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An Expedient and Stereoselective Route to the Perhydrophenanthrene Skeleton via Sequential Diels-Alder Reactions

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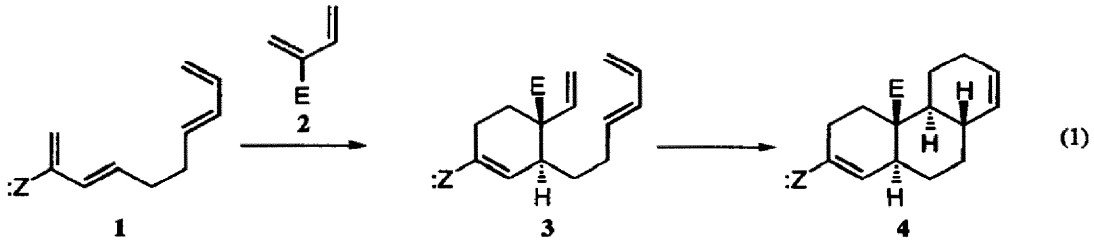
Abstract: A novel and efficient stereoselective synthesis of the perhydrophenanthrene skeleton was achieved using a sequential Diels-Alder cycloaddition strategy involving enyne **10** and bis-diene **8**.

The perhydrophenanthrene skeleton is extremely common in natural product chemistry being embodied, in particular, in the carbon framework of most steroids and triterpenoids. Many synthetic methodologies have been developed to construct this core structure among which the Robinson annelation and the intramolecular Diels-Alder cycloaddition stand as some of the most successful.[1] We report herein a novel approach to this skeleton that utilizes sequential Diels-Alder reactions between two tethered diene units and an enyne.

Eq 1 summarizes our approach. We believed that it should be possible to adjust the electronic properties of each of the three dienes in **1** and **2** in order to favor one of the 18 possible Diels-Alder cycloadditions (DAC). For example, an electron-withdrawing group (EWG) at position 2 on diene **2** (E=EWG) should increase the dienophilicity of the C_1-C_2 double bond whereas an electron-releasing group (Z=ERG) at position 2 on bisdiene **1** should increase the enophilicity of the C_1-C_3 diene.[2] It was expected that the cycloadduct **3** would thus be favored. Then, an intramolecular Diels-Alder cycloaddition (IMDAC) of **3** would close the perhydrophenanthrene ring system while leaving valuable functionalities for further elaboration into several types of natural products. Steroids are targets of choice for this methodology because of the C_3 oxygen and the C_{10}-ester (steroid numbering) which offer the possibility of transforming the left-hand ring of intermediate **4** into several types of steroid A-rings. It was anticipated that both cycloadditions would proceed with stereoselectivity to give a tricyclic structure with the correct stereochemistry for steroid and triterpene synthesis (vide infra).

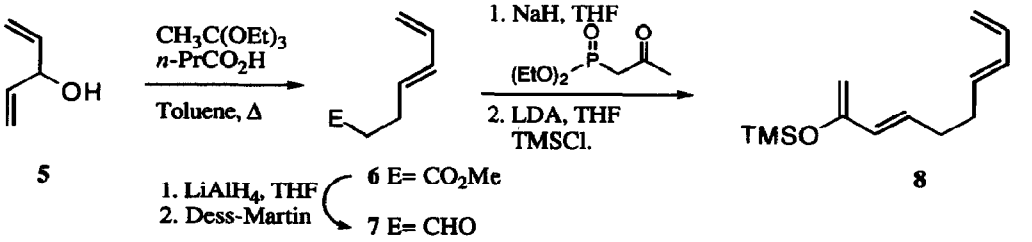


1 **3** **4** (1)

E=electron-withdrawing group, Z=electron-releasing group

To that end, the required bis-diene **8** was prepared in 5 steps from the commercial 1,4-pentadien-3-ol **5**. The orthoester Claisen rearrangement of **5** proceeded in refluxing toluene to give 73% of the distilled diene-

