Design and Synthesis of Simplified Analogs of the Natural Product Sordarin As Potential Antifungal Agents

Yibiao Wu
Marquette University

DESIGN AND SYNTHESIS OF SIMPLIFIED ANALOGS OF THE NATURAL PRODUCT SORDARIN AS POTENTIAL ANTIFUNGAL AGENTS

By
Yibiao Wu, M. Sc.

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ABSTRACT

DESIGN AND SYNTHESIS OF SIMPLIFIED ANALOGS OF THE NATURAL PRODUCT SORDARIN AS POTENTIAL ANTIFUNGAL AGENTS

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Invasive fungal infection is a life-threatening illness that causes high mortality, and is especially common among patients with compromised immune systems. However, currently there are only three major classes of clinically useful drugs capable of treating such infections. In addition, due to the fact that drug resistance has become a serious issue especially among patients who suffer from chronic infections, it is urgent to identify new drug candidates, particular those of new classes.

The discovery of the natural product sordarin and its novel mechanism of action of inhibiting fungal protein synthesis via the fungal eukaryotic elongation factor 2 (eEF2) led to the development of a new class of antifungal agents that target eEF2. Despite the extensive efforts of multiple pharmaceutical companies striving to identify a clinically useful agent from this class, there has been no analog that has successfully reached clinical trials, perhaps due to unsatisfactory pharmacokinetic profiles or limited spectra of activity.

This study mainly focused on the synthesis of a series of simplified bicyclic sordarin analogs. By switching the parent sordarin molecule's metabolically unstable cyclopentane to a more metabolically stable substituent, an improved pharmacokinetic profile could be achieved. This function-oriented synthesis approach also allows a more facile synthesis as compared with reported total syntheses.

Two generations of novel bicyclic sordarin analogs were synthesized featuring a Diels-Alder reaction using a functionalized silyloxy-cyclopentadiene. The 1st-generation synthesis furnished an analog maintaining the minimum pharmacophore of a bicyclic carboxylic acid vicinal to a nitrile or aldehyde. In subsequent studies, five different strategies for constructing a C-2 quaternary center on the bicyclo[2.2.1]heptane core were studied in detail, and a synthetic route featuring a stereoselective alkylation at C-2 was developed, which gives access to more sophisticated bicyclic sordarin analogs, including

those with glycone moieties.

Five bicyclic sordarin analogs were synthesized and assessed against *C. albicans, C. parapsilosis, P. variotii and A. fumigatus*. Although no antifungal activities were observed up to 8 μg/mL, the established synthetic route will enable unique structure-activity relationship (SAR) studies that could generate promising antifungal agents targeting eEF2.

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TABLE OF ABBREVIATION

MIC: minimum inhibitory concentration

PK: pharmacokinetics

SAR: structure-activity relationships

RCM: ring-closing metathesis

IC_{50}: half maximal inhibitory concentration

ED_{50}: median effective dose

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

DCM: Dichloromethane

THF: Tetrahydrofuran

TEA: Triethylamine

DMP: Dess-Martin Periodinane

LDA: Lithium diisopropylamide

PCC: Pyridinium chlorochromate

PPTS: Pyridinium p-toluenesulfonate

1.0 Background

Fungal infection caused by pathogenic fungi is now a more fatal disease than malaria or tuberculosis, causing 1.5 to 2 million death each year[1]. Generally, fungal infections can be divided into two major categories, superficial or subcutaneous infection where the pathogenic fungi live in the skin, nail, or hair of the host, and systemic infection which is often caused by inhalation of spores produced by invasive fungal species. The first kind of infection is often not life-threatening and to a large extent curable by using current antifungal drugs, however in the latter type the fungi will affect host organs or even the CNS. Such infections are typically observed in patients who are under the influence of immunosuppressant drugs, including many chemotherapies for cancer.

There are only three common classes of antifungal agents currently on market that are approved to treat systemic fungal infections: the polyenes, the azoles, and the echinocandins. (**Figure 1.0.1**)

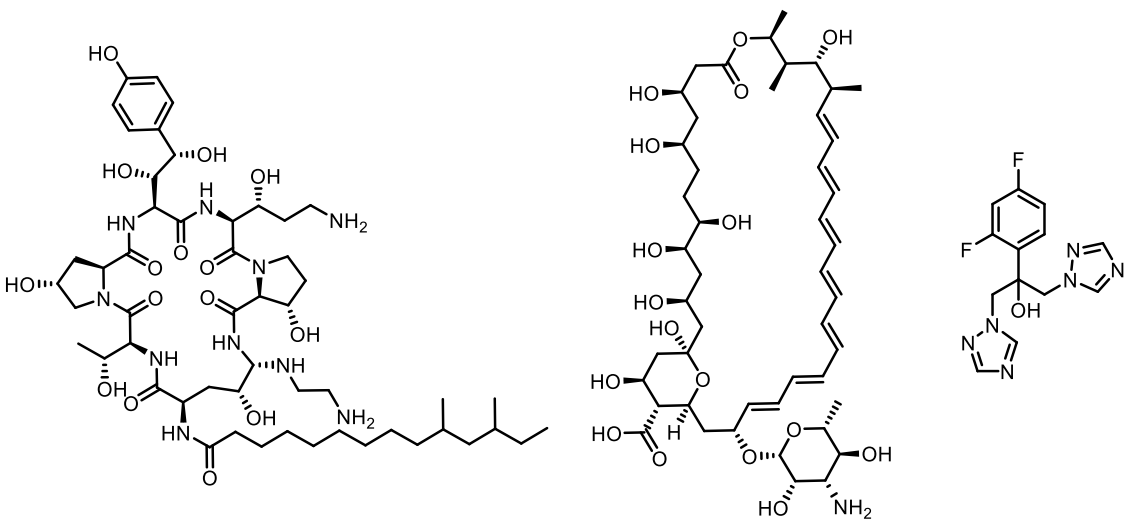


Figure 1.0.1: Representative antifungal agents of three clinically approved classes for systemic infections

These three classes have a common feature, namely, they all ultimately affect the integrity of the fungal cell wall or membrane, either by directly binding to or by disrupting the synthesis of key components of the cell membrane or wall. For example, the azole class acts by inhibiting fungal 14α-demethylase which is the enzyme responsible for converting lanosterol to ergosterol, which in turn alters the permeability and rigidity of plasma membranes. The inhibition thus causes changes in the permeability of the cell membrane and eventually leads to cell lysis.[2] The polyene class causes the formation of pores on fungal cell membrane by directly binding to ergosterol embedded within.[3] The echinocandin class act as a 1,3-beta-glucan synthase inhibitor so that the fungal cell can no longer synthesize 1,3-beta-glucan, which is a key component of fungal cell wall.[4] However,

these three classes all have different limitations in clinical use.

Severe side effects and resistance is rarely seen in the echinocandin class, however one limitation is the fact that it's only available via IV administration, which can be problematic for patients who need prolonged treatment.[5]

The polyene class represented by amphotericin B is well-known for its severe nephrotoxicity, which can lead to kidney failure. While the azoles generally do not have side effects as severe as the polyene class, development of drug resistance in various fungal species toward this type of drug has been reported more and more frequently in recent years.[5-6]

Therefore, new classes of antifungal agents may provide alternative options for the treatment of systemic fungal infections which could overcome the weaknesses of pre-existing antifungal drugs, such as high cytotoxicity, lack of oral activity, and developed drug resistance.

1.1 Sordarin and Its Medicinal Chemistry

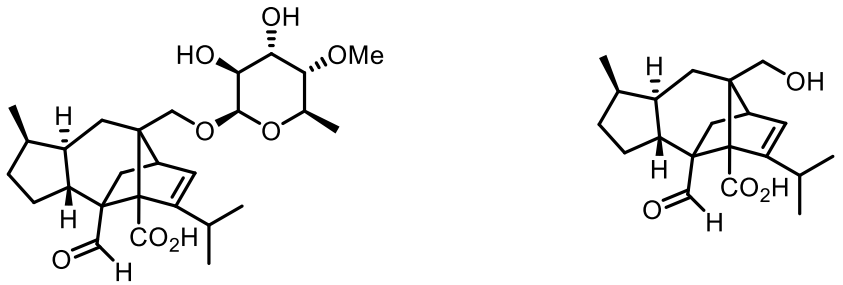


Figure 1.1.1: Sordarin and its aglycone sordaricin

Sordarin is a natural product isolated from the fungus *Sordaria araneosa*, reported in 1967 by the Swiss pharmaceutical company Sandoz[7], which has a unique tetracyclic diterpene core structure and a carbohydrate moiety (**Figure 1.1.1**). In the late 1990s, people started to discover new members of this family and recognize their antifungal activities. In the meantime, the fungal resistance toward pre-existing antifungal drugs such as fluconazole has become more and more serious, and thus efforts to find a more potent and stable sordarin analog against pathogenic fungi increased after 1998 when Merck and Glaxo obtained evidence to rationalize the high selectivity of this compound toward fungi.[8] Sordarin acts by selectively binding to the fungal protein eukaryotic elongation factor 2 (eEF2) which is a cofactor required for the translocation process during protein synthesis. In a binding assay examination, ribosomes and eEF2 from 3 different species were used to form different ribosome-eEF2 complexes, it has been shown that inhibition of protein

synthesis by sordarin only happens significantly when fungal eEF2 is present regardless of what species of the ribosome is used.[8] Selective binding to fungal eEF2 is possible despite the high sequence similarity between human and fungal eEF2. When a sordarin-eEF2 complex is formed it will not be able to disengage the ribosome easily, thus inhibiting the translocation step of ribosomal protein synthesis.

Another important structural biological finding is the role of a motif of the ribosome 40S subunit called rpP0 in the development of resistance to sordarin. García-Bustos et al.[8b] have shown that fungi use two strategies to counteract sordarin, mutating eEF2 or mutating rpP0: the first type of mutant has no affinity for sordarin, and the second type of mutant may be able to force the ribosome to distort the sordarin-eEF2 complex so that eEF2 can still function.

The effort of building sordarin analogs has been dominated semisynthesis whereby the original carbohydrate moiety is replaced with other groups such as the morpholino ester reported by Glaxo.[9] (**Figure 1.1.2**) Tremendous efforts at modifying the parent compound[10] have led to the discovery of highly potent synthetic sordarins, but only a few of them showed therapeutically useful potency in vivo and PK profile,[11] and none of them have reached clinical trials. Moreover, despite these intensive efforts, there are still several important areas remaining to be explored, such as the modification of the sordarin core

structure,[12] which is problematic due to the inert nature of the unfunctionalized aliphatic core, or the challenge of de novo syntheses. Novel modifications to the core structure may lead to more potent and/or more stable sordarin analogs with the potential for clinical utility. This is the focus of our current efforts.

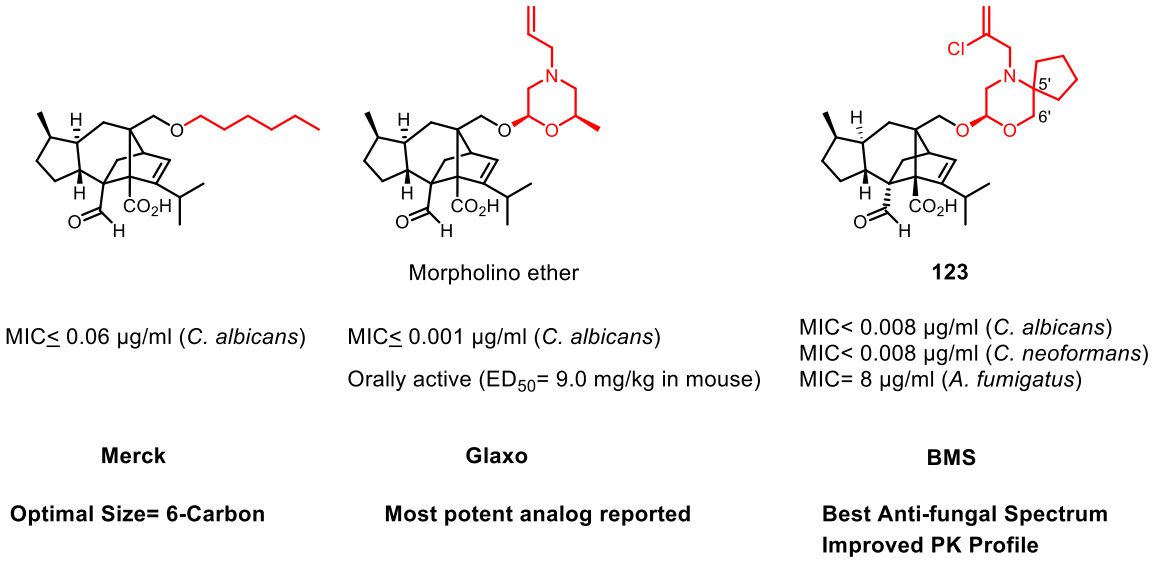


Figure 1.1.2: Representative sordarin analogs

A summary of semi-synthetic or natural sordarin derivatives categorized by different pharmaceutical companies is given below:

1.1.1 Merck

In the late 1990s, Merck published some fundamental SAR studies showing that the sugar unit of the sordarin molecule is not essential for the inhibition of *S. cerevisiae* a

non-pathogenic fungal species.[13] By substituting the sugar moiety with an aliphatic chain of optimal length, dramatic increases in antifungal activity were observed (**Figure 1.1.1.1**). These alkyl ethers were later shown by Regueiro-Ren et al., in pathogenic fungal species such as *C. albicans* and *C. glabrata*, to have MICs 1000-fold lower than to sordarin.[14] This could be due to the metabolic instability of the alkyl ether.

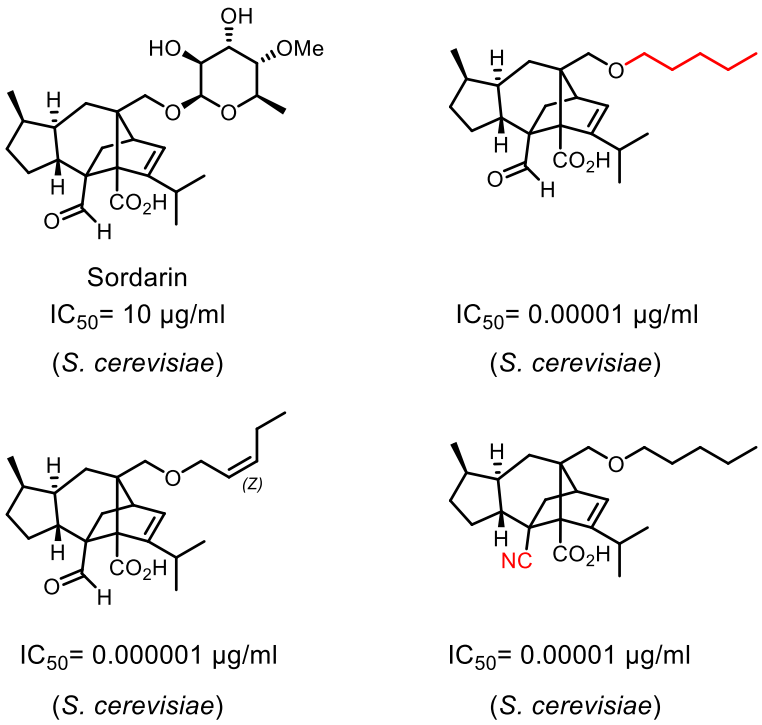


Figure 1.1.1.1: Merck's semi-synthetic sordarins

Another important finding in the same study was that it is essential for the sordarin core to have an aldehyde or nitrile group adjacent to the bridgehead carboxylic acid. Other functional group beyond this scope abolished the antifungal activity. This pharmacophore

can be explained with the x-ray crystal structure of sordarin-eEF2 complex reported by Andersen,[15] showing that the carboxylic acid (mediated by two water molecules) and the aldehyde form hydrogen bonds with Glu-524 and Ala-562 respectively. (**Figure 1.1.1.2**)

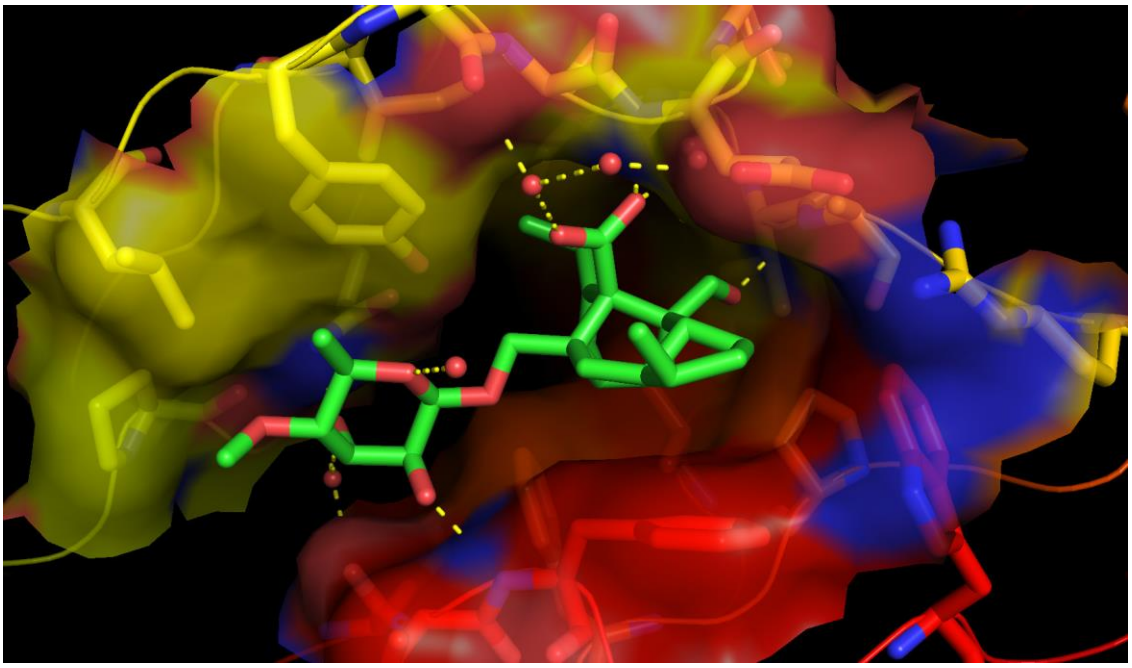
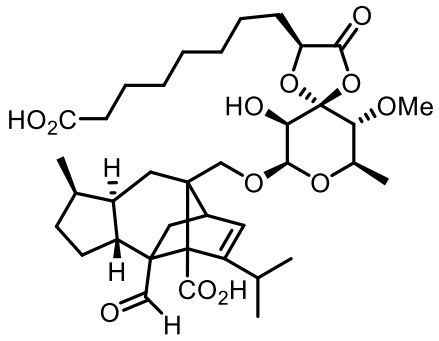


Figure 1.1.1.2: X-ray crystal structure of sordarin-eEF2 complex

Apart from the semi-synthetic sordarin studies, another important contribution of Merck is the discovery of the natural sordarin family member moriniafungin[16] (**Figure 1.1.1.3**). This natural sordarin is produced by *M. pestalozzioides*, and has a relatively broad antifungal spectrum that includs *C. albicans*, *C. glabrata*, and *S. cerevisiae*. Despite the fact that this is the most potent natural sordarin to date, this compound did not show any in

vivo efficacy. In a murine model of disseminated candidiasis with enhanced susceptibility to *C. albicans*, Moriniafungin did not produce any reduction in the number of c.f.u. (colony forming units), even at high doses.[16]



Moriniafungin

IC_{50}= 1.2 µg/mL (*S. cerevisiae*)
0.9 µg/mL (*C. albicans*)

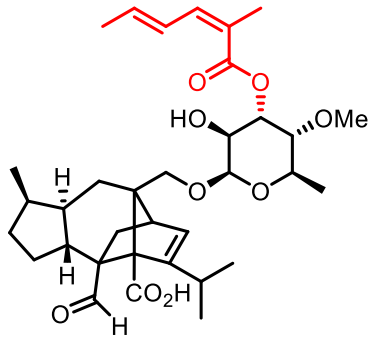
Figure 1.1.1.3: Moriniafungin

1.1.2 Glaxo

Researchers from Glaxo Wellcome (presently "GlaxoSmithKline") developed a series of azasordarins[9, 17] represented by GW471558 (**Figure 1.1.2.1**), which are the most potent semi-synthetic sordarins against Candida species to date (best MIC < 0.001 ug/mL (*C. albicans*)). In all Candida species tested except for *C. krusei* which is intrinsically resistant to azasordarins, azasordarins are significantly more potent than amphotericin B or fluconazole. In addition, they also showed oral activity with relatively low dosage (ED_{50}=

9.0 mg/kg in mice), and they are safer to mammalian cells than amphotericin B in terms of cytotoxicity.

In the same period, researchers from Glaxo were also able to isolate a reasonably potent natural sordarin family member GR135402 (**Figure 1.1.2.1**) from a fermentation broth of *Graphium putredinis*, which although is not toxic at high doses in animals, lacked activity against a series of *Candida* species as well as *A. fumigatus*.[18]

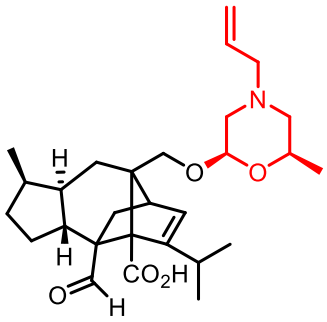


GR135402

MIC= 0.008 μg/mL (*C. albicans*)

High *in vivo* dose required (100 mg/kg)

Limited antifungal spectrum



GW471558

MIC≤ 0.001 μg/mL (*C. albicans*)

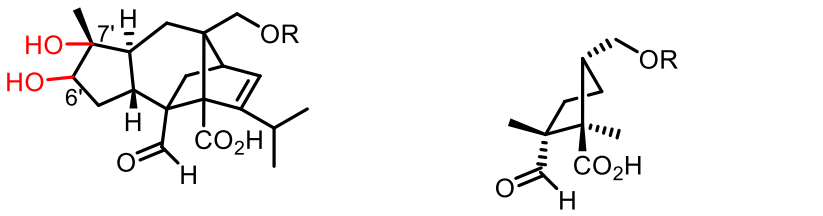
Orally active (ED_{50}= 9.0 mg/kg in mouse)

Less toxic than polyene and azole

Figure 1.1.2.1: Glaxo's sordarin derivative GW135402 and azasordarin GW471558

In a rodent hepatic S9 fraction stability study, HPLC-MS analysis revealed that the major metabolites through P450 oxidation are C-6/C-7 hydroxy or 6,7-dihydroxy sordarin (**Figure 1.1.2.2**). based on this finding, an effort of reducing the complexity of the sordarin molecule was also made by Glaxo.[12] This work examined the possibility of

whether modifying the oxidation site of P450, namely the aliphatic 5-membered ring and 6-membered rings, would increase the bioavailability, and whether a simpler structure could maintain the pharmacophoric groups in the orientation required for antifungal activity.

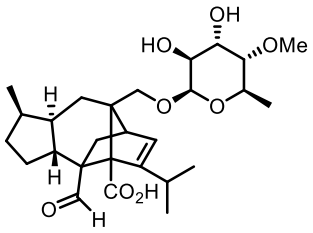


cytochrome P-450 metabolized product

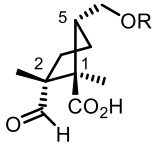
Simplified Sordarin derivative

Figure 1.1.2.1: P-450 metabolite of sordarin and simplified sordarin

However, this approach showed that such a modification will lead to at least 28-fold lower potency compared to the parent tetracyclic molecule (sordaricin, the aglycone of sordarin) which in turn is already much less potent than sordarin. This is probably because the non-bridged cyclopentane (Figure 1.1.2.1) is not able to maintain the OHC-C-C-COOH dihedral angle. Based on their molecular modeling result using INSIGHT software, although the distance between pharmacophoric groups OHC-C-C-COOH are maintained, the dihedral angle of them has changed more than 25 degrees. (**Figure 1.1.2.2**)



Sordarin



Simplified Sordarin derivative

compound	C-C distance (Å) (COOH, CH_2OH)	C-C distance (Å) (COOH, CHO)	dih. angle (COOH, C1, C5, CH_2OH)	dih. angle (CHO, C2, C1, COOH)
Sordarin	3.1	3.2	60.3°	67.3°
Simplified Sordarin	3.3	3.4	85.5°	94.9°

Figure 1.1.2.2: Geometry comparison between sordaricin and simplified sordaricin[19]

Since the outcome of an antimicrobial agent in vivo is a function of two important factors, the intrinsic antimicrobial ability of the agent and the pharmacokinetic profile of the agent,[20] PK studies are an important part of preclinical development. Glaxo also performed detailed PK studies on the sordarins, mainly with a series of sordarin derivatives with a sugar unit containing 3',4'-fused tetrahydrofuran ring with a methyl or an exomethylene group[21] (**Figure 1.1.2.3**). The compounds represented by GM237354 showed a linear correlation of efficacy with dosage as well as low cytotoxicity in mice and rat.[21b] Histological observations also showed significant efficacy in the infected tissue of immunosuppressed rats.[21g]

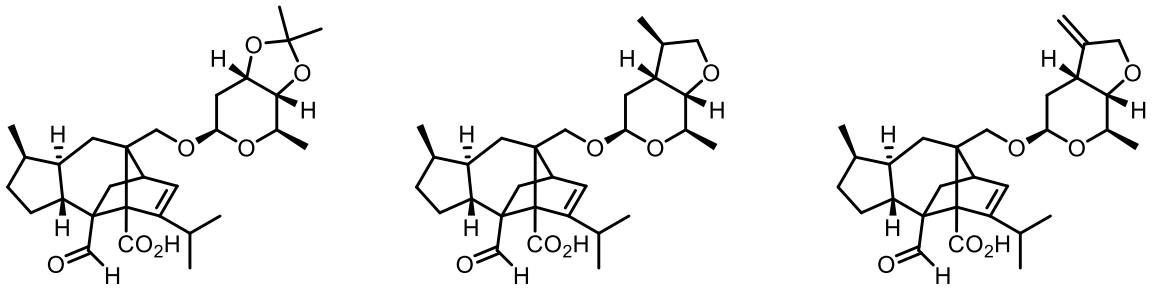


Figure 1.1.2.3: 3',4'-fused tetrahydrofuran derivatives

1.1.3 Sankyo

Sankyo patented a natural sordarin family member called Zofimarin[22] isolated from *Zofiella marina* in 1987. It showed potent in vitro activity but had no activity in vivo. Later Sankyo patented a series of Zofimarin derivatives[23] featuring an oxime ether or thioether structure at the sugar unit position of sordarin, some of which had good in vitro potency. (**Figure 1.1.3.1**)

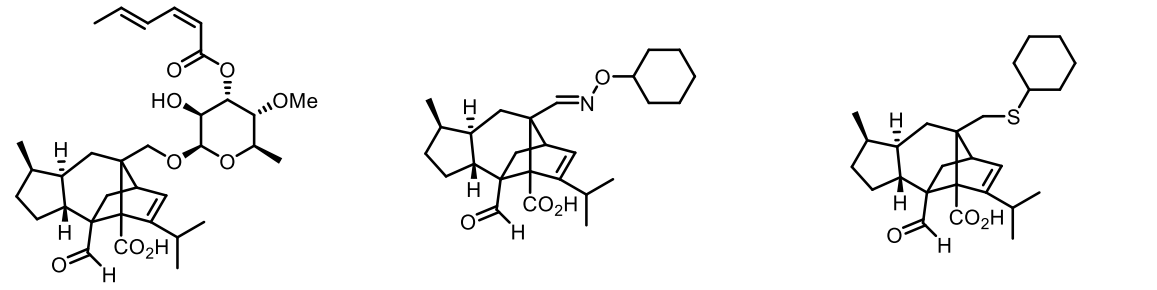


Figure 1.1.3.1: Zofimarin and derivatives

Inspired by Glaxo's azasordarin derivatives which showed promising in vivo efficacy,[9, 17, 24] Sankyo synthesized a series of N-substituted 1,4-oxazepanyl sordaricins from Zofimarin (**Figure 1.1.3.2**). Those analogs are represented by R-135853, which showed good in vitro efficacy against *C. albicans* (best MIC= 0.016 ug/mL), but still poor activity against *A. fumigatus* (best MIC> 4 ug/mL). Later R-135853 was subjected to in vivo efficacy examination and PK studies in mice, it had good absorption and efficacy by oral administration, however it suffered from short $t_{1/2}$ (1.1 h, oral) and rapid clearance in IV administration.[25]

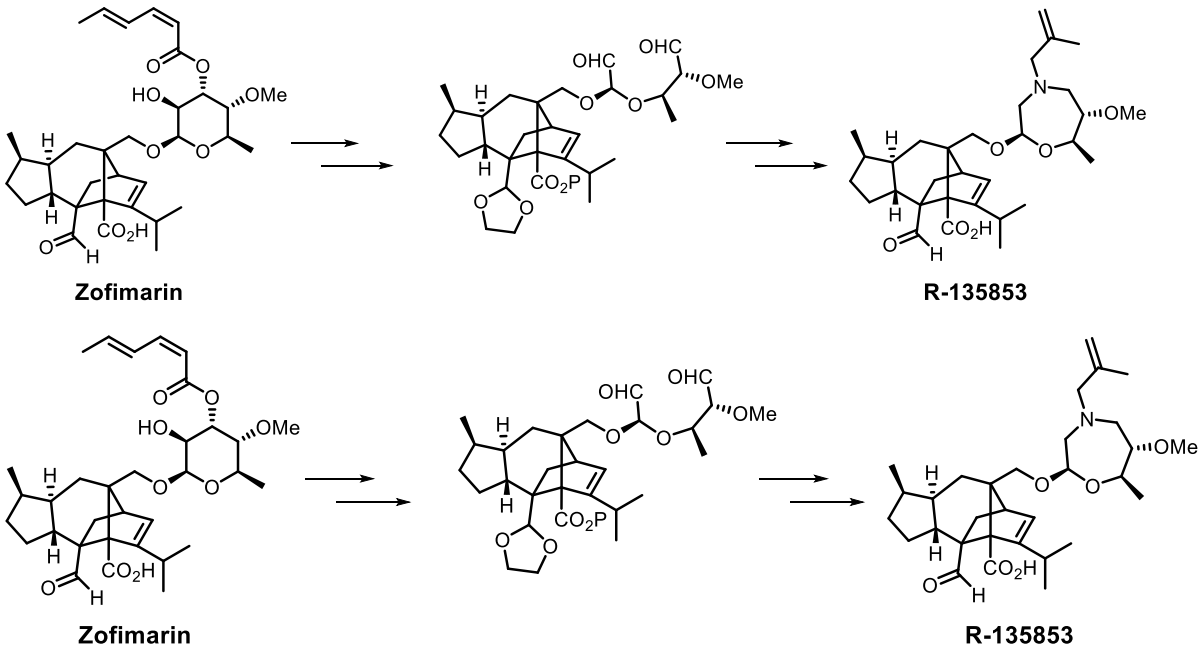


Figure 1.1.3.2: Synthesis of N-substituted 1,4-oxazepanyl sordaricin R-135853

Sankyo attempted to find better sordarin derivatives by modifying the chemically inert sordarin core skeleton through biotransformation[26] (**Figure 1.1.3.3**). Although they were able to hydroxylate the C-6 position of the core to give 6-hydroxyzofimarin and from which derived 6-fluro and 6-acetoxyzofimarin, none of these compounds showed better efficacy than the parent compound zofimarin. They soon realized that the metabolite of sordarin in mouse was 6- and/or 7-hydroxysordarin which might have lower activity. Their conclusion was that it might be possible to find a compound with a better PK profile if the C-6 position can be converted to some enzymatically inert substituent.

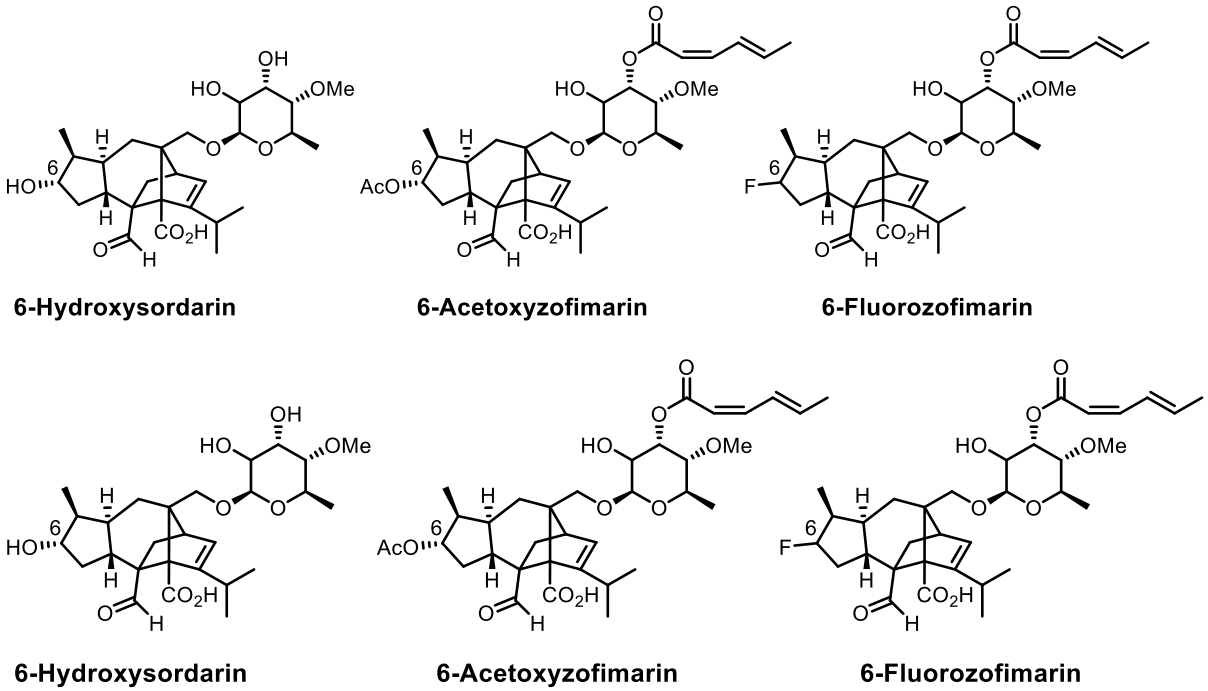


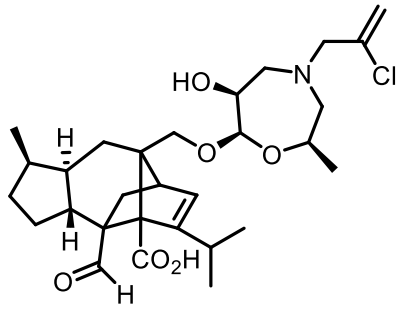
Figure 1.1.3.3: Sankyo's 6-oxidized (6'-oxidized in conventional numbering) sordarins

1.1.4 Bristol-Myers Squibb

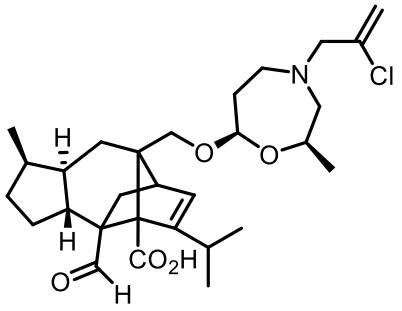
BMS did extensive SAR studies on glycosyl replacements,[27] and early efforts included 3 major categories: oxazepine derivatives, oxime derivatives, and alcohol and ketone derivatives. Although no compounds with superior potency to previous examples were identified, these works have confirmed the observation made by Merck earlier, that is, when a non-cyclic glycosyl replacement is used, a nonpolar medium sized sidechain group is needed to have good potency, which could suggest a large lipophilic pocket in the target enzyme eEF2.

Some oxazepine derivatives (**Figure 1.1.4.1**)[27a] had a balanced antifungal spectrum including reasonable activity against *C. neoformans*, and SAR studies showed that removing the hydroxyl group at the oxazepine C-2 position will give the most balanced compound in terms of potency and interspecies antifungal spectra.

The oximes (**Figure 1.1.4.1**)[27b] didn't give any better derivatives in terms of in vitro antifungal activity compared to the simple ether derivatives reported by Merck (**Figure 1.1.1.1**), but the SAR study clearly confirmed the observation made by Merck that the best activity was achieved when a 5 or 6 carbon aliphatic chain is attached (**Figure 1.1.4.1**, lower left).

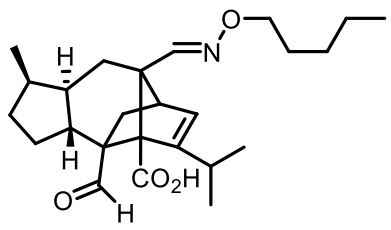


MIC= 4 μg/mL (C. neoformans)
MIC= 0.5 μg/mL (*C. albicans*)

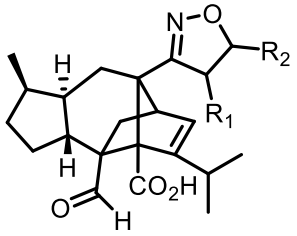


MIC= 1 μg/mL (C. neoformans)
MIC= 0.125 μg/mL (*C. albicans*)

Sordarin Oxazepine Derivatives



MIC= 0.06 μg/mL (*C. albicans*)



MIC= 1 μg/mL (*C. albicans*)

Oxime Derivatives of Sordaricin

Figure 1.1.4.1: Sordarin Oxazepine Derivatives and Oxime Derivatives

Additionally, three types of sordarin derivatives were prepared by organometallic additions to a fully protected sordaricin aldehyde.[27d] The alkyl alcohol and ketone derivatives had not only lower potency but also higher cytotoxicity (cell type not specified). With the propargylic alcohol and ketone derivatives, it is clear that the ketone derivatives are more potent than the alcohol counterparts. Only 2 carbon-homologated sordaricin

derivatives (**Figure 1.1.4.2**, bottom) were able to maintain good activity against *C. albicans*, and compounds with bigger and more polar sidechains were poorly active.

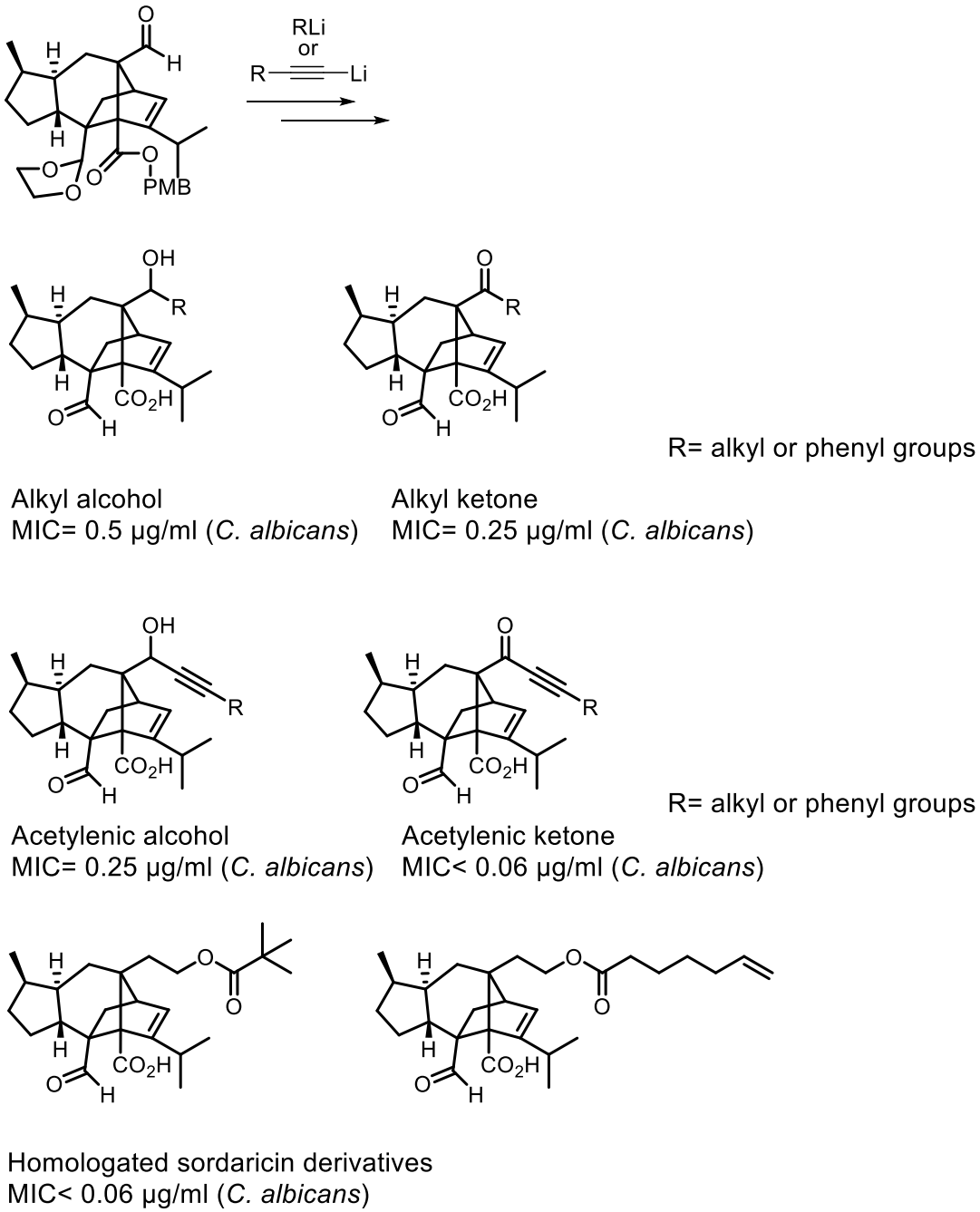
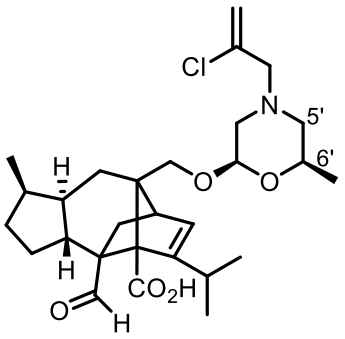


Figure 1.1.4.2: Sordarin derivative prepared from sordaricin aldehyde

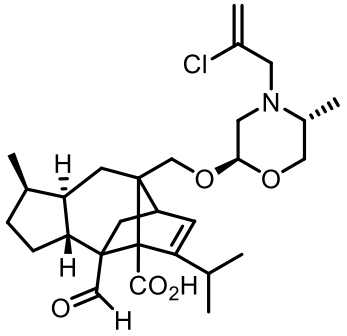
One major success of BMS in this field was the identification of a broad-spectrum azasordarin inspired by Glaxo's azasordarin derivative GW513920 (**Figure 1.1.4.3**).[27c] By shifting the methyl group from C-6' to C-5' on the morpholine ring, the compound started to show activities against *C. neoform*ans and *A. fumigatus*, which GW513920 was not able to inhibit. Next, based on the observation that the metabolism process of this kind of azasordrarin involves a N-dealkylation, they increased the bulk of the C-5' substituent from a methyl to an isopropyl or spirocyclopentyl group, leading to a reduction in the total clearance from 95 mL/min/kg to 20 mL/min/kg.



