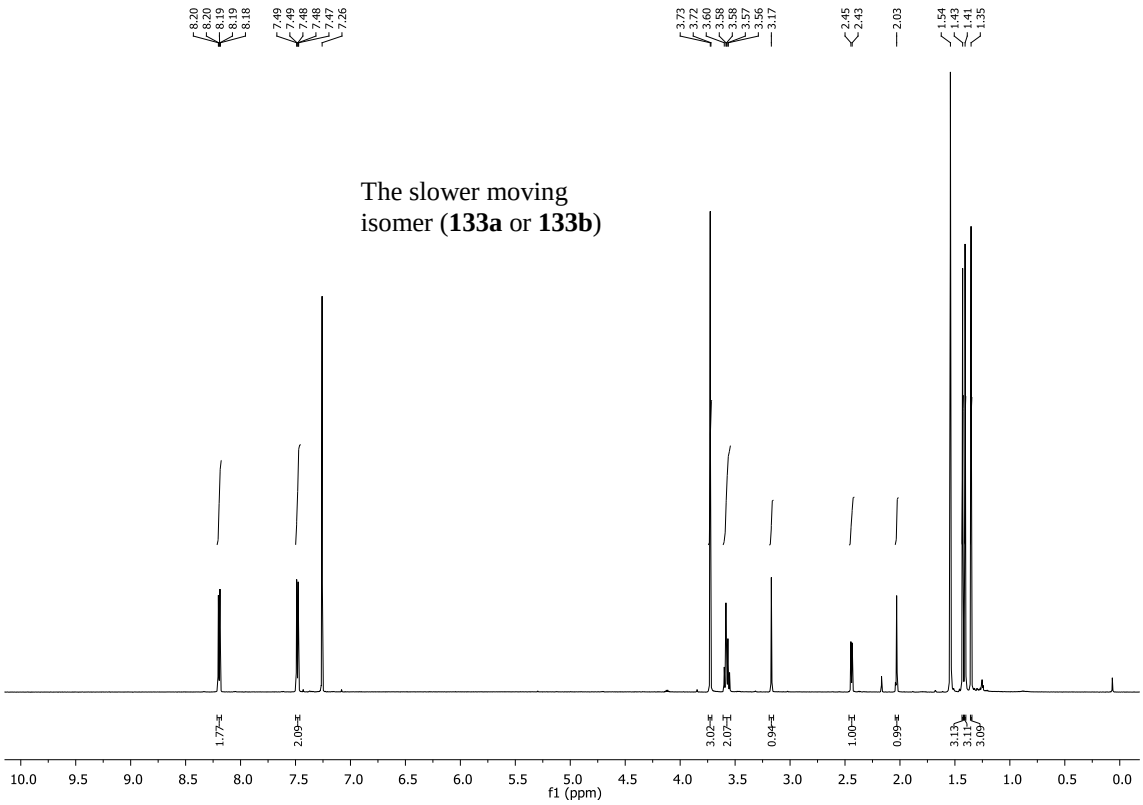


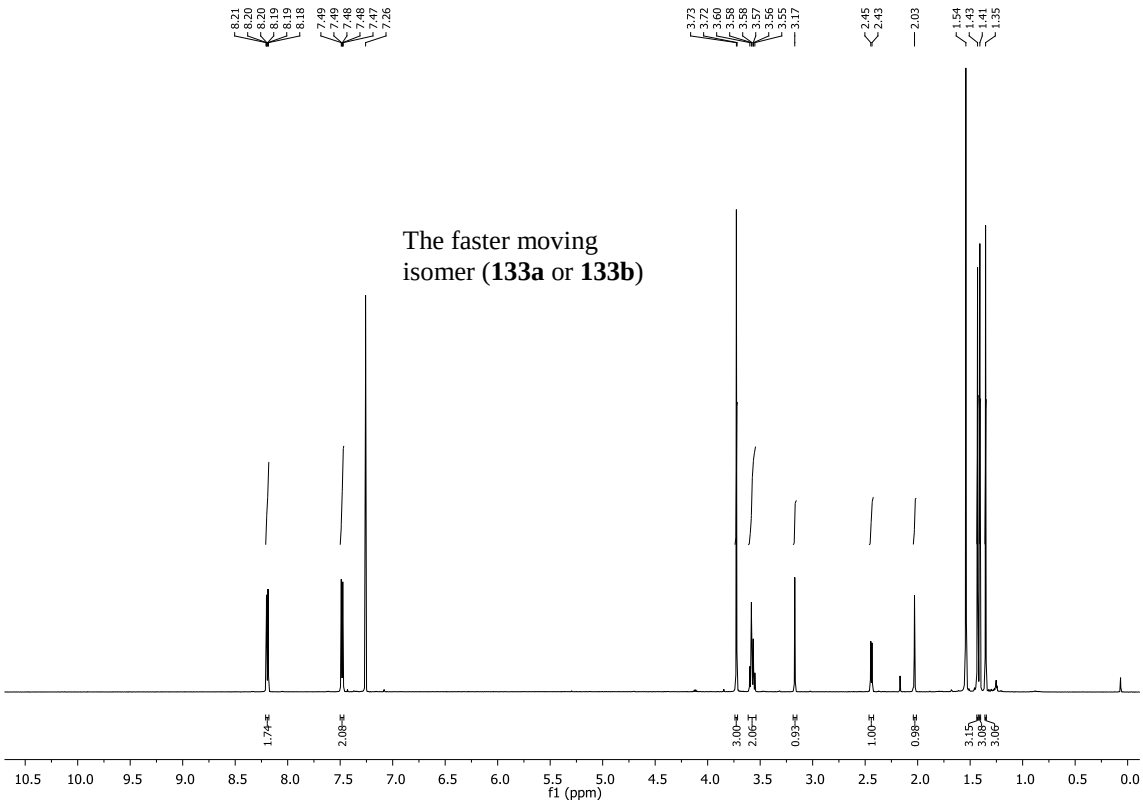
132

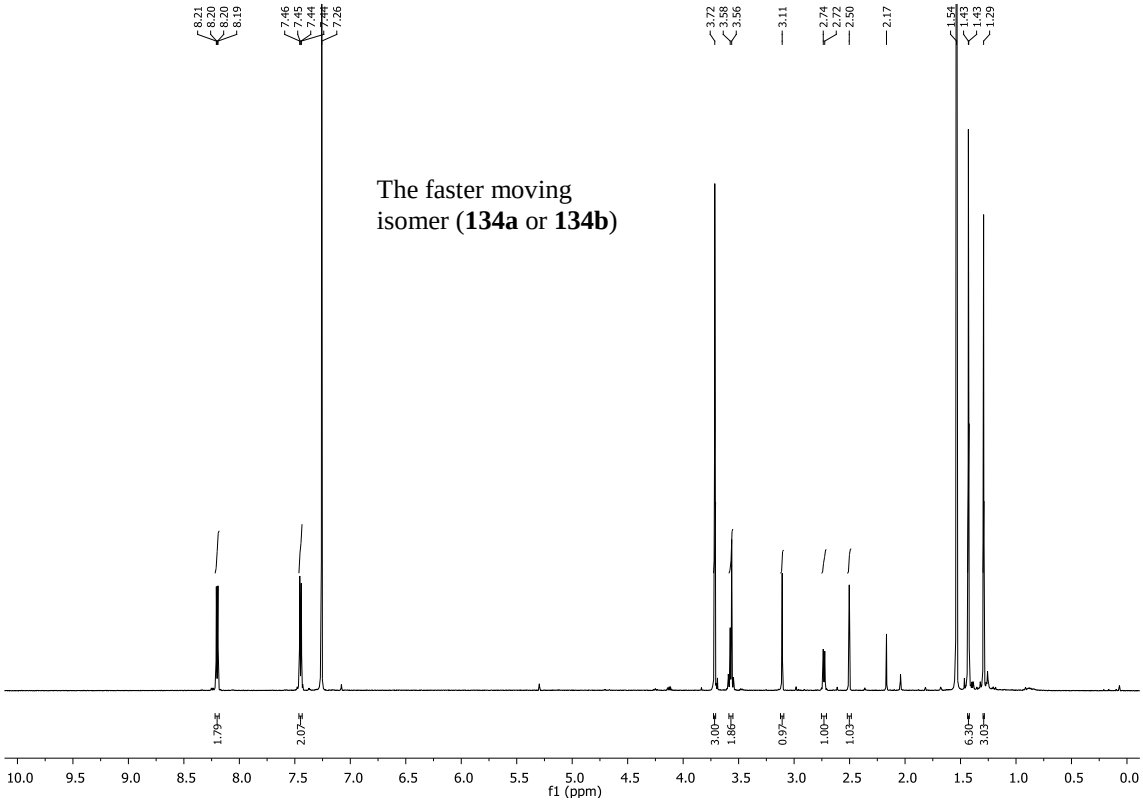

Reaction mixture from the mixture of **128** and **129**
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

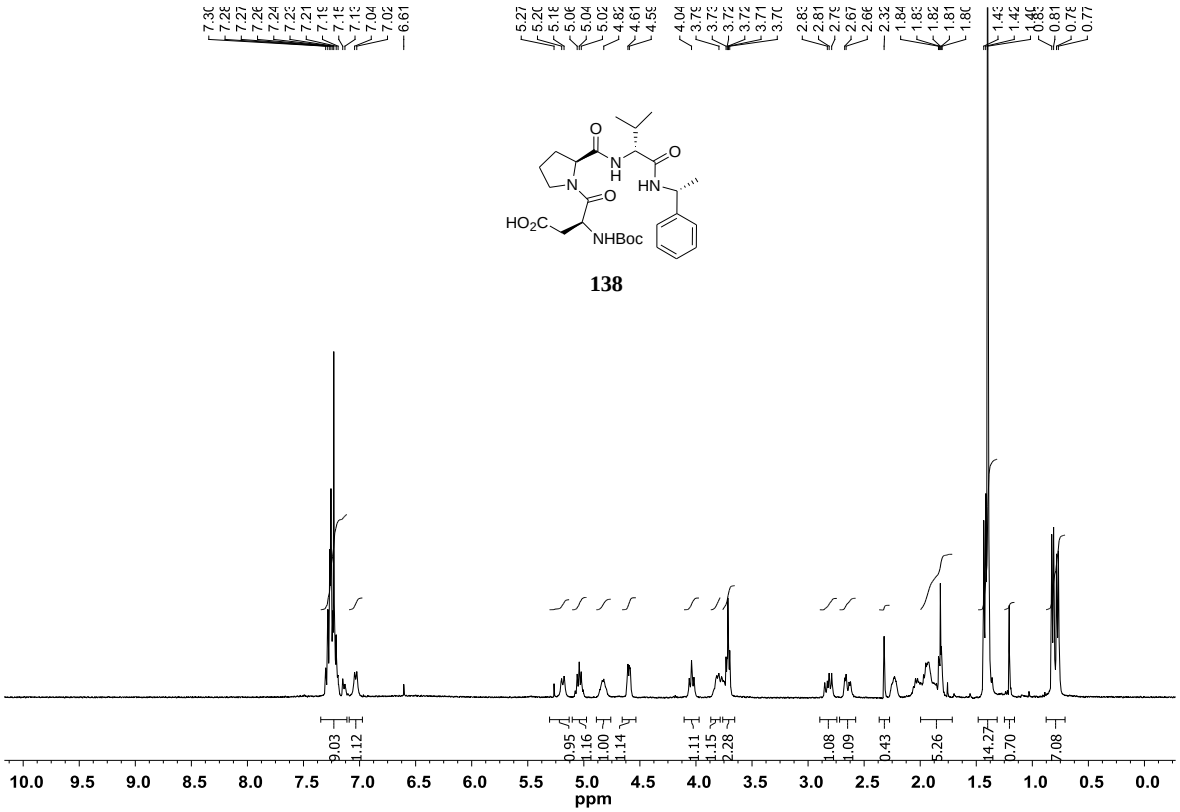

Recovered bicyclooctadienes **128** and **129** from the mixture of **128** and **129**
4.68 5.80 1.00 1.27 2.56 1.32 5.19 1.13 1.10 1.56 17.03 2.68 5.46 18.61 5.38
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


