A Study of Gold Catalyzed Transannular \([4+3]\) Cycloaddition Reactions

Specific Aim

This creative project in organic chemical synthesis is ultimately aimed at further developing a reaction that can produce multiple fused carbon ring frameworks in a single transformation. This method could then be applied toward the total synthesis of biologically active natural products containing fused ring structures with a center seven-membered ring.

Background

The transannular \([4+3]\) cycloaddition reaction has hardly been studied unlike its counterpart in the Diels-Alder reaction.\(^1\) The structures of the highly potent cytostatic cortistatins\(^2\) and several other natural products suggest that efficient construction of the carbon skeletons could be most efficiently achieved by a transannular \([4+3]\) cycloaddition reaction. However, relatively few reports have dealt with the possibilities for initiating any type of \([4+3]\) cycloaddition reactions.\(^3\) This project offers an opportunity for expanding gold-catalyzed reactions to transannular \([4+3]\) cycloadditions and should spur further interest in this area of research.

The carbon frames of the natural products depicted in Figure 1 can be constructed rapidly through a transannular \([4+3]\) cycloaddition reaction as the key step. Allene macrocylcles needed to perform this study will be prepared using a ring-closing metathesis reaction (RCM) as the key step. The RCM reaction has proven to be invaluable for the synthesis of macrocycles.\(^4\)

![Figure 1](image)

**Figure 1.** Potent cytostatic agents cortistatin A, B and J from the marine sponge *Corticium Simplex*. Brevifoliol is a natural diterpene isolated from *Taxus baccata* Nutt. The new dolastane (6) was isolated from the brown alga *Dilophus spiralis*. 
Research Plan

The goal of this project is to test the reaction using different ring systems and also to try and optimize the reaction for higher yields of the [4+3] adduct. In this study, we will try to prepare the 5,7,5,5 and 7,7,5,5 ring systems. The macrocycles will be synthesized efficiently using well known reactions (Scheme 2). 2,5-Dibromofuran will be coupled to THP protected 2-propyn-1-ol or 4-propyn-1ol using the Sonogashira reaction to establish the differing side chain lengths (Scheme 2). The alkynes will then undergo complete hydrogenation in the presence of hydrogen.
gas with a catalytic amount of Palladium on carbon. The THP protecting groups will then be removed using a catalytic amount of p-Toluenesulfonic acid in methanol giving a diol. The diol will then be converted to the dibromide 8 with Triphenylphosphine and Carbon tetrabromide. 8 will undergo a dialkylation reaction with lithiated allene to give 9. At this point an RCM reaction\(^4\) using Grubbs’ 1\(^{\text{st}}\) generation catalyst will provide the macrocycles 10 with the varying chain lengths.

When macrocycles 10 have been synthesized, the study of the transannular [4+3] cycloaddition can take place. The yields of the products will be compared to the preliminary results already discussed. Various Gold catalysts with different ligands and oxidation states can be surveyed to determine the optimal conditions for the transannular cycloaddition to take place. This study is depicted in Scheme 3.

![Scheme 3](image)

**Experimental Procedure for the Transannular [4+3] cycloaddition**\(^5\)

Gold(I) catalyst (9 mg, 17 µmol) and silver hexafluoroantimonate (6 mg, 17 µmol) were loaded to a flask before dry methylene chloride (1 mL) was added to the reaction flask. A solution of 10 (1 mmol) in dry methylene chloride (1 mL) was added drop wise to the flask. After 2 h, the reaction was diluted with Et\(_2\)O and filtered through a pad of silica and Celite. The ethereal layers were concentrated and the residue was purified via silica gel chromatography (10% EtOAc:Hex) to yield 35 mg (70%) of a white solid.

**Anticipated Results**

The proposed plan is based on the Gung group’s recent discovery that a Pd(II) and a Au(I) catalyst systems initiated a transannular [4+3] cycloaddition reaction. Although both transannular Diels-Alder reactions and intramolecular [4+3] cycloadditions have been extensively investigated, the proposed transannular [4+3] cycloaddition has hardly been studied. The various catalyst systems will be surveyed and optimal conditions will be determined. As a part of studying this reaction, the
stereochemistry of the products will also be determined. Methods including X-ray crystallography and NMR studies can be used to solve this problem. The results of the methodology study can be applied to the total synthesis of the strongly cytostatic natural products cortistatins A and J.

Budget

Reagents:

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<tr>
<th>Reagent</th>
<th>Quantity</th>
<th>Price</th>
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<tr>
<td>Furan</td>
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<td>3,4-dihydro-2H-pyran</td>
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<td>Propargyl Alcohol</td>
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<td>4-Penyn-1-ol</td>
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<td>Dichloro(2-pyridinecarboxylato)gold</td>
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<td>Gold(I) Chloride</td>
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<td>Gold(III) Chloride</td>
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**Total:** $1022.40

Prices are provided by the Sigma Aldrich chemical company.

References:

1. Gung, B. W.; Conyers, R. *Synlett* **2010**, 2797-2801, "Transannular [4C+3C]-cycloaddition reactions of oxyallyl cation to furan".