PROGRESS TOWARD THE SYNTHESIS OF A *XENIA* DITERPENOID COMMON INTERMEDIATE AND THE PREPARATION OF INOTILONE DERIVATIVES

by

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ABSTRACT

Xenia diterpenoid natural products (or xenicanes), isolated from the crude organic extracts of coelentrates, have been shown to possess cytotoxic, antiangiogentic, antimicrobial and anti-inflammatory effects against a number of animal cell lines. Structurally, these molecules feature a nine-membered ring containing an endocyclic (*E*)-olefin between C-6 and C-7 and *trans* substituents at C-2 and C-3. Snowden proposed the synthesis of a common xenicane intermediate employing tandem Reformatskii/Grob chemistry. Such a route can allow for a divergent synthesis of a library of *Xenia* diterpenoids. The synthetic strategy mandates beginning from the 1,3-ketol *trans*-3-hydroxy-2-vinyl-2-methylcyclopentan-1-one, a common motif found in the synthesis of medium-sized carbocycles and natural products.

An array of cyclic-2,2-disubstituted-1,3-alkanediones were reduced to the corresponding 1,3-ketols using $NaBH_4$/DME or LTBA/THF to study reaction progress and diastereomeric outcomes. These analyses show that both reducing systems favor formation of the *cis*-ketol; the degree of diastereoselectivity was largely found to be a function of steric bulk in the 2-position. Additionally, both reducing systems minimize over-reduction to the corresponding diol, though this effect is more pronounced with LTBA/THF.

In the investigation of conjugate reduction conditions for the synthesis of Snowden's common intermediate, Stryker's reagent was found to effect reductive aldol cyclization of our enoate dione starting materials to the corresponding β-hydroxy ester. Experimentation with catalytic quantities of Stryker's reagent using hydrosilanes as the stoichiometric reductant on

enoate ketone substrates offered excellent conversions at room temperature with little control of diastereoselectivity. Attempts to expand the bicyclic products via Wharton-type Grob fragmentation resulted in diasteromeric racemization and/or saponification of the ester moiety.

Suppression of the COX-2 isoenzyme has been found to lessen the risk of colorectal cancer onset in epidemiological studies. The natural product inotilone, isolated by Hertweck in 2006 and first synthesized by Snowden in 2007, acts as a potent COX-2 inhibitor. An array of structurally related analogs was prepared by the Mukaiyama aldol reaction of 5-methyl-3-trimethylsiloxyfuran and commercially available benzaldehyes in 14-71% yield. These derivatives will be screened against a number of cancer cell lines to assess biological activity relative to the parent inotilone compound.

LIST OF ABBREVIATIONS AND SYMBOLS

AA	arachidonic acid
Ac	acetyl
acac	acetylacetone
Am	amyl
9-BBN	9-borabicyclo[3.3.1]nonane
BDP	1,2-bis(diphenylphosphino)benzene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Bu	butyl
CBz	carbobenzyloxy
COX	cyclooxygenase
CRC	colorectal cancer
δ	chemical shift in parts per million
d	doublet (spectral)
dd	doublet of doublet (spectral)
DBU	diazabicycloundecene
DCM	dichloromethane or methylene chloride
DEAD	diethylazodicarboxylate

DIBAH	diisobutylaluminum hydride
dimsyl	dimethylsulfoxide anion
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMS	dimethylsulfide
DPPF	1,1'-dis(diphenylphosphino)ferrocene
dr	diasteromeric ratio
eu	entropy units
Et	ethyl
equiv	equivalent
FDA	Food and Drug Administration
g	grams
GI	gastrointestinal
h	hours
HBC	hexabromocyclopentadiene
HMBC	heteronuclear multiple bond correlation
HRMS	high resolution mass spectrometry
HSD	hydroxysteroid deoxygenase
IC_{50}	50% inhibitory concentration
Im	imidazole
IR	infrared
kcal	kcal
L	liter(s)

LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LTBA	lithium tri-*tert*-butoxyaluminum hydride
LUMO	lowest unoccupied molecular orbital
*m*CPBA	*meta*-chloroperoxybenzoic acid
m	milli- (measurement), multiplet (spectral)
Me	methyl
min	minute(s)
mol	mole(s)
MOM	methoxymethyl ether
Ms	methanesulfonyl
n	normal
NaO*t*-Pen	sodium tert-pentoxide
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NSAID	nonsteroidal anti-inflammatory drug
OAc	acetate
OTf	trifluoromethanesulfonate
P_2-Et	1-Ethyl-2,2,4,4,4-pentakis(dimethylamino)-2λ^5,4λ^5-catenadi(phosphazene)
PCC	pyridinium chlorochromate
Pen	pentyl
Ph	phenyl

PhMe	toluene
PMHS	polymethylhydrosiloxane
ppm	parts per million
Pr	propyl
rt	room temperature
s	singlet (spectral)
SSRI	selective serotonin reuptake inhibitor
t	triplet (spectral)
TBAF	tetra-*n*-butylammonium fluoride
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBS	*tert*-butyl-dimethylsilyl
TEA	triethylamine
TES	triethylsilane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMDS	tetramethyldisiloxane
TMEDA	tetramethylethylenediamine
TMS	tetramethylsilane (spectral); trimethylsilyl (synthetic)
Ts	toluenesulfonyl
XO	xanthine oxidase
XRD	X-ray diffraction

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CHAPTER 1

AN OVERVIEW OF *XENIA* DITERPENOIDS AND THE SYNTHETIC STRATEGY TOWARD A COMMON STRUCTURE

1.1 Introduction

Since the beginning of recorded history, nature has played a vital role in the treatment of a wide array of ailments.[1] Oils derived from natural sources have been administered to combat infections, mitigate inflammation and even treat common colds. We now know that these "therapies" were impure concoctions—mixtures containing several compounds in addition to the active ingredient. By comparison, singular, pure natural products are relatively new, and their interest arguably began with the isolation of morphine in 1816.[2] Since then, thousands of molecules have been isolated from natural sources for medicinal, industrial and scientific purposes.

Beginning with Wohler's synthesis of urea from ammonia,[3] arguably marking the origins of research-based natural product synthesis,[4] chemists have awakened to the opportunity to mimic nature in the laboratory—a practice now considered a cornerstone of organic chemistry.[5] Apart from supplying chemists with structurally interesting targets, nature's molecules are also

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[1] Newman, D. J.; Cragg, G. M.; Snader, K. M. "The influence of natural products upon drug discovery." *Nat. Prod. Rep.* **2000**, *17*, 215-234.
[2] Bhat, S. V.; Nagasampagi, B. A.; Sivakumar, M. *Chemistry of Natural Products*, 1st ed, Springer, 2004; p 5.
[3] Wohler, F. "Ueber künstliche Bildung des Harnstoffs." *Ann. Phys. Chem.* **1828**, *88*, 253-256.
[4] Cohen, P. S.; Cohen, S. M. "Wohler Synthesis of Urea: How Do the Textbooks Report It?" *J. Chem. Ed.* **1996**, *73*, 883.
[5] Banwell, M. "Research in natural product synthesis: a vital and dynamic global enterprise." *Tetrahedron* **2008**, *64*, 4669-4670.

known to be biologically active and in fact capable of treating ailments such as pain and inflammation and diseases such as neurosis and certain cancers. One desire of organic chemists lies in the preparation or modification of natural products to develop new medicines.

The combination of discovery, synthesis and modification of natural products has provided the pharmaceutical industry with a vast arsenal of potential lead compounds capable of treating a wide array of diseases. Between the years 1981 and 2006, approximately 1000 new therapeutic agents were brought to market.[6] As seen in Figure 1.1, the majority of these compounds are totally synthetic—the outcome of random biological screening or modification of an existing target—or entirely/partially prepared from a natural product (including semi-synthetics). Despite this prevalence, therapeutic development in recent years has shifted away from natural product research.[7] The purportedly dismal productivity[8] plaguing the development of new medicines could be resolved by the continued "exploration of Nature as a source of novel active agents that may serve as leads and scaffolds." The root of this endeavor lies in the identification, synthesis, modification and screening of biologically active natural products.

[6] (a) Newman, D. J.; Cragg, G. M.; Snader, K. M. "Natural Products as Sources of New Drugs over the Period 1981-2002." *J. Nat. Prod.* **2003**, *66*, 1022-1037. (b) Newman, D. J.; Cragg, G. M. "Natural Products as Sources of New Drugs over the Last 25 Years." *J. Nat. Prod.* **2007**, *70*, 461-477.

[7] Baker, D. D.; Chu, M.; Oza, U.; Rajgarhia, V. "The value of natural products to the future of pharmaceutical discovery." *Nat. Prod. Rep.* **2007**, *24*, 1225-1244.

[8] Rouhi, M. A. "Rediscovering Natural Products." *Chem. Eng. News.* **2003**, *81*, 77-78.

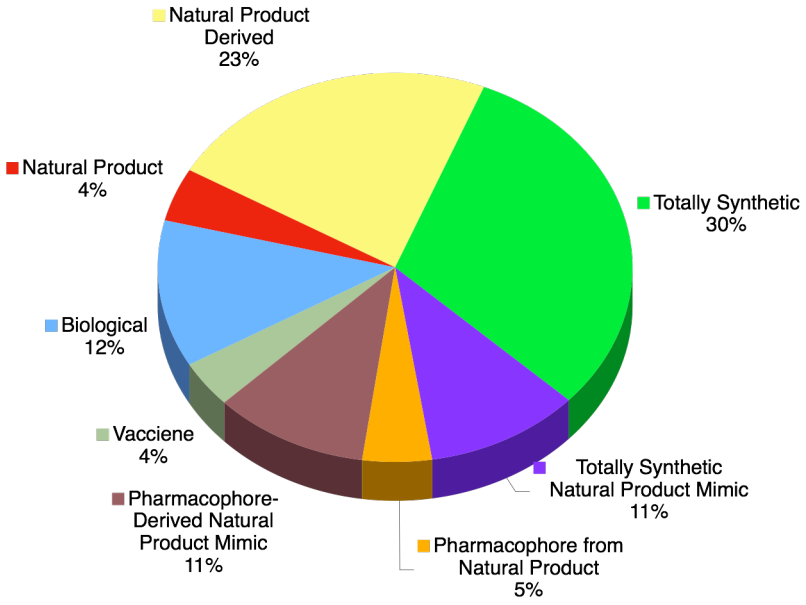


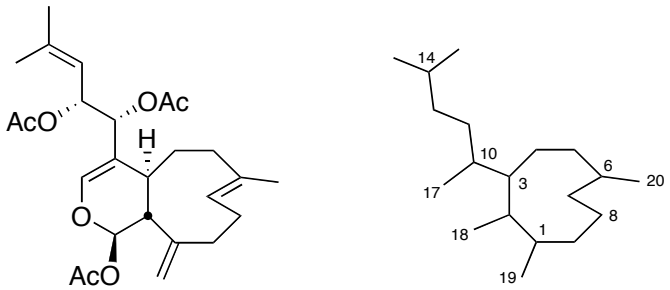
Figure 1.1. New chemical entities and medical indications by source of compound 01/1981-06/2006.[6]

1.1.1. Xenicanes and their Potential Medical Value

Coelentrates of the genus *Xenia* are known to contain a wide range of biologically active natural products. Of these, the diterpenoids have gained interest from the scientific community in the past 20 years due to their structural and pharmacological value. The first of these compounds, xenicin (**1.1**), was reported by Schmitz and van der Helm in 1977 (Figure 1.2).[9] Xenicin was isolated from the crude organic extracts of the soft coral *Xenia elongata*, an organism common to Southern Australia. Structurally, xenicanes contain a complex carbon framework, possessing varying degrees of oxidation and unsaturation throughout their structure. The numbering of the carbon framework (**1.2**) was proposed by Schmitz and van der Helm,[9] and

[9] Vanderah, D. J.; Steudler, P. A.; Ciereszko, L. S.; Schmitz, F. J.; Ekstrand, J. D.; van der Helm, D. "Marine Natural Products. Xenicin: a Diterpenoid Possessing a Nine-Membered Ring from the Soft Coral, *Xenia elongata.*" *J. Am. Chem. Soc.* **1977**, *99*, 5780-5784.

is still widely used to date. Considering **1.1** as an example, xenicanes commonly share a 6,7-trisubsituted (*E*)-cyclononene ring attached to *trans*-fused substituents at C-2 and C-3 in addition to an exocyclic methylene function.



1.1 **1.2**

Figure 1.2. Xenicin (**1.1**) and Vanderah's proposed numbering system (**1.2**).[9]

Some time after Schmitz and van der Helm's seminal contribution,[9] Kashman and Groweiss reported several new structures isolated from the same genus of soft corals.[10,11] Since then, structurally similar, biologically active xenicanes have been reportedly isolated from specimens such as *Xenia elongata*, *X. faraunensis*, *X. florida* and *X. corallium*. This molecular-organism relationship suggests a "distinctive chemotaxonomic feature."[12] The Pfander group later proposed that *Xenia* diterpenoids could be classified into the following four main groups (Figure 1.3):[13] xeniolides (**1.3**, lactone ring), xenicins (**1.4**, acetal ring), xeniaphyllanes (**1.5**, cyclobutane ring) and dictyotadials (**1.6**).

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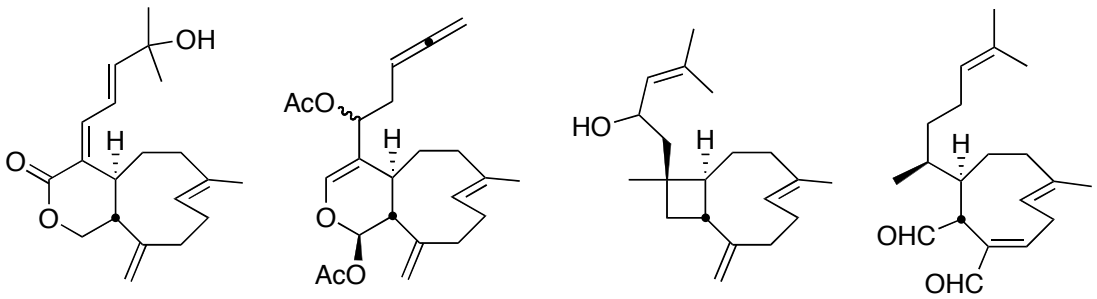
[10] Kashman, Y.; Groweiss, A. "New diterpenoids from the soft corals Xenia macrospiculata and Xenia obscuronata." *J. Org. Chem.* **1980**, *45*, 3814-3824.
[11] Kashman, Y.; Saltoun M.; Rudi, A.; Benayahu, Y. "Xeniafaraunol A and B, and Faraunatin; Three New Cytotoxic Diterpenes from the Soft Coral *Xenia faraunensis*." *Tetrahedron Lett.* **1994**, *35*, 8855-8858.
[12] Kashman, Y.; Groweiss, A.; Carmely, S.; Kinomoni, Z.; Czarkie, D.; Rotem, M. "Recent Research in Marine Natural Products from the Red Sea." *Pure Appl. Chem.* **1982**, *54*, 1995-2010.
[13] Liu, G.; Smith, T. C.; Pfander, H. "Synthesis of Optically Active *trans*-Cyclononenes A Possible Approach to Xenicanes." *Tetrahedron Lett.* **1995**, *36*, 4979-4982.



9-deoxyxeniolide A (Xeniolide group) **1.3** | ginamallene (Xenicin group) **1.4** | xeniaphyllenol A (Xeniaphyllane group) **1.5** | dictyotadial **1.6**

Figure 1.3. Representative *Xenia* diterpenoids depicted to highlight their structural diversity.

Structurally similar xenicane derivatives have also been reportedly isolated from the organic extracts of brown algae.[14,15] Though, these xenicane derivatives possess the opposite absolute configurations relative to xenicin.[16] A similar observation was made when comparing the absolute arrangement of atoms in plant-derived β-caryophyllene against soft coral-derived antheliolide A.[17]

Xenicanes and corresponding analogs have demonstrated impressive pharmacological properties that include cytotoxic,[18,19,20] antiangiogenic,[21] antimicrobial[22], and anti-inflammatory[23]

[14] Awad, N. E.; Selim, M. A.; Metawe, H. M.; Matloub, A. A. "Cytotoxic Xenicane Diterpenes from the Brown Alga *Padina pavonia* (L.) Gaill." *Phytotheraphy Res.* **2008**, *22*, 1610-1613.
[15] Konig, G. B.; Wright, A. D.; Sticher, O. "New xenicane and hydroazulenoid diterpenes from an Australian collection of *Dictyota divaricata*." *Tetrahedron* **1991**, *47*, 1399-1410.
[16] Ohtani, I.; Kusumi, T.; Ishitsuka, M. O.; Kakisawa, H. "Absolute Configurations of Marine Diterpenes Possessing a Xenixane Skeleton. An Application of an Advanced Mosher's Method." *Tetrahedron Lett*. **1989**, *30*, 3147-3150.
[17] Mushti, C. S.; Kim, J.-H.; Corey, E. J. "Total Synthesis of Antheliolide A." *J. Am. Chem. Soc.* **2008**, *128*, 14050-14052.
[18] Fusetani, N.; Asano, M.; Matsunaga, S.; Hashimoto, K. "Acalycizeniolides, novel norditerpenes with inhibit cell division of fertilized starfish eggs, from the gorgonian *Acalycigorgia inermis*." *Tetrahedron Lett.* **1987**, *28*, 5837-5840.
[19] Bouaicha, N.; Pesando, D.; Puel, D. "Cytotoxic diterpenoids from the brown alga *Dilophus ligulatus*." *J. Nat. Prod.* **1993**, *56*, 1747-1752.
[20] Ishitsuka, M.; Kusumi, T.; Kakisawa, H. "Antitumor xenicane and norxenicane lactones from the brown algae *Dictyota dichotoma*." *J. Org. Chem.* **1988**, *53*, 5010-5013.

effects. Xenicanes cytotoxic effects against a number of animal cell lines are briefly summarized in Table 1. The data suggests that xenicanes may provide a promising avenue of exploration in the realm of cancer treatment. Relative to the currently employed anti-cancer drugs, xenicanes have reportedly exhibited cytotoxicity greater than or equal to that of cisplatin in human lung and liver carcinoma assays.[14]

Table 1.1. Potencies of select *Xenia* diterpenoids against animal cancer cell lines.

Xenia Diterpenoid	*Biological Activity*	*Potency (μg/mL)*
Acalycigorgin E	Brine shrimp lethality	LC_{50} 1.5
Acalycixeniolide A	*Asterina peclimifera* (starfish) eggs	ED_{50} 20
Acalycixeniolide B	*Asterina peclimifera* (starfish) eggs	ED_{50} 5
Acalycixeniolide E	K562 (human leukemia cell line)	LC_{50} 4.7
	Farnesyl protein transferase	IC_{50} 10
	HUVEC (angiogenesis) inhibition	IC_{50} 10
9-Deoxyxeniolide A	K562 (human myelogenous leukemia)	LC_{50} 0.04
Farauntain	P-388 (murine lymphocytic leukemia)	IC_{50} 1.2
Ginamallene	P-388	ED_{50} 0.27
	Sea urchin egg division	IC_{50} 1.0
Umbellacin F	P-388	ED_{50} 3.7
Xeniafauranol A	P-388	IC_{50} 1.2
Xeniafauranol B	P-388	IC_{50} 1.2
Xenitacin	A549 (human lung adenocarcinoma)	ED_{50} 3.3
	HT-29 (human colon cancer)	ED_{50} 1.1
	P-388	ED_{50} 1.1

The limitation regarding the exploration of *Xenia* diterpenoids as potential medicines has chiefly been the difficulty in obtaining these compounds in sufficient quantities.[24,25] Many of the

[21] Rho, J.-R.; Oh, M.-S.; Jang, K. H.; Cho, K. W.; Shin, J. "New Xenicane Diterpenoids from the Gorgonian *Acalycigorgia inermis*." *J. Nat. Prod.* **2001**, *64*, 540-543.
[22] Iwagawa, T.; Kawasaki, J.; Hase, T. "New Xenia Diterpenes Isolated from the Soft Coral, *Xenia florida*." *J. Nat. Prod.* **1998**, *61*, 1513-1515.
[23] Hooper, G. J.; Davis-Coleman, M. T.; Schleyer, M. "New diterpenes from the South African soft coral *Eleutherobia aurea*." *J. Nat. Prod.* **1997**, *60*, 889-893.
[24] Andrianasolo, E. H.; France, D.; Cornell-Kennon, S.; Gerwick, W. H. "DNA Methyl Transferase Inhibiting Halogenated Monoterpenes from the Madagascar Red Marine Alga *Portieria hornemanni*." *J. Nat. Prod.* **2006**, *69*, 576-579.

host organisms are endangered and/or grow in complex environments which are difficult to mimic in a laboratory setting. Additionally, the yield of pure xenicane relative to the mass of dried organism is generally unuseful for pharmaceutical development. For example, Fusetani and co-workers yielded 40 mg (or 0.02%) of **1.4** from a 200 g sample of dried *Acalycigorgia inermis*.[26]

Despite the prominance of *Xenia* diterpenoids in the literature, there is relatively little information outlining an effective strategy towards accessing a library of these molecules.[27] To date, the synthesis of a *Xenia* diterpenoid has been limited to a few examples. The next section will provide background information in discussing the several strategies used to synthesize xenicanes and their structurally related derivatives. Because the nine-membered ring is a common feature in each target, the synthetic strategies described below are organized into two categories. The first category describes routes employing a Grob fragmentation to access the nine-membered ring. The second category identifies syntheses that do not involve fragmentation approaches to access the nine-membered ring.

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[25] Andrianasolo, E. H.; Haramaty, L.; Degenhardt, K.; Mathew, R.; White, E.; Lutz, R.; Falkowski, P. "Induction of Apoptosis by Diterpenes from the Soft Coral *Xenia enlongata*." *J. Nat. Prod.* **2007**, *70*, 1551-1557.

[26] Hokama, S.; Tanaka, J.; Higa, T.; Fusetani, N.; Asano, M.; Matsunaga, S.; Hashimoto, K. "Ginamallene, a New Norditerpene with Allene Functionality from Four Gorgonians of the Genus Acalycigorgia."*Chem Lett.* **1988**, 855-856.

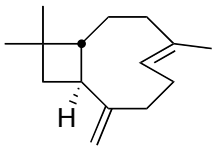
[27] Pollex, A.; Hiersemann, M. "Catalytic Asymmetric Claisen Rearrangement in Natural Product Synthesis: Synthetic Studies toward (-)-Xeniolide F." *Org. Lett.* **2005**, *7*, 5705-5708.

1.2 Background

1.2.1. Xenicane and Analog Syntheses Involving Grob Fragmentations

1.2.1.1. Corey's β-Caryophyllene

The first synthesis of a natural product containing the xenicane-like cyclononene framework was, in fact, not a *Xenia* diterpenoid. In 1964, Corey and co-workers reported the total synthesis of racemic β-caryophyllene (**1.7**),[28] a [7.2.0]-bicyclic compound that, like xenicanes, possesses an endocyclic (*E*)-olefin and *trans* substitutents at C-2 and C-3 (Figure 1.4). Though the structural details are reminiscent of molecules classified as *Xenia* diterpenoids, caryophyllenes are a completely different class of molecules, naturally occurring in plants such as clove (*Syzygium aromaticum*), hemp (*Cannabis sativa*) and rosemary (*Rosmarinus oficinalis*). Despite the taxonomic disparity between β-caryophyllenes and *Xenia* diterpenoids, Corey's synthesis of the former would provide a useful paradigm in future syntheses attempting to access xenicanes.



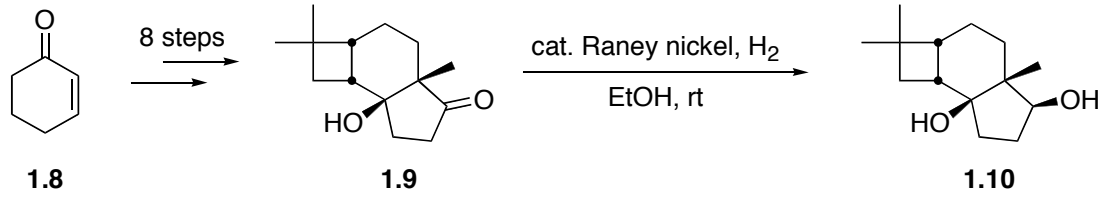
1.7

Figure 1.4. β-Caryophyllene.

Corey's synthesis of β-caryophyllene began with the construction of tricyclic ketol **1.9** from commercially available cyclohexanone (**1.8**) over the course of 8 steps (Scheme 1.1). Reduction of the **1.9** with catalytic quantities of Raney-nickel under an atmosphere of hydrogen

[28] Corey, E. J.; Mitra, R. B.; Uda, H. "Total Synthesis of d,l-Caryophyllene and d,l-Isocaryophyllene." *J. Am. Chem. Soc.* **1964**, *85*, 485-492.

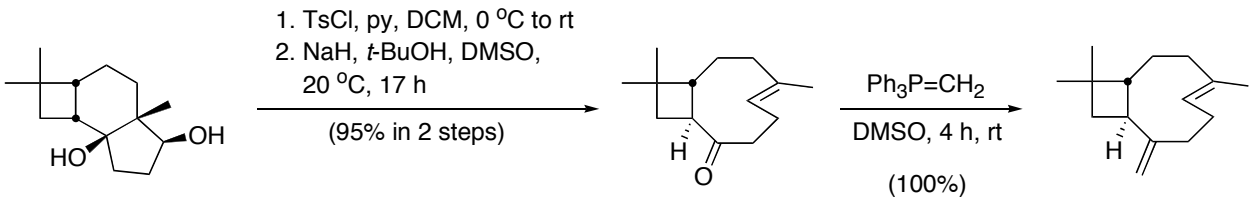
provided diol **1.10** along with some of its *anti*-diastereomer. A combination of column chromatography and repeated recrystallizations provided the *cis*-diol (**1.10**) in its pure form.



1.8 **1.9** **1.10**

Scheme 1.1. Early steps in Corey's synthesis of β-caryophyllene.[28]

Conversion of the secondary alcohol **1.10** to the corresponding sulfonyl ester proceeded smoothly (Scheme 1.2). Subsequent treatment of the tosylate with NaH in *t*-BuOH/DMSO for prolonged reaction times promoted the Wharton-type Grob fragmentation step,[29] effecting isomerization and providing cyclononone **1.11** in excellent yield over two steps. The relative placement of the hydroxyl and methyl substitutents about the cyclopentane moiety in **1.10** proved critical to the stereospecific formation of the (*E*)-olefin in **1.11**. Corey noted that the *trans*-diol furnished the (*Z*)-olefin, which served as the basis for accessing *iso*-caryophyllene. Methylenation of the cyclononone provided β-caryophyllene (**1.7**) in reportedly quantitative yield.



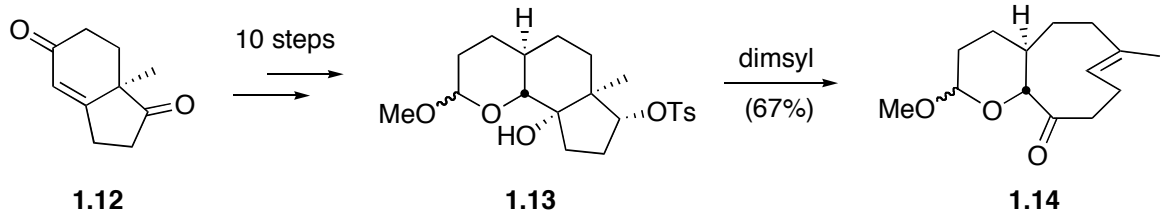
1.10 **1.11** **1.7**

Scheme 1.2. The late stages of Corey's synthesis of β-caryophyllene (**1.7**).[28]

[29] Wharton, P. "Stereospecific Synthesis of 6-Methyl-trans-5-cyclodecenone." *J. Org. Chem.* **1961**, *26*, 4781-4782.

1.2.1.2. Pfander and Leumann's Coraxeniolide A

Pfander and co-workers reported a synthetic route to the optically active xeniolide carbon skeleton **1.14**.[13] His communication marked the first synthetic efforts toward synthesizing a *Xenia* diterpenoid by highlighting a single compound that may be used to access a library of structurally related natural products. Beginning from (-)-Hajos-Parrish ketone (**1.12**),[30] Pfander accessed tosylate (**1.13**) in ten steps, as seen in Scheme 1.3. Then, inspired by Corey's β-caryophyllene synthesis,[28] Pfander initiated the dimsyl-mediated Wharton-type Grob fragmentation[29] to afford **1.14** in modest yield.[13]



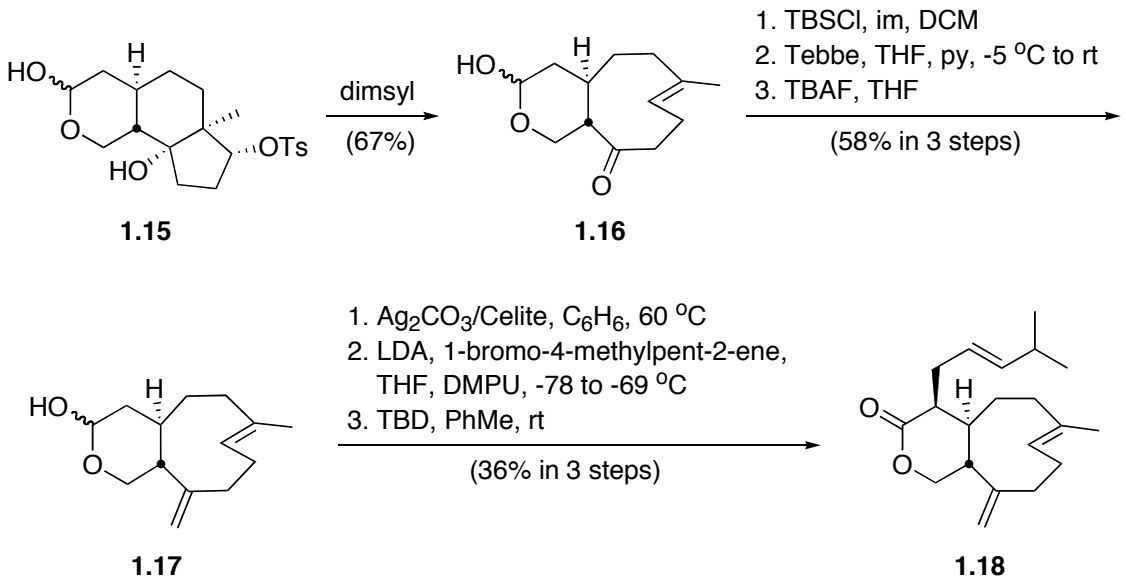
1.12 **1.13** **1.14**

Scheme 1.3. An excerpt of Pfander's synthesis of xenicane carbon skeleton **1.14** from (-)-Hajos-Parrish ketone (**1.12**).[13]

Leumann, Pfander and Renneburg employed a variation of Pfander's initial strategy in the total synthesis of coraxeniolide A,[31] a xenicane reportedly isolated from the pink coral *Xenia corallium* by Scheuer and co-workers in 1981.[32] Like Pfander's seminal synthetic route, Leumann's began from (-)-Hajos-Parrish ketone (**1.12**),[30] ultimately synthesizing tosylate **1.15** over the course of 15 steps (Scheme 1.4). Sulfonyl ester **1.15** was expanded to a nine-membered ring through the introduction of dimsyl. Protection of the alcohol as the TBS ether allowed for methylenation of the carbonyl in 70% yield. Ensuing deprotection provided the cyclononene

[30] Hajos, Z. G.; Parrish, D. R. "Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry." *J. Org. Chem.* **1974**, *39*, 1615-1621.
[31] Renneberg, D.; Pfander, H.; Leumann, C. J. "Total Synthesis of Coraxeniolide-A." *J. Org. Chem.* **2000**, *65*, 9069-9079.
[32] Schwartz, R. E.; Scheuer, P. J.; Zabel, V.; Watson, W. H. "The Coraxeniolides, Constituents of Pink Coral, *Corallium* Sp." *Tetrahedron* **1981**, *37*, 2725-2733.

ring in **1.17**, which upon treatment with Fetizon's reagent resulted in clean formation of the lactone. Finally, installation of the *iso*-hexene arm was accomplished through alkylation of the corresponding lithium enolate with 1-bromo-4-methylpent-2-ene. A 1:5.7 diasteromeric mixture of coraxeniolide A diasteromers (**1.18**) was isolated in 50% yield in favor of the undesired epimer. However, equilibration of **1.18** with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) provided the desired product. Leumann's synthetic efforts marked the first example of a xenicane total synthesis.



1.15 **1.16** **1.17** **1.18**

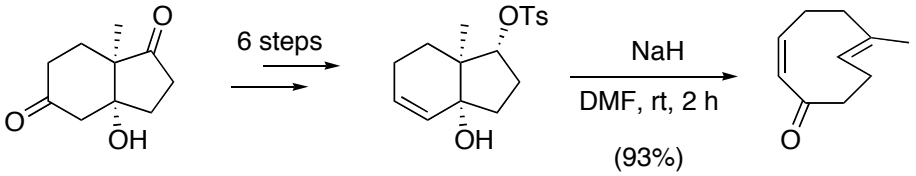
Scheme 1.4. The late stages of Leumann's synthesis of coraxeniolide A (**1.18**).[31]

1.2.1.3. Corey's Synthesis of Coraxeniolide A and Second Approach to β-Caryophyllene

Recently, Corey and Larionov published a concise synthesis of coraxeniolide A[33] beginning from enantiomerically pure Hajos-Parish ketol **1.19**.[30] As seen in Scheme 1.5, sulfonyl ester **1.20** was prepared from **1.19** over the course of six steps in 24% overall yield.

[33] Larionov, O. V.; Corey, E. J. "An Unconventional Approach to the Enantioselective Synthesis of Caryophylloids." *J. Am. Chem. Soc.* **2008**, *130*, 2954-2955.

Allylic alcohol **1.20** was subjected to alkoxide-promoted Wharton-type Grob fragmentation[29] to provide optically active dienone **1.21** in excellent reported yield.



1.19 **1.20** **1.21**

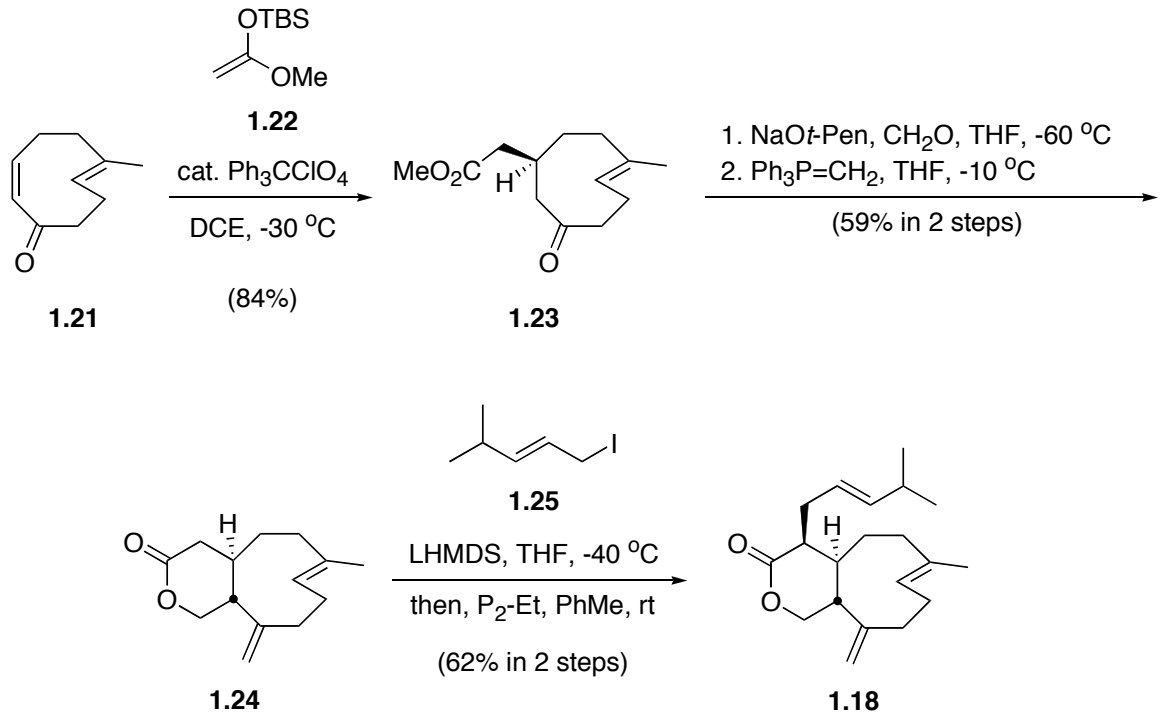
Scheme 1.5. An excerpt of Corey's synthesis of cyclononadienone **1.21**.[33]

Mukiayama aldol addition of silyl ketene acetal **1.22** to **1.21** in the presence of trityl perchlorate[34] provided conjugate adduct **1.23** in good yield (Scheme 1.6). Regioselective deprotonation of ketone **1.23** followed by enolate trapping with formaldehyde resulted in lactonization. Ensuing Wittig-type olefination with methylene triphenylphosphorane gave diene **1.24**. Finally, α-alkylation of lactone **1.24** was achieved through trapping of the corresponding lithium enolate with iodide **1.25**. This process provided the undesired coraxeniolide A epimer, which was converted to the desired natural product (**1.18**) by treatment with Schwesinger's reagent (P_2-Et).[35]

---

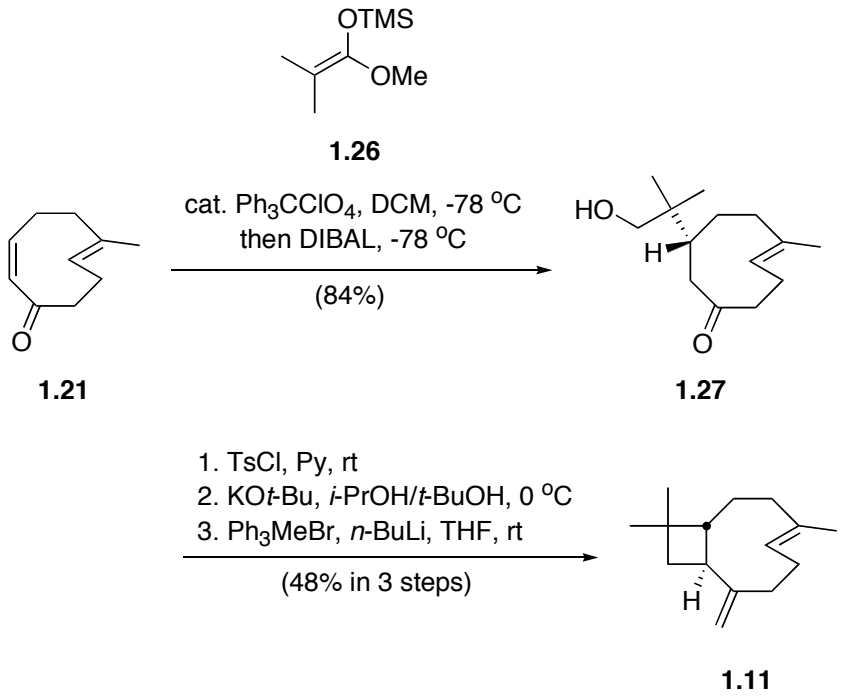
[34] (a) Kobayashi, S.; Mukaiyama, T. "Trityl perchlorate catalyzed tandem Michael-aldol reaction. A facile method for the stereoselective synthesis of γ-acyl substituted δ-hydroxy ketone derivatives." *Chem. Lett.* **1986**, *15*, 221-224. (b) Mukaiyama, T.; Tamura, M.; Kobayashi, S. "The stereoselective Michael reaction between silyl enol ethers and α,β-unsaturated ketones by use of trityl perchlorate as a catalyst." *Chem. Lett.* **1986**, *15*, 1017-1020

[35] (a) Schwesinger, R.; Schlemper, H. "Peralkylierte Polyaminophosphazine –extrem starke neutrale Stickstoffbasen." *Angew. Chem.* **1987**, *99*, 1212-1214. (b) Pietzonka, T.; Seebach, D. "Allylations of (*R*,*R*)-2-*t*-Butyl-6-methyl-1,3-dioxan-4-ones which are not Possible with Lithium Amides may be Achieved with a Schwesinger P4 Base." *Chem. Ber.* **1991**, *124*, 1837-1843. (c) Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. "Novel, Very Strong, Uncharged Auxiliary Bases; Design and Synthesis of Monomeric and Polymer-Bound Triaminoiminophosphorane Bases of Broadly Varied Steric Demand." *Chem. Ber.* **1994**, *127*, 2435-2454.



Scheme 1.6. Corey's synthesis of coraxeniolide A (**1.18**) from cyclononone **1.21**.[33]

Corey's attempt at synthesizing coraxeniolide A enantioselectively offered a significant development in the realm of xenicane syntheses. Creation of a common intermediate allowed for divergent syntheses of more than one diterpenoid, evidenced in the total synthesis of (-)-β-caryophyllene (**1.11**) from enone **1.21** over the course of four steps (Scheme 1.7).[33] Perchlorate-mediated Mukaiyama aldol addition[34] and ensuing selective reduction of the ester over the in situ-generated silyl enol ether provided alcohol **1.27** after desilylative workup with TEA•3HF. Tosylation, intermolecular α-alkylation followed by olefination provided **1.11** in good yield over three steps.



Scheme 1.7. An excerpt of Corey's synthesis of β-caryophyllene (**1.11**) from intermediate cyclononone **1.21**.[33]

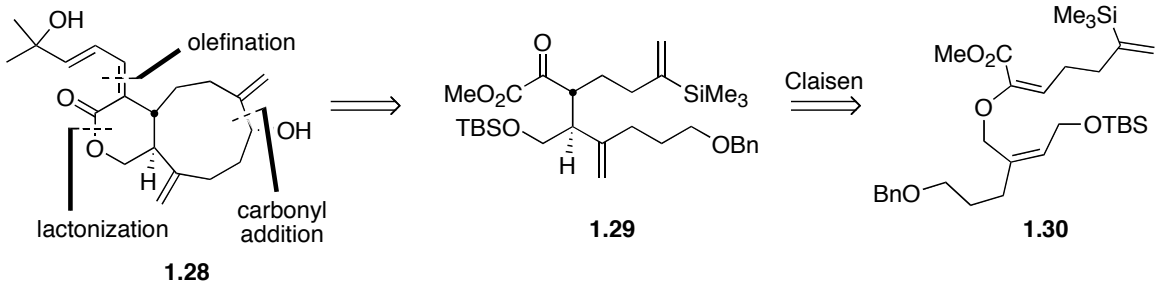
Corey's recent approach to coraxeniolide A and β-caryophyllene added a new chapter to the xenicane total synthesis saga. Through the construction of intermediate **1.21** from a known compound (**1.19**) in good yield over seven steps, Corey was able to expediently access two natural products in a divergent manner.

1.2.2. Xenicane and Analog Syntheses not Involving Grob Fragmentations

1.2.2.1. Hiersemann's Route to (-)-Xeniolide F

Hiersemann and Pollex reported the construction of intermediate **1.29**, which they argued would be used to access (-)-xeniolide F (**1.28**).[27] Though the absolute configuration of the antipode of **1.28** has not been entirely determined, it has demonstrated strong inhibitory effects

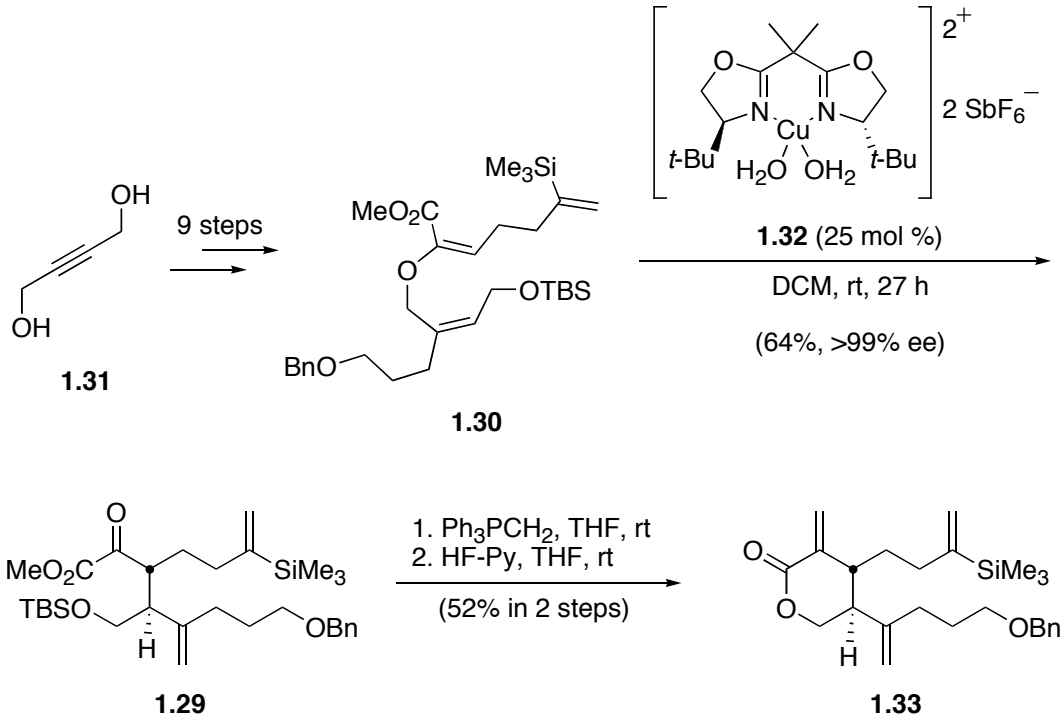
of mouse and human tumor cell lines,[36] making its synthesis interesting from a chemical, structural and medicinal standpoint. Compound **1.28** would be constructed to compare the stereochemistry at the fused bicycle against its enantiomer. Retrosynthetically, the cyclononene ring in **1.28** would hypothetically derive from **1.29** through a stereoselective carbonyl addition reaction (Scheme 1.8). Additionally, α-keto ester **1.29** derives from **1.30** through a copper-catalyzed asymmetric Claisen rearrangment,[37] the featured reaction in the synthesis.



Scheme 1.8. An excerpt of Hiersemann's retrosynthetic analysis of (-)-xeniolide F (**1.28**).[27]

As seen in Scheme 1.9, allyl vinyl ether **1.30** was synthesized in 9 steps beginning from commercially available 2-butyne-1,4-diol (**1.31**). Use of Evan's catalyst (**1.32**)[38] to mediate the asymmetric Claisen rearrangement of **1.30** provided **1.29** in modest yield and excellent enantioselectivity. Olefination and ensuing desilylative lactonization funished lactone **1.33** in a sequence employed to demonstrate progress toward (-)-xeniolide F.

[36] Anta, C.; González, N.; Santafé, G.; Rodríguez, J.; Jiménez, C. "New Xenia Diterpenoids from the Indonesian Soft Coral *Xenia* sp." *J. Nat. Prod.* **2002**, *65*, 766-768.
[37] Abraham, L.; Korner, M.; Hiersemann, M. "Highly Enantioselective Catalytic Asymmetric Claisen Rearrangement of 2-Alkoxycarbonyl-substituted allyl vinyl ethers." *Tetrahedron Lett.* **2004**, *45*, 3647-3650.
[38] Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. "Chiral Bis(oxazoline)copper(II) Complexes as Lewis Acid Catalystis for the Enantioselective Diels-Alder Reaction." *J. Am. Chem. Soc.* **1999**, *121*, 7559-7573.

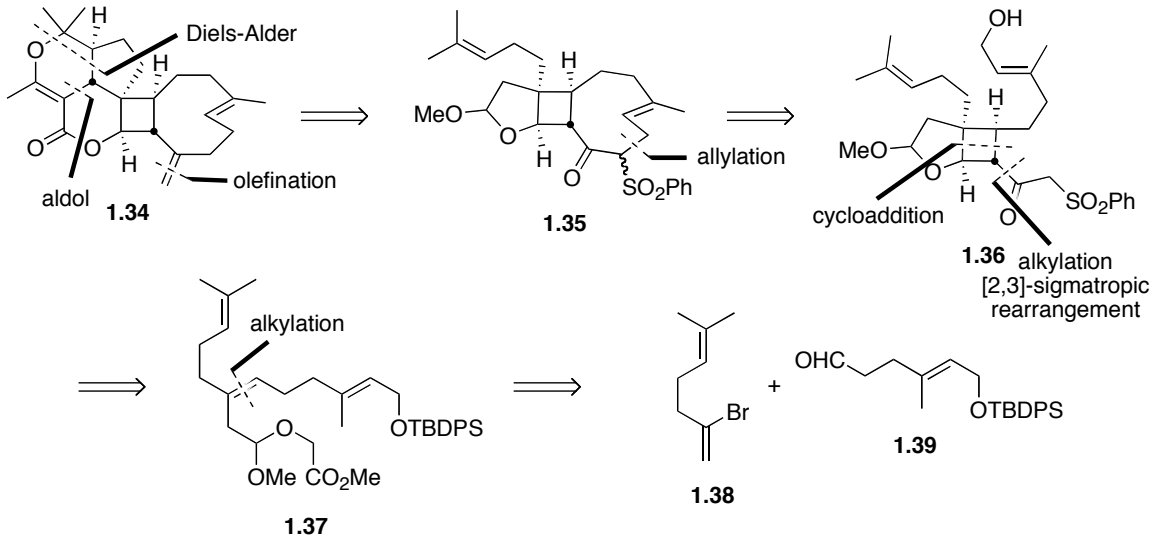


Scheme 1.9. Hiersemann's approach to lactone **1.33**.[27]

1.2.2.2. Corey's Antheliolide A

The Corey group reported an enantioselective total synthesis of the optically active *Xenia* diterpenoid antheliolide A (**1.34**), a complex, tetracyclic structure.[17] They noted that their strategy differed in several ways from the syntheses of similar compounds, particularly in the construction of the nine-membered ring in **1.34** using a method other than the commonly employed Grob fragmentation (Scheme 1.10). Retrosynthetically, antheliolide A derived from α-methoxytetrahydrofuran **1.35** through a complex series of annulation steps, carbonyl olefination and reductive sulfonate cleavage. Cyclononenone **1.35** was derived from bicycle

1.36 through [2+2]-cycloaddition and a palladium-catalyzed Hiroi-type rearrangement.[39] Ultimately, **1.37** derived from known compounds **1.38** and **1.39**.



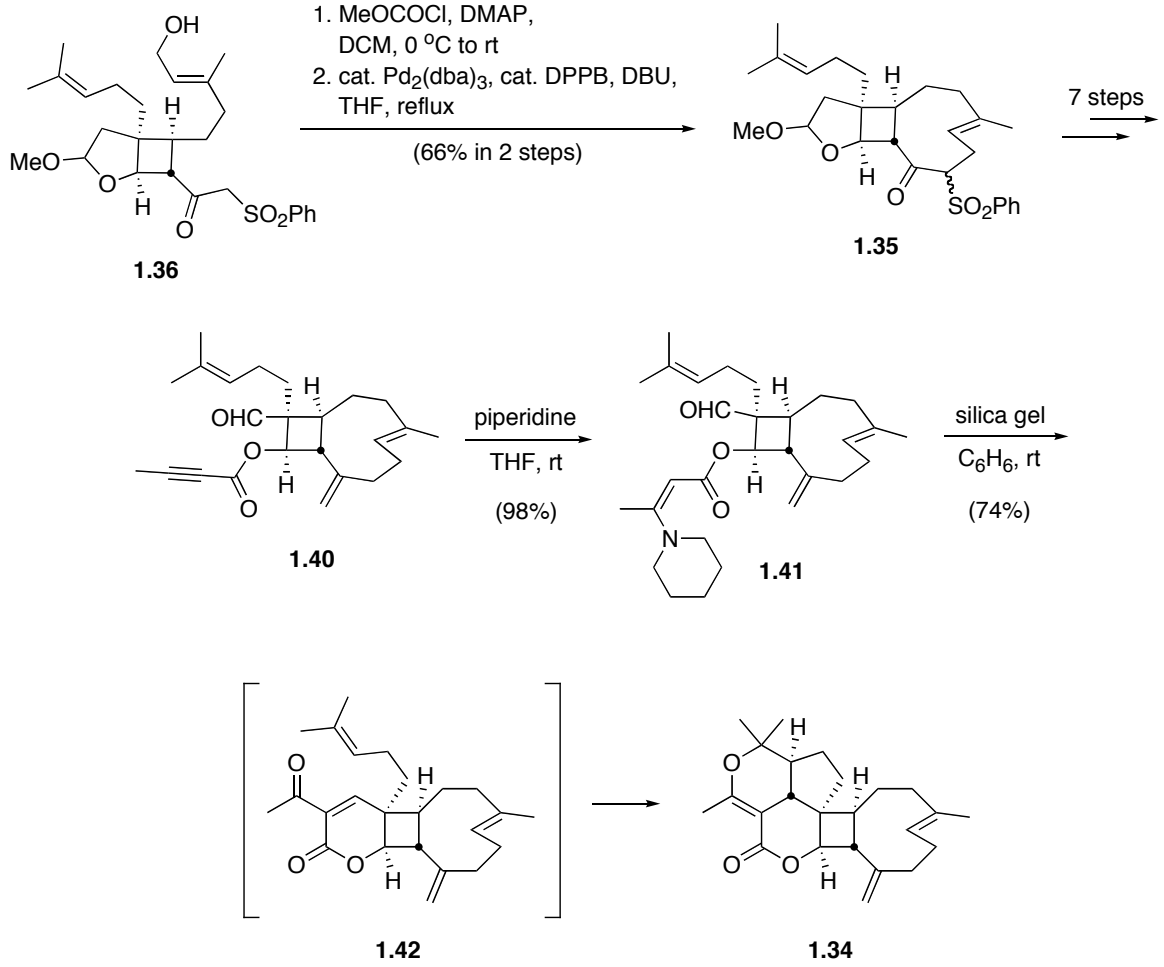
Scheme 1.10. Corey's retrosynthesis of antheliolide A (**1.34**).[17]

Corey and co-workers accessed **1.36** in 14 steps beginning from known compounds **1.38** and **1.39**.[17] As seen in Scheme 1.11, esterification of allylic alcohol **1.36** with methyl chloroformate followed by Tsuji-type allylation afforded the desired nine-membered ring (**1.35**) in good yield as an inconsequential diastereomeric mixture of sulfones. This allylation chemistry had been featured in a previous synthesis also conducted by the Corey group.[40] Tricycle **1.35** was eventually converted to aldehyde **1.40** over a series of seven steps. The reaction of piperidine and **1.40** resulted in formation of the conjugate adduct **1.41** in excellent yield.

[39] For examples see: (a) Hiroi, K.; Kato, F. "Stereochemical studies of palladium-catalyzed rearrangements of chiral 2-alkynyl sulfinates into chiral allenyl sulfones." *Tetrahedron* **2001**, *57*, 1543-1545. (b) Hiroi, K.; Kato, F.; Nakasato, H. "Stereochemistry of Palladium-catalyzed Asymmetric Transformation of Chiral 2-Alkynyl Sulfinates into Allenyl Sulfones." *Chem. Lett.* **1998**, *27*, 553-554.

[40] Hu, T.; Corey, E. J. "Short Syntheses of (±)-δ-Araneosene and Humulene Utilizing a Combination of Four-Component Assembly and Palladium-Mediated Cyclization." *Org. Lett.* **2002**, *4*, 2441-2443.

Treatment of **1.41** with silica gel in benzene at room temperature afforded intermediate lactone **1.42**, which underwent intramolecular [2+2]-cycloaddition to provide antheliolide A (**1.34**).



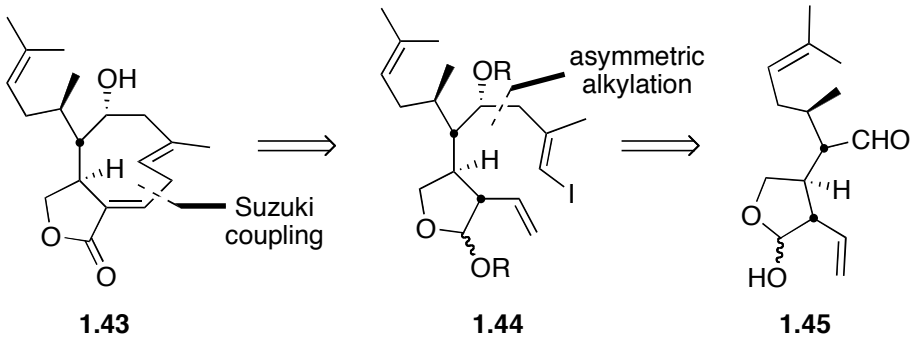
Scheme 1.11. An excerpt of Corey's synthesis of antheliolide A (**1.34**).[17]

1.2.2.3. Williams' Efforts Toward 4-Hydroxydictyolactone

Recently, Williams and co-workers reported their efforts to synthesize 4-hydroxydictyolactone (**1.43**),[41] a *Xenia* diterpenoid originally classified as a semi-synthetic

[41] Williams, D. R.; Walsh, M. J.; Claeboe, C. D.; Zorn, N. "Studies for the synthesis of marine natural products." *Pure Appl. Chem.* **2009**, *81*, 181-194.

compound in 1982[42] but now known as a natural product.[43] Their strategy, seen in Scheme 1.12, retrosynthetically makes use of an intramolecular Suzuki reaction to construct the cyclononene ring. Vinyl iodide **1.44** was derived from aldehyde **1.45** through substrate-controlled asymmetric alkylation.

