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TETRAHEDRON

3-Phenylselanylfuran-2(5*H*)-one: a Versatile Building Block in the Synthesis of Lignans. A New Approach Towards 3,4-Dibenzyl γ-Butyrolactones

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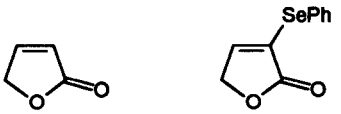
Abstract:

Ready available 3-phenylselanylfuran-2(5*H*)-one undergoes tandem conjugate addition-alkylation by organocopper reagents to afford, with good yields and diastereoselectivities, 3,4-disubstituted-3-phenylselanyl-γ-butyrolactones, which can be transformed into naturally occurring compounds, such as lignans.

Keywords: furanones; lignans; selenium compounds.

Stereocontrolled bond-forming reactions by conjugate additions in cyclic α,β-unsaturated carbonyl compounds are challenging areas of current importance in organic synthesis.[1] Direct organocopper addition to furan-2(5*H*)-one **1** is a problematic reaction.[2] The addition of simple organocuprates, such as lithium dimethyl cuprate, requires the use of the highly toxic HMPA as cosolvent, while the reaction of other organocopper reagents, such as benzylmagnesium chloride in the presence of Cu(I) salts, proceeds in low yields.[3a] In recent years, both 3-phosphorous[3b] and sulfur[3c] substituted furanones, though not easy available, have been shown to undergo Michael additions, allowing circumvention of these problems.



1 **2**

We report a new and efficient synthesis of 3-phenylselanylfuran-2(5*H*)-one **2**, readily available now in large amount, and its use as an efficient Michael acceptor for the ready preparation of naturally occurring 3,4-disubstituted-butyrolactones, such as lignans. There is an increasing interest in developing new synthetic routes to these compounds, due to their biological properties.[4] To our knowledge, these substances have generally been prepared by a multi-step sequence, where the construction of the γ-lactone ring is usually the last step.[5]

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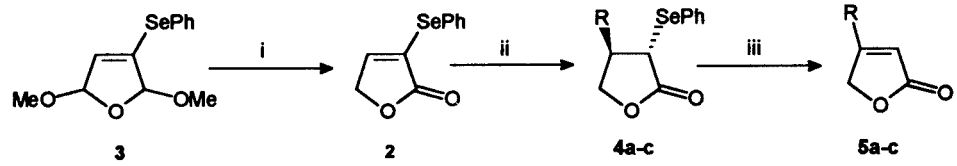
The preparation of **2** was carried out by acid catalysed treatment of 2,5-dimethoxy-3-phenylselanyl-2,5-dihydrofuran **3**[6a] (yield: 81%, Scheme 1). Due to the presence of the phenylselenium group, **2** was obtained as a single regioisomer. It is important to observe that 3-substituted-2,5-dimethoxy-2,5-dihydrofurans by reaction with acids usually give rise to the formation of a mixture of regioisomeric furan-2(5*H*)-ones.[6b,c] Only a two step synthesis of compound **2** (23% overall yield) was previously described.[7] Unlike furan-2(5*H*)-ones, **2** was shown to be very reactive both in mono- and dialkylation reactions of the conjugate double bond.

Scheme 1



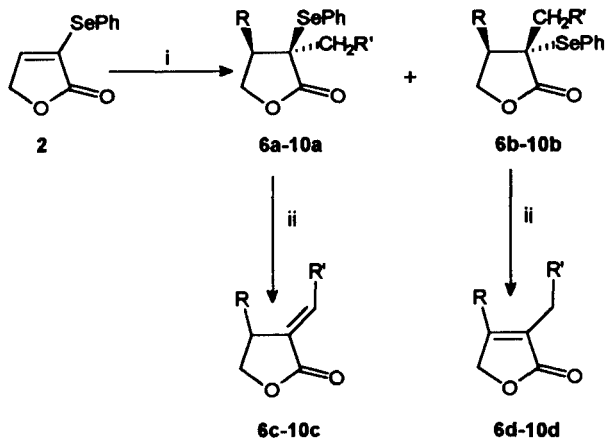
Reagents and conditions: i, 1M HCl:CH_3CN 1:10, 0° C, 10 min.; ii, R_2CuLi or RMgBr/CuI, ether, -78° C, (**a**: R= CH_3, **b**: R= 3,4-(methylenedioxy)benzyl, **c**, R= benzyl) 10 min. then H_2O (**4a**: 90%, **4b**: 80%, **4c**, 90%); iii, $NaIO_4$, MeOH/H_2O, 6/1(**5a**: 95%, **5b**: 93%, **5c**, 94%).

