Synthesis of Resveratrol and Its Analogs, Phase-Transfer Catalyzed Asymmetric Glycolate Aldol Reaction, and Total Synthesis of 8,9-Methylamido-Geldanamycin

Jing Liu
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SYNTHESIS OF RESVERATROL AND ITS ANALOGS, PHASE-TRANSFER CATALYZED ASYMMETRIC GLYCOLATE ALDOL REACTIONS, AND TOTAL SYNTHESIS OF 8,9-METHYLAMIDO-GELDANAMYCIN

by

Jing Liu

A thesis submitted to the faculty of

Brigham Young University

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry and Biochemistry

Brigham Young University

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BRIGHAM YOUNG UNIVERSITY

GRADUATE COMMITTEE APPROVAL

of a thesis submitted by

Jing Liu

This thesis has been read by each member of the following graduate committee and by majority vote has been found to be satisfactory.

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As chair of the candidate’s graduate committee, I have read the thesis of Jing Liu in its final form and have found that (1) its format, citations, and bibliographical style are consistent and acceptable and fulfill university and department style requirements; (2) its illustrative materials including figures, tables, and charts are in place; and (3) the final manuscripts is satisfactory to the graduate committee and is ready for submission to the university library.

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Accepted for the College
Thomas W. Sederberg, Associate Dean
College of Physical and Mathematical Sciences
The phytoalexin resveratrol and its acetyl analogs have been made using a decarbonylative Heck reaction. The acid chloride derived from 3,5-dihydroxybenzoic acid was coupled with suitable protected 4-hydroxystyrene in the presence of palladium acetate and N,N-bis-(2,6-diisopropylphenyl)-4,5-dihydro imidazolium chloride to give the substituted stilbene in good yield as the key step. Human HL-60 cell assays showed the 4'-acetyl resveratrol variant improved activity (ED$_{50}$ 17 µM) relative to resveratrol (24 µM).

Cinchona phase-transfer catalysts (PTC) were developed for glycolate aldol reactions to give differentially protected 1,2-diol products. Silyl enol ether of diphenylmethoxy-2,5-dimethoxyacetophenone reacted to generate benzhydryl-protected
products. O- Allyl trifluorobenzyl cinchonium hydrodifluoride (20 mol %) catalyzed the addition of the silyl enol ether to benzaldehyde to give aldol product as a single syn-product in 76% yield and 80% ee. Recrystallization enriched the product to 95% ee, and a Baeyer-Villiger reaction transformed the product into useful ester intermediates.

A novel unnatural product, 8,9-Methylamido-Geldanamycin, has been designed and synthesized. Using a convergent route, the total synthesis of the molecule involved only 27 longest linear steps. New synthesis methodologies, including auxiliary controlled asymmetric anti-glycolate aldol, syn-norephedrine aldol, and selective p-quinone formation, were used.
I am particularly grateful to my mentor Professor Merritt B. Andrus for his guidance throughout my graduate studies in Brigham Young University. He has provided me an optimum research environment. His constant encouragement, support, and invaluable suggestions made my research success.

I would like to thank all of my committee members, Dr. Paul B. Savage, Dr. Matt A. Peterson, Dr. Young Wan Ham, Dr. Roger G. Harrison and Dr. Morris J. Robins, for their guidance and suggestions.

I would also like to acknowledge all the members of Andrus group for their friendship. I am grateful for the help of Jiuqing Zhang and Dr. Ziniu Zhou for their initial training. My collaboration with Zhifeng Ye and Yong Wang has been a wonderful experience. I wish to thank Mike Christiansen for providing proofreading. Dr. Guoping Xue and Dr. Erik Meredith have provided many useful discussions.

I thank my wife Jianping for her overwhelming love and unconditional support. I thank my parents for teaching me to be independent, diligent, and honest.

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<td>DMP</td>
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<td>$N$-Methylpyrrolidinone</td>
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<td>PDC</td>
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Chapter 1. Synthesis of Resveratrol and Its Acetyl and Fluoro Analogs Using Decarbonylative Heck Reaction

1.1. Introduction

1.1.1. Discovery

Resveratrol (3,4',5-trihydroxystilbene) \( \text{I} \), a naturally occurring phytoalexin, was first identified in 1940 as an off-white powder from the extractions of roots of white hellebore lily (\textit{Veratrum grandiflorum} O. Loes).\(^1\) Since that time, it has been detected in more than seventy plant species, including grapes, blueberries, cranberries, mulberries, peanuts, jackfruit, scots pine, corn lilies, etc. The richest natural source is the root of \textit{Polygonum cuspidatum} and the extract of the root of \textit{Polygonium cuspidatum} is the source of most of the marketed resveratrol-containing supplements in the U.S. Plants are induced to produce higher levels of the phytoalexin resveratrol under stress from injury, ultraviolet irradiation, or fungal infection as a defense mechanism.

The use of resveratrol to treat human disease can be tracked back to 600 B.C. Grapes are the principal ingredient of Darakchasava (fermented juice of red grapes), an ayurvedic herbal remedy, which is mainly used in ayurvedic medicine as a cardiotonic.\(^2\) The dried root and stem of \textit{Polygonium cuspidatum} is used in traditional Chinese and Japanese medicine as a circulatory tonic, among other things.\(^3\) This traditional Chinese and Japanese remedy is also known as Hu Zhang and ko-jo-kon.
1.1.2. Biological Activity

Most diseases are caused by dysregulation of multiple genes instead of a single gene. Recent studies have shown that drugs targeted to a specific gene are not likely to cure a disease. Resveratrol can modulate multiple cellular targets and thus it may prove suitable for the prevention and treatment of a wide variety of diseases.

Extensive research work has been carried out with resveratrol after it was discovered to be a causative agent of the “French paradox”, the molecule most responsible for the Mediterranean diet effect where high fat intake coupled with moderate wine consumption leads to abnormally low rates of heart disease and cancer. Growing evidence has demonstrated that resveratrol at reasonable dietary concentrations plays an important role in mitigating numerous and diverse human pathological processes including inflammation, atherosclerosis, and carcinogenesis. Specific properties of resveratrol include antioxidant; radical scavenging activity; cyclooxygenase inhibition; lipid modification; platelet aggregation inhibition and vasodilation; inhibition of tumor initiation, promotion, and progression; neuroprotection; and antiviral activity. While various biological targets have been implicated and identified, the mechanism of resveratrol’s integrated effect on various cellular pathways remains unclear. Many studies have shown its ability in modulation of gene expression, signal transduction, cell cycle progression, prostaglandin biosynthesis, and angiogenesis.

Recently, resveratrol has also been shown to extend the lifespan of yeast
*Saccharomyces cerevisiae*, worm *Caenorhabditis elegans*, the fruit fly *Drosophila melanogaster*, a short-lived fish *Nothobranchius furzeri*, and obese mice. Lifespan extension is believed to arise through activation of sirtuin (SIRT-1, 2), an NAD dependent histone deacetylase that has been shown to directly correlate with cellular longevity. Another research study shows that mice fed resveratrol demonstrated enhanced treadmill endurance compared with controls. This study also supports the effects of resveratrol via activation of SIRT1.

1.1.3. Synthesis of Resveratrol

Although resveratrol’s natural sources are abundant, isolation from plant sources in pure form is not efficient, as reported from dried *Cassia q*. Rich (30 mg/kg) or from dried grape skins (92 mg/kg).

The first synthesis of resveratrol was reported by Takaoka using a Perkin condensation of sodium 3,5-dihydroxyphenylacetate 2 with 4-hydroxybenzaldehyde 3 in acetic anhydride (Figure 1.1). The resulting 3,5,4'-triacetoxystillbene-α-carboxylic acid 4 was converted to triacetoxystillbene by decarboxylation and then to resveratrol 1 by hydrolysis. Unfortunately, no yield was reported for any step.

![Figure 1.1](image-url)
The majority of the recent published synthetic routes rely on Wittig and Horner–Emmons couplings that give mixtures of olefin isomers and require 7–8 steps. Most routes use methyl or benzyl ether protecting groups that require the use of boron tribromide or other inconvenient reagents for removal. Recently, a palladium catalyzed isomerization of *cis*-alkenes to *trans*-alkenes was used to convert a mixture of *trans* and *cis* 3,5,4′-trimethoxystillbene 5 to the corresponding *trans* form 6 (Figure 1.2).17a

Figure 1.2 Resveratrol synthesis using a Wittig reaction.

A palladium catalyzed Heck reaction route has been reported that utilized a costly starting material, 3,5-dihydroxybenzaldehyde 7, together with a Wittig reaction to form the styrene coupling partner 8 (Figure 1.3).18 Heck coupling of this styrene with 4-iodophenylacetate 9 gave 3,5,4′-triacetoxystillbene 10, which was converted to resveratrol 1 by treatment with sodium methoxide.

Figure 1.3 Resveratrol synthesis using a Heck reaction.
Recently, a vinylsilane Heck based coupling route using 4-methoxyiodobenzene has been reported that uses methyl ether protecting groups (Figure 1.4).\(^{19}\) Arylation of vinyltrimethylsilane \(^{12}\) with 4-methoxyiodobenzene \(^{11}\) gave the 4-methoxystyrene intermediate. After removal of an excess amount of vinyltrimethylsilane \(^{12}\), Heck coupling of the 4-methoxystyrene with 3,5-dimethoxyiodobenzene yielded methyl ether protected resveratrol \(^{6}\). The methyl ether protecting groups were removed by boron trichloride.

**Figure 1.4** Resveratrol synthesis using a one-pot vinylsilane Heck coupling.

### 1.1.4. Decarbonylative Heck Reactions

Carbon-carbon bond formation is a fundamental goal in organic synthesis. The palladium catalyzed Mizoroki-Heck reaction using aryl halides and olefins has become a powerful and versatile means to accomplish this demand.\(^{20}\) Besides the commonly used aryl halides, other arylating reagents have been developed,\(^{21}\) including aryl triflates,\(^ {22}\) aryl sulfonyl halides,\(^ {23}\) aryl diazonium salts,\(^ {24}\) aroyl halids,\(^ {25}\) aryl anhydrides,\(^ {26}\) aryl esters,\(^ {27}\) arenecarboxylates,\(^ {28}\) arylboronic acids,\(^ {29}\) arylsilanols,\(^ {30}\) arylstannanes,\(^ {31}\) organic tellurides and tellurium salts,\(^ {32}\) organoantimony compounds,\(^ {33}\) and
Among these arylating reagents, aroyl halides, aryl anhydrides, aryl esters, and arenecarboxylates are readily available from commercial sources or are particularly easy and inexpensive to make.

Blaser and Spencer reported that with catalytic palladium acetate, aroyl chlorides reacted with activated alkenes to give (E)-arylation products at 130 °C in p-xylene (Figure 1.5).\textsuperscript{25a-d} \textit{N}-Benzyldimethylamine was used as base for most of the substrates, except when strongly electron-withdrawing groups were present in the aroyl chlorides. In these cases, \textit{N}-ethylmorpholine was alternatively used. Although \textit{N}-ethylmorpholine led to a much slower coupling reaction, it did not react with the aroyl chlorides. The reaction tolerated various substituents on the aroyl chloride. In general electron-withdrawing groups on the aroyl chloride hindered the reaction and electron-donating groups favored the reaction. Aliphatic acid chlorides and vinylic acid chlorides did not show reactivity. Aroyl bromides and iodides did not improve reactivity. Activated alkenes gave good reactivity whereas non-activated alkenes, except ethylene, gave none or poor reactivity. A reaction mechanism was also proposed. Palladium acetate is reduced to palladium(0) species by alkene or base. After oxidative addition of the aroyl chloride and aryl group migration to palladium, the carbonyl forms an $\eta^2$ complex with palladium. Carbon monoxide release is favored at high temperature. After alkene coordination with the resulting palladium intermediate, alkene insertion, $\beta$-hydride elimination and palladium(0) regeneration are followed as proposed by Heck.
Miura and coworkers reported a \([\text{RhCl(C}_2\text{H}_4)_2]\)\(_2\) catalyzed decarbonylative Heck coupling of aroyl chlorides with styrene or \(n\)-butyl acrylate in refluxing \(o\)-xylene at 145 °C (Figure 1.6).\(^{25c,f}\) Without phosphine ligand and base, the reaction preceded more smoothly. A slow stream of nitrogen was used to remove generated hydrogen chloride and carbon monoxide. The purification procedure involved filtration, evaporation, and washing with methanol or ethyl acetate. The initial step of the mechanism is oxidative addition of the Rh(I)Cl to the aryl acid chloride. Aryl group migration and decarbonylation give \(\text{ArRh(III)Cl}_2\). Alkene coordination, 1,2-insertion, and \(\beta\)-hydride elimination give product and Rh(III)(H)Cl\(_2\). The last step was conversion to Rh(I)Cl by
reductive elimination with release of HCl.

Figure 1.6 Rhodium catalyzed decarbonylative Heck reaction with aroyl chloride.

A base-free decarbonylative Heck reaction was developed by de Vries and coworkers with aromatic carboxylic anhydrides as arylating agents (Figure 1.7). Under a catalytic amount of palladium chloride and sodium bromide, aromatic carboxylic anhydrides coupled with alkenes at 140-190 °C in N-methylpyrrolidinone (NMP). Aromatic carboxylic acid and carbon monoxide were by-products. Although a catalytic amount of sodium chloride salt was needed, phosphine ligands were not required in this reaction. Aromatic carboxylic anhydrides, such as benzoic anhydrides, p-methoxybenzoic
anhydride and furanoic anhydride, reacted similarly. Olefins with electron-withdrawing
groups showed higher reactivity than olefins with electron-donating groups. However, at
this relatively high temperature, double bond isomerization and internal arylation
occurred for some substrates.

\[ \text{O}_2 \text{O} \quad + \quad 0.25 \% \text{PdCl}_2 \quad 1 \% \text{NaBr} \quad \text{NMP} \quad 160^\circ \text{C} \]

\[ \text{87\%} \quad \beta/\alpha = 8:1 \]

**Figure 1.7** Palladium catalyzed decarbonylative Heck reaction with aromatic carboxylic
anhydride.

Further investigation of this reaction by Shmidt and Smirnov showed that the nature
of the catalytic amount of salt had an important effect on the reactivity and
regioselectivity (Figure 1.8). Lithium chloride was found to be superior to other
alkaline halide salts and ammonium halide salts. The effect of lithium chloride is due to
carboxylate ligand substitution for a halide anion. Palladium chloride is initially reduced
to palladium(0). Oxidative addition of benzoic anhydride to the palladium(0) give an
aryl palladium benzoate complex. Benzoate ligand substitution for the halide anion give
an aryl palladium halide complex, which is the same oxidative addition complex for
aryl halides substrates. The cation of the salt showed an important effect on the
reactivity in water free NMP as solvent. And the anion of the salt showed an important
effect on regioselectivity. Aryl group migration, decarbonylation, olefin coordination, 1,2-insertion, and \(\beta\)-hydride elimination give the coupling product. The catalyst was again regenerated by reductive elimination of hydrogen halide.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
1.6 \% \text{PdCl}_2 & \quad 16 \% \text{LiCl} \\
\text{NMP} 140^\circ \text{C} & \quad 85\% \quad \beta/\alpha = 33:1
\end{align*}
\]

**Figure 1.8** The effect of the halide salt on the palladium catalyzed decarbonylative Heck reaction with aromatic carboxylic anhydride.

Gooßen and coworkers reported a palladium catalyzed decarbonylative Heck reaction with an in situ generated mixed anhydride (Figure 1.9).\textsuperscript{26d} Aromatic carboxylic acid was activated with Boc\(_2\)O to form a mixed anhydride, which coupled with the olefin via catalytic palladium chloride, lithium chloride, and \(\gamma\)-picoline at 120 \(^\circ\)C in NMP. The
byproducts of the reaction were carbon monoxide, carbon dioxide and tert-butanol.

Figure 1.9 Palladium catalyzed decarbonylative Heck reaction with an in situ generated mixed anhydride.

Gooßen and coworkers also developed a Heck reaction with aryl esters as arylating agents at 160 °C (figure 1.10).\textsuperscript{27a} Palladium chloride was found to be the best precatalyst. The addition of lithium chloride and isoquinoline improved the reactivity. Phosphine is not a suitable ligand due to its strong coordination with the catalyst. Benzoates of electron-deficient phenols gave good reactivity. Electron-deficient carboxylic esters also gave better yields than the electron-rich derivatives. Both electron-rich and electron-poor olefins gave similar yields. The palladium (0) inserts to the ester carbon-oxygen bond and enters a catalytic cycle similar to the decarbonylative Heck reaction with carboxylic anhydride as the arylating agent.
Further studies by Gooßen and coworkers extended the reaction to the use of isopropenyl arenecarboxylates at 160 °C (Figure 1.11). Isopropenyl arenecarboxylates were synthesized by a ruthenium catalyzed addition of the carboxylic acids to propyne or allene. Tri-n-butyl(2-hydroxyethyl)ammonium bromide additive was found to stabilize the palladium catalyst and gave better yields. Strong coordination ligands such as phosphines and amines decreased the reactivity. By adding celite, the reduced palladium(0) was precipitated on the celite. After the reaction, Pd(0) on celite was filtered and converted back to palladium bromide with bromine. The recycled PdBr₂ showed similar reactivity for this coupling. NMP was the best solvent for this reaction. The high
reactivity of the reaction allowed coupling of electron-rich and electron-deficient aryl, heteroaryl, and vinyl carboxylic acid esters with various olefins in good yields. The reaction tolerated esters, ethers, nitro, keto, trifluoromethyl, and formyl functional groups. The workup procedure was convenient because the only side products were carbon monoxide and acetone.

![Figure 1.11 Palladium catalyzed decarbonylative Heck reaction with isopropenyl arenecarboxylic acid.](image)

**Figure 1.11** Palladium catalyzed decarbonylative Heck reaction with isopropenyl arenecarboxylic acid.

Myers and coworkers reported a palladium catalyzed decarboxylative Heck olefination of arene carboxylic acids (Figure 1.12). With three equivalent of silver carbonate additive, 20% palladium trifluoroacetate catalyzed the olefin coupling reaction of a variety of ortho-substituted arene carboxylates with alkenes between 80 and 120 °C in a short period of time (0.5-3 hours). The silver carbonate salt was believed to function as both a base to deprotonate the carboxylic acid and a stoichiometric oxidant and was believed to extend the catalyst lifetime. Both electron-rich and electron-deficient arene carboxylic acids gave good yields. However, at least one ortho substituent was necessary for a successful decarboxylative Heck reaction and to avoid apparent C-H insertion at the
ortho position (ortho-palladation). Styrene, acrylates, (E)-ethyl crotonate, and
cyclohexenone were all successful alkene partners. With a stoichiometric amount of
palladium trifluoroacetate, the mechanism of generation of the arylpalladium(II) species
is different from the standard Heck reaction, which involves oxidative addition of
palladium(0) into the carbon-halide bond. The mechanism is initiated with a carboxyl
exchange between palladium(II) trifluoroacetate and the arene carboxylic acid substrate to
form a trifluoroacetato palladium(II) benzoate complex. Intramolecular coordination of
the electron-deficient palladium(II) to the ipso-carbon of the arene forms a four
membered palladacyclic species, which is converted to an arylpalladium(II)
trifluoroacetate intermediate by releasing carbon dioxide. After olefin coordination,
insertion and β-hydride elimination, the Heck coupling product is generated. Although
these steps are common in all Heck reactions, the decarboxylative pathway generated
arylporpalladium(II) trifluoroacetate coupled preferentially with electron-rich olefins,
whereas the standard Heck pathway caused the arylpalladium(II) species to couple
preferentially with electron-deficient olefins. The σ-aralkylpalladium(II) trifluoroacetate
intermediates also are relatively more stable than the corresponding intermediate
produced in the normal Heck reaction. These differences are due to the electron-deficient
nature of the palladium(II) intermediates.
**Figure 1.12** Palladium catalyzed decarbonylative Heck reaction with arene carboxylate and mechanism study with stoichiometric amount of catalyst.

### 1.2. Results and Discussions

#### 1.2.1. Synthesis of Resveratrol Using a Direct Decarbonylative Heck Approach

The novel resveratrol synthesis route involved only four steps from inexpensive resorcylic acid 15, converted to its acid chloride 13, and 4-acetoxystyrene 14 (Figure 1.13). A decarbonylative Heck reaction catalyzed by palladium acetate with an imidazolium carbene ligand 16 was used for stilbene formation. The hydroxyls were conveniently protected as acetate esters which were easily removed with hydroxide.35
Figure 1.13 Retrosynthetic analysis of resveratrol.

3,5-Dihydroxybenzoic acid 15 (~$25/100$ g) was reacted with 5 equiv. of acetic anhydride in the presence of pyridine to give the protected acid, following treatment with aqueous formic acid and recrystallization, in 90% isolated yield (Figure 1.14). Use of 2.6 equiv. of acetic anhydride gave a reduced yield of 75%. Thionyl chloride at 80 °C was then used to convert the protected acid to the acid chloride 13. The product was recrystallized from hexane in 91% isolated yield. Alternatively, oxalyl chloride could be used with catalytic DMF to give 3,5-diacetoxybenzoyl chloride 13 in 94% isolated yield. Spencer and coworkers reported that aryl acid chlorides react with styrene under palladium(II) acetate catalysis with added base to give styrenes in good yield via a decarbonylative Heck type process. This approach held particular promise in this case, since the acid chloride was readily made and the styrene coupling partner is readily available and inexpensive. It was shown that the nature of the added base was critical for the success of the transformation. Added phosphine ligand inhibited the reaction, giving greatly lowered yields. Non-coordinating amine bases, $N$-ethylmorpholine (NEM) and $N,N$-dimethylbenzylamine, proved optimal. Smaller amines capable of palladium coordination retarded the release of carbon monoxide leading to lower stilbene
formation.\textsuperscript{37} 3,5-Diacetoxy benzyol chlorides \textbf{13} were not explored previously. We reported the use of \(N,N\)-bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride (H\textsubscript{2}IPr) \textbf{16} as a carbene-type ligand with palladium(II) acetate for efficient catalysis of Suzuki and Heck couplings with aryl diazonium ions.\textsuperscript{38} Using palladium(II) acetate catalyst (1 mol\%) and ligand \textbf{16}, acid chloride \textbf{13} was coupled with styrene \textbf{14} (1.2 equiv.) with added \(N\)-ethylmorpholine in \(p\)-xylene at 120 °C for 3.5 h. Following standard workup and silica gel chromatography, resveratrol triacetate \textbf{10} was obtained in 73% yield. Resveratrol \textbf{1} was then obtained in pure form following basic hydrolysis in THF and acidification in 88% yield. The total overall yield was 53%, requiring only four steps from resorcylic acid performed on multigram scale.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{synthesis_diagram.png}
\caption{Synthesis of resveratrol using decarbonylative Heck reaction.}
\end{figure}

Variations were explored using the methyl ether protected version of \textbf{13}, together with changes in the amount of palladium(II) acetate catalyst, ligand \textbf{16}, and the use of other bases to form stilbene \textbf{10} (Table 1.1). With dimethyl ether benzoyl chloride \textbf{13}
(P=Me) and 5 mol% palladium(II) acetate, an extended reaction time of 18 h was needed to achieve a yield of 75%. *N,N*-Dimethylbenzylamine and Hünig’s base gave lower yields. Diacetate acid chloride 13 (P=Ac) coupled with good reactivity using one mol% catalyst in less time, 3.5 h. When ligand 16 was left out, the product was obtained in lower yield, 63%. When the catalyst loading was lowered to 0.1 mol%, the yield again dropped to 57%. Use of *N*-methylmorpholine (NMM) was only slightly less effective, while added triethylamine gave product with lowered 57% yield.

**Table 1.1 Decarbonylative Heck coupling.**

<table>
<thead>
<tr>
<th>P</th>
<th>mol% Pd</th>
<th>mol% ligand</th>
<th>base</th>
<th>time (h)</th>
<th>yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>5</td>
<td>0</td>
<td>NEM</td>
<td>18</td>
<td>75</td>
</tr>
<tr>
<td>Me</td>
<td>5</td>
<td>0</td>
<td>BnNMe₂</td>
<td>18</td>
<td>52</td>
</tr>
<tr>
<td>Me</td>
<td>5</td>
<td>0</td>
<td>EtN(i-Pr)₂</td>
<td>18</td>
<td>35</td>
</tr>
<tr>
<td>Ac</td>
<td>1</td>
<td>1</td>
<td>NEM</td>
<td>3.5</td>
<td>73</td>
</tr>
<tr>
<td>Ac</td>
<td>1</td>
<td>0</td>
<td>NEM</td>
<td>3.5</td>
<td>63</td>
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<tr>
<td>Ac</td>
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<td>0.1</td>
<td>NEM</td>
<td>3.5</td>
<td>57</td>
</tr>
<tr>
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<td>1</td>
<td>NMM</td>
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<td>70</td>
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<tr>
<td>Ac</td>
<td>1</td>
<td>1</td>
<td>Et₃N</td>
<td>3.5</td>
<td>57</td>
</tr>
</tbody>
</table>
The efficiency of the decarbonylative Heck approach was compared to an aryl diazonium ion approach. Phloroglucinol 17 was converted to 5-azido-1,3-resorcinol 18 using a three-step sequence (Figure 1.15).\(^\text{39}\) Acetate protection, aniline formation, and diazotization using tert-butyl nitrite, according to the procedure of Doyle, generated the aryl diazonium salt 19.\(^\text{40}\) Coupling of 4-acetoxystyrene with the palladium acetate–imidazolium catalyst gave stilbene 10 product in very low 12% isolated yield. The low efficiency of this coupling and the lengthy route to the aryldiazonium ion illustrated the superiority of the decarbonylative route.

![Fig1](image)

**Figure 1.15** Synthesis of resveratrol using aryl diazonium ion approach.

Recently the decarbonylative Heck-type coupling was extended to mixed anhydrides.\(^\text{26}\) To explore this option, mixed anhydride 21 was formed from the protected acid using pivaloyl chloride and triethylamine in 92% yield. Reaction under the coupling conditions with styrene 14 again gave a low 20% yield of stilbene product 10 (Figure
Figure 1.16 Synthesis of resveratrol using decarbonylative Heck coupling with mixed anhydride.

The decarbonylative route was also compared to an optimized Horner–Emmons based route using a diisopropyl phosphonate 24 (Figure 1.17). Resorcylic acid 15 was benzylated and hydrolyzed to give 3,5-dibenzylxoybenzoic acid 22 in good yield. Treatment with lithium aluminum hydride gave a benzyl alcohol that was then converted to benzyl bromide 23 using phosphorous tribromide. Arbuzov reaction with neat isopropyl phosphate produced phosphonate 24 in high yield. Coupling with 4-benzyloxybenzaldehyde 25 using sodium methoxide as base in DMF gave the protected stilbene in 80% yield. Boron tribromide was then used to give resveratrol 1. The Horner–Emmons step using the diisopropyl phosphonate in this case gave only the E-stilbene in contrast to previous phosphonate routes that have produced mixtures. This route required seven steps and gave product in 36% overall yield.
Figure 1.17 Synthesis of resveratrol using an optimized Horner–Emmons approach.

The decarbonylative Heck approach required only four steps from inexpensive resorcylic acid and gave resveratrol in excellent 53% overall yield. The palladium catalyzed coupling allowed for the use of acetate esters, which were easily removed. Aryl diazonium and mixed anhydride based routes were far less efficient. An improved Horner–Emmons synthesis was lower in overall yield and required more steps.

1.2.2. Synthesis of Ester and Fluoro Analogs of Resveratrol Using Decarbonylative Heck Couplings

Numerous closely related resveratrol analogs, derivatives and conjugates have been found from natural sources.42 In addition, due to its simple structure and broad bioactivity, various resveratrol analogs have been designed to study the structure-activity relationships and to improve its therapeutic activity.43

We developed systematic, selective syntheses of acetate and fluoro analogs of resveratrol using decarbonylative Heck couplings25 with protected resorcylic acid derivatives and styrenes under palladium-$N$-heterocyclic carbene conditions. Suitable
protecting groups were employed that allow for efficient cross-couplings with appropriate partners for the selective synthesis of specific resveratrol analogs.

4'-Acetylresveratrol was synthesized in five steps beginning with resorcylic acid 15 (Figure 1.18). Treatment with sodium hydride followed by MOMCl (methoxymethyl chloride) and exposure to sodium hydroxide gave MOM protected resorcylic acid in 91% isolated yield. A stock solution of thionyl chloride and benzotriazole in CH₂Cl₂ was slowly added to a solution of MOM protected resorcylic acid. After filtration of the benzotriazolium chloride by-product and evaporation of solvents, acid chloride 26 was generated.⁴⁴ Thionyl chloride on its own, without adding benzotriazole, was found to be ineffective for this transformation, and multiple products were formed. Decarbonylative Heck coupling with 4-acetoxy styrene 14 was performed using palladium(II) acetate (1 mol %) and H₂IPr 16 with N-ethylmorpholine as base in p-xylene at 120 °C following the previous decarbonylative Heck route.³⁵ The di-MOM stilbene 27 was isolated in 56% yield for the two steps, from MOM protected resorcylic acid. The MOM groups were removed using TMSI, generated from TMSCl and sodium iodide, to give 4'-acetylresveratrol 28.
Figure 1.18 Synthesis of 4-acetylresveratrol.

The 3,5-diacyl analog was generated from the unstable intermediate, 4-vinylphenol\textsuperscript{45} which was accessed from 4-acetoxytyrene \textsuperscript{14} (Figure 1.19). To differentiate between the 3,5 and 4'-hydroxyls in this case, the chloroacetate protecting group\textsuperscript{46} was found to be superior to the MOM ether. Chloroacetate \textsuperscript{29} was formed in high yield using chloroacetyl chloride. 3,5-Diacetoxybenzoyl chloride \textsuperscript{13} was reacted under palladium–NHC conditions to give stilbene \textsuperscript{30} (70%). Efficient removal of the chloroacetate, in the presence of the 3,5-diacylates, was performed using 50% aqueous pyridine (pH 6.7) to give 3,5-acetylresveratrol \textsuperscript{31} in 90% isolated yield.
To begin the synthesis of 3,4'-diacetylresveratrol 36, resorcylic acid 15 was mono-acetylated in 60% yield using acetic anhydride (1 equiv) and sodium hydroxide (3 equiv) to give mono-acetyl protected resorcylic acid (Figure 1.20). Protection of the 5-hydroxyl was found to be most efficient using the seldomly employed levulinate (Lev, 4-oxopentanoate) group. This group was found to be stable to various reaction conditions, including acid chloride formation and the palladium coupling step, and is readily removed using sodium sulfite via the hydroxysulfite adduct. Mono-acetyl resorcylic acid was treated with levulinic anhydride in the presence of pyridine to give differentially protected resorcylic acid 33 in 96% isolated yield. Formation of the acid chloride 34 was then performed using thionyl chloride again with added benzotriazole. Coupling under palladium–NHC conditions, as before, generated levulinic ester 35 (70%). The Lev group was then removed by sodium sulfite and thiosulfate to access the desired 3,4'-diacetylresveratrol analog 36.
The levulinate strategy also proved to be most effective for the synthesis of the 3-acetyl analog 39 (Figure 1.21). 4-Hydroxystyrene was treated with levulinic acid under DCC, DMAP coupling conditions to give the Lev-protected hydroxystyrene 37. Coupling with differentially protected resorcylic acid chloride 34 under the decarbonylative Heck conditions gave the protected stilbene 38 in 72% yield. Removal of the two Lev groups gave 3-acetylresveratrol 39.
Fluoro analogs were also produced using the decarbonylative coupling reaction. Resveratrol has been found to have a limited cellular lifetime.\textsuperscript{49} Fluoride is isosteric with hydroxyl and the stability of the substituted C–F bond can lead to improved activity and resistance to metabolism.\textsuperscript{50} 3,5-Difluorobenzoyl chloride 40 reacted with 4-fluorostyrene 41 to give 3,4',5-trifluorostilbene 42 in 80% yield. Coupling of 3,5-Difluorobenzoyl chloride 40 with 4-acetoxy styrene 14 occurred in 74% yield and the difluoro analog 43 was generated in 88% isolated yield (Figure 1.22). 3,5-Diacetoxybenzoyl chloride 13 was also coupled using 4-fluorostyrene 41 to generate 4'-fluoro analog 44 in good overall yield (Figure 1.23).

![Synthesis of fluoro analogs using decarbonylative Heck reaction.](image)

**Figure 1.22** Synthesis of fluoro analogs using decarbonylative Heck reaction.

To complete the synthesis of the fluoro analog series, it was found that use of bromobenzene substrates under standard Heck coupling conditions known to produce
stilbenes\textsuperscript{51} was superior to the previous decarbonylative conditions (Figure 1.23). 1-Bromo-3,5-difluorobenzene 45 was reacted with benzyl alcohol under sodium hydride conditions to give the benzyloxy substituted product 46.\textsuperscript{52} Heck coupling with 4-fluorostyrene 41 and catalytic palladium acetate with tri-\textit{o}-toluylphosphine gave benzyloxy stilbene. Boron tribromide mediated removal of the benzyl ether generated the 3,4'-(difluoro analog 47. Treatment of the benzyloxy adduct 46, formed from 1-Bromo-3,5-difluorobenzene 45, with 4-acetoxystyrene 14 gave substituted stilbene which was converted to the 3-fluoro analog 48 following protecting group removal.

![Chemical structures and reactions](image-url)

\textbf{Figure 1.23 Synthesis of fluoro analogs using Heck coupling.}

The analogs were tested with human leukemia HL-60 cells to determine anti-cancer potential related to resveratrol. The cells were cultured over various times (24, 48, and 72 h) exposed to compounds (5–100 µM), and ED\textsubscript{50} values were determined using an established protocol.\textsuperscript{53} Triacetyl 10 and 3-acetyl 39 were found to be comparable to resveratrol (23 µM), while the 3,5- and 3,4'-diacetyl anallogs, 31 and 36, were less potent.
Only the 4’-acetyl variant 28 showed somewhat improved anti-cancer activity at 17 µM.

In general, the fluoro analogs were found to be toxic to this and other cell lines, limiting their potential for future investigations.

Table 1.2 Bioactivity of the acetate analogs with leukemia HL-60 cells.

