REACTIVITY STUDIES OF ARENE-CIS-DIOLS IN CYCLOADDITIONS AND POTASSIUM PERMANGANATE OXIDATIONS: SYNTHESIS OF THE CORRESPONDING ARENE-TRANS-DIOLS AND AN APPROACH TO THE SYNTHESIS OF (+)-PANCRTISTATIN.

by

Bryan P. McKibben

Dissertation submitted to the Faculty of the Virginia Polytechnic Institute and State University in partial fulfillment of the requirements for the degree of

Doctor of Philosophy in Chemistry

Approved:

Dr. Tomas Hudlicky, Chairman

Dr. James Tanko

Dr. Joseph Merola

Dr. David Kingston

Dr. Richard Gandour

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Dr. Tomas Hudlicky, Chairman
Chemistry

(Abstract)

Potassium permanganate oxidations and novel cycloaddition chemistry of the arene-cis-diols (7) were investigated. It was found that permanganate oxidation of arene-cis-diols yielded a mixture of 2 products, (157a) and (157b) in low yield. The influence of the C1-substituent on the outcome of the reaction was found to be a complex mixture of steric and electronic effects. In the area of cycloaddition chemistry of protected (7), this thesis describes novel [4+2] cycloadditions with quinones along with the first published report of benzyne and nitrile oxide cycloadditions of these homochiral molecules. The structure of the cycloadducts were elucidated by nOe as well as 2D-NMR analysis and were supported by Frontier Molecular Orbital theory. Finally, arene-trans-diols (200) were synthesized from (7) by a multistep stereoselective protection/deprotection sequence utilizing the Diels-Alder reaction. These compounds serve as intermediates in an approach to the amaryllidaceae alkaloid (+)-pancratistatin (12).
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...to the four most important people in my life-

my wife - Denise
my father and mother - Robert and Janice McKibben
and my grandmother - Mary Louise Pflaum

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I. INTRODUCTION

The area of biotransformations is a growing field. It represents a unification of two distinct areas of research, chemistry and microbiology. Biotransformations or biocatalysis\textsuperscript{1} are chemical transformations mediated by either purified enzymes or by whole cell organisms (for example, bacteria, fungi, plant or mammalian tissue culture). Included under this broad title are stereoselective hydrolysis, esterification, oxidation, and reduction reactions catalyzed by enzymes. There are several advantages and disadvantages involved with using biocatalysis in chemical synthesis.\textsuperscript{2}

Advantages

1. Enzymes catalyze a broad spectrum of reactions with high turnover numbers. Rate enhancements approach 10\textsuperscript{12} fold.
2. Enzymes may accept a wide range of substrates.
3. Enzymes are highly regio and stereoselective.
4. Enzyme reactions take place under mild conditions, room temperature at pH 6-8, this minimizes problems of isomerization, racemization and epimerization.

Disadvantages

1. Instability of some enzyme systems, which can be overcome by immobilization/membrane encapsulation
2. Cofactor requirements for some enzyme systems.

Despite these disadvantages, biotransformations have become a primary means of generating chiral starting materials which otherwise would be impossible to make. Organic chemists have utilized biotransformations to generate chiral starting materials or intermediates for stereospecific syntheses.\textsuperscript{3} Robert's\textsuperscript{4} synthesis of carbovir (4), a potential HIV inhibitor, and the preparation of (5), a synthon for hypocholesteremics, exemplify their use (Figure 1). The key step in the synthesis of both (4) and (5) is the
enzyme mediated hydrolysis of the racemic propyl ester which yields two asymmetric products (3 and 2; each possessing > 95% enantiomeric excess (ee)).

![Chemical Reaction Diagram]

Figure 1. Use of Biocatalysis in Organic Synthesis

Recently, it has been suggested that biotransformations could be used to remove toxic aromatic waste from the environment.\textsuperscript{5} It has been known for years that the soil bacterium \textit{Pseudomonas putida} oxidatively degrades aromatic compounds (6) to catechols (8) and ultimately to muconates (Figure 2). In 1970 Gibson\textsuperscript{6} isolated a mutant strain of bacteria (\textit{Pseudomonas putida} 39D) that arrested the oxidation to catechols at the stage of the substituted cyclohexadiene-cis-diol or arene-cis-diol (7). These bacterial metabolites are >95\% enantiomerically pure. Industrially, aromatic waste such as benzene and chlorobenzene (over 3 million tons of each produced annually)\textsuperscript{7} could be converted into chiral synthons of type (7) which is useful to organic chemists as a chiral synthon.
Figure 2. Biooxidation of Aromatic Compounds by *Pseudomonas putida*

Chemists have realized the synthetic utility of compounds possessing the general structure (7). In 1986, Ley\(^8\) published the total synthesis of (+/-)-pinitol (10) utilizing the *meso*-cyclohexadiene-*cis*-diol as a chiral synthon. Since then, the use of these synthons in enantioselective synthesis has grown dramatically (Graph 1). Compounds such as (7) have found use in the enantioselective synthesis of a structurally diverse set of compounds, included are PGE\(_2\)\(\alpha\) (9),\(^9\) (+)-pinitol (10)\(^10\) and (+)-kifunensine (11) (Figure 3).\(^11\) Because demand for these chiral synthons has increased appreciably, some of the arene-*cis*-diols are now available commercially.\(^12\)

Figure 3. Use of Arene-**Cis**-Diols in Organic Synthesis
This thesis describes the synthetic utility of the arene-\textit{cis}-diols in several oxidative and cycloaddition processes culminating in an enantioselective approach to the synthesis of the potential chemotherapeutic compound (+)-pancratistatin (12). Also included in this thesis is a general methodology for the synthesis of arene-\textit{trans}-diols (13), possessing high enantiomeric excess, from the arene-\textit{cis}-diols through a protection-deprotection sequence. Arene-\textit{trans}-dial (13) represents the key intermediate in the synthesis of (+)-pancratistatin (12).

![Figure 4. Retrosynthetic Analysis of (+)-Pancratistatin (12)](image-url)
Graph 1. Growth of Arene-Cis-Diol Use in Synthesis and Isolation
II. HISTORICAL

1. Cycloaddition Chemistry of Arene-Cis-Diols
   1.1 Diels-Alder Cycloadditions

   Over the last five years there has been a plethora of research published concerning [4 +2] cycloadditions with substituted arene-cis-diols. Most of the work describes the reactivity trends of these diene systems in cycloaddition reactions. Some of these complex, polycyclic cycloadducts have been used in the synthesis of natural products. Presented in this section is a comprehensive review of the [4+2] cycloaddition chemistry of 1-substituted-arene-cis-diols.

   The dimerization of the isopropylidene protected arene-cis-diols shows that the diene system can act both as a diene and a dienophile in [4+2] cycloaddition chemistry. Three research groups have reported the dimerization of these compounds. In general, the dimerization is stereoselective and yields a single isomeric product (Table 1). Hudlicky et al. studied the rate of such dimerizations with compounds (14b) and (14c). Table 1 shows dimerization occurs readily neat at 0°C and in solution at elevated temperature. The dimers (15) result from bond formation anti to the sterically bulky isopropylidene group with the electron rich 3-4 olefin acting as the dienophile. NMR methods and X-ray crystallography have been used for structural assignment. X-Ray crystallography of (15b) also confirmed the absolute configuration of the 1-bromo-arene-cis-diol.
Table 1. Dimerization of Substituted Arene-Cis-Diols

![Diagram showing dimerization of substituted arene-cis-diols.]

<table>
<thead>
<tr>
<th>Isopropyldiene</th>
<th>Dimerization Conditions</th>
<th>Yield (recovered 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14b</td>
<td>neat, 0°C, 15d</td>
<td>32 (61)</td>
</tr>
<tr>
<td>14c</td>
<td>neat, 0°C, 23d</td>
<td>49 (51)</td>
</tr>
<tr>
<td>14b</td>
<td>neat, rt, 8d</td>
<td>80</td>
</tr>
<tr>
<td>14c</td>
<td>neat, rt, 8d</td>
<td>71</td>
</tr>
<tr>
<td>14b</td>
<td>CDCl₃, 60°C, 8d (sealed tube)</td>
<td>70</td>
</tr>
<tr>
<td>14b</td>
<td>CDCl₃, 100°C, 2d (sealed tube)</td>
<td>---</td>
</tr>
<tr>
<td>14c</td>
<td>CDCl₃, 100°C, 6d (sealed tube)</td>
<td>95</td>
</tr>
</tbody>
</table>

1-Ethenyl-cyclohexadiene-5,6-cis-diol protected as the isopropyldiene (14d) has been shown to dimerize stereoselectively but not regioselectively (Figure 5). Dimerization occurs over two to three weeks at room temperature and yields three products; (16a), (16b) and (16c), in a 4:3:3 ratio, respectively. The lack of regioselectivity can be attributed to the reactive exocyclic diene system. The structure of adducts (16b) and (16c) were established by ¹H-NMR studies. The structure of compound (16a) was assigned on the basis of ¹H-NMR studies and confirmed by X-ray crystallography.
Hetero-[4 + 2] cycloaddition chemistry has been used to establish the absolute configuration of other *P. putida* 39-D metabolites. Protected or unprotected arene-cis-diols have reacted readily under mild conditions with 4-aryl-1,2,4-triazoline-3,5-diones, which have been previously described as one of the most reactive dienophiles known. In 1973, Gibson published the cycloaddition of the diacetoxy derivative of i-methyl-arene-cis-diol (17) with 4-(p-bromophenyl)-1,2,4-triazoline-3,5-dione (18). The reaction occurred instantaneously at 0°C to yield stereoselectively one cycloadduct (19). The absolute configuration of (19) was proven by X-ray crystallography. X-Ray diffraction confirmed initial speculation that cycloaddition occurred from the less hindered α-face of the diene.
Years later, Boyd showed that various unprotected arene-cis-diols react with 4-phenyl-1,2,4-triazoline-3,5-dione (20) (Figure 7). Esterification of the resulting cycloadduct with Mosher acid chloride (MTPA-Cl) produced the Mosher diester. Cycloaddition occurs from the β-face, directed by the hydroxyls as shown by X-Ray crystallography.

![Diagram of cycloaddition](image)

7 a: R = CH₃  
b: R = F  
c: R = CF₃  

Figure 7. Cycloaddition of (7) with (20) and Mosher Diester Formation

The Diels-Alder reactions of other dienophiles with substituted arene-cis-diols and their derivatives have not been as selective. N-phenyl and N-ethylmaleimide (NPM and NEM) react to give various ratios of cycloadducts. The product ratio of the cycloadducts was found to be determined by a combination of solvent and steric factors (Table 2). These results contrast the results of cycloadditions with 4-phenyl-1,2,4-triazoline-3,5-dione (20). Burnell hypothesized that the difference may arise in the transition state leading to the products. As (20) approaches in an endo manner and syn to the hydroxyls, Burnell believes this must lead to an unfavorable electrostatic interaction between the nitrogen's and the oxygen's lone pairs of electrons. This hypothesis does not fit with the X-ray crystallography data showing (20) reacted syn to the unprotected arene-cis-diols. As in epoxidation reactions, the hydroxyls must direct (20) to the β-face through electrostatic interactions.
Table 2. Cycloaddition of (14e) with Substituted Maleimides

![Chemical Structures]

<table>
<thead>
<tr>
<th>Dienophile</th>
<th>Solvent</th>
<th>Product Ratio (endo-syn:endo-anti)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPM</td>
<td>CHCl3</td>
<td>60:40</td>
<td>---</td>
</tr>
<tr>
<td>NPM</td>
<td>C₆H₆</td>
<td>52:48</td>
<td>86</td>
</tr>
<tr>
<td>NPM</td>
<td>H₂O</td>
<td>33:67</td>
<td>85</td>
</tr>
<tr>
<td>NPM</td>
<td>(CH₂OH)₂</td>
<td>27:73</td>
<td>95</td>
</tr>
<tr>
<td>NEM</td>
<td>CHCl₃</td>
<td>50:50</td>
<td>98</td>
</tr>
<tr>
<td>NEM</td>
<td>C₆H₆</td>
<td>39:61</td>
<td>96</td>
</tr>
<tr>
<td>NEM</td>
<td>H₂O</td>
<td>18:82</td>
<td>79</td>
</tr>
<tr>
<td>NEM</td>
<td>(CH₂OH)₂</td>
<td>12:88</td>
<td>73</td>
</tr>
</tbody>
</table>

The nitrosyl-Diels-Alder reaction of 1-substituted-arene-cis-diols has been one of the most useful cycloaddition reactions. The resulting cycloadducts have been used in the synthesis of aminoconduritols²⁶-²⁹ and alkaloids³⁰ through short enantiospecific reaction sequences.

The Diels-Alder reaction of nitroso compounds with 1-substituted-arene-cis-diols has been shown to be regioselective. Hudlicky and Olivo²⁶,²⁷ studied the reactions of substituted-arene-cis-diols with various nitrosyl compounds. The results are shown in Figure 8. The halogenated dienes all reacted in a similar manner generating cycloadducts where the nitrosyl oxygen is bonded to C1. This contradicts FMO theory which predicted the bromo (14b) and fluoro derivatives (14f) would yield compounds of opposite
regiochemistry. The regiochemistry was proven by reductive cleavage of the labile N-O bond of the two cycloadducts (24a) and (24c) yielding a common intermediate (25). Confident of the regiochemistry of cycloaddition, Hudlicky and Olivo synthesized conduramine A1(29),26 dihydroconduramine A126 and lycoricidine30 using the nitrosyl-Diels-Alder reaction as the key step in the reaction sequences.

![Figure 8. Proof of Nitrosyl Cycloaddition Regiochemistry](image)

An asymmetric nitrosyl-Diels-Alder reaction with the *meso*-arene-cis-diols has been used by both Piepersburg, (26a) (R = -(CH₃)₃),28 and Werbitzky, (26b) (R = Ac).29 The dienophile, nitrosyl-α-D-manno-furanosyl chloride (27), reacted with the protected arene-cis-diols to yield cycloadducts (28a) and (28b). The bicyclic dihydro-1,2-oxazines (28a, 28b) were then used by both groups in the synthesis of conduramine A1 (29).

![Figure 9. Route to Conduramine A1 (29)](image)
The stereochemistry of addition, syn or anti mode, has been shown to depend on the nature of the arene-cis-diol protecting group, substrate, and reaction conditions. Table 3 shows examples of the isopropylidene protected arene-cis-diol reacting with some linear dienophiles. In all of these cases, cycloaddition occurs anti to the sterically demanding isopropylidene group.

Table 3. Diels-Alder Reactions with Various Linear Dienophiles

<table>
<thead>
<tr>
<th>R</th>
<th>R₁</th>
<th>W</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>% Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>C(CH₃)₂</td>
<td>CH₂</td>
<td>CHCO₂Me</td>
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</tr>
<tr>
<td>H</td>
<td>C(CH₃)₂</td>
<td>CHCN</td>
<td>CHCO₂Me</td>
<td>--</td>
<td>--</td>
<td>52</td>
<td>18</td>
</tr>
<tr>
<td>H</td>
<td>C(CH₃)₂</td>
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<td>CHCO₂Me</td>
<td>--</td>
<td>--</td>
<td>70</td>
<td>18</td>
</tr>
<tr>
<td>H</td>
<td>C(CH₃)₂</td>
<td>C(CN)₂</td>
<td>C(CN)₂</td>
<td>--</td>
<td>--</td>
<td>71</td>
<td>18</td>
</tr>
<tr>
<td>H</td>
<td>C(CH₃)₂</td>
<td>NCCO₂Et</td>
<td>NCCO₂Et</td>
<td>--</td>
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<td>18</td>
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<td>H</td>
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<td>--</td>
<td>CCO₂Me</td>
<td>CCO₂Me</td>
<td>--</td>
<td>70</td>
<td>18</td>
</tr>
<tr>
<td>CF₃</td>
<td>C(CH₃)₂</td>
<td>--</td>
<td>CH</td>
<td>CCO₂Me</td>
<td>--</td>
<td>54</td>
<td>19</td>
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<tr>
<td>CF₃</td>
<td>C(CH₃)₂</td>
<td>--</td>
<td>CCO₂Me</td>
<td>CCO₂Me</td>
<td>--</td>
<td>83</td>
<td>18</td>
</tr>
<tr>
<td>F</td>
<td>C(CH₃)₂</td>
<td>--</td>
<td>CCO₂Et</td>
<td>CH</td>
<td>--</td>
<td>78</td>
<td>20</td>
</tr>
<tr>
<td>Cl</td>
<td>C(CH₃)₂</td>
<td>--</td>
<td>CCO₂Et</td>
<td>CH</td>
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<td>Br</td>
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<td>--</td>
<td>CCO₂Et</td>
<td>CH</td>
<td>--</td>
<td>61</td>
<td>20</td>
</tr>
<tr>
<td>I</td>
<td>C(CH₃)₂</td>
<td>--</td>
<td>CCO₂Et</td>
<td>CH</td>
<td>--</td>
<td>58</td>
<td>20</td>
</tr>
</tbody>
</table>

The 1-substituted-arene-cis-diol has been used in the intramolecular Diels-Alder reaction. This reaction has been used as a model system directed towards the total synthesis of morphine (30) and as a method for the determination of absolute stereochemistry of an o-chlorostyrene metabolite. Figure 10 (path a) was envisioned for the synthesis of the non-aromatic portion of morphine (31) from 1-methyl-arene-cis-
diol (7a). However, the intramolecular Diels-Alder reaction did not proceed as expected. Instead, the tricyclodecene system (33) was produced via cycloaddition of the cyclic diene system (C1-C2, C3-C4) with the sorbyl olefin (C9-C10). The tricyclic system (31) was produced in two more steps by oxidation of the alcohol to the ketone followed by a Cope rearrangement of the ketone.

Figure 10. Intramolecular Diels-Alder Reaction as a Model for Morphine (30)

A similar intramolecular Diels-Alder reaction has been conducted with metabolites of the biooxidation of o-chlorostyrene (34) and styrene (7d). In a proof of the absolute stereochemistry and enantiopurity of the o-chlorostyrene metabolite, both (34) and (7d) were transformed in three steps to the same tricyclic intermediate (36). In this convergent synthesis, the intramolecular Diels-Alder reaction was the key step.
Figure 11. Intramolecular Diels-Alder Reaction in a Proof of Stereochemistry

Hudlicky and Seoane have published a formal total synthesis of (-) zeylena (Figure 12), a unique hydrocarbon, through a Diels-Alder strategy. The synthesis began with 1-ethenyl-arene-cis-diol (7d). Mitsunobu inversion at C3 in the presence of the reactive triene system proved problematic. Protection of the triene system through the Diels-Alder reaction solved the problem. The more reactive diene (C1-C2, C7-C8) reacted with diethyl azodicarboxylate or its derivatives (37b: bis-(2,2,2-trichloroethyl)-azodicarboxylate, 37c: bis-((trimethylsilyl)-ethyl)-azodicarboxylate) at 0°C. Manipulation of the diols gave compound (38) in four steps. The latent diene system was regenerated (39) in low yield by the treatment with Zn(Cu) in 90% AcOH (38b) or Bu₄NF in THF (38c). The tetrane (39) underwent an intramolecular Diels-Alder reaction in 94% yield in benzene at 110°C. The synthesis of zeylena acetate (41) was accomplished in two more steps. This represented a formal synthesis of (-) zeylena.

The arene-cis-diols also underwent 1,4 reaction with singlet oxygen, which can be perceived as a hetero-Diels-Alder reaction (Table 4). Contrasting most [4+2] reactions of the free diols, singlet oxygen adds preferentially from the α-face (anti to the hydroxyls). Prior to reaction with singlet oxygen, protection of both alcohols as t-butyldimethylsilyl ethers or as an isopropylidene leads to exclusive formation of the anti-endo-peroxide (43e, 43g) and in the case of the t-butyldimethylsilyl ethers, the hydroperoxide.
(44) was also formed. These highly oxygenated bicyclic compounds have been used in the synthesis of conduritol. 40,41,42

![Chemical reactions and structures]

Figure 12. Total Synthesis of (-)-Zeylena

Table 4. Diels-Alder Reaction of (42) with Singlet Oxygen

<table>
<thead>
<tr>
<th>R</th>
<th>R_1</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>R=R_1=H</td>
<td></td>
<td>42a</td>
<td></td>
</tr>
<tr>
<td>R=CH_3, R_1=H</td>
<td></td>
<td>42b</td>
<td></td>
</tr>
<tr>
<td>R=H, R_1=SiMe_2Bu</td>
<td></td>
<td>42c</td>
<td></td>
</tr>
<tr>
<td>R=H, R_1=C(CH_3)_2</td>
<td></td>
<td>42d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>43a (74)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>43c (61)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>43d (39)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
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<td></td>
<td>43g</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>

15
Arene-cis-diols and their derivatives have been used extensively in the Diels-Alder reaction. The [4+2] cycloadditions have been used to determine the reactivity characteristics of these 1,3-diene systems. Application of these cycloadducts to the synthesis of natural products has been limited to a few examples (Table 7).

1. Cycloaddition Chemistry of Arene-Cis-Diols
   1.2 Miscellaneous Cycloadditions

In the cycloaddition chemistry of arene-cis-diols, the Diels-Alder reaction or the [4+2] cycloaddition reaction has been the most thoroughly investigated. However, there are some cases of [2+2] and higher order cycloadditions of the arene-cis-diols in the literature. This section will give a comprehensive review of cycloadditions reactions, other than the [4+2] variety, involving the arene-cis-diols.

Isopropylidene protected arene-cis-diols reacted with carbenes in what formally can be considered a [2+1] cycloaddition reaction. Dichlorocarbene generated in situ reacted with protected arene-cis-diols (Table 5). Addition of the carbene always proceeds selectively anti to the isopropylidene protecting group. Regioselectivity is determined by the electronic effect of the substituent on the cyclohexadiene ring. Protected 1-trifluoromethyl-arene-cis-diol reacted with dichlorocarbene regioselectively at the less substituted olefin to give compound (46a). 1-Substituents consisting of hydrogen, methyl and fluoro yielded mixtures of the two regioisomeric products.
The reaction of arene-cis-diols with ketenes has been briefly investigated. Diphenylketene reacted with protected meso-arene-cis-diol to yield a mixture of [2+2] and [4+2] cycloadducts (48a, 49a). Compound (49a) was unexpected since dienes and ketenes rarely react in a [4+2] manner. Interestingly, the reaction of protected 1-fluorocyclohexadiene-2,3-cis-diol with diphenyl ketene gave more of the [4+2] cycloadduct, whereas methylphenyl ketene reacted with meso-arene-cis-diol to give exclusively [2+2] product formation.
Meso-cyclohexadiene-2,3-cis-diol (7e) has been shown to undergo a photosensitized [2+2] dimerization (Figure 13)\textsuperscript{44} to yield an interesting tricyclic compound (50). Deoxygenation of (50) leads to the benzene dimer (51).

