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 Substituted γ-Butyrolactones: β-Hydroxymethyl-, β-Methylene and Cyclopropane Derivatives

Paulo Marcos Donate [a], Mauricio Gomes Constantino [a], Rosangela da Silva [a] & Susimaire Pedersoli [a]

[a] Departamento de Quimica Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto Universidade de São Paulo, Avenida Bandeirantes, 3900, 14040-901, Ribeirão Preto, SP, Brazil

Published online: 25 Sep 2007.

To cite this article: Paulo Marcos Donate, Mauricio Gomes Constantino, Rosangela da Silva & Susimaire Pedersoli (1999) Synthesis of Substituted γ-Butyrolactones: β-Hydroxymethyl-, β-Methylene and Cyclopropane Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:17, 2923-2936, DOI: 10.1080/00397919908086464

To link to this article: http://dx.doi.org/10.1080/00397919908086464

SYNTHETIC COMMUNICATIONS, 29(17), 2923-2936 (1999)

SYNTHESIS OF SUBSTITUTED γ-BUTYROLACTONES: β-HYDROXYMETHYL-, β-METHYLENE AND CYCLOPROPANE DERIVATIVES

Paulo Marcos Donate,* Mauricio Gomes Constantino, Rosangela da Silva and Susimaire Pedersoli

Departamento de Química
Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto
Universidade de São Paulo
Avenida Bandeirantes, 3900, 14040-901-Ribeirão Preto-SP, Brazil

ABSTRACT: A β-hydroxymethyl-γ-butyrolactone, which is a useful intermediate for the synthesis of several natural products with biological activity, was synthesized with good yield and a reduced number of steps from simple commercially available starting materials. Model compounds of natural products containing the unsaturated γ-butyrolactone unit, such as butenolides and β-methylene-γ-butyrolactones, were also conveniently synthesized from this hydroxymethyl-lactone.

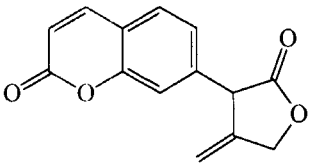
The structural unit γ-butyrolactone is widely distributed in nature; a large number of terpenes and other natural products containing the γ-butyrolactone moiety has been isolated in the last 30 years from plants and animals.[1] Many of these natural products have important biological activities, which have been frequently associated with the presence of the lactone ring in the molecular structure.[2] Particularly prominent are α-methylene-γ-butyrolactones, whose chemical properties and methods for synthesis have been reviewed extensively.[3] Their β-methylene counterparts, however, even though present in natural products[4] and potentially important for their biological activity, have been subject of much less attention by synthetic organic chemists.[5]

* To whom correspondence should be addressed.

Rahmani *et al.* recently reported[6] a novel natural product, microminutinin (**1**), (**2**), which belongs to a class of coumarins that are useful in the treatment of malaria and show cytotoxic activity.[6,7]

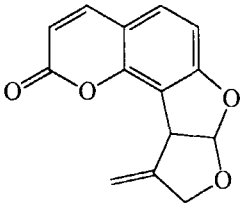
Microminutinin

First proposed structure:



1

Revised structure:



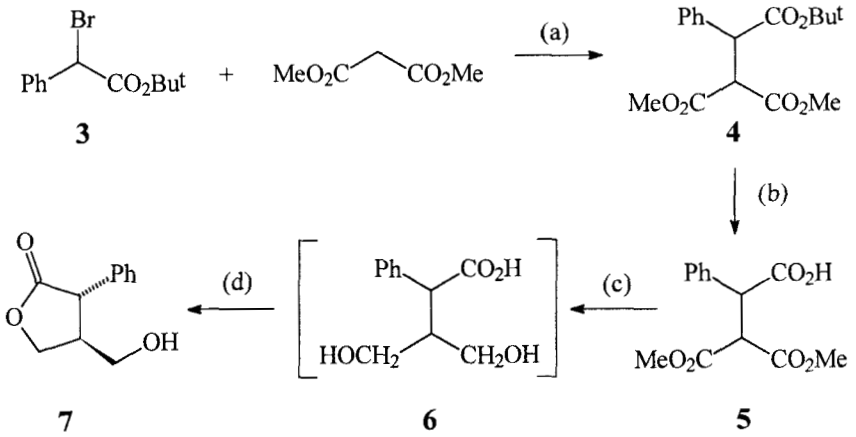
2

The structure first proposed for microminutinin (**1**) has drawn our attention mainly because it contained a β-methylene-γ-butyrolactone, usually stable only when the α-carbon atom is fully substituted. One would expect that the *endo* double bond, being conjugated to the carbonyl group and, in this case, also conjugated to the aromatic ring, would be much more stable. We thus decided to study the synthesis of this kind of structures to determine whether they can be prepared and how stable they are.

