Total Syntheses of (+)-Geldanamycin, (-)-Ragaglitazar, and (+)-Kurasoin A and Phase-Transfer-Catalyzed Asymmetric Alkylation

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TOTAL SYNTHESES OF (+)-GELDANAMYCIN, (−)-RAGAGLITAZAR, AND
(+)-KURASOIN A AND PHASE-TRANSFER-CATALYZED
ASYMMETRIC ALKYLATION

By

Erik J. Hicken

A dissertation submitted to the faculty of

Brigham Young University

in partial fulfillment of the requirements for the degree of

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Department of Chemistry and Biochemistry

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December 2005
of a dissertation submitted by

Erik J. Hicken

This dissertation 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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ABSTRACT

TOTAL SYNTHESES OF (+)-GELDANAMYCIN, (−)-RAGAGLITAZAR, AND (+)-KURASOIN A AND PHASE-TRANSFER-CATALYZED ASYMMETRIC ALKYLATION

Erik J. Hicken
Department of Chemistry and Biochemistry
Doctor of Philosophy

Geldanamycin possess various biological activities as seen in the NCI 60 cell line panel (13 nM avg., 70 nM SKBr-3 cells). The predominant mode of action providing these unique results arises from the ability of geldanamycin (GA) to bind to the chaperone heat shock protein 90 (Hsp90). Despite its complicated functionality, the first total synthesis of GA was accomplished, which included two new reactions developed specifically to address the stereochemical features. The final step in the synthesis of GA was a demethylation-oxidation sequence to generate the desired para-quinone. This step could only be accomplished with HNO$_3$/AcOH, producing GA in 5% yield.

A GA model study, which closely resembled the aromatic core was extensively investigated to solve this critical oxidation issue. A protected hydroquinone model
compound was determined to be the optimum choice. Using Pd in the presence of air with a 1,4-hydroquinone provided the desired para-quinone quickly and nearly quantitatively in 98% yield. This study formulated the recipe of success for para-quinone formation of GA and future synthetic analogs.

Asymmetric glycolate alkylation has been developed using phase-transfer-catalysis (PTC). Diphenylmethoxy-2,5-dimethoxyacetophenone with trifluorobenzyl cinchonidinium catalyst and cesium hydroxide provided alkylation products at –35 °C in high yield (80-99%) and with excellent enantioselectivity (up to 90% ee). Useful α-hydroxy products were obtained using bis-TMS peroxide Baeyer–Villiger conditions and selective transesterification. The intermediate aryl esters can be obtained with >99% ee after a single recrystallization.

The newly developed PTC glycolate alkylation was applied to the asymmetric syntheses of ragaglitazar and kurasoin A. Ragaglitazar is a potent antihyperglycemic and lipid modulator, currently in phase II clinical trials. Kurasoin A is a potent protein farnesyltransferase (PFTase) inhibitor with an IC$_{50}$ value of 59.0 µM. PTC glycolate alkylation was optimized to provide 4-benzyloxy glycolate intermediates in excellent overall yield and with 96% ee after recrystallization. Ragaglitazar was then synthesized after considerable experimentation to provide the potent lipid modulator with yields and enantiopurity rivaling the best known routes produced by industry standards. Kurasoin A was produced through an α-triethylsiloxy Weinreb amide to provide the highest overall yielding route to this PFTase inhibitor currently disclosed.
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Chapter 1. Background

1.1. Geldanamycin

1.1.1. Isolation

Geldanamycin was isolated in 1970 as yellow crystalline needles from the culture filtrates of *Streptomyces hygroscopicus* var. *geldanus* var. *nova* (UC-5208) by workers at Upjohn.\(^1\) Originally isolated as a moderately active antibiotic compound it showed a unique profile compared to other ansamycin antimicrobials, as its principal activity is against protozoa rather than against gram-positive bacteria. Geldanamycin displayed a broad antimicrobial spectrum with MIC (minimal inhibitory concentration) values ranging from 2–100 µg/ml for a variety of bacteria, fungi, and protazoa *in vitro*. Geldanamycin was also found to be extremely active against nasopharynx KB (<0.001 µg/ml) and leukemia L–1210 (<0.002 µg/ml) tumor cells.

![Geldanamycin structure](image)

**Figure 1.1.** Benzoquinone ansamycin antibiotics.

Shortly thereafter, the structure was determined by Rinehart.\(^2\) His report showed geldanamycin to be the first ansamycin isolated containing a benzoquinone nucleus. Related ansamycin family members previously disclosed contained a napthoquinone,
such as the rifamycins, streptovaricins and tolypomycins. Other benzoquinone ansamycins (e.g. macbecins and herbimycins) were subsequently isolated and characterized. Although geldanamycin is the most potent member of the benzoquinone family it is also more structurally complex. In particular, the additional methoxy group in the quinone nucleus at C17 and the lack of a methoxy group at C15 pose significant challenges to synthetic routes.

1.1.2. Biological Activity

Geldanamycin possesses various biological activities as seen in the NCI 60 cell line panel (13 nM avg., 70 nM SKBr-3 cells).\(^3\) The predominant mode of action providing these unique results arises from the ability of geldanamycin to bind to the chaperone heat shock protein 90 (Hsp90).\(^4\) This was established by Neckers when he precipitated geldanamycin in a stable manner using a geldanamycin–affigel–10 affinity column.\(^5\)

Geldanamycin binds specifically to the ATP binding site of Hsp90 inhibiting its ability to perform its protein folding and ATPase activities. Hsp90’s ATPase activity is vital for \textit{in vivo} function. Inhibiting Hsp90 causes degradation of client proteins and disrupts the cell cycle. The broad range of antitumor effects, caused by Geldanamycin, have been attributed to its ability to selectively bind to Hsp90, causing a lower level of various growth-regulatory proteins.

Most proteins in a cell only interact with Hsp90 after a heat shock or stress induced unfolding event. A few proteins must interact with Hsp90 for normal function, such as the membrane bound Src family Wee 1, Lck that control cell proliferation.\(^7\) One
of the most sensitive oncogenic kinases to degradation via Hsp90–Geldanamycin complexes is human epidermal receptor, HER–2. This kinase is typically over-expressed in a variety of cancers and plays a prominent role in breast and ovarian cancer. Assays show that 50% of HER–2 is lost from SKBR3 cells within 90 minutes of geldanamycin treatment. Geldanamycin does not effect the cellular levels of the serine/threonine kinases PKA or PKC.

Hsp90 is highly expressed in most cells. Its abundance in both tumor and normal cells raises concerns that the treatment of tumor cells with geldanamycin may be toxic to patients. However, in phase I clinical trials 17-allylaminogeldanamycin, a semi–synthetic geldanamycin derivative, is well tolerated by patients and has been found to have up to 100 times greater affinity for cancer cells over normal cells.

![Figure 1.2. 3D view of bound geldanamycin with key Hsp90 residues.](image)

A significant development resulting from a collaboration of research groups is the X-ray crystal structure of the Hsp90-Geldanamycin complex. The complex shows that geldanamycin adopts a ‘C–clamp’ shaped conformation, which is higher in energy (~14 kcal/mol) than its extended conformation in solution. Figure 1.2 shows the shape of
geldanamycin and the key residues of Hsp90 that it interacts with. The bound conformation requires a change from an \textit{s-trans} amide with a dihedral angle of 8° (C22–N–CO) to an \textit{s-cis} arrangement (-165°). With the energy barrier between these two conformations being too great to allow for a spontaneous conversion, the change must be catalyzed.\textsuperscript{11}

It has been proposed that Ser 113 of Hsp90 catalyzes this conformation change via an enol-keto tautomerism pathway, thereby overcoming the amide rotational barrier.\textsuperscript{12}

A feasible explanation as to why 17-allylaminogeldanamycin is not toxic to patients yet lethal to cancer cells lies in this conformational change issue. In order to perform its protein folding and heat shock response functions, Hsp90 forms complexes with up to 10 different proteins. These protein complexes play an essential role in preventing damage to regulatory client proteins. Recent studies have confirmed that the majority of Hsp90 in cancer cells is contained in multi-chaperone complexes.\textsuperscript{6} On the other hand, Hsp90 in normal cells exist primarily in a free-form. The lack of normal cell toxicity exhibited by 17-allylaminogeldanamycin has been attributed to Hsp90 existing as a super-chaperone complex in cancer cells, which catalyzes the conformational change in the drug better than the free-form of Hsp90 found in normal cells.\textsuperscript{6}

\textbf{1.1.3. Related Synthetic Efforts}

Members of the benzoquinone ansamycin family have received considerable attention. In particular, two total syntheses of herbimycin A and three total syntheses of macbecin I have been reported. Despite the higher level of antitumor activity associated
with geldanamycin, when compared to the other family members, no complete synthetic route to this natural product had been disclosed prior to the work described herein.

The lack of synthetic interest may be two-fold. First, as alluded to earlier, the subtle structural differences between geldanamycin and herbimycin A or macbecin I are significant. The lack of a methoxy group at C15 forces a distinct disconnection and requires special methods to install the C14 stereocenter without the aid of the vicinal C15 center. The additional methoxy group at C17 contained in the quinone core may appear trivial at first glance. However, this small addition greatly complicates the aromatic core synthesis and nearly destroys the ability to create the para-quinone functionality via a conclusive oxidative demethylation sequence. The second reason may be that only recently has the cellular target been identified as discussed previously.

Macbecin I was first synthesized by Baker in 1990. His convergent approach focused on a C15-C16 disconnection, which was formed in the forward direction using a cyanocuprate epoxide opening. The two requisite pieces both employed the syn–aldol methodology developed by Evans to set the C6-C7 and C14-C15 stereocenters. The Evans’ auxillary was also used to introduce the C12 methoxy group via an enolate oxidation using an oxaziridine. Common threads through the following syntheses include the use of Wittig and Horner–Emmons reagents to install the $E,Z$–diene and the use of oxidizing (e.g. CAN, DDQ, etc.) reagents to form the para-quinone via an oxidative demethylation strategy. Baker’s route, though convergent, still required ~45 steps to complete the synthesis.

Evans then employed his aldol methodology toward macbecin I. Evans also used a convergent approach; his route employs a substrate controlled aldol reaction to
form the C12–C13 bond followed by decarbonylation to form the C13 methylene. Both
coupling fragments used the Evans aldol chemistry at three separate junctures to
introduce the syn stereochemistry at C15–C14, C11–C10, and at C6–C7. The endgame of
macrolactamization and oxidation produced the desired compound in the shortest linear
sequence known to date of ~25 steps.

![Synthetic approaches to macbacin I.](image)

**Figure1.3.** Synthetic approaches to macbacin I.

Panek also produced a concise route to macbacin I. Panek’s approach was linear
in fashion but used the crotylsilane methodology he had recently developed.\(^\text{15}\) This
method provided a disconnection at C14–C15 and at C6–C7. Panek also relied heavily on
diastereoselective hydroboration to install stereocenters at C12 and C10. A similar endgame to Evans’ approach was employed producing macbecin I in 37 steps.

Herbimycin A was first synthesized in 1991 by Tatsuta. He initiated the synthesis using a D-mannose derivative to install the stereocenters at C11, C12, and C14. He pioneered the diastereoselective hydroboration method used by Panek to install the C10 stereocenter. A mildly selective methoxy-allylborane addition formed the C6–C7 centers. Tatsuta was able to accomplish his synthesis in ~39 steps.

![Diagram](image)

**Figure 1.4.** Total syntheses of Herbimycin A.

Panek recently disclosed his synthesis of herbimycin A following a similar sequence that he had used previously in the synthesis of macbecin I. He again employed the *syn*-crotylation methodology to introduce the C10, C11, C14, and C15 stereocenters. A diastereoselective hydroboration was employed to set the C12 arrangement. Brown’s α-pinene-derived γ-methoxy allylborane reagent was used to establish the *syn* relationship at C6–C7. This route concluded with 31 steps and an overall yield of ~1%. 
1.2. Ragaglitazar

1.2.1. Discovery

Ragaglitazar (3) was found as the result of a discovery program initiated to find novel compounds that could activate both PPARα and PPARγ receptors for the treatment of type 2 diabetes.\textsuperscript{18} The research stemmed from a report that found β–aryl α–hydroxy propanoic acids to be useful in the treatment of hyperglycemia and hyperlipidemia (e.g. 4).\textsuperscript{19} Starting from the base motif of 4, a structure-activity study commenced which found ragaglitazar (3), a phenoxazine derivative, to be especially active in an \textit{in vitro} transactivation assay. Other groups followed the same course finding other related, highly active agonists 5 and 6.\textsuperscript{20}

![Chemical structures](image)

**Figure 1.5.** β–aryl α–hydroxy propanoic acids as PPARα and PPARγ agonists.

The assay showed that the racemate of 3 could activate both PPARα and PPARγ as desired. Resolution of (±)3 using (+)-2-phenyl glycinol afforded the separate enantiomers. The (+) enantiomer (\textit{R} configuration) showed only weak activation for both
isoforms. (S)-(−)3 on the other hand displayed excellent activity with significantly reduced plasma glucose and triglyceride levels in the assay. The study showed ragaglitazar to have great potential as a new drug for diabetes.

1.2.2. Biological Activity

Ragaglitazar is a potent antihyperglycemic and lipid modulator. It improves insulin sensitivity and decreases hyperlipidemia. Ragaglitazar showed 56% reduction in plasma glucose and 62% reduction in triglyceride levels of genetically diabetic, insulin resistant, hyperlipidemic mice. The observed activity is the result of its ability to activate both PPARα and PPARγ (peroxisome proliferator-activated receptor α/γ). This dual acting agonist transactivates PPARα and PPARγ with EC₅₀ = 3.2 µM and EC₅₀ = 0.6 µM respectively. Ragaglitazar has recently entered phase III clinical trials for the treatment of diabetes mellitus type 2 and is co-licensed by Novo Nordisk.

Type 2 diabetes is a multifaceted metabolic disorder. It is illustrated by hyperglycemia, insulin resistance, defects in insulin secretion and associated with dyslipidemia, hypertension, and obesity. The cause is currently being redefined as an abnormality in fat metabolism rather than a disorder in carbohydrate metabolism.

Peroxisome proliferators-activated receptors (PPARs) are receptors that are members of the steroid/thyroid/retinoid receptor superfamily. These receptors serve as ligand-activated transcription factors. There are three PPAR subtypes, PPARα, PPARγ, and PPARδ, which are created by separate genes. Their primary difference lies in the significant variation of the residues that line the ligand-binding pocket. These PPARs
regulate the expression of target genes (e.g. acyl-CoA synthetase and lipoprotein lipase) that encode proteins involved in lipid metabolism and energy balance.

PPARα plays an essential role in the uptake and oxidation of fatty acids and also in lipoprotein metabolism. It is abundant in metabolically active tissues such as the liver, kidney and heart. Selective PPARα ligands display significant lipid lowering capabilities and are used to reduce triglycerides (TG) and free fatty acid levels as well as increase high-density lipoprotein cholesterol (HDL).

PPARγ is a transcription factor involved with fat cell differentiation. It also regulates the production of many genes that encode proteins, which are involved in lipid metabolism and hormones that affect body energy metabolism. It is also found in active tissue such as skeletal muscle, adipose tissue and kidney. Selective PPARγ ligands are used to reduce plasma glucose levels and are currently used to treat diabetes, they are known as thiazolidinediones (TZDs).

While PPARγ ligands have many beneficial properties for people suffering from type 2 diabetes, they also have undesirable side effects. A significant problem is the typical weight gain observed in most patients (3–5 kg) due to an increase in fat mass. This not only poses negative psychological effects but also prevents patients from taking the drugs if they are at risk for cardiac complications.

The ability to control both glucose and lipid levels by a single compound can eliminate these problems associated with current treatments for diabetes. The discovery of compounds (e.g. 3–6) that serve as a PPARα/γ dual agonist can accomplish this goal. Therefore, the recent developments that produced ragaglitazar and others (Figure 1.5)
should provide an exciting entry to additive, and possibly synergistic, pharmacology for new agents used to treat type 2 diabetes.

1.2.3. Ragaglitazar Syntheses

The initial synthesis of 3 was disclosed in 2001 by workers at Dr. Reddy’s Research Foundation (Figure 1.6). Their work began with commercially available \( p \)-hydroxybenzaldehyde (7), which is reacted with 1,2-dibromoethane to form the bromoethoxy benzaldehyde. This compound is then treated with the sodium phenoxazine anion to produce 9 in 87% yield over 2 steps. Compound 9 then undergoes a Horner-Emmons olefination reaction which is followed by reduction using magnesium/methanol to provide 11 in racemic form.

![Figure 1.6](image-url)  
*Figure 1.6. First synthesis of ragalitazar.*
Hydrolysis of 11 was followed by diastereomeric resolution of the racemic acid using (S)-2-phenyl glycinol. The diastereomers could easily be separated using standard chromatography. Finally, the glycinol auxiliary was removed via acidic hydrolysis to afford 3 in 7 scaleable steps with a 6% overall yield and 94% ee.

The second synthesis was produced when ragaglitazar was co-licensed by Novo Nordisk.28,22 Their route to 3 began with the synthesis of a novel phenoxazine derivative. Phenoxazine (8) was treated with n-butyllithium, followed by bubbling ethylene oxide through the reaction mixture to provide the N-alkylated product 13. Then the primary alcohol of compound 13 was converted to the mesylate leaving group in preparation for the sequence seen in Figure 1.8.

![Figure 1.7. Phenoxazine intermediate synthesis.](image)

With 14 in hand the bulk of the synthesis could commence. Compound 10 was produced on large scale when commercially available 15 was chlorinated with acetyl chloride and a catalytic amount of I₂ followed by treatment with triethyl phosphite to give 10 in 96% yield. Compound 10 was then treated with t-BuOK and 4-benzyloxybenzaldehyde (16) to produce the Horner–Emmons adduct. This was followed by hydrogenation of the alkene with concomitant removal of the phenolic benzyl protecting group to provide racemic 17.
The resolution of 17 was then attempted via enzymatic methods. Over 80 hydrolases were screened in order to obtain suitable selectivity and yields. It was determined after many attempts that the hydrolase from *Aspergillus oryzea* was the best candidate for this step. After optimization of both the fermentation process and the resolution conditions, 18 was obtained in up to 48% yield with 99% ee. Acid 18 was then treated with thionyl chloride and 2-propanol to provide the isopropyl ester. Alkylation of the isopropyl ester with 14 and K$_2$CO$_3$ in refluxing toluene was followed by saponification, which afforded ragaglitazar (3) in 8 steps and with a 26% overall yield and 98% ee.

![Chemical reaction diagram](figure1.png)

**Figure 1.8.** Novo Nordisk route to ragaglitazar.

The route reported by Novo Nordisk is being used to produce large amounts (~50g batches) of 3 for phase III clinical trials. In principal, the selective synthesis of 18 can also be applied to the synthesis of other related PPAR$\alpha$/γ agonists such as 5 and 6.
Both of the outlined procedures employ a resolution of racemic materials, while no enantioselective carbon-carbon bond forming routes have been established.

1.3. Kurasoin A and B

1.3.1. Isolation

Kurasoin A and B were isolated in 1996 as white powders during a search for protein farnesyltransferase (PFTase) inhibitors.\textsuperscript{29} Soil samples taken from Kurashiki City, Okayama Prefecture, Japan were found to contain a fungus of \textit{Paecilomyces} sp. The particular strain was named FO-3684, which was amplified via culture fermentation and the broth extracted and purified to obtain kurasoin A and B in 0.09\% and 0.19\% yields respectively, from dried culture extracts.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structures.png}
\caption{Structures of kurasoin A and B.}
\end{figure}

The PFTase inhibitory activity was measured showing IC\textsubscript{50} values of 59 and 58 \textmu M for 19 and 20 respectively. Due to the significant level of activity for the promising anticancer drug target of farnesyltransferase the structure was quickly elucidated.\textsuperscript{30} A variety of spectroscopic techniques were employed to determine the topology. This was followed by a racemic synthesis, which unambiguously determined the carbon skeleton. The absolute configuration was then established via enantioselective synthesis and
comparison of the optical rotations of the synthetic and isolated materials.\textsuperscript{31} Although kurasoins A and B have been known for nearly 10 years they still stand as two of the more promising leads for PFTase inhibition.\textsuperscript{32}

1.3.2. Biological Activity\textsuperscript{33}

One of the most common mutations in cancer cells is the alterations found in \textit{ras} genes.\textsuperscript{34} These genes encode the 21-kDa proteins, p21 or Ras (e.g. Ki4B-, Ha- and N-Ras), which are found within the inner face of the plasma membrane. When Ras proteins are activated they promote cell proliferation.\textsuperscript{35} The mutations found in cancerous \textit{ras} genes inhibit the pathway that deactivates Ras proteins. In other words, the switch that stimulates cell growth is stuck in the ‘on’ position. With this knowledge in hand the task has been to find pathways that inhibit the function of oncogenic Ras proteins and the cell proliferation induced by these mutant \textit{ras} genes.

A promising pathway to this goal has been developing novel chemotherapeutics focused on inhibiting the enzyme protein farnesyltransferase. PFTase catalyzes the inclusion of a farnesyl isoprene group to various cellular proteins including the Ras family. The addition of a farnesyl group is essential to convert Ras proteins from a cytoplasmic and inactive precursor to a fully mature membrane assimilated form.\textsuperscript{36} This reaction is critical to the Ras protein cellular growth activity. Therefore, inhibition of PFTase would prevent Ras from becoming a biologically active protein.

A study aimed at supporting the PFTase antagonist theory found that if PFTase in yeast cells were mutated such that farnesylation could not occur, oncogenic Ras proteins no longer had the ability to transform cells.\textsuperscript{36} Significantly, these tests also found that
although PFTase activity was suppressed the yeast cells did not die. Human mammary tumor cells in mice have been effectively treated with PFTase inhibitors. A daily treatment of animals bearing small tumors resulted in 100% regression within a few days. Furthermore, toxicity has not been seen in mice being treated with PFTase inhibitors. This result is much different than the findings of cytotoxic antitumor agents which must be used at their maximally tolerated dose. Therefore, antagonists such as 19 and 20 represent a potentially selective drug with reduced toxicity issues for tumor treatment by inhibiting the cell proliferation pathway induced by mutant ras enzymes.

1.3.3. Total Syntheses

The first synthesis of the kurasoins was a racemic synthesis aimed at establishing the carbon skeleton. (±)-p-Hydroxyphenyllactic acid (21) was first treated with gaseous HCl in MeOH to produce the methyl ester. The ester was then treated with a mixture of N,O-diemthylhydroxylamine hydrochloride and AlMe₃ to afford Weinreb amide 22.

![Chemical structure](image1)

**Figure 1.10.** Racemic synthesis of the kurasoins.
Subsequent treatment with benzylmagnesium chloride in THF provided racemic kurasoin A. The validity of this final step and yield will be called into question later in this work. The synthesis of kurasoin B followed the analogous route (Figure 1.10) with lower yields for each step but inevitably reaching the desired compound.

The next synthesis was developed to produce a stereospecific route to the kurasoins and to determine their absolute stereochemistry. The synthesis of kurasoin A began with phenol 25, which was oxidized to an aldehyde using Doering-Parikh conditions. Nucleophilic addition of vinylmagnesium bromide provided allylic alcohol 26 in 45% yield for the two steps. Kinetic resolution of racemic 26 was accomplished via Sharpless asymmetric epoxidation to give the desired epoxide. Subsequent treatment with TBSCl and base then afforded (−)27 in 25% yield. Regiospecific opening of epoxide 27 with PhMgBr in the presence of CuI was followed by Moffat oxidation to afford (S)-28. A final global deprotection with HF-pyridine gave kurasoin A in a total of 7 steps and 5% overall yield.

![Chemical structures and reactions](image)

**Figure 1.11.** Total synthesis of kurasoin A.
The synthesis of kurasoin B was more concise, beginning with aldehyde 29. Addition of vinylmagnesium bromide and a kinetic resolution using the Sharpless epoxidation gave epoxide 30. Oxidation of the homobenzylic alcohol using CrO₃ under acidic conditions was followed by the regiospecific epoxide alkylation using indole with a lewis acid to provide kurasoin B. Although the route was expeditious requiring only 4 steps the overall yield was poor at 6%. Compounds 30 and TBS free 27 were found to have >90% ee as determined by (+)-MTPA ester analysis.

![Reaction Scheme](image)

**Figure 1.12.** Total synthesis of kurasoin B.

Both kurasoins were found to possess the (S)-configuration and a (+)-optical rotation. These total syntheses allowed the enantiomers to be tested for their activity and (R)-(−)-kurasoin B was found to be >6 times less potent than its natural antipode with an IC₅₀ = 400 µM. This suggests that the absolute configuration is critical for maximal inhibition of PFTase.
1.4. Catalytic Asymmetric Phase-Transfer Alkylation

1.4.1. Background

Catalysts used in phase-transfer systems are ionic compounds, traditionally quaternary ammonium salts, which have significant hydrocarbon appendages that deliver good solubility of the salt in organic solvents. In the case of asymmetric phase-transfer systems (phase-transfer catalysis, PTC), the ammonium salts are based on enantiopure amines (e.g. cinchonidine) that can be quaternized to form the requisite salt. Phase-transfer reactions are typically run in a biphasic (organic/aqueous or organic/solid) mode, yet homogenous conditions have been developed.

![Reaction Mechanism Diagram](image)

**Figure 1.13.** Phase-transfer catalyzed reaction mechanism.

The process for alkylation under biphasic liquid/liquid conditions is summarized in Figure 1.13. The organic substrate and electrophile are dissolved in a water-immiscible solvent such as toluene or CH$_2$Cl$_2$ while the base is dissolved in water. Once the phase-transfer catalyst is added, the first step proceeds as deprotonation at the interface by base, which generates the enolate. The enolate then coordinates with the catalyst as an ion pair and the enolate is transported to the organic phase.

The coordination of the enolate and cationic ammonium salt is the critical step for asymmetric induction. In the case of an enantioselective PTC alkylation, the binding of a
rigid, chiral catalyst to the enolate in a preferred arrangement produces a unique conformation that allows a single face of the enolate to interact with the electrophile. The selectivity of the alkylation is believed to arise from the steric screening provided by the catalyst. Increasingly selective catalysts have been developed by strengthening the preferred conformation and enhancing the steric shielding. After the enolate and electrophile react, the ammonium ion dissociates and is left available to participate in the cycle again.

1.4.2. Early Developments

Catalytic enantioselective alkylation under phase-transfer conditions was pioneered by workers at Merck and by the O’Donnell group. At Merck a project directed toward the synthesis of the uricosuric (+)-indacrinone 34 revealed that a chiral phase transfer catalyst was highly selective for the methylation of 31 providing the product 33 in 95% yield and 92% ee. The group used a cinchona alkaloid based catalyst (32) and chloromethane in a biphasic mixture of toluene and 50% aqueous NaOH. The mild reagents and the unprecedented high level of selectivity displayed for this substrate caused this reaction to become a prime example of the untapped potential of phase-transfer catalysts in asymmetric synthesis.

Figure 1.14. The first catalytic, highly enantioselective alkylation.
Surprisingly, little progress in this area was reported until five years later when O’Donnell published his initial findings using a related system.\textsuperscript{39,41} His goal was to synthesize non-natural amino acids with high levels of enantioselectivity using \textit{catalytic} quantities of an enantiocontrol element. He had been investigating the selective monoalkylation of prochiral protected glycine derivatives under \textit{achiral} phase-transfer conditions.

![Chemical structure](image)

\textbf{Figure 1.15.} O’Donnell’s stereoselective synthesis of amino acids by PTC.

Synthetic variations of a protected glycine derivative were screened with catalyst \textbf{36} to determine the optimum structure for an enantioselective alkylation. O’Donnell found that imine \textbf{35} could be alkylated in 75\% yield and 66\% ee using benzyl bromide when 10 mol\% of catalyst \textbf{36} was employed. A variety of alkyl-, allylic-, and benzyl bromides could be used to provide the product in 42–66\% ee and with good overall yields. Additionally, O’Donnell also found that when the pseudo-enantiomer of \textbf{36} (cinchonidine based) was used the products were obtained with similar enantiocontrol but with the opposite configuration. This report was the first example of a practical asymmetric synthesis of $\alpha$–amino acids using phase-transfer catalysis. The limitation of this work was that the enantiomeric excess peaked at 66\%, yet this issue became the foundation of study for many others seeking its remedy.
1.4.3. Synthesis of Enantiopure α–Amino Acids

The next breakthrough in PTC methodology was the development of a new catalyst that was reported simultaneously by two groups working independently. The basis of the new catalyst was to increase the steric shielding offered to the benzophenone imine (35) by substituting the benzyl group with an anthracenylmethyl group. The groups of Corey and Lygo both found that this modification provided a catalyst that was superior to 36.

![Chemical structures](image)

**Figure 1.16.** Development of N-9-anthracenylmethyl cinchonidium catalysts.

The Corey conditions deviated from those used by O’Donnell in that solid cesium hydroxide monohydrate was employed as the basic phase. This change allowed for minimal water content in the organic phase and use of lower temperatures. Under these conditions, catalyst 38 provided 37 with excellent enantioselectivity and in high yield. Lygo used the conditions originally employed by O’Donnell but with catalyst 39. Lygo was able to alkylate 35 with results similar to those reported by Corey, albeit with slightly
lower enantioselectivity and yield. The advantage to Lygo’s conditions was that the alkylation could be run at ambient temperature, avoiding the need for cryogenic temperatures.

![Proposed model for stereoinduction.](image)

Figure 1.17. Proposed model for stereoinduction.

The mode of enhanced selectivity was proposed by Corey in his initial communication. He felt that the alkylation proceeded via an early transition state through the most stable geometry of the tight ion pair of cation 38 and enolate 35. The electrophile approaches from the si (front) face of the ion-paired enolate for steric reasons. The transition-state analysis shown in Figure 1.17 (O-allyl group omitted for clarity) invokes π-stacking with the extended E-enolate over the quinoline with the fixed orientation of the bulky anthracenylmethyl substituent enforcing a selective pairing of cation 38 and enolate 35 in the most stable conformation shown.

The next advance in this area was the development of homogeneous reaction conditions that avoided the need for biphasic mixtures. The rate of a PTC reaction is greatly influenced by the rate at which the reaction can be stirred. When employing solid CsOH•H2O at or near freezing temperatures of 50% aqueous KOH or NaOH, the desired high rate of stirring can be difficult to achieve. Thus, O’Donnell sought reaction
conditions that would eliminate the problems associated with stirring by using an organic soluable base that could be used in the presence of an alkyl halide and a chiral catalyst without eroding selectivity.\textsuperscript{45}

![Schwesinger bases and homongeous reaction results.](image)

**Figure 1.18.** Schwesinger bases and homongeous reaction results.

In order to maintain high levels of enantioselectivity, it is essential that the ion-exchange from the initially formed ion-pair to the chiral, non-racemic ion-pair to be fast relative to the rate of alkylation of the initial ion-pair. In addition, the base must be sufficiently strong so as to form a small amount of the enolate while avoiding self-alkylation so that both the base and electrophile can be present at the outset of the reaction. The organic-soluble, nonionic Schwesinger bases met all of the desired criteria. The phosphazene bases, BEMP (\textit{40}, 2-\textit{tert}-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine) and BTPP [\textit{41}, \textit{tert}-butylimino-tri(pyrrolidino) phosphorane], have a pK\textsubscript{a}=16.2 and 17.0 respectively (DMSO). Their corresponding cations were deemed (via molecular modeling) too small and convex to interact effectively with the enolate anion. O'Donnell showed that when catalyst \textit{38} was used with ester \textit{35} high levels of enantioselectivity were maintained under homogenous conditions when the Schwesinger bases were employed at −50 °C. All electrophiles
screened displayed high levels of enantioselectivity and isolated yields with 37 being obtained in 88% yield and 91% ee.

From this background a number of new catalysts have been developed that further improve selectivity under altered reaction conditions and reduced catalyst loading. Maruoka reported the rational design of a unique C₂-symmetric chiral quaternary ammonium salt 42. Despite its lengthy synthesis, this new chiral phase transfer catalyst has shown remarkable efficiency with only 1 mol% typically being required. Catalyst 42 provides excellent levels of enantiocontrol for the alkylation of 35 as well as with various other ketone and ester substrates, which are discussed below.

Co-workers Park and Jew have also been active in this area developing four new catalysts based on cinchona alkaloids. The first is based on the dimerization concept that has been successfully applied to asymmetric dihydroxylation developed by Sharpless. Park and Jew found that a dimeric ammonium salt using a naphthalene group 43 could provide optimal enantioselectivity for producing 37 while employing 1 mol% of 43.

![Figure 1.19. New catalysts developed for phase-transfer alkylation.](image)

Park & Jew:

Maruoka:

Shibasaki:

Ar = C₆H₄-4-OMe 45
Park and Jew also studied the importance of electronic effects associated with nitrogen substituents in cinchona based phase-transfer catalysts. They discovered an unusual electronic effect of fluorinated benzyl catalysts. It was determined that catalysts containing a 2’-F benzyl methyl unit on the nitrogen greatly enhanced the selectivity. Further refinement of possible substitution patterns revealed that the 2,3,4-trifluorobenzyl group (44) provided optimum selectivity. It is important to note that although 10 mol% of the catalyst is required that the incorporation of three fluorine atoms provides nearly enantiopure product (98% ee) compared to catalyst 36 prepared by O’Donnell that provided product in 66% ee.

The enhanced levels of stereoinduction were originally attributed to potential internal hydrogen bonding, providing a more rigid catalyst. Evidence for this postulate was obtained by further varying the $N^+-$aryl methyl unit. $N$-oxy-pyridine and cyanobenzene 44b and 44c have been reported to form a stable crystal structure by internal hydrogen bonding, similar to fluorobenzenes 44 and 44a. When the ammonium salts were prepared containing either an $N$-oxy-pyridine (44c) and cyanobenzene (44b) at the 2’ position, 37 was obtained with 96% ee and 94% yield at 0 °C. In contrast, when the cyano nitrogen is replaced by a carbon (i.e. alkyne) then levels of enantioselectivity fall to 75% ee. Similarly, when the $N$-oxy-pyridine moiety is replaced by the simple pyridine derivative the enantioselectivity is reduced to 61% ee. The results of this study not only culminated in the determination of two new highly selective catalysts, but also support the hypothesis that hydrogen bonding between water and the cinchona catalyst could provide a more rigid conformation leading to high levels of enantioselectivity.
Another recent phase-transfer catalyst was developed by Shibasaki.\textsuperscript{49} He designed a new two-centered catalyst based on L- or D-tartrate (45). These catalysts have two-cationic centers and are designed to simplify the process of catalyst modification in order to improve selectivity or reactivity. Standard conditions (50% KOH/PhMe) are used with 10 mol\% of the catalyst. These catalysts are easily recoverable and show high levels of enantioselectivity, Figure 1.19. The catalysts described above show the diverse nature and high levels of enantioselectivity that can be attained with phase-transfer alkylations.

Another class of nonproteinogenic amino acids are $\alpha,\alpha$-dialkyl-$\alpha$-amino acids. These noncoded amino acids have displayed significant activity as enzyme inhibitors and occupy a unique role on the conformation of peptides that incorporate them. These amino acids possess a stereochemically stable quaternary carbon that can be derived from the dialkylation of a compound such as 35. Two groups have developed the requisite methods to accomplish this task. The first to do so was Maruoka and co-workers. They employed a derivate of Schiff base 35, which replaced the benzophenone imine portion with a $p$-chlorobenzaldehyde imine (46). Using this substrate in conjunction with catalyst 42 provided the desired products 47 with excellent selectivity.\textsuperscript{50} Substrate 46 undergoes alkylation by the sequential addition of two different electrophiles at a regular interval
and stochiometry. When the halides are added in the reverse order the absolute configuration of the product is also reversed. In addition to this sequential alkylation the substrate can be prepared with an alkyl group already present (48) and thus a single alkylation can afford the same products with slightly higher selectivity (Figure 1.21).

**Maruoka**

\[
\begin{align*}
\text{Cl} & \quad \text{N} & \quad \text{O} & \quad \text{Or-Bu} \\
46 & \quad & & \\
\text{PhCH}_2\text{Br (1.0 eq)} & \quad \text{then} & \quad \text{Br (1.2 eq)} & \quad \text{42 (1 mol\%), CsOH(H}_2\text{O)} & \quad \text{PhMe, -10°C} & \quad \text{citric acid} & \quad \text{THF} & \quad \text{H}_2\text{N} & \quad \text{O} & \quad \text{Or-Bu} & \quad 47 & \quad 74\%, 92\% \text{ ee}
\end{align*}
\]

**Park & Jew**

\[
\begin{align*}
\text{Cl} & \quad \text{N} & \quad \text{O} & \quad \text{Or-Bu} \\
48 & \quad & & \\
\text{PhCH}_2\text{Br (1.2 eq)} & \quad \text{42 (1 mol\%), CsOH(H}_2\text{O)} & \quad \text{PhMe, -10°C} & \quad \text{citric acid} & \quad \text{THF} & \quad \text{47} & \quad 71\%, 97\% \text{ ee}
\end{align*}
\]

**Figure 1.21.** Enantioselective synthesis of \(\alpha,\alpha\)-dialkyl-\(\alpha\)-amino acids.

Park and Jew also determined an appropriate protocol to accomplish the quaternary carbon formation. They also used a derivative of 35 and by changing the imine portion they could induce the desired reactivity.\(^{51}\) They found that imine 49 could be alkylated with RbOH and benzyl bromide in excellent selectivity when catalyst 44 was employed. Both of these examples display the distinct feature of enabling the formation of various \(\alpha,\alpha\)-dialkyl-\(\alpha\)-amino acids in a straightforward manner, making these otherwise inaccessible amino acids available for general use.
In an attempt to stereoselectively produce α-alkylserines, Park and Jew were able to selectively alkylate the phenyl oxazoline 51a. The oxazoline moiety served to enhance the acidity of the α proton of the ester and as an efficient protecting scheme for both the amino and hydroxy groups. Catalysts 38, and 42-44 were screened for their ability to elicit high levels of enantioselectivity and reactivity. Catalyst 42 developed by Maruoka was found to be optimal, providing product 52a in 98% yield and 99% ee in 5 hours. By modifying the substrate (e.g. 51b) they found that the more readily available cinchona-derived catalysts related to 38 could be employed to provide (R)-α-alkylserines such as 52b with excellent enantioselectivity. Various activated halides display high levels of selectivity; in addition, the isolated products can be hydrolyzed with 6M HCl to generate the desired α-alkyl serines.

More recently, Maruoka has extended his work on the alkylation of β-keto esters (Figure 1.23) to include aza-cyclic keto esters. This alkylation can be used to obtain nonproteinogenic aza-cyclic α-amino acids with quaternary stereogenic centers. Compounds 54 and 55 could be alkylated with high levels of enantioselectivity when

![Figure 1.22. Asymmetric alkylation of aryl oxazolines.](image-url)
using 2 mol% of catalyst 56. In addition to the direct isolation of aza-cyclic amino acids, products can be chemoselectively functionalized at the 3-keto carbonyl position. Using either NaBH₄ or Grignard reagents provides a single diastereomer of densely functionalized material in high yield.

Figure 1.23. Asymmetric alkylation of aza-cyclic keto esters.

Maruoka has also described the alkylation of the benzophenone Schiff base of N-benzhydrolglycinamide (64). This compound is closely related to 35, and although applicable to amino acids this method was designed to provide a practical route to enantiopure diamines. Alkylation of 64 in the presence of catalyst 65 with various electrophiles gave the desired products in excellent yield and enantiomeric excess. The products could then be hydrolyzed with acid followed by carbonyl reduction to provide compounds such as 67 with excellent selectivity. This process was also extended to the alkylation of amides related to 48 to afford vicinal diamines with congested quaternary stereogenic centers.

In summary, a large amount of work has been devoted to the synthesis of non-natural amino acids via asymmetric phase-transfer catalyzed alkylation. A variety of carbonyl containing compounds have been effectively used to create enantioenriched products that can be used to study biologically active compounds and the systems they
interact with. Although amino acids targets have been the general focus in the literature, phase-transfer alkylation can also be applied to other related synthetic needs.

![Chemical reactions](image)

**Figure 1.24.** Maruoka’s route to optically active diamines.

1.4.4. Additional Asymmetric Phase-Transfer Alkylations

Few examples of catalytic, asymmetric alkylations exist in the chemical literature that do not use glycine based substrates. Due to the surprising existence of this fundamental problem, phase-transfer-catalyzed enantioselective alkylations of carbonyl compounds have also been studied. Although the number of examples is relatively small, they represent the potential of phase-transfer catalyzed alkylations.

