Synthesis and Study of Regenerative Natural Products

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Our research is directed at the synthesis and study of natural products with proven or potential regenerative properties, which may open avenues for developing treatments for nervous system disorders. The natural products, which are the subject of our studies, increase the biosynthesis of neurotrophic factors or neurotransmitters, promote neuronal network formation, or lead to recovery from Aβ-induced neuronal injury. The mechanism by which they induce biological function is, however, still unknown owing to a lack of material for evaluation. By developing synthetic routes to these natural products, we seek to allow wide access to them for research, and for the study of structurally related compounds.

Complanadine A was the first dimeric compound of the *Lycopodium* class to be isolated. The alkaloid was obtained from the club moss *Lycopodium complanatum* in 0.003% yield along with complanadines B (0.0002%) and D (0.00007%).[1-3] Complanadine A is able to induce the secretion of neurotrophic factors from human astrocytoma cells, promoting the differentiation of PC-12 cells. Comparisons of cells treated with complanadine A and phorbol 12-myristate 13-acetate (PMA), a known activator of neurotrophic factor biosynthesis, showed the compounds to possess similar activities as judged by morphological changes in PC-12 cells.[1] In addition, the structurally related natural products complanadine B and D also possess the ability to induce the secretion of neurotrophins.[1,3] Both compounds are capable of enhancing the expression of nerve growth factor (NGF) mRNA in 1321N1 human astrocytoma cells relative to controls.

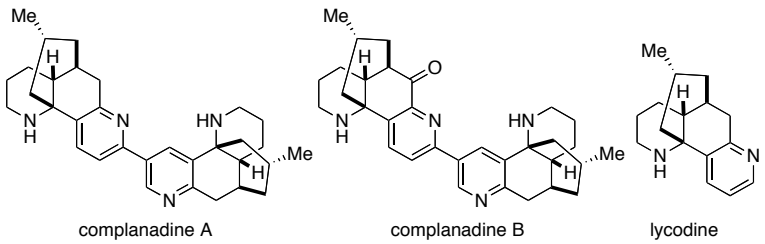


Figure 1. Structures of complanadine A, complanadine B, and lycodine.

In addition to their varied biological activities, the lycopodium alkaloids have attracted the interest of the synthetic chemists leading to several creative methods for their laboratory preparation including the related alkaloid lycodine (Figure 1).[4] In addition to our synthetic efforts, the Sarpong research group has completed a synthesis of complanadine A, as well as several structurally related alkaloids.[5]

In developing a synthesis of complanadine A the pseudosymmetry of the molecule allows the application of a simplifying metal catalyzed [2+2+2] + [2+2+2] sequence using a silyl-diyne and the two equivalents of the corresponding alkyne-nitrile (Figure 2).

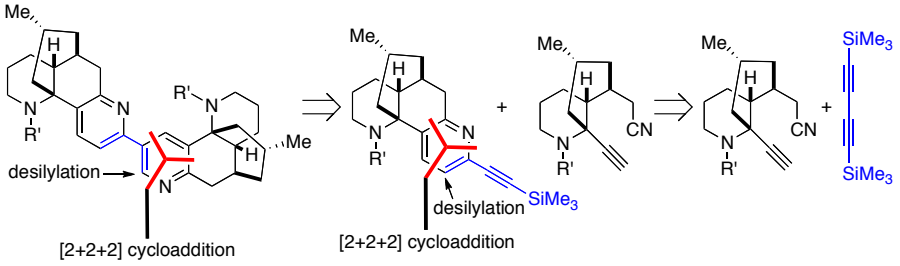
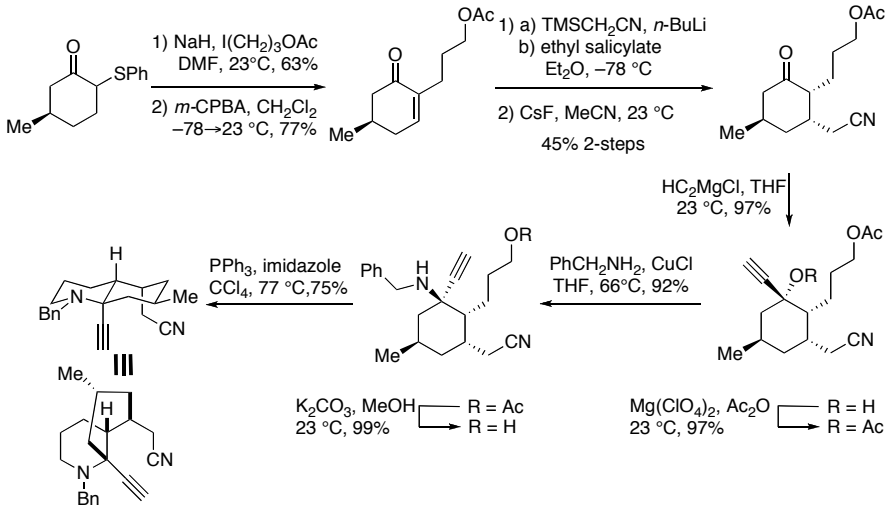


