The Enantioselective Synthesis of (-)-Rocaglamide core structure via an "Interrupted" Feist-Bénary Reaction

by

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Abstract

The National Cancer Institute estimated that in the United States in 2018, ~24,000 people would die of leukemia and ~60,000 new cases would be detected.\(^1\) Thus, discovering and synthesizing new antileukemic compounds is essential to allow treatment of this disease. Therefore, this thesis describes a novel, faster, cheaper, and greener route for synthesizing an antileukemic natural product found in low levels in the roots and stems of *Aglia elliptifolia* in southeast Asia.\(^2\) Rocaglamide’s significant anti-cancer activity relies heavily on its structural complexity, containing five stereocenters. While total syntheses of (-)-rocaglamide have been developed, all of the current total syntheses are long, have poor yields, and utilize expensive and very toxic compounds.\(^2\)

Through an asymmetric organocatalytic Interrupted Feist-Bénary-like synthesis, the enantioselectivity of two substituted cinchona alkaloid-derived pyrimidine catalysts have been tested under various reaction conditions. After the reaction conditions were optimized, the phenyl-phenyl derived catalyst proves to be the most effective with an enantioselectivity of 45-51% enantiomeric excess at room temperature. Though high enantioselectivity has not yet been achieved, the phenyl-phenyl derived catalyst proves to be effective at room temperature independently of the solvent used to run the IFB-like reaction. Once a potential chiral organocatalyst yields an enantiomer at greater excess of rocaglamide’s core structure, we will have two controlled stereocenters that will facilitate the total enantioselective synthesis of rocaglamide. In developing this new synthetic pathway for the total synthesis of rocaglamide.
rocaglamide, we will not only provide new insight into green, synthetic chemistry but also enable sufficient quantities of potential low-cost therapeutic treatments.
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I could not have asked for a better support system. Thank y’all!
List of Abbreviations

aq            aqueous
cat           catalytic
DABCO         1,4-diazabicyclo[2.2.2]octane
DCM           Dichloromethane
ee            enantiomeric excess
eq.           equivalents
EtOAc         Ethyl acetate
EtOH          Ethyl alcohol
h             hour(s)
Hz            Hertz
HPLC          High-performance liquid chromatography
IFB           "Interrupted" Feist-Bénary
IFB-like      "Interrupted" Feist-Bénary-like
IPA           isopropanol
J             coupling constant
m-CPBA        meta-chloroperoxybenzoic acid
Me            Methyl
min           minutes
mL            milliliters
mol           moles(s)
mmol          millimoles(s)
n-Bu          n-butyl
NMR           Nuclear Magnetic Resonance
Nu            nucleophile
Ph            Phenyl
ppm           parts per million
QD            quinidine
QN            quinine
rt            room temperature
TLC           Thin Layer Chromatography
1. Introduction

1.1 Introduction to Chirality and Stereochemistry
Chiral objects are almost everywhere and unavoidable! Consider our hands, one of the many physical features humans possess that is chiral. Chiral objects are asymmetrical, in other words, non-superimposable on their mirror image.

Figure 1: The right-hand and left hand (palm view) are non-superimposable on their mirror image.

The origin of the word “chiral” derives from the Greek word “cheir”, which means ‘handedness’. As illustrated in Figure 1, the right hand is the mirror image of the left hand, both have the same number of fingers, however when we put our hands (palms) on top of each other, we notice that our hands are not identical. Therefore, if the object cannot be matched with its mirror image by either translation or rotation, it is a chiral object.

In 1850, Louis Pasteur was the first chemist to study chirality and the first to achieve resolution of a racemic mixture. Pasteur’s study and novel findings of chiral, natural occurring compounds were in later years termed as “stereochemistry”. Stereochemistry is the study of the spatial configuration of atoms that compose a molecule. The three-dimensional analysis of a compound provides essential characterization of a compound when the molecular and constitutional formula fall short in explicitly indicating what molecule is being studied or synthesized. For
example, Figure 2, shows two possible compounds that can account for the molecular formula CHFClBr and where the constitutional formula cannot specifically indicate the spatial orientation of the atoms linked to the stereocenter, carbon. Therefore, in Figure 2, there are two distinct chiral compounds that have in common the same number of atoms, albeit with no symmetries just as our hands.

![Figure 2](image)

*Figure 2:* Two chiral molecules with the same molecular formula of CHFClBr that contain the same atoms but in different spatial environments.

On the other hand, symmetrical objects are called achiral. Achiral compounds are superimposable and such molecules do not contain a stereocenter that can interfere with its symmetry. In Figure 3, the two compounds have the same molecular formula and atom connectivity therefore, identical. Therefore, B1 and B2 are the same compound and not stereoisomers.