Our synthetic strategy was based on the synthesis of the model hydroxymethyl-lactone **7** which we expected would give initially an *exo* double bond through water elimination. Starting with *t*-butyl α-bromophenylacetate (**3**) (Scheme 1), nucleophilic substitution with dimethyl sodiomalonate furnished the tri-ester **4** in 84% yield. Selective acidic hydrolysis[8] of the *t*-butyl ester produced compound **5** (99% yield). Reduction of the ester groups of **5** with $LiBH_4$ gave intermediate **6** (not isolated) which, upon acidic work-up, furnished the desired lactone **7** (83% yield from **5**), as a mixture of *trans* and *cis* isomers in 13:1 ratio.

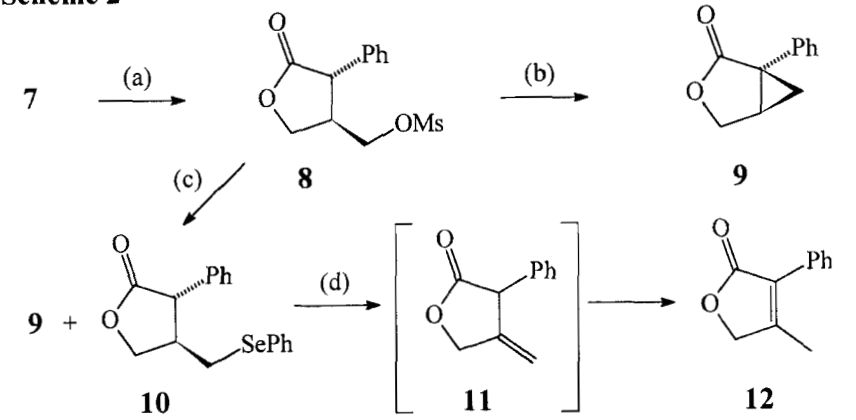
Rather surprisingly, although the mesylate **8** could be easily prepared from **7** (92% yield), a normal β-elimination of HOMs from **8** to give an *exo* double bond could not be performed. Upon treatment of **8** with DBU,[9] γ-elimination took place and the cyclopropane derivative **9** was obtained in 70% yield (Scheme 2).

Scheme 1



(a): NaOMe/MeOH, reflux 1.5 h, 84%; (b): TFA, r. t., 1 h, 99%; (c): $LiBH_4$, ethyl ether, r. t., 5 h; (d): 1 N HCl, 15 min, 83% from **5**.

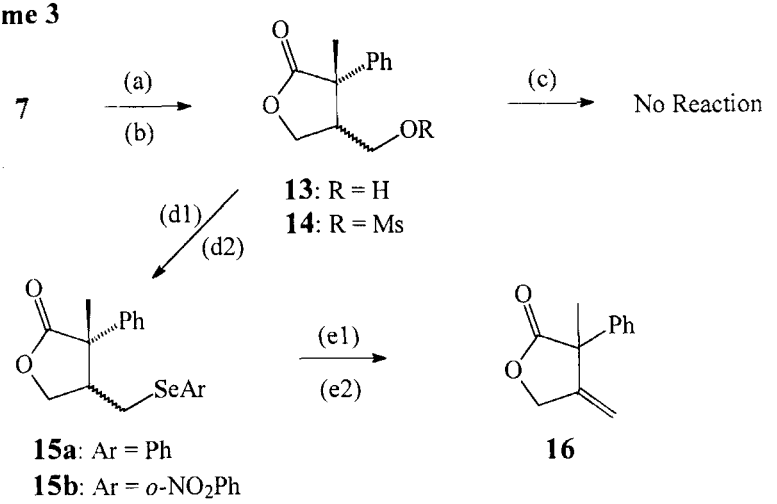
Scheme 2



(a): MsCl, Et_3N, CH_2Cl_2, r. t., 1 h, 92%; (b): DBU, CH_2Cl_2, r. t., 1 h, 70%; (c): PhSeSePh, $NaBH_4$, EtOH/THF, r. t., 3 h, 50% yield of compound **10**; (d): 30% H_2O_2, THF, $MgSO_4$, r. t., 24 h, 31%.

However, treatment of **8** with diphenyl diselenide[10] and sodium borohydride gave the selenide **10** together with a equimolar amount of **9**. When submitted to oxidation[11] by H_2O_2, selenide **10** furnished the compound with the *endo* double bond **12**.