Glaxo' GW 513920

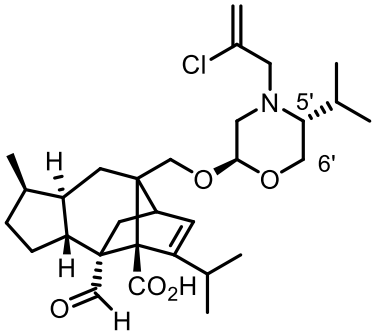
Not active against *C. neoformans, A. fumigatus,* short $t_{1/2}$

Shifting methyl group from C-6' to C-5'

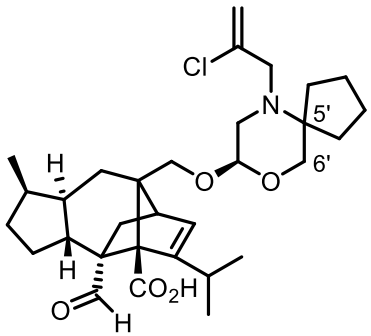


MIC< 0.06 µg/mL (*C. albicans*)
MIC< 0.06 µg/mL (*C. neoformans*)
MIC= 32 µg/mL (*A. fumigatus*)

Broadened antifungal spectrum



MIC< 0.06 µg/mL (*C. albicans*)
MIC< 0.06 µg/mL (*C. neoformans*)
MIC= 32 µg/mL (*A. fumigatus*)



MIC< 0.008 µg/mL (*C. albicans*)
MIC< 0.008 µg/mL (*C. neoformans*)
MIC= 8 µg/mL (*A. fumigatus*)

Better PK profiles

Figure 1.1.4.3: Broad-spectrum azasordarin with improved pharmacokinetic properties

1.2 Total Synthesis of Sordarin

This section will mainly focus on the total synthesis work towards sordarin and its congeners. The synthesis of sordarin analogs by Ciufolini et al.[28] will be discussed together with Diels-Alder reaction literature in chapter 2.

There are three sordarin total syntheses to date, systematically reviewed by Liang.[29] The first two total synthesis by Kato[30] and Mander[31] featured the same strategy for the key step of constructing the tetracyclic sordaricin skeleton, namely an intramolecular Diels-Alder reaction, while Narasaka[32] later took a different approach by featuring a Tsuji-Trost reaction. (**Figure 1.2.1**)

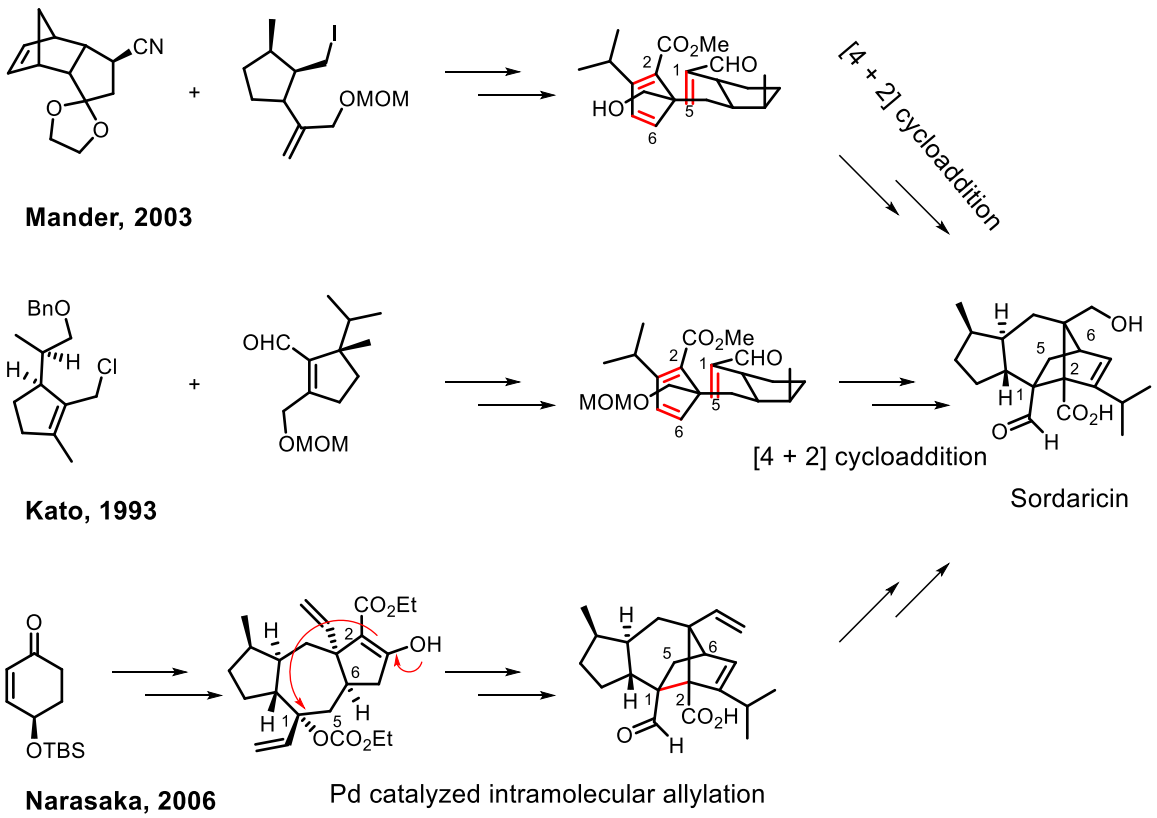


Figure 1.2.1: Overview of approaches to the total synthesis of sordarin.

1.2.1 Kato's Total Synthesis of Sordaricin Methyl Ester

Kato's synthesis (**Figure 1.2.1.1**)[30] commenced by condensing two chiral synthons **1** and **2** via a Grignard-type carbonyl addition,[33] the resulting alcohol was then converted to methyl ether **3**. A subsequent Cope rearrangement was smoothly conducted at 200 ºC to give enol ether **4**. Singlet-oxygen oxidation[34] and AcCl-promoted rearrangement, followed by deprotected with Pearlman's catalyst and a selective syn-reduction of the non-conjugated alkene using iridium black furnished ester **5**, the free alcohol of which was then re-protected with TBSCl. The cyclopentene was further oxidized to cyclopentadiene **6** by

MoO_5-mediated α-hydroxylation following by dehydration condition using $SOCl_2$. Next, the cyclopentane was elaborated into the Diels-Alder dienophile **8** by TBS removal, converting the resulting enol to TMS enol ether followed by a Saegusa oxidation. Diels-Alder precursor **8** performed the key intramolecular DA reaction smoothly at 40 °C to give the desired tetracycle **9**. Kato did not proceed further to synthesize the fully elaborated sordarin molecule (**Figure 1.2.1.1**).

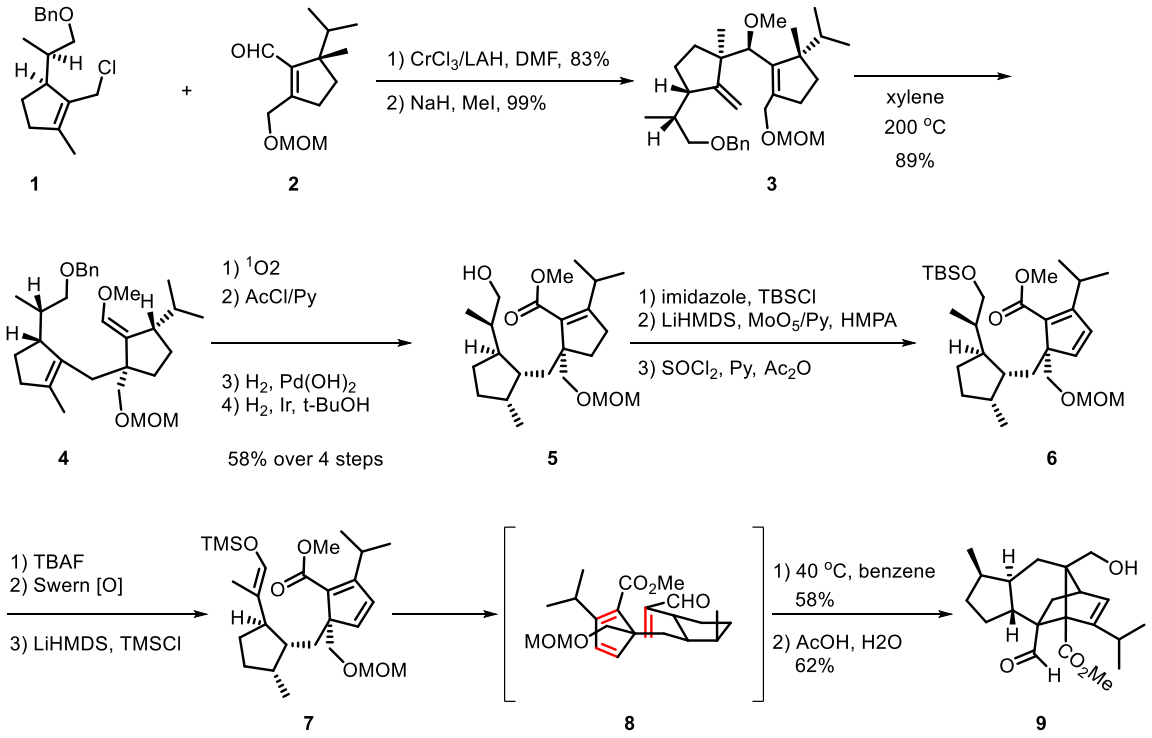


Figure 1.2.1.1: Kato's Total Synthesis of Sordaricin Methyl Ester

1.2.2 Mander's Total Synthesis of Sordaricin

Mander's strategy in constructing the tetracyclic skeleton is very similar with Kato's synthesis described above. In that they both featured the intramolecular [4+2] cycloaddition, although their strategy of preparing the precursor was different. Mander's synthesis (**Figure 1.3.2.1**)[31] used enone (+)-**10** and (-)-**10** as the initial starting materials. First, iodide **12** was prepared from (+)-**10** through a 13 step synthesis, then (-)-**10** was converted to **11** by 1,4-addition of KCN. Alkylation was then performed using **11** and **12** to give a single diastereomer **13**. The nitrile group of **13** was then reduced twice to give its corresponding alcohol, which is in turn protected with MOM. Glycol protected ketone was then released under acid condition to give **14**. **14** underwent a retro-Diels-Alder reaction smoothly at 180 ^{o}C giving enone **15**. Acylation at the α-position of enone **15** was achieved by enolization and addition to MeOC(O)CN. Then the resulting ketone was converted to its corresponding enol triflate by using McMurry's triflating reagent, followed by the addition of the higher order cuprate derived from 2-Th(Cu)CNLi[35] and isopropylmagnesium chloride. This furnished the cyclopentadiene moiety to give **16**. Then a double MOM deprotection and subsequent allylic oxidation furnished the Diels-Alder reaction predursor **17**. The key Diel-Alder reaction went smoothly at 40 ^{o}C to give the desired tetracyclic skeleton (**Figure 1.3.2.1**).

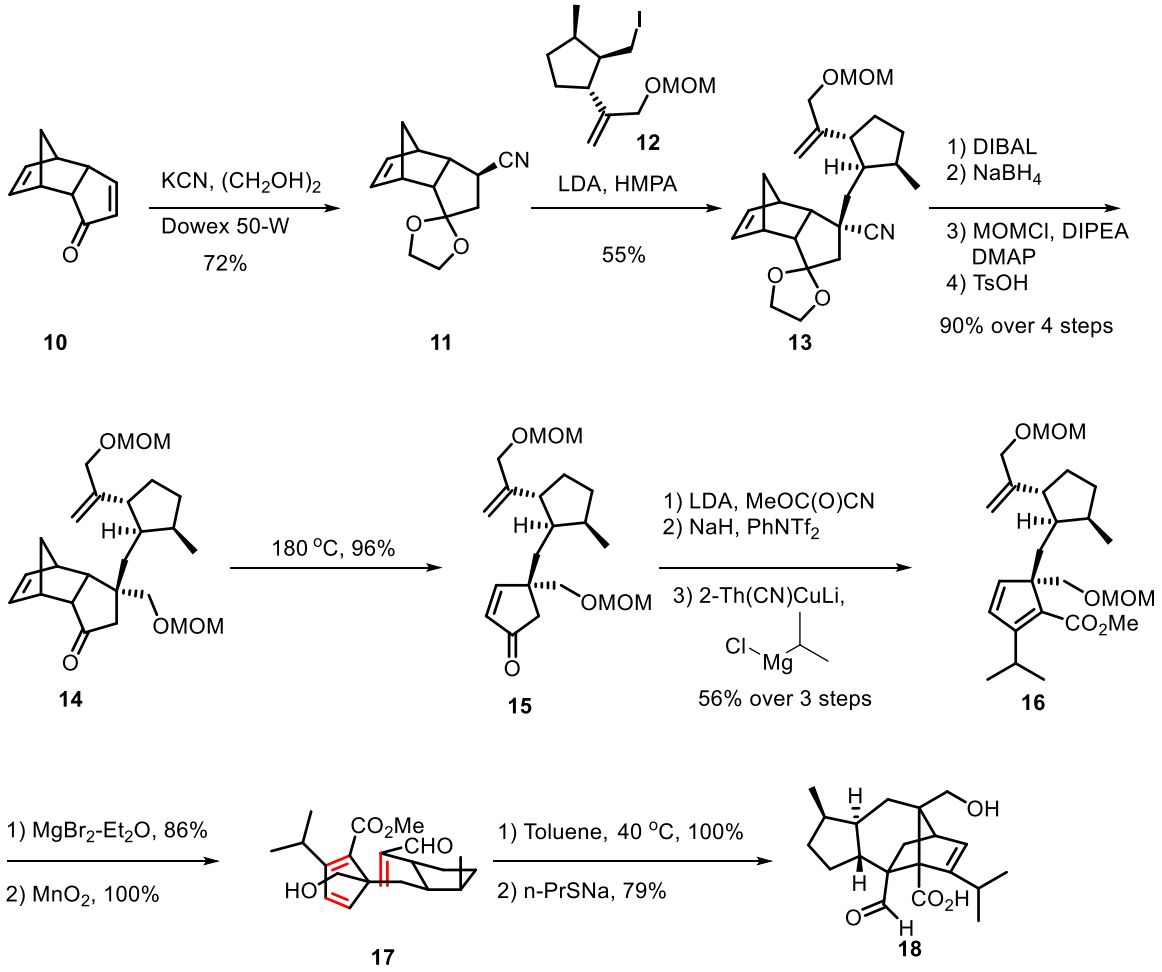


Figure 1.3.2.1: Mander's Total Synthesis of Sordaricin

1.2.3 Narasaka's Total Synthesis of Sordarin

Narasaka[32] not only synthesized the tetracyclic skeleton using Tsuji-Trost reaction rather than Diels-Alder cycloaddition, but they were also able to synthesize the novel sugar unit in the original sordarin molecule and perform a β-selective glycosylation to finish the first enantioselective synthesis of the complete sordarin molecule.

Narasaka's key step of constructing the sordarin tetracyclic skeleton featured a Tsuji-Trost addition which called for the tricycle **6** as the precursor. Chiral enone **19** was used as the initial starting material, which was first converted to bicyclo[5.3.0]decan-3-one **21** by subjecting the intermediate **20** to oxidative radical cyclization using a $AgNO_3$-$(NH_4)_2S_2O_8$-pyridine catalytic system.[36] To construct the tricyclic system, they started with a stereo- and regioselective allylation at C-3 of **22** using a hydrazine intermediate derived from ketone **21**. Olefin **22** was then subjected to oxidative cleavage to give the corresponding aldehyde, which was then converted to a β-keto ester,[37] which in turn performed a Knoevenagel condensation to give **23**. To furnish the Tsuji-Trost precursor **27**, from **23** two vinyl groups were introduced as equivalents of the hydroxy methyl and formyl parts of sordaricin to give **26**, finally ethoxy carbonylation of **26** and TBS deprotection gave the Tsuji-Trost precursor **27**. The key Tsuji-Trost addition was performed smoothly in the presence of NaH giving only 5% of β-hydride elimination byproduct. The tetracyclic compound thus generated was further elaborated to give sordarin ethyl ester **28**.

With the sordaricin core in hand, they then focused on the β-selective glycosylation of **28**. After a model study, they concluded that by attaching a 4-methoxybenzoyl group to the C-3 hydroxyl group of the carbohydrate unit, 1,3-anchimeric assistance can be utilized to favor a β-selective glycosylation under

Mukaiyama's glycosylation conditions.[38] Compound **29** was thus synthesized from D-mannose and coupled with **28** resulting a 6.5:1 β:α mixture, which was then deprotected by DDQ. The β isomer was isolated and the 4-methoxybenzoyl protecting group removed to give sordarin (**30**).

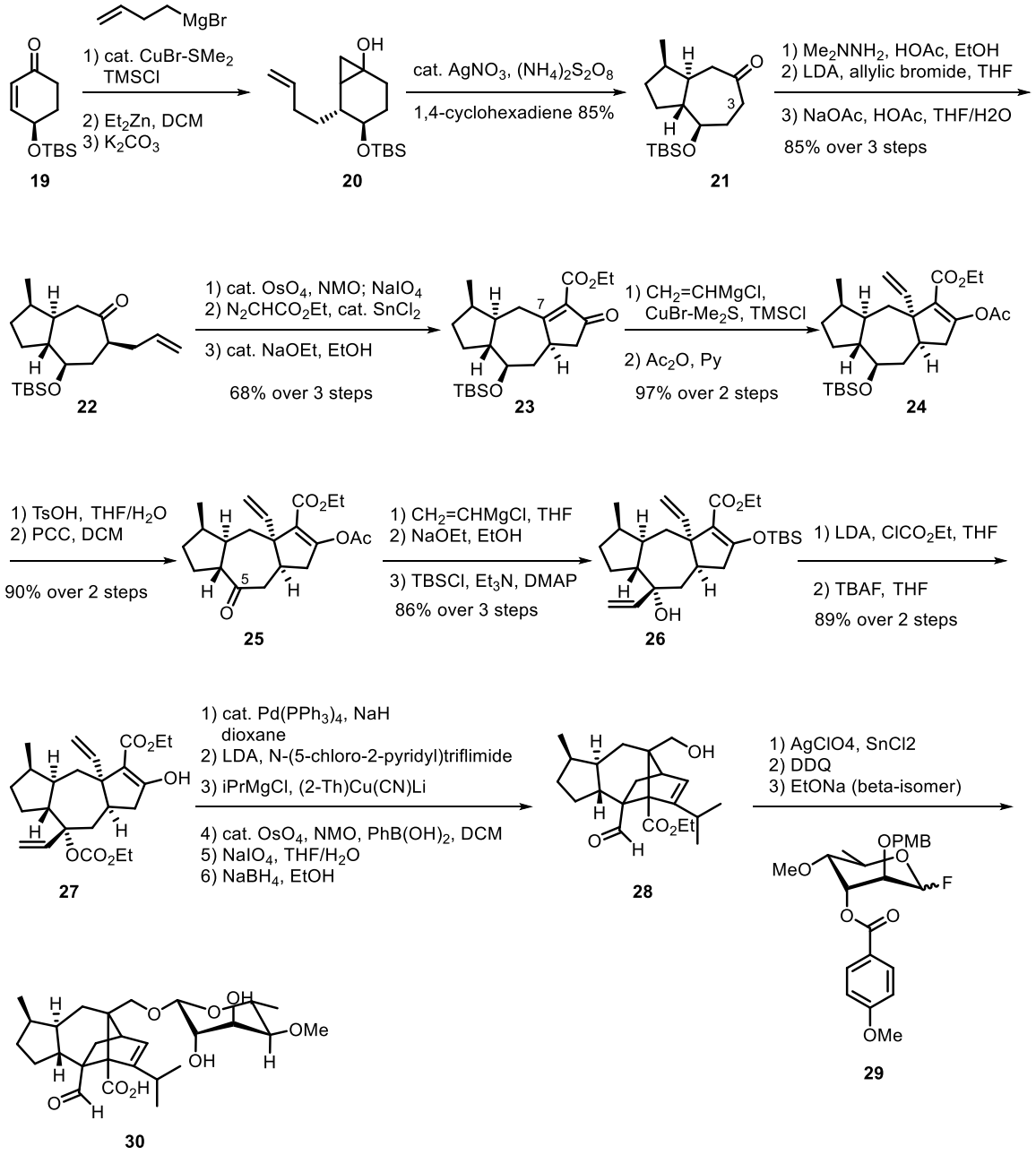


Figure 1.3.3.1: Narasaka's Total Synthesis of (-)-Sordarin

In conclusion, the total synthesis efforts described above all have more than 20 linear steps, and even very small changes in the final compound may require tremendous changes in prior steps. In medicinal chemistry studies, functional groups and substituents

of interest need to be switched quickly to establish SARs, and these approaches are generally not amenable to such SAR studies.

2.0 Research Proposal

2.1 Design of Novel Sordarin Derivatives

Based on previous medicinal chemistry studies on sordarin and its derivatives (Chapter 1.2), a clear SAR map can be drawn (**Figure 2.1.1**). The glycosyl moiety of sordarin is the most intensively studied part due to its ease of replacement. By far, Glaxo's "azasordarin" analogs represented by GW471558[39] with their morpholino glycone are the most potent analogs against *C. albicans,* with a MIC typically lower than 0.001 μg/mL (**Figure 1.1.2.1**), and a C-5' substituted version of the same kind of sordarin made by BMS has the most balanced profile in terms of potency, PK, and antifungal spectrum[40] (**Figure 1.2.4.3**).

The adjacent aldehyde and carboxylic acid groups on the norbornene core were clearly essential both from Merck's substitution study[13] and the crystal structure published by Andersen.[15]

There is currently no clear evidence whether the isopropyl group on the norbornene core is essential or not. The C-6 and C-7 position on the cyclopentane ring was proved to be the oxidation site when sordarin is subjected to P-450 metabolism[19] (**Figure 2.1.1**), and thus substitution or replacement of the cyclopentane moiety with an inert group

may slow down drug metabolism, resulting in a better pharmacokinetic (PK) profile.

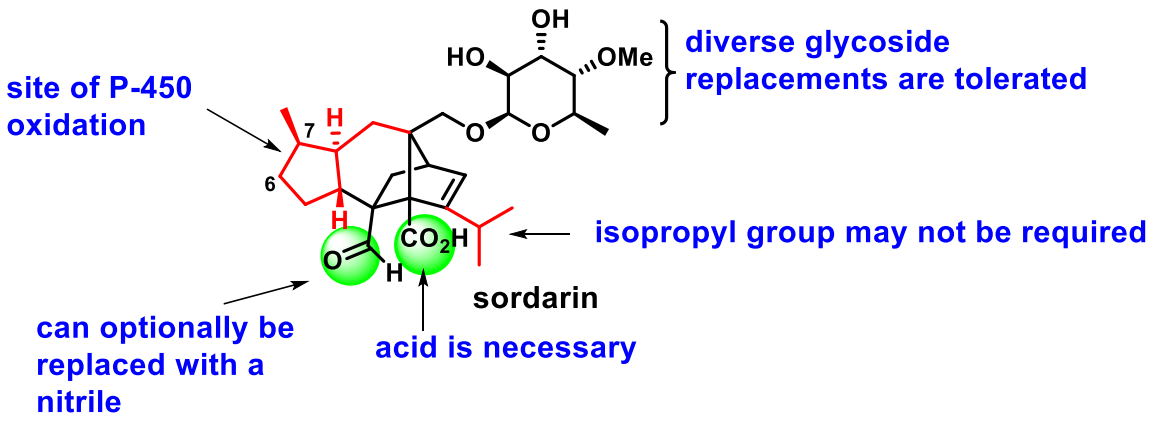


Figure 2.1.1: SAR map of sordarin

The previous SAR studies discussed in the first chapter included some glycoside replacements that are able to deliver compounds with very high potency against various fungal species. Nonetheless, none of those candidates were advanced into clinical trials, presumably because of poor PK profiles such as high clearance rate, and thus, the main goal of this research is to identify a novel class of sordarin analogs that have improved PK profiles while maintaining a high potency against various fungal species.

There are still very few reported SAR studies that focus on modifications of the sordarin core bicycle. To substitute the P-450 oxidation site on C-6 and C-7 with an oxidation-resistant replacement, a total synthetic strategy must be taken to construct the core. In a semi-synthetic approach, such as those reported previously, it is difficult to

modify the unfunctionalized cyclopentane moiety on the genuine sordarin core. A bicyclic-sordarin analog is thus proposed (**Figure 2.1.2**).

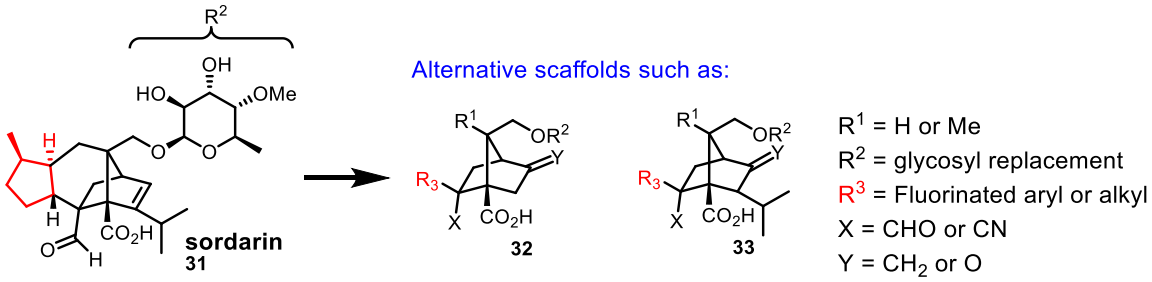


Figure 2.1.2: Aryl/Alkyl bicyclic sordarin analogs

By deleting the six-membered ring on the western side of the norbornene core and replacing the cyclopentane ring fused to it with an aryl or alkyl group, the synthetic route can be largely shortened while still keeping the essential pharmacophoric groups in correct positions. Most importantly, blocking the metabolically labile site of the molecule with a fluorine would most likely make the molecule more inert to P-450 oxidation, and thus improve the agent's half-life and result in a lower clearance rate.

This approach is based on the concept of Function-Oriented Synthesis (FOS) advocated by Wender.[41] FOS focuses on reproducing the parent molecule's (usually a natural product) biological activity with simpler analogs, and thus, reducing the amount of synthetic work required, and permitting better access to diverse analogs that may have

improved properties. Multiple successful examples were reported using this strategy. Selected examples are given below (**Figure 2.1.3**).

Based on pharmacophoric analysis, the anticancer agent bryostatin 1 was divided into a spacer domain and a recognition domain. The spacer domain was then simplified to contain an unsubstituted tetrahydropyran ring and a 1,3-dioxane ring. The recognition domain was kept mostly intact. The resulting analog required only 29 synthetic steps compared to 70 steps for the parent molecule. Additionally, it was able to show an improved binding affinity with PKC **(Equation (a), Figure 2.1.3)**.[42]

The FOS approach with the anticancer agent laulimalide highlights the ability of this strategy to address stability issues. The epoxide at the C-16 position which is responsible for a nucleophilic ring-opening that causes a dramatic loss of activity against MDA-MB-435 cells was eliminated. The resulting analog, although not as potent as its parent molecule, allowed for an investigation of the features of laulimalide that control its activity **(Equation (b), Figure 2.1.3)**.[43]

The FOS approach was applied briefly to sordarin as well. The monocyclic analog **316** reported by Glaxo[19] retained only the minimum required pharmacophores. Despite the fact that the rigidity of the analog was largely lost comparing to its parent molecule, it was able to show weak activity against *C. albicans* **(Equation (c), Figure 2.1.3)**.

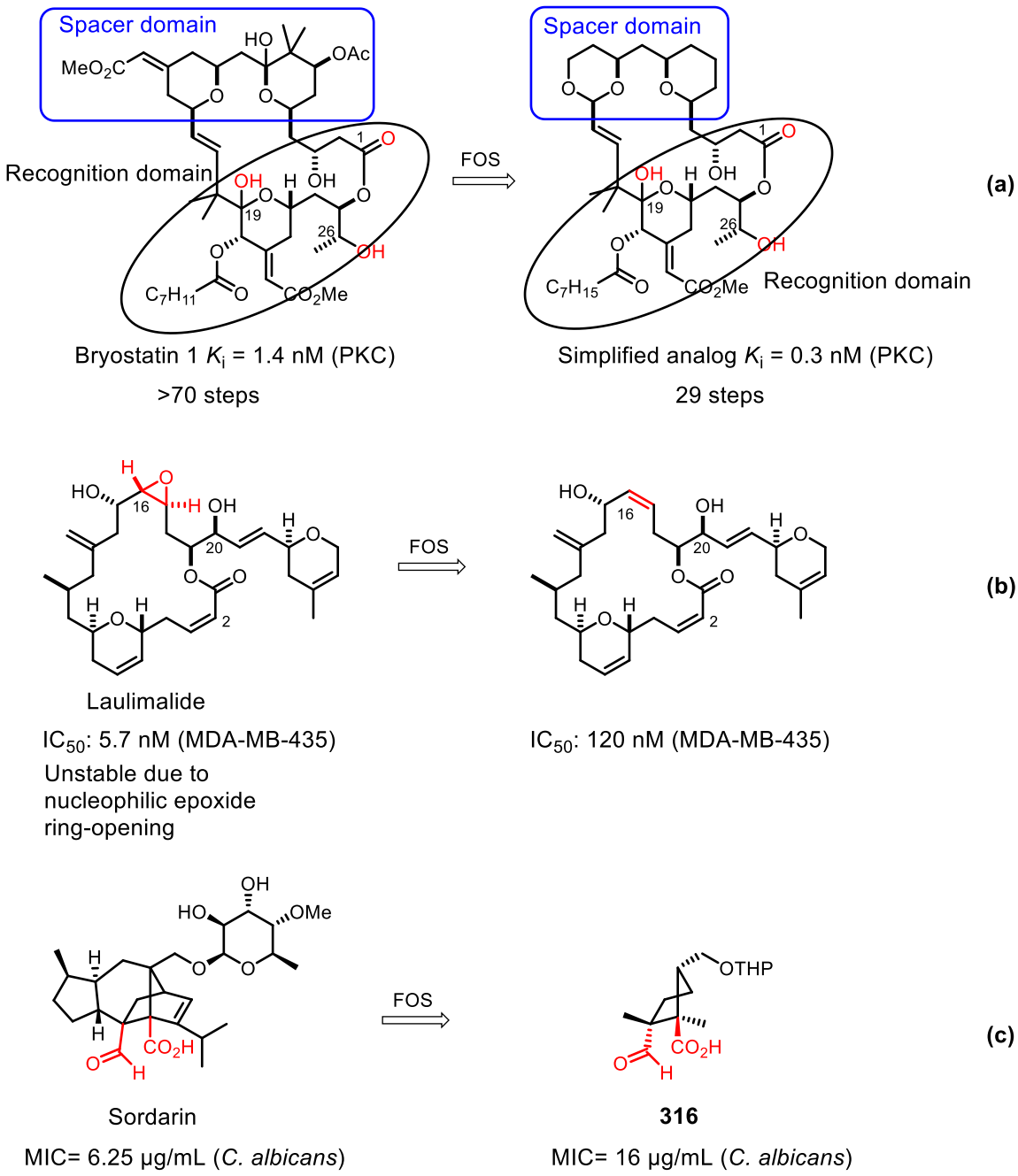


Figure 2.1.3: Examples of Function-Oriented Synthesis

2.2 Synthetic Route Proposals

To access a novel bicyclic sordarin scaffold such as **32** in Figure 2.1.2, a

retrosynthetic analysis is outlined below (**Figure 2.2.1**). The glycosyl group can be easily installed by conventional glycosylation or anomeric alkylation. The key step to construct the C-2 quaternary center of the bicyclo[2.2.1]heptane core is envisaged to be achieved by one of five different strategies (**Figure 2.2.2**). These strategies all require cyclopentenone **38** as a common intermediate. **38** can be prepared from unsaturated ester **39** by allylic oxidation and silyl enolation. Ester **39** in turn, can be accessed by two different synthetic routes, depending on what method is used to introduce the chiral center. One of these routes, as described below, also provides an option for synthesis of racemic **38** and eventually racemic **32** for a faster and cheaper validation of concept.

The five different strategies to furnish a quaternary chiral center at the C-2 position of **35** (**Figure 2.2.1**) is depicted in detail in Figure 2.2.2. These strategies can be grouped into two general categories depending on whether the C-2 quaternary center is formed at the same time as the formation of the bicyclo[2.2.1]heptane core, or afterwards. Stereoselective Diels-Alder reaction and double Michael addition belong to the first category (**48**, **49**, **52**, **Figure 2.2.2**). The C-2 quaternary center can also be formed after the formation of the bicyclo[2.2.1]heptane core by trapping a C-2 carbocation with cyanide or using a C-2 anion to conduct a S_N2- or S_NAr-type substitution (**51**, **52**, **Figure 2.2.2**).

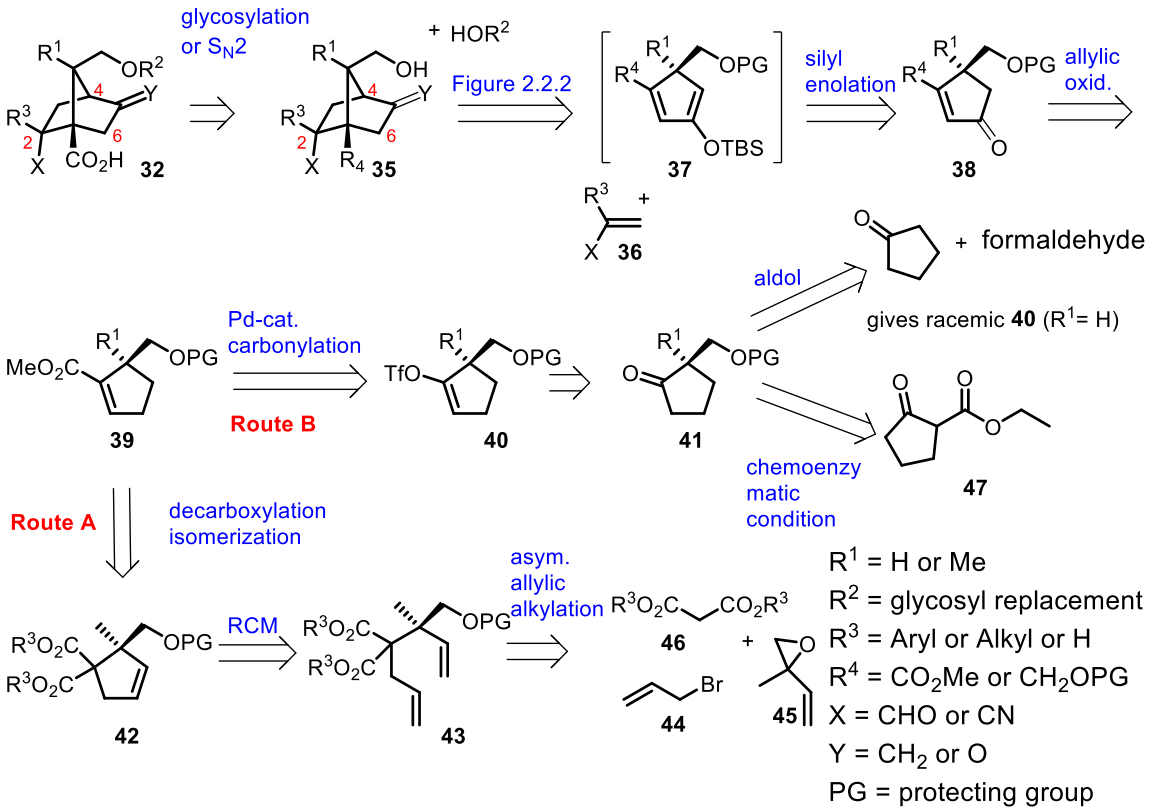


Figure 2.2.1 Retrosynthetic analysis for bicyclic sordarin analog **32**

The chiral center of **38** can be introduced by Trost asymmetric allylic alkylation (AAA) reaction (**Route A, Figure 2.2.1**).[44] Unsaturated ester **39** can be accessed by applying Krapcho decarboxylation[45] of diester/acid **42** followed by olefin isomerization. **42** is in turn made by RCM of diene **43**. Chiral diene **43** can be made enantioselectively by using Trost asymmetric allylic alkylation where vinyloxirane **45** and malonic ester **46** serve as electrophile and nucleophile respectively.

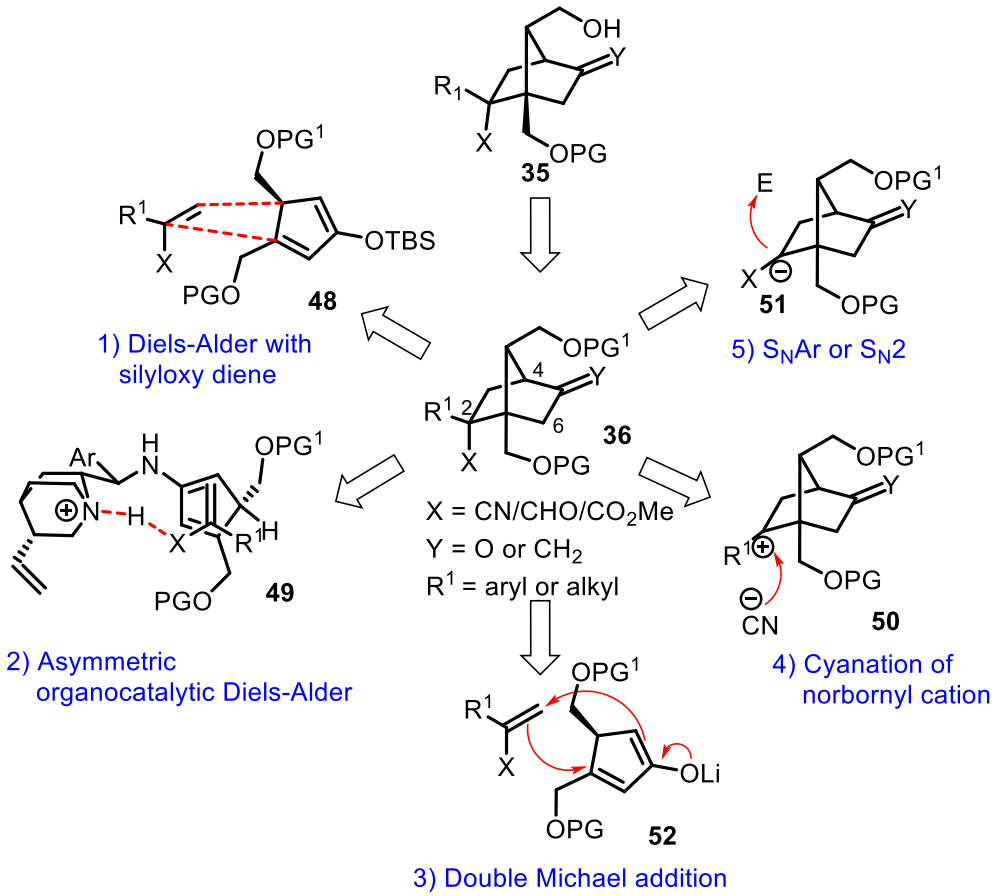


Figure 2.2.2 Proposed strategies for constructing the desired bicyclo[2.2.1]heptane core with quaternary center at C-2. PG = protecting group.

Another route features palladium catalyzed carbonylation to give **39** (**Route B**, **Figure 2.2.1**), which can access either chiral or racemic **41**. For the chiral approach, a chemoenzymatic resolution of **47** using Baker's yeast[46] or Amano PS[47] will furnish the chiral center of **41**. Chemoenzymatic resolution is advantageous to use in early stage of the synthesis for its lower cost and robustness. Optionally, the chiral center of **41** can be introduced by direct asymmetric α-hydroxymethylation such as examples reported by

Mlynarski,[48] but the cost will be higher compare to chemoenzymatic resolution for its relatively high catalyst load (10 mol%) and commercially unavailable ligand. For a racemic approach, *rac*-**41** can simply be made from cyclopentanone and formaldehyde via aldol reaction.

2.2.1 Cyclopentanone and Cyclopentadiene Synthesis

Two different routes used to synthesize the common intermediates **37** and **38** are described in this chapter.

2.2.1.1 Trost Asymmetric Allylic Alkylation Route (Route A)

To build a chiral primary alcohol that has a quaternary center at its C-2 position, the application of asymmetric allylic alkylation (AAA) developed by Trost[44] was chosen in this first proposed route (**Figure 2.2.1.1.1**). Methyl malonate under Trost AAA conditions could asymmetrically add to vinyloxirane **45** to generate a chiral quaternary center and a primary alcohol, which could then be protected with TBS. The malonic position is deprotonated by NaH and allylated to give compound **53**. **53** will then be subjected to Krapcho decarboxylation resulting in diene **54**, which after ring closing metathesis and tandem olefin isomerization will give α,β-unsaturated ester **55**. From **55**, allylic oxidation, such as under the conditions developed by Corey,[49] will be used to oxidize

the C-3 position to a ketone. This ketone is then converted into silyl enol ether **57**, which is the cyclopentadiene needed for the key Diels-Alder reaction. (**Figure 2.2.1.1.1**)

There are, however, some disadvantages for this route. The Trost AAA reaction requires use of the expensive Trost ligand. From a synthetic point of view, this may not be ideal for large scale synthesis. More importantly is that the final cyclopentadiene product **57** intrinsically has to bear a methyl group at C-5 position for this type of Trost AAA reaction doesn't tolerate 2-vinyloxirane as an electrophile. If the stereochemical outcome of the key bicyclo[2.2.1]heptane core forming step is proven to give the undesired diastereomer at C-2 position, then to eliminate the steric effect of the C-5 methyl group of **57**, a 5-demethyled analog of **57** would be required, which cannot be easily made through this route (see discussion in chapter 3).

