

PROGRESS REPORT

**Coalification by Clay-Catalyzed Oligomerization of Plant
Monomers.**

July 1, 1990 to September 30, 1990

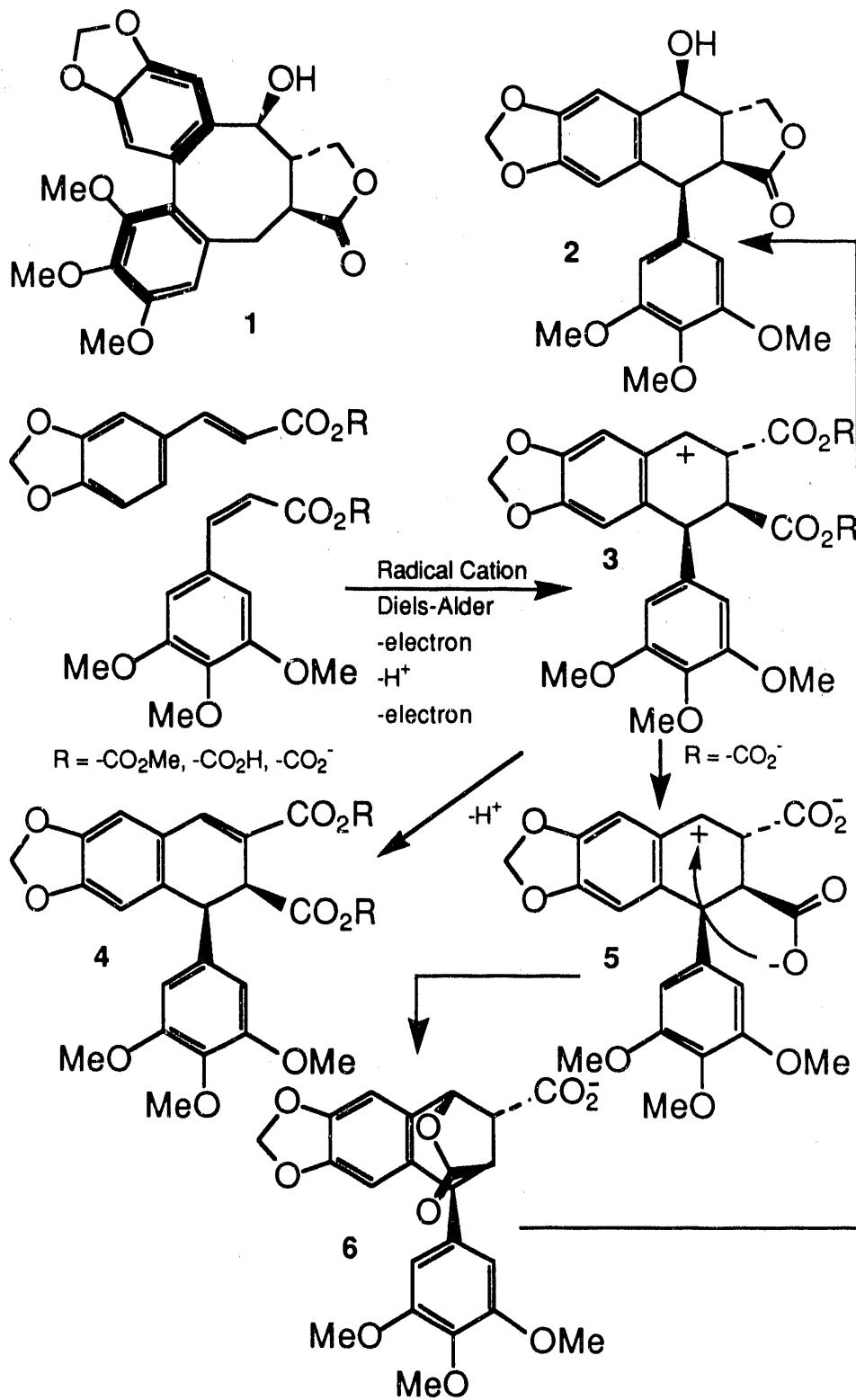
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One of the main objectives of this research program is to explore the possibility that radical cation Diels-Alder reactions are involved in the biosynthesis of lignans in plants. If this hypothesis is valid, then it should be possible to prepare representatives of the various classes of lignans under radical cation conditions. Two of the most highly sought after classes of lignans are the dibenzocyclooctadienes represented in Scheme 1 by steganol (1) and the aryltetralins represented by podophyllotoxin (2). Both of these lignans are powerful anticancer agents and have structures that might be assembled from C₆-C₃ units via radical cation processes. A possibly significant and common feature of both of these molecules is the benzylic hydroxyl group. In both of these molecules, this hydroxyl group is cis to the lactone carbonyl carbon. While this hydroxyl group might be introduced in the biosynthesis after the carbon skeleton has been constructed, we have often wondered whether this hydroxyl group was an artifact of a radical cation biosynthesis of these materials. The hypothetical mechanism by which

