Thermally-Induced One-Step Construction of the Tetracyclic Steroidal Skeleton from Acyclic Enyne–Allenes

Yemane W. Andemichael, Ying Huang, and Kung K. Wang*

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506

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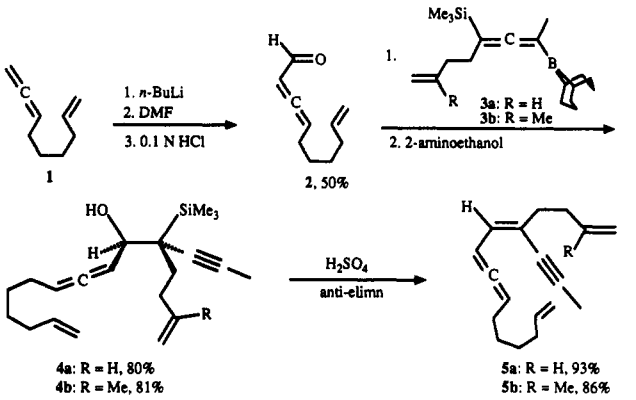
Summary: On heating, acyclic enyne–allenes **5** underwent a sequence of intramolecular transformations with a cascade of energy to produce **9** having the tetracyclic steroidal skeleton in a single step.

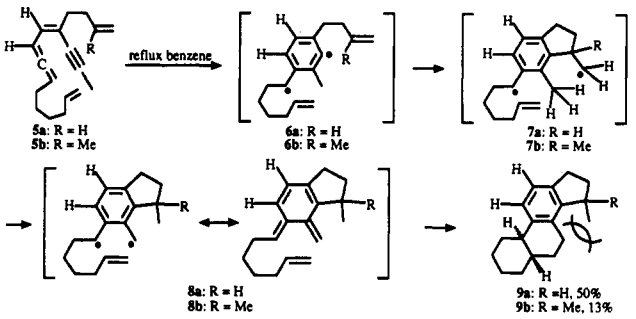
Cycloisomerization of polyolefins is an efficient and attractive synthetic strategy for the construction of polycyclic structures.[1] The versatility of such an approach has been amply demonstrated in the cationic-initiated polyolefin cyclization reaction.[2] Recent development has focused on the use of transition metals,[3] free radicals,[4] and alkyllithiums[5] to promote ring formation. We recently reported a new synthetic route to *o*-quinodimethanes,[6] a class of reactive intermediates finding many useful synthetic applications,[7] via the thermally-induced Myers cycloaromatization reaction of conjugated enyne–allenes.[8] We now have successfully extended this pathway to the preparation of synthetically useful *o*-quinodimethanes for the subsequent intramolecular Diels–Alder reactions, producing the tetracyclic steroidal skeleton from acyclic enyne–allenes in a single step.

The acyclic enyne–allene **5a**, serving as a precursor to the steroidal skeleton, was synthesized as outlined in Scheme I. The conjugated allenic aldehyde **2** was prepared by sequential treatment of the readily available 1,2,8-nonatriene (**1**)[9] with *n*-butyllithium and *N,N*-dimethylformamide followed by acidic workup.[10] Condensation of **2** with allenylborane **3a**[6] proceeded smoothly and afforded, after treatment with 2-aminoethanol, hydroxy propargyl silane **4a** in 80% isolated yield. The diastereoselectivity of the two newly formed asymmetric centers was high (de = 94%), whereas an essentially random selection of the allenic chiral axis, which was of no chemical consequence, was observed. The subsequent H_2SO_4-induced Peterson olefination reaction[11] produced **5a** in high geometric purity (*Z*:*E* = 96:4). Similarly, enyne–allene **5b** (*Z*:*E* = 97:3) was

Scheme I



Scheme II



prepared by using allenylborane **3b**, derived from 2-methyl-5-(trimethylsilyl)-1,5,6-octatriene, for condensation with **2**.

