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New Methods for the Preparation of Hydrophenanthrenes

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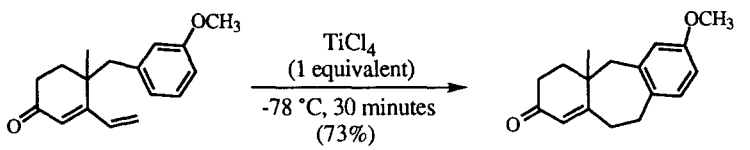
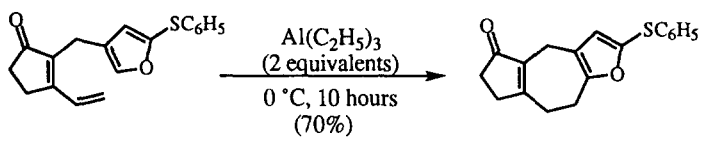
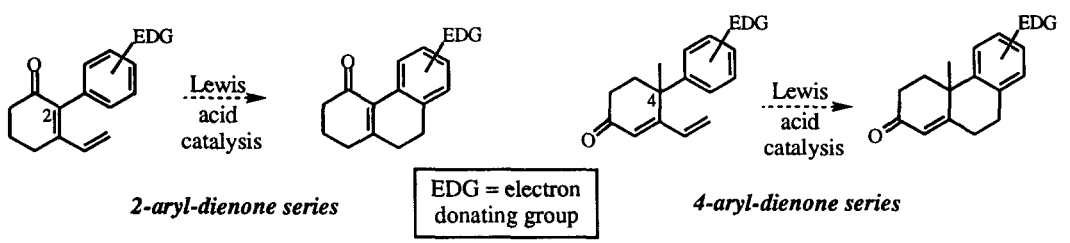
Abstract: Functionalized hydrophenanthrenes can be prepared using a cyclialkylation-based strategy. These annulations are highly dependent on the directing effects of the arene substitutents and on conformational considerations. General routes were devised for the facile preparation of the requisite cyclization precursors.

Intramolecular Friedel-Crafts alkylations, known as cyclialkylations,[1] are useful for the preparation of tricyclic compounds that have a central seven-membered ring fused to either an arene[2] or furan ring,[3] as shown below.

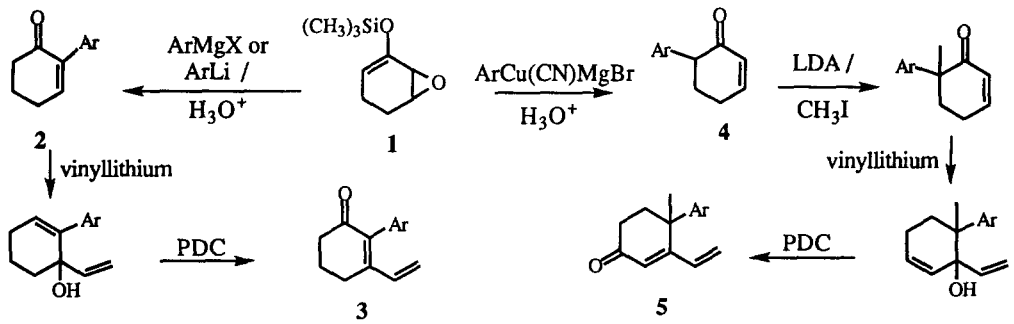




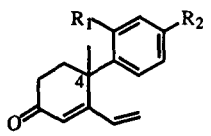
We wanted to determine whether a cyclialkylation-based strategy could also be used to make hydrophenanthrenes, as generalized below. If so, this annulation procedure would represent a new method for the formation of diterpenes, steroids and triterpenes containing a 6,6,6-fused subunit. Towards this end, we examined the cyclialkylations of a series of 2- and 4-functionalized aryl-dienones and we report our preliminary findings herein.



Research by Wender[4] and Marino,[5] coupled with our own methodology, allowed us to devise a three-step sequence for the preparation of most of the substrates used in this study.[6] In the first step, treatment of epoxide **1** with either aryl Grignard reagents or aryllithium reagents furnished 2-aryl-2-cyclohexenones in high yield (cf. **2**); alternatively, the use of aryl cuprates gave 6-aryl-2-cyclohexenones in comparable yield (cf. **4**). Previously, we reported that 3-vinyl-2-cycloalkenones can be prepared from 2-cycloalkenones in good yield by oxidizing the appropriate *bis*-allylic tertiary alcohol with pyridinium dichromate (PDC).[7] This oxidative procedure allowed the conversion of analogues of enones **2** and **4** to many of the required cyclization precursors.

