Synthetic Progress Toward Parvistemonine, Spiroxins A and B, and Generation of Palmarumycin Analogues

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Synthetic Progress Toward Parvistemonine, Spiroxins A and B,

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Natural products can both challenge synthetic chemists and guide biologists. In this work, they prompted the extension of oxidative methodology to new systems, inspired the systematic modification of the palmarumycin scaffold to produce potent thioredoxin/thioredoxin reductase (Trx/TrxR) inhibitors, and demanded creative synthetic solutions to the structural challenges Mother Nature provided. The first pursuit was the total synthesis of parvistemonine, a pentacyclic azacycle isolated from *Stemona* plants. These plants have been used in Chinese folk medicine, and the isolated *Stemona* alkaloids possess therapeutic uses that range from antitussive to antiparasitic activity. The oxidative cyclization of tyrosine was incorporated into the syntheses of several natural products, and the extension of this methodology to homotyrosine for construction of the azacyclic core was investigated. Ultimately, the desired cyclization was not optimized to give synthetically viable yields, but the competing pathways and preferred reactivity was elucidated. In a separate project, a library of palmarumycin based prodrugs was synthesized. The bisnaphthospiroketal functionality, which is present in palmarumycin, is a lucrative scaffold that potently inhibits thioredoxin/thioredoxin reductase (Trx/TrxR). Some of the analogues suffered from low solubility, so various amino ester and sugar containing prodrugs were investigated. A prodrug library with improved solubility and greater plasma stability was successfully generated. One gram of the lead prodrug was needed for further biological testing, which would have been challenging with the first generation synthesis. An alternative synthesis

was developed that afforded 1 g of the prodrug and decreased the total number of steps by half while significantly improving the overall yield. Finally, the total synthesis of spiroxins A and B was pursued. The spiroxins were isolated from an unidentified marine fungus and only spiroxin A was tested for biological activity. These highly oxygenated octacyclic compounds only differ in their degree of chlorination. A synthetic route was proposed that allowed access to both spiroxin A and B, and only diverged in the final chlorination step. Through a series of oxidations and reductions, this challenging core was accessed.

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so far away. I can not imagine what my time in Pittsburgh would have been like without him. In all honesty, there is nothing more that I could ask for.

LIST OF ABBREVIATIONS

Ac……....acyl

Acac……acetylacetonate

AIB…….α-aminoisobutyric acid

AIBN……..2,2'-azobis(2-methylpropionitrile)

ATR……Attenuated total reflection

BCNU……1,3-bis(2-chloroethyl)-1-nitrosourea

B-I-9-BBN……9-iodo-9-borabicyclo[3.3.1]nonane

Bn……...benzyl

Boc…….*tert*-butyloxycarbonyl

Bu……...butyl

CAN……...ceric ammonium nitrate

CD……..circular dichroism

CDI…….carbonyl diimidazole

Choi……2-carboxy-6-hydroxyoctahydroindole

d…….day

Dba…….dibenzylideneacetone

DBB……4,4-di-*tert*-butylbiphenyl

DBU…….....1,8-diazabicyclo[5.4.0]undec-7-ene

DCC.....1,3-dicyclohexylcarbodiimide

DDQ.....dichlorodicyanoquinone

DEAD……diethylazodicarboxylate

DIAD.....diisopropylazodicarboxylate

DIBALH.....diisobutylaluminum hydride

DMAP .....4-(dimethylamino)pyridine

DMDO.....dimethyldioxirane

DMF.....dimethylformamide

DMP.....Dess-Martin periodane

DMSO.....dimethylsulfoxide

DTNB…….dithionitrobenzoic acid

ee.....enantiomeric excess

equiv.…….equivalent

Et.....ethyl

FAD……...flavin adenine dinucleotide

GI_{50}……half of growth inhibition

h……..hour

HMPA.....hexamethylphosphoramide

IC_{50}……half of inhibitory concentration

Im……...imidazole

LAH.....lithium aluminum hydride

LC_{50}.....median lethal concentration

LDA.....lithium diisopropylamide

LHMDS.....lithium hexamethyldisilazane

mCPBA.....*meta*-chloroperoxybenzoic acid

Me.....methyl

min.....minute

MOM.....methoxymethyl ether

MTT……..3-[4,5]-dimethylthiazol-2-yl-2,5-diphenyltetrazolium bromide

NADPH…….nicotinamide adenine dinucleotide phosphate

N-BCC.....*N*-benzyl cinchonidinium chloride

NBS.....*N*-bromosuccinimide

NCS.....*N*-chlorosuccinimide

NMO.....4-methylmorpholine *N*-oxide

NMR.....nuclear magnetic resonance

n.r……...no reaction

PCC.....pyridinium chlorochromate

PDC.....pyridinium dichromate

Ph.....phenyl

PIDA.....iodobenzene diacetate

PIFA.....[bis(trifluoroacetoxy)iodo]benzene

Piv…….....pivaloyl

PPA.....polyphosphoric acid

PPTS.....pyridinium *para*-toluenesulfonate

r.t…….room temperature

TBAF.....tetrabutylammonium fluoride

TBHP.....*tert*-butyl hydrogen peroxide

TBSCl.....*tert*-butyldimethylsilyl chloride

TCE.....tetrachloroethane

TESOTf…….triethylsilyl trifluoromethane sulfonate

TFA.....trifluoroacetic acid

TFAA.....trifluoroacetic anhydride

TFE…….trifluoroethanol

THF……tetrahydrofuran

TIBA.....triisobutylaluminum

TMSOTf…….trimethylsilyl trifluoromethanesulfonate

Tos.....*para*-toluene sulfonate

TPAP…….tetra-*n*-propylammonium perruthenate

Trx/TrxR……thioredoxin/thioredoxin reductase

Ts……*para*-toluene sulfonyl

1.0 INTRODUCTION TO THE *STEMONA* ALKALOIDS

1.1 THE *STEMONA* ALKALOID FAMILY

Parvistemonine (**1**, Figure **1.1**) is a member of the *Stemona* class of alkaloids. The structural features of two lactones, a 4-azaazulene ring and ten stereocenters pose interesting synthetic challenges in a relatively compact arrangement. This structural complexity, along with the diverse biological activity found among members of this class of natural products, has prompted synthetic interest in this compound. Diels-Alder reactions,[1] oxidative cyclization[2,3] and the Staudinger[4] reaction have all been explored in efforts to construct the 4-azaazulene ring system. At this time, there have been no other reports of partial or total synthetic approaches to parvistemonine outside of those from the Wipf group.

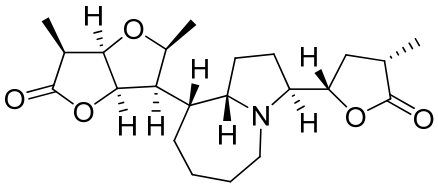


Figure 1.1. Structure of parvistemonine (**1**)

The source of *Stemona* alkaloids are the *Stemona* plants, also known as Roxburghia. They are found in South Asia, Malaysia and North Australia and are classified as subshrubs, or

twining herbs, with thick and tuberous roots.[5] This family can be divided into three genera: *Stemona*, *Croomia*, and *Stichoneuron*. The *Stemona* genera, which contains parvistemonine, is the largest of the three groups and contains more than 25 species.[6] This family of plants has a history of medicinal applications.

Stemona and *Croomia* plants are used in both Japanese and Chinese folk medicine to treat an array of medical conditions. The roots are boiled in water and the extracts consumed to treat illnesses as diverse as pulmonary bronchitis, tuberculosis and intestinal parasites.[5] The roots of the *Stemona* plants are still sold for their medicinal properties. On the internet, these roots are being advertised for conditions as varied as head lice, scabies, colds, and pulmonary tuberculosis.[7] These traditional applications prompted further investigation into the source of this biological activity.

There have been several reports exploring the details of the biological activities of the various components of the *Stemona* plants. Many biological studies have focused on the roots, but there have also been studies on the leaf and rhizome extracts along with individually isolated alkaloids.[8,9] Tuberostemonine, stemofoline, didehydrostemofoline and other *Stemona* alkaloids all show insecticidal activity against larvae.[10] In another study, tuberostemonine was shown to act as a glutamate inhibitor at the neuromuscular junction of crayfish with a potency that matches clinically proven glutamate inhibitors.[11] Neostenine and neotuberostemonine both show antitussive activity in guinea pigs.[12]

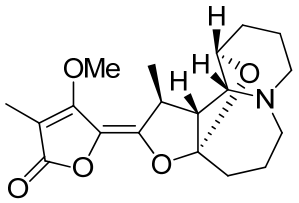


Figure 1.2. Structure of a recently isolated *Stemona* alkaloid, stemocurtisine (**2**)

Stemona alkaloids have some common structural features. Their most distinct component is the 1-azabicyclo[5.3.0]-decane, or 4-azaazulene, ring system. An exception to this generalization was reported in 2003. Stemocurtisine (**2**, Figure **1.2**) contains the [1,2-*a*]azepine core[13] and exhibits larvicidal activity.[14] Excluding the structural variability in some of the most recently isolated members, there have been several proposed ways to further subdivide this class. One proposal classifies the *Stemona* alkaloids into five groups, each named after a representative member: stenine, stemoamide, tuberostemospironine, stemonamine and parvistemoline (Figure **1.3**).[5] These groups predominantly distinguish themselves from one another by the presence and arrangement of the lactone and furan moieties.

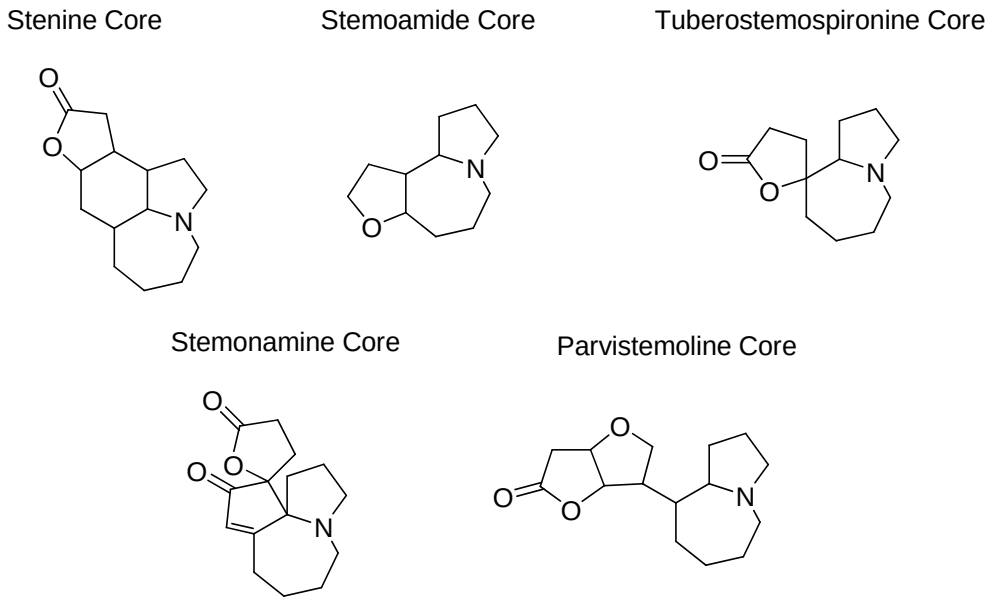


Figure 1.3. Five groups of *Stemona* alkaloids

1.2 *STEMONA* ALKALOIDS' ISOLATION, STRUCTURE ELUCIDATION AND SYNTHESES

The scientific community was first introduced to the family of *Stemona* alkaloids with the isolation of tuberostemonine (**3**, Figure **1.4**) in 1934.[15] However, its structure was not elucidated until 1968 by ^{1}H NMR, mass spectrometry, X-ray studies, UV, IR and degradation studies.[16] Throughout the 1980s, Ren-Sheng Xu led an extensive investigation into the structure determination and isolation of new *Stemona* alkaloids. Through the collective work of him and others, about 42 *Stemona* alkaloids have been described.[5] In 1990, Ren-Sheng Xu and coworkers published the isolation and characterization of parvistemonine. The structure was elucidated by ^{1}H and ^{13}C NMR, MS, COSY, NOESY, IR and various two dimensional techniques.[17]

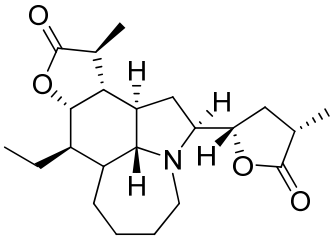
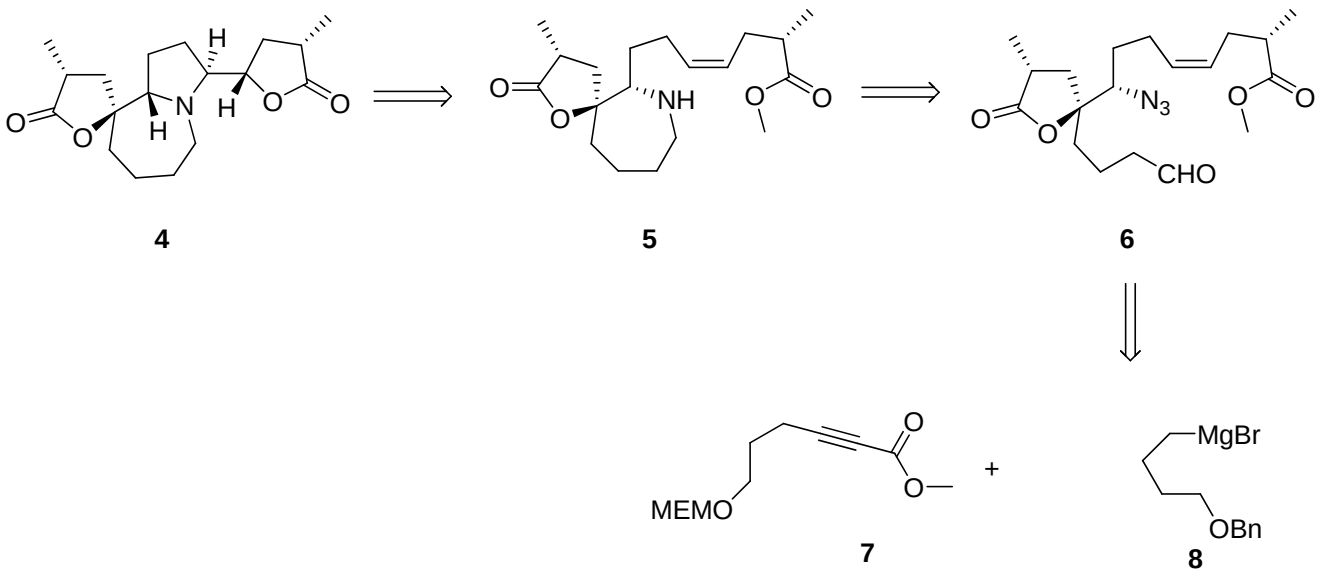


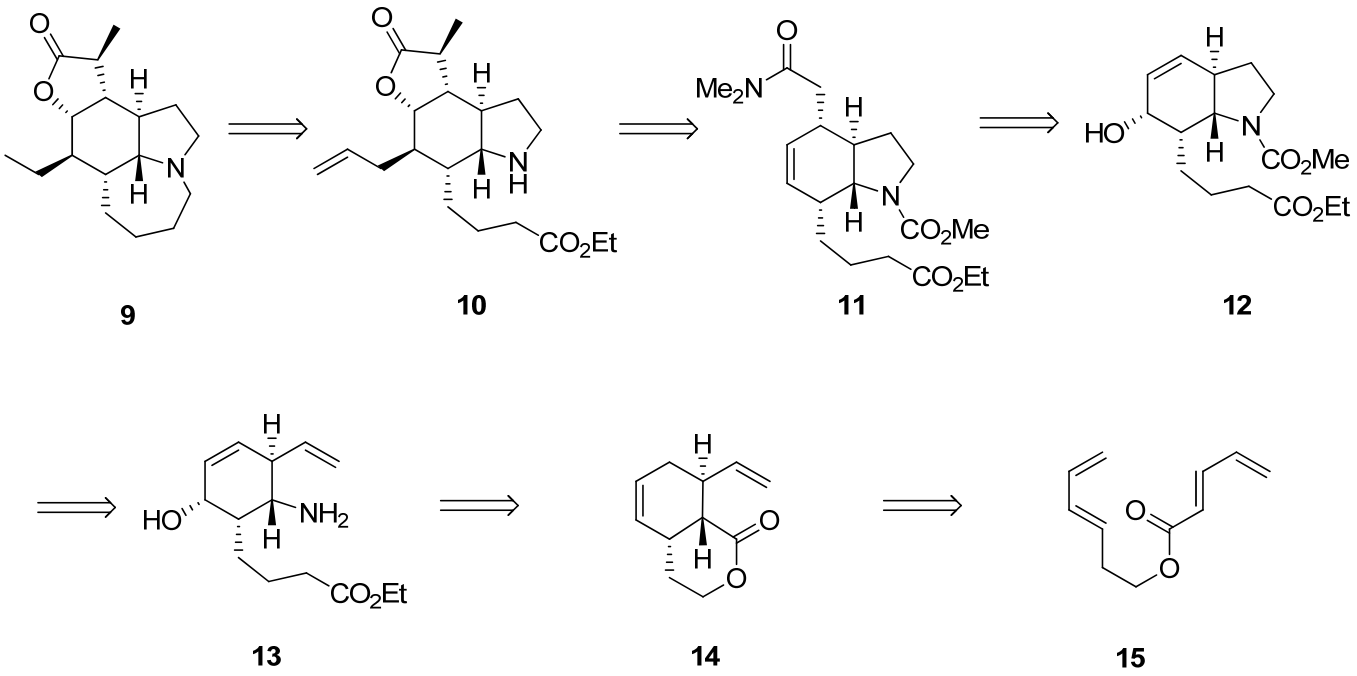
Figure 1.4. First isolated *Stemona* alkaloid, tuberostemonine (**3**)

The synthetic history of *Stemona* alkaloids is relatively short, but well developed. The first *Stemona* alkaloid to be synthesized was (±) croomine (Scheme **1.1**).[4] The Williams group chose to form much of the structure via a linear route and reserved the key steps of ring construction for the end game. (±) Croomine (**4**) was constructed through treatment of **5** with iodine to afford both the lactone and 4-azaazulene moieties. Intermediate **5** was obtained from a Staudinger reaction with azide **6**. The azide moiety in this synthesis proved to be particularly recalcitrant and was carried through five synthetic steps unaffected. The early steps in the synthesis were devoted to functionalizing the linear components of this key intermediate starting from **7** and **8**. (±) Croomine (**4**) was synthesized in 16 steps with an overall yield of 0.02%.



Scheme 1.1. Williams' retrosynthetic analysis of (±) croomine (**4**)

In 1993, Chen and Hart reported the first racemic synthesis of stenine (**9**) in 39 steps with a 9% overall yield using an intramolecular Diels-Alder reaction as the key step.[1] In the retrosynthetic analysis (Scheme **1.2**), the azepine in **9** was formed from substrate **10** by amide formation, conversion to the thioamide and reduction. The lactone formation was accomplished by electrophilic cyclization of the amide in **11**. This substrate was prepared via the Claisen rearrangement of **12**. The hydroindole core was synthesized through hydroboration of **13**, oxidation, conversion of the resultant alcohol to a mesylate and nucleophilic displacement. The synthesis was initiated with the key intramolecular Diels-Alder reaction of substrate **15**.



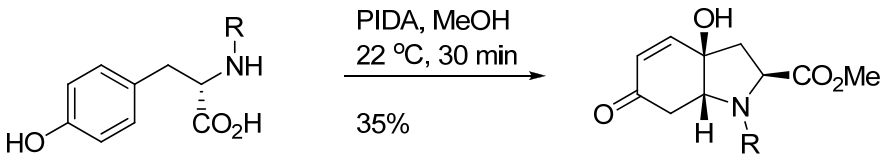
Scheme 1.2. Chen and Hart's retrosynthetic analysis of stenine (**9**)

These alkaloids are an enticing target to many groups. One of the more recent total syntheses of a *Stemona* alkaloid reported in the literature is didehydrostemofoline by Overman.[18] Total syntheses and synthetic approaches have also been reported for croomine,[19,20] stemoamide,[21] stemonine,[22] stemospironine,[23] isostemonamide,[24] isostemofoline,[25] stemonamide[26] and tuberostemonine.[3]

1.3 *STEMONA* ALKALOID SYNTHESIS IN THE WIPF GROUP

The Wipf group first became involved in the synthetic pursuit of *Stemona* alkaloids in 1992, demonstrating that the hydroindole core **17** can be produced in good yield and excellent diastereoselectivity through the oxidative cyclization of tyrosine with phenyl iodoniumdiacetate

(Scheme **1.3**).[27] This reaction was performed with the amine protected either as Boc or Cbz (R = Cbz or Boc). This azacycle can be envisioned as the synthetic starting point for many *Stemona* alkaloids along with other natural products. The 6,5-system delivers three stereocenters from the original one and offers several sites available for further functionalization.



16 **17**

Scheme 1.3. Oxidative cyclization of tyrosine (**16**)

Two transition states were proposed (**18** and **19**) that could account for the observed diastereoselectivity (Figure **1.5**). The diastereoselectivity was attributed to the minimization of allylic strain in **18** compared to **19** with respect to the placement of the ester moiety. Other groups have explored the diastereoselective oxidation of phenols utilizing substrate control[28] or organocatalysis,[29] but have rarely seen the same high level of diastereoselectivity.

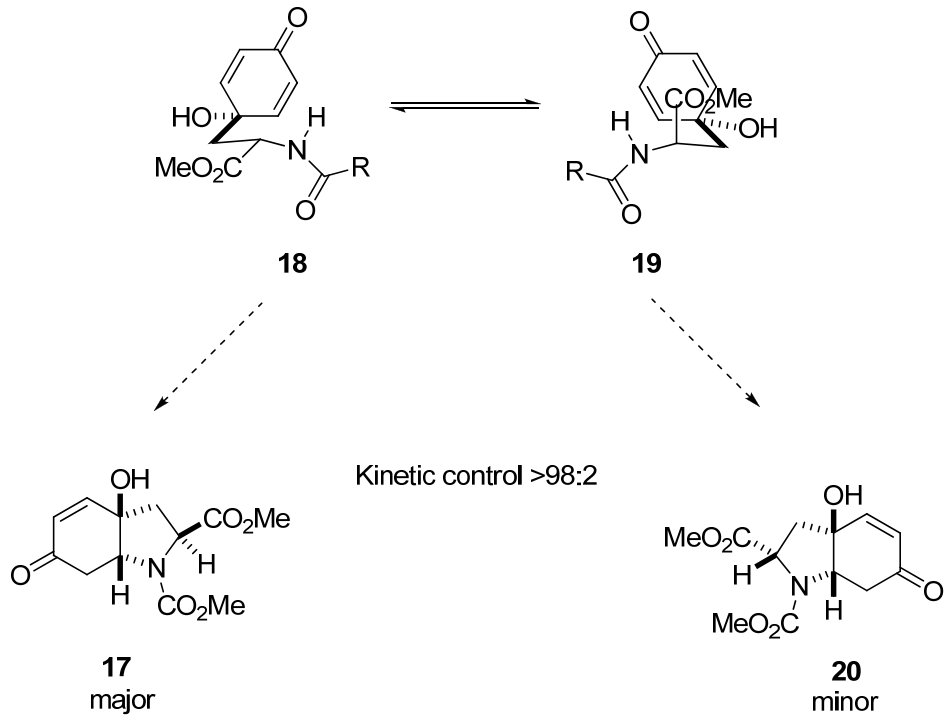


Figure 1.5. Proposed transition states in oxidative cyclization of tyrosine

The construction of this core provided access to a valuable scaffold that has been utilized in several natural product syntheses from the Wipf group. The list of targets includes natural products outside of the *Stemona* family: aranorosin (**21**)[30] and aeruginosin 298-A (**22**)[31] (Figure **1.6**). Other groups have also incorporated the oxidative cyclization of tyrosine and tyrosine derivatives into the syntheses of various alkaloids.[32-36]

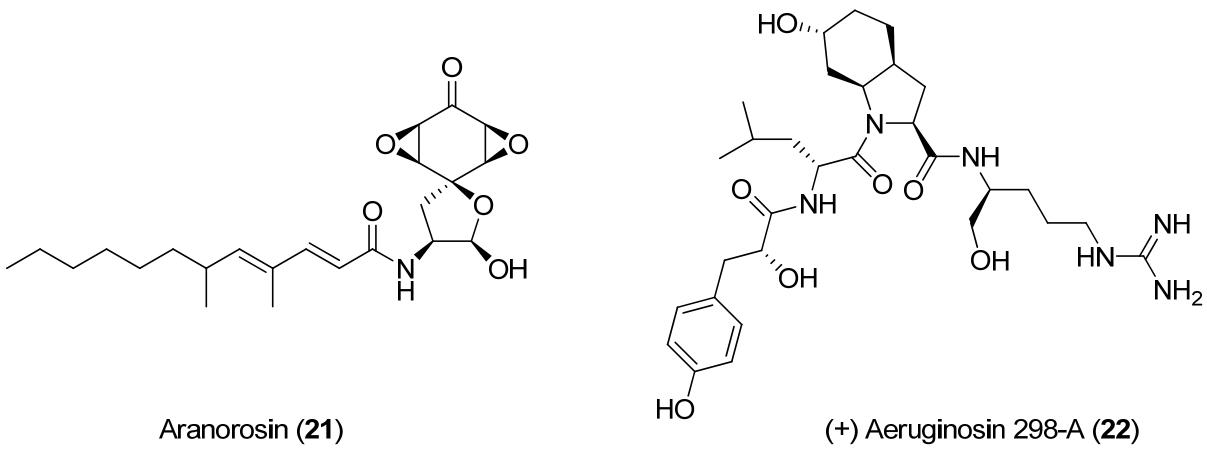
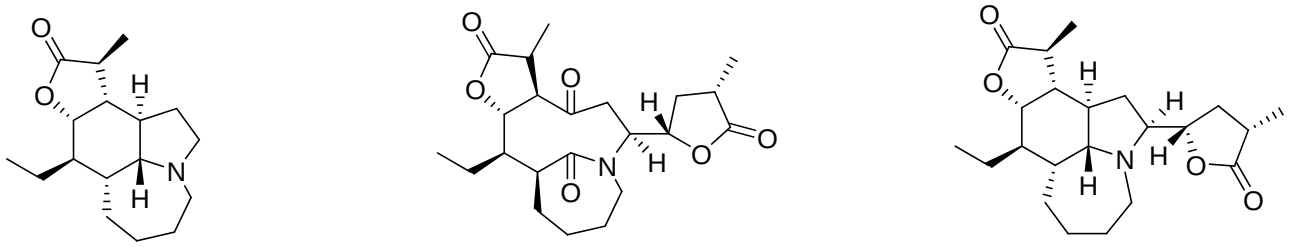


Figure 1.6. Structures of aranorosin (**21**) and aeruginosin 298-A (**22**)

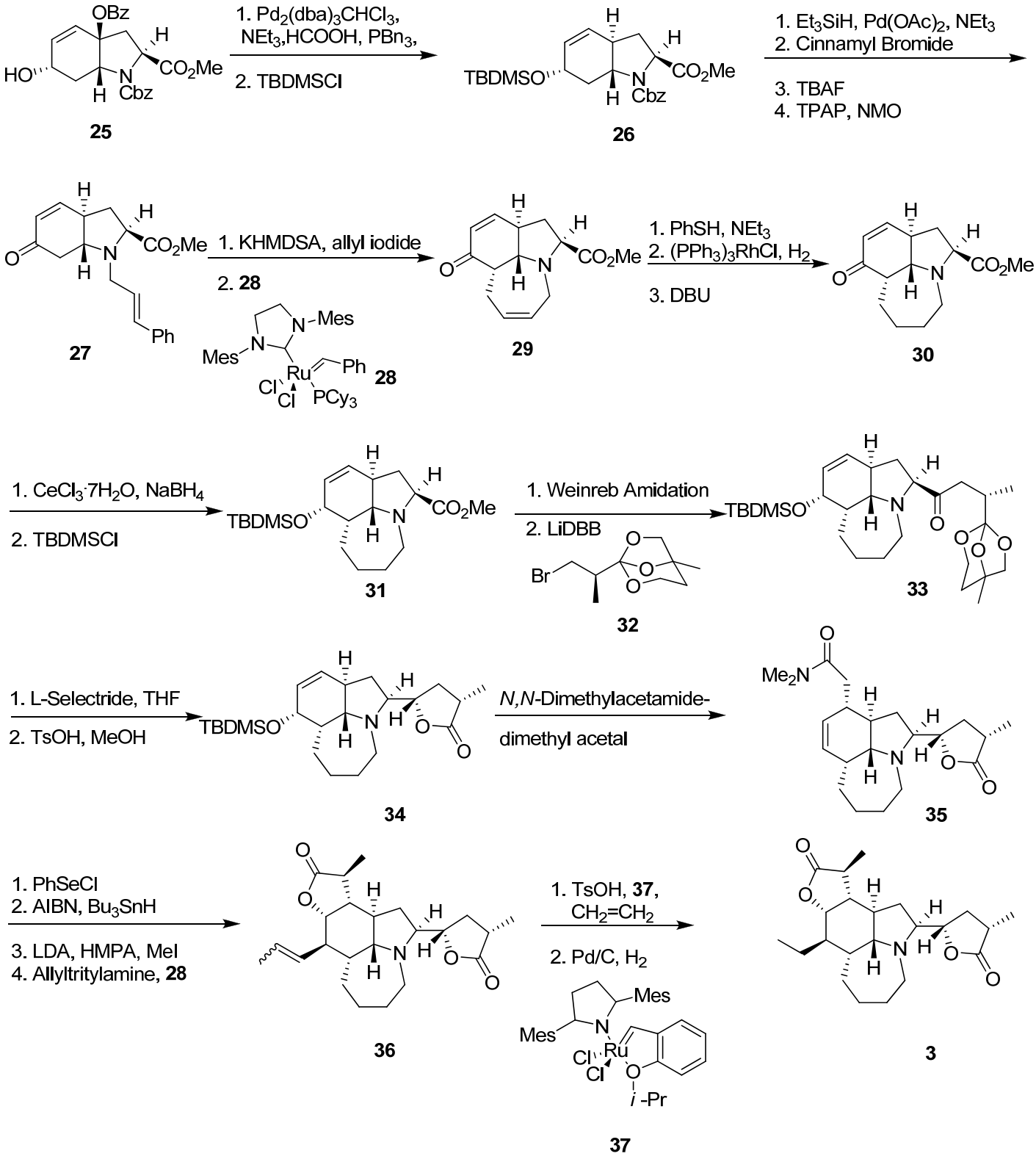
The oxidative cyclization shown in Scheme **1.3** has been applied to two syntheses of *Stemona* alkaloids: stenine (**23**) and tuberostemonine (**3**) and an approach towards the synthesis of tuberostemonone (**24**, Figure **1.7**). In 1995, the Wipf group reported the first asymmetric synthesis of stenine in 26 steps and 1.2% overall yield.[2] In 1999, the possibility of combining the hypervalent iodine chemistry with a biomimetic approach to yield the tuberostemonone core was discussed.[37] The postulation was that the core of tuberostemonone could come from an oxidative cleavage of the tuberostemonine scaffold. These studies used PIDA and iodine for successful oxidative cleavage of the desired bond and construction of the core. These *Stemona* alkaloid studies were further expanded with the asymmetric total synthesis of tuberostemonine in 2002 (Scheme **1.4**).[3]



Stenine (**23**) Tuberostemonone (**24**) Tuberostemonine (**3**)

Figure 1.7. Structures of *Stemona* alkaloid synthetic targets in the Wipf group

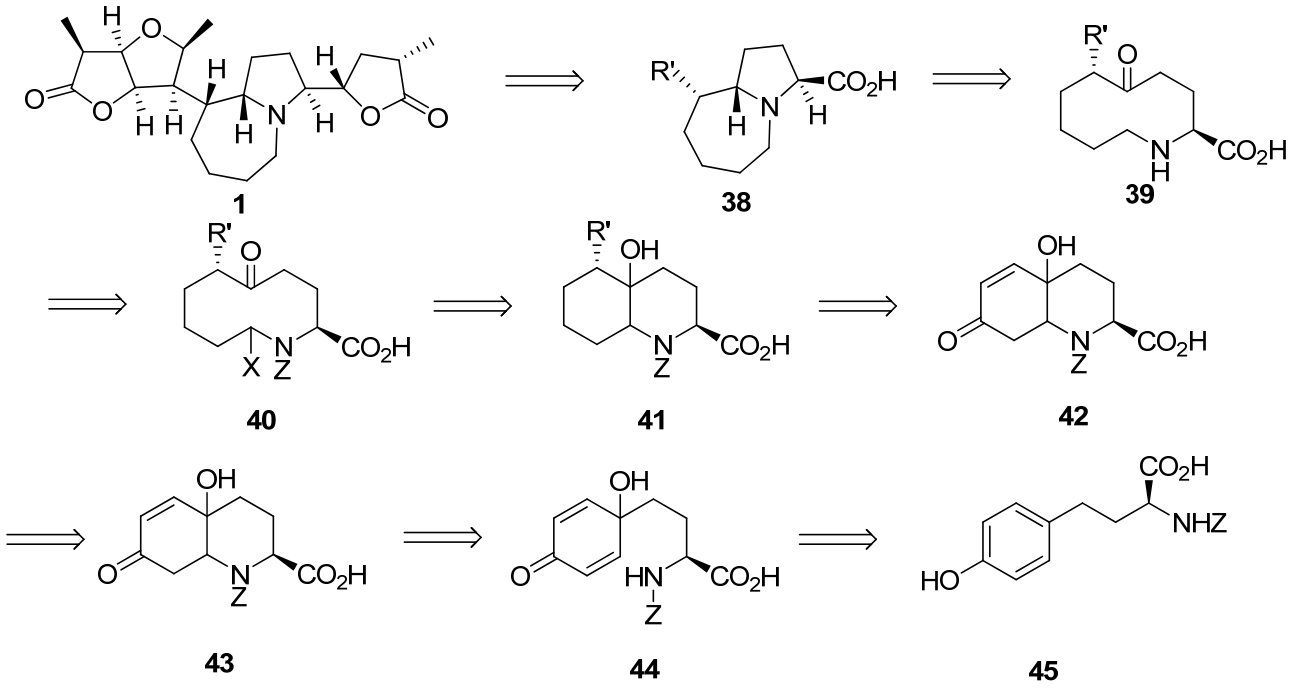
There are numerous points of interest in the total synthesis of tuberostemonine (**3**). The first maneuver to highlight is the use of the same hydroindole core **25** that had served as the key scaffold in the total synthesis of stenine. In both syntheses, **25** was readily prepared from **17** in three steps (Scheme **1.4**). A π-allyl palladium reaction was used to both remove the benzyl ether and simultaneously reduce the ring carbon with overall inversion of configuration to provide **26**. The next key step was the ring closing metathesis with Grubbs' catalyst **28** to afford **29**. Following hydrogenation to **30**, the core of the natural product had successfully been constructed and the remaining lactone moieties were the only necessary additions. The eastern lactone in **34** was formed from a Claisen rearrangement and selenolactonization. The western lactone in **36** was formed via the introduction of the orthoester, reduction and cyclization. This synthesis provided the natural product in 27 steps with a 1% overall yield.



Scheme 1.4. Total synthesis of tuberostemonine (**3**)

1.4 EARLY SYNTHETIC STUDIES TOWARD PARVISTEMONINE

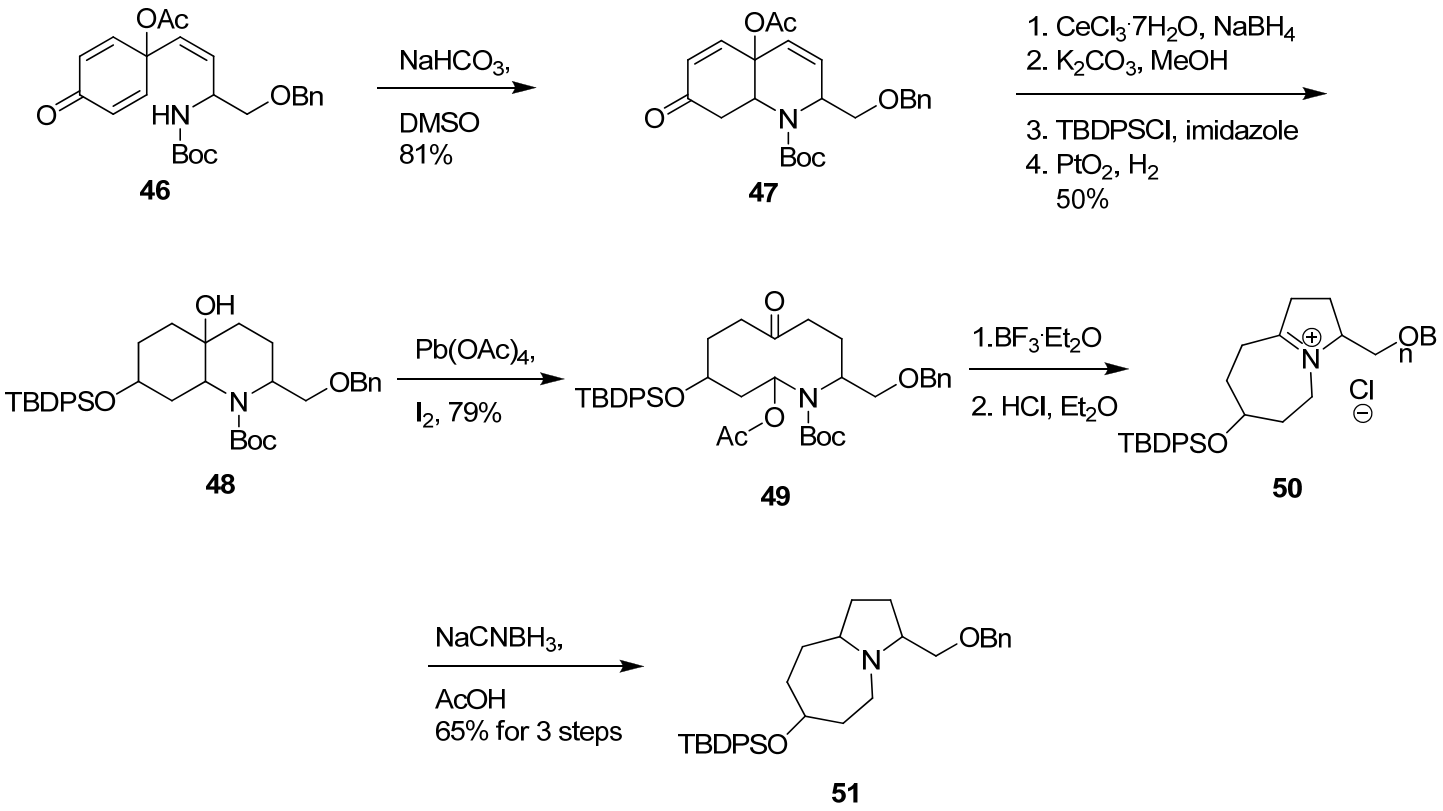
The synthetic studies toward parvistemonine (**1**) in the Wipf group commenced with the work of Dr. David Mareska.[38] The initial goals were to extend some of the methodology that was applied in the total syntheses of stenine (**23**) and tuberostemonine (**3**) along with the development of novel methodology that could be applied to this unique core.



Scheme 1.5. Retrosynthetic analysis of parvistemonine (**1**)

Among the required adjustments of the earlier methodology for **1** was the substitution of homotyrosine (**45**) for tyrosine in the PIDA mediated oxidative cyclization. The key step in the initial retrosynthetic analysis of the 4-azaazulene core **38** was the reductive amination of **39** following oxidative fragmentation of **41** (Scheme **1.5**). This substrate would have been derived

from the oxidative cyclization of **45**. Unfortunately, the synthesis of **45** proved challenging and there were difficulties with the oxidative cyclization. At this point, the retrosynthetic analysis was modified and synthetic studies concentrated on a model system in which the carboxylic acid functionality was replaced with hydrogen. A second generation model system was later explored that replaced the carboxylic acid functionality with benzyl ether (Scheme **1.6**).



Scheme 1.6. Synthesis of parvistemonine model **51**

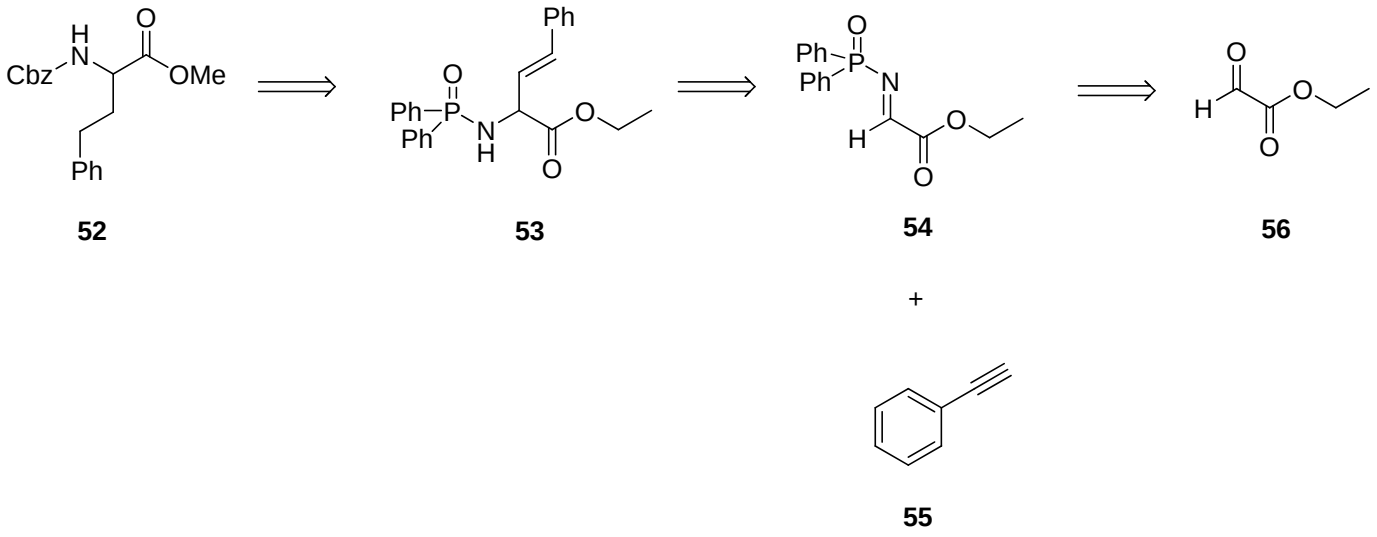
Although this model system would offer a substantially simplified version of the parvistemonine core, its primary focus was to offer a proof of concept for some of the proposed latter steps, in particular the oxidative fragmentation. After testing various analogues and conditions, the model system was converted to the desired azaazulene core **51** (Scheme **1.6**).

Dienone **46** was synthesized as the analogue of **44** from the original retrosynthetic analysis (Scheme **1.5**). Under basic conditions this substrate successfully cyclized to provide **47**, which after several synthetic manipulations, including oxidative cleavage, afforded **49**. Reductive amination led to the desired azaazulene core **51**. The relative stereochemistry of **51** was not established. This scheme provided answers concerning the synthetic manipulations of the modified azaazulene core, but an extension of this approach towards the much more highly substituted natural product was needed.

2.0 SYNTHETIC APPROACHES TO HOMOTYROSINE

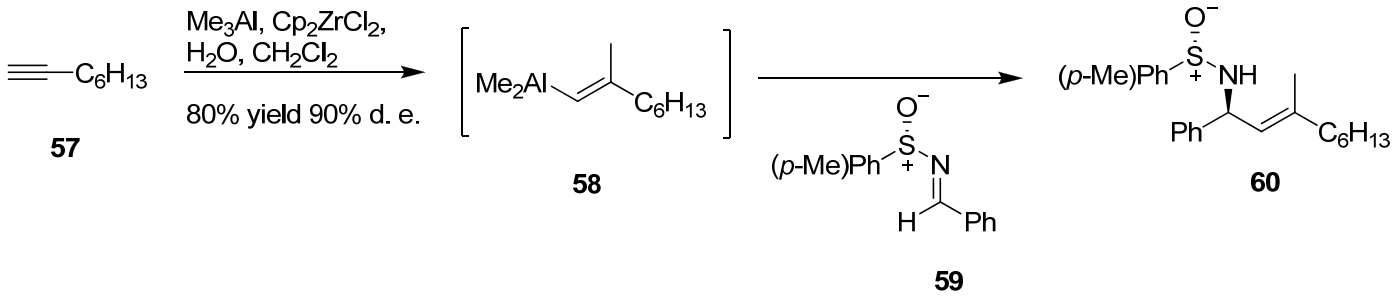
2.1 RETROSYNTHETIC ANALYSIS OF HOMOTYROSINE

The first objective of this project was to synthesize homotyrosine. This would permit investigation into some of the reactions that had been optimized on the model system (Scheme **1.6**). In particular, the oxidative cyclization of a more functionalized intermediate could be explored and studies could continue toward the total synthesis of parvistemonine.



Scheme 2.1. Homotyrosine retrosynthetic analysis

The first retrosynthetic analysis (Scheme **2.1**) of homotyrosine **52** involved hydroalumination of phenylacetylene **55** followed by addition into imine **54**, which is synthesized from ethyl glyoxylate (**46**). This methodology is an extension of similar work explored in the Wipf group (Scheme **2.2**).[39] This earlier work had provided a methodology for the generation of chiral allylic amines. Zirconium in combination with trimethylaluminum reacts with alkyne **57** to form reactive intermediate **58** containing the vinylic dimethyl aluminum moiety. Stoichiometric water was incorporated for its ability to greatly accelerate the reaction. This species was then treated with chiral imine **59** to afford the final chiral allylic amine **60** in good yields and high diastereoselectivity. Such adaptation of this methodology would forego the transmetallation from zirconium to aluminum and instead proceed by direct hydroalumination of the alkyne followed by immediate imine addition.

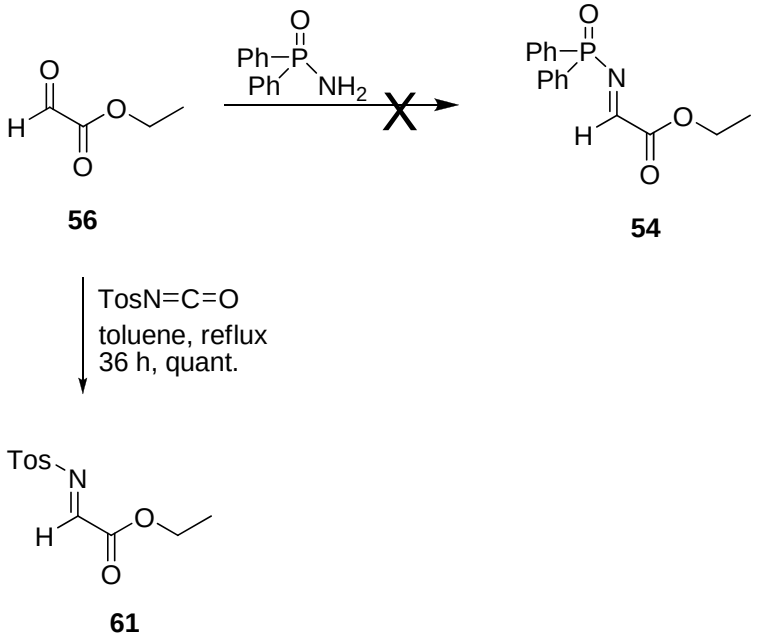


Scheme 2.2. Prior Wipf group work with imine additions

2.2 ALKYNE HYDROALUMINATION AND IMINE SNTHESIS

The first step was to synthesize phosphinamide **54**. This imine protecting group had been used very successfully in another Wipf group methodology that utilized hydrozirconation and zinc

transmetallation for the addition to imines.[40] The condensation reaction never went to completion for the imine formation using the standard conditions with $TiCl_4$ (Scheme **2.3**). A different approach was explored for formation of an imine bearing a tosyl protecting group, as in **61**. Heating tosyl isocyanate at reflux for 36 h with **56** gave quantitative conversion to **61** according to ^1H NMR analysis of the reaction mixture.[41,42] The imine possessed marginal stability and was susceptible to hydrolysis back to the aldehyde. Once the imine was generated, it needed to be submitted directly to the hydroalumination conditions.



Scheme 2.3. Imine **61** formation from ethyl glyoxylate (**56**)

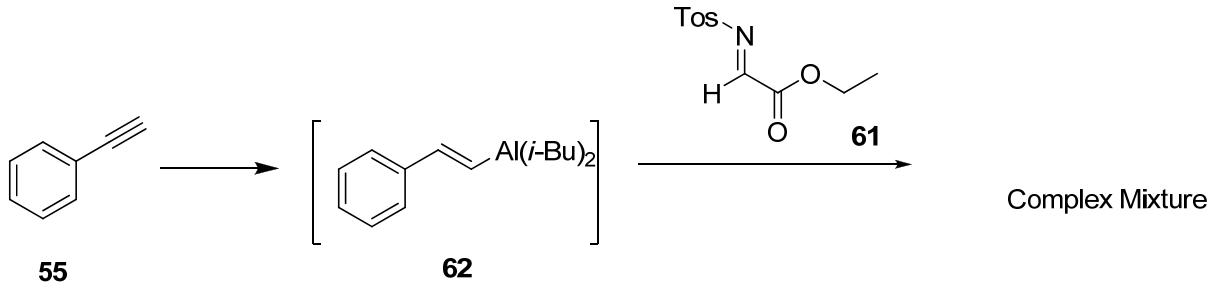
With the synthesis of **61** resolved, the hydroalumination of phenylacetylene needed to be resolved. DIBALH was first examined as the aluminum source.[43,44] Various conditions were explored for hydroalumination with varying success (Table **2.1**). Additives such as Pd or Cu were investigated (entries 2 and 4),[45-47] but these only produced trace amounts of product. The

effect of temperature on yield was also investigated (entries 1 and 3). Ultimately, the best result was observed for the reaction of phenylacetylene and DIBALH in heptane at 55 °C (entry 3).

Table 2.1. Hydroalumination of phenylacetylene conditions

Entry	**Additives**	**Al source**	**Solvent**	**Yield** [%]	**Temp** [°C]
1	None	DIBALH (1equiv)	Heptane	Trace	0-55
2	$Cl_2(PPh_3)_2Pd$	TIBA (1.1 equiv)	CH_2Cl_2	Trace	23
3	None	DIBALH (1 equiv)	Heptane	96	55
4	LiCl, CuBr	DIBALH (2 equiv)	THF	Trace	23

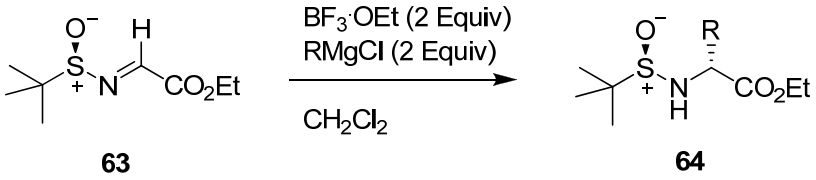
After the successful hydroalumination of phenylacetylene, addition to the imine was attempted. Tosyl imine **61**, as a 6 mmol solution in toluene, was added dropwise to a solution of **62** in heptane at −78 °C. Unfortunately, this sequence only afforded a complex mixture (Scheme **2.4**). The difficulties encountered prompted an investigation of a new methodology for the synthesis of homotyrosine.



Scheme 2.4. Addition of hydroaluminated phenylacetylene to tosylimine **61**

2.3 GRIGNARD ADDITION TO IMINE 63

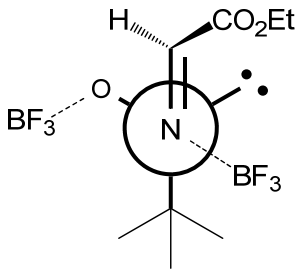
An alternative approach was needed and the possibility of a Grignard addition into a protected imine was explored. The stereoselectivity of similar organometallic additions has been documented by the Davis group using a chiral sulfonylimine generated from the condensation of a sulfinamide with ethyl glyoxylate **63**.[48,49] They reported the Grignard additions of methyl, ethyl and benzyl nucleophiles (59, 27, and 70% yield, respectively) (Scheme **2.5**). They initially investigated the *p*-toluenesulfonyl imine, but found that side reactions due to Grignard addition into the sulfoxide resulted in a low yield. The switch to the *t*-butyl moiety on the sulfoxide was credited with providing the desired steric bulk to significantly reduce the side reactions and resulted in preferential imine addition.



63 **64**

Scheme 2.5. Grignard addition to imine **63**

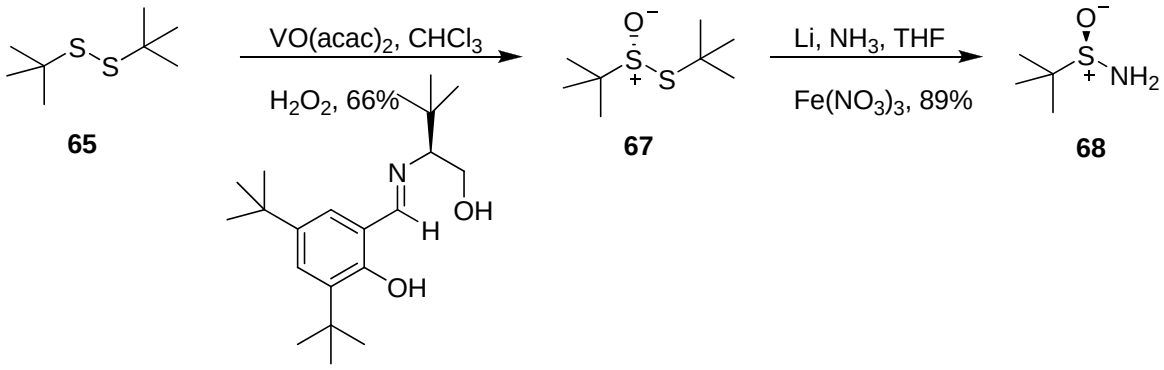
The stereoselectivity of the addition is based on the proposed transition state in Figure **2.1**. One equivalent of $BF_3{\cdot}OEt_2$ coordinates to the oxygen of the sulfoxide providing additional steric bias to increase the diastereoselectivity. The second equivalent of $BF_3{\cdot}OEt_2$ coordinates to the nitrogen of the imine and increases activation towards nucleophilic addition.



63

Figure 2.1. Proposed conformation of BF_3 complexed **63**

The new approach for the synthesis of homotyrosine would utilize the chemistry shown in Scheme **2.5** with (*p*-OMe)phenethyl magnesium chloride as the nucleophile. A model study was first explored with phenethyl magnesium chloride as the nucleophile. The new synthesis of homotyrosine first required preparation of the chiral sulfonylimine. The synthesis of sulfinamide **68** followed a procedure published by Ellman (Scheme **2.6**).[50-53]

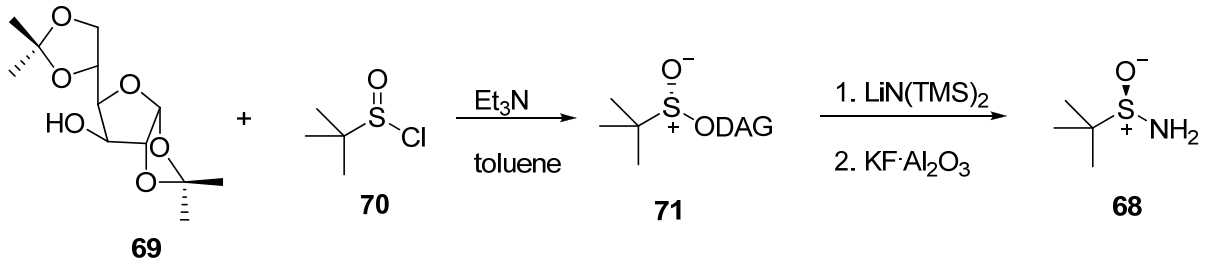


Scheme 2.6. Ellman's synthesis of sulfinamide **68**

Sulfoxide **67** was formed through the oxidation of *t*-butyl disulfide with $VO(acac)_2$ using methodology developed by the Ellman group. Ammonia and dissolving metal conditions

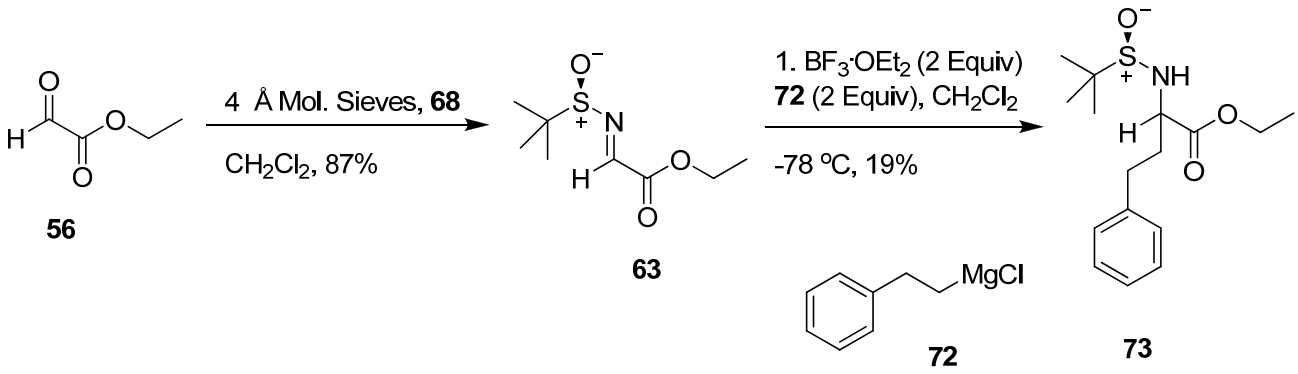
afforded **68** in good yields and this product could be scaled up to gram quantities. Sulfinamide **68** is the identical substrate that the Davis group had used to generate their chiral sulfonylimines of ethyl glyoxylate.

Of particular note is the catalytic oxidation of *t*-butyl disulfide with $VO(acac)_2$, H_2O_2 and chiral ligand **66** to provide **67** (Scheme **2.6**). The enantiomer of **66** can be readily synthesized and likewise allows access to the enantiomer of **67**. This procedure was both an extension and optimization of earlier work from the Alcudia group. They had enantioselectively generated **68** through the incorporation of the chiral auxiliary DAG (**69**).[54] This had the obvious drawback of being stoichiometric in the chiral auxiliary (Scheme **13**).



Scheme 2.7. Chiral auxiliary mediated enantioselective synthesis of sulfonamide **68**

With the chiral sulfinamide **68** in hand, imine formation proceeded smoothly by treating ethyl glyoxylate with 4 Å molecular sieves and **68**, which afforded good yields of **63** (Scheme **2.8**). 1,2-Addition into the imine was then explored with 2 equiv of $BF_3{\cdot}OEt_2$ and 2 equiv of the Grignard reagent.



Scheme 2.8. Grignard addition into sulfonyl imine **63**

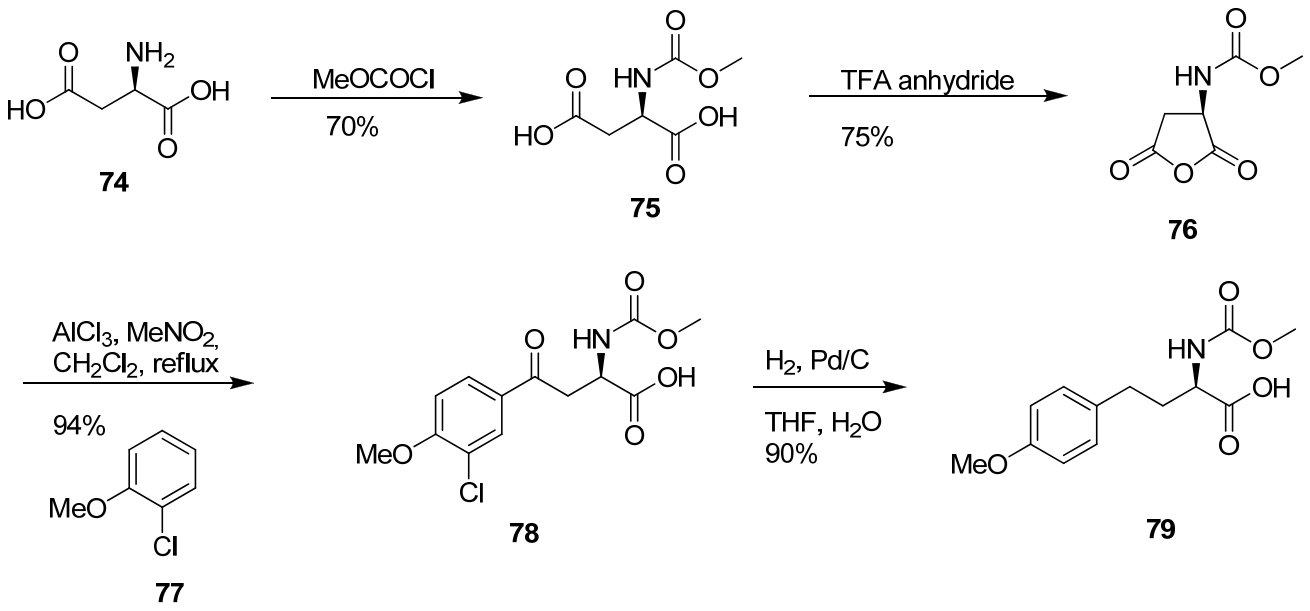
Various conditions were explored in hopes of improving the yield of **73** (Table **2.2**). The imine bearing the *t*-butyl sulfoxide protecting group, **63**, afforded the best yields whereas the tosyl protecting group, **61**, only afforded complex mixtures (entries 1 and 2). This was analogous to the Davis group findings with the *p*-toluene sulfoxide protecting group. The yield was influenced by the scale of the reaction. The highest yield was 30% (entry 5) and was performed on the largest scale, 6 mmol. However, the various conditions explored did not deliver marked improvement in the yield.

Table 2.2. Grignard conditions for addition into imine **63**

Entry	**Imine**	**72** [equiv]	**BF_3·OEt_2** [equiv]	**Solvent**	**Time**	**Yield** [%]	**Scale** [mmol]
1	**61**	1	0	Et_2O	1 h	Decomp	12
2	**61**	1	0	THF	8 h	Decomp	7
3	**63**	2	2	CH_2Cl_2	10 min	19	0.5
4	**63**	1	1	CH_2Cl_2	10 min	9	2
5	**63**	2	2	CH_2Cl_2	10 min	30	6
6	**63**	2	2	CH_2Cl_2	10 min	26	2
7	**63**	2	2	CH_2Cl_2	30 min	Mixture	2

The difficult scalability of the imine formation combined with the low yields of the Grignard addition were sizeable dilemmas for the first step in a synthesis. In order to circumvent these problems, the literature procedure for the production of homotyrosine was followed (Scheme **2.9**).[55]

2.4 LITERATURE SYNTHESIS OF HOMOTYROSINE



Scheme 2.9. Literature synthesis of homotyrosine (**79**)

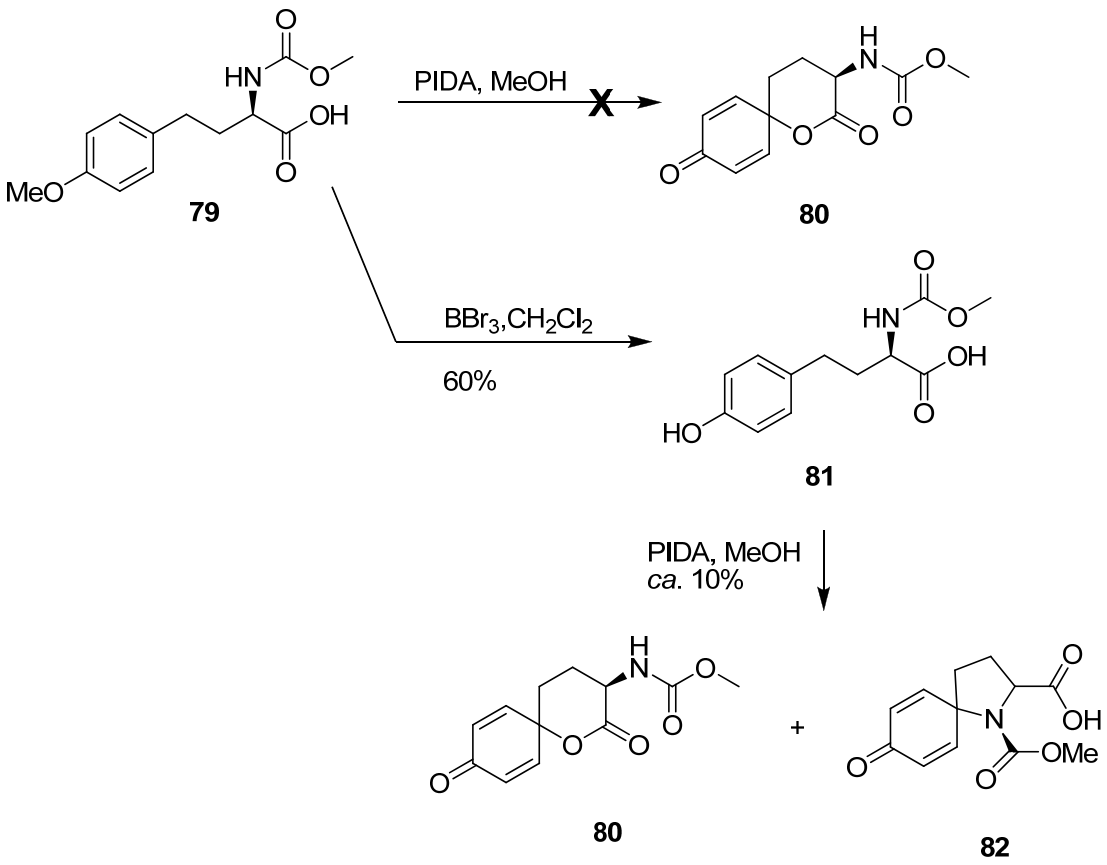
The reported synthesis began with the protection of the nitrogen in aspartic acid (**74**) with methyl chloroformate, followed by TFA anhydride promoted dehydration of **75** to afford anhydride **76** (Scheme **2.9**).[55] A Friedel-Crafts reaction with anhydride **76** and aryl **77** led to the functionalized homotyrosine precursor **78**. The incorporation of chlorine in **77** was important to improve the para-selectivity of the Friedel-Crafts reaction. The chlorine blocks the ortho site next to the methoxy group and can minimize acylation at the other orthoposition via a buttressing effect.[56] Hydrogenation of **78** at 40 p.s.i. removed both the benzylic carbonyl group and the aromatic chlorine to afford **79** in multigram quantities as a single isomer.

Several alternative approaches have been published for the enantioselective synthesis of homotyrosine. Approaches have utilized the organocatalytic diastereoselective Mannich reaction,[57] and chiral auxilariary mediated diastereoselective alkylation.[58]

3.0 OXIDATION OF HOMOTYROSINE

3.1 OXIDATION OF HOMOTYROSINE TO DIENONE

With **79** in hand, the hypervalent iodine chemistry could be explored (Scheme **3.1**). The one pot procedure of tyrosine oxidation, saponification of the lactone and aza-Michael addition has been reported previously.[59] The goal was to apply this same sequence to homotyrosine, but the early studies focused first on the oxidation of homotyrosine to **80**. Saponification of **80** would afford dienone **44** (scheme **1.5**), which would undergo conjugate addition to afford the azacyclic core **43** (Scheme **1.5**). The oxidation was first attempted with PIDA, but the presence of the methyl ether prevented the cyclization from occurring, necessitating deprotection to the phenol. The deprotection to phenol **81** was not trivial due to the hydrophilicity of the product, yet with careful workup conditions, the yield was improved to 60%. The oxidative cyclization with hypervalent iodine chemistry under standard conditions with PIDA gave low yields of the desired product **80** (Scheme **3.1**).