The mono-alkylation of **2** proceeded both with lithium dialkyl cuprates and with Grignard reagents in presence of Cu(I) salts to give the corresponding 4-substituted derivatives **4** (Scheme 1). It is worth noting that all the addition reactions were completely regioselective, giving *trans* 4-substituted-3-phenylseleno-γ-butyrolactones **4a-c** in nearly quantitative yields. As a result of this reaction, selenium has proven to be particularly effective as a directing and activating atom in conjugate addition.[8]

However, for the efficiency of the reaction, better results were obtained using a large excess of the organocuprates (3:1 with respect to the substrate), that sometimes could interfere in the purification step. The usual selenoxide *syn*-elimination, carried out with $NaIO_4$ in MeOH/H_2O at room temperature, restored the double bond, giving 4-substituted butenolides **5** (Scheme 1). It is known that compounds **5**, where R is an aryl group, exhibit pharmacological activities[9a] and that this structural moiety is present in some naturally occurring substances.[9b]

The anion resulting from the Michael addition to **2** can be easily trapped by adding primary alkyl halides (Scheme 2). However, the second alkylation reaction proceeded only after warming the mixture to room temperature and the presence of a cosolvent was necessary, while it was not required in the monoalkylation procedure. DMPU could effectively be used instead of HMPA.

Scheme 2



Reagents and conditions: i, R_2CuLi or RMgBr/CuI, ether, -78° C, then DMPU, $R'CH_2X$, room temperature; ii, $NaIO_4$, $MeOH/H_2O$, 6/1.

Table 1. Tandem Michael conjugate addition/alkylation of 3-phenylselanylfuran-2(5*H*)-one **2**

Entry	Compounds	R	R'	*trans:cis* [a]	yield, %
1	**6a-6b**	CH_3	H	1:2	65
2	**7a-7b**	CH_3	CH_2=CH	1:2	60
3	**8a-8b**	CH_3	Ph	4:1	62
4	**9a-9b**	Bn	Bn	>7:1	70
5	**10a-10b**	3,4-(methylenedioxy)benzyl	3,4-(methylenedioxy)phenyl	>10:1	45

[a] *Trans/cis* with respect to alkyl groups.

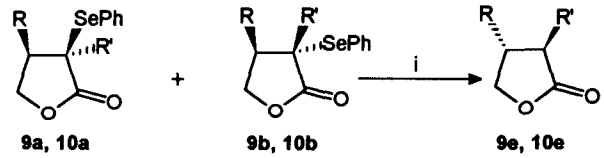
Using electrophiles, such as benzylic bromides, the dialkylation gives a mixture of diastereoisomers, where the *trans* isomer was preferentially formed (Scheme 2; Table 1, entries 4, 5). On the other hand, the double alkylation procedure, adding first lithium dimethyl cuprate and then electrophiles with lower steric hindrance, such as either methyl iodide or allyl iodide, showed a poor diastereoselectivity, with a 2:1 *cis/trans* ratio (Scheme 2; Table 1, entries 1,2). The *trans* relationship between the two alkyl groups of compounds **6a-10a** was unambiguously established by the oxidative *syn*-elimination of the PhSe group, which by treatment with $NaIO_4$ led to the unsaturated γ-lactones with only the *E* exocyclic double bond, such as **6c-10c** in nearly quantitative yields. The same reaction carried out on the *cis* isomers **6b-10b** led to the formation of 2-furanones **6d-10d**. Interestingly, the above results pointed out that the oxidation/elimination of the phenylselanyl group proceeded both regio and stereoselectively.

Table 2. Selenoxide elimination on 3,4-disubstituted-3-phenylselanyl-γ-butyrolactones.

Entry	Substrate	Product	R	R''	yield, %
1	**6a**	**6c**	CH_3	H	95
2	**8a**	**8c**	CH_3	H	91
3	**9a**	**9c**	Bn	Ph	94
4	**10a**	**10c**	3,4-(methylenedioxy)benzyl	3,4-(methylenedioxy)phenyl	94
5	**6b**	**6d**	CH_3	CH_3	93
6	**8d**	**8d**	CH_3	Bn	95

The above described compounds, such as **10a**, can be considered versatile intermediates for a straightforward access to biologically active natural lignans. (±)-Savinin **10c** [R=3,4-(methylenedioxy)benzyl, [R'=3,4-(methylenedioxy)phenyl] was easily obtained by treatment of **10a** with $NaIO_4$ in very high yields (Scheme 2, Table 2, entry 4).[10]

The reductive elimination of the phenylselanyl group, carried out by reaction with $NiCl_2/NaBH_4$ in THF directly on the mixture of the compounds **9a-9b**, afforded predominantly (>10:1) the *trans* saturated γ-butyrolactone **9e**. Similarly, the 3,4-bis-[3,4-(methylenedioxy)benzyl]-γ–butyrolactone, (±)-hinokinin **10e**, was easily obtained starting from the compounds **10a-10b**. The reductive elimination is known to proceed *via* a radical mechanism, leading to more stable *trans* isomer; stereochemical assignments have been confirmed by comparison with literature spectral data.



