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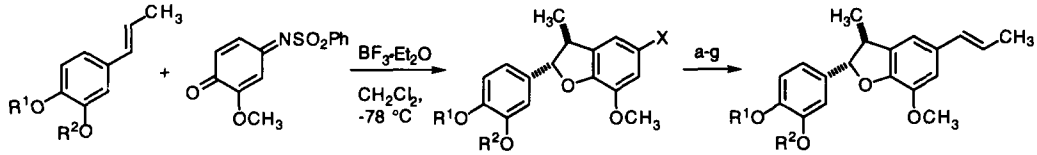
Synthesis of (±)-Licarin B and Eupomatenoids-1 and -12: A General Approach to 2-Aryl-7-alkoxy-benzofuranoid Neolignans

Thomas A. Engler* and Wenying Chai

Department of Chemistry
University of Kansas
Lawrence, Kansas 66045-2506

Abstract: *New syntheses of the title compounds are described using Lewis acid-promoted reactions of styrenes with N-phenylsulfonyl-1,4-benzoquinone monoimines to regioselectively form the 2-arylbenzofuranoid ring system followed by conversion of the aromatic N-phenylsulfonyl moiety into a propenyl substituent.*

(±)-Licarin B (**9a**) and eupomatenoids-1, -12 (**11a/b**) are benzofuranoid neolignans possessing alkoxy substituents at C-7.[1] Members of this class of natural products show varied biological activity as antibacterial, cytotoxic, antiproliferative and potential immunosuppressant agents, and insecticides.[2] Recently, we reported an efficient and regioselective method for synthesis of highly substituted 2-aryl-2,3-dihydrobenzofurans by Lewis acid-promoted reactions of styrenes with 1,4-benzoquinones.[3a] Unfortunately, 2-aryl-2,3-dihydrobenzofurans bearing C-7 alkoxy groups were not generally accessible via this methodology.[3b] Herein we report an alternative method for synthesis of this substructure culminating in the total synthesis of the title compounds.



1a, $R^1/R^2=CH_2$
1b, $R^1=R^2=CH_3$

2

3, X=$NHSO_2Ph$ **6**, X=NH_2
4, X=$N(SO_2Ph)BOC$ **7**, X=$N{=}NNEt_2$
5, X=NHBOC **8**, X=I

9

For **3-9**: **a**, $R^1/R^2=CH_2$; **b**, $R^1=R^2=CH_3$

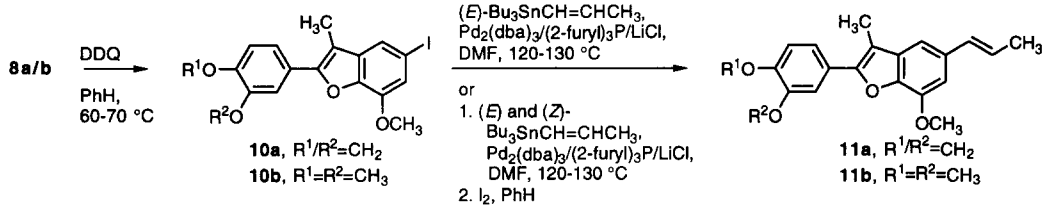
a) KOtBu/$(tBuO_2C)_2O$, THF, 60-70 °C. b) Na/anthracene, THF, 23 °C. c) F_3CCO_2H, CH_2Cl_2, 23 °C. d) $NaNO_2$/50% aq HOAc, 0 °C e) $HNEt_2/K_2CO_3$, H_2O, 0 °C. f) $Me_3SiCl/NaI/CH_3CN$. g) (*E*)-$Bu_3SnCH{=}CHCH_3$/ $Pd_2(dba)_3$/(2-furyl)$_3P$/LiCl, DMF, 120-130 °C.