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Analogs</th>
<th>( ED_{50} ) (µM)</th>
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<td>OAc</td>
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<tr>
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<td>33</td>
</tr>
<tr>
<td>OH</td>
<td>OAc</td>
<td>OAc</td>
<td><img src="image36" alt="Image of compound 36" /></td>
<td>30</td>
</tr>
<tr>
<td>OH</td>
<td>OAc</td>
<td>OH</td>
<td><img src="image39" alt="Image of compound 39" /></td>
<td>24</td>
</tr>
</tbody>
</table>

1.3. Conclusion and Future Work

The decarbonylative Heck approach required only four steps from inexpensive
resorcylic acid and gave resveratrol in excellent 53% overall yield. The palladium catalyzed coupling allowed for the use of acetate esters, which are easily removed. The same coupling approach was applied to the synthesis of resveratrol analogs from substituted acid chlorides and styrenes. Chloro acetate and levulinate protecting groups have been shown to be suitable for this transformation, facilitating selective routes to mono- and di-acetoxyl analogs. Heck coupling conditions were found to be more effective for 3-fluoro and 3,4'-difluoro resveratrol synthesis. The 4'-acetoxy variant was found to be more potent than resveratrol using an HL-60 cell assay. Further investigations of the biological activities of these compounds, together with the synthesis of a range of 4'-analogs, can now be pursued using this approach.

1.4. References

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34.


Chapter 2. Asymmetric Glycolate Aldol Reactions Using Cinchonium Phase-Transfer Catalysts

2.1. Introduction

Phase transfer catalysts (PTC) are chemical agents that accelerate reaction rates through transferring a reagent or substrate ion from one phase to another. Anion transfer agents have been used in organic transformation as early as the 1950s. Phase transfer catalyzed reactions have undergone great developments since the 1970s, when the foundations of PTC were laid by Starks, Makosza, and Brandstrom. The most common phase transfer process is the “normal” biphasic phase transfer reaction, in which the phase transfer catalyst coordinates with a reagent or substrate ion and transports the ion into the organic phase. Depending on the reaction conditions, the ion exchange process can occur in the aqueous phase, the interfacial region, or in the organic phase. Despite these mechanism variations, phase transfer catalyzed reactions have many advantages, including operational simplicity, mild reaction conditions with aqueous media, environmental consciousness, and suitability for large-scale production.

The great demand for non-racemic chemicals in both industrial and academic laboratories has led to the rapid development of enantioselective processes using enantiopure phase transfer catalysts, such as chiral quaternary ammonium salts and chiral crown ethers. Crown ethers are usually less favorable as a chemical reagent due to their toxicity and synthetic complexity. Instead, chiral quaternary ammonium salts,
derived from the naturally occurring chiral pool, have been widely used because of their low cost and synthetic simplicity. Chiral quaternary ammonium catalysts have also been successfully designed from non-natural substrates. While these catalysts are expensive, they have been effective in a large variety of reactions. Since the pioneering work of the Merk research group and O’Donnell in the 1980s (Figure 2.1), catalytic asymmetric phase transfer reactions have been applied in alkylations, aldol and Mannich reactions, Michael additions, Darzens condensations, Horner-Wadsworth-Emmons reactions, epoxidations, reductions, Robinson annulations, fluorinations, cyclopropanations, aziridinations, Strecker reactions, and esterifications.

**Figure 2.1** Pioneering works in PTC catalyzed asymmetric alkylation.

PTC alkylation, aldol, and Michael additions have mainly focused on the
benzophenone imine \( t \)-butyl glycine substrate 49, due to its \( t \)-butyl ester stability, extended enolate delocalization (\( pK_a \) 18, DMSO), and aromatic \( \pi-\pi \) interaction with the catalyst. Inexpensive cinchona alkaloid derived catalysts are most commonly employed. Variation of the catalyst and conditions has shown steady improvement in selectivity and efficiency.

Although there are numerous reports in asymmetric phase transfer alkylation of the prochiral glycine derivative 49, reports for aldol reactions are limited. The first catalytic asymmetric aldol condensation of the glycine Schiff base 49 under phase transfer condition was described by Miller (Figure 2.2). 9 Under catalyst \( N \)-benzyl-cinchonium chloride 50, benzophenone imine \( t \)-butyl glycine 49 reacted with heptanal at ambient temperature in a biphasic mixture of \( CH_2Cl_2 \) and 5% aqueous NaOH to give 81% product 51. With hydrocinnamaldehyde as substrate, the yield was 76%. Unfortunately, the diastereoselectivities and enantioselectivities were poor.

Figure 2.2 Miller’s PTC catalyzed aldol reaction.
Shioiri and co-workers reported an N-benzyl-cinchonium fluoride 53 catalyzed aldol reaction between silyl enol ether 52 and aldehydes (Table 2.1). The N-benzyl-cinchonium chloride was first converted to its corresponding hydroxide by passing through an Amberlyst A-26 OH⁻ ion exchange column. Then the hydroxide was neutralized with aqueous hydrofluoric acid. In the present of this fluoride catalyst, the silyl enol ethers of 2-methyl-1-tetralone derivatives 52 reacted with benzaldehydes in THF at -78 °C to give asymmetric aldol products 54 in good yield and stereoselectivity. The same conditions were also applied to the silyl enol ethers 55 of acetophenone and pinacolone to give aldol products 56 in 65% yield, 39% ee and 62% yield, 62% ee, respectively (Figure 2.3).

**Table 2.1** Shioiri’s Mukaiyama-type PTC catalyzed aldol reaction.

<table>
<thead>
<tr>
<th>R</th>
<th>% yield</th>
<th>erythro/threo</th>
<th>% ee (erythro)</th>
<th>% ee (threo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>74</td>
<td>3.5/1</td>
<td>70</td>
<td>22</td>
</tr>
<tr>
<td>MeO</td>
<td>73</td>
<td>3.2/1</td>
<td>68</td>
<td>30</td>
</tr>
<tr>
<td>Cl</td>
<td>73</td>
<td>4.6/1</td>
<td>66</td>
<td>21</td>
</tr>
<tr>
<td>Br</td>
<td>67</td>
<td>4.3/1</td>
<td>66</td>
<td>15</td>
</tr>
</tbody>
</table>
Further studies by the same group showed that the stereochemical results of the aldol reaction mainly depended on the hydroxymethyl-quinuclidine fragment.Usually, the cinchonium fluorides were more efficient than cinchonidinium fluorides. In the reactions of silyl enol ethers of 2-methyl-1-tetralone derivatives with benzaldehyde, cinchonium and quinidium fluorides gave *erythro* isomers with (2*R, 2'S*)-configuration as major products and *threo* isomers with (2*R, 2'R*)-configuration as minor products. Interestingly cinchonidinium and quininium fluorides gave *erythro* isomers with (2*R, 2'S*)-configuration as minor products and *threo* isomers with (2*S, 2'S*)-configuration as major products. With silyl enol ethers of acetophenone and pinacolone as substrates, *N*-benzyl-cinchonidinium fluoride *CN* gave aldol products with the opposite absolute configuration compared with the products from *N*-benzyl-cinchonium fluoride *CD* (Figure 2.4).
To facilitate a stereoselective synthesis of the HIV protease inhibitor amprenavir, Corey and Zhang developed a nitroaldol reaction with \textit{N}-anthracenylmethyl-\textit{O-}
benzylcinchonidinium fluoride catalyst 58 (Figure 2.5). Since the reaction only 
needed a catalytic amount of base, a catalytic amount of ammonium fluoride was 
basic enough to fulfill this requirement. \textit{N},\textit{N}-dibenzyl-(\textit{S})-phenylalaninal 57 reacted 
with nitromethane with a catalytic amount of cinchonium fluoride 58 and 12.5 
equivalents of potassium fluoride in THF at -10 °C to give 86% of the desired 
\textit{syn}-nitro alcohol 59 and 5% of its diastereomer. The diastereoselectivity was about 
17:1. When achiral phase transfer catalyst, tetra-\textit{n}-butylammonium fluoride, was used, 
only 4:1 diastereoselectivity was obtained. The C-2 diastereomer of amprenavir was 
also synthesized using \textit{N}-tert-butoxycarbonyl-(\textit{S})-phenylalaninal 60 as a substrate. 
The fluoride catalyst was generated in situ from its corresponding bromide 61. The 
nitroaldol product 62 was obtained in an 88% yield with a 9:1 diasteromeric ratio. In 
the presence of tetra-\textit{n}-butylammonium fluoride as catalyst, the diasteromeric ratio of 
the reaction was 1:1.

\textbf{Figure 2.4} Shioiri’s Mukaiyama-type cinchonidinium PTC catalyzed aldol reaction.
Later, Corey and coworkers developed a Mukaiyama-type aldol reaction to synthesize chiral β-hydroxy-α-amino acids in a homogenous organic solution (Table 2.2).<sup>13</sup> Using the cinchonidine derived ammonium bifluoride catalyst 64, the trimethylsilyl ketene acetal derivative of benzophenone imine 63 reacted with aliphatic aldehydes at -78 °C in a mixed solvent of hexanes and methylene chloride. The yields and enantioselectivity were good to excellent. The diastereoselectivity depended on the aldehyde substrate. Branched aldehydes gave better diastereoselectivity than unbranched aldehydes.
Table 2.2 Corey’s PTC catalyzed Mukaiyama-type aldol reaction.

<table>
<thead>
<tr>
<th>R</th>
<th>Hex.-CH₂Cl₂</th>
<th>temp (°C)</th>
<th>% yield</th>
<th>syn/anti</th>
<th>% ee (syn)</th>
<th>% ee (anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-Pr</td>
<td>3:1</td>
<td>-78</td>
<td>70</td>
<td>6/1</td>
<td>95</td>
<td>83</td>
</tr>
<tr>
<td>c-Hex</td>
<td>5:1</td>
<td>-50</td>
<td>81</td>
<td>13/1</td>
<td>88</td>
<td>46</td>
</tr>
<tr>
<td>n-Hex</td>
<td>3:1</td>
<td>-78</td>
<td>79</td>
<td>3/1</td>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td>Cl(CH₂)₃</td>
<td>5:1</td>
<td>-78</td>
<td>48</td>
<td>1/1</td>
<td>82</td>
<td>86</td>
</tr>
<tr>
<td>Ph(CH₂)₂</td>
<td>3:1</td>
<td>-78</td>
<td>64</td>
<td>1/1</td>
<td>72</td>
<td>86</td>
</tr>
<tr>
<td>i-Bu</td>
<td>5:1</td>
<td>-45</td>
<td>61</td>
<td>3/1</td>
<td>76</td>
<td>70</td>
</tr>
</tbody>
</table>

Cinchona alkaloids and brucine derived chiral ammonium fluorides were used in catalytic asymmetric vinylogous Mukaiyama aldol reactions. Campagne and Bluet reported that sily dienolate 66 reacted with isobutyraldehyde in the presence of 10 mol% of chiral ammonium fluoride 53 to give the vinylogous aldol product 67 in 70% yield with unsatisfactory enantioselectivity (Figure 2.6).¹⁴

Figure 2.6 Campagne’s PTC catalyzed vinylogous Mukaiyama-type aldol reaction.
Castle and coworkers developed an effective direct aldol reaction between benzophenone imine $t$-butyl glycine 49 and aliphatic aldehydes with an $N$-trifluorobenzyl-cinchonidinium bromide catalyst 68 (Table 2.3). Phosphazene base, BTTP, was used under homogeneous conditions. Although the diastereoselectivity was still unsatisfying, the enantioselectivity was much better than Miller’s results. Due to a facile retro-aldol process, benzaldehyde was not a suitable substrate. With the pseudoenantiomeric catalyst derived from cinchonine, reversed enantioselectivity was obtained with lower stereoselectivity.

**Table 2.3** Castle’s PTC catalyzed direct aldol reaction.

<table>
<thead>
<tr>
<th>R</th>
<th>%yield</th>
<th>syn/anti</th>
<th>%ee (syn)</th>
<th>%ee (anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCH$_2$CH$_2$</td>
<td>64</td>
<td>1.3/1</td>
<td>80</td>
<td>33</td>
</tr>
<tr>
<td>BnOCH$_2$</td>
<td>70</td>
<td>1/1</td>
<td>83</td>
<td>45</td>
</tr>
<tr>
<td>$p$-NO$_2$PhCH$_2$CH$_2$</td>
<td>74</td>
<td>1.3/1</td>
<td>75</td>
<td>60</td>
</tr>
<tr>
<td>$p$-OMePhCH$_2$CH$_2$</td>
<td>78</td>
<td>1.2/1</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>CH$_2$=CHCH$_2$CH$_2$</td>
<td>46</td>
<td>1.2/1</td>
<td>60</td>
<td>19</td>
</tr>
<tr>
<td>CH$_3$(CH$_2$)$_4$CH$_2$</td>
<td>34</td>
<td>1.2/1</td>
<td>52</td>
<td>6.5</td>
</tr>
</tbody>
</table>
Arai and coworkers investigated asymmetric aldol reactions between tert-butyl diazoacetate 70 and aldehydes using \(N\)-anthracenylmethyl-cinchonidinium chloride 71 as a catalyst at -40 °C (Table 2.4). The substituents on the benzene ring of benzaldehydes had an important electronic effect. Electron-withdrawing groups increased the reactivity and enantioselectivity, and electron-donating groups decreased the reactivity and enantioselectivity. The substituents on aliphatic aldehydes had a strong steric effect. With a bulky substituent, the yield and enantioselectivity was improved. Since the enantioselectivity of the aldol reaction kept increasing for the first several hours, it was believed that the asymmetric induction was enhanced from both the C-C formation process and the retroaldol step.

**Table 2.4** Arai’s PTC catalyzed aldol reaction.

<table>
<thead>
<tr>
<th>(R)</th>
<th>time (h)</th>
<th>%yield</th>
<th>%ee</th>
<th>(R)</th>
<th>time (h)</th>
<th>%yield</th>
<th>%ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>12</td>
<td>91</td>
<td>56</td>
<td>Ph(CH(_2)CH(_2)(_2))</td>
<td>72</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>(p)-MePh</td>
<td>66</td>
<td>66</td>
<td>39</td>
<td>(i)-Bu</td>
<td>72</td>
<td>85</td>
<td>20</td>
</tr>
<tr>
<td>(p)-MeOPh</td>
<td>120</td>
<td>56</td>
<td>0</td>
<td>(i)-Pr</td>
<td>20</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>(p)-CF(_3)Ph</td>
<td>140</td>
<td>81</td>
<td>73</td>
<td>(c)(i)-Hex</td>
<td>10</td>
<td>88</td>
<td>33</td>
</tr>
<tr>
<td>1-naphthyl</td>
<td>94</td>
<td>86</td>
<td>79</td>
<td>(t)-Bu</td>
<td>72</td>
<td>83</td>
<td>78</td>
</tr>
</tbody>
</table>
Maruoka and coworkers designed a novel type of $N$-spiro C$_2$-symmetric chiral phase transfer catalyst derived from (S)- or (R)-1,1'-bi-2-naphthol. Without $\beta$-hydrogens, these catalysts were more stable than the cinchona derived quaternary ammonium catalysts, which degrade under basic condition through Hofmann elimination. Consequently, less than 1 mol\% catalyst loading was required. Although they required 12 steps to be synthesized from expensive substrates, these catalysts have been applied in a wide variety of transformations.

Maruoka and coworkers successfully used an in situ generated C$_2$-symmetric chiral quaternary ammonium fluoride salt from the corresponding hydrogen sulfate 73 to catalyze aldol reactions between tetralone-derived trimethyl silyl enol ether 74 and aromatic aldehydes (Table 2.5). 17 The electron-withdrawing effect of the trifluoromethyl groups on the 3,3'-aryl substituents of the catalyst helped form a tight contact ion pairing with the ammonium enolate, thus providing excellent stereoselectivity.
Table 2.5 Maruoka’s PTC catalyzed Mukaiyama-type aldol reaction with tetralone derived silyl enol ethers.

<table>
<thead>
<tr>
<th>R</th>
<th>% yield</th>
<th>erythro/threo</th>
<th>% ee (erythro)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>90</td>
<td>83/17</td>
<td>84</td>
</tr>
<tr>
<td>α-Naph</td>
<td>90</td>
<td>94/6</td>
<td>91</td>
</tr>
<tr>
<td>9-phenanthryl</td>
<td>88</td>
<td>95/5</td>
<td>90</td>
</tr>
</tbody>
</table>

The same in situ fluoride catalyst generation strategy was applied to aldol couplings with glycine-derived silyl ketene acetal 75 and aliphatic aldehydes (Table 2.6). With 3,5-bis(3,5-bis(trifluoromethyl)phenyl)phenyl substituents at the 3,3’-position of the catalyst 74, both the diastereo- and enantioselectivities were enhanced.
Table 2.6 Maruoka’s PTC catalyzed Mukaiyama-type aldol reaction with glycine derived silyl ketene acetal.

<table>
<thead>
<tr>
<th>R</th>
<th>% yield</th>
<th>anti/syn</th>
<th>% ee (anti)</th>
<th>R</th>
<th>% yield</th>
<th>anti/syn</th>
<th>% ee (anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph(CH₂)₂</td>
<td>77</td>
<td>8.3/1</td>
<td>92</td>
<td>i-Bu</td>
<td>70</td>
<td>7.2/1</td>
<td>90</td>
</tr>
<tr>
<td>CH₃(CH₂)₄</td>
<td>58</td>
<td>8.4/1</td>
<td>91</td>
<td>i-Pr</td>
<td>65</td>
<td>6.7/1</td>
<td>97</td>
</tr>
<tr>
<td>CH₃(CH₂)₅</td>
<td>72</td>
<td>11/1</td>
<td>90</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

An asymmetric nitro aldol reaction was also investigated by Maruoka’s group, using their $N$-spiro C₂-symmetric ammonium bifluoride catalyst 78 (Table 2.7).¹⁹ Silyl nitronates 77 reacted with aromatic aldehydes to give the corresponding nitoalkanol products 79 with excellent stereoselectivities at low temperature (-98 °C to -78 °C) in THF (m.p. -108.5 °C).
Table 2.7 Maruoka’s PTC catalyzed Mukaiyama-type nitroaldol reaction.

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>% yield</th>
<th>anti/syn</th>
<th>% ee (anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>Ph</td>
<td>92</td>
<td>12/1</td>
<td>95</td>
</tr>
<tr>
<td>CH₃</td>
<td>p-FPh</td>
<td>94</td>
<td>5/1</td>
<td>90</td>
</tr>
<tr>
<td>CH₃</td>
<td>β-Np</td>
<td>88</td>
<td>12/1</td>
<td>93</td>
</tr>
<tr>
<td>Et</td>
<td>Ph</td>
<td>94</td>
<td>9/1</td>
<td>91</td>
</tr>
<tr>
<td>BnO(CH₂)₂</td>
<td>Ph</td>
<td>70</td>
<td>7/1</td>
<td>91</td>
</tr>
</tbody>
</table>

A direct aldol reaction was also developed with catalyst 80 (Table 2.8).²⁰,²¹ With benzophenone imine t-butyl glycine 49 as the substrate, a variety of aliphatic aldehydes gave excellent enantioselectivity at 0 °C in a biphasic system, where toluene and 1% aqueous NaOH served as solvents.²⁰ Further mechanistic studies regarding this aldol process revealed an unfavorable yet inevitable retro aldol reaction under this basic asymmetric condition.²¹ By reducing the addition of aqueous base to a catalytic amount of 15 mol% NaOH, with addition of NH₄Cl (10 mol%) to control the pH of the reaction, a wider aliphatic aldehyde scope was obtained with better diastereo- and enantioselectivity. Unfortunately, aromatic aldehydes gave poor yields and poor stereoselectivities.
Table 2.8 Maruoka’s PTC catalyzed direct aldol reaction.

<table>
<thead>
<tr>
<th>R</th>
<th>% yield</th>
<th>anti/syn</th>
<th>% ee (anti)</th>
<th>R</th>
<th>% yield</th>
<th>anti/syn</th>
<th>% ee (anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph(CH₂)₂</td>
<td>82</td>
<td>24/1</td>
<td>98</td>
<td>i-PrCH₂</td>
<td>64</td>
<td>&gt;24/1</td>
<td>96</td>
</tr>
<tr>
<td>CH₃(CH₂)₄</td>
<td>79</td>
<td>&gt;24/1</td>
<td>97</td>
<td>AllylCH₂</td>
<td>82</td>
<td>24/1</td>
<td>98</td>
</tr>
<tr>
<td>CH₃(CH₂)₅</td>
<td>80</td>
<td>16/1</td>
<td>97</td>
<td>CH₃</td>
<td>54</td>
<td>&gt;24/1</td>
<td>99</td>
</tr>
<tr>
<td>TIPSOCH₂</td>
<td>73</td>
<td>&gt;24/1</td>
<td>98</td>
<td>i-Pr</td>
<td>39</td>
<td>&gt;24/1</td>
<td>98</td>
</tr>
<tr>
<td>BnO(CH₂)₃</td>
<td>83</td>
<td>24/1</td>
<td>96</td>
<td>Ph</td>
<td>58</td>
<td>1/1.1</td>
<td>25</td>
</tr>
</tbody>
</table>

Similar to aldol reactions, direct Mannich reactions of benzophenone imine $t$-butyl glycine 49 with imine derivative 82 were accomplished with high enantioselectivity using $N$-spiro C₂-symmetric ammonium bromide 83 as the catalyst to give differentially protected 3-aminoaspartate 84 (Figure 2.7).²² The catalyst with a 3,4,5-trifluorophenyl group at the 3,3'-position gave enhanced enantioselectivity. Switching solvent from toluene to mesitylene further improved the yield and the diastereo- and enantioselectivity.

Figure 2.7 Maruoka’s PTC catalyzed direct Mannich reaction.
Shibasaki reported another successful phase transfer catalyzed Mannich reaction using a tartrate-derived diammonium salt (TaDiAS) 86 (Table 2.9). Fluorobenzene and cesium carbonate were the best solvent and base, respectively. The electron-withdrawing imine-protecting group, Boc, gave excellent reactivity and diastereoselectivity. Both aromatic and acetal moieties on the catalyst strongly affected the enantioselectivity. Placing a 4-fluorophenyl group at the C2 position of the acetal side chain improved enantioselectivity. A variety of aromatic and α,β-unsaturated imines 85 were suitable substrates. Because of the synthetic difficulty, N-Boc C-aliphatic imines were not applied.

Table 2.9 Shibasaki’s PTC catalyzed direct Mannich reaction.

<table>
<thead>
<tr>
<th>R</th>
<th>% yield</th>
<th>syn/anti</th>
<th>% ee (syn)</th>
<th>R</th>
<th>% yield</th>
<th>syn/anti</th>
<th>% ee (syn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>98</td>
<td>99:1</td>
<td>70</td>
<td>p-FPh</td>
<td>99</td>
<td>49:1</td>
<td>72</td>
</tr>
<tr>
<td>p-MeOPh</td>
<td>95</td>
<td>19:1</td>
<td>82</td>
<td>p-ClPh</td>
<td>87</td>
<td>49:1</td>
<td>58</td>
</tr>
<tr>
<td>p-MePh</td>
<td>98</td>
<td>49:1</td>
<td>80</td>
<td>o-Np</td>
<td>87</td>
<td>&gt;19:1</td>
<td>60</td>
</tr>
<tr>
<td>m-MePh</td>
<td>96</td>
<td>19:1</td>
<td>70</td>
<td>o-HSPh</td>
<td>98</td>
<td>19:1</td>
<td>80</td>
</tr>
<tr>
<td>o-MePh</td>
<td>99</td>
<td>32:1</td>
<td>68</td>
<td>(E)-PhCH=CH</td>
<td>86</td>
<td>19:1</td>
<td>66</td>
</tr>
</tbody>
</table>
2.2. Results and Discussions

In an effort to extend the PTC process to oxygenated glycolate products, we previously reported asymmetric PTC-catalyzed alkylations with oxygenated substrates using the novel alkoxyacetophenone 88 (Figure 2.8). The nature of the protecting group and substitution pattern on the aryl ketone proved to be critical for high selectivity and good reaction rates. This method provides a convenient route to a variety of alkylated hydroxy products with high selectivity. Previous to this work, asymmetric glycolate alkylation was limited to chiral auxiliaries.

Figure 2.8 PTC-catalyzed glycolate alkylation.

2.2.1. Direct PTC Catalyzed Glycolate Aldol Reactions

Initially the direct aldol reaction of DPM (diphenylmethyl)-protected 2,5-dimethoxyacetophenone derivative 88 was explored using the N-trifluorobenzyl cinchonidinium catalyst of Park and Jew 68-CD\(^+\)Br. Solid-liquid-phase conditions with either cesium hydroxide or sodium methoxide in THF gave product 90 from
dihydrocinnamaldehyde with poor diastereoselectivity and no enantioselectivity at -40 °C (Table 2.10). In toluene, the yield was decreased. Relatively weaker bases such as sodium hydroxide and sodium carbonate did not give any product at this temperature. The phosphazine base, BTPP, also failed to give desired product.

Table 2.10 PTC catalyzed solid-liquid-phase glycolate aldol reaction.

<table>
<thead>
<tr>
<th>base</th>
<th>solvent</th>
<th>time</th>
<th>yield%</th>
<th>syn:anti</th>
<th>ee% syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsOH·H₂O</td>
<td>THF</td>
<td>1 day</td>
<td>45</td>
<td>3:1</td>
<td>0</td>
</tr>
<tr>
<td>NaOMe</td>
<td>THF</td>
<td>1 day</td>
<td>83</td>
<td>2.5:1</td>
<td>0</td>
</tr>
<tr>
<td>NaOMe</td>
<td>Tol.</td>
<td>1 day</td>
<td>61</td>
<td>3:1</td>
<td>0</td>
</tr>
<tr>
<td>NaOH</td>
<td>THF</td>
<td>1 day</td>
<td>N. R.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na₂CO₃</td>
<td>THF</td>
<td>1 day</td>
<td>N. R.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BTPP</td>
<td>THF</td>
<td>1 day</td>
<td>No desired prod.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Liquid-liquid conditions with 1% aqueous sodium hydroxide showed slight improvement in enantioselectivity at 0 °C (Table 2.11). THF solvent gave the best syn/anti selectivity (3.9:1) and 1,2-dimethoxyethane gave the best yield (66%). Benzaldehyde gave a very low yield (15%) in toluene under these conditions.
Table 2.11 PTC catalyzed liquid-liquid-phase glycolate aldol reaction.

<table>
<thead>
<tr>
<th>solvent</th>
<th>yield%</th>
<th>syn:anti</th>
<th>ee% syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tol.</td>
<td>53</td>
<td>3.7:1</td>
<td>7</td>
</tr>
<tr>
<td>CH₂Cl₂+Hexanes (1:5)</td>
<td>40</td>
<td>3.9:1</td>
<td></td>
</tr>
<tr>
<td>THF</td>
<td>63</td>
<td>2:1</td>
<td></td>
</tr>
<tr>
<td>CH₂Cl₂</td>
<td>8.4</td>
<td>3.5:1</td>
<td></td>
</tr>
<tr>
<td>DME</td>
<td>66</td>
<td>2.5:1</td>
<td></td>
</tr>
<tr>
<td>Dioxanes</td>
<td>51</td>
<td>2:1</td>
<td></td>
</tr>
</tbody>
</table>

The catalyst was then changed to the pseudo-enantiomeric 68-CN⁺Br⁻ with only slight improvement in the enantioselectivity, 22% ee for the syn-product (Table 2.12). Surprisingly, this change to the cinchonium catalyst 68 resulted in production of the same enantiomeric product. Use of Maruoka’s bis-binaphthyl catalyst 91 gave only trace product with little selectivity (7%, 6% ee). Corey’s catalyst 61-CD gave opposite stereoselectivity. Self condensation products were not observed under any conditions with dihydrocinnamaldehyde as substrate.
Table 2.12 Different PTCs catalyzed liquid-liquid-phase glycolate aldol reaction.

<table>
<thead>
<tr>
<th>PTC</th>
<th>yield%</th>
<th>syn:anti</th>
<th>ee% syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maruoka 91</td>
<td>7</td>
<td>4.1:1</td>
<td>6</td>
</tr>
<tr>
<td>Corey (CD) 61</td>
<td>15</td>
<td>5.7:1</td>
<td>-20</td>
</tr>
<tr>
<td>R= Allyl 68</td>
<td>50</td>
<td>4.9:1</td>
<td>8</td>
</tr>
<tr>
<td>Park-Jew (CD)</td>
<td>53</td>
<td>4.9:1</td>
<td>7</td>
</tr>
<tr>
<td>R= Bn 92</td>
<td>53</td>
<td>4.9:1</td>
<td>7</td>
</tr>
<tr>
<td>Park-Jew (CN) 68</td>
<td>45</td>
<td>3.8:1</td>
<td>22</td>
</tr>
</tbody>
</table>

With Park-Jew’s cinchonium bromide catalyst 68-CN, use of catalytic amount of aqueous NaOH as base and ammonium chloride as an additive in toluene did not improve the yield or selectivity (Table 2.13). Decreasing the reaction time (2 h) lowered the yield. Switching the solvent to THF induced no enantioselectivity. Benzaldehyde did not show enantioselectivity under these conditions.
Table 2.13 Effect of NH₄Cl on PTC catalyzed liquid-liquid-phase glycolate aldol.

<table>
<thead>
<tr>
<th>R</th>
<th>additive</th>
<th>solvent</th>
<th>time (h)</th>
<th>% yield</th>
<th>syn:anti</th>
<th>ee% syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph(CH₂)₂</td>
<td>none</td>
<td>tol.</td>
<td>24</td>
<td>51</td>
<td>3.9:1</td>
<td>25</td>
</tr>
<tr>
<td>Ph(CH₂)₂</td>
<td>NH₄Cl</td>
<td>tol.</td>
<td>24</td>
<td>55</td>
<td>3.8:1</td>
<td>25</td>
</tr>
<tr>
<td>Ph(CH₂)₂</td>
<td>NH₄Cl</td>
<td>tol.</td>
<td>2</td>
<td>9</td>
<td>3.6:1</td>
<td>21</td>
</tr>
<tr>
<td>Ph(CH₂)₂</td>
<td>NH₄Cl</td>
<td>THF</td>
<td>2</td>
<td>10</td>
<td>1:1</td>
<td>0</td>
</tr>
<tr>
<td>Ph</td>
<td>NH₄Cl</td>
<td>tol.</td>
<td>24</td>
<td>35</td>
<td>7:1</td>
<td>0</td>
</tr>
</tbody>
</table>

2.2.2. PTC Catalyzed Mukaiyama-Type Glycolate Aldol Reactions

The silyl enol ether of 88 was then made and explored under Corey’s cinchonium fluoride catalyst conditions. Compound 88 was treated with LDA and trapped with TMSCl to give 93 as a stable white solid, which is simply purified by filtration and crystallization (Figure 2.9). Fortunately, as a silyl en ether, 93 is easily manipulated, unlike the corresponding silyl ketene acetal of the protected glycine used in previous PTC aldol studies, which is easily hydrolyzed. The difluoride catalyst 94-CN⁺HF₂⁻ was easily made from its corresponding bromide salt 68 by passing it through an Amberlyst A-26 (OH⁻) ion exchange column, followed by acidification (Figure 2.9).
Figure 2.9 Preparation of substrate and catalyst.

Reaction of 93 with benzaldehyde under PTC conditions gave the differentially protected aldol product 90 following treatment with cesium fluoride and water (Table 2.14). In dry THF with the hydrogen difluoride catalyst 68-CN’HF₂⁻ at -45 °C, the yield of 90 was low (35%); however, the selectivity was dramatically improved to 75% ee. In all cases with this substrate, a single syn-diastereomer was obtained. Protected glycine PTC aldol reactions typically give a mixture of diastereomers. Various solvents and combinations were also explored under these aldol conditions. Use of toluene, a mixture of dichloromethane and hexanes, and DME did not improve the yield. Surprisingly, use of reagent grade THF with 68-CN’HF₂⁻ improved the rate of the reaction, requiring 1.5 h for completion, and the yield and selectivity also increased (78%, 75% ee). Trace water in this case appears to improve the catalyst turnover and the selectivity. Use of a 1/1 reagent THF/DMF solvent mixture with
68-CN’HF₂ proved to be superior, with an 87% yield and an 80% ee for the syn-product 90. Reagent grade THF used alone proved to be the most practical and general solvent for the other aldehyde substrates.

**Table 2.14** Effect of solvents on the PTC catalyzed glycolate aldol reaction.

<table>
<thead>
<tr>
<th>solvent</th>
<th>aldehyde load.</th>
<th>time</th>
<th>temp. (°C)</th>
<th>yield%</th>
<th>ee%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tol.</td>
<td>8 eq.</td>
<td>&gt; 1day</td>
<td>-45</td>
<td>Trace</td>
<td></td>
</tr>
<tr>
<td>DCM:Hex (3:1)</td>
<td>8 eq.</td>
<td>&gt; 1day</td>
<td>-45</td>
<td>Trace</td>
<td></td>
</tr>
<tr>
<td>THF</td>
<td>8 eq.</td>
<td>1 day</td>
<td>-45</td>
<td>35</td>
<td>75</td>
</tr>
<tr>
<td>THF</td>
<td>8 eq.</td>
<td>2 days</td>
<td>-45</td>
<td>49</td>
<td>67</td>
</tr>
<tr>
<td>THF (MS 4Å)</td>
<td>8 eq.</td>
<td>1 day</td>
<td>-45</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>reagent THF</td>
<td>2 eq.</td>
<td>1.5 h</td>
<td>-45</td>
<td>78</td>
<td>75</td>
</tr>
<tr>
<td>reagent DME</td>
<td>8 eq.</td>
<td>1 day</td>
<td>-45</td>
<td>62</td>
<td>78</td>
</tr>
<tr>
<td>DME</td>
<td>8 eq.</td>
<td>1 day</td>
<td>-45</td>
<td>19</td>
<td>37</td>
</tr>
<tr>
<td>reagent DME + 3% H₂O</td>
<td>8 eq.</td>
<td>1 day</td>
<td>-45</td>
<td>TMS removal</td>
<td></td>
</tr>
<tr>
<td>reagent THF</td>
<td>2 eq</td>
<td>1 day</td>
<td>-55</td>
<td>76</td>
<td>80</td>
</tr>
<tr>
<td>THF/DMF</td>
<td>8 eq.</td>
<td>19 h</td>
<td>-78</td>
<td>87</td>
<td>80</td>
</tr>
</tbody>
</table>
Using the corresponding cinchonidinium catalyst 68-CD⁺HF₂⁻, the isolated yield increased to 52%; however the selectivity dropped to 41% ee (Table 2.15). Use of the Corey-Lygo catalyst 61-CN⁺HF₂⁻ extended the reaction time and improved the selectivity (78% ee), but gave a lower yield (52%). Using the optimal catalyst 68-CN⁺HF₂⁻, the temperature was lowered to -55 °C, to give 90 in 76% yield and 80% ee. Use of the novel difluoroanthracenyl catalyst 94-F₂-CN⁺HF₂⁻, recently found in the bromide form to give highly selective glycine alkylation⁷, improved the aldol reaction in 90 with an 83% ee. Unfortunately, the isolated yield dropped to 40% in this case.
Table 2.15 Effect of silyl enol ether substrates and catalysts on the PTC aldol.

