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Synthesis of the Spirocyclic Cyclohexadienone Ring System of the Schiarisanrins

Robert S. Coleman,* Jason M. Guernon, and Jason T. Roland

Department of Chemistry, The Ohio State University, 100 West 18th Avenue, Columbus, Ohio 43210-1185

coleman@chemistry.ohio-state.edu

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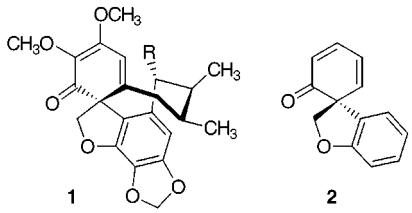
ABSTRACT



Studies on the synthesis of the spirocyclic cyclohexadienone ring system 2 of the schiarisanrin family of natural products 1 are described and were based on the Lewis acid-promoted C-alkylation of the corresponding phenolic precursor.

Schiarisanrins A−D (**1a**−**d**) are a structurally unique family of homolignan natural products isolated from the fruit of the Taiwanese medicinal plant *Schizandra arisanensis* (*Schizandraceae*)[1] and are related to the dibenzocyclooctadiene lignans (Figure 1).[2,3] Schiarisanrin C exhibits interesting cytotoxicity against several standard cell lines at μg/mL levels. A truly unique feature of these agents is the unprecedented 2,4-cyclohexadienone-6-spiro-3′-(2′,3′-dihydrobenzo[*b*]furan) substructure **2**. This spirocyclic ring system could arise biosynthetically by oxidation of the methyl ether precursor **4** to the oxonium ion **3** (or its equivalent radicaloid species[4]), which undergoes spirocyclization by nucleophilic attack of the adjacent phenolate to afford the substructure **2** (Scheme 1).

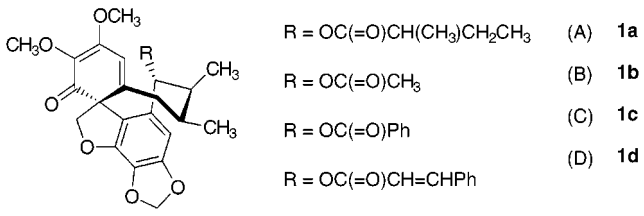
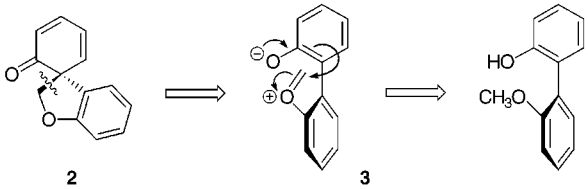


Figure 1. Structures of the schiarisanrins.

Scheme 1. Formation of the Spirocyclic Ring System



Taking this biosynthetic clue from nature, we set out to investigate the ionic version of this bond formation strategy.

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(3) For recent synthetic work on dibenzocyclooctadiene lignans, see: Dhal, R.; Landais, Y.; Lebrun, A.; Lenain, V.; Robin, J.-P. *Tetrahedron* **1994**, *50*, 1153−1164. Carroll, A. R.; Taylor, W. C. *Aust. J. Chem.* **1994**, *47*, 937−941. Warshawsky, A. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1990**, *112*, 8090−8099.

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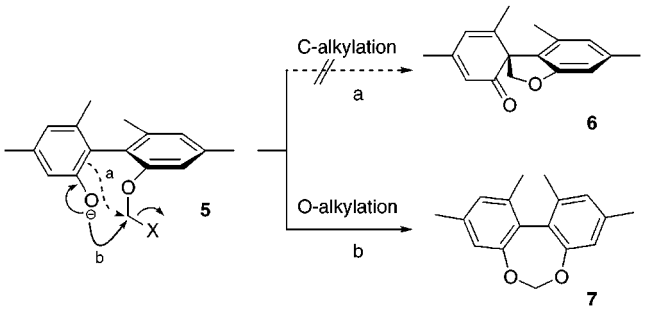
Formally, our synthetic strategy amounts to an intramolecular C-alkylation of a phenolate ion by way of a 5-endo-trig ring closure. C-Alkylation of phenols is not common in the literature, and the most relevant example of an intramolecular version was found in the recent work from Mukherjee and co-workers in their synthesis of (±)-isolongifolene.[5] In their system, there is no possibility of competing O-alkylation. 2,4-Cyclohexadienones bearing 6,6-dialkyl substitution are largely unknown.[6]

In our initial examination of this bond construction pathway (Scheme 2), we prepared simple 3,3′,5,5′-tetra-

