JOC*Note*

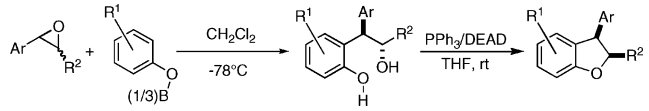
Synthesis and Cyclodehydration of Hydroxyphenols: A New Stereoselective Approach to 3-Aryl-2,3-dihydrobenzofurans

Ferruccio Bertolini, Paolo Crotti, Valeria Di Bussolo, Franco Macchia, and Mauro Pineschi*

Dipartimento di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy

pineschi@farm.unipi.it

Received February 22, 2007

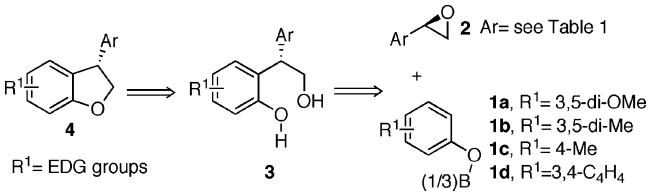


R^1= EDG groups
R^2=H, alkyl, aryl or ester groups

A novel and simple method for the stereoselective synthesis of substituted 3-aryl-2,3-dihydrobenzofurans by intramolecular cyclization of hydroxyphenols is described. The stereoselective *ortho*-*C*-alkylation of phenols allows a novel and stereoselective access to a diverse array of polyfunctionalized products containing a diarylmethane stereogenic center without the need for time-consuming protection−deprotection steps.

2,3-Dihydrobenzofuran derivatives are common in natural products and have attracted considerable attention as a result of their biological activity.[1] There are several approaches to the synthesis of the 2,3-dihydrobenzofuran ring system,[2] but no method is general, and rapid access to highly functionalized 2,3-dihydrobenzofurans not accessible through current techniques is an important synthetic tool. Although various methods for the preparation of 3-unsubstituted 2,3-dihydrobenzofurans have been reported,[2] there are few reports about the synthesis of 3-aryl-2,3-dihydrobenzofurans,[3] and none of them is able to give these biologically significant compounds in an enantioenriched form. Known approaches to the synthesis of enantioenriched 2,3-dihydrobenzofurans involve asymmetric quinone−styrene reactions,[4] Sharpless asymmetric dihydroxylation or epoxidation followed by cyclization reactions,[5] enantioselective rhodium- or ruthenium-catalyzed insertion processes,[6] Jacobsen hydrolytic kinetic resolution followed by intramolecular epoxide ring opening,[7] lipase-catalyzed kinetic resolution,[8] and intramolecular carbolithiation of allyl *o*-lithioaryl ethers.[9] Moreover, despite the several methods available for the synthesis of *trans*-2,3-disubstituted dihydrobenzofuran,[4,9,10] only a few methods are suitable for the stereoselective obtainment of *cis*-2,3-disubstituted dihydrobenzofurans,[6] and none of these are able to give 3-aryl-substituted derivatives. We recently reported a new regio- and stereoselective ring opening of aryl epoxides with aryl borates bearing electron-donating groups to give hydroxyphenols with high levels of retention of configuration at the cleaved benzylic center.[11]

SCHEME 1. Retrosynthetic Approach to 3-Aryl-2,3-dihydrobenzofurans



Now we report that the ring-opening process of aryl-substituted epoxides occurs with *syn*-stereoselectivity only when particular stereoelectronic issues are matched. Moreover, we envisioned that hydroxyphenols of type **3** obtained, which contain a diarylmethine stereogenic center, were suitable precursors to prepare 3-aryl-2,3-dihydrobenzofurans such as **4** by simple cyclodehydration (Scheme 1). The ready availability of aryl epoxides also in enantioenriched forms,[12] together with the high regio- and stereoselectivity associated with their ring-opening reaction, gives a reliable method for the preparation of these important heterocyclic targets.

