Partial Asymmetric Synthesis of the Core of Mahuannin D

By

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Abstract

Many studies have focused on the isolation and study of the biologically active molecules present in herbal Chinese medicines in an effort to determine their therapeutic potential. One such drug that has been investigated is the ephedra, or ma huang, derived “mao-kon”. From the ephedra plant was isolated mahuannin D, a bisflavanoid natural product that demonstrates hypotensive activity. This project focuses on the asymmetric synthesis of the core of mahuannin D in conjunction with the development of asymmetric, cinchona alkaloid organocatalyzed conjugate addition reactions and Michael addition reactions that lead to advanced intermediates along the synthetic pathway to the bisflavanoid core of mahuannin D.

We developed the asymmetric conjugate addition addition of 3, 5-bis(benzyloxy)phenol to (E)-ethyl 4-(2,4-dihydroxyphenyl)-2-oxo-but-3-enoate at room temperature in toluene to afford 81% yield and 74% ee. We also developed the asymmetric Michael addition of 1,5-dioxaspiro[5.5]undecane-8,10-dione to (E)-ethyl 4-(2,4-dihydroxyphenyl)-2-oxo-but-3-enoate at -30°C in THF to afford 41% yield and >99% ee. The synthetic chemistry leading to the core of mahuannin D was also developed while maintaining the enantiomeric excess imbued through the asymmetric transformation.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>°C</td>
<td>Degrees Celsius</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Cat</td>
<td>Catalyst</td>
</tr>
<tr>
<td>DIBAL</td>
<td>Diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DHQD</td>
<td>Dihydroquinidine</td>
</tr>
<tr>
<td>DHQN</td>
<td>Dihydroquine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiometric excess</td>
</tr>
<tr>
<td>eq</td>
<td>Equivalents</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>h</td>
<td>Hours</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IFB</td>
<td>Interrupted Feist-Benary</td>
</tr>
<tr>
<td>in vacuo</td>
<td>Under reduced pressure</td>
</tr>
<tr>
<td>iPr</td>
<td>Isopropyl</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium Diisopropylamide</td>
</tr>
<tr>
<td>M</td>
<td>Molar</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>min</td>
<td>Minutes</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliters</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimoles</td>
</tr>
<tr>
<td>nBu</td>
<td>n-Butyl</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>OTf</td>
<td>Trifluoromethanesulfonate</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>PTC</td>
<td>Phase Transfer Catalyst</td>
</tr>
<tr>
<td>PYR</td>
<td>Pyrimidine</td>
</tr>
<tr>
<td>QD</td>
<td>Quinidine</td>
</tr>
<tr>
<td>QN</td>
<td>Quinine</td>
</tr>
<tr>
<td>rfx</td>
<td>Reflux</td>
</tr>
<tr>
<td>tBu</td>
<td>tert-Butyl</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
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1. Introduction

1.1 Natural Product Synthesis

Nature abounds with molecules that can be exploited for countless uses in the fields of medicine, industry, entertainment, and nutrition. These compounds can themselves be useful such as artemisinin, a drug that represents the state of the art in antimalarial medication,\(^1\) or vitamin B12, whose role is vital in brain functioning, blood formation and DNA synthesis (Figure 1-1). Other molecules such as amino acids, sugars, carbohydrates, and hydroxy acids prove useful as starting points or intermediates along synthetic routes to more structurally complex molecules of import.

Figure 1-1

![Artemisinin and Vitamin B12](image-url)
Demand for such natural products frequently exceeds the supply that can be readily extracted from their original source in nature. For instance, there is only enough taxol, a potent anticancer treatment, in the yew tree from which it is derived for the extraction of a single dose. This predicament leaves organic chemists the task of orchestrating their syntheses.

As many of these compounds are chiral, often displaying drastically different biological and chemical activity between their various stereoisomers, the stereospecific construction of natural products is of paramount importance to insure the molecule’s intrinsic reactivity. Chiral molecules, defined as molecules that are not superimposable over their mirror image, exhibit the same physical characteristics such as crystal stucture, boiling point, melting point, polarity, NMR spectra, and they interact identically with achiral molecules. They interact differently with polarized light, leading enantiomers to rotate light in equal magnitudes but opposite directions. They will also interact with each enantiomer of chiral compounds differently.

Countless molecules in nature and our bodies are chiral, and so interact with each enantiomer of other chiral molecules differently. Examples of such substances include olfactory receptors, amino acids, and enzymes, fitting like hands in a glove to make different enantiomers smell differently and enzymes selectively react with one enantiomer over the other. The ubiquity of chiral molecules in our bodies necessitates the stereocontrolled production of pharmaceutical drugs. A tragic testament to the importance of chirality can be
found in the history of the drug thalidomide (Figure 1-2). A racemate of thalidomide (though thalidomide also racemizes in vivo) was sold as a sedative to treat women with morning sickness from 1957-1961. While the R enantiomer of thalidomide alleviates nausea, the S enantiomer inhibits angeogenesis, which impacts the development of limbs, eyes and ears.³ This led to mutation in the unborn fetuses, causing over 10,000 babies to be born with deformities. The potentially drastic difference in reactivity between enantiomers has led to the development of enantioselective reactions.

**Figure 1-2**

![Diagram of R-Thalidomide and S-Thalidomide](image)

**R-Thalidomide** (sleep-inducing) **S-Thalidomide** (teratogenic)

### 1.2 Michael Reaction

The Michael addition stands as a fundamental method of carbon-carbon bond formation. The Michael class of reactions describes reactions in which stabilized carbanions alkylate unsaturated electrophiles in the position β to an electron-withdrawing group. First published in 1883 by T. Komnenos with the
addition of deprotonated diethyl malonate to ethylidene malonate, it wasn’t until later that the addition of a carbon nucleophile to an electron-deficient double bond was thoroughly investigated by Arthus Michael. The Michael reaction was first coined in 1887 by Arthur Michael, an American chemist who discovered the addition of diethyl malonate to the β position of ethyl cinnamate in the presence of sodium ethoxide (Scheme 1-1).

Scheme 1-1

In 1894 Michael expanded the scope of the reaction by illustrating the efficacy of electron-deficient triple bonds as electrophilic acceptors in the Michael reaction. Michael donors are generally created through the deprotonation of ketones, nitriles, aldehydes, β-dicarbonyls, and other CH-activated compounds. The Michael reaction is base catalyzed, and can be run with relatively weak bases such as triethylamine in cases where the electron withdrawing group on the nucleophile is strong enough. Michael acceptors can be constructed through the activation of the alkene or alkyne moiety with almost any electron-withdrawing group. The reaction can occur intramolecularly as well as intermolecularly, and can be diasteroselective or enantioselective when the reagents have defined stereochemistry. Though it is possible for side
reactions leading to 1, 2-addition and self-condensation of the nucleophile, it is possible to tailor reaction conditions to favor the 1, 4-addition through optimization of such variables as solvent, temperature, additives and reagents.

The first step of the reaction proceeds through the enolization of the diethyl malonate through deprotonation at the \( \alpha \) position by ethoxide. The enolate, stabilized by various resonance structures allowed by the two ethyl ester electron withdrawing groups, attacks the unsaturated electrophile with 1, 4-regioselectively at the \( \beta \) position. The resulting carbanion, with the enolate transferred to the electrophilic moiety of the adduct, then abstracts a proton from ethanol to form the final Michael adduct (Scheme 1-2).

**Scheme 1-2**

Since its discovery, the Michael reaction has proved an invaluable method of carbon-carbon bond formation, and plays an integral role in many asymmetric natural product syntheses. In 1995 D.L. Boger performed the synthesis of the antitumor-antibiotic fredericamycin A through a cascade Michael addition-Dieckmann condensation. The substituted 4-methylpyridine was reacted with an excess of LDA, followed by the addition to the Michael acceptor
cyclopentenone. Intramolecular acylation then occurred between the enolate and ester moieties of the Michael adduct in situ to afford the resulting tricycle (Scheme 1-3).

Scheme 1-3

![Scheme 1-3](image)

*Fredericamycin A*

Stereocontrol is often of paramount importance in the synthesis of biologically active organic molecules; therefore much attention has recently been devoted to the development of asymmetric Michael addition reactions. A new stereocenter is created through the 1, 4-addition of Michael donors to activated alkenes with the possibility of another being formed through subsequent O-alkylation of an unreacted carbonyl, Dieckmann condensation, or any number of intramolecular reactions. The activating groups on both nucleophiles and electrophiles can be exploited as functional handles through which chirality can be induced. Michael reactions provide a useful transformation along the pathways to many privileged structures so
enantioselective and diastereoselective renditions of the reaction would simultaneously expand the scope of the reaction while providing a powerful tool in such realms as drug discovery, natural product synthesis, and industry.

In 1961, Walborsky demonstrated the efficacy of the Michael reaction in the chiral pool method of asymmetric induction through the addition of (-)-menthyl chloroacetate to ethyl acrylate in the presence of catalytic, achiral alkoxides.⁷

In 1973, Langstrom and Bergson reported the first example of an asymmetric Michael reaction between achiral starting materials in the presence of a catalytic amount of a chiral tertiary amine base.⁸

In 1979 Hermann and Wynberg employed cinchona alkaloid phase transfer catalysts (PTC) as a means of chiral induction into the Michael reaction.⁹ Since then such prolific chemists as E. J. Corey have investigated cinchona alkaloid catalyzed Michael reactions.¹⁰

### 1.3 Cinchona Alkaloids as Chiral Catalysts

Isolated from the barks of various cinchona trees, cinchona alkaloids were first discovered in 1820 when Pierre-Joseph Pelletier and Joseph Bienaimé Caventou found quinine (QN) to possess potent antimalarial activity.¹¹ Since then cinchona alkaloids have had a profound impact many facets of human society including medicine, chemistry, and the food industry. Of the roughly 700
metric tons of cinchona alkaloids extracted from the bark of *Cinchona ledgeriana* each year, most are used as food additives or, in the cases of quinine and a pseudoenantiomer quinidine (QD) respectively, are employed for their medicinal antimalarial and muscle relaxant and antiarrhythmic qualities (Figure 1-3).

**Figure 1-3**

Cinchona alkaloids impacted the world of chemistry as early as 1853, when Pasteur discovered their potential as racemate resolving agents through the crystallization of diastereiomic salts. They have since been a valued tool in the fields of enantioseparation, enantioselective analysis and, more recently, enantioselective catalysis. Pursuit of the asymmetric synthesis of quinine, sought initially to augment the potent antimalarial drug's limited supply, has itself contributed greatly to the field of organic chemistry through the discovery of
powerful synthetic methodologies. Woodward and Doering completed the first synthesis of quinine in 1944;\textsuperscript{13} however it wasn't until 2000 that Stork accomplished the first \textit{stereocontrolled} synthesis of quinine.\textsuperscript{14}

Today, cinchona alkaloids such as quinine and their various pseudoenantiomers represent some of the most powerful inducers of chirality in the realm of asymmetric organocatalysis. The efficacy of this cheap and abundant class of organocatalytic ligands can be traced back to the functional diversity of their chiral skeletal structures. Much of the catalytic functionality of cinchona alkaloids is imbued through the presence of a 1, 2-aminoalcohol moiety. The basic and bulky tertiary quinuclidine group allows cinchona alkaloids to bind to metals as chiral ligands, making them effective ligands in metal-catalyzed reactions.

The quinuclidine nitrogen can also act as a chiral nucleophile catalyst or base; facilitating innumerable asymmetric organocatalyzed reactions often through coordination of the quaternary ammonium salt of the cinchona alkaloid with achiral reagents under phase transfer conditions. The secondary 9-hydroxyl group can undergo hydrogen bonding (H-bonding) or act as a weak acid. It can also be further functionalized with bulky groups or transformed into ureas, amides or other functional groups to respectively alter the steric or electronic conditions surrounding the chiral locus of catalytic activity of the alkaloid. The free OH or thiourea derivatives of the 6'-methoxy group of quinine and quinidine can also be exploited to add another site of H-bond donation.
While the influence of each active site varies between each reaction, in general they all work in tandem to induce asymmetry.

