Tetrahedron Letters,Vol.30,No.19,pp 2541-2544,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A STEREOSELECTIVE ACCESS TO THE BASIC SKELETON OF PHYLLOCLADANE TYPE DITERPENES: [3+2], [2+2+2], and [4+2] CYCLOADDITION

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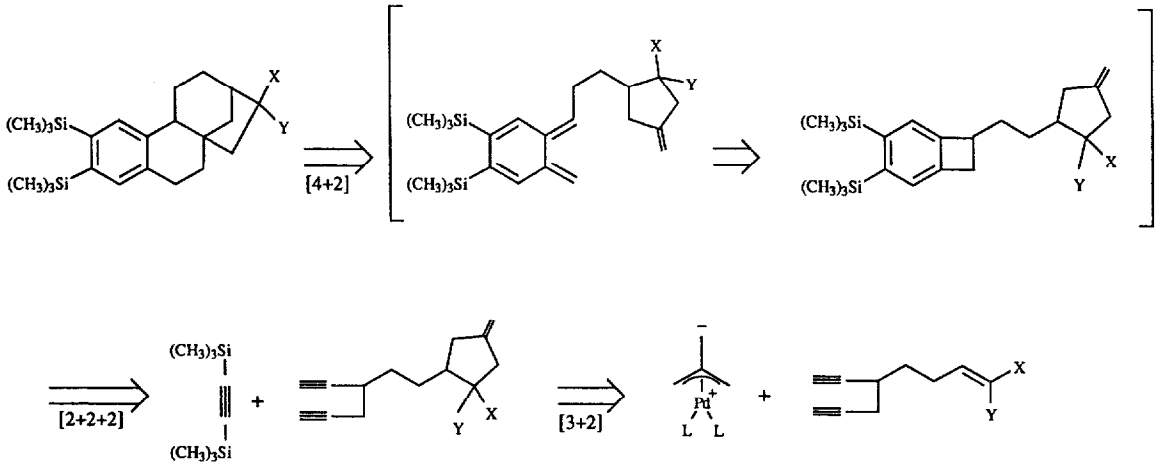
Abstract: A strategy based upon a "cascade" of three consecutive cycloaddition reactions [3+2], [2+2+2] and [4+2] allowed a stereoselective and straightforward access to the phyllocladane basic skeleton in eight high yield steps starting from 1,5-hexadiyne.

