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Short Report

Racemic Synthesis of 1,2-*Seco*microminutinin

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A 1,2-*seco*microminutinina (**25**) racêmica foi sintetizada empregando-se a reação de cicloadição intramolecular de um alceniloxiceteno, preparado a partir do correspondente tosilato. O alceniloxiceteno sofre reação de cicloadição [2+2] intramolecular originando uma benzociclobutafuranona tricíclica (**16**) que, por oxidação de Bayer-Villiger, fornece uma benzofurofuranona (**17**). Reação desta última com propiolato de metila, catalisada por trifenilfosfina, produziu o derivado de éster cinâmico (**25**).

The racemic 1,2-*seco*microminutinin (**25**) was synthesized employing the intramolecular cycloaddition reaction of an (alkenyloxy)ketene, prepared from the corresponding tosylate. The (alkenyloxy)ketene undergoes intramolecular [2+2] cycloaddition to give tricyclic benzocyclobutafuranone (**16**), which by Baeyer-Villiger oxidation gives a benzofuranofuranone (**17**). Reaction of the latter compound with methyl propiolate, catalyzed by triphenylphosphine, produced the cinnamic ester derivative (**25**).

Keywords: 1,2-*seco*microminutinin, benzofuranofuran, intramolecular cycloaddition, synthesis

Introduction

The skeleton of the tricyclic compound 3a,8a-dihydro-2H,3H,3aH,8aH-benzo[*b*]oxolano[3,2-*d*]furan (**1**) appears as a moiety in a large number of natural products[1-4] (Figure 1).

These compounds are of special interest since they show very interesting properties depending on their chemical constitution. Many of them are highly toxic, mutagenic or carcinogenic, like aflatoxin B2 (**2**), a secondary fungal metabolite produced by certain strains of *Aspergillus flavus*.[1] They can also have useful properties due to their biological and pharmaceutical activity, like the antimalarial activity[2] presented by pseudosemiglabrin derivatives (**3** and **4**), two flavonoid metabolites isolated from a subtropical plant of the genus *Tephrosia*. And there still is the anticoagulant activity[3] of coumarins **5** and **6**.

Several biologically active compounds, some of which with the basic structure **1**, were isolated from *Micromelum* species, of the family Rutaceae, which are plants encountered in Asia, where they are traditionally used in folk medicine in the treatment of rheumatism, muscular atrophy and fever of different origins.[4] The coumarin microminutinin (**7**), and the dihydrocinnamic acid derivatives 3,4-dihydro-1,2-*seco*microminutinin (**8a**) and 3,4-dihydro-1,2-*seco*microminutinin methyl ester (**8b**) are three natural products that contain the same 3-methylene-

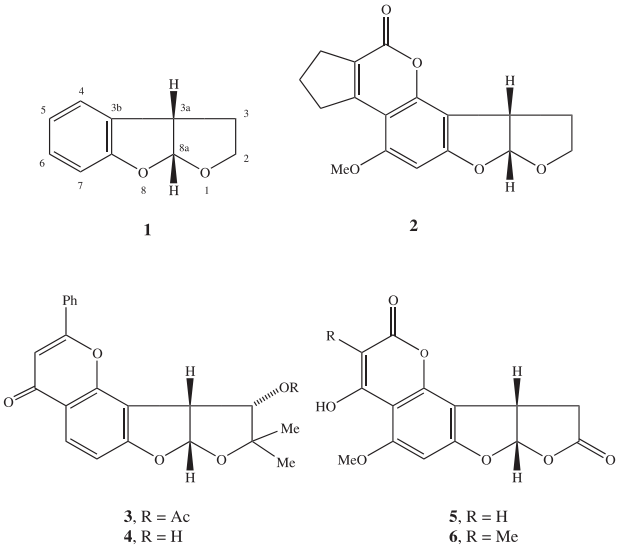

Figure 1. Benzo[*b*]furano[3,2-*d*]furan compounds.

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2,3a,8a-trihydrobenzo[*b*]furano[3,2-*d*]furan moiety in their structures (Figure 2), which have been recently isolated[4] from the leaves of the shrub *Micromelum falcatum*.