![Figure 13. Dimerization of Arene-Cis-Diols](image)

Protected 1-trifluoromethyl-arene-cis-diol (14a) reacted as a dienophile with cyclopentadiene to yield a single cycloadduct (52).\textsuperscript{48}

![Figure 14. [4+2] Reaction with Cyclopentadiene](image)

Roberts\textsuperscript{24} (53e) and Hudlicky\textsuperscript{33} (53e) have independently reported the [6+4] cycloaddition of arene-cis-diols with tropone.
The substituted-arene-\textit{cis}-diols react in [2+1], [2+2] and [6+4] manners to yield interesting polycyclic compounds. Application of these cycloadditions to the synthesis of natural products is expected in the near future.
Table 7. Natural Products Synthesized by Cycloaddition with Substituted Arene-Cis-Diols

<table>
<thead>
<tr>
<th>Diene</th>
<th>Cycloadduct</th>
<th>Natural Product</th>
<th>References</th>
</tr>
</thead>
<tbody>
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<td><img src="image1" alt="diene" /></td>
<td><img src="image2" alt="cycloadduct" /></td>
<td><img src="image3" alt="natural_product" /></td>
<td>41</td>
</tr>
<tr>
<td>conduitol A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image4" alt="diene" /></td>
<td><img src="image5" alt="cycloadduct" /></td>
<td><img src="image6" alt="natural_product" /></td>
<td>40</td>
</tr>
<tr>
<td>conduitol D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image7" alt="diene" /></td>
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<td>50</td>
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<td>(-)conduramine A1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image10" alt="diene" /></td>
<td><img src="image11" alt="cycloadduct" /></td>
<td><img src="image12" alt="natural_product" /></td>
<td>49</td>
</tr>
<tr>
<td>(-)conduramine A1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 7. Natural Products Synthesized by Cycloaddition with Substituted Arene-Cis-Diols

<table>
<thead>
<tr>
<th>Diene</th>
<th>Cycloadduct</th>
<th>Natural Product</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Diene 1" /></td>
<td><img src="image2" alt="Cycloadduct 1" /></td>
<td><img src="image3" alt="Natural Product 1" /></td>
<td>37</td>
</tr>
<tr>
<td><img src="image4" alt="Diene 2" /></td>
<td><img src="image5" alt="Cycloadduct 2" /></td>
<td><img src="image6" alt="Natural Product 2" /></td>
<td>42</td>
</tr>
<tr>
<td><img src="image7" alt="Diene 3" /></td>
<td><img src="image8" alt="Cycloadduct 3" /></td>
<td><img src="image9" alt="Natural Product 3" /></td>
<td>26, 28, 29</td>
</tr>
<tr>
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<td><img src="image11" alt="Cycloadduct 4" /></td>
<td><img src="image12" alt="Natural Product 4" /></td>
<td>30</td>
</tr>
</tbody>
</table>

pinitol

(-) dihydroconduritol C

conduramine A1

(+)-lycoricide
Table 7. Natural Products Synthesized by Cycloaddition with Substituted Arene-Cis-Diols

<table>
<thead>
<tr>
<th>Diene</th>
<th>Cycloadduct</th>
<th>Natural Product</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Diene" /></td>
<td><img src="image2" alt="Cycloadduct" /></td>
<td><img src="image3" alt="Natural Product" /></td>
<td>36</td>
</tr>
<tr>
<td>(-) zeylena</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| ![Diene](image4) | ![Cycloadduct](image5) | ![Natural Product](image6) | 36         |
| (-) zeylena | -          |                |            |
2. Potassium Permanganate Oxidations in Organic Synthesis
2.1 Oxidation of Mono-Alkenes

The potassium permanganate oxidation of alkenes dates back to the nineteenth century. Wagner\textsuperscript{51} published the dihydroxylation of alkenes using potassium permanganate in 1895. Since then, the use of potassium permanganate in organic chemistry has been underutilized as noted by a recent review on the subject.\textsuperscript{52} The reason for its underuse is that a great deal of functional groups are either incompatible with or are themselves oxidized by potassium permanganate. Selectivity is therefore a problem. The experimental,\textsuperscript{52} mechanistic,\textsuperscript{54} and synthetic\textsuperscript{53} aspects of alkene oxidation have been addressed. Recently, the addition of organic cosolvents (i.e. acetone and ethanol), magnesium sulfate,\textsuperscript{55} and phase transfer catalysis (PTC)\textsuperscript{56} has optimized the permanganate oxidation of some alkenes.

The mechanism of potassium permanganate oxidation of alkenes has drawn widespread attention.\textsuperscript{54} It is generally accepted that the cyclic manganese ester (55) is the first intermediate in the oxidation (Figure 16, path b). Recently, Sharpless, Rappe and Goddard\textsuperscript{57} have proposed the initial formation of a metallocyclooxetane intermediate (54) via [2+2] insertion of the alkene π bond into the metal oxo bond of the manganese (path a). The metallo intermediate then undergoes rearrangement to the cyclic manganese ester (55). Once the intermediate cyclic manganese ester (55) is formed, pH values, substrate structure as well as other factors determine the structure of the product. These possible products include glycols (56), α-hydroxy ketones (57) and products resulting from C-C bond cleavage (58).
The Lemieux-von Rudloff reagent (sodium periodate-potassium permanganate) gives selective C-C bond cleavage of alkenes. Mechanistically, the reaction proceeds through the cyclic manganese ester (55).\(^{58}\) The permanganate is the actual oxidant in the reaction and is continuously being regenerated from its reduced state by sodium periodate.

![Chemical Reaction Diagram]

Figure 16. Mechanism of Alkene Oxidation by Potassium Permanganate
As mentioned above, the selectivity of potassium permanganate oxidation in moderately functionalized molecules is very low. Potassium permanganate has been reported to oxidize alcohols, aldehydes, ketones, sulfides, thiols, alkynes and alkenes among other functional groups. However, there are published examples of selective oxidations using potassium permanganate. For example, homogeneous PTC selectively generate oxidation products in high yield. In these systems the product is protected against further oxidation by permanganate through the formation of a stable organomanganese species in non-aqueous media. The oxidation of dicyclopentadiene illustrates this point. Ogino selectively oxidized dicyclopentadiene (59) under homogeneous PTC in high yield to either tricyclic diol (60) or the bicyclic dialdehyde (61). Ogino manipulated the pH of the reaction to selectively give the two desired products.

![Diagram](image)

Figure 17. Selective Oxidation of Dicyclopentadiene Using PTC
The oxidation of alkenes with potassium permanganate is a synthetically useful yet underutilized reaction. Experimental improvements such as PTC catalysis\textsuperscript{56} have readily improved yields and selectivity of this reaction and such improvements are expected to increase the use of potassium permanganate in organic synthesis. The oxidation of highly functionalized compounds is still troublesome due to unwanted functional group oxidations. The next section describes the oxidation of bifunctional molecule, i.e., unconjugated and conjugated dienes.

\section*{2. Potassium Permanganate Oxidations in Organic Synthesis}
\subsection*{2.2 Oxidation of Conjugated and Unconjugated Dienes}

The potassium permanganate oxidation of dienes has been briefly studied. Potassium permanganate oxidation of conjugated dienes at one time was reported to be uncontrollable and the only products isolated were the result of full oxidative cleavage.\textsuperscript{60} The mechanism in the oxidation of unconjugated dienes is usually identical to the oxidation of simple alkenes (Section II.1). However, the permanganate oxidation of acyclic 1,5-dienes and cyclic 1,3-dienes yield products which do not fit the accepted mechanism for mono-alkenes. Several theories have been developed to explain these anomalies.

There are several publications which describe the potassium permanganate oxidation of unconjugated alkenes. The oxidation of dicyclopentadiene (59) was mentioned earlier.\textsuperscript{59} In this case, products resulted from oxidation of only one olefin in the diene system. In 1965, Sable \textit{et al.}\textsuperscript{61} studied the oxidation of 1,4-cyclohexadiene and reported the isolation of two products in low yield, the tetraol (62) and diol (63).
The oxidation of acyclic 1,5 dienes has also been studied. In general, only tetrahydrofuran adducts are isolated in yields up to 80% (Figure 19). Rojahn\textsuperscript{62} proposed a mechanism which involved the internal migration in the initially formed manganese ester (65) (path a). The cyclic Mn\textsuperscript{IV} ester (66) is then hydrolyzed to yield the tetrahydrofuran skeleton. In this mechanism Rojahn believed the permanganate is the sole source of the oxygens in tetrahydrofuran product. However, five years later, Ingold\textsuperscript{63} provided indirect evidence by \textsuperscript{18}O labelling experiments that the reaction may proceed through a penta-coordinated (67a) or hexa-coordinated (67b) manganese species (path b). The resulting tetrahydrofurans were found to possess two oxygens from the permanganate and one from the solvent (H\textsubscript{2}\textsuperscript{18}O). The mechanism of rearrangement from the highly coordinated manganese species to the resulting tetrahydrofuran has not been proposed.
Conjugated systems are known to react much faster than the unconjugated variety.\textsuperscript{61} There are four examples of potassium permanganate oxidation of 1,3 dienes. Sable \textit{et al.} has described the oxidation of cyclopentadiene (69a) and cyclohexadiene (69b).\textsuperscript{61,64} Both reacted to give \textit{cis}-epoxy-diols (70) as the major products in low yield. Sable proposed that the initial manganese ester (72) rearranged to an anhydride species of mixed oxidation states (73) which acts to oxidize the vicinal olefin intramolecularly (Figure 21). In support of their mechanism the minor product, (71a), was further subjected to potassium permanganate oxidation and less than 5\% of the epoxy-diol (70a) was formed. Therefore, diol (71a) is not an intermediate in the oxidation as Sable had originally believed.
In most cases, the epoxy-diols are isolated in less than 30% yield. Occidentalol (75) was subjected to potassium permanganate oxidation and yielded the epoxy diol (76). In a third example, the epoxy diol (78) was generated from the 1,3 diene system of a steroid (77).
Recently, Hudlicky and Mandel have subjected the protected-arene-\textit{cis}-diol (14c) to potassium permanganate oxidation conditions. They found the product distribution to be very sensitive to the reaction conditions. For example, epoxy diol (80) (Table 8) formation was favored by high concentrations, low reaction temperatures and short reaction times whereas glycol (79) was favored by lower concentrations, higher reaction temperatures and slower addition of reagents. Along with (80), PTC also produced products (81) and (82) which were isolated in less than 15% yield (82 was only isolated under PTC conditions). Hudlicky and Mandel proposed a mechanism in which the product distribution depends on the rate of 1,2 vs 1,4 addition of the permanganate to the polarized diene system. In this case, 1,4 addition can be considered formally as a [4+2] cycloaddition reaction. Support for 1,4 addition lies in the ease and regioselectivity with which (14) undergoes [4+2] cycloaddition reactions. The competition between 1,4 and 1,2-addition serves to explain the sensitivity of the product distribution on the reaction.
conditions. Hudlicky believes that kinetic 1,4 addition of permanganate to the diene is followed by rearrangement to either of the normal 1,2 adducts, which establishes equilibrium of the proposed intermediates (83), (84) and (85) (Figure 23), compounds from which all observed products can be easily derived. In all cases, it is believed that reoxidation of the manganese species occurs fast from another equivalent of permanganate. Further mechanistic studies need to be performed to explain these fascinating oxidations.

Table 8. Effect of Varying Conditions on the Oxidation of 1,3-Dienes

<table>
<thead>
<tr>
<th>T/°C</th>
<th>KMnO₄ (equiv)</th>
<th>%79</th>
<th>%80</th>
<th>%81 + %82</th>
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<tbody>
<tr>
<td>-5</td>
<td>0.85</td>
<td>45</td>
<td>45</td>
<td>10</td>
</tr>
<tr>
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<td>10</td>
</tr>
<tr>
<td>25</td>
<td>0.85</td>
<td>60</td>
<td>30</td>
<td>10</td>
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</tbody>
</table>
Figure 23. Hudlicky et al. Mechanism of 1,3-Diene Oxidation

The potassium permanganate oxidation of olefins has been used sparingly since its inception in the late nineteenth century. The major problem lies in functional group compatibility. Experimental methods including PTC have been used to improve selectivity and ultimately the yields of the products. The mechanism of the oxidation of 1,3-dienes or 1,5-dienes is not completely understood at the time of this writing.
3. Arene-Trans-Diols
3.1 Biological Activity

The interest in arene-trans-diols originates in their proposed intermediacy in the metabolism of aromatic compounds in eukaryotic cells. The multistep pathway of metabolic activation of benzene to the toxic compound that ultimately is responsible for its carcinogenic effects is not fully understood. It has been established that benzene is metabolized to benzene oxide (86) by a class of nonspecific monoxygenases known as cytochrome P-450 (Figure 24).

![Chemical structures and reactions]

Figure 24. Metabolism of Benzene in Eukaryotic Cells

In the metabolic pathway, benzene oxide can undergo several distinct reactions: a spontaneous isomerization to phenol (87) via a NIH shift (path a) or an enzyme catalyzed
hydration to the *trans*-dihydrodiol (88) (path b) or an addition of glutathione which occurs both nonenzymatically and through catalysis by soluble glutathione-S-epoxide transferases (path c) or addition of cellular macromolecules such as DNA, RNA and proteins (path d). It has been accepted that pathways a, b and c act to eliminate toxic benzene oxide from the cell and prevent cell mutagenesis which occurs by the reaction of (86) with DNA, RNA and proteins (path d). Recently Berchtold has suggested that the true toxic agents are the epoxydiols (89a and 89b). His studies involving bacterial mutagenesis indicate that these compounds are toxic towards cells and may also play a role in the carcinogenic effect of benzene.

According to the accepted theory, epoxide hydrases play a major role in removing the toxic benzene oxides and other arene oxides from the cell. It has been suggested and experimentally supported that the monoxygenases and epoxide hydrases are closely associated in the microsomal membranes. This association allows the cell to remove the toxic oxides immediately upon their formation.

The specificity and selectivity of these epoxide hydrases have drawn considerable attention in the literature. Various epoxide hydrases have been isolated and experimentally examined for both specificity and selectivity. Jerina has carried out hydration studies involving rabbit liver hydrase (RLH) (Table 9).

Table 9. Studies on Epoxide Hydration using Rabbit Liver Hydrase

<table>
<thead>
<tr>
<th>Substrate (µmol)</th>
<th>% conversion to diol</th>
<th>Observed $\alpha_D^{25}$ of diol (deg)</th>
<th>$\alpha_D^{25}$ of resolved diol (deg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclohexene oxide (250)</td>
<td>2</td>
<td>-32.6</td>
<td>-46.5</td>
</tr>
<tr>
<td>benzene oxide (110)</td>
<td>11</td>
<td>-250+/− 25</td>
<td>250</td>
</tr>
<tr>
<td>1,2-naphthalene oxide (100)</td>
<td>30</td>
<td>-47+/− 5</td>
<td>-159</td>
</tr>
<tr>
<td>9,10-phenanthrene oxide (50)</td>
<td>38</td>
<td>-87</td>
<td>-138</td>
</tr>
<tr>
<td>styrene oxide (100)</td>
<td>18</td>
<td>18</td>
<td>62</td>
</tr>
</tbody>
</table>
The stereospecificity of RLH was investigated by examining the stereochemistry of optically active \textit{trans}-dial produced from various oxides. In the carefully controlled reaction conditions, nonenzymatic opening of the oxides did not occur in any appreciable amount. These studies indicate that the stereospecificity of enzymatic hydration of oxides is very substrate dependent. The optical purities of the resulting \textit{trans}-dial range from 70\% (cyclohexene oxide) to < 1\% (styrene oxide) with benzene oxide estimated to be approximately 50\% optically pure.

3. Arene-\textit{Trans}-Diols
3.2 Synthesis

The synthetic utility of arene-\textit{trans}-dials has been slower to mature than that of the corresponding arene-\textit{cis}-dials. The reason for this is the fact that \textit{Psuedomonas putida} 39D oxidizes a wide variety of aromatic compounds in high enantiomeric excess. To date, over 200 arene-\textit{cis}-dials have undergone biooxidation. Contrasting this, Section III.1 showed the substrate dependence of the epoxide hydrase and low enantiomeric excess of the resulting arene-\textit{trans}-dials. Several chemical syntheses of arene-\textit{trans}-dials have been reported.\textsuperscript{36,69,71,72} These syntheses will be presented in this section along with their reactivity and synthetic utility as chiral synthons.

Plah and Oesch\textsuperscript{71} in 1977 published the synthesis of \textit{trans}-1,2-dihydroxy-1,2-dihydrobenzene or simply benzene-\textit{trans}-dial (Figure 25). The five step synthesis uses cheap starting materials and reagents and is designed to produce large amounts of racemic benzene-\textit{trans}-dial (96) (51\% overall yield). The synthesis begins with the Birch reduction of benzene producing 1,4-cyclohexadiene which is then monobrominated at
-70°C to yield (92) in 92% yield. The olefin (92) was then trans-dihydroxylated by the action of performic acid in formic acid followed by acidic methanolation. Attempts to debrominate (93) under various basic conditions proved unsuccessful. However, debromination of the diacetoxy-protected dibromide (94) with lithium chloride and lithium carbonate produced diene (95) in 80% yield. Removal of the acetates takes place at -30°C upon treatment with lithium tetrahydroaluminate. This method has been utilized for the synthesis of benzene-trans-diol and Carless ⁷³ has applied this methodology to the synthesis of racemic conduritol B, myo-inositol, chiro-inositol and other chiro-inositol derivatives (Table 10).

![Chemical Structures]

Figure 25. Racemic Synthesis of Benzene-Trans-Diol (96)

There have been two methods developed for the synthesis of chiral arene-trans-diols. Both methods are limited in that they have been specifically tailored for the production of a single trans-diol. The first method ⁶⁹ involves sequential enzymatic hydrolysis of the diacetate (95) derived from benzene (Figure 26). Porcine liver esterase
(PLE) hydrolyzes only one diacetate isomer in modest enantiomeric excess. Repeating the hydrolysis procedure on the enriched product yields both enantiomers of benzene-
trans-diol in high optical purity.

95 \[\text{AcCl, DMAP, Pyridine} \rightarrow 96a(97\text{% ee})\]

96a \[\text{NaOH, H}_2\text{O} \rightarrow 97(63\text{% ee}) + 98(62\text{% ee})\]

97 \[\rightarrow 98\] i) PLE ii) AcCl, Pyridine, DMAP iii) NaOH, H\(_2\)O

Figure 26. Synthesis of Chiral Benzene-
trans-diol with PLE

Another specialized enantioselective synthesis of an arene-
trans-diol (99) has been developed as an intermediate in the synthesis of (+)-pipoxide (100) and (+)-\(\beta\)-senepoxide (101).72

99

100

101
The synthesis begins with carboxylic acid (102) which undergoes bromolactonization to produce (103). Compound (103) is reduced with LiAlH₄ and acetylated to produce the diacetate (104). Cleavage of the anhydro-ring with HBr in acetic acid at 90°C gave the tribromide (105). The arene-trans-diol (99) was produced from (105) through a four-step sequence involving debromination, bromination, benzoate formation and subsequent debromination.

![Chemical Reaction Diagram]

i) Br₂, CHCl₃, 0°C ii) a) LiAlH₄ b) AcCl, Pyridine, 0°C, 84% iii) HBr, AcOH, 90°C, 71% iv) Zn, AcOH, 80% v) a) NBS, CCl₄, AIBN, 80°C b) sodium benzoate, DMF, 44% vi) Zn, AcOH, 70°C, 91%

Figure 27. Synthesis of an Arene-Trans-Diol (99)

The three enantioselective syntheses of arene-trans-diois (99), (100) and (101) represent specialized methods which gain access to these highly functionalized compounds. However, a general method which could be applied to the synthesis of a
wide range of arene-trans-diols is needed. Section III.4 will describe a general methodology for producing arene-trans-diols from the corresponding arene-cis-diols.

3. Arene-Trans-Diols
3.3 Reactivity and Utility

Since the initial synthesis of benzene-trans-diol in 1977,\textsuperscript{71} there has not been a great deal of effort describing the reactivity of arene-trans-diols. Few papers have been published which describe the reactivity and synthetic utility of these chiral synths.\textsuperscript{73} This section will describe the known reactivity of these compounds.

Ogawa\textsuperscript{72} utilized selective epoxidation as the last step in the synthesis of (+)-pipoxide (108). As expected, epoxidation of mono-protected trans-diol (106) results in oxidation of the β-face (Figure 28). In general, the regiochemistry of epoxidation is controlled by the C1-substituent. Similar selectivity has been ascribed to the arene-cis-diols.

![Reaction Scheme](image)

i) m-CPBA, ClCH\textsubscript{2}CH\textsubscript{2}Cl, phosphate buffer (pH 8), 87%

Figure 28. Selective Epoxidation of Arene-Trans-Diol (106)

Carless and Piepersburg\textsuperscript{73} have both utilized the hetero-Diels-Alder reaction in the synthesis of natural products. Carless showed that the arene-trans-diol undergoes
cycloaddition with singlet oxygen. The *endo*-peroxide (108) is reduced to the diol ether (109) *in situ* by the action of thiourea in methanol. This diol ether (109) served as a useful intermediate in the synthesis of various inositol phosphates (Table 10).

![Cycloaddition of (107) with Singlet Oxygen](image)

Piepersburg\textsuperscript{73} has utilized the hetero-Diels-Alder reaction with racemic *trans*-dual (110) to give the bicyclic dihydro-1,2-oxazine (111) which was reduced to the amino alcohol and subsequently acetylated to give (112). Compound (112) served as an intermediate in the synthesis of various aminocyclitols (Table 10). These three examples serve to show the synthetic utility of these molecules in organic synthesis.