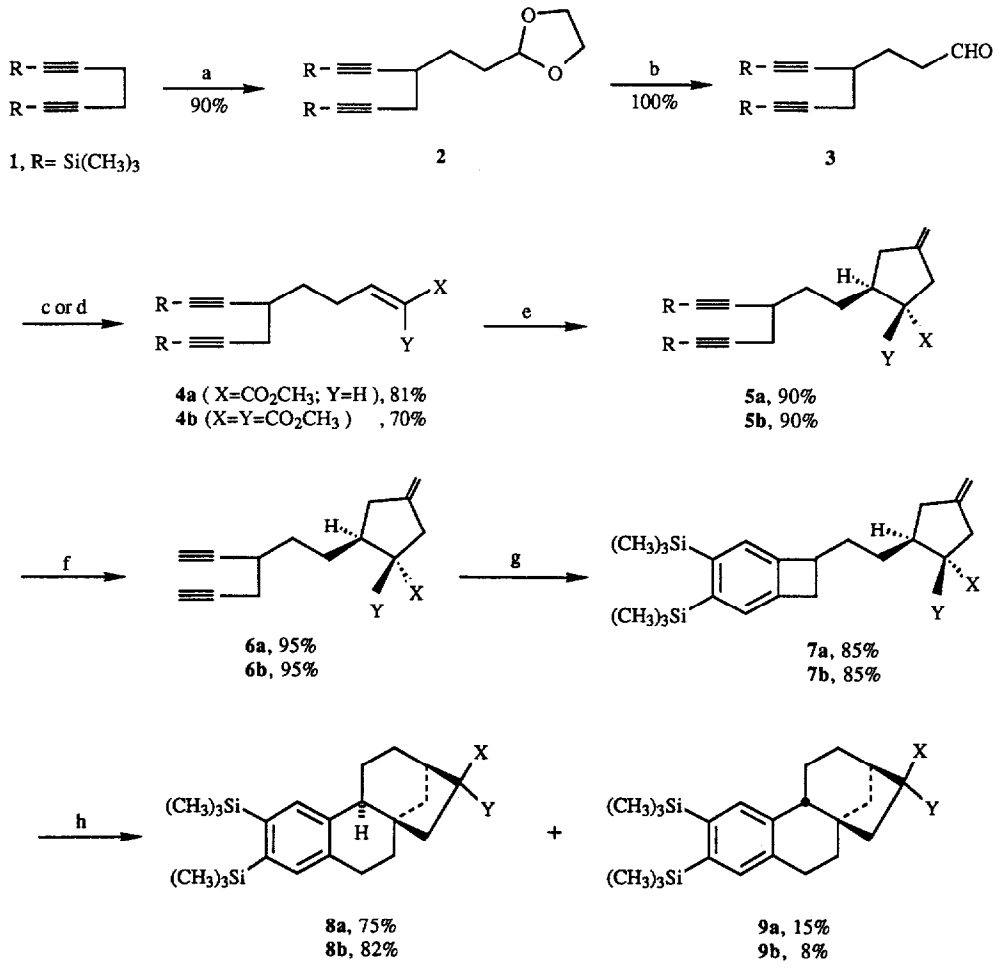
The bicyclo [3.2.1] octane system is a common subunit in many natural products. It is present in diterpene families such as kauranes, phyllocladanes and gibbanes[1]. There is a myriad of naturally occurring compounds belonging to these groups with very important biological activities[2]. Moreover it is worthy of note that the ent-Kaurane group has a fundamental biological importance as a biosynthetic precursor of the plant growth hormone gibberellins[3]. As a consequence, several synthetic approaches to these diterpenoids have been used, and among them the syntheses of (±)hibaol by Kametani[4] and of (±)cafestol[5a],(±)kaweol[5b], and (±)atractyligenin[5c] by Corey.

In this communication, we wish to report a stereoselective synthesis of the basic skeleton of the (±) phyllocladane family in only eight steps, starting from the commercially available 1,5-hexadiyne. Based upon the powerful [2+2+2] cobalt mediated cycloadditions of α,ω-diynes, developed by Vollhardt and coworkers[6a] in the synthesis of complex molecules, our strategy, retrosynthetically depicted in Scheme I, used a "cascade" of three consecutive cycloaddition reactions: palladium catalyzed [3+2][6b]; cobalt catalyzed [2+2+2] and intramolecular [4+2][6c], starting from an acyclic enediyne.



Scheme I

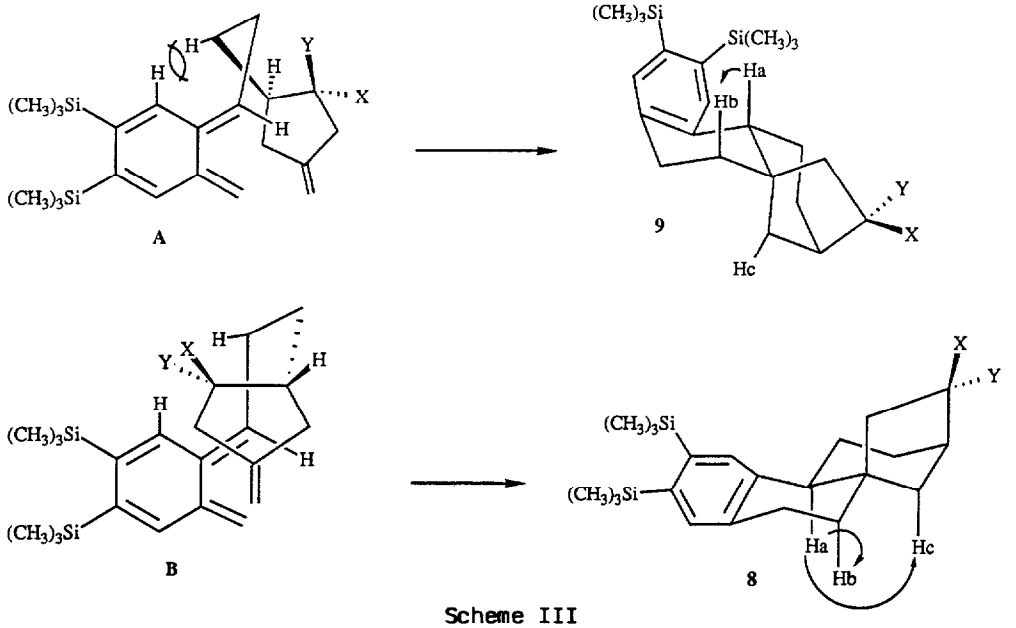
The straightforward and efficient synthesis of the two cyclization precursors **6** is outlined in Scheme II[7]. 1,5-hexadiyne was first converted quantitatively into the 1,6-[bis(trimethylsilyl)]1,5-hexadiyne[8]. Alkylation of the lithio derivative of **1** with 3-iodopropanal ethylene acetal[9] gave **2** which was subsequently hydrolyzed[10] to yield the aldehyde **3**. A Wittig-Horner[11a] or a Knoevenagel reaction[11b] achieved the preparation of **4a** and **4b** respectively. Treatment of these compounds in the presence of two equivalents of 2-acetoxymethyl-3-allyltrimethylsilane, 5 mol% of palladium acetate, and 20 mol% of tris-isopropylphosphite in refluxing tetrahydrofuran afforded the substituted methylenecyclopentane adducts **5a** and **5b** in excellent yields and in a complete diastereoselective manner in the case of **5a**. Protodesilylation of the resulting cycloadducts ended the preparation of **6a** and **6b**.