The first deviation from phase-transfer catalyzed amino acid synthesis was developed by Corey. He found that alkene could be selectively alkylated with allyl bromide and catalyst in high yield. A variety of electrophiles can be used each providing products with excellent selectivity. The isolated products can then be elaborated to useful intermediates such as chiral propane-1,3-diol derivatives, 3-oxygenated propionic aldehydes, and chiral tetrahydropyrans.
Figure 1.25. Phase-transfer catalyzed alkylation of propionic ester equivalent.

Ester 59 closely resembles the core structure of 35. A significant aspect of 59 is the retention of unsaturation at the β-carbon in order to create an extended enolate and thereby produce a lower pKₐ to enable deprotonation with suitable bases. Another important structural aspect was the inclusion of the dimethylamino moiety on the phenyl groups. These electron donating groups help increase the electron density/charge on the enolate oxygen of the conjugate base. The enhancement of selectivity can then be understood on the basis of the contact ion pair model, which would predict that a more electron rich oxygen would help strengthen the Coulombic force between the counterions and favor a very tight ion pairing. Thus, when the dimethylamino groups are changed the selectivity is altered dramatically (e.g. 4-OMe, 91% ee, 4-H, 67% ee).

Maruoka has also described the application of his catalysts to β-keto esters toward the production of chiral quaternary carbon centers. He reports the use of 3 cyclic β-keto esters, reminiscent of ketone 31 used in the Merck studies, as well as an acyclic substrate that displays high selectivity as well. Using catalyst 56 with any of the substrates shown in Figure 1.25 and benzyl bromide produces α,α-dialkyl-β-keto esters in high yield and with excellent selectivity. The products thus obtained can be readily converted to their
corresponding β-hydroxy and β-amino acid derivatives without loss of chirality. Others have worked in this area using cinchonine based catalysts, unfortunately they have not achieved the consistent high levels of enantioselectivity that are observed when catalyst 56 is employed.\textsuperscript{58}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.26.png}
\caption{Phase-transfer alkylation of β-keto esters.}
\end{figure}

A final example of a phase transfer catalyzed alkylation leading to products other than amino acids is the alkylation of α-fluorotetralone.\textsuperscript{59} In this case a new catalyst based on cinchonine (69) was used as the optimal catalyst for α-fluorotetralone, although the communication does not report whether catalysts such as 38 were screened.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.27.png}
\caption{Asymmetric alkylation of α-fluorotetralone.}
\end{figure}
Shioiri found that catalyst 69 could provide high levels of selectivity under the biphasic KOH/PhMe conditions at −10 °C. A variety of benzyl halides showed high levels of enantioselectivity (80-91% ee) while allylic bromides showed lower levels of selectivity (70% ee).

1.5. References and Notes


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Chapter 2. Total Synthesis of Geldanamycin

2.1. Introduction

The first total synthesis of geldanamycin was a multi-year task requiring the full-time attention of up to four graduate associates and an undergraduate student.\(^1\) The synthesis entails the development of two novel asymmetric glycolate aldol reactions and was pursued from a myriad of approaches including a ring closing metathesis macrcyclization.\(^2\) The primary student responsible for this synthesis was Dr. Erik L. Meredith, who graduated from Brigham Young University in 2002. The developments leading to the eventual total synthesis of geldanamycin are described in exhaustive detail within the dissertation he provided in defense of his Ph.D. requirement.\(^3\) In order to avoid duplication of such work this chapter will describe only those synthetic protocols that culminate in the first total synthesis of geldanamycin.

The synthetic overview of the route toward 1 is depicted in Figure 2.1. The total syntheses of herbimycin and macbecin (see Chapter 1, Section 1.1) had successfully employed an oxidative demethylation step to reveal the desired para-quinone. Following this precedent it was anticipated that the quinone functionality could be masked as trimethoxy benzene 71, and be revealed in the final step of the synthesis. The next disconnection is opening the macrolactam, revealing seco-carboxylic acid 72. The aniline group would be obtained by selective reduction of the aryl nitro functional group to provide the cyclization precursor. 72 reveals the linear, dense functionality required for the synthesis of 1, as well as the challenge of finding a midpoint disconnection.

A linear approach was adopted after several convergent routes failed to provide sufficient progress. This approach employs aldehyde 73 to form the requisite E,Z-diene
acid via phosphonate mediated olefin installation. Enal 74 would be treated with the
enolate of 75 to set the C6 and C7 stereocenters, using a recently described
enantioselective syn-glycolate aldol reaction. The C8,9 olefin and C10 methyl
stereocenter were eventually installed by means of an asymmetric hydroboration route
used previously in the synthesis of herbimycin and macbecin. Intermediate 76 would be
obtained by employing the recently developed enantioselective anti-glycolate aldol
reaction which uses dioxanone 78 and aldehyde 77. The synthesis of the aryl core could
be produced by elaboration of trimethoxy benzene followed by an Evans alkylation to
install the C14 methyl stereocenter.

Figure 2.1. Retrosynthetic analysis of geldanamycin.
2.2. Synthesis of Aromatic Core and C₁₅–C₇ Segment

The first task was to create an aryl core that would be prepared for the extension of a stereocenter-rich carbon chain as well as mask the aromatic functionality, such that it can withstand the synthetic steps of the carbon skeleton synthesis and be selectively revealed at the appropriate time. The process began with commercially available 1,2,4-trimethoxybenzene. Using a selective lithiation procedure developed by Gilman, treatment of 79 with n-butyllithium followed by the addition of DMF and subsequent hydrolysis produced the aryl aldehyde. Interestingly, this procedure provides nearly exclusive formylation at the 3 position, presumably due to the complex induced proximity effect provided by the 2,4 disposed methoxy groups. Selective nitration of the electron rich aldehyde was produced by standard treatment with nitric acid in warm acetic acid to provide crystalline nitrobenzene 80.

With the aromatic ring substituted at the desired positions the next task consisted of extending the long stereocenter-rich carbon chain from the aldehyde position. Facile reduction of aldehyde 80 with NaBH₄ proceeded uneventfully in excellent yield. Following an aqueous workup the material was sufficiently pure to be carried on directly
to the next step. Subsequent treatment of the benzylic alcohol with PBr₃ and catalytic pyridine resulted in the isolation of the highly crystalline compound 81.⁵ Once again the yield was excellent and the material of sufficient purity to be carried on directly to the next step without purification.

At this point introduction of the C14 methyl stereocenter was installed using the ubiquitous Evans’ oxazolidinone-based asymmetric alkylation.⁶ Toward this goal, (S)-3-(1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone 82 was prepared by reported procedures.⁷ Subsequent treatment of 82 with NaHMDS at –78 °C produced the corresponding (Z)-sodium enolate, which was then treated with benzyl bromide 81. The aryl bromide underwent selective alkylation (>19:1) with excellent mass conversion to provide 83. This alkylation proceeds with excellent selectivity despite the potential issue of steric congestion produced by the neighboring methoxy groups of bromide 81.

In order to advance this intermediate to aldehyde 77 a one carbon homologation was necessary. This transformation was accomplished using a cyano group as a masked aldehyde. Removal of the auxiliary from 83 was accomplished by reduction with LiBH₄ to afford the corresponding primary alcohol. The alcohol then underwent cyanation using Mitsunobu conditions with acetone cyanohydrin, DEAD and PPh₃ to directly give cyanide 84.⁸ Using two equivalents of DIBAL-H at –78 °C followed by warming to ambient temperature and subsequent in situ hydrolysis with pH 7 buffer, the key aldehyde 77 was produced in excellent yield.

With intermediate 77 in hand the stage was set for the first glycolate aldol reaction to set the C11 and C12 anti-diol stereocenters. Dioxanone 78 had been previously developed to provide high levels of selectivity for anti aldol reactions. It could
be prepared on large scale by dihydroxylation of 4-4′-dimethoxystilbene using Sharpless
conditions to provide diol 86 with excellent enantioselectivity (98% ee).

Treatment of 86 with di-n-butyltin oxide produced a tin acetal which was then treated with tert-butyl bromoacetate to afford 78.

The optimal conditions employ di-cyclohexylboron triflate (2.6 equiv.), added as a standardized methylene chloride solution, with triethyl amine (2.6 equiv.) at −78 °C followed by addition of the aldehyde (1.5 equiv.) with warming to room temperature.

**Figure 2.3.** Asymmetric anti-glycolate aldol reaction.

The reaction gives good yields of isolated products with high to excellent selectivity for the anti-adduct as determined by 1H NMR. X-ray crystal structure analysis and optical rotation comparison to known products were used to establish the S,S,S,S- stereochemistry as shown for 87. Various classes of aldehydes including alkyl, aryl, branched, unsaturated, etc. show high selectivity with the exception of aryl aldehydes.
The origin of the asymmetry of the reaction is due to the enolate of 78 being constrained to the E-isomer and the proximity of the C5-aryl group on the dioxanone, which directs the aldehyde to the si-enolate face in the closed, Zimmerman-Traxler type transition state.

Following this method, 78 was exposed to dicyclohexylboron triflate and triethylamine to give the boron enolate. Addition of aldehyde 77 produced the (S,S)-anti-aldol adduct 88 in 70% yield and with 10:1 selectivity. The diastereomers were readily separated by column chromatography and recovered starting materials could be resubjected to the reaction conditions. The free alcohol of 88 was then methylated with Meerwien’s salt and proton sponge to give the corresponding methyl ether product. The lactone ring was then opened using catalytic NaOMe in MeOH to cleanly produce methyl ester 89 in excellent overall yield without loss of optical purity. The benzylic ether was easily cleaved using CAN to give the \( \alpha \)-hydroxy ester. Protection of the \( \alpha \)-hydroxy group as a TBS ether involved using the mild conditions of TBSCl and imidazole in DMF.

![Figure 2.4](image-url). Synthesis of disubstituted olefin intermediate.
In order to prepare for the installation of the C10 methyl stereocenter, 76 was then elaborated to 91 using a series of steps related to those previously reported by Tatsuda and Panek. Accordingly, methyl ester 76 was carefully reduced directly to the aldehyde in high yield using 2 equivalents of DIBAL-H at low temperature. The aldehyde was then treated with an excess of trimethylaluminum at low temperature to provide an inconsequential 2:1 mixture of alcohol diastereomers. The free secondary alcohol of 90 was then oxidized using Dess-Martin periodinane (DMP) to provide the corresponding ketone. Wittig olefination of the ketone was accomplished using methyl triphenylphosphonium bromide and sodium bis-trimethylsilylamide (NaHMDS). Cleavage of the silyl protecting group was then accomplished using aqueous HF in acetonitrile to provide allylic alcohol 91.

2.3. Completion of Geldanamycin Carbon Skeleton

The stereoselective hydroboration of an olefin highly related to 91 by Tatsuda showed that BH$_3$-DMS complex produced the C10 methyl stereocenter of herbimycin A in 4:1 (syn/anti) selectivity. In his synthesis of macbacin, Panek had investigated a variety of other hydroboration conditions and reagents but ultimately relied on the same reagent as Tatsuda, due to its simplicity and mild yet reproducible selectivity. In the present case, when alkene 91 was exposed to BH$_3$-THF complex at –10 °C, followed by a basic hydrogen peroxide oxidation of the resulting borane, the reaction yielded a 5:1 mixture of separable diastereomers in 94% combined yield. Despite evidence suggesting that the major product was the syn isomer, the acetonides of the isolated isomers were formed. The major product provided an acetonide (94) with a $J_{ab}$ coupling constant of 2.5
Hz while the minor isomer provided a $J_{ab}$ coupling constant of 12.0 Hz, indicating that the syn isomer was indeed obtained as the major product.

The origin of this selective induction is not clear, however Houk has proposed a transition-state model.\textsuperscript{14} Computations suggest that conformations which adopt a free hydroxyl group at the inside position over an outside position are favored slightly by ~0.1 kcal/mol. This minimal difference is reflected in the reaction providing 92. Although this example provides additional evidence for Houk’s model it is unknown whether other conformational issues enhance or exclusively produce the observed selectivity. Attempts to improve the selectivity were unsuccessful. In addition, the uncatalyzed hydroboration only provides the desired product if the alcohol is left unprotected. This forces a number of protecting group changes to be made, which adds to the length of the route.

Figure 2.5. Diastereoselective hydroboration.
Syn-diol 92 was doubly protected as TBS ethers using TBSOTf and 2,6-lutidine to provide the di-protected adduct in 90% yield. Selective removal of the primary TBS ether was accomplished by employing camphorsulfonic acid in methanol at 0 °C in good yield. With the C11 hydroxyl group now selectively protected, the primary alcohol was oxidized with DMP to smoothly provide aldehyde 93. Treatment with the stabilized Wittig reagent at 90 °C in toluene provided the trisubstituted olefin as a 16:1 mixture of E and Z isomers. The crude ratio could be enhanced by chromatography to afford exclusively the E isomer. The ethyl ester was then reduced to its allylic alcohol by reduction with DIBAL-H. Subsequent Swern oxidation (DMSO, oxalyl chloride and NEt₃) provided the highest yield of 74, whereas DMP provided a slightly lower 70-80% yield.

With aldehyde 74 in hand, a syn-glycolate aldol reaction was used to set the C6 and C7 stereocenters. Initially, Evans’ auxiliary was chosen as the ideal candidate since it had received considerable attention for such a transformation and displayed promising results.¹⁵ Unfortunately, use of this auxiliary provided only a ~2:1 mixture of diastereomers. These results forced us to look for a new solution to the desired stereochemistry that resulted in the following development.

Masamune had reported the use of norephedrine based auxiliaries to affect an anti selective propionate aldol reaction.¹⁶ In addition, he had demonstrated that by judicious choice of dialkyl boron triflate and base, the anti/syn ratio could be rigorously controlled. These reaction conditions were then screened for their efficacy in relation to a glycolate aldol reaction. The substrate was quickly prepared on large scale by treating the known alcohol 95¹⁶a with methoxyacetic acid in the presence of 1-ethyl-3-[3-(dimethylamino)-
propyl]-carbodimide hydrochloride (EDCI) and 4-dimethylaminopyridine (4-DMAP) to provide 75 in excellent yield. Using auxiliary 75 with various aldehydes in the presence of different boron triflates and bases quickly established that the reaction was syn-selective regardless of reagent choice.\textsuperscript{17} The lack of tunable selectivity in this case is proposed to arise from coordination of the Lewis basic ether at the α-position ensuring that the enolate geometry is \textit{Z}-96, leading to \textit{syn}-product. The \textit{S,R}-stereochemistry was confirmed by direct comparison. The method was found to be general and useful for a wide range of aldehyde substrates. The exceptions are alkynyl and β-branched enals at only 2:1 selectivity. Fortunately α-branched enals, as needed for geldanamycin, typified by α-methyl cinnamaldehyde give good selectivity (9:1) and 83\% yield.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2_6.png}
\caption{Norephedrine based glycolate aldol reaction.}
\end{figure}
Using the optimized conditions shown in Figure 2.6 with aldehyde 74 and auxiliary 75 provided the syn-aldol adduct 98 in excellent yield and with >20:1 selectivity. The development of the syn-glycolate aldol reaction proved to be very rewarding and provided a new solution for this challenging transformation. The ester auxiliary was then removed by hydrolysis using LiOH in THF and H₂O. The crude reaction mixture was then treated with trimethylsilyldiazomethane. Column chromatography provided pure hydroxy ester 99 along with the recovered auxiliary in excellent yield for the two steps.

The C7 alcohol was then protected as a triethylsilyl ether using TESOTf and 2,6-lutidine to provide a group that could be selectively removed in the presence of a secondary TBS ether at a later stage. The methyl ester was then reduced directly to its corresponding α-methoxy aldehyde using DIBAL-H at −78 °C in CH₂Cl₂. The resulting aldehyde then underwent Still-Gennari olefination with the anion derived from bis-(2,2,2-trifluoroethyl)-phosphonate, KHMDS, and 18-crown-6. This reaction provided diene 100 in excellent yield and as a 13:1 mixture of Z/E isomers. Unfortunately the isomers
were not readily separable until the following stage. The next step was reduction of the methyl ester to intercept the aldehyde functionality. Reduction with DIBAL-H proved more troublesome than anticipated. Initially, DIBAL-H reduction in THF provided trace product formation even when a large excess of DIBAL-H was employed. Interestingly, solvent changes provided large variations in reactivity. Using CH₂Cl₂ the reaction gave complete reduction of the ester and concomitant TES deprotection. Finally, using Et₂O gave the desired product in 91% yield. Subsequent oxidation using DMP cleanly provided the desired enal. The E-trisubstituted olefin was installed using the Roush-Masamune olefination with phosphonate 103. The E,Z diene ester 104 was obtained in excellent yield and selectivity.

Figure 2.8. Completion of the geldanamycin carbon backbone.
At this point revealing the aniline and carboxylic acid groups was necessary in order to form the macrolactam. The nitro group was selectively reduced in the presence of three alkenes using the reagent developed by Lalancette.\textsuperscript{21} NaBH\textsubscript{2}S\textsubscript{3} was prepared \textit{in situ} by adding elemental sulfur to NaBH\textsubscript{4} followed by introducing 104 in THF. This reaction smoothly produced the aniline compound without disturbing the existing olefins. The resulting aniline was treated with Pd(PPh\textsubscript{3})\textsubscript{4} and morpholine at ambient temperature to produce amino acid 105 in 85% yield.\textsuperscript{22} The specific use of an allyl ester was critical to revealing the acid moiety. Previous attempts toward the synthesis of 105 had employed the ethyl ester of 104, which gave decomposition products when the hydrolysis was carried out using LiOH.

The next step was to create the macrolactam via amide bond formation. Previous work on herbimycin and macbecin had shown that (bis(2-oxo-3-oxazolidinyl)phosphinic chloride) (BOP-Cl) was an effective reagent. Accordingly, exposure of amino acid 105 to BOP-Cl with iPr\textsubscript{2}NEt in dilute warm toluene (0.001M) produced the desired macrolactam 106 in 76\% isolated yield. The NMR data of 106 suffers significantly from severe line broadening due to the various ansa ring conformations. Alternating solvent and using variable temperature NMR experiments did not improve the resolution. Attention then turned to the formation of the urethane at C7. Selective removal of the TES protecting group was first attempted using HF•pyridine which provided ~80\% of the desired product along with the remaining double (TBS and TES) silyl ether deprotection product. Conversely, employing TBAF in THF at 0 °C provided exclusively the mono deprotection product in 90\% yield. Installation of the carbamate moiety was then attempted using the commercially available trichloroacetyl isocyanate reagent following
the lead of Kocovsky. This method had been used with excellent results in a number of hindered and complex settings but had not been applied to ansamycin syntheses. Using this method the protected carbamate was installed smoothly and underwent methanolysis upon the addition of MeOH and K$_2$CO$_3$ to provide the urethane adduct. The remaining step prior to quinone formation was removal of the TBS protecting group. The TBS group proved practically inert under standard TBAF or HF•pyridine conditions. Eventually using the more reactive aqueous HF in acetonitrile successfully removed the TBS group in 95% yield.

2.4. The Oxidative Demethylation Quinone Formation

As described in the previous chapter, an oxidative demethylation strategy had been employed in order to selectively produce the desired *para*-quinone for the other members of the ansamycin family. The primary difference of those routes in relation to the current study is that an additional methoxy group is present on the aromatic core at C17 of geldanamycin. These syntheses had primarily employed CAN to provide the desired quinone arrangement, while other oxidizing reagents such as AgO/HNO$_3$ and MnO$_2$ impregnated with HNO$_3$ had also been useful.

Initially the oxidative demethylation strategy was employed using these reagents. Discouragingly, treatment of 71 with CAN provided rapid decomposition even at –10 °C. Relying next on AgO/HNO$_3$ procedures, it was found that when this reagent mixture was employed, 71 was quickly oxidized to a quinone product in 77% yield with minimal byproducts. In addition, HNO$_3$-impregnated MnO$_2$ also provided a quinone product but with a lower yield of 40%. Despite a successful oxidation, direct comparison with
authentic 1 (TLC, NMR and high resolution mass spec) suggested that the product was not the desired para-quinone. Subsequent reduction of the quinone with Na$_2$S$_2$O$_4$ provided hydroquinone 108. Analysis by NMR and most importantly by nOe studies revealed that an unusual aza-quinone had been formed in the oxidation step. In anticipation of further problems with the oxidation step, a model study was pursued to establish an optimal reagent for para-quinone formation.

Figure 2.9. Oxidation strategies toward geldanamycin.

The model employed in this study (109) was prepared from benzaldehyde 80. Acetamide 109 was exposed to a variety of oxidants as seen in Figure 2.10. Both CAN in aqueous acetonitrile and AgO/HNO$_3$ in dioxane provided complete conversion to a quinone product. Other reagents (DDQ, MnO$_2$/HNO$_3$, CoF$_3$, CrO$_3$/AcOH and PhI(OAc)$_2$) provided little or no quinone product. The quinone product obtained was originally assigned as the desired para-quinone. The NMR data for 110 was consistent with that observed with related para-quinone systems. This original assignment was determined to be incorrect after significant effort was exerted to obtain a crystal suitable for X-ray analysis. The crystal analysis proved unambiguously that the product was actually
ortho-quinone 110. It was later found that the quinone arrangement of 110 could be deduced with greater certainty (i.e. when compared to NMR data) by comparing the UV spectrum of 110 with that of geldanamycin. UV data was obtained for 110, $\lambda_{\text{max}}$ at 300 nm for the $\pi-\pi^*$ (CHCl$_3$, K-band). The corresponding value for geldanamycin is much higher at 311 nm.

![ortho-quinone](image)

<table>
<thead>
<tr>
<th>Reagent</th>
<th>quinone % yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAN</td>
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<tr>
<td>AgO/HNO$_3$</td>
<td>quant.</td>
</tr>
<tr>
<td>CoF$_3$</td>
<td>50%</td>
</tr>
<tr>
<td>MnO$_2$/HNO$_3$</td>
<td>25%</td>
</tr>
<tr>
<td>Phil(OAc)$_2$</td>
<td>trace</td>
</tr>
<tr>
<td>DDQ</td>
<td>NR</td>
</tr>
<tr>
<td>CrO$_3$/AcOH</td>
<td>NR</td>
</tr>
</tbody>
</table>

Not formed:  

---

**Figure 2.10.** Oxidation model study.

Different strategies were pursued to overcome the para-quinone formation dilemma. These included attempting the oxidation prior to removal of the TBS protecting group (106) and prior to urethane formation. Both procedures failed to provide the para-quinone, giving instead the undesired aza-quinone product. Additionally, derivatives of 71 were synthesized that could decrease the participation of the amide lone pairs in
quinone formation. This led to the synthesis of 71 with both the amide and urethane groups BOC protected (i.e. three BOC protecting groups were incorporated). Oxidation of this intermediate provided a quinone product that was either the ortho- or para-quinone product in only 40% yield. Encouraged by this, attempted deprotection of the tri-BOC intermediate was screened using multiple reagents. Unfortunately, all conditions provided a mixture of decomposition products. 29

![Figure 2.11. Successful oxidation completing the synthesis of geldanamycin.](image)

Finally, a report by Musgrave was followed employing HNO₃ to affect quinone formation. 30 A glacial acetic acid solution of 71 was treated with 70% nitric acid for 1 min followed by quenching with sodium bicarbonate. Longer reaction times led to extensive decomposition. The more polar, red-orange ortho-geldanamycin 111 (UV λ max at 303 nM) was the major product 10:1 over the less polar, yellow-orange natural product geldanamycin (1), which was shown to be identical in all respects to natural material (NMR, TLC, UV). Multiple runs on 10 mg scale were performed with reproducible results. Success in this case over the other conditions may be attributed to protonation of
the amide prior to oxidation, which renders the nitrogen lone pair less available to participate in quinone formation.

The route outlined above created sufficient material to allow biological activity assays to be run. The results are shown in Table 2.1. Cell assays were performed in collaboration with Kosan Biosciences. The assays were performed using SKBr3 human cancer cells, known to rely on Hsp90 kinase signaling. None of the geldanamycin derivatives obtained in this synthesis showed toxicity levels equal to the parent compound. This data reveals the essential nature of the para-quinone moiety for full potency to be realized. A reliable route to this key functionality is vital for the synthesis of simplified geldanamycin derivatives and their development as novel antiproliferative agents.

<table>
<thead>
<tr>
<th>compound</th>
<th>SKBr3 IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geldanamycin (GA)</td>
<td>40</td>
</tr>
<tr>
<td>o-GA-111</td>
<td>1272</td>
</tr>
<tr>
<td>tri-MeO-GA-71</td>
<td>&gt;5000</td>
</tr>
<tr>
<td>aza-GA-107</td>
<td>838</td>
</tr>
</tbody>
</table>

Table 2.1. Cytotoxicity and Hsp90 binding.

2.5. References and Notes


14. Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row, M. N. 


17. Andrus, M. B.; Sekhar Soma, B. B. V.; Turner, T. M.; Meredith, E. L. 


29. BOC deprotection was attempted using dilute HCl, HF and the mild Mg(ClO<sub>4</sub>)<sub>2</sub> reagent.


Chapter 3. Selective Synthesis of the para–Quinone Region of Geldanamycin

3.1. Introduction

The final step in the synthesis of geldanamycin (1) was a demethylation-oxidation sequence to generate the desired para-quinone. Unfortunately, the anticipated final reaction, amply preceded in the literature, could not be realized using standard conditions. The unforeseen conformational and electronic issues proved nearly impenetrable after exhaustive studies with either the aza- (107) or ortho-quinone (111) being isolated as the major product. Finally, employing HNO₃ in AcOH produced a 5% yield of geldanamycin (1). The oxidation challenge was overcome but at a significant cost of efficiency. In order to establish a more practical route to natural 1 and simplified derivatives, a solution to this critical issue became a study of paramount importance.

Using the acyclic model compound 109 as an example, the mechanism of dealkylative quinone formation, proposed by Kochi,¹ involves one-electron removal to give a radical cation (Figure 3.1). In this case, either the ortho- or para-disposed methoxyls are best able to stabilize the charge. Addition of water, loss of methanol and a proton, followed by additional loss of an electron then gives an allyl cation 112.

![Figure 3.1. Mechanism of quinone formation.](image-url)
Water can then attack at either the *ortho* or *para* positions relative to the carbonyl, leading to quinone formation (e.g. 110). Preferred attack at the *ortho* position seems to be due to steric factors. In addition, possible destabilization of the allylic cation at the *para* position may be due to the adjacent amide, forcing the methyl ether to adopt a conformation that does not optimize lone-pair donation.

The difficulty of *p*-quinone formation of 1, and other related lactams, under the common oxidation conditions, may be rationalized using a conformational argument (Figure 3.2). As discussed in Section 2.4, *p*-quinone formation was minor while the *aza*-quinone 107 was the major product. A stereoelectronic rationale is made difficult by the presence of many low energy conformations that the lactam seems to adopt, as seen by line broadening in the NMR. An important clue can be found by placing lactam 111 in the Hsp90 bound conformation for geldanamycin as shown (Figure 3.2). The amide nitrogen is found in a twisted conformation where the lone-pair on nitrogen is not fully conjugated with the carbonyl oxygen due to the constraints of the large ring. Instead of being coplanar, the amide and aromatic ring are twisted out of plane showing a dihedral angle of 12°. This conformation suggests that delocalization of the amide nitrogen lone pair is decreased and has the potential for strong cation stabilization upon ring oxidation. The less electronegative nitrogen, compared to oxygen, is then more able to donate its lone-pair leading to *aza*-quinone formation instead of either *p*- or *o*-quinone products. In the case of the acyclic model 109, the amide is flat and the nitrogen lone pair is not available due to full amide bond resonance.
3.2. Selective para-Quinone Construction Strategies

A review of literature accounts regarding the synthesis of para-quinone products revealed a number of interesting strategies. Four main routes were ultimately recognized as effective procedures toward obtaining para-quinone products. They include a) using 1,4-dimethoxy benzene substrates (i.e. 71) as quinone precursors, b) protected phenolic compounds with a methoxy substituent oriented para, c) using protected 1,4-diphenols (hydroquinone) compounds, and d) using a benzene ring devoid of any functionality at either one or both of the desired quinone positions. The examples given below are representative and are not meant to serve as an exhaustive review of all known examples.

As the trimethoxy quinone precursor (71) failed to provide a reasonable yield of geldanamycin, this strategy was abandoned. Alternatively, the use of protected phenols has received considerable attention and has provided a wide range of para-quinone products. A number of reagents have been reported to provide p-quinones in high yield using this strategy. Both Danishefsky and Fukuyama have employed 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an effective oxidant for quinone formation.
Danishefsky employed a triethylsilyl protected phenol (113), the silyl ether was removed prior to oxidation. Subsequent use of DDQ in aqueous THF at room temperature provided 114 in nearly quantitative yield. Fukuyama used the stable benzyl protecting group for a similar transformation. After deprotection of the benzyl ether with H₂ and Pd/C the resulting phenol was oxidized to quinone 116 in 77% yield using DDQ in a 1:5:40 mixture of H₂O:DMSO:acetone at −78 °C.

The benzyl ether proved to be an effective protecting group as earlier in the synthesis a 3,4-dimethoxy benzyl ether was selectively removed using DDQ in aqueous CH₂Cl₂ in near quantitative yield.

![Figure 3.3. DDQ oxidation of phenols.](image)

Ceric ammonium nitrate [Ce(NH₄)₂(NO₃)₆, CAN] has been used extensively as an effective oxidant of phenols. Rapoport has shown that di-methoxy substituted phenols can be transformed to p-quinone products in good to excellent yields using this reagent. When a solution of phenol 117 in acteonitrile was exposed to an aqueous solution of CAN, quinone 118 was formed in excellent yield. Conversely, when dibromo phenol 119 was exposed to the same conditions, only a modest yield of the p-quinone was obtained while 46% was isolated as the ortho-isomer. This strategy was also pursued by Stoltz for
the synthesis of (−)-lemonomycin.⁶ Using a tosylate-protected phenol (deprotection earlier in synthesis with KOTMS) the synthetic route arrived at intermediate 120. A final oxidation with CAN in an aqueous environment provided the desired p-quinone product in 51% yield. These examples provide additional support for using this method as a potential route to 1, although the aromatic ring substituents appear to effect whether ortho- or para-quinone formation will be favored.

An interesting comparison of various oxidants was provided by Boger during the syntheses of mitomycin and duocarmycin analogues.⁷ Phenol 121 was obtained in eight steps while using the methoxy methyl ether (MOM) protecting group. Deprotection of MOM using 4M HCl in EtOAc provided 121 in 80%. It was found that bis(salicyclidene)-ethyenediiminocobalt (II) (salcomine) provided the most selective oxidation to the p-quinone with only trace o-quinone obtained. Despite the overwhelming evidence supporting the use of CAN and DDQ, in this setting these reagents were found
to be less successful. Both oxidants provided the \( o \)-quinone as the major product.

Fremy’s salt has been used extensively as a selective \( p \)-quinone oxidant, although it is no longer widely used due to its detonation hazard. In this case, Fremy’s radical provided the quinones in a 2:1 ratio favoring the desired \( p \)-quinone arrangement, but in lower yield.

The mild oxidant PhSeO\(_2\)H yielded a very selective reaction for the \( o \)-quinone product.

Differentiation between \( 122 \) and \( 123 \) was difficult similar to the challenges described with the model system \( 109 \) (Figure 2.10). Boger found that key IR and NMR peaks were too close to be considered diagnostic, while UV data (\( \lambda_{\text{max}} = 314 \text{ nm} \) and 332 nm for \( 122 \) and \( 123 \), respectively) and 1D GOESY experiments provided more conclusive results and were used to establish the quinone pattern.

Most recently hypervalent iodine reagents have found utility for the selective oxidation of phenolic compounds to \( p \)-quinones. In particular, iodosylbenzene has been used to oxidize phenols to their respective quinones. During the total synthesis of (−)-saframycin A, Myers used this reagent successfully as the last step in a complex setting.\(^8\)
The synthesis of intermediate 124 was accomplished while employing TBS ethers to protect the phenolic oxygens. Addition of PhIO to 124 in wet acetonitrile provided (–)-saframycin A in good yield. The biomimetic synthesis of (–)-longithorone A presented by Shair also employed this valuable oxidant.\(^9\) Removal of both TBS groups using TBAF provided the corresponding phenols. This material was directly oxidized with iodosylbenzene to afford the bisquinone. This intermediate underwent a spontaneous transannular Diels-Alder cycloaddition to generate (–)-longithorone A in excellent yield.

![Diagram of chemical reactions](image)

**Figure 3.6.** Oxidation to \(p\)-quinones using iodosylbenzene.

A less commonly employed reagent for the synthesis of \(p\)-quinones was developed by Matsumoto and Kobayashi. This report explores the scope of a Cu(II) mediated oxidation of methoxyphenols to \(para\)-quinones.\(^{10}\) All the reactions shown required the use of a full equivalent of CuCl\(_2\) relative to the substrate and were mixed in
the indicated solvent under an oxygen atmosphere. The results show that a wide variety of substrates provide the \( p \)-quinone products in good yield under the reaction conditions. Reaction side products were primarily halogenation at the \( \text{ortho} \) position.

![Diagram of reaction](image)

<table>
<thead>
<tr>
<th>( R_1 )</th>
<th>( R_2 )</th>
<th>( R_3 )</th>
<th>Temperature</th>
<th>Quinone Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>OMe</td>
<td>OMe</td>
<td>Ambient</td>
<td>95%</td>
</tr>
<tr>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>70 °C</td>
<td>94%</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
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<td>OMe</td>
<td>H</td>
<td>Ambient</td>
<td>87%</td>
</tr>
</tbody>
</table>

**Table 3.1.** Phenol oxidation with \( \text{CuCl}_2 \).

The strategy discussed next can be considered the most selective toward \( p \)-quinone formation. This procedure uses 1,4-hydroquinone compounds to produce \( p \)-quinone products in high yield and with excellent selectivity. Due to their susceptibility to air oxidation they must be protected throughout a synthetic route. Although their synthesis can be more complex, they provide a reliable source of \( p \)-quinone products. Two excellent examples of air oxidation following hydroquinone deprotection are given in Figure 3.7. The first example using this procedure is the total synthesis of damavaricin D disclosed by Roush.\(^{11}\) He found that if the phenolic MOM ethers of 128 were replaced with methyl ethers, oxidation to damavaricin was unsuccessful. Modification of the synthesis to intercept 128 allowed the final oxidation step to proceed with a much
different result. Hydrolysis of 128 with 9:1 TFA/H₂O in CH₂Cl₂ and subsequent air oxidation of the resulting hydroquinone provided (+)-damavaricin D in 70% yield.

Boger’s synthesis of fredericamycin A employs an interesting series of deprotections and subsequent air oxidation.¹² A two step deprotection of 129 with air oxidation served admirably to provide the desired natural product. BBr₃ treatment of 129 cleanly removed the two MOM ethers, the two benzyl ethers and the activated methyl ether leaving the required methyl intact. Deprotection of the pyridone ethyl ether was accomplished by the further use of TsOH-NaBr. Exposure of the crude material to air lead to the direct formation of fredericamycin A. Boger concludes that the deliberate use of labile protecting groups throughout the synthesis permitted a dependably clean final deprotection sequence.

Figure 3.7. Air oxidation of hydroquinones.

One of the more mild reagents used for direct oxidation of hydroquinone compounds is palladium on carbon. An early report of this type was provided by
Rapoport in his synthesis of mitomycins.\textsuperscript{13} When 10\% palladium on carbon was added to a solution of 130 in EtOAc followed by stirring in the presence of air, quinone 131 was obtained quantitatively in just 75 minutes. The product was sufficiently pure after simple filtration to be carried on to the next step. Boger has also reported excellent results when employing this method.\textsuperscript{7} Hydroquinone 132 was surprisingly air- and acid-stable. Simply treating 132 with the Rapoport conditions provided 133 in near quantitative yield, without competitive oxidation of the trimethoxy indole subunit.

\textbf{Figure 3.8.} Hydroquinone oxidation activated with palladium.

In addition to palladium catalyzed oxidations of hydroquinones, other reagents can be used directly with protected hydroquinone ethers. One such reagent that has been used successfully in this context is pyridinium chlorochromate (PCC). Miller first reported using the mildly acidic PCC reagent for the oxidation of hydroquinone silyl ethers in 1981.\textsuperscript{14} This study revealed that a variety of silyl ethers underwent direct oxidation to their corresponding hydroquinone products in good to excellent yield. Both TMS and TBS ethers could be readily transformed to \textit{p}-quinones in 2 h. The reaction was unsuccessful if the aromatic ring was nonactivated or contained electron-withdrawing
groups. Additionally, methyl ether substitution apparently decreased the isolated yields. This method is particularly useful because TBS ethers are stable to many reaction conditions and the deprotection step in concert with quinone formation is relatively mild when compared to oxidative demethylation.

![Chemical structure](image)

**Table 3.2.** PCC mediated oxidation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>% yield</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>TMS</td>
<td>OMe</td>
<td>H</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>TMS</td>
<td>CH₃</td>
<td>CH₃</td>
<td>93</td>
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<td>t-Bu</td>
<td>99</td>
</tr>
</tbody>
</table>

Jimenez then applied this strategy to the synthesis of an aziridinomitosene analog. Treatment of 135 with two equivalents of PCC in CH₂Cl₂ at ambient temperature provided an excellent yield of 136. Despite the mild yield of methoxy substituted hydroquinones in Miller’s synthesis (Table 3.2), oxidation of 135 provides a particularly high yield of the p-quinone adduct. Another example of direct quinone formation from protected hydroquinones is the use of CAN with MOM ethers to produce the corresponding quinone in high yield. During Noland’s synthesis of aflatoxin B₂, sulfoxide 137 was treated directly with CAN to provide quinone 138 in excellent yield. Noland reported that using MOM protecting groups was critical to the success of this
reaction that gave very poor results when the hydroquinone was protected with the more
typical methyl ether groups. These examples show that other synthetic efforts have found
outstanding success with hydroquinone oxidation when an oxidative demethylation
strategy of methyl ethers has failed to provide good yields of \( p \)-quinone products.

A final strategy widely employed for the formation of \( p \)-quinones is using a
benzene ring void of functionality at either one or both of the desired quinone positions.
Potassium nitrosodisulfonate \([\text{ON(SO}_3\text{K)}_2]\) was prepared in 1845 by Fremy and was
later shown by Teuber to selectively oxidize phenols to either \( p \)- or \( o \)-quinones.\(^\text{17}\) The
presence or absence of a substituent \( \text{para} \) to the phenol controls which type of quinone
will be formed. If the \( \text{para} \) position is unsubstituted (\( R = \text{H} \)) then \( p \)-quinones are
produced. If the \( \text{para} \) position is substituted (\( R = \text{OR, alkyl} \)) then oxidation leads to \( o \)-quinones. A summary of these results are displayed in Table 3.3. Fremy’s salt shows
excellent selectivity and yields under mild conditions for the formation of \( p \)- or \( o \)-quinones. Unfortunately, because of its radical nature and the presence of nitrite ion,
Fremy’s salt is a detonation hazard and has been reported to undergo spontaneous
decomposition resulting in a potentially violent explosion, thus discouraging its continued application for synthetic needs.

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>R₁</th>
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<td>H</td>
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<tr>
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<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>-</td>
<td>80</td>
</tr>
</tbody>
</table>

**Table 3.3.** Oxidation using Fremy’s salt.

A more stable reagent that has been useful for this class of oxidations is the versatile Dess–Martin Periodinane (DMP). Nicolaou recently developed the use of this mild, chemoselective, and direct route to \( p \)-quinones from anilides.\(^{18}\) Optimized reaction conditions employ four equivalents of DMP and two equivalents of H\(_2\)O in CH\(_2\)Cl\(_2\) at 25 °C. A variety of \( p \)-substituted anilides were converted to \( p \)-quinones (Figure 3.10). Significantly, the reaction is not limited to simple anilides, as even the naphthalene amide 144 led smoothly to the corresponding benzoquinone 145 in 30% yield. Nicolaou aptly applied this method to the total synthesis of the type II-collagen-induced arthritis inhibitor, epoxyquinomycin B. The route only required four synthetic steps from readily available starting materials, providing a 38% overall yield. The workup and isolation
procedures are critical to the success of these reactions. In order to isolate the \( p \)-quinone products in optimum yield, a neutral workup procedure was necessary. The instability of these products may be a link to the suppressed isolated yields observed.