Scheme 3



(a): LDA, CH_3I, THF, -78°C, 6 h, 74%; (b): MsCl, Et_3N, CH_2Cl_2, r. t., 2 h, 97%; (c): DBU, CH_2Cl_2, reflux; (d1): PhSeSePh, $NaBH_4$, EtOH/THF, r. t., 35 h, 59%; (d2): *o*-NO_2PhSeSePh-*o*-NO_2, $NaBH_4$, EtOH/THF, r. t., 25 h, 30%; (e1): 30% H_2O_2, THF, $MgSO_4$, r. t., 24 h, 25%; (e2): 30% H_2O_2, THF, r. t., 24 h, 70%.

To demonstrate that a fully substituted α-carbon atom is critical to obtain stable β-methylene-γ-lactones we alkylated lactone **7** and submitted the product **13**[12] to the reactions previously described (Scheme 3).

Again, elimination by treatment of the mesylate **14** with DBU could not be performed (only unchanged starting material was recovered from the reaction medium). The desired β-methylene-γ-lactone **16**, however, was obtained through the selenides **15a** or **15b**.

Experimental Section

Melting points were determined on a Reichert Kofler block melting point apparatus and are uncorrected. NMR spectra were measured 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 analysis were carried out on a CE instrument EA-1110. Analytical gas chromatography

(GLC) separations were performed on a Varian GC 3400 instrument with a fused silica capillary column (30 m length × 0.25 mm i. d.) coated with DB 1701 (phase thickness 0.25 μm) operating at temperatures in the range 50-200°C. 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.

2-Methoxycarbonyl-3-phenyl-butanedioic acid-4-*tert*-butyl-1-methyl ester (4). To a solution of sodium methoxide, prepared from sodium metal (65.1 mg, 2.8 mmol) and anhydrous methanol (3 mL), was added a solution of dimethyl malonate (370.4 mg, 2.8 mmol) in methanol (1 mL). After refluxing for 15 minutes, a solution of *tert*-butyl 2-bromo-2-phenylacetate (**3**) (700.3 mg, 2.6 mmol) in methanol (1 ml) was added dropwise and the resulting mixture was refluxed for 1.5 hour. Methanol was removed by distillation, water (1 mL) was added, and the reaction mixture was diluted with water and extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography through silica gel, eluting with hexane/ethyl acetate (8:2) to give compound **4**. Yield 701 mg (2.18 mmol, 84%); IR (neat film) 1130, 1400, 1600, 1672, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.3 (m, 5H), 4.3 (d, J = 12.5 Hz, 1H), 4.2 (d, J = 12.5 Hz, 1H), 3.8 (s, 3H), 3.5 (s, 3H), 1.5 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170 (C=O), 168.1 (C=O), 167.5 (C=O), 135.2 (C), 128.6 (CH), 128 (CH), 127.8 (CH), 55.1 (CH), 52.7 (CH), 52.3 (CH_3O), 52.2 (C), 52.6 (CH_3O), 27.8 (CH_3); MS *m/z* (rel. intensity) 248 (5), 222 (12), 189 (8), 162 (17), 121 (32), 107 (11), 77 (12), 57 (100).

2 - Methoxycarbonyl - 3 - phenyl - butanedioic acid - 1 - methyl ester (5). Trifluoroacetic acid (1.5 mL) was added to a solution of compound **4** (718 mg, 2.23 mmol) in dichloromethane (3 mL), and the reaction mixture was stirred at room temperature for 1 hour. Evaporation of the solvent and subsequent

recrystallization from petroleum ether afforded compound **5** as a white crystalline solid: mp 133-135°C. Yield 593 mg (2.22 mmol, 99%); IR (KBr) 775, 1132, 1302, 1432, 1590, 1692, 1742, 3447 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.7 (br. s, 1H), 7.3 (s, 5H), 4.3 (d, J = 12.5 Hz, 1H), 4.2 (d, J = 12.5 Hz, 1H), 3.7 (s, 3H), 3.4 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.2 (C=O), 168.1 (C=O), 167.2 (C=O), 133.9 (C), 129 (CH), 128.4 (CH), 128.3 (CH), 54.7 (CH), 53.1 (CH_3O), 52.6 (CH_3O), 50.5 (CH); MS *m/z* (rel. intensity) 248 (70), 216 (36), 189 (82), 161 (39), 131 (42), 121 (100), 103 (42), 77 (33).