In 1912 Bregid and Fiske published the first asymmetric reaction catalyzed by a cinchona alkaloid.\textsuperscript{12} They performed the hydrocyanation of benzaldehyde in the presence of catalytic amounts of quinine and quinidine to yield products with opposite optical activity. While the asymmetric induction was minimal, amounting to \(<10\%\) ee for both the R and S products, their chemistry proved that cinchona alkaloids could affect catalytic stereocontrol in reactions.

The first cinchona alkaloid catalyzed reaction to accomplish substantial chiral induction was performed by Pracejus and Mätje in 1960 (Scheme 1-5). In the presence of as little at 1 mol\% of $O$-acetylquinine, they were able to asymmetrically add methanol to phenylmethylketene to afford \((-\text{-})\text{-}\text{\(\alpha\)}\)-phenyl methyl-propionate in 93\% yield and 74\% ee.\textsuperscript{15}

**Scheme 1-5**
Another landmark in the evolution of cinchona alkaloid catalysis was marked by their use in the development of asymmetric thiol-conjugate additions, Michael additions, and β-lactone synthesis performed by Wynberg et al (Scheme 1-6) in the late 1970’s. Using various cinchona alkaloids, Wynberg was able to achieve impressive asymmetric catalysis in both the β-lactone synthesis and thiol-conjugate additions, at 98% and 75% ee respectively, as well as the modest enantioselectivity in the Michael addition of 25% ee.\textsuperscript{16,17,9}

**Scheme 1-6**

A powerful example of the importance and scope of cinchona alkaloids in the field of asymmetric catalysis can be found in its modification of the osmium
tetraoxide-induced asymmetric dihydroxylation of olefins. The asymmetric dihydroxylation of olefins in the presence of stoichiometric amounts of cinchona alkaloid-substituted osmium tetraoxide was first discovered by Sharpless and Hentges in 1980. Soon afterwards, Sharpless modified the reaction to require only catalytic amounts of cinchona alkaloid functionalized osmium,\textsuperscript{18} a monumental achievement that contributed to his receiving of the Nobel Prize in Chemistry in 2001.

In order to better understand the mechanisms of asymmetric chiral induction, computational and spectroscopic studies have illuminated the conformational structure of cinchona alkaloids in solution. In 1989 Dijkstra determined through a combination of NMR and molecular mechanics (MM) calculations that the overall conformation was most strongly influenced by rotation around the C8-C9 and C4-C9 bonds (Figure 1-4).\textsuperscript{19} The lowest energy confirmations can be described as syn-closed, syn-open, anti-closed and anti-open. Both ab initio and MM calculations indicated that the anti-open conformation is adopted in nonpolar solvents. Polar solvents are able to stabilize the relatively large dipole moments of the anti-closed and syn-closed conformers, so in polar solvents they prevail over the relatively apolar anti-open structure. However, protonated cinchona alkaloids exist solely as the anti-open conformation due to inhibited rotation about the C8-C9 and C4-C9 bonds. It is this anti-open conformation that concerns the molecule's catalytic potential. The pocket formed between the quinuclidine and quinoline groups forces hydrogen
bonded electrophiles into relatively rigid geometries while simultaneously restricting the angles of nucleophilic addition.

**Figure 1-4**

Since Bredig and Fiske first discovered their potential as asymmetric inducers, cinchona alkaloids have proven a prolific class of organocatalysts. Abundant and versatile, they continue to contribute to the field of organic chemistry through the asymmetric modification of such ubiquitous synthetic transformations as Aldol, the Diels-Alder, epoxidation, and dihydroxilation reactions to name a few. Their potency at affecting stereocontrol over a vast range of synthetic reactions made them ideal candidates for use as chiral catalysts in our project.
1.4 Enantioselective Michael Reaction

Motivated by the success of cinchona alkaloid catalyzed asymmetric IFB reactions,\textsuperscript{20} Profesor Calter and Jun Wang set out to investigate the asymmetric Michael reaction (Scheme 1-7). Initially interested in synthesizing advanced intermediates along the path to hexahydroquinoline calcium channel blockers, Calter and Wang set out to develop the asymmetric Michael addition of cyclic diones to enones.

Scheme 1-7

\[\begin{align*}
\text{R}_1 & \text{R}_2 \quad + \quad \text{R}_3 & \rightarrow & \text{R}_1 \text{R}_2 \text{R}_3 \text{R}_4 \\
\text{chiral} & \text{catalyst} & \text{NH}_3 & \rightarrow & \text{R}_1 \text{R}_2 \text{R}_3 \text{R}_4
\end{align*}\]

\(\beta,\gamma\)-unsaturated \(\alpha\)-ketoesters were chosen as the generic electrophile in order to mimic the reagent structure of proven IFB electrophiles.\textsuperscript{20, 21} 5, 5-dimethyl-1, 3-cyclohexadione (dimedone) was initially used as the nucleophile as it is a cyclic dione with methyl substitutions that sterically resemble functional groups at the 5 position that can be used to aromatize the ring. The Michael addition of dimedone to the various ketoesters yields lactones with an ester handle that can be exploited for further synthetic potential. The resulting
fused ring system structure is commonly observed in many biologically active natural products, making this class of asymmetric Michael addition reactions a powerful new synthetic tool in the realm of natural product synthesis. Pyrimidine-bis-cinchona alkaloid functionalized PTCs proved effective at inducing high levels of enantioselectivity in the IFB reaction, and so were the logical starting point of catalyst screening for the asymmetric Michael reaction.

Initial catalyst screening of the phenyl-substituted ketoester proved promising, giving yields as high as 95% and enantiomeric excesses (ee’s) of up to 84% (Table 1-1). Both results were achieved with the catalyst 5, illustrating the correlation between increased steric bulk at the C2 and C5 positions and enhanced ee’s. Screening of catalysts 2-5 showed that chiral induction was more heavily impacted by the increased bulk at the C2 position than at the C5 position. As larger groups at the C2 position led to increased ee’s, Calter and Wang decided to test the logical extrapolation of this trend by substituting the C2 position with the relatively large triethylmethyl group while retaining the C5 t-Bu substitution.
**Table 1-1.** Wang’s Michael Addition Catalyst Screening

<table>
<thead>
<tr>
<th>Catalyst (A,B,C,D)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 quinuclidine</td>
<td>85</td>
<td>0</td>
</tr>
<tr>
<td>2 (QD, QD, Ph, H)</td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td>3 (QD, QD, Ph, t-Bu)</td>
<td>69</td>
<td>65</td>
</tr>
<tr>
<td>4 (QD, QD, t-Bu, Ph)</td>
<td>55</td>
<td>74</td>
</tr>
<tr>
<td>5 (QD, QD, t-Bu, t-Bu)</td>
<td>95</td>
<td>84</td>
</tr>
<tr>
<td>6 (DHQD, DHQD, Ph, Ph)</td>
<td>47</td>
<td>63</td>
</tr>
</tbody>
</table>

Screening of this new generation of catalyst verified Calter and Wang’s hypothesis, leading to ee’s exceeding 90% with the quinidine-substituted catalyst (7a) (Table 1-2). The dihydroquinidine rendition of the catalyst, 7b, offered similar ee’s (7b: 90% vs. 7a: 92%), but at substantially higher yield (97% vs. 60%). The pseudoenantiomer catalysts 8a and 8b led to impressive, yet slightly less effective results (84 and 88% ee respectively). Temperature screening revealed that while warming the reaction to room temperature sped up the reactions, it led to a loss of ee’s. It was found that by running the addition at 0°C they were able to increase the speed and yield of the reaction without
sacrificing asymmetric induction, so Calter and Wang performed the solvent screening at 0°C. While the asymmetric Michael reaction performed well in a variety of common solvents (dichloromethane, diethyl ether, THF, MeOH), toluene provided the highest ee's for both pseudoenantiomers of the catalyst, bumping the enantioselectivity of 8b (entry 16) to the synthetically useful level of 92% ee, thereby offering a viable method of forming the S-enantiomer.
Table 1-2. Wang’s Michael Addition Solvent and Temperature Screening

<table>
<thead>
<tr>
<th>catalyst (A, B, C, D)</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a (QD, Cl, CETS, t-Bu)</td>
<td>DCM</td>
<td>-20</td>
<td>72</td>
<td>60</td>
<td>92</td>
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<tr>
<td>7b (DHQD, Cl, CETS, t-Bu)</td>
<td>DCM</td>
<td>-20</td>
<td>72</td>
<td>97</td>
<td>90</td>
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<tr>
<td>8a (QN, Cl, CETS, t-Bu)</td>
<td>DCM</td>
<td>-20</td>
<td>72</td>
<td>65</td>
<td>-84</td>
</tr>
<tr>
<td>8b (DHQN, Cl, CETS, t-Bu)</td>
<td>DCM</td>
<td>-20</td>
<td>72</td>
<td>97</td>
<td>-88</td>
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<tr>
<td>7a (QD, Cl, CETS, t-Bu)</td>
<td>DCM</td>
<td>0</td>
<td>24</td>
<td>78</td>
<td>92</td>
</tr>
<tr>
<td>7a (QD, Cl, CETS, t-Bu)</td>
<td>DCM</td>
<td>25</td>
<td>24</td>
<td>81</td>
<td>88</td>
</tr>
<tr>
<td>7a (QD, Cl, CETS, t-Bu)</td>
<td>toluene</td>
<td>0</td>
<td>24</td>
<td>97</td>
<td>96</td>
</tr>
<tr>
<td>7a (QD, Cl, CETS, t-Bu)</td>
<td>toluene</td>
<td>25</td>
<td>24</td>
<td>81</td>
<td>88</td>
</tr>
<tr>
<td>7a (QD, Cl, CETS, t-Bu)</td>
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<td>0</td>
<td>24</td>
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<td>94</td>
</tr>
<tr>
<td>7a (QD, Cl, CETS, t-Bu)</td>
<td>Et2O</td>
<td>0</td>
<td>24</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>7a (QD, Cl, CETS, t-Bu)</td>
<td>THF</td>
<td>0</td>
<td>24</td>
<td>71</td>
<td>92</td>
</tr>
<tr>
<td>7a (QD, Cl, CETS, t-Bu)</td>
<td>MeOH</td>
<td>0</td>
<td>24</td>
<td>89</td>
<td>73</td>
</tr>
<tr>
<td>7a (QD, Cl, CETS, t-Bu)</td>
<td>CH3CN</td>
<td>0</td>
<td>24</td>
<td>90</td>
<td>77</td>
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<tr>
<td>7a (QD, Cl, CETS, t-Bu)</td>
<td>DMF</td>
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<td>24</td>
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<tr>
<td>8b (DHQN, Cl, CETS, t-Bu)</td>
<td>DCM</td>
<td>0</td>
<td>24</td>
<td>97</td>
<td>-88</td>
</tr>
<tr>
<td>8b (DHQN, Cl, CETS, t-Bu)</td>
<td>toluene</td>
<td>0</td>
<td>24</td>
<td>89</td>
<td>-92</td>
</tr>
</tbody>
</table>
The scope of this asymmetric Michael addition was then probed through altering the electrophile at the γ-position with excellent results. Substituting the γ-position with alkyl groups, as well as aromatic moieties of varying electronic nature had inconsequential effects on the rate, yield, and enantioselectivities of the reaction (Table 1-3). Calter and Wang were also able to transform the Michael adducts into their corresponding hexahydropyridines without compromising the optical activities of the resulting compounds (Scheme 1-8).