![Chemical structures]

**Figure 3.10.** Nicolaou’s use of DMP toward \( p \)-quinones.

Two other reagents have shown excellent selectivity and high levels of isolated yields. Both salcomine and Co(salen) can be used in catalytic quantities with an oxygen atmosphere to provide \( p \)-quinones. Boger used this method in the synthesis of duocarmycin analogues (Figure 3.11).\(^7\) Naphthol 146 was oxidized using catalytic salcomine in acetonitrile with bubbling oxygen to provide the bright yellow naphthoquinone 147 in high yield. Impressively, 147 was cleanly formed without competitive oxidation of the trimethoxy indole subunit (see also Figure 3.8). In a related context, Lipshutz developed an excellent synthesis of Coenzyme Q\(_{10}\) using a selective oxidation as the final step.\(^{19}\) Intermediate 148 was detosylated using 2 equivalents of \( n \)-BuLi at 0 \(^\circ\)C, generating the free phenol. Subsequent oxidation of the phenol using a catalytic quantity of Jacobsen’s Co(salen) complex under an oxygen atmosphere at ambient temperature provided the yellow-orange CoQ\(_{10}\) product in 86% over two steps.
The reagents used in these examples are valuable and the reactions disclosed significant as they display the ability to provide excellent levels of \( p \)-quinone formation. Additionally, they are employed in catalytic quantity and are stable benchtop compounds.

![Chemical structures](image)

**Figure 3.11.** Selective \( p \)-quinone formation with salcomine and Co(salen).

Due to the complexity of the final oxidation step toward 1, it was determined that the most reliable method for \( para \)-quinone formation would be the oxidation of a phenol or a 1,4-dihydroquinone. Accordingly, model compounds were synthesized that would closely resemble the aromatic core of geldanamycin and provide the crucial data requisite for selective installation of the \( para \)-quinone. In order to avoid the potential pitfall of \( aza \)-quinone formation the phenol substrate was made with the phenol being eventually revealed \( meta \) to the amide group, thus precluding its participation in quinone formation.

### 3.3. Synthesis of Geldanamycin Model Compounds

Despite the evidence suggesting that hydroquinone oxidation could cleanly provide geldanamycin, we decided to synthesize both a 4-OMe phenolic derivative as
well as a protected hydroquinone, to comparatively investigate their ability to selectively provide the desired p-quinone product. A benefit to using a protected 4-OMe phenol model compound versus using a protected p-hydroquinone is that the 4-OMe phenol compound requires only a single protecting group to be carried out throughout the synthesis. Thus, a potentially unavoidable loss of the protecting group and subsequent reprotection would be less troublesome. Also, starting materials containing a phenol are available in greater variety whereas p-hydroquinone compounds are less abundant.

With this task at hand we looked at potential phenolic protecting groups that would be useful. The phenolic ether employed needs to be stable to a variety of synthetic manipulations, be readily removed under mild conditions and facilitate the introduction of functional groups onto the aromatic ring. While many protecting groups meet the first two requirements, the third limits the choices dramatically. The specific step in question requires the installation of a formyl group onto the aromatic ring via directed o-lithiation (e.g. 79→80). In particular, both the 2-(trimethylsilyl)ethoxymethyl (Me₃SiCH₂CH₂OCH₂; SEM)²⁰ and methoxymethyl (CH₃OCH₂O; MOM)²¹ ethers have displayed excellent results in this regard and show good stability to a variety of reaction conditions. The bulky TIPS ether is considered a rugged protecting group and does direct metellation, but it directs metellation to the meta position.²² With this data in hand the synthesis of geldanamycin model compounds was first attempted by the synthesis of hydroquinone derivatives employing both the SEM and MOM ethers.

The study began with commercially available methoxy hydroquinone. Protection of the p-diol was accomplished using excess NaH and MOM-Cl in DMF to provide 149 in excellent yield. Other procedures using weaker bases such 3M NaOH and CH₂Cl₂
under phase transfer conditions or Hünig’s base in CH$_2$Cl$_2$ provided poor results. Regiospecific formylation was first attempted using $n$-BuLi in Et$_2$O at reflux or at ambient temperature. This procedure provided a mixture of regioisomers and failed to give a useful yield of 150. It was found that when $n$-BuLi in THF with TMEDA was added to 149 at 0 °C that site specific lithiation could be obtained. 149 was subsequently treated with DMF and hydrolyzed with dilute HCl to provide benzaldehyde 150.

![Synthesis of MOM protected aryl core](image)

**Figure 3.12.** Synthesis of MOM protected aryl core.

Regiospecific nitration of 150 was particularly challenging due to the acid-sensitive nature of the MOM ethers. A variety of mild nitration conditions were screened which included, TFAA/NH$_4$NO$_3$, Cu(NO$_3$)$_2$/Ac$_2$O, NO$_2^+$/BF$_4^-$/DMF, NaNO$_3$/La(NO$_3$)$_3$ and nitropyridinium salts. All conditions produced multiple product formation or mixtures of deprotection products. Fortuitously, it was found that treatment of 150 at 0 °C with glacial acetic acid and 70% nitric acid for 5 min provided a single yellow, crystalline product. After extensive attempts, a crystal suitable for X-ray analysis was obtained, which unambiguously determined the product to be 151, obtained in 76%
isolated yield. This analysis not only established the site of MOM ether removal but also demonstrated that the nitro moiety had been incorporated at the desired position. The product was sufficiently pure after an aqueous alkaline quench and CH$_2$Cl$_2$ extraction that it could be used directly in the subsequent step.

With the identity of 151 clearly established, we focused on finishing the aromatic region of 1 by reinstalling the MOM ether. This step proved to be surprisingly difficult. Attempts to use the same conditions as before (NaH and DMF) provided low yields (41%) even after extended reaction times. Using NaH in THF or NaHMDS in THF did not significantly improve the yield. Finally, using excess KH in THF with the phase-transfer catalyst n-Bu$_4$NI provided 152 in 79% yield after 2 days.

The next step was to synthesize a SEM-protected hydroquinone aromatic core. As in the previous study, the investigation began with commercially available methoxy hydroquinone. The diol was added as a DMF solution to a dry suspension of NaH in DMF at 0 °C. Treating this mixture with a slight excess of SEM-Cl provided the protected hydroquinone 153 in excellent yield. The next step was to selectively introduce the formyl group. This transformation proved to be more challenging than anticipated. Initial experiments using n-BuLi in THF at 0 °C or ambient temperature with or without the addition of TMEDA provided little or no desired product formation. It was then determined that by using n-BuLi in Et$_2$O at reflux followed by quenching the reaction after 30 min of DMF addition provided the desired benzaldehyde 154 in 84% yield.

The final step in preparation of the aryl ring is aromatic nitration. Again, the typically acidic conditions of nitration would invariably cleave the acid labile SEM ether. A series of nitration procedures were then screened to determine which set of conditions
would be useful for this transformation. Unfortunately, all conditions studied, including TFAA/NH$_4$NO$_3$, Cu(NO$_3$)$_2$/Ac$_2$O, NH$_4$NO$_3$/Ac$_2$O, NO$_2$BF$_4$/DMF, NaNO$_3$/La(NO$_3$)$_3$, nitropyridinium salts and Sc(OTf)$_3$/LiNO$_3$/Ac$_2$O$^{29}$ provided either multiple products or low yields (< 50%) of SEM deprotection products. Finally, employing nitric acid and glacial acetic acid, which had been used successfully earlier, only provided a 53% yield of a phenol. Due to these disappointing results and the success found earlier, we decided to carry out the synthesis of geldanamycin model compounds employing MOM ethers.

**Figure 3.13.** Attempted synthesis of SEM aryl core.

Attention then focused on the synthesis of an aromatic core that had a methyl ether substituent placed at the *para* position, in relation to the MOM ether. The synthesis began with readily available 2,4-dimethoxyphenol.$^{30}$ Exposure of phenol 155 to the MOM ether protection conditions used earlier provided 156 in excellent yield. Adapting the procedure developed earlier in the synthesis of 150, provided the selective formylation of 156 in good yield. Once again, a series of nitration conditions were screened to determine a reagent mixture capable of aromatic nitration without disturbing the MOM ether. When benzaldehyde 157 was treated with Ac$_2$O/Cu(NO$_3$)$_2$, NO$_2$BF$_4$ /DME, or HNO$_3$/Ac$_2$O multiple reaction products were observed by TLC analysis. We were pleased to find that when 157 was treated with one equivalent of NH$_4$NO$_3$ and
excess trifluoroacetic anhydride in CHCl₃, the desired nitro benzene product 158 was isolated in 36% yield. After further optimization of this reaction it was found that when CH₃CN is used in place of CHCl₃, the reaction cleanly provides 158 in 88% yield.

![Chemical Structure]

**Figure 3.14.** Synthesis of MOM phenol.

Intermediates 152 and 158 could then be elaborated using similar conditions to eventually arrive at the desired geldanamycin model compounds. The synthetic endeavor began with reduction of the aldehyde using NaBH₄ in THF to cleanly provide the benzyl alcohol in excellent yield. Attempts to convert the benzyl alcohol of 158 to bromide 159b gave varied results. Employing PBr₃ and pyridine in Et₂O gave multiple products with 159b being isolated in only 24% yield.³¹ When CBr₄ and PPh₃ were employed in CH₂Cl₂ 159b was provided in 37% yield. Further investigation revealed that when Et₂O is used in place of CH₂Cl₂ that 159b is produced with a high yield of 81%. Unfortunately, when this protocol was followed on gram scale the reaction gave an attenuated yield of 60%.³² In order to obtain a more reliable and scaleable route to 159b further investigations ensued. Kajiwara has reported that when LiBr and methanesulfonyl chloride (Ms-Cl) are employed with NEt₃, excellent yields of activated bromides are obtained.³³ In practice this procedure provided both 159a and 159b in excellent yield.
With benzyl bromides 159 in hand the next step was to set the first methyl stereocenter, corresponding to C14 of geldanamycin. Accordingly, Evans asymmetric alkylation with S-oxazolidinone 82 proceeded with high yield and excellent selectivity for both substrates.\textsuperscript{34} Reductive removal of the auxiliary using lithium borohydride proceeded uneventfully. Mitsunobu one carbon homologation with acetone cyanohydrin under the conditions of Ito gave the desired cyano compounds 162 in good yield.\textsuperscript{35} Subsequent reduction with Dibal-H followed by water hydrolysis provided aldehydes 163 in good isolated yields.

![Chemical Structures](image_url)

**Figure 3.15.** Elaboration of geldanamycin model compounds.

Nucleophilic addition to the aldehydes 163 could potentially be diastereoselective, providing alcohols such as 164. In practice, addition of various nucleophiles gave mixed
results. Use of Et₂Zn and TBSOTf at 0 °C gave complete decomposition of 163.

Employing TiCl₄ and allyltrimethyl silane gave MOM ether cleavage while AlMe₃ at –78 °C gave only a 44% yield of a 1.2:1 mixture of diastereomers. Finally, we resorted to using Brown’s asymmetric allylborane reagent to provide homoallylic alcohols 164 in good yield and diastereoselectivity. The workup procedure in this reaction was critical to obtaining the maximum isolated yields. If the reaction was quenched with the standard NaOH and aqueous H₂O₂ procedure reported by Brown, then yields of 164 did not exceed 50%. In contrast, when the reaction was quenched with MeOH followed by the addition of ethanolamine and stirred overnight, the desired product was isolated in >80% yield.

![Chemical Structure]

**Figure 3.16.** Completion of geldanamycin model compounds.

Compounds 164 were then treated with TBSOTf and 2,6-lutidine to afford the secondary silyl ethers cleanly in excellent yield. Concomitant reduction of the aryl nitro
and terminal alkene of 165 was quickly accomplished with H₂ (balloon pressure) and 10% wt Pd/C in absolute ethanol. This procedure gave a clean reaction and provided the aniline intermediates in high isolated yields. The final step was acylation of the aryl amine to mimic the geldanamycin aryl core. Treatment of 166 with tigloyl chloride\textsuperscript{38} and triethylamine gave the unsaturated benzamides in excellent yield.\textsuperscript{39} Initial attempts to acylate amine 166b with tiglic acid in conjunction with the coupling reagents EDCI and HOBr provided lower yields of 167b.\textsuperscript{40}

3.4. Selective Oxidation to para–Quinone

With fully protected model compounds 167 available and useful routes established, the deprotection-oxidation sequence could be studied. In order to demonstrate that the TBS ether could be selectively removed in the presence of the MOM ethers, deprotection protocols were investigated. Treatment of 167a (R = MOM) with excess TBAF in THF or Et₃N•HF in CH₃CN gave incomplete reactions with modest yields based on recovered starting materials. Alternatively, employing HF•pyridine in THF gave the selective TBS ether removal product in 82%. Focus then turned to the study of concomitant MOM and TBS ether removal in a single transformation prior to oxidation. Compound 167b (R = Me) could be converted to 168 in 78% yield by treatment with TFA:H₂O (9:1) in CH₂Cl₂ at ambient temperature. Further investigation found that when TMSI was generated \textit{in situ} (TMSCl and NaI) in CH₂Cl₂ that 168 was formed cleanly in 80% yield.\textsuperscript{41}
Table 3.4. Deprotection and oxidation of the phenol model compound.

With phenol 168 in hand, oxidation to the desired \( p \)-quinone compound was evaluated. The standard oxidants CAN and DDQ gave the desired \( p \)-quinone in an unacceptably low yield (entries 1 and 2). Using potassium ferricyanide provided a low yield of quinone 169. Further investigation found that iodosobenzene, which was very successful in the syntheses of saframycin and logithorone, gave a poor yield of the \( p \)-quinone product. Employing argentic oxide and \( \text{HNO}_3/\text{AcOH} \) gave products that could not be identified as 169. Next, reagents which use various catalysts with \( \text{O}_2 \) as the oxidant were screened. Employing a full equivalent of \( \text{CuCl}_2 \) in \( \text{EtOAc} \) and \( \text{H}_2\text{O} \) followed by adding \( \text{O}_2 \) (balloon pressure) provided incomplete reactivity after prolonged reaction times. Finally, using catalytic salcomine or Co(salen) in DMF provided up to 27% of 169.
after chromatography. Although these results are disappointing they further exemplify the significant challenge of selectively forming the \( p \)-quinone region of geldanamycin.

The model oxidation study then turned to the deprotection of di-MOM hydroquinone 167a. Attempting a deprotection protocol using TFA:H\(_2\)O in CH\(_2\)Cl\(_2\) gave a complex mixture of products. Gratifyingly, the use TMSCl and NaI in a 1:1 CH\(_3\)CN:CH\(_2\)Cl\(_2\) mixture provided the surprisingly air-stable hydroquinone 170 in 79% isolated yield. To our delight, simply treating 170 with catalytic palladium on carbon, following the conditions of Rapoport, with the flask open to air gave \( p \)-quinone 169 in near quantitative yield. This procedure provides a new route to the \( p \)-quinone portion of geldanamycin. It represents the first example of selective access to this unique trisubstituted quinone. New routes to this important target can now be undertaken with confidence.

![Diagram of chemical reactions](https://via.placeholder.com/200)

**Figure 3.17.** Deprotection and oxidation of hydroquinone model.

The structural assignment of \( p \)-quinone adduct 169 proceeded with great care, especially in light of the first trimethoxy model study (Figure 2.10) in which the \( p \)-quinone structure had initially been assigned, only to determine later that the correct structure was the undesired \( o \)-quinone. The earlier trimethoxy model study showed that \(^1\)H and \(^{13}\)C NMR spectra could not be used to assign the quinone pattern. We thereby
relied on a combination of UV and HRMS spectra obtained from the isolated products with additional support from NMR spectra. The UV spectrum of 169 shows a $\lambda_{\text{max}}$ at 310 nm, consistent with the same $\pi-\pi^*$ bands observed for geldanamycin (311 nm). These $p$-quinone UV bands are distinctly different from those observed for $o$-quinones 110 and 111 (300 and 303 nm, respectively). An additional NMR experiment was performed to confirm the structure of 169. HMBC was used to establish the connectivity with correlation to DEPT and HETCOR experiments verifying the assignment of signals. The results were consistent with the assignment given to 169. Figure 3.18 displays the ambiguity of quinone assignment resulting from $^1$H NMR values and the more convincing data associated with UV $\lambda_{\text{max}}$ values.

Figure 3.18. Para vs Ortho: $^1$H NMR and UV data.
3.5. References and Notes


30. 2,4-dimethoxy phenol is made in one step from 2,4-dimethoxy benzaldehyde via Baeyer-Villiger oxidation, for excellent examples see: (a) Matsumoto, M.; Kobayashi, H.; Hotta, Y. *J. Org. Chem.* **1984**, *49*, 4740. (b) Syper, L. *Synthesis*
1989, 167. (c) Zeng, L.; Fukai, T.; Nomura, T.; Zhang, R.-Y.; Lou, Z.-C. J. Chem. Soc. Perkin Trans. 1 1993, 1153. In our hands yields of ~70% were obtained when these procedures were employed on multi-gram scale.


38. O’Hare, D.; Green, J. C.; Marder, T.; Collins, S.; Stringer, G.; Kakkar, A. K.;


Chapter 4. Enantioselective Phase–Transfer–Catalyzed Glycolate Alkylation

4.1. Asymmetric Glycolate Alkylation

A commonly occurring motif in biologically active and pharmacologically important compounds is the α-hydroxy acid.\(^1\) Consequently, an assortment of procedures have arisen to fulfill the demand for this fundamental unit. These procedures include asymmetric dihydroxylation of enones\(^2\) and silyl enol ethers,\(^3\) asymmetric enolate hydroxylations using optically active auxiliaries or enantiopure reagents,\(^4\) and the asymmetric hydrogenation of enol esters\(^5\) or α-keto esters.\(^6\) Another common method adopted for this purpose is the alkylation of chiral glycolic acid equivalents. A wide range of chiral auxiliaries have been developed which display excellent levels of selectivity.

An early report of asymmetric glycolate alkylation was provided by Helmchen.\(^7\) This study found that \(O\)-protected glycolates such as 171, which are readily accessible from \((+)-\)camphor, could be alkylated with very high diastereoselectivity. Addition of lithium cyclohexylisopropylamide (LICA) in THF/hexamethylphosphoramide (HMPA, 4:1) at \(-78\,^\circ\text{C}\) to 171 provided almost exclusive \(Z\)-enolate generation.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>(R_2)</th>
<th>% yield</th>
<th>% de</th>
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<tr>
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<td>97</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>86</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>(n)-C(_{10})H(_21)</td>
<td>82</td>
<td>93</td>
</tr>
</tbody>
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**Table 4.1.** Glycolate alkylation using a camphor derived auxiliary.
To this mixture is added the alkyl iodide to produce 172 in up to 97% yield and with excellent diastereomeric excess (de). It was also demonstrated that when the synthesis of 172 begins with (−)-camphor in place of (+)-camphor, the complimentary R stereocenter of the glycolate adduct can be produced with the same level of selectivity.

Katsuki has disclosed a highly effective asymmetric synthesis of α-hydroxy acids by using a chiral pyrrolidine auxiliary. This auxiliary had previously been used successfully for alkylation, acylation and aldolization. The N-acylbenzyloxy derivative 173 was then tested for its efficacy toward diastereoselective alkylation. The amide enolate could be generated with either n-BuLi or LDA (1.05 eq) in THF, with both protocols providing the same level of selectivity. After enolate formation the electrophiles were added neat (1.1 eq) at −78 °C. Both benzylic and alkyl halides were effective alkylating agents. Alkyl iodides other than iodomethane required warming to −20 °C to complete the reaction. Table 4.2 shows the results from the alkylation with 173.

<table>
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<th>RX</th>
<th>% yield</th>
<th>% de</th>
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<td>n-BuLi</td>
<td>CH₃I</td>
<td>88</td>
<td>97</td>
</tr>
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<td>n-BuLi</td>
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<td>LDA</td>
<td>BnOC₆H₁₂I</td>
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</tr>
<tr>
<td>5</td>
<td>LDA</td>
<td>n-Octl</td>
<td>73</td>
<td>96</td>
</tr>
</tbody>
</table>

Table 4.2. Pyrrolidine based glycolate alkylation.
Protecting groups other than the benzyl moiety were also studied. If the O-benzyl group was replaced with O-phenyl then a 90% de was obtained, whereas the TBS group gave only a 35% de. Significantly, if the hydroxyl group was left unprotected, the de was still high at 90%, although 2.1 equivalents of LDA were required. The products were easily hydrolyzed using a 1:1 mixture of 1M HCl : dioxane at reflux for 4 h, to provide the corresponding carboxylic acids of 174 without detectable racemization. At the time of publication 173 provided the highest known levels of de obtained for the asymmetric alkylation of glycolic acid derivatives. Unfortunately, the synthesis of 173 is a multi-step process, which detracts from the general utility of this method.

Newcomb then released a study using α-hydroxy amides in acyclic and cyclic settings.9 In this report auxiliaries based on known enantiopure amino alcohols were employed. Unfortunately, these auxiliaries provided mixed results. Using the cyclic carboxamide 175 with LDA in THF at –78 °C provided products 176 in high yield and up to 96% de.

![Figure 4.1. Glycolate alkylation using amino alcohol auxiliaries.](image)

Compound 175 provided good results, however, methylation (MeI) was unsuccessful in this case. Additionally, it was found that the conversion of products 176
into α-hydroxy acids was problematic. As a result of these issues, the acyclic compound 177 was studied for its utility in this transformation. Employing similar conditions for enolate generation compounds 178 were produced in excellent yield but suffered from reduced levels of selectivity. Unfortunately, variations of 175 and 177 did not overcome these limitations.

Pearson then developed spiro-fused dioxolanones to serve as chiral glycolate enolate equivalents.\textsuperscript{10} The requisite dioxolanones were prepared from 8-phenylmenthone with trimethylsilyl((trimethylsilyl)oxy)acetate and catalytic TMSOTf. This step produces an undesirable mixture of spiro-diastereomers that are formed in nearly equal quantity. Fortunately, they are readily separable by column chromatography and the diastereomers can be used to create α-hydroxy acid products with opposite absolute configurations. Deprotonation of 179 with LDA in THF at \(-78\, ^\circ\text{C}\) followed by the addition of alkyl, allylic or benzylic halides provides products in excellent yield and with high levels of diastereofacial selectivity. The incorporation of a rigid auxiliary to both the hydroxyl and carboxyl group results in a well-defined steric environment, providing excellent selectivity. Products 180 were exposed to refluxing ethanolic hydrogen chloride to liberate the respective α-hydroxy acid compounds in a single step in high yield (84–95\%) without epimerization. In addition, the 8-phenylmenthone auxiliary could be recovered in 95\% yield from this step without epimerization. Excellent levels of selectivity are obtained and the auxiliary can be recovered in good yield. However, the expense of 8-phenylmenthol and lack of selectivity in the synthesis of 179 detracts from its general application for synthesis of α-hydroxy acid derivatives.
Using a similar method, Uang developed a unique dioxolanone to overcome some of these limitations. It was found that (1S)-N,N-diisopropyl-10-camphorsulfonamide served as an excellent chiral auxiliary for the enantioselective synthesis of α-hydroxy acids.\textsuperscript{11} In this case, spiro-fused dioxolanones could not be formed using the procedure developed by Pearson. As a consequence, a two-step procedure was followed, first forming the dimethoxy acetal then exposing this material to glycolic acid and BF$_3$•OEt$_2$ to form 181. Dioxolanone 181 was formed as a 12:1 mixture of diastereomers that were readily separated by column chromatography. Treatment of 181 with LDA in THF at −78 °C in the presence of HMPA followed by addition of the alkyl halide provides products 182 in good yield and with excellent % de. By conducting the reaction at a temperature of −100 °C then warming to −78 °C, the product was formed essentially as a single diastereomer. The major product presumably arises from the alkylation of the enolate on the less hindered \textit{re} face. In addition to mono alkylation, products 182 could undergo a second alkylation to provide a quaternary stereocenter in high yield and with excellent diastereomeric excess. The alkylated products were hydrolyzed in one-step via

\begin{table}[h]
\centering
\begin{tabular}{llll}
\hline
entry & RX & \% yield & dr \\
\hline
1 & Mel & 99\% & 24:1 \\
2 & Allyl-I & 96 & >100:1 \\
3 & BnBr & 92 & >100:1 \\
4 & \textit{n}-BuI & 82 & 28:1 \\
\hline
\end{tabular}
\caption{Alkylation of spiro dioxolanones.}
\end{table}
ethanolysis using anhydrous HCl in EtOH at reflux for 6 h to provide the \( \alpha \)-hydroxy acid products along with recovered auxiliary in >80% and >90% yield respectively. The benefit to this approach is that dioxolanone 181 is made diastereoselectively. With both enantiomers of 10-camphorsulfonamide readily available, this procedure is highly effective for the synthesis of either the \( S \) or \( R \) enantiomer of \( \alpha \)-hydroxy acid compounds.

\[
\begin{align*}
\text{entry} & \quad \text{R} & \quad \% \text{ yield} & \quad \% \text{ de} \\
1 & \text{Me} & 86 & >98 \\
2 & \text{Allyl} & 83 & >98 \\
3 & \text{Benzyl} & 70 & >98 \\
4 & \text{Et} & 65 & >98 \\
\end{align*}
\]

Table 4.4. Asymmetric synthesis of \( \alpha \)-hydroxy acids using 10-camphorsulfonamide.

Orena has reported successfully using imidazolidinones prepared from (+)- or (−)-ephedrine for the selective alkylation of glycolate enolates.\(^{12}\) This approach provides 2-benzyloxyalcohols or acids having a stereogenic center at C-2 with excellent levels of diastereomeric excess. The imidazolidinone 183 is commercially available or it can be prepared in a single step from ephedrine. Treating the lithium anion of 183 in THF with an equimolar amount of benzyloxyacetyl chloride provides 184 in 85% yield. Deprotonation of 184 with LDA in THF at \(-78 \, ^\circ \text{C}\) is followed by the addition of an alkyl halide at the same temperature. Alkylated products are obtained in good yield and with excellent diastereomeric excess. In addition to the examples depicted in Figure 4.2., the
enantiomers of 183-185 can be prepared with almost identical yields and selectivity, providing access to both series of enantiomers. The auxiliary can be cleaved with LiBH₄ in THF at 0 °C to produce the corresponding alcohol in excellent yield which allows the auxiliary to be recovered in good yield. Advantages to this method are that the auxiliary is commercially available and alkylated products are obtained with >90% de. The utility of this method was demonstrated during a recent synthesis of a key building block for epothilone and its derivatives.¹³

Figure 4.2. Asymmetric glycolate alkylation using ephedrine based auxiliary.

The well-documented Evans alkylation of N-acyl 4-substituted oxazolidinones has been applied extensively in asymmetric synthesis.¹⁴ Surprisingly this method had not been studied for its general application to asymmetric glycolate alkylation until Crimmins thoroughly explored its use for this transformation in 2000.¹⁶ Prior to Crimmins’ work the Evan’s auxiliary had only been used in a limited number of cases such as the synthesis of epothilone and its derivatives by Danishefsky²⁴ and in a complex setting toward the synthesis of halichondrin B, provided by Burke.¹⁵

The oxazolidinone auxiliaries are available commercially or they can be prepared from their respective amino acids (i.e. valine and phenylalanine). Acylation of the
auxiliary with the appropriate alkoxyacetyl chloride provides a general procedure for the production of 186. Crimmins varied the hydroxy protecting group, the oxazolidinone auxiliary, and the allylic halide alkylating agent. It was found that the Me, allyl, and MOM protecting groups resulted in substantial deacylation, providing excellent selectivity but with modest yields. The use of allylic iodides was essential to product formation as rates with allylic bromides were slow and yields suffered. Using valine-derived oxazolidinone 186 provides slightly higher yields than the phenylalanine derivative. Alkylations were performed by treating 186 with NaHMDS in THF at −78 °C and stirring for 30 min. Subsequent addition of 3–5 equivalents of the alkylating agent and warming the reaction mixture to −45 °C provided products 187 in 81-88% yield and with excellent diastereoselectivity (>96% de).

![Chemical structure](image)

**Table 4.5.** Evans oxazolidinone directed glycolate alkylation.

<table>
<thead>
<tr>
<th>entry</th>
<th>P</th>
<th>RI</th>
<th>% yield</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>Allyl-I</td>
<td>82</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>2</td>
<td>TES</td>
<td>Allyl-I</td>
<td>88</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>3</td>
<td>TBS</td>
<td>Allyl-I</td>
<td>84</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>Allyl-I</td>
<td>81</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>Allyl-I</td>
<td>84</td>
<td>&gt;98:2</td>
</tr>
</tbody>
</table>

Since this report, Crimmins has used this methodology in the total synthesis of (+)-laurencin,\(^{17}\) (−)-isolaurallene,\(^{18}\) (−)-laulimalide,\(^{19}\) (+)-rogioloxepane A,\(^{20}\) (+)-
obtusenyne,\textsuperscript{21} (+)-gigantecin,\textsuperscript{22} and ophirin B\textsuperscript{23}. Other groups have also employed this procedure for the synthesis of α-hydroxy acid products. They include Kim in his synthesis of (+)-laurencin,\textsuperscript{25} and recently Falck in his synthesis of 12(S),20-DiHETE.\textsuperscript{26}

All of the chiral auxiliaries discussed thus far are attached to the carboxyl group or to both the hydroxy and carboxyl groups. As a variant from these protocols, Kim has described the utility of using an auxiliary attached exclusively to the hydroxyl group which directs the diastereoselective glycolate alkylation.\textsuperscript{27} Due to the potential conformational flexibility of such an auxiliary, it was anticipated that a rigid ether ligand would be needed. The proposed solution was to use an ether ligand that could participate in bidentate chelation by interacting with both the metal enolate and the auxiliary.

This chelation effect provided a rigid metalocycle which shields one face of the enolate. The auxiliary was synthesized from (R)-glyceraldehyde acetonide, which can be synthesized in two steps from mannitol. Addition of the 4-methoxyphenyl organocopper reagent provided 188. This was followed by O-alkylation with ethyl bromoacetate to provide compound 189 in good yield. Studies revealed that using LiHMDS in THF at –78 °C followed by addition of an alkylation agent provided optimum selectivity and yields.
Results proved that a chiral auxiliary attached to the hydroxyl group can provide excellent levels of selectivity. The auxiliary is removed by treating compounds 190 with CAN in wet acetonitrile. This method oxidizes the auxiliary to the corresponding aryl ketone, which can be treated with L-selectride to produce 188 for reuse. This procedure provides α-hydroxy acid products with excellent selectivity. The multi-step synthesis of the auxiliary and oxidation of the auxiliary during cleavage causes this protocol to be somewhat unpractical. Nonetheless, Kim has aptly applied this method to the synthesis of (+)-lauthisan and avoided the auxiliary issues by incorporating it into the final product, displaying a unique and practical application of this methodology.28

Recently, Ley has developed a new cyclic building block for the stereoselective synthesis of enantiopure α-hydroxy acids.29 This approach uses a butane diacetal (BDA) glycolate equivalent produced through a stereoselective protection step. Accordingly, the commercially available and relatively cheap (S)-3-chloropropane-1,2-diol 191 was used to produce the BDA adduct 192 as a single enantiomer in 56% overall yield. This route was amenable to large-scale batches and 192 could be produced in multi-gram quantities. Subsequent exposure of 192 to a substoichiometric quantity of LiHMDS (0.95 eq) in THF at –78 °C followed by the addition of an alkyl, allylic or benzylic halide and warming to –30 °C provided 193 in good yield and with high to excellent diastereoselectivity. The selectivity appears to improve with increasing size of the electrophile. For example, when benzyl bromide and 2-(bromomethyl)naphthalene (not shown in Table 4.6) were used the minor diastereomer could not be detected in the crude reaction mixture. Single-crystal X-ray determination of products confirmed the stereochemical outcome shown for 193. This outcome suggests that attack of the alkyl
halide on the enolate proceeds from the side opposing the 1,3-disposed axial methoxy group. In addition, products 193 could be dialkylated to provide excellent levels of selectivity. The α-hydroxy acid products could be readily liberated by removal of the BDA protecting group through an acid mediated hydrolysis using TFA/H₂O (9:1) or transesterification using TMSCl and an appropriate alcohol. This procedure is general for a variety of electrophiles and provides high to excellent levels of selectivity, producing both tertiary and quaternary stereocenters. Ley has displayed the synthetic utility of the methodology by applying it in a complex setting during the synthesis of Herbarumin II.³⁰

![Chemical Structure](image)

**Table 4.6.** Butane-2,3-diacetal-desymmetrized glycolic acid alkylation.

<table>
<thead>
<tr>
<th>entry</th>
<th>RX</th>
<th>% yield</th>
<th>dr</th>
</tr>
</thead>
<tbody>
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<td>61</td>
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<tr>
<td>2</td>
<td>Cl-O-OMe</td>
<td>64</td>
<td>10:1</td>
</tr>
<tr>
<td>3</td>
<td>AllylBr</td>
<td>89</td>
<td>60:1</td>
</tr>
<tr>
<td>4</td>
<td>Br-CN</td>
<td>85</td>
<td>10:1</td>
</tr>
<tr>
<td>5</td>
<td>BnBr</td>
<td>96%</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>6</td>
<td>t-BuO-C=Br</td>
<td>92%</td>
<td>18:1</td>
</tr>
</tbody>
</table>

Wang has disclosed a study employing an auxiliary derived from fructose.³¹ This report stems from interest in finding an auxiliary that could be cleaved under mildly basic conditions and which was useful for reactive electrophiles, such as allylic halides, as well as less reactive halides, such as ethyl iodide. Starting from commercially available and inexpensive D-fructose, 194 can be prepared in a single step. The hydroxyl group of 194
is then coupled with an appropriately protected glycolic acid derivative. Optimization of reaction conditions found that using LiHMDS in THF with 5% HMPA at –95 °C provided the best compromise of yield and selectivity. Compounds 195 were made using a variety of protecting groups, including Bn, PMB, Me, MOM, BOM, TBS, TES and TIPS.

Table 4.7. Asymmetric glycolate alkylation using a carbohydrate derivative.

<table>
<thead>
<tr>
<th>entry</th>
<th>P</th>
<th>RX</th>
<th>% yield</th>
<th>% de</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>BnBr</td>
<td>58</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>EtI</td>
<td>74</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>PhCH₂CH₂I</td>
<td>52</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>TES</td>
<td>BnBr</td>
<td>75</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>TES</td>
<td>Allyl</td>
<td>71</td>
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<td>6</td>
<td>TES</td>
<td>EtI</td>
<td>83</td>
<td>88</td>
</tr>
</tbody>
</table>

The results imply that the hydroxyl protecting group has little effect on the selectivity but significantly affects the yield. Generally, the highest yields were obtained when either a benzyl or silyl ether was used. Methylation of 195 when employing Me, MOM, or BOM gave yields ranging from 66–68%, whereas Bn and TBS gave yields of 73 and 76% respectively. Using these results a variety of electrophiles were employed during the alkylation of 195 using either the Bn or silyl ethers. The products were obtained in moderate to high yield and with good to excellent levels of selectivity. The auxiliary is cleaved by LiOH in an aqueous mixture of THF/MeOH after removing the
hydroxyl protecting group. This protocol benefits from using a simple and readily available auxiliary. Unfortunately, the yields and level of diastereoselectivity fail to provide a practical route to enantiomerically enriched α-hydroxy acid products when compared to the auxiliaries previously described.

At this point it is important to note that the practical pseudoephedrine auxiliary studied in depth by Myers was not found to be useful for the alkylation of glycolate derivatives. In a single case when pseudopehedrine α-hydroxy-acetamide 197 was used in excess with limiting benzyl bromide the product 198 was obtained in 84% yield and 82% de.

![Figure 4.4. Pseudoephedrine as an auxiliary for glycolate alkylation.](image)

Myers reports that alkylation reactions were studied using a series of O-protected derivatives (TBS, TBDPS, THP, Bn, BOM, Piv, and methyl(1-methoxyethyl)), but none of them provided satisfactory results. Interestingly, in a study toward the total synthesis of (+)-laurenyne, Clark successfully employs this auxiliary to help control the stereoselective outcome of an alkylation with allyl iodide in 75% yield and with complete control of the resulting stereogenic center. The selectivity in this case may arise from a combination of effects since the α-hydroxyl ether contains an adjacent stereocenter (see also Figure 4.3).
Although these examples provide a wide range of α-hydroxy acid products with excellent selectivity their common drawback is that an auxiliary must be employed. Prior to our work, described below, a catalytic enantioselective glycolate alkylation protocol was unknown. A single example has been reported since that provides an α-hydroxy acid product via a catalytic enantioselective alkylation. Evans used a Ni(II) tol-BINAP-catalyzed orthoester alkylation of an N-acylthiazolidinethione to provide such a compound.\textsuperscript{34} Using \(199\) with 5 mol\% of the Ni-BINAP complex, trimethyl orthoformate, 2,6-lutidine, and BF\(_3\)•Et\(_2\)O in CH\(_2\)Cl\(_2\) at –78 °C provided \(200\) with excellent yield and enatioselectivity. Products such as \(200\) can be converted into a range of functional groups including Weinreb amides, alcohols and β-ketoesters in a single step. This protocol provides excellent results for a variety of alkyl-substituted thiazolidinethiones. Disappointedly, this method was developed using a single electrophile and a single glycolate based substrate (\(199\)).

\textbf{4.2. Development of a Suitable Glycolate Substrate}

The excellent success displayed by phase-transfer catalyzed (PTC) protocols for catalytic asymmetric alkylation (see Chapter 1, Section 1.4) prompted a study to develop a PTC reaction using a glycolate substrate. The benzophenone imine \textit{tert}-butyl glycine,
with its extended enolate conjugation and low pK$_a$ value (18.7, DMSO), continues to be a popular substrate for amino acid synthesis.\textsuperscript{35} If the nitrogen of 35 could be replaced with an oxygen (201), PTC alkylation may lead to results similar to those seen in the alkylation of 35.

![Figure 4.6. Attempted alkoxy ester alkylation.](image)

As depicted in Figure 4.6, alkoxyester substrates, which would provide a direct route to glycolate esters, were synthesized and subjected to various PTC conditions. Unfortunately, all attempts to obtain alkylation products from this reaction were unsuccessful. The hydroxyl protecting group was then varied to include the benzhydrol (201), benzyl, $p$-anisole, pivalate, and trityl groups. None of the alkoxyester substrates would undergo alkylation as reaction analysis by thin layer chromatography (TLC) revealed that only starting materials were present even after prolonged reaction times at ambient temperature. The high pK$_a$ values of these substrates (~28) could be the reason for such inactivity. Glycolate surrogates that would provide access to $\alpha$-hydroxy acid products and lower the pK$_a$ value, were subsequently investigated.

The coordination of the enolate and cationic ammonium salt is the critical step for asymmetric induction. As such, a limited number of bases can be used, as the counterions
of most strong bases (e.g. LDA, NaHMDS, etc.) commonly employed for enolate generation will compete with the cationic ammonium salt for enolate ion pairing. Bases typically employed in PTC reactions include aqueous solutions of NaOH and KOH in biphasic liquid-liquid mode, CsOH or RbOH in solid-liquid mode or phosphazene bases used in a homogenous mode. Subsequently, we synthesized the more acidic benzyloxy acetophenones (203, $pK_a \sim 22$) and screened them for reactivity under standard PTC conditions.

