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# Synthesis of Tenuifolin via Intramolecular Nicholas Reaction

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**Abstract:** The synthesis of the *Cinnamomum* homosesquiterpenoid tenuifolin (**1**) has been accomplished by way of an intramolecular Nicholas reaction of the $Co_2(CO)_6$ complex of an alkyne- substituted biaryl for construction of the seven- membered ring. The cyclization features reaction of a non- activated arene ring with the propargyldicobalt cation to give the dibenzocycloheptyne-$Co_2(CO)_6$.

**Key words:** alkynes, total synthesis, carbocation, fused-ring systems, carbonyl complexes, electrophilic aromatic substitution, transition metals

The *Cinnamomum* homosesquiterpenoids are a series of dibenzocycloheptenemethanol derivatives including tenuifolin (**1**), subamol (**2**), reticuol (**3**), burmanol (**4**), and several glycosidic subavenosides (Figure 1). They have been isolated recently from several trees of the genus *Cinnamomum* that have been used in folk medicine.[1] The sesquiterpenoid tenuifolin itself has been isolated from the stems of *Cinnamomum tenuifolium* and *Cinnamomum reticulatum*, and has been shown to possess weak activity against the prostate tumor cell line LNCaP.[1a,b] Reticuol has also shown inhibitory activity towards microsome CYP3A4.[1c]

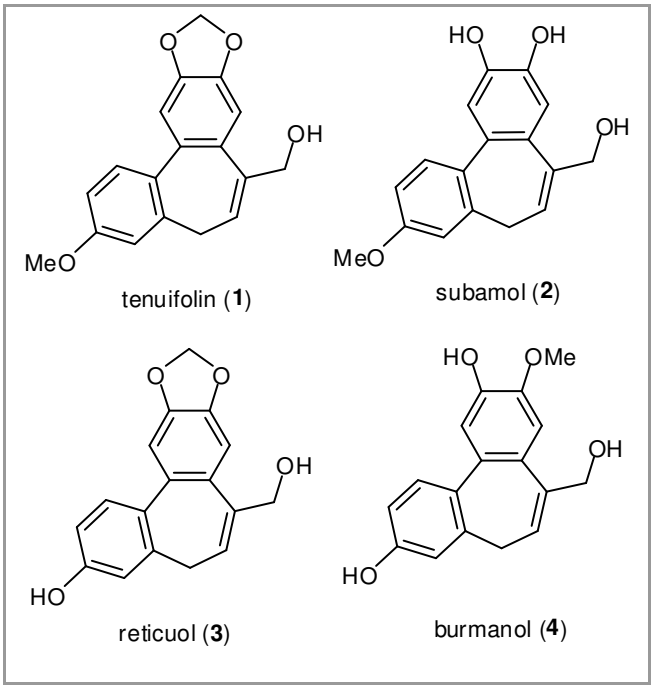
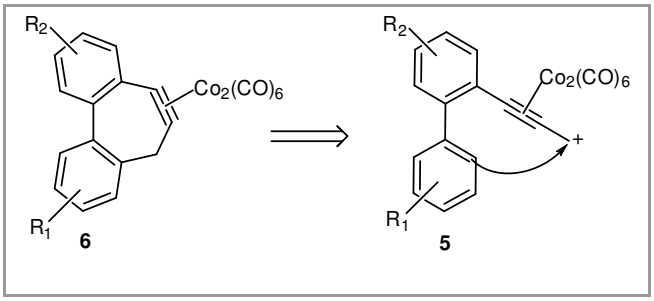


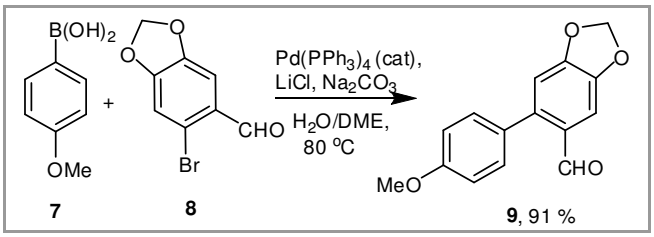

**Figure 1** *Cinnamomum* debenzocycloheptanoids.

Synthetic studies towards members of this group of compounds have been limited. The first total synthesis of tenuifolin was reported recently by Wu and coworkers; this synthesis centred on a PIFA mediated oxidative biaryl coupling to afford the seven-membered ring of the dibenzocycloheptene.[2] The other members of this class of compounds have not been the subject of published synthetic work.