The thermally-induced cyclization of **5a** to the tetracyclic structure **9a** was carried out by dropwise introduction of a solution of **5a** (0.156 g, 0.65 mmol) in 100 mL of benzene into 300 mL of refluxing benzene over a period of 1 h followed by an additional 1.5 h of reflux to afford 0.080 g (0.33 mmol, 50%) of **9a** having predominantly the trans ring junction (trans:cis = 92:8) (Scheme II). The assignment of the trans ring junction to **9a** is based on the chemical shift correlation of the ^{13}C NMR signals with those of other similar systems.[12] Such a stereochemical outcome of the transformation from **8a** to **9a** is also consistent with earlier reports of other closely related intramolecular Diels–Alder reactions of *o*-quinodimethanes.[12,13] Because the asymmetric center on the five-membered ring did not exert a significant influence on the facial selection of the Diels–Alder reaction, a 1:1 mixture of the two diastereomeric pairs of **9a** was produced. However, only a small amount (ca. 1%) of **10**, derived from the [1,5]-sigmatropic hydrogen shift of **8a**, was

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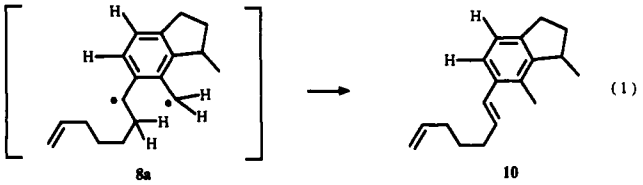
detected by the ^1H NMR (eq 1). Similarly, **9b** (trans:cis



8a 10 (1)

= 95:5) was produced from **5b** in 13% isolated yield. In comparison with **9a**, the absence of an asymmetric center on the five-membered ring in **9b** reduces the complexity of the ^1H and ^{13}C NMR spectra and makes it easier for structural elucidation.

The sequence of events leading to **9a** is a subject of interest. It is most likely that ring closure to form **7a** is the first event that occurs following the Myers cycloaromatization reaction because aryl radicals are very reactive toward cyclization ($k_{5\text{-exo}}$ = ca. 5×10^8 s^{-1} at 50 °C).[14] It also seems likely that the subsequent 1,5-hydrogen transfer[6] to form **8a** is faster than the possible intramolecular trapping of the benzylic radical center in **7a** by the carbon–carbon double bond. The heat of formation of **8a** is estimated to be ca. 13 kcal/mol less than that of **7a**, representing the difference in the bond dissociation energies of primary alkyl and benzylic C–H bonds.[15] Furthermore, the rigid structure of **7a** should also enhance the rate of the hydrogen transfer. The possible intramolecular trapping of the benzylic radical center in **7a** by the carbon–carbon double bond is favored by only ca. 7 kcal/mol, representing a gain of ca. 20 kcal/mol by trading a carbon–carbon π bond for a σ bond[16] but a loss of 13 kcal/mol by going from a benzylic radical to a primary alkyl radical.[15] The entropy factor should also make such a conversion less favorable. It was recently reported that attempts to induce cyclization of *o*-allylbenzyl chloride by a free-radical route were unsuccessful.[17] Therefore, it is most likely that *o*-quinodimethane **8a** was also produced in the present case and then intramolecularly captured by the carbon–carbon double bond.

There are two factors that might contribute to the low efficiency in converting **5b** to **9b**. The presence of a methyl substituent at the internal position of a double bond in **6b** could increase the amount of the undesirable 6-*endo* cyclization.[18] The transition state leading to **9b** suffered from a severe allylic 1,3-strain[19] as depicted in **9b**, which would reduce the efficiency of the intramolecular Diels–Alder reaction. Indeed, the ^1H NMR spectrum of the crude product exhibited strong signals attributable to the vinylic hydrogens of the monosubstituted double bond together with signals due to other vinylic as well as aromatic hydrogens.

In conclusion, the synthetic strategy outlined in Scheme II represents a new approach to a one-step 0 → ABCD ring construction of the tetracyclic steroidal skeleton having an aromatic C-ring.[20] In comparison with the cationic polyolefin cyclization reactions[2] and the more recent transition metal-mediated reactions,[3a–c] this strategy is unique in that cyclization is induced thermally and does not require an acid or a transition-metal catalyst. We are currently extending this synthetic strategy to other fused ring systems by varying the length of the tether connecting the two carbon–carbon double bonds to the eyne–allene system and by using other dienophiles for the intramolecular Diels–Alder reaction.

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Supplementary Material Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of 2-methyl-5-(trimethylsilyl)-1,5,6-octatriene, **2**, **4a,b**, **5a,b**, and **9a,b** (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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