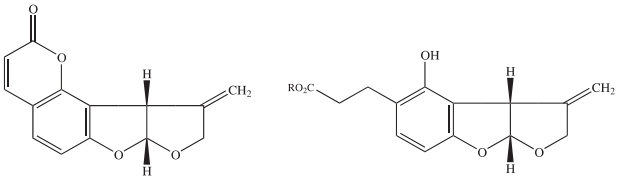


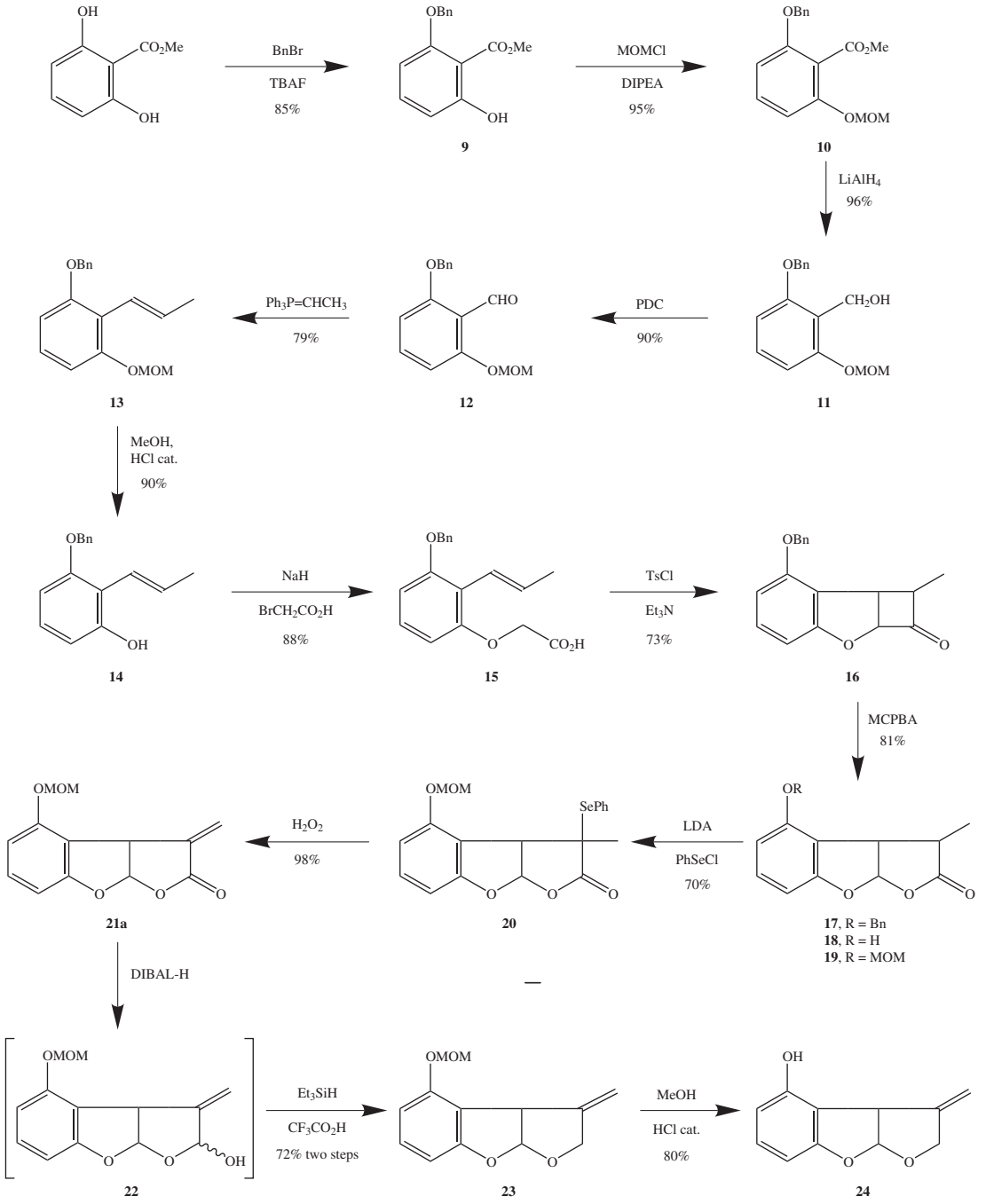
Figure 2. 3-Methylene-2,3a,8a-trihydrobenzo[*b*]furano[3,2-*d*]furan compounds.

Although the relevant biological and chemical properties of these natural products have translated into considerable synthetic interest; the syntheses of the natural products **7** and **8** have not been reported yet. Recently, we described the syntheses and the conformational studies[5] of several model compounds of natural products containing the basic benzofuranofuran skeleton. The intramolecular [2+2] cycloaddition of alkoxyketenes with alkenes, developed by Snider *et al.*[6] and by Brady *et al.*,[7] was used as a useful synthetic method in the preparation of these polycyclic compounds. As part of our interest in the synthesis of a family of compounds bearing the benzofuranofuran moiety, this methodology was also used to synthesize, for the first time, the racemic cinnamic ester derivative 1,2-*seco*microminutinin (**25**).

Results and Discussion

The synthesis started with the treatment of commercial methyl 2,6-dihydroxybenzoate with benzyl bromide and tetrabutylammonium fluoride (TBAF), to selectively protect only one of the hydroxyl groups,[8] producing compound **9** in 85% yield (Scheme 1). Attempts to use other bases (NaH, KOH, *t*-BuOK) instead of TBAF favors the protection of both hydroxyl groups. The protection of the second hydroxyl group[9] by reaction of **9** with methoxymethyl chloride and *N,N*-diisopropylethylamine (DIPEA)[10] furnished compound **10** in 95% yield. The reduction of the carboxyl group[11] of compound **10** with $LiAlH_4$ furnished the corresponding alcohol **11** in 96% yield. The aldehyde **12** was obtained in 90% yield after the oxidation of **11** with pyridinium dichromate (PDC).[12] Wittig reaction[13] of **12** with ethylidenetriphenylphosphorane furnished compound **13** in 79% yield. Compound **14**, with only one of the hydroxyl group deprotected, was obtained in 90% yield after selective cleavage of the methoxymethyl group of **13** with HCl in methanol.[14] Reaction of **14** with bromoacetic acid produced compound **15** in 88% yield, which, after intramolecular [2+2] cycloaddition reaction,[6,7] furnished the tricyclic benzocyclobutafuranones **16** in 73% yield. The benzofuranofuranone **17** (R = Bn) was obtained in 81% yield through a Baeyer-Villiger oxidation of **16**. Studies on the Baeyer-Villiger reaction indicate that the regioselectivity of asymmetric ketones is directed by the migratory aptitude of the groups adjacent to the carbonyl, reflecting the ability of the migrant group to accept a partial positive charge in the transition states.[15] In the case of compound **16**, the cation-stabilizing effect of the unshared oxygen electron pairs increases the relative migratory aptitude of the attached carbon. Hydrogenolysis of the benzyl group of **17** produced the corresponding hydroxybenzofuranofuranone **18** (R = H), in 97% yield, and **18** is an analogue of the biologically active compounds **5** and **6**. Attempts to remove the protective benzyl group resulted in hydrogenation of the exocyclic double bond. Because of that, the hydroxyfuranone **18** was reacted with methoxymethyl chloride and *N,N*-diisopropylethylamine (DIPEA)[10] to furnish the protected compound **19** (R = MOM) in 95% yield. Reaction of **19** with phenylselenenyl chloride, using LDA as a base,[16] produced the selenophenyl derivative **20** in 70% yield. Reaction of compound **20** with H_2O_2 at 0 °C furnished 98% of a mixture of the unsaturated furanone **21a** with an exocyclic methylene group, and its isomer **21b** with an endocyclic double bond (ratio 2:1). After the separation of the two isomers, the treatment of lactone **21a** with diisobutylaluminium hydride (DIBAL-H) yielded lactol **22** (not isolated), which, by reaction with triethylsilane and trifluoroacetic acid, furnished ether **23** in 72% yield in two steps.[17] The use of this two-step procedure, which joins a low-temperature reduction followed by a highly chemoselective deoxygenation, was more favorable in terms of operational simplicity and overall yield when compared with other methods.[17] The methoxymethyl protective group in compound **23** was cleaved in 80% yield by treatment with HCl in methanol[14] to produce 3-methylene-2,3a,8a,trihydro-benzo[*b*]furano[3,2-*d*]furan-4-ol (**24**), which is a precursor of the natural products **7** and **8**.

