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Synthetic Approach to Aphidicolan and Stemodan Basic Skeletons Using a "Tandem Principle" [2+2+2] and [4+2] Cycloaddition Reactions.

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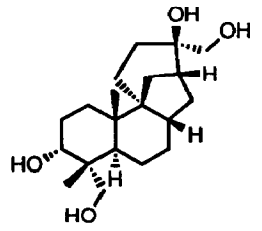
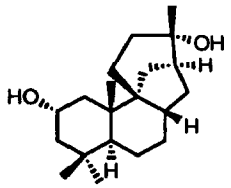
Abstract : *A strategy based upon the "Tandem Principle" : coupling of the cobalt catalyzed [2+2+2] cycloaddition and an intramolecular [4+2] Diels-Alder reaction allowed the formation of the stemodan skeleton in 11 high yield steps starting from 4-ethoxycarbonyl cyclohexanone.*

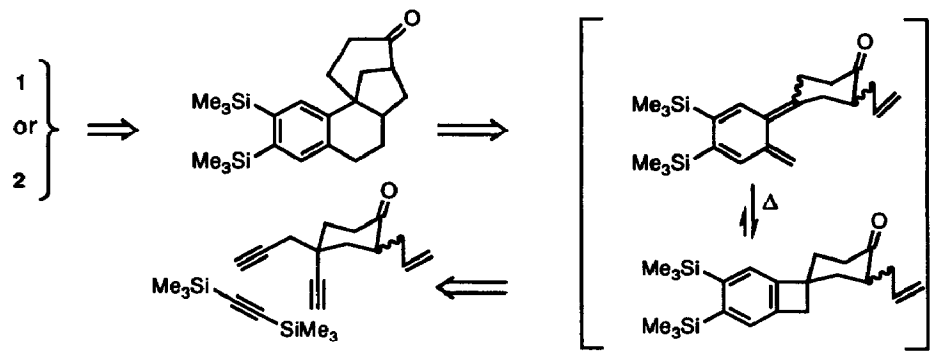
In connection with our ongoing program aimed at the rapid construction of the basic skeleton of tetracyclic diterpenes,[1] we were interested in a quest of a common synthetic route which would allow, at will, a stereoselective access to aphidicolin **1**[2] and stemodin **2**[3]. Because of their unique structural features and alleged medicinal properties, both compounds have received considerable attention as ultimate targets for syntheses.[4] Our approach, retrosynthetically depicted in the scheme I, is based on the very powerful Vollhardt's cobalt catalyzed cooligomerization of substituted 1,5-hexadiynes and bis(trimethylsilyl)ethyne (btmse)[5] combined with an intramolecular Diels-Alder reaction.



