Racemic Synthesis of 1,2-Secomicrominutinin

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

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

Keywords: 1,2-secomicrominutinin, benzfuranofuran, 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 products1-4 (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 activity2 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 activity3 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-secomicrominutinin (8a) and 3,4-dihydro-1,2-secomicrominutinin methyl ester (8b) are three natural products that contain the same 3-methylene-
2,3a,8a-trihydrobenzo[b]furano[3,2-d]furan moieties in their structures (Figure 2), which have been recently isolated 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 of several model compounds of natural products containing the basic benzofuranofuran skeleton. The intramolecular [2+2] cycloaddition of alkoxymethanes with alkenes, developed by Snider et al. and by Brady et al., 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-secomicrominutinin (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, 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 by reaction of 9 with methoxymethyl chloride and N,N-diisopropylethylamine (DIPEA) furnished compound 10 in 95% yield. The reduction of the carboxy group of compound 10 with LiAlH₄ 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). Wittig reaction of 12 with ethyldienetriphenylphosphorane 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. Reaction of 14 with bromoacetic acid produced compound 15 in 88% yield, which, after intramolecular [2+2] cycloaddition reaction, 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. 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) to furnish the protected compound 19 (R = MOM) in 95% yield. Reaction of 19 with phenylselenenyl chloride, using LDA as a base, produced the selenophenyl derivative 20 in 70% yield. Reaction of compound 20 with H₂O₂ 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 diisobutylalumimum 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. 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. The methoxyhexyl protective group in compound 23 was cleaved in 80% yield by treatment with HCl in methanol to produce 3-methylene-2,3a,8a-trihydrobenzo[b]furano[3,2-d]furan-4-ol (24), which is a precursor of the natural products 7 and 8.

The traditional Pechmann reaction 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. 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. obtained coumarins in good yields by the reaction between phenols and dimethyl
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-secoemicrinminitin 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)\textsuperscript{20} on the aromatic ring of 24 is influenced by the strong ortho/para activating groups on the aromatic ring.

Stereochemical assignment of the acrylate double bond is usually based on the magnitude of the vicinal coupling constant of the corresponding hydrogens in the \textsuperscript{1}H NMR spectra. The range for \textit{E} isomers is 12 to 18 Hz, and 6 to 12 Hz for \textit{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,\textsuperscript{21} we can suggest that the prepared compounds are \textit{E} isomers.

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

Conclusions

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

Experimental

All \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using a Bruker DPX-300 instrument and chloroform-\textit{d} (CDCl\textsubscript{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\textsuperscript{-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 electrospray ionization (ESI), using a Micromass Quattro LC spectrometer. Solutions were infused into the Z-spray source at 10 µL min\textsuperscript{-1} (0.5 mg mL\textsuperscript{-1}), and the protonated parent ions were observed at \textit{m}/\textit{z} 275. TLC was performed on plates precoated with silica gel 60 F\textsubscript{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.

\textit{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\textsubscript{4}, filtered and evaporated to give the crude product, which was purified by column chromatography through silica gel, using \textit{n}-hexane:ethyl acetate (8:2) as eluent, to afford 9 (1.3075 g, 85%) as a colorless oil; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 11.5 (s, 1H), 7.5 (s, 5H), 7.3-6.5 (m, 3H), 5.2 (s, 2H), 4.0 (s, 3H); IR \textit{v}_{\text{max}}/\text{cm}^{-1}: 3337, 3008, 1732, 1200, 1030, 841; MS \textit{m}/\textit{z} (relative intensity) 210 [M\textsuperscript{+}-(OMe + OH), 10], 180 (2), 91 (100), 65 (12), 45 (50), 28 (31).

\textit{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\textsubscript{3}Cl\textsubscript{2} (5 mL), cooled to 0 °C under anhydrous conditions. The

![Scheme 2. Reaction of compound 24 with methyl propiolate in the presence of triphenylphosphine.](image-url)
mixture was stirred at room temperature for 24 h, and it was diluted with water (3 x 10 mL) and CH$_2$Cl$_2$ (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$_3$) $\delta$ 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$_3$) $\delta$ 116.7, 106.0, 101.1, 78.2, 16.6; IR $\nu$ max/cm$^{-1}$: 3005, 1615, 1572, 1503, 1475. 1,2,4,5-Tetrachlorobenzene ($\delta$ 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; MS m/z (relative intensity) 257 [(M$^+$ - CH$_2$OCH$_3$), 7], 121 (5), 91 (100), 65 (12), 45 (55) 28 (50).