The traditional Pechmann reaction[18] cannot be used to prepare the coumarinic ring of microminutinin (**7**) and its derivatives directly from compound **24** because this compound is very sensitive to the acidic conditions generally used in that reaction. Hoefnagel *et al.*[19] synthesized several coumarins in moderate yields through the reaction of resorcinol and propynoic acid catalyzed by Amberlyst-15 or zeolite H-beta, at 150 °C. However, the ketal function of compound **24** was cleaved under these conditions. Yavari *et al.*[20] obtained coumarins in good yields by the reaction between phenols and dimethyl

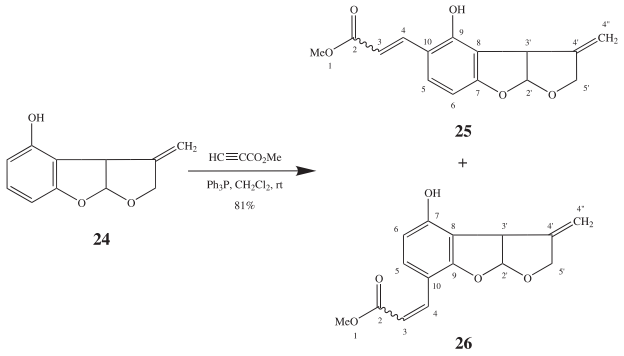


Scheme 1. Synthesis of 3-methylene-2,3a,8a,trihydro-benzo[*b*]furano[3,2-*d*]furan-4-ol (**24**) from methyl 2,6-dihydroxybenzoate.

acetylenedicarboxylate in the presence of triphenylphosphine under reflux in dichloromethane. Nevertheless, decomposition of the starting material was also observed when this reaction was carried out with compound **24**. Therefore, this latter methodology was adapted to be employed in very mild conditions. Under these milder conditions, the coumarinic ring is not produced, but instead, very interesting 1,2-*seco*microminutinin derivatives are obtained. These cinnamic ester derivatives are the unsaturated analogues of the natural product **8**, and may be used as very valuable intermediates for the synthesis of natural products with the benzofuranofuran skeleton.

Thus, compound **24** and triphenylphosphine were dissolved in dichloromethane and a solution of methyl propiolate in dichloromethane was slowly added, maintaining the reaction mixture under stirring for 24 hours at room temperature. Analysis by ^{1}H NMR, ^{13}C NMR, MS,

and IR revealed that the product obtained in 81% yield was a mixture of the unsaturated isomers **25** and **26** in the proportion of 2:1, respectively (Scheme 2). Presumably, these two isomers are formed because the electrophilic attack of the vinyltriphenylphosphonium cation (resulting from the initial addition of triphenylphosphine to the acetylenic ester followed by concomitant protonation)[20] on the aromatic ring of **24** is influenced by the strong *ortho*/*para* activating groups on the aromatic ring.



Scheme 2. Reaction of compound **24** with methyl propiolate in the presence of triphenylphosphine.

Stereochemical assignment of the acrylate double bond is usually based on the magnitude of the vicinal coupling constant of the corresponding hydrogens in the ^{1}H NMR spectra. The range for *E* isomers is 12 to 18 Hz, and 6 to 12 Hz for *Z* isomers. In this work, the measured values for compounds **25** and **26** were 12.1 and 12.4 Hz, respectively, making an unequivocal attribution difficult. On the other hand, the chemical shifts of the hydrogens on the acrylic β-carbons of these compounds were 7.80 and 7.66, respectively. Based on numerous examples from the literature,[21] we can suggest that the prepared compounds are *E* isomers.

All attempts to obtain microminutinin (**7**) either straightforward from compound **24** by reaction with several kinds of reagents,[18-20] or by the ring closure of the 1,2-*seco*microminutinin (**25**) were unproductive. This failure can be another evidence for the fact that the double bond of compound **25** has an *E* configuration, since it is well-known that *E* isomers of 3-(2-hydroxyaryl)propenoic esters are difficult to cyclize to the corresponding coumarins by traditional methods.[21] The lability of the ketal function present in the compounds under investigation prevents the use of more drastic methods such as heating or pyrolisis.

