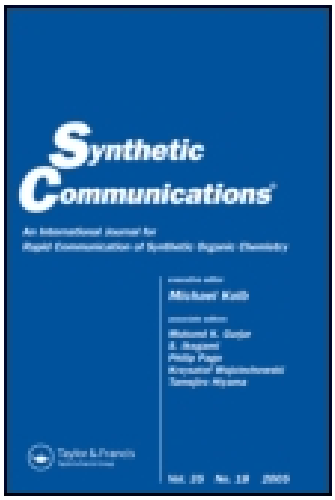

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 09 Nov 2006.

To cite this article: Paulo Marcos Donate , Rosangela da Silva , Gil Valdo José da Silva & Carlos Alemán (2001) SYNTHESIS OF BENZOFURANOFURAN DERIVATIVES: MODEL OF NATURAL PRODUCTS, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:1, 151-154, DOI: 10.1081/SCC-100000191

To link to this article: http://dx.doi.org/10.1081/SCC-100000191

SYNTHETIC COMMUNICATIONS, 31(1), 141–150 (2001)

SYNTHESIS OF BENZOFURANOFURAN DERIVATIVES: MODEL OF NATURAL PRODUCTS

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ABSTRACT

Several benzofuranofuran derivatives were synthesized employing intramolecular cycloaddition reactions of ketenes with alkenes. (Alkenyloxy)ketenes, prepared from the tosylate by treatment with triethylamine, easily undergo intramolecular $[2 + 2]$ cycloaddition to give tricyclic benzocyclobutafuranones. Baeyer-Villiger oxidation of the cycloadducts gives benzofurano-furanones, which are closely related to natural products with anticoagulant and antimalarial properties.

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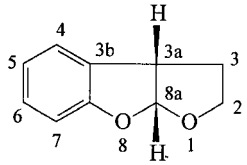

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Figure 1.

The skeleton of the tricyclic compound 3a,8a-dihydro-2H,3H,3aH,8aH-benzo[b]oxolano[3,2-d]furan **1** (see Fig. 1) appears as a moiety in a large number of natural products (1–6).

These compounds show very interesting properties that depend on their chemical constitution (see Fig. 2). Many of them are highly toxic, mutagenic, or carcinogenic, among other activities. Aflatoxin B_1 (**2**) belongs to a group of acutely toxic and highly carcinogenic mold metabolites produced by *Aspergillus flavus* (1). Pseudosemiglabrin (**3**) and semiglabrin (**4**) have anticoagulant and antimalarial activities (2). Microminutinin (**5**) pertains to a class of compounds that displays in vivo activity in the lymphocytic leukemia test system (3–5), while several other compounds with the benzofuranofuranone unit, e.g., **6** and **7**, have anticoagulant activity (6). Furthermore, very recent theoretical studies have revealed that the five-membered rings of the benzofuranofuran derivatives present complex conformational properties (7). The relevant biological and chemical properties render these compounds interesting as synthetic targets. In this work, the intramolecular

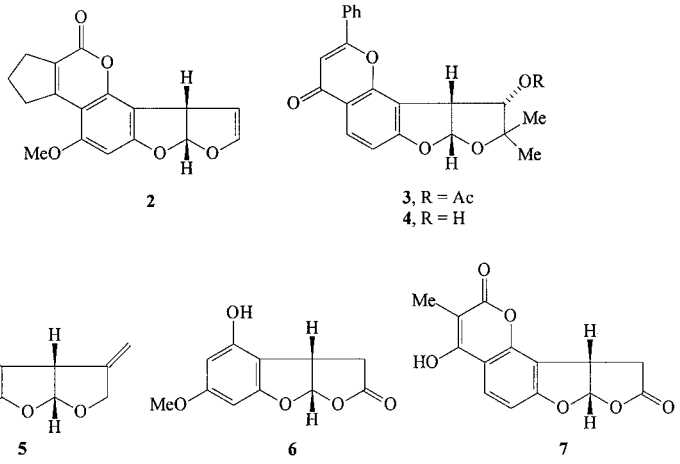

Figure 2.