***trans*-4-Hydroxymethyl-3-phenyl-dihydro-2(3H)-furanone (7).** To a solution of compound **5** (80 mg, 0.30 mmol) in anhydrous ether (4 mL), maintained under nitrogen atmosphere, was added $LiBH_4$ (16 mg, 0.72 mmol). The reaction mixture was stirred at room temperature for 5 hours and then quenched with water (1 mL) and 6M HCl (2 mL). After stirring for 15 minutes, the mixture was diluted with water and extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography through silica gel, eluting with ethyl acetate/hexane (7:3) to give compound **7**. Yield 48.4 mg (0.25 mmol, 83%). IR (neat film) 758, 1222, 1363, 1400-1500, 1772, 1706, 3472 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.3 (m, 5H), 4.5 (dd, J_1 = 9.02 Hz, J_2 = 9.0 Hz, 1H), 4.25 (dd, J_1 = 9.02 Hz, J_2 = 9.0 Hz, 1H), 3.8 (dd, J_1 = 10.8 Hz, J_2 = 4.0 Hz, 1H), 3.75 (d, J = 10 Hz, 1H), 3.7 (dd, J_1 = 10.8 Hz, J_2 = 5.8 Hz, 1H), 2.8 (m, 1H), 2.6 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.9 (C=O), 135.8 (C), 129 (CH), 128.5 (CH), 127.7 (CH), 68.9 (CH_2), 60.3 (CH_2), 47.8 (CH), 46.6 (CH); MS *m/z* (rel. intensity) 192 (12) (M^+), 161 (20), 133 (9), 115 (72), 117 (98), 91 (59), 77 (22), 32 (100). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68,66; H, 6.54.

***trans* - 4 - Methylsulfonyloxymethyl - dihydro - 2 (3 H) - furanone (8).** Methanesulfonyl chloride (63 mg, 0.54 mmol) was added to a previously cooled (0 °C) solution of compound **7** (99.8 mg, 0.52 mmol) and triethylamine (59 mg,

0.58 mmol) in dichloromethane (8 mL). After stirring for 1 hour, the resulting mixture was diluted with water and extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography through silica gel, eluting with ethyl acetate/hexane (7:3) to give compound **8**. Yield 130.4 mg (0.48 mmol, 92%); IR (neat film) 700, 1000, 1173, 1357, 1400, 1603, 1767 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.4 (m, 5H), 4.5 (dd, J_1 = 9.7 Hz, J_2 = 7.7 Hz, 1H), 4.3 (dd, J_1 = 9.7 Hz, J_2 = 5 Hz, 1H), 4.2 (dd, J_1 = 10.3 Hz, J_2 = 5.7 Hz, 1H), 4.1 (dd, J_1 = 10.3 Hz, J_2 = 9.0 Hz, 1H), 3.6 (d, J = 10.3 Hz, 1H), 3.0 (m, 1H), 2.9 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.7 (C=O), 134.7 (C), 129.1 (CH), 128.3 (CH), 128.1 (CH), 67.7 (CH_2), 66.7 (CH_2), 47.9 (CH), 44.2 (CH), 37.4 (CH_3S); MS *m/z* (rel. intensity) 271 (17) (M^+), 174 (24), 161 (78), 144 (20), 129 (94), 115 (100), 91 (53), 32 (18).

1-Phenyl-3-oxa-bicyclo[3.1.0]hexan-2-one (9). A solution of compound **8** (50.1 mg, 0.185 mmol) and DBU (0.033 mL, 0.23 mmol) in dichloromethane (3 mL) was stirred at room temperature for 1 hour. The reaction mixture was diluted with water and extracted with dichloromethane. The organic solution was washed with water and saturated brine, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography through silica gel, eluting with ethyl acetate/hexane (1:1) to give compound **9** as a solid: mp 48-49 °C. Yield 22.6 mg (0.129 mmol, 70%); IR (neat film) 706, 1046, 1363, 1400, 1446, 1600, 1761 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.3 (m, 5H), 4.5 (dd, J_1 = 10 Hz, J_2 = 6 Hz, 1H), 4.25 (dd, J_1 = 10 Hz, J_2 = 10 Hz, 1H), 2.6 (m, J_1 = 6 Hz, J_2 = 10 Hz, J_3 = 5.3 Hz, 1H), 1.6 (dd, J_1 = 8 Hz, J_2 = 5.3 Hz, 1H), 1.3 (dd, J_1 = 8 Hz, J_2 = 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.0 (C=O), 134.1 (C), 128.6 (CH), 128.3 (CH), 127.7 (CH), 68.1 (CH_2), 31.7 (C), 25.1 (CH), 20.1 (CH_2); MS *m/z* (rel. intensity) 174 (81) (M^+), 144 (48), 129 (40), 116 (48), 115 (100), 103 (23), 77 (14), 63 (13). Anal. Calcd for $C_{11}H_{12}O_3$: C, 75.84; H, 5.78. Found: C, 75.50; H, 5.89.