To have a better understanding of the stereoselectivity of the ring-opening process, several diastereoisomerically pure aryl-substituted epoxides have been allowed to react at a low temperature with freshly prepared tris(3,5-dimethoxyphenyl borate) (**1a**) and tris(3,5-dimethylphenyl borate) (**1b**). These reaction conditions are able to maximize the *C*-alkylation pathway, and the less polar *O*-alkylated byproducts were easily removed by chromatography (see the Supporting Information for details). The stereoselectivity of the Friedel−Crafts-type carbon−carbon coupling proved to be rather peculiar. For example, *trans*-epoxides **2a** and **2b** in the reaction with **1b** afforded the corresponding hydroxyphenols **3ab** and **3bb** with a high *syn*-stereoselectivity (Table 1, entries 1 and 2), while the stereoselectivity of the ring openings of *trans*-phenyl glycidate **2c** was considerably lower (entries 3 and 4).[13] The *syn*-stereoselectivity of the ring-opening process can be rationalized by the occurrence of an advanced carbocationic intermedi-

(1) A January 2007 SCIFinder Scholar survey indicated the presence of 837 patents out of 2333 total hits associated with the preparation and biological activity of molecules containing a dihydrobenzofuran moiety.

(2) For a recent report including an extensive list of references about the synthesis of 2,3-dihydrobenzofurans, see: Kuethe, J. T.; Wong, A.; Journet, M.; Davies, I. W. *J. Org. Chem.* **2005**, *70*, 3727.

(3) Yamashita, M.; Ono, Y.; Tawada, H. *Tetrahedron* **2004**, *60*, 2843 and references therein.

(4) Engler, T. A.; Combrink, K. D.; Letavic, M. A.; Lynch, K. O., Jr.; Ray, J. E. *J. Org. Chem.* **1994**, *59*, 6567.

(5) de Carvalho e Silveira, G. P.; Coelho, F. *Tetrahedron Lett.* **2005**, *46*, 6477.

(6) Kurosawa, W.; Kobayashi, H.; Kan, T.; Fukuyama, T. *Tetrahedron* **2004**, *60*, 9615.

(7) Bhoga, U. *Tetrahedron Lett.* **2005**, *46*, 5239.

(8) Juhász, L.; Visy, J.; Simonyi, M.; Krohn, K.; Antus, S. *Tetrahedron: Asymmetry* **2002**, *13*, 1219.

(9) Barluenga, J.; Fananas, F. J.; Sanz, R.; Marcos, C. *Chem.−Eur. J.* **2005**, *11*, 5397.

(10) Ohara, H.; Kiyokane, H.; Itoh, T. *Tetrahedron Lett.* **2002**, *43*, 3041 and references therein.

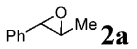
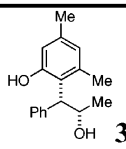
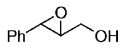
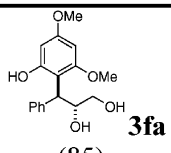
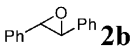
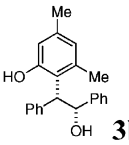
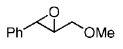
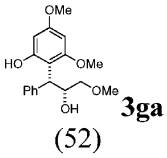
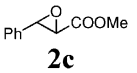
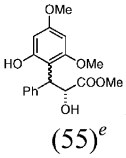
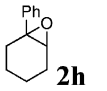
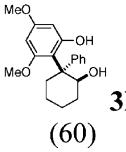
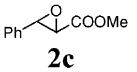
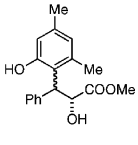
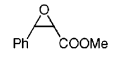
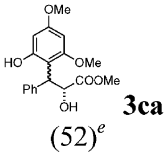
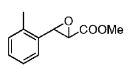
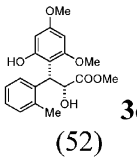
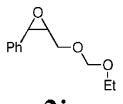
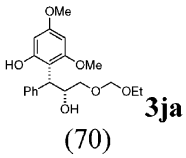
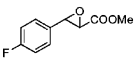
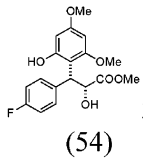
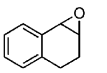
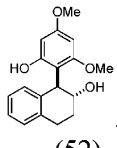
(11) Bertolini, F.; Crotti, P.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **2006**, *47*, 61.