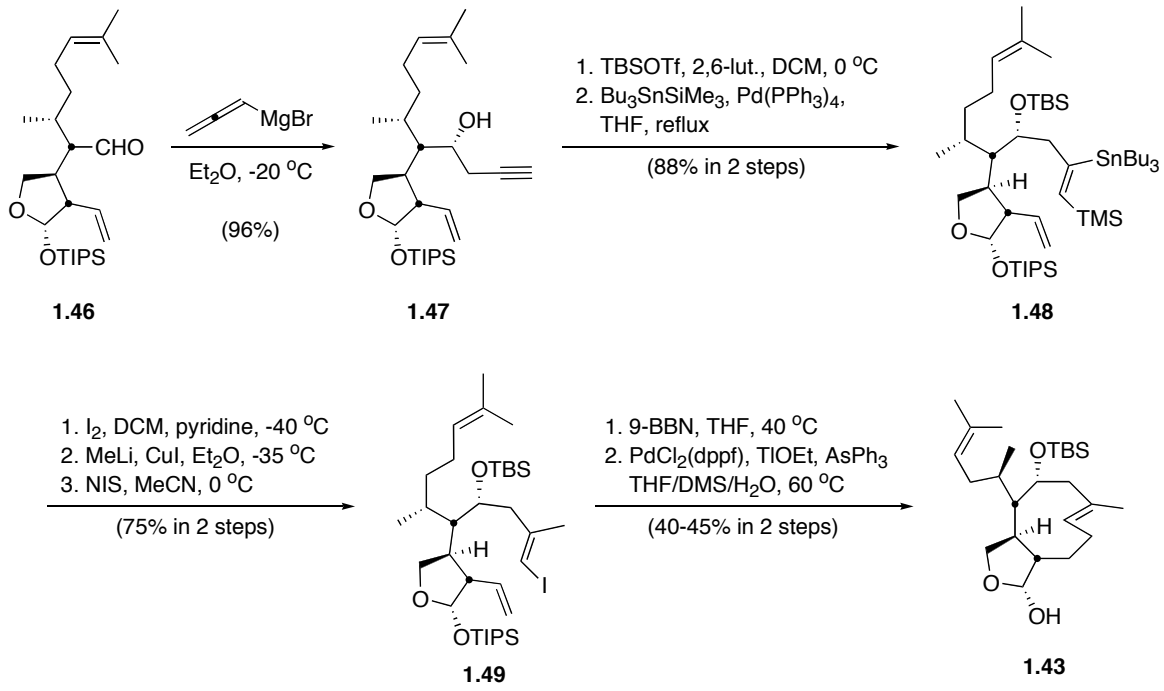


Scheme 1.12. An excerpt of Williams' retrosynthesis of 4-hydroxydictyolactone (**1.43**).[41]

As seen in Scheme 1.13, aldehyde **1.46** was diastereoselectively converted to butynol **1.47** (dr 5:1) in excellent yield. Protection of the alcohol followed by palladium-catalyzed silylstannylation provided organosilane **1.48**. Consecutive iodo-destannylation,[44] methylation and iodination smoothly afforded alkenyl iodide **1.49** in good yield over three steps. Hydroboration of **1.49** with 9-BBN followed by β-alkyl Suzuki-Miyaura coupling[45] employing a

[42] Ochi, M.; Masui, N.; Kotsuki, H.; Miura, I.; Tokoroyama, T. "The Structures of Fukurinolal and Fukurinal, Two New Diterpenoids from the Brown Seaweed *Dilophus Okaimurai* Dawson." *Chem. Lett.* **1982**, 1927-1930.
[43] Guella, G.; Pietra, F. "Photochemical Conversion of Xenicane into the Crenulatane Skeleton with Diterpenoids of the Brown Seaweed *Dictyota* sp. from the Coasts of Senegal." *Chem. Commun.* **1993**, 1539.
[44] Liron, F.; Gervais, M.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. "Palladium-catalyzed stereoselective synthesis of *E*- and *Z*-1,1-diaryl or triarylolefins." *Tetrahedron Lett.* **2003**, *44*, 2789-2794.
[45] Miyaura, N.; Ishiyama, T.; Ishikawa, M.; Suzuki, A. "Palladium-Catalyzed Cross-Coupling Reactions of B-alkyl-9-BBN or Trialkylboranes with Aryl and 1-Alkenyl Halides." *Tetrahedron Lett.* **1986**, *27*, 6369-6372.

variation of Johnson's protocol[46] afforded 4-hydroxydictyolactone (**1.43**). Thalium bases are known to enhance reaction rates in Suzuki reactions due to their excellent solubility and halophilicity.[47] Williams' decision to employ thallium ethoxide over commonly used K_2CO_3 in the synthesis of **1.43** aided in product formation.



Scheme 1.13. An excerpt of Williams' total synthesis of 4-hydroxydictyolactone (**1.43**).[41]

The efforts to construct xenicane systems by the Hiersemann, Corey and Williams groups offer an alternative route to accessing their respective natural products *in lieu* of the examples by only two groups' Wharton-type Grob fragmentations. These routes appear useful for targets not readily susceptible to ring expansions, yet their drawback typically involves unfavorable

[46] See: Johnson, C. P.; Braun, M. P. "A Two-Step, Three-Component Synthesis of PGE_1: Utilization of α-Iodoenones in Pd(0)-Catalyzed Cross-Couplings of Organoboranes." *J. Am. Chem. Soc.* **1993**, *115*, 11014-11015.
[47] Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. "Use of Thallium(I) Ethoxide in Suzuki Cross Coupling Reactions." *Org. Lett.* **2000**, *2*, 2691-2694.

medium-sized carbocycle formation and lengthy syntheses relative to methods employing ring expansions.

1.3. Research Aims

Corey's synthesis of **1.21** is currently the only known route to a divergent synthesis of *Xenia* diterpenoids,[33] a strategy allowing for access to a library of *Xenia* diterpenoids. Employing Corey's intermediate,[33] both coraxeniolide A (**1.18**) and β-caryophyllene (**1.11**) were synthesized stereoselectively and in good yield. However, the lack of established stereocenters at C-2 and C-3 in **1.21** makes this specific strategy generally unappealing for synthesizing xenicanes and corresponding analogs. As seen in Figure 1.5, we have identified an intermediate structure (**1.50**) common to several xenicanes. This molecule features the characteristic cyclononene ring, *trans*-substitution at C-2 and C-3 and versatile synthetic handles at C-10 and C-18.

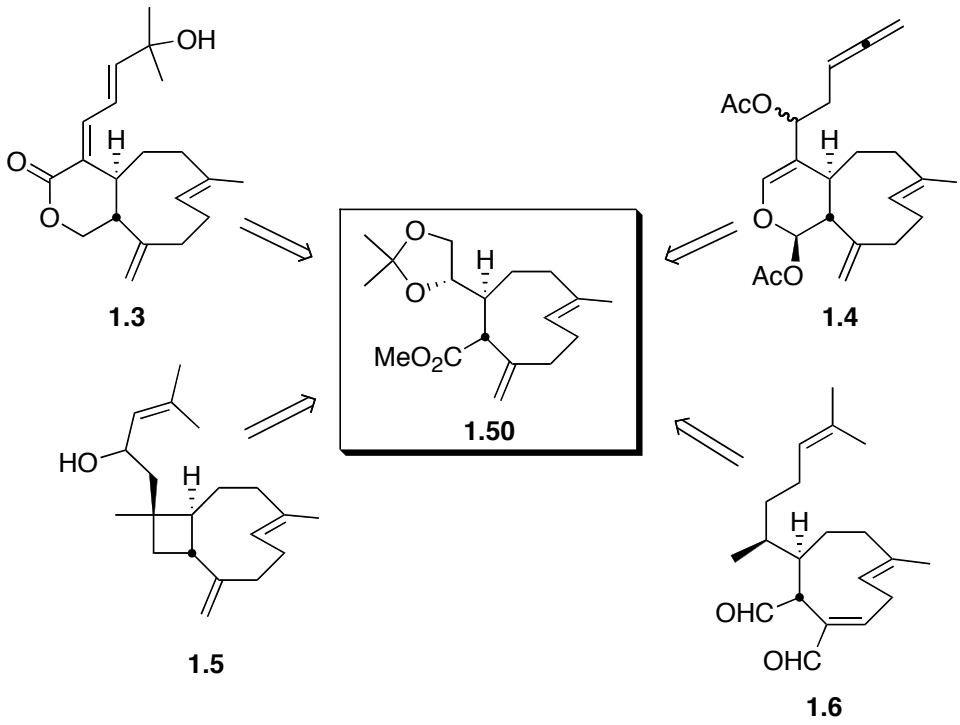
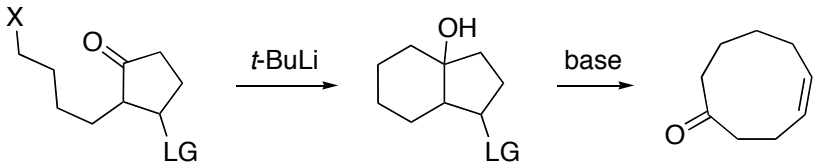


Figure 1.5. Snowden's xenicane common intermediate **1.50**.

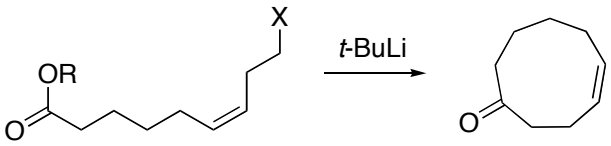
1.3.1. Cyclononone Ring Formation

Accessing the nine-membered carbocycle is the focal point of preparing xenicanes and corresponding analogs. Despite the argument that there is no "single synthetic approach to medium ring compounds,"[48] several methodologies developed to access medium-sized carbocycles hinge on synthesis of an intermediate smaller, bicyclic ring system followed by fragmentation (Equation 1.1). Such a strategy appears more favorable than a direct formation of the medium-sized ring by cyclization (Equation 1.2) due to the severe penalties from activation entropy and transannular strain.

[48] Molander, G. A. "Diverse Methods for Medium Ring Synthesis." *Acc. Chem. Res.* **1998**, *31*, 603-609.



Equation 1.1



Equation 1.2

In comparing the two routes, the rate of cyclization is a significant factor. Rate is defined as the amount of time it requires to orient the open chain structure into a product-like transition state leading to product formation.[49] In examining cyclization rates of lactones, Illuminati and Mandolini reported that six-membered rings cyclize five orders of magnitude faster than nine-membered rings.[50]

One must take into account substrate reactivity when comparing the cyclization event between six- and nine-membered rings. Reactivity is typically defined in terms of activation enthalphy ($\Delta H^{\neq}$) and the probability of end-to-end encounters ($\Delta S^{\neq}$ or entropy of activation).

1.3.1.1. Enthalpic considerations

The enthalpy of activation required to cyclize a ring is defined by the strain energy experienced by the activated complex. This energy derives from the following three specific types of strain: Pitzer, Baeyer and transannular. Torsional or Pitzer strain accounts for the nonoptimal arrangement of vicinal bonds (i.e. eclipsing and gauche interactions) in the transition state. Angle or Baeyer strain accounts for the angular discrepancies exerted on the atoms in the

[49] Illuminati, G.; Mandolini, L. "Ring Closure Reactions of Bifunctional Chain Molecules." *Acc. Chem. Res.* **1981**, *14*, 95-102.
[50] Casadei, M. A.; Galli, G.; Mandolini, L. "Ring-Closure Reactions. 22. Kinetics of Cyclization of Diethyl (ω-Bromoalkyl)malonates in the Range of 4- to 21-Membered Rings. Role of Ring Strain." *J. Am. Chem. Soc.* **1984**, *106*, 1051-1056.

ordered transition state. Six-membered rings are generally considered strain-free due to each atom's adoption of the optimal 109.5° bond angle.[51] By comparison, larger more complex systems (specifically medium-sized rings) have increased strain due to torsional and transannular strain experienced in the molecule. Transannular strain takes into account the repulsive interactions experienced by atoms across the forming ring. Illuminati and Mandolini contend that of the three types of strain, torsional and transannular are of chief importance in medium-sized (e.g., nine-membered) ring formation.[49,50]

1.3.1.2. Entropic Considerations

The entropic difference between the cyclization of a six- and nine-membered ring is considerable.[48] Ruzicka's postulate states that in comparing the cyclization of two differently sized rings, a shorter chain has a higher probability of end-to-end encounters relative to a longer chain.[52] This end-to-end encounter must allow for proper alignment, or trajectory approach,[53] of the orbitals in the transition state. To this end, several atoms involved in the cyclization must be properly aligned in the reactive conformer. Longer chains have more degrees of freedom to overcome relative to their shorter analogs. Illuminati and Mandolini demonstrated in their lactonization experiments the relative difference between a six- and nine-membered ring formation accounts for approximately -9 eu in favor of six-membered ring formation.[49,50] Thus cyclization of the six-membered ring is entropically favorable relative to the nine-membered ring.

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[51] Wiberg, K. B. "The Concept of Strain in Organic Chemistry." *Angew. Chem. Int. Ed.* **1986**, *25*, 312-322.
[52] Ruzicka, L.; Brugger, W.; Pfeiffer, M.; Schinz, H.; Stoll, M. "Zur Kenntnis des Kohlenstoffringes VI. Über die relative Bildungsleichtigkeit, die relative Bestandigkeit und den räumlichen Bau der gesättigten Kohlenstoffringe." *Helv. Chim. Acta.* **1926**, *9*, 499-520.
[53] Baldwin, J. E. "Approach Vector Analysis: a Stereochemical Approach to Reactivity." *J. Chem. Soc., Chem. Commun.* **1976**, 738-740.

1.3.1.3. Favorability of Cyclization

The cyclization of a six-membered ring is kinetically and thermodynamically more favorable than the formation of a nine-membered ring. The enthalpic difference between nine- and six-membered lactones is approximately 3 kcal/mol.[49,50] One could infer that a nine-membered ring would experience more Pitzer strain by the number of ring members relative to a six-membered ring. Since the activation enthalpy is greater and the activation entropy is restricted in the cyclization of nine-membered rings, the process becomes less favorable (i.e., a greater $\Delta G^{\neq}$) assuming the temperature remains constant (Equation 1.3).

$$\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq} \qquad \textbf{Equation 1.3}$$

1.3.2 Synthetic Strategy

Variations in SmI_2-mediated tandem Barbier/Grob processes developed by Molander and co-workers appear ideal for the construction of **1.50**.[54] Samarium diiodide is a mild and selective reagent used to promote reductive coupling reactions through single electron transfer. In numerous instances, Molander has employed SmI_2 in the presence of catalytic quantities of Fe(III)[55] or Ni(II)[56] salts to synthesize an array of different carbocycles. Most notably, seen in Scheme 1.14, the tandem Barbier/Grob chemistry provided medium-sized carbocycles (**1.53**) through the formation of alkoxide intermediates (**1.52**) beginning from the *cis*-mesylate (**1.51**).

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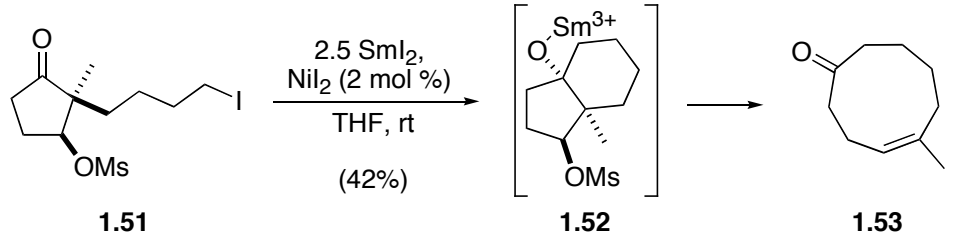
[54] Molander, G. A.; Le Huerou, Y.; Brown, G. A. "Sequenced Reactions with Samarium(II) Iodide. Sequential Intramolecular Barbier Cyclization/Grob Fragmentation for the Synthesis of Medium-Sized Carbocycles." *J. Org. Chem.* **2001**, *66*, 4511-4516.

[55] Molander, G. A.; McKie, J. A. "Intramolecular Nucleophilic Acyl Substitution Reactions of Halo-substituted Esters and Lactones. New Applications of Organosamarium Reagents." *J. Org. Chem.* **1993**, *58*, 7216-7227.

[56] Machrouhi, F.; Hamann, B.; Namy, J.-L.; Kagan, H. B. "Improved Reactivity of Diiodosamarium by Catalysis with Transition Metal Salts." *Synlett* **1996**, 633-634.

As reported by Wharton,[29] the relative placement of the leaving group in **1.51** determines the stereochemical outcome of the olefin in **1.53**.

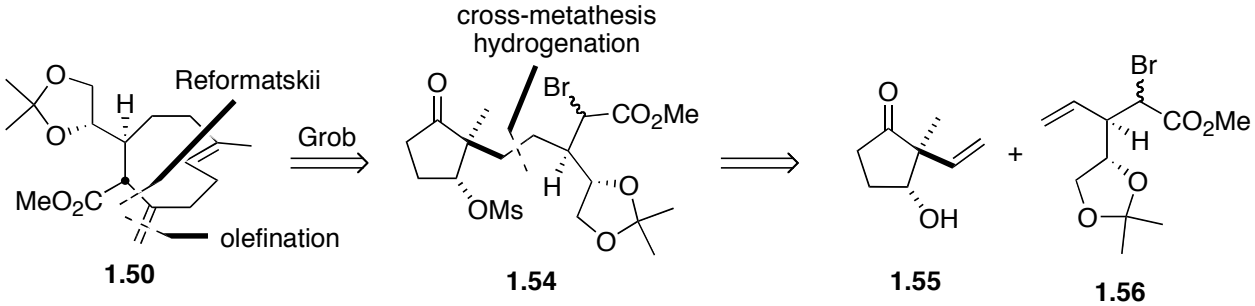


1.51 **1.52** **1.53**

Scheme 1.14. Application of Molander's tandem Barbier/Grob chemistry to convert sulfonyl ester **1.51** into cyclononenone **1.53**.[54]

1.3.2.1. Retrosynthetic Analysis

We envisioned applying a variation of Molander's Barbier/Grob chemistry[54] toward the synthesis of **1.50**. The presence of the ester moiety at C-2 would make the Barbier reaction, by definition, a Reformatskii reaction. Thus, we hypothesized that **1.50** would derive from **1.54** through a samarium(II)-mediated tandem Reformatskii/Grob reaction and ensuing methylenation (Scheme 1.15). Apart from mesylation, **1.54** would derive from 1,3-ketol **1.55** and α-bromo ester **1.56**.

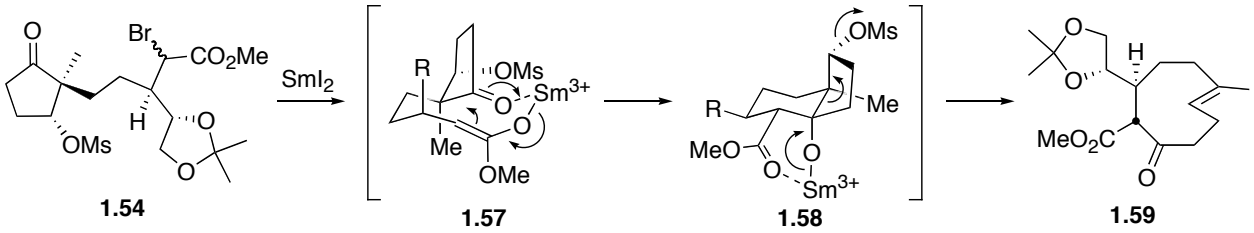


1.50 **1.54** **1.55** **1.56**

Scheme 1.15. An excerpt of the retrosynthetic analysis of common intermediate **1.50**.

We hypothesized that use of SmI_2 would aid in the diastereoselective Reformatskii step. Stereogenic control is dependent upon Lewis acid chelation to ensure proper diastereomer

formation at C-2 in **1.50**. Similar effects have been reported in samarium-mediated carbon-carbon bond forming reactions.[57] Given the strong oxophilicity of samarium(III) cations, we envisioned a chelating effect in **1.57** leading to the diastereoselective formation of bicyclic intermediate **1.58** (Scheme 1.16).



1.54 **1.57** **1.58** **1.59**

Scheme 1.16. Application of the proposed Reformatskii/Grob chemistry to access cyclononone **1.59** from α-bromo ester **1.54**.

Furthermore, the stereochemistry of the 3º-alkoxide in **1.58** plays no role in the diastereoselectivity or the effectiveness of the olefin formation. Given that Grob fragmentations are stereospecific processes dependent upon the relative placement of the leaving group and neighboring atoms, we predict formation of the (*E*)-alkene in **1.59**.

Acetonide **1.56** derives from ester enoate **1.57** through a diastereoselective, copper-mediated conjugate addition (Scheme 1.17).[58] Stereochemical outcomes have been rationalized by both the Ullenius and Yamamoto groups exploring similar systems.[59] Alternatively, Hruby

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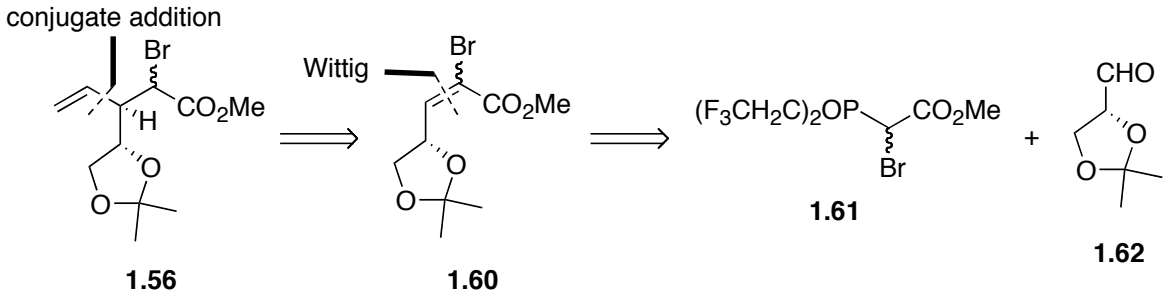
[57] For examples see: (a) Kawatsura, M.; Matsuda, F.; Shirahama, H. "Samarium(II) Iodide Promoted Intermolecular Ketone-Olefin Couplings Chelation-Controled by α-Hydroxyl Groups." *J. Org. Chem.* **1994**, *59*, 6900-6901. (b) Yeh, M.-C. Y.; Wang, F.-C.; Tu, J.-J.; Chang, S.-C.; Chou, C.-C.; Liao, J.-W. "Samarium Diiodide-Promoted Intramolecular Radical Cyclization of (η^4-Diene)Fe(CO)$_3$ Complexes Bearing Keto Side Chains." *Organomet.* **1998**, *17*, 5656-5662. (c) Zriba, R.; Bezzenine-Lafollée, S.; Guibé, F.; Magnier-Bouvier, C. "A new access to ring-fused cyclopropanols through samarium diiodide-induced 3-*exo*-trig-cyclizations." *Tetrahedron Lett.* **2007**, *48*, 8234-8237.

[58] Wang, W. Ph.D. Thesis, University of Montreal, Montreal, Canada, 1996.

[59] (a) Nilsson, K.; Ullenius, C. "Stereoselectivity in the 1,4-Addition Reaction of Organocopper Reagents to Ethyl 3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]propenoate." *Tetrahedron* **1994**, *50*, 13173-13180. (b) Yamamoto, K.; Ogura, H.; Jukuta, J.; Inoue, H.; Hamada, K.; Sugiyama, Y.;

and Han[60] reported excellent yields and diastereoselectivities resulting from the treatment of α,β-unsaturated oxazolidinones with vinylmagnesium bromide in the presence of TMEDA and TMSCl or *n*-Bu_2BOTf. Bromo enoate **1.60** would derive from known reactants α-bromo phosphane **1.61**[61],[62] and aldehyde **1.62**.[63]



Scheme 1.17. Retrosynthetic analysis of α-bromo enoate **1.56**.

Previous efforts by a former group member, Dr. Murali K. Urlam, have allowed us to access enoate **1.60**. As seen in Scheme 1.18, treatment of ester **1.63** with DIBAH resulted in formation of the intermediate aldehyde **1.62**. Introduction of methyl bis(2,2,2-trifluoroethyl)bromophophonoacetate (**1.61**) effected the olefination of **1.62** providing **1.60** in 50% yield over two steps.

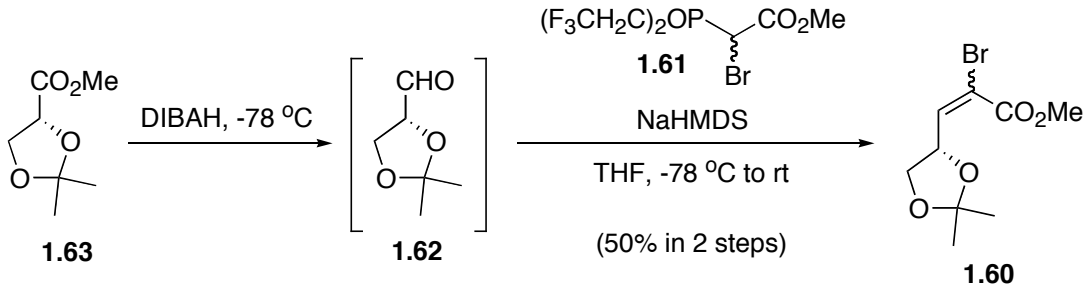
Yamada, S. "Stereochemical and Mechanistic Studies on Conjugate Addition of Organocuprates to Acyclic Enones and Enoates: Simple Rules for Diastereofacial Selectivity." *J. Org. Chem.* **1998**, *63*, 4449-4458.

[60] Han, Y.; Hruby, V. J. "Lewis acid promoted conjugate addition of vinylmagnesium bromide to chiral α,β-unsaturated *N*-acyl oxazolidinones." *Tetrahedron Lett.* **1987**, *38*, 7317-7320.

[61] Märkl, G. "Synthese von α-halogenierten, α,β-ungesättigten Carbonsäuren mit Triphenylphosphin-halogen-carbomethoxy-methylenen." *Chem Ber*, **1961**, *94*, 2996-3004.

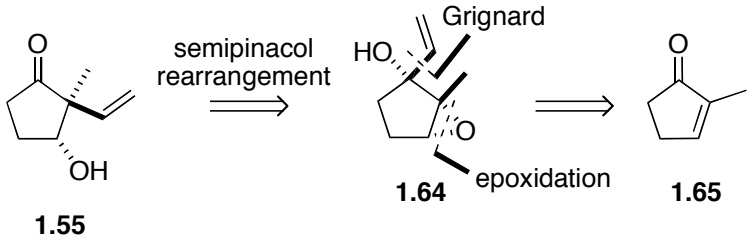
[62] Denny, D. B.; Ross, S. T. "The Preparation and Reactions of Some Halophosphoranes." *J. Org. Chem.* **1961**, *27*, 998-999.

[63] Schmid, C. R.; Bryant, J. D. "D-(*R*)-Glyceraldehyde Acetonide." *Org. Syn.* **1995**, *72*, 6-9.



Scheme 1.18. Synthesis of α-bromo enoate **1.60**.

As seen in Scheme 1.19, ketol **1.55** would derive from epoxy carbinol **1.64** through a Lewis-acid promoted semipinacol rearrangement.[64] This method has been known to provide *trans*-1,3-ketols diastereospecifically from precursor α-epoxyalcohols in good yield. Carbinol **1.63** derives from commercially available 2-methyl-2-cyclopente-1-one (**1.65**) through epoxidation and Grignard vinylation.



Scheme 1.19. Retrosynthetic analysis of *trans*-1,3-ketol **1.55**.

1.4. Conclusions

Xenicanes are important, biologically active natural products. They have demonstrated an impressive array of pharmacological properties at micro- or nanomolar concentrations in biological screenings. To date, only a few xenicanes have been synthesized and these routes are generally classified by how the nine-membered ring is formed. A Wharton-type Grob

[64] For a similar example see: Jeon, S.-J.; Walsh, P. J. "Asymmetric Addition of Allylzinc Reagents to Cyclic α,β-Unsaturated Ketones and a Tandem Enantioselective Addition/Diastereoselective Epoxidation with Dioxygen." *J. Am. Chem. Soc.* **2003**, *125*, 9545.

fragmentation used to diastereospecifically form the (*E*)-cyclononene ring is far superior to any other method available. Snowden's structure common to xenicanes (**1.50**), which derives from commercially available starting materials, hypothetically makes use of a tandem Reformatskii/Grob chemistry to access the nine-membered ring, thereby facilitating access to a broad range of biologically active *Xenia* diterpenoids.

CHAPTER 2

A COMPARATIVE STUDY OF THE REDUCTIVE DESYMMETRIZATION OF CYCLIC-2,2-DISUBSTITUTED-1,3-ALKANEDIONES

2.1 Introduction and Background

The monoreduction of 2,2-disubstituted-cycloalkane-1,3-diones is an important protocol for the synthesis of steroids, terpenoid natural products and substrates used to establish new synthetic protocols. Although several alternatives now exist for the enantioselective monoreduction of such diones,[65] the cost and inconvenience of these approaches is unwarranted for applications where a stereospecific modification, (e.g. ring fragmentation) is desired. We sought to develop a facile, inexpensive and diastereoselective approach for forming cyclic 2,2-disubstituted-1,3-ketols applicable toward the synthesis of our *Xenia* diterpenoid common intermediate (Chapter 1). This subchapter reviews several pertinent methods surrounding the reductive desymmetrization of cyclic 2,2-disubtituted-1,3-diones and discusses the advantages and disadvantages of each protocol.

[65] For examples see: (a) Watanabe, H.; Iwamoto, M.; Nakada, M. "Preparation of New Chiral Building Blocks: Highly Enantioselective Reduction of Prochiral 1,3-Cycloalkanediones Possessing a Methyl Group and a Protected Hydroxymethyl Group at Their C2 Position with Baker's Yeast or CBS Catalyst." *J. Org. Chem.* **2005**, *70*, 4652-4658; (b) Butler, B.; Schultz, T.; Simpkins, N. S. "Chiral base mediated transformation of cyclic 1,3-diketones." *Chem. Commun.* **2006**, 3634-3636; (c) Yeung, Y.-Y.; Chein, R.-J.; Corey, E. J. "Conversion of Torgov's synthesis of Estrone into a Highly Enantioselective and Efficient Process." *J. Am. Chem. Soc.* **2007**, *129*, 10346-10347.

2.1.1. Enantioselective Monoreductions

2.1.1.1. Microbial-Mediated Processes

Pasteur is credited with reporting the first ever biotransformation,[66] the oxidation of ethanol to acetic acid by *Bacterium xylinum*. Since Pasteur's seminal contribution, countless examples of microbial-mediated biotransformations have emerged in the literature, including enantioselective ketone reductions. Microbial-mediated reductions are a subset of biotransformations. In its broadest sense, a biotransformation is a process wherein an organism alters the chemical and physical properties of a substrate.

The appeal of employing microbes in organic chemistry lies in the highly enantioselective outcome of the biotransformation, frequently in carbonyl reductions. Although the general mechanisms of microbial-mediated transformations are not definitively understood, it is widely believed that stereochemical outcome is often predicated on how the substrate binds in the active site of the microbe,[67] a result rationalized by application of Prelog's rule.[68] In considering a hypothetical ketone where stereochemical priority is established based on the steric size of the R-groups adjacent to the carbonyl, Prelog's rule suggests that microbial mediated reductions favor hydride delivery to the *Re* face of the substrate (Figure 2.1). As a result, these reductions often favor formation of the *S*-alcohol. It should be noted that facial selectivity, according to Prelog's rule,[68] is a function of steric bulk and not necessarily IUPAC priority.

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[66] Csuk, R.; Glanzer, B. I. "Baker's Yeast Mediated Transformations in Organic Chemistry." *Chem. Rev.* **1991**, *91*, 49-97.
[67] MacLeod, R.; Prosser, H.; Fikentscher, L.; Lanyi, J.; Mosher, H. S. "Asymmetric Reductions. XII. Stereoselective Ketone Reductions by Fermenting Yeast." *Biochemistry* **1964**, *3*, 838-846.
[68] Prelog, V. "Specification of the stereospecificity of some oxido-reductases by diamond lattice sections." *Pure and Applied Chemistry* **1964**, *9*, 119-130.

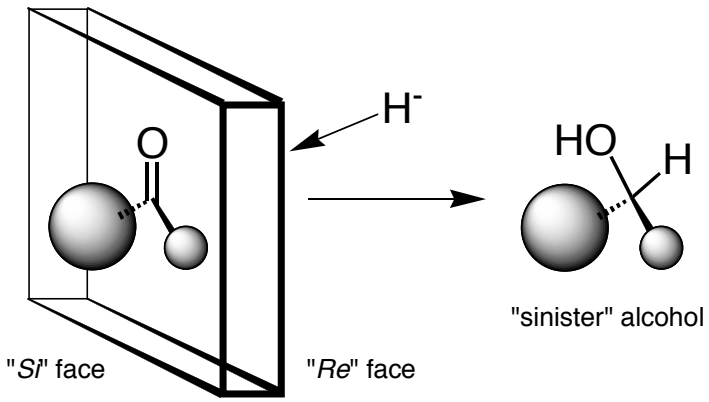


Figure 2.1. The facial selective microbial-mediated hydride addition to a ketone.

Microbial-mediated ketone reductions have been employed in the synthesis of a number of natural products. Gibian,[69] Mathieu,[70] Kogan[71] and Lanzilotta[72] employed various microbes in the synthesis of optically active 2,2-disubstituted-1,3-ketols for the preparation of naturally occurring steroids. Additionally, as seen in Scheme 2.1, Sugai and co-workers used yeast strain *Torulaspora delbrueckii* to enantioselectively access cyclic 1,3-ketols as the corresponding hemiketal (**2.3**).[73] As predicted by Prelogs' rule,[68] the (*S*)-enantiomer was accessed in high

[69] (a) Gibian, H.; Kieslich, K.; Koch, H.-J.; Kosmol, H.; Rufer, C.; Schröder, E.; Vossing, R. "Totalsynthese von natürlichem östradiolmethyläther." *Tetrahedron Lett.* **1966**, *7*, 2321-2330. (b) Kosmol, H.; Kieslich, K.; Vössing, R.; Koch, H.-J.; Petzoldt, K.; Gibian, H. "Total synthesis of optically active steroids. I. Microbiological stereospecific reduction of 3-methoxy-8,14-seco-1,3,5(10),9-estratetraene-14,17-dione." *Liebigs Ann. Chem.* **1967**, *701*, 198-205.

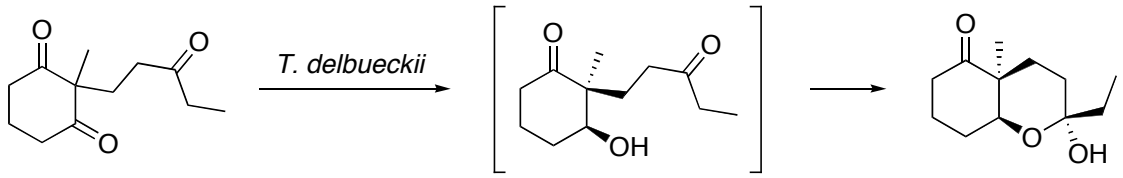
[70] Bellet, P; Nomine, G.; Mathieu, Y. "Asymmetric reduction by a microbiological route in the total synthesis of steroids." *C. R Acad. Sci.* **1966**, *263*, 88-92.

[71] Kogan, L. M.; Gulaya, V. E.; Torgov, I. V. "Structures of spiroethers derived from products of the yeast fermentation of the 3-methoxy-14-seco-D-homo-1,3,5(10),9(11)-estratetraendione-14,17a." *Tetrahedron Lett.* **1967**, *47*, 4673-4676.

[72] Lanzilotta, R. P.; Bradley, D. G.; Beard, C. C. "Microbial Reduction of 1,3-Dioxo-2-Methyl-2-(3'-Oxo-6'-Carbomethoxyhexyl)-Cyclopentane to Form 1β-Hydroxy-3-Oxo-2β-Methyl-2α-(3'-Oxo-6'-Carbomethoxyhexyl)-Cyclopentane, an Intermediate for Steroid Total Synthesis." *Appl. Microbio*. **1975**, *29*, 427-429.

[73] (a) Fuhshuku, K.; Funa, N.; Akeboshi, T.; Ohta, H.; Hosomi, H.; Ohba, S.; Sugai, T. "Access to Wieland-Miescher ketone in an enantiomerically pure form by a kinetic resolution with yeast-mediated reduction." *J. Org. Chem.* **2000**, *65*, 129-135. (b) Fuhshuku, K.; Tomita, M.; Sugai, T. "Enantiomerically pure octahydronaphthalenone and octahydroindenone: Elaboration of the

enantioselectivity (98.7% ee) in albeit modest yield (56%). Although these microbial-mediated monoreductions reportedly gave poor yields, the enantioselectivity clearly could not be accomplished using conventional reducing agents such as $NaBH_4$ or $LiAlH(OtBu)_3$.



2.1 **2.2** **2.3**

Scheme 2.1. Microbial-mediated preparation of hemi-ketal **2.3** by Sugai et. al.[73b]

Brooks and co-workers made significant contributions in the field of microbial-mediated reductions in a series of methodological studies wherein they reported the synthesis of several optically active cyclic 2,2-disubsituted-1,3-ketols from the corresponding diones.[74] Brooks employed bakers' yeast (*Saccharomyces cerevisiae*) as the biological organism due to its accessibility and well-documented history in the enantioselective reduction of carbonyls. An overview of these studies is listed in Table 2.1. All substrates (**2.4**) were converted in modest yield, though the cyclopentanediones (entries 1-5) had an affinity for forming the corresponding *cis* diastereomers. This effect appears to be a function of the steric bulk of the R-group. By comparison, the cyclohexanediones (entries 6-10) favored *trans*-ketol formation. The degree of selectivity in the cyclohexanedione substrates is lower relative to the cyclopentanedione analogs,

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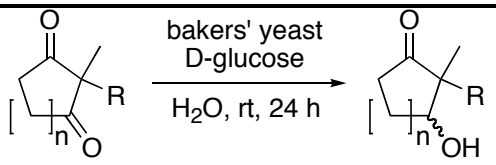
substrate overcame the specificity of yeast-mediated reduction." *Adv. Synth. Catal.* **2003**, *345*, 766-774.

[74] (a) Brooks, D. W.; Grothaus, P. G.; Irwin, W. L. "Chiral cyclopenanoid synthetic intermediates via asymmetric microbial reduction of prochiral 2,2-disubstituted cyclopentanediones." *J. Org. Chem.* **1982**, *47*, 2820-2821. (b) Brooks, D. W.; Mazdiyasni, H.; Chakrabarti, S. "Chiral cyclohexanoid synthetic precursors via asymmetric microbial reduction of prochiral cyclohexanediones." *Tetrahedron Lett.* **1984**, *25*, 1241-1244. (c) Brooks, D. W.; Mazdiyasni, H.; Grothaus, P. G. "Asymmetric microbial reduction of prochiral 2,2-disubstituted cycloalkanediones." *J. Org. Chem.* **1987**, *52*, 3223-3232.

though Brooks was not able to rationalize this effect. Nevertheless, enantioselectivity was predicated by the application of Prelog's rule.[68]

Table 2.1. Application of Brooks' method in the enantioselective desymmetrization of cyclic-2,2-disubstituted-1,3-diones (**2.4**).[74]



2.4 **2.5**

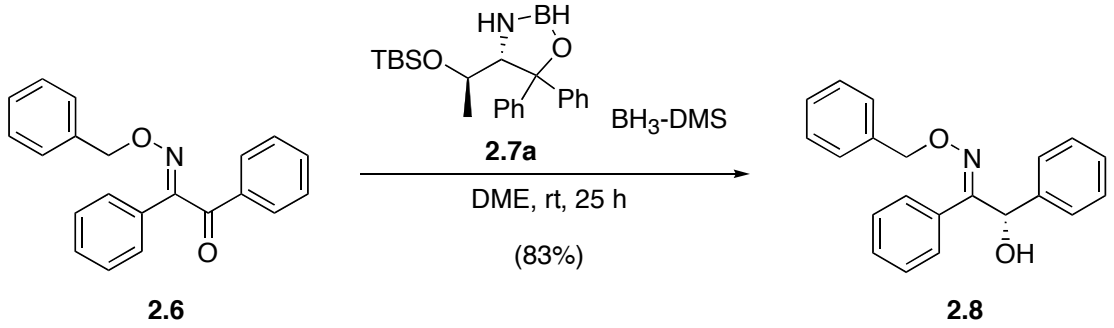
Entry	*n*	*R*	*Yield* (%)[a]	*Diastereoselectivity* (*cis*:*trans*)
1	1	$CH_2CH_2CH_3$	60	100:0
2	1	$CH_2CH{=}CH_2$	75	90:10
3	1	$CH_2C{\equiv}CH$	60	67:33
4	1	$CH_2C(CH_3){=}CH_2$	75	100:0
5	1	$CH_2CH_2C{\equiv}N$	71	96:4
6	2	$CH_2CH_2CH_3$	80	22:78
7	2	$CH_2CH{=}CH_2$	80	45:55
8	2	$CH_2C{\equiv}CH$	75	27:73
9	2	$CH_2C(CH_3){=}CH_2$	49	40:60
10	2	$CH_2CH_2C{\equiv}N$	49	30:70

[a]All ketol products exhibited >98% ee.

Microbial-mediated reductive desymmetrizations are a class of reactions that can provide optically active alcohols with a high degree of enantioselectivity. Although these processes are typically limited in synthetic utility by the yield of isolated product, they do offer an interesting degree of diastereoselectivity. In cyclic-2,2-disubstituted-1,3-dione substrates, diastereoselectivity appears to be a function of the steric bulk of the R-group. This effect predominates in the cyclopentanediones relative to other cycloalkanediones.

2.1.1.2. Desymmetrizations Involving a Chiral Reagent or Catalyst

Oxazaborolidines have played a large role in diastereo- and enantioselective reductions of 2,2-disubstituted-1,3-diones. In particular, Fujisawa's L-threonine-derived ligand[75] was used to prepare 1,3-ketols from precursor diones. Prior to its application in reductive desymmetrization reactions, Fujisawa sought to prepare of β-imino alcohols (**2.8**) from the corresponding β-imino ketones (**2.6**). As seen in Scheme 2.2, optimal conditions, involving one molar equivalent of the ligand in DME with BH_3-DMS as the stoichiometric reducing agent, provided β-imino alcohol **2.6** in 83% yield with 98% ee.



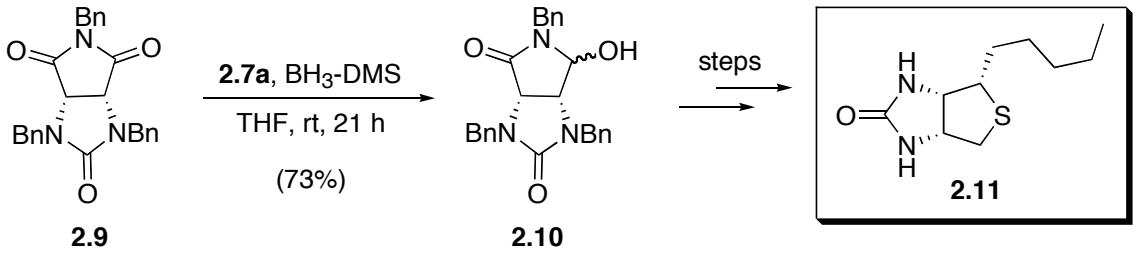
2.6 **2.8**

Scheme 2.2. Preparation of β-imino alcohol **2.6** using Fujisawa's ligand (**2.7a**).[75]

Shimizu employed Fujisawa's ligand and method to enantioselectively desymmetrize *meso*-imide **2.9** in the synthesis of (+)-deoxybiotin **2.11**.[76] As seen in Scheme 2.3, the corresponding β-hydroxy lactam (**2.10**) was isolated in 73% yield and 92% ee. Although the conditions allowed for complete conversion, inseparable diol formation accounted for the remaining 27% of the mass balance. Lactam **2.10** was then converted to (+)-deoxybiotin in six

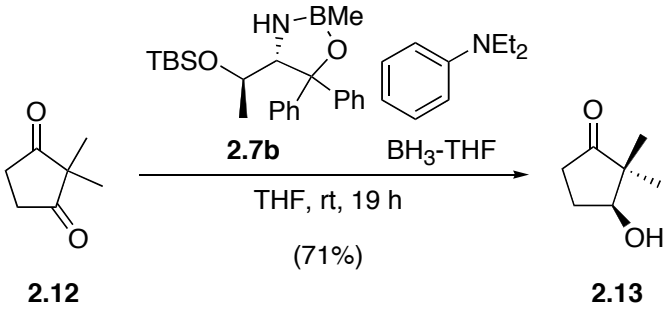
[75] Shimizu, M.; Tsukamoto, K.; Matsutani, T.; Fujisawa, T. "Oxazaborolidine-Mediated Asymmetric Reduction of 1,2-Diaryl-2-benzyloxyiminoethanones and 1,2-Diarylethanediones." *Tetrahedron* **1998**, *54*, 10265-10274.
[76] Shamizu, M.; Nishigaki, Y.; Wakabayashi, A. "Stereocontrol in the reduction of *meso*-imides using oxazaborolidine, leading to the facile synthesis of (+)-deoxybiotin." *Tetrahedron Lett.* **1999**, *40*, 8873-8876.

additional steps. Though plagued by diol formation, Shimizu noted that the methodology offered a "convenient approach to biologically important materials."



Scheme 2.3. Shimizu's preparation of lactam **2.10**.[76]

Shimizu endeavored to prepare optically active β-hydroxyketones from the corresponding 2,2-disubstituted-1,3-diones in one step.[77] Although exploring various conditions to harness over-reduction to the diol, the addition of catalytic quantities of aniline derivatives was found to increase the enantioselectivity in 1,3-ketol formation while suppressing over-reduction. As seen in Scheme 2.4, for example, optimal conditions provided optically active 3-hydroxy-2,2-dimethylcyclopenanone (**2.13**) in 71% yield and 88% ee.



Scheme 2.4. Shimizu's preparation of 1,3-ketol **2.13** using ligand **2.7b**.[77]

The stereochemical outcome using Fujisawa's ligand was initially rationalized with the six-membered transition state proposed by Corey et al. to explain the stereochemical outcome in

[77] Shimizu, M.; Yamada, S.; Fujita, Y.; Kobayashi, F. "Highly stereocontrolled reduction of 1,3-cyclopentanediones using oxazaborolidine-BH_3." *Tetrahedron: Asymmetry* **2000**, *11*, 3883-3886.

CBS-type reductions.[78] As seen in Figure 2.2, a combination of the steric bulk and the inherent chirality of the ligand accounted for the stereofacial hydride transfer, which was the rate determining step for the transformation.[79] However, this model does not account for inclusion of the aniline derivatives as deemed beneficial by Shimizu.

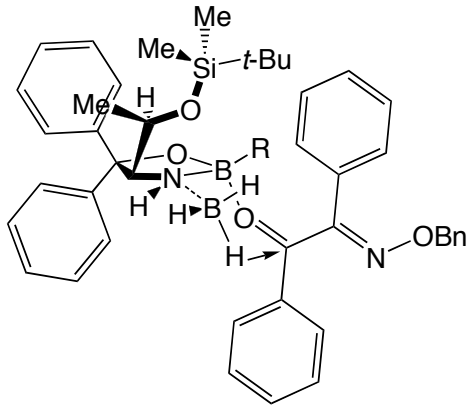
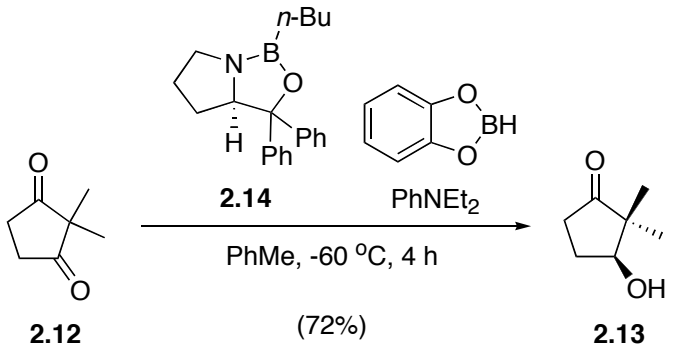


Figure 2.2. Proposed six-membered transition state used to explain the stereochemical outcome using Fujisawa/Shimizu ligands **2.7**.[75]

Corey and co-workers employed an oxazaborolidine catalyst (**2.14**) in the presence of substoichiometric quantities of $PhNEt_2$ using catecholborane as the stoichiometric reductant to prepare optically active 2,2-disubtituted-1,3-ketols from the corresponding diones.[80] As seen in Scheme 2.5, optimal reaction conditions provided 3-hydroxy-2,2-dimethylcyclopentanone (**2.13**) in 72% yield after 4 h at -60 ^{o}C.

[78] Corey, E. J.; Bakshi, R. K.; Shibata, S. J. "Highly enantioselective borane reduction of ketones catalyzed by chiral oxazaborolidines. Mechanism and synthetic implications." *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553.
[79] Saaverda, J.; Stafford, S. E.; Meyer, M. P. "Experimental transition state for the Corey-Bakshi-Shibata reduction." *Tetrahedron Lett.* **2009**, *50*, 1324-1327.
[80] Yeung, Y.-Y.; Chein, R.-J.; Corey, E. J. "Conversion of Torgov's Synthesis of Estrone into a Highly Enantioselective and Efficient Process." *J. Am. Chem. Soc.* **2007**, *129*, 10346-10347.



Scheme 2.5. Corey's CBS-type monoreduction of **2.12**.[80]

Interestingly, inclusion of the additive $PhNEt_2$ provided the opposite stereoisomer expected through normal CBS-type reductions[81] and an increase in reaction rate.[82] This reversal in stereochemical outcome was explained through the pre-transition state assembly of a catecholborane-$PhNEt_2$ complex (Figure 2.3).[80] Carbonyl activation by the CBS catalyst allowed for enantioselective hydride addition. Corey argued that the pre-transition state was found to be "of lower energy than the various alternative geometries."

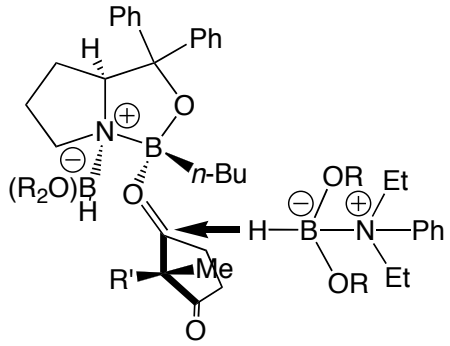


Figure 2.3. Corey's proposed pretransition state complex used to explain reversal of stereochemical outcome in the monoreduction of **2.12**.[80]

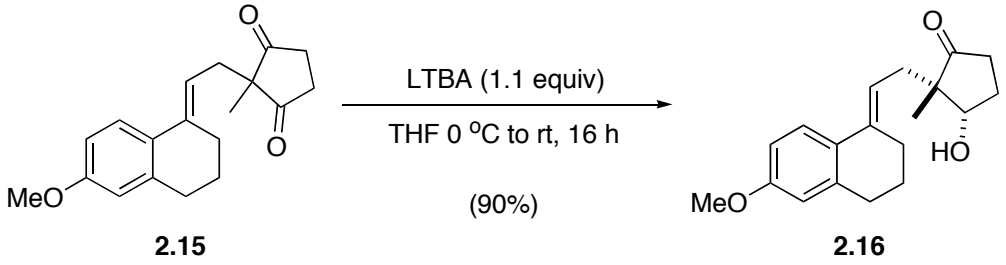
[81] Corey, E. J.; Helal, C. J. "Reduction of carbonyl compounds with chiral oxazaborolidine catalysts: A new paradigm for enantioselective catalysis and a powerful new synthetic method." *Angew. Chem. Int. Ed.* **1998**, *37*, 1986-2012

[82] Chien, R. J.; Yeung, Y.-Y.; Corey, E. J. "Highly Enantioselective Oxazaborolidine-Catalyzed Reduction of 1,3-Dicarbonyl Compounds: Role of the Additive Diethylaniline." *Org. Lett.* **2009**, *11*, 1611-1614.

Chiral oxazaborolidines used to facilitate monoreductions offer modest yields and useful stereoselectivities. These transformations, as in the case with microbial-mediated processes, offer useful enantiomeric outcomes. However, the reported chiral reagents are either costly (e.g., CBS-type molecules) or commercially unavailable (e.g., Fujisawa/Shimizu ligands). Though collectively interesting transformations, high costs or inconvenience make the use of oxazaborolidines undesirable for some reductive desymmetrizations of cyclic diones.

2.1.2. Diastereoselective Monoreductions

Few methodological studies have been published regarding the diastereoselective reductive desymmetrization of 2,2-disubstituted-cyclic-1,3-diones. Kuo and co-workers first employed lithium tri-*tert*-butoxyaluminum hydride (LTBA) in the racemic total synthesis of estrone.[83] As seen in Scheme 2.6, their method predominantly gave *cis*-ketol **2.16** as the major product in 90% yield using a slight stoichiometric excess of reductant.



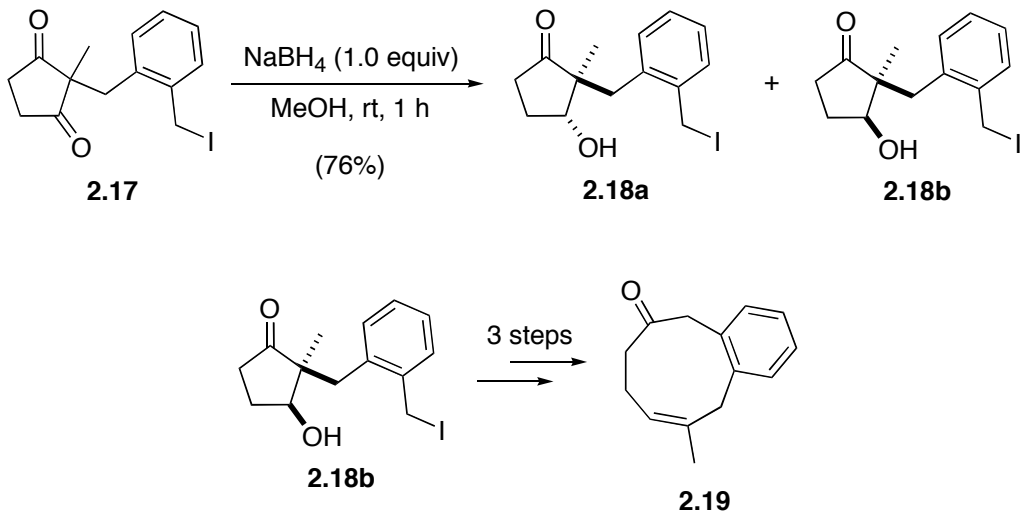
2.15 **2.16**

Scheme 2.6. The diastereoselective preparation of ketol **2.16**.[83]

Molander and co-workers employed $NaBH_4$ to reductively desymmetrize cyclic 2,2-disubstituted-1,3-diones in modest yields.[54] These reactions typically provided both diastereomers in equal amounts (**2.18a/b**). The over-reduced diol typically accounted for the

[83] Kuo, C. H.; Taub, D.; Wendler, N. L. "Synthesis of estrone via novel intermediates. Mechanism of the coupling reaction of vinyl carbinol with a β-diketone." *J. Org. Chem.* **1968**, *33*, 3126-3132.

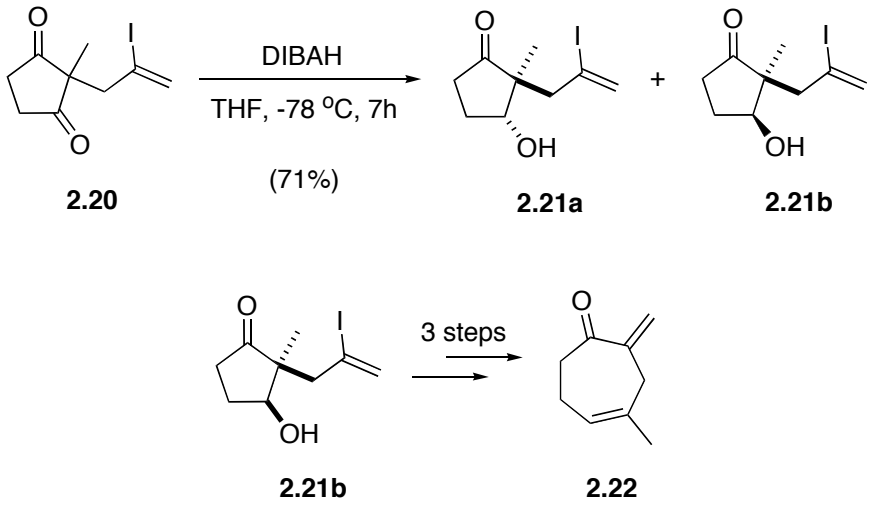
remaining mass balance. As seen in Scheme 2.7, isolation of the *cis* ketol (**2.18b**) was followed by mesylation then a samarium-mediated, sequential Barbier cyclization/Grob fragmentation to access carbocycle **2.19**.



Scheme 2.7. Molander's preparation of carbocycle **2.19** through the reductive desymmetrization of dione **2.17**.[54]

The Mori group employed DIBAH as well as $NaBH_4$ in monoreductions of cyclopentane- and cyclohexanediones (Scheme 2.8).[84] Like Molander,[54] Mori employed the resulting cyclc-1,3-ketols to establish new methods for the preparation of 7- and 8-membered carbocycles. DIBAH was found to work best for the cyclopentanedione substrates (**2.20**), providing good diastereoselectivity (1.0:6.1, *trans*:*cis*) and modest yields with low diol formation but poor substrate conversion. Ketol **2.21** was mesylated then converted to cycloheptadienone **2.22** using a stannous-mediated cyclization protocol.

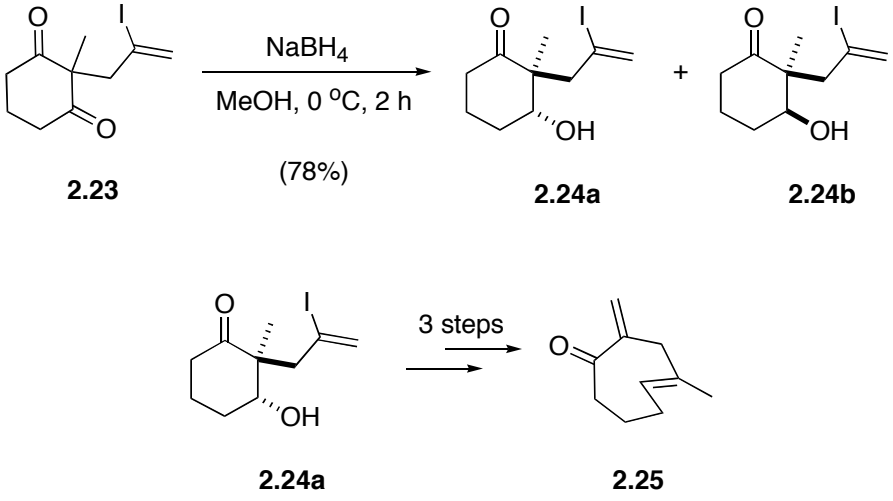
[84] Imai, A. E.; Sato, Y.; Nishida, M.; Mori, M. "Stereospecific Synthesis of (+)- and (-)-Cyclooctenone Derivatives Using a Ring Expansion Reaction with $Me_3SiSnBu_3$ and CsF." *J. Am. Chem. Soc.* **1999**, *121*, 1217-1225.



2.20 **2.21a** **2.21b** **2.21b** **2.22**

Scheme 2.8. The DIBAH-mediated reductive desymmetrization of dione **2.20** used to access carbocycle **2.22**.[84]

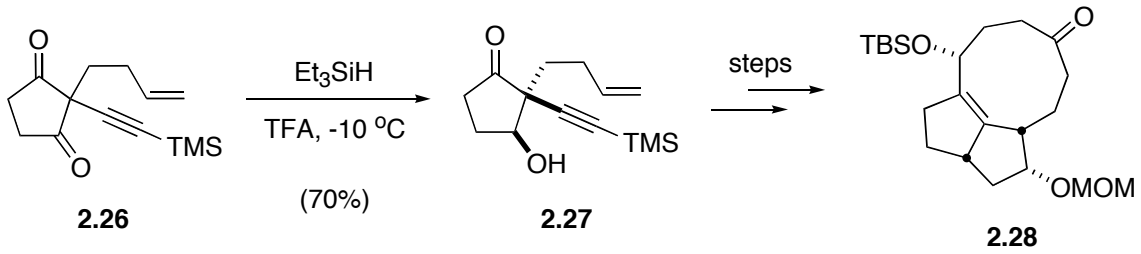
By comparison, sodium borohydride in methanol provided the best results when used to reductively desymmetrize Mori's cyclohexanedione substrates,[84] as seen in Scheme 2.9. Application of this protocol provided the desired ketols in good yields with excellent selectivities (8:70 **2.24a**:**2.24b**), though the drawback to this method was over-reduction. Again, Mori applied the stannous methodology to transform *trans*-ketol **2.24** into (*E*)-cyclooctenone **2.25**.



2.23 **2.24a** **2.24b** **2.24a** **2.25**

Scheme 2.9. Mori's $NaBH_4$-mediated reductive desymmetrization of dione **2.23** used to access carbocycle **2.25**.[84]

As seen in Scheme 2.10, Burnell monoreduced sterically biased 2,2-disubstituted-cyclopentane-1,3-dione **2.26** with Et_3SiH in concentrated TFA in the synthesis of an aquariane ring system (**2.28**).[85] Although able to provide the desired *cis*-ketol (**2.27**) in excellent diastereoselectivity (40:1 *cis*:*trans*), the method was limited by diol formation. Additionally, the harsh conditions are not compatible with many substrates making this method less versatile than other options. Interestingly, when LTBA was employed to reduce **2.26**, a diastereomeric mixture of ketols was obtained in 95% yield favoring *trans* product formation (dr = 4:1).