![Figure 3](image)

*Figure 3:* Two identical compounds (CH₂FBr) that are superimposable.
Stereoisomers are compounds that have the same molecular formula but differ in the spatial arrangement of their constituents. Stereoisomers must contain a stereocenter in order to eliminate symmetry. A stereocenter (chiral center) is an asymmetric atom bonded to different moieties. For example, a carbon atom when bonded to four different atoms or groups of atoms is a chiral center (*Figure 2*). The Cahn-Ingold-Prelog system rules are utilized to define the stereochemical configuration of a chiral center, using the (R) (right hand) or (S) (left hand) nomenclature.\textsuperscript{4}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{limonene.png}
\caption{Enantiomer pair of limonene, the isomer on the left rotates clockwise (+) on its stereocenter while the isomer on the right side rotates counterclockwise (-) on its stereocenter.}
\end{figure}

*Note:* The stereocenters are marked with an (*).

Stereoisomers can be classified as either enantiomers or diastereomers. Enantiomers are stereoisomers that are non-superimposable mirror images as observed in *Figure 4*. Enantiomers are optically active molecules in chiral environments, that is to say that these molecules have the ability to rotate plane polarized light. The isomer that rotates counter clockwise is called “levorotary” and is indicated as a (-) sign.\textsuperscript{4} The isomer that rotates clockwise is called “dextrorotary” and is designated by a (+) sign.\textsuperscript{5}
The R-(-)-limonene is what causes an orange to smell, while the S-(-)-limonene causes the smell of lemons, thus these two enantiomers are found in different fruits that our chiral nose can distinguish. However, when two enantiomers are present in a one to one (equimolar) mixture, a racemic mixture, there is zero optical activity, the two isomers become indistinguishable since the pair of enantiomers in an achiral environment have the same chemical and physical properties.5

Figure 5: Diastereomers of 2-bromo-3-chlorobutane, where one stereocenter is inverted.

Note: “S” and “R” indicate the nomenclature to a stereocenter.

Unlike enantiomers, diastereomers have different chemical and physical properties in chiral and achiral environments which facilitate chiral separation.5 As illustrated in Figure 5, diastereomers are not mirror images of each other due to the inversion of one stereocenter. Diastereomers are stereoisomers that require a minimum of two stereocenters, where compounds can have the same molecular formula but have at least one inverted stereocenter to eliminate any mirror image of each other.

1.2 Stereochemistry and Small Molecules

Stereochemistry has been a significant concern for both the pharmaceutical industry and the Food and Drug Administration.4 A prime example of the importance of stereochemistry in medicine occurred after the distribution of the racemic mixture of thalidomide in Europe.4 In the late 1950s, thalidomide was administered to pregnant women as a morning sickness sedative.4,5,6 The small molecule was marketed as a
racemate at the time, which caused phocomelia and its ban.\textsuperscript{3,5} However, after careful studies on chiral resolution and effectiveness of the thalidomide enantiomers in the biological system, it was resolved that (R)-thalidomide is the eutomer (gives the sedative effects) while the (S)-thalidomide is the distomer (causes birth defects). R-thalidomide is now avowed as one of the best cancer treatments for multiple myeloma and for other chronic diseases.\textsuperscript{6,7}

![Chemical Structures of R-thalidomide and S-thalidomide](image)

\textbf{Figure 6:} Thalidomide isomers, the (R)-isomer is the major bioactive enantiomer (eutomer) and the S-isomer is the terotogen (distomer).

Biological systems (proteins, enzymes, amino acids, carbohydrates, nucleosides and hormones) are chiral compounds.\textsuperscript{4} Proteins are chiral and are able to very specifically recognize and bind to small molecules.\textsuperscript{4} Consider cereblon, a chiral protein that binds differently with the R- and S-enantiomers of thalidomide.\textsuperscript{7} \textbf{Figure 7}, is a hypothetical illustration of how a chiral protein such as cereblon can interact with a small, chiral molecule. The black, right hand glove represents the protein while the right hand (palm) represents the R-enantiomer and the left hand represents the S-enantiomer of a given therapeutic binding with the chiral protein. As observed, only one enantiomer of the small molecule (hand) can bind correctly to the protein (right hand glove) due to selectivity of chiral compounds in chiral environments.
Small molecule chiral drugs can bind with various biomolecules selectively.\textsuperscript{3} Small, chiral molecules can bind deep into cavities of a protein or DNA and can target extra-cellular, intra-cellular, and intra-nuclear targets through diffusion.\textsuperscript{8} For example, when pregnant women would take the racemic mixture of thalidomide, the R-enantiomer would stop nausea while the S-enantiomer would enter the placenta and affect the cells in limb development in embryos. Therefore, chiral resolution is important in order to eliminate the distomer from penetrating through other cells and causing serious side effects.\textsuperscript{4,5}