<table>
<thead>
<tr>
<th>Ar</th>
<th>R</th>
<th>catalyst</th>
<th>% yield</th>
<th>syn:anti</th>
<th>ee% syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,5-diMePh</td>
<td>DPM</td>
<td>68-CN⁻HF₂⁻</td>
<td>76</td>
<td>&gt; 99:1</td>
<td>80</td>
</tr>
<tr>
<td>2,5-diMePh</td>
<td>DPM</td>
<td>68-CD⁻HF₂⁻</td>
<td>52</td>
<td>&gt; 99:1</td>
<td>41</td>
</tr>
<tr>
<td>2,5-diMePh</td>
<td>DPM</td>
<td>61-CN⁻HF₂⁻</td>
<td>52</td>
<td>&gt; 99:1</td>
<td>78</td>
</tr>
<tr>
<td>2,5-diMePh</td>
<td>DPM</td>
<td>94-F₂-CN⁻HF₂⁻</td>
<td>40</td>
<td>&gt; 99:1</td>
<td>83</td>
</tr>
<tr>
<td>2,5-diMePh</td>
<td>Bn</td>
<td>68-CN⁻HF₂⁻</td>
<td>41</td>
<td>&gt; 99:1</td>
<td>86</td>
</tr>
<tr>
<td>Ph</td>
<td>DPM</td>
<td>68-CN⁻HF₂⁻</td>
<td>58</td>
<td>6.3:1</td>
<td>15</td>
</tr>
<tr>
<td>2-MePh</td>
<td>DPM</td>
<td>68-CN⁻HF₂⁻</td>
<td>23</td>
<td>&gt; 99:1</td>
<td>52</td>
</tr>
<tr>
<td>4-MePh</td>
<td>DPM</td>
<td>68-CN⁻HF₂⁻</td>
<td>18</td>
<td>3:1</td>
<td>6</td>
</tr>
<tr>
<td>2,4-diMePh</td>
<td>DPM</td>
<td>68-CN⁻HF₂⁻</td>
<td>16</td>
<td>&gt; 99:1</td>
<td>60</td>
</tr>
</tbody>
</table>

Variations of the aryl group of the silyl enol ether 93 were also explored. With phenyl in place of the 2,5-dimethoxyphenyl group, the aldol product with benzaldehyde was obtained in a 58% yield with a greatly reduced enantiomeric excess of 15%. With the 2-methoxyphenyl substrate variation, a 52% ee was obtained with a 23% yield. 4-Methoxy- and 2,4-methoxy variants gave only trace aldol product (18%) with poor diastereoselectivity (syn/anti = 3:1) (Table 2.15).

Optimized conditions with 68-CN⁻HF₂⁻ in reagent grade THF were used with a
wide range of aldehydes (Table 2.16). In most cases, a single syn-diastereomer 90 was again produced. Aromatic aldehydes all reacted with good to excellent results. 4-Biphenylcarboxaldehyde and o-methoxybenzaldehyde with yields and selectivities from 70% to 80% were typical. 2-Naphthaldehyde was also efficient again, with a single syn-diastereomer in 79% ee. Unfortunately, alkyl and α,β-unsaturated aldehydes reacted with lower yield and selectivity. Although conclusions concerning mechanistic details are premature at this time, it can be pointed out that the C2 stereocenter in the product 90 is S using either the cinchonine catalyst 68-CN or cinchonidine 68-CD as demonstrated below. This is consistent with the major S-isomer obtained previously for alkylation of 88 using 68-CD.
Table 2.16 The scope of the PTC catalyzed glycolate aldol reaction.

<table>
<thead>
<tr>
<th>RCHO</th>
<th>% yield</th>
<th>syn:anti</th>
<th>ee% syn</th>
<th>RCHO</th>
<th>% yield</th>
<th>syn:anti</th>
<th>ee% syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>76</td>
<td>&gt;99:1</td>
<td>80</td>
<td>Napth</td>
<td>69</td>
<td>&gt;99:1</td>
<td>79</td>
</tr>
<tr>
<td>4-MeOPh</td>
<td>30</td>
<td>&gt;99:1</td>
<td>78</td>
<td>2-MeOPh</td>
<td>70</td>
<td>&gt;99:1</td>
<td>77</td>
</tr>
<tr>
<td>4-MePh</td>
<td>58</td>
<td>&gt;99:1</td>
<td>78</td>
<td>2-MePh</td>
<td>57</td>
<td>&gt;99:1</td>
<td>75</td>
</tr>
<tr>
<td>4-PhPh</td>
<td>77</td>
<td>&gt;99:1</td>
<td>75</td>
<td>2-PhPh</td>
<td>45</td>
<td>20:1</td>
<td>83</td>
</tr>
<tr>
<td>4-ClPh</td>
<td>85</td>
<td>10:1</td>
<td>65</td>
<td>4-NO₂Ph</td>
<td>20</td>
<td>4:1</td>
<td>35</td>
</tr>
<tr>
<td>3-furyl</td>
<td>33</td>
<td>&gt;99:1</td>
<td>62</td>
<td>2-furyl</td>
<td>86</td>
<td>6:1</td>
<td>53</td>
</tr>
<tr>
<td>Ph(CH)₂</td>
<td>36</td>
<td>&gt;99:1</td>
<td>44</td>
<td>Ph(CH)₂</td>
<td>23</td>
<td>2:1</td>
<td>45</td>
</tr>
<tr>
<td>²Pr</td>
<td>11</td>
<td>2:1</td>
<td>43</td>
<td>BnOCH₂</td>
<td>25</td>
<td>1:1</td>
<td>33</td>
</tr>
<tr>
<td>³Hex</td>
<td>11</td>
<td>5:1</td>
<td>39</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fortunately, the enantioselectivity of the aldol product was significantly increased on crystallization (Figure 2.10). The major (2S,3R) syn-diastereomer 90, obtained from addition to benzaldehyde originally at 80% ee, was enriched to 95% ee (65%) following crystallization and filtration of a racemic, conglomerant solid. Elaboration to differentially protected products and proof of the absolute stereochemistry were carried out from this intermediate. Treatment with acetyl chloride and pyridine gave an acetate intermediate, which was unambiguously confirmed by single-crystal X-ray
analysis (Figure 2.11). This intermediate was then subjected to titanium chloride at low temperature to effect removal of the diphenylmethyl (DPM) group. The resultant hydroxy ketone 95 (Ar = 2,5-dimethoxyphenyl) was subjected to Shibizaki modified Baeyer-Villiger conditions, involving stiochiometric TMS peroxide, catalytic tin tetrachloride, and (±)-cyclohexyl bis-sulfonamide, to give aryl ester 96 with a 79% isolated yield. Transesterification, with concomitant acetate hydrolysis, gave the known (S,R)-diol methyl ester 97.29

![Chemical structure](image)

**Figure 2.10** Structural proof and elaboration.
2.3. Conclusion

In summary, a new approach to asymmetric glycolate aldol additions has been developed using readily available catalysts under mild PTC conditions. Differentially protected syn-1,2-diols are produced with very high diastereoselectivity and good
enantioselectivity. Simple recrystallization and Baeyer-Villiger oxidation generate highly enantioenriched ester diol products. Refinements to the substrate and catalyst are anticipated to lead to further improvements and synthetic applications.

2.4. References


Chapter 3. Design and Synthesis of 8,9-Methylamido-Geldanamycin, an Amide Isostere for a Macrolide Antitumor Antibiotic

3.1. Introduction

3.1.1. Isolation and Bioactivity

Geldanamycin 98, an anti-tumor Hsp90 inhibitor, was isolated from *Streptomyces hygroscopicus* var. *geldanus* var. *nova* (UC5208) in 1970 by researchers at Upjohn. Its structure was determined by Rinehart and coworkers shortly thereafter. Different from previously discovered anasamycin antibiotics (e.g. rifamycins, streptovaricins, tolypomycins), which have napthoquinone nuclei, it is the first member containing a benzoquinone nucleus. Other benzoquinone anasamycin antibiotics 99, such as macbecin and herbimycin, were disclosed later (Figure 3.1).

![Geldanamycin](image)

**Figure 3.1** Benzoquinone anasamycins.

Geldanamycin demonstrated moderate activity in vitro against protazoa, bacteria, and fungi (MIC: 2-100 μM/ml), and extreme activity against KB cells (<0.001 μM/ml).
and L1210 (<0.002 µM/ml). In vivo, geldanamycin was found to be orally active against the parasite *syphacia oblevata* at 0.5 mg/mouse/day for 4 days.\textsuperscript{1} Later studies have found that geldanamycin was the most potent member of the ansamycin family, showing broad activity against the NCI 60 cell-line panel (13 nM avg., 70nM SKBr-3 cells).\textsuperscript{9} 17-Allylamino-geldanamycin, a semi-synthetic compound, is currently in phase-III clinical trials.\textsuperscript{10}

While initially thought to be a tyrosine kinase inhibitor, Neckers and coworkers showed that geldanamycin binds to Hsp90, an abundant cytosolic heat shock chaperone protein that regulates cell signaling.\textsuperscript{11} Subsequent studies showed that geldanamycin binds to the ATP binding site (775 nM) of the 25 kD N-terminal domain of Hsp90, leading to inhibition of its protein folding and ATPase activities, which causes client protein degradation and cell death.\textsuperscript{12} Hsp90’s ATPase activity is essential for function in vivo, which includes complex formation with many other cofactor proteins such as Hsp70, Hsp40, and FKBP53.\textsuperscript{13} Although Hsp90 is abundantly present in both tumor and normal cells, recent studies have confirmed that nearly all Hsp90 in cancer cells is found in multi-chaperone complexes.\textsuperscript{14} In contrast, Hsp90 in normal cells primarily exists in free, uncomplexed form. A complexed form of Hsp90, consisting of the proteins Hsp70, Hsp40, Hop, and p23, is bound by geldanamycin with high affinity (12 nM), while Hsp90, isolated from normal cells, is bound by geldanamycin much less tightly (2-6 µM). It is believed that a conformational change, imposed by the other chaperone complex members, occurs in Hsp90 to cause to tighter geldanamycin binding.
3.1.2. Design of Geldanamycin Diamide Analog

X-ray crystal structures of the Hsp90-geldanamycin complex show that geldanamycin adopts a “C-clamp” shaped conformation that is higher in energy (+14.9 kcal/mol) than its free, unbound solution conformation (Figure 3.2).\textsuperscript{9,15} The bound conformation possesses an \textit{s-cis} amide with a dihydral angle (C22-N-C-O) of -165° while the free conformation possesses a more stable \textit{s-trans} arrangement (8°). It was proposed that the Ser113 residue of Hsp90 catalyzed this conformational change, breeching the amide rotation barrier (>20 kcais) through an enol-keto tautomeration pathway.\textsuperscript{16} It may be that the chaperone-complexed Hsp90 is a better catalyst for this conformation change process than the free form of Hsp90.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structure.png}
\caption{Structure of geldanamycin-Hsp90 binding complex.}
\end{figure}

Our plan is to create and test compounds that are biased toward the chaperone complexed form of Hsp90. Analogs that favor the \textit{s-cis} “C-clamp” conformation should show improved activity and selectivity for binding complexed Hsp90. Targeted high affinity binding for complexed Hsp90 will allow for lower dosage
levels and possess lower activity in normal cells, leading to lowered toxicity.\textsuperscript{17}

The CLogP of geldanamycin at 2.06 is well below the Lipinski “rule of five” limit of 5 and it might be considered ideal, yet water solubility (0.05 mg/mL) and bioavailability present significant problems with assays and in clinical work.\textsuperscript{17} Pharmokinetics, tissue distribution, and metabolism studies have shown that injected geldanamycin and 17-Allylamino-geldanamycin have moderate to good bioavailability (50-100%), from monitoring plasma levels following a subtoxic dosage (5 min, 10 mg/kg), while oral administration is poor (<24%).\textsuperscript{17, 18} Hepatic, gastrointestinal, and nephrotoxicity have been noted in these studies with intravenous injection (2-60 mg/kg) in animals, showing poor to moderate tolerance. Studies with cytochrome P-450 reductase and super oxide formation suggest that most cellular geldanamycin toxicity is independent of Hsp90 kinase complex inhibition.\textsuperscript{19} The hypothesis is that a more potent, water soluble analog of geldanamycin, constrained to the bound “C-clamp” conformation, can bind selectively to the kinase complexed form of Hsp90 with higher affinity, allowing for lower dosage levels.

Based on both the binding mechanism and an energetics bias, the C8,9 olefin is substituted by an $N$-methylamide surrogate. Conformational analysis and ab-initio quantum chemical calculations have been performed to assess the suitability of this amide substitution. The geometry of geldanamycin and the analog were optimized with density functional theory at the B3LYP/6-31G* level by Dr. Y. S. Lee (NIH, NCI). The Hsp90 bound amide $s$-cis “C-clamp” conformation of geldanamycin is 14 kcals/mol higher in energy than the unbound $s$-trans conformation ($K_{eq}>10^{11}$). The C8
Methyl occupies an axial position with the double bond adopting a typical \( \text{sp}^2 \) edgewise orientation. The C8,9-\textit{trans} amide will enforce the bound conformation with the carbonyl and the C10 hydrogen coplanar and the \( N \)-methyl and C7-H coplanar.\textsuperscript{20} We were pleased to find that the energy difference between the bound \textit{s-cis} amide conformation and the free form dramatically reduces to +6.3 kcal/mol. This amide substitution also services to both simplify the synthesis and to create a more polar, water soluble template. The C8,9 amide analog shows a CLog P of 1.07. The analog synthesis is convergent with the additional amide, allowing for intermolecular amide formation, followed by macrolactam formation.

\[
\Delta \Delta G_{\text{cis-trans}}: +14 \text{ kcal/mol} \\
\text{CLogP: 2.06}
\]

\[
\Delta \Delta G_{\text{cis-trans}}: +6.3 \text{ kcal/mol} \\
\text{CLogP: 1.07}
\]

\textbf{Figure 3.3} Geldanamycin and geldanamycin diamide analog.

\[\text{3.1.3. Synthesis of Geldanamycin}\]

As a most potent antitumor antibiotic ansamycin family member, geldanamycin has ironically received less synthetic attention than the closely related macbecnin and herbimycin, for which four total syntheses have been done.\textsuperscript{21} The first and only total
synthesis of geldanamycin was accomplished by Andrus’ group using a 41-step linear route from 1,2,4-trimethoxybenzene 101. The key steps involved a chiral dioxanone auxiliary (102)-controlled asymmetric anti-glycolate aldol reaction to set the C11,12 hydroxyl-methoxyl stereochemistry; also a chiral norephendrine auxiliary (103)-controlled syn-aldol to set the methoxy-urethane stereochemistry at C6,7. The macrolactam ring was formed by amide coupling reagent Bop-Cl. Using the previously reported oxidative demethylation with simpler trimethoxybenzene, azaquinone was obtained instead of the desired p-quinone. Finally, nitric acid was able to form o-quinone geldanamycin as the major product 10:1 over the desired p-quinone geldanamycin 98.

Figure 3.4 Total synthesis of geldanamycin.
A ring-closing metathesis strategy was also explored to develop a more efficient and convergent synthetic route. The Grubbs imidazolium benzylidene ruthenium catalyst failed to give the ring closing product under various solvents, concentrations, modes of addition, and additives. Although this strategy has been successfully applied to close medium and large rings, the combination of the ring size of geldanamycin and a bulky trisubstituted olefin substrate led to an unsuccessful result.

**Figure 3.5** Ring-closing metathesis strategy.

A solution to the problem of selective \(p\)-quinone formation was developed using a 1,4-di-MOM protected model substrate \(105\). The MOM protecting groups were selectively removed with in situ generated TMSI. The resulting hydroquinone intermediate was oxidized to \(p\)-quinone \(106\) using mild Rapoport conditions with Pd/C in the presence of air.
3.2. Results and Discussions

3.2.1. Retro-Synthesis of 8,9-Methylamido-Geldanamycin Analog

With our newly developed selective para-quinone formation strategy, the desired diamide product 100 was planned from di-MOM precursor 107 (Figure 3.7). With the introduction of the new amide bond, an efficient and convergent route was successfully used to assemble the precursor 107 from diamine 108 and diacid 109. The 8,9-methylamide bond was formed first to couple these two pieces together, followed by deprotection of the aniline and acid and another amide coupling to form the macrolactam 107. The right-hand piece 108 was synthesized using Evans oxazolidinone auxiliary-controlled alkylation, dioxanone auxiliary-controlled anti-glycolate aldol reaction, and substrate controlled asymmetric reductive amination. The left-hand piece 109 was assembled with Horner-Wadsworth-Emmons olefin coupling, Ando olefin coupling, and norephendrine auxiliary controlled syn-glycolate aldol.
3.2.2 Synthesis of the Left Hand Piece of the 8,9-Methylamido-Geldanamycin

The anti-glycolate aldol substrate 114 was made from methoxy hydroquinone 110 according to our previously published procedure (Figure 3.8). A variety of reaction conditions for the nitration and MOM reprotction were also explored to improve yields. Because of the strong acidic condition in the nitration step, removal of one MOM protecting group was inevitable. Recently, Blagg and Shen used a nitration reaction to synthesize an unnatural Hsp90 binding compound, radester, a hybrid of radicicol and geldanamycin. The di-MOM protecting group on their substrate was intact under ammonium nitrate and trifluoroacetic anhydride conditions (Figure 3.9). A very similar nitration substrate 117 was obtained from benzaldehyde 111 by
reduction with NaBH₄. Subjecting benzyl alcohol 117 to the same reaction condition, only a small amount of desired product 118 was formed, together with the benzyl alcohol recovered (Figure 3.9). Extended reaction time, higher nitration reagent loading, and various temperature ranges did not result in a higher yield. Other mild nitration conditions, such as Cu(NO₃)₂/Ac₂O and NO₂BF₄/DMF, produced multiple products or decomposition.

Figure 3.8 Synthesis of the anti-aldol aldehyde substrate.

Figure 3.9 Nitration of the aromatic core.
Using excess amount of KH in THF with phase transfer catalyst \( n\text{Bu}_4\text{N}^+\text{I}^- \) as indicated in our previous publication,\(^{28}\) we were not able to achieve a good yield. After extended reaction time (two days), a significant amount of decarbonylative product 119 was isolated, and the structure was confirmed by NMR and X-ray analysis (Figure 3.10). With a milder organic base (\( \text{Et}_3\text{N} \)) and a shorter time period (one hour), the di-MOM protected product 113 was obtained with an 81% yield. Switching the triethylamine to inorganic base potassium carbonate further increased the yield to 91% (Figure 3.8).

\[
\text{KH, MOMCl} \quad \text{MeO} \quad \text{OMOM} \quad \text{MeO} \quad \text{OMOM} \\
\text{OHC} \quad \text{OH} \quad \text{NO}_2 \quad \text{OHC} \quad \text{OH} \quad \text{NO}_2 \\
112 \quad 113 \quad 119
\]

**Figure 3.10** MOM ether reinstallation.

\( S,S\)-Bis-4-methoxyphenyldioxanone 102 was treated with 2 equiv of dicyclohexylboron triflate and 2.5 equiv of \( \text{Et}_3\text{N} \) to give the locked \( E \)-boron enolate (Figure 3.11). Aldehyde 114 was then added to the enolate solution to generate the *anti*-glycolate aldol adduct 120 in 70% yield with 8:1 selectivity.\(^{23}\) The attack of the aldehyde is constrained to a closed Zimmerman-Traxler chair arrangement on the *si*-enolate face away from the C5 methoxyphenyl. The amount of the boron triflate and triethylamine is critical. Too much boron triflate (3 equiv) led to very poor...
reactivity and only a tiny amount of aldol product. Converting the newly generated secondary alcohol as a methoxy group with Meerwein salt gave 121 with quantitative yield. NaOMe (1 mol%) catalyzed lactone-ester exchange provided methylester 122. A higher amount of NaOMe (10 mol%) generated multiple products. The benzyl ether was then oxidatively removed using CAN and the resulting alcohol was protected with TBSCI to give 123. Other benzyl ether protecting group cleavage methods, such as DDQ or Pd/C catalyzed hydrogenation, gave multiple products.

![Figure 3.11 Application of the anti-glycolate aldol reaction.](image)

The methyl ketone intermediate 125 was obtained through a three-step sequence from ester 123. DIBAL-H reduced the ester 123 to aldehyde 124 at low temperature (-78 °C) in CH₂Cl₂. A 1.5 M DIBAL-H toluene solution was added to the reaction along the flask’s inside wall to prevent formation of the over-reduced alcohol product.
Methylation with trimethylaluminum to the aldehyde 124 gave a pair of secondary alcohol diastereomers, which were oxidized to methyl ketone 125 by Dess-Martin periodinane.\textsuperscript{35} The success of the reduction of nitrobenzene 125 to aniline 126 using Pd/C catalyzed hydrogenation depended on the nature of the alcohol solvent. Primary alcohols, such as methanol or ethanol, gave \textit{N}-methyl or \textit{N}-ethyl anilines in quantitative yield. With isopropyl alcohol as the solvent, the desired aniline 126 was obtained. The nitro reduction \textit{N}-alkylation cascade process was unprecedented with methyl and ethyl alcohol. It is believed that primary alcohols were oxidized to aldehydes through a palladium catalyzed oxidation reaction. The resulting aldehydes reacted with aniline 126 to give imine intermediates, which were then reduced to the \textit{N}-alkyl aniline under hydrogenation conditions. Bulkier alcohols, however, may be more slowly oxidized to ketones. Or, the resulting ketones were not as favorable as aldehydes to form imine intermediates. Aniline 126 was protected as the allylcarbamate 127. The ketone group was converted to secondary amine 108 through a titanium(IV) isopropoxide mediated asymmetric reductive amination using the modified conditions of Bhattacharyya.\textsuperscript{31} The diastereoselectivity was high (>20:1), and the absolute configuration of the newly generated C10 stereocenter was assumed to be \textit{syn} in accord with a chelation controlled model. This assignment is tentative, awaiting an unambiguous X-ray crystal structure of derivatives of this intermediate.

Magnesium perchlorate was also tried in this amination transformation\textsuperscript{36} as a chelation metal reagent in the presence of methylamine and sodium borohydride or sodium cyanoborohydride; however, poor yield and selectivity were obtained.
A Weinreb amide\textsuperscript{37} approach was also explored to access the methyl ketone \textsuperscript{125}. Attempts to synthesize Weinreb amides through trimethylaluminum or Grignard reagents following one-step ester-amide exchange have failed with intermediates \textsuperscript{121}, \textsuperscript{123}, and \textsuperscript{128} (Figure 3.13). Finally, ester \textsuperscript{123} was hydrolyzed to acid \textsuperscript{129} in the presence of potassium trimethylsilylolate (Figure 3.14).\textsuperscript{38} Other bases, such as LiOH, NaOH or KOH were not able to hydrolyze this ester in dioxane-H\textsubscript{2}O, with or without H\textsubscript{2}O\textsubscript{2}. Weinreb amide \textsuperscript{130} was then successfully prepared from acid \textsuperscript{129} with 1,1\textsuperscript{'}-carbonyldiimidazole (CDI) as the amide coupling reagent. Surprisingly, EDCI was not be able to produce the desired amide product, and multiple products were generated. Attempts to convert the Weinreb amide \textsuperscript{130} to methyl ketone were unsuccessful with Grignard reagent or methyl lithium. It is known that nitro aryl
compounds are able to react with Grignard reagents.

Figure 3.13 Weinreb amide synthesis using one-step ester-amide exchange strategy.

Figure 3.14 Weinreb amide approach to synthesis the methyl ketone intermediate.

3.2.3. Synthesis of the Right Hand Piece of the 8,9-Methylamido-Geldanamycin

4-Methoxybenzyl protected α-hydroxyacetaldehyde 131 was prepared according to Smith’s procedure (Figure 3.15). Using flash chromatography instead of distillation to purify the ozonolysis product greatly improved the yield to 93% from 53%. Our previously developed (−)-norephedrine-derived glycolate 103 reacted with
dicyclohexyl boron triflate and triethylamine, followed by addition of aldehyde 131, to generate syn aldol product 132 in 91% yield and >20:1 selectivity (Figure 3.15). The resulting free alcohol was then protected by TMSCl. The norephedrine auxiliary was removed by DIBAL-H mediated half-reduction, and aldehyde 134 was obtained. Although the yield of the half-reduction step was high enough, it took an extremely long time to purify the product by flash chromatography because the unreacted substrate, desired product, and norephedrine have similar Rf values and coelute. A two-step process was also developed by reducing the ester 133 into a primary alcohol intermediate and then oxidizing the alcohol to aldehyde 134. While lithium borohydride in THF did not provide a good yield (56%), addition of 3 equiv of methanol in the presence of 3 equiv of lithium borohydride in refluxing diethyl ether resulted in an 82% yield. It was believed that methanol was a good proton source for this reduction through hydrogen-bonding. Another possibility was that methoxy-substituted lithium borohydrides formed in situ were the actual reducing species. The alcohol was conveniently separated from the unreacted substrate and norephedrine. Dess-Martin periodinane successfully oxidized the alcohol to aldehyde 134 with a 90% yield. The combination of TPAP and NMO gave a much lower 67% yield.
To synthesize the Z-olefin intermediate 137, a Touchard modified Ando reagent 135 was successfully performed with aldehyde 134 in the presence of TMG and sodium iodide additive at -78 °C (Figure 3.16). Excellent yield (98%) and Z/E selectivity (>20:1) were obtained. For comparison, 2 equiv of the common Still-Gennari hexafluorophosphonate42 in the presence of KHMDS and 18-crown-6 did not completely convert the aldehyde 134 to olefin 136 after extended time. The ester 136 was reduced to a primary alcohol by DIBAL-H in diethyl ether at low temperature (-78 °C). Dess-Martin periodinane then oxidized the resulting alcohol to the enal 137.

Figure 3.16 Z-Olefination using Ando phosphonate.
Following Roush’s procedure, enal 137 was reacted with allyl ester phosphonate 138 together with lithium chloride and DBU at 0 °C to give the desired $E,Z$ diene ester 139 with excellent yield (98%) and selectivity (>20:1) (Figure 3.17). The PMB protecting group on diene ester 139 was oxidatively cleaved by DDQ in a mixed solvent of methylene chloride and water. CAN in acetonitrile and water was not a good alternative reagent for this deprotection, as the TES protecting group was removed before the PMB group. The newly generated alcohol 140 was oxidized to acid 142 through a two-step oxidation procedure. DMP oxidized the alcohol to aldehyde 141, which was further oxidized to acid 142 by sodium chlorite and sodium dihydrogen phosphate in a mixture of $t$-butanol, water, and 2-methyl-2-butene. One-step oxidation from alcohol 140 to acid 142 using PDC in DMF, or the combination of diacetoxyiodobenzene and TEMPO were futile. Other oxidation reagents, such as AgO or H$_2$O$_2$, were also tried in various solvents and temperatures; however, decomposition was observed.

**Figure 3.17** Completion of the left-hand piece of the geldanamycin diamide analog.
A more convergent route was also explored to synthesize the \( E,Z \)-dienoate 139 by a Horner-Wadsworth-Emmons reaction of the aldehyde 134 with unsaturated Still-Gennari\(^{42} \) or Touchard modified Ando phosphonates 144-146 (Figure 3.18).\(^{33} \) This strategy was recently applied in the total synthesis of (+)-macbecin\(^{21c} \) and (+)-damavaricin D\(^{44} \) with low selectivities (2.7:1, and 4:1, respectively) using the unsaturated Still-Gennari hexafluorophosphonates.

![Figure 3.18 Retrosynthetic analysis of the olefin coupling with unsaturated phosphonates.](image)

According to Nicolaou’s procedure,\(^{45} \) intermediate 149 was synthesized from (Z)-but-2-ene-1,4-diol through THP protection, Wittig reaction and THP deprotection (Figure 3.19). The bromination of the allyl alcohol 149 was accomplished by slowly adding methanesulfonyl chloride into a mixture of 149, lithium bromide and triethylamine in THF.\(^{46} \) The resulting bromide 150 was then submitted to Arbuzov conditions with 2,2,2-trifluoroethyl phosphite in the presence of a catalytic amount of tetrabutylammonium iodide to provide the unsaturated ethyl phosphonate 151 in 45%
Figure 3.19 Synthesis of the Still-Gennari ethyl phosphonate.

To synthesize the unsaturated allyl phosphonates 144 and 145, ethyl ester 148 was converted to allyl ester 152 in the presence of lithium bromide, DBU, and allyl alcohol, to give an 88% yield (Figure 3.20). Deprotection, bromination and Arbuzov reaction with tris(2,2,2-trifluoroethyl) phosphite and bis(2-tert-butylphenyl)ethyl phosphite provided unsaturated allyl phosphonates 144 and 145, respectively. Olefination between aldehyde 147 or 154 and Horner-Wadsworth-Emmons reagent 138, unfortunately, gave poor E/Z selectivity (4:1 or 1.2:1).
Aldehyde 134 was slowly added to an ether solution of Still-Gennari phosphonate anion, which was generated by deprotonation of the corresponding phosphonate in the presence of KHMDS or n-BuLi, at -78 °C, over one hour (Figure 3.21).44 When KHMDS was used as base, 1.4 equivalents of allyl phosphonate 146 gave a better yield than ethyl phosphonate 144 with the same E,Z-selectivity. Switching the base to n-BuLi, eight equivalents of allyl phosphonate 146 gave better selectivity (4:1) but lower yield (50%). Deprotonation of Ando phosphonate 145 by TMG in THF at 0 °C gave a solution of the corresponding phosphonate anion.33 Aldehyde 134 was slowly added to this anion solution at -78 °C to generate the dienoate 139 with a 61% yield devoid of selectivity.
Table 3.1 Olefin coupling with unsaturated phosphonates.

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>conditions</th>
<th>% yield</th>
<th>(E,Z): (E,E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et</td>
<td>CH₂CF₃</td>
<td>KHMDS, Et₂O, -78 °C</td>
<td>30</td>
<td>2:1</td>
</tr>
<tr>
<td>Allyl</td>
<td>CH₂CF₃</td>
<td>KHMDS, Et₂O, -78 °C</td>
<td>76</td>
<td>2:1</td>
</tr>
<tr>
<td>Allyl</td>
<td>CH₂CF₃</td>
<td>n-BuLi, Et₂O, -78 °C</td>
<td>50</td>
<td>4:1</td>
</tr>
<tr>
<td>Allyl</td>
<td>o-tBuPh</td>
<td>NaI, THF, TMG (0 °C), aldehyde (-78 °C)</td>
<td>61</td>
<td>1:1</td>
</tr>
</tbody>
</table>

3.2.4. Coupling, Cyclization, and Completion of Geldanamycin Diamide

Initially, methyl ketone 125 was converted to secondary amine 155 with 85% yield by titanium(IV) isopropoxide mediated reductive amination.³¹ HATU and N,N-diisopropylethylamine coupled the resulting amine 155 and acid 109 to give intermediate 156. Other amide coupling reagents, such as PyBrop, BOP-Cl, and DEPC, did not give good reactivity.⁴⁹ A variety of reductive reagents, such as NaBH₄, Zn/NH₄Cl/MeOH, SnCl₂, and Pd/C/(NH₄)O₂CH, failed to convert the nitrobenzene 156 to aniline 157. Allyl ester 156 was then removed using palladium tetrakistriphenylphosphine and morpholine to generate the acid 158.⁵⁰ Unfortunately,
under all reductive conditions attempted, the aniline 159 was not obtained.

Figure 3.21 Reduction of the nitro benzene after 8,9-amide bond formation.

Amine 108 was then successfully coupled with acid 109 through an amide bond formation under HATU and DIPEA at 0 °C to generate the protected amino acid 160 as a pair of rotamers, which complicated the NMR analysis. Simultaneously removing both allyl ester and allylcarbamate protecting groups by Pd(PPh₃)₄ and morpholine
produced an amino acid intermediate.\textsuperscript{50} Use of HATU with DIPEA and catalytic amount of DMAP in methylene chloride (0.0005M) provided the macrolactam 161. Following Kocovsky’s procedure,\textsuperscript{51} trichloroacetyl isocyanate was employed to form the protected carbamate. Deprotection with potassium carbonate produced the C7 urethane 107 in 86\% yield. Deprotection of both MOM and TBS ether protecting groups with in situ generated TMSI provided the dihydroxyquinone, which was oxidized to the desired \textit{p}-quinone macrolactam 100 by a catalytic amount of palladium on carbon and with the flask open to air.\textsuperscript{28,29}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{geldanamycin_diamide.png}
\caption{Figure 3.22 coupling, cyclization, and completion of Geldanamycin diamide.}
\end{figure}
3.3. Conclusion and Future Work

In summary, the first geldanamycin diamide analog has been made through a convergent route, involving 27 greatly simplified steps in its longest linear sequence. New synthesis methodologies, including auxiliary controlled asymmetric anti-glycolate aldol, syn-norephedrine aldol, and selective p-quinone formation, were used. This route can be applied to the synthesis of other GA-diamide analogs. Preliminary bioactivity assessment of this analog showed 100 times less potency than the geldanamycin natural product in cell and Hsp90 assays. This may due to the newly introduced 8,9-methylamido group, or the configuration of the C10 stereocenter. More analogs can be designed and synthesized to improve the bioactivity and further simplify the synthesis. Such might include inverting the C14 stereocenter, removing the C10 methyl group, removing the N-methyl group, and substitution of the Z, E diene by benzene.