![Cycloaddition of (110) with 1-Chloro-1-nitrosocyclohexane](image)
Table 10. Natural Products Synthesized by Cycloaddition with Arene-Trans-Diols

<table>
<thead>
<tr>
<th>Trans-diol</th>
<th>Natural Product</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+/-) OMEM OMEM</td>
<td>HO OR OR OR HO OR OR</td>
<td>73b</td>
</tr>
<tr>
<td>R = H or PO₃H₂</td>
<td>R = H or PO₃H₂</td>
<td></td>
</tr>
<tr>
<td>(+/-) OMe OMe</td>
<td>HO OR OR OR HO OR OR</td>
<td>73a</td>
</tr>
<tr>
<td>R = PO₃H₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+/-) OMe OMe</td>
<td>NH₂ OH OH *2HCl</td>
<td>73e</td>
</tr>
<tr>
<td>H₂N OH OH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NH₂ OH OMe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂N OH OMe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

41
Table 10. Natural Products Synthesized by Cycloaddition with Arene-Trans-Diols

<table>
<thead>
<tr>
<th>Trans-diol</th>
<th>Natural Product</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td><img src="image2.png" alt="Structure 2" /></td>
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</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>72</td>
</tr>
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<td><img src="image5.png" alt="Structure 5" /></td>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>72</td>
</tr>
<tr>
<td><img src="image7.png" alt="Structure 7" /></td>
<td><img src="image8.png" alt="Structure 8" /></td>
<td>36</td>
</tr>
</tbody>
</table>

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4. Pancreatistatin: An Amaryllidaceae Alkaloid
4.1 Isolation, Structure Determination and Biological Activity

The treatment of cancer with Amaryllidaceae family of plants dates back to the fourth century BC. Greek physician Hippocrates of Cos used the oil of the daffodil Narcissus poeticus L. to treat cancer. More than thirty other plants of the Amaryllidaceae family representing eleven genera have also found application in folk medicinal management of cancer. The first chemical investigations of the Amaryllidaceae family of plants (Hymenocallis littoralis species) were performed by Gorter in 1920. Gorter describes the isolation of an alkaloid, lycorine (114), which was the first alkaloid isolated from the Amaryllidaceae family of plants. Compound (114) is known to inhibit growth of the murine P-388 lymphocytic leukemia (PS system). H. littoralis activity was reevaluated by Pettit et al. 55 years later. They found that the antineoplastic activity resides in the n-butanol fraction rather than the lycorine containing methylene chloride fraction (Figure 33). Further purification of the extract guided by a bioassay (PS in vivo and in vivo systems) led to the isolation of two principle antineoplastic components, 7-deoxynarciclisine (115a, 0.022%) and pancreatistatin (12, 0.014%).

The structure of pancreatistatin (12), a phenanthridone alkaloid, was determined by detailed NMR and mass spectral analysis. A X-ray crystal structure of its 7-methyl ester derivative was utilized to make the stereochemical assignments and confirm the overall structure.
Figure 31. Several Biologically Active Amaryllidaceae Alkaloids

Narciclasine (115b), 7-deoxynarciclasine and pancratistatin, compounds bearing highly oxygenated phenanthridone nucleus, are all biologically active compounds. 7-deoxynarciclasine and narciclasine have been shown to inhibit growth of *Avena coleoptile* (rice seedling test), tobacco plant tissue cultures and murine Ehrlich carcinoma. Narciclasine has displayed other types of antineoplastic activity and is undergoing evaluation by NCI. Pancratistatin displays antineoplastic activity that is more potent and diverse than narciclasine. Pancratistatin shows activity against murine P-388 lymphocytic leukemia (38-106% life extension at 0.75-12.5 mg/kg dose levels) and *in vivo* murine M5076 ovarian sarcoma (53-84% life extension at 0.38-3.0 mg/kg dose levels). Pettit suggests that the activity displayed by the hydroxylated phenanthridone units in pancratistatin and narciclasine may become useful as a chemotherapeutic drug and/or other medicinal areas.

To date there is no information on the mechanism of antineoplastic action of pancratistatin (12). However, the mechanism of action of narciclasine (115b), a structurally similar but less pronounced antineoplastic compound has been deduced. Studies indicate that the mechanism of action of narciclasine involves the inhibition of
the growth of eukaryotic cells by the disruption of protein biosynthesis. In eukaryotic cells, it has been concluded that narciclamine inhibits the binding of t-RNA to the peptidal transferase center of the 60S ribosomal subunit. The correlation the biological activities between narciclamine and pancratistatin remains to be determined.

4. Pancratistatin: An Amaryllidaceae Alkaloid

4.2 Biogenesis

The biogenesis of pancratistatin (12) has not yet been elucidated; however, the biosynthesis of a structurally related and more abundant alkaloid, narciclamine (115b), has been evaluated. Fuganti has deciphered the biosynthesis through elegant radioactive feeding experiments of $^3$H and $^{13}$C labeled compounds. Fuganti’s data suggests that norbelladine (118), which is biosynthesized ultimately from phenylalanine (116) and tyrosine (117), is a precursor to narciclamine (115b). Narciclamine is biosynthesized from norbelladine through alkaloid intermediates oxocrinine (120) and crinine (121).
Figure 32. Biogenesis of Narciclasine
Figure 33. Isolation of 7-Deoxynarciclasine and Pancreatistatin
4. Pancreatin: An Amaryllidaceae Alkaloid
4.3 Total Synthesis and Synthetic Approaches

Total Synthesis

To date, there has been only one total synthesis of racemic pancreatin by Danishefsky and Lee. They began the synthesis of pancreatin with pyrogallol (122a). Protection with triethyl orthoformate, carbamoylation and cyclization to the dioxolane (123b). Anionic Fries rearrangement of the trisubstitued system yielded (124a) in modest yield. Protection of the phenol as the t-butyldimethylsilyl (TBDMS) ether (124b), ortho-lithiation followed by alkylation with dimethylformamide (DMF) produced the desired piperonal derivative. The synthesis of the C-ring was begun by allylmagnesium bromide addition, elimination and Diels-Alder reaction with a masked acetylene ultimately gave the 1,4-cyclohexadiene derivative (128). At this point iodolactonization was attempted and proved problematic. The problem was reasoned to be the steric interaction between the TBS and the diethylamide portion of the molecule. Therefore, the TBS was deprotected and iodolactonization occurred under forced conditions via stannylation and subsequent cyclization to yield (129a). The benzyl ether protected compound (129b) was treated with osmium followed by a Moffat-like transformation to yield a mixture of (133) and its allylic isomer (132). The former was again dihydroxylated. A four step protection-deprotection sequence yielded the monobenzylated diol (135e). Reductive elimination furnished (136) which reacted to form the imidate (137). An Overman rearrangement was affected using the combination of high temperature and vacuum to yield (138) in 56%. Dihydroxylation followed by methanolic potassium carbonate generated the amino acid which underwent cyclization under standard DCC conditions. The total synthesis of pancreatin (12) was completed.
Figure 34. Danishefsky Synthesis of Pancreatistatin Part A
Figure 35. Daminofsky Synthesis of Pancreatatin Part B
with deprotection of the benzyl groups using hydrogenation to give a spectra which identically matched the natural product. Danishefsky and Lee completed the synthesis of pancratistatin in 26 steps with an overall yield of 0.183%. Danishefsky comments that the synthesis is not very efficient due to several key low yielding steps and goes on to state that a more practical route is needed.

**Synthetic Approaches**

There have been only two synthetic approaches to pancratistatin published; however, it should be noted that Ohta, Paulsen and Kallmerten proceed through the 7-deoxy system (142), a derivatized version of pancratistatin, in their syntheses of (+/-) and (+)-lycoricidine (143b). In each case dehydration of the C1 was used to complete the synthesis of lycoricidine. These syntheses should be considered as model systems for pancratistatin. Excluding these, two other approaches to pancratistatin have been published by Heathcock and Clark.

![Figure 36. 7-Deoxypancratistatins as Intermediates in the Synthesis of Lycoricidine](image)

Clark and Souchet published a model study directed toward the total synthesis of pancratistatin in 1990. Retrosynthetically, they had hoped to use (145) as the key
intermediate. Compound (144) would be synthesized from (145) by carbon-carbon bond formation and furnish pancrestatin (12) in several steps.

![Chemical structures](image)

Figure 37. Retrosynthetic Analysis of Clark and Souchet Model Study

The short synthesis of (145) begins with the condensation of (146) with the functionalized imine (147) in refluxing methylene chloride. This generates a 1:1 mixture of diastereomers. It was found that the reaction occurred by Lewis acid induced chelation controlled addition of (146) to (147). Table 11 shows that in varying Lewis acid and temperature, a good ratio is achieved. Thus, addition of trimethylaluminum to the reaction at low temperatures increased the stereoselectivity of the chelation product. The ratio of the desired isomer was increased from 1:1 (no LA) to 10:1 (Me₃Al).
Table 11. Optimization of Lewis Acid Catalysis Conditions

<table>
<thead>
<tr>
<th>Lewis Acid (LA)</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Ratio 148a:148b</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>CH₂Cl₂</td>
<td>reflux</td>
<td>10 min</td>
<td>50:50</td>
</tr>
<tr>
<td>Li⁺</td>
<td>THF</td>
<td>reflux</td>
<td>10 min</td>
<td>60:40</td>
</tr>
<tr>
<td>ZnCl₂</td>
<td>CH₃CN</td>
<td>rt</td>
<td>2 hr</td>
<td>82:18</td>
</tr>
<tr>
<td>MgCl₂</td>
<td>THF</td>
<td>0°C</td>
<td>2 hr</td>
<td>70:30</td>
</tr>
<tr>
<td>MgCl₂</td>
<td>THF</td>
<td>-50 to 0°C</td>
<td>2 hr</td>
<td>80:20</td>
</tr>
<tr>
<td>MgCl₂</td>
<td>CH₃CN</td>
<td>0°C</td>
<td>2 hr</td>
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<tr>
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<td>CH₃CN</td>
<td>-30 to 0°C</td>
<td>24 hr</td>
<td>93:7</td>
</tr>
<tr>
<td>AlMe₃</td>
<td>CH₂Cl₂</td>
<td>-78 to 0°C</td>
<td>5 hr</td>
<td>91:9</td>
</tr>
</tbody>
</table>

Clark and Souchet then used a racemic, but more functionalized imine (150) and studied the Lewis Acid chelation controlled condensation. Again, the addition of trimethylaluminum gave a similar ratio of diastereomers and furnished (151) in a 50% yield.

Figure 38. Optimized Conditions for Condensation
Heathcock et al. 82 published an expedient method to the synthesis of the A, B and C rings of pancreatinstatin in a model study (Figure 39). The synthesis began with the corresponding diethylamide of piperonal (152). Compound (152) was deprotonated, trapped as the borane ester, and oxidized to the corresponding phenol (153a) in one pot. The phenol was protected as the silyl ether (153b). The protected phenol again was subjected to ortho-lithiation conditions and reacted with 1-nitrocyclohexene to yield a pair of isomers (154). The cis isomer was epimerized to the thermodynamically stable trans isomer (155) upon treatment with triethylamine in refluxing ethanol. Reduction of the nitro group to the amine was accomplished using sonication of (155) in the presence of sodium borohydride-nickel chloride which was subsequently cyclized upon treatment with s-BuLi. Deprotection under acidic conditions furnished the desired tetracyclic phenanthridone skeleton (156).
Several model studies and one racemic total synthesis have been achieved. The Danishefsky total synthesis is economically unfeasible for pharmaceutical generation of pancreatestatin. An enantioselective synthesis of pancreatestatin is therefore needed, possibly general enough to permit the preparation of structurally related molecules.
III. DISCUSSION
  1. Introduction

The oxidation of substituted benzenes by the mutant bacteria *Psuedomonas putida* 39D produces arene-cis-diols (7) in > 95% ee. These biooxidation products have been used as chiral synthons in organic synthesis. Their synthetic utility is exemplified by the directing/hindering effect that the hydroxyl groups, both free and protected, have on subsequent stereochemical events. This manipulation is the basis for all stereospecific reactions of the arene-cis-diols and controls the topography of the molecule.

Cycloaddition reactions and potassium permanganate oxidations are examples of reactions in which the stereoselectivity is dictated by the chiral centers at C5 and C6. Several new modes of cycloaddition involving 1-chloro-arene-cis-diol have been investigated. Thermal reactions with quinones yield [4+2] cycloadducts resulting from addition to the less hindered face and in an *endo* fashion. Photolytically, benzoquinone undergoes a hetero-[4+2] cyclization with the diene system. Generation of benzyne and nitrile oxide *in situ* lead to the isolation of their [4+2] and [3+2] cycloadducts. The potassium permanganate mediated oxidation of various protected 1-substituted arene-cis-diols has been briefly examined. In general, compounds (157a) and (157b), where oxidation occurs *anti* to the acetonide group, were the only isolated products (Figure 40). The effect of the R substituent both electronically and sterically on the reactive diene system and thus the ratio of (157a):(157b) will be presented.
Figure 40. Potassium Permanganate Oxidation of Arene-Cis-Diols

Also included in this thesis will be a discussion detailing the development of a protection, inversion and cycloreversion methodology of arene-cis-diols as a route to the desired arene-trans-diol. An arene-trans-diol (159) serves as a chiral intermediate in an enantioselective approach to the amaryllidaceae alkaloid (+)-pancratistatin (12). The two key steps in this approach are the generation of the arene-trans-diol system and the cross coupling between the arene-trans-diol (159) and appropriate functionalized piperonylic acid derivative to give (158).

Figure 41. Retrosynthetic Analysis of (+)-Pancratistatin (12)
2. Novel Cycloadditions of a 1-Chloro-Arene-Cis-Diol Derivative

As discussed in Section II.1, some cycloadditions of 1-chloro-5,6-cis-isopropylidenedioxy-1,3-cyclohexadiene or acetonide protected 1-chloro-arene-cis-diol (14c) have already been examined. In general, the cycloadducts result from approach of the dienophile from the less hindered face and in an endo manner. The cycloadducts from [4+2] nitrosyl Diels-Alder reaction have found use in the total synthesis of several natural products, i.e. aminocyclitols\textsuperscript{26,49,50} and lycoricidine.\textsuperscript{30} This section focuses on a preliminary investigation of novel cycloaddition reactions of (14c) with various compounds. Frontier molecular orbital (FMO) theory and electron density will be used to support spectroscopic evidence concerning regiochemistry and stereochemistry of both [4+2]\textsuperscript{87,88} and [3+1]\textsuperscript{89-91} cycloaddition reactions.

![Cycloaddition reaction](image)

14c

2. Novel Cycloadditions of a 1-Chloro-Arene-Cis-Diol Derivative

2.1. With Quinones, Thermal and Photolytic

In general, 1,4-benzoquinone reacts photolytically with olefins to yield the oxetanes and/or cyclobutane adducts.\textsuperscript{92} Reports of 1,3-dienes reacting with 1,4-benzoquinone under photolytic conditions also exist.\textsuperscript{93}
In 1965, Baltrop et al. showed in an elegant study that 1,4-benzoquinone undergoes cycloaddition with various dienes to yield spiropyrans of type (161) (Figure 42). They discovered that the product distribution is directly related to the wavelength of light used in the reaction. Irradiation below 400nm results in excitation of the carbonyl moiety of the quinone (n→π* transition), and isolation of spiropyrans in low yield (30%). Irradiation above 400nm led to a complex mixture of products. In mechanistic terms, 1,4 addition of radicals to 2,3-dimethylbutadiene via a resonance stabilized diradical, (162), can be invoked to rationalize the formation of the spiropyran (Figure 43).

As expected, a degassed benzene solution containing 1,4-benzoquinone and (14c) reacted under photolytic conditions (360nm monochromatic light) to yield one spiropyran adduct (163) (16%) and unreacted starting material (45%). Increase in the number of equivalents of 1,4-benzoquinone did not lead to a higher yield of (163) and the excess 1,4-benzoquinone made flash chromatographic purification difficult. [It should be noted that irradiation with a 400 watt Hanovia gave an intractable mixture of products.]
Regiochemistry of photolytic cycloaddition was assumed to be (163a) on the grounds of steric factors. In the transition state leading to (163b), there is a steric interaction between the chlorine atom and the approaching quinone. This interaction is not present in the transition state that produces compound (163a).
The regiochemistry was proven by heteronuclear multibond correlation (HMBC). HMBC is a 2D NMR technique that gives long range proton-carbon correlations (up to three bonds). The HMBC of compound (163) shows a correlation between C-4 and C-10. This is possible in (163a) but not in its regioisomer (163b).

Because they are planar and contain the electron withdrawing carbonyls, quinones make excellent dienophiles in the Diels-Alder reaction. In refluxing benzene, 1,4-benzoquinone and 1,4-napthoquinone reacted with (14c) to yield the polycyclic compounds (164) and (165) in 53% and 40% respectively. The stereoselectivity of this reaction merits some discussion. The quinones approach the diene from the less hindered face. FMO theory supports the experimental evidence that quinones react through the more stable endo transition state. This is due to secondary orbital interactions of the carbonyl moiety with the diene. This reaction proved to be no exception as shown by a positive nuclear Overhauser effect (nOe) in the product. In the benzoquinone cycloadduct, irradiation of H₃ showed 6-10% enhancement of signals due to H₂, H₅ and H₆. This nOe enhancement of proximal protons is only possible with the endo structure. The napthoquinone cycloadduct was shown to be endo following similar reasoning and spectroscopic analysis.
These cycloadditions with quinones generated interesting polycyclic molecules which are possibly applicable to natural product synthesis. Specifically compound (165) could undergo stoichiometric ozonolysis to yield (166), which is structurally similar to a class of anthraquinone antibiotics of which atlersolanol A and dactylariol are members (Figure 44).

![Structural diagrams of compounds 165 and 166]

Figure 44. Naphthoquinone Cycloadduct (165) and Structurally Similar Antitibiotics

2. Novel Cycloadditions of a 1-Chloro-Arene-Cis-Diol Derivative

2.2. With Benzyne

Dehydrobenzene or benzyne is a reactive intermediate which is useful in organic synthesis. Benzyne has an unperurbed aromatic system with a weak extra double bond orthogonal to its plane. Because of its inherent ring strain, benzyne undergoes substitution and cycloaddition reactions readily.
Benzyne is readily prepared from anthranilic acid which undergoes diazotization and concomitant loss of carbon dioxide and nitrogen. In the presence of (14c), benzyne (Figure 45) reacted to give the expected cycloadduct (167) in respectable yield (66%).

2. Novel Cycloadditions of a 1-Chloro-Arene-Cis-Diol Derivative
2.3. With Acetonitrile Oxide

Nitrile oxides can also be viewed as dipolar species.\textsuperscript{97} They are ambivalent intermediates composed of two resonance forms, a propargyl (168a) and an allenyl (168b) hybrids. The carbon-nitrogen bond length of nitrile oxides, in general, approaches that of hydrogen cyanide, suggesting that the nitrilium oxide (168a) structure predominates.\textsuperscript{89} This fact is responsible for the relatively high dipole moment (3.15D). 1,3-Dipolar species, such as nitrile oxides, react with polarized olefins to yield products resulting from [3 + 2] cycloaddition reactions. The rate of the reaction depends directly upon the extent of polarization of the olefin.

Mukaiyama and Hoshino developed a mild method for the generation of nitrile oxides \textit{in situ}.\textsuperscript{97}
Following this protocol, nitroethane was dehydrated and formed the intermediate nitrile oxide which reacted with (14c) to yield the novel bicyclic isoxazole (Figure 46). Electron density (Appendix) obtained from AM1 calculations have shown the C3-C4 olefin to be the more polarized olefin in the 1,3-diene of (14c). Regiochemistry was rationalized by invoking the dominant nitriilium oxide hybrid (168a) and an incipient positive charge at C-3 of the diene, as predicted by electron density calculations. FMO theory also supports this regiochemistry. In order to predict regiochemistry, the FMO energy and coefficients of the dipole and the dipolarophile must be known or approximated. Houk has shown that the coefficients and energy of the FMOs of unsubstituted nitrile oxide are similar to those of substituted cases and therefore constitute a good qualitative measure in predicting regiochemistry. The olefin must be classified as electron deficient (dipole-LUMO controlled, i.e., lower energy of HOMO/LUMO) or electron rich (dipole-HOMO controlled, i.e., raise energy of HOMO/LUMO). The C3-C4 olefin is electronically neutral due to an inductive electron withdrawing effect and conjugation which counteract each other. The olefin is similar in energy to ethylene where the smallest energy gap is between the HOMO (dipolarophile) and LUMO (dipole), as illustrated in Figure 47. This is supported by the calculated energy of the HOMO and the LUMO (Appendix, Figure 48). The lowest energy gap is between the HOMO of the diene and the LUMO of the dienophile.
The largest coefficients (appendix) of the HOMO (dipolarophile) and LUMO (dipole) interact in the transition state and lead to the regiochemistry shown (Figure 48). This regiochemistry was proven by $^1$H-NMR decoupling studies.

Figure 48. FMO Interaction of the Dipole with the Dipolarophile
Presented here are the first examples of quinones, benzyne or acetonitrile oxide reacting with the homochiral 1-chloro-arene-cis-diol (14e). These and other stereoselective cycloadditions of (14) generate highly functionalized polycyclic molecules. Future work involving cycloaddition chemistry of (14) will focus on the utilization of the resulting cycloadducts in organic synthesis. Section III.4 works towards this end. It describes the development of a cycloaddition-cycloreversion strategy to the synthesis of arene-trans-diols. One of these arene-trans-diols will serve as an intermediate in an enantioselective approach to the synthesis of the amaryllidaceae alkaloid (+)-pancratistatin. The next section discusses the potassium permanganate oxidations of 1-substituted-arene-cis-diols, which can be formally considered as a [3+2] cycloaddition reaction.
3. Oxidation of Arene-Cis-Diols by Potassium Permanganate

The potassium permanganate oxidation of alkenes dates back to 1895.\textsuperscript{51} Section II.2.1 showed how the structure of the resulting product is dependent on pH, substrate structure as well as other factors. Selectivity in the potassium permanganate oxidation is a major concern. Potassium permanganate oxidizes a wide variety of functional groups and therefore has been used little in the area of organic synthesis. The oxidation of 1,3-diienes has only been investigated relatively recently. Section II.2.2 described two mechanisms for the oxidation of 1,3-diienes which are theoretically based on the product distribution. Mandel and Hudlicky\textsuperscript{67} have reported that the oxidation of 1-halo-arene-cis-diols yield a mixture of products, diol (157a) and epoxydiol (157b). The product distribution was found to be very sensitive to the reaction conditions (ie. temperature, concentration etc.). These halo-epoxydiols have been used extensively in the synthesis of inositol.\textsuperscript{67} This section will describe the effect the diene substituent has on the course of the oxidation. Also, the effect of solvent will be briefly discussed.