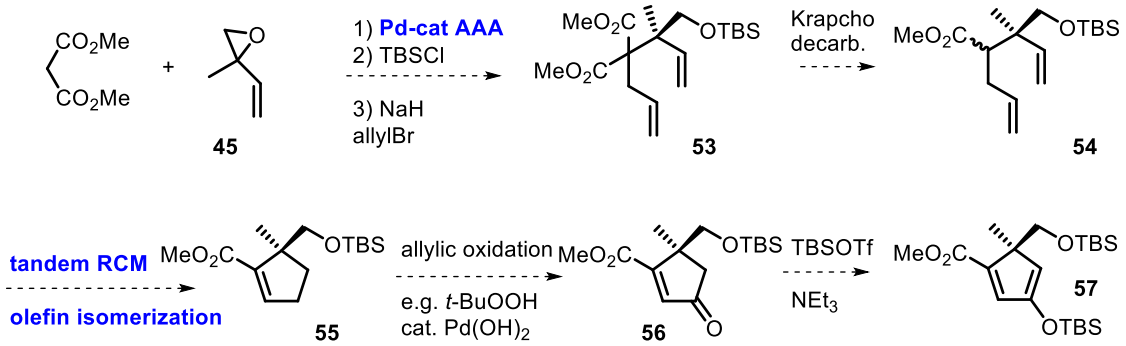


Figure 2.2.1.1.1: Proposed Trost asymmetric allylic alkylation route to cyclopentadiene **57**

2.2.1.2 Palladium-Catalyzed Carbonylation Route

(Route B)

In order to improve the Trost AAA route in terms of cost, and also prepare for the potential need of a 4-monosubstituted cyclopentenone **38** (R_1 = H), two chemoenzymatic routes were proposed.

First, to synthesized the 4-monosubstituted cyclopentanone **63**, racemic β-ketoester **47** will be subjected to Baker's yeast asymmetric reduction. Baker's yeast is known to be able to catalyze the reduction of **(R)-47** much more faster than its enantiomer to give (1R, 2S)-2-hydroxycyclopentanecarboxylate (**59**).[46] The desired **(S)-47** will remain intact while the ketone of **(R)-47** will be reduced to alcohol **59**. **(S)-47** will then be reduced to diol whose primary alcohol is selectively protected with TBDPS, then a Dess-Martin oxidation[50] will furnish chiral ketone **60**. **60** will then be converted into enol triflate **61** using McMurry's triflating reagent.[51] **61** will then be homologated into α,β-unsaturated ester **62** by Pd-catalyzed carbonylation. Allylic oxidation conditions, such as those developed by Corey,[49] will be used to oxidize the C-3 position of **62** to α, β-unsaturated ketone **63**. Finally **63** can be converted into an enol ether such as **64,** if a Diels-Alder reaction is used for the construction of the bicyclo[2.2.1]heptane core (**Figure 2.2.1.2.1**).

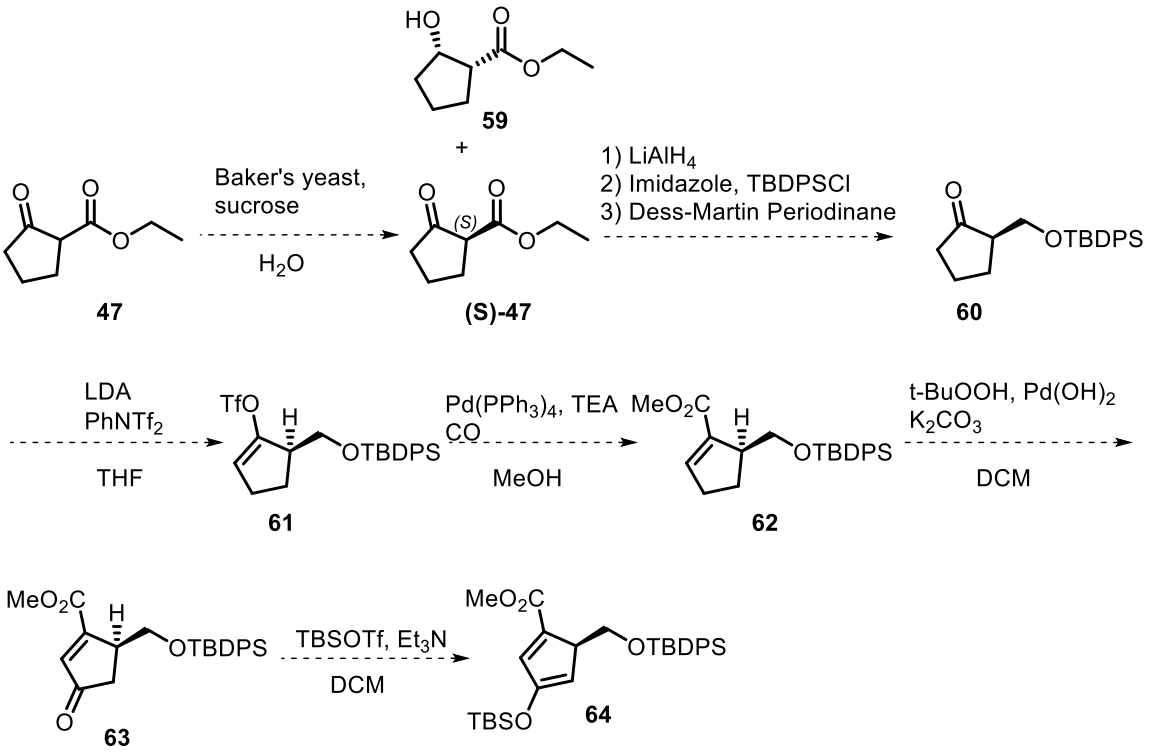


Figure 2.2.1.2.1: Baker's yeast route to chiral cyclopentadiene **64**

Enzymatic transesterification using a suitable lipase provides a way of synthesizing 4-disubstituted cyclopentenone **69** (**Figure 2.2.1.2.2**). Starting from the same starting material, racemic β-ketoester **47** will be methylated at the α-position. After protecting its ketone as a ketal, the ester is reduced to the primary alcohol, followed by hydrolysis of the ketal, generating racemic alcohol **65**. **65** is then subjected to enzymatic transesterification where the (R)-**65** will be able to perform the transesterification much faster with vinyl acetate giving highly enantioenriched ketone **66**.[47] From **66**, the subsequent steps will be the same as described above in the Baker's yeast approach, giving

access to a 4-disubstituted cyclopentennone such as **69** (**Figure 2.2.1.2.2**).

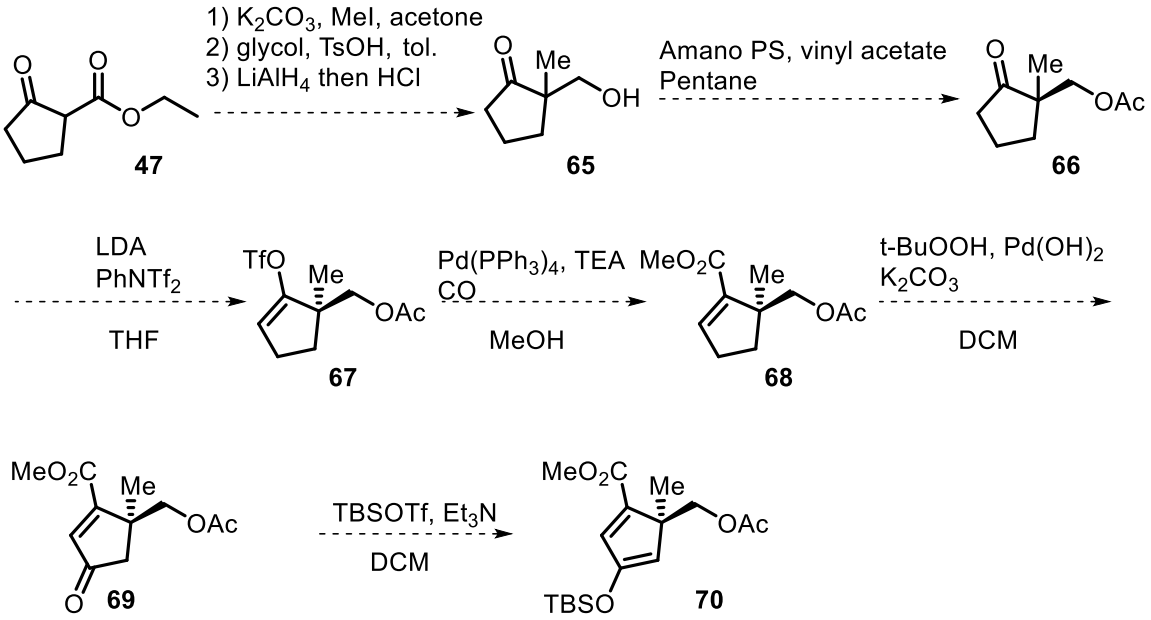


Figure 2.2.1.2.2: Amano lipase route to chiral cyclopentadiene **70**

In addition, a cheaper and faster synthesis of the racemic building block cyclopentenone **74** and cyclopentadiene **75** can be achieved by preparing racemic ketone **71** from cyclopentanone via aldol reaction with formaldehyde. The process after **71** will be the same as described above in the chiral approach (**Figure 2.2.1.2.3**).

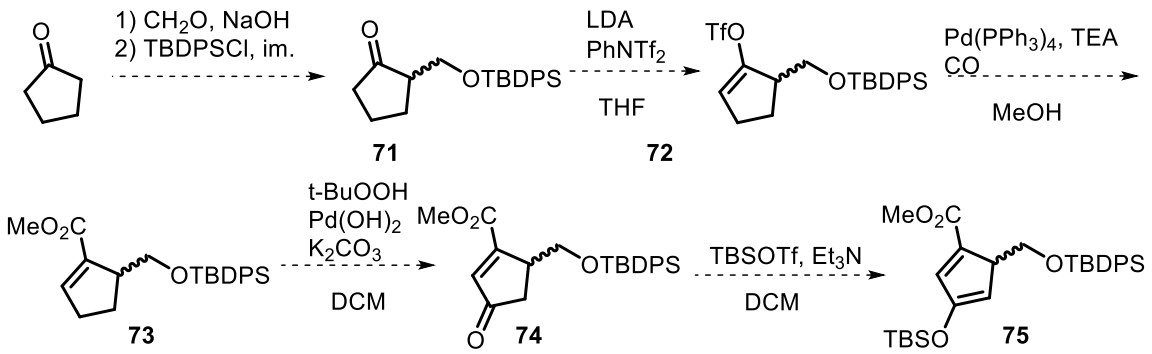


Figure 2.2.1.2.3: Aldol route to racemic cyclopentadiene **75**

2.2.2 Construction of Quaternary Center at C-2 of Bicyclo[2.2.1]heptane core

2.2.2.1 Diels-Alder Reaction using Functionalized Cyclopentadiene and 1,1-Disubstituted Dienophile

The Diels–Alder reaction is a [4+2] cycloaddition between a conjugated diene and an alkene, commonly termed the dienophile, to form a cyclohexene system. It was discovered in 1928 by Otto Diels and Kurt Alder,[52] and its application in total synthesis can be backdated to Woodward's landmark 1952 syntheses of the steroids cortisone and cholesterol.[53]

In the Diels-Alder reaction approach to our desired bicyclo[2.2.1]heptane core, the diastereoselectivity (endo/exo) is anticipated to be the most challenging part. Since prior SAR and crystallographic studies suggest that the carboxylic acid and its adjacent aldehyde/nitrile group must maintain a specific orientation for compounds to be active (**Figure 2.1.1**), this means that in our strategy the endo diastereomer is required and the

Diels-Alder reaction should be endo-selective so that these two pharmacophores can be placed in the same relative orientation as in sordarin. Uncertainty remains at this stage about the stereoselectivity when a cyclopentadiene such as **76b** is paired with **77** (**Figure 2.2.2.2**). Especially when R^3 = Ar, due to the steric hindrance caused by the aryl group on **77**, it is anticipated that the aryl group may be forced to the undesired endo position when two substituents are present on the bridge proximal to the dienophile carbons.

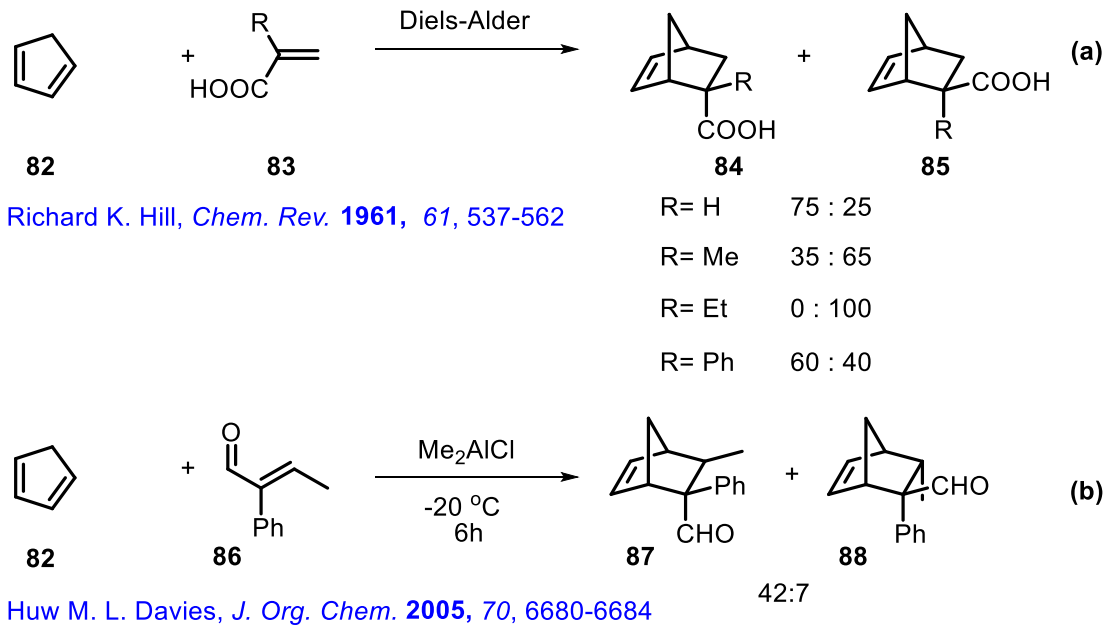


Figure 2.2.2.1: Steric effect of 1,1-disubstituted dienophile with phenyl substituent.

However, there are some evidences that a phenyl substituent on the dienophile might actually benefit endo-selective Diels-Alder reaction. In a review summarized by

Hill,[54] it was evident that as the size of substituent on the dienophile α-position increases, the percentage of endo adducts decreases. But phenyl substituent in this context is an exception, giving better endo-selectivity compared to α-methylacrylic acid (**eq. (a) Figure 2.2.2.1**). Davies[55] reported a Lewis acid catalyzed Diels-Alder reaction using similar dienophile. In his case, the endo-selectivity was further improved (**eq. (b), Figure 2.2.2.1**). It should be remembered though, in these examples there are no significant steric bulk on the diene side.

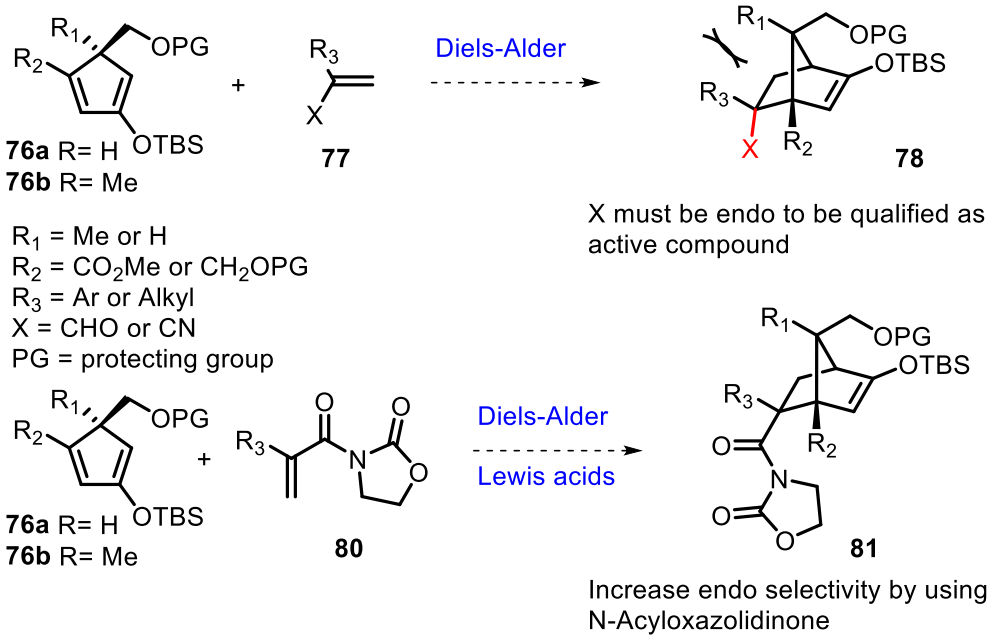


Figure 2.2.2.2: Steric effect caused by aryl group on the dienophile

To circumvent this issue, as described above in chapter 2.2.1.2, cyclopentadiene

76a without a methyl group at its C-5 will be synthesized. There is however, another potential issue if a 5-monoalkylated cyclopentadiene is used in a Diels-Alder reaction, namely an undesired [1,5]-sigmatropic shift (usually hydride), which leads to a more substituted diene.[56] (**Figure 2.2.2.3**)

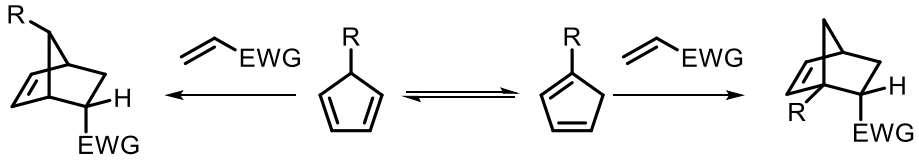


Figure 2.2.2.3: [1,5]-sigmatropic shift

These [1,5]-sigmatropic shifts can in some cases be minimized by handling the cyclopentadienes at low temperatures. One milestone synthesis using a Diels-Alder reaction with such a cyclopentadiene was reported by Corey,[57] in which a copper catalyst was used to accelerate the reaction at 0 ºC without observing an appreciable amount of cycloadduct generated from the isomerized 2-substituted cyclopentadiene.[57] (**Figure 2.2.2.4**)

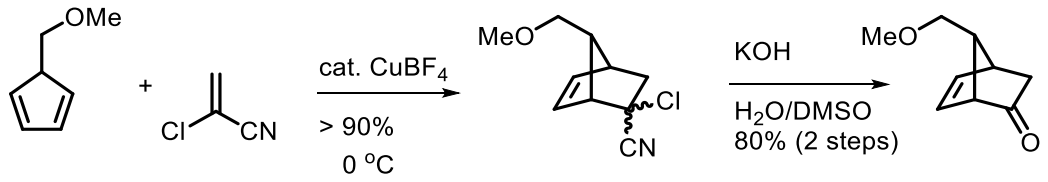


Figure 2.2.2.4: Corey's DA reaction used in the synthesis of prostaglandins

The half-life of 5-monoalkylated cyclopentadiene shown above is short at room temperature, measured at 1.2 h for 5-methylcyclopentadiene.[58] Gleason has reported that a cyclopentadiene with an electron-donating 2-silyloxy group has greatly increased stability towards isomerization (**Figure 2.2.2.5**).[59] Also noteworthy is that in the same work, Gleason conducted a Diels-Alder reaction using this cyclopentadiene with a 1,1-disubstituted dienophile with and without a mild Lewis acid. In both cases the exo-product dominated, which is consistent with the example shown in Figure 2.2.2.1 eq. (a). Nonetheless, when a Lewis acid is present the amount of endo product is increased slightly (**Figure 2.2.2.5**).

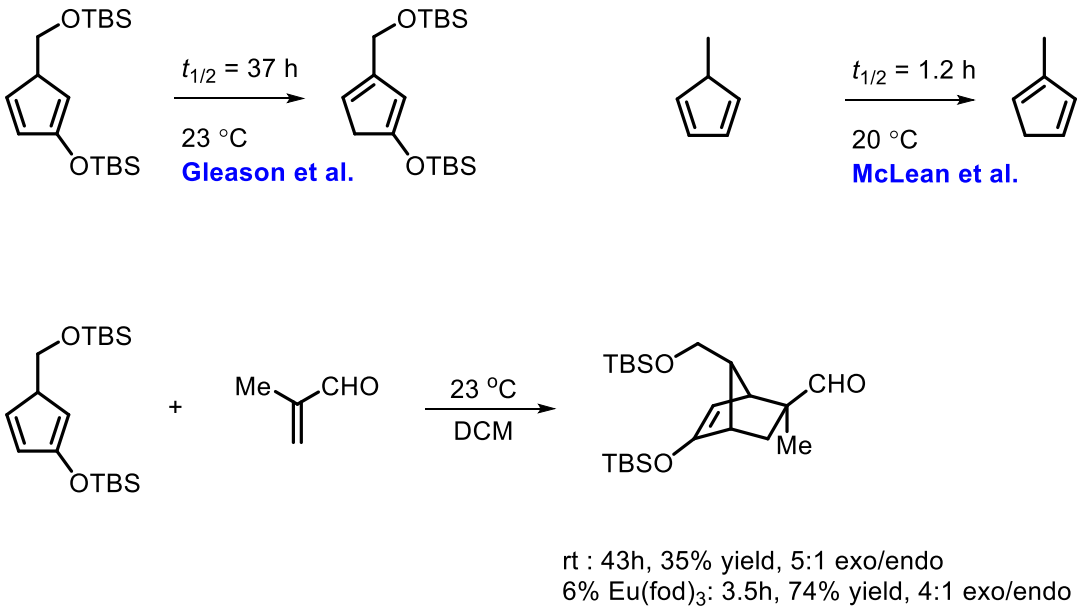


Figure 2.2.2.5: Expanded half-life of Gleason's diene and its Diels-Alder reaction example

At the same time, if a substrate like **76a-b** turns out to favor the undesired exo adduct, as a backup plan, α,β-unsaturated *N*-acyloxazolidinones developed by Narasaka[60] such as **80** can be used to increase the activity and endo selectivity by its steric effect and/or its ability to chelate a Lewis acid, with the increased electron deficiency correlated with increased endo selectivity[61] (**Figure 2.2.2.2**).

A close example of a 5,5-dialkylated cyclopentadiene performing a DA reaction with dienophile disubstituted with electron-withdrawing groups at C-1 was reported by Ciufolini,[28] in an effort to synthesize sordarin analogs by both inter- and intramolecular Diels-Alder reactions (**Figure 2.2.2.6**). An analog of Danishefsky's diene was used in their

intermolecular Diels-Alder reaction, where cyclopentadiene **89** substituted by electron donating groups at C-1 and C-3 is paired with dienophile **83**. This reaction went smoothly at 60 °C to give desired adduct **90**. Interestingly, when they tried to introduce an alkyl group at C-2 on the cyclopentadiene, even a methyl group could prevent the Diels-Alder reaction from taking place. They attributed this failure to the adjacent bulky TIPS group (**Figure 2.2.2.6**).

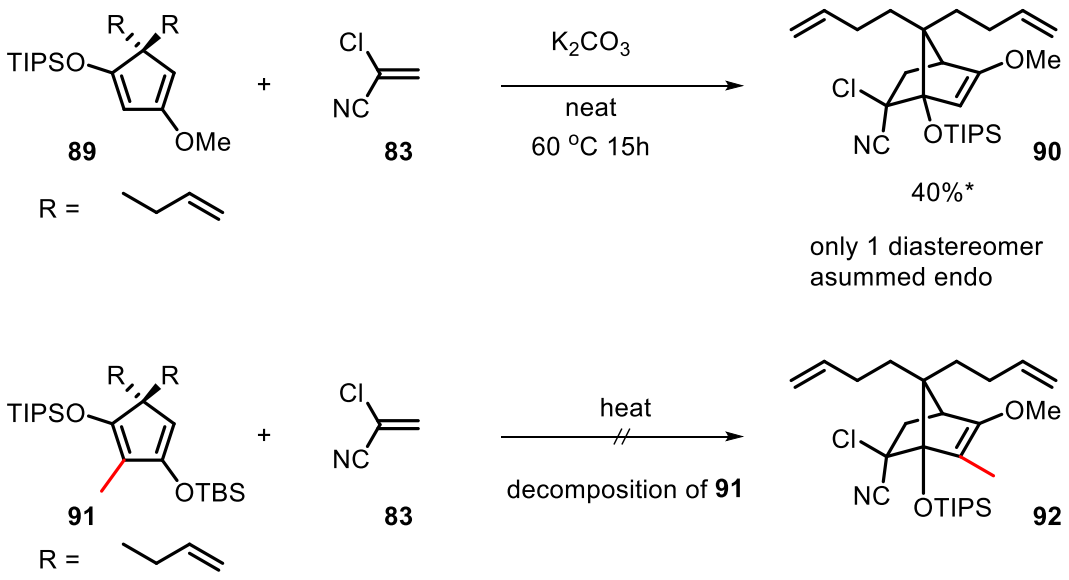


Figure 2.2.2.6: Ciufolini's intermolecular DA examples

In Ciufolini's intramolecular DA reaction examples, there are great similarities with the diene and dienophile proposed in this research. Compound **95** has a silyloxy diene,

which is proven in his example to be able to increase the diene's HOMO energy level and enabled a Diels-Alder reaction that was otherwise inert (**Figure 2.2.2.7**).

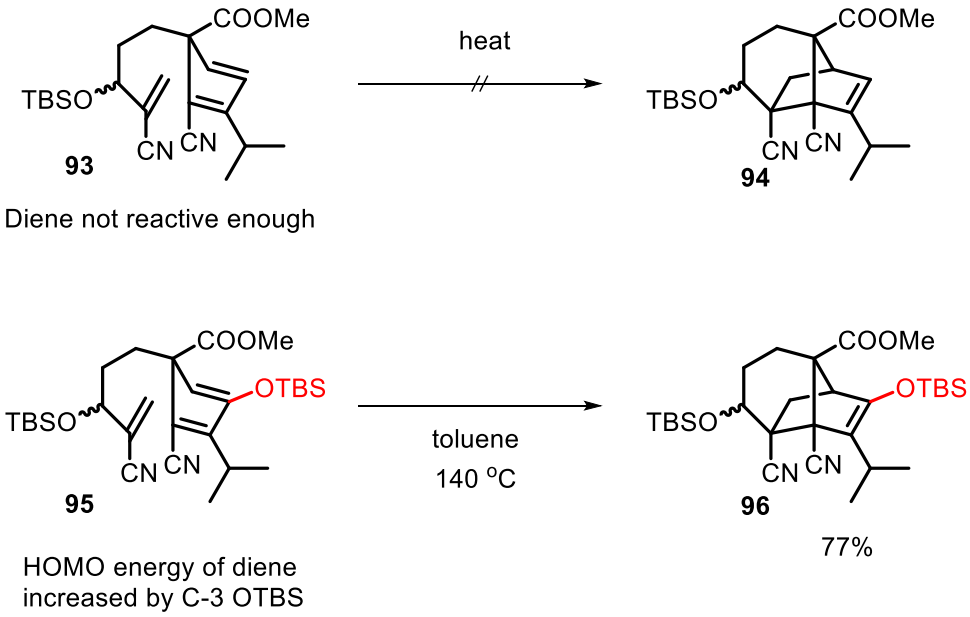


Figure 2.2.2.7: Ciufolini's intramolecular DA examples

Other than the conventional type of Diels-Alder approach described above, an organocatalytic asymmetric Diels-Alder reaction[62] could also provide a promising path to the desired bicyclo[2.2.1]heptane core. An example of such a Diels-Alder reaction reported by Jørgensen is depicted in **Figure 2.2.2.8**.[63] This strategy uses a quinidine-derived amine catalyst **98** to form an intermediate dienamine from cyclopentenone. In the transition state, the tertiary ammonium directs and activates a dienophile by acting as a hydrogen bond

donor (**eq. (a), Figure 2.2.2.8**). This method can give high diastereo- and enantioselectivities and doesn't need a separate step to convert the cyclopentenone to a diene. A cyclopentenone such as **100** could be used to examine this approach (**eq. (b), Figure 2.2.2.8**).

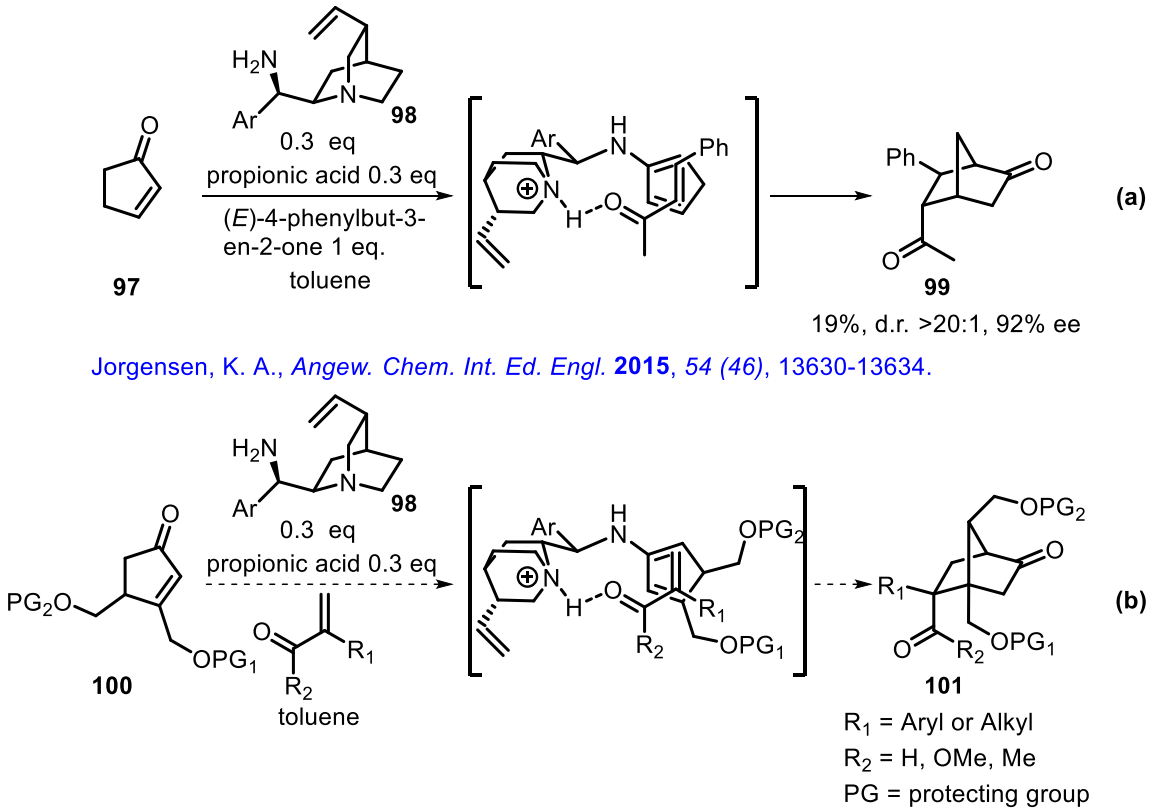


Figure 2.2.2.8: Jørgensen's organocatalytic asymmetric Diels-Alder reaction

In conclusion, to construct the bicyclo[2.2.1]heptane core with an endo-selective Diels-Alder reaction, two general approaches could be taken. For a conventional intermolecular Diels-Alder reaction, using a Lewis acid with or without the N-

acyoxazolidinone decorated dienophile could be a useful method if a thermal Diels-Alder reaction leads to an undesired exo-adduct. If a 5-monosubstituted cyclopentadiene is to be used, undesired [1,5]-sigmatropic shifts could can be prevented by increasing the electron density on the cyclopentadiene with silyloxy substitution or handling the cyclopentadiene at lower temperature in the presence of a Lewis acid catalyst. For an organocatalytic Diels-Alder approach, the cyclopentenone precursor **100** can be used directly to examine its validity.

2.2.2.2 Double Michael Addition

Yamada[64] has reported a double Michael addition to construct a similar bicyclo[2.2.1]heptane skeleton using a 3-alkoxyl cyclopentanone **102** together with a chiral Michael acceptor **103** (**eq. (a), Figure 2.2.2.2.1**). This addition afforded in high yield the bicyclo[2.2.1]heptane scaffolds **104a-b**, with the high stereoselectivity induced by the chirality of **103**.

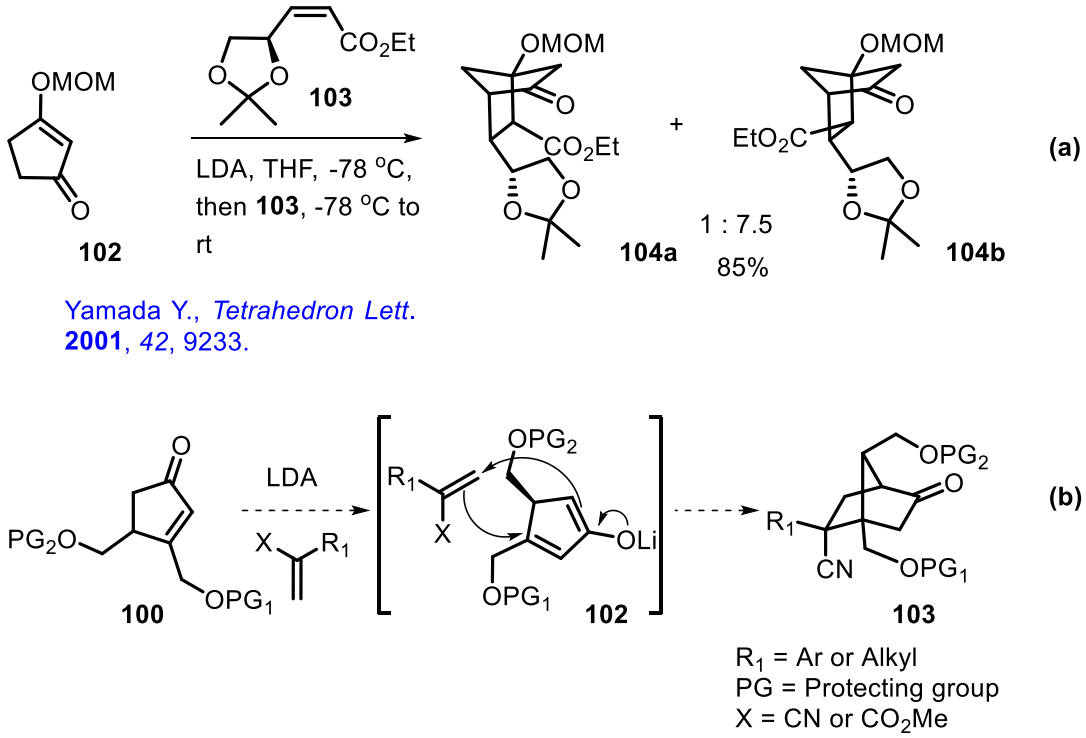


Figure 2.2.2.2.1: Yamada's double Michael example and proposal to construct scaffold **103**

If the C-2 diastereochemistry turns out to be undesirable with the Diels-Alder approach described in chapter 2.2.2.1, the double Michael strategy will be a good alternative to reach scaffold **103** (**eq. (b), Figure 2.2.2.2.1**).

2.2.2.3 S_NAr/S_N2 using C-2 Anion

As described in section 2.2, the C-2 quaternary center of the bicyclo[2.2.1]heptane core can also be furnished using a C-2 anion to conduct S_NAr- or S_N2-type substitution reactions. This approach is based on the examples reported by Caron, in which he reported

that 2-cyano-5-norbornene **105** can undergo S_NAr with aryl fluorides exclusively from the exo face to furnish a tertiary nitrile at the C-2 position of the skeleton (**eq. (a), Figure 2.2.2.3.1**).[65] This stereoselectivity was also seen in a S_N2 reaction using the same starting material with BnBr, and the C-2 anion attacked the electrophile exclusively from the exo face to give **107**.

To take this approach, the silyloxy diene **108** described in previous chapters can be paired with acrylonitrile to simply form a diastereomeric mixture of secondary nitriles at C-2 to give scaffold **109**. **109** can then be subjected to the same conditions reported by Caron to furnish the C-2 quaternary center of **110** (**eq. (b), Figure 2.2.2.3.1**).

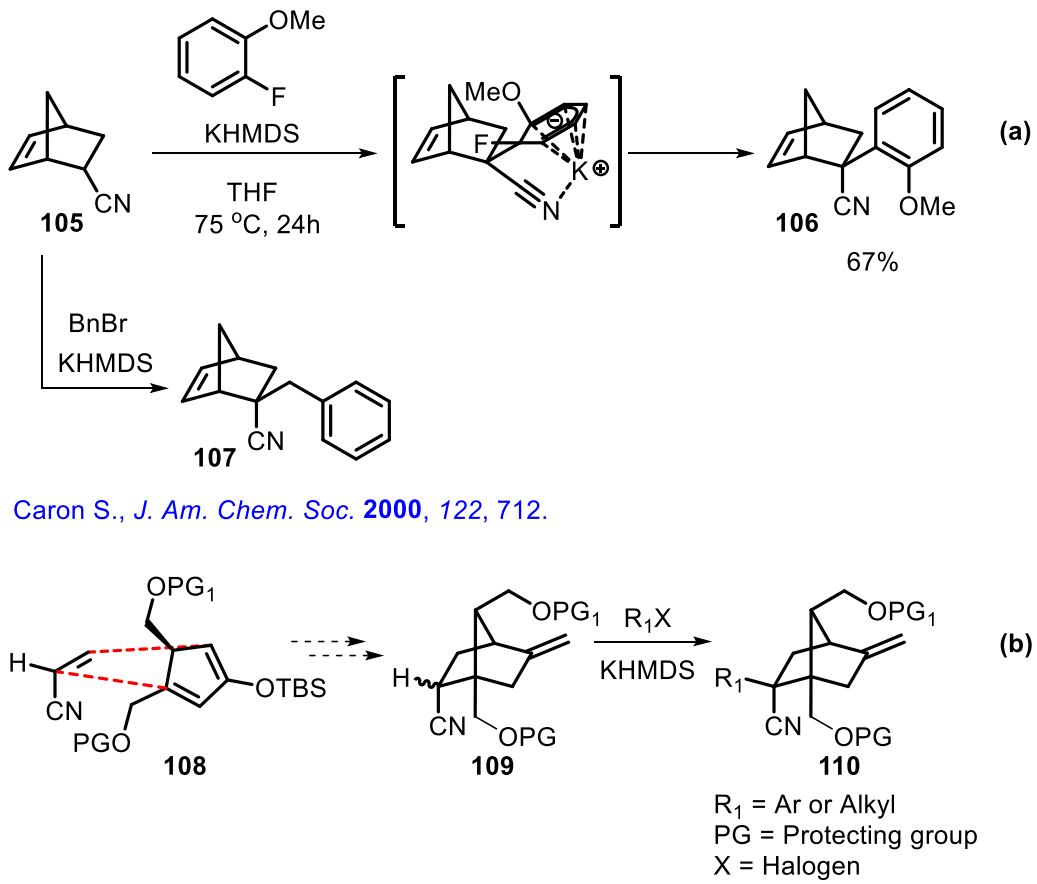


Figure 2.2.2.3.1: SNAr/SN2 using C-2 anion of bicyclo[2.2.1]heptane scaffold

2.2.2.4 Nucleophilic Trapping of C-2 Cation

In the case of an aryl tertiary nitrile, the C-2 tertiary center may also be furnished via a nucleophilic trapping of a stabilized C-2 cation. As shown in equation (a) in **Figure 2.2.2.4.1**, Yanagisawa[66] showed that in a monocyclic system, a tertiary benzylic carbocation can be trapped with a cyanide source such as TMSCN to give aryl tertiary nitriles **112**. There is a clear trend in these examples that cations stabilized by a more electron-donating aryl group give higher yields. There are also some examples of

nucleophilic trapping of this type of carbocation on a bicyclic system, one pertinent example reported by Lattanzi[67] where a camphor derived C-2 cation was successfully trapped with hydroperoxide (**eq. (b), Figure 2.2.2.4.1**). However, this method is also highly dependent on the substituent used to stabilize the cation. If a phenyl substituent is used instead of a furan-2-yl group to stabilize the cation, the trapping was unsuccessful. Instead, it leads to dehydration and Wagner–Meerwein rearrangement to give olefins **121** and **122** respectively (**eq. (c), Figure 2.2.2.4.1**). Therefore, the validity of this strategy should be examined in a model system using substrates easily derived from camphor before an approach depicted in equation (d) can be tested.