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar</th>
<th>catalyst</th>
<th>conditions</th>
<th>% yield</th>
<th>% ee</th>
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<td>38</td>
<td>50% Aq. KOH, 0 °C PhMe:CHCl$_3$ (7:3)</td>
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<td>13</td>
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<tr>
<td>2</td>
<td>Ph</td>
<td>44</td>
<td>&quot;</td>
<td>74</td>
<td>25</td>
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<td>p-anisyl</td>
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<td>&quot;</td>
<td>64</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>p-anisyl</td>
<td>44</td>
<td>CsOH, CH$_2$Cl$_2$, -40 °C</td>
<td>82</td>
<td>54</td>
</tr>
</tbody>
</table>

**Table 4.8.** Initial PTC alkylation using benzyloxy acetophenones.

To our delight, when 203 was treated with 50% aqueous KOH in a 7:3 ratio of toluene:chloroform with benzyl bromide and the commercially available Corey/Lygo catalyst 38, alkylated product 204 was obtained in 58% yield and with 13% ee. Encouraged by these results the enantiopure ammonium salt was varied. When Park/Jew catalyst 44 was employed under the same conditions, the reaction product could be
obtained with an improved yield of 74% and with 25% ee after 26 hours at 0 °C. The phenyl group was then changed to p-anisyl and the reaction was run again. This time the reaction yield was decreased to 64% but the selectivity increased to 30% ee. The lower yield may be due to the extended reaction time of 50 h at 0 °C. In order to find reaction conditions that would provide 204 in a shorter time frame the solid-liquid phase conditions employing CsOH in CH₂Cl₂ at –40 °C, developed by Corey, were screened. Under these reaction conditions and employing the Park/Jew catalyst product, 204 was produced in 82% yield and with 54% ee. With these encouraging results, the next step was to employ these reaction conditions to find the optimum aryl group of 203.

4.3. Reaction Optimization

4.3.1. Aryl Ketone Variation

![Figure 4.7. Synthesis of benzyloxy acetophenones.](image)

The aryl group of 203 could be quickly varied via a simple two-step process. Beginning with benzyloxyacetyl chloride in a chloroform solution, N,O-dimethylhydroxylamine hydrogen chloride was added followed by excess (2.2 equiv.) pyridine. Simply stirring this mixture overnight at ambient temperature followed by extractive workup, 206 could be obtained routinely in >90% yield on gram scale. The product was isolated with sufficient purity that chromatography was not required and 206
could be used directly in the next step. Weinreb amide 206 was then cooled to –40 °C as a THF solution, which was followed by the addition of a commercially available aryl Grignard reagent to provide compounds 203, isolated in varying yields (avg. ~60%) after column chromatography.

With a convenient procedure for obtaining a variety of benzyloxy acetophenones a library of compounds was synthesized and screened for their utility in the PTC alkylation reaction. Using acetophenones 203 with 10 mol% of catalyst 44 in CH\textsubscript{2}Cl\textsubscript{2} at –40 °C and with excess CsOH \textcdot H\textsubscript{2}O and benzyl bromide (5 equiv each) the various aryl

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar</th>
<th>time (hr)</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>4-anisyl</td>
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<td>82</td>
<td>54</td>
</tr>
<tr>
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<td>3-anisyl</td>
<td>16</td>
<td>50</td>
<td>50</td>
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<td>3</td>
<td>2-anisyl</td>
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<td>78</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>2-\textit{N},\textit{N}-dimethyl aniline</td>
<td>13</td>
<td>87</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>2-toluyl</td>
<td>12.5</td>
<td>72</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>2,3-diMePh</td>
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</tr>
<tr>
<td>7</td>
<td>2,4-diMePh</td>
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<td>66</td>
</tr>
<tr>
<td>8</td>
<td>2,5-diMePh</td>
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<td>80</td>
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</tr>
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<td>2-OMe-5-MePh</td>
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<td>8</td>
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<tr>
<td>13</td>
<td>2-Naphthyl</td>
<td>9</td>
<td>72</td>
<td>50</td>
</tr>
</tbody>
</table>

**Table 4.9.** Effect of aryl variation on glycolate PTC alkylation.
groups gave interesting results. Changing the position of the methoxy group on the aryl ring proved that substitution at the 2-position was most effective, providing an increase in selectivity to 66% ee. Changing the methoxy group to a \(N,N\)-dimethyl amine drastically affected the selectivity (entry 4). If a methyl group was used instead of a methoxy substituent the enantioselectivity remained high but slightly depressed. Further variations included employing dimethyl phenyl groups (entries 6–9). Maintaining the optimal 2 position and varying the second methyl position improved the yield to 80% and the selectivity peaked at 66%. The dimethyl strategy was extended to dimethoxy substrates. This found that the 2,5-dimethoxy aryl group could provide 204 with high selectivity and yield at 71% ee and 83%. Further variations using combinations of methyl and methoxy substituents as well as naphthyl substrates did not improve the selectivity.

4.3.2. Hydroxyl Protecting Group Screening

With the optimum aryl moiety in place, the effect of different hydroxyl protecting groups was investigated. Changing the benzyl group to \(p\)-methoxybenzyl (PMB) slightly lowered the selectivity of the reaction. Using an aryl protecting group drastically lowered the enantioselectivity to less than 30%. The 2-naphthylmethyl (NAP) group has recently been developed as an alternative to the benzyl protecting group.\(^{39}\) Employing this group provided an increase in selectivity to 75% ee. Finally, by switching to the diphenylmethyl (DPM) group based on benzhydrol product 206 was obtained in 80% yield and with high enantioselectivity at 90:10 er. Unfortunately, all further attempts to improve the selectivity with different protecting groups failed. All forms of substitution on the DPM aryl groups gave the same level of selectivity and were thus abandoned.
As the remaining optimization reaction would require the use of DPM 205 a highly efficient synthesis that would be amenable to large-scale reactions was developed. Benzhydryloxy acetic acid (207) is commercially available in only milligram quantities, therefore a convenient, large-scale synthesis was necessary for our needs. In attempting to follow known protocols for the synthesis of 207 we found that in our hands these procedures did not provide the desired product in reasonable yield or under mild conditions. Therefore, a unique, mild, and efficient method for the synthesis of 207 was developed. When a solution of benzhydrol in benzene was treated with tetrabutylammonium hydrogensulfate, ethyl bromoacetate and 50% aqueous NaOH, a thick, white solution was produced. Dilution with H₂O and subsequent washing with hexanes was followed by careful acidification and extraction with diethyl ether to directly provided 207 cleanly in 95% yield. No impurities could be detected by NMR analysis and the product was taken on to the next step. Next, Weinreb amide 208 was formed by EDCI

### Table 4.10. Hydroxyl protecting group variations.

<table>
<thead>
<tr>
<th>entry</th>
<th>P</th>
<th>time</th>
<th>% yield</th>
<th>% ee</th>
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<td>71</td>
</tr>
<tr>
<td>2</td>
<td>PMB</td>
<td>9</td>
<td>83</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>2-OMePh</td>
<td>23</td>
<td>70</td>
<td>&lt;30</td>
</tr>
<tr>
<td>4</td>
<td>2-NapCH₂⁺</td>
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<tr>
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<td>DPM</td>
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<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>
mediated coupling of 207 with $N,O$-dimethylhydroxylamine hydrogen chloride. The reaction was then quenched and the crude product obtained after extractive workup.

Figure 4.8. Synthesis of optimized substrate.

Following filtration and evaporation of solvent 208 was treated with lithiated 2,5-dimethoxybenzene to produce 209 in 91% yield. Using commercially available 2,5-dimethoxyphenyl magnesium bromide Grignard reagent was not considered practical due to its high cost (50 mL of 0.5 M solution = ~$100, Aldrich). Whereas 2,5-dimethoxy phenyl lithium could be easily obtained by treating 1-bromo-2,5-dimethoxybenzene with $n$-BuLi in THF and stirring for 1 h at $-40 \, ^\circ\mathrm{C}$. This procedure provided large quantities of 209 in 86% overall yield, and required only a single use of column chromatography.

4.3.3. Solvent Effects

With multi-gram quantities of 209 available the effect of solvent variation was investigated. Using THF in the reaction caused the rate to decrease tremendously, with the reaction being incomplete even after 48 h, analysis of the crude product revealed that
210 was formed with slightly depressed selectivity. Changing the solvent to chloroform caused multiple product formation and thus an attenuated yield, with the selectivity also significantly affected. Changing to a toluene/chloroform mixture typically used by Park and Jew37 provided yet again attenuated results from those employing just methylene chloride. By using pure toluene the enantioselectivity was improved to 86% ee while maintaining a high yield. Although the selectivity had been improved the reaction rate was again reduced, as the reaction required a four-fold increase in time to run to completion. By using mixtures of CH₂Cl₂ with either Et₂O or hexanes to decrease the solvent polarity, it was determined that a 1:1 mixture of hexanes and CH₂Cl₂ was optimal, providing 210 in excellent yield and with excellent enantioselectivity (86% ee). Further dilution with hexanes did not improve the selectivity.

Table 4.11. Solvent effect on glycolate PTC alkylation.
4.3.4. Base and Temperature Optimization

At this point the effect of changing the base and reaction temperature were studied. The only other base that was effective for the alkylation of 209 was rubidium hydroxide hydrate. This provided 210 with a slightly lower level of stereoselectivity. Using barium hydroxide or the phosphazene base BTTP provide only trace product formation even after prolonged reaction times. The temperature profile of the reaction was then investigated. Conducting the reaction in an ice bath at ~0 °C provided an excellent yield and retained a high level of selectivity. Cooling the reaction further found that the reaction temperature could be maintained at ~35 °C while retaining the optimum selectivity. Using lower temperatures did not improve the selectivity and at ~60 °C the rate became prohibitively slow.

![Image of chemical structures](image)

<table>
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<tr>
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<th>temp. (°C)</th>
<th>time (h)</th>
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<th>% ee</th>
</tr>
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<td>96</td>
<td>86</td>
</tr>
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<td>3</td>
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<td>75</td>
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<td>5</td>
<td>&quot;</td>
<td>-20</td>
<td>12</td>
<td>86</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>-30</td>
<td>12</td>
<td>95</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>&quot;</td>
<td>-35</td>
<td>14</td>
<td>94</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>&quot;</td>
<td>-60</td>
<td>52</td>
<td>69</td>
<td>84</td>
</tr>
</tbody>
</table>

**Table 4.12.** Variation of base and temperature.
4.3.5. Catalyst Loading and Screening

The level of catalyst loading was screened to determine if smaller quantities of 44 could be used while providing 210 with excellent enantiocontrol. While 1 mol% of ammonium salt 44 could be employed to provide useful levels of selectivity, 5 mol% was required to nearly reach the optimum level. It was determined that at least 8 mol% of catalyst 44 was required to provide the highest level of enantioselectivity. Increasing the catalyst loading to more than 10 mol% did not provide further improvements of the reaction results.

![Chemical structure of 209 and 210](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst loading</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 mol%</td>
<td>87</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>5 mol%</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>8 mol%</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>10 mol%</td>
<td>94</td>
<td>86</td>
</tr>
</tbody>
</table>

Table 4.13. Effect of catalyst loading on PTC glycolate alkylation.

With this data a series of cinchonidinium salts were investigated to determine the effect of catalyst structure for the selective synthesis of 210. A number of different catalysts were synthesized and their results displayed in Table 4.14. Changing the counteranion from bromine to tetrafluoroborate appeared to have little effect on the catalysts capabilities (entry 2). Replacing the allyl hydroxyl protecting group with a benzyl ether and/or using cinchonidine or hydrocinchonidine also appeared to have little
effect on the reaction results (entries 3 and 4). On the other hand using a benzoate ester for hydroxyl protection had a negative impact on the reaction selectivity and yield. Using a 2-nitrobenzyl salt instead of the standard triflurobenzyl group drastically hampered the enantioselectivity. Whereas the 2-cyanobenzyl cinchonidinium catalyst 44b developed by Park and Jew provided a high level of selectivity but slightly lower than 44 (entry 7). 41

\[
\begin{align*}
&\text{DPMO} & & \text{O} & & \text{OMe} & & \text{O} & & \text{OMe} & & \text{O} & & \text{OMe} \\
&\text{209} & & \text{cat, BnBr, CsOH} & & \text{CH}_2\text{Cl}_2: \text{hex}, -35 \, ^\circ\text{C} & & \text{210} & & \text{ODPM} & & \text{OMe} & & \text{OMe} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>P</th>
<th>X^-</th>
<th>Y</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2,3,4-tri-F-benzyl</td>
<td>allyl</td>
<td>Br</td>
<td>CH\text{2CH}_3</td>
<td>94</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>allyl</td>
<td>BF_4</td>
<td>CH\text{2CH}_3</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>benzyl</td>
<td>Br</td>
<td>CH\text{2CH}_3</td>
<td>95</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>benzyl</td>
<td>Br</td>
<td>CH\text{2CH}_2</td>
<td>96</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>benzoate</td>
<td>Cl</td>
<td>CH\text{2CH}_2</td>
<td>66</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>2-nitro-benzyl</td>
<td>benzyl</td>
<td>Br</td>
<td>CH\text{2CH}_2</td>
<td>96</td>
<td>32</td>
</tr>
<tr>
<td>7</td>
<td>2-cyano-benzyl</td>
<td>allyl</td>
<td>Br</td>
<td>CH\text{2CH}_2</td>
<td>quant</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>9-anthracenyl methyl</td>
<td>allyl</td>
<td>Br</td>
<td>CH\text{2CH}_2</td>
<td>72</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>2,6-F-9-anthracenyl methyl</td>
<td>allyl</td>
<td>Br</td>
<td>CH\text{2CH}_3</td>
<td>80</td>
<td>73</td>
</tr>
</tbody>
</table>

**Table 4.14.** Catalysts used in the glycolate PTC alkylation of 209.

Employing the commercially available Corey/Lygo catalyst 38 provided 210 with only moderate enantioselectivity (entry 8). Using the fluoro- substituted anthracenyl methyl
group recently disclosed by our group provided high selectivity,\textsuperscript{42} but again not to the
level provided by \textbf{44} (entry 9). Other catalysts screened, which are not shown in Table
4.14 include the Maruoka β-naphthyl catalyst (i.e. \textbf{42})\textsuperscript{43} recently made available from
Aldrich and the tartrate derived catalyst \textbf{45} developed by Shibasaki\textsuperscript{44} both provided poor
levels of enantioselectivity. These results suggest that the reaction is best run using the
well-established Park/Jew catalyst \textbf{44}.

\textbf{4.3.6. Electrophile Variation}

With the optimal procedure determined the scope of the procedure was studied by
varying the electrophile in the reaction. Treatment of \textbf{209} with CsOH in a 1:1 mixture of
CH\textsubscript{2}Cl\textsubscript{2} in the presence of catalyst \textbf{44} (10 mol\%) and various electrophiles provided
products \textbf{210} in good to excellent yield and with up to 90\% enantiomeric excess (Table
4.15). Allyl bromides (entries 2–5) reacted with high isolated yields and selectivities in
4–5 h. Allyl iodide reacted at a faster rate; however, the selectivity was reduced.
Methallyl bromide gave the highest selectivity at 89\% ee. Geranyl bromide was
somewhat slower at 8 h. Propargyl bromides substituted at the γ-position (entries 6,7)
were also effective with high selectivity in 4 h. Yields and selectivities were uniformly
high with benzyl bromides (entries 9, 10, 13–16). The reaction times varied depending on
the substitution pattern. Benzyl bromide required 13 h for completion, while 4-\textit{tert}-butyl
BnBr terminated in 5 h with high selectivity (84\% ee). \textit{o}-Phenyl BnBr gave a quantitative
yield after 9 h with excellent selectivity (90\% ee). Benzyl chlorides gave attenuated
yields but retained the general high selectivity seen with benzyl bromides. Entries 2, 4, 7,
and 9 have been run multiple times and on gram scale with reproducible results.
Table 4.15. PTC alkylation with a variety of electrophiles.

Extensive attempts were made to use alkyl halides in the PTC alkylation of 209. Many variations of the optimized reaction conditions were attempted with iodomethane, which only provided displeasing results. Using MeI in excess (10 equiv) at –20 °C did provide the methylated product in good yield but with only moderate enantioselectivity (entry 1). Additional alkyl halides and various leaving groups were studied, including \(n\)-hexyl iodide, ethyl bromide, ethyl triflate, and ethyl tosylate, all of which failed to give the desired product in reasonable yield (< 50%) under a variety of conditions.
4.4. Product Elaboration to α-Hydroxy Acid Products

The elaboration of products 210 to useful α-hydroxy acid products can be accomplished via a Baeyer–Villiger-type oxidation to give an aryl ester. Early explorations into this step had shown that the DPM group was unstable to variety of Lewis (e.g. TiCl₄, SnCl₄, and Sc(OTf)₃) and Brønsted acids (e.g. catalytic quantities of TFA, triflic acid) typically used in conjunction with Baeyer–Villiger oxidations. Accordingly, the DPM group was quickly and cleanly removed by the addition of TiCl₄ (1 equiv) in CH₂Cl₂ and stirring at −78 °C for 30 min prior to fully screening potential Baeyer–Villiger oxidations. The free hydroxyl group was then protected as a benzoate ester as an attempt to differentiate between the hydroxyl and impending aryl ester. Exposure of 211 to benzoyle chloride in CHCl₃ with pyridine provided 212 in excellent yield.

![Diagram of oxidation process](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>oxidation conditions</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>m-CPBA (8 equiv), NaH₂PO₄, dichloroethane, 50 °C</td>
<td>No Reaction</td>
</tr>
<tr>
<td>2</td>
<td>(TMSO)₂ (4 eq), SnCl₄ (1 eq), 214 (1 eq), CH₂Cl₂, 0 °C</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>(TMSO)₂ (4 eq), SnCl₄ (0.5 eq), 214 (0.5 eq), K₂CO₃ (2.0 eq), CH₂Cl₂, 0 °C</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>(TMSO)₂ (2.5 eq), SnCl₄ (0.5 eq), 214 (0.5 eq), K₂CO₃ (2.0 eq), CH₂Cl₂, 0 °C</td>
<td>74</td>
</tr>
</tbody>
</table>

Figure 4.9. Baeyer–Villiger oxidation to aryl ester.
With 212 in hand the oxidation step to provide aryl ester 213 was studied. Initial reactions employing m-CPBA with added NaH₂PO₄ as buffer provided no reaction even at elevated temperatures overnight, as monitored by TLC. A unique set of conditions developed by Shibasaki was then explored. By using a SnCl₄•bis-sulfonamide (214) complex formed in situ followed by the addition of bis-TMS peroxide and 212 aryl ester 213 was generated in moderate yield. The reaction was then probed in depth to find conditions that would provide 213 in high yield. Eventually it was discovered that using a catalytic quantity of the SnCl₄•bis-sulfonamide complex with added K₂CO₃ to sequester any HCl generated in the reaction could improve the yield to 63% (entry 3). Finally, by reducing the amount of bis-TMS peroxide from 4 equivalents to 2.5, 213 was obtained in 74% yield (entry 4).

![Diagram](image-url)

<table>
<thead>
<tr>
<th>entry</th>
<th>oxidation conditions</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>m-CPBA (3 eq), Triflic Acid (0.1 eq), CH₂Cl₂, 0 °C</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>m-CPBA (3 eq), TFA (1 eq), CH₂Cl₂, 0°C</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>m-CPBA (3 eq), Sc(OTf)₃ (0.1 eq), CH₂Cl₂, 0 °C</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>(TMSO)₂ (2.5 eq), SnCl₄ (0.5 eq), 214 (0.5 eq), K₂CO₃ (2.0 eq), CH₂Cl₂, 0 °C</td>
<td>Incomplete Reaction</td>
</tr>
<tr>
<td>5</td>
<td>(TMSO)₂ (2.0 eq), SnCl₄ (1.0 eq), 214 (1.0 eq), K₂CO₃ (2.0 eq), CH₂Cl₂, 0 °C</td>
<td>79</td>
</tr>
</tbody>
</table>

Table 4.16. Direct Baeyer–Villiger oxidation to aryl ester.
In order to eliminate the benzoate protection step and the dependance on a hydroxyl protection, the direct oxidation of 211 was investigated. Again, protocols using \( m \)-CPBA as the oxidant were explored, this time looking at reagent mixtures activated with either Lewis or Brønsted acids.\(^{47}\) Using both triflic acid and trifluoracetic acid (TFA) provided only a minimal amount of 215. Using scandium triflate the same results were seen by TLC analysis and the product was not isolated (entry 3). In all cases the alcohol 211 was consumed during the reaction but only poor yields of 215 resulted. Resorting to the Shibasaki Baeyer–Villiger-type oxidation conditions optimized in Figure 4.9, only minimal product was formed as seen by TLC analysis. Since the starting material was not consumed during prolonged exposure to these conditions investigation of its utility continued. Gratifyingly, it was determined that if slightly less bis-TMS peroxide (from 2.5 equivalents to 2.0) was employed and a full equivalent of the SnCl\(_4\)•bis-sulfonamide complex was used crystalline 215 was obtained in 79% yield (entry 5). We were very pleased to find that a single recrystallization of hydroxyester 215 (mp 128–130 °C) from warm Et\(_2\)O gave further enantioenrichment to >99% ee.

![Figure 4.10. Oxidation of allylic hydroxy ketone.](image)
The Baeyer–Villiger oxidation was also applied to hydroxy ketone 216. Following the conditions described previously, the DPM group was replaced with a benzoate ester to provide 218 in 82% overall yield for the two steps. Subsequently using the oxidation conditions with catalytic quantity of the SnCl₄•bis-sulfonamide complex provided 219 in 74% yield. A key benefit to using these peroxide conditions over the standard peracid protocols is that these conditions do not affect alkene epoxidation and thus allow for expansion of the scope of the process to include unsaturated substrates. Thus, the formation of 219 proceeded such that no epoxidation products were seen. Attempts to directly oxidize 217 were met with low yields (~30%) that could not be improved by varying the relative equivalents of the reagents, which had been successful previously.

![Diagram](image)

**Figure 4.11.** Selective transesterification.

Selective transesterification conditions were also developed for the aryl ester intermediate 213 to establish the stereochemistry and to demonstrate multistep utility. When 213 was exposed to catalytic NaOMe (20 mol%) in MeOH/THF, (S)-methyl ester 220 was obtained in 81% yield with the benzoate ester intact and without racemization.
In complementary fashion, when excess NaOMe (2 equiv) is added to 213 both the aryl and benzoate groups are removed, providing (S)-2-hydroxy methyl ester 221 in 82% yield. A combination of attenuated lone-pair n-π carbonyl resonance by the O-aryl oxygen and greater stability of the aryloxy leaving group appears to be the origin of this useful chemoselectivity.\textsuperscript{48} Comparison of literature optical rotation values to those obtained from 220 and 221 ([\alpha]_D^{23} -35.5^\circ \text{ (c 0.45, MeOH)}, \text{lit. } [\alpha]_D^{20} = -40.2^\circ \text{ (c 1.85, MeOH)};\textsuperscript{49} and [\alpha]_D^{23} -8.8^\circ \text{ (c 0.4, CHCl}_3\text{), lit. } [\alpha]_D^{24} = -6.8^\circ \text{ (c 1.39, CHCl}_3\text{),}\textsuperscript{50} respectively) established the S-stereoinduction. In addition to these comparisons, a single-crystal X-ray structure was solved for benzoate 212, which unambiguously determined the stereochemical assignment as S.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.12.png}
\caption{One-pot hydrogenation/DPM removal.}
\end{figure}

While the alkylation of 209 was unsuccessful with alkyl halides, unsaturated alkylation products could be quickly transformed to alkyl products. Unsaturated ketone 216 was simply treated with H\textsubscript{2} at balloon pressure overnight with activated Pd/C. This procedure provided a mixture of 222 and hydrogenated 216 without DPM removal. Simply filtering off the Pd/C and switching the solvent to CH\textsubscript{2}Cl\textsubscript{2} was followed by the addition of trifluoroacetic acid to quickly provided 222 in 80% yield after column chromatography.
4.5. References and Notes


32. Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. 

33. Clark, J. S.; Freeman, R. P.; Cacho, M.; Thomas, A. W.; Swallow, S.; Wilson, C. 


35. For a review see: (a) O’Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3. (b) 


38. For an excellent example, see: Williams, R. M.; Ehrlich, P. P.; Zhai, W.; Hendrix, 

   Abbas, S. A.; Locke, R. D.; Piskorz, C. F.; Alderfer, J. L.; Matta, K. L. 

40. For an example, see: Carceller, E.; Merlos, M.; Giral, M.; Almansa, C.; Bartroli, 


44. (a) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, 


Chapter 5. Total Synthesis of Ragaglitazar

5.1. Retrosynthetic Analysis

Ragaglitazar (3) is a potent antihyperglycemic and lipid modulator. It improves insulin sensitivity and decreases hyperlipidemia. Ragaglitazar showed 56% reduction in plasma glucose and 62% reduction in triglyceride levels of genetically diabetic, insulin resistant, hyperlipidemic mice.\(^1\) The current synthetic route to ragaglitazar (3) employs 8 steps with a 26% overall yield and 98% ee. The route reported by Novo Nordisk is being used to produce large amounts (~50g batches) of 3 for phase II clinical trials.\(^2\) The selective synthesis of 3 can theoretically be applied to the synthesis of other related PPAR\(\alpha/\gamma\) agonists such as 5, 6, and 223.\(^3\) All reported routes to 3 employ a resolution of racemic materials, and no enantioselective carbon-carbon bond forming routes have been established.

![Figure 5.1. β–aryl α–hydroxy propanoic acids as PPAR\(\alpha\) and PPAR\(\gamma\) agonists.](image)

The high standard created for the synthesis of 3 by Novo Nordisk and the potential application of a successful synthesis to this and other related drugs provides an
excellent challenge for the PTC alkylation methodology we had developed. The successful synthesis would be the first catalytic enantioselective route to 3 as well as a significant synthetic alternative to the method developed by Novo Nordisk. With this goal in mind we embarked on the synthesis of 3 using the PTC method described in Chapter 4.

![Figure 5.2. Retrosynthesis of ragaglitazar.](image)

The initial disconnection was determined to be the phenol ether. This would break 3 into two large pieces, the phenoxazine derivative 224 and the α-ethoxy methyl ester 225. Derivatives of 224 have been reported with $X$ = either a halogen or sulfonate leaving group. Additionally, 225 could arise from α-hydroxy methyl ester 226 by a mild introduction of the ethyl group. This could be traced back to the aryl ketone 227 via an enatioselective PTC alkylation with judicious choice of a suitable phenolic protecting group. The synthesis of 3 was envisioned to begin with the aryl ketone 209 that was available in multi-gram quantities.
5.2. PTC Alkylation of 4-Oxy-Benzyl Halides

The first challenge was to establish the 4-oxy-phenyl moiety found in 3. The protecting group (P) of 227 would need to be stable to the PTC alkylation step and the ethyl ether formation while not affecting the selectivity of the PTC alkylation. The triisopropyl silyl (TIPS), benzyl (Bn), benzoate (Bz), and pivolate (Piv) protecting groups were selected as prime candidates. Their corresponding 4-OP-benzyl bromides were synthesized and used in the PTC alkylation reaction under standard conditions.

![Chemical structure]

Table 5.1. Effect of 4-substituent on benzyl halide alkylation.

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>equivalents</th>
<th>time (h)</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>2.0</td>
<td>14</td>
<td>86</td>
<td>83</td>
</tr>
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<td>2</td>
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<td>5.0</td>
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<td>3</td>
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<td>10.0</td>
<td>8</td>
<td>93</td>
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</tr>
<tr>
<td>13</td>
<td></td>
<td>5.0</td>
<td>24</td>
<td>95</td>
<td>83</td>
</tr>
</tbody>
</table>
First the 4-OBn benzyl bromide\textsuperscript{6} electrophile was studied under the standard reaction conditions. Surprisingly, while a high yield was obtained, poor selectivity was uncharacteristically produced (40\% ee, entry 6). The poor solubility of this electrophile prompted us to vary the equivalents of electrophile added to the reaction. Unexpectedly, the level of selectivity varied dramatically with equivalents of benzyl halide added, with a maximum of 74\% ee obtained (entries 4 and 5). For a comparison the equivalents of benzyl bromide and its effect on the reaction selectivity was investigated. As expected only slight deviations were seen when this parameter was varied (entries 1–3) with 5 equivalents being optimum. Next, the effect of the leaving group was examined, thus the commercially available 1-(benzyloxy)-4-(chloromethyl)benzene was utilized. The results indicate that this electrophile also displays varying levels of enantioselectivity based on equivalents employed. In this case optimum selectivity was produced when the standard 5 equivalents of the benzyl chloride was used (entries 7 and 8).

With these disappointing results our attention turned to the more bulky TIPS protecting group with (4-(bromomethyl)phenoxy)triisopropylsilane being employed for this purpose.\textsuperscript{7} Despite the electrophile having improved solubility and using a protecting group with different steric properties the product was again obtained with lower than expected selectivity at only 70\% ee (entry 9). It was anticipated that by changing the electronic property of the aromatic ring, from an electron rich (P = Bn, TIPS) to a comparatively electronically withdrawn (P= Bn, Piv) benzyl halide that the stereoselective outcome could be altered. Unfortunately, 4-benzoate benzyl bromide also reacted at a slow rate, displaying poor solubility in the reaction conditions and provided only moderate selectivity (entries 10 and 11). Finally, when 4-(bromomethyl)phenyl
pivalate was employed the desired product was obtained in 95% yield and with 83% ee. It appears that the pivolate group provides the optimal combination of both solubility in the reaction media and attenuated lone-pair contribution from the phenolic oxygen. This alkylation has been performed numerous times on gram scale to provide reproducible results (avg results = 93% yield, 82.5% ee).

![Chemical Structure]

**Figure 5.3.** Large-scale synthesis of requisite benzyl bromide.

Although the reaction requires 5 equivalents of the benzyl halide to obtain optimum levels of enantioselectivity, it can be recovered in 94% after column chromatography and reused in the PTC alkylation with identical results. The requisite 4-(bromomethyl)phenyl pivalate has been made in up to 20 grams batches following a simple two-step protocol. Beginning with commercially available 4-hydroxybenzyl alcohol (228) as a THF solution NaH is added and stirred at ambient temperature for 30 min. Subsequent addition of trimethylacetyl chloride produces 229 in 80% yield after brief flash column chromatography. Treatment of 229 with LiBr and NEt₃ followed by methanesulfonyl chloride at 0°C for 2 h gave the crystalline adduct 230 in 80% yield.

5.3. Enantioselective Synthesis of Ragaglitazar

With significant quantities of 231 in hand, and a convenient procedure available for scale-up needs, we proceeded with our synthesis of ragaglitazar (3). Deprotection of
with TiCl$_4$ at $-78 \, ^\circ C$ provided 232 uneventfully in 92% yield. Aryl ketone 232 was then treated with the Shibasaki Baeyer–Villiger-type oxidation protocol using bis-TMS peroxide (2.0 equivalents) and a full equivalent of the SnCl$_4$-bis-sulfonamide complex to provide 233 as colorless needles in 83% yield. We were very pleased to find that a single recrystallization of hydroxyester 233 (mp 94–96 °C) from warm Et$_2$O:hexanes (1:1) gave further enantioenrichment to 96% ee and in 75% yield.

Figure 5.4. Synthesis of key aryl ketone intermediate.

The next goal was to install the ethyl ether without epimerization of our nearly enantiopure material. This transformation was more difficult that expected. Despite intense research, significant epimerization has been seen with a variety of alkylation procedures in related systems. In our hands, standard protocols were ineffective for the stereoretentive formation of 234. Repeated attempts to alkylate 233 provided only complex mixtures by TLC analysis. Oxonium salts have been successfully employed for the alkylation of optically labile secondary alcohols. The most common of these is Meerwein’s trimethyloxonium tetrafluoroborate salt for the installation of methyl ethers, which we had used previously in the total synthesis of geldanamycin.
An extension of this work has been reported by Fry for the formation of ethyl ethers. He showed that the triethyloxonium salt can be employed in conjunction with nonnucleophilic amine bases to effect the alkylation of optically active alcohols. Accordingly, Et$_3$OBF$_4$ was employed with proton sponge (bis(dimethylamino)-naphthalene) in CH$_2$Cl$_2$ to cleanly afford 234 in good yield and with minimal loss of enantiopurity. Discouragingly, after running this reaction multiple times we found that the results were not reproducible. At times the product enantiomeric purity was nearly identical to that of the starting material while at other times the product purity had significantly eroded as much as 9% ee.

While the exact cause of this discrepancy was not determined, it was noticed that after 24 h at room temperature if a significant loss of solvent had occurred that a solid material would precipitate out of solution. It was when this solid came out of solution that the enantiopurity appeared to suffer. Although the composition of the solid formed was

<table>
<thead>
<tr>
<th>reaction conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaH, DMF, Et-I</td>
<td>Multiple Products</td>
</tr>
<tr>
<td>Hunigs Base, Et-OTf</td>
<td>&quot;</td>
</tr>
<tr>
<td>Ag$_2$O, Et-I, CH$_3$CN</td>
<td>&quot;</td>
</tr>
<tr>
<td>SO$_4$(Et)$_2$, Cs$_2$CO$_3$, Toluene</td>
<td>&quot;</td>
</tr>
<tr>
<td>Et-I, Cs$_2$CO$_3$, Toluene</td>
<td>&quot;</td>
</tr>
<tr>
<td>Et$_3$OBF$_4$, Proton Sponge, CH$_2$Cl$_2$</td>
<td>73-80% yield, 94-87% ee</td>
</tr>
<tr>
<td>Et$_3$OBF$_4$, Proton Sponge, CHCl$_3$</td>
<td>79% yield, 95% ee</td>
</tr>
</tbody>
</table>

**Table 5.2.** Installation of the ethyl ether.
never determined, it could possibly arise from the formation of a quaternary ammonium salt via alkylation of proton sponge\textsuperscript{12}, from the condensation of an aniline group with the aryl ester providing a less soluble material\textsuperscript{13} or from simple precipitation of proton sponge. Regardless of its composition, additional solvents were screened that had a higher boiling point than CH\textsubscript{2}Cl\textsubscript{2} in order to overcome this evaporation issue. When THF was used only a polymeric material was obtained that could not be characterized. By switching to chloroform we found that the enantiopurity of the product was still high while the problem of solvent volatility had been reduced. Using these conditions \textbf{234} could be provided in 79\% yield and with minimal erosion of the enantiomeric excess. Significantly, we found that the issue of reproducibility was overcome as we could routinely obtain \textbf{234} with 95\% ee using these conditions.

At this juncture the phenol was revealed, in order to incorporate the phenoxazine moiety. We used 2 equivalents of NaOMe/MeOH to remove the pivolate ester and concomitantly convert the aryl ester to its corresponding methyl ester. This procedure provided \textbf{235} in 94 \% yield without any detectable racemization of the \(\alpha\)-ethoxy stereocenter (determined by HPLC analysis with comparison to racemic materials).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure55.png}
\caption{Attempted synthesis of 3-methyl ester.}
\end{figure}
With the phenol selectively exposed the \( O \)-alkylation of 235 was attempted using primary chloride 236. Chloride 236 was prepared in a single step by treating phenoxazine with \( n \)-BuLi at ambient temperature for 30 min followed by the addition of 2-chloroethyl-\( p \)-toluene sulfonate. Unfortunately, treatment of 235 with 236 failed to provide any alkylation product, even at elevated temperatures and for prolonged reaction times, as monitored by TLC. The failure of 236 to give the desired phenyl ether 237 prompted us to investigate an approach that employed mesylate 241 which had been used successfully for the synthesis of 3 (see Chapter 1, Section 1.2).\(^\text{14}\). We found that a three-step procedure could provide 241 in significant quantities.\(^\text{15}\) Treatment of 238 with ethyl bromoacetate in 1-methyl-2-pyrrolidinone at 70 °C provided 239 in 78% yield after column chromatography. Subsequent reduction of ethyl ester 239 with lithium aluminum hydride produced the primary alcohol adduct 239 cleanly, such that it could be used directly in the next step without further purification. Crude 239 was then treated with methanesulfonyl chloride in \( \text{CH}_2\text{Cl}_2 \) with \( \text{NEt}_3 \) to provide mesylate 241 in high yield.

Exhaustive screening of potential reaction conditions to provide 240 in a single step from phenoxazine (238) via nucleophilic displacement of alkyl halides or sulfonates did not afford useful yields (\(<40\%) or produced multiple reaction products.

\[ \text{Figure 5.6. Synthesis of } 2-(10H-\text{phenoxazin}-10-yl)\text{ethyl methanesulfonate (241).} \]
With this phenoxazine derivative in hand the synthesis of \( ^{237} \) was again attempted. When \( ^{235} \) was treated with potassium carbonate and \( ^{241} \) in toluene at 100 °C \( ^{237} \) was produced in 85% yield with complete retention of enantiopurity as determined by chiral HPLC analysis. In an attempt to improve the yield of this step we tried the same reaction conditions but instead of using \( \text{K}_2\text{CO}_3 \) we employed cesium carbonate. These conditions provided \( ^{237} \) in 98% yield but eroded the enantiomeric excess to 91%.

![Chemical reaction diagram](image)

**Figure 5.7.** Final steps in the synthesis of ragaglitazar.

The final step was hydrolysis of methyl ester \( ^{237} \) using 3N NaOH in MeOH, which provided (–)-ragaglitazar in 92% yield. Although significant reaction optimization of 4-hydroxy benzyl halides was necessary to produce high levels of selectivity in the PTC alkylation, the synthesis of \( ^{3} \) was accomplished for the first time using a catalytic enantioselective route requiring a single recrystallization. The route we have developed provides \( ^{3} \) in 26.5% overall yield in 8 steps from benzhydryloxy-acetic acid and with 95% ee. This procedure rivals that developed by Novo Nordisk while eliminating the need for enzyme catalysis and provides a new avenue for the synthesis of related derivatives (e.g. \( ^{5} \), \( ^{6} \), and \( ^{223} \)).
5.4. References and Notes


6. For synthetic preparations, see: (a) Colobert, F.; Des Mazery, R.; Solladie, G.;
7. For a synthetic preparation, see: Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.;
   examples, see: (a) Sawada, D.; Shibasaki, M. Angew. Chem. Int. Ed. 2000, 39,
   10521. (c) Trost, B. M.; Terrell, L. R. J. Am. Chem. Soc. 2003, 125, 338. (d)
    1937, 147, 257.
   Chem. 2003, 46, 1306.
6.1. Introduction and Retrosynthesis

Kurasoin A and B were isolated in 1996 as white powders during a search for protein farnesyltransferase (PFTase) inhibitors.¹ Soil samples taken from Kurashiki City, Okayama Prefecture, Japan were found to contain a fungus of Paecilomyces sp. The particular strain was named FO-3684, which was amplified via culture fermentation, the broth was extracted and purified to obtain kurasoin A and B in 0.09% and 0.19% yields respectively, from dried culture extracts.

![Figure 6.1](image_url) Structures of kurasoin A and B.

The PFTase inhibitory activity was measured providing IC₅₀ values of 59.0 and 58.7 µm for 19 and 20 respectively. Only a single enantioselective route to kurasoin A and B has been reported. The total synthesis of kurasoin A requires a total of 7 steps and produces a 5% overall yield.² While the synthesis of kurasoin B was accomplished via an expeditious route requiring only 4 steps but the overall yield was poor at only 6%.

We felt that the synthesis of 19 and 20 provided another challenging target for the asymmetric PTC glycolate alkylation methodology we had developed. In this instance the target would be an α-hydroxy ketone, which would further display the synthetic utility of our PTC methodology for the synthesis of α-hydroxy carbonyl compounds other than α-hydroxy acids and esters. Initially, work focused on the synthesis of kurasion A as it
embodied the 4-hydroxy benzyl group that had been obtained in the enantioselective synthesis of ragaglitazar.

**Figure 6.2.** Retrosynthesis of kurasoin A.

The racemic synthesis of kurasoin A had required only 2 steps from (+)-238 to provide 19 in good yield.\(^{1b}\) Ester (+)-238 had been treated with a mixture of N,O-diemethylhydroxylamine hydrochloride and AlMe\(_3\) to afford the Weinreb amide (+)-22. Subsequent treatment with benzylmagnesium chloride in THF provided racemic kurasoin A, as reported by Omura. Simple NaOMe/MeOH treatment of intermediate 233, which we had previously intercepted could directly provide \(\alpha\)-hydroxy ester 238. Using the PTC glycolate alkylation of 209 with our optimized 4-OPiv-Benzyl bromide alkylating agent would again provide significant quantities of 233. With this plan in mind, the enantioselective synthesis of kurasoin A commenced.

### 6.2. Initial Endeavor

As described previously the synthesis of 233 proceeded, starting with the alkylation of 209, catalyzed by 10 mol % of the Park/Jew chiral ammonium salt 44.
Product 231 was obtained in 95% yield and with 83% ee. Removal of the diphenylmethyl (DPM) group was accomplished using TiCl$_4$ in CH$_2$Cl$_2$ at $-78 \, ^\circ$C for 30 min followed by basic quenching to produce 232 in excellent yield. Hydroxy ester 232 was then treated with the TMS peroxide and SnCl$_4$ Baeyer–Villiger conditions to produce 233 in high yield. This was followed by an overnight recrystallization from warm Et$_2$O:hexanes (1:1) to provide 233 in 96% ee.