Table 1-3. Wang’s Michael Addition Substrate Screening

<table>
<thead>
<tr>
<th>catalyst</th>
<th>nucleophile</th>
<th>electrophile (R₃)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>dimedone</td>
<td>4-OMe-Ph</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>7a</td>
<td>dimedone</td>
<td>4-NO₂-Ph</td>
<td>96</td>
<td>99</td>
</tr>
<tr>
<td>7a</td>
<td>dimedone</td>
<td>4-Br-Ph</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>7a</td>
<td>dimedone</td>
<td>Hex</td>
<td>74</td>
<td>95</td>
</tr>
<tr>
<td>7a</td>
<td>dimedone</td>
<td>iPr</td>
<td>64</td>
<td>94</td>
</tr>
<tr>
<td>7a</td>
<td>dimedone</td>
<td>Ph</td>
<td>97</td>
<td>96</td>
</tr>
<tr>
<td>7a</td>
<td>1,3-cyclohedadione</td>
<td>Ph</td>
<td>89</td>
<td>97</td>
</tr>
</tbody>
</table>
Scheme 1-8

With the optimized pyrimidine-functionalized cinchona alkaloid PTC Michael reaction conditions in hand for a variety of electrophiles, attention was then focused on expanding the scope of the reaction through varying the nucleophile to tailor such reactions to natural product synthesis.

1.5 Mahuannin D

Chiral chromans (Figure 1-5) make up the skeletal structure of many biologically active natural products and synthons. Chromans have recently become the focus of medicinal and pharmaceutical research due to their therapeutic potentials in the realms of diabetes, cancer, hypertension, obesity, central nervous system and endocrine disorders, and cardiovascular disorders.22, 23, 24, 25
Chromans of interest include α-tacopherol, a prominent component of the vitamin E family which is a lipophilic antioxidant and radical scavenger (Figure 1-6). Similar in structure to α-tacopherol, both trolox and MDL-73404 are being investigated for their ability to treat cardiovascular diseases thought to be associated with antioxidant activity. Englitazone and troglitazone are both antagonists of PPARs, and are being looked at as medications to control glucose levels in people with diabetes. (+)-Catechin wards off intestinal tumors and has been shown to reduce atherosclerotic plaques in animal testing.
The myriad biological activities associated with chromans have sparked interest in the development of viable enantioselective synthetic pathways to their various analogues. My research has focused on the synthesis of polyphenolic chromans via asymmetric catalysis as it provides an atom-economical method of chiral induction that requires only a small and reusable amount of readily available chiral material that can be tailored to provide either enantiomer by simply switching between enantiomers of the chiral ligand of the catalyst. While the original focus of the project was the asymmetric synthesis of the core of the molecule Mahuannin D, the chemistry developed herein could easily be modified to synthesize countless chromans of similar structure.

Much research has focused on the isolation and study of the biologically active molecules present in herbal Chinese medicines in an effort to determine their therapeutic potential. One such drug that has been investigated is the ephedra, or ma huang, derived “mao-kon”. Mahuannin A, B, C, and D, a series of
bisflavanoid compounds that demonstrate hypotensive activity, were isolated from the roots of the ephedra plant. Mahuannin D (Figure 1-7) is unique within this series of bisflavanoids as it is the only molecule of the four that contains different monomeric units. We chose mahuannin D as the target of our research because it is composed of a flavane and a flavanol, mahuannin A-C are isomeric bisflavanols, and so structurally resembles conceivable asymmetric, conjugate adducts. Though the project was conceived to focus on the synthesis of the core of mahuannin D in the highest enantiomeric excess in order to determine the minimum pharmacophore of the mahuannin D bisflavanoid, the chemistry we have developed can be applied to the wider scope of enantioselective chroman, and more specifically flavanoid synthesis.

**Figure 1-7**
References

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2. Proof of Concept Synthesis

2.1 Retrosynthesis:

We began the project by exploring the synthesis of a relatively simple derivative of the core of Mahuannin D using cheap, readily available substrates. Our retrosynthesis of the core of mahuannin D (Scheme 2-1) used the asymmetric conjugate addition as the vital transformation that induces the requisite stereochemistry. Target molecule 1 can be formed via aryl-metal addition to lactone 2, preceded by the oxidation of lactol 3 in the presence of PCC, reaction of diol 4 with sodium periodate, and treatment of the conjugate adduct 5 with sodium borohydride. The conjugate addition reaction would occur between (E)-ethyl 4-(2-methoxyphenyl)-2-oxobut-3-enoate 7, synthesized via aldol condensation of 2-methoxybenzaldehyde with ethyl pyruvate, and 3,5-dimethoxyphenol. 3,5-dimethoxyphenol is a cheap, commercially available compound.
2.2 Synthesis

Methoxy substituted substrates were chosen for the proof of concept synthesis as they are robust protecting groups that would withstand the reaction conditions that follow the initial conjugate addition. Protecting groups are
necessary to stop the free phenols of the reactants from complexing with the catalysts. Such binding would severely diminish the efficacy of the catalyst, as it would alter the structure of the transition state of the reaction, placing the chiral centers of the catalyst farther from the reaction center. Assuming the hydroxyl group at the para position of the aromatic moiety of the electrophile would have little steric effect on the synthesis of the desired molecule, the electrophile was singly substituted at the ortho position. This group was important to include as it exists in close proximity to the site of conjugate addition, thereby possibly effecting the asymmetric induction, speed or yield of the reaction. The substitution also resembles the electronic structure of the fully substituted electrophile more than would an unsubstituted phenyl moiety. The methoxy group at the ortho position of the electrophile is also positioned in close spatial proximity to the functionalized lactol resulting from the conjugate addition reaction, and so could possibly affect the reactivity of the region.

3,5-dimethoxyphenol was chosen in the hopes that the conjugate addition would lead to the more sterically and statistically favorable product, which could then undergo intramolecular O-alkylation at the unreacted ketone, leaving no free phenols.

The synthesis of electrophile 7 was initially performed through the aldol condensation of ethyl orthoformate with o-methoxybenzaldehyde in the presence of trimethyl orthoformate (reaction a) and copper (II) triflate (Scheme
However, this reaction yielded a mixture of the ethyl and methyl ketoesters so triethylorthoformate was substituted in place of trimethyl orthoformate to insure the formation of the ethyl ketoester 7 (reaction a').

**Scheme 2-2:**

\[
\text{Scheme 2-2:}
\]

3, 5-dimethoxyphenol is commercially available, so reactants in hand, the symmetric DABCO catalyzed conjugate addition to 7 was performed. While the desired cyclized adduct was the major regioisomer formed (22% yield), the improper adduct was also found in significant yields (cyclized/uncyclized adduct, 3:1) (Scheme 2-3).

**Scheme 2-3:**

The reaction proceeds through the initial deprotonation of the free phenolic moiety of 3, 5-dimethoxyphenol by the basic quinuclidine nitrogen on the DABCO catalyst (Scheme 2-4). The now protonated catalyst is able to doubly
coordinate with the two carbonyl oxygens of the ketoester, simultaneously activating the electrophile through induction while creating a coordinated molecular scaffold that will allow for asymmetric induction through chiral modification of the quinuclidine structure in future catalysts. Resonance localizes electron density on the 2, 4, and 6 carbons of the phenolic nucleophile, any of which can then undergo conjugate addition to the β position of the coordinated catalyst-electrophile scaffold.

**Scheme 2-4:**

The resulting enol tautomerizes to a ketone by one of two methods. The enol can abstract the proton from the carbon that recently added to the electrophile, reforming the aromaticity of the nucleophilic moiety. It can also tautomerize with the proton of the enol, breaking the hydrogen-bonding that
coordinates the catalyst to the conjugate adduct. In the latter case, the quinuclidine nitrogen most likely deprotonates the nucleophilic moiety and reforms the hydrogen-bonding between the catalyst and the new ketoester. This marks the terminus of the conjugate addition reaction if the new carbon-carbon bond was formed through addition at the 4-carbon of the nucleophile as neither of the methoxy protected phenols can affect O-alkylation to the ketone. This product is less favorable both statistically, there are half the number of reaction sites, and sterically as the 4-carbon is surrounded by two methoxy groups instead of one methoxy group and a phenol. Should either the 2 or 6 carbons bond to the electrophile the conjugate adduct then undergoes a spontaneous intramolecular O-alkylation cyclization between the free phenol and the ketone to form the desired lactol.

The next step along the synthetic pathway was the reduction of the conjugate adduct with sodium borohydride in order to form the diol lactol (Scheme 2-5). The reduction led to a mixture of the singly and doubly reduced products, yielding both the cyclized and unyclized diols.

Scheme 2-5:
At the time it was thought that 4b was 4a, and 4a was structure z, which we believed would not undergo the necessary sodium periodate cleavage reaction. We did not discover this distinction until the products of the actual synthesis were isolated and analyzed. For this reason we ran the next reaction on 4b only, which led to an 89% yield (Scheme 2-6).

Scheme 2-6:

Lactol 3 was oxidized in the presence of pyridinium chlorochromate (PCC) to lactone 2 in dichloromethane at room temperature in 55% yield (Scheme 2-7).
Scheme 2-7:

Lactone 2 was reacted with phenyl lithium, made through the metal-halogen exchange of nBuLi and iodobenzene at -10°C in diethyl ether, to produce lactol 1 in ~40% yield (Scheme 2-8).²

Scheme 2-8:

Believing that the chemistry thus far developed using the proof of concept substrates was sufficiently promising to warrant attempting that actual synthesis, we decided not to optimize the aryl-lithium addition and set out to synthesize the actual core of the molecule with the fully substituted reactants.
REFERENCES

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3. Conjugate Addition Synthetic Route

3.1 Retrosynthesis of Mahuannin D Core

Our retrosynthesis of the core of mahuannin D (Scheme 3-1) used the asymmetric conjugate addition as the vital transformation that induces the requisite stereochemistry. Target molecule 10 can be formed via the acid promoted cyclization of flavanoid 11a, which could subsequently be derived from the benzyl ether protected 11b. The protected flavanoid 11b can be traced back to the aryl-metal addition to lactone 12, the oxidation of lactol 13 in the presence of PCC, reaction of diol 14 with sodium periodate, and treatment of the Michael adduct 15 with sodium borohydride. The conjugate addition reaction would occur between dibenzyl protected (E)-ethyl 4-(2,4-dihydroxyphenyl)-2-oxo-butyric enoate, synthesized via aldol condensation of 2, 4-dihydroxybenzaldehyde with ethyl pyruvate, and 3, 5-bis(benzyloxy)phenol. Both substrates were protected with benzyl ether protecting groups by reacting the initial phenols with benzyl bromide.
Scheme 3-1:

3.2 Synthesis

The bis benzyl-substituted nucleophile 16 was prepared as per the literature procedure by first treating anhydrous phloroglucinol with benzyl bromide in the presence of K₂CO₃ to yield the trisubstituted phloroglucinol derivative (Scheme 3-2), which in turn was debenzylated using benzylmercaptan and NaH. The resulting anion inhibits further deprotection by the benzylmercaptan, which would lead to an electronically unstable 2⁻ ion, thereby favoring the bis-benzylated substrate as the final product.¹
Scheme 3-2:

Ketoester 17 was synthesized by similarly reacting 2, 4-dihydroxybenzaldehyde with benzyl bromide to yield the bis benzyloxy benzaldehyde (Scheme 3-3). As illustrated in Scheme 3-3, the protected benzaldehyde then underwent an aldol condensation with ethyl pyruvate in the presence of triethyl orthoformate and copper (II) triflate to afford compound 17.²

Scheme 3-3:

With nucleophile 16 and electrophile 17 in hand, the DABCO catalyzed conjugate addition reaction was attempted at room temperature in dry conditions beneath N₂ at 0.5 M in toluene (Scheme 3-4). Unfortunately, the bulky benzyloxy protecting groups inhibited the reaction to give yields after 7 days of reaction of less than 5%.
Scheme 3-4:

![Chemical structure](image)

To investigate the extent to which each substrate hindered the conjugate addition reaction, we ran the reaction under identical conditions while varying the nucleophile-electrophile combinations. Substituting the bis-methoxy nucleophile into the reaction significantly improved the rate of the reaction, leading to 60% conversion to a mixture of the conjugate adduct regioisomers (15a:15a', 3:1) after 5 days (Scheme 3-5).

