Progress towards intramolecular Diels-Alder model study towards (+-) polyandrol
by Amogh G Boloor

A thesis submitted in partial fulfillment Of the requirements for the degree of Master of Science in Chemistry
Montana State University

Abstract:
The Grieco group was interested in the total synthesis of the C19 quassinoid polyandrol. It was realized that the carbon framework could be constructed from an intramolecular Diels-Alder reaction of a 1, 6, 8, nonatriene, resulting in construction of six of the ten stereocenters. Before the synthesis was undertaken, a model study of the essential reaction was to be studied. Synthesis of the Diels-Alder adduct was accomplished in thirteen continuous steps. The Diels-Alder can now be studied, with the triene in hand.

PROGRESS TOWARDS INTRAMOLECULAR DIELS-ALDER MODEL STUDY TOWARDS (±) POLYANDROL

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APPROVAL

of a thesis submitted by

Amogh Govind Boloor

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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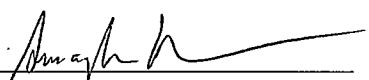
Signature 

Date 12/16/98

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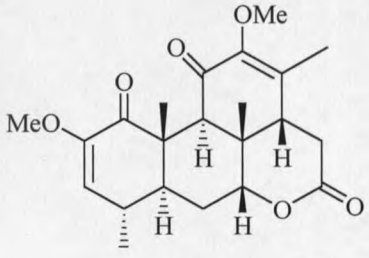
ABSTRACT

The Grieco group was interested in the total synthesis of the C_{19} quassinoid polyandrol. It was realized that the carbon framework could be constructed from an intramolecular Diels-Alder reaction of a 1, 6, 8, nonatriene, resulting in construction of six of the ten stereocenters. Before the synthesis was undertaken, a model study of the essential reaction was to be studied. Synthesis of the Diels-Alder adduct was accomplished in thirteen continuous steps. The Diels-Alder can now be studied, with the triene in hand.

INTRODUCTION

Quassinoids are a diverse group of highly oxygenated polycyclic natural products.[1] Collectively, these natural products are the bitter constituents of the *Simaroubaceae* botanical family, which possesses medical properties that have been recognized long before the advances of modern medicine. They are known to treat a variety of illnesses such as dysentery, fever, amoebiasis, malaria, and arthritis.[2] More recently, quassinoids have received intense attention from the scientific community as antitumor agents. The mechanism of their biological activity has been investigated, and extensive studies concerning structure-activity relationships have been conducted.[3]

The oldest of the *Simaroubaceae* species known is *Quassia amara.*[4] Its two major constituents, quassin (**1**) and neoquassin (**2**), were isolated by Clark in 1939.[5] Robertson reported the separation of the two compounds in the early 1950's,[6] but it was not until 1961 that both structures were finally determined by Valenta and coworkers by means of NMR spectroscopy.[7]



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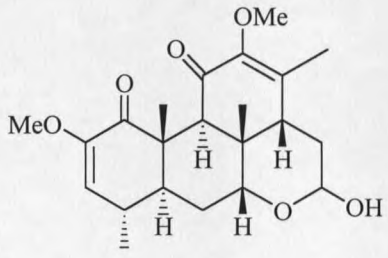

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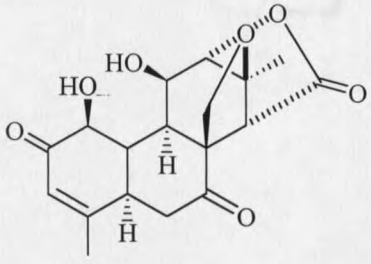
The vast majority of quassinoids possess a C_{20} picrasane-like skeleton represented by the tetracyclic framework of quassin (**1**). Consequently, all biological studies conducted to date, as well as the synthetic work published in this area, have been almost exclusively concerned with C_{20} quassinoids. To this date, Grieco's synthesis of samaderin B (**3**) [8] has been the only published account of a total synthesis of a C_{19} quassinoid. In 1994 research efforts by the Grieco group culminated in the isolation and characterization of a new C_{19} quassinoid, (+)- polyandrol (**4**), from the root bark of *Castela polyandra*.[9]



