A Convergent Route to Dihydrobenzofuran *Neolignans* via a Formal 1,3-Cycloaddition to Oxidized Phenols

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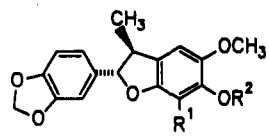
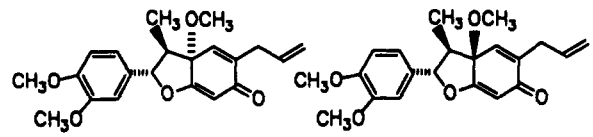
Summary: Oxidation of *p*-methoxy-substituted phenols with iodobenzene bis-trifluoroacetate in the presence of electron-rich styrene derivatives affords *trans*-dihydrobenzofurans stereoselectively.

Neolignans are a group of secondary plant metabolites structurally characterized by the presence of two arylpropanoid units.[1,2] One class of this group possesses the dihydrobenzofuran skeleton, **1a–d**, **2a,b**, all with trans stereochemistry. Of special biological interest is *kadsurenone*,[1e] **2a**, a potent and specific platelet-activating factor (PAF) antagonist.[3] Three basic approaches have been used in the preparation of these dihydrobenzofuran structures. One involved acid-catalyzed cycloaddition reactions of styrenes and quinone monoketals,[4] the second employed an abnormal Claisen arrangement of phenol allyl ether,[5] and the third used the Lewis acid, Ti(IV), catalyzed cycloaddition of benzoquinones with styrene derivatives.[6] We report herein a mild, oxidative method for preparation of the dihydrobenzofuran nucleus, the application of this chemistry to a synthesis of **1a**, and a formal synthesis of **2a**, *kadsurenone*, and *denudatin B*,[7] **2b**.

Our interest in carbon–carbon bond-forming reactions from trapping of anodically[8] and chemically[9] oxidized phenols with olefins led us to examine the oxidation of phenols in the presence of substituted styrene derivatives. The addition of iodobenzene diacetate, **3a**, to a mixture of 3,4-dimethoxyphenol, **5**, and (*E*)-3,4-dimethoxypropenylbenzene, **4** (4 equiv),[10] in acetonitrile at room

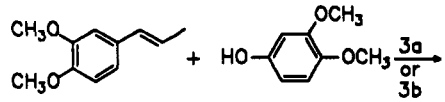


1a, $R^1 = H$; $R^2 = C_3H_5$
b, $R^1 = CH_2CH{=}CH_2$; $R^2 = H$
c, $R^1 = CH_2CH{=}CH_2$; $R^2 = CH_3$
d, $R^1 = R^2 = H$

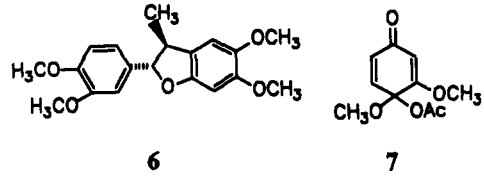


2a, *Kadsurenone* **2b**, *Denudatin B*

temperature resulted in the isolation of **6** (24%). The *trans*-dihydrobenzofuran structure **6** was strongly suggested by its ^1H NMR spectrum (see the supplementary material). Firm evidence for this structure is presented later. The monoketal derivative **7**, obtained in 24% yield from oxidation of **5** with **3a** in acetonitrile, is stable *under the reaction conditions* and thus itself is not an intermediate in this particular oxidation.



4 **5**



6 **7**

One possible factor contributing to the low yield of **6** was reaction of acetic acid with the oxidized phenol intermediate. Thus, iodobenzene bis(trifluoroacetate),[11] **3b**, was investigated as the oxidant since the generated trifluoroacetic acid would be a poorer nucleophile and this side reaction would be less important. Indeed, oxidation with iodobenzene bis(trifluoroacetate) under essentially the same conditions gave **6** (65% yield). The subsequent reactions reported herein were performed with both iodobenzene diacetate and iodobenzene bis(trifluoroacetate), with high yields always observed with the latter reagent.