Scheme 3.1. Oxidative cyclization of homotyrosine

The one side product formed was discovered to be the 5-6-spirocycle **82**. This side product presumably formed from initial attack of the carbamate nitrogen instead of the carboxylic acid oxygen after phenol **81** reacted with PIDA. The crude ^{1}H NMR from entry 8 (Table **3.1**) showed nearly a 3:1 ratio of **82**:**80**. The separation of **82** from **80** through chromatography proved to be surprisingly difficult, often requiring several submissions to column chromatography. The most efficient method for separation of these two components proved to be a simple aqueous wash with sat. $NaHCO_3$ followed by a single submission to standard chromatography on silica (entry 8). Despite the efficient separation, the yield was only 7%.

Table 3.1. Oxidative cyclization of homotyrosine conditions

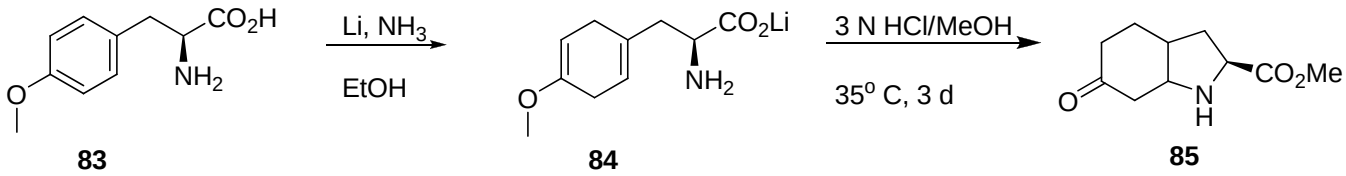
Entry	Reagent	Solvent	Yield [%]	Purification
1	PIDA	TFE	9	SiO_2
2	PIDA	MeOH	Decomp	SiO_2
3	PIDA	Nitromethane	13	Fuller's earth
4	PIDA	TFE	13	Reverse phase
5	PIDA	TFE	7	SiO_2
6	Iodosobenzene	TFE	Decomp	-
7	Iodosobenzene, phthalic anhydride	1:1, MeCN:CH_2Cl_2	8	SiO_2
8	PIFA	TFE	7	SiO_2

In order to improve the oxidation result, the solvent, time and workup conditions were modified in the hope of increasing the yield of **80** (Table **3.1**). Trifluoroethanol emerged as the solvent of choice due to its low nucleophilicity. The use of methanol was accompanied with a small degree of methanol addition into the system (entry 2). The choice of trifluoroethanol, however, did not increase the yields to a satisfactory range. Another alternative to explore for reaction optimization was the use of different forms of the hypervalent iodine reagent. Both iodosobenzene (entries 6 and7) and PIFA (entry 8) were tested and gave similar yields to PIDA. Another optimization pathway explored focused on alternative methods of purification. PIDA is used in excess in the reaction and has to be removed from the reaction mixture through chromatography. Fuller's Earth and reverse phase column chromatography (entries 3 and 4) were tested, but, once again, no improvement in yield was observed. None of the conditions explored afforded the desired yields of **80** and alternative synthetic routes needed to be explored.

4.0 BIRCH REDUCTION OF HOMOTYROSINE

4.1 BIRCH REDUCTION OF HOMOTYROSINE AND ACIDIC CYCLIZATION

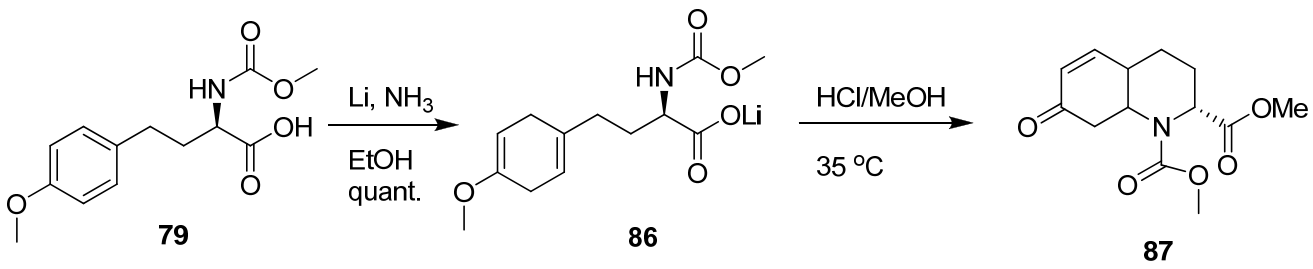
A new route that would break the aromaticity of the aromatic ring with a Birch reduction followed by an intramolecular Michael type addition was explored. This is a similar scheme to the synthesis of *L*-Choi (**85**) reported by the Bonjoch group (Scheme **4.1**). They submitted tyrosine (**83**) to the Birch reduction conditions and obtained good yields of **84**. Subsequent treatment of **84** in methanolic HCl provided **85**.



83 **84** **85**

Scheme 4.1. Bonjoch's synthesis of *L*-Choi (**85**)

The Birch reduction was performed on substrate **79** to afford the desired precursor **86** in quantitative yield (Scheme **4.2**). The lithium salts were used in the next reaction without further purification. Diene **86** was dissolved in methanolic HCl and heated for several days to initiate cyclization.[60]

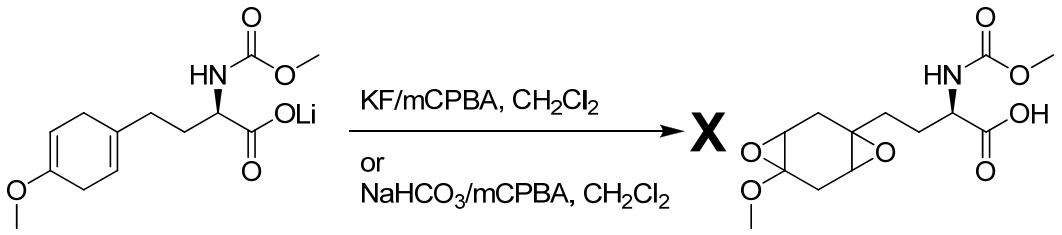


Scheme 4.2. Reduction and cyclization of homotyrosine

Problems, however, resulted in isolating the cyclized product **87** and separation of **87** from the multiple products obtained. The reaction was performed in both 3.0 and 9.0 N methanolic HCl. In both situations, multiple products were isolated and the desired product was only obtained crude and in low yields.

4.2 BIRCH REDUCTION OF HOMOTYROSINE AND EPOXIDATION

The problems with the cyclization to **87** prompted the question as to what other synthetic manipulations could be performed on **86** that could permit a more controlled reaction. One option was to epoxidize both alkenes and to explore various Lewis acids and bases to afford the desired cyclization product.



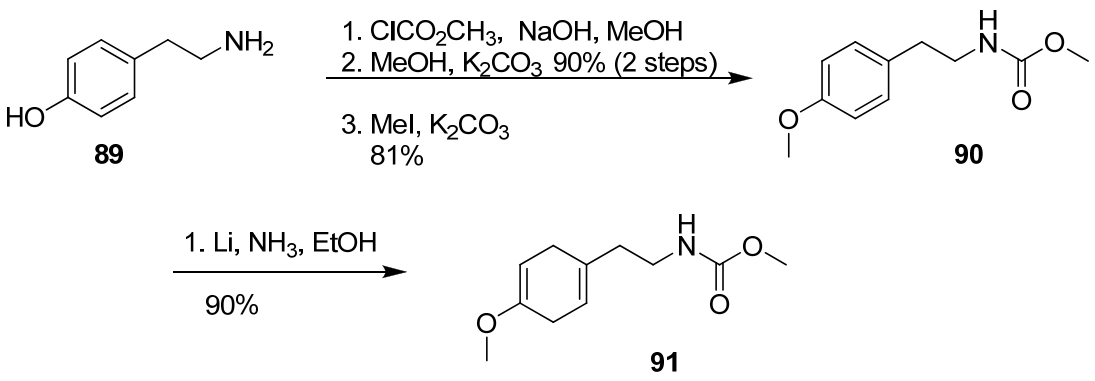
86 **88**

Scheme 4.3. Bisepoxidation of diene **86**

Modified epoxidation conditions using both a KF/mCPBA[61] and $NaHCO_3$/mCPBA[62,63] system were explored on substrate **86** (Scheme **4.3**). Both of these conditions have been demonstrated to be effective with the epoxidation of acid sensitive enol ethers, however there was no indication of formation of **88** under either of these conditions. The lack of reactivity of diene **86** was attributed to the extremely low solubility of diene **86** in dichloromethane. In an effort to improve the solubility of the system, a simplified analogue was devised that lacked the carbamate moiety (Scheme **4.4**).

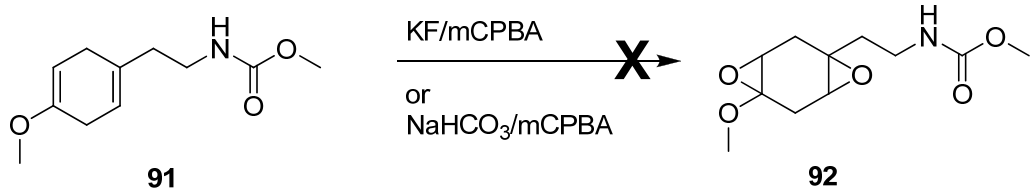
4.3 MODEL STUDIES FOR BIRCH REDUCTION AND EPOXIDE CYCLIZATION

The synthesis of the analogue **91** began with commercially available tyramine (**89**) (Scheme **4.4**). Treatment of **89** with 2 equiv of methylchloroformate afforded both the carbonate, with the phenolic oxygen, and the carbamate, with the amine. The carbonate was selectively removed with basic methanol to afford the free phenol, which was subsequently treated with methyl iodide to afford methyl ether **90** in good overall yield. Intermediate **90** was subjected to Birch conditions and afforded diene **91** in high yields.



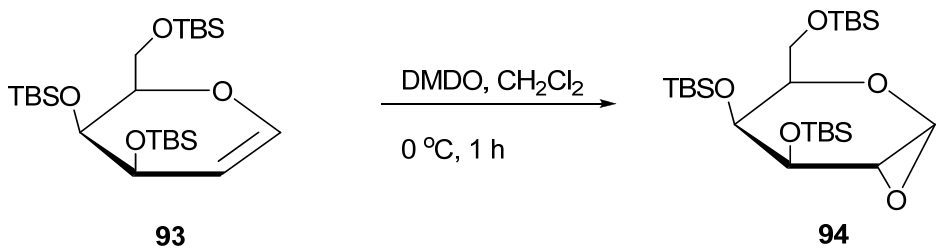
Scheme 4.4. Preparation of diene model system **91**

With **91** in hand, the epoxidation conditions were explored (Scheme **4.5**). Epoxidation was first attempted with mCPBA. In the presence of both KF[61,64] and $NaHCO_3$,[62] 5 equiv of mCPBA were needed for the epoxidation and the excess reagent was difficult to separate from the mixture apart from column chromatography. A significant problem encountered was the instability of the epoxidized enol ether. The product decomposed on alumina, silica gel, reverse phase and florisil columns.



Scheme 4.5. Bisepoxidation of **91**

Alternative epoxidation conditions needed to be explored. DMDO appeared to be a well suited reagent for this type of substrate because of the ease of purification (concentration under reduced pressure), and mild reaction conditions.[65,66]

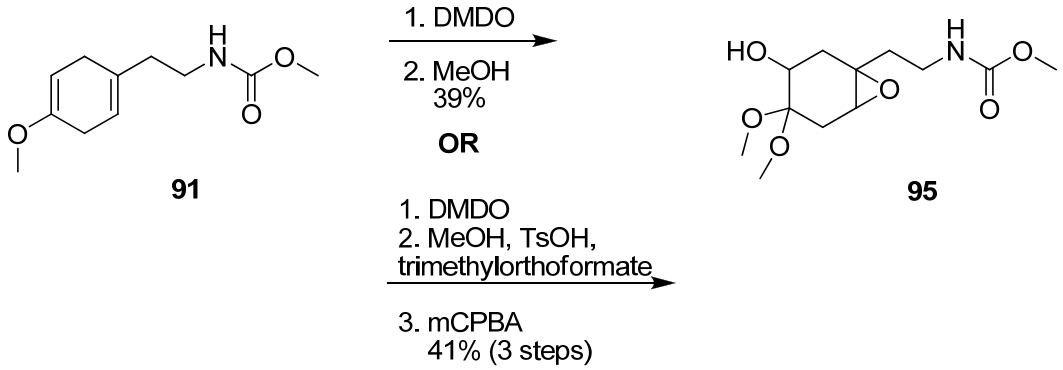


93 **94**

Scheme 4.6. Danishefsky's conditions for glycal epoxidation

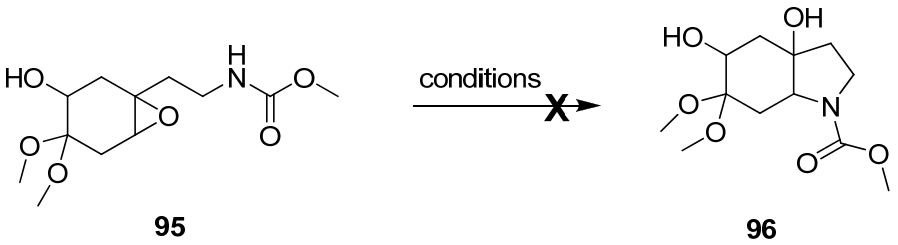
The Danishefsky group has extensively investigated the epoxidation of glycals using DMDO (Scheme **4.6**).[67,68] They initially used various peroxy acids and found that once the epoxidized product formed, it would frequently react further with either excess acid or solvent. This result initiated investigation into other epoxidizing agents. DMDO proved strong enough to quickly epoxidize the alkene, such as the one present in **93**, while also being mild enough to not further react with the product.

DMDO was prepared according to literature protocol and used immediately for reaction with **91** under the same reaction conditions reported by the Danishefsky group.[69] Unfortunately, the DMDO epoxidation was still problematic. The substrate solubility was good in both dichloromethane and acetone and the starting material was quickly consumed, but product isolation was difficult. Different silica gel, alumina and florisil columns were utilized in an attempt to purify this reaction mixture, however, it was not possible to isolate **92** cleanly. This was attributed to the reactivity of the epoxidized enol ether.



Scheme 4.7. Epoxidation and acetal formation

This problem was addressed by letting the bisepoxide **92** stir at room temperature in methanol to open the epoxide and form the α-hydroxy ketone. The subsequent acetal opening occurred upon extended methanol exposure (Scheme **4.7**). The preparation of **95** on larger scale was often hampered by the incomplete epoxidation of both alkenes and the tedious production of large quantities of DMDO. This problem was addressed by treating **91** with a slight excess of DMDO, which preferentially epoxidized the methyl enol ether alkene, and then stirring the reaction mixture overnight in MeOH. This led to opening of the epoxide to the α-hydroxy ketone accompanied with partial acetal formation of the ketone. The crude reaction mixture was then treated with TsOH and trimethylorthoformate for 2 h to drive the acetal formation to completion. The remaining alkene was readily epoxidized with mCPBA to afford the desired substrate as a 1:1 mixture of inseparable diastereomers. Both procedures afforded highly functionalized **95** in moderate yields.



Scheme 4.8. Intramolecular epoxide opening of **95**

With substrate **95** in hand, conditions were sought for the cyclization to **96** (Scheme **4.8**). A variety of Lewis acids and bases were investigated for this cyclization (Table **4.1**).

Table 4.1. Acidic and basic conditions explored for cyclization to **96**

Entry	**Additive**	**Solvent**	**Temperature** [°C]	**Yield of 96** [%]
1	BF_3OEt_2	CH_2Cl_2	−78	Trace
2	$EtAlCl_2$	CH_2Cl_2	−78	Decomp
3	$AgClO_4$	CH_2Cl_2	25	Decomp
4	NaOMe	MeOH	0	NR
5	NaOMe	MeOH	100	0
6	KO*t*-Bu	*t*-BuOH	0-25	NR
7	KO*t*-Bu	*t*-BuOH	100	Decomp

A variety of acids and bases were examined for the cyclization to **96**, but delivered limited success (Table **4.1**). The Lewis acids explored (entries 1, 2 and 3) gave complicated reaction mixtures and were abandoned in favor of Brönsted bases. The reaction with NaOMe was initially investigated at 0 °C, but there was no observed reaction (entry 4). When the system was heated to 100 °C in the microwave (entry 5), methoxide preferentially and cleanly opened

the epoxide with no trace of the cyclized product. The bulkier base KO*t*-Bu was tested (entry 6), starting at 0 °C and slowly warming to room temperature, but there was no observed reaction. The same base was also tested at 100 °C in *t*-BuOH in the microwave (entry 7). In this example, starting material was consumed according to TLC, but only 5% of the mass was recovered following aqueous workup. The reaction was tried one last time with the same conditions as entry 7 with the exception that the reaction was quenched with benzoyl chloride instead of water. The desired result was to protect the secondary alcohol in **95** as the carbonate and decrease the water solubility of the substrate. Despite a greatly improved mass recovery following aqueous workup, the desired product was still not obtained. A new approach was needed to form the ring system.

5.0 CONSTRUCTION OF BICYCLIC CORE VIA STETTER REACTION

5.1 CATALYSTS FOR STETTER REACTION

Nucleophilic carbenes are versatile reagents in synthesis. These reagents offer many new opportunities for ring construction and condensation as highlighted in two excellent recent reviews.[70,71] One reaction to which carbenes have been applied is the benzoin condensation. The mechanism (Figure **5.1**) proposed in the catalytic variant of the benzoin condensation begins with the deprotonation of a triazolium or thiazolium salt to generate a stable carbene. The mechanism is illustrated with thiazolium salt **97** in Figure **5.1**. The carbene **98** reacts with aldehyde **99**, which converts the aldehyde into a nucleophilic species (Umpolung of activity). When **101** is located in proximity of another electrophile, such as **102**, it can undergo an addition to afford **103**. After this addition, elimination of the catalyst regenerates carbene **98** and expels the benzoin condensation product **104**.

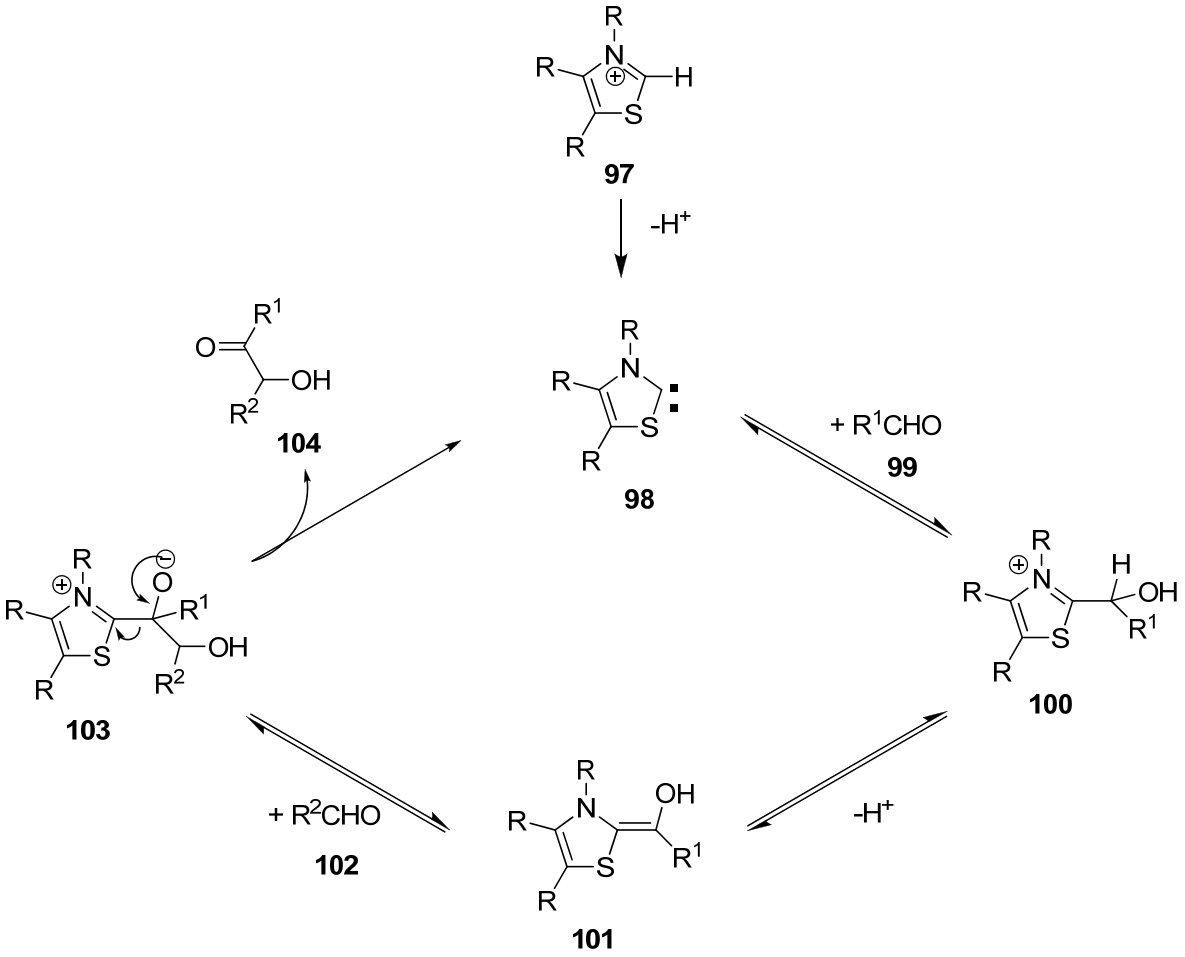
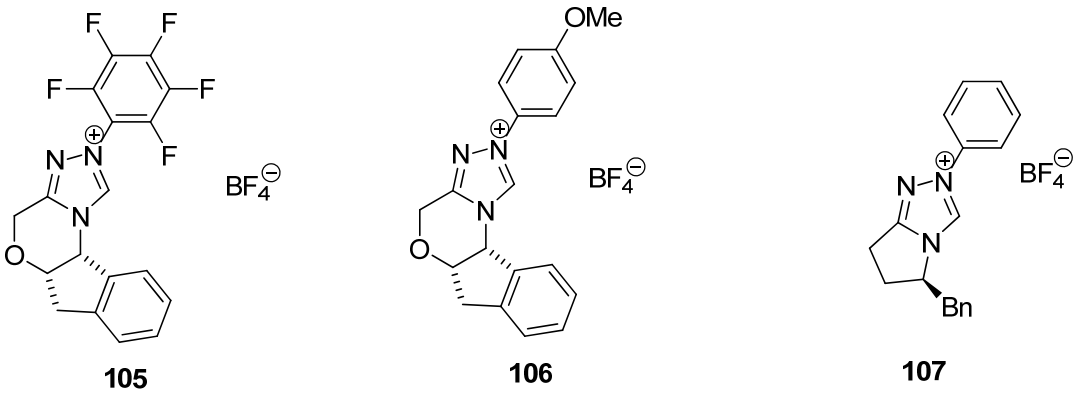


Figure 5.1. Benzoin condensation mechanism

Another reaction that incorporates a carbene reactant is the Stetter reaction. The Stetter group in the 1970's developed a process for addition of an activated aldehyde into an activated double bond in a Michael-type fashion. Recently, there have been several papers discussing both asymmetric and catalytic versions of this reaction

Rovis has published extensively on the asymmetric and catalytic variants of the Stetter reaction.[72,73] Heterocycles **105**, **106** and **107** were developed and demonstrated high enantioselectivity in this reaction (Figure **5.2**). Heterocycle **105** has the distinction of demonstrating enantioselectivity in the formation of quartenary carbon centers through the

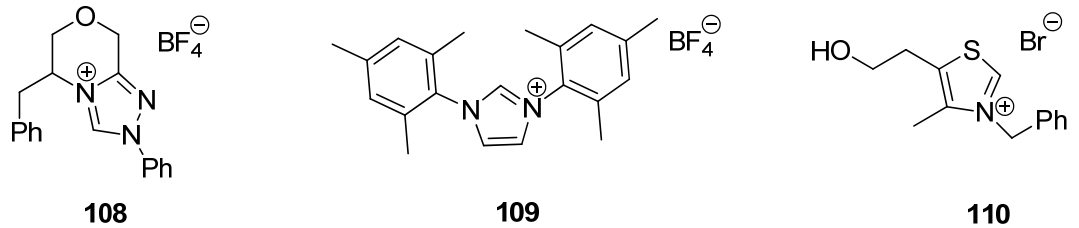
Stetter reaction.[74] These carbene precursors were synthesized according to the protocol of Leeper.[75]



105 106 107

Figure 5.2. Triazolium salts utilized by Rovis group for Stetter reaction

Catalyst **108** (Figure **11**) had been tested by the Leeper group as a catalyst for a chiral benzoin condensation.[75] They obtained low to moderate yields of product with good enantioselectivity. The Rovis group investigated both added structural complexity on the triazolium salt along with alternative counter ions in order to apply this catalyst to the Stetter reaction and obtain high yields and enantioselectivity. Catalyst **106** met these standards for a variety of substrates.

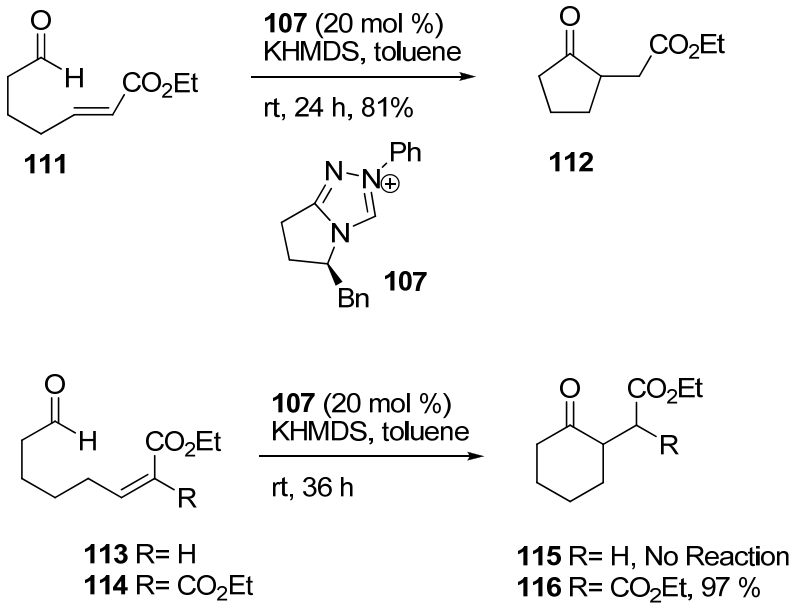


108 109 110

Figure 5.3. Catalysts investigated for Stetter reaction

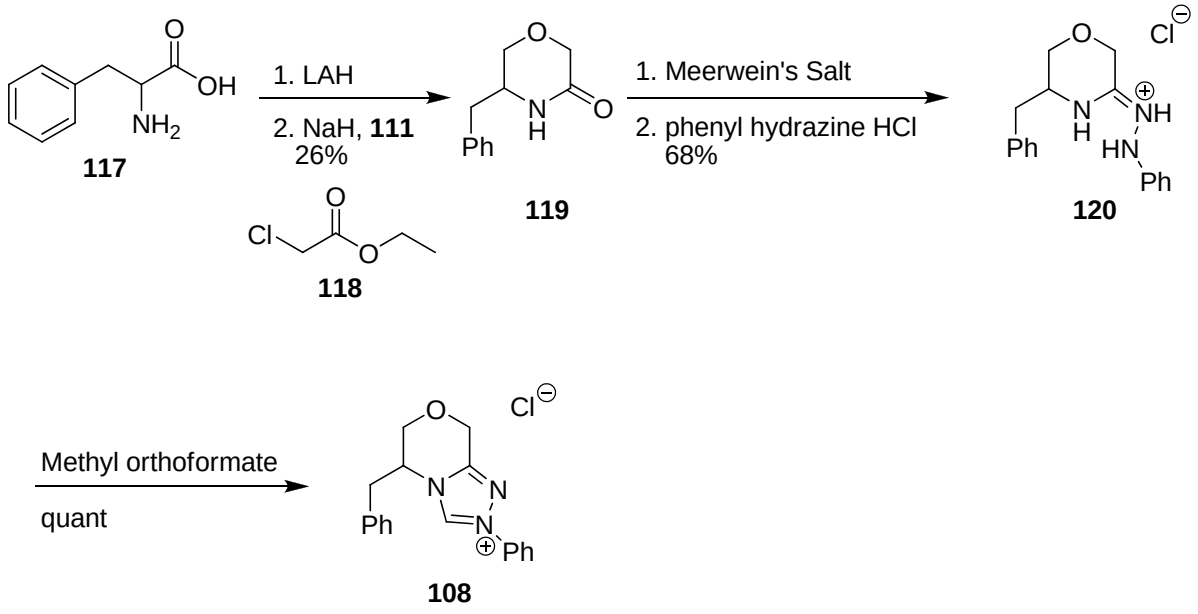
The new goal for this project was to synthesize an aldehyde bearing enone substrate and explore the intramolecular Stetter reaction with a modified version of Rovis's catalyst along with two commercially available carbene catalysts (**109** and **110**). The triazolium salt Leeper had used, **108**, was a convenient surrogate of **106** due to its ease of synthesis. The first test reactions were intended to prove that the cyclization could occur, and, after this proof, enantioselective cyclization would be pursued. Due to this ranking of priorities, the triazolium salt was synthesized as a racemic mixture.

Most of the substrates that the Rovis group has investigated have been aromatic aldehydes, which obviously lack enolizable protons. There are, however, a few examples of the asymmetric Stetter reaction being applied to readily formed 5-membered rings such as **112** (Scheme **5.1**). The scope of reactions with aliphatic aldehydes is still limited. Enoate **113** does not react to give the desired 6-membered ring. It is necessary to further activate the enoate towards Michael addition with an additional ester, as in **114**, to obtain the desired product **116**.



Scheme 5.1. Aliphatic Michael acceptors in Stetter reaction

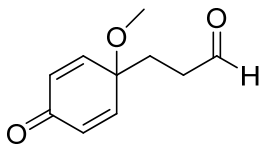
The synthetic route for **108** remained faithful to the Leeper process (Scheme **5.2**). Racemic phenylalanine (**117**) was reduced to phenylalaninol following the published literature protocol.[76] Phenylalaninol was treated with **118** to afford morpholinone **119**. The remaining steps were based on Leeper's protocol. Meerwein's salt afforded the imino ether which was used without further purification, and carried directly into the reaction with phenylhydrazine to form the amidrazone chloride salt **120**. Refluxing this substrate with methylorthoformate in methanol afforded the triazolium catalyst. Heterocycle **108**'s structure and purity were confirmed by both NMR and mass spectrometry analysis and comparison to the reported spectra. This substrate was used without further purification. With catalyst **108** in hand, the next task was to synthesize the desired enone.



Scheme 5.2. Synthesis of Stetter catalyst **108**

5.2 STETTER REACTION WITH CYCLOHEXADIENONE 121

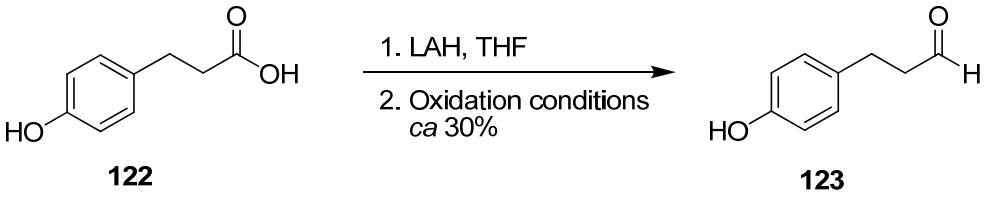
Using chemistry that had been explored previously in the Wipf group, the desired cyclohexadieneone (**121**, Figure **5.4**) could be envisioned being derived from **124** using PIDA or PIFA in methanolic solvent.



121

Figure 5.4. Target substrate for Stetter reaction

The most direct route to **121** would be a simple reduction of **120** followed by oxidation to the aldehyde. Initially, the synthesis was attempted without the aid of the TBS protecting group on the free phenol **122** (Scheme **5.3**).



122 **123**

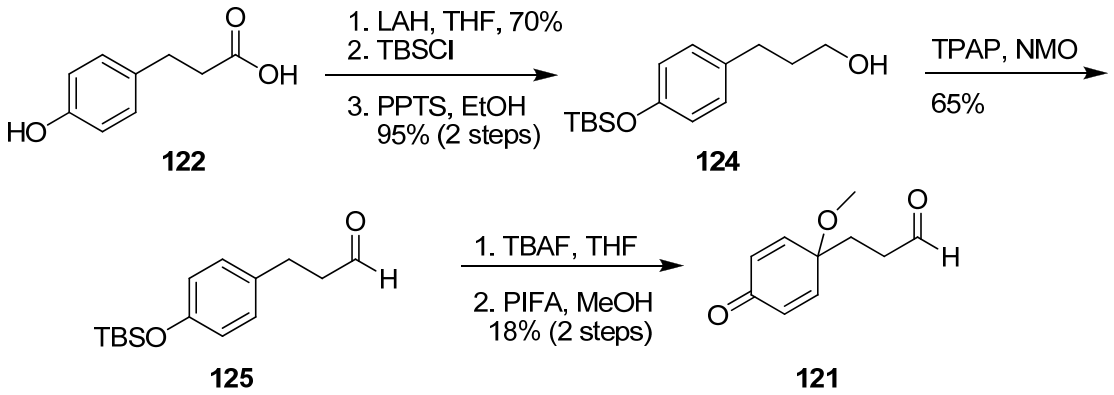
Scheme 5.3. Model system oxidation

A problem arose with the oxidation of the alcohol to aldehyde **123** and the resultant low yields (Table **5.1**). Various conditions were explored until it was deemed more time efficient to simply protect the phenol as a TBS ether for the oxidation, and then remove the TBS protecting group prior to the PIFA conditions (Scheme **5.4**).

Table 5.1. Oxidation conditions to aldehyde **123**

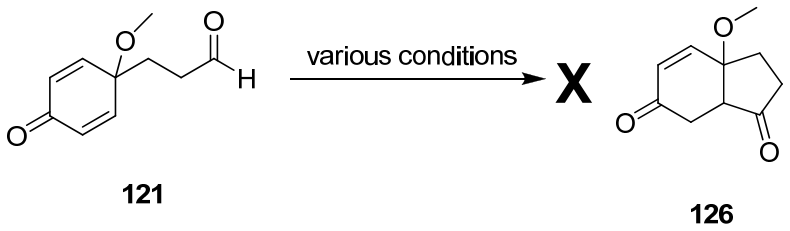
Entry	**Oxidizing Agent**	**Oxidizing Agent** [equiv]	**Yield of 123** [%]
1	TPAP/NMO	1.5	19
2	PDC (0.2 M solution)	2	30
3	PDC (0.02 M solution)	2	33
4	PDC	18	15

The commercially available acid **122** was reduced with LAH, both aliphatic and phenol alcohols were protected as TBS ethers, and then the aliphatic TBS ether was selectively deprotected with PPTS to afford **124** (Scheme **5.4**). Substrate **124** could alternatively be synthesized via the treatment of **122** with 2 equiv of TBSCl to form the TBS ester and the TBS ether from the phenol. Subsequent treatment of this globally protected intermediate with LAH afforded **124**. In this synthesis, the first major cause for concern arose once the TBS group had been removed from **125** to afford the phenol in the presence of the aldehyde. This is an unstable intermediate and can not be stored or concentrated. Once the TBS group was removed, the substrate was immediately subjected to oxidative conditions.



Scheme 5.4. Aldehyde **121** synthesis

Many of the transformations carried out in the first part of the synthesis were well documented in the literature (Scheme **5.4**). The PIFA oxidation of a phenol in the presence of an unprotected aldehyde was not reported previously. This sequence was proposed as the most direct route to **121**. The literature examples involved acetal-protected aldehydes under oxidative conditions. The initial goal was to perform these reactions with the free aldehyde. One potential side product that could result from the PIFA oxidation in the presence of the aldehyde would by the formation of a bicycle. The bicycle from aldehyde participation could be opened again, or preferentially, an unreacted aldehyde could be subjected directly to the Stetter conditions. Methanol was found to preferentially add into the substrate to afford the desired **121**. As the reaction proceeded further, the unreacted aldehyde functionality would be converted into the methoxy acetal. The formation of the acetal was minimized by keeping the reaction temperature at 0 °C.



121 **126**

Scheme 5.5. Stetter reaction with dieneone **121**

With aldehyde **121** in hand, it was possible to begin exploring the Stetter reaction (Scheme **5.5**). All three catalysts from Figure **11** were tested along with modifications in reaction conditions (Table **5.2**). Unfortunately, none of these conditions afforded any of the desired product **126**.

Table 5.2. Cyclization conditions of cyclohexadienone **121**

Entry	Catalyst	Base	Solvent	Conditions
1	**108**	KHMDS	Toluene	r.t., overnight
2	**109**	NEt_3	MeOH	r.t., overnight
3	**109**	NEt_3	THF	r.t., overnight
4	**110**	NEt_3	THF	r.t., overnight

Upon further inspection, it became clear that before the cyclization could occur, a fragmentation took place (Figure **5.5**). This hypothesis was tested by allowing **121** to stir with 0.2 equiv of triethylamine in toluene at room temperature without the Stetter catalyst. In less than 2 h, all of the starting material had been consumed. The new product isolated from base treatment was 4-methoxy phenol **128**. The proposed complementary side product from the fragmentation would be the unsaturated aldehyde **129**, which was never isolated. A literature search did not uncover any other examples of carbon-carbon bond fragmentations on similar cyclohexadienone systems. It was therefore necessary to explore a new model system substrate that would not be susceptible to such a fragmentation.

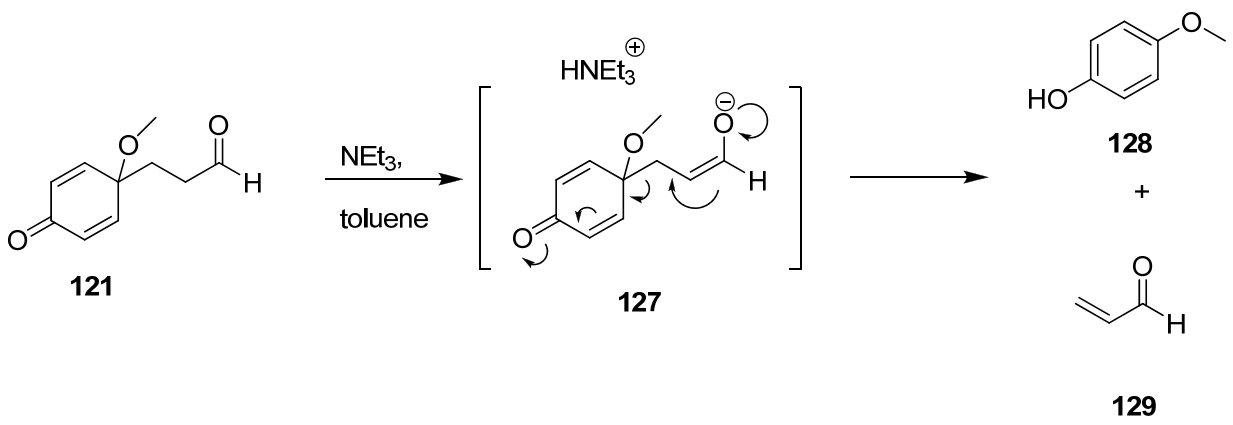
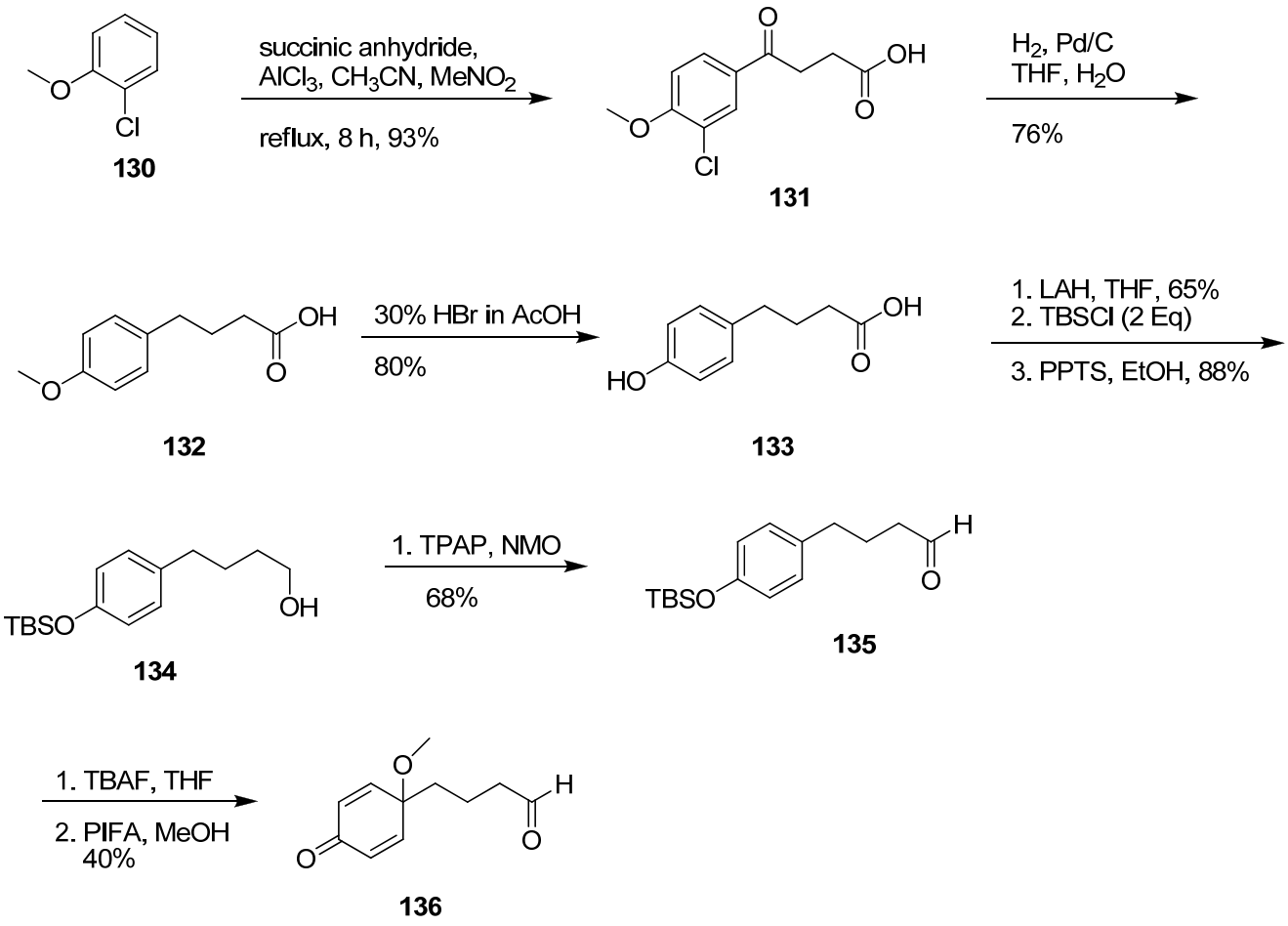


Figure 5.5. Proposed base-induced fragmentation of cyclohexadienone **121**

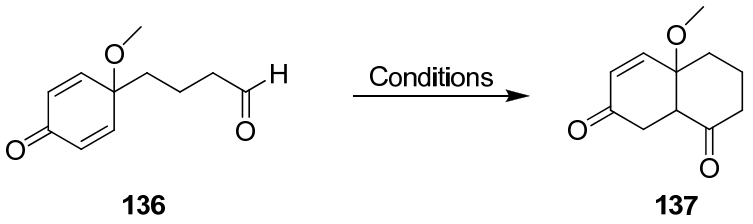
5.3 STETTER REACTION WITH MODEL SYSTEM

The new model system extended the previous model system by one methylene unit (Scheme **5.6**). Moving the cyclohexadienone moiety one carbon away from the β–position of the enolate would eliminate the fragmentation side reaction. The homologated model system was prepared in a route reminiscent of the synthesis of homotyrosine (Scheme **2.9**). The Friedel-Crafts reaction with succinic anhydride and **130** proceeded well and provided multigram quantities of **131**. The hydrogenation to **132** and the subsequent methyl ether deprotection to **133** proceeded analogously to homotyrosine. The remaining steps of reduction, TBS protection and oxidation employed the same conditions used in Scheme **5.4**.



Scheme 5.6. Synthesis of chain extended aldehyde **136**

After the PIFA oxidation, substrate **136** was submitted to the same basic conditions as **121**. After 7 h of stirring at room temperature with 0.2 equiv of base, no decomposition was observed. The base stability of **136** was very encouraging. The first Stetter reaction was run on a 4 mg scale of substrate with 0.6 equiv of triethylamine and heated to 80 °C over 2 d. In this system, no aromatic signals were observed by crude ^{1}H NMR analysis. These encouraging results prompted further investigation of the revised Stetter substrate **136**. Various Stetter conditions were explored (Scheme **5.7**) in pursuit of enone **137**.

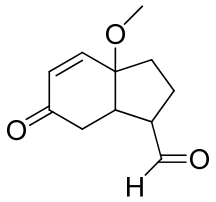


136 137

Scheme 5.7. Stetter reaction analogue

On the first large scale Stetter reactions using catalyst **110**, 0.4 equiv of the catalyst were needed. None of the desired cyclized product was isolated. A significant amount of the isolated side products were benzylated, presumably from the nucleophilic displacement of the benzyl moiety present in catalyst **110**. This result prompted the use of catalyst **109** which lacks the electrophilic benzyl group.

The propensity for the aldehyde to enolize had been demonstrated before and hence the ratio of base to catalyst had to be carefully considered. The base and catalyst were premixed and stirred initially for 15 min following the experimental protocol published by Rovis. The solids present in the reaction mixture were a cause for concern and the mixture was subsequently heated to 35 °C and stirred for an additional 2 h before **136** was added. Unfortunately, the major product isolated (30% yield and 50% of the recovered mass) was the result of the enolized aldehyde adding into the enone in a Michael fashion (**138**, Figure **5.6**).



138

Figure 5.6. Major product isolated from Stetter reaction, **138**

The enolization of the aldehyde proved problematic for the Stetter reaction with this system. Substrate **121** was incompatible with the Stetter reaction conditions due to aldehyde enolization and subsequent fragmentation. Substrate **136** was likewise incompatible with the Stetter reaction conditions due to enolization and enone addition. Therefore, the Stetter reaction was abandoned for this project.

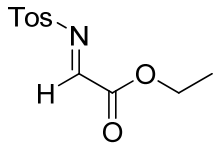
6.0 PARVISTEMONINE CONCLUSIONS

The studies towards the total synthesis of parvistemonine have yielded some interesting results. The initial attempts to synthesize homotyrosine were inundated with difficulties. Both Grignard reagents and hydroaluminated phenylacetylene were problematic due to low yields and the difficulty of producing the needed imine in large quantities. The literature procedure for the synthesis of homotyrosine opened the door to testing the subsequent synthetic steps of key interest. The oxidation of homotyrosine did not deliver the favorable results that the oxidation of tyrosine had, which prompted methodology that greatly deviated from what had been explored in previous work. The Birch reduction proceeded smoothly with homotyrosine, but acidic cyclization did not afford the desired results. The alternative pathway of bisepoxidation, likewise, proved problematic. Model studies began to further explore some of the epoxidation methodology. The bisepoxidation studies demonstrated the reactivity of the enol ether and were extended to various epoxidizing agents. DMDO gave especially satisfying results and subsequent treatment of the reaction mixture with methanol afforded the isolable acetal which allowed investigation of the cyclization. The next methodology explored was the Stetter reaction. This study demonstrated that the PIFA conditions can be compatible with a free aldehyde. This substrate was unfortunately incompatible with the Stetter reaction conditions due to quick fragmentation. The second generation Stetter reaction substrate did not suffer from the

earlier observed fragmentation difficulties, but conditions still need to be optimized for the problematic 6-membered ring formation.

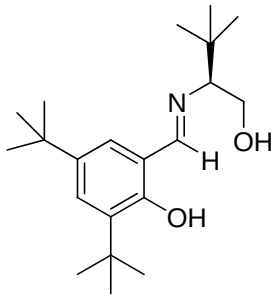
7.0 PARVISTEMONINE EXPERIMENTAL PART

General: All reactions were performed in flame-dried or oven-dried glassware under a nitrogen atmosphere. THF and Et_2O were distilled over Na/benzophenone, while pyridine and triethylamine were distilled over CaH_2. Hexanes and EtOAc were distilled prior to use. All other reagents and solvents were used as received unless otherwise noted. Analytical thin layer chromatography was performed on pre-coated silica gel 60 F-254 plates available from Merck. Flash chromatography was performed using silica gel 60 (230-400 mesh) available from Baker. NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR using a Bruker Avance 300 with XWIN-NMR software. Chemical shifts (δ) are expressed relative to the NMR solvent peak. IR spectra were obtained with a Nicolet Avatar 360 FT-IR, optical rotations were measured with a Perkin-Elmer 241 polarimeter, and mass spectra were obtained on a double focusing instrument. EI mass spectra were obtained with VG Autospec and ESI mass spectra with Q-TOF API US.

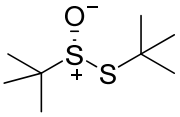


Ethyl-*N*-(*p*-toluenesulfinyl)iminoacetate (61).[48] A solution of ethyl glyoxylate (0.64 mL, 6.0 mmol) in toluene (16 mL) was treated with 4 Å activated molecular sieves (1.0 g) and *p*-toluenesulphonyl isocyanate (1.0 mL, 6.0 mmol), heated at reflux for 36 h, filtered through

celite, concentrated under reduced pressure and used without further purification.[42] The reaction progress was monitored by the appearance of the signal at δ 8.3 in the crude ^{1}H NMR corresponding to the imine proton.

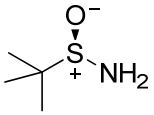


(*S*)-2-(*N*-3,5-di-*tert*-Butylsalicylidene)amino-3,3-dimethyl-1-butanol (66).[51] A solution of (*S*)-*t*-leucinol (499 mg, 4.26 mmol) and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (1.00 g, 4.26 mmol) in MeOH (28 mL) was treated with Na_2SO_4 (3.20 g) and stirred for 4 h. The reaction mixture was filtered through a pad of celite, washed with anhydrous MeOH and concentrated under reduced pressure to afford 1.44 g (100%) of **66** as a bright yellow solid. The product was pure according to TLC and ^{1}H NMR analysis and was used without further purification: ^{1}H NMR δ 8.36 (s, 1 H), 7.41 (d, 1 H, *J* = 2.5 Hz), 7.14 (d, 1 H, *J* = 2.5 Hz), 3.93 (dd, 1 H, *J* = 9.7, 2.3 Hz), 3.77 (t, 1 H, *J* = 9.5 Hz), 2.94 (dd, 1 H, *J* = 9.6, 2.7 Hz), 1.45 (s, 9 H), 1.30 (s, 9 H), 0.98 (s, 9 H).

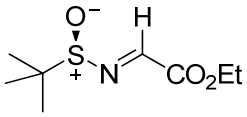


***S*-*tert*-Butyl 2-methylpropane-2-sulfinothioate (67).**[51] An Erlenmeyer flask containing $VO(acac)_2$ (333 mg, 1.25 mmol) and **66** (457 mg, 1.37 mmol) was treated with $CHCl_3$ (56 mL) and stirred for 10 min. The solution was treated with *tert*-butyl disulfide (26.3 mL, 141 mmol)

followed by a slow, steady stream of H_2O_2 (15.6 mL) along the sides of the flask. The reaction mixture was stirred for 24 h and extracted with brine. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (1:19, hexanes:EtOAc) afforded 18.1 g (66%) of **67** as a colorless solid: ^{1}H NMR δ 1.56 (s, 9 H), 1.38 (s, 9 H).

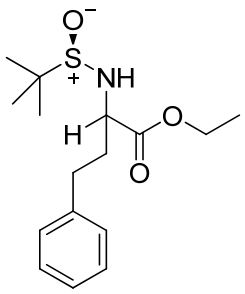


***tert*-Butylsulfinamide (68).**[51] A solution of **67** (2.40 g, 12.3 mmol) in THF (4.7 mL) was cooled to -78 °C and NH_3 (13 mL) was added followed by 5 portions of Li (214 mg, 30.8 mmol) over 0.5 h. The reaction mixture turned deep blue, was stirred for 1 h, warmed to room temperature overnight and the remaining solvent was removed under reduced pressure. The resultant solid was dissolved in EtOAc, washed with water, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (1:19, MeOH:CH_2Cl_2) afforded 1.33 g (89%) of **68** as a colorless solid: ^{1}H NMR δ 3.69 (bs, 2 H), 1.22 (s, 9 H).



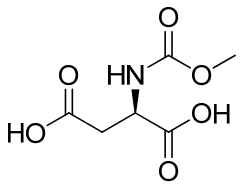
Ethyl (*R*)-(−)-N-(*tert*-butylsylfinyl)iminoacetate (63).[48] A round bottom flask containing a 50% solution of ethyl glyoxylate in toluene (1.2 mL, 6.7 mmol) was heated at 50 °C for 5 min with a heat gun, cooled to room temperature and diluted with CH_2Cl_2 (168 mL). The rapidly stirring solution was treated with **68** (817 mg, 6.70 mmol) followed by 4 Å molecular sieves

(62.0 g) and stirred for 48 h. The reaction mixture was filtered through a plug of celite, washed with EtOAc, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography through a short plug of SiO_2 (CH_2Cl_2) afforded 1.20 g (87%) of **63** as a colorless oil: ^{1}H NMR δ 8.01 (s, 1 H), 4.41 (q, 2 H, *J* = 7.1 Hz), 1.36 (t, 3 H, *J* = 7.1 Hz), 1.27 (s, 9 H).

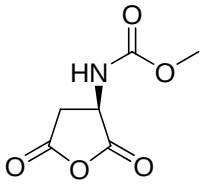


Ethyl (R_S-2-phenethyl)-(-)-N-(*tert*-butylsylfinylamine) ethyl ester (73). A solution of **63**[48] (102 mg, 0.500 mmol) in CH_2Cl_2 (10.0 ml) was cooled to -78 °C and treated with $BF_3{\cdot}OEt_2$ (0.13 mL, 1.0 mmol), and after 5 min with a 1.0 M solution of phenethyl magnesium chloride in THF (1.0 mL, 1.0 mmol). The reaction mixture was quenched after 15 min with sat. NH_4Cl (3.5 mL) and warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x), washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (2:1, hexanes:EtOAc) afforded 30 mg (19%) of **73** as a colorless oil: Rf 0.2 (1:1, hexanes:EtOAc); IR (neat) 3281, 3027, 2980, 2958, 2930, 2866, 1735, 1497, 1474, 1455, 1389, 1366, 1299, 1200, 1176, 1075, 740, 700 cm $^{-1}$; ^{1}H NMR δ 7.29 (t, 2 H, *J* = 7.1 Hz), 7.21 (d, 1 H, *J* = 7.2 Hz), 7.16 (d, 2 H, *J* = 7.2 Hz), 4.18 (q, 2 H, *J* = 7.1 Hz), 3.99-3.93 (m, 1 H), 2.69 (t, 2 H, *J* = 8.3 Hz), 2.15-1.97 (m, 2 H), 1.28 (s, 9 H); ^{13}C NMR δ 173.2, 140.9, 128.7, 128.6, 126.4, 61.9, 57.0, 56.2, 35.7, 31.3, 22.8, 14.3; MS (EI) *m/z* (rel

intensity) 312 (M^+, 1), 255 (20), 181 (14), 164 (39), 134 (29), 117 (74), 91 (94), 57 (100); HRMS (EI) calculated for $C_{16}H_{26}NO_3S$ 312.1633, found 312.1640.

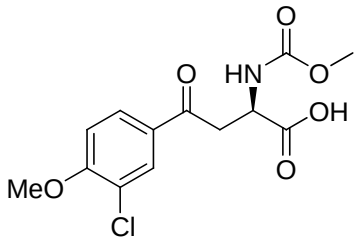


(*R*)-*N*-(Methoxycarbonyl)aspartic acid(75).[55] A solution of aspartic acid (10.5 g, 7.88 mmol) in 2.0 N NaOH (39.5 mL) was cooled to 0 °C, treated dropwise over 15 min with methyl chloroformate (9.9 mL, 13 mmol), warmed to room temperature and stirred for 1 h. The reaction mixture was cooled to 0 °C, slowly and cautiously acidified to pH 1 with 12 N HCl, concentrated under reduced pressure and the solid was extracted with 60 °C EtOAc (3x). The combined organic extracts were concentrated under reduced pressure to afford 10.7 g (70%) of **75** as a white solid: crude ^{1}H NMR (DMSO-d_6) δ 12.61 (bs, 2 H), 7.49 (d, 1 H, J = 8.4 Hz), 4.35 (td, 1 H, J = 8.2, 5.5 Hz), 3.57 (s, 3 H), 2.74 (dd, 1 H, J = 16.4, 5.5 Hz), 2.59 (d, 1 H, J = 8.1 Hz).

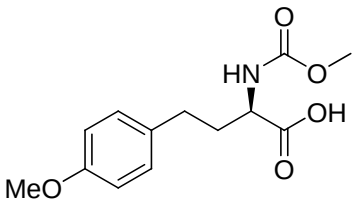


(*R*)-*N*-(Methoxycarbonyl)aspartic anhydride (76).[55] A suspension of **75** (11.5 g, 60.5 mmol) in EtOAc (230 mL) was treated dropwise over 0.5 h with trifluoroacetic anhydride (12 mL, 84 mmol), warmed to 35 °C and stirred for 1 h. The reaction mixture was cooled to room temperature, concentrated to 100 mL under reduced pressure, diluted with hexanes (460 mL), cooled to 0 °C and stirred for 1h. A precipitate formed and was filtered, washed with a solution

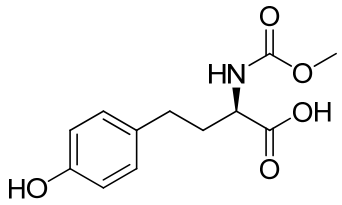
of hexanes:EtOAc (5:1, 3x) and dried under reduced pressure to afford 8.66 g (75%) of **76** as a white solid: ^{1}H NMR (DMSO-d_6) δ 8.07 (d, 2 H, J = 7.7 Hz), 4.71 (ddd, 1 H, J = 10.0, 7.7, 6.3 Hz), 3.62 (s, 3 H), 3.28 (dd, 1 H, J = 18.5, 10.0 Hz), 2.94 (dd, 1 H, J = 18.5, J = 6.3 Hz).



(2*R*)-[(Methoxycarbonyl)amino]-4-oxo-4-(3-chloro-4-methoxyphenyl)butanoic acid (78).[55] A solution of $AlCl_3$ (15.7 g, 118 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C, treated dropwise over 15 min with a solution of 2-chloroanisole (4.7 mL, 37 mmol) in nitromethane (7 mL), warmed to room temperature and treated portionwise over 0.5 h with **76** (8.91 g, 46.8 mmol). The reaction mixture was heated at reflux for 24 h with a vent for the HCl (g) that was generated, cooled to room temperature and quenched by pouring into a rapidly stirred mixture of ice (25 g), 2 M H_3PO_4 (250 mL) and EtOAc (250 mL). The organic layer was extracted and washed with 2 M H_3PO_4, brine, filtered through celite and concentrated to 120 mL under reduced pressure. The solution was diluted with hexanes (370 mL) and stirred at 0 °C for 1 h. A precipitate formed and was filtered, washed with a solution of EtOAc:hexanes (3:1, 2x) and dried under reduced pressure to afford 11.5 g (99%) of **78** as a white solid: ^{1}H NMR δ 7.98 (d, 2 H, J = 2.2 Hz), 7.86 (dd, 1 H, J = 8.7, 2.2 Hz), 6.97 (d, 1 H, J = 8.7 Hz), 5.83 (d, 2 H, J = 8.3 Hz), 4.80-4.75 (m, 1 H), 3.97 (s, 3 H), 3.76-3.73 (m, 1 H), 3.68 (s, 3 H), 3.49 (dd, 1 H, J = 18.3, 4.4 Hz).

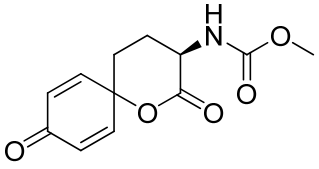


(2*R*)-[(Methoxycarbonyl)amino]-4-(4-methoxyphenyl)butanoic acid (79).[55] A solution of THF (20 mL) and water (20 mL) was added to 10% Pd/C (485 mg, 0.457 mmol) to form a suspension in a hydrogenation vessel. Acid **78** (9.77 g, 30.9 mmol) was added to the suspension and the vessel was evacuated of air under reduced pressure and charged with H_2 (2x), pressurized to 40 p.s.i with H_2 and shaken for 24 h. The reaction mixture was depressurized to atmospheric pressure and filtered through a plug of celite. The THF was removed under reduced pressure and the water was extracted with 60 °C EtOAc (3 x). The combined organic extracts were washed with brine and concentrated to 20 mL under reduced pressure. Hexanes (60 mL) were added while the solution was rapidly stirring. The reaction mixture was cooled to 0 °C, stirred for 1 h and the solid that formed was filtered, washed with hexanes:EtOAc (5:1), and dried under reduced pressure to afford 7.43 g (90%) of **79** as a white solid; ^{1}H NMR (DMSO-d_6) δ 12.47 (bs, 1 H), 7.23 (d, 1 H, J = 8.0 Hz), 7.14 (d, 2 H, J = 8.6 Hz), 6.88 (d, 2 H, J = 8.6 Hz), 3.88-3.81 (m, 1 H), 3.75 (s, 3 H), 3.65 (s, 3 H), 2.65- 2.55 (m, 2 H), 1.92-1.81 (m, 2 H).



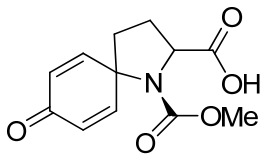
(2*R*)-[(Methoxycarbonyl)amino]-4-(4-hydroxyphenyl)butanoic acid (81). A solution of **79**[55] (1.00 g, 3.74 mmol) in CH_2Cl_2 (37 mL) was cooled to −78 °C and treated with a 1.0 M solution of BBr_3 in CH_2Cl_2 (6.9 mL, 6.9 mmol) dropwise over 10 min. The solution was stirred for 1 h at

−78 °C, 5 h at room temperature and then quenched with a mixture of CH_2Cl_2 (60 mL), sat. NH_4Cl (20 mL) and ice (10 g). The aqueous layer was extracted with EtOAc (3 x) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (1:9, MeOH:CH_2Cl_2) afforded 567 mg (60%) of **81** as a white foam: Rf 0.15 (10:90, MeOH:CH_2Cl_2); IR (neat) 3337, 2957, 1704, 1614, 1515, 1454, 1373, 1235, 1059 cm $^{-1}$; ^{1}H NMR (DMSO-d_6) δ 12.54 (s, 1 H), 9.18 (s, 1 H), 7.56 (d, 2 H, J = 8.0 Hz), 6.99 (d, 2 H, J = 8.2 Hz), 6.70 (d, 2 H, J = 8.2 Hz), 3.91-3.86 (m, 1 H), 3.65 (s, 3 H), 2.58-2.50 (m, 2 H), 1.95-1.82 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 174.2, 156.7, 155.5, 131.1, 129.2, 115.1, 53.4, 51.4, 33.2, 30.7; MS (EI) *m/z* (rel intensity) 253 (M^+, 14), 221 (8), 160 (5), 147 (13), 133 (100), 121 (40), 115 (96), 107 (93), 77 (48), 59 (32); HRMS (EI) calculated for $C_{12}H_{15}NO_5$ 253.0950, found 253.0960.

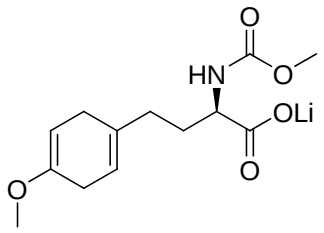


Methyl tetrahydro-6(cyclohexa-2,5-dienone)-2-oxo-2H-pyran-3-ylcarbamate (80). A solution of **81** (100 mg, 0.375 mmol) in trifluoroethanol (3.8 mL) was cooled to 0 °C, treated with PIFA (238 mg, 0.553 mmol) in a single portion and stirred for 1 h. The reaction mixture was concentrated under reduced pressure, diluted with EtOAc, washed with sat. $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography on SiO_2 (1:1, hexanes:EtOAc) afforded 7 mg (7%) of crude **80** as a colorless oil: Rf 0.3 (1:3, hexanes:EtOAc); IR (neat) 2350, 2341, 1715, 1673, 1521, 1065, 858 cm $^{-1}$; ^{1}H NMR δ 7.27 (m, 1 H), 6.83 (dd, 1 H, J = 3.5, 10.3 Hz), 6.26 (d, 2 H, J = 10.1 Hz), 5.54 (bs, 1 H), 4.13- 4.11 (m, 1 H), 3.73 (s, 3 H), 2.53- 2.43 (m, 4 H); ^{13}C NMR δ 184.0, 169.2, 146.5, 129.2, 128.9, 78.5, 52. 8,

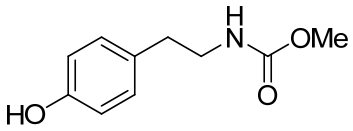
51.1, 32.7, 25.3; MS (ESI) *m/z* (rel intensity) 274 ([M+Na]$^+$,100), 206 (18); HRMS (ESI) calculated for $C_{12}H_{13}NO_5Na$ 274.0691, found 274.0730.



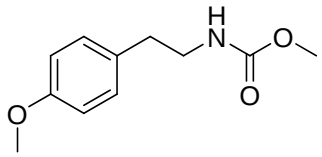
Characteristic signals for 1-(methoxycarbonyl)-5-cyclohexadienone-2-carboxylic acid (82). Rf 0.1 (10:90, MeOH:CH_2Cl_2); ^{1}H NMR (90 °C DMSO–d_6) δ 13.0 (bs, 1 H), 7.19-7.02 (m, 2 H), 6.24-6.12 (m, 2 H), 4.50 (d, 1 H, *J* = 7.2 Hz), 3.54 (s, 3 H), 2.25-2.25-2.00 (m, 4 H).



(*S*)-4-(4-Methoxycyclohexa-1,4-dienyl)-2-(methylcarbamate)butanoic acid (86). A solution of **79** (1.00 g, 3.74 mmol) in EtOH (5.2 mL) was cooled to −78 °C and ammonia (19 mL) was added. The reaction mixture was treated over 0.5 h with 5 portions of Li wire (266 mg, 38.3 mmol) and gradually turned deep blue. After 1 h, the -78 °C bath was removed and the reaction mixture was warmed to room temperature overnight with a vent for the ammonia. The remaining EtOH was removed under reduced pressure and the salts were dried under high vacuum and used without further purification. The diagnostic peaks in crude ^{1}H NMR (DMSO-d_6) were the two signals at δ 5.3 (s, 1 H) and 4.7 (s, 1 H), corresponding to the alkene protons.

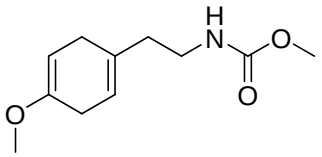


Methyl 4-hydroxyphenethylcarbamate.[77] A solution of tyramine (4.00 g, 29.2 mmol) in 4.0 N NaOH (15 mL) was cooled to 0 °C, treated with methyl chloroformate (3.6 mL, 47 mmol) dropwise over 15 min and stirred for 1 h at 0 °C. The reaction mixture was neutralized to pH 7 with 2 N HCl, extracted with EtOAc (2x), and the combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. A solution of the crude product in MeOH (31.3 mL) was treated with K_2CO_3 (0.728 g, 5.26 mmol), stirred for 12 h, filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (2:1, hexanes:EtOAc) afforded 5.12 g (90%) of the carbamate as a white solid: ^{1}H NMR δ 7.03 (d, 2 H, *J* = 8.3 Hz), 6.77 (d, 2 H, *J* = 8.3 Hz), 5.53 (bs, 1 H), 4.72 (bs, 1 H), 3.66 (s, 3 H), 3.40 (q, 2 H, *J* = 6.2 Hz), 2.73 (t, 2 H, *J* = 7.0 Hz).