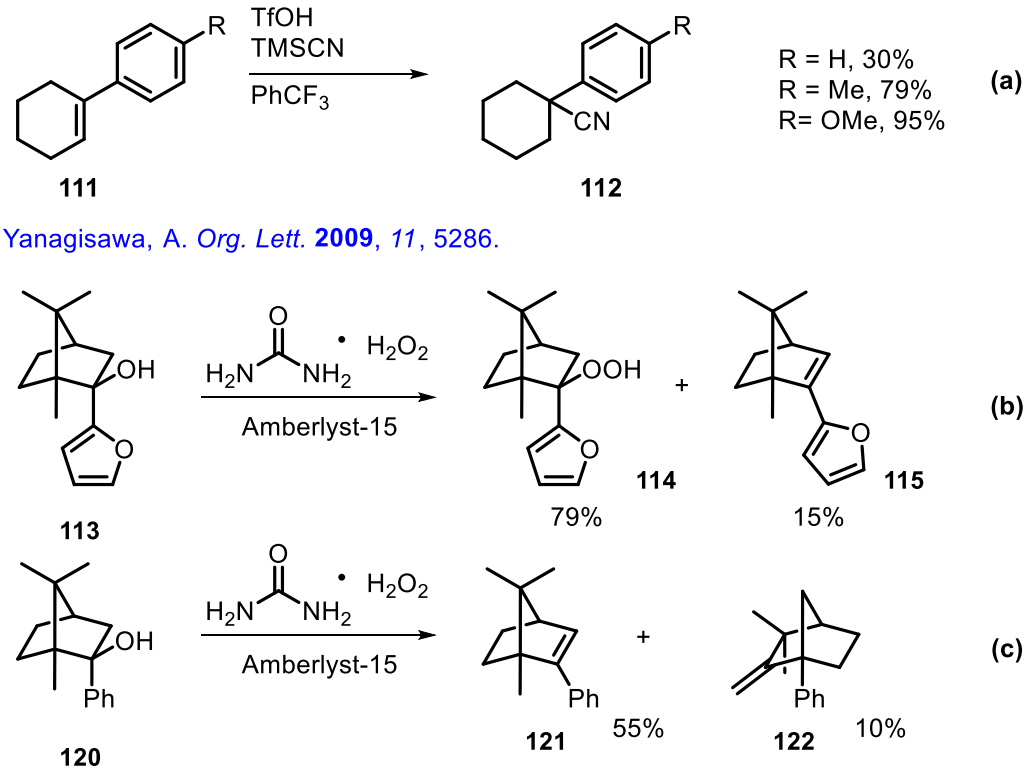


Figure 2.2.2.4.1: Nucleophilic trapping of stabilized carbocation

2.2.3 Glycosidation and Late-stage Modifications

The initial goal of this research is to synthesize a series of analogs with different R_2 groups at the C-2 exo position. Since the glycosyl moiety SAR has already been studied extensively (Chapter 1), once the desired sordaricin cores **127** or **134** are synthesized, they

will be coupled with selected glycoside replacements to give **124**, **125**, **126 (Figure 2.2.3.1)**. **124** and **126** were proposed because their known analogs **120**[68] and **121**[40] possess high potency, and the glycones are relatively easy to access. The glycone in **126** has shown both high potency and broad antifungal spectrum in sordarin derivatives, and thus, it is the most favorable glycone to use at this stage. All different R^2 variants will be tested with this glycoside first.

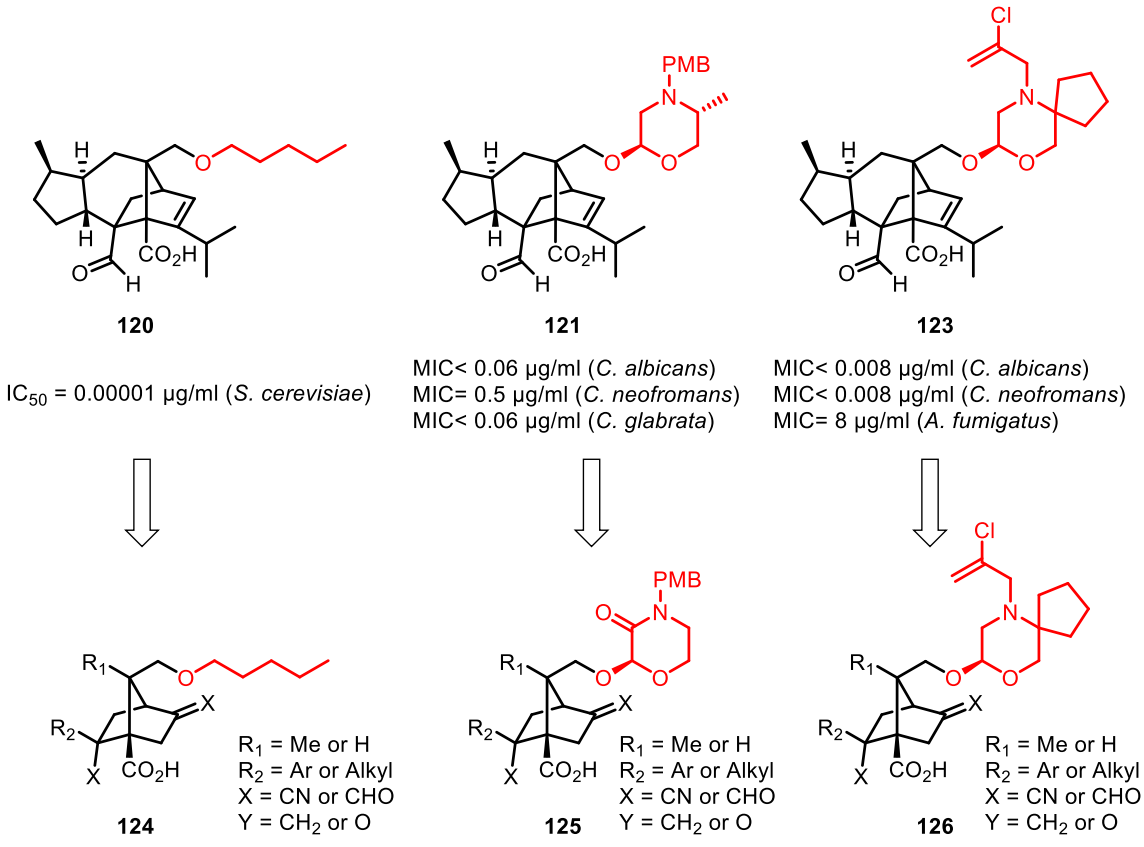


Figure 2.2.3.1: Target compounds with selected glycoside replacement

The synthesis of glycone **140** starts from cyclopentanone (**Figure 2.2.3.2**). Imine formation with ammonia followed by addition of cyanide gives aminonitrile **135**. **135** will then be hydrolyzed to acid **136**. Reduction by $LiAlH_4$ will give known amino alcohol **137**,[69] which by reductive amination with 2,2-dimethoxyacetaldehyde, gives amino alcohol **138**. The 2-chloroallyl group will then be installed by SN2 to the secondary amine giving **139**. Finally, the protected aldehyde is released to give glycone **140**. The formation of glycone **142** will follow the method reported by Brands[70] by condensing amino alcohol **141** with glyoxylic acid (**Figure 2.2.3.2**).

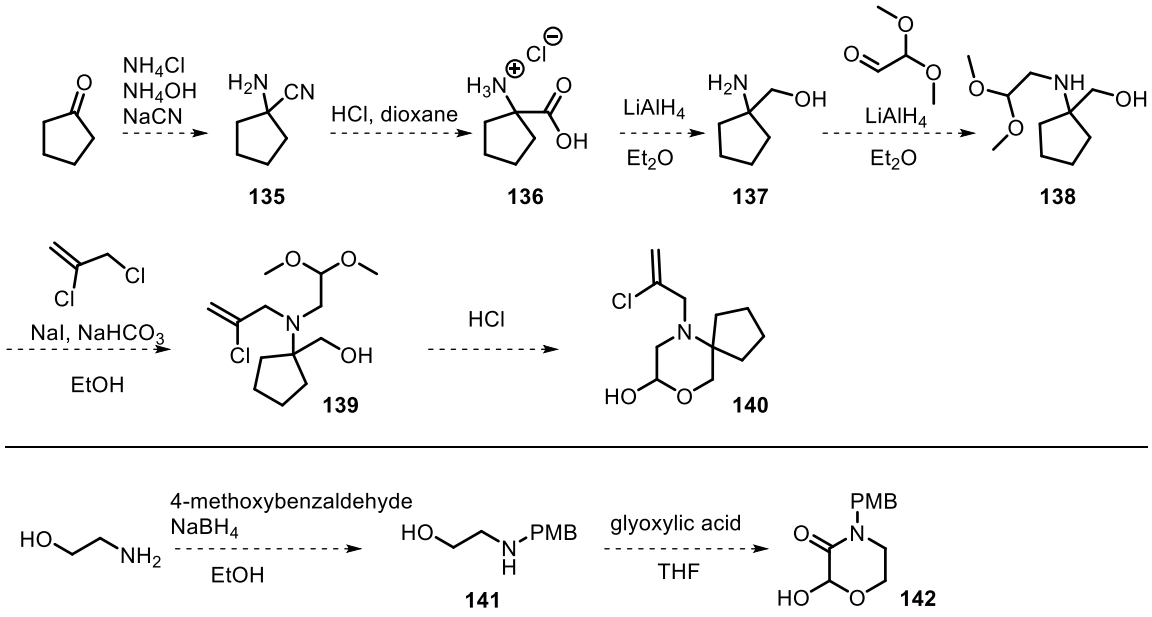


Figure 2.2.3.2: Proposed synthesis of selected glycosides

The glycosidation of the bicyclo[2.2.1]heptane core to give either nitrile **130** or

aldehyde **133** can start from alcohol **127** or **134** (**Figure 2.2.3.3**). Since the nitrile **127** may be synthetically more accessible than its aldehyde analog, the final compound **130** can potentially be reduced to its aldehyde counterpart **133**. Core structure **127** will be synthesized with highest priority.

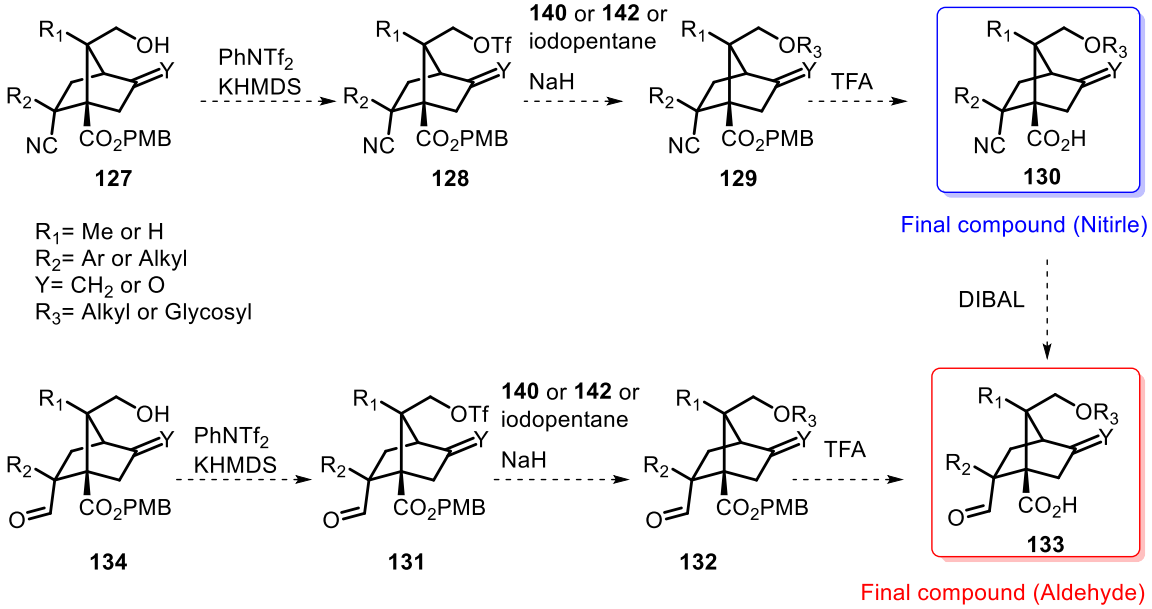


Figure 2.2.3.3: Glycosidation and protecting group manipulation

The desired bicyclo[2.2.1]heptane cores **143** and **144** can also be subjected to various late-stage modifications for SAR studies, especially at the C-5 and C-6 position of the bicyclo[2.2.1]heptane core which has never been explored before. Some proposed modifications are given in **Figure 2.2.3.4**.

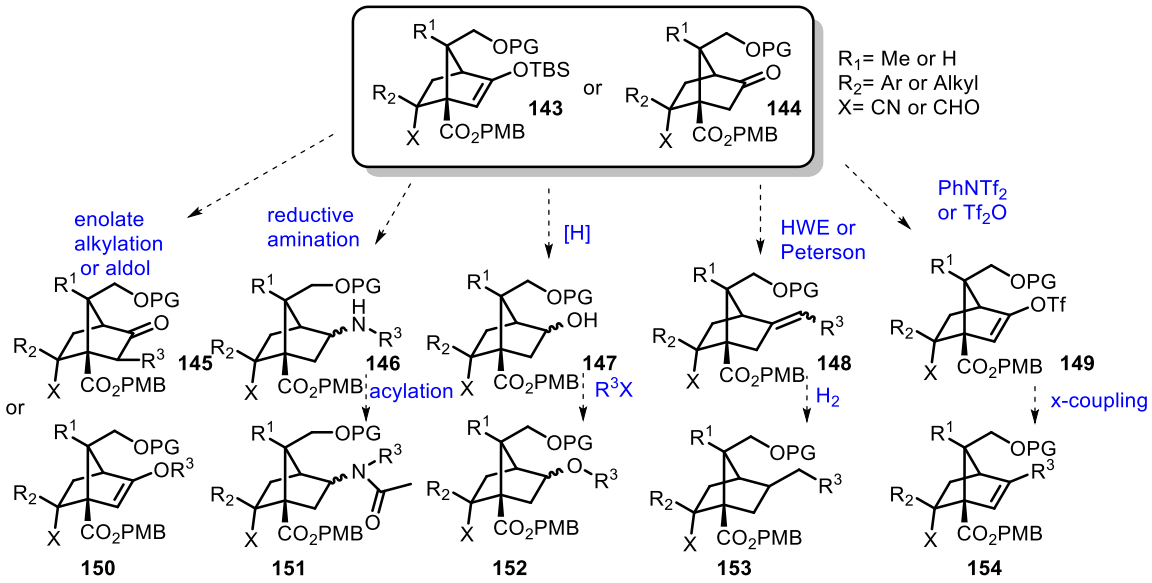


Figure 2.2.3.4: Late-stage modification on bicyclo[2.2.1]heptane core

3.0 Results and Discussion

Much of the work described in this chapter has been published in Tetrahedron Lett., ChemRxiv preprint,[71] and J. Org. Chem.[72] This chapter describes the experimental results in pursuing the synthetic proposal discussed in Chapter 2.2

3.1 Cyclopentanone and Cyclopentadiene Synthesis

Two routes featuring Trost AAA reaction and Pd-catalyzed carbonylation respectively to reach cyclopentenone **38** (**Figure 2.2.1**) are described in this chapter.

3.1.1 Trost Asymmetric Allylic Alkylation Route

This route started with a Trost AAA reaction using 2-methyl-2-vinyloxirane and dimethyl malonate. The desired alcohol **203** however, was not observed (**Figure 3.1.1.2**). Instead, lactone **204** was formed through lactonization. At this early stage, four different nucleophiles **350**-**353** were tested to examine if the lactonization could be avoided, but they either did not react or they still give a lactone product such as **230** or amino enol ether **234** (**Figure 3.1.1.1**).

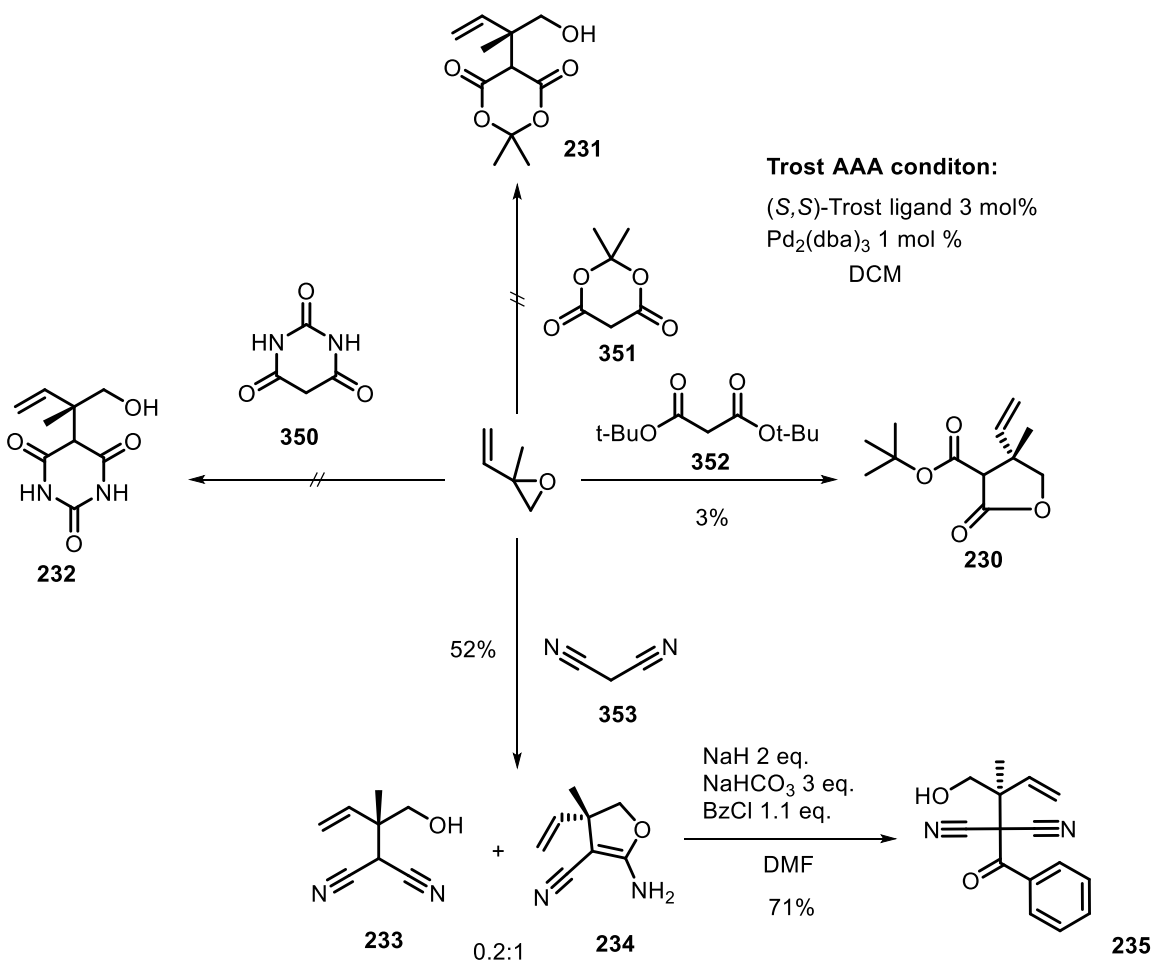


Figure 3.1.1.1: Vinyloxirane with various nucleophiles in Trost AAA reaction

The lactone product **204** was thus used as is. An α-allylation of **204** furnished racemic diene **205** in excellent yield, which was then subjected to ring-closing metathesis. Due to the fact that the lactone ring restricted the orientation of the substitutents on the two adjacent quaternary centers, only the diastereomer of **205** that had the two olefins syn to each other reacted to give bicyclic lactone **206**. The stereochemistry was assigned based on a bicyclic ketone stability study by Hudlicky,[73] which suggested in a cis- and trans-fused

bicyclic ketone equilibrium, the cis-fused bicyclic ketone dominated. Then, a Krapcho decarboxylation proceeded smoothly to give the lactone **207**. Initial attempts to isomerize the double bond to give an α,β-unsaturated lactone **229** by ruthenium hydride generated from Grubbs ruthenium carbene and MeOH[74] were not successful.

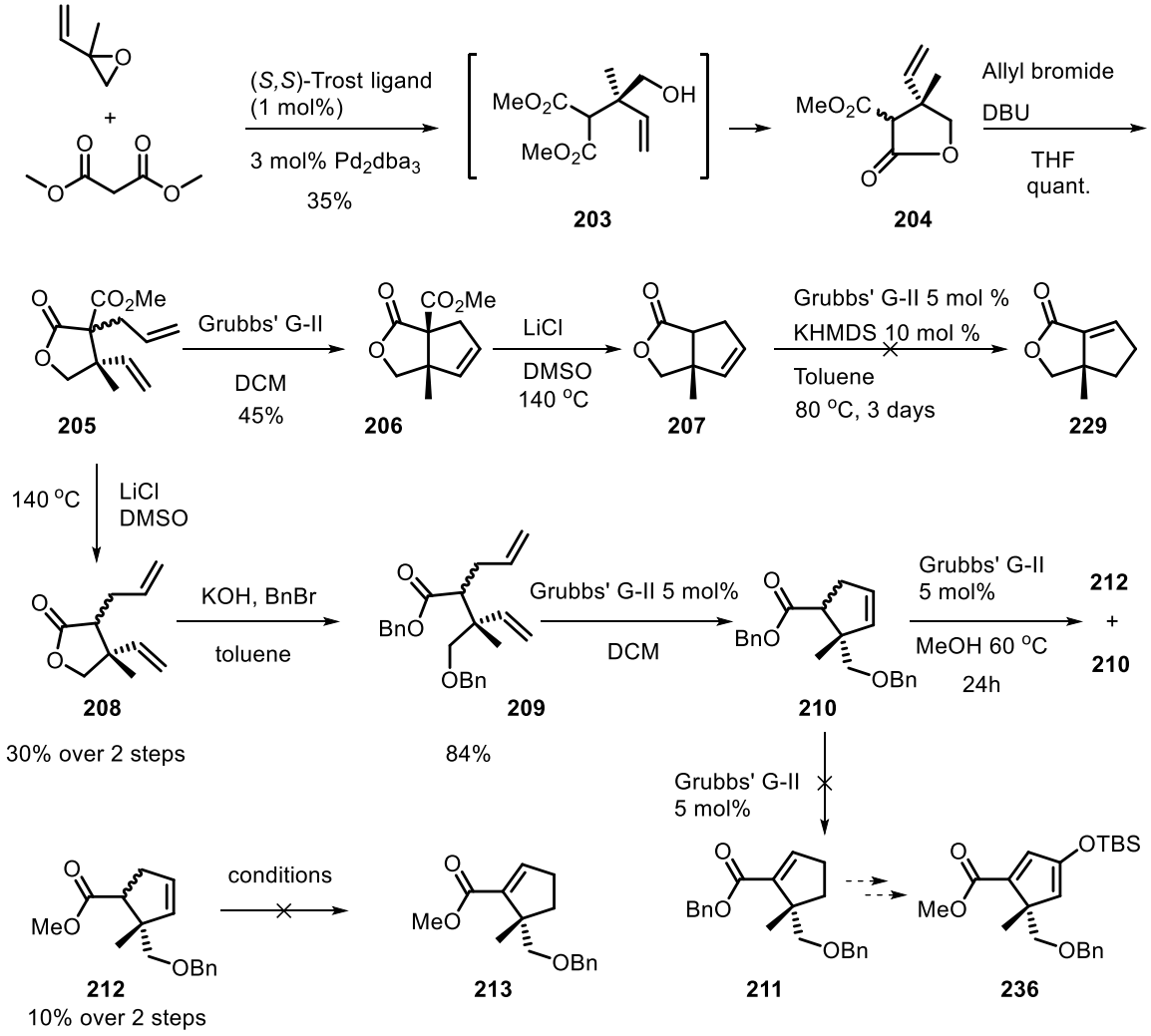


Figure 3.1.1.2: Trost AAA route to cyclopentadiene **236**

Alternatively, to avoid the issue that only one diastereomer of **205** is reactive in the RCM reaction, the lactone ring can be opened prior to the RCM step. Therefore, **205** was decarboxylated to give **208**. Then, **208** was be converted to **209** by an alkylative ring opening with hydroxide and benzyl bromide.[75] As expected, **209** gave a complete RCM conversion to **210**. A tandem alkene isomerization of **210** to α, β-unsaturated ester **211** by switching the RCM solvent from DCM to MeOH and applying heat was attempted. However, the vast majority of **210** remained intact and 10% of an unexpected transesterification product **212** was obtained after prolonged heating. Grubbs' catalyst is known to catalyze alkene isomerizations after RCM reactions,[76] especially when the newly generated alkene is at the β position to a heteroatom. However, in this case, the Grubbs' catalyst does not appear to be able to shift an alkene two bonds away to give a more conjugated structure. A ruthenium catalyst capable of doing long range alkene isomerization[77] has also been taken into consideration. It appears that this type of catalyst works best when converting an alcohol that has a remote alkene to an aldehyde or ketone. There was no reported example in which a remote alkene is shifted to give an α,β-unsaturated ester. Moreover, this type of catalyst usually bears a highly sophisticated ligand that is not trivial to synthesize. Therefore, the isomerization effort to reach **211** and this route were not pursued further.

3.1.2 Routes Containing Pd-Catalyzed Carbonylation Reactions

3.1.2.1 Lipase-Catalyzed Transesterification Route

α-Alkyl-α-hydroxymethylcycloalkanones such as **238** can undergo a lipase-catalyzed kinetic resolution reaction where the (R)-enantiomer of racemic **238** undergoes a transesterification with vinyl acetate faster than its enantiomer, to give the known chiral compound **239** (**Figure 3.1.2.1.1**).[47] Acetate **239** was smoothly synthesized from **238**. However, this route was discontinued due to the concern that a 5,5-disubstituted cyclopentadiene might be problematic in introducing bulky substituents (such as aryl) at the *exo* position of desired bicyclic intermediates. (see Section 2.2.2).

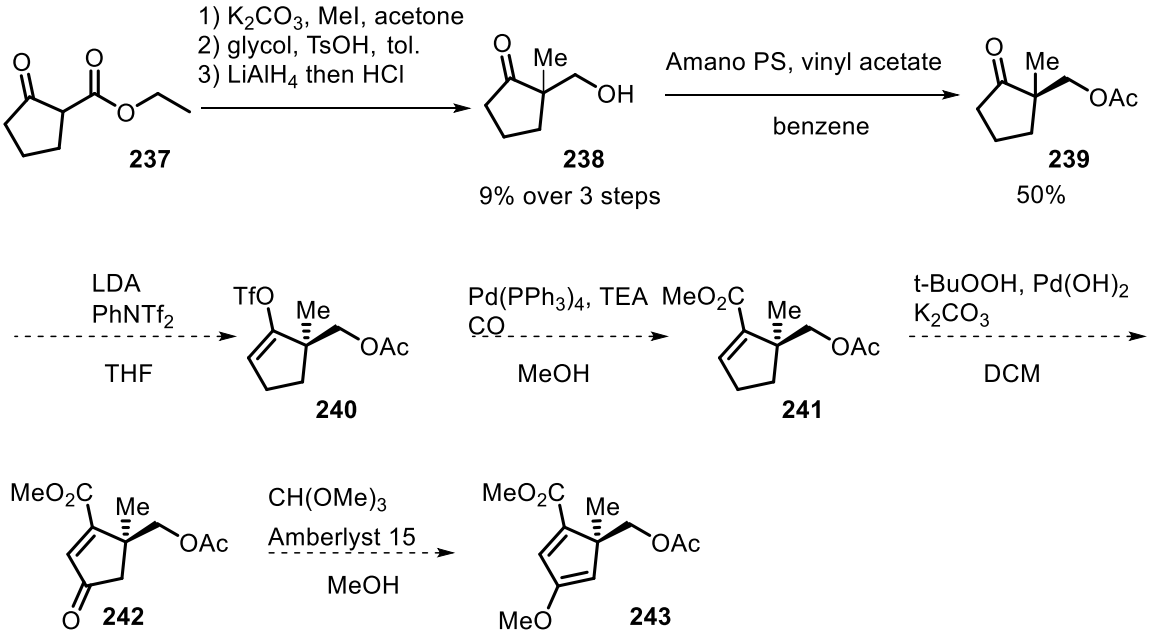


Figure 3.1.2.1.1: Lipase-catalyzed transesterification route

3.1.2.2 Baker's Yeast Reduction Route

In the original synthetic plan discussed in chapter 2.2.1.2, Baker's yeast reduction of **rac-237** was expected to give chiral alcohol **244** and the unreacted (S)-**237**. However, despite the fact that this reaction appeared to be a kinetic resolution, the assumption that (S)-enantiomer of **237** would remain intact in this reaction appeared to be invalid. after the reaction was complete, the crude NMR only showed the existence of **244** without any isolated rac-**237** or (S)-**237**. We speculate that (S)-**237** may have been hydrolyzed by the yeast esterases.

Nonetheless, compound **224** can be used as an enantiomeric starting material to validate the synthetic route to the desired cyclopentadiene. **224** was reduced to the diol,

and the primary alcohol was protected as a TBDPS ether. Next, the intermediate secondary alcohol was oxidized to ketone **245** using DMP, which was then deprotonated by LDA and converted to enol triflate **248** in 21% yield. This is likely due to the low reactivity of McMurry's triflating reagent at low temperature.[78] The Pd-catalyzed carboxylation went smoothly to give α,β-unsaturated ester **249**, which in turn gives a smooth conversion to ketone **250** under allylic oxidation conditions reported by Corey.[49] (**Figure 3.1.2.2.1**)

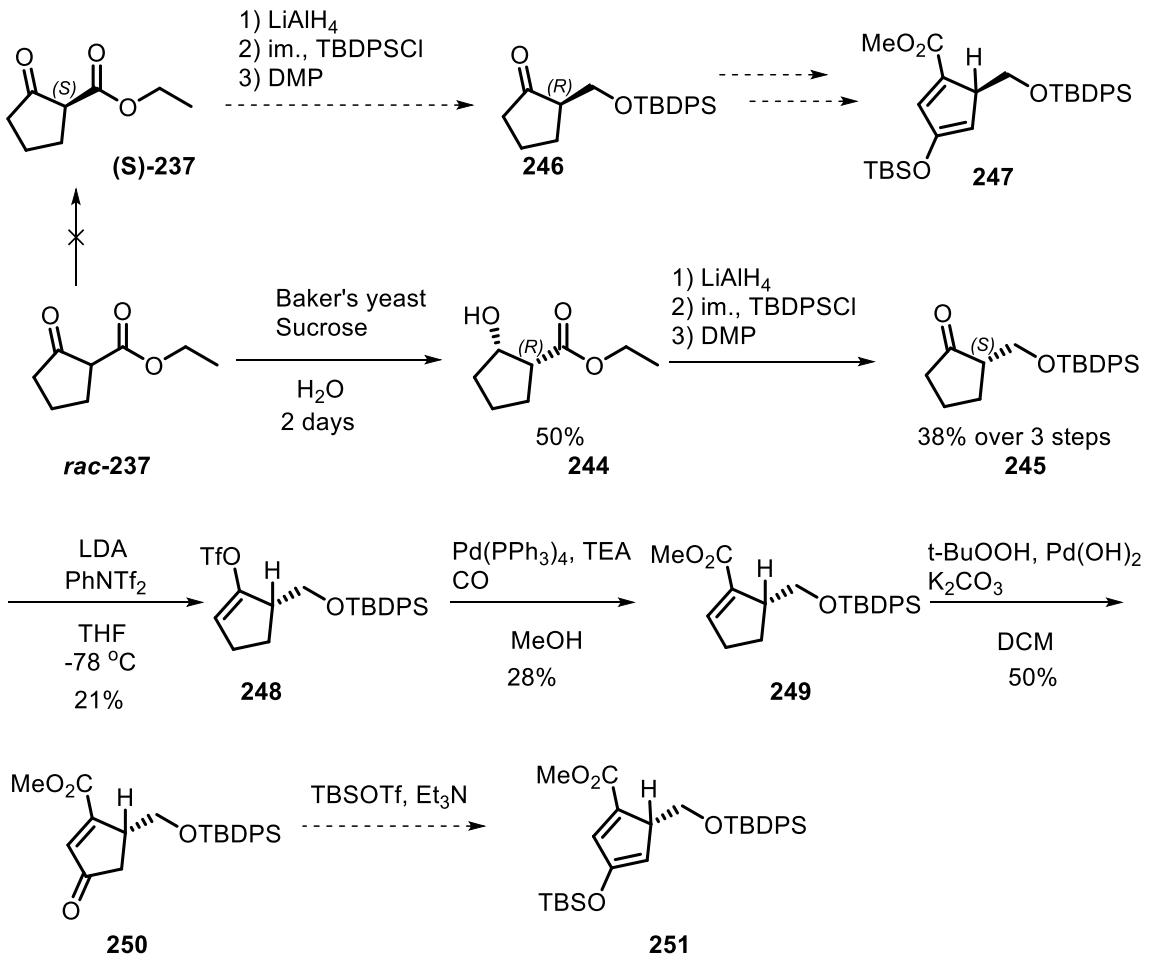


Figure 3.1.2.2.1: Baker's yeast reduction route

3.1.2.3 Racemic Aldol Route

Although an enantioselective synthesis to the desired cyclopentadiene **247** is also possible through an enantioselective aldol reaction between cyclopentanone and formaldehyde to give **246**, to quickly examine the key Diels-Alder reaction, a racemic synthesis of the racemic diene **258** was conducted (**Figure 3.1.2.3.1**). The synthesis started with an aldol reaction of cyclopentanone with formaldehyde to provide a primary alcohol,

which is then protected with TBDPS to give ketone **252**. **252** was treated with McMurry's triflating reagent to give enol triflate **253**. This triflating reaction gave the best result using NaHMDS, other bases such as LDA resulted in a very sluggish reaction. Pd catalyzed carbonylation converts **253** to α, β-unsaturated ester **254**. Allylic oxidation of **254** provided cyclopentenone **255**. Attempts were made to convert **255** into diene **259** using TBSOTf and TEA. However, based on crude NMR, the electron-withdrawing methyl ester seemed to have caused the desired diene to be extremely prone to isomerization, leading to the loss of its stereocenter. Diene **259** could not be trapped in Diels-Alder reactions with an excess of highly active dienophiles such as maleic anhydride and dimethyl acetylenedicarboxylate, presumably due to its low HOMO level. To circumvent this issue, **255** was then reduced to its corresponding diol, the primary alcohol of which was selectively protected with acetate to give **256** as a mixture of diastereomers. PCC oxidation of the secondary allylic alcohol furnished α, β-unsaturated ketone **257**, which reacted smoothly give the much more stable silyloxy diene **258** when subjected to TBSOTf and TEA. Given its acid sensitivity, **258** was not purified before being used in a Diels-Alder reaction. (**Figure 3.1.2.3.1**)

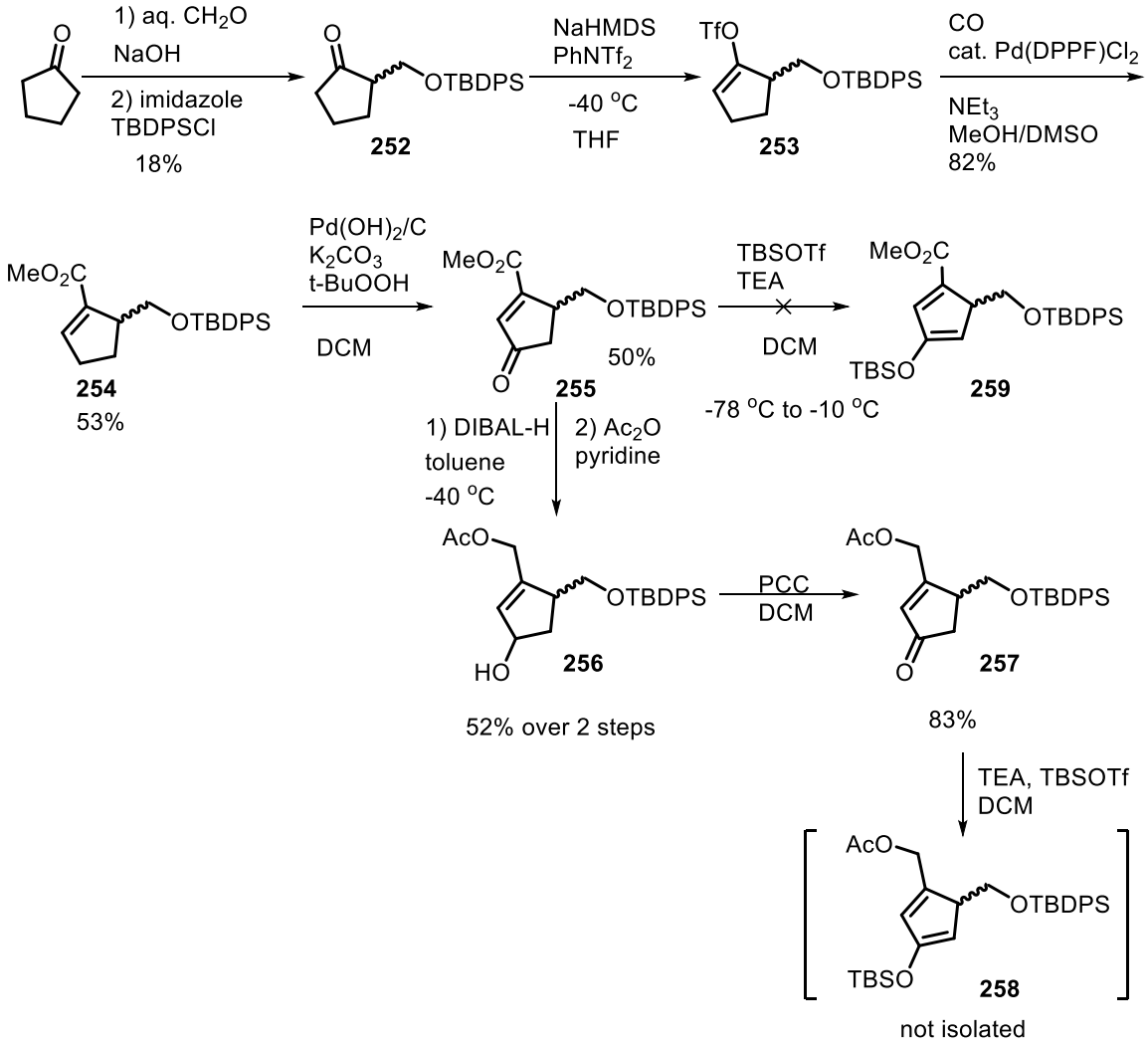


Figure 3.1.2.3.1: Racemic route to silyloxy diene **258**

3.2 Construction of Quaternary Center at C-2 of the Bicyclo[2.2.1]heptane Core

This chapter describes the experimental results in pursuing the synthetic proposal discussed in chapter 2.2.2.

3.2.1 Diels-Alder Reaction

3.2.1.1 Model Reaction

A model reaction is designed to assess the validity and stereoselectivity of a Diels-Alder reaction using 5,5-disubstituted cyclopentadiene with l,l-disubstituted ethylenes (**Figure 3.2.1.1.1**).

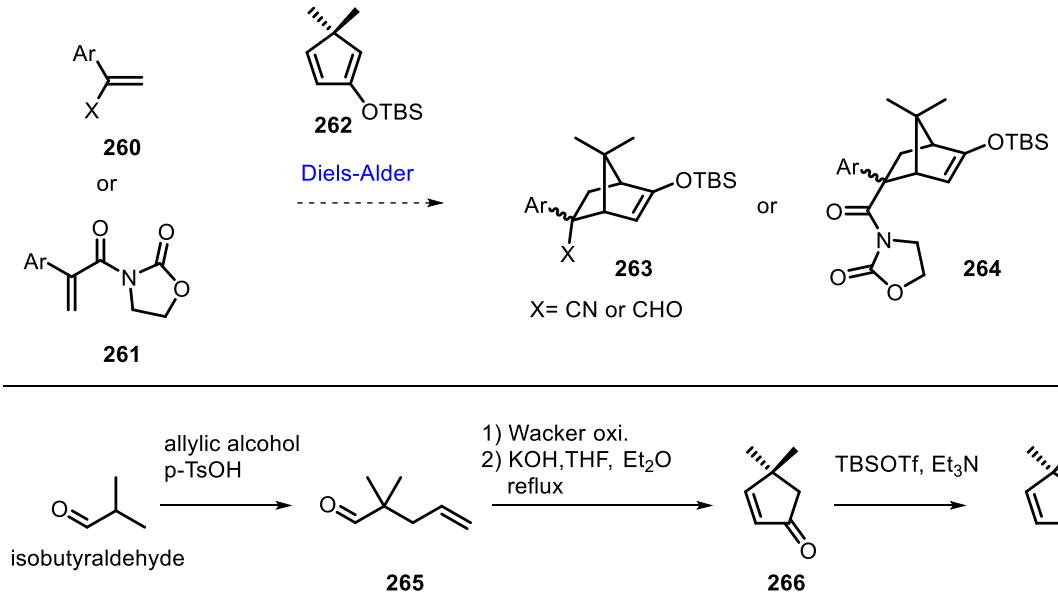


Figure 3.2.1.1.1: Model DA reactions

A simplified 5,5-disubstituted cyclopentadiene **262** can be easily synthesized from isobutyraldehyde using a protocol reported by Hudlicky in Organic Syntheses (**Figure 3.2.1.1.1**).[79] The DA reaction outcomes of the more electron-rich diene **262** with dienophile **260** or **261** were used to decide which diene (e.g. **243** or **258)** should be the first priority

for the desired *endo*-selective Diels-Alder reactions.

The key Diels-Alder reaction was examined using the model molecule cyclopentadiene **262**. **262** was paired with dienophile **270** and **267,** which may be used in synthesizing desired drug candidates. When paired with **267**, even prolonged heating in a sealed tube at 140 ºC was not able to deliver any desired DA products (**Figure 3.2.1.1.2**). When Lewis acids such as BF_3-OEt_2 or $AlCl_3$ were used, diene **262**, a silylenol ether, hydrolyzes to the α, β-unsaturated ketone. However, reaction with dienophile **270** gave a complex mixture when a strong Lewis acid such as $TiCl_4$ was used. The structure of this byproduct has yet to be determined but may be a Michael addition product between **262** and **270**.

Since diene **262** and dienophile **270** had never been reported together in a DA reaction, they were paired with commonly used dienophiles and dienes respectively to ensure that they were capable of doing a normal DA reaction. **262** was paired with maleic anhydride, and the reaction went smoothly at rt to give DA product **269**. **270** was paired with cyclopentadiene, and under conditions reported by Evans,[80] it gave a single diastereomer of the desired DA product **271**. This product is assumed to be *endo* based on the Alder Endo rule, since it is unlikely to give the *exo* product exclusively (**Figure 3.2.1.1.2**).

This series of observations using the model diene **262** suggested that a Diels-Alder reaction using 5,5-disubstituted cyclopentadiene with l,l-disubstituted alkenes is likely to be difficult, although elimination of steric bulk from either side of the pair will make the reaction feasible. Therefore, cyclopentadiene **258** was prioritized for synthesis.

