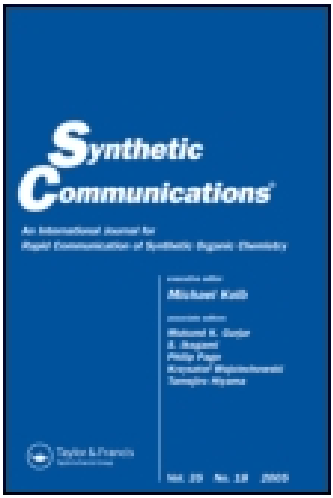


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of 5-Alkyl-2,3-dihydro-1,4-benzodio

Adriano Martendal [a] , Rafael Dias [a] , Faruk Nome [a] & César Zucco [a]
[a] Departamento de Química , Universidade Federal de Santa Catarina , 88040-900, Florianópolis, Brazil
Published online: 10 Jan 2011.

To cite this article: Adriano Martendal , Rafael Dias , Faruk Nome & César Zucco (2004) Synthesis of 5-Alkyl-2,3-dihydro-1,4-benzodioxins, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:13, 2487-2498, DOI: 10.1081/SCC-120039503

To link to this article: http://dx.doi.org/10.1081/SCC-120039503

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 13, pp. 2487–2498, 2004

Synthesis of 5-Alkyl-2,3-dihydro-1,4-benzodioxins

Adriano Martendal, Rafael Dias, Faruk Nome, and César Zucco*

Departamento de Química, Universidade Federal de Santa Catarina, Florianópolis, Brazil

ABSTRACT

An expedient synthesis of 5-alkyl-2,3-dihydro-1,4-benzodioxins by intramolecular cyclization of 2-(2-bromoethoxy)-3-alkylphenols prepared from 2-alkylphenols is described.

Key Words: Cyclization; 2-Alkyl phenols; 5-Alkyl-2,3-dihydro-1,4-benzodioxins; Enzyme–substrate complex.

INTRODUCTION

It is well established that there is a remarkable influence of the chain length on intramolecular reactivity. The reaction rate normally decreases as

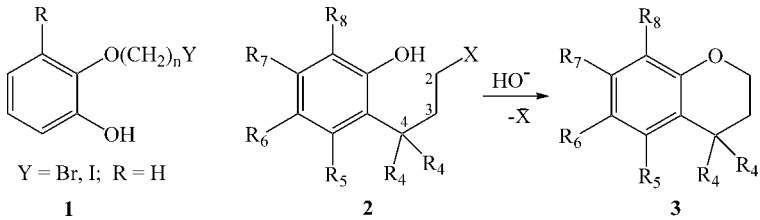
*Correspondence: César Zucco, Departamento de Química, Universidade Federal de Santa Catarina, 88040-900, Florianópolis, Brazil; E-mail: czucco@qmc.ufsc.br.

DOI: 10.1081/SCC-120039503 0039-7911 (Print); 1532-2432 (Online)

the chain increases, the retarding effect caused by each additional methylene group being smaller the larger the ring to be formed.[1,2]

Cyclizations of *o*-(ω-haloalkoxy)phenols, **1**, R = H, $n = 2–20$, and Y = Br and I, have been widely studied in various systems, especially with regard to the high reactivity of these compounds as given by the effective molarities (EM).[2–4] The effects of solvents and surfactants on the reactivity towards the cyclization as a function of the ring size have also been studied and the activation parameters determined.[5–7] The values found for the entropy of activation decrease with the cyclization rates. On the other hand, the enthalpy of activation does not normally change with the side-chain length.[4] Based on these and on solvent effects an intramolecular mechanism was postulated in which the reaction center has a S_N2-like transition state geometry although the reaction is rather a first-order process.[5]

As part of a study on the effects of stereopopulation control on rates, mechanisms and equilibria, the simple intramolecular nucleophilic displacement of 3-(*o*-hydroxyphenyl)-1-propanol monoesters, **2**, X = Mes, acetate or phosphate, to form chromans, **3**, was investigated. For a series involving an invariant leaving group, appropriate methyl substitution in both the aromatic ring and side chain produces rate-enhancement factors of almost 10^6. This methyl substitution produces partial conformational freezing of the side chain and increases greatly the population of the conformer most closely resembling the transition state.[8]



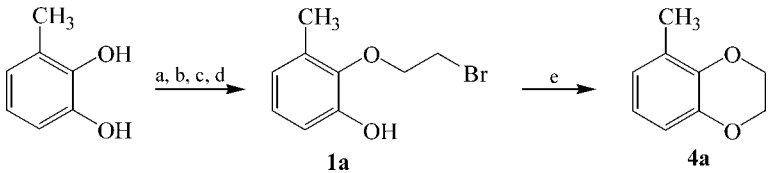
In this communication we described the synthesis of a series of 2-(2-bromoethoxy)phenols, **1a–d**, $n = 2$, R = methyl, isopropyl, *sec*-butyl, and *tert*-butyl, and their conversion to the corresponding cyclic diethers 5-alkyl-2,3-dihydro-1,4-benzodioxins, **4a–d**. The influence of the alkyl ring substitution might be used as a test for the stereopopulational theory,[9] which states that during formation of the enzyme-substrate complex the enzyme limits the substrate to one single conformation, i.e., that most favorable for the enzyme to play its catalytic role. Therefore the ring substitution effect on the intramolecular cyclization reaction mechanism will be investigated later as a model for enzyme actions and will appear elsewhere.