***trans*-3-Phenyl-4-phenylselenomethyl-dihydro - 2(3H) - furanone (10).** To a solution of diphenyl diselenide (31.2 mg, 0.1 mmol) in anhydrous ethanol (2 mL),

maintained under nitrogen atmosphere, was added a solution of $NaBH_4$ (9.3 mg, 0.24 mmol) in anhydrous ethanol (1 mL). The initially yellow solution became colorless after completing the addition. A solution of compound **8** (57 mg, 0.21 mmol) in THF (1 mL) was then added and the reaction mixture was stirred for 3 hours at room temperature. Then, aqueous 10% HCl (1 mL) was added and, after stirring for 5 minutes, the reaction mixture was diluted with water and extracted with petroleum ether. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography through silica gel, eluting with hexane/ethyl acetate (7:3) to give the phenyl selenide derivative **10** as a solid (mp 90-91 °C) and the cyclopropane derivative **9** in a ratio of ~ 1:1. Yield of compound **10** 34.9 mg (0.105 mmol, 50%); IR (neat film) 1000, 1166, 1400, 1600, 1755 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.7-7.1 (m, 10H), 4.5 (dd, J_1 = 8.7 Hz, J_2 = 7.7 Hz, 1H), 4.0 (dd, J_1 = 8.7 Hz, J_2 = 8.7 Hz, 1H), 3.5 (d, J = 11 Hz, 1H), 3.2 (dd, J_1 = 15 Hz, J_2 = 8.7 Hz, 1H), 2.9 (m, 1H), 2.9 (dd, J_1 = 15 Hz, J_2 = 9.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.4 (C=O), 135 (C), 133.1 (CH), 129.4 (CH), 129 (C), 128.8 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 71.1 (CH_2), 52.5 (CH), 45.4 (CH), 28.4 (CH_2); MS *m/z* (rel. intensity) 332 (6) (M^+), 192 (2), 172 (20), 157 (22), 129 (32), 115 (56), 91 (100), 51 (45).

4-Methyl-3-phenyl-2(5H)-furanone (12). To a solution of compound **10** (17 mg, 0.051 mmol) in THF (1 mL), cooled to 0°C, was added 30% aqueous H_2O_2 (0.05 mL) and an excess of anhydrous $MgSO_4$. The reaction mixture was stirred at 0°C for 30 minutes and at room temperature for 24 hours. THF (2 mL) was then added, and the solid phase was removed by filtration and washed with ethyl acetate. The organic phases were combined, the solvent was evaporated and the residue was purified by column chromatography through silica gel, eluting with hexane/ethyl acetate (8:2) to give compound **12** as a crystalline solid: mp 83-85°C. Yield 2.8 mg (0.016 mmol, 31%). IR (neat film) 707, 1014, 1122, 1400, 1600, 1731 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.3 (m, 5H), 4.75 (s, 2H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3 (C=O), 157.6 (=C), 129.8 (=C),

128.8 (C), 128.5 (CH), 128.48 (CH), 126.8 (CH), 72.4 (CH_2), 13.4 (CH_3); MS *m/z* (rel. intensity) 174 (59) (M^+), 131 (15), 145 (19), 131 (15), 117 (100), 115 (57), 91 (14), 63 (8). Anal. Calcd for $C_{11}H_{12}O_3$: C, 75.84; H, 5.78. Found: C, 75.65; H, 5.76.

