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LETTERS

The Synthesis of Quaternary Carbon Centers Through Cyclialkylations

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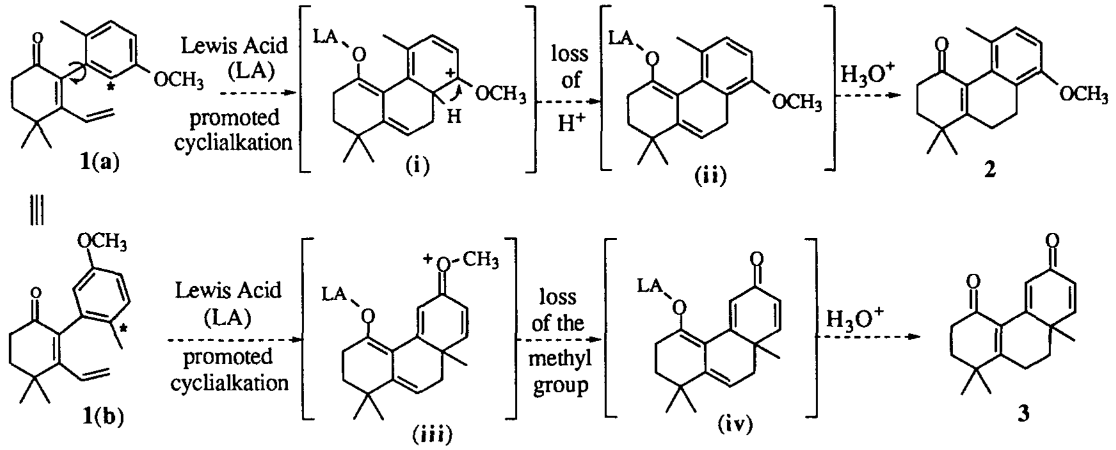
Abstract: Treatment of conjugated dienone **1** with a strong Lewis acid at -78 °C produced a hydrophenanthrene with a newly created quaternary carbon. During this transformation the arene moiety becomes a dienone system.

Previous work from our labs led us to believe that conjugated dienone **1** would cyclize via the two conformers shown below to give different products.[1] In particular, hydrophenanthrene **2** would result from conformer **1a**, after cyclization takes place at the unsubstituted position (*) ortho to the methoxyl group (cf. intermediates **i** and **ii**, Scheme 1). On the other hand, cyclialkylation via conformer **1b** at the position para to the methoxyl group (*) — despite the presence of substitution — would produce intermediate **iii**; the loss of the O-methyl group from **iii** would form species **iv**. Aqueous acidic workup of **iv** would produce dienone **3**. Note that in the course of this proposed transformation a new quaternary center would be created. The intriguing synthetic potential of this annulation process prompted us to prepare and then cyclize dienone **1**.