Two monoepoxides from the mixture of **128** and **129**
ppm

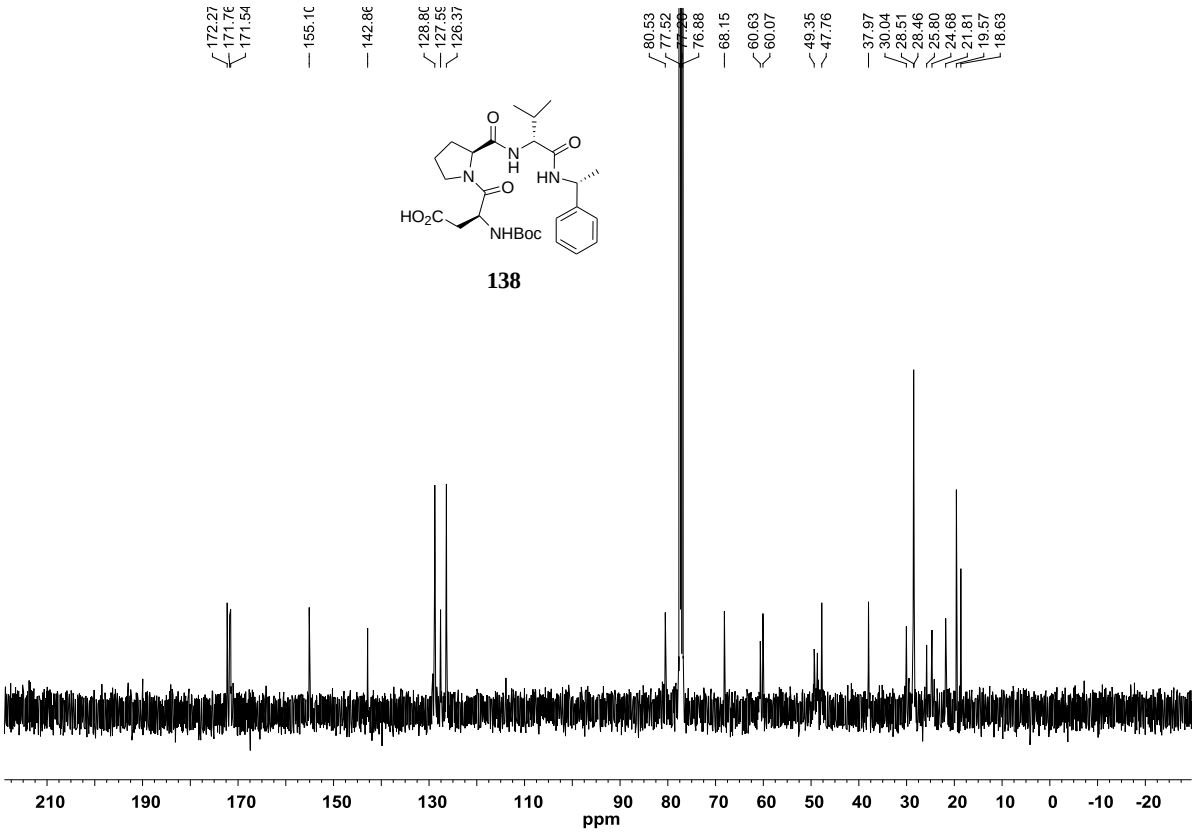

The slower moving isomer (**133a** or **133b**)
f1 (ppm)


The faster moving
isomer (**133a** or **133b**)
f1 (ppm)

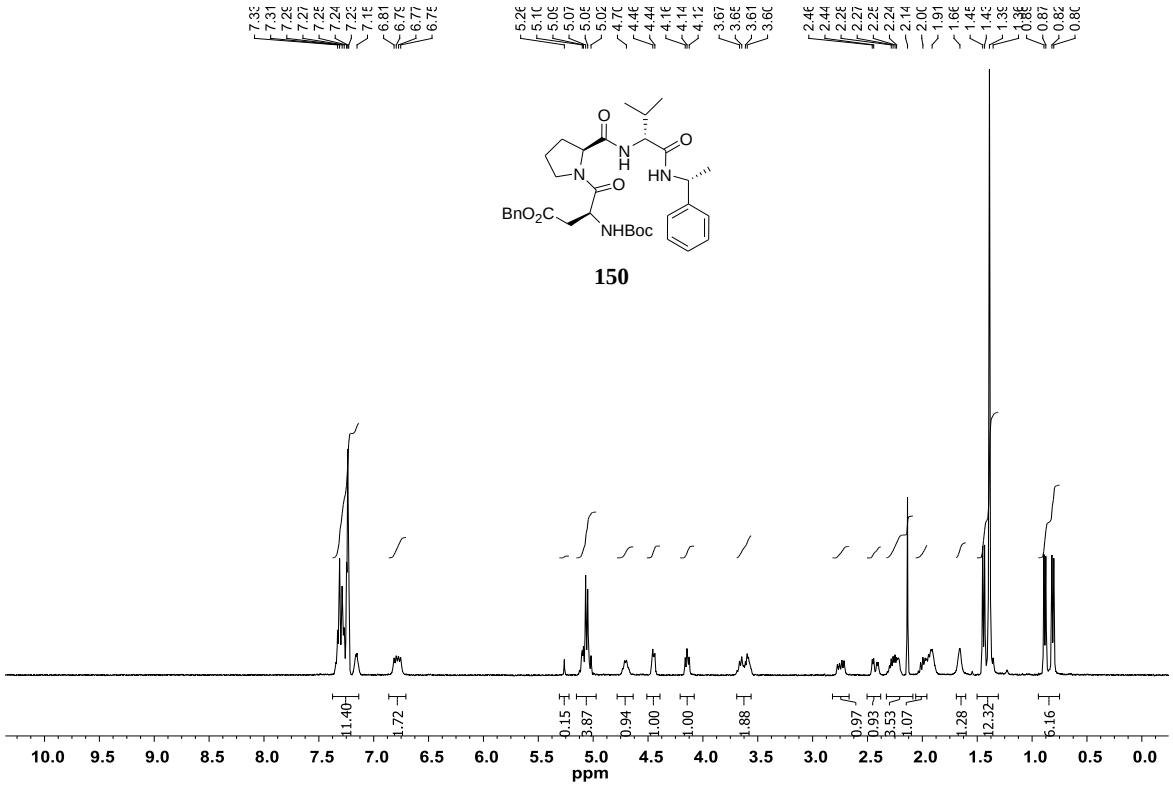

The faster moving
isomer (**134a** or **134b**)
f1 (ppm)