Since enantiomers possess differing pharmacodynamics and pharmacokinetic properties, enantioseparation of chiral drugs is vital for optimal potency of the drug and reduction off-target effects in patients.\textsuperscript{4} One approach to enantioselectivity of a small molecule is to conduct asymmetric synthesis. In this thesis project, the enantioselective synthesis of rocaglamide via an asymmetric organocatalytic “Interrupted" Feist-Bénary-like (IFB-like) reaction is explored and analyzed through high-performance liquid chromatography for the direct separation and characterization of enantiomers. The analytical method employed in this project is high-performance liquid
chromatography. High-performance liquid chromatography (HPLC) can be utilized to quantify the enantiomeric excess (enantiopurity) of one enantiomer over the other using the formula below. The enantiomeric excess (%ee) provides the percent abundance of each enantiomer, thus a racemate has 0%ee, while a pure enantiomer has 100%ee.

\[
%ee = \frac{(R - S)}{(R + S)} \times 100\%
\]

*Equation 1:* The equation for calculating the enantiomeric excess of a chiral molecule.

1.3 Cinchona Alkaloids as Organocatalysts

Asymmetric organocatalysis is one of the many methods employed to isolate the bioactive enantiomer of a racemate. Leading examples of organocatalysis for the enantioseparation of small molecules are secondary amine catalysis, tertiary amine catalysis via phase-transfer catalysis, and Bronsted base catalysis.\(^9\) The Bronsted base catalysis has been a major area of interest within the field of synthetic and medicinal chemistry due to the use of 0.1 or even 0.01 equiv. of cinchona alkaloid-derived pyrimidine catalysts that readily convert accessible achiral starting materials into potent chiral molecules.\(^9,11,12,13,14\)

Cinchona alkaloids are abundant natural products found in the bark of genus *Cinchona* trees in South America.\(^10,11,12,13\) Cinchona alkaloids exist as pseudoenantiomeric pairs of cinchonidine (CD) and cinchonine (CN) and as diastereomeric pair of quinine (QN) and quinidine (QD).\(^11,12\) In 1820, Pelletier was the first to isolate quinine, a potent antimalarial agent.\(^11,12\) A century later, Bredig and Fiske discovered that cinchona alkaloids do not only possess medicinal properties but can
also play an active role in the application of stereochemistry and in asymmetric synthesis.\textsuperscript{10,13,14,15,16}

Unlike metal catalysts, cinchona alkaloid-derived catalysts are stable, recoverable, tunable, non-toxic, inexpensive, and commercially available.\textsuperscript{11,12} Additionally, cinchona alkaloids are bifunctional organocatalysts; the tertiary amine activates and orients the nucleophile at the same time the hydroxyl group activates and orients the electrophile through hydrogen binding to achieve optimum asymmetric catalysis.\textsuperscript{11,13,14,15,16} Note, these bifunctional groups can be modified to synthesize more tunable cinchona alkaloid-derived catalysts that can increase the catalytic activity and selectivity of diverse enantioselective reactions.\textsuperscript{9,14,15,16}

The major organocatalysts explored in Dr. Michael Calter’s research laboratory are quinine and quinidine. Quinine and quinidine differ in two chiral carbons that yield opposite enantiomers.\textsuperscript{13,15} Quinine is levorotary while quinidine is dextrorotary.\textsuperscript{13}
Therefore, for this specific research project, we are only investigating quinidine’s selectivity since the two adjacent stereocenters in rocaglamide’s core structure rotate clockwise.

1.4 The "Interrupted" Feist-Bénary Reaction

The Feist-Bénary reaction yields a substituted furan through a base-catalyzed reaction between an $\alpha$-halogen ketone and a $\beta$-dicarbonyl compound in the presence of an amine catalyst.\textsuperscript{16,17} The first step is the enolization of the $\beta$-dicarbonyl compound with the amine catalyst, followed by the aldol reaction of the $\alpha$-halogen ketone to form a hydroxydihydrofuran intermediate. The intermediate then undergoes elimination of water through acid work-up to yield a furan.

**Scheme 1.1:** The Feist-Bénary reaction and its intermediate step; the "Interrupted" Feist-Bénary Reaction.

The hydroxydihydrofuran intermediate in the Feist-Bénary reaction is the "Interrupted" Feist-Bénary (IFB) reaction. In Dr. Michael Calter’s synthetic research laboratory, the IFB reaction is explored since the formation of two adjacent stereocenters can readily provide core structures of bioactive natural products such as (-)-rocaglamide. In 2005, Dr. Phillips, graduate student in Dr. Calter’s research laboratory at the time, discovered that cinchona alkaloid-derived catalyzed IFB
reactions between $\alpha$-bromopyruvate and 1,3-cyclohexandione give 94-96% yields and 92-96%ee (Scheme 1.2).  