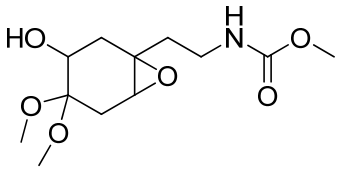


Methyl 4-methoxyphenethylcarbamate (90).[78] A solution of methyl 4-hydroxyphenethylcarbamate (5.69 g, 29.2 mmol) in acetone (180 mL) was treated with K_2CO_3 (10.2 g, 73.9 mmol) and methyl iodide (3.7 mL, 58 mmol) and the solution was heated at reflux for 24 h. The reaction mixture was filtered and concentrated under reduced pressure. The crude product was dissolved in EtOAc, washed with sat. NH_4Cl, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (3:1, hexanes:EtOAc) afforded 4.937 g (81%) of **90** as a colorless oil: ^{1}H NMR δ 7.14 (d, 2 H, *J* = 8.6

Hz), 6.85 (d, 2 H, *J* = 8.6 Hz), 4.65 (bs, 1 H), 3.79 (s, 3 H), 3.66 (s, 3 H), 3.41 (q, 2 H, *J* = 6.3 Hz), 2.75 (t, 2 H, *J* = 6.9 Hz).



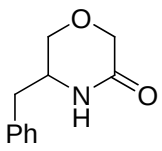
Methyl 2-(4-methoxycyclohexa-1,4-dienyl)ethylcarbamate (91). A solution of **90** (4.94 g, 23.6 mmol) in EtOH (23 mL) was cooled to −78 °C, ammonia (75 ml) was added and the solution was treated over 0.5 h with 5 portions of Li (1.26 g, 182 mmol). The reaction mixture turned deep blue and was stirred for 1 h, warmed to room temperature overnight and concentrated under reduced pressure. The salts were dissolved in H_2O and washed with EtOAc (2x). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (3:1, hexanes:EtOAc) afforded 4.40 g (90%) of **91** as a colorless oil: Rf 0.2 (75:25, hexanes:EtOAc); IR (neat) 3346, 2991, 2942, 2892, 2827, 1693, 1667, 1529, 1465, 1321, 1248, 1215, 1192, 1012, 780 cm $^{-1}$; ^{1}H NMR δ 5.43 (s, 1 H), 4.70 (bs, 1 H), 4.60 (s, 1 H), 3.64 (s, 3 H), 3.53 (s, 3 H), 3.27 (q, 2 H, *J* = 6.2 Hz), 2.71 (bs, 4 H), 2.18 (t, 2 H, *J* = 6.7 Hz); ^{13}C NMR δ 157.0, 152.9, 132.3, 120.0, 112.2, 90.2, 53.9, 52.0, 38.9, 36.8, 29.1; MS (EI) *m/z* (rel intensity) 211 (M^+, 20), 136 (35), 123 (100); HRMS (EI) calculated for $C_{11}H_{17}NO_3$ 211.1208, found 211.1203.



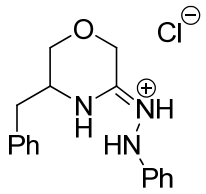
Methyl 2-(3-hydroxy-4,4-dimethoxy-7-oxa-bicyclo[4.1.0]heptan-1-yl)ethylcarbamate (95). A solution of **91** (350 mg, 1.66 mmol) in CH_2Cl_2 (33 mL) was cooled to 0 °C, treated dropwise over 5 min with a 0.1 M solution of DMDO in acetone (25 mL, 2.5 mmol) and stirred for 1 h. The reaction mixture was concentrated under reduced pressure and the highly unstable intermediate was immediately dissolved in MeOH (11.3 mL) and stirred at room temperature for 12 h. The reaction mixture was treated with trimethylorthoformate (3.3 mL, 3.3 mmol) and *p*-toluenesulphonic acid (12 mg, 0.063 mmol) and stirred for 3 h at room temperature. The solution was concentrated under reduced pressure, dissolved in EtOAc, washed with sat. $NaHCO_3$, water, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure: crude NMR (DMSO-d_6) δ 7.0 (bs, 1 H), 5.2 (s, 1 H), 4.6 (bs, 1 H), 3.8 (bs, 1 H), 3.5 (s, 3 H), 3.2 (s, 3H), 3.1 (s, 3 H), 3.07-3.01 (m, 4 H), 2.3 (d, 1 H, J = 17.4 Hz), 2.2 (bs, 2 H), 2.0 (t, 2 H, J = 8.9 Hz), 1.9 (d, 1 H, J = 17.4 Hz). A solution of the crude product in CH_2Cl_2 (16 mL) was cooled to 0 °C, treated with mCPBA (343 mg, 2.00 mmol), warmed to room temperature and stirred for 2 h. The reaction mixture was extracted with sat. $NaHCO_3$ and the aqueous layer was washed with CH_2Cl_2 (2x). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (1:3, hexanes:EtOAc) afforded 212 mg (47%) of **95** as a colorless oil and a 1:1 mixture of inseparable diastereomers: Rf 0.3 (5:95, MeOH:CH_2Cl_2); IR (neat) 3348, 2948, 2834, 1705, 1537, 1456, 1377, 1263, 1194, 1127, 1109, 1051 cm^{-1}; ^1H NMR δ 5.29 (bs, 0.5 H), 4.96 (bs, 0.5 H), 3.80 (dd, 0.5 H, J = 5.8, 4.3 Hz), 3.78-3.73 (m, 0.5 H), 3.63 (s, 1.5 H), 3.62 (s, 1.5 H), 3.52-3.35 (m, 2 H), 3.25 (s, 1.5 H), 3.21 (s, 1.5 H), 3.20 (s, 1.5 H), 3.16 (s, 1.5 H), 3.13-3.09 (m, 1 H), 3.00 (t, 0.5 H, J = 2.2 Hz), 2.55 (s, 0.5 H), 2.35 (dd, 0.5 H, J = 5.4, 1.2 Hz), 2.29 (dd, 0.5 H, J = 5.5, 1.2 Hz), 2.24-2.22 (m, 0.5 H), 2.19-2.07 (m, 3 H), 1.99 (dd, 0.5 H, J = 15.1, 6.0 Hz), 1.89-

1.76 (m, 1.5 H), 1.69-1.61 (m, 0.5 H); ^{13}C NMR δ 157.1, 157.0, 99.4 (2C), 67.6, 66.7, 61.1, 57.7, 57.1, 52.2, 52.1, 49.1, 48.8, 48.1, 47.6, 37.3, 37.0, 36.7, 35.6, 31.9, 31.5, 30.1, 28.8; MS (EI) *m/z* (rel intensity) 275 (M^+, 5), 244 (13), 225 (15), 187 (100), 173 (30), 117 (43), 101 (69), 99 (98), 88 (85); HRMS (EI) calculated for $C_{12}H_{21}NO_6$ 275.1368, found 275.1368.

Typical procedure for the preparation of DMDO: A 3-L three neck round bottom flask was equipped with a mechanical stirrer and thermometer for monitoring the internal temperature. A solution of water (254 mL) and acetone (192 mL) was treated with $NaHCO_3$ (58 g, 0.69 mol), cooled to 10 °C and treated with Oxone (120 g, 0.39 mol) in 5 portions over 15 min with rapid stirring. After the addition was complete, the ice bath was removed and the thermometer replaced with a short path distillation head connected to a 250 mL round bottom collection flask. The round bottom collection flask was cooled to −78 °C and the DMDO solution was distilled over at ~40 torr to afford a light yellow solution (~0.1 M). Approximately 100 mL of the solution was distilled over during 20 min. The quality of the DMDO solution typically diminishes during longer distillation times. The molarity was established via titration with thioanisole and ^{1}H NMR analysis. A more concentrated solution of DMDO in CH_2Cl_2 could be obtained via extraction.[79] The distilled DMDO acetone solution was treated with ice cooled water (500 mL), transferred to a separatory funnel and extracted with CH_2Cl_2 (18 mL) followed by two smaller extractions of CH_2Cl_2 (9 mL, 2x). The combined organic extracts were dried ($Na_2S_2O_4$), filtered and stored over K_2CO_3 at 0 °C and used within 24 h.

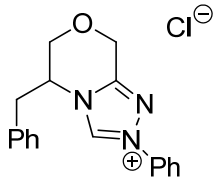


5-Benzylmorpholin-3-one (119).[80] A solution of phenylalinol (1.26 g, 8.35 mmol) in THF (97 mL) was treated portionwise over 15 min with NaH (60% dispersion in mineral oil, 366 mg, 15.3 mmol) and stirred for 0.5 h. The reaction mixture turned deep yellow and was treated dropwise over 5 min with ethylchloroacetate (0.88 ml, 8.3 mmol) and heated at reflux for 3 h. The solution was slowly and cautiously poured into a 1 L flask containing 1 N HCl (100 mL) and extracted with EtOAc (3x). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 403 mg (26%) of **119** as a colorless solid: ^{1}H NMR δ 7.37-7.27 (m, 3 H), 7.19 (d, 2 H, *J* = 6.8 Hz), 5.85 (bs, 1 H), 3.94 (dd, 1 H, *J* = 3.7, 11.6 Hz), 3.82-3.72 (m, 1 H), 3.57 (dd, 1 H, *J* = 6.7, 11.6 Hz), 2.90 (1 H, dd, *J* = 5.4, 13.5 Hz), 2.69 (dd, 1 H, *J* = 9.1, 13.5 Hz).



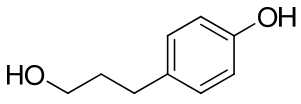
2-(5-Benzylmorpholin-3-ylidene)-1-phenylhydrazine hydrochloride (120). A solution of trimethyloxonium tetrafluoroborate (210 mg, 1.42 mmol) in CH_2Cl_2 (5 mL) was treated dropwise over 5 min with a solution of (+/-) **119**[80] (162 mg, 0.852 mmol) in CH_2Cl_2 (5 mL) and stirred for 12 h. The reaction mixture was diluted with CH_2Cl_2, washed with ice cold sat. $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 128 mg (73%) of 3-benzyl-3,6-dihydro-5-methoxy-2H-1,4-oxazine as a colorless oil: crude ^{1}H NMR δ 7.31-7.22 (m, 5H), 4.02 (dd, 2 H, *J* = 3.9, 1.5 Hz), 3.77-3.75 (m, 1 H), 3.72 (s, 3 H), 3.60 (dd, 1 H, *J* = 3.8, 11.6 Hz), 3.31 (dd, 1 H, *J* = 6.0, 11.6 Hz), 3.01 (dd, 1 H, *J* = 5.3, 13.5 Hz), 2.65 (dd, 1 H, *J* = 9.1, 13.5 Hz).

The crude product was used without further purification and carried on to the following reaction: A solution of 3-benzyl-3,6-dihydro-5-methoxy-2H-1,4-oxazine (148 mg, 0.721 mmol) in MeOH (3.5 mL) was treated with phenylhydrazine hydrochloride (104 mg, 0.721 mmol), heated at 50 °C for 3 h, concentrated under reduced pressure and recrystallized from MeOH to afford 155 mg (68%) of **120** as a colorless solid: Mp 224 °C (dec.); IR (neat) 3565, 3321, 2946, 2830, 1471, 1455, 1111, 1032 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.60 (s, 1 H), 10.36 (s, 1 H), 8.57 (s, 1 H), 7.35-7.28 (m, 5 H), 7.22 (d, 2 H, J = 7.3 Hz), 6.99 (d, 1 H, J = 7.4 Hz), 6.94 (2 H, J = 7.5 Hz), 4.73 (s, 2 H), 3.88 (dd, 1 H, J = 11.3, 3.0 Hz), 3.80-3.75 (m, 1 H), 3.74-3.69 (m, 1 H), 3.10 (dd, 1 H, J = 13.2, 3.5 Hz), 2.87 (dd, 1 H, J = 13.1, 8.9 Hz); ^{13}C (DMSO-d_6) δ 162.4, 146.1, 136.5, 129.4, 129.1, 128.6, 126.8, 121.1, 113.8, 65.2, 61.5, 50.3, 37.7; MS (EI) *m/z* (rel intensity) 282 (M^+, 100), 191 (8); HRMS (EI) calculated for $C_{17}H_{20}N_3$ 282.1606, found 282.1603.

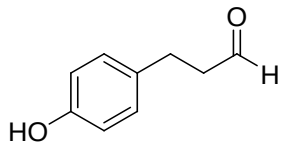


5-Benzyl-3,5,6,8-tetrahydro-2-phenyl-2H-[1,2,4]triazolo[3,4-c][1,4]oxazium chloride (108).[75] A solution of **120** (155 mg, 0.489 mmol) in a trimethylorthoformate-methanol mixture (2:1, 0.5 mL) was heated at 80 °C for 12 h in a sealed tube and concentrated under reduced pressure to afford 160 mg (quant) of **108** as a white solid: Mp 100.3-102.2 °C (MeOH); IR (KBr) 3399, 3059, 2999, 2917, 2850, 2201, 1577, 1513, 1462, 1120, 1091, 762 cm^{-1}; ^{1}H NMR (DMSO-d_6) 11.36 (bs, 1 H), 7.98 (d, 2 H, J = 7.7 Hz), 7.74 (t, 2 H, J = 7.0 Hz), 7.67-7.72 (m, 1 H), 7.47-7.37 (m, 5 H), 5.23 (d, 2 H, J = 8.8 Hz), 4.91-4.89 (m, 1 H), 4.00 (bs, 2 H), 3.63 (dd, 1 H, J = 13.5, 4.4 Hz), 3.21 (dd, 1 H, J = 13.0, 10.9 Hz); ^{13}C NMR (MeOD) δ 151.7, 136.5, 136.3, 132.1,

131.4, 130.7, 130.3, 128.9, 122.0, 66.7, 63.0, 58.7, 39.3; MS (EI) *m/z* (rel intensity) 293 ($[M+1]^+$,60) 292 (M^+, 100), 274 (8), 248 (3), 158 (10); HRMS (EI) calculated for $C_{18}H_{18}N_3O$ 292.1450, found 292.1443.

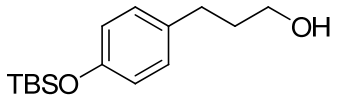


4-(3-Hydroxypropyl)phenol.[81] A suspension of lithium aluminum hydride (2.51 g, 66.2 mmol) in THF (300 mL) was cooled to 0 °C, treated with 3-(4-hydroxyphenyl)propionic acid (1.87 g, 11.2 mmol) in 3 portions over 0.5 h, stirred for 1 h and stirred at room temperature for 6 h. The reaction mixture was quenched with water (700 mL), acidified to pH 6 with conc. HCl and extracted (2x) with CH_2Cl_2. The combined organic extracts were washed with water, sat. $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (3:1, hexanes:EtOAc) afforded 1.198 g (70%) of 3-(4-hydroxyphenyl)propanol: ^{1}H NMR (DMSO-d_6) δ 9.14 (s, 1 H), 7.00 (d, 2 H, J = 8.3 Hz), 6.70 (d, 2 H, J = 8.3 Hz), 3.59 (t, 2 H, J = 6.2 Hz), 2.5 (bs, 2 H), 1.7 (pent, 2 H, J = 6.6 Hz).



3-(4-Hydroxyphenyl)propanal (123).[82] A solution of 4-(3-hydroxypropyl)phenol (430 mg, 2.84 mmol), in EtOAc (4.8 mL) and CH_2Cl_2 (9.4 mL) was treated with pyridinium dichromate (2.19 g, 5.82 mmol) and stirred for 12 h. The reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. Purification by column chromatography on SiO_2

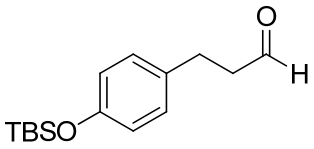
(3:1, EtOAc:hexanes) afforded 128 mg (30%) of **123**: ^{1}H NMR 9.80 (s, 1 H), 7.06 (d, 2 H, *J* = 8.4Hz), 6.76 (d, 2 H, *J* = 8.5 Hz), 2.89 (t, 2 H, *J* = 7.2 Hz), 2.72 (t, 2 H, *J* = 7.2 Hz).



3-[4-(*tert*-Butyldimethylsilyloxy)phenyl]propan-1-ol (124).[83] A solution of 4-(3-hydroxypropyl)phenol (186 mg, 1.22 mmol) in DMF (1.2 mL) was treated with imidazole (252 mg, 3.70 mmol), stirred for 15 min, treated with TBSCl (452 mg, 3.01 mmol) and stirred for 8 h. The reaction mixture was diluted with EtOAc, washed with 1.0 N HCl and the aqueous extract was washed with EtOAc (3x). The combined organic extracts were washed with water (3x), brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was used without further purification and carried on to the following reaction. A solution of the crude product in ethanol (16 mL) was treated with pyridinium *p*-toluenesulfonate (39 mg, 0.15 mmol) and stirred at 50 °C for 3 h. The reaction mixture was cooled to room temperature, concentrated, diluted with EtOAc, extracted with water (2x), brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (9:1, hexanes:EtOAc) afforded 271 mg (95%) of **124**: ^{1}H NMR δ 7.04 (d, 2 H, *J* = 8.2 Hz), 6.76 (d, 2 H, *J* = 8.3 Hz), 3.66 (t, 2 H, *J* = 6.4 Hz), 2.64 (appt, 2 H, *J* = 7.4 Hz), 1.91-1.83 (m, 2 H), 0.98 (s, 9 H), 0.18 (s, 6 H).

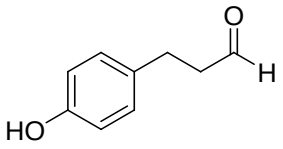
Alternative synthesis of 3-[4-(*tert*-butyldimethylsilyloxy)phenyl]propan-1-ol (124).[83] A solution of **122** (3.21 g, 19.3 mmol) in DMF (7.7 mL) was treated with imidazole (3.95 g, 57.9 mmol), cooled to 0 °C and treated with TBSCl (7.28 g, 48.3 mmol). A precipitate formed

instantly and the mixture was warmed to room temperature. The precipitate dissolved and the reaction mixture was stirred for 2 d, diluted with EtOAc, and washed with 1 N HCl. The aqueous extract was washed with EtOAc (2x). The combined organic extracts were washed with water (3x), brine, dried (Na_2SO_4), filtered and concentrated to afford the crude product which was used without further purification and carried on to the next reaction. A suspension of LAH (l89 mg, 23.5 mmol) in THF (20 mL) at 0 °C was treated portionwise over 0.5 h with crude 3-(4-*tert*-butyldimethylsilanyloxyphenyl)-propyl-*tert*-butyldimethylsilyl ether and stirred for 1 h. The reaction mixture was quenched with 1 N HCl (4 mL) and diluted with water. The aqueous layer was washed with EtOAc (2x). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography on SiO_2 (9:1, hexanes:EtOAc) afforded 4.40 g (75%) of **124** whose spectral and physical properties matched the previously synthesized material.

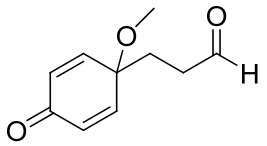


3-[4-(*tert*-Butyldimethylsilyloxy)phenyl]propanal (125). A solution of **124** (100 mg, 0.376 mmol) in acetonitrile (0.43 mL) and CH_2Cl_2 (3.9 mL) was treated with powdered activated 4 Å molecular sieves (0.22 g), TPAP (7.5 mg, 0.021 mmol) and NMO (75.7 mg, 0.646 mmol) and stirred for 0.5 h. The reaction mixture turned colors from dark green to black, was filtered through a plug of silica and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (97:3, hexanes:EtOAc) afforded 75 mg (65%) of **125** as a colorless oil: Rf 0.3 (1:10, EtOAc:hexanes); IR (neat) 3030, 2956, 2930, 2858, 2887, 2715, 1725, 1609, 1510, 1472, 1259, 917, 840, 780 cm^{-1}; ^1H NMR δ 9.81 (t, 1 H, J = 1.5 Hz), 7.04 (d, 2 H, J = 8.5

Hz), 6.76 (d, 2 H, *J* = 8.5 Hz), 2.89 (t, 2 H, *J* = 7.3 Hz), 2.79-2.71 (m, 2 H), 0.97 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR δ 202.0, 154.2, 133.0, 129.3, 120.2, 45.6, 27.5, 25.8, 18.3, −4.3; MS (EI) *m/z* (rel intensity) 264 (M^+, 30), 207 (100), 101 (67); HRMS (EI) calculated for $C_{15}H_{24}O_2Si$ 264.1545, found 264.1547.



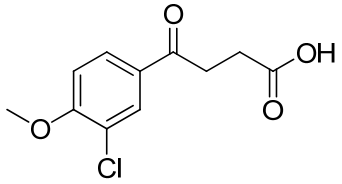
3-(4-Hydroxyphenyl)propanal (123).[82] A solution of **125** (652 mg, 2.32 mmol) in THF (20 mL) was cooled to 0 °C and treated with a 1.0 M solution of TBAF in THF (4.7 mL, 4.7 mmol). The reaction mixture was stirred for 3 h, concentrated under reduced pressure, diluted with EtOAc, washed with water and the aqueous extract was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford a colorless oil. The product slowly decomposed when concentrated and used immediately.



3-(1-Methoxy-4-oxocyclohexa-2,5-dienyl)propanal (121). A solution of crude **123** in MeOH (12.3 mL) and acetonitrile (4.9 mL) was cooled to 0 °C, treated with PIFA (2.47 g, 5.74 mmol) and stirred for 4 h. The reaction mixture was quenched with water, diluted with EtOAc, the layers were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (19:1, hexanes:EtOAc)

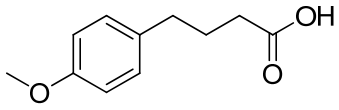
afforded 62.1 mg (18%) of crude **121** as colorless oil: Rf 0.3 (1:1, hexanes:EtOAc); IR (neat) 3411, 2935, 2828, 2729, 1721, 1670, 1633, 1084, 861 cm^{-1}; ^1H NMR δ 9.73 (t, 1 H, *J* = 1.2 Hz), 6.72 (d, 2 H, *J* = 10.3 Hz), 6.38 (d, 2 H, *J* = 10.3 Hz), 3.21 (s, 3 H), 2.49 (td, 2 H, *J* = 1.2, 7.2 Hz), 2.07 (t, 2 H, *J* = 7.6 Hz); ^{13}C NMR δ 200.3, 184.9, 150.1, 131.9, 74.8, 53.2, 38.2, 31.5; MS (EI) *m/z* (rel intensity) 180 (M^+, 25), 137 (32), 124 (40), 123 (100), 107 (37); HRMS (EI) calculated for $C_{10}H_{12}O_3$ 180.0786, found 180.0782.

Decomposition of 121. A solution of **121** (10 mg, 0.056 mmol) in toluene (0.25 mL) at room temperature was treated with NEt_3 (1.5 μL, 0.011 mmol), stirred for 1 h and concentrated under reduced pressure. Crude ^1H NMR analysis showed clean conversion of **121** to 4-methoxyphenol.

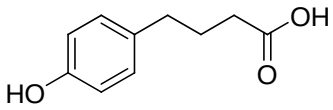


4-(3-Chloro-4-methoxyphenyl)-4-oxobutanoic acid (131). A solution of $AlCl_3$ (7.78 g, 57.4 mmol) in CH_2Cl_2 (47mL) was cooled to 0 °C, treated dropwise over 15 min with a solution of 2-chloroanisole (5.00 g, 35.0 mmol) in nitromethane (3.2 mL), warmed to room temperature and treated portionwise over 0.5 h with succinic anhydride (2.34 g, 23.3 mmol). The reaction mixture was heated at reflux for 8 h with a vent for the HCl (g) that was generated, cooled to room temperature and quenched by pouring into a rapidly stirred mixture of ice (25 g), 2N H_3PO_4 (250 mL) and CH_2Cl_2 (250 mL). A precipitate formed, the suspension was stirred for 6 h, the precipitate dissolved, and the aqueous mixture was extracted with CH_2Cl_2, washed with

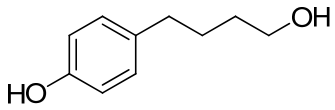
water, brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (1:19, MeOH:CH_2Cl_2) afforded 5.27g (93%) of **131** as a white solid: Rf 0.27 (10:90, MeOH:CH_2Cl_2); Mp 184 °C (CH_2Cl_2); IR (neat) 3063, 2658, 2589, 1694, 1674, 1594, 1258, 1203, 1173, 823 cm^{-1}; ^1H NMR δ 8.03 (d, 1 H, *J* = 1.7 Hz), 7.93 (dd, 1 H, *J* = 8.7, 1.7 Hz), 6.99 (d, 1 H, *J* = 8.7 Hz), 3.98 (s, 3 H), 3.26 (t, 2 H, *J* = 6.5 Hz), 2.81 (t, 2 H, *J* = 6.4 Hz); ^{13}C NMR δ 196.3, 174.0, 158.0, 130.0, 129.5, 129.0, 121.6, 112.4, 56.6, 32.9, 28.0; MS (EI) *m/z* (rel. intensity) 242 (M^+, 39), 171 (75), 169 (100); HRMS (EI) calculated for $C_{11}H_{11}O_4Cl$ 242.03459, found 242.0343.



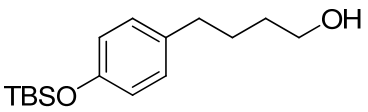
4-(4-Methoxyphenyl)butanoic acid (132).[84] A hydrogenator vessel containing 3% Pd/C (983 mg, 0.278 mmol) was treated with a mixture of THF (5 mL) and water (5 mL) to form a suspension. Acid **131** (5.27 g, 22 mmol) was added to the suspension and the vessel evacuated of air, charged with H_2 (2x), pressurized with H_2 to 40 p.s.i and shaken for 24 h. The reaction mixture was depressurized, filtered through a plug of celite, diluted with EtOAc (50 mL), washed with water, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (1:19, MeOH:CH_2Cl_2) afforded 3.20 g (76%) of **132**: ^1H NMR δ 7.07 (d, 2 H, *J* = 8.5 Hz), 6.84 (d, 2 H, *J* = 8.6 Hz), 3.79 (s, 3 H), 2.63 (t, 2 H, *J* = 7.4 Hz), 2.37 (t, 2 H, *J* = 7.4 Hz), 1.92 (p, 2 H, *J* = 7.3 Hz).



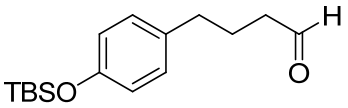
4-(4-Hydroxyphenyl)butanoic acid (133).[85] A solution of **132** (2.55 g, 13.1 mmol) in CH_2Cl_2 (187 mL) was cooled to −78 °C and treated dropwise over 10 min with a 1.0 M solution of BBr_3 in CH_2Cl_2 (59 mL, 59 mmol), stirred for 3 h at −78 °C and at room temperature for 2 h. The reaction mixture was poured into a mixture of ice, sat. NH_4Cl and CH_2Cl_2, stirred for 0.5 h and extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (1:3, hexanes:EtOAc) afforded 1.89 g (80%) of **133** as a white solid: ^{1}H NMR δ 7.05 (d, 2 H, *J* = 8.5 Hz), 6.76 (d, 2 H, *J* = 8.5 Hz), 2.61 (t, 2 H, *J* = 7.7 Hz), 2.36 (t, 2 H, *J* = 7.5 Hz), 1.93 (pentet, 2 H, *J* = 7.5 Hz).



4-(4-Hydroxybutyl)phenol. A suspension of LAH (505 mg, 2.80 mmol) in THF (40 mL) was cooled to 0 °C, treated dropwise over 5 min with a solution of **133** (0.505 g, 23.2 mmol) in THF (5 mL) and stirred at 0 °C for 1 h. The reaction mixture was warmed to room temperature, stirred for 8 h, cooled to 0 °C and slowly and cautiously quenched by dropwise addition of water. The color of the suspension turned from grey to white. The reaction mixture was warmed to room temperature and acidified to pH 7 with 1 N HCl. It was diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography on SiO_2 (1:1, hexanes:EtOAc) afforded 300 mg (65%) of the alcohol: ^{1}H NMR (DMSO-d_6) δ 9.14 (s, 1 H), 6.99 (d, 2 H, *J* = 8.2 Hz), 6.68 (d, 2 H, *J* = 8.1 Hz), 4.37 (t, 1 H, *J* = 5.2 Hz), 3.42 (q, 2 H, *J* = 6.3 Hz), 2.48 (t, 2 H, *J* = 7.2 Hz), 1.55 (m, 2 H), 1.41-1.21 (m, 2 H).

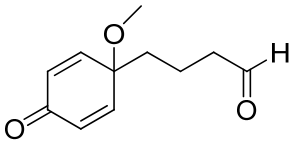


4-[4-(*tert*-Butyldimethylsilyloxy)phenyl]-1-butanol (134).[86] A solution of 4-(4-hydroxyphenyl)-1-butanol (300 mg, 1.81 mmol) in DMF (0.3 mL) was treated with imidazole (379 mg, 5.57 mmol), stirred for 15 min, treated with TBSCl (666 mg, 4.42 mmol) and stirred for 8 h. The reaction mixture was diluted with EtOAc, washed with 2 N HCl and the aqueous layer was washed with EtOAc (3x). The combined organic extracts were washed with water (3 x), brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. A solution of the crude product in ethanol (17 mL) was treated with PPTS (43 mg, 0.17 mmol) and heated at 50 °C for 3 h. The reaction mixture was concentrated under reduced pressure, diluted with EtOAc, washed with 2 N HCl, water, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (9:1, hexanes:EtOAc) afforded 420 mg (88%) of **134**: ^{1}H NMR δ 7.03 (d, 2 H, *J* = 8.4 Hz), 6.75 (d, 2 H, *J* = 8.4 Hz), 3.66 (t, 2 H, *J* = 6.3 Hz), 2.58 (t, 2 H, *J* = 7.0 Hz), 1.63 (m, 4 H), 1.39 (s, 1 H), 0.98 (s, 9 H), 0.19 (s, 6 H).



4-[4-(*tert*-Butyldimethylsilyloxy)phenyl]butanal (135). A solution of **134** (420 mg, 1.50 mmol) in MeCN (1.68 mL) and CH_2Cl_2 (17.0 mL) was treated with powdered activated 4 Å molecular sieves (0.83 g), TPAP (30.0 mg, 0.0853 mmol) and NMO (279 mg, 2.38 mmol), and stirred for 0.5 h. The reaction mixture turned from dark green to black and was filtered through a plug of silica and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (97:3, hexanes:EtOAc) afforded 284 mg (68%) of **135** as a colorless oil: Rf 0.38 (10:1, hexanes:EtOAc); IR (neat) 2955, 2930, 2858, 1726, 1510, 1256, 917, 840, 781 cm $^{-1}$; ^{1}H NMR

δ 9.74 (s, 1H), 7.01 (d, 2 H, *J* = 8.3 Hz), 6.8 (d, 2 H, *J* = 8.3 Hz), 2.58 (t, 2 H, *J* = 7.4 Hz), 2.56-2.40 (m, 2 H), 1.95-1.89 (m, 2 H), 1.0 (s, 9 H), 0.2 (s, 5 H); ^{13}C NMR δ 202.3, 154.0, 134.0, 129.4, 120.1, 43.2, 34.0, 25.9, 23. 9, 18.3, −4.4; MS (EI) *m/z* (rel intensity) 278 (M^+, 51), 221 (85), 165 (71), 151 (100), 73 (75).



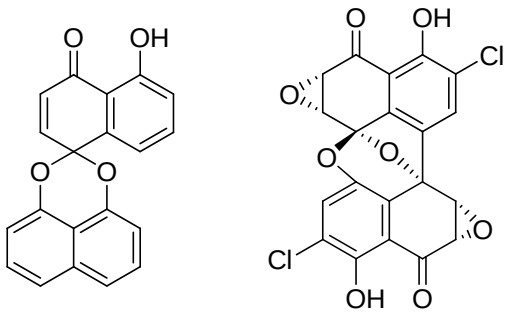
4-(1-Methoxy-4-oxocyclohexa-2,5-dienyl)butanal (136). A solution of **135** (283 mg, 1.02 mmol) in THF (10 mL) was cooled to 0 °C, treated with a 1.0 M solution of TBAF in THF (2.1 mL, 2.1 mmol) and stirred for 1 h at 0 °C. The reaction mixture was concentrated under reduced pressure, diluted with EtOAc, washed with water and the aqueous layer was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The product slowly decomposed when concentrated and was immediately carried on to the following reaction conditions. A solution of the crude product in MeOH (0.78 mL) and acetonitrile (0.30 mL) was cooled to 0 °C, treated with PIFA (140 mg, 0.326 mmol) and stirred for 1h. The reaction mixture was concentrated under reduced pressure, diluted with EtOAc, washed with water and the aqueous layer was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (1:1, hexanes:EtOAc) afforded 75 mg (40%) of **136** as a colorless oil: Rf 0.3 (1:1, hexanes:EtOAc); IR (neat) 3429, 2935, 2827, 1721, 1670, 1633, 1459, 1393, 1272, 1167, 1093, 862, 703 cm $^{-1}$; ^{1}H NMR δ 9.74 (t, 1 H, *J* = 1.3 Hz), 6.75 (d, 2 H, *J* = 10.1 Hz), 6.38 (d, 2 H, *J* = 10.3 Hz), 3.21 (s, 3 H), 2.46 (td, 2 H, *J* = 1.3, 7.0 Hz), 1.67-1.66 (m, 2 H), 1.66- 1.57 (m, 2 H); ^{13}C NMR δ 201.5,

185.4, 150.7, 131.9, 75.5, 53.2, 43.7, 38.9, 16.3; MS (EI) *m/z* (rel intensity) 194 (M^+, 3), 192 (1), 150 (23), 149 (15), 124 (43), 123 (100); HRMS (EI) calculated for $C_{11}H_{14}O_3$ 194.0943, found 194.0945.

8.0 BISNAPHTHOSPIROKETALS

8.1 INTRODUCTION

A variety of structurally intricate and biologically active bisnaphthospiroketals are found in nature.[87] The Wipf group has a history of exploring this substance class and utilizing the generated biological data to guide further synthetic investigations (Figure **8.1**). Of particular interest to us are the naphthoquinone bisnaphthospiroketals, such as the palmarumycins (**139**). This scaffold has been the starting point for a library of analogues and prodrugs that were tested as Trx/TrxR inhibitors with potential applications in cancer therapy. Initial *in vitro* results prompted the exploration of an expedited route for the prodrug synthesis to provide multi-gram quantities for biological testing. Bisnaphthospiroketals functionalized as an epoxynaphthoquinone, such as the spiroxins, are also structurally and strategically alluring to us. The total syntheses of spiroxin A and B (**140**) were pursued utilizing some key oxidative transformations to gain access to the core of these natural products.



139 **140**

Figure 8.1. Palmarumycin (**139**) and spiroxin B (**140**)

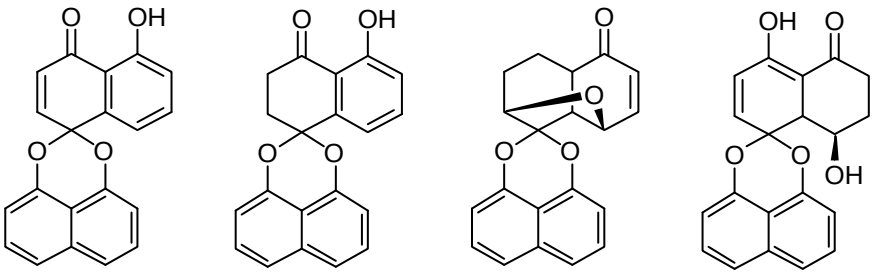
8.2 BISNAPHTHOSPIROKETAL CLASSIFICATION

Chemists immediately noted and appreciated the synthetic challenges of the bisnaphthospiroketal's compact architecture. The first member of this class was isolated in the early 1990's, and more recent additions[88] include spiro-mamakone A[89] and the decaspirones isolated from *Helicoma viridis*.[90,91] Structurally, bisnaphthospiroketals can be divided into types I, II and III; all members have a compact and highly oxygenated ring system and a spiroketal linking two naphthalenes or naphthoquinones.[92] These types differ primarily in the connectivity between the upper and lower rings.

8.2.1 Type I bisnaphthospiroketals

Type I bisnaphthospiroketals are characterized by a spiroketal moiety between a naphthoquinone and a dihydroxynaphthalene. MK 3018 was first isolated in 1989,[93] and since that report this class has grown to include many new members that primarily differ in their degree and sites of

oxidation.[94-97] A series of particularly noteworthy representatives is the palmarumycin CP family (Figure **8.2**).



139 **141** **142** **143**

Figure 8.2. Palmarumycins CP_1-CP_4 (**139**, **141-143**)

Palmarumycins CP_1-CP_4 (Figure **8.2**) were first isolated in 1994 from the endophytic fungus *Coniothurium palmarum* and numbered according to their polarities, with palmarumycin CP_1 (**139**) being the least polar and palmarumycin CP_4 (**133**) being the most polar.[94] Their structures were elucidated by ^{1}H NMR, ^{13}C NMR, DEPT, C-H COSY, H-H COSY, IR, MS and X-ray crystallography. The initial report identified the anti-fungal activity and later reports described the antibacterial activity of these compounds.[98] Members of this family subject to total synthesis include palmarumycins CP_1 (**139**),[99-101] CP_2 (**141**),[100,101] C_2 (**144**),[100] C_{11},[102] diepoxin σ (**145**),[103-105] CJ 12371,[100,101,106] CJ 12372[106] and others (Figure **8.3**).[107,108]

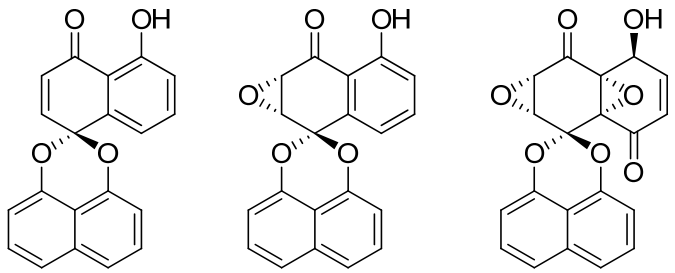
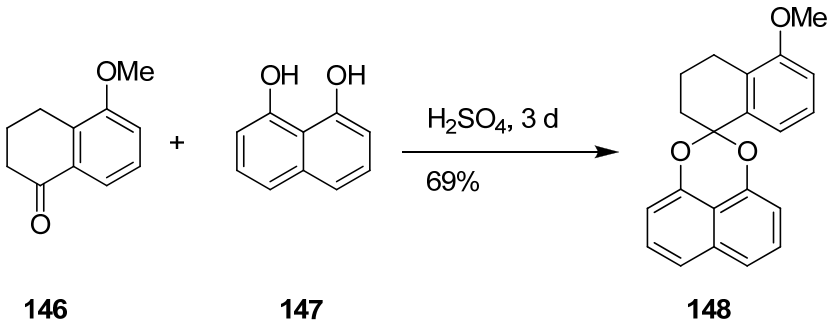


Figure 8.3. Palmarumycin CP_1 (**139**), C_2 (**144**) and diepoxin σ (**145**)

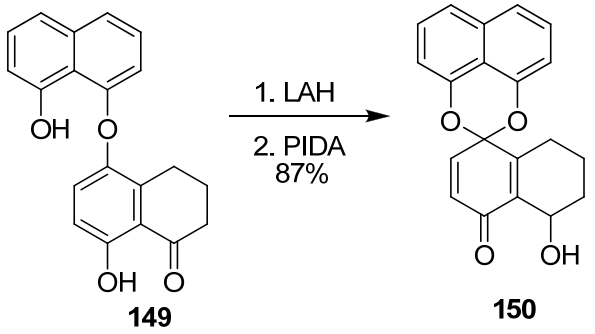
The initial report inspired further explorations of the biological activity of other type I bisnaphthospiroketals. Schering-Plough researchers isolated a number of bisnaphthospiroketals from the fungus *Nattrassia mangiferae* in pursuit of anti-tumor and phospholipase D activity.[109-113] Merck isolated several palmarumycins and preussomerins from the unidentified fungus *C. elomycetes*[114] which exhibited DNA gyrase[115] and ras farnesyl transferase inhibition.[116-118] As a testament to the versatility of this pharmacophore, unnatural type I analogues have been synthesized by the Wipf group and identified as thioredoxin/thioredoxin reductase (Trx/TrxR) inhibitors.[119,120]

The synthetic routes for type I bisnaphthospiroketals can typically be divided into two categories: acid catalyzed spiroketalizations and biaryl ether oxidative cyclizations. The Barrett[101] and Taylor[100] groups both utilized the former approach (Scheme **8.1**). The Taylor group synthesized spiroketal **148** via an acid catalyzed spiroketalization of 5-methoxytetralone (**146**) and dinaphthol **147**.



Scheme 8.1. Taylor's acid catalyzed spiroketalization

An alternative synthetic approach to this architecture is the oxidative cyclization of biaryl ethers. The Wipf group synthesized spiroketal **150** in good yield via a reduction of biaryl ether **149** and treatment with PIDA (Scheme **8.2**).[99] The primary advantage of the PIFA or PIDA mediated spiroketalization is the milder reaction conditions.



Scheme 8.2. Oxidative cyclization to spiroketal **150**

8.2.2 Type II bisnaphthospiroketals

The preussomerins are examples of type II bisnaphthospiroketals and are characterized by three oxygen bridges between the dihydronaphthoquinones (Figure **8.4**). These antifungal metabolites were isolated from *Preussia isomera* in 1990 by the Gloer group.[121] Their structures were

elucidated via HREIMS, ^{13}C NMR, ^{1}H NMR, INEPT ^{1}H-^{13}C, X-ray crystal diffraction and CD calculations.[122,123]

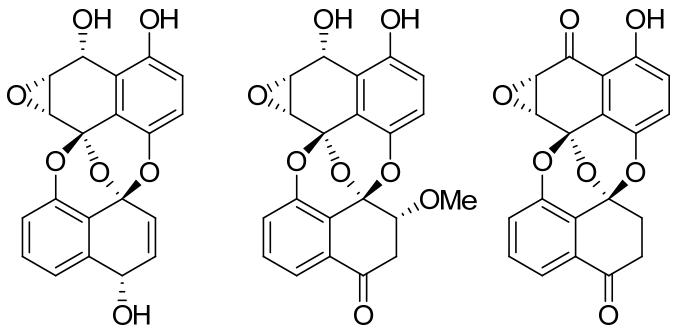


Figure 8.4. Preussomerin A (**151**), preussomerin C (**152**) and preussomerin H (**153**)

The isolation of type I and type II bisnapthospiroketals from a common source sparked some interesting biosynthetic proposals.[114] One hypothesis was that the preussomerins could be derived from the oxidation of type I bisnaphthospiroketals. There have been no reports to substantiate these hypotheses *in vivo*, but organic chemists have demonstrated that this transformation is chemically possible. The first reported preussomerin synthesis was from the Heathcock group in 1999. They calculated that the preussomerin framework **155** was energetically favored by 5 kcal/mol to the type I spiroketal **154** (Figure **8.5**)[124] Treatment of **154** with LiOH afforded **155** in 97% yield. The Barrett group likewise demonstrated a similar interconversion, except with the aid of $Pb(OAc)_4$.[125]

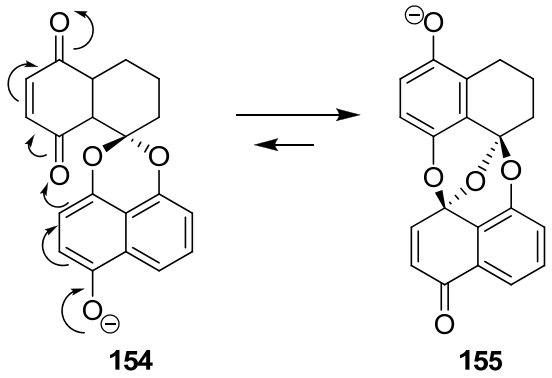
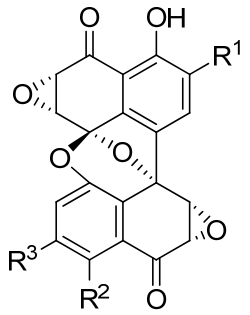


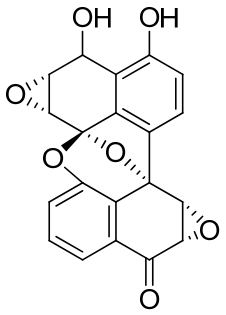
Figure 8.5. Interconversion between **154** and **155**

8.2.3 Type III bisnaphthospiroketals

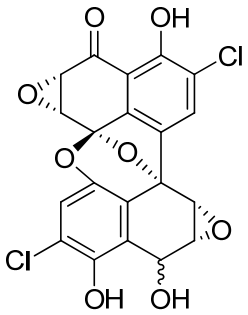
A third type of bisnaphthospiroketal is represented by the spiroxins (Figure **8.6**). This group consists of five members characterized by a spiroketal and a biaryl bond between two naphthoquinone derivatives. The spiroxins were isolated in 1999 from coral fungal strain LL-37H248 off the coast of Vancouver Island.[126-128] Only spiroxin A (**156**) was tested for biological effects and displayed anti-tumor and antibacterial activity against gram positive bacteria. Spiroxin A (**156**) induced single strand cleavage of double stranded DNA in the presence of thiols, which could account for its anti-tumor activity. The absolute configuration was determined through exciton coupled CD spectroscopy.[129]



Spiroxin A (**156**): R^1 = Cl R^2 = OH R^3 = H
Spiroxin B (**140**): R^1 = Cl R^2 = OH R^3 = Cl
Spiroxin C (**157**): R^1 = H R^2 = H R^3 = H



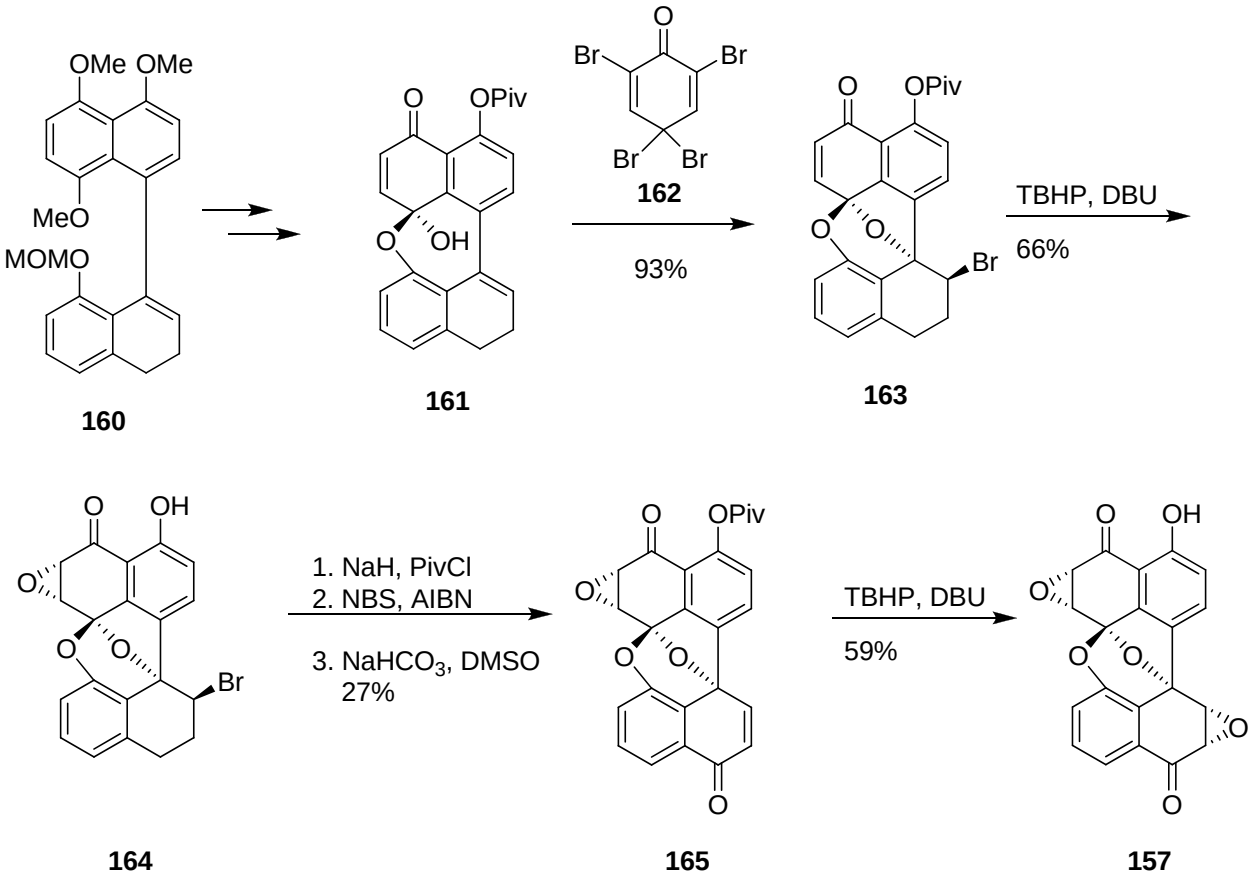
Spiroxin D (**158**)



Spiroxin E (**159**)

Figure 8.6. Type III bisnaphthospiroketals

The only reported total synthesis of a spiroxin was published in 1999 by the Imanishi group (Scheme **8.3**).[130] The synthesis of spiroxin C (**157**) commenced with standard oxidative conditions to afford hemiacetal **161** from **160**. Bromoetherification followed by epoxidation delivered bromide **163**. The epoxidation of bromide **163** occurred stereoselectively on the convex face. Protecting group manipulation, enone formation and a final stereoselective epoxidation delivered spiroxin C (**157**) in 15 steps and 0.6% overall yield.



Scheme 8.3. Imanishi's spiroxin C (**157**) synthesis

9.0 THIOREDOXIN/THIOREDOXIN REDUCTASE

9.1 TRX/TRXR BACKGROUND

The thioredoxin-thioredoxin reductase (Trx/TrxR) complex is a homodimeric flavoprotein present in both eukaryotic and prokaryotic cells.[131] The complex was first studied in *E. coli* and differences between the bacterial and human Trx/TrxR were discovered shortly afterwards.[132-139] In humans, thioredoxin is one of over 25 selenocysteine containing proteins known.[140] In other species, the Trx/TrxR selenocysteine is replaced with the more common cysteine residue.[141-143] These proteins regulate a variety of essential enzymes and processes through a series of oxidations and reductions.

Trx/TrxR is essential for cell function and survival and hence an attractive medicinal target.[144] This complex relies on thioredoxin, thioredoxin-reductase, FAD and NADPH to initiate the flow of electrons (Figure **9.1**).[141] TrxR reduces the Trx dithiane to a thiol. In the reduced state, Trx activates a plethora of different enzymes.[145] Examples include the initiation of DNA synthesis through activation of ribonucleotide reductase,[141,146] the regulation of gene transcription factor binding to DNA,[147,148] and the growth factor properties of Trx/TrxR.[131]

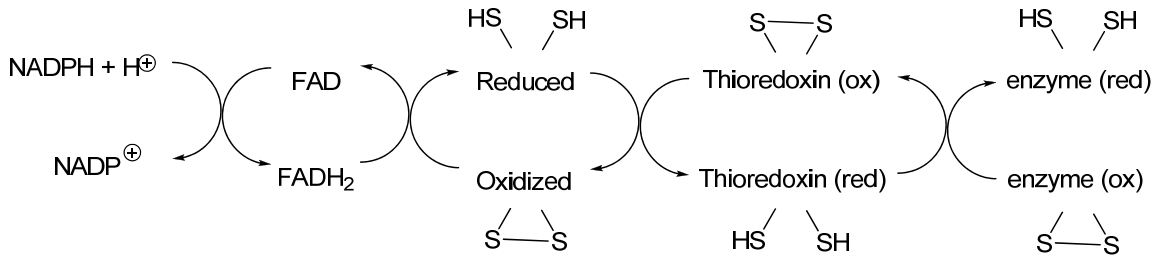


Figure 9.1. Trx/TrxR redox cycle

A crystal structure increases the appeal of an enzyme as a target for the medicinal chemist.[149] Human TrxR-1 has been crystallized in 2.8 Å resolution with bound $NADP^+$ (blue) and FAD (yellow) (Figure **9.2**).[150] The active site in thioredoxin contains a conserved Cys-Gly-Pro-Cys-Lys sequence located on the flexible solvent exposed side arm of the protein.[131] The N- and C- terminal active redox centers are displayed in green and marked as NR and CR respectively. This orientation permits access for potential inhibitors. The active site was compared to glutathione reductase, another common and important cellular anti-oxidant protein involved in the synthesis of proteins, catalysis, metabolism and transport.[151] Binding site comparisons revealed unique binding pockets available to Trx inhibitors and could assist in the systematic development of selective inhibitors.

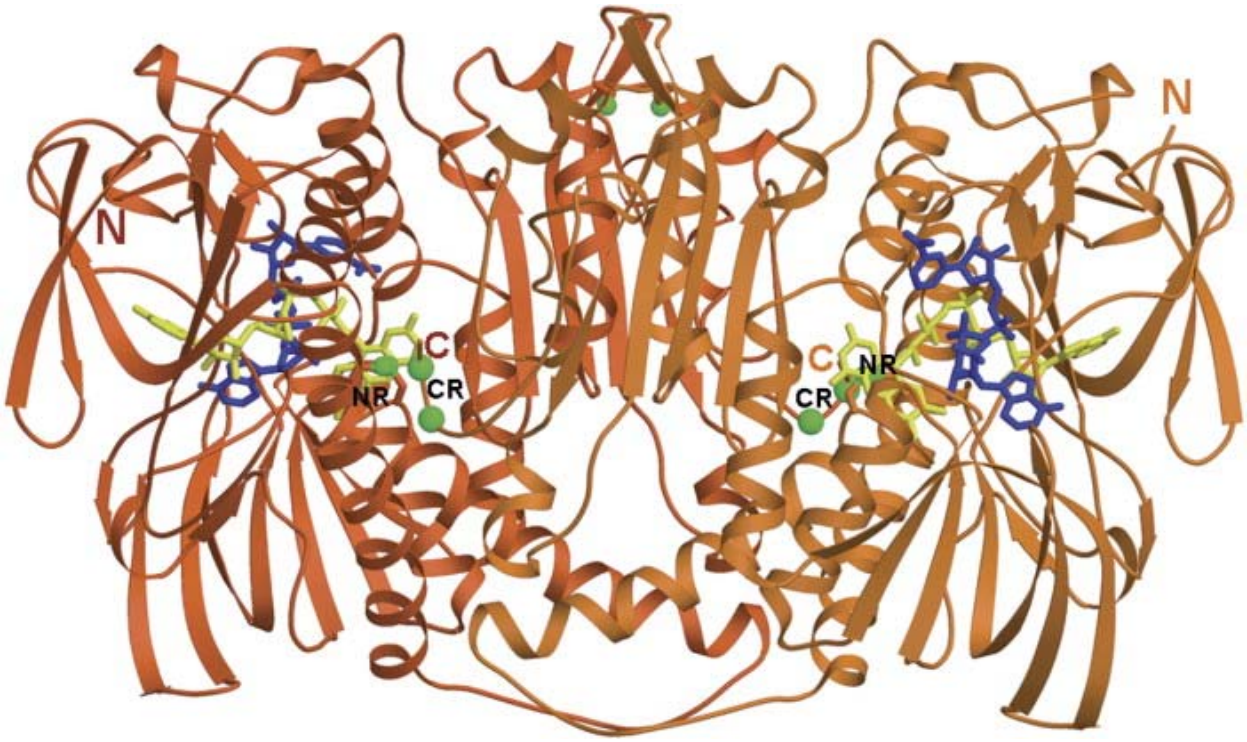


Figure 9.2. Crystal structure of hTrx homodimer[150]

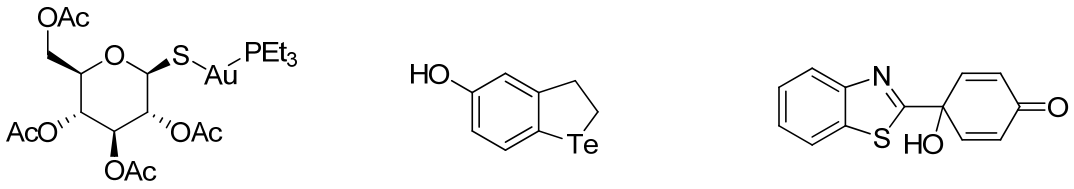
9.2 TRX/TRXR AS THERAPEUTIC TARGET

Trx/TrxR is increasingly considered a drug target because it is involved in many crucial biological pathways.[150,152-159] It has implication in cancer, HIV-AIDS, rheumatoid arthritis and other medical conditions.[160,161] There are two isoforms of thioredoxin: Trx-1 is found in the cytoplasm and the nucleus of cancer cells, and Trx-2 is found in the mitochondria.[141,162] Trx-1 and Trx-2 differ in size, 105 and 166 amino acids, respectively, and each have distinct TrxR's associated with them.

The dichotomy of thioredoxin's role in cancer proliferation is noteworthy. Trx/TrxR protects against cancer by disabling DNA damaging oxidizers, activating gene transcription for antioxidative proteins and activating p53.[163] P53 is a crucial transcription factor that acts as a

guardian for the genome via cell cycle regulation and tumor suppression. P53 is critical to the cell's anticancer measures because it signals DNA repair proteins, pauses the cell cycle at the G1/S regulation point for DNA damage repair and initiates apoptosis.[164,165] After tumor formation, Trx/TrxR's role shifts from protector to bad actor. The complex acts as a tumor growth factor, becomes responsible for supplying deoxyribonucleotides for tumor growth and protects the tumor against NK lysin tumor necrosis factor[166] and the immune system.[167] The expression of Trx-1 is 10 fold higher in cancer cells than in normal cells, making this system a natural target to combat the growing tumor.[168-170]

A myriad of Trx/TrxR inhibitors have been developed for cancer therapy (Figure **9.3**). One series of Au (I) and Au (III) compounds inhibits Trx/TrxR in the low μM range.[171-173] A well known example is auronafin (**166**), which traditionally has been used in arthritis therapy.[174,175] Palmarumycin CP_1 (**139**),[176,177] BCNU,[178] organotellerium **167**[179] curcumin,[180] a wide assortment of quinones and naphthoquinones,[181-183] quinol **168**[184,185] and many other examples[186-191] have been shown to inhibit the Trx/TrxR complex.



166 **167** **168**

Figure 9.3. Trx/TrxR inhibitors

Quinol **168** is one member from a library of heteroaromatic substituted quinols synthesized in pursuit of anticancer activity from the laboratory of Dr. Malcolm Stevens (Figure **9.3**).[185] Phenols are susceptible to first pass metabolism and there are numerous *in vivo*

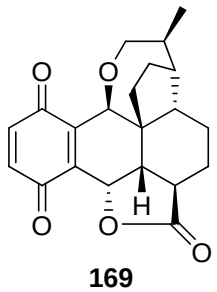
processes that can modify the phenol moiety such as methylation, oxidation, glucuridination or acetylation.[192-194] These phenolic modifications can be the source of inconsistencies between *in vivo* and *in vitro* data or a short plasma half life.[195,196] However, in some systems these cellular modifications of the phenol are the true source of biological activity. There are reports where the biological activity is dependent on phenol oxidation to a quinine or quinol.[197,198] The Stevens group investigated the phenol oxidation to the quinine or quinol of a series of biologically active phenols in pursuit of enhanced biological activity.[185] Quinol **168** was one of the synthesized compounds and found to have a very good antiproliferative and cytotoxic profile with a mean GI_{50} of 0.23 μM and a mean LC_{50} of 3.39 μM. This work highlights how small molecule quinones or quinols can be very potent anticancer agents.

A diverse set of *in vitro* Trx/TrxR inhibitors has been developed, but *in vivo* data are scarce. Selectivity, solubility, potency and ease of synthetic availability are obstacles that need to be overcome to produce a viable drug. The therapeutic potential of this target combined with as of yet unmet clinical applications inspired the Wipf group to become involved in this area of research.

9.3 EARLY WIPF GROUP WORK WITH TRX/TRXR INHIBITORS

The Wipf group previously reported that the type I bisnaphthospiroketal pharmacophore leads to promising biological activity.[176] In 2001, deoxypreussomerin A, palmarumycin CP_1 (**139**) and a library of palmarumycin analogues were synthesized and tested against two human breast cancer cell lines.[177] Several analogues were more cytotoxic and as potent as pleurotin (**169**, Figure **9.4**)

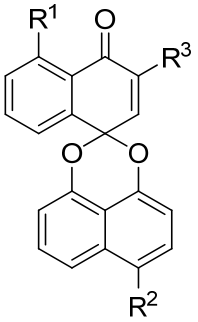
at inhibiting Trx/TrxR.[176,177] Pleurotin was the most potent Trx/TrxR inhibitor known at the time with an IC_{50} of 0.17 μM.[176,199,200]



169

Figure 9.4. Pleurotin, a potent Trx/TrxR inhibitor

The Wipf group recently reported a new series of palmarumycin CP_1 analogues. The compound identification number from the published paper is shown in parentheses (Figure **9.5**).[119] The double bond of the enone was functionalized with substituents such as bromine (**171**), 2-furyl (**172**) and pyridyl (**173**). The lower naphthalene moiety was functionalized with a methyl ether (**170**-**174**), benzyl ether (**175**) and a free hydroxyl group (**176** and **177**). The synthesized compounds were submitted to the laboratory of Dr. Garth Powis for biological testing.



170 (S1): R^1=H, R^2=OMe, R^3=H
171 (S2): R^1=H, R^2=OMe, R^3=Br
172 (S3): R^1=H, R^2=OMe, R^3=2-furyl
173 (S4): R^1=H, R^2=OMe, R^3=2-pyridyl
174 (S9): R^1=OH, R^2=OMe, R^3=H
175 (S10): R^1=OH, R^2=OBn, R^3=H
176 (S11): R^1=H, R^2=OH, R^3=H
177 (S12): R^1=OH, R^2=OH, R^3=H

Figure 9.5. Early palmarumycin analogues

The palmarumycin CP_1 (**139**) analogues were similarly potent inhibitors, but the two most potent analogues were **176** and **177** (Table **9.1**). Although **176** and **177** shared a similar biological profile, the limited solubility of **177** raised questions concerning its actual activity and prevented efficacy in mouse models. A library of prodrugs of **177** was synthesized to address the issue of low water solubility.[201]

Table 9.1. IC_{50} (μM) values for Trx-1/TrxR inhibition and cell growth inhibition

Entry	Compound	Trx/TrxR	MCF-7
1	Pleurotin	0.17	4.1
2	Palmarumycin CP_1	0.35	1.0
3	**170**	3.2	9.2
4	**171**	3.1	2.6
5	**172**	6.4	6.0
6	**173**	5.0	1.6
7	**174**	1.0	14.0
8	**175**	5.2	14.2
9	**176**	0.34	2.8
10	**177**	0.2	2.6

9.4 SYNTHESIS OF PALMARUMYCIN PRODRUGS

9.4.1 Introduction and history of prodrugs

A variety of factors can hinder the application of a potential drug.[202,203] Among these factors are low aqueous solubility,[204] poor absorption and distribution,[205] low patient acceptability and formulation problems.[206,207] Additional attributes that hurt a potential drug are lack of selectivity for the target tissue, taste and odor or volatility.[208] A way to bypass several of these pitfalls is via the synthesis of prodrugs.

The term prodrug was first coined in 1958 by Albert[209] and defined as a pharmacologically inactive, or less active, compound that is converted into a biologically active drug via a metabolic biotransformation by, for example, cytochrome P 450,[210] antibodies[211,212] esterases,[213,214] or a non-enzymatic process, such as hydrolysis.[206] Prodrugs can be designed to improve physiochemical properties, increase oral absorption,[215] increase site specificity by only being unmasked by enzymes located at the target site[216-218] and attenuate the desired dose through slow release of the active compound.[219-221]

A plethora of groups have been used to convert drugs into prodrugs such as phosphonate or phosphate esters,[222,223] amino acid esters,[224] phenolic acetates[225-228] and others.[229,230] There are many prodrugs on the market (Figure **9.6**).[202,231] Merck's ACE inhibitor enalapril (**178**)[232] and Glaxo Smith Klein's anti-viral valaciclovir (**179**)[233] are both converted to their active form by esterases for improved oral bioavailability and activity, respectively. The anti-Parkinson's drug levodopa (**180**) is converted to dopamine by DOPA decarboxylase[234] after crossing the blood-brain barrier.[235,236] The anti-microbial chloramphenicol (**181**) succinate ester has improved water solubility over the active compound, chloramphenicol (**181**).[237] Codeine (**182**) is demethylated by the liver enzyme CYP2D6 to give morphine.[238,239] These are only a few examples where a prodrug improves the properties and pharmacological profile of a drug.