3.4. References


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Chapter 4. Experimental Details and Data

4.1. General Method and Materials

Air and water sensitive reactions were performed in flame-dried glassware under a nitrogen atmosphere. Water sensitive reagents were introduced via dry syringe or cannula. Methylene chloride, toluene, benzene, THF, diethyl ether, acetonitrile, DMSO, DMF, methanol, triethylamine and pyridine were dried by passing through columns of activated alumina. Hexanes, 1,2-dimethoxyethane, p-xylene were distilled with CaH₂. Other solvents, such as ethanol, isopropyl alcohol, acetone, and chloroform, were stored over molecular sieves. Reagents were purchased from Aldrich and Lancaster. Flash chromatography was carried out using 60-230 mesh silica gel. Radial chromatography was performed using 1, and 2 mm plates loaded with 230-400 mesh PF-254 gypsum bound silica. Analytical thin-layer chromatography (TLC) was performed with Merck silica gel 60 F₂₅₄, 0.25 mm pre-coated TLC plates. TLC plates were visualized using UV₂₅₄ and cerium molybdate with charring. All ¹H NMR spectra were obtained with either 300 or 500 MHz Varian spectrometers using TMS (0.0 ppm) or chloroform (7.27 ppm) as an internal reference. Signals are reported as m (multiplet), s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), and dd (doublet doublet); and coupling constants are reported in Hertz (Hz). ¹³C NMR spectra were obtained with either 75 or 125 MHz Varian spectrometers using chloroform (77.23 ppm) as the internal standard. Mass spectral data (HRMS, CI, EI, FAB) were obtained from the Brigham Young
University mass spectrometry facility. Optical rotations were obtained on a Perkin Elmer 241 polarimeter using the sodium D line at ambient temperature. Low temperatures were maintained using an immersion cooler with a cooling probe placed in an acetone bath. Combustion analysis was performed by M-H-W Laboratories, Phoenix, AZ.

4.2. Synthesis of Resveratrol and Its Acetyl and Fluoro Analogs

4.2.1. Synthesis of Resveratrol

\[
\begin{align*}
\text{AcO} & \quad \text{OAc} \\
& \quad \text{OH} \\
& \quad \text{OAc}
\end{align*}
\]

Preparation of 3,5-diacetoxybenzoic acid

To a stirred solution of 3,5-dihydroxybenzoic acid (7.71 g, 50 mmol) in EtOAc (110 mL) were added acetic anhydride (12.25 mL, 130 mmol) and pyridine (8.08 mL, 100 mmol) in an ice-water bath under a nitrogen atmosphere. The mixture was stirred at 0 °C for 40 min and then stirred at ambient temperature for 4 h. 98% Formic acid (2.36 mL, 60 mmol) was added and the resulting mixture was stirred for 1 h. Then, the mixture was poured into water and extracted with EtOAc. The organic phase was washed with water and brine, dried over Na₂SO₄, filtered, and evaporated under vacuum. Purification of the residue via recrystallization from n-heptane/EtOAc provided 3,5-diacetoxybenzoic acid (8.97 g, 75%) as a white solid. Data are: \(^1\)H NMR (CDCl₃, 300 MHz) \(\delta\) 12.1 (bs, 1H), 7.73 (d, \(J = 2.1\) Hz, 2H), 7.21 (t, \(J = 2.1\) Hz, 1H),
2.32 (s, 6H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 170.4, 169.0, 151.2, 131.5, 121.3, 121.0, 21.2; mp = 161–162 °C; HRMS (EI$^+$) found 238.0475 M$^+$, calcd 238.0477 for C$_{11}$H$_{10}$O$_6$; Anal. Calcd for C$_{11}$H$_{10}$O$_6$: C, 55.47; H, 4.23. Found: C, 55.62; H, 4.37.

Preparation of 3,5-diacetoxybenzoyl chloride (13)

To a mixture of 3,5-diacetoxybenzoic acid (8.00 g, 33.59 mmol) and DMF (5 drops) added fresh distilled thionyl chloride (16 mL). The mixture was stirred for 15 min under nitrogen atmosphere at ambient temperature. Then it was refluxed for 2 h at 80 °C in a hot water bath. The excess thionyl chloride was evaporated under vacuum and toluene was added. Insoluble yellow solid was discarded. Toluene was evaporated under reduced pressure to give 3,5-diacetoxybenzoyl chloride 13 (8.23g, 96%) as a white solid. Data are: $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.75 (d, $J = 2.1$ Hz, 2H), 7.29 (t, $J = 2.1$ Hz, 1H), 2.34 (s, 6H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 168.8, 167.0, 151.4, 135.3, 122.8, 122.0, 21.2; mp = 89.5–91 °C; HRMS (EI$^+$) found 256.0130 M$^+$, calcd 256.0139 for C$_{11}$H$_9$O$_5$Cl; Anal. Calcd for C$_{11}$H$_9$O$_5$Cl: C, 51.48; H, 3.53. Found: C, 51.60; H, 3.68.
Preparation of resveratrol triacetate (10)

A 100 mL round bottom flask was charged with p-xylene (56 mL), Pd(OAc)$_2$ (62.86 mg, 0.28 mmol), $N,N$-bis-(2,6-diisopropylphenyl)-4,5-dihydro imidazolium chloride 16 (119.53 mg, 0.28 mmol), 3,5-diacetoxybenzoyl chloride 13 (7.19 g, 28 mmol), 4-acetoxystyrene 14 (5.35 mL, 33.6 mmol), and $N$-ethyl morpholine (4.2 mL, 33.6 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to ambient temperature. And the whole mixture was purified by a flash chromatography (20% EtOAc/hexanes) to give resveratrol triacetate 10 (6.95 g, 70%) as a white solid. Data are: $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.50 (d, $J = 9.0$ Hz, 2H), 7.12-6.94 (m, 6H), 6.82 (t, $J = 2.1$ Hz, 1H), 2.31 (s, 9H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 169.6, 169.2, 151.5, 150.6, 139.7, 134.7, 129.9, 127.9, 127.4, 122.1, 117.1, 114.6, 21.4; mp = 116-118 °C; HRMS (EI$^+$) found 354.1118 M$^+$, calcd 354.1103 for C$_{20}$H$_{18}$O$_6$; Anal. Calcd for C$_{20}$H$_{18}$O$_6$: C, 67.79, H, 5.12. Found: C, 67.93, H, 5.26.

Preparation of resveratrol (1)

To a stirred solution of resveratrol triacetate 10 (6.02 g, 17 mmol) in THF (170 mL) added a solution of NaOH (4.67 g, 119 mmol) in water (170 mL). The mixture was
stirred at ambient temperature for 2 h. Then 5 N HCl was added until the pH is 4. The solution is evaporated in vacuo to remove THF. Then it was extracted with EtOAc. The organic phase was washed with water and brine and dried over Na₂SO₄. The dried solution was filtered and evaporated. Purification via flash chromatography (35% EtOAc/hexane) gave resveratrol 1 (3.43 g, 88%) as a pale yellow solid. Data are: ¹H NMR (aceton-d₆, 300 MHz) δ 8.45 (s, 1H), 8.18 (s, 2H), 7.41 (d, J = 12.6 Hz, 3H), 7.05-6.82 (m, 6H), 6.53 (d, J = 3.3 Hz, 3H), 6.27 (t, J = 3.3 Hz, 1H); ¹³C NMR (aceton-d₆, 75 MHz) δ 159.8, 158.4, 140.7, 129.8, 129.0, 128.7, 126.8, 116.5, 105.5, 102.7; mp = 259-261 °C; HRMS (EI⁺) found 228.0780 M⁺, calcd 228.0786 for C₁₄H₁₂O₃; Anal. Calcd for C₁₄H₁₂O₃: C, 73.67, H, 5.30. Found: C, 73.67, H, 5.52.

Preparation of 5-aminobenzene-1,3-diol hydrochloride

Ammonium hydroxide (30%, 30 mL) was added to phloroglucinol dihydrate (5.18 g, 31 mmol) at 0 °C over 3 min. Ammonia gas was bubbled in for 30 min. Then the mixture was allowed to warm to ambient temperatures and stirred for 2 days, at which time it was concentrated under vacuum at 50 °C. The resulting solid was dissolved in 5 N HCl (10 mL). After evaporation, the crude product was obtained as a yellow solid. Purification by crystallized in acetone to gave 5-aminobenzene-1,3-diol hydrochloride (2.77 g, 55%). Data are: ¹H NMR (acetone-d₆, 300 MHz) δ 7.71 (s, 2H), 5.71 (d, J = 1.8 Hz, 2H), 5.67 (t, J = 1.8 Hz, 1H), 4.39 (bs, 2H); HRMS (EI⁺) found 125.0476 M⁺,
Preparation of 5-azidobenzene-1,3-diol (18)

To a stirred solution of 5-aminobenzene-1,3-diol hydrochloride (1.00 g, 6.19 mmol) and concentrated HCl (2.5 mL) in water (25 mL) was added a solution of NaNO₂ (0.39 g, 5.71 mmol) in water (2.5 mL) over 5 min at 0 °C. The mixture was stirred for 10 min before a solution of NaN₃ (0.41 g, 6.25 mmol) in water (2.5 mL) was added. After 1 h, the reaction was extracted 3 times with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. Purification with flash chromatography (30% EtOAc/hexanes) gave 0.52 g (60%) desired product. Data are: HRMS (EI⁺) found 151.0378 M⁺, calcd 151.0382 for C₆H₅N₃O₂.

Preparation of 5-azido-1,3-phenylene diacetate

To a stirred solution of 5-azidobenzene-1,3-diol 18 (0.52 g, 3.43 mmol) in EtOAc (7 mL) were added acetic anhydride (1.05 g, 10.29 mmol) and pyridine (0.54 g, 6.86 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 30 min and then warmed to ambient temperature and stirred for 3 h. The reaction mixture was poured in to water and extracted 3 times with EtOAc. The combined organic
layers were dried over Na₂SO₄ and concentrated. Flash chromatography (30% EtOAc/hexanes) gave 0.70 g (87%) desired product. Data are: ¹H NMR (acetone-d₆, 300 MHz) δ 6.80 (m, 3H), 2.26 (s, 6H); ¹³C NMR (acetone-d₆, 75 MHz) δ 169.3, 153.4, 142.7, 113.6, 111.2, 21.0; HRMS (EI⁺) found 235.0584 M⁺, calcd 235.0593 for C₁₀H₉N₃O₄.

Preparation of 5-amino-1,3-phenylene diacetate

In a Parr hydrogenation tube filled with Ar were charged with 5-azido-1,3-phenylene diacetate (0.63 g, 2.66 mmol), EtOAc (30 mL), and Pd/C (10%, 0.17 g). The tube was sealed, vacuumed and purged with H₂. The reaction was carried out at 50 psi of hydrogen atmosphere for 17 h, at which time the solution was passed through a celite cup and eluted with MeOH. After solvent evaporation, 5-amino-1,3-phenylene diacetate (0.56 g, 100%) was obtained. Data are: ¹H NMR (acetone-d₆, 300 MHz) δ 6.29 (d, J = 2.1 Hz, 2H), 6.12 (t, J = 2.1 Hz, 1H), 4.98 (bs, 2H), 2.19 (s, 6H); HRMS (EI⁺) found 209.0675 M⁺, calcd 209.0688 for C₁₀H₁₁NO₄.

Preparation of 3,5-diacetoxybenzenediazonium borotetrafluoride (19)

A flame dried flask was charged with BF₃·Et₂O (0.54 g, 3.80 mmol). A solution of
5-amino-1,3-phenylene diacetate (0.53 g, 2.53 mmol) in THF (5 mL) was added at -15 °C. More THF was needed if solid precipitated. Tert-butyl nitrite (0.36 mL, 3.04 mmol) was dropwisely added over 10 min as a THF (2.5 mL) solution. The mixture was stirred at -15 °C for 10 min, at which time it was warmed to 5 °C over 20 min. Pentane was added to precipitate the diazonium product. Filtration, wash with cold ether, and air-dry generated desired product 19 0.68 g (88%). Data are: ¹H NMR (DMSO-d₆, 300 MHz) δ 8.57 (d, J = 2.1 Hz, 2H), 8.07 (t, J = 2.1 Hz, 1H), 2.37 (s, 6H); ¹³C NMR (acetone-d₆, 75 MHz) δ 168.4, 151.0, 129.8, 123.6, 117.7, 20.7.

Preparation of 3,5-diacetoxybenzoic pivalic anhydride (21)

To a mixture of 3,5-diacetoxybenzoic acid (0.238 g, 1 mmol) and pivaloyl chloride (0.145 g, 1.2 mmol) in CH₂Cl₂ (5 mL) was added Et₃N (0.152 g, 1.5 mmol). The resulting solution was stirred for 30 min at ambient temperature and then the solvent was evaporated in vacuo. The concentrated crude product was dissolved in benzene and filtrated. After evaporation, the desired product was obtained in 92% yield (0.296 g). Data are: ¹H NMR (CDCl₃, 300 MHz) δ 7.65 (d, J = 2.4 Hz, 2H), 7.23(t, J = 2.4 Hz, 1H), 2.33 (s, 6H), 1.36 (s, 9H); HRMS (EI+) found 322.1036 M⁺, calcd 322.1053 for C₁₆H₁₈O₇.
4.2.2. Synthesis of Resveratrol Acetyl Analogs

Preparation of 3,5-bis(methoxymethoxy)benzoic acid

A flame dried flask was charged with dry DMF (75 mL) and 60% oil dispersion NaH (3.8 g, 95 mmol). The mixture was cooled to 0 °C before a solution of 3,5-dihydroxybenzoic acid 5 (4.6 g, 30 mmol) in DMF (25 mL) was added dropwisely over 20 min. The mixture was allowed to stir for 1 h under N₂. MOMCl (7.5 mL, 100 mmol) was added slowly at 0 °C. The mixture was then slowly warmed to ambient temperature. After 30 h, the insoluble material was filtered and the filtrate was concentrated to an oil residue, which was partitioned between benzene and water. The water layer was extracted 3 times with benzene. The combined benzene extracts were dried by Na₂SO₄ and concentrated to pale yellow oil, which was dissolved in 50 mL methanol. And 2 N aqueous NaOH (25 mL, 50 mmol) was added. The solution was stirred for 3 h before it was concentrated and dissolved in 30 mL water. The aqueous solution was washed with benzene and acidified with 10% aqueous HCl. The white solid precipitate was filtered and washed with water and dried to give 6.6 g (91%) of product 6, which can be further purified by recrystallization from EtOAc-hexanes.

Data are: ¹H NMR (CDCl₃, 300 MHz) δ 7.44 (d, 2H), 6.98 (t, 1H), 5.21 (s, 4H), 3.50 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 170.9, 158.4, 131.4, 111.5, 110.7, 94.7, 56.4;
mp = 129-130 °C; HRMS (EI⁺) found 242.0796 M⁺, calcd 242.0790 for C₁₁H₁₄O₆.

Preparation of 3,5-bis(methoxymethoxy)benzoic chloride (26)

A stock solution was prepared by dissolving benzotriazol (1.49 g, 12.5 mmol), thionyl chloride (0.91 mL, 12.5 mmol) in 8.0 mL CH₂Cl₂. The reaction was carried out by adding the stock solution into a stirred solution of 3,5-bis(methoxymethoxy)benzoic acid (2.60 g, 10 mmol) in 200 mL CH₂Cl₂. Before the addition was complete, benzotriazole hydrochloride started to precipitate out as a white solid. The mixture was stirred for another 12 min. After filtration, the filtrate was stirred with MgSO₄·7H₂O (5 g) to destroy excess thionyl chloride. The white solid was filtered and the filtrate was concentrated, at which time more white solid was generated. The mixture was redissolved in benzene, filtrated and concentrated to give 2.5 g (97%) crude product 26. Data are: ¹H NMR (CDCl₃, 300 MHz) δ 7.44 (d, J = 2.4 Hz, 2H), 7.04 (t, J = 2.4 Hz, 1H), 5.20 (s, 4H), 3.49 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 168.1, 158.5, 135.3, 112.6, 111.9, 94.7, 56.4; HRMS (EI⁺) found 260.0465 M⁺, calcd 260.0452 for C₁₁H₁₃O₅Cl.
**Preparation of 3,5-bis(methoxymethoxy)-4'-acetoxy stilbene (27)**

A 50 mL round bottom flask was charged with *p*-xylene (20 mL), Pd(OAc)$_2$ (22.5 mg, 0.1 mmol), *N*,*N*-bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride 16 (42.7 mg, 0.1 mmol), 3,5-bis(methoxymethoxy)benzoic chloride 26 (2.42 g, 10 mmol), 4-acetoxystyrene 14 (1.94 g, 12 mmol), and *N*-ethyl morpholine (1.38 g, 12 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to ambient temperature. And the whole mixture was purified by a flash chromatography (20% EtOAc/hexanes) to give the product 27 (2.1 g, 59%) as a white solid. Data are: $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.48 (d, $J = 8.4$ Hz, 2H), 7.08-6.93 (m, 4H), 6.86 (d, $J = 2.1$ Hz, 2H), 6.66 (t, $J = 2.1$ Hz, 1H), 5.19 (s, 4H), 3.50 (s, 6H), 2.30 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 169.5, 158.7, 150.3, 139.5, 135.0, 128.7, 128.5, 127.6, 121.9, 108.0, 104.5, 94.6, 56.2, 21.2; HRMS (EI$^+$) found 358.1409 M$^+$, calcd 358.1416 for C$_{20}$H$_{22}$O$_6$.

**Preparation of 3,5-dihydroxy-4'-acetoxy stilbene (28)**

To a stirred solution of 3,5-bis(methoxymethoxy)-4'-acetoxy stilbene 27 (0.358 g, 1 mmol) in dry CH$_2$Cl$_2$ (50 mL) and dry CH$_3$CN (50 mL) was added NaI (0.18 g, 2.4
mmol) and freshly distilled trimethylsilyl chloride (0.15 g, 2.4 mmol) at 0 °C. The mixture was stirred under argon for 15 min. The solution was diluted with CH₂Cl₂ (50 mL) and washed with a freshly prepared saturated Na₂S₂O₄ (3 x 40mL) solution, saturated NaHCO₃, and water. The organic layer was dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by flash column and gave 0.20 g product **28** (72%). Data are: ¹H NMR (Aceton-d₆, 300 MHz) δ 8.25 (s, 1H), 7.60 (m, 2H), 7.13-7.08 (m, 4H), 6.59 (d, J = 2.1 Hz, 2H), 6.32 (t, J = 2.1 Hz, 1H), 2.25 (s, 3H); ¹³C NMR (Aceton-d₆, 75 MHz) δ 169.7, 159.7, 151.4, 140.4, 136.0, 130.0, 128.3, 128.3, 123.0, 106.1, 103.3, 21.1; HRMS (EI⁺) found 270.0889 M⁺, calcd 270.0892 for C₁₆H₁₆O₄.

![Structure of 29](image)

**Preparation of 4-chloroacetoxystyrene (29)**

To a round bottom flask was charged 4-acetoxystyrene **14** (10.00 g, 61.73 mmol), methanol (30 mL), and KOH (0.13 g, 2.23 mmol), and 1 drop of water. After the mixture was stirred for 5 min under N₂, the temperature was raised to 65 °C. The mixture was stirred for 1.5 h and then cooled to ambient temperature. Acetic acid (0.14 g, 2.44 mmol) in methanol (0.5 mL) was added slowly over 5 min. The mixture was stirred for another 5 min and then concentrated. The residue was dissolved in toluene and filtered. The filtrate was cooled to -78 °C and the 4-hydroxystyrene was precipitated, filtered and dried to give 4.5 g product (60%).

To a stirred solution of 4-hydroxystyrene (1.22 g, 10 mmol) in ethyl ether (140 mL)
was added chloroacetyl chloride (2.26 g, 20 mmol) and Et$_3$N (1.62 g, 16 mmol). After 2 h, the mixture was washed with NaHCO$_3$ and water. The ether solution was dried by Na$_2$SO$_4$ and concentrated. After purification by flash column, 4-chloroacetoxystyrene 29 (1.8 g, 92%) was obtained. Data are: $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.46 (d, $J = 8.4$ Hz, 2H), 7.11 (d, 2H, $J = 8.4$ Hz), 6.73 (dd, $J = 11.1$, 18 Hz, 1H), 5.74 (d, $J = 18$ Hz, 1H), 5.29 (d, $J = 11.1$ Hz, 1H), 4.31 (s, 2H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 166.0, 150.0, 136.0, 135.8, 127.4, 121.3, 114.6, 41.0.

![Image](AcO-Cl.png)

**Preparation of 3,5-diacetoxy-4'-chloroacetoxy stilbene (30)**

A 10 mL round bottom flask was charged with $p$-xylene (4 mL), Pd(OAc)$_2$ (4.5 mg, 0.02 mmol), $N,N$-bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride 16 (8.6 mg, 0.02 mmol), 3,5-diacetoxybenzoyl chloride 13 (0.77 g, 3.0 mmol), 4-chloroacetoxystyrene 29 (0.393 g, 2.0 mmol), and $N$-ethyl morpholine (0.28 g, 2.4 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to ambient temperature. The whole mixture was purificid by a flash chromatography (20% EtOAc/hexanes) to give the product 30 (0.54 g, 70%) as a white solid. Data are: $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.47 (d, $J = 8.7$ Hz, 2H), 7.14-6.89 (m, 6H), 6.83 (t, $J = 2.1$ Hz, 1H), 4.29 (s, 2H), 2.29 (s, 6H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 169.1, 165.9, 151.4, 150.1, 139.5, 135.1, 129.5, 127.9, 127.7, 121.6, 117.1, 114.7, 41.0, 21.2; HRMS (EI$^+$) found 388.0710 M$^+$, calcd 388.0714 for
C_{20}H_{17}ClO_6.

**Preparation of 3,5-diacetoxy-4'-hydroxy stilbene (31)**

A solution of 3,5-diacetoxy-4'-chloroacetoxy stilbene 30 (0.388 g, 1 mmol) in 50% aqueous pyridine, which was adjusted to pH 6.7 with hydrochloric acid, was stirred for 6 h at ambient temperature. The mixture was concentrated and diluted with EtOAc. The mixture was washed with 1 N aqueous HCl, saturated NaHCO₃ and water. The EtOAc layer was dried and concentrated. After purification by radial chromatography, the product 31 (0.28 g, 90%) was obtained. Data are: $^1$H NMR (Aceton-d₆, 300 MHz) δ 8.55 (bs, 1H), 7.47 (m, 2H), 7.25-7.00 (m, 4H), 6.86 (m, 2H), 6.82 (t, $J = 2.1$Hz, 1H), 2.27 (s, 3H); $^{13}$C NMR (Aceton-d₆, 75 MHz) δ 169.5, 158.7, 152.7, 141.2, 131.4, 129.5, 129.2, 124.8, 117.5, 116.6, 115.1, 21.0; HRMS (EI⁺) found 312.0993 M⁺, calcd 312.0998 for C₁₈H₁₆O₅.

**Preparation of 3-acetoxy-5-hydroxybenzoic acid**

To 3,5-dihydroxybenzoic acid 15 (20 g, 129 mmol) added NaOH (15.6 g, 390 mmol) in 100 mL water. After the mixture was cooled to 0 °C, Ac₂O (13.2 g, 129 mmol) was
added. The solution was stirred for 40 min and then acidified with 10% H₂SO₄ at 0 °C. The precipitate was filtered and washed with cold water. The crude product was recrystallized from water to give 3-acetoxy-5-hydroxybenzoic acid (15.2 g, 60%).

Data are: ¹H NMR (Aceton-d₆, 300 MHz) δ 8.96 (s, 1H), 7.40 (dd, J = 1.5Hz, 1H), 7.26 (dd, J = 1.5Hz, 1H), 6.86 (t, J = 2.1H, 1H), 2.27 (s, 3H); HRMS (EI⁺) found 196.0380 M⁺, calcd 196.0372 for C₉H₈O₅.

Preparation of 3-acetoxy-5-levulinoxy-benzoic acid (33)

To a stirred solution of 3-acetoxy-5-hydroxybenzoic acid (2.45 g, 12.5 mmol) in CH₂Cl₂ (25 mL) were added levulinic anhydride (5.4 g, 25 mmol) and pyridine (1.22 mL, 15 mmol) at 0 °C. The mixture was stirred at 0 °C for another 0.5 h, at which time it was warmed to ambient temperature. After 3 h, 98% formic acid was added and stirred for 1 h. The mixture was washed with 1 N HCl, saturated NaHCO₃ and water. Then it was dried with Na₂SO₄ and concentrated. The crude product was purified by flash column chromatography to give 3-acetoxy-5-levulinoxy-benzoic acid 33 (3.52 g, 96%). Data are: ¹H NMR (CDCl₃, 300 MHz) δ 7.72 (d, J = 1.2Hz, 2H), 7.20 (t, J = 1.2Hz, 1H), 2.85 (m, 4H), 2.32 (s, 3H), 2.24 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 206.6, 177.6, 171.0, 170.0, 169.0, 151.2, 131.7, 121.1, 121.1, 121.0, 38.1, 30.0, 28.3, 21.2; HRMS (EI⁺) found 294.0741 M⁺, calcd 294.0740 for C₁₄H₁₄O₇.
Preparation of 3-acetoxy-5-levulinoxy-benzoic chloride (34)

A stock solution was prepared by dissolving benzotriazole (1.49 g, 12.5 mmol), thionyl chloride (0.91 mL, 12.5 mmol) in 8.0 mL CH₂Cl₂. The reaction was carried out by adding the stock solution intermittently into a stirred solution of 3-acetoxy-5-levulinoxy-benzoic acid 33 (2.94 g, 10 mmol) in 200 mL CH₂Cl₂. Before the addition was complete, benzotriazole hydrochloride started to precipitate out as a white solid. The mixture was stirred for another ten min. After filtration, the filtrate was stirred with MgSO₄·7H₂O (5 g) to destroy excess thionyl chloride. After concentration, the residue was extracted several times with hot dry hexane and recrystallized from hexanes to give 3-acetoxy-5-levulinoxy-benzoic chloride 34 (1.4 g, 45%). Data are: ¹H NMR (CDCl₃, 300 MHz) δ 7.75 (d, J = 2.1Hz, 2H), 7.28 (t, J = 2.1Hz, 1H), 2.86 (m, 4H), 2.33 (s, 3H), 1.24 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 206.3, 170.9, 168.7, 167.1, 151.42, 151.38, 135.3, 122.8, 122.1, 121.9, 38.0, 30.0, 28.3, 21.2; HRMS (EI⁺) found 312.0390 M⁺, calcd 312.0401 for C₁₄H₁₃O₆Cl.

Preparation of 3,4'-diacetoxy-5-levulinoxystillbene (35)
A 25 mL round bottom flask was charged with \(p\)-xylene (6 mL), Pd(OAc)\(_2\) (6.9 mg, 0.03 mmol), \(N,N\)-bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride 16 (12.9 mg, 0.03 mmol), 3-acetoxy-5-levulinoxy-benzoic chloride 34 (0.94 g, 3.0 mmol), 4-acetoxy styrene 14 (0.58 g, 3.6 mmol), and \(N\)-ethyl morpholine (0.42 g, 3.6 mmol). The mixture was heated at 120 \(^\circ\)C for 3.5 h under nitrogen atmosphere. Then it was cooled to ambient temperature. The whole mixture was purified by a flash chromatography (20% EtOAc/hexanes) to give the product 35 (0.86 g, 70%) as a white solid. Data are: \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.48 (m, 2H), 7.12 (m, 6H), 6.81 (t, \(J = 1.2\) Hz, 1H), 2.85 (m, 4H), 2.31 (s, 1H), 2.30 (s, 1H), 2.23 (s, 1H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 206.4, 171.2, 169.5, 169.1, 151.5, 150.6, 140.0, 134.7, 129.8, 127.8, 127.4, 122.1, 117.14, 117.09, 114.6, 38.1, 30.0, 28.4, 21.32, 21.29.

### Preparation of 3,4'-diacetoxy-5-hydroxystilbene (36)

To a stirred solution of 3,4'-diacetoxy-5-levulinoxy stilbene 35 (0.72 g, 1.75 mmol) in THF (5 mL) was added a solution of Na\(_2\)SO\(_3\) (0.26 g, 2.1 mmol) and Na\(_2\)S\(_2\)O\(_5\) (0.1 g, 0.53 mmol) in water (5 mL). The reaction mixture was stirred for 9 h at ambient temperature under N\(_2\). Then the mixture was poured into water and extracted 3 times with EtOAc and dried over Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure and purified by radial chromatography to give 3,4'-diacetoxy-5-hydroxystilbene 36 (0.40 g, 73%). Data are: \(^1\)H NMR (Aceton-d\(_6\), 300 MHz) \(\delta\) 8.66 (bs, 1H), 7.63 (m,
2H), 7.25 (m, 4H), 6.94 (t, J = 1.8Hz, 1H), 6.86 (t, J = 1.8Hz, 1H), 6.54 (t, J = 2.1Hz, 1H), 2.26 (s, 3H), 2.25 (s, 3H); \(^{13}\)C NMR (Aceton-d\(_6\), 75 MHz) \(\delta\) 169.7, 169.6, 159.2, 153.2, 151.6, 140.4, 135.6, 129.4, 128.8, 128.3, 122.9, 111.85, 111.79, 109.4, 21.07, 21.02; HRMS (EI\(^{+}\)) found 312.0996 M\(^{+}\), calcd 312.0998 for C\(_{18}\)H\(_{16}\)O\(_{5}\).

**Preparation of 4-levulinoxystyrene (37)**

A flame dried flask was charged with dioxane (120 mL), 4-hydroxystyrene (3.66 g, 30 mmol), levulinic acid (6.97 g, 60 mmol), DCC (12.39 g, 60 mmol), and DMAP (300 mg). The mixture was stirred under N\(_2\) for 3.5 h. and the mixture was washed with water, dried over Na\(_2\)SO\(_4\), concentrated under reduced pressure, and purified by flash column to give 4-levulinoxystyrene 37 (5.9 g, 90%). Data are: \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.39 (m, 2H), 7.04 (m, 2H), 6.68 (dd, J = 10.8, 17.7 Hz, 1H), 5.69 (d, J = 17.7 Hz, 1H), 5.69 (d, J = 10.8Hz, 1H), 2.82 (m, 4H), 2.20 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 206.5, 171.5, 150.4, 136.0, 135.5, 127.3, 121.7, 114.1, 38.0, 30.0, 28.3; HRMS (EI\(^{+}\)) found 218.0955 M\(^{+}\), calcd 218.0943 for C\(_{13}\)H\(_{14}\)O\(_{3}\).

**Preparation of 3-acetoxy-4',5-dilevulinoxystillbene (38)**
A 25 mL round bottom flask was charged with \( p \)-xylene (6 mL), Pd(OAc)\(_2\) (6.9 mg, 0.03 mmol), \( N,N \)-bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride \( 16 \) (12.9 mg, 0.03 mmol), 3-acetoxy-5-levulinoxy-benzoic chloride \( 34 \) (0.936 g, 3.0 mmol), 4-levulinoxy styrene \( 37 \) (0.786 g, 3.6 mmol), and \( N \)-ethyl morpholine (0.42 g, 3.6 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to ambient temperature. The whole mixture was purified by a flash chromatography (20% EtOAc/hexanes) to give the product \( 38 \) (1.0 g, 72%) as a white solid. Data are: \(^1\)H NMR (CDCl\(_3\), 300 MHz) \( \delta \) 7.47 (m, 2H), 7.11-6.92 (m, 6H), 6.81 (t, \( J = 2.1 \)Hz, 1H), 2.89-2.80 (m, 8H), 2.29 (s, 3H), 2.224 (s, 3H), 2.221 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \( \delta \) 206.6, 206.5, 171.5, 171.2, 169.1, 151.4, 151.5, 150.6, 139.7, 134.6, 129.8, 127.8, 127.3, 122.0, 117.10, 117.05, 114.5, 38.07, 38.02, 30.01, 30.00, 28.32, 28.30, 21.3; HRMS (EI\(^+\)) found 466.1636 M\(^+\), calcd 466.1628 for C\(_{26}\)H\(_{26}\)O\(_8\).

\[ \text{HO} \]
\[ \text{OAc} \]
\[ \text{39} \]

**Preparation of 3-acetoxy-4',5-dihydroxystillbene (39)**

To a stirred solution of 3-acetoxy-4',5-dilevulinoxy stillbene \( 38 \) (0.47 g, 1.0 mmol) in THF (3 mL) was added a solution of Na\(_2\)SO\(_3\) (0.30 g, 2.4 mmol) and Na\(_2\)S\(_2\)O\(_5\) (0.11 g, 0.6 mmol) in water (3 mL). The reaction mixture was stirred for 7 h at ambient temperature under N\(_2\). Then the mixture was poured into water and extracted 3 times with EtOAc and dried over Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure.
and purified by radial chromatography to give 3-acetoxy-4',5- dihydroxystillbene 39 (0.19 g, 70%). Data are: \(^1\)H NMR (Aceton-d\(\delta\), 300 MHz) \(\delta\) 8.56 (s, 1H), 8.48 (s, 1H), 7.45 (m, 2H), 7.04 (m, 2H), 6.90-6.80 (m, 4H), 6.50 (t, \(J = 2.1\)Hz, 1H), 2.24 (s, 1H); \(^13\)C NMR (Aceton-d\(\delta\), 75 MHz) \(\delta\) 169.6, 159.2, 158.5, 153.3, 141.1, 129.8, 130.3, 129.0, 116.5, 111.5, 111.4, 108.8, 21.1; HRMS (EI\(^+\)) found 270.0896 M\(^+\), calcd 270.0892 for C\(_{16}\)H\(_{16}\)O\(_4\).