Scheme 1.2: IFB reaction of $\alpha$-bromopyruvate and 1,3-cyclohexandione with bis-quinidine-catalyst.

The transition states of the proposed IFB mechanism, shows the activation of the electrophile followed by the nucleophilic attack due to the ion pair of the protonated chiral catalyst with the carbonyl moieties of the $\alpha$-bromopyruvate. The front and back groups, labeled as “R1” and “R2” in Scheme 1.3, play a pivotal role in the enantioselectivity of the IFB reaction.
Scheme 1. 3: Proposed mechanism of the IFB reaction.

The study of the organocatalytic IFB reactions have been a success in Dr. Calter’s lab, which have further helped develop new synthetic methodology of electrophiles that can expand the scope of novel asymmetric syntheses. For example, in 2011, Dr. Korotkov and Dr. Calter designed a new class of non-highly functionalized electrophiles for IFB reactions. This new class of electrophile, 1,4-diketone electrophiles, pertain to the IFB-like reaction since the mechanism of the IFB reaction undergoes a different path to close the furan ring. Nonetheless, these 1,4-diketones prove to be as effective as the previous developed electrophiles in Dr. Calter’s lab since they still yield hydroxydihydrofurans in high efficacy with two adjacent stereocenters. As a result, this thesis focuses on one of the IFB-like reactions that yields the substituted hydroxydihydrofuran ring of rocaglamide’s core structure.
1.5 Rocaglamide

(-)-Rocaglamide or also known as rocaglamide is a natural compound found in trees of genus *Aglaia* in Southeast Asia. Rocaglamide was first isolated in 1982 by King *et al.* and reported to be a potent antileukemic agent.

![Rocaglamide](image)

**Figure 1.9:** Rocaglamide

Rocaglamide’s therapeutic properties and stereochemistry has been of great interest for synthetic and medicinal chemists. Over 20 total syntheses have been reported, however no organocatalytic asymmetric synthesis has been yet accomplished yet.9 Rocaglamide has five continuous stereocenters as illustrated in **Figure 1.9**. Therefore, through an enantioselective IFB-like reaction, we will make two of the continuous stereocenters in one step through the creation of a hydroxydihydrofuran. We will also shorten the synthetic pathway by having a four-step electrophile reaction. Additionally, our organocatalytic reaction will only contain 0.1 equiv. of a cheap, recoverable, and non-toxic catalyst. Our ultimate goal is to provide a more efficient synthetic pathway towards the total synthesis of rocaglamide, in order to facilitate its production and minimize its cost to current patients who rely on this potent therapeutic agent.
2. The "Interrupted" Feist-Bénary Reaction with a Cyclic Triketone

2.1 Introduction of the Cyclic Triketone and its Synthesis

Dr. Ednyasheva inspired by the IFB-like electrophiles explored by Dr. Korotkov, proposed the use of a cyclic ene-triketone electrophile for the asymmetric IFB-like reaction of rocaglates. A key aspect of this new type of triketone electrophile is its rigid nature that maintains the stereochemistry of the product after the aldol addition reaction. Furthermore, the three ketones render the electrophile highly reactive with aromatic nucleophiles which ultimately shortens the number of steps required for the total synthesis of rocaglamide (Figure 2.1).

![Figure 2.1: The five electrophilic sites of unsaturated cyclic triketones.](image)

The cyclic triketone electrophile, 4-phenylcyclopent-4-ene-1,2,3-trione, was designed and first synthesized by Dr. Ednyasheva, which consists of a four-step reaction as illustrated in Scheme 2.1. The first step consists of a Grignard reaction to make a secondary alcohol. The secondary alcohol is then converted into an allylic alcohol that is then submitted as a diketone through activated manganese (IV) dioxide. However, it is important to note that the allylic alcohol does not fully convert to a diketone with activated manganese (IV) dioxide. This specific reaction must be resubmitted three times in order to consume starting material that hinders activation.
The last step to make the electrophile is carried by using selenium dioxide to install the third ketone group on the highly reactive electrophile.

Scheme 2.1: Synthesis of 4-phenylcyclopent-4-ene-1,23-trione electrophile.

2.2 IFB-like reaction with 4-phenylcyclopent-4-ene-1,23-trione Electrophile

The triketone electrophile, 8, was submitted with 3,5-dimethoxyphenol (nucleophile) and DABCO (catalyst) to test the IFB-like reaction proposed by Dr. Ednyasheva. According to NMR analysis, the reaction was a success. The next step we took was to consider the selectivity DABCO was providing as the organocatalysts. Therefore, we developed a chiral HPLC assay to resolve the enantiomers of the IFB-like product racemate.

Scheme 2.2: IFB-like reaction using DABCO.