(12) Katsuki, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Eds.; Wiley-VCH: New York, 2000; p 287.

(13) *syn*/*anti* ratio determined by ^{1}H NMR after cyclization to the corresponding 2,3-dihydrobenzofurans (vide infra and the Supporting Information for details).

10.1021/jo070316q CCC: $37.00
Published on Web 09/07/2007

TABLE 1. New Hydroxyphenols by Coupling of Aryl Epoxides with Aryl Borates 1a and 1b[a]

Entry	Substrate	Product[b]	*Syn*/*anti*[c]	Entry	Substrate	Product[b]	*Syn*/*anti*[c]
1	 **2a**	 **3ab** (45)	>95/<5	7	 **2f**	 **3fa** (85)	<5/<95
2[d]	 **2b**	 **3bb** (38)	>95/<5	8	 **2g**	 **3ga** (52)	74/26
3	 **2c**	 **3ca** (55)[e]	60/40	9	 **2h**	 **3ha** (60)	>95/<5[g]
4[d]	 **2c**	 **3cb**[f]	89/11	10	 **2i**	 **3ca** (52)[e]	13/87
5	 **2d**	 **3da** (52)	>95/<5	11	 **2j**	 **3ja** (70)	<5/>95
6	 **2e**	 **3ea** (54)	>95/<5	12	 **2k**	 **3ka** (52)	<5/>95

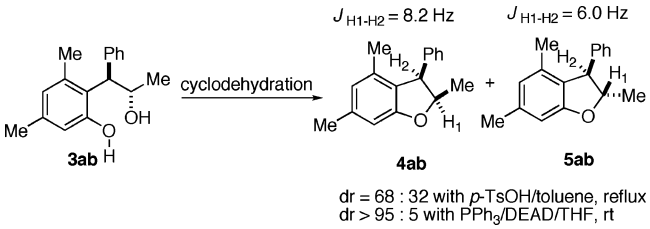
[a] All reactions were performed in accordance with the general procedure reported in the Experimental Section unless stated otherwise. [b] Isolated yields of the pure product after chromatographic purification indicated in parentheses. [c] Determined by ^{1}H NMR of the crude reaction mixture after Mitsunobu-type cyclization to 2,3-substituted 2,3-dihydrobenzofurans (vide infra). [d] Reaction carried out at rt. [e] Isolated yield of an inseparable mixture of diastereoisomers. [f] The inseparable mixture of diastereoisomers was directly cyclized to the corresponding mixture of dihydrobenzofurans **4cb** and **5cb**. [g] Determined by ^{1}H and ^{13}C NMR and HPLC analysis of the crude mixture.

ate in which the nucleophilic attack occurs by the internal nucleophile (i.e., the aryl borate tethered with the oxirane oxygen) from the same side as the oxygen atom of the former epoxide ring, as recently reported by us.[11] Probably, the electron-withdrawing methoxycarbonyl group present in compound **2c** destabilizes the incipient carbocation, thus rendering the S_N2-type process (i.e., an *anti*-attack) competitive. However, the presence of aryl moieties bearing electron-donating *o*-methyl or *p*-fluoro substituents (compounds **2d** and **2e**) is sufficient to restore a completely *syn*-stereoselective ring-opening process (entries 5 and 6). On the other hand, when 1-aryl-2,3-epoxy alcohol **2f** was employed, the corresponding phenol diol **3fa** was obtained with a high yield and complete *anti*-stereoselectivity (entry 7). Probably, with this substrate the boron atom is engaged in the formation of an ate complex with the free primary hydroxyl group, thus delivering the nucleophile (i.e., the aryl moiety) in *anti*-fashion.[14]