4.2.3. Synthesis of Resveratrol Fluoro Analogs

![Resveratrol Fluoro Analogs](image)

**Preparation of 3,5,4'-trifluorostillbene (42)**

A 25 mL round bottom flask was charged with \(p\)-xylene (10 mL), Pd(OAc)\(_2\) (11.3 mg, 0.05 mmol), \(N,N\)-bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride 16 (21.4 mg, 0.05 mmol), 3,5-difluorobenzoyl chloride 40 (0.89 g, 5 mmol), 4-fluorostyrene 41 (0.74 g, 6 mmol), and \(N\)-ethyl morpholine (0.69 g, 6 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to ambient temperature. The whole mixture was purified by a flash chromatography (20% EtOAc/hexanes) to give the product 42 (0.94g, 80%) as a white solid. Data are: \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.47 (m, 2H), 7.08-6.88 (m, 6H), 6.70 (tt, \(J = 2.4, 9.0\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 163.52 (dd), 162.98 (d), 140.82 (t), 132.77, 130.26, 128.58 (d), 126.53, 116.03 (d), 109.20 (q), 102.98(t); \(^19\)F NMR (CDCl\(_3\), 282
Preparation of 4'-acetoxy-3,5-difluorostilbene

A 25 mL round bottom flask was charged with \( p \)-xylene (10 mL), \( \text{Pd(OAc)}_2 \) (11.3 mg, 0.05 mmol), \( \text{N,N-bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride} \) (21.4 mg, 0.05 mmol), 3,5-difluorobenzoyl chloride (0.89 g, 5 mmol), 4-acetoxystyrene (0.97 g, 6 mmol), and \( \text{N-ethyl morpholine} \) (0.69 g, 6 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to ambient temperature. The whole mixture was purified by a flash chromatography (20% EtOAc/hexanes) to give the product (1.02 g, 74%) as a white solid. Data are: \( ^1H \) NMR (CDCl\(_3\), 300 MHz) \( \delta 7.51 \) (d, \( J = 8.4 \) Hz, 2H), 7.12-6.97 (m, 6H), 6.70 (t, 1H), 2.31(s, 3H).

Preparation of 3,5-difluoro-4'-hydroxystilbene (43)

To a stirred solution of 3,5-difluoro-4'-acetoxy-stilbene (0.69 g, 2.5 mmol) in MeOH (10 mL) were added 5 mL 4 N HCl in 1,4-dioxane. The mixture was stirred for 20
min at ambient temperature. After purification by flash chromatography, 3,5-difluoro-4'-hydroxystilbene 43 (0.51 g, 88%) was obtained. Data are: $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.40 (m, 2H), 7.05-6.83 (m, 6H), 6.67 (tt, $J = 2.1$, 8.7 Hz, 1H), 4.88 (s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 164.49(d), 162.47, 156.01, 141.29, 130.90, 128.53, 124.74, 115.96, 109.03 (t), 102.53 (t); $^{19}$F NMR (CDCl$_3$, 282 MHz) $\delta$ -31278.95 (t, $J = 1720.2$ Hz, 2F); HRMS (EI$^+$) found 232.0715 M$^+$, calcd 232.0700 for C$_{14}$H$_{10}$F$_2$O.

Preparation of 3,5-diacetoxy-4'-fluorostilbene

A 25 mL round bottom flask was charged with $p$-xylene (10 mL), Pd(OAc)$_2$ (11.3 mg, 0.05 mmol), $N,N$-bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride 16 (21.4 mg, 0.05 mmol), 3,5-diacetoxybenzoyl chloride 13 (1.28 g, 5 mmol), 4-fluorostyrene 41 (0.73 g, 6 mmol), and $N$-ethyl morpholine (0.69 g, 6 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to ambient temperature. The whole mixture was transferred to a flash chromatography (20% EtOAc/hexanes) to give the product (1.15 g, 73%) as a white solid. Data are: $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.45 (m, 2H), 7.11-6.91 (m, 6H), 6.82 (t, $J = 1.95$ Hz, 1H), 2.31 (s, 6H).
Preparation of 4'-fluoro-3,5-dihydroxystilbene (44)

To a stirred solution of 3,5-diacetoxy-4'-fluoro-stilbene (0.79 g, 2.5 mmol) in MeOH (10 mL) was added 10 mL 4 N HCl in 1,4-dioxane. The mixture was stirred for 30 min at ambient temperature. After purification by flash chromatography, 3,5-difluoro-4'-hydroxystilbene 44 (0.49 g, 85%) was obtained. Data are: $^1$H NMR (Aceton-$d_6$, 300 MHz) $\delta$ 8.25 (s, 1H), 7.61 (m, 2H), 7.16-7.00 (m, 4H), 6.58 (d, $J = 2.4$ Hz), 6.31 (t, $J = 2.4$ Hz); $^{13}$C NMR (Aceton-$d_6$, 75 MHz) $\delta$; $^{19}$F NMR (Aceton-$d_6$, 282 MHz) $\delta$ -32881.41 (m); HRMS (EI$^+$) found 230.0737 M+, calcd 230.0743 for C$_{14}$H$_{11}$FO$_2$.

Preparation of 3-benzyloxy-5-fluorophenyl Bromide (46)

To a stirred solution of benzyl alcohol (3.86 g, 20 mmol) in DMA (30 mL), NaH (0.80 g, 20 mmol, 60% dispersion in oil) was dropwisely added. After 1 h, 1-bromo-3,5-difluorobenzene 45 (3.86 g, 20 mmol) was added at such a rate to maintain the temperature no higher than 40 °C. The mixture was stirred at ambient temperature overnight. The reaction was quenched with water and extracted with EtOAc. Purification by flash chromatography gave the product 46 (4.17 g, 74%) as colorless oil. Data are: $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.41-7.43 (m, 5H), 6.94 (m, 1H), 6.86 (dt, $J = 2.1$, 8.1 Hz, 1H), 6.63 (dt, $J = 2.4$, 8.1 Hz, 1H), 5.02 (s, 2H); $^{13}$C NMR (CDCl$_3$,}
75 MHz) δ 165.20, 161.89, 160.72, 160.56, 136.01, 128.94, 128.57, 127.77, 127.73, 122.99, 122.83, 114.58, 114.53, 112.18, 111.84, 102.29, 101.96, 70.76; 19F NMR (CDCl₃, 282 MHz) δ -31129.40 (t, J = 2583.12 Hz, 1F).

Preparation of 3-benzyloxy-5, 4'-difluorostilbene

A mixture of 3-benzyloxy-5-fluorophenyl bromide 46 (2.81 g, 10 mmol), Pd(OAc)₂ (0.067 g, 0.3 mmol), tri-o-tolyolphosphine (0.18g, 0.6mmol), 4-fluorostyrene 41 (1.53 g, 12.5 mmol), and Et₃N (1.26 g, 12.5 mmol) in 20 mL dry DMF was stirred under N₂ at 100 °C for 24 h. The dark mixture was distributed between EtOAc and 1 N HCl. The organic layer was separated and washed with water and brine, dried over Na₂SO₄, filtered, and evaporated. After flash chromatography, the desired product (2.93g, 91%) was obtained. Data are: 1H NMR (CDCl₃, 300 MHz) δ 7.49-7.34 (m, 7H), 7.08-6.81 (m, 6H), 6.60 (dt, J = 2.4, 10.5 Hz, 1H), 5.08 (s, 2H); 19F NMR (CDCl₃, 282 MHz) δ -31666.54 (t, J = 2583.12, 1F), -32136.54 (t, J = 2580.3 Hz, 1F). HRMS (EI⁺) found 322.1169 M⁺, calcd 322.1169 for C₂₁H₁₆F₂O.

Preparation of 3, 4'-difluoro-5-hydroxystilbene (47)
A solution of BBr₃ (9 ml, 9 mmol, 1 M in CH₂Cl₂) was added to a well-stirred solution of 5-benzyloxy-3, 4'-difluorostillbene (0.97g, 3 mmol) in dry CH₂Cl₂ (120 mL) at –78 °C. The mixture was warmed to –20 °C and stirred for 10 min. Then MeOH was added at –78 °C. The mixture was washed with saturated NaHCO₃, and water. Flash chromatography gave 5-hydroxy-3, 4'-difluorostillbene 47 (0.60 g, 86%) as white solid. Data are: ¹H NMR (CDCl₃, 300 MHz) δ 7.46 (m, 2H), 7.08-6.73 (m, 6H), 6.48 (dt, \( J = 2.4, 9.6 \) Hz, 1H), 4.85 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 165.05 (d), 161.78 (d), 157.06 (d), 140.43 (d), 133.06 (d), 129.40 (s), 128.45 (d), 127.25 (t), 115.95 (d), 109.42 (d), 105.91 (d), 102.60 (d); ¹⁹F NMR (CDCl₃, 282 MHz) δ -31703.17 (t, \( J = 2583.12 \) Hz, 1F), -32099.92 (t, \( J = 2583.12 \), 1F); HRMS (EI⁺) found 232.0714 M⁺, calcd 232.0700 for C₁₄H₁₀F₂O.

Preparation of 4'-acetoxy-3-benzyloxy-5-fluorostillbene

A mixture of 3-benzyloxy-5-fluorophenyl bromide 46 (2.81 g, 10 mmol), Pd(OAc)₂ (0.067 g, 0.3 mmol), tri-o-tolylphosphine (0.18 g, 0.6 mmol), 4-acetoxystyrene 14 (2.03 g, 12.5 mmol), and Et₃N (1.26 g, 12.5 mmol) in 20mL dry DMF, was stirred under N₂ at 100 °C for 24 h. The dark mixture was distributed between EtOAc and 1 N HCl. The organic layer was separated and washed with water and brine, dried over Na₂SO₄, filtered, and evaporated. After flash chromatography, the desired product (3.19 g, 88%) was obtained. Data are: ¹H NMR (CDCl₃, 300 MHz) δ 7.51-7.34 (m,
Preparation of 3-fluoro-5,4′-dihydroxystilbene (48)

A solution of BBr$_3$ (9 mL, 9 mmol, 1 M in CH$_2$Cl$_2$) was added to a well-stirred solution of 5-benzyloxy-3-fluoro-4′-acetoxystilbene (1.09 g, 3 mmol) in dry CH$_2$Cl$_2$ (120 mL) at -78 °C. The mixture was warmed to -20 °C and stirred for 10 min. Then MeOH was added at -78 °C. The mixture was washed with saturated NaHCO$_3$, and water, dried over Na$_2$SO$_4$, and evaporated. The intermediate 4′-acetoxycarbonyl-3-fluoro-5-hydroxystilbene (0.50 g, 61%) was obtained as a white solid. To a stirred solution of the crude 4′-acetoxycarbonyl-3-fluoro-5-hydroxystilbene (0.50 g, 1.8 mmol) in MeOH (7.5 mL) was added HCl (3.7 mL, 4 M in 1,4-dioxane). The mixture was stirred for 20 min at ambient temperature. After purification by flash chromatography, 3-fluoro-5,4′-dihydroxystilbene 48 (0.33 g, 78%) was obtained. Data are: $^1$H NMR (Aceton-d$_6$, 300 MHz) δ 8.62 (s, 2H), 7.46 (m, 2H), 7.06 (q, 2H), 6.84 (m, 4H), 6.66 (dt, $J = 2.1$, 10.5 Hz, 1H); $^{13}$C NMR (Aceton-d$_6$, 75 MHz) δ 164.90 (d), 159.96 (d), 158.57, 142.02 (d), 130.84, 129.63, 129.10, 125.55 (d), 116.53, 110.28 (d), 104.44 (d), 102.00
4.3. Asymmetric Phase-Transfer-Catalyzed Glycolate Aldol Reaction

4.3.1. Substrate Preparation

(Z)-(2-(Benzyldroxy)-1-(2,5-dimethoxyphenyl)ethenyl)oxy)trimethyl silane (93).

To a stirred solution of 2-Benzhydryloxy-1-(2,5-dimethoxy-phenyl)-ethanone 88 (3 mmol, 1.09 g) in 10 ml dry THF was dropwisely added LDA (2.5 mL) at -78 °C. After 1 h, TMSCl (2.5 mL) was added slowly. The mixture was stirred for another 1 h and the color was changed to pale yellow from orange. The reaction was warmed to ambient temperature. After THF was removed under reduced pressure, dry hexanes were added. The resulting white precipitates were removed by filtration. After concentration, the residue was purified by recrystallization with hexanes to give 2 as white solid (0.80 g, 61%). Data are: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.41 (d, $J = 7.5$ Hz, 4 H), 7.34 (t, $J = 7.5$ Hz, 4 H), 7.26-7.28 (m, 2 H), 7.07 (d, $J = 0.3$ Hz, 1 H), 6.72 (d, $J = 9.0$ Hz, 1 H), 6.63 (dd, $J = 3.0$, 9.0 Hz, 1 H), 5.79 (s, 1 H), 3.75 (s, 3 H), 3.61 (s, 3 H), 0.17 (s, 9 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 153.8, 150.1, 141.5, 135.4, 131.0, 128.6, 127.9, 127.5, 126.9, 112.94, 112.91, 112.1, 85.7, 56.2, 55.8, 0.8; HRMS (FAB$^+$) found 457.1806, calcd 457.1811 for C$_{26}$H$_{30}$O$_4$SiNa.
(Z)-(2-(Benzyloxy)-1-(2,5-dimethoxyphenyl)vinyloxy)trimethylsilane

Data are: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.41-7.29 (m, 5H), 7.11 (d, $J = 3.5$ Hz, 1H), 6.94 (s, 1H), 6.76 (d, $J = 9$ Hz, 1H), 6.66 (dd, $J = 3.5$, 9 Hz, 1H), 4.88 (s, 2H), 3.76 (s, 3H), 3.74 (s, 3H), 0.18 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 153.9, 150.1, 137.6, 136.1, 131.1, 128.6, 128.5, 128.4, 128.22, 128.19, 126.7, 113.0, 112.6, 112.0, 77.5, 77.3, 77.0, 74.5, 56.3, 55.8, 0.80; HRMS (FAB$^+$) found 358.1591, calcd 358.1600 for C$_{20}$H$_{26}$O$_4$Si.

(Z)-(2-(Benzhydryloxy)-1-phenylvinyloxy)trimethylsilane

Data are: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.41-7.40 (m, 4H), 7.36-7.32 (m, 6H), 7.29-7.21 (m, 4H), 7.16-7.11 (m, 1H), 6.41 (s, 1H), 5.77 (s, 1H), 0.18 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 141.3, 137.2, 134.9, 130.2, 128.7, 128.3, 128.0, 127.3, 126.8, 123.8, 85.9, 0.84; HRMS (FAB$^+$) found 397.1597, calcd 397.1600 for C$_{24}$H$_{26}$O$_2$SiNa.
(Z)-(2-(Benzhydryloxy)-1-(2-methoxyphenyl)vinyloxy)trimethylsilane

Data are: $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.43-7.40 (m, 4H), 7.34-7.31 (m, 4H), 7.28-7.24 (m, 3H), 7.15-7.10 (m, 1H), 6.90-6.87 (m, 1H), 6.80-6.78 (m, 1H), 6.74 (s, 1H), 5.77 (s, 3H), 3.68 (s, 3H), 0.15 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 156.1, 141.6, 134.6, 131.5, 128.5, 128.41, 128.36, 128.3, 128.1, 127.9, 127.6, 127.4, 127.3, 126.0, 120.7, 111.3, 85.7, 55.5, 0.84; HRMS (FAB$^+$) found 427.1714, calcd 427.1705 for C$_{25}$H$_{28}$O$_3$SiNa.

(Z)-(2-(Benzhydryloxy)-1-(4-methoxyphenyl)vinyloxy)trimethylsilane

Data are: $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.40-7.38 (m, 2H), 7.34-7.30 (m, 4H), 7.27-7.23 (m, 5H), 6.78-6.76 (m, 3H), 6.27 (s, 1H), 3.75 (s, 3H), 0.17 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 158.9, 141.5, 135.1, 130.6, 130.0, 128.9, 128.6, 128.5, 128.0, 127.8, 127.7, 127.6, 127.4, 127.2, 125.3, 113.8, 85.8, 55.5, 0.85; HRMS (FAB$^+$) found 427.1697, calcd 427.1705 for C$_{25}$H$_{28}$O$_3$SiNa.
(Z)-(2-(Benzhydryloxy)-1-(2,4-dimethoxyphenyl)vinyl)oxy)trimethylsilane

Data are: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.44-7.42 (m, 4H), 7.36-7.33 (m, 4H), 7.32-7.26 (m, 3H), 6.57 (s, 1H), 6.44 (dd, $J = 2.5, 8.5$ Hz, 1H), 6.40 (d, $J = 2.5$ Hz, 1H), 5.76 (s, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 0.16 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 159.6, 157.3, 141.7, 133.1, 131.6, 129.0, 128.5, 128.3, 127.8, 127.7, 127.6, 127.5, 127.2, 118.9, 104.1, 99.1, 85.5, 55.5, 55.4, 0.8; HRMS (FAB$^+$) found 434.1902, calcd 434.1913 for C$_{26}$H$_{30}$O$_4$Si.

4.3.2. Bifluoride Salt Preparation

$N$-2',3',4'-trifluorobenzylhydrocinchonium bromide.

To a flame dried 50 mL round bottom flask was added hydrocinchonine (5.0 g, 16.81 mmol) and 35 mL toluene. Then 2,3,4-trifluorobenzylbromide (2.25 mL, 17.11 mmol) was dropwisely added. The resulting mixture was stirred at 100 °C for 7 h. After cooling to ambient temperature, the product was precipitated out. Filtration and wash 3 times with Et$_2$O gave desired title compound (8.49 g, 97%).
The catalyst was prepared according to the published procedure with the exceptions that the product was purified by flash column instead of recrystallization.

Amberlyst A-26 (Br⁻ form, 1.6 g, 9.6 meq) column was flushed with 1 N aqueous NaOH until all of the Br⁻ was exchanged by OH⁻. The column was washed with H₂O until it was neutral. Then it was flushed with MeOH. A solution of Cinchonium bromide 68-CN⁺Br⁻ (0.5 mmol) in 10 mL MeOH was slowly passed through the column and eluted with MeOH. The eluent was neutralized with 1 N HF (1 mL). The solvents were removed under reduced pressure to provide the title product in quantitative yield. Data for 68-CN⁺HF₂⁻ are: 

\[ ^1H \text{NMR (CDCl}_3, 500 \text{ MHz): } \delta 8.98 (d, J \text{ }) \]
= 4.5, 1H), 8.59 (d, J = 8 Hz), 8.15 (d, J = 9 Hz, 1H), 8.02 (m, 1H), 7.90 (bs, 1H), 7.79 (t, J = 7.5 Hz, 1H), 7.61 (bs, 1H), 7.21 (m, 1H), 6.22 (bs, 1H), 6.07 (m, 1H), 5.82 (d, J = 12 Hz, 1H), 5.42 (d, J = 1.5 Hz, 1H), 5.39 (d, J = 1 Hz, 1H), 4.78 (d, J = 12.5 Hz, 1H), 4.55 (t, J = 11 Hz, 1H), 4.49 (m, 1H), 4.26 (m, 1H), 4.04 (m, 1H), 4.00 (m, 1H), 3.22 (t, J = 10.5 Hz, 1H), 2.88 (q, J = 10 Hz, 1H), 2.31 (t, J = 11.5 Hz, 1H), 2.01 (m, 1H), 1.94 (m, 1H), 1.76 (m, 2H), 1.58 (m, 2H), 1.11 (m, 1H), 0.94 (t, J = 7 Hz, 3H); 13C NMR (CDCl3, 125 MHz): δ 153.9, 152.3, 152.2, 151.9, 150.3, 150.2, 149.7, 148.7, 141.0, 140.0, 139.1, 139.0, 132.4, 131.3, 130.4, 130.1, 129.2, 129.0, 128.4, 125.7, 125.4, 124.2, 120.3, 119.8, 119.1, 114.1, 113.9, 113.1, 74.2, 70.7, 70.5, 66.8, 57.5, 56.7, 54.6, 36.2, 24.7, 24.5, 24.3, 22.1, 11.5; HRMS (FAB+) found 504.2364, calcd 504.2359 for C29H32F3N2NaO.

4.3.3. Asymmetric Aldol Reaction

\[
\text{2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-3-phenylpropan-1-one (90).}
\]

\(\text{O(9)-Allyl-N-2',3',4'-trifluorobenzylhydrocinchonium bifluoride salt 68-CN^+HF_2^-}\) (15 mg, 0.003 mmol) was dissolved in reagent grade 1.5 mL THF. Benzaldehyde (0.3 mmol, 0.0318g) was added and the mixture was cooled to -55 °C. (Z)-(2-(benzhydryloxy)-1-(2,5-dimethoxyphenyl)ethenyloxy)trimethyl silane (0.15
mmol, 0.0652 g) 93 was added. After 24 h, the reaction was quenched with CsF and H2O. The solution was extracted 5 times with CH2Cl2. The combined organic layers were washed with water and brine, and dried over MgSO4. The mixture was filtered and concentrated *in vacuo*. Radial chromatography afforded the desired compound 90 (0.054 g, 76%). Its enantioselectivity can be enriched by recrystallization with EtOH and hexanes. The crystals were racemic and the residue was the enantio-enriched product. Data are: 1H NMR (CDCl3, 500 MHz): δ 7.10-7.31 (m, 14 H), 6.98-7.00 (m, 1 H), 6.78-6.85 (m, 3 H), 5.48 (s, 1 H), 5.28 (d, J = 2.5 Hz, 1 H), 5.03 (s, 1 H), 3.77 (s, 3 H), 3.55 (s, 3 H), 3.13 (b, 1 H); 13C NMR (CDCl3, 125 MHz): δ 200.1, 154.0, 152.5, 142.2, 141.2, 140.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 127.3, 127.1, 126.2, 121.1, 114.3, 113.3, 84.7, 82.5, 73.9, 55.99, 55.97; HRMS (FAB+) found 491.1844, calcd 491.1834 for C30H28O5Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): tR = 23.1 (minor). tR = 33.0 (major).

![Chemical structure](image)

**2-(Benzyloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-3-phenylpropan-1-one**

Data are: 1H NMR (CDCl3, 500 MHz): δ 7.33-7.22 (m, 8H), 7.19 (d, J = 3.0 Hz, 1H), 7.08 (m, 2H), 7.00 (dd, J = 3.5, 9.0 Hz, 1H), 6.83 (d, J = 9.0 Hz, 5.26 (d, J = 3.0 Hz, 1H), 5.01 (dd, J = 3.0, 7.5 Hz, 1H), 4.73 (d, J = 11.5 Hz, 1H), 4.38 (d, J = 11.5 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.04 (d, J = 7.5 Hz, 1H); 13C NMR (CDCl3, 125 MHz): δ 200.1, 154.0, 152.6, 141.0, 137.7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7,
2-(Benzhydryloxy)-3-hydroxy-1,3-diphenylpropan-1-one

Data (major) are: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.68-7.66 (m, 2H), 7.49-7.45 (m, 1H), 7.32-7.15 (m, 15H), 7.05-7.03 (m, 2H), 5.41 (s, 1H), 5.01 (t, 1H), 4.88 (d, $J = 5.0$ Hz, 1H), 3.15 (d, $J = 5.0$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 199.1, 141.6, 140.2, 139.6, 136.4, 133.5, 128.8, 128.7, 128.6, 128.5, 128.4, 128.20, 128.17, 127.8, 127.7, 127.4, 126.7, 83.2, 75.2; HRMS (FAB$^+$) found 431.1636, calcd 431.1623 for C$_{28}$H$_{24}$O$_3$Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): $t_R = 51.1$ (minor). $t_R = 60.1$ (major).

2-(Benzhydryloxy)-3-hydroxy-1,3-diphenylpropan-1-one

Data (minor) are: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.76-7.74 (m, 2H), 7.50-7.47 (m, 1H), 7.35-7.17 (m, 15H), 6.98-6.96 (m, 2H), 5.27 (s, 1H), 5.18 (dd, $J = 3.0$, 7.0 Hz, 1H), 4.83 (d, $J = 7.0$ Hz, 1H), 2.51 (d, $J = 4.0$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz):
\[ \delta 200.1, 141.7, 140.7, 140.5, 137.1, 130.33, 128.8, 128.64, 128.55, 128.5, 128.4, 128.0, 127.73, 127.68, 127.4, 127.3, 127.2, 83.2, 75.7; \text{HRMS (FAB$^+$) found} \ 431.1624, \text{calcd} \ 431.1623 \text{ for } C_{28}H_{24}O_3Na; \text{HPLC (DAICEL Chiralpack AD, 10\% EtOH/hexane, flow rate 1.0 mL/min): } t_R = 12.6 \text{ (major). } t_R = 14.8 \text{ (minor).} \]

![Image of 2-(Benzhydryloxy)-3-hydroxy-1-(2-methoxyphenyl)-3-phenylpropan-1-one](image1)

**2-(Benzhydryloxy)-3-hydroxy-1-(2-methoxyphenyl)-3-phenylpropan-1-one**

Data are: \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta 7.64 \text{ (dd, } J = 1.5, 7.5 \text{ Hz, 1H)}, 7.44-7.40 \text{ (m, 1H)}, 7.31-7.23 \text{ (m, 9 H)}, 7.21-7.17 \text{ (m, 2H)}, 7.15-7.12 \text{ (m, 2H)}, 6.99 \text{ (dt, } J = 1.5, 7.5 \text{ Hz, 1H)}, 6.87-6.83 \text{ (m, 3H)}, 5.50 \text{ (s, 1H)}, 5.26 \text{ (d, } J = 3.0 \text{ Hz, 1H)}, 5.01 \text{ (dd, } J = 3.0, 7.5 \text{ Hz, 1H)}, 3.60 \text{ (s, 3H)}, 3.11 \text{ (d, } J = 3.0 \text{ Hz, 1H)}; ^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz): } \delta 200.7, 158.0, 142.2, 141.1, 140.5, 134.1, 131.1, 128.4, 128.3, 128.2, 127.9, 127.7, 127.6, 127.5, 127.3, 127.1, 126.3, 121.4, 111.6, 84.8, 82.6, 73.9, 55.4; \text{HRMS (FAB$^+$) found} 461.1729, \text{calcd} 461.1729 \text{ for } C_{29}H_{26}O_4Na; \text{HPLC (DAICEL Chiralpack AD, 10\% EtOH/hexane, flow rate 1.0 mL/min): } t_R = 52.3 \text{ (major). } t_R = 57.5 \text{ (minor).} \]

![Image of 2-(Benzhydryloxy)-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpropan-1-one](image2)

**2-(Benzhydryloxy)-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpropan-1-one**

Data (major) are: \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta 7.72-7.70 \text{ (m, 2H)}, 7.28-7.19 \text{ (m, 13H)}, 7.07-7.04 \text{ (m, 2H)}, 6.81-6.78 \text{ (m, 2H)}, 5.39 \text{ (s, 1H)}, 5.09 \text{ (t, } J = 3.5 \text{ Hz, 1H),} \)
4.82 (d, \( J = 5.5 \) Hz, 1H), 3.83 (s, 3H), 3.20 (d, \( J = 4.0 \) Hz, 1H); \(^{13}\)C NMR (CDCl\textsubscript{3}, 125 MHz): \( \delta \) 197.2, 163.9, 141.7, 140.3, 139.7, 131.1, 129.4, 128.8, 128.4, 128.18, 128.15, 127.8, 127.7, 126.8, 113.9, 83.0, 82.9, 75.4, 55.7; HRMS (FAB\textsuperscript{+}) found 461.1728, calcd 461.1729 for C\textsubscript{29}H\textsubscript{26}O\textsubscript{4}Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): \( t_R \) = 22.0 (major). \( t_R \) = 26.9 (minor).

![Structure](image)

2-(Benzhydryloxy)-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpropan-1-one

Data (minor) are: \(^1\)H NMR (CDCl\textsubscript{3}, 500 MHz): \( \delta \) 7.80-7.78 (m, 2H), 7.36-7.34 (m, 2H), 7.31-7.28 (m, 3H), 7.23-7.17 (m, 8H), 6.96-6.94 (m, 2H), 6.81-6.79 (m, 2H), 5.27 (s, 1H), 5.17 (m, 1H), 4.77 (d, \( J = 6.5 \) Hz, 1H), 3.84 (s, 3H), 2.58 (d, \( J = 3.5 \) Hz, 1H); \(^{13}\)C NMR (CDCl\textsubscript{3}, 125 MHz): \( \delta \) 198.3, 163.9, 141.8, 140.8, 140.6, 131.3, 130.1, 128.6, 128.5, 128.4, 128.3, 128.0, 127.71, 127.68, 127.2, 113.8, 82.8, 81.8, 75.7, 55.7; HRMS (FAB\textsuperscript{+}) found 461.1728, calcd 461.1729 for C\textsubscript{29}H\textsubscript{26}O\textsubscript{4}Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): \( t_R \) = 22.3 (major). \( t_R \) = 32.3 (minor).

![Structure](image)

2-(Benzhydryloxy)-1-(2,4-dimethoxyphenyl)-3-hydroxy-3-phenylpropan-1-one

Data are: \(^1\)H NMR (CDCl\textsubscript{3}, 500 MHz): \( \delta \) 7.78 (d, \( J = 8.5 \) Hz, 1H), 7.33-7.24 (m, 9H),
7.21-7.17 (m, 2H), 7.14-7.11 (m, 2H), 6.85 (d, $J = 7.5$ Hz, 2H), 6.53 (dd, $J = 2.5$, 8.5 Hz, 1H), 6.32 (d, $J = 2.5$ Hz, 1H), 3.84 (s, 3H), 3.59 (s, 3H), 3.16 (d, $J = 8.0$ Hz, 1H);

$^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 198.3, 165.0, 160.3, 142.3, 141.3, 140.7, 133.6, 128.4, 128.3, 128.2, 127.9, 127.7, 127.51, 127.45, 127.3, 126.3, 120.0, 106.0, 98.5, 84.3, 82.3, 74.1, 55.8, 55.4; HRMS (FAB$^+$) found 491.1843, calcd 491.1834 for C$_{30}$H$_{28}$O$_5$Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): $t_R = 31.8$ (minor). $t_R = 34.6$ (major).

2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-3-0-tolylpropan-1-one.

Data are: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.51 (m, 1 H), 7.12-7.32 (m, 10 H), 7.00 (m, 2 H), 6.93 (m, 1 H), 6.84 (m, 2 H), 6.71 (d, $J = 9.5$ Hz, 1 H), 5.47 (s, 1 H), 5.28 (d, $J$ = 3.5 Hz, 1 H), 5.12 (dd, $J$ = 3.5, 7.0 Hz, 1 H), 3.75 (s, 3 H), 3.41 (s, 3 H), 3.07 (d, $J$ = 7.0 Hz, 1 H), 1.94 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 202.0, 153.8, 151.8, 142.2, 140.8, 138.3, 134.3, 130.3, 128.44, 128.35, 128.1, 127.73, 127.65, 127.62, 127.57, 127.3, 127.2, 125.8, 120.0, 114.1, 112.5, 82.7, 82.6, 71.3, 56.0, 55.5, 18.6; HRMS (FAB$^+$) found 505.1986, calcd 505.1991 for C$_{31}$H$_{30}$O$_5$Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): $t_R = 12.2$ (minor). $t_R = 21.3$ (major).
2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-(furan-3-yl)-3-hydroxypropan-1-one.

Data are: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.15-7.36 (m, 15 H), 7.00 (q, $J = 2.5$ Hz, 1 H), 6.79 (d, $J = 9.5$ Hz, 1 H), 6.21 (s, 1 H), 5.60 (s, 1 H), 5.23 (d, $J = 2.5$ Hz, 1 H), 4.96 (dd, $J = 2.5$, 8.5 Hz, 1 H), 3.77 (s, 3 H), 3.56 (s, 3 H), 2.95 (d, $J = 8.5$ Hz, 1 H); $^1$C NMR (CDCl$_3$, 125 MHz): $\delta$ 199.7, 154.0, 152.6, 143.0, 142.1, 140.6, 140.0, 128.5, 128.3, 128.2, 128.0, 127.6, 127.3, 126.9, 126.3, 121.2, 114.1, 113.3, 109.2, 83.8, 82.6, 68.1, 56.0; HRMS (M$^+$) found 458.1723, calcd 458.1729 for C$_{28}$H$_{26}$O$_6$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): $t_R = 43.0$ (minor), $t_R = 47.7$ (major).

2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-(furan-2-yl)-3-hydroxypropan-1-one.

Data (major) are: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.21-7.37 (m, 10 H), 7.00-7.05 (m, 3 H), 6.81 (d, $J = 8.5$ Hz, 1 H), 6.29-6.35 (m, 2 H), 5.53 (s, 1 H), 5.42 (d, $J = 2.5$ Hz, 1 H), 5.04 (dd, $J = 2.5$, 9.0 Hz, 1 H), 3.78 (s, 3 H), 3.62 (s, 3 H), 3.09 (d, $J = 9.0$ Hz, 1 H); $^1$C NMR (CDCl$_3$, 125 MHz): $\delta$ 198.9, 154.1, 153.9, 153.0, 142.1, 141.8, 140.6,
128.5, 128.3, 127.9, 127.7, 127.4, 126.3, 121.5, 114.1, 113.3, 110.6, 107.2, 82.7, 82.6, 69.2, 56.0, 55.9; HRMS (FAB^+) found 481.1637, calcd 481.1627 for C_{28}H_{26}O_{6}Na;

HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 21.4 (minor). t_R = 38.3 (major).

\[
\text{OMe} \quad \text{OMe} \\
\text{DMPO} \quad \text{OH} \\
\text{anti}
\]

\[\begin{align*}
\text{2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-(furan-2-yl)-3-hydroxypropan-1-one.}
\end{align*}\]

Data (minor) are: \(^1\text{H NMR (CDCl}_3, 500 MHz)\): \(\delta 7.17-7.30 (m, 11 H), 6.95-6.99 (m, 2 H), 6.76 (d, J = 9.5 Hz, 1 H), 6.32 (s, 1 H), 6.28 (s, 1 H), 5.47 (s, 1 H), 5.43 (d, J = 5.5 Hz, 1 H), 5.04 (dd, J = 5.5, 8.5 Hz, 1 H), 3.73 (s, 3 H), 3.58 (s, 3 H), 2.94 (d, J = 8.5 Hz, 1 H); \(^{13}\text{C NMR (CDCl}_3, 125MHz)\): \(\delta 200.6, 153.9, 153.2, 152.5, 142.04, 142.0, 141.0, 128.6, 128.3, 128.1, 128.0, 127.96, 127.6, 127.4, 120.8, 113.8, 113.4, 110.6, 108.5, 82.9, 82.0, 69.1, 56.2, 56.0; \]

HRMS (FAB^+) found 481.1624, calcd 481.1627 for C_{28}H_{26}O_{6}Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 27.5 (minor). t_R = 31.0 (major).

\[
\text{OMe} \quad \text{OMe} \\
\text{Cl} \quad \text{DMPO} \\
\text{OMe} \\
\begin{align*}
\text{2-(Benzhydryloxy)-3-(4-chlorophenyl)-1-(2,5-dimethoxyphenyl)-3-hydroxypropan-1-one.}
\end{align*}
\]
n-1-one.