The HPLC assay developed consists of 10% Ethanol/ 90% Hexanes with a flow of 1.00, (1+2) Range of 0.05, and a wavelength of 280nm. The chiral columns tested on these...
protocols were a Chiralcel OD-H column and a ChiralPAk AD-H column. The first chiral column was more efficient than the latter one since the two enantiomers were readily observed at an earlier retention time interval which further facilitated the process. Once, the protocols for the HPLC assay were optimized, we screened our first IFB-like reaction with the triketone electrophile and DABCO as the organocatalyst. As illustrated in Figure 2.2, the presence of DABCO shows our racemic mixture, giving 0%ee.

![Figure 2.2](image)

**Figure 2.2**: Chromatogram of IFB-like reaction using DABCO.

Since the IFB-like reaction in the presence of DABCO gave the racemate product, we started synthesizing bis(QD)cinchona alkaloid catalysts to start identifying the selectivity of the reaction in presence of quinidine.
2.3 Chiral catalyst synthesis

The chiral catalysts employed in optimizing the IFB-like reaction were all cinchona alkaloid-derived pyrimidine catalysts since quinidine’s selectivity matches the dextrorotary rotation of the two adjacent stereocenters in rocaglamide’s core structure (hydroxydihydrofuran ring). Only the front group (R1) in the bis-substituted catalysts was changed to determine if high enantioselectivity would be achieved with a non-steric (hydrogen) or steric group like phenyl.

2.4 Catalyst Screening and Reaction Optimization

This thesis focuses on increasing the enantioselectivity of the IFB-like reaction using a triketone, a cyclohexadione, and an aromatic nucleophile to synthesize
roca glam ide’s core structure. Below, is tabulated the different solvent and reaction conditions explored using H-Ph and Ph-Ph-derived organocatalysts. The key point explored in this specific part of the project is to consider solubility characteristics and the effect of temperature.

Scheme 2.3: IFB-like reaction.

The first set of IFB-like reactions were ran under DCM at various temperatures using the phenyl-phenyl derived catalyst. According to HPLC chromatograms, we obtain the highest enantioselectivity of the IFB-like reaction at room temperature in DCM. We then slowed the IFB-like reaction by running it at -78°C, however this change in temperature had a negative influence on the rate of the reaction. Note, this negative affect was observed for all IFB-like reactions at -78°C independently of the solvent is was dissolved in. We then questioned if the rate of addition had any influence in the enantioselctivity of the IFB-like reaction. After testing this new approach with DCM, we realized that adding our reactants dropwise did not influence the selectivity of our desired enantiomer. Thus, we did not continue to run reactions where either the electrophile or nucleophile were added dropwise with other solvents. Below are tables that show several experiments with DCM, DCE, and Chloroform.
### Table 1: IFB-like reaction with Ph-Ph catalyst in DCM.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>Temp</th>
<th>Dropwise Addition</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>-78°C</td>
<td>-</td>
<td>98</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Ph</td>
<td>-78°C</td>
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<td>47</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>Ph</td>
<td>RT</td>
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<td>31</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Ph</td>
<td>RT</td>
<td>Nucleophile</td>
<td>98</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>Ph</td>
<td>40°C</td>
<td>-</td>
<td>98</td>
<td>44</td>
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</tbody>
</table>

### Table 2: IFB-like reaction with Ph-Ph catalyst in DCE.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>Temp</th>
<th>% yield</th>
<th>% ee</th>
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<tbody>
<tr>
<td>1</td>
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<td>Ph</td>
<td>-78°C</td>
<td>98</td>
<td>31</td>
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<td>Ph</td>
<td>183°C</td>
<td>98</td>
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### Table 2: IFB-like reaction with Ph-Ph catalyst in chloroform.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>Temp</th>
<th>% yield</th>
<th>% ee</th>
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<tbody>
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<td>Ph</td>
<td>-78°C</td>
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<td>28</td>
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<td>Ph</td>
<td>61°C</td>
<td>98</td>
<td>42</td>
</tr>
</tbody>
</table>

The H-Ph catalyst was the second catalyst to be tested. However, the H-Ph catalyst does not show much selectivity than the Ph-Ph catalyst when at room temperature in DCM. The H-Ph catalyst gave 21%ee and there no further experiments were undertaken using this catalyst. Nonetheless, other catalysts are being employed in the IFB-like reaction to test if selectivity will increase with more steric hindrance in the R1 group of the bis(QD)pyrimidine catalyst.

### 4. Conclusions and Future Directions

The IFB-like reaction has higher enantioselectivity with the Ph-Ph bis(QD)pyrimidine catalyst which has helped change our perspective in analyzing other steric groups to
be placed as R1 groups. After the reaction conditions were optimized, we have concluded that independent of the solvent used, the phenyl-phenyl derived catalyst proves to be the most effective with an enantioselectivity of 45-51% enantiomeric. Our next approach is now to synthesize more organocatalysts and try slowing the reactions by running the IFB-like at °C and -50°C to identify if in the range of -78°C to room temperature there is a favorable temperature that bring higher selectivity.