Scheme 3-5:

![Chemical structure](image)

Similarly, using the ortho-methoxy ketoester led to almost total conversion (>95%) to a mixture of the regioisomers (15b:15b', 3:2) after 7 days under the same conditions (Scheme 3-6).
Scheme 3-6:

These test reactions indicated that while both the benzyloxy substituted substrates functioned as useful electrophiles and nucleophiles, using them in tandem slowed the reaction significantly due to their combined steric bulk. Specifically, the benzyloxy groups of the ketoester, most likely at the ortho position, greatly slow the reaction by blocking nucleophilic attack at the π* orbital β to the ketone.

As the desired, fully protected conjugate adduct 15 was observed to have formed at room temperature, albeit in small quantities, we decided to run the reaction at 72°C (Scheme 3-7) in an attempt to speed up the reaction and increase the yield and, satisfyingly, the reaction provided 81% yield of exclusively the desired regioisomer.

Scheme 3-7:
A reliable HPLC assay was developed for product 15 and racimicity of the products was confirmed. The reaction was then attempted in the presence of the commercially available (DHQD)_2Pyr catalyst, yielding the promising ee of 61%. Having achieved a significant yields and ee’s with the asymmetric conjugate addition reaction, we were then ready to proceed with the next steps of the synthesis with the fully functionalized substrates.

The DABCO catalyzed, symmetric synthesis was first investigated in order to develop reliable HPLC assays for subsequent steps along the synthetic pathway. In an attempt to speed up the reaction further, a large-scale conjugate addition reaction (1.11 mmol 17, 1.01 mmol 16) was run at the elevated temperature of 100°C. While complete conversion of 17 was observed after 5 days, it led to an isolated yield of only 40%. This is most likely attributed to polymer formation at such elevated temperatures.

The conjugate adduct 15 was isolated and reduced in an excess of NaBH₄ at rt for 5.5 h to give a mixture of the products similar to that achieved during the proof of concept synthesis. NMR analysis of the resulting products led to the previously mentioned conclusion that the reduction led to the formation of the singly and doubly reduced products, and not a mixture of the cyclized and uncyclized singly reduced product.

As only the reactivity of the uncyclized product had been probed, both reductants were isolated and underwent the sodium periodate cleavage.
Interestingly, after 30 minutes the cleavage reaction using the doubly reduced substrate produced the desired lactol 13 in >97% yield while the analogous reaction using the singly reduced substrate indicated no lactol formation. In an attempt to increase the reactivity of the cyclized reductant, the same reaction was run in acidic conditions (pH adjusted to 2-3 using concentrated HCl). Unfortunately, NMR analysis of the crude reaction mixture showed no presence of the product or starting materials, indicating the molecule’s sensitivity to acidic conditions in this reaction.

Focus was then shifted from reacting the cyclized, singly reduced substrate to increasing the ratio of doubly to singly reduced products from the preceding sodium borohydride reduction. The reduction was allowed to run overnight which gratifyingly drove the reaction to produce the desired doubly reduced product 14 in quantitative yield.

**Scheme 3-8**
Having optimized the reaction conditions for the reduction, the next step was to perform the sodium periodate cleavage. While running the cleavage on the unpurified product from the previous reduction yielded only 84% of desired lactol 13, it was pure enough to use for the subsequent oxidation, leading us to believe that the reaction went to completion and that the remaining product was lost during the work up.

**Scheme 3-9**

Lactol 13 was oxidized with PCC in DCM at rt, leading to an isolated yield of lactone 12 of 90%. HPLC assays were developed for substrates 15 and 13, but attempts to separate lactone 12 with our equipment proved fruitless.

**Scheme 3-10**
With lactone 12 in hand, we were then ready to add the last ring through a metal-aryl addition. We first tried adding 4-iodoanisole to the lactone to probe the reactivity of the molecule. This was performed at -78°C in THF by first performing the metal halogen exchange between nBuLi and 4-iodoanisole, thereby forming the aryl-lithium, and then adding the subsequent mixture to a solution containing lactone 12.3

**Scheme 3-11**

This attempt led to no detectable product formation and almost complete recovery of the starting material 12 once the reaction was treated with NaHCO3 and extracted with EtOAc after 1 hr. Concerned that the metal-halogen exchange was the issue, we attempted reacting lactone 12 with commercially available phenyl lithium in diethyl ether at -78°C. No aryl-lithium adduct was observed after an hour. The reaction was reproduced, this time allowing it to run for 2h, however only a slight amount of the desired adduct was observed.
Scheme 3-12

We began exploring the Weinreb-amination of lactone 12 in an attempt to simultaneously activating the electrophile while insuring formation of only the mono-adduct. To a mixture of N,O-dimethylhydroxylamine and 12 in DMF at 90° C was added triethylamine under N₂. The reaction was stirred for 24 hours, then treated with saturated NH₄Cl and extracted with EtOAc. The combined organic layers were dried over sodium sulfate, concentrated in vacuo and subjected to proton NMR to reveal that no reaction had occurred. The reaction was repeated substituting distilled diethylisopropylamine for triethylamine with identical results.⁵,⁶

Scheme 3-13
We then attempted the Weinreb-amination in the presence of triethylaluminum, instead of triethylamine, at room temperature in DCM. The reaction was run for 2.5h, treated with sat. NH₄Cl and extracted with EtOAc to reveal that while lactone 12 was no longer present, numerous biproducts had formed. We were unable to isolate the Weinreb-amide, and so refocused upon the development of an aryl-lithium addition directly to substrate 12.

To further probe the efficacy of the metal-halogen exchange, we attempted the addition of 4-iodoanisole to distilled benzaldehyde. 4-iodoanisole and nBuLi were mixed in THF and allowed to stir for 10 min after which benzaldehyde was added via syringe. After 60 min the reaction was quenched with NaHCO₃, extracted with EtOAc and purified via flash column chromatography (hexanes/EtOAc, 3:2) to give a 30% isolated yield.⁴

**Scheme 3-14**

Proton NMR of the 4-iodoanisole indicated the significant presence of water. Similarly significant levels of water were found in lactone 12 and so the aryl-lithium addition to compound 12 was attempted after azeotroping both the 4-iodoanisole and 12 in toluene *in vacuo*. The addition was run in diethyl ether
under N₂ at 0°C to increase the rate of reaction. After 75 minutes proton NMR indicated almost complete conversion of lactone 12 and was purified via flash column chromatography to afford the mono-aryl adduct 11b as a white solid in 38% yield.

Scheme 3-15

Removal of the benzyloxy protecting groups to reform the free phenols was performed by treating compound 11b with cyclohexa-1,4-diene in the presence of palladium on carbon in ethanol at room temperature for 24 hrs. The reaction mixture was filtered through celite, and a proton NMR of the crude product indicated complete deprotection of all benzyloxy groups. Furthermore, the NMR spectrum indicated the presence of three distinct methoxy groups, which suggests the presence of the predicted diastereomers of 11a and the final cyclized core of Mahuannin D, compound 10. Isolation and characterization of the resulting compounds is currently underway.
Scheme 3-16

The asymmetric conjugate addition reaction was run on a large scale, 2.0 mmol of substrate 8 with 1.1 eq. of substrate 7, in the presence of 0.2 eq. of the bis-phenyl, phenyl dihydroquinine, (DHQN)$_2$Pyr, catalyst at 85°C to give 79% yield and 40% ee.

Scheme 3-17

The reaction proceeds through the initial deprotonation of the free phenolic moiety of 16 by the basic quinuclidine nitrogen on the chiral catalyst. The now protonated catalyst is able to doubly coordinate with the two carbonyl oxygens of the ketoester, simultaneously activating the electrophile through induction while creating a coordinated molecular scaffold that will determine the chirality of the product. Stereocontrol of the reaction is primarily determined
by the orientation with which the electrophile coordinates with the catalyst. The electrophile preferentially binds with the protonated catalyst such that the relatively small ester moiety points towards the pyrimidine scaffold, thereby minimizing the steric interaction between the electrophile and the catalyst. The 6-methoxyquinoline group on the catalyst blocks one side of the electrophile from nucleophilic attack, promoting Re facial nucleophilic addition. The electrophile can also bind with the catalyst such that the aromatic moiety is placed in close proximity to the pyrimidine ring. This coordination is less favorable due to the increased steric interaction between the electrophile and catalyst, and ideally reverses before the disfavored Si facial addition occurs.

**Scheme 3-18**
This enantioenriched conjugate adduct was then transformed to lactone 12 via the developed synthetic pathway. When Wang attempted the oxidation of an enantioenriched lactol from the proof of concept synthesis she reported that the resulting lactone existed as a racemate of the enantiomers. While no assay was developed for lactone 12, it was shown that the oxidation did not lead to racemization of the product by reducing 12 back to 13 with DIBAL and confirming the maintained enantioenrichment (40% ee) using that assay.

Scheme 3-19

3.3 Catalyst Screening

With much of the required synthetic chemistry developed, catalyst screening became a parallel focus of the project. Having experienced moderate success at 80°C with the commercial (DHQD)$_2$Pyr catalyst (61% ee), we began testing similar catalysts at elevated temperatures (75-110°C) to discern the correlation between catalyst structure and asymmetric induction.

We began with the commercial (QD)$_2$Pyr and (DHQD)$_2$Pyr catalysts, which immediately revealed the relatively elevated enantioselective potential of
the saturated catalysts (40%:61% ee at 80°C). This hypothesis was confirmed through the results yielded by the (DHQN)₂PYR-Ph, (R=1-NPTH) and (QN)₂PYR-Ph, (R=1-NPTH) (-39%: -31% at 80°C). Comparison between various pseudoenantiomers of catalysts revealed the superiority of quinidine-based catalysts (entries 6: 10, 43%: -31% and entries 1: 7, 61%: -40%) (Table 3-1).

In contrast with Wang’s findings using the methoxy substituted substrates, we found that the C=D=t-Bu and catalysts were less effective than the aromatic counterparts. Similarly, the (DHQD)₂PYR-CEt₃, (R=t-Bu) catalyst afforded the modest enantioselectivity of 39% at 80°C.

The (QD)₂PYR-Ph, (R=H) catalyst led to similarly diminished chiral induction. This result could further indicate the need for an aromatic functionality at the D position or illustrate the need for a greater steric presence in close proximity to the site of catalysis. To examine the affect of an aromatic group of substantial steric bulk we tried using the (QD)₂PYR-Ph, (R=3, 5-propyloxybenzene) catalyst (entry 8), which afforded the racemate of the conjugate adducts at 80°C. To probe whether this result arose from the size of the aromatic moiety or the electron-donating groups with which it was substituted, we ran the reaction with the para-methoxy substituted entry 12 (37% ee at 80°C). The (QD)₂PYR-Ph, (R=Ph-OMe para) catalyst (entry 12) indicated that it was most likely the massive size of entry 8, and not the electron-donating character of the substituents that impeded asymmetric induction. To examine the affect of an electron-poor phenyl ring at position D, we ran the
reaction in the presence of the trifluoromethyl-functionalized entry 9 to yield an ee of 52% at rt. Ultimately, comparison of the (QD)$_2$PYR-Ph, (R=3, 5-propyloxybenzene) and (QD)$_2$PYR-Ph, (R=Ph-OMe para) (entries 8 and 12) with their unsubstituted counterparts indicated that neither electron-donating nor withdrawing groups increased the enantioselective capacity of the catalysts.

