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Intramolecular 4+3 Cycloadditions. A Total Synthesis of Aphanamol†

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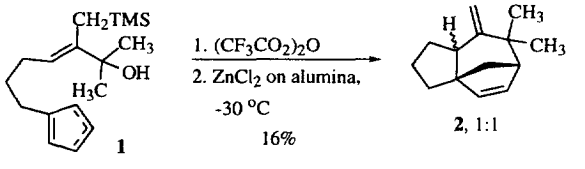
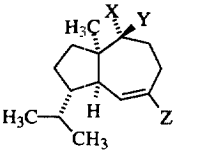
Summary: Treatment of the easily prepared allylic alcohol **11** with triflic anhydride gives the cycloadduct **12** in 32% yield. Deprotection results in the formation of racemic aphanamol I.

The intramolecular 4+3 cycloaddition reaction of allylic cations and dienes is a potentially general and powerful approach to the synthesis of polycyclic, fused-ring systems, especially those containing seven-membered rings.[1,2] Despite this potential, there has been only one application of this general approach to the synthesis of a class of natural products. Hoffmann and Henning reported that chromatography of **1** on alumina



(1)



3a: X, Y=O, Z=-CH_2OH
3b: X= -OH, Y=H, Z= -CHO

(1)

coated with $ZnCl_2$ afforded the cycloadduct **2** as an approximately 1:1 mixture of stereoisomers in 16% yield (equation 1).[3] Hydrogenation with diimide afforded 2-norzizaene and the corresponding ring fusion isomer.

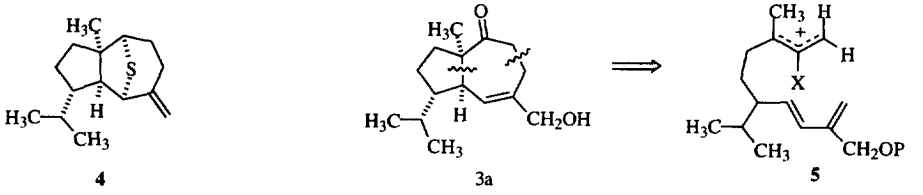
As part of our program involving the study of 4+3 cycloaddition reactions, we have begun to examine the utility of the process in the synthesis of natural products. This report details our synthesis of the sesquiterpene aphanamol I (**3a**). To the best of our knowledge, there has been no report of a total synthesis of a natural product which has made use of an intramolecular 4+3 cycloaddition reaction.

Aphanamol I was isolated from the fruit peel of the Indonesian timber tree *Aphanamixis grandifolia* as one of the minor toxic principles.[4] The structure and relative stereochemistry were assigned on the basis of the NMR data. The carbocyclic skeleton of aphanamol I is that of the relatively rare isodaucane group of sesquiterpenes which includes such compounds as mintsulfide (**4**).[5]

Two syntheses of aphanamol I have appeared. The first, by Mehta and co-workers, made use of limonene as a starting material and involved a strategy sufficiently flexible to be applicable to isodaucane sesquiterpenes as well as dolastane diterpenes.[6] The second synthesis, by Hansson and Wickberg, involved a 2+2 photocycloaddition followed by a base-catalyzed fragmentation to produce the seven-membered ring.[7] A biomimetic synthesis of racemic aphanamol II has also been published.[8]

Our approach took advantage of the direct formation of seven-membered rings made possible by the 4+3 cycloaddition reaction as illustrated in the retrosynthesis shown in Scheme 1. Thus, it became a matter of how to generate the allylic cation **5**. We chose to investigate an alkoxyallylic alcohol for this purpose. Alkoxyallylic

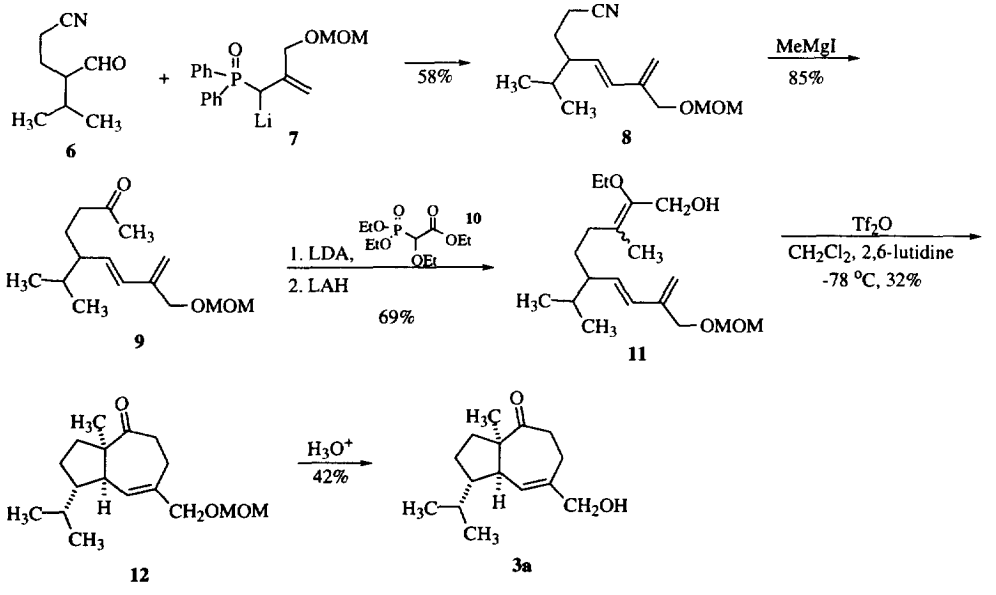
alcohols have been investigated to a limited extent in both inter- and intramolecular 4+3 cycloaddition