9a, 10a **9b, 10b** **9e, 10e**

Reagents and conditions: i, $NiCl_2$, $NaBH_4$, THF, 0° C, **9e**, R=R'=Bn, 90% ; **10e**, R=R'=3,4-(methylenedioxy)benzyl, 95%.

In conclusion, we have developed a novel methodology for a facile and diastereoselective synthesis of natural substances, such as lignans **10c** and **10e**. Furthermore this strategy allows good flexibility and could be successfully used for the synthesis both of natural or unnatural compounds based on the 3,4-disubstituted butyrolactone moiety. Development of a stereocontrolled protocol to prepare enantiomerically pure compounds *via* this sequential strategy is in progress in our laboratory.

Experimental Section

General Experimental

^{1}HNMR and ^{13}CNMR spectra were recorded on a Varian Gemini 200 spectrometer at room temperature with $CDCl_3$ as solvent and as internal standard. Coupling constants are quoted in Hertz. IR spectra were obtained with a Shimazu IR 435 grating infrared spectrophotometer. Flash chromatography was executed with Merck Kiesegel 60 (230-400 mesh) using a mixture of ethyl acetate and hexane as eluant.

DHDMF, (commercially available as *cis-trans* mixture of diastereoisomers), PhSeCl, $NaIO_4$, CuI were utilised as purchased. Commercially available methyllithium, (1.4 M solution in diethyl ether), benzylmagnesium chloride, (2.0 M solution in tetrahydrofuran), were titrated prior to use. THF and diethyl ether were dried over sodium wires.

Melting points were taken on a Mettler -FP-61 apparatus and are uncorrected. All selenium containing compounds (except compound **2**) are viscous oils and only in some cases they could be crystallised at -15°.

2,5-Dimethoxy-3-phenylselanyl-2,5-dihydrofuran **3**:

This compound was prepared with a slight modification of the literature procedure[6a]:

To a stirred solution of 2,5-dimethoxy 2,5-dihydrofuran (2.00 g, 15.38 mmol) in 20 ml of dry CH_2Cl_2, ZnF_2 (500 mg) and PhSeCl (2.95 g, 15.38 mmol) were added portionwise during 5 minutes and the mixture was stirred at room temperature for 2 hours.

The colour of the solution changed from deep brownish to light yellow. The mixture was poured into a separating funnel, diluted with ethyl acetate (200 ml) and washed once with water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo to give 4.90 g of crude 3-chloro-2,5-dimethoxy-3-phenylselanyl-tetrahydrofuran as a viscous reddish oil. *t*-BuOK (5 g in 5 ml of anhydrous *t*-BuOH) was added to this compound and the mixture was warmed to 80° for 25 minutes. The reaction was cooled to room temperature and diluted with ethyl acetate (200 ml). The organic layer was washed with water and then with brine, and dried over anhydrous Na_2SO_4. After solvent evaporation, the oil residue was purified *via* flash chromatography on silica gel (hexane first, then hexane: ethyl acetate 6/1) to give **3** (4.08 g) as colourless oil (mixture of diastereoisomers) in 93% overall yield. Spectral data are completely in agreement with ref. 6a.

B.p.: decomposes on heating.

δ_H($CDCl_3$) 7.7-7.6 (2H, m), 7.4-7.3 (3H, m), 5.56 (1H, s), 5.50 (2H, s), 3.37 (3H, s), 3.33 (3H, s);

and 7.7-7.6 (2H, m), 7.4-7.3 (3H, m), 5.80 (1H, d, J=3.8), 5.72 (1H, d, J=3.8), 5.50 (1H, s), 3.36 (3H, s), 3.34 (3H, s).

3-Phenylselanylfuran-2(5H)-one **2**:

To a cooled (0° C) solution of **3** (1.00 g, 3.508 mmol) in 30 ml of CH_3CN, 1M HCl solution (1 ml) was added dropwise. The colour of the solution changed from colourless to light yellow instantaneously.

After 10 minute, the mixture was diluted with ethyl acetate (100 ml) and washed once with water and then with brine and dried over anhydrous Na_2SO_4.

The solvent was evaporated to give a brown solid (790 mg) that was purified *via* flash chromatography on silica gel (hexane: ethyl acetate 3/1) to obtain 680 mg of **2** (2.84 mmol, 81%) as an oil that could be crystallised to give a pale yellowish solid. M.p.: 57-58° (ether/hexane).

Direct crystallisation of the crude product gives 495 mg (59%) of **2**.

Spectral data are completely in agreement with ref. 7.

δ_H ($CDCl_3$) 7.7-7.6 (2H, m), 7.4-7.3 (3H, m), 6.81 (1H, J=2.0), 4.77 (2H, J=2.0); δ_c ($CDCl_3$) 171.63, 145.24, 135.65, 129.93, 129.30, 127.66, 125.55, 72.61.