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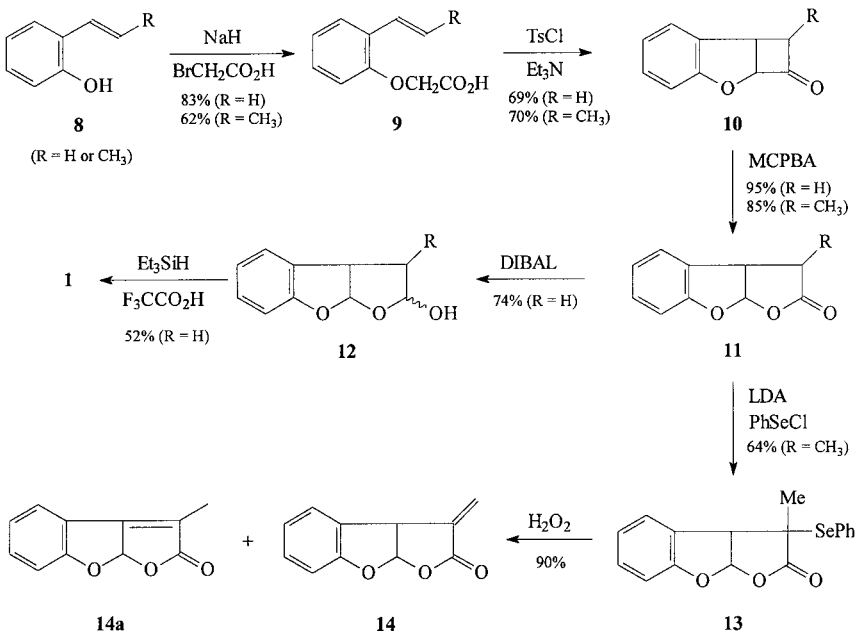
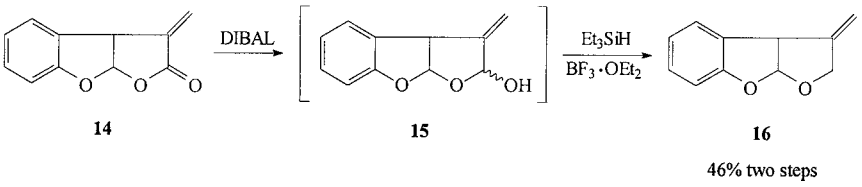


Scheme 1.

[2 + 2] cycloaddition of alkoxyketenes with alkenes developed by Snider and Hui (8) and by Brady and Giang (9) was used as a useful synthetic method to obtain these polycyclic compounds.

The syntheses of model compounds of the natural products shown in Figure 2 were carried out by the procedure presented in Schemes 1–2.

Reaction of the alkoxide from 2-alkenylphenol **8** (R = H or CH_3) with bromoacetic acid (8,9) furnished the acid **9** [yield: 83% (R = H), 62% (R = CH_3)]. Compound **9**, by reaction with tosyl chloride and triethylamine (10), afforded the tricyclic ketone **10** [yield: 69% (R = H), 70% (R = CH_3)], an



Scheme 2.

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intramolecular [2 + 2] cycloaddition product. Lactone **11**, which can be regarded as a model compound of natural products **6** and **7**, was obtained through a Baeyer-Villiger reaction of compound **10** [yield: 95% (R = H), 85% (R = CH_3). Lactol **12** (R = H), was prepared from the reduction of lactone **11** (R = H) with DIBAL (11) (yield: 74%). The latter compound provided the compound **1** (yield: 52%) (12) after treatment with triethylsilane/trifluoroacetic acid (11). Treatment of **11** (R = CH_3) with LDA/PhSeCl (13,14) afforded compound **13** (yield: 64%), which, after treatment with H_2O_2, furnished a mixture of the compounds **14** and **14a** in a 2:3 ratio (yield: 90%). It was observed that the α-methylene-γ-butyrolactone **14** isomerizes to the butenolide **14a** during the chromatographic purification on a silica gel column.

The treatment of compound **14** with DIBAL (11) yielded compound **15** (not isolated), which, by reaction with $Et_3SiH/BF_3 \cdot OEt_2$ (15), furnished compound **16** (yield: 46% over two steps). This compound is the model of microminutinin (**5**).

The synthesis of natural product microminutinin and its analogues by applying this methodology is in progress (16).

EXPERIMENTAL

Melting points were determined on a Reichert Kofler block melting point apparatus and are uncorrected. NMR spectra were recorded using a Bruker DPX-300 (300 MHz ^{1}H NMR and 75 MHz ^{13}C NMR) instrument. GC-MS spectra were obtained by EI ionization at 70 eV on a HP-5988-A spectrometer. IR spectra were measured with a Perkin-Elmer 1600 FT spectrometer. Elemental analyses were carried out on a CE instrument EA-1110. TLC was performed on precoated silica gel 60 F254 (0.25 mm thick, Merck), and for column chromatography silica gel 60 70-230 mesh (Merck) was used. Given yields correspond to materials with the same purity as the samples used in the subsequent steps. The reaction products were isolated from solution by evaporation under water-aspirator vacuum at room temperature, using a rotary evaporator.