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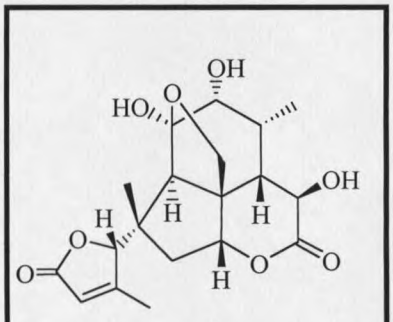

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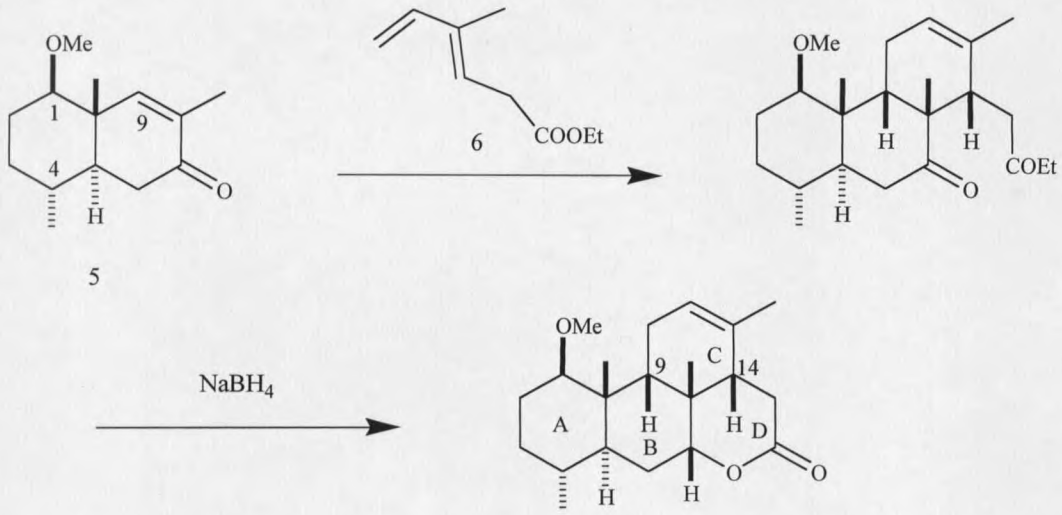
The intriguing structural features of polyandrol (**4**), as well as the virtual lack of studies regarding its biological activity, prompted the initiation of a research project aimed at the total synthesis of (+)-polyandrol.

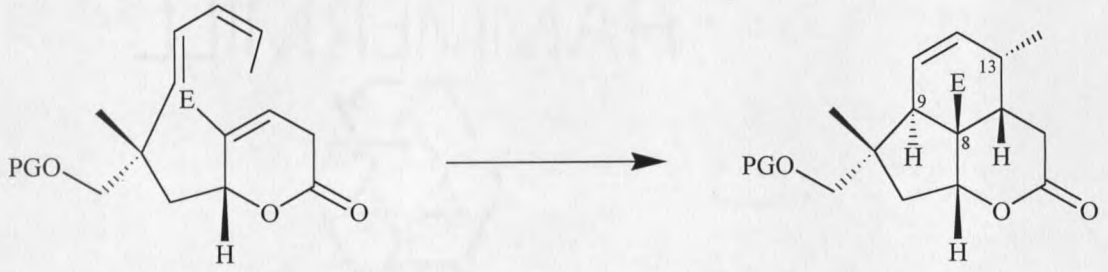
Synthetic strategies by the Grieco group toward the synthesis of quassin[10] as well as a variety of other quassinoids have focused first on the construction of the A and B rings. Then the C ring is then constructed by cycloaddition of dienophile **5** with ethyl (*E*)-4-methyl-3,5-hexadienoate (**6**) (Scheme 1). Hydride reduction and subsequent lactonization provides the intact carbon framework of quassin.

Scheme 1: Preparation of C_{20} quassinoid framework



The Diels-Alder strategy correctly establishes six of the seven stereocenters found in quassin.