4-Hydroxymethyl-3-methyl-3-phenyl-dihydro-2(3H)-furanone (13). To a solution of diisopropylamine (363 mg, 3.43 mmol) and HMPA (560 mg, 3.12 mmol) in anhydrous THF (12 mL), maintained at 0°C under nitrogen atmosphere, was added a solution of butyllithium in hexane (3.28 mmol). After stirring for 10 minutes at 0°C, the solution was cooled to –78°C and, after 15 minutes, a solution of compound **7** (300 mg, 1.56 mmol) in anhydrous THF (2 mL) was added. Stirring was continued for 30 minutes, and then a solution of methyl iodide (243 mg, 1.7 mmol) in THF (1 mL) was added. After being stirred for 6 hours at –78°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 $MgSO_4$ and evaporated. The residue was purified by column chromatography through silica gel, eluting with ethyl acetate/hexane (7:3) to give compound **13** as a mixture (2:1) of *trans* and *cis* stereoisomers. Yield 238.3 mg (1.16 mmol, 74%). Analytical data for the major (*trans*) stereoisomer: IR (neat film) 707, 1012, 1183, 1400, 1600, 1758, 3415 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.3 (m, 5H), 4.25 (dd, J_1 = 9.1 Hz, J_2 = 5.3 Hz, 1H), 4.25 (dd, J_1 = 9.1 Hz, J_2 = 8.0 Hz, 1H), 3.8 (dd, J_1 = 11.4 Hz, J_2 = 5.7 Hz, 1H), 3.7 (dd, J_1 = 11.4 Hz, J_2 = 3.4 Hz, 1H), 2.8 (m, 1H), 2.2 (s, 1H), 1.5 (s, 3H); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.3 (m, 5H), 4.45 (dd, J_1 = 9.1, J_2 = 6.8 Hz, 1H), 4.42 (dd, J_1 = 9.1, J_2 = 6.8 Hz, 1H), 3.3 (dd, J_1 = 11.4, J_2 = 6.8 Hz, 1H), 3.1 (dd, J_1 = 11.3, J_2 = 8 Hz, 1H), 2.65 (m, 1H), 2.2 (s, 1H), 1.7 (s, 3H); MS *m/z* (rel. intensity) 206 (10) (M^+), 147 (16), 131 (100), 129 (33), 115 (18), 105 (15), 91 (59), 77 (22). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.52; H, 7.01.

3-Methyl-4-methylsulfonyloxymethyl-3-phenyl-dihydro-2(3H)-furanone (14). Methanesulfonyl chloride (130 mg, 1.13 mmol) was added to a cooled (0°C) solution of compound **13** (mixture of stereoisomers) (220.3 mg, 1.07 mmol) and triethylamine (125 mg, 1.24 mmol) in dichloromethane (5 mL). After stirring at room temperature for 2 hours, the reaction mixture was diluted with water and extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography through silica gel, eluting with ethyl acetate/hexane (7:3) to give compound **14** as a mixture (2:1) of *trans* and *cis* stereoisomers. Yield 298 mg (1.04 mmol, 97%). Analytical data for the major (*trans*) stereoisomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.3 (m, 5H), 4.5 (dd, J_1 =10.4 Hz, J_2 = 7.8 Hz, 1H), 4.4 (dd, J_1 = 10.4 Hz, J_2 = 5.2 Hz, 1H), 4.3 (dd, J_1 = 10.4 Hz, J_2 = 7.8 Hz, 1H), 4.2 (dd, J_1 = 10.4 Hz, J_2 = 4.7 Hz, 1H), 3.1 (m, 1H), 1.5 (s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.7 (C=O), 140.5 (C), 129.1 (CH), 127.8 (CH), 125.8 (CH), 67.3 (CH_2), 66.8 (CH_2), 49.9 (C), 46.4 (CH), 37.6 (CH_3-S), 23.6 (CH_3); MS *m/z* (rel. intensity) 284 (4) (M^+), 144 (21), 131 (19), 129 (100), 115 (11), 103 (10), 91 (24), 77 (10).

3-Methyl-3-phenyl-4-phenylselenomethyl-dihydro - 2(3H) - furanone (15a). To a solution of diphenyl diselenide (156 mg, 0.5 mmol) in anhydrous ethanol (2 mL), maintained under nitrogen atmosphere, was added a solution of $NaBH_4$ (33 mg, 0.87 mmol) in anhydrous ethanol (1 mL). The initially yellow solution became colorless after completing the addition. A solution of compound **14** (mixture of stereoisomers) (284 mg, 1.0 mmol) in THF (1 mL) was added, and the reaction mixture was stirred for 35 hours. Then, 10% HCl (1 mL) was added and, after stirring for 5 minutes, the reaction mixture was diluted with water and extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography through silica gel, eluting with hexane/ethyl acetate (7:3) to give compound **15a** as a mixture (6:1) of *trans* and *cis* stereoisomers. Yield 203.5 mg (0.59 mmol, 59%). Analytical data for the major (*trans*) stereoisomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.3 (m, 10H),

4.4 (dd, J_1 = 7.5 Hz, J_2 = 6.3 Hz, 1H), 4.1 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 1H), 3.2 (dd, J_1 = 10 Hz, J_2 = 3.7 Hz, 3H), 2.9 (m, 1H), 2.77 (dd, J_1 = 10 Hz, J_2 = 10 Hz, 1H), 1.5 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.8 (C=O), 140.7, 136.5, 132.8, 129.3, 128.8, 127.6, 127.5, 126.3, 69.9 (CH_2), 51.3 (C), 48 (CH), 24.8 (CH_2), 17.4 (CH_3); MS *m/z* (rel. intensity) 346 (57) ($M^{+\cdot}$), 157 (30), 143 (50), 129 (60), 132 (54), 105 (47), 91 (100), 77 (52).