RESULTS

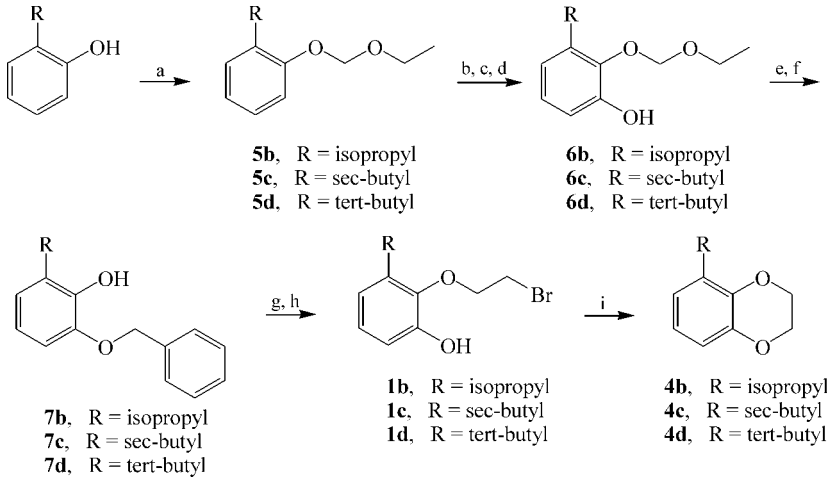
Compound 2,3-dihydro-5-methyl-1,4-benzodioxin, **4a**, was obtained by reacting equimolecular amounts of 3-methylcatechol and chloromethyl ethyl ether forming a mixture of 2-(ethoxymethoxy)-3-methylphenol, 2-(ethoxymethoxy)-6-methylphenol, and unreacted 3-methylcatechol, which was removed by column chromatography. The resulting mixture was then treated with 1,2-dibromoethane and the protecting group was removed by acid catalysis. Compounds 2-(2-bromoethoxy)-3-methylphenol, **1a**, and 2-(2-bromoethoxy)-6-methylphenol (small amount) were isolated by column chromatography. The two isomers were identified by NOESY spectra and readily converted to the cyclic **4a** in alkali medium (Sch. 1).

The synthetic route to the titled compounds **4b–d** was chosen to permit the variation of the 5-alkyl substituents on the aromatic ring. The basic skeleton was 3-alkylcatechols obtained from the appropriate 2-alkylphenols by oxygen-directed metalation group and metalation–boronation–oxidation strategies.[10–13] In this manner 2-alkylphenols were reacted with chloromethyl ethyl ether giving the corresponding 1-alkyl-2-(ethoxymethoxy)benzenes, **5b–d**, followed by ortho-lithiation (butyl lithium and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) and treatment with trimethyl borate and hydrogen peroxide to give the 3-alkyl-2-(ethoxymethoxy)phenols, **6b–d**. The reaction of **6** with benzylbromide and the acid catalyzed removal of the ethoxymethoxy protecting group afforded **7**, which by alkylation with 1,2-dibromoethane and catalytic hydrogenation to remove the benzyl group, gave **1b–d**, immediately cyclized to **4b–d** by addition of alkali solution, Sch. 2.

In conclusion, this communication described convenient methods for the preparation of new 3-alkylsubstituted phenols, **1a–d**, and their corresponding cyclic diethers, **4c–d**, despite the need for protecting/deprotecting steps. All the spectral data are consistent with the structural assignments made for each compound. The yields of the products may not be optimal, especially the alkylation step, but the current general procedures readily afforded multi-gram



Scheme 1. a: $ClCH_2OEt$, CH_2Cl_2, NaOH–H_2O, Aliquat 336; b: $BrCH_2CH_2Br$, K_2CO_3, acetone, reflux; c: MeOH/HCl; d: column chromatography; e: NaOH 1 M/ethanol.



Scheme 2. a: $ClCH_2OEt$, CH_2Cl_2, NaOH–H_2O, Aliquat 336; b: *n*-BuLi, TMEDA, THF, 0°C; c: $B(OMe)_3$; d: H_2O_2; e: BnBr, K_2CO_3, acetone, reflux; f: MeOH/HCl; g: $BrCH_2CH_2Br$, K_2CO_3, acetone, reflux; h: Pd-C [H_2]; i: NaOH 1 M/ethanol.

quantities of pure products, which were sufficient amounts for our purposes. All the prepared compounds were high b.p. oils.

EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer FT-IR 16PC; NMR spectra were obtained with a Bruker AC200 spectrometer, employing tetramethylsilane as internal reference; MS were obtained on Shimadzu CGMS-QP2000A spectrometer. The reagents were purchased from commercial suppliers and were used without further purification.

2-(2-Bromoethoxy)-3-methylphenol, 1a, and 2-(2-bromoethoxy)-6-methylphenol. To 3-methylcatechol (3.0 g, 24 mmol), in dichloromethane (25 mL), and NaOH (0.96 g, 24 mmol), in H_2O (25 mL), in a 125 mL round-bottom flask, was added methyltrioctylammonium chloride (0.45 , 1 mmol). The flask was stoppered with a rubber septum and under vigorous stirring chloromethyl ethyl ether (2.18 mL, 24 mmol) was added via a syringe. The stirring was maintained for 1 hr. The organic layer was separated and rotary evaporated. The residue was passed through a column of silica gel eluted with hexane/chloroform, 1 : 1, to remove unreacted 3-methylcatechol. The resultant solution was refluxed for 24 hr with 1,2-dibromoethane (4.1 mL,

48 mmol) and K_2CO_3 (6.6 g, 48 mmol) in acetone (40 mL). The residues were removed by filtration and the rotary evaporated organic phase was refluxed in methanol (40 mL) and 6 M HCl (3 mL). The reaction was accompanied by TLC. The organic layer was separated and evaporated. Column chromatography on silica gel and elution with hexane/chloroform, 1 : 1, gave 0.99 g (18%) of **1a**, a viscous liquid. Anal. calcd. for $C_9H_{11}BrO_2$: C, 46.78; H, 4.80. Found: C, 46.92; H, 4.75. MS: *m/e* (%) 51(26), 66(30), 77(40), 95(22), 107(68), 109(69), 123(100), 230(33), and 232(33). IR (KBr): 3417, 2959, 2929, 1580, 1472, 1277, 1214, 1177, 1072, 772 and 742 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 6.90-6.55$ (m, 3H, aromatic), 5.93 (s, 1H), 4.11 (m, 2H), 3.61 (m, 2H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 16.75$, 32.23, 73.03, 114.24, 123.08, 125.81, 131.67, 144.26, and 149.74.

2-(2-Bromoethoxy)-6-methylphenol. 0.38 g (7%), m.p. 71°C. Anal. calcd. for $C_9H_{11}BrO_2$: C, 46.78; H, 4.80. Found: C, 46.74; H, 4.82. MS: *m/e* (%) 51(14), 77(27), 95(17), 107(57), 109(60), 123(100), 230(25), and 232(24). IR (KBr): 3399, 2969, 2925, 1625, 1597, 1492, 1454, 1269, 1214, 1095, 760, and 733 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 6.82-6.71$ (m, 3H, aromatic), 5.81 (s, 1H), 4.34 (t, 2H, $J = 5.7$ Hz), 3.66 (t, 2H, $J = 5.7$ Hz), 2.26 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 16.17$, 30.37, 69.79, 111.09, 119.88, 124.97, 125.39, 145.08, and 145.25.

Procedure 1

1-(Ethoxymethoxy)-2-isopropylbenzene, 5b. To isopropylphenol (2.7 mL, 20 mmol) in dichloromethane (25 mL) and NaOH (0.8 g, 20 mmol) in water (25 mL), in a round-bottom flask, was added methyltrioctylammonium chloride (0.45 mL, 1 mmol). Under vigorous stirring, chloromethyl ethyl ether (1.82 mL, 20 mmol) was slowly added through a rubber septum. Stirring was continued for 1 hr. The organic phase was separated and evaporated under reduced pressure. The product was passed through a column of silica gel eluted with hexane and yielded 2.33 g (61%) of **5b**, b.p. 232°C. Anal. calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.35; H, 9.61. MS: *m/e* (%) 59(100), 77(13), 91(18), 121(26), 149(12), and 194(11). IR (KBr): 3034, 2965, 1593, 1489, 1450, 1388, 1285, 1227, 1190, 1153, 1107, 1081, 1003, and 751 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.00-7.30$ (m, 4H, aromatic), 5.30 (s, 2H), 3.80 (q, 2H), 3.41 (m, 1H), 1.28 (m, 9H). ^{13}C NMR ($CDCl_3$): $\delta = 15.17$, 22.82, 26.90, 64.23, 93.30, 114.05, 121.73, 126.14, 126.61, 137.54, and 154.63.