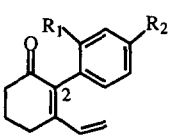


Simple aryl-dienones, such as **6** and **9**, are not sufficiently electron-rich to cyclize. Alternatively, the directing nature of the methoxy group prevents the precursors **7**, **8**, **10** and **11** from cyclizing. In substrate **7**, for example, the methoxy substituent activates positions which are geometrically precluded from intramolecular



4-arene-dienone series

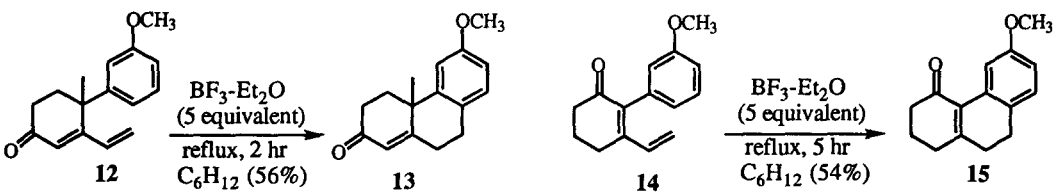
$R_1 = R_2 = H$ (**6**)
$R_1 = OCH_3$, $R_2 = H$ (**7**)
$R_1 = H$, $R_2 = OCH_3$ (**8**)



2-arene-dienone series

$R_1 = R_2 = H$ (**9**)
$R_1 = OCH_3$, $R_2 = H$ (**10**)
$R_1 = H$, $R_2 = OCH_3$ (**11**)

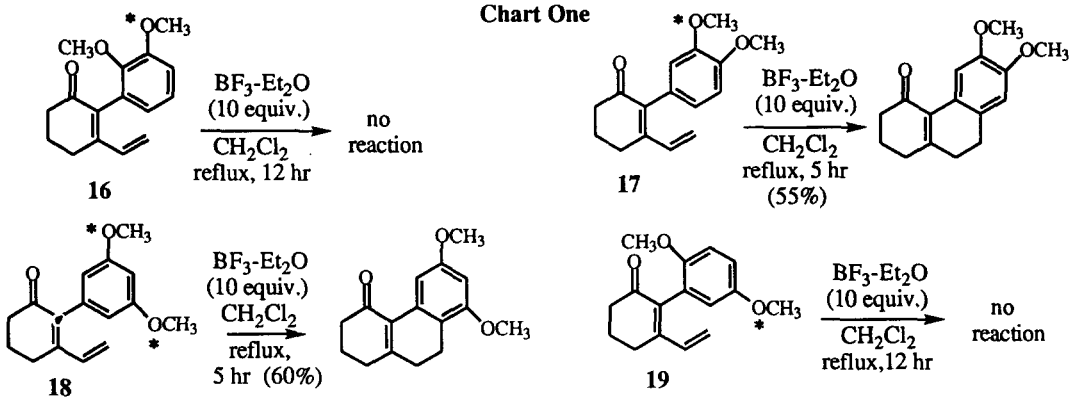
reaction with the Lewis acid-activated conjugated dienone. In contrast to these examples, treatment of aryl-dienone **12** with boron trifluoride etherate in refluxing cyclohexane (81 °C) produces enone **13** in 56% yield within two hours. 2-Aryl-dienone **14** also cyclizes under comparable conditions and yield.



Four 2-aryl-dienones with two methoxy groups were prepared using the Grignard-based protocol

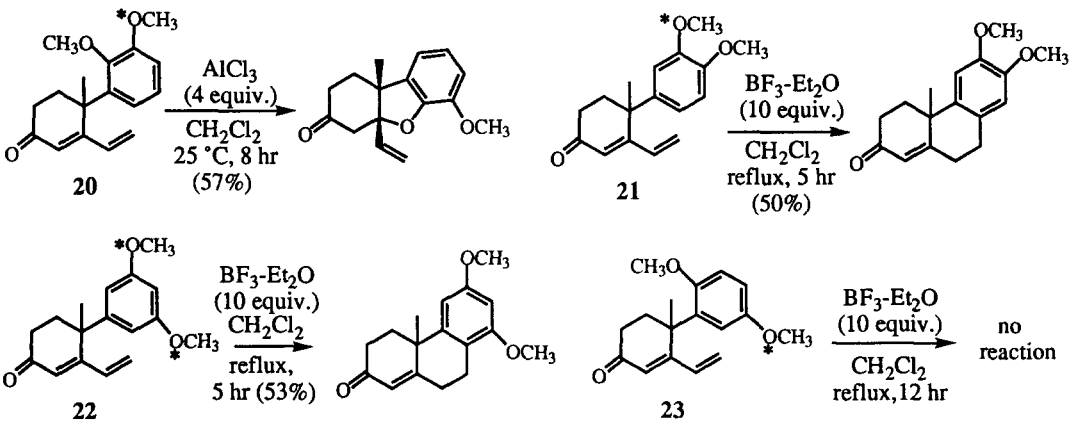
presented earlier (c.f., **1** → **2** → **3**). Each of the substrates shown in Chart One was expected to cyclize because of the favorable directing effects of the indicated (*) substituent(s); however, two substrates did not.