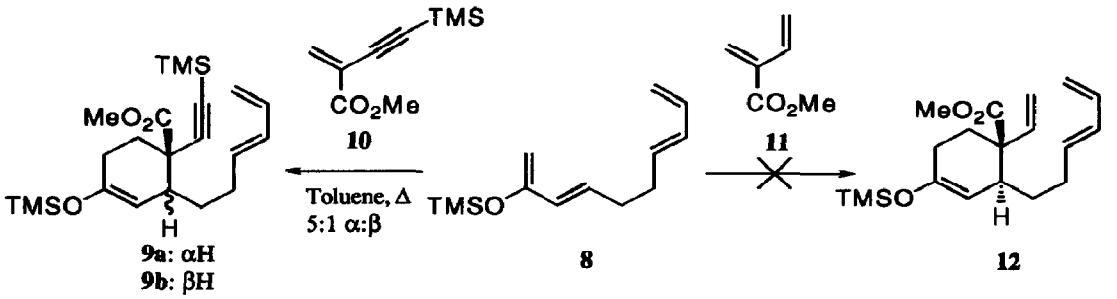
ester **6**. Reduction of **6** to the aldehyde **7** was more efficiently carried out in two steps as shown . The reduction proceeded in 83% yield and the unstable aldehyde was used directly in the reaction with the anion of diethyl 2-oxopropylphosphonate to afford 85% of the desired α,β-unsaturated ketone.[3] Kinetic enolization of the enone with LDA in THF, and trapping of the resulting dienolate with trimethylsilylchloride furnished the desired bis-diene **8** in 81% yield.



Scheme 1

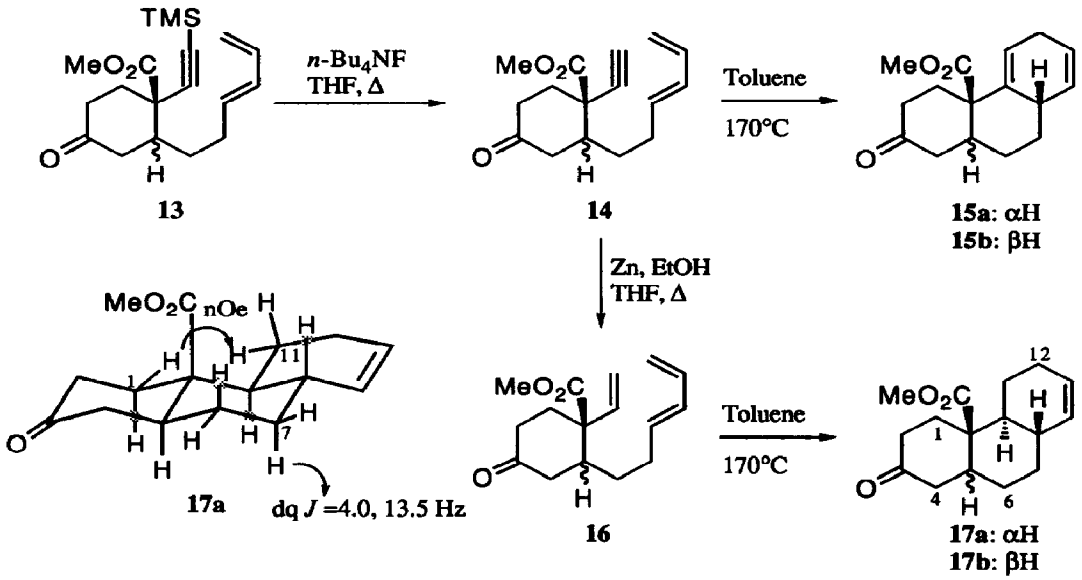
When 2-carbomethoxy-2,5-dihydrothiophene-1,1-dioxide is heated in refluxing toluene, sulfur dioxide is extruded over a period of 3-4 h, thus generating 2-carbomethoxy-1,3-butadiene **11**.[4] When this was carried out in the presence of the bis-diene **8** (Scheme 2, right), only the cyclodimerization product of diene **11** was isolated. Diene **11** is known to dimerize rapidly, even at room temperature.[4,5] However, the preference for its dimerization over its cross Diels-Alder reaction with **8** was a surprise. We have investigated this phenomenon in more detail and those results are reported elsewhere.[6] Even a slow addition of the sulfolene precursor to **11** via a syringe pump did not lead to synthetically useful amounts of the desired adduct **12**. We were therefore forced to use a substitute for **11**, one in which dimerization would be impaired or stopped.