3. Oxidation of Arene-Cis-Diols by Potassium Permanganate
3.1 Effect of Diene Substituent

Hudlicky and Mandel\textsuperscript{67} have reported on the potassium permanganate oxidation of 1-halo-arene-cis-diols. Since the original oxidations were performed only on halo-diols, we postulated that the 1,3-diene substituent may play a key role in the oxidative mechanism and thus on the product distribution. We set out to oxidize several acetonide protected arene-cis-diols each possessing a different C1-substituent. These were chosen because of availability and the nature of the C1-substituent, both steric and electronic.
The parent diols of (14h) and (14i) were obtained from Genencor International Inc. Compounds (14g) and (14j) were prepared in our labs.

At the outset, it was reasoned that the electronics of potassium permanganate dihydroxylation should be similar to osmium tetroxide (OsO₄) dihydroxylation. It has been shown in our labs that in osmium tetroxide dihydroxylation reactions of the arene-cis-diols, electron withdrawing groups at the C1-position (R = Cl) deactivate the 1,2-alkene and the 3,4-alkene is selectively oxidized (157a). However, when the C1-position possesses an electron donating group (R = CH₃), a mixture of oxidation products is isolated (157a:170; 1:2).

![Diagram](image)

Figure 49. C1-Substituent Effect on the Selectivity of OsO₄ Dihydroxylation

We believe that initially the regiochemistry of the manganese ester formation should parallel that of the osmate ester. From the intermediate manganese ester, it is expected to
rearrange and oxidize the second olefin following the Hudlicky or Sable mechanisms (Section II.2, Figures 21 and 23). Therefore, it is our presupposition that electron donating R groups should increase the amount of (171a) and (171b) (Figure 50, path a) and electron withdrawing R groups should increase the amount of (157a) and (157b) (Figure 50, path b).

![Chemical Structures](image)

**Figure 50** Expected Substituent Effect on Permanganate Oxidation

Examining the product distribution of the permanganate oxidations, this rationale seems to be unsubstantiated (Figure 51). As in all permanganate mediated oxidations of (14), the yields of products are low and this makes any hypothesis involving substitution effects suspect. However, examining the yields and ratios of products we believe that electronically the substituent plays little role in the oxidation. A possible reason for this irregularity may be steric effects. Permanganate has been shown to be very sensitive to sterics.\(^{52}\) These effects may play an important role in the oxidation of an electron rich disubstituted olefin in the presence of an equally electron rich trisubstituted one.
3. Oxidation of Arene-Cis-Diols by Potassium Permanganate

3.2 Effect of Solvent

Potassium permanganate oxidation reactions can be performed in a number of aqueous solvent systems. However, there are several requirements. The solvent must be inert towards permanganate oxidation, miscible with water and potassium permanganate must show appreciable solubility in the solvent system. Common solvents include acetone/water and ethanol/water mixtures. Other solvents have been reported, for example, pyridine/water and THF/water. Keeping all other variables constant, the effect of different aqueous solvents on the permanganate oxidation of 1-chloro-arene-cis-diol was examined. The results are shown in Table 12. Entry 3 appears to be an exciting result; however, the yield of permanganate oxidation product was less than 5%. Entries 1, 2 and 4 show an interesting effect. All yield products in approximately 20% yield but
in a different ratio. This solvent effect can be explained by the solubility of the permanganate in the aqueous solvent system. It seems permanganate is most soluble in aqueous acetone and least soluble in aqueous THF. Mandel\textsuperscript{67} found that the concentration of permanganate in solution has a direct effect on the product distribution.

Table 12. Solvent Effect on Potassium Permanganate Oxidation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent(aq)</th>
<th>Ratio (176a):(176b)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>acetone/water</td>
<td>1:4.5</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>ethanol/water</td>
<td>1:1.5</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>pyridine/water</td>
<td>100:0</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>THF/water</td>
<td>2:1</td>
<td>20</td>
</tr>
</tbody>
</table>

The potassium permanganate oxidation has been used sparingly in the area of organic synthesis. Selectivity is the fundamental problem with permanganate oxidations. This section described the potassium permanganate oxidation of substituted arene-cis-diols. Diols and epoxydiols were isolated as the major products in low yields. Substituent changes alter the product ratio which suggests that a complex mixture of electronic and steric effects are operating. The oxidation of 1,3-dienes remains a perplexing reaction. Although the potassium permanganate oxidation of (14) is mechanistically interesting, it will not be a practical reaction in organic synthesis because of low yields and complex mixtures of products. The next section will describe the application of [4+2] cycloaddition chemistry of arene-cis-diols to the synthesis of arene-
trans-diols. One of these molecules serves as an intermediate in an enantioselective approach to the alkaloid (+)-pancratistatin.
4. Arene-Trans-Diols

The availability of arene-cis-diols through the biooxidation of substituted aromatic compounds has led to their common use as chiral synths.\textsuperscript{101} Sections II.1, II.2, III.2 and III.3 described their use in the areas of cycloaddition and permanganate mediated oxidation. Both of these areas have produced highly functionalized intermediates which have been used in short, enantioselective synthesis of a variety of natural products, including alkaloids\textsuperscript{30,37} and inositols.\textsuperscript{67}

The synthetic methods available for producing arene-trans-diols were discussed in Section II.3. These specific methods are limited to the synthesis of three arene-trans-diols. Benzene-trans-diol (96) has proven to be a valuable intermediate in the synthesis of several inositol phosphates\textsuperscript{73} and aminocyclitols\textsuperscript{73} (Section II.3). The development of a general methodology for the synthesis of arene-trans-diols will enhance their use as chiral synthons in natural product synthesis.

Presented in this section are the syntheses of arene-trans-diols from the corresponding 1-chloro or 1-bromo arene-cis-diols. The methodology employed in this synthesis is shown in Figure 52. Protection of the 1,3-diene moiety through the Diels-Alder reaction, selective inversion at the C5 hydroxyl, followed by cycloreversion will produce the desired arene-trans-diol (180). Included in this discussion will be the choice of protecting groups, inversion of the sterically hindered alcohol (178) as well as optimum conditions found for the cycloreversion reaction. Mechanistic interpretations explaining the product distribution of the cycloreversion will also be given. Finally, the
arene-trans-diols serve as an intermediate in an approach to the chemotherapeutic agent (+)-pancreatistatin (Section II.4).

![Chemical structure](image)

Figure 52. Synthetic Methodology for the Production of Arene-Trans-Diols

4. Arene-Trans-Diols

4.1 Development of the Methodology

In the development of a general methodology for the synthesis of arene-trans-diols from the corresponding arene-cis-diol an important restriction becomes evident at the outset. Attempts at inversion of either hydroxyl group on the cyclohexadiene ring leads to immediate aromatization. Upon the generation of a leaving group at C5 or C6 (182), elimination occurs which is driven by the enthalpic force of aromatization (Figure 53). Therefore, in order to synthesize the arene-trans-diols, the 1,3-diene system must be protected. Diels-Alder cycloaddition, selective inversion at C5 and subsequent cycloreversion will produce the required arene-trans-diol in enantioselective fashion.
Several reviews\textsuperscript{102} have been written about the cycloreversion reaction. Many methods involving cycloreversion, which lead to the generation of 1,3-dienes, have been developed. However, most cycloreversions occur under harsh conditions and in most cases require temperatures exceeding 200°C. It is questionable whether the labile arene-\textit{trans}-diols would survive such strenuous reaction conditions. In this methodology, three known methods were tried for the protected/deprotection sequence of the 1,3-cyclohexadiene system. These methods were selected according to their comparatively mild conditions.

The choice of the 1,3-diene protecting group is critical to the success of the synthetic methodology. In 1989 Hudlicky and Seoane\textsuperscript{36} published the synthesis of (-)-zeylena (Section II.1, Figure 12). In this synthesis, the diene system was protected under mild conditions utilizing the Diels-Alder reaction with DEAD derivatives. After inversion of the C5 hydroxyl, the diene system was regenerated upon treatment with zinc/copper couple in acetic acid. The synthesis of (-)-zeylena was finished in several subsequent steps. The major problem encountered in the (-)-zeylena synthesis was the reproducibility of the cycloreversion reaction. Yields of the cycloreverted products ranged from 10% to 60% which depended directly on the activity of the zinc/copper couple.
Even with the problem of reproducibility in the (-)-zeylena synthesis, the DEAD protection-deprotection sequence served as the initial idea in the development of the methodology for the synthesis of arene-\( \text{trans} \)-diols. We believed that the DEAD cycloreversion step could be optimized and therefore began the synthesis by trying the first step in the reaction sequence, the DEAD cycloaddition reaction. Problems immediately arose with the DEAD protection sequence. The diene system in these halogenated cyclohexadiene systems was found to be much less reactive than the triene system encountered in the (-)-zeylena synthesis. All attempts to generate Diels-Alder cycloadducts of arene-\( \text{cis} \)-diols with DEAD led to the isolation of starting material, aromatic byproducts and/or products of arene-\( \text{cis} \)-diol dimerization (Table 13). The use of DEAD as a protecting group in the methodology for the production of arene-\( \text{trans} \)-diols was abandoned. Other 1,3-diene protecting groups were subsequently attempted.

Table 13. Attempts at Cycloaddition of Arene-\( \text{Cis} \)-Diols with DEAD

![Diagram of cycloaddition reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diene</th>
<th>DEAD Equivalents</th>
<th>Conditions</th>
<th>Product (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>184a</td>
<td>1.1</td>
<td>THF, 0°C-&gt;rt, 1day</td>
<td>184a (90)</td>
</tr>
<tr>
<td>2</td>
<td>184a</td>
<td>5.0</td>
<td>Benzene, reflux, 6 hours</td>
<td>Aromatics</td>
</tr>
<tr>
<td>3</td>
<td>184b</td>
<td>2.2</td>
<td>THF, 0°C, 4 days</td>
<td>Dimer (70) + 184a (20)</td>
</tr>
<tr>
<td>4</td>
<td>184b</td>
<td>2.2</td>
<td>THF, reflux, 2 days</td>
<td>Dimer (87)</td>
</tr>
</tbody>
</table>

Since before 1950\(^{102}\) sulfur dioxide has been reported as a protecting group for 1,3-dienes. Sulfur dioxide undergoes a six electron [4+2] cycloaddition with 1,3-dienes to yield sulfolenes. Sulfolenes undergo thermal cycloreversion at temperatures near
150°C. It has been reported that sulfur dioxide reacts with both reactive dienes and unreactive dienes. However, in the case of the free arene-cis-diol or its protected version, starting material or aromatic compounds were the only compounds isolated upon reaction with sulfur dioxide at atmospheric pressure. Obviously, the dienes were not reactive enough to furnish cycloadducts with sulfur dioxide. In the presence of moderate pressures of sulfur dioxide, normally unreactive dienes can be forced to react. Sealed in a stainless steel bomb under 40 psi of sulfur dioxide, the arene-cis-diols still did not undergo cycloaddition (Table 14, entries 2 and 4). The arene-cis-diols only aromatize under these forcing conditions. It was initially believed that any moisture would react with sulfur dioxide and produce sulfonic acid which could catalyze deprotection and subsequent elimination of the arene-cis-diol. Even with the addition of 2 equivalents of triethyl amine, aromatization still occurred (entry 4). Protection of the arene-cis-diols with 4-phenyl-1,2,4-triazoline-3,5-dione (20) was examined next and proved successful.

Table 14. Attempts at Cycloaddition of Arene-Cis-Diols with Sulfur Dioxide

![Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diene</th>
<th>Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>186b</td>
<td>Et₂O, bubbling SO₂, rt, 2hr</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>186b</td>
<td>Et₂O, SO₂ (40 psi), rt, 2 days</td>
<td>Aromatics</td>
</tr>
<tr>
<td>3</td>
<td>186a</td>
<td>Benzene, bubbling SO₂, rt, 1hr</td>
<td>Aromatics</td>
</tr>
<tr>
<td>4</td>
<td>186a</td>
<td>Benzene, SO₂ (40 psi), NE₃, 1 day</td>
<td>Aromatics</td>
</tr>
<tr>
<td>5</td>
<td>186c</td>
<td>Benzene, bubbling SO₂, rt, 12hr</td>
<td>NR</td>
</tr>
</tbody>
</table>
In 1970, Barton\textsuperscript{103} published his first in a series of seminal papers\textsuperscript{104} relating to a Diels-Alder/retro-Diels-Alder strategy in the synthesis of steroids and steroidal metabolites. In this paper, ergosterol acetate reacted readily with 4-phenyl-1,2,4-triazoline-3,5-dione (20) at room temperature in 87% yield. The cycloreversion step was found to proceed under a variety of conditions (Table 15). Treatment of the cycloadduct with excess lithium aluminum hydride gave the best yields in the cycloreversion reaction. The mechanism of cycloreversion is reagent dependent and will be discussed in Section III.4.3.

Table 15. Protection/Deprotection of Ergosterol with 4-Phenyl-triazoline-3,5-dione

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Conditions</th>
<th>Yield of Ergosterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiAlH\textsubscript{4}</td>
<td>THF, reflux, 8 hr</td>
<td>99 (188a)</td>
</tr>
<tr>
<td>2</td>
<td>Heat</td>
<td>235\textdegree C, 0.045 mm Hg</td>
<td>36 (188b)</td>
</tr>
<tr>
<td>3</td>
<td>Na</td>
<td>EtOH, reflux, 24 hr</td>
<td>53 (188a)</td>
</tr>
<tr>
<td>4</td>
<td>NH\textsubscript{2}NH\textsubscript{2}•H\textsubscript{2}O</td>
<td>EtOH, reflux, 14 hr</td>
<td>30 (188a)</td>
</tr>
</tbody>
</table>

Since 1970, many other research groups have utilized this protection/deprotection sequence.\textsuperscript{102} In that time period, researchers have developed more conditions which effect cycloreversion. A complete list of cycloreversion conditions to date is presented below (Table 16). The yields of product (1,3-diene) range from 99% to 60%.
Table 16. Cycloreversion Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiAlH₄</td>
<td>THF, 67°C, 18hr</td>
</tr>
<tr>
<td>2</td>
<td>15N KOH</td>
<td>EtOH, 78°C, 15hr</td>
</tr>
<tr>
<td>3</td>
<td>2.1 N KOH</td>
<td>EtOH, 78°C, 1.5hr</td>
</tr>
<tr>
<td>4</td>
<td>2.1 N KOH</td>
<td>EtOH, rt. 36hr</td>
</tr>
<tr>
<td>5</td>
<td>K₂CO₃</td>
<td>DMSO, 120°C, 7hr</td>
</tr>
<tr>
<td>6</td>
<td>DBN</td>
<td>Pyridine, 115°C, 18hr</td>
</tr>
<tr>
<td>7</td>
<td>Imidazolidinone</td>
<td>120°C, 1-5-hr</td>
</tr>
<tr>
<td>8</td>
<td>Collidine</td>
<td>175°C, 15min</td>
</tr>
<tr>
<td>9</td>
<td>tetramethylguanidine</td>
<td>180°C, 15min</td>
</tr>
</tbody>
</table>

4. Arene-Trans-Diols
4.2 Successful Synthesis

In the beginning, we believed that using the methodology depicted in Figure 52, we would successfully gain access to arene-trans-diols. In this methodology (Figure 52), the C5- and C6-hydroxyl protecting groups play an important role. Both hydroxyls must be selectively protected in order to avoid the separation of mixtures. Also, the C5-hydroxyl protecting group ultimately must be deprotected and inverted in the presence of the C6-protecting group (ie. stable to bases and fluoride ion). A protection route similar to the (-)-zeylena synthesis\textsuperscript{36} was chosen. The 1-bromo or chloro-arene-cis-diol (190) was selectively protected with thexyldimethylsilyl chloride (THSCI) at the least hindered C5-hydroxyl. The C6-hydroxyl was then protected as a methoxymethyl (MOM) derivative following a procedure developed by Stork.\textsuperscript{105} Both of these protection steps proceeded selectively and in high yield (Figure 54).
Cycloaddition of (192) with 4-phenyl-1,2,4-triazoline-3,5-dione (20) proceeds stereoselectively at low temperatures and in high yield. The two bulky protecting groups shield the β-face and only allow cycloaddition to occur selectively from the α-face. Experimentally, the triazolium is added dropwise to a cold solution of the (192) in methylene chloride. The reaction is complete when the characteristic red color of the triazoline persists in the reaction medium. The product (193) displays the characteristic $^1$H-NMR, $^{13}$C-NMR and IR of these cycloadducts (Section VI).

The THS-protecting group was readily deprotected upon treatment with tetrabutylammonium fluoride (TBAF) at low temperatures. At this point, the inversion of the free hydroxyl was carried out but proved to be problematic.
The Mitsunobu reaction is the standard method for inverting an alcohol. There have been several recent reviews published on the Mitsunobu reaction. These reviews describe at great lengths its mechanism and usefulness in organic synthesis. However, alcohol (194a), under standard Mitsunobu conditions, was never inverted (Table 17, entry 1). Other carboxylic acids used in place of benzoic acid gave similar results (Table 17, entries 2 and 3). A possible explanation for the inability of (194a) to react under Mitsunobu conditions is that the alcohol is in a sterically demanding environment that impedes the intermediate alkoxy-phosphonium salt formation. The Mitsunobu reaction was abandoned in the hope that other inversion techniques would prove successful.

Sulfonate formation followed by inversion with a nucleophile was the next obvious choice. This technique has been described to work even on sterically hindered alcohols. Hart found that treatment of a mesylate with potassium acetate in hot DMF produced inversion products in cases where the Mitsunobu reaction failed. In our hands, this method returned only unreacted mesylate (Table 17, entry 4). However, formation of a triflate followed by inversion with cesium acetate in the presence of 18-crown-6 proceeded in 15 minutes to give inverted products in hot DMF (Table 17, entry 5).
Table 17. Inversion Conditions

\[
\begin{align*}
\text{Entry} & & \text{Inversion Conditions} & & \% \text{Product} \\
1 & & \text{THF, PPH3, benzoic acid, DEAD, } 0^\circ \text{C} & & \text{NR} \\
2 & & \text{Benzene, PPH3, p-nitrobenzoic acid} \\
& & \text{DEAD, } 0^\circ \text{C-rt} & & \text{NR} \\
3 & & \text{THF, PPH3, NaO2CH, DEAD, } 0^\circ \text{C-rt} & & \text{NR} \\
4 & & a) \text{ Tf2O, pyridine, CH2Cl2, } 0^\circ \text{C} \\
& & b) \text{ KOAc, 18-crown-6, DMF, } 0^\circ \text{C-rt} & & \text{NR} \\
5 & & a) \text{ Tf2O, pyridine, CH2Cl2, } 0^\circ \text{C} \\
& & b) \text{ DMSO, KO2, 18-crown-6, rt} & & \text{---} \\
6 & & a) \text{ Tf2O, pyridine, CH2Cl2, } 0^\circ \text{C} \\
& & b) \text{ CsOAc, 18-crown-6, DMF, } 70^\circ \text{C} & & 95
\end{align*}
\]

Comparison of the $^1$H-NMR of (194a) with (196a) showed expected differences in the splitting patterns and coupling constants of the C5 and C6-protons. In this rigid system, the coupling constants suggest that the C5- and C6-substituents are forced into an eclipsed conformation (Figure 57). The inversion step was later optimized so that triflate formation, inversion and subsequent acetate hydrolysis were accomplished in >90% combined yield.

\[
\begin{align*}
\text{Figure 57. } ^1\text{H-NMR Evaluation of (194a) and (196a)}
\end{align*}
\]
At this point, the cycloversion reaction was attempted. Treatment of (196a) with 2.1N KOH in EtOH (Table 16, entry 4) led to the isolation of an unknown product in low yield. Analysis by $^1$H-NMR showed the compound contained a disubstituted alkene, the N-phenyl moiety of the triazoline and the ether linkage of the MOM group. According to this spectroscopic data, the product was assumed to be (198), resulting perhaps from intramolecular hydrolysis of a portion of the triazoline (Figure 58).

![Chemical Structure](image)

Figure 58. First Attempt at Cycloversion

In order to prevent this intramolecular hydrolysis, the inverted hydroxyl was protected as a t-butyldimethylsilyl (TBDMS) ether (199). Treatment of this diprotected cycloaduct (199a) under cycloversion conditions (2.1N KOH in EtOH) furnished an inseparable 11:1 mixture of arene-trans-diols (200c) and (200a) in 68% yield. The other 32% of the mass balance was accountable as aromatic byproducts resulting from decomposition of
the products. Interestingly, subjecting (199b) to the cycloreversion conditions yielded chloro-trans-diol (200b) exclusively in 65% isolated yield. None of the dechlorinated compound (200c) was isolated.