Conclusions

We have reported the first successful racemic synthesis of the cinnamic ester derivative 1,2-*seco*microminutinin (**25**) by the intramolecular cycloaddition of an (alkenyloxy)ketene followed by the reaction, under mild conditions, of a benzofuranofuran moiety with methyl propiolate.

Experimental

All ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using a Bruker DPX-300 instrument and chloroform-*d* ($CDCl_3$) as solvent; chemical shifts are in ppm downfield from tetramethylsilane internal standard. IR spectra were measured KBr) with a Perkin Elmer Spectrum RX IFTIR System, and the most intense or representative bands are reported (in cm^{-1}). Mass spectra were determined at an ionizing voltage of 70 eV, using a HP 5988-A spectrometer. The mass spectra of compounds **25** and **26** were performed by electronspray ionization (ESI), using a Micromass Quattro LC spectrometer. Solutions were infused into the Z-spray source at 10 μL min^{-1} (0.5 mg mL^{-1}), and the protonated parent ions were observed at *m/z* 275. TLC was performed on plates precoated with silica gel 60 F_{254} (0.25 mm thick, Merck) and column chromatography separations were performed with silica gel 60 (70-230 mesh, Merck). Melting points were determined on a Reichert Kofler block apparatus and are uncorrected.

*Methyl 2-(benzyloxy)-6-hydroxybenzoate (**9**).* A solution of methyl 2,6-dihydroxybenzoate (0.1002 g, 0.596 mmol) and tetrabutylammonium fluoride (TBAF) (0.3751 g, 1.190 mmol) in DMF (5 mL) was stirred under nitrogen atmosphere for 15 min. Benzyl bromide (0.1119 g, 0.650 mmol) was then added and the reaction mixture was stirred at room temperature for 3 h, and it was subsequently diluted with water (5 mL) and ethyl ether (10 mL). The organic phase was separated, washed with water and with saturated brine. The combined extracts were dried over $MgSO_4$, filtered and evaporated to give the crude product, which was purified by column chromatography through silica gel, using *n*-hexane:ethyl acetate (8:2) as eluent, to afford **9** (1.3075 g, 85%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.5 (s, 1H), 7.5 (s, 5H), 7.3-6.5 (m, 3H), 5.2 (s, 2H), 4.0 (s, 3H); IR ν_{max}/cm^{-1}: 3337, 3008, 1732, 1200, 1030, 841; MS *m/z* (relative intensity) 210 [M^+ - (OMe + OH), 10], 180 (2), 91 (100), 65 (12), 45 (50), 28 (31).

*Methyl 2-(benzyloxy)-6-(methoxymethoxy)benzoate (**10**).* ***N,N*-**Diisopropylethylamine (DIPEA) (0.0319 g, 0.247 mmol) was added slowly to a stirred solution of compound **9** (0.0525 g, 0.204 mmol) and chloromethyl methyl ether (MOMCl) (0.0181 g, 0.225 mmol) in CH_2Cl_2 (5 mL), cooled to 0 °C under anhydrous conditions. The

mixture was stirred at room temperature for 24 h, and it was diluted with water (3 x 10 mL) and CH_2Cl_2 (10 mL). The phases were separated, and the organic phase was dried over $MgSO_4$, filtered and evaporated to give the crude product, which was purified by column chromatography through silica gel, using *n*-hexane:ethyl acetate (1:1) as eluent, to afford **10** (0.0585 g, 95%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 (s, 5H), 7.4-6.7 (m, 3H), 5.2 (s, 2H), 5.1 (s, 2H), 3.8 (s, 3H), 3.5 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 164.2 (2 C-O arom), 140.8, 134.8, 128.4 (2 CH arom), 127.3 (2 CH arom) , 127.2, 106.1 (2 CH arom), 101.7, 100.7, 77.8, 50.2, 50.1; IR ν_{max}/cm^{-1}: 3005, 1603, 1730, 1200, 1151, 1033, 841; MS *m/z* (relative intensity) 257 [(M^+ - CH_2OCH_3), 7], 121 (5), 91 (100), 65 (12), 45 (55) 28 (50).

*[2-(Benzyloxy)-6-(methoxymethoxy)phenyl]methanol (**11**).* A solution of compound **10** (2.5402 g, 8.41 mmol) in THF (2 mL) was added to a stirred suspension of $LiAlH_4$ (0.5370 g, 14.0 mmol) in THF (30 mL), under anhydrous conditions. The mixture was refluxed for 3 h, cooled to 0 °C, and then water (2.5 mL) and a solution of NaOH 3 mol L^{-1} (0.640 mL) were added. The precipitate was separated by filtration and the resulting solution was extracted with ethyl ether. The organic phase was dried over $MgSO_4$, filtered and evaporated to give the crude product, which was purified by column chromatography through silica gel, using with *n*-hexane:ethyl acetate (1:1) as eluent, to afford **11** (2.2126 g, 96%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 (m, 5H), 7.4-6.7 (m, 3H), 5.2 (s, 2H), 5.1 (s, 2H), 4.8 (s, 2H), 3.5 (s, 3H), 2.5 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8 (2 C-O arom), 140.9, 129.4, 128.7 (2 CH arom), 127.4 (2 CH arom), 127.3, 112.1, 106.6 (2 CH arom), 101.0, 78.1, 50.2, 48.7; IR ν_{max}/cm^{-1}: 3300, 3005, 1600, 1475, 1200, 1151, 1033, 841, 735; MS *m/z* (relative intensity) 213 [(M^+ - OCH_2OCH_3), 5], 91 (100), 45 (53), 28 (19).