The logical step was to then functionalize position D with a different aromatic group. Entries 3 and 6, as well as 5 and 7 yielded almost identical results (40:43% ee and -39: -40% ee respectively), indicating the similarity between 1-NPTH and phenyl groups at position D on both saturated and unsaturated catalysts. Though the napthyl moiety did not increase the efficacy of the catalysts, it provides ample room for future exploration into catalyst modification through functionalization of the napthyl group, binding it to the catalyst at different positions, and substitution of position D with larger fused-aromatic systems.

It was determined that the reaction rate was highly concentration dependent as similar yields were achieved in half the time in cases in which the reaction mixtures were allowed to dry out over the first two hours of reaction. With this in mind, the room temperature conjugate addition reaction was set up in a minimum amount of solvent, which was dried by flushing N$_2$ through the reaction flask. Happily, the (DHQD)$_2$Pyr catalyzed reaction produced a yield of 55% after 7 days and an ee of 74%. With no clear path to attaining synthetically useful levels of asymmetric induction, we expanded the scope of our research
beyond the conjugate addition reaction to investigate alternate asymmetric transformations and the use of different nucleophiles

**Table 3-1. Conjugate Addition Catalyst Screening**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (A, B, C, D)</th>
<th>% ee (rt)</th>
<th>% ee (80°C)</th>
<th>% ee (100°C)</th>
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</thead>
<tbody>
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<td>24</td>
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</tr>
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<td>5</td>
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<td>-39</td>
<td>-43</td>
</tr>
<tr>
<td>6</td>
<td>QD, QD, Ph, 1-NPTH</td>
<td>-</td>
<td>43</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
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<td>-40</td>
<td>-</td>
</tr>
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<tr>
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<td>-</td>
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<tr>
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<td>QN, QN, Ph, 1-NPTH</td>
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<td>-31</td>
<td>-19</td>
</tr>
<tr>
<td>11</td>
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<td>39</td>
<td>25</td>
</tr>
<tr>
<td>12</td>
<td>QD, QD, Ph, Ph-OMe (para)</td>
<td>-</td>
<td>37</td>
<td>-</td>
</tr>
</tbody>
</table>
References


6 Thomas, E.; Bradshaw, B. *Organic & Biomolecular Chem.* **2008**, 6, 12, 2138-57
4. Alternate Synthetic Exploration

Before attempting the Michael addition, the unsatisfying initial results of the fully substituted conjugate addition reaction prompted us to investigate alternate routes to the core of Mahuannin D. Through altering the electrophile we hoped to achieve facile synthesis of intermediates that more closely resembled the core of Mahuannin D. Hoping to avoid cleaving a carbon-carbon bond, we devised reactions that would lead to molecules resembling either the lactol 13 or the aryl-substituted lactol 11b.

4.1 Cinnamaldehyde Route

We first attempted the addition of various cyclic nucleophiles to the alpha-beta unsaturated aldehyde, cinnamaldehyde to determine the feasibility of directly forming the unsubstituted lactol 13 through either a conjugate or Michael reaction.

Scheme 4-1
Reacting 3,5-dimethoxyphenol with cinnamaldehyde in DCM in the presence of DABCO at rt under N₂ led to only slight conversion after 96 hrs. Similar results were found when using the bis-benzylxyloxy protected nucleophile in otherwise identical conditions.

**Scheme 4-2**

Hoping to combat the obviously diminished reactivity of the electrophile by stripping the nucleophile of all extraneous steric bulk, we ran the reaction again using phloroglucinol as the nucleophile, this time in DMF to solvate the relatively polar triphenol. Disappointingly, after 169 hrs no product formation was observed.

**Scheme 4-3**
To further increase the reactivity of the nucleophile, we switched from substituted phenols to 5,5-dimethylcyclohexane-1,3-dione (dimedone). After 96 hrs under the above conditions the reaction formed what we think to be a mixture of both the aldol adduct as well as the aldol condensate in a 1:1 ratio in modest yields.

**Scheme 4-4**

While these reactions could prove synthetically useful given methodological optimization, they did not provide results immediately helpful to the synthesis of our target molecule, and so we moved on to investigate the potential of different electrophiles. There were also concerns that affecting enantioselectivity using such electrophiles in tandem with our quinuclidine based catalysts would prove fruitless due to the relatively less rigid nature of a coordinated catalyst-electrophile structure bound by a single point of hydrogen bonding.
4.2 IFB Analogue

The Calter group has performed and published an impressive array of synthetic and methodological chemistry stemming from the asymmetric Interrupted Feist-Benary (IFB) reaction. Though the IFB reaction forms highly substituted tetrahydrofurans, it is conceivable that such chemistry could be modified to produce a six-membered lactol analogue. This could be acheived by extending the framework of the electrophile by a single methylene group between the carbonyl moiety and the leaving group, effectively substituting the electrophile at the beta position instead of the alpha position. While the carbonyl group of such a molecule would not be activated by the electron-withdrawing nature of leaving group to the same degree as its alpha-substituted predecessor, such an electrophile would be able to doubly coordinate through bifurcated hydrogen-bonding to the protonated catalyst.

Scheme 4-5

We synthesized 1-(4-methoxyphenyl)propan-1-ol to test the electrophilicity of a benzylic leaving group that was not activated by an adjacent
carbonyl moiety. Unfortunately, this compound proved unstable and was prone to degradation.

**Scheme 4-6**

\[
\text{MeO} - \text{H} + \text{Me} - \text{MgBr} \xrightarrow{4.7 \text{ ether:toluene} \ 0^\circ C} \text{MeO} - \text{Me} \text{OH}
\]

Still curious to try the IFB analogue reaction, we made 3-hydroxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one through the aldol addition of 4-methoxybenzaldehyde to acetophenone in the presence of magnesium bromide and Hunig’s base.

**Scheme 4-7**

\[
\text{MeO} - \text{H} + \text{Me} - \text{O} \xrightarrow{\text{MgBr}^2- \text{EtN(iPr)}^2- \text{DCM, rt}} \text{MeO} - \text{OH} - \text{C}
\]

This compound proved stable enough for subsequent experimentation, so we attempted to tosylate the benzylic alcohol by treating it with sodium hydride and tosyl chloride. To our surprise these reaction conditions drove the reverse-aldol reaction to give us quantitative yields of acetophenone and 4-methoxybenzaldehyde.
**Scheme 4-8**

\[
\text{MeO} - \text{CH} = \text{C} - \text{CH} - \text{OH} \quad \xrightarrow{\text{NaH, TsCl, DCM}} \quad \text{MeO} - \text{CH} = \text{C} - \text{CH} - \text{O} \\
\]

Believing the poor chelating ability of sodium to contribute to the reverse-aldol reaction, we tried performing the tosylation reaction with tosic anhydride and different bases. The use of pyridine led to some reverse-aldol reaction and no tosylation, while the use of calcium hydride led to the reverse-aldol reaction as well as elimination. Concerned with the obvious problems associated with the stability of such electrophiles, as well as their predictably lower reactivity to nucleophilic attack when compared with the already unreactive alpha-beta unsaturated ketoesters, we decided to leave the development of the “six-membered” IFB analogue to future generations of Calter laboratory chemists.

### 4.3 Chalcone Route

Chalcones represented a promising class of electrophiles. Depending upon the nucleophile, their successful participation in an asymmetric conjugate or Michael addition reaction and successive O-alkylation would complete almost the entire synthesis in one fell swoop.
We attempted the Michael addition of dimedone to \((E)\)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one in the presence of DABCO in toluene at room temperature. No reaction was observed after 48 hrs.

We then synthesized \((E)\)-3-(4-methoxyphenyl)-1-(4-nitrophenyl)prop-2-en-1-one to increase the electrophilicity of the Michael acceptor moiety. Reacting the nitro-chalcone with dimedone in toluene at room temperature led to no reaction after 23 hrs, but it was observed that the chalcone did not seem to dissolve thoroughly in toluene and so the reaction was replicated in DCM. Proton NMR revealed this reaction to run to 45% conversion by 48 hrs. After 96 hrs the
reaction was purified via flash chromatography (DCM/MeOH, 99:1) to afford the uncyclized Michael adduct as a yellow solid in 58% yield.

Scheme 4-11

Exploration into asymmetric renditions of this Michael addition using chiral cinchona based catalysts is currently underway.

In spite of the great success of these initial findings, at this point we redoubled our efforts to develop the conjugate addition between the benzylxyx protected substrates for multiple reasons. As with the cinnamaldehyde, we were again concerned that insufficient hydrogen-bonding sites on the electrophile would inhibit the development of an enantioselective version of this new Michael reaction. Also, though using the nitro substituted chalcone as an electrophile in the Michael addition eliminated multiple steps along the initially conceived synthetic pathway to the core of Mahuannin D, it would possibly add just as many to transform the nitro group into a phenol.
5. Michael Addition Synthetic Route

5.1 Retrosynthesis of Mahuannin D Core

The alternate retrosynthesis of the core of mahuannin D (Scheme 3-1) used the asymmetric Michael addition as the vital transformation that induces the requisite stereochemistry. Target molecule 27 can be formed via the acid promoted cyclization of flavanoid 28a, which could subsequently be derived from the benzyl ether protected 28b. Substrate 28b could be formed through the deprotection of the propanol substituted 28c. The protected flavanoid 28c can be traced back to the aryl-metal addition to lactone 29, the oxidation of lactol 30 in the presence of PCC, and the reaction of diol 31 with sodium periodate. Diol 31 is formed through the reduction of compound 32', which would be formed through the aromatization of the Michael adduct 32 with potassium tertbutoxide. The Michael addition reaction would occur between dibenzyl protected (E)-ethyl 4-(2,4-dihydroxyphenyl)-2-oxo-but-3-enoate, synthesized via aldol condensation of 2, 4- dihydroxybenzaldehyde with ethyl pyruvate, and 1,5-dioxaspiro[5.5]undecane-8,10-dione. Both substrates were protected with benzyl ether protecting groups by reacting the initial phenols with benzyl bromide.
5.2 Michael Addition

Calter and Wang published significant yields and ee's reacting similar ketoester electrophiles with cyclic 1, 3-cyclohexadiones so we first investigated the Michael addition using the commercially available nucleophile dimedone. Dimedone is highly enolizable with a pKa=5.23, making it a more reactive nucleophile than its aromatic predecessor (pKa~10). Also, the methyl substitutions at the 5 position act as a geometric and steric placeholder for a dioxane protecting group. Such a functionality would be used on future nucleophiles to allow aromatization of the anomeric ring, making dimedone a
representative proof of concept substrate in terms of both reactivity and asymmetric catalysis. Gratifyingly, the DABCO catalyzed (30 mol %) Michael addition between (E)-ethyl 4-(2,4-dihydroxyphenyl)-2-oxo-but-3-enoate and dimeredone in dichloromethane went to complete conversion after 4 days at room temperature.

Scheme 5-2

An HPLC assay was developed to confirm the racemicity of the product and catalytic screening began.

5.3 Catalyst Screening:

Wang and Calter published that the Michael addition between dimeredone and similar ketoester electrophiles achieved the highest levels of enantioselectivity when run in the presence of functionalized pyrimidine catalysts substituted with bulky anomic groups at the C2 and C5 positions. Using their research as a starting point, we attempted the Michael reaction using the \((QD)_{2}\)PYR-t-Bu, \((R=t-Bu)\) catalyst at room temperature in a minimum of
DCM, which gave a yield of 42% and ee of 80% after 20 hrs. Curious to what extent this new reaction mirrored those published by Calter and Wang, we then ran the Michael addition using the commercially available (QD)$_2$PYR-Ph, (R=Ph) catalyst under the same conditions to find little difference in both yield and asymmetric induction (40% yield and 77% ee). These results were reassuring as the Calter lab possesses an extensive library of substituted phenyl, phenyl catalysts coupled with the fact that making anomerically substituted catalysts requires a non-trivial multistep synthesis.