This oxidative carbon–carbon bond-forming reaction occurs with a number of *p*-methoxy-substituted phenols. Thus, oxidation of *p*-methoxyphenol (**8a**), 2-allyl-4-meth-

(1) (a) Lima, O. A.; Gottlieb, O. R.; Magalhaes, M. T. *Phytochemistry* **1972**, *11*, 2031. (b) von Bulow, M. V.; Franca, N. C.; Gottlieb, O. R.; Suarez, A. M. P. *Phytochemistry* **1973**, *12*, 1805. (c) Gottlieb, O. R.; da Silva, M. L.; Ferreira, Z. S. *Phytochemistry* **1975**, *14*, 1825. (d) Aiba, C. J.; Fernandes, J. B.; Gottlieb, O. R.; Sores Maia, J. G. S. *Phytochemistry* **1975**, *14*, 1597. (e) Shen, T. Y.; Hwang, S.-B.; Chang, M. N.; Doeber, T. W.; Lam, M.-H. T.; Wu, M. S.; Wang, X.; Han, G. Q.; Li, R. Z. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 672. (f) Iida, T.; Ichino, K.; Ito, K. *Phytochemistry* **1982**, *21*, 2939.

(2) For a discussion of the biosynthesis of *neolignans*, see: (a) Gottlieb, O. R.; *Phytochemistry* **1972**, *11*, 1537. (b) Angle, S. R.; Turnbull, K. D. *J. Am. Chem. Soc.* **1990**, *112*, 3698 and references cited therein.

(3) (a) Demopoulos, C. A.; Pinckard, R. N.; Hanahan, D. J. *J. Biol. Chem.* **1979**, *254* 9355. (b) Pinkcard, R. N.; McManus, M. L.; Hanahan, D. J. *Adv. Inflam. Res.* **1982**, *4*, 147. (c) Vargaftig, B. B.; Benveniste, J. *Trends Pharmacol. Sci.* **1983**, 341. (d) Snyder, F. *Med. Res. Rev.* **1985**, *5*, 107. Venuti, M. C. *Annu. Rep. Med. Chem.* **1985**, *20*, 193.

(4) (a) Buchi, G.; Mak, C.-P. *J. Am. Chem. Soc.* **1977**, *99*, 8073. (b) Buchi. G.; Chu, P.-S. *J. Org. Chem.* **1978**, *43*, 3717. See also: (c) Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1983**, *24*, 5011; (d) Mortlock, S. V.; Seckington, J. K.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* 1988, 2305.

(5) (a) Ponpipom, M. M.; Yue, B. Z.; Bugianesi, R. L.; Brooker, D. R.; Chang, M. N.; Shen, T. Y. *Tetrahedron Lett.* **1986**, *27*, 309. (b) For the original report of this rearrangement see: Schmid, E.; Frater, G.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1972**, *55*, 1625.

(6) (a) Engler, T. A.; Combrink, K. D.; Ray, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 7931. (b) Engler, T. A.; Combrink, K. D.; Takusagawa, F. *J. Chem. Soc., Chem. Commun.* **1989**, 1573. (c) Engler, T. A.; Reddy, J. P.; Combrink, K. D.; Vander Velde, D. *J. Org. Chem.* **1989**, *55*, 1248. (d) Engler, T. A.; Letavic, M. A.; Combrink, K. D.; Takusagawa, T. *J. Am. Chem. Soc.* **1990**, *55*, 5810 and references cited therein.

(7) For a synthesis of *denudatin B*, see ref 4c.

(8) Morrow, G. W.; Swenton, J. S. *Tetrahedron Lett.* **1987**, *28*, 5445. Morrow, G. W.; Chen, Y.; Swenton, J. S. *Tetrahedron*, in press.