General Procedure for Preparation of (2-Alkenylphenoxy) Acetic Acids (8,9)

The alkenylphenol (30 mmol) was dissolved in anhydrous THF under N_2 and treated with NaH (65 mmol, 60% dispersion in mineral oil). The mixture was stirred for 20 min and treated with 1 equiv of bromoacetic acid. After effervescence had subsided, the mixture was heated at reflux for 4–6 h and stirred at room temperature overnight. The reaction was diluted with ether and quenched with saturated brine and enough water to dissolve all the salts. The aqueous layer was adjusted to pH 10.5 with Na_2CO_3 solution. The aqueous layer was separated, washed twice

with ether, acidified to pH 1 with concentrated HCl, and extracted with three portions of ether. The combined extracts were washed with water and brine, dried (Na_2SO_4), and evaporated in vacuum to give the pure (alkenylphenoxy) acetic acids.

2-(2-Vinylphenoxy)acetic acid (**9**, R = H)

4.43 g (83% yield) of this acid were obtained with mp 124°–127°C (8); IR (KBr) 3415, 2924, 1455, 1713, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20 (br.s, 1H); 7.51–6.97 (m, 4H), 7.10 (dd, 1H, J = 17.7 Hz, J = 11.3 Hz) 5.80 (dd, 1H, J = 17.7 Hz, J = 1.5 Hz), 5.31 (dd, 1H, J = 11.3 Hz, J = 1.5 Hz), 4.70 (s, 2H); MS m/z (rel. intensity) 178 (M^+, 72), 133 (53), 105 (76), 91 (100), 77 (49).

2-[(2-Prop-1-enyl)phenoxy)]acetic acid (**9**, R = CH_3)

3.57 g (62% yield) of this acid were obtained with mp 101°–102°C (lit. (9): 101°–102°C); ^1H NMR ($CDCl_3$) δ 8.70 (br.s, 1H), 7.55–6.95 (m, 5H), 6.30 (m, 1H), 4.65 (s, 2H), 1.89 (dd, 3H, J = 1.7 Hz, J = 6.6 Hz); MS m/z (rel. intensity) 192 (M^+, 100), 133 (71), 131 (64), 105 (84), 91 (63), 77 (37).

General Procedure for Conversion of Acids into Tosylates and Subsequent Intramolecular Cycloaddition (10)

A solution of (2-alkenylphenoxy)acetic acid (4.5 mmol) in benzene (50 mL) was added over 5 h through a syringe to a refluxing solution of trietylamine (22.5 mmol) and *p*-toluenesulfonyl chloride (9 mmol) in benzene (50 mL). After addition was completed, the mixture was gently refluxed for 2–6 h. Upon cooling, the mixture was washed with water (3 × 50 mL) and then concentrated under water aspirator vacuum to about 30 mL. This concentrate was stirred with 3% aqueous sodium NaOH solution (250 mL) for 10 h to remove excess tosyl chloride. The benzene layer was dried with anhydrous magnesium sulfate, filtered, and the benzene evaporated. The residue was purified by column chromatography on silica gel, eluting with 3% ethyl acetate in hexane, to give cycloaddition product.

1,2a,7b-Trihydrobenzo[b]cyclobuta[1,2-d]furan-2-one (**10**, R = H)

Acid **9** (R = H) (92.3 mg, 0.518 mmol) was converted to the tosylate and added to trietylamine in benzene at reflux for 2 h as described above. Normal workup, followed by chromatography on silica gel, eluting with CH_2Cl_2, gave

57.6 mg (69%) of pure **10** (R = H) as white solid mp 30°–32°C (lit. (8): 31°–32°C); IR (KBr) 2907, 1744, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–6.85 (m, 4H), 5.65 (dt, 1H, J = 7.5 Hz, J = 3.0 Hz, J = 3.0 Hz), 4.20 (ddd, 1H, J = 7.5 Hz, J = 3.8 Hz, J = 8.4 Hz), 3.65 (ddd, 1H, J = 8.4 Hz, J = 3.0 Hz, J = 17.7 Hz), 3.05 (ddd, 1H, J = 3.8 Hz, J = 3.0 Hz, J = 17.7 Hz); ^{13}C NMR ($CDCl_3$) δ 205.6 (C), 160.9 (C), 129.1 (C), 127.9 (CH), 125.8 (CH), 125.8 (CH), 110.7 (CH), 94.4 (CH), 55.8 (CH), 35.1 (CH_2); MS m/z (rel. intensity) 160 (M^+, 2), 131 (30), 118 (100), 103 (9), 90 (20), 77 (14).