APHIDICOLIN **1**

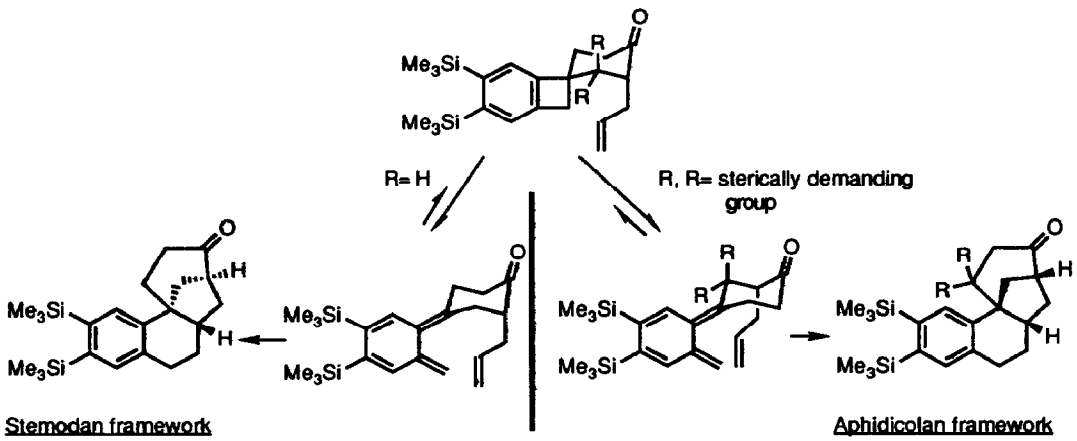


STEMODIN **2**



Scheme 1

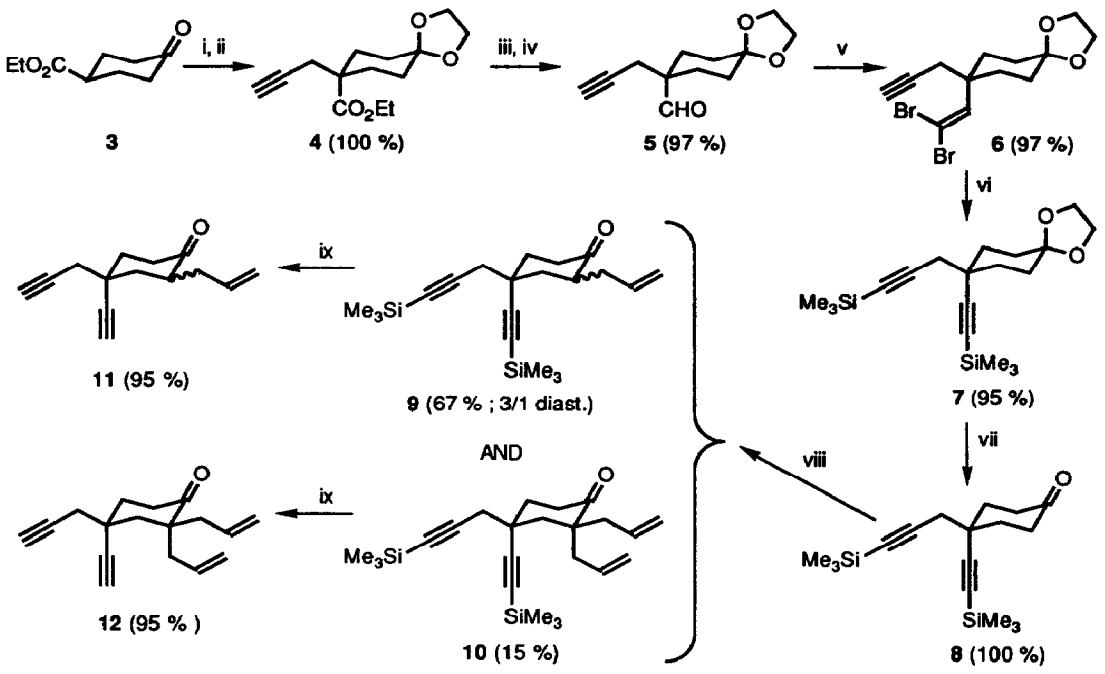
On stereochemical considerations, examination of molecular models deserves various comments : i) both *E* and *Z* orthoquinodimethanes could give a cycloadduct, and, it is important to note that cyclization of the *E* stereoisomer would led to the aphidicolane framework, whereas, the *Z* stereoisomer should deliver the stemodan basic skeleton; ii) the intramolecular [4+2] cycloaddition reaction between the orthoquinodimethanes and the dienophile will be possible only if the allyl substituent is in an axial orientation ; iii) based on the orbital overlapping requirement, the cyclization of the *Z*-orthoquinodimethane seems to be favored. Therefore, if we can control the stereoselective opening of the benzocyclobutene by a judicious choice of the substituents R (Scheme 2), this sequence would afford a very fast and stereoselective new entry to these interesting families of diterpene compounds.



Scheme 2

In this communication, we report the results of our initial efforts aimed at exploring the feasibility of our proposed synthetic strategy.

The required monocyclic enediyne was prepared in nine steps from 4-ethoxycarbonyl cyclohexanone **3**[6] in 56 % overall yield as outlined in the Scheme 3. After acetalization of the starting material with ethylene glycol, the resulting ester was treated with LDA, and then, with propargyl bromide[7] to afford **4**. Diisobutylaluminium hydride reduction[8] followed by Swern oxidation[9] furnished the aldehyde **5**. The Fuchs-Corey reaction[10] provided the dibromoolefin **6** which was treated with butyl lithium. The resulting dialkynide was quenched with chlorotrimethylsilane to afford the diyne **7**. Deprotection to the ketone **8** was readily achieved with formic acid in ligroïne.[11] Introduction of the allyl substituent was a little troublesome and finally we obtained the monoallyl derivative **9** in 67 % yield as a 3/1 mixture of diastereoisomers beside a 15 % yield of the bis allylated compound **10**. Products **9** and **10** were easily separated by flash chromatography on silica gel. Desilylation using KF in DMSO[12] ended the preparation of the desired enediynes **11** and **12**.[13]