1-*sec*-Butyl-2-(ethoxymethoxy)benzene, 5c. Prepared according to Procedure 1, to 2-*sec*-butylphenol (3.1 mL, 20 mmol) in dichloromethane (25 mL) and NaOH (0.8 g, 20 mmol) in water (25 mL), under stirring, was

added methyltrioctylammonium chloride (0.45 mL, 1 mmol) followed by chloromethyl ethyl ether (1.82 mL, 20 mmol), yielding 2.7 g (65%) of **5c**, b.p. 251°C. Anal. calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.48; H, 9.31. MS: *m/e* (%) 59(100), 77(14), 91(19), 121(25), 149(13), and 208(9). IR (KBr): 3032, 2964, 2929, 2874, 1593, 1489, 1453, 1386, 1225, 1153, 1083, 1004, 751 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.26-6.95$ (m, 4H, aromatic), 5.30 (s, 2H), 3.80 (q, 2H), 3.19 (m, 1H), 1.67 (m, 2H), 1.29 (m, 6H), 0.91 (t, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 12.87$, 15.78, 21.32, 30.58, 34.29, 64.83, 93.96, 114.78, 122.33, 127.13, 127.48, 137.10, and 155.57.

1-*tert*-Butyl-2-(ethoxymethoxy)benzene, 5d. Prepared according to Procedure 1, to 2-*tert*-butylphenol (3.1 mL, 20 mmol) in dichloromethane (25 mL) and NaOH (0.8 g, 20 mmol) in water (25 mL), under stirring, was added methyltrioctylammonium chloride (0.45 mL, 1 mmol) followed by chloromethyl ethyl ether (1.82 mL, 20 mmol). The dried product yielded 2.54 g (61%) of 5d, b.p. 247°C. Anal. calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.42; H, 9.59. MS: *m/e* (%) 59(100), 77(7), 91(18), 107(12), 135(9), 163(9), and 208(7). IR (KBr): 3059, 2957, 2909, 1597, 1488, 1444, 1391, 1219, 1154, 1108, 1079, 1003, and 752. ^1H NMR ($CDCl_3$): $\delta = 7.23-6.80$ (m, 4H, aromatic), 5.20 (s, 2H), 3.67 (q, 2H, $J = 7.0$ Hz), 1.31 (s, 9H), 1.17 (t, 3H, $J = 7.0$ Hz). ^{13}C NMR ($CDCl_3$): $\delta = 15.86$, 30.58, 35.61, 64.97, 93.56, 115.15, 121.93, 127.34, 127.83, 138.94, and 157.13.

Procedure 2

2-(Ethoxymethoxy)-3-isopropylphenol, 6b. To 1-(ethoxymethoxy)-2-isopropylbenzene, **5b** (2.0 g, 10 mmol), in a three-neck 125 mL round-bottom flask, equipped with a nitrogen inlet tube, was added dry THF (20 mL) through a rubber septum. The flask was cooled to 0°C in an ice-water bath and the solution was vigorously stirred. With a syringe via the septum a solution at 0°C of *N*,*N*,*N*′,N′-tetramethylethylenediamine (1.66 mL, 11 mmol) and butyllithium, 1.6 M in hexanes (6.87 mL, 11 mmol), in dry THF (20 mL) was added. After stirring for 1 hr, trimethyl borate (1.14 mL, 10 mmol) was slowly added through the septum. The solution was stirred for an additional hour. The ice-water cooling bath was removed and a 30% hydrogen peroxide solution (3 mL) was added. The stirring was then continued for 30 min. The organic phase was separated, rotary evaporated, and the product was purified by column chromatography on silica gel (hexane/chloroform, 1 : 1) to give 1.56 g (72%) of **6b** as a viscous liquid. Anal. calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.38; H, 8.59. MS: *m/e* (%) 59(100), 77(12), 91(12), 137(19), and 210(10). IR (KBr): 3334, 3045, 2966, 2894, 1590, 1465, 1390, 1323, 1287, 1225, 1195, 1157, 1104, 1054, 985, 790, and 748 cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 7.68$ (s, 1H), 7.06–6.77 (m, 3H, aromatic), 5.08 (s, 2H), 3.91 (q, 2H, $J = 7.0$ Hz), 3.25 (sep, 1H, $J = 6.9$ Hz), 1.36 (t, 3H, $J = 7.0$ Hz), 1.23 (d, 6H, $J = 6.9$ Hz). ^{13}C NMR ($CDCl_3$): $\delta = 14.96$, 23.23, 27.05, 65.73, 98.61, 114.41, 117.15, 125.26, 141.87, 143.74, and 148.81.

