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Synthesis of (+)-Complanadine A, an Inducer of Neurotrophic Factor Excretion

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Gene therapy-based approaches to increasing the production of neurotrophic factors, while promising, have not overcome the limitations of short-lived effects, undesirable immune responses, intracranial delivery, and challenges of viral vectors.[1] Small molecules provide an attractive alternative to the biologics-based strategies to regenerative medicine. Able to mimic neurotrophic factors, or to induce neurotrophic factor biosynthesis, small molecules possess the pharmacological advantage.[2] The natural product complanadine A (**1**) and complanadine B (**2**) were identified in a screen of compounds from the club moss *Lycopodium complanatum* and reported to induce the secretion of neurotrophic factors from 1321N1 cells, promoting the differentiation of PC-12 cells.[3] While this activity is promising, additional material is needed to test complanadine A in primary glial cell cultures to discover if enhanced expression of neurotrophic factors occurs and if so which are produced.

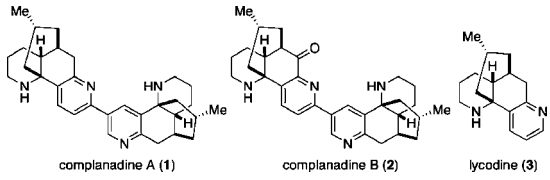


Figure 1. Structures of complanadine A, complanadine B, and lycodine.

Complanadine A is a member of the large family of lycopodium alkaloids.[4] Aside from their varied and interesting biological activities, the compounds have attracted the interest of the synthetic community leading to several creative methods for their laboratory preparation including the related alkaloid lycodine (**3**) (Figure 1).[5] In addition to our efforts, Sarpong and co-workers have concurrently completed a synthesis of complanadine A, as well as several structurally related alkaloids.[6]

In Nature, complanadine A is likely synthesized through the union of two molecules of lycodine (**3**). In the laboratory setting the pseudosymmetry of the molecule has allowed the implementation of a simplifying metal mediated [2+2+2] + [2+2+2] sequence using a substituted diyne and 2 equiv of the corresponding alkyne-nitrile (Figure 2).

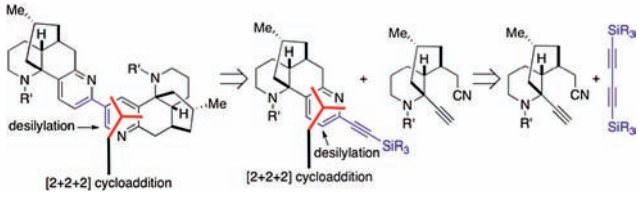
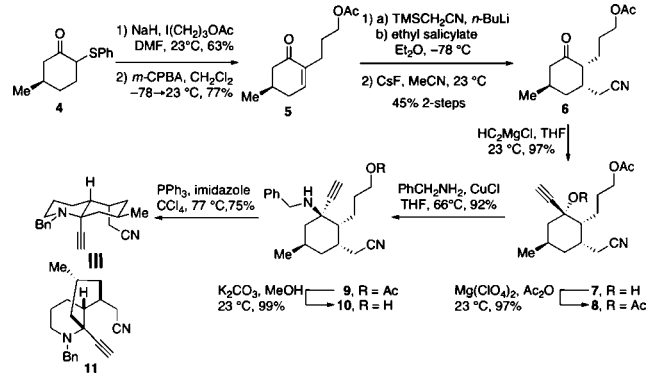


Figure 2. Synthetic disconnections.

The synthesis of the requisite alkyne-nitrile was initiated by the alkylation of the thermodynamically favored enolate of thioether **4** with 3-iodopropyl acetate (Scheme 1).[7] The product was transformed into cyclohexenone **5** through *m*-CPBA mediated oxidation of the thioether and a mild sulfoxide elimination (occurring at 23 °C). Treatment of enone **5** with the anion of trimethylsilyl acetonitrile at −78 °C followed by careful quenching with ethyl salicylate furnished the Michael adduct as a mixture of diastereomers.[5,8,9] Desilylation of the crude mixture with cesium fluoride facilitated the separation of isomers and provided cyclohexanone **6**. Diastereoselective delivery of ethynylmagnesium chloride into the ketone cleanly provided the corresponding propargyl alcohol **7** as a single isomer. Activation of the propargyl alcohol of **7** as the corresponding acetate **8** by treatment with neat acetic anhydride and magnesium perchlorate provided a precursor for a copper mediated amination reaction.[10] Displacement of the tertiary acetate was examined under a variety of conditions. After optimization, heating a thoroughly degassed THF solution of diacetate **8** and benzylamine with a catalytic amount of CuCl provided propargyl amine **9** in 92% yield.[11] Notably, the reaction proceeded with complete diastereoselectivity. Thorough degassing of the solvent prevented an otherwise rapid Glaser dimerization. Secondary amine **9** was transformed into the desired alkyne-nitrile **11** in a two-step sequence initiated by cleavage of the acetate followed by cyclization using PPh_3/CCl_4/imidazole, forming alkne-nitrile **11** in a 75% yield over two steps.[12] The structure of **11**, determined by NMR, was corroborated by X-ray crystallography (see Supporting Information).