2-(Benzyloxy)-6-(methoxymethoxy)phenylmethanol (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 ºC, 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 the solvent was 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 11 (2.2126 g, 96%) as a colorless oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 128.4, 127.4, 127.3 (2 CH arom), 121.7, 107.9, 107.7, 101.7, 101.6, 77.8, 50.2, 50.1; IR $\nu$ max/cm$^{-1}$: 3300, 3005, 1607, 1478, 1200, 1151, 837, 729; MS m/z (relative intensity) 213 [(M$^+$ - OCH$_2$OCH$_3$), 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$_3$) $\delta$ 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, 9.0 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 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 $\nu$ max/cm$^{-1}$: 3005, 1607, 1478, 1200, 1151, 837, 729; MS m/z (relative intensity) 239 [(M$^+$ - CH$_2$OCH$_3$), 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$_3$) $\delta$ 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, 9.1 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 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 $\nu$ 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]phenoxycetic 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 6 mol 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 MgSO₄, filtered, and the solvent was evaporated to furnish compound 15 (0.4381 g, 88% yield) as a viscous oil. ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ 176.0, 160.7 (2 C-atom), 140.7, 129.5, 128.6 (2 CH-atom), 128.4, 127.4, 127.3 (2 CH-atom), 121.7, 106.2 (2 CH-atom), 106.0, 78.2, 78.0, 15.3; IR ν max/cm⁻¹: 2994, 1727, 1475, 1200, 1160, 1033, 845, 735; MS m/z (relative intensity) 280 (M⁺, 3), 251 (5), 211.3, 176.0, 160.7, 155.4, 131.6, 111.9, 107.8, 107, 104.7, 94.9, 56.8, 45.9, 38.1, 13.6; 1H NMR (300 MHz, CDCl₃) δ 177.6, 159.5, 156.5, 136.3, 131.2, 128.7 (2 CH-atom), 127.4, 127.3 (2 CH-atom), 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. ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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, 1203, 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-Diisopropylamidemethylamine (DIPEA) (0.020 mL, 0.12 mmol) was added to a stirred solution of compound 18 (0.0201 g, 0.098 mmol) in CH₂Cl₂ (2 mL). After stirring for 10 min at room temperature, the residue was purified by column chromatography through silica gel, using n-hexane:ethyl acetate (1:1) as eluent, to afford 19 (0.0233 g, 95% yield) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ 177.9, 159.8, 156.4, 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⁺ - CH₂OCH₃, 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 disopropylamine (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 (0.084 mmol) was added, and the resulting mixture was stirred at room temperature for 1 h under anhydrous conditions. After 20 min, the mixture was stirred at −78 °C for an additional 30 min. Phenylselenenyl bromide (0.0055 g, 44% yield) as a colorless oil; 1H NMR (300 MHz, CDCl₃) 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); 13C NMR (75 MHz, CDCl₃) 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]benzo-furan-2(3H)-one (21a). To a stirred solution of compound 20 (0.0210 g, 0.050 mmol) in CHCl₃ (2 mL), cooled to 0 °C, H₂O₂ (30% of 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 MgSO₄, 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; 1H NMR (300 MHz, CDCl₃) 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); 13C NMR (75 MHz, CDCl₃) 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⁺ - CH₂OCH₃), 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]benzo-furan (23). Diisobutylaluminium 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 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 CHCl₃, (7 mL) was added. This mixture was stirred for 30 min, the organic phase was separated, washed with saturated solution of NaHCO₃, and with saturated brine, and dried over MgSO₄. 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 CH₂Cl₂ (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% NaHCO₃ (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 NaHCO₃, and with saturated brine, dried over MgSO₄, 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; 1H NMR (300 MHz, CDCl₃) 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); 13C NMR (75 MHz, CDCl₃) δ 160.2, 154.7, 146.6, 130.3, 112.7, 106.1, 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⁺ - CH₃CO₂H), 8], 134 (28), 89 (70), 45 (54).

3-Methylene-2,3,3a,8a-tetrahydrofuro[2,3-b][1]benzo-furan-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; 1H NMR (300 MHz, CDCl₃) δ 7.0-6.3 (m, 4H), 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); 13C NMR (75 MHz, CDCl₃) 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-methylen-2,3,3a,8a-tetrahydrofuro[2,3-b][1]benzo-furan-5-yl)acrylate (25) and methyl (2Z)-3-(4-hydroxy-3-methylen-2,3,3a,8a-tetrahydrofuro[2,3-b][1]benzo-furan-7-yl)acrylate (26).** A solution of methyl propiolate (0.0005 g, 0.006 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (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: 1H NMR (300 MHz, CDCl₃) δ 7.80 (d, J 12.1 Hz, H₄), 6.61 (d, J 8.2 Hz, H₃), 6.53 (d, J 8.2 Hz, H₂), 6.36 (d, J 5.8 Hz, H₆), 5.63 (d, J 12.1 Hz, H₅), 5.28 (dd, J 2.3, 1.6 and 1.5 Hz, 1 H₄ –), 5.06 (m, 1 H₂ –), 4.41 (d, J 12.4 Hz, H₃), 5.15 (m, 1 H₄ –), 5.11 (m, 1 H₄ –), 4.48 (d, J 12.3 and 1.6 Hz, 1 H₅'), 4.32 (m, 3 H₃ –), 3.73 (s, 3 H₁ –); 13C NMR (75 MHz, CDCl₃) δ 177.8 (C₇), 160.2 (C arom), 154.6 (C arom), 146.2 (C₂), 131.2 (CH arom), 116.7 (C₃), 113.7 (C arom), 111.6 (C₄), 109.0 (C arom), 108.9 (C₃ –), 104.8 (CH arom), 70.5 (C₅'), 6.68 (d, J 7.66 Hz, H₆), 6.36 (d, J 8.2 Hz, H₅), 6.53 (d, J 12.4 Hz, H₄), 7.18 (d, J 8.1 Hz, H₃), 6.68 (d, J 8.1 Hz, H₂), 6.43 (d, J 5.6 Hz, H₆), 5.34 (d, J 12.4 Hz, H₅), 5.15 (m, 1 H₂ –), 5.11 (m, 1 H₂ –), 4.48 (d, J 5.6 Hz, H₄), 4.42 (m, 2 H₂ –), 3.73 (s, 3 H₃ –); 13C NMR (75 MHz, CDCl₃) δ 178.0 (C₇), 161.8 (C arom), 159.9 (C arom), 148.3 (C₇ –), 139.9 (C₉), 131.5 (CH arom), 114.8 (C arom), 113.9 (C₂), 113.1 (C₃), 112.2 (CH arom), 109.9 (C₄), 108.7 (C arom), 71.1 (C₂), 55.4 (C₃ –), 51.9 (C₁). 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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