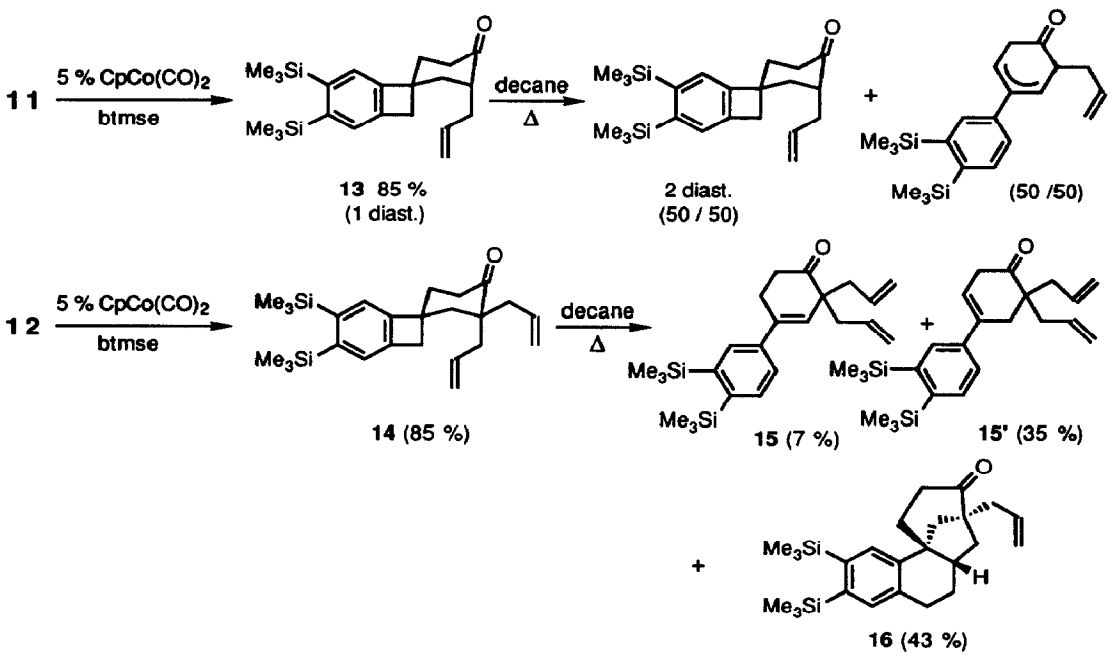
Reagents : i, $(CH_2OH)_2$, CSA, $PhCH_3$; ii, LDA, THF, C_3H_3Br ; iii, DIBAlH, $PhCH_3$; iv, DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 ; v, CBr_4, PPh_3, CH_2Cl_2 ; vi, *n*-BuLi, THF, $ClSiMe_3$; vii, HCO_2H, ligroin ; viii, LDA, THF, C_3H_5Br ; ix, KF, DMSO.

Scheme 3

Exposure of **11** and **12** to a catalytic amount of (η^5-cyclopentadienyl) cobalt dicarbonyl in boiling bis(trimethylsilyl)ethyne with simultaneous irradiation furnished the corresponding benzocyclobutenes in high yields. The intramolecular Diels-Alder reaction was then carried out in refluxing decane. After 60 h, **13** delivered an equal amount of styrene derivatives (in a 1/1 ratio) resulting from a (1,5) hydrogen shift and recovered starting material in a diastereomeric ratio 1/1 showing that the formation of orthoquinodimethane occured but no cycloadducts were formed.

We suspected that this unsuccessful conversion resulted from the difficulty of having the allyl moiety in an axial position. We supported this finding by studying the behavior of **14** in the same conditions.

After 120 h, the starting material **14** was totally consumed. We observed the formation of the styrene derivatives **15** and **15'** in 42 % yield (in a 1/5 ratio) and interestingly 43 % of the tetracyclic compound **16** as a single diastereoisomer having the stemodan skeleton[14] (the structure elucidation was based on NOE experiments) (Scheme 4).



Scheme 4

Active efforts in our laboratory are currently devoted to the optimization of the cyclization process and the application of this methodology for the synthesis of stemodin.

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(13) All new compounds gave satisfactory spectroscopic data.
(14) Spectral data for **16** : IR ($CHCl_3$) 3080, 2960, 1710, 1640, 1250, 990, 920, 850, 760 cm^{-1} ; ^1H NMR (400 MHz ; $CDCl_3$) δ 8.01(s, 1H), 7.66 (s, 1H), 5.99 (m, 1H), 5.03 (m, 2H), 2.66 (m, 2H), 2.40 (m, 2H), 2.24 (d, 2H, J = 7.5 Hz), 2.13 (ddd, 1H, J = 13.0, 8.5, 2 Hz), 2.03 (m, 2H), 1.92 (ddd, 1H, J = 13.0, 8.0, 3.5 Hz), 1.81 (dd, 1H, J = 7.5, 3.0 Hz), 1.80 (dd, 1H, J = 13.0, 5.0 Hz), 1.63 (dd, 1H, J = 11.5, 3.0 Hz), 1.30 (m, 1H), 0.43 (s, 9H), 0.41 (s, 9H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 143.5, 143.0, 142.3, 136.6, 136.4, 136.2, 135.1, 116.7, 51.3, 46.0, 44.6, 42.6, 39.4, 39.1, 36.0, 31.3, 31.2, 30.1, 2.0, 1.9 ; Anal. Calcd. for $C_{25}H_{38}OSi_2$: C, 73.10 ; H, 9.33. Found : C, 73.24 ; H, 9.28.

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