*2-(Benzyloxy)-6-(methoxymethoxy)benzaldehyde (**12**).* A solution of compound **11** (1.8303 g, 6.68 mmol) in anhydrous CH_2Cl_2 (10 mL) was added to a stirred solution of pyridinium dichromate (PDC) (5.0021 g, 13.3 mmol) in anhydrous CH_2Cl_2 (50 mL). The reaction mixture was stirred at room temperature for 48 h, then the suspension was filtered through Celite®, and the solvent was evaporated to give the crude product, which was purified by column chromatography through silica gel, using dichloromethane:ethyl acetate (8:2) as eluent, to afford **12** (1.6358 g, 90%) as a white solid; mp 38-40 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.5 (s, 1H), 7.5 (m, 5H), 7.4-6.7 (m, 3H), 5.2 (s, 2H), 5.1 (s, 2H), 3.5 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 164.2 (2 C-O arom), 140.7, 136.3, 128.7 (2 CH arom), 127.4, 127.3 (2 CH arom), 107.9, 106.9 (2 CH arom), 100.7, 77.8, 50.1; IR ν_{max}/cm^{-1}: 3010, 2825, 1705, 1603, 1475, 1200, 1157, 841, 730; MS *m/z* (relative intensity) 211 [(M^+ - OCH_2OCH_3), 2], 180 (2), 91 (100), 56 (12), 45 (50).

*1-(Benzyloxy)-3-(methoxymethoxy)-2-[(1E)-prop-1-en-1-yl]benzene (**13**).* *n*-Butyllithium (8.720 mL, 8.46 mmol, 0.97 mol L^{-1} in *n*-hexane) was added to a stirred solution of (ethyl)triphenylphosphonium bromide (3.1398 g, 8.46 mmol) in THF (5 mL) at –78 ºC, under anhydrous conditions. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 20 min. The reaction mixture was cooled again at –78 ºC, and a solution of compound **12** (1.1552 g, 4.25 mmol) in THF (4 mL) was added. The reaction mixture was then stirred at room temperature for 1 h, diluted with water (5 mL) and extracted with ethyl ether (15 mL). The organic phase was washed with water and with saturated brine, dried over $MgSO_4$, filtered, and the solvent was evaporated to give the crude product, which was purified by column chromatography through silica gel, using *n*-hexane:ethyl acetate (9:1) as eluent, to afford **13** (0.9540 g, 79% yield) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (m, 5H), 7.40-6.71 (m, 3H), 6.30-5.90 (m, 2H), 5.21 (s, 2H), 5.10 (s, 2H), 3.50 (s, 3H), 1.90 (d, *J* 9.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8 (2 C-O arom), 140.7, 129.7, 128.7 (2 CH arom), 128.4, 127.4, 127.3 (2 CH arom), 121.7, 106.3 (2 CH arom), 106.0, 101.1, 78.2, 50.2, 16.6; IR ν_{max}/cm^{-1}: 3005, 1607, 1478, 1200, 1151, 837, 729; MS *m/z* (relative intensity) 239 [(M^+ - CH_2OCH_3), 4], 193 (4), 161 (15), 91 (100), 65 (15), 45 (62), 28 (38).

*3-(Benzyloxy)-2-[(1E)-prop-1-en-1-yl]phenol (**14**).* One drop of concentrated HCl was added to a stirred solution of compound **13** (0.1002 g, 0.353 mmol) in methanol (20 mL). The reaction mixture was stirred at room temperature for 24 h, the solvent was evaporated, and the residue was purified by column chromatography through silica gel, using *n*-hexane:ethyl acetate (8:2) as eluent, to afford **14** (0.0763 g, 90%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 (m, 5H), 7.4-6.7 (m, 3H), 6.3-5.9 (m, 2H), 5.2 (s, 2H), 4.5 (s, 1H), 1.9 (d, *J* 9.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 156.0, 140.9, 130.1, 128.7 (2 CH arom), 128.4, 127.4, 127.3 (2 CH arom), 121.7, 107.9, 107.7, 106.6, 78.2, 16.4; IR ν_{max}/cm^{-1}: 3370, 3005, 1603, 1475, 1200, 1151, 841, 735; MS *m/z* (relative intensity) 240 (M^+, 100), 199 (7), 161 (15), 149 (50), 91 (98), 66 (15).

*{3-(Benzyloxy)-2-[(1E)-prop-1-en-1-yl]phenoxy}acetic acid (**15**).* **A** solution of compound **14** (0.4002 g, 1.67 mmol) in THF (2 mL) was added to a stirred suspension of NaH (0.1659 g, 4.15 mmol) in THF (15 mL), under anhydrous conditions. The reaction mixture was stirred at room temperature for 20 min, and then a solution of bromoacetic acid (0.2540 g, 1.66 mmol) in THF (1 mL)

was added. The reaction mixture was refluxed for 6 h, and it was then, stirred overnight at room temperature, diluted with ethyl ether and quenched with saturated brine (8 mL). The aqueous phase was separated, washed with ethyl ether, acidified with HCl 6mol L^{-1} until pH 1 and extracted with ethyl ether (3 x 15 mL). The organic phase was washed with water and with saturated brine, dried over $MgSO_4$, filtered, and the solvent was evaporated to furnish compound **15** (0.4381 g, 88% yield) as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.0 (s, 1H), 7.5 (m, 5H), 7.4-6.7 (m, 3H), 6.3-5.9 (m, 2H), 5.2 (s, 2H), 4.7 (s, 2H), 1.7 (d, *J* 9.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 160.7 (2 C-O-arom), 140.7, 129.5, 128.6 (2 CH arom), 128.4, 127.4, 127.3 (2 CH arom), 121.7, 106.2 (2 CH arom), 106.0, 78.2, 78.0, 15.3; IR ν_{max}/cm^{-1}: 3294, 3005, 1717, 1408, 1200, 1151, 932, 841, 735; MS *m/z* (relative intensity) 298 (M^+, 2), 207 (20), 161 (30), 147 (6), 91 (100), 65 (16), 28 (40).