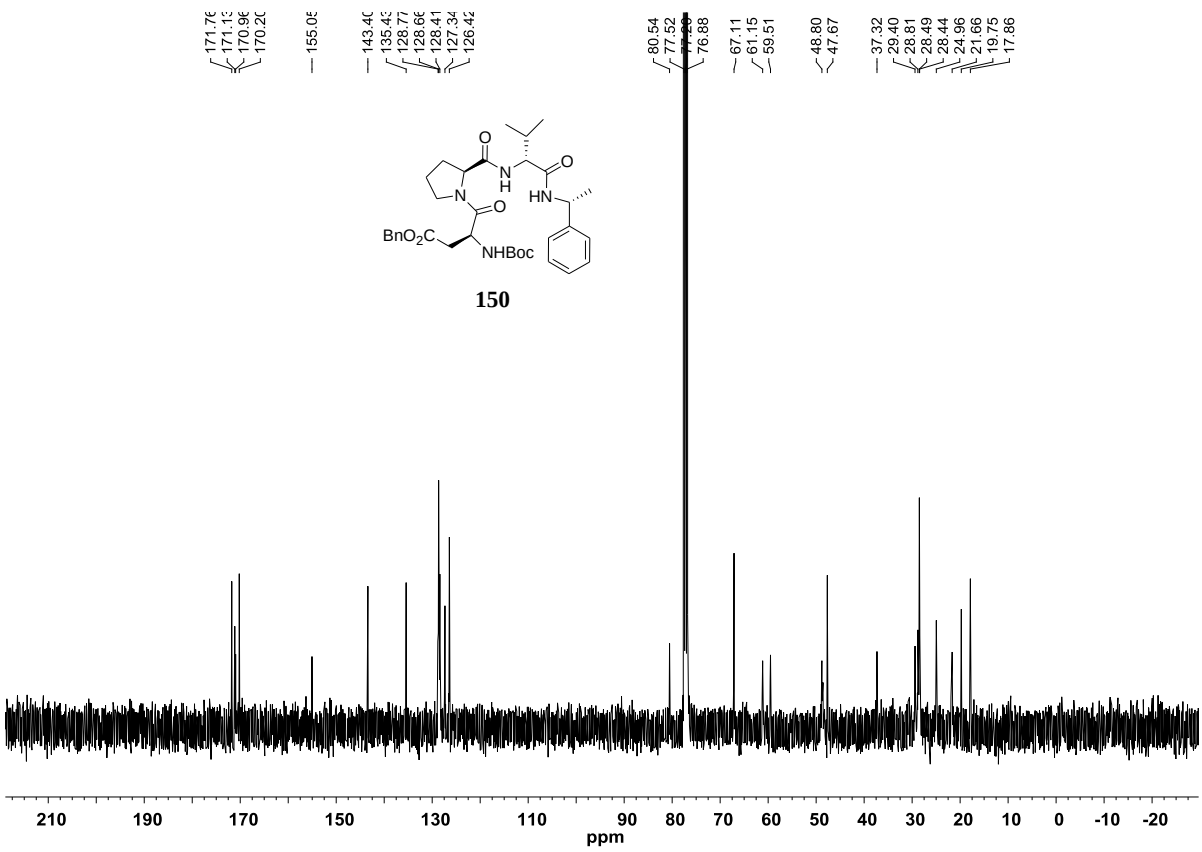
138



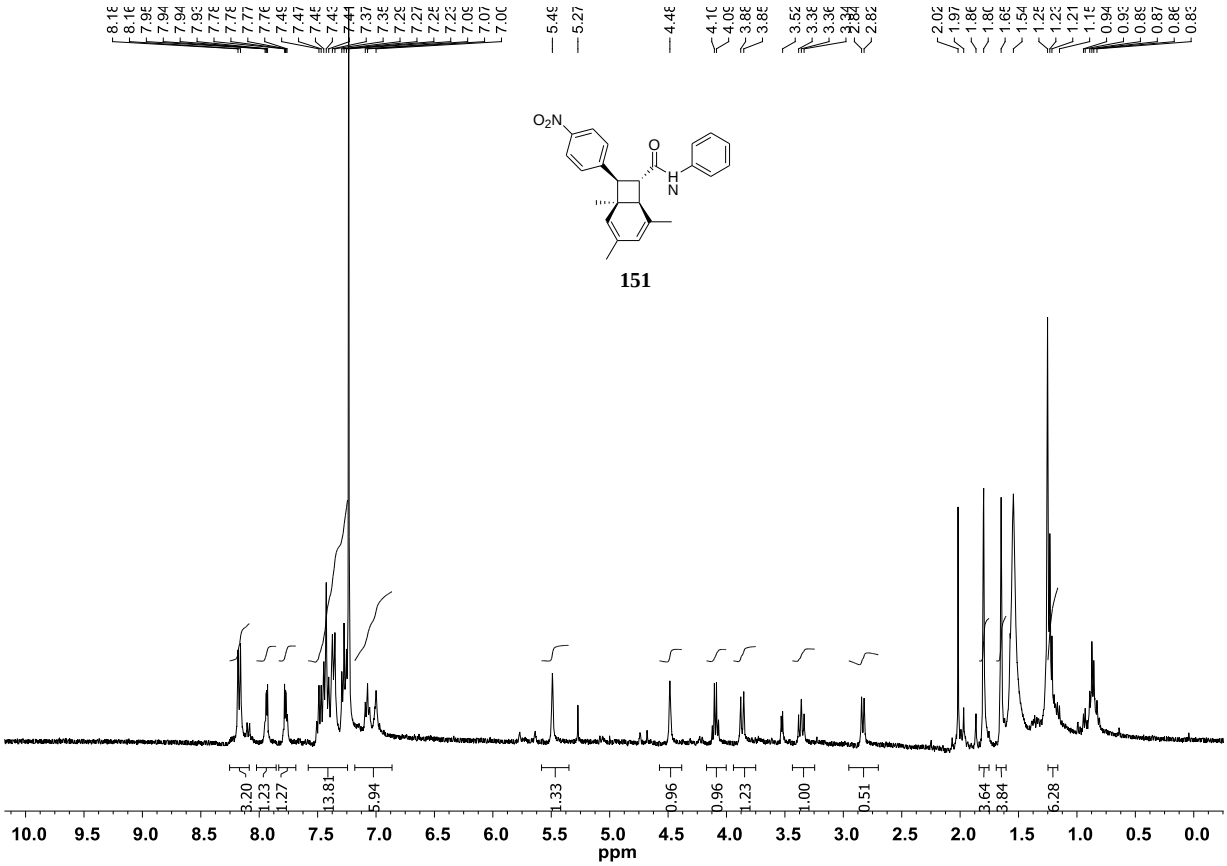
138

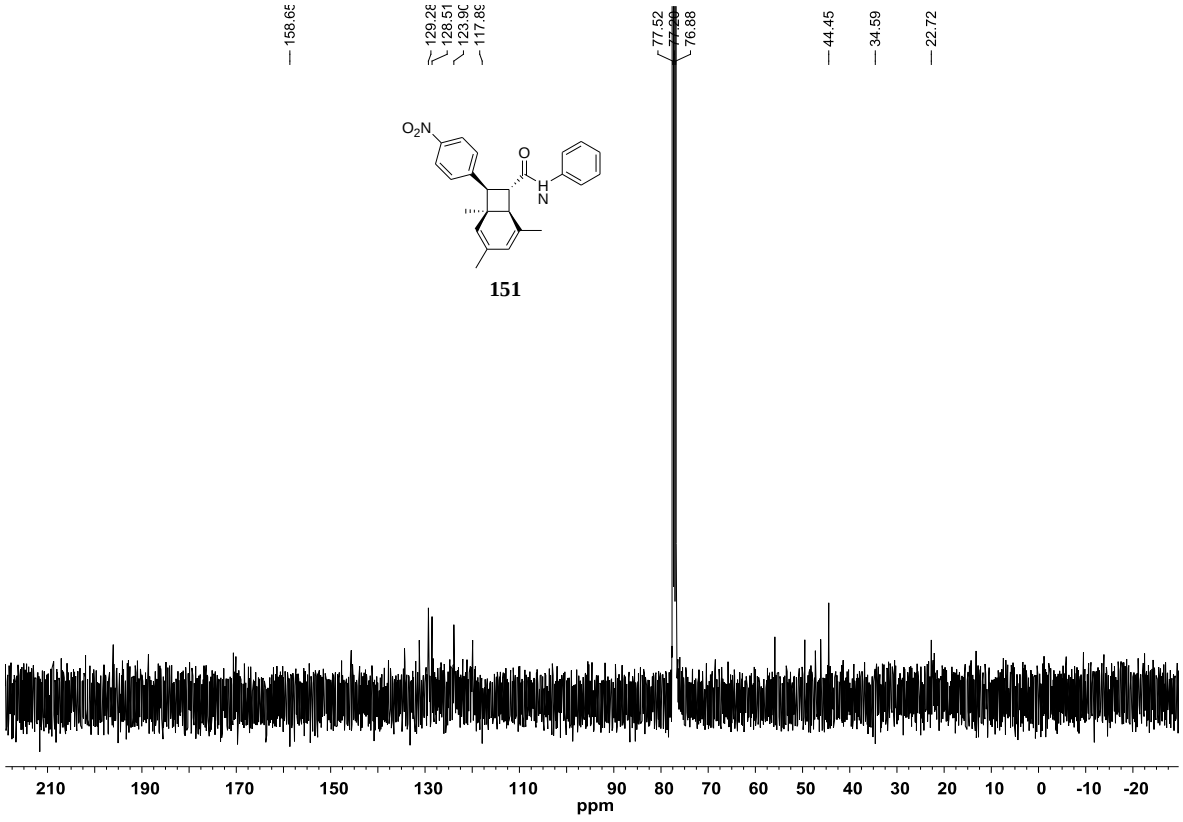


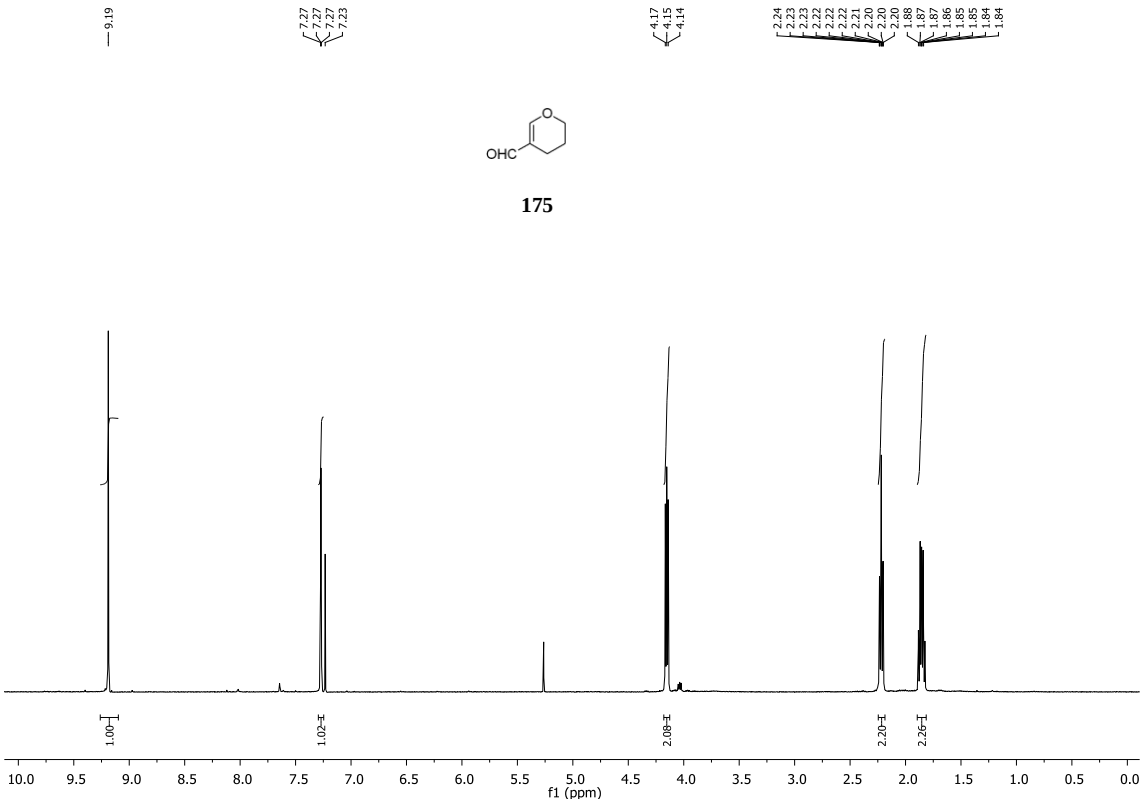
150



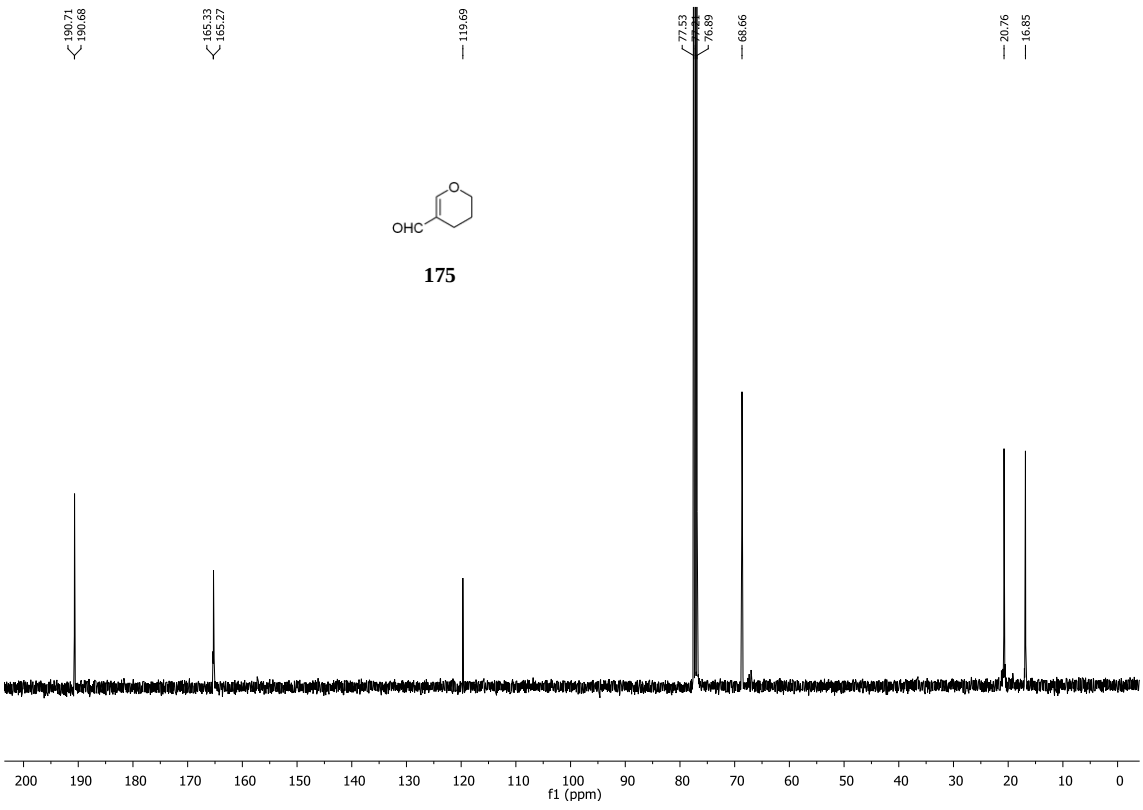
150


O2N
O
H
N
151
3.20
1.23
1.27
13.81
5.94
1.33
0.96
0.96
1.23
1.00
0.51
3.64
3.84
6.28
ppm

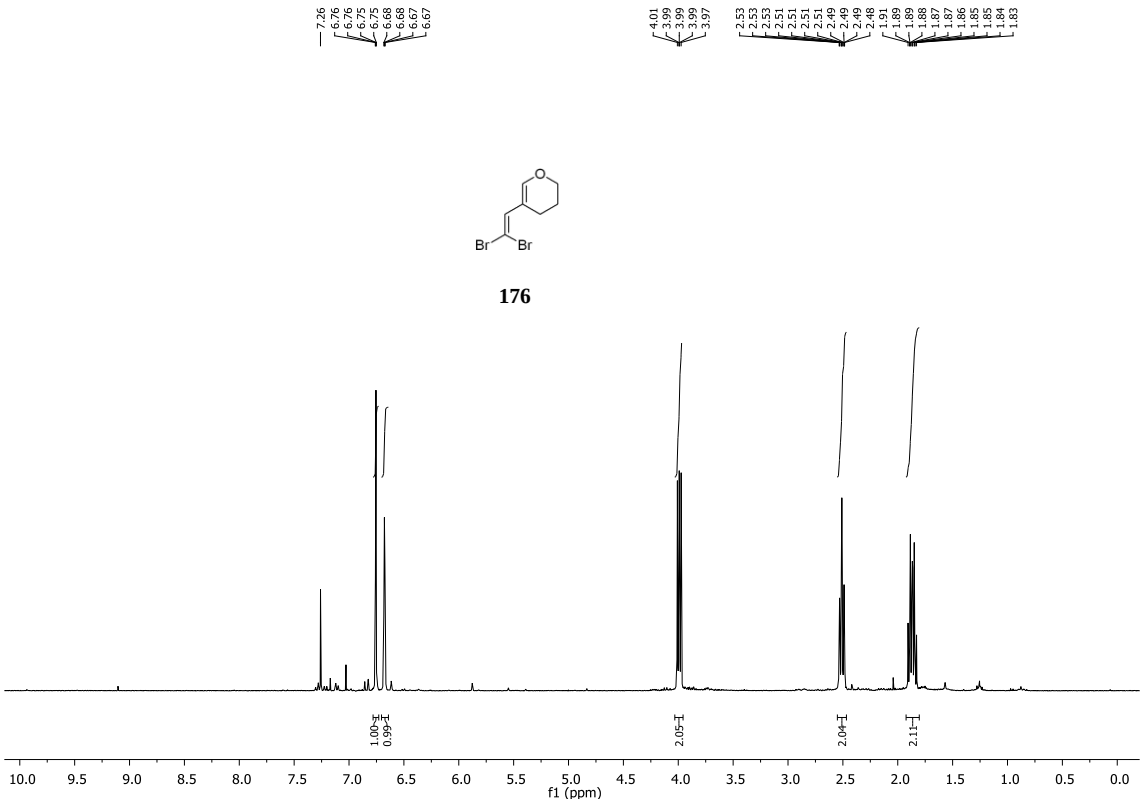

158.65
129.28
128.51
123.90
117.85
77.52
76.88
44.45
34.59
22.72
O2N
O
H
N
151
ppm