General procedure for alkylation of 3-phenylselanylfuran-2(5H)-one **2**:

To a cold (-78 °C) solution of dialkyl cuprate or benzylic magnesium cuprate in 15 ml of ether (2.50 mmol), an ethereal solution (2ml) of **2** (200 mg, 0.836 mmol) was added dropwise. After 10 minutes, TLC showed that all starting material had been consumed. Aqueous NH_4Cl/NH_3 (10 ml) solution was added and the mixture extracted once with ethyl acetate (100 ml). The organic layer was washed with brine (5 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give a viscous oil that was purified by flash chromatography on silica gel (hexane: ethyl acetate 6/1) to give pure products.

(3S, 4R*)-4-Methyl-3-phenylselanyl-γ-butyrolactone* **4a**:

Yield : 90% ; viscous oil. δ_H ($CDCl_3$) 7.7-7.6 (2H, m), 7.4-7.2 (3H, m), 4.27 (1H, dd, J_1=7.0, J_2=8.8), 3.82 (1H, dd, J_1=6.0, J_2=8.8), 3.46 (1H, d, J=6.6), 2.6-2.4 (1H, m), 1.19 (3H, t, J=6.8); δ_c ($CDCl_3$) 175.33, 135.87, 129.34, 129.03, 126.41, 72.98, 44.31, 37.57, 17.37 ; ν_{max} ($CHCl_3$)/cm^{-1} 1771 (C=O). Anal. Calcd. for $C_{11}H_{12}O_2Se$: C, 51.77%, H, 4.74%. Found : C, 51.82% H, 4.70%.

(3S, 4R*)-4-[(3,4-Methylenedioxy)benzyl]-3-phenylselanyl-γ-butyrolactone* **4b:**

Yield : 80% ; viscous oil. δ_H ($CDCl_3$) 7.7-7.6 (2H, m), 7.4-7.2 (3H, m), 6.8-6.7 (1H, m), 6.55-6.45 (2H, m), 5.94 (s, 2H), 4.17 (1H, dd, J_1=6.2, J_2=9.0), 3.97 (1H, dd, J_1=4.2, J_2=9.0), 3.62 (1H, d, J=4.6), 2.9-2.6 (3H, m); δ_c ($CDCl_3$) 175.51, 147.54, 146,51, 135.89, 130.88, 129.42, 129.17, 126.37, 121.87, 108.97, 108.47, 101.04, 70.97, 44.26, 41.63, 38.12; ν_{max} ($CHCl_3$)/cm^{-1} 1763 (C=O). Anal. Calcd. for $C_{18}H_{16}O_4Se$: C, 57.61%, H, 4.30%.

Found : C, 57.80% H, 4.34%.

(3S, 4R*)-4-Benzyl-3-phenylselanyl-γ-butyrolactone* **4c**:

Yield : 90% ; viscous oil. δ_H ($CDCl_3$) 7.75-7.65 (2H, m), 7.45-7.15 (6H, m),), 7.1-7.0 (2H, m); 4.17 (1H, dd, J_1=6.2, J_2=9.1), 4.00 (1H, dd, J_1=4.2, J_2=9.1), 3.64 (1H, d, J=4.8), 3.0-2.6 (3H, m); δ_c ($CDCl_3$) 175.55, 137.19, 135.78, 129.39, 129.07, 128.76; 128.66; 126.87, 126.31, 71.58; 43.98; 41.74; 38.27; ν_{max} ($CHCl_3$)/cm^{-1} 1766 (C=O). Anal. Calcd. for $C_{17}H_{16}O_2Se$: C, 61.64%, H, 4.87%. Found : C, 61.54% H, 4.93%.

Tandem Michael conjugate addition/alkylation of 3-phenylselanylfuran-2(5H)-one **2**. *General procedure.*

To a cold (-78 °C) solution of dimethyl lithium cuprate in 15 ml of THF (2.51 mmol), a THF solution (2ml) of **2** (200 mg, 0.836 mmol) was added dropwise. After 10 minutes, DMPU (2ml) and an alkyl halide (5.02 mmol) were added and the reaction mixture was allowed to warm up to room temperature. After 5 hr, aqueous NH_4Cl/NH_3 solution (10 ml) was added and the mixture extracted once with ethyl acetate (100 ml). The organic layer was washed with water (10 ml) and then brine (10 ml), dried over anhydrous sodium sulphate and concentrated *in vacuo* to give an oil that was purified by flash chromatography on silica gel (hexane: ethyl acetate 5:1) to give pure products.

(3R, 4R*)-3,4-Dimethyl-3-phenylselanyl-γ-butyrolactone* **6a** and *(3S*, 4R*)-3,4-Dimethyl-3-phenylselanyl-γ-butyrolactone* **6b**:

These compounds were obtained in a 65% overall yield as viscous oils and in *ca.* 1 : 2 diastereoisomeric ratio.