Scheme II (a) 1. $CH_3CH_2CH_2CH_2Li$ (1 equiv), $(CH_3)_2NCH_2CH_2N(CH_3)_2$ (1 equiv), THF, -78°C ;
2. 3-iodopropanal ethylene acetal, -78°C; (b) HCO_2H, petroleum ether, 20°C ;
(c) 1. $(CH_3O)_2P(=O)CH_2CO_2CH_3$ (1.1equiv), tBuOK (2.2 equiv), THF, 0°C ;
2. **3**, -78 to 0°C; (d) $CH_2(CO_2CH_3)_2$ (1 equiv), $TiCl_4$ (2 equiv), Pyridine (4 equiv), CH_2Cl_2, 0°C then 20°C ;
(e) $AcOCH_2C(=CH_2)CH_2TMS$ (2 equiv), 20 mol% $(i\text{-}C_3H_7O)_3P$, 5 mol% $Pd(OAc)_2$,THF, Δ ;
(f) KF (10 equiv), DMSO, 20°C; (g) 5 mol% $CpCo(CO)_2$, btmse,Δ, hν (ELH, 300W, slide projector lamp), 30 min ;
(h) Decane, Δ, 10h.

When these compounds were exposed to refluxing bis(trimethylsilyl)ethyne (btmse) with simultaneous irradiation in the presence of a catalytic amount of (η_5 -cyclopentadienyl)cobalt dicarbonyl [$CpCo(CO)_2$], benzocyclobutenes **7a** and **7b** were the only cyclization products formed. It is interesting to note that the enediyne system having a methylenecyclopentane unit, which has never been tested in such a reaction, gave a total and chemoselective reaction in less than one hour without migration of the double bond to an endocyclic, thermodynamically more stable position (Scheme II). The thermal intramolecular [4+2] cycloaddition reaction, involving an ortho-quinodimethane and an exocyclic non activated double bond, was carried out in refluxing decane to furnish the tetracyclic products **8** and **9** in a diastereoselective manner (5 to 1 and 10 to 1 respectively), the overall yields for **8a** and **8b** being, respectively, 40% and 38% from 1,5-hexadiyne (Scheme II).

The major isomer **8b** and the minor **9b** were separated by flash chromatography on silica gel. The complete structural and stereochemical assignment of **8b** was made on the basis of conventional high resolution and 2D NMR methods. Proton chemical shifts were assigned by COSY and decoupling experiments, allowing for the determination of coupling constants. NOeSY spectral analysis indicated a NOe effect for Ha-Hb and Ha-Hc in **8b**, establishing a trans B, C rings junction configuration characteristic of the phyllocladane skeleton(Scheme III). Finally, the assigned structure of **8b** was unambiguously confirmed by a single crystal X-ray analysis[12].