9.19
7.27
7.27
7.27
7.23
4.17
4.15
4.14
2.24
2.23
2.23
2.22
2.22
2.22
2.21
2.20
2.20
2.20
1.88
1.87
1.87
1.86
1.85
1.85
1.84
1.84
OHC
1.00
1.02
2.08
2.20
2.26
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

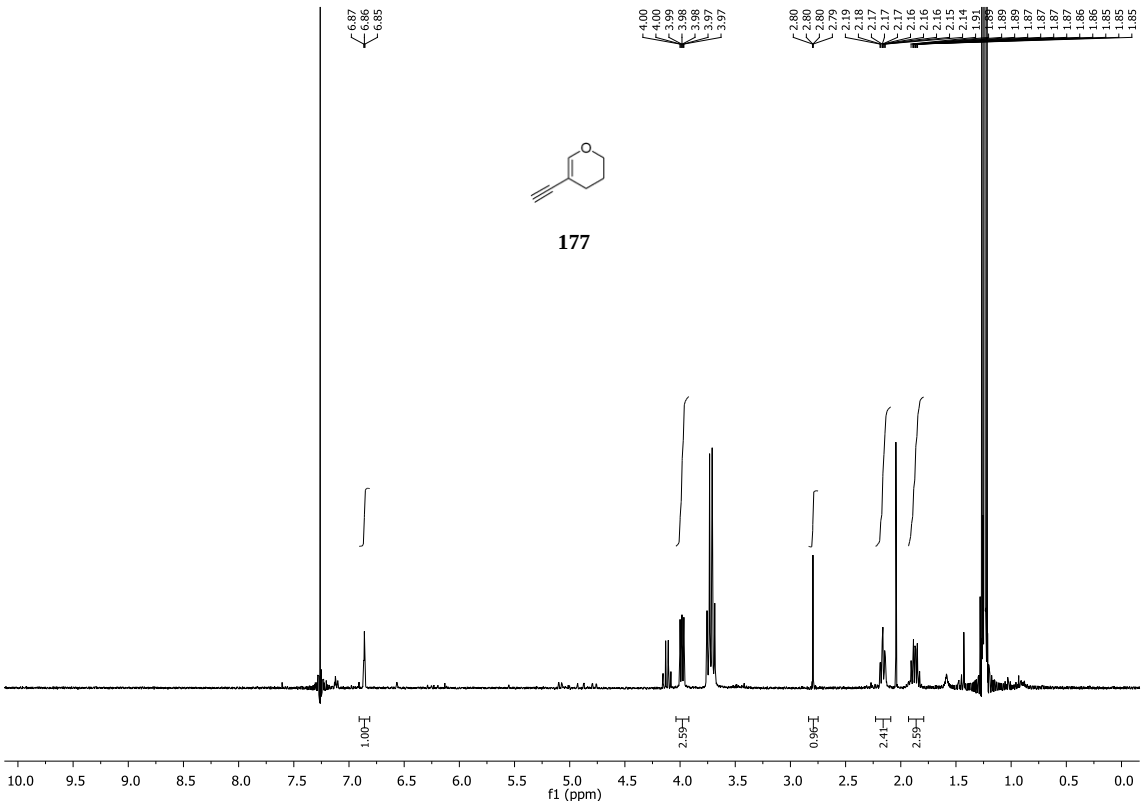
175


190.71
190.68
165.33
165.27
119.69
77.53
77.21
76.89
68.66
20.76
16.85
OHC
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

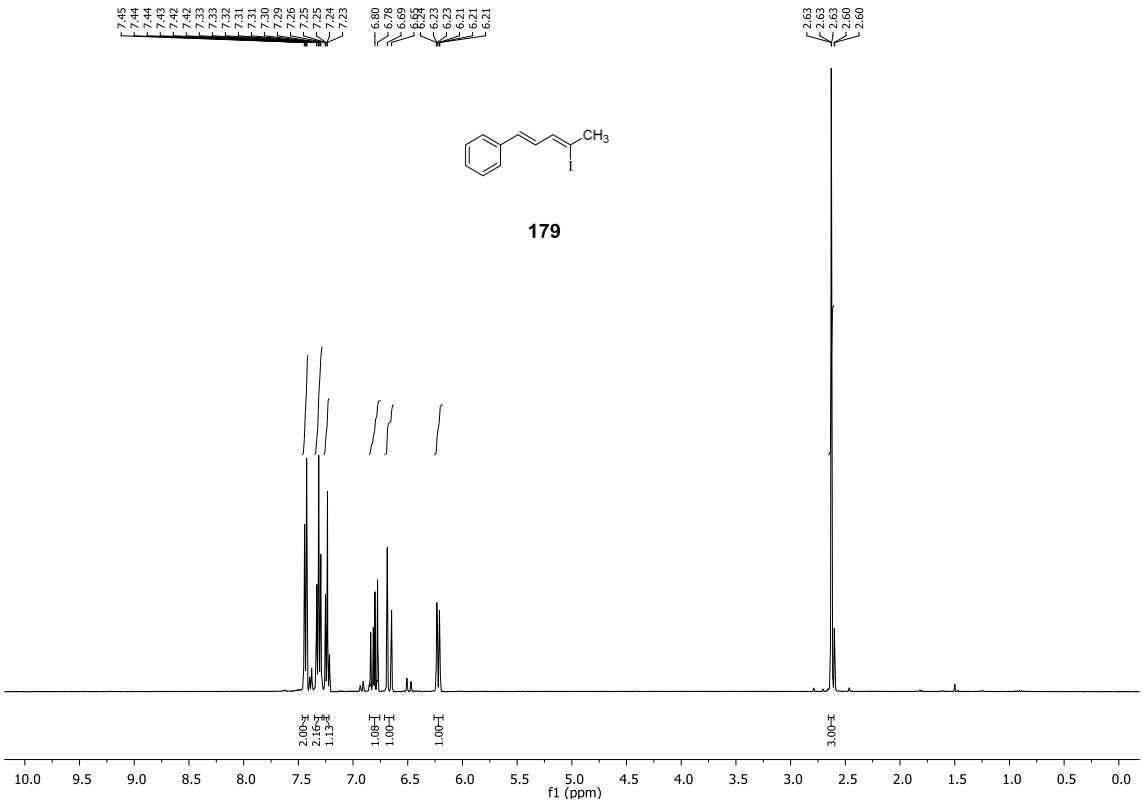
175


7.26
6.76
6.76
6.75
6.75
6.68
6.68
6.67
6.67
4.01
3.99
3.99
3.99
3.97
2.53
2.53
2.53
2.51
2.51
2.51
2.51
2.49
2.49
2.48
1.91
1.89
1.89
1.88
1.87
1.87
1.86
1.85
1.85
1.84
1.83
Br
Br
1.00
0.99
2.05
2.04
2.11
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

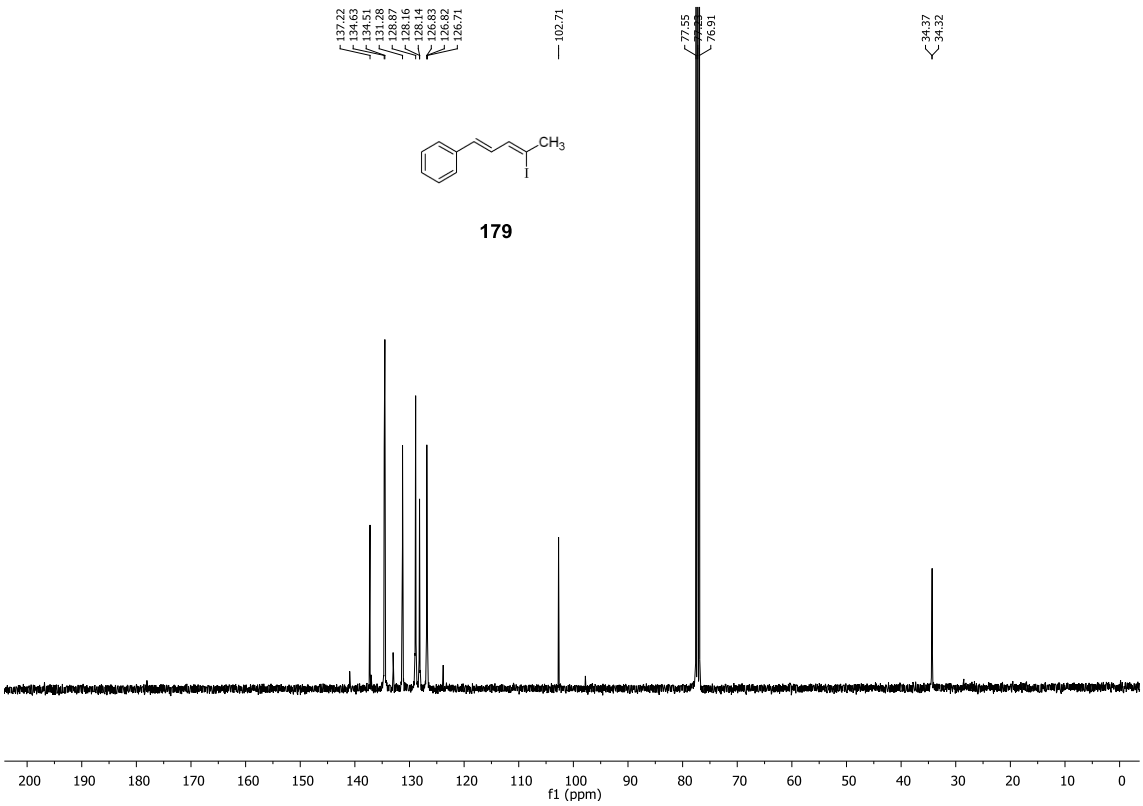
176


6.87
6.86
6.85
4.00
4.00
3.99
3.98
3.98
3.97
3.97
2.80
2.80
2.80
2.79
2.19
2.18
2.17
2.17
2.17
2.16
2.16
2.16
2.15
2.14
1.91
1.89
1.89
1.89
1.87
1.87
1.87
1.87
1.86
1.86
1.85
1.85
1.85
1.00
2.59
0.96
2.41
2.59
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

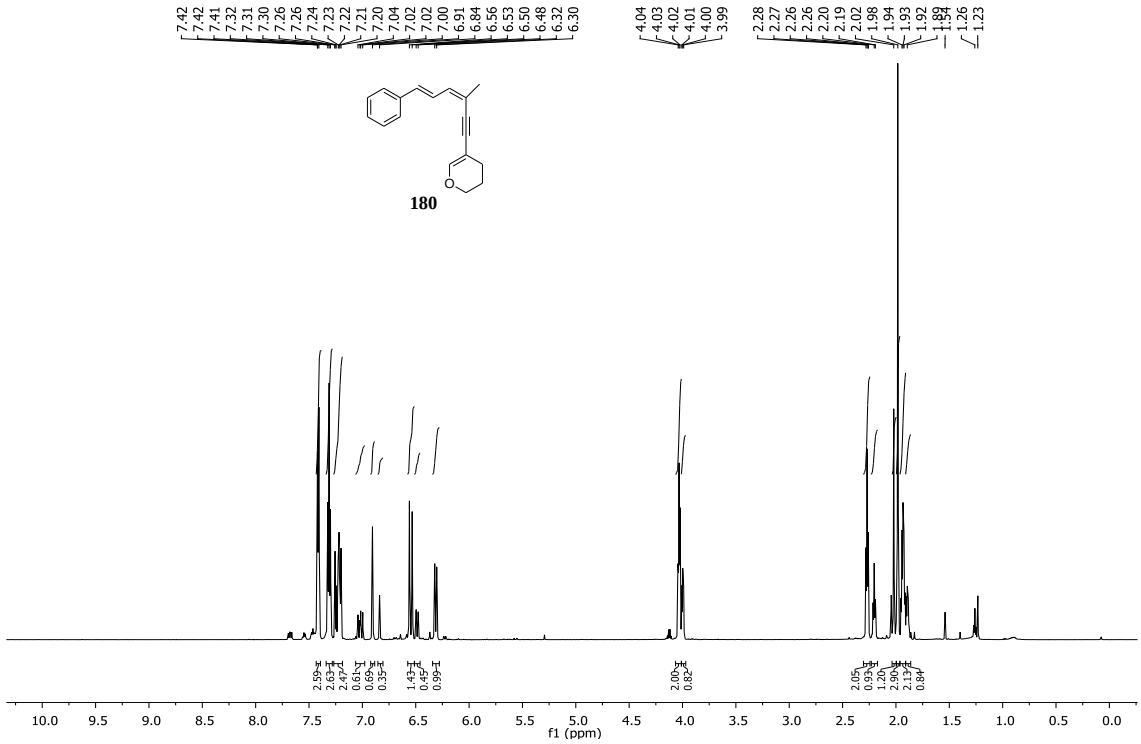
177


7.45
7.44
7.44
7.43
7.42
7.42
7.33
7.32
7.31
7.31
7.30
7.29
7.26
7.25
7.25
7.24
7.23
6.80
6.78
6.69
6.23
6.23
6.21
6.21
6.21
2.63
2.63
2.63
2.60
2.60
CH3
I
2.00
2.16
1.13
1.08
1.00
1.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

