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Studies on Inducers of Nerve Growth Factor: Synthesis of the Cyathin Core

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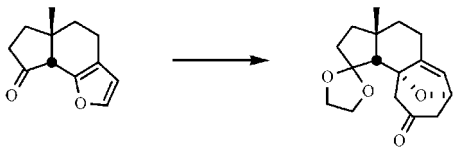
ABSTRACT



Compounds that induce the synthesis of nerve growth factor (NGF) are of interest as alternatives to the administration of the native peptide. We have initiated a program to study the NGF synthesis stimulating activity of the erinacine and scabronine diterpenes. Herein, we report an approach to the core cyathin system by sequential application of an oxidative coupling and [4 + 3] cycloaddition.

The past several decades have witnessed impressive efforts to develop highly effective methods for the treatment of several neurodegenerative disorders.[1] An emerging area of interest has centered upon the potential therapeutic role of endogenous neurotrophic molecules such as nerve growth factor (NGF).[2] These small peptidic factors are important for growth, development, and maintenance of the central and peripheral nervous systems (CNS and PNS).[3]

Studies suggest that supplemental NGF administration can offer cytoprotection and stimulate the outgrowth of neuritic projections.[4] Attempted clinical applications by direct administration of exogenous NGF have primarily failed owing to the inability of the polar peptide to penetrate the blood-brain barrier and to rapidly degrade in vivo.[5] These severe pharmacological limitations have prompted the search for small-molecule inducers of NGF, compounds that can stimulate the natural production of NGF as an alternative to administration of the peptide.[6]

Recently two classes of related natural products, the erinacines[7] and scabronines[8], have been shown to have significant NGF synthesis stimulating activity (Figure 1).

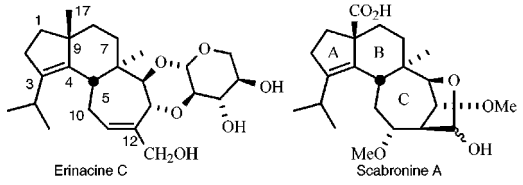


Figure 1. Representative cyathins, chemical inducers of nerve growth factor.

These diterpenoid natural products share a common core structure endemic to the well-known cyathin class of antibiotics.[9] We have initiated a program to study the structure−activity relationships of these natural products and the mechanisms by which they promote the synthesis of nerve growth factor. The core of this program centers on the development of a synthetic strategy to access a wide

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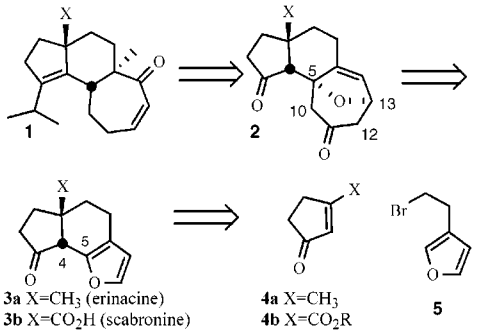
range of modified structures for biological assay.[10] Herein, we wish to report our first generation strategy for the assembly of the cyathin framework.

We have selected the advanced cyathin core **1** which will provide access to a variety of related natural products and analogous structures (Scheme 1). Oxo-bridged tricyclic

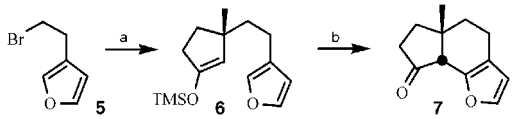
Scheme 1. Retrosynthetic Analysis of the Cyathins



compound **2** was targeted as an advanced intermediate in an approach to **1**. We envisioned an efficient preparation of this tricyclic building block by formation of the C5−C10 and C12−C13 bonds through an oxyallyl cation cycloaddition involving furan **3**. An additional ring closure through oxidative coupling of the C4−C5 bond is key for the synthesis of **3**. The known compounds **4** and **5** served as convenient starting points for the synthesis.