Our ultimate goal is to synthesize a potential chiral organocatalyst that can yield an enantiomer at greater excess of rocaglamide’s core structure, in order to have two controlled stereocenters that can facilitate the total enantioselective synthesis of rocaglamide. In developing this new synthetic pathway for the total synthesis of rocaglamide, we hope not only to provide new insight into green, synthetic chemistry but also enable sufficient quantities of potential low-cost therapeutic treatments.

5. Experimental

General Methods

All commercial reagents were used directly as received unless otherwise indicated. Toluene, pyridine, dichloromethane, and tetrahydrofuran were filtered through an activated alumina column in a solvent purification system. Thin-layer chromatography (TLC) was achieved using SiliCycle 0.25mm thickness, 60Å pore size silica gel plates or basic alumina (III) plates. Visualization of the developed TLC plates was accomplished using fluorescence quenching. Flash chromatography employed Dynamic Adsorbent Inc. 60Å, 32-63μm or SiliCycle 60Å, 32-63μm silica gel, and Dynamic Adsorbent Inc. 60Å, 32-63μm basic alumina activity III.
Proton NMR spectra were recorded on Varian Mercury-300BB (300MHz) and Varian-400 (400 MHz) spectrometers.

HPLC analyses were obtained using a Thermo Separation Product Spectra Series P200 HPLC, coupled with a Dynamax Absorbance UV-D detector, a Hewlett-Packard 3395 integrator, and a Chiralcel OD-H chiral column.

**Synthesis of 2-furyl(phenyl)methanol**

To a flame-dried 250mL round-bottom flask, equipped with a stir bar, 100mL of DCM were added followed by 4mL of 2-furaldehyde at 0°C under nitrogen. With a dry syringe, 18mL of phenyl magnesium bromide were added dropwise. The reactants were stirred for an hour at room temperature. At completion, the reaction was quenched by an acid work-up using 1M HCl and DCM. The organic solution was dried over anhydrous sodium sulfate and concentrated in vacuo. Product was purified by flash chromatography (10% Ethyl Acetate/90% Hexanes) to yield a brown oil of 8.878g (5.1x10^{-2} mol) of 2-furyl(phenyl)methanol (98% yield).

^1H NMR (CDCl3, 300MHz) δ 7.395 (m, 6H), 6.326 (s, 1H), 6.12 (s, 1H), 5.804 (s, 1H), 2.041 (s, 2H).

**Synthesis of 4-hydroxy-2-phenylcyclopent-2-en-1-one**
To a 500mL round-bottom flask, equipped with a stir bar, 60mL of 1,4-dioxane were added to 5.7g ($3.3\times10^{-2}$ mol) of 2-furyl(phenyl)methanol and stirred at 95°C. Subsequently, 80mL of water and 17.5g ($1.28\times10^{-1}$ mol) of zinc chloride were added. After twenty-four hours of reflux, TLC analysis was conducted to test full completion of reaction. Once the mixture was at room temperature, the organic layer was extracted using DCM. The organic solution was dried over anhydrous sodium sulfate and concentrated in vacuo. Product was purified by flash chromatography (10% Ethyl Acetate/90% Hexanes) to yield a brown residue of 2.91g ($1.67\times10^{-2}$ mol) of 4-hydroxy-2-phenylcyclopent-2-en-1-one (52% yield).

$^1$H NMR (CDCl$_3$, 300MHz) $\delta$ 7.706 (d, 2H), 7.638 (s, 1H), 7.383 (d, 3H), 5.083 (s, 1H), 3.017 (dd, 1H), 2.524 (d, 1H), 2.008 (d, 1H).

### Synthesis of 4-phenylcyclopent-4-ene-1,3-dione

To a 250mL round-bottom flask, equipped with a stir bar, 2.47g ($1.67\times10^{-2}$ mol) of 4-hydroxy-2-phenylcyclopent-2-en-1-one, 180mL of ethyl acetate, and 6.17g ($7.09\times10^{-2}$ mol) of manganese dioxide were stirred for two hours at room temperature. TLC
analysis was conducted to test full completion of reaction. The mixture was filtrated using ethyl acetate. The product was concentrated in vacuo. The brown crude was purified by flash chromatography (30% Ethyl Acetate/70% Hexanes) to yield a yellow solid of 1.59g (9.25x10^{-3} mol) of 4-phenylcyclopent-4-ene-1,3-dione (65% yield). (Note: This reaction was submitted three times in order to reuse the starting material that was not converted to desired product.)