Our point of entry for these syntheses were $BF_3{\cdot}Et_2O$-promoted cycloadditions of styrenes **1** with quinone monoimide **2** which afforded dihydrobenzofurans **3**, as ~95:5 mixtures of trans:cis isomers, in 86-88% yields.[3c,4] In these experiments, small amounts of the regioisomeric *N*-phenylsulfonyl-2-aryl-3-methyl-5-hydroxy-2,3-dihydroindoles were also found in 2-10% yields. Because the free amine **6** proved difficult to handle, desulfonation of **3** was effected by first conversion to t-Boc-sulfonamide **4**[4] followed by reductive desulfonation[5] which gave t-Boc-amines **5**, again as 95:5 trans:cis mixtures, in 61-81% yields for the two steps. Removal of the Boc group provided the unstable amines **6**, which were directly subjected to diazotization followed by treatment with $HNEt_2$.[6] The again difficult to purify product triazenes **7** were recovered by simple extraction (Et_2O) and the crude products were reacted directly with Me_3SiCl/NaI to produce ~10:1 trans:cis mixtures of aryl iodides **8** in 40-60% overall yields from **5**. Recrystallization afforded nearly pure (>97%) trans-**8**.[4] Stille coupling[7] of iodides **8** with (*E*)-propenyltributyltin[8] gave (±)-licarin B (**9a**) and analog **9b**[4] in 84-86% yield. Although amides **3** and **5** could be obtained free of their cis-dihydrobenzofuran isomers by recrystallization, in the conversion of pure trans-**5**[4] to iodides **8** some epimerization was observed resulting in ~10:1 mixtures of trans-**8**:cis-**8**.

Because of the expense of pure (*E*)-1-bromopropene, the starting material for preparation of (*E*)-propenyltributyltin,[8] reactions of mixtures of (*E*)- and (*Z*)-propenyltributyltin in the Stille-coupling step with **8a**

were also explored. The isomeric mixtures of propenyl-tin reagents were readily available from inexpensive mixtures of (*E*)- and (*Z*)-1-bromopropene (2:3),[8] and the coupling with **8a** afforded the propenyl-dihydrobenzofuran product as a 3:2 (*E*):(*Z*) mixture of double bond isomers. Simple treatment of this mixture with I_2 in benzene at rt effected clean and complete isomerization to the (*E*)-isomer **9a**.

For synthesis of eupomatenoids-1 and -12 (**11a/b**), DDQ oxidation of iodides **8a/8b** afforded benzofurans **10a/b**[4] in 73% yields, and Stille coupling of these iodo-benzofurans with (*E*)-1-propenyltributyltin gave **11a/b** in 97-98% yields. Again, Stille coupling of **10b** with (*E*):(*Z*) mixtures of propenyltributyltin followed by treatment of the mixture of double bond isomers with I_2/PhH gave (*E*)-**11b**[4] in 90% overall yield. Attempted DDQ oxidations of **9** to **11** failed due to competing oxidation of the propenyl side chain.[1f]



This approach holds considerable promise for synthesis of other similarly substituted 2-arylbenzofuranoid neolignans.[1] Although the conversions of sulfonamides **3** to iodides **8** entail a number of steps, the individual steps are generally efficient, some of the intermediates are not isolated, and the final products are easily purified. Indeed, the sequence **5** -> **8** can be effected in a matter of hours.[9]

References and Notes

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4. This compound was identified by high field (500/125 MHz) $^1H/^{13}C$ NMR, IR, and mass spectra, including HRMS and/or combustion analysis, on chromatographically homogeneous material.

5. For a similar desulfonation procedure, see Tian, X.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc.* **1995** *117*, 3643-3644. A number of methods for direct desulfonation of **3** to **6** were examined without success, most likely due to our inability to purify the product (for a summary, see Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley-Interscience: New York, 1991).

6. Ku, H.; Barrio, J.R. *J. Org. Chem.* **1981** *46*, 5239-5241.

7. Numerous recipes for these couplings have been reported for specific applications. Similarly, the conditions used herein were developed empirically after considerable experimentation. For leading references and helpful discussions, see a) Echavarren, A.M.; Stille, J.K. *J. Am. Chem. Soc.* **1987** *109*, 5478-5486. b) Kalivretenos, A.; Stille, J.K.; Hegedus, L.S. *J. Org. Chem.* **1991** *56*, 2883-2894. c) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991** *113*, 9585-9595. d) Hegedus, L.S. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: Chichester, England, 1994; Chapter 5. e) Ciattini, P.G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1994** *35*, 2405-2408.

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