The use of a pivotal [4 + 3] cycloaddition to construct the seven-membered C-ring requires a highly substituted furan ring fused to a suitable AB ring system. In designing a route to the annulated furan **3**, we were intrigued by reports from Moeller and co-workers[11] who had shown that furan rings could be coupled to pendant electron rich olefins such as methyl enol ethers and allylsilanes under electrochemical conditions. Based upon these elegant studies, we examined an annulation strategy through a tandem conjugate addition/anodic oxidation sequence (Scheme 2)

Scheme 2. Two-Step Annulation via Cuprate Addition/Anodic Oxidation



Key: a) Mg, CuI, TMSCl then **4a** b) carbon anode, iPrOH, CH_3CN, $LiClO_4$, lut., 65% overall from **4a**

Commercially available 3-methylcyclopentenone **4a** provided a convenient A-ring precursor and was efficiently coupled with the organocuprate reagent derived from 3-bromoethylfuran **5**, prepared via the method of Tanis.[12] The addition of chlorotrimethylsilane to the cuprate addition step not only resulted in the regioselective formation of the silyl enol ether **6** but also served to greatly accelerate addition to the disubstituted enone. The structure of the sensitive silyl enol ether **6** was confirmed by NMR, but attempted purification resulted in extensive hydrolysis to the corresponding ketone; therefore, the crude silyl enol ether was used directly. Initial attempts to effect oxidative cyclization by constant-current anodic oxidation in acetonitrile−methanol with lithium perchlorate as the supporting electrolyte led to instantaneous desilylation to the corresponding ketone. It was surmised that the use of a more sterically demanding nucleophile might increase the lifetime of the silyl enol ether and permit productive cyclization. This was realized when anodic oxidation of a solution of the silyl enol ether **6** in acetonitrile with 20% isopropyl alcohol and lithium perchlorate (carbon anode, 100 mA) produced the corresponding tricyclic ketone **7** in 65% overall yield for the two-step annulation from 3-methylcyclopentenone. The stereochemistry of the newly formed ring junction was found to be the more thermodynamically stable *cis* isomer as predicted by molecular modeling.[13] The *cis* relationship of the C9 methyl group and the proton at C4 was suggested by a strong NOE enhancement of the methine proton upon irradiation of the methyl group. Although this relationship ultimately proves inconsequential since the C4 stereocenter will be removed during a synthesis of the natural product, the *cis* fusion of rings A and B was considered critical to enforcing facial bias in the ensuing [4 + 3] cycloaddition.

Examination of a minimized model of tricyclic ketone **7** suggested that the *cis* fusion produces a cup-shaped confor-

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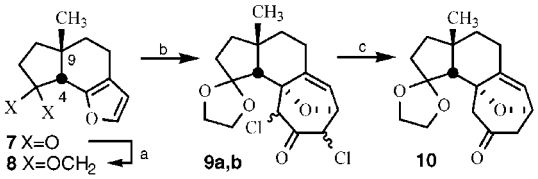
(13) AM1 calculations on the alternate epimers predict the *cis* isomer to be more stable by 2−3 kcal/mol. Calculations were conducted on Spartan running on a Silicon Graphics workstation. Wavefunction, Inc., Spartan version 5.0, 18401 Von Kaarman Avenue, Suite 370, Irvine, CA 92612.

mation and that the addition of an oxyallyl cation across the furan should preferentially occur from the convex face, *syn* to the C4 proton. Although it appeared that addition would occur from this face, a possible directing effect exerted by the C9 methyl group would give the opposite selectivity. Additionally, it appeared that conversion of the C3 ketone to an sp^3 center in the form of a cyclic ketal could provide additional steric bulk on the α-face. The ketone **7** was converted to the C3 acetal **8** under standard conditions (ethylene glycol, tosic acid) as a prelude to cycloaddition (Scheme 3).

Scheme 3. Synthesis of a Cyathin Skeleton by [4 + 3] Cycloaddition.