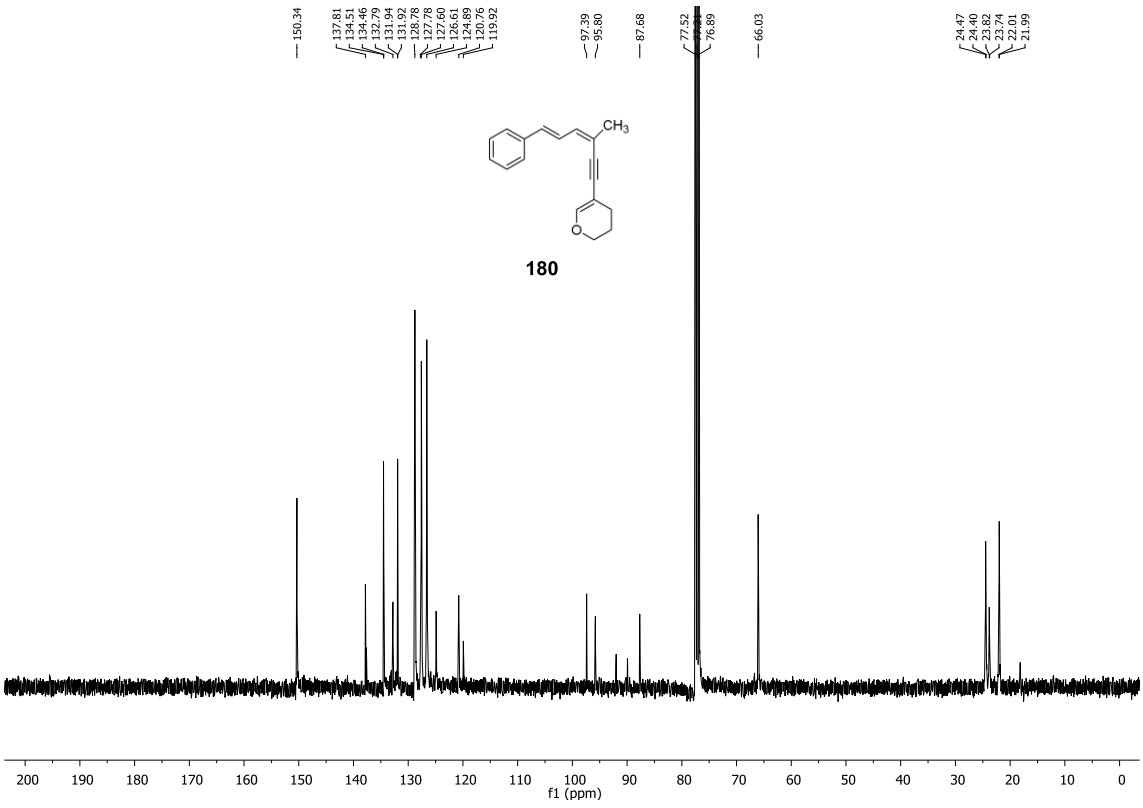
179


137.22
134.63
134.51
131.28
128.87
128.16
128.14
126.83
126.82
126.71
102.71
77.55
77.23
76.91
34.37
34.32
CH3
I
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

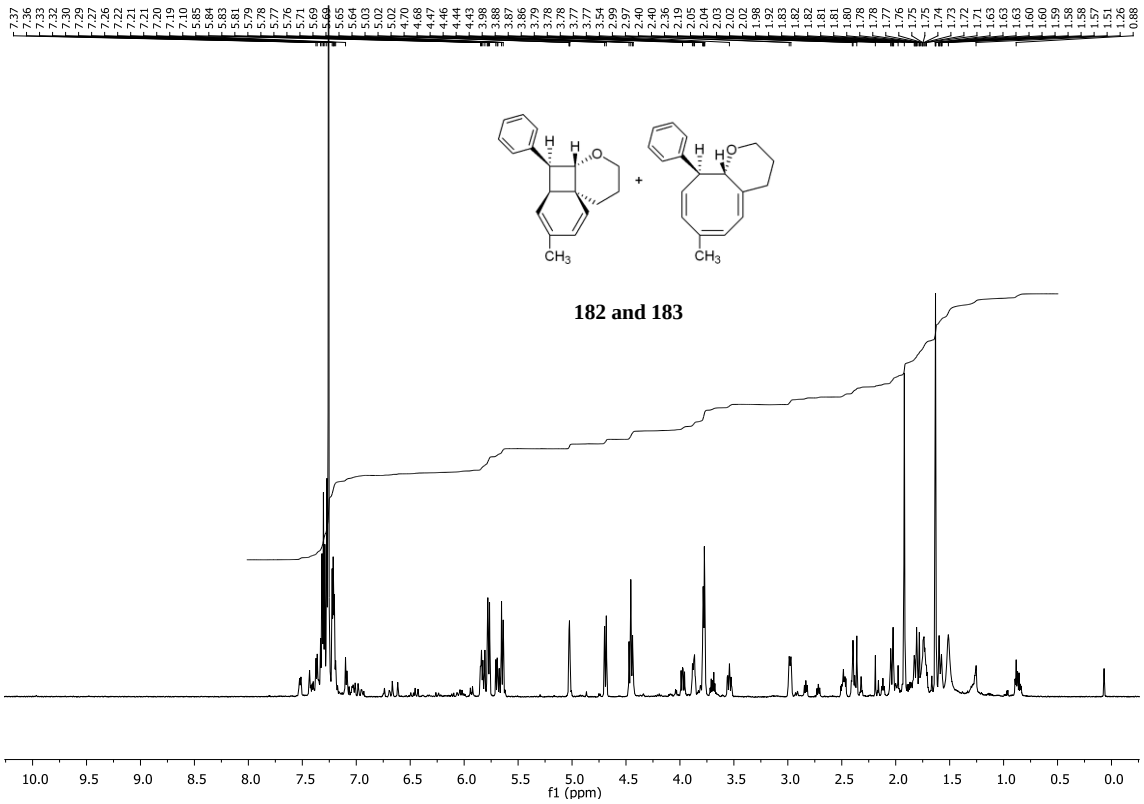
179


7.42
7.42
7.41
7.32
7.31
7.30
7.26
7.26
7.24
7.23
7.22
7.21
7.20
7.04
7.02
7.02
7.00
6.91
6.84
6.56
6.53
6.50
6.48
6.32
6.30
4.04
4.03
4.02
4.01
4.00
3.99
2.28
2.27
2.26
2.26
2.20
2.19
2.02
1.98
1.94
1.93
1.92
1.89
1.54
1.26
1.23
2.59
2.63
2.47
0.61
0.69
0.35
1.43
0.45
0.99
2.00
0.82
2.05
0.93
1.20
2.90
2.13
0.84
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

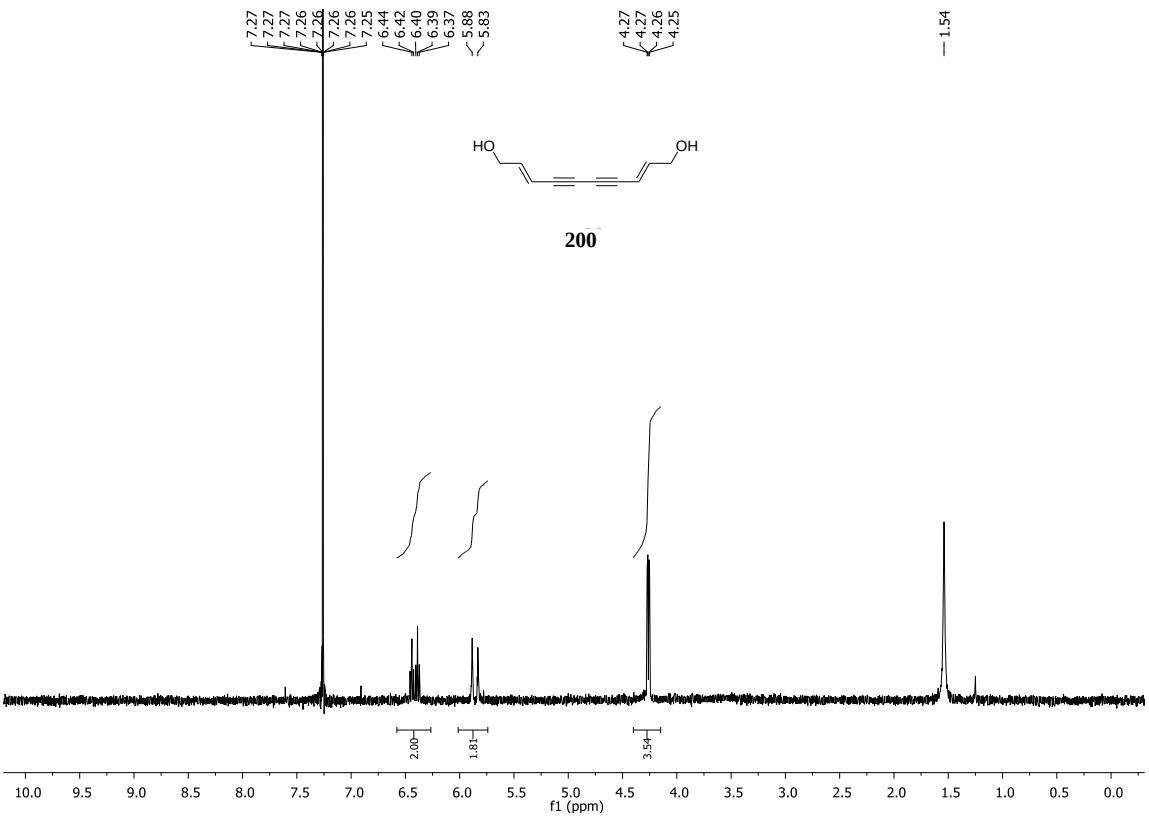
180


150.34
137.81
134.51
134.46
132.79
131.94
131.92
128.78
127.78
127.60
126.61
124.89
120.76
119.92
97.39
95.80
87.68
77.52
77.21
76.89
66.03
24.47
24.40
23.82
23.74
22.01
21.99
CH3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