Scheme 1



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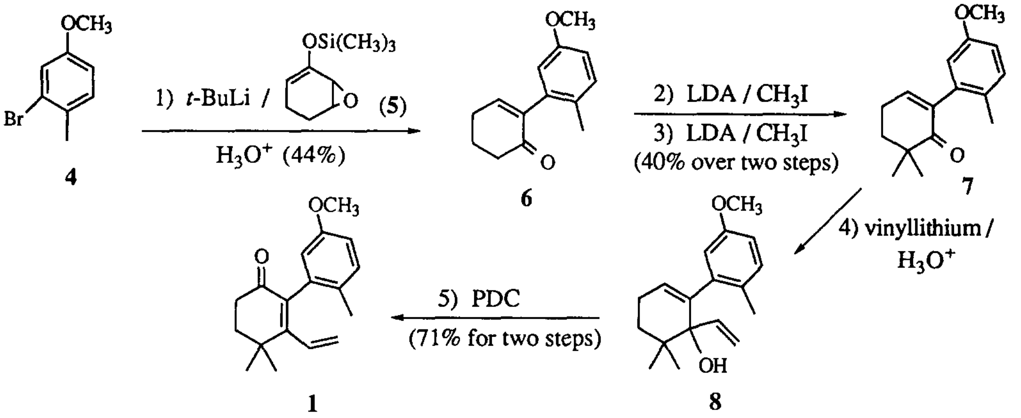
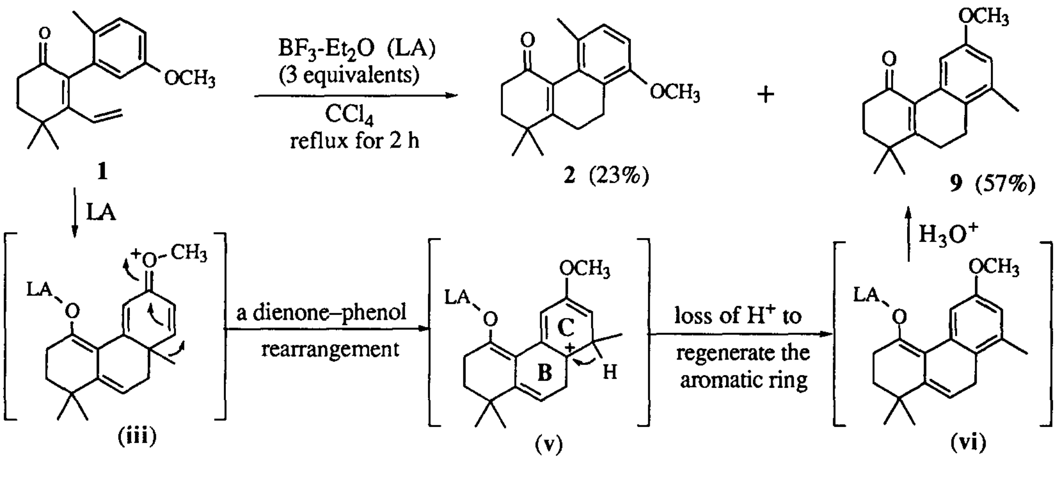
The preparation of cyclization precursor **1** involved five steps as shown in Scheme 2.[2] In the first step the lithio anion derived from aryl bromide **4** [3] was treated with Wender's epoxide (**5**) to produce the 2-aryl-2-cyclohexenone **6**.[4] This enone was then bis-alkylated to introduce a geminal dimethyl unit (cf. **7**).[5] We were aware that 3-vinyl-2-cycloalkenones (cf. **1**) can be efficiently prepared from 2-cycloalkenones in good yield by oxidizing the appropriate bis-allylic tertiary alcohol with pyridinium dichromate (PDC).[6] Treating enone **7** with vinyllithium gave the 2-aryl-1-vinyl-2-cycloalkenol (**8**) required for oxidation.

Scheme 2



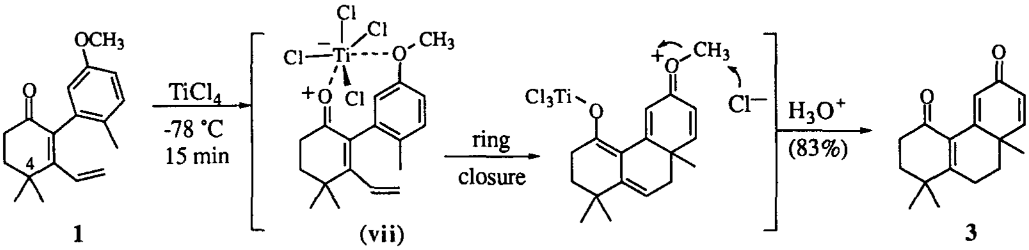
Treatment of **1** with boron trifluoride etherate in refluxing CCl_4 gave hydrophenanthrene **2** and an unexpected isomer **9** (Scheme 3). Tricycle **9**, however, must result from intermediate **iii**, which has a

Scheme 3



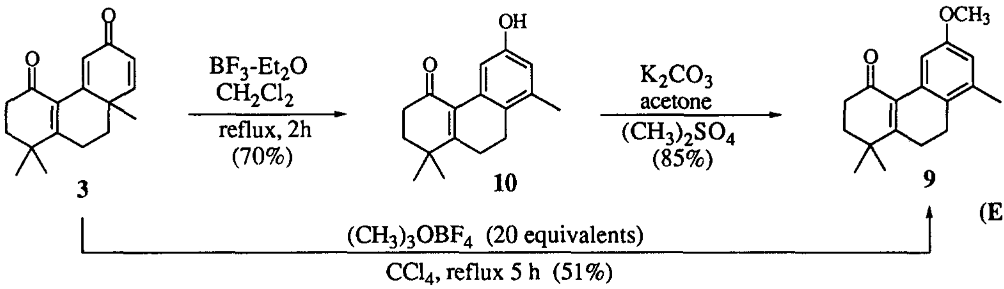
quaternary center at the B/C ring fusion. The subsequent 1,2- migration of the methyl group (cf. **v**) and rearomatization is consistent with the well-established acid-catalyzed dienone–phenol rearrangement.[7,8]