In an attempt to mimic the steric bulk of the anumeric (QD)$_2$PYR-t-Bu, (R=t-Bu) catalyst we ran the reaction using the (QD)$_2$PYR-Ph, (R=3,5-bis-t-Bu phenyl) catalyst. This catalyst gave an ee of only 68%. Such poor asymmetric induction could result from the relatively massive steric interaction between the two new t-Bu groups on the phenyl ring and the coordinated electrophile, or possibly from a change in the angle of the pryimidine ring arising from substituting it with such different aromatic moieties. To probe the opposite extreme we then ran the reaction with the (QD)$_2$PYR-Ph, (R=H) catalyst. Interestingly, this provided the worst ee to date at 57%. These results led us to believe that optimal catalysis would be achieved when R is a group of moderate size, or when the substituents at C2 and C5 are of similar size.

This hypothesis was strengthened by results from the use of the (QD)$_2$PYR-Ph, (R=nBu) catalyst, which gave an enantiomeric excess of 71%. While these results were impressive, they still fell short of the initial asymmetric
induction affected by the initial bis t-Bu and bis phenyl catalysts, leading us to posit that the angle of the pyrimidine scaffold is optimized by substituting both sides with the same functionality.

The success of the \((\text{QD})_2\text{PYR-Ph}, (R=\text{Ph})\) catalyst prompted us to try the saturated \((\text{DHQD})_2\text{PYR-Ph}, (R=\text{Ph})\) version, yielding the diminished ee of 67\% in comparison to the ee of 77\% from the unsaturated catalyst. This substantial loss of ee could be attributed to the interaction between the hydrogens of the saturated catalyst and the back phenyl group of the pyrimidine ring, thereby altering the angle of the pyrimidine ring with respect to the reaction site. This would affectively aim the front phenyl ring towards the reaction site, which could alter or weaken the coordinated catalyst-electrophile scaffold, thereby allowing for more opportunity for nucleophilic attack from the disfavored side. Furthermore it lends merit to the assertion that the angle of the pyrimidine scaffold affects the highest levels of enantioselectivity when the front and back groups are of similar size on the unsaturated catalysts.

We tried catalysts \((\text{QD})_2\text{PYR-Ph}, (R=\text{SMe})\) and \((\text{QD})_2\text{PYR-Ph}, (R=\text{1-NPTH})\) to examine the affect of altering the electronic structure of the front group on asymmetric induction. Substitution of the naphthyl group proved ineffective, yielding the modest ee of 59\% under standard conditions, while the SMe group led to an ee of 75\%, similar results to those of the initial commercial catalyst. While the SMe catalyst proved almost as useful as the QD QD bis phenyl, it was not considered as a candidate as it required a more extensive synthesis and
afforded less opportunity for substitution. This development seemed to indicate that a phenyl moiety was the optimal size and electronic structure for the front group of the catalyst.

**Table 5-1. Dimedone Michael Addition Catalyst Screening**

<table>
<thead>
<tr>
<th>catalyst (A, B, C, D)</th>
<th>ee %</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>QD, QD, t-Bu, t-Bu</td>
<td>80</td>
<td>39</td>
</tr>
<tr>
<td>QD, QD, Ph, Ph</td>
<td>77</td>
<td>40</td>
</tr>
<tr>
<td>QD, QD, Ph, 3, 5-t-Bu-Ph</td>
<td>68</td>
<td>42</td>
</tr>
<tr>
<td>QD, QD, Ph, H</td>
<td>57</td>
<td>38</td>
</tr>
<tr>
<td>DHQD, DHQD, Ph, Ph</td>
<td>67</td>
<td>36</td>
</tr>
<tr>
<td>QD, QD, Ph, nBu</td>
<td>71</td>
<td>42</td>
</tr>
<tr>
<td>QD, QD, Ph, SMme</td>
<td>75</td>
<td>39</td>
</tr>
<tr>
<td>QD, QD, Ph, Me</td>
<td>64</td>
<td>43</td>
</tr>
<tr>
<td>QD, QD, Ph, 1-NPTH</td>
<td>59</td>
<td>37</td>
</tr>
</tbody>
</table>

Unable to glean better ee values than those found with the initial bis-t-Bu and bis-phenyl QD catalysts, we then investigated the affect of temperature on both the yield and enantioselectivity of the Michael reaction. Traditionally, lower temperatures amplify the enantioselectivity imbued in a reaction by a catalyst by decreasing the energy of the system, thereby making the catalyst-electrophile structure more rigid. This increased rigidity allows the catalyst to more reliably block unfavorable venues of attack by the nucleophile, leading to increased asymmetric induction. Having yet to try a quinine based catalyst, reactions
catalysed by the (QN)$_2$PYR-Ph, (R=Ph) and (QD)$_2$PYR-t-Bu, (R=t-Bu) version of the catalyst were run in tandem at 4°C. While the QN catalyst gave an ee of only 63%, a surprising result considering the success of the QD version coupled with the depressed temperature reaction conditions, the (QD)$_2$PYR-Ph, (R=Ph) catalyst afforded a 5% bump in ee to 83%. Encouraged by these results, we replicated the reaction at -30°C to achieve a yield of 39% and an enantiomeric excess of 90%. Having developed the asymmetric Michael addition reaction of dimedone to (E)-ethyl 4-(2,4-dihydroxyphenyl)-2-oxo-but-3-enoate, we then set out to perform the reaction using the 1,5-dioxaspiro[5.5]undecane-8,10-dione nucleophile 33.

**Table 5-2. Dimedone Michael Addition Temperature Screening**

<table>
<thead>
<tr>
<th>catalyst (A, B, C, D)</th>
<th>% ee (4°C)</th>
<th>% ee (-30°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QN, QN, t-Bu, t-Bu</td>
<td>63</td>
<td>-</td>
</tr>
<tr>
<td>QD, QD, Ph, Ph</td>
<td>83</td>
<td>90</td>
</tr>
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The synthesis of 33 began with the protection of propan 1,3-diol with trimethylsilyl chloride in the presence of triethylamine in DCM at room temperature. Diethyl 3-oxopentanedioate was then reacted with this protected
diol in the presence of catalytic trimethylsilyl triflate under N₂ in DCM at -78°C then warmed to room temperature for 24 hrs, converting the central ketone moiety to a dioxane protecting group. Methyl Grignard addition to diethyl 2,2'- (1,3-dioxane-2,2-diyl)diacetate at -78°C in DCM for 15 hrs then afforded ethyl 2- (2-(2-oxopropyl)-1,3-dioxan-2-yl)acetate. Lithium diisopropylamine was then formed by mixing nBuLi and diisopropylamine in THF at -78°C for 30 min, and was subsequently cannulated into a solution of ethyl 2-(2-(2-oxopropyl)-1,3- dioxan-2-yl)acetate in THF. The reaction mixture was heated to reflux for 3 hrs to affect the Deikman cyclization that would afford the desired 1,5-dioxaspiro[5.5]undecane-8,10-dione nucleophile.¹

Scheme 5-3

The symmetric, DABCO catalyzed Michael addition of nucleophile 33 to 17 was then attempted at room temperature in THF. After 24 h the reaction was observed to have gone to completion, indicated by the absence of ketoester 17.
The crude $^1$H NMR indicated the presence of multiple products, including the desired cyclized Michael adduct 32. When subjected to flash chromatography, however, only product 32 was isolated, indicating that the other product could potentially have been the uncyclized adduct which was then transformed by the acidic conditions of the column. An HPLC assay was then developed to confirm the racimicity of the product. Having formed the symmetric Michael adduct 32, we then attempted to reproduce the success of the asymmetric Michael addition of dimedone to 17. Happily, the Michael addition of nucleophile 33 to 17 at -30°C in THF gave a yield of 41% after 3 days and an ee of >99%.

Scheme 5-4

5.4 Synthesis

With the asymmetric Michael addition reaction in hand, the next step was the aromatization of the dioxane-protected ring. Calter and Li developed multiple methods of deprotecting and aromatizing similarly protected substrates, so we began with these conditions. Reacting Michael adduct 32 with
potassium tertbutoxide in THF under N₂ at 0°C for 120 min led to complete conversion of the starting material as indicated by proton NMR.¹

**Scheme 5-5**

While we were able to confirm that compound 32 had been depleted, the NMR spectral data of the resulting product was undecipherable. It is possible that the resulting aromatized compound isomerizes between the open and closed forms of the product too quickly to allow for proper NMR analysis. Should this be the case, the product could also isomerize between different O-alkylation products as it recyclizes.

**Scheme 5-6**
Reducing the aromatized product to the corresponding diol would hypothetically solve the problem of isomerization, so we attempted the sodium borohydride reduction under the same conditions developed for the conjugate addition product 15. While multiple new compounds were indicated both by proton NMR and TLC analysis, we have yet to be able to adequately isolate and identify the resulting compounds.

**Scheme 5-7**

Dissatisfied with the progress afforded through the potassium tertbutoxide aromatization, we then attempted to deprotect 32 with lithium diisopropyl amine.\(^1\) Compound 32 was treated with iPr\(_2\)NLi at -45\(^\circ\)C for 60 min in THF under N\(_2\), and while complete conversion was again observed, it remains unclear whether any of the compounds isolated via flash chromatography (DCM/MeOH, 99:1) are the desired aromatized product 31. This mode or aromatization is currently being explored.
References

1 Calter, M.; Li, N. Org. Lett. 2011, 13, 14, 3686-9
6. Future Studies and Conclusion

Having developed a method of asymmetric induction through the Michael addition of 33 to 17, as well as the synthetic chemistry to all but finish the synthesis of the core of our target molecule, our efforts now focus on combining the two accomplishments to complete the asymmetric total synthesis of the core of Mahuannin D. This begins with the aromatization of Michael adduct 32 into an intermediate that resembles conjugate adduct 15. The chemistry developed during the conjugate addition synthetic route can then be applied to the aromatized Michael adduct in order to transform it into the aryl lithium adduct, the deprotection of which is currently underway.
Further study should be devoted to the optimization and chiral catalysis of the conjugate addition reaction. While enantiomeric excesses greater than 74% were not achieved through our screening, there remains a wealth of catalysts and conditions to explore. Few catalysts have been synthesized with anomeric groups functionalizing the pyrimidine ring, and preliminary work has begun towards the synthesis of novel catalysts substituted with cyclic moieties.
like cyclopentane and cyclohexane. Alteration of groups at position D of the pyrimidine ring has been of primary focus as they offer direct interaction with the site of catalysis, but there is room for experimentation with groups at position C as well. The variability afforded through functionalized, fused aromatic systems at position D gives further hope for the discovery of a potent catalyst for this reaction.

Altering the β-substituent and the electron withdrawing groups of the electrophile should be looked into. As Wang found through her work on enantioselective Michael additions, yields and ee's suffered little from modest modification of the electrophile. It is also possible that the scope of the asymmetric Michael addition developed herein could be expanded to the use of further substituted nucleophiles. Such chemistry could lead to more densely functionalized aromatic moieties, as well as possible sites for new stereocenters should the nucleophile go unaromatized.

**Scheme 6-2**

![Scheme 6-2](image-url)
Preliminary results from the dimedone addition to cinamaldehyde were unexpected, however they warrant further investigation. A cinchona alkaloid catalyzed asymmetric aldol addition of cyclic diones to cinamaldehyde derivatives would prove a powerful method of forming polycyclic synthons. Continued work could also possibly yield the desired asymmetric Michael addition, which would cut multiple steps from the chiral synthesis of chromans.