Table 18. Protection and Second Attempt at Cycloreversion

\[
\begin{align*}
\text{OCH}_2\text{OEt} & \quad \text{OCH}_2\text{OEt} & \quad \text{OCH}_2\text{OEt} \\
\text{Ph} & \quad \text{Ph} & \quad \text{R} \\
196 & \quad 199 & \quad 200 \\
\text{i) TBDMSI}, 2,6-lutidine, \text{CH}_2\text{Cl}_2, 0^\circ\text{C} \rightarrow \text{rt}, 90\% & \quad \text{a) } R = \text{Br} \\
& \quad \text{b) } R = \text{Cl} & \quad \text{c) } R = \text{H} \\
\end{align*}
\]

\(i\) TBDMSI, 2,6-lutidine, CH₂Cl₂, 0°C–rt, 90% ii) see below

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Conditions</th>
<th>Product (a:b:c)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>199a</td>
<td>2N KOH (aq), EtOH, air</td>
<td>1:0:11</td>
<td>65%</td>
</tr>
<tr>
<td>199a</td>
<td>Collidine, 175°C, 22hr</td>
<td>100:0:0</td>
<td>22%</td>
</tr>
<tr>
<td>199b</td>
<td>2N KOH (aq), EtOH, air</td>
<td>0:100:0</td>
<td>60%</td>
</tr>
</tbody>
</table>

Attempts at cycloreversion using other conditions also yielded interesting results. When (199a) was dissolved in collidine and heated to 175°C for 22 hours, purification of the reaction mixture yielded (200a) in low yield. Due to the different ratios of products in the case of (199a), we believe that the two cycloreversion conditions (KOH, EtOH or Collidine at 175°C) are mechanistically distinct from one another. Presented in the next section is a mechanistic discussion on the cycloreversion reaction.
4. Arene-Trans-Diols
4.3 Mechanistic Interpretations of Cycloreversion

This section will present what is known about the triazoline cycloreversion along with experiments which were run to discern the mechanism of debromination. The mechanism for cycloreversion of (199a) in collidine at 175°C is believed to occur through a retro-[4+2] reaction followed by decomposition of the 4-phenyl-1,2,4-triazoline-3,5-dione (Figure 59). The thermally unstable triazoline would not survive such high temperatures. We propose that the triazoline (20) decomposed at 175°C and produced one molecule of nitrogen, carbon dioxide and phenyl isocyanate.

\[
\begin{align*}
\text{199a} & \xrightarrow{i} \text{200a} + \text{20} \\
\end{align*}
\]

\(i\) Collidine, 175°C, 22hrs, 22%

Figure 59. Mechanism for Cycloreversion at Elevated Temperature

Mechanistic insights into the cycloreversion reaction of triazoline cycloadducts come from two sources. First, in the cycloreversion with lithium aluminum hydride (LAH), Barton\textsuperscript{104} used gas chromatographic (GC) analysis of the reaction mixture to gain some understanding of the reaction. The GC showed three compounds were present in a 1:7:1 ratio. These compounds were found to be N,N-dimethylaniline, N-methylaniline, aniline and accounted for 62% of the N-phenyl-triazoline system. The mechanism which accounts for these anilines being formed is shown in Figure 60. It involves complete reduction of the triazolo system to the corresponding hydrazine (202). Barton proposed
that the intermediate hydrazine (202) undergoes cycloversion through air oxidation to the azo compound followed by loss of nitrogen or loss of hydrazine via a retro-Diels-Alder reaction to regenerate the 1,3-diene system.

![Diagram of chemical reaction]

Figure 60. General Mechanism of LAH Mediated Cycloversion

Alkaline mediated cycloversion can be postulated to follow a similar mechanism due to the work of Gilani and Triggle (Figure 61). They were interested in the synthesis of steroidal hydrazines. Prior to hydrolysis, the olefin (204) was hydrogenated. Alkaline hydrolysis yielded the desired hydrazine (205) in quantitative yield. The two pieces of information concerning the hydrolytic mechanism lead us to believe that hydrolysis proceeds through the semicarbazide (206). The semicarbazide is further hydrolyzed to the hydrazine (202) with loss of another of CO₂ molecule and one molecule of aniline. Similarly, oxidation with concomitant loss of nitrogen or loss of hydrazine via retro-[4+2] cycloaddition can be invoked to regenerate the 1,3-diene (203) (Figure 62).
The mechanism depicted in Figure 62 is straightforward in nature; however, it will not account for debromination in the case of (199a). Experimentally, it was found that changing the reaction conditions had a profound effect on the ratio of (200a) to (200c) and thus on the mechanism of the reaction. First, 1-bromo-trans-diol (200a) was subjected to the reaction conditions (2.1N KOH, EtOH). The only products isolated from the reaction mixture contain bromine and were aromatic in nature. There was no
spectroscopic evidence implicating the formation of (200c). Therefore, it is our presupposition that debromination must occur during the cycloreversion step.

Table 19. Experimental Variations in Hydrolytic Cycloreversion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product Ratio (200a):(200c)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2N KOH (aq), EtOH, air</td>
<td>1:11</td>
<td>65%</td>
</tr>
<tr>
<td>2</td>
<td>2N KOH (aq), EtOH, O₂</td>
<td>1:6</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>2N KOH (aq), EtOH, degassed</td>
<td>0:100</td>
<td>51%</td>
</tr>
<tr>
<td>4</td>
<td>2N KOH (aq), t-BuOH, air</td>
<td>0:100</td>
<td>58%</td>
</tr>
<tr>
<td>5</td>
<td>2N KOH (aq), THF, 80°C, air</td>
<td>1:2</td>
<td>45%</td>
</tr>
<tr>
<td>6</td>
<td>2N KOH (aq), EtOH, degassed, galvinoxyl free radical (1 equiv)</td>
<td>1:1</td>
<td>50%</td>
</tr>
</tbody>
</table>

Others variations in reaction conditions are shown in Table 19. Interestingly, when the EtOH solution was degassed, (200c) was isolated exclusively. From this result it was believed oxygen may play a role in the debromination. Oxygen can either act as an oxidant or as a radical scavenger. In order to rule out or support the formation of radical intermediates, (199a) was first subjected to the cycloreversion conditions in the presence of oxygen. This caused a slight change in the product ratio. Next, the reaction was run in the presence of a stabilized free radical (galvinoxyl). The ratio changed again, but not drastically. If radicals are involved, we expected the presence of galvinoxyl free radical would trap any radicals and severely alter the product ratio. We believe the experimental results (Table 19) neither support nor rule out a radical mechanism. Solvent also seems to play a role in the debromination. When t-BuOH was used in place of EtOH, (200c)
was formed exclusively. A heterogeneous system (entry 5), also changed the ratio of products.

At this point in studying the cycloreversion of (199a), we have come up with three plausible mechanisms which account for the debromination (Figure 63). First, a carbenoid intermediate is proposed to result from attack of hydroxide on the bromine atom (path A). Fragmentation and quenching give the desired debrominated product (200c). Second, alkaline hydrolysis of (199a) yields the corresponding hydrazine which undergoes deprotonation and loss of bromide forming the ubiquitous bridgehead olefin (path B). Compound (208) rearranges to the azo compound (210) and subsequently looses nitrogen to give the desired trans-diol (200c). Lastly, we envisioned hydroxide attack on the bromine atom forming hypobromite and a stabilized anion (211). The anion is quenched and hydrolysis of the triazoline portion proceeds as previously described to give (200c). We believe all of the proposed mechanisms are possible and further experimental evidence is needed to support or rule out any of the mechanisms. The next section describes the use of (200a) in an enantioselective approach to the alkaloid (+)-pancratistatin (12).

Figure 63. Plausible Mechanisms for Debromination During Cycloreversion
Figure 63. Plausible Mechanisms for Debromination During Cycloreversion
4. Arene-Trans-Diols

4.4 Approach to the Synthesis of (+)-Pancreatistatin

Section II.4 described the potent biological activity of (+)-pancreatistatin (12) along with several synthetic ventures directed towards its synthesis. An efficient total synthesis of (+)-pancreatistatin is an ongoing project of several synthetic organic groups throughout the United States.\(^{110}\) Retrosynthetically we disconnected (12) into two pieces, the stannyI-trans-diol (213) and the aryl triflate (214), which would be coupled using the Stille cross coupling reaction to yield (158). The coupled product would then be stereoselectively manipulated to give the target molecule (12).

\[
\begin{align*}
\text{Figure 64. Retrosynthesis of (+)-Pancreatistatin (12)}
\end{align*}
\]

The two intermediates (213) and (214) were easily synthesized by known methods. The synthesis of the aryl triflate (214) was completed in several steps by use of an ortho-lithiation methodology. The synthesis begins with the known isopropyl ester of piperonylic acid (215).\(^{111}\) Compound (215) was subjected to lithium tetramethylpiperidine (LiTMP) and trimethylborate under the internal quench conditions.
which were developed by Corey\textsuperscript{112} and later used by Martin\textsuperscript{113} followed by acidic hydrolysis and subsequent oxidation yielded the corresponding phenol (216a) in 83\% yield. Protection of the phenol as the MOM derivative proceeded in high yield. Similarly, (216b) reacts under internal quench conditions to yield the mono protected diphenol (217). Treatment of (217) with triflic anhydride at low temperature yielded the desired aryltriflate (214).

\[
\begin{align*}
\text{215} & \xrightarrow{\text{i}} \text{216a} \quad \text{R}_3 = \text{H} \\
\text{216b} & \quad \text{R}_3 = \text{OCH}_2\text{OEt} \\
\text{214} & \quad \text{R}_2 = \text{Tf} \\
\text{217} & \quad \text{R}_2 = \text{H} \\
\text{215} & \xrightarrow{\text{ii}} \text{216a} \quad \text{R}_3 = \text{H} \\
\text{216b} & \quad \text{R}_3 = \text{OCH}_2\text{OEt} \\
\text{214} & \quad \text{R}_2 = \text{Tf} \\
\text{217} & \quad \text{R}_2 = \text{H}
\end{align*}
\]

\text{i) a) } \text{B(OMe)}_3, \text{THF, LiTMP, -78\textdegree C} \quad \text{b) } \text{AcOH, H}_2\text{O}_2, 83\% \\
\text{ii) } \text{EtNiPr}_2, \text{CH}_2\text{Cl}_2, 0\textdegree C, 98\% \\
\text{iii) } \text{Tr}_2\text{O, pyridine, 0\textdegree C, 98\%}

\text{Figure 65. Synthesis of Aryltriflate (214)}

The easily synthesized 1-bromo-arene-cis-diol (192a) was used as a model compound in the cross coupling reactions because of the scarcity of the corresponding arene-trans-diol. The stannyl-derivative (218) was synthesized in low yield following conditions described by Ley (Figure 81).\textsuperscript{114} Cross coupling of (218) and (214) under standard Stille\textsuperscript{115} and modified Stille conditions developed by Farina\textsuperscript{116} and others\textsuperscript{117} resulted in the isolation of the deprotected phenol (220), (219) and (221). The free phenol (220) should still have undergone cross coupling with (214). These preliminary results indicate that much more work is needed to gain access to coupled molecules such as (158).
This section accessed the recent results obtained in an enantioselective approach to (+)-pancratistatin. The approach hinges on the synthesis of two intermediate compounds the aryl unit (214) and the arene-trans-diol (213). The Stille coupling protocol of (214) and (218) gave unfortunate results. Future work in the area of pancratistatin synthesis as well as other uses for the arene-trans-diols are given in the next section.

4. Arene-Trans-Diols
4.5 Future Work

Section III.4.4 detailed the unsuccessful results of coupling (214) and (218) using the Stille methodology. Future work will focus on the coupling reaction. The Suzuki\textsuperscript{118} or other organometallic coupling procedures\textsuperscript{119} will be attempted and will hopefully succeed in providing ample quantities of the coupled product (158). Once the coupled
product is in hand, we believe that the synthesis of (+)-pancratistatin would be completed in 7 subsequent steps. The key step in finishing the synthesis is the stereoselective dihydroxylation of (158). We believe that osmylation will occur selectively on the β-face of the 3-4 olefin due to the steric crowding of the equally electron rich 1-2 olefin. The dihydroxylation product would next undergo selective deprotection of the MOM derivative followed by protection of the diol as an acetonide which would yield (222). Compounds similar to (222) have been found to exist in a bisected conformation because of functional group crowding, this makes further olefin functionalization impossible. Adapting the methodology of Danishefsky, the two six-membered rings of (222) would be tied back as a lactone (223). Treatment of (223) with diborane followed by hydroxylamine-O-sulfonic acid would give (224) in which the new amine and hydrogen are in the required β-face, syn-disposition. Opening the lactone followed by cyclization to the amide using the Danishefsky protocol would yield the protected phenanthridone skeleton (225). Acidic deprotection would the produce (+)-pancratistatin (12) in 16 steps from commercially available 1-bromo-arene-cis-diol (190a). If this approach is successful, it compares favorably with the published 26 step synthesis of racemic pancratistatin by Danishefsky in 0.183% overall yield.
Ultimatey, it is believed that with a general methodology to the differentially protected arene-trans-diols completed, these molecules will find extensive use as a chiral synthon in organic synthesis. Future studies involving the monoprotected arene-trans-diols will examine the availability of possible stereoselective reactions. Figure 68 shows the selective Diels-Alder, dihydroxylation and epoxidation reactions which are feasible.
Figure 68. Potential Stereoselective Reactions of Arene-Trans-Diols (200)
IV. CONCLUSION

This thesis depicts the usefulness of the arene-cis-diols in organic synthesis. Their commercial availability in high enantiomeric excess and predictable reactivity make these molecules effective asymmetric building blocks. Sections III.2 and III.3 described the highly functionalized molecules available via cycloaddition and potassium permanganate oxidation reactions. In the area of cycloaddition chemistry this thesis reports the first photolytic cycloaddition and [3+2] cycloaddition yielding (163a) and (169). The regiochemistry of the cycloadducts were reasoned by NMR analysis and supported by FMO theory. The first cycloaddition of these homochiral compounds with benzyne was also described (167).

Potassium permanganate oxidation of the arene-cis-diols were found to give in most cases a mixture of diol (157a) and epoxydiol (157b) in low yield. The substituent effect on the product ratio of (157a):(157b) was found to be a complex interaction of both steric and electronics.
Finally, a general enantioselective route to the synthesis of arene-\textit{trans}-diols from the corresponding arene-\textit{cis}-diol was developed. This thesis discussed the evolution of a methodology and described how to choose a 1,3-diene protecting group, how to invert a sterically hindered alcohol and how to affect cycloreversion. The 7-step protection-deprotection sequence produced enantiopure arene-\textit{trans}-diols (200a), (200b), and (200c).

Compound (200a) is a key intermediate in an approach to the synthesis of (+)-pancratistatin, an amaryllidaceae alkaloid with potent biological activity toward cancer cells. Preliminary studies indicate that the Stille coupling route to intermediate (158) is not a viable one. Future work (Section III.4.5) will investigate the synthetic utility of (200) as a chiral synthon in natural product synthesis and continue with the synthesis of (+)-pancratistatin, the approach to which was fully described in this thesis.
V. EXPERIMENTAL

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF), benzene and diethyl ether (Et₂O) were distilled from sodium/benzophenone ketyl under argon immediately prior to use. Methylene chloride (CH₂Cl₂) was distilled from CaH₂ under argon immediately prior to use. Diisopropylethylamine (i-Pr₂NEt), pyridine, 2,6-lutidine, tetramethylpiperidine (TMP), triethylamine (Et₃N) and collidine were distilled from CaH₂ and stored over KOH pellets in a desiccator until use. Reactions involving air and/or moisture sensitive reagents were executed under an inert atmosphere of dry argon and the glassware was flame dried under vacuum. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh) and indicated solvents. Infrared (IR) spectra were reported in wavenumbers (cm⁻¹) and referenced to the 1601.8 cm⁻¹ absorption of polystyrene film. The ¹H and ¹³C-nuclear magnetic resonance (NMR) spectra were obtained as solutions in deuterio-chloroform (CDCl₃) unless otherwise indicated. Chemical shifts were reported in parts per million (ppm, δ) and were referenced to CHCl₃ at δ 7.24 for ¹H-NMR or to the center line of the CDCl₃ triplet at δ 77.0 for ¹³C-NMR. Coupling constants were reported in hertz (Hz). Splitting patterns were designated as s, singlet; d, doublet; t, triplet; q, quartet; h, heptet; m, multiplet; br, broad.

Photolytic reactions were performed using a Rayonet RPR-240 reactor equipped with four 12.5-W bulbs which irradiated at 360nm. Melting points were determined on a Thomas Hoover capillary apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 1600 FTIR or Perkin-Elmer 283B. NMR spectra were recorded on Bruker WP-270 or Varian Unity 400. Optical rotations were measured on Perkin-Elmer 241 digital polarimeter. Mass spectra were determined on Varian MAT-112 instrument (low
(1'R, 4'R, 5'S, 6'S)-Spiro-[2,5-cyclohexadiene-4-one-1'-chloro-5',6'- (isopropylidenedioxy)-1,3'-[2]-oxabicyclo[2.2.2]oct-7'-ene] (163a).

To a solution of protected (14c) (301 mg, 1.62 mmol) in benzene (10 ml, degassed) was added 1,4-benzoquinone (192 mg, 1.78 mmol). The solution was stirred until the 1,4-benzoquinone dissolved and then transferred via cannula to a quartz photolysis apparatus. The yellow solution was photolyzed at 3600°A. After 11 hours, the reaction was diluted with Et₂O (25 ml) and washed with brine (25 ml). The aqueous layer was extracted with Et₂O (3 x 25 ml) and the combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude amorphous solid was chromatographed (silica, 10:1 Hexane/EtOAc) to yield 75 mg of a yellow oil (16%).

Rf: 0.20 (Hexane/EtOAc 15:1)
[α]D²⁵: +163.8° (c = 0.57; CHCl₃)

IR: (CCl₄) cm⁻¹ 3005, 1680, 1640, 1360, 1390

¹H-NMR: (CDCl₃) δ 1.41 (s, 3H), 1.42 (s, 3H), 3.76 (d, 1H, J = 6.0 Hz), 4.43 (dd, 1H, J = 5.6, 0.8 Hz), 4.83 (m, 1H), 5.59 (ddd, 1H, J = 10.4, 5.6, 2.0 Hz), 6.04 (dt, 1H, J = 10.4, 0.8 Hz), 6.20 (dd, 1H, J = 10.2, 2.0 Hz), 6.26 (dd, 1H, J = 10.4, 2.0 Hz), 6.65 (dd, 1H, J = 10.4, 3.2 Hz), 7.82 (dd, 1H, J = 10.4, 3.2 Hz)

¹³C-NMR: (CDCl₃) δ 26.7 (CH₃), 27.9 (CH₃), 51.3 (CH), 72.6 (CH), 75.8 (CH), 79.7 (C), 101.9 (C), 110.7 (C), 120.1 (CH), 128.7 (CH), 130.9 (CH), 131.5 (CH), 143.6 (CH), 146.1 (CH), 184.0 (C)

MS: (Cl, 70eV) m/z (rel. intensity) 295 (M + 1) (15), 259 (15), 237 (50), 201 (100)

HRMS calcd for C₁₅H₁₅ClO₄: 294.0659  Found: 294.0658 error -0.4 ppm.

(1S, 2S, 3S, 4S, 4aR, 8aS)-1-Chloro-1,4-etheno-2,3-(isopropylidenedioxy)-1,2,3,4,4a,8a-hexahydro-naphthalene-5,8-dione (164).

Benzoquinone (483 mg, 4.47 mmol) was added to a stirred solution of (14c) (554 mg, 2.98 mmol) in benzene (15 ml). The solution was refluxed. After 22 hours, the solution was cooled to room temperature and the solid precipitate was filtered to yield 464 mg of a pale yellow amorphous solid (53%).

Rf: 0.20 (CHCl₃/MeOH 100:1)
Mp: 196.5-197.5°C
[α]D^25: -155.8° (c=0.62, CHCl₃)
IR: (KBr) cm⁻¹ 3000, 1730, 1620, 1390, 1080
¹H-NMR: (CDCl₃) δ 1.30 (s, 3H), 1.34 (s, 3H), 2.88 (d, 1H, J = 8.8 Hz), 2.98 (dd, 1H, J = 2.7, 8.8 Hz), 3.46 (m, 1H), 4.28 (d, 1H, J = 7.0 Hz), 4.40 (dd, 1H, J = 2.8, 7.1 Hz), 6.06 (m, 2H), 6.63 (d, 1H, J = 10.5 Hz), 6.74 (d, 1H, J = 10.5 Hz)
¹³C-NMR: (CDCl₃) δ 25.1 (CH₃), 25.3 (CH₃), 40.2 (CH), 45.9 (CH), 51.2 (CH), 67.7 (C), 77.6 (CH), 84.3 (CH), 110.2 (C), 130.5 (CH), 133.7 (CH), 141.8 (CH), 143.0 (CH), 193.2 (C), 195.9 (C)
MS: (Cl, 70 eV) m/z (rel. intensity) 297 (M+1) (2), 295 (10), 267 (6), 259 (8), 237 (8)
HRMS calc'd for C₁₅H₁₆ClO₄: 295.0737 Found: 295.0725, error 3.90 ppm
Calcd for C₁₅H₁₅ClO₄: C 61.13% H 5.13% Found: C 61.16% H 5.11%

(1S, 2S, 3S, 4S, 4aR, 9aS)-1-Chloro-1,4-etheno-2,3-(isopropylidenedioxy)-1,2,3,4,4a,9a-hexahydro-anthracene-9,10-dione (165).

Napthoquinone (689 mg, 4.35 mmol) was added to a stirred solution of (14c) (578 mg, 3.11 mmol) in 1,4 dioxane (15 ml). The solution was refluxed. After 22 hours, the solution was diluted with Et₂O (20 ml) and washed with water (20 ml). The aqueous layer was extracted with Et₂O (2 x 20 ml). The organic phases were combined, dried over MgSO₄ and concentrated under reduced pressure. Chromatography (silica, gradient Hexanes/EtOAc 10:1-4:1) yielded 430 mg of a white crystalline compound (40%).

Rf: 0.16 (Hexanes/EtOAc 4:1)

Mp: 181-182°C
[α]D^25: -99.2° (c=0.6, CHCl₃)
IR: (KBr) cm⁻¹ 2950, 1680, 1595, 1375
¹H-NMR: (CDCl₃) δ 1.31 (s, 3H), 1.32 (s, 3H), 3.10 (d, 1H, J = 9.0 Hz), 3.21 (dd, 1H, J = 9.0, 2.8 Hz), 3.54 (dddd, 1H, J = 6.2, 3.1, 3.1, 1.2 Hz), 4.35 (dd, 1H, J = 7.0, 1.4 Hz), 4.48 (ddd, 1H, J = 7.1, 3.1, 1.2 Hz), 5.79 (dd, 1H, J = 8.6, 0.61 Hz), 5.91 (ddd, 1H, J = 8.6, 6.4, 1.1 Hz), 7.68 (m, 2H), 7.88 (m, 2H)
¹³C-NMR: (CDCl₃) δ 25.1 (CH₃), 25.3 (CH₃), 40.7 (CH), 46.9 (CH), 52.3 (CH), 67.9 (C), 77.8 (CH), 84.3 (CH), 110.2 (C), 126.3 (CH), 126.9 (CH), 130.4 (CH), 133.6 (CH), 134.1 (CH), 134.6 (CH), 136.0 (C), 137.1 (C), 193.1 (C), 195.0 (C)
MS: (EI) m/z (rel. intensity) 345 (M⁺)(2), 329 (20), 286 (35), 104 (100)
HRMS calcd for C₁₉H₁₈ClO₄: 345.0894  Found: 345.0903, error 2.80 ppm
Calcd for C₁₉H₁₇ClO₄: C 66.19%  H 4.97%  Found: C 66.09%  H 4.95%.

(1R, 2S, 3S, 4R)-1-Chloro-1,4-etheno-2,3-(isopropylidenedi oxy)-1,2,3,4-tetrahydro-napthalene (167).