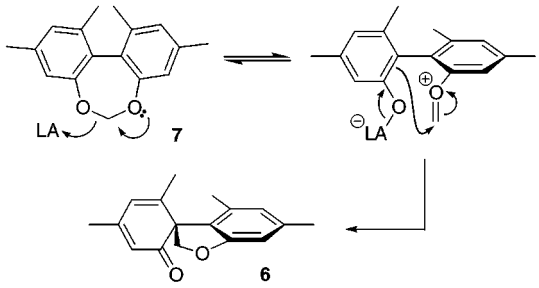
Scheme 2. C- versus O-Alkylation of Phenolate



methyl-2,2′-biphenol systems **5** with one phenolic oxygen bearing an oxonium ion precursor (e.g., X = Cl, S(O)Ph, OCH_3, $OCH_2CH_2OCH_3$). In all cases, once a phenolic oxygen or the corresponding phenolate anion was liberated from the appropriately protected precursor, rapid O-alkylation via pathway b proceeded to afford the dibenzodioxepin **7**, at the expense of the desired C-alkylation pathway a to spirocycle **6**. No evidence was observed for formation of the cyclohexadienone product **6** with X = Cl (basic conditions), S(=O)Ph (AcCl), OCH_3 (Lewis acid), or $OCH_2CH_2OCH_3$ (Lewis acid).

Assuming that the O-alkylation could be reversible but that the corresponding C-alkylation pathway would not be, we examined the Lewis acid-promoted conversion of dibenzodioxepin **7** to the presumed ring-opened oxonium ion, which could cyclize by a 5-endo-trig pathway to the desired spirocyclic product **6** (Scheme 3). We examined this reaction pathway with the model system **7**, where the aryl methyl

Scheme 3. Lewis Acid-Promoted Acetal Cleavage/ C-Alkylation



substituents served as surrogates of the four-carbon chain of the natural products and provided an impediment to dimerization of the cyclohexadienone product.[7]

A variety of Lewis acids promoted this process effectively, many of them in high yield (Table 1). For example, $AlCl_3$ in CH_2Cl_2 afforded **6** in 95% yield, and the cyclization was equally successful with $EtAlCl_2$ although with a decreased rate of cyclization.

Table 1. Yields of Spirocyclization Reaction of **7**

Lewis acid	reaction conditions	yield of **6** (%)
$AlCl_3$	1.25 equiv, CH_2Cl_2, 25 °C, 5 min	95
$EtAlCl_2$	1.25 equiv, CH_2Cl_2, 25 °C, 24 h	91
Et_2AlCl	1.25 equiv (5 × 0.25 equiv at 4 h intervals), CH_2Cl_2, reflux, 30 h	65
Me_3SiOTf	1.25 equiv, CH_2Cl_2, 25 °C, 48 h	74
$SnCl_4$	1.25 equiv, CH_2Cl_2, 25 °C, 36 h	56
$FeCl_3$	1.25 equiv, CH_2Cl_2, 25 °C, 30 min	53

With Et_2AlCl, the cyclization was significantly slower, and under carefully controlled reaction conditions with incremental addition of Et_2AlCl, the yields of **6** were modest. Me_3SiOTf, $SnCl_4$, and $FeCl_3$ were less than optimal. Protic acids such as camphorsulfonic acid and the Lewis acids $BF_3{\cdot}OEt_2$, $TiCl_4$, $LiClO_4$, and $LiBF_4$ did not promote the cyclization.

The ^1H NMR of **6** was indicative of the rigid spirocyclic structure, and the diastereotopic furan methylene protons were observed as a characteristic AB pattern. Irradiation of the cyclohexadienone C5-methyl group that is proximal to the furan resulted in a reciprocal NOE of the *syn*-methylene hydrogen. Single-crystal X-ray analysis confirmed the spirobicyclic structure (Figure 2).

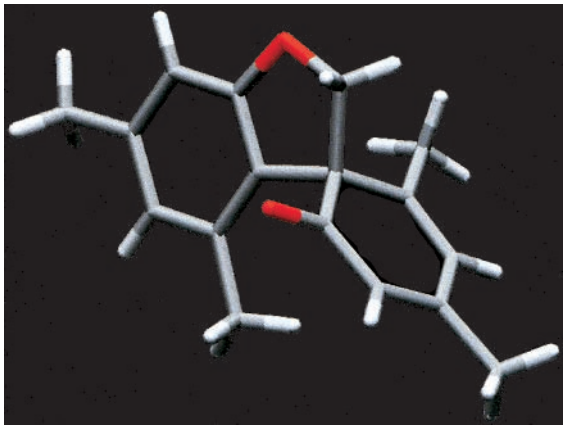
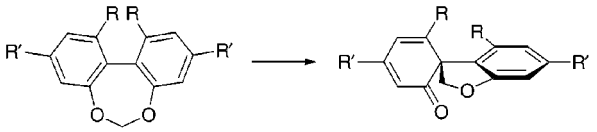


Figure 2. X-ray crystal structure of spirobicyclic cyclohexadienone **6** (hydrogens added for clarity).