3-*sec*-Butyl-2-(ethoxymethoxy)phenol, 6c. Prepared according to Procedure 2, to 1-*sec*-butyl-2-(ethoxymethoxy)benzene, **5c** (2.08 g, 10 mmol), in dry THF (20 mL), was added a cold (0°C) solution of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (1.66 mL, 11 mmol) and butyllithium, 1.6 M solution in hexanes (6.87 mL, 11 mmol), in dry THF (20 mL). After 1 hr trimethyl borate (1.14 mL, 10 mmol) was added. The solution was stirred for an additional hour. The ice-water cooling bath was removed and a 30% hydrogen peroxide solution (3 mL) was added, to yield 1.68 g (75%) of **6c**, as a viscous liquid. Anal. calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.31; H, 9.09. MS: *m*/*e* (%) 59(100), 77(7), 91(9), 123(5), 137(13), and 224(9). IR (KBr): 3337, 3043, 2964, 2930, 2876, 1589, 1463, 1387, 1333, 1288, 1194, 1156, 1056, 984, 788, and 749 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 7.62$ (s, 1H), 7.02–6.67 (m, 3H, aromatic), 5.03 (s, 2H), 3.87 (q, 2H, $J = 7.1$ Hz), 2.98 (m, 1H), 1.56 (m, 2H), 1.35 (t, 3H, $J = 7.1$ Hz), 1.18 (d, 3H), 0.87 (t, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 149.36$, 144.29, 142.42, 125.77, 117.69, 114.93, 99.13, 66.19, 34.35, 30.65, 21.52, 15.64, 12.68.

3-*tert*-Butyl-2-(ethoxymethoxy)phenol, 6d. Prepared according to Procedure 2, to 1-*tert*-butyl-2-(ethoxymethoxy)benzene, **5d** (2.08 g, 10 mmol), in dry THF (20 mL), was added a cold (0°C) solution of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (1.66 mL, 11 mmol) and butyllithium, 1.6 M solution in hexanes (6.87 mL, 11 mmol), in dry THF (20 mL). After 1 hr trimethyl borate (1.14 mL, 10 mmol) was added. The solution was stirred for an additional hour. The ice-water cooling bath was removed and a 30% hydrogen peroxide solution (3 mL) was added, to afford 1.75 g (78%) of **6d**, as a viscous liquid. Anal. calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.98; H, 8.68. MS: *m*/*e* (%) 59(100), 77(11), 123(10), 151(8), and 224(7). IR (KBr): 3338, 2960, 1587, 1451, 1283, 1227, 1058, 984, 786, and 745 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 8.27$ (s, 1H), 6.97–6.78 (m, 3H, aromatic), 5.07 (s, 2H), 3.94 (q, 2H), 1.36 (m, 12H). ^{13}C NMR ($CDCl_3$): $\delta = 15.51$, 31.14, 35.31, 66.34, 99.21, 116.41, 118.09, 125.13, 143.63, 146.60, and 150.19.

Procedure 3

2-(Benzyloxy)-6-isopropylphenol, 7b. The mixture 2-(ethoxymethoxy)-3-isopropylphenol, **6b** (3.57 g, 17 mmol), benzyl bromide (8.1 mL, 68 mmol) and K_2CO_3 (4.7 g, 34 mmol), in acetone (40 mL), was refluxed in a 125 mL round-bottom flask until completion of the reaction followed by TLC.

The reaction mixture was filtered off and the filtrate was rotary evaporated. The remainder was refluxed in methanol (40 mL) and 3 M HCl (3 mL) and the removal of the ether protecting group was accompanied by TLC. The organic layer was separated, rotary evaporated, and purified by column chromatography on silica gel eluted with hexane/chloroform, 1 : 1, to give 3.91 g of **7b** (95%), a viscous liquid decomposing above 250°C. Anal. calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.29; H, 7.46. MS: *m/e* (%) 65(13), 77(5), 91(100), 123(2), 150(2), and 242(4). IR (KBr): 3534, 3035, 2960, 2871, 1611, 1469, 1271, 1211, 1043, 735, and 699 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.49–7.43$ (m, 5H, C_6H_5), 6.95–6.85 (m, 3H, aromatic), 5.90 (s, 1H), 5.14 (s, 2H), 3.42 (sep, 1H, $J = 6.9$ Hz), 1.33 (d, 6H, $J = 6.9$ Hz). ^{13}C NMR ($CDCl_3$): $\delta = 22.46$, 27.05, 71.12, 109.42, 118.91, 119.31, 127.75, 128.27, 128.65, 134.56, 136.54, 143.00, and 145.44.

2-(Benzyloxy)-6-*sec*-butylphenol, 7c. Prepared according to Procedure 3, using 3-*sec*-butyl-2-(ethoxymethoxy)phenol, **6c** (3.36 g, 15 mmol), benzyl bromide (7.1 mL, 60 mmol), and K_2CO_3 (4.1 g, 30 mmol) in acetone (40 mL). The remainder was refluxed in methanol (40 mL) and 3 M HCl (3 mL) to give 3.46 g of **7c** (90%), a viscous liquid decomposing above 250°C. Anal. calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.35; H, 7.68. MS: *m/e* (%) 65(10), 91(100), 123(2), 164(2), and 256(4). IR (KBr): 3535, 3035, 2961, 2928, 2871, 1592, 1469, 1269, 1212, 1049, 736, and 699 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.38–7.34$ (m, 5H, C_6H_5), 6.81–6.75 (m, 3H, aromatic), 5.75 (s, 1H), 5.06 (s, 2H), 3.10 (m, 1H), 1.60 (m, 2H), 1.21 (d, 3H), 0.85 (t, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 12.86$, 21.02, 30.33, 34.66, 71.85, 110.00, 119.93, 120.37, 128.46, 128.97, 129.34, 134.14, 137.25, 144.08, and 146.17.