![Figure 6.3. Synthesis of key aryl ester intermediate.](image)

With 233 in hand we continued with the outlined synthesis of kurasoin A. Treating 233 with 3 equivalents of NaOMe in MeOH/THF cleanly removed the pivolate ester with concomitant transesterification of the aryl ester to methyl ester 238 in excellent yield. At this point we intercepted the route described by Omura in his racemic synthesis of kurasoin A.$^{1b}$ Following his conditions exactly, with 6 equivalents each of N,O-dimethylhydroxylamine hydrochloride and trimethylaluminum in CH$_2$Cl$_2$ for 5 hours 22 was produced in only 30% yield with a 35% recovery of the starting material (46% yield based on recovered starting material, BORSM). This was discouraging when compared to
the 67% yield reported by Omura for the same transformation. Despite this result attempts were made to optimize the reaction. Using less equivalents of these reagents with 238 produced an inactive reaction mixture as starting materials were the only isolable material. Next, the equivalents of \( N,O \)-dimethylhydroxylamine hydrochloride and trimethylaluminum were increased to 7 equivalents and the reaction was allowed to proceed for 64 h at ambient temperature. This protocol provided Weinreb amide 22 in 76% isolated yield along with complete consumption of the starting material.

![Figure 6.4. Total synthesis of kurasoin A.](image)

Again following the lead of Omura, the addition of benzyl magnesium chloride to Weinreb amide 22 was investigated. Following the reported conditions exactly, employing 5 equivalents of benzyl magnesium chloride as a 2.0 M solution in THF at 0 °C kurasoin A was isolated with only a 15% yield and in 30% BORSM. Again, work began to improve the reaction by looking at various parameters. First different reaction concentrations were investigated, running the reaction at 0.007, 0.01, 0.02 and 0.05 M in THF, provided no improvement. Using benzyl magnesium chloride in Et\(_2\)O also provided poor results. Attempts were made using benzyl lithium formed \textit{in situ} from toluene and \( n-\)
BuLi with added TMEDA. This protocol also provided kurasoin A but again in a poor yield of only 16%. These results are in direct conflict with those reported by Omura who reports obtaining a 65% yield directly from 22.

N-methoxy-N-methylamides are also known as Weinreb amides. In contrast to alkyl esters and amides, the addition of alkyl Grignard or lithium reagents to the carbonyl of a Weinreb amide produces a coordinated tetrahedral intermediate that is stable at low temperatures. The desired ketone product is revealed after an aqueous workup. In relation to the synthesis of kurasoin A, the addition of organometallic reagents to α-hydroxy Weinreb amides is frequently accomplished with the hydroxy group masked as either a benzyl, or silyl ether. Following this precedent both the phenol and hydroxyl groups would be masked as either a p-methoxy benzyl (PMB) or tert-butyl dimethyl silyl (TBS) ethers. Due to the large excess of reagents and the long reaction time required to provide 22 the protecting groups would be installed prior to Weinreb amide formation.

![Figure 6.5. Attempted Weinreb amide formation with different α-hydroxy ethers.](image_url)

Addition of TBSCI and imidazole to 238 in DMF provided 239 in excellent yield. Unfortunately, all attempts to produce the corresponding Weinreb amide from 239 failed,
as only complex mixtures were obtained. Turning to the PMB protecting group scheme, addition of \( p \)-methoxybenzyl trichloroacetimidate to 238 with catalytic 10-camphorsulfonic acid provided 240 in quantitative yield.\(^7\) As with 239, all attempts to form the Weinreb amide failed. In each attempt, an inactive reaction mixture was produced as only the starting material was seen by TLC analysis.

At this point, additional routes to kurasoin A from 233 were considered. Fukuyama has described the palladium-mediated synthesis of aldehydes and ketones from thioesters.\(^8\) He has shown that a variety of ketones can be prepared by a Pd-catalyzed reaction of ethane or dodecanethiol esters with organozinc reagents. In addition, Fukuyama has shown that this method can be applied to the synthesis of \( \alpha \)-amino ketones without racemization.\(^9\) Following his lead we decided to attempt the synthesis of kurasoin A via this method.

![Figure 6.6. Palladium-mediated synthesis of kurasoin A from thiol esters.](image)

It was quickly determined that 233 could be directly converted to thioester 241. Accordingly, 233 was treated with excess 1-dodecane thiol and AlMe\(_3\) in CH\(_2\)Cl\(_2\). This
reaction removed the pivolate ester and gave the thiol transesterification product in 74% yield. At this point different protecting groups were installed. Treatment of 241 with either Ac₂O and pyridine along with catalytic DMAP or TBSCI and imidazole provided the acetate and TBS compounds 242 and 243 in 90 and 84% yield, respectively. Compounds 241-243 were then exposed to the standard coupling protocols. Using 10 mol% PdCl₂(PPh₃)₂ in toluene followed by the addition of commercially available benzylzinc bromide did not provide the desired product. Using 241 and 242 produced complex mixtures that provided major products whose spectral data did not match that of expected products and whose identity could not be determined. Intermediate 243 resisted activity completely with only starting material being observed by TLC analysis after an extended reaction time at ambient temperature.

6.3. Asymmetric Synthesis of Kurasoin A

Undeterred from our goal we decided to return to a Weinreb amide protocol. With the success of directly forming thiol ester 241 directly from 233 a similar route aimed at the direct formation of the corresponding Weinreb amide was investigated. Gratifyingly, addition of aryl ester 233 to a CH₂Cl₂ solution of N,O-dimethylhydroxylamine hydrochloride and trimethylaluminum provided 244 in excellent yield. Following this procedure the pivolate ester is left unscathed while the Weinreb amide is installed cleanly in 92% yield. Due to the inactivity of the α-OTBS intermediates previously described we installed the relatively more labile and less bulky triethyl silyl ether (TES). The TES group has also been used successfully for the addition of organometallic reagents to α-siloxy Weinreb amides.¹⁰
Treatment of 244 with TESCl and imidazole in DMF provided 245 uneventfully in 91% yield. At this point the intermediate was ready for the critical addition of the benzyl moiety to produce the requisite benzyl ketone. We were pleased to find that addition of benzylmagnesium chloride in THF to amide 245 at 0 °C afforded the desired benzyl ketone 246 in 81% yield. Finally, a procedure for the formation of the benzyl ketone had been found. All that was left for the preparation of kurasoin A was the removal of the pivolate ester and the silyl ether.

Figure 6.7. Benzyl addition to weinreb amide.

The global deprotection of 246 was much more challenging than originally anticipated. While the TES ether is labile using either fluoride sources or Lewis acids, the pivolate ester is quite stable to these conditions. The pivolate ester is typically removed under basic conditions.11 The newly formed benzyl ketone is now considerably more prone to epimerization than before, thereby precluding the use of strong bases. A variety of one-pot reactions were screened that could concomitantly remove the protecting groups while maintaining the integrity of the α-hydroxy stereocenter.
A report by Bengtsson showed that an aryl pivaloyl group could be cleaved by acidic hydrolysis using 6 M HCl at 80 °C.\textsuperscript{12} As the TES silyl ether is also labile under aqueous acidic conditions this procedure was tested first. Unfortunately, exposure of 246 to 3 M HCl in dioxane at reflux provided complete decomposition of the starting materials. A one-pot procedure that would remove the protecting groups sequentially was investigated next. In our first attempt addition of 3 N NaOH and dioxane to 246 at ambient temperature, was followed by careful acidification with 1 N HCl until a pH of ~1.6 was obtained. The procedure provided a single spot by TLC and was purified by column chromatography. Analysis of the product by \textsuperscript{1}H NMR revealed that two compounds had been isolated together. The inseparable mixture provided a spectrum, which contained peaks corresponding to those reported for kurasoin A along with a minor product that had a number of nearly superimposable peaks. Carbonyl migration has been observed in a variety of highly related α-hydroxy ketone systems, occurring in either acidic or basic media.\textsuperscript{13} In accord with these observations, the minor product has been tentatively assigned as ketone 247, presumably formed via a keto/enol tautomerism mechanism, although this has not been unambiguously confirmed by a separate synthesis of 247.

In an attempt to minimize this byproduct formation and prevent racemization of the hydroxy stereocenter, we decided to first remove the TES silyl ether followed by pivalate ester cleavage under less basic conditions. By first treating 246 with TBAF in THF followed by the addition of 1 M NaOH, kurasoin A was obtained with drastically reduced levels of tautomer 247 (entry 3). Finally, by using TBAF in THF followed by the addition of the relatively more nucleophilic base LiOOH (compared to NaOH) kurasoin
A was isolated in 65% yield. Using this procedure 247 could not be detected by NMR analysis.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>combined % yield</th>
<th>ratio (19 : 247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3M HCl, dioxane, reflux</td>
<td>Decomposition</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>3N NaOH, dioxane then 1N HCl</td>
<td>63%</td>
<td>75 : 25</td>
</tr>
<tr>
<td>3</td>
<td>TBAF, THF then 1M NaOH</td>
<td>51%</td>
<td>92 : 8</td>
</tr>
<tr>
<td>4</td>
<td>TBAF, THF then LiOH/H2O2</td>
<td>65%</td>
<td>100 : 0</td>
</tr>
</tbody>
</table>

Table 6.1. Deprotection producing kurasoin A.

Product 19 matched all reported data for (+)-kurasoin A (1H and 13C NMR, optical rotation and appearance). The route described herein provides kurasoin A in 8 steps from benzhydryloxy-acetic acid with a 22% overall yield. In contrast, the enantioselective route reported by Omura requires a total of 7 steps and produces a 5% overall yield. This new route provides a more practical synthesis of kurasoin A for further biological testing and provides a convenient route for the synthesis of structural analogues.

6.4. Studies Toward the Asymmetric Synthesis of Kurasoin B

With a concise route determined for the enantioselective total synthesis of kurasoin A, our attention turned to its family member, kurasoin B. It was anticipated that the route culminating in the synthesis of kurasoin A could be applied to the synthesis of kurasoin B. The first step toward this goal was to determine a suitable electrophile, which could be applied to the PTC glycolate alkylation reaction. This study began with the
synthesis of a series of 3-(bromomethyl)-indole derivatives. The N-Piv, and –Bz derivatives 249 and 250 were made in two steps from 3-methyl-1\(H\)-indole, while 248 is commercially available.

![Figure 6.8. PTC glycolate alkylation with indole derivatives.](image)

When the PTC alkylation reaction was run using either 249 or 250 the reaction rate was extremely sluggish with incomplete starting material consumption after 2 days. In addition to the slow rate, multiple products were formed and the reaction was abandoned. We were pleased to find that using commercially available 248, the alkylated product 251 could be obtained in excellent yield and in 82% ee. With 251 in hand removal of the DPM protecting group ensued.

![Figure 6.9. Elaboration of alkylated indole intermediate.](image)
Exposure of 251 to one equivalent of TiCl₄ in CH₂Cl₂ at −78 °C provided 252 in 79% yield along with other minor byproducts that were easily removed via column chromatography. The next step was the Baeyer–Villiger oxidation to provide 253. Unfortunately, employing this reaction using the standard conditions we had employed previously, the reaction produced complete decomposition of the starting material with multiple products being formed in less than 1h. This result prompted us to investigate the Baeyer–Villiger oxidation with the hydroxyl group protected as a benzoate ester. Previous experiments had shown that when the hydroxyl group was modified as such that a catalytic quantity of the SnCl₄•bis-sulfonamide (214) complex could be employed.

When 252 was treated with benzoyl chloride and pyridine in CHCl₃ product 254 was obtained in near quantitative yield. The Baeyer–Villiger oxidation was again attempted using this intermediate. Exposure of 254 to a catalytic quantity of the SnCl₄•bis-sulfonamide complex (0.5 equiv) with added K₂CO₃ and 2.5 equivalents of bis-TMS peroxide provided a complex mixture of products. These results suggest that the indole unit is responsible for the poor results of the Baeyer–Villiger oxidation. As such, the oxidation step must be run prior to the installation of the indole moiety.
Larock reported an efficient synthesis of indoles via a palladium-catalyzed heteroannulation of internal alkynes. A wide variety of internal alkynes have been successfully employed in this process. Additionally, the annulation of unsymmetrical alkynes has proven to be highly regioselective, with the more sterically bulky group on the alkyne ending up nearer to indole nitrogen. An excellent directing group in the annulation step is a TMS group, located on the alkyne terminus. As discussed in Chapter 4, TMS propargyl bromide can be used with success in the PTC glycolate alkylation reaction and therefore represents a possible alternative for the synthesis of kurasoin B.

**Figure 6.11.** Exploration of Pd-catalyzed indole formation.

In an exploration of this potential route, product 256 was obtained by employing the PTC alkylation of 209 with (3-bromoprop-1-ynyl)trimethylsilane. Alkyne 256 was then treated with catalytic palladium (II) acetate, 2-idoaniline, LiCl and Na₂CO₃ in DMF at 90 °C overnight. This procedure provided indole adduct 257 cleanly in 69% yield. This process provides hope that kurasoin B can be obtained using this alternative pathway. Studies are currently in progress using this avenue for the total synthesis of kurasoin B.
6.5. References and Notes


   Omura, S. *J. Antibiotics* **1997**, *50*, 453. (b) Hirose, T.; Sunazuka, T.; Zhi-Ming,
   T.; Handa, M.; Uchida, R.; Shiomi, K.; Harigaya, Y.; Omura, S. *Heterocycles*

3. For the preparation of benzyl lithium, see: Bernardi, L.; Bonini, B. F.; Dessole,


6. For excellent examples using these groups, see: (a) Jones, T. K.; Reamer, R. A.;

7. For the preparation of *p*-methoxybenzyltrichloroacetimidate, see: (a) Audia, J. E.;
   54*, 3738. (b) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Daeffler, R.; Osmani,


Chapter 7. Experimental Details and Data

7.1. General Methods and Materials

Air and water sensitive reactions were performed in flame-dried glassware under a nitrogen atmosphere. Air and moisture sensitive reagents were introduced via dry syringe or cannula. Methylene chloride, toluene, THF, diethyl ether, DMSO, DMF, methanol, triethylamine and acetonitrile were dried by passing through columns of activated alumina. Chloroform, benzene and pyridine were stored over molecular sieves. Reagents were purchased from Aldrich, Lancaster and TCI America. Flash chromatography was carried out using 60-230 mesh silica gel. Radial chromatography was performed using 1, 2, and 4 mm plates loaded with 230-400 mesh PF-254 gypsum bound silica. Analytical thin-layer chromatography (TLC) was performed with Merck silica gel 60 F\textsubscript{254}, 0.25 mm pre-coated TLC plates. TLC plates were visualized using UV\textsubscript{254} and cerium molybdate with charring. All \textsuperscript{1}H NMR spectra were obtained with either 200, 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), ABq (AB quartet) obs (obscured); and coupling constants are reported in hertz (Hz). \textsuperscript{13}C NMR spectra were obtained with either 75 or 125 MHz Varian spectrometers using chloroform (77.2 ppm) as the internal standard. Infrared spectra were obtained on a Perkin Elmer FTIR instrument. Mass spectral data (HRMS, CI, EI, FAB) were obtained from the Brigham Young University mass spectrometry facility. Optical rotations were obtained with 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.

### 7.2. Geldanamycin Oxidation Model

![Chemical structures](image)

**Preparation of (+)-Geldanamycin (1) and (-)-ortho-Quinone Geldanamycin (111).**

To a solution of alcohol 71 (0.013 g, 0.022 mmol) and 0.68 mL of glacial acetic acid in a 10 mL round bottom flask at ambient temperature was added 0.068 mL of 70% HNO₃ drop wise. The solution immediately turned yellow and then gradually to red-orange. The mixture was allowed to stir for 1 min further before being diluted with EtOAc (3 mL) and then quenched by the careful addition of saturated NaHCO₃ solution (3 mL). The mixture was allowed to stir until the evolution of gas had ceased and then the organic layer was removed and added to a 25 mL separatory funnel containing 5 mL of saturated NaHCO₃ solution. Again 3 mL of EtOAc was allowed to stir in the round bottom flask and the organic layer was removed and added to the separatory funnel. The mixture in the separatory funnel was carefully mixed until gas evolution had ceased and the layers were separated. This entire process was repeated 4 times and the combined organic layers were then dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude residue was then purified via prep TLC (two 0.25 mm precoated TLC plates, 75% EtOAc/hexanes) to
provide (+)-geldanamycin 1, 0.6 mg (5%), as an orangish-yellow solid, and (-)-ortho-quinone-geldanamycin 111, 6.2 mg (50%), as a red-orange solid. The data are: (+)-
geldanamycin 1 TLC $R_f = 0.40$ (75% EtOAc/hexanes), authentic sample $R_f = 0.40$ (75%
EtOAc/hexanes); $[\alpha]_D^{23} = +29.7^\circ$ (c 0.064, CHCl$_3$), lit. $[\alpha]_D^{25} = + 55^\circ$ (c 0.64, CHCl$_3$); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.71 (bs, 1H), 7.29 (s, 1H), 6.94 (bd, $J = 12.0$ Hz, 1H), 6.57 (t, $J = 11.0$ Hz, 1H), 5.88 (t, $J = 10.5$ Hz, 1H), 5.19 (s, 1H), 5.00-4.50 (bs, 2H), 4.31 (d, $J = 9.5$ Hz, 1H), 4.13 (s, 3H), 3.55-3.52 (m, 1H), 3.40-3.38 (m, 1H), 3.36 (bs, 3H), 3.30 (s, 3H), 3.07-3.06 (m, 1H), 2.81- 2.69 (m, 1H), 2.50 (dd, $J = 9.0$, 13.0 Hz, 1H), 2.43 (dd, $J = 3.5$, 13.0 Hz, 1H), 2.03 (s, 3H), 1.84- 1.81 (obscured m, 1H), 1.79 (app d, $J = 1.0$ Hz, 3H), 1.78-1.74 (m, 1H), 1.69-1.62 (m, 1H), 0.97 (app t, $J = 7.5$ Hz, 6H); UV-Vis $\lambda_{max} = 260, 311, 405$ nm (CHCl$_3$) HRMS (FAB$^+$) found 583.2632 [M$^+$+Na$^+$], calcd 583.2631 for
C$_{29}$H$_{40}$N$_2$O$_9$Na.  (-)-ortho-quinone-geldanamycin 111 TLC $R_f = 0.10$ (75%
EtOAc/hexanes); $[\alpha]_D^{22} = -26.7^\circ$ (c .015, CHCl$_3$); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.49 (bs, 1H), 7.27 (s, 1H), 6.88 (bd, $J = 12.0$ Hz, 1H), 6.52 (t, $J = 11.5$ Hz, 1H), 5.92 (app t, $J = 11.0$ Hz, 1H), 5.52 (d, $J = 9.5$ Hz,1H), 5.22 (bs, 1H), 5.00-4.50 (bs, 1H), 4.34 (bd, $J = 7.0$ Hz, 1H), 3.94 (s, 3H), 3.66-3.58 (m, 1H), 3.36 (bs, 3H), 3.35 (s, 3H), 3.31-3.65 (obscured m, 1H), 3.21-3.16 (m, 1H), 2.88-2.79 (m, 1H), 2.62-2.55 (m, 1H), 2.39-2.33 (m, 1H), 2.05 (s, 3H), 1.89-1.81 (obscured m, 1H), 1.76 (s, 3H), 1.42-1.47 (m, 2H), 1.02 (d, $J = 6.0$ Hz, 3H), 0.96 (d, $J = 6.5$ Hz, 3H); UV-Vis $\lambda_{max} = 266, 303, 439$ nm (CHCl$_3$); HRMS (FAB$^+$) found 585.2780 [M$^+$+Na$^+$+2H]$^+$ (for dihydroquinone), calcd 585.2789
C$_{29}$H$_{44}$N$_2$O$_9$Na.
Model Oxidation System (110). To a stirring solution of 109 (0.020 g, 0.062 mmol) in 1,4-dioxane (4.0 ml) was added AgO (0.031 g, 0.248 mmol) and an aqueous 1 M solution of HNO₃ (0.25 mL). The mixture was then stirred at ambient temperature for 15 minutes before being diluted with a 1:1 mixture of saturated aqueous solutions of NaCl/NaHCO₃ (10 mL). The mixture was then diluted further with EtOAc (10 mL) and the layers were separated. The aqueous phase was then extracted with additional EtOAc (3x10 mL), the combined organic layers were then dried over Na₂SO₄, filtered and concentrated. The crude residue was then purified by preparative TLC (EtOAc). The title compound was obtained in approx. quantitative yield. A crystal of analytical purity sufficient for X-Ray crystallography was obtained when crystals were grown in EtOAc/Hexanes. Data for ortho-110 are: "H NMR (CDCl₃, 500 MHz) δ 8.00 (s, 1H), 7.41 (s, 1H), 4.09 (s, 3H), 3.69 (s, 3H), 2.56 (t, J = 8.0 Hz, 2H), 2.42 (t, J = 7.0 Hz, 3H), 2.28 (s, 3H), 1.84-1.78 (m, 2H); "C NMR (CDCl₃, 125 MHz) δ 180.3, 179.7, 173.8, 169.3, 158.4, 143.9, 127.1, 109.4, 63.0, 51.8, 33.6, 25.7, 23.9, 23.6; UV-Vis λₘₐₓ = 242, 300, 431 nm (CHCl₃); HRMS (EI⁺) found 297.1211 [M⁺+ 2H]⁺ (for hydroquinone), calcd 297.1212 for C₄H₁₉NO₆, and found 295.1067 M⁺ (for quinone), calcd 295.1056 for C₄H₁₇NO₆.
2,4-Dimethoxy-1-methoxymethoxy-benzene (156). To a flame dried 500 mL round bottom flask was added NaH (1.97 g, 77.8 mmol) followed by DMF (150 mL). The solution was then stirred and cooled to 0 °C under a nitrogen atmosphere. Then 2,4-dimethoxyphenol 155 (6.0 g, 38.9 mmol) was added to the stirring suspension in one portion. The reaction mixture was then warmed to ambient temperature and stirred for 30 min. The solution was then cooled to 0 °C again and chloromethyl methyl ether (5.91 mL, 77.84 mmol) was carefully added dropwise. After 30 min of additional stirring the solution was allowed to warm to ambient temperature and stirred for an additional 13.5 h. The reaction mixture was again cooled to 0 °C and then quenched by the addition of 50 mL of a saturated NaHCO₃ solution and then 50 mL of H₂O. The resulting mixture was then extracted (4 x 75 mL) with EtOAc. The combined organic layers were then washed with H₂O, a saturated NaCl solution and then dried over MgSO₄. The solution was then filtered and the solvent removed in vacuo. The crude product was purified by column chromatography (30% EtOAc/hexanes) to provide 6.98 g (90%) of the desired compound as a faint yellow oil. Data are: ¹H NMR (CDCl₃, 300 MHz) δ 7.06 (d, J = 8.7 Hz, 1H), 6.52 (d, J = 2.7 Hz, 1H), 6.39 (dd, J = 11.4 Hz, 2.7 Hz, 1 H) 5.14 (s, 2H), 3.85 (s, 3H), 3.78 (3H), 3.52 (s, 3H) ; ¹³C NMR (CDCl₃, 50 MHz) δ 155.7, 151.0, 140.6, 118.0, 103.4, 100.3, 96.4, 56.1, 55.8, 55.6.
2,6-Dimethoxy-3-methoxymethoxy-benzaldehyde (157). To a flame dried 100 mL round bottom flask was added 156 (0.500 g, 2.53 mmol). Then 25 mL of THF was added followed by TMEDA (0.460 mL, 3.04 mmol). The solution was then cooled to 0 °C at which time n-BuLi (1.9 mL, 1.6 M Hexanes) was added dropwise. The reaction was then allowed to slowly warm to ambient temperature and then stirred for 4 h. Then DMF (0.785 mL, 10.12 mmol) was added dropwise to the stirring solution. The resulting clear, light green solution was then stirred for 1 h. Then 3 mL of 0.5 M HCl was added and the clear yellow/orange solution stirred for 5 min. Next 10 mL of H₂O was added and the solution was extracted (4 x 20 mL) with Et₂O. The combined Et₂O layers were then washed with a sat NaCl solution and dried over MgSO₄. The solution was then filtered and the solvent removed. The crude oil was initially purified by radial chromatography (4mm plate, 30% EtOAc/hexanes) to provide only 0.205 g of the title compound. Impure fractions were combined and subjected to column chromatography (20% EtOAc/hexanes) to provide an additional 0.197 g (0.402 g total, 70%) of the desired compound as a yellow oil which solidified upon exposure to cold conditions. Data are: TLC Rₚ = 0.24 (30% EtOAc/hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 10.45 (s, 1H), 7.33 (d, J = 9.0 Hz, 1H), 6.65 (d, J = 9.0 Hz, 1H), 5.15 (s, 2H), 3.94 (s, 3H), 3.86 (s, 3H), 3.53 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 189.6, 156.5, 153.1, 144.2, 124.5, 119.7, 106.8, 96.4, 62.3, 56.4, 56.3.
2,6-Dimethoxy-3-methoxymethoxy-5-nitro-benzaldehyde (158). A flame dried 25 mL round bottom flask was charged with 2,6-dimethoxy-3-methoxymethoxy-benzaldehyde (1.07 g, 4.71 mmol) and 5 mL CH₃CN. The solution was then cooled to 0 °C and with stirring NH₄NO₃ (0.40 g, 4.95 mmol) was added in one portion. This was followed by the dropwise addition of trifluoroacetic anhydride (2.30 ml, 16.48 mmol). The reaction was then stirred at 0 °C for 12 min, at which time it was transferred directly to a separatory funnel containing H₂O and CH₂Cl₂. The organic layer was removed and the aqueous phase extracted further with CH₂Cl₂. The combined organic layers were washed with a copious amount of a saturated NaHCO₃ solution followed by a saturated NaCl solution. The resulting organic phase was dried over MgSO₄, filtered, and the solvent reduced to ~5 mL by evaporation. The mixture was then purified via flash chromatography (5:1:4, CH₂Cl₂: Et₂O: hexanes) to afford 1.13 g (88%) of the title compound as fluffy pale yellow needles. Data are: TLC Rₜ = 0.38 (5:1:4, CH₂Cl₂:Et₂O: hexanes); ¹H NMR (CDCl₃, 200 MHz) δ 10.39 (s, 1H), 7.91 (s, 1H), 5.27 (s, 2H), 4.06 (s, 3H), 3.99 (s, 3H), 3.54 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 188.1, 156.4, 149.8, 146.4, 139.4, 125.4, 117.6, 95.8, 65.0, 62.8, 56.9; HRMS (EI⁺) found 271.0696 M⁺, calcd 271.0692 for C₁₁H₁₃NO₇.
(2,6-Dimethoxy-3-methoxymethoxy-5-nitro)benzyl alcohol. To a flame dried 25 mL round bottom flask was added 158 (0.500 g, 1.85 mmol) and 9.25 mL of THF. To this stirring solution at ambient temperature was added NaBH₄ (0.07 g, 1.85 mmol) in one portion. The solution was stirred for 1 h at which time 5 mL H₂O was added followed by 0.5 mL of 0.5 M HCl. The solution was allowed to stir for 10 min at which time 10 mL of Et₂O was added and the layers separated. The aqueous phase was extracted further with Et₂O and the combined Et₂O layers were washed with a saturated NH₄Cl solution. The organic layer was then dried over MgSO₄, filtered and the solvent removed in vacuo to provide 0.498 g (99%) of the title compound as a light orange oil. Data are: TLC Rᵣ = 0.26 (50% EtOAc/hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 7.70 (s, 1H), 5.21 (s, 2H), 4.72 (bs, 2H), 3.99 (s, 3H), 3.91 (s, 3H), 3.50 (s, 3H) 2.65-2.75 (bs, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 153.6, 148.2, 146.0, 130.5, 113.2, 95.6, 68.0, 63.9, 61.9, 56.7, 55.1.

3-Bromomethyl-2,4-dimethoxy-1-methoxymethoxy-5-nitro-benzene (159b, R=Me). A 100 mL flame dried round bottom flask was charged with LiBr (3.14 g, 36.10 mmol) and 9.9 mL of THF. To this stirring solution was added freshly distilled NEt₃ (1.26 mL, 9.03 mmol). Then a solution of (2,6-dimethoxy-3-methoxymethoxy-5-nitro)benzyl alcohol (0.986 g, 3.61 mmol) in 9.9 mL of THF is added. The mixture was then stirred at ambient
temperature until LiBr had completely dissolved. Then the solution was cooled to 0 °C and methane sulfonyl chloride (0.590 mL, 7.58 mmol) was added dropwise. The reaction was stirred at 0 °C for 2 h at which time it was quenched by the addition of H₂O. The resulting solution was extracted 3 times with Et₂O. The combined Et₂O layers were then washed with a saturated NaHCO₃ solution and then a saturated NaCl solution. The organic phase was then dried over MgSO₄, filtered and the solvent removed in vacuo. The crude mixture was purified by column chromatography (30% EtOAc/hexanes) to provide 1.08 g (88%) of the title compound. Data are: TLC Rf = 0.44 (30% EtOAc/hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 7.78 (s, 1H), 5.25 (s, 2H), 4.62 (s, 2H), 4.12 (s, 3H), 4.02 (s, 3H), 3.54 (s, 3H); HRMS (EI⁺) found 335.0017 M⁺, calcd 335.0005 for C₁₁H₁₄O₆NBr.

(4S)-4-Benzyl-3-[3-(2,6-dimethoxy-3-methoxymethoxy-5-nitro-phenyl)-(2R)-2-methyl-propionyl]-oxazolidin-2-one (160b, R = Me). To a flame dried 50 mL round bottom flask was added (4S)-4-benzyl-3-propionyl-oxazolidin-2-one (82) (0.678 g, 2.91 mmol) and 10 mL of THF. The stirring solution was then cooled to −78 °C under a nitrogen atmosphere. Then NaHMDS (3.20 mL, 1.0 M THF) was added dropwise. The solution was then allowed to stir at −78 °C for 10 min. Then 159b (R= Me) (1.075 g, 3.199 mmol) was added as a solution in THF (6 mL). Stirring continued for an additional 4 h before being quenched by the addition of a saturated NH₄Cl solution (5 mL). Upon
warming to ambient temperature the solution was diluted with 20 mL of Et₂O and 10 mL of a saturated NH₄Cl solution. The organic layer was then removed and the aqueous layer was extracted with Et₂O (3 x 25 mL). The combined organic layers were then dried over MgSO₄, filtered, and concentrated. The crude reaction materials were the purified via flash chromatography (30% EtOAc/hexanes) to provide 1.24 g (87%) of the desired compound as a >20:1 mixture of diastereomers and as a light yellow, sticky foam. Data are: TLC Rf = 0.18 (30% EtOAc/hexanes); [α]D²² = +19.5° (c 0.24, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) 7.66 (s, 1H), 7.35-7.20 (m’s, 5H), 5.22 (s, 2H), 4.70-4.62 (m, 1H), 4.20-4.10 (m, 3H) 4.00 (s, 3H), 3.86 (s, 3H), 3.52 (s, 3H), 3.33 (dd, J = 13.2 Hz, 3.3 Hz, 1H), 3.11 (dd, J = 13.2 Hz, 6.6 Hz, 1H), 3.01 (dd, J = 13.2 Hz, 8.1 Hz, 1H), 2.73 (dd, J = 13.5 Hz, 9.9 Hz, 1H) 1.17 (d, J = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 176.8, 153.9, 153.1, 148.7, 145.7, 138.5, 135.7, 129.6, 129.1, 127.4, 112.1, 95.7, 66.2, 62.7, 61.3, 56.7, 55.6, 37.8, 37.6, 28.0, 17.5; HRMS (EI⁺) found 488.1788 M⁺, calcd 488.1795 for C₂₄H₂₈N₂O₉.

3-(2,6-Dimethoxy-3-methoxymethoxy-5-nitro-phenyl)-(2R)-2-methyl-propan-1-ol (161b, R= Me). A 50 mL flame dried conical flask containing 160b (0.165 g, 0.338 mmol) and 6.75 mL Et₂O was cooled to 0 °C under a nitrogen atmosphere. Then with stirring LiBH₄ (0.015 g, 0.676 mmol) was added in one portion. The reaction stirred at 0 °C for 1 h at which time it was quenched by the addition of 10 mL of a saturated NH₄Cl
solution and allowed to stir for an additional 20 min. The solution was then allowed to warm to ambient temperature at which point the mixture was extracted with Et₂O (3 x 10 mL). The combined organic layers were then washed with a saturated NaCl solution and then dried over MgSO₄. The mixture was then filtered and the solvent removed in vacuo. Purification via radial chromatography (1mm plate, gradient 30-40% EtOAc/hexanes) afforded 0.085 g (80%) of the title compound as a thick golden oil. Data are: TLC Rᵣ = 0.2 (40% EtOAc/hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 7.63 (s, 1H), 5.22 (s, 2H), 3.95 (s, 3H), 3.85 (s, 3H), 3.51 (s, 3H), 3.38 (d, J = 4.8 Hz, 2H), 2.73 (dd, J = 12.9 Hz, 8.1 Hz, 1H), 2.61 (dd, J = 12.9 Hz, 6.3 Hz, 1H), 2.19 (bs, 1H), 1.96-1.85 (m, 1H), 0.99 (d, J = 6.9 Hz, 3H); ¹³C NMR (CDCl₃) δ 153.3, 148.3, 146.0, 138.8, 130.9, 111.5, 95.6, 66.7, 62.8, 61.3, 56.7, 36.6, 27.9, 17.4.

4-(2,6-Dimethoxy-3-methoxymethoxy-5-nitro-phenyl)-(3R)-3-methyl-butyronitrile (162b). To a 500 mL round bottom flask containing primary alcohol 161b (R= Me) (1.86 g, 5.90 mmol) was added 20 mL of Et₂O. The solution was then cooled to 0 °C under a nitrogen atmosphere. Then with stirring triphenylphosphine (3.09 g, 11.8 mmol) was added followed by the dropwise addition of DEAD (1.86 mL, 11.8 mmol) over 10 min. The thick light yellow mixture was stirred for at least 10 min at which time acetone cyanohydrin (1.08 mL, 11.8 mmol) was added as an Et₂O (6.5 mL) solution. The mixture was allowed to stir at ambient temperature for 22 h. Then the entire reaction mixture was filtered directly over a silica plug eluting with 200 mL of 50% EtOAc/hexanes. The
resulting filtrate was then concentrated and the crude oil purified by flash chromatography (30% EtOAc/hexanes) to afford 1.242 g of the title compound. Impure fractions were concentrated and purified again using radial chromatography (2mm plate, 30% EtOAc/hexanes) to provide an additional 0.213 g (total 1.455 g, 76%) of the desired compound. Data are: TLC Rf = 0.3 (30% EtOAc/hexanes); 1H NMR (CDCl3, 500 MHz) δ 7.61 (s, 1H), 5.18 (s, 2H), 3.93 (s, 3H), 3.79 (s, 3H), 3.47 (s, 3H), 2.70 (dd, J = 12.5 Hz, 7.5 Hz, 1H), 2.66 (dd, J = 13.0 Hz, 6.5 Hz, 1H), 2.28 (dd, J = 16.5 Hz, 6.5 Hz, 1H), 2.23 (dd, J = 16.5 Hz, 6.5 Hz, 1H), 2.17-2.09 (m, 1H), 1.05 (d, J = 6.5 Hz, 3H); 13C NMR (CDCl3, 125 MHz) δ 153.2, 148.1, 145.7, 138.4, 129.1, 118.8, 111.7, 95.3, 62.4, 61.1, 56.5, 31.4, 30.5, 24.1, 19.6; HRMS (EI+) found 324.1321 M+, calcd 324.1321 for C_{15}H_{20}N_{2}O_{6}.

4-(2,6-Dimethoxy-3-methoxymethoxy-5-nitro-phenyl)-(3R)-3-methyl-butyraldehyde (163b). To a stirring solution of butyronitrile 162b (0.200 g, 0.617 mmol) in 7.7 mL of toluene at −78 °C was added DIBAL-H (1.23 mL, 1.0 M toluene) dropwise over 15 min. The solution was stirred for 20 min and then allowed to slowly warm to ambient temperature over at least 1 h. Then 0.3 mL of acetone, 0.3 mL of EtOAc, and 0.4 mL of pH 7 phosphate buffer were added in sequence. After 30 min of vigorous stirring a generous amount of anhydrous Na2SO4 was added followed by another 20 min of vigorous stirring. The entire reaction mixture was then filtered through a plug of silica gel over anhydrous Na2SO4. The plug was washed thoroughly with 50% EtOAc/hexanes. The
resulting filtrate was concentrated and then purified by radial chromatography (2mm plate, gradient 10-30% EtOAc/hexanes) to afford 0.145 g (72%) of the title compound as a thick golden oil. Data are: TLC R\textsubscript{f} = 0.32 (30% EtOAc/hexanes); \textsuperscript{1}H NMR (CHCl\textsubscript{3}, 300 MHz) \textdelta 9.72 (app t, J = 1.8 Hz, 1H), 7.67 (s, 1H), 5.23 (s, 2H), 3.96 (s, 3H), 3.84 (s, 3H), 3.53 (s, 3H), 2.67 (d, J = 6.6 Hz, 2H), 2.44-2.31 (m, 3H) 0.99 (d, J = 6.6 Hz, 3H); HRMS (EI\textsuperscript{+}) found 327.1317 M\textsuperscript{+}, calcd 327.1318 for C\textsubscript{15}H\textsubscript{21}NO\textsubscript{7}.

\begin{center}
\begin{tikzpicture}
\node (163b) at (0,0) {\begin{minipage}{0.4\textwidth}
\centering
\includegraphics[width=\textwidth]{163b}
\end{minipage}};
\node (164b) at (3,0) {\begin{minipage}{0.4\textwidth}
\centering
\includegraphics[width=\textwidth]{164b}
\end{minipage}};
\node (+) at (1.5,1) {\small (+) Ip\textsubscript{c}\textsubscript{2}B(allyl)};
\draw[->] (163b) -- (164b);
\end{tikzpicture}
\end{center}

7-(2,6-Dimethoxy-3-methoxymethoxy-5-nitro-phenyl)-(6R)-6-methyl-hept-1-en-(4R)-4-ol (164b, R= Me). To a flame dried 25 mL round bottom flask charged with (+)-Ipc\textsubscript{2}B(OMe) (0.375 g, 1.187 mmol) was added 6 mL of Et\textsubscript{2}O. Then with stirring the solution was cooled to –78 °C under a nitrogen atmosphere. Then allyl magnesium bromide (1.13 mL, 1.0 M Et\textsubscript{2}O) was added dropwise and the reaction stirred at –78 °C for 15 min then warmed to ambient temperature and stirred for an additional hour. The mixture with precipitated magnesium salts was cooled back down to –78 °C where the previous butyraldehyde (0.185 g, 0.565 mmol) was added dropwise as an Et\textsubscript{2}O (2.0 mL) solution. Stirring continued for 3 h at –78 °C and then 0.4 mL MeOH was added and the solution allowed to warm to ambient temperature. The reaction mixture was then filtered through a Buchner funnel to remove the magnesium salts. The magnesium salts were washed with Et\textsubscript{2}O and then ethanol amine (0.340 mL, 5.65 mmol) was added to the diluted reaction mixture. The mixture was then stirred for 18 h at ambient temperature.
Then 20 mL of a saturated NH₄Cl solution was added and the layers were separated. The aqueous phase was then further extracted with Et₂O. The combined organic layers were then washed with a saturated NaHCO₃ solution and dried over MgSO₄. The mixture was then filtered, the solvent removed in vacuo and the crude product purified using radial chromatography (1mm plate, 1:8:11 EtOAc:Et₂O:hexanes) to afford 0.172 g (82%) of the title compound as a 9:1 mixture of inseparable diastereomers. Data are: TLC Rᵣ = 0.3 (50% EtOAc/hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 7.64 (s, 1H), 5.90-5.76 (m, 1H), 5.22 (s, 2H), 5.16 (d, J = 1.2 Hz, 1H), 5.11 (d, J = 2.1 Hz, 1H), 3.94 (s, 3H), 3.84 (s, 3H), 3.82-3.75 (obs m, 1H), 3.53 (s, 3H), 2.69 (dd, J = 12.3 Hz, 6.0 Hz, 1H), 2.57 (dd, J = 12.6 Hz, 8.1 Hz, 1H), 2.35-2.27 (m, 1H), 2.20-2.04 (m, 2H), 1.55-1.44 (m, 2H), 1.38-1.26 (m, 1H), 0.89 (d, J = 6.6 Hz, 3H); HRMS (FAB⁺) found 392.1693 [M⁺+Na]⁺, calcd 392.1686 for C₁₈H₂₇NO₇Na.

tert-Butyl-{(1R)-1-[3-(2,6-dimethoxy-3-methoxymethoxy-5-nitro-phenyl)-(2R)-2-methyl-propyl]-but-3-enyloxy}-dimethyl-silane (165b). To a 25 mL round bottom flask containing the previous homoallylic alcohol 164b (R= Me) (0.021 g, 0.056 mmol) was added 0.40 mL of CH₂Cl₂. Then the solution was cooled to 0 °C under a nitrogen atmosphere. Then with stirring 2,6-lutidine (0.016 mL, 0.140 mmol) was added followed by TBDMSOTf (0.019 mL, 0.084 mmol). The mixture was then stirred for 1 h at 0 °C and then 1 h at ambient temperature. The reaction was then diluted with a saturated
NH₄Cl solution and the layers separated. The aqueous phase was further extracted with CH₂Cl₂. The combined CH₂Cl₂ layers were then dried over MgSO₄, filtered, and the solvent removed in vacuo. The crude oil was then purified by radial chromatography (1mm plate, 10% EtOAc/hexanes) to provide 0.026 g (96%) of the title compound as a faint yellow oil. Data are: TLC R_f = 0.3 (10% EtOAc/hexanes); [α]D²³ = −13.6° (c 0.5, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 7.62 (s, 1H), 5.86-5.72 (m, 1H), 5.21 (s, 2H), 5.04 (d, J = 4.5 Hz, 1H), 5.00 (s, 1H), 3.93 (s, 3H), 3.82 (s, 3H), 3.8 (obs m, 1H), 3.52 (s, 3H), 2.62 (dd, J = 12.6 Hz, 6.0 Hz, 1H), 2.51 (dd, J = 12.3 Hz, 8.4 Hz, 1H), 2.23 (app t, J = 6.3 Hz, 2H), 1.99 (m, 1H), 1.51-1.42 (m, 1H), 1.36-1.21 (m, 1H), 0.85 (s, 9H), 0.82 (d, J = 6.6 Hz, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 153.6, 148.7, 145.8, 138.7, 135.4, 131.4, 116.9, 111.5, 95.7, 70.1, 62.5, 61.1, 56.7, 44.7, 42.7, 32.5, 29.9, 26.0, 19.8, 18.2, -4.1, -4.4; HRMS (FAB⁺) found 506.2546 [M⁺+Na]⁺, calcd 506.2550 for C₂₄H₄₁NO₇SiNa.