Figure 2. Synthetic disconnections.

The synthesis of the alkyne-nitrile was initiated by alkylation of the thermodynamically favored enolate of a thioether, prepared from pulegone, with 3-iodopropyl acetate (Scheme 1).[6] The diasteromeric mixture of product were converted to the corresponding cyclohexenone by *m*-CPBA mediated oxidation of the thioether followed by a mild sulfoxide elimination (occurring at 23°C). Treatment of the enone with the lithium anion of trimethylsilyl acetonitrile followed by careful quenching with ethyl salicylate furnished the desired Michael adduct as a mixture of diastereomers.[4,7,8] Desilylation of the crude mixture with cesium

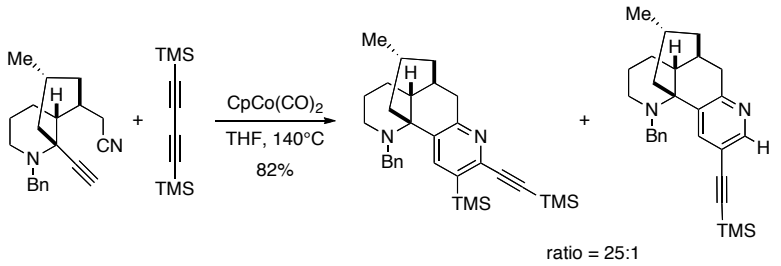
fluoride allowed the separation of the isomers and provided the desired cyclohexanone. Diasteroselective, equitorial delivery of ethynylmagnesium chloride into the ketone cleanly provided the corresponding propargyl alcohol as a single isomer. Activation of the resulting propargyl alcohol as the corresponding acetate occurred upon treatment with neat acetic anhydride and magnesium perchlorate providing the precursor for a key copper mediated amination reaction.[9] Displacement of the tertiary acetate was examined under a variety of conditions. After optimization, heating a thoroughly degassed THF solution of the diacetate and benzylamine with a catalytic amount of CuCl provided the propargyl amine in 92% yield.[10] Notably, the reaction proceeded with complete diastereoselectivity. Thorough degassing of the solvent was needed to prevented an otherwise rapid Glaser dimerization. The secondary amine was transformed into the desired alkyne-nitrile in a two-step sequence initiated by cleavage of the acetate followed by cyclization using PPh_3/CCl_4/imidazole, forming the alkne-nitrile in a 74% yield over two steps.[11] The structure of the bicyclic subtarget was determined by NMR and corroborated by X-ray crystallography.



Scheme 1. Synthesis of the bicyclic subtarget.

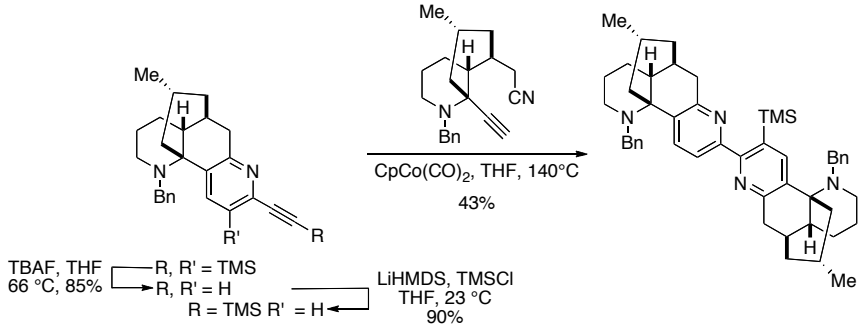
The first [2+2+2] cycloaddition of the alkyne-nitrile and bis(trimethylsilyl)butadiyne proceeded smoothly under thermal conditions using $CpCo(CO)_2$, providing the expected [2+2+2] cycloadduct as the major

regioisomer (Scheme 2).[12] Unfortunately, even under the influence of a variety of conditions and catalysts the pyridyl-alkyne proved resistant to undergoing a second [2+2+2] cycloaddition reactions with the starting alkyne-nitrile.



