Asymmetric Conjugate Addition of ortho-Quinone Methides as a Pathway to the Core of Nomofungin

Joshua Kubiak
Leukemia, cancer of the blood or hematopoietic bone marrow, causes hundreds of thousands of deaths every year.

A class of natural products called the communesins has been investigated as a potential treatment for leukemia and other cancers.

Communesins, which are classified from A-H, have been obtained from aquatic species of the *Penicillium* fungus found growing on certain green algae and sponges and have shown potent cytotoxic activity against leukemia cell lines\(^1\) and also some useful insecticidal activity.\(^2\)

Although a lot of work has been done on secretions such as Penicillin that come from terrestrial fungi, the secretions of aquatic fungi are a relatively new topic of investigation.


Since these products cannot be obtained in high yield from nature, much work has been done on the synthesis of the communesins in the lab resulting in the creation of only a select few due to their challenging polycyclic frameworks.

However, the communesins share a core tetracyclic structure which is easier to access and is found in many natural products.

Similar to Communesin B is the analog nomofungin which has a slightly altered core structure with a dihydropyran ring instead of a tetrahydropyridine ring.³

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Nomofungin was hypothesized in a mistaken identification of Communesin B, and the paper detailing its discovery was retracted. This mistake testifies to the striking similarity between the two structures.

Pathak et al. recently synthesized the nomofungin core structure in a palladium-catalyzed disubstitution reaction and found that derivatives of it caused G1 and G2 arrests in breast cancer tumor cells.\(^4\)

We were interested in the nomofungin core structure because derivatives of the compound and compounds very similar to it have many useful applications.
Objective

- Pathak et al.’s method relies on the presence of two hydroxyl groups on the substrate and also uses complex metal catalysis which is costly. In addition, the palladium metal used is highly toxic and is unfavorable for medicinal applications.

- My objective was to search for an alternate synthetic pathway to access the core structure of nomofungin that avoids these restrictions.
**ortho-Quinone Methides**

- *ortho*-Quinone methides are highly reactive and susceptible to the 1,4-addition of nucleophiles.
- Through the conjugate addition of an indole onto an *ortho*-quinone methide, a new molecule can be created which can then be cyclized to create the four-ringed core structure of nomofungin.
- *ortho*-Quinone methides are a good base since they can be synthesized from sesamol, a relatively cheap material, using methods that are already established.\(^5\)

ortho-Quinone Methide Synthesis

Sesamol + Acetic Anhydride → Friedel-Crafts Acetylation

Claisen Condensation

Benzaldehyde + 1) Et₃N, CICO₂Et → 2) NaBH₄ → Decarbonylation

Oxidation

41% Yield

82% Yield
Sesamol + 4-methoxybenzyl alcohol

1% Ascorbic Acid
2% Citric Acid

Friedel-Crafts Addition

59% Yield

Oxidation

41% Yield
Although the addition of an indole onto an *ortho*-quinone methide occurs readily, it forms a new chiral center, and two enantiomers of the product are created.

In most biological systems, only one enantiomer of a compound is active.

We hypothesized that chiral BINOL phosphoric acids could be used to control the enantioselectivity of the reaction.

Many reaction conditions were varied to try to induce selectivity:
- Temperature
- Catalyst
- *ortho*-Quinone methide substrate
- Indole
Reactions were run on a 0.1 mmol scale.

1. The ortho-quinone methide and a magnetic stir bar were added to a reaction tube which was then cooled to the desired temperature.

2. Two equivalents of the desired indole were dissolved in 1 mL of the selected solvent inside a test tube. This solution was also cooled.

3. The selected amount and type of catalyst was added to the initial reaction tube, and the indole solution was pipetted in immediately afterwards.

4. The tube was capped, and the reaction was stirred.

5. Structures were confirmed via NMR, and er was measured via HPLC.
Conjugate addition reaction stirring in a dry ice and acetone bath.
The indole forms a resonance structure creating a carbon with a negative charge. This makes an excellent nucleophile.

The indole can now attack the unblocked face of the ortho-quinone methide and from a bond with the methylene carbon. This causes a shift of electrons that forms a complete aromatic system and gives the oxygen of the ortho-quinone methide a negative charge.

To eliminate the unfavorable positive charge on the nitrogen atom of the indole, a hydrogen atom is expelled allowing electrons to migrate back to the nitrogen atom.