3-[(4R)-4-(tert-Butyl-dimethyl-silanyloxy)-(2R)-2-methyl-heptyl]-2,4-dimethoxy-5-methoxymethoxy-phenylamine (166b). To a 50 mL round bottom flask containing the previous TBS protected alcohol 165b (0.173 g, 0.358 mmol) was put under vacuum and then filled with H₂ three times. Then 6.0 mL of absolute ethanol was added followed by activated Pd/C (0.027 g). The system was then put under vacuum and then filled with H₂.
three times. The solution was then stirred vigorously for 5 hours under a hydrogen atmosphere. The entire reaction mixture was then filtered directly over a silica gel plug, eluting with Et$_2$O. The filtrate was then taken and the solvent removed \textit{in vacuo}. The crude mixture was then purified by radial chromatography (2mm, 20% EtOAc/hexanes) to afford 0.144 g (88%) of the title compound as a golden oil. Data are: TLC $R_f = 0.2$ (20% EtOAc/hexanes); $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 6.48 (s, 1H), 5.14 (s, 2H), 3.78 (obs m, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.61 (s, 2H), 3.51 (s, 3H), 2.58 (dd, $J = 12.6$ Hz, 5.7 Hz, 1H), 2.40 (dd, $J = 12.3$ Hz, 8.7 Hz, 1H), 2.03 (m, 1H), 1.55-1.23 (m, 6H), 0.89 (d, $J = 3$ Hz, 3H), 0.87 (s, 9H), 0.83 (d, $J = 6.6$ Hz, 3H), 0.04 (s, 6H); HRMS (FAB+) found 455.3063 $M^+$, calcd 455.3067 for C$_{24}$H$_{45}$NO$_5$Si.

(2E)-2-Methyl-but-2-enoic acid {3-[(4R)-4-(tert-butyl-dimethyl-silanyloxy)-(2R)-2-methyl-heptyl]-2,4-dimethoxy-5-methoxymethoxy-phenyl}-amide (167b, R= Me). To a 50 mL round bottom flask containing the previous aryl amine 166b (0.143 g, 0.314 mmol) was added 1.6 mL of THF. Then freshly distilled NEt$_3$ (0.109 mL, 0.786 mmol) was added and the mixture stirred at ambient temperature for 15 min. Then tiglic acid chloride (0.075 g, 0.628 mmol) was added as a THF (2.1 mL) solution. The reaction was then stirred at ambient temperature for 1 h. The reaction mixture was then poured into H$_2$O and the solution extracted with EtOAc 3 times. The combined organic layers were
washed with a saturated NH₄Cl solution and a saturated NaCl solution. The organic layer was then dried over MgSO₄, filtered, and the solvent then removed in vacuo. The crude oil was purified by radial chromatography (2mm plate, 20% EtOAc/hexanes) to provide 0.152 g (90%) of the title compound. Data are: TLC Rf = 0.5 (30% EtOAc/hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 8.09 (s, 1H), 7.92 (s, 1H), 6.57 (dq, J = 7.2 Hz, 1.2 Hz, 1H), 5.19 (s, 2H), 3.80 (s, 3H), 3.75 (obs m, 1H), 3.69 (s, 3H), 3.51 (s, 3H), 2.59 (dd, J = 12.9 Hz, 6.0 Hz, 1H), 2.42 (dd, J = 12.6 Hz, 8.4 Hz, 1H), 2.00 (obs m, 1H), 1.95 (s, 3H), 1.82 (dd, J = 6.9 Hz, 0.9 Hz, 3H), 1.50-1.19 (m, 6H), 0.88 (d, J = 3.0 Hz, 3H), 0.85 (s, 9H), 0.81 (d, J = 6.6 Hz, 3H), 0.02 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 167.0, 146.6, 145.0, 143.0, 132.6, 131.7, 128.2, 127.5, 107.6, 95.8, 70.4, 61.0, 60.9, 56.6, 45.2, 40.1, 32.5, 30.2, 26.0, 20.1, 18.6, 18.2, 14.5, 14.3, 12.5, -4.2, -4.3.

2-Methyl-but-(2E)-2-enoic acid [5-hydroxy-3-((4R)-4-hydroxy-(2R)-2-methylheptyl)-2,4-dimethoxy-phenyl]-amide (168). To a 25 mL round bottom flask containing the previous aryl amide 167b (R= Me)(0.048 g, 0.089 mmol) and 8.90 mL of CH₂Cl₂ was added a freshly prepared solution of (9:1, v:v) trifluoroacetic acid:H₂O (0.900 mL). The reaction was allowed to stir for 3 h at ambient temperature, at which time the reaction was quenched by the addition of a saturated NaHCO₃ solution (20 mL). The layers were then separated and the aqueous phase was further extracted with EtOAc. The combined
EtOAc layers were then dried over MgSO₄, filtered and concentrated in vacuo. The crude residue was purified by radial chromatography (1mm plate, 50 % EtOAc/hexanes) to afford 0.022 g (65%) of the desired compound. Also obtained was 0.008 g (18%) of the MOM deprotected phenol without removal of the TBS group. Data are: ¹H NMR (CDCl₃, 500 MHz) δ 8.08 (s, 1H), 8.04 (s, 1H), 7.60 (bs, 1H), 6.59 (q, J = 7 Hz, 1H), 3.81 (s, 3H), 3.77-3.72 (obs m, 1H), 3.70 (s, 3H), 2.65 (dd, J = 13.0 Hz, 6.5 Hz, 1H), 2.52 (dd, J = 13.0 Hz, 8.0 Hz, 1H), 2.10-2.05 (m, 1H), 1.98 (s, 3H), 1.84 (d, J = 6.5 Hz, 3H), 1.48-1.23 (m’s, 7H), 0.92 (app t, J = 6.5 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H).

2-Methoxy-1,4-bis-methoxymethoxy-benzene (149). To a flame dried 500 mL round bottom flask was added NaH (3.61 g, 142.8 mmol) and 100 mL of DMF. The stirring solution was then cooled to 0 °C and methoxyhydroquinone (5.0 g, 35.7 mmol) was added as a solution in DMF (50 mL). Rinsing the flask containing the hydroquinone with an additional 10 mL of DMF completed the addition. The mixture was then warmed to ambient temperature and stirred for 0.5 h. The solution was again cooled to 0 °C and then chloromethyl methyl ether (10.85 mL, 142.8 mmol) was added dropwise to the stirring solution. The reaction mixture was stirred for 0.5 h at which time it was warmed to ambient temperature where it stirred for an additional 1 h. The reaction was again cooled to 0 °C where it was quenched by the addition of H₂O (50 mL) followed by a saturated NaHCO₃ solution (50 mL). The solution was then extracted with EtOAc (5 x 75 mL),
washed with a saturated NaCl solution (150 mL) and then dried over MgSO₄. The mixture was then filtered and the solvent removed in vacuo. The crude oil was purified by column chromatography (20% EtOAc/hexanes) to provide 7.69 g (94%) of the desired compound as a light yellow oil. Data are: TLC Rᵣ = 0.41 (20% EtOAc/hexanes); ¹H NMR (CDCl₃, 200 MHz) δ 7.02 (d, J = 8.8 Hz, 1H), 6.62 (d, J = 2.5 Hz, 1H), 6.54 (dd, J = 8.8, 3.0 Hz, 1H), 5.20 (s, 2H), 5.10 (s, 2H), 3.82 (s, 3H), 3.49 (s, 3H), 3.45 (s, 3H); ¹³C NMR (CDCl₃, 50 MHz) δ 153.2, 150.8, 141.5, 139.3, 117.9, 107.1, 102.0, 96.3, 95.1, 56.1, 55.9; HRMS (EI⁺) found 228.0991 M⁺, calcld 228.0998 for C₁₁H₁₆O₅.

2-Methoxy-3,6-bis-methoxymethoxy-benzaldehyde (150). To a round bottom flask containing 2-methoxy-1,4-bis-methoxymethoxy-benzene 149 (7.99 g, 35.0 mmol) was added 117 mL of dry THF followed by TMEDA (6.34 mL, 42.0 mmol). The mixture stirred at ambient temperature for 10 minutes and then the solution was cooled to 0 °C under a nitrogen atmosphere. Then n-BuLi (26.25 mL, 1.6 M hexanes) was added dropwise to the stirring solution. The reaction mixture was removed from the ice bath and allowed to warm to ambient temperature; stirring continued for 4 h. To the resulting dark golden mixture was added DMF (10.8 mL, 140 mmol) dropwise. The reaction was allowed to stir for another 1 h at which time the reaction was acidified by the addition of a 0.5 M HCl solution until the reaction had a pH between 7 and 8. The reaction stirred for another 15 min at which time it was extracted with EtOAc (5 x 50 mL). The
combined EtOAc layers were then dried over MgSO₄, filtered and the solvent removed in vacuo. The crude oil was purified by column chromatography (40% EtOAc/hexanes) to afford 7.14 g (79%) of the desired compound as a yellow oil. Data are: \(^1\)H NMR (CDCl₃, 200 MHz) \(\delta\) 10.47 (s, 1H), 7.31 (d, \(J = 9.2\) Hz, 1H), 6.90 (d, \(J = 9.2\) Hz, 1H), 5.22 (s, 2H), 5.17 (s, 2H), 3.95 (s, 3H), 3.53 (s, 3H), 3.51 (s, 3H); HRMS (EI⁺) found 256.0941 M⁺, calcld 256.0947 for C\(_{12}\)H\(_{16}\)O\(_6\).

**3-Hydroxy-2-methoxy-6-methoxymethoxy-5-nitro-benzaldehyde (151).** A 500 mL round bottom flask containing 150 (7.05 g, 27.5 mmol) was cooled to 0 °C and then 13.7 mL of glacial acetic acid was added. Then immediately following, a premixed solution of glacial acetic acid (54.4 mL) and 70% nitric acid (14.3 mL) was added. The reaction stirred for precisely 5 min, at which time the ice bath was replaced by a clean glass dish. The reaction was then rapidly quenched with the careful addition of a saturated NaHCO₃ solution until bubbling ceased. The product precipitated out of the solution with the gas evolution, while the spill over from the round bottom was collected by the glass dish. Then CH\(_2\)Cl\(_2\) was added to the round bottom and the glass dish, the combined contents were then extracted with CH\(_2\)Cl\(_2\) (6 × 75 mL). The combined CH\(_2\)Cl\(_2\) layers were then dried over MgSO₄, filtered and the solvent removed in vacuo to afford 5.44 g (76%) of a single mono deprotected product, as orange flakes, which is assumed to be the title compound. Data are: \(^1\)H NMR (CDCl₃, 300 MHz) \(\delta\) 12.53 (s, 1H), 10.33 (s, 1H), 8.16 (s, 1H), 5.21 (s, 2H), 4.19 (s, 3H), 3.54 (s, 3H); \(^1^3\)C NMR (CDCl₃, 75 MHz) \(\delta\) 193.9, 158.8,
153.2, 140.9, 130.8, 122.3, 115.5, 96.4, 62.9, 56.9; HRMS (EI) found 257.0536 M⁺, calcd 257.0536 for C₁₀H₁₁NO₇.

2-Methoxy-3,6-bis-methoxymethoxy-5-nitro-benzaldehyde (152). To a flame dried 50 mL round bottom flask was added KH (0.210 g, 1.56 mmol) as a 30 wt% suspension in mineral oil. The suspension was washed with dry hexanes (2 x 3 mL), and the residual hexanes were removed by vacuum. Then 7.8 mL of THF was added followed by cooling to 0 °C. Then with stirring the solid, nitro phenol 151 (0.200 g, 0.78 mmol) was added in one portion. Then n-Bu₄NI (0.03 g, 0.078 mmol) was added and the mixture was warmed to ambient temperature. After 0.5 h of stirring the solution was again cooled to 0 °C and chloromethyl methyl ether (0.120 mL, 1.56 mmol) was added dropwise to produce a red/orange mixture. The reaction stirred at 0 °C for 30 min and then at ambient temperature for 50 h. The reaction was then quenched by the addition of a saturated NH₄Cl solution (5 mL) followed by H₂O (15 mL). The resulting mixture was then extracted with EtOAc (3 x 30 mL). The combined organic layers were then washed with H₂O (50 mL) and then a saturated NaCl solution (25 mL) and dried over MgSO₄. The mixture was then filtered and the solvent removed in vacuo. The crude oil was then purified using column chromatography (40% EtOAc/hexanes) to afford 0.186 g (79%) of the title compound as a pale yellow solid. Data are: TLC Rf = 0.43 (40% EtOAc/hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 10.32 (s, 1H), 7.84 (s, 1H), 5.25 (s, 2H),
5.08 (s, 2H), 4.03 (s, 3H), 3.51 (s, 3H), 3.49 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 188.3, 155.8, 146.7, 146.3, 140.3, 125.7, 117.0, 103.0, 95.7, 62.7, 58.2, 56.8; HRMS (FAB+) found 324.0704 [M+Na]$^+$, calcd 324.0696 for C$_{12}$H$_{15}$NO$_8$Na.

![Chemical Structure](image)

(2-Methoxy-3,6-bis-methoxymethoxy-5-nitro-phenyl)-methanol. A flame dried 100 mL round bottom flask was charged with 152 (0.760 g, 2.52 mmol) and 12.5 mL of THF. Then NaBH$_4$ was added in one portion and the reaction was stirred for 2.5 h at ambient temperature. The reaction was then quenched by the addition of 20 mL of H$_2$O followed by 7 mL of a 0.5 M HCl solution. The reaction mixture was then stirred for 15 min, at which time 30 mL of Et$_2$O was added. The layers were then separated and the aqueous phase extracted 3 times with Et$_2$O. The combined Et$_2$O layers were washed with a saturated NH$_4$Cl solution and dried over MgSO$_4$. The mixture was then filtered and the solvent removed in vacuo. The crude oil was then passed through a silica gel plug, eluting with EtOAc. The solvent was then removed from the filtrate to provide 0.715 g (94%) of the title compound as an orange oil which solidified upon exposure to cold conditions. Data are: $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 7.75 (s, 1H), 5.25 (s, 2H), 5.13 (s, 2H), 4.70 (d, $J$ = 7.2 Hz, 2H), 4.02 (s, 3H), 3.66 (s, 3H), 3.53 (s, 3H), 3.31 (t, $J$ = 7 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 153.7, 146.8, 146.3, 139.2, 131.7, 113.1, 102.1, 95.6, 62.3, 58.1, 56.7, 54.6.
3-Bromomethyl-2-methoxy-1,4-bis-methoxymethoxy-5-nitro-benzene (159a, R= MOM). To a flame dried 25 mL round bottom flask charged with LiBr (0.29 g, 3.29 mmol) was added 0.9 mL of THF. To this reaction mixture was added freshly distilled NEt₃ (0.115 mL, 0.82 mmol) followed by (2-methoxy-3,6-bis-methoxymethoxy-5-nitrophenyl)-methanol (0.10 g, 0.329 mmol) as a THF solution (0.9 mL). The mixture was stirred at ambient temperature until all the LiBr has dissolved, and then the reaction was cooled to 0 °C. Then methane sulfonyl chloride (0.054 mL, 0.822 mmol) was added dropwise to the stirring solution. The solution was stirred at 0 °C for 0.5 h and then quenched by the addition of H₂O. The mixture was then extracted 3 times with Et₂O and the combined organic layers were washed with a saturated NaHCO₃ solution followed by a saturated NaCl solution. The organic layer was then dried over MgSO₄, filtered and the solvent removed in vacuo. The crude oil was purified by radial chromatography (1mm plate, 30% EtOAc/hexanes) to provide 0.0822 g (69%) of the desired compound as a light orange oil. Data are TLC R̵ = 0.52 (30% EtOAc/hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 7.70 (s, 1H), 5.23 (s, 2H), 5.16 (s, 2H), 4.64 (s, 2H), 4.09 (s, 3H), 3.60 (s, 3H), 3.51 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 153.3, 146.4, 145.2, 139.7, 128.6, 113.4, 101.8, 95.6, 61.6, 58.1, 56.7, 22.0; HRMS (EI⁺) found 365.0108 M⁺, calcd 365.0110 for C₁₂H₁₆BrNO₇.
(4S)-4-Benzyl-3-[3-(2-methoxy-3,6-bis-methoxymethoxy-5-nitro-phenyl)-(2R)-2-methyl-propionyl]-oxazolidin-2-one (160a). To a flame dried 50 mL round bottom flask containing (4S)-4-benzyl-3-propionyl-oxazolidin-2-one (82) (0.31 g, 1.33 mmol) was added 4.5 mL of THF. Then with stirring the solution was cooled to –78 °C under a nitrogen atmosphere. Then NaHMDS (1.46 mL, 1.0 M THF) was added dropwise and the reaction was allowed to stir for 10 min. Then 159a (R= MOM) (0.536 g, 1.46 mmol) was added dropwise as a THF solution (3.0 mL). The stirring continued at –78 °C for 4 h at which time the reaction was quenched by the addition of 3 mL of a saturated NH$_4$Cl solution. The reaction was then allowed to warm to ambient temperature where it was diluted with an additional 5 mL of a saturated NH$_4$Cl solution and 10 mL of Et$_2$O. The layers were separated and the aqueous phase was extracted 3 times with Et$_2$O. The combined organic layers were then dried over MgSO$_4$, filtered and the solvent removed in vacuo. The crude oil was then purified using column chromatography (gradient 30 – 40% EtOAc/hexanes) to afford 0.594 g (86%) of the title compound as a golden foam.

The product was obtained with >16:1 ds as seen by $^1$H NMR. Data are: TLC R$_f$ = 0.29 (30% EtOAc/hexanes); [α]$_D^{23}$ = +2.57° (c 0.35, CHCl$_3$); $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.62 (s, 1H), 7.34-7.25 (m, 3H), 7.21-7.19 (m, 2H), 5.22 (s, 2H), 5.03 (s, 2H), 4.71-4.63 (m, 1H), 4.21-4.07 (m, 3H), 4.01 (s, 3H), 3.56 (s, 3H), 3.50 (s, 3H), 3.34 (dd, J = 13.5, 3.0 Hz, 1H), 3.16 (dd, J = 13.2, 6.6 Hz, 1H), 3.07 (dd, J = 13.2, 7.5 Hz, 1H), 2.72 (dd, J = 13.8, 9.9 Hz, 1H), 1.19 (d, J = 6.9 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 176.6, 153.4,
153.0, 146.0, 145.6, 139.5, 135.6, 129.4, 129.3, 128.9, 127.2, 111.5, 101.7, 95.4, 66.1, 61.2, 57.8, 55.4, 37.6, 28.4, 17.3; HRMS (EI) found 518.1907 M\(^+\), calcd 518.1900 for C\(_{25}\)H\(_{30}\)N\(_2\)O\(_{10}\).

3-(2-Methoxy-3,6-bis-methoxymethoxy-5-nitro-phenyl)-(2R)-2-methyl-propan-1-ol (161a, R= MOM). To a round bottom flask containing oxazolidinone 160a (0.576 g, 1.11 mmol) was added 22.0 mL of Et\(_2\)O. Then with stirring the solution was cooled to 0 °C and then LiBH\(_4\) (0.048 g, 2.22 mmol) was added in one portion. The mixture was then stirred for 1.5 h at 0 °C, at which time the reaction was quenched with 25 mL of a saturated NH\(_4\)Cl solution and allowed to warm to ambient temperature. The solution was stirred for 30 min and then extracted 3 times with Et\(_2\)O. The combined Et\(_2\)O layers were washed with a saturated NaCl solution and then dried over MgSO\(_4\). The mixture was then filtered, the solvent removed, and the crude oil purified by column chromatography (50% EtOAc/hexanes) to afford 0.287 g (75%) of the desired compound. The product was isolated as a light yellow/orange oil. Data are: TLC R\(_f\) = 0.26 (50% EtOAc/hexanes); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.59 (s, 1H), 5.21 (s, 2H), 5.01 (s, 2H), 3.93 (s, 3H), 3.56 (s, 3H), 3.50 (s, 3H), 3.39 (bs, 2H), 2.77 (dd, \(J = 12.9, 8.1\) Hz, 1H), 2.65 (dd, \(J = 12.9, 6.6\) Hz, 1H), 2.28 (bs, 1H), 1.99-1.89 (m, 1H), 0.98 (d, \(J = 6.9\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 153.0, 146.3, 145.4, 139.7, 131.2, 111.1, 101.9, 95.5, 66.6, 61.3, 58.0, 56.6, 36.5, 28.2, 17.3.
4-(2-Methoxy-3,6-bis-methoxymethoxy-5-nitro-phenyl)-(3R)-3-methyl-butyronitrile (162a). To a 100 mL round bottom flask containing 161a (R= MOM) (0.28 g, 0.81 mmol) was added 2.7 mL of Et₂O. The solution was then cooled to 0 °C and then with stirring triphenylphosphine (0.425 g, 1.624 mmol) was added followed by the dropwise addition of DEAD (0.255 mL, 1.624 mmol) over 5 min. The thick milky white mixture was stirred for at least 10 min then acetone cyanohydrin (0.148 mL, 1.624 mmol) was added as an Et₂O solution (0.95 mL). The solution was then allowed to stir at ambient temperature for 23 h. The entire reaction mixture was then filtered directly over a silica gel plug and washed with 50 mL of Et₂O. Removal of the solvent provided the crude product which was purified by column chromatography (5:1:4, CH₂Cl₂:Et₂O:hexanes) to provide 0.204 g (71%) of the title compound as a golden oil. Data are: TLC R_f = 0.38 (5:1:4, CH₂Cl₂:Et₂O:hexanes); [α]_D²³ = −24.9° (c 0.28, CHCl₃); ^1H NMR (CDCl₃, 300 MHz) δ 7.63 (s, 1H), 5.22 (s, 2H), 5.01 (ABq, 2H), 3.95 (s, 3H), 3.55 (s, 3H), 3.51 (s, 3H), 2.77 (d, J = 6.9 Hz, 2H), 2.29 (m, 2H), 2.26-2.15 (m, 1H), 1.11 (d, J = 6.6 Hz, 3H); ^13C NMR (CDCl₃, 75 MHz) δ 153.0, 146.2, 145.7, 139.5, 129.6, 118.9, 111.6, 102.0, 95.5, 61.2, 58.0, 56.7, 31.4, 31.1, 24.2, 19.8; HRMS (FAB+) found 377.1335 [M + Na⁺], calcd 377.1325 for C₁₆H₂₂O₇N₂Na.
4-(2-Methoxy-3,6-bis-methoxymethoxy-5-nitro-phenyl)-(3R)-3-methyl-butraldehyde (163a). To a 100 mL round bottom flask containing nitrile 162a (0.20 g, 0.565 mmol) was added 7.0 mL of toluene. Then with stirring the solution was cooled to −78 °C under a nitrogen atmosphere. Then DIBAL-H (1.13 mL, 1.0 M toluene) was added slowly over 10 min. The red/orange solution was then allowed to slowly warm from −78 °C to −20 °C over 1 h. The solution was then quenched by the sequential addition of 0.3 ml of acetone, 0.3 mL of EtOAc and 0.4 mL of pH 7 phosphate buffer. The solution was then warmed to ambient temperature where it stirred vigorously for 0.5 h. Then anhydrous powdered Na₂SO₄ was added and the solution stirred for 20 min. The entire reaction mixture was then filtered through a bed of silica gel over anhydrous Na₂SO₄ and washed with 50% EtOAc/hexanes. After generous washing the filtrate was concentrated and then purified using radial chromatography (2 mm plate, 30% EtOAc/hexanes) to afford 0.159 g (79%) of the desired compound as a viscous golden oil. Data are: TLC Rᵢ = 0.28 (30% EtOAc/hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 9.69 (app t, J = 2.1, 1H), 7.61 (s, 1H), 5.21 (s, 2H), 4.99 (ABq, 2H), 3.93 (s, 3H), 3.54 (s, 3H), 3.51 (s, 3H), 2.71 (d, J = 7.5 Hz, 2H), 2.49-2.24 (m, 3H), 0.98 (d, J = 6.3 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) 202.6, 153.1, 146.3, 145.7, 139.6, 130.5, 111.4, 101.9, 95.5, 61.2, 57.9, 56.7, 50.4, 31.8, 29.0, 20.4; HRMS (FAB+) found 380.1335 [M + Na⁺], calcd 380.1322 for C₁₆H₂₃NO₈Na.
7-(2-Methoxy-3,6-bis-methoxymethoxy-5-nitro-phenyl)-(6R)-6-methyl-hept-1-en-(4R)-4-ol (164a, R = MOM). To a flame dried 25 mL round bottom flask charged with (+)-Ipc₂B(OMe) (0.279 g, 0.882 mmol) was added 4.4 mL of Et₂O. Then with stirring the solution was cooled to −78 °C under a nitrogen atmosphere. Next, allyl magnesium bromide (0.840 mL, 1.0 M Et₂O) was added dropwise and the stirring continued at −78 °C for 15 min. The solution was then warmed to ambient temperature where it stirred for an additional 1 h. The solution was then cooled to −78 °C again and then (without removing the precipitated magnesium salts) the previous aldehyde (0.150 g, 0.420 mmol) was added as an Et₂O solution (1.4 mL). Stirring then proceeded at −78 °C for 4 h, at which time 0.4 mL MeOH was added. The solution was then warmed to ambient temperature and filtered through a buchner funnel to remove the white salts, and washed with dry Et₂O. Then with stirring ethanol amine (0.253 mL, 4.20 mmol) was added to the filtrate and stirring continued for 17 h. Then 15 mL of a saturated NH₄Cl solution was added and the layers separated. The aqueous phase was then extracted 1 time with Et₂O. The combined organic layers were then washed with a saturated NaHCO₃ solution and dried over MgSO₄. The mixture was then filtered, the solvent removed and the crude product purified by radial chromatography (2 mm plate, 1:8:11, EtOAc:hexanes:Et₂O) to afford 0.145 g (86%) of the desired compound as a golden oil. The product was obtained as a 5:1 mixture of inseperable diastereomers. Data are: TLC Rf = 0.30 (1:8:11, EtOAc:hexanes:Et₂O); [α]D²³ = −12.7° (c .27 CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ...
7.58 (s, 1H), 5.88-5.74 (m, 1H), 5.20 (s, 2H), 5.12-5.07 (m, 2H), 4.98 (s, 2H), 3.91 (s, 3H), 3.79-3.71 (m, 1H), 3.54 (s, 3H), 3.50 (s, 3H), 2.71 (dd, J = 12.6, 6.3 Hz, 1H), 2.61 (dd, J = 12.9, 8.4 Hz, 1H), 2.31-2.02 (m, 3H), 1.77-1.76 (m, 1H), 1.52-1.28 (m, 2H), 0.88 (d, J = 6.6 Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 153.2, 146.2, 145.7, 139.7, 135.1, 131.7, 118.1, 111.0, 101.7, 95.5, 68.6, 61.1, 57.9, 56.6, 44.3, 42.8, 32.8, 30.4, 19.5; HRMS (FAB+) found 422.1775 [M+Na\(^+\)], calcd 422.1791 for C\(_{19}\)H\(_{29}\)NO\(_8\).

tert-Butyl-\{(1R)-1-[3-(2-methoxy-3,6-bis-methoxymethoxy-5-nitro-phenyl)-(2R)-2-methyl-propyl]-but-3-enyloxy\}-dimethyl-silane (165a). To a 50 mL round bottom flask containing 164a (R= MOM) (0.133 g, 0.333 mmol) was added 2.5 mL of CH\(_2\)Cl\(_2\). Then 2,6-lutidene (0.097 mL, 0.833 mmol) was added and the reaction mixture cooled to 0 \(^\circ\)C. Then TBSOTf (0.115 mL, 0.500 mmol) was added dropwise to the stirring solution. The solution was stirred for 1.5 h, then another 0.5 eq of TBSOTf (0.040 mL, 0.17 mmol) was added. The mixture was then warmed to ambient temperature and stirred for 3 h. The reaction was then diluted with 10 mL of a saturated NH\(_4\)Cl solution and 10 mL CH\(_2\)Cl\(_2\). The layers were separated and the aqueous phase was extracted 2 times with CH\(_2\)Cl\(_2\). The combined organic layers were then dried over MgSO\(_4\), filtered and the solvent removed \(\textit{in vacuo}\). The crude oil was then purified by radial chromatography (2 mm plate, 10% EtOAc/hexanes) to afford 0.154 g (90%) of the title compound as a pale yellow oil. Data
are: TLC R_f = 0.35 (10% EtOAc/hexanes); ^1^H NMR (CDCl_3, 300 MHz) δ 7.59 (s, 1H), 5.86-5.72 (m, 1H), 5.21 (s, 2H), 5.06-4.95 (obs m, 2H), 4.99 (app d, J = 0.9 Hz, 2H), 3.92 (s, 3H), 3.82-3.76 (m, 1H), 3.55 (s, 3H), 3.52 (s, 3H), 2.67 (dd, J = 12.6, 6.3 Hz, 1H), 2.58 (dd, J = 12.6, 8.1 Hz, 1H), 2.23 (t, J = 6.6 Hz, 2H), 2.03 (s, 1H), 1.51-1.21 (m, 2H), 0.86 (s, 9H), 0.84 (d, J = 6.6 Hz, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^13^C NMR (CDCl_3, 75 MHz) δ 153.3, 146.2, 146.0, 139.7, 135.4, 131.8, 116.9, 111.1, 101.8, 95.6, 70.0, 61.0, 57.8, 56.7, 44.6, 42.8, 32.9, 29.9, 26.0, 19.7, 18.2, -4.1, -4.4; HRMS (FAB+) found 536.2659 [M+Na]^+ , calcd 536.2656 for C_{25}H_{43}O_8NSiNa.

3-[(4R)-4-(tert-Butyl-dimethyl-silanyloxy)-(2R)-2-methyl-heptyl]-4-methoxy-2,5-bismethoxymethoxy-phenylamine (166a). A 50 mL round bottom flask containing TBS protected alcohol 165a (0.149 g, 0.290 mmol) was put under high vacuum then filled with H_2 three times. Then 5.0 mL of absolute EtOH was added followed by activated Pd/C (0.022 g, 0.20 mmol). The system was then put under vacuum and filled with H_2 three more times. The solution was then stirred vigorously for 5 h under a H_2 atmosphere. The entire reaction mixture was then filtered through a silica gel plug and washed with Et_2O. The solvent was then removed from the filtrate and the crude product purified by radial chromatography (2 mm plate, 20% EtOAc/hexanes) to provide 0.121 g (87%) of the title compound as an off-white clear oil. Data are: TLC R_f = 0.25 (20%
EtOAc/hexanes); $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 6.47 (s, 1H), 5.14 (s, 2H), 4.92 (s, 2H), 3.80 (bs, 2H), 3.76 (obs m, 1H), 3.74 (s, 3H), 3.60 (s, 3H), 3.51 (s, 3H), 2.56 (dd, $J = 12.3, 5.7$ Hz, 1H), 2.42 (dd, $J = 12.6, 8.7$ Hz, 1H), 2.00 (m, 1H), 1.54–1.24 (m, 6H), 0.89 (app d, $J = 1.8$ Hz, 3H), 0.87 (s, 9H), 0.82 (d, $J = 6.6$ Hz, 3H), 0.03 (s, 6H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 147.5, 140.7, 139.0, 136.1, 129.4, 102.7, 99.7, 95.6, 70.5, 61.0, 57.5, 56.3, 45.3, 40.2, 32.9, 30.1, 26.1, 20.0, 18.7, 18.3, 14.5, -4.1, -4.2; HRMS (EI$^+$) found 485.3170 M$^+$, calcd 485.3173 for C$_{25}$H$_{47}$NO$_6$Si.

2-Methyl-but-(2E)-2-enoic acid {3-[4R)-4-(tert-butyl-dimethyl-silanyloxy)-(2R)-2-methyl-heptyl]-4-methoxy-2,5-bis-methoxymethoxy-phenyl]-amide (167a, R= MOM). To a 50 mL round bottom flask containing aryl amine 166a (0.199 g, 0.245 mmol) was added 1.3 mL of THF followed by freshly distilled NEt$_3$ (0.085 mL, 0.613 mmol). The mixture was then stirred at ambient temperature for 15 min, at which time tiglic acid chloride (0.058 g, 0.490 mmol) was added as a THF solution (1.6 mL). The reaction was then stirred at ambient temperature for 1 h. The reaction mixture was then poured into water and the solution extracted 3 times with EtOAc. The combined organic layers were then washed with a saturated NaHCO$_3$ solution and then with a saturated NaCl solution. The organic layer was then dried over MgSO$_4$, filtered, and concentrated. The crude product was purified by radial chromatography (2 mm plate, 20%
EtOAc/hexanes) to afford 0.125 g (90%) of the title compound as a colorless oil. Data are: TLC $R_f = 0.48$ (30% EtOAc/hexanes); $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 8.64 (s, 1H), 8.15 (s, 1H), 6.56 (dq, $J = 6.9$, 1.2 Hz, 1H), 5.21 (s, 2H), 4.93 (ABq, 2H), 3.81 (s, 3H), 3.77-3.71 (m, 1H), 3.55 (s, 3H), 3.53 (s, 3H), 2.55 (dd, $J = 12.6$, 5.7 Hz, 1H), 2.41 (dd, $J = 12.6$, 9.0 Hz, 1H), 1.99 (obs m, 1H), 1.94 (app t, $J = 1.2$ Hz, 3H), 1.82 (dd, $J = 6.6$, 0.9 Hz, 3H), 1.51-1.23 (m, 6H) 0.89 (app d, $J = 2.7$ Hz, 3H), 0.87 (s, 9H), 0.81 (d, $J = 6.6$ Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H), $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 167.6, 146.8, 144.7, 141.7, 133.3, 131.2, 128.5, 128.1, 107.7, 101.0, 95.7, 70.3, 60.9, 57.6, 56.6, 45.2, 40.3, 33.0, 30.0, 26.1, 19.9, 18.6, 18.3, 14.5, 14.3, 12.5, -4.1, -4.2; HRMS (FAB+) found 567.3606 M$^+$, calcd 567.3591 for C$_{30}$H$_{53}$NO$_7$Si.

![Chemical Structure](image)

2-Methyl-but-(2E)-2-enoic acid [2,5-dihydroxy-3-((4R)-4-hydroxy-(2R)-2-methylheptyl)-4-methoxy-phenyl]-amide (170). To a 10 mL round bottom flask charged with 167a (R= MOM) (0.035 g, 0.0617 mmol) was added 4.1 mL of CH$_3$CN and 4.1 mL of CH$_2$Cl$_2$. Then with stirring NaI (0.093 g, 0.617 mmol) was added to the solution followed by chlorotrimethylsilane (0.078 mL, 0.617 mmol). The solution became cloudy and then yellow, and the mixture was then stirred for 0.5 h. The reaction was then diluted with 10 mL of CH$_2$Cl$_2$ and washed with a saturated Na$_2$S$_2$O$_4$ solution (3 x 15 mL). The organic phase was then washed with H$_2$O and dried over MgSO$_4$, then filtered and concentrated.
The crude product was purified using radial chromatography (1 mm plate, 50% EtOAc/hexanes) to afford 0.018 g (79%) of the title compound as a yellow oil. Data are:
TLC R<sub>f</sub> = 0.2 (50% EtOAc/hexanes); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.24, (bs, 1H), 7.75 (s, 1H), 6.84 (app d, J = 2.5 Hz, 1H), 6.65 (dq, J = 6.5, 0.5 Hz, 1H), 5.50 (bs, 1H), 3.80-3.74 (obs m, 1H), 3.75 (s, 3H), 2.75 (dd, J = 13.0, 5.0 Hz, 1H), 2.59 (dd, J = 13.0, 8.5 Hz, 1H), 2.04-1.98 (obs m, 1H), 1.96 (s, 3H), 1.83 (d, J = 7.0 Hz, 3H), 1.50-1.32 (m, 7H), 0.95-0.91 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 168.7, 144.2, 142.4, 141.0, 133.8, 131.2, 124.8, 122.4, 106.8, 71.4, 61.4, 44.6, 40.6, 32.7, 31.3, 20.7, 19.1, 14.5, 14.3, 12.7.

2-Methyl-but-(2E)-2-enoic acid [5-((4R)-4-hydroxy-(2R)-2-methyl-heptyl)-4-methoxy-3,6-dioxo-cyclohexa-1,4-dienyl]-amide (169). To a vial containing 170 (0.0047 g, 0.0129 mmol) was added 1.5 mL of EtOAc. Then activated Pd/C (0.007 g, 150 wt %) was added and the mixture stirred at ambient temperature, open to the air, and vigorously for 45 min. The mixture was then filtered through a silica gel plug and the product eluted with EtOAc. The filtrate was then concentrated to afford 0.0046 g (98%) of the desired compound as a yellow/orange oil. Data are: TLC R<sub>f</sub> = 0.54 (50% EtOAc/hexanes); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.65 (s, 1H), 7.39 (s, 1H), 6.63 (dq, J = 7.5, 1.5 Hz, 1H), 4.12 (s, 3H), 3.75-3.69 (m, 1H), 2.44 (dd, J = 12.5, 6.0 Hz, 1H), 2.37 (dd, J = 12.5, 8.5 Hz, 1H), 1.94 (app t, J = 1.5 Hz, 3H), 1.90 (obs m, 1H), 1.85 (dd, J =...
7.0, 1.0 Hz, 3H), 1.49-1.36 (m, 6H), 1.29-1.24 (m, 1H), 0.95-0.93 (m, 3H), 0.90 (d, J = 6.5 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 184.5, 184.2, 167.6, 157.3, 138.4, 134.7, 132.1, 127.3, 112.5, 69.7, 61.7, 44.9, 40.7, 31.1, 29.7, 19.8, 19.1, 14.6, 14.3, 12.4; UV-Vis $\lambda_{\text{max}}$ = 242, 310, 423 nm (CHCl$_3$); HRMS (El$^+$) found 363.2047 M$^+$, calcd 363.2046 for C$_{20}$H$_{29}$NO$_3$.