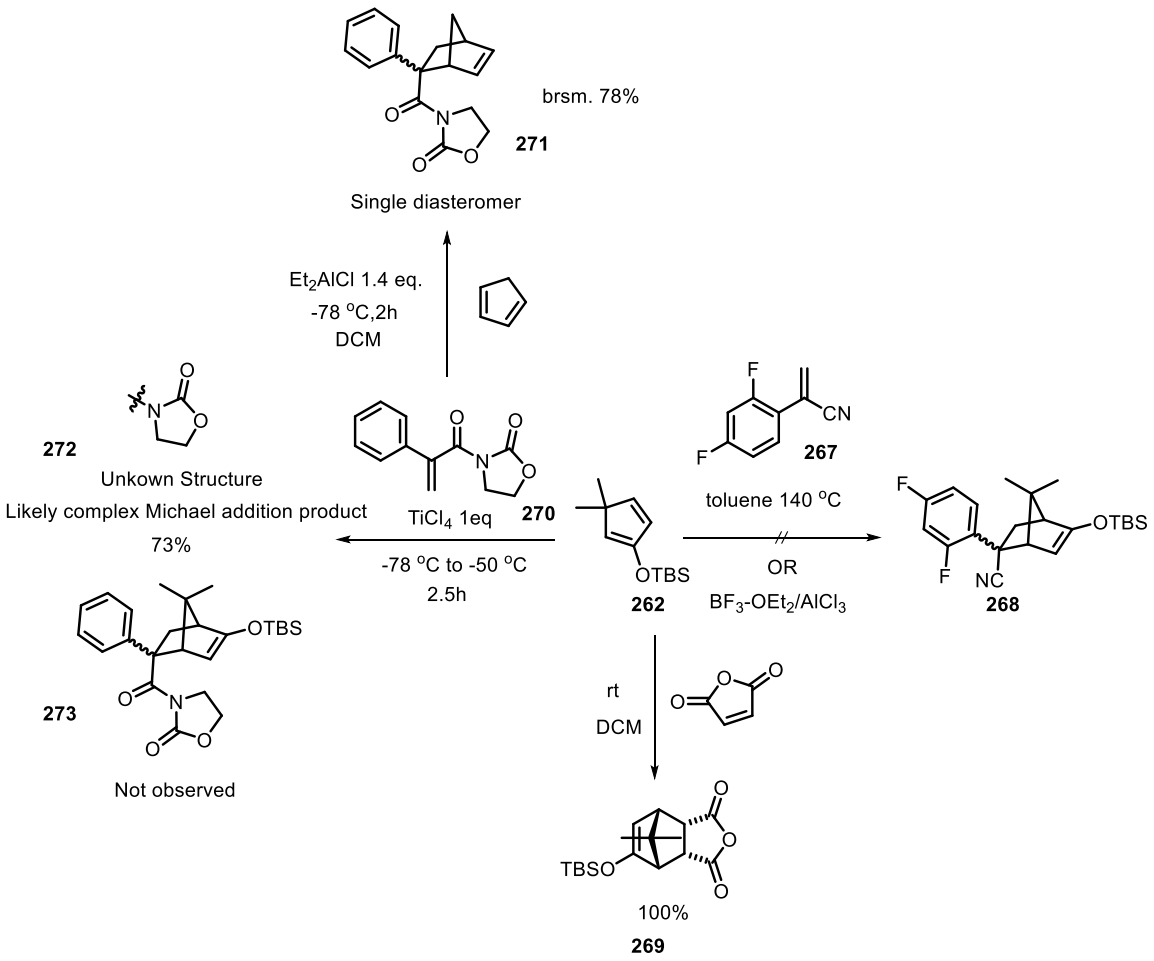


Figure 3.2.1.1.2: Diels-Alder model reaction

3.2.1.2 Diels-Alder Reaction using Functionalized Cyclopentadiene and 1,1-Disubstituted Dienophile

Initially the most desirable target compounds possess a fluorinated aryl group at C-2 exo position (**32**, **Figure 2.1.2**), which we hypothesize should fit into the lipophilic portion of the eEF2 binding pocket occupied by the cyclopentane ring of sordarin. The installation of such aryl substituents has proven to be challenging. The initial attempt used the 2-aryl-acrylaldehyde **274**, but instead of the desired adduct **275**, the unexpected dihydropyran **276** was obtained (**Figure 3.2.1.2.1**). This product could be generated from either a retro-Claisen rearrangement of **275** or an inverse electron demand, hetero Diels–Alder reaction. Davies has published a comprehensive study on a similar system,[55] although there appears to be no reported example of this rearrangement/DA$_{INV}$ with a silyl enol ether. One notable difference in this case comparing with Davies' study is that the dihydropyran was the only product observed. The ratio of the DA adduct and its rearranged product are known to be determined by extent of ring strain and extent of conjugation to the involved carbonyl.[81] In this case, an electron rich silyl enol ether and the electron-withdrawing aryl group may both contribute to this outcome. Silyl ketal **276** is an unstable species that decomposed to racemic aldehyde **277** upon treatment with formic acid in methanol, or sitting in the freezer for a month dissolved in DCM under neutral conditions. The most straightforward way to circumvent the undesired hetero Diels-Alder reaction

appeared to be using the nitrile or ester counterparts of **274**, but unfortunately these dienophiles failed to give any Diels-Alder adducts with **258**.

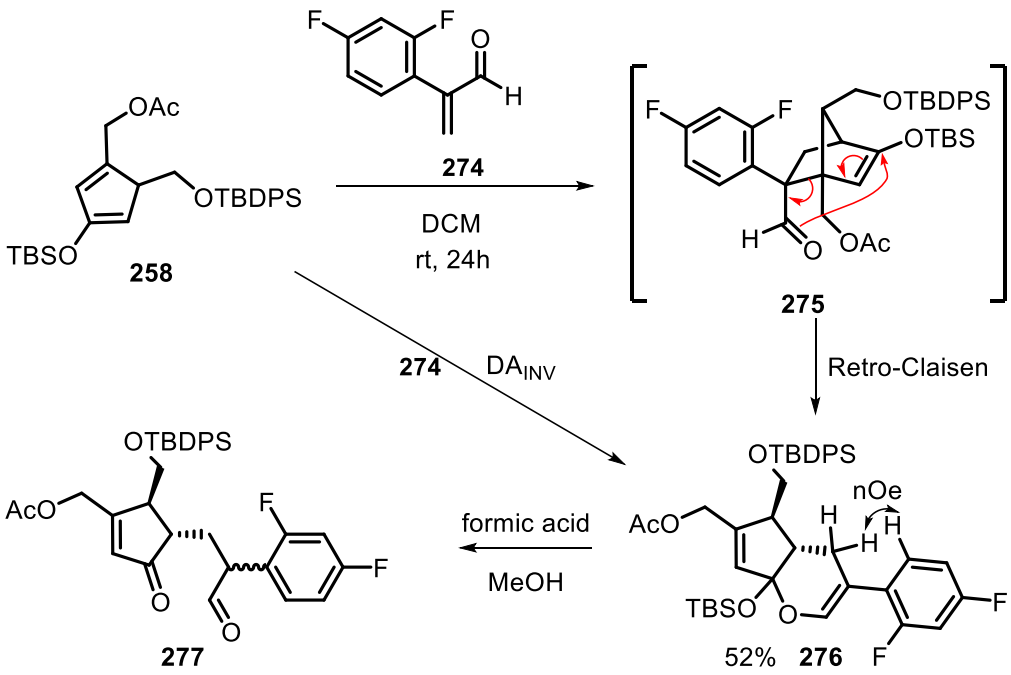
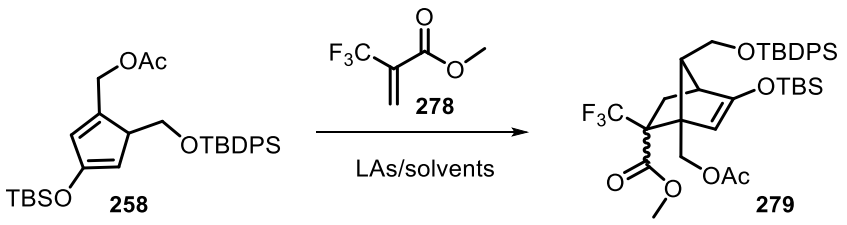


Figure 3.2.1.2.1: Diels-Alder reaction using **258** and **274**

To potentially circumvent the lack of Diels-Alder reactivity of acrylates, α,β-unsaturated ester **278** with a more highly activating trifluoromethyl methyl group to decrease the LUMO level of the dienophile. The trifluoromethyl group is also a desirable substituent for our medicinal chemistry studies due to its lipophilic but metabolically stable profile. After extensive screening of different solvents and Lewis acids, we learned that diene **258** was indeed not compatible with most Lewis or Brønsted acids (e.g.

trifluoroethanol, **Table 3.2.1.2.1**, entry 15), as reported by Gleason for a related OTBS-substituted cyclopentadiene.[82] Lewis acids that were compatible with **258** ($Mg(OTf)_2$, $Mg(ClO_4)_2$, and $Eu(hfc)_3$; entries 4, 18 and 19) did not give any *endo* selectivity. The diastereomers were tentatively assigned based on a report by Ishihara characterizing *endo*/*exo* isomers with the same dienophile.[83] The diastereoselectivity can be tilted slightly by using different solvents; the highest *exo* selectivity was achieved in DCM (**Table 3.2.1.2.1**, entries 8, 9), and the most *endo* selective reaction was in hexanes (**Table 3.2.1.2.1**, entry 11). Due to the low tolerance of **258** to Lewis acids, alternative dienophile/Lewis acid combinations were not pursued to increase the proportion of the desired *endo* cycloadducts, though it was anticipated that bulkier substituents than CF_3 may favor the desired *endo* cycloadducts.

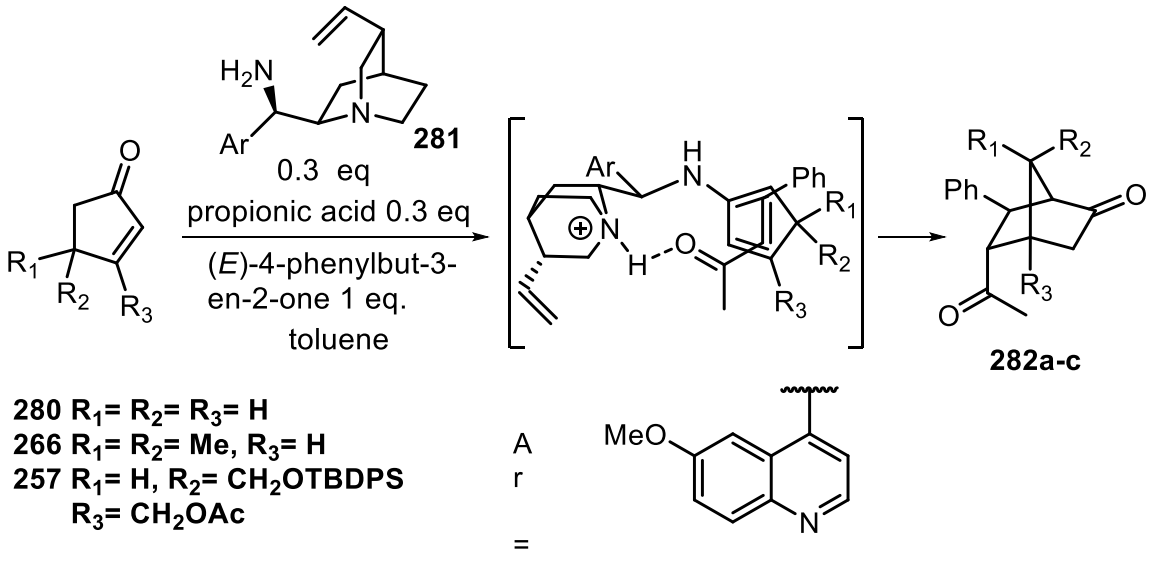


Entry	Solvent	Temp. (ºC)	Lewis Acid[e]	Endo /Exo[b]	Yield[c]
1	DCM	–78 to rt	$InCl_3$	N/A	decomp.
2	DCM	–78 to rt	$ZnBr_2$	N/A	decomp.
3	DCM	–78 to rt	$Yb(OTf)_3$	N/A	decomp.
4	DCM	–78 to rt	$Mg(OTf)_2$	0.75	68%
5	DCM	–78 to rt	$Zn(OTf)_2$	N/A	decomp.
6	DCM	–78 to rt	$Eu(OTf)_3$	N/A	decomp.
7	DCM	–78 to rt	K-10	N/A	decomp.
8	DCM	–78 to rt	–	0.67	83%
9	DCM	rt	–	0.71[d]	40%[d]
10	THF	rt	–	0.82	85%
11	hexanes	rt	–	1.04	96%
12	MeCN	rt	–	0.85	91%
13	acetone	rt	–	0.8	63%
14	MeOH	rt	–	0.93	86%
15	F_3CCH_2OH	rt	–	N/A	decomp.
16	$PhCF_3$	rt	–	0.83	100%
17	EtOAc	rt	–	0.78	74%
18	MeCN	rt	$Mg(ClO_4)_2$	0.87	98%
19	$CDCl_3$	rt	$Eu(hfc)_3$	0.62	trace

[a]Diene was washed with phosphate buffer (pH 7) before using; all experiments were run for 24 h. [b]Diastereomers were assigned based on a previously reported analog,[83] and the ratio was determined with ^{19}F NMR. [c]NMR yield using pentachloroethane as internal standard, unless otherwise specified. [d]Isolated yield. [e]1 eq. except for entry 18 (0.9 eq.) and entry 19 (0.2 eq.). decomp. = diene decomposed to **257**. K-10 = Montmorillonite K-10. $Eu(hfc)_3$ = europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]. rt = room temperature (22–23 ºC).

Table 3.2.1.2.1. Solvent and Lewis acid screening for Diels-Alder using **278**

In order to achieve an *endo*-selective Diels-Alder reaction and avoid the acid sensitivity of diene **258**, the organocatalytic asymmetric Diels-Alder reaction reported by Jørgensen[63] was examined. Using quinidine-derived amine catalyst **281**, this catalyst worked smoothly with 4-unsubstituted cyclopentenone (**Table 3.2.1.2.2**, entry 1), as was reported. However, the scope couldn't be extended to include the 4-substituted cyclopentenone (**Table 3.2.1.2.2**, entry 2, 3). When the C-4 position of the cyclopentenone is disubstituted, the reaction didn't proceed (entry 2), likely because the transition state is disrupted by the steric repulsion between the dienamine intermediate and the dienophile. When the C-4 position is monosubstituted, the dienamine intermediate rearranged to cause the loss of the stereogenic center at C-4 of enone **257** (entry 3), and no cycloaddition products were observed.



Entry	Enone	T/t	Result
1	**280**	60 ºC, 3d	100% conversion to **282a**[a]
2	**266**	60 ºC 3d; 100 ºC, 24h	N.R.[a]
3	**257**	60 ºC, 2d	Decomposed **257**[b]

[a] Determined by GC-MS, [b] Determined by ^{1}H NMR.

Table 3.2.1.2.2: Organocatalytic Diels-Alder reaction using **281**

3.2.2 Double Michael Addition

Inspired by Yamada's reports of stereoselective sequential Michael reactions using enolates generated from 3-alkoxy-cyclopentenones to generate [2.2.1] bicyclic adducts (**Figure 3.2.2.1**),[64] an analogous reaction starting from enone **257** and model enone **266**. These were treated with LDA to give their corresponding lithium enolates, followed by the addition of an initial Michael acceptor. However, all enolates were unreactive in the presence of several Michael acceptors under a number of different conditions (**Table 3.2.2.1**). Despite the fact that the cyclopentanone can be smoothly deprotonated (entry 8),

use of Michael acceptors with different reactivities ranging from methyl 2-(4-fluorophenyl)acrylate to acrylonitrile did not result in any difference. The addition of HMPA (entries 2, 15, 11, 13) or heating (Entry 10–13) were not able to initiate this reaction as well. Upon work up, the cyclopentenones **257**, **266** were recovered. This inactivity could be explained by the lack of an electron-donating alkoxy group at C3 of **257**, **266**. In the case of **266**, the methyl group at C-4 proximal to the approaching Michael acceptor likely prevented its reaction due to steric hindrance (entries 9–11).

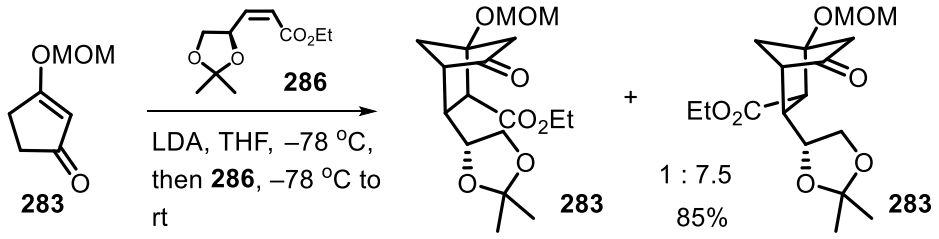
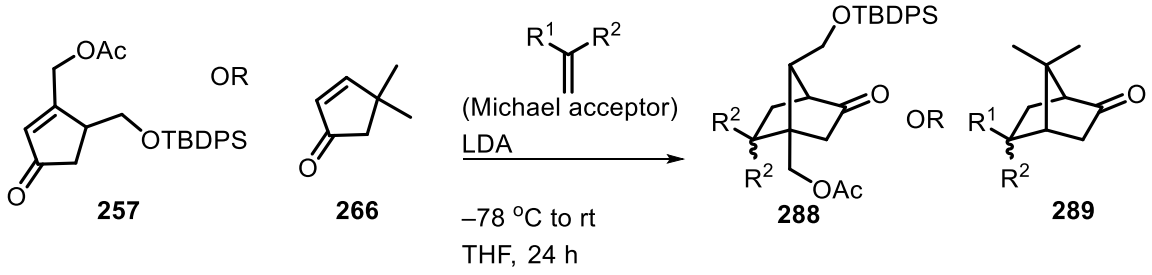


Figure 3.2.2.1 Sequential Michael reaction reported by Yamada[64]

Table 3.2.2.1 Attempted double Michael addition



Entry	enone	Michael acceptor[b]	conditions[a]	additive	result[c]
1	**257**	R^1= 4-FPh, R^2= CO_2Me	A	None	N.R.

2	**257**	R^1= 4-FPh, R^2= CO_2Me	A	HMPA (1 eq.)	N.R.
3	**257**	R^1= 4-FPh, R^2= CO_2Me	A	None	N.R.
4	**257**	R^1= CF_3, R^2= CO_2Me	A	None	N.R.
5	**257**	R^1= CF_3, R^2= CO_2Me	A	HMPA (1 eq.)	N.R.
6	**257**	R^1= CF_3, R^2= CO_2Me	A	None	N.R.
7	**257**	acrolein	A	None	N.R.
8	**257**	none, quenched with D_2O	A	None	deut.[d]
9	**257**	R^1= H, R^2= CO_2Et	A	None	N.R.
10	**257**	R^1= 4-FPh, R^2= CO_2Me	B	None	N.R.
11	**257**	R^1= 4-FPh, R^2= CO_2Me	B	HMPA (1 eq.)	N.R.
12	**257**	R^1= CF_3, R^2= CO_2Me	B	None	N.R.
13	**257**	R^1= CF_3, R^2= CO_2Me	B	HMPA (1 eq.)	N.R.
14	**266**	R^1= H, R^2= CO_2Et	A	None	N.R.
15	**266**	acrylonitrile	A	None	N.R.
16	**266**	R^1= 4-FPh, R^2= CO_2Me	A	None	N.R.

[a]Condition A: Enones were deprotonated at –78 ºC, followed by the addition of the Michael acceptor. All experiments except for entry 8 were kept at –78 ºC for 2 h, then warmed up to rt and stirred for 22 h. Entry 8 was quenched at –78 ºC after LDA deprotonation; Condition B: Enones were deprotonated at –78 ºC, followed by the addition of the Michael acceptor, then warmed up to rt and refluxed for 3h. [b]2 eq. of Michael acceptor were used in entries 1–13, each, and 1.2 eq. in entries 14–16. [c]N.R. = no reaction; [d]deut. = deuteration

of α-carbon confirmed by ^{1}H NMR.

3.2.3 Nucleophilic Trapping of C-2 Cation

The use of a bicyclic[2.2.1]ketone substrate could be advantageous, because it could permit the ready generation of varied aryl-containing analogs (e.g. **290**) via arylmetal 1,2-addition reactions, followed by the conversion of the resulting alcohols to nitriles via intermediate carbocations (**Figure 2.2.2**, **51**). However, one disadvantage of the tertiary alcohol to nitrile conversion is that it may only be high yielding for electron-rich arenes able to facilitate the S_N1-type transformation. Cyanation of a *p*-methoxylphenyl-stabilized tertiary cation has been reported with monocyclic substrates,[66] and there are also several examples of trapping tertiary 2-norbornyl cations with nucleophiles.[67, 84] This strategy was examined by using model systems formed by treating camphor with 4-methoxyphenyl magnesium bromide to generate alcohol **290**, followed by acidic dehydration to generate **291**. These were separately reacted with two different acids and TMSCN (**Figure 3.2.3.1**). Upon treatment with BF_3-OEt_2 and TMSCN, **290** quickly dehydrated and rearranged to give an inseparable mixture of dehydration product **291** and three other inseparable alkene products with GC-MS and NMR analysis consistent with Wagner–Meerwein and Nametkin rearrangements.[85] The desired cyanation product **295** was not observed. Trapping of 2-

norbornyl cation generated from **291** using TfOH[66a] was also not successful at a higher temperature (-20 °C).

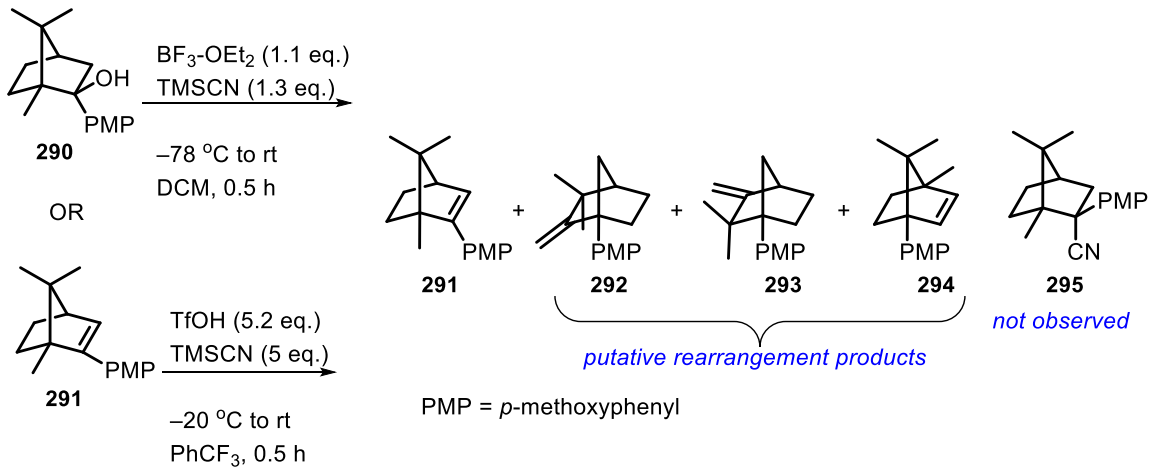


Figure 3.2.3.1 Attempted cyanation of camphor-derived alcohol **290** and alkene **291**.

3.2.4 S_NAr/S_N2 using C-2 Anion

An *endo*-selective S_NAr reaction with 2-cyano-5-norbornene and aryl fluoride reported by Caron suggested a promising path to desirable α-arylated nitriles (**Figure 3.2.4.1**).[65] In this approach, nitriles can be deprotonated with KHMDS and reacted with both electron-rich and electron-poor aryl fluorides, with **297** reported as a single (*endo*), presumably thermodynamic, diastereomer. Nitrile **298** was chosen to examine this approach (**Table 3.2.4.1**). Under Caron's optimal conditions, **298** did not undergo the S_NAr substitution with 1,2-difluorobenzene (entry 1). When forcing conditions were applied (1,2-difluorobenzene as solvent, 115 ºC), only a trace amount of **299a** was observed via

LC-MS, and most of **298** was decomposed, as followed by TLC (entry 2). The substituted bridgehead next to the reaction center has likely obstructed the approach of the arene electrophile. However, alkylation reactions were successful using iodomethane and benzyl bromide as electrophiles with quantitative conversion (entries 4, 5). CN-endo diastereomers were the only products observed.

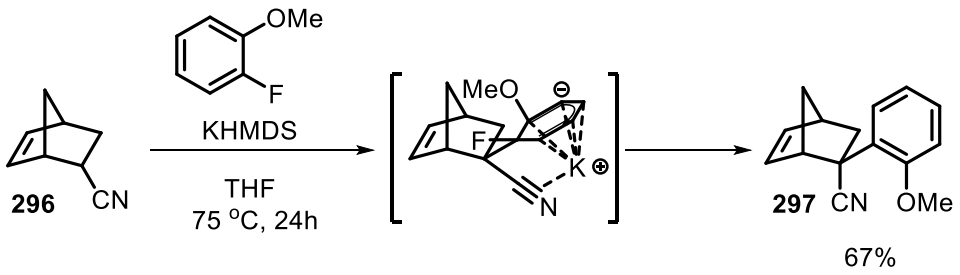
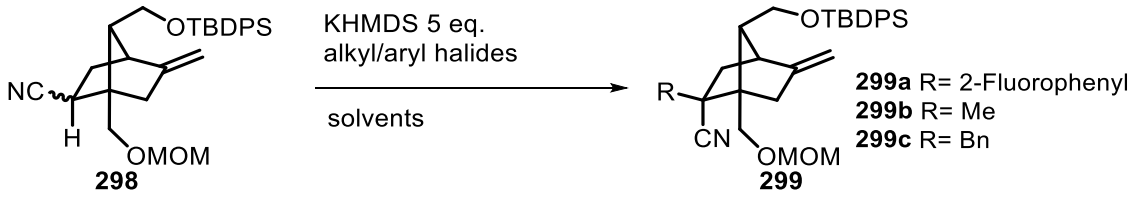


Figure 3.2.4.1 SNAr reported by Caron[65] using 2-cyano-5-norbornene



Entry[a]	Electrophile	Solvent	Conditions	Results
1	1,2-difluorobenzene (4 eq.)	THF	75 ºC, 12 h	N.R.[b]
2	1,2-difluorobenzene (excess)	neat	90–115 ºC, 24 h	trace **299a**[b]
3	1,2-difluorobenzene (50 eq.)	toluene	18-crown-6 (1 eq.), 100 ºC, 12 h	N.R.[b]
4	MeI (45 eq.)	toluene	55 ºC, 12 h	quant. **299b**[c]
5	BnBr (5.5 eq.)	toluene	55 ºC, 12 h	quant. **299c**[c]

[a]To a solution of **298** (2 mg, 0.01 M) was added the indicated amount of electrophile followed by KHMDS. [b]Observed by LC-MS. [c]Estimated NMR yield using pentachloroethane as internal standard. N.R. = no reaction.

Table 3.2.4.1 Aryl/alkylation of secondary nitrile **298**

3.3 Endgame Synthesis to 1st and 2nd Generation Bicyclic Sordarin Analogs

This chapter describes the final stage synthesis toward two generations of bicyclic sordarin analogs, starting from diene **258** described in chapter 3.1.2.3.

3.3.1 1st Generation Bicyclic Sordarin Analog

The first generation bicyclic sordarin (**306**, **Figure 3.3.1.1**) maintained the minimum pharmacophore in a bicyclo[2.2.1]heptane skeleton and possessed a pentyl group as the glycone substituent. This structure was designed mainly for the purpose of quick

access and validation of a bicyclic sordarin analog. Therefore, the C-2 position was kept as a secondary nitrile instead of a tertiary nitrile/aldehyde.

The synthesis commenced with a Diels-Alder reaction using silyloxy diene **258** and acrylonitrile which furnished the norbornene core **300** with approximately 1:1 d.r. The TBS enol ether of **300** was selectively hydrolyzed to give ketone **301**. The acetate of **301** was then hydrolyzed to give its corresponding primary alcohol. At this stage the two diastereomers **302a** and **302b** were separated by chromatography, the stereochemistry was assigned based on NMR analysis of **302b**. As shown in Figure 3.3.1.1, in **302b**, H_c and H_b can be differentiated by observing their coupling constant with bridgehead proton H_d. No coupling constant will be observed between H_b and H_d due to a dihedral angle approaching 90°.[86] $^3J_{ab}$ (9.2 Hz) is consistent with the cis coupling reported by Williamson for a nitrile-substituted bicyclo[2.2.1]heptene (9.3 Hz).[87] The primary alcohol of the CN-endo diastereomer **302a** was then protected with THP to give **303**. An efficient Wittig reaction converting **303** to **304** required generation of ylide under 90 °C. This was likely due to the steric bulkiness from the neighboring TBDPS. To install the pentyl group as a glycone substituent, TBDPS protected primary alcohol in **304** was cleaved by TBAF followed by an alkylation to give **305**. Finally, the THP protecting group was cleaved and oxidized to a carboxylic acid to give the final bicyclic sordarin analog **306**.

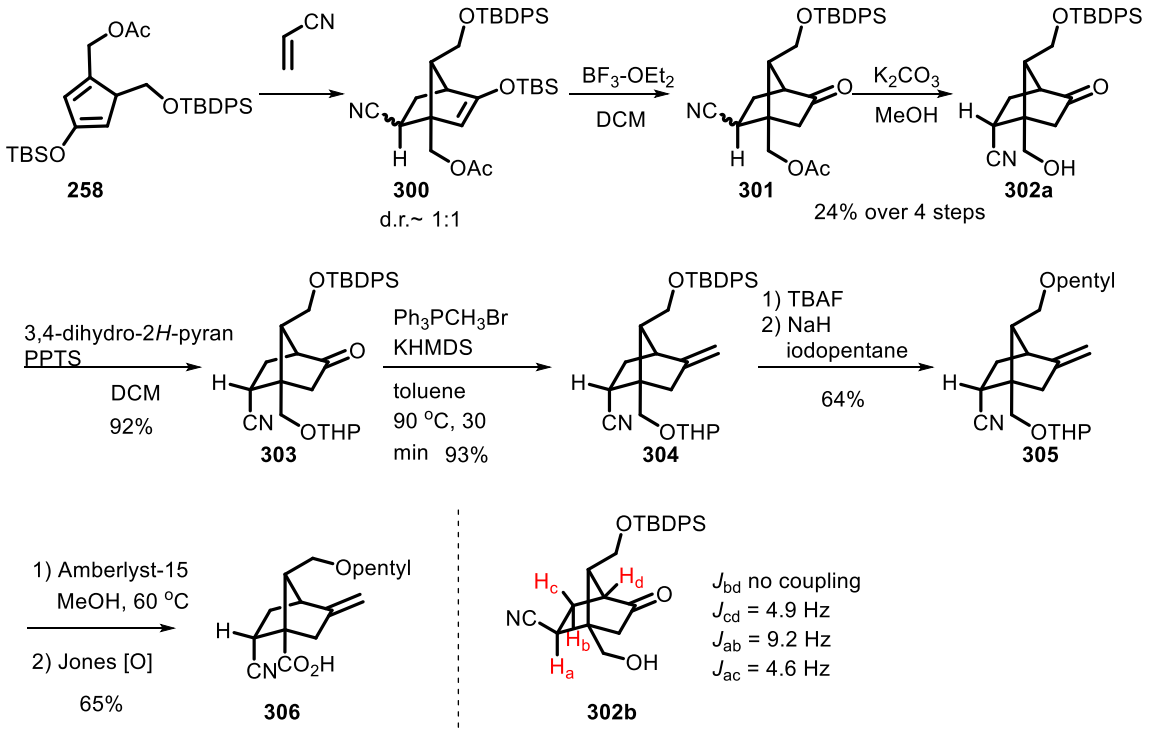


Figure 3.3.1.1 Synthesis of the 1st generation bicyclic sordarin

3.3.2 2nd Generation Bicyclic Sordarin Analogs

The inactivity of the first-generation analog (See chapter 3.4) led to the hypothesis that maybe a tertiary center at C-2 and/or a sophisticated glycone is needed for high antifungal potency. Therefore, analogs with these two traits **312** and **313a-c** were synthesized (**Figure 3.3.2.1**).

The synthesis commenced with the intermediate **302** from the first-generation synthesis. The primary alcohol of **302** was first oxidized to carboxylic acid and protected as an PMB ester to give ester **307**. **307** was then subjected to Wittig reaction to give olefin

308. As was anticipated from the alkylation results discussed in chapter 3.2.4, direct alkylation of **308** at the C-2 position gave the CN-endo product **309a-c** exclusively. After a TBAF deprotection of **309a-c**, the stereochemistry was confirmed by observing nOe between the C-2 alkyl groups and its neighboring protons as depicted in **310a-c**. To conduct the glycosidation, the primary alcohol was first converted into its corresponding triflate **311a-c**, then reacted with deprotonated **314** or **315** to give final target compound **312** and **313a-c**. The newly formed anomeric bond in **313a-c** from this substitution was tentatively assigned as equatorial based on NMR analysis on the chemical shift (4.5-4.6 ppm) and coupling constants (4-6 Hz) of the anomeric proton from known analog.[88] This result is also consistent with a report from Schmidt,[89] in which he demonstrated that sodium alkoxide of glucopyranose prefers equatorial alkylation in room temperature. Since this is a racemic synthesis, the final compounds each represent a racemic mixture of diastereomers.

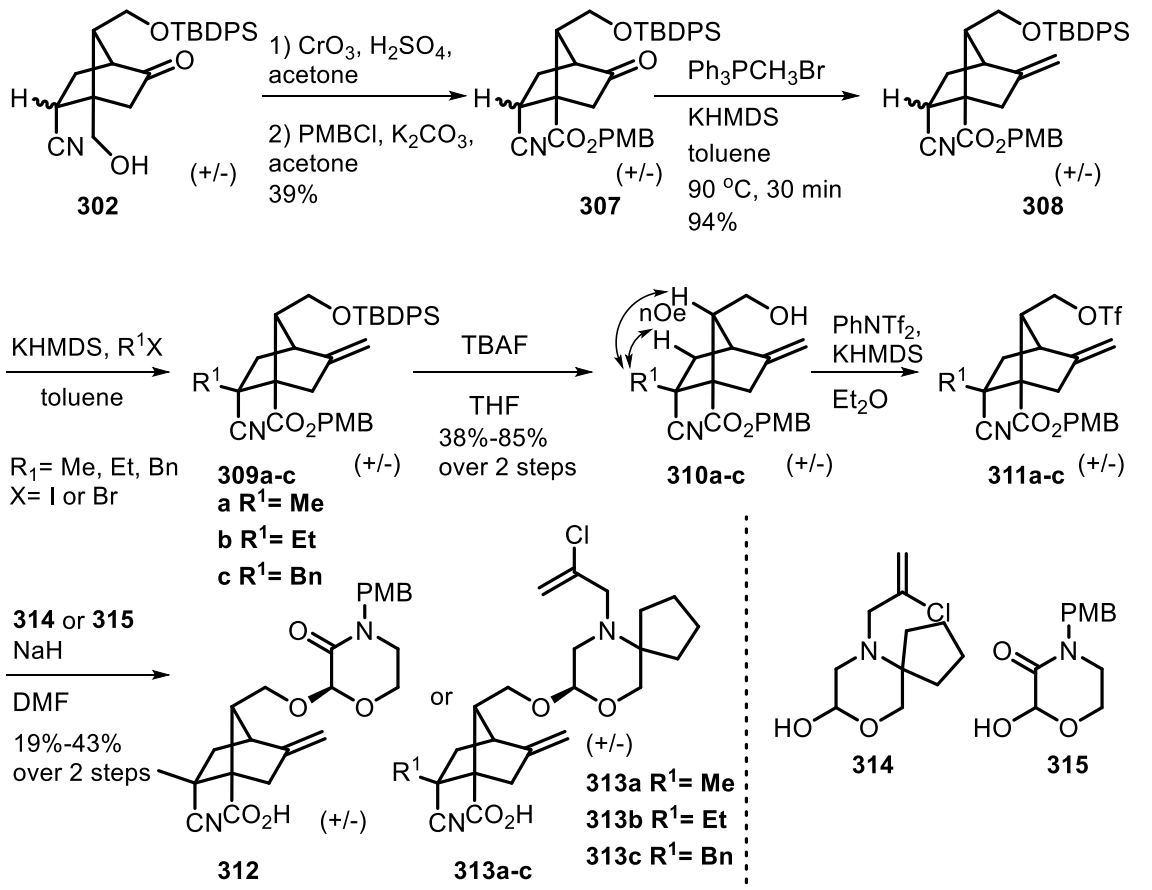


Figure 3.3.2.1 Synthesis of the 2nd generation bicyclic sordarin analogs

3.4 Biological Results and Docking Studies

The antifungal activity of compounds **306**, **312**, **313a-c** were assessed against *C. albicans, C. parapsilosis, P. variotii,* and *A. fumigatus*. No antifungal activities were observed at 8 µg/mL for compounds **306**, **312**, **313a** and **313b**. The assay for **313c** only went up to 4 µg/mL, and no antifungal activities were observed as well. (**Figure 3.4.1**) Although it should be taken into consideration that these tested samples each contained four isomers and only one is supposed to be active, it nonetheless suggested that their

potencies are not in the same range as optimal analogs such as azasordarin **123** (**Figure 2.2.3.1**).

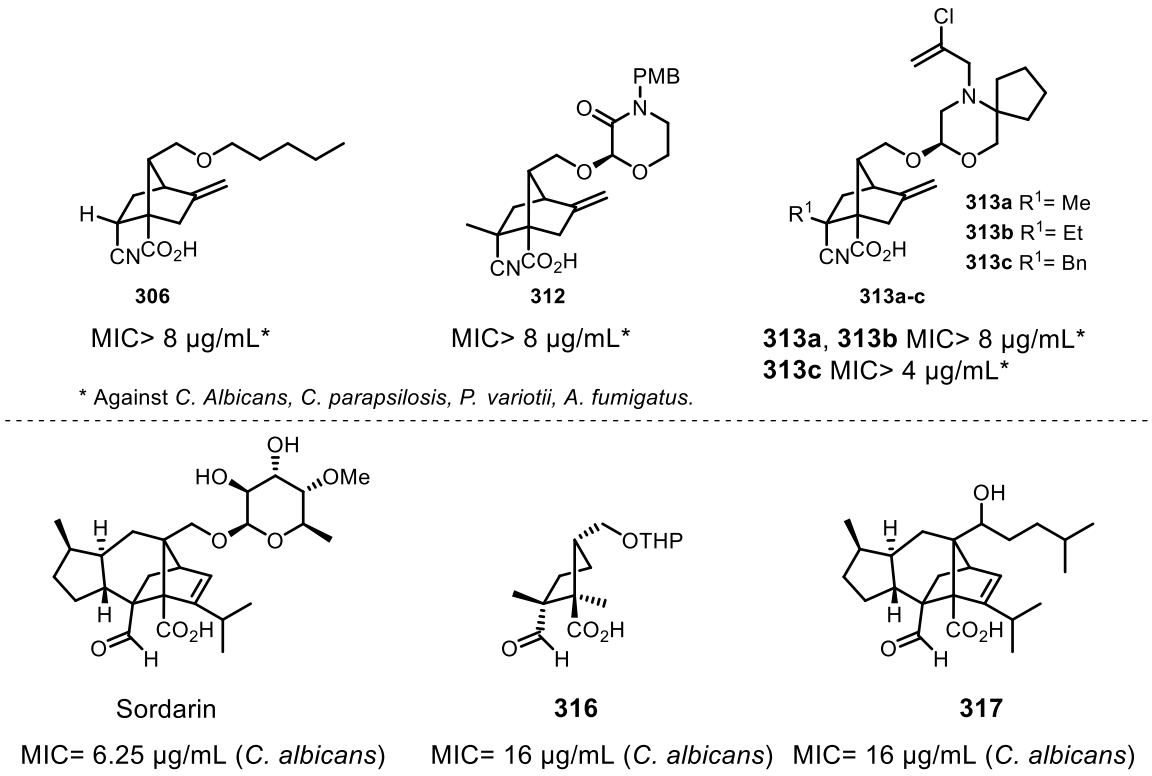


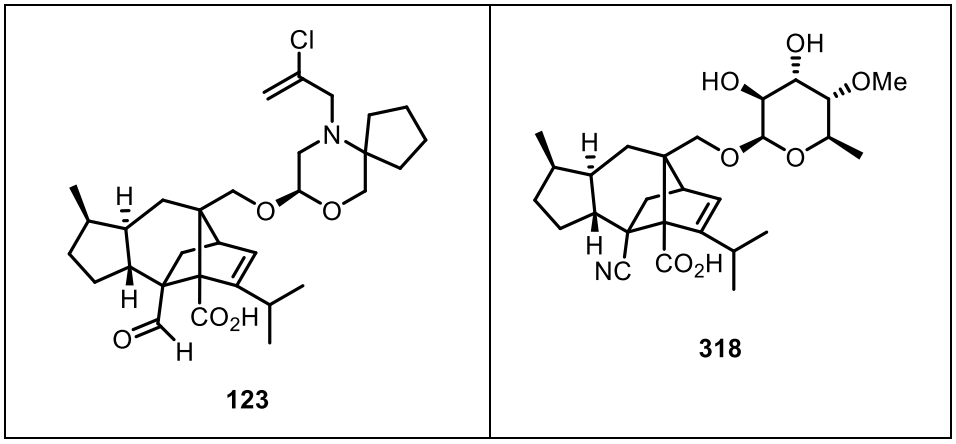
Figure 3.4.1 Antifungal assay result of **306**, **312**, **313a-c** and reported low-potency compound **316**,[12] **317**.[90]

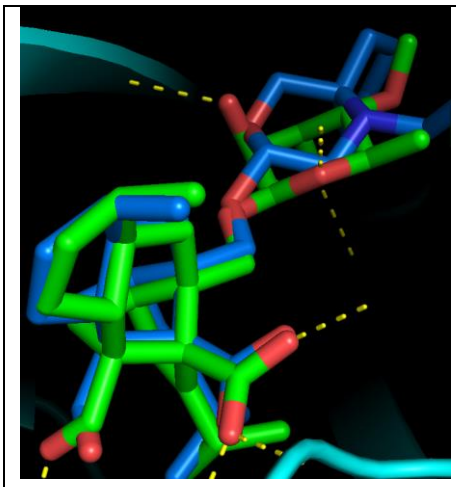
The inactivity of these analogs led to their examination with docking studies. The docking results are summarized in Table 3.4.1 below. The study is mainly aimed to elucidate the extent of the carboxylic acid–aldehyde/nitrile pharmacophore's deviation from the parent sordarin molecule. Each picture shows a pose of sordarin (green) in eEF2

binding site that is identified from the X-ray structure,[15] and a superimposing sordarin analog (various colors except green), whose poses were calculated by Molecular Forecaster software.[91]

The sordarin molecule was docked first to benchmark the software. The resulting pose is in great agreement with the reported crystal structure (last row, **Table 3.4.1**). The high-potency azasordarin reported by BMS[40] superposed its pharmacophore well with the sordarin molecule (**123**, **Table 3.4.1**). This suggests that the docking calculation is consistent with experimental data. The substitution of the aldehyde group in sordarin to a nitrile did not appear to have a major impact in the poses of the molecules in eEF2 (**318**, **Table 3.4.1**). This is also consistent with SAR studies reported by Merck.[68] However, bicyclic sordarin analogs **313b**, **313c** and **319** showed major deviations in the positioning of the nitrile/carboxylic acid pharmacophore from the parent sordarin molecule. The monocyclic analog **316** also gave similar poses with the second-generation analogs, with the carboxylic acid deviating largely from its counterpart of the parent molecule. These results could be attributed to two possibilities: The deletion of the C1-C2-C7 embedded ring, or the deletion of the isopropyl group and the introduction of a terminal alkene. To examine these hypotheses, analogs **320–324** were docked. The deletion of an isopropyl group and the introduction of a terminal alkene on the bicyclo[2.2.1]heptane (**320**, **321**) did

not result in distortion of the molecule's optimal pose and the docking scores are very close to genuine sordarin. The deletion of the cyclopentane ring in sordarin also caused no major pharmacophore deviation (**322**). In addition, the C1-C2-C7 embedded ring can be changed from 6-membered to 5-membered without a major impact on the poses (**323**, **324**). In conclusion, the docking study suggests that a more rigid multicyclic ring system with a 5 or 6-membered ring enclosing C1-C2-C7 may be essential to keep the pharmacophore in its optimal position when bound to eEF2.