1-Methyl-1,2a,7b-trihydrobenzo[b]cyclobuta[1,2-d]furan-2-one (**10**, R = CH_3)

Acid **9** (R = CH_3) (517.2 mg, 2.69 mmol) was converted to the tosylate and added to trietylamine in benzene at reflux for 3 h as described above. Normal workup, followed by chromatography on silica gel, eluting with CH_2Cl_2, gave 330.6 g (70%) of pure **10** (R = CH_3) as white solid mp 65°–67°C (lit. (9): 65°–66°C); ^1H NMR ($CDCl_3$) δ 7.30–6.85 (m, 4H), 5.75 (dd, 1H, J = 8.3 Hz, J = 2.8 Hz), 4.29 (dd, 1H, J = 8.3 Hz, J = 8.9 Hz), 3.80 (m, 1H), 1.05 (d, 3H, J = 7.3 Hz); MS m/z (rel. intensity) 174 (M^+, 3), 145 (5), 118 (100), 103 (2), 90 (9), 63 (6), 39 (5).

General Procedure for Baeyer-Villiger Oxidation (8)

Solid $NaHCO_3$ (3 equiv) and *m*-chloroperoxybenzoic acid (85% pure, 1.05 equiv) were added rapidly to a solution of tricyclic ketone (34 mmol) in dry CH_2Cl_2 (5 mL) under stirring. The reaction mixture was stirred for 2 h, diluted with CH_2Cl_2 (20 mL), and quenched with 10% aqueous Na_2CO_3 solution. The organic layer was washed with 10% Na_2CO_3 solution and brine, dried over anhydrous sodium sulfate, and evaporated to give the product.

3,3a,8a-Trihydrobenzo[b]furano[3,2-d]furan-2-one (**11**, R = H)

Baeyer-Villiger oxidation of ketone **10** (R = H) (45.5 mg, 0.284 mmol) as described above gave 47.7 mg (95%) of pure **11** (R = H) as white solid mp 123°–126°C (lit. (8): 124°–126°C); IR (KBr) 2994, 1782, 1221 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33–6.90 (m, 4H), 6.55 (d, 1H, J = 9.7 Hz), 4.24 (dt, 1H, J = 9.7 Hz, J = 2.4 Hz, J = 9.7 Hz), 3.10 (dd, 1H, J = 9.7 Hz, J = 17.9 Hz), 2.83 (dd, 1H, J = 2.4 Hz, J = 17.9 Hz); ^{13}C NMR ($CDCl_3$) δ 173.6 (C), 157.2 (C), 129.9 (CH_3), 126.6 (C), 124.7 (CH), 122.9 (CH), 110.9 (CH), 107.6 (CH), 42.3 (CH), 34.6 (CH_2); MS m/z (rel. intensity) 176 (M^+, 46), 147 (100), 131 (12), 103 (70), 91 (37).

3-Methyl-3,3a,8a-trihydrobenzo[b]furano[3,2-d]furan-2-one (**11**, R = CH_3)

Baeyer-Villiger oxidation of ketone **10** (R = CH_3) (261.0 mg, 1.5 mmol) as described above gave 242.2 mg (85%) of pure **11** (R = CH_3) as white solid mp 140°–142°C; ^{1}H NMR ($CDCl_3$) δ 7.33–6.90 (m, 4H arom), 6.55 (d, 1H, J = 7.0 Hz), 4.25 (dd, 1H, J = 7.0 Hz, J = 11.6 Hz), 3.22 (m, 1H), 1.42 (d, 3H, J = 9.1Hz); MS m/z (rel. intensity) 190 (M^+, 69), 161 (100), 145 (22), 115 (45), 105 (55), 91 (19), 77 (30); Anal. calcd for $C_{11}H_{10}O_3$: C, 69.47; H, 5.26. Found: C, 69.41; H, 5.04.