2-(Benzyloxy)-6-*tert*-butylphenol, 7d. Prepared according to Procedure 3, using 3-*tert*-butyl-2-(ethoxymethoxy)phenol, **6d**, benzyl bromide (4.8 mL, 40 mmol) and K_2CO_3 (2.8 g, 20 mmol), in acetone(40 mL). The remainder was refluxed in methanol (40 mL) and 3 M HCl (3 mL) to give 2.28 g of **7d** (89%), a viscous liquid decomposing above 250°C. Anal. calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.43; H, 7.80. MS: *m/e* (%) 65(10), 91(100), 107(2), 123(2), 200(2), and 256(2). IR (KBr): 3534, 3035, 2961, 2928, 2872, 1592, 1469, 1271, 1211, 1049, 735, and 699 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.32–7.25$ (m, 5H, C_6H_5), 6.84–6.65 (m, 3H, aromatic), 5.96 (s, 1H), 4.96 (s, 2H), 1.32 (s, 9H). ^{13}C NMR ($CDCl_3$): $\delta = 30.06$, 35.35, 71.99, 110.52, 119.34, 120.04, 128.46, 128.97, 129.34, 136.47, 137.18, 145.18, and 146.62.

Procedure 4

2-(2-Bromoethoxy)-3-isopropylphenol, 1b. In a 125 mL round-bottom flask 2-(benzyloxy)-6-isopropylphenol, **7b** (2.42 g, 10 mmol), 1,2-dibromoethane

(2.6 mL, 30 mmol) and K_2CO_3 (4.1 g, 30 mmol) in acetone (20 mL) were refluxed, for 48 hr. The solution was filtered and the organic phase evaporated under vacuum. The residue was mixed with 10% wt. palladium on activated carbon (0.05 g) in methanol (20 mL) and hydrogenated at 60 psi. The reaction was monitored to completion by TLC. The organic layer was separated, evaporated under vacuum, and column chromatographed on silica gel using hexane/chloroform, 1 : 1, as eluent to afford 0.73 g (27%) of **1b**, a viscous liquid. Anal. calcd. for $C_{11}H_{15}BrO_2$: C, 50.98; H, 5.83. Found: C, 51.22; H, 5.71. MS: *m/e* (%) 51(29), 66(24), 77(47), 91(27), 107(100), 109(83), 123(57), 137(22), 151(63), 163(29), 216(8), 218(8), 243(30), 245(30), 258(43), and 260(45). IR (KBr): 3481, 2962, 2922, 2863, 1585, 1464, 1279, 1183, 1065, 997, 779, and 742 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 6.94–6.70$ (m, 3H, aromatic), 5.90 (s, 1H), 4.10 (m, 2H), 3.64 (m, 2H), 3.18 (sep, 1H, $J = 6.9$ Hz), 1.16 (d, 6H, $J = 6.9$ Hz). ^{13}C NMR ($CDCl_3$): $\delta = 24.48$, 27.32, 32.22, 74.13, 113.98, 118.49, 126.28, 142.82, 143.00, and 149.64.

2-(2-Bromoethoxy)-3-*sec*-butylphenol, 1c. Prepared according to Procedure 4, a solution of 2-(benzyloxy)-6-*sec*-butylphenol, **7c** (2.82 g, 11 mmol), 1,2-dibromoethane (2.6 mL, 30 mmol) and K_2CO_3 (4.1 g, 30 mmol) in acetone (20 mL) was refluxed for 48 hr. The residue was mixed with 10% wt. palladium on activated carbon (0.05 g) in methanol (20 mL) and hydrogenated at 60 psi to give 0.57 g (19%) of **1c**, a viscous liquid. Anal. calcd. for $C_{12}H_{17}BrO_2$: C, 52.76; H, 6.27. Found: C, 53.67; H, 6.02. MS: *m/e* (%) 51(58), 77(49), 91(44), 107(96), 109(84), 123(69), 136(50), 163(46), 215(10), 217(10), 243(99), 245(100), 272(53), and 274(52). IR (KBr): 3481, 2960, 2922, 2863, 1579, 1465, 1277, 1177, 1067, 997, 779, and 742 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.07–6.70$ (m, 3H, aromatic), 5.98 (s, 1H), 4.16 (m, 2H), 3.72 (m, 2H), 3.00 (m, 1H), 1.59 (m, 2H), 1.21 (d, 3H), 0.84 (t, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 13.05$, 22.46, 31.42, 32.26, 34.24, 74.13, 113.82, 118.73, 126.25, 141.72, 143.56, and 149.57.