To a two-necked flask fitted with an addition funnel and a reflux condenser was added a
solution of (14c) (502 mg, 3.01 mmol) dissolved in dimethoxyethane (DME, 5.5 ml).
Isoamyl nitrite (960 mg, 8.2 mmol) was added and the reaction was brought to reflux. A
solution of anthranilic acid (1.40 g, 10.4 mmol) dissolved in DME (5.5 ml) was added
dropwise over a period of 20 minutes to the refluxing solution. After the addition was
complete the solution was refluxed for another 40 minutes. The reaction was cooled to
room temperature, diluted with Et₂O (25 ml) and washed with a 5% NaOH (aq) solution.
The aqueous layer was extracted with Et₂O (3 x 25 ml). The combined organic layers
were dried over MgSO₄ and concentrated at reduced pressure. Chromatography (silica.
Hexane/EtOAc 25:1) yielded 521 mg of a pale yellow oil (66%).
Rᶠ: 0.18 (Hexane/EtOAc 25:1)
[α]D²⁵: +59.7° (c= 0.83, CHCl₃)
IR: (neat) cm⁻¹ 2995, 2940, 1620, 1470, 1270, 1100
¹H-NMR: (CDCl₃) δ 1.28 (s, 3H), 1.44 (s, 3H), 4.13 (m, 1H), 4.22 (dd, 1H, J = 7.0,
1.2), 4.36 (ddd, 1H, J = 7.1, 3.6, 1.1), 6.43 (m, 2H), 7.22 (m, 3H), 7.64 (m, 1H)
¹³C-NMR: (CDCl₃) δ 25.3 (CH₃), 25.7 (CH₃), 44.6 (CH), 71.7 (C), 79.7 (CH), 84.5
(CH), 113.0 (C), 123.0 (CH), 124.3 (CH), 126.6 (CH), 127.1 (CH), 132.0 (CH), 136.2
(CH), 137.6 (C), 139.6 (C)
MS: (CI, 70eV) m/z (rel. intensity) 263 (M + 1) (25), 247 (20), 233 (15), 205 (100)
HRMS calcd for C₁₅H₁₆ClO₂: 263.0839  Found: 263.0843, error 1.7 ppm
Calcd for C₁₅H₁₅ClO₂: C 68.57%  H 5.75%  Found: C 68.50%  H 5.78%.

(3aR, 4S, 5S, 7aS)-6-Chloro-4,5-(isopropylidenedi oxy)-3-methyl-3a, 4, 5, 7a-
tetrahydro-1,2-benzisoxazole (169).

Phenyl isocy anate (636 mg, 5.38 mmol) was added to a stirred solution of (14c) (1.0 g,
5.38 mmol), nitroethane (408 mg, 5.38 mmol) and catalytic triethylamine (3 drops) in
benzene (6 ml). A total of two more equivalents (phenyl isocyanate, nitroethane and 6
drops triethylamine) were added in one equivalent increments after 2 and 15 hours. After 27 hours, the reaction was washed with water (2 x 20 ml) and once with 10% NaOH aqueous solution (10 ml). The benzene solution was dried over MgSO4 and concentrated under reduced pressure to give a brown crystalline solid. Recrystallization (Hexane/EtOAc 6:1) yields 955 mg of a white crystalline solid (73%).

\[ \text{Rf: 0.17 (Hexane/EtOAc 4:1)} \]

\[ \text{Mp: 152-153.5°C} \]

\[ \left[ \alpha \right]_{D}^{25}: +285.2 \text{ (c=0.54, CHCl3)} \]

\[ \text{IR: (KBr) cm}^{-1} 3005, 2950, 1660, 1632, 1115, 920 \]

\[ \text{\textsuperscript{1}H-NMR: (CDCl3)} \delta 1.39 \text{ (s, 3H), 1.40 (s, 3H), 2.00 (s, 3H), 3.80 (br d, 1H, J = 9.0 Hz), 4.35 (d, 1H, J = 4.9 Hz), 4.60 (dd, 1H, J = 5.0, 3.1 Hz), 5.12 (dd, 1H, J = 9.0, 3.2 Hz), 5.80 (d, 1H, J = 3.3 Hz)} \]

\[ \text{\textsuperscript{13}C-NMR: (CDCl3)} \delta 12.5 \text{ (CH3), 26.4 (CH3), 27.6 (CH3), 49.2 (CH), 72.5 (CH), 72.7 (CH), 75.0 (CH), 110.2 (C), 123.2 (CH), 135.2 (C), 154.2 (C)} \]

\[ \text{MS: (Cl, 70 eV) m/z (rel. intensity) 244 (M+ 1) (40), 228 (10), 186 (40), 59 (100)} \]

\[ \text{HRMS calculated for C}_{11}\text{H}_{15}\text{ClNO}_{3}: 244.0740 \text{ Found: 244.0741, error 0.1 ppm}} \]

\[ \text{Calcd for C}_{11}\text{H}_{14}\text{ClNO}_{3}: \text{C 54.22% H 5.79% N 5.75% Found: C 54.20% H 5.80%. N 5.76%}} \]

\((3R, 4R, 5S, 6S)-1\text{-Cyano-3,4-dihydroxy-5,6-(isopropylidenedioxy)-1,2-cyclohexene (172a).}

To a cooled flask (-10°C) charged with KMnO4 (300 mg, 1.90 mmol), MgSO4 (168 mg, 1.4 mmol), acetone (6.3 ml) and water (7.3 ml) was added (14h) (305 mg, 1.72 mmol) dissolved in acetone (6 ml) over 35 minutes. After stirring 1 hour, sodium metabisulfite (50 mg) was added and the solution was warmed to room temperature. The solution was filtered through Celite and the solid residue was washed with water (10 ml) and acetone (15 ml). The solution was saturated with NaCl and extracted with EtOAc (4 x 25 ml). The combined extracts were dried over MgSO4 and concentrated under reduced pressure to yield a colorless oil. Chromatography (silica, CHCl3/MeOH 30:1) yielded 110 mg of a white solid (30%).

\[ \text{Rf: 0.10 (CHCl3/MeOH 20:1)} \]

\[ \text{Mp: 110-112°C} \]

\[ \left[ \alpha \right]_{D}^{24}: -60.3^\circ \text{ (c = 0.68; MeOH)} \]
IR: (CCl₄) cm⁻¹ 3400, 2990, 2915, 2210, 1370, 1222

¹H-NMR: (CDCl₃) δ 1.38 (s, 6H), 2.92 (s, 1H), 2.98 (d, 1H, J = 7.6 Hz), 4.31 (dd, 1H, J = 6.6, 3.2 Hz), 4.44 (m, 1H), 4.48 (t, 1H, 4.8 Hz), 4.63 (dd, 1H, J = 5.1, 1.3 Hz), 6.51 (t, 1H, J = 1.7 Hz)

¹³C-NMR: (CDCl₃) δ 26.0 (CH₃), 27.5 (CH₃), 65.1 (CH), 69.1 (CH), 70.7 (CH), 75.1 (CH), 110.8 (C), 114.3 (C), 117.0 (C), 144.8 (CH)

MS: (EI, 70eV) ml/z (rel. intensity) 212 (M⁺) (50), 196 (100), 184 (10), 136 (70)

HRMS calculc for C₁₀H₁₄NO₄: 212.0923 Found: 221.0929 error + 2.8 ppm.

Calcd for C₁₀H₁₄NO₄ C 56.87% H 6.20% N 6.63% Found C 56.17% H 6.15% N 6.55%

(1S, 2S, 3S, 4R, 5S, 6S)-3,4-dihydroxy-1,2-epoxy-5,6-(isopropylidenedioxy)-1-phenycyclohexane (173).

To a cooled (0°C) and stirred solution of KMnO₄ (890 mg, 5.61 mmol), MgSO₄ (166 mg, 1.40 mmol), acetone (9.0 ml) and water (10 ml) was added (14i) in solution (196 mg, 0.86 mmol in 9.0 ml of acetone) over ten minutes. After fifteen minutes, sodium metabisulphite was added until the excess KMnO₄ was quenched. The reaction was warmed to room temperature. The brown reaction was then filtered through Celite and the solid residue was washed with water (20 ml) and acetone (20 ml). The solution was saturated with NaCl and was extracted with CHCl₃ (5 x 20 ml). The combined extracts were dried over MgSO₄ and concentrated under reduced pressure to yield 230 mg of a pale yellow oil. Chromatography (silica, gradient, CHCl₃/MeOH 100:1, 60:1) yields 55 mg (23%) of a white crystalline material.

Rf: 0.11 (CHCl₃/MeOH 80:1)

Mp: 115 -117°C

αD²⁵: +84.2° (c = 0.66, CHCl₃)

IR: (CHCl₃) cm⁻¹ 3300, 2980, 1320, 1200

¹H-NMR: (CDCl₃) δ 1.30 (s, 3H), 1.44 (s, 3H), 3.10 (d, 1H, J = 10.0 Hz), 3.19 (d, 1H, J = 12.0 Hz), 3.70 (s, 1H), 4.06 (brd, 1H, J = 11.8 Hz), 4.36 (dd, 1H, J = 9.8, 3.7 Hz), 4.61 (dd, 1H, J = 6.4, 2.7 Hz), 4.76 (dd, 1H, J = 6.3, 1.0 Hz), 7.35 (m, 3H), 7.43 (m, 2H)

¹³C-NMR: (CDCl₃) δ 24.2 (CH₃), 27.0 (CH₃), 64.6 (CH), 64.8 (CH), 65.0 (C), 69.5 (CH), 73.2 (CH), 77.6 (CH), 109.5 (C), 127.5 (2 x CH), 128.3 (2 x CH), 128.6 (CH), 136.6 (C)
**MS:** (EI, 70 ev) m/z (rel. intensity) 278 (M+) (2), 263 (14), 220 (70)

**Calcd. for C\textsubscript{15}H\textsubscript{18}O\textsubscript{5}:** C 64.74% H 6.52% **Found:** C 64.48% H 6.42%.

(3R, 4R, 5S, 6S)-3,4-Dihydroxy-1-(ethynylphenyl)-5,6-(isopropylidenedioxy)-cyclohexene (174a).

To a cooled (0°C) and stirred solution of KMnO\textsubscript{4} (890 mg, 5.61 mmol), MgSO\textsubscript{4} (450 mg, 3.74 mmol), acetone (9.0 ml) and water (11.0 ml) was added (14j) in solution (472 mg, 1.87 mmol in 9.0 ml of acetone) over ten minutes. After fifteen minutes, sodium metabisulfite was added until the excess KMnO\textsubscript{4} was quenched. The reaction was warmed to room temperature. The brown reaction was then filtered through Celite and the solid residue was washed with water (20 ml) and acetone (20 ml). The solution was saturated with NaCl and was extracted with EtOAc (4 x 30 ml). The combined extracts were dried over MgSO\textsubscript{4} and concentrated under reduced pressure. Chromatography (silica, CHCl\textsubscript{3}/MeOH 20:1) yielded 30 mg of a colorless oil (6%).

**Rf:** 0.20 (CHCl\textsubscript{3}/MeOH 20:1)

\(\alpha_d^{28} = -20.9^\circ \) (c = 0.58, CHCl\textsubscript{3})

**IR:** (CHCl\textsubscript{3}) cm\(^{-1}\) 3416, 2928, 1745, 1679

**\(^1\)H-NMR:** (CHCl\textsubscript{3}) \(\delta\) 1.40 (s, 3H), 1.44 (s, 3H), 2.50 (s, 1H), 4.10 (dd, 1H, \(J = 4.6, 4.7\) Hz), 4.42 (m, 2H), 4.68 (d, 1H, \(J = 5.3\) Hz), 6.18 (d, 1H, \(J = 3.7\) Hz), 7.29 (m, 3H), 7.45 (m, 2H)

**\(^{13}\)C-NMR:** (CHCl\textsubscript{3}) \(\delta\) 26.0 (CH\(_3\)), 27.7 (CH\(_3\)), 66.0 (CH), 70.3 (CH), 73.6 (CH), 75.4 (CH), 87.3 (C), 90.3 (C), 109.9 (C), 122.7 (CH), 128.2 (2 x CH), 128.5 (CH), 131.8 (CH), 134.9 (CH)

**MS:** (CI, 70 ev) m/z (rel. intensity) 286 (M+) (10), 269 (20), 211 (100), 183 (100).

(1S, 2S, 3S, 4R, 5S, 6S)-3,4-Dihydroxy-1,2-epoxy-1-(ethynylphenyl)-5,6-(isopropylidenedioxy)-cyclohexane (174b).

To a cooled (0°C) and stirred solution of KMnO\textsubscript{4} (890 mg, 5.61 mmol), MgSO\textsubscript{4} (450 mg, 3.74 mmol), acetone (9.0 ml) and water (11.0 ml) was added (14j) in solution (472 mg, 1.87 mmol in 9.0 ml acetone) over ten minutes. After fifteen minutes, sodium metabisulfite was added until the excess KMnO\textsubscript{4} was quenched. The reaction was warmed to room temperature. The brown reaction was then filtered through Celite and
the solid residue was washed with water (20 ml) and acetone (20 ml). The solution was saturated with NaCl and was extracted with EtOAc (4 x 30 ml). The combined extracts were dried over MgSO4 and concentrated under reduced pressure. Chromatography (silica, CHCl3/MeOH 20:1) yielded 80 mg of a pale yellow solid (14%).

Rf: 0.25 (CHCl3/MeOH 20:1)

Mp: 123 -126°C

αD25: +98.3° (c = 0.48, CHCl3)

IR: (CHCl3) cm\(^{-1}\) 3450, 3000, 2210, 1495, 1220

\(^1\)H-NMR: (CHCl3) δ 1.38 (s, 3H), 1.48 (s, 3H), 2.66 (d, 1H, J = 12.2 Hz), 2.85 (d, 1H, J = 10.3 Hz), 3.81 (m, 1H), 4.07 (ddt, 1H, J = 12.2, 3.8, 1.4 Hz), 4.29 (dd, 1H, J = 10.2, 4.0, 0.8 Hz), 4.54 (dd, 1H, J = 5.6, 3.6 Hz), 4.60 (dd, 1H, J = 5.6, 1.2 Hz), 7.30 (m, 3H), 7.47 (m, 2H)

\(^13\)C-NMR: (CHCl3) δ 25.2 (CH3), 27.3 (CH3), 55.9 (C), 63.9 (CH), 65.6 (CH), 68.2 (CH), 71.6 (CH), 77.1 (CH), 84.2 (C), 85.6 (C), 110.3 (C), 121.5 (C), 128.2 (2 x CH), 129.0 (CH), 132.0 (2 x CH)

MS: (EI, 70 ev) m/z (rel. intensity) 302 (M+) (2), 287 (5), 244 (30), 185 (60)

HRMS calc'd for C\(_{17}\)H\(_{19}\)O\(_5\): 303.1232 Found: 303.1222, error 3.2 ppm.

(1S, 2S, 3S, 4R, 5S, 6S)-3,4-Dihydroxy-1,2-epoxy-5,6-(isopropylidenedioxy)-1-methylcyclohexane (175).

To a cooled (0°C) and stirred solution of KMnO\(_4\) (656 mg, 4.15 mmol), MgSO\(_4\) (350 mg, 2.90 mmol), acetone (8 ml) and water (9 ml) was added (14g) in solution (300 mg, 1.80 mmol in 5.0 ml acetone) over ten minutes. After fifteen minutes, sodium metabisulfite was added until the excess KMnO\(_4\) was quenched. The reaction was warmed to room temperature. The brown reaction was then filtered through Celite and the solid residue was washed with water (20 ml) and acetone (20 ml). The solution was saturated with NaCl and was extracted with EtOAc (4 x 30 ml). The combined extracts were dried over MgSO\(_4\) and concentrated under reduced pressure. Chromatography (silica, Hexane/EtOAc gradient; 2.5:1 -> 1:1) yielded 20 mg of a pale yellow solid (5%).

Rf: 0.26 (CHCl3/MeOH 25:1)

Mp: 105 -107°C

αD24: +25.3° (c = 0.15, CHCl3)

IR: (CHCl3) cm\(^{-1}\) 3455, 2987, 2934, 1380, 1165, 1100
1H-NMR: (CDCl3) δ 1.32 (s, 3H), 1.39 (s, 3H), 1.42 (s, 3H), 2.96 (d, 1H, J = 10.2 Hz), 3.04 (d, 1H, J = 12.0 Hz), 3.35 (d, 1H, J = 1.1 Hz), 3.98 (dddd, 1H, J = 1.7, 3.7, 3.7, 12.1 Hz), 4.17 (dd, 1H, J = 4.0, 10.1 Hz), 4.36 (dd, 1H, J = 1.1, 6.0 Hz), 4.48 (dd, 1H, J = 3.4, 6.0 Hz)

13C-NMR: (CDCl3) δ 19.4 (CH3), 24.8 (CH3), 27.1 (CH3), 62.2 (C), 64.4 (CH), 65.2 (CH), 68.8 (CH), 73.3 (CH), 77.1 (CH), 109.5 (C)

MS: (EI, 70eV) m/z (rel. intensity) 201 (M-15) (100), 123 (90), 115 (20)

HRMS calcd for C10H17O5: 217.1076 Found: 217.1077 error + 0.7 ppm.

(5S, 6S)-1-Bromo-6-hydroxy-5-(thexyldimethylsilyloxy)-cyclohexa-1,3-diene (191a). (190a) (7.0 g, 36.65 mmol) and imidazole (3.0 g, 43.97 mmol) were dissolved in CH2Cl2 (80 ml). The flask was cooled to 0°C and the xyldimethylsilyl chloride (7.86 g, 43.97 mmol) was added dropwise. After 2 days at 0°C, the solution was concentrated under reduced pressure. Water (25 ml) and Et2O (150 ml) were added to the crude reaction mixture. The layers were separated and the aqueous layer was extracted with Et2O (3 x 50 ml). The Et2O extracts were combined, dried over MgSO4 and concentrated under reduced pressure. Chromatography (silica, Hexane/EtOAc, 25:1) yielded 11.48 g of a colorless oil (94%).

Rf: 0.19 (Hexane/EtOAc, 10:1)
[^2]D: +92.0° (c=0.79, CHCl3)

IR: (neat) cm⁻¹ 3550, 2975, 1600, 1440

1H-NMR: (CDCl3) δ 0.14 (s, 3H), 0.15 (s, 3H), 0.85 (s, 6H), 0.87 (d, 3H, J = 1.8 Hz), 0.88 (d, 3H, J = 1.8 Hz), 1.62 (m, 1H), 2.74 (d, 1H, J = 4.5 Hz), 4.12 (dd, 1H, J = 4.6, 6.2 Hz), 4.54 (d, 1H, J = 6.1 Hz), 5.76 (d, 2H, J = 3.8 Hz), 6.34 (dd, 1H, J = 2.5, 4.1 Hz)

13C-NMR: (CDCl3) δ -3.0 (CH3), -2.5 (CH3), 18.5 (CH3), 18.6 (CH3), 20.1 (CH3), 20.3 (CH3), 25.0 (C), 34.1 (CH), 70.5 (CH), 72.6 (CH), 123.4 (CH), 125.6 (C), 126.8 (CH), 129.4 (CH)

MS: (Cl, 70 eV) m/z (rel. intensity) 334 (M+1) (0.5), 317 (12), 231 (50), 75 (100)

Calcd for C14H25BrO2Si: C 50.44% H 7.56% Found: C 50.23% H 7.47%.
(5S, 6S)-1-Chloro-6-hydroxy-5-(thexyldimethylsilyloxy)-cyclohexa-1,3-diene (191b) (92%).

**Rf:** 0.33 (Hexane/EtOAc, 10:1)

**[α]D**^25_25: +58.7° (c=1.06, CHCl₃)

**IR:** (neat) cm⁻¹ 3540, 2990, 1650, 1475

**¹H-NMR:** (CDCl₃) δ 0.14 (s, 3H), 0.15 (s, 3H), 0.85 (s, 6H), 0.87 (d, 3H, J =1.8 Hz), 0.89 (d, 3H, J =1.8 Hz), 1.62 (m, 1H), 2.76 (s, 1H), 4.03 (d, 1H, J = 6.3 Hz), 4.56 (m, 1H), 5.69 (dd, 1H, J = 2.9, 9.6 Hz), 5.85 (ddd, 1H, J = 2.0, 5.8, 9.6 Hz), 6.10 (d, 1H, J = 5.6 Hz)

**¹³C-NMR:** (CDCl₃) δ -3.0 (CH₃), -2.5 (CH₃), 18.5 (CH₃), 18.6 (CH₃), 20.1 (CH₃), 20.3 (CH₃), 25.0 (C), 34.1 (CH), 70.6 (CH), 71.5 (CH), 122.7 (2xCH), 129.0 (CH), 134.6 (C).

(5S, 6S)-1-Bromo-6-(2-ethoxymethyloxy)-5-(thexyldimethylsilyloxy)-cyclohexa-1,3-diene (192a).

(191a) (11.08 g, 28.10 mmol) was dissolved in i-Pr₂NEt (21.8 g, 168.60 mmol). After 5 minutes, chloromethyl ethylether (5.74 g, 60.69 mmol) was added dropwise over several minutes. The reaction was stirred at 0°C for 1 hour and then warmed to room temperature. After 2.5 hours, CH₂Cl₂ (10 ml) was added to the heterogeneous reaction. The reaction was stirred for 1 hour and then diluted with water (50 ml) and Et₂O (75 ml). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 50 ml). The organic extracts were combined, dried over MgSO₄ and concentrated under reduced pressure. Chromatography (silica, Hexanes/EtOAc 20:1) yielded 12.32 g of a colorless oil (93%).