Nevertheless, the isolation of tricycle **9** suggested that the dienone–phenol rearrangement could be precluded under milder conditions. Indeed, treatment of **1** with $TiCl_4$ at -78 °C for 15 minutes, followed by aqueous workup, gave the single product (**3**) with its new quaternary center in 83% yield. Here the formation of an eight-membered ring chelate (cf. **vii**) restricts **1** to a single conformation (i.e., **1b**) prior to ring closure.



(Eq. 1)

The mechanism of the dienone–phenol rearrangement dictates that exposure of **3** to acidic catalysts would produce a rearranged phenol. This was verified when dienone **3** was treated with BF_3-Et_2O to produce phenol **10**; methylation of **10** gave hydrophenanthrene **9** (Eq. 2). Moreover, only **9** was produced when excess trimethyloxonium tetrafluoroborate was used to promote the dienone–phenol rearrangement.

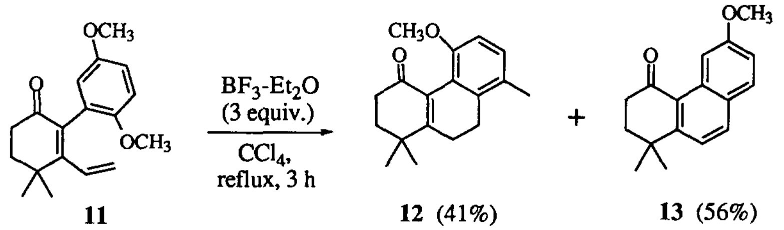


(Eq. 2)

The ability to predictably annulate a new cyclohexane ring and at the same time create a quaternary center at the ring fusion holds considerable promise for natural product synthesis. Further applications of this methodology are under investigation.

REFERENCES AND NOTES

1. The cyclialkylation of conjugated dienone **11** occurred via two conformers of **11** to produce hydrophenanthrene **12** and naphthalene **13**. For a discussion of this study, see: Majetich, G.; Liu, S.; Fang. J.; Siesel, D.; Zhang, Y. *J. Org. Chem.* **1997**, *62*, 6928.



2. a) The spectroscopic data obtained for all compounds were consistent with the assigned structures.

   b) Reaction conditions have not been optimized. c) All yields are isolated yields.

3. a) Delawanna, N. J. *J. Org. Chem.* **1955**, *20*, 401. b) Bellamy, F. D.; Du, K. *Tetrahedron Lett.* **1984**, *25*, 839.

4. Wender, P. A.; Erhardt, J. M.; Letendre, L. *J. Am. Chem. Soc.* **1981**, *103*, 2114.

5. Conjugated 2-aryl-dienones, such as **1**, require a *cisoid* conformation in order to react with the electron-rich arene moiety. The presence of alkyl substituents at C(4) causes a distinct conformational bias towards the *cisoid* conformation. For a more detailed discussion, see ref. 1.

6. Majetich, G.; Condon, S.; Hull, K.; Ahmad, S. *Tetrahedron Lett.* **1989**, *30*, 1033.

7. For the use of Lewis acids, instead of protic ones, to catalyze the dienone–phenol rearrangement, see: a) Chalais, S.; Laszlo, P.; Mathy, A. *Tetrahedron Lett.* **1986**, *27*, 2627. For recent examples of this transformation, see: b) Greca, M. D.; Fiorentino, A.; Pinto, G.; Pollio, A.; Previtera, L. *J. Org. Chem.* **1996**, *61*, 7178. c) Frimer, A. A.; Marks, V.; Sprecher, M.; Gilinsky-Sharon, P. *Ibid.* **1994**, *59*, 1831.

8. For an example of a cyclialkylation occurring at the para position of an arene to generate a spiro-cyclohexadienone *in situ* (previously described as a "Ar_1-5 participation"), followed by ring expansion via a dienone–phenol rearrangement, to generate a tetralin, see: Haddon, V. R.; Jackman, L. M. *J. Am. Chem. Soc.* **1971**, *93*, 3832.