The enyne **10** was a perfect candidate for that purpose. While it should retain a similar dienophilicity to **11** it cannot cyclodimerize because of the triple bond. We prepared the trimethylsilyl enyne **10** from the palladium-catalyzed coupling of methyl 2-bromoacrylate and trimethylsilylacetylene in 76% yield.[7] The product was contaminated with ~20% of the starting bromoacrylate. This mixture underwent a facile DAC with bis-diene **8** over a 12 h period in refluxing toluene to yield 82% of the inseparable cycloadducts **9a** and **b** in a 6:1 ratio (nmr analysis, yield based on **8**).



Scheme 2

Repeated flash column chromatography of **9** was needed in order to remove polymeric materials, presumably emanating from the starting materials. During chromatography the silyl enol ether was partially hydrolyzed to the corresponding ketone **13**. It was therefore more practical to completely hydrolyze it (SiO_2-ethyl acetate, 1 drop conc. HCl) prior to chromatography. This procedure afforded a 73% yield of compounds **13a** and **b** after a single column (ratio 6:1 by ^{1}H-NMR). Although the stereochemistry of the major isomer **9a** could not be ascertained, we strongly suspected that the ester-*endo* adduct would be the predominant one for steric and electronic reasons. We thus decided to carry on, hoping that we would be able determine it at a later stage. After removal of the TMS group in **13** with fluoride ion (TBAF, THF, 0°C, 98%), the intramolecular Diels-Alder reaction of **14** (as a 5.5:1 mixture of stereoisomers) was performed in toluene at 170°C in a sealed tube for 48 hrs to afford 64% of two tricyclic molecules **15a** and **15b** as a 5:1 mixture (Scheme 3). Recrystallization furnished 51% of a single adduct **15a**, in greater than 99% isomeric purity (GC analysis). The stereochemistry of the major isomer of **15a** is as shown and was derived from a single crystal X-ray crystallographic analysis. This result confirmed the stereochemistry of the major isomer **9a**. Although we do not know the stereochemistry of the newly formed methine in the minor isomer **15b** we suspect that it is as shown from consideration of the possible transition states (vide infra). Nevertheless, the intramolecular Diels-Alder of both isomers of **14** proceeded with complete stereoselectivity.



Scheme 3

Zinc metal reduction of the triple bond in **14** gave the alkenes **16a** and **b** (Zn, LiBr. CuBr, EtOH, 72 hrs, 68% yield)[8] which underwent an IMDAC in toluene at 170°C in a sealed tube giving 64% yield of two tricyclic products **17a** and **b** as a 5.3:1 mixture of stereoisomers. Recrystallization furnished 53% of pure **17a** in greater than 95% isomeric purity (NMR analysis). Though we could not grow crystals of good enough quality for X-Ray analysis, a strong nOe between the equatorial protons at C_1 and C_{11} plus a clear ^{1}H-NMR signal for the axial proton at C_7 as a large dq [d (J = 4.0 Hz) of q (J = 13.5 Hz)] provide strong evidence for

the proposed structure (Scheme 3). The IMDAC of **14** and **16** presumably proceeds via an *exo* chair-like transition state **A** (Figure 1, shown for **16**).[9] The interaction between the ester group and the diene unit in **B** is probably responsible for its destabilization. The *exo*- and *endo*-boat-like transition states should be even more destabilized. The IMDAC of the minor isomers of **14** and **16** likely proceeds via a transition state similar to **A**.

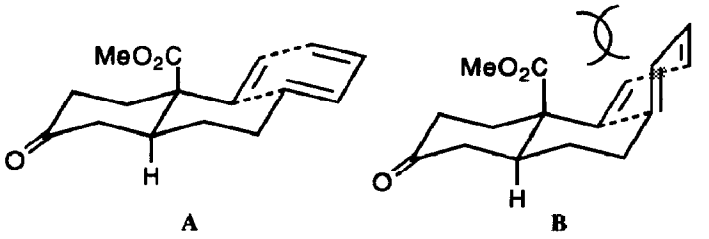


Figure 1

In conclusion, we have developed a very short and stereoselective route to the perhydrophenanthrene ring system using a sequential Diels-Alder cycloaddition strategy. The strategy should be usable with different bis-dienes and create adequate functionality around the ring system for further elaboration. We are currently undertaking the total synthesis of steroids and triterpenoids using this strategy and the results of our efforts will be reported in due course.

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