Data are: major: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.13-7.32 (m, 13 H), 7.00-7.02 (m, 1 H), 6.79-6.86 (m, 3 H), 5.47 (s, 1 H), 5.22 (dd, $J = 1.0$ Hz), 4.99 (s, 1 H), 3.77 (s, 3 H), 3.56 (s, 3 H), 3.20 (bs, 1 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 199.8, 154.0, 152.5, 142.0, 140.2, 139.8, 133.1, 128.4, 128.3, 128.2, 127.9, 127.6, 127.2, 121.1, 114.3, 113.4, 84.5, 82.6, 73.3, 56.0, 55.9; HRMS (FAB$^+$) found 525.1457, calcld 525.1445 for C$_{30}$H$_{27}$O$_5$ClNa; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): $t_R = 23.2$ (minor). $t_R = 28.9$ (major).

\[
\text{2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-3-(2-methoxyphenyl) propan-1-one.}
\]

Data are: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.43-7.45 (m, 1 H), 7.09-7.31 (m, 9 H), 6.92-7.02 (m, 3 H), 6.68-6.81 (m, 4 H), 5.45 (s, 1 H), 5.35 (d, $J = 2.0$ Hz, 1 H), 5.19 (dd, $J = 2.0, 9.0$ Hz, 1 H), 3.74 (s, 1 H), 3.47 (s, 1 H), 3.465 (s, 1 H), 3.23 (d, $J = 9.0$ Hz, 1 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 202.3, 156.0, 153.7, 152.0, 142.4, 141.0, 129.0, 128.5, 128.4, 128.3, 128.2, 127.7, 127.5, 127.4, 127.2, 120.5, 119.3, 114.2, 112.6, 110.0, 82.8, 82.3, 70.2, 55.9, 55.7, 54.9; HRMS (FAB$^+$) found 521.1954, calcld 521.1940 for C$_{31}$H$_{30}$O$_6$Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): $t_R = 19.0$ (minor). $t_R = 31.8$ (major).
2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-3-p-tolylpropan-1-one.

Data are: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.07-7.32 (m, 13 H), 6.96-6.99 (m, 1 H), 6.88-6.90 (m, 2 H), 6.78 (d, $J = 9$ Hz, 1 H), 5.48 (s, 1 H), 5.26 (d, $J = 3.0$ Hz, 1 H), 4.99 (dd, $J = 3.0$, 7.5 Hz, 1 H), 3.76 (s, 3 H), 3.54 (s, 3 H), 3.05 (d, $J = 7.5$ Hz, 1 H), 2.35 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 200.3, 154.0, 152.5, 142.3, 140.7, 138.1, 137.1, 128.9, 128.7, 128.4, 128.3, 127.9, 127.7, 127.5, 127.3, 126.2, 120.9, 114.3, 113.3, 84.9, 82.6, 73.9, 56.0, 21.3; HRMS (M$^+$) found 482.1078, calcd 482.2093 for C$_{31}$H$_{30}$O$_5$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): $t_R = 21.0$ (minor). $t_R = 32.3$ (major).

2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-3-(4-methoxyphenyl)propan-1-one.

Data are: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.14-7.33 (m, 11 H), 6.93-6.99 (m, 3 H), 6.76-6.81 (m, 3 H), 5.26 (d, $J = 3.5$ Hz, 1 H), 4.97 (dd, $J = 3.5$, 7.5Hz, 1 H), 3.81 (s, 3 H), 3.76 (s, 3 H), 3.54 (s, 3 H), 3.06 (d, $J = 7.5$ Hz, 1 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 200.4, 159.2, 154.0, 152.5, 142.3, 140.7, 133.1, 128.7, 128.5, 128.3, 128.0, 127.8, 127.6, 127.4, 120.9, 114.3, 113.6, 113.3, 84.9, 82.6, 73.8, 56.0, 55.5; HRMS
(FAB\(^+\)) found 521.1940, calcd 521.1940 for C\(_{31}\)H\(_{30}\)O\(_6\)Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t\(_R\) = 36.1 (minor). t\(_R\) = 49.8 (major).

\[
\text{2-(Benzhydryloxy)-3-(biphenyl-2-yl)-1-(2,5-dimethoxyphenyl)-3-hydroxypropan-1-one.}
\]

Data (major) are: \(^1\)H NMR (CDCl\(_3\), 500MHz): \(\delta\) 7.73 (d, \(J = 8.0\) Hz, 1 H), 7.02-7.42 (m, 14 H), 6.80-6.82 (m, 1 H), 6.74-6.78 (m, 4 H), 6.64 (d, \(J = 3.0\) Hz, 1 H), 6.50 (d, \(J = 9\) Hz, 1 H), 5.38 (s, 1 H), 5.26 (dd, \(J = 2.5, 7.5\) Hz, 1 H), 4.76 (d, \(J = 2.5\) Hz, 1 H), 3.71 (s, 3 H), 3.29 (s, 3 H),, 3.06 (d, \(J =7.5\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 202.9, 153.5, 151.0, 142.3, 140.9, 140.44, 140.37, 137.7, 130.3, 128.9, 128.5, 128.3, 128.2, 128.1, 127.8, 127.71, 127.68, 127.55, 127.49, 127.3, 126.9, 118.5, 113.2, 112.3, 83.1, 82.4, 70.4, 56.0, 55.5 \(;\) HRMS (FAB\(^+\)) found 567.2161, calcd 567.2147 for C\(_{36}\)H\(_{32}\)O\(_5\)Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t\(_R\) = 16.8 (minor). t\(_R\) = 21.0 (major).

\[
\text{2-(Benzhydryloxy)-3-(biphenyl-2-yl)-1-(2,5-dimethoxyphenyl)-3-hydroxypropan-}
\]
1-one.

Data (minor) are: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.07-7.49 (m, 18 H), 6.97-7.00 (dd, $J = 3.5, 9.0$ Hz, 1 H), 6.86-6.89 (m, 2 H), 6.78 (d, $J = 9.0$ Hz, 1 H), 5.51 (s, 1 H), 5.34 (d, $J = 3.0$ Hz, 1 H), 5.09 (dd, $J = 3.0, 8.5$ Hz, 1 H), 3.75 (s, 3 H), 3.55 (s, 3 H), 3.14 (d, $J = 8.5$ Hz, 1 H); HRMS (FAB$^+$) found 567.2158, calcd 567.2147 for C$_{36}$H$_{32}$O$_5$Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): $t_R = 33.8$ (major). $t_R = 44.3$ (minor).

![2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-5-phenylpentan-1-one.](image)

$2$-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-5-phenylpentan-1-one.

Data are: major $^1$H NMR (CDCl$_3$, 500MHz): $\delta$ 7.43 (d, $J = 7.5$ Hz, 2 H), 7.15-7.36 (m, 12 H), 7.07 (d, $J = 7.0$ Hz, 2 H), 6.99 (dd, $J = 3.5, 8.5$ Hz, 1 H), 6.76 (d, $J = 9.5$ Hz, 1 H), 5.64 (s, 1 H), 5.01 (d, $J = 1.5$ Hz, 1 H), 3.84 (dd, $J = 1.5, 10$ Hz, 1 H), 3.76 (s, 3 H), 3.46 (s, 3 H), 2.63 (m, 1 H), 2.44 (m, 1 H), 2.35 (d, $J = 10$ Hz, 1 H), 2.00 (m, 1 H), 1.78 (m, 1 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 201.6, 154.0, 152.5, 142.3, 142.0, 141.0, 128.7, 128.60, 128.57, 128.5, 128.30, 128.27, 127.6, 127.3, 127.2, 126.0, 120.9, 114.2, 113.2, 83.0, 82.2, 71.6, 56.0, 55.8, 36.5, 32.0; HRMS (FAB$^+$) found 519.2149, calcd 519.2147 for C$_{32}$H$_{32}$O$_5$Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): $t_R = 38.0$ (minor). $t_R = 51.0$ (major).
(E)-2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-5-phenylpent-4-en-1-one.

Data are: major $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.15-7.41 (m, 16 H), 6.98 (dd, $J = 3.0$, 8.5 Hz, 1 H), 6.79 (d, $J = 9.5$ Hz, 1 H), 6.56 (d, $J = 16$ Hz, 1 H), 6.13 (dd, $J = 5.5$, 16 Hz, 1 H), 5.62 (s, 1 H), 5.12 (d, $J = 3.0$ Hz, 1 H), 4.56 (bs, 1 H), 3.72 (s, 3 H), 3.56 (s, 3 H), 2.73 (d, $J = 8.5$ Hz, 1 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 200.0, 154.1, 152.6, 142.1, 140.8, 136.8, 131.2, 129.4, 128.7, 128.6, 128.4, 128.3, 128.2, 127.8, 127.6, 127.5, 127.2, 126.7, 121.0, 114.2, 113.3, 84.1, 82.8, 73.0, 56.05, 55.96; HRMS (M$^+$) found 494.2091, calcd 494.2093 for C$_{32}$H$_{30}$O$_5$; HPLC (DAICEL Chiralpack AD, 10% IPA/hexane, flow rate 1.0 mL/min): $t_R = 30.8$ (minor). $t_R = 35.7$ (major).

2-(Benzhydryloxy)-3-(biphenyl-4-yl)-1-(2,5-dimethoxyphenyl)-3-hydroxypropan-1-one.

Data are: $^1$H NMR (CDCl$_3$, 500MHz): $\delta$ 7.60 (d, $J = 8.0$ Hz, 2 H), 7.45-7.52 (m, 4 H), 7.10-7.38 (m, 12 H), 7.00 (dd, $J = 3.0$, 9.0 Hz, 1 H), 6.88-6.90 (m, 2 H), 6.80 (d, $J = 9.0$ Hz, 1 H), 5.50 (s, 1 H), 5.31 (d, $J = 3.0$ Hz, 1 H), 5.07 (dd, $J = 3.0$, 8.0 Hz, 1 H), 3.77 (s, 3 H), 3.60 (s, 3 H), 3.14 (d, $J = 8.0$ Hz, 1 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$
200.2, 154.0, 152.6, 142.2, 141.2, 140.5, 140.2, 129.0, 128.43, 128.36, 127.9, 127.8, 127.6, 127.5, 127.32, 127.27, 127.1, 126.9, 126.7, 121.0, 114.4, 113.3, 84.9, 82.6, 73.8, 56.1, 56.0; HRMS (FAB\(^+\)) found 567.2141, calcd 567.2147 for C\(_{36}\)H\(_{32}\)O\(_5\)Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): \(t_R = 33.6\) (minor). \(t_R = 38.2\) (major).

\[
\begin{align*}
\text{2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-3-(naphthalen-2-yl)propan-1-one.}
\end{align*}
\]

Data are: \(^1\)H NMR (CDCl\(_3\), 500MHz): \(\delta 7.80\text{-}7.82 \text{ (m, 1 H)}, 7.71\text{-}7.76 \text{ (m, 3 H)}, 7.45\text{-}7.48 \text{ (m, 2 H)}, 7.09\text{-}7.35 \text{ (m, 8 H)}, 6.92\text{-}6.96 \text{ (m, 3 H)}, 6.74\text{-}6.80 \text{ (m, 3 H)}, 5.48 \text{ (s, 1 H)}, 5.39 \text{ (d,} J = 2.5 \text{ Hz, 1 H)}, 5.18 \text{ (bs, 1 H)}, 3.71 \text{ (s, 3 H)}, 3.57 \text{ (s, 3 H)}, 3.23 \text{ (d,} J = 8.0 \text{ Hz, 1 H}); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta 200.2, 154.0, 152.5, 142.1, 140.4, 138.6, 133.3, 133.1, 128.3, 128.2, 127.9, 127.84, 127.75, 127.5, 127.3, 127.2, 126.2, 126.0, 125.3, 124.3, 120.9, 114.3, 113.3, 84.7, 82.7, 74.1, 56.0, 55.9; HRMS (FAB\(^+\)) found 541.1998, calcd 541.1991 for C\(_{34}\)H\(_{30}\)O\(_5\)Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): \(t_R = 31.8\) (minor). \(t_R = 41.4\) (major).

\[
\begin{align*}
\text{2-(Benzhydryloxy)-1-(2,4-dimethoxyphenyl)-3-hydroxy-3-(4-nitrophenyl)propan-1-one.}
\end{align*}
\]
1-one

Data are: $^1$H NMR (CDCl$_3$, 500MHz): δ 8.14 (m, 2H), 7.41 (d, $J = 8.0$ Hz, 2H), 7.29-7.25 (m, 5H), 7.24-7.20 (m, 2H), 7.10 (d, $J = 7.5$ Hz, 2H), 7.06 (dd, $J = 4.0$ Hz, 9.0 Hz, 1H), 6.86 (d, $J = 9.0$ Hz, 1H), 6.80 (d, $J = 7.5$ Hz, 2H), 5.46 (s, 1H), 5.29 (d, $J = 2.0$ Hz, 1H), 5.11 (dd, $J = 2.0$ Hz, 8.5 Hz, 1H), 3.80 (s, 3H), 3.64 (s, 3H), 3.22 (d, $J = 8.5$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 199.1, 154.3, 152.7, 149.1, 147.4, 141.7, 140.0, 128.5, 128.4, 128.2, 128.1, 127.8, 127.2, 127.1, 126.6, 123.5, 121.6, 114.4, 113.7, 83.9, 82.7, 73.2, 56.3, 56.1; HRMS (FAB$^+$) found 536.1679, calcd 536.1685 for C$_{30}$H$_{27}$NO$_7$Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): $t_R = 45.2$ (minor). $t_R = 49.9$ (major).

![2-(Benzhydryloxy)-3-cyclohexyl-1-(2,4-dimethoxyphenyl)-3-hydroxypropan-1-one](image)

2-(Benzhydryloxy)-3-cyclohexyl-1-(2,4-dimethoxyphenyl)-3-hydroxypropan-1-one

Data (major) are: $^1$H NMR (CDCl$_3$, 500MHz): δ 7.50-7.47 (m, 2H), 7.39-7.31 (m, 7H), 7.27-7.24 (m, 2H), 7.01 (dd, $J = 3.0$, 8.5 Hz, 1H), 6.81 (d, $J = 8.5$ Hz, 1H), 5.61 (s, 1H), 5.21 (d, $J = 1.5$ Hz, 1H), 3.78 (s, 3H), 3.59 (s, 3H), 3.33 (t, $J = 10$ Hz, 1H), 2.06 (m, 1H), 1.73-1.50 (m, 4H), 1.19-0.96 (m, 4H), 0.82-0.79 (m, 1H), 0.61-0.57 (m, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 201.6, 154.1, 152.3, 142.4, 141.1, 129.1, 128.5, 128.34, 128.27, 127.5, 127.3, 127.2, 120.8, 114.2, 113.0, 82.0, 80.8, 76.6, 56.0, 55.8, 40.8, 29.9, 29.7, 29.0, 26.5, 26.2, 26.1; HRMS (FAB$^+$) found 497.2297, calcd
497.2304 for C$_{30}$H$_{34}$O$_5$Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): $t_R = 10.5$ (minor). $t_R = 23.6$ (major).

2-(Benzhydryloxy)-3-cyclohexyl-1-(2,4-dimethoxyphenyl)-3-hydroxypropan-1-one

Data (minor) are: $^1$H NMR (CDCl$_3$, 500MHz): $\delta$ 7.37-7.29 (m, 8H), 7.28-7.26 (m, 1H), 7.22-7.19 (m, 1H), 7.13 (d, $J = 3.5$ Hz, 1H), 7.00 (dd, $J = 3.5$, 9.0 Hz, 1H), 6.81 (d, $J = 9.0$ Hz, 1H), 5.45 (s, 1H), 5.16 (d, $J = 6.0$ Hz, 1H), 3.76 (s, 3H), 3.56 (s, 3H), 2.27 (d, $J = 7.0$ Hz, 1H), 1.64-0.87 (m, 11H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 202.8, 153.9, 152.4, 142.2, 141.4, 129.0, 128.6, 128.3, 128.2, 128.1, 127.6, 127.4, 120.5, 113.9, 113.3, 96.4, 82.6, 81.2, 77.7, 56.1, 40.0, 30.0, 27.0, 26.6, 26.5, 26.2; HRMS (FAB$^+$) found 497.2300, calcd 497.2304 for C$_{30}$H$_{34}$O$_5$Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): $t_R = 12.7$ (minor). $t_R = 21.4$ (major).

2-(Benzhydryloxy)-1-(2,4-dimethoxyphenyl)-3-hydroxy-4-methylpentan-1-one

Data (major) are: $^1$H NMR (CDCl$_3$, 500MHz): $\delta$ 7.48-7.46 (m, 2H), 7.37-7.31 (m, 7H), 7.26-7.25 (m, 2H), 7.01 (dd, $J = 3.5$, 9.0 Hz, 1H), 6.81 (d, $J = 8.5$ Hz, 1H), 3.78 (s, 3H), 3.57 (s, 3H), 3.27 (t, $J = 10.5$ Hz, 1H), 2.18 (d, $J = 10.5$ Hz, 1H), 1.92 (m,
$^{1}H$, 0.95 (d, $J = 6.5$ Hz, 3H), 0.51 (d, $J = 7.0$ Hz, 3H); $^{13}C$ NMR (CDCl$_3$, 125 MHz): δ 201.3, 154.1, 152.3, 142.4, 141.0, 129.1, 128.6, 128.35, 128.28, 127.6, 127.5, 127.2, 127.1, 120.9, 114.3, 113.0, 81.8, 81.0, 77.8, 56.0, 55.7, 31.5, 19.6, 18.8; HRMS (FAB$^+$) found 457.1974, calcd 457.1991 for C$_{27}$H$_{30}$O$_5$Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): $t_R = 13.6$ (minor). $t_R = 39.8$ (major).

![Chemical structure](image-url)

**2-(Benzhydryloxy)-1-(2,4-dimethoxyphenyl)-3-hydroxy-4-methylpentan-1-one**

Data (minor) are: $^{1}H$ NMR (CDCl$_3$, 500MHz): δ 7.36-7.29 (m, 7H), 7.27-7.24 (m, 2H), 7.21-7.18 (m, 1H), 7.13 (d, $J = 3.0$ Hz, 1H), 7.00 (dd, $J = 3.0$, 9.0 Hz, 1H), 6.81 (d, $J = 9.0$ Hz, 1H), 5.46 (s, 1H), 5.17 (d, $J = 6.0$ Hz, 1H), 3.77 (s, 3H), 3.76-3.73 (m, 1H), 3.56 (s, 3H), 2.28 (d, $J = 8.0$ Hz, 1H), 1.85 (m, 1H), 0.83 (apparent t, $J = 7.0$ Hz, 6H); $^{13}C$ NMR (CDCl$_3$, 125 MHz): δ 202.5, 153.9, 152.5, 142.2, 141.3, 128.8, 128.7, 128.3, 128.2, 128.1, 127.5, 127.3, 120.6, 113.9, 113.4, 95.0, 82.5, 81.7, 78.2, 56.0, 30.2, 30.0, 19.8, 16.8; HRMS (FAB$^+$) found 457.1989, calcd 457.1991 for C$_{27}$H$_{30}$O$_5$Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): $t_R = 11.0$ (minor). $t_R = 12.2$ (major).
2-(Benzhydryloxy)-4-(benzyloxy)-1-(2,4-dimethoxyphenyl)-3-hydroxybutan-1-one

Data are: $^1$H NMR (CDCl$_3$, 500MHz): $\delta$ 7.41 (d, $J = 7.0$ Hz, 2H), 7.34-7.32 (m, 4H), 7.31-7.23 (m, 7H), 7.20-7.17 (m, 3H), 6.98 (dd, $J = 3.0$, 8.5 Hz, 1H), 6.76 (d, $J = 9.0$ Hz, 1H), 5.64 (s, 1H), 5.26 (d, $J = 2.0$ Hz, 1H), 4.42 (ABq, $J = 11.5$ Hz, 1H), 4.38 (ABq, $J = 11.5$ Hz, 1H), 4.09-4.04 (m, 1H), 3.75 (s, 3H), 3.62-3.54 (m, 2H), 3.44 (s, 3H), 2.48 (d, $J = 9.0$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 200.6, 153.9, 152.7, 142.3, 141.0, 138.2, 128.7, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6, 127.4, 127.0, 120.9, 114.0, 113.2, 82.3, 80.8, 73.4, 71.4, 70.8, 56.0, 55.8; HRMS (FAB$^+$) found 535.2114, calcd 535.2097 for C$_{32}$H$_{32}$O$_6$Na; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): $t_R = 35.9$ (minor). $t_R = 45.2$ (major).

2-(Benzhydryloxy)-4-(benzyloxy)-1-(2,4-dimethoxyphenyl)-3-hydroxybutan-1-one

Data are: $^1$H NMR (CDCl$_3$, 500MHz): $\delta$ 7.33-7.17 (m, 15H), 7.10 (d, $J = 3.5$ Hz, 1H), 6.97 (dd, $J = 3.5$, 9.0 Hz, 1H), 6.77 (d, $J = 9.0$ Hz, 1H), 5.52 (s, 1H), 5.29 (d, $J = 5.5$ Hz, 1H), 4.43 (s, 2H), 4.16-4.14 (m, 1H), 3.70 (s, 3H), 3.70-3.60 (m, 2H), 3.46 (s, 3H), 2.61 (d, $J = 8.0$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 201.0, 153.8, 152.8, 142.2,
141.3, 138.2, 128.7, 128.5, 128.3, 128.1, 127.9, 127.6, 127.5, 120.8, 113.9, 113.5, 82.7, 81.1, 73.6, 72.1, 70.8, 56.0, 55.9; HRMS (EI⁺) found 535.2203, calcd 512.2199 for C₃₂H₃₂O₆; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): tᵣ = 84.4 (minor). tᵣ = 95.1 (major).

4.3.4. Product Elaboration and Absolute Configuration Determination

\[ \text{2-(Benzhydryloxy)-3-(2,5-dimethoxyphenyl)-3-oxo-1-phenylpropyl acetate} \]

To a stirred solution of 2-(benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-3-phenylpropan-1-one 90 (0.6 g, 1.28 mmol) in EtOAc (3 mL) were added pyridine (0.31 mL, 3.84 mmol), DMAP (20 mg), and acetyl chloride (0.27 mL, 3.84 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 30 min and then stirred at ambient temperature for overnight. The reaction was quenched by 1 N HCl. The resulting mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered, and evaporated in vacuo. The product (0.64 g, 97%) was used for the next step without further purification, although it can be recrystallized with ethyl acetate and hexanes. Data are: ¹H NMR (CDCl₃, 500 MHz): δ 7.10-7.32 (m, 13 H), 7.03 (d, J = 3.0 Hz, 1 H), 6.96-6.99 (m, 1 H), 6.79-6.85 (m, 3 H), 6.14 (d, J = 3.5 Hz, 1 H), 5.48 (s, 1 H), 5.26 (d, J = 3.5 Hz, 1 H), 3.74 (s, 3 H), 3.59 (s, 3 H), 2.04 (s, 3 H); ¹³C NMR (CDCl₃, 75
3-(2,5-Dimethoxyphenyl)-2-hydroxy-3-oxo-1-phenylpropyl acetate (95)

A solution of 2-(benzhydryloxy)-3-(2,5-dimethoxyphenyl)-3-oxo-1-phenylpropyl acetate (0.51 g, 1 mmole) in 25 mL CH₂Cl₂ was cooled to –78 °C. TiCl₄ (1.1 mL, 1.0 M CH₂Cl₂) was added dropwisely. The resulting dark red solution was stirred at -78 °C for 2 h, at which time the reaction was quenched by saturated NaHCO₃ solution. The aqueous layer was extracted 3 times with ether. The combined organic layers were washed with water and brine, dried over MgSO₄. The solution was then filtered and concentrated in vacuo. Radial chromatography afforded the desired compound 95 (0.27 g, 77%). Data are: ¹H NMR (CDCl₃, 500 MHz): δ 7.27-7.44 (m, 6 H), 7.13 (dd, J = 3.0, 9.0 Hz, 1 H), 6.98 (d, J = 9.0 Hz, 1 H), 6.13 (d, J = 1.5 Hz, 1 H), 5.44 (dd, J = 1.5, 7.0 Hz, 1 H), 3.97 (d, J = 7.0 Hz, 1 H), 3.95 (s, 3 H), 3.81 (s, 3 H), 1.99 (s, 3 H); ¹³C NMR (CDCl₃, 125 MHz): δ 199.2, 169.8, 154.1, 153.6, 137.9, 128.6, 128.3, 127.0, 122.3, 114.8, 113.5, 79.3, 75.0, 56.3, 56.1, 20.9; HRMS (FAB⁺) found 367.1156, calcd 367.1158 for C₁₀H₁₀O₆Na.
2,5-Dimethoxyphenyl 3-acetoxy-2-hydroxy-3-phenylpropanoate (96)

To a flame dried round bottom flask was added activated 4 angstrom molecular sieves (1.0 g), K₂CO₃ (0.2142 g, 1.55 mmol), trans-N,N-bis(p-toluenesulfonyl)-1,2-cyclohexanediamine (0.3275 g, 0.775 mmol) and 10 mL of CH₂Cl₂. The mixture was cooled to 0 °C and SnCl₄ (0.78 mL, 1 M in CH₂Cl₂) was added followed by bis(trimethylsilyl) peroxide (0.33 mL, 1.55 mmol). The mixture was stirred at 0 °C for 15 min, then 3-(2,5-dimethoxyphenyl) -2-hydroxy-3-oxo-1-phenylpropyl acetate 95 (0.2669 g, 0.775 mmol) was added as a CH₂Cl₂ solution (7.5 mL). The reaction stirred at 0 °C for 50 min, at which time the reaction was quenched by the addition of a saturated NaHCO₃ followed by a saturated Na₂S₂O₃ solution. The mixture was stirred at ambient temperature for 30 min then diluted with EtOAc and the layers separated. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with H₂O and brine. The mixture was then filtered, concentrated and purified by radial chromatography to provide the desired product 96 (0.22 g, 79%). Data are:

¹H NMR (CDCl₃, 500 MHz): δ 7.32-7.48 (m, 5 H), 6.90 (d, J = 8.5 Hz, 1 H), 6.76 (dd, J = 3.0, 9.5 Hz, 1H), 6.59 (d, J = 3.0 Hz, 1H), 6.30 (d, J = 3.0 Hz, 1H), 4.70 (dd, J = 3.0, 8.5 Hz, 1H), 3.752 (s, 3 H), 3.747 (s, 3 H), 3.05 (d, J = 8.5 Hz, 1H), 2.15 (s, 3 H);

¹³C NMR (CDCl₃, 125 MHz): δ 170.0, 169.8, 153.9, 145.3, 139.5, 136.6, 128.8, 128.7, 127.2,113.6, 112.3, 109.3, 75.7, 73.9, 56.6, 56.0, 21.1; HRMS (M⁺) found 360.1223, calcd 360.1209 for C₁₉H₂₀O₇.
Methyl 2,3-dihydroxy-3-phenylpropanoate (97).

To a flame dried round bottom flask containing 2,5-dimethoxyphenyl-3-acetoxy-2-hydroxy-3-phenylpropanoate 96 (0.1 g, 0.28 mmol) was added 2.8 mL of MeOH and 2.8 mL of THF. The solution was cooled to 0 °C and then a freshly prepared NaOMe solution (5.8 mL, 0.1 M in MeOH) was added. The solution was stirred at 0 °C for 1 h then at ambient temperature for 17 h, at which time the reaction was quenched by the addition of a saturated NH₄Cl solution. The resulting solution was extracted with Et₂O and the combined organic layers were dried over MgSO₄, filtered and concentrated. The crude residue was purified by flash column chromatography to provide the title compound 97 (0.0182 g, 85%). Data are: [α]$_{23}^D$ -7.6 (c 0.3, CHCl₃); [Lit. -10.7 (c 1.0, CHCl₃)]; $^1$H NMR (CDCl₃, 500 MHz): δ 7.30-7.41 (m, 5 H), 5.01 (dd, $J = 3.0$, 6.5 Hz, 1 H), 4.37 (dd, $J = 3.0$, 6.5 Hz, 1 H), 3.80 (s, 3 H), 3.17 (d, $J = 5.5$ Hz, 1 H), 2.83 (d, $J = 6.5$ Hz, 1 H); $^{13}$C NMR (CDCl₃, 125 MHz): δ 173.4, 140.1, 128.7, 128.3, 126.4, 74.9, 74.6, 53.1; HRMS (FAB$^+$) found 219.0635, calcd 219.0633 for C$_{10}$H$_{12}$O$_4$Na.
4.4. Total Synthesis of 8,9-Methylamido-Geldanamycin

4.4.1. Preparation of Intermediates for Successful Route

(2R,3S)-((1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl)
3-hydroxy-2-methoxy-4-(4-methoxybenzyloxy)butanoate (132)

A 500 mL flame dried flask was charge with auxiliary 103 (4.957 g, 10 mmol) and 300 mL dry CH₂Cl₂. The solution was cooled to -78 °C under N₂ atmosphere. NEt₃ (3.4 mL, 25 mmol) was added dropwisely over 5 min, followed by slow addition of c-Hex₂BOTf (20 mL, 1 M hexanes) over 30 min. The resulting mixture was stirred at -78 °C for 2.5 h at which time aldehyde 131 (2.7 g, 15 mmol) was added as a CH₂Cl₂ (5 mL) solution over 5 min. The mixture was stirred for another 2 h, at which time it was quenched with pH 7 buffer (10 mL), MeOH (10 mL) and 30% H₂O₂ (2 mL). The mixture was warmed to ambient temperature and NaHCO₃ aqueous solution was added. The layers were separated and aqueous layer was extracted 3 times with CH₂Cl₂. The organic layers were combined and dried over Na₂SO₄, filtered and concentrated. Chromatograph (20-30% EtOAc/hexanes) provides the desired product 132 (6.14 g, 91%). Data are: TLC Rₜ = 0.3 (30% EtOAc/hexanes); [α]D²³ = +39.2° (c 3.8, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.30 (d, J = 7.0 Hz, 2H), 7.23-7.13 (m, 8H), 6.88-6.83 (m, 6H), 5.87 (d, J = 5.0 Hz, 1H), 4.75 (A of AB q, J = 16.5 Hz, 1H), 4.51 (B of AB q, J = 16.5 Hz, 1H), 4.42 (apparent q, J = 11.5 Hz, 2H), 4.15 (m, 2H),
3.83 (d, J = 3.5 Hz, 1H), 3.77 (s, 3H), 3.47 (d, J = 7.0 Hz, 2H), 3.35 (s, 3H), 2.56 (d, J = 7.5 Hz, 1H), 2.47 (s, 6H), 2.27 (s, 3H), 1.21 (d, J = 7.0 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 169.6, 159.4, 142.7, 140.4, 138.5, 138.0, 133.3, 132.3, 129.9, 129.5, 128.4, 128.1, 127.9, 127.3, 126.4, 113.9, 80.4, 78.7, 77.5, 77.2, 77.0, 73.2, 70.8, 69.7, 59.5, 56.9, 55.3, 48.3, 23.0, 21.0, 14.0; HRMS (FAB+) found 675.3533 M$, \text{calcd } 675.2866 \text{ for } \text{C}_3\text{H}_4\text{NO}_8\text{S}$.

(2$R$,3$S$)-((1$R$,2$S$)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl)

2-methoxy-4-(4-methoxybenzyloxy)-3-(triethylsilyloxy)butanoate 133

A 100 mL dry flask was charged with the aldol product 132 (6.24 g, 9.1 mmol) and DMF (50 mL). To the stirring solution was added imidazole (1.86 g, 27.3 mmol) followed by TESCl (3.1 mL, 18.2 mmol). The mixture was stirred for 4 h at ambient temperature and then quenched with H$_2$O (200 mL). The layers were separated and aqueous layer was extracted 3 times with Et$_2$O. The organic layers were combined, dried and concentrated. Chromatograph (20% EtOAc/hexanes) provided the desired product 133 (6.75 g, 94%). Data are: TLC $R_f$ = 0.6 (20% EtOAc/hexanes); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.32 (d, $J$ = 6.5 Hz, 2H), 7.26-7.18 (m, 6H), 7.10 (t, $J$ = 7.5 Hz, 2H), 6.85-6.83 (m, 6H), 5.81 (d, $J$ = 5 Hz, 1H), 4.77 (A of AB q, $J$ = 16 Hz, 1H), 4.51 (B of AB q, $J$ = 16 Hz, 1H), 4.35 (m, 2H), 4.13-4.11 (m, 2H), 3.79 (s, 3H), 3.73 (d, $J$ = 5 Hz, 1H), 3.51-3.48 (m, 1H), 3.33 (m, 4H), 2.41 (s, 6H), 2.29 (s, 3H), 1.18 (d, $J$ =
7 Hz, 3H), 0.81 (t, J = 7 Hz, 9H), 0.48-0.43 (m, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 169.9, 159.4, 142.7, 140.5, 138.7, 138.0, 138.3, 132.3, 130.3, 129.5, 128.6, 128.4, 128.2, 128.1, 127.5, 126.9, 82.5, 78.8, 73.1, 72.1, 70.6, 59.8, 56.9, 55.5, 48.2, 23.1, 21.1, 14.7, 6.9, 5.0; HRMS (FAB+) found 812.3633 [M+Na]$^+$, calcd 816.3628 for C$_{44}$H$_{59}$NO$_8$SiNa.