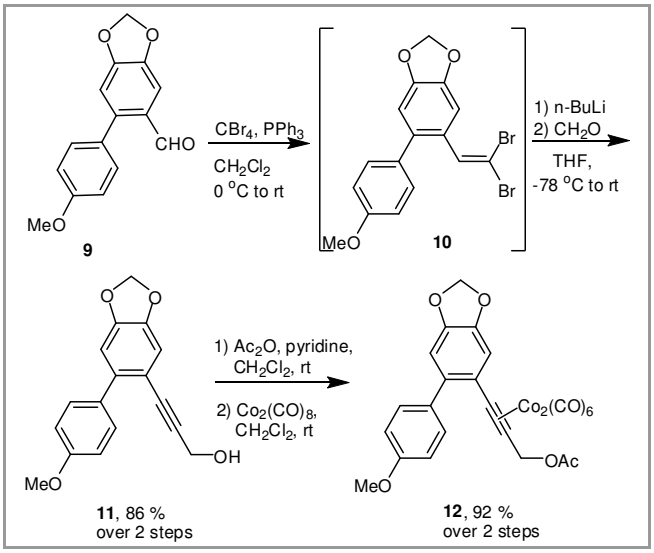

**Equation 1** Generalized approach to dibenzocycloheptynedicobalt complexes

Our group has developed several protocols of seven-membered ring synthesis based on cycloheptynedicobalt complexes,[3,4] and recently applied this to dibenzocycloheptane and allocolchicine synthesis by way of intramolecular Nicholas reaction chemistry (Equation 1).[5,6,7] These normally involve reaction of a very electron rich arene ($R_1$ = electron donating group(s)) attacking the propargyldicobalt cation (**5** → **6**), appropriate since the bimolecular reactions of propargyldicobalt cations require a partner with the nucleophilicity greater than that of *m*-xylene for successful reaction.[8] Conversely, the corresponding approach to tenuifolin or subamol would involve attack of a considerably less electron rich arene ring site (*m*- to methoxy) on the propargyldicobalt cation. Given that this approach would test the reactivity limits of Nicholas reaction – based dibenzocycloheptane synthesis, that this is a distinct ring closure approach to the tenuifolins relative to the work of Wu, and that there is a paucity of synthetic work in the *Cinnamomum* dibenzocycloheptanoids in general, we have begun a programme to investigate the viability of the intramolecular Nicholas reaction approach to this group of compounds. This report describes our synthesis of tenuifolin (**1**) based on this chemistry.




**Equation 2** Suzuki-Miyaura biaryl formation

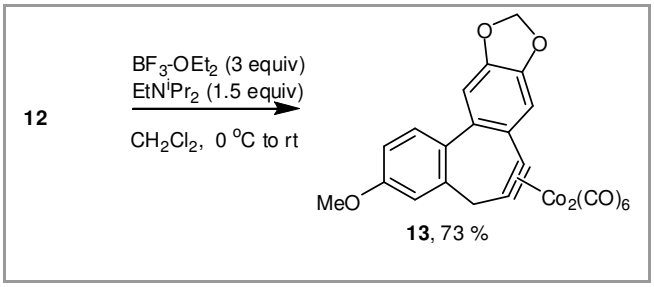
The intramolecular Nicholas reaction approach relies on the prior construction of an alkyne- substituted biaryl substrate. The initial biaryl formation was accomplished by Suzuki-Miyaura cross-coupling[9] of 4-methoxyphenylboronic acid **(7)** and 6-bromo-1,3-benzodioxole-5-carboxaldehyde **(8)**; this proceeded smoothly and afforded the intended biaryl **(9)** in 91% yield (Equation 2). Extension of the aldehyde function in **9** to a propargylic alcohol was then accomplished by Corey-Fuchs chemistry.[10] Subjecting the former to $CBr_4$ and $PPh_3$ afforded the dibromoalkene **10**, which was not purified rigourously but subjected to reaction with *n*-BuLi (2.5 equiv) followed by the addition of paraformaldehyde at low temperature; subsequent workup afforded produced the intended propargyl alcohol **(11)** in good yield (86 %) over two steps (Scheme 1).