\(^1\)H NMR (CDCl\(_3\), 300MHz) \(\delta\) 7.886 (s, 2H), 7.493 (s, 3H), 7.383 (s, 1H), 3.113 (s, 2H).

**Synthesis of 4-phenylcyclopent-4-ene-1,2,3-trione**

```
O
\Ph
\ SeO\textsubscript{2}
\textsubscript{1,4-dioxane}
\textsubscript{90°C}
\textsubscript{12h reflux}
```

To a 50mL round-bottom flask, equipped with a stir bar, 1.59g of (9.24x10^{-3} mol) 4-phenylcyclopent-4-ene-1,3-dione, 8mL of 1,4-dioxane, 1.12g (1.00x10^{-2} mol) of selenium dioxide were stirred at 90°C for twelve hours under reflux. The product was purified through flash chromatography (35% Ethyl Acetate/65% Hexanes) to yield an orange powder of 0.44g (2.37x10^{-3} mol) of 4-phenylcyclopent-4-ene-1,2,3-trione (26% yield).

\(^1\)H NMR (CDCl\(_3\), 300MHz) \(\delta\) 7.953 (s, 2H), 7.539 (s, 3H), 6.622 (s, 1H).
6. References


7. Spectra
furan-2-yl(phenyl)methanol
4-hydroxy-2-phenylcyclopent-2-en-1-one
4-phenylcyclopent-4-ene-1,2,3-trione
January 04, 201
Column: ODH0 CE - IF0 80; Chiral OD-H
Assay: 10% Ethanol / 90% Hexanes
Flow: 1.00 (l/h) Range: 0.05 A: 280nm
Attn's:
Sample: JA - I - 47 (IFB + Ph-Pn in CHCl3 @ -78°C)
(1.5 ul injection)
RUNH 4081  JAN 4, 1916  19:20:38

AREA

RT  AREA  TYPE  WIDTH  AREA
4.065  17457  PB  .999  .98193
22.356  132250600  PU  1.160  72.67516
26.585  45577856  UU  1.356  27.24386

TOTAL AREA=1.8196E+06
MUL FACTOR=1.0000E+00

January 04, 2019
Column: 05-HCE - IFP 30; third OD-H
Assay: 10% Ethanol / 90% Hexanes
Flow: 2.00 (1+2) Range: 0.05  λ: 280nm
Attn.: B
Sample: JA-I-47 (IFB + Ph-Pi in CHCl3 @ -78°C)
* (1.5µL injection)
**January 04, 2019**

**Column:** ODHUC1-IF03a; Chiral OD-H

**Assay:** 10% EtOH and 90% Hexanes

**Flow:** 1.00 (1+2) Range: 0.05 2:280nm

**HtIn:** 8

**Sample:** JA-1-4+/IPhPh in CHCl3 @ -78°C

#(1 Bull injection)

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**MUL FACTOR=1.0000E+00**
**RUN 1847**  
**DEC 28, 1915 15:02:**

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December 28, 1915  
**Column:** UA-11, 8 ft, 100 Å, 0.5 mm I.D.  
**Flow:** 1.00 mL/min  
**Column Temperature:** 60.5 °C  
**Injection:** 5 μL  
**Sample:** 3α, 5α-14a-3-Hydroxy Androsterone  
**Expiration:** 08/01/97  
**Dissolved:** 300 mg/mL in ethanol / 3% aqueous  
**OIL INJECTION**  

451.66
December 20, 2014

Column: NAPL-TRAP; OD-H Unit (Sub)
Assay: 1.1. Ethanol / Hz.

Flow 1.00 (112) Range: 0.05 4 2.00 cm

Area:

| Area | RT   | Width | Area |
|------|------|-------|------|-------|
| 21.092 | 149.76164 | 1.362 | 72.7906 |
| 25.203 | 353.90541 | 1.362 | 27.23533 |

Total Area: 1.4409E+08

Input Factor: 1.0000E+08

451.00
eee
\[
\frac{213.93}{4155.59} \times 100\% = 5\% \text{ ee}
\]
December 21, 2019

Column: ODHCE - IF038; Chiral OD-H
Assay: 10% Ethanol / 90% Hexanes
Flow: 1.00 mL/min
Range: 0.55 - 280 nm
Attm: 8
Sample: JA - I - 48 - IFB (IFB + Meth in DCE under reflux)

\[
\frac{206.08}{1159.52} \times 100\% = 18\% \text{ ee}
\]

18% ee
December 26, 2018

Column: OD-H, CE-IFB30, Chiral OD-H
Assay: 10% Ethanol / 90% Hexanes
Flow: 1.00 (1+2), Range: 0.05 A; 280 nm
Att: 3
Sample: JA-I-42-IFB (IFBIPH in DCE under reflux)