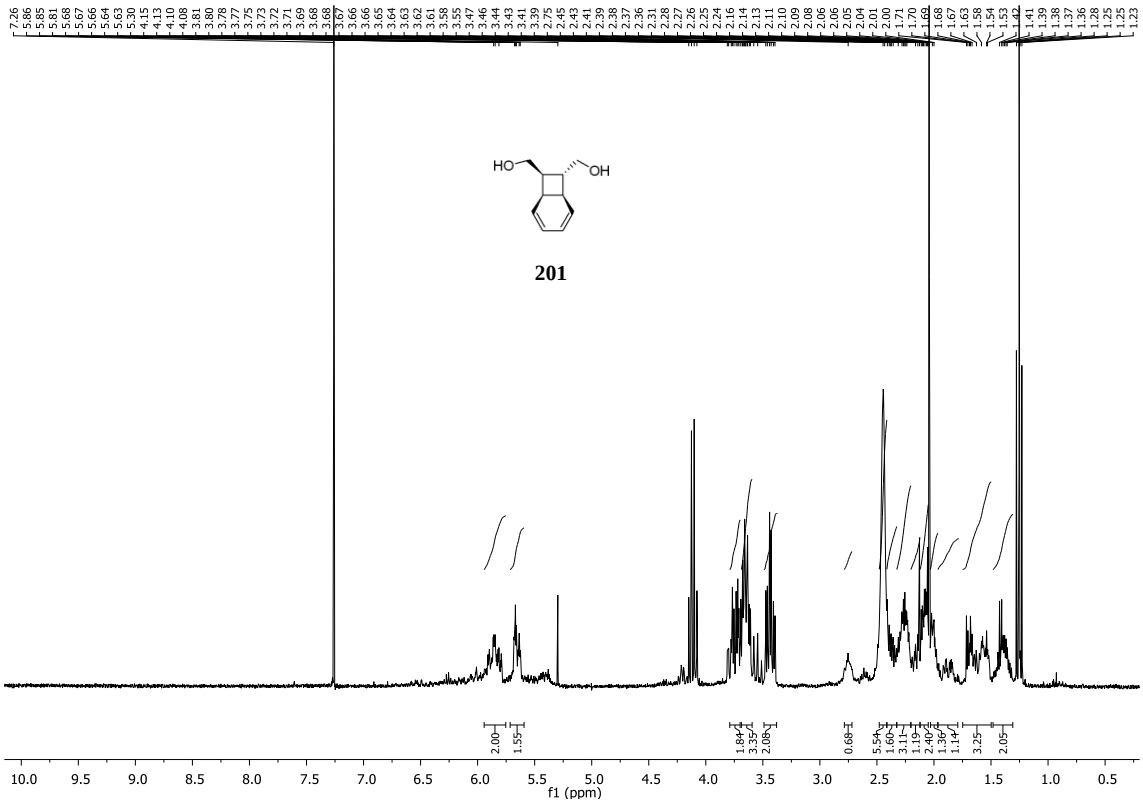
180



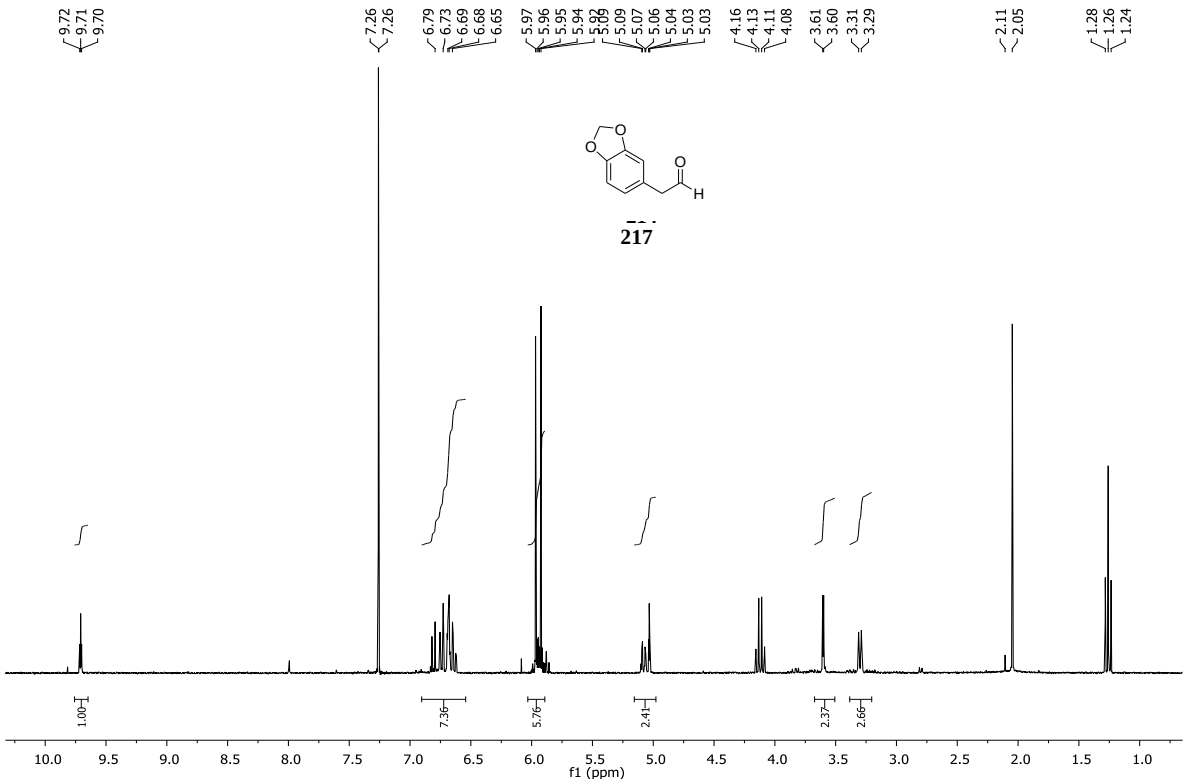
182 and 183



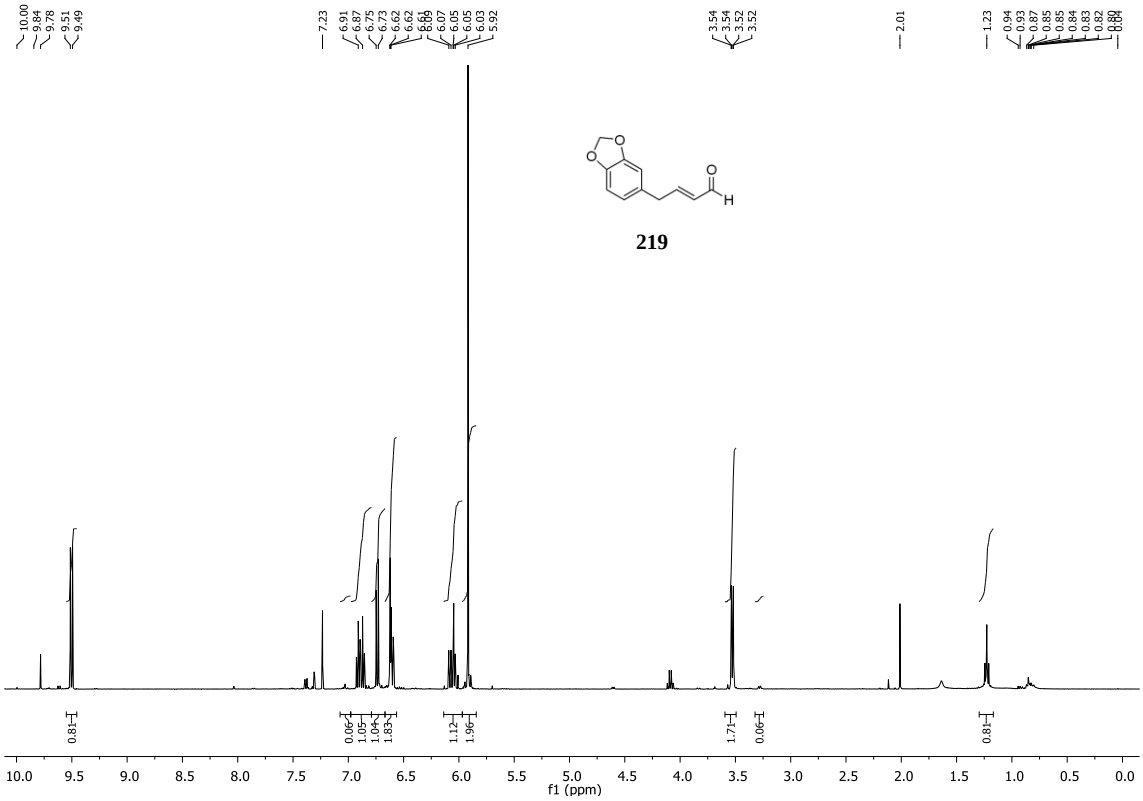
200



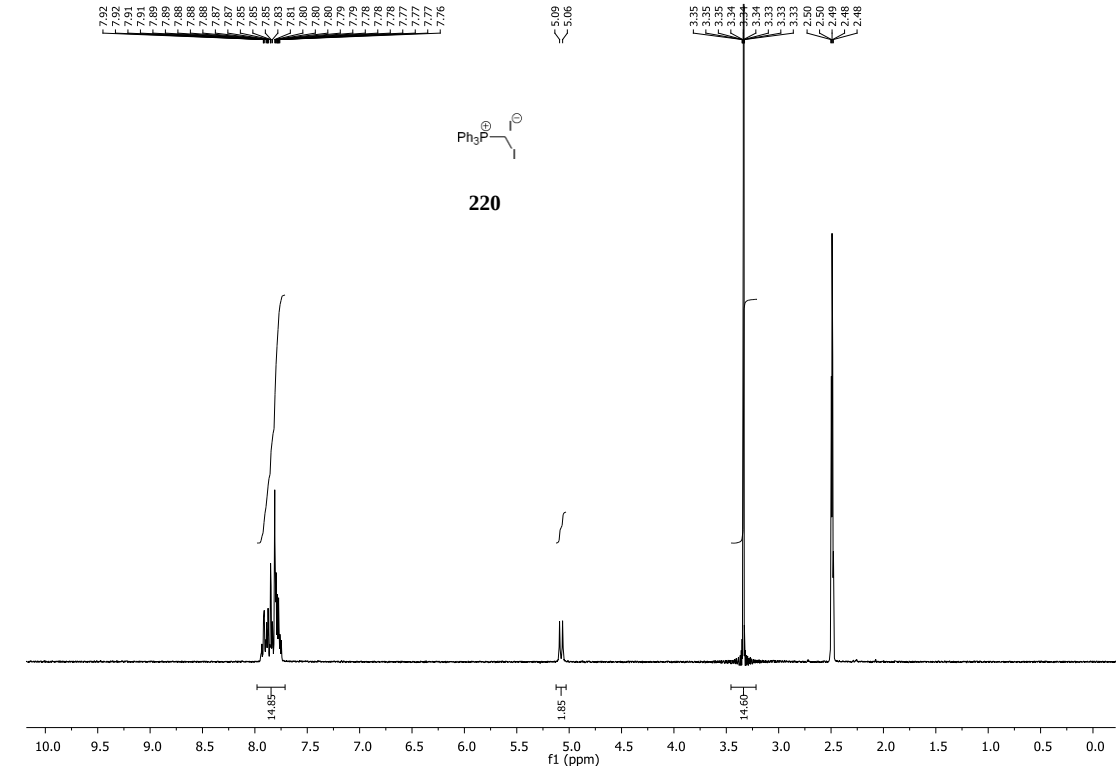
201



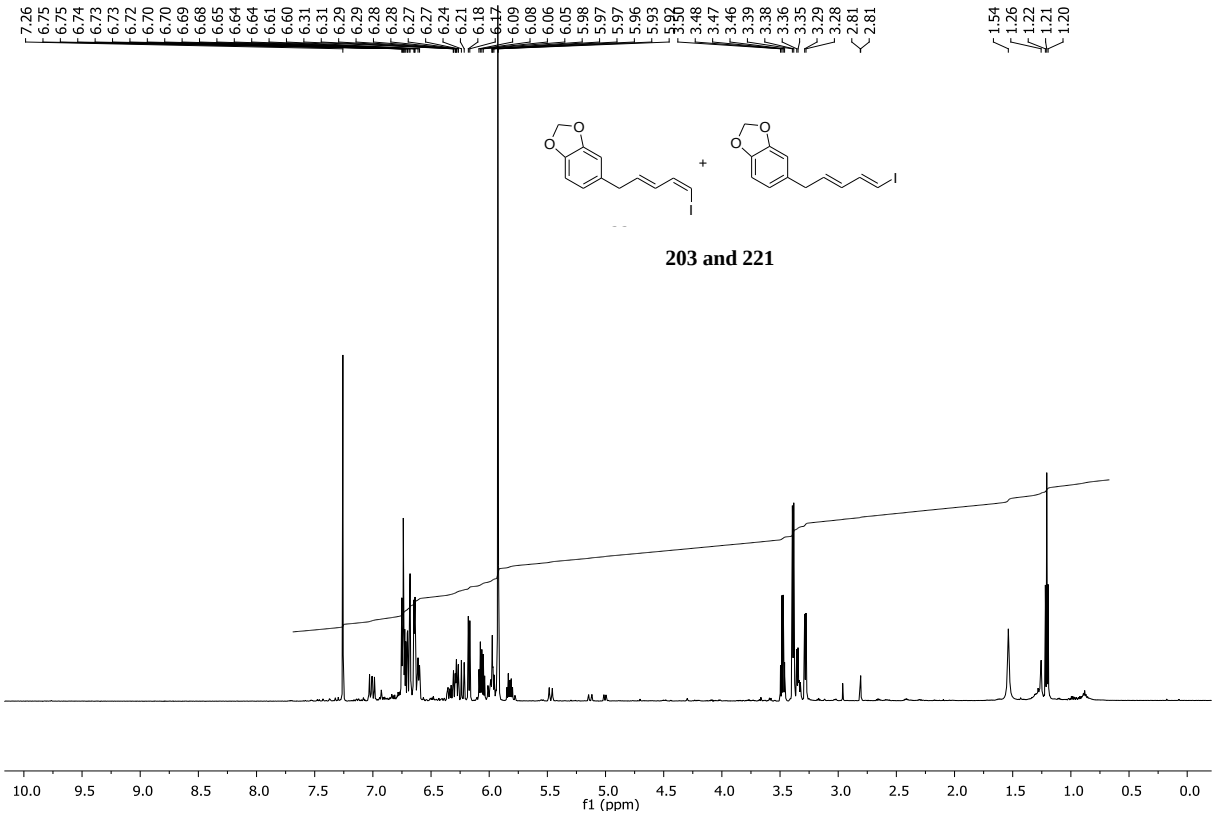
217

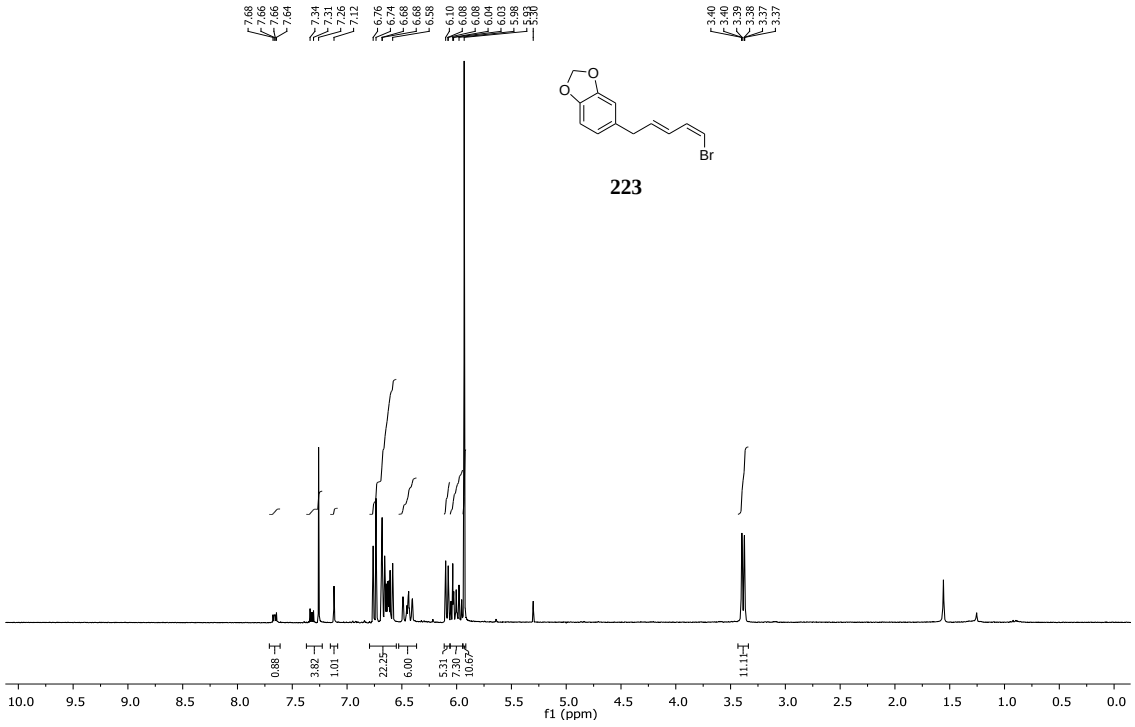


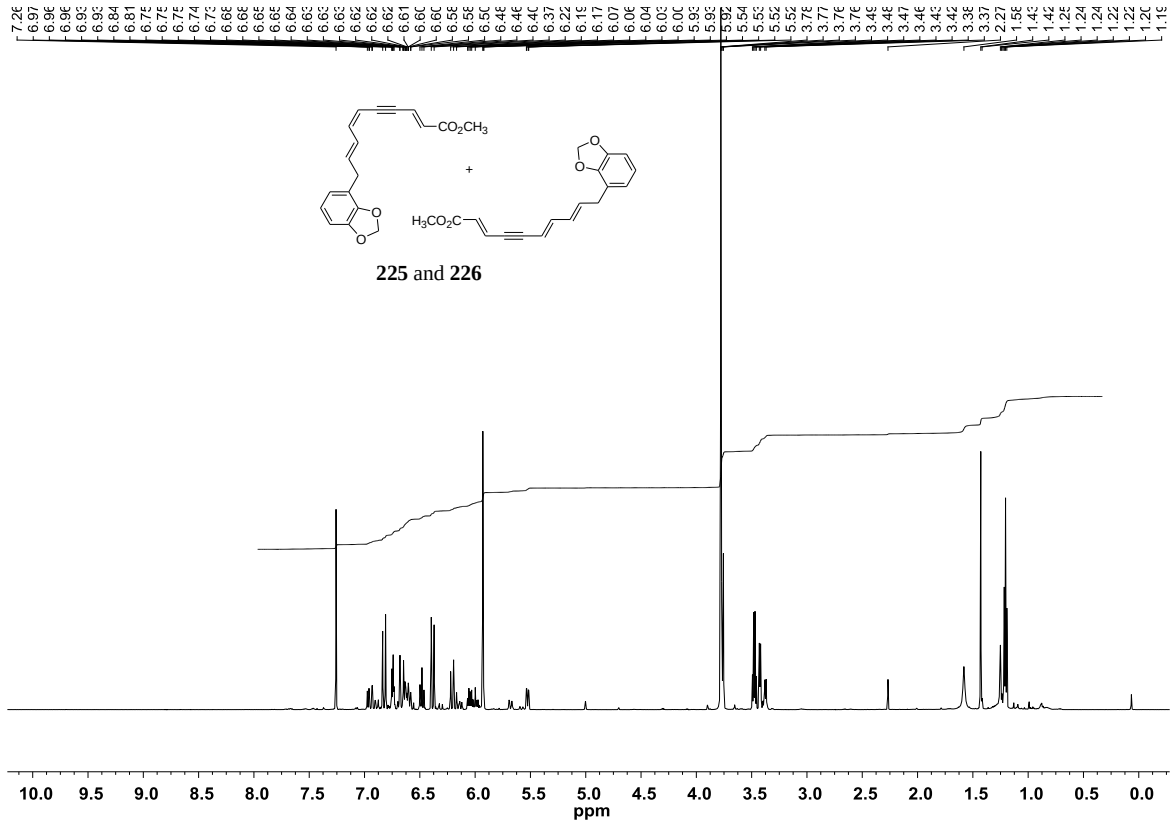
219



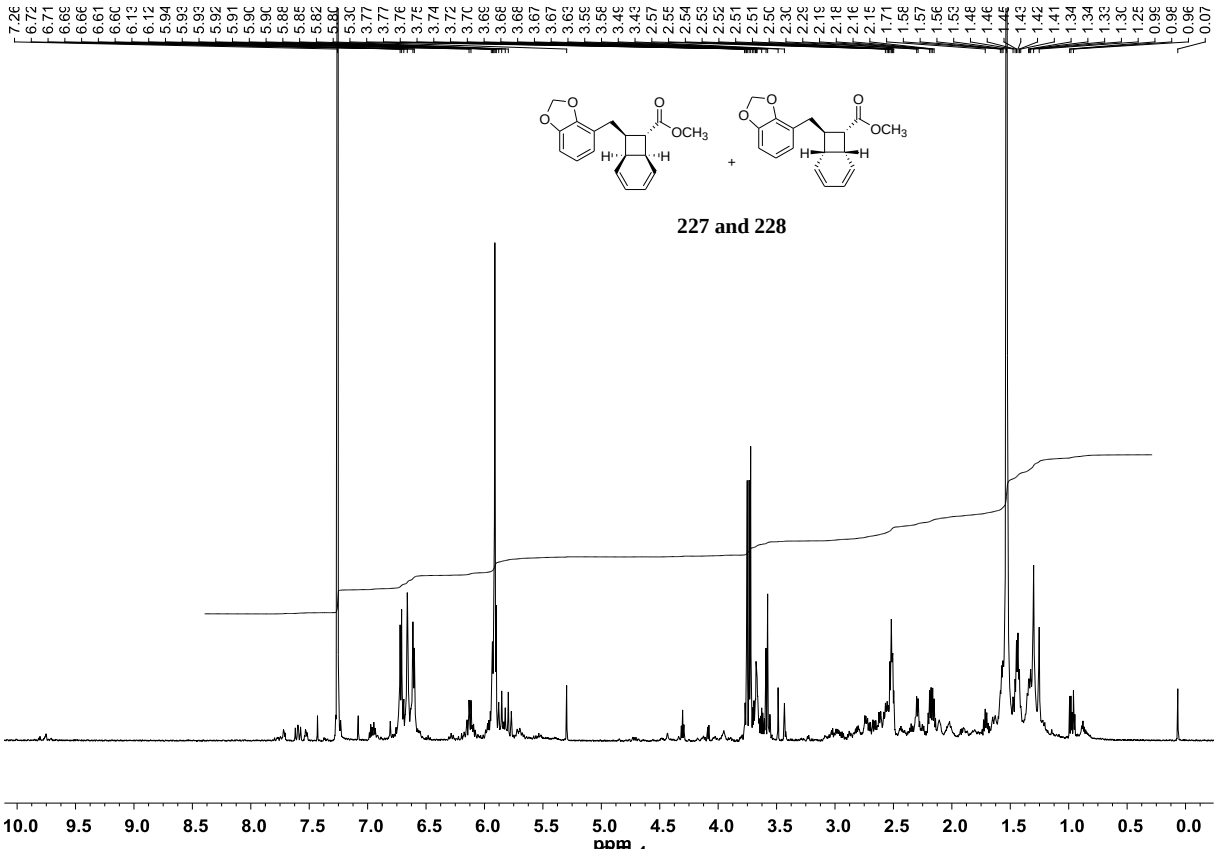
220


7.26 6.75 6.75 6.74 6.73 6.73 6.72 6.70 6.70 6.69 6.68 6.65 6.64 6.64 6.61 6.60 6.31 6.31 6.29 6.29 6.28 6.28 6.27 6.27 6.24 6.21 6.18 6.17 6.09 6.08 6.06 6.05 5.98 5.97 5.97 5.96 5.93 5.92 3.50 3.48 3.47 3.46 3.39 3.38 3.36 3.35 3.29 3.28 2.81 2.81 1.54 1.26 1.22 1.21 1.20
I
I
203 and 221
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