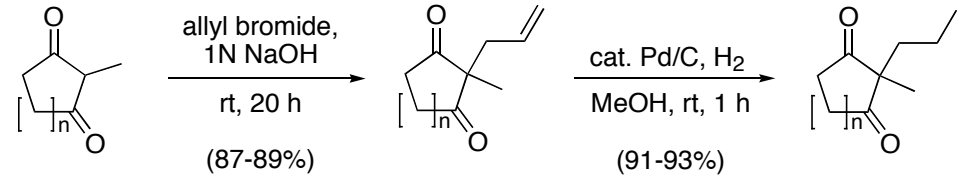
Scheme 2.10. Burnell's highly diastereoselective monoreduction of dione **2.25**.[85]

[85] Thornton, P. D.; Burnell, D. J. "A Pauson-Khand and Ring-Expansion Approach to the Aquariane Ring System." *Org. Lett.* **2006**, *8*, 3195-3198

2.2 Results and Discussion

2.2.1. Substrate Preparation

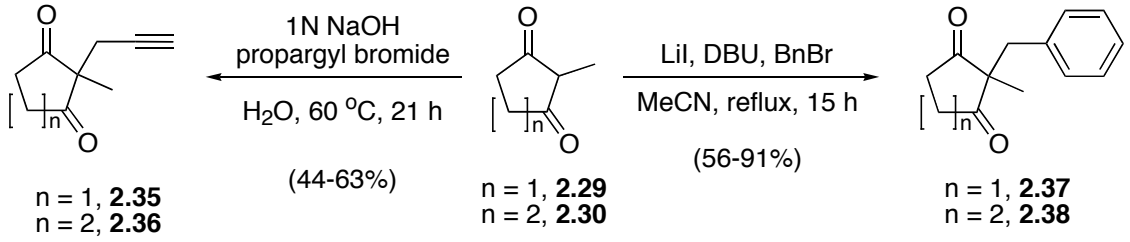
We chose to prepare an array of dione substrates to experiment with various monoreduction protocols. Ultimately, a high yielding and scaleable method was sought to diastereoselectively access cyclic 2,2-disubsitututed-1,3-ketols from precursor diones. The surveyed substrates were selected for examination based on varying steric and electronic parameters as well as ease of preparation. Several of the surveyed cyclic 2,2-disubstituted-1,3-diones were prepared from commercially available diones (**2.29** and **2.30**) using published procedures. As seen in Scheme 2.11, allyl derivatives **2.31** and **2.32** were accessed via Tsuji-Trost allylation[86] or base-mediated allylic substitution[74c] in good overall yields. Though the reaction times were longer, we found that the cleanest product formation occurred when using alkaline conditions. The allyl functional group was cleanly reduced to the corresponding *n*-propyl alkyl group using catalytic hydrogenation providing substrates **2.33** and **2.34** in excellent yield.



Scheme 2.11. Transformation of diones **2.28** and **2.29** into the corresponding allyl (**2.30**, **2.31**) and propyl (**2.32**, **2.33**) substrates.

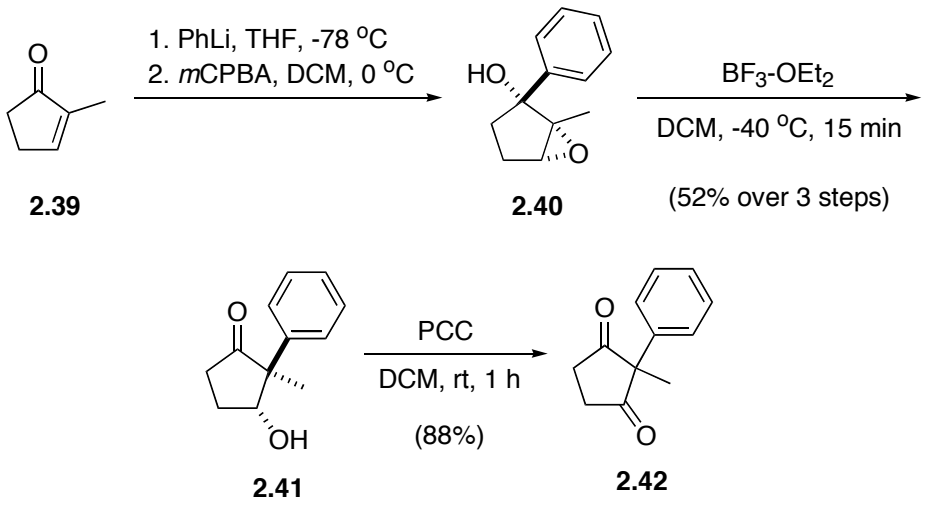
[86] Mandai, T.; Kaihara, Y.; Tsuji, J. "A New Candidate for a Properly Substituted CD Ring Component of Vitamin D3 via Intramolecular Asymmetric Olefination of a 1,3-Cyclopentanedione Derivative." *J. Org. Chem.* **1994**, *59*, 5847-5849.

Installation of the propargyl moiety to provide substrates **2.35** and **2.36** was accomplished in modest yields using alkaline conditions with gentle heating (Scheme 2.12).[74c] Additionally, treatment of **2.29** and **2.30** with DBU in the presence of LiI followed by introduction of benzyl bromide resulted in the formation of diones **2.37** and **2.38** in good yield. The best benzylation yields were obtained when the LiI was meticulously dried using a vacuum oven prior to use.



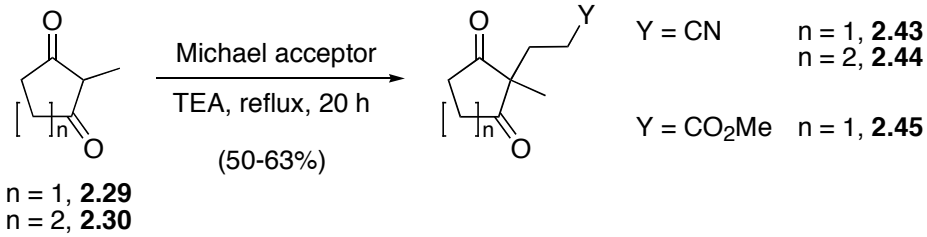
Scheme 2.12. Transformation of diones **2.29** and **2.30** into the corresponding propargyl (**2.35**, **2.36**) and benzyl (**2.37**, **2.38**) substrates.

We additionally prepared 2-methyl-2-phenylcyclopentane-1,3-dione (**2.41**) for examination in our study, which is outlined in Scheme 2.13. Commercially available **2.39** was treated with phenyllithium then epoxidized with *m*CPBA to provide the desired racemic epoxycarbinol (**2.40**). Lewis-acid mediated semipinacol rearrangement[64] of **2.40** diastereospecifically afforded *trans*-1,3-ketol **2.41** in good yield over three steps. Finally, PCC oxidation of **2.41** cleanly provided dione **2.42**.



Scheme 2.13. Preparation of phenyl dione **2.42** from **2.39**.

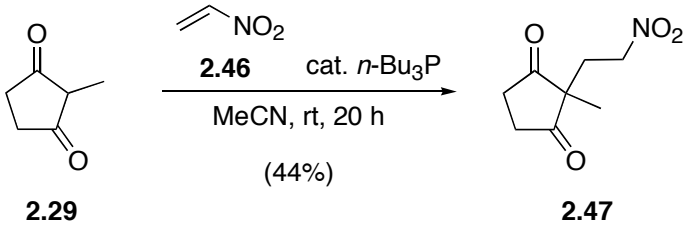
Installation of terminal electron-withdrawing groups was readily accomplished through conjugate addition with various Michael acceptors. Several examples of Michael reactions to cyclic-1,3-diones have been reported, including use of KO*t*Bu/crown ethers,[87] dimsyl[88] or lanthanides under microwave irradiation.[89] We employed Brooks' procedure[74c] for ease, cost and convenience (Scheme 2.14). Exposure of a ten-fold excess of acrylonitrile or methyl acrylate to **2.29** or **2.30** in refluxing triethylamine provided compounds **2.43**, **2.44** and **2.45**.



Scheme 2.14. Preparation of diones **2.43**, **2.44** and **2.45**.

[87] Cram, D. J.; Sogah, G. D. Y. "Chiral crown complexes catalyze Michael addition reactions to give adducts in high optical yields." *J. Chem. Soc., Chem. Commun.* **1981**, 625-628.
[88] Danishefsky, S.; Koppel, G.; Levine, R. "Reactions of methyl β-vinylacrylate with β-dicarbonyl compounds a new route to functionalized bridged ring systems." *Tetrahedron Lett.* **1968**, *18*, 2257-2260.
[89] Boruah, A.; Baruah, M.; Prajapati, D.; Sandhu, J. S. "Cerium catalyzed Michael addition of 1,3-dicarbonyl compounds under microwave irradiation." *Synth. Commun.* **1998**, *28*, 653-658

Preparation of nitroethyl **2.47** proved surprisingly difficult. Nitroethylene (**2.46**) was prepared from nitromethane over two steps according to literature procedures.[90] Exposure of **2.46** to Brooks' Michael reaction conditions[74c] resulted in flash-polymerization of the material and the formation of an acrid brown/red gas. An identical result was observed when the solution was cooled to -78 ^{o}C prior to addition of Michael acceptor **2.46**. However, treatment of **2.28** and **2.45** with *n*-Bu_3P in MeCN at room temperature provided dione **2.46** in 44% yield (Scheme 2.15).[91]



Scheme 2.15. Preparation of nitroethyl dione **2.47**.

2.2.2. Initial Monoreduction Screening

Early progress in the identification of a high yielding, facile, diastereoselective monoreduction protocol focused on screening several established methods. We used allyl dione **2.31** as a test substrate for the reaction screening studies due to its simplicity in preparation. This section discusses these experiments in two parts, namely methods involving diastereoselective hydride addition facilitated by chiral reagents and methods involving substrate-controlled delivery.

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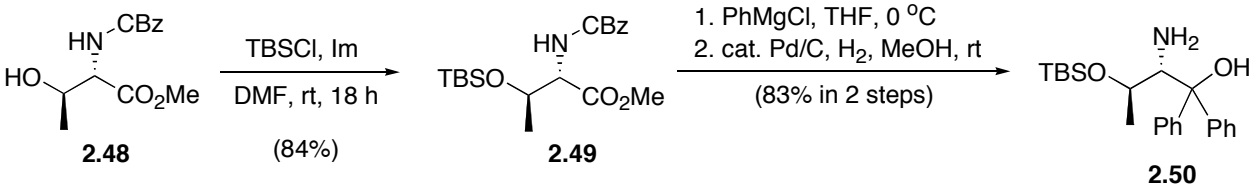
[90] Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, A. K.; Iyengar, R. "Nitroethylene: a stable, clean, and reactive agent for organic synthesis." *J. Org. Chem*. **1980**, *45*, 1185-1189

[91] Nakashita, Y.; Watanabe, T.; Benkert, E.; Lorenzi-Riatsch, A.; Hesse, M. "Studies on the Synthetic Usefulness of the Nitro Function. Part I. A Novel Cyclopentenone Ring Annelation." *Helv. Chim. Acta* **1983**, *67*, 1204-1207.

2.2.2.1. Ligated Enantioselective Monoreductions

The earliest iterations of the monoreduction experiments involved the use of the Fujisawa/Shimizu ligand (**2.7**),[75] which was not commercially available. The ligand derives from CBz-protected L-threonine methyl ester (**2.48**), which was protected as TBS ether **2.49** in 84% yield (Scheme 2.16). Treatment of the ether with three equivalents of phenylmagnesium chloride provided the diphenylcarbinol. Ensuing catalytic hydrogenation cleaved the CBz functional group and thus cleanly afforded α-amino alcohol **2.50**. The Fujisawa/Shimizu ligand (**2.7**) is prepared through the reaction of α-amino alcohol **2.50** with alkylated boric acids in the presence of 4 Å molecular sieves[77] or BH_3-DMS.[75] For our purposes, we heated **2.50** with methyl boronic acid for 5 h to prepare the methylated ligand (**2.7b**)

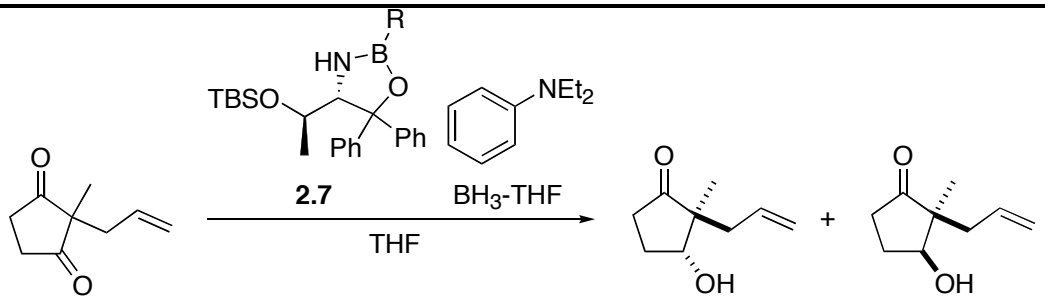


Scheme 2.16. Preparation of α-amino alcohol **2.50**.

As seen in Table 2.2, treatment of **2.31** with a modified variation of Shimizu's conditions provided the corresponding 1,3-ketol (**2.31a**/**b**) in 32% yield after 12 h when BH_3•THF was introduced as the stoichiometric reducing agent through syringe pump addition. Incomplete conversion of the starting material accounted for the low yield. Repetition of the experiment for a longer time allowed for greater conversion providing a diastereomeric mixture of ketols (3:1 **2.31a**:**2.31b**) in 65% yield. This stereochemical outcome was contrary to the isomer reported by Shimizu and co-workers.[77] Lowering the temperature appeared to hinder conversion and had a negative effect on the yield and diastereoselectivity (Entry 3). Additionally, pre-treatment of α-

amino alcohol **2.49** with *n*-butylboronic acid resulted in a decrease in yield and diastereoselectivity relative to methylated ligand **2.7b** (Table 2.2, entries 4-5).

Table 2.2. Application of the Fujisawa/Shimizu ligand (**2.7**) in the monoreduction of allyl dione **2.31**.



2.31 **2.31a** **2.31b**

Entry	*R*	*T* (°C)	*t* (h)	*Yield* (%)[a]	*d.r.* (**a**:**b**)[b]
1	Me	rt	11	32	2:1
2	Me	rt	21	65	3:1
3	Me	0	30	20	2:1
4	Bu	rt	20	40	2:1
5	Bu	0	15	31	2:1

[a]Combined isolated yield of ketols **2.31a** and **2.31b**.
[b]Determined by ^{1}H-NMR analysis of the crude reaction mixture.

Other chiral catalysts were screened to study the diastereoselective monoreduction of allyl dione **2.31**. Treatment of the substrate with L-proline and addition of several equivalents of BH_3-THF resulted in no conversion even after heating for several hours at reflux.[92] Similarly, employing the (*R*)-methyl CBS catalyst[33] in the presence of borane had no effect on the conversion after several hours even with inclusion of the $PhNEt_2$ additive. Though, similar experiments with catecholborane furnished the desired ketol (**2.31a/b**), these results had little advantage over the Fujisawa/Shimizu methodology. With little success coming from the use of chiral auxiliaries, we opted to explore other monoreduction methods.

[92] Brunel, J. M.; Maffei, M.; Maffei, M.; Buono, G. "Enantioselective reduction of ketones with borane, catalyzed by (*S*)-(-)-proline or (*S*)-(+)-prolinol." *Tetrahedron: Asymmetry* **1993**, *4*, 2255-2260.

2.2.2.2. Aluminum- and Boron-Based Reducing Agents

We initially began experimenting with a variety of other reducing agents commonly found in our laboratory. The reaction of **2.31** with strong reductants such as LAH and DIBAH promoted diol formation even at -78 ^{o}C. Despite this outcome, use of 9-BBN resulted in starting material recovery (even with gentle warming to 40 ^{o}C). Although 9-BBN is normally a versatile reducing agent capable of reducing a ketone, the combination of its steric bulk and the presence of an adjacent quaternary center may preclude hydride addition to **2.31**.

We eventually experimented with $NaBH_4$ to reduce **2.31** to the corresponding ketol while hypothesizing that the reactivity of the ketone might be harnessed through temperature moderation. Molander's methodology purportedly furnished 1,3-ketols as a 1:1 diastereomeric mixture in modest yields when MeOH was used as the solvent. Experimentation with this method on **2.31** provided ketols **2.30a** and **2.30b** in 53% yield as a 2.3:1 diastereomeric mixture in favor of the *trans* isomer. By comparison, Luche conditions[93,94] at -78 ^{o}C resulted in a slight increase in diastereoselectivity (2.5:1, **2.30a**:**2.30b**) while offering no advantage in the yield. Additionally, the cost of $CeCl_3$ makes Luche conditions largely unappealing.

2.2.3. $NaBH_4$/DME Method for Monoreduction of Cyclopentanedione Substrates.

In considering an economical method for effecting the monoreduction of cyclic 2,2-disubstituted-1,3-diones, we reasoned that successes using $NaBH_4$ could be improved by moderating the reactivity of the reductant rather than the substrate. Brown reported that 1,2-dimethoxyethane (DME) retards the rate of borohydride-mediated reductions compared to

[93] Krief, A.; Surleaux, D. "Unusual stereofacial differentiation in the reduction of bicyclo[3.1.0]hexanones by Luche's reagent (sodium borohydride-cerium trichloride)." *Synlett* **1991**, 273-275.
[94] Jeanmart, S. "Trends in chrysanthemic acid chemistry: A survey of recent Pyrethrum syntheses." *Aust. J. Chem.* **2003**, *56*, 559-566.

reactions conducted in lower alcohols.[95] Given the reportedly poor ability of $NaBH_4$ to reduce ketones in DME, we were curious to determine whether the harnessed reactivity could lead to controlled monoreduction of substituted 2,2-disubstituted-cyclic-1,3-diones. The affordability, simplicity, and functional group compatibility of such a method would offer obvious benefits.

2.2.3.1. Development of a NaBH4/DME Monoreduction Protocol

Examination of the reaction progress of $NaBH_4$ and **2.31** in DME at various temperatures provided interesting results. Experimentally, a solution of the substrate in DME, equilibrated at a given temperature for one hour, was treated with a predetermined portion of $NaBH_4$. At random time intervals, aliquots of the reaction mixture were removed by glass pipette, quenched with 1N HCl then extracted with EtOAc. The resultant organic layers were dried ($MgSO_4$) and concentrated then analyzed by ^{1}H-NMR to monitor substrate conversion.

As seen in Figure 2.4, allyl dione **2.31** was completely consumed within 1 h using 0.5 equivalents of $NaBH_4$. During this same time, nearly 30% of the desired 1,3-ketol was also reduced to the diol. The observed over-reduction appeared maximized at ~35% with no change after 7 h.

[95] Brown, H. C.; Krishnamurthy, S. "Forty years of hydride reductions." *Tetrahedron* **1979**, *35*, 567-607.

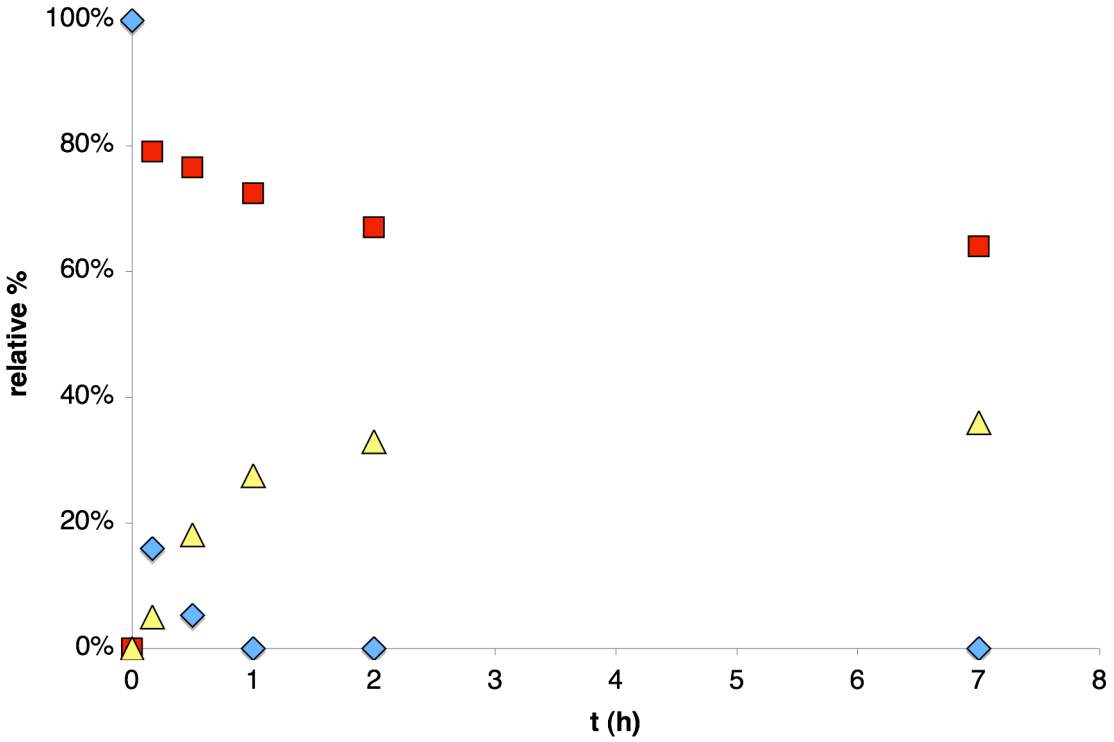


Figure 2.4. Data plot of the ^{1}H-NMR analysis of the reaction progress of $NaBH_4$ (0.5 equiv) and **2.31** in DME at room temperature. The symbols above are as follows: ◆ - dione; ■ - ketol; ▲ - diol.

Repetition of the experiment at lower temperatures offered expected advantages. Decreasing the reaction temperature to -60 ^{o}C afforded superior control of diol formation (<5%) even after 12 h (Figure 2.5). Also, increasing the amount of reductant from 0.5 to 1.0 equivalents resulted in greater conversion and rate of reaction. However, this increase also resulted in an increase in diol formation and a notable decline in diastereoselectivity. For these reasons, we elected to use 0.5 equivalents of $NaBH_4$ in -60 ^{o}C DME as our optimal reaction conditions for the cyclopentanedione experiments.

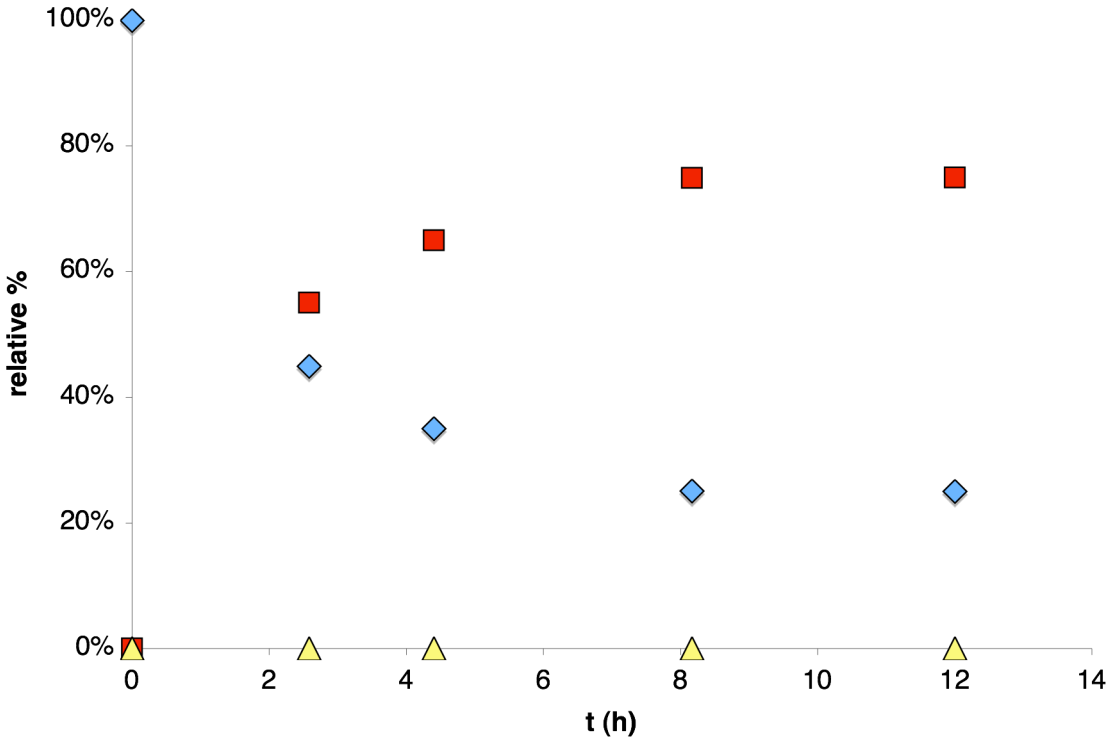
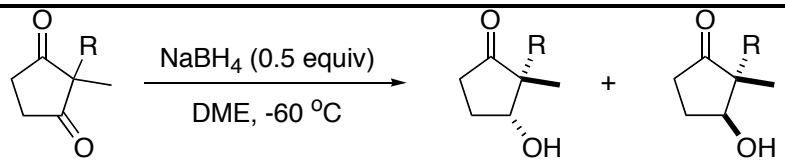


Figure 2.5. Data plot of the ^{1}H-NMR analysis of the reaction progress of $NaBH_4$ (1.0 equiv) and **2.31** in DME at -60 ^{o}C. The symbols above are as follows: ◆ - dione; ■ - ketol; ▲ - diol.

Encouraged by the results of our optimization studies, we applied the newly devised conditions to our array of different cyclopentanediones to ascertain the degree of diastereoselectivity furnished during the monoreductions. Treatment of the substituted cyclopentanediones at -60 ^{o}C with 0.5 molar equivalents of $NaBH_4$ in DME produced high yields of ketols (Table 2.3). Routine monitoring of reaction progress by TLC indicated that the diones were consumed within 24 h. Given the sluggish reduction rates for **2.31**, **2.33**, **2.35**, **2.37** and **2.42**, we were surprised to find that cyanoethyl dione **2.43** was consumed within two hours. We observed a similar rate enhancement in the $NaBH_4$ reduction of the nitroethyl dione (**2.47**) and a slight rate enchantment with the methyl ethanoate substrate (**2.45**).

Table 2.3. Application of optimized reaction conditions for the $NaBH_4$/DME-mediated monoreduction of a variety of cyclopentyl-2,2-disubstituted-1,3-diones.



			a		**b**	
Entry	*Compound*	*Substituent* (R)	*Equiv*	*t* (h)	*dr*[a] (**a**:**b**)	*Yield* (%)[b]
1	**2.31**	Allyl	0.5	20	3.3 : 1	86
2	**2.33**	Propyl	0.5	20	5.1 : 1	82
3	**2.35**	Propargyl	0.5	24	1.0 : 1	79
4	**2.37**	Benzyl	0.5	24	4.9 : 1	83
5	**2.42**	Phenyl	0.5	20	16 : 1	93
6	**2.43**	Cyanoethyl	0.5	2	1 : 1.1	82
7	**2.45**	Methyl Ethanoate	0.5	17	1.6 : 1	80
8	**2.47**	Nitroethyl	0.5	3	1 : 1.4	76

[a]Determined by ^{1}H NMR analysis of crude reaction mixture and/or nOe difference spectroscopy of purified materials.
[b]Isolated yield of purified combined ketols **a** and **b**.

The results suggest that steric hinderance and diastereoselectivity are intimately related. As the R-substitutent increases in steric bulk, there is a diastereoselective preference for formation of the *cis*-ketol (**a**). This is particularly apparent when comparing the phenyl (**2.42**) and benzyl (**2.37**) substrates (Table 2.3, Entries 4 and 5). As the aryl ring becomes distal to the carbonyls, there is a decrease in diastereoselectivity.

2.2.3.2. Rate Enhancement in Electron-Withdrawing Substrates

We remained puzzled by the diastereoselective outcome of the electron-withdrawing substrates and endeavored to examine the accompanying rate enhancement. As seen in our optimized results, both the cyanoethyl (**2.43**) and nitroethyl (**2.47**) substrates are consumed under 3 h. Analysis of the crude reaction mixtures of these two substrates by ^{1}H-NMR, as a function of time, confirms this rate enhancement (Figure 2.6, 2.7). Longer reaction times resulted in an increased formation of diol. However, in both cases, starting material was still present in the

reaction mixture indicating incomplete substrate conversion, even after 20 h. A similar rate enhancement was observed for ethanoate dione **2.45** (Figure 2.8). Though, this effect was less pronounced relative to **2.43** and **2.47**.

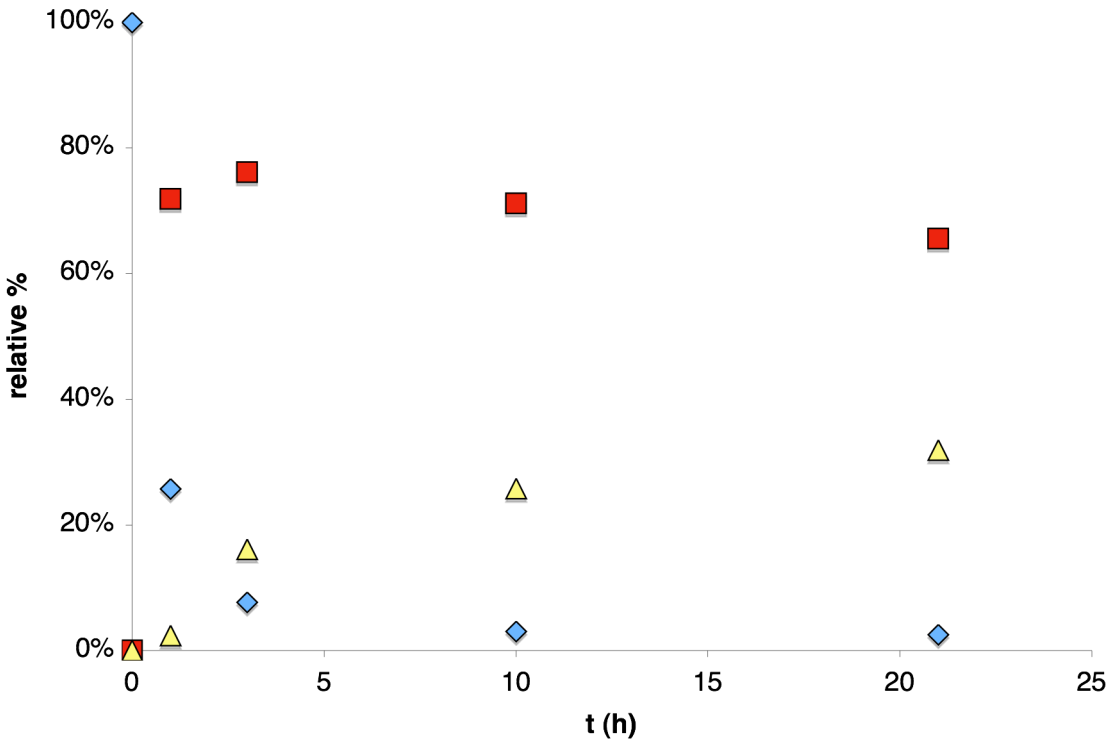


Figure 2.6. Data plot of the ^{1}H-NMR analysis of the reaction progress of $NaBH_4$ (0.5 equiv) and cyanoethyl dione **2.43** in DME at -60 ^{o}C. The symbols above are as follows: ◆ - dione; ■ - ketol; ▲ - diol.

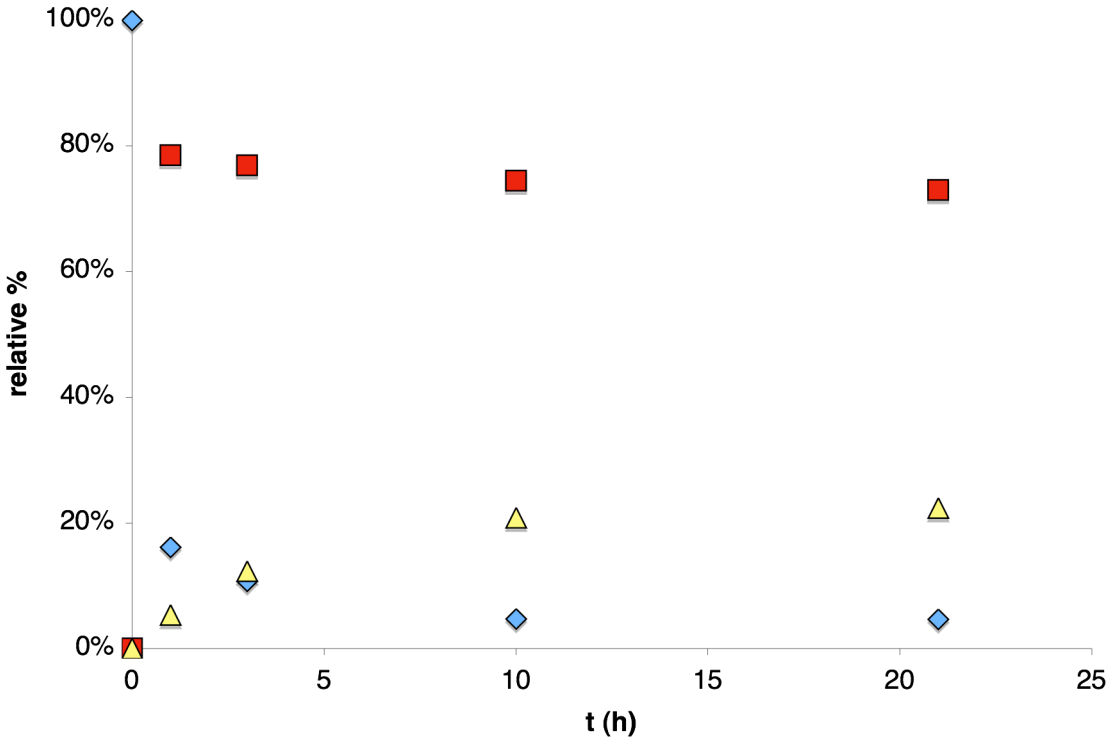


Figure 2.7. Data plot of the ^{1}H-NMR analysis of the reaction progress of $NaBH_4$ (0.5 equiv) and nitroethyl dione **2.47** in DME at -60 ^{o}C. The symbols above are as follows: ◆ - dione; ■ - ketol; ▲ - diol.

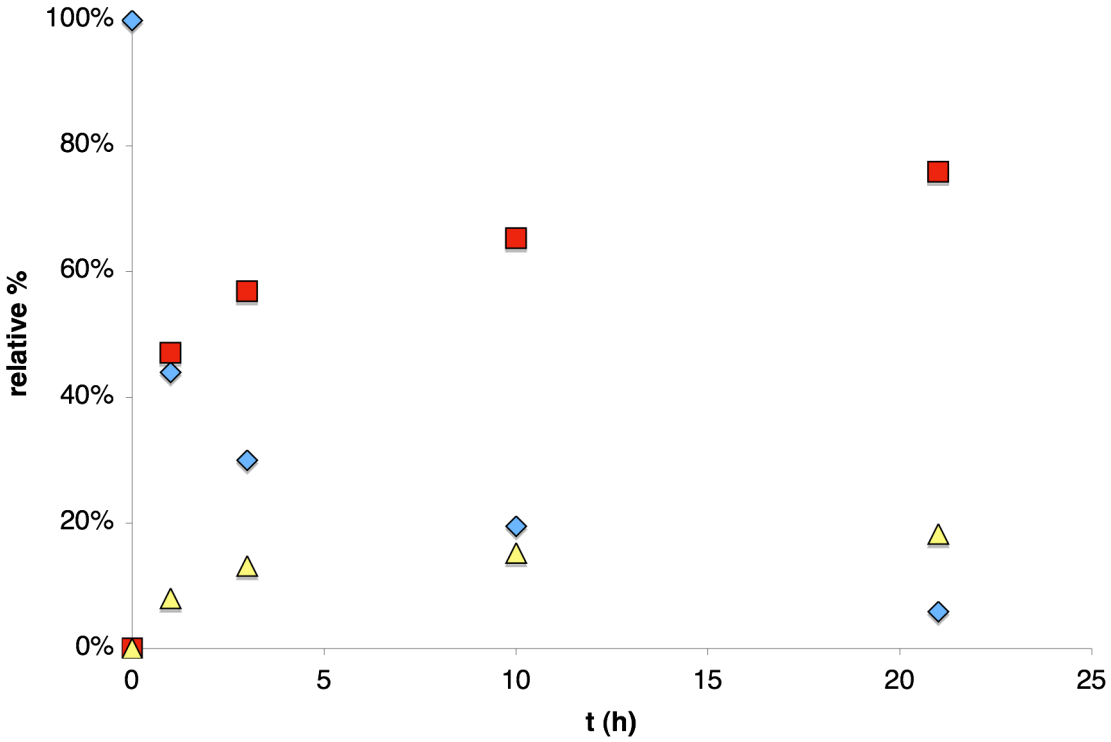


Figure 2.8. Data plot of the ^{1}H-NMR analysis of the reaction progress of $NaBH_4$ (0.5 equiv) and methyl ethanoate dione **2.45** in DME at -60 ^{o}C. The symbols above are as follows: ◆ - dione; ■ - ketol; ▲ - diol.

We elected to construct LUMO maps of propyl substrate **2.33** and nitro substrate **2.47** to compare the electron density surfaces. Similar calculations have been used to explain the stereoselectivity of carbonyl addition reactions.[96] The LUMO maps reveal both the molecular van der Waals surface and the positions most susceptible to nucleophilic attack (blue regions). The surfaces readily account for facial selectivity among similar systems, and these theoretical results have shown good correlation with experimental findings. Compounds **2.33** and **2.47** were

[96] (a) Hehre, W. J. *A Guide to Molecular Mechanics and Quantum Chemical Calculations*; Wavefunction Inc.: Irvine, CA, 2003, Chapter 19. (b) Fraga, C. A. M.; Teixeira, L. H. P.; Mendezes, C. M. de S.; Sant'Anna, C. M. R.; Ramos, M. C. K. V.; Neto, F. R. A.; Barreiro, E. J. *Tetrahedron* **2004**, *60*, 2745-2755. (c) Höltje, H.-D.; Folkers, G. *Molecular Modeling. Basic principles and applications*; Manhold, R., Kubinyi, J., Timmerman, H., Eds.; VCH: Weinheim, 1997; Vol. 5., p 194

selected because of their steric similarities but disparate facial selectivities during the experimental monoreductions. A conformational search was conducted using the semiempirical PM3 method[97] and then a single-point energy LUMO map was established for the lowest energy ground-state conformer using an HF 6-31G* basis set.

Examination of the LUMO maps for structures **2.33** and **2.47** aided in rationalizing the observed diastereoselectivities in the reduction of these substrates (Figure 2.9). The methyl face of **2.33** (right structure) shows a clear preference (deep blue at carbonyl carbons) for hydride addition relative to the opposite face bearing the *n*-propyl group (left structure). A possible electronic (steric) repulsion (red-orange of the propyl group) is also evident in the leftmost compound. Conversely, both faces of **2.47** show similar electronic and steric susceptibilities to hydride addition, thereby reflecting little facial differentiation. The electronic and steric information highlighted by these LUMO maps is in excellent agreement with the experimental observations.

[97] (a) Stewart, J. J. P. "Optimization of parameters for semiempirical methods I. Method." *J. Compu. Chem.* **1989**, *10*, 209-220. (b) Stewart, J. J. P. "Optimization of parameters for semiempirical methods II. Applications." *J. Compu. Chem.* **1989**, *10*, 221-264. (c) Stewart, J. J. P. "Optimization of parameters for semiempirical methods. III Extension of PM3 to Be, Mg, Zn, Ga, Ge, As, Se, Cd, In, Sn, Sb, Te, Hg, Tl, Pb and Bi." *J. Compu. Chem.* **1991**, *12*, 320-341

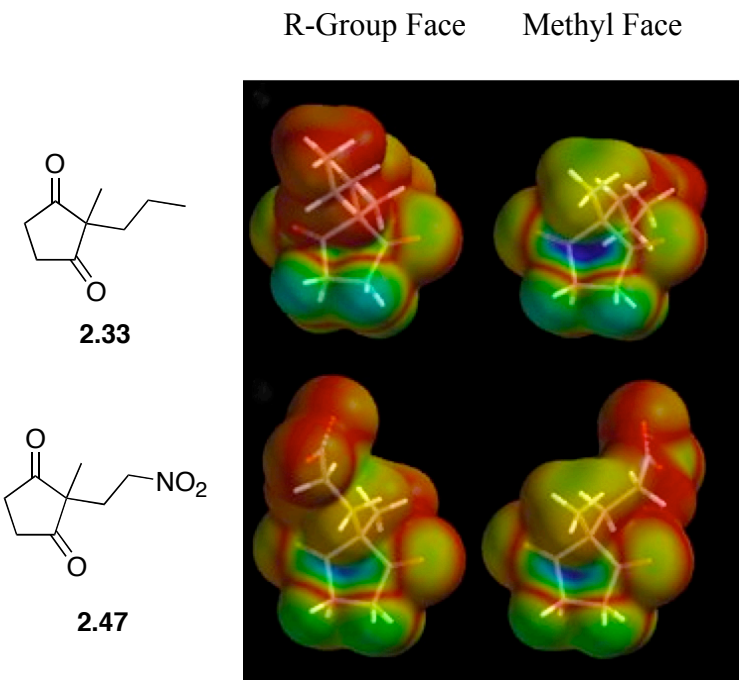


Figure 2.9. LUMO maps of propyl dione **2.33** and nitro dione **2.47** plotted over their respective lowest energy conformers.

2.2.4. $NaBH_4$/DME Methodological Studies for Cyclohexanedione Substrates.

Allyl dione **2.32** was selected as our model substrate to establish conditions for our cyclohexanedione analogs. We initially discovered that 0.5 equivalents of $NaBH_4$ in DME at -60 ^oC led to incomplete substrate conversion. Increasing the reductant loading to 0.75 equivalents resulted in better conversion and good overall yields in pilot reactions (Figure 2.10). Spectroscopic analysis of the crude reaction mixture as a function of time confirmed substrate consumption at a much faster rate relative to allyl dione analog **2.31**, an effect documented previously.[98] Unlike with the cyclopentanedione substrates, the concentration of the diol

[98] (a) Guyon, R.; Villa, P. "Stereoselectivity and relative reaction rates in the reduction of substituted cyclohexanones and cyclopentanones by various hydrides." *Bull. Soc. Chim. Fr.* **1977**, II-145-151. (b) Caro, B.; Boyer, B.; Lamaty, G.; Jaouen, G. "Reactivity factors and stereochemistry of metal borohydride reduction of carbonyl compounds." *Bull. Soc. Chim. Fr.* **1983**, II-281-303.

continually increased with time for hexanedione **2.32**. This observation suggested that the monoreduction should be terminated at 30 minutes to afford optimal results.

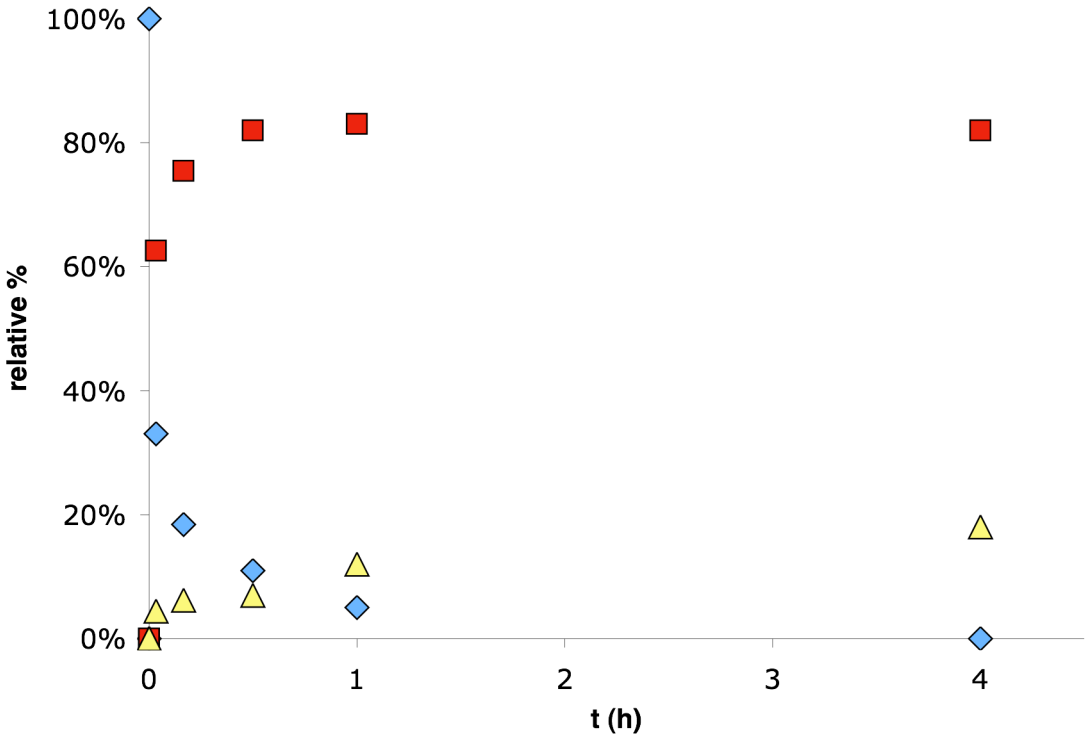
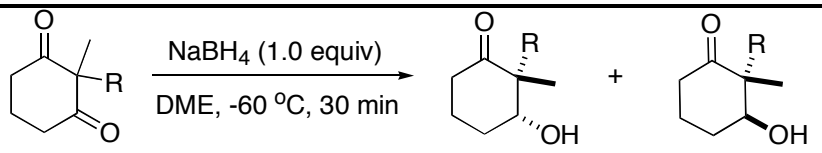


Figure 2.10. Data plot of the ^{1}H-NMR analysis of the reaction progress of $NaBH_4$ (0.75 equiv) and allyl dione **2.31** in DME at -60 ^{o}C. The symbols above are as follows: ◆ - dione; ■ - ketol; ▲ - diol.

Despite the outcome of our initial analyses, we found that employing up to 1.0 equivalent of $NaBH_4$ in the cyclohexanedione substrates effected optimal conversion of the diones without a significant increase in the rate of diol formation (Table 2.4). In all cases, the diones were quickly reduced (within 30 min) giving good combined isolated yields of diastereomeric ketols. The results feature interesting levels of diastereoselectivity for the favored *cis*-stereoisomer, with benzyl-substituted compound **2.38** offering the highest stereocontrol (dr = 8.6:1)

Table 2.4. Application of optimized reaction conditions for the $NaBH_4$/DME-mediated monoreduction of a variety of cyclohexyl-2,2-disubstituted-1,3-diones.



			a	**b**
Entry	*Compound*	*Substituent* (R)	*dr*[a] (**a**:**b**)	*Yield* (%)[b]
1	**2.36**	Propargyl	1.4 : 1	77
2	**2.32**	Allyl	3.3 : 1	82
3	**2.34**	Propyl	4.3 : 1	81
4	**2.38**	Benzyl	8.6 : 1	81
5	**2.44**	Cyanoethyl	1.1 : 1	85

[a]Determined by ^{1}H NMR analysis of crude reaction mixture and NOE difference spectroscopy of purified materials.
[b]Isolated yield of purified combined ketols **a** and **b**.

As seen in Figure 2.11, we constructed LUMO maps for cyclohexanedione analogs **2.34** and **2.36**. The LUMO map of the pseudo-chair equatorial and axial faces of **2.34** displays a clear electronic preference for hydride approach from the methyl face, leading to the *cis*-ketol. However, a similar preference is indicated by the LUMO map of **2.36**, despite that substrate's poor experimentally observed diastereoselectivity.

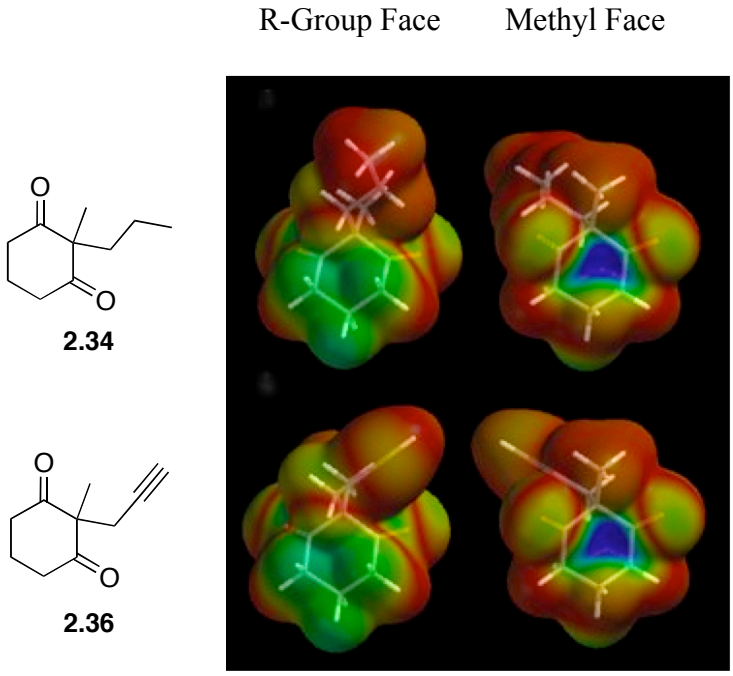


Figure 2.11. LUMO maps of propyl dione **2.34** and propargyl dione **2.36** plotted over their respective lowest energy conformers.

It is important to recognize that factors other than those reflected in LUMO maps affect facial selectivity, especially with the cyclohexane-1,3-diones. Depending upon the substrate and the precise reaction conditions, transition state position, steric and torsional effects related to product-development control, the steric impact of the axial hydrogen at C-5, and conformational isomerization also contribute to facial selectivity.[99] The latter factor may be particularly relevant to substrates **2.32**, **2.34**, **2.36**, and **2.44** where conformational isomerization may occur even at -60 ^{o}C leading to higher energy, more reactive conformers that are susceptible to hydride addition.

[99] (a) Ashby, E. C.; Boone, J. R. "Stereochemistry of Reduction of Ketones by Simple and Complex Metal Hydrides of the Main Group Elements." *J. Org. Chem.* **1976**, *41*, 2890-2903. (b) Wigfield, D. C. "Stereochemistry and mechanism of ketone reductions by hydride reagents." *Tetrahedron* **1979**, *35*, 449-462. (c) Houk, K. N.; Wu, Y.-D.; Paddon-Row, M. N. "Effect of Torsional Strain and Electrostatic Interactions on the Stereochemistry of Nucleophilic Additions to Cyclohexanone and Related Systems." *Angew. Chem. Int. Ed.* **1992**, *31*, 1019-1021

2.2.5. LTBA/THF Reduction Applied to Dione Substrates

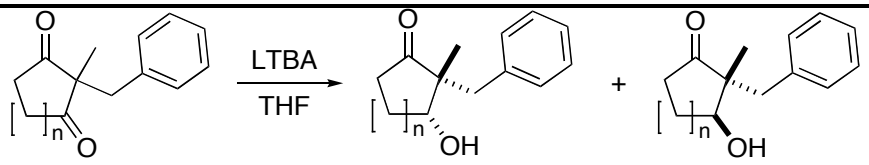
Given our observations in the monoreductions using $NaBH_4$ in DME at reduced temperature, we proceeded to evaluate the ability of lithium tri-*tert*-butoxyaluminum hydride (LTBA) to furnish ketols from our substrates. These experiments would not only offer a comparative measure of the performance of $NaBH_4$ in DME but also provide the first extensive investigation concerning the capabilities of LTBA to monoreduce variably substituted cyclic 1,3-diones. Although the utility of the reductant has been marginally investigated relative to $NaBH_4$,[100] LTBA is known to offer superior reactivity.[101] Additionally, LTBA is notably less violent than similar aluminum-based reducing agents (e.g., LAH).

Concerned that the bulky *tert*-butoxy ligands on LTBA might retard the desired reduction of substrates bearing large substituents, we elected to examine benzyl substrates **2.37** and **2.38** in our initial optimization studies (Table 2.5). The optimization studies suggested an increase in diastereoselective formation of *cis*-ketols with decreasing temperature. Although this effect was minor with cyclopentanedione **2.37**, the results were pronounced with cyclohexanedione **2.38**.

[100] Wigfield, D. C.; Gowland, F. W. "Kinetics and Activation Parameters for the Reduction of Alkylcyclohexanones by Lithium Tri-*tert*-butoxyaluminohydride." J. *Org. Chem.* **1980**, *45*, 653-658.

[101] Brown, H. C.; McFarlin, R. F. "The Reaction of Lithium Aluminum Hydride with Alcohols. Lithium Tri-*t*-butoxyaluminohydride as a New Selective Reducing Agent." *J. Am. Chem. Soc.* **1958**, *80*, 5372-5376.

Table 2.5. Optimization of monoreduction of benzyl diones **2.37** and **2.38** using LTBA/THF.



n = 1, **2.37**
n = 2, **2.38**

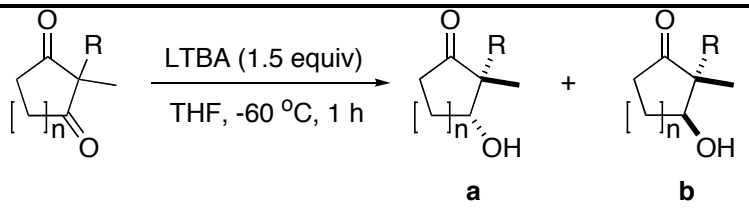
a **b**

Entry	*Dione*	*LTBA* (equiv)	*T* (°C)	*t* (h)	*Selectivity* (**a**:**b**)[a]	*Conversion* (%)[a]
1	**2.37**	1.1	rt	0.5	3.2:1	86
2		1.1	-20	2	3.3:1	87
3		1.1	-60	2	3.4:1	72
4		1.2	-60	2	3.9:1	89
5		1.5	-60	2	3.9:1	>95
6	**2.38**	1.1	rt	0.5	5.0:1	88
7		1.1	-20	2	5.4:1	82
8		1.1	-60	2	5.8:1	69
9		1.5	-60	2	9.8:1	88

[a]Determined by ^{1}H-NMR analysis of the crude reaction mixture.

Unlike the monoreductions with $NaBH_4$ in DME, all reactions involving LTBA were completed within two hours independent of ring size (Table 2.6). We also found that conducting the reactions at -60 °C mandated employment of 1.5 equivalents of LTBA to provide desired levels of conversion. Temperatures below -60 °C limited the solubility of LTBA in THF.

Table 2.6. Desymmetrization of 2-methyl-2-substitutedcycloalkane-1,3-diones using LTBA/THF.



a **b**

Entry	*Compound*	*n*	*Substituent* (R)	*dr*[a] (**a**:**b**)	*Yield* (%)[b]
1	**2.31**	1	Allyl	2.2 : 1	85
2	**2.33**	1	Propyl	4.0 : 1	93
3	**2.35**	1	Propargyl	1.3 : 1	83
4	**2.37**	1	Benzyl	3.9 : 1	84
5	**2.42**	1	Phenyl	11 : 1	95
6	**2.43**	1	Cyanoethyl	1 : 1.2	91
7	**2.45**	1	Methyl Ethanoate	1.9 : 1	82
8	**2.47**	1	Nitroethyl	1 : 1.4	88
9	**2.32**	2	Allyl	5.0 : 1	87
10	**2.34**	2	Propyl	5.9 : 1	91
11	**2.36**	2	Propargyl	1.4 : 1	77
12	**2.38**	2	Benzyl	9.8 : 1	83
13	**2.44**	2	Cyanoethyl	1.1 : 1	85

[a]Determined by ^{1}H NMR analysis of crude reaction mixture and nOe difference spectroscopy of purified materials.
[b]Isolated yield of purified combined ketols **a** and **b**.

Implementing LTBA in THF at -60 °C gave consistently high yields with all substrates evaluated. Interestingly, LTBA-mediated monoreduction did not result in diol formation with any evaluated substrates. This observation corroborates reported results for other dione monoreductions involving the reagent.[83,102] As expected, LTBA displays greater stereoselectivity in the monoreductions of the cyclohexanedione substrates. The reagent's propensity for axial

[102] (a) Boeckman, Jr., R. K.; Arvanitis, A.; Voss, M. E. "Synthetic Studies Directed Toward Naturally Occurring Cyclooctanoids. 1. A Total Synthesis of (±)-Ceroplastol I." *J. Am. Chem. Soc.* **1989**, *111*, 2737-2739. (b) Yuan, P.; Plourde, R.; Shoemaker, M. R.; Moore, C. L.; Hansen, D. E. "A Mimic of Both a Torsionally-Distorted Peptide Ground State and the Transition State for Peptide Bond Hydrolysis: Synthesis of a Spiro[4.4]nonyl Derivative." *J. Org. Chem.* **1995**, *60*, 5360-5364.

attack in the reduction of cyclohexanones is superior to that of $NaBH_4$.[103] However, we were surprised to find that the $NaBH_4$/DME protocol afforded enhanced diastereoselectivity in the monoreduction of the cyclopentane-1,3-dione derivatives. Perhaps the reduced reactivity of $NaBH_4$ in DME affords greater selectivity toward these rigid substrates.

2.2.6. Conclusion

A new approach to the reductive desymmetrization of 2,2-disubstitutedcycloalkane-1,3-diones using $NaBH_4$ in DME at -60 ^oC shows yields and levels of stereocontrol comparable to those found using LTBA. The $NaBH_4$ in DME approach offers slightly greater facial selectivity in the monoreduction of 2,2-disubstitutedcyclopentane-1,3-diones while LTBA is superior with 2,2-disubstitutedcyclohexane-1,3-diones. Both conditions minimize subsequent reduction to diols thereby furnishing high yields of 1,3-ketols though this effect is more pronounced with the LTBA/THF reducing system.

This comparative study is the first of its kind with this popular class of diones and provides important data for the longstanding campaign to better understand and predict the reactivity and selectivity of hydride-based additions to carbonyl compounds.

[103] Brown, H. C.; Deck, H. R. "Selective Reductions. VIII. The Stereochemistry of Reduction of Cyclic and Bicyclic Ketones by the Alkoxy-Substituted Lithium Aluminum Hydrides." *J. Am. Chem. Soc.* **1965**, *87*, 5620-5625.

2.3. Experimental Details

2.3.1. General Remarks

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone ketyl radical under argon. 1,2-Dimethoxyethane (DME) was purchased from Aldrich (99.8%), shipped in a SureSeal bottle and used as received. Dichloromethane (DCM) was distilled over CaH_2. Sodium borohydride (99%) was purchased from Sigma and LTBA (93-98%) was purchased from Acros, and both were used as received. Starting materials **2.29** and **2.30** were purchased from Aldrich and used directly. Enone **2.39** was purchased from SAFC and used directly. CBz-protected L-threonine methyl ester (**2.48**) was purchased from Aldrich and used directly. Alkyl lithium reagents were titrated with 2,5-dimethoxybenzylalcohol (Aldrich) in anhydrous THF immediately before use.[104] Air-sensitive materials were handled using standard anoxic transfer techniques employing argon.

Proton magnetic resonance spectra (^{1}H-NMR) were recorded at either 360 or 500 MHz. Carbon magnetic resonance spectra (^{13}C-NMR) were recorded on spectrometers operating at either 91 or 127 MHz. Nuclear Overhauser enhancement (nOe) difference spectroscopy experiments were performed on a 500 MHz spectrometer. Infrared spectroscopy data (IR) was recorded on a Jasco FT/IR-4100. High-resolution mass spectrometry (HRMS) was performed on an AutoSpec-Ultima NT. Flash column chromatography was performed using Silicycle silica gel (230-400 mesh). TLC visualization was achieved by ultraviolet light (254 nm), I_2 vapors, or an acidic *p*-anisaldehyde or vanillin stain. Temperature for monoreduction experiments was controlled using an immersion cooler (NESLAB CC-100) or a $CHCl_3$:CO_2 bath.