Scheme III

Although the isomers **8a** and **9a** were not separated by flash chromatography, the stereochemistry of **8a** was assigned by elucidating the ^{13}C NMR spectrum of the mixture which shows chemical shifts of major component similar to those of **8b**.

The diastereoselectivity observed can be explained if we consider the only two possible approaches **A** and **B** for the intramolecular cycloaddition reaction (Scheme III). In **A**, a severe H-H non bonding interaction exists, and implies that the reaction proceeds via the approach **B**, which seems to be more strained and compact, to allow the stereoselective formation of **8b**.

In summary, this ready access to the phyllocladane skeleton correctly functionnalized allowed us to envisage the synthesis of natural occurring diterpenoids belonging to this family. In addition, we are currently investigating a possible stereoselective synthesis of the (±) kaurane skeleton by removing the H-H non bonding interaction and we are considering a possible asymmetric synthesis of these compounds by taking advantage of an enantioselective construction of the 3,4-substituted methylenecyclopentane moiety[13].

Acknowledgements. We are indebted to Professor K.Peter C. VOLLHARDT (University of California at Berkeley) for helpful advice and his continuous interest in this work. This study is part of a collaborative program: Conférences des Grandes Ecoles Françaises- University of California at Berkeley. We thank CNRS, NSF and Roussel-Uclaf to G.J.P. for financial support. G.Massiot (University of Reims) and A.Belguise (Bruker company) are thanked for recording the 2D NMR spectra and R.Faure for carrying out the X-ray analysis of **8b**.

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7. Structures **1-9** represent racemates. Satisfactory elemental analysis, ^{1}H NMR, ^{13}C NMR, infrared and mass spectral data were obtained for each isolated intermediate described here in. For example: **8b** ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.52 (brs,1H), 7.34 (brs,1H), 3.71 (s,3H), 3.69 (s,3H), 2.88 (dd,J=4.7,3Hz,1H), 2.83 (brddd,J=13,12.7,5.3Hz,1H), 2.76 (brdd,J=13,6.2Hz,1H), 2.70 (brdd,J=12.45,5.5Hz,1H), 2.50 (dd,J=11.5,2.3Hz,1H), 2.31 (brddd,J=13.8,5.7,5.5Hz,1H), 1.97 (ddd,J=11.5,4.7,2.1Hz,1H), 1.89 (dd,J=12.45,5.9Hz,1H), 1.73 (tdd,J=12.45,5.7,3Hz,1H), 1.64 (d,J=14.8Hz,1H), 1.61 (ddd,J=12.7,5.3,2.1Hz,1H), 1.52 (dd,J=11.5,2.3Hz,1H), 1.41 (brdtd, J=13.8,12.45,5.9Hz,1H), 0.35 (s,9H), 0.34 (s,9H); ^{13}C NMR(75MHz,CDCl3) δ 173.23, 170.81, 146.61, 142.31, 138.60, 136.22, 135.49, 133.90, 63.25, 52.54, 52.45, 46.48, 45.49, 42.70, 42.34, 37.39, 34.50, 28.92, 27.44, 24.90, 1.99, 1.97; m.p. 156-157°C.

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12. The structure of compound **8b** was determined by X-ray analysis using a crystal of 0.25 x 0.50 x 0.50 mm. Diffraction measurements were made on an Enraf-Nonius CAD-4 fully automated diffractometer using graphite-monochromated CuK radiation (λ = 1.542Å). The space group, based on the observed systematic extinctions, was assigned as $P2_1/c$, with a = 16.432(2)Å, b = 9.597(3)Å, c = 17.029(2)Å, β = 93.727(9)°, V = 2680(1)Å^3, Z = 4 with one molecule of composition $C_{26}H_{40}O_4Si_2$ in the asymmetric unit. The calculated density was 1.172 g cm^{-3}. There were 5353 reflections collected with $2\theta \leq 146°$; of those reflections, 4523 with $I \geq 3\sigma(I)$ were adjuged observed. The structure was solved using the SPD procedure. An anisotropic least squares refinement yielded an unweighted R of 0.108 and a weighted R of 0.135.

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(Received in France 20 February 1989)