1. ee = \frac{184.24}{179.8} \times 100\% = 16.7\% ee
% ee = \frac{330.48}{1104.1} \times 100\% = 32.1\%
\[
\text{I/e} = \frac{203.83}{27} \times 100\% = 31.17
\]
ee = \frac{318.33}{1104.03} \times 100\% = 32.1\%
KUH 4688  JUL 23, 2018  12:18:21

Column #: 0DH0CE-1F280; Chiral OD-H Column
Assay: 100% Ethanol / 10% Hexanes
Flow: 1.00 mL/min  Range: 0.05  At: 250nm  Atm: 8
Sample: JA-I-39- Fr 25-53 (IFB + Ph-Me @ Reflux)

Ignore

KUR 4688  JUL 23, 1913  12:18:21

24.285

TRIP

KUH 4688  JUL 23, 2018  12:18:21

Column #: 0DH0CE-1F280; Chiral OD-H Column
Assay: 100% Ethanol / 10% Hexanes
Flow: 1.00 mL/min  Range: 0.05  At: 250nm  Atm: 8
Sample: JA-I-39- Fr 25-53 (IFB + Ph-Me @ Reflux)

Ignore

KUR 4688  JUL 23, 1913  12:18:21

24.285

TRIP
\[ \% \text{ ee} = \frac{545.75}{1247.37} \times 100\% = 44\% \text{ ee} \]
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\[ \text{ee} = \frac{248.54}{1100.3} \times 100\% = 21\% \]
\[
\% \text{ee} = \frac{461.78}{1177.84} \times 100\% = 39\%
\]
\[ \% \text{ee} = \frac{451.4}{1127.52} \times 100\% = 40\% \]
\[ \% \text{ee} = \frac{393.32}{971.06} \times 100\% = 41.1 \]
$\frac{y_{ce}}{y_{ce}} = \frac{367.84}{1190.7} \times 100\% = 31$
She = 368.59 x 1001 = 3.1

July 17, 2019

Column: OD-HILIC 100Å 2.0 x 150mm
Mobile Phase: A = 10% CH3CN, B = 90% CH3CN
Flow: 1.0 mL/min
Injection Volume: 8 µL

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Total Area = 1.7944E+08
HIL Factor = 1.0000E+00

*(85 µL injection)
\[ \% ee = \frac{368.78}{1143.48} \times 100\% = 31\% \]
ee = $\frac{443.95}{923.95} \times 100\% = 48\%$

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TOTAL AREA = 1.4179E+08
MULT FACTOR = 1.0000E+09

July 13, 2018

Column #: ODH0CE-1F030
Chiral OD-H Column
Assay: 107. Ethanol / 90%. Hexanes
Flow: 1.00 (1+2) Range: 0.05 A: 280 nm
Sample: JAI-1-33- Fr 45-58 (IFB + Ph-Pn θ = 38°C; el diprole)
~ 1mg of IFB + Ph-Pn θ = 38°C; el diprole; addition in 1ml of Ethanol /2 Hexanes
$\pm$ (3ul injection)
$\theta = \frac{418.93}{988.89} \times 100\% = 42.1\%$

**Run Information**

- **Run #: 4539**
- **Date: JUL 13, 1915**
- **Time: 18:44:06**

**Graph Data**

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  - Type: PP
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- **Area:**
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  - Type: PU
  - Width: 0.492
  - Area: 6.38878

**Total Area:** 1.1711E+08

**Multiplier Factor:** 1.0998E+08

**Sample Information:**

- **Sample:** JA-I-33-Fr-45 - 68 (IFB + Ph-Mh @ -78°C, el drywise)
- **Assay:** 10% Ethanol / 90% Hexanes
- **Flow:** 1.00 (1st) Range: 0.05 h: 2.80nm

**Additional Notes:**

- 1mg at IFB + Ph-Mh @ -78°C, el drywise addition in Ethanol / 2 Hexanes
- 3μL injection
**Chemical Analysis Report**

**Sample:** SA-1-33-H-45-58 (IFB + Pn-Ph @ -78°C, dropwise addition of Cl2 in 1mL of Ethanol/2 Hexanes)

**Assay:** 10% Ethanol/90% Hexanes

**Flow:** 1.00 L/min

**Column:** 6DHCE-1F @ 30° C

**Chromatographic Data**

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**Total Area:** 1.2486E-06

**Multiplier Factor:** 1.0000E-00

**Date:** July 13, 2018

**Note:** 1mL injection
\[ \% \text{ee} = \frac{424.06}{894.48} \times 100 = 47\% \]
% ee = \frac{360.49}{720.49} \times 100 = 50\%
\[
A = 52.07 \text{ mm}^2
\]

\[
A = 169.71 \text{ mm}^2
\]