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[104] Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. "2,5-Dimethoxybenzyl alcohol: a convenient self-indicating standard for determination of organolithium reagents." *J. Chem. Soc., Chem. Commun.* **1980**, *3*, 87-88.

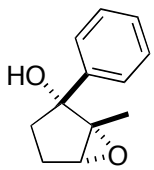
2.3.2. Molecular modeling

Molecular modeling was conducted using SPARTAN '04 v.1.0.1 (Wavefunction Inc., Irvine, CA, 2003). A ground state conformer distribution search was conducted on compounds **2.33**, **2.47**, **2.34** and **2.36** with the PM3 method.[97] The lowest energy conformers were submitted to single-point energy calculations using the Hartree-Fock 6-31G* basis set. The calculated absolute value of the LUMO was plotted onto the electron density surface (0.002 e/au^3) of each structure to produce the LUMO maps.

2.3.3. Preparation of Known Compounds

Substrates **2.31** and **2.32**,[74a,86] **2.35** and **2.36**,[105] **2.37** and **2.38**,[106] **2.43**, **2.44** and **2.45**[74a] were prepared according to known procedures starting from **2.29** and **2.30**, respectively. Amino alcohol **2.50** was prepared from **2.48** according to known procedure.[75]

2.3.4. Substrate Preparation



(±)-2,3-Epoxy-2-methyl-1-phenylcyclopentan-1-ol (2.40). A stirred solution of freshly distilled bromobenzene (2.1 mL, 20 mmol) and diethyl ether (100 mL) was treated with 1.5 M *tert*-butyl lithium (44 mL, 66 mmol, 3.3 equiv) at -78 ^{o}C dropwise via glass syringe over 30 min. Upon transfer of the reagent, the orange solution was allowed to warm to rt for approximately 30 min then cooled to -78 ^{o}C. Enone **2.38** (1.96 mL, 20.0 mmol, 1 equiv) was added dropwise to the reaction mixture over 15 min via addition funnel.

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[105] Schick, H.; Schwarz, H.; Finger, A.; Schwarz, S. "2,2-disubtituierte cyclopentan-1,3-dione—2: Untersuchung der regioselektivität von alkylierungs-reaktionen an 2-methyl-cyclopentan-1,3-dion." *Tetrahedron* **1982**, *9*, 1279-1283.

[106] Fuji, K.; Bedekar, A. V.; Watanabe, T.; Tanaka, K. "A convenient method for selective C-alkylation of 2-methyl-1,3-diketones." *Synthesis* **1995**, 1069-1070.

After stirring for an additional 10 min, the solution was removed from the -78 ^{o}C bath and quenched by slow addition of saturated NH_4Cl solution (25 mL). Upon an initial separation, the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic layers were then washed with brine (1 x 25 mL), dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by flash chromatography (9:1 hexanes:EtOAc) removed major impurities but left traces of unidentified compounds.

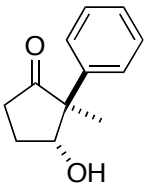
The recovered semi-pure carbinol (3.21 g, 16.9 mmol) was diluted in DCM (40 mL), vigorously stirred and cooled to -78 °C (~20 min). In a separate vessel, a solution of *m*CPBA (5.38 g, 23.1 mmol, 1.37 equiv) and DCM (31 mL) was warmed to 40 °C to induce solubility. The peroxy acid solution was transferred to the cold carbinol dropwise via cannulation over 30 min. The reaction mixture was then allowed to warm to room temperature. After 3 h, the starting material appeared consumed (TLC), and the reaction mixture was quenched by slow addition of a saturated aqueous $NaHCO_3$ (20 mL). Upon an initial separation, and the aqueous layer was extracted with DCM (3 x 25 mL). The combined organic layers were then washed with brine (1 x 25 mL), dried ($MgSO_4$) and concentrated to give a yellow oil which was purified by flash chromatography (9:1 hexanes:EtOAc) to give the title compound (3.60 g, 18.9 mmol, 94.6%) as an essentially pure white solid (mp: 61-63 ^{o}C). The material was used directly in the next reaction.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.28 (m, 5H, Ar), 3.64 (s, 1H), 2.34 (s, 1H), 2.27-2.23 (m, 1H), 2.08-1.98 (m, 1H), 1.90-1.85 (m, 1H), 1.23 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$): δ 144.1; 128.4; 127.0; 124.4; 82.0; 69.3; 65.0; 38.9; 26.7; 12.7.

IR (thin film cm^{-1}): 3475; 3084; 3058; 3026; 2975; 2932; 2860; 1493; 1450; 1375; 1200; 764; 703.

HRMS (EI): calcd. for $C_{12}H_{14}O_2$ $[M]^+$ 190.0994, found 190.1001.



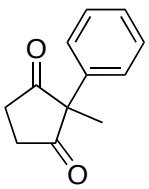
***cis*-(±)-1-Keto-2-methyl-2-phenylcyclopentan-3-ol (2.41)**.[64] A stirred solution of precursor epoxide **2.40** (3.60 g, 18.9 mmol) and DCM (95 mL) was cooled to -40 ^oC for 30 min. To this solution was added BF_3•OEt_2 (4.8 mL, 38 mmol, 2.0 equiv) slowly causing the reaction mixture to turn from yellow to deep red. After 35 min, the starting material was consumed (TLC), and the reaction was quenched by the addition of dH_2O (40 mL). The phases were separated, and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (1 x 25 mL) and dried ($MgSO_4$). Upon concentration, the crude oil was purified by flash chromatography (7:3 hexanes:EtOAc) to afford the title compound (1.96 g; 10.3 mmol; 52% over 3 steps) as a cloudy, colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.19 (m, 5H); 4.58 (m, 1H); 2.60-2.49 (m, 1H); 2.40-2.27 (m, 2H); 2.16-2.06 (m, 1H); 1.95-1.86 (m, 2H); 1.36 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$): δ 219.4; 141.9; 128.8; 127.1; 126.5; 78.2; 58.9; 35.2; 27.5; 17.6.

IR (thin film cm^{-1}): 3442; 2972; 2926; 1735; 734; 701.

HRMS (EI): calcd. for $C_{12}H_{14}O_2$ $[M]^+$ 190.0994, found 190.1001.



2-Methyl-2-phenyl-1,3-cyclopentanedione (2.42). To a stirred solution of **2.41** (954 mg; 5.01 mmol) and DCM (17 mL) was added activated 4 Å molecular sieves (~2 g). The solution was cooled to 0 ^oC and PCC (2.699 g; 12.5 mmol, 2.50 equiv) was added portionwise over 5 min. When the starting material appeared consumed (TLC, ~10 h),

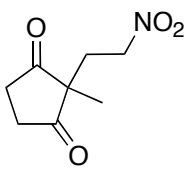
the reaction was diluted with diethyl ether (5 mL) and DCM (5 mL) followed by the addition of Celite (~3 g). The solution was vigorously stirred at rt for an addtional 1 h then the contents of the flask were filtered over a pad of Celite. The filter cake was rinsed with additional Et_2O (100 mL). The filtrate was then concentrated to give a brown oil, which was purified by flash chromatography (8:2 hexanes:EtOAc) to afford the title compound (830 mg; 4.41 mmol; 88% yield) as a clear, yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (t, 2H, J = 7.3 Hz); 7.29 (t, 1H, J = 7.3 Hz); 7.21 (d, 2H, J = 7.0 Hz); 2.96-2.85 (m, 2H); 2.79-2.68 (m, 2H); 1.44 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$): δ 213.1; 137.0; 129.4; 128.1; 126.4; 62.1; 35.3; 19.9.

IR (thin film, cm^{-1}): 2930; 1724; 749; 699.

HRMS (EI): calcd. for $C_{12}H_{12}O_2$ $[M]^+$ 188.0837, found 188.0844.



2-Methyl-2-(2-nitroethyl)-1,3-cyclopentanedione (2.47). To a stirred solution of 2-methyl-1,3-cyclopentanedione (**2.29**, 2.02 g; 18.0 mmol) and dry MeCN (35 mL) was added freshly distilled nitroethylene (**2.46**, 2.04 g; 35.7 mmol, 1.98 equiv) followed by the slow addition of *n*-Bu_3P (440 mL; 1.76 mmol, 9.78 mol %) at rt over 30 min. The reaction was stirred for 20 h at which point the mixture was concentrated and purified by flash chromatography (7:3 hexanes:EtOAc) to afford the title compound (1.48 g, 7.99 mmol, 44%) as an orange-yellow oil, which solidified on standing.

^{1}H NMR (360 MHz, $CDCl_3$): δ 4.41 (t, 2H, J = 7 Hz); 2.95-2.76 (m, 4h); 2.33 (t, 2H, J = 7 Hz); 1.19 (s, 3H).

^{13}C NMR (91 MHz, $CDCl_3$): δ 214.1; 70.7; 54.0; 34.5; 29.6; 21.9.

IR (thin film, cm^{-1}): 3466; 2976; 2931; 2875; 1764; 1719; 1639; 1552.

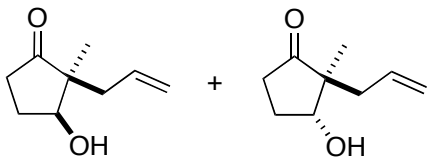
HRMS (EI): calcd. for $C_8H_{11}NO_4$ $[M]^+$ 185.0688, found 185.0686.

2.3.5. Monoreduction Experiments

Method A: General procedure for $NaBH_4$/DME-mediated reductions. To a stirred solution of 2,2-disubstitutedcycloalkane-1,3-dione (0.5 mmol) in DME (1 mL) cooled to -60 ^oC (1 h) was added $NaBH_4$ (9.0 mg, 0.25 mmol, 0.50 equiv) in one portion. The reaction proceeded at -60 ^oC until judged complete (TLC) at which point it was quenched with 1 N HCl (1 mL). The mixture was diluted with EtOAc (5 mL) and the resultant solution was allowed to warm to room temperature. Upon an initial separation, the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organics were washed with brine (1 x 10 mL), dried ($MgSO_4$) and concentrated to afford a crude oil that was examined by ^1H NMR spectroscopy then purified by flash chromatography.

Method B: General procedure for LTBA/THF-mediated reductions. To a stirred solution of 2,2-disubstitutedcycloalkane-1,3-dione (0.5 mmol) in THF (4 mL) cooled to -60 ^oC (1 h) was added a solution of LTBA (191 mg; 0.751 mmol, 1.50 equiv) and THF (5 mL) also at -60 ^oC via glass syringe over 5 min. Once judged complete (TLC), the reaction was quenched by the addition of 1 N HCl (5 mL) then diluted with EtOAc (5 mL) and allowed to warm to room temperature. After initial separation, the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) then concentrated. The resulting crude compound was examined by ^1H NMR spectroscopy then purified by flash chromatography.

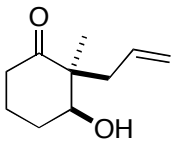
2.3.6. Monoreduction products



Diastereomeric mixture of *cis*- and *trans*-2-allyl-3-hydroxy-2-methylcyclopentanone (2.31a and 2.31b). Allyl dione **2.31** (76 mg, 0.5 mmol) was reductively desymmetrized to provide a diastereomeric mixture of 3.1:1 (*cis*:*trans*, **2.31a**:**2.31b**) employing Method A or 2.2:1 employing Method B as evidenced by crude ^{1}H-NMR analysis of the reaction mixture. Purification of the crude product by flash chromatography (8:2 hexanes:EtOAc) provided the desired ketols (Method A: 66 mg, 0.43 mmol, 86%; Method B: 66 mg, 0.43 mmol, 85%) as a clear, colorless oil. Repurification of the mixture of ketols by flash chromatography (8:2 hexanes:EtOAc) provided an inseparable mixture of **2.31a** and **2.31b**, both of which exhibited physical properties previously reported in the literature.[74c]

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.81-5.71 (m, 1H); 5.19-5.09 (m, 2H); 4.28 (m, 1H, *trans*); 4.22 (m, 1H, *cis*); 2.50-2.44 (m, 1H); 2.31-2.13 (m, 3H); 1.96-1.88 (m, 1H, *trans*); 1.86-1.82 (m, 1H, *cis*); 1.63 (br s, 1H); 1.15 (s, 3H, *trans*); 1.02 (s, 3H, *cis*).

^{13}C NMR (127 MHz, $CDCl_3$): δ 220.5 (*cis*); 219.8 (*trans*); 134.3 (*cis*); 133.5 (*trans*); 118.6 (*trans*); 118.1 (*cis*); 77.4 (*cis*); 75.4 (*trans*); 53.1 (*cis*); 52.9 (*trans*); 39.8 (*trans*); 35.4 (*cis*); 34.8 (*trans*); 34.0 (*cis*); 27.7 (*cis*); 27.5 (*trans*); 19.7 (*cis*); 15.0 (*trans*).

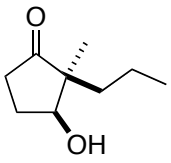


***cis*-3-Hydroxy-2-allyl-2-methylcyclohexanone (2.32a).** Allyl dione **2.32** (83 mg, 0.5 mmol) was reductively desymmetrized to provide a diastereomeric mixture of 3.3:1 (*cis*:*trans*, **2.32a**:**2.32b**) employing Method A or 5.0:1 employing Method B as evidenced by crude ^{1}H-NMR analysis of the reaction mixture. Purification of the crude product by flash chromatography (8:2 hexanes:EtOAc) provided the

desired ketols (Method A: 69 mg, 0.41 mmol, 82%; Method B: 73 mg, 0.44 mmol, 87%) as a clear, colorless oil. Repurification of the mixture of ketols by flash chromatography (8:2 hexanes:EtOAc) provided **2.32a** as the major product, which exhibited physical properties previously reported in the literature.[74c]

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.80-5.71 (m, 1H); 5.14-5.07 (m, 1H); 3.81 (m, 1H); 2.49-2.34 (m, 4H); 2.06-2.02 (m, 2H); 1.92-1.86 (m, 2H); 1.69 (m, 1H); 1.17 (s, 3H).

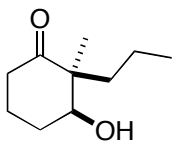
^{13}C NMR (127 MHz, $CDCl_3$): δ 213.6; 133.9; 118.1; 76.7; 54.0; 37.7; 36.7; 28.5; 20.6; 19.9.



***cis*-3-Hydroxy-2-propyl-2-methylcyclopentanone (2.33a).** Propyl dione **2.33** (77 mg, 0.5 mmol) was reductively desymmetrized to provide a diastereomeric mixture of 5.1:1 (*cis*:*trans*, **2.33a**:**2.33b**) employing Method A or 4.0:1 employing Method B as evidenced by crude ^{1}H-NMR analysis of the reaction mixture. Purification of the crude product by flash chromatography (9:1 hexanes:EtOAc) provided the desired ketols (Method A: 64 mg, 0.41 mmol, 82%; Method B: 73 mg, 0.47 mmol, 93%) as a clear, colorless oil. Repurification of the mixture of ketols by flash chromatography (9:1 hexanes:EtOAc) provided **2.33a** as the major product, which exhibited physical properties previously reported in the literature.[74c]

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.11 (m, 1H); 2.52-2.42 (m, 1H); 2.33-2.15 (m, 2H); 1.98-1.92 (m, 1H); 1.77 (br s, 1H); 1.51-1.23 (m, 4H); 1.00 (s, 3H); 0.94 (t, 3H, J = 10 Hz);

^{13}C NMR (127 MHz, $CDCl_3$): δ 220.8, 77.7, 53.2, 34.0, 32.3, 27.8, 19.3, 17.2, 14.8.

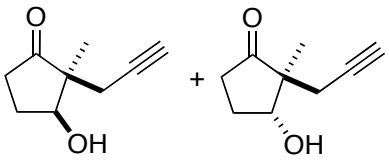


***cis*-3-Hydroxy-2-propyl-2-methylcyclohexanone (2.34a).** Propyl dione **2.34** (84 mg, 0.5 mmol) was reductively desymmetrized to provide a diastereomeric

mixture of 4.3:1 (*cis*:*trans*, **2.34a**:**2.34b**) employing Method A or 5.9:1 employing Method B as evidenced by crude ^{1}H-NMR analysis of the reaction mixture. Purification of the crude product by flash chromatography (9:1 EtOAc:hexanes) provided the desired ketols (Method A: 77 mg, 0.41 mmol, 81%; Method B: 87 mg, 0.46 mmol, 91%) as a clear, colorless oil. Repurification of the mixture of ketols by flash chromatography (9:1 EtOAc:hexanes) provided **2.34a** as the major product, which exhibited physical properties previously reported in the literature.[74c]

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.60 (m, 1H); 2.35-2.28 (m, 2H); 1.96-1.82 (m, 3H); 1.67-1.47 (m, 3H); 1.24-1.16 (m, 2H); 1.08 (s, 3H); 0.96-0.94 (m, 1H); 0.85 (t, 3H, J = 3 Hz).

^{13}C NMR (127 MHz, $CDCl_3$): δ 213.9; 77.6; 54.8; 37.6; 33.7; 28.8; 20.7; 18.9; 16.6; 14.8.



***cis*-3-Hydroxy-2-propargyl-3-methylcyclopentanone (2.35a) and *trans*-3-Hydroxy-2-propargyl-3-methylcyclopentanone (2.35b).** Propargyl dione **2.35** (75 mg, 0.5 mmol) was reductively desymmetrized to provide a diastereomeric mixture of 1.0:1 (*cis*:*trans*, **2.35a**:**2.35b**) employing Method A or 1.3:1 employing Method B as evidenced by crude ^{1}H-NMR analysis of the reaction mixture. Purification of the crude product by flash chromatography (8:2 hexanes:EtOAc) provided the desired ketols (Method A: 60 mg, 0.40 mmol, 79%; Method B: 63 mg, 0.42 mmol, 83%) as a clear, colorless oil. Repurification of the mixture of ketols by flash chromatography (8:2 hexanes:EtOAc) provided **2.35a** and **2.35b**, both of which exhibited physical properties previously reported in the literature.[74c]

2.35a:

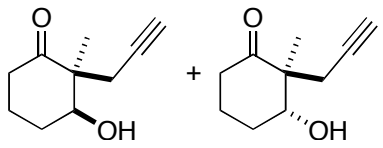
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.27 (m, 1H); 2.54-2.17 (m, 6H); 2.08-2.02 (m, 2H); 1.13 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$): δ 219.6, 81.1, 76.7, 70.6, 53.2, 34.0, 27.4, 20.8, 19.9.

2.35b:

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.42 (m, 1H); 2.53-2.47 (m, 1H); 2.41-2.28 (m, 3H); 2.20-2.13 (m, 2H); 2.06 (t, 1H, *J* = 3 Hz); 1.91-1.83 (m, 1H); 1.08 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$): δ 218.2, 80.6, 75.4, 71.1, 51.7, 34.8, 27.1, 25.0, 15.0.



***cis*-3-Hydroxy-2-propargyl-2-methylcyclohexanone (2.36a) and *trans*-3-Hydroxy-2-propargyl-2-methylcyclohexanone (2.36b).** Propargyl dione **2.36** (82 mg, 0.5 mmol) was reductively desymmetrized to provide a diastereomeric mixture of 1.4:1 (*cis*:*trans*, **2.36a**:**2.36b**) employing Method A or Method B as evidenced by crude ^{1}H-NMR analysis of the reaction mixture. Purification of the crude product by flash chromatography (17:3 hexanes:EtOAc) provided the desired ketols (Method A: 63 mg, 0.39 mmol, 77%; Method B: 64 mg, 0.39 mmol, 77%) as a clear, colorless oil. Repurification of the mixture of ketols by flash chromatography (17:3 hexanes:EtOAc) provided **2.36a** and **2.36b**, both of which exhibited physical properties previously reported in the literature.[74c]

2.36a:

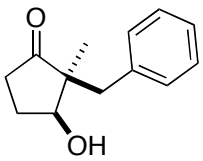
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.21 (m, 1H); 2.73 (d, 1H, *J* = 14 Hz); 2.59-2.49 (m, 2H); 2.38-2.31 (m, 1H); 2.13-2.03 (m, 4H); 1.90-1.83 (m, 2H); 1.29 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$): δ 212.9; 81.1; 75.0; 71.1; 52.4; 37.6; 28.1; 22.9; 21.1; 20.6.

2.36b:

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.08 (m, 1H); 2.62-2.51 (m, 3H); 2.36-2.29 (m, 1H); 2.20 (m, 1H); 2.08-1.81 (m, 4H); 1.65-1.52 (m, 1H); 1.23 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$): δ 211.6, 81.6, 74.7, 71.3, 54.2, 37.1, 29.1, 24.8, 20.0, 17.1.



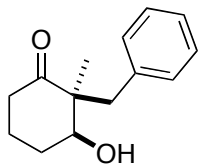
***cis*-3-Benzyl-2-hydroxy-2-methylcyclopentanone (2.37a).** Phenyl dione **2.37** (101 mg, 0.5 mmol) was reductively desymmetrized to the corresponding ketols to provide a diastereomeric mixture of 4.9:1 (*cis*:*trans*, **2.37a**:**2.37b**) employing Method A or 3.9:1 employing Method B as evidenced by crude ^{1}H-NMR analysis of the reaction mixture. Purification of the crude product by flash chromatography (8:2 hexanes:EtOAc) provided the desired ketols (Method A: 85 mg, 0.42 mmol, 83%; Method B: 85 mg, 0.42 mmol, 84%) as a clear, colorless oil. Repurification of the mixture of ketols by recrystallization (EtOAc:hexanes) provided **2.37a**, the major product, as beige needles (mp: 65-66 ^{o}C).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.10 (m, 5H, Ar); 4.05 (m, 1H); 3.06 (d, 1H, J = 14 Hz); 2.73 (d, 1H, J = 14 Hz); 2.55-2.47 (m, 1H); 2.40-2.33 (m, 1H); 2.20-2.14 (m, 1H); 2.04 (br s, 1H); 1.92-1.86 (m, 1H); 0.87 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$): δ 220.4; 137.9; 130.4; 128.1; 126.2; 76.4; 54.8; 35.7; 33.7; 28.2; 19.6.

IR (thin film, cm^{-1}): 3433; 3086; 3062; 3028; 2967; 2928; 2875; 1728; 1647; 1496; 1454; 1159; 1143; 1073; 1034; 736; 704.

HRMS (EI): calcd. for $C_{13}H_{16}O_2$ $[M]^+$ 204.1150, found 204.1150.



***cis*-2-Benzyl-3-hydroxy-2-methylcyclohexanone (2.38a).** Benzyl dione **2.38** (108 mg, 0.5 mmol) was reductively desymmetrized to provide a diastereomeric mixture of 8.6:1 (*cis*:*trans*, **2.38a**:**2.38b**) employing Method A or 9.8:1 employing Method B as evidenced by crude ^{1}H-NMR analysis of the reaction mixture. Purification of the crude product by flash chromatography (9:1 hexanes:EtOAc) provided the

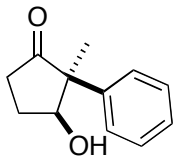
desired ketols (Method A: 88 mg, 0.41 mmol, 81%; Method B: 91 mg, 0.42 mmol, 83%) as a clear, colorless oil. Repurification of the mixture of ketols by recrystallization (CH_2Cl_2:hexanes) provided **2.38a** as a white solid (mp: 64-66 ^oC).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.16 (m, 5H), 3.76 (m, 1H), 3.11 (d, 1H, *J* = 14 Hz), 2.96 (d, 1H, *J* = 14 Hz); 2.55 (t, 2H, *J* = 6 Hz), 2.18-1.99 (m, 2H); 1.91-1.72 (m, 3H); 1.08 (s, 3H);

^{13}C NMR (127 MHz, $CDCl_3$): δ 213.7; 137.5; 130.5; 128.0; 126.; 75.7; 54.5; 37.7; 37.4; 28.5; 20.7; 20.4.

IR (thin film cm^{-1}): 3449; 3084; 3061; 3028; 2941; 2874; 1698; 1603; 1495; 1453; 758; 705.

HRMS (EI): calcd. For $C_{14}H_{18}O_2$ $[M]^+$ 218.1307, found 218.1308.



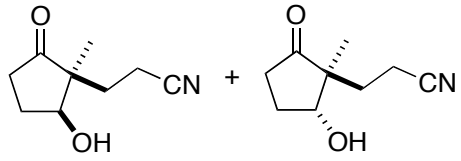
***cis*-3-Hydroxy-2-phenyl-2-methylcyclopentanone (2.42a).** Phenyl dione **2.42** (94 mg, 0.5 mmol) was reductively desymmetrized to provide a diastereomeric mixture of 16:1 (*cis*:*trans*, **2.42a**:**2.42b**) employing Method A or 11:1 employing Method B as evidenced by crude ^{1}H-NMR analysis of the reaction mixture. Purification of the crude product by flash chromatography (8:2 hexanes:EtOAc) provided the desired ketols (Method A: 88 mg, 0.47 mmol, 93%; Method B: 90 mg, 0.48 mmol, 95%) as a clear, colorless oil. Repurification of the mixture of ketols by flash chromatography (8:2 hexanes:EtOAc) provided **2.42a** as the major product.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H); 4.22 (m, 1H); 2.72-2.64 (m, 1H); 2.54-2.48 (m, 1H); 2.31-2.23 (m, 1H); 2.10-2.07 (m, 1H); 1.44 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$): δ 219.0; 138.2; 128.8; 128.0; 127.4; 78.9; 59.0; 35.4; 26.9; 22.0.

IR (thin film cm^{-1}): 3442; 2972; 2926; 1735; 1447; 1157; 1055; 734; 701.

HRMS (EI): calcd. for $C_{12}H_{14}O_2$ $[M]^+$ 190.0994, found 190.1001.



***cis*-2-Cyanoethyl-3-hydroxy-2-methylcyclopentanone (2.43a) and *trans*-2-Cyanoethyl-3-hydroxy-2-methylcyclopentanone (2.43b).** Cyanoethyl dione **2.43** (83 mg, 0.5 mmol) was reductively desymmetrized to the corresponding ketols providing a diastereomeric mixture of 1:1.1 (*cis*:*trans*, **2.43a**:**2.43b**) employing Method A or 1:1.2 employing Method B as evidenced by crude ^{1}H-NMR analysis of the reaction mixture. Purification of the crude products by flash chromatography (9:1 DCM:EtOAc) provided the desired ketols (Method A: 69 mg, 0.41 mmol, 82%; Method B: 76 mg, 0.46 mmol, 91%) as a clear, colorless oil. Repurification of the mixture of ketols by flash chromatography (9:1 DCM:EtOAc) provided **2.43a** and **2.43b**, both of which exhibited physical properties previously reported in the literature.[74c]

2.43a:

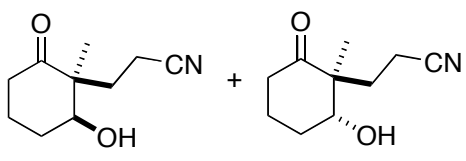
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.22 (m, 1H); 2.53-2.28 (m, 5H); 2.00-1.87 (m, 4H); 1.02 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$): δ 219.2; 120.3; 76.8; 52.2; 33.6; 28.5; 26.5; 19.0; 12.5.

2.43b:

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.20 (m, 1H); 2.55-2.44 (m, 3H); 2.32-2.18 (m, 2H); 1.93-1.78 (m, 4H); 1.03 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$): δ 218.3; 120.0; 75.6; 51.7; 35.0; 30.8; 27.9; 14.1; 12.3.

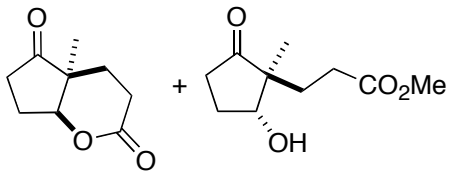


Diastereomeric mixture of *cis*- and *trans*-2-cyanoethyl-3-hydroxy-2-methylcyclopentanone (2.45a and 2.45b). Cyanoethyl dione **2.44** (90 mg, 0.5 mmol) was reductively desymmetrized to provide a diastereomeric mixture of 1.1:1 (*cis*:*trans*, **2.44a**:**2.44b**) employing

Method A or Method B as evidenced by crude ^{1}H-NMR analysis of the reaction mixture. Purification of the crude product by flash chromatography provided the desired ketols (Method A: 77 mg, 0.43 mmol, 85%; Method B: 77 mg, 0.43 mmol, 85%) as a clear, colorless oil. Repurification of the mixture of ketols by flash chromatography provided an inseparable mixture of **2.44a** and **2.44b**, both of which exhibited physical properties previously reported in the literature.Purification of the crude reaction mixture by flash chromatography (9:1 DCM:EtOAc) yielded an inseparable mixture of ketols as a clear, colorless oil.[74c]

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.22-4.07 (m, 1H); 2.74-1.57 (m, 11 H); 1.29-1.23 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$): δ 213.7 (*cis*); 213.2 (*trans*); 120.3; 76.3 (*cis*); 73.2 (*trans*); 53.9 (*trans*); 52.6 (*cis*); 37.4 (*cis*); 37.1 (*trans*); 30.1 (*trans*); 29.3 (*cis*); 28.9 (*trans*); 28.7 (*cis*); 20.3 (*cis*); 19.9 (*trans*); 19.5 (*cis*); 17.0 (*trans*); 12.5 (*trans*); 12.1 (*cis*).



6-Methyl-2-oxabicyclo[4.3.0]nonane-3,7-dione (2.45a) and *trans*-Methyl 3-(2-hydroxy-1-methyl-5-oxocyclopentyl)propanoate (2.45b). Methyl ethanoate dione **2.45** (99 mg, 0.5 mmol) was reductively desymmetrized to the corresponding lactone and ketol to provide a diastereomeric mixture of 1.6:1 (lactone:ketol, **2.45a**:**2.45b**) employing Method A or 1.9:1 employing Method B as evidenced by crude ^{1}H-NMR analysis of the reaction mixture. Purification of the crude product by flash chromatography (1:1 EtOAc:hexanes) provided the desired ketols (Method A: 80 mg, 0.40 mmol, 80%; Method B: 82 mg, 0.41 mmol, 82%) as a clear, colorless oil. Repurification of the mixture of ketols by flash chromatography (1:1 EtOAc:hexanes) provided **2.45a**, a compound previously reported in the literature,[74c] and **2.45b** as a clear, colorless oil.

2.45a:

^{1}H NMR (360 MHz, $CDCl_3$): δ 4.67 (m, 1H); 2.48-2.32 (m, 6H); 2.16-2.08 (m, 1H); 1.86 (dt, 1H, J = 6 Hz, J = 14 Hz); 1.17 (s, 3H).

^{13}C NMR (91 MHz, $CDCl_3$): δ 218.5, 171.8, 85.7, 48.0, 33.9, 27.8, 27.0, 26.3, 21.5.

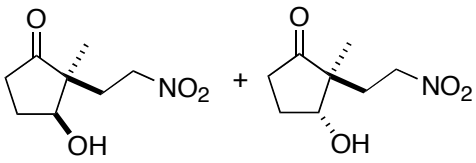
2.45b:

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.09 (m, 1H); 3.68 (s, 3H); 2.51-2.43 (m, 1H); 2.39-2.26 (m, 3H); 2.23-2.17 (m, 1H); 2.06 (d, 1H, J = 4.0 Hz); 1.92-1.74 (m, 2H); 1.00 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$): δ 219.3; 174.5; 75.6; 52.5; 51.9; 34.8; 29.3; 28.8; 27.2; 14.7.

IR (thin film cm^{-1}): 3421; 2957; 2924; 2853; 2360; 2341; 1734; 1073.

HRMS (EI): calcd. for $C_{10}H_{16}O_4$ $[M]^+$ 200.1049, found 200.1046.



***cis*-3-Hydroxy-1-methyl-2-(nitroethyl)-cyclopentanone (2.47a) and *trans*-3-Hydroxy-1-methyl-2-(nitroethyl)-cyclopentanone (2.47b).** Nitroethyl dione **2.47** (93 mg, 0.5 mmol) was reductively desymmetrized to the corresponding ketols thus providing a diastereomeric mixture of 1:1.4 (*cis*:*trans*, **2.47a**:**2.47b**) employing Method A or Method B as evidenced by crude ^{1}H-NMR analysis of the reaction mixture. Purification of the crude product by flash chromatography (23:2 DCM:EtOAc) provided the desired ketols (Method A: 71 mg, 0.38 mmol, 76%; Method B: 82 mg, 0.44 mmol, 88%) as a clear, colorless oil. Repurification of the mixture of ketols by flash chromatography (23:2 DCM:EtOAc) provided **2.47a** and **2.47b** as a clear, slightly yellow oils.

2.47a:

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.54-4.50 (m, 2H); 4.13 (m, 1H); 2.55-2.49 (m, 1H); 2.32-2.08 (m, 5H); 1.92-1.85 (m, 1H); 1.02 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$): δ 218.3; 75.9; 71.4; 51.1; 34.8; 32.1; 27.7; 14.2.

IR (thin film cm^{-1}): 3432; 2971; 2926; 1733; 1638; 1552.

HRMS (EI): calcd. for $C_8H_{13}NO_4$ $[M\text{-}OH]^+$ 170.0817, found 170.0818.

2.47b:

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.61-4.50 (m, 2H); 4.13 (m, 1H); 2.53 (m, 1H); 2.38 (m, 4H); 2.00 (m, 1H); 1.84 (br s, 1H); 1.03 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$): δ 219.0; 77.1; 72.1; 51.7; 33.4; 28.4; 28.2; 19.3.

IR (thin film cm^{-1}): 3432; 2971; 2926; 1733; 1638; 1552.

HRMS (EI): calcd. for $C_8H_{13}NO_4$ $[M]^+$ 187.0845, found 187.0841.

CHAPTER 3

COPPER-CATALYZED TANDEM REDUCTIVE ALDOL/GROB FRAGMENTATION EN ROUTE TO A *XENIA* DITERPENOID COMMON INTERMEDIATE.

3.1 Copper(I) Hydrides

This subchapter concisely reviews the pertinent historical aspects of Stryker's reagent and chemically similar copper(I) hydrides. Additionally, the utility of copper(I) hydrides is discussed including catalytic processes, mechanistic details and the application to reductive aldol chemistry.

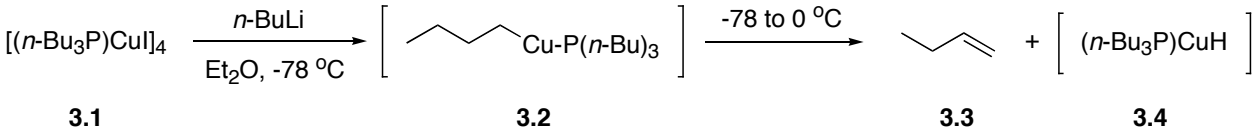
3.1.1. Historical Aspects and Development of Stryker's Reagent

Würtz, credited as the father of copper(I) hydride chemistry,[107] reported the first copper(I) hydride complex from the reaction of $CuSO_4$ and dilute hypophosphorous acid[108] in the mid-19th century (Equation 3.1).[109] The resultant brown powder was thermally unstable, air-sensitive and possessed a chemical formula of Cu_2H_2.

$$2\ CuSO_4 + 2\ H_3PO_2 \longrightarrow Cu_2H_2$$ **Equation 3.1**

[107] Deutsch, C.; Krause, N.; Lipshutz, B. H. "CuH-Catalyzed Reactions." *Chem. Rev.* **2008**, *108*, 2916-2927.
[108] Hood, G. F.; Carpenter, J. A. *A Textbook of Practical Chemistry*; Plakiston's Son & Co.: Philadelphia, PA, 1921; pp 41-42.
[109] Würtz, A. "Sur l'hydure de cuivre." *Ann. Chim. Phys.* **1844**, *11*, 250-252.

Over a century later, Whitesides and co-workers reported the first instance of thermal decomposition of an alkyl cuprate to the corresponding copper(I) hydride.[110] Treatment of tetramer **3.1** with *n*-BuLi resulted in formation of intermediate alkylcuprate **3.2**, which, when gradually warmed to 0 °C, decomposed as evidenced by the detection of *n*-butene (**3.3**) in the reaction mixture. In fact, copper(I) hydride **3.4** was found to reduce alkyl cuprate **3.2** as evidenced by the detection of n-butane. The fact octane was not detected in the reaction mixture ruled out a radical-based process. Whitesides argued that the mechanism of decomposition occurred via concerted β-hydride elimination to provide an air-sensitive copper(I) hydride species (**3.4**). A copper(I) hydride, prepared from the reaction of *n*-Bu_3P, CuBr and DIBAH in pyridine, was shown to reduce alkylmercuric halides to the corresponding alkane in later experiments.[111]



3.1 **3.2** **3.3** **3.4**

Scheme 3.1. Whitesides' thermal decomposition experiment of alkyl cuprate **3.2**.[110]

Soon thereafter, Osborn and co-workers isolated the first air-stable copper(I) hydride complex (**3.6**).[112] The reaction of $[(Ph_3P)CuCl]_4$ (**3.5**) with an excess of $NaBH(OMe)_3$ yielded bright, red crystals in poor yield (Scheme 3.2). X-ray diffraction analysis (Figure 3.1) confirmed

[110] Whitesides, G. M.; Stedronsky, E. R.; Casey, C. P.; San Filippo, J. "Mechanism of Thermal Decomposition of *n*-Butyl(tri-*n*-butylphosphine) Copper(I)." *J. Am. Chem. Soc.* **1970**, *92*, 1426-1427.
[111] Whitesides, G. M.; San Filippo, J. "Mechanism of Reduction of Alkylmercuric Halides by Metal Hydrides." *J. Am. Chem. Soc.* **1970**, *92*, 6611-6624.
[112] Bezman, S. A.; Churchill, M. R.; Osborn, J. A.; Wormald, J. "Preparation and Crystallographic Characterization of a Hexameric Triphenylphosphinecopper Hydride Cluster." *J. Am. Chem. Soc.* **1971**, *93*, 2063-2065.

the formation of a hexameric phosphine-ligated copper(I) complex.[113] The pattern suggested strong steric repulsion from the aryl rings of the Ph_3P ligand but failed to account for the location of the hydride atoms with respect to the copper metal centers. However, the reaction of complex **3.6** with deuterobenzoic acid resulted in the formation of HD, a result that supported copper(I) hydride formation.

$$\underset{\textbf{3.5}}{[(Ph_3P)CuCl]_4} \xrightarrow[\text{DMF, rt, 0.5 h}]{NaBH(OMe)_3} \underset{\textbf{3.6}}{[(Ph_3P)CuH]_6}$$

Scheme 3.2. Osborn's synthesis of **3.6**.[112]

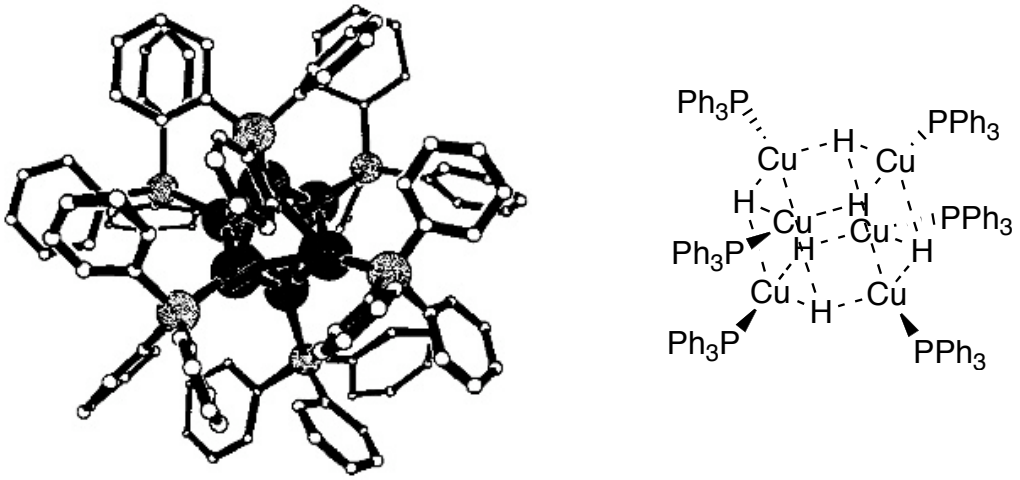
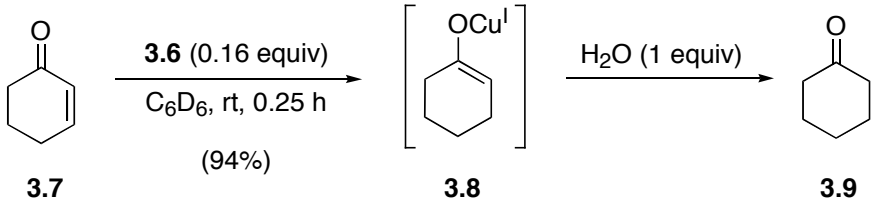


Figure 3.1. Osborn's reported complex **3.6**.[113] The left graphic is the crystal structure reported by Osborn in 1972. The right graphic is a pictorial representation of the crystal structure.

[113] Churchill, M. R.; Bezman, S. A.; Osborn, J. A. "Synthesis and Molecular Geometry of Hexameric Triphenylphosphinocopper(I) Hydride and the Crystal Structure of $H_6Cu_6(PPh_3)_6$-$HCONMe_2$." *Inorg. Chem.* **1972**, *11*, 1818-1825.

Despite some progress in the field of cuprate chemistry[114] **3.6** went relatively unused for ten years after Osborn's seminal contribution. Stryker is credited with first applying Osborn's complex to the conjugate reduction of α,β-unsaturated carbonyls.[115] Stoichiometric quantities of **3.6** were found to selectively reduce activated olefins (i.e. enones, alkyl enoates, α,β-unsaturated nitriles) in the presence of a variety of functional groups (Scheme 3.3). The typical reaction conditions involved use of non-coordinating solvents (i.e. benzene, toluene) often accompanied by a stoichiometric equivalent of water to quench the intermediate copper enolate (**3.8**).



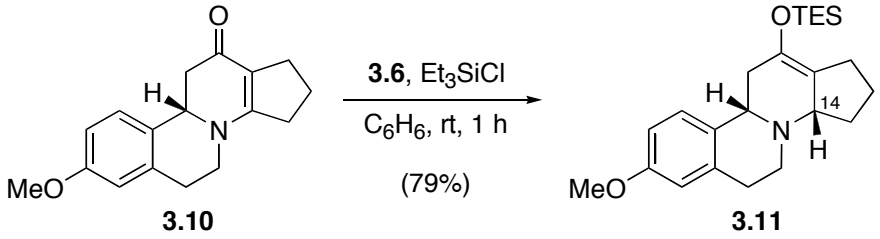
Scheme 3.3. The conjugate reduction of enone **3.7** with copper(I) hydride **3.6**.[115]

Additionally, treatment of enolate **3.8** with silyl halides (e.g. Me_3SiCl) was found to result in silyl enol ether formation under anhydrous conditions.[115] Meyers and Elworthy

[114] For examples see: (a) Boeckman, Jr., R. K.; Michalak, R. "Reduction of α,β-unsaturated carbonyl compounds by "ate" complexes of copper(I) hydride." *J. Am. Chem. Soc.* **1974**, *96*, 1623-1625. (b) Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. "Reductions of Conjugated Carbonyl Compounds with Copper Hydride-Preparative and Mechanistic Aspects." *J. Org. Chem.* **1977**, *42*, 3180-3188. (c) Ashby, E. C.; Korenowski, T. F.; Schwartz, R. D. "Preparation of the first stable complex metal hydride of copper, $LiCuH_2$." *J. Chem. Soc., Chem Commun.* **1974**, 157. (d) Ashby, E. C.; Lin, J. J.; Goel, A. B. "Reactions of Complex Metal Hydrides of Copper with Alkyl Halides, Enones, and Cyclic Ketones." *J. Org. Chem.* **1978**, *43*, 183-188. (e) Tsuda, T.; Fuji, T.; Kawasaki, K. Saegusa, T. "Copper(I)-catalysed Conjugate Reduction of αβ-Unsaturated Carbonyl Compounds by Lithium Aluminum Hydride." *J. Chem. Soc., Chem. Commun.* **1980**, 1013-1014.

[115] Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. "Selective Hydride-Mediated Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds Using $[(Ph_3P)CuH]_6$." *J. Am. Chem. Soc.* **1988**, *110*, 291-293

employed such a transmetallation in the synthesis of oxasteroids (Scheme 3.4).[116] Incorporation of TESCl under Stryker's conditions provided silyl enol ether **3.11** in good yield as a 32:1 mixture favoring the β-H at C-14. The bulkiness of the Ph_3P ligand significantly contributes to the excellent diastereoselective outcome by favoring hydride delivery to the least hindered face.[115]



Scheme 3.4. Preparation of silyl enol ether **3.11** using **3.6** and TESCl.[116]

Stryker's reagent (**3.6**) demonstrates amazing chemoselectivity,[115] making it a particularly useful reagent for synthesizing complex natural products. As seen in Scheme 3.5, Chiu and Lam relied on Stryker's reagent in the late stages of their total synthesis of (-)-indicol (**3.13**).[117] Treatment of enone **3.12** with stoichiometric quantities of **3.6** afforded the corresponding saturated ketone quantitatively. Cleavage of the MOM protecting group cleanly furnished hemiketal **3.13**. Other examples of the use of stoichiometric quantities of Stryker's reagent in natural product syntheses include *trans*-kumausyne,[118] (+)-pinnatoxin A[119] and (-)-lycopodine.[120]

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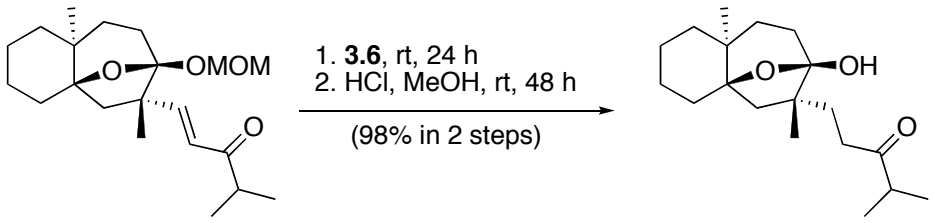
[116] Meyers, A. I.; Elworthy, T. R. "Chiral Formamidines. The Total Asymmetric Synthesis of (-)-8-Azaestrone and Related (-)-8-Aza-12-oxo-17-desoxoestrone." *J. Org. Chem.* **1992**, *57*, 4732-4740

[117] Lam, S. K.; Chiu. P. "Asymmetric Total Synthesis of (-)-Indicol by a Carbene Cyclization-Cycloaddition Cascade Strategy." *Chem. Eur. J.* **2007**, *13*, 9589–9599

[118] Chandler, C. L.; Phillips, A. J. "A Total Synthesis of (±)-*trans*-Kumausyne." *Org. Lett.* **2005**, *7*, 3493-3495.



3.12 **3.13**

Scheme 3.5. Chiu's use of Stryker's reagent (**3.6**) to synthesize (-)-indicol (**3.13**).[117]

3.1.2. Conjugate Reductions Catalytic in Stryker's Reagent.

3.1.2.1. Hydrogen

Significant breakthroughs have been reported in the field of Stryker's reagent-catalyzed conjugate reductions of α,β-unsaturated carbonyls. Stryker demonstrated that **3.6** could catalytically reduce α,β-unsaturated carbonyls in the presence of excess Ph_3P under hydrogen pressure.[115,121] Though quite novel, these conditions typically required the use of high hydrogen pressure (>70 bar) to result in complete conversion. Such conditions also furnished over-reduction products formed in varying amount.

3.1.2.2. Silanes or Stannanes.

Most notable have been the contributions of the Lipshutz group who reported that catalytic quantities of **3.6** (as low as 0.5 mol %) could reduce enones to their corresponding

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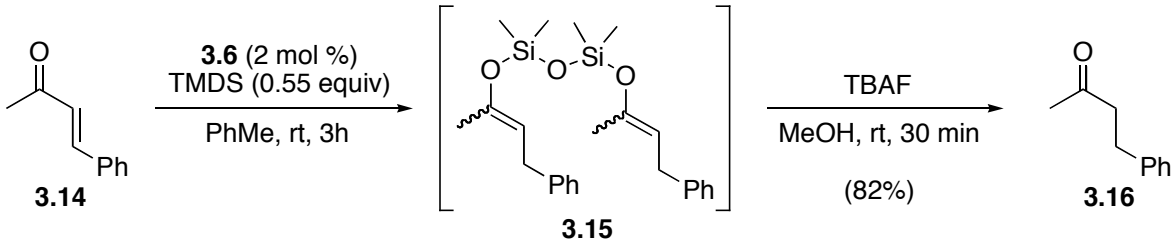
[119] Sakamoto, S.; Sakazaki, H.; Hagiwara, K.; Kamada, K.; Ishii, K.; Noda, T.; Inoue, M.; Hirama, M. "A Formal Total Synthesis of (+)-Pinnatoxin A." *Angew. Chem.* **2004**, *116*, 6667-6672.

[120] Yang, H.; Carter, R. G.; Zakharov, L. N. "Enantioselective Total Synthesis of Lycopodine." *J. Am. Chem. Soc.* **2008**, *130*, 9238-9239.

[121] Mahoney, W. S.; Stryker, J. M. "Hydride-Mediated Homogeneous Catalysis. Catalytic Reduction of α,β-Unsaturated Ketones Using $[(Ph_3P)CuH]_6$ and H_2." *J. Am. Chem. Soc.* **1989**, *111,* 8818-8823.

ketones using silanes or stannanes as the stoichiometric reducing agent.[122] Treament of enone **3.14** with Lipshutz's conditions resulted in formation of intermediate **3.15**,[123] which upon exposure to stoichiometric quantities of methanolic TBAF resulted in isolation of the corresponding ketone (**3.16**) in 82% yield (Scheme 3.6). Silanes were favored for optimal conditions due to their cost, ease of handling and low toxicity[124] relative to stannanes. Moreover, careful choice of silane resulted in rate enhancements using catalytic quantities of **3.6**.[123] When polymethylhydrosiloxane (PMHS) was used as the stoichiometric reducing agent, starting material conversion occurred under two minutes, which was a marked improvement from the hour or two using other silanes including tetramethyldisiloxane (TMDS) and $PhMe_2SiH$.



Scheme 3.6. Conjugate reduction of **3.14** using catalytic quantities of **3.6**.[123]

[122] Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. "A Convenient, Efficient Method for Conjugate Reductions Using *Catalytic* Quantities of Cu(I)." *Tetrahedron Lett.* **1998**, *39*, 4627-4630.

[123] Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Scalfani, J. A.; Vivian, R. W.; Keith, J. M. "Copper Hydride-*Catalyzed* Tandem 1,4-Reduction/Alkylation Reactions." *Tetrahedron* **2000**, *56*, 2779-2788.

[124] (a) Senapati, K. K. Polymethylhydrosiloxane (PMHS). *Synlett* **2005**, 1960-1961. (b) Chandrasekhar, S.; Chandrashekar, G.; Babu, B. N.; Vijeender, K.; Reddy, K. V. Reductive etherification of carbonyl compounds with alkyl trimethylsilylesters using polymethylhydrosiloxane (PMHS) and catalytic $B(C_6F_5)_3$. *Tetrahedron Lett.* **2004**, *45*, 5497-5499.

3.1.3 Conjugate Reductions Catalytic in Other Copper(I) Hydride Complexes.

Other conjugate reduction methodologies have been developed using catalytic quantities of copper(I) hydrides apart from **3.6**. Alternatives typically involve catalytic quantities of the metal while changing various aspects of the ligand. Examples of NHC[125] and *bis*-phosphine-ligated[126] copper complexes have been shown to effect conjugate reductions of α,β-unsaturated carbonyls in excellent yields.

3.1.3.1. BINAP-ligated Copper(I) Hydride Catalysts

Perhaps the most important contributions made in the field of copper(I)-catalyzed conjugate reductions have come from the Buchwald group. Their method involves enantioselective reduction of α,β-unsaturated carbonyls using chiral BINAP-type ligands.[127] Furthermore, the addition of stoichiometric quantities of alcohol (specifically *t*-AmOH) allowed for protonation of the copper enolate[107] enhancing catalyst turnover and thereby offering rate acceleration. As seen in Scheme 3.7, the utility of this method was evidenced in the synthesis of the selective serotonin reuptake inhibitor (-)-paroxetine (**3.19**). Treatment of α,β-unsaturated lactam **3.17** with Buchwald's conditions resulted in preparation of lactam **3.18** in 90% yield and

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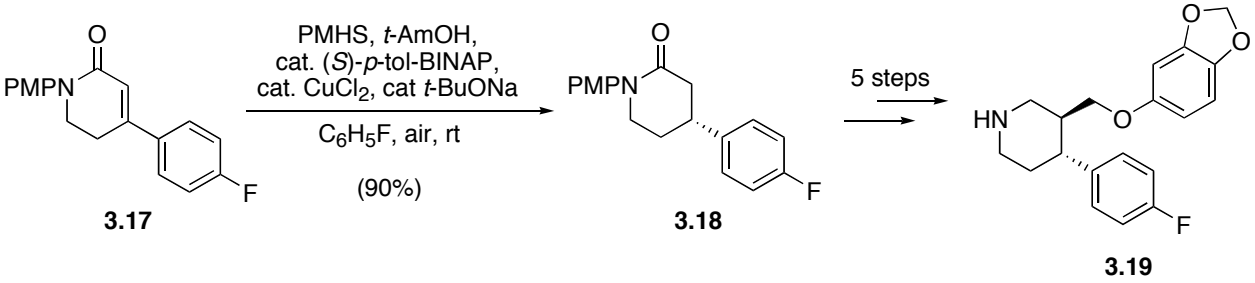
[125] (a) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L., "Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds Catalyzed by a Copper Carbene Complex." *Org. Lett.* **2003**, *5*, 2417-2420. (b) Yun, J.; Kim, D.; Yun, H. "A new alternative to Stryker's reagent in hydrosilylation: synthesis, structure, and reactivity of a well-defined carbene-copper(II) acetate complex." *Chem. Commun.* **2005**, 5181-5183.

[126] For recent examples see: (a) Baker, B. A.; Boskovic, Z. V.; Lipshutz, B. H. "(BDP)CuH: A "Hot" Stryker's Reagent for Use in Achiral Conjugate Reductions." *Org. Lett.* **2008**, *11*, 289-292. (b) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. "Highly Diastereo- and Enantioselective Copper-Catalyzed Domino Reduction/Aldol Reaction of Ketones with Methyl Acrylate." *Angew. Chem. Int. Ed.* **2006**, *45*, 1292-1297.

[127] Jurkauskas, V.; Buchwald, S. L. "Dynamic Kinetic Resolution via Asymmetric Conjugate Reduction: Enantio- and Diastereoselective Synthesis of 2,4-Dialkyl Cyclopentanones." *J. Am. Chem. Soc.* **2002**, *124*, 2892-2893. (b) Hughes, G.; Kimura, M.; Buchwald, S. L. "Catalytic Enantioselective Conjugate Reduction of Lactones and Lactams." *J. Am. Chem. Soc.* **2003**, *125*, 11253-11258.

90% ee.[127b] Similar methods have been applied to the conjugate reduction of phosphinyl-substituted imines,[128] α,β-unsaturated nitriles[129] and α,β-unsaturated sulfones.[130,131]



Scheme 3.7. The conjugate reduction step in Buchwald's synthesis of (-)-paroxetine (**3.19**).

3.1.4. Proposed Mechanistic Details

Although not definitively verified, experimental details from Stryker[121] have served to establish a generally accepted mechanism for copper-mediated conjugate reductions. Like most copper-mediated conjugate additions, the process is believed to involve a coordination-insertion-dissociation pathway.[132] As seen in Figure 3.2,[107] the initial copper-hydride species (**A**) reacts

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[128] Lipshutz, B. H.; Shimizu, H. "Copper(I)-Catalyzed Asymmetric Hydrosilylations of Imines at Ambient Temperatures." *Angew. Chem. Int. Ed.* **2004**, *43*, 2228-2230.

[129] (a) Lee, D.; Yang, Y.; Yun, J. "Copper-Catalyzed Asymmetric Reduction of 3,3-Diarylacrylonitriles." *Org. Lett.* **2007**, *9*, 2749-2751. (b) Ren, Y.; Xu, X.; Sun, K.; Xu, J. *Tetrahedron: Asymmetry* "A new and effective method for providing optically active monosubstituted\malononitriles: selective reduction of α,β-unsaturated dinitriles catalyzed by copper hydride complexes." **2005**, *16*, 4010-4014.

[130] Lamas, T.; Arrayás, R. G.; Carretero, J. C. "Catalytic Asymmetric Conjugate Reduction of β,β-Disubstituted α,β-Unsaturated Sulfones." *Angew. Chem. Int. Ed.* **2007**, *46*, 3329-3332.

[131] Desrosiers, J.-N.; Charette, A. B. "Catalytic Enantioselective Reduction of β,β-Disubstituted Vinyl Phenyl Sulfones by Using Bisphosphine Monoxide Ligands." *Angew. Chem. Int. Ed.* **2007**, *46*, 5955-5957.

[132] (a) Krauss, S. R.; Smith, S. G. "Kinetics and Mechanism of the Conjugate Addition of Lithium Dimethylcuprate to α,β-Unsaturated Ketones." *J. Am. Chem. Soc.* **1981**, *103*, 141-148 (b) Corey, E. J.; Boaz, N. W. "Evidence for a reversible d,π*-complexation, β-cupration sequence in the conjugate addition reaction of Gilman reagents with α,β-enones." *Tetrahedron Lett.* **1985**, *26*, 6015-6018. (c) Corey, E. J.; Hannon, F. J. "A possible transition state assembly

with a Michael acceptor (**B**) to form π-complex **C**. The resulting organocopper species inserts into the substrate adding the hydride at the β-carbon and tautomerization provides copper enolate **E**. A stoichiometric hydride source (**F**) intercepts the copper enolate through a slow σ-bond metathesis (**G**)—often regarded as the rate-determining step. The active catalyst (**A**) is regenerated while species **H** may transform to the keto tautomer (**I**) if X = H.