Scheme 1



The first [2+2+2] cycloaddition of alkyne-nitrile **11** and bis(trimethylsilyl)butadiyne proceeded smoothly under thermal conditions using $CpCo(CO)_2$, providing the [2+2+2] cycloadduct **13** as the major regioisomer (25:1, **13**:**14**, eq 1).[13] Unfortunately, even under the influence of a variety of conditions and catalysts pyridyl-alkyne **13** proved resistant to undergoing a second [2+2+2] cycloaddition reaction with alkyne-nitrile **11**.

As a result of the low reactivity of pyridyl-alkyne **13**, both silicon groups were removed with TBAF in THF heated to reflux, generating alkyne **15** (Scheme 2). However, attempts at the second

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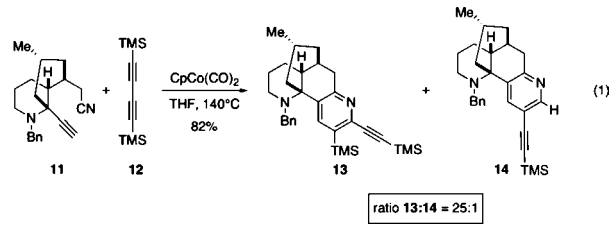
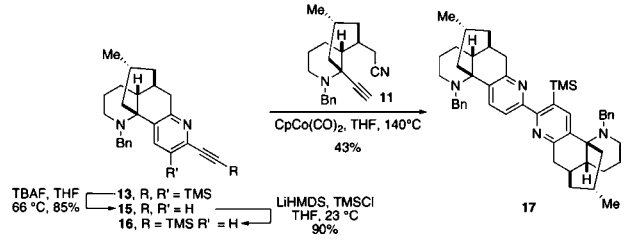


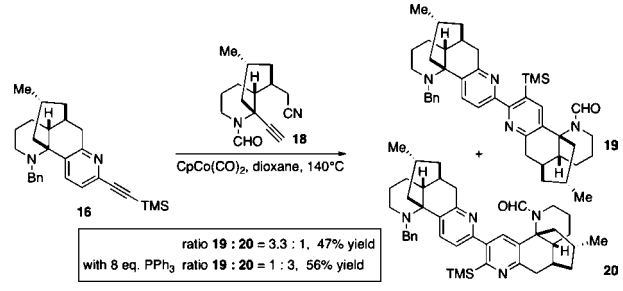
[2+2+2] annulation of **15** with the bicycle **11** led only to decomposition of **15** and recovery of **11**. Other transition-metal catalysts examined, such as $Ru(COD)Cl_2$ and $Cp_2Zr/NiCl_2$, were also ineffective. After routinely noting the unproductive consumption of **15** the reactivity of the alkyne was attenuated by the reinstallation of the alkynyl trimethylsilyl group providing pyridylalkyne **16**. A mixed result was obtained in the cobalt-catalyzed [2+2+2] annulations of **16** and **11** as the reaction provided a single compound, symmetric 2,2′-bipyridinyl **17** rather than the desired 2,3′-bipyridinyl isomer (Scheme 2).

Scheme 2



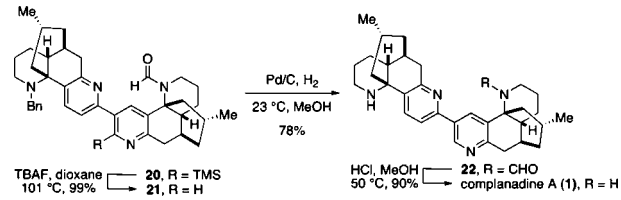
After significant experimentation it was discovered that a remarkable switch in regioselectivity, providing **20** as the major isomer (1:3, **19**/**20**), was possible by the addition of an excess PPh_3 to the reaction using the formyl derivative **18** (Scheme 3).[14] The use of formyl in place of the benzyl group was required as **16** and **11** failed to react in the presence of PPh_3. The ability of PPh_3 to change the regioselectivity warrants further study.

Scheme 3



With access to bipyridyl **20**, fluoride mediated removal of the aryl-trimethylsilyl group yielded **21** (Scheme 4). Debenzylation of **21** by hydrogenation and subsequent deformylation using a heated acidic methanol solution generated (+)-complanadine A (**1**), fully matching with the spectroscopic data reported for the natural product.[3]

Scheme 4



The successful synthesis of complanadine A provided several transformations of utility; the formation of a challenging quaternary center by Cu(I)-catalyzed amine substitution of propargyl acetate **8** and two late-stage Co(I)-mediated [2+2+2] cycloadditions with good to excellent regioselectivities. With access to synthetic complanadine A we are currently examining the effects of the compound on primary cultures of rat glial cells and examining the effects on the biosynthesis of neurotrophin mRNAs.

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Supporting Information Available: Complete references, detailed experimental procedures, and full spectroscopic characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) See Supporting Information for the preparation of **18**.

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