It is a fact that when the same reaction was carried out on the corresponding methyl ether (epoxide **2g**), *syn*-hydroxyphenol **3ga** was again the major product (entry 8).[13] The ring opening with **1a** of the semirigid cyclic epoxide **2h**, bearing a tertiary benzylic position, afforded the corresponding ring-opened adduct **3ha**, containing a *benzylic all-carbon quaternary stereocenter*, with a remarkably high *syn*-stereoselectivity (entry 9).[15] On the other hand, *cis*-epoxides **2i**, **2j**, and **2k** underwent a highly *anti*-stereoselective ring opening when allowed to react with aryl

(14) Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M. *Org. Lett.* **2003**, *5*, 1789.
(15) Taber, D. F.; He, Y. *J. Org. Chem.* **2005**, *70*, 7711.

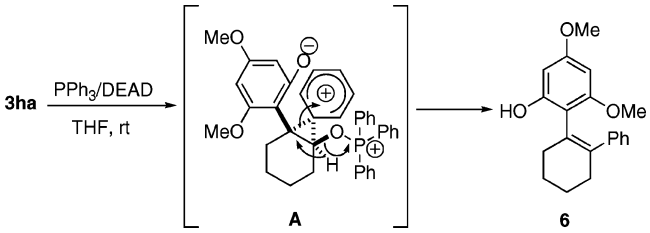
SCHEME 2. Cyclodehydration Reactions on Hydroxyphenol 3ab



borate **1a** (entries 10−12, Table 1). Reasonably, in *cis*-aliphatic systems, the phenyl substituent is substantially twisted out of conjugation with the benzylic carbenium ion, creating a steric inhibition to the formation of a discrete carbocationic species,[16] thus favoring the *anti*-attack by the highly nucleophilic arene.[17] In all cases no carbonyl-containing rearranged products were detected in the reactions carried out by means of our protocol with the substrates listed in Table 1.[18]

In preliminary experiments aiming to synthesize 2,3-dihydrobenzofurans, the treatment of hydroxyphenol **3ab** with catalytic amounts of *p*-TsOH in refluxing toluene gave an inseparable 68/32 mixture of diastereoisomeric *cis*- and *trans*-2-methyl-3-phenyl-5,7-dimethyl-2,3-dihydrobenzofurans (**4ab** and **5ab**, respectively) (Scheme 2).[19] When the cyclodehydration was effected by means of an intramolecular Mitsunobu-type protocol (PPh_3, DEAD, THF, rt), which generally occurs with inversion of configuration, the diastereoselectivity was improved up to synthetically useful levels (dr >95/<5), and compound **4ab** was isolated with an 80% yield (Scheme 2).[20] The Mitsunobu procedure gave high levels of diastereoselectivity for the cyclization of differently substituted hydroxyphenols (Table 2).[21] For example, compounds **3dc** and **3bc**, which can readily be prepared with a high diastereoisomeric purity starting from the corresponding *trans*-epoxides **2d** and **2b** by *ortho*-selective carbon−carbon *syn*-stereoselective coupling with borate **1c**, afforded good yields of the corresponding *cis*-3-phenyl-2,3-dihydrobenzofurans **4dc** and **4bc** (Table 2, entries 1 and 2). The application of Mitsunobu cyclization to compounds **3la**, **3lb**, **3mb**, and **3nb**, all bearing a primary alcohol functionality, gave quantitative yields of the corresponding 3-aryl-2,3-dihydrobenzofurans (entries 3−6). In particular, the use of enantioenriched hydroxyphenol **3lb**, in turn obtained from the reaction of optically active (*R*)-styrene oxide (**2l**) (99/1 er) with borate **1b**,[11] afforded the corresponding enantioenriched dihydrobenzofuran **4lb** with 94% isolated yield, with a reduced overall extent of epimerization (92/8 er), as determined by HPLC on CSPs (entry 4). Also dihydronaphthobenzofurans can be accessed by this method.[22] The nuclear alkylation of borate **1d** derived from *β*-naphthol with optically active styrene oxide and subsequent Mitsunobu-type cyclization afforded the corresponding (*S*)-1-phenyl-1,2-dihydronaphtho[2,1-*b*]furan (**4ld**) with a high yield (entry 7).[23] However, an increased extent of racemization (78/22 er) was observed with respect to the same reaction carried out with more electron-rich aryl borates, such as **1a** and **1b**. To our surprise, the application of the Mitsunobu cyclodehydration to phenol diol **3fa** turned out to be completely regioselective with formation in good yields of the corresponding *trans*-dihydrobenzofuran **5fa** deriving from the intramolecular substitution of the secondary, instead of the primary, alcohol functionality (entry 8). Compound **3qa**, bearing a tertiary alcohol functionality, was directly used in the cyclization step due to a difficult chromatographic purification with the unreacted 3,5-dimethylphenol. As no diastereoselectivity issues exist, the more atom-economic *p*-TsOH-catalyzed cyclodehydration was used, and 2,2-dimethyl-3-phenyl dihydrobenzofuran (**4qa**) was obtained with a 55% yield (entry 9). Hydroxyphenols **3ja** and **3ka** afforded upon cyclization the corresponding 2,3-*cis*-configurated dihydrobenzofurans **4ja** and **4ka**, respectively, the latter containing a novel tetrahydrobenzonaphthofuran tetracyclic structure (entries 10 and 11). The application of the Mitsunobu cyclization to compound **3ha**, in which the two reacting termini (i.e., the phenol moiety and the hydroxyl group) are on the same side of the cyclohexane ring, proved to be problematic, and tetrasubstituted alkene **6** was obtained (Scheme 3).