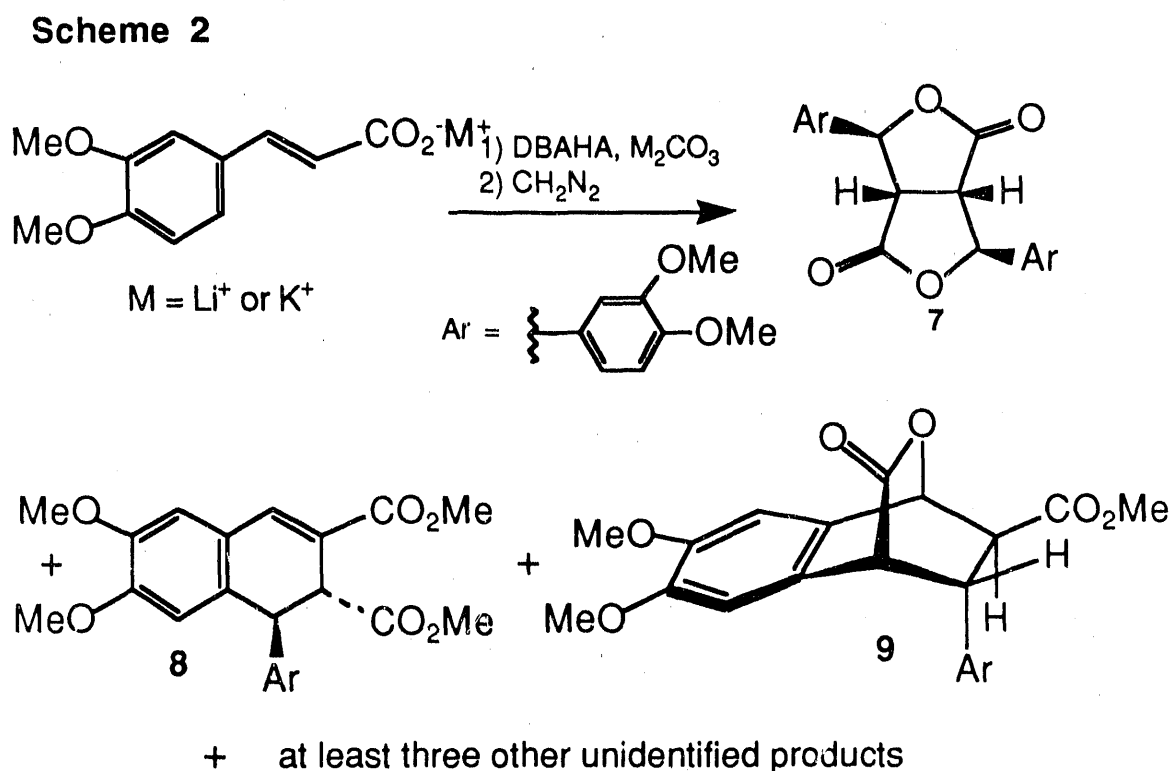
Scheme 1



this hydroxyl group might be introduced into the aryltetralins is outlined in Scheme 1. A radical cation Diels-Alder reaction between two C₆-C₃ units will afford the cation **3**. This mechanism has been detailed in many of the previous reports. Once formed, **3** might lose a proton to form the dihydronaphthalene **4** or the cation might be attacked by an oxygen nucleophile such as water to introduce the hydroxyl group in question here. With these considerations in mind, we have periodically added water and other potential oxygen nucleophiles to radical cation reactions. However, in no case have we isolated any products that contained a hydroxyl group or any other oxygen functionality in this benzylic position. With the observation of the radical cation Diels-Alder reactions of cinnamic acids and their esters, a further possibility presents itself. Perhaps this hydroxyl group might be introduced via an intramolecular lactonization between this cation center and one of the carboxylate groups in **3**. To date, we have not observed this type of reaction in the radical cation Diels-Alder reaction of cinnamic acids. We have rationalized this as being due to the poor nucleophilicity of the carboxylic acid group. On the other hand, the carboxylate anion in **5** should be a much better nucleophile than the corresponding carboxylic acid, and might trap this cation to form the lactone **6**. In a synthesis of podophyllotoxin (**2**), **6** could be easily converted to **2**, and in the hypothetical biosynthesis of **2** under consideration here, an unsymmetrical radical cation Diels-Alder reaction between a C₆-C₃ alcohol functioning as the diene and a cinnamate salt functioning as the dienophile could lead to **2** in a single step. Finally, it should be added that a related [4+4] cycloaddition between the same two C₆-C₃ components might lead to steganol (**1**) through an identical sequence of steps. Furthermore, this intramolecular delivery of the oxygen

nucleophile would establish the cis stereochemistry between the lactone carboxyl group and the hydroxyl group in both stegnosol (1) and podophyllotoxin (2).

With these correlations in mind, we have now begun to study the radical cation Diels-Alder chemistry of cinnamate salts, and the preliminary results of this work are extremely interesting (Scheme 2).