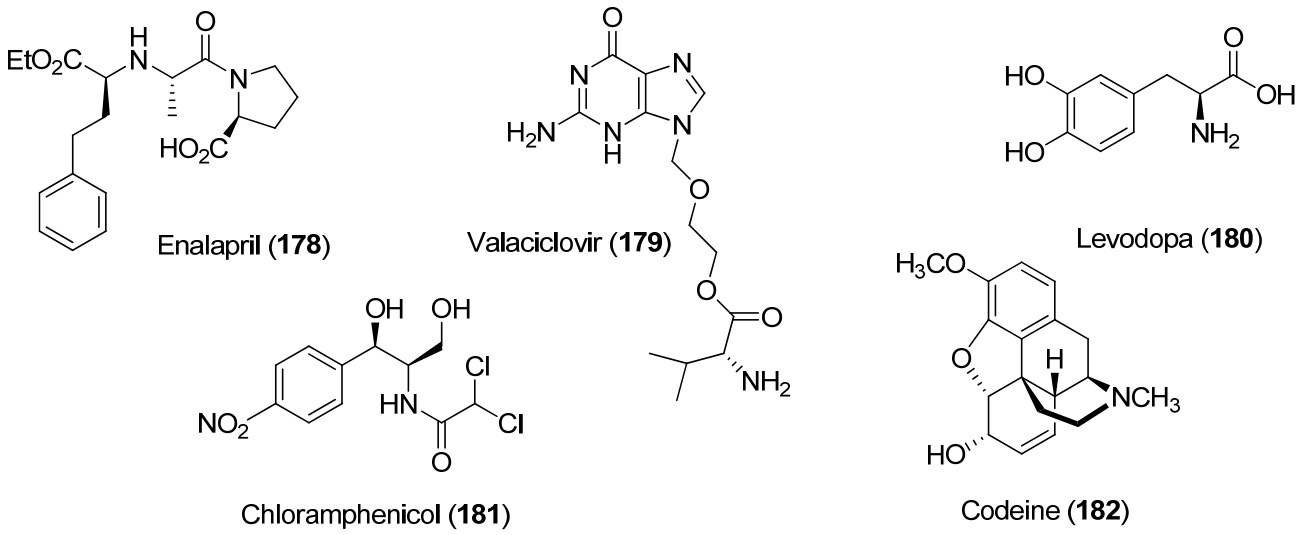
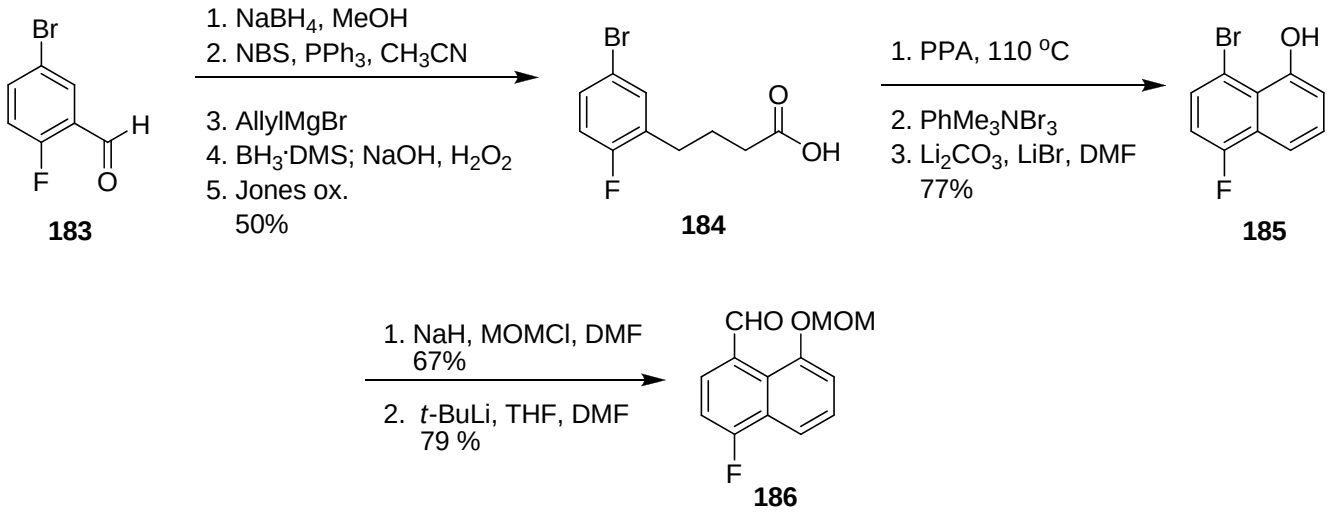


Figure 9.6. Commercially available prodrugs

In order to increase the *in vivo* activity of these promising, yet very hydrophobic, spiroketal agents, these compounds were functionalized with charged moieties at the phenol oxygen for improved water solubility.[240] The palmarumycin core **177** was first synthesized according to the reported protocol.[119]

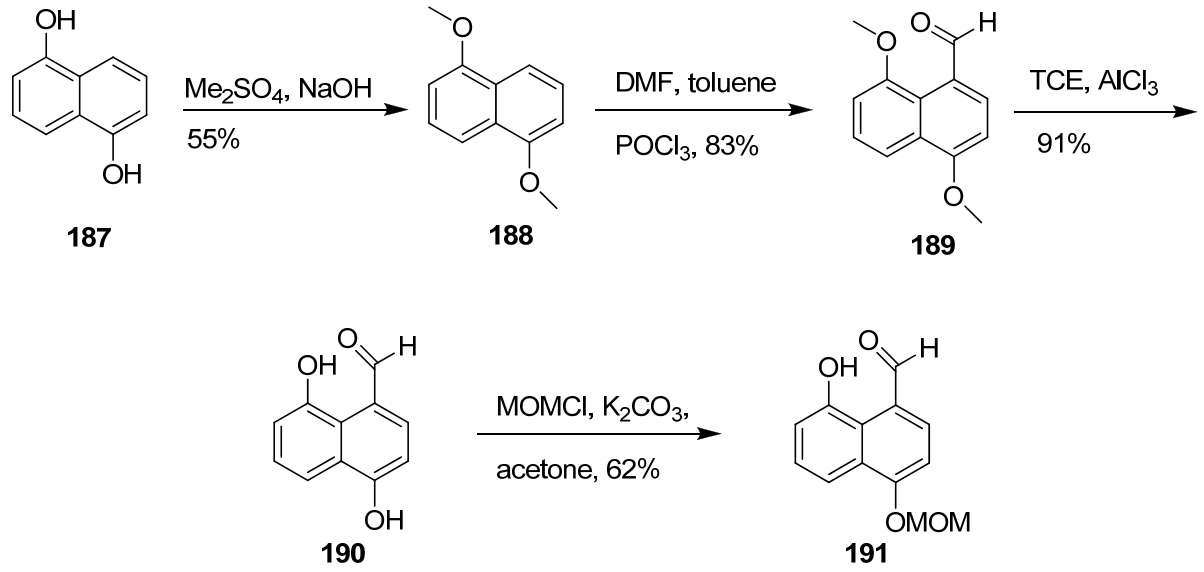
9.4.2 Synthesis of spiroketal 177

The synthesis of **177** followed the previously reported synthetic route (Scheme **9.1**).[119] Bromofluorobenzaldehyde **183** was reduced, brominated and treated with allyl magnesium bromide to afford the alkene. Hydroboration of the introduced alkene and Jones oxidation afforded acid **184**. Cyclodehydration with PPA, α-bromination and subsequent elimination afforded naphthol **185**. MOM protection of the naphthol followed by formylation readily delivered naphthaldehyde **186** in 10 steps and 31% overall yield.



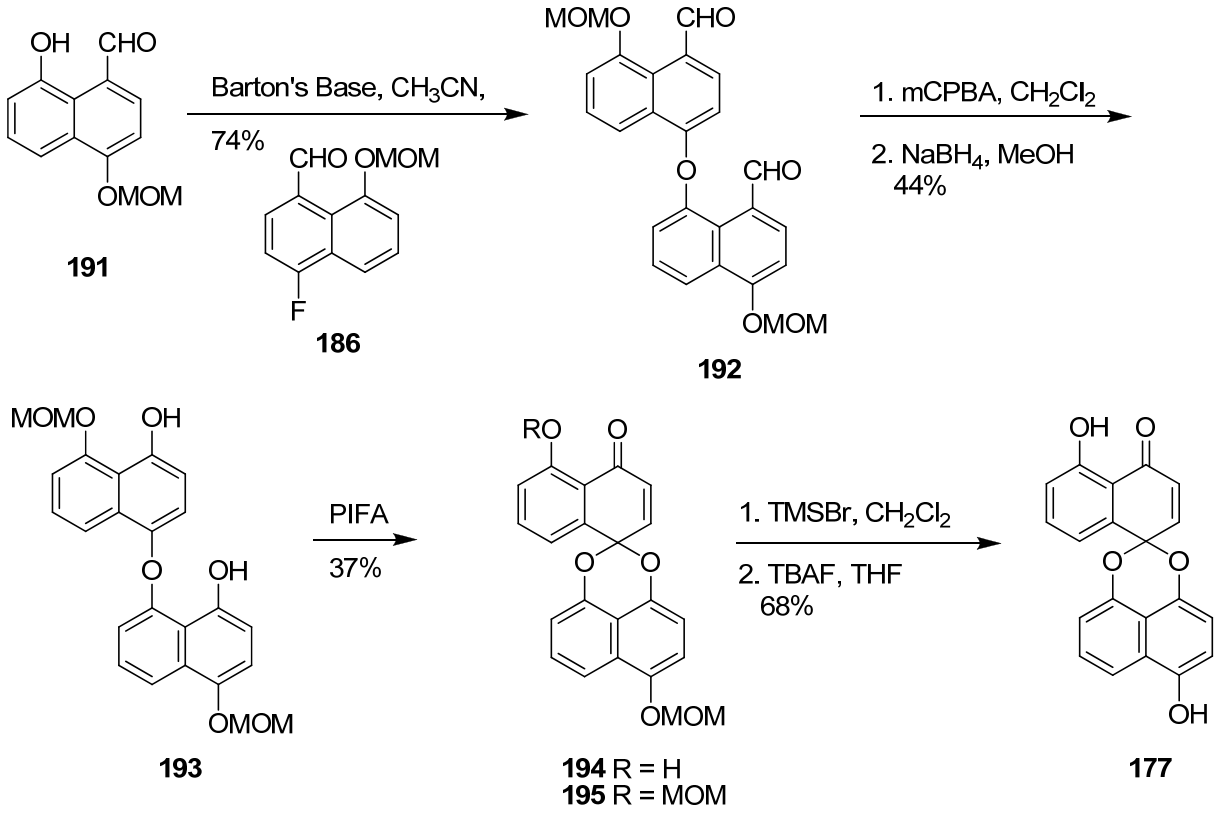
Scheme 9.1. Synthesis of naphthyl fluoride **186**

The second etherification component, **191**, was rapidly synthesized starting with 1,5-dihydroxynaphthalene (**187**) (Scheme **9.2**). Methylation, Vilsmeier-Haack formylation and deprotection of **187** afforded the needed naphthaldehyde **190**. This compound was selectively MOM protected to deliver naphthol **191** in four steps and 47% overall yield.



Scheme 9.2. Synthesis of naphthaldehyde **191**

Using both substrates, the S_NAr biaryl ether synthesis was performed (Scheme **9.3**). The etherification of **191** and **186** proceeded smoothly with Barton's base to deliver **192** in 54% yield.[241] A Dakin reaction delivered naphthol **193** which was oxidized with PIFA to afford spiroketal **194**. One MOM group was lost during the cyclization, which can be attributed to trace amounts of water and the acidity of the PIFA conditions. Treatment of **194** with TMSBr followed by TBAF deprotected the MOM group and delivered the target structure **177**.



Scheme 9.3. Synthesis of palmarumycin analogue **177**

The PIFA or PIDA mediated oxidative cyclization has been used in many Wipf group publications.[59,242-244] The proposed mechanism for the formation of **194** is that an attack of the naphthol oxygen on PIFA (**196**) affords the reactive O-I bonded intermediate **197** (Figure **9.7**).[245] The naphthol oxygen on the lower ring in **197** then attacks para to the O-I bond generating naphthoquinone **195**. As stated earlier, the MOM group on the naphthoquinone is acid sensitive and is hydrolyzed under standard PIFA conditions to afford **194**.

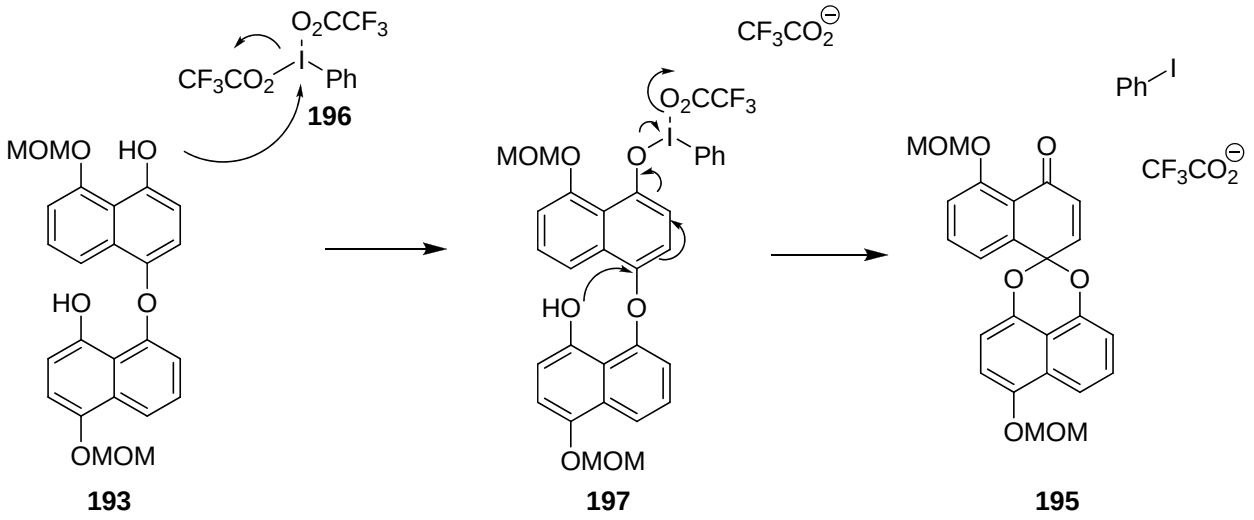
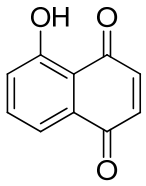


Figure 9.7. PIFA mediated oxidative cyclization of **193**[245]

PIFA is an environmentally benign, commercially available and relatively non-toxic oxidant, but the reaction conditions are sometimes difficult to optimize.[246] The major side product isolated was juglone (**198**, Figure **9.8**), presumably from oxidation and fragmentation of **193**. Quinones are ubiquitous building blocks in synthesis and a wide variety of preparations are available.[247] Various oxidants, solvents, bases and temperatures were screened with hopes of improving the yield (Table **9.2**). PIFA (entries 1-9), Ag_2O (entry 10),[248] DDQ (entry 11),[249] benzoquinone (entry 12),[125,250] $Pb(OAc)_4$ (entry 13)[251] and $LiClO_4$ (entry 14)[252] were investigated. Water could mediate at least one decomposition pathway. If water reacted with **197** preferential to the naphthol, the resultant hemiketal would hydrolyze to the quinone during the reaction workup. If this was the primary decomposition pathway, addition of a dehydrating agent, such as 4 Å molecular sieves, should improve the reaction efficiency. The yield did not greatly improve with 4Å molecular sieves, and the primary difference was the isolation of both **195** and **194** (entry 15).



198

Figure 9.8. Oxidation side product, juglone (**198**)

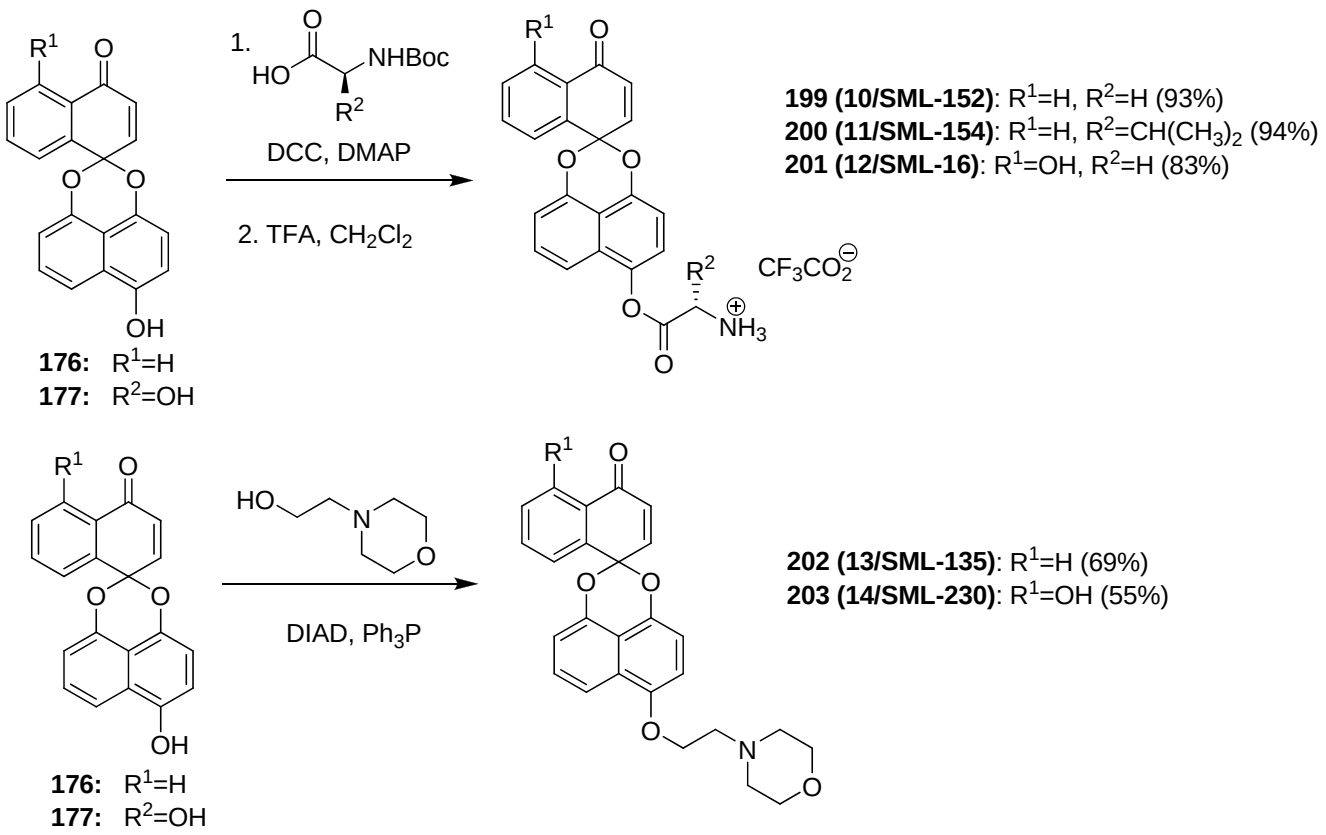
Table 9.2. Oxidative cyclization of **193**

Entry	**Conditions**	**Yield of 194** [%]/**Result**
1	PIFA (3 equiv), Cs_2CO_3, CH_3CN, −20 °C	28
2	PIFA (3 equiv), Cs_2CO_3 (6 equiv), CH_3CN, 0 °C	32
3	PIFA (3 equiv), K_2CO_3 (6 equiv), CH_3CN, 0 °C	21
4	PIFA (5 equiv), K_2CO_3 (10 equiv), CH_3CN, 0 °C	15
5	PIFA (1.3 equiv), K_2CO_3 (2.6 equiv), CH_3CN, 0 °C	15
6	PIFA (2 equiv), CH_3CN, THF, H_2O (1:4:4)	Juglone (**198**)
7	PIFA (2 equiv), TEMPO (0.5 equiv), CH_3CN, rt	Decomp
8	TBS protected phenol, PIFA (2 equiv)	NR
9	PIFA (1 equiv), TMSOTf, CH_3CN	Decomp
10	Ag_2O	NR
11	DDQ	Decomp
12	Benzoquinone	NR
13	$Pb(OAc)_4$	No desired product
14	CH_3CN, H_2O, $LiClO_4$, 1.5 V	NR
15	PIFA, CH_3CN, 4Å mol sieves	26

Despite the extensive search for alternative conditions, the yields could not be increased nor could the major side reaction to juglone (**198**) be avoided. The equivalents of PIFA in the presence of either K_2CO_3 or Cs_2CO_3 were varied. The other oxidants screened either resulted in decomposition or no reaction (entries 10-14). The original PIFA conditions were used for the synthesis **177**. Using these conditions, the synthesis was completed to produce 100 mg of **177**.

9.4.3 Generation I prodrugs

Selective functionalization of spiroketals **176** and **177** at the phenol moiety with various Boc-protected amino acids was desired.[119,253] The esterification occurred selectively at the non-hydrogen bonded naphthol even when two hydroxyl groups were present. This selectivity was due to the attenuated nucleophilicity of the phenol hydrogen bonded to the carbonyl, which is a trend witnessed in other similarly functionalized scaffolds.[254-256] This methodology was followed to functionalize both **176** and **177** with glycine, valine and morpholine side chains. In Scheme **9.4**, the first number in parentheses correlates to the numbers of the compounds in the published paper and the SML number correlates to the sample numbers the compounds were given prior to biological testing.[201] Following esterification, 20% TFA in CH_2Cl_2 was used to remove the BOC group and afford the prodrug as the TFA salt. These salts were pure according to ^1H and ^{13}C NMR spectral analysis and submitted directly to the biological assays.



Scheme 9.4. Synthesis of **177** prodrugs

In addition to amino esters, the introduction of a tertiary amine in the form of a morpholine was likewise pursued (Scheme **9.4**). Once again, monoetherification at the hydroxyl group distal from the carbonyl was observed. Unlike the amino esters, the ether linkage is not readily cleaved to release the parent compound. The morpholine moiety was selected to improve water solubility and decrease plasma protein binding.[257] Previous SAR studies indicated that the naphthalene diol substructure is primarily solvent exposed and can tolerate modifications without adversely affecting the biological activity.[119,176,177] Hence, it was believed that the role of the morpholine moiety would be solely to improve the water solubility.

All prodrugs were submitted to the laboratory of Dr. Garth Powis for biological testing. The tests were performed with an estrogen positive, p53 positive human breast cancer cell line.[258] The cells were seeded at 4,000 cells/well in 96 well titer plates and allowed to attach overnight. After the cells were exposed to the prodrugs for 72 h, the viable cells were stained with 3-[4,5]-dimethylthiazol-2-yl-2,5-diphenyltetrazolium bromide (MTT). When MTT is reduced by the mitochondria, it forms non-water soluble violet crystals in the cell.[259,260] The plates were incubated for three h in the dark and the reduced MTT in the cells was measured spectrophotometrically at 540 nm.[261] All compounds were cytotoxic against the MCF-7 cell line with activities in the low μM range with compounds **200** and **202** being the most active (Table **9.3**).

The Trx/TrxR inhibition of the prodrugs was also measured. All of the Trx/TrxR activities were measured in microtiter plate calorimetric assays using purified human placenta Trx and recombinant human Trx.[262] In these assays, dithionitrobenzoic acid (DTNB), also known as Ellman's reagent,[263] is reduced via the enzyme mediated transfer of electrons from NADPH. The reduction of DTNB correlates to the increase of absorbance at 405 nm and indicates TrxR activity. Trx activity was measured via the Trx dependent reduction of insulin in the presence of TrxR and NADPH. DTNB reduction at the end of incubation was used to detect Trx activity. The *in vitro* tests of the prodrugs generated greater variability (Table **9.3**). The *in vitro* results of **201** were equipotent with **177**, but many of the other prodrugs did not match the activity of **177**.

Table 9.3. IC_{50} values (μM) for TrxR and human breast cancer growth inhibition

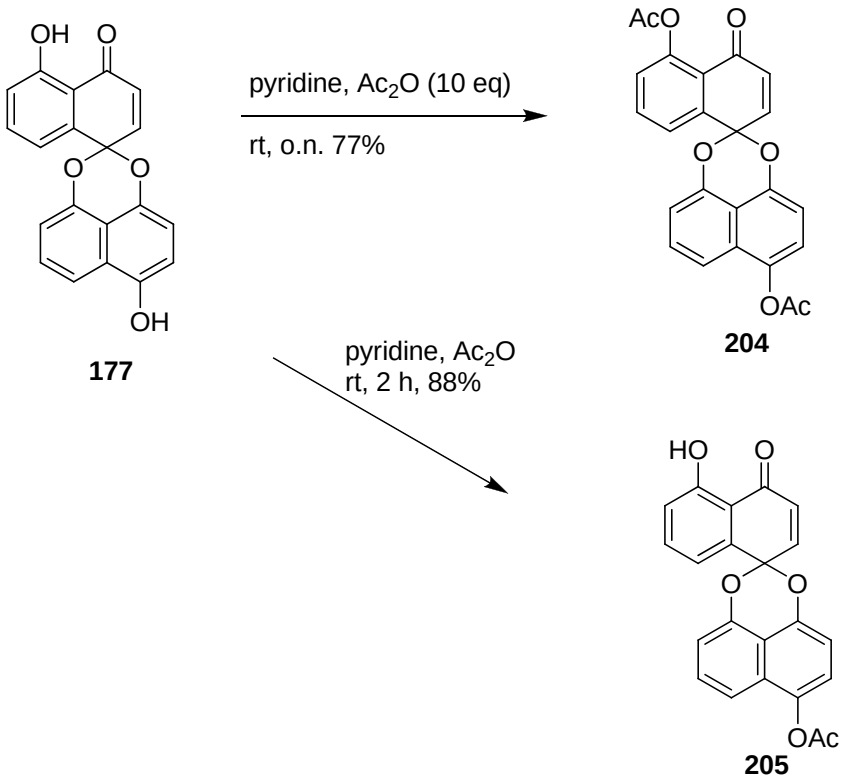
Entry	Compound	TrxR inhibitory activity (±SEM)	MCF-7 Growth Inhibition (±SEM)
1	**177**	0.20 ± 0.01	2.6 ± 0.1
2	**199** (SML-152)	1.8 ± 0.1	2.4 ± 0.1
3	**200** (SML-154)	0.62 ± 0.06	2.2 ± 0.1
4	**201** (SML-16)	0.28 ± 0.04	3.1 ± 0.3
5	**202** (SML-135)	1.6 ± 0.1	1.2 ± 0.3
6	**203** (SML-230)	4.2 ± 0.3	2.6 ± 0.6

SEM = the standard error of the mean from three separate experiments

The spontaneous hydrolysis of **201** during the enzyme assays was likely the source of some of the released active drug. The $t_{1/2}$ of **201** in water at room temperature with different pHs was measured.[119] At pH 4 and 7 the $t_{1/2}$ was 37 h and <1 h respectively. The $t_{1/2}$ in mouse plasma was <2 min. The short $t_{1/2}$ at pH 7 does not present a problem clinically because a formulation of **201** at pH 4 can be administered to patients. It was established according to HPLC analysis that the consumed prodrug was releasing **177**, as opposed to proceeding via an unproductive pathway or decomposing. The water solubility of **201** and **177** was measured to be 0.7 and <0.1 mg/mL, respectively. The improved water solubility of **201** validated the hypothesis that incorporation of amino esters can deliver prodrugs of greater water solubility than **177**. The excellent water solubility and promising *in vitro* results led to the selection of **201** for further biological testing *in vivo* against A-673 rhabdomyosarcoma in beige nude mice.

9.5 SEPARATION OF ENANTIOMERS OF 177

All chiral spiroketals were submitted for biological testing as racemic mixtures. Separation of the enantiomers of spirocycle **177** and testing of their individual biological activity was of interest. The most direct approach was a separation by chiral column HPLC. A Chiralcel AD-H column separated the enantiomers of **177** with retention times of 8.5 and 11.24 min. However, a preparative separation was limited by the low solubility of **177** of 1 mg/1.5 mL in a 15% *i*-PrOH/ hexanes solution. The low solubility that plagued the biological testing likewise hampered efforts towards chiral separation on quantities larger than several milligrams. A series of related analogues was therefore synthesized with the goal of improved solubility and good separation on the chiral column.



Scheme 9.5. Mono and bis-acetylated **177**

The mono- and bis-acetylation of **177** was first synthesized for improved solubility and ultimate separation of the enantiomers during chiral chromatography (Scheme **9.5**). The mono-acetate **205** was readily synthesized in 2 h by treating **177** with Ac_2O in pyridine. The assigned regioselectivity was based upon the chemical shifts of the phenol protons in ^{1}H NMR. The phenol hydrogen bonded to the carbonyl in **177** is at δ 12.18 whereas the non-hydrogen bonded phenol is at δ 8.99 in the ^{1}H NMR. The only phenol signal in the ^{1}H NMR spectra of **205** is at δ 12.15 which correlates to the hydrogen bonded phenol and hence the non-hydrogen bonded phenol is presumably acetylated. The bis-acetate **204** required 12 h for the less reactive phenol to be acetylated. Chiral HPLC conditions were screened with varying concentrations of *i*-PrOH in hexanes, but separation was not achieved. Bis-acetate **204** eluted in 10% *i*-PrOH in hexanes at

31.2 min as a single peak. Mono-acetate **205** eluted in 10% *i*-PrOH in hexanes as 2 unresolved peaks at 17.0 and 17.5 min. Other groups tethered to the **177** core were also explored. Mono-MOM protected **194** possessed a prohibitively long retention time for the separation of enantiomers, 35.8 min in 0.5% *i*-PrOH in hexanes. The free-based glycine prodrug **201** was unsuitable for chiral separation due to decomposition on the column. Ultimately, the best option was to separate **177** in small batches until 1 mg of each enantiomer was collected. The back up option would have been to esterify **177** with a chiral resolving agent, such as Mosher's ester.[264] Isolation of 0.5 mg of each **177** enantiomer was achieved on the Daicel AD-H analytical column, and *in vitro* biological testing established that both enantiomers demonstrated comparable activity. This supports the earlier stated hypothesis that the naphthalene diol does not participate in active site bonding or engage in any interactions critical for efficacy.[119]

In conclusion, a library of palmarumycin CP_1 analogues was synthesized in a rapid and efficient manner. The biological activity of the members was tested, and many members had improved solubility compared to spirocycle **177** while maintaining good to moderate biological activity in the inhibition of thioredoxin-thioredoxin reductase system. As a follow up to earlier studies, the enantiomers of **177** were separated and shown to exhibit similar biological activity.

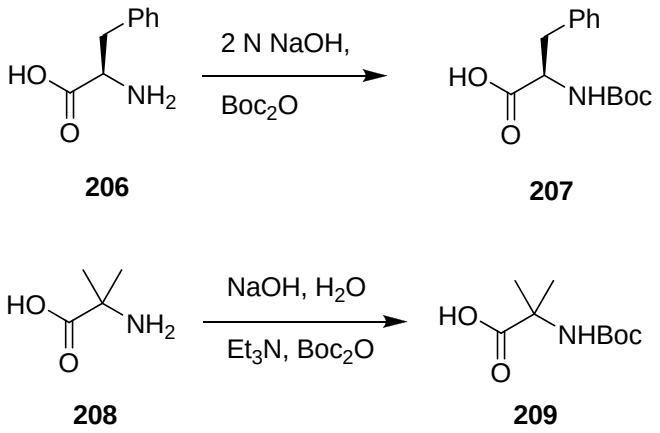
9.6 GENERATION II PRODRUGS

9.6.1 Amino acid containing prodrugs

The biological results from the first batch of prodrugs shown in Table **9.3** led to the pursuit of the synthesis of a series of prodrugs that was more resistant to metabolic cleavage.[201] The primary

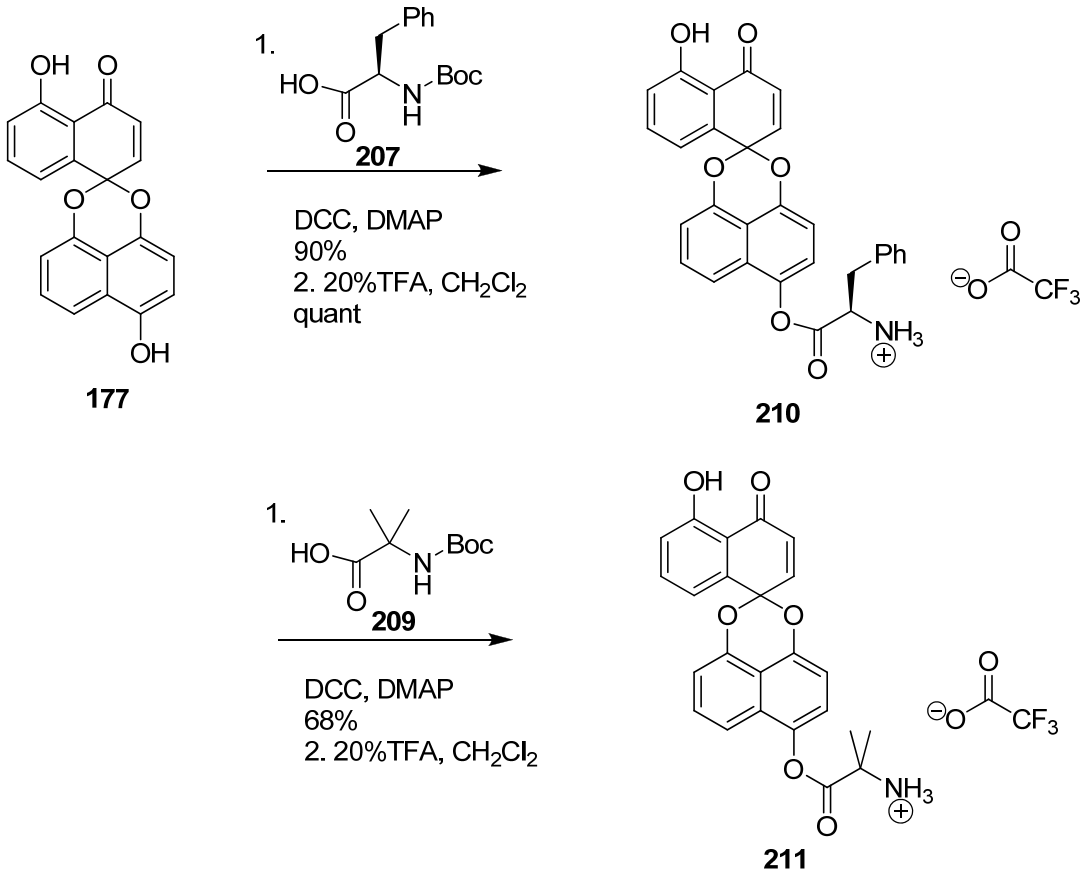
reason was to address the inconsistencies between the Trx inhibitory action and the MCF-7 growth inhibition. The rapid degradation of amino acids by peptidases can account the inconsistencies. For greater stability against proteolytic enzymes, there is a history of incorporating nonproteinogenic amino acids into the prodrug scaffold.[265,266] Clinically, sterically hindered amino esters can assist the prodrug in withstanding the acidic environment of the stomach and alkaline conditions of the intestines, and result in the absorption of the intact prodrug into the plasma.[267] For greater stability in aqueous buffer, sterically hindered amino acids have been utilized to increase the half life of the prodrug to clinically viable times needed for administration to a patient.[268] The goal was to synthesize a second generation library of prodrugs of **177** to overcome the low water solubility of **177** and produce an even stronger inhibitor of Trx/TrxR in both *in vitro* and *in vivo* assays.

As an extension of the prodrug studies, a second generation series of esters of **177** with phenylglycine (**206**) and α-aminoisobutyric acid (AIB, **207**) was synthesized. Both substituents, in particular the AIB residue, add to the steric hindrance near the ester functionality and decrease the rate of hydrolytic cleavage.[267] The amino esters were prepared using a similar protocol as for the generation I prodrugs. BOC-protection of both amino acids afforded **207** and **209** in good yields (Scheme **9.6**).



Scheme 9.6. BOC-protection of AIB (**208**) and phenylalanine (**206**)

DCC was the coupling reagent of choice for the esterification between the amino esters and **177** due to its previous success. Protected phenylalanine (**207**) was esterified in good yield and the more hindered AIB analogue was obtained in moderate, but acceptable yield (Scheme **9.7**). Once again, selective coupling occurred at the phenol that was not deactivated. 20% TFA in CH_2Cl_2 removed the Boc group and concentration under reduced pressure delivered the salts **210** and **211**. These salts were pure according to ^{1}H and ^{13}C NMR analysis and submitted directly to the biological assays without further purification.

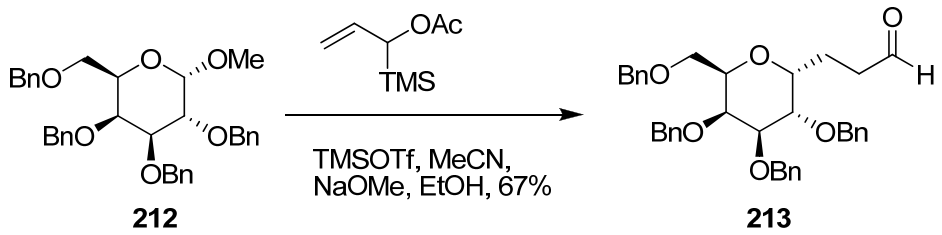


Scheme 9.7. Prodrugs containing amino acids **207** and **209**

9.6.2 Carbohydrate linked prodrugs

Prodrugs that were not based on amino ester substituents were also considered, such as glycosides. A carbon-linked *C*-glycoside was of particular interest.[269] This modification would introduce a very polar, non-cleavable group. There are numerous approaches for *C*-glycoside synthesis, including the Stille coupling between tin glycals and sulfonyl chlorides[270] or a cross metathesis between two olefins.[271] The Wipf group has a history of *C*-glycoside synthesis and a

recent example involves the allyl silane addition into sugar **212** to afford *C*-glycoside **213** (Scheme **9.8**).[272]



Scheme 9.8. Synthesis of C-glycoside **213**

Glycosylated palmarumycin prodrugs are interesting for several reasons. A variety of sugar containing cancer inhibitors has been reported in the literature, and the anti-cancer activity of *N*-acetyl-D-mannosamine *n*-butyrate esters was found to be dependent on the glycosyl residue (**214**, Figure **9.9**).[273] Carbohydrates have been used as prodrugs for a variety of applications including, but not limited to, improving solubility,[274,275] biological site specificity,[276] tumor therapy,[277] GLUT-1 assisted transport across the blood brain barrier,[278] and colon specific targeting.[279] The improved water solubility of sugar-based prodrugs was of greatest interest.[280]

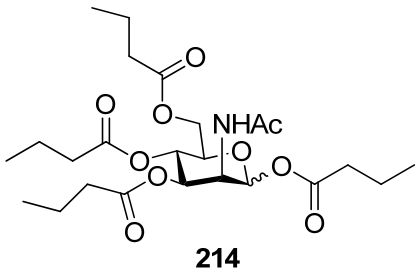
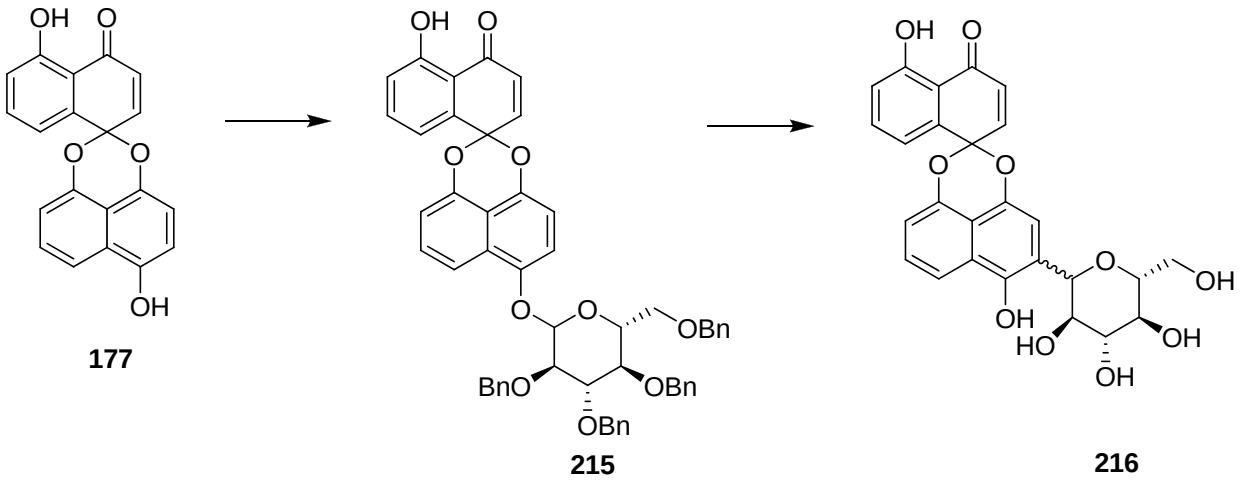


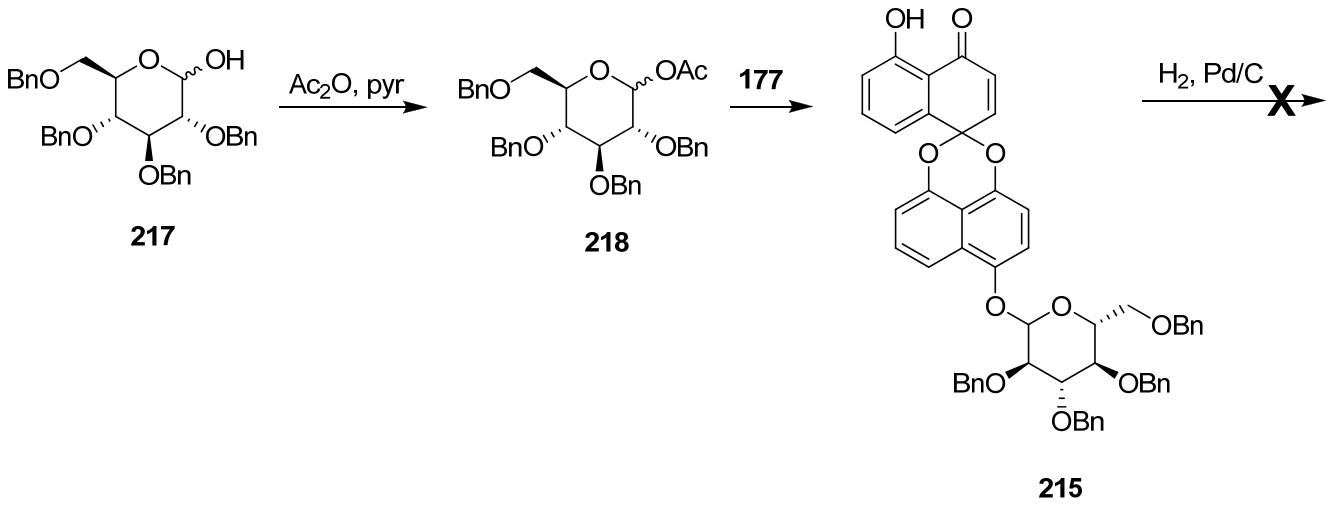
Figure 9.9. Sugar based cancer inhibitor

The phenol moiety was taken advantage of for glycosylation (Scheme **9.9**). Acidic conditions can be used to catalyze a sugar migration from the phenolic oxygen to the aromatic carbon.[281] These protocols commenced with phenol glycosylation with glycosyl phosphates[282] fluorides[283] or chloroimidates followed by acid promoted migration.[284-286] The synthesis of *C*-glycosides utilizing various sugars[287] such as *O*-benzyl glucals,[288] the 2-deoxy variants,[289-291] and tetra-protected glucose were considered. Ultimately, the most direct, readily modified and commercially available D-glucose was selected to glycosylate **177**.



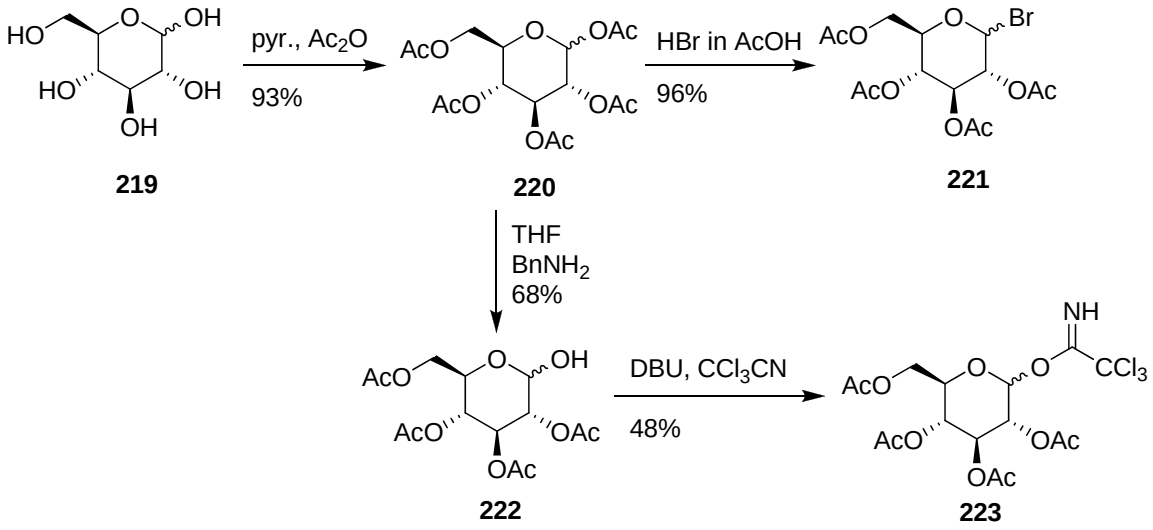
Scheme 9.9. Proposed path to *C*-glycosylated **177**

The synthesis began with benzyl protected glucose **217** (Scheme **9.10**).[282] Treatment of **217** with Ac_2O and pyridine provided the anomeric acetate **218**. The glycosylation of **177** in the presence of $BF_3{\cdot}OEt_2$,[292] $Sc(OTf)_3$[293] and various drying agents[294] failed to deliver the desired pyran migration. *O*-glycosylated **215** could still provide the desired solubilizing effect and hence the removal of the benzyl protecting groups to generate the final prodrug was explored.



Scheme 9.10. Glycosylation of **177**

Problems were encountered with the hydrogenation of the benzylic ethers.[295] Palladium on carbon[296] and Wilkinson's catalyst[297] were screened, but the starting material either remained or there was poor mass recovery. The possibility of reducing the enone was a concern which could be addressed by transiently protecting the double bond with methanol[123] or thiophenol.[298] However, these modifications were also unsuccessful.

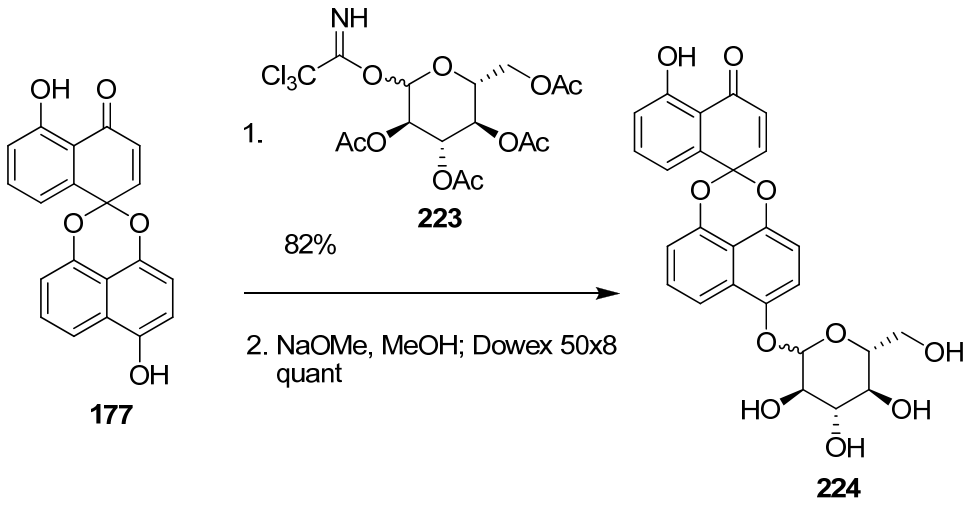


Scheme 9.11. Synthesis of acetylated imidate **223**

D-Glucose can be protected with acetyl groups and converted to the anomeric chloroimidate, fluoride[287] or bromide[299] in preparation for coupling. Acetate **220** was synthesized by treating D-glucose (**219**) with acetic anhydride in pyridine (Scheme **9.11**), but did not glycosylate **177**. The bromo derivative **221** was synthesized in good yield by treatment of **220** with HBr in AcOH, but this compound also did not glycosylate **177**.[300] Acetate **220** was mono-deprotected with benzyl amine to give **222**, and subsequently treated with trichloroacetonitrile to deliver the chloroimidate **223** in modest yield.

Chloroimidate **223** was used to glycosylate **177** under standard Schmidt glycosylation conditions (Scheme **9.12**).[301] Instead of the desired O-C migration, only the *O*-glycosylated product was isolated. The limitation of this migration with acetylated sugars has previously been noted in the literature and attributed to the electron withdrawing nature of the acetates.[302] When the acetates were exchanged to benzyl protecting groups, the migration proceeded. *O*-Glycosylated **224** was also a suitably soluble prodrug, and the acetate groups were removed with base. There are some very mild methods for acetate removal. It is possible to deprotect the

acetates from a sugar in the presence of sensitive moieties, such as a β-lactam, with NEt_3, H_2O and MeOH.[303,304] NaOMe is also a common base used for the removal of acetate groups on a sugar.[305,306] The deprotection was performed with NaOMe and a Dowex 50 x 8 quench to afford **224**, which was found to be soluble in water at a concentration of 1.4 mg/mL.



Scheme 9.12. Glycosylation of **177** and deprotection

9.6.3 Biological data for generation II prodrugs

The second generation prodrugs were submitted to the laboratory of Dr. Garth Powis for biological testing. The relative metabolic stabilities of the new prodrugs were compared to the first generation glycine prodrug **201** (Table **9.4**). The entry numbers in parentheses in the table correspond to the code names given to the compounds prior to biological testing. The prodrugs were incubated at 33 °C at a concentration of 1 mg/mL in ES1 mouse and human plasma and their stability was measured by calculating the formation of the parent drug over the first 20 min of incubation. HPLC analyses of the mixture and comparison of the relative areas under the

generated peaks for the parent compound and starting prodrug provided information about the rate of hydrolysis. The unit of "area/20 min" in the table refers to the area under the peak in the HPLC trace corresponding to parent compound **177** relative to the area under the peak in the HPLC trace corresponding to the prodrug after 20 min of incubation. Therefore, a large area/20 min value correlates to lower metabolic stability. The two most promising new prodrugs were carbohydrate **224** and the AIB derivative **211**. Both agents were more stable in plasma than the lead compound **177** and were therefore selected for further biological testing. The phenylalanine prodrug **210** had low water solubility and was not studied in mouse plasma.

Table 9.4. Relative plasma stabilities of prodrugs (in area/20 min)

Entry	**Mouse plasma** (area/20 min)	**ES1 mouse plasma** (area/20 min)	**Human plasma** (area/20 min)
201 (3-SML-16)	350	210	135
224 (EEE-86-III)	20	17	70
211 (EEE-263-II)	42	82	81
210 (EEE-273-II)	19	n.a.	n.a

In addition to the biological studies, the logP values of the prodrugs were calculated. The LogP value predicts the water solubility of a molecule. The logP is a partition coefficient for the concentration of a given compound between octanol and water. Most optimally soluble drugs fall into the logP range of 0-3,[215] and the Lipinski rules state that the logP of a viable drug candidate should be less than 5.[307] One method to calculate logP is based on work by Cates and evaluates the hydrophobic and hydrophilic properties of each functional group.[308] There are also various computer programs available for the calculation of log P such as ALOGPs at the Virtual Computational Chemistry Lab (www.vcclab.org). This program was developed with 12908

molecules from the PHYSPROP database using 75 E-state indices. Sixtyfour neural networks were trained using 50% of molecules selected by chance from the whole set.[309-311] The logP values for **201**, **211**, **210** and **224** were calculated to be 1.90 ± 1.49, 2.53 ± 1.53, 3.64 ± 1.73 and 2.24 ± 0.89. A low level calculation of log P using ChemBioDraw Ultra 11.0 predicted the logP values of **201**, **211**, **210** and **224** to be 1.74, 2.14, 3.13 and 1.95 respectively. Both programs predicted that the phenylalanine prodrug **210** would be the least soluble in water, which is an attribute that was observed experimentally (Table **9.5**).

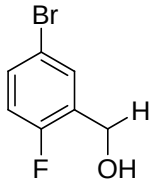
The water solubilities of the AIB **211**, sugar **224** and phenylalanine **210** prodrugs were experimentally determined and compared to the solubility of the glycine prodrug **201** (Table **9.5**).[119] Compound **177** and generation I prodrug **201** have a water solubility of <0.1 mg/mL and 0.7 mg/mL, respectively. The water solubilities of the generation II prodrugs **211**, **224** and **210** were 4.5, 1.4 and <0.1 mg/ mL, respectively. Prodrug **210** had a low water solubility, a property that hampered biological testing, of <0.1 mg/mL. Gratifyingly, the other prodrugs had improved water solubility.

Table 9.5. Water solubility of prodrugs

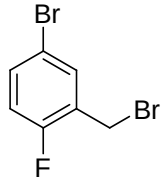
Compound	**Solubility** (mg/mL)
201	0.7
211	4.5
224	1.4
210	<0.1

10.0 SYNTHESIS OF 177 & PRODRUGS EXPERIMENTAL PART

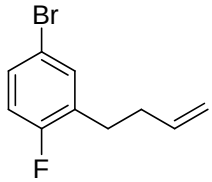
General: All moisture sensitive reactions were performed in flame-dried or oven-dried glassware under a nitrogen atmosphere. THF and Et_2O were distilled over Na/benzophenone, while pyridine and triethylamine were distilled over CaH_2. Hexanes and ethyl acetate were distilled prior to use. All other reagents and solvents were used as received unless otherwise noted. Analytical thin layer chromatography was performed on pre-coated silica gel 60 F-254 plates available from Merck. Flash chromatography was performed using silica gel (230-400 mesh) available from Baker. NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR using a Bruker Avance 300 with XWIN-NMR software. Chemical shifts (δ) are expressed relative to the NMR solvent peak. IR spectra were obtained with a Nicolet Aviator 360 FT-IR, ATR-IR spectra were measured with a Smiths IdentifyIR, optical rotations were measured with a Perkin-Elmer 241 polarimeter and mass spectra were obtained on a double focusing instrument. EI mass spectra were obtained with VG Autospec and ESI mass spectra with Q-TOF API US.



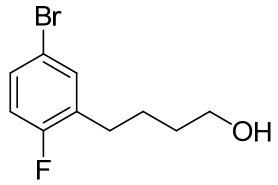
(5-Bromo-2-fluorophenyl)methanol.[312] A solution of 5-bromo-2-fluorobenzaldehyde (**183**) (25 g, 0.12 mol) in MeOH (310 mL) was cooled to 0 °C and treated with $NaBH_4$ (6.1 g, 0.16 mol) in 4 batches over 10 min. The reaction mixture was stirred for 20 min, quenched with 1.0 M HCl and extracted with Et_2O (2x). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the benzyl alcohol **183** as a light yellow oil which was used without further purification: Rf 0.1 (19:1, hexanes:EtOAc); ^{1}H NMR δ 7.59 (dd, 1 H, *J* = 6.6, 2.4 Hz), 7.41-7.36 (m, 1 H), 6.93 (t, 1 H, *J* = 9.0 Hz), 4.96 (bs, 1 H), 2.02 (bs, 2H).



4-Bromo-2-(bromomethyl)-1-fluorobenzene.[312] A solution of (5-bromo-2-fluorophenyl)methanol (25.0 g, 0.123 mol) in THF (245 mL) was cooled to 10 °C and treated with PPh_3 (33.1 g, 0.126 mol) followed by NBS (21.5 g, 0.121 mol). The reaction mixture was warmed to room temperature, stirred for 30 min, concentrated under reduced pressure and purified by column chromatography on SiO_2 (19:1, hexanes:EtOAc) to afford 22.8 g (68%) of the benzyl bromide as an orange oil: Rf 0.7 (19:1, hexanes:EtOAc); ^{1}H NMR δ 7.52 (dd, 1H, *J* = 6.6, 2.5 Hz), 7.41 (dd, 1 H, *J* = 9.0, 6.6, 2.5 Hz), 6.96 (t, 1 H, *J* = 9.0 Hz), 4.44 (s, 2H).

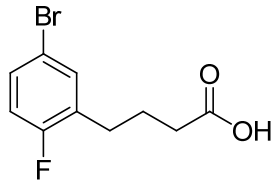


4-Bromo-2-(but-3-enyl)-1-fluorobenzene. A solution of 4-bromo-2-(bromomethyl)-1-fluorobenzene (22.8 g, 83.8 mmol) in THF (95 mL) was cooled to 0 °C, treated with a 1.0 M solution of allyl magnesium bromide in THF (125.4 mL, 0.1254 mol), warmed to room temperature and stirred for 1 h. The reaction mixture was cooled to 0 °C, quenched with sat. NH_4Cl, diluted with H_2O, and extracted with Et_2O (2x). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 19.2 g (quant.) of the olefin as a clear oil which was used without further purification. An analytically pure sample was obtained by column chromatography on SiO_2 (9:1, hexanes:EtOAc): Rf 0.8 (9:1, hexanes:EtOAc); ^{1}H NMR δ 7.32-7.25 (m, 2H), 6.89 (t, 1H, *J* = 9.0 Hz), 5.89-5.73 (m, 1 H), 5.11-4.96 (m, 2 H), 2.70 (t, 2 H, *J* = 7.7 Hz), 2.38-2.25 (m, 2 H); MS (EI) *m/z* (rel intensity) 228 (M^+,6), 189 (70), 187 (73), 108 (100), 107 (80); HRMS (EI) calculated for $C_{10}H_{10}BrF$ 227.9950, found 227.9948.



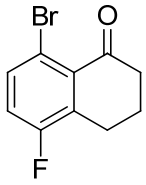
4-(5-Bromo-2-fluorophenyl)butan-1-ol. A solution of 4-bromo-2-(but-3-enyl)-1-fluorobenzene (19.20 g, 84.21 mmol) in THF (76 mL) was slowly transferred to a 2.0 M solution of BH_3·DMS in THF (82.9 mL, 0.166 mol) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 2 h, cooled to 0 °C and quenched with 2.0 N NaOH (136.9 mL), which resulted in a large amount of gas evolution. The reaction mixture was treated with 30% H_2O_2 (91.24 mL), stirred at room temperature for 12 h, diluted with H_2O and extracted with Et_2O (2x). The combined organic extracts were washed with sat. NH_4Cl , H_2O and brine, dried ($MgSO_4$), filtered

and concentrated under reduced pressure to afford the alcohol as a clear oil which was used without further purification: Rf 0.4 (7:3, hexanes:EtOAc); ^{1}H NMR δ 7.32-7.23 (m, 2 H), 6.88 (t, 1 H, *J* = 9.0 Hz), 3.66 (t, 2 H, *J* = 6.2 Hz), 2.63 (t, 2 H, *J* = 7.1 Hz), 1.70-1.55 (m, 4 H); MS (EI) *m/z* (rel intensity) 246 (M^+, 22), 200 (85), 187 (54), 149 (53), 134 (35), 109 (58), 108 (90), 107 (100); HRMS (EI) calculated for $C_{10}H_{12}BrFO$ 246.0056, found 246.0464.

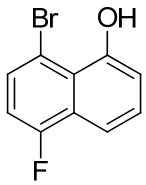


4-(5-Bromo-2-fluorophenyl)butanoic acid (184). A solution of CrO_3 (16.72 g, 0.1672 mol) in H_2O (60.8 mL) was cooled to 0 °C and treated with concentrated H_2SO_4 (15.2 mL). A solution of 4-(5-bromo-2-fluorophenyl)butan-1-ol (84.21mmol) in acetone (380 mL) was cooled to 0 °C, treated with the chromium solution dropwise via addition funnel, stirred for 1 h, warmed to room temperature and stirred for 1 h. The reaction mixture was cooled back to 0 °C and quenched dropwise with *i*-PrOH until the precipitation of dark green solids ceased. The reaction mixture was filtered through celite, washed with acetone and concentrated under reduced pressure. The filtrate was dissolved in Et_2O and extracted with 10% NaOH. The aqueous extract was washed with Et_2O, acidified to pH 2 with HCl (conc.) and extracted with Et_2O (2x). The combined acidified organic extracts were dried ($MgSO_4$), filtered and concentrated. Recrystallization (hexanes) of the crude product afforded 6.9 g (36%) of acid **184** as a white solid: Rf 0.3 (7:3, hexanes:EtOAc); ^{1}H NMR δ 7.33-7.27 (m, 2 H), 6.91 (t, 1 H, *J* = 9.0 Hz), 2.68 (t, 2 H, *J* = 7.6 Hz), 2.40 (t, 2H, *J* = 7.5 Hz) 1.95 (app pent, 2 H, *J* = 7.5 Hz); MS (EI) *m/z* (rel intensity) 260

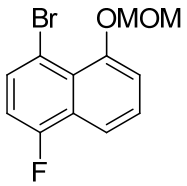
(M^+, 25), 201 (71), 200 (72), 189 (52), 187 (54), 108 (87), 107 (100); HRMS (EI) calculated for $C_{10}H_{10}BrFO_2$ 259.9848, found 259.9852.



8-Bromo-5-fluoro-3,4-dihydronaphthalen-1(2*H*)-one. H_3PO_4 (sat, 30.8 mL) was treated with P_2O_5 (69.3 g, 0.488 mol) with continuous stirring to afford a thick solution of PPA. Acid **184** (3.84 g, 14.8 mmol) was added to the freshly prepared PPA solution, heated to 120 °C for 1.5 h, cooled to room temperature and poured into an ice/H_2O mixture. The suspension was agitated until all the solids dissolved and extracted with Et_2O (2x). The combined organic extracts were washed with 5% NaOH, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 2.281 g (64%) of the product as an orange solid which was used without further purification. An analytically pure sample was attained by column chromatography on SiO_2 (4:1, hexanes:EtOAc): Rf = 0.6 (7:3, hexanes:EtOAc); ^{1}H NMR δ 7.54 (dd, 1H, *J* = 8.7, 5.1 Hz), 7.05 (t, 1 H, *J* = 8.7 Hz), 2.97 (t, 2H, *J* = 6.2 Hz), 2.71 (t, 2 H, *J* = 6.2 Hz), 2.14 (pent, 2 H, *J* = 6.2 Hz); MS (EI) *m/z* (rel intensity) 242 (M^+, 37), 227 (5), 216 (46), 214 (49), 186 (24), 133 (35), 107 (100), 81 (39); HRMS (EI) calculated for $C_{10}H_8BrFO$ 241.9743, found 241.9733.

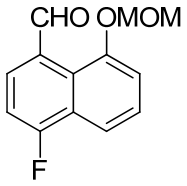


8-Bromo-5-fluoronaphthalen-1-ol (185). A solution of 8-bromo-5-fluoro-3,4-dihydronaphthalen-1(2*H*)-one (2.28 g, 9.43 mmol) in THF (42 mL) was treated with trimethylphenylammonium tribromide (3.52 g, 9.37 mmol) and white solids precipitated out of solution. The reaction mixture was stirred for 30 min, quenched with H_2O and extracted with EtOAc (2x). The combined organic extracts were washed with H_2O, dried ($MgSO_4$), filtered and concentrated under reduced pressure. A solution of the crude product in DMF (42 mL) was treated with LiBr (1.70 g, 19.6 mmol) and Li_2CO_3 (2.22 g, 30.0 mmol), and heated to 130 °C for 1 h. The reaction mixture was cooled to room temperature, filtered and washed with EtOAc (80 mL, 3x). The EtOAc filtrate was washed with H_2O (80 mL, 3x), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 0.850 g (40%) of the naphthol as an off white solid: Rf 0.4 (4:1, hexanes:EtOAc); ^{1}H NMR δ 8.10 (s, 1 H), 7.73 (d, 1 H, *J* = 8.3 Hz), 7.56 (dd, 1H, *J* = 8.3, 5.8 Hz), 7.48 (t, 1 H, *J* = 8.1 Hz), 7.15 (d, 1 H, *J* = 8.1 Hz), 6.97 (dd, 1 H, *J* = 9.6, 8.3 Hz).

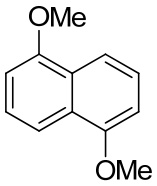


4-Bromo-1-fluoro-5-(methoxymethoxy)naphthalene. A solution of naphthol **185** (0.850 g, 3.73 mmol) in DMF (17.8 mL) was cooled to 0 °C, treated with NaH (60% dispersion in mineral oil, 0.14 g, 3.6 mmol) warmed to room temperature, stirred for 30 min and cooled back to 0 °C. The reaction mixture was treated with MOMCl (0.38 mL, 5.0 mmol), warmed to room temperature, stirred for 30 min, cooled to 0 °C and quenched with H_2O. It was extracted with EtOAc (3x), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by

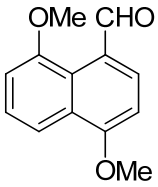
column chromatography on SiO_2 (9:1, hexanes:EtOAc) afforded 0.709 g (67%) of the naphthalene as a yellow solid: Rf 0.6 (9:1, hexanes:EtOAc); ^{1}H NMR δ 7.79 (dt, 1 H, *J* = 8.4, 1.0 Hz), 7.69 (dd, 1 H, *J* = 8.3, 5.4 Hz), 7.47 (t, 1 H, *J* = 8.1 Hz), 7.26 (bd, 1 H, *J* = 7.7 Hz), 6.97 (dd, 1 H, *J* = 9.6, 8.3 Hz), 5.34 (s, 2 H), 3.60 (s, 3 H).



4-Fluoro-8-(methoxymethoxy)naphthalene-1-carbaldehyde (186). A solution of 4-bromo-1-fluoro-5-(methoxymethoxy)naphthalene (4.589 g, 1.616 mmol) in Et_2O (92 mL) was cooled to −78 °C and treated with a 1.7 M solution of *t*-BuLi in pentane (20.7 mL, 35.2 mmol) dropwise. The reaction mixture was stirred for 15 min, treated with DMF (3.68 mL, 53.3 mmol), warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with H_2O, extracted with EtOAc (2x), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (7:3, hexanes:EtOAc) afforded 3.0 g (79%) of **186** as a yellow solid: Rf 0.3 (7:3, hexanes:EtOAc); ^{1}H NMR δ 11.08 (s, 1 H), 7.99 (dd, 1 H, *J* = 8.4, 5.7 Hz), 7.85 (d, 1 H, *J* = 8.4 Hz), 7.53 (t, 1 H, *J* = 8.1 Hz), 7.37 (d, 1 H, *J* = 7.5 Hz), 7.22 (d, 1 H, *J* = 8.4 Hz), 5.40 (s, 2 H), 3.54 (s, 3 H); MS (EI) *m/z* (rel intensity) 234 (M^+, 4), 189 (24), 133 (100), 81 (39); HRMS (EI) calculated for $C_{13}H_{11}O_3F$ 234.0692, found 234.0698.

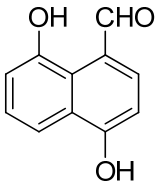


1,5-Dimethoxynaphthalene (188).[313] A dark purple solution of 1,5-dihydroxynaphthalene (**187**) (100 g, 0.63 moles) in 2.0 N NaOH (125 mL) at 0 °C was slowly treated with dimethyl sulfate (120 mL, 1.26 moles) in two 60 mL batches over 10 minutes. The addition was very exothermic and light beige solids precipitated out of solution. Additional H_2O (100 mL) was added to the thick suspension. The reaction mixture was stirred for 2 h, quenched with 2.0 M NaOH (120 mL), diluted with water and extracted with CH_2Cl_2 (2x). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by chromatography on SiO_2 (CH_2Cl_2) to afford 64 g (55%) of **188** as a beige solid: Rf 0.6 (7:3, hexanes:EtOAc); ^{1}H NMR δ 7.83 (d, 2 H, *J* = 8.4 Hz), 7.38 (t, 2 H, *J* = 8.1 Hz), 6.79 (d, 2 H, *J* = 8.1 Hz), 4.00 (s, 6 H); MS (EI) *m/z* (rel intensity) 188 (M^+, 100), 173 (65), 115 (46); HRMS (EI) calculated for $C_{12}H_{12}O_2$ 188.0837, found 188.0833.

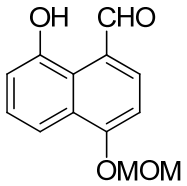


4,8-Dimethoxynaphthalene-1-carbaldehyde (189).[314] A suspension of naphthaldehyde **188** (9.70 g, 50.6 mmol) in toluene (9.83 mL) and DMF (5.93 mL, 6.36 mmol) was cooled to 0 °C and treated with $POCl_3$ (5.89 mL, 63.2 mol) dropwise. The reaction mixture was stirred at 0 °C for 30 min, heated to reflux for 12 h, cooled to room temperature, poured into 2.0 N NaOH and extracted with EtOAc. The combined organic extracts were washed with 1.0 N HCl, H_2O and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 9.26 g (83%) of **189** as a light yellow solid: Rf 0.4 (7:3, hexanes:EtOAc); ^{1}H NMR δ 11.06 (s, 1 H), 8.08 (d, 1 H, *J* = 8.4 Hz), 7.96 (dd, 1 H, *J* = 8.4, 0.9 Hz), 7.45 (t, 1 H, *J* = 8.1 Hz), 7.04 (d, 1 H, *J* = 7.8 Hz),

6.92 (d, 1 H, J = 8.4 Hz), 4.06 (s, 3 H), 4.02 (s, 3 H); MS (EI) *m/z* (rel intensity) 216 (M^+, 100), 201 (31), 185 (26), 173 (25), 115 (80), 102 (34); HRMS (EI) calculated for $C_{13}H_{12}O_3$ 216.0786, found 216.0785.