SCHEME 3. Rearrangement Induced by Mitsunobu Cyclodehydration



Although there are no reports of this kind, the 1,2-phenyl migration observed might be reasonably explained by the intermediate occurrence of a phenonium ion, such as **A**, assisting the concerted exit of the leaving group and the contemporary loss of the proton.[24] In this case, the application of the *p*-TsOH-catalyzed cyclodehydration gave the corresponding new 2,3-dihydrofuran **4ha** as a single diastereoisomer with a high yield (entry 12).[25]

In summary, the ring opening of diastereoisomerically pure aryl-substituted epoxides with electron-rich aryl borates afforded hydroxyphenols, which are very difficult to access by other routes, with interesting levels of diastereoselectivity. These compounds, containing a diarylmethane stereogenic center, can easily be cyclodehydrated to differently substituted 3-aryl-2,3-

(16) Balsamo, A.; Crotti, P.; Macchia, B.; Macchia, F. *Tetrahedron* **1973**, *29*, 199.

(17) The alternative occurrence of a fully developed carbenium ion does not appear to be supported by the present and previously obtained results on closely related systems: Crotti, P.; Di Bussolo, V.; Macchia, F.; Favero, L.; Pineschi, M.; Lucarelli, L.; Roselli, G.; Renzi, G. *J. Phys. Org. Chem.* **2005**, *18*, 321 and references cited therein.

(18) It should be noted that alternative Friedel−Crafts-type procedures making use of electron-rich phenols and Lewis acids afforded mixtures of regio- and stereoisomeric hydroxyphenols and gave substantial amounts of carbonyl-rearranged products.

(19) In general, diastereoisomeric 2,3-substituted 2,3-dihydrobenzofurans can easily be distinguished by ^{1}H NMR examination of the coupling constants of the corresponding benzylic proton (J_{H1-H2} = 8.0−9.5 Hz in *cis*-systems, J_{H1-H2} = 4.0−6.5 Hz in *trans*-systems).

(20) (a) Aristoff, P. A.; Harrison, A. W.; Huber, A. M. *Tetrahedron Lett.* **1984**, *25*, 3955. (b) Trost, B. M.; Saulnier, M. G. *Tetrahedron Lett.* **1985**, *26*, 123. (c) Stafford, J. A.; Valvano, N. L. *J. Org. Chem.* **1994**, *59*, 4346.