**Scheme 1** Preparation of intramolecular Nicholas reaction precursor

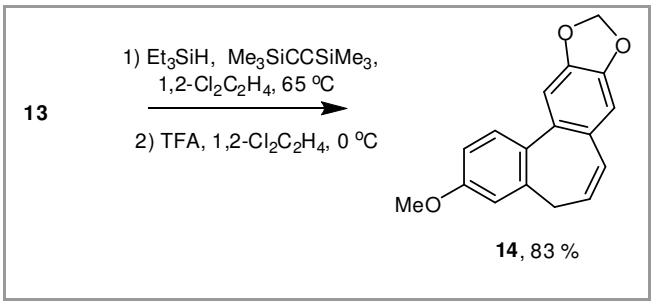
Before complexation of the alkyne function with dicobalt octacarbonyl, the alcohol function was converted to the corresponding acetate. Complexation of the propargyl acetate then afforded the intended **12** in 92 % yield over the two steps.

When complex **(12)** was subjected to a cyclization reaction attempt with $BF_3$-$OEt_2$ (3 equiv, 5 x $10^{-3}$ M) a reaction proceeded over 4 h to give dibenzocycloheptynedicobalt complex **(13)**. However, the reaction produced some baseline material on TLC and the maximum yield obtained under these conditions was 61 %. In some cases the addition of $EtN^iPr_2$ has been shown to reduce decomposition in our intramolecular Nicholas reaction chemistry,[5] and in this case addition of $EtN^iPr_2$ (1.5 equiv) to the reaction mixture caused the rate of cyclization to decrease slightly but to result in an increase of yield to 73 % over a period of 6 h (Equation 3). Despite the relatively electron- poor C ring, this rate of cyclization reaction was roughly in line with other dibenzocycloheptynedicobalt derivatives synthesized previously by our group.[5]




**Equation 3** Intramolecular Nicholas reaction of **12**

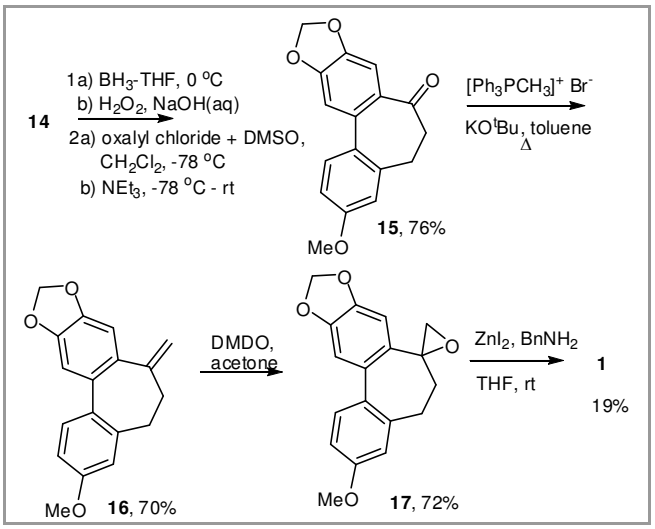
Reductive decomplexation of dibenzocycloheptynedicobalt complex **(13)** was accomplished by means of the two step procedure involving a hydrosilylation mediated by $Et_3SiH$ and bis(trimethylsilyl)acetylene, followed by addition of $CF_3CO_2H$ (TFA) at 0 °C to induce protodesilylation of the intermediate vinylsilane mixture;[5,11] this produced the intended alkene **(14)** in 83 % yield (Equation 4). Some care was required in the TFA addition step, as extended reaction times or higher temperatures resulted in reduced yield, likely due to competing deprotection of the methylenedioxy group.