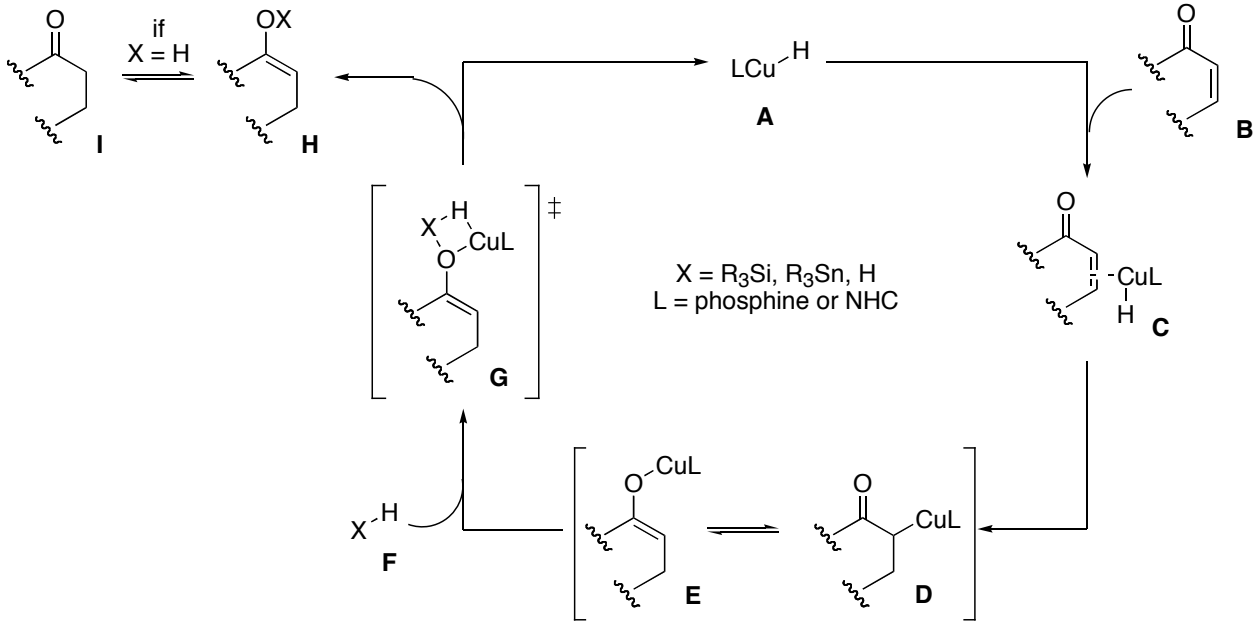

Figure 3.2. Mechanistic aspects of copper-mediated conjugate reduction.[107]

Similar mechanistic details have been reported by Buchwald to account for the rate enhancement in their method (Figure 3.3).[127b] In their specific case, inclusion of the alcohol additive (**J**) protonates the copper enolate (**E**) providing enol tautomer **K** and eventually ketone **I** (Figure 3.3). Protonation also likely results in fast generation of the copper-alkoxide species **L**, which can undergo σ-bond metathesis with a stoichiometric hydride (**E**) regenerating the copper-hydride species (**A**).

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for highly diastereoselective conjugate addition reactions of lithium dimethylcuprate with α,β-enones." *Tetrahedron Lett.* **1990**, *31*, 1393.

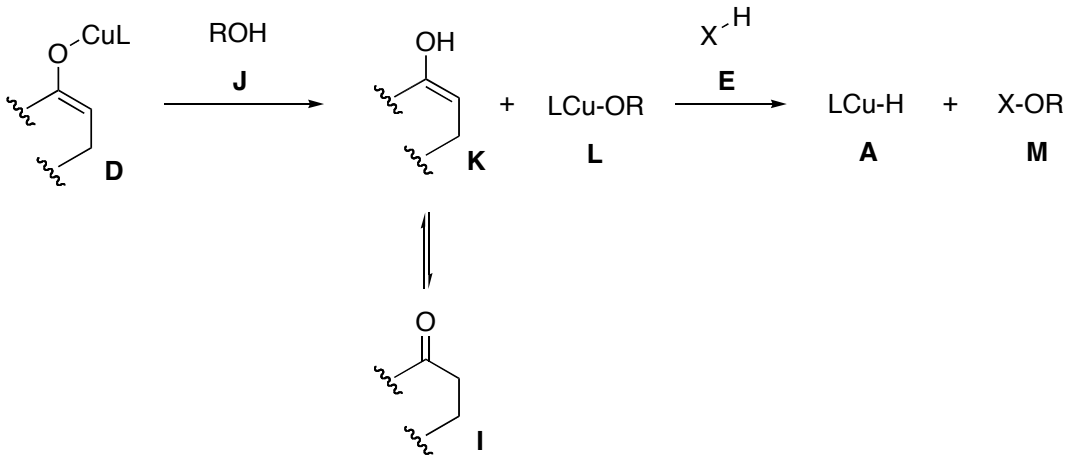


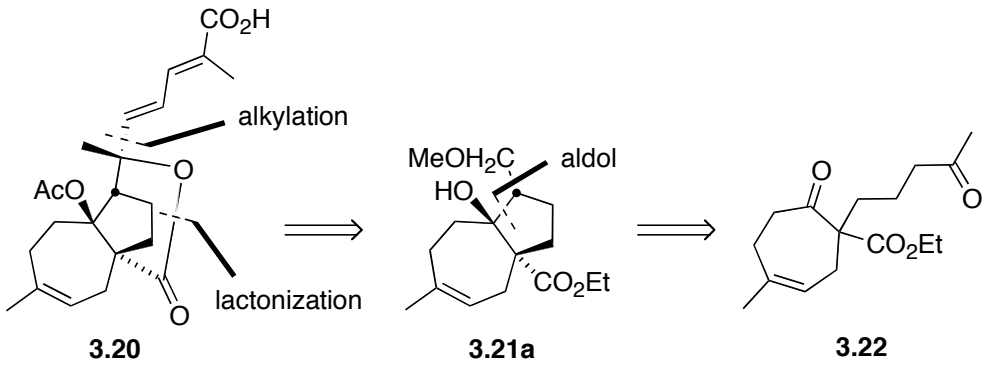
Figure 3.3. The role of stoichiometric quantities of alcohol (**J**) in Buchwald-type copper-catalyzed conjugate reductions.[127b]

3.1.5. Copper(I) Hydride-Mediated Reductive Aldol Chemistry

3.1.5.1. Stryker's Reagent

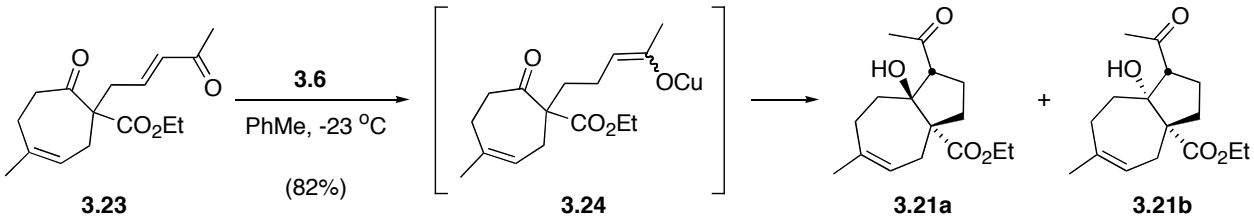
In recent applications of copper(I) hydride chemistry, Stryker's reagent (**3.6**) has been used to promote conjugate reductions in concert with carbon-carbon bond formation processes. Chiu and co-workers are credited with reporting the first example of a copper-mediated tandem conjugate reduction/aldol reaction in an attempting to synthesize pseudolaric acid A (**3.20**).[133] Initially, Chiu hypothesized that **3.21a** would derive from *trans*-bicycle **3.22** through a base-mediated aldol reaction (Scheme 3.8). Such a transformation, reported by Pan and co-workers,[134] was known to provide the desired product diastereoselectively and in high yield.

[133] Chiu, P.; Chen, B.; Cheng, K. F. "A conjugate reduction-intramolecular aldol strategy toward the synthesis of pseudolaric acid A." *Tetrahedron Lett.* **1998**, *39*, 9229-9232.
[134] Pan, B.-P.; Chang H.-Y.; Cai G.-L.; Guo Y.-S. "Synthetic studies on pseudolaric acid A." *Pure Appl. Chem.* **1989**, *61*, 389-392.



Scheme 3.8. Chiu's retrosynthetic analysis of pseudolaric acid A (**3.20**).[133]

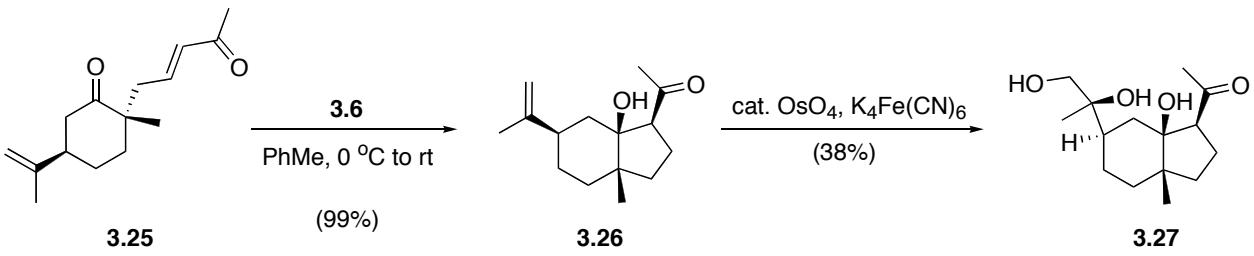
After numerous attempts of the base-mediated aldol chemistry failed, Chiu turned to Stryker's reagent to access the copper enolate[135] (**3.24**) from the precursor enone to ultimately induce intramolecular aldolization. As seen in Scheme 3.9, treatment of enone **3.23** with stoichiometric quantities of **3.6** provided the desired bicycle in good yield but favored *cis* product formation (4:1, **3.21b/a**). Although the method did not furnish the desired natural product, it represented the first example of an intramolecular reductive aldol reaction mediated by a copper(I) hydride complex.



Scheme 3.9. Chiu's synthesis of bicycle **3.21a/b**.[133]

[135] Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. "Reductions of Conjugated Carbonyl Compounds with Copper Hydride-Preparative and Mechanistic Aspects." *J. Org. Chem.* **1977**, *42*, 3180-3188.

Chiu and co-workers employed tandem reductive cyclization in the enantioselective total synthesis of (*R*)-lucinone (**3.27**) beginning from (+)-dihydrocarvone.[136] As seen in Scheme 3.10, Chiu accessed bicyclic core **3.26** while setting four of the five stereocenters in the final product in reportedly quantitative yield using stoichiometric quantities of Stryker's reagent (**3.6**). The excess copper presumably created a chelation effect[137] thereby exclusively furnishing the *syn*-β-hydroxy ketone in **3.26**. Substrate-controlled asymmetric dihydroxylation afforded antispasmodic **3.27** in 38% yield. This synthesis marked the first instance where copper(I) hydride-mediated reductive aldol chemistry had been applied in the preparation of a natural product.



Scheme 3.10. An excerpt of Chiu's synthesis of (*R*)-lucinone (**3.32**).[136]

The Lipshutz group prepared 1,3-ketols from the corresponding enones in good yields employing their catalytic Stryker's reagent reductive aldol method (Scheme 3.11).[123] Generation of a silyl enol ether intermediate from enone **3.28** allowed for Mukaiyama-type aldolization when an electrophile was introduced in the presence of a strong Lewis acid. As a result (Scheme 3.11), ketol **3.30** was prepared from enone **3.28** in 83% yield by way of intermediate **3.29**.

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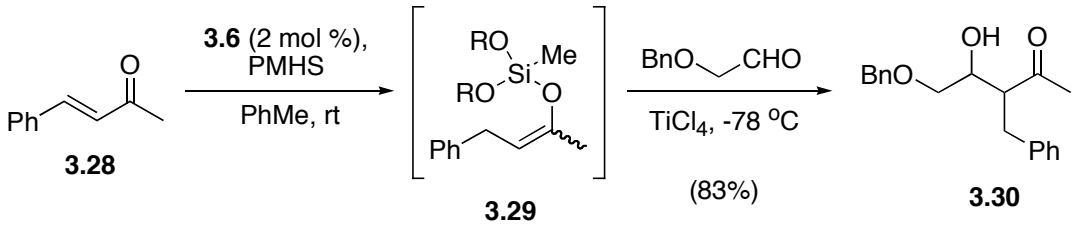
[136] Chiu, P.; Szeto, C. P.; Geng, Z.; Cheng, K. F. "Application of the tandem Stryker reduction-aldol cyclization strategy to the asymmetric synthesis of lucinone." *Tetrahedron Lett.* **2001**, *42*, 4091-4093

[137] Arrowsmith, J. E.; Greengrass, C. W.; Newman, M. J. "Copper (I) catalysed reactions of 6-bromopenicinllanoyl magnesium bromide: A synthesis of 6-spirocyclopropyl penicillanates." *Tetrahedron* **1983**, *39*, 2469-2475.



Scheme 3.11. Preparation of 1,3-ketol **3.30** using **3.6**-catalyzed reductive aldol chemistry.[123]

3.1.5.2. Analogs

Several intermolecular reductive aldol reactions have been reported. The majority of these processes involve commercially unavailable copper(I) salts and require the use of chiral *bis*-phosphino-type ligands[138] to afford products in good yield with high levels of diastereo- and enantioselectivity.

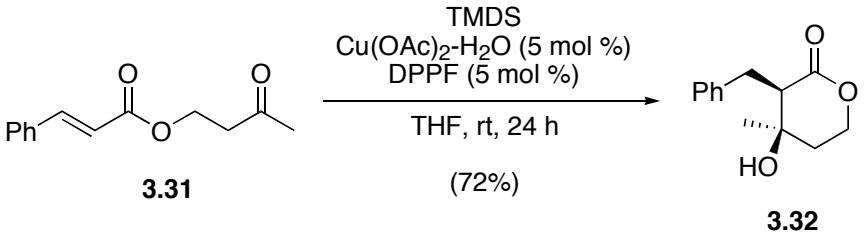
Lam and co-workers demonstrated the preparation of β-hydroxylactones from precursor enoates using a bis-phosphine-ligated copper(I) hydride species.[139] This reductive aldol method employed catalytic quantities of copper in the presence of silicon hydrides to effect the desired transformation. Optimized conditions, though reminiscent of Yun's work,[140] diastereoselectively provided β-hydroxylactone (**3.32**) from the corresponding enoate (**3.31**) in 72% yield (Scheme 3.13).[139] This method suffered from long reaction times (upwards of 30 h in some cases) and

[138] For examples see: (a) Deschamps, J.; Chuzel, O.; Hannedouche, J.; Riant, O. "Highly Diastereo- and Enantioselective Copper-Catalyzed Domino Reduction/Aldol Reaction of Ketones with Methyl Acrylate." *Angew. Chem. Int. Ed.* **2006**, *45*, 1292-1297. (b) Chuzel, O.; Deschamps, J.; Chausteur, C.; Riant, O. "Copper(I)-Catalyzed Enantio- and Diastereoselective Tandem Reductive Aldol Reaction." *Org. Lett.* **2006**, *8*, 5943-5946. (c) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. "Catalytic enantioselective intermolecular reductive aldol reaction to ketones." *Tetrahedron Lett.* **2006**, *47*, 1403-1407.

[139] Lam, H. W.; Joensuu, P. M. "Cu(I)-Catalyzed Reductive Aldol Cyclizations: Diastereo- and Enantioselective Synthesis of β-Hydroxylactones." *Org. Lett.* **2005**, *7*, 4225-4228.

[140] Lee, D.-W.; Yun, J. "Direct Synthesis of Stryker's Reagent from a Cu(II) Salt." *Tetrahedron Lett.* **2005**, *46*, 2037-2039.

competitive 1,2-hydride addition products.[141] Similar methodology has been applied to the diastereoselective preparation of β-hydroxypiperidinones also in modest yields with similar limitations.[142]



Scheme 3.12. Lam's preparation of lactam **3.32**.[139]

3.2. Wharton-Type Grob Fragmentations

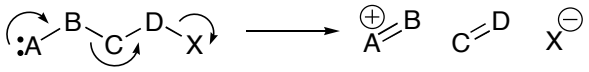
3.2.1. General Aspects of Grob Fragmentations

A Grob fragmentation is a heterolytic cleavage of a five-atom system. The process, occurring in molecules containing certain combinations of carbon and heteroatoms, is generically represented by the following generic reaction as seen in Equation 3.2. The A-B component, defined as the electrofuge, supplies the lone pair of electrons to drive the process. By comparison the nucleofuge, the X or leaving group, carries away the electron pair. The middle group, a saturated or unsaturated element, (C-D) is involved in forming the newly formed double

[141] Joensuu, P. M.; Murray, G. J.; Fordyce, E. A. F.; Luebbers, T.; Lam, H. W. "Diastereoselective Nickel-Catalyzed Reductive Aldol Cyclizations Using Diethylzinc as the Stoichiometric Reductant: Scope and Mechanistic Insight." *J. Am. Chem. Soc.* **2008**, *130*, 7328-7338.

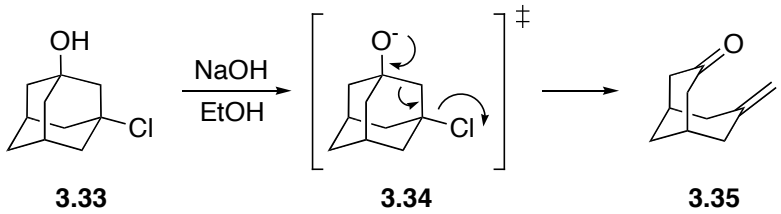
[142] Lam, H. W.; Murray, G. J.; Firth, J. D. "Diastereoselective Synthesis of 4-Hydroxypiperidin-2-ones via Cu(I)-Catalyzed Reductive Aldol Cyclization." *Org. Lett.* **2005**, *7*, 5743-5746.

or triple bond. Note that the actual fragmentation occurs between atoms B and C and the process yields the creation of two new π-bonds.[143]



Equation 3.2

Variations of the Grob fragmentation include acid- or base-mediated processes. Additionally, Matsuda and coworkers reported that Grob fragmentations have been observed biosynthetically.[144] An example of a Grob fragmentation is the conversion of 3-chloroadamantanol (**3.33**) to unsaturated [3.3.1]-bicycle **3.35**, as seen in Scheme 3.13.[145] These experiments, as is the case with all Grob fragmentations, suggest a concerted fragmentation mechanism, though deprotonation in this particular case helps mediate the process. As such, the reaction chiefly involves synchronous heterolytic cleavage in the transition state.



3.33 **3.34** **3.35**

Scheme 3.13. Preparation of bicyclic olefin **3.35** from **3.33**.[145]

Grob transformations have an important role in organic chemistry. These fragmentations have been used in the development of several complex molecules,[13,146] natural products[28,31,33]

[143] Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier, Inc.: Oxford, UK, 2005; p 480.
[144] Xoing, Q.; Wilson, W. K.; Matsuda, S. P. T. "An Arabidopsis Oxidosqualene Cyclase Catalyzes Iridal Skeleton Formation by Grob Fragmentation." *Angew. Chem.* **2006**, *118*, 1307-1310.
[145] Fischer, W.; Grob, C. A. "Concerted fragmentation and anchimerically assisted elimination in the solvolysis of 3-chloropropanols." *Tetrahedron Lett.* **1975**, *16*, 3547-3550.
[146] For examples see: (a) Tada, N.; Miyamoto, K.; Ochiai, M. "Oxidation of 3-Hydroxypiperidines with Iodosylbenzene in Water: Tandem Oxidation Grob Fragmentation-Cyclization Reaction." *Chem. Pharm. Bull.* **2004**, *52*, 1143-1144. (b) De Giacomo, M; Bettolo,

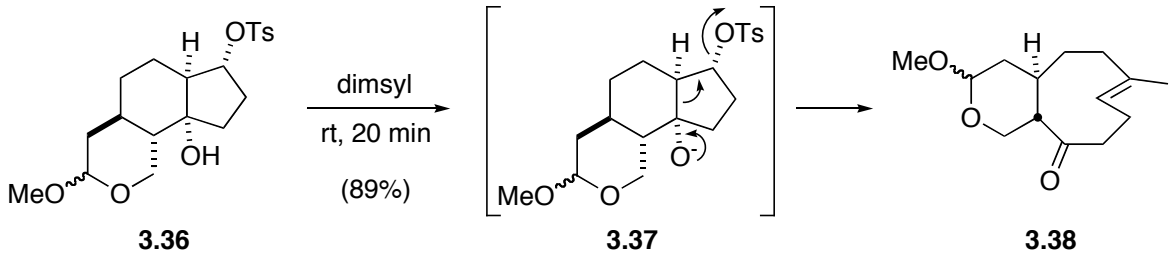
and medium-sized carbocycles.[29,54,84] The later aspect is significantly important because where direct cyclization reactions fail due to unfavorable entropic processes, Grob fragmentations have been shown to be quite effective.

3.2.2. Classical Wharton-type Grob Fragmentations

Classical Wharton-type Grob fragmentations involve the synchronous fragmentations of 1,3-diol monosulfonate esters,[29] though variations include dithioketal leaving groups.[147] Historically, Wharton substrates are rigid, bicyclic compounds that fragment to provide unsaturated, medium-sized rings.[143] The process typically involves treatment of the substrate with strong non-nucleophilic bases such as dimsyl or KO*t*-Bu in polar solvents to cause an initial intermediate alkoxide formation followed by concerted fragmentation. The polar solvent system serves to separate the metal from the alkoxide thus promoting fragmentation. Apolar solvents such as THF or benzene often require the addition of crown ethers to separate the ionic interaction between the metal and alkoxide. An example of a Wharton-type Grob fragmentation is seen in Leumann's synthesis of coraxeniolide A (Scheme 3.14).[31] Treatment of β-hydroxy tosylate **3.36** with dimsyl provided the corresponding cyclononene ring **3.38**. Presence of DMSO aided reaction progress in creating a "naked" alkoxide by sequestering the cation.

R. M.; Scarpelli, R. "Unprecedented Grob-type fragmentation of 5-dioxolan-bicyclo[4.2.0]octan-2-ones into 3-(methyoxycarbonylmethyl) cyclohexanones." *Tetrahedron Lett.* **1997**, *38*, 3469-3470. (c) French, L. G.; Charlton, T. P. "Rearrangement of exo-1,4:2,3-diepoxy-1,2:3,4-tetrahydronaphthalene: formation of a novel isochromene via Grob fragmentation." *Heterocycles* **1993**, *35*, 305-313. (d) Harmata, M.; Elahmad, S. "An intramolecular 4+3 cycloaddition-vinylogous grob fragmentation route to a tricyclo[6.3.0.$0^{2,4}$] undecene ring system." *Tetrahedron Lett.* **1993**, *34*, 789-792.

[147] De Dobbeleer, C.; Ates, A.; Vanherk, J.-C.; Marko, I. E. "Efficient access to functionalised medium-ring systems by radical fragmentation/radical addition to α-iodoketones." *Tetrahedron Lett.* **2005**, *46*, 3889-3893.

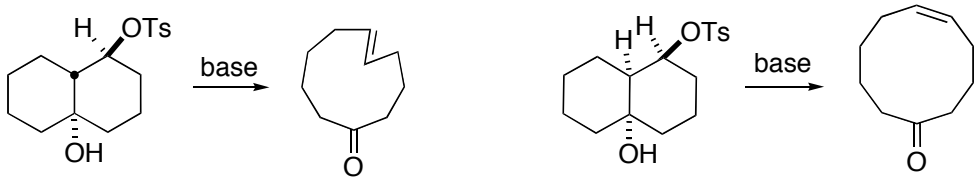


3.36 **3.37** **3.38**

Scheme 3.14. The synthesis of coraxeniolide A core **3.38** from tricycle **3.36**.[31]

3.2.2.1. Stereoelectronic Effects

In seminal experiments, Wharton reported that the possibility of fragmentation depended upon proper alignment of the fractioning bond and leaving group at the unsaturated element (Scheme 3.15). Treatment of β-hydroxy tosylate *trans*-decalin system **3.39a** with KO*t*-Bu provided (*E*)-cyclodecenone **3.40a** stereospecifically. Similarly, the *cis*-decalin analog (**3.39b**) provided (*Z*)-cyclodecenone **3.40b**. The difference in these two substrates was the relative placement of the hydrogen atoms on the unsaturated element. An *anti* arrangement of the hydrogen atoms (**3.39**a) stereospecifically gave the (*E*)-olefin whereas a *syn* arrangement (**3.39b**) furnished the (*Z*)-olefin.[148]

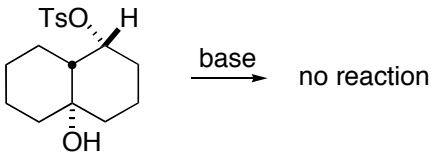


3.39a **3.40a** **3.39b** **3.40b**

Scheme 3.15. Wharton-type Grob fragmentation of tosylates **3.39a/b**.[148]

[148] Wharton, P. S.; Hiegel, G. A.; Coombs, R. V. "*trans*-5-Cyclodecenone." *J. Org. Chem.* **1963**, *28*, 3217. (c) Wharton, P. S.; Hiegel, G. A. "Fragmentation of 1,10-Decalindiol Monotosylates." *J. Org. Chem.* **1965**, *30*, 3254.

By comparison, treatment of *trans*-decalin **3.39a** under the same conditions resulted in recovery of unreacted starting material (Scheme 3.16).[148] In fact, use of a stronger base (e.g. dimsyl) with heating could not effect the desired fragmentation. Wharton noted that such harsh conditions resulted in isolation of trace quantities of 1,2-elimination products.



3.39c

Scheme 3.16. Wharton-type Grob fragmentation of tosylate **3.39c**.[148]

In examining the C-6/C-5 Newman projection of **3.39a**, it is obvious that the sulfonyl ester bond and the fractioning bond (i.e. electron density shared between C-1 and C-6) possess a ~180° dihedral angle (Figure 3.4), a similar requirement necessary for E2 mechanisms.[149] However, Wharton-type Grob fragmentations are widely considered $E1_{CB}$ due to the initial deprotonation step followed by concerted heterolytic cleavage.

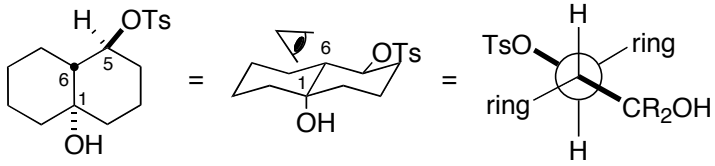
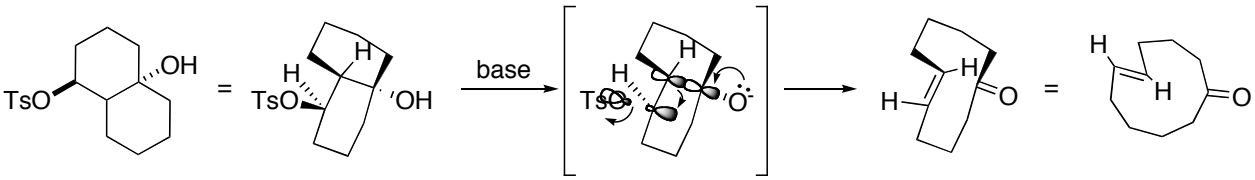


Figure 3.4. Newman projection of the C-6/C-5 bond in tosylate **3.39a**.

An antiperiplanar conformation allows for optimal orbital overlap in the transition state. The elimination step necessarily creates a new π-bond in the product. As the alkoxide forms a new carbonyl, electron density between C-1 and C-6 pushes electron density into the σ* orbital at C-5 in **3.41a** (Scheme 3.17). This movement of electrons simultaneously weakens the

[149] DePuy, C. H.; Morris, G. F.; Smith, J. S.; Smat, R. J. "Electronic Effects in Elimination Reactions. V. Bimolecular *cis* Eliminations. 2-Arylcyclopenyl Tosylates." *J. Am. Chem. Soc.* **1965**, *87*, 2421.

sulfonyl ester bond resulting in heterolytic cleavage of the C-5-O bond. The net result is the formation of four sp^2-hybridized atoms and two new π-bonds. The optimal orbital alignment in the transition state situates the hydrogens in an antiperiplanar conformation. This relative positioning is maintained in the olefination step providing the (*E*)-alkene.[148]



3.39a **3.41a** **3.40a**

Scheme 3.17. Wharton-type Grob fragmentation of tosylate **3.39a**.

By comparison, the syn *trans*-decalin system (**3.39c**) does not undergo fragmentation when exposed to a strong base.[148] Looking down the C-6/C-5 bond, the Newman projection in Figure 3.5 suggests that the fragmenting bond and the leaving group are gauche, possessing a dihedral angle of 60°.

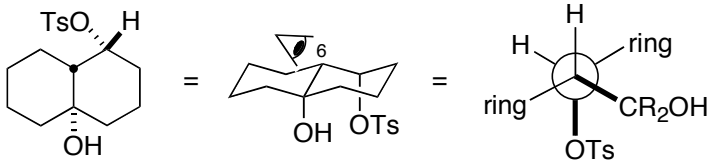


Figure 3.5. Newman projection of the C-6/C-5 bond in tosylate **3.39c**.

As seen in the three-dimensional representation of the **3.39c**, the gauche conformation precludes the π* and σ* orbitals from overlapping (Figure 3.6). This nearly orthogonal orientation makes the π* bond incapable of donating electron density into the neighboring σ* orbital. Thus, inclusion of a strong base results in starting material recovery or, as reported by Wharton, trace quantities of 1,2-elimination products.

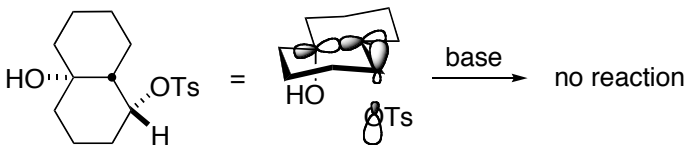
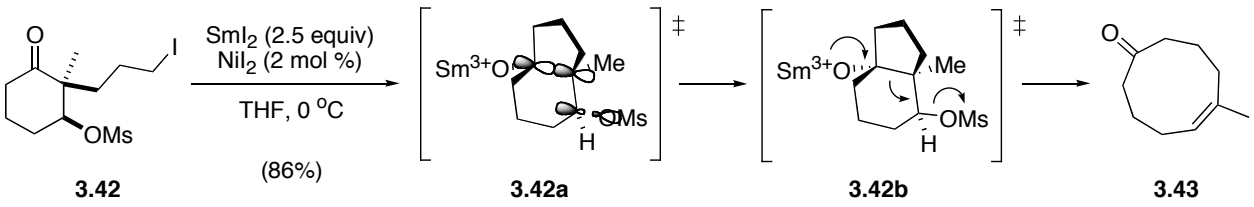


Figure 3.6. Misalignment of the π* and σ* orbitals in tosylate **3.39c**.

3.2.3. Representative Transformations

3.2.3.1. Molander's Tandem Barbier/Grob Chemistry

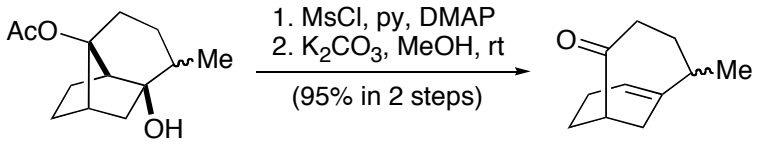
Molander and co-workers employed Sm(II)-mediated tandem Barbier/Grob chemistry to access medium-sized carbocycles from precursor 1,3-ketols.[54] Treatment of ω-iodo-1,3-ketols with SmI_2 and catalytic quantities of NiI_2 provided the cyclononene ring **3.43** through the formation of the samarium alkoxide intermediate (Scheme 3.18). As seen in the intermediate structure **3.42a**, the antiperiplanar arrangement of the fragmenting carbon-carbon and leaving carbon-oxygen bond allowed for the heterolytic cleavage to proceed. This methodology was applied to a number of substrates providing a wide array of carbocycle products in yields ranging from 42-92%



Scheme 3.18. Sm(II)-mediated Barbier/Grob chemistry used to access carbocycle **3.43**.[54]

3.2.3.2. Wood's Synthetic Strategy toward CP-263,114

Wood and co-workers employed Wharton-type Grob fragmentations to access the carbocyclic core of CP-263,114 (**3.45**).[150] As seen in Scheme 3.19, mesylation and ensuing methanolysis of norbornane-based core **3.44** smoothly provided the [4.3.1]-bicyclic sytem. The antiperiplanar arrangement of the fractioning C-C bond and the C-O bond in **3.44a** allow for optimal alignment of the π* and σ* orbitals.



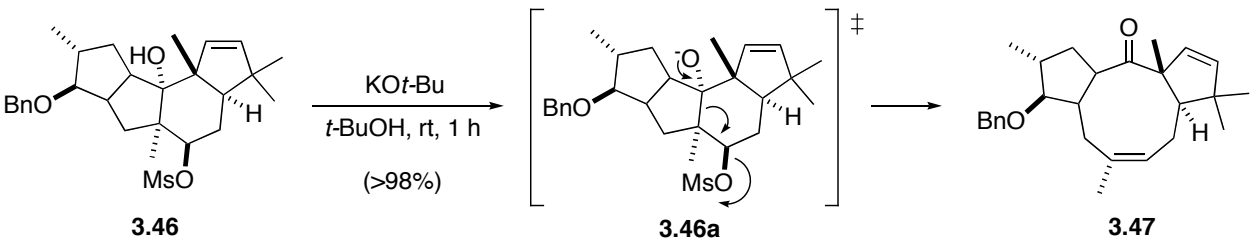
3.44 **3.45**

Scheme 3.19. Synthesis of alcohol **3.45** from alcohol **3.44**.[150]

3.2.3.3. Paquette's Synthesis of Jatrophatrione.

Paquette made use of a Wharton-type Grob fragmentation in the total synthesis of jatrophatrione .[151] Treatment of mesylate **3.46** with KO*t*-Bu provided the desired cyclononone core (**3.47**) in quantitative yield. Use of the protic solvent assisted in segregating the potassium cation from the alkoxide thus allowing for fragmentation to occur.

[150] Njardarson, J. T.; Wood, J. L. "Evolution of a Synthetic Approach to CP-263,114." *Org. Lett.* **2001**, *3*, 2421-2434.
[151] Yang, J.; Long, Y. O.; Paquette, L. A. "Concise Total Synthesis of the Bioactive Mesotricyclic Diterpenoids Jatrophatrione and Citlalitrione." *J. Am. Chem. Soc.* **2003**, *125*, 1567-1574.



3.46 **3.46a** **3.47**

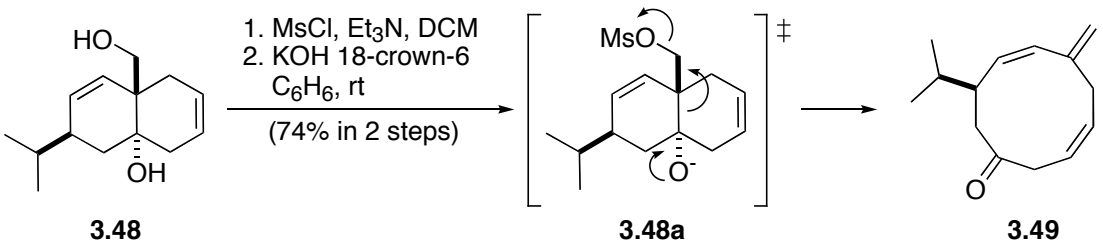
Scheme 3.20. Synthesis of cyclononone **3.47** from mesylate **3.46**.

Analysis of the lowest energy conformer of the substrate suggests that the fractioning bond and C-OMs bond have a dihedral angle of approximately 129°, short of the requisite 180°.[152] The computational analysis suggests that the cyclohexane ring adopts a twisted boat at its ground state. However, the fact that the sulfonyl ester is situated on a cyclohexane ring suggests that optimal orbital alignment may occur with a twisted conformation.

3.2.3.4. Saicic's Synthesis of Periplanone C.

Saicic and co-workers reported the use of Wharton-type Grob chemistry in the racemic synthesis of periplanone C.[153] Chemoselective mesylation of 1,3-diol *trans*-decalin **3.48** followed by deprotonation furnished decanone triene **3.49** in good yield (Scheme 3.21). Use of the crown ether in the fragmentation step aided in segregating the potassium ion from the alkoxide allowing the reaction to proceed. Free rotation of the mesylate allowed for an antiperiplanar alignment in the transition state.

[152] Determined using an MM2 calculation of the lowest energy conformer of **3.46**. *CS Chem3D Pro*, version 5.0; CambridgeSoft Corp.: Cambridge, MA, 1999.
[153] Matovic, R.; Ivkovic, A.; Manojlovic, M.; Tokic-Vujosevic, Z.; Saicic, R. N. "Ring Closing Metathesis/Fragmentation Route to (*Z*)-Configured Medium Ring Cycloalkenes. Total Synthesis of (±)-Periplanone C." *J. Org. Chem.* **2006**, *71*, 9411-9419.

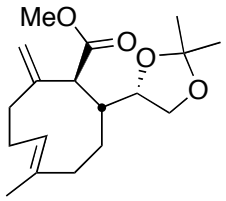


3.48 **3.48a** **3.49**

Scheme 3.21. Synthesis of decanone **3.49**.

3.3. Research Goals

We sought to develop a method to synthesize common intermediate **3.50** using tandem reactions. As is shown in the Results and Discussion section (*vide infra*), this method would incorporate copper-catalyzed reductive aldol chemistry and a Wharton-type Grob fragmentation[29] to stereoselectively access the nine-membered ring. Though the research goals would deviate from the original plan of developing a Reformatskii/Grob process (discussed in Chapter 1), this new direction could offer a viable alternative toward the synthesis of **3.50**.



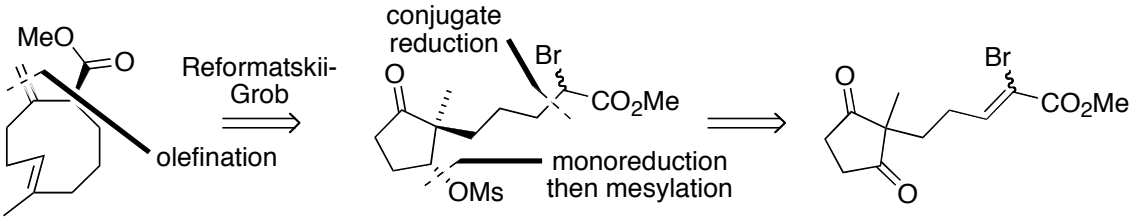
3.50

Figure 3.7. Snowden's xenicane common intermediate.

3.3.1. Initial Retrosynthetic Analysis and Strategy

Prior to the investigation of reductive aldol chemistry, our strategy focused on the preparation of common intermediate analog **3.51a** *vis-à-vis* our initial goal of demonstrating our proposed Reformatskii/Grob reaction (Scheme 3.22). Application of our proposed chemistry on a simple, model substrate carries obvious benefits toward eventually synthesizing **3.50**—a

densely functionalized target. We hypothesized that Reformatskii/Grob substrate **3.52** would derive from known dione enoate **3.53**[154] through a monoreduction/mesylation sequence and a chemoselective conjugate reduction. Although the examples of 1,4-hydride delivery methods are numerous, to our knowledge, the conjugate reduction of an α-bromo-α,β-unsaturated carbonyl had not been reported in the literature. We planned to explore a variety of reactions to develop optimal conditions for this transformation.



3.51a **3.52** **3.53**

Scheme 3.22. Retrosynthetic analysis of simplified common intermediate **3.51a**.

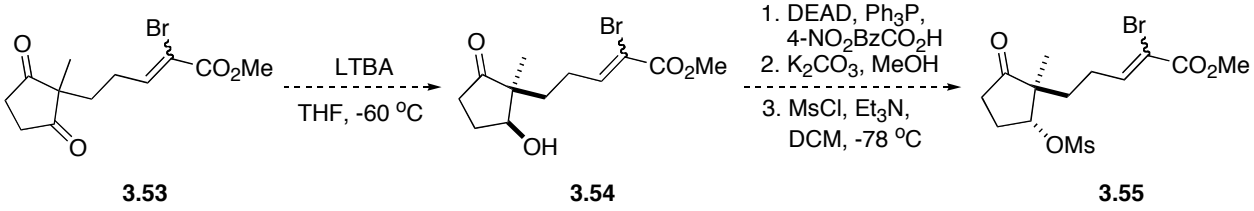
Based on reported experimental data, we hypothesized that subjection of **3.55** to our optimized diastereoselective LTBA-mediated monoreduction conditions[155] would provide the undesired *cis*-ketol **3.56** as the major isomer (Scheme 3.23) without promoting diol formation. Inversion of the alcohol would involve classical[156] or Martin-type[157] Mitsunobu reaction

[154] Chapdelaine, D.; Belzile, J.; Deslongchamps, P. "A Convergent Synthesis of the Cardenolide Skeleton: Intramolecular Aldol Condensation via Reduction of α-Bromoketones." *J. Org. Chem.* **2002**, *67*, 5669-5672.

[155] Carr, J. M.; Snowden, T. S. Comparative reductive desymmetrization of 2,2-disubstituted-cycloalkane-1,3-diones. *Tetrahedron* **2008**, *64*, 2897-2905.

[156] (a) Mitsunobu, O.; Yamada, M.; Mukaiyama, T. "Preparation of Esters of Phosphoric Acid by the Reaction of Trivalent Phosphorous Compounds with Diethyl Axodicarboxylate in the Presence of Alcohols." *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935-939. (b) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* "Preparation of Carboxylic Esters and Phosphoric Esters by the Activation of Alcohols." **1971**, *44*, 3427-3430. (c) Bose, A. K.; Lal, B.; Hoffman, W. A.; Manhas, M. S. "Steroids. IX. Facile inversion of unhindered sterol configuration." *Tetrahedron Lett.* **1973**, *18*, 1619-1622. (d) Manna, S.; Falck, J. R. "A convenient preparation of alkyl halides and cyanides from alcohols by modification of the Mitsunobu procedure." *Synth. Commun.* **1985**, *15*, 663-668.

conditions and ensuing saponification using alkaline methanol to provide the requisite *trans*-ketol. Finally, formation of the sulfonyl ester (**3.57**) would involve classic mesylation conditions.[158] This four-step sequence would provide the requisite positioning of substituents about the cyclopentanone moiety to access the desired (*E*)-olefin in the Wharton-type Grob fragmentation step.



3.53 **3.54** **3.55**

Scheme 3.23. The proposed synthesis of sulfonyl ester **3.55**.

3.4. Results and Discussion

3.4.1. Starting Material Preparation

3.4.1.1. Dione Enoate Substrates

Deslongchamps and co-workers reported the synthesis of bromo dione **3.53** from the Wittig reaction of aldehyde **3.56** and commercially unavailable phosphane **3.59**,[154] as seen in Scheme 3.24. Aldehyde **3.56** derives from commercially available 2-methylcyclopentane-1,3-dione (**3.57**) and acrolein (**3.58**). Bromophosphane **3.59** derives from the Wittig reaction of commercially available **3.60** through a chemoselective bromination.

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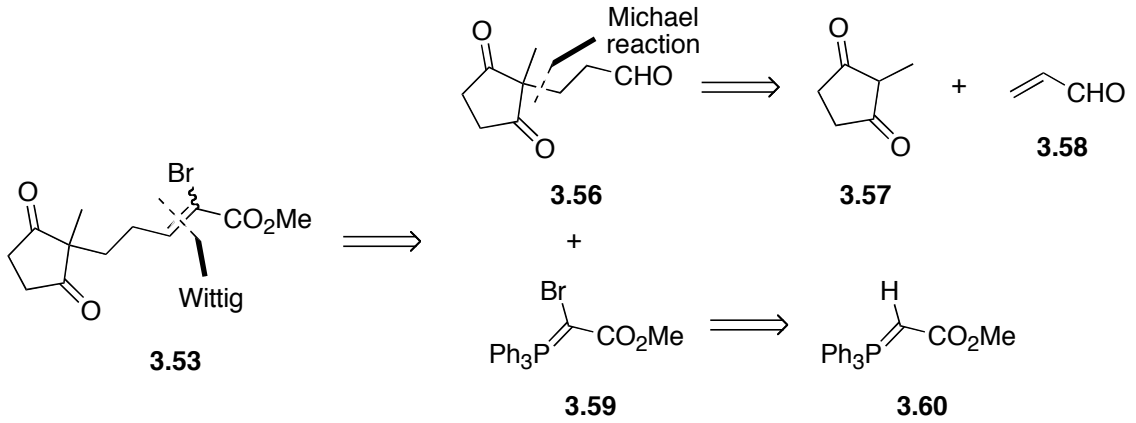
[157] (a) Martin, S. F.; Dodge, J. A. "Efficacious modification of the Mitsunobu reaction for inversions of sterically hindered secondary alcohols." *Tetrahedron Lett.* **1991**, *32*, 3017-3020. (b) Kaufman, T. S. "The Mitsunobu reaction of *ortho*-ethers of secondary benzylic alcohols. Concise enantioselective synthesis of a key intermediate of the novel b-adrenergic receptor antagonist MY336-a." *Tetrahedron Lett.* **1996**, *37*, 5329-5332. (c) Nicolaou, K. C.; Zhang, H.; Ortiz, A.; Dagneau, P. "Total Synthesis of the Originally Assigned Structure of Vannusal B." *Angew. Chem. Int. Ed.* **2008**, *47*, 8605-8610.

[158] Mesnard, P.; Gibirila, B.; Bertucat, M. "Action du chlorure de *p*-toluènesulfonyle sure la fonction hydroxyle, indice de tosylation pyridinée." *Chimie Analytique* **1963**, *45*, 491-498.

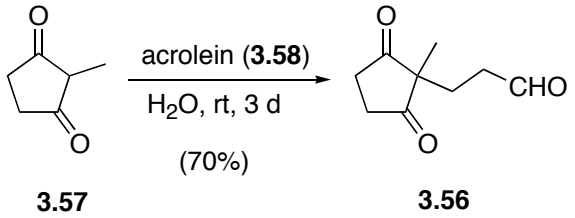


Scheme 3.24. Deslongchamps' retrosynthesis of dione **3.53**.[154]

As seen in Delongchamps' retrosynthesis (Scheme 3.25), aldehyde **3.56** is prepared through a Michael reaction of commercially available dione **3.57**[159] and acrolein (**3.58**) in aqueous media.[160,161,162] In practice, we found this reaction cleanly provided the desired *C*-alkylation product in good yields after mixing for three days (Scheme 3.25). Aqueous solvent systems are known to accelerate the rates of Michael addition due to the creation of a hydrophobic effect,[163] the aggregation of nonpolar species in water resulting in the decrease of

[159] Also readily prepared from succinic acid: Meister, P. G.; Sivik, M. R.; Paquette, L. A. "2-Methyl-1,3-Cyclopentanedione." *Org. Synth.* **1992**, *70*, 226-228.
[160] Katoh, T.; Mizumoto, S.; Fudesaka, M.; Nakashima, Y.; Kajimoto, T.; Node, M. "Inversion of Diastereoselectivity Depending on Substrate Concentration in Baker's Yeast Catalyzed Reduction of sigma-Symmetrical 1,3-Cyclopentadiones and 1,3-Cyclohexadiones." *Synlett* **2006**, 2176-2182.
[161] Lavallée, J.-F.; Deslongchamps, P. "One-step construction of a 13α-methyl 14α-hydroxy steroid via a new anionic polycyclization method" *Tetrahedron Lett.* **1988**, *29*, 6033-6036.
[162] Bocknack, B. M.; Wang, L.-C.; Krische, M. J. "Desymmetrization of enone-diones via rhodium-catalyzed diastereo- and enantioselective tandem conjugate addition-aldol cyclization." *Proc. Nat. Acad. Sci.* **2004**, *101*, 5421-5424.
[163] (b) Lubineau, A. "Water-Promoted Organic Reactions: Aldol Reaction under Neutral Conditions." *J. Org. Chem.* **1986**, *51*, 2142-2144 (b) Lubineau, A.; Auge, J.; Queneau, Y. "Water-Promoted Organic Reactions." *Synthesis* **1994**, 741-760.

hydrocarbon-water interfacial area.[164] The water also presumably mitigates *O*-alkylation[165] by hydrogen bonding to both carbonyls, thus chemoselectively favoring the formation of **3.56**.



3.57 **3.56**

Scheme 3.25. Preparation of aldehyde **3.56**.

Bromo phosphane **3.59** was prepared from commercially available **3.60** using previously reported procedures. Märkl first reported the first synthesis of **3.59** in 1961,[61] a reaction that involved treatment of **3.60** with $KBrO_3$ and KBr in acidic media. The reduction of $KBrO_3$ in strong acid formed Br_2 in situ formation (Equation 3.3)[166] thus providing a stoichiometric bromine source for the reaction. Ensuing neutralization of the reaction mixture provided the α-bromo Wittig reagent (**3.59**) in reportedly 90% yield.

$$5\ KBr + KBrO_3 + 3\ H_2SO_4 \longrightarrow 3\ Br_2 + 3\ K_2SO_4 + 3\ H_2O \qquad \textbf{(Equation 3.3)}$$

Denny and Ross reported a similar preparation of bromo phosphane **3.59**.[62] Their method involved treatment of phosphane **3.60** with elemental Br_2 in methylene chloride followed by an alkaline workup. More recently, Kayser, Zhu and Hooper reported a method wherein α-bromo

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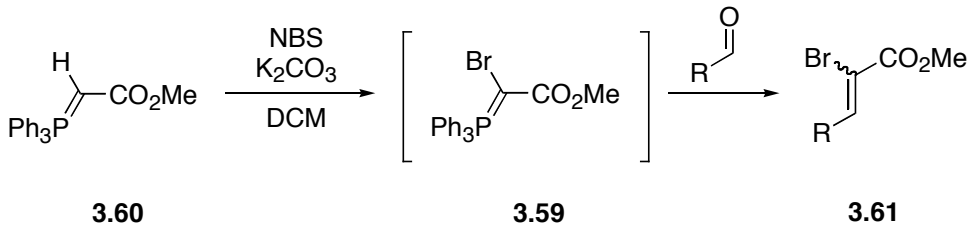
[164] Breslow, R. "Hydrophobic Effects on Simple Organic Reactions in Water." *Acc. Chem. Res.* **1991**, *24*, 159-164.

[165] For example see: Bertelsen, S.; Dinér, P.; Johansen, R. L.; Jørgensen, K. A. "Asymmetric Organocatalytic β-Hydroxylation of α,β -Unsaturated Aldehydes." *J. Am. Chem. Soc.*, **2007**, *129*, 1536-1537.

[166] For examples of the preparation of Br_2 from $KBrO_3$ in acidic media, see the following references: (a) Krafft, F.; Merz, V. Vorläufige Mittheilung. *Chem. Ber.* **1875**, *8*, 1045. (b) Derbyshire, D. H.; Waters, W. A. "108. The significance of the bromine cation in aromatic substitution." *J. Chem. Soc.* **1950**, 573-577. (c) Gilow, J. M.; Ridd, J. H. "Mechanism of aromatic bromination by hydrobromous acid in aqueous perchloric acid. Kinetic evidence against the prior formation of positive bromine." *J. Chem. Soc., Perkin Trans. 2*, **1973**, 1321-1327. (d) Harrison, J. J.; Pellegrini, J. P.; Selwitz, C. M. "Bromination of deactivated aromatics using potassium bromate." *J. Org. Chem.* **1981**, *46*, 2169-2171.

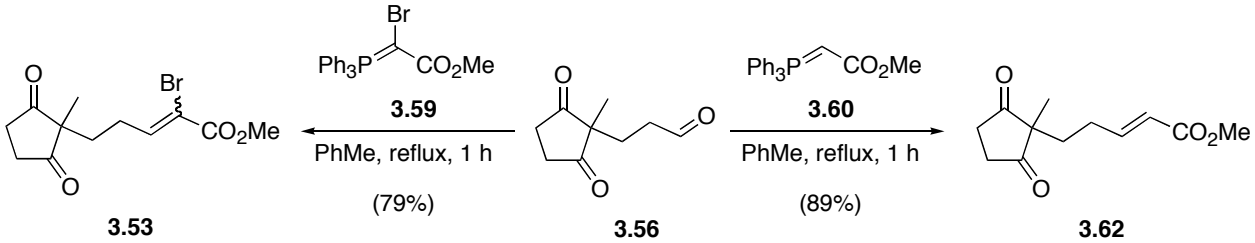
phosphane **3.59** was prepared in situ by treatment of commercially available **3.60** with NBS in methylene chloride (Scheme 3.26).[167] Introduction of an aldehyde furnished the desired α-bromo enoate (**3.63**) in yields ranging from 40-92%.



3.60 **3.59** **3.61**

Scheme 3.26. Preparation of α-bromo enoates (**3.61**) from **3.60**.[167]

The Deslongchamps route to **3.53**[154] made use of Märkl's procedure[61] for preparing **3.59**. In early experiments, we found that the procedure suffered from byproduct formation, which may be attributed to the harsh reaction conditions. Recrystallization of crude **3.59** from EtOAc/hexanes provided the pure product in 62% yield. By comparison, we observed no significant improvements in yield in the direct bromination of **3.59** using the Denny and Ross method.[62] The reaction of **3.56** and **3.59** in refluxing toluene furnished **3.53** in 79% yield as an inseparable mixture of (*E*)- and (*Z*)-isomers (Scheme 3.27). Additionally, dione **3.62** was prepared in 89% yield from the reaction of **3.56** and **3.60** in refluxing toluene.

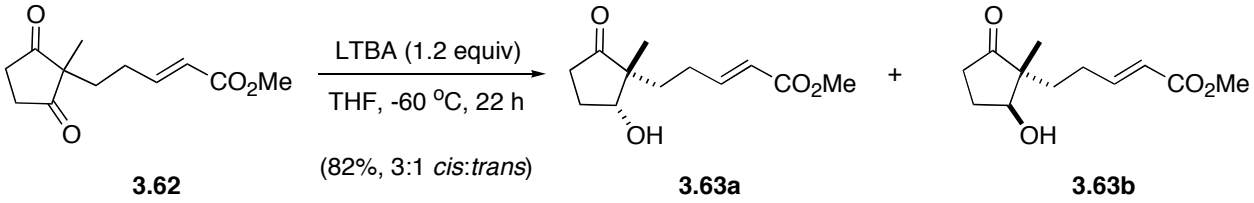


Scheme 3.27. The synthesis of **3.53** and **3.62**.

[167] Kayser, M. M.; Zhu, J.; Hooper, D. L. "Stabilized haloylides: synthesis and reactivity." *Can. J. Chem.* **1997**, *75*, 1315-1321.

3.4.1.2. Diastereoselective Substrate Preparation

Though shown to provide excellent yields in the monoreduction of cyclopentanediones, use of the $NaBH_4$/DME methodology at -60 ^oC (described in Chapter 2) promoted diol formation. Reaction of **3.62** with 0.5 equivalents of $NaBH_4$ in DME at -60 ^oC furnished the desired ketols in 64% yield after purification by column chromatography. The choice to use the LTBA/THF method became ideal due to the reagent's inability to over-reduce cyclic-2,2-disubtituted-1,3-diones to the corresponding diols.[155] As seen in Scheme 3.28, dione **3.62** was cleanly converted to the corresponding 1,3-ketol as a diastereomeric mixture (3:1 **3.63a**:**3.63b**) in 82% yield. Repurification of the isolated material provided the pure *cis*-ketol (**3.65a**) in 52% yield.



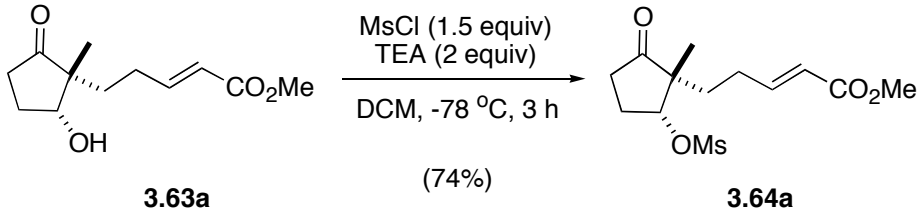
3.62 **3.63a** **3.63b**

Scheme 3.28. Preparation of ketols **3.63a/b**.

Attempted conversion of *cis*-ketol **3.63a** to the corresponding *trans*-isomer using a variety of transformations such as classical and Martin-type Mitsunobu chemistry resulted in starting material recovery. These results suggest that the quaternary carbon may hinder addition of the Mitsunobu reagents. Additionally, treatment of **3.63a** with Appel conditions resulted in slight consumption of the starting material after refluxing for several days when CCl_4 was used as the solvent. By contrast, reactions with CBr_4 in warm DMF resulted in recovery of the starting material.

We eventually abandoned inversion chemistry. Initial experiments suggested that both the substrate (**3.63a**) and the product (**3.64a**) had identical R_f values in TLC analysis using

several different solvent systems. Nevertheless, pure **3.63a** was subjected to mesylation conditions[54] and monitored reaction progress by crude ^{1}H-NMR analysis as a function of time (Scheme 3.29). The transformation proceeded smoothly providing sulfonyl ester **3.64a** in quantitative yield, yet flash chromatography was employed to remove any residual impurities resulting in diminished yields.



3.63a **3.64a**

Scheme 3.29. Mesylation of *cis*-ketol **3.63a**.

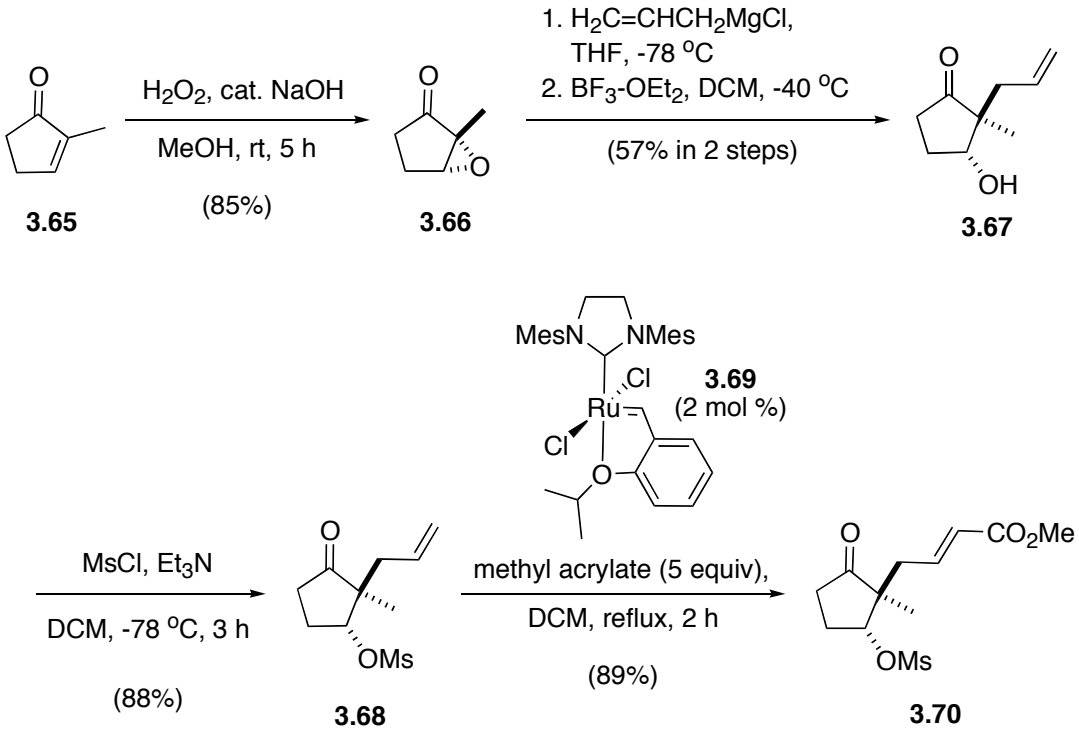
3.4.1.3. Diastereospecific Substrate Preparation

There is only one established method for the diastereospecific preparation of *trans*-ketols, namely semi-pinacol rearrangement of the precursor α-epoxycarbinol. In Chapter 2, we demonstrated such a transformation beginning from commercially available 2-methyl-2-cyclopenten-1-one. A similar strategy was used to diastereoselectively synthesize a *cis*-methanesulfonyl enoate.