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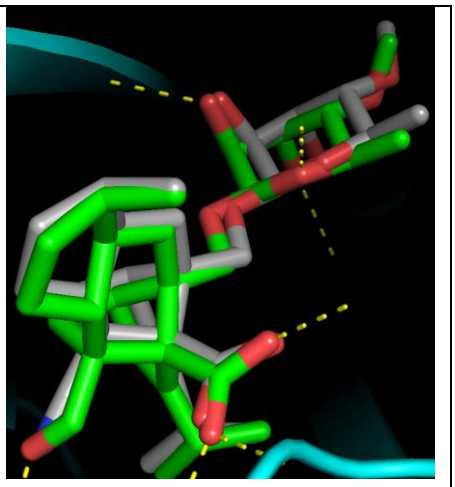

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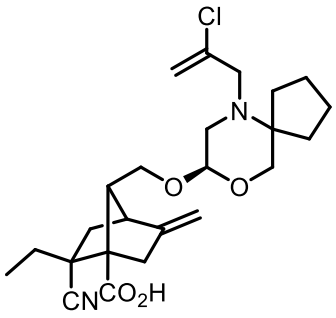

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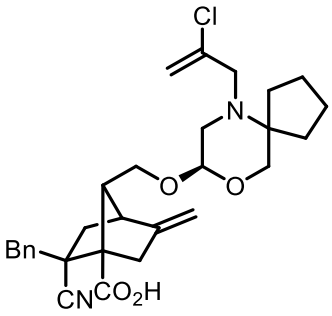

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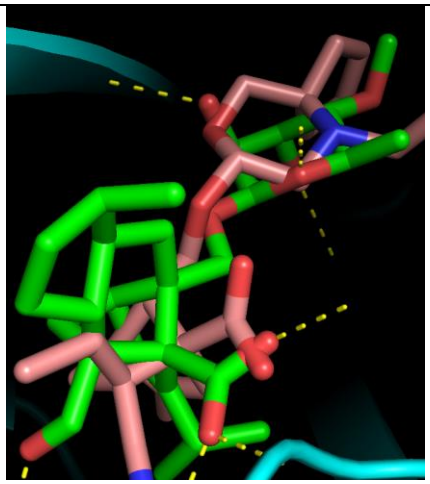

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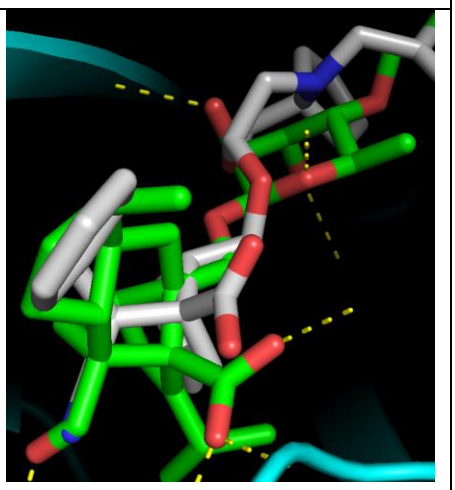

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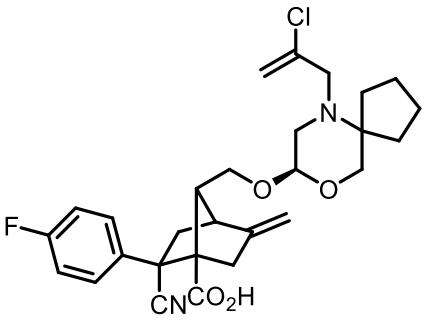

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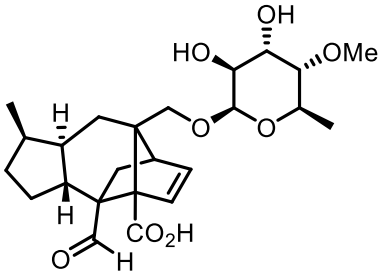

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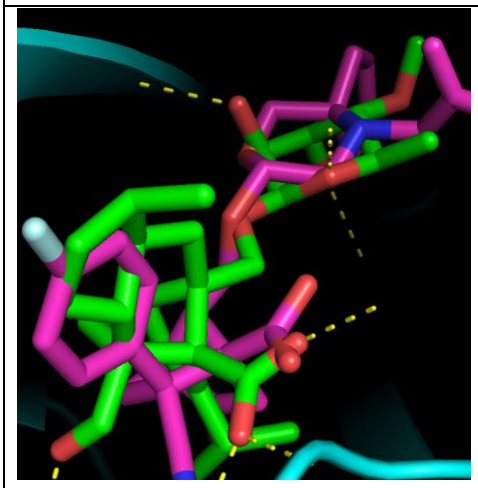

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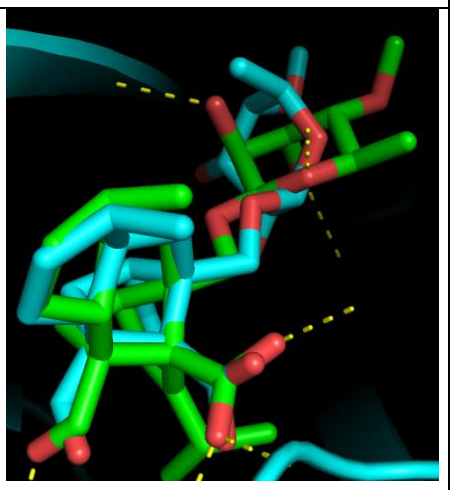

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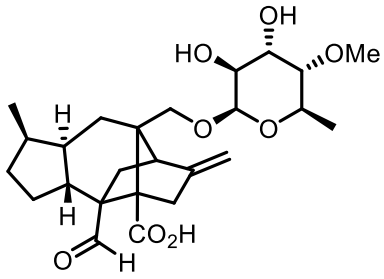

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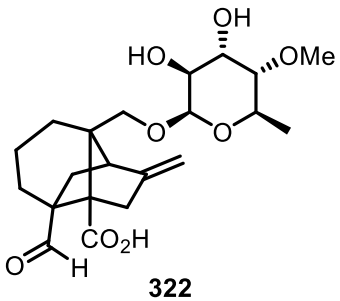

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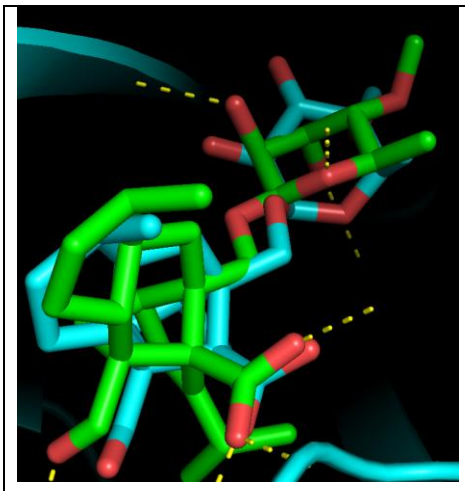

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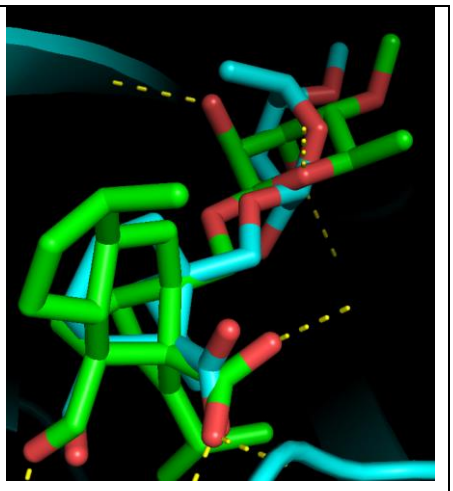

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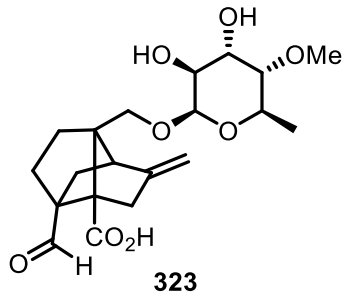

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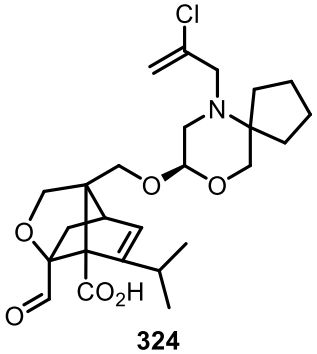

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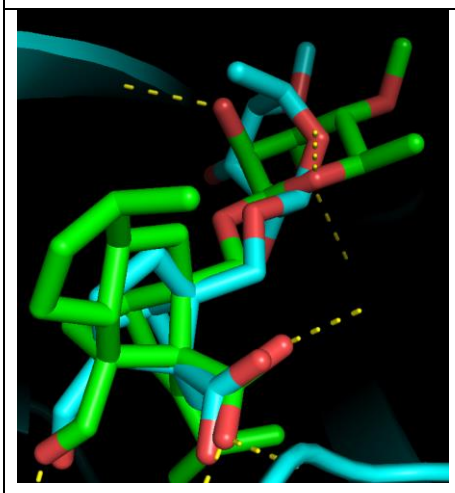

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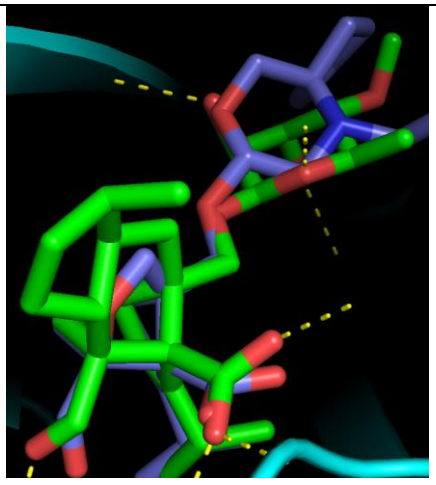

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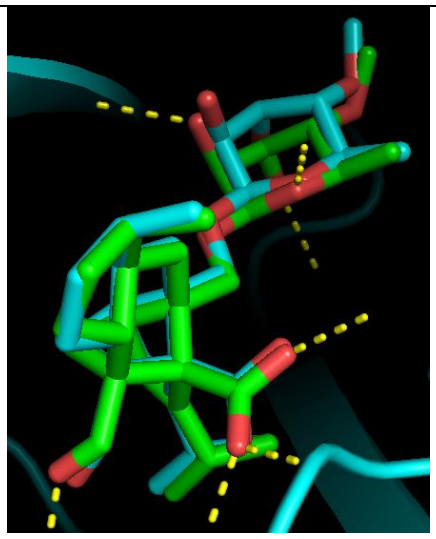
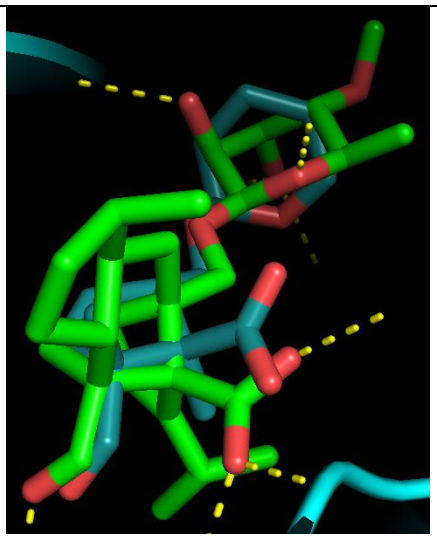
Sordarin	316
	
Score: -30.097	Score: -20.836

Table 3.4.1 Docking results of sordarin analogs with eEF2. Sordarin x-ray structure is shown in green, and lowest energy poses of docked analogs are shown in alternative colors

3.5 Future Work

Based on the antifungal testing of **306**, **312**, and **313a-c**, and the docking studies described in Chapter 3.4, it is hypothesized that a rigid 5 or 6-membered ring embedding C1-C2-C7 of the bicyclo[2.2.1]heptane core may be needed for the carboxylic acid-aldehyde/nitrile pharmacophore to assume optimal orientations when binding eEF2.

Therefore, two strategies to introduce such a rigid ring system are proposed.

A synthesis from (S)-camphor to introduce a 5-membered ring is proposed in Figure 3.5.1. This strategy could provide an enantiopure sordarin analog from a cheap starting material. Trans-π-bromocamphor **325** can be prepared from a known protocol using (S)-camphor.[92] A substitution using BnOH will give benzyl ether **326**. Despite the fact that the primary bromide is next to a quaternary center, a S_N2 reaction is feasible at this position as was demonstrated in Corey's report.[92b] Chelate-directed C-H activation using oxime reported by Sanford[93] could be used to oxidize the bridgehead methyl group to give acetate **327**, and the oxime can then be hydrolyzed to give ketone **328**. The acetate of **328** is then cleaved and oxidized to carboxylic acid, followed by formation of the *t*-butyl ester **329**. Cyanohydrin **330** can then be derived from ketone **329** by using TMSCN as a cyanide source, with related reactions furnishing the desired CN-*endo* diastereomer in at least a 2:1 ratio.[94] Alcohol **330** will then be subjected to Suárez oxidative cyclization to give ether **331**.[95] The benzyl protected primary alcohol will then be released to give **332**. Following the same glycosidation procedure described in chapter 3.3.2, a final testable nitrile **333** can be obtained, and it can be optionally reduced to the aldehyde analog **334**.

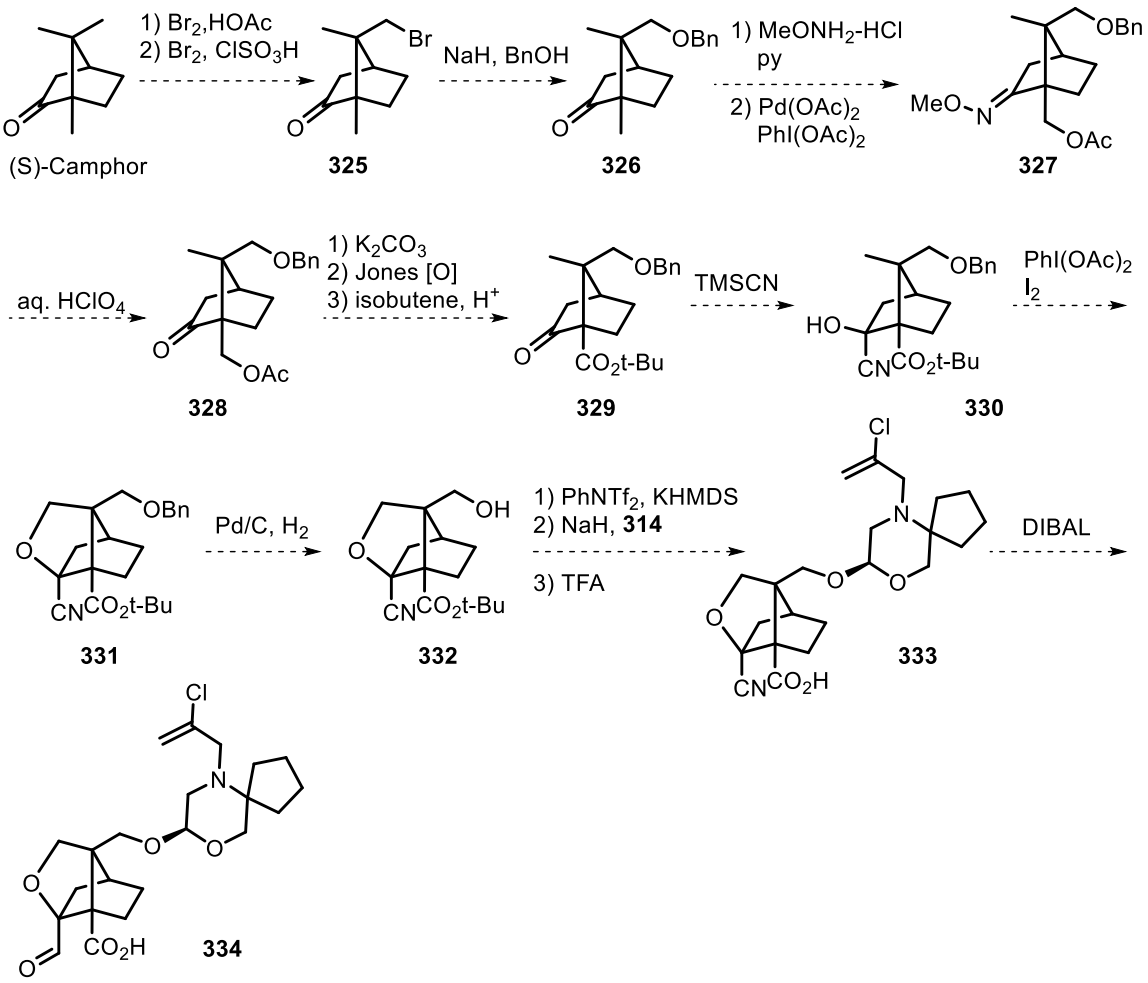


Figure 3.5.1 Proposed synthetic scheme for analogs with C1-C2-C7 embedded 5-membered ring

Another strategy which could introduce a C1-C2-C7 embedded 6-membered ring can be taken by using secondary nitrile **308** (**Figure 3.5.2**). **308** was a key intermediate described in the 2nd-generation analog synthesis. A direct alkylation of **308** with PMBBr is expected to happen exclusively on the *exo*-face, giving tertiary nitrile **336**. The TBDPS protected alcohol will then be released and oxidized to aldehyde **337**. Tollens conditions

will convert **337** to diol **338**.[96] The primary alcohol *cis* to the PMB group will be able to add to the oxidized benzylic position upon treatment with DDQ. Trauner has reported a similar example.[96a] This conversion will furnish a C1-C2-C7 embedded 6-membered ring giving ether **339**. Following the same glycosidation procedure described in chapter 3.3.2. glycone **314** can be installed to give the final sordarin analog **340**.

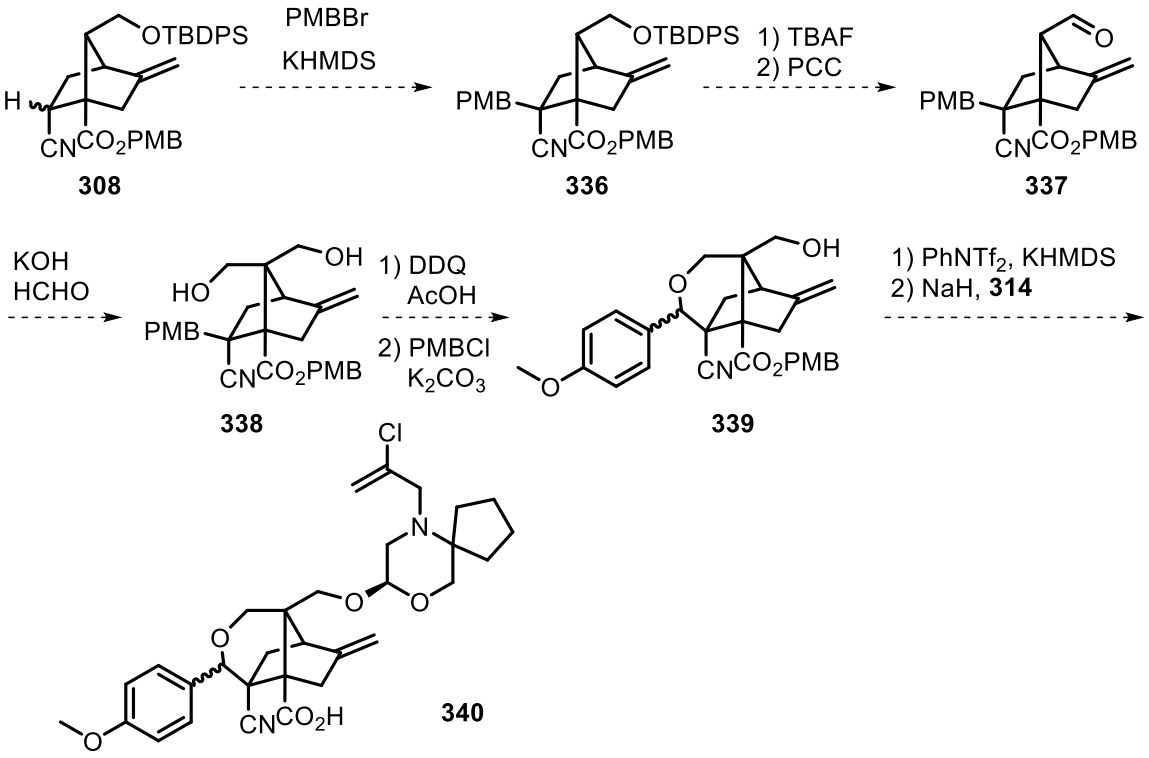


Figure 3.5.2 Proposed synthetic scheme for analogs with C1-C2-C7 embedded 6-membered ring

4.0 Experimental Procedures and Characterization Data

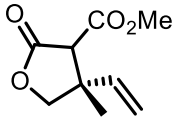
General Information. Unless otherwise noted, all reagents and solvents, including anhydrous solvents, were purchased from commercial vendors and used as received. Reactions were performed in ventilated fume hoods with magnetic stirring and heated in oil baths, unless otherwise noted. Reactions were performed in air, unless otherwise noted. Chilled reactions (below –10 °C) were performed in an acetone bath in a vacuum dewar, using a Neslab CC 100 immersion cooler. Unless otherwise specified, reactions were not run under N_2 atmosphere. Deionized water was purified by charcoal filtration and used for reaction workups and in reactions with water. NMR spectra were recorded on Varian 300 MHz or 400 MHz spectrometers as indicated. Proton and carbon chemical shifts are reported in parts per million (ppm; δ) relative to tetramethylsilane (^{1}H δ 0), or $CDCl_3$ (^{13}C δ 77.16), $(CD_3)_2CO$ (^{1}H δ 2.05, ^{13}C δ 29.84), d_6-DMSO (^{1}H δ 2.50, ^{13}C δ 39.5), or CD_3OD (^{1}H δ 3.31, ^{13}C δ 49.00). NMR data are reported as follows: chemical shifts, multiplicity (obs = obscured, app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex overlapping signals); coupling constant(s) in Hz; integration. Unless otherwise indicated, NMR data were collected at 25 °C. Filtration was performed by vacuum using VWR Grade 413 filter paper, unless otherwise noted.

Analytical thin layer chromatography (TLC) was performed on Agela Technologies glass plates with 0.20 mm silica gel with F254 indicator. Visualization was accomplished with UV light (254 nm) and $KMnO_4$ stain, unless otherwise noted. Flash chromatography was performed using Biotage SNAP cartridges filled with 40-60 μm silica gel on Biotage Isolera automated chromatography systems with photodiode array UV detectors. Unless otherwise mentioned, columns were loaded with crude compounds as DCM solutions. Tandem liquid chromatography/mass spectrometry (LC-MS) was performed on a Shimadzu LCMS-2020 with autosampler, photodiode array detector, and single-quadrupole MS with ESI and APCI dual ionization, using a Peak Scientific nitrogen generator. Unless otherwise noted, a standard LC-MS method was used to analyze reactions and reaction products: Phenomenex Gemini C18 column (100 x 4.6 mm, 3 μm particle size, 110 A pore size); column temperature 40 °C; 5 μL of sample in MeOH or CH_3CN at a nominal concentration of 1 mg/mL was injected, and peaks were eluted with a gradient of 25−95% CH_3CN/H_2O (both with 0.1% formic acid) over 5 min., then 95% CH_3CN/H_2O for 2 min. Purity was measured by UV absorbance at 210 or 254 nm. Preparative liquid chromatography was performed on a Shimadzu LC-20AP preparative HPLC with autosampler, dual wavelength detector, and fraction collector. Samples purified by preparative HPLC were loaded as DMSO solutions. Chemical names were generated

and select chemical properties were calculated using either ChemAxon Marvin suite or ChemDraw Professional 15.1. NMR data were processed using either MestreNova or ACD/NMR Processor Academic Edition software. High-resolution mass spectra (HRMS) were obtained at the University of Cincinnati Environmental Analysis Service Center (EASC) with an Agilent 6540 Accurate-Mass with Q-TOF. Catalyst **281** was prepared according to a published protocol.[97]

4.1 Cyclopentanone Synthesis

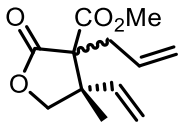
4.1.1 Trost AAA Route



204

Methyl (4S)-4-methyl-2-oxo-4-vinyltetrahydrofuran-3-carboxylate. To a 100 mL round bottom flask was added $Pd_2(dba)_3$ (140 mg, 0.153 mmol), (S,S)-Trost Ligand (316.8 mg, 0.459 mmol), and a stirbar. The flask was then placed under reduced pressure (vacuum pump) for 10 seconds and refilled with argon. This purging process was repeated for 5 times, after being placed under an argon atmosphere, dry DCM (30 mL) was added and the resulting dark purple solution was stirred at room temperature until it turned into a deep

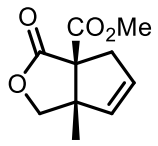
orange color (5 min). During this time, neat dimethyl malonate (1.93 mL, 16.82 mmol) was added. Finally, 2-methyl-2-vinyloxirane (1.5 mL, 15.29 mmol) was added to the reaction mixture. Stirring was continued for 30 min at rt, at which point, the color of the solution turned into orange again. The solvent was removed in vacuo to give a crude yellow oil, the crude sample was then purified by chromatography (0-40% EtOAc/Hexane) to give **204** as a clear colorless oil, 973 mg, 35% yield. ESI+APCI LC-MS: m/z 185 (M+H+). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.02 – 5.76 (m, 1H), 5.32 – 5.08 (m, 2H), 4.53 – 3.98 (m, 1H), 4.24 – 4.13 (m, 1H), 3.79 (s, 1H), 3.74 (s, 1H), 3.48 (s, 1H), 3.29 (s, 1H), 1.40 (s, 1H), 1.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 171.8, 167.1, 166.9, 140.3, 136.9, 117.0, 115.5, 76.6, 76.6, 58.5, 56.1, 52.9, 52.9, 46.4, 46.2, 24.4, 19.4.



205

Methyl (4S)-3-allyl-4-methyl-2-oxo-4-vinyltetrahydrofuran-3-carboxylate. 204 (14 mg, 0.076 mmol) was dissolved in 1 mL THF in a 20 mL vial. Allyl bromide (13 uL, 0.152 mmol) was added, followed by the addition of DBU (23 uL, 0.152 mmol). The mixture was stirred for 5 h, then the mixture was diluted with 3 mL EtOAc and washed with water (2 mL). The organic phase was separated and the aqueous phase was extracted with 3 x 1

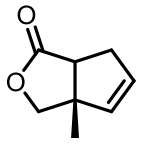
mL EtOAc. The combined organic phase was dried over Na_2SO_4 and concentrated to give crude **205** as a colorless oil. The crude NMR indicated crude **205** contains mostly the desired product with very little impurity, the sample was recovered and used in the next step without any further purification. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.16 – 5.68 (m, 2H), 5.39 – 4.90 (m, 4H), 4.32 (dd, *J* = 34.1, 8.8 Hz, 1H), 4.03 (dd, *J* = 39.9, 8.9 Hz, 1H), 3.83 – 3.64 (m, 3H), 2.69 – 2.34 (m, 2H), 1.44 – 1.11 (m, 3H).



206

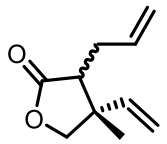
Methyl (3aR,6aS)-6a-methyl-3-oxo-4,6a-dihydro-1H-cyclopenta[c]furan-3a(3H)-carboxylate. Crude **205** (6.7 mg) was dissolved in 2 mL DCM in a 20 mL vial. Grubbs' G-II catalyst (3.2 mg, 0.004 mmol) was added, the vial was then purged 3 times with N_2, the mixture was then stirred overnight. The mixture was concentrated to give a black oil, this crude sample was then dissolved in 5 mL 30% EtOAc in hexane and passed through a silica gel packed pipette and eluted with additional 5 mL 30% EtOAc in hexane solution. The resulted solution was then concentrated to give a gray oil. The sample was purified by chromatography (5%-8%-20% EtOAc/Hexane) to give unreacted **205** as a colorless oil, 3.2

mg 19% yield, and **206** as a colorless oil, 6.7 mg 45% yield over 2 steps. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.79 (ddd, *J* = 5.7, 2.6, 1.9 Hz, 1H), 5.46 (ddd, *J* = 5.7, 2.7, 1.6 Hz, 1H), 4.31 (d, *J* = 8.9 Hz, 1H), 4.22 – 4.16 (m, 1H), 3.81 – 3.77 (m, 3H), 3.30 – 3.20 (m, 1H), 2.99 – 2.89 (m, 1H), 1.13 (s, 3H).



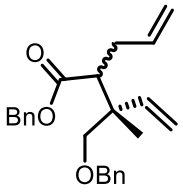
207

(3aS)-3a-methyl-3,3a,6,6a-tetrahydro-1H-cyclopenta[c]furan-1-one. 206 (6.7 mg, 0.034 mmol) was dissolved in 2 mL DMSO in a 20 mL vial. LiCl (2.9 mg, 0.068 mmol) was added, the mixture was then heated to 140 ºC and stirred for 48h. To the mixture was added 5 mL EtOAc and 10 mL water, the organic phase was separated and washed with another 5 mL of water and 5 mL of brine. The resulting organic phase was dried over Na_2SO_4 and concentrated to give crude **207** as a yellow oil. The crude NMR indicated the desired product was formed without any other byproducts. The crude sample was recovered and used in next step directly. 1H NMR (400 MHz, Chloroform-d) δ 5.80 – 5.73 (m, 1H), 5.57 (dd, J = 5.5, 1.9 Hz, 1H), 4.28 (d, J = 9.2 Hz, 1H), 4.18 – 4.06 (m, 1H), 2.83 – 2.63 (m, 3H), 1.44 – 1.04 (m, 3H).



208

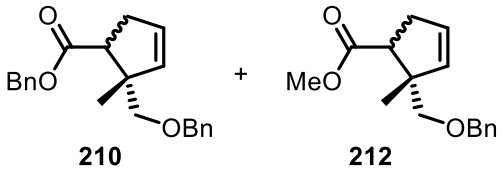
(4S)-3-allyl-4-methyl-4-vinyldihydrofuran-2(3H)-one. Crude **205** (923 mg, 4.116 mmol) was dissolved in 30 mL DMSO in a 100 mL flask. LiCl (348.9 mg, 8.232 mmol) was added, the flask was then purged with N_2 capped with plastic cap loosely and heated to 140 ºC and stirred for 24 h. The mixture was then added 30 mL EtOAc and 30 mL water, the organic phase was separated and washed with another 20 mL of water and 20 mL of brine. The resulting organic phase was dried over Na_2SO_4 and concentrated to give crude **208** as a brown oil, 261 mg, 38% yield over 2 steps. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.97 – 5.72 (m, 2H), 5.32 – 4.93 (m, 4H), 4.21 – 3.82 (m, 2H), 2.58 – 2.04 (m, 3H), 1.40 – 1.02 (m, 3H).



209

Benzyl (3S)-2-allyl-3-((benzyloxy)methyl)-3-methylpent-4-enoate. Crushed KOH (193.2 mg, 3.444 mmol) was added to a toluene (6 mL) solution of **208** (108 mg, 0.650

mmol) and benzyl bromide (0.49 mL, 4.127 mmol). The reaction mixture was stirred at 110 ºC for 24 h. TLC indicated complete consumption of the starting material, the reaction mixture was diluted with 3 mL EtOAc and added sat. aq. NH_4Cl solution (3 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 3 mL). The combined organic phase was dried over Na_2SO_4 and concentrated to give a crude oil sample which is purified by chromatography (0-8% EtOAc/Hexane) to give **209** as a colorless oil, 199 mg, 84% yield. ESI+APCI LC-MS: m/z 365 (M+H+). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.24 (m, 10H), 6.09 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.87 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.74 – 5.60 (m, 1H), 5.17 – 4.88 (m, 6H), 4.51 – 4.29 (m, 2H), 3.36 – 3.14 (m, 2H), 2.75 (ddd, *J* = 13.4, 11.9, 3.2 Hz, 1H), 2.41 – 2.25 (m, 1H), 2.25 – 2.11 (m, 1H), 1.12 (d, *J* = 10.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 174.1, 142.4, 141.9, 138.6, 138.6, 136.3, 136.3, 136.2, 136.1, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.3, 127.7, 127.6, 116.8, 116.7, 114.6, 114.1, 76.6, 73.4, 73.4, 66.2, 66.1, 51.3, 50.8, 43.7, 43.4, 32.4, 32.2, 18.6, 17.8.



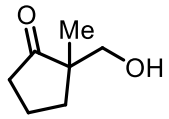
210 **212**

4:1 mixture

Benzyl (2S)-2-((benzyloxy)methyl)-2-methylcyclopent-3-ene-1-carboxylate and methyl (2S)-2-((benzyloxy)methyl)-2-methylcyclopent-3-ene-1-carboxylate. 209 (293.1 mg, 0.804 mmol) was dissolved in 10 mL DCM in a 20 mL vial. Grubbs' G-II catalyst (34.1 mg, 0.04 mmol) was added, the vial was then purged 3 times with N_2, the mixture was then stirred 16h. LCMS indicated complete consumption of the starting material, the mixture was concentrated to give a black oil. This crude sample was then dissolved in 10 mL MeOH and stirred at 60 ºC for 24h, then the mixture was concentrated to give a dark oil and purified by chromatography (0-5% EtOAc/Hexane) to give an inseparable 4:1 mixture of **210** and **212** as a yellow oil, 138 mg, 54% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.19 (m, 8H), 5.75 – 5.65 (m, 1H), 5.53 – 5.39 (m, 1H), 5.18 – 4.82 (m, 2H), 4.64 – 4.27 (m, 2H), 3.74 – 3.37 (m, 2H), 3.33 – 3.15 (m, 1H), 3.00 – 2.72 (m, 1H), 2.62 – 2.41 (m, 1H), 1.35 (d, *J* = 23.2 Hz, 1H), 0.87 (d, *J* = 18.9 Hz, 2H); ^{13}C NMR (101 MHz, $cdcl_3$) δ 174.4, 173.8, 173.7, 138.6, 138.6, 138.6, 136.7, 136.7, 136.3, 136.2, 136.1, 129.2, 128.5, 128.5, 128.4, 128.3, 128.3, 128.3, 128.2, 128.1, 128.1, 128.0, 127.5, 127.3, 127.3, 127.3, 76.2, 74.1, 73.3, 73.2, 73.1, 66.2, 66.1, 53.0, 52.9, 52.8, 51.9, 51.4, 47.8, 47.8, 35.2, 35.1, 33.9, 33.9, 30.0, 24.3, 18.8, 18.8.

4.1.2 Pd. Catalyzed Carbonylation Route

4.1.2.1 Lipase-catalyzed Transesterification Route



238

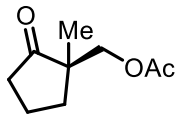
2-(hydroxymethyl)-2-methylcyclopentan-1-one. To a 250 mL round bottom flask was charged with ethyl 2-oxocyclopentanecarboxylate (10 mL, 69.1 mmol) dissolved in 150 mL acetone. K_2CO_3 (28.6 g, 207 mmol) and MeI (8.2 mL, 131 mmol) was added subsequently. The mixture was then heated to reflux for 1 h. LCMS indicated completion of the reaction, the mixture was passed through a Celite pad. The filtrate was concentrated and re-dissolved in EtOAc (100 mL) washed with 50 mL NH_4Cl solution and brine (50 mL). The resulting solution was dried over Na_2SO_4 and concentrated to give a colorless crude oil which is used in next step without any further purification.

To a 250 mL round bottom flask was charged with the crude sample from the previous step (10.4 g, 61.1 mmol) dissolved in 100 mL toluene, ethylene glycol (10.2 mL, 183 mmol) and p-TsOH monohydrate (1.16 g,6.11 mmol) was added subsequently. The flask was fitted with a Dean-Stark trap and heated to 120 ºC for 24h, to the mixture was then added K_2CO_3 (5g) and filtered through a Celite pad rinsed with 50 mL toluene, the resulting mixture was

then concentrated to give a crude colorless oil, 13.1 g, 36%. The crude sample was used directly in the next step.

To a 500 mL round bottom flask was charged with $LiAlH_4$ (2.78 g, 73.3 mmol) dissolved in Et_2O (100 mL). The mixture was cooled down to 0 ºC, crude sample from the previous step (4.79 g, 22.4 mmol) in 15 mL Et_2O was added to the mixture over 5 min. The mixture was then stirred at 0 ºC for 1 h. TLC indicated completion of the reaction, the mixture was quenched by adding EtOAc dropwise until no more gas was released. To this suspension was added sat aq. potassium sodium tartrate (300 mL) and stirred for 6 h. Then the organic phase was separated and the aqueous phase was extracted with 3 x 100 mL EtOAc. The combined organic phase was washed with brine (100 mL) and dried over Na_2SO_4, concentrated to give a colorless crude oil. This crude oil was then dissolved in Et_2O (100 mL). 2N HCl (11.2 mL) was added. The mixture was stirred at rt for 2h, then $NaHCO_3$ (50 mL) was added. The organic phase was separated and the aqueous phase was extracted with 3 x 50 mL Et_2O, the combined organic phase was washed with brine (100 mL) and dried over Na_2SO_4, concentrated to give a crude oil which is then purified by chromatography (0%-40% EtOAc/Hexane) to give **238** as a colorless oil, 783 mg, 3% over 4 steps. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.16 (qd, *J* = 7.1, 1.3 Hz, 2H), 2.63 – 2.22 (m, 3H), 2.14 – 1.76 (m, 3H), 1.38 – 1.14 (m, 6H). Product previously characterized in the

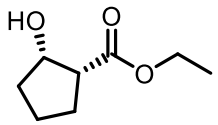
literature[98].



239

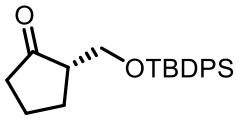
(R)-(1-methyl-2-oxocyclopentyl)methyl acetate. 238 (47.9 mg, 0.374 mmol) was dissolved in 20 mL benzene, to this mixture was added vinyl acetate (0.1 mL, 1.121 mmol) and Amano PS lipase (29.2 mg). The mixture was then heated to 50 ºC and stirred for 24 h. After 24h at 50 ºC, 1 mL of the mixture was taken and filtered through a syringe filter concentrated and a crude NMR was taken. NMR indicated the ratio of desired product : SM= 1:2. the mixture was then filtered through syringe filter, concentrated and re-dissolved in benzene (5 mL). Vinyl acetate (0.1 mL, 1.121 mmol) and Amano PS lipase (29.2 mg) was added. The mixture was then heated to 50 ºC and stirred for another 24 h. 1 mL of the mixture was taken and filtered through a syringe filter concentrated and a crude NMR was taken. NMR indicated ratio of desired product **239** : SM= 1:1, suggesting a 50% conversion. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.04 (d, *J* = 1.8 Hz, 2H), 2.46 – 2.14 (m, 2H), 2.04 (s, 3H), 2.02 – 1.69 (m, 4H), 1.04 (s, 3H). Product previously characterized in the literature[47].

4.1.2.2 Baker's yeast Reduction Route



244

Ethyl (1R,2S)-2-hydroxycyclopentane-1-carboxylate. To a 2L Erlenmeyer flask was charged with sucrose (180 g, 0.53 mol), dissolved in 900 mL warm water (30 ºC). Baker's yeast (90 g) was added, upon which, large amount of bubble and foam was observed. The mixture was stirred at 30 ºC for 30 min, ethyl 2-oxocyclopentanecarboxylate (10 mL, 69.09 mmol) was added, then the mixture was stirred for 48h at 25 ºC. The mixture was filtered through a Bucher funnel with filter paper to give a slightly yellow filtrate. To the filter cake was added 200 mL MeOH to elute the emulsion. The combined filtrate was then extracted with 200 mL EtOAc, then the aqueous phase was saturated with NaCl and extracted with 3 x 200 mL EtOAc. The combined organic phase was dried over Na_2SO_4 and concentrated to give a brown oil crude product (8.2 g), which is then purified by chromatography (0-20% EtOAc/Hexane) to give **244** as a yellow oil, 5.7 g, 50% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.44 (q, *J* = 3.9 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.17 (s, 1H), 2.68 (ddd, *J* = 10.1, 8.7, 4.3 Hz, 1H), 2.08 – 1.87 (m, 3H), 1.83 – 1.73 (m, 2H), 1.70 – 1.57 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H); Product previously characterized in the literature[99].

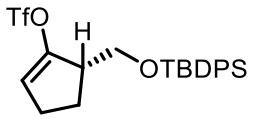


245

(S)-2-(((tert-butyldiphenylsilyl)oxy)methyl)cyclopentan-1-one. To a 500 mL round bottom flask was charged $LiAlH_4$ (65.3 mg, 1.721 mmol) and Et_2O (200 mL). This mixture was cooled to 0 ºC, **244** (4.767 g, 30.13 mmol) in Et_2O (50 mL) was added and the mixture was stirred at the same temperature for 1h, at which point, TLC indicated complete consumption of the starting material. The reaction was quenched by adding EtOAc dropwise until no gas was forming, then saturated potassium sodium tartrate solution (50 mL) was added. The mixture was stirred for 4h, the mixture was transferred to a separatory funnel. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic phase was washed with brine (30 mL) dried over Na_2SO_4, concentrated to give a colorless oily crude product which is used directly in next step without any further purification.