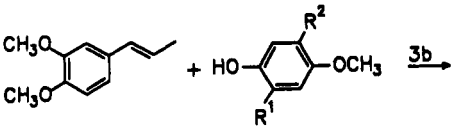
(9) Callinan, A.; Chen, Y.; Morrow, G. W.; Swenton, J. S. *Tetrahedron Lett.* **1990**, *31*, 4551. For older examples of iodobenzene diacetate and iodobenzene bis(trifluoroacetate) oxidation, see references cited therein.

(10) Four equivalents of the styrene derivative was used throughout these studies, allowing a convenient purification of the product and recovery of unreacted styrene by silica gel chromatography.

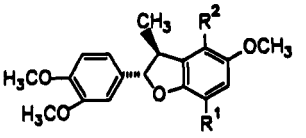
(11) Loudon, G. M.; Radhakrishna, A. S.; Almond, M. R.; Blodgett, J. K.; Boutin, R. H. *J. Org. Chem.* **1984**, *49*, 4272.

0022-3263/91/1956-1979$02.50/0

oxyphenol (**8b**), and 2-allyl-4-methoxy-5-chlorophenol[12] with iodobenzene bis(trifluoroacetate) in the presence of 4 furnished **9a–c** as shown below. We were not able to isolate an analogous product using *m*-methoxyphenol, although a 4-allyl substituent on 3-oxygenated phenols did furnish the cycloaddition product, vide infra.



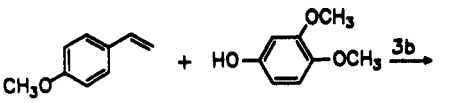
4 **8a**, $R^1 = R_2 = H$
8b, $R^1 = C_3H_5$; $R^2 = H$
8c, $R^1 = C_3H_5$; $R^2 = Cl$



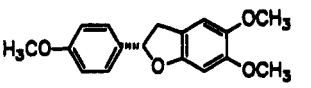
9a (71%)
9b (68%)
9c (40%)

Although the detailed steps in the cycloaddition are unknown, the reaction is not stereospecific. Photoisomerization of **4** furnished a 40:60 mixture of the trans/cis isomer from which the pure cis isomer could be obtained in >98% purity.[14] Oxidation of a mixture of **5** and the cis isomer of **4** using **3b** as oxidant furnished **6** (23% yield); a cis adduct could not be isolated from the reaction mixture.[15] The lower yield for reaction of the cis versus the trans isomer probably reflects the importance of the electron-donating character of the benzene ring on the reaction. Models suggest that the methyl group in the cis isomer sterically interferes with the coplanarity of the aromatic ring with the double bond. This is supported by the lower intensity of the long wavelength transition in the ultraviolet spectrum of the cis isomer of **4** versus **4**. Such a barrier to coplanarity of the *p*-methoxy-substituted ring and styrene double bond would make the double bond less nucleophilic; thus, side reactions would consume the oxidized phenol intermediate. The effect of substituents on the styrene double bond has not been studied extensively, but *p*-methoxystyrene does furnish the corresponding dihydrobenzofuran **11** (34% yield) using **3b** as oxidant.

Additional research needs to be performed before the steps in the reaction can be defined more clearly. Similar dihydrobenzofurans have been produced from reacting electron-rich olefins with the following: quinone monoketals using a strong acid catalyst (2,4,6-trinitrobenzenesulfonic acid, trifluoromethanesulfonic acid, etc.),[2b,4a,b] *p*-quinol derivatives and methanesulfonyl chloride,[4d] and quinones and titanium tetrachloride.[6] Except for the latter

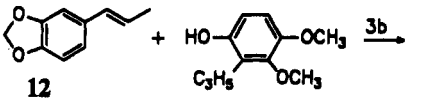


10 **5**

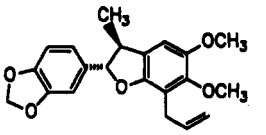


11

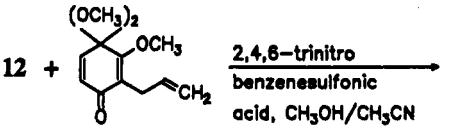
case, the yields of dihydrobenzofurans were 20–40%, substantially less than those typically noted here. In addition, two of these methods involve the use of strong acids which in some cases leads to secondary reactions.[4a] In one exact comparison, oxidation of phenol **13** with **3b** in the presence of styrene **12** gave **14** in 71% yield, whereas reaction of monoketal **15** with acid afforded a mixture of **14** and **16**.[4b] We have not been able to detect products