(2R,3S)-2-Methoxy-4-(4-methoxybenzylxylo)-3-(triethylsilyloxy)butanal (134)

A flame dried 250 mL round bottom flask was charged with the TES protected aldol product 133 (2.25 g, 2.8 mmol) and 80 mL dry CH$_2$Cl$_2$. The resulting solution was cooled to -78 °C under nitrogen atmosphere. DIBAL-H (4.7 mL, 1.5 M in toluene) was added along the inner wall of the flask over 20 min. The mixture was stirred for 3 h before being quenched with 4 mL MeOH and 12 mL Na/K tartrate aqueous solution at -78 °C. The mixture was allowed to warm to ambient temperature and stirred for another 1.5 h, at which time it was diluted with 80 mL Na/K tartrate salt solution and extracted 4 times with CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$, filtered, concentrated, and chromatographed (10% acetone/hexanes) to give the title compound 134 (0.86 g, 87%). Data are: TLC R$_f$ = 0.6 (20% EtOAc/hexanes); $[\alpha]_D^{23}$ = +31.7° (c 3.3, CHCl$_3$); $^1$H NMR (CDCl$_3$, 500 MHz) δ 9.76 (d, J = 1.5 Hz, 1H), 7.23 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 4.45 (A of AB q, J = 11.5 Hz, 1H), 4.41 (b of AB q, J = 11.5 Hz, 1H), 4.20-4.17 (m, 1H), 3.81 (s, 3H), 3.69-3.68 (m, 1H),
3.59-3.56 (m, 1H), 3.48 (s, 3H), 3.45-3.43 (m, 1H), 0.93-0.89 (m, 9H), 0.61-0.56 (m, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 203.6, 159.4, 130.2, 129.6, 113.9, 87.0, 73.2, 72.1, 70.1, 59.6, 55.5, 6.9. 4.9; HRMS (FAB+) found 391.1916 [M+Na]$^+$, calcd 391.1917 for C$_{19}$H$_{32}$O$_5$SiNa.

(4S,5S,Z)-Ethyl 4-methoxy-6-(4-methoxybenzylxylo)-5-(triethylsilyloxy)hex-2-enoate (136)

To a mixture of phosphonate 135 (1.17 g, 2.71 mmol) and NaI (1.69 g, 11.3 mmol) in 20 mL THF was slowly added tetramethylguanidine (0.37 mL, 2.94 mmol) at -78 °C. After the mixture was stirred for 30 min, aldehyde 134 (0.83 g, 2.26 mmol) was added as a THF (3 mL) solution. The mixture was stirred for another 5 h and then quenched with NH$_4$Cl aqueous solution. The layers were separated. Aqueous layer was extracted 3 times with Et$_2$O. The organic layers were combined, dried over Na$_2$SO$_4$, filtered and concentrated. The crude product was purified by chromatograph (5% EtOAc/hexanes) and provided 136 (0.97 g, 98%, 16:1–28:1 selectivity). Data are:

TLC R$_f$ = 0.6 (10% EtOAc/hexanes); $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.27 (d, $J = 9.0$ Hz, 2H), 6.87 (d, $J = 9.0$ Hz, 2H), 6.25 (dd, $J = 8.3$ and 12 Hz, 1H), 5.97 (d, $J = 12$ Hz, 1H), 4.92 (m, 1H), 4.50 (A of AB q, $J = 12$ Hz, 1H), 4.42 (B of AB q, $J = 12$ Hz, 1H), 4.21- 4.15 (m, 2H), 4.03-4.00 (m, 1H), 3.80 (s, 3H), 3.62 (dd, $J = 6$ and 10 Hz, 1H), 3.43 (dd, $J = 6$ and 10 Hz, 1H), 3.29 (s, 3H), 1.28 (t, $J = 7.5$ Hz, 3H), 0.91 (t, $J$
= 8 Hz, 9H), 0.60-0.55 (m, 6H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 166.0, 159.2, 149.0, 130.7, 129.4, 122.5, 113.7, 77.8, 73.9, 73.0, 71.5, 60.4, 57.7, 55.4, 14.3, 7.0, 5.0; HRMS (FAB+) found 461.2330 [M+Na\(^+\)], calcd 461.2335 for C\(_{23}\)H\(_{38}\)O\(_6\)SiNa.

\[(\text{4S,5S,Z})-4\text{-methoxy-6-(4-methoxybenzyloxy)-5-(triethylsilyloxy)hex-2-en-1-ol.}\]

A solution of ester 136 (0.814 g, 1.86 mmol) in 30 mL Et\(_2\)O was cooled to -78 °C. DIBAL-H (3.1 mL, 1.5 M in toluene) was added dropwise. After the mixture was stirred for 30 min, it was quenched with Na/K tartrate aqueous solution. The mixture was warmed to ambient temperature and stirred for 15 min, at which time the two layers were clear. The two layers were separated and aqueous layer was extracted 5 times with Et\(_2\)O. The combined Et\(_2\)O solution was dried over Na\(_2\)SO\(_4\), filtered and concentrated. Chromatograph column (10-20% EtOAc/hexanes) provided the title compound (0.6 g, 82%). Data are: TLC \(R_f = 0.2\) (20% EtOAc/hexanes); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.24 (d, \(J = 8.5\) Hz, 2H), 6.87 (d, \(J = 8.5\) Hz, 2H), 5.96 (m, 1H), 5.4 (t, \(J = 10\) Hz, 1H), 4.48 (q, \(J = 11.5\) Hz, 2H), 4.21-4.17 (m, 1H), 4.13-4.10 (m, 1H), 4.09-4.05 (m, 1H), 3.82-3.80 (m, 1H), 3.80 (s, 3H), 3.53 (dd, \(J = 7\) and 10.5 Hz, 1H), 3.43 (dd, \(J = 5\) and 10.5 Hz, 1H), 3.28 (s, 3H), 2.58 (bs, 1H), 0.94 (t, \(J = 8.0\) Hz, 9H), 0.63 (q, \(J = 8.0\) Hz, 6H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 159.3, 133.6, 130.3, 130.2, 129.6, 113.9, 78.6, 74.6, 73.6, 71.7, 58.5, 56.9, 55.4, 7.0, 5.0; HRMS (+TOF MS) found 419.1859 [M+Na\(^+\)], calcd 419.22130 for C\(_{21}\)H\(_{36}\)O\(_5\)SiNa.
To a stirred solution of the above alcohol (1.05 g, 2.65 mmol) in 20 mL CH₂Cl₂ was added Dess-Martin periodinane (1.68 g, 3.97 mmol) in one portion at ambient temperature. The solution was stirred for 45 min, at which time it was diluted with Et₂O and quenched with Na₂S₂O₃ (6.58 g, 26.5 mmol) aqueous solution. The resulting mixture was stirred for another 20 min. The layers were separated and organic layer was washed 3 times with Na₂S₂O₃ and NaHCO₃ aqueous solution. Chromatograph (10% EtOAc/hexanes) provided 137 (0.98 g, 94%). Data are: TLC Rₜ = 0.6 (20% EtOAc/hexanes); $^1$H NMR (CDCl₃, 500 MHz) δ 10.11 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 6.47 (m, 1H), 6.11 (m, 1H), 4.56 (m, 1H), 4.43 (A and B of AB q, J = 11.5 Hz, 2H), 3.91 (dd, J = 5.5 and 7.8 Hz, 1H), 3.80 (s, 3H), 3.58 (m, 1H), 3.77 (m, 1H), 3.34 (s, 3H), 0.92 (t, J = 8.0 Hz, 9H), 0.60 (q, J = 8.0 Hz, 6H); $^{13}$C NMR (CDCl₃, 125 MHz) δ 192.0, 159.4, 148.6, 132.8, 130.2, 129.6, 113.9, 78.8, 73.7, 73.3, 71.0, 57.7, 55.4, 7.0, 5.0; HRMS (+TOF MS) found 412.2631 [M+NH₄]⁺, calcd 412.2514 for C₂₁H₃₈NO₅Si.
To a stirred solution of phosphonate 138 (0.83 g, 3.32 mmol) in 25 mL CH₃CN was added LiCl (0.14 g, 3.32 mmol) at ambient temperature. The mixture was stirred for 15 min before it was cooled to 0 °C. After it was stirred for another 10 min, DBU (0.45 mL, 2.98 mmol) was added slowly. The mixture was stirred for 15 min and aldehyde 137 (0.65 g, 1.66 mmol) was added as a CH₃CN (3 mL) solution. After 2 h at 0 °C, the reaction was quenched with NH₄Cl aqueous solution. These two layers were separated and the aqueous layer was extracted 3 times with Et₂O. The combined ether layers was dried over Na₂SO₄, filtered and concentrated. Chromatograph (5% EtOAc/hexanes) provided 139 (0.80 g, 98%, 25:1 selectivity) product. Data are: TLC Rf = 0.6 (10% EtOAc/hexanes); ¹H NMR (CDCl₃, 500 MHz) δ 7.56 (d, J = 12 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 6.55 (t, J = 11.5 Hz, 1H), 5.96 (m, 1H), 5.72 (t, 10.5 Hz, 1H), 5.34 (d, J = 10.5 Hz, 1H), 5.23 (d, J = 9.0 Hz, 1H), 4.67 (m, 2H), 4.45 (q, J = 12 Hz, 2H), 4.26 (m, 1H), 3.83 (q, J = 5.5 Hz, 1H), 3.80 (s, 3H), 3.56 (m, 1H), 3.36 (m, 1H), 3.27 (s, 3H), 1.99 (s, 3H), 0.93 (t, J = 8.0 Hz, 9H), 0.60 (q, J = 8.0 Hz, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 168.1, 159.2, 136.1, 132.7, 132.6, 130.5, 129.5, 129.2, 127.6, 118.1, 113.8, 78.2, 74.3, 73.2, 71.5, 65.5, 57.1, 55.4, 12.7, 7.0, 5.0; HRMS (+TOF MS) found 513.2649 [M+Na]+, calcd 513.2643 for
C_{27}H_{42}O_{6}SiNa.

(2E,4Z,6S,7S)-Allyl 8-hydroxy-6-methoxy-2-methyl-7-(triethylsilyloxy)octa-2,4-dienoate (140)

To a stirred solution of allyl ester 139 (0.39 g, 0.8 mmol) in 16 mL CH₂Cl₂ and 0.8 mL H₂O was added DDQ at ambient temperature. The resulting green colored mixture was stirred for 1.5 h before being quenched with saturated NaHCO₃ aqueous solution. The aqueous layer was extracted 3 times with CH₂Cl₂. And the combined organic layers were washed 3 times with aqueous NaHCO₃. The resulting organic layer was dried over Na₂SO₄, filtered and concentrated. Chromatograph (10% EtOAc/hexanes) provided 140 (0.25 g, 84%). Data are: TLC Rₓ = 0.2 (10% EtOAc/hexanes); ¹H NMR (CDCl₃, 500 MHz) δ 7.54 (d, J = 12 Hz, 1H), 6.61 (t, J = 11.0 Hz, 1H), 5.96 (m, 1H), 5.68 (t, J = 11.0 Hz, 1H), 5.35 (d, J = 17 Hz, 5.25 (d, J = 12 Hz, 1H), 4.69-4.67 (m, 2H), 4.24 (m, 1H), 3.82 (m, 1H), 3.63 (m, 1H), 3.53 (m, 1H), 3.28 (s, 3H), 2.16 (m, 1H), 1.99 (s, 3H), 0.96 (t, J = 8.0 Hz, 9H), 0.64 (q, J = 8.0 Hz, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 168.1, 135.0, 132.6, 132.5, 129.7, 128.6, 118.1, 79.2, 74.5, 65.6, 64.0, 56.9, 12.7, 7.0, 5.1; HRMS (+TOF MS) found 371.2255 [M+H]+, calcd 371.2248 for C₁₉H₃₅O₅Si.
(2E,4Z,6S,7R)-Allyl 6-methoxy-2-methyl-8-oxo-7-(triethylsilyloxy)octa-2,4-dienoate (141)

A flame dried flask was charged with alcohol 140 (0.8 g, 2.16 mmol) and 10 mL CH₂Cl₂. Dess-Martin periodinane (1.37 g, 3.24 mmol) was added in one portion at ambient temperature. The solution was stirred for 1 h and diluted with Et₂O and quenched with Na₂S₂O₃ (5.36 g, 21.6 mmol) aqueous solution. The mixture was stirred for 15 min before the layers were separated and organic layer was washed 3 times with Na₂S₂O₃ and NaHCO₃ aqueous solution. Chromatograph (10% EtOAc/hexanes) provided 141 (0.76 g, 95%). Data are: TLC Rf = 0.5 (10% EtOAc/hexanes); ¹H NMR (CDCl₃, 300MHz) δ 9.69 (d, J = 1.5 Hz, 1H), 7.49 (d, J = 12.0 Hz, 1H), 6.62 (t, J = 12.0 Hz, 1H), 5.96 (m, 1H), 5.77 (t, J = 10.2 Hz, 1H), 5.33 (m, 2H), 4.69 (d, J = 6.0 Hz, 2H), 4.53 (m, 1H), 3.27 (s, 3H), 1.99 (s, 3H), 0.95 (t, J = 8.1 Hz, 9H), 0.62 (q, J = 8.1 Hz, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 203.0, 168.0, 133.8, 132.5, 131.8, 130.4, 128.6, 118.3, 79.9, 78.4, 65.7, 57.3, 12.8, 6.9, 4.9; HRMS (+TOF MS) found 391.1897 [M+Na]+, calcd 391.1911 for C₁₀H₃₂O₅SiNa.
(2R,3S,4Z,6E)-8-(Allyloxy)-2-hydroxy-3-methoxy-7-methyl-8-oxoocta-4,6-dienoic acid (142)

A 50 mL flask was charged with aldehyde 141 (0.68 g, 1.85 mmol), NaH₂PO₄·H₂O (0.61 g, 4.44 mmol), 16 mL t-BuOH, 4 mL H₂O, and 4 mL 2-methyl-2-butene. NaClO₂ (0.52 g, 5.74 mmol) was added at 0 °C. The resulting mixture was warmed to ambient temperature and allowed to stir for 2 h. The reaction was quenched with aqueous NH₄Cl and extracted 10 times with EtOAc. The organic layers were combined, dried over Na₂SO₄, filtered, and concentrated. The crude product was passed through a silicon plug eluting with 30% EtOAc/hexanes to get rid of some yellow impurities, and then eluting with MeOH to get the product. After MeOH solvent was removed in vacuo, the residue was dissolved in CH₂Cl₂. The insoluble silicon was removed by filtration. The product 142 (0.45 g, 90% yield) was recovered after CH₂Cl₂ removal. Data are: TLC Rf = 0.2 (20% MeOH/CH₂Cl₂); [α]D²³ = -33.7° (c 4.2, CHCl₃); ¹H NMR (CD₃OD, 300MHz) δ 7.64 (d, J = 12.0 Hz, 1H), 6.69 (t, J = 11.4 Hz), 6.06-5.89 (m, 2H), 5.37-5.21 (m, 2H), 4.69-4.67 (m, 2H), 4.64 (bs, 1H), 4.00 (bs, 1H), 3.28 (s, 3H), 1.99 (s, 3H); ¹³C NMR (CD₃OD, 75 MHz) δ 178.1, 169.4, 136.3, 134.0, 133.5, 130.9, 128.6, 118.4, 79.4, 76.2, 66.6, 57.5, 12.8; HRMS (+TOF MS) found 293.0996 [M+Na]⁺, calcd 293.0996 for C₁₃H₁₈O₆Na.
A flame dried flask was charged with dioxanon 102 (0.93 g, 2.97 mmol) and 80 mL CH₂Cl₂. The solution was cooled to -78 °C under nitrogen atmosphere. Et₃N (1.03 mL, 7.43 mmol) was added dropwise, followed by cis-hex2BOTf (6 mL, 1M in hexanes) over 0.5 h. The resulting mixture was stirred at -78 °C for 3 h, at which time aldehyde 114 (1.2 g, 3.56 mmol) was added in 3 mL CH₂Cl₂ dropwise over 10 min. The reaction was stirred for another 3 h at -78 °C and then quenched with pH 7 buffer (10 mL), MeOH (10 mL) and 30% aqueous H₂O₂ (3 mL). The mixture was warmed to ambient temperature and NaHCO₃ aqueous solution was added. The layers were separated and aqueous layer was extracted 3 times with CH₂Cl₂. The organic layers were combined and dried over Na₂SO₄, filtered and concentrated. Chromatograph (30-40% EtOAc/hexanes) provided the desired product 120 (1.26 g, 63%) and an isomer (0.16 g, 8%). Data are: TLC Rf = 0.2 (30% EtOAc/hexanes); [α]D²³ = -103.7° (c 3.5, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.58 (s, 1H), 7.00-6.94 (m, 4H), 6.78-6.74 (m, 4H), 5.37 (d, J = 9.0 Hz, 1H), 5.19 (s, 2H), 5.00 (q, J = 6.0 Hz, 2H), 4.93 (d, J = 9.0 Hz, 1H), 4.54 (d, J = 5.5 Hz, 1H), 4.26 (m, 1H), 3.93 (s, 3H), 3.757 (s, 3H), 3.756 (s, 3H), 3.52 (s, 3H), 3.50 (s, 3H), 2.88 (d, J = 5.5 Hz, 1H), 2.71 (m, 2H), 2.13 (m, 1H), 1.75 (m, 1H), 1.65 (m, 1H), 0.95 (d, J = 6.5 Hz, 3H); ¹³C NMR (CDCl₃,
125 MHz) δ 170.0, 160.2, 159.9, 153.3, 146.2, 145.8, 139.6, 131.5, 129.0, 128.7, 128.1, 126.8, 113.9, 111.1, 101.8, 95.6, 85.2, 78.2, 76.8, 71.5, 61.2, 57.9, 56.6, 55.3, 40.4, 32.9, 30.2, 19.2; HRMS (FAB+) found 694.2474 [M+Na]+, calcd 694.2476 for C_{34}H_{41}NO_{13}Na.

(3S,5S,6S)-3-((1S,3R)-1-Methoxy-4-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-3-methylbutyl)-5,6-bis(4-methoxyphenyl)-1,4-dioxan-2-one (121)

A flame dried 100 mL flask was charged with the aldol product 120 (1.7 g, 2.53 mmol) and 40 mL CH_{2}Cl_{2}. The solution was cooled to 0 °C before proton sponge (1.09 g, 5.06 mmol) was added, followed by Me_{3}OBF_{4} (0.75 g, 5.06 mmol). The resulting mixture was warmed to ambient temperature and stirred for 5 h, at which time another portion of proton sponge (0.54 g, 2.53 mmol) and Me_{3}OBF_{4} (0.37 g, 2.53 mmol) was added. The reaction was stirred for overnight, at which time it was filtered through a silicon plug eluting with Et_{2}O and concentrated. Chromatograph (20-30% EtOAc/hexanes) provided 121 (1.73 g, 100%). Data are: TLC R_{f} = 0.5 (30% EtOAc/hexanes); \textsuperscript{1}H NMR (CDCl_{3}, 500 MHz) δ 7.57 (s, 1H), 6.99 (t, J = 9.0 Hz, 4H), 6.75 (q, J = 9.0 Hz, 4H), 5.38 (d, J = 9.0 Hz, 1H), 5.17 (s, 2H), 5.01 (s, 2H), 4.97 (d, J = 9.0 Hz, 1H), 4.87 (d, J = 2.5 Hz, 1H), 3.93 (s, 3H), 3.91 (m, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.54 (s, 3H), 3.48 (s, 3H), 3.44 (s, 3H), 2.71 (m, 2H), 2.08 (m, 1H), 1.92
1H, 1.58 (m, 1H), 0.98 (d, J = 6.5 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 168.1, 160.0, 159.8, 153.2, 146.2, 145.6, 139.6, 131.2, 128.9, 128.8, 128.1, 127.3, 113.81, 113.77, 111.0, 101.8, 95.4, 85.5, 82.7, 77.9, 74.4, 61.1, 57.9, 57.6, 56.6, 55.3, 37.9, 32.7, 30.4, 19.7; HRMS (FAB+) found 708.2637 [M+Na]$^+$, calcld 708.2632 for C$_{35}$H$_{43}$NO$_{13}$Na.

(2S,3S,5R)-Methyl 2-((1S,2S)-2-hydroxy-1,2-bis(4-methoxyphenyl)ethoxy)-3-methoxy-6-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-5-methylhexanoate (122)

A solution of the protected aldol product 121 (1.73 g, 2.53 mmol) in 20 mL dry THF and 20 mL dry MeOH was cooled to 0 °C. A freshly prepared NaOMe (0.25 mL, 0.1 M in MeOH) was added. The resulting mixture was stirred at 0 °C for 3 h, at which time it was quenched with NH$_4$Cl solution. The mixture was extracted 5 times with Et$_2$O. The combined organic layer was dried over Na$_2$SO$_4$, filtered and concentrated. Chromatograph (30% EtOAc/hexanes) provided desired product 122 (1.60 g, 88%).

Data are: TLC R$_f$ = 0.4 (50% EtOAc/hexanes); $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.62 (s, 1H), 6.94 (apparent q, J = 8.5 Hz, 4H), 6.70 (t, J = 8.5 Hz, 4H), 5.22 (s, 2H), 5.03 (q, J = 6.5 Hz, 2H), 4.71 (d, J = 9.0 Hz, 1H), 4.31 (d, J = 8.0 Hz, 1H), 4.23 (d, J = 3.5 Hz, 1H), 3.99 (s, 1H), 3.95 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.65 (m, 1H), 3.59 (s, 3H), 3.52 (s, 3H), 3.46 (s, 3H), 3.30 (s, 3H), 3.24 (s, 3H), 3.16 (s, 3H), 3.09 (s, 3H), 3.00 (s, 3H), 2.95 (s, 3H), 2.88 (s, 3H), 2.81 (s, 3H), 2.73 (s, 3H), 2.66 (s, 3H), 2.59 (s, 3H), 2.52 (s, 3H), 2.45 (s, 3H), 2.38 (s, 3H), 2.30 (s, 3H), 2.23 (s, 3H), 2.16 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H), 1.95 (s, 3H), 1.88 (s, 3H), 1.80 (s, 3H), 1.73 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H), 1.52 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H), 1.17 (s, 3H), 1.10 (s, 3H), 0.98 (d, J = 6.5 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 168.1, 160.0, 159.8, 153.2, 146.2, 145.6, 139.6, 131.2, 128.9, 128.8, 128.1, 127.3, 113.81, 113.77, 111.0, 101.8, 95.4, 85.5, 82.7, 77.9, 74.4, 61.1, 57.9, 57.6, 56.6, 55.3, 37.9, 32.7, 30.4, 19.7; HRMS (FAB+) found 708.2637 [M+Na]$^+$, calcld 708.2632 for C$_{35}$H$_{43}$NO$_{13}$Na.
3H), 3.52 (s, 3H), 3.50 (s, 3H), 3.40 (s, 3H), 2.76 (m, 1H), 2.66 (m, 1H), 2.12 (m, 1H),
1.92 (m, 1H), 1.32 (m, 1H), 0.86 (d, J = 6.0 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ
171.2, 159.4, 159.1, 153.3, 146.3, 145.9, 139.7, 131.5, 129.6, 129.4, 128.5, 113.4,
113.3, 111.2, 101.8, 95.6, 90.1, 81.0, 79.1, 78.6, 61.2, 58.2, 57.9, 56.6, 55.2, 51.9,
38.3, 33.0, 30.2, 19.0; HRMS (+TOF MS) found 740.2888 [M+Na]⁺, calcd 740.2889
for C₃₆H₄₇O₁₄Na.

(2S,3S,5R)-Methyl 2-hydroxy-3-methoxy-6-(2-methoxy-3,6-bis(methoxymethoxy)
-5- nitrophenyl)-5-methylhexanoate

To a stirred solution of the methyl ester 122 (1.36 g, 1.89 mmol) in 25 mL CH₃CN
and 2.7 mL H₂O was added ceric ammonium nitrate (2.59 g, 4.72 mmol) at 0 °C. The
resulting mixture was stirred at 0 °C for 30 min, at which time the reaction was
diluted with H₂O and Et₂O. The two layers were separated and aqueous layer was
extracted 5 times with Et₂O. The Et₂O layers were combined, dried, filtered,
concentrated, and chromatographed (30% EtOAc/hexanes) to provide the title
compound (0.68 g, 78%). Data are: TLC Rₓ = 0.3 (50% EtOAc/hexanes); ¹H NMR
(CDCl₃, 500 MHz) δ 7.60 (s, 1H), 5.22 (s, 2H), 5.00 (s, 2H), 4.45 (m, 1H), 3.93 (s,
3H), 3.81 (s, 3H), 3.60-3.57 (m, 1H), 3.56 (s, 3H), 3.52 (s, 3H), 3.42 (s, 3H), 2.87 (d,
J = 5.5 Hz, 1H), 2.72-2.69 (m, 1H), 2.63-2.59 (m, 1H), 2.05 (m, 1H), 1.76 (m, 1H),
1.12 (m, 1H), 0.86 (d, J = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 173.4, 153.3,
(2S,3S,5R)-Methyl 2-(tert-butyldimethylsilyloxy)-3-methoxy-6-(2-methoxy-3,6-bis (methoxymethoxy)-5-nitrophenyl)-5-methylhexanoate (123)

A flame dried 25 mL flask was charge with the previous α-hydroxyl ester (0.33 g, 0.72 mmol), 5 mL DMF, and imidazole (0.25 g, 3.61 mmol). The resulting solution was cooled to 0 °C before TBSCl (0.22 g, 1.44 mmol) was added in portions. The reaction was stirred for overnight, at which time it was quenched with NH₄Cl and diluted with Et₂O. The two layers were separated and aqueous layer was extracted 3 times with ether. Ether layers were combined, dried, filtered, concentrated, and chromatographed (10% EtOAc/hexanes) to give desired product 123 (0.36 g, 87%).

Data are: TLC Rf = 0.7 (30% EtOAc/hexanes); [α]D²³ = -22.0° (c 3.1, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.60 (s, 1H), 5.22 (s, 2H), 5.00 (q, J = 6.0 Hz, 2H), 4.28 (d, J = 4.5 Hz, 1H), 3.93 (s, 3H), 3.73 (s, 3H), 3.56 (s, 3H), 3.52 (s, 3H), 3.51-3.48 (m, 1H), 3.45 (s, 3H), 2.72- 2.60 (m, 2H), 2.05 (m, 1H), 1.70-1.65 (m, 1H), 1.26-1.19 (m, 1H), 0.89 (s, 9H), 0.86 (d, J = 6.0 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 173.0, 153.4, 146.3, 146.0, 139.6, 131.7, 111.1, 101.8, 95.6, 81.5, 73.8, 61.2, 58.3, 57.9, 56.7, 52.0, 38.2, 33.1, 30.0, 25.8, 19.3, 18.4, -5.0, -5.1; HRMS
(+TOF MS) found 593.3101 [M+NH₄]⁺, calcld 593.3100 for C₂₆H₄₉N₂O₁₁Si.

(2S,3S,5R)-2-(tert-Butyldimethylsilyloxy)-3-methoxy-6-(2-methoxy-3,6-bis(methoxy)methoxy)-5-nitrophenyl)-5-methylhexanal (124)

A flame dried flask was charged with ester 123 (0.82 g, 1.42 mmol) and 25 mL CH₂Cl₂. The solution was cooled to -78 °C. DIBAL-H (1 mL, 1.5 M in toluene) was added slowly along the flask inside wall. After 2 h, another portion of DIBAL-H (1 mL, 1.5 M in toluene) was added slowly. The mixture was stirred for another 2 h at which time it was quenched with 1 mL MeOH and aqueous Na/K tartrate. The mixture was warmed to ambient temperature and stirred until the layers became clear. The two layers were separated and the aqueous layer was extracted 5 times with Et₂O. The combined ether layers were dried, filtered, concentrated and chromatographed (10% EtOAc/hexanes) to provide aldehyde 124 (0.76 g, 98%). Data are: TLC Rf = 0.5 (20% EtOAc/hexanes); ¹H NMR (CDCl₃, 500 MHz) δ 9.66 (s, 1H), 7.61 (s, 1H), 5.22 (s, 2H), 5.00 (q, J = 6.0 Hz, 2H), 4.10 (s, 1H), 3.92 (s, 3H), 3.56 (s, 3H), 3.52 (s, 3H), 3.49-3.46 (m, 1H), 3.37 (s, 3H), 2.71-2.60 (m, 2H), 2.05 (m, 1H), 1.78-1.72 (m, 1H), 1.14-1.11 (m, 1H), 0.90 (s, 9H), 0.85 (d, J = 7.0 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 204.7, 153.4, 146.3, 146.0, 139.6, 131.6, 111.1, 101.9, 95.6, 81.5, 79.2, 61.2, 58.4, 57.9, 56.7, 38.2, 33.0, 29.9, 38.1, 33.0, 29.9, 25.9, 19.3, 18.4, -4.7; HRMS (+TOF MS) found 568.2552 [M+Na]⁺, calcld 568.2548 for
C$_{25}$H$_{43}$NO$_{10}$SiNa.

(3$R$,#S,#S)-3-(tert-Butyldimethylsilyloxy)-4-methoxy-7-(2-methoxy-3,6-bis(methoxy)methoxy)-5-nitrophenyl)-6-methylheptan-2-ol

A flame dried 50 mL flask was charged with aldehyde 124 (0.77 g, 1.41 mmol) and 20 mL CH$_2$Cl$_2$. The resulting solution was cooled to -78 °C before AlMe$_3$ (2.1 mL, 2 M in hexanes) was slowly added. After 1.5 h, another portion of AlMe$_3$ (2.1 mL, 2 M in hexanes) was added and the mixture was allowed to stir for 6 h, at which time the reaction was quenched with aqueous NH$_4$Cl and was warmed to ambient temperature. Aqueous Na/K tartrate was added and the resulting mixture was stirred for another 20 min. The layers were separated and aqueous layer was extracted 5 times with CH$_2$Cl$_2$. The combined organic layers were dried, filtered, concentrated, and filtered through a silica plug (20% EtOAc/hexanes) to provide 0.79 g products (100%) as a pair of diastereomers. Data are: TLC $R_f$ = 0.3 and 0.4 (30% EtOAc/hexanes); HRMS (+TOF MS) found 584.2861 [M+Na]$^+$, calcd 584.2861 for C$_{26}$H$_{47}$NO$_{10}$SiNa.

(3$S$,#S,#S)-3-(tert-Butyldimethylsilyloxy)-4-methoxy-7-(2-methoxy-3,6-bis(methoxy)methoxy)methoxy)-5-nitrophenyl)-6-methylheptan-2-ol
xymethoxy)-5-nitrophenyl)-6-methylheptan-2-one (125)

To a stirred solution of the previous alcohol (0.79 g, 1.41 mmol) in 20 mL CH₂Cl₂ was added Dess-Martin periodinane (0.90 g, 2.12 mmol) at 0 °C. The resulting mixture was warmed to ambient temperature and stirred for 1 h. It was diluted with ether and quenched with saturated NaHCO₃ and Na₂S₂O₃ (5.26 g, 21.2 mmol). The mixture was stirred for 20 min at which time the layers were separated. The organic layer was washed 3 times with aqueous NaHCO₃ and Na₂S₂O₃. The organic layer was dried, filtered, concentrated, and chromatographed (10% EtOAc/hexanes) to provide desired methyl ketone product 125 (0.75 g, 95%). Data are: TLC Rᵥ = 0.7 (30% EtOAc/hexanes); [α]D²³ = -36.2° (c 3.1, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.60 (s, 1H), 5.21 (s, 2 H), 5.00 (q, J = 6.5 Hz, 2H), 4.14 (d, J = 3.0 Hz, 1H), 3.92 (s, 3H), 3.55 (s, 3H), 3.52 (s, 3H), 3.44-3.40 (m, 1H), 3.35 (s, 3H), 2.67-2.60 (m, 2H), 2.22 (s, 3H), 2.05-2.02 (m, 1H), 1.72-1.67 (m, 1H), 1.00-0.95 (m, 1H), 0.89 (s, 9H), 0.84 (d, J = 6.5 Hz, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 212.7, 153.4, 146.3, 146.0, 139.6, 131.7, 111.1, 101.8, 95.6, 81.9, 80.0, 61.2, 58.2, 57.9, 56.7, 37.3, 33.1, 29.8, 27.7, 25.9, 19.3, 18.3, -4.6, -5.1; HRMS (+TOF MS) found 582.2716 [M+Na]+, calcd 582.2705 for C₂₆H₄₅NO₁₀SiNa.

(3S,4S,6R)-7-(3-Amino-6-methoxy-2,5-bis(methoxymethoxy)phenyl)-3-(tert-butyl dimethylsilyloxy)-4-methoxy-6-methylheptan-2-one (126)
To a stirred solution of previous prepared methyl ketone 125 (0.25 g, 0.45 mmol) in 20 mL i-PrOH was added Pd/C (0.1 g, 10 wt%). The reaction was put under high vacuum and then purged with H₂. After the reaction was stirred for 5 h under H₂ balloon, the mixture was filtered through a celite plug eluting with MeOH. The solvent was evaporated to provide the aniline product 126 (0.24 g, 100%). Data are: TLC Rf = 0.2 (20% EtOAc/hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 6.47 (s, 1H), 5.13 (s, 2H), 4.91 (m, 2H), 4.12 (d, J = 2.7 Hz, 1H), 3.78 (s, 2H), 3.74 (s, 3H), 3.59 (s, 3H), 3.50 (s, 3H), 3.45-3.40 (m, 1H), 3.35 (s, 3H), 2.56-2.48 (m, 2H), 2.22 (s, 3H), 2.02 (m, 1H), 1.77-1.68 (m, 1H), 1.04-0.97 (m, 1H), 0.91 (s, 9H), 0.82 (d, J = 6.6 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); HRMS (+TOF MS) found 552.2947 [M+Na]+, calcd 552.2963 for C₂₆H₄₇NO₈SiNa.