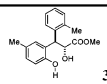
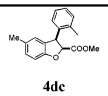
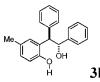
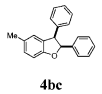
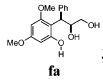
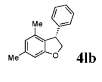
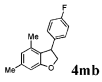
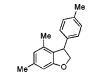
(21) See the Supporting Information for details.

(22) Haselgrove, T. D.; Jevric, M.; Taylor, D. K.; Tiekink, E. R. T. *Tetrahedron* **1999**, *55*, 14739.

(23) (a) Guss, C. O.; Jules, L. H. *J. Am. Chem. Soc.* **1950**, *72*, 3462. (b) Guss, C. O.; Jules, L. H. *J. Am. Chem. Soc.* **1950**, *72*, 3878.

(24) The anchimeric assistance of neighboring groups in Mitsunobu reactions has been admitted to explain the obtainment of products with retention of configuration.

TABLE 2. Mitsunobu Cyclodehydration of Hydroxyphenols of Type 3[a]

Entry	Substrate	Product	Yield (%)[b]	Entry	Substrate	Product	Yield (%)[b]
1	 **3dc**	 **4dc**	62	7	 **3ld**	 **4ld** *er* = 78/22	95
2	 **3bc**	 **4bc**	65	8	 **fa**	 **5fa**	60[c]
3	 **3la**	 **4la**	95	9[d]	 **3qa**	 **4qa**	55
4	 **3lb**	 **4lb** *er* = 92/ 8	94	10	 **3ja**	 **4ja**	78
5	 **3mb**	 **4mb**	88	11	 **3ka**	 **4ka**	40
6	 **3nb**	 **4nb**	85	12[d]	 **3ha**	 **4ha**	95

[a] All reactions were performed in accordance with the general procedure reported in the Experimental Section. [b] Isolated yields after chromatographic purification. [c] Isolated after acetylation of the crude reaction mixture. [d] Cyclization performed with *p*-TsOH in toluene.

dihydrobenzofurans, which can now be accessed also in an enantioenriched form, starting from readily available chiral nonracemic aryl-substituted epoxides.

Experimental Section

Aryl borates **1a**−**d** were prepared following a previously described procedure[26] and were used immediately after their preparation.

General Procedure for the Preparation of Hydroxyphenols (Table 1). A solution of aryl borate (1.5 mmol) in CH_2Cl_2 (1.0 mL) was added to a stirred solution of the aryl epoxide (1.0 mmol) in CH_2Cl_2 (0.5 mL) under argon. The reaction was followed by TLC and was quenched with brine (2.0 mL) after complete consumption of the starting epoxide. The solution was diluted with Et_2O or CH_2Cl_2 (20 mL) and washed with brine. Evaporation of the dried organic solution afforded a crude reaction mixture which was purified by silica gel column chromatography.

2-((1*R,2*S**)-2-Hydroxy-1-phenylcyclohexyl)-3,5-dimethoxyphenol (3ha) (Table 1, Entry 9).** Using the general procedure, a solution of borate **1a** (705 mg, 1.5 mmol) in CH_2Cl_2 (1.0 mL) was added at −78 °C to a solution of 1-phenyl-1-cyclohexene oxide (**2h**) (174 mg, 1.0 mmol) in CH_2Cl_2 (0.5 mL). The mixture was allowed to react for 4.5 h at −78 °C. Column chromatography eluting with hexanes/AcOEt (8/2) afforded pure **3ha** (196.8 mg, 60%) as a white solid: mp 140−142 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.98−2.00 (m, 7H), 2.12−2.28 (m, 1H), 2.96 (CH*OH*, br s, 1H), 3.12−3.22 (m, 1H), 3.28 (s, 3H), 3.67−3.75 (m, 1H), 3.76 (s, 3H), 5.98 (s,1H), 6.16 (s,1H), 7.12−7.28 (m, 5H), 10.19 (Ar*OH*, br s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.7, 26.0, 29.8, 34.2, 54.9, 55.0, 55.3, 81.2, 93.47, 95.6, 110.0, 126.1, 126.4, 128.4, 147.2, 157.7, 159.7, 160.6. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.21; H, 7.33.