**Scheme 6-3**

![Scheme 6-3 Diagram](image)

The six-membered IFB analogue was never attempted during this project and merits development. More stable and reactive electrophiles than those whose construction was attempted for this synthesis could lead to the discovery of a new enantioselective method of forming functionalized six-membered heterocycles.
Scheme 6-4

\[
\begin{align*}
R_1R_2R_3 & \quad + \quad R_7R_8R_9R_{10} \\
\text{L} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

The promising results stemming from the Michael addition of dimedone to chalcones also deserve investigation. The asymmetric rendition of the previously performed addition, catalyzed with (QD)₂PYR, is also currently underway.

Scheme 6-5

In conclusion, we are close to completing the catalytic, asymmetric total synthesis of the core of Mahuangnin D, using the novel enantioselective Michael addition of 33 to 17 to imbue the requisite stereochemistry. The commercial
catalyst (QD)$_2$PYR was found to affect the greatest enantioselectivity, yielding >99% ee at -30°C. Substantial work was also put towards the development of the asymmetric conjugate addition of 16 to 17, achieving yields as high as 81% and ee’s as high as 74%. Conditions were developed for the reduction of the conjugate adduct in the presence of sodium borohydride, leading to quantitative yields of the resulting diol. Reaction conditions for the oxidative cleavage of diol 14 were established, leading to the similarly impressive yield of 97%. Oxidation of lactol 13 was carried out in the presence of PCC with great efficacy, and the aryl-lithium addition of the final aromatic ring was developed. Other reactions involved in this project included alkyl-cuprate and Grignard additions, Dieckmann cyclization, tosylation, aldol additions and condensations, benzyloxy protection and deprotection, frustration, aromatization, elation, and alkylation.

The enantioselective Michael addition of dioxane 33 to ketoester 17 is a powerful new addition to the asymmetric synthesis of highly functionalized chromans. Its use towards the completion of the total synthesis of the core of Mahuannin D is underway, and modification of both the nucleophile and electrophile promises to expand the scope of the reaction to the synthesis of other densely functionalized natural products.
7. Methods

All commercial chemicals and materials were used as they were received unless otherwise indicated. DMF, toluene, DCM, pyridine, diethyl ether and THF were filtered through an activated alumina column in a solvent purification system. When needed anhydrous, diisopropylamine and DCM were distilled over calcium hydride. $^{13}$C and $^1$H NMR spectral data were taken on Varian-300 (300 Hz and 75 Hz) and 400 (400 Hz and 100 Hz) spectrometers. Flash chromatography employed Silicycle 60 Å, 32-63 μm and Dynamic Absorbants 60 Å, 32-63 μm. SiliCycles 0.25 mm, 60 Å pore sized silica gel plates were used for thin-layer chromatography (TLC). Ceric ammonium molybdate stains and UV/Vis. lamps were used to visualize TLC plates. A Thermo Separation Product Spectra Series P200 HPLC, coupled with a Spectra 100 variable UV/Vis. detector and Hewlett Packard HP-3394a integrator was used to take HPLC spectra. Elemental analyses were performed by Robertson Microlit Laboratories.

![Chemical Reaction Diagram]

**Ethyl 4-(2-methoxyphenyl)-2-oxobut-3-enoate (7):** Triethyl orthoformate (3.990 ml, 24 mmol) was added to a solution of 2-methoxybenzaldehyde (2.779 g, 20 mmol), ethyl pyruvate (4.536 g, 40 mmol), and copper (II) triflate (0.868 g,
2.4 mmol) in 100 ml of dichloromethane. The solution was heated to 45°C and stirred for 36 hrs. The crude product was washed with deionized water (3 x 20 ml). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The product was purified via flash column chromatography (hexanes/EtOAc, 10:1) to afford 7 (4.56 g, 63%) as a yellow oil. \(^1\)H NMR (300 MHz, CDCl₃) \(\delta 8.22\) (d, \(J = 18.2\) Hz, 1H), \(7.63\) (d, \(J = 9.1\) Hz, 1H), \(7.39\) (d, \(J = 9.1\) Hz, 1H), \(7.00\) (d, \(J = 9.1\) Hz, 1H), \(6.95\) (d, \(J = 9.1\) Hz, 1H), \(4.40\) (q, \(J = 9.1\) Hz, 2H), \(3.92\) (s, 3H), \(1.42\) (t, \(J = 9.1\) Hz, 3H).

\[
\begin{align*}
&\text{O} &\text{Me} \\
&\text{Me} &\text{O} \\
&\text{OH} + \text{DABCO, toluene, rt} \\
&\text{O} &\text{Me} &\text{O} &\text{Me} \\
&\text{5} &\text{5'} \\
\end{align*}
\]

**Ethyl 2-hydroxy-5,7-dimethoxy-4-(2-methoxyphenyl)chroman-2-carboxylate (5):** (144 mg, 0.94) was added to a solution of 3, 5-dimethoxyphenol (200 mg, 0.85 mmol) and DABCO (10 mg, 0.01 mmol) in 10 ml toluene at room temperature. The reaction mixture was stirred for 160 hrs then concentrated in vacuo. The crude product was purified via flash column chromatography (hexanes/EtOAc, 4:1) to afford a mixture of diastereomers of 5 (0.08 g, 22%) as a brown oil. \(^1\)H NMR (300 MHz, CDCl₃) \(\delta 7.19\) (d, \(J = 9.1\) Hz, 1H), \(6.89\) (m, 3H), \(6.22\) (d, \(J = 3.2\) Hz, 1H), \(6.16\) (d, \(J = 3.2\) Hz, 1H), 4.70 (t, \(J = 9.1\) Hz,
1H), 4.30 (q, J = 6.2 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 2.58 (d, J = 3.2 Hz, 1H), 2.43 (m, 1H), 1.33 (t, J = 6.0 Hz, 1H).

![Chemical structure](image)

### 4-(2-hydroxy-4,6-dimethoxyphenyl)-4-(2-methoxyphenyl)butane-1,2-diol (4b)

Sodium borohydride (40 mg, 1.00 mmol) was added to a solution of 2a (40 mg, 0.1 mmol) in 2 ml anhydrous EtOH at 0°C. The reaction mixture warmed to room temperature and stirred for 15 h. The reaction mixture was concentrated in vacuo and treated with 0.1 M HCl to bring the pH=4. The aqueous layer was extracted with EtOAc (3 x 5 ml). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The crude product was purified via flash column chromatography (hexanes/EtOAc, 1:2) to afford 4b (16 mg, 40%) as a white solid. \(^1\)H NMR (300 MHz, CDCl₃) 7.52 (d, J = 9.1 Hz, 1H), 7.17 (t, J = 9.1 Hz, 1H), 6.96 (t, J = 9.1 Hz, 1H), 6.83 (d, J = 9.1 Hz, 1H), 6.07 (d, J = 18.0 Hz, 2H), 4.76 (d, J = 9.1 Hz, 1H), 3.79-3.44 (m, 9H), 2.55 (t, J = 12.0 Hz, 2H), 2.05 (d, J = 3.2 Hz, 1H), 1.92 (m, J = 9 Hz, 2H).
5,7-dimethoxy-4-(2-methoxyphenyl)chroman-2-ol (3): Sodium periodate (9 mg, 0.006 mmol) was added to 3 (10 mg, 0.003 mmol) in a mixture of MeOH/H₂O (4:1) at room temperature. The reaction mixture was allowed to stir for 30 min. The reaction mixture was filtered through filter paper, which was washed with EtOAc. The crude product was then concentrated in vacuo to afford 3 (8.9 mg, 89%), which was pure enough to proceed to the next step. ¹H NMR (300 MHz, CDCl₃) 7.18 (t, J = 9.1 Hz, 1H), 6.90 (d, J = 9.1 Hz, 1H), 6.77 (t, J = 9.1 Hz, 1H), 6.66 (d, J = 9.1 Hz, 1H), 6.17 (d, J = 3.2 Hz, 1H), 6.09 (d, J = 3.2 Hz, 1H), 5.18 (d, J = 9.1 Hz, 1H), 4.64 (d, J = 3.2 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.58 (s, 3H), 2.33 (d, J = 9.1 Hz, 1H), 2.02 (m, 2H).
5,7-dimethoxy-4-(2-methoxyphenyl)chroman-2-one (2): Pyridinium chlorochromate (20 mg, 0.01 mmol) was added to 4 (10 mg, 0.003 mmol) in 1 ml dichloromethane. The reaction mixture was stirred for 24 hrs. The reaction mixture was then concentrated in vacuo and purified via flash column chromatography (hexanes/EtOAc, 4:1) to afford 5 (9 mg, 90%) ¹H NMR (300 MHz, CDCl₃) 7.21 (m, 2H), 6.87 (d, J = 9.1 Hz, 1H), 6.79 (d, J = 3.2 Hz, 1H), 6.33 (d, J = 3.2 Hz, 1H), 6.26 (d, J = 3.2 Hz, 1H), 4.75 (d, J = 9.1 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.71 (s, 3H), 3.05 (d, J = 18.0 Hz, 1H), 2.91 (dd, J = 9.1 Hz, 1H).

2,4-bis(benzyloxy)benzaldehyde was prepared according to the literature procedure.

(E)-ethyl 4-(2,4-bis(benzyloxy)phenyl)-2-oxobut-3-enoate (17): Triethyl orthoformate (4.94 ml, 29.8 mmol) was added to a solution of 2,4-
bis(benzyloxy)benzaldehyde (7.9 g, 24.8 mmol), ethyl pyruvate (5.6 ml, 50 mmol), and copper (II) triflate (1.8 g, 5.0 mmol) in 100 ml of dichloromethane. The solution was heated to 45°C and stirred for 21 hrs. The crude product was washed with deionized water (3 x 50 ml). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The product was purified via flash column chromatography (hexanes/EtOAc, 10:1) to afford 11 (4.95 g, 48%) as a yellow oil. ¹H NMR (300 MHz, CDCl₃) 8.16 (d, J = 18.0 Hz, 1H), 7.58 (d, J = 9.1 Hz, 1H), 7.40 (m, 11H), 6.64 (d, J = 9.1 Hz, 1H), 6.60 (s, 1H), 5.13 (s, 2H), 5.08 (s, 2H), 4.33 (q, J = 9.1 Hz, 2H), 1.33 (t, J = 9.1 Hz, 3H).

Ethyl 5,7-bis(benzyloxy)-4-(2,4-bis(benzyloxy)phenyl)-2-hydroxychroman-2-carboxylate (15): 17 (0.144 g, 0.94) was added to a solution of 3, 5-dimethoxyphenol (0.2 g, 0.85 mmol) and (QD)₂PYR-Ph, (R=Ph) (0.01 g, 0.01 mmol) in 10 ml toluene at 80°C. The reaction mixture was stirred for 160 hrs then concentrated in vacuo. The crude product was purified via flash column chromatography (hexanes/EtOAc, 4:1) to afford 15 (0.08 g, 81%) as a brown oil. ¹H NMR (300 MHz, CDCl₃) 7.34-7.12 (m, 20H), 6.87 (m, 1H), 6.79 (d, /
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\begin{align*}
= 9.1 \text{ Hz, 1H}, 6.49 (d, J = 3.2 \text{ Hz, 1H}), 6.45 (d, J = 9.1 \text{ Hz, 1H}), 6.30 (d, J = 9.1 \text{ Hz, 1H}), 6.28 (s, 1H), 5.08-4.60 (m, 8H), 4.28 (d, J = 18.0 \text{ Hz, 1H}), 4.11 (q, J = 9.1 \text{ Hz, 2H}), 2.59 (d, J = 9.1 \text{ Hz, 1H}), 2.37 (d, J = 9.1 \text{ Hz, 1H}), 1.30 (d, J = 9.1 \text{ Hz, 1H}), 1.27 (t, J = 9.1 \text{ Hz, 3H}). \end{align*}
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$^{13}$C NMR (75 MHz, CDCl$_3$) 171.51, 170.17, 170.04, 159.48, 159.18, 158.71, 158.30, 157.89, 157.68, 157.08, 154.03, 137.59, 137.52, 137.47, 137.43, 137.19, 137.15, 137.13, 136.95, 129.53, 128.99, 128.87, 128.78, 128.68, 128.41, 128.30, 128.27, 128.22, 128.21, 127.97, 127.94, 127.90, 127.86, 127.79, 127.77, 127.69, 127.57, 127.48, 127.25, 127.13, 126.99, 126.97, 125.85, 107.28, 106.17, 105.41, 105.34, 101.00, 100.67, 95.64, 95.60, 95.23, 95.18, 94.91, 94.82, 70.39, 70.34, 70.08, 69.92, 63.03, 62.91, 60.71, 33.40, 21.33, 14.49, 14.23.