The presence or absence of the aryl methyl groups was found to exert a significant influence on the success or failure

of the spirocyclization (Scheme 4). With two methyl groups ortho to the biaryl bond (**8**; R = CH_3, R′ = H), the cyclization proceeded with modest yield (60%) to afford **11**

Scheme 4. Effect of Substituents on Cyclization

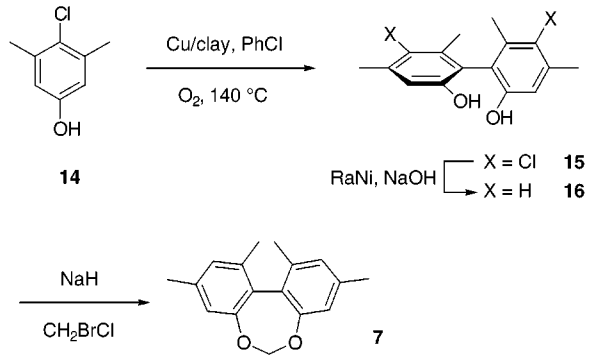


8	R = CH_3; R′ = H	**11**
9	R = H; R′ = CH_3	**12**
10	R = R′ = H	**13**

and was accompanied by small amounts of the corresponding bis-phenol. With two methyl groups para to the biaryl bond (**9**, R = H, R′ = CH_3), no cyclization to **12** was observed but only small amounts of the bis-phenol were present; the multiple products formed were unidentifiable. In the absence of all four methyl groups (**10**, R = R′ = H), the cyclization to **13** failed completely, and the corresponding bis-phenol was isolated in 25% yield, among numerous unidentifiable products. The origin of this effect may arise either from decreased stability of less substituted cyclohexadienone products as in **12** or from an effect similar to the Thorpe−Ingold effect where the ortho methyl groups preorganize the system for cyclization as in **8** → **11**.

Construction of the tetramethyldibenzodioxepin system **7** used in these studies (Scheme 5) relied on the Cu-promoted

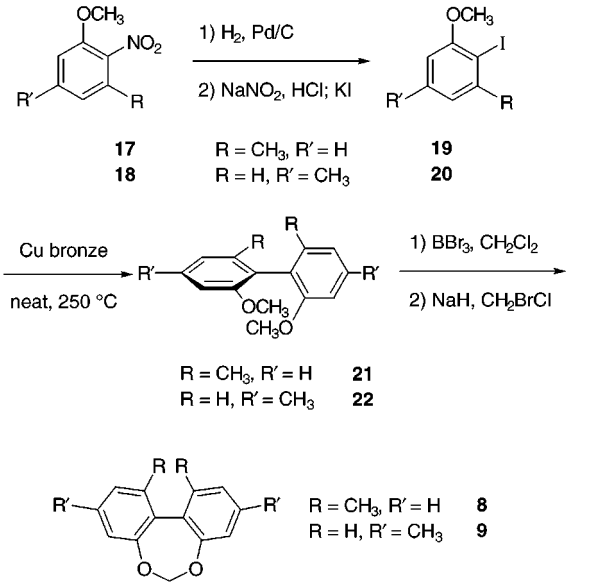
Scheme 5. Synthesis of Tetramethylbenzodioxepin Precursor



phenoxy radical coupling[8] of commercially available phenol **14** (70%) followed by removal of the aryl chlorides of **15** with Raney nickel[9] to afford **16** (96%). Methylene introduction with CH_2BrCl and NaH afforded **7** (64%).[10] The 4-chloro substituent was used to block the *p*-phenoxy radical coupling pathway[11] in the dimerization of **14**.

The other spirocyclization substrates were prepared as illustrated in Scheme 6 starting from the corresponding

Scheme 6. Synthesis of Dibenzodioxepin Precursors



17	R = CH_3, R′ = H	**19**
18	R = H, R′ = CH_3	**20**

R = CH_3, R′ = H	**21**
R = H, R′ = CH_3	**22**

R = CH_3, R′ = H	**8**
R = H, R′ = CH_3	**9**

nitroaromatic systems **17** and **18**. Nitro to amine reduction to the anilines[12] followed by diazotization and Sandmeyer reaction to the iodide[13] afforded aryl iodides **19**[14] and **20** in 84% and 78%, respectively, for the two steps. Copper bronze coupling[15] was performed in the absence of solvent, and although the yields to biaryls **21** and **22** were quite modest (15−20%), suitable quantities of these biaryl systems could be isolated for subsequent studies. Demethylation in the presence of boron tribromide (91% for **21**; 85% for **22**) afforded the corresponding bis-phenols[16] and methylenation with CH_2BrCl and NaH afforded the dibenzodioxepins **8**

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(53%) and **9** (73%). These yields were not optimized. The parent dibenzo[*d*,*f*][1,3]dioxepin (**10**) was prepared by simple phenoxy radical coupling followed by methylenation as above.

We have described a synthetic approach to the spirobicyclic ring system of the schiarisanrin family of homolignan natural products that was based on a Lewis acid-promoted intramolecular C-alkylation of a phenol. Cyclization yields were near quantitative when methyl groups were present on the aromatic systems ortho to the biaryl bond.

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Supporting Information Available: Experimental procedures and spectral characterization of synthetic intermediates and products. This information is available free of charge via the Internet at http://pubs.acs.org.

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