The complexity of the A and B rings of quassin dictated an approach through dienophile **5**. The framework for polyandrol displays a simplification in the A and B rings. It was realized that an intramolecular Diels-Alder approach could provide a direct route to the tricyclic core of polyandrol,[11] correctly establishing four

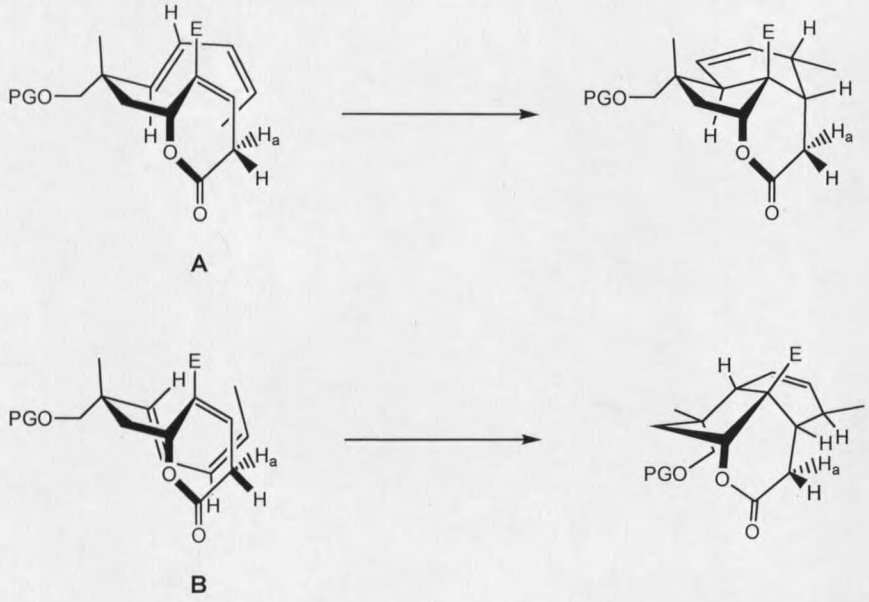


E= EWG

stereocenters in polyandrol in a single transformation.

Careful scrutiny of the Diels-Alder strategy reveals that there are only two possible cycloadducts that can be derived from triene **7**. An exo-bridging transition state (A) would provide the desired tricycle (scheme 2). The endo-bridging transition

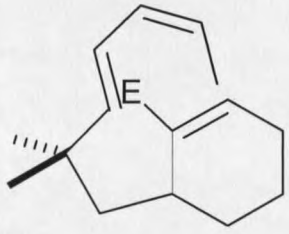
Scheme 2: Exo (A) and Endo (B) bridging transition states



state (B), which would provide the undesired tricycle possessing the wrong configuration at C(9) and C(13). The 1,6,8-nonatriene transition state (A) appears to suffer from nonbonding interactions of the C(5) methyl substituent with the C(2) substituent and the diene hydrogen at C(7). Although, the nonbonding interaction of the C(5) substituent and the diene hydrogen is relieved, transition state (B) appears to suffer from the unfavorable interaction between the olefinic hydrogen atom of the diene and the axial (H_a) hydrogen atom of the lactone ring.

MODEL STUDY

In order to test this methodology, a model study was to be investigated with model triene **8**.



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Cyclohexanone was converted to the corresponding enamine and alkylated with methyl methacrylate using the Stork procedure[12] (45% from cyclohexanone) (Scheme 3). Resulting keto ester **9** was protected as its ketal with ethylene glycol and pyridinium *p*-toluene sulfonic acid in refluxing benzene (>98%). [11a] Alkylation of the ester was accomplished by generation of the lithium enolate and subsequent trapping with methyl iodide to provide dimethyl ester **10** (94%). [11a] The ester was reduced to the alcohol with lithium aluminum hydride (98%) and then protected with *tert*-butylchlorodiphenylsilane and imidazole in DMF forming silyl ether **11a** (89%). Subsequent deketalization with wet acetone and pyridinium *p*-toluene sulfonic acid provided the desired ketone **11b** (99%). A Stille like palladium catalyzed alkoxy-carbonylation[13] was undertaken to install the dienophile alkene. Enol triflate **12** was formed by generation of the lithium enolate in tetrahydrofuran and subsequent trapping with *N*-phenyltriflouromethanesulfonimide[14] in 94% yield. The resulting enol triflate was converted to unsaturated ester **13** in