6a (22%) . δ_H ($CDCl_3$) 7.7-7.6 (2H, m), 7.5-7.2 (3H, m), 4.50 (1H, dd, J_1=6.0, J_2=8.8), 3.87 (1H, dd, J_1=2.6, J_2=8.8), 2.6-2.4 (1H, m), 1.49 (3H, s) 1.12 (3H, d, J=7.4); δ_c ($CDCl_3$) 177.05, 137.88, 129.77, 129.08, 125.82, 72.98, 46.40, 40.28, 18.68, 15.02 ; ν_{max} ($CHCl_3$)/cm^{-1} 1760 (C=O). Anal. Calcd. for $C_{12}H_{14}O_2Se$: C, 53.54%, H, 5.24%. Found : C, 53.44% H, 5.22%.

6b (43%) : δ_H ($CDCl_3$) 7.7-7.6 (2H, m), 7.5-7.2 (3H, m), 4.27 (1H, dd, J_1=7.6, J_2=8.8), 3.93 (1H, dd, J_1=11.0, J_2=8.8), 2.5-2.3 (1H, m), 1.55 (3H, s), 1.24 (3H, d, J=6.6); δ_c ($CDCl_3$) 176.78, 138.36, 129.74, 128.99, 124.28, 70.74, 50.95, 43.27, 22.03, 11.89; ν_{max} ($CHCl_3$)/cm^{-1} 1760 (C=O). Anal. Calcd. for $C_{12}H_{14}O_2Se$: C, 53.54%, H, 5.24%. Found : C, 53.30% H, 5.22%.

(3R, 4R*)-3-Allyl-4-methyl-3-phenylselanyl-γ-butyrolactone* **7a** and *(3S*, 4R*)-3-Allyl-4-methyl-3-phenylselanyl-γ-butyrolactone* **7b**

These compounds were obtained in a 60% overall yield as viscous oils and as an inseparable *ca.* 1 : 2 diastereoisomeric mixture (ratio determined by ^{1}H-NMR analysis).

7a (20%) : δ_H ($CDCl_3$) 7.7-7.6 (2H, m), 7.5-7.2 (3H, m), 6.2-5.9 (1H, m); 5.3 (2H, m); 4.57 (1H, dd, J_1=5.6, J_2=9.0), 3.90 (1H, dd, J_1=2.0, J_2=9.0), 2.6-2.4 (3H, m), 1.14 (3H, d, J=7.2); δ_c ($CDCl_3$) 176.40, 138.02, 133.62, 133.46, 125.90, 124.57, 119.57, 72.88, 53.34; 40.02, 34.75, 15.42.

7b (40%) : δ_H ($CDCl_3$) 7.7-7.6 (2H, m), 7.5-7.2 (3H, m), 6.2-5.9 (1H, m) 5.3-5.1 (2H, m) 4.25 (1H, dd, J_1=8.8, J_2=8.8), 3.95 (1H, dd, J_1=11.0, J_2=8.8), 2.6-2.4 (3H, m), 1.18 (3H, d, J=8.8); δ_c ($CDCl_3$) 176.04, 139.12, 138.91, 138.40; 130.37, 129.57, 120.06, 119.57, 71.23, 53.99; 39.55, 39.01, 12.41.

7a-7b (mixture of diastereoisomers) ν_{max} ($CHCl_3$)/cm^{-1} 1757 (C=O). Anal. Calcd. for $C_{14}H_{16}O_2Se$: C, 56.95%, H, 5.46%. Found : C, 56.99% H, 5.54%.

(3R, 4R*)-3-Benzyl-4-methyl-3-phenylselanyl-γ-butyrolactone* **8a** and *(3S*, 4R*)-3-Benzyl-4-methyl-3-phenylselanyl-γ-butyrolactone* **8b**:

These compounds were obtained in 62% overall yield as viscous oils and in 4 :1 diastereoisomeric ratio.

8a: (50%); δ_H ($CDCl_3$) 7.7 (2H, m), 7.5-7.1 (8H, m), 4.09 (1H, dd, J_1=8.6, J_2=8.6), 3.90 (1H, dd, J_1=10.8, J_2=8.6), 3.36 (1H, d, J=13.8), 3.14 (1H, d, J=13.8), 2.45-2.25 (1H, m), 1.15 (3H, d, J=6.6); δ_c ($CDCl_3$) 175.34, 138.53, 136.31, 130.16, 129.87, 129.03, 128.55, 127.04, 124.26, 70.54, 55.30, 40.40, 36.91, 11.58; ν_{max} ($CHCl_3$)/cm^{-1} 1757 (C=O). Anal. Calcd. for $C_{18}H_{18}O_2Se$: C, 62.61%, H, 5.25%. Found: C, 62.75% H, 5.20%.