![Chemical structures](image)

**DEPT Data**

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**HETCOR Data**

**HMBC (Partial Data)**

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* $^1$H attached to specified $^{13}$C
7.3. Asymmetric Phase-Transfer-Catalyzed Glycolate Alkylation

Park & Jew – \(O(9)\)-allyl-N-2’,3’,4’-trifluorobenzylhydrocinchonidinium bromide (44).\(^1\) The catalyst was prepared according to the published procedure with the exceptions that in the workup of \(N\)-(2’,3’,4’-Trifluoro)benzylhydrocinchonidinium bromide the reaction mixture was diluted with a 1:40 ratio of MeOH : diethyl ether to precipitate the catalyst. Also the purification of \(O(9)\)-allyl-N-2’,3’,4’-trifluorobenzyl-hydrocinchonidinium bromide 44 was accomplished via column chromatography (5% MeOH/CH\(_2\)Cl\(_2\)) rather than by recrystallization.

Benzhydryloxy-acetic acid (207). To an oven dried round bottom flask was added benzhydrol (5.07 g, 27.5 mmol) and 270 ml of benzene. Then tetrabutylammonium hydrogensulfate (0.465 g, 1.37 mmol) was added with stirring followed by 50 mL of a 50% aq. (w/w) NaOH solution. The reaction was stirred for 30 min then ethyl bromoacetate (4.6 mL, 41.3 mmol) was added dropwise. The solution was allowed to stir at ambient temperature for 24 h. The resulting thick white solution was then diluted with H\(_2\)O and hexanes, the layers were mixed and then separated. The aqueous layer was then carefully acidified, while stirring vigorously, with 6 M HCl until a pH of ~ 7 was obtained. Then 1 M HCl was added until the pH was ~ 1.4, as monitored by pH 0 – 2.5 indicator strips. Next, the resulting white, cloudy solution was extracted with CH\(_2\)Cl\(_2\) (5 x
100 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated to provide 6.32 g (95%) of the title compound as a white powder. Observations by TLC and ¹H NMR concluded that the product was analytically pure and carried on to the next step. Data are: ¹H NMR (DMSO-­d₆, 300 MHz) δ 12.76 (bs, 1H), 7.40-­7.22 (m, 10H), 5.60 (s, 1H), 3.99 (s, 2H); ¹³C NMR (DMSO-­d₆, 75 MHz) δ 171.3, 141.7, 128.4, 127.5, 126.8, 82.1, 65.2.

2-Benzhydryloxy-­1-(2,5-dimethoxyphenyl)-ethanone (209). To a flame dried round bottom flask was added benzhydryloxy-­acetic acid 207 (1.94 g, 8.01 mmol) and 32 mL of CH₂Cl₂. The solution was cooled to 0 °C and N,O-­dimethylhydroxylamine hydrochloride (1.17 g, 12.02 mmol) was added in one portion followed by N,N-diisopropylethylamine (2.09 mL, 12.02 mmol). Then 4-(dimethylamino)pyridine (0.146 g, 1.20 mmol) was added followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.70 g, 12.02 mmol). The reaction was stirred at 0 °C for 1 h then warmed to ambient temperature where it stirred for an additional 24 h. The solution was then diluted with CH₂Cl₂ and H₂O. The layers were mixed and separated, and the aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were washed with an aqueous 1 M H₃PO₄ solution, then with a saturated aqueous NaHCO₃ solution and finally with a saturated aqueous NaCl solution. The organic layer was then dried over MgSO₄,
filtered and concentrated *in vacuo*. Dry THF (40.0 mL) was added to the crude mixture followed by cooling to −40 °C. To a separate flame dried round bottom flask was added 1-bromo-2,5-dimethoxybenzene (2.41 mL, 16.02 mmol) and 40.0 mL of THF. The solution was cooled to −40 °C and then, with stirring, *n*-BuLi (9.56 mL, 1.6 M in hexanes, 15.3 mmol) was added dropwise. The solution was allowed to stir for 1 hr then added via cannula to the previously described, pre-cooled solution of the crude 2-benzhydryloxy-\(N\)-methoxy-\(N\)-methyl-acetamide solution. The resulting solution was allowed to stir for 15 min at −40 °C then quenched by the addition of a 5% HCl/EtOH solution. The reaction was warmed to ambient temperature and the solution partitioned between a saturated aqueous NaCl solution and a 1:1 mixture of Et\(_2\)O:CH\(_2\)Cl\(_2\). The layers were separated and the aqueous layer extracted with (1:1) Et\(_2\)O:CH\(_2\)Cl\(_2\) (3 x 50 mL). The combined organic layers were dried over MgSO\(_4\), filtered and concentrated. The crude product was purified via column chromatography (10% EtOAc/hexanes) to produce 2.63 g (91%) of the desired compound as an off-white crystalline solid. Data are: TLC \(R_f = 0.23\) (20% EtOAc/hexanes); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.43-7.20 (m, 11H), 7.00 (dd, \(J = 3, 9\)Hz, 1H), 6.81 (d, \(J = 9\)Hz, 1H), 5.62 (s, 1H), 4.71 (s, 1H), 3.75 (s, 3H), 3.69 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 197.7, 153.7, 141.8, 128.5, 127.7, 127.5, 125.9, 121.1, 113.7, 113.1, 83.4, 75.1, 56.0, 55.9; mp = 82–86 °C; HRMS (FAB\(^+\)) found 385.1412 [M+Na]\(^+\), calcd 385.1410 for C\(_{23}\)H\(_{22}\)O\(_4\)Na; Anal. calcd for C\(_{23}\)H\(_{22}\)O\(_4\) : C, 76.22; H, 6.12. Found: C, 75.98; H, 6.09.
Representative Procedure for the Enantioselective Catalytic Phase-Transfer

Alkylation of 2-Benzhydryloxy-1-(2,5-dimethoxy-phenyl)-ethanone.

(S)-2-(benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-phenylpropan-1-one (Table 4.15, entry 9). To a flame dried round bottom flask was added 2-benzhydryloxy-1-(2,5-dimethoxyphenyl)-ethanone 209 (0.10 g, 0.276 mmol), O(9)-allyl-N-2',3',4'-trifluorobenzylhydrocinchonidinium bromide (15.7 mg, 0.028 mmol), CH₂Cl₂ (1.4 mL) and hexane (1.4 mL). The solution was cooled to –35 °C and then CsOH•H₂O (0.232g, 1.38 mmol) was added in one portion. The mixture stirred for 10 min at which time benzyl bromide (0.165 mL, 1.38 mmol) was added dropwise. The mixture stirred at –35 °C for 14 h at which time the reaction was diluted with Et₂O (40 mL) and H₂O (15 mL). The layers were mixed and then separated and the organic layer was washed with H₂O (2 x 15 mL) followed by a saturated aqueous solution of NaCl, then dried over MgSO₄. The mixture was filtered, the solvent removed in vacuo and the crude residue purified by column chromatography (15% EtOAc/hexane) to afford 0.116 g (93%) of the desired compound as a colorless oil. Data are: TLC Rₕ = 0.35 (20% EtOAc/hexanes); [α]D 23° = −6.7° (c 2.14, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 7.32-7.07 (m, 14H), 7.00 (dd, J = 3.0, 9.0 Hz, 1H), 6.88-6.80 (m, 3H), 5.41 (s, 1H), 5.14 (dd, J = 3.0, 9.6 Hz, 1H), 3.76 (s, 3H), 3.58 (s, 3H), 3.06 (dd, J = 2.7, 13.8 Hz, 1H), 2.88 (dd, J = 9.6, 14.1 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 201.2, 153.9, 152.7, 142.7, 141.4, 138.5, 129.9, 128.29, 128.27, 127.8, 127.5, 127.4, 127.3, 127.2, 126.5, 120.5, 114.3, 113.4, 82.8, 82.5, 56.1,
56.0, 39.1; HRMS (EI') found 452.1982 M', calcd 452.1988 for C$_{30}$H$_{28}$O$_4$; Anal. calcd for C$_{30}$H$_{28}$O$_4$: C, 79.62; H, 6.24. Found: C, 79.59; H, 6.24. The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 1.0 mL/min, 23°C, $\lambda = 254$ nm, retention times: $S$ (major) 7.3 min, $R$ (minor) 6.4 min, 86% ee). The absolute configuration was determined by elaboration of the product to known compounds described below.

**Physical Data for Enantioselective Phase Transfer Alkylation (Table 4.15)** $^2$

(2S)-2-Benzhydryloxy-1-(2,5-dimethoxyphenyl)-4-methyl-pent-4-en-1-one (Table 4.15, entry 3). Following purification via chromatography the product was obtained in 78% yield as a colorless oil. TLC $R_f = 0.36$ (20% EtOAc/hexanes); $[\alpha]_D$ $^{23} -26.5^\circ$ (c 1.0, CHCl$_3$); $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.42-7.16 (m, 11H), 6.98 (dd, $J = 3.3$, 9.0 Hz, 1H), 6.79 (d, $J = 9.0$ Hz, 1H), 5.52 (s, 1H), 5.12 (dd, $J = 4.8$, 7.5 Hz, 1H), 4.82-4.77 (m, 2H), 3.75 (s, 3H), 3.55 (s, 3H), 2.40-2.35 (m, 2H), 1.61 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 202.5, 153.8, 152.6, 144.0, 142.8, 141.8, 141.7, 128.6, 128.4, 128.3, 128.2, 127.8, 127.7, 127.5, 127.3, 127.2, 126.7, 120.3, 114.3, 113.9, 113.2, 82.2, 80.1, 56.0, 55.9, 41.1, 22.5; HRMS (FAB') found 439.1878 [M+Na]$^+$, calcd 439.1880 for C$_{27}$H$_{28}$O$_4$Na. The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 1.0 mL/min, 23°C, $\lambda = 254$ nm, retention times: $S$ (major) 5.9 min, $R$ (minor) 5.4 min, 89% ee).
(2S)-2-Benzhydroyloxy-1-(2,5-dimethoxyphenyl)-pent-4-en-1-one (Table 4.15, entry 2).

Following purification via chromatography the product was obtained in 83% yield as a colorless oil. TLC $R_f = 0.31$ (20% EtOAc/hexanes); $[\alpha]_D^{23} -10.8^\circ$ (c 1.0, CHCl$_3$); $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.40-7.16 (m, 10H), 7.12 (d, $J = 3.0$ Hz, 1H), 6.98 (dd, $J = 3.0$, 9.0 Hz, 1H), 6.79 (d, $J = 9.0$ Hz, 1H), 5.95-5.81 (m, 1H), 5.53 (s, 1H), 5.05-4.97 (m, 3H), 3.75 (s, 3H), 3.55 (s, 3H), 2.55-2.32 (m, 2H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 202.2, 153.8, 152.6, 142.7, 141.8, 134.5, 128.6, 128.5, 128.2, 128.1, 127.8, 127.7, 127.4, 127.3, 126.7, 120.1, 117.3, 114.2, 113.2, 82.3, 81.4, 56.0, 55.9, 37.2; HRMS (FAB$^+$) found 425.1715 [M+Na]$^+$, calcd 425.1723 for C$_{26}$H$_{26}$O$_4$Na; Anal. calcd for C$_{26}$H$_{26}$O$_4$: C, 77.59; H, 6.51. Found: C, 77.61; H, 6.57. The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 0.5 mL/min, 23°C, $\lambda = 254$ nm, retention times: S (major) 12.6 min, R (minor) 11.2 min, 83% ee).

(2S)-2-Benzhydroyloxy-1-(2,5-dimethoxyphenyl)-5-(trimethyl-silanyl)-pent-4-yn-1-one (Table 4.15, entry 7). Following purification via chromatography the product was obtained in 88% yield as a colorless oil. TLC $R_f = 0.34$ (20% EtOAc/hexanes); $[\alpha]_D^{23} +26.3^\circ$ (c 1.95, CHCl$_3$); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.46-7.28 (m, 10H), 7.15 (d, $J = 3.0$Hz, 1H), 7.01 (dd, $J = 3.0$, 9.0 Hz, 1H), 6.81 (d, $J = 9.0$ Hz, 1H), 5.65 (s, 1H), 5.16
(dd, J = 5.5, 7.0 Hz, 1H), 3.78 (s, 3H), 3.58 (s, 3H), 2.71-2.69 (m, 2H), 0.16 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 201.1, 153.8, 152.8, 142.3, 141.5, 128.5, 128.3, 127.8, 127.7, 127.6, 127.5, 127.4, 120.5, 114.1, 113.2, 103.4, 86.5, 82.6, 80.0, 56.0, 55.9, 24.6, 0.19; HRMS (EI\(^+\)) found 472.2078 M\(^+\), calcld 472.2070 for C\(_{29}\)H\(_{32}\)O\(_4\). The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% IPA/hexane, 1.0 mL/min, 23°C, \(\lambda\) = 254 nm, retention times: \(S\) (major) 4.7 min, \(R\) (minor) 6.0 min, 81% ee).

![Chemical Structure](attachment:image)

\((S)\)-2-(benzhydryloxy)-1-(2,5-dimethoxyphenyl)hex-4-yn-1-one (Table 4.15, entry 6).

Following purification via chromatography the product was obtained in 89% yield as a colorless oil. TLC \(R_f = 0.23\) (20% EtOAc/hexanes); \([\alpha]_D^{23}\) +10.3° (c 0.93, CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.45-7.19 (m, 10H), 7.12 (d, \(J = 3.3\) Hz, 1H), 6.97 (dd, \(J = 3.0, 9.0\) Hz, 1H), 6.78 (d, \(J = 9.0\) Hz, 1H), 5.58 (s, 1H), 5.06 (dd, \(J = 5.1, 6.9\) Hz, 1H), 3.75 (s, 3H), 3.57 (s, 3H), 2.59-2.56 (m, 2H), 1.72 (t, \(J = 2.7\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 201.7, 153.9, 152.7, 142.4, 141.7, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 120.2, 114.3, 113.2, 82.8, 80.8, 75.5, 56.2, 56.0, 23.5, 3.8; HRMS (FAB\(^+\)) found 437.1725 [M+Na]\(^+\), calcld 437.1723 for C\(_{27}\)H\(_{26}\)O\(_4\)Na. Anal. calcld for C\(_{27}\)H\(_{26}\)O\(_4\)Na: C, 78.24; H, 6.32. Found: C, 78.24; H, 6.17. The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 0.5 mL/min, 23°C, \(\lambda\) = 254 nm, retention times: \(S\) (major) 16.8 min, \(R\) (minor) 15.7 min, 81% ee).
(2S)-2-Benzhydryloxy-3-(4-tert-butyl-phenyl)-1-(2,5-dimethoxyphenyl)-propan-1-one

(Table 4.15, entry 10). Following purification via chromatography the product was obtained in 96% yield as a colorless oil. TLC $R_f = 0.34$ (20% EtOAc/hexanes); $[\alpha]_D^{23} +18.7^\circ$ (c 1.26, CHCl$_3$); $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.33-6.97 (m, 14H), 6.87-6.79 (m, 3H), 5.41 (s, 1H), 5.12 (dd, $J = 3.3, 9.6$ Hz, 1H), 3.75 (s, 3H), 3.58 (s, 3H), 3.02 (dd, $J = 3.3, 13.8$ Hz, 1H), 2.86 (dd, $J = 9.6, 13.8$ Hz, 1H), 1.35 (s, 9H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 202.4, 153.9, 152.7, 149.3, 142.8, 141.5, 135.3, 129.6, 128.3, 128.2, 127.8, 127.4, 127.3, 125.1, 120.4, 114.3, 113.4, 83.0, 82.6, 56.0, 55.9, 38.6, 34.6, 31.7; HRMS (FAB$^+$) found 531.2530 [M+Na]$^+$, calcd 531.2506 for C$_{34}$H$_{36}$O$_4$Na. The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 0.5 mL/min, 23°C, $\lambda = 254$ nm, retention times: $S$ (major) 11.2 min, $R$ (minor) 10.5 min, 84% ee).

(2S)-2-Benzhydryloxy-3-biphenyl-2-yl-1-(2,5-dimethoxyphenyl)-propan-1-one

(Table 4.15, entry 13). Following purification via chromatography the product was obtained in 99% yield as a colorless oil. TLC $R_f = 0.27$ (20% EtOAc/hexanes); $[\alpha]_D^{23} -58.9^\circ$ (c 1.35, CHCl$_3$); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.35-7.11 (m, 15H), 7.00-6.98 (m, 2H), 6.88-6.76 (m, 4H), 6.62 (d, $J = 9.0$ Hz, 1H), 5.33 (s, 1H), 4.87-4.85 (m, 1H), 3.68 (s,
3H), 3.36 (s, 3H), 3.12 (dd, J = 3.0, 14.0 Hz, 1H), 2.94 (dd, J = 10.0, 14.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 203.9, 153.5, 151.9, 142.7, 142.5, 141.5, 141.4, 135.3, 131.3, 130.3, 129.4, 128.3, 128.1, 128.0, 127.7, 127.4, 127.3, 126.7, 126.5, 119.1, 113.8, 112.8, 82.3, 81.8, 55.9, 55.7, 36.1; HRMS (FAB$^+$) found 551.2198 [M+Na]$^+$, calcd 551.2193 for C$_{36}$H$_{32}$O$_4$Na. The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 1.0 mL/min, 23°C, $\lambda = 254$ nm, retention times: S (major) 7.5 min, R (minor) 6.8 min, 90% ee).

(2S)-2-Benzhydryloxy-1-(2,5-dimethoxyphenyl)-3-naphthalen-2-yl-propan-1-one (Table 4.15, entry 14). Following purification via chromatography the product was obtained in 91% yield as a colorless oil. TLC $R_f$ = 0.3 (2:1:7, CH$_2$Cl$_2$:Et$_2$O:hexanes); $\lbrack \alpha \rbrack_D^{23}$ +40.6° (c 1.1, CHCl$_3$); $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.83-7.69 (m, 3H), 7.58 (s, 1H), 7.45-7.41 (m, 2H), 7.33-6.79 (m, 14H), 5.43 (s, 1H), 5.25 (dd, J = 3.3, 9.3 Hz, 1H), 3.72 (s, 3H), 3.59 (s, 3H), 3.22 (dd, J = 3.0, 14.1 Hz, 1H), 3.05 (dd, J = 9.3, 13.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 202.1, 153.9, 152.7, 142.6, 141.2, 135.9, 133.6, 132.4, 128.5, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.4, 127.3, 127.2, 126.0, 125.5, 120.5, 114.3, 113.4, 82.7, 82.6, 56.1, 55.9, 39.2; HRMS (FAB$^+$) found 525.2048 [M+Na]$^+$, calcd 525.2036 for C$_{34}$H$_{30}$O$_4$Na. The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 1.0 mL/min, 23°C, $\lambda = 254$ nm, retention times: S (major) 9.9 min, R (minor) 8.9 min, 85% ee).
(2S)-2-Benzhydryloxy-1-(2,5-dimethoxyphenyl)-5,9-dimethyl-deca-4,8-dien-1-one (Table 4.15, entry 5). Following purification via chromatography the product was obtained in 80% yield as a colorless oil. TLC R_{f} = 0.39 (20% EtOAc/hexanes); [\alpha]_{D}^{23} +9.5^\circ (c 1.0, CHCl_{3}); ^1H NMR (CDCl_{3}, 300 MHz) \delta 7.41-7.18 (m, 10H), 7.10 (d, J = 3.0 Hz, 1H), 6.96 (dd, J = 3.0, 9.0 Hz, 1H), 6.78 (d, J = 9.0 Hz, 1H), 5.52 (s, 1H), 5.22-5.17 (m, 1H), 5.11-5.07 (m, 1H), 4.97 (t, J = 6.0 Hz, 1H), 3.74 (s, 3H), 3.54 (s, 3H), 2.42 (t, J = 6.3 Hz, 2H), 2.06-1.92 (m, 4H), 1.67 (d, J = 0.9 Hz, 3H), 1.59 (d, J = 0.9 Hz, 3H), 1.49 (d, J = 1.2 Hz, 3H); ^13C NMR (CDCl_{3}, 75 MHz) \delta 202.9, 153.8, 152.5, 142.8, 141.9, 137.6, 131.5, 128.4, 128.2, 128.0, 127.7, 127.4, 127.3, 124.5, 119.9, 119.8, 114.2, 113.2, 82.3, 81.9, 56.0, 55.9, 39.9, 31.7, 26.8, 25.8, 17.9, 16.4; HRMS (FAB\(^{+}\)) found 521.2676 [M+Na]^{+}, calcd 521.2662 for C_{33}H_{38}O_{4}Na. The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 0.5 mL/min, 23°C, λ = 254 nm, retention times: S (major) 10.1 min, R (minor) 9.1 min, 84% ee).

(2S)-2-Benzhydryloxy-1-(2,5-dimethoxyphenyl)-3-(2-methoxy-5-nitro-phenyl)-propan-1-one (Table 4.15, entry 15). Following purification via chromatography the product was obtained in 91% yield as a white solid. TLC R_{f} = 0.2 (30% EtOAc/hexanes);
[α]_D^{23} -35.6° (c 1.2, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 8.09 (dd, J = 2.7, 9.0 Hz, 1H), 8.01 (d, J = 3.0 Hz, 1H), 7.31-7.10 (m, 9H), 6.99-6.93 (m, 3H), 6.79-6.75 (m, 2H), 5.42 (s, 1H), 5.25 (dd, J = 5.4, 8.4 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.58 (s, 3H), 3.13-2.99 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 202.2, 162.8, 153.8, 152.5, 142.3, 141.4, 141.1, 128.3, 128.2, 127.9, 127.7, 127.3, 127.1, 127.0, 124.2, 120.0, 114.4, 113.0, 109.7, 82.4, 80.3, 56.0, 55.9, 33.1; HRMS (FAB⁺) found 550.1844 [M+Na]⁺, calcd 550.1836 for C₃₁H₂₉NO₇Na. The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 2.0 mL/min, 23°C, λ = 254 nm, retention times: S (major) 12.2 min, R (minor) 15.8 min, 88% ee).

(2S)-2-Benzhydryloxy-1-(2,5-dimethoxyphenyl)-hept-4-en-1-one (Table 4.15, entry 4). Following purification via chromatography the product was obtained in 85% yield as a colorless oil. TLC Rᵣ = 0.35 (20% EtOAc/hexanes); [α]_D^{23} +1.0° (c 1.8, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 7.41-7.18 (m, 10H), 7.10 (d, J = 3.3 Hz, 1H), 6.97 (dd, J = 3.3, 9.0 Hz, 1H), 6.79 (d, J = 9.0 Hz, 1H), 5.53 (s, 1H), 5.46-5.43 (m, 2H), 4.96 (dd, J = 4.2, 7.5 Hz, 1H), 3.75 (s, 3H), 3.55 (s, 3H), 2.48-2.30 (m, 2H), 2.02-1.94 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 202.6, 153.8, 152.5, 142.7, 141.8, 135.0, 134.1, 128.4, 128.2, 128.1, 127.7, 127.4, 127.3, 124.8, 119.9, 114.2, 113.2, 82.3, 82.0, 56.0, 55.9, 36.1, 25.7, 13.8; HRMS (FAB⁺) found 453.2040 [M+Na]⁺, calcd 453.2036 for C₂₈H₃₀O₄Na. The enantioselectivity was determined by chiral HPLC (DAICEL
Chiralpack AD column, 10% EtOH/hexane, 0.5 mL/min, 23°C, λ = 254 nm, retention times: S (major) 12.2 min, R (minor) 12.9 min, 82% ee).

\( \text{(S)-}\text{tert-butyl 3-(benzhydryloxy)-4-(2,5-dimethoxyphenyl)-4-oxobutanoate} \) (Table 4.15, entry 8). Following purification via chromatography the product was obtained in 70% yield as a colorless oil. \([\alpha]_D^{23} = -7.4^\circ \text{ (c 2.0, CHCl}_3\text{); } \)\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.34–7.16 (m, 10H), 7.10 (d, \(J = 3.0\) Hz, 1H), 6.98 (dd, \(J = 3.0, 9.0\) Hz, 1H), 6.78 (d, \(J = 9.0\) Hz, 1H), 5.60 (s, 1H), 5.33 (dd, \(J = 5.1, 7.5\) Hz, 2H), 3.75 (s, 3H), 3.59 (s, 3H), 2.71-2.57 (m, 2H), 1.42 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 200.9, 169.9, 153.8, 152.6, 142.4, 141.7, 128.4, 128.2, 127.9, 127.7, 127.4, 127.3, 120.4, 114.2, 113.2, 83.0, 80.9, 79.0, 56.0, 55.9, 39.1, 28.2; HRMS (FAB\(^{+}\)) found 499.2100 [M+Na]\(^{+}\), calcd 499.2097 for C\(_{29}\)H\(_{32}\)O\(_6\)Na. The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 0.5 mL/min, 23°C, λ = 254 nm, retention times: S (major) 13.7 min, R (minor) 14.6 min, 89% ee).

\( \text{(2S)-2-Benzhydryloxy-1-(2,5-dimethoxyphenyl)-3-(2,3,6-trimethoxy-5-nitro-phenyl)-propan-1-one} \) (Table 4.15, entry 16). Following purification via chromatography the
product was obtained in 83% yield as a yellow oil. TLC $R_f = 0.12$ (20% EtOAc/hexanes); $[\alpha]_D^{23} = -37.4^\circ$ (c 1.3, CHCl$_3$); $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.32-7.14 (m, 9H), 6.99-6.95 (m, 3H), 6.91 (dd, $J = 3.0$, 8.7 Hz, 1H), 6.74 (d, $J = 9.0$ Hz, 1H), 5.42 (s, 1H), 5.32 (dd, $J = 4.8$, 9.3 Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.69 (s, 3H), 3.59 (s, 3H), 3.53 (s, 3H), 3.22 (dd, $J = 9.6$, 13.2 Hz, 1H), 2.95 (dd, $J = 5.1$, 13.2 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 204.1, 153.6, 153.2, 152.3, 148.3, 148.2, 142.2, 141.2, 128.6, 128.3, 128.1, 127.8, 127.76, 127.73, 127.5, 127.4, 119.3, 114.2, 112.7, 107.6, 82.7, 80.2, 62.3, 60.9, 56.4, 55.9, 28.3; HRMS (FAB$^+$) found 610.2051 [M+Na]$^+$, calcd 610.2047 for C$_{33}$H$_{33}$NO$_9$Na. The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% IPA/hexane, 1.0 mL/min, 23°C, $\lambda = 254$ nm, retention times: S (major) 13.0 min, R (minor) 15.5 min, 74% ee).

(S)-2-(benzhydryloxy)-1-(2,5-dimethoxyphenyl)propan-1-one (Table 4.15, entry 1).

Following purification via chromatography the product was obtained in 70% yield as a colorless oil. TLC $R_f = 0.44$ (30% EtOAc/hexanes); $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.39-7.19 (m, 10H), 7.11 (d, $J = 3.3$ Hz, 1H), 6.97 (dd, $J = 3.3$, 9.0 Hz, 1H), 6.79 (d, $J = 9.0$ Hz, 1H), 5.54 (s, 1H), 4.99 (q, $J = 6.9$, 13.8 Hz, 1H), 3.75 (s, 3H), 3.56 (s, 3H), 1.37 (d, $J = 7.2$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 203.8, 153.8, 152.4, 142.5, 141.9, 128.6, 128.3, 127.7, 127.6, 127.5, 127.4, 126.7, 119.7, 114.2, 113.1, 82.4, 78.1, 56.0, 55.9, 18.4. The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD
column, 10% EtOH/hexane, 1.0 mL/min, 23°C, \( \lambda = 254 \) nm, retention times: \( S \) (major) 6.9 min, \( R \) (minor) 6.3 min, 66% ee).

(2S)-1-(2,5-dimethoxyphenyl)-2-hydroxy-3-phenyl-propan-1-one (211). To a flame dried round bottom flask was added (3S)-2-benzhydroxylo-1-(2,5-dimethoxyphenyl)-3-phenyl-propan-1-one 210 (0.625 g, 1.38 mmol) and 27 mL of CH\(_2\)Cl\(_2\). The solution was cooled to –78 °C and then TiCl\(_4\) was added dropwise (0.75 mL, 1.0 M CH\(_2\)Cl\(_2\)). The resulting dark red/orange solution was stirred at –78 °C for 15 min, at which time additional TiCl\(_4\) was added dropwise (0.65 mL, 1.0 M CH\(_2\)Cl\(_2\)). The reaction was stirred for another 15 min, then the reaction was quenched by the addition of a saturated aqueous NaHCO\(_3\) solution (25 mL). The layers were separated and the aqueous layer was washed with Et\(_2\)O (2 x 25 mL). The combined organic layers were washed with H\(_2\)O followed by a saturated aqueous NaCl solution, then dried over MgSO\(_4\), filtered and concentrated in vacuo. Chromatography (radial, 4mm plate, 20% EtOAc/hexanes) afforded the title compound, 0.361 g (91%), as a colorless oil. Data are: TLC \( R_f = 0.33 \) (20% EtOAc/hexanes); \( [\alpha]_D^{23} = -42.2^\circ \) (c 1.15, CHCl\(_3\)) \( ^1\)H NMR (CDCl\(_3\), 300 MHz) \( \delta 7.34 \) (d, \( J = 3.3 \) Hz, 1H), 7.28-7.08 (m, 6H), 6.93 (d, \( J = 9.0 \) Hz, 1H), 5.42-5.36 (m, 1H), 3.87 (s, 3H), 3.86 (obs m, 1H), 3.78 (s, 3H), 3.14 (dd, \( J = 3.6, 14.1 \) Hz, 1H), 2.70 (dd, \( J = 7.5, 14.1 \) Hz, 1H); \( ^{13}\)C NMR (CDCl\(_3\), 75 MHz) \( \delta 202.0, 153.8, 153.4, 137.8, 129.5, 128.3, \)
126.6, 124.4, 121.9, 114.7, 113.3, 77.6, 56.1, 55.9, 40.8; HRMS (EI') found 286.1200 M', calcd 286.1205 for C_{17}H_{18}O_{4}.

(2S)-2-Hydroxy-3-phenyl-propionic acid 2,5-dimethoxyphenyl ester (215). To a flame dried round bottom flask containing activated 4 angstrom molecular sieves and K_{2}CO_{3} (0.097 g, 0.70 mmol) was added trans-N,N-bis(p-toluenesulfonyl)-1,2-cyclohexanediamine 214 (0.148 g, 0.35 mmol), followed by CH_{2}Cl_{2} (2.5 mL). The mixture was cooled to 0 °C and then SnCl_{4} (0.350 mL, 1.0 M in CH_{2}Cl_{2}) was added followed by bis(trimethylsilyl) peroxide (0.150 mL, 0.70 mmol). The mixture was stirred at 0 °C for 15 minutes, then (2S)-1-(2,5-dimethoxyphenyl)-2-hydroxy-3-phenyl-propan-1-one 211 (0.100 g, 0.35 mmol) was added dropwise as a CH_{2}Cl_{2} (3.5 mL) solution. The reaction mixture was stirred at 0 °C for 1.5 h, at which time it was quenched by the addition of a saturated aqueous NaHCO_{3} solution (9 mL) followed by the addition of a saturated aqueous Na_{2}S_{2}O_{3} solution (9 mL). The mixture stirred for 0.5 h at ambient temperature then diluted with CH_{2}Cl_{2} (10 mL). The layers were mixed and separated; then the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were then washed with H_{2}O followed by a saturated aqueous NaCl solution, then dried over Na_{2}SO_{4}, filtered, and concentrated. The crude product was purified by column chromatography (50% Et_{2}O/hexanes) to provide 0.083 g (79%) of the title compound as a white solid. The product was put into a round bottom flask, then dissolved in a minimal
amount of warm diethyl ether. The flask was then capped loosely and allowed to cool to ambient temperature where it sat for ~5 h. The remaining solution was then decanted from the needle-like crystals and the residual crystals were washed quickly with cold diethyl ether. The crystals were then analyzed by chiral HPLC which revealed the product was enantiomerically enriched to >99% ee. Data are: TLC Rf = 0.23 (50% Et₂O/hexanes); [α]D 23 –15.9° (c 0.17, CHCl₃); mp = 128-130 °C; ¹H NMR (CDCl₃, 300 MHz) δ 7.37-7.25 (m, 5H), 6.91 (d, J = 9.0 Hz, 1H), 6.76 (dd, J = 3.3, 9.3 Hz, 1H), 6.57 (d, J = 3.0 Hz, 1H), 4.76-4.70 (m, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.34 (dd, J = 4.5, 14.1 Hz, 1H), 3.15 (dd, J = 7.2, 14.1 Hz, 1H), 2.77-2.74 (m, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 172.5, 153.9, 145.3, 139.9, 136.6, 129.9, 128.7, 127.2, 113.6, 112.1, 109.4, 71.5, 56.6, 56.0, 40.7; HRMS (EI⁺) found 302.1155 M⁺, calcd 302.1154 for C₁₇H₁₉O₅. The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 20% IPA/hexane, 1.0 mL/min, 23°C, λ = 254 nm, retention times: S (major) 19.0 min, R (minor) 17.2 min, >99 : 1 er).

**Benzoic acid-(1S)-1-benzyl-2-(2,5-dimethoxyphenyl)-2-oxo-ethyl ester (212).** To a flame dried round bottom flask was added benzoyl chloride (0.200 mL, 1.73 mmol), 6.0 mL of CHCl₃, and pyridine (0.465 mL, 5.75 mmol). The solution was cooled to 0 °C, then (2S)-1-(2,5-dimethoxyphenyl)-2-hydroxy-3-phenyl-propan-1-one 211 (0.330g, 1.15 mmol) was added slowly as a solution in CHCl₃ (2.0 mL). The reaction was stirred at 0°C for 2.0 h, then quenched by the addition of H₂O (30 mL). The layers were separated and
the aqueous layer was extracted with CHCl₃ (2 x 15 mL). The combined organic layers were washed with a saturated aqueous NH₄Cl solution, then dried over MgSO₄, filtered and concentrated. The title compound was obtained after radial chromatography (4mm plate, gradient 10 – 20% EtOAc/hexanes) as a white solid, 0.407 g (90%), which could be recrystallized from CH₂Cl₂. Data are: TLC Rₚ = 0.37 (30% EtOAc/hexanes); FTIR (film) 3088-2836, 1714, 1669, 1600, 1582, 1495, 1463, 1313, 1276, 1115, 1039, 991 cm⁻¹; [α]D⁺²³ +13.6° (c 1.0, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 8.04-8.01 (m, 2H), 7.57-7.51 (m, 1H), 7.44-7.20 (m, 8H), 7.10 (dd, J = 3.3, 9.0 Hz, 1H), 6.95 (d, J = 9.3 Hz, 1H), 6.41 (dd, J = 3.0, 9.3 Hz, 1H), 3.93 (s, 3H), 3.79 (s, 3H), 3.37 (dd, J = 3.3, 14.4 Hz, 1H), 3.13 (dd, J = 9.3, 14.4 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 196.3, 166.3, 154.0, 153.4, 137.6, 133.2, 130.1, 130.0, 129.5, 128.6, 128.5, 126.9, 125.5, 121.9, 114.7, 113.4, 80.1, 56.4, 56.0, 36.9; HRMS (EI⁺) found 390.1459 M⁺, calcd 390.1467 for C₂₄H₂₂O₅.

Benzoic acid-(1S)-1-(2,5-dimethoxyphenoxy carbonyl)-2-phenyl-ethyl ester (213). To a flame dried round bottom flask was added activated 4 angstrom molecular sieves (0.200 g), trans-N,N-bis(p-toluenesulfonyl)-1,2-cyclohexanedi amine (0.026 g, 0.062 mmol), K₂CO₃ (0.034 g, 0.246 mmol) and 1.25 mL of CH₂Cl₂. The mixture was cooled to 0 °C and SnCl₄ (0.062 mL, 1.0 M in CH₂Cl₂) was added followed by bis(trimethylsilyl) peroxide (0.066 mL, 0.308 mmol). The mixture was stirred at 0 °C for 15 minutes, then benzoic acid-(1S)-1-benzyl-2-(2,5-dimethoxy-phenyl)-2-oxo-ethyl ester 212 (0.048 g, 204
0.123 mmol) was added as a CH₂Cl₂ solution (3.0 mL). The reaction stirred at 0 °C for 1.0 h at which time the reaction was quenched by the addition of a saturated aqueous NaHCO₃ (6 mL) followed by a saturated aqueous Na₂S₂O₃ solution (6 mL). The mixture was then stirred at ambient temperature for 30 minutes and diluted with 10 mL of CH₂Cl₂ and the layers separated. The aqueous phase was extracted with EtOAc (2 x 20 mL) and the combined organic layers were washed with H₂O followed by a saturated aqueous NaCl solution. The mixture was then filtered, concentrated and purified via flash column chromatography (30% EtOAc/hexanes) to provide 0.037 g (74%) of the title compound as an oil. Data are: TLC Rf = 0.37 (30% Et₂O/hexanes); [α]D²³ +13.6° (c 1.0, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 8.07-8.04 (m, 2H), 7.58-7.53 (m, 1H), 7.45-7.24 (m, 7H), 6.89 (d, J = 9.3 Hz, 1H), 6.73 (dd, J = 3.0, 9.0 Hz, 1H), 6.61 (d, J = 3.3 Hz, 1H), 5.72-5.67 (m, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.54 (dd, J = 4.2, 14.4 Hz, 1H), 3.43 (dd, J = 9.0, 14.4 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 167.9, 166.0, 153.9, 145.4, 139.9, 136.3, 133.6, 130.1, 129.8, 129.5, 128.8, 128.6, 127.3, 113.8, 112.2, 109.3, 73.6, 56.8, 56.0, 37.8; HRMS (EI⁺) found 406.1418 M⁺, calcd 406.1416 for C₂₄H₂₂O₆.

(2S)-2-Hydroxy-3-phenyl-propionic acid methyl ester (221). To a flame dried round bottom flask containing benzoic acid-(1S)-1-(2,5-dimethoxy-phenoxy carbonyl)-2-phenyl-ethyl ester 213 (0.023 g, 0.057 mmol) was added 0.57 mL of MeOH and 0.57 mL of THF. The solution was cooled to 0 °C and then a freshly prepared NaOMe/MeOH
solution (1.19 mL, 0.1 M) was added. The solution stirred at 0 °C for 1 h then at ambient temperature for 13 h at which time the reaction was quenched by the addition of a saturated aqueous NH₄Cl solution (0.5 mL) and further diluted with 10 mL of H₂O. The resulting solution was extracted with Et₂O (3 x 10 mL) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The crude residue was purified via flash column chromatography (40% Et₂O/hexanes) to provide 0.0084 g (82%) of the title compound as an oil that slowly became a white solid. Data are: TLC Rₖ = 0.21 (40% Et₂O/hexanes); [α]D₂³ = –8.8° (c 0.4, CHCl₃), lit. [α]D₂⁴ = –6.8° (c 1.39, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 7.35-7.21 (m, 5H), 4.50-4.45 (m, 1H), 3.79 (s, 3H), 3.14 (dd, J = 4.5, 13.8 Hz, 1H), 2.98 (dd, J = 6.9, 13.8 Hz, 1H), 2.70 (d, J = 6.3 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 174.8, 136.5, 129.7, 128.7, 127.2, 71.5, 52.7, 40.8; product verification and absolute configuration were obtained by comparison to: Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. J. Am. Chem. Soc. 1999, 121, 4168.