![Chemical structure of 127](image)

**Allyl 3-((2R,4S,5S)-5-(tert-butyldimethylsilyloxy)-4-methoxy-2-methyl-6-oxoheptyl)-4-methoxy-2,5-bis(methoxymethoxy)phenylcarbamate (127)**

A flame dried 50 mL flask was charged with aniline 126 (0.24 g, 0.45 mmol) and 10 mL CH₂Cl₂. The solution was cooled to 0 °C before pyridine (0.11 mL, 1.35 mmol) was added dropwisely, followed by AllocCl (0.14 mL, 1.35 mmol) and DMAP (0.02 g). The mixture was stirred at 0 °C for 2 h, at which time it was warmed to ambient temperature. After another 3 h, the reaction was quenched with diluted HCl, and extracted 3 times with EtOAc. The combined organic layers were dried, filtered,
concentrated and chromatographed (20% EtOAc/hexanes) to provide product 127 (0.23 g, 83%). Data are: TLC R_f = 0.4 (20% EtOAc/hexanes); [α]D^23 = -26.2° (c 3.6, CHCl_3); ^1H NMR (CDCl_3, 500 MHz) δ 7.79 (bs, 2H), 5.97-5.92 (m, 1H), 5.33 (d, J = 19 Hz, 1H), 5.21 (d, J = 10.5 Hz, 1H), 5.17 (s, 2H), 4.88 (s, 2H), 4.64 (d, J = 6.0 Hz, 2H), 4.10 (d, J = 2.5 Hz, 1H), 3.78 (s, 3H), 3.58 (s, 3H), 3.50 (s, 3H), 3.41-3.38 (m, 1H), 3.33 (s, 3H), 2.51-2.46 (m, 2H), 2.19 (s, 3H), 1.97-1.94 (m, 1H), 1.70-1.64 (m, 1H), 0.98-0.93 (m, 1H), 0.87 (s, 9H), 0.80 (d, J = 7.0 Hz, 3H), 0.01 (s, 3H), 0.00(s, 3H); ^13C NMR (CDCl_3, 125 MHz) δ 212.4, 153.4, 147.0, 144.2, 141.0, 132.8, 128.5, 127.7, 117.7, 106.3, 100.6, 95.6, 82.0, 80.1, 65.6, 60.9, 58.1, 57.4, 56.5, 37.5, 33.1, 29.9, 27.6, 25.8, 19.3, 18.2, -4.7, -5.2; HRMS (+TOF MS) found 636.3157 [M+Na]⁺, calcd 636.3174 for C_{30}H_{51}NO_{10}SiNa.

![Chemical structure](image)

**Allyl 3-((2R,4S,5R,6R)-5-(tert-butyldimethylsilyloxy)-4-methoxy-2-methyl-6-(methylamino)heptyl)-4-methoxy-2,5-bis(methoxymethoxy)phenylcarbamate (108)**

A flame dried 25 mL flask was charged with the Alloc protected aniline 127 (0.178 g, 0.29 mmol) and 5 mL dry ethanol. To this stirred solution was added CH_3NH.HCl (0.077 g, 1.16 mmol), Et_3N (0.16 mL, 1.16 mmol), and Ti(O-iPr)_4 (0.35 mL, 1.16 mmol). The mixture was stirred overnight at ambient temperature before being cooled to -78 °C. NaBH_4 (0.033 g, 0.87 mmol) was added and the resulting mixture was
stirred for 8 h. The reaction was diluted with Et₂O and quenched with saturated Na/K tartrate and 10% ammonium aqueous solution. The mixture was separated and the aqueous layer was extracted 3 times with Et₂O and 5 times with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, concentrated and chromatographed (2% MeOH/CH₂Cl₂ and 6 drops of NH₃·H₂O) to provide 108 (0.1249 g, 68%). Data are: TLC Rᵣ = 0.7 (10% MeOH/CH₂Cl₂); [α]D²³ = -9.8° (c 3.1, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.81 (bs, 1H), 7.78 (bs, 1H), 5.98-5.91 (m, 1H), 5.32 (d, J = 17 Hz, 1H), 5.21 (d, J = 10.5 Hz, 1H), 5.18 (s, 2H), 4.90 (s, 2H), 4.64 (d, J = 5.5 Hz, 2H), 3.79 (s, 3H), 3.61-3.59 (m, 1H), 3.59 (s, 3H), 3.50 (s, 3H), 3.35-3.31 (m, 1H), 3.28 (s, 3H), 2.56-2.46 (m, 3H), 2.36 (s, 3H), 2.01-1.97 (m, 1H), 1.58-1.53 (m, 1H), 1.29-1.24 (m, 1H), 1.22 (bs, 1H), 1.05 (d, J = 6.5 Hz, 3H), 0.85 (s, 9H), 0.84 (d, J = 7.5 Hz, 3H), 0.02 (s, 3H), 0.00 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 153.5, 147.0, 144.2, 141.1, 132.9, 128.9, 127.7, 117.7, 106.3, 100.7, 95.6, 80.7, 76.3, 65.6, 60.9, 57.6, 57.4, 56.5, 38.1, 34.4, 33.3, 30.4, 26.2, 19.4, 18.4, 16.3, -4.1, -4.5; HRMS (+TOF MS) found 651.3639 [M+Na]+, calcd 651.3647 for C₃₁H₅₆N₂O₉SiNa.

(2E,4Z,6S,7R)-Allyl 8-(((2R,3R,4S,6R)-7-(3-(allyloxycarbonylamino)-6-methoxy-2,5-bis(methoxymethoxy)phenyl)-3-(tert-butyldimethylsilyloxy)-4-methoxy-6-methylheptan-2-yl)(methyl)amino)-7-hydroxy-6-methoxy-2-methyl-8-oxoocta-2,4-dienoate (160)
A solution of acid \textit{109} (0.054 g, 0.20 mmol) and amine \textit{108} (0.125 g, 0.20 mmol) in 4 mL CH$_2$Cl$_2$ was cooled to 0 °C. HATU (0.091 g, 0.24 mmol) was added followed by iPr$_2$NEt (0.077 g, 0.1 ml). After 3 h, acid \textit{109} (0.011 g, 0.04 mmol) and HATU (0.015 g, 0.04 mmol) were added. After another 2 h, more acid \textit{109} (0.011 g, 0.04 mmol) and HATU (0.015 g, 0.04 mmol) were added. After another 3 h, the reaction mixture was passed through a silica plug eluting with EtOAc. The filtrate was concentrated and purified with radial chromatograph (20% EtOAc/hexanes + 1% MeOH) to provide amide products \textit{160} (0.13 g, 74%) as a pair of rotamers (2:1). Data are: TLC \( R_f = 0.7 \) (50% EtOAc/hexanes); \([\alpha]_D^{23} = +4.5^\circ \) (c 3.2, CHCl$_3$); $^1$H NMR (CDCl$_3$, 500 MHz) \( \delta \)

7.85 (bs, 1H), 7.77 (bs, 1H), 7.55 (d, \( J = 12.0 \) Hz, 1/3H), 7.53 (d, \( J = 12.0 \) Hz, 2/3H), 6.67-6.61 (m, 1H), 5.98-5.91 (m, 2H), 5.68 (t, \( J = 10.0 \) Hz, 2/3H), 5.62 (t, \( J = 10.0 \) Hz, 1/3H), 5.32 (apparent d, \( J = 17.0 \) Hz, 2H), 5.22 (apparent t, \( J = 10.5 \) Hz, 2H), 5.17 (s, 2H), 4.90 (s, 2H), 4.73-4.41 (m, 7H), 3.97-3.92 (m, 1H), 3.79 (s, 2/3 x 3H), 3.77 (s, 1/3 x 3H), 3.74-3.71 (m, 1H), 3.59 (s, 2/3 x 3H), 3.57 (s, 1/3 x 3H), 3.50 (s, 3H), 3.29-3.23 (m, 6H), 3.10 (d, \( J = 11.0 \) Hz, 1H), 2.98 (s, 2/3 x 3H), 2.84 (s, 1/3 x 3H), 2.51-2.47 (m, 2H), 2.02 (m, 1H), 1.97 (s, 3H), 1.69-1.65 (m, 2/3H), 1.54-1.50 (m, 1/3H), 1.29 (d, \( J = 6.0 \) Hz, 1/3 x 3H), 1.18 (d, \( J = 6.0 \) Hz, 2/3 x 3H), 1.14-1.12 (m, 2/3H), 0.95-0.89 (m, 1/3H), 0.84-0.78 (m, 12 H), 0.02- -0.06 (m, 6H); HRMS (+TOF MS) found 903.4647 [M+Na]$^+$, calcd 903.4645 for C$_{44}$H$_{72}$N$_2$O$_{14}$SiNa.
To a stirred solution of previous amide 160 (0.13 g, 0.15 mmol) in 4 mL dry THF was added morpholine (0.26 mL, 2.92 mmol) and Pd(PPh₃)₄ (0.068 g, 0.058 mmol). The resulting solution was stirred 4 h at ambient temperature before being diluted with Et₂O and quenched with NaH₂PO₄ and water. The mixture was separated and aqueous layer was extracted twice with Et₂O and 8 times with EtOAc. The combined organic layers were dried, filtered, concentrated and radial chromatographed (50% EtOAc/hexanes + 10 drops AcOH) to get crude amino acid product. This crude amino acid was dissolved in 300 mL CH₂Cl₂ (0.0005M). HATU (0.13 g, 0.35 mmol), DIPEA (0.16 mL, 0.88 mmol) and DMAP (0.010 g) were added at ambient temperature. The resulting mixture was stirred for 2 days, at which time the mixture was concentrated and passed through a silica plug eluting with EtOAc. The concentrated crude product was purified with radial chromatograph (50% EtOAc/hexanes) to provide desired product 161 (0.056 g, 51%). Data are: TLC Rₜ = 0.2 (50% EtOAc/hexanes); [α]D²³ = -7.3° (c 2.2, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 8.62 (bs, 1H), 7.98 (bs, 1H), 6.84 (bs, 1H), 6.46 (t, J = 11.0 Hz, 1H), 5.86 (m, 1H), 5.19 (m, 4H), 4.96 (bs, 1H), 4.66 (d, J = 5.5 Hz, 2H), 4.46 (bs, 1H), 3.84 (s, 4H), 3.52 (s, 3H), 3.42-3.31 (m, 12H), 2.89 (m, 2H), 2.69 (bs, 1H), 2.03 (s, 3H), 1.76 (bs, 1H), 1.45-1.37 (m, 1H), 1.32 (bs, 3H), 1.20-1.16 (m, 1H), 1.06 (m, 3H), 0.89 (s, 9H), 0.13-0.00 (m, 6H); HRMS (+TOF MS)
found 761.4017 [M+Na]+, calcd 761.4015 for C_{37}H_{62}N_{2}O_{11}SiNa.

A 25 mL round bottom flask was charged with the previous diamide 161 (0.044 g, 0.06 mmol) trichloroacetyl isocyanate (0.014 mL, 0.12 mmol) and 4 mL CH_{2}Cl_{2}. The mixture was allowed to stir for 30 min before MeOH (6 mL) and K_{2}CO_{3} (0.041 g, 0.30 mmol) was added. The mixture was stirred for 2 h before it was quenched with water and 3 drops of 1 N HCl aqueous solution. The mixture was extracted 5 times with CH_{2}Cl_{2} and 5 times with EtOAc. The combined organic layers were dried over Na_{2}SO_{4}, filtered and concentrated. The crude product was purified by radial chromatograph (50% EtOAc/hexanes + 1% MeOH) to provide desired product 107 (0.04 g, 86%). Data are: TLC R_{f} = 0.7 (5% MeOH/CH_{2}Cl_{2}); [\alpha]_{D}^{23} = -4.4^o (c 1.8, CHCl_{3}); \textsuperscript{1}H NMR (CDCl_{3}, 500 MHz) \delta 8.78 (bs, 1H), 7.67 (bs, 1H), 7.12 (bs, 1H), 6.46 (t, J = 11.0 Hz, 1H), 5.81 (bs, 1H), 5.19 (s, 4H), 5.07-4.76 (m, 3H), 4.75 (d, J = 4.5 Hz, 2H), 4.67 (s, 1H), 3.83 (s, 3H), 3.53 (s, 3H), 3.43-3.32 (m, 11H), 3.00 (s, 3H), 2.73 (bs, 1H), 2.35 (bs, 1H), 2.03 (s, 3H), 1.81 (bs, 1H), 1.60 (bs, 1H), 1.19 (s, 4H), 1.01 (bs, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H); HRMS (+TOF MS) found 804.4071 [M+Na]+, calcd 804.4073 for C_{38}H_{63}N_{3}O_{12}SiNa.

To a stirred solution of compound 107 (0.011 g, 0.014 mmol) in 2 mL CH₂Cl₂ and 2 mL CH₃CN was added NaI (0.021 g, 0.14 mmol) and TMSCl (0.18 mL, 0.14 mmol). The resulting mixture was stirred 1 h before being quenched with saturated Na₂S₂O₃ solution. The organic layer was washed 3 times with Na₂S₂O₃ solution. And the combine aqueous layers were extracted 3 times with CH₂Cl₂ and 5 times with EtOAc. The combined organic layers were dried, filtered, concentrated and radial chromatographed (7% MeOH/CH₂Cl₂) to provide deprotected product. This intermediate was dissolved in 3 mL EtOAc. And Pd/C (0.012 g, 10 wt%) was added. The mixture was stirred at ambient temperature, open to the air for 45 min. The mixture was then filtered through a celite plug eluting with EtOAc. The crude product was further purified by radial chromatograph (5% MeOH/CH₂Cl₂) to provide desired product 100 (0.0065 g, 80%). Data are: TLC Rf = 0.4 (10% MeOH/CH₂Cl₂); [α]D²³ = +8.3° (c 2.4, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 8.82 (s, 1H), 7.38 (d, J = 10.8 Hz, 1H), 7.27 (s, 1H), 6.56 (t, J = 11.1 Hz, 1H), 5.79 (t, J = 11.1 Hz, 1H), 5.53 (d, J = 4.5
Hz, 1H), 4.87 (m, 3H), 4.31 (m, 1H), 4.08 (s, 3H), 3.96 (m, 1H), 3.66 (bs, 1H), 3.39 (s, 3H), 3.34 (s, 3H), 3.32 (m, 1H), 3.07 (s, 3H), 2.52-2.46 (m, 1H), 2.36-2.29 (m, 1H), 2.01 (s, 3H), 1.98 (m, 1H), 1.62 (m, 1H), 1.26 (m, 1H), 1.15 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.3 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 184.5, 184.4, 168.4, 168.1, 157.3, 155.8, 138.9, 136.1, 133.8, 129.9, 127.9, 127.4, 111.3, 81.3, 76.6, 73.8, 73.1, 68.6, 61.7, 57.9, 57.2, 55.0, 31.3, 29.9, 27.4, 22.7, 12.4, 11.4; HRMS (+TOF MS) found 578.2708 [M+H$^+$], calcd 578.2708 for C$_{28}$H$_{40}$N$_3$O$_{10}$.

4.4.2. Preparation of Intermediates for Unsuccessful Routes

(2-Methoxy-3,6-bis(methoxymethoxy)phenyl)methanol

To a stirred solution of 2-methoxy-3,6-bis(methoxymethoxy)benzaldehyde 111 (0.51 g, 2 mmol) in THF (10 mL) was added NaBH$_4$ (0.23 g, 6 mmol) in portions. The resulting mixture was stirred at ambient temperature for 3.5 h, at which time the reaction was quenched with H$_2$O. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. Chromatography (30% EtOAc/hexanes) provided 117 (0.47 g, 91%). Data are: TLC $R_f$ = 0.2 (30% EtOAc/hexanes); $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.03 (d, J = 9.0 Hz, 1H), 6.81 (d, J = 9.0 Hz, 1H), 5.17 (s, 2H), 5.15 (s, 2H), 4.77 (d, J = 4.0 Hz, 2 H), 3.91 (s, 3H), 3.51 (s, 3H), 3.49 (s, 3H), 2.56 (bs, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$
1-Methoxy-2,5-bis(methoxymethoxy)-4-nitrobenzene (119)

It is the byproduct from MOM reprotection step. Data are: TLC Rf = 0.3 (30% EtOAc/hexanes); 1H NMR (CDCl3, 500 MHz) δ 7.81 (s, 1H), 6.84 (s, 1H), 5.27 (s, 2H), 5.20 (s, 2H), 3.95 (s, 3H), 3.56 (s, 3H), 3.52 (s, 3H); 13C NMR (CDCl3, 125 MHz) δ 155.3, 148.5, 140.7, 132.8, 114.3, 101.8, 107.8, 96.6, 96.3, 56.9, 56.6; HRMS (+TOF MS) found 274.0910 [M+H]+, calcd 274.0921 for C11H16NO7.

(2S,3S,5R)-2-(tert-Butyldimethylsilyloxy)-3-methoxy-6-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-5-methylhexanoic acid (129)

A flame dried flask was charged with methyl ester 123 (0.05 g, 0.087 mmol) and Et2O (2 mL). After TMSOK (0.025 g, 0.19 mmol) was added, the color changed to orange. The resulting mixture was stirred at ambient temperature for overnight. Then it was diluted with EtOAc and quenched with 1 N HCl. The mixture was washed 3 times with water and the organic layer was dried over Na2SO4 and concentrated. The
concentrated solution was passed through a silica cup eluting with EtOAc. After solvent evaporation, the desired acid **129** was obtained (0.042, 85%). Data are: TLC \( R_f = 0.1 \) (40% EtOAc/hexanes); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \( \delta \) 7.60 (s, 1H), 5.21 (s, 1H), 5.00 (m, 1H), 4.44 (d, \( J = 1.8 \) Hz, 3.92 (s, 3H), 3.55 (s, 3H), 3.52 (s, 3H), 3.45-3.40 (m, 1H), 3.39 (s, 3H), 2.65 (dd, \( J = 3.0, 7.5 \) Hz, 2H), 2.05 (m, 1H), 1.70 (m, 1H), 1.08-1.01 (m, 1H), 0.95-0.82 (m, 12 H), 0.10 (s, 3H), 0.05 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \( \delta \) 172.67, 153.4, 146.3, 146.0, 139.6, 131.6, 111.2, 101.8, 95.7, 81.2, 73.8, 61.2, 58.4, 57.9, 56.7, 36.7, 33.0, 29.7, 25.8, 19.3, 18.3, -4.6, -5.4; HRMS (+TOF MS) found 584.2488 [M+H]\(^+\), calcd 584.2498 for C\(_{25}\)H\(_{43}\)NO\(_{11}\)SiNa.

![Chemical Structure](image)

**(2S,3S,5R)-2-(tert-Butyldimethylsilyloxy)-3-methoxy-6-(2-methoxy-3,6-bis(methoxy)methoxy)-5-nitrophenyl)-5-methylhexanoic acid (130)**

A flame dried round bottom flask was charged with acid **129** (0.03 g, 0.053 mmol) and CH\(_2\)Cl\(_2\) (1 mL). \( 1,1'-\)Carbonyldiimidazole (0.014 g, 0.086 mmol) was then added slowly. The resulting solution was stirred for 25 min at ambient temperature before \( N,O \)-dimethylhydroxylamine hydrochloride (0.013 g, 0.13 mmol) was added. After the mixture was stirred for overnight, it was diluted with ether and washed with 5% citric acid aqueous solution. The organic layer was dried over MgSO\(_4\) and concentrated. Radial chromatography (20% EtOAc/hexanes) provided **130** (0.016 g, 50%). Data are: TLC \( R_f = 0.5 \) (40% EtOAc/hexanes); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \( \delta \)
7.60 (s, 1H), 5.22 (s, 2H), 5.00 (A and B of ABq, \( J = 6.5 \text{ Hz}, 2\text{H} \)), 4.55 (bs, 1H), 3.93 (s, 3H), 3.72 (s, 3H), 3.54 (s, 3H), 3.51 (s, 3H), 3.50-3.47 (m, 1H), 3.32 (s, 3H), 3.22 (bs, 3H), 2.71-2.63 (m, 2H), 2.09-2.03 (m, 1H), 1.57-1.45 (m, 2H), 0.89 (s, 9H), 0.89-0.88 (m, 3H), 0.060 (s, 3H), 0.057 (s, 3H); \(^{13}\text{C NMR (CDCl}_3\text{, 125 MHz)}\) \( \delta \) 153.4, 146.3, 146.1, 139.7, 131.9, 111.1, 101.9, 95.6, 80.8, 70.5, 61.2, 58.7, 57.9, 56.7, 39.0, 33.4, 30.2, 26.0, 19.4, -4.7, -4.9; HRMS (+TOF MS) found 627.2897 [M+H]^+ , calcd 627.2920 for \( \text{C}_{27}\text{H}_{48}\text{N}_2\text{O}_{11}\text{SiNa} \).

\[ \text{O} \quad \text{O} \]

\[ \text{Br} \quad \text{O}_{\text{Et}} \]

2-(Benzyl oxy)acetaldehyde (131)

A round bottom flask was charged with 1,4-bis(benzyl oxy)but-2-ene (3.54 g, 10.8 mmol) and 110 mL CH\(_2\)Cl\(_2\). The resulting solution was cooled to -78 °C before ozone was bubbled in until the color changed to blue. After purging with argon, PPh\(_3\) (4.24 g, 16 mmol) was added slowly. The solution was warmed to ambient temperature. After it was stirred for 7 h, the solution was concentrated in vacuo and purified by silica chromatography (20% EtOAc/hexanes) to give 131 (3.62 g, 93%). Data are: TLC \( R_f = 0.2 \) (20% EtOAc/hexanes); \(^1\text{H NMR (CDCl}_3\text{, 500 MHz)}\) \( \delta \) 9.71 (s, 1H), 7.29 (d, \( J = 8.5 \text{ Hz}, 2\text{H} \)), 6.90 (d, \( J = 8.5 \text{ Hz}, 2\text{H} \)), 4.57 (s, 2H), 4.07 (s, 2H), 3.82 (s, 3H).

\[ \text{Br} \quad \text{O}_{\text{Et}} \]

\((E)\)-Ethyl 4-bromo-2-methylbut-2-enoate (150)
A flame dried round bottom flask was charged with LiBr (4.34 g, 50 mmol) and THF (14 mL). The solution was stirred until LiBr dissolved, at which time Et$_3$N (1.74 mL, 12.5 mmol) was added. To this stirred solution was added a solution of (E)-ethyl 4-hydroxy-2-methylbut-2-enoate 149 (0.72 g, 5 mmol) in 14 mL THF. The resulting solution was cooled to 0 °C, and MsCl (0.81 mL, 10.5 mmol) was dropwisely added. The reaction was stirred at 0 °C for 2 h, at which time it was quenched by water. The mixture was extracted 3 times with ether. And the combined ether solution was washed with a saturated NaHCO$_3$ solution, followed with a saturated NaCl solution. The ether solution was then dried over MgSO$_4$ and concentrated in vacuo. Purification with column chromatography (10% EtOAc/hexanes) provided 150 (0.94 g, 90%).

Data are: TLC $R_f = 0.7$ (20% EtOAc/hexanes); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.93 (t, $J = 8.0$ Hz, 1H), 4.20 (q, $J = 7.5$ Hz, 2 H), 4.04 (d, $J = 8.0$ Hz, 2H), 1.93 (s, 3H), 1.31 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 167.3, 134.9, 132.3, 61.1, 26.2, 14.3, 12.3; HRMS (FAB+) found 228.9834 [M+Na]$^+$, calcd 228.9840 for C$_7$H$_{11}$BrO$_2$Na.

(F$_3$CH$_2$CO)$_2$POEt

(E)-Ethyl 4-(bis(2,2,2-trifluoroethoxy)phosphoryl)-2-methylbut-2-enoate (151)

To a mixture of (E)-ethyl 4-bromo-2-methylbut-2-enoate 150 (0.41 g, 2 mmol) and tris(2,2,2-trifluoroethyl) phosphate (6.56 g, 20 mmol) was added catalytic amount of tetra-$n$-butylammonium iodide (0.074 g, 0.2 mmol). The resulting mixture was stirred
for 1 day at 125 °C. The whole mixture was purified by a column chromatography
(10% EtOAc/hexanes) to give the title compound 151 (0.34 g, 45%). Data are: TLC
R_f = 0.7 (20% EtOAc/hexanes); ^1H NMR (CDCl_3, 500 MHz) δ 6.69 (dd, J = 1.5, 7.5
Hz, 1H), 4.44-4.37 (m 4H), 4.24-4.20 (q, J = 7.0 Hz, 2H), 2.93 (dd, J = 7.5, 24.5 Hz,
2H), 1.91 (d, J = 5.0 Hz, 3H), 1.31 (t, J = 7.0, 3H); ^13C NMR (CDCl_3, 125 MHz) δ
167.1, 134.2 (d), 126.9 (d), 123.7 (d), 121.5 (d), 62.6 (dq), 61.2, 27.9, 26.8, 14.3, 12.7;
HRMS (FAB+) found 395.0448 [M+Na]^+ , calcd 395.0459 for C_{11}H_{15}F_6PO_5Na.

(E)-Allyl 2-methyl-4-(tetrahydro-2H-pyran-2-yloxy)but-2-enoate (152)

To a stirred solution of (E)-ethyl 2-methyl-4-(tetrahydro-2H-pyran-2-yloxy)but-2-
enoate 148 (1.14 g, 5 mmol) in allyl alcohol (5 mL) was added LiBr (2.17 g, 25
mmol). DBU (1.12 mL, 7.5 mmol) was dropwisely added and the resulting mixture
was stirred for 9 h at ambient temperature. After evaporation of the allyl alcohol
solvent under reduced pressure, a saturated NH_4Cl solution was added. The resulting
mixture was extracted 3 times with Et_2O. The combined ether solution was condensed
in vacuo and purified by column chromatography (3% EtOAc/hexanes) to give
product 152 (1.06 g, 88%). Data are: TLC R_f = 0.3 (10% EtOAc/hexanes); ^1H NMR
(CDCl_3, 500 MHz) δ 6.89 (m, 1H), 5.95 (m, 1H), 5.34 (m, 1H), 5.24 (m, 1H), 4.65 (m,
3H), 4.40 (m, 1H), 4.19 (m, 1H), 3.87 (m, 1H), 3.52 (m, 1H), 1.87 (s, 3H), 1.86-1.53
(m, 6H); ^13C NMR (CDCl_3, 125 MHz) δ 167.4, 138.6, 132.6, 129.2, 118.2, 98.5, 65.5,
64.1, 62.3, 30.7, 25.6, 19.4, 13.0; HRMS (FAB+) found 241.1425 [M+H]^+ , calcd
241.1400 for C\textsubscript{13}H\textsubscript{21}O\textsubscript{4}.

\((E)\)-Allyl 4-hydroxy-2-methylbut-2-enoate

To a stirred solution of THP ether 152 (0.90 g, 3.74 mmol) in MeOH (15 mL) was added catalytic amount of \(p\)-TsOH (0.036 g, 0.187 mmol). The resulting solution was stirred at ambient temperature for 3 h, at which time 0.3 mL Et\textsubscript{3}N was added to quench the reaction. After concentration in vacuo, the residue was dissolved in EtOAc and washed with a saturated NaHCO\textsubscript{3} solution. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were dried and concentrated. Column chromatography (10-20% EtOAc/hexanes) provided the title compound (0.51 g, 88%). Data are: TLC \(R_f = 0.2\) (20% EtOAc/hexanes); \(^1\)H NMR (CDCl\textsubscript{3}, 500 MHz) \(\delta 6.87\) (m, 1H), 5.96-5.92 (m, 1H), 5.36-5.32 (m, 1H), 5.26-5.23 (m, 1H), 4.65 (m, 2H), 4.35 (s, 2H), 2.52 (bs, 1H), 1.85 (s, 3H); \(^13\)C NMR (CDCl\textsubscript{3}, 125 MHz) \(\delta 167.6, 140.9, 132.3, 128.4, 118.2, 65.6, 59.8, 12.8\); HRMS (FAB+) found 157.0863 [M+H]\(^+\), calcd 157.0865 for C\textsubscript{8}H\textsubscript{13}O\textsubscript{3}.

\((E)\)-Allyl 4-bromo-2-methylbut-2-enoate (153)

A flame dried round bottom flask was charged with LiBr (9.26 g, 106.67 mmol) and THF (35 mL). The solution was stirred until LiBr dissolved, at which time Et\textsubscript{3}N (3.72
mL, 26.67 mmol) was added. To this stirred solution was added a solution of \( (E) \)-Allyl 4-hydroxy-2-methylbut-2-enoate (1.67 g, 10.67 mmol) in 35 mL THF. The resulting solution was cooled to 0 °C before MsCl (1.73 mL, 22.4 mmol) was dropwisely added over 5 min. After the mixture was stirred at 0 °C for 2 h, it was quenched by water and extracted 3 times with ether. The combined ether solution was washed with a saturated NaHCO₃ solution and then a saturated NaCl solution. The ether solution was then dried over MgSO₄ and concentrated in vacuo. Purification with column chromatography (10% EtOAc/hexanes) provided \( 153 \) (2.18 g, 99%). Data are: TLC \( R_f = 0.7 \) (20% EtOAc/hexanes); \(^1\)H NMR (CDCl₃, 500 MHz) \( \delta \) 6.96 (t, \( J = 9.0 \) Hz, 1H), 5.99-5.92 (m, 1H), 5.34 (m, 1H), 5.25 (m, 1H), 4.67 (m, 2H), 4.04 (d, \( J = 9.0 \) Hz, 2H), 1.94 (s, \( J = 3 \)H); \(^13\)C NMR (CDCl₃, 125 MHz) \( \delta \) 167.0, 135.4, 132.3, 132.2, 118.4, 65.8, 26.1, 12.4; HRMS (EI+) found 217.9941 [M]+, calcd 217.9942 for C₈H₁₁O₂Br.

\( (E) \)-Allyl 4-(bis(2,2,2-trifluoroethoxy)phosphoryl)-2-methylbut-2-enoate (144)

To a mixture of \( (E) \)-Allyl 4-bromo-2-methylbut-2-enoate \( 153 \) (1.10 g, 5 mmol) and tris(2,2,2-trifluoroethyl) phosphate (8.20 g, 25 mmol) was added catalytic amount of tetra-\( n \)-butylammonium iodide (0.18 g, 0.5 mmol). The resulting mixture was stirred at 125 °C for 1 day, at which time the whole mixture was purified by a column chromatography (10% EtOAc/hexanes) to give the title compound \( 144 \) (0.97 g, 51%). Data are: TLC \( R_f = 0.7 \) (20% EtOAc/hexanes); \(^1\)H NMR (CDCl₃, 500 MHz) \( \delta \)
6.75-6.71 (m, 1H), 5.98-5.93 (m, 1H), 5.33 (dd, \( J = 1.5, 17 \) Hz, 1H), 5.25 (dd, \( J = 1.5 \) Hz, 5.0 Hz, 1H), 4.67 (d, \( J = 6.0 \) Hz, 2H), 4.45-4.37 (m, 4H), 2.98-2.90 (m, 2H), 1.93 (d, \( J = 5.0 \) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 166.6 (d), 133.9 (d), 132.2, 127.5 (d), 126.9 (d), 125.9 (d), 123.7 (d), 121.5 (d), 118.2, 65.7, 62.4 (dq), 61.1, 27.9, 26.7, 14.2, 12.7; HRMS (FAB+) found 385.0642 [M+H]+, calcd 385.0640 for C\(_{12}\)H\(_{16}\)F\(_6\)O\(_5\)P.

\( (o\text{-}t\text{BuPhO})_2\text{P} \)

(E)-Allyl 4-((bis(2-tert-butylphenoxy)phosphoryl)-2-methylbut-2-enoate (145)

A mixture of (E)-Allyl 4-bromo-2-methylbut-2-enoate 153 (0.22 g, 1 mmol) and bis(2-tert-butylphenyl) ethyl phosphite (0.75 g, 2 mmol) was stirred at 130 °C for 9 h. The whole mixture was purified by column chromatography to give the title compound 145 (0.37 g, 76%). Data are: TLC \( R_f = 0.3 \) (20% EtOAc/hexanes); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \( \delta \) 7.63 (d, \( J = 8.5 \) Hz, 2H), 7.36 (d, \( J = 7.5 \) Hz, 2H), 7.16-7.13 (m, 2H), 7.10-7.07 (m, 2H), 6.98-6.95 (m, 1H), 5.93-5.87 (m, 1H), 5.31-5.21 (m, 2H), 4.61 (d, \( J = 6.0 \) Hz, 2H), 3.22-3.16 (m, 2H), 1.79 (d, \( J = 4.0 \) Hz, 3H), 1.36 (s, 18H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 166.7, 150.2, 150.1, 139.3, 139.3, 132.9, 132.8, 132.3, 129.2, 129.1, 127.9, 127.6, 124.7, 119.7, 118.4, 65.7, 34.9, 30.2, 29.1, 28.0, 12.9; HRMS (FAB+) found 485.2459 [M+H]+, calcd 485.2379 for C\(_{28}\)H\(_{38}\)O\(_3\)P.
A flame dried 25 mL flask was charged with the methyl ketone 125 (0.10 g, 0.18 mmol) and 5 mL dry ethanol. To this stirred solution was added CH$_3$NH.HCl (0.048g, 0.72 mmol), Et$_3$N (0.10 mL, 0.72 mmol), and Ti(O-iPr)$_4$ (0.22 mL, 0.72 mmol). The mixture was stirred overnight at ambient temperature before being cooled to -78 °C. NaBH$_4$ (0.02g, 0.54 mmol) was added and the resulting mixture was stirred for 8 h at -78 °C. The reaction was diluted with Et$_2$O and quenched with saturated Na/K tartrate and 10% ammonium aqueous solution. The mixture was separated and the aqueous layer was extracted 3 times with Et$_2$O and 5 times with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$, filtered, concentrated, and chromatographed (2% MeOH/CH$_2$Cl$_2$ and 6 drops of NH$_3$.H$_2$O) to provide 155 (0.088 g, 85%). Data are:

TLC R$_f$ = 0.6 (10% MeOH/CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.57 (s, 1H), 5.2 (s, 2H), 4.98 (m, 2H), 3.91 (s, 3H), 3.60 (m, 1H), 3.54 (s, 3H), 3.50 (s, 3H), 3.33 (m, 1H), 3.28 (s, 3H), 2.7-2.60 (m, 2H), 2.54-2.51 (m, 1H), 2.37 (s, 3H), 2.07-2.04 (m, 1H), 1.57-1.53 (m, 1H), 1.31-1.26 (m, 2H), 1.05 (d, $J$ = 6.5 Hz, 3H), 0.86 (d, $J$ = 7.0 Hz, 3H), 0.84 (s, 9H), 0.02 (s, 3H), -0.018 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 153.4, 146.3, 146.0, 139.7, 131.9, 111.0, 101.8, 95.6, 95.0, 80.2, 76.5, 61.1, 57.9, 57.6, 57.3, 56.7, 36.5, 33.8, 33.3, 29.9, 26.3, 26.1, 19.6, 18.6, 15.6, -3.9, -5.0; HRMS (+TOF MS) found 575.3358 [M+H]$^+$, calcd 575.3364 for C$_{23}$H$_{51}$N$_2$O$_9$Si.