*7-(Benzyloxy)-1-methyl-2a,7b-dihydrobenzo[b]cyclobuta[d]furan-2(1H)-one (**16**).* A solution of acid **15** (0.4502 g, 1.51 mmol) in benzene (50 mL) was added slowly (5 h) to a stirred solution of triethylamine (2.110 mL, 15.1 mmol), tosyl chloride (0.5741 g, 3.01 mmol) in benzene (50 mL), under reflux. After 6 h under reflux, the reaction mixture was washed with water (3 x 10 mL) and concentrated to 10 mL, under reduced pressure. This concentrated solution was stirred for 10 h at room temperature, with a solution of 3% NaOH (20 mL), to remove excess tosyl chloride. The organic phase was separated, dried over $MgSO_4$, filtered, the solvent was evaporated, and the residue was purified by column chromatography through silica gel, using *n*-hexane:ethyl acetate (8:2) as eluent, to afford **16** (0.3088 g, 73%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 (m, 5H), 7.3-6.8 (m, 3H), 5.6 (dd, *J* 8.4 and 2.9 Hz, 1H), 5.2 (s, 2H), 4.3 (dd, *J* 8.4 Hz and 8.7 Hz, 1H), 3.8 (m, 1H), 1.1 (d, *J* 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.3, 162.4, 159.6, 140.9, 128.7 (2 CH arom), 127.4 (2 CH arom), 127.3 (2 CH arom), 110.1, 106.3, 105.9, 85.2, 78.1, 43.0, 30.2, 13.3; IR ν_{max}/cm^{-1}: 2995, 1725, 1475, 1205, 1033, 841, 735; MS *m/z* (relative intensity) 280 (M^+, 3), 251 (5), 160 (15), 91 (100), 66 (15), 45 (51).

*4-(Benzyloxy)-3-methyl-3a,8a-dihydrofuro[2,3-b][1]benzofuran-2(3H)-one (**17**).* Solid $NaHCO_3$ (0.0990 g, 1.17 mmol) and solid *m*-chloroperoxybenzoic acid (MCPBA) 85% (0.0831 g, 0.409 mmol) were quickly added to a stirred solution of compound **16** (0.1101 g, 0.393 mmol) in anhydrous CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 30 min and then it was diluted with CH_2Cl_2 (10 mL) and with a solution of 10% $NaHCO_3$ (5 mL). The organic phase was washed with saturated brine, dried over $MgSO_4$, filtered, the solvent was evaporated, and the residue was purified by column chromatography through silica gel, using *n*-hexane:ethyl acetate (8:2) as eluent, to afford **17** (0.0943 g, 81%) as a white solid: mp 82-85 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 (m, 5H), 7.3-6.5 (m, 3H), 6.5 (d, 1H, *J* 6.6 Hz, 1H), 5.1 (s, 2H), 4.4 (dd, *J* 6.6 and 10.3 Hz, 1H), 3.1 (m, 1H), 1.3 (d, *J* 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 159.5, 156.5, 136.3, 131.2, 128.7 (2 CH arom), 127.4, 127.3 (2 CH arom), 111.0, 106.7, 105.5, 103.8, 77.2, 45.6, 37.7, 13.3; IR ν_{max}/cm^{-1}: 2998, 1727, 1475, 1200, 1023, 841, 735; MS *m/z* (relative intensity) 296 (M^+, 3), 91 (100), 65 (12), 28 (73).

*4-Hydroxy-3-methyl-3a,8a-dihydrofuro[2,3-b][1]benzofuran-2(3H)-one (**18**).* A solution of compound **17** (0.1502 g, 0.507 mmol) in methanol (10 mL) was hydrogenated under 1 atm at room temperature, with a catalyst containing 5% palladium on activated carbon powder (amount not determined). When one equivalent of hydrogen had been consumed (about 1h), the catalyst was removed by filtration through Celite®, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography through silica gel, using *n*-hexane:ethyl acetate (1:1) as eluent, to afford **18** (0.1014 g, 97% yield) as a white solid: mp 166-168 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3-6.5 (m, 3H), 6.5 (d, *J* 6.6 Hz, 1H), 6.0 (br s, 1H), 4.4 (dd, *J* 6.6 and 10.3 Hz, 1H), 3.1 (m, 1H), 1.3 (d, *J* 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 160.3, 153.8, 131.4, 110.0, 109.8, 107.4, 103.8, 45.0, 38.4, 13.5; IR ν_{max}/cm^{-1}: 2995, 1728, 1475, 1207, 1023, 845, 735; MS *m/z* (relative intensity) 206 (M^+, 17), 177 (43), 147 (9), 121 (13), 105 (21), 45 (100).