**Rf:** 0.38 (Hexane/EtOAc, 10:1)

**[α]D**^26_26: +33.5° (c=1.00, CHCl₃)

**IR:** (neat) cm⁻¹ 2990, 1600, 1580, 1260

**¹H-NMR:** (CDCl₃) δ 0.13 (s, 3H), 0.15 (s, 3H), 0.85 (s, 6H), 0.86 (d, 3H, J = 1.1 Hz), 0.88 (d, 3H, J = 1.1 Hz), 1.20 (t, 3H, J = 7.1 Hz), 1.64 (m, 1H), 3.49 (dq, 1H, J = 2.3, 7.0 Hz), 3.87 (dq, 1H, J = 2.3, 7.0 Hz), 4.04 (d, 1H, J = 5.8 Hz), 4.65 (m, 1H), 4.75 (d, 1H, J = 6.9 Hz), 4.87 (d, 1H, J = 6.9 Hz), 5.76 (ddd, 1H, J = 2.8, 5.6, 9.6 Hz), 5.84 (ddd, 1H, J = 1.1, 1.1, 9.7 Hz), 6.40 (d, 1H, J = 5.6 Hz)

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\textbf{13C-NMR:} (CDCl\textsubscript{3}) \(\delta\) -2.8 (CH\subscript{3}), -2.7 (CH\subscript{3}), 14.8 (CH\subscript{3}), 18.5 (CH\subscript{3}), 18.6 (CH\subscript{3}), 20.0 (CH\subscript{3}), 20.2 (CH\subscript{3}), 25.0 (C), 34.0 (CH), 63.5 (CH\subscript{2}), 72.6 (CH), 77.9 (CH), 95.5 (CH\subscript{2}), 122.2 (CH), 123.0 (C), 128.5 (CH), 132.6 (CH)

\textbf{MS:} (Cl, 70 eV) \(m/z\) (rel. intensity) 391 (M\textsuperscript{+}) (1), 317 (100), 259 (40), 231 (100)

\textbf{HRMS calcd for C\textsubscript{17}H\textsubscript{31}BrO\textsubscript{3}Si:} 390.1226 \textbf{Found:} 390.1246, error 5.1 ppm.

(5S, 6S)-1-Chloro-6-(2-ethoxymethyloxy)-5-(thexyldimethylsilyloxy)-cyclohexa-1,3-diene (192b).

\textbf{1H-NMR:} (CDCl\textsubscript{3}) \(\delta\) 0.12 (s, 3H), 0.14 (s, 3H), 0.85 (s, 6H), 0.86 (d, 3H, \(J = 1.1\) Hz), 0.88 (d, 3H, \(J = 1.1\) Hz), 1.19 (t, 3H, \(J = 7.0\) Hz), 1.63 (m, 1H), 3.48 (dq, 1H, \(J = 2.3, 7.0\) Hz), 3.83 (dq, 1H, \(J = 2.3, 7.0\) Hz), 3.95 (d, 1H, \(J = 5.8\) Hz), 4.65 (d, 1H, \(J = 5.8\) Hz), 4.74 (d, 1H, \(J = 6.9\) Hz), 4.86 (d, 1H, \(J = 6.9\) Hz), 5.80 (m, 2H), 6.16 (d, 1H, \(J = 5.3\) Hz).

(1R, 7R, 8S, 9S)-1-Bromo-9-(2-ethoxymethyloxy)-4-phenyl-8-(thexyldimethylsilyloxy)-2,4,6-triazolotricyclo-[5.2.2.0]-undec-10-ene-3,5-dione (193a).

(192a) (1.35 g, 3.46 mmol) was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (16 ml). The flask was cooled to -50°C. In another flask triazoline (20) (637 mg, 3.63 mmol) was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (12 ml). The triazoline solution was then added dropwise via cannula to the cold diol (192a) solution over 10 minutes. The reaction was then warmed to room temperature. After 20 minutes, the reaction was diluted with water (20 ml). The layers were separated and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 20 ml). The organic layers were combined, dried over MgSO\textsubscript{4} and concentrated under reduced pressure. Chromatography (silica, Hexanes/EtOAc 8:1) yielded 1.74 g of a white foam (89%).

\textbf{Rf:} 0.33 (Hexane/EtOAc 4:1)

[\(\alpha\)]\textsubscript{D}\textsuperscript{26}: +83.3° (c=0.83, CHCl\textsubscript{3})

\textbf{IR:} (CHCl\textsubscript{3}) \textsuperscript{cm\textsuperscript{-1}} 2995, 1790, 1735, 1608, 1509, 1410, 1265

\textbf{1H-NMR:} (CDCl\textsubscript{3}) \(\delta\) 0.19 (s, 3H), 0.26 (s, 3H), 0.85 (m, 12H), 1.24 (t, 3H, \(J = 7.0\) Hz), 1.62 (m, 1H), 3.59 (dq, 1H, \(J = 2.3, 7.0\) Hz), 4.11 (dq, 1H, \(J = 2.3, 7.0\) Hz), 4.38 (dd, 1H, \(J = 0.8, 6.7\) Hz), 4.47 (dd, 1H, \(J = 0.8, 3.7, 6.7\) Hz), 4.73 (d, 1H, \(J = 7.0\) Hz), 4.77 (d, 1H, \(J = 7.1\) Hz), 4.87 (ddd, 1H, \(J = 1.4, 3.7, 5.8\) Hz), 6.34 (dd, 1H, \(J = 5.7, 8.5\) Hz), 6.66 (d, 1H, \(J = 8.4\) Hz), 7.41 (m, 5H)
$^{13}$C-NMR: (CDCl$_3$) δ -3.1 (CH$_3$), -2.5 (CH$_3$), 14.8 (CH$_3$), 18.4 (CH$_3$), 18.4 (CH$_3$), 19.9 (CH$_3$), 20.0 (CH$_3$), 24.8 (C), 33.8 (CH), 53.5 (CH), 64.6 (CH$_2$), 69.1 (CH), 69.7 (C), 78.8 (CH), 94.8 (CH$_2$), 125.5 (2xCH), 128.5 (CH), 128.7 (CH), 129.0 (2xCH), 130.8 (C), 135.6 (CH), 153.7 (C), 154.3 (C)

MS: (Cl, 70 eV) m/z (rel. intensity) 567 (M$^+$+1) (1), 487 (5), 305 (45)

Caled for C$_{25}$H$_{36}$BrN$_3$O$_5$Si: C 53.00%  H 6.40%  N 7.42%  Found: C 53.03%  H 6.39%  N 7.39%

(1R, 7R, 8S, 9S)-1-Chloro-9-(2-ethoxymethyloxy)-4-phenyl-8-(thexydimethylsilyleoxy)-2,4,6-triazolotricyclo-[5.2.2.0]undec-10-ene-3,5-dione (193b) (76%)

R$_f$: 0.12 (Hexane/EtOAc 10:1)

[α]$_D^{24}$: +79.6° (c=1.18, CHCl$_3$)

IR: (CHCl$_3$) cm$^{-1}$ 2960, 1738, 1716, 1504

$^1$H-NMR: (CDCl$_3$) δ 0.15 (s, 3H), 0.24 (s, 3H), 0.83 (s, 6H), 0.84 (s, 3H), 0.88 (s, 3H), 1.22 (t, 3H, J = 7.0 Hz), 1.62 (m, 1H), 3.54 (dq, 1H, J = 2.3, 7.0 Hz), 4.00 (dq, 1H, J = 2.3, 7.0 Hz), 4.33 (d, 1H, J = 0.8, 6.8 Hz), 4.48 (dd, 1H, J = 0.8, 3.6, 7.7 Hz), 4.70 (d, 1H, J = 7.0 Hz), 4.74 (d, 1H, J = 7.0 Hz), 4.84 (dd, 1H, J = 1.4, 3.6, 5.7 Hz), 6.40 (d, 1H, J = 5.7, 8.5 Hz), 6.53 (d, 1H, J = 8.5 Hz), 7.40 (m, 5H)

$^{13}$C-NMR: (CDCl$_3$) δ -3.0 (CH$_3$), -2.4 (CH$_3$), 14.8 (CH$_3$), 18.5 (CH$_3$), 20.0 (CH$_3$), 20.1 (CH$_3$), 24.8 (C), 33.9 (CH), 53.8 (CH), 64.4 (CH$_2$), 69.0 (CH), 76.5 (CH), 79.7 (C), 94.9 (CH$_2$), 125.7 (2xCH), 128.6 (CH), 128.8 (CH), 129.1 (2xCH), 130.9 (C), 134.0 (CH), 153.9 (C), 154.8 (C)

MS: (Cl, 70 eV) m/z (rel. intensity) 522 (M$^+$) (100), 477 (50), 363 (80)

HRMS caled for C$_{25}$H$_{37}$ClN$_3$O$_5$Si: 522.2191 Found: 522.2190, error 0.2 ppm.

(1R, 7R, 8S, 9S)-1-Bromo-9-(2-ethoxymethyloxy)-8-hydroxy-4-phenyl-2,4,6-triazolotricyclo-[5.2.2.0]undec-10-ene-3,5-dione (194a).

(193a) (1.08 g, 1.90 mmol) was dissolved in THF (45 ml). The reaction flask was cooled to -60°C and TBAF (2.2 ml of a 1M solution, 2.2 mmol) was added dropwise. The reaction was slowly warmed to -50°C over 1 hour, quenched with water (20 ml) and warmed to room temperature. Brine was added to the emulsion and the organic layer was
separated. The aqueous layer was extracted with EtOAc (4 x 25 ml). The organic layers were combined, dried over MgSO₄ and concentrated under reduced pressure. Chromatography (silica, Hexanes/EtOAc 1.5:1) yielded 754 mg of a white foam (94%).

Rf: 0.22 (Hexane/EtOAc 1:1)
[α]D²⁵: -87.9° (c=0.59, CHCl₃)

IR: (CHCl₃) cm⁻¹ 3500, 2490, 1790, 1735, 1410

¹H-NMR: (CDCl₃) δ 1.26 (t, 3H, J = 7.0 Hz), 3.13 (d, 1H, J = 5.6 Hz), 3.74 (q, 2H, J = 7.0 Hz), 3.74 (q, 2H, J = 7.0 Hz), 4.33 (dd, 1H, J = 1.0, 7.3 Hz), 4.46 (m, 1H), 4.96 (d, 1H, J = 6.4), 4.99 (d, 1H, J = 6.4 Hz), 5.11 (ddd, 1H, J = 1.5, 4.0, 5.6 Hz), 6.40 (ddd, 1H, J = 0.9, 5.6, 8.4 Hz), 6.62 (ddd, 1H, J = 1.2, 1.2, 8.5 Hz), 7.42 (m, 5H)

¹³C-NMR: (CDCl₃) δ 15.0 (CH₃), 53.2 (CH), 65.2 (CH₂), 67.7 (CH), 69.4 (C), 78.7 (CH), 97.8 (CH₂), 125.7 (2xCH), 128.6 (CH), 129.1 (2xCH), 129.6 (CH), 130.9 (C), 135.2 (CH), 154.0 (C), 154.5 (C)

MS: (CI, 70 eV) m/z (rel. intensity) 424 (M⁺+1) (1), 366 (10), 307 (70), 119 (100)

Calcd for C₁₇H₁₈BrN₃O₅: C 48.13%  H 4.28%  Found: C 48.20%  H 4.31%.

(1R, 7R, 8S, 9S)-1-Chloro-9-(2-ethoxymethyloxy)-8-hydroxy-4-phenyl-2,4,6-triazolo[5.2.2.0]-undec-10-ene-3,5-dione (194b) (89%).

Rf: 0.25 (Hexane/EtOAc 1:1)
[α]D²⁹: -64.2° (c=1.10, CHCl₃)

IR: (CHCl₃) cm⁻¹ 3500, 2495, 1788, 1730, 1407

¹H-NMR: (CDCl₃) δ 1.23 (t, 3H, J = 7.2 Hz), 3.12 (d, 1H, J = 5.8 Hz), 3.70 (q, 2H, J = 7.0 Hz), 4.30 (dd, 1H, J = 1.0, 7.4 Hz), 4.45 (m, 1H), 4.91 (d, 1H, J = 6.6 Hz), 4.96 (d, 1H, J = 6.6 Hz), 5.08 (ddd, 1H, J = 1.7, 3.8, 5.5 Hz), 6.46 (ddd, 1H, J = 0.9, 5.5, 8.4 Hz), 6.50 (ddd, 1H, J = 1.1, 1.7, 8.4 Hz), 7.39 (m, 5H)

¹³C-NMR: (CDCl₃) δ 15.0 (CH₃), 53.4 (CH), 65.2 (CH₂), 67.4 (CH), 77.9 (CH), 79.3 (C), 97.6 (CH₂), 125.7 (2xCH), 128.7 (CH), 129.1 (2xCH), 129.6 (CH), 129.0 (C), 133.9 (CH), 154.0 (C), 154.9 (C)

MS: (CI, 70 eV) m/z (rel. intensity) 380 (M⁺+1) (50), 334 (50), 261 (50)

(1R, 7R, 8R, 9S)-1-Bromo-9-(2-ethoxymethyloxy)-8-hydroxy-4-phenyl-2,4,6-triazolotricyclo-[5.2.2.0]undec-10-ene-3,5-dione (196a).

(194a) (506 mg, 1.2 mmol) was dissolved in CH₂Cl₂ (13 ml). The reaction mixture was cooled to 0°C. Pyridine (650 mg, 7.74 mmol) and triflic anhydride (839 mg, 3.0 mmol) were then added dropwise. After 1.5 hours, water (8 ml) was added and the reaction mixture was warmed to room temperature. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (4 x 30 ml). The organic layers were combined, dried over MgSO₄ and concentrated under reduced pressure to yield 700 mg of the corresponding crude triflate as a foam.

**¹H-NMR:** (CDCl₃) δ 1.25 (t, 3H, J = 6.9 Hz), 3.74 (dq, 1H, J = 2.1, 7.1 Hz), 3.86 (dq, 1H, J = 2.1, 7.1 Hz), 4.49 (dd, 1H, J = 6.9 Hz), 4.93 (d, 1H, J = 6.6 Hz), 5.01 (d, 1H, J = 6.6 Hz), 5.25 (m, 1H), 5.49 (dd, 1H, J = 4.0, 6.6 Hz), 6.38 (dd, 1H, J = 5.8, 8.5 Hz), 6.81 (d, 1H, J = 8.5 Hz), 7.44 (m, 5H).

The crude triflate (700 mg), 18-crown-6 (1.26 g, 4.77 mmol) and cesium acetate (915 mg, 4.77 mmol) were dissolved in DMF (19.8 ml). The reaction mixture was heated to 70°C. After 15 minutes, the reaction was cooled to room temperature and diluted with water (15 ml) and EtOAc (45 ml). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 45 ml). The organic layers were combined, dried over MgSO₄ and concentrated under reduced pressure to yield 596 mg of the crude acetate.

**¹H-NMR:** (CDCl₃) δ 1.16 (t, 3H, J = 7.0 Hz), 2.10 (s, 3H), 3.60 (q, 2H, J = 7.0 Hz), 4.15 (s, 1H), 4.79 (d, 1H, J = 7.1 Hz), 4.87 (d, 1H, J = 7.1 Hz), 4.90 (m, 1H), 5.10 (dd, 1H, J = 2.4, 6.3 Hz), 6.49 (dd, 1H, J = 6.4, 8.3 Hz), 6.61 (d, 1H, J = 8.3 Hz), 7.40 (m, 5H).

The crude acetate was placed in a flask followed by 95% EtOH (40 ml) and K₂CO₃ (1.59 g). After 2.5 hours of vigorous stirring, the reaction was diluted with water (15 ml) and CHCl₃ (45 ml). The layers were separated and the aqueous layer was extracted with CHCl₃ (3 x 45 ml). The organic layers were combined, dried over MgSO₄ and concentrated under reduced pressure. Chromatography (silica, Hexanes/EtOAc 1:1) yielded 475 mg of a white foam (94%).

**Rf:** 0.20 (Hexane/EtOAc 1:1)

**[α]D²⁵:** +50.3° (c=0.90, CH₃OH)

**IR:** (CHCl₃) cm⁻¹ 3440 (br), 2995, 1780, 1720, 1600, 1500

**¹H-NMR:** (CDCl₃) δ 1.22 (t, 3H, J = 7.0 Hz), 3.21 (d, 1H, J = 5.6 Hz), 3.684 (q, 1H, J = 7.0 Hz), 3.687 (q, 1H, J = 7.0 Hz), 3.87 (m, 1H), 3.94 (s, 1H), 4.84 (s, 2H), 4.95 (dd, 1H, J = 2.7, 5.6 Hz), 6.41 (dd, 1H, J = 6.2, 8.4 Hz), 6.54 (d, 1H, J = 8.4 Hz), 7.39 (m, 5H)
13C-NMR: (CDCl3) δ 14.9 (CH3), 56.3 (CH), 64.4 (CH2), 68.4 (C), 74.9 (CH), 83.4 (CH), 95.4 (CH2), 126.0 (2xCH), 128.2 (CH). 128.7 (CH), 129.1 (2xCH), 131.0 (C), 136.4 (CH), 153.4 (C), 155.5 (C)  
MS: (Cl, 70 eV) m/z (rel. intensity) 424 (M+1) (1), 366 (14), 305 (60)  
Calcd for C_{17}H_{18}BrN_{3}O_{5}: C 48.13%  H 4.28%  Found: C 48.41%  H 4.48%.

(1R, 7R, 8R, 9S)-1-Chloro-9-(2-ethoxymethoxy)-8-hydroxy-4-phenyl-2,4,6-triazolotricyclo-[5.2.2.0]-undec-10-ene-3,5-dione (196b) (86%).

RF: 0.22 (Hexane/EtOAc 1:1)  
[α]D^{26}: -51.8° (c=1.03, CHCl3)  
IR: (CHCl3) cm^{-1} 3445 (br), 2976, 1770, 1716, 1698, 1503  
1H-NMR: (CDCl3) δ 1.20 (t, 3H, J = 7.0 Hz), 3.64 (m, 2H), 3.83 (m, 1H), 3.94 (s, 1H), 4.82 (d, 1H, J = 7.0 Hz), 4.84 (d, 1H, J = 7.0 Hz), 4.94 (ddd, 1H, J = 1.5, 2.8, 5.1 Hz), 6.41 (d, 1H, J = 7.9 Hz), 6.46 (dd, 1H, J = 6.0, 8.4 Hz), 7.40 (m, 5H)  
13C-NMR: (CDCl3) δ 14.8 (CH3), 56.4 (CH), 64.2 (CH2), 74.8 (CH), 79.2 (C), 82.8 (CH), 95.3 (CH2), 125.9 (2xCH), 128.0 (CH), 128.7 (CH), 129.1 (2xCH), 130.9 (C), 135.0 (CH), 153.4 (C), 155.8 (C)  
MS: (Cl, 70 eV) m/z (rel. intensity) 380 (M+1) (40), 316 (80), 304 (80), 261 (70)  
HRMS calcd for C_{17}H_{19}ClN_{3}O_{5}: 380.1013  Found: 380.1000, error 3.8 ppm.

(1R, 7R, 8R, 9S)-1-Bromo-8-(t-butyldimethylsilyloxy)-9-(2-ethoxymethoxy)-2,4,6-triazolotricyclo-[5.2.2.0]-undec-10-ene-3,5-dione (199a).

(196a) (580 mg, 1.37 mmol) was dissolved in CH2Cl2 (13 ml). The reaction was cooled to 0°C. 2,6-Lutidine (732 mg, 6.84 mmol) and t-butyldimethylsilyl chloride (1.08 g, 4.10 mmol) were added dropwise. After 4 hours, water (15 ml) was added and the reaction was warmed to room temperature. The layers were separated and the aqueous layer was extracted with CH2Cl2 (3 x 50 ml). The organic layers were combined, dried over MgSO4 and concentrated under reduced pressure. Chromatography (silica, gradient: Hexanes/EtOAc 10:1->5:1) yielded 662 mg of white solid (90%).

RF: 0.27 (Hexane/EtOAc 4:1)  
Mp: 137–138° C  
[α]D^{26}: +68.4° (c=0.90, CHCl3)
IR: (CHCl₃) cm⁻¹ 2910, 1770, 1715, 1590, 1395, 1250

¹H-NMR: (CDCl₃) δ 0.12 (s, 3H), 0.13 (s, 3H), 0.84 (s, 9H), 1.21 (t, 3H, J = 7.0 Hz), 3.68 (m, 2H), 3.96 (dd, 1H, J = 0.9, 3.0 Hz), 4.03 (s, 1H), 4.82 (ddd, 1H, J = 1.2, 2.9, 8.9 Hz), 4.89 (s, 2H), 6.45 (dd, 1H, J = 6.3, 8.4 Hz), 6.54 (ddd, 1H, J = 1.0, 1.1, 8.2 Hz), 7.32 (m, 1H), 7.44 (m, 4H)

¹³C-NMR: (CDCl₃) δ -5.0 (CH₃), -4.5 (CH₃), 14.9 (CH₃), 18.0 (C), 25.6 (3xCH₃), 56.4 (CH), 64.6 (CH₂), 68.0 (C), 76.2 (CH), 84.4 (CH), 95.8 (CH₂), 125.5 (2xCH), 128.1 (CH), 128.3 (CH), 128.9 (2xCH), 131.4 (C), 137.0 (CH), 152.4 (C), 153.7 (C)

MS: (CI, 70 eV) m/z (rel. intensity) 540 (M⁺+1) (40), 492 (40), 464 (100), 406 (50)

HRMS calcd for C₂₃H₃₃BrN₃O₅Si: 538.1372 Found: 538.1357, error 2.90 ppm
Calcd for C₂₃H₃₂BrN₃O₅Si: C 51.30% H 5.99% N 7.80% Found: C 51.47% H 6.09% N 7.73%.

(1R, 7R, 8R, 9S)-1-Chloro-8-(t-butyldimethylsilyloxy)-9-(2-ethoxymethoxy)-2,4,6-triazolotricyclo-[5.2.2.0]undec-10-ene-3,5-dione (199b) (86%).

Rf: 0.22 (Hexane/EtOAc 4:1)

Mp: 137–138° C

[α]D²⁹: +35.1° (c=1.13, CHCl₃)

IR: (CHCl₃) cm⁻¹ 3019, 2930, 1775, 1720, 1600, 1403

¹H-NMR: (CDCl₃) δ 0.13 (s, 6H), 0.87 (s, 9H), 1.21 (t, 3H, J = 7.0 Hz), 3.66 (m, 2H), 3.93 (dd, 1H, J = 0.9, 2.9 Hz), 3.99 (s, 1H), 4.81 (ddd, 1H, J = 1.3, 3.0, 6.2 Hz), 4.87 (d, 1H, J = 6.7 Hz), 4.90 (d, 1H, J = 6.7 Hz), 6.41 (d, 1H, J = 8.4 Hz), 6.51 (dd, 1H, J = 6.3, 8.4 Hz), 7.33 (m, 1H), 7.44 (m, 4H)

¹³C-NMR: (CDCl₃) δ -5.0 (CH₃), -4.5 (CH₃), 14.8 (CH₃), 17.9 (C), 25.6 (3xCH₃), 56.4 (CH), 64.4 (CH₂), 76.0 (CH), 79.0 (C), 83.9 (CH), 95.8 (CH₂), 125.5 (2xCH), 128.0 (CH), 128.1 (CH), 128.9 (2xCH), 131.3 (C), 135.5 (CH), 152.6 (C), 154.2 (C)

MS: (CI, 70 eV) m/z (rel. intensity) 495 (M⁺+1) (50), 418 (100), 362 (60), 316 (60)

HRMS calcd for C₂₃H₃₂ClN₃O₅Si: 494.1878 Found: 494.1866, error 2.5 ppm.
(5R, 6S)-1-Bromo-5-(t-butyldimethylsilyloxy)-6-(2-ethoxymethyloxy)-1,3-cyclohexadiene (200a).