12 **13**



14 (71%)



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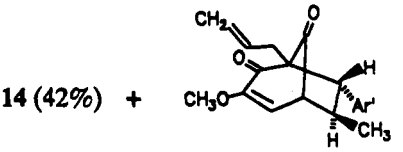


14 (42%) + **16** (20%)

analogous to **16** in our reactions. To check if compounds similar to **16** are formed and then undergo acid-catalyzed rearrangements to the dihydrobenzofuran isolated, the reaction of **4** and **5** was performed using pyridine (>2 equiv) to neutralize the trifluoroacetic acid generated in the oxidation. Since the yield is comparable (50% vs 65%) with and without pyridine being present, it appears unlikely that a stable intermediate is formed in the reaction which undergoes subsequent acid-catalyzed rearrangement to the dihydrobenzofuran.[15b] The formation of **6** in the reaction of the cis isomer of **4** indicates loss of stereochemistry about the double bond during some stage of the reaction. The sequence **4** → **17** → **18** → **6** serves as a useful working hypothesis for the steps in the reaction.

The synthetic potential associated with this interesting reaction is apparent from the chemistry outlined below. Oxidative cycloaddition of **12** and **19**[16] using **3b** afforded

(12) This phenol was prepared (73% yield) by reaction of 3-chloro-4,4-dimethoxy-2,5-cyclohexadienone[13] with allylmagnesium bromide.

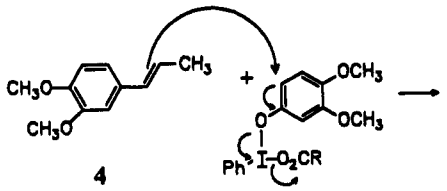
(13) Stern, A. J.; Rohde, J. J.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 4413.

(14) This isomerization was performed by irradiating *trans*-3,4-dimethoxypropenylbenzene (2.0 g, 11.2 mmol) in hexane (450 mL) for 3.5 h with Corex-filtered light from a 450-W Hanovia medium-pressure source. The cis isomer was obtained by silica gel chromatography (hexane as eluent).

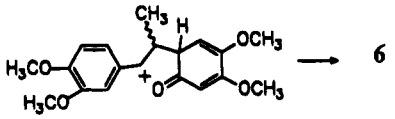
(15) (a) An impure sample of a very minor product was detected which showed an ^1H NMR spectrum similar to what would be expected for the cis isomer of **6**. There was no detectable isomerization of the recovered olefin. (b) The ^1H NMR spectrum of the reaction mixture showed **6** to be present before chromatography; **6** is not formed from rearrangement of an intermediate during chromatography.

(16) The phenol was prepared by anodic oxidation of resorcinol diallyl ether followed by monohydrolysis and zinc–copper hydrolysis of the resulting quinone monoketal.[17]

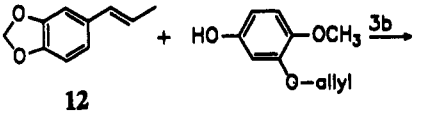
(17) Henton, D. R.; Anderson, K.; Manning, M. J.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 3422.