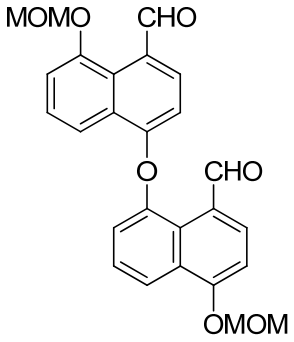


4,8-Dihydroxynaphthalene-1-carbaldehyde (190). A solution of naphthaldehyde **189** (9.26 g, 42.9 mmol) in tetrachloroethane (89 mL) was treated with $AlCl_3$ (26.88 g, 0.2013 mol) and heated to 75 °C for 1 h. The reaction mixture was cooled to room temperature, poured into an ice and 1.0 M HCl mixture and stirred while dark green solids precipitated out of solution. The solids were filtered, washed with H_2O and dried under high vacuum to afford 7.784 g (91%) of carbaldehyde **190** as an off white solid: ^{1}H NMR (DMSO-d_6) δ 11.51 (s, 1 H), 11.38 (s, 1 H), 10.51 (s, 1 H), 8.05 (d, 1 H, J = 8.1 Hz), 7.78 (d, 1 H, J = 8.1 Hz), 7.43 (t, 1 H, J = 8.0 Hz), 7.11 (d, 1 H, J = 7.5 Hz), 7.02 (d, 1 H, J = 8.1 Hz); MS (EI) *m/z* (rel intensity) 188 (M^+, 44), 187 (34), 117 (100), 115 (69), 91 (51); HRMS (EI) calculated for $C_{11}H_8O_3$ 188.0473, found 188.0469.



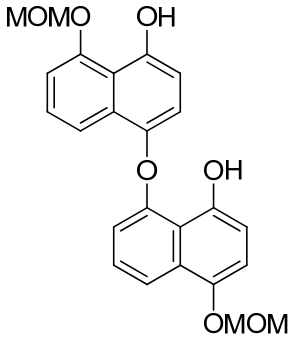
8-Hydroxy-4-(methoxymethoxy)naphthalene-1-carbaldehyde (191).[119] A solution of naphthaldehyde **190** (5.00 g, 26.7 mmol) in acetone (125 mL) was treated with K_2CO_3 (8.82 g, 88.8 mmol) followed by MOMCl (2.6 mL, 0.034 mol) and stirred for 1.5 h. The reaction

mixture was quenched with H_2O, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by column chromatography through a 3 cm plug of SiO_2 (CH_2Cl_2) to afford 3.78 g (62%) of **191** as a yellow solid: Rf 0.3 (7:3, hexanes:EtOAc); ^{1}H NMR δ 12.12 (d, 1 H, *J* = 0.9 Hz), 9.67 (d, 1H, *J* = 0.9 Hz), 8.00 (d, 1 H, *J* = 8.2 Hz), 7.90 (dd, 1 H, *J* = 8.3, 1.2 Hz), 7.51 (t, 1H, *J* = 8.0 Hz), 7.20 (dd, 1 H, *J* = 7.8, 1.2 Hz), 7.16 (d, 1H, *J* = 8.2 Hz), 5.50 (s, 2 H), 3.57 (s, 3H); MS (EI) *m/z* (relative intensity) 232 (M^+, 100), 202 (37), 131 (77), 115 (65), 102 (56), 77 (62); HRMS (EI) calculated for $C_{13}H_{12}O_4$ 232.0736, found 232.0741.



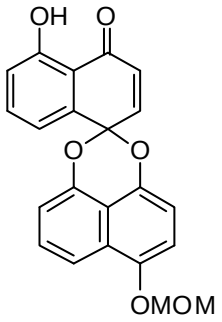
4-(1-(Methoxymethoxy)-4-formylnaphthalen-5-yloxy)-8-(methoxymethoxy)naphthalene-1-carbaldehyde (192).[119] A solution of fluoride **186** (2.00 g, 8.54 mmol) and naphthol **191** (3.00 g, 12.9 mmol) in CH_3CN (30 mL) was treated with Barton's Base (2.63 mL, 13.2 mmol) and the solution turned dark brown. The reaction mixture was stirred at 80 °C for 5 h, cooled to room temperature, poured into 1.0 M HCl and extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with H_2O, dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by column chromatography on SiO_2 (7:3, hexanes:EtOAc) to afford 2.849 g (74%) of **192** as a light yellow solid: Rf 0.4 (3:2, EtOAc:hexanes); ^{1}H NMR δ 11.09 (s, 1H), 10.94 (s, 1H), 8.31 (dd, 1H, *J* = 8.4, 1.1 Hz), 8.17 (d, 1H, *J* = 8.3 Hz), 8.11 (dd, 1H, *J* = 8.3, 1.1 Hz), 7.89

(d, 1 H, *J* = 8.1 Hz), 7.53 (t, 1H, *J* = 8.4 Hz), 7.50 (t, 1H, *J* = 7.8 Hz), 7.41 (dd, 1H, *J* = 7.8, 1.1 Hz), 7.25 (d, 1H, *J* = 8.3 Hz), 7.21 (dd, 1H, *J* = 7.7, 1.0 Hz), 6.81 (d, 1H, *J* = 8.1 Hz), 5.51 (s, 2H), 5.44 (s, 2H), 3.59 (s, 3H), 3.56 (s, 3H); MS (EI) *m/z* (rel intensity) 446 (M^+, 82), 402 (76), 401 (100), 171 (54), 117 (92), 115 (96); HRMS (EI) calculated for $C_{26}H_{22}O_7$ 446.1366, found 446.1351.



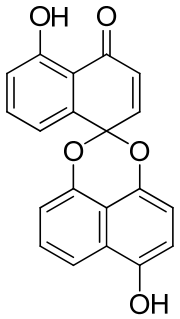
4-(1-Hydroxy-4-(methoxymethoxy)naphthalen-8-yloxy)-8-(methoxymethoxy)naphthalen-1-ol (193).[119] A solution of aldehyde **192** (2.849 g, 6.386 mmol) in CH_2Cl_2 (133 mL) was treated with mCPBA (2.85 g, 16.5 mmol), stirred for 15 h, treated with 10% $Na_2S_2O_3$ (133 mL) and stirred for 1 h. The reaction mixture was diluted (CH_2Cl_2), washed with sat. $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The reaction mixture was purified by column chromatography on SiO_2 (3:2, hexanes:EtOAc) to afford 1.857 g (61%) of the formate as a yellow foam: Rf 0.6 (3:2, EtOAc:hexanes); ^{1}H NMR δ 8.38 (s, 1H), 8.16 (d, 1H, *J* = 8.4 Hz), 8.08 (s, 1H), 7.97 (d, 1H, *J* = 8.4 Hz), 7.46 (t, 1 H, *J* = 8.0 Hz), 7.42 (t, 1H, *J* = 8.0 Hz), 7.25 (d, 1H, masked), 7.16 (d, 1H, *J* = 8.4 Hz), 7.06 (d, 1H, *J* = 8.4 Hz), 7.00 (d, 1H, *J* = 8.0 Hz), 6.68 (d, 1H, *J* = 8.0 Hz), 5.36 (s, 2H), 5.32 (s, 2 H), 3.57 (s, 3 H), 3.55 (s, 3 H); MS (ESI-Q-TOF) *m/z* (relative intensity) 501 ($[M+Na]^+$, 100); HRMS (ESI-Q-TOF) calculated for $C_{26}H_{22}O_9Na$ 501.1162, found 501.1164.

A crude solution of the formate (1.875 g, 39.23 mmol) in MeOH (44.5 mL) and THF (44.5 mL) was cooled to 0 °C and treated with $NaBH_4$ (0.339 g, 9.00 mmol). The reaction mixture was stirred at 0 °C for 3 h, quenched with H_2O, extracted with EtOAc (2x), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was immediately subjected to column chromatography on SiO_2 (3:2, hexanes:EtOAc) to afford 1.186 g (72%) of **193** as a white foam: Rf 0.5 (3:2, hexanes:EtOAc); ^{1}H NMR δ 9.36 (s, 1 H), 8.99 (s, 1 H), 7.89 (dd, 1 H, *J* = 8.5, 1.0 Hz), 7.62 (dd, 1 H, *J* = 8.5, 1.0 Hz), 7.30 (t, 1 H, *J* = 8.2 Hz), 7.25 (d, 1 H, *J* = 8.3 Hz), 7.17-7.12 (m, 2 H), 6.91 (d, 1 H, *J* = 8.3 Hz), 6.90 (d, 1 H, *J* = 8.3 Hz), 6.46 (dd, 1 H, *J* = 7.7, 0.9 Hz), 5.49 (s, 2 H), 5.32 (s, 2 H), 3.62 (s, 3 H), 3.56 (s, 3 H); MS (EI) *m/z* (rel intensity) 422 (M^+, 15), 149 (100), 117 (77), 75 (42); HRMS (EI) calculated for $C_{24}H_{22}O_7$ 422.1366, found 422.1362.



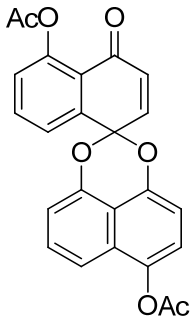
5-Hydroxy-6'-(methoxymethoxy)-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one (194).[119] A solution of **193** (0.600 g, 1.42 mmol) in CH_3CN (22 mL) was treated with activated 4 Å molecular sieves (1.3 g), cooled to 0 °C and treated with PIFA (0.733 g, 1.70 mmol). The reaction mixture was stirred at 0 °C for 30 minutes, filtered through celite and washed with EtOAc. The organic extracts were washed with H_2O, dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by column chromatography on SiO_2 (7:3,

hexanes:EtOAc) to afford 0.682 g (37%) of **194** as a yellow oil: Rf 0.6 (7:3, hexanes:EtOAc); ^{1}H NMR δ 12.17 (s, 1 H), 7.90 (dd, 1 H, *J* = 8.5, 0.7 Hz), 7.66 (t, 1 H, *J* = 8.1 Hz), 7.48 (dd, 1 H, *J* = 8.6, 7.7 Hz), 7.46 (dd, 1 H, *J* =7.7, 1.1 Hz), 7.13 (dd, 1 H, *J* = 8.7, 1.2 Hz), 7.11 (d, 1 H, *J* = 8.1 Hz), 7.02 (dd, 1 H, *J* = 7.2, 0.6 Hz), 7.01 (d, 1 H, *J* = 10.5 Hz), 6.89 (d, 1 H, *J* = 8.4), 5.36 (s, 2 H), 3.57 (s, 3 H); MS (EI) *m/z* (relative intensity) 376 (M^+, 60), 331 (56), 121 (100), 69 (66);

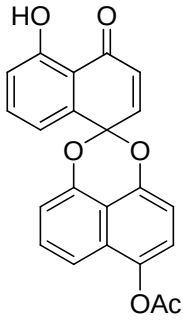


5,6'-Dihydroxy-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxin]-4-one (177).[119] A solution of **194** (0.681 g, 1.81 mmol) in CH_2Cl_2 (27 mL) was treated with 4 Å molecular sieves (1.70 g), cooled to 0 °C and treated with TMSBr (0.88 mL, 6.7 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1 h, warmed to room temperature, stirred 12 h, filtered through celite, washed (CH_2Cl_2) and concentrated under reduced pressure. A solution of the crude product in THF (40.5 mL) was treated with a 1.0 M solution of TBAF in THF (1.62 mL, 1.62 mmol) and stirred at room temperature for 15 min. The reaction was quenched with H_2O and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (CH_2Cl_2) afforded 0.366 g (68%) of **177** as a yellow solid: Rf 0.3 (7:3, hexanes:EtOAc); ^{1}H NMR δ 12.18 (s, 1 H), 8.99 (s, 1 H), 7.88 (dd, 1 H, *J* = 8.5, 0.9 Hz), 7.78 (t, 1 H, *J* = 7.9 Hz), 7.52-7.47 (m, 2 H), 7.18 (d, 1 H, *J* = 10.5 Hz), 7.16 (dd, 1 H, *J* = 8.5, 1.1 Hz), 7.03 (dd, 1 H, *J* = 7.5, 0.9 Hz), 6.93 (d, 1 H, *J* = 8.2 Hz), 6.85 (d, 1 H, *J* = 8.1 Hz), 6.44 (d, 1 H, *J* = 10.5 Hz); MS (EI) 332 (M^+,

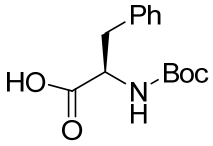
82), 256 (13), 167 (33), 121 (72), 69 (100); HRMS (EI) calculated for $C_{20}H_{12}O_5$ 332.0685, found 332.0685.



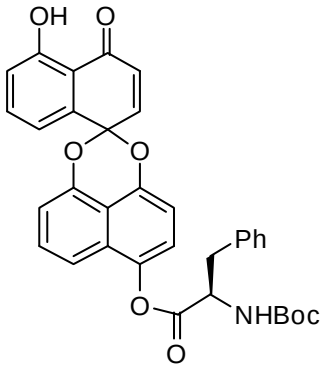
4-Oxo-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxine]-5,6'-diyl diacetate (204). A solution of spiroketal **177** (6.25 mg, 0.0188 mmol) in pyridine (0.12 mL) was treated with Ac_2O (0.04 mL, 0.4 mmol) and diluted with CH_2Cl_2 (0.12 mL). The reaction mixture was stirred for 3 h, treated with additional Ac_2O (0.04 mL, 0.4 mmol) and stirred for an additional 12 h. It was diluted with CH_2Cl_2, extracted with sat. $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (7:3, hexanes:EtOAc) afforded 3.8 mg (77%) of bis-acetate **177** as an orange oil: Rf 0.24 (7:3, hexanes:EtOAc); IR (ATR) 2917, 1765, 1674, 1640, 1606, 1323, 1265, 1193, 1111, 1032 cm^{-1}; ^1H NMR δ 7.89 (dd, 1 H, *J* = 7.9, 1.1 Hz), 7.77 (t, 1 H, *J* = 7.9 Hz), 7.52 (d, 2 H, *J* = 7.9 Hz), 7.27 (dd, 1 H, *J* = 7.9, 1.1 Hz), 7.23 (d, 1 H, *J* = 8.2 Hz), 7.04-7.01 (m, 1 H), 6.96 (d, 1 H, *J* = 8.2 Hz), 6.95 (d, 1 H, *J* = 10.5 Hz), 6.27 (d, 1 H, *J* = 10.5 Hz), 2.47 (s, 3 H), 2.45 (s, 3 H); ^{13}C NMR δ 182.0, 169.7, 169.6, 149.7, 147.5, 145.0, 141.2, 140.4, 136.6, 134.6, 131.3, 128.3, 127.3, 126.3, 125.9, 122.1, 119.9, 115.5, 113.5, 110.7, 109.5, 93.1, 21.1, 20.9; MS (EI) *m/z* (rel intensity) 416 (M^+, 21), 376 (4), 375 (6), 374 (94), 334 (40), 332 (100), 231 (14), 117 (49); HRMS (EI) calculated for $C_{24}H_{16}O_7$ 416.0896, found 416.0897.



5-Hydroxy-4-oxo-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxine]-6'-yl acetate (205). A solution of spiroketal **177** (6.25 mg, 0.0194 mmol) in pyridine (0.12 mL) was treated with Ac_2O (0.5 mL, 0.5 mmol) and stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (3 mL), washed with sat. $NaHCO_3$ (0.5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (7:3, hexanes:EtOAc) afforded 3.9 mg (88%) of mono-acetate **205** as a bright yellow oil: Rf 0.4 (7:3, hexanes:EtOAc); IR (ATR) 3054, 2920, 1761, 1661, 1606, 1418, 1346, 1265, 1195, 1073 cm^{-1}; ^1H NMR δ 12.15 (s, 1 H), 7.67 (t, 1 H, *J* = 7.8 Hz), 7.52-7.43 (m, 3 H), 7.23 (d, 1 H, *J* = 8.1 Hz), 7.15 (d, 1 H, *J* = 8.6 Hz), 7.05-6.95 (m, 3 H), 6.38 (d, 1 H, *J* = 10.6 Hz), 2.47 (s, 3 H); ^{13}C NMR δ 188.7, 169.6, 161.9, 147.4, 144.9, 141.3, 139.4, 138.6, 136.6, 129.9, 128.3, 127.3, 119.9, 119.8, 119.3, 115.6, 113.8, 113.4, 110.7, 109.5, 93.1, 20.9; MS (EI) *m/z* (rel intensity) 374 (M^+, 20), 333 (24), 332 (100), 231 (7), 117 (31); HRMS (EI) calculated for $C_{22}H_{14}O_6$ 374.0790, found 374.0790.

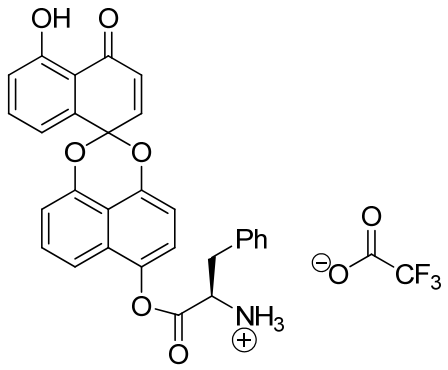


(*R*)-2-(*tert*-Butoxycarbonylamino)-3-phenylpropanoic acid (207).[315] A solution of D-phenyl alanine (0.50 g, 3.0 mmol) in 2.0 N NaOH (3 mL) was cooled to 0 °C, treated with Boc_2O (0.990 g, 4.54 mmol) and warmed to room temperature. The Boc_2O was insoluble at 0 °C, but dissolved as the reaction mixture was warmed to room temperature. The reaction mixture was stirred for 3 h, cooled to 0 °C, acidified to pH 2 with 1.0 N HCl and extracted with EtOAc (2x). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford **207** as a white solid which was used without further purification: ^{1}H NMR (DMSO-d_6) δ 12.60 (s, 1 H), 7.30-7.19 (m, 4 H), 7.12 (d, 1 H, J = 7.8 Hz), 4.08 (ddd, 1 H, J = 13.8, 10.5, 4.5 Hz), 3.01 (dd, 1 H, J = 13.8, 4.5 Hz), 2.81 (dd, 1 H, J = 13.8, 10.5 Hz), 2.50 (t, 1 H, J = 1.8 Hz), 1.31 (s, 9 H); MS (EI) *m/z* (rel intensity) 265 (M^+, 28), 237 (12), 220 (14), 176 (58), 164 (33), 148 (31), 120 (54), 91 (51), 57 (100); HRMS (EI) calculated for $C_{14}H_{19}NO_4$ 265.1314, found 265.1324.



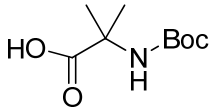
(2*R*)-5-Hydroxy-4-oxo-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxine]-6'-yl 2-(*tert*-butoxycarbonylamino)-3-phenylpropanoate. The bright orange suspension of **177** (18 mg, 0.054 mmol) in CH_2Cl_2 (0.7 mL) was treated with *N*-Boc phenyl alanine (**207**) (10.34 mg, 0.03900 mmol) followed by DCC (0.0087 g, 0.042 mmol) and DMAP (1 mg, 0.008 mmol) and stirred for 30 min at room temperature. The reaction mixture was treated with additional *N*-Boc

phenylalanine (10.34 mg, 0.03900 mmol), DCC (0.0087 g, 0.42 mol) and DMAP (1 mg, 0.008 mmol) and stirred 5 min. It was filtered, concentrated under reduced pressure and purified by column chromatography on SiO_2 (7:3, hexanes:EtOAc) to afford 17.3 mg (90%) of the amino ester as a yellow foam: Rf 0.5 (7:3, hexanes:EtOAc); IR (ATR) 3388 (bs), 2973, 2926, 2855, 1763, 1707, 1662, 1606, 1390, 1377, 1347, 1263, 1155, 1129 cm^{-1}; ^1H NMR δ 12.11 (s, 1H), 7.73 (t, 1 H, *J* = 8.1 Hz), 7.48-7.42 (m, 2 H), 7.40-7.31 (m, 2 H), 7.27-7.17 (m, 1 H), 7.15 (d, 1 H, *J* = 8.4 Hz), 7.07 (dd, 1 H, *J* = 8.1, 3.6 Hz), 7.01 (d, 1 H, *J* = 10.5 Hz), 7.01 (d, 1 H, *J* = 7.5 Hz), 6.92 (d, 1 H, *J* = 8.1 Hz), 6.38 (d, 1 H, *J* = 10.5 Hz), 5.11 (d, 1 H, *J* = 8.4 Hz), 4.99-4.95 (m, 1 H), 3.33 (d, 2 H, *J* = 6.3 Hz), 1.42 (s, 9 H); ^{13}C NMR δ 188.6, 171.1, 161.8, 155.3, 147.2, 145.0, 141.0, 139.3, 138.5, 136.6, 135.6, 129.9, 129.5, 128.9, 128.3, 127.4, 119.7, 119.5, 119.5, 119.3, 115.8, 113.7, 113.3, 110.7, 109.3, 93.1, 80.4, 54.9, 38.2, 28.2; MS (EI) *m/z* (rel. intensity) 506 ([M-O*t*-Bu]$^+$,1), 333 (22), 332 (100), 271 (20), 120 (83), 91 (72); HRMS (EI) calculated for $C_{30}H_{20}NO_7$ 506.1240, found 506.1239

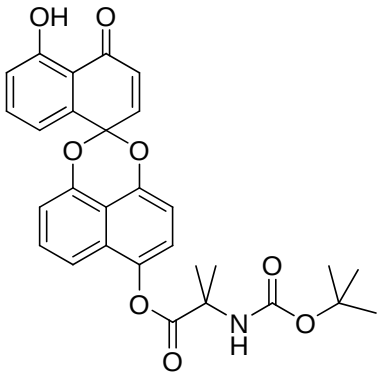


(2*R*)-1-(5-Hydroxy-4-oxo-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxine]-6'-yloxy)-1-oxo-3-phenylpropan-2-aminium 2,2,2-trifluoroacetate (210). A solution of the *N*-BOC protected phenylalanine ester of **177** (17.3 mg, 0.0489 mmol) in CH_2Cl_2 (0.6 mL) was treated with TFA (0.15 mL, 2.0 mmol), stirred at room temperature for 30 min, concentrated

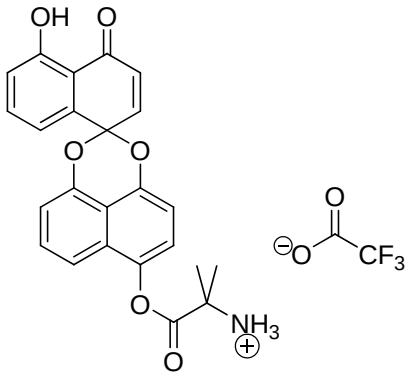
under reduced pressure and further dried under high vacuum to afford **210** as a yellow solid in quantitative yield: Mp 80.7-81.2 °C (CH_2Cl_2); IR (ATR) 2956 (bs), 1653, 1606, 1437, 1264, 1204, 1148, 1073, 1046 cm^{-1}; ^1H NMR (CD_3CN) δ 12.10 (s, 1 H), 7.73 (t, 1 H, *J* = 8.1 Hz), 7.56 (t, 1 H, *J* = 8.0 Hz), 7.49-7.39 (m, 6 H), 7.29 (dd, 1 H, *J* = 8.4, 2.4 Hz), 7.16 (dd, 1 H, *J* = 8.6, 0.8 Hz), 7.09 (d, 1 H, *J* = 8.7 Hz), 7.08 (d, 1 H, *J* = 10.5 Hz), 7.01 (d, 1 H, *J* = 8.4 Hz), 6.39 (dd, 1 H, *J* = 10.5, 1.2 Hz), 4.82 (bs, 1 H), 3.55 (bs, 2 H); ^{13}C NMR (CD_3CN) δ 189.9, 168.9, 162.7, 148.4, 146.6, 141.3, 140.3, 139.7, 137.9, 135.0, 130.9, 130.8, 130.7, 130.5, 130.3, 129.9, 129.7, 129.1, 127.8, 120.9, 120.6, 118.4, 116.4, 114.7, 111.9, 110.4, 94.3, 55.7, 37.0; MS (ESI-Q-TOF) *m/z* (relative intensity) 480 (M^+, 42), 120 (100); HRMS (ESI-Q-TOF) calculated for $C_{28}H_{18}NO_7$ 480.1082, found 480.1083.



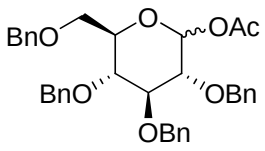
2-(*tert*-Butoxycarbonylamino)-2-methylpropanoic acid (209).[316,317] A solution of 2-aminoisobutyric acid (**208**) (2.06 g, 20.0 mmol) 1.0 M NaOH (20 mL), H_2O (40 mL), and dioxane (40 mL), cooled to 0 °C was treated with Boc_2O (4.8 g, 22 mmol) and stirred at room temperature for 3 h. The reaction mixture was partially concentrated under reduced pressure, acidified to pH 2.0 with 1.0 M $NaHSO_4$, extracted with EtOAc, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 4.0 g (99%) of **209** as a white solid. ^1H NMR (DMSO-d_6) δ 5.27 (bs, 1 H), 1.53 (s, 6 H), 1.44 (s, 9 H); MS (ESI-Q-TOF) *m/z* (rel intensity) 226 (M^+, 29), 191 (90), 170 (100); HRMS (ESI-Q-TOF) calculated for $C_9H_{17}NO_4Na$ 226.1055, found 226.1048.



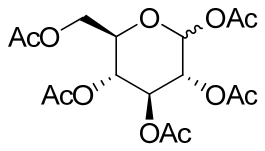
5-Hydroxy-4-oxo-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxine]-6'-yl 2-(*tert*-butoxycarbonylamino)-2-methylpropanoate. A suspension of spiroketal **177** (4.7 mg, 0.014 mmol) in CH_2Cl_2 (1.27 mL) was treated with *N*-Boc aminoisobutyric acid **209** (4.80 mg, 0.0237 mmol), DCC (4.7 mg, 0.023 mmol) and DMAP (0.47 mg, 0.0039 mmol), and stirred for 1.5 h. The reaction mixture was treated with additional *N*-Boc aminoisobutyric acid **209** (4.7 mg, 0.014 mmol) and DCC (4.0 mg, 0.019 mmol), stirred for 30 min, filtered, concentrated under reduced pressure and purified by column chromatography on SiO_2 (7:3, hexanes:EtOAc) to afford 5 mg (68%) of the AIB ester of **177** as a bright yellow foam: Rf 0.4 (7:3, hexanes:EtOAc); IR (neat) 3500 (bs), 1764, 1708, 1664, 1610, 1506, 1457, 1419, 1380, 1348, 1265, 1239, 1159, 1114, 1075, 956 cm^{-1}; ^1H NMR δ 12.16 (s, 1 H), 7.69-7.62 (m, 2 H), 7.51 (d, 1 H, *J* = 7.6 Hz), 7.45 (dd, 1 H, *J* = 7.6, 1.0 Hz), 7.23 (d, 1 H, *J* = 8.2 Hz), 7.14 (dd, 1 H, *J* = 8.4, 1.3 Hz), 7.03 (d, 1 H, *J* = 10.5 Hz), 7.01 (d, 1 H, *J* = 6.9 Hz), 6.95 (d, 1 H, *J* = 8.2 Hz), 6.38 (d, 1 H, *J* = 10.5 Hz), 5.15 (s, 1 H), 1.76 (s, 6 H), 1.49 (s, 9 H); ^{13}C NMR δ 188.7, 161.8, 154.8, 147.2, 144.8, 141.7, 138.6, 136.6, 129.8, 128.2, 127.5, 119.7, 119.6, 119.3, 113.7, 113.3, 110.6, 93.0, 56.4, 28.4, 25.7; MS (EI) *m/z* (rel intensity) 517 (M^+, 24), 458 (11), 444 (20), 443 (5), 417 (30), 401 (6), 373 (18), 334 (22), 332 (81), 58 (100); HRMS (EI) calculated for $C_{29}H_{27}NO_8$ 517.1737, found 517.1758.



1-(5-Hydroxy-4-oxo-4H-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxine]-6'-yloxy)-2-methyl-1-oxopropan-2-aminium 2,2,2-trifluoroacetate (211). A solution of the *N*-Boc AIB prodrug of **177** (5.0 mg, 0.0096 mmol) in CH_2Cl_2 (0.42 mL) was treated with TFA (0.10 mL, 1.4 mmol), stirred for 30 min at room temperature, concentrated under reduced pressure and dried further under high vacuum to afford **221** in quantitative yield as a light yellow powder: Mp 137.7-138.1 °C (CH_2Cl_2); IR (neat) 2936.1 (bs), 2860.0, 1768.2, 1666.3, 1610.5, 1456.3, 1420.0, 1378.7, 1347.4, 1267.6, 1236.9, 1166.4, 112.6 cm $^{-1}$; ^{1}H NMR (CD_3CN) δ 12.07 (bs, 1 H), 8.16 (bs, 3 H), 7.69 (t, 1 H, *J* = 8.0 Hz), 7.61-7.53 (m, 2 H), 7.45 (d, 1 H, *J* = 7.5 Hz), 7.35 (d, 1 H, *J* = 8.3 Hz), 7.13 (d, 1 H, *J* = 8.3Hz), 7.08-7.04 (m, 2 H), 7.00 (d, 1 H, *J* = 8.2 Hz), 6.35 (d, 1 H, *J* = 10.5 Hz), 1.89 (s, 6 H); ^{13}C NMR (Acetone-d6) δ 189.8, 171.6, 162.6, 148.5, 146.6, 141.4, 140.5, 139.7, 137.8, 130.9, 130.1, 127.9, 121.0, 120.5, 120.4, 116.1, 114.7, 114.3, 111.9, 110.4, 94.3, 59.1, 24.3; MS (ESI) *m/z* (rel intensity) 441 ([M+Na]$^+$, 32), 191 (42), 146 (87), 135 (100); HRMS (ESI) calculated for $C_{24}H_{20}NO_6Na$ 441.1179, found 441.1188.

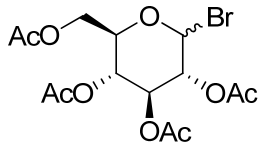


(3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-tetrahydro-2H-pyran-2-yl acetate (218).[318] A solution of 2,3,4,6 tetra-*O*-benzyl-D-glucopyranose (0.15 g, 0.35 mmol) in pyridine (2.5 mL) was cooled to 0 °C, treated with Ac_2O (0.5 mL, 6 mmol), warmed to room temperature and stirred for 20 h. The reaction mixture was cooled to 0 °C, quenched with MeOH (0.5 mL), stirred for 1h. It was diluted with EtOAc, washed with sat. $NaHCO_3$, H_2O, sat. $CuSO_4$, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 0.064 g (31%) of **218** as a colorless oil which was used without further purification: ^{1}H NMR δ 7.49-7.24 (m, 20 H), 7.14-7.12 (m, 2 H), 6.35 (d, 1 H, *J* = 3.6 Hz), 4.95 (d, 1 H, *J* = 5.7 Hz), 4.84 (d, 1 H, *J* = 6.0), 4.81 (d, 1 H, *J* = 6.3 Hz), 4.70 (d, 1 H, *J* = 11.4 Hz), 4.64 (d, 1 H, *J* = 7.5 Hz), 4.60 (d, 1 H, *J* = 8.1 Hz), 4.50 (d, 1 H, *J* = 4.2 Hz), 4.46 (d, 1 H, *J* = 5.7 Hz), 3.94 (t, 1 H, *J* = 9.3 Hz), 3.90 (appd, 1 H, *J* = 9.0 Hz), 3.76-3.62 (m, 6 H); MS (EI) *m/z* (rel intensity) 491 ([M-Bn]$^+$, 2), 431 (5), 325 (4), 253 (5), 91 (100); HRMS calculated for $C_{29}H_{31}O_7$ [M-Bn] 491.2070, found 491.2070.

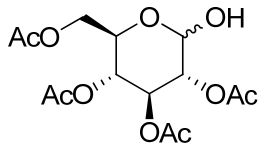


(3*R*,4*S*,5*R*,6*R*)-6-(Acetoxymethyl)tetrahydro-2*H*-pyran-2,3,4,5-tetrayl tetraacetate (220).[319] A solution of pyridine (7.5 mL) and acetic anhydride (5.0 mL, 0.053 mol) was cooled to 0 °C and treated with D-glucose (1.00 g, 5.55 mmol). The suspension was stirred at 0 °C until all of the solids dissolved (1.5 h), warmed to room temperature and stirred for 16 h. The reaction mixture was poured into ice water (20 mL) and white solids immediately precipitated out of solution. The solids were filtered through a coarse sintered glass filter, washed (H_2O) and dried under high vacuum to afford 2.003 g (93%) of **220** as a white solid and 1:1 anomeric mixture:

Rf 0.6 (4:1, hexanes:EtOAc); ^{1}H NMR δ 6.33 (d, 1 H, *J* = 3.66 Hz), 5.47 (t, 1 H, *J* = 9.6 Hz), 5.16 (d, 1 H, *J* = 9.7 Hz), 5.10 (dd, 1 H, *J* = 10.3, 3.7 Hz), 4.30-4.24 (m, 1 H), 4.15-4.06 (m, 2 H), 2.18 (s, 3 H), 2.10 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H); MS (ESI-Q-TOF) *m/z* (rel intensity) 413 ([M+Na]$^+$, 100); HRMS (ESI-Q-TOF) calculated for $C_{16}H_{22}O_{11}Na$ 412.1060, found 413.1027.

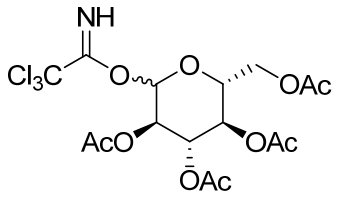


(2*R*,3*R*,4*S*,5*R*)-2-(Acetoxymethyl)-6-bromotetrahydro-2*H*-pyran-3,4,5-triyl triacetate (221).[320] A 30% solution of HBr in AcOH (1.05 mL) was cooled to 0 °C and treated with 10 portions of acetylated D-glucose **220** (0.600 g, 1.54 mmol) over the course of 10 min. The ice bath was removed and the sugar slowly dissolved to afford a light yellow solution. The reaction mixture was stirred for 45 min, quenched with ice cold H_2O (25 mL), extracted with CH_2Cl_2 (2x), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 0.607 g (96%) of **221** as a clear oil which was clean according to ^{1}H NMR analysis and used without further purification: Rf 0.8 (4:1, hexanes:EtOAc); ^{1}H NMR δ 6.60 (d, 1 H, *J* = 3.9 Hz), 5.6 (t, 1 H, *J* = 5.7 Hz), 5.15 (t, 1 H, *J* = 9.9 Hz), 4.83 (dd, 1 H, *J* = 10.0, 4.1 Hz), 4.26-4.04 (m, 2 H), 4.14-4.10 (m, 1 H), 2.10 (s, 3 H), 2.09 (s, 3 H), 2.05 (s, 3 H), 2.03 (s, 3 H).



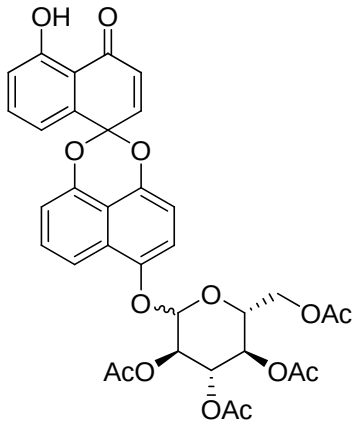
(2*R*,3*R*,4*S*,5*R*)-2-(Acetoxymethyl)-6-hydroxytetrahydro-2*H*-pyran-3,4,5-triyl triacetate (222).[321] A solution of penta-acetylated D-glucose **220** (0.290 g, 0.743 mmol) in THF (3 mL)

was treated with benzylamine (0.22 mL, 2.0 mmol) dropwise at room temperature, stirred for 6 h, diluted with EtOAc and H_2O and extracted. The organic extract was washed with H_2O (2x), 1.0 N HCl, and a final wash with H_2O. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by column chromatography on SiO_2 (4:1, hexanes:EtOAc) to afford 0.173 g (68%) of deprotected glucose **222** as a white foam: Rf 0.5 (4:1, hexanes:EtOAc); ^{1}H NMR δ 7.26 (s, 1 H), 5.55 (t, 1 H, *J* = 4.3 Hz), 5.50 (d, 1 H, *J* = 3.4 Hz), 5.09 (t, 1 H, *J* = 9.5 Hz), 4.91 (dd, 1 H, *J* = 10.2, 3.5 Hz), 4.31-4.21 (m, 2 H), 4.15-4.08 (m, 1 H), 2.10 (s, 3 H), 2.09 (s, 3 H), 2.04 (s, 3 H), 2.02 (s, 3 H); MS (ESI-Q-TOF) *m/z* (rel intensity) 371 ([M+Na]$^+$, 100), 229 (8), 198 (12), 169 (20), 127 (23); HRMS (ESI-Q-TOF) calculated for $C_{14}H_{20}O_{10}Na$ 371.0954, found 371.0918.



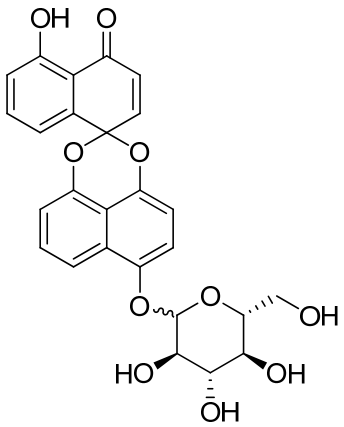
(2*R*,3*R*,4*S*,5*R*)-2-(Acetoxymethyl)-6-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (223).[322] A solution of **222** (0.301 g, 0.864 mmol) in CH_2Cl_2 (2.95 mL) was treated with DBU (0.26 mL, 1.7 mmol) followed by trichloroacetonitrile (0.87 mL, 6.9 mmol), stirred at room temperature for 4 h and concentrated under reduced pressure. The crude product was immediately purified by column chromatography on SiO_2 (1:1, EtOAc:hexanes) to afford 0.196 g (48%) of chloroimidate **223** as a 1:3 mixture of α and β anomers. Rf 0.4 (1:1, EtOAc:hexanes); ^{1}H NMR δ 8.69 (s, 1 H), 8.57 (s, 0.3 H), 6.64 (d, 0.3 H, *J* = 3.6 H), 6.56 (d, 1 H, *J* = 3.6 Hz), 5.66 (t, 0.3 H, *J* = 3.6 Hz), 5.57 (t, 1 H, *J* = 9.8 Hz), 5.19 (t, 1.3 H, *J* = 9.8 Hz),

5.13 (dd, 1.3 H, *J* = 10.2, 3.7 Hz), 4.31-4.11 (m, 3.9 H), 2.15 (s, 1 H), 2.10 (s, 1 H), 2.08 (s, 3 H), 2.05 (s, 4 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 2.00 (s, 1 H).



(2*R*,3*R*,4*S*,5*R*)-2-(Acetoxymethyl)-6-(5-hydroxy-4-oxo-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxine]-6'-yloxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate. A suspension of **177** (42.4 mg, 0.128 mmol) in CH_2Cl_2 (9.3 mL) was treated with chloroimidate **223** (90.7 mg, 0.190 mmol) and cooled to 0 °C. The reaction mixture was treated with BF_3OEt_2 (0.03 mL, 0.2 mmol) and the light yellow solution instantly turned to a deep red color. The reaction mixture was stirred for 20 min at 0 °C and quenched with H_2O which caused the color of the solution to return to light yellow. It was diluted with CH_2Cl_2, washed with H_2O (2x), dried (Na_2SO_4), filtered, concentrated under reduced pressure and purified by column chromatography on SiO_2 (3:2, hexanes:EtOAc) to afford 0.069 g (82%) of the desired O-glycosylated product as a yellow oil and 1:1 anomeric mixture: Rf 0.5 (3:2, hexanes:EtOAc); IR (ATR) 2939 (bs), 1744, 1661, 1608, 1456, 1418, 1346, 1211, 1113, 1064, 1032, 729 cm^{-1}; ^1H NMR δ 12.16 (s, 0.5 H), 12.14 (s, 0.5 H), 7.73 (d, 1 H, *J* = 8.2 Hz), 7.67 (t, 0.5 H, *J* = 7.6 Hz), 7.66 (t, 0.5 H, *J* = 7.6 Hz), 7.5 (d, 0.5 H, *J* = 7.6 Hz), 7.47 (d, 0.5 H, *J* = 7.6 Hz), 7.47 (t, 0.5 H, *J* = 7.6 Hz), 7.44 (t, 0.5 H, *J* = 7.6 Hz), 7.14 (d, 0.5 H, *J* = 8.4 Hz), 7.14 (d, 0.5 H, *J* = 8.4 Hz),

7.07 (d, 0.5 H, *J* = 8.3 Hz), 7.07 (d, 0.5 H, *J* = 8.3 z), 7.03 (d, 0.5 H, *J* = 7.5 Hz), 7.03 (d, 0.5 H, *J* = 7.5 Hz), 6.98 (d, 0.5 H, *J* = 10.5 Hz), 6.98 (d, 0.5 H, *J* = 10.5 Hz), 6.88 (d, 0.5 H, *J* = 8.3 Hz), 6.87 (d, 0.5 H, *J* = 8.3 Hz), 6.37 (d, 0.5 H, *J* = 10.5 Hz), 6.35 (d, 0.5 H, *J* = 10.5 Hz), 5.49 (dd, 0.5 H, *J* = 7.9, 1.3 Hz), 5.47 (dd, 0,5 H, *J* = 7.9, 1.3 Hz), 5.38 (0.5 H, d, *J* = 9.5 Hz), 5.35 (d, 0.5 H, *J* = 9.5 Hz), 5.25 (app d, 1 H, *J* = 9.3 Hz), 5.19 (d, 0.5 H, *J* = 7.8 Hz), 5.18 (d, 0.5 H, *J* = 7.8 Hz), 4.38-4.31 (m, 1 H), 4.21 (dd, 0.5 H, *J* = 12.4, 2.7 Hz), 4.20 (dd, 0.5 H, *J* = 12.4, 2.7 Hz), 2.10 (s, 3 H), 2.08 (s, 3 H), 2.08 (s, 1.5 H), 2.07 (s, 1.5 H), 2.07 (s, 1.5 H), 2.05 (s, 1.5 H); ^{13}C NMR δ 188.6, 170.4, 170.1, 170.1, 169.4, 169.4, 161.7, 147.8, 147.7, 147.1, 147.0, 142.7, 142.6, 139.4, 139.4, 138.6, 138.6, 136.6, 136.5, 129.7, 129.7, 127.7, 126.2, 119.6, 119.3, 119.1, 115.9, 115,9, 113.7, 113.6, 113.3, 113.3, 111.4, 111.1, 110.9, 109.2, 109.1, 100.0, 99.8, 92.9, 92.8, 72.4, 72.1, 71.0, 71.0, 68.3, 61.8, 60.3, 21.0, 20.7, 20.6, 20.6, 20.5, 14.1; MS (ESI-Q-TOF) *m/z* (rel. intensity) 685 ([M+Na]$^+$, 100), 617 (10), 415 (10); HRMS (ESI-Q-TOF) calculated for $C_{34}H_{30}O_{14}Na$ 685.1533, found 685.1542.



5-Hydroxy-6'-((3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy)-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxin]-4-one (224). A solution of *O*-glycosylated **177** (53.0 mg, 0.16 mmol) in MeOH (1.5 mL) and THF (1.5 mL) was treated with a

solution of NaOMe (25 mg, 0.46 mmol) in MeOH (2.5 mL) dropwise. The light yellow solution turned to a light orange color, was stirred for 45 min and quenched with DOWEX 50 W beads until the pH = 6.0. The reaction mixture was filtered and concentrated under reduced pressure to afford **224** as a bright yellow solid and 1:1 mixture of anomers: Rf 0.25 (9:1, CH_2Cl_2:MeOH); Mp (toluene) 189.5 (dec.); IR (ATR) 3378 (bs), 1592, 1415, 1265, 1224, 1068, 1036, 1014 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.22 (s, 1 H), 8.05-7.98 (m, 0.5 H), 7.97-7.944 (m, 0.5 H), 7.78 (t, 0.5 H, *J* = 8.1 Hz), 7.71 (t, 0.5 H, *J* = 8.1 Hz), 7.59 (d, 0.5 H, *J* = 7.8 Hz), 7.54 (d, 0.5 H, *J* = 7.8 Hz), 7.49-7.44 (m, 1 H), 7.39 (d, 1 H, *J* = 7.8 Hz), 7.28-7.22 (m, 2 H), 7.03 (dd, 1 H, *J* = 8.4, 7.8 Hz) ,6.96 (d, 0.5 H, *J* = 8.3 Hz), 6.96 (d, 0.5 H, *J* = 8.3 Hz), 6.46 (d, 0.5 H, *J* = 10.5 Hz), 6.46 (d, 0.5 H, *J* = 10.5 Hz), 5.53-5.50 (m, 1 H), 5.16-5.15 (m, 1 H), 5.07 (d, 1 H, *J* = 4.8 Hz), 4.97-4.88 (m, 2 H), 4.65-4.58 (m, 1 H) 4.10 (bs, 1 H), 3.78-3.72 (m, 2 H), 3.41-3.38 (m, 2 H); ^{13}C NMR δ 201.9, 188.4, 161.0, 150.4, 148.5, 148.2, 148.1, 147.9, 146.8, 146.6, 141.3, 141.1, 140.9, 138.7, 138.4, 137.5, 137.1, 129.8, 127.4, 127.2, 125.9, 125.7, 121.7, 119.2, 117.5, 116.2, 115.0, 113.2, 113.1, 112.7, 111.2, 110.6, 109.6, 108.9, 102.0, 98.4, 98.3, 77.2, 76.5, 75.0, 73.4, 69.8, 60.8, 59.8, 58.7, 45.7, 20.8, 14.1; MS (EI) *m/z* (rel intensity) 526 (M^+, 2), 494 (2), 332 (100), 190 (38), 160 (25); HRMS (EI) calculated for $C_{26}H_{22}O_{10}$ 494.1213, found 494.1228.

General Procedure for determination of prodrug water solubility:

A suspension of the prodrug in H_2O was agitated, allowed to sit for 15 min and filtered. The filtrate was concentrated under reduced pressure and further dried under high vacuum. The mass of both the collected filtrate and the solids were recorded to confirm that there was neither loss of sample nor a falsely high value due to residual water. The value for water solubility was determined by: mass (mg of prodrug isolated from the filtrate)/total volume of H_2O.

Phenylalanine prodrug (210): 1.9 mg of **210** was treated with H_2O (0.5 mL). Because very little of the prodrug went into solution, it was treated with additional H_2O (0.5 mL) to make the total volume of H_2O = 1.0 mL. 0.06 Mg of **210** was isolated from the filtrate. Water solubility of **210** = 0.06 mg/mL (<0.1 mg/mL).

AIB prodrug (211): 3.76 mg of **211** was treated with H_2O (0.5 mL). 2.26 mg of prodrug **211** was isolated from the filtrate. Water solubility of **211** = 4.5 mg/mL

Sugar prodrug (224): 2.1 mg of **224** was treated with H_2O (0.5 mL). 0.7 mg of prodrug **224** was isolated from the filtrate. Water solubility of **224** = 1.4 mg/ mL

11.0 PRODRUG SCALE-UP

11.1 REVISED RETROSYNTHETIC ANALYSIS OF PRODRUG 211

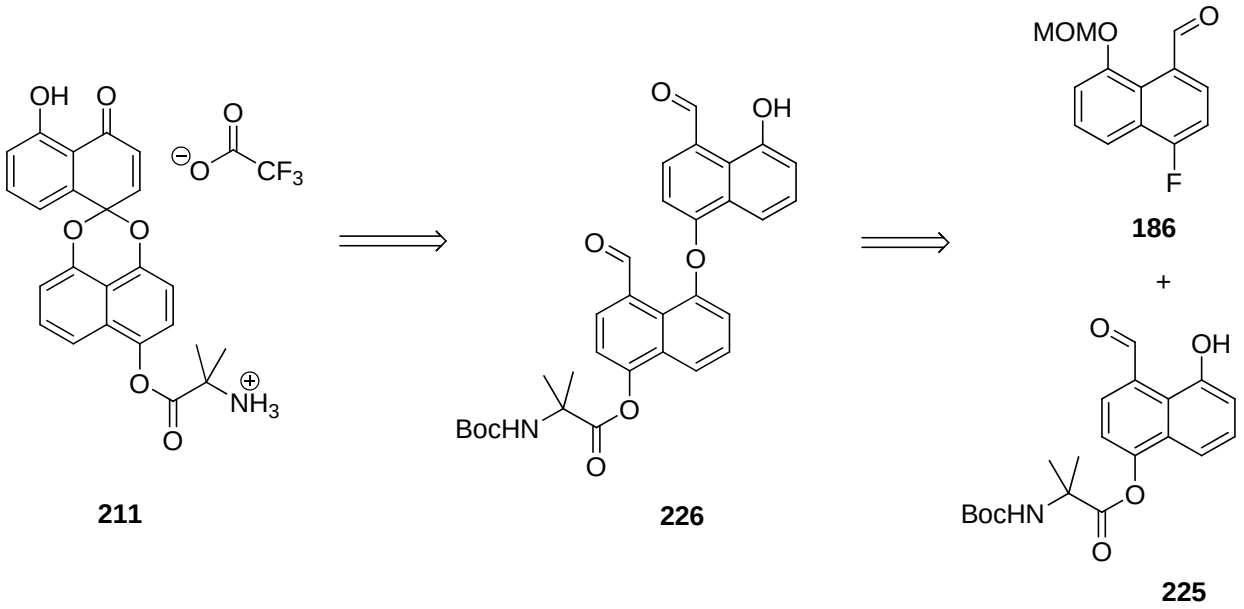
The promising biological results with **177** inspired the prodrug project. Spirocycle **177** had a Trx/TrxR inhibition of 0.20 ± 0.01 μM and MCF-7 growth inhibition of 2.6 ± 0.1 μM. Unfortunately, the low solubility limited more extensive biological studies. The undesirable physical properties of **177** inspired the investigation of prodrugs of **177**. After measuring the water solubilities of the synthesized prodrugs, it was found that prodrug **211** had significantly improved water solubility (4.5 mg/mL vs. <0.1 mg/mL for **177**). Since it improved on the poor plasma stability of the other prodrugs and poor water solubility of the parent compound, prodrug **211** was selected as a suitable candidate for animal studies. The biologists needed at least one gram of the prodrug for their proposed animal tests.[323] With any new anticancer drug, one of the most important questions is what type of tumor will respond best. Each tumor has a "standard of care" for treatment.[324] Examples are the treatment of breast cancer with doxorubicin[325] or Taxol,[326] and the treatment of lung cancer with platinum containing drugs[327] or imatinib.[328] Biologists not only test the efficacy of the synthesized drug, but they need to test the drug with a combination of the "standard of care" for each of the standard tumors. There are 8-10 mice per group for each tumor tested. The number of tests that need to be performed necessitates the delivery of 1 g of material.

It was exciting that prodrug **211** was viable for animal tests, but this also raised concerns about the best synthetic route to prepare 1 g of compound. At best, the current route allowed for the synthesis of 100 mg of **177**. An alternative route was needed, and therefore the synthetic plan had to be optimized to allow for the preparation of gram quantities.

The bottlenecks in the original synthesis were evaluated. Fluoride **186** was synthesized in 10 steps and 31% overall yield and naphthol **191** was obtained in four steps and 54% overall yield. The segment condensation and the last six steps, with an overall yield of 7%, were clearly a major problem. Primarily responsible for the mediocre efficiency was the PIFA mediated oxidation of **193**. Unfortunately, earlier attempts to optimize this oxidation were unsuccessful (Table **9.1**). The retrosynthetic analysis was changed to more efficiently arrive at **177**.

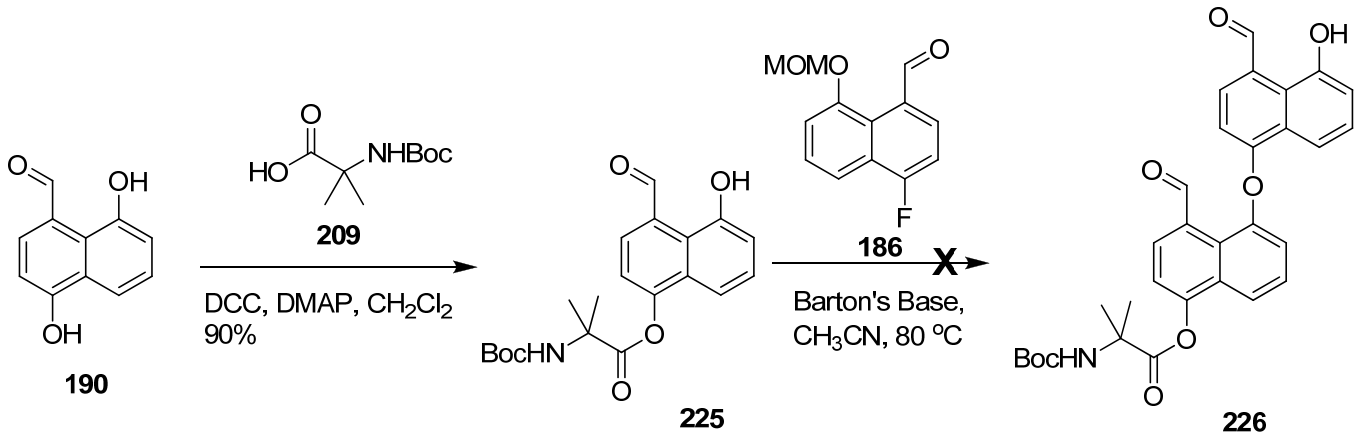
The first modified retrosynthetic analysis (Scheme **11.1**) investigated the incorporation of the AIB ester earlier in the synthesis (Scheme **9.3**). Prodrug **211** would be synthesized from **226** following Dakin conversion of the naphthaldehydes to naphthols and subsequent oxidative cyclization. The yields of hypervalent iodine mediated oxidative cyclizations can be sensitive to the electronic nature of the aromatic substituents.[329] It would be interesting to see the effect on yield during the oxidative cyclization that the amino ester substituent would exert compared to the MOM ether substituent in **193**. Biaryl ether **226** would be synthesized from an S_NAr condensation between naphthyl fluoride **186** and naphthol **225**. Naphthyl fluoride **186** was the same etherification partner used in the original synthesis of **177** (Scheme **9.1**). Naphthol **225** could be readily synthesized via esterification between *N*-Boc-AIB (**209**) and the previously synthesized naphthaldehyde **190** (Scheme **9.2**). The primary advantage of this synthesis would be the removal of one of the MOM protections early in the synthesis, and the removal of the late stage MOM deprotection and esterification. The other advantage of this revised retrosynthetic

analysis was that the majority of the proposed chemistry mirrors transformations applied in the original synthesis of **177**. Ideally, this would expedite the process of reaction optimization (Scheme **11.1**).



Scheme 11.1. Modified retrosynthetic analysis of **211**

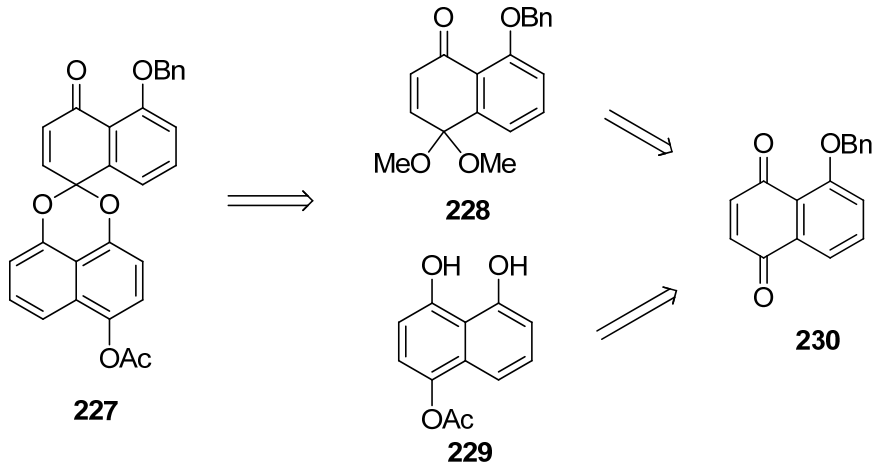
The revised synthesis commenced with the esterification between **209** and **190** (Scheme **11.2**). The esterification proceeded in excellent yield utilizing the standard DCC conditions to afford **225**. Unfortunately, problems were rapidly encountered with this route. The amino ester did not survive the standard S_NAr conditions and no **226** was isolated. Amino ester **225** rapidly decomposed during these conditions. This necessitated the development of a completely revised retrosynthetic plan.



Scheme 11.2. Failed synthesis of **226**

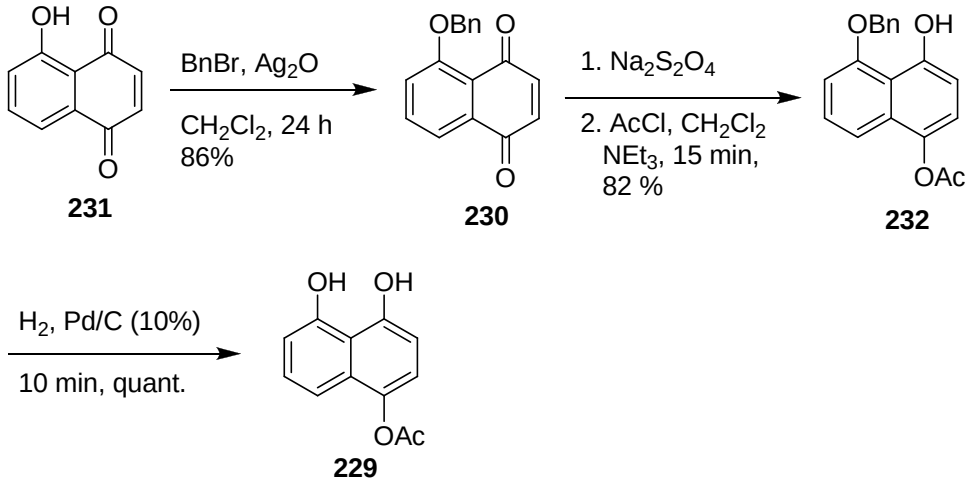
11.2 ATTEMPTED SYNTHESIS OF 227

In the new retrosynthetic analysis, the oxidative cyclization (Scheme **9.3**) was replaced with a spiroketalization between naphthalene diol **229** and ketone **228** (Scheme **11.3**). Other syntheses that performed a spiroketalization required a late stage introduction of the enone, but it would be advantageous to introduce the enone earlier in the synthesis.[125] Conveniently, both mono ketal **228** and naphthol **229** can be synthesized from benzyl protected juglone **230** (Scheme **11.3**).



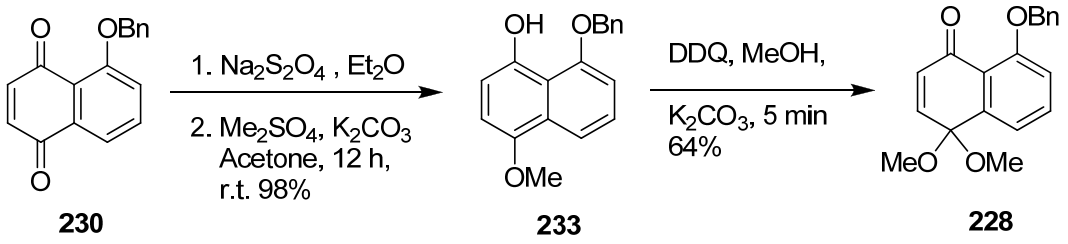
Scheme 11.3. Modified retrosynthetic analysis of **227**

The synthesis of acetate **229** commenced with the benzyl protection of juglone (**231**, Scheme **11.4**). The initial benzylation in $CHCl_3$ afforded **230** in 30% yield, but a solvent switch to CH_2Cl_2 increased the yield to 80%.[330] Naphthoquinone **230** was reduced with $Na_2S_2O_4$ in Et_2O and one of the phenol groups was acetylated with AcCl. The benzyl ether blocked the acetylation of the proximal phenol to give **232** selectively.[331] Debenzylation proceeded cleanly in 15 min with 10% Pd/C to afford diol **229** in excellent yield.



Scheme 11.4. Synthesis of acetate **229**

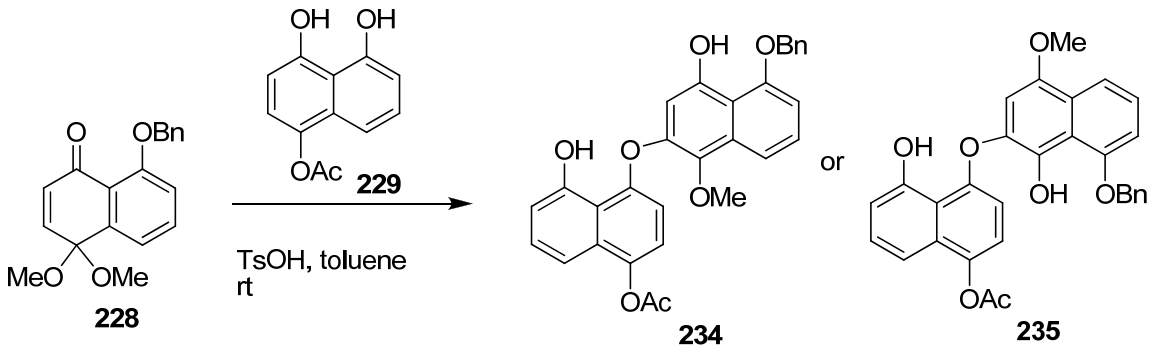
Spiroketalization ketone component **228** was also synthesized starting from **230** (Scheme **11.5**). The naphthoquinone was reduced with $Na_2S_2O_4$ and monoprotected with dimethyl sulphate to afford **233**. Monomethylated **233** was oxidized with DDQ[332-334] to afford monoacetal **228** as a single observed regioisomer in good yield.



230 **233** **228**

Scheme 11.5. Selective monoketalization

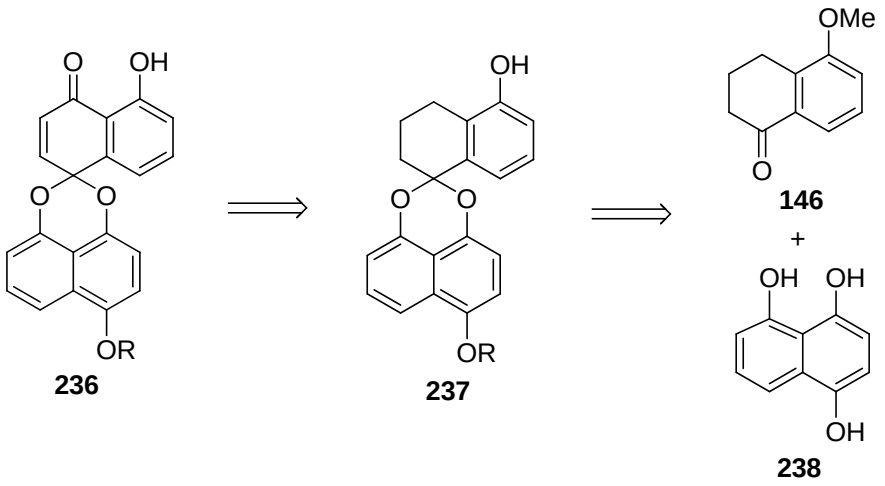
The spiroketalization between **228** and **229** with catalytic TsOH was attempted (Scheme **11.6**). Both starting materials were consumed, but the spiroketal was not observed according to ^{1}H NMR analysis of the crude reaction mixture. The conjugate addition of the naphthol to the enone was presumably the preferred pathway to afford either **234** or **235** based on ^{1}H NMR and MS analysis. A series of conditions were screened, but the enone was not preserved. Accordingly, the introduction of the enone needed to be performed after the spiroketalization.



Scheme 11.6. Conjugate addition of naphthol **229** to **228**

11.3 REVISED RETROSYNTHETIC ANALYSIS II

The new revised retrosynthetic analysis of **236** postponed the enone introduction until after the spiroketalization between 5-methoxytetralone (**146**) and naphthol **238** (Scheme **11.7**).[101,124,125] The enone could be introduced in a two step protocol. First, benzylic oxidation to the ketone could be performed with chromium, MnO_4,[335] NBS and AIBN with subsequent DMSO and $NaHCO_3$ treatment,[130,336,337] or DDQ.[125] Secondly, the alkene could be introduced by further DDQ treatment[124,338] or the Saegusa reaction. 5-Methoxytetralone (**146**) is commercially available and 1,2,5-trihydroxynaphthalene (**238**) can be synthesized via the reduction of juglone (**231**). If **238** needed to be protected, the earlier developed methodology for monoprotection could be readily employed (Scheme **11.4**).

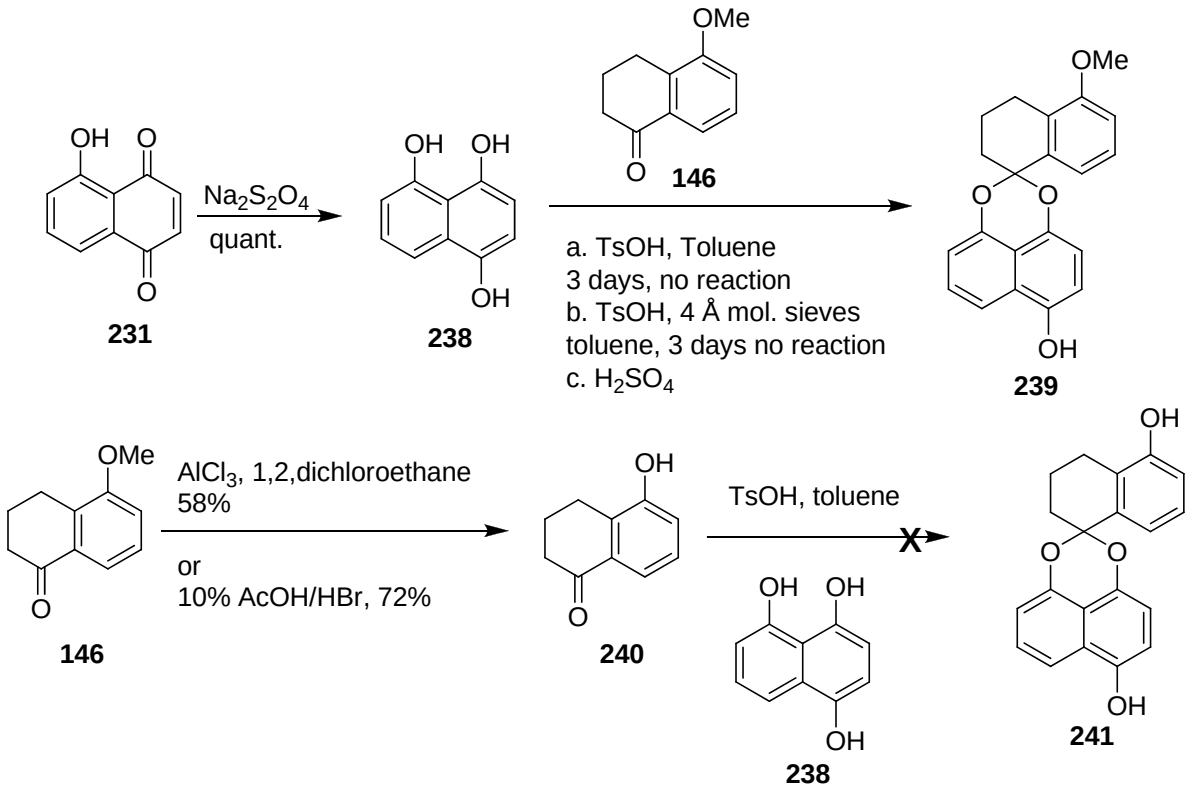


Scheme 11.7. Revised retrosynthetic analysis II

11.4 PROTECTING GROUP FREE SYNTHESIS OF BUILDING BLOCKS

The unprotected naphthol **238** was synthesized by reduction of juglone (**231**) with $Na_2S_2O_4$ (Scheme **11.8**). This electron rich aromatic ring would likely be susceptible to air oxidation and was rapidly subjected to the spiroketalization conditions with tetralone **146**.[339] The disappearance of triol **238** was observed in the ^{1}H NMR analysis of the crude reaction mixture, but **146** remained unreacted. 5-Hydroxytetralone (**240**) was synthesized by a simple demethylation of **146** with $AlCl_3$. The yield of the demethylation step was improved to 90% via treatment with 10% AcOH in HBr. However, **238** decomposed during the spiroketalization with TsOH in toluene, and tetralone **240** was recovered quantitatively. The TLC of the spiroketalization reaction showed one spot corresponding to the tetralone, disappearance of **238** and baseline material. The polar decomposition product was never isolated, but the likely decomposition pathway can be speculated on. There are numerous examples of air oxidation of electron rich naphthols to the corresponding quinones.[339,340] Juglone (**231**) would be expected if

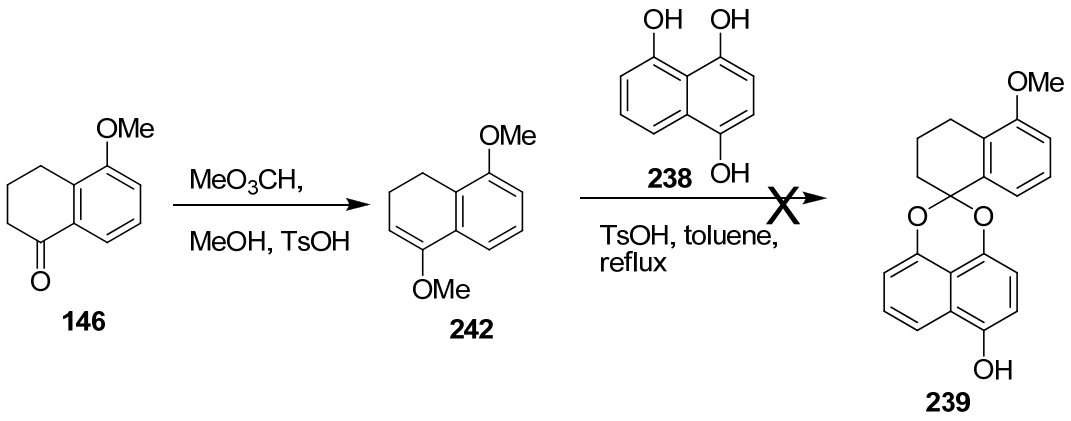
this was the lone mode for consumption of **238**, but it was not isolated. A possible explanation is that the oxidation to **231** is followed by additional reactions such as the dimerization of **231** or condensation between **231** and **238**.[341] The homocoupling of electron rich aromatics to afford various biaryl compounds has been reported and could also account for the decomposition of **238**.[342-344] Although the side product was never isolated, precedence from the literature indicates that some form of dimerization most likely accounted for the consumption of **238**.