As seen in Scheme 3.30, treatment of commercially available 2-methyl-2-cyclopenten-1-one (**3.65**) using H_2O_2 in the presence of a substiochiometric quantity of sodium hydroxide[168] provided epoxide **3.66** in good yield. Addition of allylmagnesium chloride to **3.66** furnished the desired α-epoxycarbinol, which was stereospecifically rearranged to the *trans*-2,2-disubstituted-1,3-ketol (**3.67**) using a variation of Walsh and Jeon's procedure.[64] The secondary alcohol was

[168] Winter, B. Process for the preparation of alkyl 3-oxo-2-pentyl-1-cyclopentene acetates. U.S. Patent # 5,302,745. Issued April 12, 1994.

mesylated[54] then transformated to enolate **3.70** through a cross-metathesis with methyl acrylate using catalytic quantities of Hoveyda-Grubbs-II catalyst (**3.69**).[169]



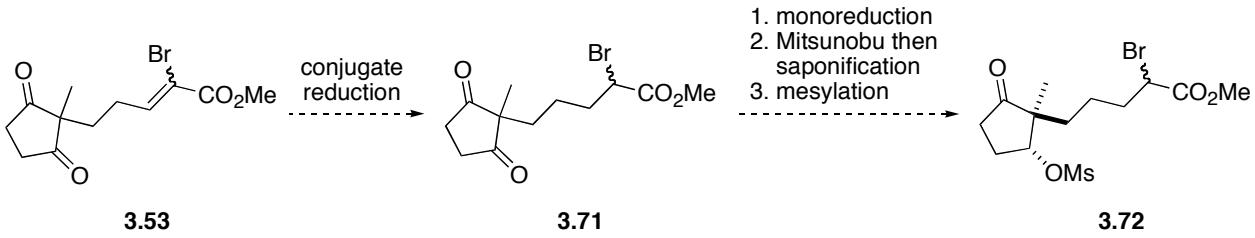
Scheme 3.30. Synthesis of enoate **3.70**.

3.4.2 Early Reductive Aldol Chemistry

3.4.2.1. The Initial Discovery

Having successfully accessed dione **3.53**, we experimented with different conjugate reduction methododologies in an attempt to convert the enoate moiety to the corresponding α-bromo ester (**3.71**) prior to applying the monoreduction/mesylation transformations en route to Reformatskii/Grob substrate **3.72** (Scheme 3.31). Since the conjugate reduction of an α-bromo-α,β-unsaturated carbonyl had not previously been reported, we assumed significant effort would be spent developing an effective methodology.

[169] For example see: Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, Jr., P. J.; Hoveyda, A. H. "A Recyclable Ru-Based Metathesis Catalyst." *J. Am. Chem. Soc.* **1999**, *121*, 791-797.



3.53 **3.71** **3.72**

Scheme 3.31. Synthetic strategy to *trans*-mesylate **3.72**.

The several examples of conjugate reductions mediated by nickel,[170] magnesium,[171] rhodium,[172] and palladium[173] metals, salts and/or organometallic complexes are reported in the literature. A brief survey of these readily available methodologies resulted in failure to obtain

[170] Examples of nickel-catalyzed conjugate reductions: (a) Jana, P. P.; Sarma, R.; Baruah, J. B. "Reduction of α,β-unsaturated carbonyl compounds by palladium(II) and nickel(II) complexes having nitrogen-containing ligands." *J. Mol. Cat. A.: Chem.* **2008**, *289*, 57-60. (b) Khurana, J. M.; Sharma, P., "Chemoselective Reduction of α,β-Unsaturated Aldehydes, Ketones, Carboxylic Acids, and Esters with Nickel Boride in Methanol–Water." *Bull. Chem. Soc. Jpn.* **2004**, *77*, 549–552. (c) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Meneses, R., "Raney Nickel: An Efficient Reagent to Achieve the Chemoseletive Hydrogenation of α,β-unsaturated carbonyl compounds." *Synlett*, **1999**, *10*, 1663-1666.

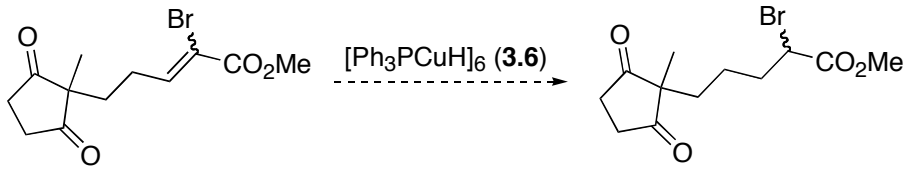
[171] Gabriëls, S.; Haver, D. V.; Vandewalle, M.; De Clercq, P.; Viterbo, D. "On the Unexpected Stereochemical Outcome of the Magnesium in Methanol—Conjugate Reduction of an Exocyclic α,β-Unsaturated Ester." *Eur. J. Org. Chem.* **1999**, 1803-1809.

[172] Examples of rhodium-catalyzed conjugate reductions: (a) Tsuchiya, Y.; Kanazawa, Y.; Shiomi, T.; Kobayashi, K.; Nishiyama, H. "Asymmetric Conjugate Reduction of α,β-Unsaturated Esters with Chiral Rhodium(bisoxazolinylphenyl) Catalysts." *Synlett* **2004**, 2493-2496. (b) Motherwell, W. B. "Curiosity and simplicity in the invention and discovery of new metal-mediated reactions for organic synthesis." *Pure Appl. Chem.* **2002**, *74*, 135-142. (c) Evans, D. A.; Fu, G. C., "Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds by Catecholborane." *J. Org. Chem.* **1990**, *55*, 5678-5680. (d) Ojima, I.; Kogure, T. "Reduction of Carbonyl Compounds via Hydrosilylation. 4. Highly Regioselective Reductions of α,β-Unsaturated Carbonyl Compounds." *Organometallics* **1982**, *1*, 1390-1399. (e) Liu, X.; West, F. G. "Construction of fused bis(pyran) units from enones *via* hydrosilylation-dihydroxylation-acetalization-reduction sequence." *Chem. Commun.* **2006**, 5036-5038. (f) Bocknack, B. M.; Wang, L.-C.; Krische, M. J. "Desymmetrization of enone-diones via rhodium-catalyzed diastereo- and enantioselective tandem conjugate addition-aldol cyclization." *Proc. Nat. Acad. Sci.* **2004**, *101*, 5421-5424.

[173] Examples of palladium-catalyzed conjugate reductions: (a) Keinan, E.; Greenspoon, N. "Highly chemoselective reductions with polymethylhydrosiloxane and palladium(0) catalyst." *J. Org. Chem.* **1983**, *48*, 3545-3548; (b) Keinan, E.; Greenspoon, N. "Highly chemoselective palladium-catalyzed conjugate reduction of α,β-unsaturated carbonyl compounds with silicon hydrides and zinc chloride catalyst." *J. Am. Chem. Soc.* **1986**, *108*, 7314-7325.

3.71. For example, application of Liu and West's procedure[172e] to hydrosilylate **3.53** using Wilkinson's catalyst and triethylsilane, PMHS or triethoxysilane resulted in starting material recovery even at high temperatures. Similarly, experimentation with nickel boride-mediated conjugate reduction[170a] and catecholborane hydroboration using Evans/Fu conditions[172c] resulted in starting material recovery. Magnesium metal in methanol[171] and palladium-mediated catalytic hydrogenation resulted in consumption of **3.53** with no isolable product.

We eventually considered experimenting with copper-based reagents. In extensive literature review, we found copper(I) hydride hexamer **3.6** (Stryker's reagent) most appealing for two reasons. First, use of Stryker's reagent in organic synthesis has been well documented since the late 1980's. Although **3.6** has not been applied to the conjugate reduction of an α-bromo enoate, we reasoned that its reported versatility would make it a viable option for effecting the desired transformation (i.e. obtaining **3.71**). Second, Yun's facile procedure for preparing **3.6** from $Cu(OAc)_2$[140] was appealing. Historically, upon synthesis of **3.6**, isolation of the complex required the use of a glovebox—a tool not readily available in our research group. Thus, as seen in Scheme 3.32, we envisioned an in situ preparation of the reagent followed by introduction of **3.53** to access **3.71**.

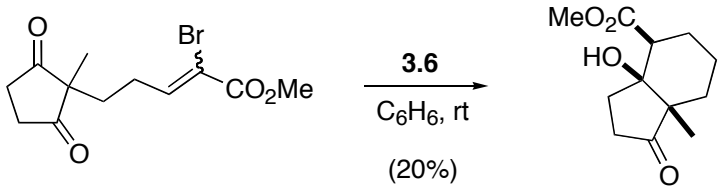


3.53 **3.71**

Scheme 3.32. The proposed synthesis of **3.71** using **3.6**.

Following Yun's procedure, Stryker's reagent (**3.6**) was prepared from the reaction of Ph_3P, PMHS and $Cu(OAc)_2$ in dry, deoxygenated benzene or toluene.[140] The reaction typically

took 5 h in total to prepare, as seen in the formation of a characteristic red color of the reaction mixture, without isolation of the copper(I) hydride complex (**3.6**). Dione **3.53** was introduced to the reaction mixture and appeared consumed, observed by TLC analysis of the crude reaction mixture, within 4 h. A mild workup with NH_4Cl followed by flash chromatography resulted in the isolation of a major spot among an array of 10-15 minor products. Spectroscopic analysis of the major product suggested the presence of 18 protons and 12 carbons. Furthermore, hi-resolution mass spectrometery detected a parent ion mass of 226.1200 g/mol. The results are consistent with desymmetrization of the starting material and the absence of the bromine atom. Based off of this evidence, we concluded that bromo enoate **3.53** had undergone cyclization to the bicyclic 1,3-ketol **3.73** in a transformation known as a reductive aldol reaction (Scheme 3.33). Initial XRD experiments of **3.73** confirmed cyclization and suggested that the ester, alcohol and methyl moieties shared a *syn*-arrangement about the face of the cyclohexane.



3.53 **3.73**

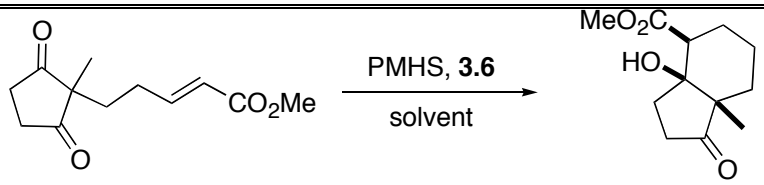
Scheme 3.33. The conversion of **3.53** to bicycle **3.73**.

The reductive aldol reaction has been reported by several groups and in each case, the presence of an α-bromide in the α,β-unsaturated carbonyl was not required for the transformation, thus raising a question over the importance of the bromine atom in **3.53**. Repetition of this experiment with dione **3.62** resulted in isolation of bicycle **3.73** in 52% yield among a mix of several minor impurities.

3.4.2.2. In Situ Stryker's Reagent Experiments

Introduction of **3.62** into the solution of active complex **3.6** (prepared in situ)[140] resulted in consumption of the starting material, optimally, in 4 h (Table 3.1). These reductive aldol reactions were found to provide bicycle **3.73** as the exclusive major product, though each reaction was accompanied by a large quantity of side products. In reaction times beyond 4 h, the yield of **3.73** was diminished, presumably due to side product formation. Increasing the amount of precatalyst used to prepare a solution of **3.6** resulted in greater by-product formation as determined by TLC and ^{1}H-NMR analyses of the reaction mixture. Interestingly, the reactions run at temperatures lower than -20 ^{o}C resulted in no conversion and recovery of **3.62**. Additionally, the isolated products were often accompanied by residual PMHS, seen as silane impurities in the ^{1}H-NMR spectrum.

Table 3.1. Reductive aldol cyclization of enoate **3.62** using in situ-prepared Stryker's reagent.



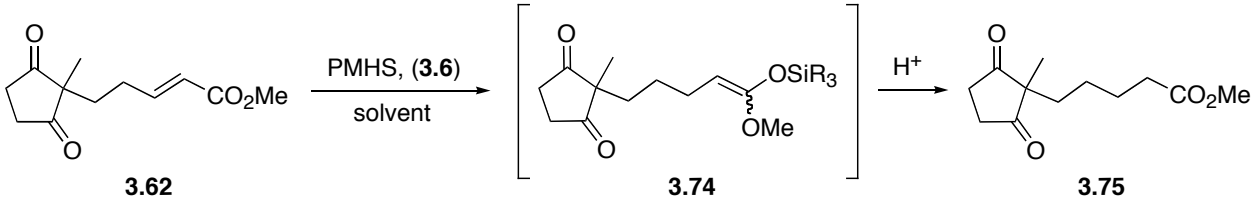
3.62 **3.73**

Substrate	*Cu* (equiv)	*Solvent*	*T* (^{o}C)	*t* (h)	*Yield* (%)[a]
1	1.0	C_6H_6	rt	0.5	22%
2	1.0	C_6H_6	rt	1	37%
3	1.0	C_6H_6	rt	1	43%
4	1.0	C_6H_6	rt	4	55%
5	1.0	C_6H_6	rt	7	42%
6	1.2	C_6H_6	rt	1.25	33%
7	1.0	PhMe	-15	6.5	14%
8	1.0	PhMe	-15	12	23%
9	1.0	PhMe	-15	20	41%
10	1.0	PhMe	-45	5	N/R
11	1.0	PhMe	-78	5	N/R

[a]Isolated yield after purification by flash chromatography.

3.4.2.3. Side Product Formation

The majority of side product formation probably occurs in one of two ways. First, as seen in Scheme 3.34, conjugate reduction of **3.62** without ensuing cyclization can provide ester **3.75**. Krische and Koech reported a similar observation in their Rh-catalyzed variation of these reactions.[174] Given the stringent reaction conditions for preparing **3.6**, protonation of silyl ketene acetal **3.74** does not seem likely. However, $Cu(OAc)_2$ is widely known to be strongly hygroscopic, often existing as the dihydrate. Though unlikely, residual molecules of water might cause enolate quenching thus providing ester **3.75**. Additionally, if **3.74** exists for an extended length of time (i.e. cyclization is not immediate), quenching of the reaction mixture with an acid source during workup would result in formation of conjugate reduction product **3.75**. This notion was evidenced by the isolation of **3.75** in trace quantities (~5% yield) from the reductive aldol reaction of **3.62**.



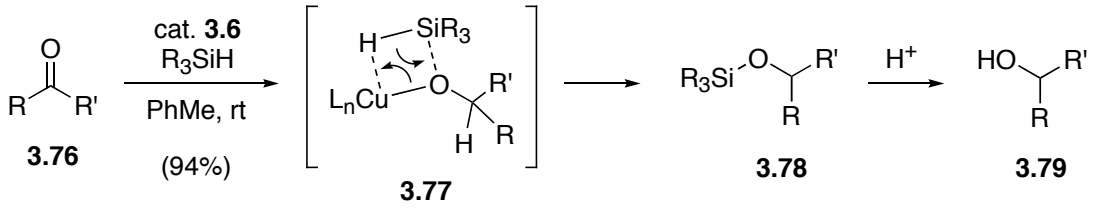
3.62 **3.74** **3.75**

Scheme 3.34. Stryker's reagent mediated conjugate reduction of enoate **3.62**.

Additionally, the 1,2-hydrosilylation of ketones and aldehydes has also been reported in reactions employing catalytic quantities of **3.6** in the presence of hydrosilanes.[175] Other examples of these reactions have been reported in the synthesis of (protected) alcohols.[176] As

[174] Koech, P. K.; Krische, M. J. Catalytic Addition of Metallo-Aldehyde Enolates to Ketones: A New C-C Bond-Forming Hydrogenation. *Org. Lett.* **2004**, *6*, 691-694.
[175] Lipshutz, B. H.; Chrisman, W.; Noson, K. "Hydrosilylation of aldehydes and ketones catalyzed by $[Ph_3P(CuH)]_6$." *J. Organomet. Chem.* **2001**, *624*, 367-371.
[176] For examples see: (a) Kantam, M. L.; Laha, S.; Yadav, J.; Likhar, P. R.; Sreedhar, B.; Jha, S.; Bhargava, S.; Udayakiran, M.; Jagadeesh, B. "An Efficient Copper-Aluminum Hydrotalcite

seen in Scheme 3.35,[175] 1,2-hydrosilyation of a carbonyl is believed to proceed through σ-bond metathesis (**3.77**) leading to the creation of a silyl ether (**3.78)**. Upon workup, the silyl group on **3.78** is cleaved furnishing the corresponding alcohol (**3.79**) in excellent yields. According to Lipshutz's seminal work on the topic, hydrosilylation occurs approximately five-times faster for aldehydes than ketones.



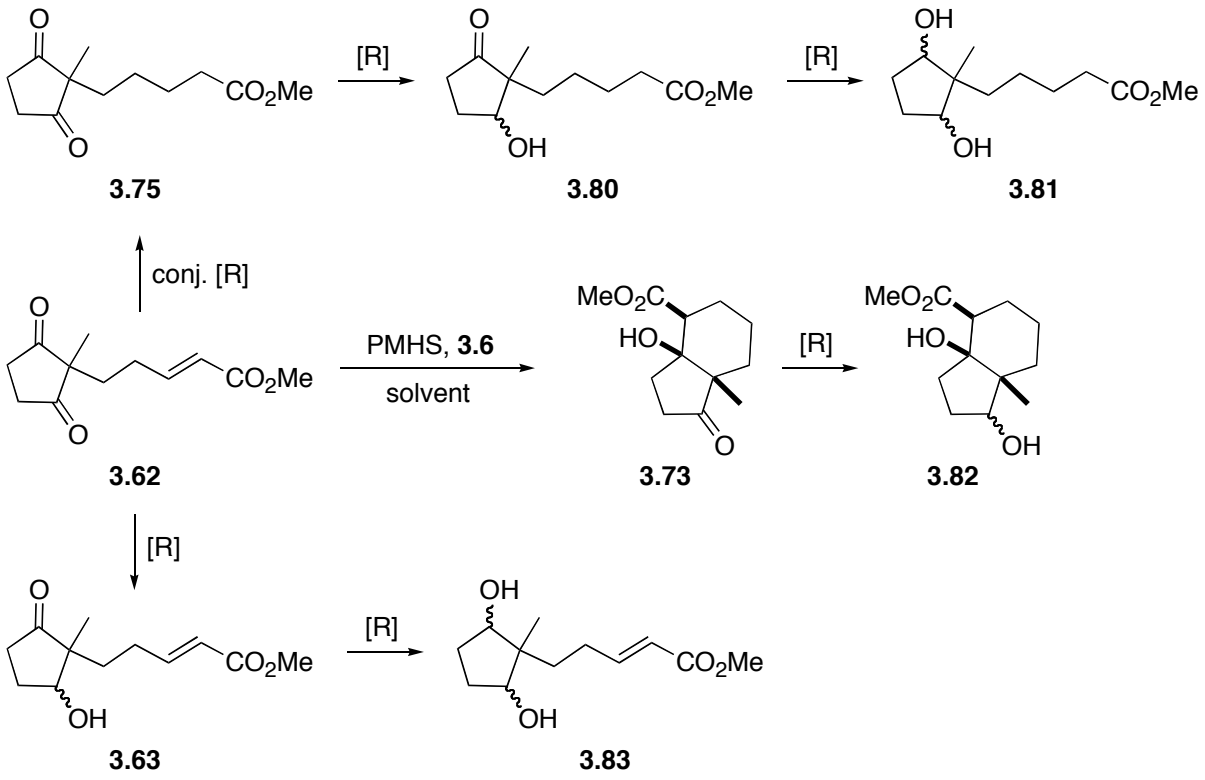
Scheme 3.35. Stryker's reagent-catalyzed 1,2-hydrosilylation.

Assuming 1,2-hydrosilylation is a possible route for biproduct formation, compounds **3.62**, **3.73** and possibly **3.75** could be reduced to complex diastereomeric mixtures of alcohols. Though Pitzer strain makes cyclopentanone reduction thermodynamically unfavorable, presence of the copper acting as a Lewis acid may lower the activation energy required to hydrosilylate the ketone as suggested by *ab initio* calculations.[177] Additionally, similar 1,2-hydrosilylation side products were reported by Lam[141] and Shibasaki.[178]

Catalyst for Asymmetric Hydrosilylation of Ketones at Room Temperature." *Org. Lett.* **2008**, *10*, 2979-2982. (b) Sirol, S.; Courmacel, J.; Mostefai, N.; Riant, O. "Efficient Enantioselective Hydrosilylation of Ketones Catalyzed by Air Stable Copper Fluoride-Phosphine Complexes." *Org. Lett.* **2001**, *3*, 4111-4113.

[177] Zipoli, R.; Bernasconi, M.; Laio, A. "Ab Initio Simulations of Lewis-Acid-Catalyzed Hydrosilylation of Alkynes." *ChemPhysChem* **2005**, *6*, 1772-1775.

[178] Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. "Catalytic enantioselective intermolecular reductive aldol reaction to ketones." *Tetrahedron Lett.* **2006**, *47*, 1403-1407.



Scheme 3.36. Hydrosilylation side products in the reductive aldol reaction of **3.62**.

In an alternate experiment, we added complex **3.6**, isolated in a glovebox, to substrate **3.64** without the presence of excess silane and observed similar results—low yields of **3.74** (< 10%) and several side products.

3.4.2.4. DPPF Experiments

We endeavored to apply Lam's protocol[139,142] to our enoate dione substrate **3.64** to determine if the method offered any significant advantages over Stryker's reagent (**3.6**). Reactions were run in dry THF using $Cu(OAc)_2$ as the precatalyst, DPPF as the ligand and PMHS as the stoichiometric reducing agent.[179] Under these condtions, substrate **3.64** was

[179] (a) Senapati, K. K. Polymethylhydrosiloxane (PMHS). *Synlett* **2005**, 1960-1961. (b) Chandrasekhar, S.; Chandrashekar, G.; Babu, B. N.; Vijeender, K.; Reddy, K. V. Reductive etherification of carbonyl compounds with alkyl trimethylsilylesters using polymethylhydrosiloxane (PMHS) and catalytic $B(C_6F_5)_3$. *Tetrahedron Lett.* **2004**, *45*, 5497-5499.

consumed quickly when 2.0 equivalents of PMHS were employed. Though, the only isolable material in these reactions was bicycle **3.74**, whose spectroscopic properties were remarkably cleaner than previous Stryker's reagent experiments. However, use of PMHS in our initial experiments provided silane impurities that were difficult to remove with multiple repurifications by flash chromatography. Additionally, lowering the temperature slowed the reaction but offered no improvement in the yield. Altering the stoichiometric reductant to triethoxysilane had no positive effect on the yields.

Table 3.2. Reductive aldol cyclizations of **3.62** using Lam's conditions.[139,141]

3.62 **3.73**

Entry	*Silane* (equiv)	*T* (°C)	*Time* (h)	*Yield* (%)[a]
1	PMHS (1.0)	rt	45	16[b]
2	PMHS (2.0)	rt	4	18
3	PMHS (2.0)	-15	46	20
4	$HSi(OEt)_3$ (2.0)	-15	12	19
5	$HSi(OEt)_3$ (1.0)[c]	rt	13	N/R
6	$HSi(OEt)_3$ (1.5)[c]	rt	20	21

[a]All reactions run to complete consumption of the starting material as evidenced by TLC analysis of the crude reaction mixture.
[b]Reaction mixture still contained S.M. at 45 h. Substrate recovery not taken into account in calculation of isolated yield
[c]Silane slowly added over 10 h.

The DPPF experiments provided some interesting insight about our reaction. First, as expected, by employing a catalytic process, spectroscopic analysis was much cleaner relative to using in situ-prepared Stryker's reagent (**3.6**). Each ^{1}H-NMR spectrum of the crude reaction mixture did not show substantial residual aryl peaks around 7 ppm, consistent with the presence of Ph_3P in Stryker's reagent. Second, a similar 1,2-hydrosilylation effect appeared to be

occurring with this method. The yields in Lam's experiments were reportedly modest, ranging from 40-78%. The mass balance difference in Lam's case accounted for "uncyclized side products" resulting from σ-bond metathesis of the intermediate copper enolate with the siloxane.

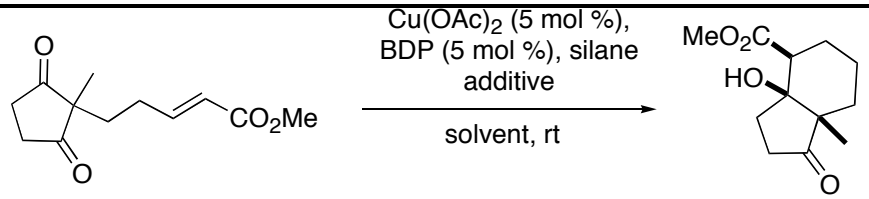
3.4.2.5. BDP Experiments

In a private conversation with Bruce Lipshutz,[180] he suggested experimenting with his 1,2-bis(diphenylphosphino)benzene (BDP) method—a catalytic, "hot" Stryker's reagent[126a]—in attempting to access bicycle **3.74**. Lipshutz's original procedure, which was optimized for conjugate reduction purposes, prescribed the addition of ^{t}BuOH to accelerate the reaction by providing a proton source to quench the silyl ketene acetal, similar to the protocol reported by Buchwald and co-workers.[127]

In employing the BDP ligand,[126a] we observed significant rate enhancement (i.e. starting material consumption) particularly when the alcohol was added (Table 3.3, Entry 2). Though, in all cases, yields were poor presumably due to formation of 1,2-hydrosilylation products evidenced by the characteristic formation of methine resonances in the ^{1}H-NMR spectrum between 4.0 and 4.3 ppm. Again, use of PMHS resulted in silane impurities observed in the ^{1}H-NMR spectrum. Switching PMHS to $HSi(OEt)_3$ resulted in a cleaner reaction mixture with fewer silylated impurities yet offered no significant effect on the yield. Treatment of these reactions with TBAF upon workup did not increase the yield of **3.74**. Additionally, lower quantities of reductant led to slightly better yields but with poorer conversion.

[180] We thank Professor Bruce Lipshutz and Ben Baker, University of California Santa Barbara Department of Chemistry, for their kind donation of the BDP ligand, in April 2008.

Table 3.3. Reductive aldol cyclization of **3.64** using Lipshutz' conditions.[126a]



3.64 **3.74**

Entry	*Silane* (equiv)	*Additive* (equiv)	*Solvent*	*t* (h)	*Yield* (%)
1	PMHS (6.0)	--	PhMe	18	9%
2	PMHS (6.0)	^{t}BuOH (6.0)	PhMe	0.5	5%
3	$HSi(OEt)_3$ (2.0)	--	THF	13	5%[a,b]
4	$HSi(OEt)_3$ (2.0)	--	PhMe	13	0%[a,b]
5	$HSi(OEt)_3$ (1.0)	--	THF	16	18%[a,c,d]

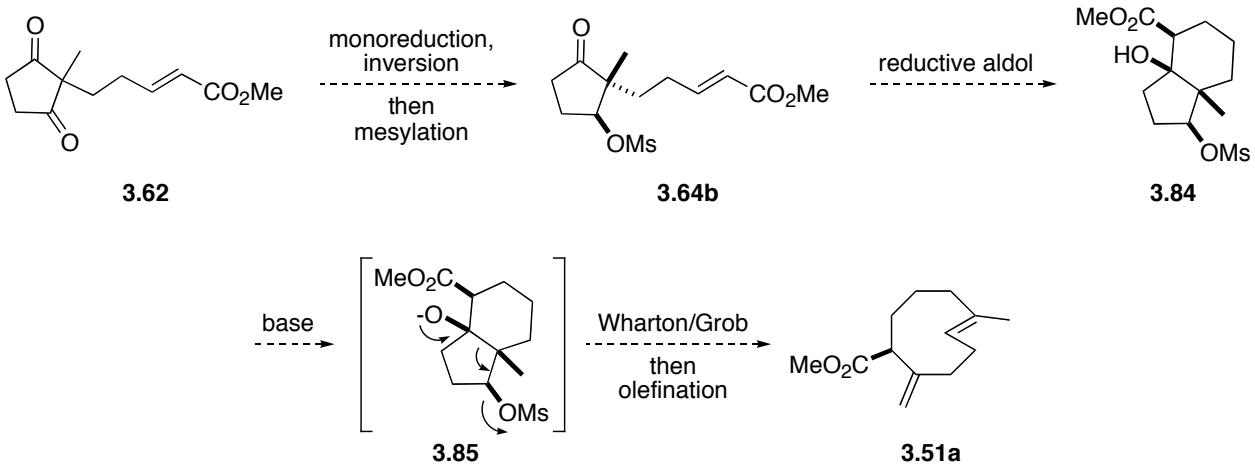
[a]Upon substrate consumption, the reaction mixture was treated with several equivalents of 1 M TBAF/THF.
[b]Major isolated material appeared to be the cyclized diol (**3.82**).
[c]Slow syringe pump addition of silane over 10 h.
[d]^{1}H-NMR of crude reaction mixture at 16 h suggested 18% bicycle formation, 40% diol formation and 42% SM remaining.

Early reductive aldol experiments were informative in identifying a protocol for reductive aldol conditions used to prepare common intermediate **3.50** and carbocycle **3.51a**. The reactions involving DPPF and BDP ligands offered good conversion, evidenced in the consumption of starting material yet poor yields. We hypothesize that 1,2-hydrosilylation of the pendant ketones in **3.64** is the major byproduct pathway. In an attempt to mitigate byproduct formation, we observed that moderation of the temperature resulted in poorer conversion.

3.4.3. Reductive Aldol on β-Keto Sulfonyl Ester Substrates

3.4.3.1. *cis*-Ketol Substrate

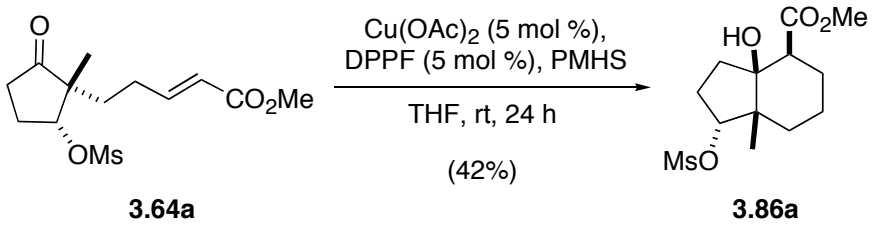
Our tentative synthetic strategy was to effect a Grob fragmentation after the Reformatskii or reductive aldol carbon-carbon bond-forming event. As seen in Scheme 3.37, the initial plan would involve monoreduction of dione **3.62** followed by Mitsunobu inversion providing the *trans*-ketol then ensuing mesylation to access **3.64b**. We saw the mesylate as a potential pseudo-protecting group[181] that could mitigate 1,2-hydrosilylation by removing one of the pendant carbonyls in **3.62**. Additionally, since we envisioned incorporating the reductive aldol chemistry with the Wharton-type Grob fragmentation (**3.85**), installation of a good nucleofuge was mandated. Positioning of the subtituents in **3.85** (i.e., a *cis* configuration) would allow for formation of the endocyclic (*E*)-olefin stereospecifically during the ring expansion step.



Scheme 3.37. Synthetic strategy toward accessing **3.51a**.

[181] Jung, M. E.; Sun, D. "Stereoselective Production of β-Amino Alcohols and β-Thioacyl Alcohols via an Application of the non-Aldol Aldol Process." *Tetrahedron Lett.* **1999**, *40*, 8343-8346.

In failing to invert the stereocenter in **3.63a** (*vide supra*), we chose to subject **3.64a** to reductive aldol conditions. Exposure of **3.64a** to Lam's conditions[139,142] using PMHS as the stoichiometric reducing agent provided bicycle **3.86a** in 42% yield (Scheme 3.38).

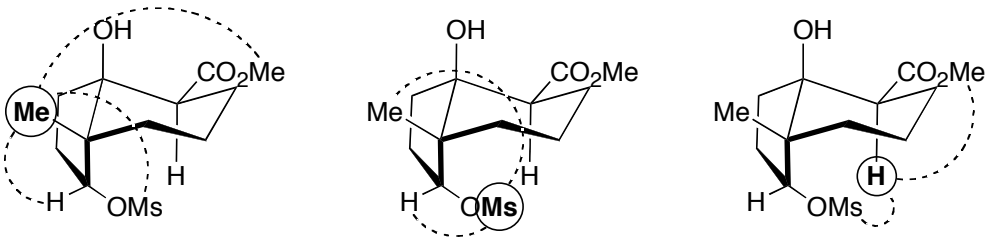


3.64a **3.86a**

Scheme 3.38. Reductive aldol cyclization of **3.64a** using Lam's conditions.[139,142]

HRMS data suggested that the major product (**3.86a**) had a molecular weight of 306.1145 g/mol, which is consistent with reductive aldolization. The most deshielded resonance (176.5 ppm) in the ^{13}C-NMR spectrum suggested presence of an ester. Additionally, a strong, broad stretch at 3483 cm^{-1} in the IR spectrum was indicative of alcohol formation, also observed in the ^{1}H-NMR spectrum as a sharp singlet at 3.27 ppm. The prominence of a strong OH might be the result of intramolecular hydrogen bonding with the proximal ester moiety. Similar hydrogen bonding was reported by Chiu in her synthesis of lucinone.[136]

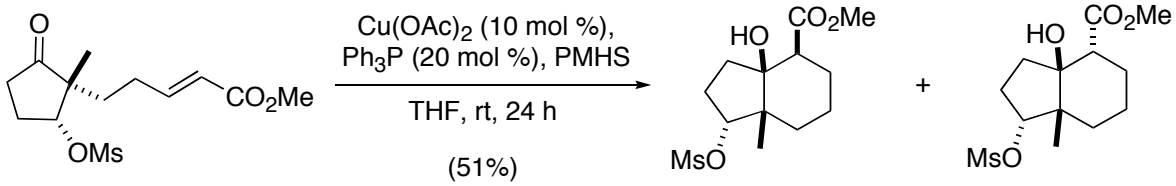
Several nOe difference experiments (Figure 3.8), supported the placement of the relative stereochemical substitutents in **3.86a**. Irradiation of the quaternary methyl (structure **A**) at 1.14 ppm resulted in enhancement of the methyl ester, methane sulfonyl ester and the adjacent methine hydrogen. Similarly, irradiation of the methane sulfonyl ester (structure **B**) caused enhancement of the methine and quaternary methyl hydrogens. Finally, irradiation of the ester methine hydrogen doublet of doublets at ~2.60 ppm (structure **C**) resulted in enhancement of the adjacent methyl ester and mesylate. Collectively, this data strongly supports formation of **3.86a**.



3.86a - A **3.86a - B** **3.86a - C**

Figure 3.8. Representitive nOe correlations of **3.86a**.

Given our laboratory's large supply of Ph_3P (relative to DPPF), we envisioned preparing a catalytic version of Stryker's reagent employing $Cu(OAc)_2$ (10 mol%) as the precatalyst and PMHS (five equivalents) as the stoichiometric reducing agent. After formation of the active copper(I) hydride, indicated by a red/brown color, introduction of **3.64a** provided bicycle **3.86a** in yields similar to those seen using Lam's conditions (Scheme 3.39). The qualitatively clean reaction mixtures (TLC) allowed for isolation of trace quantities of a minor isomer consistent with formation of **3.86b**. Addition of one molar equivalent of TBAF (per every hydride) prior to workup resulted in the best yields (51%), though it was not possible to account for the remainder of the reactant mass. ^{1}H-NMR analysis of the purged flash column and early fractions provided no additional products.



3.64a **3.86a** **3.86b**

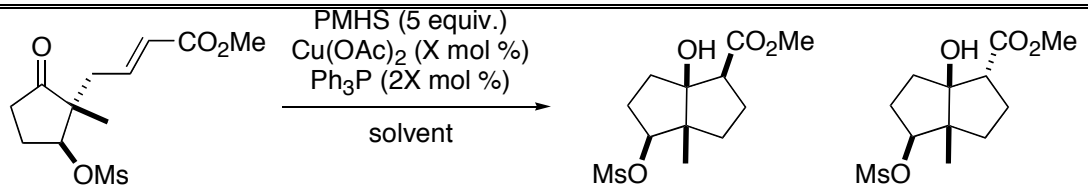
Scheme 3.39. Reductive aldol cyclization of **3.64a** employing a variation of Yun's conditions.[140]

3.4.3.2. *trans*-Ketol Substrate

Formation of the active copper(I) hydride (**3.6**) followed by introduction of enoate **3.71** resulted in good conversion after 20 h in THF when 5 mol % $Cu(OAc)_2$ was used (Table 3.5).

Though, the diastereomeric ratio of products suggested a preference for the formation of **3.87b**. Optimal conversion was observed when 10 mol % $Cu(OAc)_2$ was employed and the reaction was quenched after 20 h. In switching to non-coordinating solvents such as toluene, active catalyst formation was notably difficult due to the poor solubility of $Cu(OAc)_2$. However, substrate **3.70** was consumed over an order of magnitude faster in this solvent system while still giving slight preference to the formation of **3.87b**.

Table 3.4. Optimization of reductive cyclization method of enoate **3.70**.



3.70 **3.87a** **3.87b**

Entry	*"Cu-H"* (mol %)[a]	*Solvent*	*T* (°C)	*t* (h)	*dr* (**a**:**b**)[b]	*Conv.* (%)[b]
1	5	THF	rt	2	1:1.2	37
2	5	THF	rt	5.5	1:1.3	44
3	5	THF	rt	20	1:1.3	86
4	10	THF	rt	2	1:1.4	35
5	10	THF	rt	5.5	1:1.4	67
6	10	THF	rt	20	1:1.4	>95
7	20	THF	rt	2.5	1:1.5	>95
8	10	PhMe	rt	2	1:2.0	>95
9	10	PhMe	rt	22	1:1.7	>95
10	5	PhMe	rt	1	1:2.1	>95
11	5	PhMe	0 °C	1	1:1.1	>95
12	5	PhMe	-78 °C	7	--	0[c]

[a]Based on the amount of precatalyst added.
[b]Based on ^{1}H-NMR analysis of crude reaction mixture.
[c]Recovery of starting material

Solvation of the organocopper ketene acetal ether may create a stabilizing effect,[49] which decreases the reactivity of the enolate during cyclization. Additionally, THF could separate charged species in solution, mitigating the Lewis acidity of Cu(I) present in the solution. Non-

coordinating solvents such as toluene and benzene offer the advantage of a tighter, more compact transition state resulting in a faster conversion state versus THF.

Examination of two hypothetical transition states constructed from molecular models may account for the stereochemical outcome in the reaction, as seen in Figure 3.9. Both intermediates **3.88a** and **3.89a** adopt six-membered ring transition states. Intermediate **3.88a** appears to resemble a boat-like transition state in the carbon-carbon bond forming event, whereas the transition state in **3.89a** is chair-like and thus is likely lower in energy (~6 kcal/mol).[182] This energetic difference offers some rationalization the preference for forming **3.87b** over **3.87a**.

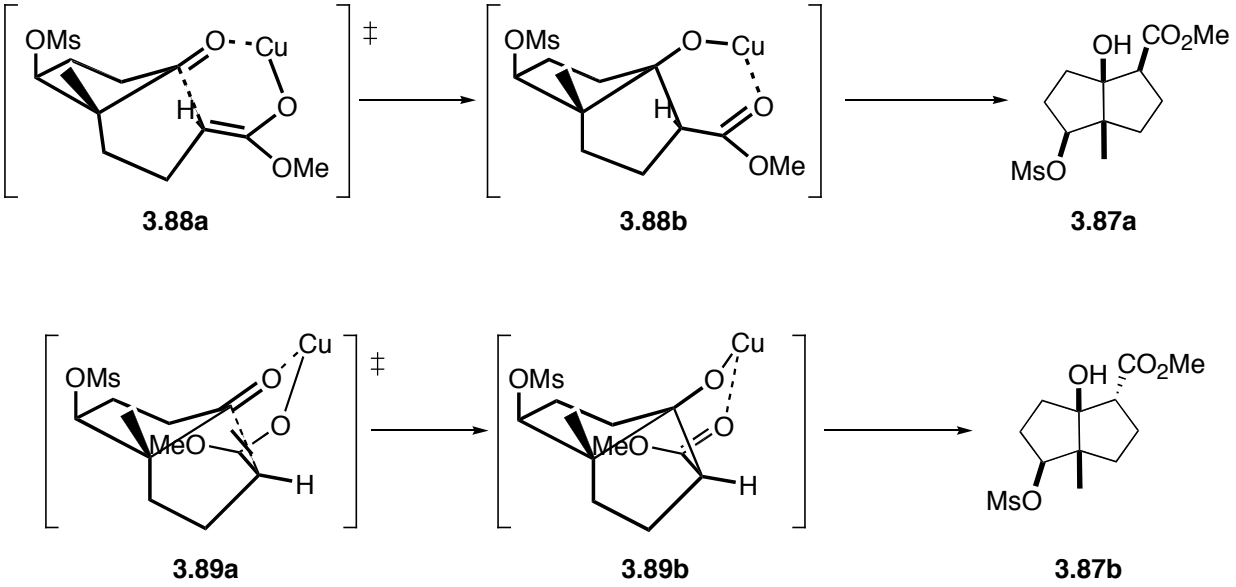


Figure 3.9. Examination of possible transition states in the carbon-carbon bond forming events in the formation of **3.87a/b**.

3.4.4. Reductive Aldol Conclusions

Though not complete, our reductive aldol experiments have established a basis protocol for effecting the desired cyclization of keto enoates to the corresponding β-hydroxy esters. Our

[182] Jones, Jr.; M. *Organic Chemistry*; 2nd ed.; W. W. Norton & Company, Inc.: New York, 2000, p 181.

substrates feature a sulfonyl ester group, which mitigates competitive 1,2-hydrosilylation and functions as a strong nucleofuge in future fragmentation reactions. Additionally, we have developed a useful copper(I)-hydride system, derived from inexpensive laboratory reagents, capable of mediating the reductive aldol chemistry, evidenced by the complete conversion of enoate **3.70**. Future experiments will include the optimization of the diastereoselectivity outcome and workup conditions thereby providing the desired bicyclic products in high yield and diastereoselectivity. Additionally, we plan to incorporate tandem Wharton-type Grob chemistry in an effort to ultimately access **3.51a** in "one pot" from **3.64a**.

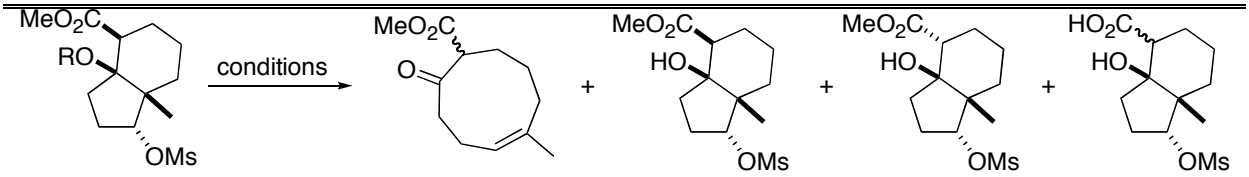
3.4.5. Wharton-Type Grob Fragmentation Experiments

Access to bicyclic mesylate **3.86a**, in albeit low yields, inspired experimentation with Wharton-type Grob fragmentation conditions. An overview of these reactions is provided in Table 3.5. Although examples are limited, fluoride-induced Grob fragmentations have been reportedly known to proceed well in highly strained systems.[183] Reductive aldol of the enoate **3.64a** followed by exposure to TBAF resulted in conversion of the starting material into a complex mixture of products (Entries 1 and 2).[184] Treatment of the alcohol with NaH in DMF resulted in demethylation of the ester as evidenced in analysis of the reaction mixture by ^{1}H-NMR. Upon workup, acidification of the aqueous layer furnished material consistent with a saponified product. Similar results were observed when the substrate was treated with KO*t*-Bu and 18-crown-6 in THF. Employing Molander's fragmentation conditions (Entry 6) resulted in

[183] (a) Tietze, L.-F.; Reichert, U. "Fluoride-Induced Fragmentation of Trimethylsiloxysuflonates to Form *cis*-Coupled Hexahydrozulenones." *Angew. Chem. Int. Ed.* **1980**, *19*, 830-831. (b) Gerlach, H. "2-(Trimethylsilyl)äthylester als Carboxylschutzgruppe; Anwendung bei der Synthese des (-)-(*S*)-Curvularins." *Helv. Chim. Acta* **1977**, *60*, 3039-3044.
[184] Zhang, W.; Dowd, P. "Double ring expansions: A new method for making medium and large cyclic ketones." *Tetrahedron Lett.* **1996**, *37*, 957-960.

the formation of a new product, believed to be the stereoisomer of the ester based on nOe experiments of the isolated material. This transformation is believed to be a result of a base-mediated retroaldol-aldol addition reaction. Though, as seen in Entry 7, saponification was observed when the solvent was switched to DMF using NaOMe as the base. Treatment of the bicycle with DBU and benzene (Entries 8 and 9) also resulted in a retroaldol-aldol addition outcome.

Table 3.5. Wharton-type Grob fragmentation experimental outcomes.



3.88/3.86a **3.54b** **3.86a** **3.86b** **3.88**

Entry	*R* (Structure)	*Base* (equiv)	*Conditions*	*Result*
1	SiR_3 (**3.88**)		TBAF, THF, 20 h	Complex Mixture
2			TBAF, THF, reflux, 2 h	Complex Mixture
3	H (**3.86a**)	NaH (1.2)	DMF, rt, 1 h	Saponification (**3.88**)
4		NaOtBu (1.2)	*t*-BuOH, 45 ^{o}C, 8 h	Saponification (**3.88**)
5		KOtBu (1.2)	18-crown-6 (1.2 equiv), THF, rt, 5 h	Saponification (**3.88**)
6		NaOMe (2)	MeOH, rt, 13 h	Retroaldol (**3.86a/b**) (2:1 **a**:**b**)
7		NaOMe (2)	DMF, rt, 24 h	Saponification (**3.88**)
8		DBU (2)	C_6H_6, rt, 48 h	SM Recovery (**3.86a**)
9		DBU (2)	C_6H_6, 45 ^{o}C, 8 h	Retroaldol (**3.86 a/b**) (1.2:1 **a**:**b**)

In examining molecular models of the lowest energy conformer, it became clear that the C-C π* and C-O σ* orbitals do not optimally align for a fragmentation (Figure 3.10). MM2 calculations of the lowest energy conformer[152] suggest that the fragmenting bond and the mesylate C-O bond have a dihedral angle of 84^{o}, well short of the requisite 180^{o} for an

antiperplanar orientation. The presumably rigid system may preclude significant bending or rotation of the orbitals thereby preventing fragmentation.

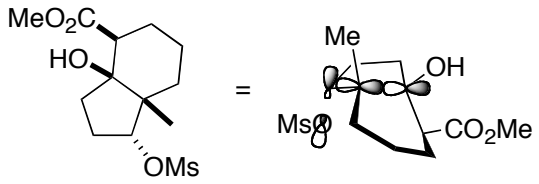
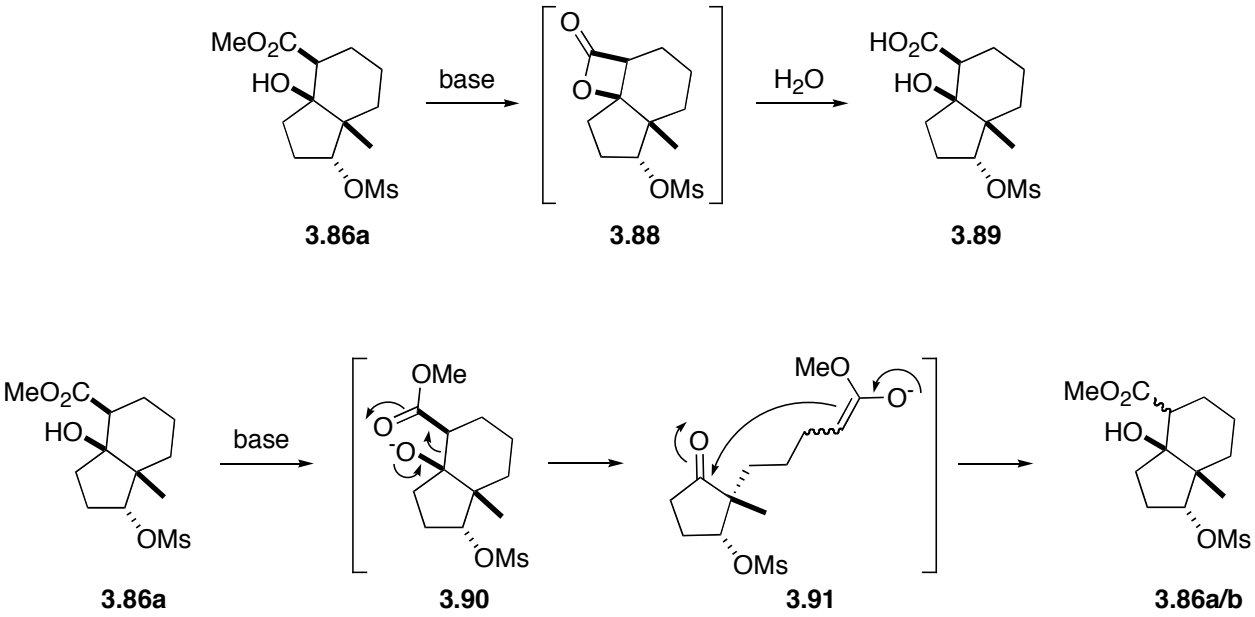


Figure 3.10. Misalignment of π* and σ* orbitals in **3.86a**.

The outcomes of the attempted Wharton-type Grob fragmentation experiments can be explained through lactonization and/or retroaldolization-aldol addition (Scheme 3.40). The saponification product (**3.88**) might be a result of formation of intermediate propiolactone (**3.89**), as described by Romo and co-workers.[185] Though β-lactonization is an unfavorable process, the inherent rigidity in the ring may optimally orient the alkoxide and methyl ester allowing for cyclization to occur upon deprotonation. Additionally, since deprotonation does not provide the desired fragmented product, C-C bond cleavage by way of carbonyl reformation (**3.90**), and retroaldolization, and aldol addition (**3.91**) can account for an alteration of stereochemistry. Similar results have been reported in the preparation of rigid bicyclic 3-hydroxy enoates.[186]

[185] Cortez, G. S.; Tennyson, R. L.; Romo, D. "Intramolecular, Nucleophile-Catalyzed Aldol-Lactonization (NCAL) Reactions: Catalytic Asymmetric Synthesis of Bicyclic β-Lactones." *J. Am. Chem. Soc.* **2001**, *123*, 7945-7946.

[186] (a) Moloney, M. G.; Yaqoob, M. "Equilibration in bicyclic pyroglutamates by ring opening-reclosure." *Tetrahedron Lett.* **2008**, *49*, 6202-6204. (b) White, J. D.; Cutshall, N. S.; Kim, T.-S.; Shin, H. "Total Synthesis of (+/-)-Euonyminol, the Sesquiterpenoid Nucleus of Cathedulin K-19, via an Epoxide Cascade Cyclization." *J. Am. Chem. Soc.* **1995**, *117*, 9780-9781.



Scheme 3.40. Representative side reactions occurring from attempted Wharton-type Grob Fragmentations in **3.86a**.

3.4.6. Conclusion

In screening several protocols for reductive aldol chemistry, **3.53** and **3.62** dione substrates were believed to undergo competitive 1,2-hydrosilylation resulting in diminished yields of reductive aldol products. This effect was mitigated when dione **3.62** was converted to sulfonyl ester **3.64a** then cyclized to **3.86a** as evidenced by the increased yield of the reaction relative to other methods tried. Attempts at expanding **3.86a** to carbocycle **3.54b** resulted in stereocenter racemization and/or saponification of the methyl ester. Additionally, treatment of mesylate **3.74** with catalytic Stryker's reagent conditions provided a diastereomeric mixture of bicyclic products in excellent conversion. We see a tandem reductive aldol/Grob fragmentation approach as a plausible route toward ultimately synthesizing common intermediate **3.50**.

3.5. Experimental Details

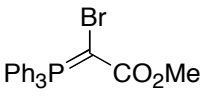
3.5.1. General Remarks

Tetrahydrofuran (THF) benzene, toluene and diethyl ether were distilled from sodium/benzophenone ketyl radical under argon prior to use. Dichloromethane (DCM) was distilled over CaH_2 under an atmosphere of argon. Acrolein (90%) was purchased from Aldrich and distilled under an atmosphere of air prior to use. Anhydrous methanol (99.8%) and *N*,*N*-dimethylformamide (DMF, 99.8%) and 1 M *n*-tetrabutylammonium fluoride in THF were purchased from Aldrich in Sure/Seal bottles and used as received. Triethoxysilane (95%), copper(II) acetate (98%), triphenylphosphine (99%) and Hoveyda-Grubbs second generation catalyst (**3.69**) were purchased from Aldrich and used directly. Polymethylhydrosiloxane (PMHS) and lithium tri-*tert*-butoxyaluminum hydride LTBA (93-98%) were purchased from Acros and used as received. Starting materials 2-methylcyclopentane-1,3-dione (99%, **3.57**) and methyl (triphenylphosphoranylidene)acetate (98%, **3.60**) were purchased from Aldrich and used directly. Enone (98%, **3.65**) was purchased from SAFC and used directly. Air sensitive materials were handled using standard anoxic transfer techniques employing argon.

Proton magnetic resonance spectra (^{1}H-NMR) were recorded at either 360 or 500 MHz. Carbon magnetic resonance spectra (^{13}C-NMR) were recorded on spectrometers operating at either 91 or 127 MHz. All spectra are referenced to TMS internal standard where applicable, otherwise referenced to solvent internal standard (C_6D_6: ^{1}H-NMR, 7.16 ppm; ^{13}C-NMR, 128.1 ppm) Nuclear Overhauser enhancement (nOe) difference spectroscopy experiments were performed on a 500 MHz spectrometer. Infrared spectroscopy data (IR) was recorded on a Jasco FT/IR-4100. High-resolution mass spectrometry (HRMS) was performed on an AutoSpec-Ultima NT. Flash column chromatography was performed using Silicycle silica gel (230-400

mesh). TLC visualization was achieved by ultraviolet light (254 nm), I_2 vapors, or an acidic *p*-anisaldehyde or vanillin stain. Temperature for monoreductions was controlled using an immersion cooler (NESLAB CC-100).

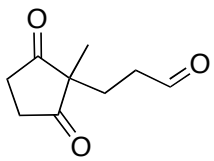
3.5.2 Substrate Preparation



Methyl bromo(triphenylphosphoranylidene)acetate (3.59). To a stirred solution of methyl (triphenylphosphoranylidene)acetate (**3.60**, 2.00 g, 5.98 mmol) in 2N HCl (18 mL) was added a solution of KBr (534 mg, 4.49 mmol) in dH_2O (25 mL) at room temperature slowly over 20 min. Upon complete addition, a solution of $KBrO_3$ (333 mg, 2.00 mmol) in dH_2O (25 mL) was slowly added through a separatory funnel at room temperature over 45 min. The reaction mixture was kept at room temperature for an additional 5 h, at which point the solution was treated with KOH (5 mL, 50% wt) resulting in precipitation of a beige solid. The resultant material was recrystallized in EtOAc/hexanes to provide the title compound (1.52 g, 3.68 mmol, 62%) as yellow/brown granules (mp: 165 ^oC; lit. 167-168 ^oC). The product exhibited physical properties consistent with those reported in the literature.[61]

^{1}H-NMR (360 MHz, C_6D_6): δ 7.68-7.62 (m, 6H); 7.06-6.93 (m, 9H); 3.62 (s, 3H).

^{13}C-NMR (91 MHz, C_6D_6): δ 134.4; 134.3; 132.1; 132.0; 127.7; 128.6; 126.8; 50.8.

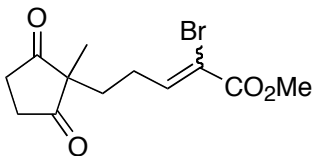


2-methyl-2-propanal-1,3-cyclopentanedione (3.56). To a vigorously stirred slurry of 2-methyl-1,3-cyclopentanedione (**3.57**, 2.00 g, 17.8 mmol) and dH_2O (4.6 mL) was added freshly distilled acrolein (2.2 mL, 33 mmol, 1.9 equiv) The reaction became homogenous and colorless after 12 h of stirring. After stirring for 3 d, the reaction mixture was diluted with DCM (10 mL) and vigorously stirred for 10 min. The

resulting emulsion was filtered over Celite and rinsed with DCM (50 mL) and dH_2O (20 mL). Upon an initial separation, the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic extracts were washed with brine (1 x 20 mL), dried ($MgSO_4$) and concentrated to give a cloudy, colorless oil. This crude material was filtered over a short plug of silica using DCM as the eluent (200 mL), which afforded the title compound (2.03 g, 12.1 mmol, 70%) as a slightly cloudy, colorless oil. This material exhibited spectroscopic properties previously reported.[154,162]

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.68 (t, 1H, J = 1.0 Hz); 2.86-2.75 (m, 4H); 2.48 (dt, 2H, J = 7.5, 1.0 Hz); 1.94 (t, 2H, J = 7.5 Hz); 1.14 (s, 3H).

^{13}C-NMR (127 MHz, $CDCl_3$): δ 215.5, 200.6, 55.1, 38.4, 34.8, 26.1, 19.3.

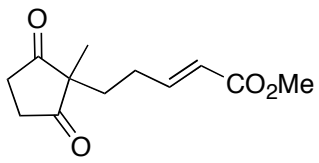


(2*Z*/*E*)-Methyl 2-bromo-5-(2'-methyl-1',3'-dioxocyclopent-2'-yl)-pent-2-enoate (3.53). To a stirred solution of aldehyde **3.56** (1.67 g, 10.0 mmol) in dry toluene (20 mL) was added Wittig reactant **3.59** (4.55 g, 11.0 mmol, 1.10 equiv). The homogeneous reaction mixture was refluxed at 150 ^{o}C for 1 h under argon then cooled to room temperature and concentrated via rotary evaporation. The resultant beige residue was purified by flash chromatography (3:1 hexanes:EtOAc) to provide an inseparable diastereomeric mixture (4:1, *Z*/*E*) of the title compound (2.40 g, 7.91 mmol, 79%) as a clear, colorless oil. The product exhibited physical properties consistent with those reported in the literature.[154]

^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.15 (t, 1H, J = 7.6 Hz, *Z* isomer); 6.52 (t, 1H, J = 7.3 Hz, *E* isomer); 3.82 (s, 3H, *Z* isomer); 3.81 (s, 3H, *E* isomer); 2.90-2.70 (m, 4H); 2.42-2.35 (m, 2H, *E*

isomer); 2.28-2.21 (m, 2H, *Z* isomer); 1.86-1.80 (m, 2H); 1.16 (s, 3H, *Z* isomer); 1.14 (s, 3H, *E* isomer).

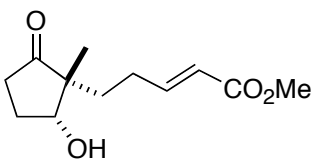
^{13}C-NMR (91 MHz, $CDCl_3$): δ 215.7 (*Z* isomer); 213.8 (*E* isomer); 163.0 (*E* isomer); 126.5 (*Z* isomer); 146.5 (*E* isomer); 144.2 (*Z* isomer); 116.8 (*Z* isomer); 111.9 (*E* isomer); 56.2 (*E* isomer); 56.0 (*Z* isomer); 53.3 (*Z* isomer); 52.7 (*E* isomer); 35.0 (*E* and *Z* isomers); 32.9 (*E* isomer); 31.8 (*Z* isomer); 27.4 (*Z* isomer); 26.7 (*E* isomer); 20.0 (*E* isomer); 19.9 (*Z* isomer).



(2*E*)-Methyl 5-(2'-methyl-1',3'-dioxocyclopent-2'-yl)-pent-2-enoate (3.62). To a stirred solution of aldehyde **3.56** (1.94 g, 11.6 mmol) in dry toluene (23 mL) was added Wittig reagent **3.60** (3.89 g, 11.6 mmol, 1.00 equiv). The homogeneous reaction mixture was refluxed at 150 ^{o}C for 1 h then cooled to room temperature and concentrated via rotary evaporation. The resultant white residue was filtered through a 2" plug of silica using a 1:1 mixture of EtOAc:hexanes as eluent (400 mL). The filtrate was concentrated by rotary evaporation to give a crude oil, which solidified on standing. The crude solid was purified by flash chromatography (7:3 hexanes:EtOAc) to afford the title compound as a cloudy, colorless oil (2.32 g, 10.3 mmol, 89%). The product exhibited physical properties previously reported in the literature.[154]

^{1}H-NMR (360 MHz, $CDCl_3$): δ 6.81 (dt, 1H, *J* = 15.6, 6.8 Hz); 5.78 (dt, 1H, 15.6, 1.5 Hz); 3.71 (s, 3H); 2.90-2.70 (m, 4H); 2.14-2.07 (m, 2H); 1.82-1.78 (m, 2H); 1.15 (s, 3H).