*4-(Methoxymethoxy)-3-methyl-3a,8a-dihydrofuro[2,3-b][1]benzofuran-2(3H)-one (**19**).* *N,N*-Diisopropylethylamine (DIPEA) (0.020 mL, 0.12 mmol) was added to a stirred solution of compound **18** (0.0201 g, 0.098 mmol) in CH_2Cl_2 (2 mL). After stirring for 10 min at room temperature, chloromethyl methyl ether (MOMCl) (0.0101 g, 0.125 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, and then it was diluted with water (5 mL) and CH_2Cl_2 (5 mL). The organic phase was separated, washed with saturated brine, dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography through silica gel, using *n*-hexane:ethyl acetate (7:3) as eluent, to afford **19** (0.0233 g, 95% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3-6.5 (m, 3H), 6.5 (d, *J* 6.6 Hz, 1H), 5.2 (s, 2H), 4.4 (dd, *J* 6.6 and 10.3 Hz, 1H), 3.5 (s, 3H), 3.1 (m, 1H), 1.3 (d, *J* 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 159.8, 155.4, 131.6, 111.9, 107.8, 107, 104.7, 94.9, 56.8, 45.9, 38.1, 13.6; IR ν_{max}/cm^{-1}: 2995, 1728, 1602, 1470, 1200, 1033, 845, 735; MS *m/z* (relative intensity) 205 [(M^+ - CH_2OCH_3), 9], 176 (43), 160 (100), 91 (55), 77 (30).

*4-(Methoxymethoxy)-3-methyl-3-(phenylsulfanyl)-3a,8a-dihydrofuro[2,3-b][1]benzo-furan-2(3H)-one (**20**).* *n*-Butyllithium (0.050 mL, 0.10 mmol, 2.2 mol L^{-1} in *n*-hexane) was added to a stirred solution of diisopropylamine (0.015 mL, 0.10 mmol) in anhydrous THF (5 mL), cooled to 0 °C under anhydrous conditions. After 20 min, the mixture was cooled at –78 °C and compound **19** (0.0211 g, 0.084 mmol) was added, and the resulting mixture was stirred for an additional 30 min. Phenylselenenyl bromide (0.0240 g, 0.10 mmol) was added, and the bath temperature was allowed to rise slowly until –20 °C. The reaction mixture was stirred for 2 h, diluted with a saturated solution of NH_4Cl (4 mL) and extracted with ethyl ether. The organic phase was dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography, using *n*-hexane:ethyl acetate (9:1) as eluent, to afford **20** (0.0239 g, 70% yield) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 (s, 5H), 7.3-6.5 (m, 3H), 6,5 (d, *J* 6.6 Hz, 1H), 5.2 (s, 2H), 4.4 (d, *J* 6.6 Hz, 1H), 3.5 (s, 3H), 1,7 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 162.7, 159.6, 128.5, 128.0 (5 CH arom), 127.2, 110.1, 106.8, 105.8, 105.0, 101.1, 50.3, 50.1, 23.1, 9.2; IR ν_{max}/cm^{-1}: 2997, 1725, 1475, 1207, 1023, 845, 735.

*4-(Methoxymethoxy)-3-methylene-3a,8a-dihydrofuro[2,3-b][1]benzofuran-2(3H)-one (**21a**).* To a stirred solution of compound **20** (0.0210 g, 0.050 mmol) in CH_2Cl_2 (2 mL), cooled to 0 °C, H_2O_2 30% (0.1 mL) was added, keeping the stirring for 2 h at 0 °C, and then, the reaction mixture was diluted with water (2 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure to furnish 98% of a mixture (ratio 2:1) of the unsaturated furanone **21a** and its isomer **21b** with an endocyclic double bond. The separation of the two isomers by column chromatography through silica gel, using *n*-hexane:ethyl acetate (8:2) as eluent, afforded **21a** (0.0055 g, 44% yield) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1-6.6 (m, 3H), 6.4 (d, *J* 6.3 Hz, 1H), 6.3 (d, *J* 1.5 Hz, 1H), 6.2 (d, *J* 1.5 Hz, 1H), 5.2 (d, *J* 6.6 Hz, 1H), 5.2 (d, *J* 6.6 Hz, 1H), 4.8 (br d, *J* 6.3 Hz, 1H), 3.4 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 158.9, 154.9, 134.0, 131.5, 126.5, 113.0, 108.1, 105.8, 104.8, 94.6, 56.7, 46.0; IR ν_{max}/cm^{-1}: 2995, 1728, 1475, 1207, 1023, 845, 735; MS *m/z* (relative intensity) 203 (M^+ - CH_2OCH_3, 100), 173 (95), 145 (98), 131 (35), 115 (37), 91 (20), 77 (16).

*4-(Methoxymethoxy)-3-methylene-2,3,3a,8a-tetrahydrofuro[2,3-b][1]benzofuran (**23**).* Diisobutyl-aluminium hydride (DIBAL-H) (0.030 mL, 0.033 mmol, 1.0 mol L^{-1} in toluene) was added to a stirred solution of compound **21a** (0.0049 g, 0.020 mmol) in toluene (2 mL), cooled at –78 °C, under anhydrous conditions. After a one-hour stirring at –78 °C, the dry ice bath was removed, and a mixture of crushed ice (1 g), acetic acid (0.3 mL) and $CHCl_3$ (7 mL) was added. This mixture was stirred for 30 min, the organic phase was separated, washed with saturated solution of $NaHCO_3$ and with saturated brine, and dried over $MgSO_4$. The solvent was filtered and evaporated under reduced pressure, to yield the crude compound **22**, which was used in the following step without further purification. Then, to a stirred solution of compound **22** in CH_2Cl_2 (4 mL), cooled at –78 °C under anhydrous conditions, triethylsilane (0.010 mL, 0.06 mmol) and trifluoroacetic acid (0.005 mL, 0.06 mmol) were added. After 1 h, a solution of 5% $NaHCO_3$ (2 mL) was added, and the mixture was quickly stirred at room temperature for 10 min. The organic phase was washed with a saturated solution of $NaHCO_3$ and with saturated brine, dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography through silica gel, using *n*-hexane:ethyl acetate (8:2) as eluent, to afford **23** (0.0034 g, 72%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.0-6.4 (m, 3H), 6.3 (d, *J* 5.6 Hz, 1H), 5.4 (br d, *J* 1.5 Hz, 1H), 5.2 (d, *J* 6.8 Hz, 1H), 5.1 (d, *J* 6.8 Hz, 1H), 5.0 (br d, *J* 1.5 Hz, 1H), 4.4 (m, 3H), 3.4 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 154.7, 146.6, 130.3, 112.7, 108.1, 106.9, 105.6, 103.8, 94.4, 70.9, 56.5, 49.8; IR ν_{max}/cm^{-1}: 2999, 1600, 1475, 1203, 1020, 845, 735; MS *m/z* (relative intensity) 189 [(M^+ - CH_2OCH_3), 8], 134 (28), 89 (70), 45 (54).