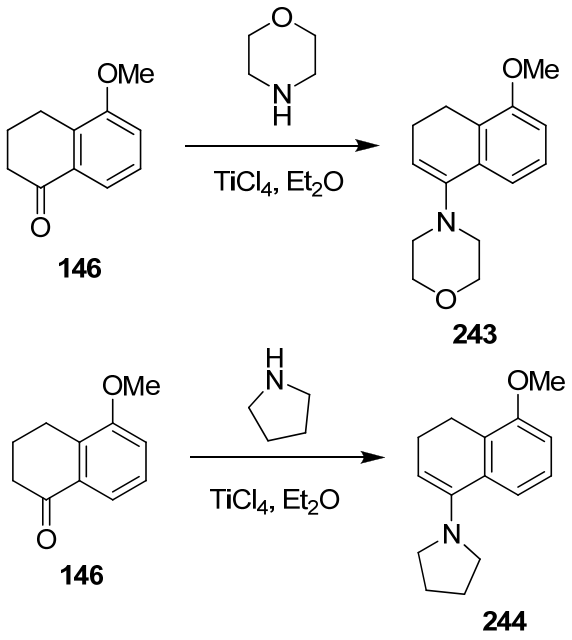
Scheme 11.8. Attempted protecting group free spiroketalization

Variants of tetralone **146** were synthesized to facilitate the desired spiroketalization. Methyl enol ether **242** was synthesized via treatment of tetralone **146** with catalytic TsOH and trimethylorthoformate (Scheme **11.9**).[345-347] Triol **238** rapidly decomposed during the

spiroketalization conditions. The pyrolidine enamine **244**[348] and morpholine enamine **243** were also synthesized from **146** with $TiCl_4$ and used without further purification for the spiroketalization reaction (Scheme **11.10**).[349,350] The same rapid decomposition of naphthol **238** was observed during the spiroketalization reaction with the enamines as had occurred with methyl enol ether **242**. In these trials, the lability of the triol was not overcome, and a suitable protecting group needed to be introduced.



Scheme 11.9. Spiroketalization with enol ether **242**



Scheme 11.10. Morpholine and pyrrolidine enamines of tetralone **146**

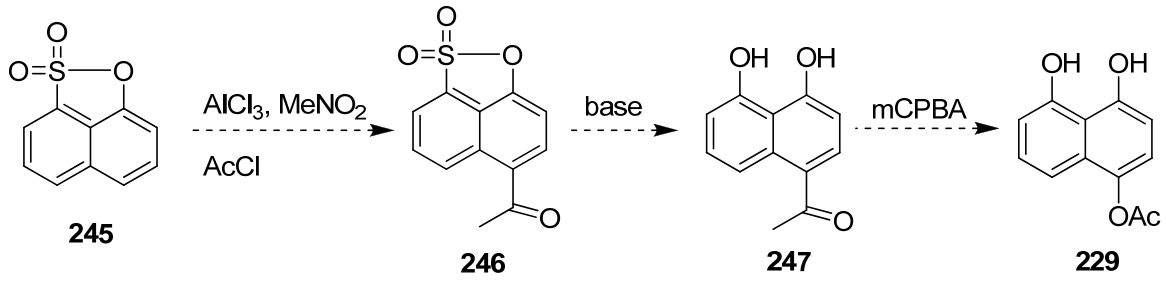
11.5 SYNTHESIS AND PROTECTION OF NAPHTHOL 238

The literature protocols to synthesize trihydroxynaphthalene **238** either proceed in low yield[351] or require the reduction of relatively expensive juglone **231** (Scheme **11.4**).[352,353] A cheap starting material and a concise synthesis of the monoprotected naphthol were desired with minimal protecting group manipulations.

11.5.1 Naphthosultone starting material

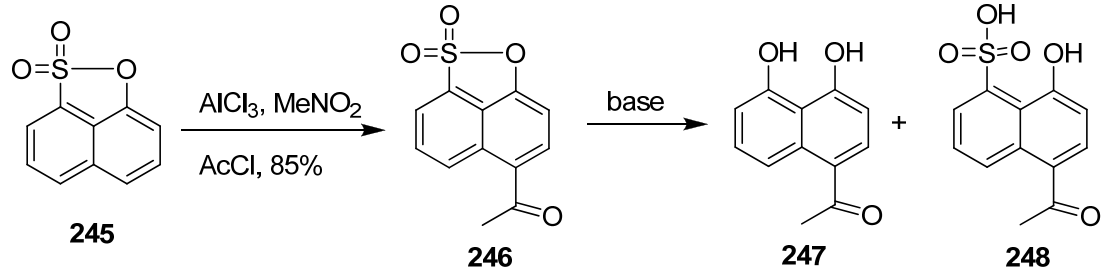
Commercially available and cheap naphthosultone **245** is a synthetic equivalent of 1,8-dihydroxynaphthalene, which is not commercially available (Scheme **11.11**).[125] Conversion of naphthosultone **245** to 1,8-dihydroxynaphthalene requires forceful conditions with strong base

and temperatures around 200 °C.[354,355] It was predicted that the acetylation of **245** to afford **246** would provide a robust enough group to withstand these conditions and also a handle to deliver acetate **229** after conversion to the diol and after Baeyer-Villiger oxidation.



Scheme 11.11. Synthesis of **229** from naphthosultone **245**

Conditions for the Friedel-Crafts acylation of **245** were first screened (Scheme **11.12**).[356] The solution in CH_2Cl_2 could not be heated high enough to promote acylation, but even at 100 °C in $MeNO_2$ no reaction was observed. This lack of conversion was attributed to the evaporation of AcCl. Lowering the temperature to 60 °C led to the successful formation of **246** in 85% yield.



Scheme 11.12. Attempted naphthosultone conversion to **247**

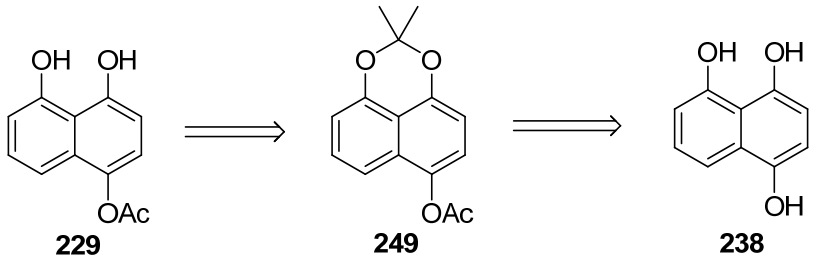
A series of basic conditions were screened for the conversion of **246** to **247** (Scheme **11.12**).[356] A one step conversion to **247** was most desirable, but there are examples in the literature where the major isolated product was naphthol **248**.[357,358] A solution of naphthosultone **246** in either aqueous KOH or NaOH was stirred at room temperature, as well as at 100 °C under conventional heating or microwave conditions, but no **247** was detected (Table **11.1**). The mass recovery for these reactions was poor and the low solubility of the isolated material made characterization and scale-up difficult.

Table 11.1. Deprotection conditions of naphthosultone **246**

Entry	Conditions
1	EtOH, KOH, r.t. to 70 °C
2	KOH, CH_2Cl_2, H_2O, rt
3	KOH, H_2O, 100 °C, 12 h
4	KOH, H_2O, 120 °C, 12 h
5	KOH, H_2O, 120 °C, μW

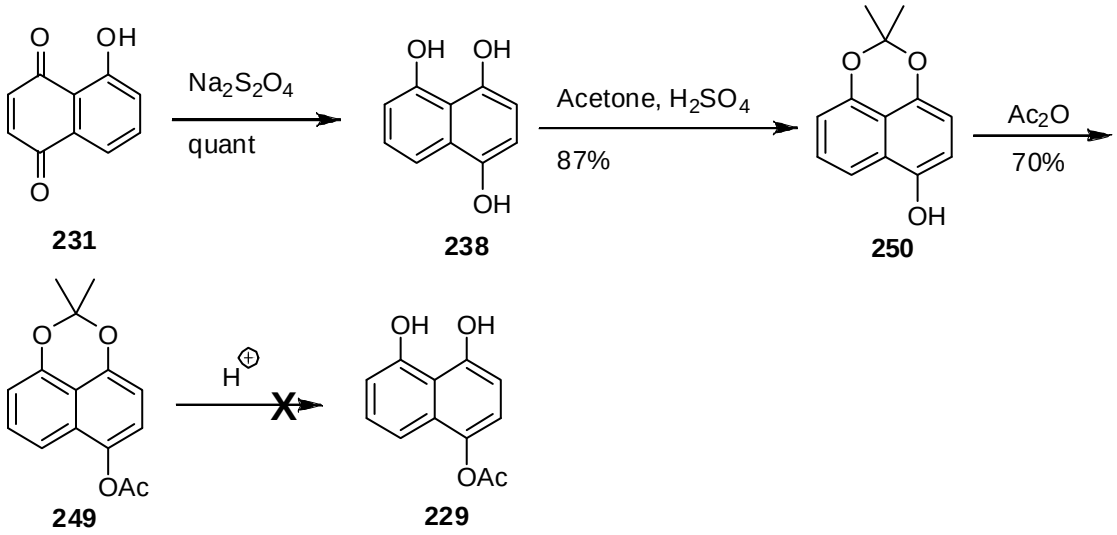
11.5.2 Acetonide protection of 238

An alternative route to monoprotected **229** was the selective deprotection of **249** (Scheme **11.13**).[342] The acetonide of **238** is a known compound and could be readily acetylated.[352] Conditions needed to be developed for selective acetonide deprotection of **229**.



Scheme 11.13. Planned synthesis of **229** via the acetonide

Juglone (**231**) was reduced to triol **238** and subjected directly to acetonide protection by treatment with H_2SO_4 in acetone to afford **250** in good yield (Scheme **11.14**). The acetylation of **250** with acetic anhydride afforded bis-protected **249**.



Scheme 11.14. Protection of naphthalene triol **238**

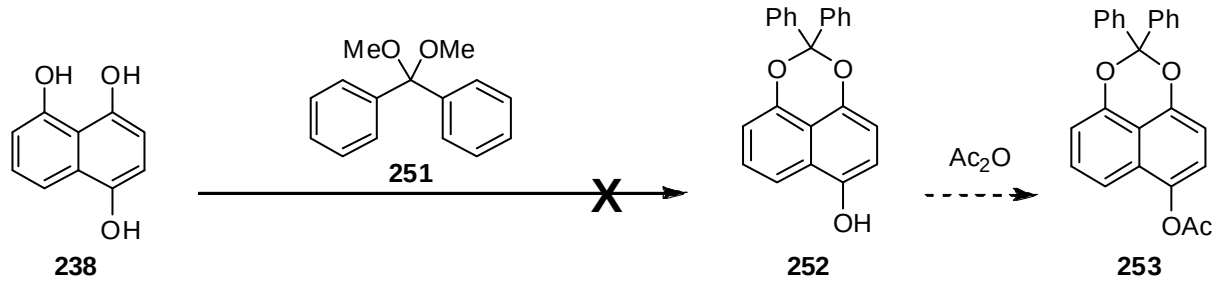
Selectivity problems were encountered with the deprotection of **249** (Table **11.2**). 10% TFA in CH_2Cl_2, 50% TFA, neat TFA, and TFA in THF and H_2O only led to recovered starting material **249** (entries 1-4).[359] Treatment with BCl_3 rapidly decomposed **249** (entry 5).[360] The acetate was lost when **249** was treated with TsOH in MeOH to afford **250** (entry 6). The lability

of the acetate was too great and selective deprotection of the acetonide in the presence of this functionality was not achieved.

Table 11.2. Conditions explored for deprotection of **249**

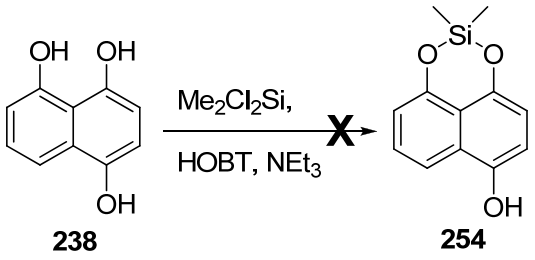
Entry	Conditions	Results
1	TFA, THF, H_2O, r.t.	Starting material
2	TFA, overnight	Starting material
3	TFA, CH_2Cl_2, reflux	Starting material
4	TFA, CH_2Cl_2, 2 days	Starting material
5	BCl_3, CH_2Cl_2, 0 °C	Decomposition
6	TsOH, MeOH	Deacetylation (**250**)
7	HCl, THF	Deacetylation (**250**)

A solution to the undesired preferential cleavage of the acetate in **249** could be identified by the synthesis of diphenylacetal **252**.[361,362] Protection of the 1,8-diol as the diphenyl acetonide and acetylation would afford **253**, a similar scaffold as in Scheme **11.14**.[363,364,365] The advantage of this sequence would be the diphenyl acetonide removal via hydrogenation which should not impact the acetate.[366] Unfortunately, **252** could not be synthesized (Scheme **11.15**).



Scheme 11.15. Failed protection of **238** with benzophenone acetal

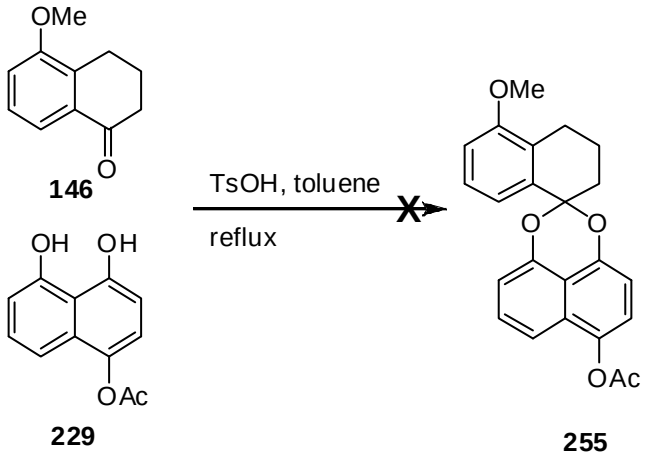
A bridging silicon ether can be synthesized from silyl chlorides,[367] triflates[367] or chlorides in the presence of additives.[368] The attempted silylation of **238** with dichlorodimethylsilane, HOBt and NEt_3 resulted in juglone (**231**) as the major product. (Scheme **11.16**)[369] The electron rich naphthalene triol **238** was a perpetually difficult substrate to handle because of its low solubility and tendency to decompose. Benzyl protected juglone **230** was returned to as the starting point in the synthesis.



Scheme 11.16. Failed protection of **238** with bridging silane

11.5.3 Spiroketalization with protected 238

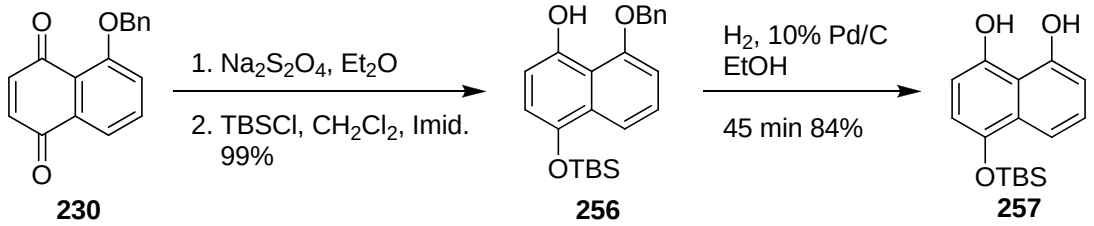
The spiroketalization between tetralone **146** and acetate **229** was investigated. The earlier failed spiroketalization attempts with **146** and **238** were attributed to the decomposition of **238**. A rapid synthesis of **229** was sought starting from cheap starting materials, as previously discussed, but ultimately the previously optimized synthesis of **229** was utilized (Scheme **11.4**). Acetate **229** was synthesized (Scheme **11.4**) and subjected to the spiroketalization conditions with 5-methoxytetralone (**146**) in toluene with catalytic TsOH (Scheme **11.17**). Once again, tetralone **146** was cleanly recovered and **229** decomposed. This is presumably due to the loss of the acetate protecting group during the reaction conditions. This process would unmask **238** which could proceed to decompose. A less labile group, such as a silyl protecting group, was needed to protect **238**.



Scheme 11.17. Acetate protected naphthol **229** in spiroketalization

The synthesis for the silyl protection of **238** followed an analogous route to acetate **229** starting from **231** (Scheme **11.4**). The TBDPS ether was first explored as a protecting group of

reduced **230**, but the reaction with TBDPSCl resulted in many side products that were difficult to characterize. The silylation of reduced **230** with TBSCl proceeded well. Reduction of naphthoquinone **230** with $Na_2S_2O_4$ and TBS protection afforded **256** in 98% yield. The benzyl group was cleaved and diol **257** was initially recovered in 31% yield when the hydrogenation was performed with hydrogen gas and 10% Pd/C in EtOAc and AcOH. A hydrogen transfer reaction with Pd/C (10%) and cyclohexadiene in EtOH improved the yield to 92%. As long as the debenzylation was performed in EtOH in the absence of acid, cyclohexadiene could be replaced by hydrogen gas to afford **257** in 91% yield (Scheme **11.18**).



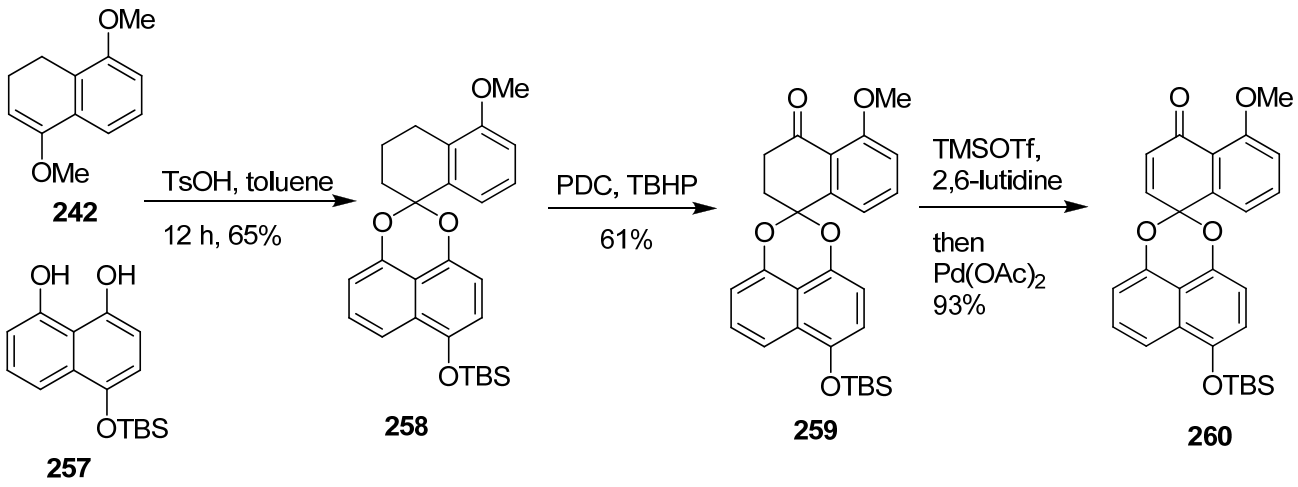
230 **256** **257**

Scheme 11.18. Silylation and debenzylation of naphthoquinone **230**

11.6 COMPLETION OF THE SYNTHESIS OF 211

With mono protected naphthol **257** in hand, the enol ether of 5-methoxytetralone (**242**) was prepared via the previously described treatment of **146** with trimethyl orthoformate and TsOH in MeOH (Scheme **11.9**). The initial attempts for the spiroketalization between **242** and **257** were plagued with either low yields or a coeluting impurity. After much optimization, the impurity could be eliminated and the yield improved by swapping the solvent from MeOH to toluene prior to introduction of diol **257**. The crude solution of **242** was treated with a toluene solution of diol

257 to afford the desired spiroketal **258** in 77%. The spiroketal was subjected to benzylic oxidation with PDC and TBHP to afford **259** in 61% yield (Scheme **11.19**).



Scheme 11.19. Spiroketalization and enone formation

Many conditions were screened for the synthesis of spiroketal **258** (Table **11.3**). The hypothesis was that the coeluting side product could be derived from the methylation of **257** with the residual trimethylorthoformate. Isolating **242** prior to spiroketalization removed the residual trimethyl orthoformate, but resulted in a slower reaction presumably due to partial hydrolysis of the enol ether (entry 2). Various Lewis acids and temperatures were screened, but these variants proceeded in low yield. The best yield and product purity was obtained by performing the solvent swap from methanol to toluene prior to the addition of **257** (entry 9). This modification eliminated the undesired side product and delivered clean spiroketal **259**.

Table 11.3. Spiroketalization to **258** conditions

Entry	Reagents	Conditions	Yield of **258** [%]
1	**257, 146**, $MgSO_4$	Toluene, r.t., 12 h	N.R.
2	**257, 242**, TsOH	**242** isolated prior to spiroketalization, toluene, r.t.	Trace
3	**257, 146**, TMSOTf	-78 °C- r.t.	15
4	**257, 242**, $BF_3{\cdot}OEt_2$	Toluene, r.t. to reflux	Decomp.
5	**257, 146**, TESOTf, $BF_3{\cdot}OEt_2$	Toluene, r.t to reflux	Decomp.
6	**257, 242**, toluene	Solvent swap (from MeOH to toluene) after 12 h	8
7	**257, 146**, TESOTf	Benzene	Decomp.
8	**257, 242**, toluene	Solvent swap (from MeOH to toluene) after addition of **257**	40
9	**257, 242**, toluene	Solvent swap (from MeOH to toluene) prior to addition of **257**	77
10	**257, 146**, TsOH, toluene	Dean-Stark	N.R.

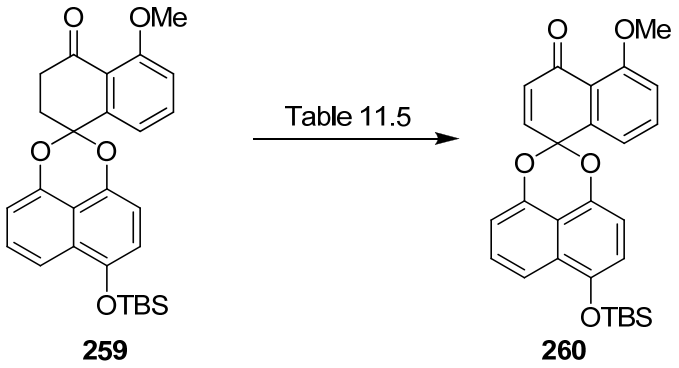
Many conditions were also screened for the benzylic oxidation of **258** to **259** (Table **11.4**). The early trials with PCC (entry 1), PDC (entries 2 and 3) and bipyridiniumchlorochromate (entry 8) with TBHP afforded clean product, albeit in low yield. Oxidation with mCPBA (entry 5), and NBS followed by basic DMSO (entry 6) only resulted in decomposition. DDQ and SiO_2 hydrolyzed **258** to 5-methoxytetralone (**146**), and there was no reaction with $FeCl_3$ and TBHP. Ultimately, PDC and TBHP at room temperature were selected due to the higher yield and the scalability of these conditions (entry 11).

Table 11.4. Benzylic oxidation optimization for conversion of **258** to **259**

Entry	Conditions	Yield [%]
1	PCC, TBHP, benzene	10
2	PDC, TBHP, benzene, 60 °C – reflux	19
3	PDC, TBHP, benzene, reflux	26
4	$FeCl_3$, TBHP, pyridine	n.r.
5	mCPBA, air, CH_2Cl_2	Decomp.
6	NBS then DMSO, Na_2CO_3	Decomp.
7	DDQ, SiO_2	Hydrolysis to **146**
8	Bipyridiniumchlorochromate, TBHP, celite, benzene	10
9	PDC (batchwise), TBHP (batchwise), celite, benzene	44
10	Bipyridiniumchlorochromate, TBHP (slow addition), celite, benzene	50
11	PDC, TBHP, celite, benzene	61

Conditions were also screened for the enone synthesis (Table **11.5**). DDQ consistently provided low yields (entries 1-2). The Saegusa reaction has been successfully employed on similarly functionalized substrates.[123,370] 1.2 Equiv of $Pd(OAc)_2$ delivered 50% of the product with some remaining starting material that closely eluted with the desired product. Lowering the catalyst loading to 0.5 equiv of $Pd(OAc)_2$ with 0.5 equiv of benzoquinone resulted in no desired product (entry 4).[338] Excess lutidine inhibited the oxidation and when the TMS enol ether was purified through a short SiO_2 plug, the reaction proceeded much more efficiently (entry 5). Ultimately, the best conditions were to azeotrope the enol ether with toluene prior to introduction

of $Pd(OAc)_2$ (entry 6). Presumably, this procedure removed the lutidine and also minimized any potential hydrolysis of the enol ether by removing residual water.



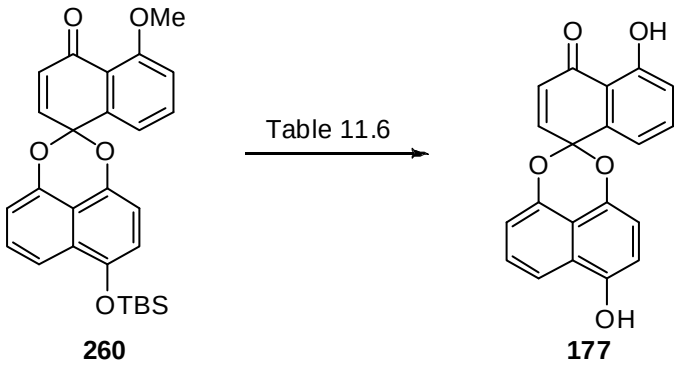
259 **260**

Table 11.5. Optimization of oxidation of **259** to enone **260**

Entry	**Conditions**	**Yield** [%] **of 260**
1	DDQ, benzene, room temperature	n.r.
2	DDQ, reflux	inconsistent
3	TMSOTf, then $Pd(OAc)_2$ (1.2 equiv), CH_3CN	50
4	TMSOTF, then $Pd(OAc)_2$ (0.5 equiv), benzoquinone (0.5 equiv), CH_3CN	n.r.
5	TMSOTf, isolate enol ether, then $Pd(OAc)_2$ (1.2 equiv), CH_3CN	44
6	TMSOTf, azeotrope with toluene, then $Pd(OAc)_2$, CH_3CN	93

With enone **260** in hand, the methyl and TBS ethers needed to be removed (Scheme **11.20**). It was predicted that the TBS group would likely be deprotected under many of the Lewis acidic conditions commonly used for demethylation, but found instead that the TBS group was quite resilient. The first reagent tried was BBr_3 (entry 6).[100] On small scale, both **177** and

TBS protected **177** were isolated according to ^{1}H NMR analysis of the crude reaction mixture. Treating the reaction mixture with TBAF for 10 min afforded 18% of **177** whose mass and ^{1}H NMR matched the previously synthesized material. Other conditions for this deprotection were screened (Table **11.6**). For example, BCl_3 (entry 1),[371,372] B-bromocatechol (entry 7) and B-I-9-BBN (entry 3)[373] were tested, but none of the yields were suitable for scale-up. Methyl deprotection with BCl_3 with Bu_4NI improved the yield ,[374] but there was some decomposition during the TBAF deprotection. Treatment of the reaction mixture with TBAF followed by AcOH did not greatly improve the yield, but the reverse addition improved the yield to 76%. Using these optimized conditions, 1 g of **177** was synthesized.



260 **177**

Scheme 11.20. Methyl ether deprotection and desilylation

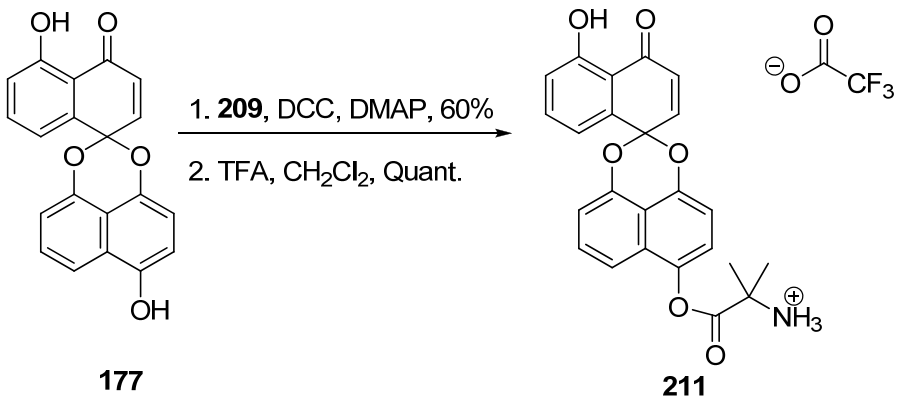
Table 11.6. Deprotection conditions of **260** to **177**

Entry	**Scale**	**Conditions**	**Yield of 177** [%]
1	50 mg	BCl_3, CH_2Cl_2	s.m. + decomp
2	50 mg	BCl_3, Bu_4NI, CH_2Cl_2 then TBAF, AcOH	22
3	50 mg	B-I-9-BBN,	— [1]
4	430 mg	BCl_3, Bu_4NI, CH_2Cl_2, then AcOH, TBAF	68
5	1.7 g	BCl_3, Bu_4NI, CH_2Cl_2, then AcOH, TBAF	76
6	5 mg	BBr_3, then TBAF	18
7	111 mg	2-Bromo-1,3,2-benzodioxaborole, then TBAF	8

[1] enone function was lost

The new synthesis provided 1.0 g of **177** from commercially available materials in 9 steps and an overall yield of 26%. This is a significant improvement from the original synthesis that was completed in 20 steps with a yield of 0.01%. The last reaction needed for completion of this project was an esterification to the AIB prodrug **211**. This esterification was performed in four 250 mg batches. The yield for the overall process was comparable to the yield observed on

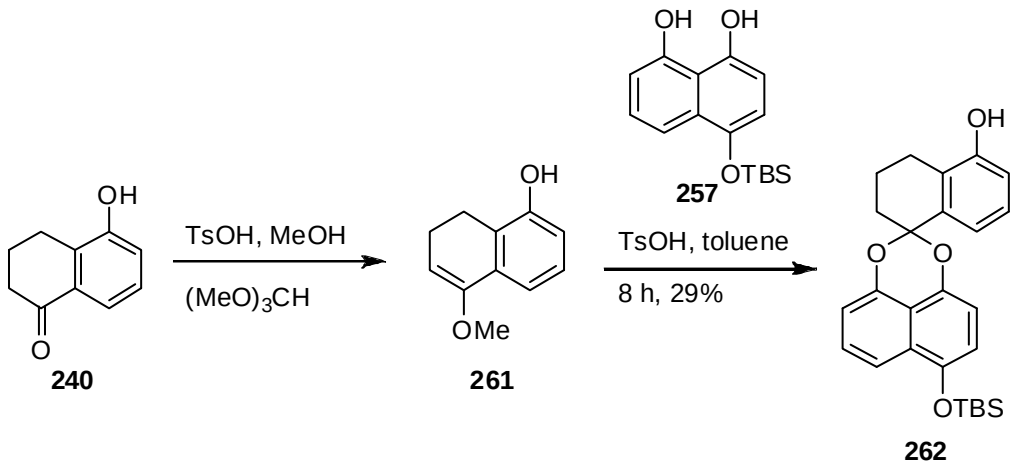
the smaller scale. A final BOC-deprotection utilizing 10% TFA in CH_2Cl_2 afforded **211** as the TFA salt.



Scheme 11.21. Synthesis of AIB prodrug **211**

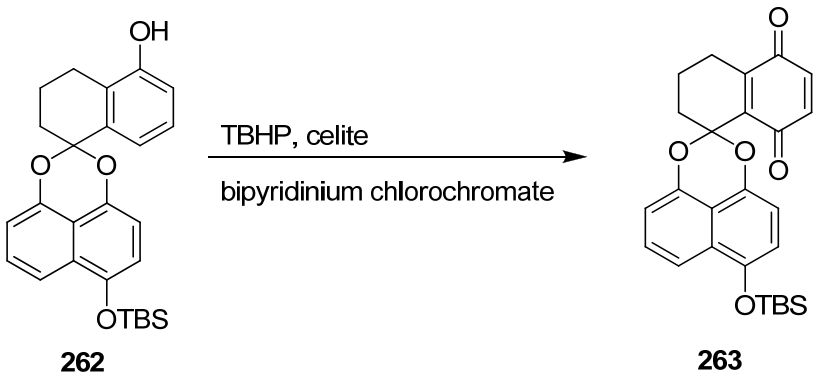
11.7 PURSUIT OF 211 STARTING FROM 240

Before the global deprotection of **260** to **177** was optimized (Scheme **11.21**), there was concern about the scalability of the late stage removal of the methyl ether in **260**. The spiroketalization starting with 5-hydroxytetralone (**240**) was concurrently being investigated (Scheme **11.22**). This modification would bypass the demethylation of the more acid sensitive spiroketal **260** to the more robust methoxytetralone **146**. With spiroketal **262** in hand, benzylic oxidation, enone introduction and a final deprotection would afford **177**. 5-Methoxytetralone **146** was deprotected with HBr and AcOH to afford tetralone **240** in good yield. The unoptimized spiroketalization afforded **262** in 20% overall yield.



Scheme 11.22. Spiroketalization with free phenol **261**

With **262** in hand, the benzylic oxidation to **260** was investigated (Scheme **11.23**). In all the references found, phenols were protected prior to oxidation. The first condition applied was catalytic bipyridinium chlorochromate with TBHP as the co-oxidant. This reaction proceeded cleanly and 80% of a bright orange oil was isolated. Characterization revealed that the product was in fact quinone **263** and not the desired tetralone. Bipyridinium chlorochromate delivered trace amounts of the desired product according to ^{1}H NMR analysis. DDQ and mCPBA in the presence of air did not lead to any conversion. Accordingly, the route described in Scheme **11.20** was pursued.

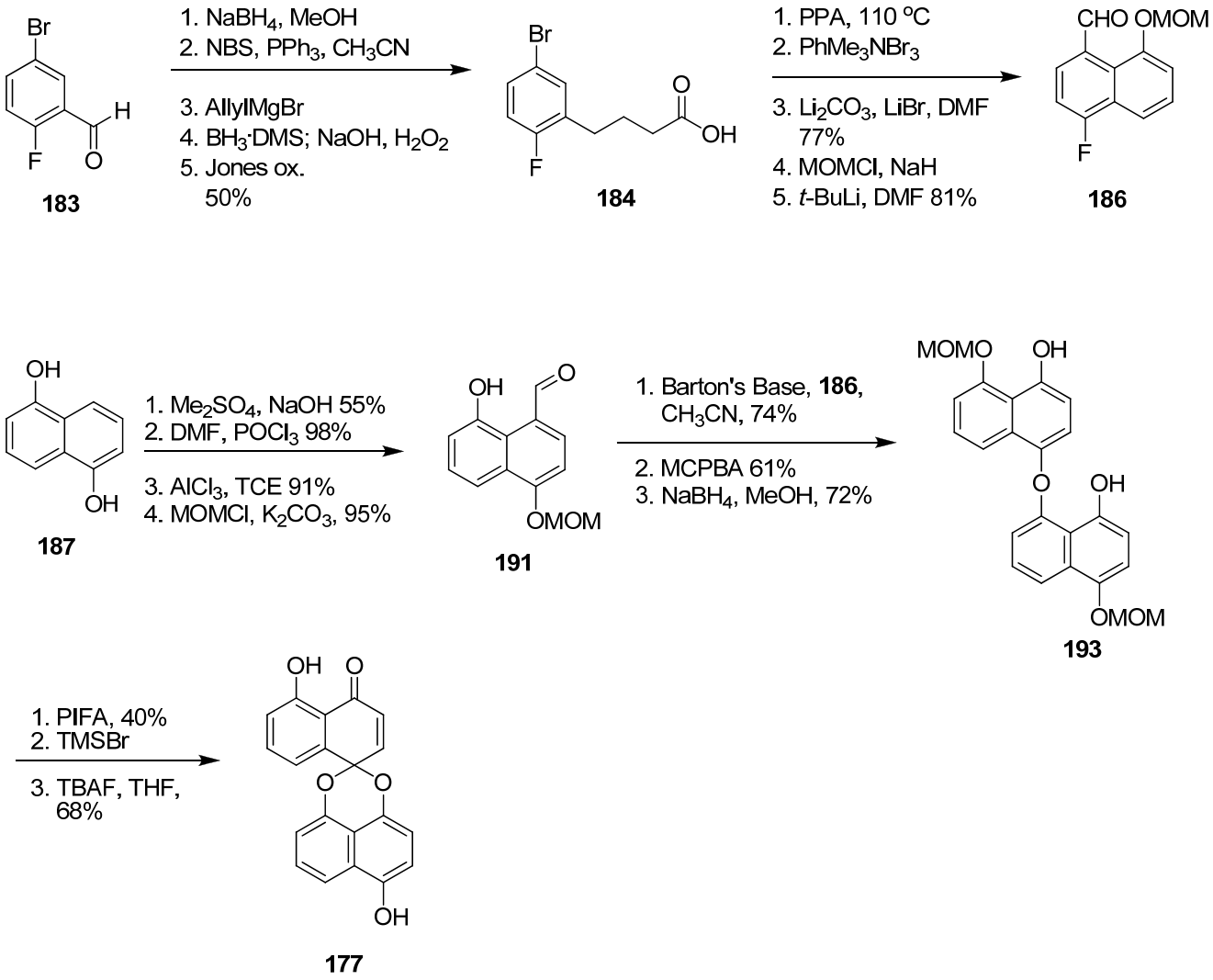


262 **263**

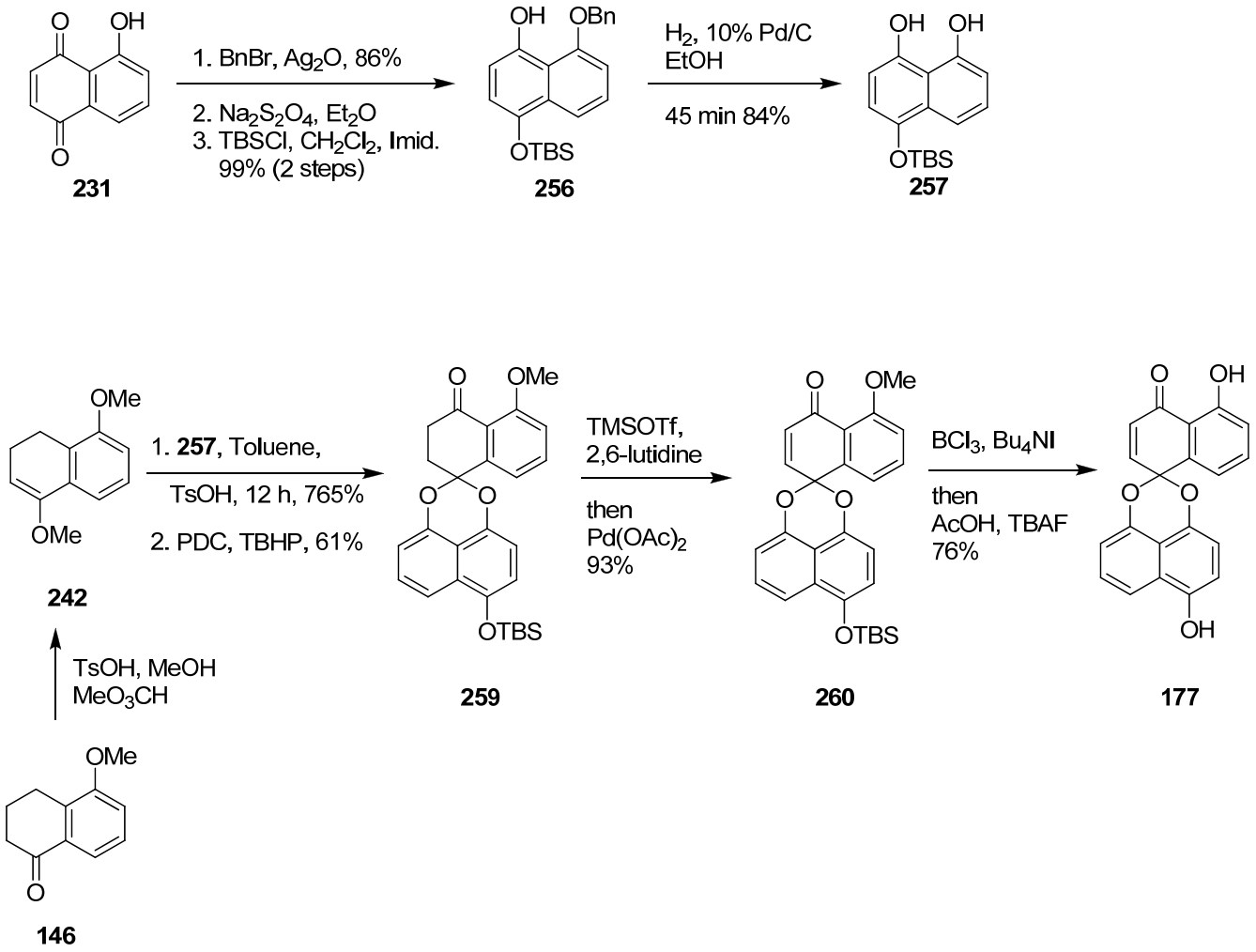
Scheme 11.23. Undesired oxidation of spiroketal to **263**

11.8 CONCLUSION

An efficient second generation route to **177** was developed. After much optimization, **177** was synthesized in 9 steps and 26% overall yield starting from commercially available material. The original route required 20 steps and provided 0.01% overall yield (Scheme **11.24**). As discussed earlier, the original route was only scaleable to 100 mg of **177**, but suffered from mediocre efficiency. One of the primary problems encountered was the PIFA mediated oxidative cyclization of **193**. It was predicted it would be beneficial to construct the spiroketal in an alternative fashion when developing a synthesis amenable to the scaleup of **177** and subsequent prodrug synthesis. Ultimately, spiroketalization between the naphthol and tetralone with catalytic amounts of acid reliably delivered the desired product and was amenable to further scaleup.



Scheme 11.24. Original synthesis of **177**



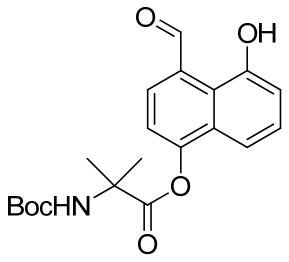
Scheme 11.25. Final route for scaleup of **177**

The revised synthesis was scaleable and readily provided 1 g of **177** (Scheme **11.25**). Conditions were developed for the selective monoprotection of the naphthalene triol and various protecting groups were screened until it was found that TBS protected **257** was robust enough for the spiroketalization conditions. The spiroketalization was optimized to eliminate the side product formation and proceeded in good yield. The addition of Bu_4NI to BCl_3 was discovered to effectively demethylate **260** in good yield. This route delivered **177** in a rapid and concise

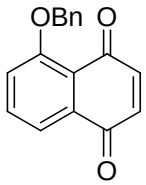
sequence. Acylation with the AIB ester and BOC-deprotection afforded 1.1 g of **211** that was delivered to the laboratory of Dr. Garth Powis for animal studies.

12.0 PRODRUG SCALE UP EXPERIMENTAL PART

General: All moisture sensitive reactions were performed in flame-dried or oven-dried glassware under a nitrogen atmosphere. THF and Et_2O were distilled over Na/benzophenone, while pyridine and triethylamine were distilled over CaH_2. Hexanes and ethyl acetate were distilled prior to use. All other reagents and solvents were used as received unless otherwise noted. Analytical thin layer chromatography was performed on pre-coated silica gel 60 F-254 plates available from Merck. Flash chromatography was performed using silica gel (230-400 mesh) available from Baker. NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR using a Bruker Avance 300 with XWIN-NMR software. Chemical shifts (δ) are expressed relative to the NMR solvent peak. IR spectra were obtained with a Nicolet Avator 360 FT-IR, ATR-IR spectra were measured with a Smiths IdentifyIR, optical rotations were measured with a Perkin-Elmer 241 polarimeter and mass spectra were obtained on a double focusing instrument. EI mass spectra were obtained with VG Autospec and ESI mass spectra with Q-TOF API US.

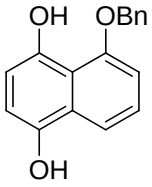


4-Formyl-5-hydroxynaphthalen-1-yl 2-(*tert*-butoxycarbonylamino)-2-methylpropanoate (225). A solution of naphthol **190** (Scheme **9.2**, 100 mg, 0.532 mmol) in CH_2Cl_2 (44.3 mL) was treated with N-Boc AIB (**209**)[316,317] (174 mg, 0.857 mmol) followed by DCC (171 mg, 0.829 mmol) and DMAP (17 mg, 0.14 mmol) and stirred for 12 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography on SiO_2 (7:3, hexanes:EtOAc) to afford 172 mg (90%) of ester **225** as a bright yellow solid: Rf 0.3 (7:3, hexanes:EtOAc); Mp 148.7-149.2 °C (EtOAc/hexanes); IR (ATR) 3409, 2982, 1756, 1697, 1666, 1517, 1500, 1470, 1452, 1387, 1270, 1150, 1213, 1149, 744 cm^{-1}; ^1H NMR δ 11.86 (s, 1 H), 9.82 (s, 1 H), 8.07 (d, 1 H, *J* = 8.1 Hz), 7.62 (dd, 1 H, *J* = 1.2, 8.1 Hz), 7.55 (d, 1 H, *J* = 7.8 Hz), 7.49 (d, 1 H, *J* = 8.1 Hz), 7.21 (dd, 1 H, *J* = 1.2, 7.5 Hz), 5.20 (bs, 1 H), 1.5 (s, 9H); ^{13}C NMR δ 196.8, 172.5, 155.6, 154.8, 142.9, 130.0, 129.8, 129.5, 122.8, 116.6, 113.1, 80.5, 56.5, 28.3, 25.6; MS (ESI-Q-TOF) *m/z* (rel intensity) 396 ($[M+23]^+$, 35), 189 (100); HRMS (ESI-Q-TOF) calculated for $C_{20}H_{23}NO_6Na$ 396.1525, found 396.1535.

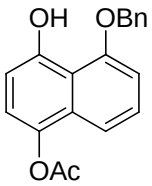


5-(Benzyloxy)naphthalene-1,4-dione (230).[290] A solution of juglone (**231**) (1.70 g, 9.76 mmol) in CH_2Cl_2 (37 mL) was treated with Ag_2O (9.14 g, 39.0 mmol) followed by benzyl bromide (3.79 mL, 31.3 mmol) and stirred at room temperature for 8 h. The reaction mixture was filtered through celite, washed (CH_2Cl_2), concentrated under reduced pressure and purified by column chromatography on SiO_2 (4:1, hexanes:EtOAc) to afford 2.57 g (86%) of **230** as a bright orange solid: Rf 0.3 (7:3, hexanes:EtOAc); ^1H NMR δ 7.74 (d, 1 H, *J* = 7.5 Hz), 7.64 (t, 1 H, *J* = 8.1

Hz), 7.58 (d, 2 H, *J* = 7.5 Hz), 7.42 (t, 2 H, *J* = 7.2 Hz), 7.53-7.33 (m, 2 H), 6.89 (s, 2 H), 5.30 (s, 2 H); MS (EI) *m/z* (rel intensity) 264 (M^+, 30), 246 (25), 174 (60), 160 (35), 105 (54), 91 (100), 77 (71); HRMS (EI) calculated for $C_{17}H_{12}O_3$ 264.0786, found 264.0786.

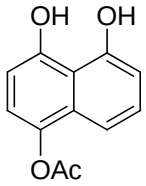


5-(Benzyloxy)naphthalene-1,4-diol. A suspension of benzyl juglone (**230**) (2.57 g, 9.72 mmol) in Et_2O (406 mL) was treated with a solution of $Na_2S_2O_4$ (22.01 g, 126.4 mmol) in H_2O (256 mL). The biphasic mixture was transferred to a separatory funnel and shaken for 10 min and separated. The organic extract was dried (Na_2SO_4), filtered, concentrated under reduced pressure to afford 2.30 g (89%) of the naphthalene diol as an off-white solid that was used without further purification: Rf 0.4 (3:2, hexanes:EtOAc); ^{1}H NMR (DMSO-d_6) δ 9.36 (s, 1H), 8.89 (s, 1 H), 7.67 (d, 1 H, *J* = 8.4 Hz), 7.56 (d, 2 H, *J* = 6.6 Hz), 7.46-7.40 (m, 3 H), 7.30 (t, 1 H, *J* = 8.3 Hz), 7.07 (d, 1 H, *J* = 7.5 Hz), 6.73 (d, 1 H, *J* = 8.4 Hz), 6.57 (d, 1 H, *J* = 8.1 Hz), 5.38 (s, 2 H); MS (EI) *m/z* (rel intensity) 266 (M^+, 16), 175 (42), 91 (100), 69 (100); HRMS (EI) calculated for $C_{17}H_{14}O_3$ 266.0943, found 266.0933,



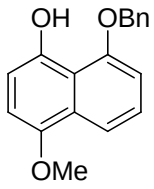
1-(Benzyloxy)-8-hydroxynaphthalen-5-yl acetate (232).[375] A solution of 5-(benzyloxy)naphthalene-1,4-diol (146 mg, 0.474 mmol) in CH_2Cl_2 (7.5 mL) and NEt_3 (0.15 mL,

11 mmol) was treated with AcCl (0.05 mL, 0.7 mmol) and stirred at room temperature for 15 min. The reaction mixture was quenched with H_2O, extracted with CH_2Cl_2 (2x), dried (Na_2SO_4), filtered, concentrated under reduced pressure and purified by column chromatography on SiO_2 (7:3, hexanes:EtOAc) to afford 0.140 g (82%) of acetate **232** as a bright orange solid: Mp 154.3-155.1 °C (EtOAc); Rf 0.4 (7:3, hexanes:EtOAc); ^{1}H NMR δ 9.35 (s, 1 H), 7.51-7.41 (m, 6 H), 7.35 (dd, 1 H, *J* = 8.4, 7.2 Hz), 7.12 (d, 1 H, *J* = 8.4 Hz), 6.91 (dd, 1 H, *J* = 7.5, 1.2 Hz), 6.82 (d, 1 H, *J* = 8.4 Hz), 5.29 (s, 2 H), 2.42 (s, 3 H); MS (EI) *m/z* (rel intensity) 308 (M^+, 41), 266 (33), 175 (77), 174 (23), 91 (100); HRMS (EI) calculated for $C_{19}H_{16}O_4$ 308.1049, found 308.1049.

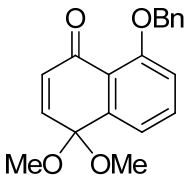


1,8-Dihydroxynaphthalen-5-yl acetate (229). A solution of acetate **232** (140 mg, 0.452 mmol) in EtOAc (14 mL) was treated with 10% Pd/C (22.5 mg, 0.0212 mmol) followed by acetic acid (0.03 mL, 0.4 mmol) and purged twice with H_2. The reaction mixture was stirred under atmospheric H_2 for 15 min, filtered through celite, washed (EtOAc), concentrated under reduced pressure and purified by column chromatography on SiO_2 (7:3, hexanes:EtOAc) to deliver 0.114 g (quant) of the diol as a light yellow oil: Rf 0.1 (7:3, hexanes:EtOAc); IR (neat) 3297 (bs), 1731, 1612, 1590, 1411, 1370, 1229, 1205, 1031, 946, 809 cm^{-1}; ^{1}H NMR δ 8.26 (bs, 1 H), 8.20 (bs, 1H), 7.19 (dd, 1 H, *J* = 8.4, 7.2 Hz), 7.14 (dd, 1 H, *J* = 8.4, 1.5 Hz) 6.92 (d, 1 H, *J* = 8.4 Hz), 6.58 (dd, 1 H, *J* = 7.2, 1.2 Hz), 6.49 (d, 1 H, *J* = 8.4 Hz), 2.49 (s, 3 H); ^{13}C NMR δ 172.1, 153.4, 151.8, 139.0, 129.0, 127.7, 118.8, 115.3, 112.8, 110.3, 108.0, 21.1; MS (EI) *m/z* (rel intensity)

218 (M^+,11), 177 (11), 176 (100), 147 (17), 86 (32), 84 (48), 57 (44); HRMS (EI) calculated for $C_{12}H_{16}O_4$ 218.0579, found 218.0580.

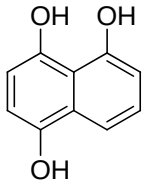


8-(Benzyloxy)-4-methoxynaphthalen-1-ol (233).[290,334] A solution of 5-(benzyloxy)naphthalene-1,4-diol (0.183 g, 0.691 mmol) in acetone (9 mL) was treated with K_2CO_3 (0.270 g, 1.95 mmol) followed by Me_2SO_4 (0.066 mL, 0.69 mmol) and stirred for 12 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography on SiO_2 (1:4, EtOAc:hexanes) to deliver 0.19 g (98%) of **233** as an off white solid: Rf 0.8 (7:3, hexanes:EtOAc); Mp 108.9-109.5 °C (EtOAc); IR (neat) 3394, 2920, 2851, 1630, 1606, 1456, 1410, 1291, 1261, 1234, 1054, 982, 819, 802, 781, 752 cm^{-1}; ^1H NMR δ 9.09 (s, 1 H), 7.87 (dd, 1 H, *J* = 8.6, 0.9 Hz), 7.51-7.40 (m, 4 H), 7.33 (t, 2 H, *J* = 8.4 Hz), 6.93 (d, 1 H, *J* = 7.8 Hz), 6.77 (s, 2 H), 5.28 (s, 2 H), 3.94 (s, 3 H); ^{13}C NMR δ 155.2, 148.2, 147.9, 135.3, 129.0, 128.8, 128.0, 125.1, 116.2, 115.7, 109.2, 106.3, 71.7, 56.0; MS (EI) *m/z* (rel intensity) 280 (M^+, 26), 190 (21), 189 (100), 91 (84), 69 (52); HRMS (EI) calculated for $C_{18}H_{16}O_3$ 280.1099, found 280.1108

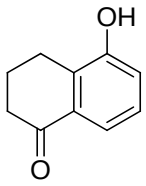


8-(Benzyloxy)-4,4-dimethoxynaphthalen-1(4*H*)-one (228).[376] A solution of methyl ether **233** (0.208 g, 0.742 mmol) in MeOH (17.6 mL) was treated with DDQ (0.250 g, 1.08 mmol)

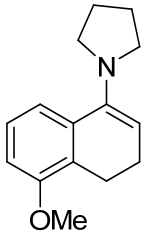
followed by K_2CO_3 (0.152 g, 1.10 mmol) and stirred at room temperature for 5 min. The reaction mixture was quenched with 10% $Na_2S_2O_3$ and extracted with EtOAc (2x). The combined organic extracts were washed with H_2O, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford **228** as a light yellow oil which was used without further purification: Rf 0.4 (7:3, hexanes:EtOAc); ^{1}H NMR δ 7.62-7.55 (m, 3 H), 7.43-7.28 (m, 4 H), 7.08 (d, 1 H, *J* = 8.4 Hz), 6.76 (d, 1 H, *J* = 10.5 Hz), 6.53 (d, 1 H, *J* = 10.5 Hz), 5.27 (s, 2 H), 3.17 (s, 6 H); MS (EI) *m/z* (rel intensity) 310 (M^+, 10), 279 (20), 266 (21), 264 (22), 189 (6), 175 (14), 91 (100); HRMS (EI) calculated for $C_{19}H_{18}O_4$ 310.1205, found 310.1189.



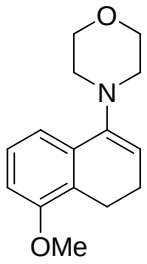
Naphthalene-1,4,5-triol (238). A suspension of juglone (**231**) (0.500 g, 2.87 mmol) in Et_2O (20 mL) was transferred to a separatory funnel, treated with a freshly prepared solution of $Na_2S_2O_4$ (2.0 g, 12 mmol) in H_2O (20 mL) and shaken for 10 min. The organic extract was separated, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Further drying under high vacuum afforded **238** as a white solid (quant.) which was used without further purification: ^{1}H NMR (DMSO-d_6) δ 10.70 (s, 1 H), 10.34 (s, 1 H), 9.35 (s, 1 H), 7.50 (d, 1 H, *J* = 8.4 Hz), 7.21 (dd, 1 H, *J* = 8.4, 7.2 Hz), 6.71 (d, 1 H, *J* = 7.2 Hz), 6.65 (d, 1 H, *J* = 8.1 Hz), 6.54 (d, 1 H, *J* = 8.1 Hz).



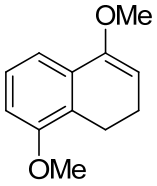
5-Hydroxy-3,4-dihydronaphthalen-1(2*H*)-one (240). A solution of 5-methoxytetralone **146** (0.100 g, 0.5675 mmol) in sat. HBr (9.0 mL) was treated with AcOH (1.0 mL, 17 mmol) and heated to 100 °C for 2 h. The reaction mixture was cooled to room temperature, poured into H_2O, extracted (EtOAc), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (7:3, hexanes:EtOAc) afforded 66.3 mg (72%) of **240** as a yellow solid: Rf 0.3 (7:3, EtOAc:hexanes); ^{1}H NMR δ 7.67 (1H, d, J = 7.8 Hz), 7.19 (1 H, t, J = 7.5 Hz), 6.97 (d, 1 H, J = 7.8 Hz), 2.90 (t, 2 H, J = 6.3 Hz), 2.65 (t, 2 H, J = 6.6 Hz), 2.16 (app, 2 H, J = 6.3 Hz); MS (EI) *m/z* (rel intensity) 162 (M^+, 100), 134 (64), 106 (30); HRMS (EI) calculated for $C_{10}H_{10}O_2$ 162.0681, found 162.0685.



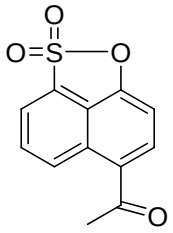
1-(1,2-Dihydro-8-methoxynaphthalen-4-yl)pyrrolidine (244). A solution of 5-methoxytetralone (**146**) (0.100 g, 0.567 mmol) in Et_2O (2.84 mL) was treated with pyrrolidine (0.16 mL, 1.9 mmol), cooled to 0 °C and treated with a freshly prepared solution of $TiCl_4$ in Et_2O (0.03 mL of $TiCl_4$ in 0.5 mL of Et_2O). The reaction mixture was warmed to room temperature, stirred for 15 h and monitored by ^{1}H NMR analysis of the crude reaction mixture. It was filtered through a plug of SiO_2, washed (Et_2O), concentrated under reduced pressure and **244** was used without further purification: Diagnostic ^{1}H NMR signal δ 5.19 (t, 1 H, J = 4.5 Hz).



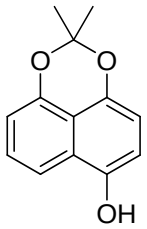
4-(1,2-Dihydro-8-methoxynaphthalen-4-yl)morpholine (243). A solution of 5-methoxy tetralone (**146**) (0.100 g, 0.567 mmol) in Et_2O (2.84 mL) was treated with morpholine (0.20 mL, 2.3 mmol). The reaction mixture was cooled to 0 °C, treated with a freshly prepared solution of $TiCl_4$ in Et_2O (0.03 mL of $TiCl_4$ in 0.5 mL of Et_2O), warmed to room temperature and stirred for 15 h. The reaction was monitored by ^1H NMR and completion was established via the appearance of the enamine signal: ^1H NMR δ 5.29 (t, 1 H, J = 4.5 Hz).



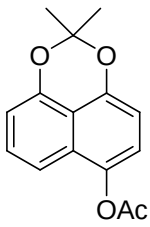
1,2-Dihydro-4,8-dimethoxynaphthalene (242). A solution of 5-methoxytetralone (**146**) (0.550 g, 3.12 mmol) in MeOH (12 mL) was treated with TsOH (17.8 mg, 0.0935 mmol) followed by trimethylorthoformate (1.20 mL, 10.9 mmol) and stirred at room temperature for 6.5 h. The mixture was monitored by TLC (7:3, hexanes:EtOAc) and used without further purification: Rf 0.5 (7:3, hexanes:EtOAc); diagnostic ^1H NMR δ 5.04 (t, 1 H, J = 4.7 Hz).



5-Acetyl-1,8-naphthosultone (246).[377] A solution of 1,8-naphthosultone (**245**) (1.0 g, 4.8 mmol) and acetyl chloride (0.6 mL, 0.66 g, 8.4 mmol) in $MeNO_2$ (48 mL) was treated with $AlCl_3$ (2.6 g, 19.4 mmol) portionwise over 10 min, stirred at room temperature for 1 h and then heated to 60 °C for 9 h. The reaction mixture was cooled to room temperature, poured into 2 M H_3PO_4 (200 mL) and extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with H_2O, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (7:3, hexanes:EtOAc) afforded 1.026 g (85%) of **246** as a white solid: Rf 0.25 (7:3, hexanes:EtOAc); Mp 159.8-160.4 °C (CH_2Cl_2); IR (ATR) 1668, 1577, 1482, 1457, 1364, 1265, 1174, 1150, 1075, 1101, 833 cm^{-1}; ^1H NMR δ 9.31 (d, 1 H, J = 8.4 Hz), 8.32 (d, 1 H, J = 8.1 Hz), 8.10 (d, 1 H, J = 7.2 Hz), 7.97 (dd, 1 H, J = 7.5, 8.4 Hz), 7.20 (d, 1 H, J = 7.8 Hz), 2.77 (s, 3 H); ^{13}C NMR (DMSO-d_6) 199.0, 148.8, 135.6, 132.1, 131.7, 129.7, 128.3, 127.2, 122.8, 120.8, 106.2, 28.6; MS (EI) *m/z* (rel intensity) 248 (M^+, 44), 233 (100), 206 (35), 176 (12), 142 (27), 114 (22), 113 (35), 57 (100); HRMS (EI) calculated for $C_{12}H_8O_4S$ 248.0143, found 248.0141.

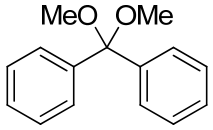


2,2-Dimethylnaphtho[1,8-*de*][1,3]dioxin-6-ol (250).[342] A solution of trihydroxynaphthalene **238** (0.175 g) in acetone (30 mL) was treated with H_2SO_4 (0.4 mL). The reaction mixture changed colors from orange to dark red over 12 h. It was diluted with H_2O, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The mixture was purified by column chromatography on SiO_2 (4:1, hexanes:EtOAc to 3:2, hexanes:EtOAc) to afford 0.186 g (87%) of **250** as a dark brown oil: Rf 0.25 (3:2, hexanes:EtOAc); ^{1}H NMR δ 7.66 (d, 1 H, *J* = 8.4 Hz), 7.41 (t, 1 H, *J* = 8.4 Hz), 6.89 (d, 1 H, *J* = 7.5 Hz), 6.76 (d, 1 H, *J* = 8.1 Hz), 6.69 (d, 1 H, *J* = 8.1 Hz), 1.64 (s, 6 H); MS (EI) *m/z* (rel intensity) 216 (M^+, 12), 176 (24), 102 (70), 96 (100), 83 (87), 74 (100); HRMS (EI) calculated for $C_{13}H_{12}O_3$ 216.0786, found 216.0868.

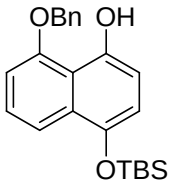


2,2-Dimethylnaphtho[1,8-*de*][1,3]dioxin-7-yl acetate (249). A solution of acetal **250** (0.175 g, 0.810 mmol) in CH_2Cl_2 (8.0 mL) was treated with acetic anhydride (0.15 mL, 1.6 mmol) and pyridine (0.15 mL, 1.9 mmol) and stirred at room temperature for 2 h. Starting material remained according to TLC (7:3, hexanes:EtOAc) and additional Ac_2O (0.05 mL, 0.5 mmol) was added. After an additional 3 h, the reaction mixture was quenched with H_2O, diluted with CH_2Cl_2, extracted, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (9:1, hexanes:EtOAc) afforded 0.146 g (70%) of the desired acetate as a colorless oil: Rf 0.6 (7:3, hexanes:EtOAc); IR (ATR) 2993, 2917, 1763, 1606, 1415, 1385, 1264, 1193, 1040 cm^{-1}; ^{1}H NMR δ 7.34-7.48 (m, 2 H), 7.15 (d, 1 H, *J* =

8.1 Hz), 6.89 (d, 1 H, *J* = 7.2 Hz), 6.82 (d, 1 H, *J* = 8.1 Hz), 2.44 (s, 3 H), 1.66 (s, 6 H); ^{13}C NMR δ 169.5, 148.1, 145.7, 140.1, 127.9, 127.2, 119.4, 114.0, 109.5, 108.1, 101.9, 25.1, 20.8; MS (EI) *m/z* (rel intensity); 258 (M^+, 22), 216 (100), 176 (38), 173 (29); HRMS (EI) calculated for $C_{15}H_{14}O_4$ 258.0892, found 258.0897.