Scheme 1

reactions.[9,10] We deemed further investigation important to begin to determine the general utility of this class of compounds as progenitors of allylic cations. Beyond this specific synthetic application, these studies would also lay the groundwork for new methodology such as the development of alkoxyallylic alcohols in which a chiral alkoxy group leads to stereocontrol in the cycloaddition reaction, i.e., an asymmetric 4+3 cycloaddition.[11]

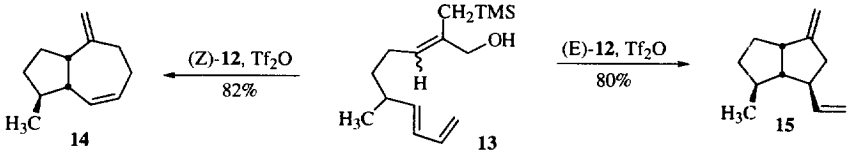
Our synthesis of aphanamol I is shown in Scheme 2. Treatment of the readily available aldehyde **6** with the lithiated phosphine oxide **7** gave **8** as a single stereoisomer in 58% yield.[12,13] The reaction of **8** with methylmagnesium iodide in THF at reflux for 24 hours gave the ketone **9** in 85% yield. Horner-Emmons homologation with phosphonate **10** and reduction gave the allylic alcohol **11** in 69% yield over two steps as an inseparable 1:1 mixture of isomers.[14,15] The key cyclization was performed according to the method of Giguere.[16] Thus, treatment of a 0.007 M dichloromethane solution of **11** with 1.5 equivalents of triflic anhydride in the presence of 2.6 equivalents of 2,6-lutidine afforded a single cycloadduct **12** in 32% yield.[17] Deprotection led to racemic aphanamol.



Scheme 2

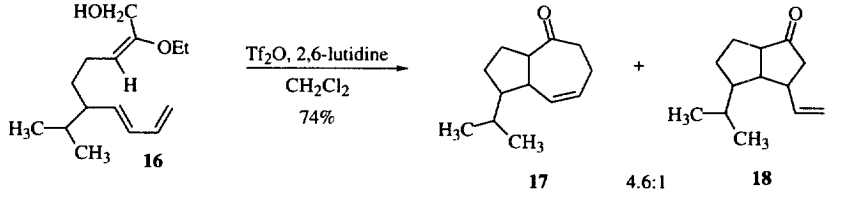
The synthetic material obtained was compared to the synthetic material prepared by Hansen and Wickberg. The 500 MHz ^1H and corresponding ^{13}C NMR spectra of both samples were essentially identical. Further, a comparison of these spectra to that of the authentic natural product confirmed that they were all in fact the same.

It is appropriate to comment on the cyclization step. Giguere and co-workers reported that the cyclization of the E and Z isomers of **13** were both regioselective and high-yielding using the same conditions we used to effect the cyclization of **11**. Thus, (Z)-**13** led to the 4+3 cycloadduct **14** in 82% yield and (E)-**13** led to the 3+2 cycloadduct **15** in 80% yield with excellent selectivity in both cases. We have observed trends similar to those reported by Giguere in some of our other work.[18] Given these data, it is interesting that despite the fact that **11** was a 1:1 mixture of stereoisomers, apparently no 3+2 cycloadducts were formed in the cycloaddition reaction of **11**. Further, the yield for the cycloaddition is poor, yet the reaction appears to be fairly clean. Finally, the lack of concentration dependence on the yield of the reaction suggests that polymerization is not a problem.[17]



Scheme 3

While satisfactory answers to the questions that these results raise remain to be elucidated, we point out that cycloadditions of alkoxyallylic alcohols related to **11** can proceed quite satisfactorily. For example, treatment of **16** with triflic anhydride resulted in the formation of the cycloadducts **17** and **18** in 74% yield in a ratio of 4.6:1 (equation 2).[19] It is interesting to note that the stereochemistry of **16** at the enol ether corresponds to that which would have been expected to give 3+2 cycloadduct as the major product based on Giguere's work. Obviously, further work on the factors which determine regiocontrol in these reactions is needed.



(2)

In summary, we have demonstrated the application of an intramolecular 4+3 cycloaddition to the synthesis of a natural product. While the yield of the cycloaddition in the total synthesis is low, we have shown in a preliminary fashion that alkoxyallylic alcohols can be effectively cyclized in an intramolecular sense. Further studies of alkoxyallylic alcohols as progenitors of allylic cations for this reaction are in progress. The determination of regio- and stereochemical features of these cycloadditions, related mechanistic studies, and applications of the methodology are underway and will be reported in due course.[20]

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Reference and Notes

†Dedicated to my mentor and friend, Professor Paul A. Wender, on the occasion of his 50th birthday.

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15. The ester precursor of the alcohol was also obtained as an inseparable mixture.
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17. Other reaction conditions gave similar results: (a) -78 °C, CH_2Cl_2, 0.10 M, 1.1 eq. 2,6- lutidine, 1.2 eq. Tf_2O; Yield: 29%. (b) -78 °C, CH_2Cl_2, 0.10 M, 2.6 eq. 2,6-lutidine, 1.5 eq. Tf_2O; Yield: 30%. (c) -78 °C, CH_2Cl_2, 0.10 M, 1.1 eq. 2,6-di-t-butylpyridine, 1.2 eq. Tf_2O; Yield: 18%.
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19. The ratio was determined by ^1H NMR and capillary GC. The determination of structural and stereochemical assignments is in progress and will be reported elsewhere.
20. All new compounds exhibited satisfactory ^1H and ^{13}C NMR and IR spectral data as well as satisfactory combustion analysis or high resolution exact mass data.

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