3-Methyl-4-(2-nitrophenyl)selenomethyl-3-phenyl-dihydro - 2(3H) - furanone (15b). To a solution of 2,2'-dinitrodiphenyl diselenide (96 mg, 0.27 mmol), prepared from *o*-nitrophenyl selenocyanate as described by Bauer,[14] in anhydrous ethanol (2 mL), under nitrogen atmosphere, was added a solution of $NaBH_4$ (21 mg, 0.55 mmol) in anhydrous ethanol (1 mL). The initially yellow solution became red after completing the addition. A solution of compound **14** (mixture of stereoisomers) (150.4 mg, 0.53 mmol) in THF (1 mL) was then added and the reaction mixture was stirred at room temperature for 25 hours. After quenching with 10% HCl (1 mL) and stirring for 5 minutes, the solution was diluted with water and extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography through silica gel, eluting with hexane/ethyl acetate (7:3) to give compound **15b** as a mixture (6:1) of *trans* and *cis* stereoisomers. Yield 61.9 mg (0.16 mmol, 30%). Analytical data for the major (*trans*) stereoisomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.3 (dd, J_1 = 9.4 Hz, J_2 = 2.0 Hz, 1H); 7.3 (m, 7H), 6.9 (dd, J_1 = 8.0 Hz, J_2 = 1.3 Hz, 1H), 4.5 (dd, J_1 = 7.5 Hz, J_2 = 6.2 Hz, 1H), 4.2 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 1H), 3.2 (dd, J_1 = 10 Hz, J_2 = 3.75 Hz, 1H), 3.0 (m, 1H), 2.7 (dd, J_1 = 10 Hz, J_2 = 10 Hz, 1H), 1.6 (s, 1H); MS *m/z* (rel. intensity) 391 (14) (M^+), 186 (28), 143 (75), 130 (21), 128 (35), 115 (56), 91 (100), 41 (62).

3-Methyl-4-methylene-3-phenyl-dihydro-2(3H)-furanone (16)

Method A (from phenyl selenide (15a)):

To a solution of compound **15a** (mixture of stereoisomers) (32 mg, 0.093 mmol) in THF (2 mL), cooled to 0°C, was added 30% aqueous H_2O_2 (0.15 mL)

and an excess of anhydrous $MgSO_4$. The reaction mixture was stirred at 0°C for 30 minutes and at room temperature for 24 hours. THF (2 mL) was then added, the $MgSO_4$ was filtered and washed with ethyl acetate. The solvent was evaporated and the residue was purified by column chromatography through silica gel, eluting with hexane/ethyl acetate (8:2) to give compound **16**. Yield 4.4 mg (0.023 mmol, 25%).

Method B (from *o*-nitrophenyl selenide (15b)):

To a solution of compound **15b** (mixture of stereoisomers) (9 mg, 0.03 mmol) in THF (1 mL), cooled to 0°C, was added 30% aqueous H_2O_2 (0.05 mL). The reaction mixture was stirred at room temperature for 24 hours and then diluted with water and extracted with ether. The ethereal solution was washed with water, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography through silica gel, eluting with hexane/ethyl acetate (8:2) to give compound **16**. Yield 3.4 mg (0.018 mmol, 70%). IR (neat film) 1000, 1188, 1400, 1600, 1777 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.3 (m, 5H), 5.38 (dt, J_1 = 4.5 Hz, J_2 = 1.9 Hz, J_3 = 1.50 Hz, 1H), 5.2 (dt, J_1 = 4.5 Hz, J_2 = 2.2 Hz, J_3 = 2.6 Hz, 1H), 4.8 (dt, J_1 = 12.4 Hz, J_2 = 1.9 Hz, J_3 = 2.2 Hz, 1H), 4.7 (dt, J_1 = 12.4 Hz, J_2 = 2.6 Hz, J_3 = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.5 (C=O), 147.5 (=C), 139.4 (C), 128.9 (CH), 127.8 (CH), 126.1 (CH), 110.2 (=CH_2), 70.2 (CH_2), 65.9 (C), 24 (CH_3); MS m/z (rel. intensity) 188 (2) (M^+), 144 (16), 129 (100), 128 (40), 115 (14), 91 (5), 77 (10), 51 (9). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.18; H, 6.36.