General Procedure for the Preparation of 2,3-Dihydrobenzofurans via Mitsunobu Cyclodehydration (Table 2). Triphenylphosphine (262.3 mg, 1.0 mmol) and diethyl azodicarboxylate (130.5 mg, 118 μL, 0.75 mmol) were added to a stirred solution of hydroxyphenol of type **3** (0.5 mmol) in anhydrous THF (2.0 mL) under argon. The reaction was followed by TLC to complete consumption of the starting hydroxyphenol, and the solvent was removed in vacuo. The crude reaction mixture was purified by silica gel column chromatography.

(3*S*)-3-Phenyl-4,6-dimethyl-2,3-dihydrobenzofuran (4lb) (Table 2, Entry 4). Using the general procedure, triphenylphosphine (262.3 mg, 1.0 mmol) and diethyl azodicarboxylate (130.5 mg, 118 μL, 0.75 mmol) were added to a solution of 2-((1*S*)-2-hydroxy-1-phenylethyl)-3,5-dimethylphenol[11] **(3lb)** (121 mg, 0.5 mmol, er = 92/8) in anhydrous THF (2.0 mL). The mixture was allowed to react for 2 h at rt. The product was isolated (105.3 mg, 94%) by column chromatography eluting with hexanes/Et_2O (9/1) as a semisolid: $[\alpha]_D^{20} = -17.8$ (c = 1.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.96 (s, 3H), 2.34 (s, 3H), 4.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.9 Hz), 4.56 (dd, 1H, J_1 = 8.8 Hz, J_2 = 4.9 Hz), 4.90 (t, 1H, J = 8.6 Hz), 6.53 (br s, 1H), 6.62 (br s, 1H), 7.14−7.39 (m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 18.5, 21.5, 47.6, 79.7, 107.8, 123.1, 126.0, 126.7, 127.5, 128.7, 135.1, 138.9, 143.3, 160.3; enantiomeric ratio determined by chiral HPLC (Chiralcel OD-H), hexanes/IPA (95/5), retention times (min) 8.85 (*R*, minor stereoisomer) and 9.50 (*S*, major stereoisomer).

(4a*S,9b*R**)-7,9-Dimethoxy-1,2,3,4,4a,9b-hexahydrodibenzo-[*b*]furan (4ha) (Table 2, Entry 12).** *p*-Toluensulfonic acid monohydrate (2.7 mg, 0.014 mmol) was added at rt to a solution of (1*S**,2*S**)-2-(2-hydroxy-4,6-dimethoxy)-2-phenylcyclohexen-1-ol **(3ha)** (90.2 mg, 0.275 mmol) in toluene (5.0 mL). The mixture was allowed to react for 18 h at rt, quenched with an aqueous $NaHCO_3$ saturated solution, and filtered. Evaporation of the organic layer afforded pure compound **4ha** (79.5 mg, 95%) as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.50−1.78 (m, 4H), 1.81−1.98 (m, 2H), 2.13−2.40 (m, 2H), 3.61 (s, 3H), 3.78 (s, 3H), 4.76−4.83 (m, 1H), 6.03 (d, 1H, J = 2.0 Hz), 6.12 (d, 1H, J = 2.0 Hz), 7.10−7.38 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 18.6, 20.6, 26.6, 30.7, 52.4, 55.2, 55.4, 88.9, 90.6, 91.6, 113.2, 125.9, 126.6, 128.0, 147.1, 157.5, 161.4, 161.7.

Acknowledgment. This work was supported by the Ministero dell'Università e della Ricerca (PRIN 2004, PRIN 2006) and by the University of Pisa. We also acknowledge Merck (2005 ADP Chemistry Award to P.C.).

Supporting Information Available: Text giving detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070316Q

(25) The stereochemistry of compound **4ha**, and as a consequence of its precursor **3ha**, was demonstrated by 1D NOESY experiments (see the Supporting Information for details).

(26) Brown, C. A.; Krishnamurthy, S. *J. Org. Chem.* **1978**, *43*, 2731.