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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: alkenes, total synthesis, carbocation, fused-ring systems, carbonyl complexes, electrophilic aromatic substitution, transition metals

The Cinnamomum homosesquiterpenoids are a series of dibenzocycloheptanemethanol 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. 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.$^{1c}$

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 ($5 \rightarrow 6$), 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.

Figure 1 Cinnamomum debenzocycloheptanoids.

Synthetic studies towards members of this group of compounds have been limited. The first total synthesis
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 of 4-methoxyphenylboronic acid (7) and 6-bromo-1,3-benzodioxole-5-carboxyaldehyde (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. Subjecting the former to CBr₄ and PPh₃ afforded the dibromoalkene 10, which was not purified rigorously but subjected to reaction with n-BuLi (2.5 equiv) followed by the addition of parafomaldehyde at low temperature; subsequent workup afforded the intended propargyl alcohol (11) in good yield (86%) over two steps (Scheme 1).

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 precursor 12 in 92% yield over the two steps.

When complex (12) was subjected to a cyclization reaction attempt with BF₃·OEt₂ (3 equiv, 5 x 10⁻³ M) a reaction proceeded over 4 h to give dibenzocycloheptenedicobalt 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 EtNPr₂ has been shown to reduce decomposition in our intramolecular Nicholas reaction chemistry, and in this case addition of EtNPr₂ (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 was roughly in line with other dibenzocycloheptenedicobalt derivatives synthesized previously by our group.

Reductive decomplexation of dibenzocycloheptenedicobalt complex (13) was accomplished by means of the two step procedure involving a hydroxysilylation mediated by Et₃SiH and bis(trimethylsilyl)acetylene, followed by addition of CF₃CO₂H (TFA) at 0°C to induce protodesilylation of the intermediate vinylsilanemixture. 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.

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 vinyl lithium by way of its tosylhydrazone and subsequent Shapiro reaction resulted in gross decomposition. Wittig reaction on 15 did afford exo-methylene substituted 16 (70% yield). Epoxidation of 16 with dimethylidioxirane (DMDO) gave 17 (72% yield).

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**Equation 2** Suzuki-Miyaura biaryl formation

**Equation 3** Intramolecular Nicholas reaction of 12

**Equation 4** Reductive decomplexation of cycloheptenedicobalt complex 13
This epoxide could be opened by ZnI$_2$-benzylamine$^4$ to give tenuifolin 1, but in unacceptable yield (19%).

Ultimately, it was found that the most effective route towards tenuifolin involved an initial bromination – dehydrobromination protocol employing Br$_2$ and KO$_2$Bu, respectively, to give brominated dibenzocycloheptene 18 in 86% yield (Scheme 3). Direct attempts to incorporate the CH$_2$OH 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).

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 benzocycloheptanoid 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.

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References


(7) For the original Nicholas publications, see: (a) Nicholas, K. M.; Pettit, R. J. Organomet. Chem. 1972, 44, C21.


(15) Use of Bu₂SnCH₂OH/Pd(PPPh₃)₄ did afford tenuifolin in modest (35%) yield.


(17) Attempted use of paraformaldehyde as electrophile gave largely decomposed material, along with small amounts of 14.


(19) By comparison, the Yao and Wu group synthesis is in 15% overall yield in 7 steps.9b
Nicholas reaction tenuifolin.