8b: (12%); δ_H ($CDCl_3$) 7.5-7.2 (10H, m), 4.49 (1H, dd, J_1=6.0, J_2=8.8), 3.77 (1H, dd, J_1=3.4, J_2=8.8), 3.16 (s,1H, s), 2.6-2.7 (1H, m), 1.21 (3H, d, J=7.0); δ_c ($CDCl_3$) 176.41, 137.83, 137.25, 136.50, 129.79, 129.68, 129.06, 128.42, 126.93, 72.01, 54.07, 40.17, 36.29, 14.69; ν_{max} ($CHCl_3$)/cm^{-1} 1757 (C=O). Anal. Calcd. for $C_{18}H_{18}O_2Se$: C, 62.61%, H, 5.25%. Found: C, 62.77% H, 5.22%.

(3R, 4R*)-3,4-Dibenzyl-3-phenylselanyl-γ-butyrolactone* **9a** and *(3S*, 4R*)-3,4-Dibenzyl-3-phenylselanyl-γ-butyrolactone* **9b** :

Compound **9a** was obtained according to the general procedure in a 70% yield as a viscous oil with only a minor amount of the minor diastereoisomer **9b** (**9a**:**9b** ratio >7:1 determined by ^{1}H-NMR analysis). This mixture can be crystallised at -30° C (ether/hexane) to give pure **9a**.

9a : δ_H ($CDCl_3$) 7.8-7.7 (2H, m), 7.6-7.2 (9H, m), 7.1-7.0 (4H, m), 4.00 (1H, dd, J_1=10.6, J_2=8.8), 3.89 (1H, dd, J_1=7.4, J_2=8.8), 3.43 (d, J=13.8), 3.20 (1H, d, J=13.8), 3.10 (1H, dd, J_1=4.6, J_2=13.4), 2.76 (1H, dd, J_1=10.4, J_2=13.4), 2.65-2.25 (1H, m); δ_c ($CDCl_3$) 175.27, 138.52, 137.87, 136.26, 130.17, 130.03, 129.52, 129.14,

128.78, 128.49, 127.23, 126.86, 69.56, 54.47, 43.88, 40.62, 34.40; ν_{max} ($CHCl_3$)/cm^{-1} 1758 (C=O). Anal. Calcd. for $C_{24}H_{22}O_2Se$: C, 68.40%, H, 5.26%. Found: C, 68.30% H, 5.34%.

9b : δ_H ($CDCl_3$) 7.8-7.7 (2H, m), 7.6-7.2 (9H, m),7.1-7.0 (4H, m), 4.21 (1H, dd, J_1=6.0, J_2=11.0), 3.86 (1H, dd, J_1=3.8, J_2=11.0), 3,27 (2H, s), 3.07 (1H, dd, J_1=9.0, J_2=13.0), 2.54 (1H, dd, J_1=13.0, J_2=13.0), 2.6-2.5 (1H, m); only discerned signals.

(3R, 4R*)-3,4-Bis[(3,4 methylenedioxy)benzyl]-3-phenylselanyl-γ-butyrolactone* **10a**:

The compound was obtained according to the general procedure in a 45% yield as a viscous oil, with only a minor amount of **10b** (**10a**:**10b** ratio >10:1 determined by ^{1}H-NMR analysis). This mixture can be crystallised at -30° C (ether: hexane) to give pure **10a** as a single diastereoisomer.

10a :δ_H ($CDCl_3$) 7.8-7.7 (2H, m), 7.6-7.5 (3H, m), 6.75-6.65 (2H, m), 6.6-6.5 (m, 4H), 5.93 (2H, s), 5.91 (1H, J=1.4), 5.90 (1H, d, J=1.4), 4.12 (1H, dd, J_1=7.0, J_2=8.0), 3.95 (1H, dd, J_1=9.0, J_2=8.0), 3.34 (1H, d, J=14.0), 3.09 (1H, d, J=14.0), 2.8-2.4 (3H, m); δ_c ($CDCl_3$) 175.26, 147.87, 147.80, 146.69, 146.40, 138.45, 135.72, 131.48, 135.72, 131.48, 129.81, 124.32, 123.21, 121.40, 110.26, 108.79, 108.36, 108.14, 100.97, 69.49, 54.39, 43.92, 40.27, 34.08 ; ν_{max} ($CHCl_3$)/cm^{-1} 1757 (C=O). Anal. Calcd. for $C_{26}H_{22}O_6Se$: C, 61.30%, H, 4.35%. Found: C, 61.20% H, 4.35%.

General procedure for selenoxide elimination:

To a solution of the selenides (0.5 mmol) in 5ml of methanol/water 6:1, $NaIO_4$ (214 mg) and $NaHCO_3$, (100 mg) were added. The mixture was stirred at room temperature until TLC showed no traces of starting material (1 hour), then ethyl acetate (50 ml) was added and the mixture washed with brine (10ml).

The organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give pure products.