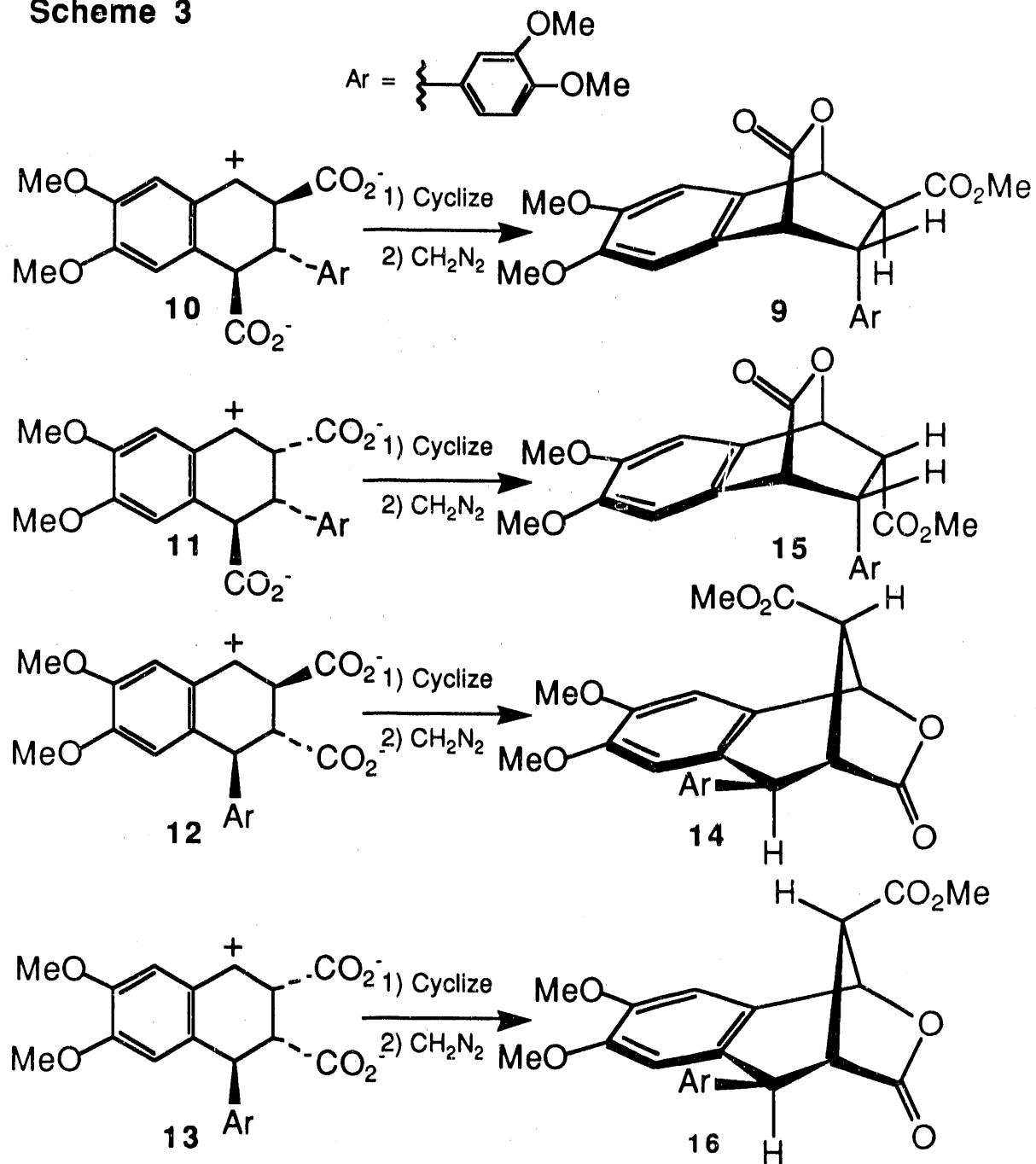


The major product of the reaction shown in Scheme 2 is the bis-lactone 7. This same product has been isolated previously by E. C. Taylor in the reaction of cinnamic acids with $Tl(OAc)_3$ and CoF_3 ,¹ and related bis-lactones have been isolated by R. Stevenson in reactions of cinnamic acids with $FeCl_3$ and oxygen.² Furthermore, it has previously been observed that heating bis-lactones related to 7 with acid leads to their conversion to dihydronaphthalenes related to 8. We also have isolated 8 from the

radical cation reaction shown in Scheme 2. Both of the bis-lactones and the dihydronaphthalenes belong to classes of natural products. The dihydronaphthalene class is found in the wood of elm trees infected with the Dutch elm disease. These observations not only represent the first demonstration that bis-lactones such as **7** can be formed via radical cation chemistry, but they also provide the first link between our radical cation work and the phenolic coupling chemistry done previously by other workers in the lignan area.

The isolation of **7** and **8** in the reaction described in Scheme 2, the known correlation between compounds related to **7** and **8** via acid-catalyzed rearrangements, and the failure of previous workers to detect products that arise from radical cation Diels-Alder reactions has caused us to question the involvement of radical cation Diels-Alder reactions in this reaction of the salts of cinnamic acid. However, at least four other products are present in this radical cation reaction mixture. Judging from HPLC, there are three closely related products, and one of these has now been isolated and its structure determined by X-ray crystallography. The structure of this material is **9** (Scheme 2), and **9** is clearly formed via a radical cation Diels-Alder reaction terminated by a cation trapping step of the type shown in Scheme 1. Therefore, there can be little doubt that radical cation Diels-Alder chemistry is active in these cinnamic acid salt systems. Unfortunately, **9** is not one of the lactones that correlates with the naturally occurring aryltetralins. If one takes into consideration the known stereochemistries of this type of radical cation Diels-Alder reaction, there are four aryltetralin cations that might be formed: **10**, **11**, **12**, and **13** shown in Scheme 3. The cation **10** should afford the lactone **9** and this cation belongs to the regiogalbulin family which is not known in