Acknowledgments: the authors wish to thank the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and the Coordenadoria de Aperfeiçoamento de Pessoal do Ensino Superior (CAPES) for financial support. Useful discussions with Prof. Dr. Gil Valdo José da Silva are also acknowledged.

References and Notes

1. Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. *J. Org. Chem.* **1994**, *59*, 365; Koch, S. S. C.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725.
2. LaLonde, R. T.; Perakyla, H.; Hayes, M. P. *J. Org. Chem.* **1990**, *55*, 2847; Harrison, T.; Myers, P. L.; Pattenden, G. *Tetrahedron* **1989**, *45*, 5247; Mattes, H.; Hamada, K.; Benezra, C. *J. Med. Chem.* **1987**, *30*, 1948.
3. Grieco, P. A. *Synthesis* **1975**, 67; Newaz, S. S. *Aldrichimica Acta* **1977**, *10*, 64; Kano, S.; Shibuya, S.; Ebata, T. *Heterocycles* **1980**, *14*, 661; Petragnani, N.; Ferraz, H. M. C.; Silva, G. V. J. *Synthesis* **1986**, 157.
4. Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*, Volume II, Academic Press: New York, **1972**.
5. Campbell, S. F.; Constantino, M. G.; Brocksom, T. J.; Petragnani, N. *Synth.Commun.* **1975**, *5*, 353; Haslouin, J.; Rouessac, F. *Tetrahedron Lett.* **1976**, *17*, 4651; McMurry, J. E.; Donovan, S. F. *Tetrahedron Lett.* **1977**, *18*, 2869; Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Chou, K. J. *J. Am. Chem. Soc.* **1977**, *99*, 4778; Evans, D. A.; Sims, C. L.; Andrews, G. C. *J. Am. Chem. Soc.* **1977**, *99*, 5453; Brocksom, T. J.; Constantino, M. G.; Ferraz, H. M. C. *Synth. Commun.* **1977**, *7*, 483; Petragnani, N.; Brocksom, T. J.; Ferraz, H. M. C.; Constantino, M. G. *Synthesis* **1977**, 112; Inoue, Y.; Hibi, T.; Satake, M.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.* **1979**, 982; Okabe, M.; Tada, M. *J. Org. Chem.* **1982**, *47*, 5382; Greene, A. E.; Coelho, F.; Deprés, J. P.; Brocksom, T. J. *J. Org. Chem.* **1985**, *50*, 1973; Greene, A. E.; Deprés, J. P.; Coelho, F.; Brocksom, T. J. *J. Org. Chem.* **1985**, *50*, 3943; Greene, A. E.; Coelho, F.; Deprés, J. P.; Brocksom, T. J. *Tetrahedron Lett.* **1988**, *29*, 5661; Coelho, F.; Deprés, J. P.; Brocksom, T. J.; Greene, A. E. *Tetrahedron Lett.* **1989**, *30*, 565.
6. Rahmani, M.; Hin, T. Y. Y.; Ismail, H. B. M.; Sukari, M. A.; Manas, A. R. *Planta Med.* **1993**, *59*, 93; Rahmani, M.; Hin, T. Y. Y.; Ismail, H. B. M.; Sukari, M. A.; Waterman, P. G. *Phytochemistry* **1994**, *37*, 561.
7. Tantivatana, P.; Ruangrungsi, N.; Vaisiriroj, V.; Lankin, D. C.; Bhacca, N. S.; Borris, R. P.; Cordell, G. A.; Johnson, L. F. *J. Org. Chem.* **1983**, *48*, 268.
8. Bryan, D. B.; Hall, R. F.; Holden, K. G.; Huffman, W. F.; Gleason, J. G. *J. Am. Chem. Soc.* **1977**, *99*, 2353.
9. Williams, R. M.; Maruyama, L. K. *J. Org. Chem.* **1987**, *52*, 4044.
10. Reich, H. J.; Shah, S. K. *J. Org. Chem.* **1977**, *42*, 1773.
11. Grieco, P. A.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 1717.
12. Compound **13** was obtained and used in the subsequent steps as a mixture of

trans and *cis* isomers (ratio ~ 2:1), as the relative stereochemistry is lost in the last step of formation of **16**.

13. Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947.

14. Bauer, H. *Ber.* **1913**, *46*, 92.

(Received in the USA 17 February 1999)