Chart One

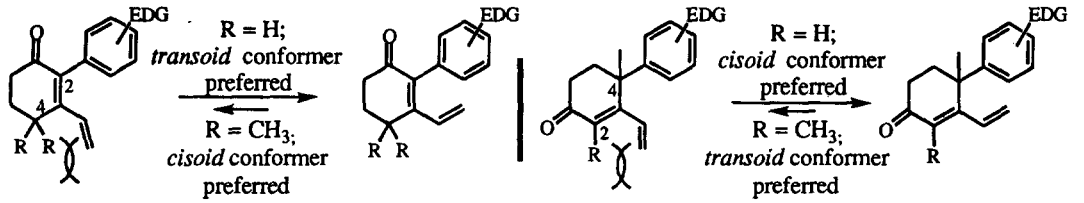


Four analogous 4-aryl-dienones were also synthesized. The cuprates required by the route presented earlier (cf. **1** → **4** → **5**) were difficult to work with. Instead, a tandem Michael addition / mixed Claisen condensation sequence, starting with the appropriately functionalized phenylacetone derivative, was employed.[8,9] Once again, two of the cyclialkylations failed despite the favorable directing effects of the methoxy substituents. Note that in the case of dienone **20**, demethylation of one of the ethers occurred, followed by ring closure.

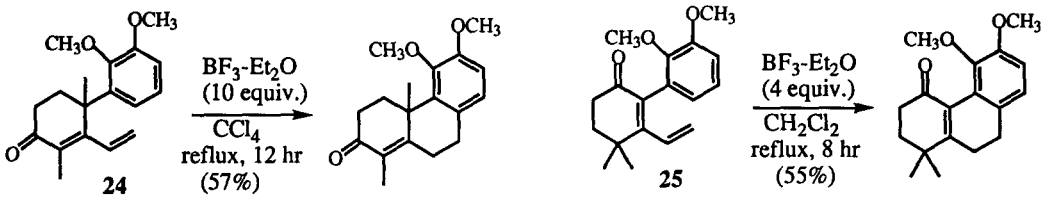
Chart Two



We reasoned that the four reactions listed in Charts One and Two which failed did so because these substrates preferred a diene conformation which precludes cyclization. This suggested that the introduction of steric hindrance at either the 4-position of a 2-aryl-dienone or at the 2-position of a 4-aryl dienone would favor



a dienone orientation leading to ring closure. The cyclialkylations of dienones **24** and **25** support this conjecture. Recall that substrates **16** and **20**, which lack these steric influences, failed to cyclize.



To summarize, we have shown that a cyclialkylation-based strategy can be used to prepare functionalized hydrophenanthrenes. These annulations occur in synthetically useful yields with electron-rich arenes and substrates in which conformational effects favor cyclization.[10]

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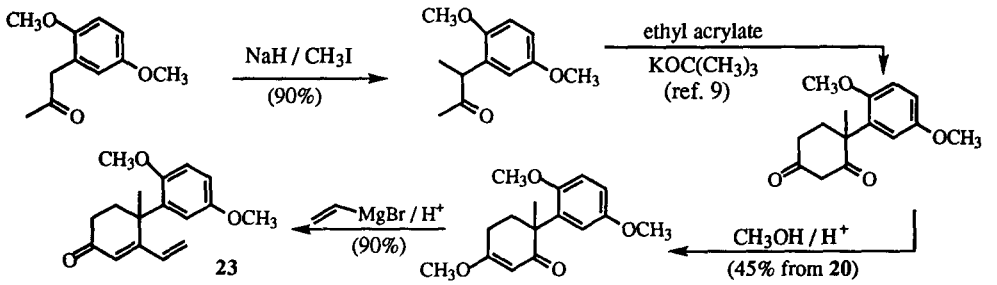
References and Notes:

1. Brunson, H. A.; Kroeger, J. W. *J. Am. Chem. Soc.* **1940**, *62*, 36.
2. Majetich, G.; Zhang, Y.; Feltman, T. L.; Belfoure, V. *Tetrahedron Lett.* **1993**, *34*, 441.
3. Majetich, G.; Zhang, Y.; Liu, S. *Tetrahedron Lett.* **1994**, *35*, 4887.
4. Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114.
5. Marino, J. P. ; Jaen, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 3165.
6. a) Spectroscopic data obtained for all new compounds were fully consistent with the assigned structures. b) All yields are isolated yields. c) Reaction conditions have not been optimized.
7. Majetich, G.; Condon, S.; Hull, K.; Ahmad, S. *Tetrahedron Lett.* **1989**, *30*, 1033.
8. The synthesis of dienone **23**, shown below, typifies this approach.



9. Zimmerman, H. E.; Pasteris, R. J. *J. Org. Chem.* **1980**, *45*, 4876.
10. This methodology has been featured in a stereoselective synthesis of the diterpenoid nimbidiol. See: Majetich, G.; Siesel, D. *SynLett.* **1995**, 0000.

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