Benzoic acid-(1S)-1-methoxycarbonyl-2-phenyl-ethyl ester (220). To a round bottom flask containing benzoic acid-(1S)-1-(2,5-dimethoxy-phenoxycarbonyl)-2-phenyl-ethyl ester 213 (0.012 g, 0.0295 mmol) was added 0.30 mL of MeOH and 0.30 mL of THF. The solution was cooled to 0 °C and then a freshly prepared solution of NaOMe/MeOH (0.006 mL, 0.1 M) was added. The solution was then warmed to ambient temperature and stirred for 1 hour, then an additional 0.06 mL of the NaOMe/MeOH solution was added
and the solution stirred for 16 h. The reaction was then quenched by the addition of a saturated aqueous NH$_4$Cl solution (0.25 mL) and then further diluted with H$_2$O (5 mL). The solution was then extracted with Et$_2$O (3 x 10 mL) and the combined organic layers were dried over MgSO$_4$, filtered and concentrated. Purification of the product via preparative TLC (0.25 mm precoated plate, 50% Et$_2$O/hexanes) produced 0.007 g (81%) of the title compound as a colorless oil. Data are: TLC R$_f$ = 0.45 (40% Et$_2$O/hexanes); $[\alpha]_{D}^{23}$ = –35.5° (c 0.45, MeOH), lit. $[\alpha]_{D}^{20}$ = –40.2° (c 1.85, MeOH); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.03-8.01 (m, 2H), 7.58-7.55 (m, 1H), 7.45-7.42 (m, 2H), 7.33-7.29 (m, 3H), 7.26-7.24 (m, 1H), 5.45 (dd, $J$ = 5.0, 8.5 Hz, 1H), 3.74 (s, 3H), 3.31 (dd, $J$ = 5.0, 14.0 Hz, 1H), 3.26 (dd, $J$ = 8.0, 14.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 170.3, 166.1, 136.2, 133.6, 130.1, 129.6, 129.5, 128.8, 128.6, 127.3, 73.7, 52.6, 37.8; product verification and absolute configuration were obtained by comparison to: Burk, M. J.; Kalberg, C. S.; Pizzano, A. J. Am. Chem. Soc. 1998, 120, 4345.

(2S)-1-(2,5-Dimethoxy-phenyl)-2-hydroxy-hept-4-en-1-one (217). To a round bottom flask containing (2S)-2-Benzhydroxyloxy-1-(2,5-dimethoxy-phenyl)-hept-4-en-1-one (0.189 g, 0.439 mmol) was added CH$_2$Cl$_2$ (8.8 mL). The solution was then cooled to –78 °C and TiCl$_4$ (0.44 mL, 1.0 M CH$_2$Cl$_2$) was added dropwise. The resulting dark red/orange solution was stirred at –78 °C for 30 min. The reaction was then quenched by the addition of a saturated aqueous NaHCO$_3$ solution (10 mL). The layers were separated
and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 15 mL). The combined organic layers were washed with H$_2$O followed by a saturated aqueous NaCl solution, then dried over MgSO$_4$, filtered and concentrated in vacuo. Chromatography (radial, 1mm plate, 20% EtOAc/hexanes) afforded the title compound, 0.103 g (89%), as a colorless oil. Data are: TLC R$_f$ = 0.23 (20% EtOAc/hexanes); $[\alpha]_D^{23}$–64.5$^\circ$ (c 1.0, CHCl$_3$) $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.31 (d, $J$ = 3.3 Hz, 1H), 7.09 (dd, $J$ = 3.0, 9.0 Hz, 1H), 6.93 (d, $J$ = 9.3 Hz, 1H), 5.42-5.39 (m, 2H), 5.21-5.16 (m, 1H), 3.88 (s, 3H), 3.82 (obs d, $J$ = 6.3 Hz, 1H), 3.80 (s, 3H), 2.57-2.49 (m, 1H), 2.23-2.14 (m, 1H), 2.02-1.93 (m, 2H), 0.93 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 202.7, 153.8, 153.3, 135.7, 124.8, 123.7, 121.5, 114.6, 113.2, 76.8, 56.1, 55.9, 37.8, 25.8, 13.9; HRMS (EI$^+$) found 287.1250 M$^+$, calcd 287.1254 for C$_{15}$H$_{20}$O$_4$Na.

(1S)-Benzoic acid 1-(2,5-dimethoxy-benzoyl)-hex-3-enyl ester (218). To a round bottom flask containing (2S)-1-(2,5-dimethoxy-phenyl)-2-hydroxy-hept-4-en-1-one 217 (0.073 g, 0.276 mmol) was added 1.4 mL of CHCl$_3$ and pyridine (0.112 mL, 1.38 mmol). The solution was cooled to 0 °C, then benzoyl chloride (0.048 mL, 0.414 mmol) was added slowly. The reaction was stirred at 0 °C for 2.5 h, then quenched by the addition of H$_2$O (10 mL). The layers were separated and the aqueous layer was extracted with CHCl$_3$ (2 x 10 mL). The combined organic layers were washed with a saturated aqueous NH$_4$Cl solution, then dried over MgSO$_4$, filtered and concentrated. The title compound was
obtained after radial chromatography (1mm plate, 20% EtOAc/hexanes) as a white solid, 0.094 g (92%). Data are: mp = 68-72 °C ; [α]_D^23 +25.2° (c 1.0, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 8.11-8.08 (m, 2H), 7.59-7.54 (m, 1H), 7.47-7.42 (m, 2H), 7.38 (d, J = 3.3 Hz, 1H), 7.08 (dd, J = 3.0, 9.0 Hz, 1H), 6.92 (d, J = 9.3 Hz, 1H), 6.25-6.21 (m, 1H), 5.63-5.47 (m, 2H), 3.89 (s, 3H), 3.79 (s, 3H), 2.76-2.70 (m, 1H), 2.62-2.53 (m, 1H), 2.06-1.97 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 196.5, 166.3, 153.8, 153.2, 136.0, 133.2, 129.9, 128.5, 125.7, 123.7, 121.4, 114.5, 113.2, 79.3, 56.3, 55.9, 34.2, 25.8, 13.9.

(1S)-Benzoic acid 1-(2,5-dimethoxy-phenoxycarbonyl)-hex-3-enyl ester (219). To a flame dried round bottom flask was added activated 4 angstrom molecular sieves (0.100 g), trans-Ν,Ν-bis(p-toluenesulfonyl)-1,2-cyclohexanediamine (0.027 g, 0.065 mmol), K₂CO₃ (0.036 g, 0.260 mmol) and 1.25 mL of CH₂Cl₂. The mixture was cooled to 0 °C and SnCl₄ (0.065 mL, 1.0 M in CH₂Cl₂) was added followed by bis(trimethylsilyl) peroxide (0.070 mL, 0.325 mmol). The mixture was stirred at 0 °C for 5 minutes, then (1S)-benzoic acid 1-(2,5-dimethoxy-benzoyl)-hex-3-enyl ester 218 (0.048 g, 0.130 mmol) was added as a CH₂Cl₂ solution (2.0 mL). The reaction stirred at 0 °C for 20 min, at which time the reaction was quenched by the addition of a saturated aqueous NaHCO₃ (5 mL) followed by a saturated aqueous Na₂S₂O₃ solution (5 mL). The mixture was stirred at ambient temperature for 30 minutes then diluted with 10 mL of CH₂Cl₂ and the layers
separated. The aqueous phase was extracted with CH₂Cl₂ (2 x 20 mL) and the combined organic layers were washed with H₂O followed by a saturated aqueous NaCl solution. The mixture was then dried over Na₂SO₄, filtered, concentrated and purified via flash column chromatography (30% Et₂O/hexanes) to provide 0.037 g (74%) of the title compound as a colorless oil. Data are: [α]D²³ -11.1° (c 1.0, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 8.14-8.11 (m, 2H), 7.62-7.57 (m, 1H), 7.49-7.44 (m, 2H), 6.90 (d, J = 9.0 Hz, 1H), 6.75 (dd, J = 3.0, 9.0 Hz, 1H), 6.70 (d, J = 3.0 Hz, 1H), 5.82-5.72 (m, 1H), 5.65-5.50 (m, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 2.90-2.86 (m, 2H), 2.08 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 168.1, 166.1, 153.9, 145.4, 140.0, 137.1, 133.5, 130.1, 129.7, 128.6, 122.5, 113.7, 112.1, 109.4, 72.6, 56.8, 56.0, 34.9, 25.9, 13.9.

(S)-1-(2,5-dimethoxyphenyl)-2-hydroxyheptan-1-one (222). To a 100 mL round bottom flask containing (S)-2-benzhydryloxy-1-(2,5-dimethoxy-phenyl)-hept-4-en-1-one 216 (0.150 g, 0.348 mmol) was added dry toluene. Then 10% Pd on activated carbon (0.030 g) was carefully added to the solution and the mixture stirred at ambient temperature under a H₂ atmosphere (balloon pressure). After 30 h the mixture was filtered through a silica gel plug, eluting with EtOAc. The solvent was removed in vacuo and the residue dissolved in CH₂Cl₂ (3.5 mL). Then trifluoroacetic acid (0.060 mL, 0.70 mmol) was added dropwise. The reaction was stirred at ambient temperature for 30 min. then quenched by the addition of a saturated aqueous NaHCO₃ solution (10 mL).
layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 20 mL). The combined organic layers were washed with a saturated aqueous NaCl solution, then dried over MgSO$_4$, filtered and concentrated in vacuo. Chromatography (radial, 1 mm plate, 20% EtOAc/hexanes) afforded the title compound, 0.074 g (80%), as a colorless oil. Data are: TLC $R_f$ = 0.26 (20% EtOAc/hexanes); [$\alpha$]$_D^{23}$ –51.0° (c 1.0, CHCl$_3$); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.34 (d, $J$ = 2.5 Hz, 1H), 7.09 (dd, $J$ = 3.5, 9.0 Hz, 1H), 6.92 (d, $J$ = 9.0 Hz, 1H), 5.12-5.09 (m, 1H), 3.87 (s, 3H), 3.81 (obs s, 1H), 3.80 (s, 3H), 1.80-1.73 (m, 1H), 1.52-1.18 (m, 7H), 0.85 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 203.5, 153.8, 153.4, 124.6, 121.5, 114.5, 114.5, 113.3, 56.1, 56.0, 34.7, 31.8, 25.4, 22.7, 14.2; HRMS (EI$^+$) found 266.1531 M$^+$, calcd 266.1518 for C$_{15}$H$_{22}$O$_4$.

7.4. Synthesis of Ragaglitazar

4-(hydroxymethyl)phenyl pivalate (229). To a flame dried 500 mL round bottom flask was added NaH (dry 95%, 2.13 g, 88.9 mmol) and 400 mL of THF. The suspension was cooled to 0 °C under N$_2$. Then 4-hydroxybenzyl alcohol (10.06 g, 80.9 mmol) was added in one portion. The mixture stirred at 0 °C until bubbling ceased at which time the reaction was warmed to ambient temperature and stirred for an additional 30 min. The mixture was again cooled to 0 °C and trimethylacetyl chloride (10.95 mL, 88.9 mmol) was added slowly. After stirring for 30 min at 0 °C the mixture was warmed to ambient temperature and stirred for 2 h. Then 100 mL of a saturated aqueous NaHCO$_3$ solution was added followed by 300 mL of H$_2$O. The mixture was extracted with EtOAc (3 x 100
mL), the combined organic layers were washed with a saturated aqueous NaCl solution, dried over MgSO₄, filtered, and concentrated. The crude product was purified via column chromatography (40% EtOAc/hex) to afford 13.40 g (80%) of the title compound as a pale yellow oil which solidified in cold storage. Data are: ¹H NMR (CDCl₃, 300 MHz) δ 7.38-7.36 (m, 2H), 7.06-7.03 (m, 2H), 4.67 (s, 2H), 1.84 (bs, 1H), 1.37 (s, 9H).

4-(bromomethyl)phenyl pivalate (230). To an oven dried 500 mL round bottom flask was added LiBr (55.84 g, 643 mmol), THF (120 mL) and NEt₃ (22.4 mL, 160.8 mmol). Then 4-(hydroxymethyl)phenyl pivalate 229 (13.4 g, 64.3 mmol) was added as a THF solution (200 mL). The mixture was cooled to 0 °C and methanesulfonyl chloride (10.45 mL, 135 mmol) was added dropwise. The solution stirred at 0 °C for 2 h at which time H₂O (200 mL) was added. The solution was warmed to ambient temperature and extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were washed with a saturated aqueous NaHCO₃ solution, dried over MgSO₄, filtered and concentrated. The crude product was purified via column chromatography (10% EtOAc/hex) to provide 14.15 g (81%) of the desired compound as a white solid. Data are: mp = 58-60 °C; ¹H NMR (CDCl₃, 500 MHz) δ 7.41-7.40 (m, 2H), 7.05-7.03 (m, 2H), 4.50 (s, 2H), 1.36 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 177.1, 151.2, 135.3, 130.4, 122.1, 39.3, 33.0, 27.3; HRMS (EI⁺) found 270.0255 M⁺, calcd 270.0255 for C₁₂H₁₅O₂Br.
Ethyl 2-(10H-phenoxazin-10-yl)acetate (239). To a flame dried 25 mL round bottom flask was added phenoxazine 238 (0.300 g, 1.64 mmol) followed by 1-methyl-2-pyrrolidinone (5.50 mL). Ethyl bromoacetate (0.910 mL, 8.20 mmol) was then added and the reaction warmed to 70 °C where it stirred for 20 h. The reaction mixture was then purified directly by column chromatography (10% Et₂O/hex) to afford 0.343 g (78%) of the title compound as an off-white powder. Data are: ¹H NMR (CDCl₃, 300 MHz) δ 6.89-6.76 (m, 6H), 6.42 (d, J = 7.5 Hz, 2H), 4.30 (obs q, J = 6.9, 14.1 Hz, 2H), 4.26 (s, 2H), 1.33 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 169.4, 145.3, 133.4, 123.6, 121.7, 115.5, 111.7, 61.5, 46.8, 14.2; HRMS (EI⁺) found 269.1053 M⁺, calcd 269.1052 for C₁₆H₁₅O₃N.

2-(10H-phenoxazin-10-yl)ethanol (240). To a flame dried 50 mL round bottom flask was added lithium aluminum hydride (95% powder, 0.120 g, 3.15 mmol) and THF (5 mL). Then ethyl 2-(10H-phenoxazin-10-yl)acetate 239 was added as a THF solution (10 mL + 3 mL rinse) and the mixture stirred at ambient temperature fro 2 h. Then additional lithium aluminum hydride (95% powder, 0.050 g, 1.32 mmol) was added and the reaction stirred for one hour. H₂O (50 mL) was then added followed by 1 M HCl aqueous solution (5 mL). Then mixture was then extracted with EtOAc (3 x 20 mL) and the combined
organic layers were washed with H₂O, a saturated aqueous NaCl solution then dried over 
Na₂SO₄, filtered, and concentrated. The crude title compound (0.279 g, 97%) was 
isolated as a pale orange/brown solid and carried on to the next step without further 
purification. Data are: ¹H NMR (CDCl₃, 300 MHz) δ 6.83-6.77 (m, 2H), 6.71-6.59 (m, 
6H), 3.89 (t, J = 6.3 Hz, 2H), 3.73 (t, J = 6.0 Hz, 2H), 2.07 (bs, 1H); ¹³C NMR (CDCl₃, 
75 MHz) δ 144.9, 133.6, 123.8, 121.4, 115.6, 112.0, 59.3, 46.9.

2-(10H-phenoxazin-10-yl)ethyl methanesulfonate (241).³ To a 100 mL round bottom 
flask containing 2-(10H-phenoxazin-10-yl)ethanol (0.274 g, 1.20 mmol) was added 
CH₂Cl₂ (24 mL) and NEt₃ (0.835 mL, 6.0 mmol). Then methanesulfonyl chloride (0.390 
mL, 5.04 mmol) was added dropwise and the reaction stirred at ambient temperature for 2 
h. Then H₂O (25 mL) was added and the layers separated. The organic layer was washed 
with another 25 mL of H₂O, then dried over MgSO₄, filtered and concentrated. The crude 
product was then purified by radial chromatography (2 mm plate, 3:1:6 CH₂Cl₂:Et₂O:hex 
mixture) to afford 0.318 g (86%) of the desired compound as a fluffy off-white solid. 
Data are: mp = 90-92 °C; ¹H NMR (CDCl₃, 500 MHz) δ 6.85-6.81 (m, 2H), 6.73-6.70 (m, 
2H), 6.67 (dd, J = 1.5, 7.5 Hz, 2H), 6.58 (d, J = 7.5 Hz, 2H), 4.42 (t, J = 7.0 Hz, 2H), 
3.95 (t, J = 7.0 Hz, 2H), 3.00 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 145.0, 132.7, 124.0, 
122.0, 116.0, 111.7, 64.5, 43.6, 37.8; HRMS (EI⁺) found 305.0721 M⁺, calcd 305.0722 
for C₁₅H₁₅O₄NS.
(S)-4-(2-(benzhydryloxy)-3-(2,5-dimethoxyphenyl)-3-oxopropyl)phenyl pivalate (231). To a flame dried round bottom flask was added 2-benzhydryloxy-1-(2,5-dimethoxy-phenyl)-ethanone 209 (1.0g, 2.76 mmol), O(9)-allyl-N-2’,3’,4’-trifluorobenzyl hydrocinchonidinium bromide 44 (0.157g, 0.28 mmol), CH₂Cl₂ (14 mL) and hexane (14 mL). The solution was cooled to −35 °C and then CsOH•H₂O (2.32g, 13.8 mmol) was added in one portion. The mixture stirred for 10 min at which time 4-(bromomethyl)phenyl pivalate 230 (3.74g, 13.8 mmol) was added. The mixture stirred at −35 °C for 24 h at which time the reaction was diluted with Et₂O (400 mL) and H₂O (150 mL). The layers were mixed and then separated and the organic layer was washed with H₂O (2 x 50 mL) followed by a saturated aqueous solution of NaCl, then dried over MgSO₄. The mixture was filtered, the solvent removed in vacuo and the crude residue purified by column chromatography (10 - 20% EtOAc/hexane gradient) to afford 1.45 g (95%) of the desired compound as a colorless oil. Early column fractions were collected and concentrated to produce 2.82 g (94% recovery) of analytically pure 4-(bromomethyl)phenyl pivalate. Data are; [α]D²³ +14.0° (c 1.3, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.32-6.81 (m’s, 17H), 5.42 (s, 1H), 5.12 (dd, J = 3.0, 10.0 Hz, 1H), 3.76 (s, 3H), 3.56 (s, 3H), 3.03 (dd, J = 3.0, 14.0 Hz, 1H), 2.86 (dd, J = 10.0, 13.5 Hz, 1H), 1.37 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 202.0, 177.4, 154.0, 152.8, 150.0, 142.7, 141.3, 135.9, 130.8, 128.5, 128.4, 127.9, 127.7, 127.4, 127.3, 121.4, 120.7, 114.3, 113.6, 82.7, 82.6, 56.1, 56.0, 39.3, 38.5, 27.5; HRMS (FAB⁺) found 575.2420 [M+Na]⁺, calcd
575.2404 for C_{35}H_{36}O_{6}Na; The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 1.0 mL/min, 23°C, λ = 254 nm, retention times: S (major) 7.9 min, R (minor) 6.1 min, 91.4 : 8.6 er, 83% ee). The absolute configuration was determined by elaboration of the product to known compounds described below.

(S)-4-(3-(2,5-dimethoxyphenyl)-2-hydroxy-3-oxopropyl)phenyl pivalate (232). To a 250 mL round bottom flask containing (S)-4-(2-(benzhydryloxy)-3-(2,5-dimethoxyphenyl)-3-oxopropyl)phenyl pivalate 231 (1.315 g, 2.38 mmol) was added CH_{2}Cl_{2} (48 mL) and the solution was cooled to −78 °C. Then TiCl_{4} (1.0 M in CH_{2}Cl_{2}, 2.38 mL) was added dropwise over 5 min and the reaction stirred at −78 °C for 20 min. Then a saturated aqueous NaHCO_{3} solution was added (50 mL) and the mixture warmed to ambient temperature. The layers were separated and the aqueous phase extracted with CH_{2}Cl_{2} (3 x 30 mL). The combined organic layers were washed with a saturated aqueous NaCl solution, dried over Na_{2}SO_{4}, filtered and concentrated. The crude product was purified via radial chromatography (4 mm plate, 20% EtOAc/hex) to afford 0.843 g (92%) of the title compound as a colorless viscous oil. Data are: [α]_{D}^{23} −34.4° (c 1.4, CHCl_{3}); {\text{1H NMR (CDCl}_{3}, 500 MHz) δ 7.34 (d, J = 3.5 Hz, 1H), 7.17-7.11 (m, 3H), 6.97-6.94 (m, 3H), 5.38-5.37 (m, 1H), 3.89 (s, 3H), 3.87 (obs m, 1H), 3.81 (s, 3H), 3.13 (dd, J = 3.0, 14.0 Hz, 1H), 2.73 (dd, J = 7.0, 14.0 Hz, 1H), 1.35 (s, 9H); {\text{13C NMR (CDCl}_{3}, 125
MHz) δ 201.9, 177.2, 154.0, 153.5, 149.9, 135.2, 130.5, 124.4, 122.1, 121.2, 114.7, 113.4, 77.5, 56.2, 56.0, 40.3, 39.2, 27.3; HRMS (FAB+) found 409.1613 [M+Na]+, calcd 409.1622 for C_{22}H_{26}O_{6}Na.

(S)-2,5-dimethoxyphenyl 2-hydroxy-3-(4-phenylpivalate)propanoate (233). To a flame dried round bottom flask was added activated 4 angstrom molecular sieves (0.500 g), trans-\(\text{N,N-bis}(p\text{-toluenesulfonyl})\)-1,2-cyclohexanediamine (0.840 g, 1.99 mmol), K_{2}CO_{3} (0.550 g, 3.98 mmol) and 15.0 mL of CH_{2}Cl_{2}. The mixture was cooled to 0 °C and SnCl_{4} (2.0 mL, 1.0 M in CH_{2}Cl_{2}) was added followed by bis(trimethylsilyl)peroxide (0.855 mL, 3.98 mmol). The mixture was stirred at 0 °C for 5 minutes, then (S)-4-(3-(2,5-dimethoxyphenyl)-2-hydroxy-3-oxopropyl)phenyl pivalate 232 (0.770 g, 1.99 mmol) was added as a CH_{2}Cl_{2} solution (16.0 mL + 4.0 mL round bottom rinse). The reaction stirred at 0 °C for 75 min, at which time the reaction was quenched by the addition of a saturated aqueous NaHCO_{3} (20 mL) followed by a saturated aqueous Na_{2}S_{2}O_{3} solution (15 mL). The mixture was warmed to ambient temperature and filtered through a celite pad. The product was rinsed off the celite with CH_{2}Cl_{2} (150 mL) and the layers were then separated. The organic layer was washed with a saturated aqueous NaCl solution, dried over Na_{2}SO_{4}, filtered, concentrated and purified via flash column chromatography (50% Et_{2}O/hexanes) to provide 0.665 g (83%) of the title compound as a fluffy white solid. Then, 0.510 g of the white solid was dissolved in a minimal amount of warm
Et₂O:hexanes (1:1) and the product was allowed to recrystallize overnight. Removal of the residual solvent and subsequent drying of the needle-like crystals provided 0.380 g (75%) of the title compound with 95.8% ee. Data are: \([\alpha]_D^{23} -7.3^\circ\) (c 1.0, CHCl₃); mp = 94-96 °C; \(^1\)H NMR (CDCl₃, 500 MHz) \(\delta\) 7.38-7.37 (m, 2H), 7.05-7.02 (m, 2H), 6.92 (d, \(J = 8.5\) Hz, 1H), 6.77 (dd, \(J = 3.0, 9.0\) Hz, 1H), 6.59 (d, \(J = 3.0, 1H\)) , 4.73-4.70 (m, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.34 (dd, \(J = 3.5, 14.0\) Hz, 1H), 3.15 (dd, \(J = 7.0, 14.0\) Hz, 1H), 2.79-2.76 (m, 1H), 1.36 (s, 9H); \(^{13}\)C NMR (CDCl₃, 125 MHz) \(\delta\) 177.2, 172.4, 153.9, 150.3, 145.2, 139.8, 133.9, 130.9, 121.6, 113.6, 112.1, 109.3, 71.4, 56.6, 56.0, 40.0, 39.3, 27.3; HRMS (FAB⁺) found 425.1583 [M+Na]⁺, calcd 425.1571 for C₂₂H₂₆O₇Na. The enantiomeric excess was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% IPA/hexane, 1.9 mL/min, 23°C, \(\lambda = 254\) nm, retention times: S (major) 14.4 min, R (minor) 11.4 min, 96% ee).

![Reagents and products](image)

(S)-2,5-dimethoxyphenyl 2-ethoxy-3-(4-pivalatephenyl)propanoate (234). To a flame dried 25 mL round bottom flask was added (S)-2,5-dimethoxyphenyl 2-hydroxy-3-(4-phenylpivalate)propanoate 233 (0.200 g, 0.497 mmol) and CHCl₃ (10.0 mL). The solution was cooled to 0 °C and proton sponge (0.425 g, 1.99 mmol) was added followed by triethylxonium tetrafluoroborate (0.380 g, 1.99 mmol). The mixture was stirred for 60 min at 0 °C then warmed to ambient temperature where it stirred for 24 h. The mixture was then quickly passed through a small silica gel plug, eluting with EtOAc (75 mL). The
eluent was then concentrated and purified via column chromatography (30% Et₂O/hex) to afford 0.169 g (79%) of the title compound as a white solid with 94.8% ee. Data are: TLC R_f = 0.40 (30% EtOAc/hex); [α]_D

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–1.4° (c 1.9, CHCl₃); mp = 100-102 °C; ¹H NMR (CDCl₃, 500 MHz) δ 7.37-7.34 (m, 2H), 7.04-7.01 (m, 2H), 6.90 (d, J = 9.0 Hz, 1H), 6.74 (dd, J = 3.0, 9.0 Hz, 1H), 6.52 (d, J = 3.0 Hz, 1H), 4.27 (dd, J = 4.0, 8.0 Hz, 1H), 3.85-3.76 (obs m, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.50-3.44 (m, 1H), 3.23 (dd, J = 5.0, 14.0 Hz, 1H), 3.15 (dd, J = 9.0, 14.0 Hz, 1H), 1.36 (s, 9H), 1.22 (t, J = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 177.2, 170.6, 154.0, 150.2, 145.4, 140.2, 134.8, 130.7, 121.5, 113.8, 112.0, 109.4, 80.1, 66.7, 56.7, 56.0, 39.3, 39.0, 27.4, 15.3; HRMS (FAB⁺) found 453.1892 [M+Na]⁺, calcd 453.1884 for C₂₄H₃₀O₇Na. The enantiomeric excess was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 1.0 mL/min, 23°C, λ = 254 nm, retention times: S (major) 10.1 min, R (minor) 8.3 min, 95% ee).

(S)-methyl 2-ethoxy-3-(4-hydroxyphenyl)propanoate (235). To a 25 mL round bottom flask containing (S)-2,5-dimethoxyphenyl 2-ethoxy-3-(4-pivalatephenyl)propanoate 234 (0.078 g, 0.181 mmol) was added THF (1.80 mL) and the solution was cooled to 0 °C. Then a freshly prepared NaOMe/MeOH (0.1 M, 5.45 mL) solution was added and the mixture was allowed to slowly warm to ambient temperature over 2h. The reaction was stirred at ambient temperature for 24 h at which time a saturated aqueous NH₄Cl solution (10 mL) was added followed by H₂O (10 mL). The solution was then extracted with EtOAc (3 x 15 mL), the combined organic layers were then dried over Na₂SO₄, filtered,
and concentrated. The product was isolated via radial chromatography (1 mm plate, 20% EtOAc/hex) to provide 0.038 g (94%) of the title compound as a yellow oil with 95.0% ee. Data are: [α]D<sup>23</sup> −18.7° (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.10-7.08 (m, 2H), 6.75-6.73 (m, 2H), 5.12 (m, 1H), 4.01 (dd, J = 6.0, 7.5 Hz, 1H), 3.71 (s, 3H), 3.63 (m, 1H), 3.39-3.33 (m, 1H), 2.98-2.91 (m, 2H), 1.17 (t, J = 7.0 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 173.4, 154.6, 130.7, 129.2, 115.4, 80.6, 66.5, 52.1, 38.7, 15.2; HRMS (EI<sup>+</sup>) found 224.1043 M<sup>+</sup>, calcld 224.1049 for C<sub>12</sub>H<sub>16</sub>O<sub>4</sub>. The enantiomeric excess was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 0.5 mL/min, 23°C, λ = 254 nm, retention times: S (major) 14.8 min, R (minor) 14.1 min, 95% ee).

![Chemical structure](image)

(S)-methyl 3-(4-(2-(10H-phenoxazin-10-yl)ethoxy)phenyl)-2-ethoxypropanoate (237).

To a 25 mL round bottom flask containing (S)-methyl 2-ethoxy-3-(4-hydroxyphenyl) propanoate 235 (0.069 g, 0.308 mmol) was added toluene (4.0 mL) and K<sub>2</sub>CO<sub>3</sub> (0.085 g, 0.620 mmol). Then 2-(10H-phenoxazin-10-yl)ethyl methanesulfonate 241 (0.125 g, 0.400 mmol) was added and the mixture warmed to 100–105°C where it stirred for 45 h, with additional toluene being added at various intervals to maintain the reaction volume. The reaction was then cooled to ambient temperature where H<sub>2</sub>O was added (10 mL) followed by a saturated aqueous NH<sub>4</sub>Cl solution (10 mL). The mixture was then extracted with EtOAc (3x20 mL). The combined organic layers were washed with a saturated aqueous NaCl solution, dried over MgSO<sub>4</sub>, filtered and concentrated. The crude product
was purified via radial chromatography (1mm plate, 10% EtOAc/hex) to afford 0.113 g (85%) of the desired product as an off-white solid in 94.6% ee. Data are: TLC R_f = 0.44 (50% Et_2O/hex); [α]_D^{23} = -9.6° (c 1.9, CHCl_3); mp = 96-98 °C; ^1H NMR (CDCl_3, 500 MHz) δ 7.17-7.15 (m, 2H), 6.85-6.79 (m, 4H), 6.70-6.63 (m, 6H), 4.18 (t, J = 7.0 Hz, 2H), 4.00 (dd, J = 5.5, 7.5 Hz, 1H), 3.97 (t, J = 7.0 Hz, 2H), 3.72 (s, 3H), 3.64-3.58 (m, 1H), 3.39-3.33 (m, 1H), 3.01-2.93 (m, 2H), 1.18 (t, J = 7.5 Hz, 3H); ^13C NMR (CDCl_3, 125 MHz) δ 173.1, 157.4, 145.0, 133.3, 130.6, 130.0, 123.8, 121.5, 115.7, 114.5, 111.8, 80.5, 66.5, 63.6, 52.0, 44.1, 38.6, 15.2; HRMS (FAB^+) found 456.1797 [M+Na]^+, calcd 456.1781 for C_{26}H_{27}O_5NNa. The enantiomeric excess was determined by chiral HPLC (DAICEL Chiralpack AD column, 5% IPA/hexane, 1.0 mL/min, 23°C, λ = 254 nm, retention times: S (major) 11.1 min, R (minor) 10.4 min, 95% ee).

(--)-Ragaglitazar. To a 25 mL round bottom flask containing (S)-methyl 3-(4-(2-(10H-phenoxazin-10-yl)ethoxy)phenyl)-2-ethoxypropanoate 237 (0.10 g, 0.230 mmol) was added MeOH (2.30 mL) followed by 3N NaOH (2.0 mL). The reaction mixture was stirred at ambient temperature for 6 h at which time H_2O (35 mL) was added and the mixture washed with Et_2O (15 mL). Then 1M HCl was added dropwise until a pH of 2 was obtained. The mixture was then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with H_2O followed by a saturated aqueous NaCl solution, then dried over Na_2SO_4, filtered and concentrated to provide 0.089 g (92%) of the title compound as a foaming viscous oil that solidified into a white solid which matched the
following reported values. Data are: $[\alpha]_D^{23} -8.7^\circ$ (c 1.0, CHCl$_3$); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 9.74 (bs, 1H), 7.18 (d, $J = 7.5$ Hz, 1H), 6.85-6.79 (m, 4H), 6.70-6.63 (m, 6H), 4.17 (t, $J = 7.0$ Hz, 2H), 4.05 (dd, $J = 4.5$, 8.0 Hz, 1H), 3.97 (t, $J = 7.0$ Hz, 2H), 3.66-3.60 (m, 1H), 3.46-3.40 (m, 1H), 3.08 (dd, $J = 4.5$, 14.5 Hz, 1H), 2.97 (dd, $J = 8.5$, 14.0 Hz, 1H), 1.19 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 176.4, 157.5, 145.0, 133.3, 130.8, 129.5, 123.8, 121.5, 115.7, 114.6, 111.8, 79.9, 67.0, 63.6, 44.1, 38.1, 15.2.

7.5. Synthesis of Kurasoin A

(S)-4-(2-hydroxy-3-(methoxy(methyl)amino)-3-oxopropyl)phenyl pivalate (244). To a flame dried 10 mL round bottom flask was added $N,O$-dimethylhydroxylamine hydrochloride (0.073 g, 0.750 mmol) and CH$_2$Cl$_2$ (1.3 mL). Then AlMe$_3$ (0.370 mL, 2.0$M$ in hex) was added dropwise and the solution stirred at ambient temperature for 30 min. Then (S)-2,5-dimethoxyphenyl 2-hydroxy-3-(4-phenylpivalate)propanoate 233 (0.050 g, 0.124 mmol) was added as a CH$_2$Cl$_2$ solution (1.0 mL + 0.3 mL rinse) and the mixture was stirred for 5 h at ambient temperature. The reaction was then quenched by the addition of a 0.5M HCl solution (2 mL) then diluted with CH$_2$Cl$_2$ and H$_2$O. The layers were mixed and separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were washed with a saturated aqueous NaCl solution, dried over Na$_2$SO$_4$, filtered and concentrated. The residual oil was purified via radial chromatography (1mm plate, 60% EtOAc/hex) to afford 0.036 g (92%) of the title
compound as a yellow oil. Data are: TLC R<sub>f</sub> = 0.34 (80% EtOAc/hex); [α]<sub>D</sub><sup>23</sup> = –38.0° (c 1.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.24-7.22 (m, 2H). 6.99-6.98 (m, 2H), 4.61 (bm, 1H), 3.71 (s, 3H), 3.32 (bm, 1H), 3.24 (s, 3H), 3.05, (dd, J = 3.5, 13.5 Hz, 1H), 2.86 (dd, J = 7.5, 14.0 Hz, 1H), 1.35 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 177.3, 174.2, 150.1, 134.8, 130.5, 121.5, 69.8, 61.6, 40.6, 39.2, 32.6, 27.3.

(S)-4-(3-(methoxy(methyl)amino)-3-oxo-2-(triethylsilyloxy)propyl)phenyl pivalate (245). To a 25 mL round bottom flask containing (S)-4-(2-hydroxy-3-(methoxy(methyl)amino)-3-oxopropyl)phenyl pivalate 244 (0.032 g, 0.104 mmol) was added DMF (1.0 mL) followed by imidazole (0.028 g, 0.416 mmol). Then chlorotriethylsilane (0.035 mL, 0.208 mmol) was added and the reaction was stirred at ambient temperature for 5 h at which time a H<sub>2</sub>O (10 mL) was added and the mixture extracted with EtOAc (3 x 10 mL). The combined organic layers were then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The product was isolated via radial chromatography (1 mm plate, 20% EtOAc/hex) to provide 0.040 g (91%) of the title compound as a colorless oil. Data are: TLC R<sub>f</sub> = 0.52 (40% EtOAc/hex); [α]<sub>D</sub><sup>23</sup> = +3.1° (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.24-7.21 (m, 2H), 6.97-6.94 (m, 2H), 4.69 (bm, 1H), 3.52 (s, 3H), 3.17 (s, 3H), 3.05 (dd, J = 5.4, 13.2 Hz, 1H), 2.87 (dd, J = 7.8, 13.2 Hz, 1H), 1.35 (s, 9H), 0.89-0.84 (m, 9H), 0.55-0.46 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 177.4, 150.1,
135.4, 130.8, 121.5, 70.9, 41.0, 39.3, 32.7, 27.4, 6.8, 4.8; HRMS (FAB+) found 446.2344 [M+Na]+, calcd 446.2333 for C_{22}H_{37}O_{5}NSiNa.

(S)-4-(3-oxo-4-phenyl-2-(triethylsilyloxy)butyl)phenyl pivalate (246). To a 25 mL round bottom flask containing (S)-4-(3-(methoxy(methyl)amino)-3-oxo-2-(triethylsilyloxy) propyl)phenyl pivalate 245 (0.114 g, 0.269 mmol) was added THF (4.5 mL) and the solution cooled to 0 °C. Then benzylmagnesium chloride (0.540 mL, 2.0 M in THF) was added slowly over 5 min. The reaction stirred at 0 °C for 2.5 h at which time H_{2}O was added (15 mL) and the mixture was then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_{2}SO_{4}, filtered and concentrated. The crude product was purified via radial chromatography (1mm plate, 5% EtOAc/hex) to afford 0.100 g (82%) of the desired product as colorless oil. Data are: TLC R_{f} = 0.75 (40% EtOAc/hex); [α]_{D}^{23} = -46.0° (c 2.0, CHCl_{3}); { }^{1}H NMR (CDCl_{3}, 500 MHz) δ 7.31-7.22 (m, 3H), 7.19-7.16 (m, 2H), 7.07 (d, J = 7.0 Hz, 2H), 6.98-6.96 (m, 2H), 4.36 (dd, J = 4.5, 7.5 Hz, 1H), 3.77 (d, J = 16.5 Hz, 1H), 3.67 (d, J = 17.0 Hz, 1H), 2.92 (dd, J = 4.5, 13.5 Hz, 1H), 2.84 (dd, J = 7.5, 13.5 Hz, 1H), 1.36 (s, 9H), 0.90-0.87 (m, 9H), 0.54-0.45 (m, 6H); { }^{13}C NMR (CDCl_{3}, 125 MHz) δ 210.7, 177.2, 150.2, 134.3, 134.0, 131.0, 130.0, 128.6, 127.0, 121.5, 79.6, 45.1, 41.2, 39.2, 27.3, 6.9, 4.8; HRMS (FAB+) found 455.2608 [M+H]+, calcd 455.2612 for C_{27}H_{39}O_{4}Si.


**(+)-Kurasoin A.** To a 25 mL round bottom flask containing (S)-4-(3-oxo-4-phenyl-2-(triethylsilyloxy)butyl)phenyl pivalate (0.038 g, 0.084 mmol) was added THF (2.0 mL) and the solution was cooled to 0 °C. Then tetrabutylammonium fluoride (0.090 mL, 1.0 M in THF) was added and the reaction stirred at 0°C for 15 min. Then H₂O (1.0 mL) was added followed by H₂O₂ (0.038 mL, 30% aqueous). Then LiOH(H₂O) (0.007 g, 0.167 mmol) was added and the reaction stirred for an additional 25 min at 0 °C. Then a saturated aqueous Na₂S₂O₃ solution (2 mL) was added followed by a saturated aqueous NH₄Cl solution (20 mL). The mixture was then extracted with EtOAc (1 x 15 mL) and CH₂Cl₂ (3 x 15 mL). Then combined organic layers were dried Na₂SO₄, filtered and concentrated. The crude product was then dissolved in a minimal amount of CH₂Cl₂ and purified via column chromatography (40% EtOAc/hex) to provide 0.014 g (65%) of the title compound as a white solid. Data are: TLC Rᵋ = 0.39 (50% EtOAc/hex); [α]D⁺23 = +8.4° (c 0.5, CH₃OH), lit.⁴ synthetic = [α]D⁺22 = +9° (c 1.0, CH₃OH), natural = [α]D⁺22 = +7° (c 0.1, CH₃OH); mp = 120–122 °C, lit.² mp = 121–123 °C; ¹H NMR (CD₂OD, 500 MHz) δ 7.28-7.01 (m, 7H), 6.70-6.68 (m, 2H), 4.33 (dd, J = 5.0, 7.5 Hz, 1H), 3.78 (d, J = 17.0 Hz, 1H), 3.72 (d, J = 16.5 Hz, 1H), 2.95 (dd, J = 5.0, 14.5 Hz, 1H), 2.75 (dd, J = 7.5, 14.0 Hz, 1H); ¹³C NMR (CD₂OD, 125 MHz) δ 212.4, 157.3, 135.6, 131.7, 131.0, 129.6, 129.5, 127.9, 116.3, 78.9, 46.7, 40.4. HRMS (FAB⁺) found 279.0989 [M+Na]⁺, calcd 279.0992 for C₁₆H₁₆O₃Na.
7.6. References


7.7. Selected NMR Spectra