2-(2-Bromoethoxy)-3-*tert*-butylphenol, 1d. Prepared according to Procedure 4, a solution of 2-(benzyloxy)-6-*tert*-butylphenol, **7d** (1.50 g, 5.8 mmol), 1,2-dibromoethane (1.3 mL, 15 mmol) and K_2CO_3 (2.0 g, 15 mmol) in acetone (15 mL) was refluxed for 72 hr. The residue was mixed with 10 % wt. palladium on activated carbon (0.05 g) in methanol (20 mL) and hydrogenated at 60 psi to yield 0.19 g (12%) of **1d**, a viscous liquid. Anal. calcd. for $C_{12}H_{17}BrO_2$: C, 52.76; H, 6.27. Found: C, 53.08; H, 6.07. MS: *m/e* (%) 55(60), 65(35), 80(99), 82(100), 91(41), 107(81), 109(60), 123(22), 137(27), 149(48), 177(95), 192(38), 257(58), 259(54), 272(18), and 274(14). IR (KBr): 3448, 2957, 2922, 2863, 1584, 1445, 1276, 1220, 1159, 1078, 1000, 934, 779, and 743 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 6.90–6.75$ (m, 3H, aromatic), 5.60 (s, 1H), 4.16 (m, 2H), 3.67 (m, 2H), 1.32 (s, 9H). ^{13}C NMR ($CDCl_3$): $\delta = 31.84$, 32.20, 72.65, 115.44, 119.63, 125.25, 144.18, 145.28, and 150.24.

Procedure 5

2,3-Dihydro-5-methyl-1,4-benzodioxin, 4a. A solution of 2-(2-bromoethoxy)-3-methylphenol, **1a** (0.11 g, 0.47 mmol) in ethanol (100 mL) was added to 1 M NaOH (5 mL). The resulting reaction mixture was stirred for 1 hr. Evaporation to dryness and extraction with chloroform afforded 0.07 g (100%) of **4a**. B.p. (lit) 74°C/1.4 mmHg.[14] Anal. calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.58; H, 6.69. MS: *m/e* (%) 51(13), 66(70), 77(10), 94(85), 135(14), and 150(100). IR (KBr): 3038, 2978, 2925, 2877, 1606, 1482, 1380, 1280, 1201, 1101, 950, 889, 769, and 724 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 6.64–6.65$ (m, 3H, aromatic), 4.19 (m, 4H), 2.12 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 16.07$, 64.83, 64.98, 115.51,121.06, 123.38, 127.39, 142.42, and 143.94.

2,3-Dihydro-5-isopropyl-1,4-benzodioxin, 4b. Prepared according to Procedure 5, 2-(2-bromoethoxy)-3-isopropylphenol, **1b** (0.13 g, 0.5 mmol) in ethanol (100 mL) and 1 M NaOH (5 mL) were stirred for 1 hr to give 0.09 g (100%) of **4b**, a viscous liquid. Anal. calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73. 89; H, 7.97. MS: *m/e* (%) 51(10), 65(8), 77(14), 83(20), 91(20), 107(8), 119(4), 135(2), 149(3), 163(100), and 178(33). IR (KBr): 3042, 2965, 2875, 1602, 1472, 1300, 1280, 1259, 1194, 1084, 963, 781, and 733 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 6.71–6.66$ (m, 3H, aromatic), 4.14 (m, 4H), 3.16 (sep, 1H, $J = 6.9$ Hz), 1.12 (d, 6H, $J = 6.9$ Hz). ^{13}C NMR ($CDCl_3$): $\delta = 23.37$, 27.27, 64.88, 115.44, 118.82, 121.46, 138.13, 141.54, and 144.04.

5-*sec*-Butyl-2,3-dihydro-1,4-benzodioxin, 4c. Prepared according to Procedure 5, 2-(2-bromoethoxy)-3-*sec*-butylphenol, **1c** (0.13 g, 0.48 mmol) in ethanol (100 mL) and 1 M NaOH (5 mL) were stirred for 1 hr to afford 0.092 g (100%) of **4c**, a viscous liquid. Anal. calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.54; H, 8.33. MS: *m/e* (%) 51(10), 65(10), 77(16), 91(21), 107(7), 119(3), 135(2), 149(9), 163(100), 177(2), and 192(24). IR (KBr): 3039, 2963, 2928, 2873, 1597, 1467, 1300, 1280, 1257, 1193, 1087, 947, 776, and 734 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 6.79–6.71$ (m, 3H, aromatic), 4.24 (m, 4H), 3.00 (m, 1H), 1.56 (m, 2H), 1.18 (d, 3H), 0.85 (t, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 12.85$, 21.06, 30.50, 33.98, 64.83, 115.23, 119.49, 121.36, 137.07, 141.81, and 143.97.