**Equation 4** Reductive decomplexation of cycloheptynedicobalt complex **13**

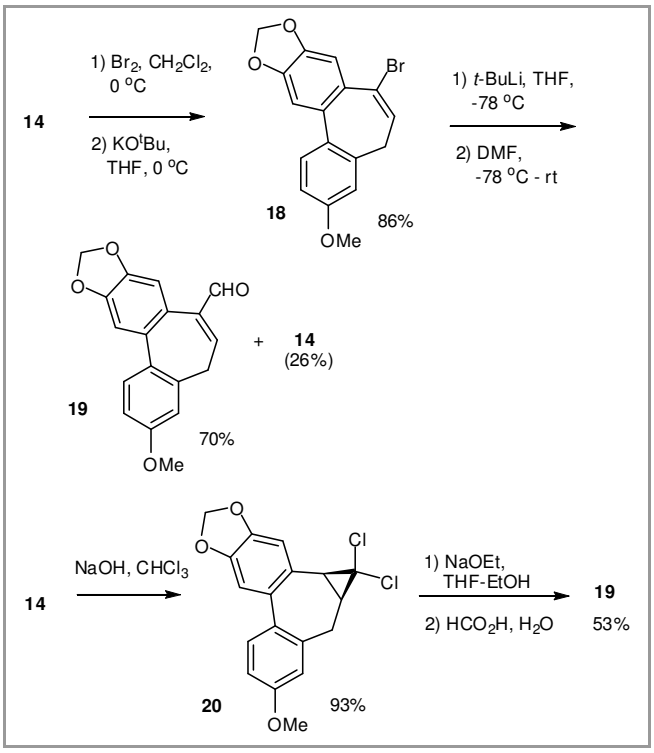
Conversion of **14** into tenuifolin required considerable experimentation. Hydroboration-oxidation resulted in the ready formation of ketone **15** (76% yield) (Scheme 2). All attempts to convert **15** into a vinyllithium by way of its tosylhydrazone and subsequent Shapiro reaction[12] resulted in gross decomposition. Wittig reaction on **15** did afford exo- methylene substituted **16** (70% yield). Epoxidation of **16** with dimethyldioxirane (DMDO)[13] gave **17** (72% yield).

This epoxide could be opened by $ZnI_2$-benzylamine[14] to give tenuifolin **1**, but in unacceptable yield (19%).

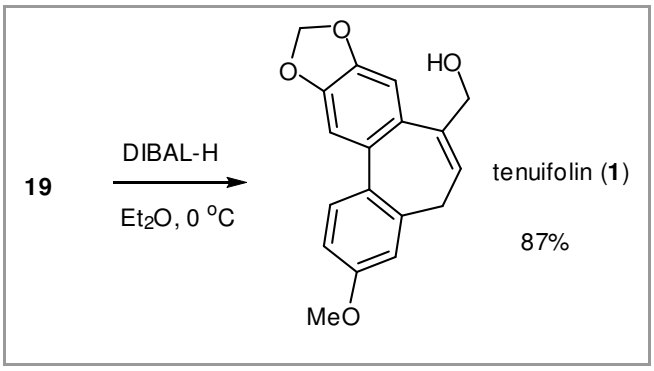



**Scheme 2**

Ultimately, it was found that the most effective route towards tenuifolin involved an initial bromination – dehydrobromination protocol employing $Br_2$ and KO*t*-Bu, respectively, to give brominated dibenzocycloheptene **18** in 86% yield (Scheme 3). Direct attempts to incorporate the $CH_2OH$ function or its acetate by Stille or Suzuki-Miyaura protocols[15,16] resulted in predominant reduction to **14**. Conversely, metal – halogen exchange employing *t*-BuLi, followed by addition DMF gave formylated **19** in 70% yield, along with some **14** (26%).[17] A less efficient, but still synthetically useful alternative proved to be cyclopropanation with dichlorocarbene to afford **20** (93% yield), followed by base induced (NaOEt-THF-EtOH) ring opening and subsequent acetal hydrolysis[18] to give **19** in 53% yield. The aldehyde **19** was then subjected to reduction with DIBAL-H, which afforded tenuifolin (**1**) readily (87% yield) (Equation 5).




**Scheme 3** Conversion of dibenzocycloheptene to aldehyde derivative **19**




**Equation 5** Completion of the tenuifolin synthesis

In summary, we have been able to synthesize tenuifolin successfully in 23% overall yield over 12 steps,[19] with construction of the seven-membered ring by way of intramolecular Nicholas reaction chemistry. This cyclization has been accomplished successfully on the least electron rich nucleophilic arene partner that has been attempted in benzocycloheptynedicobalt formation to date. As this general approach is likely amenable to the other *Cinnamomum* dibenzocycloheptanoids, investigation towards their syntheses is in progress and will be reported in due course.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

**Primary Data** for this article are available online at http://www.thieme-connect.com/ejournals/toc/synlett and can be cited using the following DOI: (number will be inserted prior to online publication).

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(19) By comparison, the Yao and Wu group synthesis is in 15% overall yield in 7 steps.[2a]

**Nicholas reaction tenuifolin.**