^{13}C-NMR (91 MHz, $CDCl_3$): δ 215.9; 166.5; 147.2; 121.6; 55.9; 51.3; 34.8; 32.4; 27.0; 19.6.



Methyl 5-[*cis*-3'-hydroxy-2'-methylcyclopentan-1'-one]-pent-2-enoate (3.63a). To a stirred solution of dione **3.62** (1.02 g, 4.54 mmol)

in THF (23 mL) cooled to -60 ^{o}C was added LTBA (1.39 g, 5.45 mmol, 1.20 equiv) in one portion. The reaction proceeded at -60 ^{o}C until starting material was judged consumed by TLC (~22 h). The cold reaction was quenched with 1 N HCl (9 mL) then diluted with dH_2O (10 mL) and EtOAc (20 mL). Upon initial separation, the aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine (1 x 20 mL), dried ($MgSO_4$) then concentrated by rotary evaporation to give a clear colorless oil. The resultant crude product was purified by flash chromatography over silica (1:1 EtOAc:hexanes) to provide a diasteromeric mixture of **3.63a** and **3.63b** (842 mg, 3.72 mmol, 82%, 3:1 **a**:**b**). Repurification of the material by flash chromatography (1:1 EtOAc:hexanes) provided the title compound (566 mg, 2.50 mmol, 55%) as a clear, colorless oil. The isolated ketol exhibited physical properties previously reported in the literature.[187]

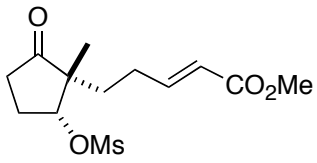
^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.99 (dt, 1H, *J* = 15.5, 6.9 Hz); 5.86 (dt, 1H, *J* = 15.5, 1.4 Hz); 4.12 (dd, 1H, *J* = 8.0, 3.9 Hz); 3.72 (s, 3H); 2.51-2.44 (m, 1H); 2.34-2.19 (m, 4H); 2.13 (d, 1H, *J* = 3.5 Hz); 1.98-1.91 (m, 1H); 1.76-1.70 (m, 1H); 1.66-1.61 (m, 1H); 1.01 (s, 3H).

^{13}C-NMR (127 MHz, $CDCl_3$): δ 220.3; 167.2; 149.4; 120.9; 77.2; 52.7; 51.5; 33.9; 28.4; 28.2; 26.8; 19.2.

IR (thin film cm^{-1}): 3464; 2954; 1724; 1655.

HRMS: calcd. For $C_{12}H_{18}O_4$ $[M]^+$ 226.1999, found 226.2001.

[187] Katoh, T.; Mizumoto, S.; Fudesaka, M.; Nakashima, Y.; Kajimoto, T.; Node, M. "Inversion of Diastereoselectivity Depending on Substrate Concentration in Baker's Yeast Catalyzed Reduction of σ-Symmetrical 1,3-Cyclopentadiones and 1,3-Cyclohexadiones." *Synlett* **2006**, 2176-2182.



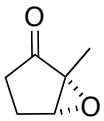
Methyl 5-[*cis*-3'-(methanesulfonyloxy)-2'-methylcyclopentan-1'-one]-pent-2-enoate (3.66a). To a stirred solution of 2,2-disubstituted-1,3-ketol **3.63a** (42 mg, 0.186 mmol) in DCM (6 mL) cooled to -78 ^{o}C for 20 min was added TEA (52 μL, 0.37 mmol, 2.0 equiv) then MsCl (22 μL, 0.28 mmol, 1.5 equiv). The solution proceeded at -78 ^{o}C until starting material was judged consumed by ^{1}H-NMR analysis of an aliquot of the crude reaction mixture (~3 h). The cold solution was quenched with brine (3 mL) then thoroughly mixed while warming to rt. Upon an initial separation, the aqueous layer was extracted with Et_2O (2 x 10 mL) resulting in the formation of a white precipitate (Et_3N•HCl) in the organic layer, which was removed by decantation. The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$) then concentrated by rotary evaporation. The resultant oil was purified by flash chromatography over SiO_2 (6:4 hexanes:EtOAc) to provide the title compound (42 mg, 0.19 mmol, 74%) as a clear, slightly yellow oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.94 (dt, 1H, *J* = 15.6, 6.8 Hz); 5.86 (dt, 1H, *J* = 15.6, 1.4 Hz); 5.06 (dd, 1H, *J* = 4.0 Hz); 3.72 (s, 3H); 3.06 (s, 3H); 2.56-2.49 (m, 1H); 2.45-2.21 (m, 5H); 1.77-1.70 (dq, 1H, *J* = 14.1, 11.8, 5.5 Hz); 1.67-1.61 (dq, 1H, *J* = 14.1, 11.8, 5.1 Hz); 1.11 (s, 3H)

^{13}C-NMR (127 MHz, $CDCl_3$): δ 216.4; 166.9; 148.2; 121.4; 85.5; 52.0; 51.5; 38.9; 33.7; 28.9; 26.3; 26.2; 19.2.

IR (thin film cm^{-1}): 3465; 3026; 2951; 1722; 1657.

HRMS: calcd. For $C_{13}H_{18}O_6S$ $[M]^+$ 304.0975, found 304.0976.



2,3-Epoxy-2-methylcyclopentan-1-one. (3.66) To a stirred solution of 2-methyl-2-cyclopenten-1-one (**3.65**, 2.4 mL, 24 mmol) in anhydrous MeOH (25 mL) cooled to 0

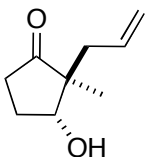
^{o}C was added 50% H_2O_2 (1.50 mL, 26.5 mmol, 1.09 equiv) and NaOH (200 mg, 5.00 mmol, 0.205 equiv). The reaction proceeded at 0 ^{o}C for 10 min, then was allowed to gradually warm to room temperature. After 3 h at rt, the reaction was cooled to 0 ^{o}C and a second portion of 50% H_2O_2 (1.50 mL) and NaOH (200 mg) was added, mixed at 0 ^{o}C for 10 min then allowed to gradually warm to rt. At 8 h (total reaction time), the reaction was treated with anhydrous K_2CO_3 (517 mg, 3.74 mmol, 0.156 equiv) and stirred at rt for 30 min. The reaction mixture was diluted with dH_2O (10 mL) and DCM (20 mL). Upon an initial separation, the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL), dried ($MgSO_4$) and concentrated by rotary evaporation to give a clear, colorless oil. Flash chromatography (1:1 DCM:hexanes) of the crude product provided the title compound (2.31 g, 20.4 mmol, 85%) as a clear colorless oil.

^{1}H-NMR (360 MHz, $CDCl_3$): δ 3.78 (s, 1H); 2.40-2.26 (m, 2H); 2.14-2.08 (m, 1H); 2.03-1.96 (m, 1H); 1.45 (s, 3H).

^{13}C-NMR (127 MHz, $CDCl_3$): δ 210.8; 64.1; 60.9; 31.2; 22.3; 10.0.

IR (thin film cm^{-1}): 1741; 1260; 1235.

HRMS: calcd. For $C_6H_8O_2$ $[M]^+$ 112.0524, found [M+H] 113.0603.



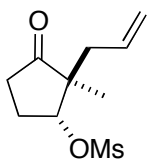
(±)-*trans*-3-hydroxy-2-allyl-2-methylcyclopentanone (3.67). To a stirred solution of epoxide **3.66** (1.76 g, 15.7 mmol) in THF (47 mL, 0.33 M) cooled at -78 ^{o}C was added 2.0 M allylmagnesium chloride (7.9 mL, 16 mmol, 1.0 equiv) via glass syringe slowly over 10 min. The reaction proceeded at -78 ^{o}C for 1.5 h at which point another equivalent of allylmagnesium chloride (7.9 mL, 16 mmol, 1.0 equiv) was slowly added over 10 min via glass syringe. Upon consumption of the starting material (TLC, ~30 min), the

reaction was slowly quenched with the addition of sat. solution of NH_4Cl (20 mL). The solution was then diluted with dH_2O (20 mL) and EtOAc (20 mL). Upon an initial separation, the aqueous layer was extracted with EtOAc (3 x 30 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated by rotary evaporation. The resultant crude oil was purified by flash chromatography (8:2 hexanes:EtOAc) to provide an inseparable mixture (9.7:1, *cis*:*trans*) of **(±)-**1-allyl-2-methyl-2,3-epoxycyclopentan-1-ol (1.99 g, 12.9 mmol, 82.0%) as a clear, colorless oil.

To a stirred solution of the semi-pure epoxy-carbinol (1.99 g, 12.9 mmol) in DCM (65 mL, 0.2 M) cooled to -78 ^oC was slowly added BF_3•OEt_2 from a glass syringe. The reaction mixture gradually warmed to rt over 16 h adopting a dark red/purple color. The reaction mixture was quenched with the addition of a saturated aqueous solution of $NaHCO_3$ (20 mL) and dH_2O (20 mL). Upon an initial separation, the organic layer was washed with brine (1 x 20 mL). The combined aqueous layers were reextracted with DCM (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated by rotary evaporation to give a dark, purple oil. Purification of the crude product by flash chromatography (7:3 hexanes:EtOAc) provided **3.67** as an orange/yellow oil (1.39 g, 9.01 mmol, 57% over 2 steps). The compound exhibited spectroscopic properties previously reported in the literature.[74c]

^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.81-5.72 (m, 1H); 5.13-5.09 (m, 2H); 4.24-4.21 (m, 1H); 2.51-2.44 (m, 1H); 2.29-2.14 (m, 4H); 1.90-1.83 (m, 1H); 1.69 (d, 1H, J = 3.8 Hz); 1.02 (s, 3H).

^{13}C-NMR (127 MHz, $CDCl_3$): δ 219.8; 133.6; 118.7; 75.4; 52.9; 39.8; 34.9; 27.5; 15.0.



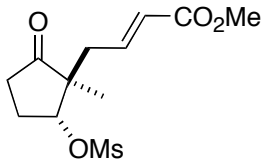
(±)-*trans*-3-methanesulfonyloxy-2-allyl-2-methylcyclopentan-1-one (3.68). To a stirred solution of 2,2-disubstituted-1,3-ketol **3.67** (1.00 g, 6.49 mmol) in DCM (32 mL) cooled to -78 ^{o}C for 20 min was added TEA (1.8 mL, 13 mmol, 2.0 equiv) then MsCl (0.77 mL, 9.7 mmol, 1.5 equiv). The solution proceeded at -78 ^{o}C until starting material was judged consumed by ^{1}H-NMR analysis of and aliquot of the crude reaction mixture (~3 h). The cold solution was quenched with brine (30 mL) then thoroughly mixed while warming to rt. Upon an initial separation, the aqueous layer was extracted with Et_2O (3 x 30 mL) resulting in the formation of a white precipitate (Et_3N•HCl) in the organic layer, which was removed by decantation. The combined organic layers were washed with brine (1 x 30 mL), dried ($MgSO_4$) then concentrated by rotary evaporation. The resultant oil was purified by flash chromatography over SiO_2 (6:4 hexanes:EtOAc) to provide the title compound (1.33 g, 5.71 mmol, 88%) as a pale, yellow oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.72-5.63 (m, 1H); 5.19-5.11 (m, 3H); 3.05 (s, 3H); 2.57-2.50 (m, 1H); 2.48-2.40 (m, 1H); 2.31-2.17 (m, 4H); 1.09 (s, 3H).

^{13}C-NMR (127 MHz, $CDCl_3$): δ 216.5; 132.0; 120.1; 83.6; 52.6; 39.4; 38.6; 34.7; 26.3; 16.4.

IR (thin film cm^{-1}): 3634; 3529; 3473; 3081; 3023; 2982; 1741; 1638.

HRMS: calcd. For $C_{10}H_{16}O_4S$ $[M]^+$ 232.0769, found 232.0772.



Methyl 4-[*trans*-3'-(methanesulfonyloxy)-2'-methylcyclopentan-1'-one]-but-2-enoate (3.70). A solution of mesylate **3.68** (785 mg, 3.38 mmol) in dry DCM (17 mL) and methyl acrylate (1.52 mL, 16.9 mmol, 5 equiv) was sparged with Ar while stirring for 30 min. Hoveyda-Grubbs second-generation catalyst (43 mg, 0.068 mmol, 2 mol %) was added in one portion to the reaction mixture. The

reaction was refluxed at 75 ^{o}C under an atmosphere of argon until the starting material was judged consumed by TLC analysis (3 h). The reaction mixture was concentrated by rotary evaporation and the resultant dark green was purified by flash chromatography (1:1 EtOAc:hexanes) to provide the title compound (874 mg, 3.01 mmol, 89.0%) as a dark green oil.

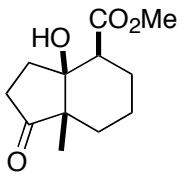
^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.79 (dt, 1H, *J* = 7.8, 15.4 Hz); 5.94 (dt, 1H, *J* = 1.2, 15.4 Hz); 5.05 (t, 1H, *J* = 6.1 Hz); 3.73 (s, 3H); 3.07 (s, 3H); 2.62-2.55 (m, 1H); 2.49-2.44 (m, 1H); 2.41 (d, 2H, *J* = 7.8 Hz); 2.31-2.19 (m, 2H); 1.11 (s, 3H).

^{13}C-NMR (127 MHz, $CDCl_3$): δ 216.4; 166.9; 148.2; 121.4; 85.5; 52.0; 51.5; 38.9; 33.7; 28.9; 26.3; 26.2; 19.2.

IR (thin film cm^{-1}): 3465; 3026; 2951; 1722; 1657.

HRMS: calcd. For $C_{12}H_{18}O_6S$ $[M]^+$ 290.0824, found 290.0836.

3.5.3. Reductive Aldol Products



(1*S,2*S**,6*S**)-2-Methoxycarbonyl-1-hydroxy-6-methylbicyclo[4.3.0]-nonan-7-one (3.67a).** To a stirred homogeneous solution of $Cu(OAc)_2$ (183 mg, 1 mmol), Ph_3P (525 mg, 2 mmol, 2 equiv) and dry C_6H_6 (5 mL, degassed by three freeze-pump-thaw cycles) was added polymethylhydrosiloxane (0.35 mL, 7.2 mmol, 7.2 equiv). The aqua blue reaction mixture adopted a strong red color after 3 h of mixing at rt. The reaction was mixed for an additional hour at rt, then a solution of the enoate **3.62** (224 mg, 1.00 mmol) diluted in dry, deoxygenated benzene (1 mL), prepared in a separate vessel, was cannulated to the cuprate solution with the aid of vacuum (over 5 min) and caused the reaction to immediately adopt a black/red color. The reaction proceeded at rt until the starting substrate appeared consumed by TLC analysis (4 h). The reaction was quenched with the addition of NH_4Cl (5 mL)

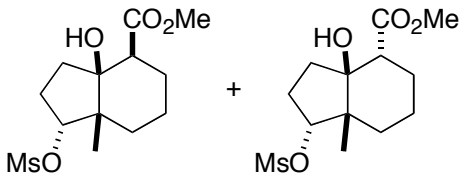
and mixed for an additional 30 min. Upon an initial separation, the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were concentrated and the resulting crude product was filtered over a sand/celite. The filtrate was concentrated by rotary evaporation then purified by flash chromatography flash chromatography (8:2 hexanes:EtOAc) to provide the title compound (124 mg, 0.549 mmol, 55%) as an off-white solid (mp: 76-78 ^{o}C).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.50 (s, 1H); 3.76 (s, 3H); 2.60-2.53 (m, 1H); 2.28-2.10 (m, 3H); 1.98-1.71 (m, 4H); 1.63-1.60 (m, 1H); 1.41-1.35 (m, 1H); 1.24-1.16 (m, 1H); 1.06 (s, 3H).

^{13}C-NMR (127 MHz, $CDCl_3$): δ 218.0; 176.4; 76.8; 53.6; 52.1; 47.8; 34.4; 31.2; 28.7; 25.1; 22.1; 19.0.

IR (thin film cm^{-1}): 3483; 2943; 1711.

HRMS: calcd. For $C_{12}H_{18}O_4$ $[M]^+$ 226.1208, found 226.1205.



(1*S,2*S**,6*S**,7*R**) -7-Methylsulfonyloxy-2-methoxycarbonyl-1-hydroxy-6-methylbicyclo [4.3.0]-nonane (3.86a) and (1*S**,2*R**,6*S**,7*R**)-7-Methylsulfonyloxy-2-methoxycarbonyl-1-hydroxy-6-methylbicyclo[4.3.0]-nonane (3.86b).**[140]

To a stirred solution of $Cu(OAc)_2$ (2.7 mg, 0.015 mmol, 5 mol %) and Ph_3P (7.9 mg, 0.030 mmol, 10 mol %) in THF (1 mL) was added polymethylhydrosiloxane (0.098 mL, 1.5 mmol, 5 equiv) causing a color change from aqua blue to red (~2 h). The methanesulfonyl enoate **3.66a** (100 mg, 0.329 mmol) was diluted in anhydrous PhMe (4 mL) then introduced to the reaction mixture via plastic syringe. The reaction proceeded at rt until the starting material was judged consumed by TLC analysis. The reaction was quenched with the addition of 1N TBAF/THF (5 mL, 5 equivalents) then vigorously stirred for an additional 3 h. The reaction was then treated

with NH_4Cl (5 mL) and stirred for an additional 30 min. Upon an initial separation, the aqueous layer was extracted with EtOAc (5 x 5 mL). The combined organic layers were washed with brine (1 x 20 mL), dried ($MgSO_4$) then concentrated to provide a crude product, which was purified by flash chromatography (7:3 hexanes:EtOAc) to give the **3.86a** (34 mg, 0.11 mmol, 33%) and **3.86b** (18 mg, 0.059 mmol, 18%) as clear, brown/yellow oils.

3.86a:

^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.90 (dd, 1H, *J* = 8.6, 5.3 Hz); 4.55 (brs, 1H); 3.74 (s, 3H); 2.99 (s, 3H); 2.71 (dd, 1H, J = 6.0, 5.0 Hz); 2.47-2.39 (m, 1H); 2.12-2.07 (m, 2H); 1.92-1.84 (m, 1H); 1.81-1.68 (m, 2H); 1.65-1.59 (m, 1H); 1.54-1.51 (m, 3H); 1.06 (s, 3H).

^{13}C-NMR (127 MHz, $CDCl_3$): δ 176.5; 90.5; 79.1; 52.1; 47.6; 46.3; 38.1; 34.7; 29.8; 27.2; 25.3; 19.8; 19.5.

IR (thin film cm^{-1}): 3483; 2943; 1711.

HRMS: calcd. For $C_{13}H_{22}O_6S$ $[M]^+$ 306.1137, found 306.1132.

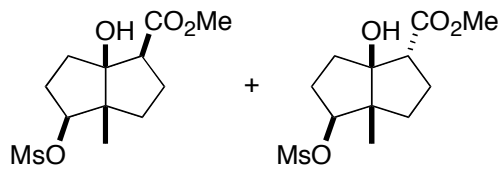
3.86b:

^{1}H-NMR (500 MHz, $CDCl_3$): 5.07 (dd, 1H, *J* = 8.8, 7.6 Hz); 3.71 (s, 3H); 3.21 (s, 1H); 3.00 (s, 3H); 2.59 (dd, 1H, *J* = 12.4, 4.3 Hz); 2.46-2.38 (m, 1H); 2.26-2.20 (m, 1H); 2.04-2.01 (m, 1H); 1.94-1.87 (m, 1H); 1.68-1.61 (m, 2H); 1.53-1.39 (m, 3H); 1.32-1.26 (m, 1H); 1.14 (s, 3H)

^{13}C-NMR (127 MHz, $CDCl_3$): 174.7, 90.1, 80.1, 52.0, 48.0, 47.4, 37.9, 30.7, 29.0, 26.1, 26.0, 20.0, 16.0

IR (thin film cm^{-1}): 3516, 2945, 2873, 1722, 1643

HRMS: calcd. For $C_{13}H_{22}O_6S$: 306.1137; found 306.1145



(1*S,2*S**,6*S**,7*S**) -7-Methylsulfonyloxy-2-methoxycarbonyl-1-hydroxy-6-methylbicyclo[3.3.0]-octane (3.87a) and (1*S**,2*R**,6*S**,7*S**)-7-Methylsulfonyloxy-2-methoxycarbonyl-1-hydroxy-6-methylbicyclo[3.3.0]-octane (3.87b).**[140] To a stirred solution of $Cu(OAc)_2$ (2.7 mg, 0.015 mmol, 5 mol %) and Ph_3P (7.9 mg, 0.030 mmol, 10 mol %) in THF (1 mL) was added polymethylhydrosiloxane (0.098 mL, 1.5 mmol, 5 equiv) at rt causing a color change from aqua blue to red (~2 h). The methanesulfonyl enoate **3.68** (96 mg, 0.33 mmol) was diluted in anhydrous THF (4 mL) in a separate vessel then introduced to the reaction mixture drop wise (over 5 min) via plastic syringe. The reaction proceeded at rt and at random time intervals (2, 5.5 and 20 h), a 0.5 mL aliquot was removed with a plastic syringe, concentrated by rotary evaporation and analyzed by ^{1}H-NMR spectroscopy to monitor reaction progress. At 21 h, the starting material appeared consumed (^{1}H-NMR analysis), and the reaction mixture was quenched with the addition of 1N TBAF/THF (3.5 mL, 3.5 mmol, 3.5 equivalents) then vigorously stirred at rt for an additional 3 h. The reaction was then treated with NH_4Cl (5 mL) and stirred for an additional 30 min. Upon an initial separation, the aqueous layer was extracted with EtOAc (5 x 5 mL). The combined organic layers were washed with brine (1 x 20 mL), dried ($MgSO_4$) then concentrated by rotary evaporation to provide a crude, oily residue which was purified by flash chromatography (6:4 hexanes:EtOAc) thus furnishing **3.87a** (11 mg, 0.038 mmol, 12%) and **3.87b** (16 mg, 0.054 mmol, 16%) as clear, colorless oils.

3.87a:

^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.71 (t, 1H, *J* = 4.0 Hz); 3.73 (s, 3H); 3.06 (s, 1H); 3.03 (s, 3H); 2.69 (dd, 1H, *J* = 6.9, 9.7 Hz); 2.12-1.84 (m, 6H); 1.74-1.70 (dq, 1H, *J* = 4.4, 6.9, 13.0 Hz); 1.54-1.48 (m, 1H); 1.09 (s, 3H).

^{13}C-NMR (127 MHz, $CDCl_3$): δ 174.0; 88.7; 88.2; 55.0; 54.8; 52.0; 38.5; 37.8; 37.2; 29.3; 26.7; 17.1.

IR (thin film cm^{-1}): 3419; 2936; 1747; 1197.

HRMS: calcd. For $C_{12}H_{20}O_6S$ $[M]^+$ 292.0975, found 292.0973.

3.87b:

^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.70 (t, 1H, *J* = 5.4 Hz); 3.74 (s, 3H); 3.03 (s, 3H); 2.85 (dd, 1H, *J* = 7.3, 11.7 Hz); 2.18 (brs, 1H); 2.12-1.99 (m, 2H); 1.93-1.87 (m, 1H); 1.83 (t, 2H, *J* = 7.5 Hz); 1.77-1.66 (m, 2H); 1.62-1.55 (m, 1H); 1.11 (s, 3H).

^{13}C-NMR (127 MHz, $CDCl_3$): δ 173.5; 89.3; 88.2; 54.4; 54.1; 51.9; 38.5; 36.2; 34.7; 30.4; 23.5; 17.9.

IR (thin film cm^{-1}): 3419; 2936; 1747; 1197.

HRMS: calcd. For $C_{12}H_{20}O_6S$ $[M]^+$ 292.0975, found 292.0973.

CHAPTER 4

THE PREPARATION OF INOTILONE DERIVATIVES

4.1 Introduction, Background and Significance

4.1.1. COX enzymes and their interactions with NSAIDs

In most mammalian cells, with the exception of erythrocytes,[188] prostaglandin synthase H_2 (PGH_2 synthase) biosynthetically converts arachidonic acid to prostanoids—hormones that mediate inflammatory reactions and maintain gastrointestinal (GI) mucosal integrity among other functions. Stimulation of cytosolic and secretory phospholipase A_2 causes saponification of glycerol on the luminal surface of the endoplasmic reticulum membrane to form arachidonic acid (AA).[189] As seen in Figure 4.1, AA is converted to the highly unstable intermediate prostaglandin G_2 (PGG_2), also known as cyclic endoperoxidase,[190] via a free radical mechanism initiated by Tyr-385.[191] PGG_2 is then reduced by the heme peroxidase active site of PGH_2 synthase to prostaglandin H_2 (PGH_2).

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[188] Biochemical Pathways: an atlas of biochemistry and molecular biology. Michal, G. Editor. Copyright 1999 by John Wiley & Sons, New York, NY. p. 200.
[189] Marnett, L. J.; Rowlinson, S. W.; Goodwin, D. C.; Kalgutkar, A. S.; Lanzo, C. A. Arachidonic Acid Oxygenation by COX-1 and COX-2. *J. Biol. Chem.* **1999**, *274*, 22903-22906.
[190] Eling, T. E.; Glasgow, W. C.; Curtis, J. F.; Hubbard, W. C.; Handler, J. A. Studies on the Reduction of Endogenously Generated Prostaglandin G2 by Prostaglandin H Synthase. *J. Biol. Chem.* **1991**, *266*, 12348-12355.
[191] Seibold, S. A.; Ball, T.; His, L. C.; Mills, D. A.; Abeysinghe, R. D.; Micielli, R.; Rieke, C. J.; Cukier, R. I.; Smith, W. L. Histidine 386 and Its Role in Cyclooxygenase and Peroxidase Catalysis by Prostaglandin-endoperoxidase H Synthases. *J. Biol. Chem.* **2003**, *278*, 46163-46170.

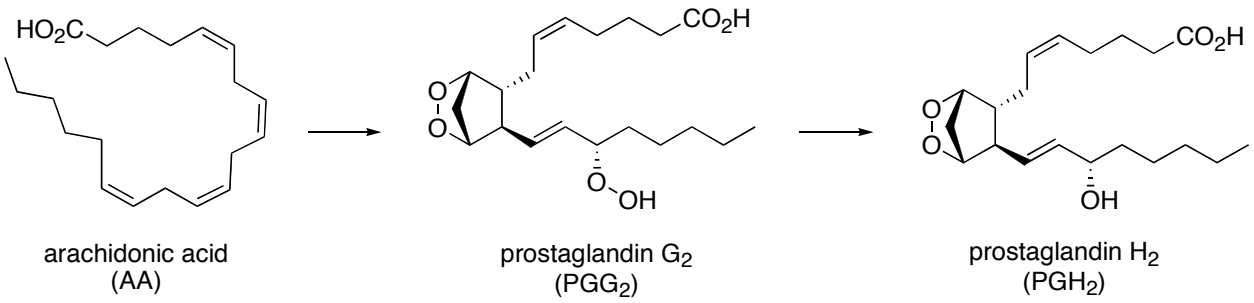
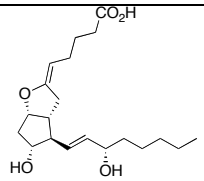
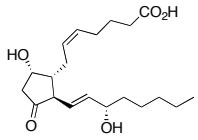
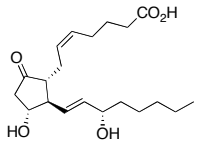
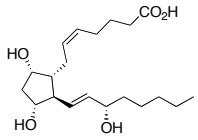
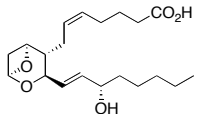


Figure 4.1. The conversion of AA to PGH_2.

"Post COX" transformations involve the conversion of PGH_2 into specific series-2 prostaglandins and thromboxanes. These processes are catalyzed by a myriad of different prostaglandin and thromboxane enzymes (Table 4.1). Each prostanoid signals specific receptors to effect major metabolic responses in humans including, but not limited to, vasodilatation, suppression of gastric acid secretion, inflammation and tissue growth.[192] Ultimately, the biological response is a function of the type of prostanoid or thromboxane synthesized.

[192] Bakhle, Y. S. COX-2 and cancer: a new approach to an old problem. *British J. Pharmacol.* **2001**, *134*, 1137-1150.

Table 4.1. Prostanoids biosynthesized from PGH_2.[188]

Prostanoid Structure	*Name*	*Receptor Occurrence*	*Major Metabolic Effect in Human*
	Prostacyclin I_2 (PGI_2)	Arterial endothelium, platelets, nerves	Vasodilation, inhibition of platelet aggregation, increase of water reabsorption in small intestine
	Prostaglandin D_2 (PGD_2)	Platelets, vascular smooth muscle, nerves	Inhibition of platelet aggregation, renal vasodilation, increased water reabsorption in small intestine
	Prostaglandin E_2 (PGE_2)	Ubiquitous: smooth muscle, adipocytes, kidney, lung, brain, veins	Inhibition of autonomic neurotransmitter release, lipolysis in adipocytes, suppression of gastric acid secretion, initiates endothelial growth factors and angiogenesis.
	Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)	Corpus lutenum, smoothe muscle, kidney, lung	Increase of uterus muscle tone, contraction of bronchial smooth muscle, inhibition of water reabsorption in the small intestine
	Thromboxane A_2 (TxA_2)	Vascular tissue, platelets, bronchial muscle, thymus	Vasoconstriction, induction of platelet aggregation, strong contraction of bronchial smooth muscle

Nonsteroid anti-inflammatory drugs (NSAIDs) inhibit COX activity of prostaglandin H_2 synthase.[193] As seen in Equation 4.1, an NSAID, such as ibuprofen, acts as a competitive inhibitor (I) to the COX active site of prostaglandin synthase (E) forming a reversible enzyme-inhibitor (E-I) complex.[194] Formation of this complex precludes AA from binding in the COX active site of PGH_2 synthase thus hindering prostanoid biosynthesis. Unreacted AA is metabolized through alternate biochemical routes (e.g., leukotriene synthesis). The ultimate biological response of COX inhibition is the temporary mitigation of inflammation and other

[193] Vane, J. R. "Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs." *Nat. New Biol.* **1971**, *231*, 232–235

[194] Selinsky, B. S.; Gupta, K.; Sharkey, C. T.; Loll, P. J. Structural Analysis of NSAID Binding by Prostaglandin H Synthase: Time-Dependent and Time-Independent Inhibitors Elicit Identical Enzyme Conformations. *Biochem.* **2001**, *40*, 5172-5180.

"housekeeping" chores, which includes gastrointestinal (GI) maintenance. Often, the side effects associated with chronic use of NSAIDs include gastric ulceration because the GI mucosal and pH regulatory mechanism is suspended while the COX-1 enzyme is inhibited.

$$E + I^A \longrightarrow [E\text{-}I^A] \xrightarrow{AA} [E\text{-}AA] + I^A \qquad \textbf{(Equation 4.1)}$$

By contrast, other NSAIDs effect a two-step process to result in a time-independent inhibitory effect (Equation 4.2). COX inhibitors such as flurbiprofen and indomethacin (I^B) form reversible complexes ($E\text{-}I^B$) within the hydrophobic pocket of the enzyme. This binding imparts a perturbation on the enzyme conformation allowing an adjacent active site to open, a process requiring approximately 10 kcal/mol.[195] Inhibitor binding in this active site results in irreversible enzyme complex ($E\text{-}I^B$*), preventing AA from entering and thus preventing the biosynthesis of prostaglandings or thromboxanes.

$$E + I^B \underset{}{\overset{I^B}{\rightleftharpoons}} [E\text{-}I^B] \longrightarrow [E\text{-}I^{B*}] \xrightarrow{AA} [E\text{-}AA] + I^B \qquad \textbf{(Equation 4.2)}$$

4.1.2. The Two Major COX Isozymes

Most higher organisms possess three separate isoforms of PGH_2 synthase. Although the literature commonly refers to the most of these enzymes as COX-1 and COX-2, these terms specifically refer to distinct cyclooxygenase active sites of PGH_2 synthases. The first discovered PGH_2 synthase (COX-1), reported by Vane and co-workers in the early 1971,[196] is constitutively expressed in most cells and responsible for the cellular "housekeeping" processes (e.g., GI maintenance, platelet upkeep, etc.). By comparison, the second discovered PGH_2 synthase

[195] So, O.-Y.; Scarafia, L. E.; Mak, A. Y.; Callan, O. H.; Swinney, D. C. "The dynamics of prostaglandin H synthase 2 Y355F unmask mechanisms of time-dependent inhibition and allosteric activation." *J. Biol. Chem.* **1996**, *273*, 5801-5807.
[196] Ferreira, S. H.; Moncada, S.; Vane, J. R. "Indomethacin and aspirin abolish prostaglandin release from the spleen." *Nature New Biol.* **1971**, *231*, 237-239.

(COX-2), reported by Simmons and co-workers in 1991,[197] is generally found at the sights of inflammation, tumors and cells comprising the central nervous system. In 2002, Simmons and co-workers reported two additional variations of PGH_2 synthase, COX-3 and partial cyclooxygenase-1 (PCOX-1).[198] These enzymes structurally resemble COX-1 and COX-2 and are typically found in the brain, though little is understood about their function.

Although COX-1 and COX-2 catalyze the transformation of AA to PGH_2, their biochemical role is actually dependent upon their cellular location *in vivo*. For example, COX-2 is responsible for the generation of PGH_2 in the perinuclear membrane, an organelle abundant with PGE_2 synthase.[199] The PGH_2 synthesized by COX-2 is used by PGE_2 synthase to make PGE_2. Thus COX-2 ultimately aids in converting AA to PGE_2 in the perinuclear membrane. By comparison, biosynthesis of PGH_2 in platelets is catalyzed by COX-1; TxA_2 synthase is largely abundant in platelets. Thus in platelets, PGH_2 are converted to TxA_2. More broadly, COX-1 is responsible for the synthesis of TxA_2.

4.1.2.1. Selective Inhibition

The discovery of COX-2 sparked the hypothesis that certain molecules could selectively inhibit one COX enzyme over another.[200] This idea is validated by studies[201] that demonstrated

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[197] Xie, W.; Chipman, J. G.; Robertson, D. L.; Erikson, R. L.; Simmons, D. L. "Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing." *Proc. Natl. Acad. Sci.* **1991**, *88*, 2692-2696.

[198] Chandrasekharan, N. V.; Dai, H.; Roos, K. L. T.; Evanson, N. K.; Tomsik, J.; Elton, T. S.; Simmons, D. L. "COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure and expression." *Proc. Natl. Acad. Sci.* **2002**, *99*, 13926-13931.

[199] Murakami, M; Naraba, H.; Tanioka, T.; Semmyo, N.; Nakatani, Y.; Kojima, F.; Ikeda, T.; Fueki, M; Ueno, A.; Oh-ishi, S.; Kudo, I. "Regulation of Prostaglandin E2 Biosynthesis by Inducible Membrane-associated Prostaglandin E2 Synthase That Acts in Concert with Cyclooxygenase-2." *J. Biol. Chem.* **2000**, *275*, 32783-32792.

[200] (a) Fu, J.-Y., Masferrer, J. L., Seibert, K., Raz, A., and Needleman, P. "The induction and suppression of prostaglandin H2 synthase (cyclooxygenase) in human monocytes." *J. Biol.*

the suppression of inflammation in rats treated with dexamethasone while retaining normal "housekeeping" functions. Today, several COX-2 inhibitors (coxibs) are prescribed to mimic the same effects in humans. It is notable that several coxibs (e.g., Vioxx™ and Bextra™) have come under fire in recent years due to their association with a 1% increased risk of myocardial infarction in those suffering from cardiovascular diseases. In cases where specific coxibs are prescribed as chronic therapies, patients have been shown to have an increased risk for heart attacks, stroke and heart infarctions. In 2004, Merck voluntarily recalled their blockbuster drug Vioxx™ after research conducted by the United States Food and Drug Administration (FDA) supported early epidemiological findings that the pharmaceutical caused an increased risk of heart attack. FDA estimations suggest that Vioxx was related to anywhere from 90,000 to 150,000 heart attacks, 30-40% which were probably fatal, in the 5 years it had been on the market as a physician-prescribed medication.[202]

COX-1 and COX-2 share roughly 60% protein sequence identity.[203] Fundamentally, differences in the peptide sequences account for the propensity of coxibs to inhibit COX-2 over

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Chem. **1990**, *265*, 16737–16740. (b) Xie, W., Chipman, J. G., Robertson, D. L., Erikson, R. L., and Simmons, D. L. "Expression of mitogen-responsive gene encoding prostaglandidn synthase is regulated by mRNA splicing." *Proc. Natl Acad. Sci.* **1991**, *88*, 2692–2696 (c) Kujubu, D. A., Fletcher, B. S., Varnum, B. C., Lim, R. W., and Herschman, H. R. "TIS10, a phorbol ester tumor promoter-inducible mRNA from Swiss 3T3 cells, encodes a novel prostaglandin synthase/cyclooxygenase homologue." *J. Biol. Chem.* **1991**, *266*, 12866 –12872 (d) O'Banion, M. K., Sadowski, H. B., Winn, V., and Young, D. A. "A serum- and glocorticoid-regulated 4-kilobase mRNA encodes a cyclooxygenase-related protein." *J. Biol. Chem.* **1991**, *266*, 23261–23267

[201] Masferrer, J. L.; Zweifel, B. S.; Manning, P. T.; Hauser, S. D.; Leahy, K. M.; Smith, W. G.; Isakson, P. C.; Seibert, K. "Selective inhibition of inducible cyclooxygenase 2 in vivo is antiinflammatory and nonulcerogenic." *Proc. Natl. Acad. Sci.* **1994** *91*, 3228-3232.

[202] Testimony of David J. Graham, MD, MPH, http://www.senate.gov/~finance/hearings/testimony/2004test/111804dgtest.pdf (accessed May 27, 2009)

[203] Kurumbail, R. G.; Stevens, A. M.; Gierse, J. K.; McDonald, J. J.; Stegeman, R. A.; Pak, J. Y.; Gildehaus, D.; Miyashiro, J. M.; Penning, T. D.; Seibert, K.; Isakson, P. C.; Stallings, W. C.

COX-1. The long hydrophobic active site in COX-1[204] contains several alkyl-substituted residues, specifically isoleucines at positions 434 and 523.[205] By comparison, the residues at positions 434 and 523 in COX-2 are valines. Comparitively, crowding in the active site of COX-1 precludes most coxibs from binding. This gating effect is lessened in COX-2, which allows coxibs to bind and thus competively prevent the conversion of AA to PGH_2. Additionally, COX-2 features more aromatic and polar residues in the binding pocket.[206]

4.1.3. The Link Between COX-2 Inhibition and Cancer

Several studies link NSAID use with the prevention of colorectal cancer (CRC).[207,208,209,210] As seen in Table 4.2, these studies demonstrated that patients who regularly take aspirin, an indiscriminate COX inhibitor, had a significantly reduced risk of developing

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"Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory agents." *Nature* **1996**, *384*, 644-648.

[204] Picot, D.; Loll, P. J.; Garavito, R. M. "The X-ray crystal structure of the membrane protein prostaglandin H2 synthase-1." *Nature* **1994**, *367*, 243-249.

[205] Marnett, L. J.; Rowlinson, S. W.; Goodwin, D. C.; Kalgutkar, A. S.; Lanzo, C. A. "Arachidonic Acid Oxygenation by COX-1 and COX-2." *J. Biol. Chem.* **1999**, *274*, 22903-22906.

[206] Llorens,O.; Perez, J. J.; Palomer, A.; Mauleon, D. "Structural basis of the dynamic mechanisms of ligand binding to cyclooxygenase." *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2779-2784.

[207] Kune, G. A.; Watson, A. J.; Watson, L. F. "Colorectal cancer risk, chronic illness, operations and medications: case control results from the Melbourne Colorectal Cancer Study." *Cancer Res.* **1998**, *48*, 4399-4404.

[208] Rosenberg, L.; Palmer, J.; Zauber, A.; Warshauer, M; Stolley, P.; Shapiro, S. "A hypothesis: non-steroidal anti-inflammatory drugs reduce the incidence of large bowel cancer." *J. Natl. Cancer Inst.* **1991**, *83*, 355-358.

[209] Suh, O.; Mettlin, C.; Petrelli, N. J. "Aspirin use, cancer and polyps of the large bowel." *Cancer* **1993**, *72*, 1171-1177.

[210] Giovannucci, E.; Rimm, E. B.; Stampfer, M. J.; Colditz, G. A.; Ascherio, A.; Willett, W. C. "Aspirin use and the risk for colorectal cancer and adenoma in male health professionals." *Ann. Intern. Med.* **1994**, *121*, 241-246.

CRC versus patients who did not regularly take aspirin. At the time, the results could not be explained scientifically because the idea of two distinct COX enzymes had not yet been realized.

Table 4.2. The risk of CRC onset in patients regularly taking aspirin.

Country	*Year*	*Patients Surveyed*	*Risk Ratio*[a]
Australia	1988	715	0.57
USA	1991	1,326	0.50
USA	1993	830	0.40-0.80
USA	1994	47,900	0.68

[a]Defined as the measure of risk of a certain group relative to the risk of the same event in another group.[211] A risk ratio of 1 suggests there is no difference between two groups.

Although the relationship between NSAIDs and CRC is still frequently reviewed,[212] breakthrough studies occurred in the 1980's. Narisawa, a Japanese surgeon, is credited with first reporting the chemoprevention of CRC in rats with indomethacin, an NSAID.[213] In 1989 Waddell and co-workers reported that sulindac had halted polyp formation in patients diagnosed with familial adenomatous polyposis (FAP).[214] In a similar study, Eberhart and co-workers reported a decrease in polyp size and number in patients diagnosed with FAP when sulindac was administered after cancer treatment was stopped.[215] These results collectively strengthened the argument that there was a positive correlation between COX inhibition and colon cancer. Importantly, Eberhart also reported significant differences in COX-2 levels in carcinoma cells

[211] Zhang, J.; Yu, K. F. "What's the Relative Risk? A Method of Correcting the Odds Ratio in Cohort Studies of Common Outcomes." *J. Am. Med. Assoc.* **1998**, *280*, 1690-1691.
[212] Iwama, T. "NSAIDs and colorectal cancer prevention." *J. Gastroenterol.* **2009**, *44*, 72-76.
[213] Narisawa, T.; Sato, M.; Tani, M.; Kudo, T.; Takahashi, T.; Goto, A. "Inhibition of development of methylnitrosourea-induced rate colon tumors by indomethacin treatment." *Cancer Res.* **1981**, *41*, 1954-1957.
[214] Waddell, W. R.; Ganser, G. F.; Cerise, E. J.; Loughry, R. W. "Sulindac for polyposis of the colon." *Am. J. Surg.* **1989**, *157*, 175-179.
[215] Eberhart, C. E.; Coffey, R. J.; Radhika, A.; Giardiello, F. M.; Ferrenbach, S.; DuBois, R. N. "Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas." *Gastroenterology* **1994**, *107*, 1183-1188.

versus normal mucosal cells, although the levels of COX-1 were identical between the cancer and normal cells.[215] Ultimately, DuBois concluded that COX-2 could be an "attractive therapeutic target" in treating CRC.

Relatively recent epidemiological studies suggest that various human cancerous cells are abundant in prostaglandin E2 (PGE_2), most commonly synthesized biochemically in cells containing COX-2.[216] The presence of high cellular quantities of PGE_2 is purportedly linked with cellular proliferation and resistance to apoptosis, two necessary conditions for cancer cell growth. The enzyme PGE_2 has been reportedly associated with cell proliferation, angiogenesis, resistance to apoptosis and immunomodulation.[217] Additionally, stimulation of endothelial migration and tube formation—necessary components in angiogenesis[218]—contribute to unregulated cellular growth (i.e., cancer).

The inhibition of COX-2 in turn mitigates angiogenesis and cell proliferation, two major components in tumor growth. Recently, Johnsen and co-workers reported that tumors in the sympathetic nervous system are associated with abnormally high levels of COX-2.[219] In this case, the high concentration of COX-2 affects tumor suppressor p53. Johnsen demonstrated that treating carcinomic rats with celecoxib, a COX-2 inhibitor, "significantly inhibited tumor growth in vivo." Further, the FDA has approved Celebrex for the treatment of familial adenomatous polyposis (FAP)—polyp formation in the epithelium of the large intestine. Most of these polyps

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[216] Taketo, M. M. "Cyclooxygenase-2 Inhibitors in Tumorigenesis (Part I)." *J. Natl. Cancer Inst.* **1998**, *90*, 1529-1536.
[217] Rishikesh, M. K.; Sadhana, S. S. "Prostaglandins and Cyclooxygenase: Their Probable Role on Cancer." *Indian J. Pharmacol.* **2003**, *35*, 3-12.
[218] Tsuji, M.; Kawano, S.; Tsuji, S.; Sawaoka, H.; Hori, M.; DuBois, R. N. "Cyclooxygenase Regulates Angiogenesis Induced by Colon Cancer Cells." *Cell* **1998**, *93*, 705-716.
[219] Johnsen, J. I.; Linkskog, M.; Ponthan, F.; Pettersen, I.; Elfman, L.; Orrego, A.; Sveinbjörnsson, B.; Kogner, P. "Cyclooxygenase-2 Is Expressed in Neuroblastoma, and Nonsteroidal Anti-Inflammatory Drugs Induce Apoptosis and Inhibit Tumor Growth *In vivo*." *Cancer Research* **2004**, *64*, 7210-7215.

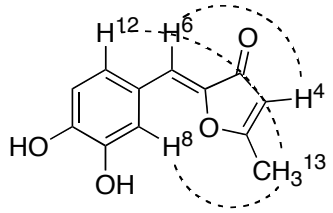
are benign; however, left untreated, FAP can turn malignant resulting in the onset of colon cancer. Besides the management of pain, there is an interest in developing newer COX-2 inhibitors that will also aid in cancer research. New aspirin analogs such as phosphoaspirin have demonstrated inhibition of 10 human cancer cell lines and is 18- to 144-times more potent than aspirin.[220]

4.1.4. Inotilone

4.1.4.1. Discovery

In 2006, Hertweck and co-workers first reported the structure and preliminary biological studies of 2-(3,4-dihydroxybenzylidene)-5-methylfuran-3-one, inotilone (**4.1**), a phenylpropanoid-derived polyketide extracted from the fruiting body of the Vietnamese *Inonotus* species mushroom.[221] Structurally, inotilone contains an aryl hemisphere and a furanone hemisphere linked by an olefin as the (*Z*)-isomer. Hertweck established the identity of the double bond through a combination of molecular modeling and NOESY. Inotilone demonstrated a correlation between the H_6 and H_3 in addition to a correlation between the aryl protons H_8 and H_{12} with the methyl protons of H_{13}. This data was consistent with the (*Z*)-stereochemistry (Figure 4.2).

[220] Zhao, W.; Mackenzie, G. G.; Murray, O. T.; Zhang, Z.; Rigas, B. "Phosphoaspirin (MDC-43), a novel benzyl ester of aspirin, inhibits the growth of human cancer cell lines more potently than aspirin: a redox-dependent effect." *Carcinogenesis* **2009**, *30*, 512-519.
[221] Wangun, H. V. K.; Härti, A.; Keit, T. T.; Hertweck, C. "Inotilone and related phenylpropanoid polyketides from *Inonotus* sp. And their identification as potent COX and XO inhibitors." *Org. Biomol. Chem.* **2006**, *4*, 2545-2548

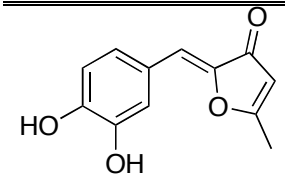


4.1

Figure 4.2. Inotilone (**4.1**) and its reported nOe correlations.[221]

Inotilone showed a COX-2 enzyme assay IC_{50} value of 0.03 uM and selective inhibition of COX-2 over COX-1 at submicromolar concentrations. By comparison, this inhibitory potency rivals currently available inhibitors meloxicam and nimesulide[222] and is superior to rofecoxib.[223] Additionally, inotilone is a relatively poor inhibitor of 3α-hydroxysteroid dehydrogenase (3α-HSD) and xanthine oxidase (XO). Collectively, this data suggests that inotilone is an attractive lead compound as a potential COX-2 inhibitor with potential applications for treatment of chronic inflammatory pain and cancer chemoprevention.

Table 4.3. Reported pharmocological properties of inotilone (**4.1**).[221]



4.1

	$IC_{50}/\mu M$			
3α-HSD[a]	*COX-1*	*COX-2*	*COX-2/COX-1*	*XO*[b]
50.4	0.36	0.03	0.08	9.1

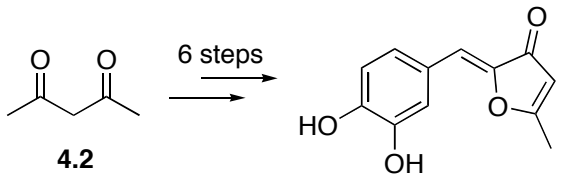
[a]3α-hydroxysteroid dehydrogenase
[b]Xanthine oxidase

[222] Vane, J. R.; Bakhle, Y. S.; Botting, R. M. "Cyclooxygenases 1 and 2." *Annu. Rev. Pharmacol. Toxicol.* **1998**, *38*, 97-120.

[223] Chan, C.-C.; Boyce, S.; Brideau, C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J.; Ford-Hutchinson, A. W.; Forrest, M. J.; Gauthier, J. Y.; Gordon, R.; Gresser, M.; Guay, J.; Kargman, S.; Kennedy, B.; Leblanc, Y.; Leger, S.; Mancini, G.; O'Neill, G. P.; Ouellet, M.; Patrick, D.; Percival, M. D.; Perrier, H.; Prasit, P.; Rodger, I. W.; Tagari, P.; Therien, M.; Vickers, P.; Visco, D.; Wang, Z.; Webb, J.; Wong, E.; Xu, L.-J.; Young, R. N.; Zamboni, R.; Riendau, D. "Rofecoxib [Vioxx, MK-0966; 4-(4'-Methylsulfonylphenyl)-3-phenyl-2-(5*H*)-furanone: A Potent and Orally Active Cyclooxygenase-2 Inhibitor. Pharmacological and Biochemical Profiles." *J. Pharmacol. Exp. Ther.* **1999**, *290*, 551–560.

4.1.4.2. First Synthesis

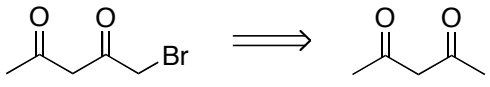
Shamshina and Snowden are credited with the first total synthesis of **4.1**.[224] Beginning from acetylacetone (**4.2**), they prepared **4.1** in approximately 50% yield over the course of six steps using a route largely inspired by Winkler and co-workers.[225]



4.2 **4.1**

Scheme 4.1. An overview of Snowden's synthesis of inotilone (**4.1**).[224]

The Shamshina and Snowden total synthesis of inotilone began by forming highly unstable 1-bromoacetylacetone (**4.3**).[224] As seen in Scheme 4.2, **4.3** could derive from acetylacetone (**4.2**) through the obvious disconnect of the C-Br bond. However, direct halogenation of **4.3** reportedly gave a complex mixture of polybrominated products and/or 3-bromoacetylacetone.[226]



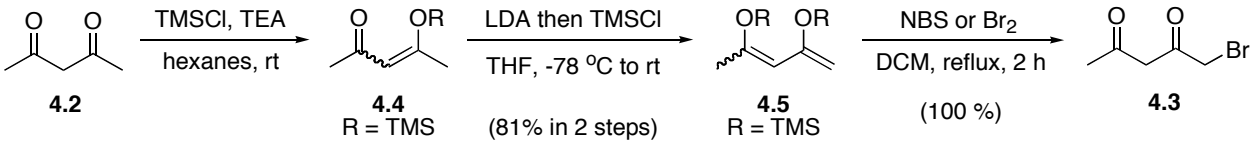
4.3 **4.2**

Scheme 4.2. Retrosynthesis of 1-bromoacetylacetone (**4.3**).

Eventually, the synthesis of **4.3** involved a new and superior approach proceeding through formation of bis-silyl enol ether formation (**4.5**). Using the method established by

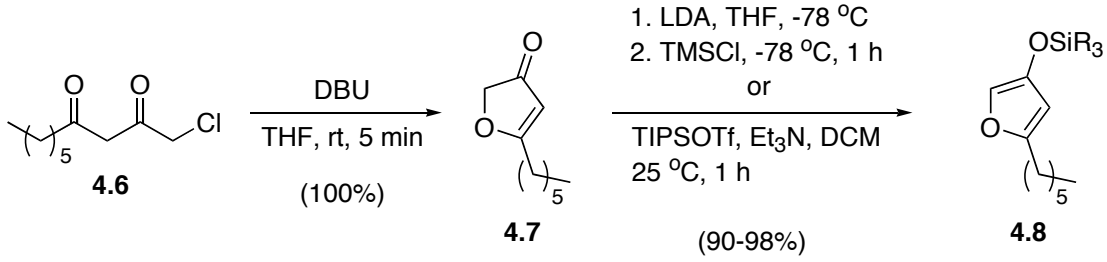
[224] Shamshina, J. L.; Snowden, T. S. "Convergent synthesis of potent COX-2 inhibitor inotilone." *Tetrahedron Letters* **2007**, *48*, 3767-3769.
[225] Winkler, J. D.; Oh, K.; Asselin, S. M. "Synthesis of Highly Functionalized Furanones via Aldol Reaction of 3-Silyloxyfurans." *Org. Lett.* **2005**, *7*, 387-389.
[226] Shamshina, J. L. New Synthetic Applications of Trichlorocarbinols. Syntheses of Small Molecule Natural Products. Ph.D. Thesis, The University of Alabama, Tuscaloosa, AL, 2008.

Molander,[227] Shamshina and Snowden treated **4.2** with triethylamine in the presence of trimethylsilyl chloride to give silyl enol ether **4.4** (Scheme 4.3). Treatment of **4.4** with LDA followed by transmetallation with TMSCl provided bis-silyl enol ether **4.4** in 81% yield over two steps after distillation. Shamshina and Snowden then brominated **4.9** with NBS in refluxing DCM to give 1-bromoacetylacetone (**4.3**) in reportedly quantitative yield.



Scheme 4.3. The synthesis of 1-bromoacetylacetone (**4.3**).[224]

Winkler and co-workers reported the conversion of α-chloro dione **4.6** to the corresponding furanone, via 5-*exo-tet* cyclization, in quantitative yield using DBU to effect the requisite deprotonation,[225] a procedure first reported by Yamaguchi and co-workers.[228] As seen in Scheme 4.4, furanone **4.7** was then transformed to the silyl enol ether (**4.8**) using either a combination of LDA and TMSCl or triethylamine and TIPSOTf in excellent yields.



Scheme 4.4. Winkler's synthesis of siloxyfuranone **4.8**.[225]

Borrowing from Winkler's procedure, Shamshina and Snowden reported a similar sequence where the α-halo dione would be converted to the silyloxyfuranone in two steps.[224]

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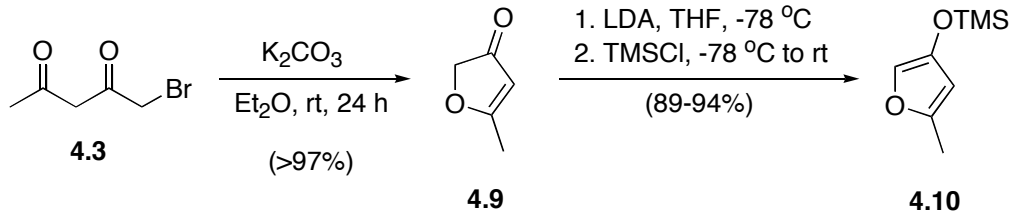
[227] Molander, G. A.; Cameron, K. O. "Neighboring Group Participation in Lewis Acid-Promoted [3 + 4] and [3 + 5] Annulations. The Synthesis of Oxabicyclo[3.*n*.1]alkan-3-ones." *J. Am. Chem. Soc.* **1993**, *115*, 830-846.

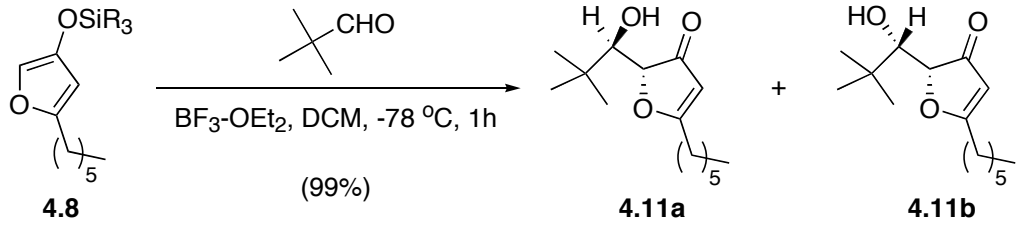
[228] Yamaguchi, M.; Shibato, K.; Nakashima, H.; Minami, T. "Synthesis of phenols by the intramolecular condensation of β,β',δ,δ'-tetraoxoalkanedioates. A novel BF_3-promoted Claisen condensation of acetoacetate dianion with esters and amides." *Tetrahedron* **1988**, *44*, 4767-4776.

Bromoacetylacetone **4.3** was treated with K_2CO_3 in anhydrous diethyl ether to form furanone **4.9** in quantitative yield after 24 h. The solvent was ideal because of its inability to dissolve salts, and thus on workup the reaction mixture could be filtered over celite then carefully concentrated to provide the pure product without problematic aqueous workup. The method was particularly useful due to the instability of both **4.3** and **4.9**—two volatile compounds prone to polymerization and decomposition during distillation. Finally, treatment of **4.9** with LDA and TMSCl gave the corresponding siloxyfuranone **4.10** in excellent yield. Shamshina and Snowden further noted that **4.10** could be purified by vacuum distillation.



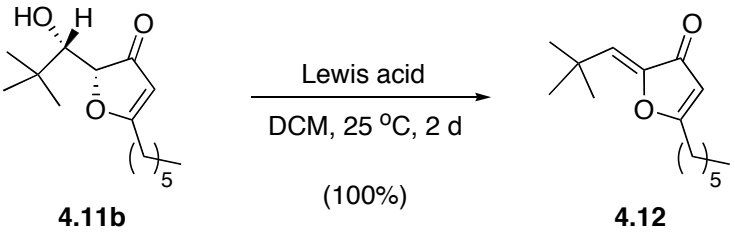
Scheme 4.5. Shamshina/Snowden synthesis of siloxyfuranone **4.10**.[224]

The aim of Winkler's experiments was to determine whether silyl enol ether **4.8** would undergo aldol reactions or [4+2]-cycloaddition when exposed to an aldehyde in the presence of a Lewis acid.[225] The reaction of silyloxyfuranone **4.8** with an array of different aldehydes gave **4.11** quantitative yields and a wide range of diastereoselectivities when either $TiCl_4$ or BF_3•OEt_2 were used as the Lewis acids. When **4.8** was reacted with sterically hindered aldehydes, such as *tert*-butanal, the diastereoselectivity shifted to >5:95, *anti*:*syn* without sacrificing the excellent yield (Scheme 4.6). Winkler and co-workers ultimately concluded that Mukaiyama conditions exclusively gave the aldol product and steric hindrance provided the driving force for the diastereoselectivity.