![Chemical structures](image)

**4-(2,4-bis(benzyloxy)-6-hydroxyphenyl)-4-(2,4-bis(benzyloxy)phenyl)butane-1,2-diol (14):** Sodium borohydride (0.07 g, 1.90 mmol) was added to a solution of **15** (0.2 g, 0.28 mmol) in 2 ml anhydrous EtOH at 0°C. The reaction mixture warmed to room temperature and stirred for five hours. The reaction mixture was concentrated *in vacuo* and treated with 0.1 M HCl to bring the pH=4. The aqueous later was extracted with EtOAc (3 x 5 ml).
The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo.
The crude product was purified via flash column chromatography (hexanes/EtOAc, 1:2) to afford 3 as a white solid. ¹H NMR (300 MHz, CDCl₃) 7.33 (m, 20H), 7.14 (m, 2H), 6.57 (s, 1H), 6.44 (d, J = 9.1 Hz, 1H), 6.17 (d, J = 3.2 Hz, 1H), 6.11 (d, J = 3.2 Hz, 1H), 5.00-4.72 (m, 8H), 4.54 (d, J = 9.1 Hz, 1H), 3.52-3.33 (s, 3H), 2.20 (m, 3H), 1.86 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) 158.80, 158.49, 156.76, 156.03, 155.74, 137.17, 137.15, 136.94, 136.42, 136.06, 129.63, 128.95, 128.87, 128.82, 128.78, 128.74, 128.66, 128.44, 128.42, 128.40, 128.35, 128.32, 128.27, 128.21, 127.80, 127.74, 124.19, 111.87, 111.02, 106.40, 105.54, 100.97, 96.32, 94.32, 94.23, 71.34, 70.73, 70.43, 70.43, 70.40, 70.21, 66.92, 36.03.

5,7-bis(benzyloxy)-4-(2,4-bis(benzyloxy)phenyl)chroman-2-ol (13):
Sodium periodate (10 mg, 0.006 mmol) was added to 14 (10 mg, 0.003 mmol) in a mixture of MeOH/H₂O (4:1) at room temperature. The reaction mixture was allowed to stir for 30 min. The reaction mixture was filtered through filter paper, which was washed with EtOAc. The crude product was then concentrated in vacuo to afford 13 (8.9 mg, 89%), which was pure enough to proceed to the next
step. $^1$H NMR (300 MHz, CDCl$_3$) 7.37-7.13 (m, 20H), 6.91 (d, $J = 9.1$ Hz, 1H), 6.66 (d, $J = 3.2$ Hz, 1H), 6.63 (d, $J = 3.2$ Hz, 1H), 6.41 (dd, $J = 9$ Hz, 1H), 6.23 (d, $J = 3.2$ Hz, 1H), 6.21 (d, $J = 3.2$ Hz, 1H), 5.29 (m, 1H), 5.06-4.76 (m, 8H), 2.96 (d, $J = 9.1$ Hz, 1H), 2.32 (dd, $J = 9$ Hz, 1H), 2.28 (m, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) 159.57, 159.55, 158.92, 158.63, 152.68, 157.51, 157.35, 156.89, 155.80, 154.53, 137.39, 137.30, 137.25, 137.14, 129.36, 128.86, 128.78, 128.38, 128.29, 128.28, 128.23, 128.04, 128.00, 127.92, 127.82, 127.64, 127.29, 127.23, 127.17, 127.02, 126.93, 105.47, 105.15, 100.82, 94.69, 94.16, 92.78, 92.75, 70.42, 70.40, 70.37, 70.28, 69.79, 35.50, 29.52, 29.48.

5,7-bis(benzyloxy)-4-(2,4-bis(benzyloxy)phenyl)chroman-2-one (12):

Pyridinium chlorochromate (20 mg, 0.01 mmol) was added to 13 (10 mg, 0.003 mmol) in 1 ml dichloromethane. The reaction mixture was stirred for 24 hrs. The reaction mixture was then concentrated in vacuo and purified via flash column chromatography (hexanes/EtOAc, 4:1) to afford 12 (9 mg, 90%) $^1$H NMR (300 MHz, CDCl$_3$) 7.38-7.11 (m, 20H), 6.63 (d, $J = 9.1$ Hz, 1H), 6.57 (d, $J = 3.2$ Hz, 1H), 6.39-6.35 (m, 3H), 5.04-4.90 (m, 8H), 3.03 (d, $J = 9.1$ Hz, 1H), 2.89 (ds, $J = 9.1$ Hz,
1H). $^{13}$C NMR (100 MHz, CDCl$_3$) 168.22, 159.75, 159.32, 156.96, 156.62, 153.88, 137.11, 137.05, 136.68, 136.61, 128.91, 128.82, 128.77, 128.58, 128.43, 128.22, 128.06, 128.01, 127.84, 127.74, 127.39, 127.16, 122.58, 106.58, 105.46, 100.91, 97.31, 95.28, 70.61, 70.30, 67.43, 35.85, 29.66.

5,7-bis(benzyloxy)-4-(2,4-bis(benzyloxy)phenyl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-2-ol (13): Butyl lithium (0.12 ml, 0.19 mmol) was added dropwise under N$_2$ to a stirring solution of 4-iodoanisole (45 mg, 0.2 mmol) in diethyl ether (2 ml) at -78°C. The reaction mixture was stirred for 10 min and then cannulated into a solution of 12 (25 mg, 0.038 mmol) in diethyl ether (2 ml). The reaction was warmed to room temperature and then stirred for 60 minutes. The reaction mixture was treated with saturated NaHCO$_3$ (3 ml) and extracted with EtOAc (3 x 5 ml). The crude product concentrated in vacuo and then purified via flash column chromatography (hexanes/EtOAc, 7:3) to afford 11b (11 mg, 38%) as a white solid. $^1$H NMR (400 MHz, CDCl$_3$) 7.36-7.21 (m, 20H), 6.72 (d, $J = 9.1$ Hz, 1H), 6.69 (d, $J = 9.1$ Hz, 1H) 6.48 (d, $J = 3.2$ Hz, 1H), 6.39 (dd, $J = 9.1$ Hz, 1H), 6.30 (s, 1H), 6.05 (s, 1H), 4.96-4.84 (m, 8H), 4.73 (m, 1H),
3.75 (s, 3H), 3.28 (dd, J = 9.1 Hz, 1H), 3.06 (dd, J = 9.1 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) 158.88, 158.34, 158.23, 155.95, 155.36, 140.19, 139.58, 137.21, 137.16, 136.76, 135.73, 130.33, 128.93, 128.85, 128.80, 128.80, 128.66, 128.45, 128.34, 128.25, 128.19, 128.17, 127.78, 127.74, 127.33, 127.29, 125.42, 113.42, 113.33, 112.24, 166.47, 100.80, 96.33, 94.13, 78.92, 71.20, 70.66, 70.38, 70.19, 55.42, 44.57.

![Chemical structure](attachment:image)

**Representative procedure for Michael addition of cyclohexadiones to 17:**

To 17 (20 mg, 0.050) and (QD)$_2$Pyr (13 mg, 0.014 mmol) in 1 ml THF at -30°C was added 33 (13 mg, 0.070 mmol). The reaction was stirred for 72 h then concentrated in vacuo. The crude product was purified via flash chromatography (hexanes/EtOAc, 1:4) to afford 32 (13 mg, 39%) as a white solid.

**(4R)-ethyl 4-(2,4-bis(benzyloxy)phenyl)-2-hydroxy-5-oxo-2,3,4,5,6,8-hexahydrospiro[chromene-7,2'-[1,3]dioxane]-2-carboxylate (32):** $^1$H NMR 7.40 (m, 10H), 6.92 (d, J = 9.1 Hz, 1H), 6.69 (dd, J = 3.2 Hz, 1H), 6.44 (dd, J = 9.1 Hz, 1H), 5.08 (s, 2H), 5.02 (m, 1H), 4.96 (s, 2H), 4.37 (q, J = 9.1 Hz, 2H), 3.96 (m, 3H), 2.92 (m, 2H), 2.76 (d, J = 18.0 Hz, 1H), 2.25 (m, 1H), 1.85 (m, 1H), 1.69 (m,
1H), 1.31-1.21 (m, 3H), 0.87 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) 193.61, 169.02, 166.07, 158.92, 157.00, 156.87, 137.48, 137.46, 137.35, 137.31, 137.28, 128.80, 128.74, 128.71, 128.43, 128.18, 127.99, 127.87, 127.82, 127.81, 127.35, 127.16, 123.08, 112.33, 105.20, 100.84, 97.49, 97.27, 96.62, 70.28, 63.23, 60.36, 44.75, 39.43, 32.84, 25.34.

(4R)-ethyl 4-(2,4-bis(benzyloxy)phenyl)-2-hydroxy-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate: $^1$H NMR 7.47-7.17 (m, 10H), 6.75 (d, $J = 9.1$ Hz, 1H), 6.65 (dd, $J = 9.1$ Hz, 1H), 6.45 (m, 1H), 5.19 (s, 2H), 4.88 (s, 2H), 4.33 (d, $J = 9.1$ Hz, 1H), 4.15 (q, $J = 9.1$ Hz, 2H), 2.27-2.48 (m, 6H), 1.23 (t, $J = 9.1$ Hz, 3H), 0.77-0.57 (m, 6H).

3-hydroxy-2-(1-(4-methoxyphenyl)-3-(4-nitrophenyl)-3-oxopropyl)-5,5-dimethylcyclohex-2-enone (14) and (2S,4R)-2-hydroxy-4-(4-methoxyphenyl)-7,7-dimethyl-2-(4-nitrophenyl)-3,4,7,8-tetrahydro-2H-
**chromen-5(6H)-one (15):** (E)-3-(4-methoxyphenyl)-1-(4-nitrophenyl)prop-2-en-1-one (300 mg, 1.08 mmol) was added to a solution of dimedone (187 mg, 1.33 mmol) and DABCO (61 mg, 0.54 mmol) in DCM (15 ml) at room temperature under N₂. The reaction was stirred for 96 hours and was then condensed *in vacuo*. The crude product was purified via flash column chromatography (DCM/MeOH, 99:1) to afford 14 (292 mg, 64%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃) 8.26 (d, J = 9.1 Hz, 2H), 7.94 (d, J = 9.1 Hz, 2H), 7.26 (d, J = 9.1 Hz, 2H), 6.73 (d, J = 9.1 Hz, 2H), 4.26 (t, J = 7.2 Hz, 1H), 3.76 (s, 3H), 3.56 (dd, J = 7.2 Hz, 1H), 3.30 (m, 2H), 3.05 (d, J = 7.2 Hz, 1H), 2.44 (dd, J = 7.2 Hz, 2H), 1.26 (s, 3H), 1.24 (s, 3H).