3a,8a-Dihydro-2H,3H,3aH,8aH-benzo[b]oxolano[3,2-d]furan (**12**)

Lactone **11** (R = H) (41 mg 0.233 mmol) was dissolved in dry toluene (2 mL) under N_2 and then cooled at −78°C. DIBAL-H (0.35 mL, 0.349 mmol, 1 M in toluene) was added, and the solution was stirred for 1.5 h. After addition of crushed ice, acetic acid (0.15 mL), and chloroform (3 mL), the mixture was stirred for another 30 min. The organic layer was separated, washed with saturated $NaHCO_3$ solution and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure gave 30.7 mg (74%) of lactol **12** (R = H) as colorless oil. This oil was dissoved in CH_2Cl_2 (3 mL), and cooled at −78°C under nitrogen atmosphere. Triethylsilane (60.1 mg, 0.517 mmol) and trifluoroacetic acid (58.9 mg, 0.517 mmol) were added, and the solution was stirred for 3.5 h at 0°C. Then 5% $NaHCO_3$ solution (2 mL) was added and the mixture stirred for 10 min. The organic layer was separated, washed with brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure gave 17.1 mg of crude **1**. Chromatography on silica gel, eluting with a mixture of dichlorometane:hexane (1:1), gave 14.4 mg (52%) as colorless oil (12); IR 3047, 2975, 1595, 1458, 1241, 1076 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33–6.85 (m, 4H), 6.42 (d, 1H, J = 5.7 Hz), 4.05 (m, 1H), 4.02 (m, 1H), 3.65 (m, 1H), 2.30 (m, 1H), 2.05 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 159.4 (C), 128.7 (CH), 127.6 (C), 124.7 (CH), 121.1 (CH), 110.9 (CH), 109.2 (CH), 67.2 (CH_2), 46.5 (CH), 29.0 (CH_2); MS m/z (rel. intensity) 162 (M^+, 100), 147 (63), 119 (29), 105 (50), 91 (40), 77 (50); Anal. calcd for $C_{10}H_{10}O_2$: C, 74.07; H, 6.17. Found: C, 74.32; H, 6.32.

3-Methyl-3-(phenylselenamethyl)3,3a,8a-trihydrobenzo[b]furano[3,2-d]furan-2-one (**13**)

A solution of *n*-butyllithium (1.16 mmol, 1.1 M in hexane) was added to a solution of diisopropylamine (122.5 mg, 1.21 mmol) in anhydrous THF (5 mL),

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maintained at 0°C under nitrogen atmosphere. After stirring for 10 min at 0°C, the solution was cooled to −78°C and, after 15 min, a solution of compound **11** (R = CH_3) (200.7 mg, 1.05 mmol) in anhydrous THF (2 mL) was added. Stirring was continued for 30 min, and then a solution of phenylselenenyl chloride (201 mg, 1.05 mmol) in THF (1 mL) was added. After stirring for 2 h at −20°C, the reaction mixture was quenched by addition of a saturated aqueous solution of NH_4Cl, diluted with water, and extracted with ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by column chromatography through silica gel, eluting with hexane:ethyl acetate (9:1), to give 231.8 mg (64%) compound **13** as yellow solid mp 122°–124°C; ^{1}H NMR ($CDCl_3$) δ 7.82–6.90 (m, 9H), 5.91 (d, 1H, J = 5.7 Hz), 4.25 (d, 1H, J = 5.7 Hz), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 175.1 (C), 157.2 (C), 138.1 (CH), 130.5 (CH), 130.2 (CH), 129.5 (CH), 126.8 (C), 122.3 (CH), 111.3 (CH), 104.7 (CH), 54.7 (CH), 47 (C), 20.5 (CH_3); MS m/z (rel. intensity) 346 (M^+, 17), 161 (100), 158 (28), 145 (13), 77 (29); Anal. calcd for $C_{17}H_{14}O_3Se$: C, 59.3; H, 4.07. Found: C, 59.54; H, 4.21.

3-Methylene-3a,8a-dihydrobenzo[b]furano[3,2-d]furan-2-one (**14**)
and 3-methyl-8a-hydrobenzo[b]furano[3,2-d]furan-2-one (**14a**) (13,14)

Aqueous H_2O_2 (30%, 0.5 mL) was added to a solution of compound **13** (226.1 mg, 0.65 mmol) in dichlorometane (2 mL), and cooled at 0°C. The reaction mixture was stirred at room temperature for 40 min and then diluted with water. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by column chromatography through silica gel, eluting with hexane:ethyl acetate (9:1), to give the compounds **14** (48.4 mg, 39%) and **14a** (62.4 mg, 51%).