5-*tert*-Butyl-2,3-dihydro-1,4-benzodioxin, 4d. Prepared according to Procedure 5, 2-(2-bromoethoxy)-3-*tert*-butylphenol, **1d** (0.14 g, 0.52 mmol) in ethanol (100 mL) and 1M NaOH (5 mL) were stirred for 1 hr to yield 0.10 g (100%) of **4d**, a viscous liquid. Anal. calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.68; H, 8.41 MS: *m/e* (%) 51(13), 65(10), 77(18), 91(15), 105(9), 149(45), 163(1), 177(100), and 192(37). IR (KBr): 2957, 2926, 2874, 1590, 1468, 1443, 1379, 1300, 1282, 1241, 1094, 953, 782, and

734 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 6.85-6.73$ (m, 3H, aromatic), 4.23 (m, 4H), 1.36 (s, 9H).^{13}C NMR ($CDCl_3$): $\delta = 30.35$, 35.54, 64.13, 64.72, 116.17, 119.30, 121.01, 130.28, 139.59, and 144.55.

ACKNOWLEDGMENTS

We are grateful to Brazilian CNPq and PRONEX for supporting this work.

REFERENCES

1. Illuminati, G.; Mandolini, L.; Masci, B. Ring-closure reactions. II. Kinetics of six- to ten-membered ring formation from *o*-*ω*-bromoalkoxyphenoxides. J. Am. Chem. Soc. **1974**, *96* (5), 1422–1427.
2. Illuminati, G.; Mandolini, L.; Masci, B. Ring-closure reactions. 19. Kinetics of formation of benzo-crown etheres by intramolecular nucleophilic substitution. A comparison between poly(oxyethylene) and polymethylene chains. J. Am. Chem. Soc. **1981**, *103* (14), 4142–4145.
3. Illuminati, G.; Mandolini, L.; Masci, B. Ring-closure reactions. V. Kinetics of five- to ten-membered ring formation from *o*-*ω*-bromoalkylphenoxides. The influence of the O-heteroatom. J. Am. Chem. Soc. **1975**, *97* (17), 4960–4966.
4. Illuminati, G.; Mandolini, L.; Masci, B. Ring-closure reactions. 9. Kinetics of ring formation from *o*-*ω*-bromoalkoxy phenoxides and *o*-*ω*-bromoalkyl phenoxides in the range of 11- to 24-membered rings. A comparison with related cyclization series. J. Am. Chem. Soc. **1977**, *99* (19), 6308–6312.
5. Cerichelli, G.; Luchetti, L.; Mancini, G.; Muzzioli, M.N.; Germani, R.; Ponti, P.P.; Spreti, N.; Savelli, G.; Bunton, C.A. Solvent and micellar effects upon the cyclisation of *o*-3-halopropyloxyphenoxide ions. J. Chem. Soc. Perkin Trans. II **1989**, (8), 1081–1085.
6. Cerichelli, G.; Mancini, G.; Luchetti, L.; Savelli, G.; Bunton, C.A. Surfactant effects upon cyclization of *o*-(*ω*-haloalkoxy)phenoxide ions. The role of premicellar assemblies. Langmuir **1994**, *10* (11), 3982–3987.
7. DiProfio, P.; Germani, R.; Savelli, G.; Cerichelli, G.; Spreti, N.; Bunton, C.A. Cyclisation and decarboxylation in zwitterionic micelles: effects of head group structure. J. Chem. Soc. Perkin Trans. 2 **1996**, (7), 1505–1508.

8. Borchardt, R.T.; Cohen, L.A. Stereopopulation control. II. Rate enhancement of intramolecular nucleophilic displacement. J. Am. Chem. Soc. **1972**, *94* (26), 9166–9174.
9. Milstien, S.; Cohen, L.A. Stereopopulation control. I. Rate enhancement in the lactonizations of *o*-hydroxyhydrocinnamic acids. J. Am. Chem. Soc. **1972**, *94* (26), 9158–9165.
10. Nerdinger, S.; Kendall, C.; Marchhart, R.; Riebel, P.; Johnson, M.R.; Yin, C.-F.; Eltis, L.D.; Snieckus, V. Directed *ortho* metalation and Suzuki–Miyaura cross-coupling connections: Regiospecific synthesis of all isomeric chlorodihydroxybiphenyls for microbial degradation studes of PCBs. Chem. Commun. **1999**, (22), 2259–2260.
11. Snieckus, V. Directed ortho metalation. Tertiary amide and *O*-carbamate directors in synthetic strategies for polysubstituted aromatics. Chem. Ver. **1990**, *90*, 879–933.
12. Posner, G.H.; Canella, K.A. Phenoxide-directed ortho lithiation. J. Am. Chem. Soc. **1985**, *107* (8), 2571–2573.
13. Parker, K.A.; Koziski, K.A. Directed hydroxylation of aromatics. J. Org. Chem. **1987**, *52* (4), 674–676.
14. Haruta, A.M.; Satoh, J.Y. The reaction of alkylcyclohexanones with copper(II) bromide and 1,2-glycols. Chem. Lett. **1980**, *5*, 473–476.

Received in the USA March 2, 2004