4-Methylfuran-2(5H)-one **5a**:

Obtained from **4a** in a 95% yield as an oil. The spectral data are completely in agreement with those reported in literature.[11a]

δ_H ($CDCl_3$) 5.78 (1H, s), 4.73 (2H, s), 2.12 (3H, s).

4-[3,4-(Methylenedioxy)benzyl]furan-2(5H)-one **5b**:

Obtained from **4b** in a 93% yield as white solid. M.p.: 56-57° (methanol). δ_H ($CDCl_3$) 6.3-6.2 (1H, m), 5.97 (2H, s), 5.84 (1H, t, J=1.8), 4.70 (2H, d, J=1.8), 3.66 (2H, s); δ_c ($CDCl_3$) 169.04, 147.98, 146.85, 142.49,

129.04, 121.81, 116.83, 108.99, 108.68, 101.24, 72.61, 39.90, 34.97; ν_{max} ($CHCl_3$)/cm^{-1} 1777, 1746 (C=O), 1687, 1659 (C=C). Anal. Calcd. for $C_{12}H_{12}O_4$: C, 66.05%, H, 4.62%. Found: C, 66.15% H, 4.62%.

4-Benzylfuran-2(5H)-one **5c** :

Obtained from **4c** in a 94% yield as white solid. M.p.: 46-47° (methanol). Lit. 48°. The spectral data are completely in agreement with those reported in literature.[9b,c]

δ_H ($CDCl_3$) 7.4-7.2 (5H, m), 5.81 (1H, tt, J_1=1.8 J_2=1.8), 4.8-4.7 (2H, m), 3.74 (1H, s).

(±)-4-Methyl-3-methylene-γ-butyrolactone **6c** :

Obtained from **6a** in a 95% yield as an oil. The spectral data are completely in agreement with those reported in literature.[4c]

δ_H ($CDCl_3$) 6.20 (1H, d, J=3.5), 5.58 (1H, d, J=3.5), 4.7-3.6 (2H, m), 3.5-2.9 (1H, m), 1.25 (3H, d, J=7.0).

4,3-Dimethylfuran-2(5H)-one **6d** :

Obtained from **6b** in a 93% yield as white solid. M.p.: 36-37° (methanol). Lit. 36-38°. The spectral data are completely in agreement with those reported in literature.[4c,11a]

δ_H ($CDCl_3$) 4.62 (2H, s), 2.01 (3H, s), 1.68 (3H, s).

(E)-(±)-3-Benzylidene-4-methyl-γ-butyrolactone **8c** :

Obtained from **8a** in a 91% yield as colourless viscous oil. δ_H ($CDCl_3$) 7.7-7.6 (3H, m), 7.6-7.5 (3H, m), 4.46 (1H, dd, J_1=7.2, J_2=8.8), 4.10 (1H, dd, J_1=2.2, J_2=8.8), 3.8-3.6 (1H, d, m), 1.33 (3H, d, J=7.0); δ_c ($CDCl_3$) 172.38, 137.98, 136.68, 133.87, 129.94, 129.79, 128.90, 72.79, 32.80, 18.29 ; ν_{max} ($CHCl_3$)/cm^{-1} 1744 (C=O), 1653 (C=C). Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57%, H, 6.42%. Found: C, 76.55% H, 6.29%.

3-Benzyl-4-methylfuran-2(5H)-one **8d** :

Obtained from **8b** in a 95% yield as colourless viscous oil. δ_H ($CDCl_3$) 7.3-7.2 (5H, m), 4.63 (2H, s), 3.61 (2H, s), 2.01 (3H, s); δ_c ($CDCl_3$) 157.52, 138.51, 130.14, 128.55, 128.45, 126.44, 126.39, 72.46, 29.38, 12.39; ν_{max} ($CHCl_3$)/cm^{-1} 1748, (C=O) 1679 (C=C). Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57%, H, 6.42%. Found: C, 76.57% H, 6.55%.

(E)-(±)-4-Benzyl-3-benzylidene-γ-butyrolactone **9c** :

Obtained from **9a** in a 94% yield as colourless viscous oil. The spectral data are completely in agreement with those reported in literature.[3b]

δ_H ($CDCl_3$) 7.7-7.0 (11H, m), 4.26 (2H, d, J=4.0), 4.1-3.6 (1H, m), 3.3-2.3 (2H, m).

(±)-Savinin **10c** :

Obtained from **10a** in a 93% yield as white solid. M.p.: 145-148° (methanol). Lit. 147-148°. Spectral data are completely in agreement with those reported in literature.[10]

General procedure for deselenylation[12]

To a THF solution (5ml) of the 3,4-disubstituted-3-phenylselanyl butyrolactones **9a-9b** or **10a-10b** (0.47 mmol), $NiCl_2$ (1.41 mmol, 3 eq) and $NaBH_4$ (4.23 mmol, 9 eq) were added at 0° C. After 5 minutes, the mixture was diluted with ethyl acetate (50 ml) and filtered over celite to give, after evaporation of the solvent, the corresponding saturated butyrolactone **9e** or **10e** (*trans/cis* ratio >10:1).