Compound 14: mp 120°–122°C; ^{1}H NMR ($CDCl_3$) δ 7.32–6.81 (m, 4H), 6.55 (d, 1H, J = 6.2 Hz), 6.35 (d, 1H, J = 1.8 Hz), 6.01 (d, 1H, J = 1.8 Hz), 4.70 (d, 1H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 167.4 (C), 157.3 (C), 135.4 (C), 130.1 (CH), 125.0 (C), 124.2 (CH), 123.7 (CH_2), 122.9 (CH), 111.0 (CH), 105.0 (CH), 47.1 (CH); MS m/z (rel. intensity) 188 (M^+, 23), 159 (100), 131 (40), 115 (57), 105 (13), 77 (29), 63 (12); Anal. calcd for $C_{11}H_8O_3$: C, 70.21; H, 4.26. Found: C, 70.35; H, 4.16.

Compound 14a: mp 92°–94°C; ^{1}H NMR ($CDCl_3$) δ 7.32–7.01 (m, 4H), 6.57 (q, 1H, J = 1.9 Hz), 2.07 (d, 3H, J = 1.9 Hz); ^{13}C NMR ($CDCl_3$) δ 172.7 (C), 163.6 (C), 160.6 (C), 133.3 (CH), 124.2 (CH), 123.1 (CH), 122.5 (C), 120.6 (C), 112.5 (CH), 106.9 (CH), 9.86 (CH_3); MS m/z (rel. intensity) 188 (M^+, 54), 160 (19), 131 (100), 115 (27), 103 (23), 77 (30), 63 (20), 51 (26); Anal. calcd for $C_{11}H_8O_3$: C, 70.21; H, 4.26. Found: C, 70.32; H, 4.31.

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3-Methylene-2,3a,8a-trihydrobenzo[b]furano[3,2-d]furan (**16**) (15)

DIBAL-H (0.3 mL, 0.3 mmol, 1 M in toluene) was added to a solution of compound **14** (48.1 mg, 0.26 mmol) in toluene (2 mL), maintained at −78°C under nitrogen atmosphere. After stirring for 1 h at −78°C, the reaction mixture was quenched by addition of crushed ice and acetic acid (0.3 mL). Chloroform (7 mL) was added and the mixture was stirred for 30 min. Then the layers were separated, and the organic layer was washed with saturated Na_2CO_3 solution and brine, and dried over anhydrous magnesium sulfate. The crude product, assumed to be the lactol **15**, obtained by evaporation of the solvent under reduced pressure, was dissolved in CH_2Cl_2 (3 mL), cooled at −78°C under nitrogen atmosphere, and treated with triethylsilane (45.3 mg, 0.39 mmol) and $BF_3 \cdot OEt_2$ (55 mg, 0.39 mmol). The solution was stirred for 1 h at 0°C and then a 5% $NaHCO_3$ solution (2 mL) was added. The organic layer was separated, washed with brine, and dried over anhydrous magnesium sulfate. The residue was purified by column chromatography through silica gel, eluting with a mixture of hexane:ethyl acetate (9:1), to give 20.5 mg (46%) of compound **16** as a white solid mp 36°–37°C; IR (KBr) 2968, 1671, 1596, 1478, 1461, 1220, 1072 cm^{-1}; ^1H NMR (benzene) δ 7.01–6.70 (m, 4H), 6.10 (d, 1H, J = 5.7 Hz), 4.85 (dt, 1H, J = 2.6 Hz, J = 1.6 Hz), 4.55 (dt, 1H, J = 2.2 Hz, J = 1.6 Hz), 4.08 (ddt, 1H, J = 12.3 Hz, J = 2.4 Hz, J = 1.6 Hz); 3.99 (dt, 1H, J = 12.3 Hz, J = 1.6 Hz), 3.67 (br.d, 1H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 158.6 (C), 147.9 (C), 129.1 (CH), 126.7 (C), 124.3 (CH), 121.3 (CH), 111.4 (CH), 109.7 (CH), 106.2 (CH_2), 70.5 (CH_2), 51.4 (CH); MS m/z (rel. intensity) 174 (M^+, 100), 145 (99), 131 (36), 115 (37), 91 (20), 77 (16), 51 (23), 39 (17); Anal. calcd for $C_{11}H_{10}O_2$: C, 75.86; H, 5.74. Found: C, 75.92; H, 5.78.

ACKNOWLEDGMENTS

The authors wish to thank to Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) and to Coordenadoria de Aperfeiçoamento de Pessoal do Ensino Superior (CAPES) for financial support.

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Received April 2, 2000

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