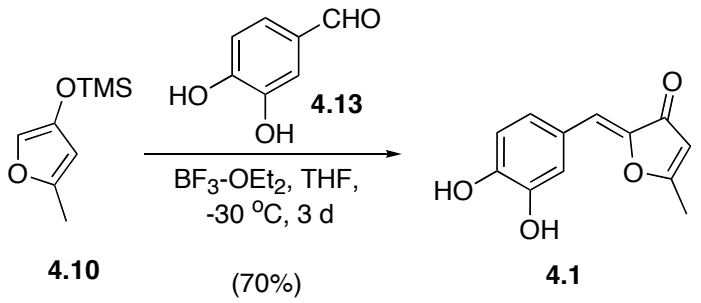
Scheme 4.6. Winkler's Mukiayama aldol chemistry.[225]

Winkler and co-workers noted that allowing *t*-butyl adduct **4.11b** to stand for 48 h resulted in stereoselective dehydration of the carbinol to the *Z*-olefin in quantitative yield.[225] Again, steric hindrance presumably acted as the driving force for the stereochemical outcome.



Scheme 4.7. Winkler's elimination reaction of alcohol **4.11b**.[225]

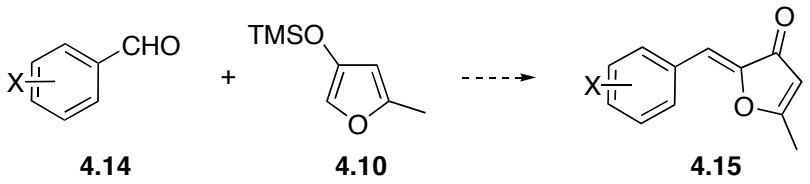
In the total synthesis of inotilone (**4.1**), Shamshina and Snowden employed a variation of Winkler's Mukaiyama aldol procedure to effect the addition of the aryl moiety. Treatment of **4.10** with **4.14** in the presence of four equivalents of BF_3•OEt_2 provided **4.1** in 70% yield after 3 days at -30 °C (Scheme 4.8). The excessive quantities of Lewis acid are needed to coordinate every heteroatom in both **4.10** and **4.14**. It was particularly significant that only the (*Z*)-diastereomer was observed in the reaction mixture, similar to the transformation reported by Winkler. Shamshina and Snowden noted that the steric interaction of the aromatic C-6 hydrogen and the furanone carbonyl prevented formation of the (*E*)-diastereomer. The authors also noted that other Lewis acids, such as Ti(O*i*Pr)$_4$ or Et_2AlCl, gave poorer conversions in the preparation of **4.1**.



Scheme 4.8. The Mukaiyama aldol step in the synthesis of inotilone (**4.1**).[224]

4.1.5. Experimental Goals and Strategy

We endeavored to prepare several inotilone analogs for biological screening to compare against the parent natural product **4.1**. Since Winkler and Snowden had success using Mukaiyama aldol chemistry to promote carbon-carbon bond formation, we envisioned applying a similar strategy in the preparation of various analogs. Our route would involve reacting various commercially available 3- and/or 4-substituted benzaldehydes (**4.14**) with siloxyfuranone **4.10** to prepare an array of inotilone analogs (**4.15**) convergently (Scheme 4.9).



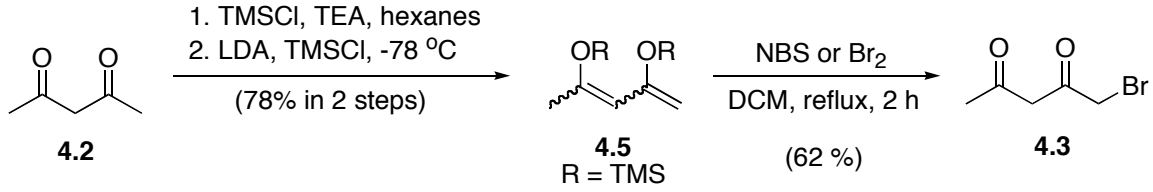
Scheme 4.9. Synthetic strategy in preparing inotilone analogs (**4.15**).

4.2 Results and Discussion

4.2.1. A Direct Route to 1-Bromopentane-2,4-dione

In early iterations of the synthesis, we found **4.5** could be prepared from **4.2** in 78% over two steps without the need for purification (Scheme 4.10). Following Snowden's protocol, **4.5** was reacted with NBS, resulting in a complex mixture of products. Changing NBS to Br_2 had no

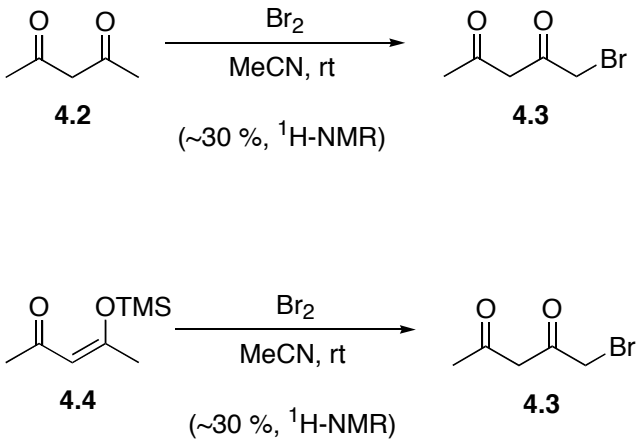
effect on the outcome of the yield or purity of the reaction. Experimentation with different solvent systems during TLC analysis eventually resulted in the resolution of two distinct, chromophoric spots. The product with the higher R_f value (~0.4 in 1:1 DCM:hexanes) was obtained as a clear, slightly yellow oil and exhibited spectroscopic properties consistent with the formation of **4.3**. The second product (R_f = 0.3 in 1:1 DCM:hexanes) was a clear, yellow oil and exhibited spectroscopic properties consistent with acetylacetone (**4.2**). Thus, it was realized that **4.3** could be isolated from **4.2** by way of column chromatography, a technique not previously reported.



Scheme 4.10. The synthesis of **4.3** from **4.2** in three steps.

Although the initial approach to 1-bromopentane-2,4-dione (**4.3**) offered a viable route from acetylacetone (**4.2**), installation of the *bis*-silyl enol ether groups (**4.5**) was undesirable for two reasons. First, the TMS group would be lost upon workup after bromination with NBS, which results in poor overall atom economy. Second, the process for accessing the bis-silyl enol ether requires a two-step preparation. Thus, through the direct bromination of **4.2**, we would expect an overall increase in atom economy while removing two steps from the synthesis of inotilone analogs, thereby facilitating material throughput in the preparation of potential inotilone analogs.

We attempted a series of experiments to chemoselectively brominate **4.2** in the 1-position using a modified version of Fuchs' method.[229] Treatment of **4.2** with Br_2 in MeCN at room temperature resulted in 50% conversion under 20 minutes as evidenced in ^{1}H-NMR analysis of the crude reaction mixture. Additionally, an unstable, white solid had formed in the reaction vessel during this time and, upon removal from anoxic reaction conditions, immediately sublimed, evolving a white gas. We attributed this solid to the formation of an acac-Br_2 complex and hypothesized that the white gas was HBr. Spectroscopic analysis of the reaction mixture after the consumption of **4.2** (approximately two days) showed formation of 1-bromoacetylacetone and a mixture of other impurities. A similar result was observed when **4.4** was employed as the substrate.

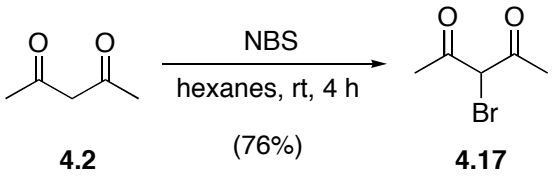


Scheme 4.11. Experimental brominations of **4.2** and **4.4**.

In an alternate series of experiments we chose to react **4.2** with NBS in MeCN. We hypothesized that NBS could act as a surrogate for **4.16** by providing the requisite electrophilic bromine and subsequent deprotonation, similar to Fuchs' method. Bromination of **4.2** and **4.4**

[229] Magen, S.; Oren, J.; Fuchs, B. "Novel bromination reagents • hexabromocyclopentadiene: bromination of activated saturated sites." *Tetrahedron Lett.* **1984**, *25*, 3369-3372.

using NBS in MeCN at room temperature gave **4.3** in roughly 50% yield with a complex mixture of polybrominated products and starting material. Warming the reaction to reflux had no effect on conversion. Additionally, as seen in Scheme 4.12, treatment of **4.2** with NBS in hexane at room temperature resulted in isolation of 3-bromopentane-2,4-dione (**4.17**) in 76% yield with trace amounts of acetylacetone remaining.

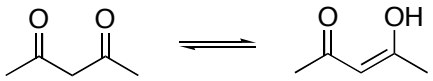


Scheme 4.12. The synthesis of 3-bromoacetylacetone (**4.17**) from **4.2**.

Since previous methods to brominate **4.2** were unsuccessful, we attempted to gain more insight into the substrate, namely its keto/enol tautomerizations. Acetylacetone (**4.2**) typically exists in one of two forms: the diketo (**4.2a**) or *cis*-enolic (**4.2b**). The solvent plays a critical role in the tautomerizim of **4.2**. *Ab initio* calculations (reference interaction site model self-consistent-field or RISM-SCF)[230] suggest that polar aprotic solvents, such as DMSO, influence **4.2** to adopt the diketo tautomer (**4.2b**) to maximize the substrate dipole, which was calculated to be 6.014 D in DMSO.[231] The calculated relative difference in enthalpies between **4.2a** and **4.2b** is positive in DMSO, which indicates an entropic driving force for the **4.2a** tautomer. Alagona and Ghio further supported this claim calculating that the diketo enol most stable form possess C2 symmetry where the carbonyls oppose each other at the B3LYP/6-31G* level.[232] Conversely, the lowest energy form of the enol tautomer (**4.2a**), observed in apolar aprotic

[230] Caminati, W.; Grabow, J.-U. "The C_{2v} Structure of Enolic Acetylacetone." *J. Am. Chem. Soc.* **2006**, *128*, 854-857.
[231] Ishida, T.; Hirata, F.; Kato, S. "Thermodynamic analysis of the solvent effect on tautomerization of acetylacetone: An *ab initio* approach." *J. Chem. Phys.* **1999**, *110*, 3938-3945.
[232] Alagona, G.; Ghio, C. "Keto-Enol Tautomerism in Linear and Cyclic b-Diketones: A DFT Study in Vacuo and in Solution." *Int. J. Quantum Chem.* **2008**, *108*, 1840-1855.

solvents such as CCl_4, favors intramolecular hydrogen bonding and thus purportedly possesses C_{2v} symmetry. The enol tautomer (**4.2a**) is calculated to be 3.24 kcal/mol more stable than the keto tautomer (**4.2**) at the B3LYP/6-31G* level. This intramolecular hydrogen bonding presumably reduces dipole-dipole repulsion of the carbonyl groups thus stabilizing **4.2**.[233] This observation was confirmed experimentally by Mills and Beak who ultimately determined that acetylacetone favors the enol tautomer over the keto tautomer 29:1 in CCl_4.[234]



4.2 **4.2a**

Scheme 4.13. Tautomerism of acetylacetone (**4.2**).

Knowledge of the tautomer formation of **4.2** became particularly useful in rationalizing bromination product outcome. The focus eventually became to effect bromination thereby affording **4.17**, which could be isomerized to **4.3** akin to methodology reported by Tavares, O'Sullivan and Hause.[235,236] The team treated **4.2** with bromine in alkaline media providing **4.17** in 55% yield. Isomerization of **4.17** using HBr in acetic acid provided the desired impure *n*-brominated **4.3** in 49% yield. This reaction sequence suggested that a two-step bromination of **4.2** was a plausible route to **4.3**, at least in aqueous media.

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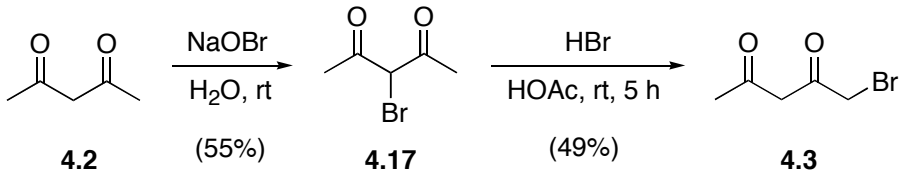
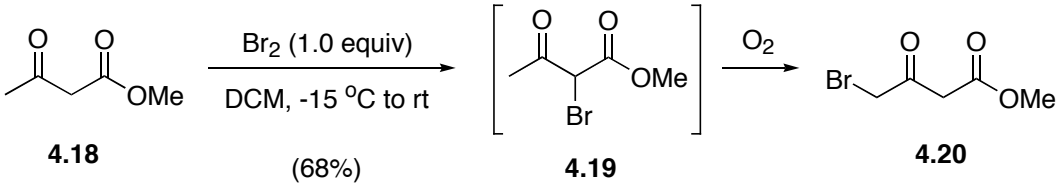
[233] Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry* 3rd Edition, pp107-108, copyright 2003 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.
[234] *J. Org. Chem.* **1985**, *50*, 1216.
[235] O'Sullivan, W. I.; Tavares, D. F.; Hauser, C. R. "Acetylation of Benzenesulfonylacetone with Acetic Anhydride by Means of Boron Fluoride to Form the Terminal Methyl Derivative." *J. Org. Chem*. **1962**, *27*, 1251-1254.
[236] O'Sullivan, W. I.; Tavares, D. F.; Hauser, C. R. "Some Condensations at the Methylene and Terminal Methyl Groups of Benzenesulfonylacetone Through its Mono- and Dipotassio Salts." *J. Am. Chem. Soc.* **1961**, *83*, 3453-3457



Scheme 4.14. Tavares/O'Sullivan/Hause method to prepare **4.3**.[235,236]

Duthaler later reported chemoselective *n*-brominaton of 1,3-dicarbonyl compounds using elemental Br_2 in DCM.[237] The reaction of methyl β-ketobutyrate (**4.18**) with one equivalent of Br_2 in cold DCM gave the intermediate 3-bromodicarbonyl (**4.19**). Treatment of the reaction mixture with oxygen facilitated isomerization to the desired *n*-brominated product (**4.20**) in 68% yield.

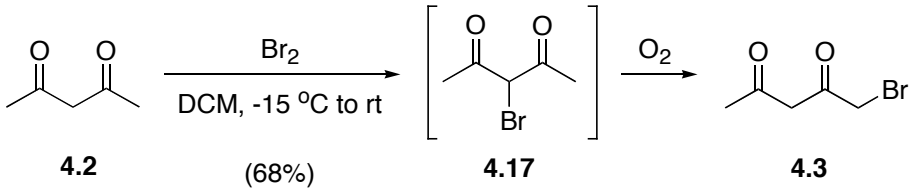


Scheme 4.15. Duthaler's methodology used to *n*-brominate 1,3-dicarbonyls.[237]

Borrowing from Duthaler's bromination protocol, Moorhoff reported the bromination of 1,3-diketone compounds.[238] Specifically, Moorhoff reported that Duthaler's procedure specifically gave intermediate **4.17**, which could be isomerized to **4.3** with the solubilized HBr. As seen in Scheme 4.16, we treated **4.2** with bromine at 0 °C and gradually warmed the reaction mixture to room temperature thus generating intermediate **4.17**. In bubbling lab air through the reaction mixture, evolution of a white gas, presumably HBr, was observed. ^{1}H-NMR analysis of the crude reaction mixture suggested a mixture of trace quantities of side products, residual **4.2**

[237] Duthaler, R. O. "Construction of Highly Substituted Nitroaromatic Systems by Cyclocondensation. Part I. Synthesis of 4-nitro-3-oxobutyrate." *Helv. Chim. Acta* **1983**, *66*, 1475-1492.
[238] Moorhoff, C. "An Efficient Separation Method for Enol Phosphate and Corresponding ß-Ketophosphonate from Their Mixtures Under Aqueous Conditions." *Synth. Commun.* **2003**, *33*, 2069-2086.

and the desired product (**4.3**) in approximately 75% yield relative to remaining **4.2**. Flash chromatography provided **4.3** in 68% yield with inseparable trace impurities (~5%). On a 200 mmol scale, **4.3** was isolated in 65% yield after successive purifications by flash chromatography.

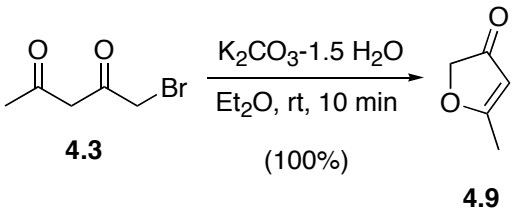


Scheme 4.16. Revised synthesis of 1-bromoacetylacetone (**4.3**).

4.2.2. Silyloxyfuran Synthesis

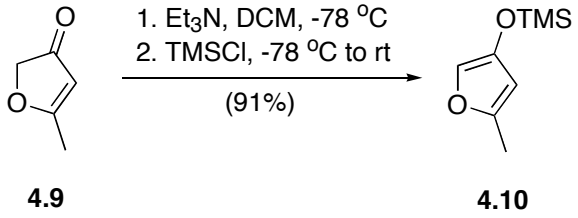
In treating **4.3** with K_2CO_3 to access **4.10** we found the yields to be low and rate of conversion to be sluggish. Reaction times greater than 20 h resulted in the formation of an unidentifiable tar. Additionally, allowing the isolated, neat material to stand for greater than 10 min at room temperature gave a similar result. Clearly, these product decompositions resulted in diminished yields.

The reaction provided the highest yield in instances where solvent-grade Et_2O was employed. We optimally determined that crystalline K_2CO_3 cyclized **4.3** under 10 min (Scheme 4.18). We reasoned that the accompanying, trace amounts of water increased the base solubility thereby enhancing the reaction rate. Filtration of the accompanying solids upon workup followed by treatment with $MgSO_4$ provided the dry, pure product in quantitative yield. In occasional cases where side products were observed, **4.10** could be chromatographed using volatile solvent systems (i.e. Et_2O/hexanes). Flash chromatography did not result in decomposition of the material.



Scheme 4.17. The synthesis of furanone **4.9**.

In converting **4.9** to **4.10**, we found that LDA gave yields ranging from 70 to 85%. In several experiments we discovered that the reaction was limited by the presence of diisopropylamine in the product and, in vacuum distilling **4.9**, heating above 90 ^{o}C resulted in product decomposition. Since **4.10** is stabilized through aromaticity, we reasoned that this effect would increase the acidity of the anomeric carbon in **4.9**. Thus, we opted to explore Winkler's other protocol (i.e., TEA/TIPSOTf)[239] to access **4.10**. Treatment of **4.9** with triethylamine in DCM at 0 ^{o}C and rt followed by inclusion of TMSCl resulted in isolation of **4.10,** albeit in low yields. Silyloxyfuranone **4.10** was obtained in higher yields when **4.9** was treated with TEA at -78 ^{o}C followed by slow addition of TMSCl (Scheme 4.19). Concentration of the reaction mixture provided a paste that comprises the desired silyl enol ether (**4.10**) and the triethylamine hydrobromide salt. Reconstitution of the paste with hexanes solublized **4.10** and allowed for the filtration of the insoluble conjugate acid. This newly optimized protocol cleanly provided silyloxyfuranone **4.10** in good yields without the need for purification.



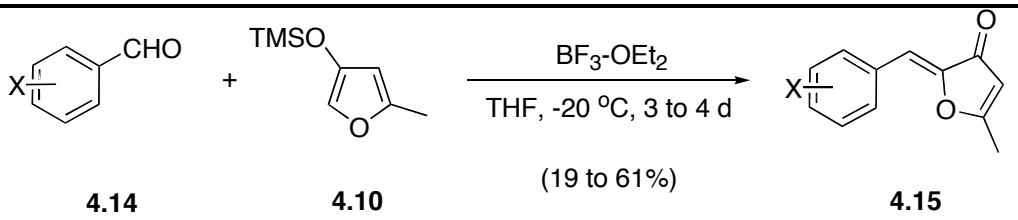
Scheme 4.18. Syntheis of siloxyfuran **4.10**.

[239] Stuart, J. G.; Nicholas, K. M. "Cobalt-mediated alkylation of siloxyfurans." *Heterocycles* **1991**, *32*, 949-963.

4.2.3. Mukaiyama Aldol Chemistry

Employing Snowden's protocol for the preparation of **4.1**,[224] inotilone derivatives **4.21**, **4.22**, **4.23** and **4.24** were synthesized in 19, 61, 25 and 42% yields, respectively. Excess quantities of Lewis acid were employed to coordinate every heteroatom present, as suggested by the published protocol. These reactions took three to four days of stirring at -20 ^{o}C to provide a singular compound after workup with a saturated solution of aqueous $NaHCO_3$. Given the success in synthesizing **4.22**, we were surprised to see that 4-*N*,*N*-dimethylaminobenzaldehyde did not provide an inotilone derivative (**4.25**). Recrystallization of the aldehyde, increased quantities of BF_3•OEt_2 and warming resulted in consumption of the starting material into a complex mixture of products, evidenced by TLC and ^{1}H-NMR analysis of the crude reaction mixture. Additionally, experimentation with the BF_3-mediated Mukaiyama aldol conditions on benzaldehydes containing electron-withdrawing substitutents (Entries 6-10) resulted in consumption of the starting material into a complex mixture of spots (evidenced by TLC analysis), presumably as a mixture of *syn*- and *anti*- aldol adducts and potentially mixtures of *E*- and *Z*-inotilone analogs.

Table 4.4. BF_3-Mediated Mukiayama aldol reactions to prepare inotilone derivatives (4.15).[a]



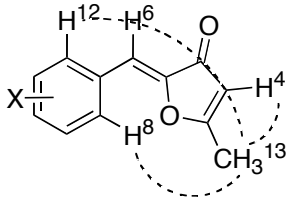
4.14 **4.10** **4.15**

Entry	*Benzaldehyde*	*BF_3•OEt_2* (equiv)	*Yield* (%)[b]	*Compound Number*
1	3-Hydroxy-	4.0	19	**4.21**
2	4-Hydroxy-	4.0	61	**4.22**
3	Benzaldehyde	3.0	25	**4.23**
4	3,4-Dimethyl-	3.0	42	**4.24**
5	4-*N*,*N*-Dimethylamino-	4.0	--	**4.25**
6	4-Fluoro-	3.0	--	**4.26**
7	3,4-Difluoro-	3.0	--	**4.27**
8	4-Cyano	4.0	--	**4.28**
9	4-Bromo	3.0	--	**4.29**
10	4-Acetyl	4.0	--	**4.30**

[a]General experimental details: Trimethylsilyl enol ether (**4.10**, 1.76 mmol) was reacted with BF_3•OEt_2 (1.1 equiv per heteroatom) in dry THF (3 mL) at -78 °C. The desired benzaldehyde (**4.14**, 1.38 mmol) was added and reaction proceeded at -24 °C until the starting material was judged consumed by TLC analysis of the reaction mixture. The reaction was quenched with the addition of a saturated aqueous solution of $NaHCO_3$ (3 mL), extracted with EtOAc then chromatographed over silica.
[b]Isolated yield after flash chromatography.

Given the stereochemical outcomes of the Winkler and Snowden experiments, we hypothesized that the analogs bearing electron-donating substitutents would adopt the (*Z*)-stereochemistry about the olefin. This hypothesis was confirmed by a series of nuclear Overhauser experiments (nOe). Hertweck and co-workers demonstrated a NOESY correlation between the methyl resonance and the aryl protons at H-8 and H-12 in **4.1**.[221] Inotilone derivatives **4.21**-**4.24** were subjected to nOe difference analysis to verify this enhancement. As seen in Figure 4.3, irradiation of the methyl singlet resulted in weak enhancement of the aryl protons at C-2 and C-6 in addition to strong enhancement of the proximal α-proton (i.e., H-4). This data confirmed the stereochemical outcome of the reaction. The fact that irradiation of the

methyl resonance did not result in enhancement of H-6 further strengthens the argument for the presence of a (*Z*)-double bond.



4.15

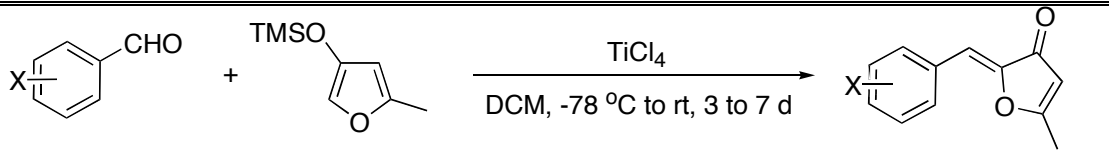
Figure 4.3. Representative nOe enhancments confirming (*Z*)-product formation in **4.15**.

In cases where the Mukaiyama aldol conditions involving BF_3•OEt_2 did not appear to provide a singular product after several days, we explored using the stronger Lewis acid $TiCl_4$. In initial experiments with benzaldehyde and **4.10**, using $TiCl_4$ as the Lewis acid, a complex reaction mixture with trace amounts of **4.23** was evidenced by ^{1}H-NMR analysis of a reaction aliquot at two hours. Warming this reaction mixture to room temperature, as suggested by Winkler's procedure,[225] provided more of the desired product after two days of stirring. Repetition of the reaction using 0.5 equivalents resulted in incomplete conversion evidenced by recovery of the starting material (48%) after several days of stirring. We found that the best workup conditions involved quenching with 2N HCl (approximately 3 molar equiv per inotilone derivative) followed by EtOAc extractions. Weaker acids such as NH_4Cl resulted in the formation of complex emulsions during workup.

The $TiCl_4$-mediated Mukaiyama aldol conditions were employed to access a variety of other inotilone derivatives (**4.15**). The highlights of these experiments are seen in Table 4.5. Treatment of a benzaldehyde/DCM solution at -78 ^{o}C with $TiCl_4$ (1.0 equiv) followed by slow addition of **4.3** over 10 min gave **4.24** in 71% yield after two days of reacting. Most notably, in cases where the BF_3-mediated Mukaiyama aldol conditions did not work, particularly with 4-fluorobenzaldehyde and 3,4-difluorobenzaldehyde, $TiCl_4$ (1.0-2.2 equiv) provided **4.26** and **4.27**

in isolated yields ranging from 14-54%. However, as when employing BF_3•OEt_2, $TiCl_4$ did not furnish the *N*,*N*-dimethylamino derivative **4.25**. Additionally, derivatives **4.31**-**4.33** were isolated in moderate, unoptimized yields (48-62%) using 1.0 to 2.0 equivalents of $TiCl_4$ and stirring at room temperature for several days.

Table 4.5. $TiCl_4$-Mediated Mukiayama aldol reactions to prepare inotilone derivatives (**4.15**).[a]



4.14 **4.10** **4.15**

Entry	*Benzaldehyde*	*$TiCl_4$* (equiv)	*Yield* (%)[b]	*Product Number*
1	Benzaldehyde	1.0	71	**4.23**
2	4-*N*,*N*-Dimethylamino-	1.0	--	**4.25**
3	4-Fluoro-	2.2	14	**4.26**
4	3,4-Difluoro-	1.1	54	**4.27**
5	4-Methoxy-	1.0	61	**4.31**
6	4-Hydroxy-3-methoxy-	2.0	62	**4.32**
7	4-Nitro-	1.1	48	**4.33**

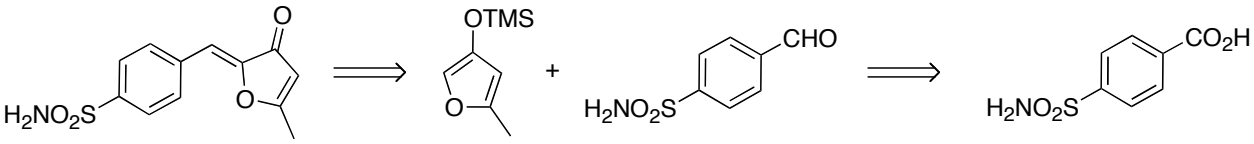
[a]General experimental details: A stirred solution of benzaldehyde (1.0 mmol) in DCM at -78 oC was treated with TiCl4/DCM (1.0-2.2 equiv) and allowed to vigorously stir for 30 min. A solution of trimethylsilyl enol ether (**4.10**, 1.5 mmol) in DCM at room temperature was slowly introduced to the reaction mixture over 5 min. Upon addition, the reaction was gradually warmed to rt and reacted until the starting material was judged consumed by TLC analysis of the mixture. The reaction was quenched with the addition of a saturated aqueous solution of 2N HCl (5 mL), extracted with EtOAc then chromatographed over silica.
[b]Isolated yield after flash chromatography.

Analysis of compounds **4.23**, **4.26**, **4.27** and **4.31-4.33** by nOe difference spectroscopy generally mirrored that of compounds **4.21**-**4.24**. All substrates, with the exception of **4.26** and **4.27**, exhibited enhancement of H-12, H-8 and H-4 when H-13 was irradiated (see Figure 4.3). This information confirms formation of the (*Z*)-olefin in compounds **4.23** and **4.31**-**4.33**. Repeated nOe experiments with **4.26** and **4.27** did not demonstrate this effect, and thus it was not

possible to confirm (Z)-olefin formation. However, initial XRD analysis of crystalline **4.27** was suggestive of (*Z*)-olefin formation. XRD analysis is ongoing for derivatives **4.26** and **4.27**.

4.2.4. Sulfonamide-substituted Inotilone Derivative

The sulfonamide moiety is prevalent in several natural products and pharmaceuticals,[240] which ultimately date back to the discovery that protonsil was effective against Streptococci infections.[2] *Para*-substitution of sulfone or sulfonamide groups on phenyl rings in known inhibitors (e.g., celecoxib, rofecoxib) has been shown to enhance COX-2 selectivity and potency.[241] The functional group is capable of hydrogen bonding[242] while remaining largely inert. Thus, it became desirable to prepare the sulfonamide-substituted inotilone derivative **4.34**. Similar to the preparation of our other derivatives, as seen in Scheme 4.20, we hypothesized that **4.34** could derive from **4.10** and 4-sulfamoylbenzaldehyde (**4.35**). Since it is sold commercially as the hydrate, which was not amenable for our purposes, we reasoned that the aldehyde **4.35** would derive from the inexpensive carboxylic acid **4.36**, known commercially as carzenide.



4.34 **4.10** **4.35** **4.36**

Scheme 4.19. Retrosynthesis of sulfonamide-substituted inotilone derivative **4.34**.

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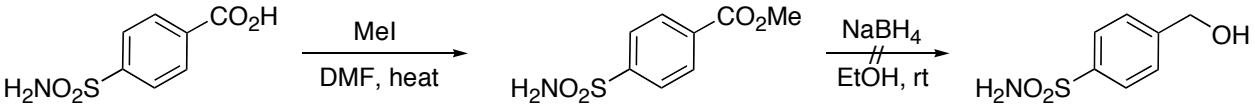
[240] Navia, M. A.; "A chicken in every pot, thanks to sulfonamide drugs." *Science* **2000**, *288*, 5474.
[241] Talley, J. J. "Selective inhibitors of cyclooxygenase-2 (COX-2)." *Prog. Med. Chem.* **1999**, *36*, 201-234.
[242] Zarghi, A.; Rao, P. N. P.; Knaus, E. E. "Sulfonamido, azidosulfonyl and *N*-acetylsulfonamido analgs of rofecoxib: 4-[4-(*N*-acetylsulfonamido)phenyl]-3-(4-methanesulfonylphenyl)-2(5*H*)furanone is a potent and selective cyclooxygenase-2 inhibitor." *Bio. Med Chem. Lett.* **2004**, *14*, 1957-1960.

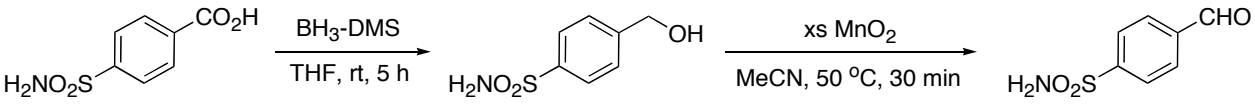
Early iterations of preparing aldehyde **4.35** were problematic. Despite heating, we immediately realized that **4.36** was insoluble in every ethereal solvent readily available. A slurry of **4.36** and THF was treated with LAH only to end up recovering starting material. We also examined methods for converting **4.36** to the corresponding methyl ester (**4.37**) followed by reduction to give intermediate benzyl alcohol **4.38** (Scheme 4.21). Methylation gave **4.36** in poor yield, and reduction became problematic due to the insolubility of the methyl ester. Addition of $NaBH_4$ to a slurry of **4.37**/EtOH resulted in recovery of the ester.[243]



4.36 **4.37** **4.38**

Scheme 4.20. Failed attempt at synthesizing benzyl alcohol **4.38** via esterification of acid **4.36**.

Experimentation with BH_3•DMS eventually provided the desired aldehyde (**4.35**). A slurry of carboxylic acid **4.36** and THF treated with an excess of BH_3•DMS provided benzyl alcohol **4.38** in 74% yield after five hours of mixing. Treatment of the benzyl alcohol with a 10-fold excess of MnO_2 in warm MeCN provided aldehyde **4.32** in 63% yield after recrystallization from EtOAc and hexanes.

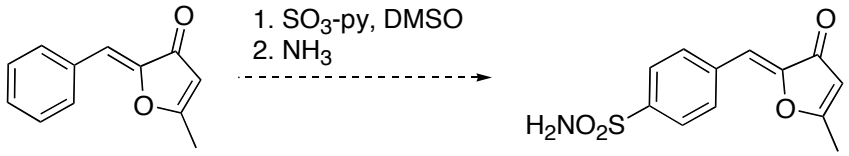


4.36 **4.38** **4.35**

Scheme 4.21. The synthesis of sulfonamide aldehyde **4.35**.

[243] For example of $NaBH_4$ reduction of an ester in polar protic solvents see: (a) Brown, M. S.; Rapoport, H. "The Reduction of Esters with Sodium Borohydride." *J. Org. Chem.* **1963**, *28*, 3261-3263; (b) Soai, K.; Oyamada, H.; Takase, M.; Ookawa, A. "Practical Procedure for the Chemoselective Reduction of Esters by Sodium Borohydride. Effect of the Slow Addition of Methanol." *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1948-1953.

Solubility played a critical role in attempting to prepare derivative **4.34**. Early experiments employing several Mukaiyama aldol protocols proved difficult because of the poor solubility of **4.35** in THF and DCM. The reaction slurry was treated with **4.10** only to observe a complex crude reaction mixture after several days with decomposition of the starting material. Mukaiyama aldol chemistry mediated by $TiCl_4$ in DCM resulted in slight conversion and the isolation of a trace crude product exhibiting a ^{1}H-NMR spectrum consistent with the formation of **4.31**. Repetition of the BF_3•OEt_2-based protocol with HMPA as a co-solvent resulted in recovery of the starting aldehyde (**4.35**). A new route to **4.34** through the reaction of **4.23** and SO_3-py[244] is currently underway (Scheme 4.23).



4.23 **4.34**

Scheme 4.22. Projected route to sulfonamide **4.34** from **4.23**.

4.2.5. Conclusions

The interesting link between NSAIDs and colorectal cancer has spawned the interest to search for new COX-2 inhibitors. Inotilone (4.1) has screened well against cancer cell lines[221,245] and as such, has sparked a desire to prepare several analogs for comparative analysis in biological screening. An tentative array of these new derivatives, available through the Lewis-acid mediated aldol condensation of siloxyfuran **4.10** and benzaldehydes were prepared using

[244] For related transformation see: Zarghi, A.; Rao, P. N. P.; Knaus, E. E. "Sulfonamido, azidosulfonyl and *N*-acetylsulfonamido analogues of rofecoxib: 4-[4-(*N*-acetylsulfonamido)phenyl]-3-(4-methanesulfonylphenyl)-2(5*H*)furanone is a potent and selective cyclooxygenase-2 inhibitor." *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1957-1960.
[245] Piazza, G. A. Southern Research Institute, Birmingham, AL. Personal communication, May 2007.

unoptimized methods. Additionally, a new, expedient synthesis of 1-bromoacetylacetone (**4.3**) was developed which circumvented bis-silyl enol ether formation (**4.5**), thereby facilitating material throughput to these and other potential inotilone derivatives.

4.3. Experimental Details

4.3.1. General Remarks

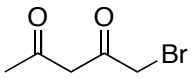
All transformations were conducted under an atmosphere of Ar. All reagents/reactants were used directly unless otherwise specified. Alkyl lithiums were titrated with diphenylacetic acid in dry THF prior to use.[104] Et_2O and THF were distilled over Na/benzophenone. Hexanes, TMSCl and DCM were distilled over CaH_2. Anhydrous MeCN (99.8%) was purchased from Aldrich in a Sure/Seal bottle and used directly. Bromine (99+%) was purchased from Acros and used directly. MnO_2 (≥99%) was purchased from Aldrich and heated (~150 ^oC) for 24 h prior to use. All glassware was either flame dried or oven-dried overnight (~120 ^oC) prior to use then cooled under an atmosphere of Ar. Silyl enol ether **4.4**,[227] *bis*-silyl enol ether **4.5**,[227] 4-nitrobenzaldehyde,[246] and 4-sulfonamidebenzaldehyde[247] were prepared identically from literature procedures. NBS was freshly recrystallized from water then dried in a vacuum oven overnight (~70 ^oC) prior to use.

Proton magnetic resonance spectra (^{1}H-NMR) were recorded at either 360 or 500 MHz. Carbon magnetic resonance spectra (^{13}C-NMR) were recorded on spectrometers operating at either 91 or 127 MHz. All spectra are referenced to TMS internal standard. Nuclear Overhauser enhancement (nOe) difference spectroscopy experiments were performed on a 500 MHz spectrometer. Infrared spectroscopy data (IR) was recorded on a Jasco FT/IR-4100. High-resolution mass spectrometry (HRMS) was performed on an AutoSpec-Ultima NT. Flash column chromatography was performed using Silicycle silica gel (230-400 mesh). TLC

[246] Hunsen, M. "Carboxylic acids from primary alcohols and aldehydes by a pyridinium chlorochromate-catalyzed oxidation." *Synthesis* **2005**, 2487-2490.
[247] Burton, H.; Hu, P. F. "Synthesis of some p-arylsulfonylbenzaldehydes and related aldehydes and ketones." *J. Chem. Soc.* **1948**, 601-603.

visualization was achieved by ultraviolet light (254 nm), I_2 vapors, or an acidic *p*-anisaldehyde or vanillin stain.

4.3.2. Starting Materials



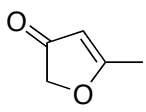
1-Bromopentane-2,4-dione (4.3). *From bis-silyl enol ether* **4.5**. To a solution of *bis*-silyl enol ether **4.5** (11.48 mg, 46.95 mmol) and freshly distilled dichloromethane (47 mL) was added recrystallized NBS (9.27 g, 52.1 mmol) slowly over 10 min at room temperature (*CAUTION!* Addition causes sudden temperature increase resulting in boiling DCM). The reaction proceeded at room temperature for 20 h at which point the dark brown solution was washed with dH_2O (2 x 30 mL). The combined aqueous layers were back extracted with DCM (1 x 20 mL). The combined organic layers were dried ($MgSO_4$) then concentrated by rotary evaporation at 30 ^oC. The resultant brown oil was purified over silica (7:3 hexanes:Et_2O). Concentration of the fractions gave the title compound (7.28 g, 40.7 mmol, 87%) with several inseparable impurities. The product exhibited physical properties consistent with those reported in the literature.[224]

^{1}H NMR ($CDCl_3$, 360 MHz): δ 14.93 (br s, 1H); 5.79 (s, 1H); 3.85 (s, 2H); 2.12 (s, 3H).

^{13}C NMR ($CDCl_3$, 127 MHz): δ 191.8; 186.5; 99.2; 30.6; 24.8.

From acetylacetone. To a stirred solution of acetylacetone (1.0 mL, 10 mmol) in DCM (9 mL) cooled to -15 ^oC for 30 min was added Br_2 (0.52 mL, 10 mmol, 1.0 equiv) via addition funnel slowly over 45 min. After addition was complete, the reaction was held at -15 ^oC for an additional 45 min then warmed to rt for an additional 1.5 h. Pressurized lab air was then bubbled through the reaction mixture using a glass pipette for 2 h (*CAUTION!* Evolution of HBr gas)

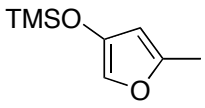
causing concentration of the reaction mixture. The crude oil was heated (65 °C) to remove residual acetylacetone (13 mm Hg, 35 °C) and the resultant deep blue crude oil was purified by flash chromatography over silica (8:2 then 6:4 hexanes:DCM) to provide semi-pure **4.3** (1.17 g, 6.51 mmol, 65%) as a yellow/orange oil.



5-Methylfuran-3-one (4.9). To a stirred solution of α-bromoacetylacetone (**4.3**, 2.171 g, 12.1 mmol) in diethyl ether (24 mL) submerged in a water bath (22 °C) was added crystalline K_2CO_3 (3.34 g, 24.2 mmol, 2 equiv). The reaction vessel was submerged in a water bath and the contents were vigorously stirred until the reaction was judged complete by the disappearance of the starting material (~10 min, TLC). The resultant heterogeneous solution was filtered over a pad of sand/celite to give a yellow filtrate. Concentration of the filtrate by rotary evaporation (25 °C) gave the desired furanone (1.187 g, 12.1 mmol, *quantitative*) as an orange oil. The material exhibited spectroscopic properties previously reported in the literature.[224]

^{1}H-NMR (360 MHz, $CDCl_3$): δ 5.49 (d, 1H, J = 0.7 Hz); 4.50 (d, 2H, J = 0.7 Hz); 2.25 (d, 3H, J = 0.7 Hz).

^{13}C-NMR (127 MHz, $CDCl_3$): δ 202.7; 191.5; 104.7; 75.3; 16.6.



5-Methyl-3-trimethylsilyloxyfuran (4.10). To a stirred solution of furanone **4.9** (1.19 g, 12.1 mmol) and DCM (41 mL) cooled at -78 °C was added Et_3N (2.1 mL, 15 mmol, 1.2 equiv). Upon addition of the base, the reaction adopted a slightly red color and proceeded at -78 °C for 1 h. The solution was treated with TMSCl (2.1 mL, 16 mmol, 1.3 equiv), which caused the reaction to fade from slightly red back to yellow. The reaction

proceeded at -78 °C for an additional 30 min after addition then was warmed to 0 °C for 2 h. The reaction mixture was concentrated by rotary evaporation to give a white paste, which was treated with hexanes (50 mL) and stirred vigorously at room temperature for 30 min. The resultant heterogeneous solution was filtered over a pad of celite/sand to provide a yellow filtrate, which was concentrated via rotary evaporation to provide the title compound (**4.10**) as brown oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.96 (s, 1H); 5.75 (s, 1H); 2.20 (s, 3H); 0.22 (s, 9H).

^{13}C NMR ($CDCl_3$, 90 MHz): δ 150.78; 143.50; 126.26; 103.06; 14.03; -0.30.

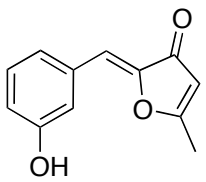
Alternatively, a solution of enone **4.9** (1.04 g, 10.6 mmol) in dry THF (5 mL) was added dropwise via cannula to a solution of freshly prepared LDA (11.7 mmol, 1.10 equiv) in THF (12 mL) at -78 °C. Addition caused a color change from orange/brown to deep, dark red. The solution was stirred at -78 °C for an additional 10 min before slowly introducing freshly distilled TMSCl (1.62 mL, 12.7 mmol, 1.20 equiv). After an additional 10 min at -78 °C, the reaction was warmed to 0 °C for 1 h. The resulting solution was concentrated by rotary evaporation to give a brown/orange oil, which was then treated with pentane (50 mL) to precipitate salts. The reaction mixture was filtered over a pad of Celite/sand and the filter cake was rinsed with additional pentane (50 mL). Concentration of the filtrate gave the title compound (**4.10**, 1.63 g, 9.59 mmol, 90.5%) as a brown oil that was pure enough for further steps. *This material is stable and storable at -20 °C for over 1 month with minimal to no decomposition.*

4.3.3. Inotilone Derivatives

Method A: general procedure for BF_3-mediated Mukaiyama aldol reactions. To a stirred solution of trimethylsilyl enol ether **4.10** (1.76 mmol) in dry THF (3 mL) and desired

benzaldehyde (1.38 mmol) cooled to -78 ^{o}C (20 min) was added BF_3•OEt_2 (1.1 equiv per heteroatom) from a plastic syringe slowly over 5 min. Upon addition, the reaction mixture was stirred at -24 ^{o}C (±3 ^{o}C) until the reaction appeared stagnant (~3-7 d). The reaction was allowed to warm to room temperature then slowly treated with a saturated solution of $NaHCO_3$ (3 mL; CAUTION! Evolution of CO_2 occurs!). The biphasic reaction mixture was treated with dH_2O (1 mL) and EtOAc (5 mL). Upon an initial separation, the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water (1 x 5 mL), brine (1 x 10 mL), dried ($MgSO_4$) then concentrated. The resultant crude material was purified by flash chromatography and/or recrystallization as specified for each product entry.

Method B: general procedure for $TiCl_4$-mediated Mukaiyama aldol reactions. To a stirred solution of the desired benzaldehyde (1.0 mmol) in DCM (3 mL) at -78 ^{o}C was added 1 M $TiCl_4$ in DCM (1 mmol, 1 mL) from a plastic syringe. The solution was stired at -78 ^{o}C for 20 min at which point a solution of silyl enol ether **4.10** (1.5 mmol) in DCM (1 mL) was introduced slowly to the reaction mixture (~5 min) via glass syringe followed by a rinse of the syringe with additional DCM (1 mL). The reaction proceeded gradually warming to room temperature and was continued to mix until the reaction appeared stagnant (~3-5 d). The reaction was then diluted with 2 N HCl (5 mL) in one portion then, upon an initial separation, the aqueous layer was extracted with EtOAc (4 x 5 mL). The combined organic layers were washed with brine (1 x 20 mL), dried ($MgSO_4$) then treated with activated charcoal. The solution was filtered through sand/Celite then concentrated by rotary evaporation providing a crude product that was purified by either flash chromatography and/or recrystallization as specified for each product entry.



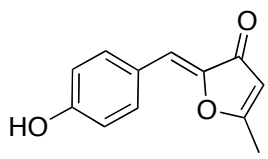
(2*Z*)-2-(3-Hydroxybenzylidene)-5-methylfuran-3-one (4.21). The title compound was prepared from the reaction of 3-hydroxybenzaldehyde (168 mg, 1.38 mmol) and **4.10** (300 mg, 1.76 mmol, 1.28 equiv) according to Method A using BF_3•OEt_2 (0.68 mL, 5.5 mmol, 4.0 equiv) as the Lewis acid. Purification of the crude product by flash chromatography (6:4 hexanes:EtOAc) afforded the title compound (53 mg, 0.26 mmol, 19%) as a yellow solid (mp: 171-172 ^{o}C)

^{1}H-NMR (500 MHz, DMSO-d6): δ 9.67 (s, 1H); 7.31-7.25 (m, 3H); 6.86-6.83 (m, 1H); 6.58 (s, 1H); 5.90 (s, 1H); 2.42 (s, 3H).

^{13}C-NMR (127 MHz, DMSO-d6): δ 187.0; 181.8; 157.5; 145.7; 132.7; 129.8; 122.4; 117.4; 117.2; 110.8; 105.3; 15.7.

IR (KBr pellet, cm^{-1}): 3083; 2362; 1686; 1641; 900; 870; 850; 789; 729.

HRMS: calcd. For $C_{12}H_9O_3$ $[M]^+$ 201.0552, found 201.0552.



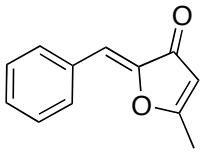
(2*Z*)-2-(4-Hydroxybenzylidene)-5-methylfuran-3-one (4.22). The title compound was prepared from the reaction of 4-hydroxybenzaldehyde (168 mg, 1.38 mmol) and **4.10** (300 mg, 1.76 mmol, 1.28 equiv) according to Method A using BF_3•OEt_2 (0.68 mL, 5.5 mmol, 4.0 equiv) as the Lewis acid. Purification of the crude product by flash chromatography (6:4 hexanes:EtOAc) afforded the title compound (169 mg, 0.841 mmol, 61% yield) as an orange/yellow solid (mp: 166-169 ^{o}C).

^{1}H-NMR (500 MHz, DMSO-d6): δ 10.14 (s, 1H); 7.74 (d, 2H, J = 8.5 Hz); 6.86 (d, 2H, J = 8.5 Hz); 6.61 (s, 1H); 5.85 (s, 1H); 2.40 (d, 3H, J = 0.5 Hz).

^{13}C-NMR (127 MHz, DMSO-d6): δ 186.6; 108.6; 159.4; 144.4; 133.3; 122.6; 116.0; 111.3; 105.4; 15.6.

IR (thin film cm^{-1}): 3411; 3290; 1683; 1638; 837.

HRMS: calcd. For $C_{12}H_{10}O_3$ $[M]^+$ 202.0632, found 202.0630



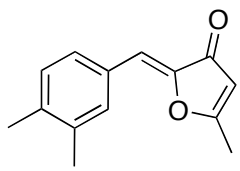
(2*Z*)-2-Benzylidene-5-methylfuran-3-one (4.23). The title compound was prepared from the reaction of benzaldehyde (0.141 mL, 1.38 mmol) and **4.10** (300 mg, 1.76 mmol, 1.28 equiv) according to Method A using BF_3•OEt_2 (0.51 mL, 4.1 mmol, 3.0 equiv) as the Lewis acid. The crude product was purified by flash column chromatography (8:2 hexanes:EtOAc) to afford the title compound (64 mg, 0.35 mmol, 25% yield) as yellow crystals (mp: 116-118 ^oC).

^{1}H-NMR (500 MHz, DMSO-d6): δ 7.89-7.87 (m, 2H); 7.51-7.42 (m, 3H); 6.70 (s, 1H); 5.91 (s, 1H); 2.43 (s, 3H).

^{13}C-NMR (127 MHz, DMSO-d6): δ 187.0; 182.0; 145.8; 131.6; 131.1; 129.8; 128.9; 110.5; 105.4; 15.7.

IR (KBr pellet, cm^{-1}): 3100; 2368; 1688; 1645; 855; 828; 764.

HRMS: calcd. For $C_{12}H_{10}O_2$ $[M]^+$ 186.0681, found 186.0675



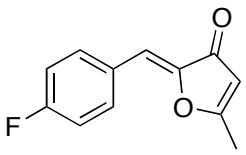
(2*Z*)-2-(3,4-Dimethylbenzylidene)-5-methylfuran-3-one (4.24). The title compound was prepared from the reaction of 3,4-dimethylbenzaldehyde (185 mg, 1.38 mmol) and **4.10** (300 mg, 1.76 mmol, 1.28 equiv) according to Method A using BF_3•OEt_2 (0.51 mL, 4.1 mmol, 3.0 equiv) as the Lewis acid. Purification of the crude product by flash chromatography (7:3 hexanes:EtOAc) afforded the title compound (124 mg, 0.580 mmol, 42%) as a yellow solid (mp: 99-100 ^oC).

^{1}H-NMR (500 MHz, DMSO-d6): δ 7.64-7.63 (m, 2H); 7.25 (d, 1H, *J* = 8.5 Hz); 6.60 (s, 1H); 5.88 (d, 1H, *J* = 0.5 Hz); 2.43 (d, 3H, *J* = 0.5 Hz); 2.26 (s, 6H).

^{13}C-NMR (127 MHz, DMSO-d6): δ 186.9; 181.5; 145.4; 138.9; 136.8; 132.2; 130.1; 129.2; 128.9; 110.8; 105.4; 19.4; 19.3; 15.7.

IR (KBr pellet, cm^{-1}): 2964; 2367; 2341; 1690; 1642; 841; 823; 793.

HRMS: calcd. For $C_{14}H_{14}O_2$ $[M]^+$ 214.0994, found 214.0998



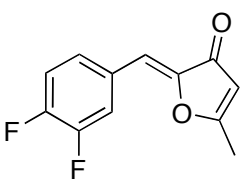
(2*Z*)-2-(4-Fluorobenzylidene)-5-methylfuran-3-one (4.26). The title compound was prepared from the reaction of 4-fluorobenzaldehyde (0.11 mL, 1.0 mmol) and **4.10** (256 mg, 1.50 mmol, 1.50 equiv) using Method B employing 1M $TiCl_4$/DCM (2.2 mL, 2.2 mmol, 2.2 equiv) as the Lewis acid. Purification of the crude product by flash chromatography (8:2 hexanes:EtOAc) afforded the desired title compound (29 mg, 14 mmol, 14%) as a brown/yellow solid (mp: 124-126 ^{o}C).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.79 (dd, 2H, *J* = 8.6, 5.6 Hz); 7.11 (t, 2H, *J* = 8.6 Hz); 6.65 (s, 1H); 5.72 (s, 1H); 2.40 (s, 3H)

^{13}C-NMR (127 MHz, $CDCl_3$): δ 188.2; 180.9; 163.4 (d, $J^{l}_{F\text{-}C}$ = 255.1 Hz); 146.1 (d, *J* = 2.7 Hz); 133.4 (d, *J* = 8.6 Hz); 128.4 (d, *J* = 3.7 Hz); 116.0 (d, *J* = 22.2 Hz); 110.8; 106.1; 16.2.

IR (KBr pellet, cm^{-1}): 1694; 1605; 844; 658.

HRMS: calcd. For $C_{12}H_9O_2F$ $[M]^+$ 204.0575, found 204.0578



(2*Z*)-2-(3,4-Difluorobenzylidene)-5-methylfuran-3-one (4.27). The title compound was prepared from the reaction of 3,4-difluorobenzaldehyde (0.11 mL, 1.0 mmol) and **4.10** (256 mg, 1.5 mmol, 1.5 equiv) using Method

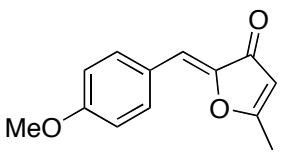
B employing 1M $TiCl_4$/DCM (1.1 mL, 1.1 mmol, 1.1 equiv) as the Lewis acid. Flash chromatography (8:2 hexanes:EtOAc) afforded the title compound (98 mg, 54 mmol, 54%) as a brown, crystalline material (mp: 141-143 ^oC).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.74-7.70 (m, 1H); 7.47-7.44 (m, 1H); 7.23-7.18 (m, 1H); 6.58 (s, 1H); 5.73 (d, 1H, *J* = 0.5 Hz); 2.42 (d, 3H, *J* = 0.5 Hz).

^{13}C-NMR (127 MHz, $CDCl_3$): δ 188.0; 181.2; 151.1 (dd, *J* = 254.6, 12.9 Hz); 150.4 (dd, *J* = 249.1, 13.0 Hz); 146.4 (d, *J* = 2.7 Hz); 129.2 (dd, *J* = 6.8, 4.2 Hz); 128.2 (dd, *J* = 6.4, 3.6); 119.6 (d, *J* = 18.3 Hz); 117.7 (d, *J* = 17.6 Hz); 109.6 (t, *J* = 2.1 Hz); 106.1; 16.2.

IR (KBr pellet, cm^{-1}): 1694; 1653; 1602; 897; 829; 792; 653.

HRMS: calcd. For $C_{12}H_9O_2F_2$ $[M]^+$ 222.0492, found 222.0486



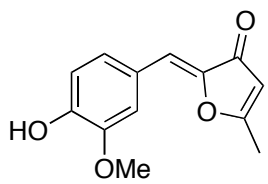
(2*Z*)-2-(4-Methoxybenzylidene)-5-methylfuran-3-one (4.31). The title compound was prepared from the reaction of 4-methoxybenzaldehyde (0.12 mL, 1.0 mmol) and **4.10** (256 mg, 1.5 mmol, 1.5 equiv) using Method B employing 1M $TiCl_4$/DCM (1.0 mL, 1.0 mmol, 1.0 equiv) as the Lewis acid. Flash chromatography (7:3 hexanes:EtOAc) of the crude reaction mixture provided the title compound (132 mg, 0.61 mmol, 61%) as a yellow/brown solid (mp: 92-95 ^oC).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.76 (d, 2H, *J* = 8.8 Hz); 6.94 (d, 2H, *J* = 8.8 Hz); 6.67 (s, 1H); 5.70 (s, 1H); 3.85 (s, 3H); 2.39 (d, 3H, *J* = 0.8 Hz).

^{13}C-NMR (127 MHz, $CDCl_3$): δ 188.1; 180.0; 160.9; 145.5; 133.2; 124.7; 114.4; 112.2; 106.1; 55.3; 16.1.

IR (thin film cm^{-1}): 3003; 2960; 2935; 2839; 1693; 1645; 1599; 1512; 831.

HRMS: calcd. For $C_{13}H_{12}O_3$ $[M]^+$ 216.0786, found 216.0787.



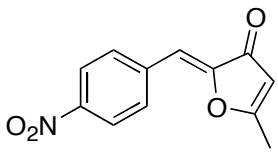
(2*Z*) -2-(3-Hydroxy-4-methoxybenzylidene)-5-methylfuran-3-one (4.32). The title compound was prepared from the reaction of 4-hydroxy-3-methoxybenzaldehyde (152 mg, 1.0 mmol) and **4.10** (256 mg, 1.5 mmol, 1.5 equiv) using Method B employing 1M $TiCl_4$/DCM (2.0 mL, 2.0 mmol, 2.0 equiv) as the Lewis acid. Flash chromatography (6:4 hexanes:EtOAc) of the crude product provided the title compound (144 mg, 0.62 mmol, 62%) as a yellow solid (mp: 159-161 ^oC). Recrystallization by slow evaporation from acetone provided orange cubes.

^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.38-7.34 (m, 2H, J = 8.2 Hz); 6.97 (d, 1H, J = 8.2 Hz); 6.66 (s, 1H); 6.13 (s, 1H); 5.72 (brs, 1H); 3.94 (s, 3H); 2.40 (d, 3H, J = 0.8 Hz).

^{13}C-NMR (127 MHz, $CDCl_3$): δ 188.2; 180.0; 147.9; 146.8; 145.5; 126.5; 124.5; 115.1; 113.4; 112.9; 106.2; 55.9; 16.1.

IR (thin film cm^{-1}): 3251; 1687; 1641; 1581; 1514.

HRMS: calcd. For $C_{13}H_{12}O_4$ $[M]^+$ 232.0736, found 232.0739.



(2*Z*)-2-(4-Nitrobenzylidene)-5-methylfuran-3-one (4.33). The title compound was prepared from the reaction of 4-nitrobenzaldehyde (151 mg, 1.0 mmol) and **4.10** (256 mg, 1.5 mmol, 1.5 equiv) using Method B employing 1M $TiCl_4$/DCM (1.1 mL, 1.1 mmol, 1.1 equiv) as the Lewis acid. Flash chromatography (8:2 hexanes:EtOAc) of the crude product provided the title compound (111 mg, 0.480 mmol, 48%) as a yellow solid (mp: 181-183 ^oC).

^{1}H-NMR (360 MHz, $CDCl_3$): δ 8.26 (d, 2H, J = 6.5 Hz); 7.94 (d, 2H, J = 6.5 Hz); 6.68 (s, 1H); 5.77 (s, 1H); 2.46 (d, 3H, J = 0.4 Hz).

^{13}C-NMR (127 MHz, $CDCl_3$): δ 187.9; 181.9; 147.7; 147.6; 138.4; 131.7; 123.9; 108.5; 106.1; 16.2.

IR (KBr pellet, cm^{-1}): 3115; 1700; 1655; 1608; 954; 882; 865; 847; 818; 749; 690.

HRMS: calcd. For $C_{12}H_9NO_4$ $[M]^+$ 231.0532, found 231.0532.