(199a) (65 mg, 0.12 mmol) was dissolved in collidine (1 ml) and heated to 175°C. After 12 hours, the reaction was cooled to room temperature and diluted with a Hexane/EtOAc solution (20:1; 2 ml). Chromatography (silica, Hexane/EtOAc 20:1) of the solution yielded 4.5 mg of a colorless oil (10% conversion, 22% based on recovered starting material).

Rf: 0.29 (Hexanes/EtOAc 25:1)
[α]D<sup>24</sup>: -220.5° (c=0.19, CHCl<sub>3</sub>)

IR: (neat) cm<sup>-1</sup> 2928, 1471, 1110, 1030

<sup>1</sup>H-NMR: (CDCl<sub>3</sub>) δ 0.81 (s, 3H), 0.10 (s, 3H), 0.87 (s, 9H), 1.22 (t, 3H, J = 7.0 Hz), 3.61 (dq, 1H, J = 2.4, 7.0 Hz), 3.78 (dq, 1H, J = 2.4, 7.0 Hz), 4.28 (d, 1H, J = 3.8 Hz), 4.36 (dd, 1H, J = 3.9, 3.9 Hz), 4.82 (s, 2H), 5.88 (m, 2H), 6.41 (d, 1H, J = 5.3 Hz)

<sup>1</sup>C-NMR: (CDCl<sub>3</sub>) δ -4.6 (CH<sub>3</sub>), -4.3 (CH<sub>3</sub>), 15.0 (CH<sub>3</sub>), 25.8 (3 x CH<sub>3</sub>), 64.0 (CH<sub>2</sub>), 70.6 (CH), 81.1 (CH), 94.6 (CH<sub>2</sub>), 123.2 (C), 123.9 (CH), 127.5 (CH), 127.7 (CH)

MS: (Cl, 70 eV) m/z (rel. intensity) 362 (M<sup>+</sup>+1) (5), 287 (25), 177 (40), 89 (100)

HRMS calculated for C<sub>15</sub>H<sub>27</sub>BrO<sub>3</sub>Si: 362.0913 Found: 362.0894, error 5.2 ppm.

(5R,6S)-5-(t-Butyldimethylsilyloxy)-1-chloro-6-(2-ethoxymethyloxy)-1,3-cyclohexadiene (200b).

(199b) (30 mg, 0.06 mmol) was dissolved in 2N KOH/95% EtOH solution. After 3 hours, the reaction was diluted with cold water (10 ml) and CH<sub>2</sub>Cl<sub>2</sub> (20 ml). The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 10 ml). The combined organic layer was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Chromatography (silica, Hexane/EtOAc 25:1) yielded 11 mg of a colorless oil (57%).

Rf: 0.29 (Hexanes/EtOAc 25:1)
[α]D<sup>29</sup>: +35.0° (c=1.13, CHCl<sub>3</sub>)

IR: (neat) cm<sup>-1</sup> 2930, 1585, 1255, 1215

<sup>1</sup>H-NMR: (CDCl<sub>3</sub>) δ 0.80 (s, 3H), 0.11 (s, 3H), 0.87 (s, 9H), 1.22 (t, 3H, J = 7.0 Hz), 3.61 (dq, 1H, J = 2.4, 7.0 Hz), 3.76 (dq, 1H, J = 2.4, 7.0 Hz), 4.18 (d, 1H, J = 3.8 Hz), 4.36 (dd, 1H, J = 4.1, 4.2 Hz), 4.82 (s, 2H), 5.83 (dd, 1H, J = 4.6, 9.5 Hz), 5.93 (dd, 1H, J = 6.0, 9.5 Hz), 6.17 (d, 1H, J = 6.0 Hz)
$^{13}$C-NMR: (CDCl$_3$) δ -4.6 (2xCH$_3$), 18.1 (C), 25.8 (4xCH$_3$), 63.8 (CH$_2$), 70.6 (CH), 79.9 (CH), 94.5 (CH$_2$), 123.3 (CH), 123.4 (CH), 127.2 (CH), 132.8 (C)

MS: (CI, 70 eV) m/z (rel. intensity) 318 (M$^+$+1) (10), 259 (25), 103 (40)

HRMS calcd for C$_{15}$H$_{27}$ClO$_3$Si: 318.1418  Found: 318.1422, error 1.3 ppm.

(5R, 6R)-5-((Butyldimethylsilyloxy)-6-(2-ethoxymethoxy)-1,3-cyclohexadiene (200c).

In a dry flask under argon, (199a) (45 mg, 0.08 mmol) was dissolved in degassed 2N KOH/95% EtOH solution. After 40 minutes, the reaction was diluted with cold water (10 ml) and CH$_2$Cl$_2$ (20 ml). The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 10 ml). The combined organic layer was dried over MgSO$_4$ and concentrated under reduced pressure. Chromatography (silica, Hexane/EtOAc 10:1) yielded 12.3 mg of a colorless oil (51%).

R$_f$: 0.29 (Hexane/EtOAc, 25:1)

[$\alpha$]$_D^{24}$: -192.24° (c=0.76, CHCl$_3$)

IR: (neat) cm$^{-1}$ 3050, 2960, 2860, 1473, 1406, 1258

$^1$H-NMR: (CDCl$_3$) δ 0.7 (s, 6H), 0.90 (s, 9H), 1.20 (t, 3H, J = 7.1 Hz), 3.59 (dq, 1H, J = 2.5, 7.1 Hz), 3.70 (dq, 1H, J = 2.5, 7.1 Hz), 4.40 (d, 1H, J = 10.5 Hz), 4.53 (dd, 1H, J = 1.8, 10.5 Hz), 4.79 (s, 2H), 5.80 (m, 3H)

$^{13}$C-NMR: (CDCl$_3$) δ -4.6 (CH$_3$), 15.1 (CH$_3$), 18.3 (C), 25.8 (CH$_3$), 63.3 (CH$_2$), 73.1 (CH), 79.7 (CH), 95.1 (CH$_2$), 123.4 (CH), 124.2 (CH), 129.1 (CH), 131.7 (CH)

MS: (CI, 70 eV) m/z (rel. intensity) 284 (M$^+$+1) (20), 225 (40), 209 (30), 151 (80)

HRMS calcd for C$_{15}$H$_{28}$O$_3$Si: 284.1808  Found: 284.1813, error 1.8 ppm.

Calcd for C$_{15}$H$_{28}$O$_3$Si: C 63.33%  H 9.92%  Found: C 63.46%  H 10.01%.

Isopropyl 2-hydroxy-3,4-methylenedioxy-benzoate (216a).

TMP (4.92 g, 34.8 mmol) was dissolved in THF (60 ml). n-BuLi (34.8 mmol) was then added dropwise at such a rate that refluxing did not occur. After the addition was complete, the LiTMP solution was stirred for another 10 minutes. In another dry flask, the (215) (4.83 g, 23.2 mmol) and trimethyl borate (3.86 g, 37.1 mmol) were dissolved in THF (115 ml). Both flasks were then cooled to -78°C and the LiTMP solution was added over 10 minutes (via cannula) to the (215) solution. The solution was stirred at -78°C for
45 minutes and then warmed to 0°C. After 45 minutes, acetic acid (3 ml) and 30% H₂O₂ (6 ml) were added. The reaction was warmed to room temperature and stirred for 18 hours. The reaction solution was then washed with a saturated solution of NH₄Cl containing 10% ferric ammonium sulfate (2 x 50 ml). The organic layer was washed with brine (1 x 100 ml), dried over MgSO₄ and concentrated under reduced pressure. Chromatography (silica, Hexane/EtOAc 20:1) yielded 4.29 g of a white solid (83%).

Rf: 0.15 (Hexane/EtOAc, 10:1)

Mp: 71.5–72.5°C

IR: (KBr) cm⁻¹ 2990, 1680, 1470, 1290

¹H-NMR: (CDCl₃) δ 1.35 (d, 6H, J = 6.3 Hz), 5.24 (heptet, 1H, J = 6.3 Hz), 6.42 (d, 1H, J = 8.0 Hz), 7.46 (d, 1H, J = 8.0 Hz), 10.88 (s, 1H)

¹³C-NMR: (CDCl₃) δ 21.8 (2 x CH₃), 69.1 (CH), 100.7 (CH), 102.3 (CH₂), 109.7 (C), 126.1 (CH), 134.2 (C), 146.0 (C), 153.3 (C), 169.4 (C)

MS: (EI, 70 eV) m/z (rel. intensity) 224 (M⁺) (10), 164 (100), 106 (20)

Calcd for C₁₁H₁₂O₅: C 58.93%  H 5.39%  Found: C 59.10%  H 5.39%.

Isopropyl 2-(2-ethoxymethoxy)-3,4-methylenedioxy-benzoate (216b).

(216a) (4.09 g, 18.24 mmol) was dissolved in CH₂Cl₂ and cooled to 0°C. EtNiPr₂ (7.50 g, 58.4 mmol) and chloromethyl ethylether (4.31 g, 45.6 mmol) were then added sequentially and the reaction was stirred. After 3 hours, the reaction was warmed to room temperature and stirred for 10 hours. The reaction was then diluted with water (100 ml). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 50 ml). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. Chromatography (silica, gradient: Hexane/EtOAc 20:1 -> 10:1) yielded 5.05 g of a colorless oil (98%).

Rf: 0.33 (Hexane/EtOAc, 10:1)

IR: (CHCl₃) cm⁻¹ 2995, 1715, 1625, 1605, 1470, 1355

¹H-NMR: (CDCl₃) δ 1.29 (t, 3H, J = 7.0 Hz), 1.31 (d, 6H, J = 6.3 Hz), 3.20 (q, 2H, J = 7.0 Hz), 5.18 (heptet, 1H, J = 6.3 Hz), 5.28 (s, 2H), 5.95 (s, 2H), 6.58 (d, 1H, J = 8.4 Hz), 7.42 (d, 1H, J = 8.4 Hz)

¹³C-NMR: (CDCl₃) δ 15.0 (CH₃), 21.9 (2 x CH₃), 65.0 (CH₂), 68.1 (CH), 96.6 (CH₂), 101.8 (CH₂), 103.6 (CH), 119.3 (C), 126.3 (CH), 139.2 (C), 140.5 (C), 152.0 (C), 164.8 (C)
MS: (EI, 70 eV) m/z (rel. intensity) 282 (M+) (5), 210 (10), 164 (100), 106 (15)

**Caled for C₁₄H₁₈O₆:** C 59.57%  H 6.43%  **Found:** C 59.36%  H 6.44%.

**Isopropyl 2-(2-ethoxymethyloxy)-6-hydroxy-3,4-methylenedioxy-benzoate (217).**
TMP (3.81 g, 27.0 mmol) was dissolved in THF (40 ml). n-BuLi (27.0 mmol) was then added dropwise at such a rate that refluxing did not occur. After the addition was complete, the LiTMP solution was stirred for another 10 minutes. In another dry flask, (216b) (4.77 g, 16.9 mmol) and trimethyl borate (2.98 g, 28.7 mmol) were dissolved in THF (85 ml). Both flasks were then cooled to -78°C and the LiTMP solution was added over 10 minutes (via cannula) to the (216b) solution. The solution was stirred at -78°C for 45 minutes and then warmed to 0°C. After 45 minutes, acetic acid (3 ml) and 30% H₂O₂ (6 ml) were added. The reaction was then warmed to room temperature and stirred for 18 hours. The reaction solution was washed with a saturated solution of NH₄Cl containing 10% ferric ammonium sulfate (2 x 50 ml). The organic layer was washed with brine (1 x 100 ml), dried over MgSO₄ and concentrated under reduced pressure. Chromatography (silica, Hexanes/EtOAc 20:1) yielded 3.28 g of a pale yellow oil (65%) which crystallized upon standing.

**Rf:** 0.45 (Hexane/EtOAc, 1:1)

**Mp:** 62–63°C

**IR:** (CHCl₃) cm⁻¹ 3350, 2995, 1705, 1640, 1460

**¹H-NMR:** (CDCl₃) δ 1.21 (t, 1H, J = 7.2 Hz), 1.31 (d, 6H, J = 6.3 Hz), 3.84 (q, 2H, J = 7.1Hz), 5.17 (hp, 1H, J = 6.3 Hz), 5.18 (s, 2H), 5.98 (s, 2H), 6.01 (brs, 1H), 7.05 (s, 1H)

**¹³C-NMR:** (CDCl₃) δ 14.9 (CH₃), 21.9 (2 x CH₃), 65.1 (CH₂), 68.5 (CH), 97.2 (CH₂), 102.5 (CH₂), 114.5 (CH), 118.7 (C), 134.8 (C), 135.3 (C), 138.9 (C), 140.9 (C), 164.9 (C)

**MS:** (Cl, 70 eV) m/z (rel. intensity) 299 (M⁺+1) (12), 269 (10), 240 (50), 180 (60)

**HRMS caled for C₁₄H₁₈O₇:** 299.1131  **Found:** 299.1139, error 2.8 ppm

**Caled for C₁₄H₁₈O₇:** C 56.37%  H 6.08%  **Found:** C 56.48%  H 6.10%.
VI. SELECTED SPECTRA

1. (1'R, 4'R, 5'S, 6'S)-Spiro-[2, 5-cyclohexadiene-4-one-1'-chloro-5',6'-(isopropylidenedioxy)-1,3'-[2]-oxabicyclo[2.2.2]oct-7'-ene] (163a).
   \[ \text{H-NMR, } ^{13}\text{C-NMR} \]
   IR, MS  
   HETCOR  
   123  
   124  
   125

2. (1'S, 2'S, 3'S, 4'S, 4aR, 8aS)-1-Chloro-1,4-etheno-2,3-(isopropylidenedioxy)-1,2,3,4,4a,8a-hexahydro-naphthalene-5,8-dione (164).
   \[ \text{H-NMR, } ^{13}\text{C-NMR} \]
   IR, MS  
   126  
   127

3. (1'S, 2'S, 3'S, 4'S, 4aR, 9aS)-1-Chloro-1,4-etheno-2,3-(isopropylidenedioxy)-1,2,3,4,4a,9a-hexahydro-anthracene-9,10-dione (165).
   \[ \text{H-NMR, } ^{13}\text{C-NMR} \]
   IR, MS  
   128  
   129

4. (1'R, 2'S, 3'S, 4R)-1-Chloro-1,4-etheno-2,3-(isopropylidenedioxy)-1,2,3,4-tetrahydro-napthalene (167).
   \[ \text{H-NMR, } ^{13}\text{C-NMR} \]
   IR, MS  
   130  
   131

5. (3aR, 4S, 5S, 7aS)-6-Chloro-4,5-(isopropylidenedioxy)-3-methyl-3a, 4, 5, 7a-tetrahydro-1,2-benzisoxazole (169).
   \[ \text{H-NMR, } ^{13}\text{C-NMR} \]
   IR, MS  
   132  
   133

6. (3R, 4R, 5S, 6S)-1-Cyano-3,4-dihydroxy-5,6-(isopropylidenedioxy)-1,2-cyclohexene (172a).
   \[ \text{H-NMR, } ^{13}\text{C-NMR} \]
   134

7. (1'S, 2'S, 3'S, 4R, 5S, 6S)-3,4-dihydroxy-1,2-epoxy-5,6-(isopropylidenedioxy)-1-phenylcyclohexane (173).
   \[ \text{H-NMR, } ^{13}\text{C-NMR} \]
   135
8. (3R, 4R, 5S, 6S)-3,4-Dihydroxy-1-(ethynylphenyl)-5,6-(isopropylidenedioxy)-cyclohexene (174a).
   $^1$H-NMR, $^{13}$C-NMR

9. (1S, 2S, 3S, 4R, 5S, 6S)-3,4-Dihydroxy-1,2-epoxy-1-(ethynylphenyl)-5,6-(isopropylidenedioxy)-cyclohexane (174b).
   $^1$H-NMR, $^{13}$C-NMR

10. (1S, 2S, 3S, 4R, 5S, 6S)-3,4-Dihydroxy-1,2-epoxy-5,6-(isopropylidenedioxy)-1-methylcyclohexane (175).
    $^1$H-NMR, $^{13}$C-NMR

11. 5S, 6S)-1-Bromo-6-hydroxy-5-(thexylidimethylsilyloxy)-cyclohexa-1,3-diene (191a).
    $^1$H-NMR, $^{13}$C-NMR

12. (5S, 6S)-1-Bromo-6-(2-ethoxymethoxy)-5-(thexylidimethylsilyloxy)-cyclohexa-1,3-diene (192a).
    $^1$H-NMR, $^{13}$C-NMR

13. (1R, 7R, 8S, 9S)-1-Bromo-9-(2-ethoxymethoxy)-4-phenyl-8-(thexylidimethylsilyloxy)-2,4,6-triazolotricyclo-[5.2.2.0]-undec-10-ene-3,5-dione (193a).
    $^1$H-NMR, $^{13}$C-NMR

14. 1R, 7R, 8S, 9S)-1-Chloro-9-(2-ethoxymethoxy)-4-phenyl-8-(thexylidimethylsilyloxy)-2,4,6-triazolotricyclo-[5.2.2.0]-undec-10-ene-3,5-dione (193b).
    $^1$H-NMR, $^{13}$C-NMR
    IR, MS

15. (1R, 7R, 8S, 9S)-1-Bromo-9-(2-ethoxymethoxy)-8-hydroxy-4-phenyl-2,4,6-triazolotricyclo-[5.2.2.0]-undec-10-ene-3,5-dione (194a).
    $^1$H-NMR, $^{13}$C-NMR

120

$^1$H-NMR, $^{13}$C-NMR

17. (1R, 7R, 8R, 9S)-1-Bromo-9-(2-ethoxymethyloxy)-8-hydroxy-4-phenyl-2,4,6-triazolo[5.2.2.0-undec-10-ene-3,5-dione (196a).

$^1$H-NMR, $^{13}$C-NMR

18. (1R, 7R, 8R, 9S)-1-Chloro-9-(2-ethoxymethyloxy)-8-hydroxy-4-phenyl-2,4,6-triazolo[5.2.2.0-undec-10-ene-3,5-dione (196b).

$^1$H-NMR, $^{13}$C-NMR


$^1$H-NMR, $^{13}$C-NMR

20. (1R, 7R, 8R, 9S)-1-Chloro-8-(t-butyldimethylsilyloxy)-9-(2-ethoxymethyloxy)-2,4,6-triazolo[5.2.2.0-undec-10-ene-3,5-dione (199b).

$^1$H-NMR, $^{13}$C-NMR

21. (5R, 6S)-1-Bromo-5-(t-butyldimethylsilyloxy)-6-(2-ethoxymethyloxy)-1,3-cyclohexadiene (200a).

$^1$H-NMR, $^{13}$C-NMR

22. (5R, 6S)-5-(t-Butyldimethylsilyloxy)-1-chloro-6-(2-ethoxymethyloxy)-1,3-cyclohexadiene (200b).

$^1$H-NMR, $^{13}$C-NMR

23. (5R, 6R)-5-(t-Butyldimethylsilyloxy)-6-(2-ethoxymethyloxy)-1,3-cyclohexadiene (200c).

$^1$H-NMR, $^{13}$C-NMR
24. Isopropyl 2-hydroxy-3,4-methylenedioxy-benzoate (216a).

$^1$H-NMR, $^{13}$C-NMR

153

25. Isopropyl 2-(2-ethoxymethoxy)-3,4-methylenedioxy-benzoate (216b).

$^1$H-NMR, $^{13}$C-NMR

154

26. Isopropyl 2-(2-ethoxymethoxy)-6-hydroxy-3,4-methylenedioxy-benzoate (217).

$^1$H-NMR, $^{13}$C-NMR

155
VII. APPENDIX

Appendix 1. Charge Distribution as Calculated by AM1$^{94}$

HOMO

\[
\begin{align*}
C1 & : +0.4984 \\
C2 & : +0.4408 \\
C3 & : -0.3538 \\
C4 & : -0.4914
\end{align*}
\]

LUMO

\[
\begin{align*}
C1 & : +0.1024 \\
C2 & : -0.1233 \\
C3 & : -0.1272 \\
C4 & : -0.1629
\end{align*}
\]

Appendix 2. FMO as Calculated by AM1$^{94}$

Appendix 3. FMO Coefficients for the Unsubstituted Nitrile Oxide$^{98}$

HOMO

\[
\begin{align*}
C & : -1.18 \\
O & : +0.17
\end{align*}
\]

LUMO

\[
\begin{align*}
C & : +0.81 \\
O & : +1.24
\end{align*}
\]
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110. In addition to our own efforts in this area, we are aware of at least 3 additional approaches: Professors Gary Keck at University of Utah, Carl Johnson at Wayne State University and Clayton Heathcock at the University of California at Berkley.


IX. VITA

Bryan Patrick McKibben was born September 18, 1968 to Mr. and Mrs. Robert George McKibben. He was raised Roman Catholic in suburban Washington D.C. Bryan graduated from Bishop McNamara High School in the spring of 1986 and enrolled at Loyola College in Maryland the following fall. In May, 1990 Bryan earned a Bachelor of Science degree in chemistry. Bryan began graduate studies at Virginia Polytechnic Institute and State University in 1990 under the direction of Dr. David Becker. His research was directed towards the synthesis of novel enediyne antibiotics and rearrangements of oxocycloalkenyloxazolium anhydrobases. In June 1993, Bryan changed research advisors from Dr. David Becker to Dr. Tomas Hudlicky because of Dr. Beckers resignation from Virginia Polytechnic Institute and State University and acceptance of a faculty position at Florida International University. In the summer of 1993, Bryan married Denise Marie Hammond. His accomplishments while at Virginia Polytechnic Institute and State University are listed below:

Publications:


Presentations:


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(Note: * denotes poster)