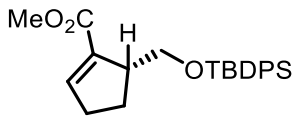
The crude product from last step was dissolve in 10 mL DCM in a 50 mL round bottom flask. To the mixture was added imidazole (47.2 mg, 0.694 mmol) and TBDPSCl (90 ul, 0.347 mmol). The mixture was stirred at rt for 24h, TLC indicated incomplete consumption of the starting material, then to the mixture was added another portion of imidazole (20.4

mg, 0.3 mmol) and TBDPSCl (104 ul, 0.4 mmol) and stirred for another 24 h. TLC indicated complete consumption of the starting material. NH_4Cl solution (10 mL) was added, the organic phase was separated and the aqueous phase was extracted with DCM 3 x 10 mL, the combined organic phase was washed with brine 10 mL, dried over Na_2SO_4 concentrated to give a colorless oily crude product which is purified through chromatography (0-15% EtOAc/Hexane) to give a colorless oil which was then dissolved in 20 mL DCM in a 100 mL round bottom flask. Dess-Martin periodinane (488 mg, 1.15 mmol) was added. The mixture was stirred at rt for 16h, LCMS indicated complete consumption of the starting material. 1:1 solution of $Na_2S_2O_3$ and $NaHCO_3$ (20 mL) was added, the organic phase was separated and the aqueous phase was extracted with DCM 3 x 20 mL. The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, concentrated to give a semi-solid crude product, which is then purified by chromatography DCM/Hexane 0-65% to give **245** as a white solid, 140 mg, 40 % yield over 3 steps. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.68 – 7.59 (m, 4H), 7.47 – 7.32 (m, 6H), 3.95 (dd, J = 10.0, 4.5 Hz, 1H), 3.76 (dd, J = 10.0, 3.1 Hz, 1H), 2.39 – 1.96 (m, 6H), 1.89 – 1.71 (m, 1H), 1.02 (s, 9H). Product previously characterized in the literature.[100]



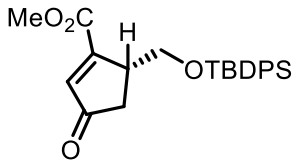
248

(S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)cyclopent-1-en-1-yl trifluoromethanesulfonate. Diisopropylamine (17 uL, 0.119 mmol) was dissolved in 1 mL THF at 0 ºC. n-BuLi 1.2 M solution in hexane (89 uL, 0.11 mmol) was added, the mixture was stirred for 5 min, cooled to -78 ºC. **245** (25.9 mg, 0.073 mol) in THF (0.5 mL) was added. The mixture was then stirred for 1 h, a solution of $PhNTf_2$ (39.4 mg, 0.11 mmol) in THF (0.5 mL) was added. The mixture was stirred at -78 ºC for 2h. $NaHCO_3$ solution (1 mL) and EtOAc (1 mL) was added, the organic phase was separated and the aqueous phase was extracted with 3 x 1 mL EtOAc. The combined organic phase was dried over Na_2SO_4 concentrated to give a crude yellow oily sample which is then purified by chromatography (0-3% EtOAc/Hexane) to give **248** as a white solid, 7.4 mg, 21% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (ddt, *J* = 7.3, 3.4, 1.6 Hz, 4H), 7.55 – 7.48 (m, 6H), 5.75 (q, *J* = 2.4 Hz, 1H), 3.74 (dd, *J* = 10.3, 4.6 Hz, 1H), 3.67 (dd, *J* = 10.3, 3.7 Hz, 1H), 3.03 – 2.90 (m, 1H), 2.52 – 2.31 (m, 2H), 2.16 (dtd, *J* = 13.1, 9.2, 5.7 Hz, 1H), 2.08 – 1.97 (m, 1H), 1.04 (s, 9H).



249

Methyl (R)-5-(((tert-butyldiphenylsilyl)oxy)methyl)cyclopent-1-ene-1-carboxylate. To a solution of **248** (23 mg, 0.047 mmol) in MeOH/DMF (4:1, 1 mL) were added Et_3N (13 ul, 0.095 mmol) and $Pd(PPh_3)_4$ (5.5 mg, 5 umol) in a 20 mL vial at room temperature. The solution was blown through by CO for 10 min, then the flask was sealed and put under vacuum and refilled with CO using a balloon. This process was repeated for 3 times, then the reaction mixture was stirred for 2.5 h at 40 °C. The reaction mixture was quenched with aq. NH_4Cl (1 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 2 mL). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give a crude product as a green oil, this crude product was dissolved in 5% EtOAc/Hexane and passed through a silica gel packed pipette concentrated to give **249** as a colorless oil, 5.3 mg, 28% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 – 7.58 (m, 4H), 7.43 – 7.34 (m, 6H), 6.89 (td, J = 2.6, 1.4 Hz, 1H), 3.81 (dd, J = 9.8, 3.6 Hz, 1H), 3.70 (dd, J = 9.8, 6.0 Hz, 1H), 3.64 (s, 3H), 3.21 – 3.03 (m, 1H), 2.62 – 2.50 (m, 1H), 2.47 – 2.34 (m, 1H), 2.16 – 2.04 (m, 2H), 1.02 (s, 9H).

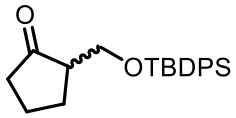


250

Methyl (R)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-3-oxocyclopent-1-ene-1-carboxylate. 249 (382.7 mg, 0.97 mmol) was dissolved in DCM (5 mL) in a 20 mL vial, $Pd(OH)_2/C$ (20%) (34 mg, 48 umol), K_2CO_3 (33.5 mg, 0.24 mmol) was added. The mixture was cooled to 4 °C and t-butylhydroperoxide (TBHP) (0.66 mL, 4.849 mmol) was added with vigorous stirring. The vial was sealed and allowed to warm up to rt. The reaction mixture was stirred at 24 °C for 48h, TLC showed incomplete consumption of starting material, t-BuOOH (0.1 mL) then $Pd(OH)_2/C$ (20%) (10 mg), K_2CO_3 (30 mg) was added, after another 48h, TLC showed small amount of starting material remaining, thus another portion of t-BuOOH (0.2 mL) was added, the mixture was stirred for another 2h, the solution was then diluted with DCM and passed through a pipette packed with silica gel and Na_2SO_4, washed with DCM, concentrated to give a colorless oil-like crude sample, which was purified by chromatography, 0-20% EtOAc/Hexane to give **250** as a colorless oil, became white solid after sitting in atmosphere, 196.4 mg, 50% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 – 7.51 (m, 4H), 7.44 – 7.33 (m, 6H), 6.82 (d, J = 1.6 Hz, 1H), 3.96 (dd, J = 10.0, 3.8 Hz, 1H), 3.89 – 3.80 (m, 1H), 3.76 (s, 3H), 3.41 – 3.30 (m, 1H), 2.64

– 2.58 (m, 2H), 0.99 (s, 9H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 208.2, 164.4, 163.2, 139.7, 135.5, 133.0, 132.9, 129.8, 129.8, 127.8, 127.7, 127.7, 63.4, 52.3, 42.5, 40.0, 26.7, 26.7, 19.2. IR (thin film) 2931, 2857, 1719, 1215, 1104, 821, 699 cm^{-1}.

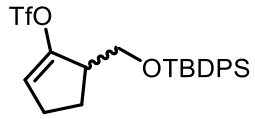
4.1.2.3 Racemic Route



252

2-(((tert-butyldiphenylsilyl)oxy)methyl)cyclopentan-1-one. 2-(Hydroxymethyl)cyclopentan-1-one prepared via a literature protocol[101] (25.81 g, 226.1 mmol) was added to a 1 L round bottom flask with stir bar in DCM (350 mL), sealed with a septum under nitrogen, and cooled in an ice bath. Imidazole (16.93 g, 248.7 mmol) was added, followed by TBDPSCl (64.7 mL, 248.7 mmol). The reaction was removed from the ice bath and stirred for 4 h, after which time TLC (30% EtOAc/hexanes) showed complete consumption of the starting material. Sat. aq. NH_4Cl (150 mL) was added, the organic phase was separated, and the aqueous phase was re-extracted with DCM (3 x 150 mL). The combined organics were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated to give a pale green solid. The crude material was recrystallized by adding

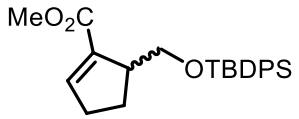
MeOH (150 mL), then heating with a heat gun until all solid dissolved. The solution was cooled for 10 min., then cooled in an ice bath for 3 h. The resulting crystals were filtered with a Buchner funnel and washed with ice-cold MeOH, then dried under vacuum, yielding silylether **252** (49.03 g, 62%) as a colorless solid, consistent with literature data.[102] $R_f = 0.5$ (5% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.60 (m, 4H), 7.48 – 7.30 (m, 6H), 3.95 (dd, J = 10.0, 4.6 Hz, 1H), 3.76 (dd, *J* = 10.0, 3.1 Hz, 1H), 2.40 – 1.97 (m, 6H), 1.90 – 1.67 (m, 1H), 1.02 (s, 9H).



253

5-(((tert-butyldiphenylsilyl)oxy)methyl)cyclopent-1-en-1-yl trifluoromethanesulfonate. Silylether **252** (3.00 g, 8.51 mmol) and $PhNTf_2$ (5.77 g, 16.1 mmol) were added to a 250 mL round bottom flask with stir bar and sealed under nitrogen. Anhydrous THF (100 mL) was added by syringe, and the resulting solution was cooled to –40 °C. NaHMDS (2 M solution in THF, 16.6 mL, 33.2 mmol) was added dropwise and the reaction was stirred at the same temperature for 45 min, at which point TLC (5% EtOAc/hexanes) showed complete consumption of the starting material. The reaction was quenched with sat. aq. NH_4Cl solution (100 mL) and extracted with EtOAc (3 x 50 mL),

then the combined organics were washed with brine, dried over Na_2SO_4, and concentrated to give a brown oil. The crude oil was then dissolved in hexanes and added by pipet to a 25 g silica gel pad in a sintered glass funnel, then eluted with hexanes (500 mL) and concentrated to give triflate **253** (4.13 g, 100%) as a yellow oil. R_f = 0.67 (3% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.61 (m, 4H), 7.45 – 7.33 (m, 6H), 5.74 (app q, *J* = 2.4 Hz, 1H), 3.75 (dd, *J* = 10.3, 4.6 Hz, 1H), 3.67 (dd, *J* = 10.3, 3.7 Hz, 1H), 3.03 – 2.89 (m, 1H), 2.53 – 2.28 (m, 2H), 2.23 – 2.09 (m, 1H), 2.09 – 1.92 (m, 1H), 1.05 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 135.8, 135.8, 133.6, 133.4, 130.0, 130.0, 128.0, 119.3, 63.6, 46.1, 27.2, 27.0, 24.8, 19.5. IR (thin film): ν = 2932, 2859, 1421, 1206, 1139, 1110, 998, 822, 699 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{23}H_{28}F_3O_4SSi$ [M+H] 485.1430; found 485.1427.

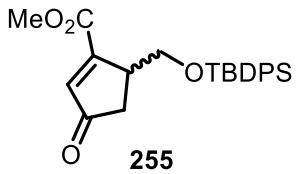


254

Methyl 5-(((tert-butyldiphenylsilyl)oxy)methyl)cyclopent-1-ene-1-carboxylate. Triflate **253** (24.4 g, 50.4 mmol) and Pd(dppf)Cl_2 · CH_2Cl_2 (1.23 g, 1.51 mmol) were charged to a 1 L round bottom flask with stir bar and sealed with a septum under nitrogen. MeOH/DMSO (1:1, 500 mL) was added by syringe, followed by NEt_3 (21.1 mL, 151

mmol). A balloon with needle adapter and 8" steel needle containing carbon monoxide (CO) (toxic; dispensed in a fume hood and transported in a sealed box) was attached to the flask, and the reaction solution was bubbled with CO for 5 min. by temporarily attaching a vent to an oil bubbler. The vent needle was removed and a new balloon of CO was attached, then the reaction was heated at 75 ºC for 4 days. TLC (3% EtOAc/hexanes) indicated complete consumption of the starting material. One-third of the reaction mixture (~170 mL) was added to a 2 L separatory funnel charged with half-saturated NH_4Cl solution (450 mL) and EtOAc (600 mL), the organic phase was separated, and the aqueous phase was extracted with EtOAc (2 x 150 mL), and the combined organics were washed with brine. This process was repeated for the other two portions of the reaction solution. The combined organics were dried over Na_2SO_4, filtered, and concentrated to give a dark tar, which was purified by column chromatography on a 300 g column (EtOAc/hexanes, 0–3%) to give ester **254** (16.2 g, 82%) as a colorless oil. R_f = 0.5 (3% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.60 (m, 4H), 7.47 – 7.33 (m, 6H), 6.90 (td, *J* = 2.6, 1.2 Hz, 1H), 3.84 (dd, *J* = 9.8, 3.6 Hz, 1H), 3.73 (ddd, *J* = 9.8, 6.0, 0.6 Hz, 1H), 3.66 (s, 3H), 3.22 – 3.08 (m, 1H), 2.64 – 2.51 (m, 1H), 2.49 – 2.36 (m, 1H), 2.18 – 2.08 (m, 2H), 1.05 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 146.3, 136.3, 135.6, 135.6, 133.9, 133.8, 129.5, 129.5, 127.6, 127.6, 65.3, 51.2, 46.9, 32.2, 27.4, 26.8, 19.3. IR (thin film): ν = 2931, 2857, 1714,

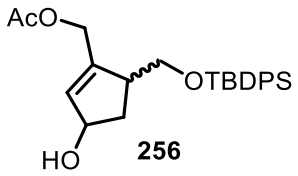
1427, 1102, 1028, 738, 698 cm^{-1}. HRMS (ESI^+): calcd for $C_{24}H_{31}O_3Si$ [M+H] 395.2042; found 395.2039.



255

Methyl 5-(((tert-butyldiphenylsilyl)oxy)methyl)-3-oxocyclopent-1-ene-1-carboxylate. Ester **254** (383 mg, 0.970 mmol) was dissolved in DCM (5 mL) in a 20 mL vial in open air with stir bar, and $Pd(OH)_2/C$ (20%) (34 mg, 0.048 mmol) and K_2CO_3 (33.5 mg, 0.242 mmol) were added. The mixture was cooled in an ice bath to 4 °C and *t*-butylhydroperoxide (TBHP) (0.66 mL, 4.85 mmol) was added with vigorous stirring. The vial was sealed and allowed to warm up to rt. The reaction mixture was stirred at 24 °C for 48 h, after which time TLC (3% EtOAc/hexanes) showed incomplete consumption of starting material. More *t*-BuOOH (0.1 mL), $Pd(OH)_2/C$ (20%) (10 mg), and K_2CO_3 (30 mg) were added, and after another 48 h, TLC showed a small amount of starting material remaining. Another portion of *t*-BuOOH (0.2 mL) was added, the mixture was stirred for another 2 h, then the solution was diluted with DCM and passed through a pipette packed with silica gel and Na_2SO_4, eluted with additional DCM. The resulting solution was concentrated to give a colorless oil, which was purified by column chromatography on a

25 g column (EtOAc/hexanes, 0–20%) to give **255** (196 mg, 50%) as a colorless oil. R_f = 0.1 (5% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.51 (m, 4H), 7.44 – 7.33 (m, 6H), 6.82 (d, *J* = 1.6 Hz, 1H), 3.96 (dd, *J* = 10.0, 3.8 Hz, 1H), 3.89 – 3.80 (m, 1H), 3.76 (s, 3H), 3.41 – 3.30 (m, 1H), 2.64 – 2.58 (m, 2H), 0.99 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2, 164.4, 163.2, 139.7, 135.5, 133.0, 132.9, 129.8, 129.8, 127.8, 127.7, 127.7, 63.4, 52.3, 42.5, 40.0, 26.7, 26.7, 19.2. IR (thin film): ν = 2931, 2857, 1719, 1215, 1104, 821, 699 cm^{-1}. HRMS (ESI$^+$) calcd for $C_{24}H_{29}O_4Si$ [M+H] 409.1835, found 409.1828.

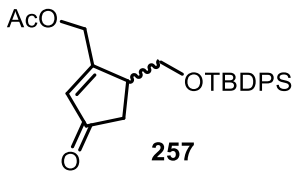


256

(5-(((tert-butyldiphenylsilyl)oxy)methyl)-3-hydroxycyclopent-1-en-1-yl)methyl acetate. Enone **255** (7.20 g, 17.6 mmol) was added to a 1 L round bottom flask with stir bar and sealed with a septum under nitrogen. Anhydrous toluene (200 mL) was added by syringe, and the resulting solution was cooled to –40 ºC. DIBAL (1.2M solution in toluene, 45.5 mL, 54.6 mmol) was added, and the mixture was stirred for 10 min, after which time TLC (5% EtOAc/hexanes) indicated complete consumption of the starting material. Saturated potassium sodium tartrate solution (300 mL) was added to quench the reaction at the same temperature, followed by EtOAc (300 mL). The mixture was stirred at rt for 24

h, then the organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated to give the crude diol intermediate as a colorless oil. This was sealed under nitrogen and dissolved in pyridine (200 mL), then the mixture was cooled to –20 ºC and acetic anhydride (1.95 mL, 20.7 mmol) was added. The reaction was stirred at –20 ºC for 24 h, after which time TLC analysis indicated that the reaction was incomplete (5% EtOAc/hexanes). Another portion of acetic anhydride (0.85 mL, 9.0 mmol) was added after 24 h, another portion (0.35 mL, 3.7 mmol) was added after 48 h, another portion (0.10 mL, 1.1 mmol) was added after 72 h, and smaller portions (0.05 mL, 0.53 mmol) were added after 96 h, 120 h, and 144 h until the starting material was consumed. The reaction mixture was concentrated to a yellow oil and purified by flash chromatography on a 100 g column (EtOAc/hexanes, 20–40%) to give **256** (3.68 g, 50%) as a yellow oil, which was an inconsequential mixture of diastereomers. R_f1= 0.15, R_f2= 0.1 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.53 (m, 4H), 7.49 – 7.28 (m, 6H), 5.96 (s, 1H), 4.71 – 4.42 (m, 1H), 3.71 – 3.54 (m, 2H), 2.82 – 2.56 (m, 2H), 2.44 (ddd, *J* = 14.2, 8.9, 7.0 Hz, 1H), 2.03 (s, 3H), 1.74 (dt, *J* = 14.1, 2.1 Hz, 1H), 1.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 142.6, 135.7, 135.6, 132.7, 132.6, 132.3, 130.0, 129.9, 127.8, 74.8, 64.3, 61.6, 46.2, 38.1, 26.9, 20.8, 19.2. IR (thin film): ν = 3435, 2930, 2857, 1739, 1222, 1110, 1017,

699 cm^{-1}. HRMS (ESI^+) calcd for $C_{25}H_{32}NaO_4Si$ [M+Na] 447.1968, found 447.1967.

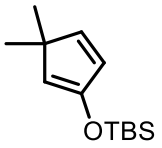


257

(5-(((tert-butyldiphenylsilyl)oxy)methyl)-3-oxocyclopent-1-en-1-yl)methyl acetate. Alcohol **256** (3.68 g, 8.67 mmol) was added to a 500 mL round bottom flask with stir bar and dissolved with DCM (200 mL). Silica gel (5.6 g) was added, followed by PCC (5.6 g, 26 mmol). The mixture was stirred for 1 h, after which time TLC (20% EtOAc/hexanes) indicated complete consumption of the starting material. The mixture was loaded directly onto a 25 g silica gel column and purified by column chromatography (100% DCM, then 10–25% EtOAc/hexanes) to give **257** (3.05 g, 83%) as a yellow oil. R_f = 0.2 (20% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.56 (m, 4H), 7.49 – 7.35 (m, 6H), 6.15 (q, *J* = 1.7 Hz, 1H), 5.02 (dd, *J* = 17.2, 1.8 Hz, 1H), 4.84 (d, *J* = 17.2 Hz, 1H), 3.77 (dd, *J* = 10.3, 4.7 Hz, 1H), 3.70 (dd, *J* = 10.3, 6.0 Hz, 1H), 3.15 – 2.99 (m, 1H), 2.52 (dd, *J* = 18.5, 6.9 Hz, 1H), 2.25 (dd, *J* = 18.6, 2.3 Hz, 1H), 2.12 (d, *J* = 0.6 Hz, 3H), 1.04 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.1, 175.2, 170.2, 135.5, 132.8, 132.7, 130.3, 130.0, 130.0, 127.9, 64.5, 62.7, 43.7, 38.7, 26.8, 20.7, 19.2. IR (thin film): ν = 2930, 2857, 1744, 1715, 1427, 1220, 1105, 701 cm^{-1}. HRMS (ESI^+) calcd for $C_{25}H_{31}O_4Si$ [M+H] 423.1992,

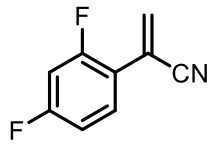
found 423.1988.

4.2 Construction of Quaternary Center at C-2 Bicyclo[2.2.1]heptane Core



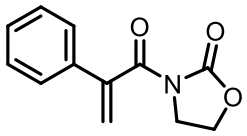
262

Tert-butyl((3,3-dimethylcyclopenta-1,4-dien-1-yl)oxy)dimethylsilane. To a solution of **266**[79] (302 mg, 2.742 mmol) in acetonitrile (4 mL) were added triethylamine (0.57 mL, 4.112 mmol), tert-butyldimethylsilyl chloride (619.8 mg, 4.112 mmol) and NaI (616.4 mg, 4.112 mmol) in this order. The reaction mixture was stirred overnight at room temperature, after which point GC-MS indicated complete consumption of the starting material and the desired mass of the desired product, PE (5 mL) and saturated $NaHCO_3$ solution (5 mL) were added. The layers were separated and the combined acetonitrile–water phases were extracted with PE 3 x 5 mL. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was dissolved in hexane and eluted through an Al_2O_3 (pH= 9.0) packed pipette, concentrated to give **262** a colorless oil, 615 mg, 93%. ^{1}H NMR (400 MHz, Acetone-d_6) δ 6.14 (dd, J = 5.4, 2.4 Hz, 1H), 5.87 (dd, J = 5.4, 1.7 Hz, 1H), 5.09 (dd, J = 2.4, 1.7 Hz, 1H), 1.09 (s, 6H), 0.89 (s, 9H), 0.12 (s, 6H).



267

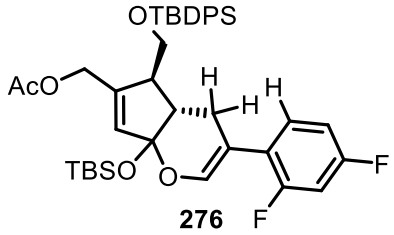
2-(2,4-difluorophenyl)acrylonitrile. A solution of 2-(2,4-difluorophenyl)acetonitrile (0.1 mL, 0.82 mmol), paraformaldehyde (37.5 mg, 1.25 mmol), K_2CO_3 (1.18 g, 1.31 mmol) and Bu_4NI (6 mg, 16 umol) in toluene (2 mL) was stirred under nitrogen atmosphere in a 20 mL vial sealed with septum at 80 °C for 5h, TLC indicated complete consumption of the starting material, The reaction mixture was poured into a saturated aqueous solution of NaCl (5 mL) and then extracted with EtOAc (3 x 10 mL). The organic layer was dried over Na2SO4 and concentrated *in vacuo*. The crude sample was purified by chromatography 0-15% EtOAc/Hexane to give **267** as a yellow oil, 2.5 mg, 2% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 (td, *J* = 8.9, 6.3 Hz, 1H), 7.04 – 6.76 (m, 2H), 6.45 (d, *J* = 0.5 Hz, 1H), 6.32 (dd, *J* = 2.1, 0.6 Hz, 1H).



270

3-(2-phenylacryloyl)oxazolidin-2-one. 2-phenylacrylic acid (1 g, 6.75 mmol),

oxazolidin-2-one (705 mg, 8.1 mmol) and DMAP (124 mg, 1.01 mmol) was dissolved in DCM (20 mL) in a 100 mL round bottom flask, DIC (3.6 mL,22.9 mmol) was added, the mixture was stirred at rt for 24h, TLC indicated the starting material was completely consumed, the suspension was then filtered through a Celite packed sintered glass, concentrated and purified by chromatography 0-50% EtOAc/Hexane to give **270** as a white solid, 638 mg, 44% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.29 (m, 4H), 5.81 (d, *J* = 0.8 Hz, 1H), 5.56 (d, *J* = 0.8 Hz, 1H), 4.52 – 4.36 (m, 2H), 4.13 (tt, *J* = 7.9, 0.7 Hz, 2H). Product previously characterized in the literature.[103]

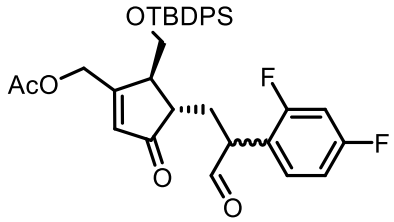


276

((4aS,5S)-7a-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-3-(2,4-difluorophenyl)-4,4a,5,7a-tetrahydrocyclopenta[b]pyran-6-yl)methyl acetate.

To a solution of enal **274** (49.7 mg, 0.296 mmol) in DCM (2.7 mL) was added cyclopentadiene **258** (94.6 mg, 176 μmol) in DCM (3 mL), and the mixture was stirred at rt for 24 h. TLC (10% EtOAc/hexanes) indicated complete consumption of the starting material, so the mixture was concentrated and purified on a 10g SiO_2 column (30%

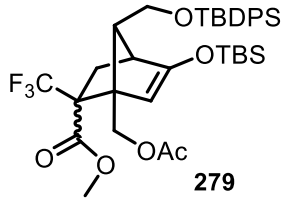
DCM/hexanes) to give **276** (64.2 mg, 52%) as a yellow oil. ^{1}H NMR (300 MHz, acetone-*d*$_6$) δ 7.76 – 7.60 (m, 4H), 7.52 – 7.33 (m, 6H), 7.26 (td, *J* = 9.0, 6.6 Hz, 1H), 7.06 – 6.90 (m, 2H), 6.78 (d, *J* = 1.7 Hz, 1H), 5.93 (d, *J* = 1.8 Hz, 1H), 4.77 (qt, *J* = 14.7, 1.4 Hz, 2H), 3.89 (dd, *J* = 10.7, 4.4 Hz, 1H), 3.80 (dd, *J* = 10.7, 4.7 Hz, 1H), 2.83 (s, 1H), 2.74 – 2.61 (comp, 3H), 2.03 (s, 3H), 1.05 (s, 9H), 0.91 (s, 9H), 0.22 (s, 3H), 0.16 (s, 3H). ^{13}C NMR (75 MHz, acetone-*d*$_6$) δ 170.7, 144.8, 144.0, 143.9, 136.5, 136.4, 134.3, 134.1, 132.0, 130.9, 130.9, 130.8, 130.7, 128.9, 128.8, 112.3, 107.7, 105.2, 104.9, 64.1, 62.4, 50.3, 46.9, 27.4, 26.2, 23.6, 20.8, 20.0, 18.5, –2.8. Decomposed to give **277** under LC-MS conditions (formic acid/MeOH).



277

((4S,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(2-(2,4-difluorophenyl)-3-oxopropyl)-3-oxocyclopent-1-en-1-yl)methyl acetate. To a solution of **276** (9.9 mg, 14 μmol) in MeOH (1 mL) in a 4 mL vial was added formic acid (50 μL, 1.2 mmol). After 5 min., TLC (10% EtOAc/hexanes) indicated complete consumption of **276**, so the reaction mixture was concentrated and purified by chromatography on a silica gel packed pipette

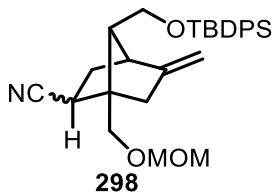
(10–20% EtOAc/hexanes) to give aldehyde **277** (1:1 diastereomeric mixture, 6.0 mg, 73%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (d, *J* = 1.4 Hz, 1H), 9.58 (t, *J* = 1.0 Hz, 1H), 7.66 – 7.49 (comp, 8H), 7.48 – 7.33 (comp, 12H), 7.25 – 7.15 (m, 1H), 7.02 (td, *J* = 8.5, 6.2 Hz, 1H), 6.89 – 6.74 (comp, 4H), 6.11 (q, *J* = 1.7 Hz, 1H), 6.06 (q, *J* = 1.7 Hz, 1H), 5.01 (d, *J* = 17.2 Hz, 1H), 4.92 (d, *J* = 17.4 Hz, 1H), 4.83 – 4.73 (m, 2H), 4.27 (dd, *J* = 9.4, 5.3 Hz, 1H), 3.95 (dd, *J* = 8.2, 5.6 Hz, 1H), 3.77 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.64 (dd, *J* = 10.5, 6.2 Hz, 1H), 3.59 (d, *J* = 5.0 Hz, 3H), 2.73 – 2.58 (m, 3H), 2.38 (ddd, *J* = 13.9, 9.9, 5.3 Hz, 1H), 2.21 – 2.14 (m, 2H), 2.13 (s, 3H), 2.11 (s, 3H), 2.05 – 1.94 (m, 1H), 1.84 (ddd, *J* = 14.5, 9.4, 5.6 Hz, 1H), 1.01 (s, 9H), 0.97 (d, *J* = 2.6 Hz, 9H). HRMS (ESI^+): calcd for $C_{34}H_{36}F_2NaO_5Si$ $[M+Na]^+$ 613.2198; found 613.2207.



279

Methyl 1-(acetoxymethyl)-5-((tert-butyldimethylsilyl)oxy)-7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(trifluoromethyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate. To a solution of cyclopentadiene **258** (10 mg, 19 μmol) in DCM (0.4 mL) was added methyl 2-(trifluoromethyl)acrylate (**278**) (4.6 μL, 37 μmol) in 1 mL DCM, and

the mixture was stirred at rt for 24 h. TLC indicated complete consumption of the starting material (20% EtOAc/hexanes), so the mixture was concentrated and purified by chromatography on a Pasteur pipette packed with silica gel (4% EtOAc/hexanes) to give cycloadduct **279** (1:1.4 diastereomeric mixture, 5.2 mg, 40%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.55 (comp, 6H), 7.46 – 7.32 (comp, 8H), 4.56 – 4.02 (comp, 5H), 3.76 (s, 3H), 3.71 (s, 2H), 3.63 (dd, *J* = 10.2, 5.0 Hz, 1H), 3.51 (dd, *J* = 10.1, 5.0 Hz, 1H), 2.92 – 2.76 (m, 3H), 2.59 (d, *J* = 13.0 Hz, 1H), 2.50 (ddd, *J* = 21.3, 9.2, 5.0 Hz, 2H), 2.19 (dd, *J* = 12.9, 3.5 Hz, 1H), 1.91 (d, *J* = 12.5 Hz, 1H), 1.77 (d, *J* = 2.0 Hz, 6H), 1.03 (d, *J* = 4.3 Hz, 18H), 0.93 (d, *J* = 3.1 Hz, 18H), 0.16 (d, *J* = 7.6 Hz, 5H), 0.12 (d, *J* = 13.8 Hz, 4H). ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.52, –64.24. ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.3, 169.8, 169.0, 162.6, 162.3, 135.7, 135.6, 133.9, 133.8, 133.8, 133.7, 129.7, 127.8, 99.6, 97.4, 62.9, 62.6, 61.8, 61.1, 60.5, 60.0, 59.5, 58.4, 52.9, 52.9, 47.4, 46.4, 34.6, 34.5, 27.0, 25.7, 20.6, 19.4, 18.1, 0.2, –4.5, –4.6. HRMS (ESI^+): calcd for $C_{36}H_{50}F_3O_6Si_2$ [M+H] 691.3098; found 691.3111.



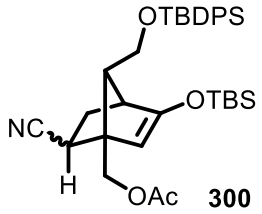
298

7-(((tert-butyldiphenylsilyl)oxy)methyl)-1-((methoxymethoxy)methyl)-5-methylenebicyclo[2.2.1]heptane-2-carbonitrile. To a solution of **302** (110 mg, 0.254 mmol) in $CHCl_3$ (5 mL) was added dimethoxymethane (224 μL, 2.54 mmol) and P_2O_5 (500 mg, 1.76 mmol).[104] The mixture was sealed under N_2 and stirred for 10 min. TLC (20% EtOAc/hexanes) indicated complete consumption of the starting material, the mixture was filtered through Celite and concentrated, and the intermediate MOM ether was used directly in the next step. To a solution of methyltriphenylphosphonium bromide (272 mg, 0.762 mmol) in toluene (5 mL) sealed under N_2 was added KHMDS (0.5 M in toluene, 1.52 mL, 0.762 mmol). The mixture was heated to 90 °C for 30 min., then the intermediate MOM ether was added (in toluene, 5 mL). The mixture was stirred at 90 °C for 10 min., after which time TLC (40% EtOAc/hexanes) indicated complete consumption of the starting material. The mixture was filtered through Celite, concentrated, and loaded as a toluene solution onto a 10 g SiO_2 column, and purified by chromatography (5–10% EtOAc/hexanes) to give alkene **298** (1:0.7 diastereomeric mixture, 75 mg, 62%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.58 (comp, 7H), 7.49 – 7.31 (comp, 10H), 4.98 (t, J = 2.5 Hz, 1H), 4.93 – 4.87 (m, 1H), 4.80 (s, 1H), 4.71 (s, 1H), 4.65 – 4.57 (m, 1H), 4.57 – 4.49 (m, 2H), 3.90 (d, J = 10.1 Hz, 1H), 3.73 (d, J = 10.1 Hz, 1H), 3.70 – 3.61 (m, 1H), 3.59 – 3.43 (comp, 4H), 3.35 (s, 2H), 3.24 (s, 3H), 3.09 (ddd, J = 12.0, 5.0,

2.5 Hz, 1H), 2.85 (d, *J* = 4.3 Hz, 1H), 2.75 (q, *J* = 5.8, 5.2 Hz, 1H), 2.47 (dd, *J* = 17.1, 2.1 Hz, 1H), 2.28 (dd, *J* = 12.3, 4.3 Hz, 1H), 2.23 – 1.96 (comp, 5H), 1.89 (dd, *J* = 12.6, 9.4 Hz, 1H), 1.69 (dd, *J* = 12.5, 5.0 Hz, 1H), 1.05 (s, 6H), 1.03 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 149.5, 135.7, 135.7, 135.7, 135.6, 133.6, 133.5, 133.4, 133.2, 129.9, 129.8, 127.9, 127.8, 127.8, 127.8, 121.5, 121.1, 107.1, 106.6, 96.9, 96.6, 69.4, 66.3, 61.1, 61.1, 55.5, 55.4, 53.1, 52.9, 52.8, 47.6, 38.0, 35.4, 34.9, 34.5, 33.7, 32.4, 26.9, 19.3, 19.3. HRMS (ESI^+): calcd for $C_{29}H_{37}NNaO_3Si$ $[M+Na]^+$ 498.2440; found 498.2452.

4.3 Endgame Synthesis

4.3.1 1st Generation Endgame Synthesis of Bicyclic Sordarin Analog

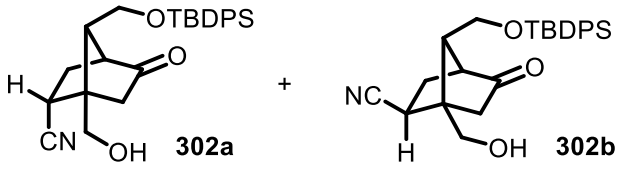


300

3-((tert-butyldimethylsilyl)oxy)-7-(((tert-butyldiphenylsilyl)oxy)methyl)-6-cyanobicyclo[2.2.1]hept-2-en-1-yl)methyl acetate. A 0.096 M solution of enone **257** in DCM (12.0 mL, 1.16 mmol) in a 50 mL round bottom flask with stir bar was sealed under nitrogen and cooled to –20 °C. NEt_3 (235 μL, 1.69 mmol) and TBSOTf (337 μL, 1.47

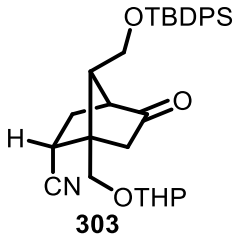
mmol) were added, and the reaction was gradually warmed up to 15 ºC over 3 h. The mixture was then quenched with aqueous phosphate buffer (10 mL, pH 7), the organic layer was separated, and the aqueous layer was then extracted with DCM (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated to an oil, then the desired product was extracted with hexanes and re-concentrated to give the crude diene **15**, which was used directly in the next step. Diene **15** was dissolved in DCM (10 mL) and acrylonitrile (passed through a column of basic alumina before use; 4.05 mL, 61.9 mmol) was added. The reaction was stirred at rt for 24 h, after which time TLC (20% EtOAc/hexanes) indicated complete consumption of the starting material. The mixture was concentrated to give crude **300** as a racemic, ~1:1 mixture of endo/exo diastereomers, and the yellow oil was used directly in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dddt, *J* = 11.2, 8.1, 3.3, 1.4 Hz, 4H), 7.48 – 7.32 (m, 6H), 4.66 – 4.24 (m, 3H), 3.84 – 3.47 (m, 2H), 2.99 (dd, *J* = 9.4, 4.1 Hz, 1H), 2.73 – 2.50 (m, 2H), 2.37 – 2.09 (m, 2H), 1.98 – 1.77 (m, 1H), 1.64 (dd, *J* = 12.6, 3.8 Hz, 1H), 1.16 – 0.98 (m, 9H), 0.98 – 0.80 (m, 9H), 0.26 – 0.05 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 170.8, 162.0, 161.7, 135.7, 135.6, 135.6, 133.5, 133.4, 133.4, 129.9, 129.8, 129.8, 127.9, 127.9, 127.8, 122.1, 121.5, 99.8, 97.9, 64.5, 63.6, 61.1, 61.1, 60.1, 59.6, 58.1, 57.7, 48.5, 48.1, 34.3, 34.2, 33.5, 33.4, 26.9, 26.9, 25.8, 25.8, 25.7, 25.7, 25.7, 20.9, 20.8, 19.3, 19.3, 18.1. IR (thin film): ν = 2930, 2857,

2234, 1744, 1616, 1227, 871, 701 cm^{-1}. HRMS (ESI^+) calcd for $C_{34}H_{47}NNaO_4Si_2$ [M+Na] 612.2941, found 612.2922.



7-(((tert-butyldiphenylsilyl)oxy)methyl)-1-(hydroxymethyl)-5-oxobicyclo[2.2.1]heptane-2-carbonitrile. The enolsilane **300** (682 mg, 1.16 mmol) was added to a 25 mL round bottom flask with stir bar and sealed under nitrogen, then $CHCl_3$ (10 mL) was added, and the solution was cooled in a bath at –10 ºC. Boron trifluoride etherate (purified by distillation prior to use; 214 µL, 1.73 mmol) was added and the solution was warmed up to 0 ºC over 30 min., after which time TLC (20% EtOAc/hexanes) indicated complete consumption of starting material. The mixture was quenched with sat. aq. $NaHCO_3$ (5 mL), then the layers were separated and the aqueous layer re-extracted with DCM (3 x 5 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated, to give the crude ketone product (61.8 mg, 0.13 mmol). This was dissolved with MeOH (5 mL), and K_2CO_3 (18 mg, 0.13 mmol) was added. The mixture was stirred at rt for 30 min., after which time TLC (20% EtOAc/hexanes) indicated complete consumption of starting material. The mixture was passed through a plug of silica gel in a

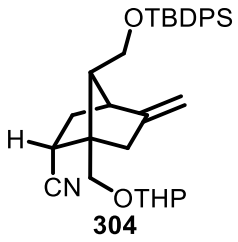
Pasteur pipette, concentrated, and then repurified by column chromatography using a Pasteur pipette packed with silica gel (EtOAc/hexanes, 21–27%) to give **302a** (20.3 mg, 24% over 4 steps), R_f = 0.5 (40% EtOAc/hexanes) and **302b** (21.4 mg, 25%), R_f = 0.38 (40% EtOAc/hexanes), both as colorless oils. **302a (endo)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.57 (m, 4H), 7.51 – 7.34 (m, 6H), 3.95 – 3.79 (m, 2H), 3.66 (dd, *J* = 11.5, 4.2 Hz, 1H), 3.54 (dd, *J* = 11.4, 9.9 Hz, 1H), 3.17 (ddd, *J* = 11.8, 5.5, 2.1 Hz, 1H), 3.04 (t, *J* = 6.7 Hz, 1H), 2.47 – 2.29 (m, 4H), 2.17 (dd, *J* = 9.9, 4.1 Hz, 1H), 1.85 – 1.75 (m, 1H), 1.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.7, 135.6, 135.6, 132.0, 131.8, 130.49, 130.45, 128.23, 128.20, 120.1, 61.5, 61.2, 54.2, 51.8, 51.6, 38.6, 31.6, 29.2, 26.89, 26.86, 19.1. IR (thin film): ν = 3458, 2931, 2858, 2239, 1751, 1427, 1112, 738, 702 cm^{-1}. HRMS (ESI$^+$) calcd for $C_{26}H_{31}NNaO_3Si$ [M+Na] 456.1971, found 456.1974. **302b (exo)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (ddt, *J* = 14.8, 7.9, 1.3 Hz, 4H), 7.51 – 7.35 (m, 6H), 4.15 (dd, *J* = 11.6, 3.0 Hz, 1H), 3.91 (dd, *J* = 11.9, 8.5 Hz, 1H), 3.67 (dd, *J* = 11.6, 4.6 Hz, 1H), 3.62 – 3.51 (m, 1H), 3.33 (dd, *J* = 8.6, 3.6 Hz, 1H), 2.77 (dd, *J* = 9.2, 4.6 Hz, 1H), 2.70 (d, *J* = 18.9 Hz, 1H), 2.44 (d, *J* = 4.9 Hz, 1H), 2.36 – 2.28 (m, 1H), 2.19 (dt, *J* = 13.8, 4.8 Hz, 1H), 2.03 (dd, *J* = 13.8, 9.3 Hz, 1H), 1.93 (dd, *J* = 18.9, 2.5 Hz, 1H), 1.06 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.4, 135.7, 135.6, 132.0, 132.0, 130.4, 130.3, 128.2, 128.2, 120.3, 62.9, 60.9, 53.2, 52.2, 51.9, 41.7, 33.8, 29.9, 26.9, 19.2.