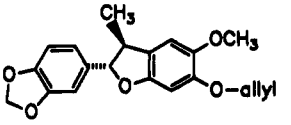
4 17



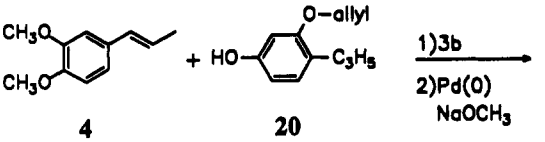
18 6



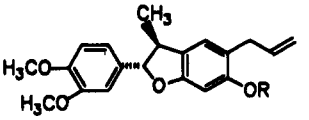
12 19



1a



4 20



21, R = allyl
22, R = H

1a (69% yield). The product 1a showed ^{1}H NMR and IR spectra in good agreement with those reported for the natural product.[1c] Finally, 4 was reacted with 20[18] to furnish 21 (R = allyl, 30% yield) which was then deblocked[20] to 22 (R = H, 90% yield). The final product 22 showed a 200-MHz ^{1}H NMR spectrum identical with an authentic spectrum of the compound.[21] The dihydrobenzofuran 22 has been converted[5] to *kadsurenone* and *denudatin B*; thus, this serves as a formal synthesis of these natural products and rigorously establishes the *trans*-dihydrofuran stereochemistry. Since the position of the methyl resonance (trans isomer $\delta \approx 1.3$, cis isomer $\delta \approx 0.7$) is indicative of the stereochemistry in these dihydrobenzofurans,[22] the other adducts reported here are assigned as having the *trans*-dihydrobenzofuran stereochemistry based on the position of their methyl resonances in their ^{1}H NMR spectra.

The scope and mechanism of this oxidative cycloaddition reaction need to be studied further; however, this chemistry establishes a novel, convergent approach to *neolignans* containing the dihydrobenzofuran unit. Especially noteworthy is that the reaction involves a one-step procedure from readily available starting materials under conditions compatible with many sensitive functional groups. The synthesis of 1a serves as a convenient entry into other compounds in this series. Thus, *neolignan* 1b is related to 1a via a Claisen rearrangement and 1c is related to 1b via a methylation. Further research will focus on defining the mechanistic aspects of this chemistry and the electrochemical version of this reaction.[23]

Acknowledgment. We acknowledge support of this work from the National Science Foundation and Dr. K. Combrink for helpful discussions and references.

Supplementary Material Available: Experimental procedure for the preparation of 9a and ^{1}H NMR spectra of 6 and 9a (5 pages). Ordering information is given on any current masthead page.

(18) This phenol was prepared by reaction of diethylaluminum chloride catalyzed Claisen rearrangement[19] of 1-(*tert*-butyldimethylsiloxy)-3-(allyloxy)benzene followed by allylation of the resulting phenol, silica gel chromatography, and desilylation with sodium methoxide.

(19) Sonnenberg, F. M. *J. Org. Chem.* **1970**, *35*, 3166.

(20) Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 230.

(21) We thank Dr. M. Ponpipom of Merck Sharp & Dohme for the authentic ^{1}H NMR spectrum.

(22) Gregson, M.; Ollis, W. D.; Redman, B. T.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1968**, 1394. See also ref 6a.

(23) All new compounds showed combustion analyses or exact mass measurements within acceptable limits. The melting points of solids were as follows: (±)-1a, 83–84.5 °C [lit.[1c] (2*S*,3*S*)-1a, oil]; (±)-6, 125.5–126 °C; (±)-9a, 99.5–100 °C; (±)-9c, 41–43 °C; (±)-11, 98–99 °C; (±)-14, mp 62–63 °C (lit.[4b] mp 67–69 °C); (±)-21, 51.5–52.5 °C (±)-22, mp 96–97 °C (lit.[5a] mp 98–99 °C).

Functionalization of Silica Gel: Application for the Catalytic Oxidation of Alkanes[1]

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Summary: Silica gel, functionalized by (*N*,*N*-dimethyl-3-aminopropyl)trimethoxysilane and complexed with Fe(II) or other metal ions in the presence of O_2 was effective for the aerobic, room temperature oxidation of a C–H bond in cyclohexane. The products were cyclohexanol and cyclohexanone.

The hydroxylation of inert C–H bonds in alkanes under mild conditions has remained a difficult challenge in organic chemistry. One possible approach to achieving this is to mimic biological conditions and systems. Mono-

(1) Contribution 102 from the Center for Photochemical Sciences.

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