*3-Methylene-2,3,3a,8a-tetrahydrofuro[2,3-b][1]benzofuran-4-ol (**24**).* A catalytic amount of concentrated HCl was added through a capillary tube to a stirred solution of compound **23** (0.0031 g, 0.013 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography through silica gel, using *n*-hexane:ethyl acetate (7:3) as eluent, to afford **24** (0.0019 g, 80%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.0 (s, 1H), 7.0-6.3 (m, 3H), 6.3 (d, *J* 5.8 Hz, 1H), 5.4 (dd, *J* 2.0 and 3.5 Hz, 1H), 5.01 (dd, *J* 2.0 and 3.2 Hz, 1H), 4.4 (br d, *J* 5.8 Hz, 1H), 4.4 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 153.4, 136.6, 130.3, 112.5, 112.3, 109.0, 108.2, 102.9, 71.0, 49.7; IR ν_{max}/cm^{-1}: 3338, 2995, 1475, 1209, 1023, 845, 735; MS *m/z* (relative intensity) 190 (M^+, 89), 134 (32), 89 (65), 77 (33), 45 (54).

*Methyl (2Z)-3-(4-hydroxy-3-methylene-2,3,3a,8a-tetrahydrofuro[2,3-b][1]benzofuran-5-yl)acrylate (**25**) and methyl (2Z)-3-(4-hydroxy-3-methylene-2,3,3a,8a-tetrahydrofuro[2,3-b][1]benzofuran-7-yl)acrylate (**26**).* A solution of methyl propiolate (0.0005 g, 0.006 mmol) in CH_2Cl_2 (2 mL) was slowly added (10 min) to a stirred solution of triphenylphosphine (0.0017 g, 0.006 mmol) and compound **24** (0.0012 g, 0.0063 mmol) in CH_2Cl_2 (1 mL), cooled at –5 °C. The ice bath was removed, and the reaction mixture was stirred at room temperature for 24 h. The solvent

was removed under reduced pressure, and the residue was purified by column chromatography through silica gel, using *n*-hexane:ethyl acetate (7:3) as eluent, to afford a mixture of compounds **25** and **26** (0.0014 g, 81%) as a colorless oil; Analytical data for compound **25**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* 12.1 Hz, H_4), 6.61 (d, *J* 8.2 Hz, H_5), 6.53 (d, *J* 8.2 Hz, H_6), 6.36 (d, *J* 5.8 Hz, $H_{2'}$), 5.63 (d, *J* 12.1 Hz, H_3), 5.28 (ddd, *J* 2.3, 1.6 and 1.5 Hz, 1 $H_{4''}$), 5.06 (m, 1 $H_{4''}$), 4.41 (d, *J* 5.8 Hz, $H_{3'}$), 4.36 (dt, *J* 12.3 and 1.6 Hz, 1 $H_{5'}$), 4.32 (m, 1 $H_{5'}$), 3.75 (s, 3 H_1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8 (C_2), 162.0 (C arom), 154.6 (C arom), 146.2 ($C_{4'}$), 142.7 (C_4), 131.2 (CH arom), 116.7 (C_3), 113.7 (C arom), 111.6 ($C_{2'}$), 109.0 (C arom), 108.9 ($C_{4''}$), 104.8 (CH arom), 70.5 ($C_{5'}$), 53.3 ($C_{3'}$), 52.0 (C_1). Analytical data for compound **26**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* 12.4 Hz, H_4), 7.18 (d, *J* 8.1 Hz, H_6), 6.68 (d, *J* 8.1 Hz, H_5), 6.43 (d, *J* 5.6 Hz, $H_{2'}$), 5.34 (d, *J* 12.4 Hz, H_3), 5.15 (m, 1 $H_{4''}$), 5.11 (m, 1 $H_{4''}$), 4.48 (d, *J* 5.6 Hz, $H_{3'}$), 4.42 (m, 2 $H_{5'}$), 3.73 (s, 3 H_1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0 (C_2), 161.8 (C arom), 159.9 (C arom), 148.3 ($C_{4'}$), 139.9 (C_4), 131.5 (CH arom), 114.8 (C arom), 113.9 (C_3), 113.1 ($C_{2'}$), 112.2 (CH arom), 109.9 ($C_{4''}$), 108.7 (C arom), 71.1 ($C_{5'}$), 55.4 ($C_{3'}$), 51.9 (C_1). IR ν_{max}/cm^{-1}: mixture of **25** and **26**: 3388, 2917-2841, 1717, 1654-1467, 1128; MS *m/z* quasi ion $[M + H]^+$ in 275.

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