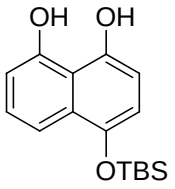


Dimethoxydiphenylmethane (251).[361] A suspension of montmorillonite K-10 (0.190 g) in anhydrous methanol (4.0 mL) was treated with trimethylorthoformate (3.0 mL, 0.027 mol) and p-TsOH (10 mg, 0.053 mmol) and stirred for 5 min before the addition of benzophenone (1.0 g, 5.5 mmol). The reaction mixture was stirred for 48 h, diluted with CH_2Cl_2, filtered over celite, washed with sat. Na_2CO_3, H_2O, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (9:1, hexanes:EtOAc) delivered 17.1 mg (2%) of **251** as a white solid: ^{1}H NMR δ 7.53 (d, 2 H, *J* = 7.5 Hz), 7.32 (m, 2H), 7.26 (m, 1 H), 3.15 (s, 3 H); MS (EI) *m/z* (rel intensity) 228 (M^+, 3), 197 (100), 151 (58), 105 (100), 91 (20), 77 (100), 51 (64); HRMS (EI) calculated for $C_{15}H_{16}O_2$ 228.1150, found 228.1149.



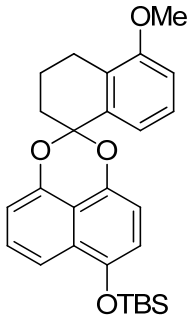
4-(*tert*-Butyldimethylsiloxy)-8-(benzyloxy)naphthalen-1-ol (256). A suspension of 5-(benzyloxy)naphthalene-1,4-diol (1.99 g, 7.47 mmol) in CH_2Cl_2 (110 mL) was treated with imidazole (0.763 g, 8.97 mmol) and stirred until all solids were dissolved. The reaction mixture

was treated with TBSCl (1.37 g, 8.97 mmol), stirred at room temperature for 2.5 h, quenched with H_2O and extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with H_2O, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (4:1, hexanes:EtOAc) afforded 2.84 g (99%) of the TBS ether **256** as a light yellow oil: Rf 0.7 (7:3, hexanes:EtOAc); IR (neat) 3428.1 (bs), 2954.8, 2930.0, 2886.4, 2857.3, 1608.0, 1512.0, 1460.5, 1411.9, 1361.5, 1282.0, 1259.0, 1237.9, 1038.5, 1014.9, 835.3 cm^{-1}; ^1H NMR δ 9.03 (s, 1 H), 7.78 (d ,1 H, J = 8.7 Hz), 7.51-7.40 (m, 5 H), 7.30 (t, 1 H, J = 8.1 Hz), 6.90 (d, 1 H, J = 7.8 Hz), 6.79 (d, 1 H, J = 9.3 Hz), 6.70 (d, 1 H, J = 8.1 H), 5.27 (s, 2 H), 1.14 (s, 9 H), 0.23 (s, 6 H); ^{13}C NMR δ 155.2, 148.4, 143.7, 135.2, 130.1, 128.9, 128.7, 127.9, 124.9, 116.8, 115.8, 114.6, 109.5, 105.7, 71.5, 26.2, 18.3, −4.3; MS (ESI-Q-TOF) *m/z* (rel intensity) 403 ($[M+Na]^+$, 100), 381 ($[M+H]^+$,47), 380 (M^+,10), 365 (25), 362 (27), 290 (88), 289 (33); HRMS (ESI- Q-TOF) calculated for $C_{23}H_{28}O_3SiNa$ 403.1705, found 403.1685.



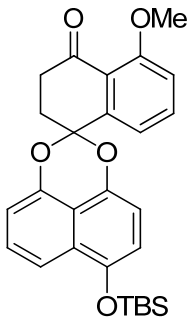
4-(*tert*-Butyldimethylsilyloxy)naphthalene-1,8-diol (257). A solution of benzyl ether **256** (1.00 g, 2.63 mmol) in EtOH (232 mL) was treated with 10% Pd/C (0.559 g, 0.526 mmol) and purged with H_2 (2x). The reaction mixture was stirred at room temperature under atmospheric H_2 for 1 h, filtered through a plug of celite and washed with CH_2Cl_2. It was concentrated under reduced pressure and purified by column chromatography on SiO_2 (4:1, hexanes:EtOAc) to deliver 0.64 g (84%) of the **257** as a light yellow oil (this material decomposes when stored concentrated): Rf 0.4 (7:3, hexanes:EtOAc); IR (neat); 3249 (bs), 2955, 2931, 2892, 2858,

1612, 1520, 1467, 1412, 1282, 1259, 1029, 963, 842, 808, 780 cm^{-1}; ^1H NMR δ 8.39 (bs, 1 H), 7.67 (d, 1 H, *J* = 8.4 Hz), 7.39 (bs, 1 H), 7.30 (t, 1 H, *J* = 8.0 Hz), 6.83 (d, 1 H, *J* = 7.2 Hz), 6.70 (d, 1H, *J* = 8.1 Hz), 6.63 (d, 1 H, *J* = 8.1 Hz), 1.07 (s, 9H), 0.23 (s, 6 H); ^{13}C NMR δ 152.8, 146.4, 145.2, 130.5, 126.3, 115.3, 115.2, 113.2, 110.0, 108.5, 25.9, 18.4, −4.3; MS (EI) *m/z* (rel intensity) 290 (M^+, 59), 234 (29), 233 (100), 217 (15), 215 (12), 73 (30); HRMS (EI) calculated for $C_{16}H_{22}O_3Si$ 290.1338, found 290.1339.



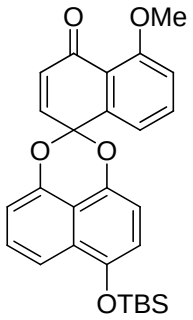
***tert*-Butyl-(5-methoxy-3,4-dihydro-2*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxine]-6'-yloxy)dimethylsilane (258).** A solution of 5-methoxytetralone (**146**) (2.30 g, 13.1 mmol) in MeOH (54 mL) was treated with TsOH (77.0 mg, 0.447 mmol) and trimethyl orthoformate (5.4 mL, 49.2 mmol) and stirred for 6 h. The crude solution was treated with toluene (225 mL) in 4 batches and concentrated down to ~50 mL. The solution turned a deep purple. The crude solution of the methyl enol ether was treated with a solution of the naphthalene diol **257** (2.60 g, 8.95 mmol) in toluene (10 mL). The reaction mixture was stirred at room temperature for 14 h, quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2, dried (Na_2SO_4), filtered, concentrated under reduced pressure and purified by column chromatography on SiO_2 (4:1, hexanes:EtOAc) to afford 2.6 g (65%) of spiroketal **258** as a light green oil: Rf 0.7 (7:3, hexanes:EtOAc); IR (ATR) 1415, 1377, 1260, 1042, 971, 779, 760 cm^{-1}; ^1H NMR δ 7.72 (d, 1 H, *J* = 8.4 Hz), 7.49 (d, 1 H, *J* = 7.8 Hz), 7.40 (t, 1 H, *J* = 8.1 Hz), 7.32 (t, 1 H, *J* = 8.1 Hz), 6.93 (d, 1 H, *J* = 7.5 Hz),

6.80 (d, 1 H, *J* = 8.1 Hz), 6.77 (d, 1 H, *J* = 7.8 Hz), 3.87 (s, 3 H), 2.81 (t, 2 H, *J* = 6.2), 2.12-2.10 (m, 2 H), 1.99-1.88 (m, 2 H); ^{13}C NMR δ 156.6, 148.3, 145.8, 142.6, 136.4, 128.1, 127.4, 127.0, 126.5, 119.1, 115.7, 114.4, 113.7, 110.2, 109.8, 109.0, 100.4, 55.5, 30.2, 25.9, 23.0, 18.8, 18.4, −4.3, −4.4; MS (ESI-Q-TOF) *m/z* (rel intensity) 449 ([M+H]$^+$, 100), 443 (23), 431 (19), 414 (11), 413 (20), 301 (10), 149 (11); HRMS (ESI-Q-TOF) calculated for $C_{27}H_{33}O_4Si$ 449.2148, found 449.2148.



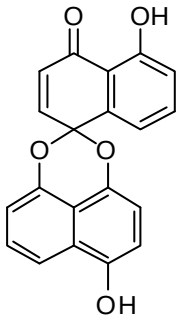
6'-(*tert*-Butyldimethylsilyloxy)-5-methoxy-2*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxin]-4(3H)-one (259). A solution of spiroketal **258** (2.85g, 6.35 mmol) in benzene (29 mL) was treated with Celite® (2.3 g), PDC (1.14 g, 3.03 mmol) and TBHP (4.7 mL, 23.5 mmol). The reaction mixture was stirred at room temperature overnight, filtered over celite, rinsed (CH_2Cl_2) and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (4:1, hexanes:EtOAc) afforded 1.78 g (61%) of **259** as a light yellow oil. Rf 0.25 (4:1, hexanes:EtOAc); IR (neat) 2932.1, 2857.0, 1690.8, 1610.6, 1507.0, 1465.3, 1379.6, 1321.6, 1267.7, 1189.7, 1136.3, 1066.7, 1047.2, 1022.0 cm $^{-1}$; ^{1}H NMR δ 7.75 (d, 1 H, *J* = 8.4 Hz), 7.66 (t, 1 H), 7.42 (t, 1 H, *J* = 8.0 Hz), 7.12 (d, 1 H, *J* = 8.1 Hz), 6.96 (d, 1 H, *J* = 7.5 Hz), 6.81 (s, 2 H), 4.09 (s, 3 H), 2.75 (t, 2 H, *J* = 6.6 Hz), 2.44 (t, 2 H, *J* = 6.6 Hz), 1.09 (s, 9 H), 0.27 (s, 6 H); ^{13}C NMR δ 195.6, 147.6, 146.2, 142.9, 141.3, 134.9, 128.2, 126.6, 117.8, 116.3, 114.2, 113.8, 113.5, 110.0, 109.2, 98.7, 56.3, 35.5, 29.3, 25.9, 18.4, −4.3; MS (ESI-Q-TOF) *m/z*

(rel intensity) 485 ([M+Na]$^+$, 100), 463 (8); HRMS (ESI-Q-TOF) calculated for $C_{27}H_{30}O_5NaSi$ 485.1760, found 485.1720.



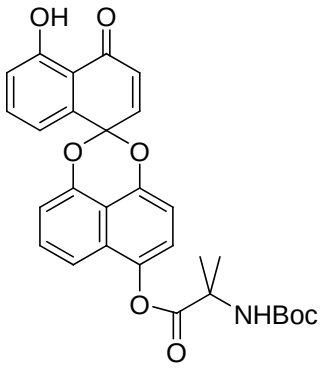
6'-(*tert*-Butyldimethylsilyloxy)-5-methoxy-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxin]-4-one (260). A solution of **259** (1.78 g, 3.66 mmol) in CH_3CN (38 mL) was cooled to 0 °C, and treated with lutidine (0.76 mL, 6.5 mmol) followed by the dropwise addition of TMSOTf (0.76 mL, 4.2 mmol) over 30 min. After 1 h, the reaction mixture was treated with additional lutidine (0.76 mL) and TMSOTf (0.76 mL), stirred for 30 min, and quenched with sat. $NaHCO_3$. The reaction mixture was extracted (CH_2Cl_2), dried ($MgSO_4$), filtered, concentrated under reduced pressure and azeotroped with toluene (3x) to give the crude enol ether. Rf 0.7 (7:3, hexanes:EtOAc). A solution of the crude enol ether in CH_3CN (19.8 mL) was treated with $Pd(OAc)_2$ (0.89 g, 3.9 mmol) stirred at room temperature for 12 h, filtered through celite and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (4:1, hexanes:EtOAc) afforded 1.7 g (93%) of the desired product as a light yellow oil: Rf = 0.3 (4:1, hexanes:EtOAc); IR (ATR) 1670, 1653, 1640, 1506, 1418, 1326, 1254, 1049, 1010 cm $^{-1}$; ^{1}H NMR δ 7.80 (dd, 1 H, *J* = 8.7, 0.6 Hz), 7.70 (t, 1 H, *J* = 8.1 Hz), 7.59 (dd, 1 H, *J* = 8.1 Hz), 7.44 (t, 1 H, *J* = 8.0), 7.17 (d, 1H, *J* = 8.4 Hz), 6.98 (d, 1 H, *J* = 7.2 Hz), 6.87-6.81 (m, 3 H), 6.28 (d, 1 H, *J* = 10.8 Hz), 4.01 (s, 3 H), 1.10 (s, 9 H), 0.29 (s, 3 H), 0.29 (s, 3 H); ^{13}C NMR δ 183.1, 159.9, 147.5, 146.6, 141.3, 141.1, 135.4, 134.9, 132.1, 128.1, 126.7, 120.2, 119.0, 116.7, 113.8, 110.4,

109.7, 93.3, 56.4, 25.9, 18.4, −4.2, −4.3; MS (ESI-Q-TOF) *m/z* (rel intensity) 461 ($[M+H]^+$, 100), 443 (5), 365 (8), 169 (10); HRMS (ESI-Q-TOF) calculated for $C_{27}H_{29}O_5Si$ 461.1784, found 461.1762.



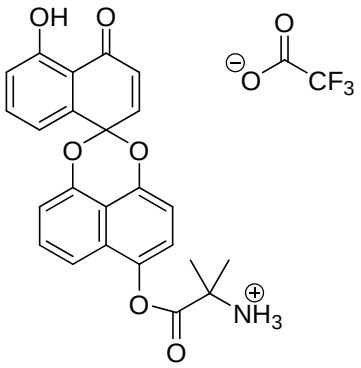
5,6'-Dihydroxy-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxin]-4-one (177). A solution of **260** (1.7 g, 3.7 mmol) in CH_2Cl_2 (100 mL) was treated with Bu_4NI (3.08 g, 8.33 mmol), cooled to −78 °C, treated with a 1.0 M solution of BCl_3 in heptane (5.4 mL, 5.4 mmol) and stirred for 30 min at −78 °C. The dry ice bath was removed and the reaction was quenched with ice after 30 min. The solution was diluted with H_2O and extracted with CH_2Cl_2 (2x). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a dark red oil. The major spot by TLC correlated to TBS protected **177**: Rf = 0.8 (7:3, hexanes:EtOAc). A solution of the crude product in CH_2Cl_2 (100 mL) was cooled to 0 °C, treated with AcOH (0.10 mL, 1.7 mmol) and a 1.0 M solution of TBAF in THF (2.33 mL, 2.33 mmol) and stirred for 30 min. After 30 min, the starting material remained and additional AcOH (0.10 mL, 1.7 mmol) and a 1.0 M solution of TBAF in THF (2.33 mL, 2.33 mmol) were added to the reaction mixture. After an additional 10 min, the reaction mixture was quenched with H_2O, extracted with CH_2Cl_2 (2x), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography through a 3 cm plug of SiO_2 (CH_2Cl_2) afforded 0.93 g

(76%) of **177** as an orange solid whose spectral and physical properties matched the previously synthesized material.



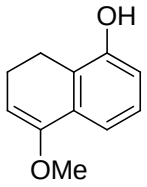
5-Hydroxy-4-oxo-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxine]-6'-yl 2-(*tert*-butoxycarbonylamino)-2-methylpropanoate. A suspension of **177** (0.208 g, 0.626 mmol) in CH_2Cl_2 (50 mL) was treated with **209** (0.208 g, 1.02 mmol), DCC (0.208 g, 1.01 mmol) and DMAP (0.021 g, 0.17 mmol), stirred for 45 min, treated with additional 209 (0.208 g, 1.02 mmol), DCC (0.208 g, 1.01 mmol) and DMAP (0.021 g, 0.17 mmol) and stirred for 1 h. The reaction mixture was quenched with H_2O and extracted (CH_2Cl_2). The organic extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by column chromatography on SiO_2 (7:3, hexanes:EtOAc) to afford 0.21 g (65%) of the AIB prodrug as a yellow oil whose physical and spectral properties matched the previously synthesized material. This reaction was run four times (with an average yield of 60%) in parallel to afford 1.07 g of the AIB prodrug whose spectral and physical properties matched the previously synthesized material (see chapter 9.6.1): ^{1}H NMR δ 12.16 (s, 1 H), 7.69-7.62 (m, 2 H), 7.51 (d, 1 H, J = 7.6 Hz), 7.45 (dd, 1 H, J = 7.6, 1.0 Hz), 7.23 (d, 1 H, J = 8.2 Hz), 7.14 (dd, 1 H, J = 8.4, 1.3 Hz), 7.03 (d, 1 H, J = 10.5 Hz), 7.01 (d, 1 H, J = 6.9 Hz), 6.95 (d, 1 H, J = 8.2 Hz), 6.38 (d, 1 H, J = 10.5 Hz), 5.15 (s, 1 H), 1.76 (s, 6 H), 1.49 (s, 9 H); ^{13}C NMR δ 188.7, 161.8, 154.8, 147.2, 144.8, 141.7, 138.6,

136.6, 129.8, 128.2, 127.5, 119.7, 119.6, 119.3, 113.7, 113.3, 110.6, 93.0, 56.4, 28.4, 25.7; MS (EI) *m/z* (rel intensity) 517 (M^+, 24), 458 (11), 444 (20), 443 (5), 417 (30), 401 (6), 373 (18), 334 (22), 332 (81), 58 (100); HRMS (EI) calculated for $C_{29}H_{27}NO_8$ 517.1737, found 517.1758.

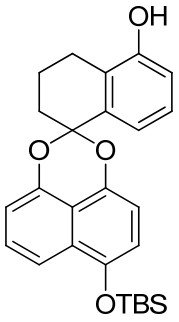


1-(5-Hydroxy-4-oxo-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxine]-6'-yloxy)-2-methyl-1-oxopropan-2-aminium 2,2,2-trifluoroacetate (211). A solution of the *N*-Boc AIB prodrug (1.07 g, 2.07 mmol) in CH_2Cl_2 (15 mL) was treated with TFA (0.5 mL), stirred 15 min treated with additional TFA (0.5 mL) and concentrated under reduced pressure. Analysis of the ^{1}H NMR indicated that some of the starting material remained. The mixture was dissolved in CH_2Cl_2 (15 mL), treated with TFA (1.5 mL), stirred 30 min and concentrated under reduced pressure. Analysis of the ^{1}H NMR indicated that trace amounts of starting material remained. A solution of the mixture in CH_2Cl_2 (15 mL) was treated with TFA (1.5 mL), stirred 30 min and concentrated under reduced pressure to afford 1.09 g (quant) of **211**. Analysis of the ^{1}H NMR spectrum indicated clean conversion to **211** and the physical and spectral properties matched the previously synthesized material (see chapter 9.6.1): ^{1}H NMR (CD_3CN) δ 12.07 (bs, 1 H), 8.16 (bs, 3 H), 7.69 (t, 1 H, *J* = 8.0 Hz), 7.61-7.53 (m, 2 H), 7.45 (d, 1 H, *J* = 7.5 Hz), 7.35 (d, 1 H, *J* = 8.3 Hz), 7.13 (d, 1 H, *J* = 8.3Hz), 7.08-7.04 (m, 2 H), 7.00 (d, 1 H, *J* = 8.2 Hz), 6.35 (d, 1 H, *J* = 10.5 Hz), 1.89 (s, 6 H); ^{13}C NMR (Acetone-d6) δ 189.8, 171.6, 162.6, 148.5, 146.6, 141.4,

140.5, 139.7, 137.8, 130.9, 130.1, 127.9, 121.0, 120.5, 120.4, 116.1, 114.7, 114.3, 111.9, 110.4, 94.3, 59.1, 24.3; MS (ESI) *m/z* (rel intensity) 441 ($[M+Na]^+$, 32), 191 (42), 146 (87), 135 (100); HRMS (ESI) calculated for $C_{24}H_{20}NO_6Na$ 441.1179, found 441.1188.

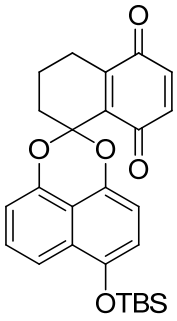


7,8-Dihydro-5-methoxynaphthalen-1-ol. A suspension of 5-hydroxytetralone (0.09 g, 0.55 mmol) in MeOH (2.16 mL) was treated with TsOH (3.2 mg, 0.017 mmol) followed by trimethylorthoformate (0.20 mL, 1.8 mmol) and stirred at room temperature for 6 h during which period the suspension turned to an orange solution. The reaction was monitored by TLC: Rf 0.5 (7:3, hexanes:EtOAc) and the product was used as a crude solution.



6'-(*tert*-Butyldimethylsilyloxy)-3,4-dihydro-2*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxin]-5-ol (262). A solution of crude 7,8-dihydro-5-methoxynaphthalen-1-ol (97.7 mg, 0.554 mmol) in MeOH (2.16 mL) containing TsOH (3.2 mg, 0.017 mmol) was treated with a solution of **257** (0.162 g, 0.558 mmol) in toluene (15 mL). The reaction mixture was partially concentrated under reduced pressure (2x) and treated with additional toluene to keep the solvent level constant at ~15 mL. The solution turned from light yellow to deep purple and was stirred

at room temperature for 20 h. The reaction mixture was quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (9:1, hexanes:EtOAc) afforded 70 mg (29%) of **262** as a white foam: Rf 0.5 (7:3, hexanes:EtOAc); IR (ATR) 3400 (bs), 2928, 1608, 1461, 1415, 1377, 1327, 1262, 1057, 837 cm^{-1}; ^1H NMR δ 7.75 (dd, 1 H, *J* = 8.4, 0.6 Hz), 7.50 (dd, 1 H, *J* = 7.8, 0.6 Hz), 7.43 (t, 1 H, *J* = 8.4 Hz), 6.96 (d, 1 H, *J* = 7.2 Hz), 6.85-6.81 (m, 3 H), 5.30 (bs, 1 H), 2.80 (t, 2 H, *J* = 6.3 Hz), 2.15-2.12 (m, 2 H), 1.99-1.93 (m, 2 H), 1.12 (s, 9 H), 0.30 (s, 3 H), 0.29 (s, 3 H); ^{13}C NMR δ 152.7, 148.2, 145.8, 141.9, 136.8, 128.1, 127.1, 126.5, 125.0, 119.6, 115.8, 115.3, 114.4, 113.8, 114.4, 113.8, 109.9, 109.1, 100.2, 30.1, 25.9, 22.8, 18.7, 18.4, −4.3, −4.3; MS (ESI-Q-TOF) *m/z* (rel intensity) 435 ($[M+Na]^+$, 100); HRMS (ESI-Q-TOF) calculated for $C_{26}H_{31}O_4Si$ 435.1992, found 435.1983



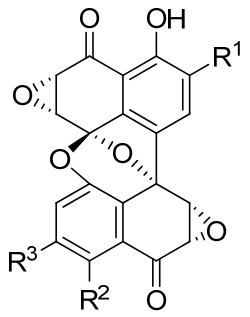
6'-(*tert*-Butyldimethylsilyloxy)-3,4-dihydro-2*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxine]-5,8-dione (263). A solution of spiroketal **262** (24.0 mg, 5.52 mmol) in benzene (0.3 mL) was treated with celite (7 mg) followed by bipyridinium chlorochromate (1.3 mg, 0.0044 mmol) and a solution of 5.0 M TBHP in nonane (0.05 mL, 0.03 mmol). The reaction mixture was stirred at room temperature for 2 h, treated with additional 5.0 M TBHP in nonane (0.05 mL, 0.03 mmol) and heated to reflux for 20 h. The mixture was cooled to room temperature, filtered through celite, washed (CH_2Cl_2), and purified by column chromatography

on SiO_2 (9:1, hexanes:EtOAc to 4:1, hexanes:EtOAc) to afford 0.021 g (84%) of quinone **263** as a red oil: Rf 0.53 (7:3, hexanes:EtOAc); IR (ATR) 2950, 2926, 2855, 1659, 1608, 1506, 1461, 1377, 1290, 1221, 1113, 971 cm $^{-1}$; ^{1}H NMR δ 7.71 (d, 1 H, *J* = 8.4 Hz), 7.39 (t, 1 H, *J* = 8.1 Hz), 6.89 (d, 1 H, *J* = 7.5 Hz), 6.82 (d, 1 H, *J* = 8.1 Hz), 6.79 (d, 1 H, *J* = 7.5 Hz), 6.77-6.72 (m, 1 H), 6.73 (d, 1 H, *J* = 8.1 Hz), 2.60 (t, 1 H, *J* = 6.0), 2.08-2.03 (m, 2 H), 1.85-1.81 (m, 2 H), 1.09 (s, 9 H), 0.26 (s, 3 H), 0.25 (s, 3 H); ^{13}C NMR δ 187.5, 183.5, 146.9, 146.8, 140.5, 138.0, 136.1, 135.0, 128.3, 126.4, 116.0, 113.8, 109.7, 109.0, 98.8, 31.5, 25.9, 23.6, 18.4, 17.7, -4.2, -4.4; MS (ESI-Q-TOF) *m/z* (rel intensity) 471 ($[M+Na]^+$, 100); HRMS (ESI-Q-TOF) calculated for $C_{26}H_{28}O_5SiNa$ 471.1604, found 471.1609.

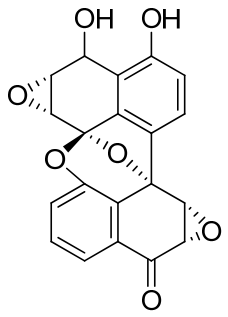
13.0 SPIROXIN

13.1 SPIROXIN ISOLATION AND CHARACTERIZATION

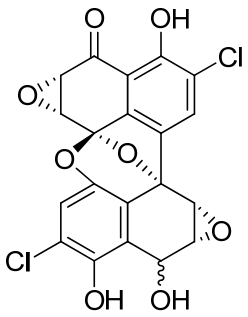
The spiroxins are marine natural products isolated from non-sporulating fungi in Dixon Bay, off the coast of Vancouver Island, Canada (Figure **13.1**).[378,379] They are compact octacyclic compounds that primarily differ in their degree of oxidation and chlorination. They showed activity as antibiotics against gram positive bacteria and marginal activity against gram negative bacteria, and displayed a mean IC_{50} value of 0.09 μG/mL in a 25 cell line cytotoxicity evaluation.[126] This activity is competitive with the epoxyquinones terreic acid (**264**)[380,381] and frenolicin (**265**, Figure **13.2**).[382]



Spiroxin A (**156**): R^1 = Cl R^2 = OH R^3 = H
Spiroxin B (**140**): R^1 = Cl R^2 = OH R^3 = Cl
Spiroxin C (**157**): R^1 = H R^2 = H R^3 = H



Spiroxin D (**158**)



Spiroxin E (**159**)

Figure 13.1. Spiroxins

The spiroxins exhibited anti-tumor activity against ovarian carcinomas with 59% inhibition of tumor growth after 21 d in nude mice. Their mode of action is postulated to involve single strand DNA cleavage. In the presence of thiols, spiroxin A (**156**) exhibited a concentration dependent nicking of pBR322-DNA. Quinones are known to be cytotoxic via a variety of mechanisms including oxidative stress, alkylation and DNA modification.[383] The exact mode of cytotoxicity is not known, but any of these mechanisms might be responsible for the bioactivity of the spiroxins.

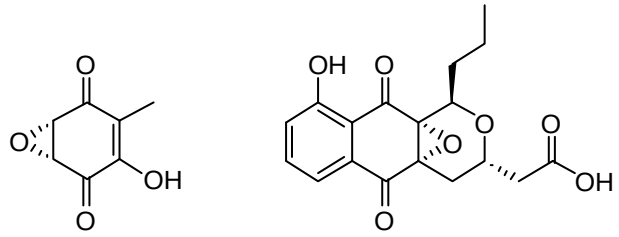


Figure 13.2. Terreic acid (**264**) and frenolicin (**265**)

The structure of spiroxin A (**156**) was elucidated spectroscopically without the aid of X-ray crystallography. Negative MS indicated the presence of both acidic functionality and chlorine. ^{1}H NMR and UV indicated an *o*-hydroxybenzoyl group and epoxide whereas IR supported the presence of the hydroxyl groups and a conjugated ketone. DEPT, HMBC, HMQC, and NOESY were also consulted to elucidate spiroxin's structure. The pivotal HMBC signal between H-7 and C-4' was the only signal that established the connectivity between the upper and lower naphthoquinone rings. The NOE signal between epoxide proton and aromatic proton established the relative stereochemistry of the epoxide (Figure **13.3**).[126]

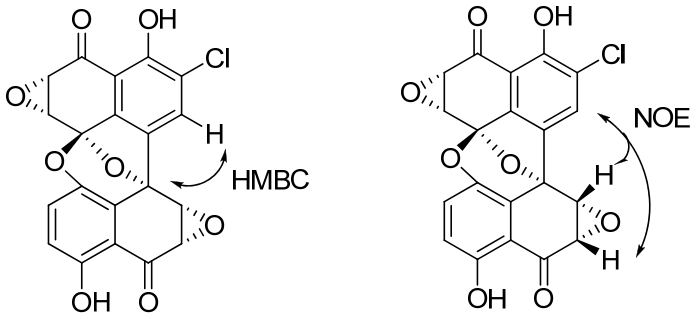
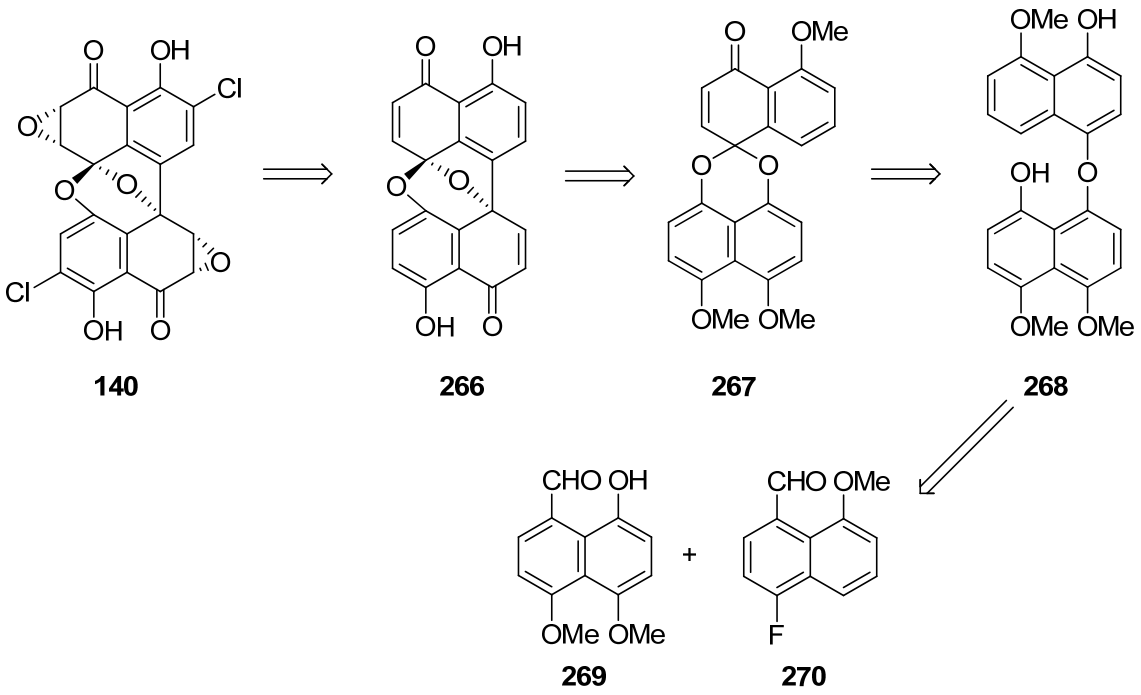


Figure 13.3. HMBC (left) and NOE (right) analyses of spiroxin A (**156**)[126]

13.2 SPIROXIN BIOSYNTHESIS AND FIRST RETROSYNTHETIC ANALYSIS

The proposed biosynthesis of the spiroxins bears similarities to the biosynthetic pathway of other bisnaphthospiroketals.[384] As previously discussed, the proposed biosynthesis of type II bisnaphthospiroketals proceeds via the oxidation of type I bisnaphthospiroketals. This hypothesis was validated as a possibility via organic synthesis (Figure **8.5**).[124] Two reports in 2000 from the Zeeck lab further examined the interconnectivity and points of divergence in the biosyntheses of other bisnaphthospiroketals. They proposed the biosynthesis of type III bisnaphthospiroketals proceeded via the introduction of a biaryl bond in type I bisnaphthospiroketals.[384,385] Thus, the spiroxin core would result from an oxidative intramolecular carbon-carbon bond formation in palmarumycin CP_1. The early retrosynthetic analysis for the spiroxins drew inspiration from the proposed biosynthesis and pursued the late stage introduction of the biaryl bond into bisnaphthospiroketal **267** (Scheme **13.1**).



Scheme 13.1. Original retrosynthetic analysis of spiroxin (**140**)

This retrosynthetic analysis aimed to exploit the methodology applied to the synthesis of the palmarumycin analogues and explore oxidative conditions on spiroketal **267** to arrive at the spiroxin core (Scheme **13.1**). Spiroxin B (**140**) would be the product from late stage chlorination and epoxidation of **266**. The key step in this retrosynthetic analysis would be the oxidative coupling of **267** to deliver the carbon-carbon bond in **266**. There are reports in the literature where PIFA[386-390] or other oxidants[391,392] mediate the oxidative biaryl coupling. This transformation has been applied to natural product synthesis[393,394] and proposed as a biosynthetic step in the production of several natural products.[395] Typically, the intramolecular variant of this methodology is applied to aromatics tethered together with an aliphatic chain. The early retrosynthetic analysis extended this methodology to the spiroketal bearing system. The early steps in this retrosynthetic analysis closely mirrored well established work with the palmarumycin analogues.[119] Spiroketal **267** would be synthesized via a PIFA or PIDA mediated

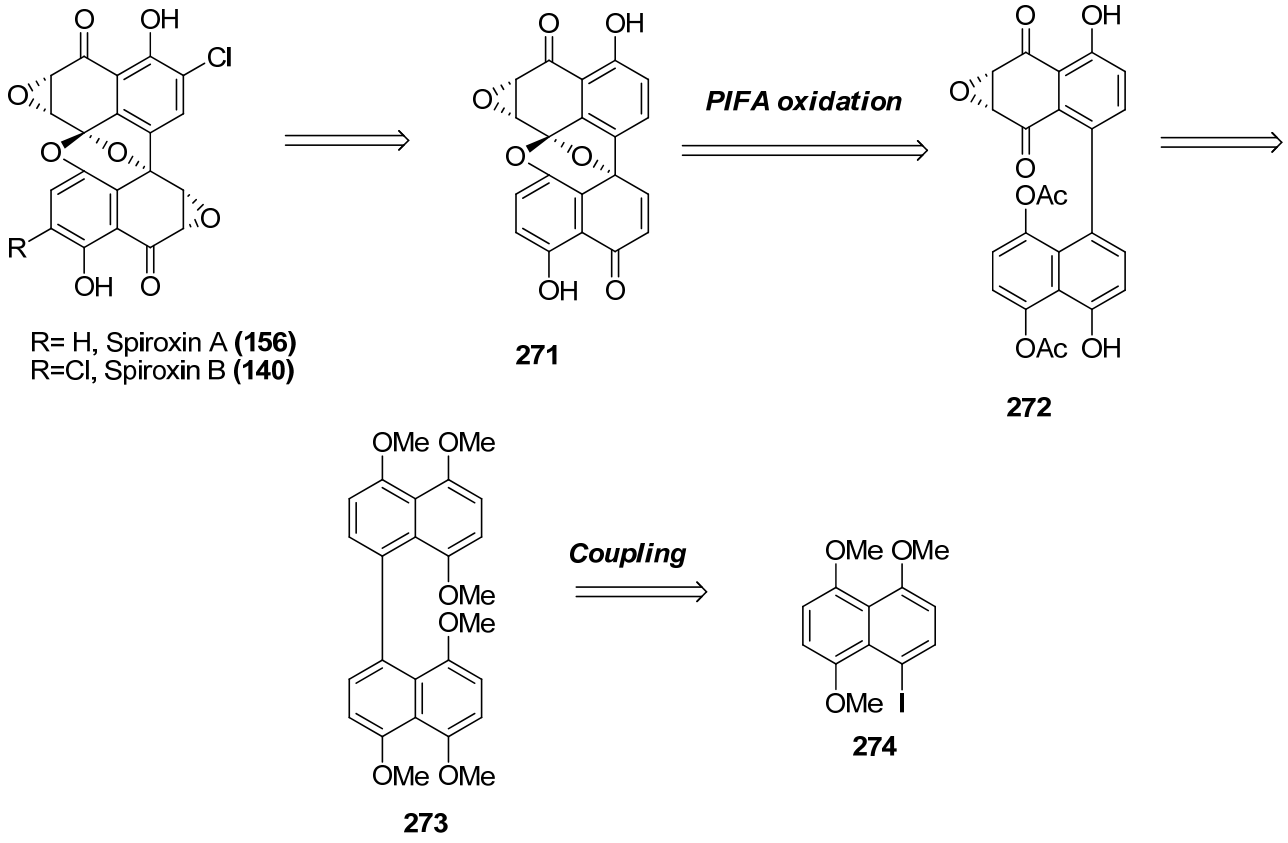
oxidative cyclization and an S_NAr reaction between **269** and **270** would deliver the biaryl ether **268**.

A model system was first explored for the key intramolecular phenolic oxidative coupling. 4'-Methoxypalmarumycin CP_1 (**174**, Scheme **9.5**) was synthesized utilizing chemistry previously applied to the palmarumycin analogue synthesis. The problem that emerged was the realization of the key oxidation step. Many oxidants were screened: PIFA, VOF_3, $VOCl_3$, Ag_2O, $FeCl_3$, $Tl(OCOCF_3)_3$ and a PIFA/$H_3[PMo_{12}O_{40}]$ mixture. However, either the starting material hydrolyzed and oxidized into two equivalents of juglone related compounds or there was no reaction. The spiroxin framework was never realized via this methodology. Extensive work with this approach led to the conclusion that it was imperative to install the carbon-carbon bond prior to spiroketalization.

13.3 MODIFIED RETROSYNTHETIC ANALYSIS OF SPIROXINS A & B

The new retrosynthetic analysis of spiroxins A (**156**) and B (**140**) diverged with the final mono- and bis-chlorination, respectively, of the penultimate spiroketal **271** (Scheme **13.2**). The chlorination to arrive at spiroxin B (**140**), with two ortho phenol chlorines, is relatively straightforward. The alternative selective mono-chlorination of spiroxin A (**156**) is difficult to predict due to the sterically and electronically related sites available for chlorination. The organic toolbox is equipped with many alternatives for chlorinating reagents.[396-400] The prediction was that with optimization and the strict use of a single equivalent of chlorinating reagent, the desired product could be obtained. Oxidation of **272** with PIFA would install the needed naphthoquinone in a fashion similar to the palmarumycin syntheses. The need for a

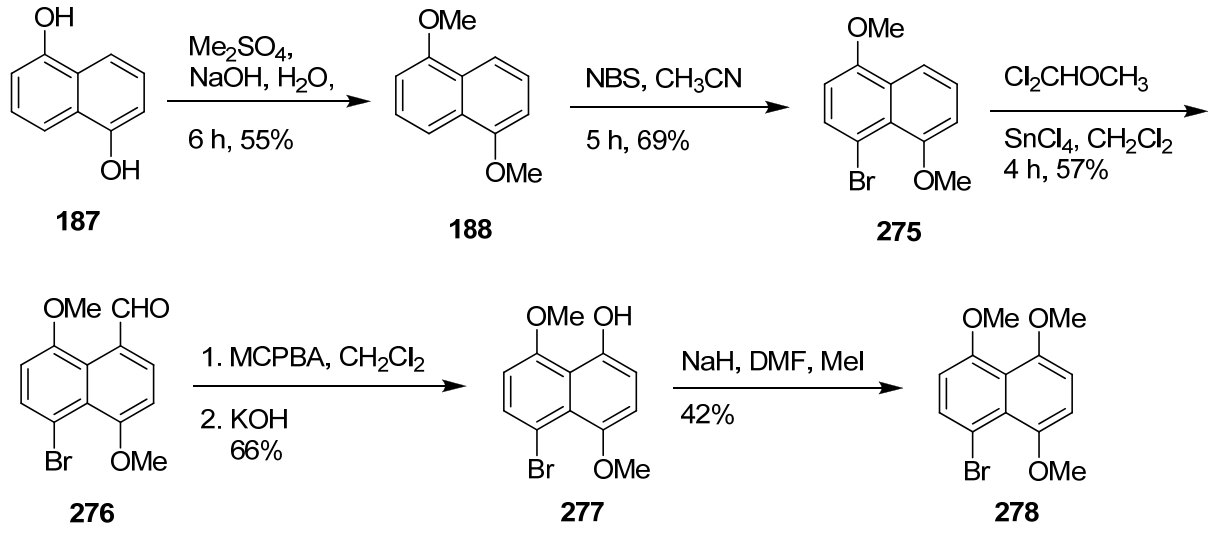
protecting group swap was anticipated to attenuate the electronics of the lower ring for the desired site specificity during oxidation. Intermediate **273** could be derived from coupling of the highly oxygenated naphthyl iodide **274** which would be synthesized from dimethoxynaphthalene.



Scheme 13.2. Updated retrosynthetic analysis of spiroxins A (**156**) and B (**140**)

13.4 SYNTHESIS OF FUNCTIONALIZED BIARYL 284

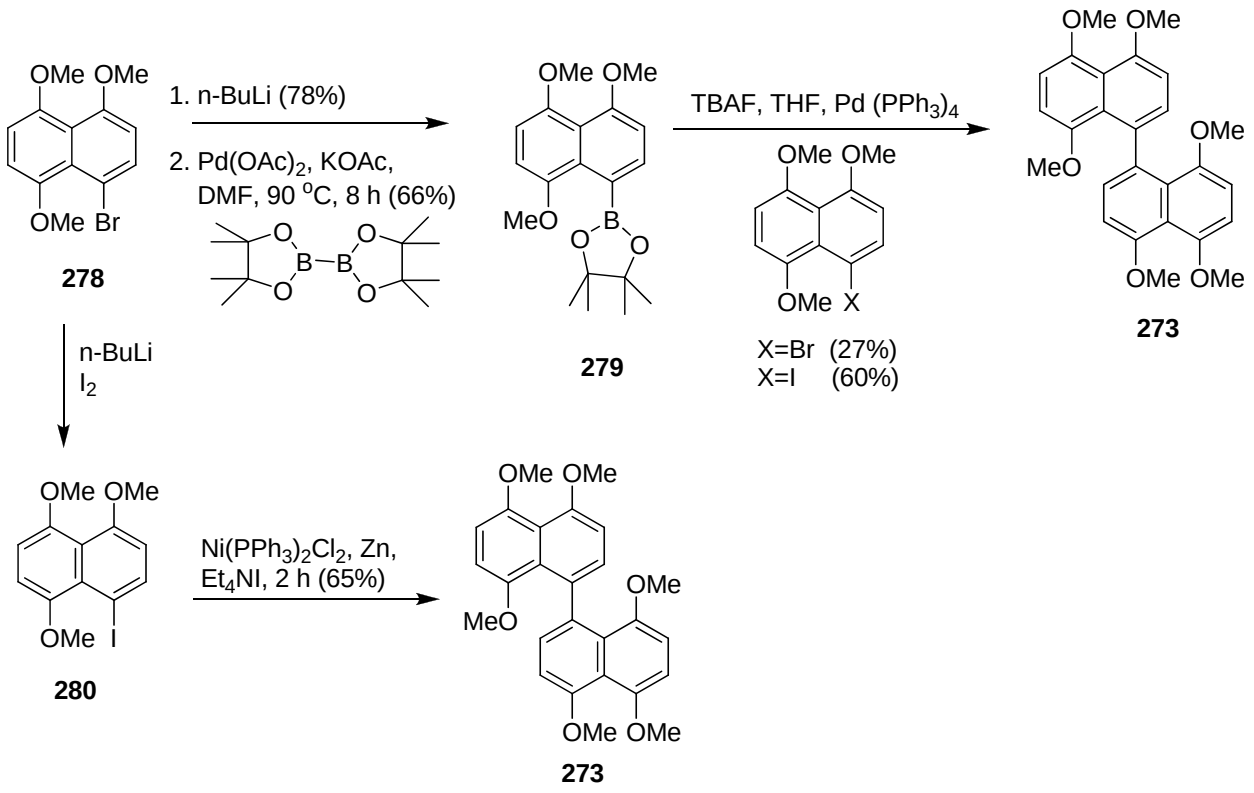
The synthesis of **278** commenced with the bis-methylation of **187** with Me_2SO_4. This reaction was extremely exothermic and required slow addition when scaled to a 100 g scale. Methylation was followed by mono-bromination with NBS,[401] formylation with α,α-dichloromethylmethyl ether delivered naphthaldehyde **276**, and a Dakin reaction with mCPBA and KOH to afford **277** (Scheme **13.3**). Alternatively, **188** could be formylated with $POCl_3$ to arrive at the same naphthaldehyde **189** utilized in the palmarumycin synthesis and brominated with NBS to afford **276**. The advantage of this alternative route was the omittance of toxic α,α-dichloromethylmethyl ether from the sequence and a comparable yield to the original sequence. The unmasked alcohol was readily methylated with MeI and NaH to deliver **278**.



Scheme 13.3. Synthesis of bromonaphthalene **278**

The synthesis of sterically hindered biaryls is a well known challenge.[402,403] Various coupling conditions were explored using bromide **278** (Scheme **13.4**). Suzuki coupling between

278 and **279** proceeded in low yield[404] whereas the Stille reaction with this sterically hindered system led to preferential reduction. The yield jumped from 27 to 53% for the Suzuki reaction when naphthyl bromide **278** was converted to the more reactive naphthyl iodide **280**. Although this Suzuki reaction provided an acceptable yield of biaryl **273**, it required the synthesis of two separate reactants, **279** and **280**. A more straightforward approach to the synthesis of **273** would be the homocoupling of a single reactant. During the 1970's, Semmelhack investigated Ni(0) aryl halide homocouplings[405] Various researchers since that initial report have altered the nickel catalyst and used additives to generate a more reactive catalyst.[406-408] Ultimately, the most promising route for us involved the homodimerization of naphthyl iodide **280**. The reaction was optimized with Iyoda's conditions of Zn, $Ni(PPh_3)_2Cl_2$ and Et_4NI.[408]



Scheme 13.4. Synthesis of **273** by biaryl coupling

After much optimization, it was found that the reductive homocoupling of **280** with 40% $Ni(PPh_3)_2Cl_2$, 2 equiv of zinc and 2 equiv of Et_4NI delivered **273** in good yield. The yield in this reaction was sensitive to the quality of zinc and the scale. The best results were obtained with zinc purchased from Strem. Additionally, when the reaction was performed with more than 20 g of naphthyl iodide **280**, it was difficult to ensure rapid stirring of the suspension which resulted in inconsistent yields. A single equivalent of PIFA oxidized **273** to **281** which was monodemethylated with lithium bromide.[409] The free phenol was protected with MOMCl for ease of removal later in the synthesis. Naphthoquinone **282** was epoxidized with hydrogen peroxide, and PIFA oxidation of **283** converted the remaining naphthalene to a naphthoquinone. Oxidative demethylation of para-dimethoxynaphthalenes with PIFA is a selective and mild procedure for demethylation.[410] This naphthoquinone was reduced with $Na_2S_2O_4$ and the resultant naphthalene diol was protected with acetic anhydride to afford **284**. It was important to protect the para-hydroxynaphthalene derived from **283** with an electron withdrawing group, such as an acetate, in order to prevent PIFA oxidation of the lower ring back to the quinone (Scheme **13.5**).

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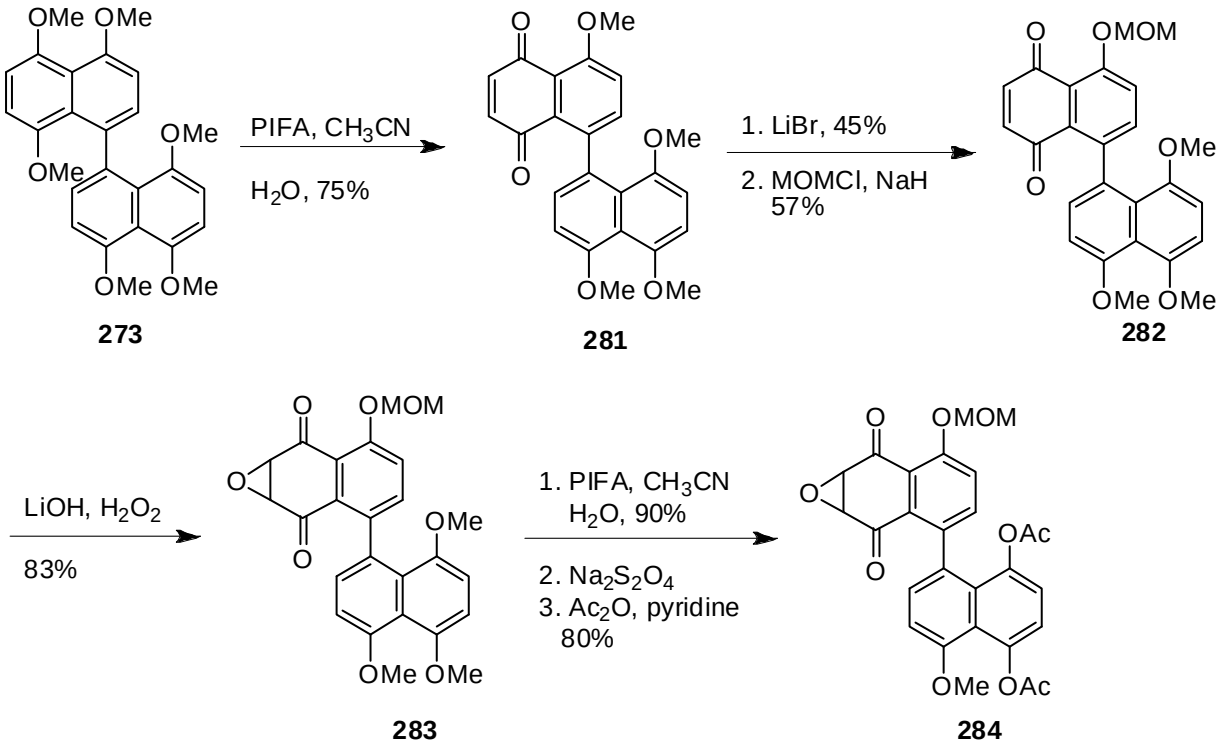
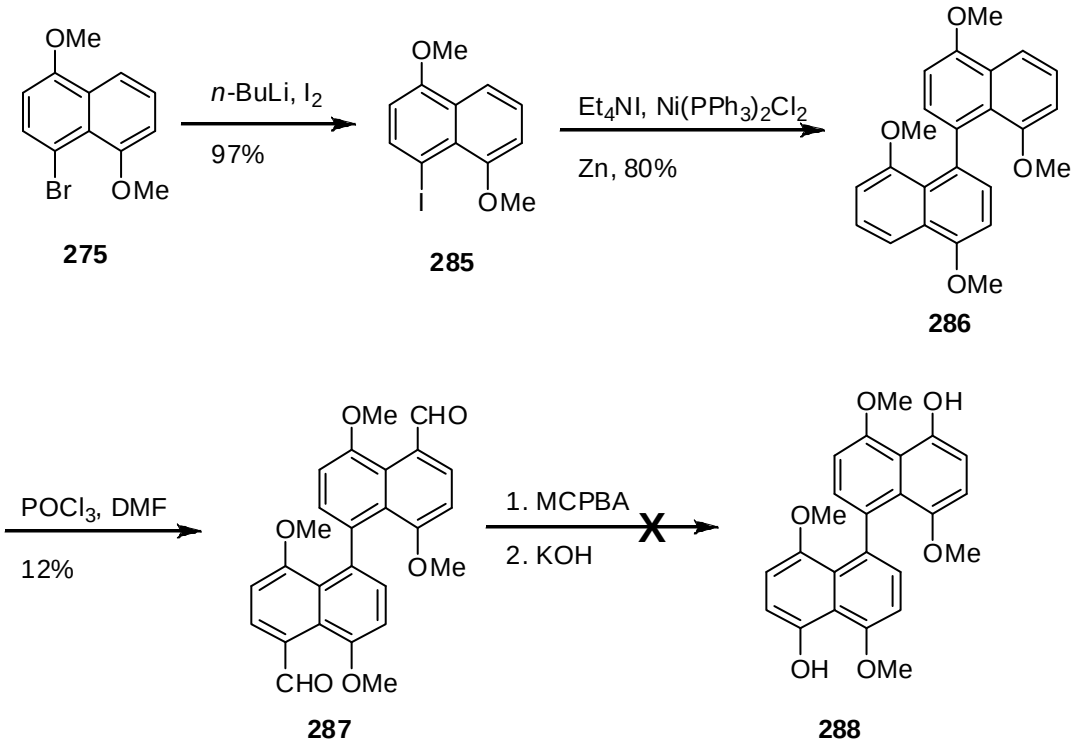


Scheme 13.5. Spiroxin core functionalization

13.4.1 Alternative biaryl synthesis

The first 10 steps of the synthesis to **282** proceeded in an overall yield of 2%. The effect on the overall yield was investigated in the modified synthesis with the homocoupling moved to an earlier stage of the synthesis (Scheme **13.6**). **275** was synthesized following the previously described protocol and the conversion to iodide **285** likewise mirrored the halogen exchange of **278** and proceeded in good yield. Gratifyingly, **285** readily underwent homocoupling in good yield, in fact in better yield than the homocoupling of **280**. The unoptimized yield for the bis-formylation to **287** was 13%. Naphthaldehyde **287** was highly insoluble and difficult to handle during both workup and purification, which could account for the low yield. Disappointingly, none of **288** was recovered. The mass recovery from the attempted Dakin reaction was poor and

although several conditions were tried, none of the diol was detected. Accordingly, it was decided that handling diol **288** was not feasible and the original route was returned to.



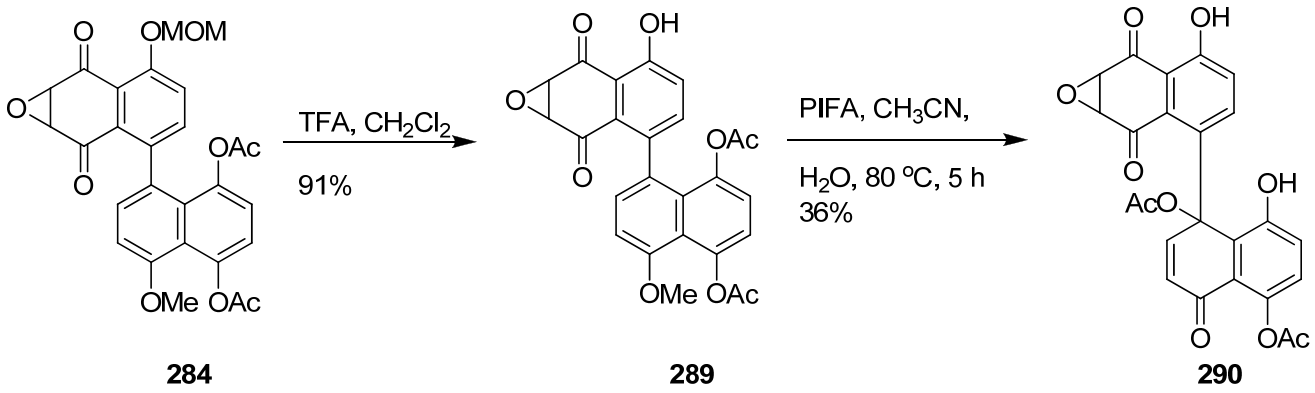
Scheme 13.6. Alternative biaryl synthesis via homocoupling of **285**

13.4.2 Studies toward the synthesis of the spiroxin core from 284

Resuming the route from **284** (Scheme **13.4**), the MOM group was deprotected and the PIFA oxidation of **289** was performed (Scheme **13.7**). The oxidation of **289** was particularly challenging. Free phenols are substantially easier to oxidize, frequently reacting at room temperature or 0 °C.[243] The most readily oxidized aryl methyl ethers are typically flanked with two or more methoxy groups.[411-414] One example of PIFA oxidation on a lone methyl protected phenol needed to be heated to 60 °C[415] and another example was ultimately optimized with the

aid of various coacids.[416] The oxidation of the naphthalene was anticipated to require forcing conditions.

A series of oxidative conditions of **289** were screened. Oxidation with PIFA in CH_3CN and H_2O at either room temperature or 50 °C failed to give conversion and clean starting material was recovered. Oxidation of **289** with CAN at room temperature proceeded quickly and, unfortunately, unselectively to deliver a mixture of unidentified products. The yield of the PIFA oxidation in CH_3CN and H_2O at 80 °C proceeded in 36% yield. While there was certainly room for improvement of the yield in the oxidation of **289**, the synthesis was proceeded with.



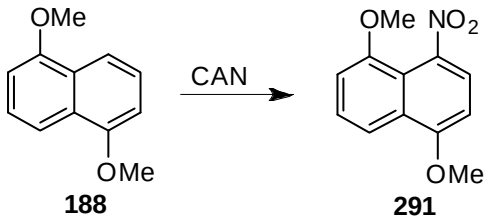
284 **289** **290**

Scheme 13.7. Oxidation of **289**

13.4.3 Model system for oxidation of 289

Dimethoxynaphthalene **188** was selected as a model system of **289** for the oxidation condition screening due to its simplicity and availability (Scheme **13.8**). Naphthalene **188** was first oxidized with CAN and the reaction went cleanly. Unfortunately, the ^{1}H NMR of the product did not match the literature ^{1}H NMR of the expected 5-methoxy naphthoquinone.[417] Instead,

mass spectrometry confirmed that the oxidized compound was the result of naphthalene nitration, **291**. The oxidation in H_2O with either THF or acetone as a co-solvent, different temperatures and various additives were explored, but consistently the same nitrated product was isolated. Although initially unexpected, aromatic nitration with CAN has been reported previously in the literature.[418-420] This led to the reevaluation of the applicability of the model system and the real system was proceeded with, **289**.



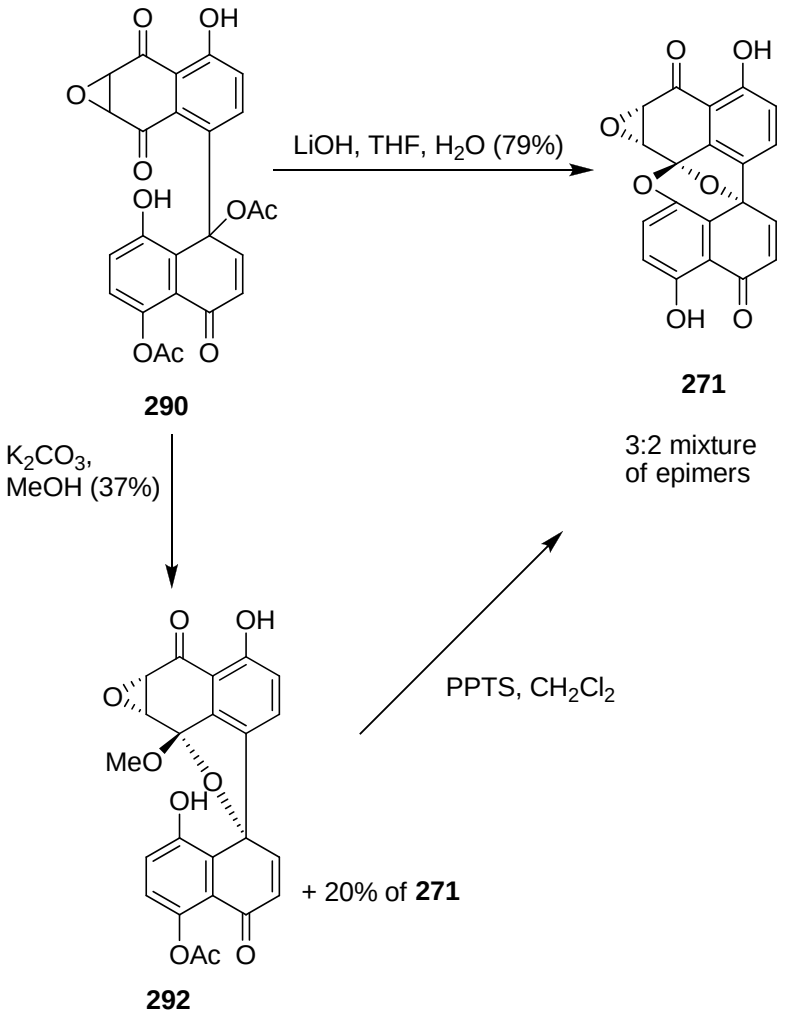
188 **291**

Scheme 13.8. CAN oxidation of model system **188**

13.4.4 Synthesis of spiroxin A core

Acetate removal and spiroketalization on this late stage intermediate would lead to the spiroxin A core (Scheme **13.9**). There are many different methods to remove acetates. Two common methods utilize NaOMe[421] or LiOH[422] under relatively mild conditions to unmask the phenol. The bis-acetate **290** was treated with LiOH in THF and water and **271** was isolated in 79% yield. These reaction conditions both globally removed the acetates and formed the spiroketal. When the deprotection was performed with 12-crown-4 and LiOH there was no change in yield. K_2CO_3 in MeOH was also investigated, but the major product isolated was the tentatively

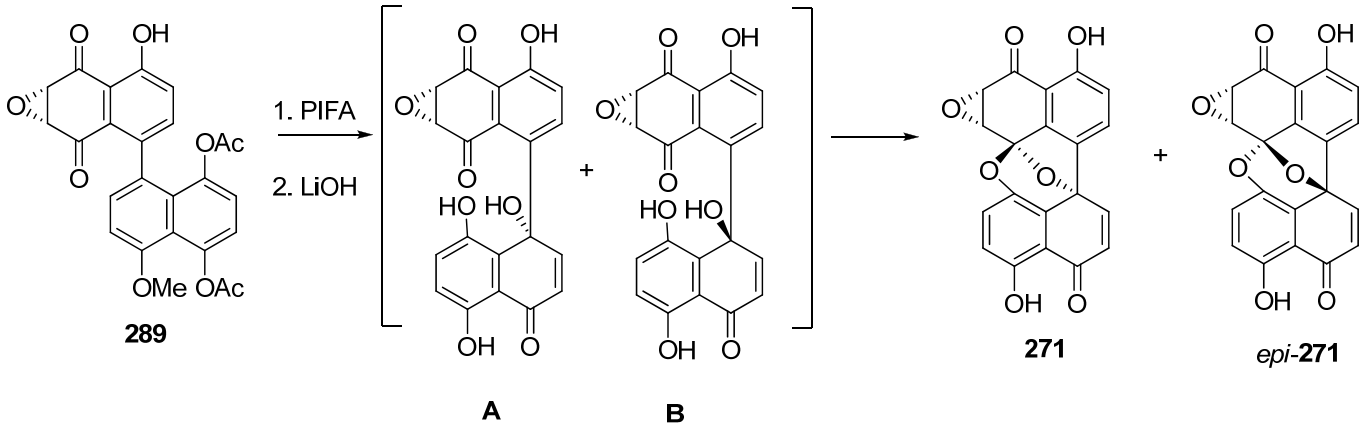
assigned mixed ketal **292** in 37% yield. Treatment of mixed ketal **292** with PPTS in CH_2Cl_2 quantitatively delivered the desired spiroketal as a 3:2 mixture of diastereomers.



Scheme 13.9. Acetate deprotection of **290**

The oxidation of **289** formed diastereomers in the product mixture. The resultant alcohol from the oxidation can either be *cis* or *trans* to the epoxide. When the acetates were removed, the predicted mechanism involved the diol intermediates of **A** or **B** to arrive at spiroketal **271** and its epimer (Scheme **13.10**). These intermediates, presumably, form spiroketal **271** and *epi*-**271**

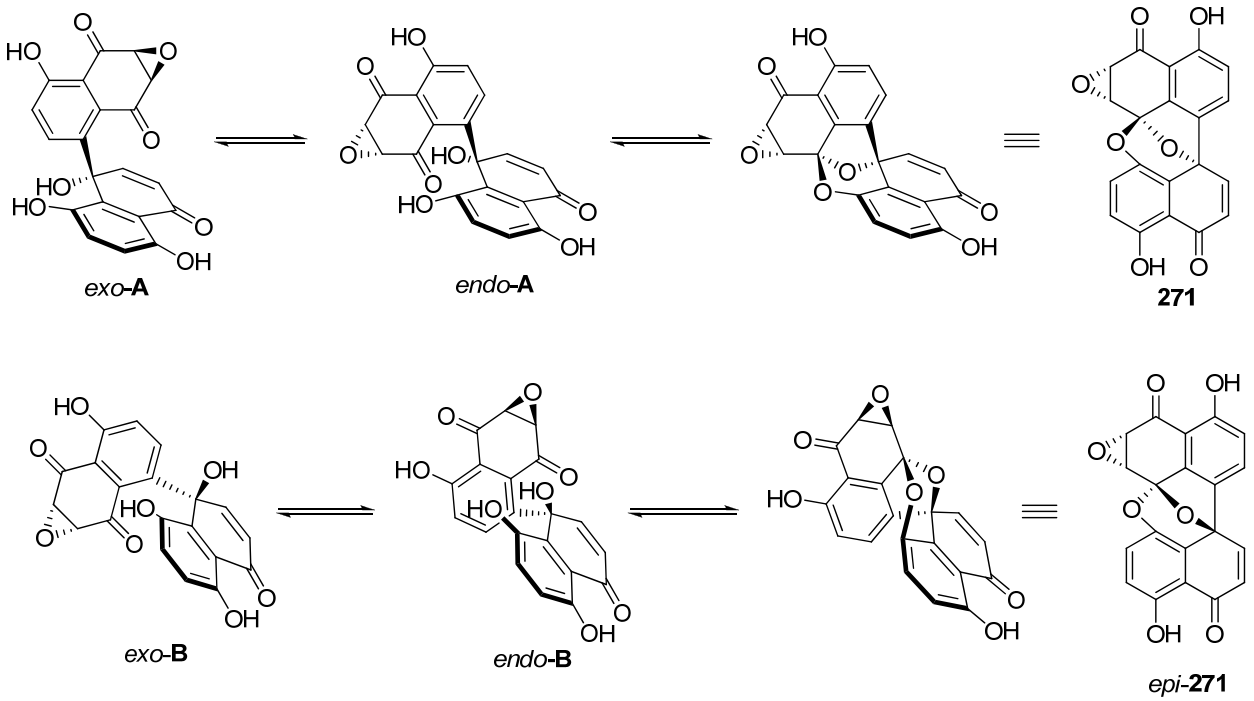
during the reaction workup and were never isolated. Spiroketal **271** and *epi*-**271** were isolated as a 3:2 mixture.



Scheme 13.10. Proposed intermediates enroute to **271**

The proposed polyol intermediates of **A** and **B** were used to propose the conformation of **271** and its epimer (Scheme **13.11**). Two possible conformations that **A** can rest in are either *endo*-**A** or *exo*-**A**. There is no experimental proof for this system, but it is likely that there is a relatively free rotation around the C-C bond connecting the two ring systems. When **A** adopts the conformation *exo*-**A**, the ketone component of the epoxyquinone is situated opposite of the tertiary alcohol making it sterically impossible to form a spiroketal. The ketone could participate in the formation of a hemi-acetal with the phenolic oxygen, but this would be reversible and ultimately an unproductive pathway. However, when **A** adopts the conformation of *endo*-**A**, the ketone is proximal to both the tertiary alcohol and the phenol and can participate in the formation of a spiroketal and ultimately form **271**. The stereochemistry depicted for **271** matches the relative stereochemistry found in the spiroxins. The arguments used for the conformations of **A**

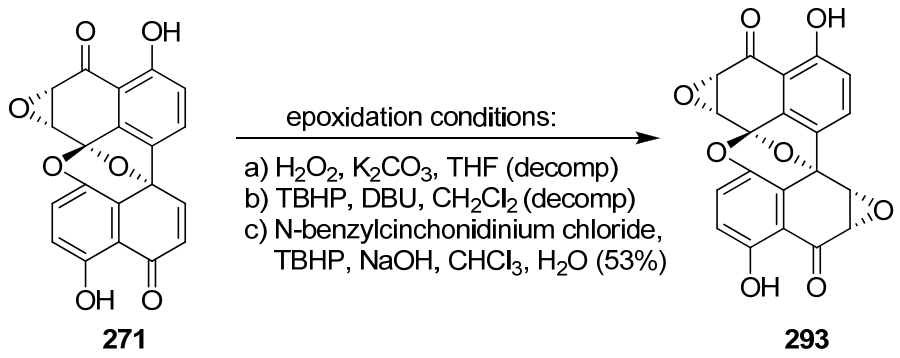
can likewise be applied to epimer **B**. When **B** adopts the conformation of *endo*-**B**, it is free to form the spiroketal with the tertiary alcohol and phenol, and results in the formation of *epi*-**271**.