Scheme 2. The first cobalt-mediated [2+2+2] cycloaddition.

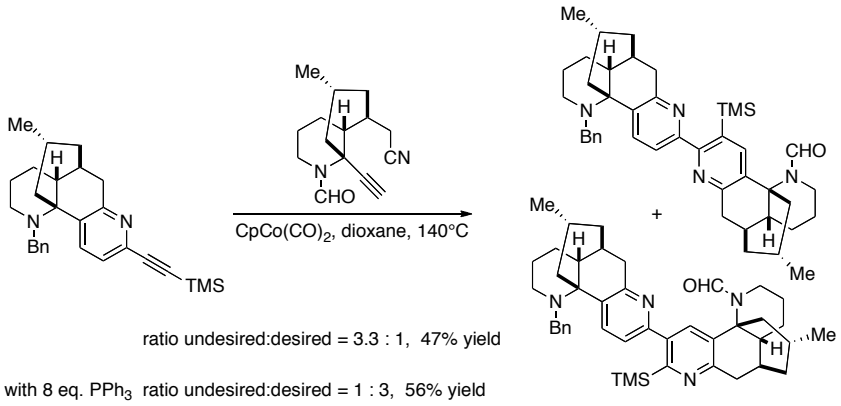
As a result of the low reactivity, both silicon groups were removed with TBAF in THF and heated to reflux, generating the monosubstituted alkyne (Scheme 3). However, attempts at the second [2+2+2] annulation of this compound led only to decomposition. Other transition-metal catalysts examined, such as $Ru(COD)Cl_2$ and $Cp_2Zr/NiCl_2$ were also ineffective.



Scheme 3*.* Synthesis and reaction of pyridyl-alkynes.

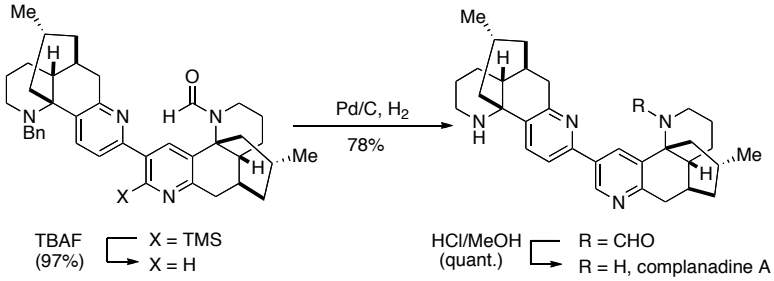
After routinely noting the unproductive consumption of the monosubstituted alkyne the reactivity was attenuated by the reinstallation of the alkynyl trimethylsilyl group. A mixed result was obtained in the cobalt-catalyzed [2+2+2] annulations of the silyl-alkyne as the reaction provided a single compound; the symmetric 2,2'-bipyridinyl rather than the desired 2,3'-bipyridinyl isomer (Scheme 3). After consideration that the amine could be made to influence the outcome of the reaction the preparation of the formyl derivative was achieved. The initial reaction of the silyl-alkyne and the formyl-bicyclic

compound using thermal conditions provided a mixture of products with the desired isomer as the minor constituent. After significant experimentation it was discovered that a remarkable switch in regioselectivity, providing the desired isomer as the major product (3:1 desired:undesired), was possible by the addition of an excess PPh_3 to the reaction (Scheme 4).



Scheme 4. Successful [2+2+2] cycloadditions providing the unsymmetric bipyridyl linkage.

With access to the unsymmetric bipyridyl, fluoride mediated removal of the aryl-trimethylsilyl group yielded protected complanadine A (Scheme 5). Debenzylation by hydrogenation and subsequent deformylation using a heated acidic methanol solution generated (+)-complanadine A, fully matching with the spectroscopic data reported for the natural product.[3]



Scheme 5. Completion of the synthesis of complanadine A.

References:
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