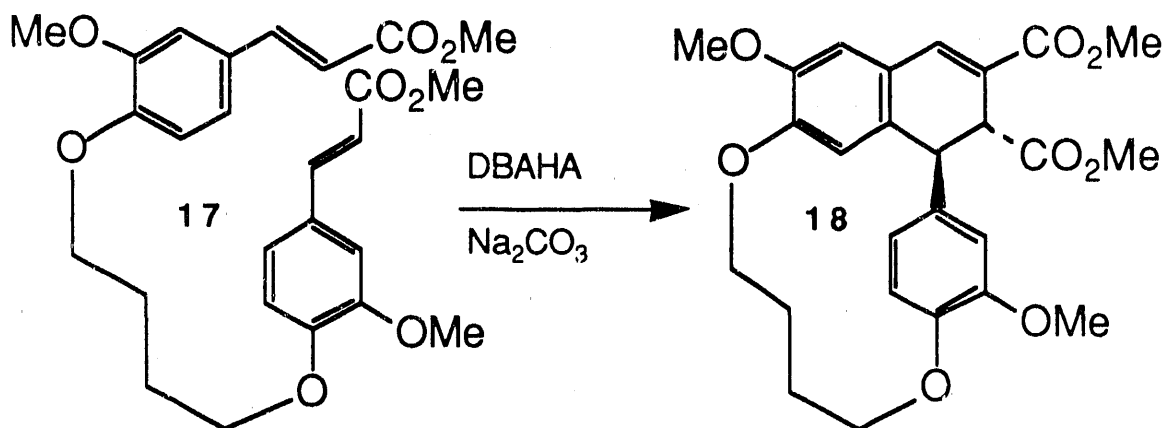
Scheme 3



nature. Similarly, cation **11** belongs to the regioisogalbulin family which also is not known in nature. However, cations **12** (galbulin family) and **13** (isogalbulin family) would provide naturally occurring stereochemistries.

The cation **12** would most closely correlate with the stereochemistry of podophyllotoxin (**2**). The difference between the stereochemistry of the lactone derived from **12** (**14**) and that of **2** is that they are epimeric at the carbon atom bearing the aryl group. Presumably this stereochemistry could be adjusted as outlined in Scheme 1. Finally, we are continuing our efforts to determine the structures of the remaining products in this reaction in the hope that we can find the other lactones **14**, **15**, or **16** shown in Scheme 3.

In an extension of our previous work with tethered cinnamates, we have returned to the tethered molecule **17** (Scheme 4) and are in the **Scheme 4**



+ Two product of unknown structure

process of reexamining its radical cation Diels-Alder chemistry in the presence of Na_2CO_3 . The addition of Na_2CO_3 eliminates or greatly reduces the acid-catalyzed reactions described in our previous report, and eliminates the formation of the regioisomers. Consequently, this reaction affords only three products, one of which has been isolated, and at this time, has tentatively been assigned the dihydronaphthalene structure **18**. When we have completed characterizing the products of this reaction, we

intend to make the disalt of this tethered system and examine its radical cation chemistry in hopes of observing lactone formation of the type described above.

Finally, we have just begun to investigate the radical cation chemistry of polycyclic aromatic hydrocarbons in an effort to find chemistry that will produce the coupling of these aromatic molecules. Our first effort in this area has been to look at naphthalene itself. Treatment of naphthalene with DBAHA seems to produce products of very similar polarity to naphthalene, and we are in the process of attempting to isolate these materials. When this initial study is complete, we shall examine the radical cation chemistry of methoxynaphthalenes related to those described in earlier reports, since methoxylated naphthalenes should provide better models for the oligomerization of the naturally occurring lignans to lignins.

References:

- 1) Taylor, E. C.; Andrade, J. G.; Rall, G. J. H.; Steliou, K.; Jagdmann, Jr., G. E. *J. Org. Chem.* **1981**, *46*, 3078.
- 2) Ahmed, R.; Lehrer, M.; Stevenson, R. *Tetrahedron Letters* **1973**, *10*, 747.

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