Scheme 13.11. Mechanistic pathway for formation of **271**

The next hurdle encountered was the epoxidation of **271** (Scheme **13.12**). The first condition explored was treatment with basic hydrogen peroxide, similar to the earlier used epoxidation conditions, but this material only decomposed. The presence of the free phenol rendered the substrate more sensitive and prone to decomposition. Several epoxidation conditions were screened with TBHP and DBU, but this only resulted in decomposition. A report was later found where the researchers tried to epoxidize various 5-hydroxynaphthoquinones with DBU and peroxide and found only decomposition.[423] The yield improved for them with a simple base switch to NaOH. Hence, a different base was likewise

explored for the epoxidation of **271**. TBHP, N-BCC and NaOH afforded the best yield of bis-epoxide **293**.[125] It was also found that this epoxidation went diastereoselectively.



271 **293**

Scheme 13.12. Epoxidation conditions of **271**

A model helps in understanding the diastereoselectivity of this process (Figure **13.4**). The MM2 energy minimized stereoviews of **271** and *epi*-**271** were generated using Chem 3D. The predicted stereoselectivity of the epoxidation was based upon the cup-shaped structure of both **271** and *epi*-**271**. This prediction was verified experimentally when the diastereomeric ratio before and after the epoxidation of **271** was the same according to ^{1}H NMR analysis. Non-selective epoxidation would result in the formation of additional stereoisomers, which would be evident during ^{1}H NMR analysis, but was not observed. During the synthesis of spiroxin C (**157**), Imanishi observed a stereoselective epoxidation of enone **165** (Scheme **8.3**) and likewise attributed it to the conformation of the core.[130]

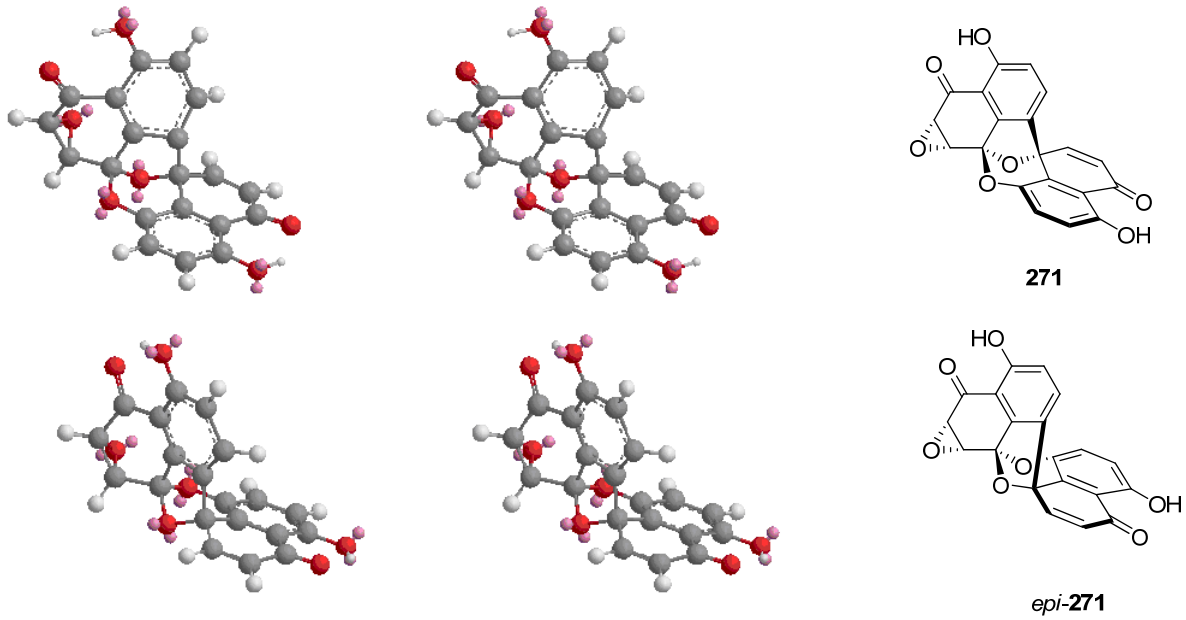


Figure 13.4. Stereoviews of **271** (top) and *epi*-**271** (bottom)

The product from the epoxidation, **293**, was also modeled (Figure **13.5**). The stereochemistry corresponding to the natural diastereomer present in the spiroxin core was represented.[129] A PM3 minimized model of dechloro-spiroxin **293** in CAChe clearly shows the retention of the cup-shaped structure after epoxidation. The newly introduced epoxide on the lower ring of **293** resides on the convex face, the face sterically most accessible to epoxidation.[424-426]

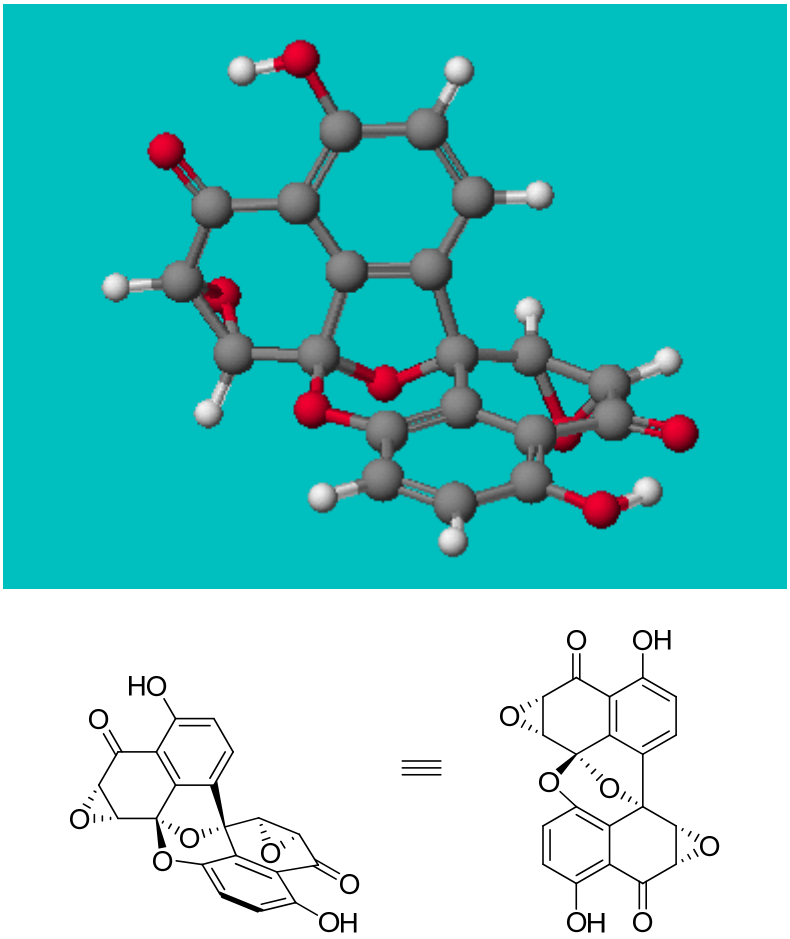


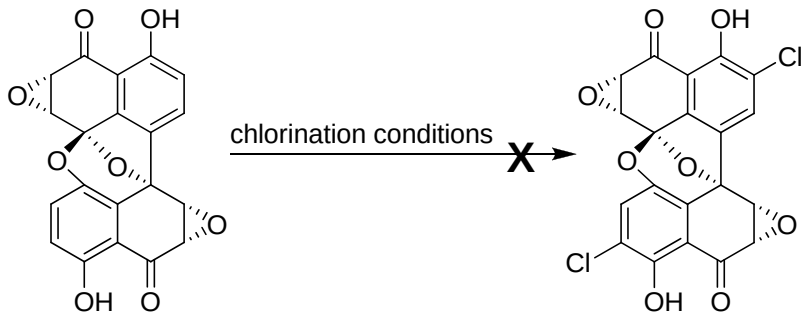
Figure 13.5. Model of spiroxin core **293**

13.4.5 Attempted chlorination of 293

The final task was to either mono- or bis-chlorinate this core to finish either spiroxin A or B (Scheme **13.13**). A diverse set of chlorinating conditions were screened with the first focus being the bischlorination.[427] *N*-chloromorpholine,[428] NCS with silica and other additives [397,429,430] NCS without additives,[431,432] and sulfuryl chloride[433,434] were all screened to no avail. Examples were found where the interaction of sulfuryl chloride with diphenyl sulfide afforded a very selective and active chlorinating agent, but this was not the case for **293**.[435,436] There are

also reports of dichlorodimethylhydantoin as a chlorinating agent.[437] These test reactions were typically run with 1-5 mg of the starting material and at least 2 equiv of chlorinating agent.

With the small amount of material used, the conversion of **293** to the chloride was monitored using the negative detection mode in the LCMS, the same condition reported in the spiroxins isolation paper.[126] Unfortunately, none of the desired bis-chloro spiroxin B **140** was detected. Either unidentified decomposition products or unreacted starting material were isolated.

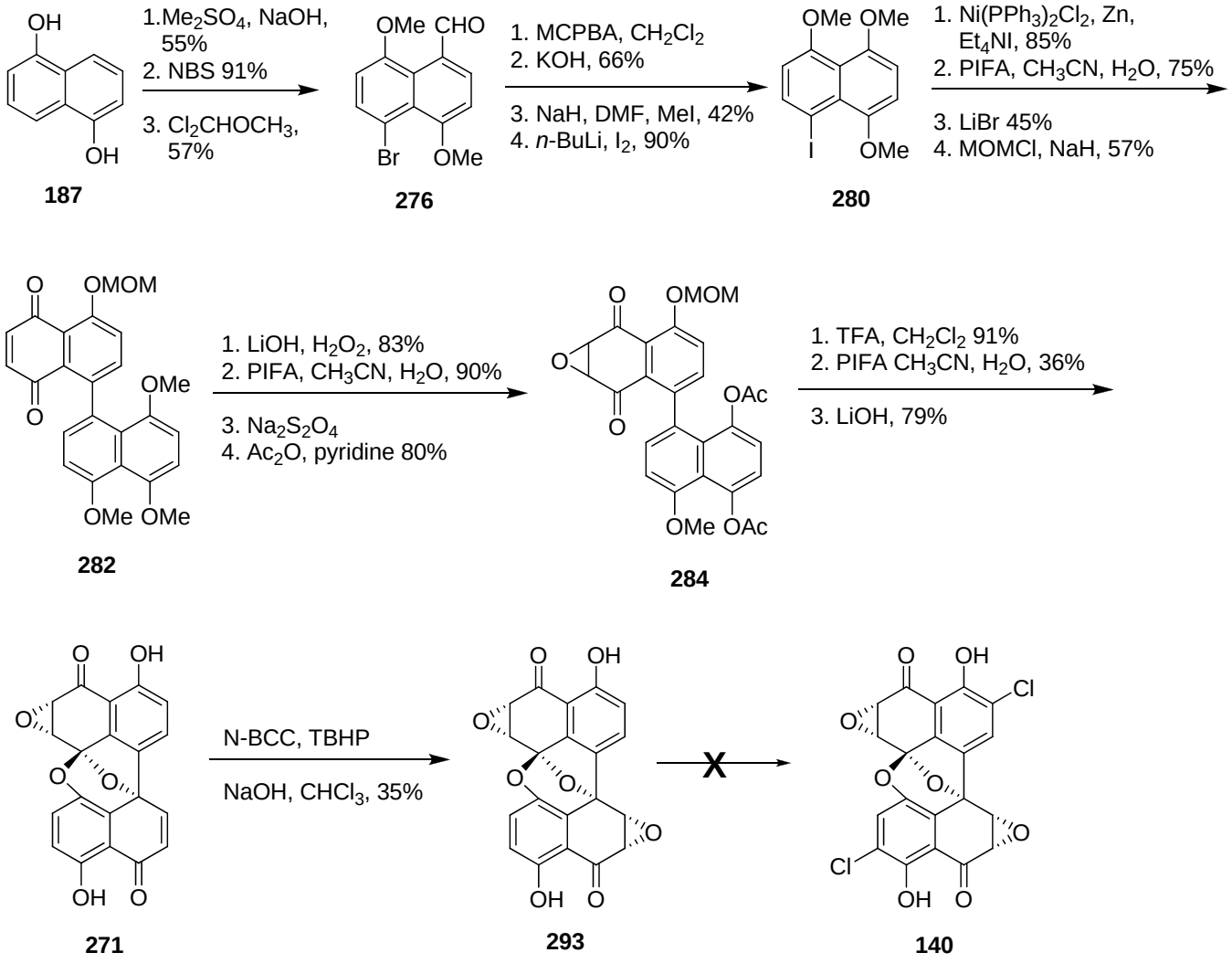


293 **140**

Scheme 13.13. Failed chlorination of **293**

13.5 CONCLUSION

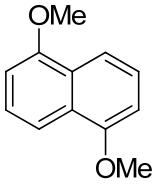
The synthesis of dechloro-spiroxin **293** proceeded in 19 steps and an overall yield of 0.15% (Scheme **13.14**). This synthesis addressed the difficult synthesis of the hindered biaryl **273** after much optimization via the reductive homocoupling of naphthyl iodide **280**. Although the PIFA mediated oxidation of **289** proceeded in low yield, it did allow access to a highly functionalized and oxygenated core that was readily deacetylated to **271**. Unfortunately, the final chlorination was never optimized to allow completion of the spiroxins' synthesis. This system either did not react or decomposed under more forcing conditions. Ultimately, this route presents an extension of PIFA mediated oxidations, optimized yields for the epoxidation of **271** without the aid of a protecting group on the phenol and an unique approach to the spiroxin core.



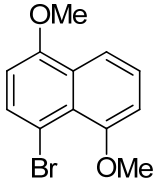
Scheme 13.14. Attempted synthesis of **140**

14.0 SPIROXIN EXPERIMENTAL PART

General: All moisture sensitive reactions were performed in flame-dried or oven-dried glassware under a nitrogen atmosphere. THF and Et_2O were distilled over Na/benzophenone, while pyridine and triethylamine were distilled over CaH_2. Hexanes and ethyl acetate were distilled prior to use. All other reagents and solvents were used as received unless otherwise noted. Analytical thin layer chromatography was performed on pre-coated silica gel 60 F-254 plates available from Merck. Flash chromatography was performed using silica gel (230-400 mesh) available from Baker. NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR using a Bruker Avance 300 with XWIN-NMR software. Chemical shifts (δ) are expressed relative to the NMR solvent peak. IR spectra were obtained with a Nicolet Avator 360 FT-IR, ATR-IR spectra were measured with a Smiths IdentifyIR, optical rotations were measured with a Perkin-Elmer 241 polarimeter and mass spectra were obtained on a double focusing instrument. EI mass spectra were obtained with VG Autospec and ESI mass spectra with Q-TOF API US.

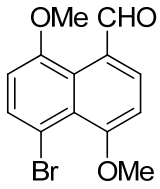


1,5-Dimethoxynaphthalene (188).[313] The dark purple solution of dihydroxynaphthalene **187** (100g, 0.63 moles) in 2.0 M NaOH (125 mL) was slowly treated with dimethyl sulfate (120 mL, 1.26 moles) in two 60 mL batches over 10 minutes. The addition was very exothermic and light beige solids precipitated out of solution. Additional H_2O (100 mL) was added to the thick suspension. The reaction mixture was stirred for 2 h, quenched with 2.0 M NaOH (120 mL), diluted with water and extracted with CH_2Cl_2 (2x). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by chromatography on SiO_2 (CH_2Cl_2) to afford 64 g (55%) of **188** as a beige solid: Rf = 0.64 (7:3, hexanes:EtOAc); ^{1}H NMR δ 7.83 (d, 2 H, *J* = 8.4 Hz), 7.38 (t, 2 H, *J* = 8.1 Hz), 6.79 (d, 2 H, *J* = 8.1 Hz), 4.00 (s, 6 H); MS (EI) *m/z* (rel intensity) 188 (M^+, 100), 173 (65), 115 (46); HRMS (EI) calculated for $C_{12}H_{12}O_2$ 188.0837, found 188.0833.



4-Bromo-1,5-dimethoxynaphthalene (275).[401] A solution of dimethoxynaphthalene **188** (64 g, 0.34 mol) in CH_3CN (1.7 L) was slowly treated with NBS (66 g, 0.37 mol) over 10 min and stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure and the succinimide byproduct was triturated ($CHCl_3$) out of solution and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography on SiO_2 (8:2, hexanes:EtOAc) to afford 100.53 g (69%) of **275** as a 1:0.3:0.3 mixture of bromonaphthalene **275**, starting material **188** and di-brominated product as an inseparable mixture: Rf 0.64 (7:3, hexanes:EtOAc); ^{1}H NMR δ 7.91 (dd, 1 H, *J* = 8.6, 1.0 Hz), 7.66 (d, 1 H,

J = 8.4 Hz), 7.40 (app t, 1 H, *J* = 8.0 Hz), 6.97 (d, 1 H, *J* = 7.5 Hz), 6.64 (d, 1 H, *J* = 8.4 Hz), 3.97 (s, 3 H), 3.95 (s, 3H); MS (EI) *m/z* (rel intensity) 266 (M^+, 100), 253 (61), 251 (82), 239 (100), 236 (66), 211 (85); HRMS (EI) calculated for $C_{12}H_{11}O_2Br$ 265.9942, found 265.9936.

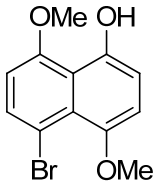


5-Bromo-4,8-dimethoxynaphthalene-1-carbaldehyde (276). A solution of α,α-dichloromethylmethyl ether (29.45 mL, 0.3261 mol) in CH_2Cl_2 (736 mL) was cooled to 0 °C, treated with $SnCl_4$ (37.85 mL, 0.3259 mol) and stirred at 0 °C for 30 min. The reaction mixture was treated with a solution of bromonaphthalene **275** (57.84 g, 0.2174 mol) in CH_2Cl_2 (315 mL) over 5 min, warmed to room temperature, stirred for 4 h, poured into ice cold H_2O and extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with H_2O, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was triturated with hexanes:EtOAc (7:3), and the solids were filtered and dried under high vacuum to afford 36.2 g (57%) of naphthaldehyde **276** as a beige solid: Rf 0.5 (7:3, hexanes:EtOAc); ^{1}H NMR δ 10.82 (s, 1 H), 7.92 (d, 1 H, *J* = 8.3 Hz), 7.75 (d, 1H, *J* = 8.4 Hz), 6.97 (d, 1 H, *J* = 8.3 Hz), 6.80 (d, 1 H, *J* = 8.4 Hz), 4.02 (s, 3 H), 3.98 (s, 3 H); MS (EI) *m/z* (rel intensity) 294 (M^+, 100), 281 (21), 279 (27), 265 (25), 115 (25); HRMS (EI) calculated for $C_{13}H_{11}O_3Br$ 293.9892, found 293.9887.

Unpublished spectral data (**276**):[438] Mp 208-209 °C (EtOAc/hexanes); IR (neat) 1668, 1570, 1517, 1370, 1063 cm $^{-1}$; ^{1}H NMR δ 10.77 (s, 1 H), 7.85 (d, 1 H, *J* = 8.3 Hz), 7.69 (d, 1H, *J* = 8.4 Hz), 6.91 (d, 1 H, *J* = 8.3 Hz), 6.75 (d, 1 H, *J* = 8.4 Hz), 3.98 (s, 3 H), 3.95 (s, 3 H); ^{13}C NMR δ

193.9, 159.3, 155.8, 133.5, 129.7, 128.5, 127.3, 124.4, 108.3, 108.0, 106.5, 56.2, 55.6; MS (EI) *m/z* (rel intensity) 294 (M^+, 100), 280 (25), 264 (26), 216 (12), 193 (14), 115 (27); HRMS (EI) calculated for $C_{13}H_{11}O_3Br$ 293. 9892, found 293. 9897.

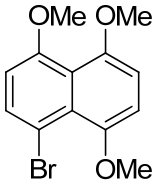
Alternative synthesis of **276**: A solution of naphthaldehyde **189** (1.400 g, 6.475 mmol) in CH_3CN (60 mL) was treated with NBS (1.164 g, 6.540 mmol) and stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography on SiO_2 (7:3, hexanes:EtOAc). Naphthaldehyde **276** and debromo starting material **189** co-elute on TLC and a trace amount of starting material was isolated from the column with **276**. Naphthaldehyde **276** was separated from **189** via trituration (Et_2O) to afford 0.774 g (41%) of **276** as a light yellow solid whose MS and ^1H NMR matched previously synthesized **276**.



5-Bromo-4,8-dimethoxynaphthalen-1-ol (277). A solution of naphthaldehyde **276** (36.2 g, 0.186 mol) in CH_2Cl_2 (1.26 L) was treated with 70% mCPBA (45.27 g, 0.211 mol) and stirred for 6 h. The reaction mixture was treated with a solution of 10% $Na_2S_2O_3$ (1.26 L), stirred for 1 h, the organic layer separated, and the aqueous extract washed with CH_2Cl_2. The combined organic extracts were washed with sat. $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated under reduced pressure. A solution of the crude product in MeOH (450 mL) and THF (40 mL) was cooled to 0 °C, treated with a solution of KOH (19.9 g, 0.354 mol) in MeOH (90 mL) and stirred

for 20 min. The reaction mixture was quenched dropwise with 1.0 M HCl until a maroon color persisted. The reaction mixture was diluted with CH_2Cl_2, extracted with H_2O, dried ($MgSO_4$), filtered and concentrated under reduced pressure. It was purified by column chromatography through a 3 cm pad of SiO_2 (CH_2Cl_2) to provide 35 g (>100%) of **277** as an off-white solid: Rf 0.4 (7:3, hexanes:EtOAc); ^{1}H NMR δ 9.29 (s, 1 H), 7.64 (d, 1 H, *J* = 8.4 Hz), 6.97 (d, 1 H, *J* = 8.5 Hz), 6.85 (d, 1 H, *J* = 8.5 Hz), 6.63 (d, 1 H, *J* = 8.4 Hz), 4.04 (s, 3 H), 3.88 (s, 3 H); MS (EI) *m/z* (rel intensity) 282 (M^+, 85), 269 (93), 267 (100), 252 (34), 189 (20); HRMS (EI) calculated for $C_{12}H_{11}BrO_3$ 281.9892, found 281.9890;

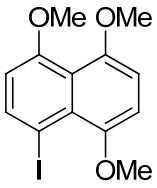
Unpublished spectral data (**277**).[438] Mp 142-143 °C (CH_2Cl_2); IR (neat) 3370 (bs), 1625, 1602, 1419, 1373, 1287, 1063 cm $^{-1}$; ^{1}H NMR δ 9.29 (s, 1 H), 7.63 (d, 1 H, *J* = 8.4 Hz), 6.97 (d, 1 H, *J* = 8.6 Hz), 6.85 (d, 1 H, *J* = 8.6 Hz), 6.62 (d, 1 H, *J* = 8.4 Hz), 4.04 (s, 3 H), 3.87 (s, 3 H); ^{13}C NMR δ 155.8, 149.0, 148.6, 132.7, 125.5, 117.4, 112.5, 111.3, 108.9, 105.4, 57.7, 56.6; MS (EI) *m/z* (rel intensity) 282 (M^+, 100), 267 (93), 252 (31), 198 (9), 172 (7), 115 (9); HRMS (EI) calculated for $C_{12}H_{11}O_3Br$ 281.9892, found 281.9896.



1-Bromo-4,5,8-trimethoxynaphthalene (278). A solution of naphthol **277** (73.5 g, 0.260 mol) in DMF (675 mL) was cooled to 0 °C and treated with NaH (60% dispersion in mineral oil, 11.4 g, 0.285 mol). The reaction mixture was warmed to room temperature, stirred for 30 min, cooled to 0 °C, treated with MeI (24.3 mL, 0.39 mol), warmed to room temperature, stirred for 30 min,

cooled to 0 °C and quenched with H_2O (1.35 L) which caused beige solids to precipitate out of solution. The suspension was filtered through a coarse sintered glass filter and washed with H_2O. The solids were collected, dried under high vacuum, dissolved in CH_2Cl_2 and purified by column chromatography though a 3 cm pad of SiO_2 (CH_2Cl_2) to afford 32.4 g (42%) of bromonaphthalene **278** as an off white solid: Rf 0.3 (7:3, hexanes:EtOAc) ^{1}H NMR δ 7.78 (d, 1H, *J* = 8.5 Hz), 6.99 (d, 1 H, *J* = 8.6 Hz), 6.92 (d, 1 H, *J* = 8.6 Hz), 6.67 (d, 1H, *J* = 8.5 Hz), 3.94 (s, 1H), 3.89 (s, 6H); MS (EI) *m/z* (rel intensity), 296 (M^+, 100), 283 (60), 282 (30), 267 (22), 202 (12), 97 (39), 57 (63); HRMS (EI) calculated for $C_{13}H_{13}BrO_3$ 296.0048, found 296.0049.

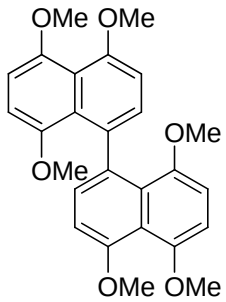
Unpublished spectral data (**278**):[438] Mp 168-169 °C; Rf 0.3 (hexanes:EtOAc, 7:3); IR (neat) 1592, 1513, 1450, 1378, 1311, 1267, 1060 cm $^{-1}$; ^{1}H NMR δ 7.68 (d, 1 H, *J* = 8.5 Hz), 6.91 (d, 1 H, *J* = 8.6 Hz), 6.84 (d, 1 H, *J* = 8.6 Hz), 6.67 (d, 1 H, *J* = 8.5 Hz), 3.92 (s, 3 H), 3.88 (s, 6 H); ^{13}C NMR δ 157.0, 151.8, 150.3, 133.8, 126.6, 121.3, 110.1, 109.4, 108.0, 107.5, 58.1, 57.2, 56.9; MS (EI) *m/z* (rel intensity) 296 (M^+, 67), 281 (38), 218 (13), 203 (14), 111, (30), 97 (52), 57 (100); HRMS (EI) calculated for $C_{13}H_{13}O_3Br$ 296.0048, found 296.0047.



1-Iodo-4,5,8-trimethoxynaphthalene (280). A solution of bromonaphthalene **278** (32.3 g, 0.109 mol) in THF (740 mL) was cooled to −78 °C and treated with a 1.6 M solution of *n*-BuLi in hexanes (77 mL, 0.12 mol). The reaction mixture was stirred for 20 min, treated with a

solution of I_2 (33 g, 0.13 mol) in THF (186 mL) over 5 min and warmed to room temperature, and stirred for 30 min. It was quenched with water and extracted with EtOAc (2x). The combined organic extracts were washed with 10% $Na_2S_2O_3$, dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by passing through a 3 cm pad of SiO_2 (CH_2Cl_2) to afford 33.6 g (90%) of iodonaphthalene **280** as a white solid: Rf 0.3 (7:3, hexanes:EtOAc); ^{1}H NMR δ 8.10 (d, 1H, *J* = 8.4 Hz), 6.90 (d, 1 H, *J* = 8.6 Hz), 6.85 (d, 1 H, *J* = 8.6 Hz), 6.53 (d, 1 H, *J* = 8.4 Hz), 3.94 (s, 3 H), 3.89 (s, 3 H), 3.89 (s, 3 H); MS (EI) *m/z* (rel intensity) 344 (M^+,100), 329 (46), 301 (13), 171 (25); HRMS calculated for $C_{13}H_{13}O_3I$ 343.9910, found 343.9892.

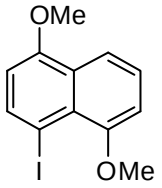
Unpublished spectral data (**280**):[438] Mp 164-165 °C (CH_2Cl_2); IR (neat) 1588, 1449, 1378, 1308, 1272, 1058 cm -1; ^{1}H NMR δ 8.09 (d, 1 H, *J* = 8.4 Hz), 6.88 (d, 1 H, *J* = 8.6 Hz), 6.84 (d, 1 H, *J* = 8.6 Hz), 6.51 (d, 1 H, *J* = 8.4 Hz), 3.92 (s, 3 H), 3.88 (s, 3 H), 3.87 (s, 3 H); ^{13}C NMR δ 157.8, 151.5, 148.6, 141.8, 127.6, 120.6, 109.0, 108.8, 108.6, 74.2, 58.0, 56.7, 55.9; MS (EI) *m/z* (rel intensity) 344 (M^+, 48), 329 (19), 218 (100), 203 (88), 115 (19); HRMS (EI) calculated for $C_{13}H_{13}O_3I$ 343.9909, found 343.9912.



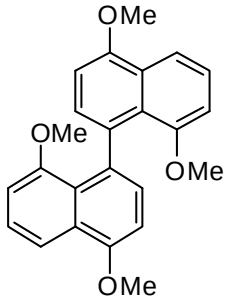
1,4,5-Trimethoxy-8-(1,4,5-trimethoxynaphthalen-8-yl)naphthalene (273). Zn (6.4 g, 98 mmol), Et_4NI (25.09 g, 97.60 mmol), and $Ni(PPh_3)_2Cl_2$ (12.8 g, 19.6 mmol) were added to a

flame dried flask and purged with N_2 (2x). THF (12.8 mL) was added to the solid mixture and N_2 was vigorously bubbled through the rapidly stirred suspension for 30 minutes as the color of the reaction mixture changed from maroon, to green, to a deep orange. Iodonaphthalene **280** (16.8 g, 48.9 mmol) was added to the reaction mixture in one batch and it was heated to 50 °C for 3 h. The reaction mixture was cooled to room temperature, filtered through a pad of celite and washed with CH_2Cl_2. The filtrate was washed with 1.0 M HCl and water, dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by column chromatography on SiO_2 (CH_2Cl_2) to afford 9.04 g (85%) of biaryl **273** as a white solid: Rf 0.16 (7:3, hexanes:EtOAc); ^{1}H NMR δ 7.08 (d, 1 H, *J* = 8.0 Hz), 6.88 (d, 1 H, *J* = 8.0 Hz), 6.78 (d, 1 H, *J* = 8.5 Hz), 6.63 (d, 1 H, *J* = 8.5 Hz), 4.01 (s, 3 H), 3.95 (s, 3 H), 2.97 (s, 3 H); MS (ESI-Q-TOF) *m/z* (rel intensity) 457 ([M+Na]$^+$, 48), 443 (100), 420 (50), 365 (20); HRMS (ESI-Q-TOF) calculated for $C_{25}H_{22}O_8Na$ 457.1627, found 457.1630.

Unpublished Spectral data (**273**):[438] Mp 196-198 °C (hexanes/EtOAc), IR (neat) 1593, 1380, 1270, 1070, 1032 cm $^{-1}$, ^{1}H NMR δ 7.09 (d, 2 H, *J* = 8.0 Hz), 6.89 (d, 2 H, *J* = 8.0 Hz), 6.81 (d, 2 H, *J* = 8.5 Hz), 6.64 (d, 2 H, *J* = 8.5 Hz), 4.02 (s, 6 H), 3.96 (s, 6 H), 2.98 (s, 6 H), ^{13}C NMR δ 155.3, 152.0, 151.4, 135.4, 128.9, 127.2, 118.7, 107.6, 107.5, 106.2, 57.9, 56.8, 56.5; MS (EI) *m/z* (rel intensity) 434 (M$^+$, 8), 246 (11), 234 (15), 218 (100), 203 (92), 175 (12), 115 (18); HRMS (EI) calculated for $C_{26}H_{26}O_6$ 434.1729, found 434.1709.

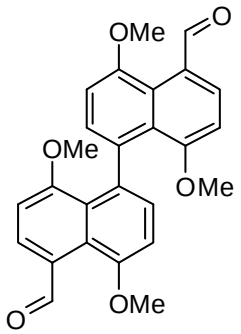


4-Iodo-1,5-dimethoxynaphthalene (285). A solution of bromonaphthalene **275** (14.0 g, 52.6 mmol) in THF (350 mL) was cooled to −78 °C and treated with a 1.6 M solution of *n*-BuLi in hexanes (36.8 mL, 57.9 mmol). The reaction mixture was stirred for 20 min, treated dropwise with a solution of I_2 (16.0 g, 63 mmol) in THF (89 mL), stirred for 5 min, warmed to room temperature, stirred for 1 h and quenched with H_2O. The reaction mixture was diluted with EtOAc, washed with H_2O and 10% $Na_2S_2O_3$, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (CH_2Cl_2) afforded 16.0 g (97%) of iodonaphthalene **285** as a beige solid: Rf 0.63 (7:3, hexanes:EtOAc); ^{1}H NMR δ 8.07 (d, 1 H, *J* = 8.1), 7.92 (dd, 1 H, *J* = 8.4, 1.0 Hz), 7.41 (t, 1 H, *J* = 8.1 Hz), 6.95 (dd, 1 H, *J* = 8.4, 1.0 Hz), 6.49 (d, 1 H, *J* = 8.1 Hz), 3.96 (s, 3 H), 3.94 (s, 3 H); MS (EI) *m/z* (rel intensity) 314 (M^+, 100), 299 (17), 241 (17), 127 (80), 114 (65), 75 (49) HRMS (EI) calculated for $C_{12}H_{11}O_2I$ 313.9804, found 313.9792.



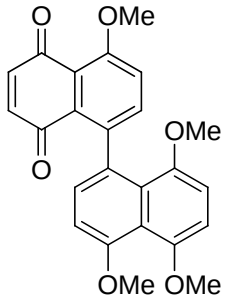
1,5-Dimethoxy-4-(1,5-dimethoxynaphthalen-4-yl)naphthalene (286). Zn (6.66 g, 101.9 mmol), Et_4NI (20.05 g, 76.40 mmol) and $Ni(PPh_3)_2Cl_2$ (10.2 g, 15.3 mmol) were added to a flame dried flask followed by THF (160 mL). N_2 was vigorously bubbled through the rapidly

stirred suspension for 30 min as the color of the reaction mixture changed from green to maroon. Iodonaphthalene **285** (16.0 g, 50.9 mmol) was added in one portion and the mixture heated to 50 °C for 3 h. The reaction mixture was cooled to room temperature, filtered through celite, washed with CH_2Cl_2, concentrated under reduced pressure and triturated with EtOAc. The solids were filtered, collected, and dried under high vacuum to afford 7.6 g (80%) of **286** as a light yellow solid. An analytically pure sample was obtained by triturating the product with (1:1, EtOAc:hexanes): Mp 218.9-216.4 °C (EtOAc); Rf 0.5 (8:2, Hex: EtOAc); IR (ATR) 1592, 1508, 1459, 1467, 1319, 1262, 1247, 1068, 1055, 759 cm $^{-1}$; ^{1}H NMR δ 7.81 (d, 1 H, *J* = 8.1 Hz), 7.35 (t, 1 H, *J* = 8.1 Hz), 6.98 (d, 1 H, *J* = 7.8 Hz), 6.96 (d, 1 H, *J* = 8.1 Hz), 6.77 (d, 1 H, *J* = 7.8 Hz), 3.99 (s, 3 H), 3.33 (s, 3 H); ^{13}C NMR δ156.8, 152.9, 134.0, 126.5, 125.9, 125.7, 124.8, 113.7, 106.5, 103.5, 55.5, 55.1; MS (EI) *m/z* relative intensity 374 (M^+, 39), 278 (41), 277 (100), 201 (14); HRMS (EI) calculated for $C_{24}H_{22}O_4$ 274.1518, found 374.1526.



4,8 Dimethoxy-5-(4,8-dimethoxy-1-formyl-5-yl)-1-carbaldehyde (287). A solution of biaryl **286** (9.50 g, 25.4 mmol) in toluene (20 mL) and DMF (12 mL) was cooled to 0 °C, treated with $POCl_3$ (6.02 mL, 63.9 mmol), warmed to room temperature and heated to reflux for 7h. The reaction mixture was quenched with 2.0 M NaOH, extracted with EtOAc, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography on

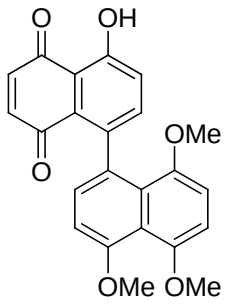
SiO_2 (1:1, EtOAc:hexanes) afforded slightly impure **287** which was triturated with Et_2O, filtered and dried under high vacuum to afford 1.3 g (12%) of **287** as an orange solid: Rf 0.5 (1:1, EtOAc:hexanes); Mp 261.8 °C (Et_2O, dec.); IR (ATR) 2961, 1662, 1584, 1573, 1511, 1401, 1310, 1128, 1059, 1025 cm^{-1}; ^1H NMR δ 11.03 (s, 2 H), 7.95 (d, 2 H, *J* = 8.1 Hz), 7.13 (d, 2 H, *J* = 8.1 Hz), 6.99 (d, 2 H, *J* = 8.1 Hz), 6.72 (d, 2 H, *J* = 8.1 Hz), 4.06 (s, 6 H), 3.11 (s, 6 H); ^{13}C NMR δ 194.9, 160.8, 154.6, 135.2, 128.8, 128.2, 127.3, 126.3, 124.7, 106.3, 105.0, 55.7, 55.3; MS (EI) *m/z* (rel intensity) 430 (M^+, 16), 278 (42), 277 (100), 201 (25), 77 (44); HRMS (EI) calculated for $C_{26}H_{22}O_6$ 430.1416, found 430.1409.



5-Methoxy-8-(1,4,5-trimethoxynaphthalen-8-yl)naphthalene-1,4-dione (281). A solution of biaryl **273** (7.56 g, 17.4 mmol) in CH_2Cl_2 (515 mL) was cooled to 0 °C and treated dropwise with a solution of PIFA (7.38 g, 17.2 mmol) in CH_3CN (172 mL), and H_2O (34 mL) over 5 min. The reaction mixture was stirred for 1 h, quenched with sat. $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by column chromatography on SiO_2 (7:3, hexanes:EtOAc) to afford 5.11 g (75%) of naphthoquinone **281** as a dark purple solid: Rf 0.5 (7:3, hexanes:EtOAc); ^1H NMR δ 7.44 (d, 1 H, *J* = 8.7 H), 7.24 (d, masked), 6.99 (d, 1 H, *J* = 7.8 Hz), 6.90 (d, 1 H, *J* = 8.1 Hz), 6.83 (d, 1 H, *J* = 8.1 Hz), 6.80 (d, 1 H, *J* = 9.9 Hz), 6.65 (d, 1 H, *J* = 8.7 Hz), 6.59 (d, 1 H, *J* = 9.9 Hz), 4.06 (s, 3 H), 4.00 (s, 3 H), 3.94 (s, 3 H), 3.30 (s, 3 H); MS (ESI-Q-TOF) *m/z*

(rel intensity) 427 ([M+Na]$^+$, 100), 405 (10), 365 (32); HRMS (ESI-Q-TOF) calculated for $C_{24}H_{20}O_6Na$ 427.1158, found 427.1138.

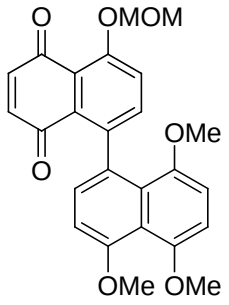
Unpublished data (**281**):[438] Mp 237-239 °C (EtOAc/hexanes); IR (neat) 1266,1590, 1288, 1275, 1247, 1108 cm $^{-1}$; ^{1}H NMR δ 7.43 (d, 1H, *J* = 8.7 Hz), 7.24 (d, 1 H, *J* = 8.7 Hz), 6.98 (d, 1 H, *J* = 8.0 Hz), 6.89 (d, 1 H, *J* = 8.0 Hz), 6.82 (d, 1 H, *J* = 8.5 Hz), 6.79 (d, 1 H, *J* = 10.1 Hz), 6.64 (d, 1 H, *J* = 8.5 Hz), 6.58 (d, 1H, *J* = 10.1 Hz), 4.04 (s, 3H), 4.00 (s, 3 H), 3.93 (s, 3 H), 3.29 (s, 3H); ^{13}C NMR δ 185.8, 185.7, 158.3, 156.5, 152.0, 150.7, 139.6, 139.3, 137.5, 137.4, 130.9, 127.1, 127.0, 119.6, 119.4, 116.1, 108.4, 107.0, 106.7, 58.1, 56.7, 56.6, 56.1; MS (EI) *m/z* (rel intensity) 404 (M$^+$, 100), 389 (6); HRMS (EI) calculated for $C_{24}H_{20}O_6$ 404.1260, found 404.1270



5-Hydroxy-8-(1,4,5-trimethoxynaphthalen-8-yl)naphthalene-1,4-dione. A solution of naphthoquinone **281** (9.28 g, 23.0 mmol) in DMF (464 mL) was treated with LiBr (99.3 g, 1.15 mol), heated to 130 °C for 3h, cooled to room temperature, poured into 1.0 M HCl and extracted with EtOAc (2x). The combined organic extracts were washed with H_2O (3x), dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by column chromatography on SiO_2 (4:1, EtOAc:hexanes) to afford 3.93 g (45%) of the demethylated product as a dark red solid: ^{1}H NMR δ 12.56 (s, 1 H), 7.43 (d, 1 H, *J* = 8.7 Hz), 7.21 (d, 1 H, *J* = 8.7 Hz), 6.99 (d, 1 H, *J* = 8.1 Hz), 6.89 (d, 1 H, *J* = 8.1 Hz), 6.89 (d, 1 H, *J* = 10.3 Hz), 6.84 (d, 1 H, *J* = 8.7 Hz), 6.67 (d, 1 H,

J = 10.2 Hz), 6.66 (d, 1 H, *J* = 8.6 Hz), 4.00 (s, 3 H), 3.93 (s, 3 H), 3.24 (s, 3 H); MS (ESI-Q-TOF) *m/z* (rel intensity) 413 ([M+Na]$^+$, 100); HRMS (ESI-Q-TOF) calculated for $C_{23}H_{18}O_6Na$ 413.1001, found 413.1001.

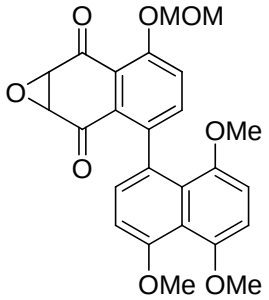
Unpublished Spectral data:[438] Mp 179-180 °C (EtOAc/Hex), IR (neat) 3431 (br), 1664, 1641, 1590, 1466, 1381, 1275 cm $^{-1}$; ^{1}H NMR δ 12.57 (s, 1 H), 7.43 (d, 1 H, *J* = 8.7 Hz), 7.21 (d, 1 H, *J* = 8.7 Hz), 6.98 (d, 1 H, *J* = 8.1 Hz), 6.89 (d, 1H, *J* = 8.1 Hz), 6.88 (d, 1 H, *J* = 10.3 Hz), 6.83 (d, 1 H, *J* = 8.6 Hz), 6.66 (d, 1H, *J* = 10.3 Hz), 6.65 (d, 1 H, *J* = 8.6 Hz), 4.00 (s, 3 H), 3.94 (s, 3 H), 3.32 (s, 3 H), ^{13}C NMR δ 191.5, 184.6, 160.8, 156.7, 152.1, 150.7, 140.8, 140.2, 140.0, 137.2, 129.6, 127.6, 126.9, 122.5, 119.5, 114.4, 108.3, 107.0, 106.6, 58.1, 56.7, 56.1; MS (EI) *m/z* (rel intensity) 390 (M$^+$, 100), 375 (11), 347 (7), 217 (13), 201 (34); HRMS (EI) calculated for $C_{23}H_{18}O_6$ 390.1103, found 390.1103



5-(Methoxymethoxy)-8-(1,4,5-trimethoxynaphthalen-8-yl)naphthalene-1,4-dione (282). A solution of 5-hydroxy-8-(1,4,5-trimethoxynaphthalen-8-yl)naphthalene-1,4-dione (3.93 g, 0.101 mol) in DMF (98.6 mL) was treated with NaH (60% dispersion in mineral oil, 0.493 g, 12.3 mmol), stirred for 30 min, treated with chloromethylmethyl ether (1.33 mL, 0.018 mol), stirred for 30 min, quenched with H_2O and extracted with EtOAc (3x). The combined organic extracts were washed with H_2O (3x), dried ($MgSO_4$), filtered, concentrated under reduced pressure and

purified by column chromatography on SiO_2 (4:1, EtOAc:hexanes) to afford 2.49 g (57%) of naphthoquinone **282** as a red solid: ^{1}H NMR δ 7.46 (d, 1 H, *J* = 8.7 Hz), 7.41 (d, 1 H, *J* = 8.7 Hz), 6.99 (d, 1 H, *J* = 8.1 Hz), 6.90 (d, 1 H, *J* = 8.1 Hz), 6.83 (d, 1 H, *J* = 8.6 Hz), 6.80 (d, 1 H, *J* = 10.2 Hz), 6.65 (d, 1 H, *J* = 8.6 Hz), 6.60 (d, 1 H, *J* = 10.2 Hz), 5.43, 5.36 (d_{AB}, 1 H, *J* = 6.9 Hz), 4.01 (s, 3 H), 3.94 (s, 3 H), 3.60 (s, 3 H), 3.30 (s, 3 H); MS (ESI-Q-TOF) *m/z* (rel intensity) 457 ($[M+Na]^+$, 100); HRMS (ESI-Q-TOF) calculated for $C_{25}H_{22}O_7Na$ 457.1263, found 457.1268.

Unpublished spectral data (**282**):[438] Mp 145-147 °C (EtOAc/hexanes); IR (neat) 1659, 1590, 1389, 1268, 1255, 1106, 1075 cm $^{-1}$; ^{1}H NMR δ 7.45 (d, 1 H, *J* = 8.7 Hz), 7.40 (d, 1 H, *J* = 8.7 Hz), 6.99 (d, 1 H, *J* = 8.1 Hz), 6.90 (d, 1 H, *J* = 8.1 Hz), 6.83 (d, 1 H, *J* = 8.6 Hz), 6.79 (d, 1 H, *J* = 10.2 Hz), 6.65 (d, 1 H, *J* = 8.6 Hz), 6.60 (d, 1 H, *J* = 10.2 Hz), 5.43, 5.37 (d_{AB}, 2H, *J* = 6.9 Hz), 4.01 (s, 3 H), 3.94 (s, 3 H), 3.60 (s, 3 H), 3.30 (s, 3 H); ^{13}C NMR δ 185.6, 185.5, 156.6, 155.7, 152.0, 150.7, 141.2, 139.2, 137.7, 137.3, 130.8, 130.3, 127.0, 120.8, 119.4, 108.4, 107.1, 106.6, 105.3, 95.6, 58.1, 56.8, 56.7; MS (ESI-Q-TOF) *m/z* (rel intensity) 457 ($[M+Na]^+$. 100), HRMS (ESI-Q-TOF), calculated for $C_{25}H_{22}O_7Na$ 457.1263, found 457.1267.

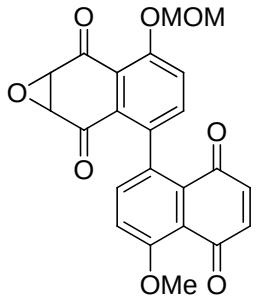


3-(Methoxymethoxy)-6-(1,4,5-trimethoxynaphthalen-8-yl)naphtho[2,3-*b*]oxirene-2,7(1a*H*,7a*H*)-dione (283). A solution of biaryl **282** (0.459 g, 1.06 mmol) in $CHCl_3$ (30.2 mL)

was treated with LiOH (0.447 g, 18.7 mol), *N*-benzylcinchonidinium chloride (48.4 mg, 0.114 mmol) and 30% H_2O_2 (6.04 mL), and the biphasic solution was stirred rapidly for 10 h. The reaction mixture was quenched with 1.0 M HCl, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by column chromatography on SiO_2 (4:1, EtOAc:hexanes) to afford 0.395 g (83%) of epoxide **283** as a yellow foam and 1:1 mixture of atropisomers: Rf 0.6 (4:1, EtOAc:hexanes); IR (ATR) 2945 (bs), 1698, 1589, 1523, 1457, 1387, 1262, 1064 cm^{-1}; ^1H NMR δ 7.41-7.40 (m, 2 H), 7.09 (d, 0.5 H, *J* = 8.1 Hz), 6.96 (d, 0.5 H, *J* = 8.1 Hz), 6.91 (d, 0.5 H, *J* = 8.0 Hz), 6.88-6.80 (m, 1.5 H), 6.72 (d, 0.5 H, *J* = 8.6 Hz), 6.67 (d, 0.5 H, *J* = 8.6 Hz), 5.38 (d, 0.5 H, *J* = 6.9 Hz), 5.35 (d, 0.5 H, *J* = 6.9 Hz), 5.31 (d, 0.5 H, *J* = 6.9 Hz), 5.30 (d, 0.5 H, *J* = 6.9 Hz), 4.04 (s, 1.5 H), 3.99 (s, 1.5 H), 3.98 (d, 0.5 H, *J* = 4.4 Hz), 3.94 (s, 1.5 Hz), 3.92 (s, 1.5 Hz), 3.82 (d, 0.5 H, *J* = 4.4 Hz), 3.75 (d, 0.5 H, *J* = 4.4 Hz) 3.65 (d, 0.5 H, *J* = 4.4 Hz), 3.59 (s, 1.5 H), 3.57 (s, 1.5 H), 3.49 (s, 1.5 H), 3.28 (s, 1.5 H); ^{13}C NMR δ 192.2, 191.8, 191.7, 191.6, 156.6, 155.0, 154.3, 154.2, 151.7, 151.5, 154.2, 151.7, 150.7, 150.0, 140.4, 139.5, 137.0, 136.1, 135.1, 131.7, 130.1, 129.8, 128.7, 128.3, 125.3, 120.9, 120.8, 119.5, 119.2, 118.4, 108.3, 108.2, 107.6, 107.4, 107.3, 106.5, 106.0, 105.9, 105.7, 95.4, 95.3, 57.9, 57.8, 57.6, 56.5, 56.4, 56.2, 55.6, 55.5, 55.4, 54.8; MS (ESI-Q-TOF) *m/z* (rel intensity) 473 ($[M+Na]^+$, 100), 457 (8); HRMS (ESI-Q-TOF) calculated for $C_{25}H_{22}O_8Na$ 473.1212, found 473.1180.

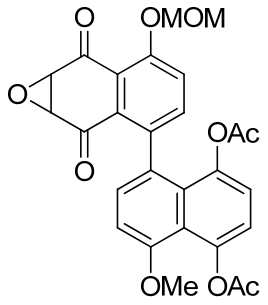
Unpublished spectral data (**283**):[438] ^1H NMR δ 7.43-7.41 (m, 2H), 7.09 (d, 0.5 H, *J* = 8.1 Hz), 6.95 (d, 0.5 H, *J* = 8.1 Hz), 6.91 (d, 0.5 H, *J* = 8.0 Hz), 6.87-6.80 (m, 1.5 H), 6.72 (d, 0.5 H, *J* = 8.6 Hz), 6.67 (d, 0.5 H, *J* = 8.6 Hz), 5.39-5.28 (m, 2 H), 4.01 (s, 1.5 H), 3.98 (s, 1.5 H), 3.96 (d, 1 H, *J* = 4.7 Hz), 3.94 (s, 1.5 H), 3.92 (s, 1.5 H), 3.81 (d, 0.5 H, *J* = 4.4 Hz), 3.75 (d, 0.5 H, *J* = 4.4 Hz), 3.59 (s, 1.5 H), 3.57 (s, 1.5 H), 3.49 (s, 1.5 H), 3.28 (s, 1.5 H); MS (EI) mz (rel intensity)

450 (M^+, 31), 406 (26), 309 (18), 176 (52), 91 (100); HRMS (EI) calculated for $C_{25}H_{22}O_8$ 450.1315, found 450.1315



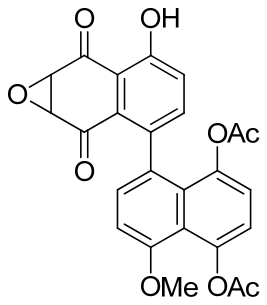
3-(1,4-Dihydro-5-methoxy-1,4-dioxonaphthalen-8-yl)-6-(methoxymethoxy)naphtho[2,3-*b*]oxirene-2,7(1a*H*,7a*H*)-dione. A solution of epoxide **283** (0.274 g, 0.611 mmol) in CH_2Cl_2 (14.1 mL) was cooled to 0 °C and treated dropwise with a solution of PIFA (0.260 g, 0.610 mmol) in CH_3CN (3.5 mL) and H_2O (0.70 mL) over 5 min. The reaction mixture was stirred for 30 min, treated with additional PIFA (0.078 g, 0.18 mmol) in CH_3CN (1.05 mL) and H_2O (0.21 mL), stirred 10 minutes, quenched with sat. $NaHCO_3$, diluted with water and extracted with CH_2Cl_2 (2x). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by column chromatography on SiO_2 (4:1, EtOAc:hexanes) to afford 0.3321 g (90%) of the oxidized product as a red oil: Rf = 0.3 (4:1, EtOAc:hexanes); IR (neat) 2939, 1700, 1658, 1618, 1584, 1560, 1465, 1279, 1248, 1150, 1084, 1025, 975 cm^{-1}; ^1H NMR δ 7.56 (d, 0.5 H, *J* = 8.5 Hz), 7.49 (d, 0.5 H, *J* = 8.5 Hz), 7.44 (d, 0.5 H, *J* = 8.8 Hz), 7.40 (d, 0.5 H, *J* = 8.8 Hz), 7.32 (d, 1 H, *J* = 8.7 Hz), 7.25 (d, 1 H, *J* = 8.5 Hz), 6.87 (d, 0.5 H, *J* = 10.2 Hz), 6.82 (d, 0.5 H, *J* = 10.2 Hz), 6.66 (d, 1 H, *J* = 10.2 Hz), 5.38 (d_{AB}, 1 H, *J* = 6.9 Hz), 5.31 (d_{AB}, 1 H, *J* = 6.9 Hz), 4.06 (s, 3 H), 4.03 (s, 3 H), 4.02 (d, 1 H, *J* = 4.3 Hz), 3.98 (d, 1 H, *J* = 4.3 Hz), 3.83 (d, 1 H, *J* = 4.3 Hz), 3.80 (d, 1 H, *J* = 4.3 Hz); ^{13}C NMR δ 192.4, 192.0, 191.0, 190.3, 186.0, 185.5, 184.5, 184.3, 159.3, 159.2, 155.5, 139.6, 138.5, 137.0, 136.9, 136.2, 136.1, 135.8,

135.5, 134.1, 133.1, 132.9, 132.0, 129.6, 121.1, 120.2, 117.6, 116.8, 95.2, 95.1, 56.6, 56.4, 55.3, 55.2, 55.1, 54.7; MS (ESI-Q-TOF) *m/z* (rel intensity) 443 ([M+Na]$^+$, 100), 427 (20), 421 (15), 365 (11); HRMS (ESI-Q-TOF) calculated for $C_{23}H_{16}O_8Na$ 443.0743, found 443.0757.

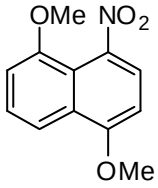


3-(1,4-Diacetoxy-5-methoxynaphthalen-8-yl)-6-(methoxymethoxy)naphtho[2,3-*b*]oxirene-2,7(1a*H*,7a*H*)-dione (284). A solution of 3-(1,4-dihydro-5-methoxy-1,4-dioxonaphthalen-8-yl)-6-(methoxymethoxy)naphtho[2,3-*b*]oxirene-2,7(1a*H*,7a*H*)-dione (0.332 g, 0.790 mmol) in $CHCl_3$ (20.1 mL) and THF (10.1 mL) was treated with sat. $Na_2S_2O_3$ and stirred rapidly for 30 min. The reaction mixture was diluted with H_2O, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The reaction mixture was carried directly onto the acetylation sequence. The crude mixture was dissolved in CH_2Cl_2 (20.2 mL) treated with pyridine (2.02 mL, 24.9 mmol), Ac_2O (0.749 mL, 7.9 mmol) and DMAP (0.020 g, 0.164 mmol) and stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and directly submitted to purification by column chromatography on SiO_2 (4:1 EtOAc: hexanes) to afford 0.3182 g (80%) of acetate **284** as an orange foam contaminated with some of the MOM deprotected product **289**: Rf 0.6 (4:1, hexanes:EtOAc); crude ^{1}H NMR δ 7.13-7.03 (m), 6.93 (d, 1 H, *J* = 7.8 Hz), 6.91 (d, 1 H, *J* = 8.1 Hz), 6.78 (d, 1 H, *J* = 8.1 Hz), 5.35-5.19 (m, 2 H), 3.94 (s, 3 H), 3.99 (d, 1 H, *J* = 4.5 Hz), 3.92 (s, 3 H), 3.82 (d, 1 H, *J* = 4.5 Hz), 3.54 (s, 3 H), 3.53 (s, 3 H), 2.37 (s, 6 H); MS (ESI-Q-TOF) *m/z* (rel intensity) 529 ([M+Na]$^+$, 100), 527

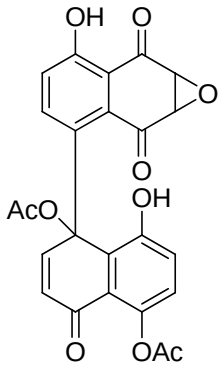
(50), 443 (73), 365 (22); HRMS (ESI-Q-TOF) calculated for $C_{27}H_{22}O_{10}Na$ 529.1111, found 529.1101.



3-(1,4-Diacetoxy-5-methoxynaphthalen-8-yl)-6-hydroxynaphtho[2,3-*b*]oxirene-2,7(1a*H*,7a*H*)-dione (289). A solution of acetate **284** (0.318 g, 0.628 mmol) in CH_2Cl_2 (18 mL) was cooled to 0 °C, treated with TFA (0.91 mL, 12 mmol) and stirred for 1 h. The reaction mixture was concentrated under reduced pressure without any aqueous workup and purified by column chromatography on SiO_2 (4:1, EtOAc:hexanes) to afford 0.265 g (91%) of **289** as a red foam: Rf 0.6 (4:1, EtOAc:hexanes); IR (neat) 3584, 2936, 2360, 1761, 1699, 1653, 1520, 1457, 1389, 1366, 1308, 1273, 1027 cm^{-1}; ^1H NMR δ 11.35 (s, 1 H), 11.32 (s, 1 H), 7.52 (d, 1 H, *J* = 8.7 Hz), 7.48 (d, 1 H, *J* = 8.7 Hz), 7.28 (d, 1 H, *J* = 9.3 Hz), 7.25 (d, 1 H, *J* = 8.8 Hz), 7.12-7.12 (m, 5 H), 6.93 (d, 1 H, *J* = 8.1 Hz), 6.92 (d, 1 H, *J* =8.1 Hz), 6.79 (d, 1 H, *J* = 8.1 Hz), 4.00 (d, 1 H, *J* = 3.9 Hz), 3.99 (d, 1 H, *J* = 3.9 Hz), 3.98 (s, 3 H), 3.94 (s, 3 H), 3.88 (d, ,1 H, *J* = 3.9 Hz), 3.86 (d, 1 H, *J* = 3.9 Hz), 2.39 (s, 3 H), 2.39 (s, 3 H); ^{13}C NMR 196.8, 196.7, 190.7, 190.4, 170.5, 170.4, 169.6, 169.0, 160.5, 160.5, 155.3, 155.3, 145.0, 144.7, 144.2, 144.0, 140.6, 140.5, 137.2, 136.2, 131.0, 129.7, 129.2, 129.0, 128.5, 126.8, 126.8, 122.5, 122.4, 120.5, 120.4, 120.2, 119.3, 119.2, 114.2, 114.0, 106.1, 105.7, 60.6, 56.2, 55.4, 55.3, 55.1, 53.4, 20.9, 20.2, 19.9, 14.1; MS (ESI-Q-TOF) *m/z* (rel intensity) 485 ($[M+Na]^+$, 100), 469 (5), 443 (4), 422 (4); HRMS (EI) calculated for $C_{25}H_{18}O_9Na$ 485.0849, 485.0866.

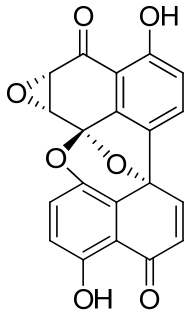


1,5-Dimethoxy-4-nitronaphthalene (291).[439] A solution of dimethoxynaphthalene **188** (0.01 g, 0.05 mmol) in acetone (0.23 mL) and H_2O (0.08 mL) was treated dropwise with a solution of CAN (73 mg, 0.13 mmol) in H_2O (0.3 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C, diluted with H_2O and EtOAc and extracted. The organic extract with dried ($MgSO_4$), filtered and concentrated under reduced pressure. Analysis of the ^{1}H NMR indicated the presence of starting material and nitro **291** (14%): Representative signals: ^{1}H NMR δ 7.91 (dd, 1 H, J = 8.5, 0.9 Hz), 7.51 (dd, 1 H, J = 8.3, 1.6 Hz), 7.49 (d, 1 H, J = 8.4 Hz), 7.02 (d, 1 H, J = 8.3 Hz), 6.75 (d, 1 H, J = 8.3 Hz), 4.03 (s, 3 H), 3.92 (s, 3H); MS (EI) *m/z* (relative intensity) 233 (M^+, 100), 203 (5), 188 (10), 172 (13), 127 (35); HRMS (EI) calculated for $C_{12}H_{11}O_4N$ 233.0688, found 233.0686.



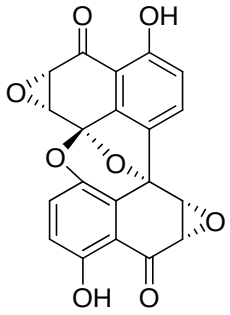
3-(1,4-Dihydro-5-hydroxy-4,8-diacetoxy-1-oxonaphthalen-4-yl)-6-hydroxynaphtho[2,3-*b*]oxirene-2,7(1a*H*,7a*H*)-dione. A solution of **289** (0.139 g, 0.300 mol) in CH_3CN (6.88 mL) and H_2O (1.11 mL) was treated with PIFA (0.140 g, 0.325 mol) and heated to 80 °C for 2 h. One

additional equivalent of PIFA (0.140 g, 0.325 mol) was added, the reaction mixture stirred for an additional h, cooled to room temperature, diluted with CH_2Cl_2, washed with water, dried ($MgSO_4$), filtered, and concentrated under reduced pressured. The reaction mixture was purified by column chromatography on SiO_2 (1:1, EtOAc:hexanes) to afford ~49.8 mg (36%) of the oxidized product as an orange film and a mixture of several coeluting deacetylated compounds: Representative ^{1}H NMR δ 11.49 (s, 1 H), 9.32 (s, 1 H), 6.27 (d, 1 H, *J* = 10.3 Hz).



De-epoxy,de-chlorospiroxin A (271). A solution of impure 3-(1,4-dihydro-5-hydroxy-4,8-diacetoxy-1-oxonaphthalen-4-yl)-6-hydroxynaphtho[2,3-*b*]oxirene-2,7(1a*H*,7a*H*)-dione (41.5 mg, 0.0894 mmol) in THF (0.5 mL) and H_2O (0.5 mL) was treated with LiOH (5.6 mg, 0.23 mmol) and stirred at room temperature for 45 minutes. The reaction mixture was treated with additional LiOH (5.6 mg, 0.23 mmol) and quenched with 1.0 M HCl after an additional 5 min. It was extracted with CH_2Cl_2, dried ($MgSO_4$) filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (7:3, hexanes:EtOAc) afforded 25.5 mg (79%) of deacetylated **271** as a dark orange foam and 1.5:1 inseparable mixture of epimers: Rf 0.3 (7:3, hexanes:EtOAc); IR (ATR) 2956 (bs), 2850, 1685, 1640, 1603, 1526, 1454, 1254, 1224, 1008 cm $^{-1}$; ^{1}H NMR δ 12.57 (s, 0.5 H), 12.50 (s, 1 H), 11.49 (s, 1 H), 11.29 (s, 0.5 H), 7.37 (s, 2 H), 7.30-7.25 (m, 5 H), 7.21 (d, 1.5 H, *J* = 8.7 Hz), 6.96 (d, 1 H, *J* = 10.2 Hz), 6.92 (d, 0.5 H, *J* = 10.2 Hz), 6.77 (d, 1.5 H, *J* = 10.2 Hz), 4.00 (d, 0.5 H, *J* = 3.9 Hz), 3.86 (d, 0.5 H, *J* = 3.9 Hz),

3.85 (d, 1.5 H, J = 3.9 Hz); ^{13}C NMR δ 196.7, 196.7, 191.3, 190.8, 190.6, 184.9, 184.6, 161.9, 161.7, 161.4, 161.0, 140.6, 140.3, 140.3, 139.3, 138.7, 138.5, 138.2, 137.8, 137.6, 134.9, 131.0, 129.6, 128.1, 124.5, 124.1, 123.9, 123.4, 115.2, 114.6, 55.5, 55.5, 55.3, 54.8; MS (EI) *m/z* (rel intensity) 362 (M^+, 34), 305 (56), 292 (51), 291 (48), 264 (100), 236 (46); HRMS (EI) $C_{20}H_{10}O_7$ calculated for 362.0427, found 362.0448.



Dechlorospiroxin A (293). A solution of N-benzylcinchonidinium chloride (0.6 mg, 0.001 mmol), a 4.0 M solution of TBHP in isooctane (0.1 mL) and H_2O (0.1 mL) was treated with a suspension of **271** (5.0 mg, 0.014 mmol) in toluene (0.14 mL) and $CHCl_3$ (0.42 mL). The reaction mixture was treated with a 0.2 M solution of NaOH (0.06 mL) and stirred for 2 h. Added an additional amount of H_2O (0.5 mL) and TBHP (0.5 mL) and worked up 1 h later. The reaction mixture was quenched with sat. NH_4Cl and extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (1:1, EtOAc:hexanes) afforded 1.8 mg (35%) of dechlorospiroxin **293** as a dark red foam and 1.5:1 mixture of epimers: Rf 0.6 (1:1, hexanes:EtOAc); IR (ATR) 2917, 2848, 1653, 1579, 1472, 1442, 1347, 1220, 1088, 1010 cm $^{-1}$; ^{1}H NMR δ 11.52 (s, 1 H), 11.39 (s, 1 H), 11.37 (s, 0.5 H), 11.24 (s, 0.5 H), 7.47 (d, 0.5 H, J = 8.8 Hz), 7.44 (d, 1 H, J = 8.8 Hz), 7.36 (d, 1.5 H, J = 8.8 Hz), 7.33 (d, 0.5 H, J = 8.8 Hz), 7.32-7.28 (m, 4 H), 4.07 (d, 0.5 H, J = 3.9 Hz), 4.04 (d, 1 H, J = 3.9 Hz), 3.99 (d, 0.5 H, J = 3.9 Hz), 3.96 (d, 0.5 H, J = 3.9 Hz), 3.91 (d, 1 H, J = 3.9 Hz),

3.94-3.92 (m, 3.5 H); MS (EI) *m/z* (rel intensity) 378 (M^+, 63), 379 (16), 293 (20), 280 (35), 252 (27), 81

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