Meanwhile, a free pair of electrons on the oxygen atom of the ortho-quinone methide attacks the hydrogen of the catalyst. This forms a hyroxyl group on the addition product and separates it from the catalyst.

The catalyst can regenerate its hyroxyl group from acid catalyst protons in solution and can then catalyze another addition.
Addition of 1-methyl indole to 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>$T$ [°C]</th>
<th>Time [h]</th>
<th>Yield</th>
<th>er</th>
<th>ee</th>
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<tbody>
<tr>
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<td>a</td>
<td>CH$_2$Cl$_2$</td>
<td>rt</td>
<td>12</td>
<td>80%</td>
<td>48:52</td>
<td>4</td>
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<tr>
<td>2</td>
<td>b</td>
<td>CH$_2$Cl$_2$</td>
<td>rt</td>
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<td>88%</td>
<td>50:50</td>
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<tr>
<td>3</td>
<td>a</td>
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<td>86%</td>
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<td>12</td>
<td>87%</td>
<td>54:46</td>
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Addition of indoles to 4 at -78°C.

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<td>53:47</td>
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<tr>
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<td>5a</td>
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<td>6</td>
<td>67%</td>
<td>52:48</td>
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<td>5a</td>
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<td>80%</td>
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<td>4</td>
</tr>
<tr>
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<td>5</td>
<td>H</td>
<td>b</td>
<td>5b</td>
<td>CH$_2$Cl$_2$</td>
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<td>48%</td>
<td>55:45</td>
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<td>7</td>
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<td>5c</td>
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<td>-78</td>
<td>6</td>
<td>0%</td>
<td>-</td>
<td>-</td>
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<td>8</td>
<td>CO$_2$Et</td>
<td>b</td>
<td>5c</td>
<td>CH$_2$Cl$_2$</td>
<td>r. t.</td>
<td>12</td>
<td>0%</td>
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Addition of indoles to 7 at -78°C.

<table>
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<th>Entry</th>
<th>R</th>
<th>Catalyst</th>
<th>Product</th>
<th>Solvent</th>
<th>$T$ [°C]</th>
<th>Time [h]</th>
<th>Yield</th>
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<td>5</td>
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<td>b</td>
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<td>6</td>
<td>61%</td>
<td>51:49</td>
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<td>6</td>
<td>H</td>
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<td>r. t.</td>
<td>12</td>
<td>0%</td>
<td>-</td>
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Further Optimization of Synthesis of 8a.

<table>
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<th>Mol %</th>
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<td>35%</td>
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<td>-98</td>
<td>6</td>
<td>19%</td>
<td>43:57</td>
<td>14</td>
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Three different methods were tried to form the full tetracyclic structure.

1. Oxidative cyclization with tert-butyl hydroperoxide
2. Oxidative cyclization with N-bromosuccinimide and pyridinium p-toluenesulfonate
3. Acid catalyzed cyclization with p-toluenesulfonic acid

Method 2 produced the desired product.
$^{1}$HNMR of Final Product
The selectivity of the conjugate addition can be controlled via BINOL phosphoric acid catalysts.

The product of the addition can be cyclized to create analogs of the core structure of communesin.

These analogs can be totally synthesized in a procedure beginning with sesamol. Although this route has restrictions, it is not limited in the same way as earlier methods.

The generated core structure can be used as a scaffold in the creation of novel compounds which may have cytotoxic effects against tumor cells or may have other useful applications.
Optimum reaction conditions:

- -78°C
- DCM
- ≥ 6 hours
- 20 mol % phosphoric acid catalyst
  - Large substituent groups
- Indole
  - Protecting group that is not strongly electron withdrawing
- ortho-Quinone methide
  - Directly attached bulky substituents
Future Work

- Design and test other catalysts
  - Triphenylsilyl substituted catalyst
- Try additional cyclization methods
  - DMDO or weak acid
- Determine the absolute stereochemistry of the addition product
  - X-ray crystallography
- Perform mechanistic studies on the conjugate addition reaction
  - Electrospray ionization mass spectroscopy
- Further develop the substrate and perform biological studies to test potency against cancer cell lines
  - Bioassays
Acknowledgements

- Boston University
- Schaus Lab Group
  - Dr. Scott Schaus
  - Yi Luan
- LSMSA Faculty
  - Dr. Mark Ward
  - Dr. Chris Hynes
  - Dr. Allison Landry
References


Add new references