(3R, 4R*)-3,4-Dibenzyl-γ-butyrolactone* **9e** :

Obtained from **9a/9b** in 90% yield as a colourless viscous oil. The spectral data are completely in agreement with those reported in literature.[11c]

(±)-Hinokinin **10e** :

Obtained from **10a/10b** in 95% yield as white solid. M.p.: 62-64° (methanol). Lit. 64-65°. Spectral data are completely in agreement with those reported in literature.[11d]

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References and notes:

1 Perlmutter, P. in *Conjugate Addition in Organic Synthesis*; ed. Pergamon Press Oxford: **1992**.

2 Hollingworth, G. J.; Lee, T.; Sweeney, J. *Synth. Comm.*, **1996**, *26*, 1117-1134.

3 (a) van Heerden, P. S.; Bezuidenhoudt, B. C. B.; Ferreira, D. *Tetrahedron*, **1996**, *52*, 12313-12322; (b)Minami, T.; Kitajima, Y.; Chikugo, T. *Chem. Lett.* **1986**, 1229-1232; (c); Wanatabe, M.; Tsukazaki, M.; Hirakawa, Y; Iwao, M.; Furukawa, S. *Chem. Pharm. Bull.* **1989**, *37*, 2914-2919; see also ref. 2 for the synthesis and organocopper addition to 3-phenylthio furanones and references cited therein.

4 (a) Ayres, D. C.; Loike, J. D. *Lignans*; ed. Cambridge University Press: **1990**. (b) MacRea, W. D.; Towers, G. H. N. *Phytochemistry*; **1984**, *23*, 1207, (c) Mattes, H.; Hamada, K.; Benezra, C. *J. Med. Chem.*, **1987**, *11*, 1948-1951.

5 (a) Knight, W. *Contemp. Org. Synth.*, **1994**, *1*, 287. (b) van Overen, A.; Jansen, J. F. G. A.; Feringa, B. L. *J. Org. Chem.*, **1994**, *59*, 5999-6007.

6 (a) D'Onofrio, F.; Margarita, R.; Parlanti, L. ; Pernazza, D.; Piancatelli G. *Tetrahedron*, **1997**, *53*, 15843-15843. (b) Abdel-Rahman, H.; Adams, J. P.; Boyes, A. L.; Kelly, M. J.; Mansfiel, D. J.; Procopiu, P.A.; Roberts, S. M.; Slee, D. H.; Watson, N. S. *J. Chem. Comm.*, **1993**, 1939-1941. (c) Hughes, M. J.; Thomas, E. J.; *J. Chem. Soc., Perkin Trans. I*, **1993**, 1493-1505.

7 Hollingworth, G. J.; Perkins, G.; Sweeney, J. *Perkin. Trans. 1*, **1996**, 1913-1919.

8 (a) Bella, M.; D'Onofrio, F.; Margarita, R.; Parlanti, L.; Piancatelli, G.; Mangoni, A. *Tetrahedron Lett.* **1997**, *45*, 7917-7918.(b) Caracciolo Torchiarolo, G.; D'Onofrio, F.; Margarita, R.; Parlanti, L.; Piancatelli, G.; Bella, M. *Tetrahedron*, **1998**, *54*, 15657-15666. (c) D'Onofrio, F.; Parlanti L.; Piancatelli, G. *Synlett*, **1996**, 63-64.

9 (a) Borguignon, J. J.; Schoenfelder, A.; Schmitt, M.; Wermuth, C. G.; Hechler, V.; Charlier, B.; Maitre, M. *J. Med. Chem.*, **1988**, *31*, 893. (b) Muraoka, O.; Tanabe, G.; Higachiura, M.; Minematsu, T.; Momose, T.; *J. Chem. Soc., Perkin Trans. I*; **1995**; 1437-1444; Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.*, **1979**, *168*, 233-240.

10 For other syntheses of savinin see Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L. *Synthesis*, **1997**, 1061-1066 and the references cited therein.

11 (a) Binger, P.; Weintz, H. J. *Chem. Ber.* **1984**, *117*, 654-665. (b) Woo, E. P.; Cheng, F.C.W. *J. Org. Chem.*; 19, **1986**, *51*, 3706-3707. (c) Momose, T.; Tanabe, G.; Tsujimori, H.; Muraoka, O. *Chem. Pharm. Bull.*, **1992**, *40*, 2525-2530. (d) Rehnberg, N. Magnusson, G. *J.Org.Chem.*; **1990**, *55*, 4340-4349.

12 Back, T. G.; Briss, V. I.; Edwards, M.; Krishna, M. V. *J. Org. Chem.*, **1988**, *53*, 3815-3822.