303

7-(((tert-butyldiphenylsilyl)oxy)methyl)-5-oxo-1-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptane-2-carbonitrile. To a solution of alcohol **302a** (34.6 mg, 0.0798 mmol) and 3,4-dihydro-2*H*-pyran (36.4 μL, 0.40 mmol) in DCM (1 mL) in a 8 mL vial, was added a spatula tip of pyridinium *p*-toluenesulfonate (unweighed, ~1 mg). The mixture was stirred at rt for 1.5 h, after which time TLC indicated complete consumption of starting material (40% EtOAc/hexanes). The reaction mixture was loaded directly onto a silica gel packed pipette and purified by column chromatography (EtOAc/hexanes, 10–15%) to give THP acetal **303** as a mixture of diastereomeric acetals (38.1 mg, 92%). R_f = 0.36 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.56 (m, 8H), 7.49 – 7.33 (m, 12H), 4.62 – 4.53 (m, 1H), 4.51 – 4.48 (m, 1H), 3.96 (d, *J* = 10.6 Hz, 1H), 3.86 (d, *J* = 10.6 Hz, 1H), 3.83 – 3.68 (m, 3H), 3.66 – 3.47 (m, 5H), 3.44 (d, *J* = 10.6 Hz, 1H), 3.38 (dt, *J* = 11.1, 4.4 Hz, 1H), 3.19 (dddd, *J* = 19.5, 11.7, 5.4, 2.1 Hz, 2H), 2.78 (dd, *J* = 23.0, 4.9 Hz, 2H), 2.49 – 2.24 (m, 6H), 2.18 – 2.09 (m, 2H), 1.82 (dt, *J* = 13.6, 4.9 Hz, 2H), 1.78 – 1.35 (m, 14H), 1.02 (d, *J* = 1.2 Hz, 18H). ^{13}C NMR (101 MHz,

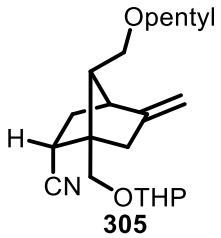
$CDCl_3$) δ 212.0, 211.9, 135.6, 132.8, 132.7, 130.0, 130.0, 130.0, 130.0, 127.9, 127.9, 127.9, 120.3, 120.3, 98.9, 98.8, 65.7, 65.6, 62.1, 62.0, 60.8, 60.6, 52.0, 51.9, 51.9, 51.9, 51.4, 51.4, 40.4, 40.2, 32.1, 31.9, 30.3, 30.2, 29.1, 26.8, 26.8, 25.4, 25.3, 19.2, 19.2, 19.1. IR (thin film): 2938, 2858, 2239, 1753, 1111, 1030, 905, 701. HRMS (ESI^+) calcd for $C_{31}H_{39}NNaO_4Si$ [M+Na] 540.2546, found 540.2527.



304

7-(((tert-butyldiphenylsilyl)oxy)methyl)-5-methylene-1-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptane-2-carbonitrile. Ph_3PMeBr (76.6 mg, 0.214 mmol) was added to an 8 mL vial with stir bar and sealed with a septum under nitrogen. Anhydrous toluene (1 mL) was added, followed by 0.5 M KHMDS in toluene (0.429 mL, 0.214 mmol) at rt. The yellow solution was heated at 90 ºC for 30 min, during which time it became a yellow slurry. Ketone **303** (37 mg, 0.072 mmol) in toluene (1 mL) was added, and the mixture was stirred at 90 ºC for 30 min., after which time TLC analysis indicated that the ketone was consumed (20% EtOAc/hexanes). The mixture was loaded directly onto a silica gel packed pipette and purified (EtOAc/hexanes, 5–15%) to give alkene **304** (34.2 mg,

93%) as a colorless oil (THP diastereomers). R_f = 0.65 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (ddt, *J* = 8.1, 5.0, 1.9 Hz, 8H), 7.50 – 7.31 (m, 12H), 4.99 (dt, *J* = 14.4, 2.6 Hz, 2H), 4.80 (d, *J* = 7.7 Hz, 2H), 4.55 (dt, *J* = 12.6, 3.1 Hz, 2H), 3.86 (d, *J* = 10.4 Hz, 1H), 3.77 – 3.56 (m, 5H), 3.53 – 3.31 (m, 6H), 3.05 (dddd, *J* = 22.0, 12.0, 5.0, 2.5 Hz, 2H), 2.90 (d, *J* = 4.2 Hz, 1H), 2.80 (d, *J* = 4.2 Hz, 1H), 2.52 (dd, *J* = 4.0, 2.0 Hz, 1H), 2.48 (dd, *J* = 3.9, 2.0 Hz, 1H), 2.26 (tdd, *J* = 12.4, 4.5, 1.7 Hz, 2H), 2.11 (d, *J* = 2.8 Hz, 1H), 2.07 (d, *J* = 2.9 Hz, 1H), 2.04 – 1.95 (m, 2H), 1.81 – 1.38 (m, 16H), 1.03 (d, *J* = 1.4 Hz, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8, 149.7, 135.7, 135.7, 135.6, 129.8, 129.8, 127.8, 127.8, 127.7, 107.1, 107.0, 98.6, 98.5, 66.5, 66.4, 61.7, 61.6, 61.4, 61.1, 53.2, 53.1, 52.9, 47.7, 47.7, 34.7, 34.6, 33.9, 33.7, 32.7, 32.7, 30.3, 26.9, 25.6, 25.5, 19.3, 19.3, 19.1, 18.9. HRMS (ESI^+) calcd for $C_{32}H_{41}NNaO_3Si$ [M+Na] 538.2753, found 538.2743.

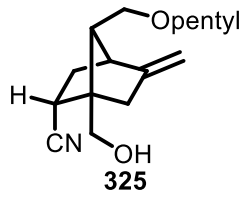


305

5-methylene-7-((pentyloxy)methyl)-1-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptane-2-carbonitrile. To a solution of **304** (16.0 mg, 0.058 mmol) in THF was added TBAF 1M solution in THF (29 µL, 0.029 mmol), the

mixture was stirred for 30 min, concentrated and dissolved in EtOAc (2 mL), washed with 1M HCl (2 mL), dried over Na_2SO_4 and concentrated to give a crude residue. This crude reside was dissolved in DMF (0.5 mL) in a 20 mL vial, NaH (~5 mg) was added at 0 ºC, the ice bath was removed, and 1-iodopentane (15.1 µL, 0.115 mmol) was added. The mixture was stirred at rt for 2 h, after which time TLC (50% EtOAc/hexanes) indicated complete consumption of the stating material. The reaction was quenched with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organics were washed with water (2 x 5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated to give a crude yellow oil. The crude was purified by column chromatography on a silica gel packed pipette (10% EtOAc/hexanes) to give ether **305** (13.1 mg, 65%) as a colorless oil (THP diastereomers). R_f = 0.2 (10% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (dd, *J* = 7.4, 2.6 Hz, 1H), 4.84 – 4.77 (m, 1H), 4.64 (q, *J* = 3.6 Hz, 1H), 3.93 – 3.75 (m, 2H), 3.60 – 3.48 (m, 1H), 3.48 – 3.29 (m, 4H), 3.26 – 3.14 (m, 1H), 3.08 (dddd, *J* = 17.1, 12.0, 5.0, 2.6 Hz, 1H), 2.74 (dd, *J* = 24.3, 4.3 Hz, 1H), 2.53 (dt, *J* = 17.1, 2.1 Hz, 1H), 2.23 (tdd, *J* = 12.3, 4.4, 2.7 Hz, 1H), 2.17 – 2.07 (m, 1H), 2.02 – 1.94 (m, 1H), 1.81 (ddt, *J* = 11.2, 8.2, 4.7 Hz, 1H), 1.71 – 1.46 (m, 9H), 1.36 – 1.21 (m, 5H), 0.93 – 0.84 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9, 149.8, 121.6, 107.0, 106.8, 99.0, 98.7, 71.7, 71.6, 68.1, 67.8, 66.4, 66.2, 61.9, 61.8, 53.3, 53.1, 50.6, 50.3, 47.9, 47.9, 34.6, 34.5, 33.9, 33.7, 32.4, 32.4, 30.5,

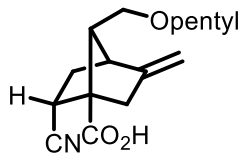
30.4, 29.5, 29.4, 28.4, 28.4, 25.6, 25.5, 22.6, 22.6, 19.2, 19.1, 14.2. HRMS (ESI^+) calcd for $C_{21}H_{33}NNaO_3$ [M+Na] 370.2358, found 370.2353.



325

1-(hydroxymethyl)-5-methylene-7-((pentyloxy)methyl)bicyclo[2.2.1]heptane-2-carbonitrile. To a solution of THP acetal **305** (12.0 mg, 34.5 μmol) in MeOH (1 mL) in a 4 mL vial was added Amberlyst® 15 (50.0 mg). The mixture was stirred at 60 °C for 45 min., after which time TLC (10% EtOAc/hexanes) indicated complete consumption of the starting material. The solution was decanted and concentrated to give a crude residue, which was purified by column chromatography (EtOAc/hexanes, 15–20%) to give alcohol **325** (7.8 mg, 86%) as a colorless oil. R_f = 0.22 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (t, *J* = 2.6 Hz, 1H), 4.78 (s, 1H), 3.69 (d, *J* = 7.0 Hz, 2H), 3.48 – 3.38 (m, 3H), 3.35 – 3.23 (m, 2H), 2.97 (ddd, *J* = 12.0, 5.1, 2.4 Hz, 1H), 2.53 (d, *J* = 4.3 Hz, 1H), 2.41 (tdd, *J* = 20.0, 16.3, 2.3 Hz, 2H), 2.26 (td, *J* = 12.3, 4.4 Hz, 1H), 1.98 – 1.90 (m, 1H), 1.70 – 1.61 (m, 1H), 1.56 (t, *J* = 6.9 Hz, 2H), 1.30 (app tt, *J* = 5.8, 3.1 Hz, 4H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.3, 121.4, 106.4, 72.0, 68.8, 62.2, 56.0,

50.9, 47.4, 34.8, 32.2, 32.1, 29.4, 28.3, 22.6, 14.1. HRMS (ESI^+) calcd for $C_{16}H_{25}NNaO_2$ [M+Na] 286.1783, found 286.1775.

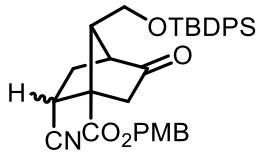


306

2-cyano-5-methylene-7-((pentyloxy)methyl)bicyclo[2.2.1]heptane-1-carboxylic acid. CrO_3 (525 mg, 5.25 mmol) was dissolved in H_2O (2 mL), and to the solution was added conc. H_2SO_4 (0.45 mL), giving Jones reagent (2.5 mL). To a solution of **325** (7.5 mg, 29 μmol) in acetone (1 mL) in a 4 mL vial at 0 ºC was added the solution of Jones reagent (28.5 μL, 71.2 μmol). The yellow solution was stirred at 0 ºC for 15 min., then at rt for 20 min., at which point the mixture was a green slurry. TLC showed complete consumption of the starting material (20% EtOAc/hexanes). The reaction was quenched with MeOH (2 mL) and concentrated to give a green oil, which was purified by column chromatography on a silica gel packed pipette (EtOAc/hexanes, 30–50%) to give acid **306** (6 mg, 76%) as a colorless oil. R_f = 0.27 (50% EtOAc/hexanes with 2 drops of AcOH in 10 mL). ^1H NMR (400 MHz, $CDCl_3$) δ 5.04 (t, *J* = 2.7 Hz, 1H), 4.91 (s, 1H), 3.49 – 3.33 (m, 5H), 2.84 (d, *J* = 4.1 Hz, 1H), 2.80 (s, 2H), 2.37 (td, *J* = 12.3, 4.2 Hz, 1H), 2.30 (t, *J* = 7.2 Hz, 1H), 1.72

(dd, *J* = 12.5, 4.9 Hz, 1H), 1.52 (p, *J* = 6.8 Hz, 2H), 1.34 – 1.15 (m, 5H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 148.0, 120.3, 107.9, 71.9, 67.6, 56.5, 54.0, 48.6, 34.9, 34.3, 33.2, 29.2, 28.3, 22.6, 14.2. HRMS (ESI^+) calcd for $C_{16}H_{24}NO_3$ [M+H] 278.1756, found 278.1742.

4.3.2 2nd Generation Endgame Synthesis of Bicyclic Sordarin Analogs

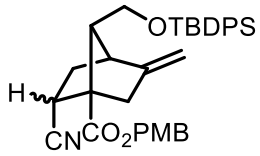


307

4-methoxybenzyl 7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-cyano-5-oxobicyclo[2.2.1]heptane-1-carboxylate. CrO_3 (525 mg, 5.25 mmol) was dissolved in H_2O (2 mL). To the solution was added concentrated H_2SO_4 (0.45 mL), to give Jones reagent (2.5 mL). To a solution of alcohol **302** (767 mg, 1.77 mmol) in acetone (20 mL) in a 50 mL round bottom flask at 0 °C was added Jones reagent (1.77 mL, 4.42 mmol), and the mixture was stirred for 30 min. at rt. TLC (40% EtOAc/hexanes) showed complete consumption of the starting material, so the mixture was quenched with MeOH (5 mL). Na_2SO_4 was added and the mixture was filtered through Celite, and the mother liquor was condensed to a green residue. The crude was dissolved in DCM (10 mL) and passed

through a 10 g silica gel pad, eluting with 80% EtOAc/hexanes. The resulting eluent was concentrated to give a crude yellow oil, which was dissolved in acetone (20 mL) in a 50 mL flask. To this solution was added PMBCl (360 μL, 2.65 mmol), K_2CO_3 (1.222 g, 8.84 mmol) and TBAI (13.1 mg, 0.0354 mmol). The mixture was stirred for 24h at rt, after which time LC-MS indicated incomplete consumption of the starting material. Additional PMBCl (0.200 mL, 1.47 mmol) was added, and the mixture was stirred for another 24 h, after which time LC-MS showed complete conversion to the desired product. The mixture was filtered through Celite, concentrated, and purified by chromatography on a 10 g SiO_2 column (0–40% EtOAc/hexanes) to give ester **307** (388 mg, 39% over 3 steps) as a colorless oil (1:1 diastereomeric mixture). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.51 (comp, 8H), 7.48 – 7.31 (comp, 12H), 7.19 (dd, *J* = 14.1, 8.7 Hz, 4H), 6.81 (dd, *J* = 8.7, 1.8 Hz, 4H), 5.18 – 4.92 (comp, 4H), 3.89 (dd, *J* = 11.3, 4.5 Hz, 1H), 3.78 (s, 6H), 3.60 (t, *J* = 6.2 Hz, 2H), 3.55 – 3.46 (m, 1H), 3.04 – 2.83 (comp, 4H), 2.82 – 2.75 (m, 2H), 2.69 – 2.59 (m, 2H), 2.46 (ddd, *J* = 13.7, 11.8, 4.9 Hz, 1H), 2.40 – 2.33 (m, 1H), 2.28 (dt, *J* = 13.8, 4.8 Hz, 1H), 2.16 – 2.06 (m, 2H), 1.79 (dd, *J* = 13.6, 5.4 Hz, 1H), 1.00 (d, *J* = 4.6 Hz, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.8, 209.7, 169.6, 169.4, 159.9, 135.7, 135.6, 132.6, 132.5, 130.5, 130.2, 130.1, 130.0, 128.8, 128.0, 127.9, 127.0, 127.0, 119.9, 119.2, 114.2, 114.1, 67.7, 60.7, 60.5, 55.6, 55.4, 54.5, 52.4, 51.7, 51.3, 43.8, 39.7, 35.2, 33.9, 29.7, 29.0, 26.8,

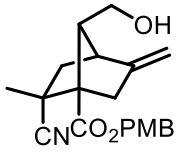
19.2. HRMS (ESI$^+$): calcd for $C_{34}H_{37}NNaO_5Si$ $[M+Na]^+$ 590.2339; found 590.2352.



308

4-methoxybenzyl 7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-cyano-5-methylenebicyclo[2.2.1]heptane-1-carboxylate. To a solution of methyltriphenylphosphonium bromide (18.9 mg, 0.0528 mmol) in dry toluene (1 mL) sealed under N_2 atmosphere was added KHMDS (0.5 M in toluene, 106 µL, 0.0528 mmol), and the mixture was heated at 90 °C for 30 min. To the reaction was added **42** (5.0 mg, 8.8 µmol) in toluene (0.5 mL), and the mixture was stirred for 10 min. at the same temperature. TLC (20% EtOAc/hexanes) indicated complete consumption of the starting material, so the mixture was filtered through Celite and concentrated, then purified by chromatography on a silica gel packed pipette (5–10% EtOAc/hexanes) to give alkene **43** (4.7 mg, 94%) as a colorless oil (1:1 diastereomeric mixture). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 – 7.53 (comp, 8H), 7.48 – 7.30 (comp, 12H), 7.17 (dd, *J* = 11.9, 8.7 Hz, 4H), 6.87 – 6.74 (comp, 4H), 5.14 – 4.90 (m, 6H), 4.82 (s, 1H), 4.78 (s, 1H), 3.99 (dd, *J* = 10.2, 4.6 Hz, 1H), 3.79 (d, *J* = 1.1 Hz, 6H), 3.66 (dd, *J* = 10.6, 6.2 Hz, 1H), 3.56 – 3.35 (m, 3H), 3.06 (d, *J* = 4.2

Hz, 1H), 2.87 (d, *J* = 4.1 Hz, 1H), 2.83 (dd, *J* = 9.3, 5.1 Hz, 1H), 2.73 (s, 2H), 2.59 (dd, *J* = 10.3, 4.6 Hz, 1H), 2.47 (d, *J* = 17.1 Hz, 1H), 2.35 (dd, *J* = 12.3, 4.2 Hz, 1H), 2.30 – 2.11 (m, 3H), 1.97 (dd, *J* = 12.6, 9.3 Hz, 1H), 1.69 (dd, *J* = 12.5, 5.0 Hz, 1H), 1.03 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 171.0, 159.9, 148.3, 147.9, 135.8, 135.7, 133.6, 133.4, 130.4, 130.2, 130.0, 129.9, 129.8, 127.9, 127.9, 127.8, 127.5, 127.5, 121.1, 120.6, 114.2, 114.1, 107.8, 67.3, 61.1, 60.9, 56.9, 56.5, 56.5, 55.5, 53.0, 48.4, 47.5, 38.3, 36.0, 35.5, 34.8, 34.5, 33.5, 29.9, 27.0, 19.5, 19.4. HRMS (ESI^+): calcd for $C_{35}H_{39}NNaO_4Si$ $[M+Na]^+$ 588.2546; found 588.2564.

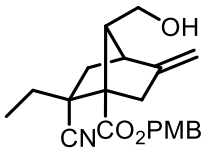


310a

4-methoxybenzyl 2-cyano-7-(hydroxymethyl)-2-methyl-5-methylenebicyclo[2.2.1]heptane-1-carboxylate. To a solution of **308** (57.3 mg, 101 μmol) in toluene (1 mL), sealed under N_2, was added iodomethane (63.0 μL, 1.01 mmol), followed by KHMDS (0.5 M in toluene, 0.61 mL, 0.30 mmol). The mixture was stirred at rt for 3 h, after which time TLC (10% EtOAc/hexanes) indicated complete consumption of the starting material. The mixture was quenched with saturated aqueous NH_4Cl (1 mL), the

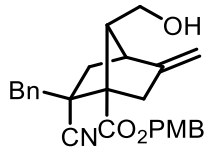
organic phase was separated, and the aqueous phase was extracted with EtOAc (3 x 1 mL). The combined organics were dried over Na_2SO_4, filtered, concentrated, and used directly in the next step. To a solution of this intermediate (**309a**) (49.0 mg, 84.5 μmol) in THF (1 mL) was added a solution of TBAF (1.00 M in THF, 127 μL, 0.127 mmol) at 0 ºC, and the mixture was removed from the ice bath and stirred at rt for 2 h. LC-MS indicated that some of the desired PMB ester product had been hydrolyzed to the carboxylic acid. The mixture was concentrated, then 1 N aqueous HCl (2 mL) was added, and the solution was extracted with EtOAc (3 x 2 mL). The combined organics were dried over Na_2SO_4, concentrated, and re-dissolved in acetone (3 mL). To the solution was added PMBCl (9.2 μL, 0.0676 mmol), K_2CO_3 (14.0 mg, 0.101 mmol), and 5 to 10 crystals of TBAI, and the mixture was stirred for 24 h at rt. TLC (100% EtOAc) indicated that the carboxylic acid was consumed. The mixture was filtered through Celite and concentrated, then purified by chromatography on a silica gel-packed Pasteur pipette (30–40% EtOAc/hexanes), to give **310a** (15.9 mg, 55%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.26 (d, J = 11.9 Hz, 1H), 5.11 (d, J = 11.9 Hz, 1H), 5.01 (t, J = 2.6 Hz, 1H), 4.87 (t, J = 2.2 Hz, 1H), 3.81 (s, 3H), 3.76 – 3.63 (m, 1H), 3.60 – 3.44 (m, 1H), 3.10 (d, J = 8.4 Hz, 1H), 2.98 (dq, J = 17.5, 2.0 Hz, 1H), 2.68 – 2.54 (m, 2H), 2.32 (t, J = 6.4 Hz, 1H), 2.12 – 1.97 (m, 1H), 1.84 (dd, J = 12.4, 3.6 Hz, 1H), 1.25 (s, 3H). ^{13}C NMR (101

MHz, $CDCl_3$) δ 172.5, 159.9, 147.1, 134.9, 130.5, 130.4, 129.7, 128.7, 127.8, 127.2, 123.4, 114.1, 114.1, 114.1, 114.0, 107.9, 67.4, 60.3, 60.2, 55.4, 50.8, 47.5, 45.0, 41.5, 36.2, 24.5. HRMS (ESI^+): calcd for $C_{20}H_{23}NNaO_4$ $[M+Na]^+$ 364.1525; found 364.1530.



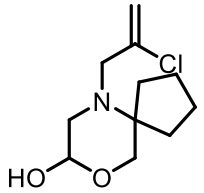
310b

4-methoxybenzyl 2-cyano-2-ethyl-7-(hydroxymethyl)-5-methylenebicyclo[2.2.1]heptane-1-carboxylate. 308 (20.0 mg, 33.7 μmol) was treated following the procedure of **310a** using EtI instead of MeI. **310b** was obtained in 4.6 mg, 38% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.22 (d, *J* = 11.9 Hz, 1H), 5.13 (d, *J* = 11.9 Hz, 1H), 5.02 (t, *J* = 2.6 Hz, 1H), 4.86 (t, *J* = 2.2 Hz, 1H), 3.81 (d, *J* = 0.5 Hz, 3H), 3.70 (dd, *J* = 11.7, 7.4 Hz, 1H), 3.60 – 3.43 (m, 1H), 3.12 – 2.94 (m, 2H), 2.70 – 2.52 (m, 2H), 2.31 (t, *J* = 6.4 Hz, 1H), 1.97 – 1.81 (m, 2H), 1.50 – 1.34 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 159.9, 147.2, 130.4, 127.2, 122.2, 114.1, 107.9, 67.3, 60.7, 60.3, 55.4, 51.3, 47.8, 47.7, 41.8, 36.6, 29.3, 8.9. HRMS (ESI^+): calcd for $C_{21}H_{25}NNaO_4$ $[M+Na]^+$ 378.1681; found 378.1687.



310c

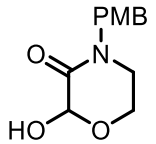
4-methoxybenzyl 2-benzyl-2-cyano-7-(hydroxymethyl)-5-methylenebicyclo[2.2.1]heptane-1-carboxylate. 308 (20.0 mg, 33.7 μmol) was treated following the procedure of **310a** using BnBr instead of MeI. **310c** was obtained in 12 mg, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.27 (comp, 5H), 7.23 – 7.13 (m, 2H), 6.96 – 6.82 (m, 2H), 5.28 (d, *J* = 11.8 Hz, 1H), 5.11 (d, *J* = 11.8 Hz, 1H), 4.97 (t, *J* = 2.6 Hz, 1H), 4.84 (t, *J* = 2.1 Hz, 1H), 3.77 (d, *J* = 0.9 Hz, 4H), 3.63 – 3.49 (m, 1H), 3.18 (s, 1H), 3.09 (d, *J* = 17.7 Hz, 1H), 2.75 – 2.55 (comp, 4H), 2.46 (t, *J* = 6.4 Hz, 1H), 2.07 (dd, *J* = 13.1, 4.3 Hz, 1H), 1.56 (d, *J* = 13.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 160.0, 147.0, 134.2, 130.6, 130.5, 128.6, 127.7, 127.2, 122.7, 114.2, 107.9, 67.4, 61.0, 60.3, 55.4, 51.4, 47.7, 47.1, 41.2, 41.0, 36.5. HRMS (ESI^+): calcd for $C_{26}H_{27}NNaO_4$ $[M+Na]^+$ 440.1838; found 440.1841.



314

6-(2-chloroallyl)-9-oxa-6-azaspiro[4.5]decan-8-ol. To a solution of (1-aminocyclopentyl)methanol[69] (3.10 g, 26.9 mmol) in EtOH (100 mL) was added 2,2-dimethoxyacetaldehyde (60% in water, 4.47 mL, 29.6 mmol). The mixture was stirred at rt for 18 h, after which time crude NMR indicated complete conversion to the intermediate imine. The mixture was quenched with 50 mL 1 N aq. NaOH followed by 50 mL H_2O, then extracted with DCM (3 x 100 mL). The combined organics were dried over Na_2SO_4, filtered, concentrated, and redissolved in Et_2O (100 mL) in a flask sealed under N_2. $LiAlH_4$ (1.02 g, 26.9 mmol) was added, and the mixture was stirred at rt for 30 min. The reaction was quenched by adding EtOAc (50 mL) and saturated aqueous Rochelle's salt (100 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated to give a colorless oil. The intermediate amine was dissolved in EtOH (60 mL) and 2,3-dichloroprop-1-ene (1.05 mL, 11.4 mol), $NaHCO_3$ (2.00 g, 23.8 mol) and NaI (114 mg, 0.763 mmol) were added. The mixture was heated to 80 °C under N_2 atmosphere for 18 h, after which time crude NMR indicated about 10% conversion to the desired product. Additional NaI (1.14 g, 7.63 mmol), $NaHCO_3$ (2.00 g, 23.8 mol), 5 to 10 crystals of TBAI and 2,3-dichloroprop-1-ene (0.1 mL, 1.09 mmol) were added. The mixture was refluxed at 87 °C under N_2 atmosphere for 24 h, after which time crude NMR

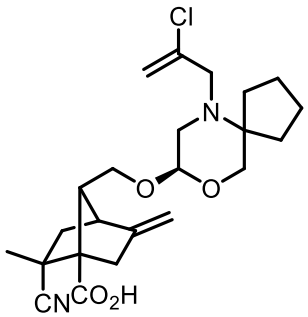
indicated about 80% conversion. The mixture was heated to 100 ºC for another 2 h, then filtered through Celite and concentrated to a yellow oil, which was dissolved in conc. HCl (60 mL). The mixture was then refluxed at 105 °C under N_2 atmosphere for 2 h, the solvent was evaporated, and 6 N NaOH (30 mL) was added. The mixture was extracted with EtOAc (3 x 30 mL), and the combined organics were washed with brine and dried over Na_2SO_4, filtered, concentrated, and purified by chromatography (10–40% EtOAc/hexanes) to give **47** (390 mg, 22% overall yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (app q, *J* = 1.2 Hz, 1H), 5.30 (app q, *J* = 1.0 Hz, 1H), 4.94 (ddd, *J* = 9.0, 3.9, 2.2 Hz, 1H), 3.82 (d, *J* = 9.1 Hz, 1H), 3.69 (dd, *J* = 11.4, 1.2 Hz, 1H), 3.25 (dd, *J* = 11.4, 0.7 Hz, 1H), 3.16 (dt, *J* = 15.0, 1.3 Hz, 1H), 2.96 (d, *J* = 14.8 Hz, 1H), 2.69 (dd, *J* = 11.6, 2.2 Hz, 1H), 2.46 (dd, *J* = 11.6, 3.9 Hz, 1H), 1.86 – 1.30 (comp, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.2, 114.2, 91.5, 69.4, 66.0, 56.4, 52.8, 31.7, 28.4, 25.9, 25.8. HRMS (ESI^+): calcd for $C_{11}H_{19}ClNO_2$ [M+H] 232.1104; found 232.1106.



315

2-hydroxy-4-(4-methoxybenzyl)morpholin-3-one. A solution of 50 wt% aqueous glyoxylic acid (9.14 g, 99.3 mmol) in THF (20 mL) was heated to reflux, then 2-(4-

methoxybenzylamino)ethanol[105] (6.00 g, 33.1 mmol) was added over 30 min, and the reaction was refluxed for another 2 h. THF was distilled off under atmospheric pressure while maintaining a constant volume by simultaneous addition of water (20 mL). The mixture was cooled to rt, then placed in an ice bath for 30 min., where the product crystallized. The solids were filtered with a Buchner funnel, washed with water, and then dried under vacuum at 60 °C for 24 h to give **48** (3.6 g, 46%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.0 Hz, 2H), 6.86 (d, *J* = 7.0 Hz, 2H), 5.34 (s, 1H), 4.91 (s, 1H), 4.65 (d, *J* = 14.4 Hz, 1H), 4.44 (d, *J* = 14.4 Hz, 1H), 4.30 – 4.18 (m, 1H), 3.80 (s, 3H), 3.78 – 3.74 (m, 1H), 3.42 (td, *J* = 11.2, 10.6, 3.9 Hz, 1H), 3.11 (d, *J* = 12.4 Hz, 1H).

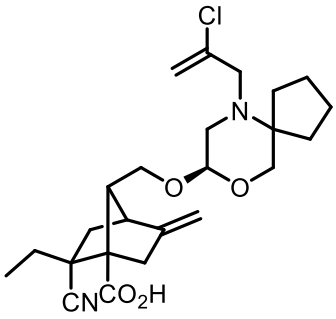


313a

7-(((-6-(2-chloroallyl)-9-oxa-6-azaspiro[4.5]decan-8-yl)oxy)methyl)-2-cyano-2-methyl-5-methylenebicyclo[2.2.1]heptane-1-carboxylic acid. To a solution of **310a** (18.0 mg, 52.7 μmol) and $PhNTf_2$ (20.7 mg, 58.0 μmol) in Et_2O (1 mL), sealed under N_2 and at –50 °C, was added KHMDS (0.5 M in toluene, 211 μL, 105 μmol), and the mixture

was stirred at the same temperature for 10 min. TLC indicated complete consumption of the starting material (40% EtOAc/hexane). The mixture was quenched with aq. NH_4Cl (1 mL) at the same temperature, then extracted with EtOAc (3 x 1 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated to give the crude triflate, which was used directly in the next step. To a solution of **47** (6.1 mg, 26 μmol) in DMF (0.2 mL) was added NaH (60% in mineral oil, 3.4 mg, 88 μmol) at 0 °C. The mixture was stirred at rt for 15 min., then a solution of the crude triflate in DMF (0.1 mL) was added. The mixture was stirred at rt for 1 h, after which time LC-MS indicated complete consumption of the starting material. The reaction was quenched with saturated aqueous NH_4Cl (3 mL) and extracted with EtOAc (3 x 3 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by preparative HPLC to give **313a** (3.3 mg, 43%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 – 5.50 (m, 2H), 5.31 (d, *J* = 1.2 Hz, 2H), 5.11 – 5.02 (m, 2H), 4.94 (s, 2H), 4.59 (dd, *J* = 4.9, 2.7 Hz, 1H), 4.54 (dd, *J* = 5.5, 2.7 Hz, 1H), 4.08 (dd, *J* = 9.7, 5.7 Hz, 1H), 3.68 (d, *J* = 7.8 Hz, 2H), 3.59 (dd, *J* = 11.1, 3.8 Hz, 2H), 3.38 – 3.17 (m, 3H), 3.04 (d, *J* = 5.5 Hz, 5H), 2.97 (s, 1H), 2.84 (d, *J* = 3.9 Hz, 1H), 2.79 (d, *J* = 4.0 Hz, 1H), 2.72 – 2.64 (comp, 3H), 2.60 (d, *J* = 2.7 Hz, 1H), 2.44 (ddd, *J* = 11.7, 9.3, 5.1 Hz, 2H), 2.16 – 2.30 (comp, 12H, presumably obs w/ H_2O), 2.13 (dd, *J* = 12.6, 2.3 Hz, 2H), 1.89 (dt, *J* = 12.7, 3.8 Hz, 2H), 1.59 (d, *J* = 10.5 Hz,

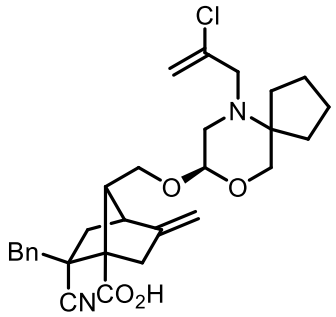
6H), 1.51 (d, J = 1.0 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 172.4, 147.2, 147.1, 140.1, 140.0, 123.4, 123.3, 113.3, 113.1, 108.6, 108.5, 98.7, 98.2, 70.8, 70.3, 68.1, 65.6, 65.5, 65.5, 65.3, 59.5, 59.5, 57.0, 56.9, 52.1, 52.0, 48.2, 48.1, 47.7, 47.6, 44.9, 44.9, 41.9, 41.8, 41.0, 36.2, 36.2, 29.9, 29.8, 25.8, 25.7, 25.0, 25.0, 22.9, 14.3. HRMS (ESI^+): calcd for $C_{23}H_{32}ClN_2O_4$ [M+H] 435.2051; found 435.2060; HPLC (Phenomenex Gemini C_{18}) (25% (0-1.5 min.) - 95% (3.5-10 min), MeCN/H_2O; flow rate, 1.0 mL/min). RT= 7.30 min.



313b

7-(((-6-(2-chloroallyl)-9-oxa-6-azaspiro[4.5]decan-8-yl)oxy)methyl)-2-cyano-2-ethyl-5-methylenebicyclo[2.2.1]heptane-1-carboxylic acid. Following the same procedure of **313a** using **310b** (5.6 mg, 16 μmol) instead of **310a**, **313b** was obtained (1.5 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 – 5.52 (m, 2H), 5.30 (s, 2H), 5.10 – 5.05 (m, 2H), 4.94 (s, 2H), 4.61 – 4.56 (m, 1H), 4.54 (dd, J = 5.5, 2.7 Hz, 1H), 4.08 (dd, J = 9.7, 5.5 Hz, 1H), 3.81 (d, J = 1.0 Hz, 1H), 3.68 (d, J = 7.0 Hz, 2H), 3.58 (dd, J = 11.0, 4.5 Hz, 2H), 3.32 (t, J = 9.2 Hz, 1H), 3.23 (dd, J = 16.4, 11.1 Hz, 2H), 3.13 – 2.96 (comp, 6H), 2.86 (s, 1H),

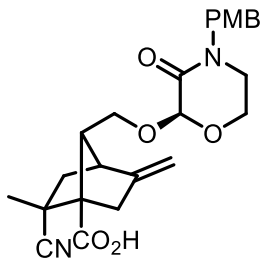
2.80 (s, 1H), 2.71 – 2.56 (m, 2H), 2.49 – 2.35 (comp, 4H), 2.07 – 1.97 (m, 1H), 1.95 (t, *J* = 3.1 Hz, 5H), 1.92 – 1.78 (m, 2H), 1.69 – 1.45 (comp, 16H, presumably obs w/ H_2O), 1.28 (s, 1H), 1.15 – 1.04 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.0, 147.2, 147.2, 140.1, 140.1, 133.8, 114.1, 113.3, 113.1, 108.6, 108.5, 98.8, 98.1, 76.9, 70.8, 70.2, 65.7, 65.5, 65.5, 65.3, 57.0, 56.9, 52.1, 52.0, 48.6, 48.0, 47.8, 47.8, 41.7, 41.6, 40.9, 37.1, 36.7, 36.7, 36.1, 32.1, 29.9, 29.8, 29.5, 29.5, 27.4, 25.8, 25.8, 25.8, 25.7, 22.9, 14.3. HRMS (ESI^+): calcd for $C_{24}H_{34}ClN_2O_4$ [M+H] 449.2207; found 449.2225; HPLC (Phenomenex Gemini C_{18}) (25% (0-1.5 min.) - 95% (3.5-10 min), MeCN/H_2O; flow rate, 1.0 mL/min). RT= 7.06 min.



313c

2-benzyl-7-(((-6-(2-chloroallyl)-9-oxa-6-azaspiro[4.5]decan-8-yl)oxy)methyl)-2-cyano-5-methylenebicyclo[2.2.1]heptane-1-carboxylic acid. Following the same procedure of **313a** using **310c** (7.8 mg, 19 μmol) instead of **310a**, **313c** was obtained (1.9 mg, 21%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (comp, 10H), 5.57 (s, 1H), 5.53 (s, 1H), 5.30 (s, 2H), 5.01 (d, *J* = 7.5 Hz, 2H), 4.89 (s, 2H), 4.64 – 4.58 (m, 1H), 4.57 – 4.50

(m, 1H), 4.25 – 4.08 (m, 1H), 3.70 (dd, *J* = 20.1, 11.3 Hz, 2H), 3.59 (t, *J* = 10.7 Hz, 2H), 3.32 (t, *J* = 9.0 Hz, 1H), 3.26 (d, *J* = 11.1 Hz, 1H), 3.20 (dd, *J* = 12.3, 6.3 Hz, 2H), 3.14 – 2.96 (comp, 6H), 2.84 (s, 1H), 2.77 (s, 1H), 2.72 (d, *J* = 12.0 Hz, 1H), 2.69 – 2.63 (m, 2H), 2.62 (d, *J* = 0.7 Hz, 1H), 2.45 (ddd, *J* = 16.5, 12.8, 7.4 Hz, 5H), 2.14 – 2.02 (m, 2H), 1.57 (comp, 20H, presumably obs w/ H_2O). HRMS (ESI^+): calcd for $C_{29}H_{35}ClN_2O_4$ [M+H] 511.2364; found 511.2370; HPLC (Phenomenex Gemini C_{18}) (25% (0-1.5 min.) - 95% (3.5-10 min), MeCN/H_2O; flow rate, 1.0 mL/min). RT= 8.27 min.



312

2-cyano-7-(((-4-(4-methoxybenzyl)-3-oxomorpholin-2-yl)oxy)methyl)-2-methyl-5-methylenebicyclo[2.2.1]heptane-1-carboxylic acid. 310a (6.0 mg, 17.6 μmol) was treated following the same procedure of **313a** using **315** instead of **314**, **312** was obtained in 1.5 mg, 19% yield. ^1H NMR (400 MHz, CD_3OD) δ 7.18 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 5.10 – 4.95 (m, 1H), 4.94 – 4.80 (m, 1H), 4.63 (t, *J* = 15.7 Hz, 1H), 4.37 (t, *J* = 16.0 Hz, 1H), 4.24 – 3.89 (m, 2H), 3.72 – 3.60 (m, 1H), 3.42 (td, *J* = 12.4, 11.7, 4.8 Hz,

1H), 3.09 (d, *J* = 12.6 Hz, 1H), 2.93 – 2.75 (m, 2H), 2.44 (d, *J* = 17.8 Hz, 1H), 2.31 (d, *J* = 9.9 Hz, 1H), 2.03 – 1.82 (m, 2H), 1.58 (s, 0H), 1.45 (s, 3H), 1.36 – 1.13 (comp, 5H). ^{13}C NMR (151 MHz, CD_3OD) δ 174.1, 174.0, 166.3, 166.2, 160.9, 160.9, 150.0, 150.0, 130.7, 130.6, 129.2, 124.8, 124.8, 115.2, 115.1, 108.4, 108.2, 97.9, 97.0, 91.7, 67.8, 67.6, 67.0, 60.8, 57.9, 57.9, 50.0, 49.7, 46.6, 46.4, 46.1, 45.9, 42.6, 37.3, 33.1, 30.6, 30.5, 30.3, 30.2, 28.1, 26.9, 25.1, 25.0, 23.8. HRMS (ESI^+): calcd for $C_{24}H_{28}N_2NaO_6$ $[M+Na]^+$ 463.1845; found 463.1855, HPLC (Phenomenex Gemini C_{18}) (25% (0-1.5 min.) - 95% (3.5-10 min), MeCN/H_2O; flow rate, 1.0 mL/min). RT= 8.10 min.

4.4 Docking Studies

Representative procedure: (Molecular Forecaster, version 5263) In the *Docking small molecules to proteins* module of the main UI, PDB file 1N0U was introduced. In the PREPARE module, the ligand molecule Residue SO1 A 843 from the PDB file was selected and other parameters were kept unchanged. In the PROCESS module, the prepare for parameter was set to docking to rigid protein, other parameters were unchanged. In the SMART module, a mol2 file containing the structure of interests was used as the source of ligand structure, other parameters were unchanged. Then in the main UI, the Run workflow bottom was clicked to start the calculation. The output sdf files were then visualized in

Pymol.

4.5 Antifungal Assay

The isomeric mixtures **306**, **312** and **313a–c** were subjected to antifungal microdilution assays using Clinical and Laboratory Standards Institute methods M27-A3 and M38-A2 at the Fungus Testing Laboratory at the University of Texas Health Science Center at San Antonio. No inhibition of fungal growth was observed at up to 8 μg/mL, or 4 μg/mL (**313c**), against *C. albicans* (isolate# CA1, CA2, CA3), *A. fumigatus* (isolate# AF1, AF2, AF3), *C. parapsilosis* (CLSI QC), and *P. variotii* (CLSI QC). Minimum inhibitory concentrations (MICs) were determined after 24 h or 48 h (*A. fumigatus*), using fluconazole and voriconazole as positive controls. For comparison, sordarin itself has a reported MIC of 16 μg/mL vs wild type *C. albicans* (strain A28235),[106] and the azasordarin **123** was <0.008 μg/mL.[40]

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