Key: a) $(HOCH_2)_2$, pTsA, 70% b) 1,1,3-trichloroacetone, $NaOCH_2CF_3$, $HOCH_2CF_3$ c) Zn-Cu couple, MeOH, 65-70% for two steps

Although several methods have been reported to generate oxyallyl cations efficiently, Föhlisch[14] reported that the combination of 1,1,3-trichloroacetone and sodium trifluoroethoxide was among the most reactive. Although [4 + 3] cycloadditions have been widely used to prepare simple cycloheptanoid systems, there are very few examples involving highly substituted furans such as **8**.[15] In fact, the use of an annulated furan as the diene component of a [4 + 3] cycloaddition during Cha's synthesis of colchicine is one of the only examples of this process.[16] Exposure of furan **8** to Föhlisch conditions led to the rapid formation of two different cycloadducts **9a**,**b** (stereochemistry of the chloroketones was not assigned). Unfortunately, under these conditions only 15−25% conversion to the cycloadduct could be realized along with a large amount of recovered starting material. Attempts to drive the reaction to completion by the use of a large excess of the oxyallyl cation precursor were ineffective, leading to the formation of insoluble byproducts. It was observed that when a slower rate of addition of the trichloroacetone component was used the reaction proceeded to a greater extent, most likely reflecting the beneficial effect of keeping the concentration of the oxyallyl cation low.[17] A more effective method was to use a slow addition of a dilute solution of the trichloroacetone in trifluoroethanol. Under these modified conditions, a more effective cycloaddition was observed which yielded the tricyclic adduct, after reductive dechlorination, in 65−70% yield over two steps. Gratifyingly, dechlorination of both isomers with a zinc−copper couple produced the single compound **10**, indicating that the two isomers arose from extensive epimerization of the α-chloroketone under basic conditions and not a lack of selectivity in the cycloaddition process (Figure 2).

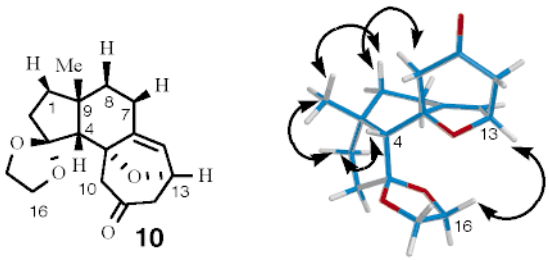


Figure 2. NOESY data summary for intermediate **10**. Key diagnostic cross-peaks are indicated.

HMQC correlation spectroscopy was used to assign carbon and hydrogen resonances, and subsequent NOESY correlations were used to assign stereochemistry. A key correlation was observed through a strong NOE from the C9 methyl group protons to the C1β proton. Subsequent correlation of C1β to the C4 methine proton established the *cis* ring fusion at the AB junction and confirmed the results of the NOE experiment with **7**. Assigning the axial protons of the methylenes at C7 and C8 (examination of coupling constants) and then the axial nature of the C9 methyl group through a positive NOE from C8β made a further confirmation. The facial selectivity of the oxyallyl addition was determined to be *syn* to the C9 methyl group by observation of NOE's between the C10 methylene group to the protons of the angular methyl group and the axial proton at C8. A final confirmation of the overall geometry was found through an additional NOE between the C13 methine proton and the *endo* proton on the C16 methylene of the A-ring ketal.

Conclusions. The structural complexity and exciting biological profile of these cyathin diterpenoids has prompted us to study the nature of their biological effects. Critical to this program is an efficient synthesis of advanced precursor molecules that can serve as general intermediates to the natural products and analogues. We have been able to assemble the tricyclic core of these natural products by using a key furan/silyl enol ether oxidative coupling followed by a [4 + 3] cycloaddition with a highly substituted furan. The high levels of stereoselectivity during the cycloaddition step and the unique conformation enforced by the oxo bridge will be useful tools for controlling the introduction of the remaining stereocenters. Current efforts are underway to convert the oxo-bridged tricycle **10** into the general precursor **1**, and results will be reported in due course.

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Supporting Information Available: Full characterization for compounds **7**, **8**, and **10** including complete NMR assignments for **10**. This material is available free of charge via the Internet at http://pubs.acs.org

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