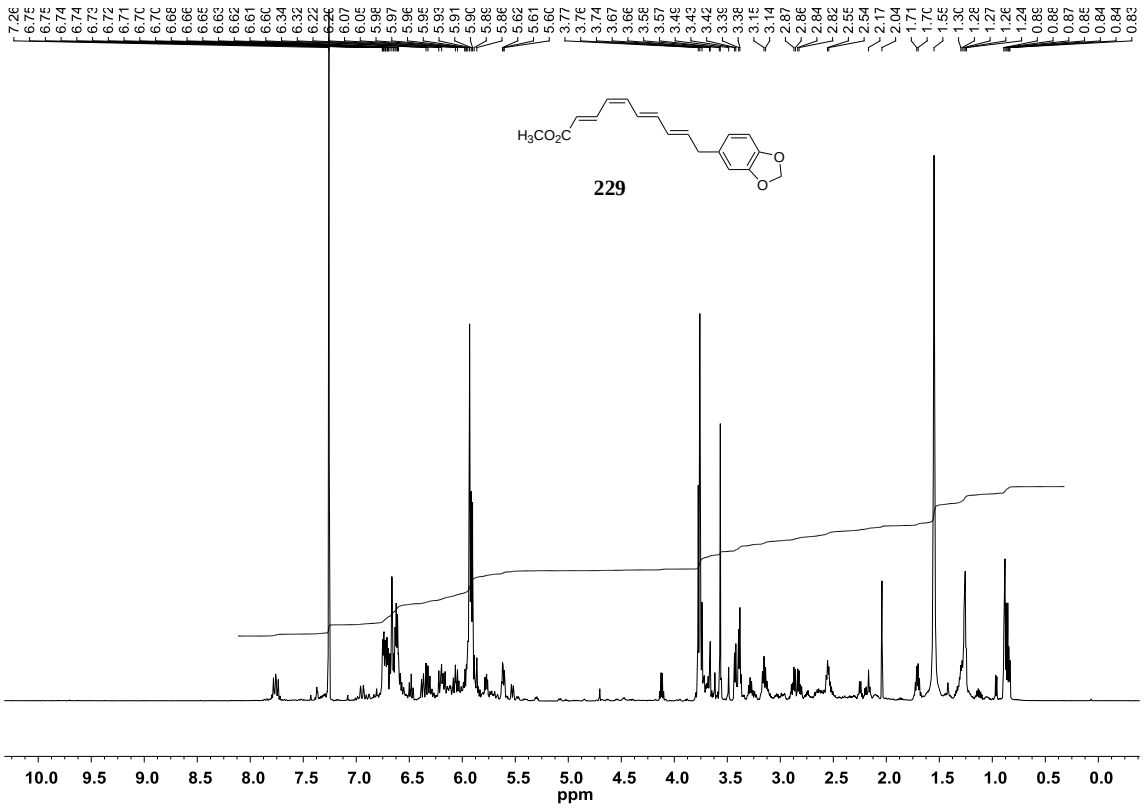

7.68 7.66 7.66 7.64 7.34 7.31 7.26 7.12 6.76 6.74 6.68 6.68 6.58 6.10 6.08 6.08 6.04 6.03 5.98 5.93 5.90 3.40 3.40 3.39 3.38 3.37 3.37
Br
223
0.88 3.82 1.01 22.25 6.00 5.31 7.30 10.67 11.11
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

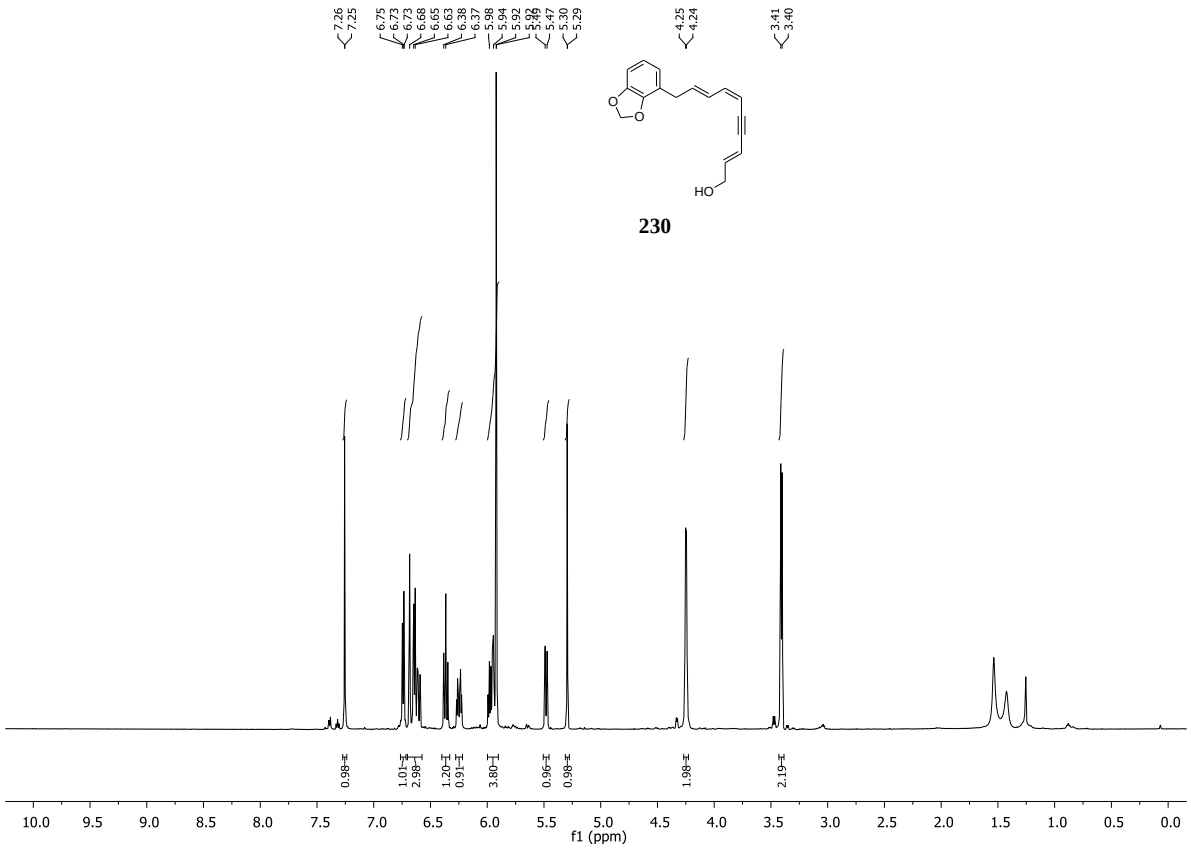


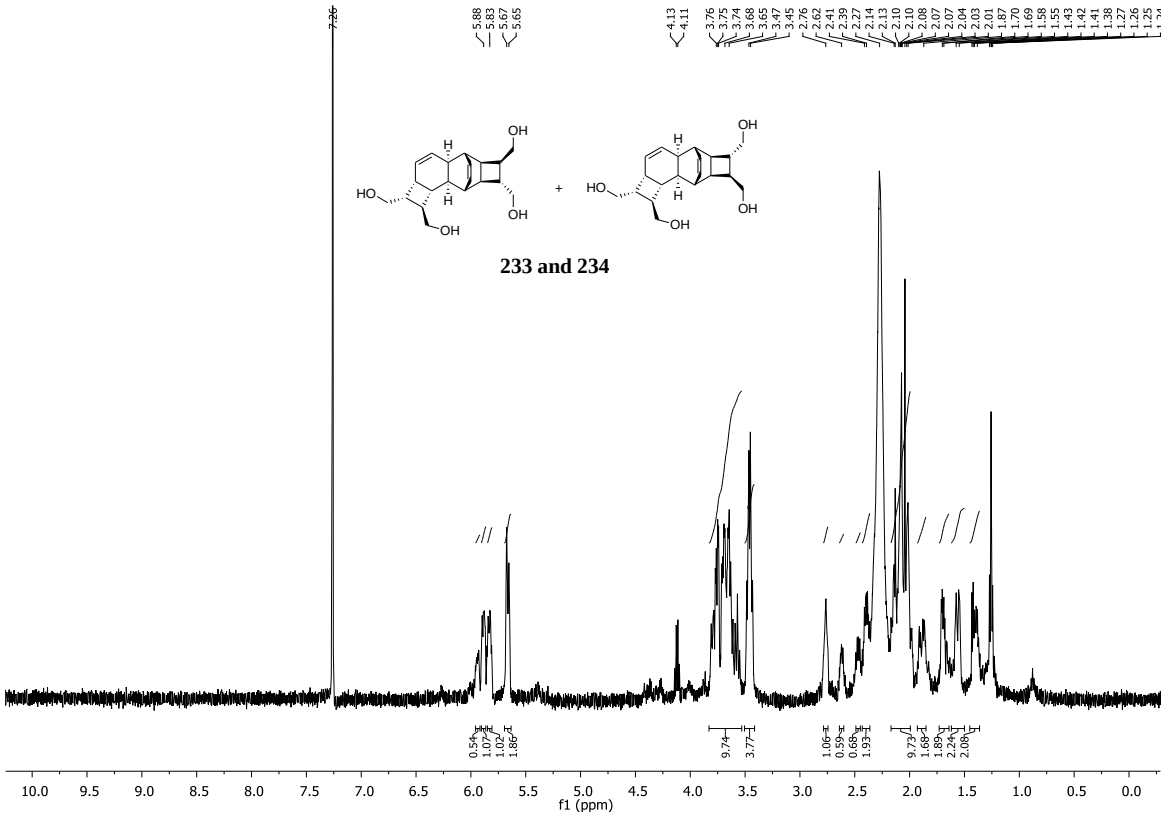
225 and **226**



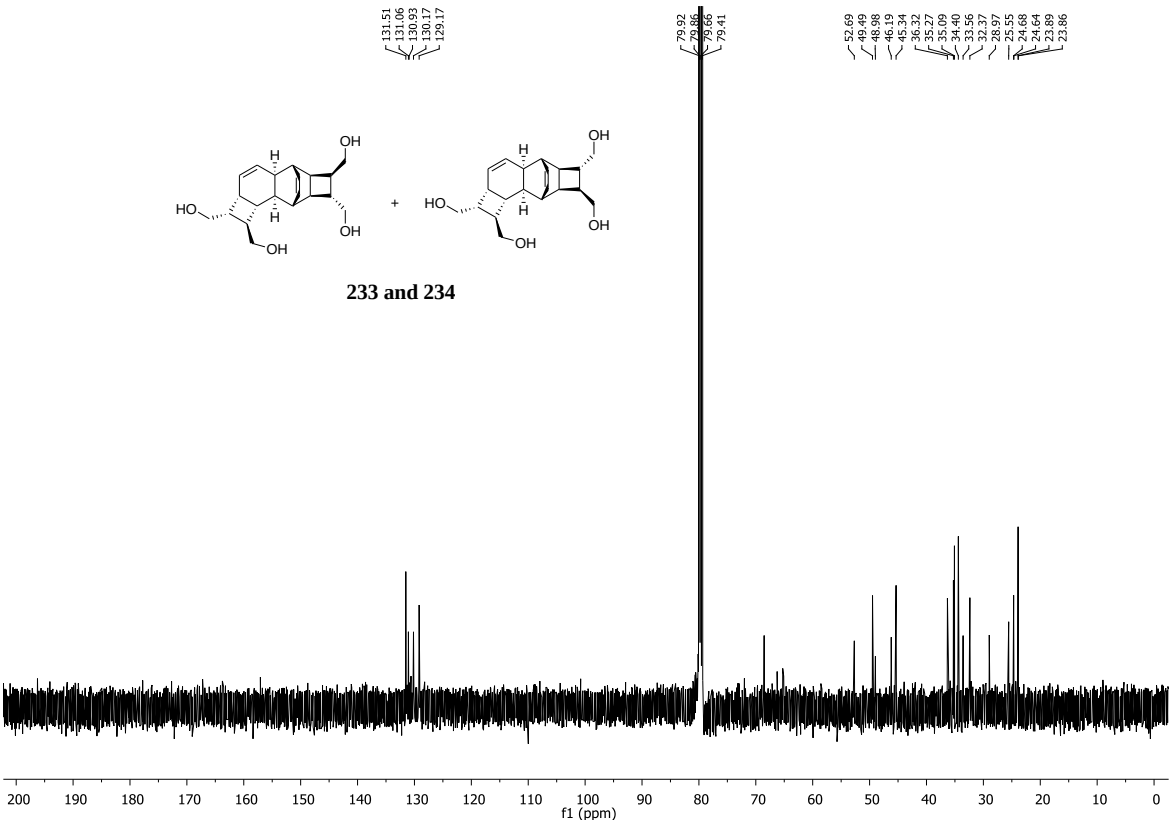
227 and 228


H3CO2C
O
O
229
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


7.26
7.25
6.75
6.73
6.73
6.68
6.65
6.63
6.38
6.37
5.98
5.94
5.92
5.47
5.30
5.29
4.25
4.24
3.41
3.40
O
O
HO
230
0.98
1.01
2.98
1.20
0.91
3.80
0.96
0.98
1.98
2.19
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



233 and 234



233 and 234